(12) 按照专利合作条约所公布的国际申请

(19) 世界知识产权组织
国 际 局

(43) 国际公布日
2019 年 8 月 15 日 (15.08.2019)

WIPO | PCT

(10) 国际公布号
WO 2019/154257 A1

(51) 国际专利分类号:
C07J 3/00 (2006.01) *A61K 31/57* (2006.01)
C07J 5/00 (2006.01) *A61K 31/573* (2006.01)
C07J 7/00 (2006.01) *A61K 31/58* (2006.01)
C07J 17/00 (2006.01) *A61P 25/00* (2006.01)
C07J 43/00 (2006.01)

(21) 国际申请号: PCT/CN2019/074134

(22) 国际申请日: 2019 年 1 月 31 日 (31.01.2019)

(25) 申请语言: 中文

(26) 公布语言: 中文

(30) 优先权:

201810141153.6	2018年2月11日 (11.02.2018)	CN
201810180543.4	2018年3月5日 (05.03.2018)	CN
201810491114.9	2018年5月21日 (21.05.2018)	CN
201810771964.4	2018年7月13日 (13.07.2018)	CN
201811408081.3	2018年11月23日 (23.11.2018)	CN

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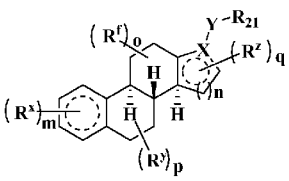
(81) 指定国(除另有指明，要求每一种可提供的国家保护): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW。

(84) 指定国(除另有指明，要求每一种可提供的地区保护): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), 欧亚 (AM, AZ, BY, KG, KZ, RU, TJ, TM), 欧洲 (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG)。

本国际公布:
一 包括国际检索报告(条约第21条(3))。

(54) **Title:** STEROID DERIVATIVE REGULATORS, METHOD FOR PREPARING THE SAME, AND USES THEREOF

(54) 发明名称: 一种甾族类衍生物调节剂及其制备方法和应用



(I)

(57) **Abstract:** The present invention relates to steroid derivative regulators, a method for preparing the same, and uses thereof. Specifically, the present invention relates to a compound of formula (I), a preparation method therefor, a pharmaceutical composition containing the compound, and uses thereof as a regulator the of GABA $_A$ receptor for treating depression, convulsion, Parkinson's disease, and nervous system diseases, wherein the substituents of the formula (I) are as defined in the description.

(57) 摘要: 本发明涉及一种甾族类衍生物调节剂及其制备方法和应用。特别地，本发明涉及通式(I)所示的化合物、其制备方法及含有该化合物的药物组合物，及其作为$GABA_A$受体调节剂在治疗抑郁症、惊厥、帕金森和神经系统疾病的用途，其中通式(I)中的各取代基与说明书中的定义相同。

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STEROID DERIVATIVE REGULATORS, METHOD FOR PREPARING THE SAME, AND USES THEREOF

FIELD OF THE INVENTION

The present invention belongs to the field of drug synthesis, and in particular relates to a steroid derivative regulator, a method for preparing the same, and a use thereof.

BACKGROUND OF THE INVENTION

$GABA_A$ receptor is a chemically-gated channel on the cell membrane and belongs to an ionic receptor. $GABA_A$ receptor is widely distributed in the nervous system, and can bind to the inhibitory neurotransmitter GABA (gamma-aminobutyric acid), leading to the opening of chloride channels and inhibition of neurons. $GABA_A$ receptor regulator (tetrahydroprogesterone) is a positive regulator of $GABA_A$ receptor. The binding of tetrahydroprogesterone and the intrasynaptic $GABA_A$ receptor regulator can increase the opening frequency of chloride channel on the receptor and the influx of chloride ion, thereby increasing the Phasic current, producing a rapid inhibitory effect, reducing nerve excitability, and providing an anti-anxiety and anti-depression effect. The binding of tetrahydroprogesterone and the extrasynaptic $GABA_A$ receptor provides a continuous chloride ion current, and mediates a lasting and sustained inhibitory effect. Tetrahydroprogesterone can also increase the content of brain derived neurotrophic factor (BDNF), promote the regeneration of hippocampal neurons, and provides a neuroprotective effect, thereby improving anxiety and depression symptoms; but the specific mechanism of action is not yet clear.

Major depressive disorder (MDD) is a common, chronic and recurrent disease. The burden and adverse consequence caused by it are becoming more and more serious. In the past 40 years, the research and clinical application of antidepressants have greatly developed. However, most antidepressants (fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, etc.) take 2 to 4 weeks to have an effect. The clinical treatment of major depressive disorder patients, especially patients with suicidal tendency, often needs to be prompt and rapid, thus there is an urgent need to develop fast-acting antidepressants.

In the past two decades, there has been little innovation in the research and development of depression treatment. The development goal of $GABA_A$ receptor regulator is to change the expectation of patients by changing the treatment regimen of MDD. If successfully developed, the $GABA_A$ receptor regulator may become the first drug that provides a truly new mechanism of action for the treatment of depression in more than two decades. At present, foreign pharmaceutical companies, including Sage Therapeutics and Marinus etc., are doing their best to develop $GABA_A$ receptor

regulators.

Published patent applications related to $GABA_A$ receptor regulators include: WO2003077919, WO2014169833, WO2016061537, WO2015180679, and WO2015027227.

$GABA_A$ receptor regulators, as a popular target in the pharmaceutical industry, currently have a good application prospect.

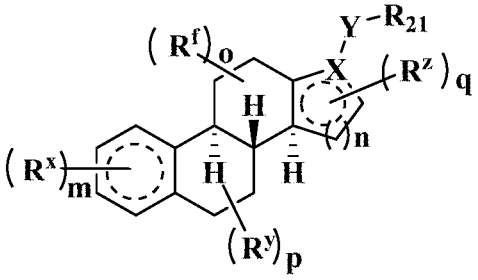
First, $GABA_A$ receptor regulators can be applied to major depressive disorder (MDD). The annual incidence of MDD in China is about 2%, thus there is a huge market potential.

Second, existing antidepressants take a long time, commonly 3 to 4 weeks, to have an effect, have a high failure rate up to 40%, and require long-term medication. $GABA_A$ receptor regulators can provide a significant antidepressant effect within 24 hours, and the effect can last for several days to two weeks.

Third, $GABA_A$ receptor regulator can meet the treatment need of MDD patients with oral administration once a day.

SUMMARY OF THE INVENTION

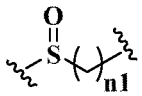
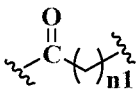
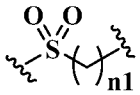
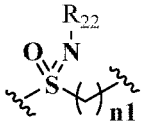
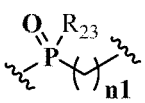
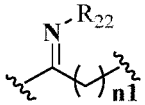
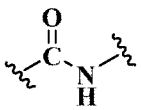
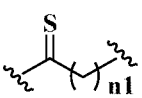
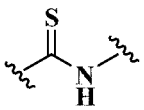
The objective of the present invention is to provide a compound of formula (I), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, wherein the structure of the compound of formula (I) is as follows:



(I)

wherein:

X is selected from the group consisting of $-CR_{17}-$ and -N-;

Y is selected from the group consisting of $-CR_{23}R_{24}-$, $-S(CH_2)_{n1}-$, $-P(CH_2)_{n1}-$, $-O(CH_2)_{n1}-$, $-(CH_2)_{n1}NR_{22}-$,  ,  ,  ,  ,  ,  ,  ,  and  ;

R^x, R^y, R^z and R^f are identical or different and are each independently selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, thiol, nitro, hydroxy, cyano, alkenyl,

alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{24}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, thiol, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

or, any two adjacent or non-adjacent groups of R^x, R^y, R^z and R^f can be bonded to form a cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{24}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$;

or, any two adjacent groups of R^x, R^y, R^z and R^f can form a double bond;

R_{21} is selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, nitro, hydroxy, cyano, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{24}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

when X is $-CR_{17}-$, R_{17} is selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, hydroxy, amino, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein the alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents

selected from the group consisting of deuterium atom, substituted or unsubstituted alkyl, halogen, hydroxy, substituted or unsubstituted amino, oxo, nitro, cyano, alkenyl, alkynyl, alkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl;

or, R_{17} and any group of R^x, R^y, R^z and R^f can be bonded to form a cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{24}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$;

R_{22} is selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, nitro, hydroxy, cyano, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{24}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

R_{23}, R_{24}, R_{25} and R_{26} are identical or different and are each independently selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, hydroxy, amino, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein the alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, substituted or unsubstituted alkyl, halogen, hydroxy, substituted or unsubstituted amino, oxo, nitro, cyano, alkenyl, alkynyl, alkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl;

m is an integer of 0, 1, 3, 4, 5, 6, 7, 8, 9 or 10;

n is an integer of 0, 1, 2 or 3;

o is an integer of 0, 1, 2, 3, 4 or 5;

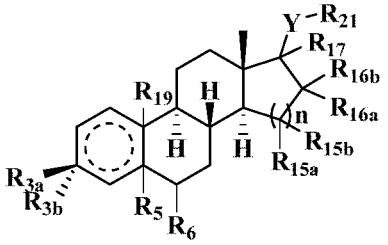
p is an integer of 0, 1, 2, 3, 4, 5 or 6;

q is an integer of 0, 1, 2, 3, 4, 5 or 6;

m_1 is an integer of 0, 1 or 2; and

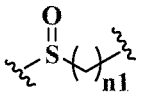
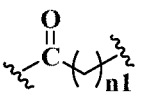
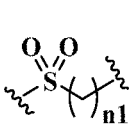
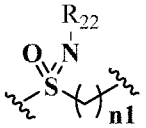
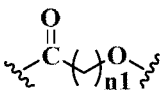
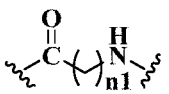
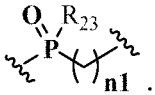
n_1 is an integer of 0, 1, 2, 3, 4 or 5.

In a preferred embodiment of the present invention, the compound of formula (I) is a compound of formula (I-A), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:



(I-A)

wherein:

Y is selected from the group consisting of $-S(CH_2)_{n1}-$,  ,  ,  ,  ,  ,  and  ;

R_{3a} and R_{3b} are identical or different and are each independently selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, thiol, nitro, hydroxy, cyano, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}S(O)NR_{23}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{23}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, thiol, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

R_5, R_6, R_{15a}, R_{15b}, R_{16a}, R_{16b} and R_{19} are identical or different and are each independently selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, nitro, hydroxy, cyano, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$,

$-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}S(O)NR_{23}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{23}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

or, any two adjacent or non-adjacent groups of R_5, R_6, R_{15a}, R_{15b}, R_{16a}, R_{16b} and R_{19} can be bonded to form a cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

R_{17} is selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, hydroxy, amino, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein the alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, substituted or unsubstituted alkyl, halogen, hydroxy, substituted or unsubstituted amino, oxo, nitro, cyano, alkenyl, alkynyl, alkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl;

or, R_{17} and any group of R_{16a} and R_{16b} can be bonded to form a cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{24}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$;

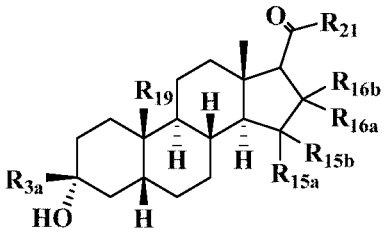
R_{21} is selected from the group consisting of hydrogen atom, deuterium atom, alkyl,

deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, nitro, hydroxy, cyano, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{24}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

n is an integer of 0, 1, 2 or 3;

R_{22}-R_{26}, m_1 and n_1 are as defined in the compound of formula (I).

In a preferred embodiment of the present invention, the compound of formula (I) is a compound of formula (II), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:



(II)

wherein:

R_{3a} is selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, thiol, nitro, hydroxy, cyano, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}S(O)(NR_{23})R_{24}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{23}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, thiol, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

R_{15a}, R_{15b}, R_{16a} and R_{16b} are identical or different and are each independently selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, nitro, hydroxy, cyano, alkenyl,

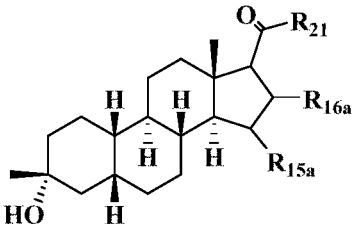
alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}S(O)(NR_{23})R_{24}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{23}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$, and R_{15a}, R_{15b}, R_{16a} and R_{16b} are not hydrogen at the same time;

or, any two adjacent or non-adjacent groups of R_{15a}, R_{15b}, R_{16a} and R_{16b} can be bonded to form a cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

R_{19} is selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, thiol, nitro, hydroxy, cyano, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}S(O)(NR_{23})R_{24}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{23}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$;

R_{21}, R_{23}-R_{26}, m_1 and n_1 are as defined in the compound of formula (I).

In a preferred embodiment of the present invention, the compound of formula (I) is a compound of formula (III), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:

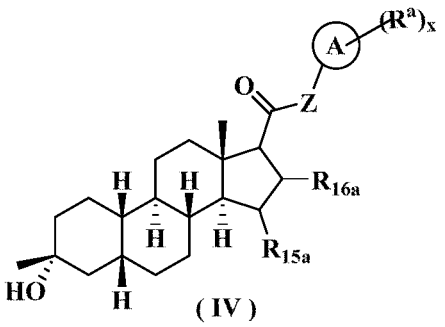


(III)

wherein:

R_{15a}, R_{16a} and R_{21} are as defined in the compound of formula (I).

In a preferred embodiment of the present invention, the compound of formula (I) is a compound of formula (IV), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:



(IV)

wherein:

Z is selected from the group consisting of $-CR_{23}R_{24}-$, $-(CH_2)_{n1}NR_{23}-$ and $-(CH_2)_{n1}O(CH_2)_{n2}-$, and preferably methylene;

ring A is selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

each R_a is identical or different and each is selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, nitro, hydroxy, cyano, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}S(O)(NR_{23})R_{24}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{23}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

R_{15a} is selected from the group consisting of hydrogen atom, alkyl, haloalkyl, alkoxy, halogen, amino, hydroxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$ and $-(CH_2)_{n1}NR_{23}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R_{16a} is selected from the group consisting of hydrogen atom, alkyl, haloalkyl, alkoxy, halogen, amino, hydroxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$,

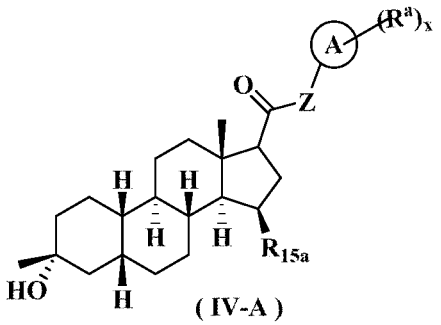
$-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$ and $-(CH_2)_{n1}NR_{23}R_{24}$;

or, R_{15a} and R_{16a} can form a cycloalkyl or heterocyclyl, wherein the cycloalkyl or heterocyclyl is optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, and R_{15a} and R_{16a} are not hydrogen at the same time;

R_{23} and R_{24} are each selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, nitro, hydroxy, cyano, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

R_{25}-R_{26}, m_1, n_1 and x are as defined in the compound of formula (II).

In a preferred embodiment of the present invention, the compound of formula (I) is a compound of formula (IV-A), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:

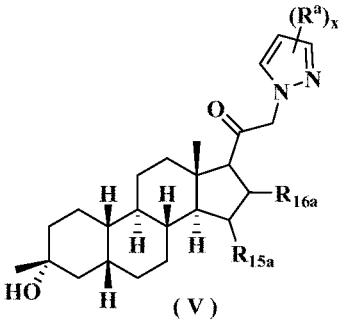


(IV-A)

R_{15a} is selected from the group consisting of hydrogen atom, alkyl, haloalkyl, alkoxy, halogen, amino, hydroxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$ and $-(CH_2)_{n1}NR_{23}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

ring A, R^a and x are as defined in the compound of formula (IV).

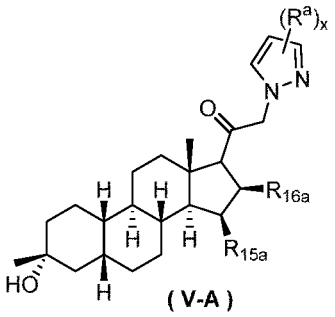
In a preferred embodiment of the present invention, the compound of formula (I) is a compound of formula (V), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:



wherein:

R_{15a}, R_{16a}, R^a and x are as defined in the compound of formula (IV).

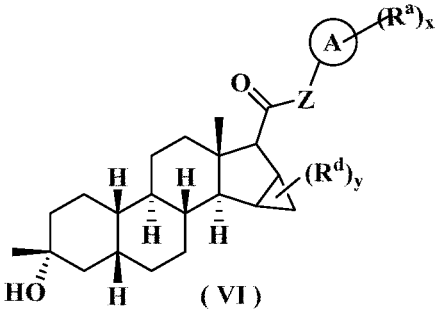
In a preferred embodiment of the present invention, the compound of formula (I) is a compound of formula (V), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:



wherein:

R_{15a}, R_{16a}, R^a and x are as defined in the compound of formula (V).

In a preferred embodiment of the present invention, the compound of formula (I) is a compound of formula (VI), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:



wherein:

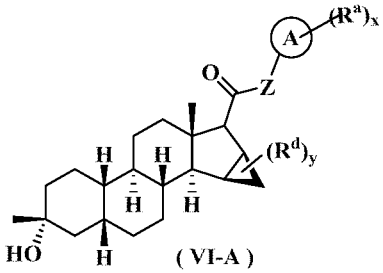
each R^d is identical or different and each is selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, nitro, hydroxy, cyano, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}S(O)(NR_{23})R_{24}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{23}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium

atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

y is an integer of 0, 1, 3 or 4;

ring A, Z, R^a, R_{23}-R_{26}, m_1, n_1 and x are as defined in the compound of formula (IV).

In a preferred embodiment of the present invention, the compound of formula (I) is a compound of formula (VI-A), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:

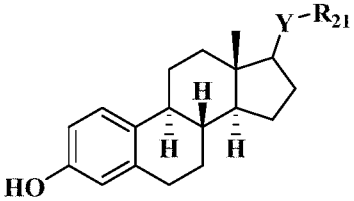


(VI-A)

wherein:

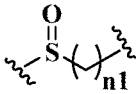
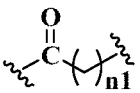
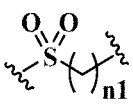
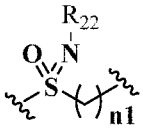
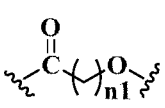
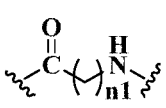
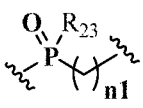
ring A, Z, R^a, R^d, R_{23}-R_{26}, m_1, n_1, x and y are as defined in the compound of formula (VI).

In a preferred embodiment of the present invention, the compound of formula (I) is a compound of formula (VII), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:



(VII)

wherein:

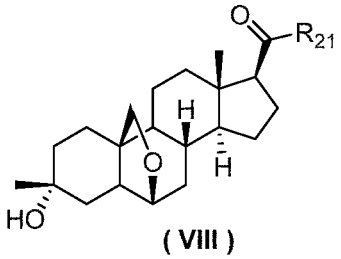
Y is selected from the group consisting of $-S(CH_2)_{n1}-$,  ,  ,  ,  ,  ,  and  ;

R_{21} is selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, nitro, hydroxy, cyano, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$,

$-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{24}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

R_{22}-R_{26}, m_1 and n_1 are as defined in the compound of formula (I).

In a preferred embodiment of the present invention, the compound of formula (I) is a compound of formula (VIII), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:



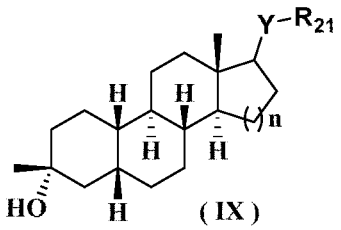
(VIII)

wherein:

R_{21} is selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, nitro, hydroxy, cyano, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{24}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

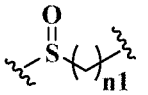
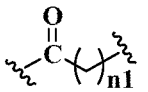
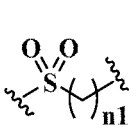
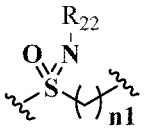
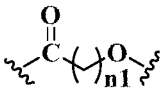
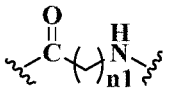
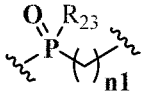
R_{23}-R_{26}, m_1 and n_1 are as defined in the compound of formula (I).

In a preferred embodiment of the present invention, the compound of formula (I) is a compound of formula (IX), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:



(IX)

wherein:

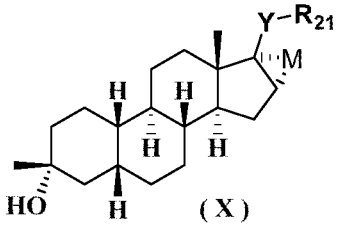
Y is selected from the group consisting of $-S(CH_2)_{n1}-$,  ,  ,  ,  ,  ,  and  ;

R_{21} is selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, nitro, hydroxy, cyano, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{24}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$; and

n is an integer of 0, 1 or 2;

R_{22}-R_{26}, m_1 and n_1 are as defined in the compound of formula (I).

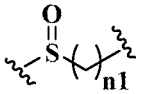
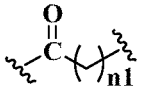
In a preferred embodiment of the present invention, the compound of formula (I) is a compound of formula (X), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:

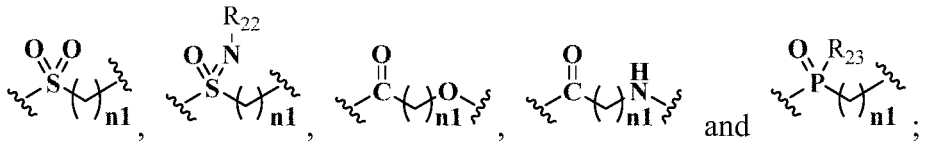


(X)

wherein:

M is selected from the group consisting of $-CR_{23}-$ and oxygen;

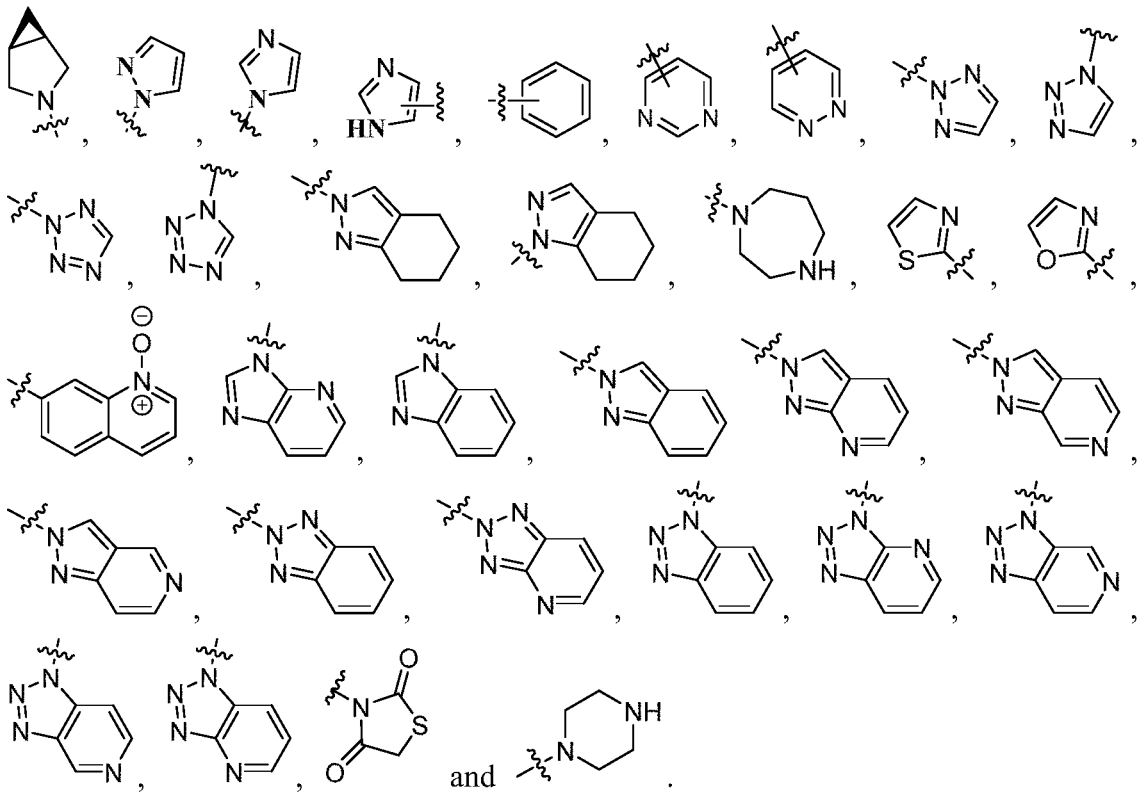
Y is selected from the group consisting of $-S(CH_2)_{n1}-$,  ,  ,



R_{21} is selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, nitro, hydroxy, cyano, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{24}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

R_{22}-R_{26}, m_1 and n_1 are as defined in the compound of formula (I).

In a preferred embodiment of the present invention, in the compound of formula (I), the stereoisomer thereof or the pharmaceutically acceptable salt thereof, the ring A is selected from the group consisting of:



In a preferred embodiment of the present invention, the compound of any formula, the stereoisomer thereof or the pharmaceutically acceptable salt thereof,

wherein:

Z is selected from the group consisting of $-CH_2-$, $-CH_2NH-$, $-CH_2O-$, $-CH_2-$, -NH- and $-NHSO_2-$;

Y is selected from the group consisting of -C(O)-, $-C(O)CH_2-$, -C(O)O-, $-C(O)CH_2NH-$, - $C(O)CH_2O-$, $-SCH_2-$, $-S(O)CH_2-$, $-S(O)_2CH_2-$, $-P(O)R_{23}-$, -C(O)NH- and $-C(O)NHSO_2-$; wherein R^a is selected from the group consisting of hydrogen atom, halogen, amino, cyano, nitro, C_{1-6} alkyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} alkoxy, C_{1-6} hydroxyalkyl, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$ and $-(CH_2)_{n1}S(O)_{m1}R_{23}$, wherein the C_{1-6} alkyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{3-6} halocycloalkyl, C_{1-6} alkoxy and C_{1-6} hydroxyalkyl are each optionally further substituted by one or more substituents selected from the group consisting of hydrogen atom, halogen, cyano, hydroxy, C_{1-6} alkyl, C_{3-6} cycloalkyl and 3 to 6 membered heterocyclyl;

R^d is selected from the group consisting of hydrogen atom, halogen, amino, cyano, nitro, C_{1-6} alkyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} alkoxy and C_{1-6} hydroxyalkyl;

R_{23} and R_{24} are identical or different and are each independently selected from the group consisting of C_{1-6} alkyl, C_{3-8} cycloalkyl and 3 to 8 membered heterocyclyl, wherein the C_{1-6} alkyl, C_{3-8} cycloalkyl and 3 to 8 membered heterocyclyl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, halogen, hydroxy, C_{1-3} alkyl, amino, oxo, nitro, cyano, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} hydroxyalkyl, C_{3-8} cycloalkyl, $-(CH_2)_{n1}NR_{25}R_{26}$, 3 to 8 membered heterocyclyl, 6 to 10 membered aryl and 5 to 12 membered heteroaryl.

In a preferred embodiment of the present invention, the compound of any formula, a stereoisomer thereof or a pharmaceutically acceptable salt thereof,

wherein:

R_{15a} is selected from the group consisting of hydrogen atom, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, halogen, amino, hydroxy, C_{3-8} cycloalkyl, C_{3-8} halocycloalkyl, 3 to 8 membered heterocyclyl, 6 to 10 membered aryl, 5 to 12 membered heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$ and $-(CH_2)_{n1}NR_{23}R_{24}$, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-8} cycloalkyl, C_{3-8} halocycloalkyl, 3 to 8 membered heterocyclyl, 6 to 10 membered aryl and 5 to 12 membered heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of hydrogen atom, halogen, cyano, hydroxy, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, $-(CH_2)_{n1}NR_{25}R_{26}$ and 3 to 6 membered heterocyclyl;

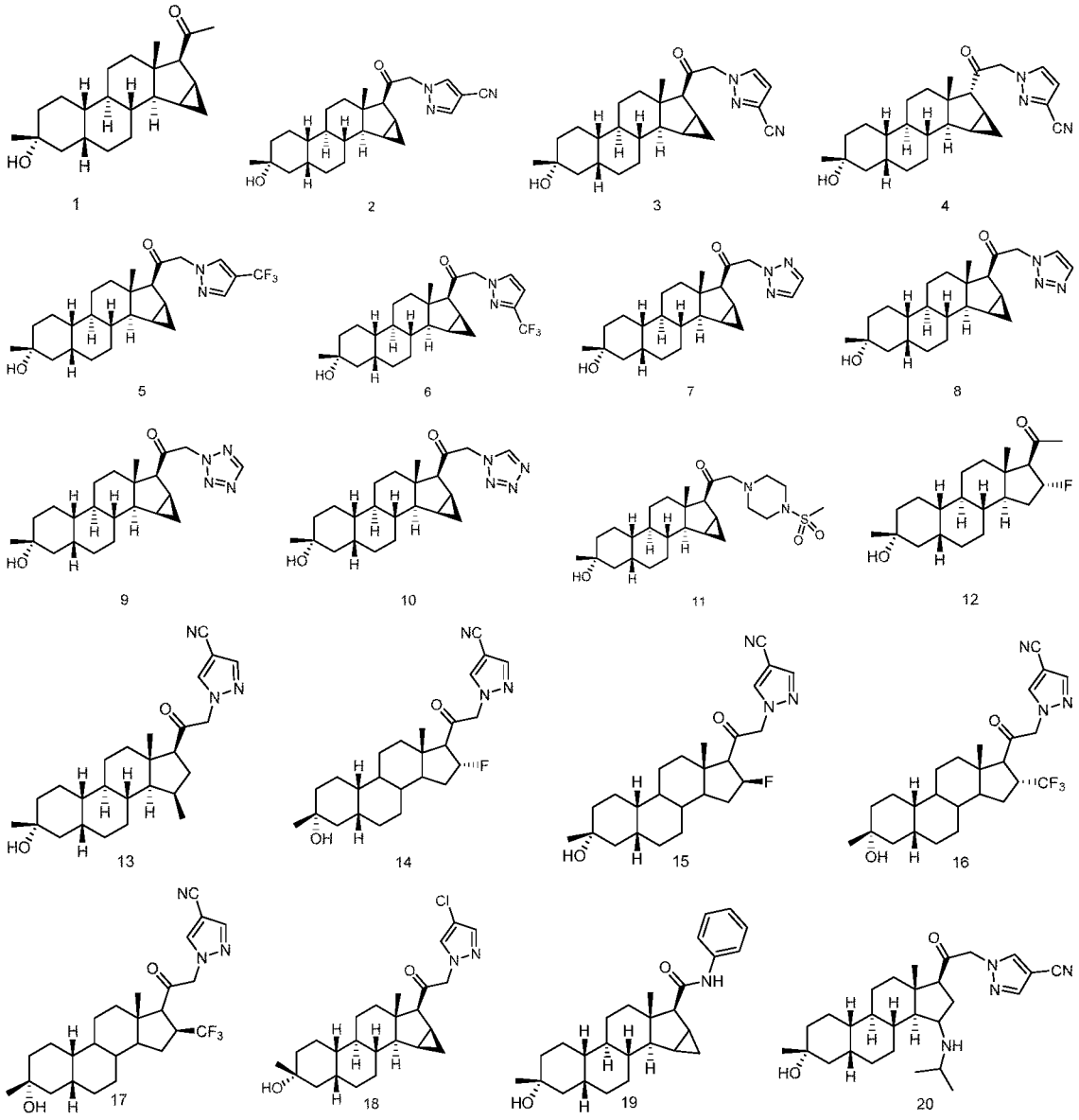
R_{16a} is selected from the group consisting of hydrogen atom, halogen, cyano, C_{1-6} alkyl and C_{1-6} haloalkyl;

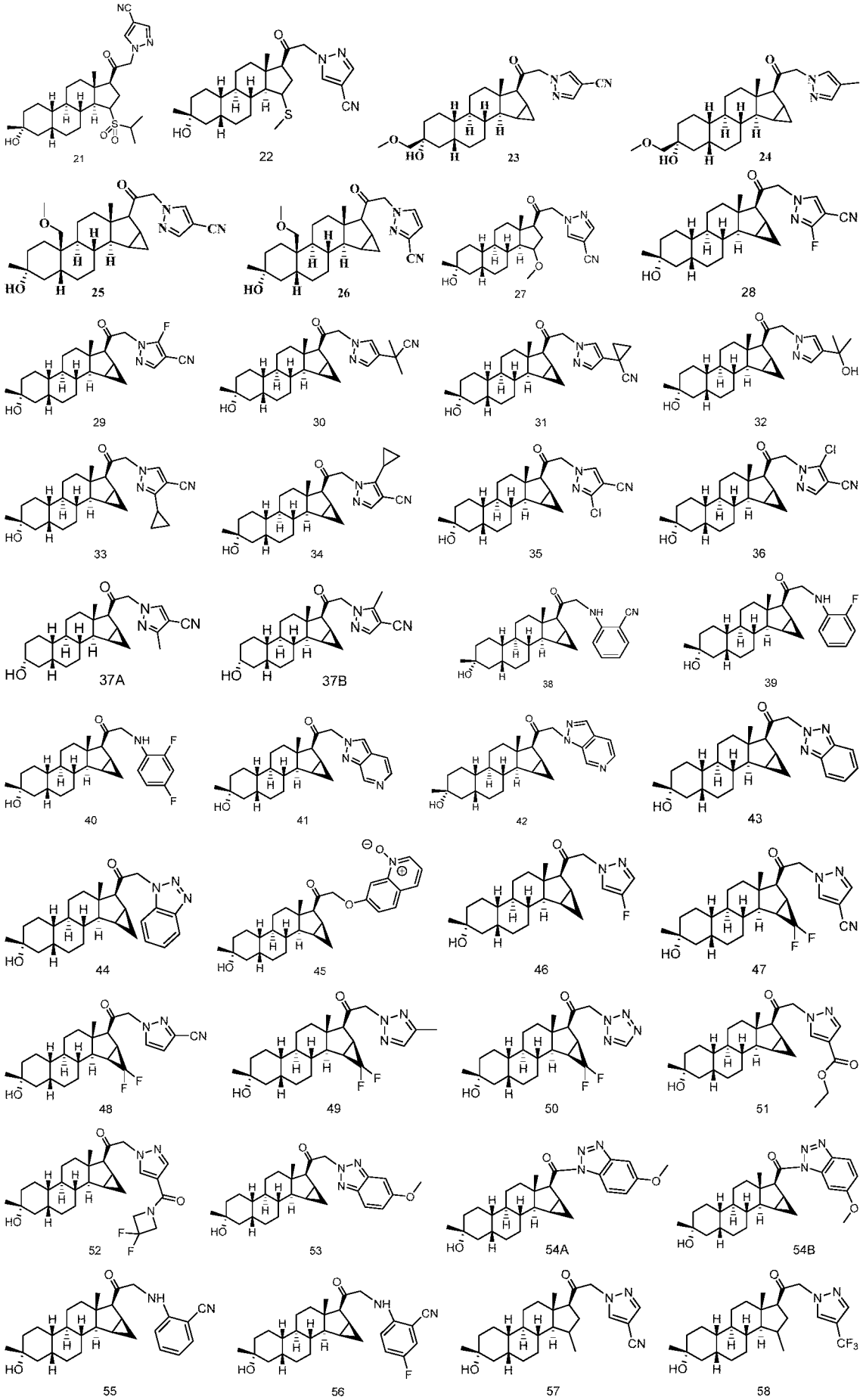
or, R_{15a} and R_{16a} can form a C_{3-8} cycloalkyl, wherein the C_{3-8} cycloalkyl is optionally further substituted by one or more substituents selected from the group

consisting of hydrogen atom, C_{1-6} alkyl, C_{1-6} haloalkyl and halogen, and R_{15a} and R_{16a} are not hydrogen at the same time;

R_{23} and R_{24} are identical or different and are each independently selected from the group consisting of hydrogen atom, C_{1-6} alkyl, C_{3-8} cycloalkyl and 3 to 8 membered heterocyclyl, wherein the C_{1-6} alkyl, C_{3-8} cycloalkyl and 3 to 8 membered heterocyclyl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, halogen, hydroxy, C_{1-3} alkyl, amino, oxo, nitro, cyano, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} hydroxyalkyl, C_{3-8} cycloalkyl, $-(CH_2)_{n1}NR_{25}R_{26}$, 3 to 8 membered heterocyclyl, 6 to 10 membered aryl and 5 to 12 membered heteroaryl.

In a preferred embodiment of the present invention, the compound of formula (I), the stereoisomer thereof, or the pharmaceutically acceptable salt thereof is selected from the group consisting of:

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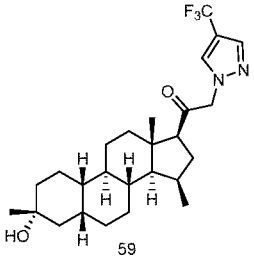
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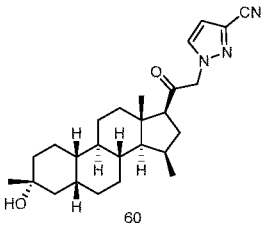
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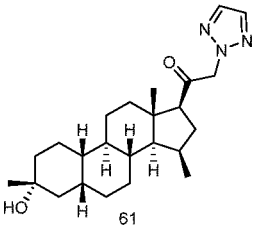
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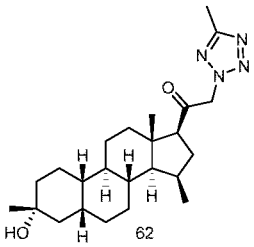
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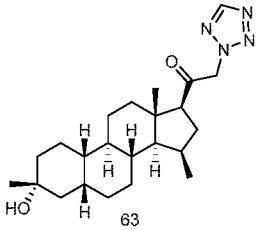
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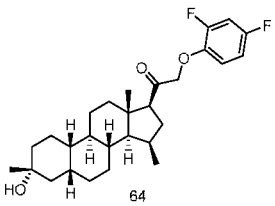
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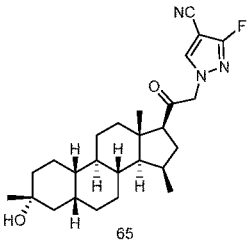
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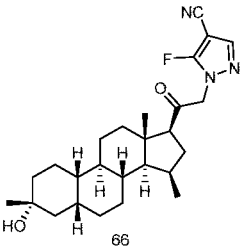
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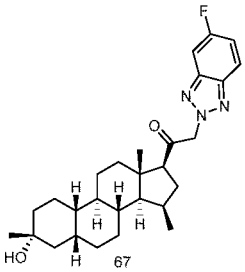
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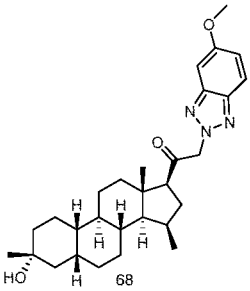
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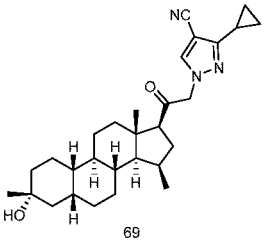
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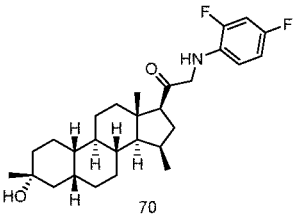
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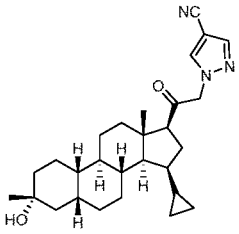
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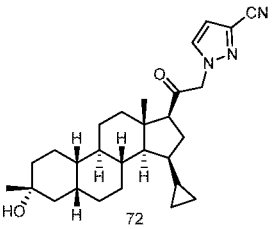
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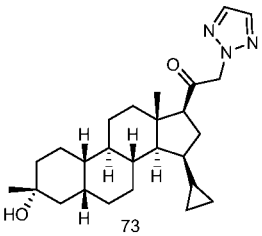
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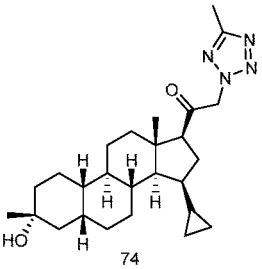
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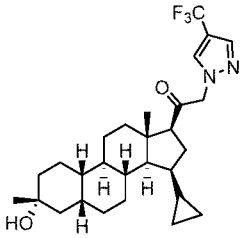
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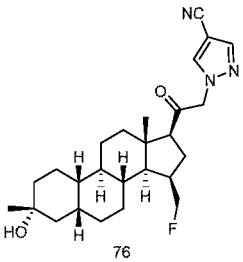
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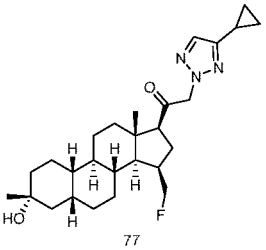
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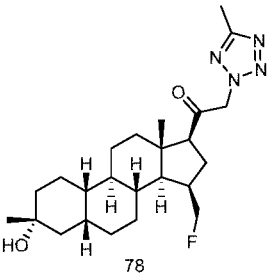
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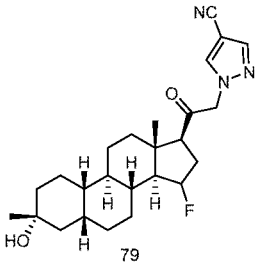
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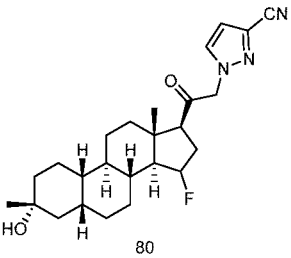
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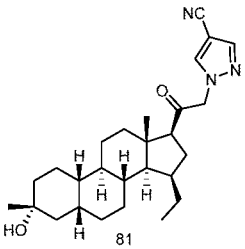
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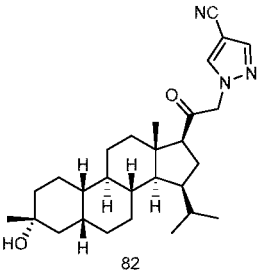
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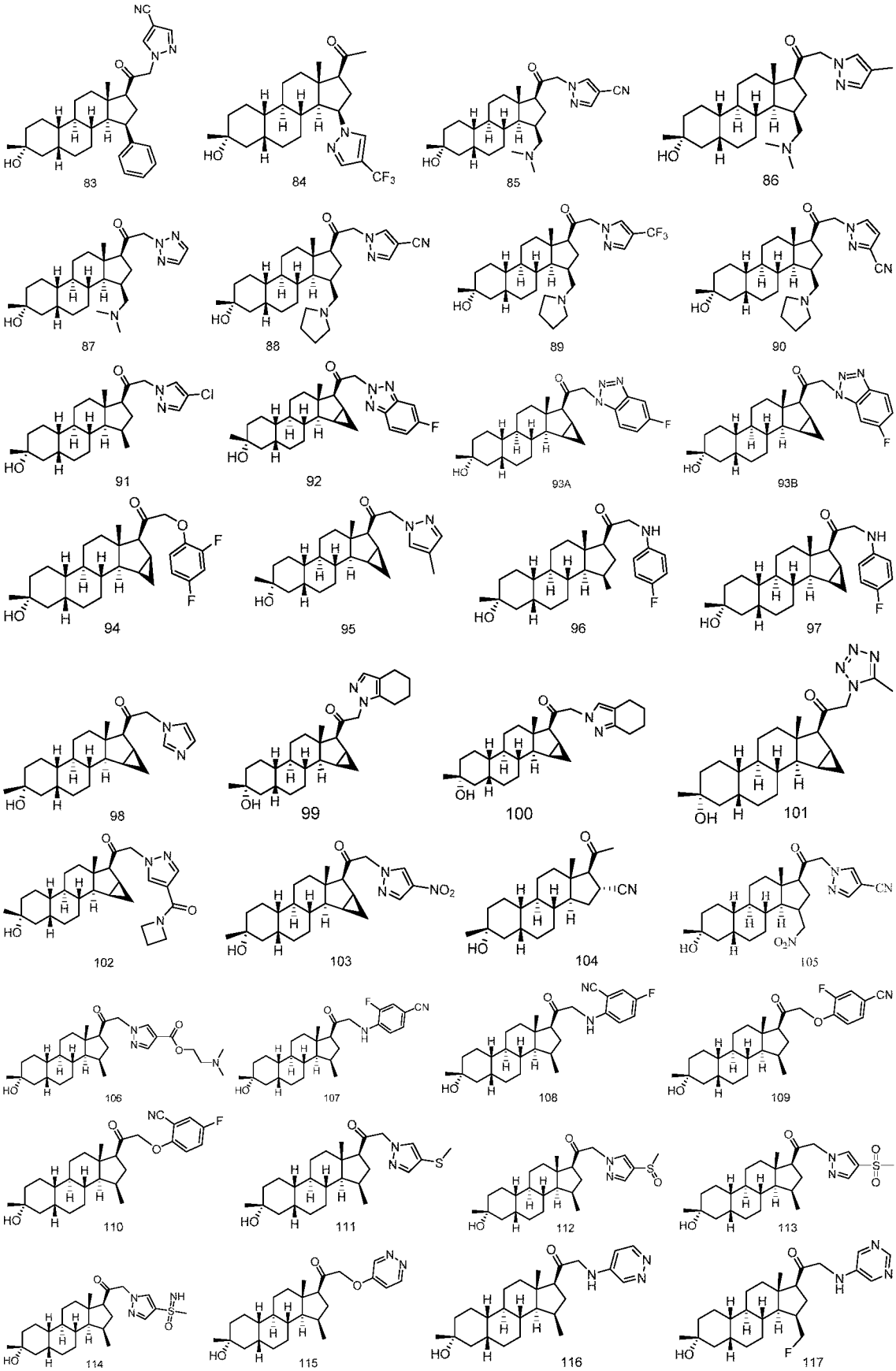
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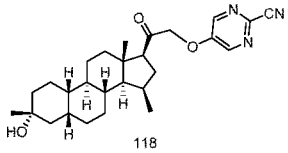
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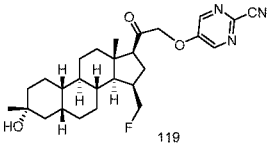
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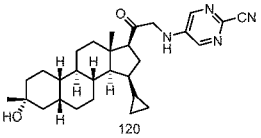
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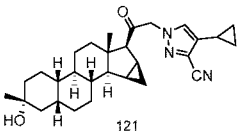
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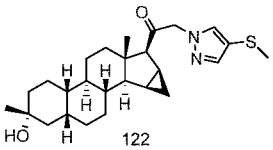
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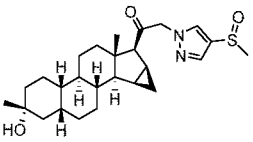
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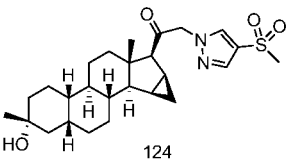
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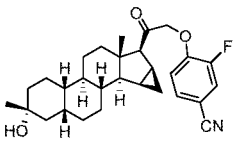
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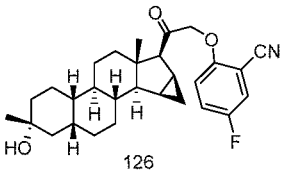
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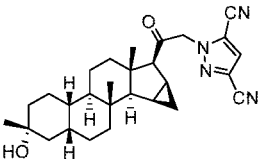
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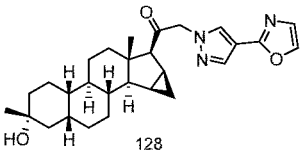
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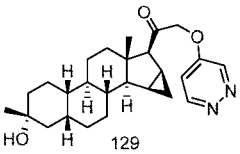
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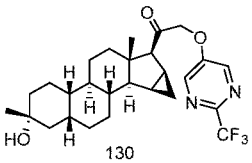
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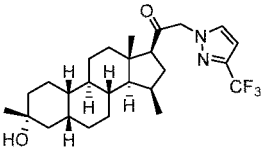
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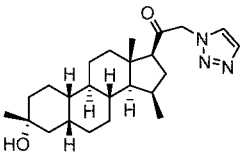
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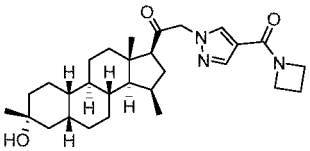
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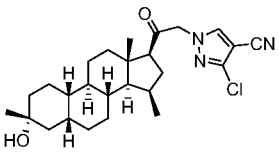
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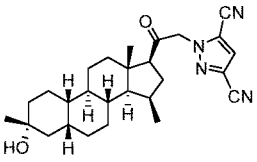
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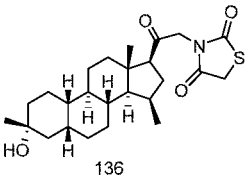
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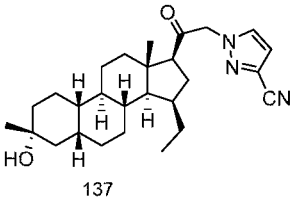
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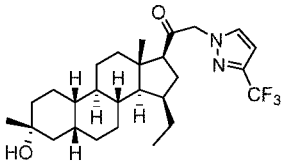
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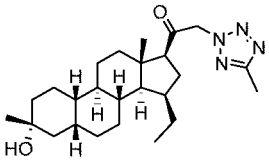
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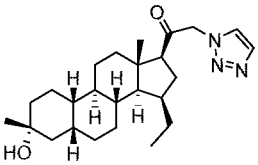
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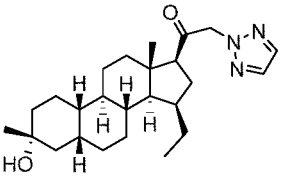
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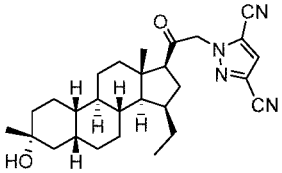
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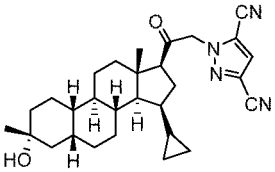
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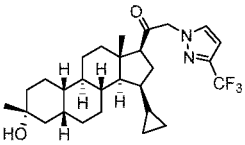
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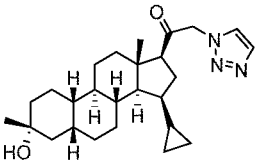
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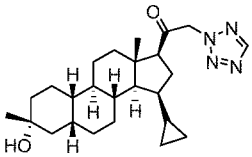
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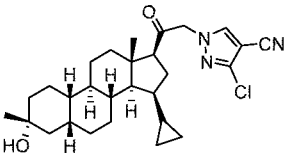
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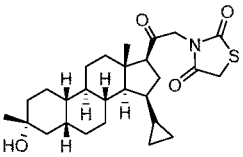
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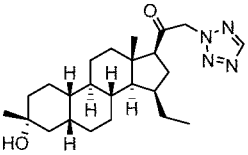
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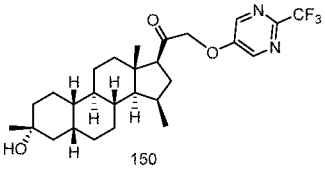
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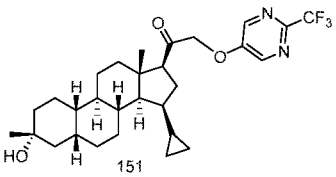
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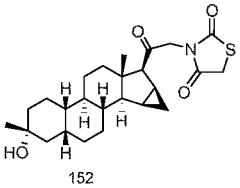
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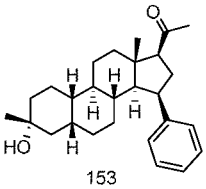
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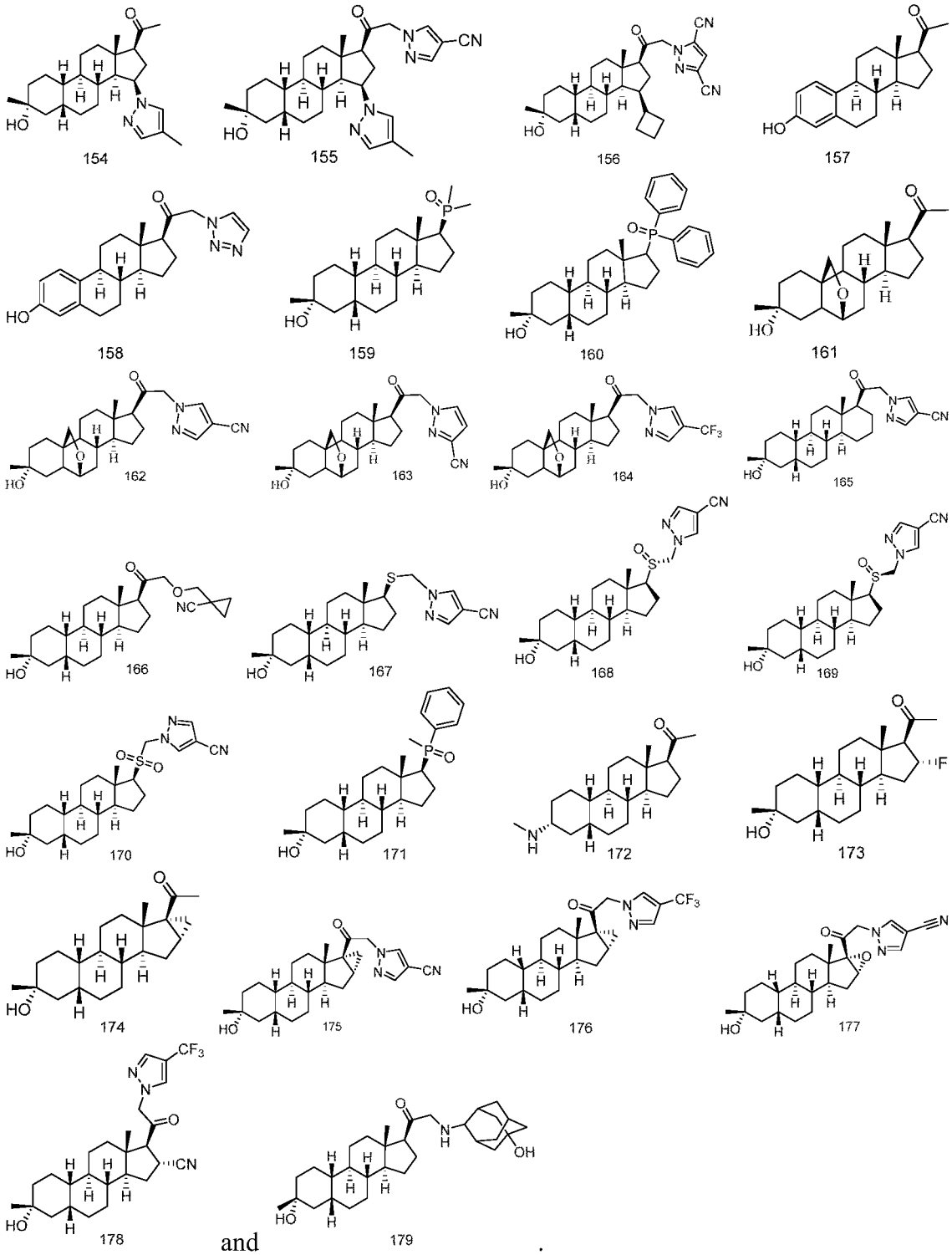


and .

The present invention further relates to a pharmaceutical composition comprising a therapeutically effective amount of any one of the compound of formula (I), the stereoisomer thereof, or the pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, diluents or excipients.

The present invention further relates to a use of any one of the compound of formula (I), the stereoisomer thereof, or the pharmaceutical composition comprsing the same in the preparation of a $GABA_A$ receptor regulator medicament.

The present invention further relates to a use of the compound of formula (I), the stereoisomer thereof, or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition comprsing the same in the preparation of a medicament for treating a Central Nervous System (CNS)-related disease, wherein the CNS-related disease is selected from the group consisting of sleep disorder, mood disorder, schizophrenia spectrum disorder, spasmodic disorder, memory disorder and/or cognitive disorder, dyskinesia, personality disorder, autism spectrum disorder, pain, traumatic brain injury, vascular disease, substance abuse disorder and/or withdrawal syndrome or tinnitus.

The present invention further relates to the compound of formula (I), the stereoisomer thereof, or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition comprsing the same for use in treating a CNS-related disease.

The present invention also relates to a method for preventing and/or treating a CNS-related disease, comprising administering to a patient a therapeutically effective amount of the compound of formula (I), the stereoisomer thereof, or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition comprsing the same.

DEFINITIONS

Unless otherwise stated, the terms used in the specification and claims have the meanings described below.

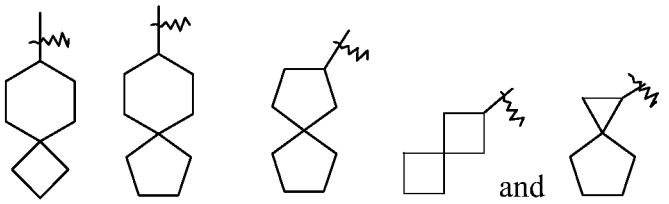
The term "alkyl" refers to a saturated aliphatic hydrocarbon group, which is a straight or branched chain group comprising 1 to 20 carbon atoms, preferably an alkyl having 1 to 8 carbon atoms, more preferably an alkyl having 1 to 6 carbon atoms, and most preferably an alkyl having 1 to 3 carbon atoms. Non-limiting examples include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, *sec*-butyl, *n*-pentyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 1-ethylpropyl, 2-methylbutyl, 3-methylbutyl, *n*-hexyl, 1-ethyl-2-methylpropyl, 1,1,2-trimethylpropyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1,3-dimethylbutyl, 2-ethylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2,3-dimethylbutyl, *n*-heptyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 2,3-dimethylpentyl, 2,4-dimethylpentyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 2-ethylpentyl, 3-ethylpentyl, *n*-octyl, 2,3-dimethylhexyl, 2,4-dimethylhexyl, 2,5-dimethylhexyl, 2,2-dimethylhexyl, 3,3-dimethylhexyl, 4,4-dimethylhexyl, 2-ethylhexyl, 3-ethylhexyl, 4-ethylhexyl, 2-methyl-2-ethylpentyl, 2-methyl-3-ethylpentyl, *n*-nonyl, 2-methyl-2-ethylhexyl, 2-methyl-3-ethylhexyl, 2,2-diethylpentyl, *n*-decyl, 3,3-diethylhexyl, 2,2-diethylhexyl, and various branched isomers thereof. The alkyl group can be substituted or unsubstituted. When substituted, the substituent group(s) can be substituted at any available connection point. The

substituent group(s) is preferably one or more groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, thiol, hydroxy, nitro, cyano, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkoxy, heterocycloalkoxy, cycloalkylthio, heterocyclylthio, oxo, carboxy and alkoxycarbonyl. The alkyl of present invention is preferably selected from the group consisting of methyl, ethyl, isopropyl, *tert*-butyl, haloalkyl, deuterated alkyl, alkoxy-substituted alkyl and hydroxy-substituted alkyl.

The term "alkylene" refers to an alkyl of which a hydrogen atom is further substituted, for example, "methylene" refers to $-CH_2-$, "ethylene" refers to $-(CH_2)_2-$, "propylene" refers to $-(CH_2)_3-$, "butylene" refers to $-(CH_2)_4-$ and the like. The term "alkenyl" refers to an alkyl as defined above that consists of at least two carbon atoms and at least one carbon-carbon double bond, for example, ethenyl, 1-propenyl, 2-propenyl, 1-, 2- or 3-butenyl and the like. The alkenyl group can be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, thiol, hydroxy, nitro, cyano, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkoxy, heterocycloalkoxy, cycloalkylthio and heterocyclylthio.

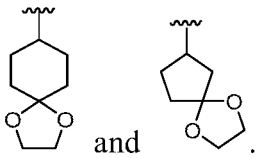
The term "cycloalkyl" refers to a saturated or partially unsaturated monocyclic or polycyclic hydrocarbon substituent group having 3 to 20 carbon atoms, preferably 3 to 12 carbon atoms, further preferably 3 to 8 carbon atoms, and more preferably 3 to 6 carbon atoms. Non-limiting examples of monocyclic cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, cycloheptyl, cycloheptatrienyl, cyclooctyl and the like. Polycyclic cycloalkyl includes a cycloalkyl having a spiro ring, fused ring or bridged ring. The cycloalkyl is preferably cyclopropyl.

The term "spiro cycloalkyl" refers to a 5 to 20 membered polycyclic group with individual rings connected through one shared carbon atom (called a spiro atom), wherein the rings can contain one or more double bonds, but none of the rings has a completely conjugated π-electron system. The spiro cycloalkyl is preferably a 6 to 14 membered spiro cycloalkyl, and more preferably a 7 to 10 membered spiro cycloalkyl. According to the number of the spiro atoms shared between the rings, the spiro cycloalkyl can be divided into a mono-spiro cycloalkyl, a di-spiro cycloalkyl, or a poly-spiro cycloalkyl, and the spiro cycloalkyl is preferably a mono-spiro cycloalkyl or di-spiro cycloalkyl, and more preferably a 4-membered/4-membered, 4-membered/5-membered, 4-membered/6-membered, 5-membered/5-membered, or 5-membered/6-membered mono-spiro cycloalkyl. Non-limiting examples of spiro cycloalkyl include:



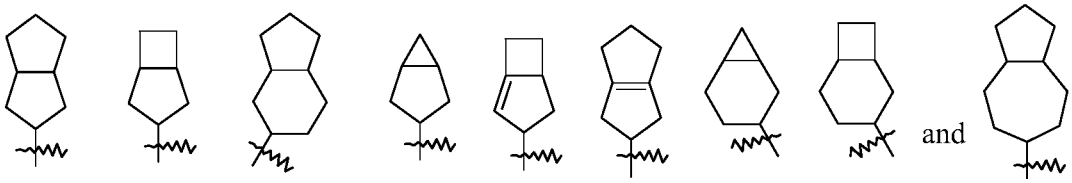
;

and also include spiro cycloalkyl in which a cycloalkyl and a heterocyclyl are connected through one spiro atom, non-limiting examples thereof include:



.

The term "fused cycloalkyl" refers to a 5 to 20 membered all-carbon polycyclic group, wherein each ring in the system shares an adjacent pair of carbon atoms with another ring, wherein one or more rings can contain one or more double bonds, but none of the rings has a completely conjugated π-electron system. The fused cycloalkyl is preferably a 6 to 14 membered fused cycloalkyl, and more preferably a 7 to 10 membered fused cycloalkyl. According to the number of membered rings, the fused cycloalkyl can be divided into a bicyclic, tricyclic, tetracyclic or polycyclic fused cycloalkyl, and the fused cycloalkyl is preferably a bicyclic or tricyclic fused cycloalkyl, and more preferably a 5-membered/5-membered, or 5-membered/6-membered bicyclic fused cycloalkyl. Non-limiting examples of fused cycloalkyl include:



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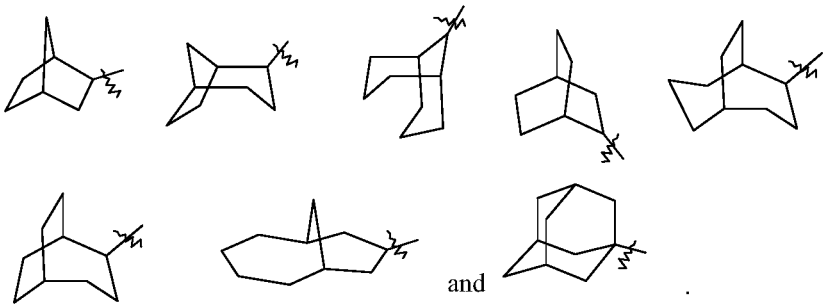
The term "bridged cycloalkyl" refers to a 5 to 20 membered all-carbon polycyclic group, wherein every two rings in the system share two disconnected carbon atoms, wherein the rings can have one or more double bonds, but none of the rings has a completely conjugated π-electron system. The bridged cycloalkyl is preferably a 6 to 14 membered bridged cycloalkyl, and more preferably a 7 to 10 membered bridged cycloalkyl. According to the number of membered rings, the bridged cycloalkyl can be divided into a bicyclic, tricyclic, tetracyclic or polycyclic bridged cycloalkyl, and the bridged cycloalkyl is preferably a bicyclic, tricyclic or tetracyclic bridged cycloalkyl, and more preferably a bicyclic or tricyclic bridged cycloalkyl. Non-limiting examples of bridged cycloalkyl include:

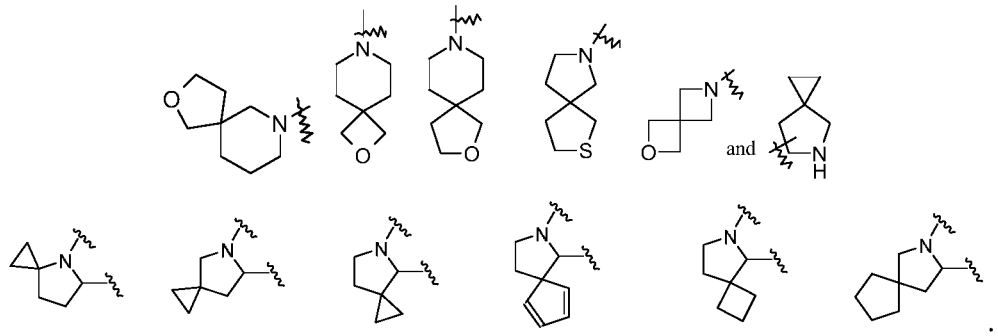


The cycloalkyl ring can be fused to the ring of aryl, heteroaryl or heterocyclyl, wherein the ring bound to the parent structure is cycloalkyl. Non-limiting examples include indanyl, tetrahydronaphthyl, benzocycloheptyl and the like. The cycloalkyl can be optionally substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more group(s) independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, thiol, hydroxy, nitro, cyano, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkoxy, heterocycloalkoxy, cycloalkylthio, heterocyclylthio, oxo, carboxy and alkoxycarbonyl.

