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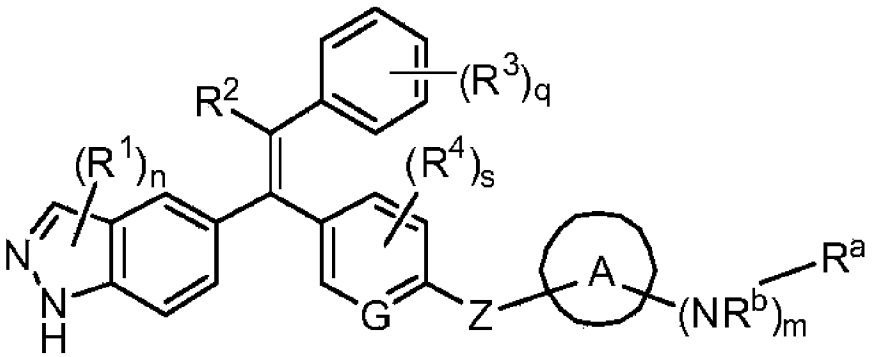
(71) Demandeurs/Applicants:
JIANGSU HENGRUI MEDICINE CO., LTD., CN;
SHANGHAI HENGRUI PHARMACEUTICAL CO., LTD., CN

(72) Inventeurs/Inventors:
FAN, XING, CN;
YANG, FANGLONG, CN;
YAN, JINGJING, CN;
...

(54) Titre : DERIVE D'INDAZOLE, SON PROCEDE DE PREPARATION ET SON APPLICATION PHARMACEUTIQUE
(54) Title: INDAZOLE DERIVATIVE, PREPARATION METHOD THEREFOR, AND PHARMACEUTICAL APPLICATION THEREOF



(I)

(57) Abrégé/Abstract:
An indazole derivative, a preparation method therefor, and a pharmaceutical application thereof. In particular, the present invention relates to an indazole derivative represented by general formula (I), a preparation method therefor, a pharmaceutical composition comprising the derivative, and a use of the derivative as an estrogen receptor modulator in the prevention and/or treatment of an estrogen receptor mediated or dependent disease or condition, the disease being particularly preferably breast cancer. The definition of each substituent in the general formula (I) is the same as that in the description.

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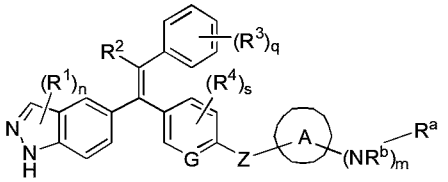
(72) Inventeurs(suite)/Inventors(continued): WU, XIAO, CN; HE, FENG, CN; TAO, WEIKANG, CN

(74) Agent: DEETH WILLIAMS WALL LLP

ABSTRACT:

An indazole derivative, a preparation method therefor, and a pharmaceutical application thereof. In particular, the present invention relates to an indazole derivative represented by general formula (I), a preparation method therefor, a pharmaceutical composition comprising the derivative, and a use of the derivative as an estrogen receptor modulator in the prevention and/or treatment of an estrogen receptor mediated or dependent disease or condition, the disease being particularly preferably breast cancer. The definition of each substituent in the general formula (I) is the same as that in the description.



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INDAZOLE DERIVATIVE, PREPARATION METHOD THEREFOR, AND PHARMACEUTICAL APPLICATION THEREOF

TECHNICAL FIELD

The present disclosure belongs to the field of medicine, and relates to an indazole derivative, a method for preparing the same, and a use thereof in medicine. The present disclosure discloses a use of the indazole derivative as an estrogen receptor modulator for preventing and/or treating estrogen receptor-mediated or estrogen receptor-dependent disease or disorder, wherein the disease is particularly preferably breast cancer.

BACKGROUND

Breast cancer is one of the most common malignant tumors in women. According to GLOBALCAN statistics in 2012 (CA CANCER J CLIN 2015; 65:87-108), there are approximately 1.7 million new cases and 520,000 deaths in the world each year. Regardless of morbidity and mortality, breast cancer ranks first among female malignancies. According to the China Cancer Registry Annual Report (2017) released by the National Cancer Center of China, breast cancer ranks first in the incidence of female malignant tumors, with about 279,000 new cases each year, and an annual increase of about 2%.

About 70% of breast cancer patients are suffered from estrogen receptor (ER)-positive breast cancer. Among the therapies for these breast cancer patients, endocrine therapy occupies an important position. There are three main types of endocrine therapy, that is, aromatase inhibitor (AI), which can inhibit the conversion of androgens into estrogen and reduce the level of estrogen in the body; selective estrogen receptor modulator (SERM), which antagonizes the activity of estrogen receptor; and selective estrogen receptor degrader (SERD), which can not only antagonize the activity of estrogen receptor, but also promote the degradation of the receptor (Pharmacol Ther. 2017 Dec 28). Although endocrine therapy is the first choice for estrogen receptor-positive breast cancer, about 30% of patients receiving adjuvant therapy will relapse, and almost all patients with metastatic breast cancer will develop resistance and progress. There are two main types of mechanisms for the resistance to endocrine therapy. One type of mechanism focuses on the estrogen receptor signaling pathway itself, including activating mutation and amplification of the ESR1 gene encoding estrogen receptor, fusion of the ESR1 gene encoding estrogen receptor with other genes, disturbance of estrogen receptor co-mediating factor and downstream factors that control cell cycle, etc. Another type of mechanism includes activation of signaling pathways that cross-react with the estrogen receptor signaling pathway, such as the growth factor receptor pathway (Nat Rev Clin Oncol. 2015 Oct; 12(10):573-83).

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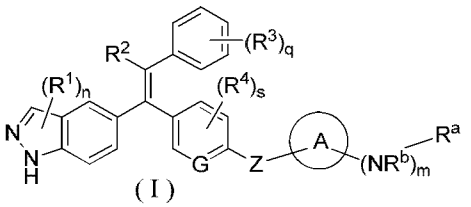
Two studies carried out in 2013 showed that ESR1 gene mutation was found in 11 to 55% of estrogen receptor-positive metastatic breast cancer patients who have received aromatase inhibitor therapy. Further studies found that the mutant receptor can be phosphorylated independently of estrogen and provide a transcription effect, so that the tumor inoculated with estrogen-dependent MCF7 can grow in the body without relying on estrogen. Moreover, the mutated receptor will reduce the activity of SERM tamoxifen and SERD fulvestrant. Therefore, ESR1 gene mutation may be one of the mechanisms of drug resistance in estrogen receptor-positive breast cancer (Nat Rev Clin Oncol. 2015 Oct; 12(10):573-83 and Nat Genet 2013; 45:1439-45). In subsequent studies, a certain proportion of ESR1 gene mutations were found in patients with estrogen receptor-positive metastatic breast cancer, and the mutation proportion was about 30%. In the BOLERO-2 clinical trial, ER Y537S and ER D538G mutations were found in the ctDNA of 29% of patients with estrogen receptor-positive metastatic breast cancer who progressed after AIs treatment. In the exemestane-only group, the progression free survival (PFS) and overall survival (OS) of patients with mutations were shorter than those of patients without mutations (Nat Genet 2013;45:1446-51).

In summary, ESR1 gene mutation mostly occurs in patients with metastatic estrogen receptor-positive breast cancer who have progressed after AIs treatment. These patients are no longer sensitive to AIs treatment. Therefore, there is a need to develop estrogen receptor antagonists that target ESR1 gene mutation.

The first-in-class estrogen receptor covalent binding antagonist H3B-6545 developed by Eisai has strong inhibitory activity on wild-type and mutant estrogen receptors, and can exert a prolonged efficacy by covalently binding with the receptor. It is currently undergoing phase I and II clinical trials. Currently published patent applications related to estrogen receptor antagonists targeting ESR1 gene mutation include WO2016196346 and WO2016196342.

SUMMARY OF THE INVENTION

The object of the present disclosure is to provide a compound of formula (I) or a tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or a pharmaceutically acceptable salt thereof:



(I)

wherein:

G is CH or N;

Z is selected from the group consisting of a bond, CR^5R^6, -O-(CH_2)t- and -NR^7-(CH_2)t-;

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ring A is selected from the group consisting of cycloalkyl and heterocyclyl;

R^a is selected from the group consisting of $-CH_2CH=CHC(O)NR^8R^9$, $-C(O)CH=CR^{10}R^{11}$ and $-C(O)C\equiv CR^{12}$;

R^b is selected from the group consisting of hydrogen atom and alkyl;

each R^1 is identical or different and each is independently selected from the group consisting of hydrogen atom, halogen, alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R^2 is selected from the group consisting of hydrogen atom, halogen, alkyl, haloalkyl, alkoxy, amino, cyano, nitro, carboxy, formyl, hydroxy, hydroxyalkyl, cycloalkyl, aryl and heteroaryl;

each R^3 is identical or different and each is independently selected from the group consisting of hydrogen atom, halogen, alkyl, haloalkyl, alkoxy, cyano, amino, nitro, carboxy, formyl, hydroxy, hydroxyalkyl, $NR^{13}C(O)R^{14}$, $C(O)NR^{13}R^{14}$, SO_2R^{15}, cycloalkyl, heterocyclyl, aryl and heteroaryl;

each R^4 is identical or different and each is independently selected from the group consisting of hydrogen atom, halogen, alkyl, haloalkyl, alkoxy, cyano, amino, nitro, carboxy, formyl, hydroxy, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R^5 and R^6 are identical or different and are each independently selected from the group consisting of hydrogen atom, halogen, alkyl, haloalkyl, alkoxy, cyano, amino, nitro, carboxy, formyl, hydroxy, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R^7 is selected from the group consisting of hydrogen atom, alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R^8 and R^9 are identical or different and are each independently selected from the group consisting of hydrogen atom, alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

or, R^8 and R^9 together with the nitrogen atom to which they are attached form a heterocyclyl, wherein the heterocyclyl optionally contains one to two identical or different heteroatoms selected from the group consisting of N, O and S in addition to the said nitrogen atom, and the said heterocyclyl is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halogen, amino, cyano, nitro, hydroxy, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R^{10} and R^{11} are identical or different and are each independently selected from the group consisting of hydrogen atom, halogen, alkyl, haloalkyl, alkoxy, cyano, amino, nitro, carboxy, formyl, hydroxy, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R^{12} is selected from the group consisting of hydrogen atom, alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R^{13} and R^{14} are identical or different and are each independently selected from the group consisting of hydrogen atom, halogen, alkyl, haloalkyl, alkoxy, cyano, amino, nitro, carboxy, formyl, hydroxy, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and

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heteroaryl;

R^{15} is selected from the group consisting of hydrogen atom, alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

m is 0 or 1;

n is 0, 1, 2 or 3;

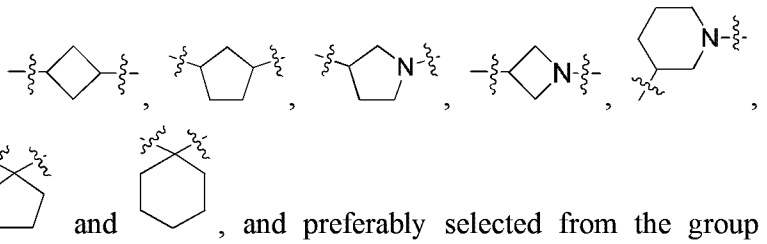
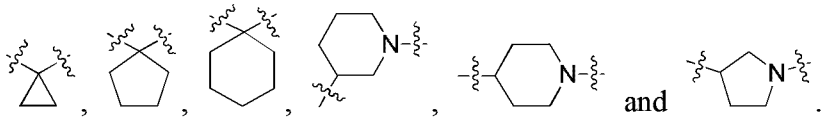
q is 0, 1, 2, 3, 4 or 5;

s is 0, 1, 2 or 3; and

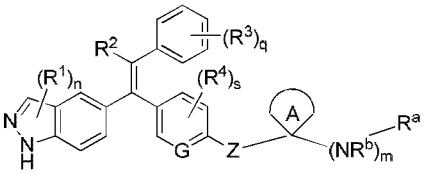
t is 0, 1, 2, 3, 4, 5 or 6.

In a preferred embodiment of the present disclosure, in the compound of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof, ring A is selected from the group consisting of C_3-C_6 cycloalkyl and 3 to 6 membered heterocyclyl, wherein the heterocyclyl contains one to three heteroatoms selected from the group consisting of N, O and S.

In another preferred embodiment of the present disclosure, in the compound of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof, ring A is selected from the group consisting of cyclopropyl, cyclopentyl, cyclohexyl, tetrahydropyrrolyl and piperidinyl.

In another preferred embodiment of the present disclosure, in the compound of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof, ring A is selected from the group consisting of  , and preferably selected from the group consisting of  .

In a preferred embodiment of the present disclosure, the compound of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof is a compound of formula (II) or a tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or a pharmaceutically acceptable salt thereof:



(II)

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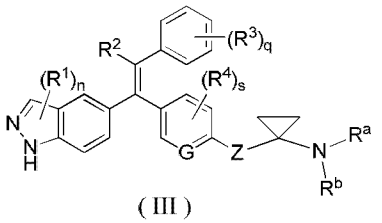
wherein

ring A, G, Z, R^1, R^2, R^3, R^4, R^a, R^b, n, m, s and q are as defined in formula (I).

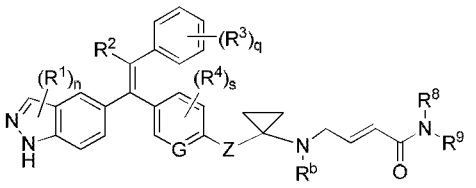
In another preferred embodiment of the present disclosure, the compound of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof, is a compound of formula (III) or a tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or a pharmaceutically acceptable salt thereof:



(III)

wherein: G, Z, R^1, R^2, R^3, R^4, R^a, R^b, n, m, s and q are as defined in formula (I).

In another preferred embodiment of the present disclosure, the compound of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof, is a compound of formula (IV) or a tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or a pharmaceutically acceptable salt thereof:



(IV)

wherein:

G, Z, R^1, R^2, R^3, R^4, R^8, R^9, R^b, n, s and q are as defined in formula (I);

preferably, R^8 and R^9 together with the nitrogen atom to which they are attached form a heterocyclyl, wherein the heterocyclyl optionally contains one to two identical or different heteroatoms selected from the group consisting of N, O and S in addition to the said nitrogen atom, and the said heterocyclyl is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halogen, amino, cyano, nitro, hydroxy, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl; more preferably, the heterocyclyl is optionally substituted by hydroxy or hydroxyalkyl; and further preferably, the heterocyclyl is optionally substituted by hydroxy.

In another preferred embodiment of the present disclosure, in the compound of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof, G is an N atom.

In another preferred embodiment of the present disclosure, in the compound of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof, R^1 is selected from the group consisting of halogen and hydrogen atom.

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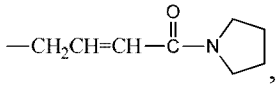
In another preferred embodiment of the present disclosure, in the compound of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof, R^2 is a haloalkyl, preferably C_1-C_6 haloalkyl, and more preferably $-CH_2CF_3$.

In another preferred embodiment of the present disclosure, in the compound of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof, R^3 is selected from the group consisting of hydrogen atom, halogen, alkyl, cyano, haloalkyl, $NR^{13}C(O)R^{14}$, $C(O)NR^{13}R^{14}$ and SO_2R^{15}; R^{13} and R^{14} are identical or different and are each independently selected from the group consisting of hydrogen atom and alkyl; and R^{15} is selected from the group consisting of hydrogen atom and alkyl.

In another preferred embodiment of the present disclosure, in the compound of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof, each R^4 is identical or different and each is independently selected from the group consisting of hydrogen atom, halogen, alkyl and alkoxy, and preferably hydrogen.

In another preferred embodiment of the present disclosure, in the compound of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof, Z is selected from the group consisting of a bond, -O-, $-O-CH_2-$ and -NH-.

In another preferred embodiment of the present disclosure, in the compound of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof, R^a is selected from the group consisting of $-CH_2CH=CHC(O)NR^8R^9$, $-C(O)CH=CR^{10}R^{11}$ and $-C(O)C\equiv CR^{12}$; R^8 and R^9 are identical or different and are each independently selected from the group consisting of hydrogen atom, alkyl, cycloalkyl and heterocyclyl; or, R^8 and R^9 together with the nitrogen atom to which they are attached form a heterocyclyl, wherein the heterocyclyl optionally contains one to two identical or different heteroatoms selected from the group consisting of N, O and S in addition to one nitrogen atom,, and the heterocyclyl is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halogen, amino, cyano, nitro, hydroxy, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl; R^{10} and R^{11} are identical or different and are each independently selected from the group consisting of hydrogen atom and alkyl; and R^{12} is selected from the group consisting of hydrogen atom and alkyl.

In another preferred embodiment of the present disclosure, in the compound of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof, R^a is selected from the group consisting of $-CH_2CH=CHC(O)N(CH_3)_2$, $-CH_2CH=CHC(O)NH(CH_3)$, $-CH_2CH=CHC(O)NHC(CH_3)_3$, $-C(O)CH=CH_2$, $-C(O)C\equiv CCH_3$,  ,

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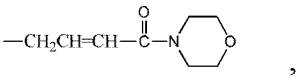
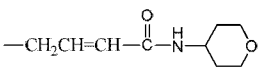
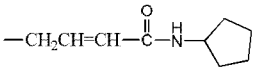
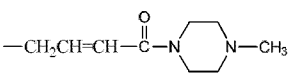
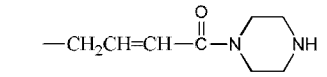
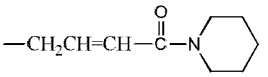
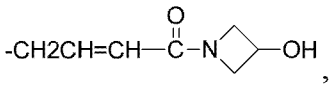
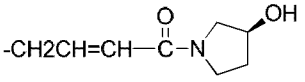
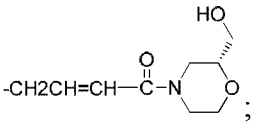
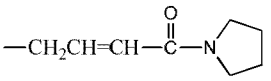
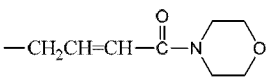
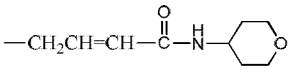
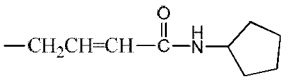
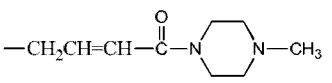
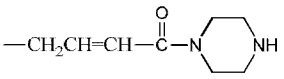
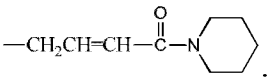
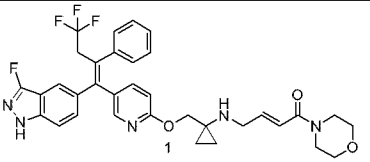
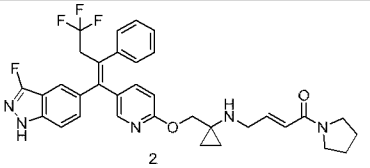
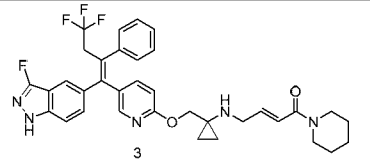
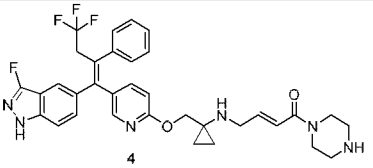
 ,  ,  ,
 ,  ,  ,
 ,  and  ;

preferably, R^a is selected from the group consisting of $-CH_2CH=CHC(O)N(CH_3)_2$, $-CH_2CH=CHC(O)NH(CH_3)$, $-CH_2CH=CHC(O)NHC(CH_3)_3$, $-C(O)CH=CH_2$, $-C(O)C\equiv CCH_3$,  ,  ,
 ,  ,  ,
 and  .

Typical compounds of formula (I) include, but are not limited to:

Example No.	Structure and name of the compound
1	
	(*E*)-1-Morpholino-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-en-1-one **1**
2	
	(*E*)-1-(Pyrrolidin-1-yl)-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-en-1-one **2**
3	
	(*E*)-1-(Piperidin-1-yl)-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-en-1-one **3**
4	

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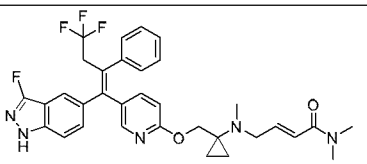
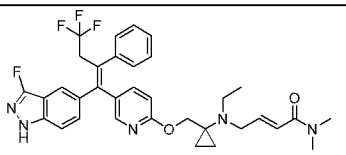
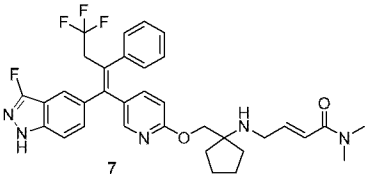
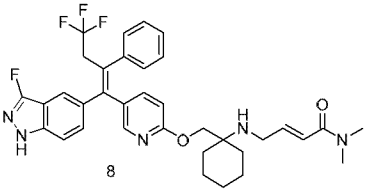
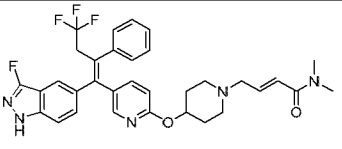
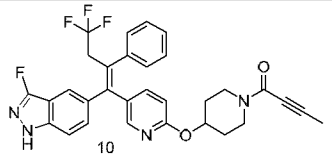
	(*E*)-1-(Piperazin-1-yl)-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-en-1-one **4**
5	 5
	(*E*)-*N*,*N*-Dimethyl-4-(methyl(1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-enamide **5**
6	 6
	(*E*)-4-(Ethyl(1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)-*N*,*N*-dimethylbut-2-enamide **6**
7	 7
	(*E*)-*N*,*N*-Dimethyl-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopentyl)amino)but-2-enamide **7**
8	 8
	(*E*)-*N*,*N*-Dimethyl-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclohexyl)amino)but-2-enamide **8**
9	 9
	(*E*)-*N*,*N*-Dimethyl-4-(4-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **9**
10	 10
	(*Z*)-1-(4-((5-(4,4,4-Trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-yn-1-one **10**

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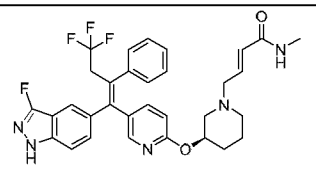
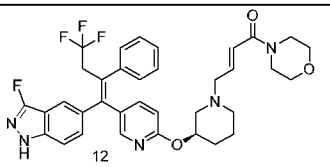
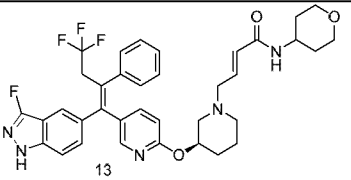
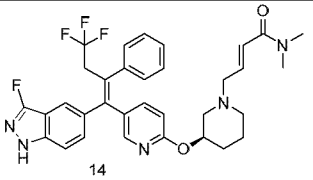
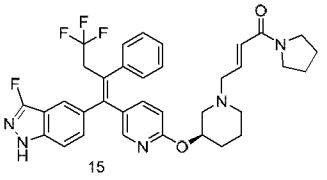
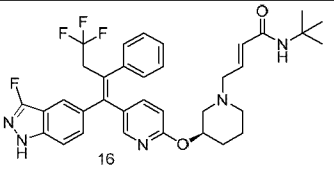
11	 11
	(*E*)-*N*-Methyl-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **11**
12	 12
	(*E*)-1-Morpholino-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-en-1-one **12**
13	 13
	(*E*)-*N*-(Tetrahydro-2*H*-pyran-4-yl)-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **13**
14	 14
	(*E*)-*N*,*N*-Dimethyl-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **14**
15	 15
	(*E*)-1-(Pyrrolidin-1-yl)-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-en-1-one **15**
16	 16
	(*E*)-*N*-(*Tert*-butyl)-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **16**