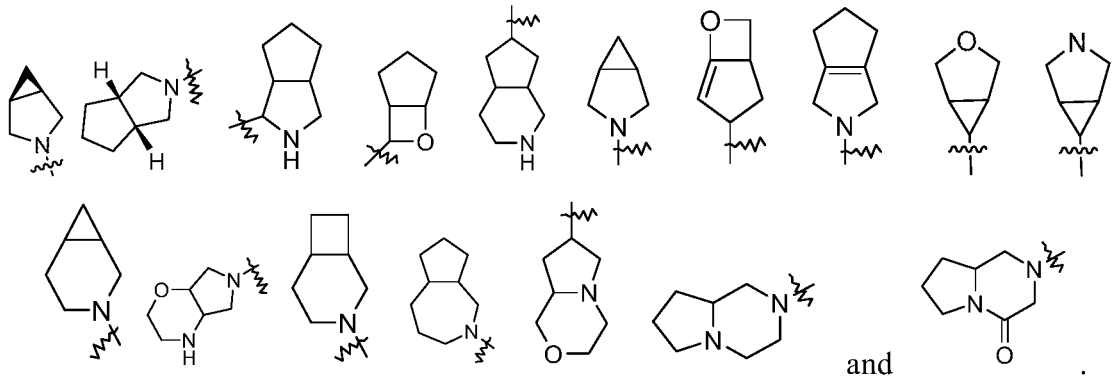
The term "heterocyclyl" refers to a 3 to 20 membered saturated or partially unsaturated monocyclic or polycyclic hydrocarbon group, wherein one or more ring atoms are heteroatoms selected from the group consisting of N, O and $S(O)_m$ (wherein m is an integer of 0 to 2), but excluding -O-O-, -O-S- or -S-S- in the ring, with the remaining ring atoms being carbon atoms. Preferably, the heterocyclyl has 3 to 12 ring atoms wherein 1 to 4 atoms are heteroatoms; more preferably, 3 to 10 ring atoms; and most preferably 3 to 8 ring atoms. Non-limiting examples of monocyclic heterocyclyl include pyrrolidinyl, imidazolidinyl, tetrahydrofuranyl, tetrahydrothienyl, dihydroimidazolyl, dihydrofuranyl, dihydropyrazolyl, dihydropyrrolyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, homopiperazinyl, pyranyl, 1,4-diazacyclyl and the like, and preferably tetrahydrofuranyl, pyrazolidinyl, morpholinyl, 1,4-diazacyclyl, piperazinyl and pyranyl. Polycyclic heterocyclyl includes a heterocyclyl having a spiro ring, fused ring or bridged ring. The heterocyclyl having a spiro ring, fused ring or bridged ring is optionally bonded to other group via a single bond, or further bonded to other cycloalkyl, heterocyclyl, aryl and heteroaryl via any two or more atoms on the ring.

The term "spiro heterocyclyl" refers to a 5 to 20 membered polycyclic heterocyclyl group with individual rings connected through one shared atom (called a spiro atom), wherein one or more ring atoms are heteroatoms selected from the group consisting of N, O and $S(O)_m$ (wherein m is an integer of 0 to 2), with the remaining ring atoms being carbon atoms, where the rings can contain one or more double bonds, but none of the rings has a completely conjugated π-electron system. The spiro heterocyclyl is preferably a 6 to 14 membered spiro heterocyclyl, and more preferably a 7 to 10 membered spiro heterocyclyl. According to the number of the spiro atoms shared between the rings, the spiro heterocyclyl can be divided into a mono-spiro heterocyclyl, di-spiro heterocyclyl, or poly-spiro heterocyclyl, and the spiro heterocyclyl is preferably

a mono-spiro heterocyclyl or di-spiro heterocyclyl, and more preferably a 4-membered/4-membered, 4-membered/5-membered, 4-membered/6-membered, 5-membered/5-membered, or 5-membered/6-membered mono-spiro heterocyclyl. Non-limiting examples of spiro heterocyclyl include:

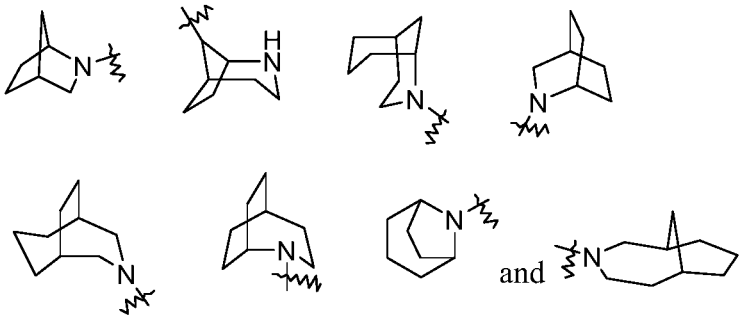


The term "fused heterocyclyl" refers to a 5 to 20 membered polycyclic heterocyclyl group, wherein each ring in the system shares an adjacent pair of atoms with another ring, wherein one or more rings can contain one or more double bonds, but none of the rings has a completely conjugated π-electron system, and wherein one or more ring atoms are heteroatoms selected from the group consisting of N, O and $S(O)_m$ (wherein m is an integer of 0 to 2), with the remaining ring atoms being carbon atoms. The fused heterocyclyl is preferably a 6 to 14 membered fused heterocyclyl, and more preferably a 7 to 10 membered fused heterocyclyl. According to the number of membered rings, the fused heterocyclyl can be divided into a bicyclic, tricyclic, tetracyclic or polycyclic fused heterocyclyl, and preferably a bicyclic or tricyclic fused heterocyclyl, and more preferably a 5-membered/5-membered or 5-membered/6-membered bicyclic fused heterocyclyl. Non-limiting examples of fused heterocyclyl include:

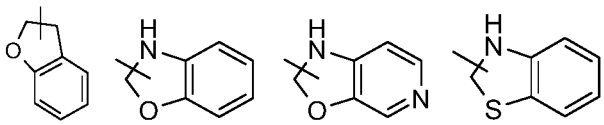


The term "bridged heterocyclyl" refers to a 5 to 14 membered polycyclic heterocyclyl group, wherein every two rings in the system share two disconnected atoms, wherein the rings can have one or more double bonds, but none of the rings has a completely conjugated π-electron system, and wherein one or more ring atoms are heteroatoms selected from the group consisting of N, O and $S(O)_m$ (wherein m is an integer of 0 to 2), with the remaining ring atoms being carbon atoms. The bridged heterocyclyl is preferably a 6 to 14 membered bridged heterocyclyl, and more

preferably a 7 to 10 membered bridged heterocyclyl. According to the number of membered rings, the bridged heterocyclyl can be divided into a bicyclic, tricyclic, tetracyclic or polycyclic bridged heterocyclyl, and the bridged heterocyclyl is preferably a bicyclic, tricyclic or tetracyclic bridged heterocyclyl, and more preferably a bicyclic or tricyclic bridged heterocyclyl. Non-limiting examples of bridged heterocyclyl include:



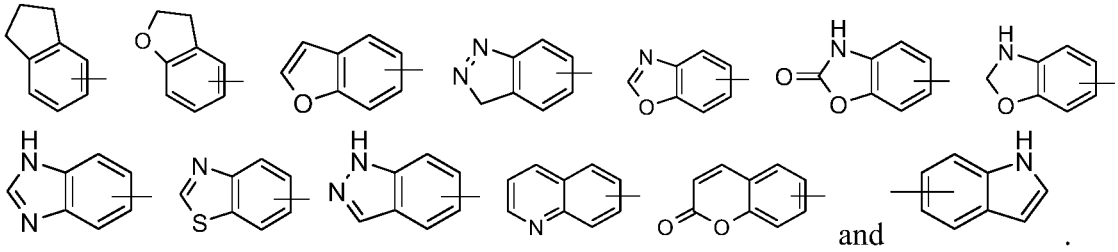
The heterocyclyl ring can be fused to the ring of aryl, heteroaryl or cycloalkyl, wherein the ring bound to the parent structure is heterocyclyl. Non-limiting examples thereof include:



and the like.

The heterocyclyl can be optionally substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more group(s) independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, thiol, hydroxy, nitro, cyano, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkoxy, heterocycloalkoxy, cycloalkylthio, heterocyclylthio, oxo, carboxy and alkoxycarbonyl.

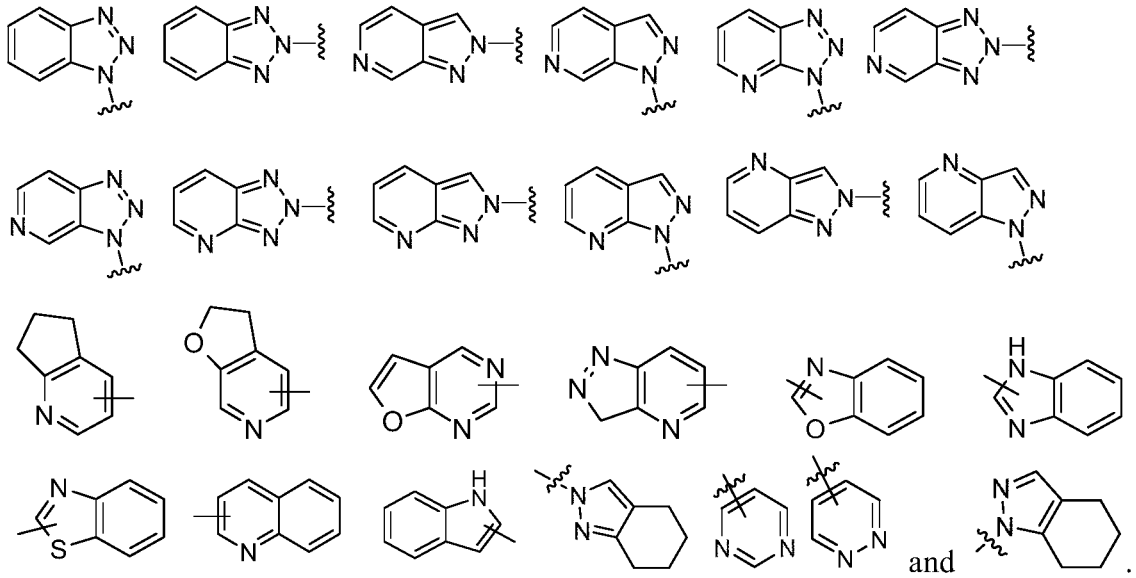
The term "aryl" refers to a 6 to 14 membered all-carbon monocyclic ring or polycyclic fused ring (i.e. each ring in the system shares an adjacent pair of carbon atoms with another ring in the system) having a conjugated π-electron system, preferably a 6 to 10 membered aryl, for example, phenyl and naphthyl. The aryl is more preferably phenyl. The aryl ring can be fused to the ring of heteroaryl, heterocyclyl or cycloalkyl, wherein the ring bound to the parent structure is aryl ring. Non-limiting examples thereof include:



The aryl can be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more group(s) independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, thiol, hydroxy, nitro, cyano, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkoxy,

heterocycloalkoxy, cycloalkylthio, heterocyclylthio, carboxy and alkoxycarbonyl.

The term "heteroaryl" refers to a 5 to 12 membered heteroaromatic system having 1 to 4 heteroatoms selected from the group consisting of O, S and N. The heteroaryl is preferably a 5 to 10 membered heteroaryl, and more preferably a 5 or 6 membered heteroaryl, for example imidazolyl, furyl, thienyl, thiazolyl, pyrazolyl, oxazolyl, pyrrolyl, triazolyl, tetrazolyl, pyridyl, pyrimidinyl, thiadiazolyl, pyrazinyl and the like, preferably triazolyl, tetrazolyl, thienyl, imidazolyl, pyrazolyl, pyridazinyl, pyrimidinyl, thiazolyl, oxazolyl, isoxazolyl or pyrimidinyl, and more preferably triazolyl, tetrazolyl, pyrazolyl, pyridyl, pyridazinyl, pyrimidinyl, thiazolyl, oxazolyl, isoxazolyl or imidazolyl. The heteroaryl ring can be fused to the ring of aryl, heterocyclyl or cycloalkyl, wherein the ring bound to the parent structure is heteroaryl ring. Non-limiting examples thereof include:



The heteroaryl can be optionally substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more group(s) independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, thiol, hydroxy, nitro, cyano, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkoxy, heterocycloalkoxy, cycloalkylthio, heterocyclylthio, carboxy and alkoxycarbonyl.

The term "alkoxy" refers to an -O-(alkyl) or an -O-(unsubstituted cycloalkyl) group, wherein the alkyl is as defined above. Non-limiting examples of alkoxy include methoxy, ethoxy, propoxy, butoxy, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy. The alkoxy can be optionally substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more group(s) independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, thiol, hydroxy, nitro, cyano, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkoxy, heterocycloalkoxy, cycloalkylthio, heterocyclylthio, carboxy and alkoxycarbonyl.

"Haloalkyl" refers to an alkyl group substituted by one or more halogens, wherein the alkyl is as defined above.

"Haloalkoxy" refers to an alkoxy group substituted by one or more halogens, wherein the alkoxy is as defined above.

"Hydroxyalkyl" refers to an alkyl group substituted by hydroxy(s), wherein the alkyl is as defined above.

"Alkenyl" refers to a chain alkenyl, also known as alkene group, which is a straight or branched chain group comprising 2 to 20 carbon atoms, preferably an alkenyl having 2 to 8 carbon atoms, more preferably an alkenyl having 2 to 6 carbon atoms, and most preferably an alkenyl having 2 to 3 carbon atoms. The alkenyl can be further substituted by other related group, for example alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, thiol, hydroxy, nitro, cyano, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkoxy, heterocycloalkoxy, cycloalkylthio, heterocyclylthio, carboxy or alkoxycarbonyl.

"Alkynyl" refers to (CH≡C-), which is a straight or branched chain group comprising 2 to 20 carbon atoms, preferably an alkynyl having 2 to 8 carbon atoms, more preferably an alkynyl having 2 to 6 carbon atoms, and most preferably an alkynyl having 2 to 3 carbon atoms. The alkynyl can be further substituted by other related group, for example alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, thiol, hydroxy, nitro, cyano, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkoxy, heterocycloalkoxy, cycloalkylthio, heterocyclylthio, carboxy and alkoxycarbonyl.

"Hydroxy" refers to an -OH group.

"Halogen" refers to fluorine, chlorine, bromine or iodine.

"Amino" refers to a $-NH_2$ group.

"Cyano" refers to a -CN group.

"Nitro" refers to a $-NO_2$ group.

"Carboxy" refers to a -C(O)OH group.

"THF" refers to tetrahydrofuran.

"EtOAc" refers to ethyl acetate.

"MeOH" refers to methanol.

"DMF" refers to N,N-dimethylformamide.

"DIPEA" refers to diisopropylethylamine.

"TFA" refers to trifluoroacetic acid.

"MeCN" refers to acetonitrile.

"DMA" refers to N,N-dimethylacetamide.

"Et_2O" refers to diethyl ether.

"DCE" refers to 1,2-dichloroethane.

"DIPEA" refers to N,N-diisopropylethylamine.

"NBS" refers to N-bromosuccinimide.

"NIS" refers to N-iodosuccinimide.

"Cbz-Cl" refers to benzyl chloroformate.

"$Pd_2(dba)_3$" refers to tris(dibenzylideneacetone)dipalladium.

"Dppf" refers to 1,1'-bisdiphenylphosphinoferrocene.

"HATU" refers to 2-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate.

"KHMDS" refers to potassium hexamethyldisilazide.

"LiHMDS" refers to lithium bis(trimethylsilyl)amide.

"MeLi" refers to methyl lithium.

"n-BuLi" refers to *n*-butyl lithium.

"$NaBH(OAc)_3$" refers to sodium triacetoxyborohydride.

Different expressions such as "X is selected from the group consisting of A, B or C", "X is selected from the group consisting of A, B and C", "X is A, B or C", "X is A, B and C" and the like, express the same meaning, that is, X can be any one or more of A, B and C.

The hydrogen atom of the present invention can be substituted by its isotope deuterium. Any of the hydrogen atoms in the compounds of the examples of the present invention can also be substituted by deuterium atom.

"Optional" or "optionally" means that the event or circumstance described subsequently can, but need not, occur, and such a description includes the situation in which the event or circumstance does or does not occur. For example, "the heterocyclyl optionally substituted by an alkyl" means that an alkyl group can be, but need not be, present, and such a description includes the situation of the heterocyclyl being substituted by an alkyl and the heterocyclyl being not substituted by an alkyl.

"Substituted" refers to one or more hydrogen atoms in a group, preferably up to 5, and more preferably 1 to 3 hydrogen atoms, independently substituted by a corresponding number of substituents. It goes without saying that the substituents only exist in their possible chemical position. The person skilled in the art is able to determine whether the substitution is possible or impossible by experiments or theory without excessive efforts. For example, the combination of amino or hydroxy having free hydrogen and carbon atoms having unsaturated bonds (such as olefinic) may be unstable.

A "pharmaceutical composition" refers to a mixture of one or more of the compounds according to the present invention or physiologically/pharmaceutically acceptable salts or prodrugs thereof with other chemical components, and other components such as physiologically/pharmaceutically acceptable carriers and excipients. The purpose of the pharmaceutical composition is to facilitate administration of a compound to an organism, which is conducive to the absorption of the active ingredient so as to exert biological activity.

A "pharmaceutically acceptable salt" refers to a salt of the compound of the present invention, which is safe and effective in mammals and has the desired biological activity.

DETAILED DESCRIPTION OF THE INVENTION

The present invention will be further described with reference to the following examples, but the examples should not be considered as limiting the scope of the present invention.

EXAMPLES

The structures of the compounds of the present invention were identified by nuclear magnetic resonance (NMR) and/or liquid chromatography-mass spectrometry (LC-MS). NMR shifts (δ) are given in parts per million (ppm). NMR was determined by a Bruker AVANCE-400 machine. The solvents for determination were deuterated-dimethyl sulfoxide (DMSO-d_6), deuterated-methanol (CD_3OD) and deuterated-chloroform ($CDCl_3$), and the internal standard was tetramethylsilane (TMS).

Liquid chromatography-mass spectrometry (LC-MS) was determined on an Agilent 1200 Infinity Series mass spectrometer. High performance liquid chromatography (HPLC) was determined on an Agilent 1200DAD high pressure liquid chromatograph (Sunfire C18 150×4.6 mm chromatographic column), and a Waters 2695-2996 high pressure liquid chromatograph (Gimini C18 150×4.6 mm chromatographic column).

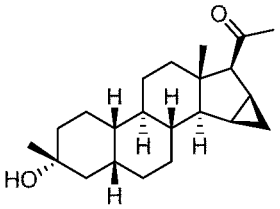
Yantai Huanghai HSGF254 or Qingdao GF254 silica gel plate was used as the thin-layer silica gel chromatography (TLC) plate. The dimension of the silica gel plate used in TLC was 0.15 mm to 0.2 mm, and the dimension of the silica gel plate used in product purification was 0.4 mm to 0.5 mm. Yantai Huanghai 200 to 300 mesh silica gel was generally used as a carrier for column chromatography.

The raw materials used in the examples of the present invention are known and commercially available, or can be synthesized by adopting or according to known methods in the art.

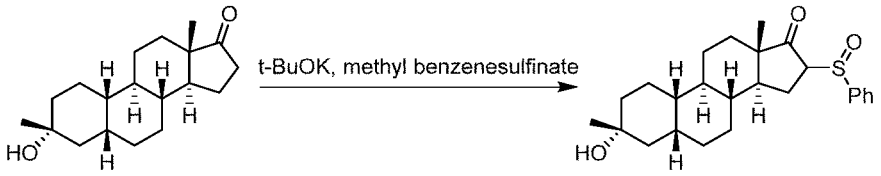
Unless otherwise stated, all reactions of the present invention were carried out under continuous magnetic stirring under a dry nitrogen or argon atmosphere, the solvent was dry, and the reaction temperature was in degrees celsius.

Example 1

1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-Hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one

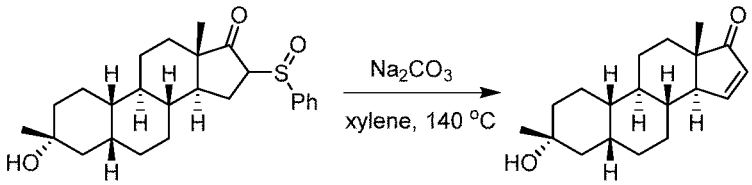


Step 1: Preparation of (3R,5R,8R,9R,10S,13S,14S)-3-hydroxy-3,13-dimethyl-16-(phenylsulfinyl)hexadecahydro-17H-cyclopenta[a]phenanthren-17-one



Potassium *tert*-butoxide (2.3 g, 20.7 mmol) was dissolved in anhydrous tetrahydrofuran (200 mL), and the reaction system was purged with nitrogen. (3R,5R,8R,9R,10S,13S,14S)-3-Hydroxy-3,13-dimethylhexadecahydro-17H-cyclopenta[a]phenanthren-17-one (3 g, 10.3 mmol) was added to the above solution to obtain an orange solution, which was then stirred at 25°C for 10 minutes. Methyl benzenesulfinate (3.2 g, 20.7 mmol) was added, and then the reaction solution was stirred at 30°C for half an hour. Water (100 mL) was added to the reaction solution to quench the reaction, and the aqueous phase was extracted with ethyl acetate (100 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtrated and concentrated. The resulting crude product was purified by column chromatography (petroleum ether/ethyl acetate: 50/1 - 3/1) to obtain (3R,5R,8R,9R,10S,13S,14S)-3-hydroxy-3,13-dimethyl-16-(phenylsulfinyl)hexadecahydro-17H-cyclopenta[a]phenanthren-17-one (3.5 g, yield: 82%).

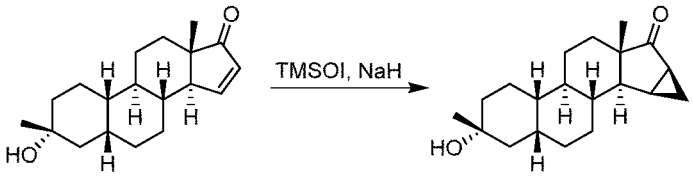
Step 2: Preparation of (3R,5R,8R,9R,10S,13S,14S)-3-hydroxy-3,13-dimethyl-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-17H-cyclopenta[a]phenanthren-17-one



(3R,5R,8R,9R,10S,13S,14S)-3-Hydroxy-3,13-dimethyl-16-(phenylsulfinyl)hexadecahydro-17H-cyclopenta[a]phenanthren-17-one (3.5 g, 8.5 mmol) was dissolved in xylene (50 mL), and the reaction system was purged with nitrogen. Sodium carbonate (24.7 g, 0.17 mol) was added, and then the reaction solution was stirred at 140°C overnight. The reaction solution was filtrated, and the organic phase was concentrated. The resulting crude product was purified by column chromatography (petroleum ether/ethyl acetate: 50/1 - 3/1) to obtain (3R,5R,8R,9R,10S,13S,14S)-3-hydroxy-3,13-dimethyl-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-17H-cyclopenta[a]phenanthren-17-one (1.5 g, yield: 62%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, J = 5.9, 1.2 Hz, 1H), 6.03 (dd, J = 6.0, 3.2 Hz, 1H), 2.42 – 2.33 (m, 1H), 1.90 – 1.79 (m, 4H), 1.76 – 1.66 (m, 2H), 1.58 – 1.48 (m, 5H), 1.47 – 1.37 (m, 4H), 1.36 – 1.23 (m, 7H), 1.08 (s, 3H).

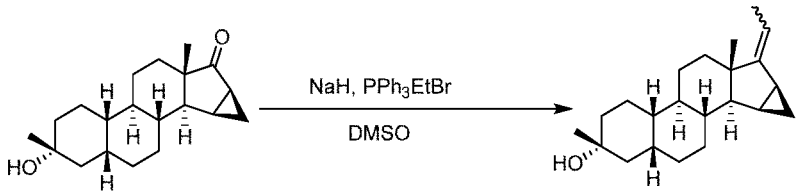
Step 3: Preparation of (2R,4aS,4bR,6aS,7aS,8aS,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethylhexadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7(1H)-one



Trimethyl sulfoxide (0.92 g, 4.2 mmol) was dissolved in anhydrous dimethyl sulfoxide (10 mL), and the reaction system was purged with nitrogen. Sodium hydride (168 mg, 4.2 mmol) was added, and then the reaction solution was stirred for 1 hour. A solution of (3R,5R,8R,9R,10S,13S,14S)-3-hydroxy-3,13-dimethyl-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-17H-cyclopenta[a]phenanthren-17-one (1.0 g, 3.5 mmol) in dimethyl sulfoxide (5 mL) was added, and then the reaction solution was stirred at room temperature overnight. Water (50 mL) was added to the reaction solution to quench the reaction, and the aqueous phase was extracted with ethyl acetate (50 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtrated and concentrated. The resulting crude product was purified by column chromatography (petroleum ether/ethyl acetate: 50/1 - 3/1) to obtain (2R,4aS,4bR,6aS,7aS,8aS,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethylhexadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7(1H)-one (0.75 g, yield: 71%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.06 – 2.00 (m, 1H), 1.97 – 1.91 (m, 1H), 1.88 – 1.79 (m, 3H), 1.78 – 1.67 (m, 6H), 1.63 – 1.54 (m, 2H), 1.48 – 1.39 (m, 3H), 1.37 – 1.25 (m, 9H), 1.15 – 1.05 (m, 2H), 0.96 (s, 3H).

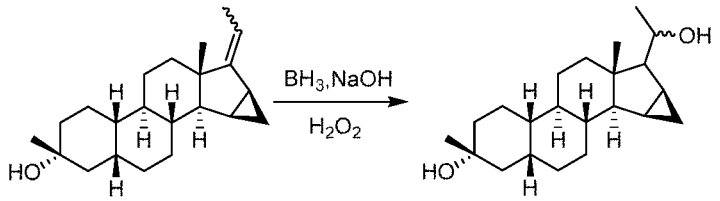
Step 4: Preparation of (2R,4aS,4bR,6aS,7aS,8aR,8bR,8cR,10aR)-7-ethylidene-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-2-ol



PPh_3EtBr (14.8 g, 40 mmol) was dissolved in anhydrous dimethyl sulfoxide (50 mL), and the reaction system was purged with nitrogen. Sodium hydride (1.6 g, 40 mmol) was added, and then the reaction solution was stirred at room temperature for 1 hour. (2R,4aS,4bR,6aS,7aS,8aS,8bR,8cR,10aR)-2-Hydroxy-2,6a-dimethylhexadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7(1H)-one (0.6 g, 2.0 mmol) was added, and then the reaction solution was stirred at 100°C overnight. The reaction solution was cooled to room temperature. Water (200 mL) was added to the reaction solution to quench the reaction, and the aqueous phase was extracted with ethyl acetate (200 mL×2). The organic phases were combined, dried over anhydrous sodium sulfate, filtrated and concentrated. The resulting crude product was purified by column chromatography (petroleum ether/ethyl acetate: 50/1 - 3/1) to obtain

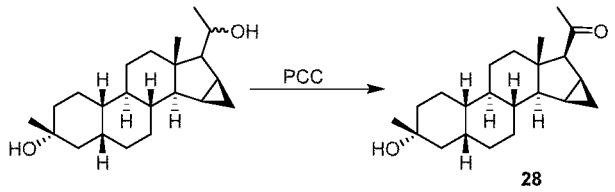
(2R,4aS,4bR,6aS,7aS,8aR,8bR,8cR,10aR)-7-ethylidene-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-2-ol (0.5 g, yield: 81%).

Step 5: Preparation of (2R,4aS,4bR,6aS,7aS,8aR,8bR,8cR,10aR)-7-(1-hydroxyethyl)-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-2-ol



(2R,4aS,4bR,6aS,7aS,8aR,8bR,8cR,10aR)-7-Ethylidene-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-2-ol (0.4 g, 1.3 mmol) was dissolved in anhydrous tetrahydrofuran (10 mL). The solution was cooled to 0°C, and then BH_3/THF (12.7 mL, 12.7 mmol) was added dropwise. The reaction solution was stirred at room temperature for 3 hours, and TLC showed that the reaction was completed. The reaction solution was cooled to 0°C, and then 3 M aqueous NaOH solution (4 mL) was slowly added, followed by the addition of H_2O_2 (3 mL). The reaction solution was stirred at room temperature for 2 hours, and TLC showed that the reaction was completed. Ethyl acetate (50 mL) was added, and then the reaction solution was washed with saturated aqueous $Na_2S_2O_3$ solution (30 mL) and water (30 mL) successively. The organic phase was dried over anhydrous sodium sulfate, filtrated and concentrated to obtain the crude product (0.4 g, yield: 100%, crude), which was used directly in the next step.

Step 6: Preparation of 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one

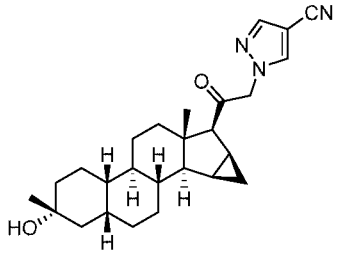


(2R,4aS,4bR,6aS,7aS,8aR,8bR,8cR,10aR)-7-(1-Hydroxyethyl)-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-2-ol (0.4 g, 1.2 mmol) was dissolved in dichloromethane (20 mL). PCC (0.52 g, 40 mmol) was added, and then the reaction solution was stirred at room temperature for 2 hours. The reaction solution was filtrated, and the organic phase was concentrated. The resulting crude product was purified by column chromatography (petroleum ether/ethyl acetate: 50/1 - 3/1) to obtain 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one (0.35 g, yield: 83%).

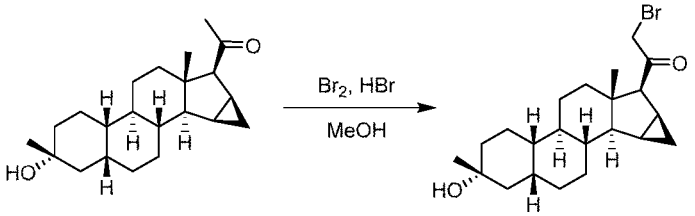
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.74 (d, J = 4.1 Hz, 1H), 2.21 (s, 3H), 1.97 – 1.91 (m, 1H), 1.87 – 1.62 (m, 7H), 1.56 – 1.50 (m, 1H), 1.44 – 1.21 (m, 15H), 1.12 – 1.00 (m, 1H), 0.90 – 0.83 (m, 1H), 0.72 (s, 3H), 0.44 – 0.36 (m, 1H).

Example 2

Preparation of 1-(2-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile

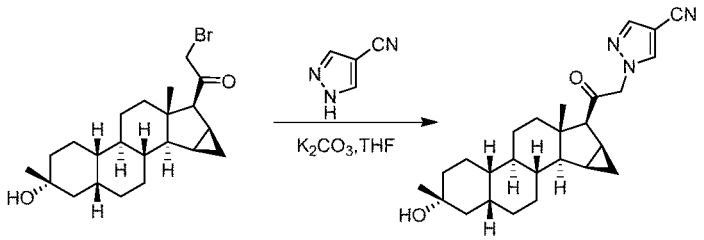


Step 1: Preparation of 2-bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one



1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-Hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one (70 mg, 0.21 mmol) was dissolved in methanol (3 mL). A drop of hydrogen bromide was added to the solution, followed by the addition of liquid bromine (41 mg, 0.25 mmol), and then the reaction solution was stirred at room temperature for 1 hour. Water (20 mL) was added to the reaction solution, and the aqueous phase was extracted with ethyl acetate (20 mL×2). The organic phases were combined, dried over anhydrous sodium sulfate, filtrated and concentrated to obtain the crude product (87 mg, yield: 100%, crude), which was used directly in the next step.

Step 2: Preparation of 1-(2-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile



2-Bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one (87 mg, 0.21 mmol), 1H-pyrazole-4-carbonitrile (59 mg, 0.64 mmol) and potassium carbonate (145 mg, 1.05 mmol) were dissolved in tetrahydrofuran (2 mL), and the resulting

reaction solution was stirred at room temperature overnight. The reaction solution was filtrated, and the filtrate was concentrated. The resulting crude product was purified by high performance liquid chromatography to obtain 1-(2-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile (33 mg, yield: 37%).

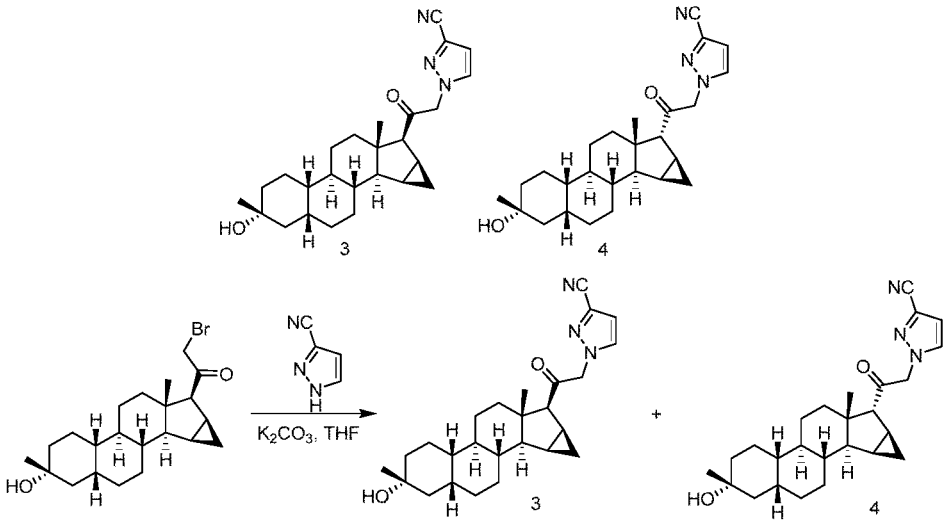
MS m/z (ESI): 404.2 $[M-H_2O+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.82 (s, 1H), 5.24-5.13 (m, 2H), 2.84 (d, J = 2.7 Hz, 1H), 1.98 – 1.92 (m, 1H), 1.87 – 1.77 (m, 4H), 1.76 – 1.66 (m, 3H), 1.57 – 1.51 (m, 1H), 1.46 – 1.24 (m, 15H), 1.12 – 1.02 (m, 1H), 1.00 – 0.96 (m, 1H), 0.78 (s, 3H), 0.54 – 0.46 (m, 1H).

Example 3 and Example 4

Preparation of 1-(2-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethyl)-1H-pyrazole-3-carbonitrile (3)

1-(2-((2R,4aS,4bR,6aS,7R,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethyl)-1H-pyrazole-3-carbonitrile (4)



2-Bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one (80 mg, 0.19 mmol), 1H-pyrazole-3-carbonitrile (55 mg, 0.58 mmol) and potassium carbonate (131 mg, 0.95 mmol) were dissolved in tetrahydrofuran (3 mL), and the resulting reaction solution was stirred at room temperature overnight. The reaction solution was filtrated, and the filtrate was concentrated. The resulting crude product was purified by high performance liquid chromatography to obtain 1-(2-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethyl)-1H-pyrazole-3-car

bonitrile (34.7 mg, yield: 42%) and 1-(2-((2R,4aS,4bR,6aS,7R,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethyl)-1H-pyrazole-3-carbonitrile (3.7 mg, yield: 4.5%).

Example 3:

MS m/z (ESI): 404.2 $[M-H_2O+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 2.4 Hz, 1H), 6.74 (d, J = 2.4 Hz, 1H), 5.29 – 5.13 (m, 2H), 2.83 (d, J = 2.9 Hz, 1H), 1.97 – 1.92 (m, 1H), 1.86 – 1.79 (m, 4H), 1.73 – 1.64 (m, 3H), 1.58 – 1.52 (m, 1H), 1.43 – 1.27 (m, 15H), 1.12 – 0.96 (m, 2H), 0.79 (s, 3H), 0.53 – 0.44 (m, 1H).

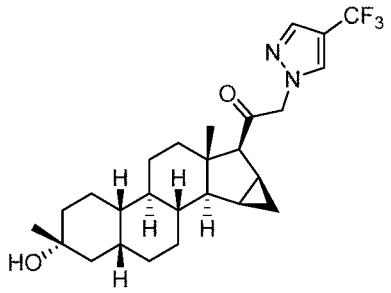
Example 4:

MS m/z (ESI): 404.2 $[M- H_2O +H]^+$.

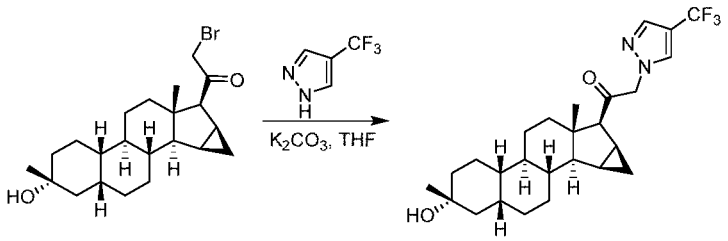
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 2.4 Hz, 1H), 6.75 (d, *J* = 2.4 Hz, 1H), 5.11-4.96 (m, 2H), 2.92 (s, 1H), 1.93 – 1.87 (m, 1H), 1.82 – 1.74 (m, 2H), 1.72 – 1.62 (m, 4H), 1.51 (s, 1H), 1.46 – 1.24 (m, 15H), 1.18 – 1.09 (m, 2H), 1.04 (s, 3H), 0.89 – 0.84 (m, 1H), 0.46 – 0.40 (m, 1H).

Example 5

1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-Hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(4-(trifluoromethyl)-1H-pyrazol-1-yl)ethan-1-one



Step 1: Preparation of 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(4-(trifluoromethyl)-1H-pyrazol-1-yl)ethan-1-one



2-Bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one (60 mg, 0.15 mmol), 4-(trifluoromethyl)-1H-pyrazole (60 mg, 0.44 mmol) and potassium carbonate (104 mg, 0.75 mmol) were dissolved in tetrahydrofuran (3 mL), and the

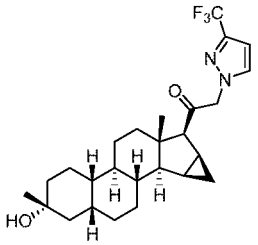
resulting reaction solution was stirred at room temperature overnight. The reaction solution was filtrated, and the filtrate was concentrated. The resulting crude product was purified by high performance liquid chromatography to obtain 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(4-(trifluoromethyl)-1H-pyrazol-1-yl)ethan-1-one (22.2 mg, yield: 33%).

MS m/z (ESI): 465.3 $[M+H]^+$.

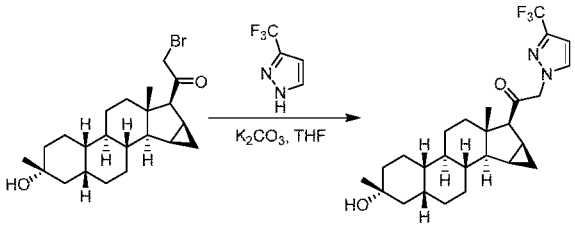
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.73 (s, 1H), 5.25 – 5.09 (m, 2H), 2.83 (d, J = 3.6 Hz, 1H), 2.00 – 1.91 (m, 1H), 1.89 – 1.79 (m, 4H), 1.78 – 1.65 (m, 3H), 1.58 – 1.52 (m, 1H), 1.47 – 1.22 (m, 15H), 1.15 – 0.95 (m, 2H), 0.79 (s, 3H), 0.52 – 0.44 (m, 1H).

Example 6

1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-Hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)ethan-1-one



Step 1: Preparation of 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)ethan-1-one



2-Bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one (80 mg, 0.2 mmol), 3-(trifluoromethyl)-1H-pyrazole (80 mg, 0.6 mmol) and potassium carbonate (138 mg, 1.0 mmol) were dissolved in tetrahydrofuran (5 mL), and the resulting reaction solution was stirred at room temperature overnight. The reaction solution was filtrated, and the filtrate was concentrated. The resulting crude product was purified by high performance liquid chromatography to obtain 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)ethan-1-one (17 mg, yield: 18%).

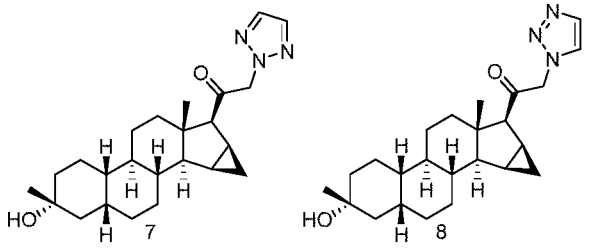
MS m/z (ESI): 447.3 $[M-H_2O+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 1.9 Hz, 1H), 6.60 (d, J = 1.9 Hz, 1H), 5.27 – 5.13 (m, 2H), 2.83 (d, J = 3.7 Hz, 1H), 1.99 – 1.90 (m, 1H), 1.89 – 1.76 (m, 4H), 1.75 – 1.61 (m, 3H), 1.58 – 1.50 (m, 1H), 1.50 – 1.21 (m, 15H), 1.13 – 0.96 (m, 2H), 0.79 (s, 3H), 0.52 – 0.45 (m, 1H).

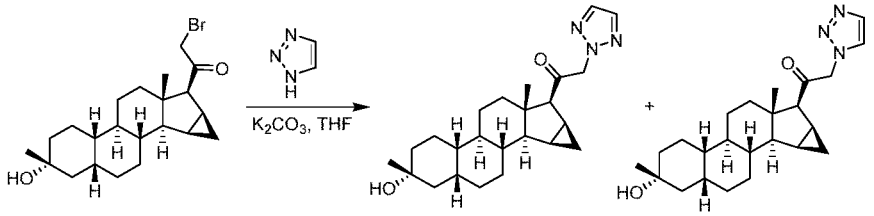
Example 7 and Example 8

1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-Hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(2H-1,2,3-triazol-2-yl)ethan-1-one (7)

1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-Hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(1H-1,2,3-triazol-1-yl)ethan-1-one (8)



Step 1: Preparation of 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(2H-1,2,3-triazol-2-yl)ethan-1-one (**7**) and 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(1H-1,2,3-triazol-1-yl)ethan-1-one (**8**)



2-Bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one (80 mg, 0.19 mmol), 1H-1,2,3-triazole (40 mg, 0.58 mmol) and potassium carbonate (131 mg, 0.95 mmol) were dissolved in tetrahydrofuran (3 mL), and the resulting reaction solution was stirred at room temperature overnight. The reaction solution was filtrated, and the filtrate was concentrated. The resulting crude product was purified by high performance liquid chromatography to obtain 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(2H-1,2,3-triazol-2-yl)ethan-1-one (**7**) (9.2 mg, yield: 12%) and

1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(1H-1,2,3-triazol-1-yl)ethan-1-one (**8**) (17.8 mg, yield: 23%).

Example 7:

MS m/z (ESI): 380.3 $[M-H_2O+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 2H), 5.55 – 5.36 (m, 2H), 2.82 (d, J = 4.1 Hz, 1H), 1.99 – 1.92 (m, 1H), 1.87 – 1.74 (m, 4H), 1.73 – 1.52 (m, 5H), 1.47 – 1.26 (m, 14H), 1.14 – 0.98 (m, 2H), 0.84 (s, 3H), 0.52 – 0.43 (m, 1H).

Example 8:

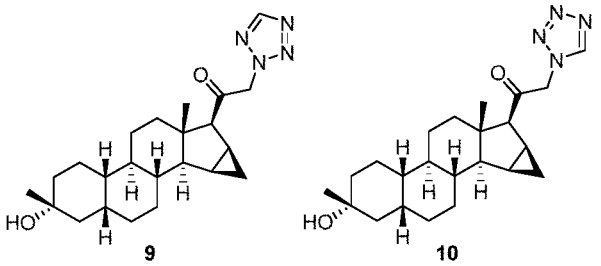
MS m/z (ESI): 398.3 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.66 (s, 1H), 5.52 – 5.35 (m, 2H), 2.87 (d, J = 3.9 Hz, 1H), 2.02 – 1.92 (m, 1H), 1.89 – 1.78 (m, 4H), 1.76 – 1.65 (m, 3H), 1.59 – 1.52 (m, 1H), 1.48 – 1.23 (m, 15H), 1.15 – 0.98 (m, 2H), 0.80 (s, 3H), 0.56 – 0.45 (m, 1H).

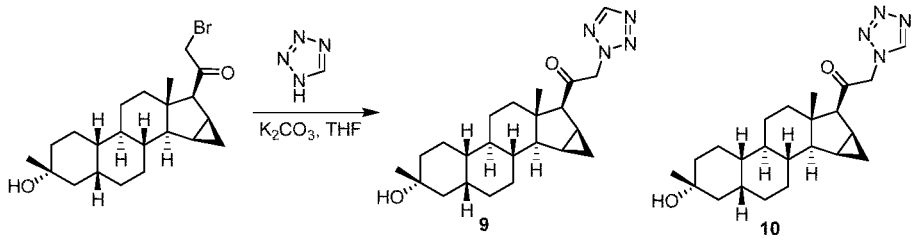
Example 9 and Example 10

1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-Hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(2H-tetrazol-2-yl)ethan-1-one (9)

1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-Hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(1H-tetrazol-1-yl)ethan-1-one (10)



Step 1: Preparation of 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(2H-tetrazol-2-yl)ethan-1-one (9) and 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(1H-tetrazol-1-yl)ethan-1-one (10)



2-Bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one (50 mg, 0.12 mmol), 1H-tetrazole (26 mg, 0.37 mmol) and potassium carbonate (83 mg, 0.6 mmol) were dissolved in tetrahydrofuran (3 mL), and the resulting reaction solution was stirred at room temperature overnight. The reaction solution was filtrated, and the filtrate was concentrated. The resulting crude product was purified by high performance liquid chromatography to obtain 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(2H-tetrazol-2-yl)ethan-1-one (**9**) (11.6 mg, yield: 24%) and 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(1H-tetrazol-1-yl)ethan-1-one (**10**) (4.4 mg, yield: 9%).

Example 9:

MS m/z (ESI): 381.2 $[M-H_2O+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ8.58 (s, 1H), 5.74 – 5.62 (m, 2H), 2.88 (d, J = 3.8 Hz, 1H), 1.97 – 1.91 (m, 1H), 1.87 – 1.79 (m, 4H), 1.75 – 1.64 (m, 3H), 1.58 – 1.55 (m, 1H), 1.45 – 1.35 (m, 7H), 1.34 – 1.24 (m, 8H), 1.14 – 1.01 (m, 2H), 0.85 (s, 3H), 0.56 – 0.48 (m, 1H).

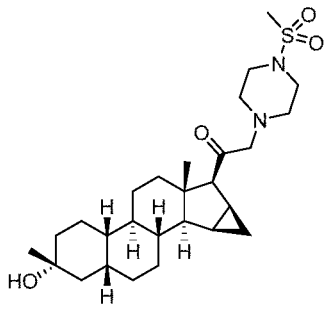
Example 10:

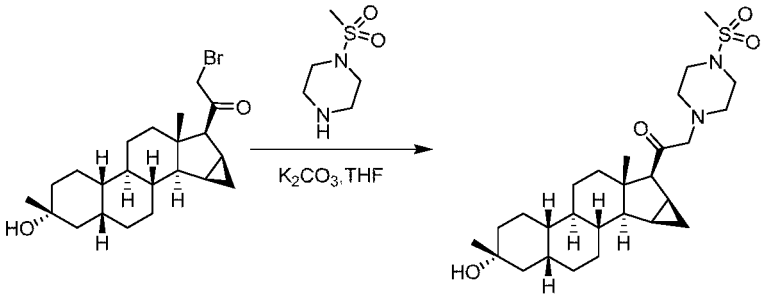
MS m/z (ESI): 399.3 $[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ8.77 (s, 1H), 5.57 – 5.39 (m, 2H), 2.90 (s, 1H), 2.00 – 1.91 (m, 1H), 1.88 – 1.79 (m, 4H), 1.76 – 1.65 (m, 3H), 1.59 – 1.56 (m, 1H), 1.46 – 1.37 (m, 7H), 1.35 – 1.24 (m, 8H), 1.13 – 0.99 (m, 2H), 0.79 (s, 3H), 0.58 – 0.49 (m, 1H).

Example 11

1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-Hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(4-(methylsulfonyl)piperazin-1-yl)ethan-1-one





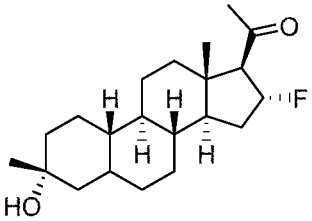
2-Bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one (50 mg, 0.12 mmol), 1-(methylsulfonyl)piperazine (60 mg, 0.36 mmol) and potassium carbonate (83 mg, 0.6 mmol) were dissolved in tetrahydrofuran (3 mL), and the resulting reaction solution was stirred at room temperature overnight. The reaction solution was filtrated, and the filtrate was concentrated. The resulting crude product was purified by high performance liquid chromatography to obtain 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(4-(methylsulfonyl)piperazin-1-yl)ethan-1-one (13.7 mg, yield: 23%).

MS m/z (ESI): 493.2 $[M+H]^+$.

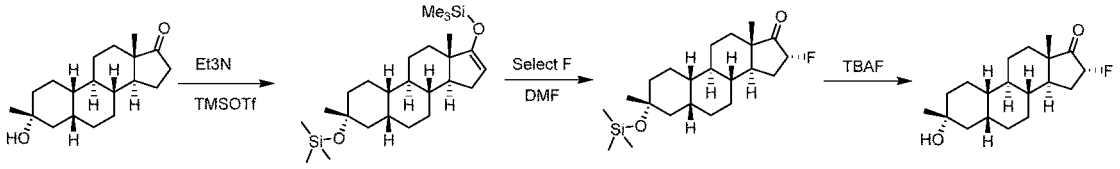
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (br, 2H), 3.47 (br, 4H), 2.93 (br, 4H), 2.82 (s, 3H), 2.73 (s, 1H), 1.90-1.88 (m, 1H), 1.86 – 1.81 (m, 2H), 1.81 – 1.70 (m, 3H), 1.70 – 1.64 (m, 2H), 1.57 – 1.50 (m, 1H), 1.41 (s, 5H), 1.34 – 1.22 (m, 10H), 1.12 – 0.99 (m, 1H), 0.92 – 0.85 (m, 1H), 0.73 (s, 3H), 0.49 – 0.39 (m, 1H).

Example 12

1-((3R,8R,9R,10S,13S,14S,16R,17S)-16-Fluoro-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one



Step 1: Preparation of (3R,5R,8R,9R,10S,13S,14S,16R)-16-fluoro-3-hydroxy-3,13-dimethylhexadecahydro-17H-cyclopenta[a]phenanthren-17-one



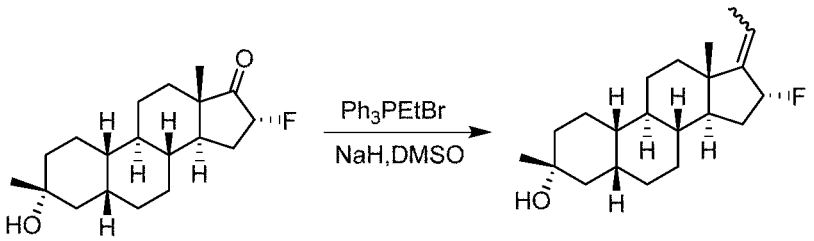
Trimethylsilyl triflate (5.6 mL, 31.0 mmol) was added dropwise to a solution of (3R,5R,8R,9R,10S,13S,14S)-3-hydroxy-3,13-dimethylhexadecahydro-17H-cyclopenta[a]phenanthren-17-one (3 g, 10.3 mmol) and triethylamine (36.0 mL, 258.2 mmol) in

toluene (45 mL), and the resulting reaction solution was heated to reflux for 2 hours. The reaction solution was cooled, washed with saturated sodium bicarbonate, and extracted with *n*-hexane. The organic phase was concentrated to dryness to obtain the crude product (((3R,5R,8R,9R,10S,13S,14S)-3,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthrene-3,17-diyl)bis(oxy))bis(trimethylsilane). A selective fluorine reagent (4.0 g, 11.4 mmol) was added to a solution of (((3R,5R,8R,9R,10S,13S,14S)-3,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthrene-3,17-diyl)bis(oxy))bis(trimethylsilane) in N,N-dimethylformamide (25 mL), and the resulting reaction solution was stirred at room temperature for 2 hours to obtain (3R,5R,8R,9R,10S,13S,14S,16R)-16-fluoro-3,13-dimethyl-3-((trimethylsilyl)oxy)hexadecahydro-17H-cyclopenta[a]phenanthren-17-one. A solution of tetrabutylammonium fluoride in tetrahydrofuran (11.4 mL, 1 M) was added, and the resulting reaction solution was stirred at room temperature overnight. The reaction solution was extracted with ethyl acetate, and washed with saturated saline three times. The organic phase was concentrated to dryness, and the resulting crude product was purified by column chromatography (petroleum ether:ethyl acetate=6:4) to obtain (3R,5R,8R,9R,10S,13S,14S,16R)-16-fluoro-3-hydroxy-3,13-dimethylhexadecahydro-17H-cyclopenta[a]phenanthren-17-one (2.0 g, yield: 50.9%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09 (dd, J = 50.6, 7.5 Hz, 1H), 2.18 – 1.58 (m, 10H), 1.54 – 1.01 (m, 14H), 0.92 (s, 3H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -192.59.

Step 2: Preparation of (3R,5R,8R,9R,10S,13S,14S,16R)-17-ethylidene-16-fluoro-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-ol



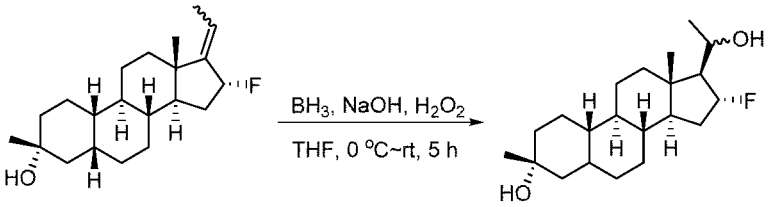
Sodium hydride (123 mg, 3.08 mmol, 60% w/w) was added to a solution of ethyltriphenylphosphonium bromide (1.2 g, 3.24 mmol) in dimethyl sulfoxide (20 mL) in batches under a nitrogen atmosphere, and the resulting reaction solution was stirred at room temperature for 1 hour. (3R,5R,8R,9R,10S,13S,14S,16R)-16-Fluoro-3-hydroxy-3,13-dimethylhexadecahydro-17H-cyclopenta[a]phenanthren-17-one (200 mg,0.65 mmol) was added, and the reaction solution was heated to 70°C under a nitrogen atmosphere overnight. The reaction solution was cooled, and saturated saline was added. 1 N hydrochloric acid was added to adjust pH to 6, and the reaction solution was extracted with ethyl acetate. The organic

phase was washed with saturated saline, and concentrated to dryness to obtain a crude product. The crude product was purified by column chromatography (petroleum ether:ethyl acetate=7:3) to obtain (3R,5R,8R,9R,10S,13S,14S,16R)-17-ethylidene-16-fluoro-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-ol (80 mg, yield: 38.5%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 – 5.59 (m, 1H), 5.12 (dt, J = 57.2, 7.0 Hz, 1H), 2.27 – 2.11 (m, 2H), 1.92 – 1.24 (m, 21H), 1.22 – 1.09 (m, 4H), 1.06 (s, 3H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -153.69.

Step 3: Preparation of (3R,8R,9R,10S,13S,14S,16R,17S)-16-fluoro-17-(1-hydroxyethyl)-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-ol

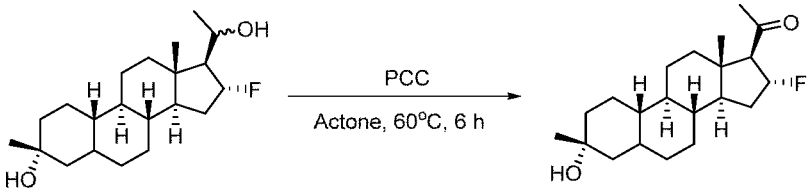


(3R,5R,8R,9R,10S,13S,14S,16R)-17-Ethylidene-16-fluoro-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-ol (80 mg, 0.25 mmol) was dissolved in anhydrous tetrahydrofuran (50 mL). A solution of borane in tetrahydrofuran (1 M, 2.5 mL) was added dropwise at room temperature, and the resulting reaction solution was stirred at room temperature for 1 hour. The reaction solution was cooled with ice water, and sodium hydroxide solution (3 M, 1 mL) was slowly added dropwise to release a large amount of gas. Hydrogen peroxide (25%, 0.58 mL) was slowly added dropwise, and then the reaction solution was stirred at room temperature for 2 hours. The reaction solution was extracted with ethyl acetate, washed with sodium thiosulfate solution and saturated saline, and dried to obtain (3R,8R,9R,10S,13S,14S,16R,17S)-16-fluoro-17-(1-hydroxyethyl)-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-ol (80 mg), which was used directly in the next step.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47 – 5.16 (m, 1H), 4.22 – 4.05 (m, 1H), 2.42 – 2.17 (m, 1H), 1.94 – 0.93 (m, 27H), 0.87 (s, 3H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -178.27.

Step 4: Preparation of 1-((3R,8R,9R,10S,13S,14S,16R,17S)-16-fluoro-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one



Pyridinium chlorochromate (102 mg, 0.47 mmol) was added to a solution of (3R,8R,9R,10S,13S,14S,16R,17S)-16-fluoro-17-(1-hydroxyethyl)-3,13-dimethylhexade

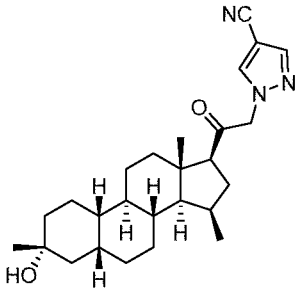
cahydro-1H-cyclopenta[a]phenanthren-3-ol (80 mg) in acetone (2 mL), and the resulting reaction solution was reacted at 60°C for 6 hours. The reaction solution was concentrated to dryness, and the resulting residue was purified by column chromatography (petroleum ether:ethyl acetate=5:2) to obtain 1-((3R,8R,9R,10S,13S,14S,16R,17S)-16-fluoro-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (22 mg, yield: 25%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.64 – 5.35 (m, 1H), 2.44 – 2.09 (m, 6H), 1.97 – 1.75 (m, 4H), 1.74 – 1.00 (m, 20H), 0.98 – 0.68 (m, 2H).

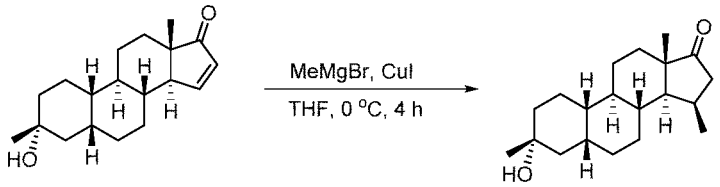
^{19}F NMR (376 MHz, $CDCl_3$) δ -168.20.

Example 13

1-(2-((3R,5R,8R,9R,10S,13S,14S,15R)-3-Hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile



Step 1: (3R,5R,8R,9R,10S,13S,14S,15R)-3-Hydroxy-3,13,15-trimethylhexadecahydro-17H-cyclopenta[a]phenanthren-17-one

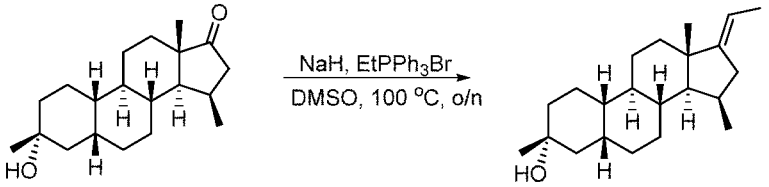


3.0 M methylmagnesium bromide (8.5 mL, 25.5 mmol) and 20 mL of anhydrous tetrahydrofuran were added to a dry 100 mL round bottom flask. The reaction system was purged with nitrogen, and cooled to 0°C. Cuprous iodide (3.94 g, 20.7 mmol) was added, and then the reaction solution was stirred at 0°C for 1 hour. (3R,5R,8R,9R,10S,13S,14S)-3-Hydroxy-3,13-dimethyl-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-17H-cyclopenta[a]phenanthren-17-one (2 g, 6.9 mmol) was dissolved in 10 ml of anhydrous tetrahydrofuran, and the resulting solution was slowly added dropwise to the reaction system. The reaction solution was stirred for 3 hours, and TLC showed that the reaction was completed. Saturated ammonium chloride solution was added to quench the reaction, and the reaction solution was extracted with ethyl acetate. The organic phase was washed with water and saturated saline, dried over anhydrous sodium sulfate, filtrated and concentrated by rotary evaporation to dryness. The resulting crude product was purified by column chromatography (petroleum ether:ethyl acetate=2:1) to obtain

(3R,5R,8R,9R,10S,13S,14S,15R)-3-hydroxy-3,13,15-trimethylhexadecahydro-17H-cyclopenta[a]phenanthren-17-one (1.56 g, yield: 75%).

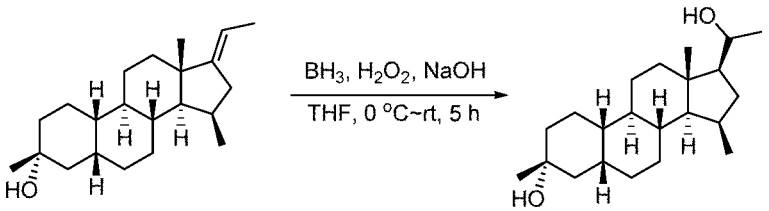
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.51-2.42 (m, 2H), 2.24 (d, J = 17.6 Hz, 1H), 1.89-1.63 (m, 7H), 1.54-1.18 (m, 16H), 1.10 (d, J = 7.6 Hz, 3H), 1.03 (s, 3H).

Step 2: (3R,5R,8R,9R,10S,13S,14S,15R,E)-17-Ethylidene-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-ol



Ethyltriphenylphosphonium bromide (18.5 g, 50 mmol) was dissolved in anhydrous dimethyl sulfoxide (50 mL), and the reaction system was purged with nitrogen. Sodium hydride (2.0 g, 50 mmol) was added, and then the reaction solution was stirred at room temperature for 1 hour. (3R,5R,8R,9R,10S,13S,14S,15R)-3-Hydroxy-3,13,15-trimethylhexadecahydro-17H-cyclopenta[a]phenanthren-17-one (1.52 g, 5 mmol) was added, and then the reaction solution was stirred at 100°C overnight. The reaction solution was cooled to room temperature. Water (200 mL) was added to the reaction solution to quench the reaction, and the aqueous phase was extracted with ethyl acetate (200 mL×2). The organic phases were combined, dried over anhydrous sodium sulfate, filtrated and concentrated. The resulting crude product was purified by column chromatography (petroleum ether/ethyl acetate: 50/1 - 3/1) to obtain (3R,5R,8R,9R,10S,13S,14S,15R,E)-17-ethylidene-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-ol (1.37 g, yield: 86%).

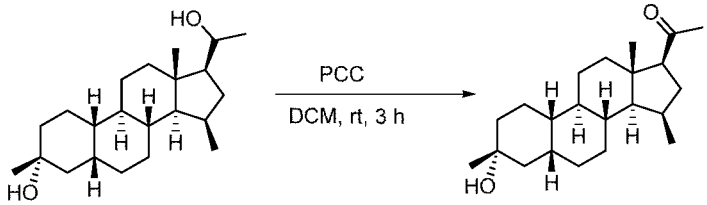
Step 3: (3R,5R,8R,9R,10S,13S,14S,15R,17S)-17-((R)-1-Hydroxyethyl)-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-ol



(3R,5R,8R,9R,10S,13S,14S,15R,E)-17-Ethylidene-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-ol (1.37 g, 4.33 mmol) was dissolved in anhydrous tetrahydrofuran (50 mL). The solution was cooled to 0°C, and then BH_3/THF (43 mL, 43 mmol) was added dropwise. The reaction solution was stirred at room temperature for 3 hours, and TLC showed that the reaction was completed. The reaction solution was cooled to 0°C, and then 3 M aqueous NaOH solution (40 mL) was slowly added, followed by the addition of H_2O_2 (30 mL). The reaction solution was stirred at room temperature for 2 hours, and TLC showed that the reaction was completed. Ethyl acetate

(50 mL) was added, and then the reaction solution was washed with saturated aqueous $Na_2S_2O_3$ solution (30 mL) and water (30 mL) successively. The organic phase was dried over anhydrous sodium sulfate, filtrated and concentrated to obtain the crude product (1.37 g), which was used directly in the next step.

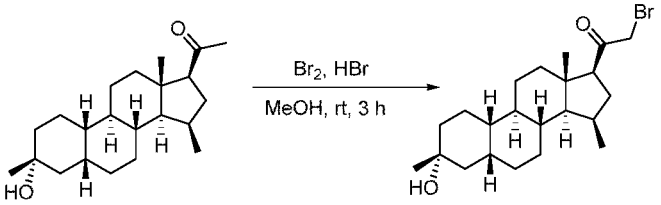
Step 4: 1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-Hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one



(3R,5R,8R,9R,10S,13S,14S,15R,17S)-17-((R)-1-Hydroxyethyl)-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-ol (1.37 g, crude) was dissolved in dichloromethane (30 mL). PCC (1.8 g, 8.66 mmol) was added, and then the reaction solution was stirred at room temperature for 2 hours. The reaction solution was filtrated, and the organic phase was concentrated. The resulting crude product was purified by column chromatography (petroleum ether/ethyl acetate: 1/1) to obtain 1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (780 mg, yield of two steps: 54.3%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (dd, J = 8.8, 10.4 Hz, 1H), 2.14-2.03 (m, 5H), 1.95-1.79 (m, 5H), 1.69-1.06 (m, 18H), 0.96 (d, J = 7.2 Hz, 3H), 0.78 (s, 3H).

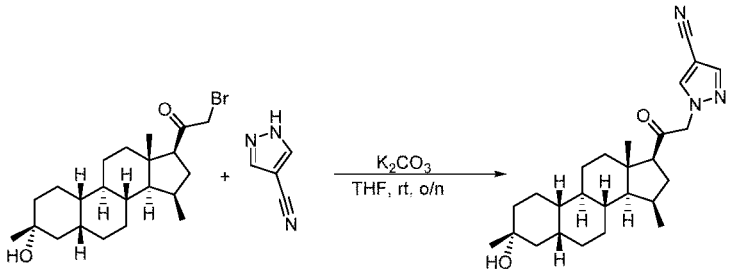
Step 5: 2-Bromo-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one



1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-Hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (333 mg, 1 mmol) was dissolved in methanol (10 mL). A drop of hydrogen bromide was added to the solution, followed by the addition of liquid bromine (176 mg, 1.1 mmol) was added, and then the reaction solution was stirred at room temperature for 1 hour. Water (20 mL) was added to the reaction solution, and the aqueous phase was extracted with ethyl acetate (20 mL×2). The organic phases were combined, dried over anhydrous sodium sulfate, filtrated and concentrated to obtain the crude product (413 mg, crude), which was used directly in the next step.

Step 6: 1-(2-((3R,5R,8R,9R,10S,13S,14S,15R)-3-Hydroxy-3,13,15-trimethylhexadecahydro-1H

-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile



2-Bromo-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (82 mg, 0.2 mmol), 1H-pyrazole-4-carbonitrile (28 mg, 0.3 mmol) and potassium carbonate (54 mg, 0.3 mmol) were dissolved in anhydrous tetrahydrofuran (5 mL), and the resulting reaction solution was stirred at room temperature overnight. The reaction solution was filtrated, and the filtrate was concentrated. The resulting crude product was purified by high performance liquid chromatography to obtain 1-(2-((3R,5R,8R,9R,10S,13S,14S,15R)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile (41 mg, yield: 48%).

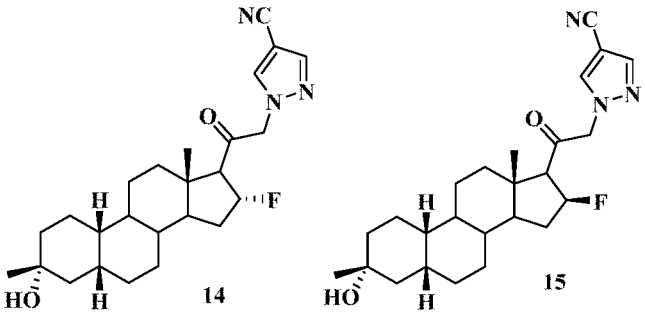
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.81 (s, 1H), 5.01 (d, J = 17.9 Hz, 1H), 4.90 (d, J = 17.9 Hz, 1H), 2.62-2.48 (m, 1H), 2.30-2.06 (m, 3H), 2.04-1.75 (m, 7H), 1.75-1.04 (m, 15H), 0.99 (d, J = 7.1 Hz, 3H), 0.84 (s, 3H).

MS m/z (ESI): 424.6 $[M+H]^+$.

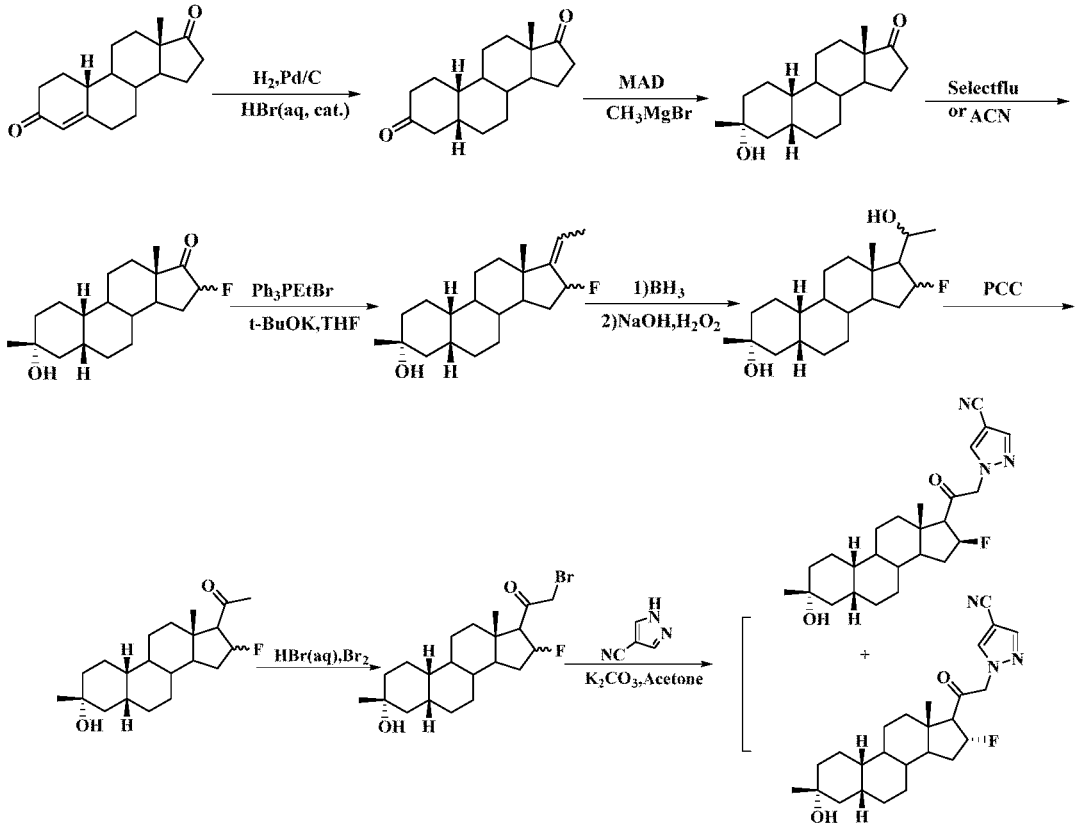
Example 14 and Example 15

1-(2-((3R,5R,10S,13S,16R)-16-Fluoro-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1*H*-pyrazole-4-carbonitrile (14)

1-(2-((3R,5R,10S,13S,16S)-16-Fluoro-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1*H*-pyrazole-4-carbonitrile (15)



Example 14 and Example 15 were synthesized by the following specific scheme:



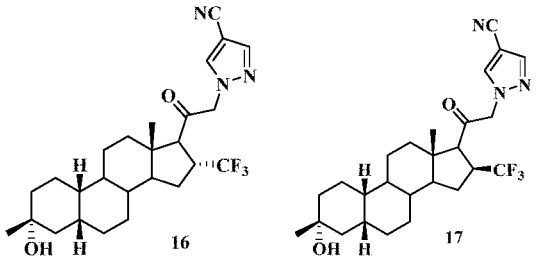
Example 14: MS m/z (ESI): 428.3 $[M+1]^+$.

Example 15: MS m/z (ESI): 428.3 $[M+1]^+$.

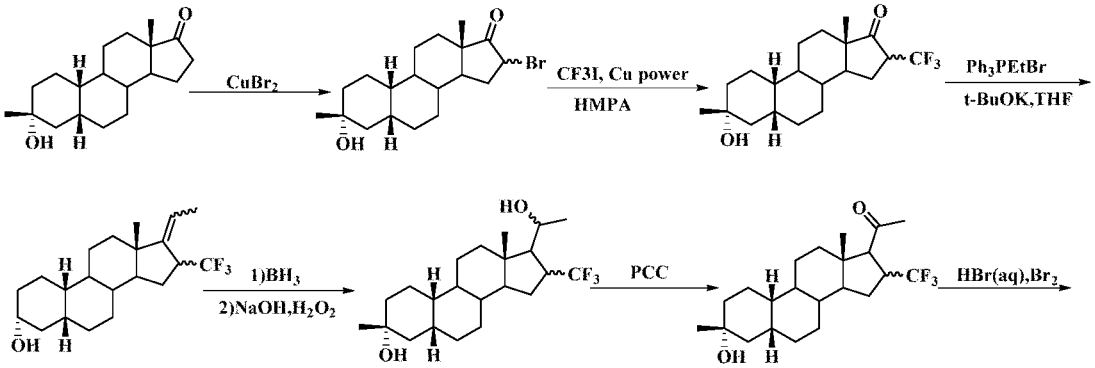
Example 16 and Example 17

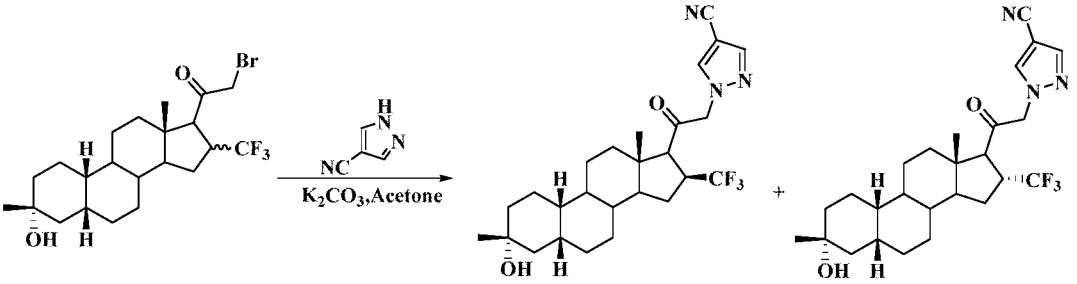
1-(2-((3R,5R,10S,13S,16R)-3-Hydroxy-3,13-dimethyl-16-(trifluoromethyl)hexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile (16)

1-(2-((3R,5R,10S,13S,16S)-3-Hydroxy-3,13-dimethyl-16-(trifluoromethyl)hexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile (17)



Example 16 and Example 17 were synthesized by the following specific scheme:



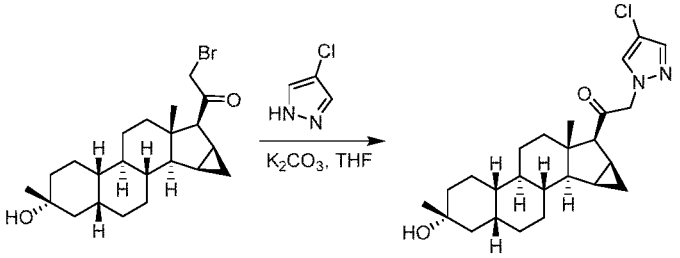


Example 16: MS m/z (ESI): 478.3 $[M+1]^+$.

Example 17: MS m/z (ESI): 478.3 $[M+1]^+$.

Example 18

2-(4-Chloro-1H-pyrazol-1-yl)-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one



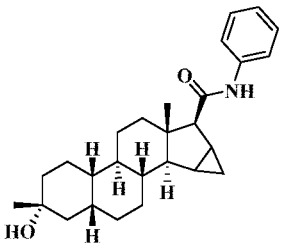
In accordance with Example 5, 2-bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one and 4-chloro-1H-pyrazole were used as the starting materials, accordingly, 2-(4-chloro-1H-pyrazol-1-yl)-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one (21.9 mg, yield: 26%) was obtained.

MS m/z (ESI): 431.2 $[M+H]^+$

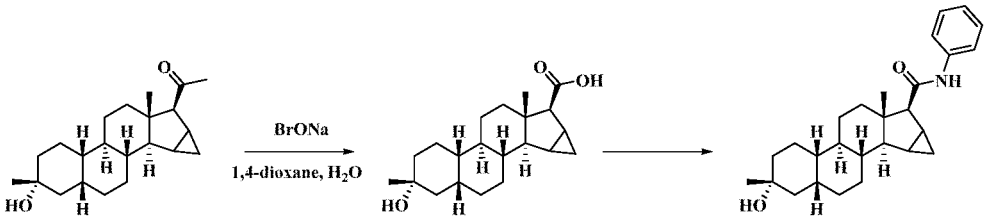
^{1}H NMR (400 MHz, $CDCl_3$) δ7.45 (d, J = 11.8 Hz, 2H), 5.17 – 5.01 (m, 2H), 2.81 (d, J = 3.5 Hz, 1H), 1.99 – 1.91 (m, 1H), 1.86 – 1.79 (m, 3H), 1.77 – 1.62 (m, 3H), 1.57 – 1.49 (m, 3H), 1.44 – 1.20 (m, 14H), 1.12 – 0.96 (m, 2H), 0.78 (s, 3H), 0.51 – 0.44 (m, 1H).

Example 19

(2R,4aS,4bR,6aS,7S,8bR,8cR,10aR)-2-Hydroxy-2,6a-dimethyl-N-phenyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthrene-7-carboxamide



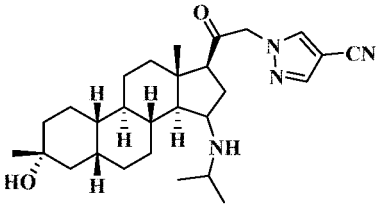
Example 19 was synthesized by the following specific scheme:



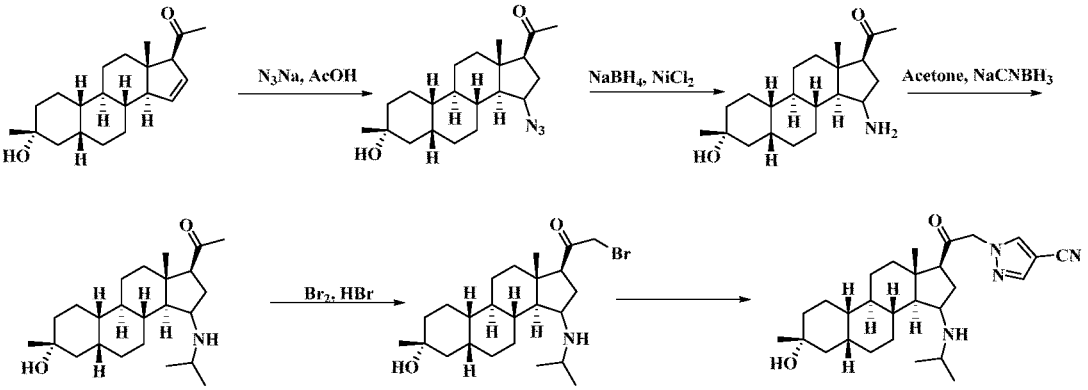
MS m/z (ESI): 408.3 $[M+1]^+$.

Example 20

1-(2-((3R,5R,8R,9R,10S,13S,14S,17S)-3-Hydroxy-15-(isopropylamino)-3,13-dimethyl hexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-4-carbon itrile



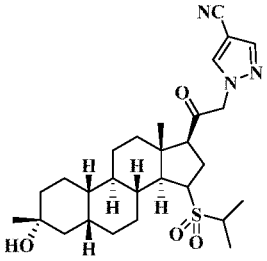
Example 20 was synthesized by the following specific scheme:



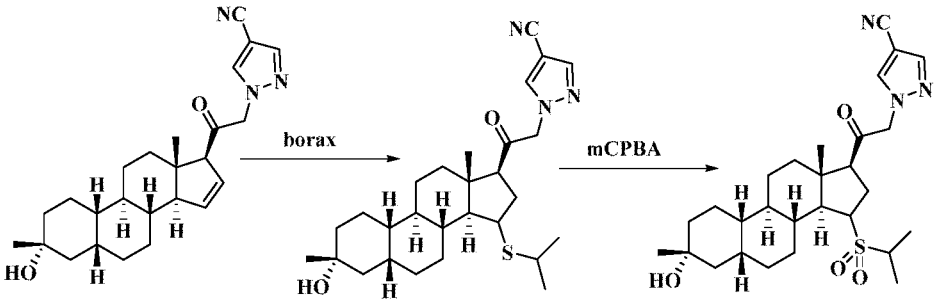
MS m/z (ESI): 467.3 $[M+1]^+$.

Example 21

1-(2-((3R,5R,8R,9R,10S,13R,14S,17S)-3-Hydroxy-15-(isopropylsulfonyl)-3,13-dimeth ylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-4-carb onitrile



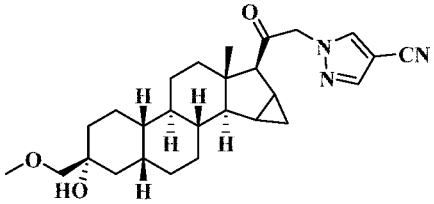
Example 21 was synthesized by the following specific scheme:



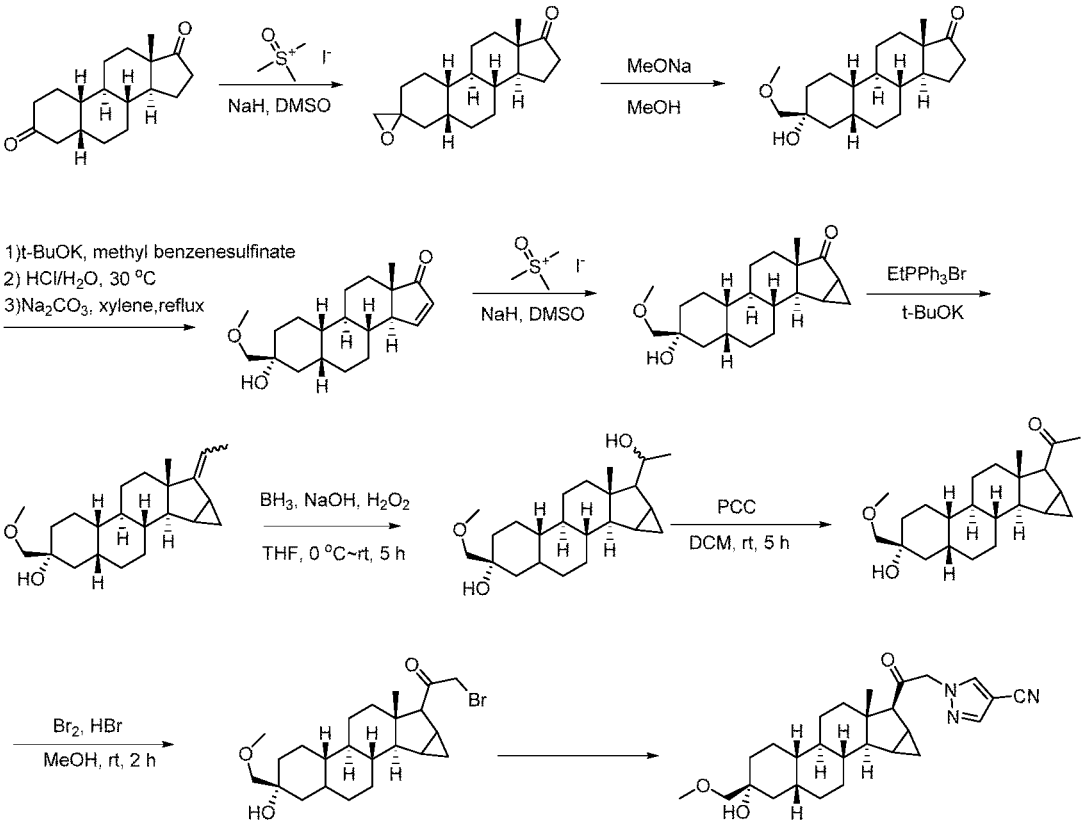
MS m/z (ESI): 516.3 $[M+1]^+$.

Example 23

1-(2-((2R,4aS,4bR,6aS,7S,8bR,8cR,10aR)-2-Hydroxy-2-(methoxymethyl)-6a-methyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile



Example 23 was synthesized by the following specific scheme:

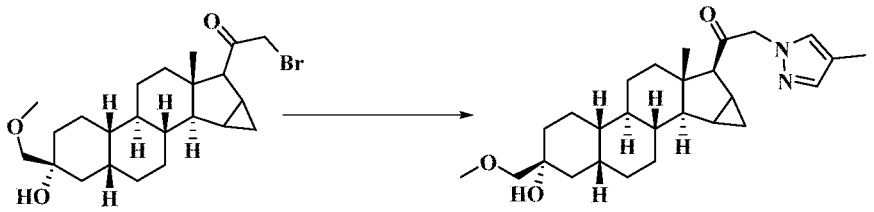


MS m/z (ESI): 452.3 $[M+1]^+$.

Example 24

1-((2R,4aS,4bR,6aS,7S,8bR,8cR,10aR)-2-Hydroxy-2-(methoxymethyl)-6a-methyloctad

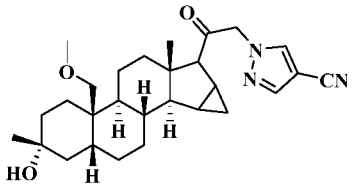
ecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(4-methyl-1H-pyrazol-1-yl)ethan-1-one



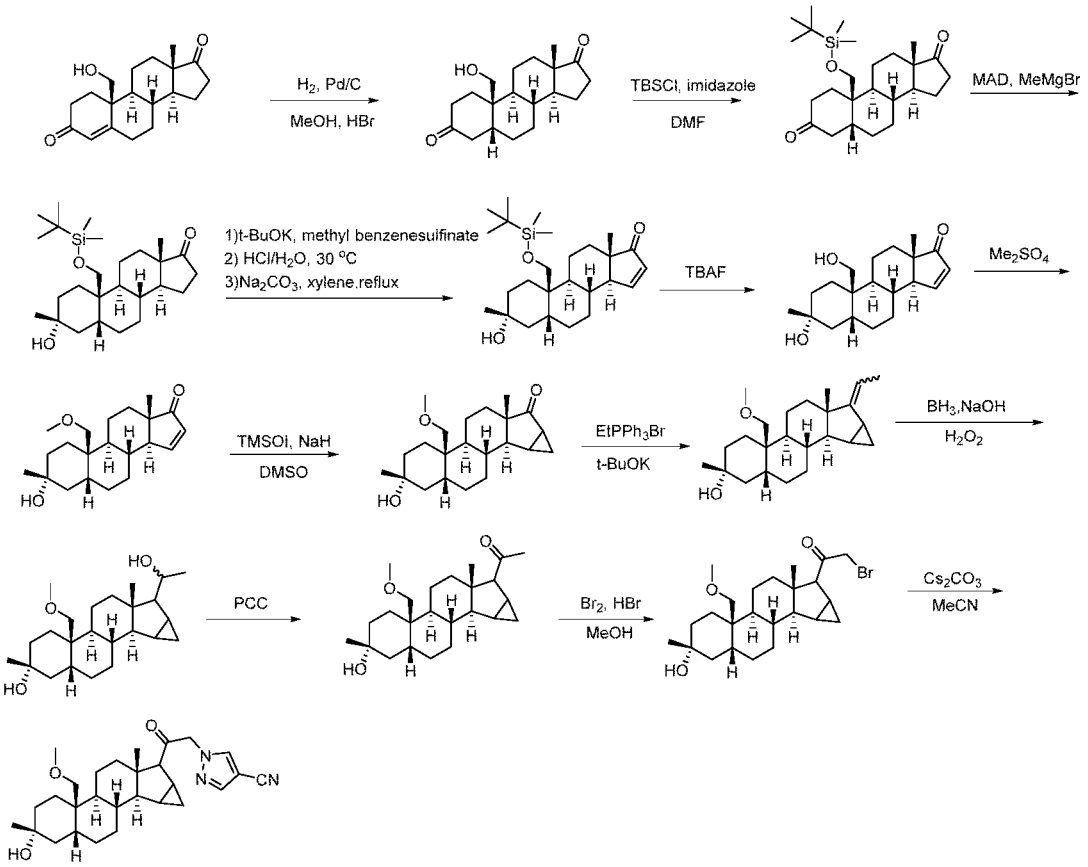
MS m/z (ESI): 441.3 $[M+1]^+$.

Example 25

1-(2-((2R,4aR,4bS,6aS,8bS,8cR,10aR)-2-Hydroxymethyl-4a-(methoxymethyl)-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile



Example 25 was synthesized by the following specific scheme:

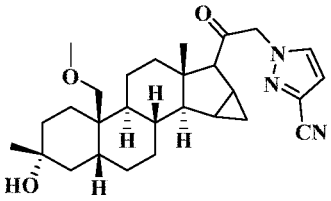


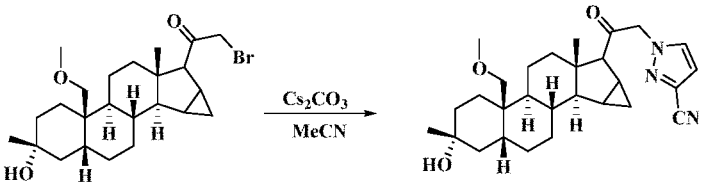
MS m/z (ESI): 466.3 $[M+1]^+$.

Example 26

1-(2-((2R,4aR,4bS,6aS,8bS,8cR,10aR)-2-Hydroxymethyl-4a-(methoxymethyl)-2,6a-di

methyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethyl)-1H-pyrazole-3-carbonitrile



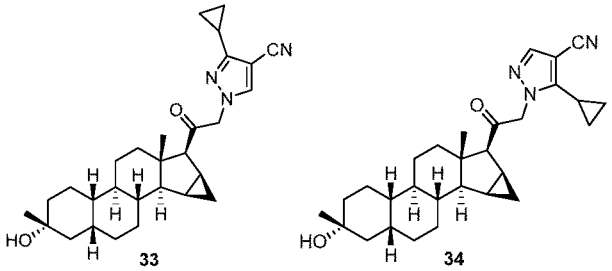


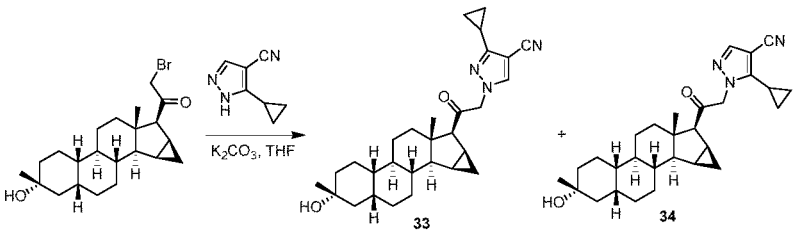
MS m/z (ESI): 466.3 $[M+1]^+$.

Example 33 and Example 34

3-Cyclopropyl-1-(2-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile (33)

5-Cyclopropyl-1-(2-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile (34)





In accordance with Example 5, 2-bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one and 5-cyclopropyl-1H-pyrazole-4-carbonitrile were used as the starting materials, accordingly, 3-cyclopropyl-1-(2-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile (**33**) (19.2 mg, yield: 21%) and 5-cyclopropyl-1-(2-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethyl)-1H-

pyrazole-4-carbonitrile (**34**) (3.0 mg, yield: 3.3%) were obtained.

Example 33:

MS m/z (ESI): 462.3 $[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ7.73 (s, 1H), 5.14 – 4.98 (m, 2H), 2.80 (d, J = 2.2 Hz, 1H), 2.05 – 1.89 (m, 2H), 1.86 – 1.78 (m, 4H), 1.75 – 1.64 (m, 3H), 1.58 – 1.52 (m, 2H), 1.46 – 1.33 (m, 7H), 1.33 – 1.20 (m, 7H), 1.14 – 0.92 (m, 6H), 0.76 (s, 3H), 0.53 – 0.43 (m, 1H).

Example 34:

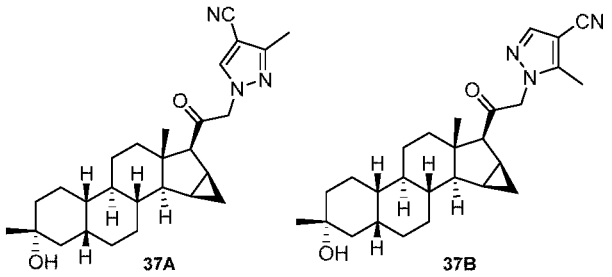
MS m/z (ESI): 462.3 $[M+H]^+$

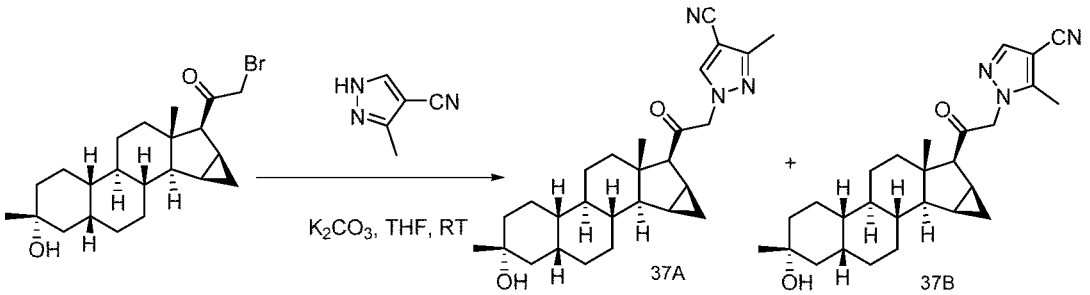
^{1}H NMR (400 MHz, $CDCl_3$) δ7.69 (s, 1H), 5.33 – 5.13 (m, 2H), 2.85 (d, J = 3.8 Hz, 1H), 2.00 – 1.92 (m, 1H), 1.86 – 1.79 (m, 3H), 1.76 – 1.62 (m, 4H), 1.60 – 1.51 (m, 2H), 1.45 – 1.34 (m, 7H), 1.34 – 1.22 (m, 7H), 1.17 – 0.94 (m, 7H), 0.81 (s, 3H), 0.54 – 0.45 (m, 1H).

Example 37A and Example 37B

1-(2-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-Hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethyl)-3-methyl-1H-pyrazole-4-carbonitrile (37A)

1-(2-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-Hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethyl)-5-methyl-1H-pyrazole-4-carbonitrile (37B)





In accordance with Example 5, 2-bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one and 3-methyl-1H-pyrazole-4-carbonitrile were used as the starting materials, accordingly, a mixture of Example 37A and Example 37B (approximately 3:1) (25.9 mg, white solid, yield: 39.3%) was obtained. The mixture was further separated by preparative chromatography to obtain

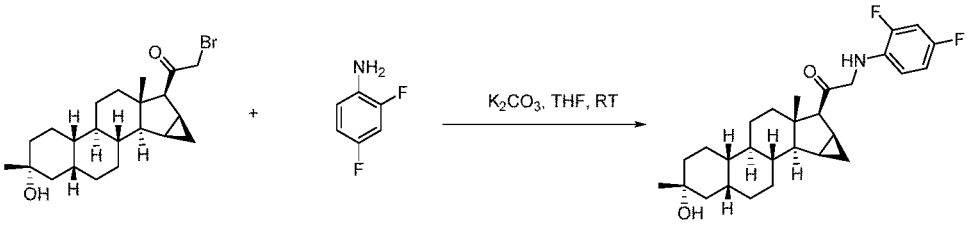
1-(2-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethyl)-3-methyl-1H-pyrazole-4-carbonitrile (37A) and 1-(2-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethyl)-5-methyl-1H-pyrazole-4-carbonitrile (37B).

Example 37A: MS m/z (ESI): 436.3$[M+H]^+$

Example 37B: MS m/z (ESI): 436.3$[M+H]^+$

Example 40

2-((2,4-Difluorophenyl)amino)-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one



In accordance with Example 5, 2-bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one and 2,4-difluoroaniline were used as the starting materials, accordingly, 2-((2,4-difluorophenyl)amino)-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one (3.9 mg, white solid, yield: 3.9%) was obtained .

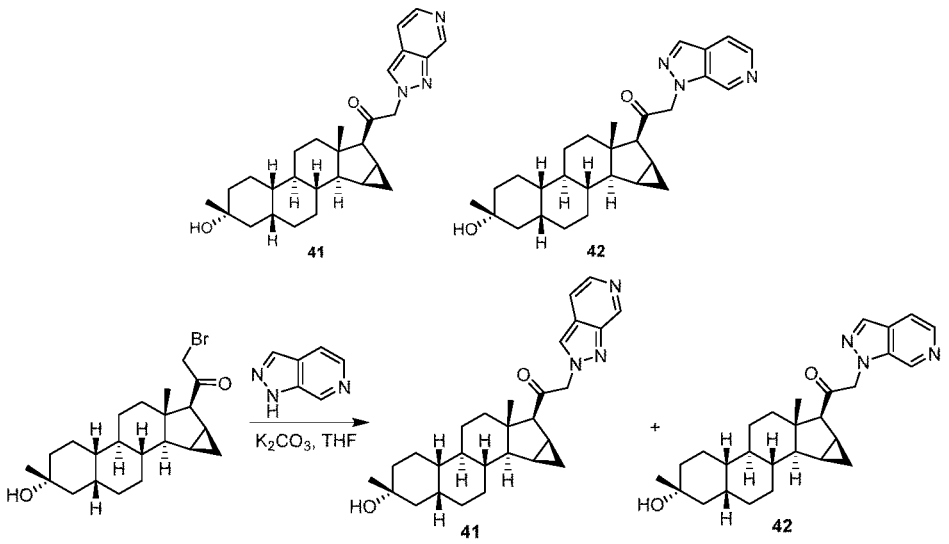
MS m/z (ESI): 458.3$[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84-6.75 (m, 2H), 6.65-6.59 (m, 1H), 4.12 (dd, J_1 = 5.2 Hz, J_2 = 24.8 Hz, 2H), 3.61-3.27 (br, 1H), 2.80 (d, J = 3.6 Hz, 1H), 2.01-1.77 (m, 10H), 1.76-1.56 (m, 3H), 1.53-1.46 (m, 1H), 1.28-1.19 (m, 10H), 1.00-0.93 (m, 2H), 0.73 (m, 3H), 0.50-0.44 (m, 1H).

Example 41 and Example 42

1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-Hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(2H-pyrazolo[3,4-c]pyridin-2-yl)ethan-1-one

1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-Hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(1H-pyrazolo[3,4-c]pyridin-1-yl)ethan-1-one



In accordance with Example 5, 2-bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one and 1H-pyrazolo[3,4-c]pyridine were used as the starting materials, accordingly, 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(2H-pyrazolo[3,4-c]pyridin-2-yl)ethan-1-one (**41**) (5.4 mg, yield: 6.2%) and 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(1H-pyrazolo[3,4-c]pyridin-1-yl)ethan-1-one (**42**) (7.0 mg, yield: 8%) were obtained.

Example 41:

MS m/z (ESI): 448.3 $[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.43 (s, 1H), 8.39 (s, 1H), 8.19 (d, J = 6.4 Hz, 1H), 8.08 (d, J = 6.4 Hz, 1H), 5.77 – 5.61 (m, 2H), 2.96 (s, 1H), 2.01 – 1.92 (m, 1H), 1.88 – 1.81 (m, 4H), 1.74 – 1.69 (m, 3H), 1.59 – 1.55 (m, 2H), 1.48 – 1.43 (m, 5H), 1.33 – 1.27 (m, 9H), 1.10 – 1.05 (m, 2H), 0.85 (s, 3H), 0.60 – 0.54 (m, 1H).

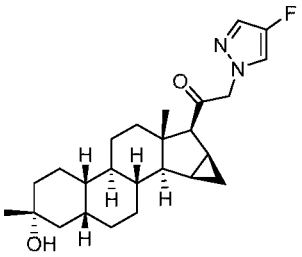
Example 42:

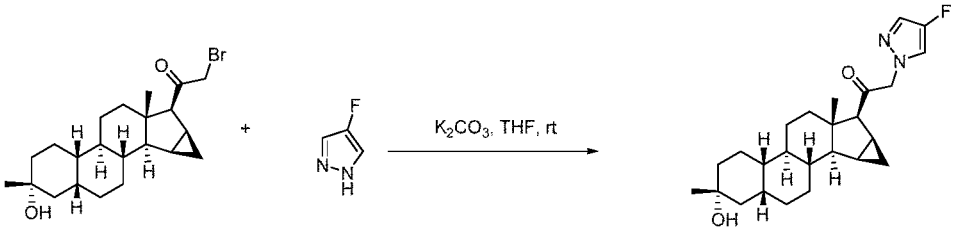
MS m/z (ESI): 448.3 $[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.34 (d, J = 5.8 Hz, 1H), 8.25 (s, 1H), 7.87 (d, J = 5.2 Hz, 1H), 5.72 – 5.60 (m, 2H), 2.96 (d, J = 3.9 Hz, 1H), 2.01 – 1.94 (m, 1H), 1.87 – 1.81 (m, 4H), 1.75 – 1.67 (m, 3H), 1.58 – 1.52 (m, 2H), 1.44 – 1.39 (m, 5H), 1.33 – 1.25 (m, 9H), 1.12 – 1.02 (m, 2H), 0.86 (s, 3H), 0.56 – 0.50 (m, 1H).

Example 46

2-(4-Fluoro-1H-pyrazol-1-yl)-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one





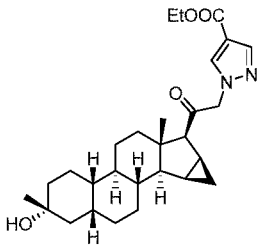
In accordance with Example 5, 2-bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one and 4-fluoropyrazole were used as the starting materials, accordingly, 2-(4-fluoro-1H-pyrazol-1-yl)-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one (6.2 mg, white solid, yield: 7.7%) was obtained .

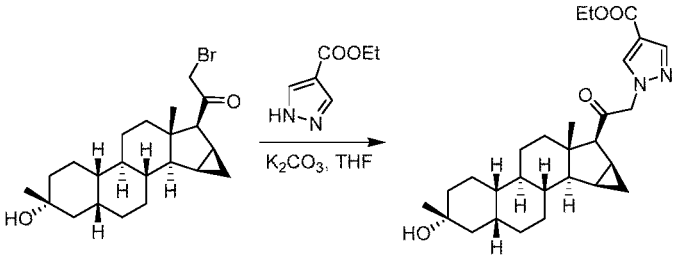
MS m/z (ESI): 415.2$[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 4.0 Hz, 1H), 7.32 (d, J = 4.0 Hz, 1H), 5.03 (d, J = 3.6 Hz, 2H), 2.80 (d, J = 3.6 Hz, 1H), 2.01-1.93 (m, 2H), 1.85-1.80 (m, 3H), 1.73-1.61 (m, 6H), 1.41-1.32 (m, 9H), 1.27 (s, 3H), 1.12-1.02 (m, 2H), 0.99-0.96 (m, 1H), 0.78 (s, 3H), 0.50-0.44 (m, 1H).

Example 51

Ethyl 1-(2-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethyl)-1H-pyrazole-4-carboxylate





In accordance with Example 5,

2-bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethylocta decahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one and ethyl 1H-pyrazole-4-carboxylate were used as the starting materials, accordingly, ethyl 1-(2-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecah ydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethyl)-1H-pyrazole-4-car boxylate (29.6 mg, white solid, yield: 43%) was obtained.

MS m/z (ESI): 469.3 $[M+H]^+$

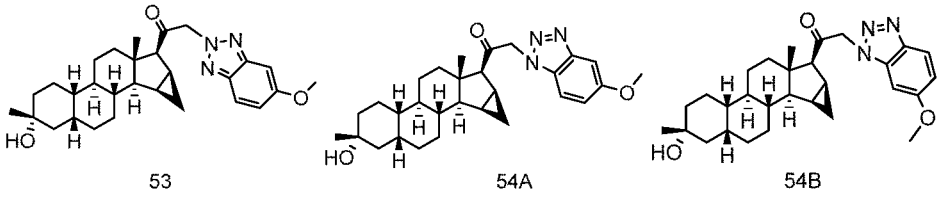
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 2H), 5.32 – 4.99 (m, 2H), 4.36 – 4.24 (m, 2H), 2.83 (s, 1H), 1.99 – 1.92 (m, 1H), 1.87 – 1.79 (m, 3H), 1.72 – 1.52 (m, 6H), 1.49 – 1.16 (m, 17H), 1.14 – 0.96 (m, 2H), 0.83 (s, 3H), 0.53 – 0.44 (m, 1H).

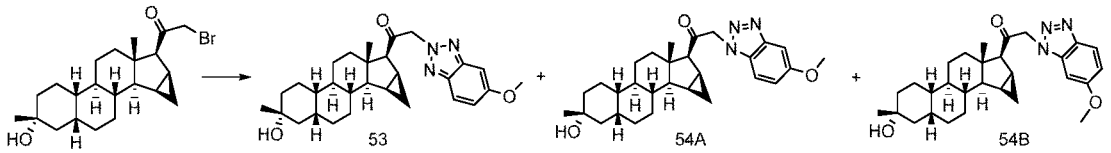
Example 53, Example 54A and Example 54B

1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-Hydroxy-2,6a-dimethyloctadecahyd rocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(5-methoxy-2H-benzo[d][1,2,3] triazol-2-yl)ethan-1-one (53)

1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-Hydroxy-2,6a-dimethyloctadecahyd rocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(6-methoxy-1H-benzo[d][1,2,3] triazol-1-yl)ethan-1-one (54A)

1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-Hydroxy-2,6a-dimethyloctadecahyd rocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(5-methoxy-1H-benzo[d][1,2,3] triazol-1-yl)ethan-1-one (54B)





In accordance with Example 5, 2-bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethylocta decahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one and 6-methoxy-1H-benzo[d][1,2,3]triazole were used as the starting materials, accordingly, 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydr ocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(5-methoxy-2H-benzo[d][1,2,3]t riazol-2-yl)ethan-1-one (11.8 mg, yield: 13.6%) and a mixture of Example 54A and Example 54B (approximately 1:1) (34 mg, yield: 39%) were obtained. The mixture was further separated by preparative chromatography to obtain 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydr ocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(6-methoxy-1H-benzo[d][1,2,3]t riazol-1-yl)ethan-1-one (54A) and

1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(5-methoxy-1H-benzo[d][1,2,3]triazol-1-yl)ethan-1-one (54B).

Example 53:

MS m/z (ESI): 478.3 $[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ7.74 (d, J = 10.1 Hz, 1H), 7.14 – 7.03 (m, 2H), 5.73 – 5.59 (m, 2H), 3.88 (s, 3H), 2.88 (d, J = 4.1 Hz, 1H), 2.01 – 1.93 (m, 1H), 1.86 – 1.78 (m, 4H), 1.74 – 1.63 (m, 3H), 1.55 – 1.51 (m, 1H), 1.46 – 1.25 (m, 15H), 1.15 – 1.00 (m, 2H), 0.88 (s, 3H), 0.53 – 0.45 (m, 1H).

Example 54A:

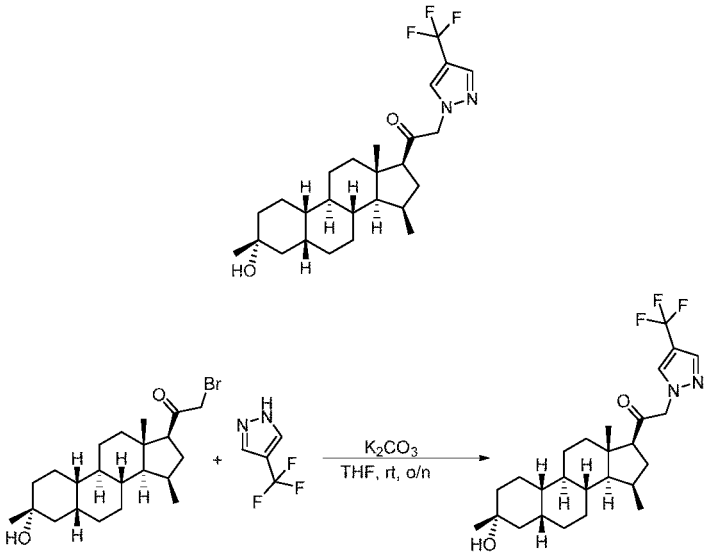
MS m/z (ESI): 478.3 $[M+H]^+$

Example 54B:

MS m/z (ESI): 478.3 $[M+H]^+$

Example 59

1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-Hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(4-(trifluoromethyl)-1H-pyrazol-1-yl)ethan-1-one



2-Bromo-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (82 mg, 0.2 mmol), 4-(trifluoromethyl)-1H-pyrazole (41 mg, 0.3 mmol) and potassium carbonate (54 mg, 0.3 mmol) were dissolved in anhydrous tetrahydrofuran (5 mL), and the resulting reaction solution was stirred at room temperature overnight. The reaction solution was filtrated, and the filtrate was concentrated. The resulting crude product was purified by high performance liquid chromatography to obtain 1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(4-(trifluoromethyl)-1H-pyrazol-1-yl)ethan-1-one (24.6 mg, yield: 26%).

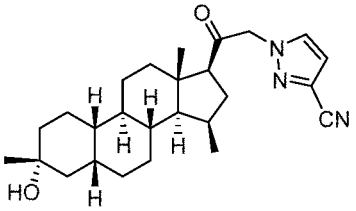
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 2H), 5.00 (d, J = 16 Hz, 1H), 4.90 (d, J = 16 Hz, 1H), 2.58-2.54 (m, 1H), 1.88-1.83 (m, 2H), 1.69-1.58 (m, 5H), 1.50-1.25 (m, 19H),

0.98 (d, J = 8.0 Hz, 3H), 0.85 (s, 3H).

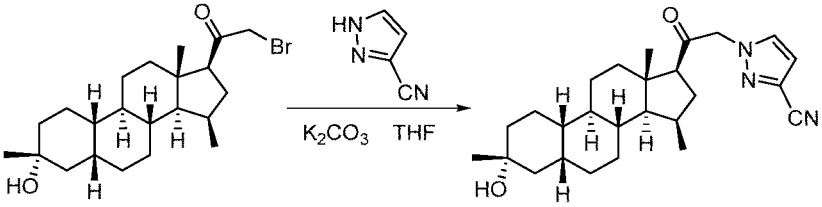
MS m/z (ESI): 467.3 $[M+H]^+$

Example 60

1-(2-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-Hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-3-carbonitrile (60)



Step 1: Preparation of 1-(2-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-3-carbonitrile



In accordance with Example 5, 2-bromo-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one was used as the starting material, accordingly, 1-(2-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-3-carbonitrile (12.5 mg, yield: 20.2%) was obtained.

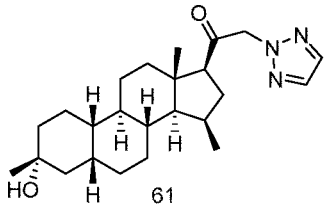
MS m/z (ESI): 424.1$[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 2.4 Hz, 1H), 6.73 (d, J = 2.4 Hz, 1H), 5.07 – 4.84 (m, 2H), 2.55 (t, J = 8.1 Hz, 1H), 2.33 – 1.06 (m, 25H), 0.98 (d, J = 7.0 Hz, 3H), 0.84 (s, 3H).

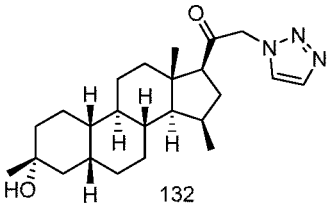
Example 61 and Example 132

1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-Hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(2H-1,2,3-triazol-2-yl)ethan-1-one (61)

1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-Hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(1H-1,2,3-triazol-1-yl)ethan-1-one (132)



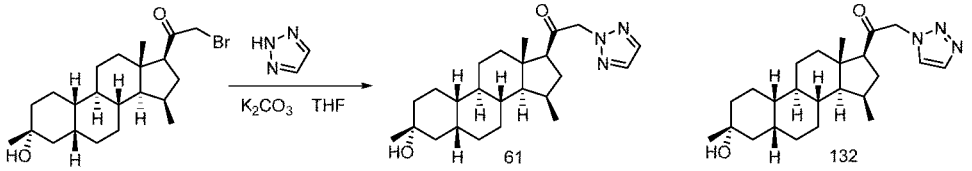
61



132

Step 1: Preparation of

1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(2H-1,2,3-triazol-2-yl)ethan-1-one and 1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(1H-1,2,3-triazol-1-yl)ethan-1-one



In accordance with Example 5, 2-bromo-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one was used as the starting material, accordingly, 1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(2H-1,2,3-triazol-2-yl)ethan-1-one (9.5 mg, yield: 16.3%) and 1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(1H-1,2,3-triazol-1-yl)ethan-1-one (13 mg, yield: 22.3%) were obtained .

Example 61:

MS m/z (ESI): 400.2[M+H]$^+$.

1H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 2H), 5.29 – 5.15 (m, 2H), 2.52 (t, J = 8.0 Hz, 1H), 2.17 – 1.29 (m, 24H), 1.15 – 1.05 (m, 1H), 0.97 (d, J = 7.0 Hz, 3H), 0.87 (s, 3H).

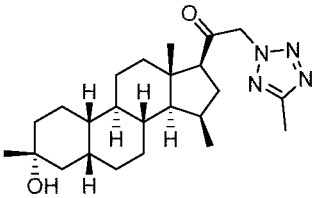
Example 132:

MS m/z (ESI): 400.2[M+H]$^+$.

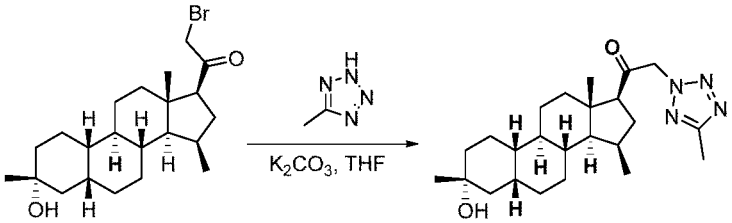
1H NMR (400 MHz, $CDCl_3$) δ7.77 (s, 1H), 7.65 (s, 1H), 5.32 – 5.02 (m, 2H), 2.60 (t, J = 9.1 Hz, 1H), 2.30 – 2.12 (m, 2H), 1.99 – 1.27 (m, 22H), 1.17 – 1.06 (m, 1H), 0.99 (d, J = 6.9 Hz, 3H), 0.84 (s, 3H).

Example 62

1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-Hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(5-methyl-2H-tetrazol-2-yl)ethan-1-one (62)



Step 1: Preparation of 1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(5-methyl-2H-tetrazol-2-yl)ethan-1-one



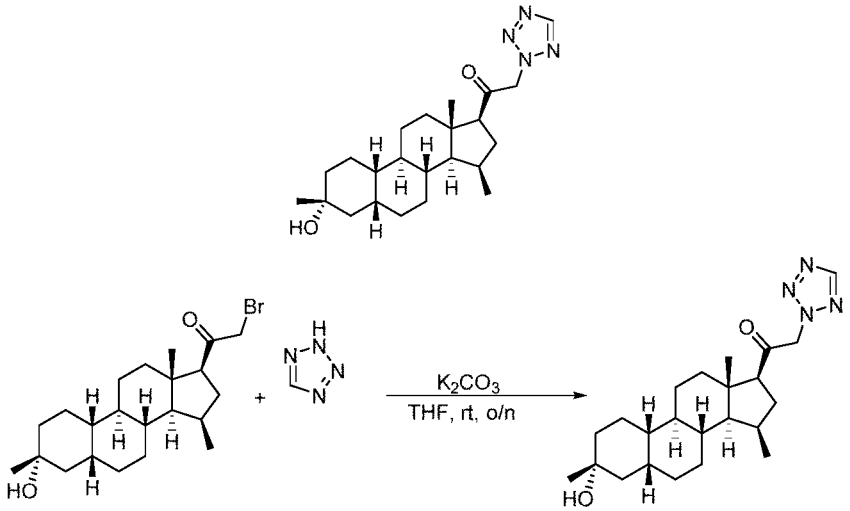
In accordance with Example 5, 2-bromo-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one was used as the starting material, accordingly, 1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(5-methyl-2H-tetrazol-2-yl)ethan-1-one (4.7 mg, yield: 7%) was obtained.

MS m/z (ESI): 415.3$[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (s, 2H), 2.57 (s, 3H), 2.27 – 2.11 (m, 2H), 2.00 –198 (m, 1H), 1.87 – 1.83 (m, 5H), 1.77 – 1.57 (m, 6H), 1.52 – 1.30 (m, 12H), 1.11 (s, 2H), 0.98 (d, J = 7.0 Hz, 3H), 0.88 (s, 3H).

Example 63

1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-Hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(2H-tetrazol-2-yl)ethan-1-one



2-Bromo-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (82 mg, 0.2 mmol), 2H-tetrazole (21 mg, 0.3 mmol) and potassium carbonate (54 mg, 0.3 mmol) were dissolved in anhydrous tetrahydrofuran (5 mL), and the resulting reaction solution was stirred at room temperature overnight. The reaction solution was filtrated, and the filtrate was concentrated. The resulting crude product was purified by high performance liquid chromatography to obtain 1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(2H-tetrazol-2-yl)ethan-1-one (15.7 mg, yield:

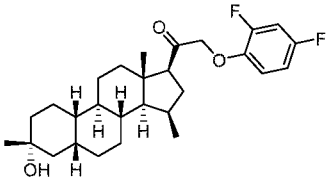
20%).

MS m/z (ESI): 401.3 $[M+H]^+$

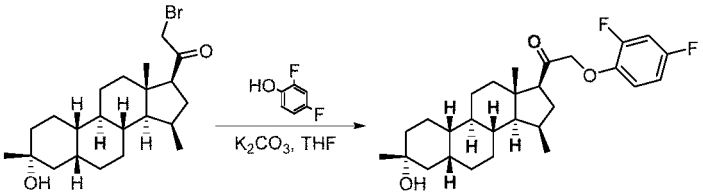
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 4.46 (s, 2H), 2.62-2.58 (m, 1H), 1.89-1.84 (m, 2H), 1.70-1.26 (m, 23H), 0.99 (d, J = 8.0 Hz, 3H), 0.88 (s, 3H).

Example 64

2-(2,4-Difluorophenoxy)-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (64)



Step 1: Preparation of 2-(2,4-difluorophenoxy)-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (64)



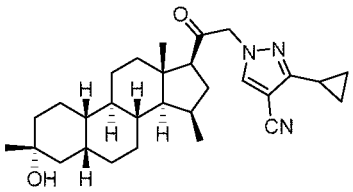
In accordance with Example 5, 2-bromo-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one was used as the starting material, accordingly, 2-(2,4-difluorophenoxy)-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (34 mg, yield: 45%) was obtained .

MS m/z (ESI): 461.3$[M+H]^+$

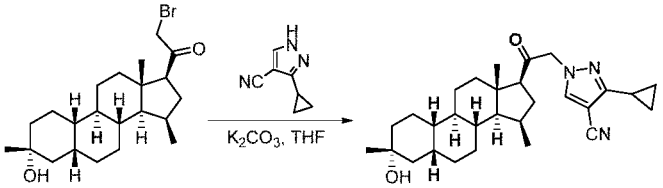
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 – 6.82 (m, 2H), 6.77 (ddd, J = 9.1, 5.3, 1.6 Hz, 1H), 4.56 (q, J = 16.7 Hz, 2H), 2.74 – 2.68 (m, 1H), 2.27 – 2.14 (m, 1H), 2.13 – 1.99 (m, 1H), 1.95 – 1.74 (m, 4H), 1.74 – 1.61 (m, 3H), 1.57 (s, 3H), 1.52 – 1.35 (m, 4H), 1.36 – 1.18 (m, 6H), 1.21 – 1.00 (m, 3H), 0.98 (d, J = 7.2 Hz, 3H), 0.82 (s, 3H).

Example 69

3-Cyclopropyl-1-(2-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile (69)



Step 1: Preparation of 3-cyclopropyl-1-(2-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethyl hexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-4-carbon itrile (69)



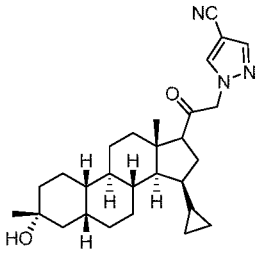
In accordance with Example 5, 2-bromo-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadec ahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one was used as the starting material, accordingly, 3-cyclopropyl-1-(2-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethyl hexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-4-carbon itrile (30 mg, yield: 41%) was obtained .

MS m/z (ESI): 464.3$[M+H]^+$

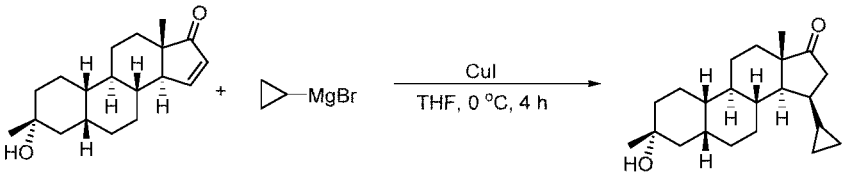
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 4.82 (q, J = 17.9 Hz, 2H), 2.51 – 2.46 (m, 1H), 2.27 – 2.18 (m, 1H), 2.19 – 2.08 (m, 1H), 2.04 – 1.91 (m, 2H), 1.90 – 1.80 (m, 4H), 1.68 – 1.60 (m, 4H), 1.57 (s, 3H), 1.51 – 1.29 (m, 8H), 1.18 – 1.03 (m, 3H), 1.02 – 0.95 (m, 7H), 0.82 (s, 3H).

Example 71

1-(2-((3R,5R,8R,9R,10S,13S,14S,15S)-15-Cyclopropyl-3-hydroxy-3,13-dimethylhexad ecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile



Step 1: (3R,5R,8R,9R,10S,13S,14S,15S)-15-Cyclopropyl-3-hydroxy-3,13-dimethylhexadecahy dro-17H-cyclopenta[a]phenanthren-17-one

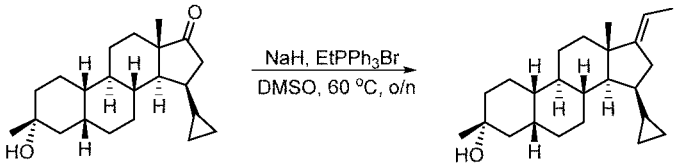


1.0 M cyclopropylmagnesium bromide (12.7 mL, 12.7 mmol) and 20 mL of anhydrous tetrahydrofuran were added to a dry 100 mL round bottom flask. The reaction system was purged with nitrogen, and cooled to 0°C. Cuprous iodide (1.97 g, 10.4 mmol) was added, and then the reaction solution was stirred at 0°C for 1 hour.

(3R,5R,8R,9R,10S,13S,14S)-3-Hydroxy-3,13-dimethyl-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-17H-cyclopenta[a]phenanthren-17-one (1 g, 3.5 mmol) was dissolved in 10 ml of anhydrous tetrahydrofuran, and the resulting solution was slowly added dropwise to the reaction system. The reaction solution was stirred for 3 hours, and TLC showed that the reaction was completed. Saturated ammonium chloride solution was added to quench the reaction, and the reaction solution was extracted with ethyl acetate. The organic phase was washed with water and saturated saline, dried over anhydrous sodium sulfate, filtrated and concentrated by rotary evaporation to dryness. The resulting crude product was purified by column chromatography (eluent: petroleum ether:ethyl acetate=2:1) to obtain (3R,5R,8R,9R,10S,13S,14S,15S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-17H-cyclopenta[a]phenanthren-17-one (1.11 g, 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45-2.30 (m, 2H), 1.85-1.76 (m, 9H), 1.59-1.52 (m, 5H), 1.59-1.27 (m, 12H), 1.11-0.98 (m, 1H), 0.67-0.64 (m, 1H), 0.47-0.43 (m, 1H), 0.22-0.18 (m, 1H), 0.09-0.07 (m, 1H).

Step 2: (3R,5R,8R,9R,10S,13S,14S,15S,E)-15-Cyclopropyl-17-ethylidene-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-ol

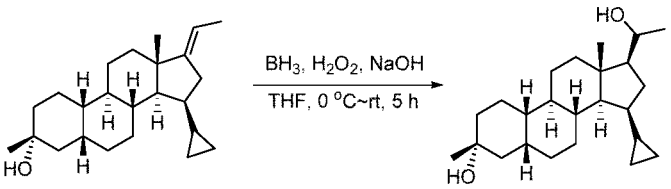


Ethyltriphenylphosphonium bromide (12.5 g, 33 mmol) was dissolved in anhydrous dimethyl sulfoxide (50 mL), and the reaction system was purged with nitrogen. Sodium hydride (1.32 g, 33 mmol) was added, and then the reaction solution was stirred at room temperature for 1 hour. (3R,5R,8R,9R,10S,13S,14S,15S)-15-Cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-17H-cyclopenta[a]phenanthren-17-one (1.1 g, 3.3 mmol) was added, and then the reaction solution was stirred at 60°C overnight. The reaction solution was cooled to room temperature. Water (200 mL) was added to the reaction solution to quench the reaction, and the aqueous phase was extracted with ethyl acetate (200 mL×2). The organic phases were combined, dried over anhydrous sodium sulfate, filtrated and concentrated. The resulting crude product was purified by column chromatography (petroleum ether/ethyl acetate: 50/1 - 3/1) to obtain (3R,5R,8R,9R,10S,13S,14S,15S,E)-15-cyclopropyl-17-ethylidene-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-ol (0.67 g, yield: 59%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15-5.09 (m, 1H), 2.45-2.38 (m, 1H), 2.38-2.18 (m, 2H), 1.90-1.07 (m, 28H), 0.86-0.78 (m, 1H), 0.56-0.50 (m, 1H), 0.38-0.32 (m, 1H), 0.12-0.02 (m, 2H).

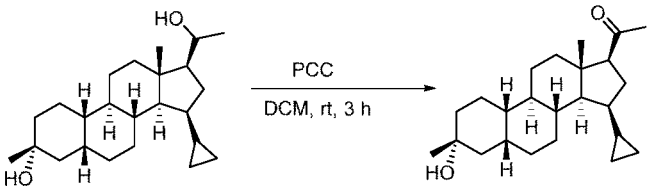
Step 3: (3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-Cyclopropyl-17-((R)-1-hydroxyethyl)-3,13-di

methylhexadecahydro-1H-cyclopenta[a]phenanthren-3-ol



(3R,5R,8R,9R,10S,13S,14S,15S,E)-15-Cyclopropyl-17-ethylidene-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-ol (0.67 g, 1.96 mmol) was dissolved in anhydrous tetrahydrofuran (20 mL). The solution was cooled to 0°C, and then BH_3/THF (9.8 mL, 9.8 mmol) was added dropwise. The reaction solution was stirred at room temperature for 3 hours, and TLC showed that the reaction was completed. The reaction solution was cooled to 0°C, and then 3 M aqueous NaOH solution (10 mL) was slowly added, followed by the addition of 30% hydrogen peroxide (8 mL). The reaction solution was stirred at room temperature for 2 hours, and TLC showed that the reaction was completed. Ethyl acetate (50 mL) was added, and then the reaction solution was washed with saturated aqueous $Na_2S_2O_3$ solution (30 mL) and water (30 mL) successively. The organic phase was dried over anhydrous sodium sulfate, filtrated and concentrated to obtain the crude product (0.71 g), which was used directly in the next step.

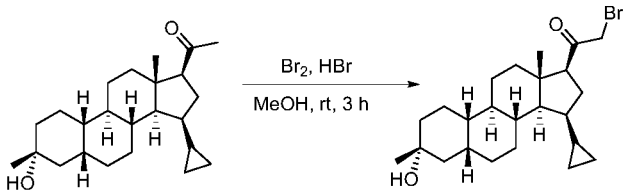
Step 4: 1-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-Cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one



(3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-Cyclopropyl-17-((R)-1-hydroxyethyl)-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-ol (0.71 g, crude) was dissolved in dichloromethane (20 mL). Pyridinium chlorochromate (1.27 g, 5.88 mmol) was added, and then the reaction solution was stirred at room temperature for 2 hours. The reaction solution was filtrated, and the organic phase was concentrated. The resulting crude product was purified by column chromatography (petroleum ether/ethyl acetate: 1/1) to obtain 1-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (480 mg, yield of two steps: 68.3%).

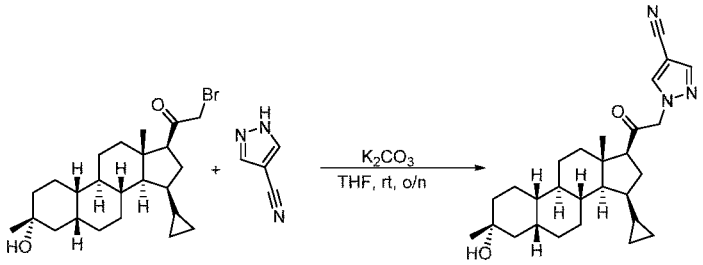
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45-2.40 (m, 1H), 2.18-2.10 (m, 4H), 1.99-1.03 (m, 24H), 0.84-0.79 (m, 4H), 0.60-0.53 (m, 1H), 0.43-0.38 (m, 1H), 0.14-0.02 (m, 2H).

Step 5: 2-Bromo-1-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one



1-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-Cyclopropyl-3-hydroxy-3,13-dimethyl hexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (107 mg, 0.3 mmol) was dissolved in methanol (5 mL). A drop of hydrogen bromide was added to the solution, followed by the addition of liquid bromine (56 mg, 0.35 mmol), and then the reaction solution was stirred at room temperature for 1 hour. Water (20 mL) was added to the reaction solution, and the aqueous phase was extracted with ethyl acetate (20 mL×2). The organic phases were combined, dried over anhydrous sodium sulfate, filtrated and concentrated to obtain the crude product (120 mg, crude), which was used directly in the next step.

Step 6: 1-(2-((3R,5R,8R,9R,10S,13S,14S,15S)-15-Cyclopropyl-3-hydroxy-3,13-dimethylhexad ecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile



1-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-Cyclopropyl-3-hydroxy-3,13-dimethyl hexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (60 mg, 0.14 mmol), 1H-pyrazole-4-carbonitrile (28 mg, 0.3 mmol) and potassium carbonate (54 mg, 0.3 mmol) were dissolved in anhydrous tetrahydrofuran (5 mL), and the resulting reaction solution was stirred at room temperature overnight. The reaction solution was filtrated, and the filtrate was concentrated. The resulting crude product was purified by high performance liquid chromatography to obtain 1-(2-((3R,5R,8R,9R,10S,13S,14S,15S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexade cahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile (31 mg, yield: 49%).

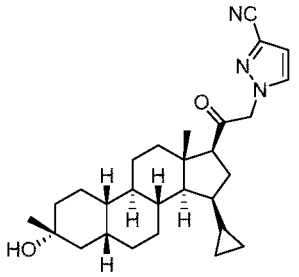
MS m/z (ESI): 450.3 $[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.81 (s, 1H), 5.02 (d, J = 16.0 Hz, 1H), 4.92 (d, J = 16.0 Hz, 1H), 2.51-2.47 (m, 1H), 2.09-1.71 (m, 9H), 1.48-1.10 (m, 16H), 0.90 (s, 3H), 0.83-0.79 (m, 1H), 0.62-0.58 (m, 1H), 0.45-0.40 (m, 1H), 0.14-0.11 (m, 1H), 0.05-0.02 (m, 1H).

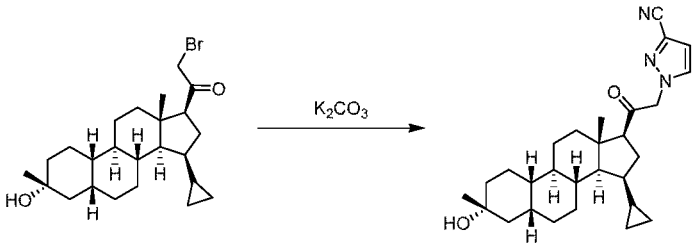
Example 72

1-(2-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-Cyclopropyl-3-hydroxy-3,13-dimethylh

exadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-3-carbonitrile (72)



Step 1: Preparation of 1-(2-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-3-carbonitrile



In accordance with Example 5, 1-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one was used as the starting material, accordingly, 1-(2-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-3-carbonitrile (20 mg, yield 20%) was obtained .

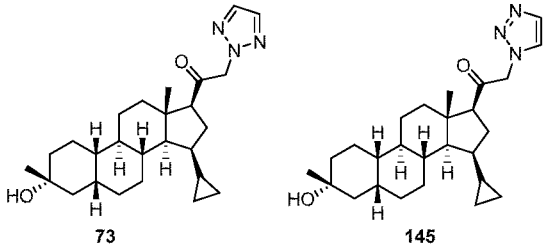
MS m/z (ESI): 432.2[M-H_2O +H]$^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 2.4 Hz, 1H), 6.73 (d, J = 2.4 Hz, 1H), 4.98 (dd, J = 40.0, 17.8 Hz, 2H), 2.52 – 2.45 (m, 1H), 2.24 – 2.13 (m, 1H), 2.11 – 2.03 (m, 1H), 2.04 – 1.95 (m, 2H), 1.90 – 1.82 (m, 2H), 1.75 – 1.66 (m, 2H), 1.54 – 1.23 (m, 16H), 1.18 – 1.05 (m, 2H), 0.93 – 0.79 (m, 4H), 0.63 – 0.55 (m, 1H), 0.45 – 0.37 (m, 1H), 0.18 – 0.09 (m, 1H), 0.08 – 0.01 (m, 1H).

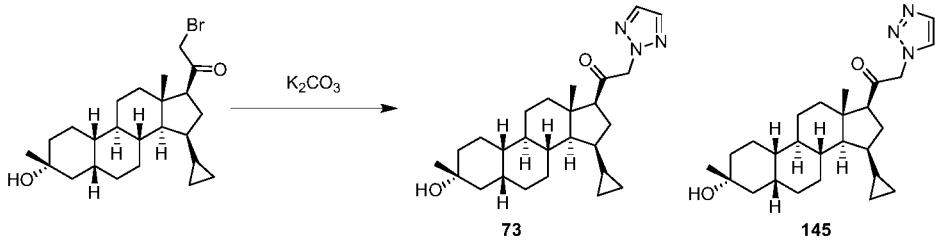
Example 73 and Example 145

1-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-Cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(2H-1,2,3-triazol-2-yl)ethan-1-one (73)

1-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-Cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(1H-1,2,3-triazol-1-yl)ethan-1-one (145)



Step 1: Preparation of 1-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(2H-1,2,3-triazol-2-yl)ethan-1-one and 1-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(1H-1,2,3-triazol-1-yl)ethan-1-one



In accordance with Example 5, 1-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one was used as the starting material, accordingly, 1-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(2H-1,2,3-triazol-2-yl)ethan-1-one (7.6 mg, yield: 7.8%) and 1-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(1H-1,2,3-triazol-1-yl)ethan-1-one (11.6 mg, yield: 11.9%) were obtained.

Example 73:

MS m/z (ESI): 408.3[M-H_2O +H]$^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 2H), 5.24 (s, 2H), 2.49 – 2.42 (m, 1H), 2.23 – 2.14 (m, 1H), 2.10 – 1.94 (m, 3H), 1.91 – 1.81 (m, 3H), 1.75 – 1.66 (m, 2H), 1.48 – 1.24 (m, 15H), 1.17 – 1.04 (m, 2H), 0.94 (s, 3H), 0.86 – 0.76 (m, 1H), 0.63 – 0.54 (m, 1H), 0.45 – 0.38 (m, 1H), 0.14 – 0.01 (m, 2H).