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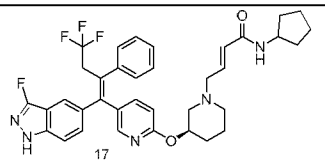
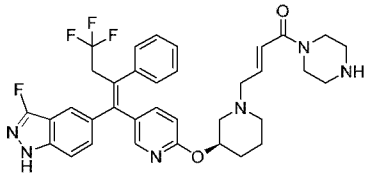
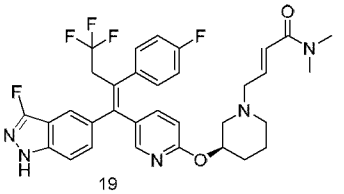
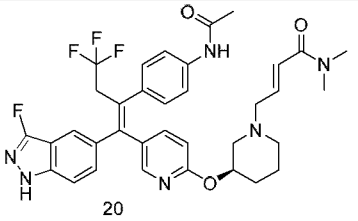
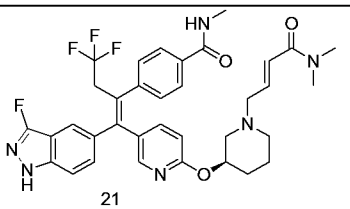
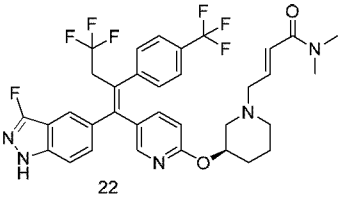
17	 17
	(*E*)-*N*-Cyclopentyl-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **17**
18	 18
	(*E*)-1-(Piperazin-1-yl)-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-en-1-one **18**
19	 19
	(*E*)-*N*,*N*-Dimethyl-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-(4-fluorophenyl)but-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **19**
20	 20
	(*E*)-4-((*R*)-3-((5-((*Z*)-2-(4-Acetamidophenyl)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)but-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)-*N*,*N*-dimethylbut-2-enamide **20**
21	 21
	4-((*Z*)-1-(6-(((*R*)-1-((*E*)-4-(Dimethylamino)-4-oxobut-2-en-1-yl)piperidin-3-yl)oxy)pyridin-3-yl)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)but-1-en-2-yl)-*N*-methylbenzamide **21**
22	 22
	(*E*)-*N*,*N*-Dimethyl-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-(4-

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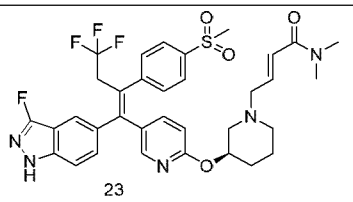
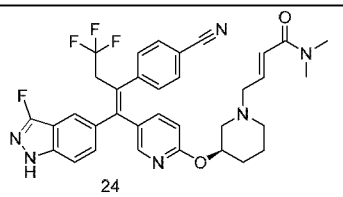
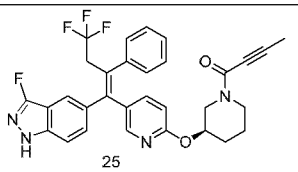
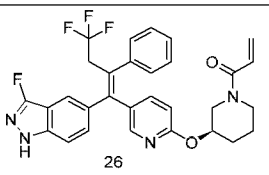
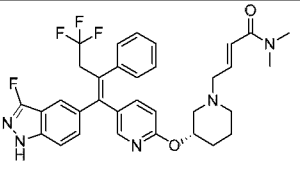
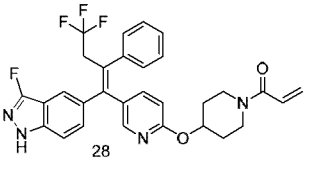
	(trifluoromethyl)phenyl)but-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **22**
23	 23
	(*E*)-*N*,*N*-Dimethyl-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-(4-(methylsulfonyl)phenyl)but-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **23**
24	 24
	(*E*)-4-((*R*)-3-((5-((*Z*)-2-(4-Cyanophenyl)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)but-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)-*N*,*N*-dimethylbut-2-enamide **24**
25	 25
	(*R*,*Z*)-1-(3-((5-(4,4,4-Trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-yn-1-one **25**
26	 26
	(*R*,*Z*)-1-(3-((5-(4,4,4-Trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)prop-2-en-1-one **26**
27	 27
	(*E*)-*N*,*N*-Dimethyl-4-((*S*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **27**
28	 28
	(*Z*)-1-(4-((5-(4,4,4-Trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyri

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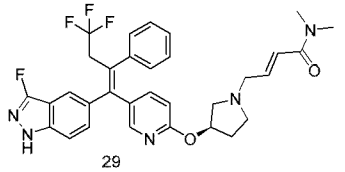
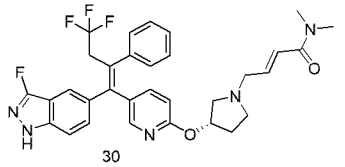
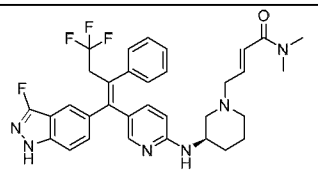
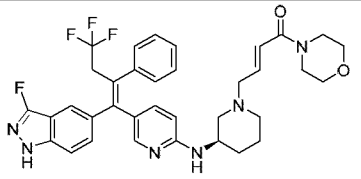
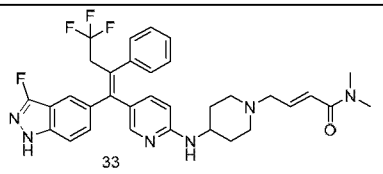
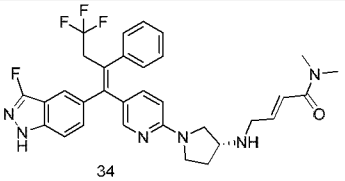
	din-2-yl)oxy)piperidin-1-yl)prop-2-en-1-one **28**
29	 29
	(*E*)-*N*,*N*-Dimethyl-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)pyrrolidin-1-yl)but-2-enamide **29**
30	 30
	(*E*)-*N*,*N*-Dimethyl-4-((*S*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)pyrrolidin-1-yl)but-2-enamide **30**
31	 31
	(*E*)-*N*,*N*-Dimethyl-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)amino)piperidin-1-yl)but-2-enamide **31**
32	 32
	(*E*)-1-Morpholino-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)amino)piperidin-1-yl)but-2-en-1-one **32**
33	 33
	(*E*)-*N*,*N*-Dimethyl-4-(4-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)amino)piperidin-1-yl)but-2-enamide **33**
34	 34
	(*E*)-*N*,*N*-Dimethyl-4-(((*R*)-1-(5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)pyrrolidin-3-yl)amino)but-2-enamide **34**

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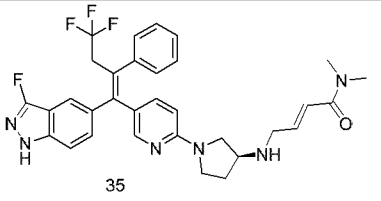
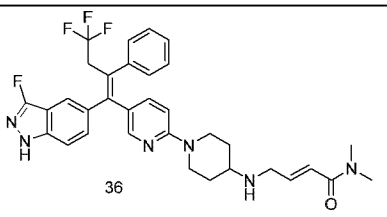
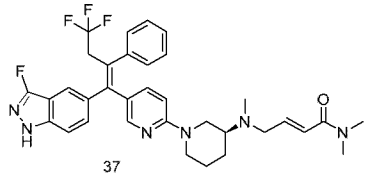
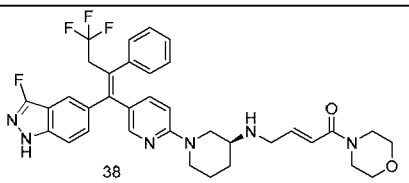
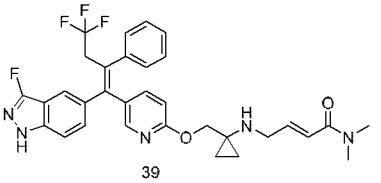
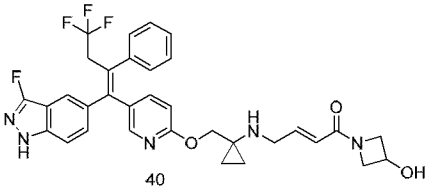
35	 35
	(*E*)-*N*,*N*-Dimethyl-4-(((*S*)-1-(5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)pyrrolidin-3-yl)amino)but-2-enamide **35**
36	 36
	(*E*)-*N*,*N*-Dimethyl-4-((1-(5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)piperidin-4-yl)amino)but-2-enamide **36**
37	 37
	(*E*)-*N*,*N*-Dimethyl-4-(methyl((*S*)-1-(5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)piperidin-3-yl)amino)but-2-enamide **37**
38	 38
	(*E*)-1-Morpholino-4-(((*S*)-1-(5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)piperidin-3-yl)amino)but-2-en-1-one **38**
39	 39
	(*E*)-*N*,*N*-Dimethyl-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-enamide **39**
40	 40
	(*E*)-1-(3-Hydroxyazetidin-1-yl)-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-en-1-one **40**

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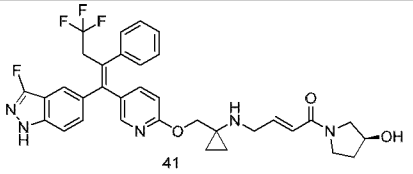
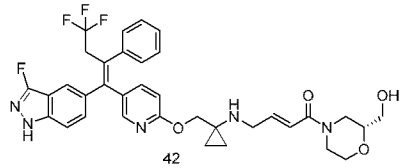
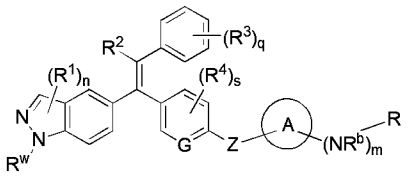
41	 41
	(*E*)-1-((*S*)-3-Hydroxypyrrolidin-1-yl)-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-en-1-one **41**
42	 42
	(*E*)-1-((*R*)-2-(Hydroxymethyl)morpholino)-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-en-1-one **42**

or a tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure provides a compound of formula (IA) or a tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or a pharmaceutically acceptable salt thereof,



(IA)

which is an intermediate for synthesizing the compound of formula (I),

wherein:

R^w is an amino protecting group, and preferably tetrahydropyranyl;

R is selected from the group consisting of $-CH_2CH=CHC(O)NR^8R^9$, $-C(O)CH=CR^{10}R^{11}$ and $-C(O)C\equiv CR^{12}$;

R^8 and R^9 are identical or different and are each independently selected from the group consisting of hydrogen atom, alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

or, R^8 and R^9 together with the nitrogen atom to which they are attached form a heterocyclyl, wherein the heterocyclyl optionally contains one to two identical or different heteroatoms selected from the group consisting of N, O and S in addition to one nitrogen atom, and the heterocyclyl is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halogen, amino, cyano, nitro, hydroxy, hydroxyalkyl, $-COOR^{16}-$, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R^{10} and R^{11} are identical or different and are each independently selected from the group consisting of hydrogen atom, halogen, alkyl, haloalkyl, alkoxy, cyano, amino,

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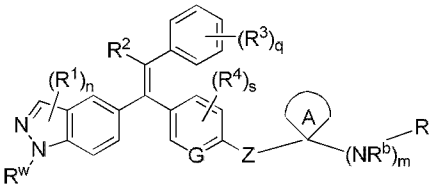
nitro, carboxy, formyl, hydroxy, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R^{12} is selected from the group consisting of hydrogen atom, alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R^{16} is selected from the group consisting of hydrogen atom, alkyl, haloalkyl and hydroxyalkyl;

ring A, G, Z, R^1, R^2, R^3, R^4, R^b, n, m, s and q are as defined in formula (I).

In another aspect, the present disclosure provides a compound of formula (IIA) or a tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or a pharmaceutically acceptable salt thereof,



(IIA)

which is an intermediate for synthesizing the compound of formula (II),

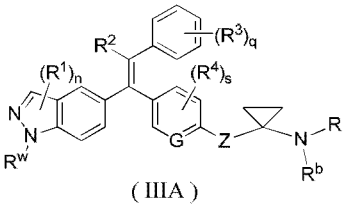
wherein:

R^w is an amino protecting group, and preferably tetrahydropyranyl;

R is as defined in formula (IA);

ring A, G, Z, R^1, R^2, R^3, R^4, R^b, n, m, s and q are as defined in formula (II).

In another aspect, the present disclosure provides a compound of formula (IIIA) or a tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or a pharmaceutically acceptable salt thereof,



(IIIA)

which is an intermediate for synthesizing the compound of formula (III),

wherein:

R^w is an amino protecting group, and preferably tetrahydropyranyl;

R is as defined in formula (IA);

G, Z, R^1, R^2, R^3, R^4, R^b, n, s and q are as defined in formula (III).

In another aspect, the present disclosure provides a compound of formula (IVA) or a tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or a pharmaceutically acceptable salt thereof,

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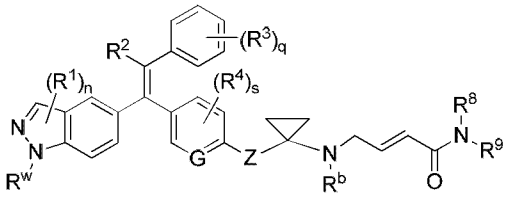


(IVA)

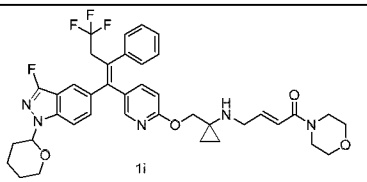
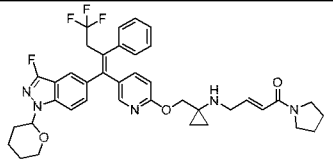
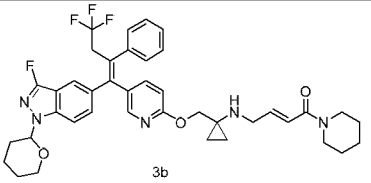
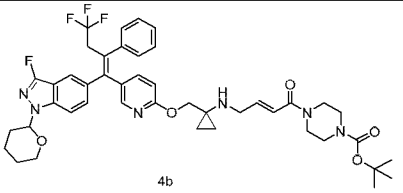
which is an intermediate for synthesizing the compound of formula (IV),

wherein:

R^w is an amino protecting group, and preferably tetrahydropyranyl;

G, Z, R^1, R^2, R^3, R^4, R^b, R^8, R^9, n, s and q are as defined in formula (IV).

Typical compounds of formula (IA) include, but are not limited to:

Example No.	Structure and name of the compound
1i	 1i
	(*E*)-1-Morpholino-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-en-1-one **1i**
2b	 2b
	(*E*)-1-(Pyrrolidin-1-yl)-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-en-1-one **2b**
3b	 3b
	(*E*)-1-(Piperidin-1-yl)-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-en-1-one **3b**
4b	 4b
	Tert-butyl

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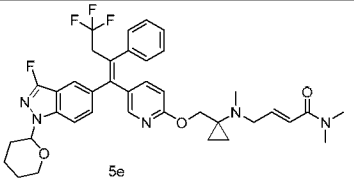
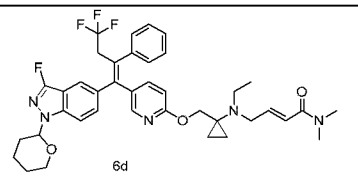
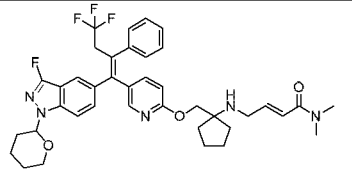
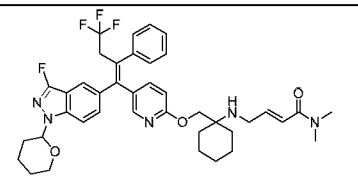
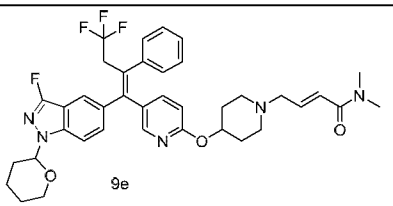
	4-((*E*)-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-enoyl)piperazine-1-carboxylate **4b**
5e	 5e
	(*E*)-*N*,*N*-Dimethyl-4-(methyl(1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-enamide **5e**
6d	 6d
	(*E*)-4-(Ethyl(1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)-*N*,*N*-dimethylbut-2-enamide **6d**
7d	 7d
	(*E*)-*N*,*N*-Dimethyl-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopentyl)amino)but-2-enamide **7d**
8d	 8d
	(*E*)-*N*,*N*-Dimethyl-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclohexyl)amino)but-2-enamide **8d**
9e	 9e
	(*E*)-*N*,*N*-Dimethyl-4-(4-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **9e**

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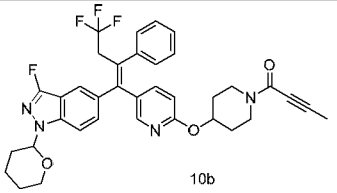
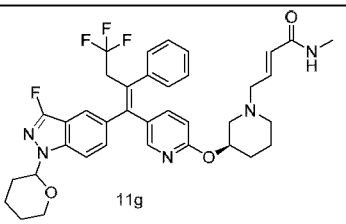
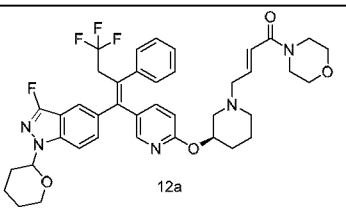
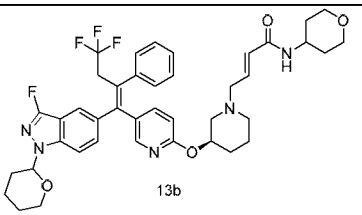
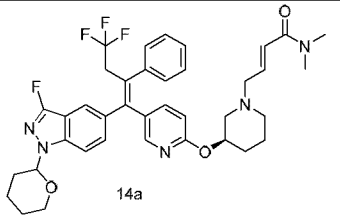
10b	 10b
	(*Z*)-1-(4-((5-(4,4,4-Trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-yn-1-one **10b**
11g	 11g
	(*E*)-*N*-Methyl-4-((3*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **11g**
12a	 12a
	(*E*)-1-Morpholino-4-((3*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-en-1-one **12a**
13b	 13b
	(*E*)-*N*-(Tetrahydro-2*H*-pyran-4-yl)-4-((3*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **13b**
14a	 14a
	(*E*)-*N*,*N*-Dimethyl-4-((3*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **14a**

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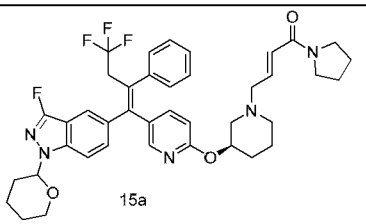
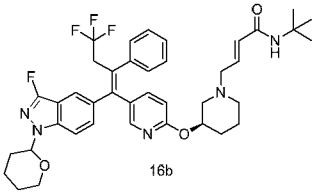
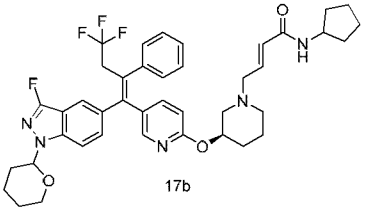
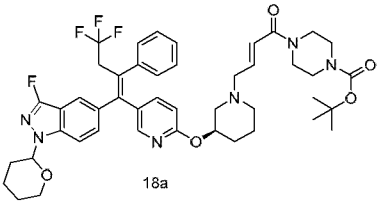
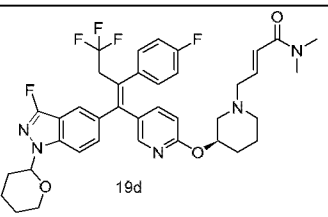
15a	 15a
	(*E*)-1-(Pyrrolidin-1-yl)-4-((3*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-en-1-one **15a**
16b	 16b
	(*E*)-*N*-(*Tert*-butyl)-4-((3*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **16b**
17b	 17b
	(*E*)-*N*-Cyclopentyl-4-((3*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **17b**
18a	 18a
	Tert-butyl 4-((*E*)-4-((3*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enoyl)piperazine-1-carboxylate **18a**
19d	 19d
	(*E*)-*N*,*N*-Dimethyl-4-((3*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-(4-fluorophenyl)but-1-en-1-yl)pyridin-2-yl)oxy)piperidin

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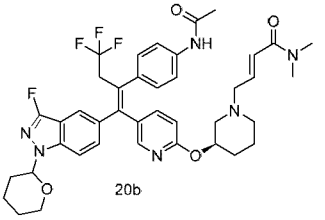
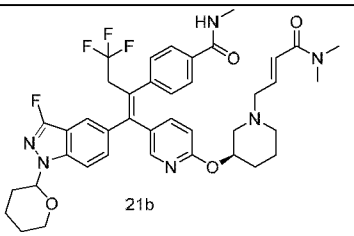
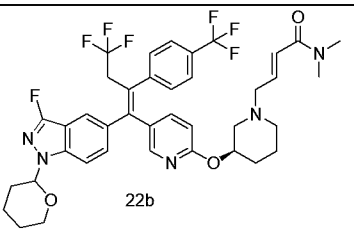
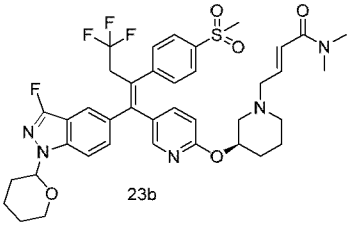
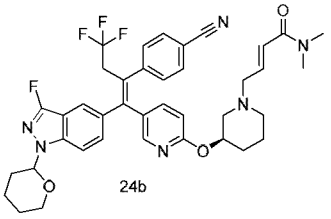
	-1-yl)but-2-enamide **19d**
20b	 20b
	(*E*)-4-((3*R*)-3-((5-((*Z*)-2-(4-Acetamidophenyl)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)but-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)-*N*,*N*-dimethylbut-2-enamide **20b**
21b	 21b
	4-((*Z*)-1-(6-(((*R*)-1-((*E*)-4-(Dimethylamino)-4-oxobut-2-en-1-yl)piperidin-3-yl)oxy)pyridin-3-yl)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)but-1-en-2-yl)-*N*-methylbenzamide **21b**
22b	 22b
	(*E*)-*N*,*N*-Dimethyl-4-((3*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-(4-(trifluoromethyl)phenyl)but-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **22b**
23b	 23b
	(*E*)-*N*,*N*-Dimethyl-4-((3*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-(4-(methylsulfonyl)phenyl)but-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **23b**
24b	 24b