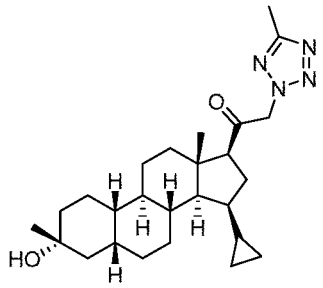
Example 145:

MS m/z (ESI): 426.3[M +H]$^+$

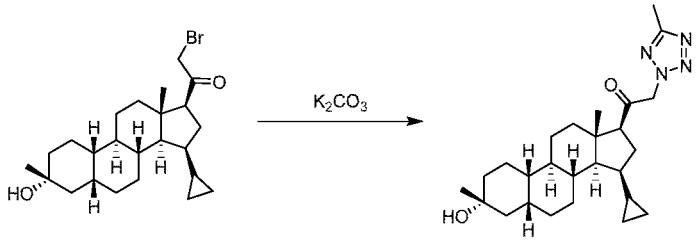
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.67 (s, 1H), 5.22 (dd, J = 47.1, 17.8 Hz, 2H), 2.59 – 2.50 (m, 1H), 2.25 – 2.15 (m, 1H), 2.14 – 1.98 (m, 2H), 1.96 – 1.79 (m, 3H), 1.76 – 1.58 (m, 6H), 1.56 – 1.25 (m, 12H), 1.22 – 1.04 (m, 2H), 0.91 (s, 3H), 0.87 – 0.77 (m, 1H), 0.62 – 0.55 (m, 1H), 0.47 – 0.36 (m, 1H), 0.18 – 0.02 (m, 2H).

Example 74

1-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-Cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(5-methyl-2H-tetrazol-2-yl)ethan-1-one (74)



Step 1: Preparation of 1-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(5-methyl-2H-tetrazol-2-yl)ethan-1-one



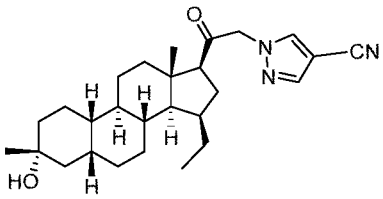
In accordance with Example 5, 1-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one was used as the starting material, accordingly, 1-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(5-methyl-2H-tetrazol-2-yl)ethan-1-one (8.5 mg, yield: 9%) was obtained.

MS m/z (ESI): 441.3[M +H]$^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (s, 2H), 2.57 (s, 3H), 2.54 – 2.47 (m, 1H), 2.25 – 2.15 (m, 1H), 2.13 – 1.95 (m, 3H), 1.92 – 1.79 (m, 3H), 1.77 – 1.66 (m, 2H), 1.50 – 1.24 (m, 15H), 1.18 – 1.05 (m, 2H), 0.94 (s, 3H), 0.87 – 0.78 (m, 1H), 0.63 – 0.55 (m, 1H), 0.45 – 0.37 (m, 1H), 0.17 – 0.02 (m, 2H).

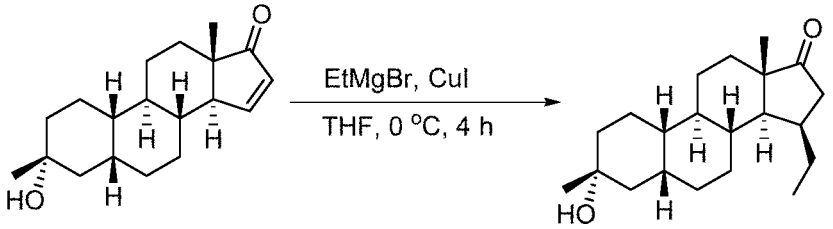
Example 81

1-(2-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-Ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile (81)



Step 1:

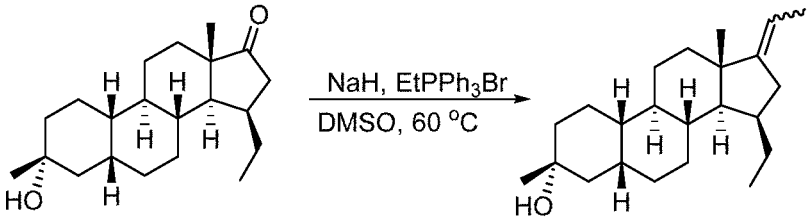
(3R,5R,8R,9R,10S,13S,14S,15R)-15-Ethyl-3-hydroxy-3,13-dimethylhexadecahydro-17 H-cyclopenta[a]phenanthren-17-one



Tetrahydrofuran (15 mL) was added to a 100 mL three-neck flask, and ethyl magnesium bromide (10 mL, 1M, 10 mmol) was then added at 0°C under a nitrogen atmosphere, followed by the addition of cuprous iodide (1.6 g, 8.4 mmol). The reaction solution was stirred at 0°C for 1 hour. (3R,5R,8R,9R,10S,13S,14S)-3-Hydroxy-3,13-dimethyl-1,2,3,4,5,6,7,8,9,10,11,12,13,14 -tetradecahydro-17H-cyclopenta[a]phenanthren-17-one (800 mg, 2.8 mmol) was dissolved in tetrahydrofuran (5 mL), and the resulting solution was slowly added dropwise to the reaction solution, which was then stirred at 0°C for 4 hours. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction solution was extracted with ethyl acetate (20 mL). The organic phase was washed with saline (10 mL×3), dried over anhydrous sodium sulfate, filtrated and concentrated by rotary evaporation to dryness. The resulting crude product was purified by column chromatography (petroleum ether/ethyl acetate: 3/1) to obtain (3R,5R,8R,9R,10S,13S,14S,15R)-15-ethyl-3-hydroxy-3,13-dimethylhexadecahydro-17 H-cyclopenta[a]phenanthren-17-one (750 mg, yield: 84.9%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 – 2.30 (m, 1H), 2.15 – 2.02 (m, 2H), 1.91 – 1.31 (m, 17H), 1.27 (s, 3H), 1.24 – 1.03 (m, 4H), 0.98 (s, 3H), 0.90 (t, J = 7.3 Hz, 3H).

Step 2: (3R,5R,8R,9R,10S,13S,14S,15R)-15-Ethyl-17-ethylidene-3,13-dimethylhexadecahydro -1H-cyclopenta[a]phenanthren-3-ol

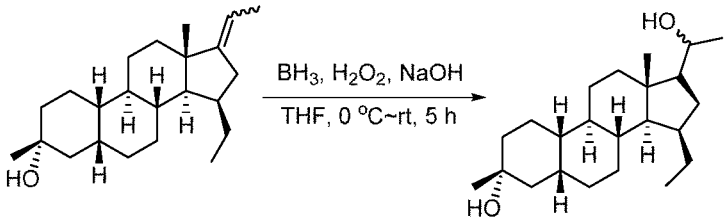


Dimethyl sulfoxide (20 mL) was added to a 100 mL three-neck flask, and ethyltriphenylphosphonium bromide (8.7 g, 23.5 mmol) was then added under a nitrogen atmosphere. Sodium hydride (60%) (940 mg, 23.5 mmol) was added in batches, and the reaction solution was stirred at room temperature for 1 hour. (3R,5R,8R,9R,10S,13S,14S,15R)-15-Ethyl-3-hydroxy-3,13-dimethylhexadecahydro-17 H-cyclopenta[a]phenanthren-17-one (750 mg, 2.35 mmol) was dissolved in dimethyl sulfoxide (5 mL), and the resulting solution was slowly added dropwise to the reaction solution, which was then stirred under a nitrogen atmosphere at 80°C for 5 hours. The reaction solution was cooled to room temperature. Saturated aqueous ammonium

chloride solution was added to quench the reaction, and the reaction solution was extracted with ethyl acetate (50 mL). The organic phase was washed with saline (20 mL×3), dried over anhydrous sodium sulfate, filtrated and concentrated by rotary evaporation to dryness. The resulting crude product was purified by column chromatography (petroleum ether/ethyl acetate: 3/1) to obtain (3R,5R,8R,9R,10S,13S,14S,15R)-15-ethyl-17-ethylidene-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-ol (580 mg, yield: 71.7%).

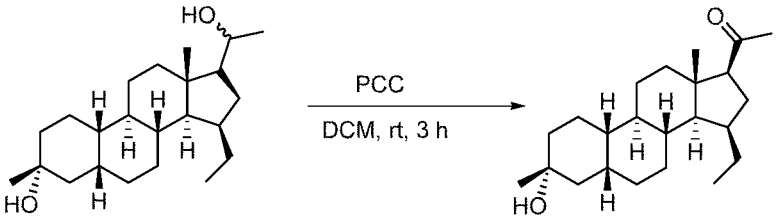
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.22 – 5.06 (m, 1H), 2.54 – 2.39 (m, 1H), 2.28 – 2.09 (m, 2H), 1.96 – 1.80 (m, 4H), 1.78 – 1.59 (m, 6H), 1.55 – 1.33 (m, 11H), 1.26 (s, 3H), 1.20 – 1.08 (m, 3H), 1.05 (s, 3H), 0.82 (t, J = 7.3 Hz, 3H).

Step 3: (3R,5R,8R,9R,10S,13S,14S,15R,17R)-15-Ethyl-17-(1-hydroxyethyl)-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-ol



In accordance with Step 3 of Example 71, (3R,5R,8R,9R,10S,13S,14S,15R)-15-ethyl-17-ethylidene-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-ol was used as the starting material, accordingly, (3R,5R,8R,9R,10S,13S,14S,15R,17R)-15-ethyl-17-(1-hydroxyethyl)-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-ol (600 mg, yield: 98.1%) was obtained.

Step 4: 1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-Ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one

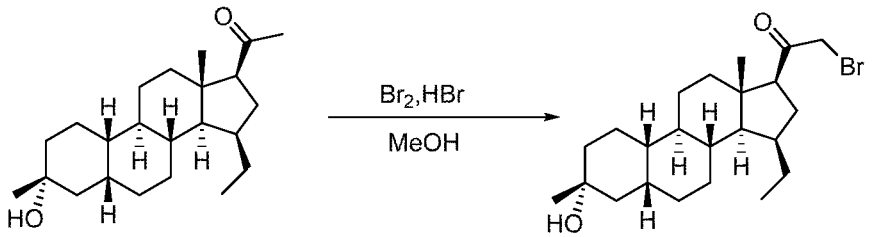


In accordance with Step 4 of Example 71, (3R,5R,8R,9R,10S,13S,14S,15R,17R)-15-ethyl-17-(1-hydroxyethyl)-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-ol was used as the starting material, accordingly, 1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (500 mg, yield: 83.8%) was obtained.

1H NMR (400 MHz, $CDCl_3$) δ 2.51 (t, J = 8.0 Hz, 1H), 2.12 (s, 3H), 2.00 – 1.30 (m, 20H), 1.28 (s, 3H), 1.25 – 1.00 (m, 4H), 0.84 (t, J = 7.2 Hz, 3H), 0.73 (s, 3H).

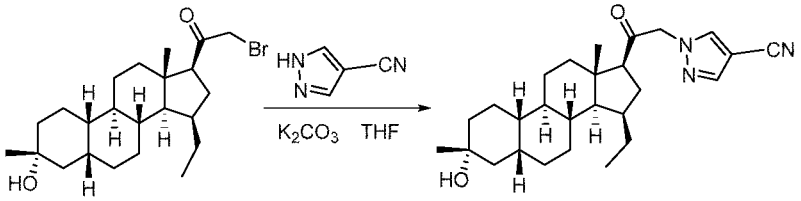
Step 5:

2-Bromo-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one



In accordance with Step 5 of Example 71, 1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one was used as the starting materials , accordingly, 2-bromo-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (500 mg, yield: 81.4%) was obtained.

Step 6: 1-(2-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-Ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile



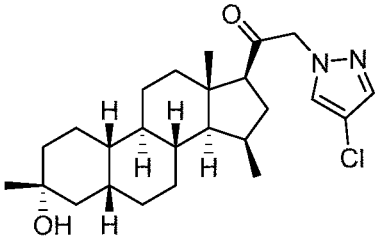
In accordance with Step 6 of Example 71, 2-bromo-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one was used as the starting material, accordingly, 1-(2-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile (24 mg, yield: 38.8%) was obtained.

MS m/z (ESI): 438.2[M+H]+.

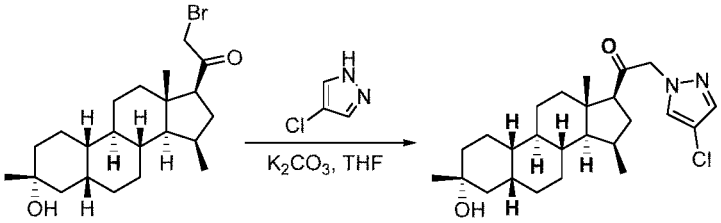
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.81 (s, 1H), 5.08 – 4.78 (m, 2H), 2.58 (t, J = 8.0 Hz, 1H), 2.07 – 1.29 (m, 20H), 1.28 (s, 3H), 1.27 – 1.06 (m, 4H), 0.85 (t, J = 7.3 Hz, 3H), 0.79 (s, 3H).

Example 91

2-(4-Chloro-1H-pyrazol-1-yl)-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (91)



Step 1: Preparation of 2-(4-chloro-1H-pyrazol-1-yl)-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one



In accordance with Example 5, 2-bromo-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one was used as the starting material, accordingly, 2-(4-chloro-1H-pyrazol-1-yl)-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (10 mg, yield: 14%) was obtained.

MS m/z (ESI): 433.3$[M+H]^+$

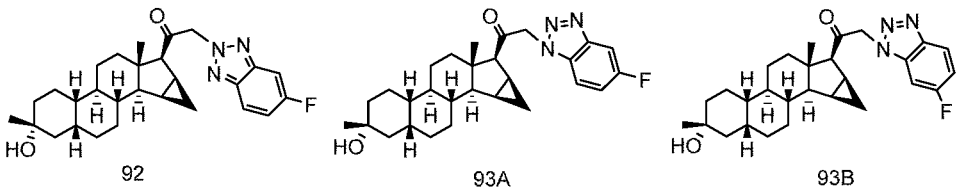
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.41 (s, 1H), 4.86 (q, J = 17.9 Hz, 2H), 2.61 – 2.44 (m, 1H), 2.30 – 2.07 (m, 2H), 2.02 – 1.91 (m, 1H), 1.86 – 1.80 (m, 4H), 1.76 – 1.57 (m, 4H), 1.51 – 1.38 (m, 6H), 1.37 – 1.20 (m, 6H), 1.20 – 1.03 (m, 2H), 0.98 (d, J = 7.1 Hz, 3H), 0.83 (s, 3H).

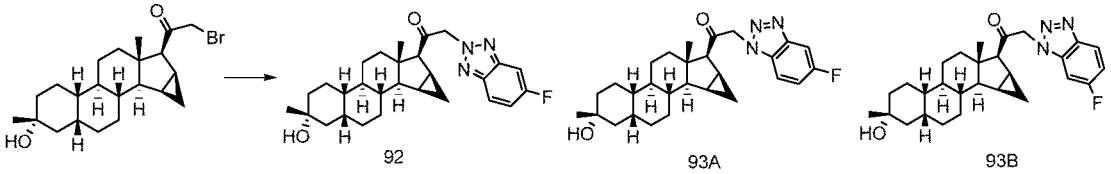
Example 92 and Example 93

2-(5-Fluoro-2H-benzo[d][1,2,3]triazol-2-yl)-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one (92)

2-(5-Fluoro-1H-benzo[d][1,2,3]triazol-1-yl)-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one (93A) and

2-(6-Fluoro-1H-benzo[d][1,2,3]triazol-1-yl)-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one (93B)





In accordance with Example 5, 2-bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one and 5-fluoro-2H-benzo[d][1,2,3]triazole were used as the starting materials, accordingly, 2-(5-fluoro-2H-benzo[d][1,2,3]triazol-2-yl)-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one (11.5 mg, white solid, yield: 12.7%) and a mixture of Example 93A and Example 93B (about 3:2) (21.6 mg, white solid, yield: 23.9%) were obtained. The mixture was further separated by preparative chromatography to obtain 2-(5-fluoro-1H-benzo[d][1,2,3]triazol-1-yl)-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one and 2-(6-fluoro-1H-benzo[d][1,2,3]triazol-1-yl)-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one.

Example 92:

MS m/z (ESI): 466.2$[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, J_1 = 9.2 Hz, J_2 = 4.8 Hz, 1H), 7.47 (dd, J_1 = 9.2 Hz, J_2 = 2.0 Hz, 1H), 7.23-7.18 (m, 1H), 5.73 (dd, J_1 = 17.6 Hz, J_2 = 4.4 Hz, 2H), 2.90 (d, J = 4.0 Hz, 1H), 1.99-1.96 (m, 1H), 1.85-1.81 (m, 4H), 1.74-1.63 (m, 3H), 1.57-1.38 (m, 10H), 1.30-1.11 (m, 6H), 1.14-1.01 (m, 2H), 0.88 (s, 3H), 0.53-0.48 (m, 1H).

Example 93A:

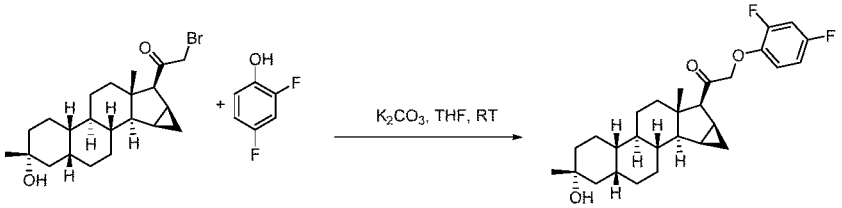
MS m/z (ESI): 466.2$[M+H]^+$

Example 93B:

MS m/z (ESI): 466.2$[M+H]^+$

Example 94

2-(2,4-Difluorophenoxy)-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one



In accordance with Example 5,

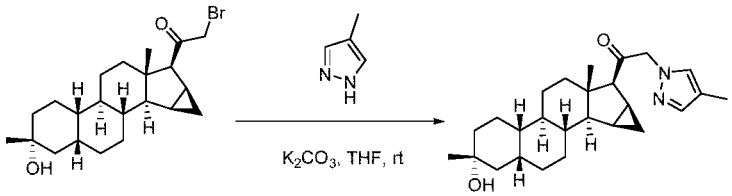
2-bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethylocta decahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one and 2,4-difluorophenol were used as the starting materials, accordingly, 2-(2,4-difluorophenoxy)-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2, 6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one (27.4 mg, white solid, yield: 38.6%) was obtained.

MS m/z (ESI): 441.2[M+H]$^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93-6.80 (m, 2H), 6.79-6.74 (m, 1H), 4.77 (dd, J_1 = 16.8 Hz, J_2 = 3.6 Hz, 2H), 2.93 (d, J = 3.2 Hz, 1H), 1.89-1.76 (m, 5H), 1.75-1.60 (m, 3H), 1.55-1.50 (m, 1H), 1.46-1.41 (m, 6H), 1.27-1.11 (m, 9H), 0.98-0.95 (m, 1H), 0.94-0.89 (m, 1H), 0.76 (s, 3H), 0.46-0.39 (m, 1H).

Example 95

1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-Hydroxy-2,6a-dimethyloctadecahyd rocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(4-methyl-1H-pyrazol-1-yl)etha n-1-one



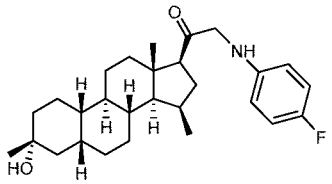
In accordance with Example 5, 2-bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethylocta decahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one and 4-methylpyrazole were used as the starting materials, accordingly, 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydr ocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(4-methyl-1H-pyrazol-1-yl)etha n-1-one (12.6 mg, white solid, yield: 15.7%) was obtained.

MS m/z (ESI): 411.3[M+H]$^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.26 (s, 1H), 5.23(m, 2H), 2.83 (d, J = 4.4 Hz, 1H), 2.13 (s, 3H), 1.98-1.85 (m, 2H), 1.83-1.69 (m, 9H), 1.60-1.56 (m, 1H), 1.40-1.27 (m, 12H), 1.09-1.01 (m, 2H), 0.80 (s, 3H), 0.48-0.45 (m , 1H).

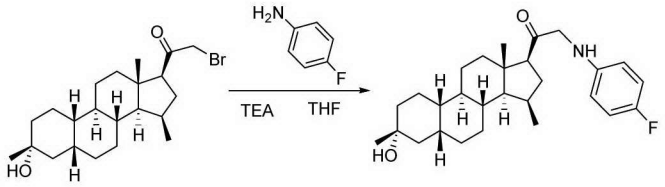
Example 96

2-((4-Fluorophenyl)amino)-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,1 5-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one



Step 1: Preparation of

2-((4-fluorophenyl)amino)-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one



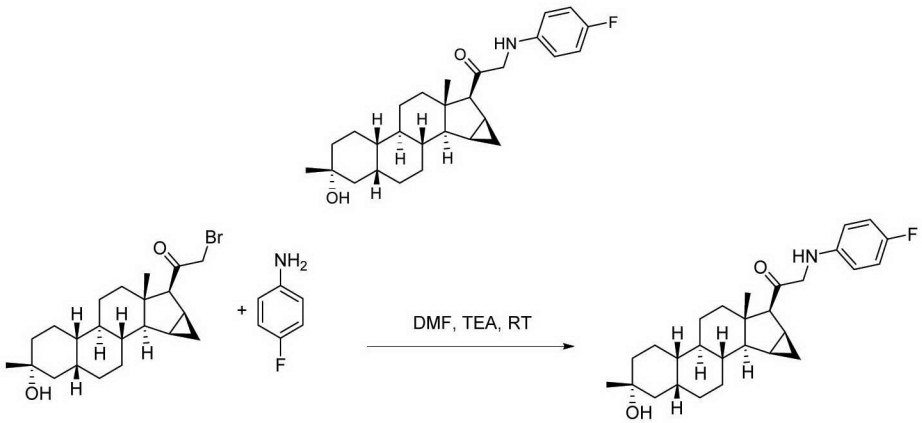
2-Bromo-1-((3R,5R,8R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (50 mg, 0.12 mmol) was dissolved in tetrahydrofuran (3 mL). 4-Fluoroaniline (42 mg, 0.2 mmol) and triethylamine (60 mg, 0.6 mmol) were added, and the reaction solution was stirred at room temperature for 12 hours. The reaction solution was concentrated, and the resulting residue was purified by high performance liquid chromatography to obtain 2-((4-fluorophenyl)amino)-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (7 mg, white solid, yield: 13%).

MS m/z (ESI): 442.3$[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95-6.86 (m, 2H), 6.59-6.53(m, 2H), 3.95-3.85(m, 2H), 2.55-2.47 (m, 1H), 2.25-2.15 (m, 2H), 1.90-1.80 (m, 5H), 1.75 – 1.25 (m, 18H), 1.00 (d, *J*=8.0 Hz, 3H), 0.81 (s, 3H).

Example 97

2-((4-Fluorophenyl)amino)-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one



In accordance with Example 5, 2-bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one and *p*-fluoroaniline were used as the starting materials, and N,N-dimethylformamide was used as the solvent, accordingly, 2-((4-fluorophenyl)amino)-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-

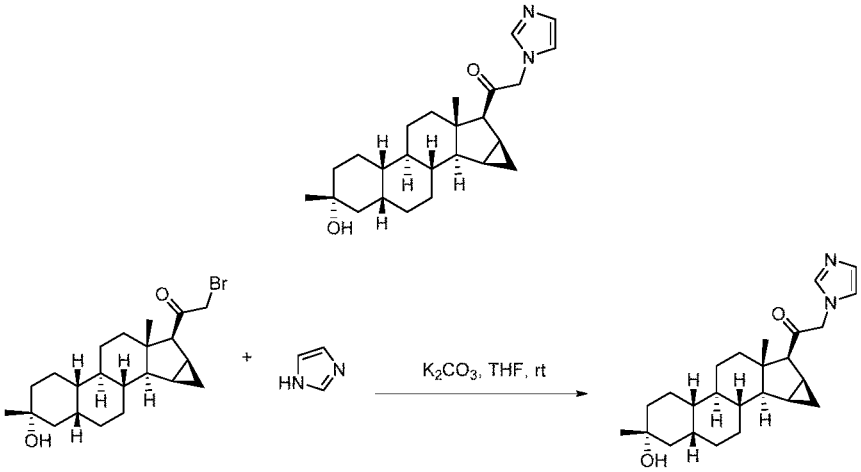
one (14.9 mg, yellow oil, yield: 26.7%) was obtained.

MS m/z (ESI): 440.2[M+H]$^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 - 6.95 (m, 2H), 6.91-6.83 (m, 2H), 4.19 (dd, J_1 = 20.0 Hz, J_2 = 2.8 Hz, 2H), 2.80 (d, J = 4.0 Hz, 1H), 1.92-1.58 (m, 14H), 1.45-1.40 (m, 8H), 1.27 (s, 3H), 1.09-0.91 (m, 2H), 0.69 (s, 3H), 0.48-0.43 (m, 1H).

Example 98

1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-Hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(1H-imidazol-1-yl)ethan-1-one



In accordance with Example 63, 2-bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one and imidazole were used as the starting materials, accordingly, 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(1H-imidazol-1-yl)ethan-1-one (23.3 mg, white solid, yield: 34.4%) was obtained.

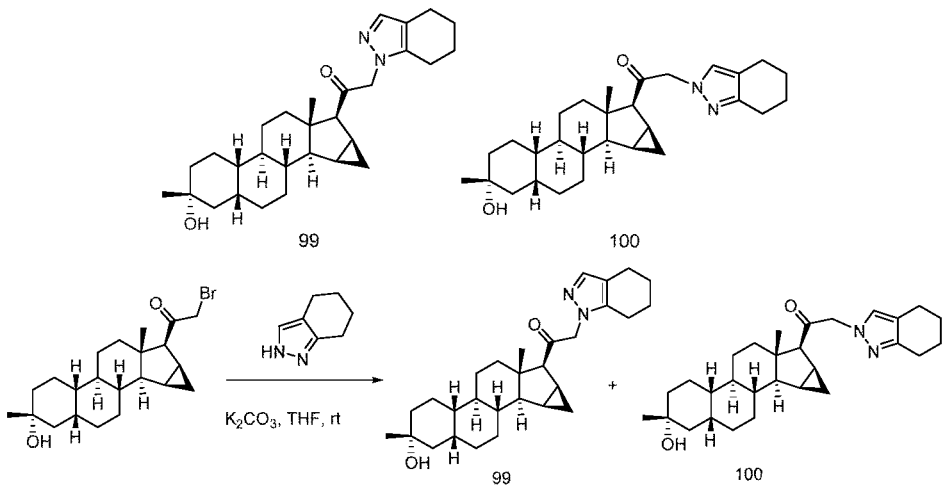
MS m/z (ESI): 397.2[M+H]$^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.12 (s, 1H), 6.88 (s, 1H), 4.98-4.87 (m, 2H), 2.82 (d, J = 2.8 Hz, 1H), 1.94-1.91(m, 1H), 1.85-1.81(m, 4H), 1.70-1.53 (m, 10H), 1.41-1.28 (m, 9H), 1.13-0.95 (m, 2H), 0.78 (s, 3H), 0.52-0.46 (m, 1H).

Example 99 and Example 100

1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-Hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(4,5,6,7-tetrahydro-1H-indazol-1-yl)ethan-1-one

1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-Hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(4,5,6,7-tetrahydro-2H-indazol-2-yl)ethan-1-one



In accordance with Example 5, 2-bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one and 4,5,6,7-tetrahydro-2H-indazole were used as the starting materials, accordingly, 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(4,5,6,7-tetrahydro-1H-indazol-1-yl)ethan-1-one (**99**) (5.5 mg, white solid, yield: 6.8%) and 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(4,5,6,7-tetrahydro-2H-indazol-2-yl)ethan-1-one (**100**) (3.1 mg, white solid, yield: 3.8%) were obtained.

Example 99:

MS m/z (ESI): 415.3$[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (s, 1H), 5.14-5.05 (m, 2H), 2.80 (d, J = 4.0 Hz, 1H), 2.69 (t, J = 6.0 Hz, 2H), 2.56 (t, J = 6.0 Hz, 2H), 1.97-1.93 (m, 1H), 1.85-1.61 (m, 12H), 1.55-1.52 (m, 2H), 1.43-1.21 (m, 13H), 1.11-0.94 (m, 2H), 0.79 (s, 3H), 0.48-0.42 (m, 1H).

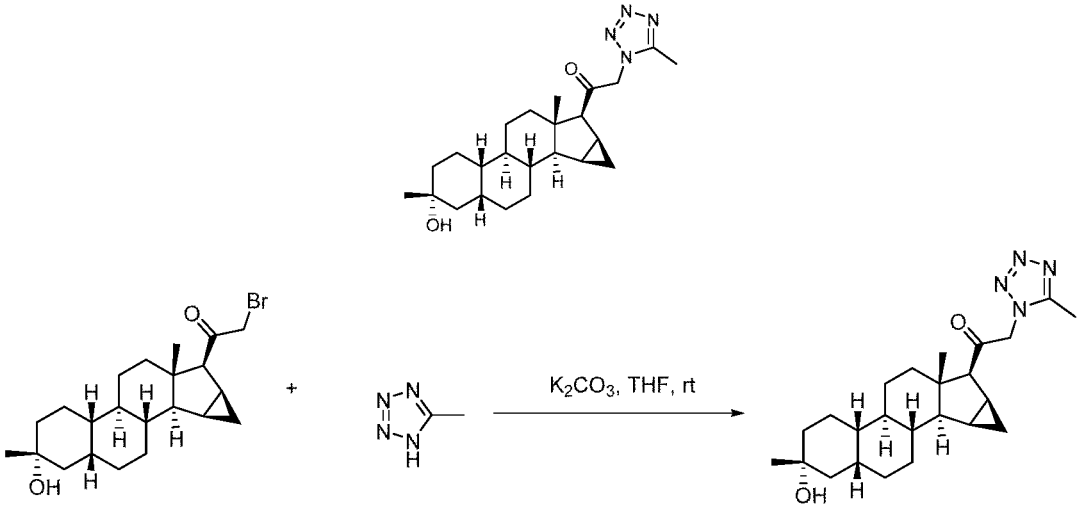
Example 100:

MS m/z (ESI): 415.3$[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 5.74-5.35 (m, 2H), 2.89 (d, J = 4.0 Hz, 1H), 2.58 (t, J = 6.0 Hz, 2H), 2.48 (t, J = 6.0 Hz, 2H), 1.96-1.91 (m, 1H), 1.80-1.72 (m, 8H), 1.40-1.22 (m, 19H), 1.12-0.99 (m, 2H), 0.82 (s, 3H), 0.51-0.45 (m, 1H).

Example 101

1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-Hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(5-methyl-1H-tetrazol-1-yl)ethan-1-one



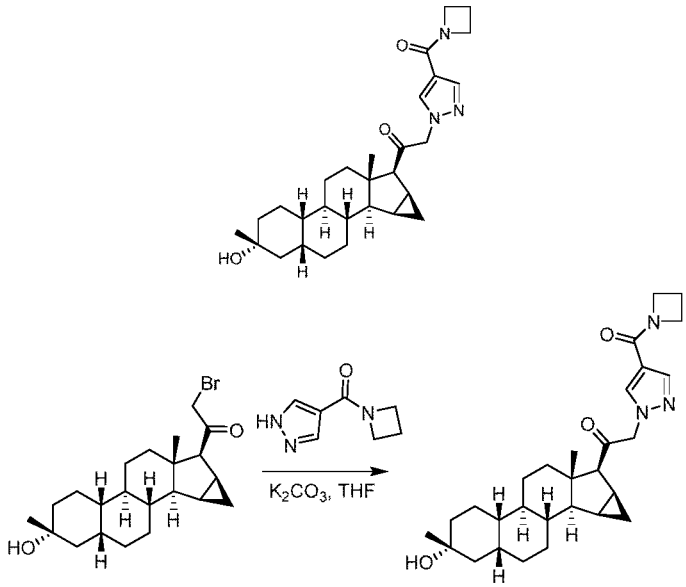
In accordance with Example 5, 2-bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one and 5-methyl-1H-4-tetrazole were used as the starting materials, accordingly, 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(5-methyl-1H-tetrazol-1-yl)ethan-1-one (19 mg, white solid, yield: 23.5%) was obtained.

MS m/z (ESI): 413.2[M+H]$^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.58 (dd, J_1 = 17.6 Hz, J_2 = 7.6 Hz, 2H), 2.86 (d, J = 4.0 Hz, 1H), 2.57 (s, 3H), 1.96-1.93 (m, 1H), 1.89-1.61 (m, 8H), 1.55-1.22 (m, 14H), 1.14-0.97 (m, 3H), 0.84 (s, 3H), 0.47-0.53 (m, 1H).

Example 102

2-(4-(Azetidine-1-carbonyl)-1H-pyrazol-1-yl)-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one



In accordance with Example 5,

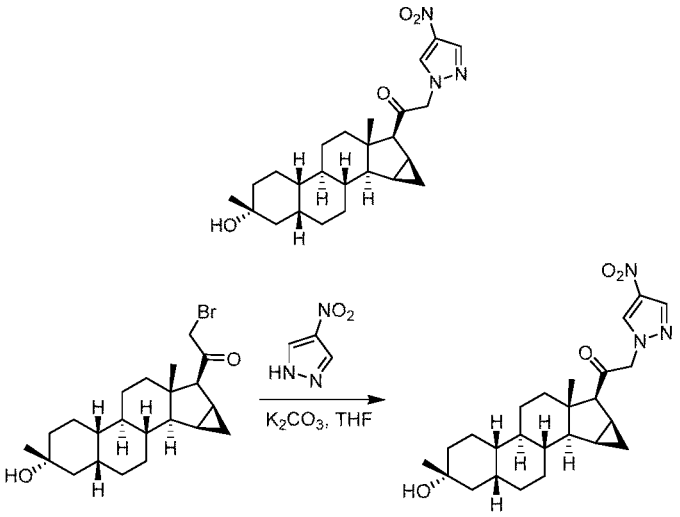
2-bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethylocta decahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one and azetidin-1-yl(1H-pyrazol-4-yl)methanone were used as the starting materials, accordingly, 2-(4-(azetidine-1-carbonyl)-1H-pyrazol-1-yl)-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR ,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenan thren-7-yl)ethan-1-one (10.0 mg, yield: 14.3%) was obtained.

MS m/z (ESI): 480.3 $[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.80 (m, 1H), 7.80 – 7.74 (m, 1H), 5.20 – 5.05 (m, 2H), 4.53 – 4.10 (m, 4H), 2.82 (d, J = 3.3 Hz, 1H), 2.44 – 2.31 (m, 2H), 1.98 – 1.90 (m, 1H), 1.86 – 1.79 (m, 3H), 1.74 – 1.64 (m, 3H), 1.57 – 1.53 (m, 2H), 1.44 – 1.24 (m, 15H), 1.13 – 0.97 (m, 2H), 0.79 (s, 3H), 0.51 – 0.44 (m, 1H).

Example 103

1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-Hydroxy-2,6a-dimethyloctadecahyd rocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(4-nitro-1H-pyrazol-1-yl)ethan-1-one



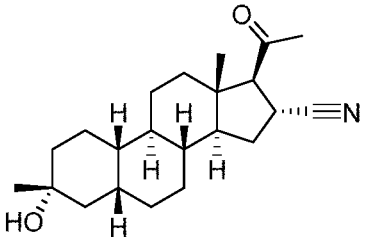
In accordance with Example 5, 2-bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethylocta decahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one and 4-nitro-1H-pyrazole were used as the starting materials, accordingly, 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydr ocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(4-nitro-1H-pyrazol-1-yl)ethan-1-one (32.5 mg, yield: 60%) was obtained.

MS m/z (ESI): 424.2 $[M+H-H_2O]^+$

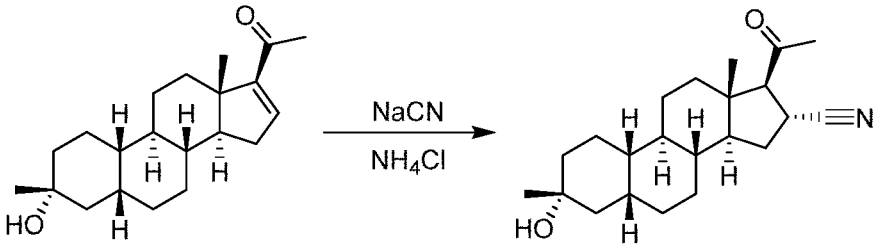
^{1}H NMR (400 MHz, $CDCl_3$) δ8.20 (s, 1H), 8.09 (s, 1H), 5.26 – 5.09 (m, 2H), 2.85 (s, 1H), 1.98 – 1.91 (m, 1H), 1.87 – 1.79 (m, 4H), 1.74 – 1.65 (m, 3H), 1.56 – 1.52 (m, 2H), 1.47 – 1.35 (m, 7H), 1.34 – 1.24 (m, 7H), 1.13 – 0.97 (m, 2H), 0.79 (s, 3H), 0.55 – 0.47 (m, 1H).

Example 104

(3R,5R,8R,9R,10S,13S,14S,16R,17S)-17-Acetyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthrene-16-carbonitrile (104)



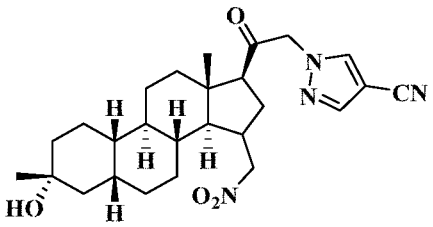
Step 1: Preparation of (3R,5R,8R,9R,10S,13S,14S,16R,17S)-17-acetyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthrene-16-carbonitrile



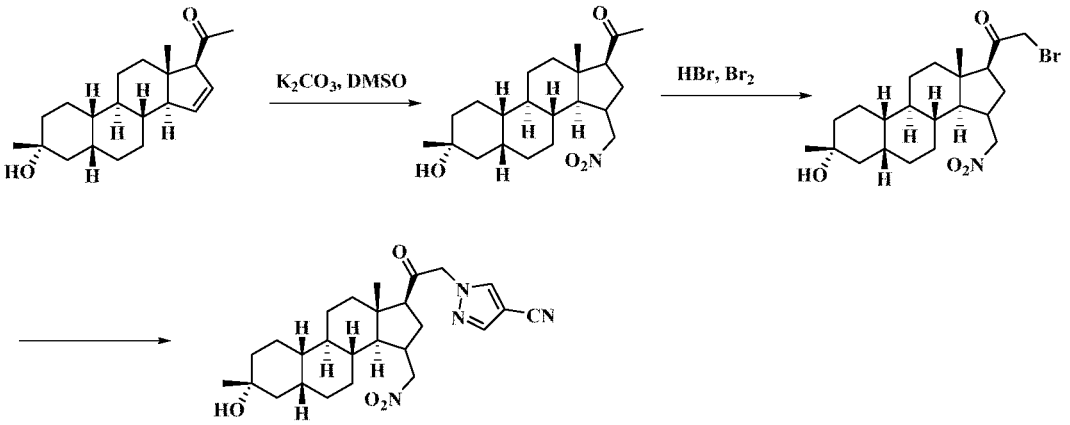
1-((3R,5R,8R,9R,10S,13S,14S)-3-Hydroxy-3,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (270 mg, 0.853 mmol), ammonium chloride (250 mg, 4.69 mmol) and 18-crown-6 (23 mg, 0.853 mmol) were added to a mixed solution of dimethyl sulfoxide (7 mL) and water (2 mL) at 85°C, followed by the addition of a mixed solution of sodium cyanide (230 mg, 4.69 mmol), dimethyl sulfoxide (4 mL) and water (1 mL). The reaction solution was stirred at 85°C for 16 hours. Water (30 mL) was added, and then the reaction solution was extracted with ethyl acetate (20 mL×3). The organic phases were combined, washed with saturated saline (30 mL), dried over anhydrous sodium sulfate and filtrated. The filtrate was concentrated under reduced pressure to dryness, and the resulting residue was purified by column chromatography (petroleum ether/ethyl acetate=1:1) to obtain (3R,5R,8R,9R,10S,13S,14S,16R,17S)-17-acetyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthrene-16-carbonitrile as a white solid (250 mg, yield: 85%).

Example 105

1-(2-((3R,5R,8R,9R,10S,13S,14R,17S)-3-Hydroxy-3,13-dimethyl-15-(nitromethyl)hexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile



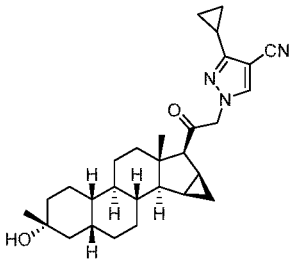
Example 105 was synthesized by the following specific scheme:



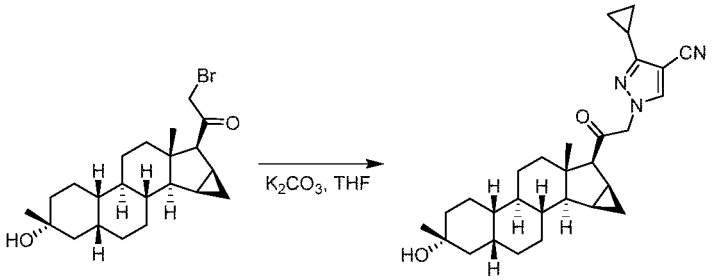
MS m/z (ESI): 469.3 $[M+1]^+$.

Example 121

3-Cyclopropyl-1-(2-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile



Step 1: Preparation of 3-cyclopropyl-1-(2-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile



In accordance with Example 5, 2-bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one was used as the starting material, accordingly, 3-cyclopropyl-1-(2-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile (19.2 mg, yield: 21%) was obtained.

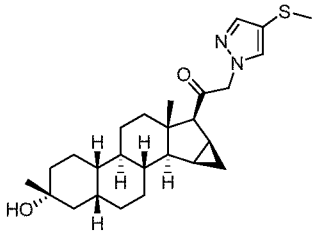
MS m/z (ESI): 462.3 $[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 5.13 – 4.95 (m, 2H), 2.80 (d, J = 2.2

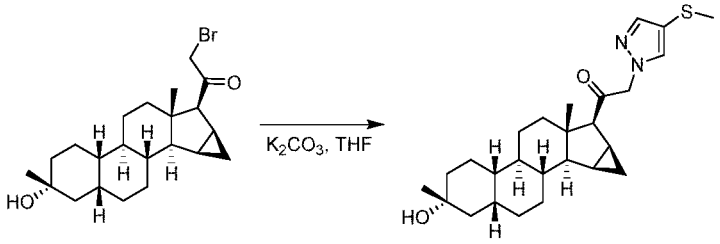
Hz, 1H), 2.04 – 1.89 (m, 2H), 1.86 – 1.79 (m, 3H), 1.76 – 1.63 (m, 3H), 1.58 – 1.49 (m, 3H), 1.46 – 1.21 (m, 14H), 1.12 – 0.93 (m, 6H), 0.76 (s, 3H), 0.51 – 0.43 (m, 1H).

Example 122

1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-Hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(4-(methylthio)-1H-pyrazol-1-yl)ethan-1-one (122)



Step 1: Preparation of 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(4-(methylthio)-1H-pyrazol-1-yl)ethan-1-one



In accordance with Example 5, 2-bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one was used as the starting material, accordingly, 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(4-(methylthio)-1H-pyrazol-1-yl)ethan-1-one (8.7 mg, yield: 16%) was obtained.

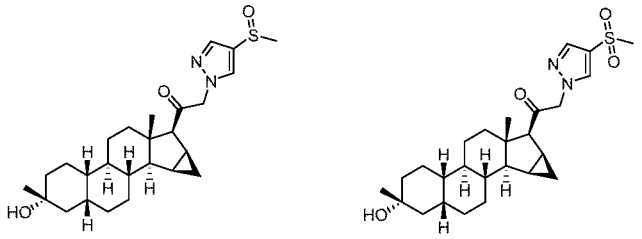
MS m/z (ESI): 443.2 $[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.45 (s, 1H), 5.17 – 5.00 (m, 2H), 2.81 (d, J = 3.8 Hz, 1H), 2.35 (s, 3H), 1.99 – 1.91 (m, 1H), 1.88 – 1.76 (m, 4H), 1.73 – 1.63 (m, 3H), 1.55 – 1.50 (m, 1H), 1.43 – 1.18 (m, 15H), 1.12 – 0.97 (m, 2H), 0.79 (s, 3H), 0.50 – 0.41 (m, 1H).

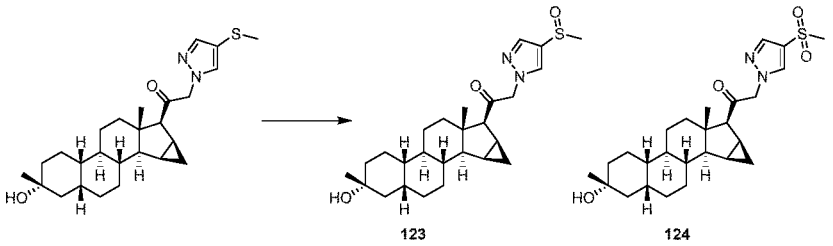
Example 123 and Example 124

1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-Hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(4-(methylsulfinyl)-1H-pyrazol-1-yl)ethan-1-one (123) and 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(4-(methylsulfonyl)-1H-pyrazol-

1-yl)ethan-1-one (124)



Step 1: Preparation of 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(4-(methylsulfinyl)-1H-pyrazol-1-yl)ethan-1-one and 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(4-(methylsulfonyl)-1H-pyrazol-1-yl)ethan-1-one



1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-Hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(4-(methylthio)-1H-pyrazol-1-yl)ethan-1-one (80 mg, 0.18 mmol) was dissolved in dichloromethane (10 mL), and the solution was cooled to -78°C. m-Chloroperoxybenzoic acid (55 mg, 0.27 mmol) was added, and the reaction solution was stirred for 1 hour. Water (10 mL) was added, and then the reaction solution was washed with saturated aqueous sodium bicarbonate solution (10 mL). The organic phase was separated, dried over anhydrous sodium sulfate, filtrated and concentrated by rotary evaporation to dryness. The resulting crude product was purified by high performance liquid chromatography to obtain 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(4-(methylsulfinyl)-1H-pyrazol-1-yl)ethan-1-one (17.2 mg, yield: 20%) and 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(4-(methylsulfonyl)-1H-pyrazol-1-yl)ethan-1-one (20.4 mg, yield: 25%).

Example 123:

MS m/z (ESI): 441.3 $[M-H_2O+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.83 (s, 1H), 5.30 – 5.09 (m, 2H), 2.91 (s, 3H), 2.85 – 2.82 (m, 1H), 1.98 – 1.90 (m, 1H), 1.87 – 1.78 (m, 3H), 1.75 – 1.50 (m, 8H), 1.47 – 1.21 (m, 12H), 1.13 – 0.96 (m, 2H), 0.79 (s, 3H), 0.54 – 0.45 (m, 1H).

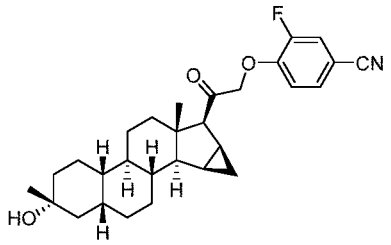
Example 124:

MS m/z (ESI): 457.2 $[M-H_2O+H]^+$

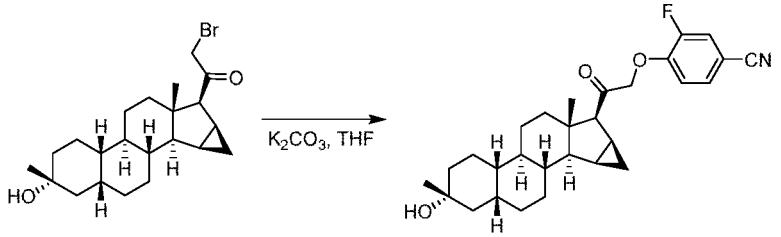
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.87 (s, 1H), 5.26 – 5.10 (m, 2H), 3.14 (s, 3H), 2.85 (d, J = 2.7 Hz, 1H), 1.98 – 1.91 (m, 1H), 1.87 – 1.79 (m, 3H), 1.76 – 1.64 (m, 3H), 1.59 – 1.52 (m, 1H), 1.50 – 1.18 (m, 16H), 1.15 – 0.96 (m, 2H), 0.79 (s, 3H), 0.55 – 0.46 (m, 1H).

Example 125

3-Fluoro-4-(2-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethoxy)benzonitrile (125)



Step 1: Preparation of 3-fluoro-4-(2-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethoxy)benzonitrile



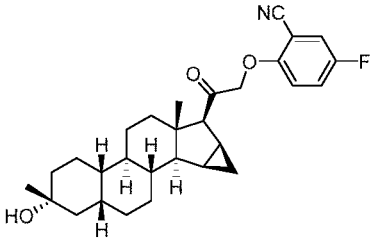
In accordance with Example 5, 2-bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethylocta decahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one was used as the starting material, accordingly, 3-fluoro-4-(2-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethoxy)benzonitrile (12.5 mg, yield: 18%) was obtained.

MS m/z (ESI): 448.2 $[M-H_2O+H]^+$

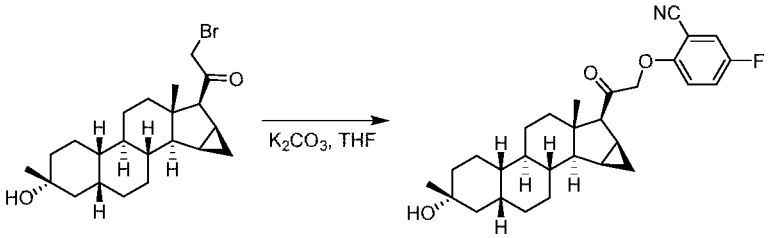
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.33 (m, 2H), 6.91 – 6.84 (m, 1H), 4.91 (s, 2H), 2.96 – 2.88 (m, 1H), 1.90 – 1.76 (m, 4H), 1.75 – 1.62 (m, 3H), 1.55 – 1.26 (m, 17H), 1.12 – 1.04 (m, 1H), 0.98 – 0.92 (m, 1H), 0.78 (s, 3H), 0.50 – 0.41 (m, 1H).

Example 126

5-Fluoro-2-(2-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethoxy)benzonitrile (126)



Step 1: Preparation of 5-fluoro-2-(2-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethoxy)benzonitrile



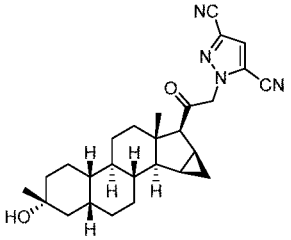
In accordance with Example 5, 2-bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one was used as the starting material, accordingly, 5-fluoro-2-(2-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethoxy)benzonitrile (11.4 mg, yield: 10%) was obtained.

MS m/z (ESI): 448.2 $[M-H_2O+H]^+$

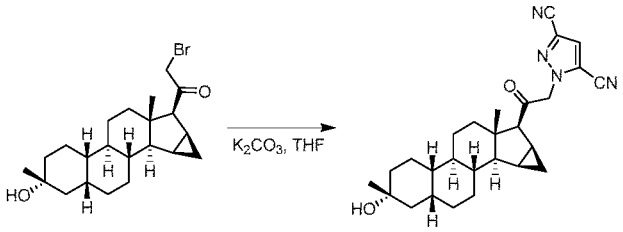
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 1H), 7.25 – 7.18 (m, 1H), 6.78 – 6.72 (m, 1H), 4.91 – 4.78 (m, 2H), 2.99 (d, J = 3.3 Hz, 1H), 1.91 – 1.78 (m, 4H), 1.76 – 1.64 (m, 3H), 1.57 – 1.25 (m, 17H), 1.08 – 0.92 (m, 2H), 0.78 (s, 3H), 0.50 – 0.40 (m, 1H).

Example 127

1-(2-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-Hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethyl)-1H-pyrazole-3,5-dicarbonitrile (127)



Step 1: Preparation of 1-(2-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethyl)-1H-pyrazole-3,5-dicarbonitrile



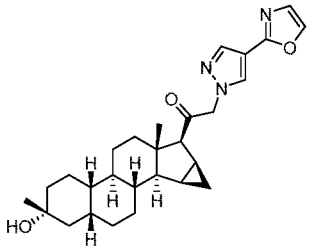
In accordance with Example 5, 2-bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one was used as the starting material, accordingly, 1-(2-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethyl)-1H-pyrazole-3,5-dicarbonitrile (18.0 mg, yield: 31.8%) was obtained.

MS m/z (ESI): 429.2 $[M-H_2O+H]^+$

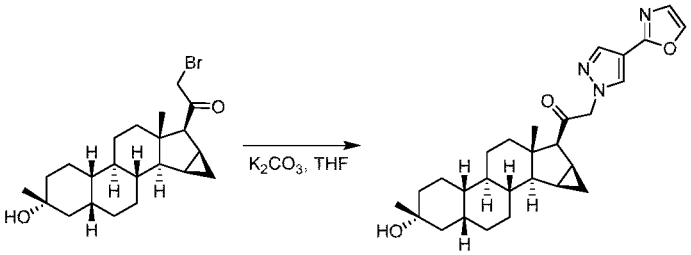
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (s, 1H), 5.38 (q, J = 18.0 Hz, 2H), 2.87 (d, J = 3.0 Hz, 1H), 1.97 – 1.91 (m, 1H), 1.88 – 1.75 (m, 4H), 1.76 – 1.64 (m, 3H), 1.58 – 1.51 (m, 1H), 1.48 – 1.26 (m, 15H), 1.15 – 0.99 (m, 2H), 0.83 (s, 3H), 0.58 – 0.48 (m, 1H).

Example 128

1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-Hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(4-(oxazol-2-yl)-1H-pyrazol-1-yl)ethan-1-one (128)



Step 1: Preparation of 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(4-(oxazol-2-yl)-1H-pyrazol-1-yl)ethan-1-one



In accordance with Example 5, 2-bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one was used as the starting material, accordingly,

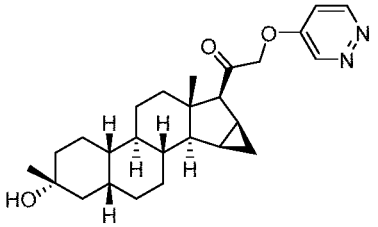
1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(4-(oxazol-2-yl)-1H-pyrazol-1-yl)ethan-1-one (16.0 mg, yield: 14%) was obtained.

MS m/z (ESI): 464.3 $[M+H]^+$

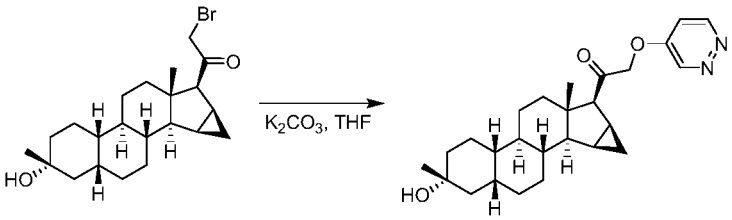
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.79 (s, 1H), 7.73 (s, 1H), 7.13 (s, 1H), 5.27 – 5.13 (m, 2H), 2.85 (d, J = 4.0 Hz, 1H), 2.01 – 1.93 (m, 1H), 1.87 – 1.65 (m, 11H), 1.58 – 1.50 (m, 1H), 1.44 – 1.22 (m, 11H), 1.14 – 0.98 (m, 2H), 0.81 (s, 3H), 0.53 – 0.44 (m, 1H).

Example 129

1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-Hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(pyridazin-4-yloxy)ethan-1-one (129)



Step 1: Preparation of 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(pyridazin-4-yloxy)ethan-1-one



In accordance with Example 5, 2-bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one was used as the starting material, accordingly, 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-(pyridazin-4-yloxy)ethan-1-one (16.0 mg, yield: 26%) was obtained.

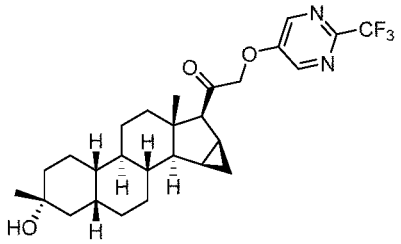
MS m/z (ESI): 425.3 $[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.61 (d, J = 6.8 Hz, 1H), 6.53 (d, J = 6.8 Hz, 1H), 5.17 – 4.85 (m, 2H), 2.83 (s, 1H), 1.99 – 1.90 (m, 1H), 1.88 – 1.78 (m, 3H), 1.76 – 1.54 (m, 10H), 1.46 – 1.25 (m, 10H), 1.14 – 0.95 (m, 2H), 0.79 (s, 3H), 0.55 – 0.46 (m, 1H).

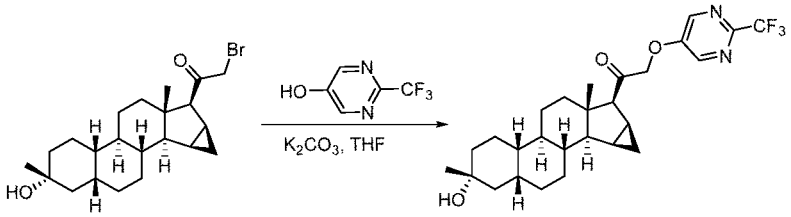
Example 130

1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-Hydroxy-2,6a-dimethyloctadecahyd

rocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)ethan-1-one



Step 1: Preparation of 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)ethan-1-one



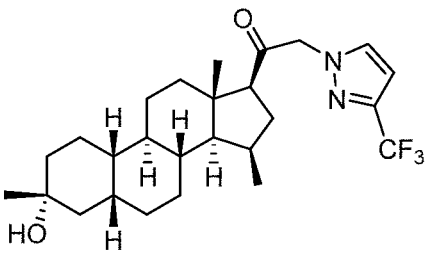
In accordance with Example 5, 2-bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one was used as the starting material, accordingly, 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)ethan-1-one (23.0 mg, yield: 38.3%) was obtained.

MS m/z (ESI): 493.2$[M+H]^+$

1H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 2H), 5.01 (s, 2H), 2.86 (s, 1H), 1.89 (m, 1H), 1.83 (m, 4H), 1.75 (dm, 1H), 1.68 (m, 2H), 1.57 (m, 1H), 1.38 (m, 8H), 1.31 (m, 2H), 1.28 (s, 3H), 1.26 – 1.20 (m, 1H), 1.13 – 1.03 (m, 1H), 0.96 (m, 1H), 0.80 (s, 3H), 0.48 (m, 1H).

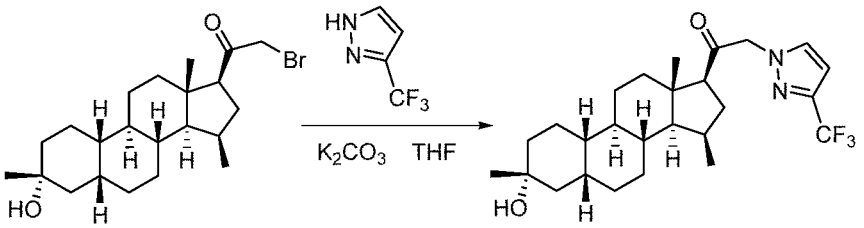
Example 131

1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-Hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)ethan-1-one (131)



Step 1: 1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-Hydroxy-3,13,15-trimethylhexadecahydro-1

H-cyclopenta[a]phenanthren-17-yl)-2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)ethan-1-one



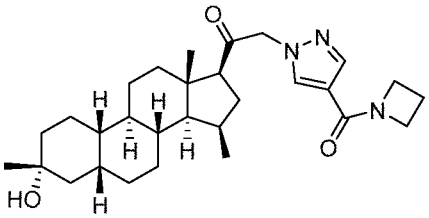
In accordance with Example 5, 2-bromo-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one was used as the starting material, accordingly, 1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)ethan-1-one (20.5 mg, yield: 30.1%) was obtained.

MS m/z (ESI): 467.2$[M+H]^+$.

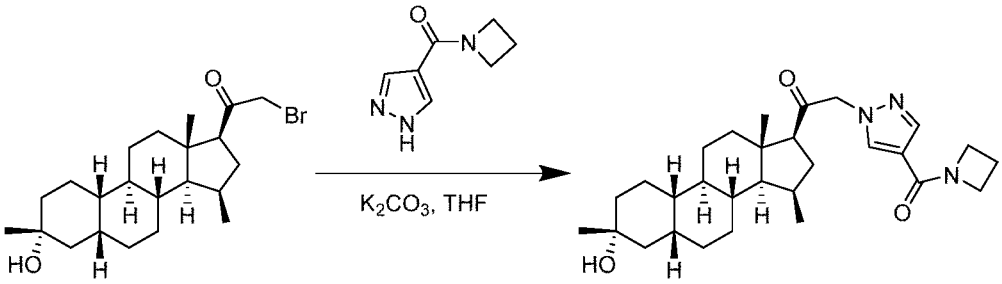
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.43 (m, 1H), 6.59 (d, J = 2.4 Hz, 1H), 5.14 – 4.85 (m, 2H), 2.54 (t, J = 8.1 Hz, 1H), 2.26 – 2.08 (m, 2H), 2.02 – 1.93 (m, 1H), 1.90 – 1.79 (m, 4H), 1.74 –1.59 (m, 3H), 1.57 – 1.19 (m, 14H), 1.21 – 1.04 (m, 1H), 0.98 (d, J = 7.0 Hz, 3H), 0.84 (s, 3H).

Example 133

2-(4-(Azetidine-1-carbonyl)-1H-pyrazol-1-yl)-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (133)



Step 1: Preparation of 2-(4-(azetidine-1-carbonyl)-1H-pyrazol-1-yl)-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one



In accordance with Example 5, 2-bromo-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadec

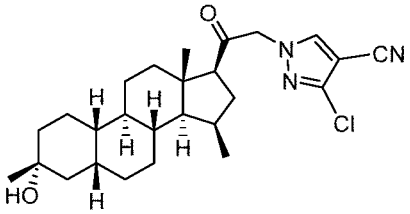
ahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one was used as the starting material, accordingly, 2-(4-(azetidine-1-carbonyl)-1H-pyrazol-1-yl)-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (12.0 mg, yield: 21%) was obtained.

MS m/z (ESI): 482.3[M+H]$^+$.

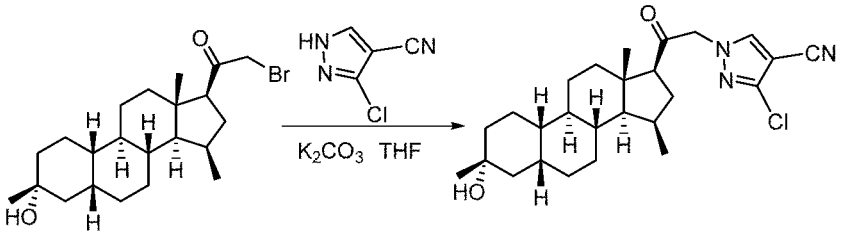
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 2H), 5.00 – 4.77 (m, 2H), 4.38-4.25 (m, 4H), 2.54 (t, J = 7.6 Hz, 1H), 2.43 – 2.32 (m, 2H), 2.26 – 2.08 (m, 2H), 1.98-1.96 (m, 1H), 1.88-1.83 (m, 3H), 1.69-1.62(m, 5H), 1.48-1.42 (m, 4H), 1.38–1.26 (m, 9H), 1.16-1.07 (m, 2H), 0.98 (d, J = 7.0 Hz, 3H), 0.84 (s, 3H).

Example 134

3-Chloro-1-(2-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile (134)



Step 1: Preparation of 3-chloro-1-(2-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile



In accordance with Example 5, 2-bromo-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one was used as the starting material, accordingly, the product 3-chloro-1-(2-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile (37 mg, yield: 55.3%) was obtained.

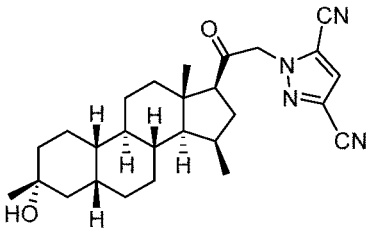
MS m/z (ESI): 456.2[M-H]-.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 5.03 – 4.75 (m, 2H), 2.54 (t, J = 8.0 Hz, 1H), 2.31 – 2.13 (m, 2H), 1.93 – 1.06 (m, 23H), 0.99 (d, J = 7.1 Hz, 3H), 0.83 (s, 3H).

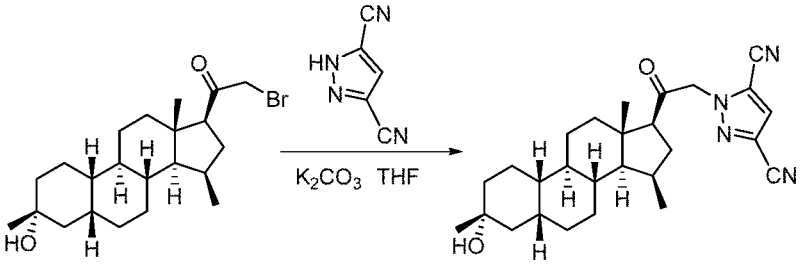
Example 135

1-(2-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-Hydroxy-3,13,15-trimethylhexadecahydr

o-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-3,5-dicarbonitrile (135)



Step 1: Preparation of 1-(2-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-3,5-dicarbonitrile



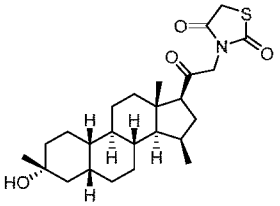
In accordance with Example 5, 2-bromo-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one was used as the starting material, accordingly, the product 1-(2-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-3,5-dicarbonitrile (18 mg, yield 27.5%) was obtained.

MS m/z (ESI): 447.2[M-H]$^-$.

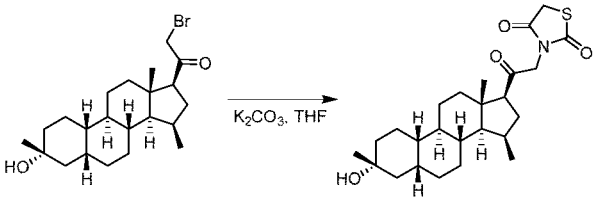
^{1}H NMR (400 MHz, $CDCl_3$) δ7.20 (s, 1H), 5.23 – 5.07 (m, 2H), 2.68 – 2.52 (m, 1H), 2.28 – 1.36 (m, 21H), 1.28 (s, 3H), 1.18 – 1.08 (m, 1H), 1.00 (d, J = 6.9 Hz, 3H), 0.88 (s, 3H).

Example 136

3-(2-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-Hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)thiazolidine-2,4-dione (136)



Step 1: Preparation of 3-(2-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)thiazolidine-2,4-dione



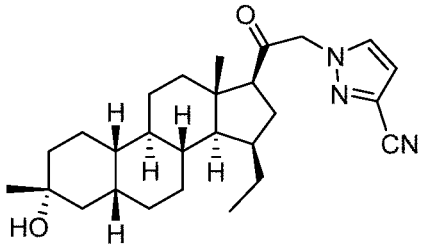
In accordance with Example 5, 2-bromo-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one was used as the starting material, accordingly, 3-(2-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)thiazolidine-2,4-dione (24.0 mg, yield: 31.5%) was obtained.

MS m/z (ESI): 430.2 $[M-H_2O+H]^+$

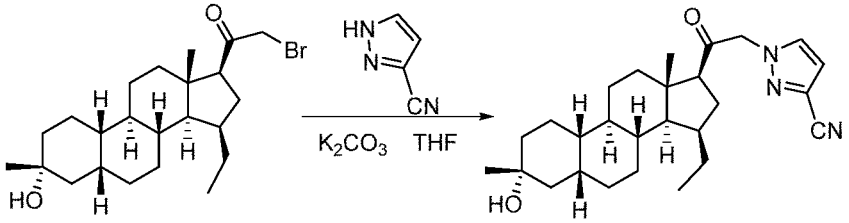
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.37 (s, 2H), 4.04 – 3.98 (m, 2H), 2.56 – 2.49 (m, 1H), 2.22 – 2.03 (m, 2H), 1.91 – 1.81 (m, 4H), 1.73 – 1.61 (m, 3H), 1.47 – 1.26 (m, 15H), 1.17 – 1.05 (m, 2H), 0.97 (d, J = 7.1 Hz, 3H), 0.81 (s, 3H).

Example 137

1-(2-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-Ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-3-carbonitrile (137)



Step 1: Preparation of 1-(2-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-3-carbonitrile



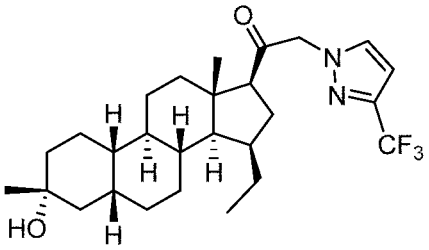
In accordance with Example 5, 2-bromo-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one was used as the starting material, accordingly, the product 1-(2-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-3-carbonitrile (16 mg, yield: 25.9%) was obtained.

MS m/z (ESI): 438.2[M+H]$^+$.

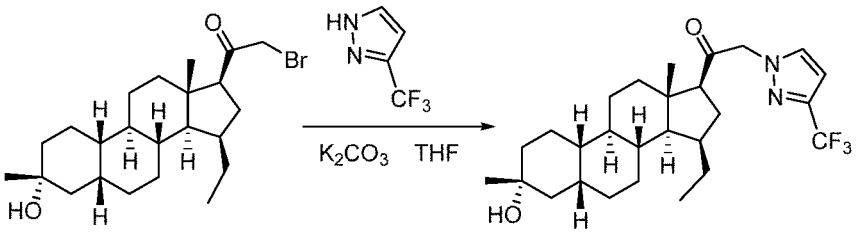
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 2.5 Hz, 1H), 6.73 (d, J = 2.4 Hz, 1H), 5.22 – 4.78 (m, 2H), 2.57 (t, J = 8.0 Hz, 1H), 2.15 – 1.30 (m, 20H), 1.28 (s, 3H), 1.16 – 1.03 (m, 4H), 0.84 (t, J= 7.3 Hz, 3H), 0.79 (s, 3H).

Example 138

1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-Ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)ethan-1-one (138)



Step 1: Preparation of 1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)ethan-1-one



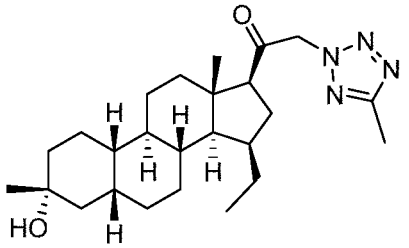
In accordance with Example 5, 2-bromo-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one was used as the starting material, accordingly, the product 1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)ethan-1-one (23 mg, yield: 33.9%) was obtained.

MS m/z (ESI): 481.3[M+H]$^+$.

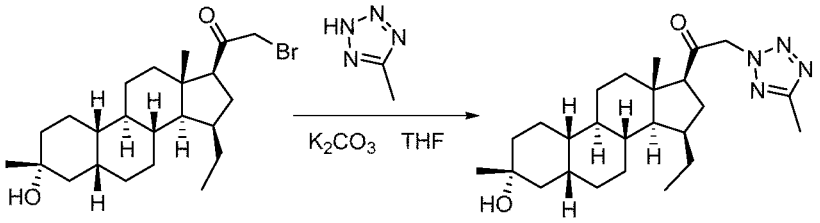
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J =4.0Hz, 1H), 6.59 (d, J = 4.0 Hz 1H), 5.07 – 4.89 (m, 2H), 2.56 (t, J = 9.3 Hz, 1H), 2.20 – 1.29 (m, 20H),1.28 (s, 3H), 1.27 – 1.03 (m, 4H),0.84 (t, J = 7.3 Hz, 3H), 0.80 (s, 3H).

Example 139

1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-Ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(5-methyl-2H-tetrazol-2-yl)ethan-1-one (139)



Step 1: Preparation of 1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(5-methyl-2H-tetrazol-2-yl)ethan-1-one



In accordance with Example 5, 2-bromo-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one was used as the starting material, accordingly, the product 1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(5-methyl-2H-tetrazol-2-yl)ethan-1-one (13.5 mg, yield: 22.3%) was obtained.

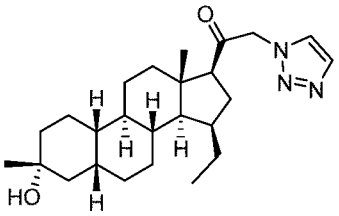
MS m/z (ESI): 429.3$[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39 – 5.29 (m, 2H), 2.63 – 2.57 (m, 1H), 2.56 (s, 3H), 2.10 – 1.30 (m, 20H), 1.28 (s, 3H), 1.27 – 1.05 (m, 4H), 0.87 – 0.81 (m, 6H).

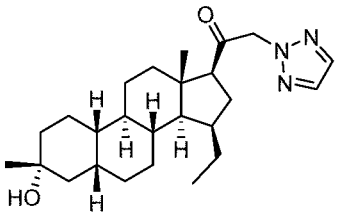
Example 140 and Example 141

1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-Ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(1H-1,2,3-triazol-1-yl)ethan-1-one (140)

1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-Ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(2H-1,2,3-triazol-2-yl)ethan-1-one (141)

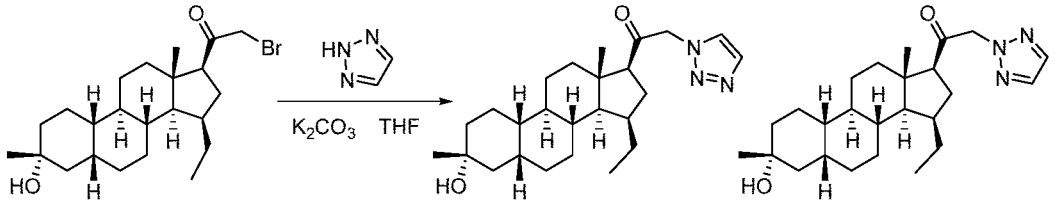


140



141

Step 1: Preparation of 1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(1H-1,2,3-triazol-1-yl)ethan-1-one and 1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(2H-1,2,3-triazol-2-yl)ethan-1-one



In accordance with Example 5, 2-bromo-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one was used as the starting material, accordingly, the products 1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(1H-1,2,3-triazol-1-yl)ethan-1-one (17 mg, yield: 29.1%) and 1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(2H-1,2,3-triazol-2-yl)ethan-1-one (9.2 mg, yield: 15.7%) were obtained.

Example 140:

MS m/z (ESI): 414.3$[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.67 (s, 1H), 5.37 – 5.09 (m, 2H), 2.62 (t, J = 9.2 Hz, 1H), 2.28 – 1.20 (m, 25H), 1.16 – 1.05 (m, 2H), 0.85 (t, J = 7.3 Hz, 3H), 0.80 (s, 3H).

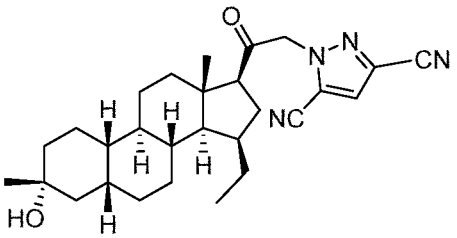
Example 141:

MS m/z (ESI): 414.3$[M+H]^+$.

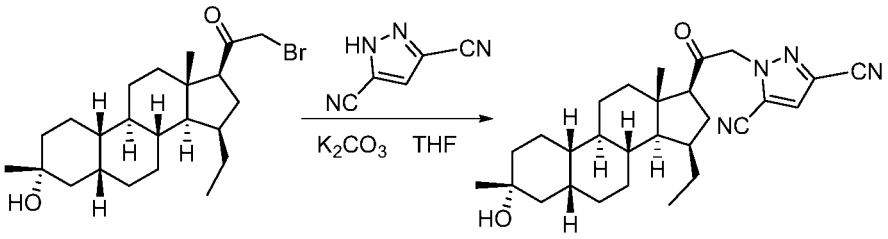
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 2H), 5.28 – 5.20 (m, 2H), 2.54 (t, J = 8.0 Hz, 1H), 1.99 – 1.23 (m, 25H), 1.13 – 1.06 (m, 2H), 0.88 – 0.78 (m, 6H).

Example 142

1-(2-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-Ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-3,5-dicarbonitrile (142)



Step 1: Preparation of 1-(2-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-3,5-dicarbonitrile



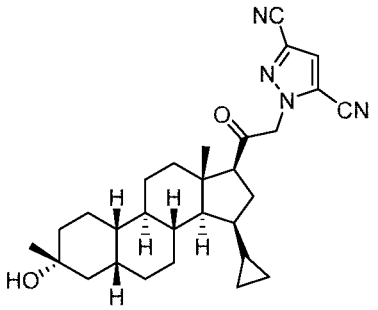
In accordance with Example 5, 2-bromo-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one was used as the starting material, accordingly, the product 1-(2-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-3,5-dicarbonitrile (5 mg, yield: 9.2%) was obtained.

MS m/z (ESI): 463.2[M+H]$^+$.

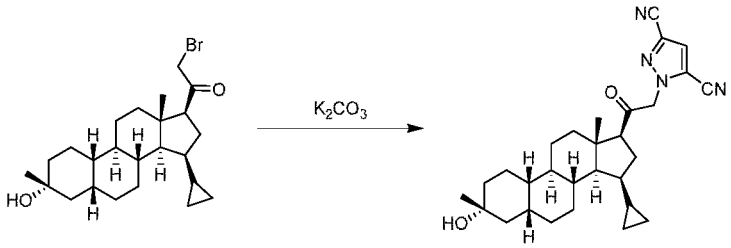
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (s, 1H), 5.29 – 5.02 (m, 2H), 2.61 (t, J = 9.3 Hz, 1H), 2.24 – 1.34 (m, 19H), 1.28 (s, 3H), 1.26 – 1.02 (m, 5H), 0.92 – 0.76 (m, 6H).

Example 143

1-(2-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-Cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-3,5-dicarbonitrile (143)



Step 1: Preparation of 1-(2-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-3,5-dicarbonitrile



In accordance with Example 5, 1-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one was used as the starting material, accordingly,

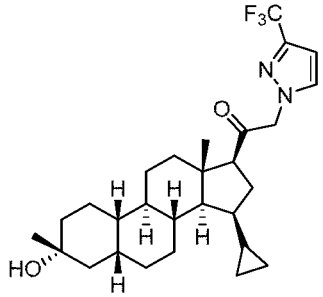
1-(2-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-3,5-dicarbonitrile (19.6 mg, yield: 18%) was obtained.

MS m/z (ESI): 473.2[M- H]$^-$

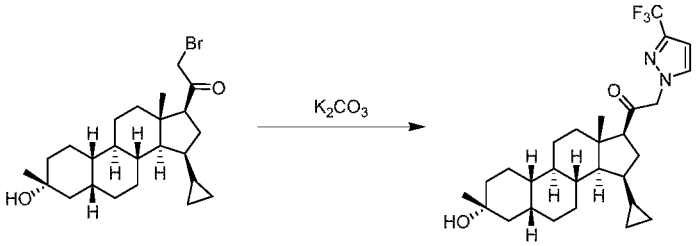
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (s, 1H), 5.24 – 5.09 (m, 2H), 2.58 – 2.50 (m, 1H), 2.26 – 2.07 (m, 2H), 2.06 – 1.95 (m, 2H), 1.90 – 1.80 (m, 2H), 1.78 – 1.66 (m, 2H), 1.58 – 1.22 (m, 16H), 1.19 – 1.06 (m, 2H), 0.94 (s, 3H), 0.87 – 0.78 (m, 1H), 0.64 – 0.56 (m, 1H), 0.45 – 0.39 (m, 1H), 0.18 – 0.02 (m, 2H).

Example 144

1-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-Cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)ethan-1-one (144)



Step 1: Preparation of 1-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)ethan-1-one



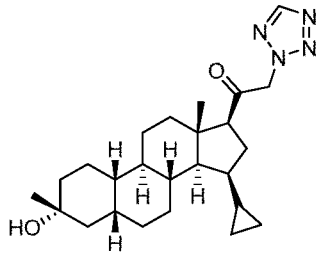
In accordance with Example 5, 1-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one was used as the starting material, accordingly, 1-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)ethan-1-one (18.0 mg, yield: 23%) was obtained.

MS m/z (ESI): 491.3[M- H]$^-$

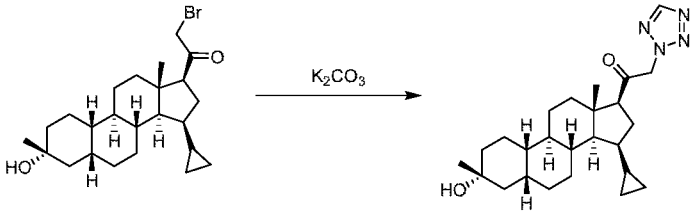
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 2.0 Hz, 1H), 6.59 (d, J = 2.0 Hz, 1H), 5.08 – 4.90 (m, 2H), 2.53 – 2.42 (m, 1H), 2.24 – 1.94 (m, 4H), 1.91 – 1.79 (m, 3H), 1.78 – 1.66 (m, 2H), 1.52 – 1.22 (m, 15H), 1.18 – 1.02 (m, 2H), 0.91 (s, 3H), 0.88 – 0.76 (m, 1H), 0.65 – 0.54 (m, 1H), 0.48 – 0.36 (m, 1H), 0.18 – 0.00 (m, 2H).

Example 146

1-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-Cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(2H-tetrazol-2-yl)ethan-1-one (146)



Step 1: Preparation of 1-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(2H-tetrazol-2-yl)ethan-1-one



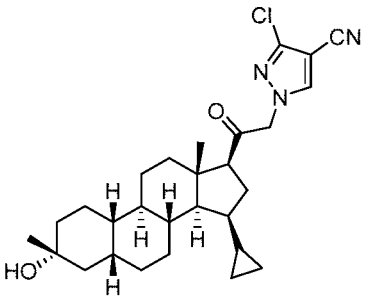
In accordance with Example 5, 1-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one was used as the starting material, accordingly, 1-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(2H-tetrazol-2-yl)ethan-1-one (12.9 mg, yield: 13.2%) was obtained.

MS m/z (ESI): 409.3[M-H_2O+ H]$^+$

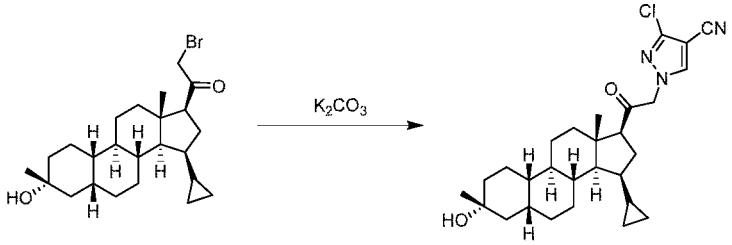
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 5.46 (s, 2H), 2.58 – 2.47 (m, 1H), 2.24 – 1.94 (m, 4H), 1.93 – 1.80 (m, 3H), 1.77 – 1.66 (m, 2H), 1.50 – 1.21 (m, 15H), 1.18 – 1.06 (m, 2H), 0.95 (s, 3H), 0.87 – 0.78 (m, 1H), 0.64 – 0.55 (m, 1H), 0.46 – 0.38 (m, 1H), 0.17 – 0.01 (m, 2H).

Example 147

3-Chloro-1-(2-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile (147)



Step 1: Preparation of 3-chloro-1-(2-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile



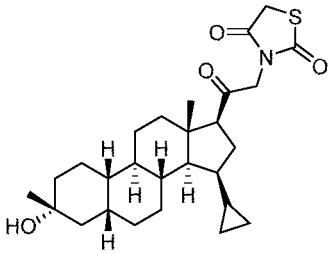
In accordance with Example 5, 1-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one was used as the starting material, accordingly, 3-chloro-1-(2-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile (13.5 mg, yield: 17.4%) was obtained.

MS m/z (ESI): 482.2[M- H]$^-$

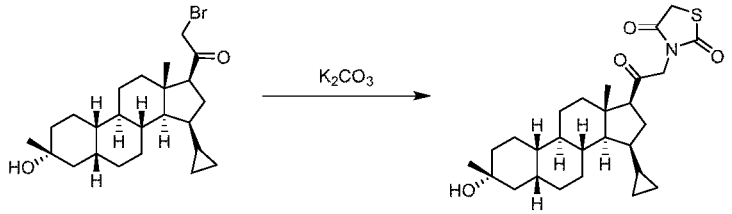
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 5.01 – 4.76 (m, 2H), 2.55 – 2.41 (m, 1H), 2.22 – 1.94 (m, 4H), 1.91 – 1.77 (m, 3H), 1.76 – 1.66 (m, 2H), 1.56 – 1.24 (m, 15H), 1.18 – 1.04 (m, 2H), 0.90 (s, 3H), 0.87 – 0.75 (m, 1H), 0.64 – 0.53 (m, 1H), 0.46 – 0.38 (m, 1H), 0.17 – 0.02 (m, 2H).

Example 148

3-(2-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-Cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)thiazolidine-2,4-dione (148)



Step 1: Preparation of 3-(2-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)thiazolidine-2,4-dione



In accordance with Example 5,

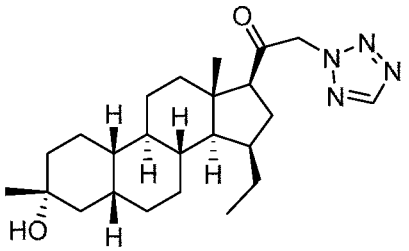
1-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one was used as the starting material, accordingly, 3-(2-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)thiazolidine-2,4-dione (10.0 mg, yield: 13%) was obtained.

MS m/z (ESI): 456.2[M-H_2O+H]$^+$

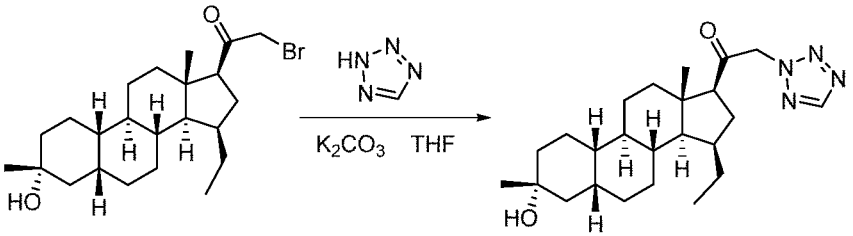
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38 (s, 2H), 4.04 (s, 2H), 2.51 – 2.43 (m, 1H), 2.24 – 2.00 (m, 4H), 1.91 – 1.80 (m, 3H), 1.75 – 1.67 (m, 2H), 1.49 – 1.27 (m, 15H), 1.17 – 1.05 (m, 2H), 0.88 (s, 3H), 0.84 – 0.78 (m, 1H), 0.62 – 0.53 (m, 1H), 0.46 – 0.36 (m, 1H), 0.15 – 0.01 (m, 2H).

Example 149

1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-Ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(2H-tetrazol-2-yl)ethan-1-one (149)



Step 1: Preparation of 1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(2H-tetrazol-2-yl)ethan-1-one



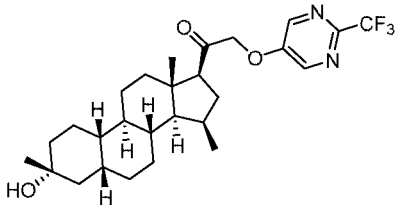
In accordance with Example 5, 2-bromo-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one was used as the starting material, accordingly, the product 1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-15-ethyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(2H-tetrazol-2-yl)ethan-1-one (11 mg, white solid, yield: 18.8%) was obtained.

MS m/z (ESI): 397.2[M-H_2O+H]$^+$

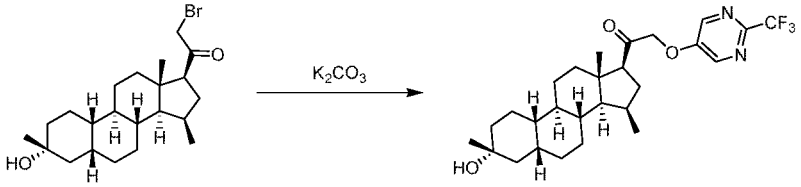
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 5.50 – 5.41 (m, 2H), 2.62 (t, J = 8.5 Hz, 1H), 2.29 – 1.30 (m, 20H), 1.28 (s, 3H), 1.27 – 1.05 (m, 4H), 0.85 – 0.82 (m, 6H).

Example 150

1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-Hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)ethan-1-one (150)



Step 1: Preparation of 1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-Hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)ethan-1-one



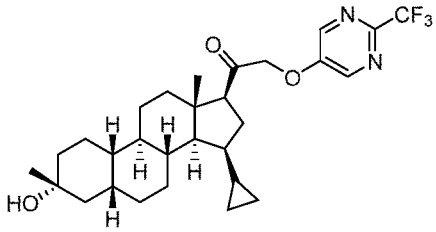
In accordance with Example 5, 2-bromo-1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one was used as the starting material, accordingly, 1-((3R,5R,8R,9R,10S,13S,14S,15R,17S)-3-hydroxy-3,13,15-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)ethan-1-one (16.1 mg, yield: 19%) was obtained.

MS m/z (ESI): 477.3[M-H_2O+ H]$^+$

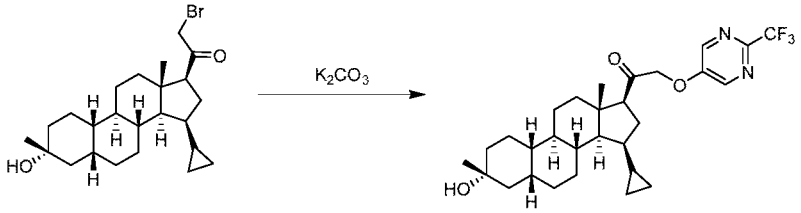
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 2H), 4.85 – 4.71 (m, 2H), 2.67 – 2.57 (m, 1H), 2.30 – 2.10 (m, 2H), 1.93 – 1.81 (m, 4H), 1.74 – 1.61 (m, 3H), 1.48 – 1.23 (m, 15H), 1.18 – 1.06 (m, 2H), 1.00 (d, J = 7.1 Hz, 3H), 0.87 (s, 3H).

Example 151

1-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-Cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)ethan-1-one (151)



Step 1: Preparation of 1-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)ethan-1-one



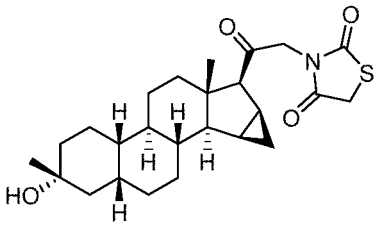
In accordance with Example 5, 1-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one was used as the starting material, accordingly, 1-((3R,5R,8R,9R,10S,13S,14S,15S,17S)-15-cyclopropyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-((2-(trifluoromethyl)pyrimidin-5-yl)oxy)ethan-1-one (22.9 mg, yield: 27.6%) was obtained.

MS m/z (ESI): 503.3[M-H_2O+ H]$^+$

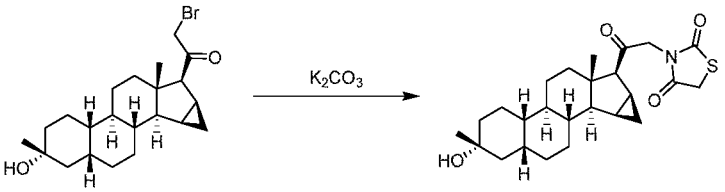
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 2H), 4.87 – 4.69 (m, 2H), 2.62 – 2.50 (m, 1H), 2.25 – 1.96 (m, 3H), 1.92 – 1.84 (m, 3H), 1.77 – 1.66 (m, 2H), 1.54 – 1.23 (m, 15H), 1.18 – 1.04 (m, 2H), 0.93 (s, 3H), 0.87 – 0.78 (m, 1H), 0.65 – 0.56 (m, 1H), 0.49 – 0.38 (m, 1H), 0.20 – 0.02 (m, 2H).

Example 152

3-(2-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-Hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethyl)thiazolidine-2,4-dione (152)



Step 1: Preparation of 3-(2-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethyl)thiazolidine-2,4-dione



In accordance with Example 5, 2-bromo-1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethan-1-one was used as the starting material, accordingly, 3-(2-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)-2-oxoethyl)thiazolidine-2,4-dio

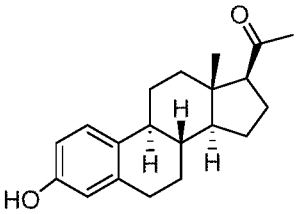
ne (7.1 mg, yield: 9.3%) was obtained.

MS m/z (ESI): 446.2[M + H]$^+$

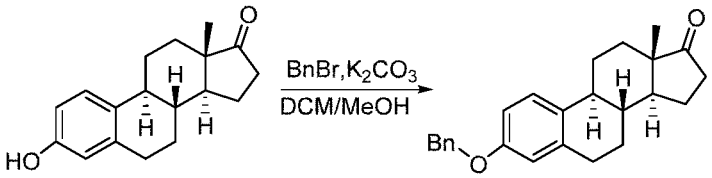
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.66 – 4.50 (m, 2H), 4.04 (s, 2H), 2.78 (d, J = 4.0 Hz, 1H), 1.98 – 1.92 (m, 1H), 1.85 – 1.52 (m, 11H), 1.44 – 1.24 (m, 12H), 1.13 – 0.97 (m, 2H), 0.77 (s, 3H), 0.49 – 0.41 (m, 1H).

Example 157

1-((8S,9S,13S,14S,17S)-3-Hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (157)



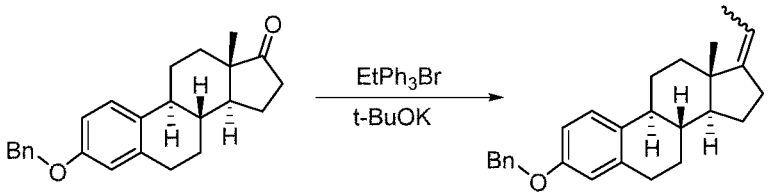
Step 1: Preparation of (8R,9S,13S,14S)-3-(benzyloxy)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one



(8R,9S,13S,14S)-3-Hydroxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one (4.1 g, 15 mmol) and a solution of dichloromethane/methanol (1/1, 50 mL) were added to a 100 mL three-neck flask, followed by the addition of potassium carbonate (6.2 g, 45 mmol) and benzyl bromide (7.6 g, 45 mmol) . The reaction solution was refluxed at 65°C for 5 hours. The reaction solution was cooled, filtrated and washed with methanol. The reaction solution was concentrated, and the resulting residue was purified by column chromatography with petroleum ether/ethyl acetate (1/3) to obtain (8R,9S,13S,14S)-3-(benzyloxy)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one (5 g, yield: 93%).

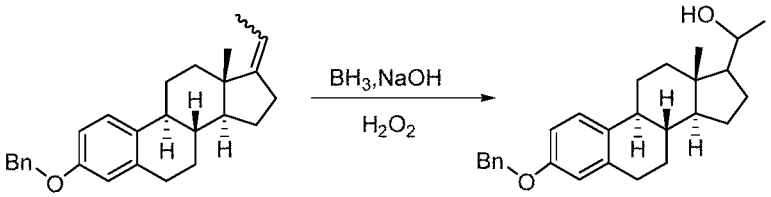
1H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.29 (m, 5H), 7.20 (d, J = 8.5 Hz, 1H), 6.79 (dd, J = 8.6, 2.7 Hz, 1H), 6.73 (d, J = 2.6 Hz, 1H), 5.04 (s, 2H), 2.95-2.85 (m, 2H), 2.50 (dd, J = 18.8, 8.5 Hz, 1H), 2.43-2.36 (m, 1H), 2.30-2.23 (m, 1H), 2.20 – 1.94 (m, 4H), 1.63 – 1.40 (m, 6H), 0.91 (s, 3H).

Step 2: Preparation of (8S,9S,13S,14S)-3-(benzyloxy)-17-ethylidene-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene



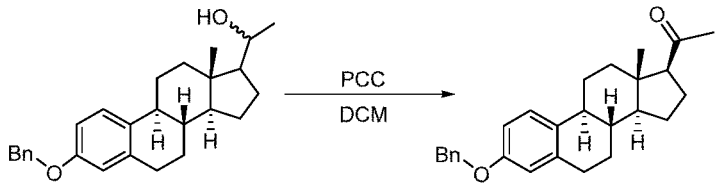
Potassium *tert*-butoxide (7.8 g, 70 mmol) was suspended in tetrahydrofuran (100 mL). Ethyltriphenylphosphonium bromide (26.3 g, 70 mmol) was slowly added at 0°C, and the reaction solution was stirred at 60°C for 2 hours. (8R,9S,13S,14S)-3-(Benzyloxy)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one (5 g, 14 mmol) was added to the above reaction solution. After reacting at 60°C for 2 hours, the reaction solution was cooled to room temperature. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction solution was extracted with ethyl acetate. The organic phase was washed with saturated saline, dried, filtrated and concentrated. The resulting residue was purified by column chromatography with petroleum ether to obtain (8S,9S,13S,14S)-3-(benzyloxy)-17-ethylidene-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene (5 g, yield: 96%).

Step 3: Preparation of 1-((8S,9S,13S,14S)-3-(benzyloxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl)ethan-1-ol



(8S,9S,13S,14S)-3-(Benzyloxy)-17-ethylidene-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene (2.5 g, 6.9 mmol) was dissolved in anhydrous tetrahydrofuran (50 mL). A solution of borane in tetrahydrofuran (1 M, 20 mL) was added dropwise at room temperature, and the resulting reaction solution was stirred at room temperature for 1 hour. The reaction solution was cooled with ice water, and sodium hydroxide solution (10%, 15 mL) was slowly added dropwise to release a large amount of gas. Hydrogen peroxide (30%, 20 mL) was slowly added dropwise, and the reaction solution was stirred at room temperature for 2 hours. The reaction solution was extracted with ethyl acetate, washed with sodium thiosulfate solution and saturated saline, and dried to obtain the product (2.5 g), which was used directly in the next step.

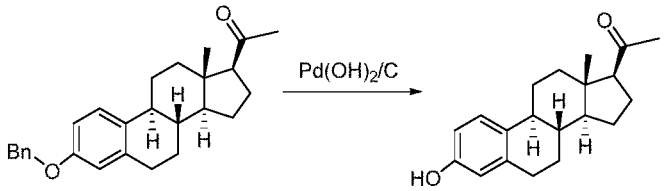
Step 4: Preparation of 1-((8S,9S,13S,14S,17S)-3-(benzyloxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl)ethan-1-one



1-((8S,9S,13S,14S)-3-(Benzyloxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl)ethan-1-ol (2.5 g, 6.5 mmol) was dissolved in dichloromethane (30 mL). Pyridinium chlorochromate (2.06 g, 9.6 mmol) was added, and the reaction solution was stirred at room temperature for 12 hours. The reaction solution was filtrated and concentrated by rotary evaporation to dryness. The resulting residue was purified by column chromatography with petroleum ether/ethyl acetate (1/5) to obtain 1-((8S,9S,13S,14S,17S)-3-(benzyloxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (1.6 g, yield: 65%).

1H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.28 (m, 5H), 7.20 (d, J = 8.6 Hz, 1H), 6.78 (dd, J = 8.5, 2.6 Hz, 1H), 6.72 (d, J = 2.6 Hz, 1H), 5.03 (s, 2H), 2.90-2.80 (m, 2H), 2.61 (t, J = 9.1 Hz, 1H), 2.40 – 2.17 (m, 4H), 2.15 (s, 3H), 1.96 – 1.27 (m, 9H), 0.65 (s, 3H).

Step 5: Preparation of 1-((8S,9S,13S,14S,17S)-3-hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl)ethan-1-one



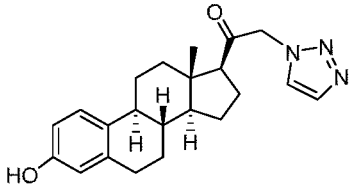
1-((8S,9S,13S,14S,17S)-3-(Benzyloxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (200 mg, 0.52 mmol) was dissolved in methanol/tetrahydrofuran (5 mL/5 mL). Palladium hydroxide on activated carbon (30 mg, 20%) was added, and the reaction solution was reacted under a hydrogen atmosphere at 45°C for 12 hours to obtain the final product 1-((8S,9S,13S,14S,17S)-3-hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (50 mg, yield: 32%).

MS m/z (ESI):298.1 [M]+.

1H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, J = 8.4 Hz, 1H), 6.63 (dd, J = 8.4, 2.6 Hz, 1H), 6.56 (d, J = 2.6 Hz, 1H), 4.62 (s, 1H), 2.92 – 2.74 (m, 2H), 2.62 (t, J = 9.1 Hz, 1H), 2.40 - 2.17 (m, 4H), 2.16 (s, 3H), 1.95-1.30 (m, 9H), 0.65 (s, 3H).

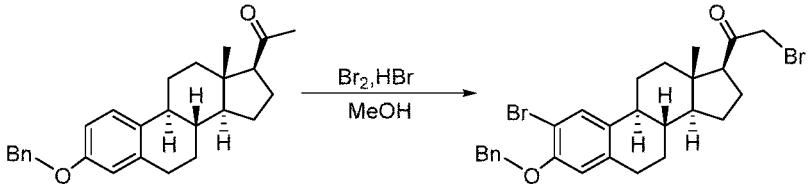
Example 158

1-((8S,9S,13S,14S,17S)-3-Hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl)-2-(1H-1,2,3-triazol-1-yl)ethan-1-one (158)



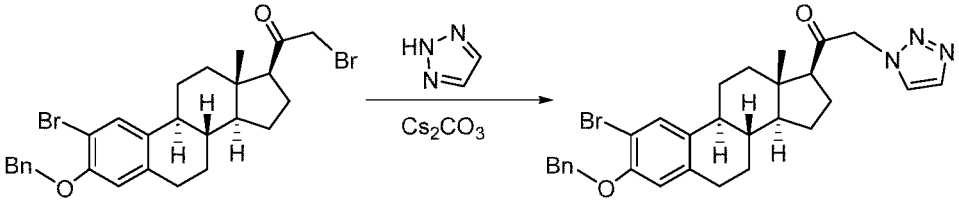
Step 1: Preparation of 1-((8S,9S,13S,14S,17S)-3-(benzyloxy)-2-bromo-13-methyl-7,8,9,11,12,13,14,15,16,17-

decahydro-6H-cyclopenta[a]phenanthren-17-yl)-2-bromoethan-1-one



1-((8S,9S,13S,14S,17S)-3-(Benzyloxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (300 mg, 0.78 mmol) was dissolved in methanol (15 mL). Five drops of hydrogen bromide solution was added, followed by the dropwise addition of liquid bromine (255 mg, 1.6 mmol). After stirring at room temperature for 2 hours, the reaction solution was poured into ice water, and extracted with ethyl acetate. The organic phase was washed with saturated saline, dried over anhydrous sodium sulfate, and concentrated by rotary evaporation to dryness to obtain 300 mg of the product 1-((8S,9S,13S,14S,17S)-3-(benzyloxy)-2-bromo-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl)-2-bromoethan-1-one, which was used directly in the next step.

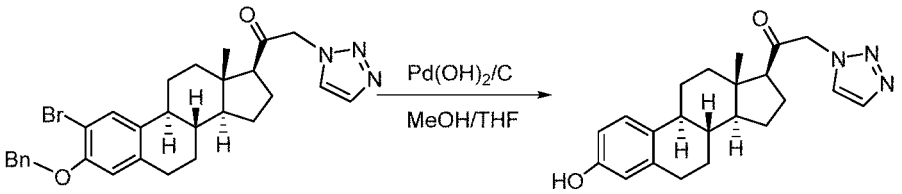
Step 2: Preparation of 1-((8S,9S,13S,14S,17S)-3-(benzyloxy)-2-bromo-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl)-2-(1H-1,2,3-triazol-1-yl)ethan-1-one



1-((8S,9S,13S,14S,17S)-3-(Benzyloxy)-2-bromo-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl)-2-bromoethan-1-one (300 mg, 0.55 mmol) was dissolved in tetrahydrofuran (10 mL). Cesium carbonate (536 mg, 1.65 mmol) and 1,2,3-triazole (190 mg, 2.7 mmol) were added, and the reaction solution was reacted at 35°C for 5 hours. The reaction solution was filtrated and concentrated. The resulting residue was purified by column chromatography with petroleum ether/ethyl acetate (1/1) to obtain 1-((8S,9S,13S,14S,17S)-3-(benzyloxy)-2-bromo-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl)-2-(1H-1,2,3-triazol-1-yl)ethan-1-one (70 mg, yellow solid, yield: 20%).

MS m/z (ESI): 534.1/536.1(50/50) [M+H]+.

Step 3: Preparation of 1-((8S,9S,13S,14S,17S)-3-hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl)-2-(1H-1,2,3-triazol-1-yl)ethan-1-one



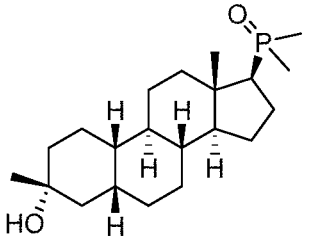
1-((8S,9S,13S,14S,17S)-3-(Benzyloxy)-2-bromo-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl)-2-(1H-1,2,3-triazol-1-yl)ethan-1-one (70 mg, 0.13 mmol) was dissolved in methanol/tetrahydrofuran (5 mL/5 mL). Palladium hydroxide on activated carbon (30 mg, 20%) was added, and the reaction solution was reacted under a hydrogen atmosphere at 45°C for 12 hours. The reaction solution was filtrated, and concentrated to obtain 1-((8S,9S,13S,14S,17S)-3-hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl)-2-(1H-1,2,3-triazol-1-yl)ethan-1-one (30 mg, white solid, yield: 62.6%).

MS m/z (ESI):366.1 [M+H]+.

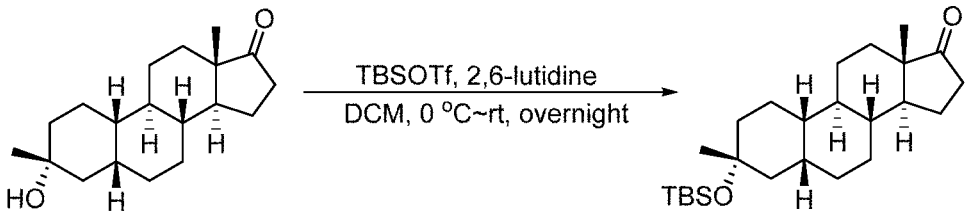
1H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.67 (s, 1H), 7.15 (d, J = 8.0 Hz, 1H), 6.65 (dd, J = 6.4, 2.4 Hz, 1H), 6.60-6.56 (m, 1H), 5.40-5.15 (m, 2H), 5.04 (s, 1H), 2.89-2.70 (m, 3H), 2.40 – 2.21 (m, 3H), 1.96 – 1.27 (m, 10H), 0.71 (s, 3H).

Example 159

((3R,5R,8R,9R,10S,13S,14S,17S)-3-Hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)dimethylphosphine oxide (159)



Step 1: Preparation of (3R,5R,8R,9R,10S,13S,14S)-3-((*tert*-butyldimethylsilyl)oxy)-3,13-dimethylhexadecahydro-17H-cyclopenta[a]phenanthren-17-one

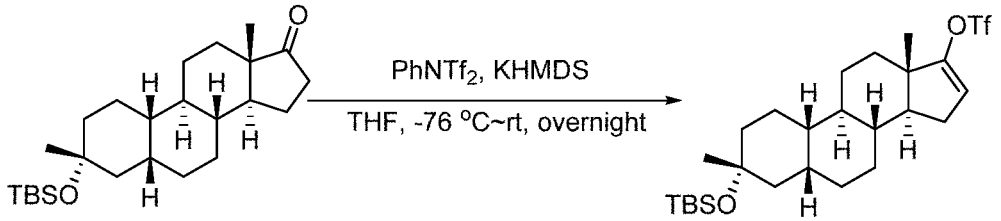


(3R,5R,8R,9R,10S,13S,14S)-3-Hydroxy-3,13-dimethylhexadecahydro-17H-cyclopenta[a]phenanthren-17-one (5 g, 17 mmol) (Shanghai Yinling Pharmaceutical Technology Co., Ltd.), 2,6-lutidine (4.5 g, 42.5 mmol) and anhydrous dichloromethane (80 mL) were successively added to a 100 mL round bottom flask. The reaction system was cooled to 0°C in an ice water bath, and *tert*-butyldimethylsilyl trifluoromethanesulfonate (9 g, 34 mmol) was added dropwise. The reaction system was

warmed up to room temperature and stirred overnight. TLC showed that the reaction was completed. The reaction solution was diluted with dichloromethane. The organic phase was washed with water and saturated saline, dried over anhydrous sodium sulfate, filtrated and concentrated by rotary evaporation to dryness. The resulting crude product was purified by column chromatography (petroleum ether:ethyl acetate=20:1) to obtain (3R,5R,8R,9R,10S,13S,14S)-3-((*tert*-butyldimethylsilyl)oxy)-3,13-dimethylhexadecahydro-17H-cyclopenta[a]phenanthren-17-one (6.2 g, yield: 90.1%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (dd, J = 18.8, 8.0 Hz, 1H), 2.06-1.97 (m, 1H), 1.90-1.84 (m, 1H), 1.75-1.68 (m, 5H), 1.59-1.55 (m, 1H), 1.47-0.89 (m, 17H), 0.80 (s, 3H), 0.79 (s, 9H), 0.00 (m, 6H).

Step 2: Preparation of (3R,5R,8R,9R,10S,13S,14S)-3-((*tert*-butyldimethylsilyl)oxy)-3,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl trifluoromethanesulfonate

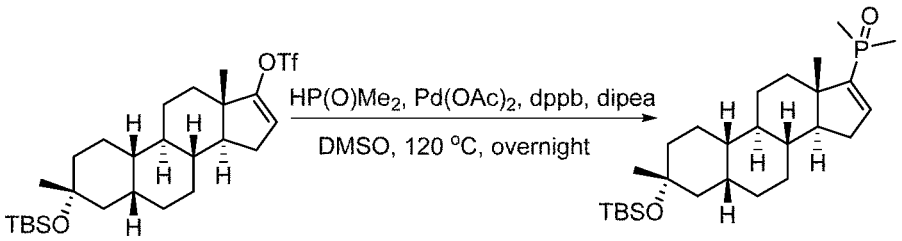


(3R,5R,8R,9R,10S,13S,14S)-3-((*tert*-butyldimethylsilyl)oxy)-3,13-dimethylhexadecahydro-17H-cyclopenta[a]phenanthren-17-one (1.2 g, 3 mmol) and 50 ml of anhydrous tetrahydrofuran were successively added to a 100 mL round bottom flask. The reaction system was cooled to -78°C, and a solution of potassium hexamethyldisilazide in tetrahydrofuran (3 mL, 3 mmol) was added dropwise to the reaction system. The reaction solution was stirred at -78°C for 1 hour, and then N-phenylbis(trifluoromethanesulfonimide) (1.29 g, 3.6 mmol) dissolved in 5 ml of anhydrous tetrahydrofuran was added dropwise to the reaction system. After completion of the addition, the reaction solution was warmed naturally up to room temperature and stirred overnight. After completion of the reaction, saturated ammonium chloride solution was added to quench the reaction, and the reaction solution was extracted with ethyl acetate. The organic phase was washed with water and saturated saline, dried over anhydrous sodium sulfate, filtrated and concentrated by rotary evaporation to dryness. The resulting crude product was purified by column chromatography (eluent: petroleum ether) to obtain (3R,5R,8R,9R,10S,13S,14S)-3-((*tert*-butyldimethylsilyl)oxy)-3,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl trifluoromethanesulfonate (1.4 g, yield: 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (s, 1H), 2.27-2.18 (m, 1H), 2.00-1.93 (m, 1H), 1.80-1.61 (m, 7H), 1.49-1.23 (m, 15H), 0.97 (s, 3H), 0.86 (s, 9H), 0.08 (s, 6H).

Step 3: Preparation of ((3R,5R,8R,9R,10S,13S,14S)-3-((*tert*-butyldimethylsilyl)oxy)-3,13-dimethyl-2,3,4,5,6,

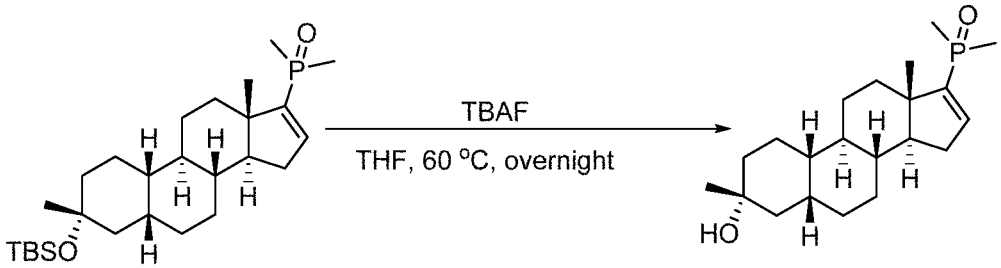
7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)dimethylphosphine oxide



(3R,5R,8R,9R,10S,13S,14S)-3-((*tert*-butyldimethylsilyl)oxy)-3,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl trifluoromethanesulfonate (840 mg, 1.57 mmol), dimethylphosphine oxide (146 mg, 1.89 mmol), palladium diacetate (35 mg, 0.16 mmol), 1,4-bis(diphenylphosphino)butane (69 mg, 0.16 mmol), N,N-diisopropylethylamine (1.6 g, 12.6 mmol) and 10 ml of anhydrous dimethyl sulfoxide were successively added to a 100 mL round bottom flask. The reaction system was purged with nitrogen, slowly warmed up to 120°C and stirred overnight. After completion of the reaction, the reaction system was cooled to room temperature. Water was added to quench the reaction, and the reaction solution was extracted with ethyl acetate. The organic phase was washed with water and saturated saline, dried over anhydrous sodium sulfate, filtrated and concentrated by rotary evaporation to dryness.The resulting crude product was purified by column chromatography (eluent: dichloromethane/methanol=10/1) to obtain ((3R,5R,8R,9R,10S,13S,14S)-3-((*tert*-butyldimethylsilyl)oxy)-3,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)dimethylphosphine oxide (642 mg, yield: 88%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (dd, J =10.8, 1.6 Hz, 1H), 2.33-2.27 (m, 1H), 2.11-2.01 (m, 2H), 1.66-1.58 (m, 12H), 1.48-1.1.13 (m, 15H), 1.00 (s, 3H), 0.86 (s, 9H), 0.07 (s, 6H).

Step 4: Preparation of ((3R,5R,8R,9R,10S,13S,14S)-3-hydroxy-3,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)dimethylphosphine oxide

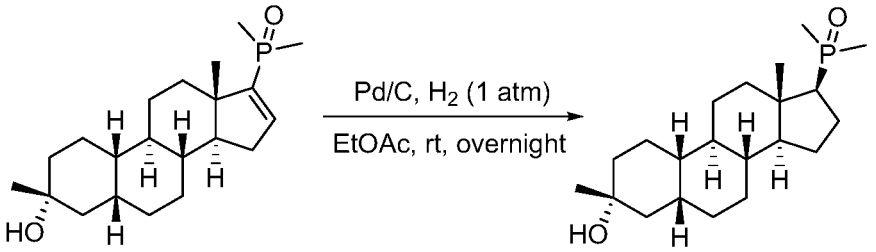


((3R,5R,8R,9R,10S,13S,14S)-3-((*tert*-butyldimethylsilyl)oxy)-3,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)dimethylphosphine oxide (642 mg, 1.38 mmol) was dissolved in 5 mL of anhydrous tetrahydrofuran in a 100 mL round bottom flask, and a 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran (5 mL) was added to the reaction

system. The reaction solution was stirred at 60°C overnight. After completion of the reaction, the reaction system was cooled to room temperature. Water was added to quench the reaction, and the reaction solution was extracted with ethyl acetate. The organic phase was washed with water and saturated saline, dried over anhydrous sodium sulfate, filtrated and concentrated by rotary evaporation to dryness. The resulting crude product was purified by column chromatography (eluent: dichloromethane/methanol=10/1) to obtain ((3R,5R,8R,9R,10S,13S,14S)-3-hydroxy-3,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)dimethylphosphine oxide (170 mg, yield: 35%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57-6.54 (m, 1H), 2.45 (br, 1H), 2.35-2.28 (m, 1H), 2.12-2.00 (m, 2H), 1.87-1.70 (m, 4H), 1.67-1.14 (m, 23H), 1.00 (s, 3H).

Step 5: Preparation of ((3R,5R,8R,9R,10S,13S,14S,17S)-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)dimethylphosphine oxide



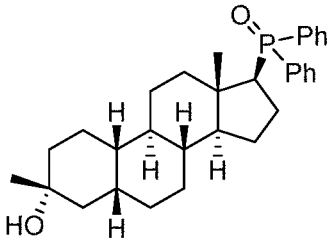
((3R,5R,8R,9R,10S,13S,14S)-3-Hydroxy-3,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)dimethylphosphine oxide (100 mg, 0.29 mmol), palladium on carbon (100 mg, 10%) and 10 mL of ethyl acetate were added to a 100 mL round bottom flask. The reaction system was purged with hydrogen three times, and reacted at 1 atmosphere overnight. After completion of the reaction, the reaction solution was filtrated through celite to remove excess palladium on carbon, and the filtrate was concentrated by rotary evaporation to dryness. The resulting crude product was purified by high performance liquid chromatography to obtain ((3R,5R,8R,9R,10S,13S,14S,17S)-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)dimethylphosphine oxide (39.5 mg, yield: 39%).

MS m/z (ESI): 353.3 $[M+H]^+$.

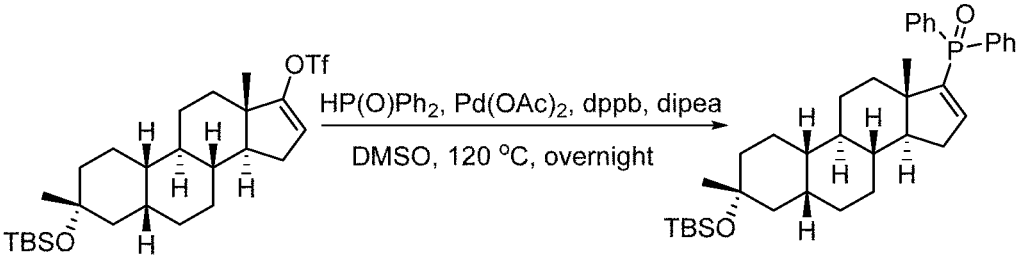
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.13-1.62 (m, 22H), 1.35-1.27 (m, 8H), 1.16-1.06 (m, 4H), 0.99 (s, 3H).

Example 160

((3R,5R,8R,9R,10S,13S,14S,17S)-3-Hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)diphenylphosphine oxide (160)



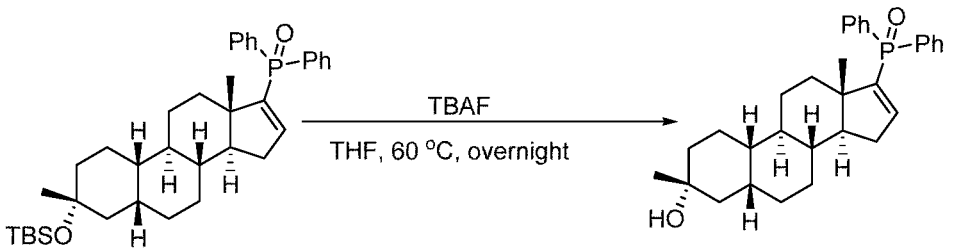
Step 1: Preparation of ((3R,5R,8R,9R,10S,13S,14S)-3-((*tert*-butyldimethylsilyl)oxy)-3,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)diphenylphosphine oxide



(3R,5R,8R,9R,10S,13S,14S)-3-((*tert*-butyldimethylsilyl)oxy)-3,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl trifluoromethanesulfonate (350 mg, 0.65 mmol), diphenylphosphine oxide (158 mg, 0.78 mmol), palladium diacetate (35 mg, 0.16 mmol), 1,4-bis(diphenylphosphino)butane (69 mg, 0.16 mmol), N,N-diisopropylethylamine (660 mg, 5.2 mmol) and 10 ml of anhydrous dimethyl sulfoxide were successively added to a 100 mL round bottom flask. The reaction system was purged with nitrogen, slowly warmed up to 120°C and stirred overnight. After completion of the reaction, the reaction system was cooled to room temperature. Water was added to quench the reaction, and the reaction solution was extracted with ethyl acetate. The organic phase was washed with water and saturated saline, dried over anhydrous sodium sulfate, filtrated and concentrated by rotary evaporation to dryness. The resulting crude product was purified by column chromatography (eluent: dichloromethane/methanol=10/1) to obtain ((3R,5R,8R,9R,10S,13S,14S)-3-((*tert*-butyldimethylsilyl)oxy)-3,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)diphenylphosphine oxide (290 mg, 76%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.80 (m, 2H), 7.67-7.62 (m, 2H), 7.59-7.40 (m, 6H), 6.01-5.98 (m, 1H), 2.31-2.25 (m, 1H), 2.09-2.02 (m, 2H), 1.89-1.10 (m, 21H), 1.07 (s, 3H), 0.86 (s, 9H), 0.07 (s, 6H).

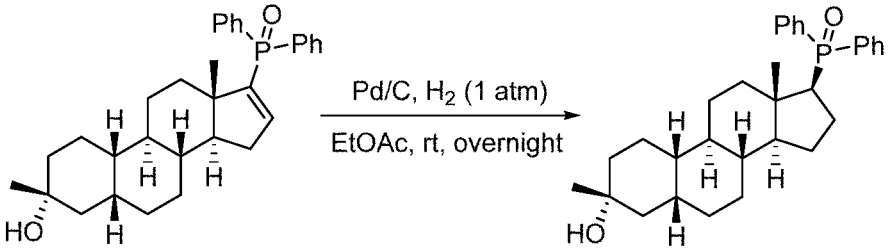
Step 2: Preparation of ((3R,5R,8R,9R,10S,13S,14S)-3-hydroxy-3,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)diphenylphosphine oxide



((3R,5R,8R,9R,10S,13S,14S)-3-((*tert*-butyldimethylsilyl)oxy)-3,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)diphenylphosphine oxide (270 mg, 0.46 mmol) was dissolved in 5 mL of anhydrous tetrahydrofuran in a 100 mL round bottom flask, and a 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran (5 mL) was added to the reaction system. The reaction solution was stirred at 60°C overnight. After completion of the reaction, the reaction system was cooled to room temperature. Water was added to quench the reaction, and the reaction solution was extracted with ethyl acetate. The organic phase was washed with water and saturated saline, dried over anhydrous sodium sulfate, filtrated and concentrated by rotary evaporation to dryness. The resulting crude product was purified by column chromatography (eluent: dichloromethane/methanol=10/1) to obtain ((3R,5R,8R,9R,10S,13S,14S)-3-hydroxy-3,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)diphenylphosphine oxide (120 mg, yield: 55%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57-6.54 (m, 1H), 2.45 (br, 1H), 2.35-2.28 (m, 1H), 2.12-2.00 (m, 2H), 1.87-1.70 (m, 4H), 1.67-1.14 (m, 26H), 1.00 (s, 3H).

Step 3: Preparation of ((3R,5R,8R,9R,10S,13S,14S,17S)-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)diphenylphosphine oxide



((3R,5R,8R,9R,10S,13S,14S)-3-Hydroxy-3,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)diphenylphosphine oxide (120 mg, 0.25 mmol), palladium on carbon (120 mg, 10%) and 10 mL of ethyl acetate were added to a 100 mL round bottom flask. The reaction system was purged with hydrogen three times, and reacted at 1 atmosphere overnight. After completion of the reaction, the reaction solution was filtrated through celite to remove excess palladium on carbon, and the filtrate was concentrated by rotary evaporation to dryness. The resulting crude product was purified by high performance liquid chromatography to obtain

((3R,5R,8R,9R,10S,13S,14S,17S)-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)diphenylphosphine oxide (40 mg, yield: 33%).

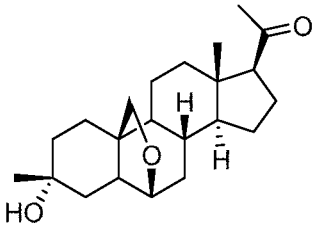
MS m/z (ESI): 477.3 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.83 (m, 4H), 7.54-7.44 (m, 6H), 2.37-2.15 (m, 2H), 2.11-2.09 (m, 1H), 2.07-1.95 (m, 6H), 1.84-1.04 (m, 22H).

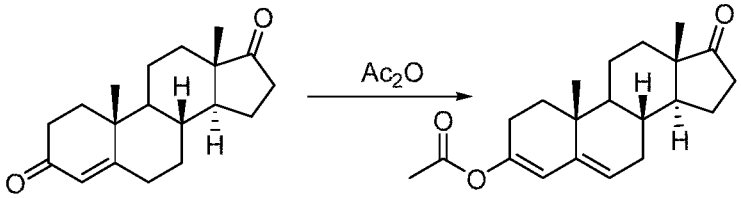
^{31}P NMR (162 MHz, $CDCl_3$) δ 30.00.

Example 161

1-((3R,6R,8S,10S,13S,14S,17S)-3-Hydroxy-3,13-dimethylhexadecahydro-6,10-(epoxymethano)cyclopenta[a]phenanthren-17-yl)ethan-1-one (161)



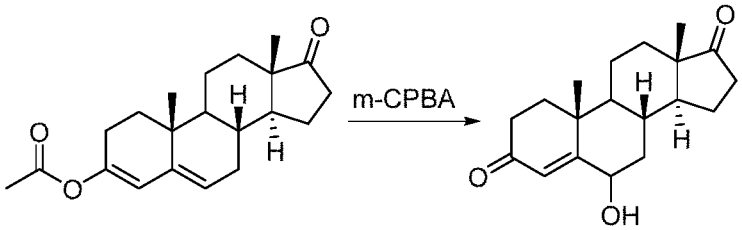
Step 1: Preparation of (8R,10R,13S,14S)-10,13-dimethyl-17-oxo-2,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl acetate



(8R,10R,13S,14S)-10,13-Dimethyl-1,6,7,8,9,10,11,12,13,14,15,16-dodecahydro-3H-cyclopenta[a]phenanthrene-3,17(2H)-dione (19.0 g, 66.43 mmol) was dissolved in ethyl acetate (500 mL), and acetic anhydride (100 mL) and perchloric acid (0.5 mL) were added. The reaction solution was stirred at room temperature for 1 hour, and TLC showed that the reaction was completed. Saturated sodium carbonate solution (300 mL) was added to the reaction solution. The organic phase was washed with saturated sodium carbonate solution (300 mL*2) and saturated saline (300 mL), dried over anhydrous sodium sulfate and concentrated. The resulting residue was purified by silica gel column chromatography (ethyl acetate: petroleum ether=0-40%) to obtain (8R,10R,13S,14S)-10,13-dimethyl-17-oxo-2,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl acetate (13.0 g, yield: 59.7%).

1H NMR (400 MHz, CDCl3) δ: 5.71 (s, 1H), 5.42 (t, J = 2.4 Hz, 1H), 2.51-2.43 (m, 2H), 2.34-2.27 (m, 1H), 2.18-2.04 (m, 5H), 2.00-1.69 (m, 6H), 1.62-1.27 (m, 5H), 1.13-1.06 (m, 1H), 1.03 (s, 3H), 0.92 (s, 3H).

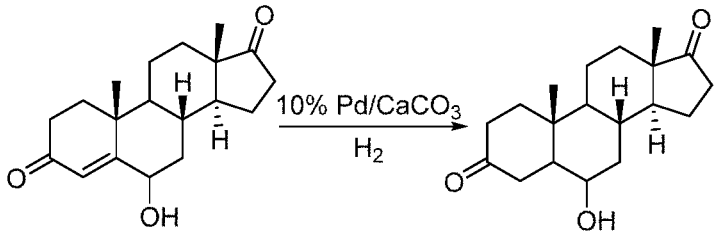
Step 2: Preparation of (8R,10R,13S,14S)-6-hydroxy-10,13-dimethyl-1,6,7,8,9,10,11,12,13,14,15,16-dodecahydro-3H-cyclopenta[a]phenanthrene-3,17(2H)-dione



(8R,10R,13S,14S)-10,13-Dimethyl-17-oxo-2,7,8,9,10,11,12,13,14,15,16,17-dodeca hydro-1H-cyclopenta[a]phenanthren-3-yl acetate (5.0 g, 15.24 mmol) was dissolved in ethanol (180 mL), and m-chloroperoxybenzoic acid (5.0 g, 24.71 mmol) was added. The reaction solution was stirred at room temperature for 3 hours, and LC/MS showed that the reaction was completed. Saturated sodium carbonate solution (200 mL) was added, and then the reaction solution was extracted with ethyl acetate (300 mL). The organic phase was washed with saturated sodium carbonate solution (200 mL*2) and saturated saline (200 mL), dried over anhydrous sodium sulfate and concentrated to obtain (8R,10R,13S,14S)-6-hydroxy-10,13-dimethyl-1,6,7,8,9,10,11,12,13,14,15,16-dodecahy dro-3H-cyclopenta[a]phenanthrene-3,17(2H)-dione (3.5 g, yield: 76.0%).

MS m/z (ESI): 303.0 $[M+H]^+$.

Step 3: Preparation of (8R,10R,13S,14S)-6-hydroxy-10,13-dimethyltetradecahydro-3H-cyclopenta[a]phenanth rene-3,17(2H)-dione

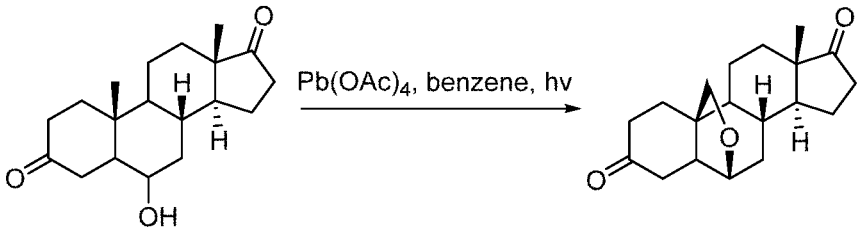


(8R,10R,13S,14S)-6-Hydroxy-10,13-dimethyl-1,6,7,8,9,10,11,12,13,14,15,16-dode cahydro-3H-cyclopenta[a]phenanthrene-3,17(2H)-dione (8.0 g, 26.5 mmol) was dissolved in pyridine (50 mL), and 10% Pd Lindlar's catalyst (2.0 g) was added to the above solution. The reaction system was equipped with a hydrogen balloon and purged with hydrogen three times, and stirred at room temperature for 16 hours. The reaction solution was filtrated, and the filter cake was washed with ethyl acetate (30 mL). The filtrate was diluted with ethyl acetate (200 mL), and washed with 1N hydrochloric acid (100 mL*2). The organic phase was washed with saturated saline (100 mL), dried over anhydrous sodium sulfate and concentrated. The resulting residue was purified by silica gel column chromatography (ethyl acetate: petroleum ether=1:1) to obtain (8R,10R,13S,14S)-6-hydroxy-10,13-dimethyltetradecahydro-3H-cyclopenta[a]phenanth rene-3,17(2H)-dione (2.0 g, yield: 25.0%).

1H NMR (400 MHz, DMSO-*d6*) δ: 4.60 (s, 1H), 3.51(m, 1H), 2.45-2.31 (m, 3H), 2.06-1.82 (m, 7H), 1.69-1.51 (m, 5H), 1.48-1.23 (m, 5H), 1.14 (s, 3H), 0.82 (s, 3H).

Step 4: Preparation of (6R,8R,10S,13S,14S)-13-methyltetradecahydro-6,10-(epoxymethano)cyclopenta[a]phen

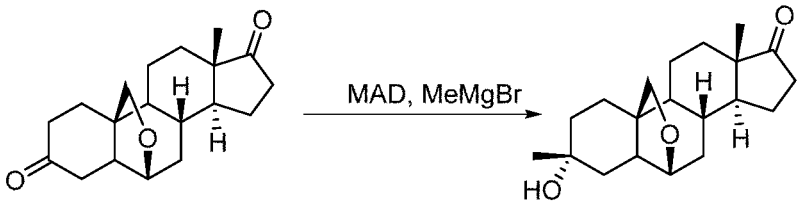
anthrene-3,17-dione



(8R,10R,13S,14S)-6-Hydroxy-10,13-dimethyltetradecahydro-3H-cyclopenta[a]phenanthrene-3,17(2H)-dione (1.0 g, 3.29 mmol) was dissolved in benzene (50 mL)/pyridine (0.8 mL), and lead tetraacetate (7.3 g, 16.5 mmol) was added to the above solution. The reaction solution was stirred under an incandescent lamp (500W) for 2 hours, and the reaction was then stopped. Ethyl acetate (100mL) was added to the reaction solution to precipitate a large amount of solid, and the reaction solution was then filtrated. The filtrate was washed with 1N hydrochloric acid (50 mL*2). The organic phase was washed with saturated saline (50 mL), dried over anhydrous sodium sulfate and concentrated. The resulting residue was purified by silica gel column chromatography (ethyl acetate: petroleum ether=1:2) to obtain (6R,8R,10S,13S,14S)-13-methyltetradecahydro-6,10-(epoxymethano)cyclopenta[a]phenanthrene-3,17-dione (600 mg, yield: 60.0%).

1H NMR (400 MHz, $CDCl_3$) δ: 4.25-4.22 (m, 1H), 4.06 (d, J = 8.4Hz, 1H,), 3.39 (d, J = 8.4 Hz, 1H), 2.63-2.44 (m, 3H), 2.35-2.06 (m, 5H), 1.98-1.80 (m, 4H), 1.72-1.24 (m, 8H), 0.96 (s, 3H).

Step 5: Preparation of (3R,6R,8R,10S,13S,14S)-3-hydroxy-3,13-dimethyltetradecahydro-6,10-(epoxymethano)cyclopenta[a]phenanthren-17(1H)-one

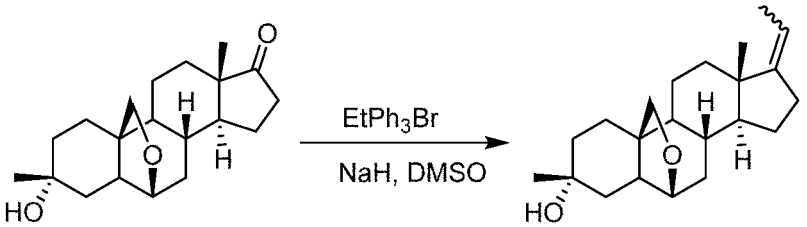


2,6-Di-*tert*-butyl-*p*-methylphenol (3.5 g, 15.9 mmol) and toluene (35 mL) were added to a three-neck flask. 2M trimethylaluminum (4 mL, 8 mmol) was added dropwise at 0-10°C under a nitrogen atmosphere. After completion of the addition, the reaction solution was stirred at room temperature for 1 hour. The reaction solution was cooled to -78°C in a dry ice/acetone bath, and (6R,8R,10S,13S,14S)-13-methyltetradecahydro-6,10-(epoxymethano)cyclopenta[a]phenanthrene-3,17-dione (0.8 g, 2.65 mmol) dissolved in toluene (30 mL) was added dropwise, and then the reaction solution was reacted at -78°C for 1 hour. 3M methylmagnesium bromide (2.3 mL, 6.9 mmol) was added, and then the reaction solution was reacted at -78°C for 1 hour. Saturated ammonium chloride solution (50 mL) was added, and then the reaction solution was extracted with ethyl acetate (120 mL). The organic phase was washed with saturated saline (50 mL), dried over anhydrous

sodium sulfate and concentrated. The resulting residue was purified by silica gel column chromatography (ethyl acetate: petroleum ether=1:1) to obtain (3R,6R,8R,10S,13S,14S)-3-hydroxy-3,13-dimethyltetradecahydro-6,10-(epoxymethano)cyclopenta[a]phenanthren-17(1H)-one (400 mg, yield: 47.5%).