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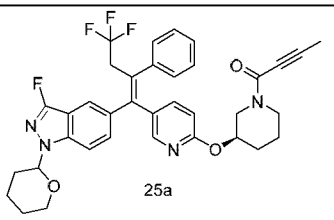
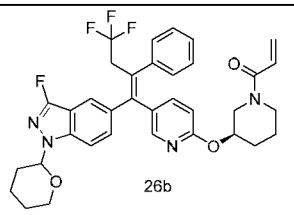
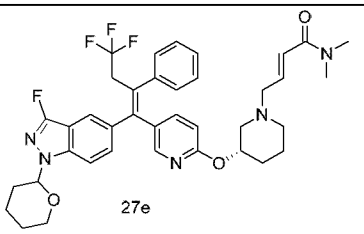
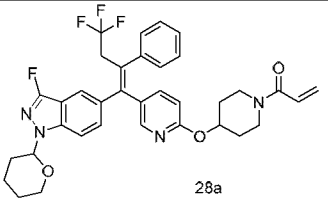
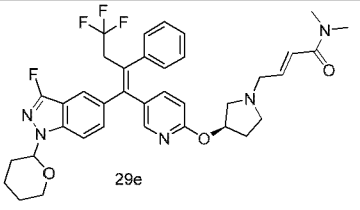
	(*E*)-4-((3*R*)-3-((5-((*Z*)-2-(4-Cyanophenyl)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)but-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)-*N*,*N*-dimethylbut-2-enamide **24b**
25a	 25a
	1-((3*R*)-3-((5-((*Z*)-4,4,4-Trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-yn-1-one **25a**
26b	 26b
	1-((3*R*)-3-((5-((*Z*)-4,4,4-Trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)prop-2-en-1-one **26b**
27e	 27e
	(*E*)-*N*,*N*-Dimethyl-4-((3*S*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **27e**
28a	 28a
	(*Z*)-1-(4-((5-(4,4,4-Trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)prop-2-en-1-one **28a**
29e	 29e
	(*E*)-*N*,*N*-Dimethyl-4-((3*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)pyrrolidin-1-yl)but-2-enamide **29e**

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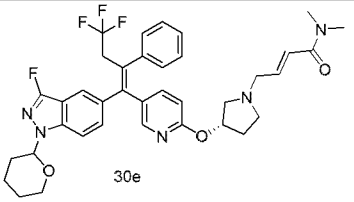
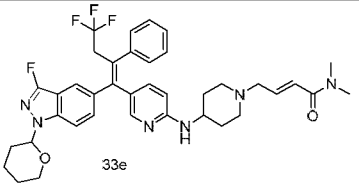
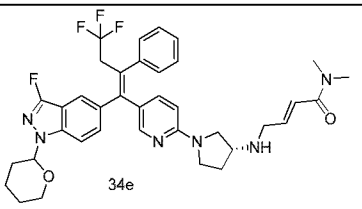
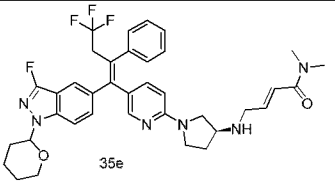
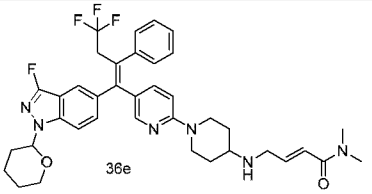
30e	 30e
	(*E*)-*N*,*N*-Dimethyl-4-((3*S*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)pyrrolidin-1-yl)but-2-enamide **30e**
33e	 33e
	(*E*)-*N*,*N*-Dimethyl-4-(4-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)amino)piperidin-1-yl)but-2-enamide **33e**
34e	 34e
	(*E*)-*N*,*N*-Dimethyl-4-(((3*R*)-1-(5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)pyrrolidin-3-yl)amino)but-2-enamide **34e**
35e	 35e
	(*E*)-*N*,*N*-Dimethyl-4-(((3*S*)-1-(5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)pyrrolidin-3-yl)amino)but-2-enamide **35e**
36e	 36e
	(*E*)-*N*,*N*-Dimethyl-4-((1-(5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)piperidin-4-yl)amino)but-2-enamide **36e**

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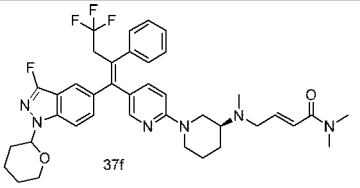
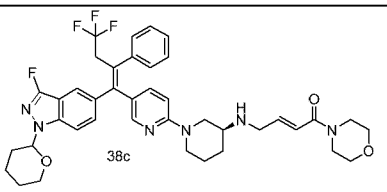
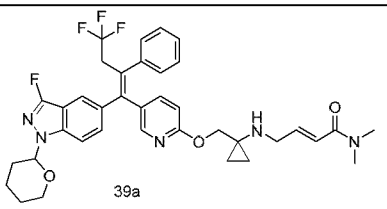
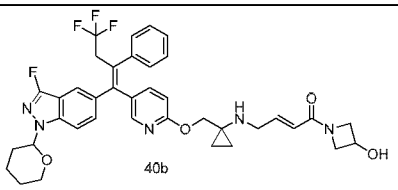
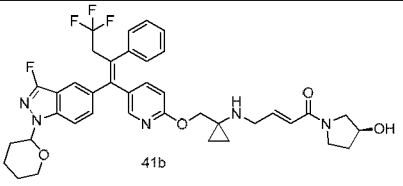
37f	 37f
	(*E*)-*N*,*N*-Dimethyl-4-(methyl((3*S*)-1-(5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)piperidin-3-yl)amino)but-2-enamide **37f**
38c	 38c
	(*E*)-1-Morpholino-4-(((3*S*)-1-(5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)piperidin-3-yl)amino)but-2-en-1-one **38c**
39a	 39a
	(*E*)-*N*,*N*-Dimethyl-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-enamide **39a**
40b	 40b
	(*E*)-1-(3-Hydroxyazetidin-1-yl)-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-en-1-one **40b**
41b	 41b
	(*E*)-1-((*S*)-3-Hydroxypyrrolidin-1-yl)-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-en-1-one **41b**

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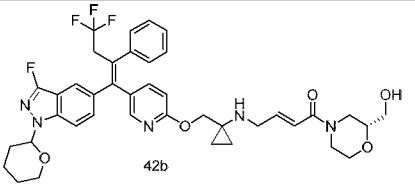
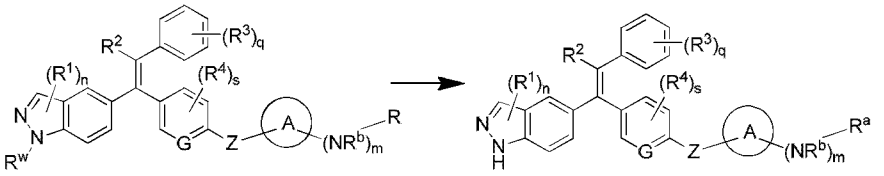
42b	
	(*E*)-1-((*R*)-2-(Hydroxymethyl)morpholino)-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-en-1-one **42b**

or a tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure provides a method for preparing the compound of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof, comprising a step of:



(IA) (I)

subjecting the compound of formula (IA) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof to a deprotection reaction under an acidic condition to obtain the compound of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof;

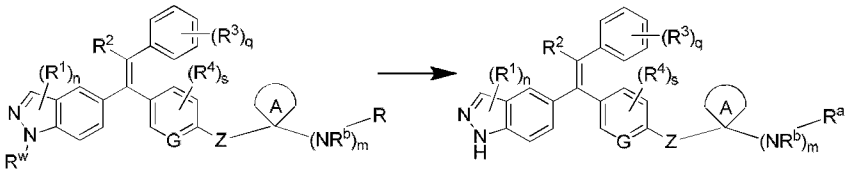
wherein:

R^w is an amino protecting group, and preferably tetrahydropyranyl or *tert*-butoxycarbonyl;

R is as defined in formula (IA);

ring A, G, Z, R^1, R^2, R^3, R^4, R^a , R^b, n, m, s and q are as defined in formula (I).

In another aspect, the present disclosure provides a method for preparing the compound of formula (II) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof, comprising a step of:



(IIA) (II)

subjecting the compound of formula (IIA) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof to a deprotection reaction under an acidic condition to obtain the compound

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of formula (II) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof;

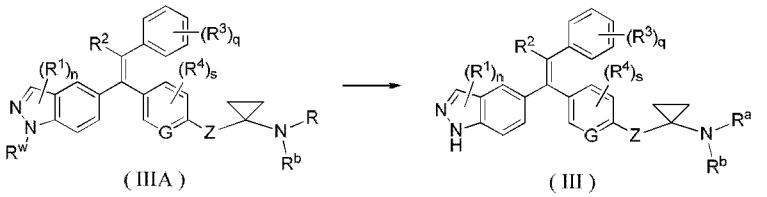
wherein:

R^w is an amino protecting group, and preferably tetrahydropyranyl or *tert*-butoxycarbonyl;

R is as defined in formula (IIA);

ring A, G, Z, R^1, R^2, R^3, R^4, R^a, R^b, n, m, s and q are as defined in formula (II).

In another aspect, the present disclosure provides a method for preparing the compound of formula (III) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof, comprising a step of:



(IIIA) (III)

subjecting the compound of formula (IIIA) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof to a deprotection reaction under an acidic condition to obtain the compound of formula (III) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof;

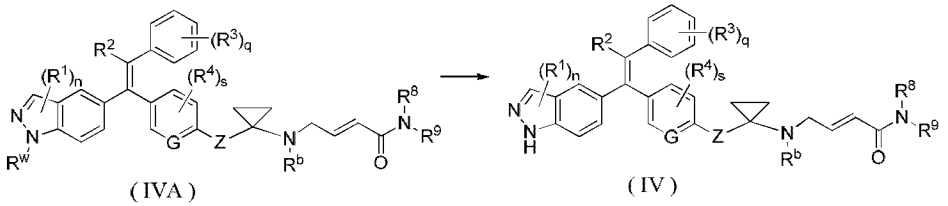
wherein:

R^w is an amino protecting group, and preferably tetrahydropyranyl or *tert*-butoxycarbonyl;

R is as defined in formula (IIIA);

G, Z, R^1, R^2, R^3, R^4, R^a, R^b, n, s and q are as defined in formula (III).

In another aspect, the present disclosure provides a method for preparing the compound of formula (IV) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof, comprising a step of:



(IVA) (IV)

subjecting the compound of formula (IVA) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof to a deprotection reaction under an acidic condition to obtain the compound of formula (IV) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof;

wherein:

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R^w is an amino protecting group, and preferably tetrahydropyranyl or *tert*-butoxycarbonyl;

G, Z, R^1, R^2, R^3, R^4, R^8, R^9, R^b, n, s and q are as defined in formula (IV).

In another aspect, the present disclosure relates to a pharmaceutical composition comprising a therapeutically effective amount of the compound of formula (I) to (IV) as defined above or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, diluents or excipients. The present disclosure also relates to a method for preparing the pharmaceutical composition as defined above, comprising a step of mixing the compound of formula (I) to (IV), or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof with the pharmaceutically acceptable carriers, diluents or excipients.

The present disclosure further relates to a use of the compound of formula (I) to (IV), or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition comprising the same in the preparation of an estrogen receptor modulator.

The present disclosure further relates to a use of the compound of formula (I) to (IV), or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition comprising the same in the preparation of a medicament for preventing and/or treating estrogen receptor-mediated or estrogen receptor-dependent disease or disorder, wherein the estrogen receptor-mediated or estrogen receptor-dependent disease or disorder is preferably cancer, more preferably breast cancer, ovarian cancer, endometrial cancer, prostate cancer or uterine cancer, and further preferably breast cancer.

The present disclosure further relates to the compound of formula (I) to (IV), or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof, for use as a medicament.

The present disclosure further relates to the compound of formula (I) to (IV), or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof, for use as a medicament for treating estrogen receptor-mediated or estrogen receptor-dependent disease or disorder, wherein the estrogen receptor-mediated or estrogen receptor-dependent disease or disorder is preferably cancer, more preferably breast cancer, ovarian cancer, endometrial cancer, prostate cancer or uterine cancer, and further preferably breast cancer.

The present disclosure further relates to a method for treating estrogen receptor-mediated or estrogen receptor-dependent disease or disorder, comprising a step of administering to a patient in need thereof a therapeutically effective amount of the compound of formula (I) to (IV) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof

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of the present disclosure. This method shows outstanding efficacy and less side effects. The estrogen receptor-mediated or estrogen receptor-dependent disease or disorder is preferably cancer, more preferably breast cancer, ovarian cancer, endometrial cancer, prostate cancer or uterine cancer, and further preferably breast cancer.

The active compound can be formulated into a form suitable for administration by any appropriate route, and the active compound is preferably in the form of a unit dose, or in a form in which the patient can self-administer in a single dose. The form of the unit dose of the compound or composition of the present invention can be tablet, capsule, cachet, bottled potion, powder, granule, lozenge, suppository, regenerating powder or liquid preparation.

The dosage of the compound or composition used in the treatment method of the present invention will generally vary according to the severity of the disease, the weight of the patient, and the relative efficacy of the compound. However, as a general guide, a suitable unit dose can be 0.1 to 1000 mg.

In addition to the active ingredients, the pharmaceutical composition of the present invention can further comprise one or more auxiliaries including filler (diluent), binder, wetting agent, disintegrant, excipient and the like. Depending on the administration mode, the composition can comprise 0.1 to 99% by weight of the active compound.

The pharmaceutical composition containing the active ingredient can be in a form suitable for oral administration, for example, a tablet, troche, lozenge, aqueous or oily suspension, dispersible powder or granule, emulsion, hard or soft capsule, syrup or elixir. An oral composition can be prepared according to any known method in the art for the preparation of pharmaceutical composition. Such a composition can contain one or more ingredient(s) selected from the group consisting of sweeteners, flavoring agents, colorants and preservatives, in order to provide a pleasing and palatable pharmaceutical formulation. The tablet contains the active ingredient in admixture with nontoxic, pharmaceutically acceptable excipients suitable for the manufacture of tablets. These excipients can be inert excipients, granulating agents, disintegrants and lubricants. The tablet can be uncoated or coated by means of a known technique to mask drug taste or delay the disintegration and absorption of the active ingredient in the gastrointestinal tract, thereby providing a sustained release over a long period of time. For example, water soluble taste masking materials can be used. An oral formulation can also be provided as soft gelatin capsules in which the active ingredient is mixed with an inert solid diluent, or the active ingredient is mixed with a water-soluble carrier.

An aqueous suspension comprises an active ingredient in admixture with excipients suitable for the manufacture of an aqueous suspension. Such excipients are suspending agents, dispersants or wetting agents. The active ingredient of the aqueous suspension can be dispersible powders or granules. The active ingredient is mixed with one or more dispersant(s), wetting agent(s) or suspending agent(s) by adding water. The aqueous suspension can also comprise one or more preservative(s), one or more colorant(s), one or more flavoring agent(s), and one or more sweetener(s).

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An oil suspension can be formulated by suspending the active ingredient in a vegetable oil or mineral oil. The oil suspension can comprise a thickener. The aforementioned sweeteners and flavoring agents can be added to provide a palatable formulation. These compositions can be preserved by adding an antioxidant.

The dispersible powders or granules suitable for the preparation of an aqueous suspension can provide the active ingredient in admixture with the dispersants or wetting agents, suspending agent or one or more preservatives by adding water. Suitable dispersants or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, such as sweeteners, flavoring agents and colorants, can also be added. These compositions can be preserved by adding an antioxidant, such as ascorbic acid.

The pharmaceutical composition of the present disclosure can also be in the form of an oil-in-water emulsion. The oil phase can be a vegetable oil, or a mineral oil, or a mixture thereof. Suitable emulsifying agents can be naturally occurring phospholipids. A sweetening agent can be used. Such formulations can also contain a demulcent, a preservative, a coloring agent and an antioxidant.

The pharmaceutical composition of the present disclosure can be in the form of a sterile injectable aqueous solution. Acceptable vehicles or solvents that can be used are water, Ringer's solution or isotonic sodium chloride solution. The sterile injectable formulation can be a sterile injectable oil-in-water micro-emulsion in which the active ingredient is dissolved in an oil phase. The injectable solution or micro-emulsion can be introduced into a patient's bloodstream by local bolus injection. Alternatively, the solution and micro-emulsion are preferably administered in a manner that maintains a constant circulating concentration of the compound of the present disclosure. In order to maintain this constant concentration, a continuous intravenous delivery device can be used. An example of such a device is Deltec CADD-PLUS. TM. 5400 intravenous injection pump.

The pharmaceutical composition of the present disclosure can be in the form of a sterile injectable aqueous or oily suspension for intramuscular and subcutaneous administration. Such a suspension can be formulated with suitable dispersants or wetting agents and suspending agents as described above according to known techniques. The sterile injectable formulation can also be a sterile injectable solution or suspension prepared in a nontoxic parenterally acceptable diluent or solvent. Moreover, sterile fixed oils can easily be used as a solvent or suspending medium. In addition, fatty acids can also be used to prepare injections.

The compound of the present disclosure can be administered in the form of a suppository for rectal administration. These pharmaceutical compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures, but liquid in the rectum, thereby melting in the rectum to release the drug.

It is well known to those skilled in the art that the dosage of a drug depends on a

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variety of factors including, but not limited to the following factors: activity of a specific compound, age of the patient, weight of the patient, general health of the patient, behavior of the patient, diet of the patient, administration time, administration route, excretion rate, drug combination and the like. In addition, the optimal treatment, such as treatment mode, daily dose of the compound of formula (I) or the type of pharmaceutically acceptable salt thereof can be verified according to traditional therapeutic regimens.

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 12 carbon atoms, and more preferably an alkyl having 1 to 6 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. More preferably, the alkyl group is a lower alkyl having 1 to 6 carbon atoms, and 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 and the like. The alkyl 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 term "alkylene" refers to a saturated linear or branched aliphatic hydrocarbon group having two residues derived from the removal of two hydrogen atoms from the

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same carbon atom or two different carbon atoms of the parent alkane. It is a linear or branched alkylene having 1 to 20 carbon atoms, preferably 1 to 12 carbon atoms, and more preferably 1 to 6 carbon atoms. Non-limiting examples of alkylene include, but are not limited to, methylene ($-CH_2-$), 1,1-ethylene ($-CH(CH_3)-$), 1,2-ethylene ($-CH_2CH_2-$), 1,1-propylene ($-CH(CH_2CH_3)-$), 1,2-propylene ($-CH_2CH(CH_3)-$), 1,3-propylene ($-CH_2CH_2CH_2-$), 1,4-butylene ($-CH_2CH_2CH_2CH_2-$) and the like. The alkylene 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 optionally 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 and oxo.

The term "alkenyl" refers to an alkyl containing carbon-carbon double bond(s) in the molecule, wherein the definition of the alkyl is as described above. The alkenyl can be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more groups independently selected from the group consisting of hydrogen atom, alkyl, alkoxy, halogen, haloalkyl, hydroxy, hydroxyalkyl, cyano, amino, nitro, cycloalkyl, heterocyclyl, aryl and heteroaryl.

The term "alkynyl" refers to an alkyl containing carbon-carbon triple bond(s) in the molecule, wherein the definition of the alkyl is as described above. The alkynyl can be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more groups independently selected from the group consisting of hydrogen atom, alkyl, alkoxy, halogen, haloalkyl, hydroxy, hydroxyalkyl, cyano, amino, nitro, cycloalkyl, heterocyclyl, aryl and heteroaryl.

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 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, carboxy and alkoxycarbonyl.

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 (for example 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 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 term "spiro cycloalkyl" refers to a 5 to 20 membered polycyclic group with

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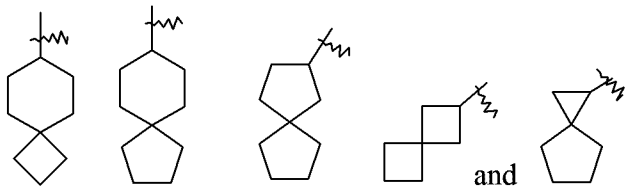
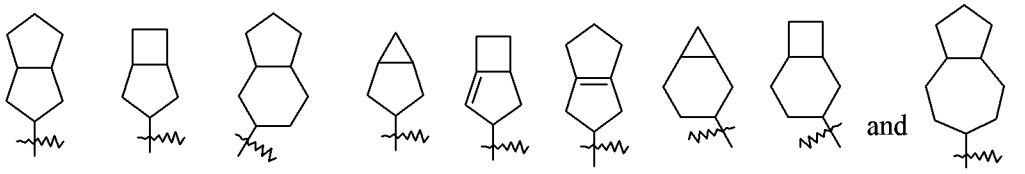
individual rings connected through one shared carbon atom (called a spiro atom), wherein the rings can contain one or more double bonds, but none of the rings has a completely conjugated π-electron system. The spiro cycloalkyl is preferably a 6 to 14 membered spiro cycloalkyl (for example 6, 7, 8, 9, 10, 11, 12, 13, 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, di-spiro cycloalkyl, or 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

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, 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 (for example 7, 8, 9 or 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:


and

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, 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 (for example 7, 8, 9 or 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

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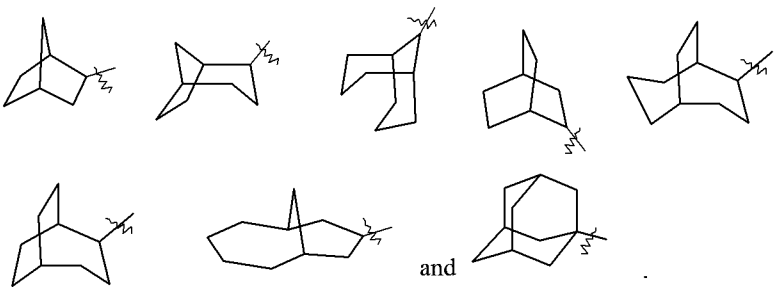
tricyclic bridged cycloalkyl. Non-limiting examples of bridged cycloalkyl include:


and

The cycloalkyl (including cycloalkyl, spiro cycloalkyl, fused cycloalkyl and bridged 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 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 term "heterocyclyl" refers to a 3 to 20 membered saturated or partially unsaturated monocyclic or polycyclic hydrocarbon substituent group, wherein one or more ring atoms are heteroatoms selected from the group consisting of N, O, S, S(O) and $S(O)_2$, 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 (for example 1, 2, 3 or 4 atoms) are heteroatoms; more preferably, 3 to 6 ring atoms (for example 3, 4, 5 or 6 ring atoms). Non-limiting examples of monocyclic heterocyclyl include pyrrolidinyl, imidazolidinyl, tetrahydrofuranyl, tetrahydrothienyl, dihydroimidazolyl, dihydrofuranyl, dihydropyrazolyl, dihydropyrrolyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, homopiperazinyl and the like, and preferably piperidinyl, pyrrolidinyl. Polycyclic heterocyclyl includes a heterocyclyl having a spiro ring, fused ring or bridged 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, S, S(O) and $S(O)_2$, 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 (for example 7, 8, 9 or 10 membered spiro heterocyclyl). According to the number of the spiro atoms shared between the rings, the spiro heterocyclyl is 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,

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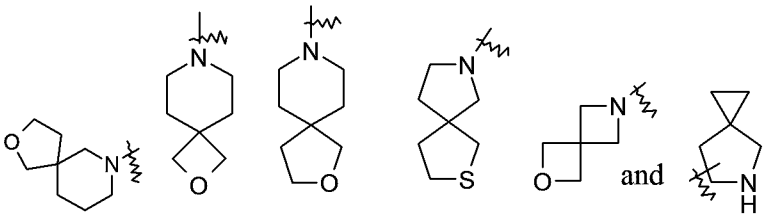
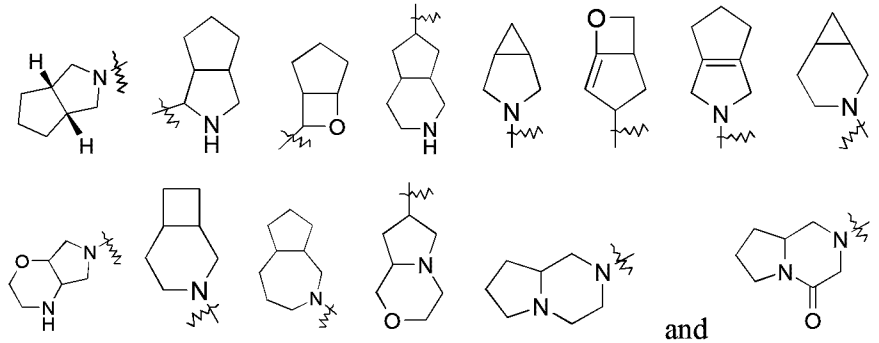
4-membered/6-membered, 5-membered/5-membered, or 5-membered/6-membered mono-spiro heterocyclyl. Non-limiting examples of spiro heterocyclyl include:



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, S, S(O) and $S(O)_2$, 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 (for example 7, 8, 9 or 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 the fused heterocyclyl is 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, S, S(O) and $S(O)_2$, 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 (for example 7, 8, 9 or 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

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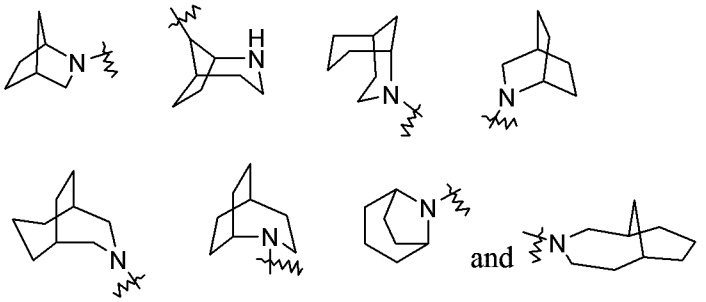
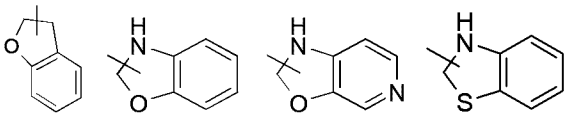
heterocyclyl include:



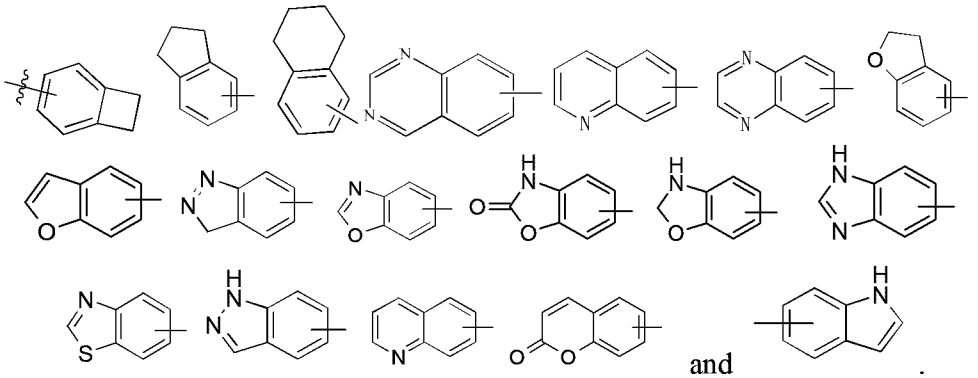
The heterocyclyl (including heterocyclyl, spiro heterocyclyl, fused heterocyclyl and bridged heterocyclyl) ring can be fused to the ring of aryl, heteroaryl or cycloalkyl, wherein the ring bound to the parent structure is heterocyclyl, and non-limiting examples thereof include:



and the like.

The heterocyclyl can be optionally substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more 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 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 ring can be fused to the ring of heteroaryl, heterocyclyl or cycloalkyl, wherein the ring bound to the parent structure is aryl ring, and non-limiting examples thereof include:



and .

The aryl 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, heterocyclylthio, carboxy and alkoxycarbonyl, and

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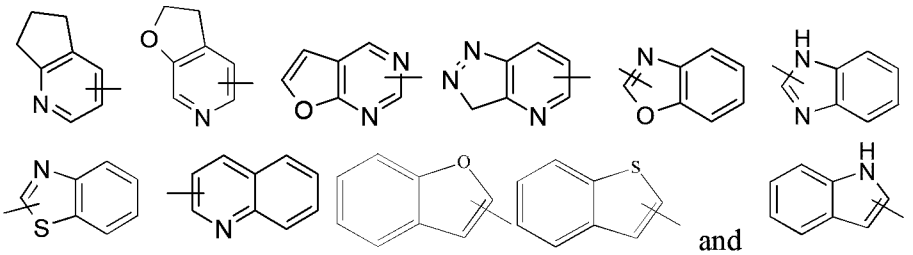
preferably phenyl.

The term "heteroaryl" refers to a 5 to 14 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 (for example 5, 6, 7, 8, 9 or 10 membered heteroaryl), more preferably a 5 or 6 membered heteroaryl, for example, imidazolyl, furyl, thienyl, thiazolyl, pyrazolyl, oxazolyl, pyrrolyl, tetrazolyl, pyridyl, pyrimidinyl, thiadiazolyl, pyrazinyl and the like, preferably imidazolyl, pyrazolyl, pyrimidinyl or thiazolyl, and more preferably pyrazolyl or thiazolyl. 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, and non-limiting examples thereof include:


and .

The heteroaryl can be optionally 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, heterocyclylthio, carboxy and alkoxycarbonyl.

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

The term "haloalkyl" refers to an alkyl group substituted by halogen(s), wherein the alkyl is as defined above.

The term "deuterated alkyl" refers to an alkyl group substituted by deuterium atom(s), wherein the alkyl is as defined above.

The term "hydroxy" refers to an -OH group.

The term "halogen" refers to fluorine, chlorine, bromine or iodine.

The term "amino" refers to a $-NH_2$ group.

The term "cyano" refers to a -CN group.

The term "nitro" refers to a $-NO_2$ group.

The term "carboxy" refers to a -C(O)OH group.

The term "formyl" refers to a -CHO group.

The term "alkoxycarbonyl" refers to a -C(O)O(alkyl) or -C(O)O(cycloalkyl) group, wherein the alkyl and cycloalkyl are as defined above.

The term "acyl halide" refers to a compound containing a -C(O)-halogen group.

"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

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optionally substituted by 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 alkyl and the heterocyclyl being not substituted by 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 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 effort. For example, the combination of amino or hydroxy having free hydrogen and carbon atoms having unsaturated bonds (such as olefinic) may be unstable.

The term "pharmaceutical composition" refers to a mixture of one or more of the compounds described herein 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 show biological activity.

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

Different expressions "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 all have the same meaning. They mean that X can be any one or more of A, B and C.

The compound of the present disclosure can also comprise isotopic derivatives thereof. The term "isotopic derivatives" refers to compounds that differ in structure only in the presence of one or more isotopically enriched atoms. For example, a compound having the structure of the present disclosure with replacing hydrogen with "deuterium" or "tritium", or replacing fluorine with an ^{18}F-fluorine labeling (^{18}F isotope), or replacing carbon with ^{11}C-, ^{13}C-, or ^{14}C-enriched carbon (^{11}C-, ^{13}C-, or ^{14}C-carbon labeling; ^{11}C-, ^{13}C-, or ^{14}C-isotope) is within the scope of the present disclosure. Such compounds can be used, for example, as analytical tools or probes in biological assays, or as tracers for *in vivo* diagnostic imaging of disease, or as tracers for pharmacodynamics, pharmacokinetics or receptor studies. Deuterated compounds can generally retain activity comparable to undeuterated compounds, and when deuterated at certain specific sites, better metabolic stability can be achieved, resulting in certain therapeutic advantages (such as increased half-life *in vivo* or reduced required dose).

For drugs or pharmacologically active agents, the term "therapeutically effective amount" refers to a sufficient amount of a drug or medicament that is non-toxic but capable of achieving the desired effect. The determination of the effective amount varies from person to person, depending on the age and general condition of the recipient, and

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also on the specific active substance. The appropriate effective amount in a case can be determined by those skilled in the art based on routine experiments.

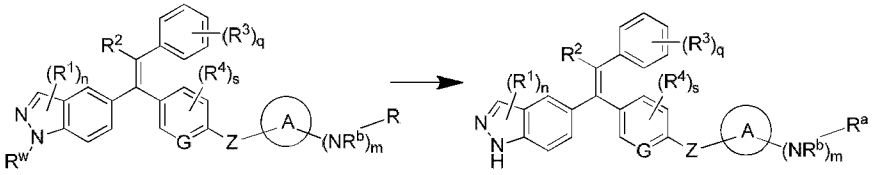
The present disclosure provides an estrogen receptor antagonist having a novel structure of formula (I). It is found that the compound having this kind of structure shows excellent *in vitro* activity. Compared with the prior art, this amide compound with α,β unsaturated bond can inactivate the estrogen receptor by specifically binding to the cysteine in the ligand binding domain of the estrogen receptor.

Synthesis Method of the Compound of the Present Disclosure

In order to achieve the object of the present disclosure, the present disclosure applies the following technical solutions:

Scheme I

A method for preparing the compound of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to the present disclosure, comprising the following step of:



(IA) (I)

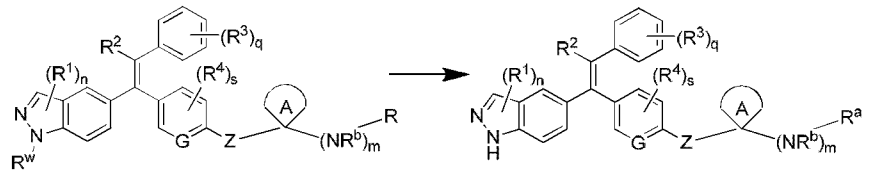
subjecting the compound of formula (IA) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof to a deprotection reaction under an acidic condition to obtain the compound of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof;

wherein:

R^w is an amino protecting group; R is as defined in formula (IA);

ring A, G, Z, R^1, R^2, R^3, R^4, R^a , R^b, n, m, s and q are as defined in formula (I).

Scheme II



(IIA) (II)

subjecting the compound of formula (IIA) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof to a deprotection reaction under an acidic condition to obtain the compound of formula (II) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof;

wherein:

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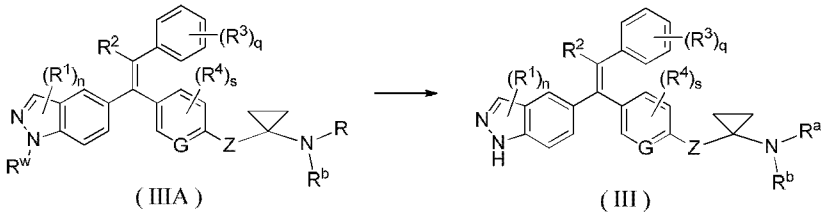
R^w is an amino protecting group;

R is as defined in formula (IIA);

ring A, G, Z, R^1, R^2, R^3, R^4, R^a, R^b, n, m, s and q are as defined in formula (II).

Scheme III



subjecting the compound of formula (IIIA) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof to a deprotection reaction under an acidic condition to obtain the compound of formula (III) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof;

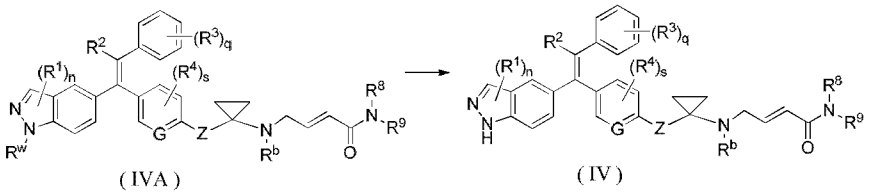
wherein:

R^w is an amino protecting group;

R is as defined in formula (IIIA);

G, Z, R^1, R^2, R^3, R^4, R^a, R^b, n, s and q are as defined in formula (III).

Scheme IV



subjecting the compound of formula (IVA) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof to a deprotection reaction under an acidic condition to obtain the compound of formula (IV) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof;

wherein:

R^w is an amino protecting group;

G, Z, R^1, R^2, R^3, R^4, R^8, R^9, R^b, n, s and q are as defined in formula (IV).

The reagent that provides an acidic condition in the above schemes includes, but is not limited to, pyridine hydrobromide, trifluoroacetic acid, formic acid, acetic acid, hydrochloric acid, sulfuric acid and methanesulfonic acid, and preferably hydrochloric acid.

The amino protecting group is selected from the group consisting of tetrahydropyranyl, *tert*-butoxycarbonyl, acetyl, benzyl, allyl and *p*-methoxybenzyl, and preferably tetrahydropyranyl.

The above reactions are preferably carried out in a solvent. The solvent used includes, but is not limited to, acetic acid, methanol, ethanol, toluene, tetrahydrofuran,

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dichloromethane, dimethyl sulfoxide, 1,4-dioxane, water, *N*,*N*-dimethylformamide and mixtures thereof.

DETAILED DESCRIPTION

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

EXAMPLES

The structures of the compounds were identified by nuclear magnetic resonance (NMR) and/or mass spectrometry (MS). NMR shifts (δ) were given in 10^{-6} (ppm). NMR was determined by a Bruker AVANCE-400 machine. The solvents for determination were deuterated-dimethyl sulfoxide (DMSO-d_6), deuterated-chloroform ($CDCl_3$) and deuterated-methanol (CD_3OD), and the internal standard is tetramethylsilane (TMS).

MS was determined by an Agilent 1200 /1290 DAD- 6110/6120 Quadrupole MS liquid chromatograph/mass spectrometer (manufacturer: Agilent, MS model: 6110/6120 Quadrupole MS), waters ACQuity UPLC-QD/SQD (manufacturer: waters, MS model: waters ACQuity Qda Detector/waters SQ Detector), THERMO Ultimate 3000-Q Exactive (manufacturer: THERMO, MS model: THERMO Q Exactive).

High Performance Liquid Chromatography (HPLC) was determined on an Agilent HPLC 1200DAD, Agilent HPLC 1200VWD and Waters HPLC e2695-2489 high pressure liquid chromatograph.

Chiral HPLC was determined on an Agilent 1260 DAD high performance liquid chromatograph.

High Performance Liquid Preparative Chromatography was carried out on Waters 2545-2767, Waters 2767-SQ Detecor2, Shimadzu LC-20AP and Gilson GX-281 preparative chromatographs.

Chiral preparative HPLC was carried out on a Shimadzu LC-20AP preparative chromatograph.

CombiFlash rapid preparation instrument used was Combiflash Rf200 (TELEDYNE ISCO).

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 silica gel column chromatography.

The average kinase inhibition rates and IC_{50} values were determined by a NovoStar microplate reader (BMG Co., Germany).

The known starting materials of the present disclosure can be prepared by the

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known methods in the art, or can be purchased from ABCR GmbH & Co. KG, Acros Organics, Aldrich Chemical Company, Accela ChemBio Inc., Dari Chemical Company etc.

Unless otherwise stated, the reactions were carried out under argon atmosphere or nitrogen atmosphere.

"Argon atmosphere" or "nitrogen atmosphere" means that a reaction flask is equipped with an argon or nitrogen balloon (about1 L).

"Hydrogen atmosphere" means that a reaction flask is equipped with a hydrogen balloon (about1 L).

Pressurized hydrogenation reaction was performed on a Parr 3916EKX hydrogenation instrument and a Qinglan QL-500 hydrogen generator or HC2-SS hydrogenation instrument.

In hydrogenation reactions, the reaction system was generally vacuumed and filled with hydrogen, and the above operation was repeated three times.

CEM Discover-S 908860 type microwave reactor was used in microwave reactions.

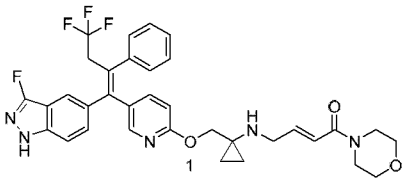
Unless otherwise stated, the solution refers to an aqueous solution.

Unless otherwise stated, the reaction temperature is room temperature from 20°C to 30°C.

The reaction process in the examples was monitored by thin layer chromatography (TLC). The developing solvent used in the reactions, the eluent system in column chromatography and the developing solvent system in thin layer chromatography for purification of the compounds included: A: dichloromethane/methanol system, B: *n*-hexane/ethyl acetate system, and C: petroleum ether/ethyl acetate system. The ratio of the volume of the solvent was adjusted according to the polarity of the compounds, and a small quantity of alkaline reagent such as triethylamine or acidic reagent such as acetic acid could also be added for adjustment.

Example 1

(*E*)-1-Morpholino-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenyl but-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-en-1-one **1**



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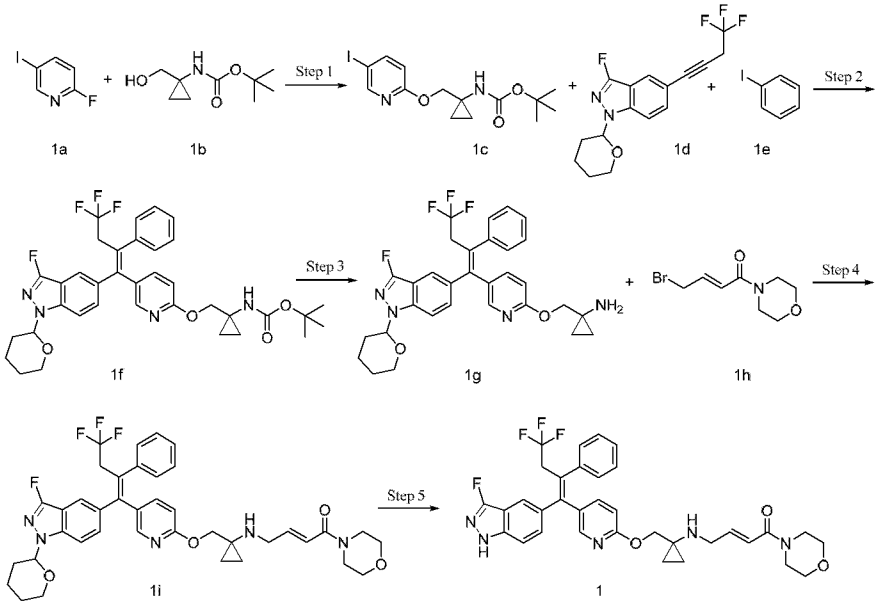

Step 1

Tert-butyl (1-(((5-iodopyridin-2-yl)oxy)methyl)cyclopropyl)carbamate **1c**

Sodium hydride (0.4 g, 10.7 mmol) was dissolved in *N*,*N*-dimethylformamide (20 mL), followed by the addition of *tert*-butyl (1-(hydroxymethyl)cyclopropyl)carbamate **1b** (1.0 g, 5.3 mmol, prepared according to the method disclosed in "*Journal of Organic Chemistry*, 2002, 67(11), 3965-3968") at room temperature. After completion of the addition, 2-fluoro-5-iodopyridine **1a** (1.8 g, 8.0 mmol) was added slowly. The reaction was stirred at room temperature for 2 hours. The reaction solution was concentrated under reduced pressure, and the resulting residues were purified by thin layer chromatography with developing system B to obtain the title product **1c** (2.4 g, yield: 86%).

MS m/z(ESI): 391.0 [M+1].

Step 2

Tert-butyl (*Z*)-(1-(((5-(4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)carbamate **1f**

3-Fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-5-(4,4,4-trifluorobut-1-yn-1-yl)-1*H*-indazole **1d** (1.8 g, 5.5 mmol, prepared according to the method disclosed in Example 3 on page 84 of the description of the patent application WO2018098305) was dissolved in methyltetrahydrofuran (40 mL), followed by the addition of bis(pinacolato)diboron (1.7 g, 6.6 mmol) and tetrakis(triphenylphosphine)platinum (137 mg, 0.1 mmol). The reaction solution was purged with argon three times, warmed up to 85°C and stirred for 3 hours. The reaction solution was cooled to room temperature, followed by the addition of compound **1c** (2.0 g, 5.2 mmol), bis(triphenylphosphine)palladium dichloride (741 mg, 1.1 mmol), cesium carbonate (3.6 g, 11.0 mmol) and water (1 mL). The reaction solution was stirred at room temperature overnight. Iodobenzene **1e** (1.2 g, 6.1 mmol) and potassium hydroxide (1.5 g, 27.6 mmol) were added. The reaction solution was

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purged with argon three times, warmed up to 85°C, stirred for 2 hours, and cooled to room temperature. The reaction solution was concentrated under reduced pressure, and the resulting residues were purified by thin layer chromatography with developing system B to obtain the title product **1f** (3.0 g, yield: 88%).

MS m/z(ESI): 667.2 [M+1].

Step 3

(*Z*)-1-(((5-(4,4,4-Trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropan-1-amine **1g**

Compound **1f** (1.8 g, 2.7 mmol) was dissolved in dichloromethane (15 mL), followed by the addition of trifluoroacetic acid (3 mL). The reaction was stirred at room temperature for 5 hours. The reaction solution was concentrated under reduced pressure, adjusted to about pH 8 with saturated sodium bicarbonate solution (100 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain the crude title product **1g** (1.4 g, yield: 89%), which was used directly in the next step without purification.

Step 4

(*E*)-1-Morpholino-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-en-1-one **1i**

Compound **1g** (1.7 g, 2.8 mmol) was dissolved in *N*,*N*-dimethylformamide (20 mL), followed by the addition of diisopropylethylamine (1.1 g, 8.5 mmol) at room temperature. (*E*)-4-Bromo-1-morpholinobut-2-en-1-one **1h** (0.7 g, 2.8 mmol, prepared according to the method disclosed in Example 15 on page 65 of the description of the patent application US2016347717) was added, and the reaction solution was stirred for 2 hours. The reaction was stopped, and the reaction solution was cooled. Saturated sodium bicarbonate solution (15 mL) was added, and the solution was extracted with ethyl acetate (50 mL×2). The organic phases were combined, washed with saturated sodium chloride solution (50 mL×4), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the resulting residues were purified by thin layer chromatography with developing system A to obtain the title product **1i** (1.3 g, yield: 65%).

MS m/z(ESI): 720.2 [M+1].

Step 5

(*E*)-1-Morpholino-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-en-1-one **1**

Compound **1i** (2.0 g, 2.8 mmol) was dissolved in methanol (5 mL), followed by the addition of hydrochloric acid (12*N*, 10 mL). The reaction solution was stirred for 3 hours. The reaction was stopped, and the reaction solution was cooled and concentrated. Saturated sodium bicarbonate solution (15 mL) was added, and the solution was extracted with dichloromethane (50 mL×4). The organic phases were combined, washed with water (30 mL×3) and saturated sodium chloride solution (50 mL) successively,

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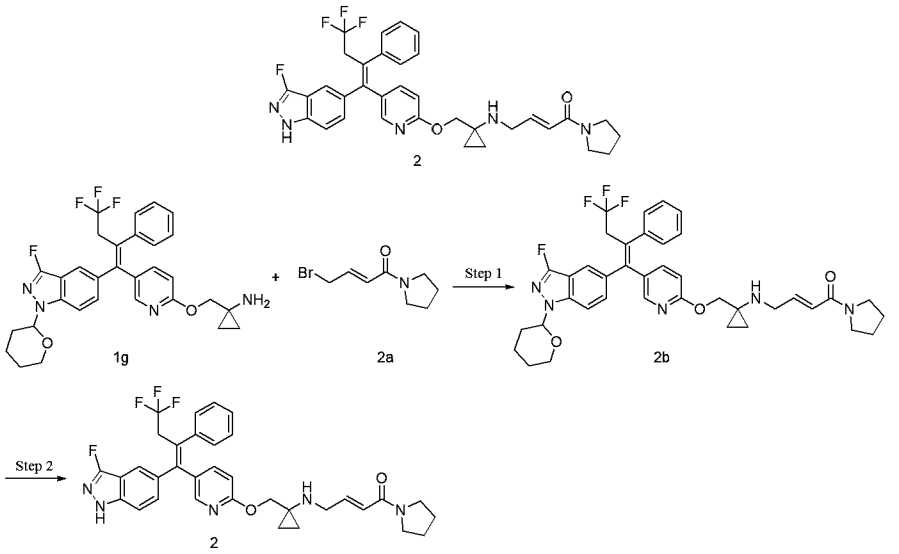
dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the resulting residues were purified by thin layer chromatography with developing system A to obtain the title product **1** (1.3 g, yield: 73%).