1H NMR (400 MHz, $CDCl_3$) δ: 4.15-4.12 (m, 1H), 3.96 (d, J = 8.0 Hz, 1H), 3.32 (d, J = 8.0 Hz, 1H), 2.48-2.41 (m, 1H), 2.13-2.03 (m, 1H), 1.92-1.79 (m, 5H), 1.75-1.63 (m, 3H), 1.60-1.43 (m, 6H), 1.38-1.10 (m, 7H), 0.92 (s, 3H).

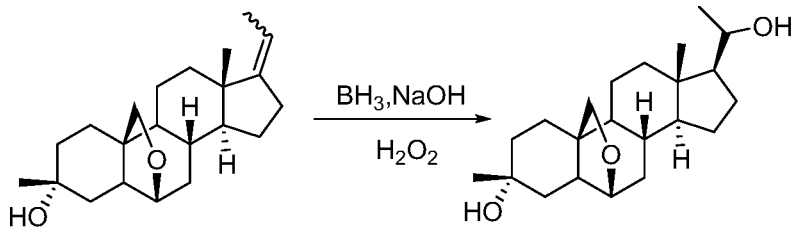
Step 6: Preparation of (3R,6R,8S,10S,13S,14S)-17-ethylidene-3,13-dimethylhexadecahydro-6,10-(epoxymethano)cyclopenta[a]phenanthren-3-ol



Ethyltriphenylphosphonium bromide (11.65 g, 31.4 mmol) was dissolved in dimethyl sulfoxide (25 mL). 60% sodium hydrogen (1.26 g, 31.4 mmol) was added, and then the reaction solution was stirred at room temperature under a nitrogen atmosphere for 1 hour. (3R,6R,8R,10S,13S,14S)-3-Hydroxy-3,13-dimethyltetradecahydro-6,10-(epoxymethano)cyclopenta[a]phenanthren-17(1H)-one (0.5 g, 1.57 mmol) dissolved in dimethyl sulfoxide (5 mL) was added, and then the reaction solution was heated to 60°C and reacted for 16 hours. Saturated ammonium chloride solution (50 mL) was added, and then the reaction solution was extracted with ethyl acetate (60 mL). The organic phase was washed with saturated sodium carbonate solution (50 mL*2) and saturated saline (50 mL) successively, dried over anhydrous sodium sulfate and concentrated. The resulting residue was purified by silica gel column chromatography (ethyl acetate: petroleum ether=1:3) to obtain (3R,6R,8S,10S,13S,14S)-17-ethylidene-3,13-dimethylhexadecahydro-6,10-(epoxymethano)cyclopenta[a]phenanthren-3-ol (350 mg, yield 67.6%).

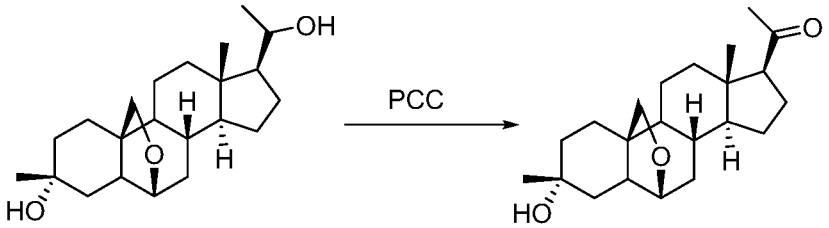
1H NMR (400 MHz, $CDCl_3$) δ: 5.12-5.09 (m, 1H), 4.15-4.12 (m, 1H), 3.96 (d, J = 8.0 Hz, 1H), 3.26 (d, J = 8.0 Hz, 1H), 2.39-2.13 (m, 3H), 1.91-1.85 (m, 3H), 1.70-1.50 (m, 12H), 1.30-1.07 (m, 8H), 0.91 (s, 3H).

Step 7: Preparation of (3R,6R,8S,10S,13S,14S,17S)-17-((S)-1-hydroxyethyl)-3,13-dimethylhexadecahydro-6,10-(epoxymethano)cyclopenta[a]phenanthren-3-ol



(3R,6R,8S,10S,13S,14S)-17-Ethylidene-3,13-dimethylhexadecahydro-6,10-(epoxy methano)cyclopenta[a]phenanthren-3-ol (250 mg, 0.76 mmol) was dissolved in tetrahydrofuran (8 mL), and the solution was cooled to 0°C. A solution of borane in tetrahydrofuran (1 M, 15 mL, 15 mmol) was added, and the reaction solution was stirred at room temperature for 3 hours. The reaction solution was cooled to 0°C, and sodium hydroxide (3M, 10 mL) was added dropwise. After completion of the dropwise addition, hydrogen peroxide (30%, 8 mL) was added, and the reaction solution was stirred at room temperature for 1 hour. The reaction solution was diluted with ethyl acetate (60 mL), and washed with saturated sodium thiosulfate solution (30 mL). The organic phase was washed with saturated saline (50 mL), dried over anhydrous sodium sulfate, and concentrated to obtain (3R,6R,8S,10S,13S,14S,17S)-17-((S)-1-hydroxyethyl)-3,13-dimethylhexadecahydro-6, 10-(epoxymethano)cyclopenta[a]phenanthren-3-ol (260 mg, yield: 100%), which was used directly in the next step without further purification.

Step 8: Preparation of 1-((3R,6R,8S,10S,13S,14S,17S)-3-hydroxy-3,13-dimethylhexadecahydro-6,10-(epoxy methano)cyclopenta[a]phenanthren-17-yl)ethan-1-one

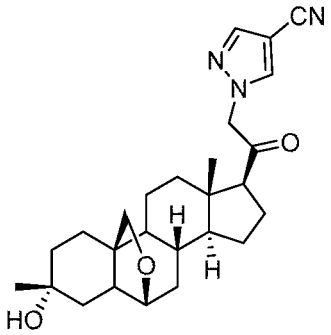


(3R,6R,8S,10S,13S,14S,17S)-17-((S)-1-hydroxyethyl)-3,13-dimethylhexadecahydr o-6,10-(epoxymethano)cyclopenta[a]phenanthren-3-ol (260 mg, 0.75 mmol) was dissolved in dichloromethane (10 mL), and the solution was cooled to 0°C. PCC (322 mg, 1.5 mmol) was added, and then the reaction solution was stirred at room temperature for 3 hours. TLC showed that the reaction was completed. The reaction solution was filtrated, and the filter cake was washed with ethyl acetate (20 mL). The filtrate was diluted with ethyl acetate (30 mL), and washed with saturated sodium thiosulfate solution (30 mL). The organic phase was washed with saturated saline (50 mL), dried over anhydrous sodium sulfate and concentrated. The resulting residue was purified by silica gel column chromatography (ethyl acetate: petroleum ether=1:2) to obtain 1-((3R,6R,8S,10S,13S,14S,17S)-3-hydroxy-3,13-dimethylhexadecahydro-6,10-(epoxy methano)cyclopenta[a]phenanthren-17-yl)ethan-1-one (150 mg, yield: 57.8%).

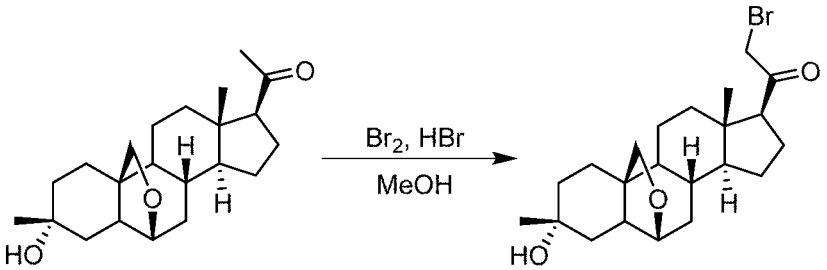
1H NMR (400 MHz, $CDCl_3$) δ: 4.14-4.12 (m, 1H), 3.94 (d, J = 7.6 Hz, 1H), 3.27 (d, J = 7.6 Hz, 1H), 2.53 (t, J = 8.8 Hz, 1H), 2.18-2.04 (m, 5H), 1.91-1.86 (m, 3H), 1.70-1.49 (m, 10H), 1.34-1.49 (m, 8H), 0.66 (s, 3H).

Example 162

1-(2-((3R,6R,8S,10S,13S,14S,17S)-3-Hydroxy-3,13-dimethylhexadecahydro-6,10-(epoxymethano)cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile (162)

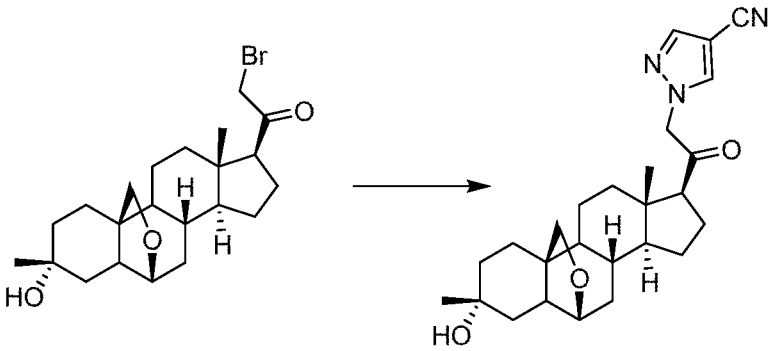


Step 1: Preparation of 2-bromo-1-((3R,6R,8S,10S,13S,14S,17S)-3-hydroxy-3,13-dimethylhexadecahydro-6,10-(epoxymethano)cyclopenta[a]phenanthren-17-yl)ethan-1-one



1-((3R,6R,8S,10S,13S,14S,17S)-3-Hydroxy-3,13-dimethylhexadecahydro-6,10-(epoxymethano)cyclopenta[a]phenanthren-17-yl)ethan-1-one (135 mg, 0.39 mmol) was dissolved in methanol (6 mL). A drop of hydrogen bromide was added, followed by the addition of 5 drops of liquid bromine under stirring at room temperature, and then the reaction solution was stirred at room temperature for 1 hour. TLC showed that the reaction was completed. Saturated sodium bicarbonate solution (30 mL) was added, and then the reaction solution was extracted with ethyl acetate (50 mL). The organic phase was washed with saturated saline (50 mL), dried over anhydrous sodium sulfate, and concentrated to obtain 2-bromo-1-((3R,6R,8S,10S,13S,14S,17S)-3-hydroxy-3,13-dimethylhexadecahydro-6,10-(epoxymethano)cyclopenta[a]phenanthren-17-yl)ethan-1-one (160 mg, yield: 96.5%), which was used directly in the next step without further purification.

Step 2: Preparation of 1-(2-((3R,6R,8S,10S,13S,14S,17S)-3-hydroxy-3,13-dimethylhexadecahydro-6,10-(epoxymethano)cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile



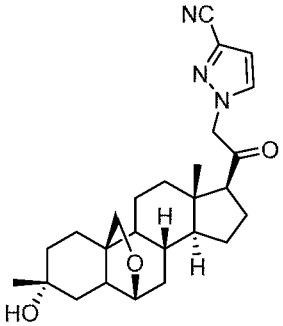
2-Bromo-1-((3R,6R,8S,10S,13S,14S,17S)-3-hydroxy-3,13-dimethylhexadecahydro-6,10-(epoxymethano)cyclopenta[a]phenanthren-17-yl)ethan-1-one (85 mg, 0.2 mmol) and 4-cyanopyrazole (92 mg, 1.0 mmol) were dissolved in tetrahydrofuran (5 mL), and potassium carbonate (138 mg, 1.0 mmol) was added. The reaction solution was stirred at room temperature for 16 hours, and TLC and LCMS showed that the reaction was completed. The reaction solution was filtrated and concentrated. The resulting residue was purified by flash preparative chromatography to obtain 1-(2-((3R,6R,8S,10S,13S,14S,17S)-3-hydroxy-3,13-dimethylhexadecahydro-6,10-(epoxymethano)cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile (29.7 mg, yield: 34.0%).

MS m/z (ESI): 438.3 [M+H]+.

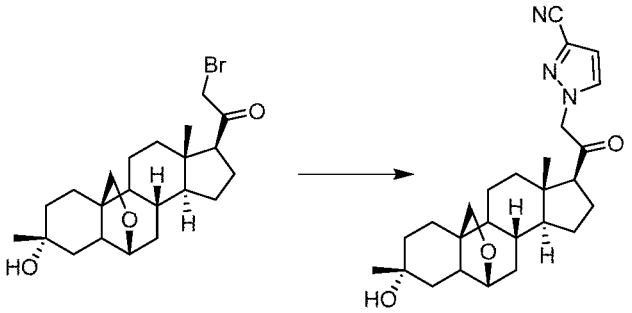
1H NMR (400 MHz, CDCl3) δ: 7.87 (s, 1H), 7.81 (s, 1H), 5.01-4.87 (m, 2H), 4.15-4.12 (m, 1H), 3.93 (d, J = 8.4 Hz, 1H), 3.28 (d, J = 8.4 Hz, 1H), 2.60 (t, J =6.8 Hz, 1H), 2.22-2.08 (m, 2H), 1.91-1.49 (m, 13H), 1.39-1.24 (m, 6H), 1.19-1.13 (m, 2H), 0.72 (s, 3H).

Example 163

1-(2-((3R,6R,8S,10S,13S,14S,17S)-3-Hydroxy-3,13-dimethylhexadecahydro-6,10-(epoxymethano)cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-3-carbonitrile (163)



Preparation of 1-(2-((3R,6R,8S,10S,13S,14S,17S)-3-Hydroxy-3,13-dimethylhexadecahydro-6,10-(epoxymethano)cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-3-carbonitrile



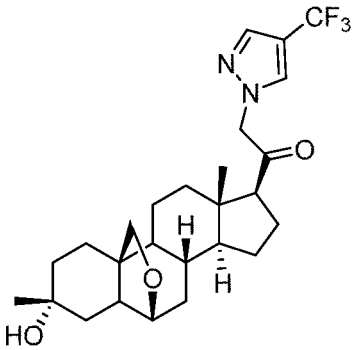
2-Bromo-1-((3R,6R,8S,10S,13S,14S,17S)-3-hydroxy-3,13-dimethylhexadecahydro-6,10-(epoxymethano)cyclopenta[a]phenanthren-17-yl)ethan-1-one (80 mg, 0.19 mmol) and 3-cyanopyrazole (88 mg, 0.95 mmol) were dissolved in tetrahydrofuran (5 mL), and potassium carbonate (130 mg, 0.95 mmol) was added. The reaction solution was stirred at room temperature for 16 hours, and TLC and LCMS showed that the reaction was completed. The reaction solution was filtrated and concentrated. The resulting residue was purified by flash preparative chromatography to obtain 1-(2-((3R,6R,8S,10S,13S,14S,17S)-3-Hydroxy-3,13-dimethylhexadecahydro-6,10-(epoxymethano)cyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-3-carbonitrile (36.5 mg, yield: 44.4%).

MS m/z (ESI): 438.3 [M+H]+.

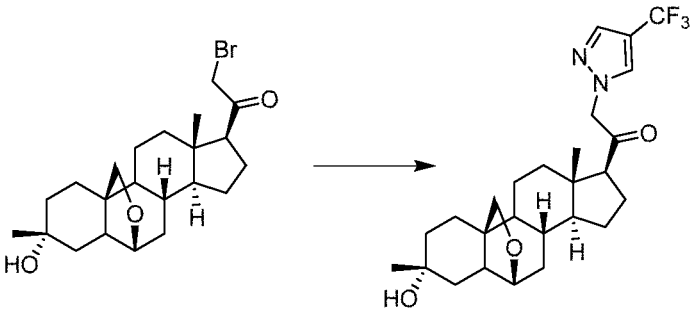
1H NMR (400 MHz, $CDCl_3$) δ: 7.49 (d, J = 2.0 Hz, 1H), 7.76 (d, J = 2.0 Hz, 1H), 5.10-4.90 (m, 2H), 4.15-4.12 (m, 1H), 3.94 (d, J = 8.0 Hz, 1H), 3.28 (d, J = 8.0 Hz, 1H), 2.60 (t, J =8.8 Hz, 1H), 2.21-2.09 (m, 2H), 1.91-1.50 (m, 13H), 1.39-1.24 (m, 6H), 1.19-1.13 (m, 2H), 0.72 (s, 3H).

Example 164

1-((3R,6R,8S,10S,13S,14S,17S)-3-Hydroxy-3,13-dimethylhexadecahydro-6,10-(epoxymethano)cyclopenta[a]phenanthren-17-yl)-2-(4-(trifluoromethyl)-1H-pyrazol-1-yl)ethan-1-one (164)



Preparation of 1-((3R,6R,8S,10S,13S,14S,17S)-3-hydroxy-3,13-dimethylhexadecahydro-6,10-(epoxymethano)cyclopenta[a]phenanthren-17-yl)-2-(4-(trifluoromethyl)-1H-pyrazol-1-yl)ethan-1-one



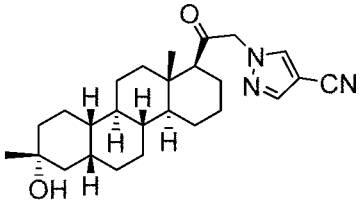
2-Bromo-1-((3R,6R,8S,10S,13S,14S,17S)-3-hydroxy-3,13-dimethylhexadecahydro-6,10-(epoxymethano)cyclopenta[a]phenanthren-17-yl)ethan-1-one (80 mg, 0.19 mmol) and 4-trifluoromethylpyrazole (128 mg, 0.95 mmol) were dissolved in tetrahydrofuran (5 mL), and potassium carbonate (130 mg, 0.95 mmol) was added. The reaction solution was stirred at room temperature for 16 hours, and TLC and LCMS showed that the reaction was completed. The reaction solution was filtrated and concentrated. The resulting residue was purified by flash preparative chromatography to obtain 1-((3R,6R,8S,10S,13S,14S,17S)-3-hydroxy-3,13-dimethylhexadecahydro-6,10-(epoxy methano)cyclopenta[a]phenanthren-17-yl)-2-(4-(trifluoromethyl)-1H-pyrazol-1-yl)ethan-1-one (29.5 mg, yield: 32.7%).

MS m/z (ESI): 481.2 [M+H]+.

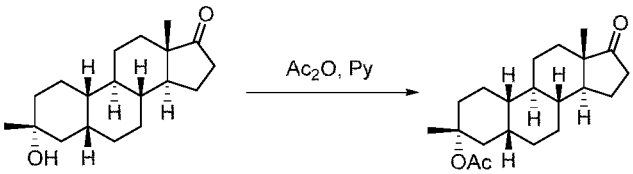
1H NMR (400 MHz, $CDCl_3$) δ: 7.72 (s, 2H), 5.01-4.87 (m, 2H), 4.15-4.12 (m, 1H), 3.94 (d, J = 8.0 Hz, 1H), 3.28 (d, J = 8.0 Hz, 1H), 2.60 (t, J =8.8 Hz, 1H), 2.22-2.09 (m, 2H), 1.91-1.49 (m, 13H), 1.39-1.24 (m, 6H), 1.19-1.13 (m, 2H), 0.73 (s, 3H).

Example 165

1-(2-((1S,4aS,4bR,6aR,8R,10aS,10bR,12aS)-8-Hydroxy-8,12a-dimethyloctadecahydrochrysen-1-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile (165)



Step 1: Preparation of (3R,5R,8R,9R,10S,13S,14S)-3,13-dimethyl-17-oxohexadecahydro-1H-cyclopenta[a]phenanthren-3-yl acetate

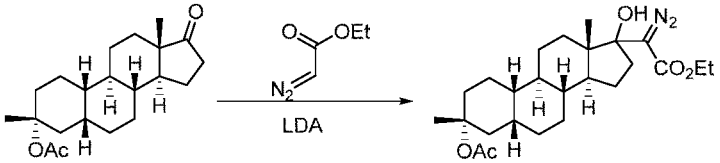


(3R,5R,8R,9R,10S,13S,14S)-3-Hydroxy-3,13-dimethylhexadecahydro-17H-cyclopenta[a]phenanthren-17-one (580 mg, 2.0 mmol) was dissolved in acetic anhydride (15 mL). Pyridine (158 mg, 2.0 mmol) was added, and the reaction solution was reacted under a N_2 atmosphere at 80°C overnight. The reaction solution was concentrated under

reduced pressure to remove acetic anhydride. H_2O (20 mL) was added to the resulting residue, and then the mixture was extracted with EA (15 mL×3). The EA phases were combined, washed successively with H_2O (20 mL) and saturated saline (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by column chromatography to obtain (3R,5R,8R,9R,10S,13S,14S)-3,13-dimethyl-17-oxohexadecahydro-1H-cyclopenta[a]phenanthren-3-yl acetate (560 mg, yield: 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (dd, J = 19.2, 8.1 Hz, 1H), 2.24-2.06 (m, 1H), 1.97 (s, 3H), 1.96-1.76 (m, 8H), 1.71 – 1.57 (m, 3H), 1.55 (s, 3H), 1.55 – 0.99 (m, 10H), 0.87 (s, 3H).

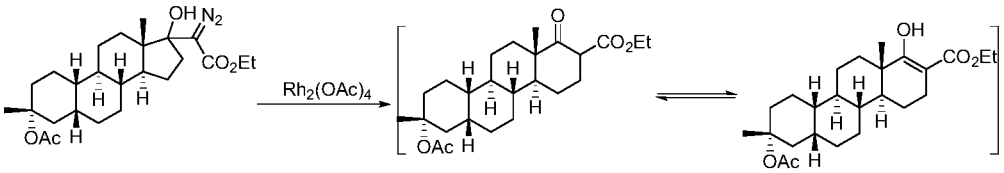
Step 2: Preparation of ethyl 2-((3R,5R,8R,9R,10S,13S,14S)-3-acetoxy-17-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-diazoacetate



(3R,5R,8R,9R,10S,13S,14S)-3,13-Dimethyl-17-oxohexadecahydro-1H-cyclopenta[a]phenanthren-3-yl acetate (400 mg, 1.2 mmol) and ethyl diazoacetate (206 mg, 1.8 mmol) were dissolved in THF (15 mL). The reaction solution was cooled to -70°C, and LDA (2 mL) was added dropwise. After completion of the dropwise addition, the reaction solution was reacted at the same temperature for 1 hour. A solution of AcOH (400 mg) in ether (20 mL) was added, and the reaction solution was warmed up to room temperature, and H_2O (50 mL) was added. The reaction solution was extracted with ether (25 mL×2). The ether phases were combined, washed successively with H_2O (50 mL), saturated $NaHCO_3$ solution (30 mL) and saturated saline (30 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to dryness. The resulting residue was purified by column chromatography to obtain ethyl 2-((3R,5R,8R,9R,10S,13S,14S)-3-acetoxy-17-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-diazoacetate (500 mg, yield: 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70 (bs, 1H), 4.36 – 4.17 (m, 2H), 2.24-2.11 (m, 1H), 2.00 (s, 3H), 1.96 – 1.87 (m, 2H), 1.85-1.83(m, 4H), 1.74 – 1.58 (m, 4H), 1.55 (s, 3H), 1.52 – 1.35 (m, 2H), 1.32 (t, J = 7.1 Hz, 3H), 1.29 – 1.17 (m, 4H), 1.17 – 0.94 (m, 5H), 0.92 (s, 3H), 0.91 – 0.81 (m, 1H).

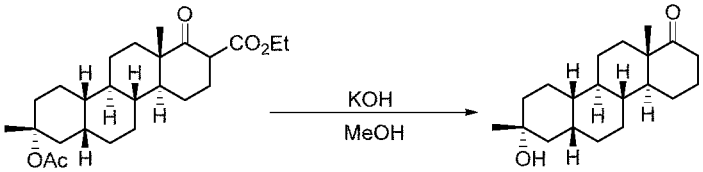
Step 3: Preparation of ethyl (4aS,4bR,6aR,8R,10aS,10bR,12aS)-8-acetoxy-8,12a-dimethyl-1-oxooctadecahydrochrysene-2-carboxylate



Ethyl 2-((3R,5R,8R,9R,10S,13S,14S)-3-acetoxy-17-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-diazoacetate (500 mg, 1.1 mmol) was dissolved in ethylene glycol dimethyl ether (10 mL). Rhodium acetate dimer (5.0 mg) was added, and the reaction solution was reacted under a N_2 atmosphere at room temperature for 0.5 hour. The reaction solution was filtrated to remove the insoluble matter, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by column chromatography to obtain ethyl (4aS,4bR,6aR,8R,10aS,10bR,12aS)-8-acetoxy-8,12a-dimethyl-1-oxooctadecahydrochrysene-2-carboxylate (436 mg, yield: 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.35 (s, 0.82H), 4.13 (q, J = 7.1 Hz, 2H), 3.63 (dd, J = 13.5, 6.0 Hz, 0.15H), 2.27 (dd, J = 16.2, 6.1 Hz, 1H), 2.14 – 1.96 (m, 2H), 1.89 (s, 3H), 1.88 – 1.65 (m, 7H), 1.58 (dd, J = 20.4, 10.4 Hz, 3H), 1.48 (s, 3H), 1.36 – 1.13 (m, 8H), 1.11 – 1.04 (m, 2H), 1.03 (s, 3H), 0.99-0.88 (m, 3H).

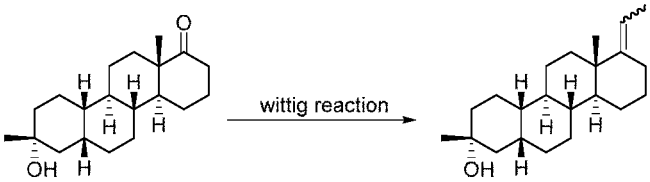
Step 4: Preparation of (4aS,4bR,6aR,8R,10aS,10bR,12aS)-8-hydroxy-8,12a-dimethylhexadecahydrochrysen-1(2H)-one



KOH (4.0 g) was dissolved in methanol (60 mL). Ethyl (4aS,4bR,6aR,8R,10aS,10bR,12aS)-8-acetoxy-8,12a-dimethyl-1-oxooctadecahydrochrysene-2-carboxylate (400 mg) was added, and then the reaction solution was heated to reflux under a N_2 atmosphere for 1 hour. The reaction solution was cooled to room temperature, and poured into ice water (150 mL). After stirring for 20 minutes, the reaction solution was filtrated. The filter cake was washed with a small amount of water and acetone, and dried to obtain (4aS,4bR,6aR,8R,10aS,10bR,12aS)-8-hydroxy-8,12a-dimethylhexadecahydrochrysen-1(2H)-one (320 mg).

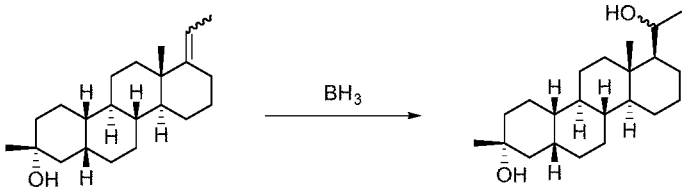
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.61 (td, J = 14.0, 6.8 Hz, 1H), 2.25 – 2.15 (m, 1H), 2.11 – 2.00 (m, 1H), 1.87 (dd, J = 9.8, 7.7 Hz, 2H), 1.84 – 1.70 (m, 5H), 1.67 – 1.57 (m, 3H), 1.56 – 1.47 (m, 2H), 1.45 – 1.27 (m, 7H), 1.26 (s, 3H), 1.20 – 1.10 (m, 1H), 1.08 (s, 3H), 1.07 – 0.91 (m, 2H).

Step 5: Preparation of (2R,4aS,4bR,6aS,10aS,10bR,12aR)-7-ethylidene-2,6a-dimethyloctadecahydrochrysen-2-ol



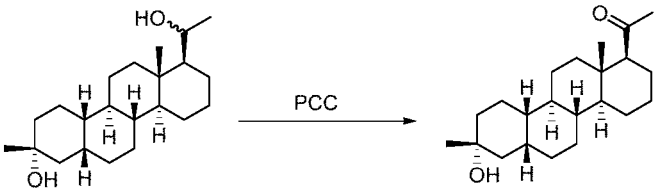
In accordance with Step 4 of Example 1, (4aS,4bR,6aR,8R,10aS,10bR,12aS)-8-hydroxy-8,12a-dimethylhexadecahydrochrysen-1(2H)-one was used as the starting material, accordingly, (2R,4aS,4bR,6aS,10aS,10bR,12aR)-7-ethylidene-2,6a-dimethyloctadecahydrochrysen-2-ol (288 mg) was obtained.

Step 6: Preparation of (2R,4aS,4bR,6aS,7S,10aS,10bR,12aR)-7-(1-hydroxyethyl)-2,6a-dimethyloctadecahydrochrysen-2-ol



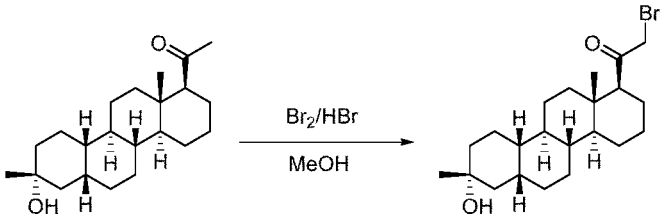
In accordance with Step 5 of Example 1, (2R,4aS,4bR,6aS,10aS,10bR,12aR)-7-ethylidene-2,6a-dimethyloctadecahydrochrysen-2-ol was used as the starting material, accordingly, (2R,4aS,4bR,6aS,7S,10aS,10bR,12aR)-7-(1-hydroxyethyl)-2,6a-dimethyloctadecahydrochrysen-2-ol (150 mg, containing a small amount of impurities) was obtained, which was used directly in the next step without purification.

Step 7: Preparation of 1-((1S,4aS,4bR,6aR,8R,10aS,10bR,12aS)-8-hydroxy-8,12a-dimethyloctadecahydrochrysen-1-yl)ethan-1-one



In accordance with Step 6 of Example 1, (2R,4aS,4bR,6aS,7S,10aS,10bR,12aR)-7-(1-hydroxyethyl)-2,6a-dimethyloctadecahydrochrysen-2-ol was used as the starting material, accordingly, 1-((1S,4aS,4bR,6aR,8R,10aS,10bR,12aS)-8-hydroxy-8,12a-dimethyloctadecahydrochrysen-1-yl)ethan-1-one (80 mg, containing a small amount of impurities) was obtained, which was used directly in the next step without purification.

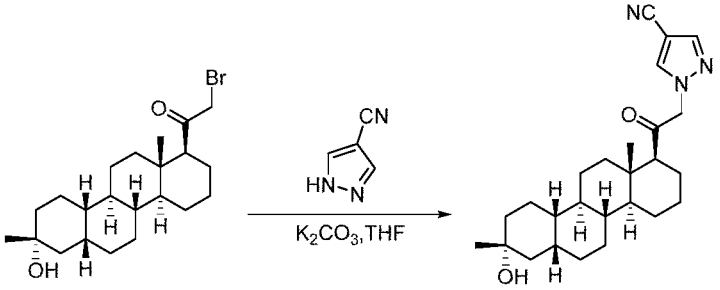
Step 8: Preparation of 2-bromo-1-((1S,4aS,4bR,6aR,8R,10aS,10bR,12aS)-8-hydroxy-8,12a-dimethyloctadecahydrochrysen-1-yl)ethan-1-one



In accordance with Step 1 of Example 2,

1-((1S,4aS,4bR,6aR,8R,10aS,10bR,12aS)-8-hydroxy-8,12a-dimethyloctadecahydrochrysen-1-yl)ethan-1-one was used as the starting material, accordingly, 2-bromo-1-((1S,4aS,4bR,6aR,8R,10aS,10bR,12aS)-8-hydroxy-8,12a-dimethyloctadecahydrochrysen-1-yl)ethan-1-one (50 mg, containing a small amount of impurities) was obtained, which was used directly in the next step without purification.

Step 9: Preparation of 1-(2-((1S,4aS,4bR,6aR,8R,10aS,10bR,12aS)-8-hydroxy-8,12a-dimethyloctadecahydrochrysen-1-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile



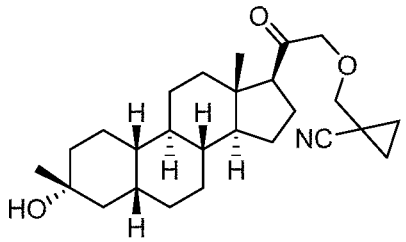
45

In accordance with Example 5, 2-bromo-1-((1S,4aS,4bR,6aR,8R,10aS,10bR,12aS)-8-hydroxy-8,12a-dimethyloctadecahydrochrysen-1-yl)ethan-1-one was used as the starting material, accordingly, 1-(2-((1S,4aS,4bR,6aR,8R,10aS,10bR,12aS)-8-hydroxy-8,12a-dimethyloctadecahydrochrysen-1-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile (5.5 mg) was obtained.

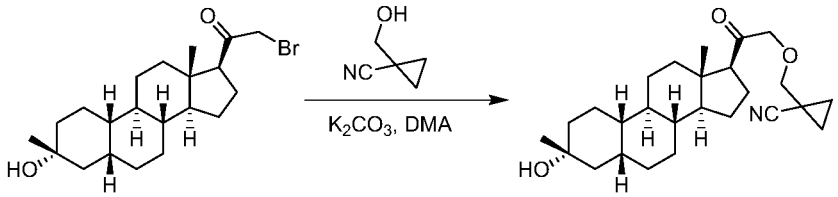
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.83 (s, 1H), 5.06-4.88 (m, 2H), 2.47 (d, J = 4.9 Hz, 1H), 1.90-1.81 (m, 2H), 1.78 – 1.67 (m, 5H), 1.58-1.50 (m, 6H), 1.41 – 1.34 (m, 4H), 1.29-1.24 (m, 9H), 0.99 (s, 3H), 0.96 – 0.83 (m, 3H).

Example 166

1-((2-((3R,5R,8R,9R,10S,13S,14S,17S)-3-Hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethoxy)methyl)cyclopropane-1-carbonitrile (166)



Step 1: Preparation of 1-((2-((3R,5R,8R,9R,10S,13S,14S,17S)-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethoxy)methyl)cyclopropane-1-carbonitrile

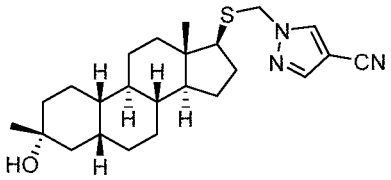


2-Bromo-1-((3R,5R,8R,9R,10S,13S,14S,17S)-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (80 mg, 0.2 mmol), 1-(hydroxymethyl)cyclopropane-1-carbonitrile (29 mg, 0.3 mmol) and potassium carbonate (138 mg, 1.0 mmol) were dissolved in N,N-dimethylacetamide (3 mL), and the resulting reaction solution was stirred at 70°C overnight. Water (20 mL) was added to the reaction solution, and the water phase was extracted with ethyl acetate (20 mL×2). The organic phases were combined, dried over anhydrous sodium sulfate, filtrated and concentrated. The resulting crude product was purified by column chromatography (petroleum ether/ethyl acetate: 50/1 - 3/1) to obtain 1-((2-((3R,5R,8R,9R,10S,13S,14S,17S)-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethoxy)methyl)cyclopropane-1-carbonitrile (10 mg, yield: 12%).

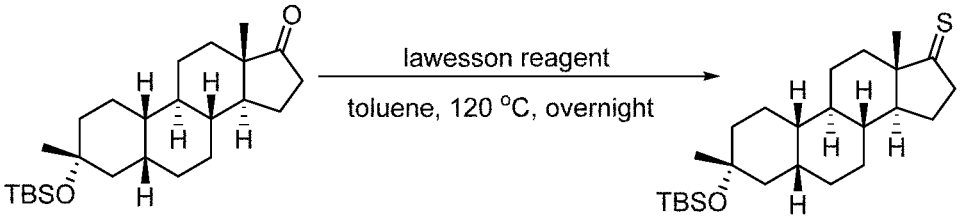
1H NMR (400 MHz, $CDCl_3$) δ 4.21 – 4.09 (m, 2H), 3.53 (s, 2H), 2.61 – 2.54 (m, 1H), 2.21 – 2.12 (m, 1H), 1.90 – 1.78 (m, 4H), 1.75 – 1.61 (m, 4H), 1.49 – 1.40 (m, 5H), 1.34 – 1.26 (m, 13H), 1.10 – 1.04 (m, 4H), 0.63 (s, 3H).

Example 167

1-((((3R,5R,8R,9R,10S,13S,14S,17S)-3-Hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)thio)methyl)-1H-pyrazole-4-carbonitrile



Step 1: Preparation of (3R,5R,8R,9R,10S,13S,14S)-3-((*tert*-butyldimethylsilyl)oxy)-3,13-dimethylhexadecahydro-17H-cyclopenta[a]phenanthrene-17-thione

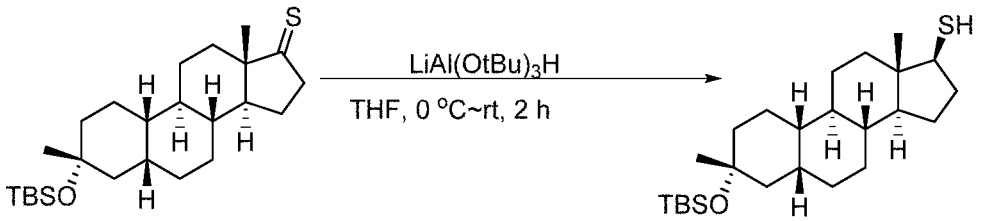


(3R,5R,8R,9R,10S,13S,14S)-3-((*tert*-butyldimethylsilyl)oxy)-3,13-dimethylhexadecahydro-17H-cyclopenta[a]phenanthren-17-thione (1.2 g, 3 mmol), 2,4-bis(*p*-methoxyphenyl)-1,3-dithiadiphosphetane-2,4-sulfide (971 mg, 2.4 mmol) and 20 mL anhydrous toluene were successively added to a dry 100 mL round bottom flask. The reaction system was purged with argon, heated to reflux and stirred overnight. After completion of the reaction, the reaction solution was filtrated through neutral alumina, and the filtrate was concentrated by rotary evaporation to dryness. The resulting crude product was purified by column chromatography (eluent: petroleum ether/ethyl acetate=50/1) to obtain (3R,5R,8R,9R,10S,13S,14S)-3-((*tert*-butyldimethylsilyl)oxy)-3,13-dimethylhexadecahy

dro-17H-cyclopenta[a]phenanthrene-17-thione (860 mg, 68%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.90 (dd, J = 8.4, 21.6 Hz, 1H), 2.63-2.55 (m, 1H), 1.97-1.93 (m, 2H), 1.73-1.17 (m, 22H), 0.84 (s, 3H), 0.79 (s, 9H), 0.07 (s, 6H).

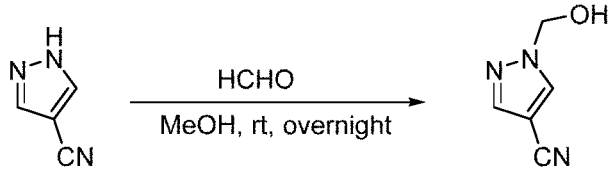
Step 2: Preparation of (3R,5R,8R,9R,10S,13S,14S)-3-((*tert*-butyldimethylsilyl)oxy)-3,13-dimethylhexadecahydro-17H-cyclopenta[a]phenanthrene-17-thiol



(3R,5R,8R,9R,10S,13S,14S)-3-((*tert*-butyldimethylsilyl)oxy)-3,13-dimethylhexadecahydro-17H-cyclopenta[a]phenanthrene-17-thione (860 mg, 2 mmol) and 30 ml of anhydrous tetrahydrofuran were added to a dry 100 mL round bottom flask. The reaction system was cooled to 0°C, and 1.0 M tri-*tert*-butoxy lithium aluminum hydride (6 mL, 6 mmol) was added dropwise. The reaction solution was stirred at 0°C for 2 hours, and stirred at room temperature for 1 hour. TLC showed that the reaction was completed. Saturated sodium bicarbonate solution was added to carefully quench the reaction, and the reaction solution was extracted with dichloromethane. The organic phases were combined, washed with water and saturated saline, dried over anhydrous sodium sulfate, filtrated, and concentrated by rotary evaporation to dryness to obtain the crude product, which was used directly in the next step without purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60-2.58 (m, 1H), 2.10-2.07 (m, 1H), 1.72-0.98 (m, 25H), 0.79 (s, 9H), 0.64 (s, 3H), 0.04(s, 6H).

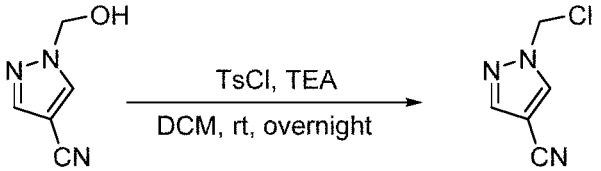
Step 3: Preparation of 1-(hydroxymethyl)-1H-pyrazole-4-carbonitrile



1H-Pyrazole-4-carbonitrile (930 mg, 10 mmol), 30% aqueous formaldehyde solution (8 g, 100 mmol) and 10 mL of methanol were added to a 100 mL round bottom flask. The reaction system was stirred at room temperature overnight. The reaction solution was concentrated by rotary evaporation to dryness to obtain 1-(hydroxymethyl)-1H-pyrazole-4-carbonitrile (900 mg, 73%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.87 (s, 1H), 4.96-4.80 (m, 2H).

Step 4: Preparation of 1-(chloromethyl)-1H-pyrazole-4-carbonitrile

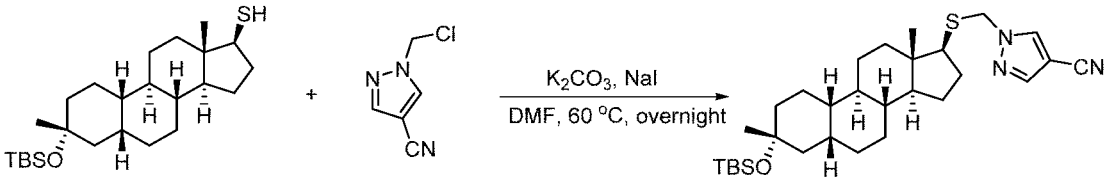


1-(Hydroxymethyl)-1H-pyrazole-4-carbonitrile (900 mg, 7.3 mmol), triethylamine

(1.5 g, 14.6 mmol) and 20 ml of dichloromethane were added to a 100 mL round bottom flask. *P*-Toluenesulfonyl chloride (2.1 g, 11 mmol) was added in batches under stirring, and the reaction system was stirred at room temperature overnight. Water was added to quench the reaction, and the reaction solution was extracted with dichloromethane. The organic phase was washed with water and saturated saline, dried over anhydrous sodium sulfate, filtrated and concentrated by rotary evaporation to dryness. The resulting crude product was purified by column chromatography (eluent: petroleum ether/ethyl acetate=10/1) to obtain 1-(chloromethyl)-1H-pyrazole-4-carbonitrile (790 mg, 76.7%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.89 (s, 1H), 5.87 (s, 2H).

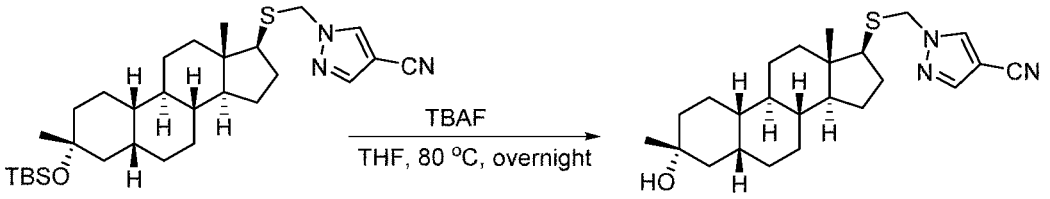
Step 5: Preparation of 1-((((3R,5R,8R,9R,10S,13S,14S,17S)-3-((*tert*-butyldimethylsilyl)oxy)-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)thio)methyl)-1H-pyrazole-4-carbonitrile



(3R,5R,8R,9R,10S,13S,14S)-3-((*tert*-butyldimethylsilyl)oxy)-3,13-dimethylhexadecahydro-17H-cyclopenta[a]phenanthrene-17-thiol (210 mg, 0.5 mmol), 1-(chloromethyl)-1H-pyrazole-4-carbonitrile (72 mg, 0.6 mmol), potassium carbonate (136 mg, 1 mmol), sodium iodide (10 mg, catalytic amount) and 5 ml of anhydrous N,N-dimethylformamide were added to a dry 100 mL round bottom flask. The reaction system was heated to 60°C and stirred overnight. The reaction solution was cooled to room temperature. Water was added to quench the reaction, and the reaction solution was extracted with dichloromethane. The organic phase was washed with water and saturated saline, dried over anhydrous sodium sulfate, filtrated and concentrated by rotary evaporation to dryness. The resulting crude product was purified by column chromatography (petroleum ether/ethyl acetate=10/1) to obtain 1-((((3R,5R,8R,9R,10S,13S,14S,17S)-3-((*tert*-butyldimethylsilyl)oxy)-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)thio)methyl)-1H-pyrazole-4-carbonitrile (170 mg, yield: 64.5%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.79 (s, 1H), 5.18 (dd, J = 14.4, 19.2 Hz, 2H), 2.62 (t, J = 7.2 Hz, 1H), 2.05-1.98 (m, 2H), 1.90-0.90 (m, 24H), 0.86 (s, 9H), 0.72 (s, 3H), 0.07 (s, 6H).

Step 6: 1-((((3R,5R,8R,9R,10S,13S,14S,17S)-3-Hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)thio)methyl)-1H-pyrazole-4-carbonitrile



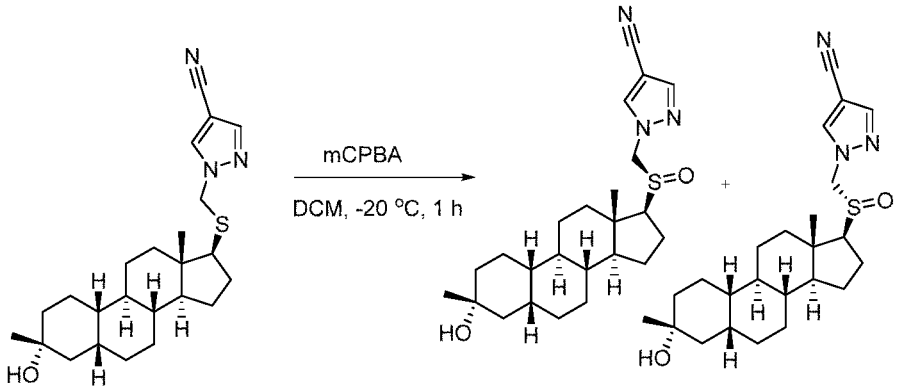
1-((((3R,5R,8R,9R,10S,13S,14S,17S)-3-((*tert*-butyldimethylsilyl)oxy)-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)thio)methyl)-1H-pyrazole-4-carbonitrile (170 mg, 0.32 mmol) was dissolved in 5 mL of anhydrous tetrahydrofuran in a 100 mL round bottom flask, and a 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran (5 mL) was added to the reaction system. The reaction solution was stirred at 60°C overnight. After completion of the reaction, the reaction system was cooled to room temperature. Water was added to quench the reaction, and the reaction solution was extracted with ethyl acetate. The organic phase was washed with water and saturated saline, dried over anhydrous sodium sulfate, filtrated and concentrated by rotary evaporation to dryness. The resulting crude product was purified by column chromatography (eluent: petroleum ether/ethyl acetate=1/1) to obtain 1-((((3R,5R,8R,9R,10S,13S,14S,17S)-3-Hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)thio)methyl)-1H-pyrazole-4-carbonitrile (100 mg, 75%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.79 (s, 1H), 5.28-5.02 (m, 2H), 2.58 (t, J = 9.4 Hz, 1H), 2.12-1.93 (m, 1H), 1.89-0.94 (m, 26H), 0.72 (s, 3H).

Example 168 and Example 169

1-(((S)-((3R,5R,8R,9R,10S,13S,14S,17S)-3-Hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)sulfinyl)methyl)-1H-pyrazole-4-carbonitrile (168)

1-(((R)-((3R,5R,8R,9R,10S,13S,14S,17S)-3-Hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)sulfinyl)methyl)-1H-pyrazole-4-carbonitrile (169)



1-((((3R,5R,8R,9R,10S,13S,14S,17S)-3-Hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)thio)methyl)-1H-pyrazole-4-carbonitrile (25 mg, 0.06 mmol) was dissolved in 5 mL of anhydrous dichloromethane in a 100 mL round bottom flask. *M*-chloroperoxybenzoic acid (15 mg, 0.073 mmol) was added at -20°C, and the reaction solution was stirred at this temperature for 1 hour. After completion of the reaction, saturated sodium bicarbonate solution was added to quench the reaction, and the reaction solution was extracted with ethyl acetate. The organic phase was

washed with water and saturated saline, dried over anhydrous sodium sulfate, filtrated and by rotary evaporation concentrated to dryness. The resulting crude product was purified by high performance liquid chromatography to obtain 1-(((S)-((3R,5R,8R,9R,10S,13S,14S,17S)-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)sulfinyl)methyl)-1H-pyrazole-4-carbonitrile (7.5 mg, 29%) and 1-(((R)-((3R,5R,8R,9R,10S,13S,14S,17S)-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)sulfinyl)methyl)-1H-pyrazole-4-carbonitrile (6.5 mg, yield: 25%).

Example 168:

MS m/z (ESI): 430.3 $[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.90 (s, 1H), 5.21 (d, J = 12.0 Hz, 1H), 5.03 (d, J = 12.0 Hz, 1H), 2.54 (t, J = 9.2 Hz, 1H), 2.12-1.93 (m, 2H), 1.85-1.02 (m, 25H), 0.89 (s, 3H).

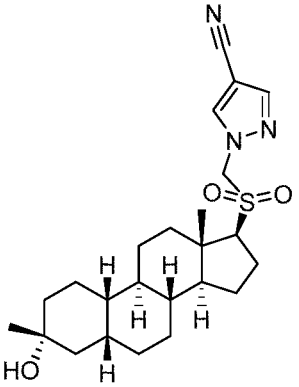
Example 169:

MS m/z (ESI): 430.3 $[M+H]^+$

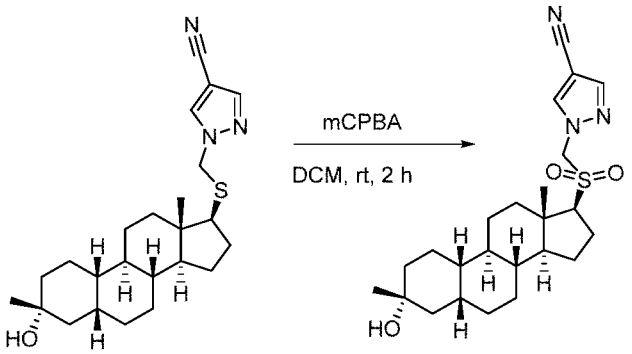
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.91 (s, 1H), 5.18 (d, J = 13.6 Hz, 1H), 5.03 (d, J = 13.6 Hz, 1H), 2.32 (t, J = 8.8 Hz, 1H), 2.05-1.94 (m, 2H), 1.85-1.12 (m, 25H), 1.05 (s, 3H).

Example 170

1-((((3R,5R,8R,9R,10S,13S,14S,17S)-3-Hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)sulfonyl)methyl)-1H-pyrazole-4-carbonitrile (170)



Step 1: Preparation of 1-((((3R,5R,8R,9R,10S,13S,14S,17S)-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)sulfonyl)methyl)-1H-pyrazole-4-carbonitrile



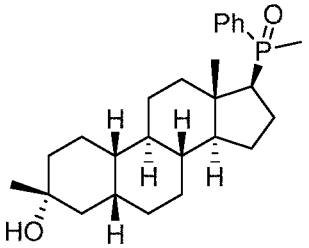
1-((((3R,5R,8R,9R,10S,13S,14S,17S)-3-Hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)thio)methyl)-1H-pyrazole-4-carbonitrile (25 mg, 0.06 mmol) was dissolved in 5 mL of anhydrous dichloromethane in a 100 mL round bottom flask. M-chloroperoxybenzoic acid (30 mg, 0.15 mmol) was added at 0°C, and the reaction solution was stirred at room temperature for 2 hours. After completion of the reaction, saturated sodium bicarbonate solution was added to quench the reaction, and the reaction solution was extracted with ethyl acetate. The organic phase was washed with water and saturated saline, dried over anhydrous sodium sulfate, filtrated and concentrated by rotary evaporation to dryness. The resulting crude product was purified by preparative high performance liquid chromatography to obtain 1-((((3R,5R,8R,9R,10S,13S,14S,17S)-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)sulfonyl)methyl)-1H-pyrazole-4-carbonitrile (9.1 mg, 34%).

MS m/z (ESI): 446.3 $[M+H]^+$

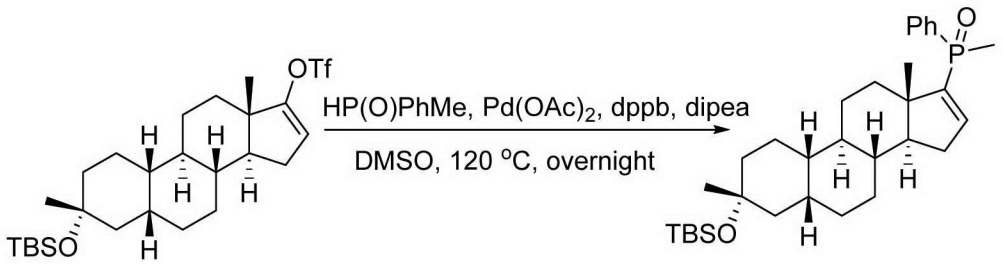
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.89 (s, 1H), 5.24 (d, J = 14.8 Hz, 1H), 5.02 (d, J = 14.8 Hz, 1H), 2.88 (t, J = 9.2 Hz, 1H), 2.24-2.18 (m, 1H), 2.11-1.92 (m, 3H), 1.84-1.00 (s, 26H).

Example 171

((3R,5R,8R,9R,10S,13S,14S,17S)-3-Hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)methylphenylphosphine oxide (171)



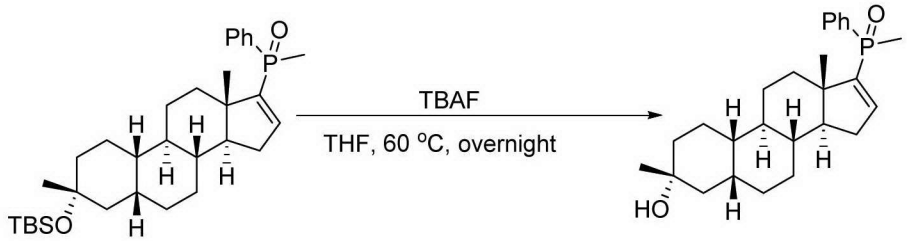
Step 1: Preparation of ((3R,5R,8R,9R,10S,13S,14S)-3-((*tert*-butyldimethylsilyl)oxy)-3,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)methylphenylphosphine oxide



(3R,5R,8R,9R,10S,13S,14S)-3-((*tert*-butyldimethylsilyl)oxy)-3,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl trifluoromethanesulfonate (230 mg, 0.43 mmol), methylphenylphosphine oxide (92 mg, 0.64 mmol), palladium diacetate (10 mg, 0.04 mmol), 1,4-bis(diphenylphosphino)butane (18 mg, 0.04 mmol), N,N-diisopropylethylamine (443 mg, 3.4 mmol) and 10 mL anhydrous dimethyl sulfoxide were successively added to a 100 mL round bottom flask. The reaction system was purged with nitrogen, slowly warmed up to 120°C and stirred overnight. After completion of the reaction, the reaction system was cooled to room temperature. Water was added to quench the reaction, and the reaction solution was extracted with ethyl acetate. The organic phase was washed with water and saturated saline, dried over anhydrous sodium sulfate, filtrated and concentrated by rotary evaporation to dryness. The resulting crude product was purified by column chromatography (eluent: dichloromethane/methanol=10/1) to obtain ((3R,5R,8R,9R,10S,13S,14S)-3-((*tert*-butyldimethylsilyl)oxy)-3,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)methylphenylphosphine oxide (170 mg, 75%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77-7.72 (m, 2H), 7.55-7.48 (m, 3H), 6.53-6.50 (m, 1H), 2.44-1.16 (m, 27H), 1.00(s, 3H), 0.86 (s, 9H), 0.05 (s, 6H).

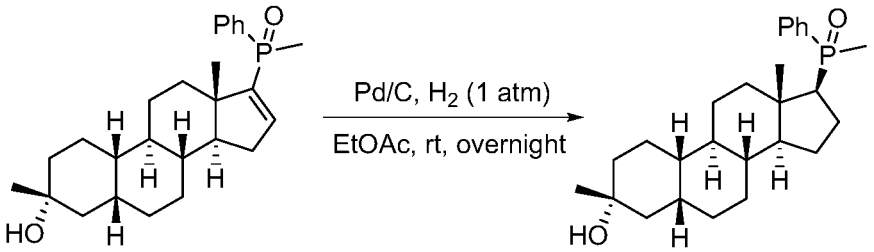
Step 2: Preparation of ((3R,5R,8R,9R,10S,13S,14S)-3-hydroxy-3,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)methylphenylphosphine oxide



((3R,5R,8R,9R,10S,13S,14S)-3-((*tert*-butyldimethylsilyl)oxy)-3,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)methylphenylphosphine oxide (170 mg, 0.32 mmol) was dissolved in 5 mL of anhydrous tetrahydrofuran in a 100 mL round bottom flask, and a 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran (5 mL) was added to the reaction system. The reaction solution was stirred at 60°C overnight. After completion of the reaction, the reaction system was cooled to room temperature. Water was added to quench the reaction, and the reaction solution was extracted with ethyl acetate. The

organic phase was washed with water and saturated saline, dried over anhydrous sodium sulfate, filtrated and concentrated by rotary evaporation to dryness. The resulting crude product was purified by column chromatography (eluent: dichloromethane/methanol=10/1) to obtain ((3R,5R,8R,9R,10S,13S,14S)-3-hydroxy-3,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)methylphenylphosphine oxide (50 mg, 38%).

Step 3: Preparation of ((3R,5R,8R,9R,10S,13S,14S,17S)-3-Hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)methylphenylphosphine oxide



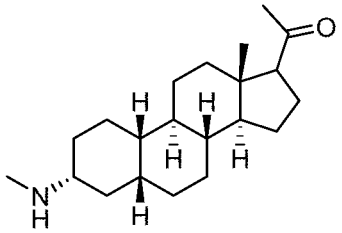
((3R,5R,8R,9R,10S,13S,14S)-3-Hydroxy-3,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)methylphenylphosphine oxide (50 mg, 0.12 mmol), palladium on carbon (50 mg, 10%) and 10 mL of ethyl acetate were added to a 100 mL round bottom flask. The reaction system was purged with hydrogen three times, and reacted at 1 atmosphere overnight. After completion of the reaction, the reaction solution was filtrated through celite to remove excess palladium on carbon, and the filtrate was concentrated by rotary evaporation to dryness. The resulting crude product was purified by high performance liquid chromatography to obtain ((3R,5R,8R,9R,10S,13S,14S,17S)-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)methylphenylphosphine oxide (10 mg, 20%).

MS m/z (ESI): 415.3 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.74 (m, 2H), 7.55-7.50 (m, 3H), 2.41-2.34 (m, 1H), 2.03-1.60 (m, 12H), 1.55-0.73 (m, 21H).

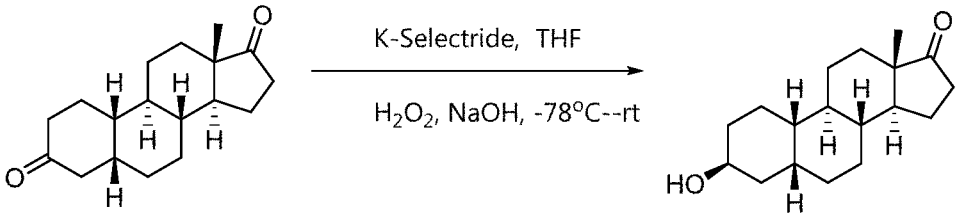
Example 172

1-((3R,5R,8R,9R,10S,13S,14S)-13-Methyl-3-(methylamino)hexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one hydrochloride



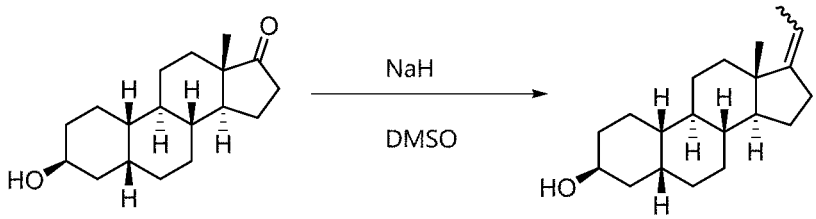
Step 1: Preparation of (3S,5R,8R,9R,10S,13S,14S)-3-hydroxy-13-methylhexadecahydro-17H-cyclopenta[a]ph

enanthren-17-one



(5R,8R,9R,10S,13S,14S)-13-Methyltetradecahydro-3H-cyclopenta[a]phenanthrene -3,17(2H)-dione (5.90 g, 21.50 mmol) was dissolved in anhydrous tetrahydrofuran (150 mL) at -78°C. The reaction system was purged with nitrogen, and potassium triisobutylborohydride (1.0 M in THF, 32.25 mL, 32.25 mmol) was added dropwise to the reaction system. The reaction solution was reacted at -78°C for 3 hours. Aqueous sodium hydroxide solution (10 wt%, 56.6 mL) and hydrogen peroxide (82.6 mL) were successively added dropwise, and then the reaction solution was stirred at room temperature for half an hour. Saturated sodium thiosulfate (100 mL) was added, and then the reaction solution was stirred at room temperature for 10 minutes. The reaction solution was extracted with ethyl acetate (100 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtrated and concentrated by rotary evaporation to dryness. The resulting crude product was purified by flash column chromatography (petroleum ether:ethyl acetate: 4:1) to obtain (3S,5R,8R,9R,10S,13S,14S)-3-hydroxy-13-methylhexadecahydro-17H-cyclopenta[a]ph enanthren-17-one (5.0 g, white solid, yield: 84%).

Step 2: Preparation of (3S,5R,8R,9R,10S,13S,14S)-17-ethylidene-13-methylhexadecahydro-1H-cyclopenta[a] phenanthren-3-ol

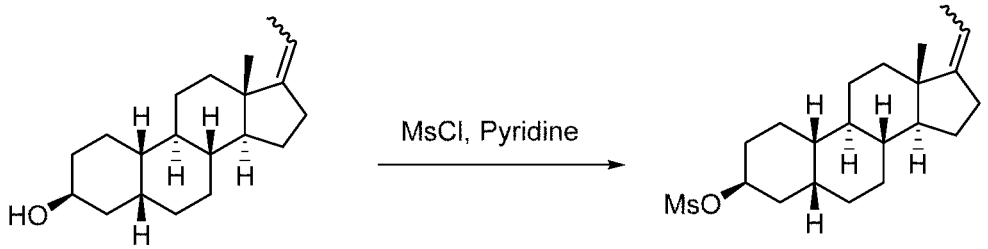


Sodium hydride (1.45 g, 36.18 mmol, 60% in mineral oil) was added in batches to a solution of ethyltriphenylphosphonium bromide (13.44 g, 36.18 mmol) in dimethyl sulfoxide (100 mL) under a nitrogen atmosphere. The reaction solution was stirred at room temperature for 1 hour, and a solution of (3S,5R,8R,9R,10S,13S,14S)-3-hydroxy-13-methylhexadecahydro-17H-cyclopenta[a]ph enanthren-17-one (2.0 g, 7.24 mmol) in dimethyl sulfoxide (40 mL) was added dropwise. The reaction solution was heated to 60°C overnight under a nitrogen atmosphere. The reaction solution was cooled to room temperature. Saturated saline (200 mL) was added, and then the reaction solution was extracted with dichloromethane (50 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtrated and concentrated by rotary evaporation to dryness. The resulting crude product was purified by flash column chromatography (petroleum ether:ethyl acetate: 10:1) to

obtain (3S,5R,8R,9R,10S,13S,14S)-17-ethylidene-13-methylhexadecahydro-1H-cyclopenta[a]phenanthren-3-ol (1.60 g, white solid, yield: 76.7%).

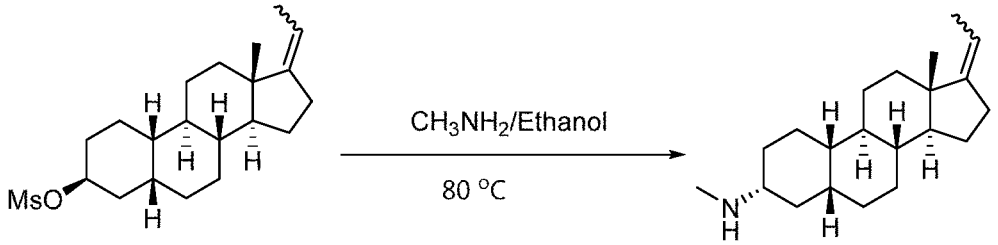
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14-5.08 (m, 1H), 4.13-4.11 (m, 1H), 2.40-2.33 (m, 1H), 2.28-2.11(m, 3H), 1.91-1.83 (m, 1H), 1.74-1.58 (m, 8H), 1.47-1.38 (m, 5H), 1.38-1.34 (m, 2H), 1.29-1.07 (m, 7H), 0.88 (s, 3H).

Step 3: Preparation of (3S,5R,8R,9R,10S,13S,14S)-17-ethylidene-13-methylhexadecahydro-1H-cyclopenta[a]phenanthren-3-yl methanesulfonate



(3S,5R,8R,9R,10S,13S,14S)-17-Ethylidene-13-methylhexadecahydro-1H-cyclopenta[a]phenanthren-3-ol (0.40 g, 1.39 mmol) was dissolved in dichloromethane (20 mL) at room temperature. Pyridine (0.33 g, 4.16 mmol) and methanesulfonyl chloride (0.32 g, 2.77 mmol) were successively added dropwise, and then the reaction solution was reacted at room temperature overnight. After completion of the reaction, the reaction solution was diluted with dichloromethane (40 mL), and washed with saturated saline (10 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtrated and concentrated by rotary evaporation to dryness. The resulting crude product was purified by flash column chromatography (petroleum ether:ethyl acetate: 10:1) to obtain (3S,5R,8R,9R,10S,13S,14S)-17-ethylidene-13-methylhexadecahydro-1H-cyclopenta[a]phenanthren-3-yl methanesulfonate (0.30 g, white solid, yield: 59%).