MS m/z(ESI): 636.2 [M+1].

^{1}H NMR (400 MHz, CD_3OD) 7.65 (d, 2H), 7.49 (d, 1H), 7.30-7.22 (m, 7H), 6.82-6.76 (m, 1H), 6.60-6.52 (m, 2H), 4.15 (s, 2H), 3.62-3.39 (m, 12H), 0.76-0.64 (m, 4H).

Example 2

(*E*)-1-(Pyrrolidin-1-yl)-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-en-1-one **2**



Step 1

(*E*)-1-(Pyrrolidin-1-yl)-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-en-1-one **2b**

In accordance with the synthetic route in Example 1, the starting material **1h** in Step 4 was replaced with (*E*)-4-bromo-1-(pyrrolidin-1-yl)but-2-en-1-one **2a** (prepared according to the method disclosed in Example 11 on page 58 of the description of the patent application US2016347717), to give the title compound **2b** (51 mg, yield: 69%).

MS m/z(ESI): 704.3 [M+1].

Step 2

(*E*)-1-(Pyrrolidin-1-yl)-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-en-1-one **2**

In accordance with the synthetic route in Example 1, the starting material **1i** in Step 5 was replaced with compound **2b**, to give the title compound **2** (20 mg, yield: 65%).

MS m/z(ESI): 620.3 [M+1].

^{1}H NMR (400 MHz, CD_3OD) 7.65 (d, 2H), 7.50 (d, 1H), 7.31-7.21 (m, 7H), 6.84-6.80 (m, 1H), 6.59 (d, 1H), 6.38 (d, 1H), 4.16 (s, 2H), 3.61-3.39 (m, 8H), 0.92-0.60

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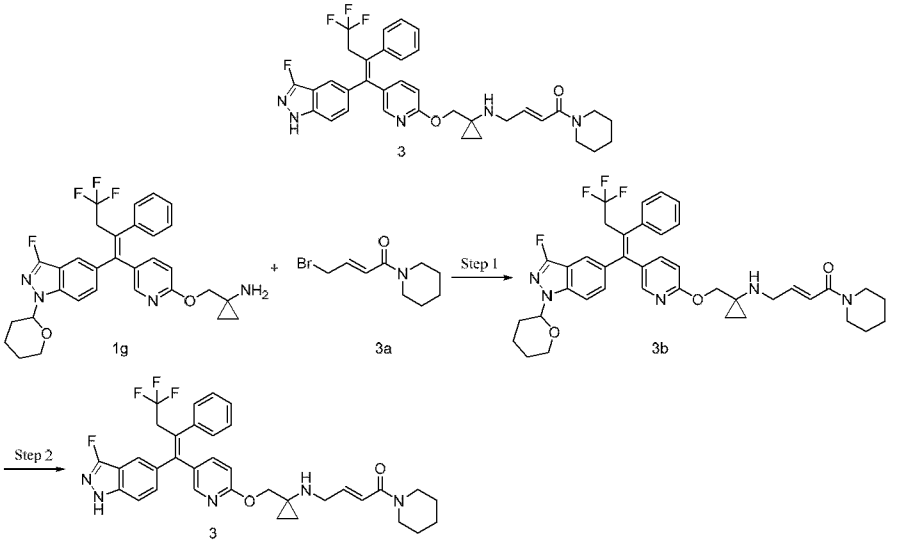
(m, 4H), 0.72-0.64 (m, 4H).

Example 3

(*E*)-1-(Piperidin-1-yl)-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-en-1-one **3**



Step 1

(*E*)-1-(Piperidin-1-yl)-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-en-1-one **3b**

In accordance with the synthetic route in Example 1, the starting material **1h** in Step 4 was replaced with (*E*)-4-bromo-1-(piperidin-1-yl)but-2-en-1-one **3a** (prepared according to the method disclosed in Example 12 on page 58 of the description of the patent application US2016347717), to give the title compound **3b** (40 mg, yield: 74%).

MS m/z(ESI): 718.4 [M+1].

Step 2

(*E*)-1-(Piperidin-1-yl)-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-en-1-one **3**

In accordance with the synthetic route in Example 1, the starting material **1i** in Step 5 was replaced with compound **3b**, to give the title compound **3** (15 mg, yield: 61%).

MS m/z(ESI): 634.3 [M+1].

^{1}H NMR (400 MHz, CD_3OD) 7.65 (d, 2H), 7.50 (d, 1H), 7.30-7.21 (m, 7H), 6.74-6.70 (m, 1H), 6.60-6.55 (m, 2H), 5.36-5.35 (m, 1H), 4.36 (s, 2H), 3.56-3.53 (m, 5H), 3.46-3.39 (m, 2H), 2.05 (s, 1H), 1.67-1.54 (m, 3H), 0.92-0.68 (m, 6H).

Example 4

(*E*)-1-(Piperazin-1-yl)-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-en-1-one **4**

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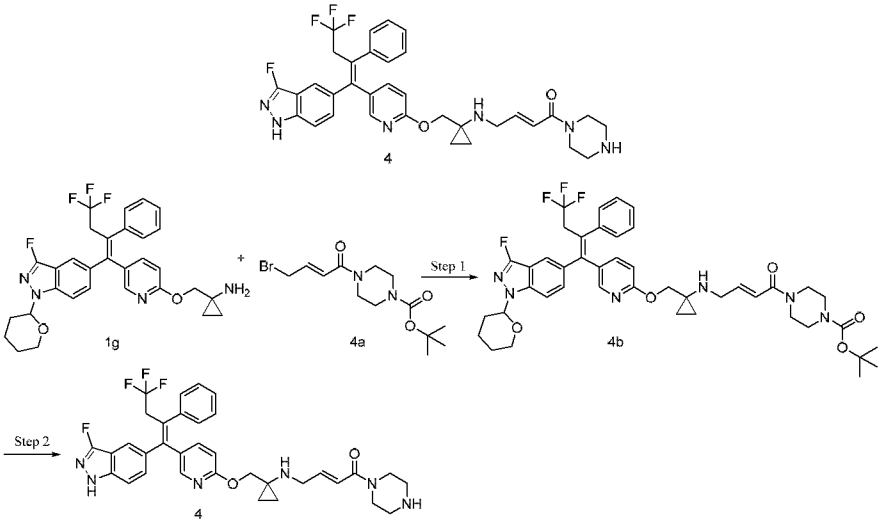


Step 1

Tert-butyl

4-((*E*)-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-enoyl)piperazine-1-carboxylate **4b**

In accordance with the synthetic route in Example 1, the starting material **1h** in Step 4 was replaced with *tert*-butyl (*E*)-4-(4-bromobut-2-enoyl)piperazine-1-carboxylate **4a** (prepared according to the method disclosed in Example 32 on page 129 of the description of the patent application WO2014160200), to give the title compound **4b** (61 mg, yield: 72%).

MS m/z(ESI): 819.4 [M+1].

Step 2

(*E*)-1-(Piperazin-1-yl)-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-en-1-one **4**

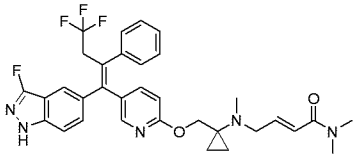
In accordance with the synthetic route in Example 1, the starting material **1i** in Step 5 was replaced with compound **4b**, to give the title compound **4** (20 mg, yield: 41%).

MS m/z(ESI): 635.3 [M+1].

^{1}H NMR (400 MHz, CD_3OD) 7.65 (d, 2H), 7.50 (d, 1H), 7.30-7.20 (m, 7H), 6.82-6.77 (m, 1H), 6.59-6.53 (m, 2H), 4.15 (s, 2H), 3.69-3.67 (m, 4H), 3.53-3.41 (m, 4H), 2.96-2.94 (m, 4H), 0.72-0.62 (m, 4H).

Example 5

(*E*)-*N*,*N*-Dimethyl-4-(methyl(1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-enamide **5**



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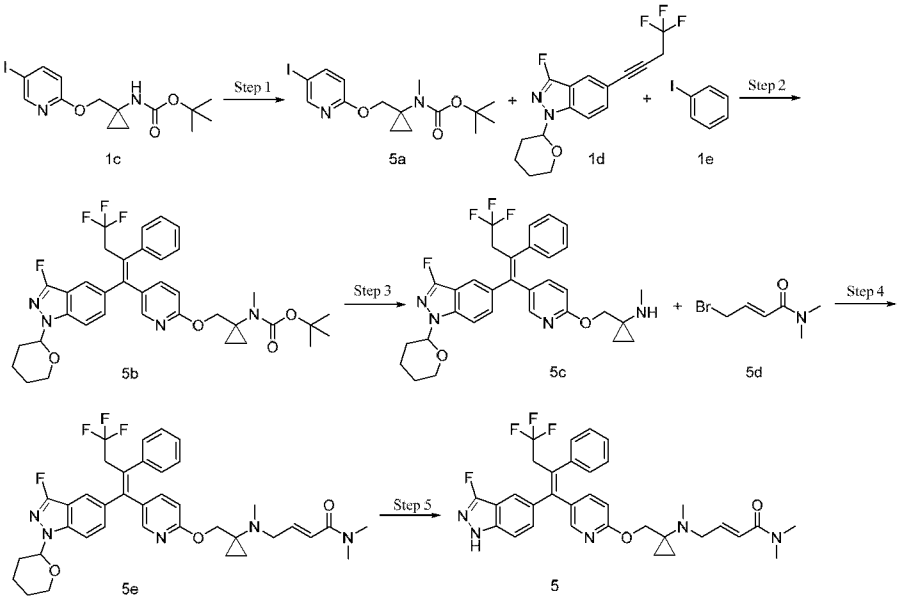

Step 1

Tert-butyl (1-(((5-iodopyridin-2-yl)oxy)methyl)cyclopropyl)(methyl)carbamate **5a**

Compound **1c** (0.5 g, 1.3 mmol) was dissolved in *N*,*N*-dimethylformamide (25 mL), followed by the addition of sodium hydride (0.1 g, 2.6 mmol) at room temperature. After completion of the addition, iodomethane (0.3 g, 1.9 mmol) was slowly added. The reaction was stirred at room temperature for 2 hours. The reaction solution was concentrated under reduced pressure, and the resulting residues were purified by thin layer chromatography with developing system B to obtain the title product **5a** (0.5 g, yield: 87%).

MS m/z(ESI): 405.1 [M+1].

Step 2

Tert-butyl (*Z*)-methyl(1-(((5-(4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)carbamate **5b**

In accordance with the synthetic route in Example 1, the starting material **1c** in Step 2 was replaced with compound **5a**, to give the title compound **5b** (89 mg, yield: 85%) was prepared.

MS m/z(ESI): 681.3 [M+1].

Step 3

(*Z*)-*N*-Methyl-1-(((5-(4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropan-1-amine **5c**

In accordance with the synthetic route in Example 1, the starting material **1f** in Step 3 was replaced with compound **5b**, to give the title compound **5c** (60 mg, yield: 70%) was prepared.

Step 4

(*E*)-*N*,*N*-Dimethyl-4-(methyl(1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)

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amino)but-2-enamide **5e**

In accordance with the synthetic route in Example 1, the starting material **1h** in Step 4 was replaced with (*E*)-4-bromo-*N*,*N*-dimethylbut-2-enamide **5d** (prepared according to the method disclosed in Example 1 on page 39 of the description of the patent application US2016347717), and the starting material **1g** was replaced with **5c**, to give the title compound **5e** (60 mg, yield: 50%).

Step 5

(*E*)-*N*,*N*-Dimethyl-4-(methyl(1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-enamide **5**

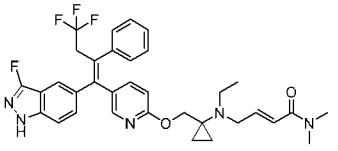
In accordance with the synthetic route in Example 1, the starting material **1i** in Step 5 was replaced with compound **5e**, to give the title compound **5** (15 mg, yield: 28%).

MS m/z(ESI): 608.2 [M+1].

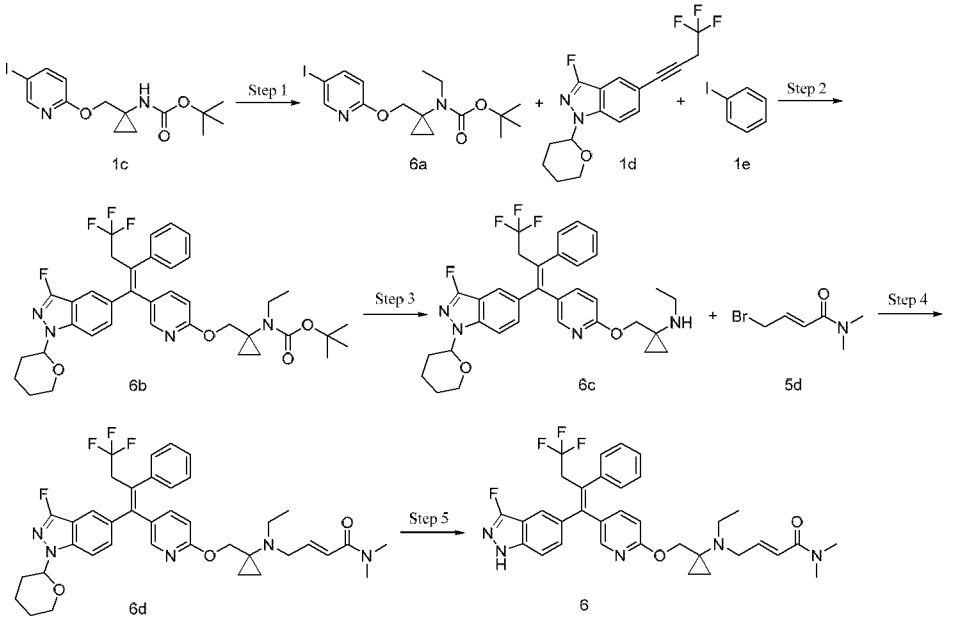
^{1}H NMR (400 MHz, $CDCl_3$) 9.59 (s, 1H), 7.65 (d, 2H), 7.33 (d, 1H), 7.28-7.23 (m, 6H), 7.10 (d, 1H), 6.79-6.75 (m, 1H), 6.46 (d, 1H), 6.35 (d, 1H), 4.22 (s, 2H), 3.48 (d, 2H), 3.38-3.35 (m, 2H), 3.05 (d, 6H), 2.38 (s, 3H), 0.73-0.63 (m, 4H).

Example 6

(*E*)-4-(Ethyl(1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)-*N*,*N*-dimethylbut-2-enamide **6**



6



Step 1

Tert-butyl ethyl(1-(((5-iodopyridin-2-yl)oxy)methyl)cyclopropyl)carbamate **6a**

In accordance with the synthetic route in Example 5, the reagent iodomethane in

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Step 1 was replaced with iodoethane, to give the title compound **6a** (58 mg, yield: 88%).

Step 2

Tert-butyl (*Z*)-ethyl(1-(((5-(4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)carbamate **6b**

In accordance with the synthetic route in Example 1, the starting material **1c** in Step 2 was replaced with compound **6a**, to give the title compound **6b** (85 mg, yield: 80%).

Step 3

(*Z*)-*N*-Ethyl-1-(((5-(4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropan-1-amine **6c**

In accordance with the synthetic route in Example 1, the starting material **1f** in Step 3 was replaced with compound **6b**, to give the title compound **6c** (65 mg, yield: 76%).

Step 4

(*E*)-4-(Ethyl(1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)-*N*,*N*-dimethylbut-2-enamide **6d**

In accordance with the synthetic route in Example 5, the starting material **5c** in Step 4 was replaced with compound **6c**, to give the title compound **6d** (70 mg, yield: 59%).

MS m/z(ESI): 706.3 [M+1].

Step 5

(*E*)-4-(Ethyl(1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)-*N*,*N*-dimethylbut-2-enamide **6**

In accordance with the synthetic route in Example 1, the starting material **1i** in Step 5 was replaced with compound **6d**, to give the title compound **6** (15 mg, yield: 28%).

MS m/z(ESI): 622.3 [M+1].

^{1}H NMR (400 MHz, $CDCl_3$) 9.74 (s, 1H), 7.66 (d, 2H), 7.31 (d, 1H), 7.28-7.25 (m, 6H), 7.21 (d, 1H), 6.86-6.82 (m, 1H), 6.46-6.36 (m, 2H), 4.19 (s, 2H), 3.53 (d, 2H), 3.35-3.30 (m, 2H), 3.06 (d, 6H), 2.73-2.70 (m, 2H), 1.05-1.02 (m, 3H), 0.73-0.61 (m, 4H).

Example 7

(*E*)-*N*,*N*-Dimethyl-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopentyl)amino)but-2-enamide **7**

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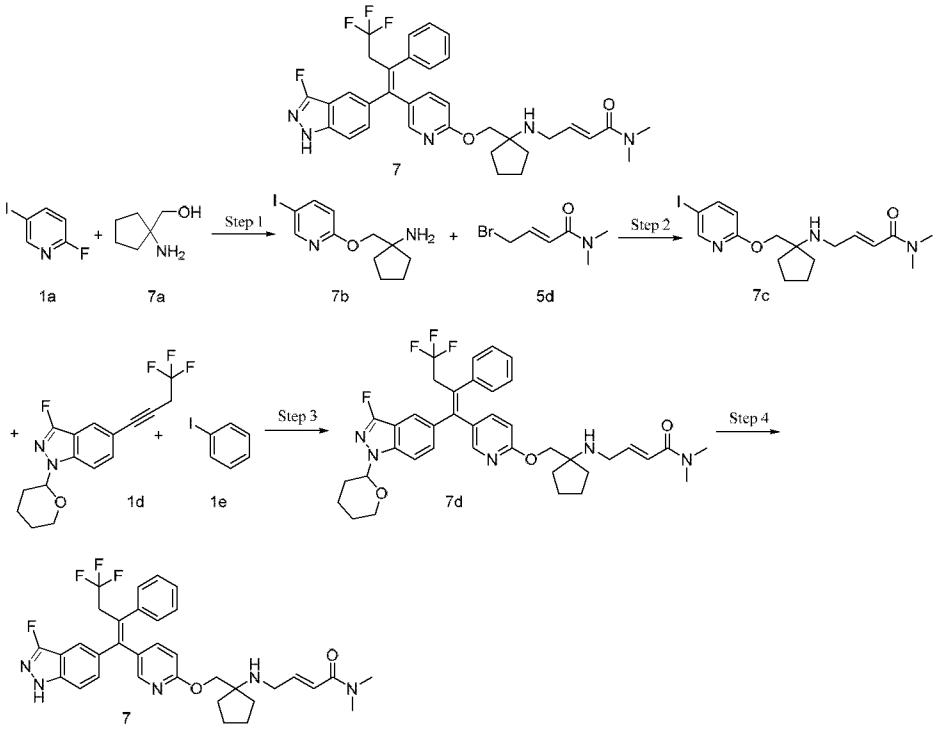

Step 1

1-(((5-Iodopyridin-2-yl)oxy)methyl)cyclopentan-1-amine **7b**

Potassium *tert*-butoxide (0.4 g, 3.5 mmol) was dissolved in tetrahydrofuran (10 mL), followed by the addition of (1-aminocyclopentyl)methanol **7a** (0.4 g, 3.5 mmol, prepared according to the method disclosed in "*Journal of the American Chemical Society*, 2004, 126(46), 15195-15201") at room temperature. After completion of the addition, compound **1a** (0.8 g, 3.5 mmol) was added slowly. The reaction was stirred at room temperature for 2 hours. The reaction solution was concentrated under reduced pressure, and the resulting residues were purified by thin layer chromatography with developing system B to obtain the title product **7b** (0.7 g, yield: 66%).

MS m/z(ESI): 319.1 [M+1].

Step 2

(*E*)-4-((1-(((5-Iodopyridin-2-yl)oxy)methyl)cyclopentyl)amino)-*N*,*N*-dimethylbut-2-enamide **7c**

Compound **7b** (100 mg, 0.3 mmol) was dissolved in *N*,*N*-dimethylformamide (10 mL), followed by the successive addition of diisopropylethylamine (41 mg, 0.3 mmol) and compound **5d** (60 g, 0.3 mmol) at room temperature. The reaction solution was stirred for 2 hours. The reaction was stopped, and the reaction solution was cooled. Saturated sodium bicarbonate solution (15 mL) was added, and the solution was extracted with ethyl acetate (50 mL×2). The organic phases were combined, washed with saturated sodium chloride solution (50 mL×4), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the resulting residues were purified by thin layer chromatography with developing system A to obtain the title product **7c** (86 mg, yield: 67%).

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Step 3

(*E*)-*N*,*N*-Dimethyl-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopentyl)amino)but-2-enamide **7d**

Compound **1d** (50 mg, 0.2 mmol) was dissolved in methyltetrahydrofuran (20 mL), followed by the addition of bis(pinacolato)diboron (47 mg, 0.2 mmol) and tetrakis(triphenylphosphine)platinum (10 mg, 0.01 mmol). The reaction solution was purged with argon three times, warmed up to 85°C and stirred for 3 hours. The reaction solution was cooled to room temperature, followed by the addition of compound **7c** (66 mg, 0.2 mmol), bis(triphenylphosphine)palladium dichloride (11 mg, 0.02 mmol), cesium carbonate (150 mg, 0.5 mmol) and water (0.2 mL). The reaction solution was stirred at room temperature overnight. Compound **1e** (63 mg, 0.3 mmol) and potassium hydroxide (26 mg, 0.5 mmol) were added. The reaction solution was purged with argon three times, warmed up to 85°C, stirred for 2 hours, and cooled to room temperature. The reaction solution was concentrated under reduced pressure, and the resulting residues were purified by thin layer chromatography with developing system B to obtain the title product **7d** (84 mg, yield: 78%).

Step 4

(*E*)-*N*,*N*-Dimethyl-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopentyl)amino)but-2-enamide **7**

Compound **7d** (30 mg, 0.04 mmol) was dissolved in methanol (1 mL), followed by the addition of hydrochloric acid (12*N*, 2 mL). The reaction solution was stirred for 3 hours. The reaction was stopped, and the reaction solution was cooled and concentrated. Saturated sodium bicarbonate solution (15 mL) was added, and the solution was extracted with dichloromethane (10 mL×4). The organic phases were combined, washed with water (10 mL×3) and saturated sodium chloride solution (10 mL) successively, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the resulting residues were purified by thin layer chromatography with developing system A to obtain the title product **7** (10 mg, yield: 41%).

MS m/z(ESI): 622.3 [M+1].

^{1}H NMR (400 MHz, $CDCl_3$) 7.61-7.45 (m, 3H), 7.29-7.01 (m, 7H), 6.54-6.42 (m, 3H), 3.95 (s, 2H), 3.42-3.39 (m, 1H), 3.17-3.14 (m, 1H), 2.91 (s, 1H), 2.77 (s, 1H), 2.62 (s, 3H), 2.26 (s, 3H), 1.63-1.52 (m, 4H), 1.49-1.38 (m, 4H).

Example 8

(*E*)-*N*,*N*-Dimethyl-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclohexyl)amino)but-2-enamide **8**

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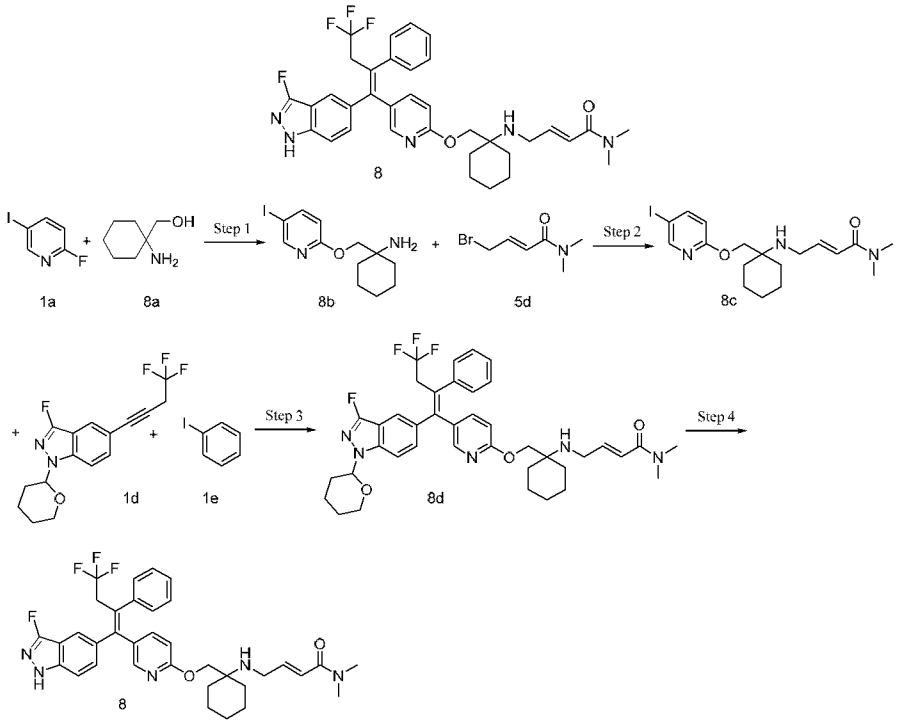

Step 1

1-(((5-Iodopyridin-2-yl)oxy)methyl)cyclohexan-1-amine **8b**

In accordance with the synthetic route in Example 7, the starting material **7a** in Step 1 was replaced with (1-aminocyclohexyl)methanol **8a** (prepared according to the method disclosed in "*Journal of Medicinal Chemistry*, 2004, 47(18), 4613-4626"), to give the title compound **8b** (650 mg, yield: 68%).

MS m/z(ESI): 333.1 [M+1].

Step 2

(*E*)-4-((1-(((5-Iodopyridin-2-yl)oxy)methyl)cyclohexyl)amino)-*N*,*N*-dimethylbut-2-enamide **8c**

In accordance with the synthetic route in Example 7, the starting material **7b** in Step 2 was replaced with compound **8b**, to give the title compound **8c** (500 mg, yield: 58%).

MS m/z(ESI): 444.2 [M+1].

Step 3

(*E*)-*N*,*N*-Dimethyl-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclohexyl)amino)but-2-enamide **8d**

In accordance with the synthetic route in Example 7, the starting material **7c** in Step 3 was replaced with compound **8c**, to give the title compound **8d** (250 mg, yield: 94%).

MS m/z(ESI): 720.4 [M+1].

Step 4

(*E*)-*N*,*N*-Dimethyl-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenyl

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but-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclohexyl)amino)but-2-enamide **8**

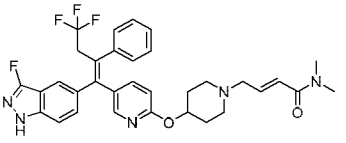
In accordance with the synthetic route in Example 7, the starting material **7d** in Step 4 was replaced with compound **8d**, to give the title compound **8** (80 mg, yield: 36%).

MS m/z(ESI): 636.2 [M+1].

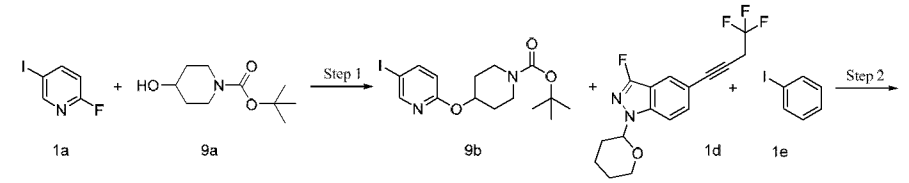
^{1}H NMR (400 MHz, CD_3OD) 7.72 (d, 1H), 7.65 (s, 1H), 7.49 (dd, 1H), 7.33 (dd, 2H), 7.31-7.24 (m, 5H), 6.80 (d, 1H), 6.68-6.65 (m, 2H), 4.53 (s, 2H), 3.85 (d, 2H), 3.46-3.38 (m, 2H), 3.08 (s, 3H), 2.98 (s, 3H), 2.06 (d, 2H), 1.75-1.64 (m, 3H), 1.64-1.47 (m, 4H), 1.31 (m, 1H).

Example 9

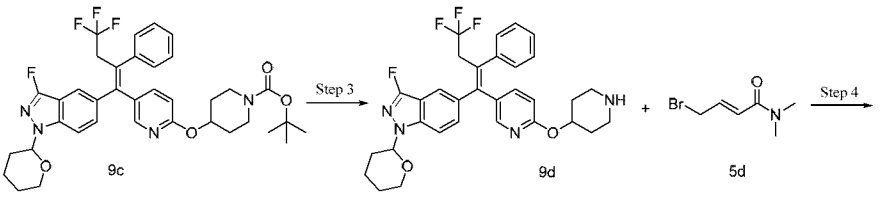
(*E*)-*N*,*N*-Dimethyl-4-(4-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **9**



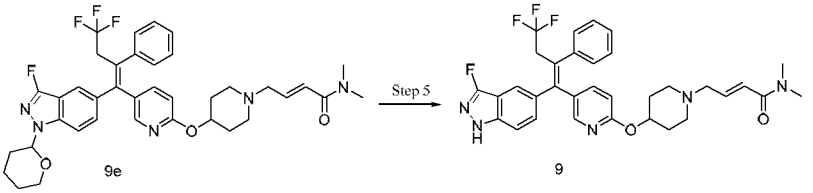
9



1a 9a 9b 1d 1e



9c 9d 5d



9e 9

Step 1

Tert-butyl 4-((5-iodopyridin-2-yl)oxy)piperidine-1-carboxylate **9b**

Sodium hydride (0.6 g, 14.9 mmol) was dissolved in *N*,*N*-dimethylformamide (30 mL), followed by the addition of *tert*-butyl 4-hydroxypiperidine-1-carboxylate **9a** (1.0 g, 5.0 mmol, prepared according to the method disclosed in "*Journal of the American Chemical Society*, 2018, 140(1), 155-158") at room temperature. After completion of the addition, compound **1a** (2.2 g, 9.9 mmol) was added slowly. The reaction was stirred at room temperature for 2 hours. The reaction solution was concentrated under reduced pressure, and the resulting residues were purified by thin layer chromatography with developing system B to obtain the title product **9b** (0.6 g, yield: 30%).

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Step 2

Tert-butyl (*Z*)-4-((5-(4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidine-1-carboxylate **9c**

Compound **1d** (150 mg, 0.5 mmol) was dissolved in methyltetrahydrofuran (15 mL), followed by the addition of bis(pinacolato)diboron (140 mg, 0.6 mmol) and tetrakis(triphenylphosphine)platinum (28 mg, 0.02 mmol). The reaction solution was purged with argon three times, warmed up to 85°C and stirred for 3 hours. The reaction solution was cooled to room temperature, followed by the addition of compound **9b** (167 mg, 0.4 mmol), bis(triphenylphosphine)palladium dichloride (31 mg, 0.05 mmol), cesium carbonate (300 mg, 0.9 mmol) and water (1 mL). The reaction solution was stirred at room temperature overnight. Compound **1e** (187 mg, 0.9 mmol) and potassium hydroxide (129 mg, 2.3 mmol) were added. The reaction solution was purged with argon three times, warmed up to 85°C, stirred for 2 hours, and cooled to room temperature. The reaction solution was concentrated under reduced pressure, and the resulting residues were purified by thin layer chromatography with developing system B to obtain the title product **9c** (210 mg, yield: 67%).

MS m/z(ESI): 681.3 [M+1].

Step 3

(*Z*)-3-Fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-5-(4,4,4-trifluoro-2-phenyl-1-(6-(piperidin-4-yloxy)pyridin-3-yl)but-1-en-1-yl)-1*H*-indazole **9d**

Compound **9c** (120 mg, 0.2 mmol) was dissolved in dichloromethane (5 mL), followed by the addition of trifluoroacetic acid (1 mL). The reaction was stirred at room temperature for 5 hours. The reaction solution was concentrated under reduced pressure, adjusted to about pH 8 with saturated sodium bicarbonate solution (10 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain the crude title product **9d** (100 mg, yield: 98%), which was used directly in the next step without purification.

Step 4

(*E*)-*N*,*N*-Dimethyl-4-(4-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **9e**

Compound **9d** (100 mg, 0.2 mmol) was dissolved in *N*,*N*-dimethylformamide (5 mL), followed by the successive addition of diisopropylethylamine (67 mg, 0.5 mmol) and compound **5d** (31 mg, 0.2 mmol) at room temperature. The reaction solution was stirred for 2 hours. The reaction was stopped, and the reaction solution was cooled. Saturated sodium bicarbonate solution (15 mL) was added, and the solution was extracted with ethyl acetate (20 mL×2). The organic phases were combined, washed with saturated sodium chloride solution (20 mL×4), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the resulting residues were purified by thin layer chromatography with developing system A

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to obtain the title product **9e** (85 mg, yield: 71%).

Step 5

(*E*)-*N*,*N*-Dimethyl-4-(4-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **9**

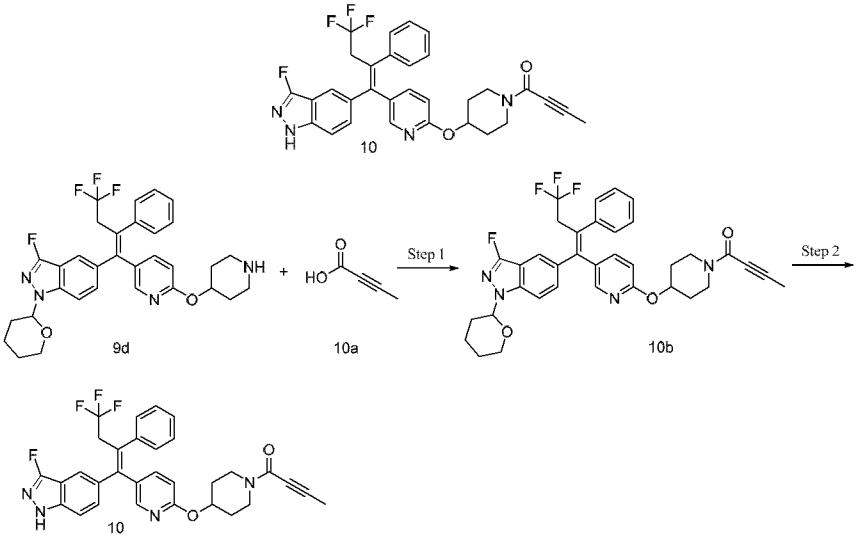
Compound **9e** (80 mg, 0.1 mmol) was dissolved in methanol (5 mL), followed by the addition of hydrochloric acid (12*N*, 3 mL). The reaction solution was stirred for 3 hours. The reaction was stopped, and the reaction solution was cooled and concentrated. Saturated sodium bicarbonate solution (15 mL) was added, and the solution was extracted with dichloromethane (10 mL×4). The organic phases were combined, washed with water (10 mL×3) and saturated sodium chloride solution (10 mL) successively, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the resulting residues were purified by thin layer chromatography with developing system A to obtain the title product **9** (25 mg, yield: 36%).

MS m/z(ESI): 608.4 [M+1].

^{1}H NMR (400 MHz, $CDCl_3$) 9.91 (br, 1H), 7.68 (d, 2H), 7.45 (d, 1H), 7.33 (s, 1H), 7.24-7.15 (m, 5H), 6.82 (s, 2H), 6.47 (d, 1H), 5.31 (s, 1H), 3.86 (s, 2H), 3.49 (s, 2H), 3.80-3.31 (m, 2H), 3.15-3.12 (s, 3H), 3.11 (s, 3H), 3.05 (s, 3H), 2.26-2.18 (m, 4H).

Example 10

(*Z*)-1-(4-((5-(4,4,4-Trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-yn-1-one **10**



Step 1

(*Z*)-1-(4-((5-(4,4,4-Trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-yn-1-one **10b**

Compound **9d** (60 mg, 0.1 mmol) was dissolved in *N*,*N*-dimethylformamide (3 mL), followed by the addition of triethylamine (52 mg, 0.5 mmol), but-2-ynoic acid **10a** (17 mg, 0.2 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (30 mg, 0.2 mmol) and 1-hydroxybenzotriazole (24 mg, 0.2 mmol) at room temperature.

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The reaction solution was stirred for 12 hours. The reaction solution was cooled. Saturated sodium bicarbonate solution (15 mL) was added, and the solution was extracted with ethyl acetate (20 mL×2). The organic phases were combined, washed with saturated sodium chloride solution (20 mL×4), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the resulting residues were purified by thin layer chromatography with developing system A to obtain the title product **10b** (45 mg, yield: 67%).

Step 2

(*Z*)-1-(4-((5-(4,4,4-Trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-yn-1-one **10**

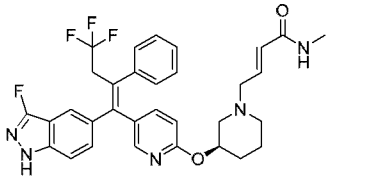
Compound **10b** (45 mg, 0.07 mmol) was dissolved in methanol (5 mL), followed by the addition of hydrochloric acid (12*N*, 3 mL). The reaction solution was stirred for 3 hours. The reaction solution was cooled and concentrated. Saturated sodium bicarbonate solution (15 mL) was added, and the solution was extracted with dichloromethane (10 mL×4). The organic phases were combined, washed with water (10 mL×3) and saturated sodium chloride solution (10 mL) successively, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the resulting residues were purified by thin layer chromatography with developing system A to obtain the title product **10** (15 mg, yield: 38%).

MS m/z(ESI): 563.3 [M+1].

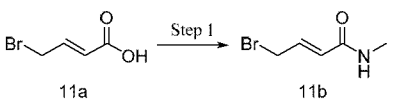
^{1}H NMR (400 MHz, $CDCl_3$) 9.67 (br, 1H), 7.65 (d, 2H), 7.45 (d, 1H), 7.34 (m, 1H), 7.21-7.17 (m, 4H), 6.50 (d, 1H), 5.11 (s, 1H), 3.94-3.92 (m, 1H), 3.80-3.71 (m, 4H), 3.37-3.29 (m, 2H), 2.02 (s, 3H), 1.94-1.75 (m, 4H).

Example 11

(*E*)-*N*-Methyl-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **11**



11



11a 11b

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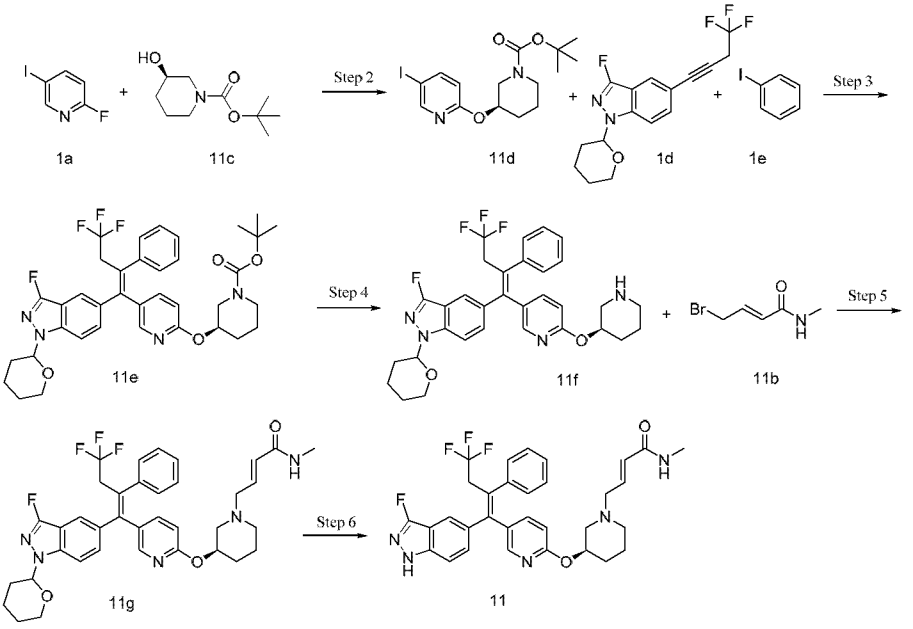

Step 1

(*E*)-4-Bromo-*N*-methylbut-2-enamide **11b**

(*E*)-4-Bromobut-2-enoic acid **11a** (0.5 g, 3.0 mmol) was dissolved in dichloromethane (5 mL), followed by the addition of triethylamine (0.3 g, 3.3 mmol), methylamine (0.1 g, 3.3 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.6 g, 3.3 mmol) and 1-hydroxybenzotriazole (0.4 g, 3.3 mmol) at room temperature. The reaction solution was stirred for 12 hours. The reaction solution was cooled. Saturated sodium bicarbonate solution (15 mL) was added, and the solution was extracted with ethyl acetate (20 mL×2). The organic phases were combined, washed with saturated sodium chloride solution (20 mL×4), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the resulting residues were purified by thin layer chromatography with developing system A to obtain the title product **11b** (0.4 g, yield: 77%).

Step 2

Tert-butyl (*R*)-3-((5-iodopyridin-2-yl)oxy)piperidine-1-carboxylate **11d**

In accordance with the synthetic route in Example 1, the starting material **1b** in Step 1 was replaced with *tert*-butyl (*R*)-3-hydroxypiperidine-1-carboxylate **11c** (prepared according to the method disclosed in "*Tetrahedron*, 2011, 67(7), 1485-1500"), to give the title compound **11d** (653 mg, yield: 91%).

Step 3

Tert-butyl

(3*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidine-1-carboxylate **11e**

In accordance with the synthetic route in Example 1, the starting material **1c** in Step 2 was replaced with compound **11d**, to give the title compound **11e** (200 mg, yield: 64%).

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MS m/z(ESI): 680.9 [M+1].

Step 4

3-Fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-5-((*Z*)-4,4,4-trifluoro-2-phenyl-1-(6-(((*R*)-piperidin-3-yl)oxy)pyridin-3-yl)but-1-en-1-yl)-1*H*-indazole **11f**

In accordance with the synthetic route in Example 1, the starting material **1f** in Step 3 was replaced with compound **11e**, to give the title compound **11f** (170 mg, yield: 100%).

Step 5

(*E*)-*N*-Methyl-4-((3*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **11g**

In accordance with the synthetic route in Example 1, the starting material **1g** in Step 4 was replaced with compound **11f**, and the starting material **1h** was replaced with **11b**, to give the title compound **11g** (50 mg, yield: 86%).

Step 6

(*E*)-*N*-Methyl-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **11**

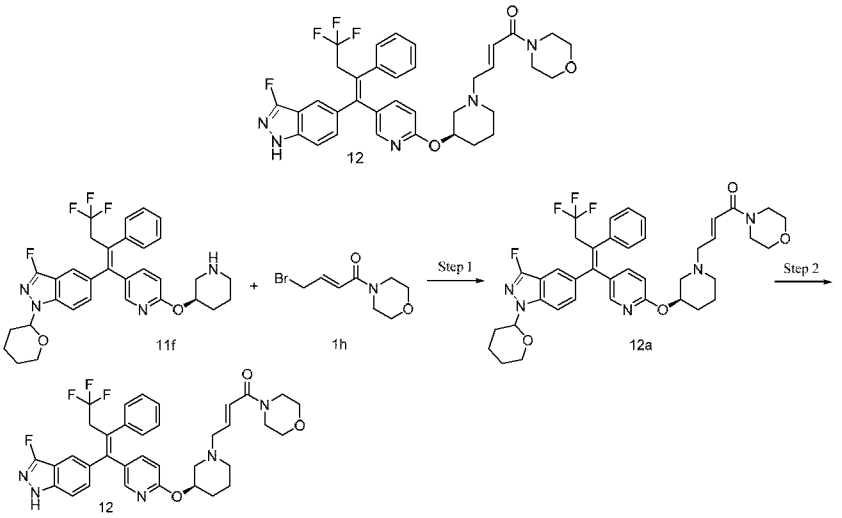
In accordance with the synthetic route in Example 1, the starting material **1i** in Step 5 was replaced with compound **11g**, to give the title compound **11** (20 mg, yield: 45%).

MS m/z(ESI): 594.2 [M+1].

^{1}H NMR (400 MHz, CD_3OD) 7.65 (d, 2H), 7.49 (d, 1H), 7.31-7.19 (m, 6H), 6.68-6.62 (m, 2H), 6.30 (d, 1H), 5.39 (s, 1H), 3.88 (s, 2H), 3.67 (s, 1H), 3.48-3.38 (m, 3H), 3.26-3.13 (m, 2H), 3.01 (s, 1H), 2.80 (s, 3H), 2.06 (s, 2H), 1.86-1.73 (m, 2H).

Example 12

(*E*)-1-Morpholino-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-en-1-one **12**



Step 1

(*E*)-1-Morpholino-4-((3*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran

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-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-en-1-one **12a**

In accordance with the synthetic route in Example 1, the starting material **1g** in Step 4 was replaced with compound **11f**, to give the title compound **12a** (50 mg, yield: 79%).

Step 2

(*E*)-1-Morpholino-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-en-1-one **12**

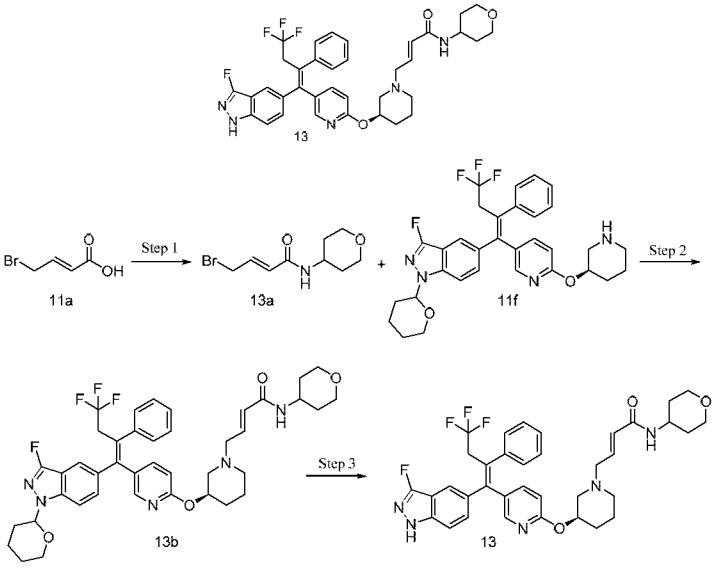
In accordance with the synthetic route in Example 1, the starting material **1i** in Step 5 was replaced with compound **12a**, to give the title compound **12** (20 mg, yield: 42%).

MS m/z(ESI): 650.3 [M+1].

^{1}H NMR (400 MHz, $CDCl_3$) 10.10 (s, 1H), 7.67-7.62 (m, 3H), 7.50 (d, 1H), 7.27-7.11 (m, 6H), 6.79 (s, 2H), 6.48 (s, 1H), 5.38 (s, 1H), 3.93 (s, 2H), 3.70 (s, 7H), 3.55 (s, 2H), 3.38-3.31 (m, 3H), 3.09-2.82 (m, 2H), 1.85-1.65 (m, 4H).