Step 4: Preparation of (3R,5R,8R,9R,10S,13S,14S)-17-ethylidene-N,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-amine

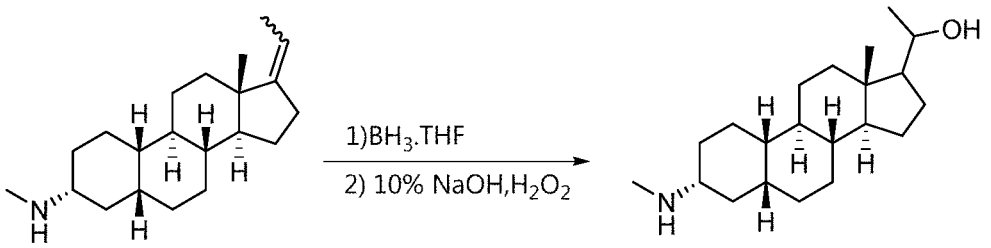


(3S,5R,8R,9R,10S,13S,14S)-17-Ethylidene-13-methylhexadecahydro-1H-cyclopenta[a]phenanthren-3-yl methanesulfonate (0.20 g, 0.55 mmol) was added to a microwave reaction tube (10 mL) at room temperature, and methylamine alcohol solution (3 mL) was added dropwise to the reaction system. The microwave reaction tube was sealed, and heated to 80°C overnight. The reaction solution was cooled to room temperature and concentrated by rotary evaporation to dryness. The resulting residue was dissolved in ethyl acetate (20 mL). The organic phases were washed with saturated saline (20

mL×3), combined, dried over anhydrous sodium sulfate, filtrated and concentrated by rotary evaporation to dryness. The resulting crude product was purified by flash column chromatography (dichloromethane: methanol: triethylamine: 300:10:3) to obtain (3R,5R,8R,9R,10S,13S,14S)-17-ethylidene-N,13-dimethylhexadecahydro-1H-cyclopent a[a]phenanthren-3-amine (70 mg, colorless oil, yield: 42.4%).

MS m/z (ESI): 302.5 $[M+H]^+$.

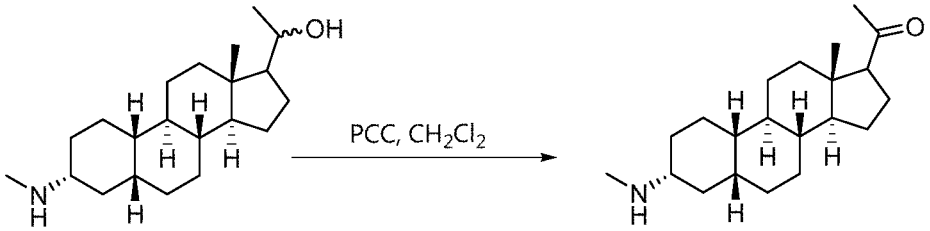
Step 5: Preparation of 1-((3R,5R,8R,9R,10S,13S,14S)-13-methyl-3-(methylamino)hexadecahydro-1H-cyclope nta[a]phenanthren-17-yl)ethan-1-ol



(3R,5R,8R,9R,10S,13S,14S)-17-Ethylidene-N,13-dimethylhexadecahydro-1H-cycl openta[a]phenanthren-3-amine (0.07 g, 0.23 mmol) was dissolved in anhydrous tetrahydrofuran (3 mL) in an ice bath, and then a solution of borane in tetrahydrofuran (1.0 M in THF, 2.32 mL, 2.32 mmol) was added dropwise. The reaction solution was reacted for 3 hours. Sodium hydroxide solution (3N, 1 mL) and hydrogen peroxide (0.3 mL) were successively added dropwise, and then the reaction solution was stirred at room temperature for half an hour. The reaction solution was diluted with ethyl acetate (20 mL), and washed with saturated saline (10 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtrated and concentrated by rotary evaporation to dryness to obtain the crude product 1-((3R,5R,8R,9R,10S,13S,14S)-13-methyl-3-(methylamino)hexadecahydro-1H-cyclope nta[a]phenanthren-17-yl)ethan-1-ol (40 mg, colorless oil, crude product).

MS m/z (ESI): 320.5 $[M+H]^+$.

Step 6: Preparation of 1-((3R,5R,8R,9R,10S,13S,14S)-13-methyl-3-(methylamino)hexadecahydro-1H-cyclope nta[a]phenanthren-17-yl)ethan-1-one



1-((3R,5R,8R,9R,10S,13S,14S)-13-Methyl-3-(methylamino)hexadecahydro-1H-cy clopenta[a]phenanthren-17-yl)ethan-1-ol (40 mg, 0.125 mmol) was dissolved in dichloromethane (5 mL) at room temperature. Pyridinium chlorochromate (54 mg, 0.25 mmol) was added, and then the reaction solution was reacted at room temperature for 3 hours. The reaction solution was diluted with dichloromethane (20 mL), and washed

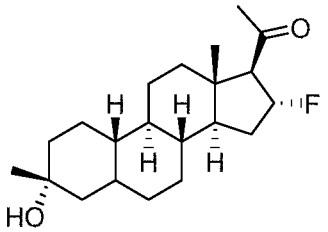
with saturated sodium thiosulfate (10 mL×3). The organic phase was dried over anhydrous sodium sulfate, filtrated and concentrated by rotary evaporation to dryness. The resulting crude product was purified by column chromatography (dichloromethane: methanol: 30:1) to obtain 1-((3R,5R,8R,9R,10S,13S,14S)-13-methyl-3-(methylamino)hexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (15 mg, white solid, yield: 37.7%).

MS m/z (ESI): 318.5 $[M+H]^+$

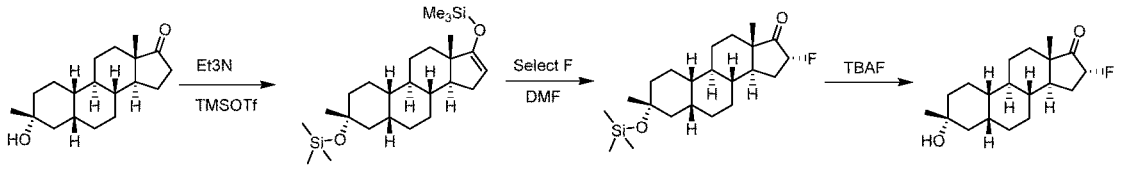
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61-3.55 (m, 1H), 2.55-2.50 (m, 1H), 2.47 (s, 3H), 2.11 (s, 3H), 2.01-1.92 (m, 3H), 1.78-1.56 (m, 8H), 1.43-1.01 (m, 13H), 0.61 (s, 3H).

Example 173

1-((3R,8R,9R,10S,13S,14S,16R,17S)-16-Fluoro-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (173)



Step 1: Preparation of (3R,5R,8R,9R,10S,13S,14S,16R)-16-fluoro-3-hydroxy-3,13-dimethylhexadecahydro-17H-cyclopenta[a]phenanthren-17-one



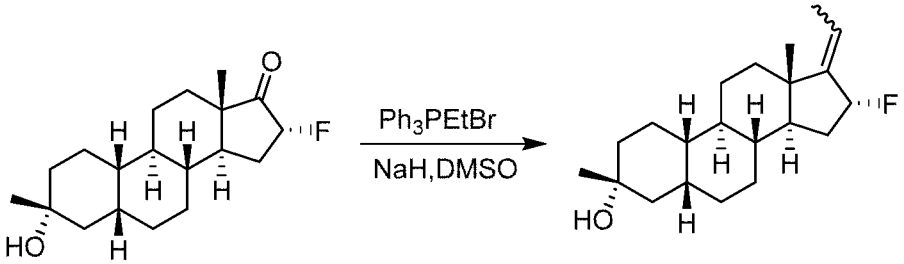
Trimethylsilyl triflate (5.6 mL, 31.0 mmol) was added dropwise to a solution of (3R,5R,8R,9R,10S,13S,14S)-3-hydroxy-3,13-dimethylhexadecahydro-17H-cyclopenta[a]phenanthren-17-one (3 g, 10.3 mmol) and triethylamine (36.0 mL, 258.2 mmol) in toluene (45 mL), and the resulting reaction solution was heated to reflux for 2 hours. The reaction solution was cooled, washed with saturated sodium bicarbonate, and extracted with *n*-hexane. The organic phase was concentrated to dryness to obtain the crude product (((3R,5R,8R,9R,10S,13S,14S)-3,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthrene-3,17-diyl)bis(oxy))bis(trimethylsilane). A selective fluorine reagent (4.0 g, 11.4 mmol) was added to a solution of (((3R,5R,8R,9R,10S,13S,14S)-3,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthrene-3,17-diyl)bis(oxy))bis(trimethylsilane) in N,N-dimethylformamide (25 mL), and the resulting reaction solution was stirred at room temperature for 2 hours to obtain (3R,5R,8R,9R,10S,13S,14S,16R)-16-fluoro-3,13-dimethyl-3-((trimethylsilyl)oxy)hexadecahydro-17H-cyclopenta[a]phenanthren-17-one. A solution of tetrabutylammonium

fluoride in tetrahydrofuran (11.4 mL, 1 M) was added, and the resulting reaction solution was stirred at room temperature overnight. The reaction solution was extracted with ethyl acetate, and washed with saturated saline three times. The organic phase was concentrated to dryness, and the resulting crude product was purified by column chromatography (petroleum ether:ethyl acetate=6:4) to obtain (3R,5R,8R,9R,10S,13S,14S,16R)-16-fluoro-3-hydroxy-3,13-dimethylhexadecahydro-17 H-cyclopenta[a]phenanthren-17-one (2.0 g, yield: 50.9%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09 (dd, J = 50.6, 7.5 Hz, 1H), 2.18 – 1.58 (m, 10H), 1.54 – 1.01 (m, 14H), 0.92 (s, 3H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -192.59.

Step 2: Preparation of (3R,5R,8R,9R,10S,13S,14S,16R)-17-ethylidene-16-fluoro-3,13-dimethylhexadecahydro -1H-cyclopenta[a]phenanthren-3-ol

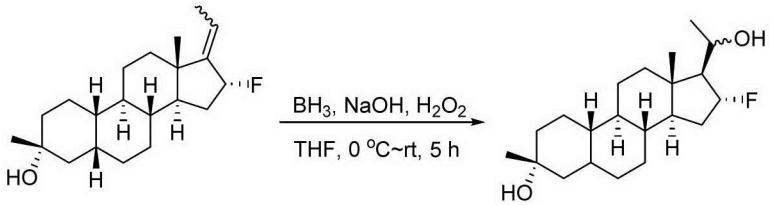


Sodium hydride (123 mg, 3.08 mmol, 60% w/w) was added to a solution of ethyltriphenylphosphonium bromide (1.2 g, 3.24 mmol) in dimethyl sulfoxide (20 mL) in batches under a nitrogen atmosphere, and the resulting reaction solution was stirred at room temperature for 1 hour. (3R,5R,8R,9R,10S,13S,14S,16R)-16-Fluoro-3-hydroxy-3,13-dimethylhexadecahydro-1 7H-cyclopenta[a]phenanthren-17-one (200 mg,0.65 mmol) was added, and the reaction solution was heated to 70°C under a nitrogen atmosphere overnight. The reaction solution was cooled, and saturated saline was added. 1 N hydrochloric acid was added to adjust pH to 6, and the reaction solution was extracted with ethyl acetate. The organic phase was washed with saturated saline, and concentrated to dryness to obtain a crude product. The crude product was purified by column chromatography (petroleum ether:ethyl acetate=7:3) to obtain (3R,5R,8R,9R,10S,13S,14S,16R)-17-ethylidene-16-fluoro-3,13-dimethylhexadecahydro -1H-cyclopenta[a]phenanthren-3-ol (80 mg, yield: 38.5%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 – 5.59 (m, 1H), 5.12 (dt, J = 57.2, 7.0 Hz, 1H), 2.27 – 2.11 (m, 2H), 1.92 – 1.24 (m, 21H), 1.22 – 1.09 (m, 4H), 1.06 (s, 3H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -153.69.

Step 3: Preparation of (3R,8R,9R,10S,13S,14S,16R,17S)-16-fluoro-17-(1-hydroxyethyl)-3,13-dimethylhexade cahydro-1H-cyclopenta[a]phenanthren-3-ol

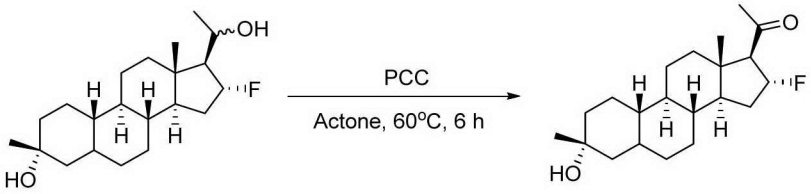


(3R,5R,8R,9R,10S,13S,14S,16R)-17-Ethylidene-16-fluoro-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-ol (80 mg, 0.25 mmol) was dissolved in anhydrous tetrahydrofuran (50 mL). A solution of borane in tetrahydrofuran (1 M, 2.5 mL) was added dropwise at room temperature, and the resulting reaction solution was stirred at room temperature for 1 hour. The reaction solution was cooled with ice water, and sodium hydroxide solution (3 M, 1 mL) was slowly added dropwise to release a large amount of gas. Hydrogen peroxide (25%, 0.58 mL) was slowly added dropwise, and the reaction solution was stirred at room temperature for 2 hours. The reaction solution was extracted with ethyl acetate, washed with sodium thiosulfate solution and saturated saline, and dried to obtain (3R,8R,9R,10S,13S,14S,16R,17S)-16-fluoro-17-(1-hydroxyethyl)-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-ol (80 mg), which was used directly in the next step.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47 – 5.16 (m, 1H), 4.22 – 4.05 (m, 1H), 2.42 – 2.17 (m, 1H), 1.94 – 0.93 (m, 27H), 0.87 (s, 3H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -178.27.

Step 4: Preparation of 1-((3R,8R,9R,10S,13S,14S,16R,17S)-16-fluoro-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one



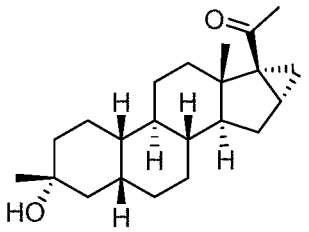
Pyridinium chlorochromate (102 mg, 0.47 mmol) was added to a solution of (3R,8R,9R,10S,13S,14S,16R,17S)-16-fluoro-17-(1-hydroxyethyl)-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-ol (80 mg) in acetone (2 mL), and the resulting reaction solution was reacted at 60°C for 6 hours. The reaction solution was concentrated to dryness, and the resulting residue was purified by column chromatography (petroleum ether:ethyl acetate=5:2) to obtain 1-((3R,8R,9R,10S,13S,14S,16R,17S)-16-fluoro-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (22 mg, yield: 25%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.64 – 5.35 (m, 1H), 2.44 – 2.09 (m, 6H), 1.97 – 1.75 (m, 4H), 1.74 – 1.00 (m, 20H), 0.98 – 0.68 (m, 2H).

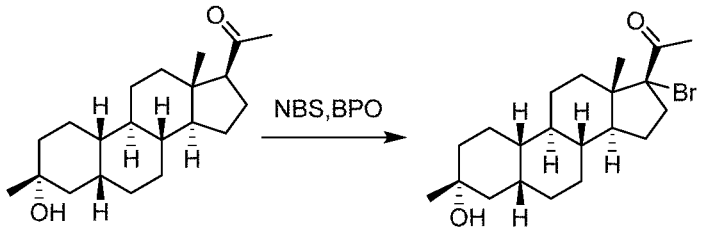
^{19}F NMR (376 MHz, $CDCl_3$) δ -168.20.

Example 174

1-((2aR,4R,6aS,6bR,8aS,8bS,9aS,10aS,10bR)-4-Hydroxy-4,8a-dimethylhexadecahydro cyclopropa[3,4]cyclopenta[1,2-a]phenanthren-8b(2H)-yl)ethan-1-one (174)



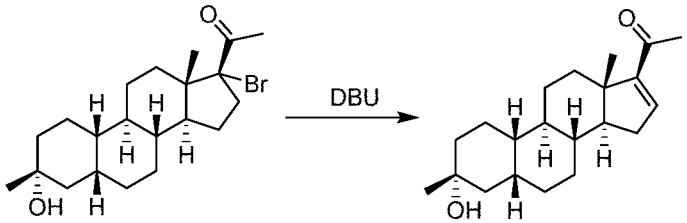
Step 1: Preparation of 1-((3R,5R,8R,9R,10S,13S,14S,17R)-17-bromo-3-hydroxy-3,13-dimethylhexadecahydro -1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one



1-((3R,5R,8R,9R,10S,13S,14S,17S)-3-Hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (600 mg, 1.872 mmol) was dissolved in carbon tetrachloride (10 mL). N-Bromosuccinimide (666 mg, 3.744 mmol) and benzoyl peroxide (48 mg, 0.187 mmol) were added, and then the reaction solution was stirred at 80°C for 2 hours. The reaction solution was cooled to room temperature. Water (30 mL) was added, and then the reaction solution was extracted with ethyl acetate (20 mL×3). The organic phases were combined, washed with saturated saline (30 mL), dried over anhydrous sodium sulfate and filtrated. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by column chromatography (petroleum ether/ethyl acetate=8/1) to obtain 1-((3R,5R,8R,9R,10S,13S,14S,17R)-17-bromo-3-hydroxy-3,13-dimethylhexadecahydro -1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (light yellow solid, 400 mg, yield: 54%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.09-3.01 (m, 1H), 2.38 (s, 3H), 2.32 – 2.20 (m, 1H), 2.10 – 1.98 (m, 1H), 1.97 – 1.72 (m, 7H), 1.71 – 1.58 (m, 1H), 1.57 – 0.94 (m, 15H), 0.89 – 0.81 (m, 1H), 0.76 (s, 3H).

Step 2: Preparation of 1-((3R,5R,8R,9R,10S,13S,14S)-3-hydroxy-3,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one

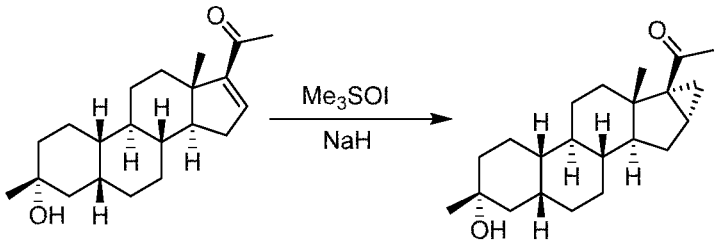


1-((3R,5R,8R,9R,10S,13S,14S,17R)-17-Bromo-3-hydroxy-3,13-dimethylhexadeca

hydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (400 mg, 1 mmol) was dissolved in anhydrous toluene (10 mL). 1,8-Diazabicycloundec-7-ene (913 mg, 6 mmol) was added, and then the reaction solution was stirred at 110°C for 16 hours. The reaction solution was cooled to room temperature. Water (20 mL) was added, and then the reaction solution was extracted with ethyl acetate (20 mL×3). The organic phases were combined, washed with saturated saline (30 mL), dried over anhydrous sodium sulfate and filtrated. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by column chromatography (petroleum ether/ethyl acetate=4/1) to obtain 1-((3R,5R,8R,9R,10S,13S,14S)-3-hydroxy-3,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (colorless oil, 160 mg, yield: 51%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (dd, J = 3.1, 1.7 Hz, 1H), 2.41 – 2.28 (m, 2H), 2.25 (s, 3H), 2.07 – 1.93 (m, 1H), 1.89 – 1.76 (m, 3H), 1.71-1.69 (m, 4H), 1.53-1.41 (m, 5H), 1.37 – 1.29 (m, 4H), 1.27 (s, 3H), 1.24 – 1.07 (m, 3H), 0.89 (s, 3H).

Step 3: Preparation of 1-((2aR,4R,6aS,6bR,8aS,8bS,9aS,10aS,10bR)-4-hydroxy-4,8a-dimethylhexadecahydrocyclopropa[3,4]cyclopenta[1,2-a]phenanthren-8b(2H)-yl)ethan-1-one

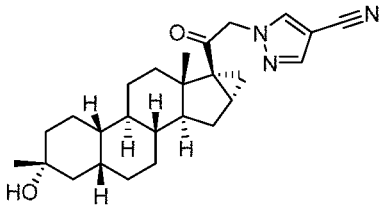


Sodium hydride (45 mg, 1.136 mmol, 60%) was suspended in dimethyl sulfoxide (2 mL). Trimethyl sulfoxide (100 mg, 0.451 mmol) was added, and then the reaction solution was stirred at room temperature for 1 hour. A mixed solution of 1-((3R,5R,8R,9R,10S,13S,14S)-3-hydroxy-3,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (90 mg, 0.284 mmol) and tetrahydrofuran (2 mL) was added, and then the reaction solution was stirred at room temperature for 16 hours. Water (15 mL) was added, and then the reaction solution was extracted with ethyl acetate (10 mL×3). The organic phases were combined, washed with saturated saline (15 mL), dried over anhydrous sodium sulfate and filtrated. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by column chromatography (petroleum ether/ethyl acetate=4/1) to obtain 1-((2aR,4R,6aS,6bR,8aS,8bS,9aS,10aS,10bR)-4-hydroxy-4,8a-dimethylhexadecahydrocyclopropa[3,4]cyclopenta[1,2-a]phenanthren-8b(2H)-yl)ethan-1-one (colorless oil, 40 mg, yield: 43%).

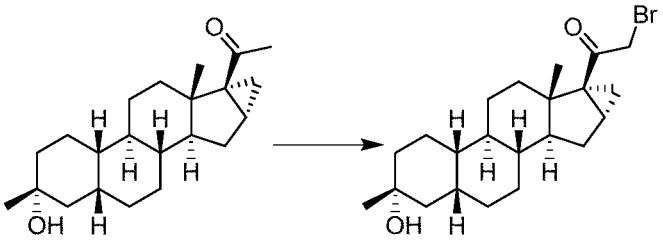
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26 – 2.18 (m, 1H), 1.95 (s, 3H), 1.92 – 1.85 (m, 1H), 1.81 (m, 2H), 1.72 – 1.53 (m, 5H), 1.46 – 1.29 (m, 7H), 1.29 – 1.17 (m, 7H), 1.16 – 1.00 (m, 3H), 0.94 (s, 3H), 0.91 – 0.78 (m, 2H).

Example 175

1-(2-((2aR,4R,6aS,6bR,8aS,8bS,9aS,10aS,10bR)-4-Hydroxy-4,8a-dimethylhexadecahydrocyclopropa[3,4]cyclopenta[1,2-a]phenanthren-8b(2H)-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile (175)

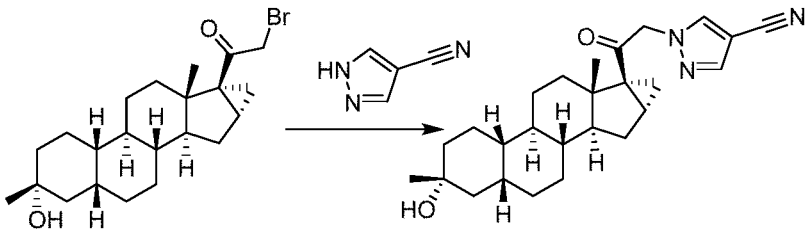


Step 1: Preparation of 2-bromo-1-((2aR,4R,6aS,6bR,8aS,8bS,9aS,10aS,10bR)-4-hydroxy-4,8a-dimethylhexadecahydrocyclopropa[3,4]cyclopenta[1,2-a]phenanthren-8b(2H)-yl)ethan-1-one



1-((2aR,4R,6aS,6bR,8aS,8bS,9aS,10aS,10bR)-4-Hydroxy-4,8a-dimethylhexadecahydrocyclopropa[3,4]cyclopenta[1,2-a]phenanthren-8b(2H)-yl)ethan-1-one (40 mg, 0.121 mmol) was dissolved in methanol (2 mL). A drop of hydrogen bromide and two drops of liquid bromine were added, and then the reaction solution was stirred at room temperature for 1.5 hours. Water (15 mL) was added, and then the reaction solution was extracted with ethyl acetate (10 mL×3). The organic phases were combined, washed with saturated saline (15 mL), dried over anhydrous sodium sulfate and filtrated. The filtrate was concentrated under reduced pressure to obtain 2-bromo-1-((2aR,4R,6aS,6bR,8aS,8bS,9aS,10aS,10bR)-4-hydroxy-4,8a-dimethylhexadecahydrocyclopropa[3,4]cyclopenta[1,2-a]phenanthren-8b(2H)-yl)ethan-1-one (50 mg, crude product).

Step 2: Preparation of 1-(2-((2aR,4R,6aS,6bR,8aS,8bS,9aS,10aS,10bR)-4-hydroxy-4,8a-dimethylhexadecahydrocyclopropa[3,4]cyclopenta[1,2-a]phenanthren-8b(2H)-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile



2-Bromo-1-((2aR,4R,6aS,6bR,8aS,8bS,9aS,10aS,10bR)-4-hydroxy-4,8a-dimethylhexadecahydrocyclopropa[3,4]cyclopenta[1,2-a]phenanthren-8b(2H)-yl)ethan-1-one (40

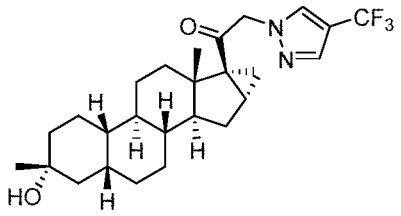
mg, 0.098 mmol) was dissolved in tetrahydrofuran (5 mL). 4-Cyanopyrazole (11 mg, 0.0118 mmol) and potassium carbonate (27 mg, 0.196 mmol) were added, and then the reaction solution was stirred at room temperature for 16 hours. Water (15 mL) was added, and then the reaction solution was extracted with ethyl acetate (10 mL×2). The organic phases were combined, washed with saturated saline (20 mL), dried over anhydrous sodium sulfate and filtrated. The filtrate was concentrated under reduced pressure, and the resulting crude product was purified by high performance liquid chromatography to obtain 1-(2-((2aR,4R,6aS,6bR,8aS,8bS,9aS,10aS,10bR)-4-hydroxy-4,8a-dimethylhexadecahydrocyclopropa[3,4]cyclopenta[1,2-a]phenanthren-8b(2H)-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile (18 mg, yield: 44%).

MS m/z (ESI): 422.2[M+H]$^+$.

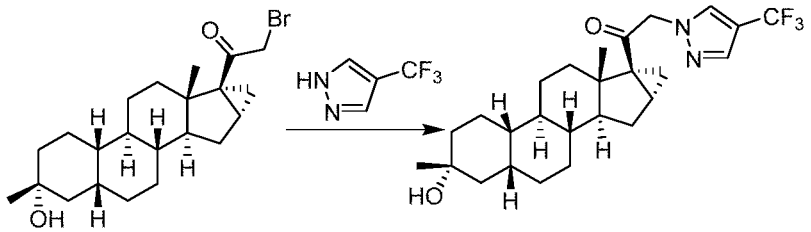
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.74 (s, 1H), 5.11 (d, J = 18.0 Hz, 1H), 4.91 (d, J = 18.0 Hz, 1H), 3.61 – 3.49 (m, 1H), 2.96 (d, J = 8.7 Hz, 1H), 2.17 – 2.05 (m, 2H), 1.90 – 1.70 (m, 5H), 1.68-1.5 (m, 7H), 1.45 – 1.35 (m, 5H), 1.34 – 1.01 (m, 7H), 0.65 (s, 3H).

Example 176

1-((2aR,4R,6aS,6bR,8aS,8bS,9aS,10aS,10bR)-4-Hydroxy-4,8a-dimethylhexadecahydrocyclopropa[3,4]cyclopenta[1,2-a]phenanthren-8b(2H)-yl)-2-(4-(trifluoromethyl)-1H-pyrazol-1-yl)ethan-1-one (176)



Step 1: Preparation of 1-((2aR,4R,6aS,6bR,8aS,8bS,9aS,10aS,10bR)-4-hydroxy-4,8a-dimethylhexadecahydrocyclopropa[3,4]cyclopenta[1,2-a]phenanthren-8b(2H)-yl)-2-(4-(trifluoromethyl)-1H-pyrazol-1-yl)ethan-1-one



2-Bromo-1-((2aR,4R,6aS,6bR,8aS,8bS,9aS,10aS,10bR)-4-hydroxy-4,8a-dimethylhexadecahydrocyclopropa[3,4]cyclopenta[1,2-a]phenanthren-8b(2H)-yl)ethan-1-one (40 mg, 0.098 mmol) was dissolved in tetrahydrofuran (5 mL). 3-Cyanopyrazole (11 mg, 0.0118 mmol) and potassium carbonate (27 mg, 0.196 mmol) were added, and then the reaction solution was stirred at room temperature for 16 hours. Water (15 mL) was added, and then the reaction solution was extracted with ethyl acetate (10 mL×2). The

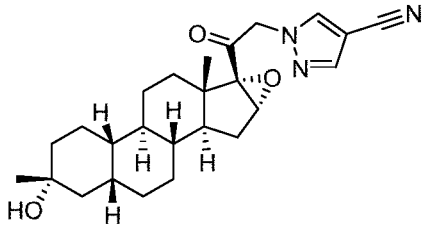
organic phases were combined, washed with saturated saline (20 mL), dried over anhydrous sodium sulfate and filtrated. The filtrate was concentrated under reduced pressure, and the resulting crude product was purified by high performance liquid chromatography to obtain 1-((2aR,4R,6aS,6bR,8aS,8bS,9aS,10aS,10bR)-4-hydroxy-4,8a-dimethylhexadecahydrocyclopropa[3,4]cyclopenta[1,2-a]phenanthren-8b(2H)-yl)-2-(4-(trifluoromethyl)-1H-pyrazol-1-yl)ethan-1-one (18 mg, yield: 44%).

MS m/z (ESI): 465.2$[M+H]^+$

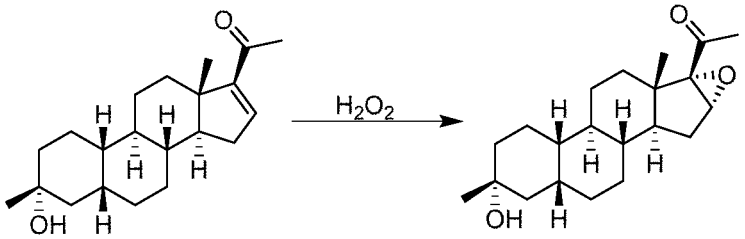
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.70 (s, 1H), 4.90 (d, J = 17.3 Hz, 1H), 4.71 (d, J = 17.3 Hz, 1H), 2.18 (m, 1H), 2.10 – 2.03 (m, 1H), 1.81 (m, 3H), 1.76 – 1.58 (m, 4H), 1.57 – 1.32 (m, 10H), 1.26 (s, 3H), 1.19 – 1.00 (m, 4H), 0.98 (s, 3H), 0.92 (m, 2H).

Example 177

1-(2-((2aR,4R,6aS,6bR,8aS,8bS,9aR,10aS,10bR)-4-Hydroxy-4,8a-dimethylhexadecahydro-8bH-naphtho[2',1':4,5]indeno[1,2-b]oxiren-8b-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile (177)



Step 1: Preparation of 1-((2aR,4R,6aS,6bR,8aS,8bS,9aR,10aS,10bR)-4-hydroxy-4,8a-dimethylhexadecahydro-8bH-naphtho[2',1':4,5]indeno[1,2-b]oxiren-8b-yl)ethan-1-one

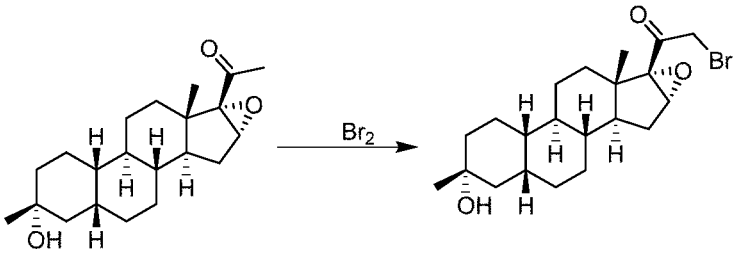


1-((3R,5R,8R,9R,10S,13S,14S)-3-Hydroxy-3,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (80 mg, 0.242 mmol) was dissolved in methanol (5 mL) and water (1 mL). Hydrogen peroxide (1.3 mL) and sodium hydroxide (30 mg, 0.75 mmol) were added, and then the reaction solution was stirred at 0°C for 16 hours. Water (15 mL) was added, and then the reaction solution was extracted with ethyl acetate (15 mL×3). The organic phases were combined, washed with saturated saline (20 mL), dried over anhydrous sodium sulfate and filtrated. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by column chromatography (petroleum ether/ethyl acetate=4/1) to obtain

1-((2aR,4R,6aS,6bR,8aS,8bS,9aR,10aS,10bR)-4-hydroxy-4,8a-dimethylhexadecahydro-8bH-naphtho[2',1':4,5]indeno[1,2-b]oxiren-8b-yl)ethan-1-one (60 mg, yield: 75%).

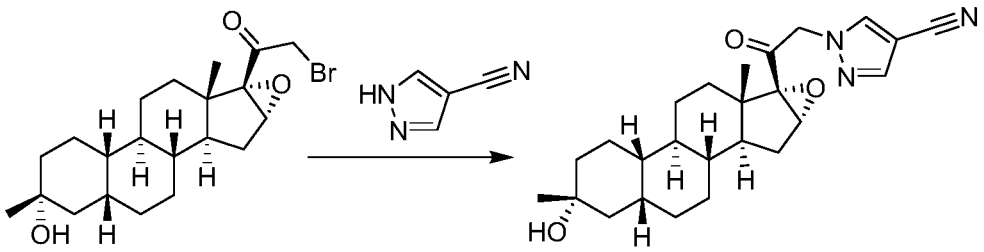
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 1H), 2.03 (s, 3H), 1.94 (m, 1H), 1.87 – 1.75 (m, 3H), 1.74 – 1.61 (m, 3H), 1.47 (m, 2H), 1.43 – 1.37 (m, 4H), 1.35 – 1.30 (m, 3H), 1.25 (s, 6H), 1.17 – 1.07 (m, 3H), 1.03 (s, 3H).

Step 2: Preparation of 2-bromo-1-((2aR,4R,6aS,6bR,8aS,8bS,9aR,10aS,10bR)-4-hydroxy-4,8a-dimethylhexadecahydro-8bH-naphtho[2',1':4,5]indeno[1,2-b]oxiren-8b-yl)ethan-1-one



1-((2aR,4R,6aS,6bR,8aS,8bS,9aR,10aS,10bR)-4-Hydroxy-4,8a-dimethylhexadecahydro-8bH-naphtho[2',1':4,5]indeno[1,2-b]oxiren-8b-yl)ethan-1-one (50 mg, 0.15 mmol) was dissolved in methanol (3 mL). A drop of hydrogen bromide and two drops of liquid bromine were added, and then the reaction solution was stirred at room temperature for 8 hours. Water (10 mL) was added, and then the reaction solution was extracted with ethyl acetate (10 mL×3). The organic phases were combined, washed with saturated saline (15 mL), dried over anhydrous sodium sulfate and filtrated. The filtrate was concentrated under reduced pressure to obtain 2-bromo-1-((2aR,4R,6aS,6bR,8aS,8bS,9aR,10aS,10bR)-4-hydroxy-4,8a-dimethylhexadecahydro-8bH-naphtho[2',1':4,5]indeno[1,2-b]oxiren-8b-yl)ethan-1-one (60 mg, crude product).

Step 3: Preparation of 1-(2-((2aR,4R,6aS,6bR,8aS,8bS,9aR,10aS,10bR)-4-hydroxy-4,8a-dimethylhexadecahydro-8bH-naphtho[2',1':4,5]indeno[1,2-b]oxiren-8b-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile



2-Bromo-1-((2aR,4R,6aS,6bR,8aS,8bS,9aR,10aS,10bR)-4-hydroxy-4,8a-dimethylhexadecahydro-8bH-naphtho[2',1':4,5]indeno[1,2-b]oxiren-8b-yl)ethan-1-one (60 mg, 0.146 mmol) was dissolved in tetrahydrofuran (3 mL). 4-Cyanopyrazole (20 mg, 0.219 mmol) and potassium carbonate (60 mg, 0.438 mmol) were added, and then the reaction solution was stirred at room temperature for 16 hours. Water (15 mL) was added, and then the reaction solution was extracted with ethyl acetate (10 mL×3). The organic

phases were combined, washed with saturated saline (15 mL), dried over anhydrous sodium sulfate and filtrated. The filtrate was concentrated under reduced pressure, and the resulting crude product was purified by high performance liquid chromatography to obtain

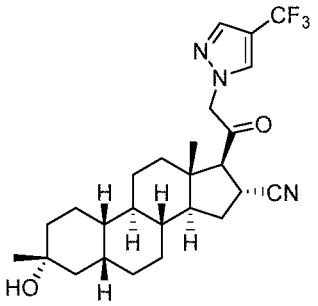
1-(2-((2aR,4R,6aS,6bR,8aS,8bS,9aR,10aS,10bR)-4-hydroxy-4,8a-dimethylhexadecahydro-8bH-naphtho[2',1':4,5]indeno[1,2-b]oxiren-8b-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile (18 mg, yield: 29%).

MS m/z (ESI): 424.2[M+H]$^+$

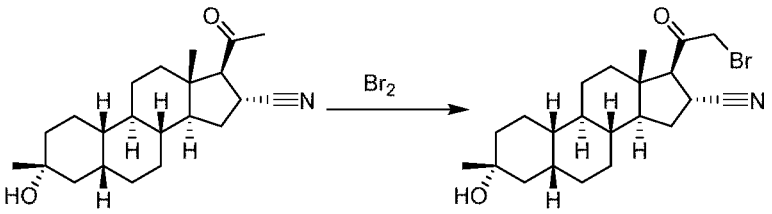
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.82 (s, 1H), 5.07 (d, J = 18.3 Hz, 1H), 4.87 (d, J = 18.3 Hz, 1H), 3.85 (s, 1H), 2.03 (dd, J = 13.1, 5.6 Hz, 1H), 1.94-1.91 (m, 1H), 1.84-1.78 (m, 3H), 1.76 – 1.64 (m, 3H), 1.52 – 1.28 (m, 10H), 1.26 (s, 4H), 1.19 – 1.09 (m, 3H), 1.07 (s, 3H).

Example 178

(3R,5R,8R,9R,10S,13S,14S,16R,17S)-3-Hydroxy-3,13-dimethyl-17-(2-(4-(trifluoromethyl)-1H-pyrazol-1-yl)acetyl)hexadecahydro-1H-cyclopenta[a]phenanthrene-16-carbonitrile (178)



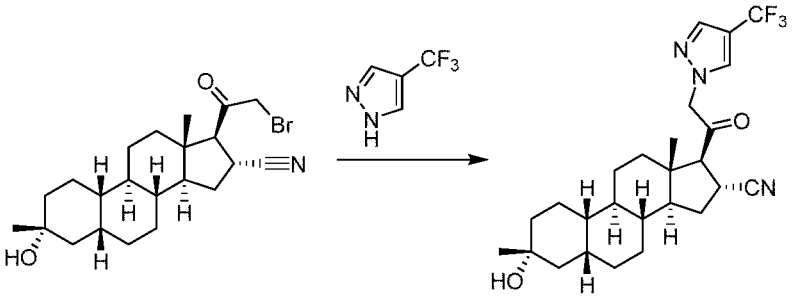
Step 1: Preparation of (3R,5R,8R,9R,10S,13S,14S,16R,17S)-17-(2-bromoacetyl)-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthrene-16-carbonitrile



(3R,5R,8R,9R,10S,13S,14S,16R,17S)-17-Acetyl-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthrene-16-carbonitrile (120 mg, 0.349 mmol) was dissolved in methanol (3 mL). Liquid bromine (83 mg, 0.524 mmol) and a drop of hydrogen bromide were added, and then the reaction solution was stirred at room temperature for 5 hours. Water (30 mL) was added, and then the reaction solution was extracted with ethyl acetate (20 mL×3). The organic phases were combined, washed with saturated saline (30 mL), dried over anhydrous sodium sulfate and filtrated. The filtrate was concentrated under reduced pressure to dryness to obtain (3R,5R,8R,9R,10S,13S,14S,16R,17S)-17-(2-bromoacetyl)-3-hydroxy-3,13-dimethylhex

adecahydro-1H-cyclopenta[a]phenanthrene-16-carbonitrile (140 mg, crude product).

Step 2: Preparation of (3R,5R,8R,9R,10S,13S,14S,16R,17S)-3-hydroxy-3,13-dimethyl-17-(2-(4-(trifluoromethyl)-1H-pyrazol-1-yl)acetyl)hexadecahydro-1H-cyclopenta[a]phenanthrene-16-carbonitrile



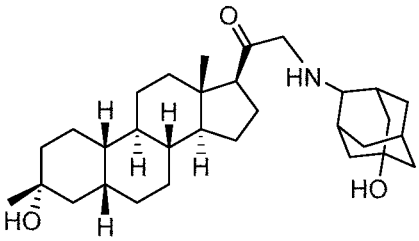
A mixture of (3R,5R,8R,9R,10S,13S,14S,16R,17S)-17-(2-bromoacetyl)-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthrene-16-carbonitrile (100 mg, 0.23 mmol), 4-(trifluoromethyl)-1H-pyrazole (63 mg, 0.46 mmol), potassium carbonate (95 mg, 0.69 mmol) and tetrahydrofuran (5 mL) was stirred at room temperature for 16 hours. Water (20 mL) was added, and then the reaction solution was extracted with ethyl acetate (20 mL×3). The organic phases were combined, washed with saturated saline (30 mL), dried over anhydrous sodium sulfate and filtrated. The filtrate was concentrated under reduced pressure to dryness, and the resulting crude product was purified by high performance liquid chromatography to obtain (3R,5R,8R,9R,10S,13S,14S,16R,17S)-3-hydroxy-3,13-dimethyl-17-(2-(4-(trifluoromethyl)-1H-pyrazol-1-yl)acetyl)hexadecahydro-1H-cyclopenta[a]phenanthrene-16-carbonitrile (25 mg, yield: 23%).

MS m/z (ESI): 478.2$[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.74 (s, 1H), 5.01 (dd, J = 77.6, 18.0 Hz, 2H), 3.65 – 3.36 (m, 1H), 2.96 (d, J = 8.7 Hz, 1H), 2.18 – 2.04 (m, 2H), 1.89 – 1.71 (m, 5H), 1.69-1.60 (m, 5H), 1.46-1.39 (m, 5H), 1.32-1.25 (m, 5H), 1.24 – 1.03 (m, 3H), 0.65 (s, 3H).

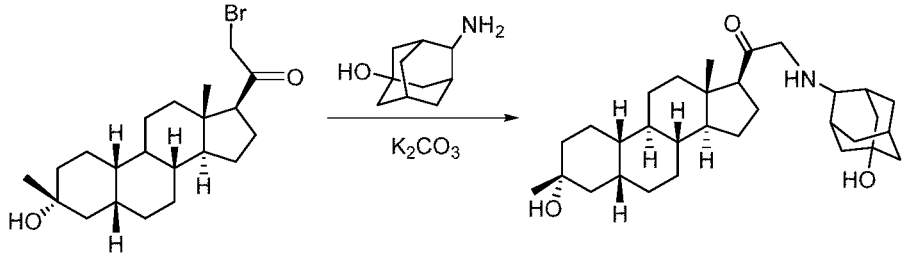
Example 179

2-(1-Hydroxy-4-aminoadamantane)-1-((3R,5R,8R,9R,10S,13S,14S,17S)-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (179)



Step 1: Preparation of 2-(1-hydroxy-4-aminoadamantane)-1-((3R,5R,8R,9R,10S,13S,14S,17S)-3-hydroxy-3,1

3-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one



In accordance with Example 5, 2-bromo-1-((3R,5R,8R,10S,13S,14S,17S)-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one was used as the starting material, accordingly, 2-(1-hydroxy-4-aminoadamantane)-1-((3R,5R,8R,9R,10S,13S,14S,17S)-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethan-1-one (7.5 mg, yield: 10.2%) was obtained .

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.55 (d, J = 2.8 Hz, 2H), 2.72 (s, 1H), 2.50 (t, J = 8.9 Hz, 1H), 2.29 – 0.93 (m, 40H), 0.64 (s, 3H).

Biological Assay and Evaluation

The present invention is further described below in combination with the following test examples, which are not intended to limit the scope of the present invention.

I. $GABA_A$ receptor binding ability test of the compound of the present invention

1.1 Experimental objective: The objective of this test example is to measure the ability of the compound to allosterically inhibit the binding of the ion channel blocker (*tert*-butylbicyclophosphorothionate (TBPS)) to the GABA-A receptor.

Experimental instruments:

Instruments/Consumables	Supplier	Model
Vortex mixer	IKA	MS3 basic
Electric thermostat incubator	Shanghai Yiheng Instrument Co., Ltd.	DHP-9032
TopCount	PerkinElmer	NTX
Universal Harvester	Perkin Elmer	UNIFILTER-96
High-speed floor-standing centrifuge	Thermo	LYNX 4000
Glass tissue homogenizer	Nanjing Luanyu Glass Instrument Co., Ltd.	50 ml
Sprague-Dawley Rat	Pharmaron	
Protease inhibitor	roche	11836170001

1.1 ml deep 96-well plate, round bottom	Axygen	P-DW-11-C
ULTIMA GOLD	Perkin Elmer	77-16061
UNIFILTER-96 GF/B filter plate	Perkin Elmer	6005177
Polyethylenimine (PEI), branched	Sigma	408727

1.2 Experimental procedures

1.2.1 Extraction of cerebral cortex cell membrane:

1. The cerebral cortex of male Sprague-Dawley rat was isolated.

2. A pre-chilled 0.32 M sucrose solution (one tablet of protease inhibitor was added per 100 ml) was added to the cerebral cortex (the volume of sucrose solution was 10 times the volume of the cerebral cortex). The mixture was crushed with a 50 mL glass tissue homogenizer in batches and mixed well.

3. The mixture was centrifuged at 1500 g, 4°C for 10 minutes, and the supernatant was collected.

4. The mixture was centrifuged at 20000 g, 4°C for 30 minutes, and the supernatant was discarded.

5. The precipitate was resuspended with the pre-chilled phosphate buffer saline (PBS) (one tablet of protease inhibitor was added per 100 ml). An average of 4 ml of PBS was added per rat, and the mixture was mixed well by a glass tissue homogenizer.

6. The mixture was centrifuged at 10000 g, 4°C for 10 minutes, and the supernatant was discarded.

7. Steps 5 and 6 were repeated three times.

8. Finally, the precipitate was resuspended with 4 volumes of PBS. The resulting solution was dispensed, frozen in liquid nitrogen, and stored at -80°C.

9. The protein concentration was measured by the bicinchoninic acid (BCA) method.

1.2.2 35S-TBPS binding assay

1. 230 μL of PBS was added to each well of a well plate with 1.1 ml volume.

2. 60 μL of the cerebral cortex cell membrane (5 μg/μL) solution was added to each well, and the mixture was mixed well.

3. The test compound (3 μL per well) was added, and the plate was incubated at 25°C for 5 minutes. The DMSO concentration was 1%. The initial compound concentration was 1 μM, and a 3-fold dilution in gradient was carried out to obtain a total of 8 gradients and 2 replicates. 1% DMSO was used as a negative control, and 10 μM P026-2 was used as a positive control.

4. GABA was added at a final concentration of 5 μM, and incubated at 25°C for 5 minutes. 1 mM GABA solution was formulated, and 1.5 μL of the solution was added to each well.

5. 35S-TBPS was added at a final concentration of 2 nM. The concentration of

isotope mother solution was 9.7 μM. After dilution with PBS for 100 times, 6 μL of the diluted isotope solution was added to each well.

6. The plate was incubated at 4°C for 20 hours.

7. The FilterMate GF/C plate was pre-treated with 0.5% PEI, and incubated at 4°C for 1 hour.

8. The FilterMate GF/C plate was washed with Universal Harvester twice, 50 ml PBS each time.

9. The reaction solution was transferred to the GF/C plate, and each well was washed 4 times with 900 μL of PBS.

10. The washed GF/C plate was placed at 55°C and dried for 10 minutes.

11. 40 μL of scintillation solution was added to each well, and the CPM value was read with TopCount.

1.2.3 Experimental data processing method:

In the experiment, the CPM (counts per minute) value was read with TopCount. According to the readings of the High control (DMSO) and the Low control (10 μM the positive compound) experimental groups, the % inhibition was calculated based on the following formula:

$$\% \text{ Inhibition} = 100 \times (CPM_{High\ control} - CPM_{Sample})/(CPM_{High\ control} - CPM_{Low\ control})$$

The IC_{50} of the compound was calculated according to the following 4-parameter nonlinear logic formula:

Y=Bottom + (Top-Bottom)/(1+10^((LogIC50-X)*HillSlope)),

wherein:

X represents the log of compound concentration,

Y represents the % Inhibition.

The effect of the compound of the present invention on the TBPS binding activity was determined by the above test, and the measured IC_{50} values are shown in Table 1.

Table 1 IC_{50} of the compound of the present invention on inhibiting the TBPS binding activity

Example No.	**35S-TBPS bindng test (nM)**	Example No.	**35S-TBPS bindng test (nM)**
1	15.0	95	34.1
2	24.3	97	30.2
3	14.9	98	37.8
5	13.5	101	11.4
6	3.1	102	65
7	14.7	103	10.2
8	42	121	18.3
9	21.3	122	46.0
13	4.6	125	30.7
18	6.4	126	4.9

33	18.3	127	6.1
34	28.1	128	15.8
37A	15.4	130	4.2
37B	15.4	131	8.0
41	22.7	132	24.6
42	38.3	133	17.8
46	28.7	134	6.7
51	5.0	135	4.3
52	65	136	26.5
53	12.3	137	16.2
54A	11.8	138	25.2
54B	11.8	139	27.0
59	6.2	140	33.1
60	8.2	141	23.9
62	5.4	142	16.2
63	6.1	143	28.5
64	8.6	144	18.6
69	7.6	145	16.9
71	7.5	146	21.4
91	9.6	147	24.4
92	10.8	149	25.6
93A	3.0	150	8.8
93B	3.0	151	26.2
94	10.2	166	38.4

Conclusion: The compounds of the examples of the present invention have a significant inhibitory effect on the TBPS binding activity.

II. Pharmacokinetic assay in Balb/c mice

1. Test objective:

Balb/c mice were used as test animals. The pharmacokinetic behavior in mice (plasma and brain tissue) of the compounds of Examples 2, 3, 5, 6, 9, 13, 59, 60, 61, 63, 71-74, 81, 103, 130, 134, 135, 137, 138, 140, 141, 143, 145 and 146 orally administered at a dose of 5 mg/kg was studied.

2. Test protocol

2.1 Test compounds:

Compounds of Examples 59, 60, 61, 63, 71-74, 81, 103, 130, 134, 135, 137, 138, 140, 141, 143, 145 and 146 of the present invention, prepared by the applicant.

2.2 Test animals:

Male Balb/c mice were purchased from Shanghai Jiesijie Laboratory Animal Co., LTD, with Certificate No.: SCXK (Shanghai) 2013-0006 N0.311620400001794.

2.3 Administration:

Each group had 24 male Balb/c mice. After an overnight fast, Balb/c mice were administered p.o. with the test compound at an administration dose of 5 mg/kg and an administration volume of 10 mL/kg.

2.4 Sample collection:

0.2 ml of blood was taken from the heart before administration and at 0, 0.5, 1, 2, 4, 6, 8 and 24 hours after administration. The samples were stored in EDTA-K_2 tubes, and centrifuged for 6 minutes at 4°C, 6000 rpm to separate the plasma. The plasma samples were stored at -80°C. The mice were sacrificed with CO_2, and the whole brain tissue was taken out, weighed, placed in a 2 mL centrifuge tube and stored at -80°C.

2.5 Sample processing:

1) 160 μL of acetonitrile was added to 40 μL of the plasma sample for precipitation, and then the mixture was centrifuged for 5-20 minutes at 3500 × g.

2) 90 μL of acetonitrile containing the internal standard (100 ng/mL) was added to 30 μL of the plasma and brain homogenate samples for precipitation, and then the mixture was centrifuged for 8 minutes at 13000 rpm.

3) 70 μL of the treated supernatant was taken and added to 70 μL of water, and mixed by vortex for 10 minutes. 20 μL of the mixture was taken to analyze the concentration of the test compound by LC/MS/MS. LC/MS/MS analysis instrument: AB Sciex API 4000 Qtrap.

2.6 Liquid chromatography analysis

- Liquid chromatography condition: Shimadzu LC-20AD pump.
- Chromatographic column: Agilent ZORBAX XDB-C18 (50×2.1 mm, 3.5 μm);
- Mobile phase: Eluent A was 0.1% formic acid in water, and Eluent B was acetonitrile.
- Flow rate: 0.4 mL/min
- Elution time: 0-4.0 minutes, the eluent is as follows:

Time/minute	Eluent A	Eluent B
0.01	90%	10%
0.5	90%	10%
0.8	5%	95%
2.4	5%	95%
2.5	90%	10%
4.0	Stop	

3. Test results and analysis

The main parameters of pharmacokinetics were calculated by WinNonlin 6.1. The results of pharmacokinetic test in mice are shown in Table 2 below:

Table 2: Results of pharmacokinetic test in mice

Example No.	Pharmacokinetic test (5 mg/kg)					
	Peak time	Plasma	Area under curve	Area under curve	Half-life	Mean

		concentration				residence time
	t_{max}(ng/mL)	C_{max}(ng/mL)	AUC_{0-t}(ng/mL×h)	$AUC_{0-\infty}$(ng/mL×h)	$t_{1/2}$(h)	MRT(h)
2 plasma	0.5	1099.3	1360.5	1374.2	0.54	1.21
2 brain tissue	0.5	636.7	839.7	913.0	2.84	2.39
3 plasma	0.5	673.3	569.7	573.8	0.50	1.01
3 brain tissue	0.5	690.3	718.9	721.8	0.50	1.10
5 plasma	0.5	461.0	1241.5	1254.2	5.12	4.80
5 brain tissue	0.5	1406.3	2303.0	3067.4	4.72	5.53
6 plasma	0.5	219.0	409.0	483.8	3.19	4.03
6 brain tissue	0.5	464.0	917.2	964.3	1.90	2.40
9 plasma	0.5	663.7	774.9	778.0	0.9	1.1
9 brain tissue	0.5	605.3	677.0	679.9	0.5	0.9
13 plasma	1.0	1210	5057.2	5065.8	2.5	3.6
13 brain tissue	1.0	1060.0	4731.4	4744.7	2.5	3.9
59 plasma	0.5	553.7	1305.0	1316.9	2.99	4.15
59 brain tissue	1.0	678.0	2642.7	2680.6	3.18	4.81
60 plasma	0.5	719.7	1704.9	1772.1	1.64	1.43
60 brain tissue	1.0	998.0	2403.0	2498.4	2.37	2.35
61 plasma	0.5	524.7	588.5	604.6	3.27	1.48
61 brain tissue	0.5	710.7	657.1	676.0	3.95	1.41
63 plasma	0.5	335.3	599	604.3	2.58	2.42
63 brain tissue	0.5	486	602.6	617.9	0.72	1.21
71 plasma	1.0	508.3	1577.3	1758.8	2.04	3.50
71	1.0	382.7	1127.8	1275.4	2.00	3.66

brain tissue						
72 plasma	0.5	1146.3	2967.0	2972.0	2.79	3.71
72 brain tissue	0.5	723.7	2051.0	2237.3	2.12	3.17
73 plasma	0.5	1303.3	2430.5	2482.0	1.40	2.06
73 brain tissue	0.5	635.7	1098.1	1117.6	1.31	1.91
74 plasma	0.5	2136.7	7156.4	8601.3	3.06	4.59
74 brain tissue	1.0	1523.3	5846.2	6511.2	2.28	3.82
81 plasma	1.0	1146.7	4643.8	5922.3	2.64	4.96
81 brain tissue	1.0	296.2	1439.7	2234.7	5.59	7.97
103 plasma	1.0	386	1034.8	1060.9	1.19	2.12
103 brain tissue	1.0	626.3	1676.2	1706.2	1.12	2.07
130 plasma	0.5	307.3	1391.8	1560	2.21	3.83
130 brain tissue	0.5	563.2	2308.8	2625.8	2.49	3.88
134 plasma	0.5	1750.0	4627.3	5132.2	1.78	3.31
134 brain tissue	1.0	892.0	3205.7	3501.3	1.59	3.22
135 plasma	2.0	640.3	4103.8	4110.3	2.06	4.38
135 brain tissue	2.0	724.0	3736.7	4450.7	2.82	4.71
137 plasma	1.0	762.7	2785.0	3792.4	3.85	5.88
137 brain tissue	1.0	613.0	2126.5	3162.6	6.02	7.58
138 plasma	0.5	432.0	661.7	729.8	1.66	2.83
138 brain tissue	0.5	314.0	772.7	934.8	1.47	2.38
140 plasma	0.5	2483.3	5982.0	6106.9	1.19	2.22
140 brain tissue	0.5	1738.0	4327.1	4539.1	1.21	2.10

141 plasma	0.5	1633.3	3545.3	3634.6	1.35	2.55
141 brain tissue	0.5	1048.0	2153.2	2251.2	1.68	2.68
143 plasma	0.5	1650.0	6287.8	6492.4	1.70	3.08
143 brain tissue	2.0	812.0	8818.0	9215.1	3.95	7.81
145 plasma	1.0	2986.7	13411.8	13415.2	1.75	3.47
145 brain tissue	1.0	1480.0	4821.6	5273.3	2.09	3.40
146 plasma	1.0	2086.7	7785.5	8000.6	1.45	2.97
146 brain tissue	1.0	1966.0	8677.8	12488.1	4.66	6.73

It can be seen from the results of the pharmacokinetic test of mice in the table that the compounds of the examples of the present invention showed good metabolic properties, and both the exposure amount AUC and the maximum blood drug concentration C_{max} performed well.

III. In vivo pharmacodynamic test in the forced swimming model in mice

3.1 Experimental objective

The antidepressant effect of the compound was evaluated by the forced swimming model in mice.

3.2 Main instruments and reagents of the experiment

3.2.1 Instruments

Forced swimming device (JLBehv-FSC-4, Shanghai Jiliang Software Technology Co., Ltd.).

3.2.2 Reagents

Sodium carboxymethyl cellulose (CMC-Na, SLBV9664, Sigma)

Tween 80 (BCBV8843, Sigma)

3.2.3 Test compounds

Compounds of Example 2, Example 3, Example 5, Example 6, Example 9, Example 13, Examples 59-63, Examples 71-74, Example 103, Example 135, Example 137, Example 145 and Example 146 of the present invention, prepared by the applicant.

3.3 Experimental procedures

3.3.1 Adaptation:

Male ICR mice (25-35 g) were adapted in the test environment for 3 days before the forced swimming test.

According to the test design, the mice were randomly grouped on the day before the test according to body weight, with 12 mice in each group. Before the test, the compounds of each example were administered intragastrically according to the Tmax

thereof in the brain in mice pharmacokinetic test as follows:

1) Model group (0.5% CMC-Na -1% Tween 80 solution, *p.o.*, 10 mL/kg);

2) Compounds of Example 2, Example 3, Example 5, Example 6, Example 9, Examples 59-63, Examples 71-73, Example 103, Example 135, Example 137, Example 145 and Example 146 (10 mg/kg, *p.o.*, 10 mL/kg); Example 13 and Example 74 (5 mg/kg, *p.o.*, 5 mL/kg).

When being administered, the compounds of each example were suspended in 0.5% CMC-Na +1% Tween 80 solution to the desired concentration.

3.3.2 Forced swimming test:

0.5-1 hour after administration, ICR mice were placed in a forced swimming device (transparent glass drum (water depth 18 cm, water temperature 25-26°C), one mouse per tank) and forced to swim for 6 minutes. The forced swimming device recorded the floating time of the ICR mice during the entire 6 minutes, and the data of the latter four minutes was used for data analysis. The mice were taken out immediately after the swimming test, wiped dry and put back in their original cages.

Note: The criterion for determining the immobility time is that the mouse stops struggling in water and floats, and there are only slight limb movements to keep the head floating on the water.

3.4 Data analysis

Floating time percentage = 100 *floating time/240s.

3.5 Test data:

Example No.	Dose (mpk)	Mean (immobility, s)	Mean (immobility, %)
Vehicle	/	163.70	68.22
Example 2	10	130.22	54.26
Example 3	10	68.39	28.50
Example 5	10	143.81	59.93
Example 13	5	138.22	57.60
Example 60	10	84.90	35.30
Example 61	10	85.8	35.75
Example 71	10	134.21	55.92
Example 72	10	85.77	35.74
Example 73	10	70.96	29.57
Example 74	5	91.21	38.00
Example 137	10	88.61	36.92
Example 145	5	73.72	30.72
Example 146	5	80.5	33.54

3.6 Test results

It can be seen from the above results that the compounds of the examples of the present application can significantly shorten the cumulative immobility time of the forced-swimming mice, and have a significant antidepressant effect.

The immobility time during the latter four minutes of the compounds of Example 3, Example 60, Example 61, Example 72, Example 73, Example 137 and Example 146

had a very significant difference compared with that of the model group.

IV. In vivo pharmacodynamic test in the PTZ-induced epilepsy model in mice

4.1 Test objective

The PTZ-induced epilepsy model in CD-1 mice was established, and the antiepileptic effect of the compounds of Example 3, Example 60, Example 61 and Example 74 was evaluated using this model.

4.2 Test method

4.2.1 Test animals

50 male CD-1 mice were purchased from Beijing Vital River Laboratory Animal Technology Co. Ltd. The test animals were adapted at the animal room in the third building of Shanghai ChemPartner Co., Ltd for 7 days before the test. The average body weight of the animals on the test day was 32.2±0.2 grams. Feeding environment: 5 animals/cage, room temperature 23±2°C, 12/12 hours of light and dark cycle, free acess to food and water.

The mice were randomly grouped for the test on the test day.

4.2.2 Test compounds

Compounds of Example 3, Example 60, Example 61 and Example 74 (prepared by the applicant). The test compounds were stored in a refrigerator at 4°C.

Table 3: Test reagent information

Name	Article number	Batch number	Property	Supplier	Total weight	Purity	Store condition
pentylenetetrazol (PTZ)	P6500	SLBD3876V	White crystal	Sigma	25 g	100%	-20°C refrigeration
Sodium carboxymethyl cellulose	9004-32-4	LAB0R36	White solid	Beijing J&K Scientific Co., Ltd.	100G	800cps	Room temperature/dry/in the dark
Tween-80	9005-65-6	P1279207	Transparent liquid	GENERAL-REAGENT®	500 mL	100%	Room temperature/dry
Hydroxypropyl β-cyclodextrin	19184C	OP1901A	White powder	Seebio Biotech	500 g	≥98%	2-8°C refrigeration
0.9% sodium chloride injection	H37022749	H18010314	Transparent liquid	Shandong Hualu Pharmaceutical Co., Ltd.	500 mL	100%	Room temperature/dry

4.2.1 Test equipments

- 1 ml sterile disposable syringe with needle (purchased from Zhejiang

Kangdelai Medical Devices Co., Ltd.)

- Pipette: Eppendorf Research Plus (100-1000μL)
- Vortex mixer: Kylin-Bell Vortex 5
- Ultrasonic instrument: JL-360 ultrasonic cleaner
- Balance: METTLER TOLEDO XS204 precision balance
- Balance: METTLER TOLEDO XS6002S electronic balance
- Plexiglass box: 25 cm length * 15 cm width * 15 cm hight with one opaque side wall, custom made by Suzhou Fengshi Laboratory Animal Equipment Co., Ltd
- 3-channel timer: Oregon/Model NO.WB-388.

4.2.2 Test animal grouping

1) Vehicle/PTZ: 0.5% CMC-Na+1% Tween-80 (10 ml/kg, p.o.), administered 0.5 hr before the PTZ administration; PTZ (120 ml/kg, s.c.), administered before the test;

2) 3 mg/kg of the compounds of Examples/PTZ: the compounds of Example 3, Example 60, Example 61 and Example 74 (3 mg/kg, 10 ml/kg, p.o.), administered 0.5 hr before the PTZ administration; PTZ (120 ml/kg, s.c.), administered before the test.

4.3 Experimental procedures

4.3.1 Solvent formulation

1) 0.5% CMC-Na+1%Tween-80 (administration volume: 10 mL/kg):

1 g of sodium carboxymethyl cellulose was precisely weighed and added to a 250 mL solvent bottle, then 150 mL of double-distilled water was added. The mixture was stirred at room temperature for 4 hours with a magnetic stirrer to obtain a uniform and clear solution. 2 mL of Tween-80 was slowly added, and the mixture was stirred at room temperature for 3 hours to obtain a uniform and clear solution. The solution was slowly transferred to a 200 mL volumetric flask, and double distilled water was added to the constant volume of 200 mL. The solution was transferred to a 250 mL solvent bottle, and stirred for 1 hour with a magnetic stirrer to obtain a uniform and clear solution.

2) 30% hydroxypropyl-β-cyclodextrin:

30.6122 g of hydroxypropyl-β-cyclodextrin (purity: 98%) was precisely weighed and added to a 100 mL solvent bottle, then 60 mL of double-distilled water was added. The mixture was mixed by vortex for 3 minutes, and treated by ultrasound at room temperature for 15 minutes to obtain a uniform and clear solution. Double distilled water was added to the constant volume of 100 mL, mixed by vortex for 1 minute, and treated by ultrasound at room temperature for 5 minutes to obtain a uniform and clear solution.

4.3.2 Test compound formulation

1) 12 mg/mL PTZ (dose: 120 mg/kg; administration volume: 10 mL/kg):

248 mg of PTZ was precisely weighed and added to a 40 mL brown flask, then 20.667 mL of physiological saline was added. The mixture was mixed by vortex for 2 minutes, and treated by ultrasound at room temperature for 2 minutes to obtain a

uniform and clear solution (concentration: 12 mg/mL).

2) 0.3 mg/mL of the compounds of Example 5 or Example 23 (dose: 3 mg/kg; administration volume: 10 mL/kg):

A certain amount of 0.5% CMC-Na+1% Tween-80 was taken and added to a flask containing a certain amount of the compounds of Example 5 or Example 23. The mixture was mixed by vortex for 3 minutes, and treated by ultrasound at room temperature for 15 minutes to obtain a uniform suspension (concentration: 0.3 mg/mL).

4.3.3 Test method

1) The test animals were transferred to the operating room to adapt to the environment 1 hour before the test;

2) The animals were randomly grouped, marked and weighed;

3) The compounds of Example 3, Example 60, Example 61 and Example 74 were administered respectively 1 hour before the PTZ administration, or 0.5% CMC-Na+1% Tween-80, the compounds of Example 3, Example 60, Example 61 and Example 74 were administered respectively 0.5 hour before the PTZ administration;

4) PTZ (120 mg/kg) was administrated subcutaneously before the test observation, and this time point was recorded as the observation start point;

5) After the administration of PTZ, the animal was immediately placed in the observation box and observed for 30 minutes, and the followings were recorded: a) the incubation period of the first clonic seizure, b) the incubation period of the first generalized tonic seizure, c) the number of clonic seizures, d) the number of generalized tonic seizures, e) the time when the animal died, 6) if the animal did not have seizures during the 30-minute observation period, the incubation period was recorded as 1800 sec and the number of seizures was recorded as 0.