Example 13

(*E*)-*N*-(Tetrahydro-2*H*-pyran-4-yl)-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **13**



Step 1

(*E*)-4-Bromo-*N*-(tetrahydro-2*H*-pyran-4-yl)but-2-enamide **13a**

(*E*)-4-Bromobut-2-enoic acid **11a** (1.0 g, 6.1 mmol) was dissolved in dichloromethane (10 mL), followed by the addition of triethylamine (1.8 g, 18.2 mmol), tetrahydropyran-4-amine (0.6 g, 6.1 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.3 g, 6.7 mmol) and 1-hydroxybenzotriazole (0.9 g, 6.7 mmol) at room temperature. The reaction solution was stirred for 12 hours. The reaction solution was cooled. Saturated sodium bicarbonate solution (15 mL) was added, and the solution was extracted with ethyl acetate (20 mL×2). The organic phases were combined, washed with saturated sodium

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chloride solution (20 mL×4), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the resulting residues were purified by thin layer chromatography with developing system A to obtain the title product **13a** (1.2 g, yield: 79%).

Step 2

(*E*)-*N*-(Tetrahydro-2*H*-pyran-4-yl)-4-((3*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **13b**

In accordance with the synthetic route in Example 1, the starting material **1g** in Step 4 was replaced with compound **11f**, and the starting material **1h** was replaced with **13a**, to give the title compound **13b** (41 mg, yield: 81%).

Step 3

(*E*)-*N*-(Tetrahydro-2*H*-pyran-4-yl)-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **13**

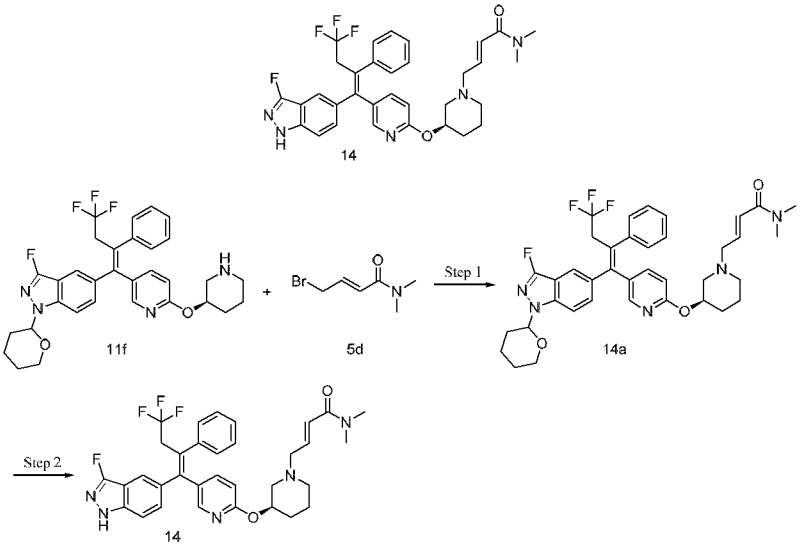
In accordance with the synthetic route in Example 1, the starting material **1i** in Step 5 was replaced with compound **13b**, to give the title compound **13** (20 mg, yield: 32%).

MS m/z(ESI): 664.3 [M+1].

^{1}H NMR (400 MHz, DMSO-d_6) 12.68 (s, 1H), 7.92-7.90 (d, 1H), 7.60-7.59 (m, 1H), 7.52-7.50 (m, 1H), 7.23-7.14 (m, 6H), 6.50-6.43 (m, 2H), 5.97-5.93 (d, 1H), 4.86-4.79 (m, 1H), 3.79-3.74 (m, 3H), 3.47-3.38 (m, 2H), 3.33-3.32 (m, 1H), 3.00-2.98 (m, 2H), 2.80-2.78 (m, 1H) , 2.55-2.50 (m, 1H) , 2.00-1.24 (m, 12H).

Example 14

(*E*)-*N*,*N*-Dimethyl-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **14**



Step 1

(*E*)-*N*,*N*-Dimethyl-4-((3*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-en

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amide **14a**

In accordance with the synthetic route in Example 1, the starting material **1g** in Step 4 was replaced with compound **11f**, and the starting material **1h** was replaced with **5d**, to give the title compound **14a** (80 mg, yield: 79%).

Step 2

(*E*)-*N*,*N*-Dimethyl-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **14**

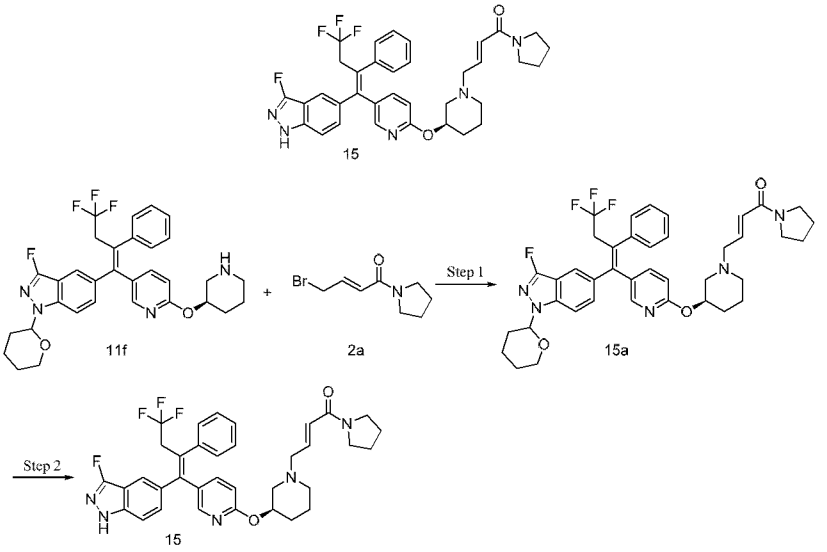
In accordance with the synthetic route in Example 1, the starting material **1i** in Step 5 was replaced with compound **14a**, to give the title compound **14** (10 mg, yield: 27%).

MS m/z(ESI): 608.3 [M+1].

^{1}H NMR (400 MHz, $CDCl_3$) 9.77-7.75 (br, 1H), 7.68-7.62 (m, 2H), 7.46-7.43 (m, 1H), 7.36-7.30 (m, 2H), 7.27-7.18 (d, 5H), 6.87-6.76 (m, 2H), 6.80-6.48 (m, 1H), 5.42-5.28 (m, 1H), 3.97-3.67 (m, 5H), 3.38-3.31 (m, 2H), 3.12-3.07 (m, 6H), 2.31-1.69 (m, 4H).

Example 15

(*E*)-1-(Pyrrolidin-1-yl)-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-en-1-one **15**



Step 1

(*E*)-1-(Pyrrolidin-1-yl)-4-((3*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-en-1-one **15a**

In accordance with the synthetic route in Example 1, the starting material **1g** in Step 4 was replaced with compound **11f**, and the starting material **1h** was replaced with **2a**, to give the title compound **15a** (49 mg, yield: 72%).

Step 2

(*E*)-1-(Pyrrolidin-1-yl)-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-en-1-one **15**

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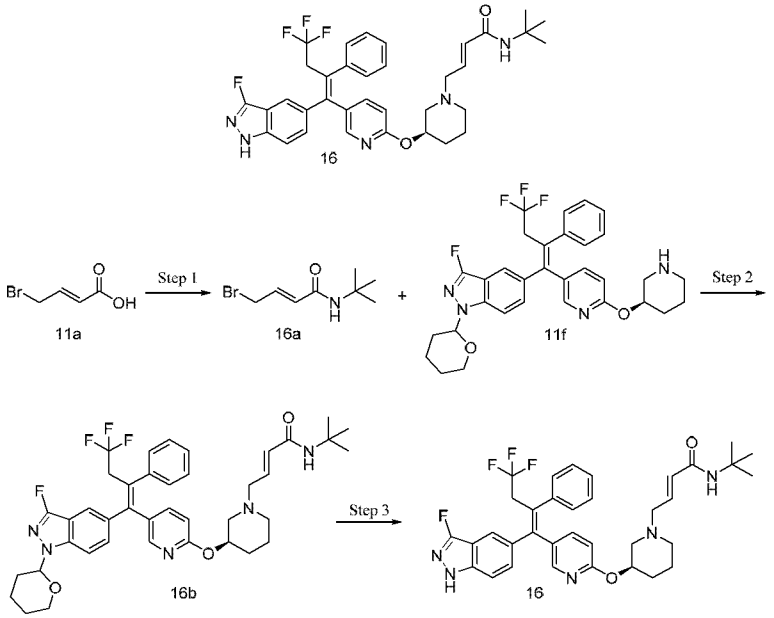
In accordance with the synthetic route in Example 1, the starting material **1i** in Step 5 was replaced with compound **15a**, to give the title compound **15** (20 mg, yield: 47%).

MS m/z(ESI): 634.3 [M+1].

^{1}H NMR (400 MHz, CD_3OD) 7.63 (d, 2H), 7.49 (dd, 1H), 7.29-7.19 (m, 7H), 6.79-6.74 (m, 1H), 6.49-6.43 (m, 2H), 5.02-4.98 (m, 1H), 3.56-3.54 (m, 2H), 3.47-3.44 (m, 4H), 3.25 (d, 2H), 2.92 (d, 1H), 2.65-2.64 (m, 1H), 2.37-2.35 (m, 2H), 1.94-1.85 (m, 6H), 1.64-1.52 (m, 2H).

Example 16

(*E*)-*N*-(*Tert*-butyl)-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **16**



Step 1

(*E*)-4-Bromo-*N*-(*tert*-butyl)but-2-enamide **16a**

Compound **11a** (0.5 g, 3.0 mmol) was dissolved in dichloromethane (10 mL), followed by the addition of triethylamine (0.4 g, 3.6 mmol), *tert*-butylamine (0.2 g, 3.0 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.7 g, 3.6 mmol) and 1-hydroxybenzotriazole (0.5 g, 3.6 mmol) at room temperature. The reaction solution was stirred for 12 hours. The reaction solution was cooled. Saturated sodium bicarbonate solution (15 mL) was added, and the solution was extracted with ethyl acetate (20 mL×2). The organic phases were combined, washed with saturated sodium chloride solution (20 mL×4), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the resulting residues were purified by thin layer chromatography with developing system A to obtain the title product **16a** (0.3 g, yield: 39%).

Step 2

(*E*)-*N*-(*Tert*-butyl)-4-((3*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran

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-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-en amide **16b**

In accordance with the synthetic route in Example 1, the starting material **1g** in Step 4 was replaced with compound **11f**, and the starting material **1h** was replaced with **16a**, to give the title compound **16b** (47 mg, yield: 83%).

Step 3

(*E*)-*N*-(*Tert*-butyl)-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **16**

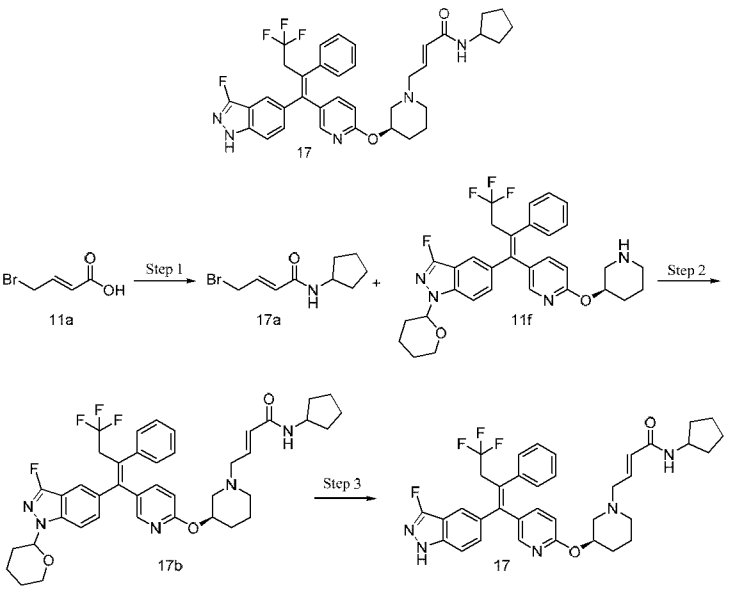
In accordance with the synthetic route in Example 1, the starting material **1i** in Step 5 was replaced with compound **16b**, to give the title compound **16** (23 mg, yield: 28%).

MS m/z(ESI): 636.5 [M+1].

^{1}H NMR (400 MHz, CD_3OD) 7.67 (d, 2H), 7.50 (dd, 1H), 7.32-7.22 (m, 7H), 6.64-6.55 (m, 2H), 6.33 (d, 1H), 5.40 (s, 1H), 3.88 (s, 2H), 3.69 (d, 1H), 3.52-3.41 (m, 3H), 3.24 (d, 1H), 3.02-2.99 (m, 1H), 2.10-2.07 (m, 2H), 1.87-1.75 (m, 2H), 1.36 (s, 9H).

Example 17

(*E*)-*N*-Cyclopentyl-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **17**



Step 1

(*E*)-4-Bromo-*N*-cyclopentylbut-2-enamide **17a**

Compound **11a** (0.5 g, 3.0 mmol) was dissolved in dichloromethane (10 mL), followed by the addition of triethylamine (0.4 g, 3.6 mmol), cyclopentylamine (0.3 g, 3.0 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.7 g, 3.6 mmol) and 1-hydroxybenzotriazole (0.5 g, 3.6 mmol) at room temperature. The reaction solution was stirred for 12 hours. The reaction solution was cooled. Saturated sodium bicarbonate solution (15 mL) was added, and the solution was extracted with ethyl

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acetate (20 mL×2). The organic phases were combined, washed with saturated sodium chloride solution (20 mL×4), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the resulting residues were purified by thin layer chromatography with developing system A to obtain the title product **17a** (0.3 g, yield: 49%).

Step 2

(*E*)-*N*-Cyclopentyl-4-((3*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **17b**

In accordance with the synthetic route in Example 1, the starting material **1g** in Step 4 was replaced with compound **11f**, and the starting material **1h** was replaced with **17a**, to give the title compound **17b** (42 mg, yield: 73%).

Step 3

(*E*)-*N*-Cyclopentyl-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **17**

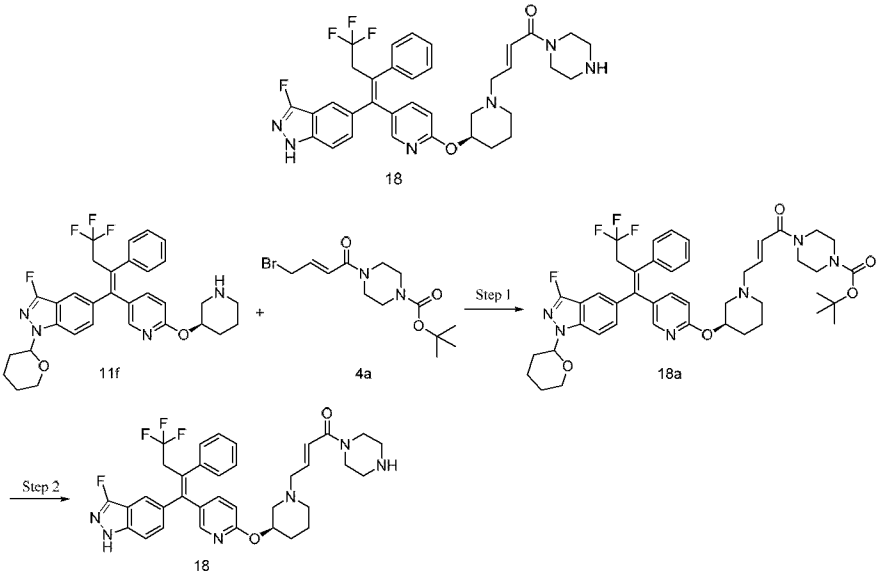
In accordance with the synthetic route in Example 1, the starting material **1i** in Step 5 was replaced with compound **17b**, to give the title compound **17** (21 mg, yield: 38%).

MS m/z(ESI): 648.3 [M+1].

^{1}H NMR (400 MHz, DMSO-d_6) 12.75-12.68 (m, 1H) 7.88-7.86 (d, 1H), 7.61-7.59 (m, 2H), 7.53-7.50 (m, 1H), 7.23-7.15 (m, 6H), 6.47-6.41 (m, 2H), 5.96-5.93 (d, 1H), 4.85-4.79 (m, 1H), 4.02-3.97 (m, 1H), 3.47-3.39 (m, 2H), 2.99-2.98 (m, 2H), 2.80-2.79 (m, 1H), 2.56-2.50 (m, 2H), 2.30-2.25 (m, 1H), 1.99-1.27 (m, 12H).

Example 18

(*E*)-1-(Piperazin-1-yl)-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-en-1-one **18**



Step 1

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Tert-butyl 4-((*E*)-4-((3*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enoyl)piperazine-1-carboxylate **18a**

In accordance with the synthetic route in Example 1, the starting material **1g** in Step 4 was replaced with compound **11f**, and the starting material **1h** was replaced with compound **4a**, to give the title compound **18a** (51 mg, yield: 76%).

Step 2

(*E*)-1-(Piperazin-1-yl)-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-en-1-one **18**

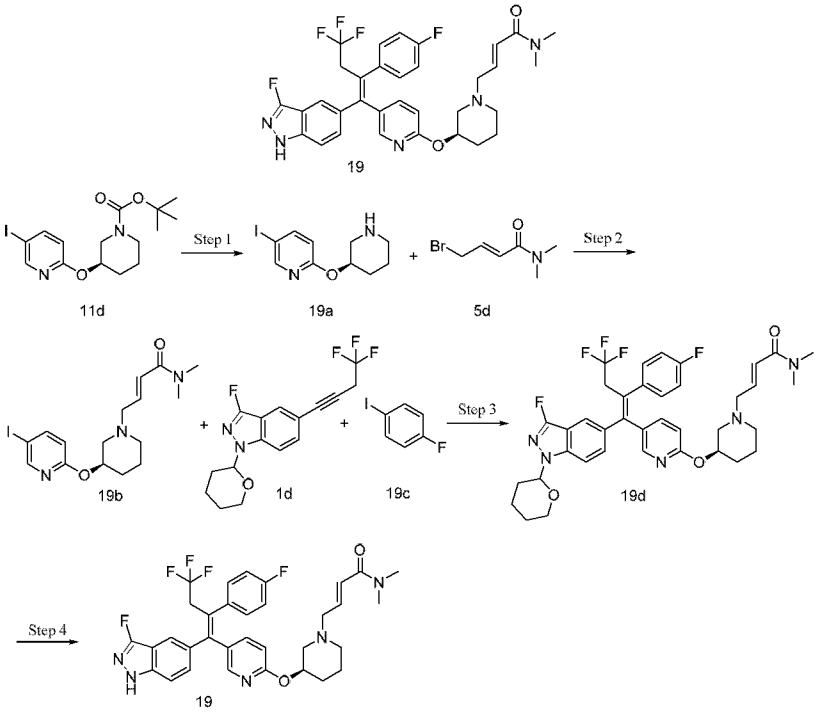
In accordance with the synthetic route in Example 1, the starting material **1i** in Step 5 was replaced with compound **18a**, to give the title compound **18** (21 mg, yield: 31%).

MS m/z(ESI): 649.3 [M+1].

^{1}H NMR (400 MHz, CD_3OD) 7.67 (d, 2H), 7.50 (d, 1H), 7.34-7.20 (m, 6H), 6.92 (d, 1H), 6.78-6.61 (m, 2H), 5.36 (s, 1H), 3.94-3.88 (m, 5H), 3.50-3.39 (m, 6H), 3.28 (s, 2H), 2.23-1.88 (m, 5H), 1.34-1.30 (m, 3H).

Example 19

(*E*)-*N*,*N*-Dimethyl-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-(4-fluorophenyl)but-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **19**



Step 1

(*R*)-5-Iodo-2-(piperidin-3-yloxy)pyridine **19a**

Compound **11d** (1.0 g, 2.5 mmol) was dissolved in dichloromethane (15 mL), followed by the addition of trifluoroacetic acid (3 mL). The reaction was stirred at room

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temperature for 5 hours. The reaction solution was concentrated under reduced pressure, adjusted to about pH 8 with saturated sodium bicarbonate solution (100 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain the crude title product **19a** (0.8 g, yield: 100%), which was used directly in the next step without purification.

Step 2

(*R*,*E*)-4-(3-((5-Iodopyridin-2-yl)oxy)piperidin-1-yl)-*N*,*N*-dimethylbut-2-enamide **19b**

Compound **19a** (752 mg, 2.5 mmol) was dissolved in *N*,*N*-dimethylformamide (20 mL), followed by the successive addition of diisopropylethylamine (1.6 g, 12.4 mmol) and compound **5d** (470 mg, 2.5 mmol) at room temperature. The reaction solution was stirred for 2 hours. The reaction solution was cooled. Saturated sodium bicarbonate solution (15 mL) was added, and the solution was extracted with ethyl acetate (50 mL×2). The organic phases were combined, washed with saturated sodium chloride solution (50 mL×4), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the resulting residues were purified by thin layer chromatography with developing system A to obtain the title product **19b** (0.7 g, yield: 68%).

MS m/z(ESI) :416.1 [M+1].

Step 3

(*E*)-*N*,*N*-Dimethyl-4-((3*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-(4-fluorophenyl)but-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **19d**

Compound **1d** (50 mg, 0.2 mmol) was dissolved in methyltetrahydrofuran (10 mL), followed by the addition of bis(pinacolato)diboron (47 mg, 0.2 mmol) and tetrakis(triphenylphosphine)platinum (4 mg, 0.003 mmol). The reaction solution was purged with argon three times, warmed up to 85°C and stirred for 3 hours. The reaction solution was cooled to room temperature, followed by the addition of compound **19b** (57 mg, 0.1 mmol), bis(triphenylphosphine)palladium dichloride (20 mg, 0.03 mmol), cesium carbonate (128 mg, 0.4 mmol) and water (0.5 mL). The reaction solution was stirred at room temperature overnight. 4-Fluoroiodobenzene **19c** (68 mg, 0.3 mmol) and potassium hydroxide (43 mg, 0.8 mmol) were added. The reaction solution was purged with argon three times, warmed up to 85°C, stirred for 2 hours, and cooled to room temperature. The reaction solution was concentrated under reduced pressure, and the resulting residues were purified by thin layer chromatography with developing system B to obtain the title product **19d** (50 mg, yield: 46%).

MS m/z(ESI): 710.3 [M+1].

Step 4

(*E*)-*N*,*N*-Dimethyl-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-(4-fluorophenyl)but-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **19**

Compound **19d** (50 mg, 0.07 mmol) was dissolved in methanol (2 mL), followed by the addition of hydrochloric acid (12*N*, 1 mL). The reaction solution was stirred for 3

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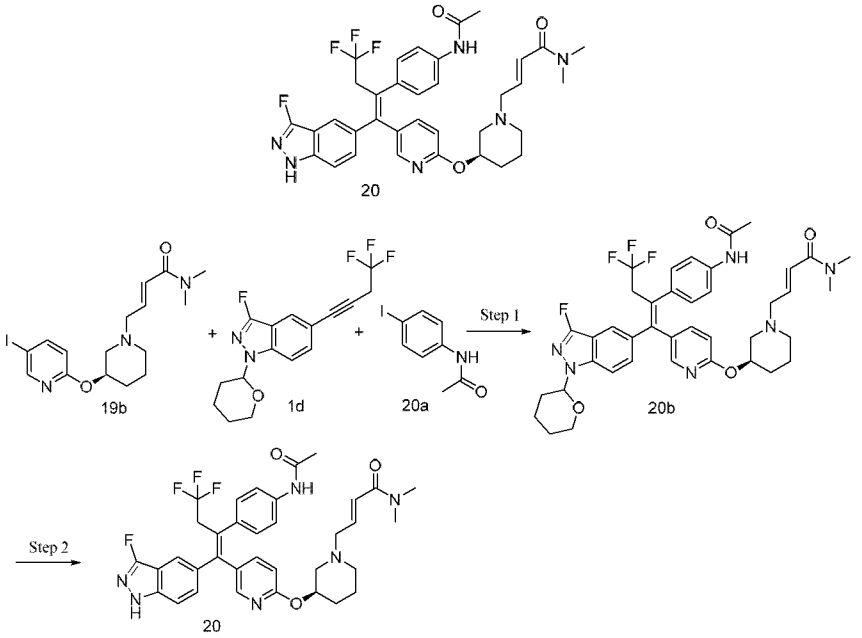
hours. The reaction solution was cooled and concentrated. Saturated sodium bicarbonate solution (15 mL) was added, and the solution was extracted with dichloromethane (10 mL×4). The organic phases were combined, washed with water (10 mL×3) and saturated sodium chloride solution (10 mL) successively, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the resulting residues were purified by thin layer chromatography with developing system A to obtain the title product **19** (15 mg, yield: 34%).