- Clonic seizure: generalized clonic seizure in animals lasts for more than 3 seconds, and is accompanied by a fall;
- Tonic seizure: the limbs straightens 90° to the body;

6) The possible side effects induced by the drug after the administration were observed and recorded, which can be divided into four levels:

- None: normal
- Mild sedation
- Moderate sedation
- Severe sedation

7) The test was carried out from 12:00 am to 16:30 pm.

4.4 Adaptation to the environment

The test animals were transferred to the operating room to adapt to the environment 1 hour before the test.

4.5 Grouping and administration

The mice were randomly grouped, marked and weighed; 10 mice per group. The test compound was administered orally at an administration volume of 10 mL/kg 30-60

minutes before the PTZ administration.

4.6 PTZ modeling and testing

PTZ (120 mg/kg) was administrated subcutaneously before the test observation, and this time point was recorded as the observation start point; after the administration of PTZ, the animal was immediately placed in the observation box and observed for 30 minutes, and the followings were recorded: a) the incubation period of the first clonic seizure, b) the incubation period of the first generalized tonic seizure, c) the number of clonic seizures, d) the number of generalized tonic seizures, e) the time when the animal died. If the animal did not have seizures during the 30-minute observation period, the incubation period was recorded as 1800 sec and the number of seizures was recorded as 0.

4.7 Data analysis

All measurement data were expressed as Mean ± SEM, and analysed with Prism 6.0 statistical software.

4.7 Test data:

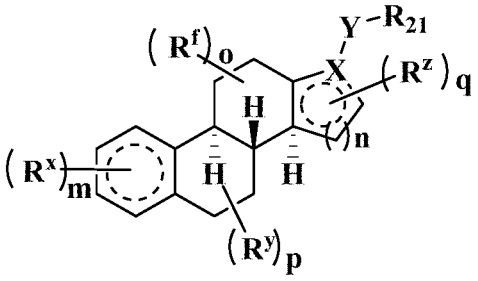
Example No.	Dose (mpk)	Incubation period of the clonic seizure (sec)	Number of clonic seizures	Incubation period of the generalized tonic seizure (sec)	Number of generalized tonic seizures	Time when the animal died (sec)	Mortality rate (%)
		Mean±SEM	Mean	Mean	Mean	Mean	
Vehicle	/	331.4±61.2	2.1±0.2	821.6±107.7	1.0±0.0	839.8±108.0	100%
3	3	902.9±200.8	1.3±0.3	1736.0±63.2	0.1±0.1	1739.8±60.2	10%
60	3	1308.1±170.1	0.5±0.2	1800.0±0.0	0.0±0.0	1800.0±0.0	0%
61	3	841.4±179.8	1.9±0.4	1497.4±124.3	0.5±0.2	1573.1±117.9	40%
74	3	635.4±149.9	1.8±0.3	1506.8±149.8	0.3±0.2	1618.1±121.3	30%

4.9 Test results

The compounds of the examples significantly prolonged the incubation period of clonic seizure and generalized tonic seizure and reduced the number of clonic seizures and generalized tonic seizures compared with the control group. The compounds of the examples can protect 60%-100% of animals from death, significantly prolong the incubation period of death, and have a good antiepileptic effect.

WHAT IS CLAIMED IS:

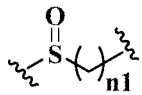
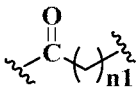
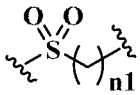
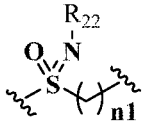
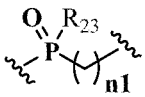
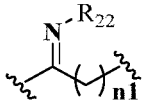
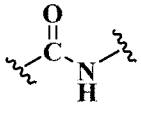
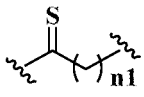
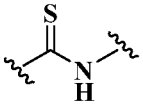
1. A compound of formula (I), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:



(I)

wherein:

X is selected from the group consisting of $-CR_{17}-$ and -N-;

Y is selected from the group consisting of $-CR_{23}R_{24}-$, $-S(CH_2)_{n1}-$, $-P(CH_2)_{n1}-$, $-O(CH_2)_{n1}-$, $-(CH_2)_{n1}NR_{22}-$,  ,  ,  ,  ,  ,  ,  ,  and  ;

R^x, R^y, R^z and R^f are identical or different and are each independently selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, thiol, nitro, hydroxy, cyano, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{24}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, thiol, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

or, any two adjacent or non-adjacent groups of R^x, R^y, R^z and R^f can be bonded to form a cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or

unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{24}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$;

or, any two adjacent groups of R^x, R^y, R^z and R^f can form a double bond;

R_{21} is selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, nitro, hydroxy, cyano, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{24}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

when X is $-CR_{17}-$, R_{17} is selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, hydroxy, amino, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein the alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, substituted or unsubstituted alkyl, halogen, hydroxy, substituted or unsubstituted amino, oxo, nitro, cyano, alkenyl, alkynyl, alkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl;

or, R_{17} and any group of R^x, R^y, R^z and R^f can be bonded to form a cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{24}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$;

R_{22} is selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, nitro, hydroxy, cyano,

alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{24}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

R_{23}, R_{24}, R_{25} and R_{26} are identical or different and are each independently selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, hydroxy, amino, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein the alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, substituted or unsubstituted alkyl, halogen, hydroxy, substituted or unsubstituted amino, oxo, nitro, cyano, alkenyl, alkynyl, alkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl;

m is an integer of 0, 1, 3, 4, 5, 6, 7, 8, 9 or 10;

n is an integer of 0, 1, 2 or 3;

o is an integer of 0, 1, 2, 3, 4 or 5;

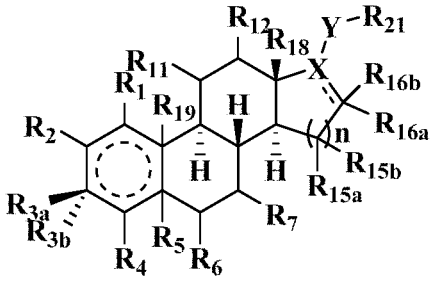
p is an integer of 0, 1, 2, 3, 4, 5 or 6;

q is an integer of 0, 1, 2, 3, 4, 5 or 6;

m_1 is an integer of 0, 1 or 2; and

n_1 is an integer of 0, 1, 2, 3, 4 or 5.

2. The compound of formula (I), the stereoisomer thereof, or the pharmaceutically acceptable salt thereof according to claim 1, being a compound of formula (II), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:



(II)

wherein:

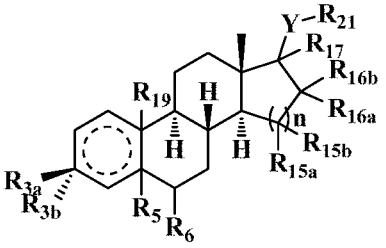
R_1, R_2, R_4, R_5, R_6, R_7, R_{11}, R_{12}, R_{15a}, R_{15b}, R_{16a}, R_{16b}, R_{18} and R_{19} are identical or different and are each independently selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, nitro, hydroxy, cyano, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}S(O)NR_{23}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{23}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

or, any two adjacent or non-adjacent groups of R_1, R_2, R_4, R_5, R_6, R_7, R_{11}, R_{12}, R_{15a}, R_{15b}, R_{16a}, R_{16b}, R_{18} and R_{19} can be bonded to form a cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

R_{3a} and R_{3b} are identical or different and are each independently selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, thiol, nitro, hydroxy, cyano, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}S(O)NR_{23}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{23}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, thiol, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

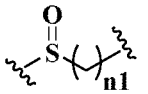
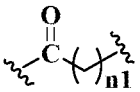
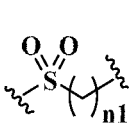
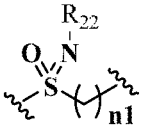
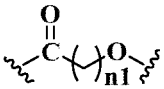
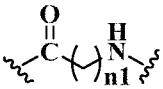
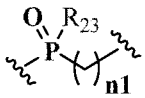
X, Y, R_{21}-R_{26}, n, m_1 and n_1 are as defined in claim 1.

3. The compound of formula (I), the stereoisomer thereof, or the pharmaceutically acceptable salt thereof according to claim 1 or 2, being a compound of formula (III), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:



(III)

wherein:

Y is selected from the group consisting of $-S(CH_2)_{n1}-$,  ,  ,  ,  ,  ,  and  ;

R_{3a} and R_{3b} are identical or different and are each independently selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, thiol, nitro, hydroxy, cyano, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}S(O)NR_{23}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{23}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, thiol, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

R_5, R_6, R_{15a}, R_{15b}, R_{16a}, R_{16b} and R_{19} are identical or different and are each independently selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, nitro, hydroxy, cyano, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}S(O)NR_{23}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{23}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and

heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

or, any two adjacent or non-adjacent groups of R_5, R_6, R_{15a}, R_{15b}, R_{16a}, R_{16b} and R_{19} can be bonded to form a cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

R_{17} is selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, hydroxy, amino, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein the alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, substituted or unsubstituted alkyl, halogen, hydroxy, substituted or unsubstituted amino, oxo, nitro, cyano, alkenyl, alkynyl, alkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl;

or, R_{17} and any group of R_{16a} and R_{16b} can be bonded to form a cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{24}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$;

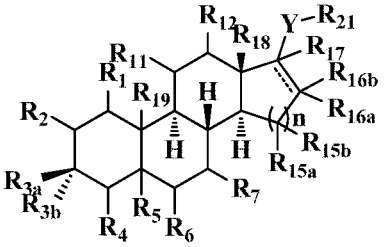
R_{21} is selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, nitro, hydroxy, cyano, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$,

$-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{24}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

n is an integer of 0, 1, 2 or 3; and

R_{22}-R_{26}, m_1 and n_1 are as defined in claim 1.

4. The compound of formula (I), the stereoisomer thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1-3, being a compound of formula (IV), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:

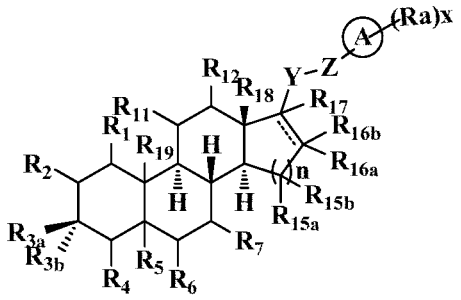


(IV)

wherein:

Y, R_1, R_2, R_{3a}, R_{3b}, R_4, R_5, R_6, R_7, R_{11}, R_{12}, R_{15a}, R_{15b}, R_{16a}, R_{16b}, R_{18}, R_{19}, R_{21} and n are as defined in claim 2.

5. The compound of formula (I), the stereoisomer thereof, or the pharmaceutically acceptable salt thereof according to claim 4, being a compound of formula (IV-1), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:



(IV-1)

wherein:

Z is selected from the group consisting of $-CR_{23}R_{24}$-, $-NR_{23}$- and -O-, and preferably methylene;

ring A is selected from the group consisting of cycloalkyl, heterocyclyl, aryl and

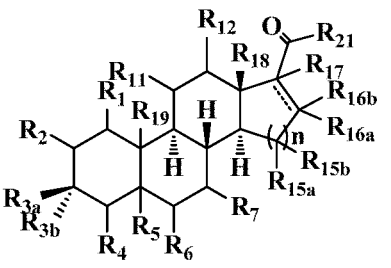
heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

each R_a is identical or different and each is selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, nitro, hydroxy, cyano, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}S(O)NR_{23}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{23}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$; and

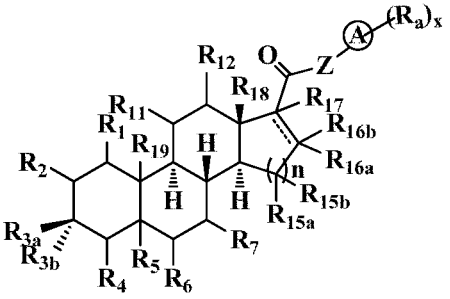
x is an integer of 0, 1, 3, 4 or 5; and

Y, R_1, R_2, R_{3a}, R_{3b}, R_4, R_5, R_6, R_7, R_{11}, R_{12}, R_{15a}, R_{15b}, R_{16a}, R_{16b}, R_{18}, R_{19}, R_{23}-R_{26}, n, m_1 and n_1 are as defined in claim 2.

6. The compound of formula (I), the stereoisomer thereof, or the pharmaceutically acceptable salt thereof according to claim 4, being a compound of formula (IV-A) or (IV-B), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:



(IV-A)



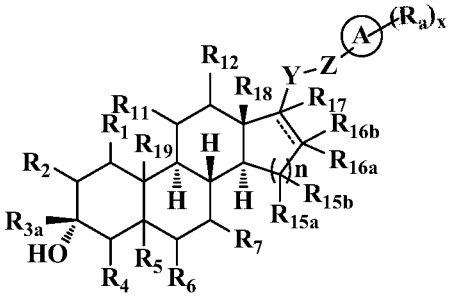
(IV-B)

wherein:

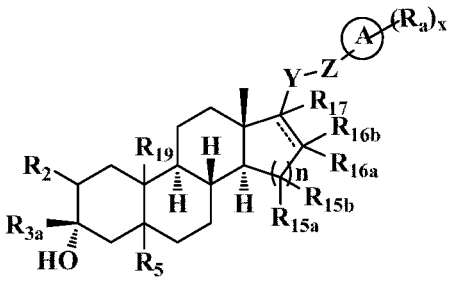
R_1, R_2, R_{3a}, R_{3b}, R_4, R_5, R_6, R_7, R_{11}, R_{12}, R_{15a}, R_{15b}, R_{16a}, R_{16b}, R_{17}, R_{18}, R_{19}, R_{21} and n are as defined in claim 3;

ring A, Z, Ra and x are as defined in claim 4.

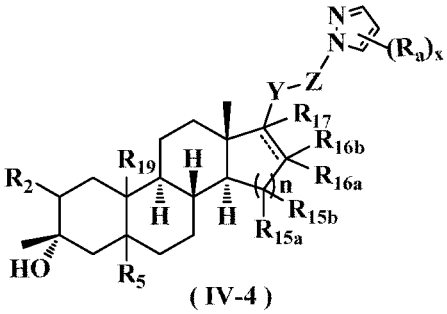
7. The compound of formula (IV), the stereoisomer thereof, or the pharmaceutically acceptable salt thereof according to claim 4, being a compound of formula (IV-2), (IV-3), (IV-4) or (IV-5), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:



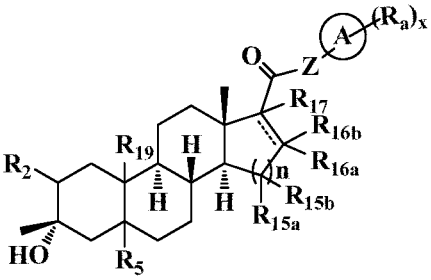
(IV-2)



(IV-3)



(IV-4)



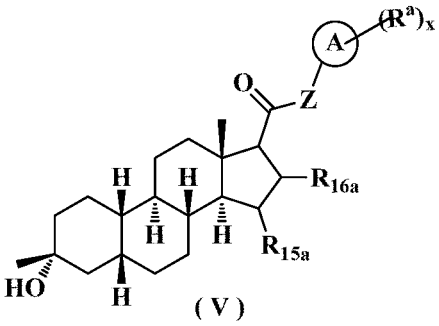
(IV-5)

wherein:

R_1, R_2, R_{3a}, R_{3b}, R_4, R_5, R_6, R_7, R_{11}, R_{12}, R_{15a}, R_{15b}, R_{16a}, R_{16b}, R_{17}, R_{18}, R_{19}, R_{21} and n are as defined in claim 4;

ring A, Z, Ra and x are as defined in claim 5.

8. The compound of formula (I), the stereoisomer thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1-4, being a compound of formula (V), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:



(V)

wherein:

Z is selected from the group consisting of $-CR_{23}R_{24}-$, $-(CH_2)_{n1}NR_{23}-$ and $-(CH_2)_{n1}O(CH_2)_{n2}-$, and preferably methylene;

ring A is selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally

further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

each R^a is identical or different and each is selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, nitro, hydroxy, cyano, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}S(O)(NR_{23})R_{24}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{23}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

R_{15a} is selected from the group consisting of hydrogen atom, alkyl, haloalkyl, alkoxy, halogen, amino, hydroxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$ and $-(CH_2)_{n1}NR_{23}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R_{16a} is selected from the group consisting of hydrogen atom, alkyl, haloalkyl, alkoxy, halogen, amino, hydroxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$ and $-(CH_2)_{n1}NR_{23}R_{24}$;

or, R_{15a} and R_{16a} can form a cycloalkyl or heterocyclyl, wherein the cycloalkyl or heterocyclyl is optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, and R_{15a} and R_{16a} are not hydrogen at the same time;

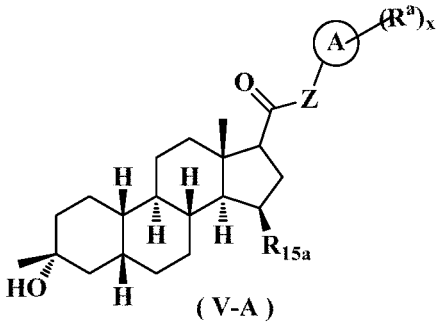
R_{23} and R_{24} are each selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, nitro, hydroxy, cyano, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, cycloalkyl, heterocyclyl,

aryl, heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

x is an integer of 0, 1, 3, 4 or 5; and

R_{25}-R_{26}, m_1 and n_1 are as defined in claim 1.

9. The compound of formula (I), the stereoisomer thereof, or the pharmaceutically acceptable salt thereof according to claim 1 or 8, being a compound of formula (V-A), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:

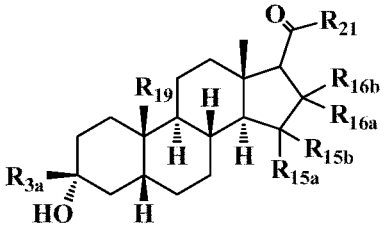


(V-A)

R_{15a} is selected from the group consisting of hydrogen atom, alkyl, haloalkyl, alkoxy, halogen, amino, hydroxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$ and $-(CH_2)_{n1}NR_{23}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

ring A, Z, R^a, R_{23}-R_{24}, m_1, n_1 and x are as defined in claim 8.

10. The compound of formula (I), the stereoisomer thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1-4, being a compound of formula (VI), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:



(VI)

wherein:

R_{3a} is selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, thiol, nitro, hydroxy, cyano, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}S(O)(NR_{23})R_{24}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{23}$

and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, thiol, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

R_{15a}, R_{15b}, R_{16a} and R_{16b} are identical or different and are each independently selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, nitro, hydroxy, cyano, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}S(O)(NR_{23})R_{24}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{23}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$, and R_{15a}, R_{15b}, R_{16a} and R_{16b} are not hydrogen at the same time;

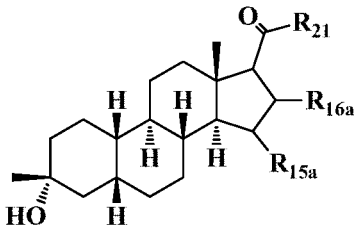
or, any two adjacent or non-adjacent groups of R_{15a}, R_{15b}, R_{16a} and R_{16b} can be bonded to form a cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

R_{19} is selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, thiol, nitro, hydroxy, cyano, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}S(O)(NR_{23})R_{24}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{23}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$;

R_{21}, R_{23}-R_{26}, m_1 and n_1 are as defined in claim 1.

11. The compound of formula (I), the stereoisomer thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1-4, being a compound of

formula (VII), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:

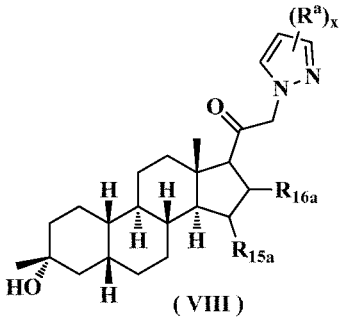


(VII)

wherein:

R_{15a}, R_{16a} and R_{21} are as defined in claim 2.

12. The compound of formula (I), the stereoisomer thereof, or the pharmaceutically acceptable salt thereof according to claim 1, being a compound of formula (VIII), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:

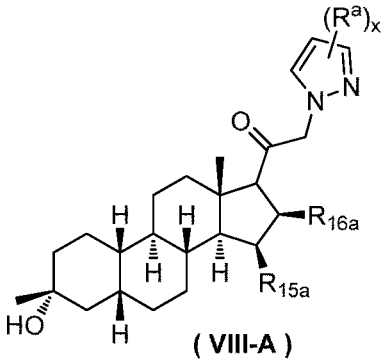


(VIII)

wherein:

R_{15a}, R_{16a}, R^a and x are as defined in claim 5.

13. The compound of formula (I), the stereoisomer thereof, or the pharmaceutically acceptable salt thereof according to claim 1 or 12, being a compound of formula (VIII-A), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:

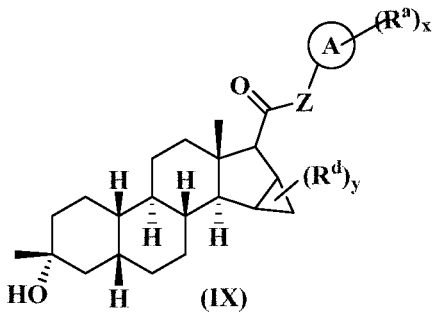


(VIII-A)

wherein:

R_{15a}, R_{16a}, R^a and x are as defined in claim 5.

14. The compound of formula (I), the stereoisomer thereof, or the pharmaceutically acceptable salt thereof according to claim 1, being a compound of formula (IX), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:



(IX)

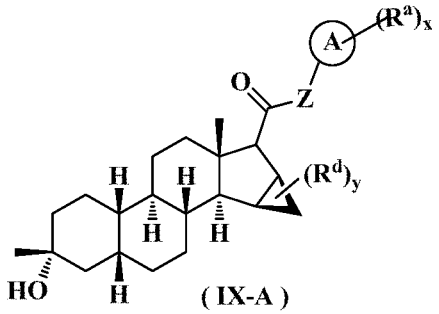
wherein:

each R^d is identical or different and each is selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, nitro, hydroxy, cyano, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}S(O)(NR_{23})R_{24}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{23}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

y is an integer of 0, 1, 3 or 4;

ring A, Z, R^a, R_{23}-R_{26}, m_1, n_1 and x are as defined in claim 5.

15. The compound of formula (I), the stereoisomer thereof, or the pharmaceutically acceptable salt thereof according to claim 1, being a compound of formula (X-A), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:



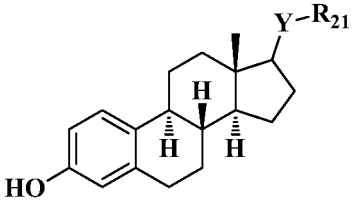
(IX-A)

wherein:

ring A, Z, R^a, R^d, R_{23}-R_{26}, m_1, n_1 , x and y are as defined in claim 14.

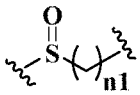
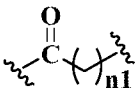
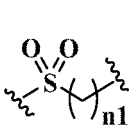
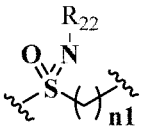
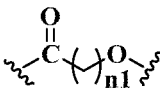
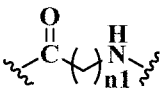
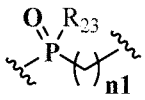
16. The compound of formula (I), the stereoisomer thereof, or the pharmaceutically

acceptable salt thereof according to claim 1, being a compound of formula (X), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:



(X)

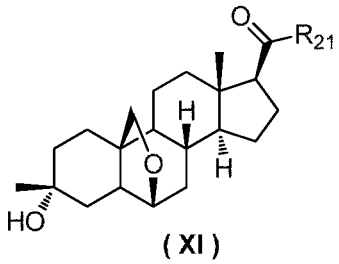
wherein:

Y is selected from the group consisting of $-S(CH_2)_{n1}-$,  ,  ,  ,  ,  ,  and  ;

R_{21} is selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, nitro, hydroxy, cyano, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{24}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

R_{22}-R_{26}, m_1 and n_1 are as defined in claim 1.

17. The compound of formula (I), the stereoisomer thereof, or the pharmaceutically acceptable salt thereof according to claim 1, being a compound of formula (XI), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:



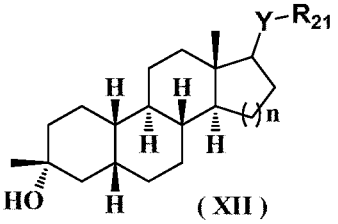
(XI)

wherein:

R_{21} is selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, nitro, hydroxy, cyano, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{24}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

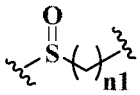
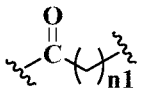
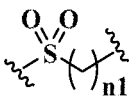
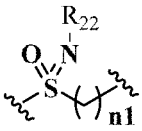
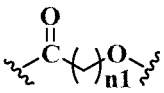
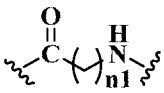
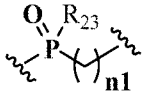
R_{23}-R_{26}, m_1 and n_1 are as defined in claim 1.

18. The compound of formula (I), the stereoisomer thereof, or the pharmaceutically acceptable salt thereof according to claim 1, being a compound of formula (XII), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:



(XII)

wherein:

Y is selected from the group consisting of $-S(CH_2)_{n1}-$,  ,  ,  ,  ,  ,  and  ;

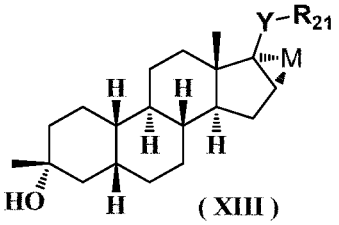
R_{21} is selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, nitro, hydroxy, cyano, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{24}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or

unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$; and

n is an integer of 0, 1 or 2;

R_{22}-R_{26}, m_1 and n_1 are as defined in claim 1.

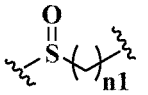
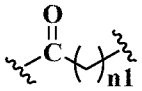
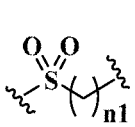
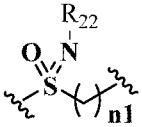
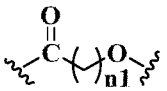
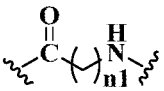
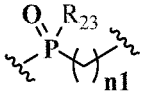
19. The compound of formula (I), the stereoisomer thereof, or the pharmaceutically acceptable salt thereof according to claim 1, being a compound of formula (XIII), a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:



(XIII)

wherein:

M is selected from the group consisting of $-CR_{23}-$ and oxygen;

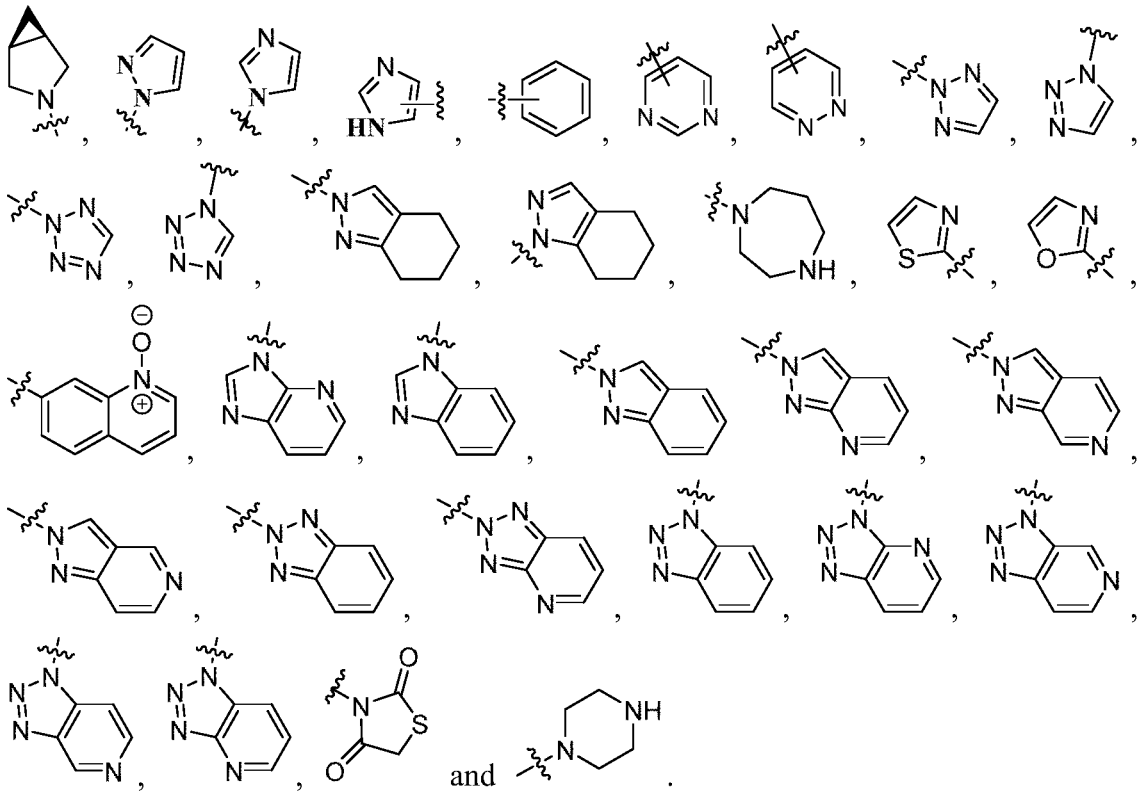
Y is selected from the group consisting of $-S(CH_2)_{n1}-$,  ,  ,  ,  ,  ,  and  ;

R_{21} is selected from the group consisting of hydrogen atom, deuterium atom, alkyl, deuterated alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, amino, nitro, hydroxy, cyano, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$, $-(CH_2)_{n1}NR_{23}R_{24}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$, $-(CH_2)_{n1}NR_{23}C(O)R_{24}$ and $-(CH_2)_{n1}NR_{23}S(O)_{m1}R_{24}$, wherein the alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, alkyl, haloalkyl, halogen, amino, oxo, nitro, cyano, hydroxy, alkenyl, alkynyl, alkoxy, haloalkoxy, hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_{n1}R_{25}$, $-(CH_2)_{n1}OR_{25}$, $-(CH_2)_{n1}SR_{25}$, $-(CH_2)_{n1}C(O)R_{25}$, $-(CH_2)_{n1}C(O)OR_{25}$, $-(CH_2)_{n1}S(O)_{m1}R_{25}$, $-(CH_2)_{n1}NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NR_{25}R_{26}$, $-(CH_2)_{n1}C(O)NHR_{25}$, $-(CH_2)_{n1}NR_{25}C(O)R_{26}$ and $-(CH_2)_{n1}NR_{25}S(O)_{m1}R_{26}$;

R_{22}-R_{26}, m_1 and n_1 are as defined in claim 1.

20. The compound of formula, the stereoisomer thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 5-9 and 14-15, wherein the ring A

is selected from the group consisting of:



21. The compound of any formula, the stereoisomer thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1-20, wherein Z is selected from the group consisting of $-CH_2-$, $-CH_2NH-$, $-CH_2O-$, $-CH_2-$, -NH- and $-NHSO_2-$;

Y is selected from the group consisting of -C(O)-, $-C(O)CH_2-$, -C(O)O-, $-C(O)CH_2NH-$, - $C(O)CH_2O-$, $-SCH_2-$, $-S(O)CH_2-$, $-S(O)_2CH_2-$, $-P(O)R_{23}-$, -C(O)NH- and $-C(O)NHSO_2-$;

R^a is selected from the group consisting of hydrogen atom, halogen, amino, cyano, nitro, C_{1-6} alkyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} alkoxy, C_{1-6} hydroxyalkyl, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}C(O)R_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}C(O)NR_{23}R_{24}$ and $-(CH_2)_{n1}S(O)_{m1}R_{23}$, wherein the C_{1-6} alkyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{3-6} halocycloalkyl, C_{1-6} alkoxy and C_{1-6} hydroxyalkyl are each optionally further substituted by one or more substituents selected from the group consisting of hydrogen atom, halogen, cyano, hydroxy, C_{1-6} alkyl, C_{3-6} cycloalkyl and 3 to 6 membered heterocyclyl;

R^d is selected from the group consisting of hydrogen atom, halogen, amino, cyano, nitro, C_{1-6} alkyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} alkoxy and C_{1-6} hydroxyalkyl;

R_{23} and R_{24} are identical or different and are each independently selected from the group consisting of C_{1-6} alkyl, C_{3-8} cycloalkyl and 3 to 8 membered heterocyclyl, wherein the C_{1-6} alkyl, C_{3-8} cycloalkyl and 3 to 8 membered heterocyclyl are each

optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, halogen, hydroxy, C_{1-3} alkyl, amino, oxo, nitro, cyano, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} hydroxyalkyl, C_{3-8} cycloalkyl, $-(CH_2)_{n1}NR_{25}R_{26}$, 3 to 8 membered heterocyclyl, 6 to 10 membered aryl and 5 to 12 membered heteroaryl.

22. The compound of any formula, the stereoisomer thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1-21,

wherein:

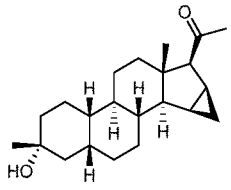
R_{15a} is selected from the group consisting of hydrogen atom, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, halogen, amino, hydroxy, C_{3-8} cycloalkyl, C_{3-8} halocycloalkyl, 3 to 8 membered heterocyclyl, 6 to 10 membered aryl, 5 to 12 membered heteroaryl, $-(CH_2)_{n1}R_{23}$, $-(CH_2)_{n1}OR_{23}$, $-(CH_2)_{n1}C(O)OR_{23}$, $-(CH_2)_{n1}SR_{23}$, $-(CH_2)_{n1}S(O)_{m1}R_{23}$ and $-(CH_2)_{n1}NR_{23}R_{24}$, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-8} cycloalkyl, C_{3-8} halocycloalkyl, 3 to 8 membered heterocyclyl, 6 to 10 membered aryl and 5 to 12 membered heteroaryl are each optionally further substituted by one or more substituents selected from the group consisting of hydrogen atom, halogen, cyano, hydroxy, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, $-(CH_2)_{n1}NR_{25}R_{26}$ and 3 to 6 membered heterocyclyl;

R_{16a} is selected from the group consisting of hydrogen atom, halogen, cyano, C_{1-6} alkyl and C_{1-6} haloalkyl;

or, R_{15a} and R_{16a} can form a C_{3-8} cycloalkyl, wherein the C_{3-8} cycloalkyl is optionally further substituted by one or more substituents selected from the group consisting of hydrogen atom, C_{1-6} alkyl, C_{1-6} haloalkyl and halogen, and R_{15a} and R_{16a} are not hydrogen at the same time;

R_{23} and R_{24} are identical or different and are each independently selected from the group consisting of hydrogen atom, C_{1-6} alkyl, C_{3-8} cycloalkyl and 3 to 8 membered heterocyclyl, wherein the C_{1-6} alkyl, C_{3-8} cycloalkyl and 3 to 8 membered heterocyclyl are each optionally further substituted by one or more substituents selected from the group consisting of deuterium atom, halogen, hydroxy, C_{1-3} alkyl, amino, oxo, nitro, cyano, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} hydroxyalkyl, C_{3-8} cycloalkyl, $-(CH_2)_{n1}NR_{25}R_{26}$, 3 to 8 membered heterocyclyl, 6 to 10 membered aryl and 5 to 12 membered heteroaryl.

23. The compound of formula (I), the stereoisomer thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1-22, selected from the group consisting of:



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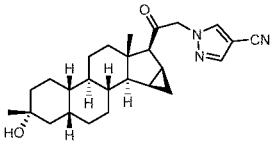

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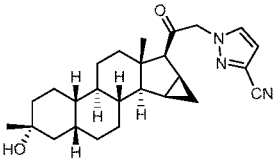

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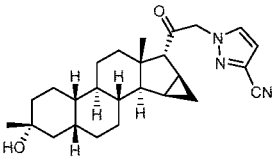

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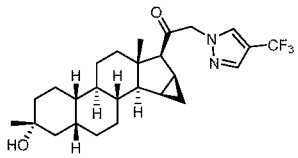

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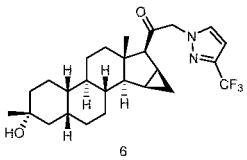

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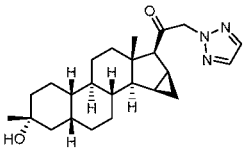

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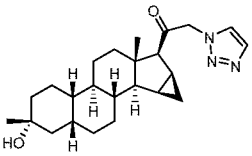

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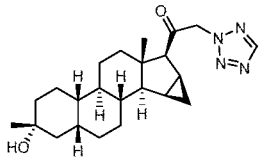

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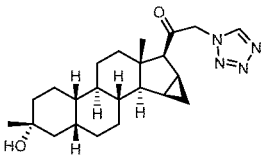

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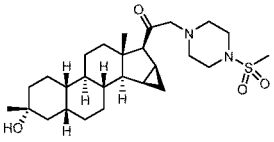

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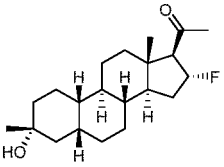

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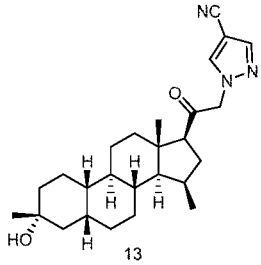

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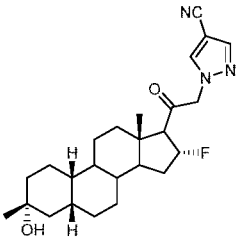

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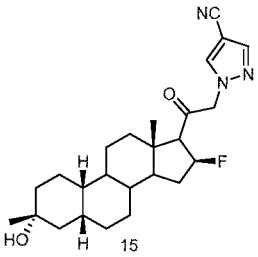

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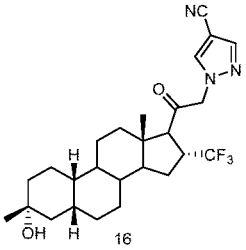

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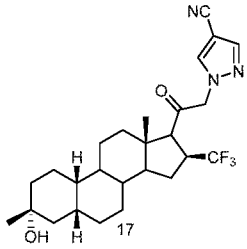

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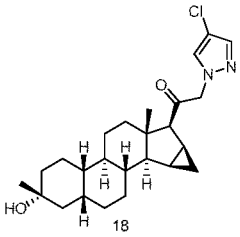

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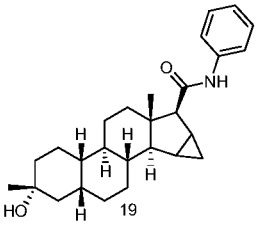

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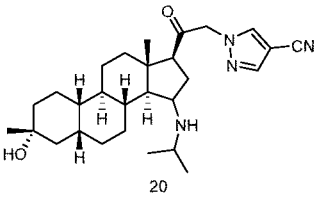

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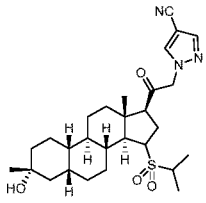

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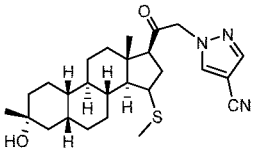

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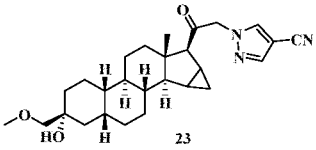

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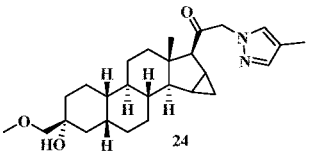

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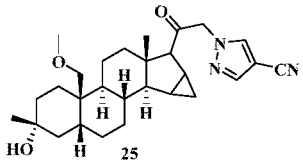

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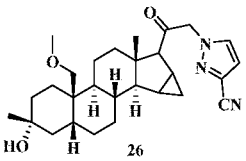

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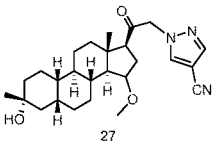

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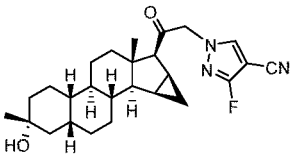

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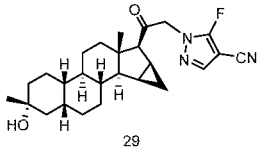

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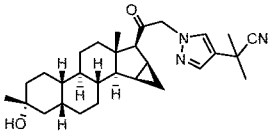

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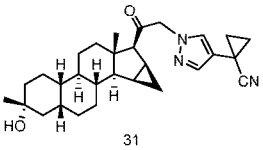

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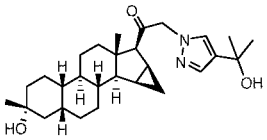

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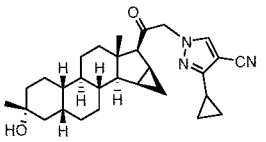
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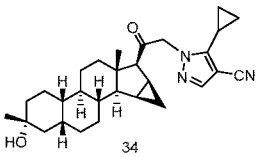
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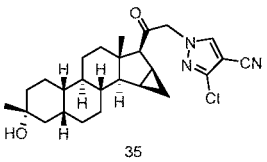
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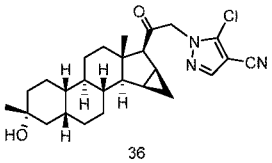
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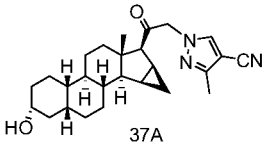
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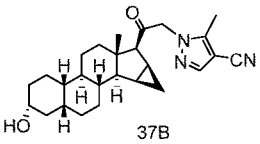
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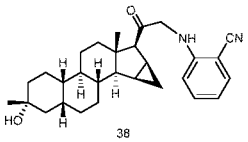
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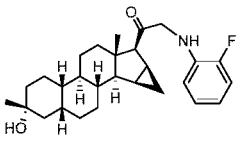
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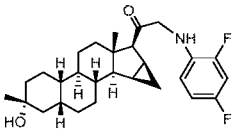
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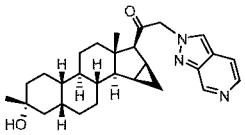
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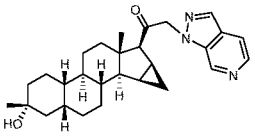
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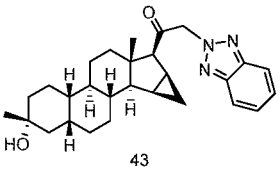
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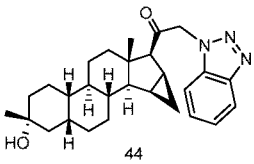
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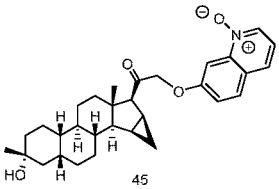
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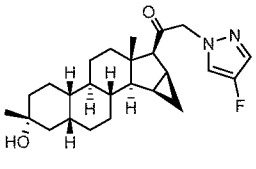
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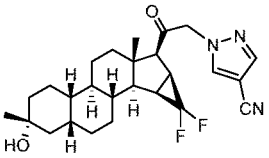
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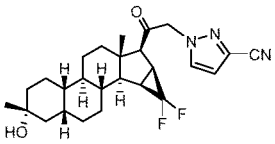
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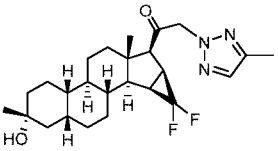
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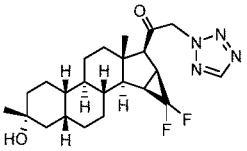
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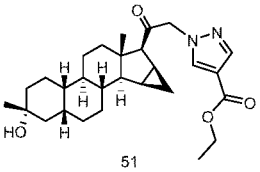
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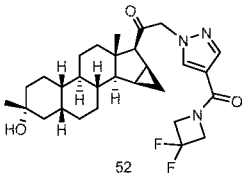
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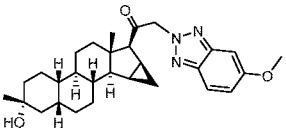
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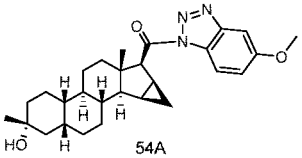
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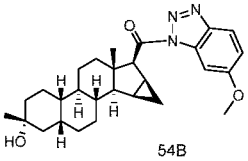
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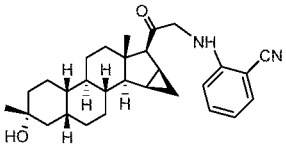
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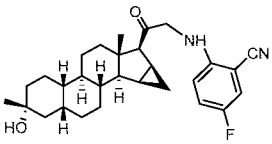
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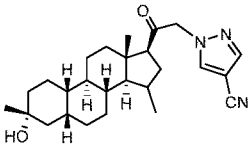
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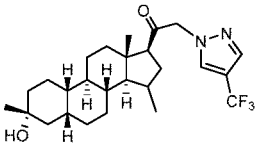
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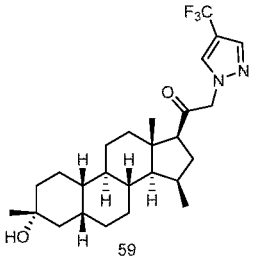
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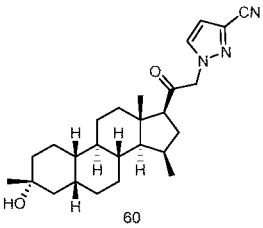
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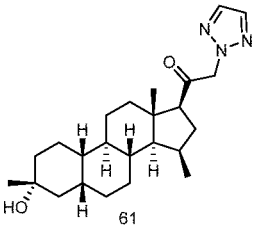
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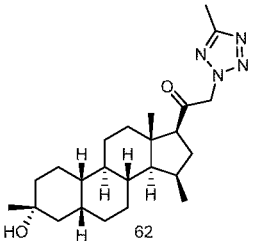
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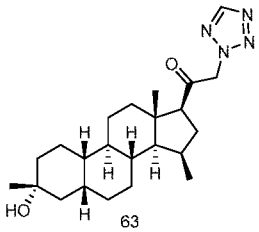
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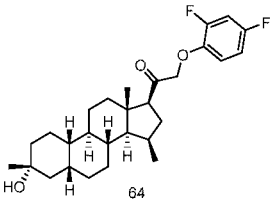
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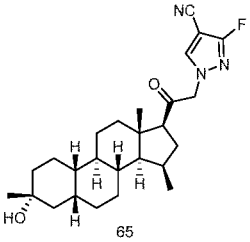
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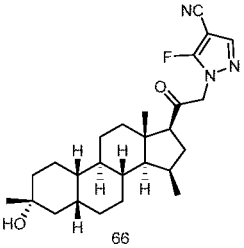
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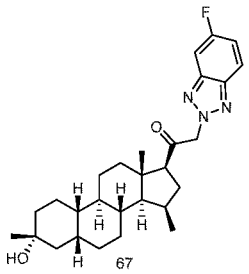
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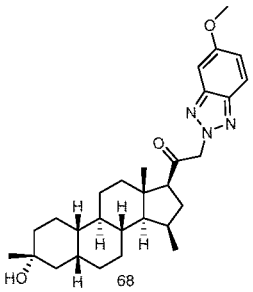
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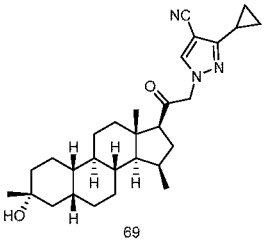
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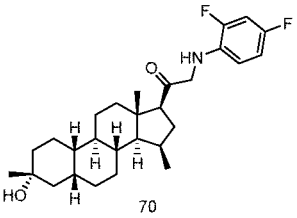
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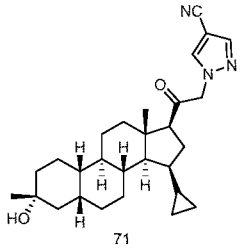
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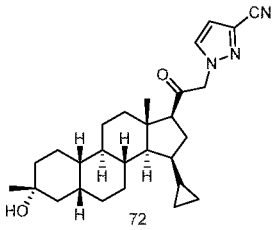
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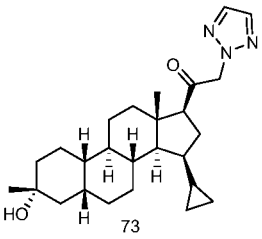
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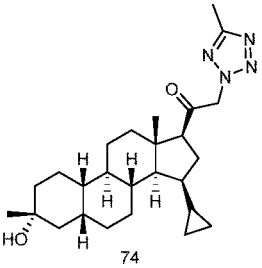
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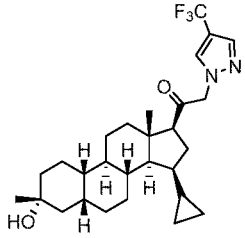
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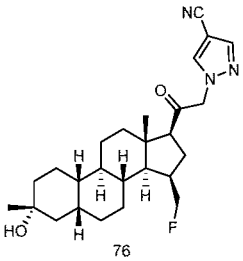
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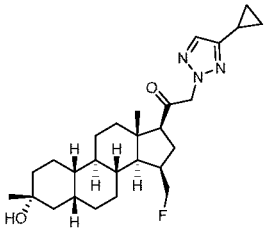
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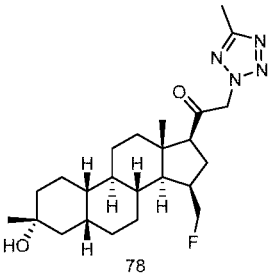
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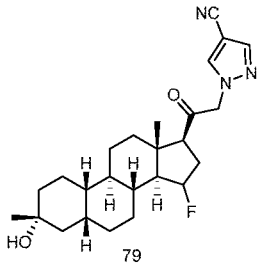
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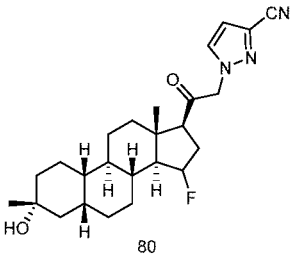
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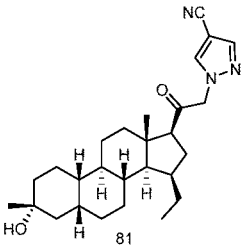
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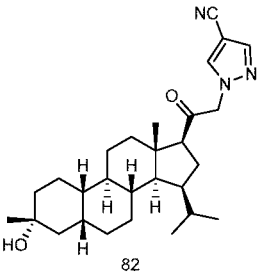
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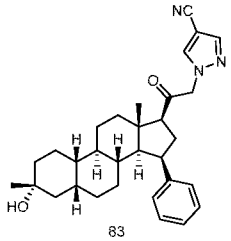
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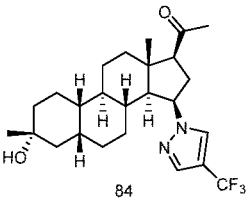
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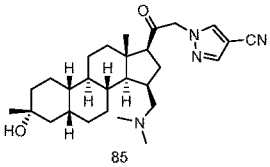
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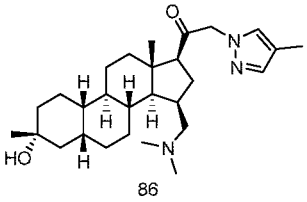
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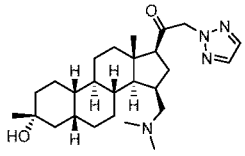
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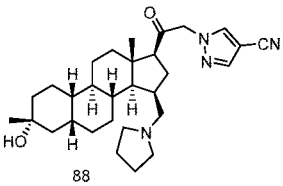
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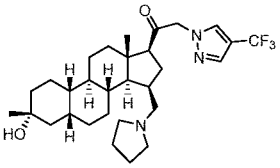
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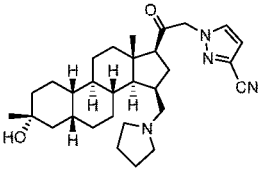
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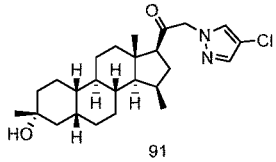
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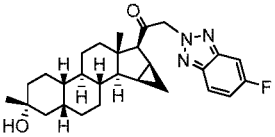
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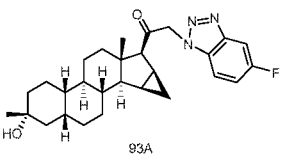
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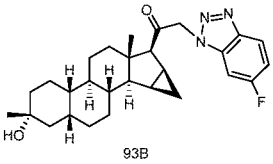
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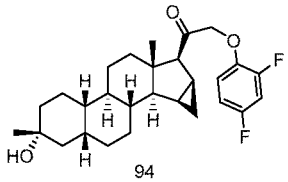
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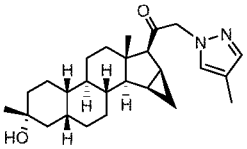
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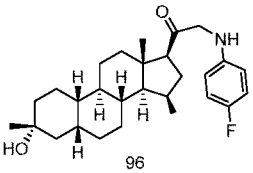
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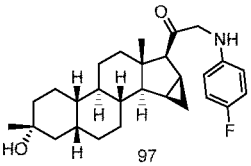
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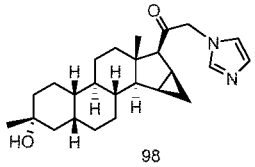
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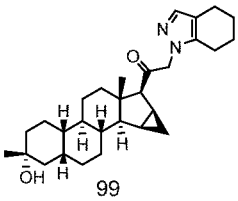
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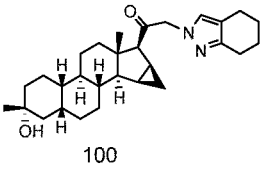
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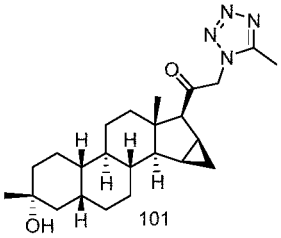
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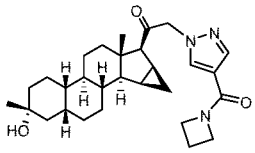
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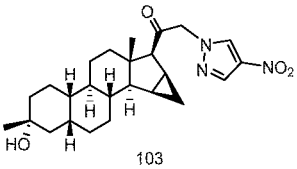
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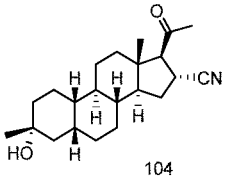
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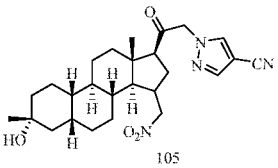
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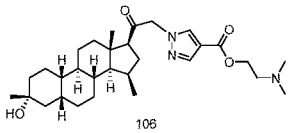
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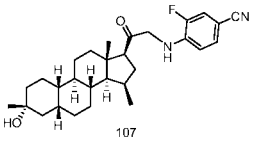
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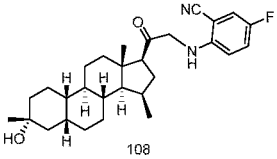
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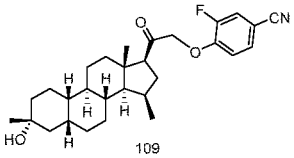
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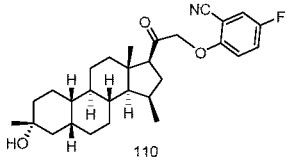
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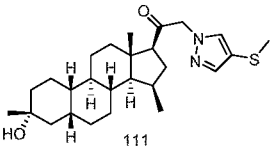
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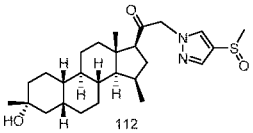
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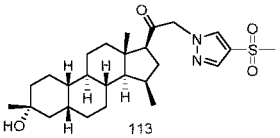
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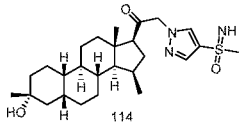
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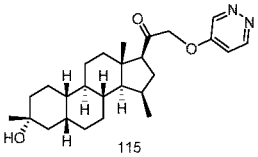
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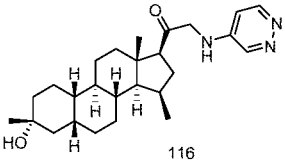
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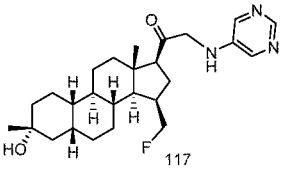
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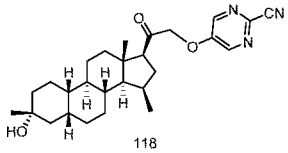
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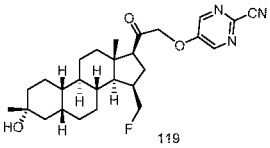
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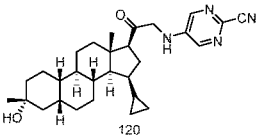
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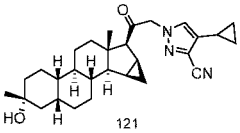
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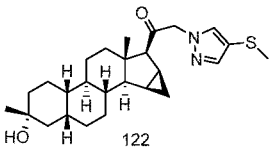
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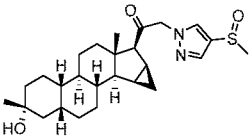
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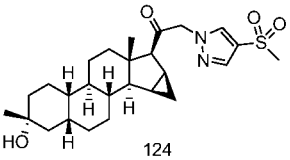
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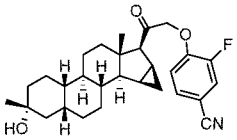
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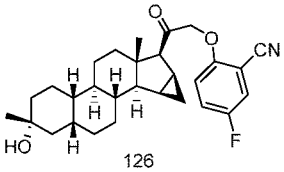
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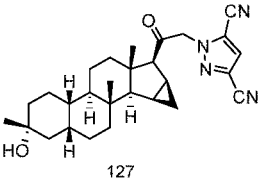
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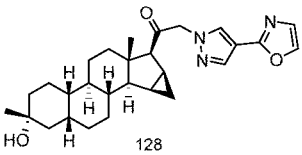
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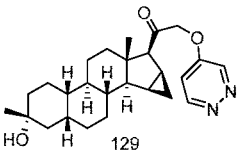
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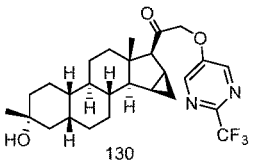
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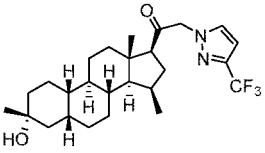
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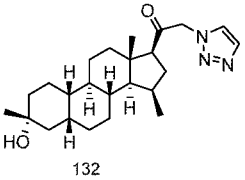
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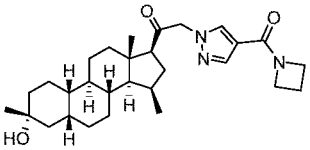
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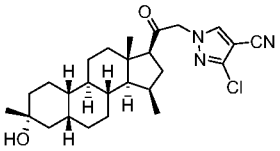
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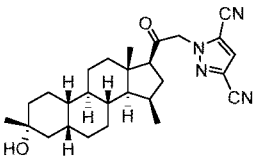
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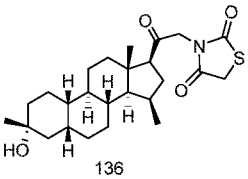
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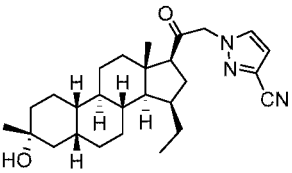
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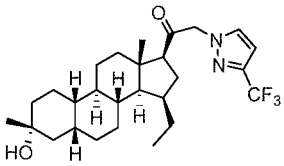
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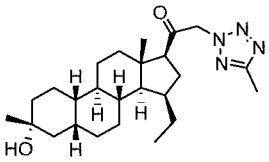
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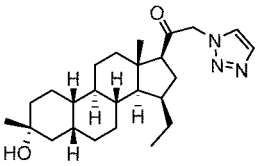
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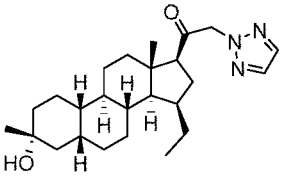
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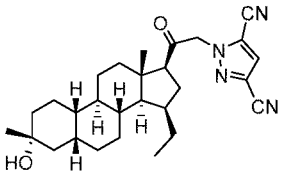
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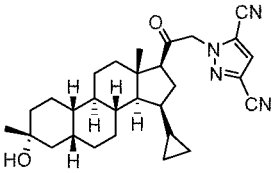
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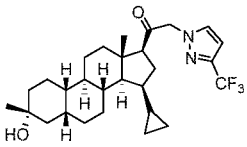
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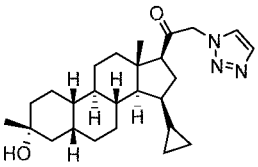
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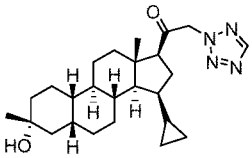
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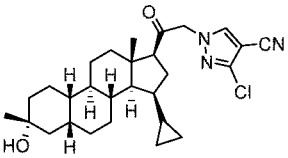
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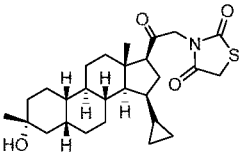
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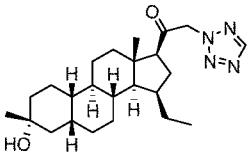
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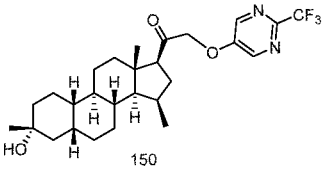
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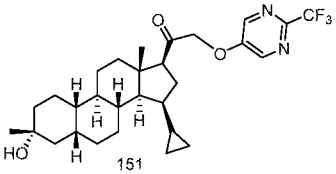
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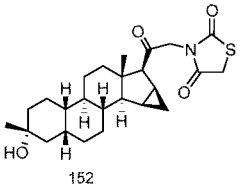
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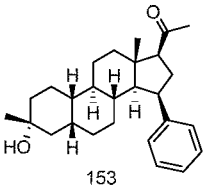
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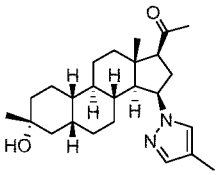
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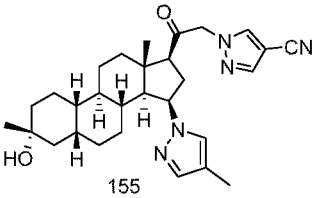
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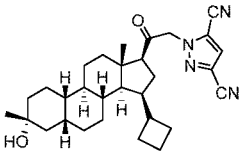
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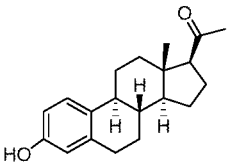
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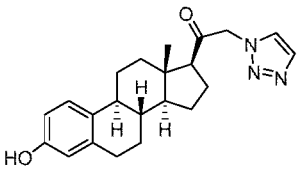
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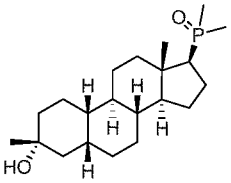
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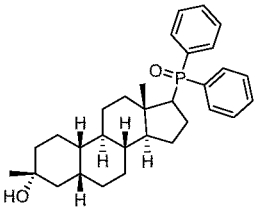
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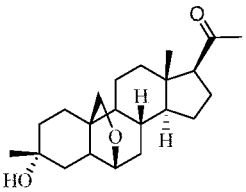
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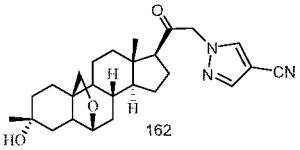
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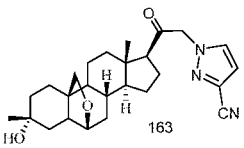
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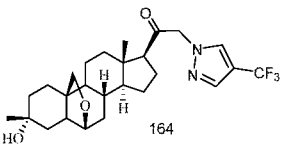
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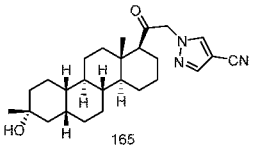
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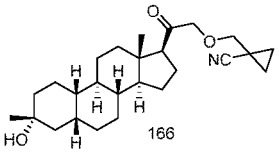
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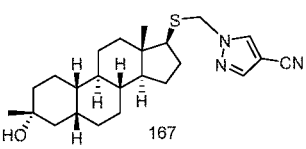
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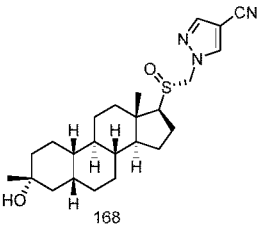
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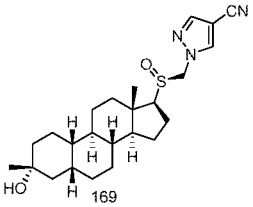
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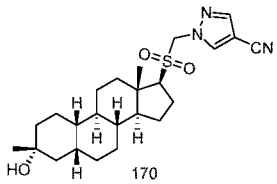
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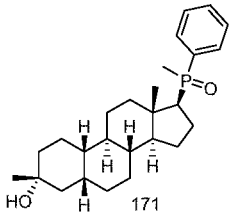
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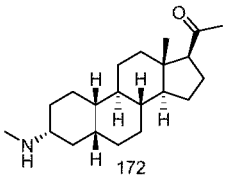
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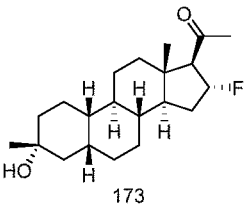
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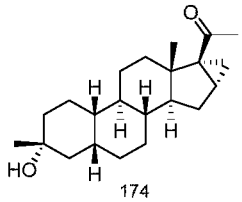
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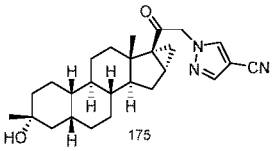
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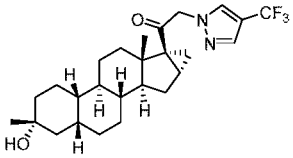
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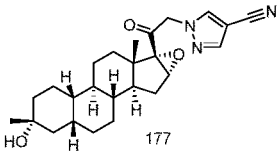
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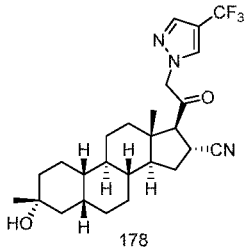
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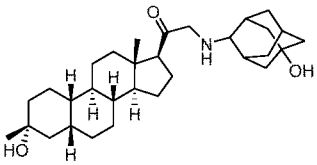
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24. A pharmaceutical composition, comprising a therapeutically effective amount of the compound of formula (I), the stereoisomer thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1-23, and one or more pharmaceutically acceptable carriers, diluents or excipients.

25. Use of the compound of formula (I), the stereoisomer thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1-23, or the pharmaceutical composition according to claim 24 in the preparation of a $GABA_A$ receptor regulator medicament.

26. Use of the compound of formula (I), the stereoisomer thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1-23, or the pharmaceutical composition according to claim 24 in treating a CNS-related disease, wherein the CNS-related disease is selected from the group consisting of sleep disorder, mood disorder, schizophrenia spectrum disorder, spasmodic disorder, memory disorder and/or cognitive disorder, dyskinesia, personality disorder, autism spectrum disorder, pain, traumatic brain injury, vascular disease, substance abuse disorder and/or withdrawal syndrome or tinnitus.