MS m/z(ESI): 626.2 [M+1].

^{1}H NMR (400 MHz, CD_3OD) 7.70 (s, 1H), 7.65 (s, 1H), 7.52 (dd, 1H), 7.32-7.26 (m, 4H), 7.02-6.97 (t, 2H), 6.91-6.87 (m, 1H), 6.65-6.61 (d, 2H), 5.44 (s, 1H), 3.94 (s, 3H), 3.50-3.38 (m, 4H), 3.14 (s, 3H), 3.12-3.05 (m, 1H), 3.01 (s, 3H), 2.11-2.09 (m, 2H), 1.89-1.77 (m, 2H).

Example 20

(*E*)-4-((*R*)-3-((5-((*Z*)-2-(4-Acetamidophenyl)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)but-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)-*N*,*N*-dimethylbut-2-enamide **20**



Step 1

(*E*)-4-((3*R*)-3-((5-((*Z*)-2-(4-Acetamidophenyl)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)but-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)-*N*,*N*-dimethylbut-2-enamide **20b**

In accordance with the synthetic route in Example 19, the starting material **19c** in Step 3 was replaced with *N*-(4-iodophenyl)acetamide **20a** (prepared according to the method disclosed in "*Journal of Organic Chemistry*, 2018, 83(2), 930-938"), to give the title compound **20b** (70 mg, yield: 61%).

Step 2

(*E*)-4-((*R*)-3-((5-((*Z*)-2-(4-Acetamidophenyl)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-y

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l)but-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)-*N*,*N*-dimethylbut-2-enamide **20**

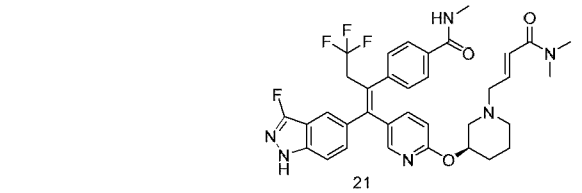
In accordance with the synthetic route in Example 19, the starting material **19d** in Step 4 was replaced with compound **20b**, to give the title compound **20** (22 mg, yield: 41%).

MS m/z(ESI): 665.2 [M+1].

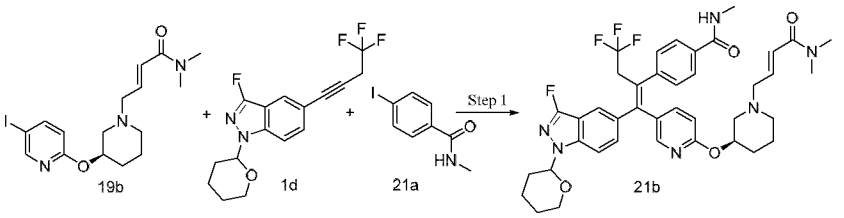
^{1}H NMR (400 MHz, CD_3OD) 7.67 (d, 2H), 7.48-7.44 (m, 3H), 7.28 (dd, 2H), 7.18 (d, 2H), 6.82 (d, 1H), 6.67-6.59 (m, 2H), 5.28 (s, 1H), 3.76 (s, 2H), 3.49-3.39 (m, 4H), 3.25 (d, 1H), 3.10 (s, 3H), 3.03 (d, 1H), 2.99 (s, 3H), 2.11 (s, 3H), 1.99-1.94 (m, 2H), 1.86-1.74 (m, 2H).

Example 21

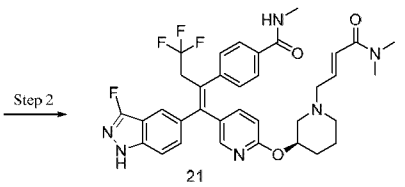
4-((*Z*)-1-(6-(((*R*)-1-((*E*)-4-(Dimethylamino)-4-oxobut-2-en-1-yl)piperidin-3-yl)oxy)pyridin-3-yl)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)but-1-en-2-yl)-*N*-methylbenzamide **21**



21



19b 1d 21a 21b



21

Step 1

4-((*Z*)-1-(6-(((*R*)-1-((*E*)-4-(Dimethylamino)-4-oxobut-2-en-1-yl)piperidin-3-yl)oxy)pyridin-3-yl)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)but-1-en-2-yl)-*N*-methylbenzamide **21b**

In accordance with the synthetic route in Example 19, the starting material **19c** in Step 3 was replaced with 4-iodo-*N*-methylbenzamide **21a** (prepared according to the method disclosed in "*Journal of the American Chemical Society*, 2013, 135(12), 4628-4631"), to give the title compound **21b** (50 mg, yield: 44%).

Step 2

4-((*Z*)-1-(6-(((*R*)-1-((*E*)-4-(Dimethylamino)-4-oxobut-2-en-1-yl)piperidin-3-yl)oxy)pyridin-3-yl)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)but-1-en-2-yl)-*N*-methylbenzamide **21**

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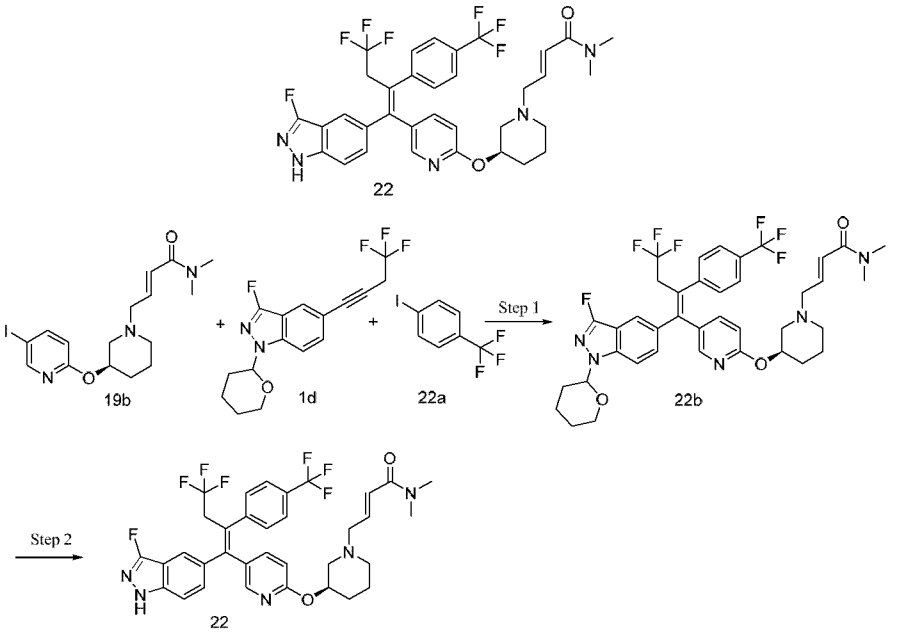
In accordance with the synthetic route in Example 19, the starting material **19d** in Step 4 was replaced with compound **21b**, to give the title compound **21** (10 mg, yield: 32%).

MS m/z(ESI): 665.3 [M+1].

^{1}H NMR (400 MHz, CD_3OD) 7.71-7.69 (m, 4H), 7.50 (d, 1H), 7.36-7.29 (m, 4H), 6.88 (d, 1H), 6.65-6.58 (m, 2H), 5.39 (s, 1H), 3.97-3.91 (m, 2H), 3.69 (d, 1H), 3.49-3.44 (m, 3H), 3.06 (s, 3H), 3.05-3.00 (m, 2H), 2.99 (s, 3H), 2.89 (s, 3H), 2.10-2.03 (m, 2H), 1.86-1.74 (m, 2H).

Example 22

(*E*)-*N*,*N*-Dimethyl-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-(4-(trifluoromethyl)phenyl)but-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **22**



Step 1

(*E*)-*N*,*N*-Dimethyl-4-((3*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-(4-(trifluoromethyl)phenyl)but-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **22b**

In accordance with the synthetic route in Example 19, the starting material **19c** in Step 3 was replaced with 1-iodo-4-(trifluoromethyl)benzene **22a**, to give the title compound **22b** (80 mg, yield: 69%).

Step 2

(*E*)-*N*,*N*-Dimethyl-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-(4-(trifluoromethyl)phenyl)but-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **22**

In accordance with the synthetic route in Example 19, the starting material **19d** in Step 4 was replaced with compound **22b**, to give the title compound **22** (20 mg, yield: 31%).

MS m/z(ESI): 676.2 [M+1].

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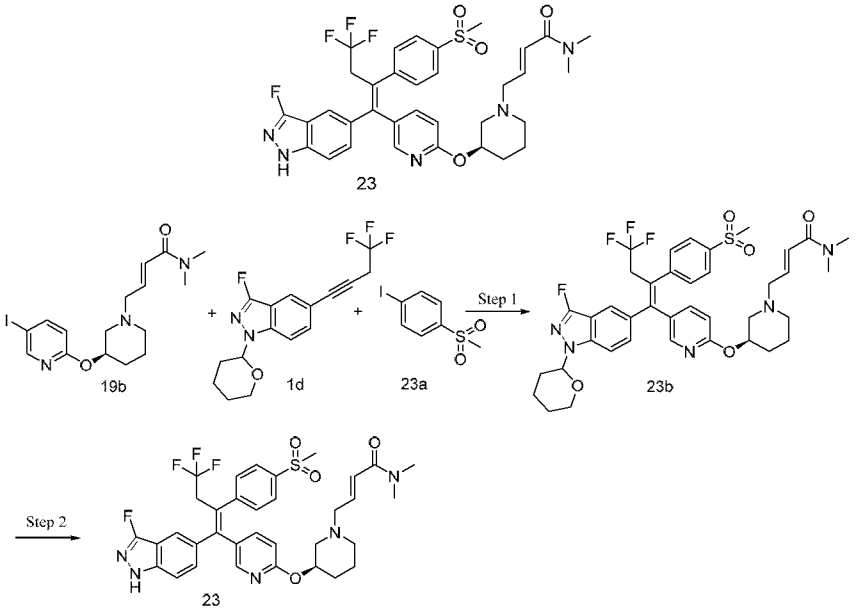
^{1}H NMR (400 MHz, CD_3OD) 7.70 (dd, 2H), 7.57-7.55 (m, 3H), 7.47 (d, 2H), 7.32 (dd, 2H), 6.88 (d, 1H), 6.65-6.59 (m, 2H), 5.37 (s, 1H), 3.91 (d, 2H), 3.50 (q, 2H), 3.32 (s, 4H), 3.12 (s, 3H), 3.00 (s, 3H), 2.09-2.04 (m, 2H), 1.84 (d, 2H).

Example 23

(*E*)-*N*,*N*-Dimethyl-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-(4-(methylsulfonyl)phenyl)but-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **23**



Step 1

(*E*)-*N*,*N*-Dimethyl-4-((3*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-(4-(methylsulfonyl)phenyl)but-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **23b**

In accordance with the synthetic route in Example 19, the starting material **19c** in Step 3 was replaced with 1-iodo-4-(methylsulfonyl)benzene **23a** (prepared according to the method disclosed in "*Organic Letters*, 2014, 16(9), 2306-2309"), to give the title compound **23b** (60 mg, yield: 51%).

Step 2

(*E*)-*N*,*N*-Dimethyl-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-(4-(methylsulfonyl)phenyl)but-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **23**

In accordance with the synthetic route in Example 19, the starting material **19d** in Step 4 was replaced with compound **23b**, to give the title compound **23** (10 mg, yield: 28%).

MS m/z(ESI): 686.2 [M+1].

^{1}H NMR (400 MHz, CD_3OD) 7.83 (d, 2H), 7.67 (s, 2H), 7.53-7.50 (m, 3H), 7.30 (d, 2H), 6.89 (dd, 1H), 6.66-6.59 (m, 2H), 5.38 (s, 1H), 3.97-3.91 (m, 3H), 3.70-3.65 (m, 1H), 3.50 (q, 3H), 3.28 (d, 1H), 3.11 (s, 6H), 2.99 (s, 3H), 2.10-2.01 (m, 2H), 1.94-1.86 (m, 2H).

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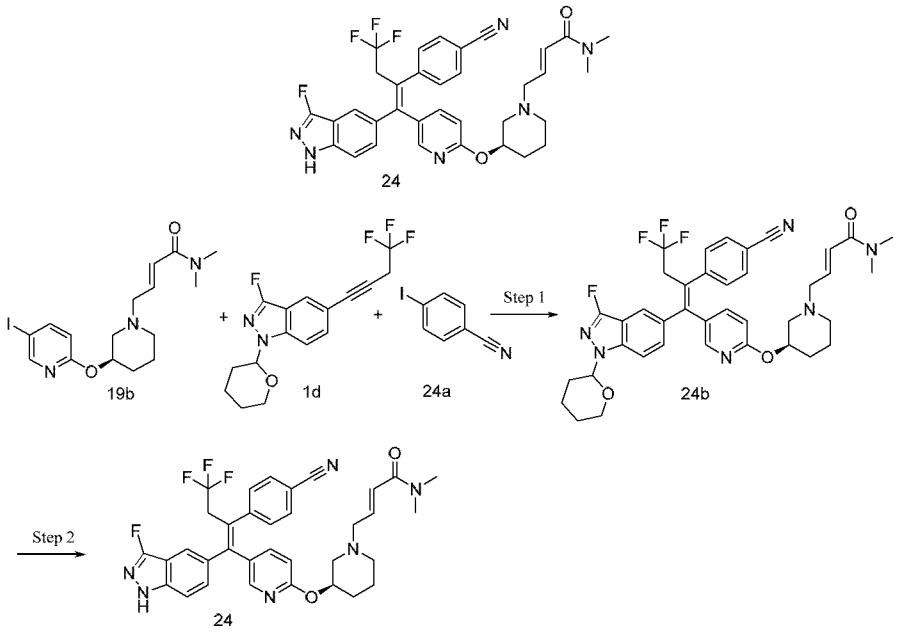
Example 24

(*E*)-4-((*R*)-3-((5-((*Z*)-2-(4-Cyanophenyl)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)but-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)-*N*,*N*-dimethylbut-2-enamide **24**



Step 1

(*E*)-4-((3*R*)-3-((5-((*Z*)-2-(4-Cyanophenyl)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)but-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)-*N*,*N*-dimethylbut-2-enamide **24b**

In accordance with the synthetic route in Example 19, the starting material **19c** in Step 3 was replaced with 4-iodobenzonitrile **24a**, to give the title compound **24b** (80 mg, yield: 73%).

Step 2

(*E*)-4-((*R*)-3-((5-((*Z*)-2-(4-Cyanophenyl)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)but-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)-*N*,*N*-dimethylbut-2-enamide **24**

In accordance with the synthetic route in Example 19, the starting material **19d** in Step 4 was replaced with compound **24b**, to give the title compound **24** (20 mg, yield: 38%).

MS m/z(ESI): 633.2 [M+1].

^{1}H NMR (400 MHz, CD_3OD) 7.67-7.61 (m, 4H), 7.47 (d, 1H), 7.45 (d, 2H), 7.33 (d, 2H), 6.89 (d, 1H), 6.66-6.61 (m, 2H), 5.44 (s, 1H), 3.94-3.91 (m, 2H), 3.71 (d, 1H), 3.52-3.45 (m, 3H), 3.25 (d, 1H), 3.12 (s, 3H), 3.05 (d, 1H), 3.01 (s, 3H), 2.11-2.04 (m, 2H), 1.90-1.77 (m, 2H).

Example 25

(*R*,*Z*)-1-(3-((5-(4,4,4-Trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-yn-1-one **25**

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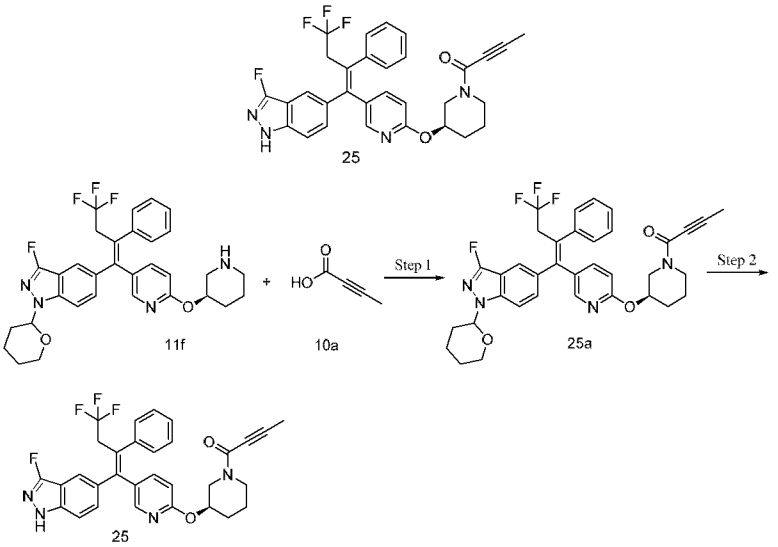


Step 1

1-((3*R*)-3-((5-((*Z*)-4,4,4-Trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-yn-1-one **25a**

In accordance with the synthetic route in Example 10, the starting material **9d** in Step 1 was replaced with compound **11f**, to give the title compound **25a** (37 mg, yield: 83%).

Step 2

(*R*,*Z*)-1-(3-((5-(4,4,4-Trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-yn-1-one **25**

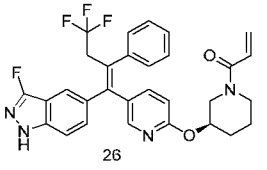
In accordance with the synthetic route in Example 10, the starting material **10b** in Step 2 was replaced with compound **25a**, to give the title compound **25** (4 mg, yield: 15%).

MS m/z(ESI): 563.2 [M+1].

^{1}H NMR (400 MHz, $CDCl_3$) 9.38 (s, 1H), 7.68-7.65 (m, 2H), 7.43-7.12 (m, 8H), 6.46-6.39 (m, 1H), 5.02 (d, 1H), 3.95-3.77 (m, 2H), 3.33-3.00 (m, 4H), 2.13-1.93 (m, 4H), 1.69 (d, 3H).

Example 26

(*R*,*Z*)-1-(3-((5-(4,4,4-Trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)prop-2-en-1-one **26**



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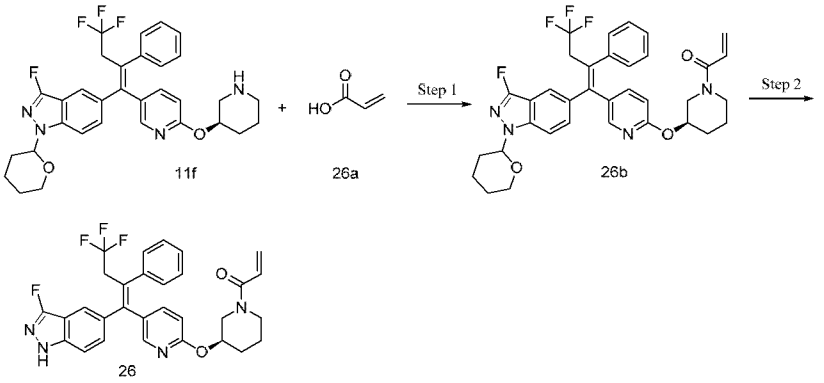


Step 1

1-((3*R*)-3-((5-((*Z*)-4,4,4-Trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)prop-2-en-1-one **26b**

In accordance with the synthetic route in Example 10, the starting material **9d** in Step 1 was replaced with compound **11f**, and the starting material **10a** was replaced with acrylic acid **26a**, to give the title compound **26b** (30 mg, yield: 73%).

Step 2

(*R*,*Z*)-1-(3-((5-(4,4,4-Trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)prop-2-en-1-one **26**

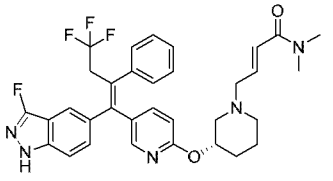
In accordance with the synthetic route in Example 10, the starting material **10b** in Step 2 was replaced with compound **26b**, to give the title compound **26** (3 mg, yield: 12%).

MS m/z(ESI): 551.2 [M+1].

^{1}H NMR (400 MHz, $CDCl_3$) 9.31 (s, 1H), 7.68 (d, 2H), 7.43 (d, 2H), 7.29-7.27 (m, 5H), 7.20-7.09 (m, 1H), 6.40 (d, 1H), 6.39-6.20 (m, 1H), 5.49-5.37 (m, 2H), 4.95 (s, 1H), 3.72(s, 1H), 3.68 (d, 2H), 3.39 (d, 1H), 3.36-3.31 (m, 2H), 2.04-1.90 (m, 4H).

Example 27

(*E*)-*N*,*N*-Dimethyl-4-((*S*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **27**



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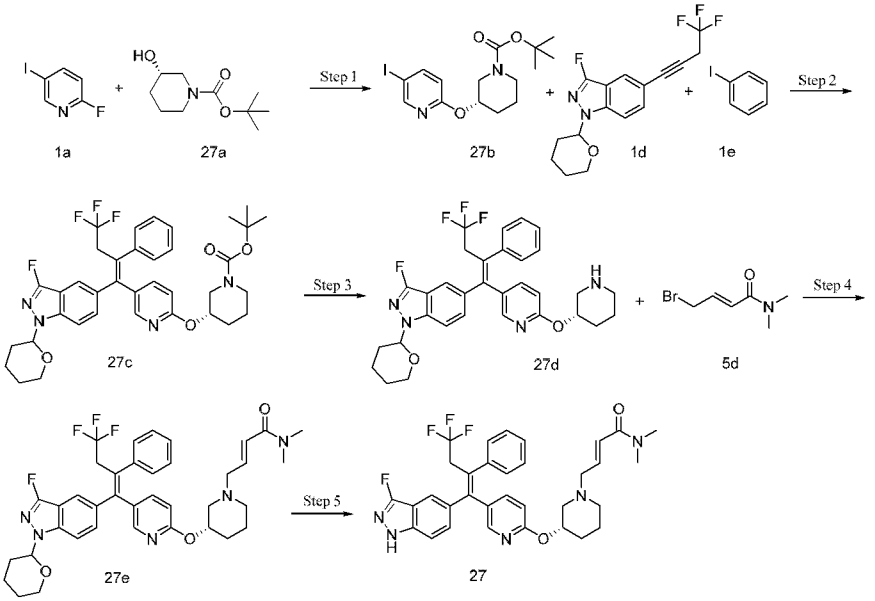

Step 1

Tert-butyl (*S*)-3-((5-iodopyridin-2-yl)oxy)piperidine-1-carboxylate **27b**

In accordance with the synthetic route in Example 1, the starting material **1b** in Step 1 was replaced with *tert*-butyl (*S*)-3-hydroxypiperidine-1-carboxylate **27a** (prepared according to the method disclosed in "*Tetrahedron*, 2007, 63(2), 331-336"), to give the title compound **27b** (531 mg, yield: 92%).

Step 2

Tert-butyl (3*S*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidine-1-carboxylate **27c**

In accordance with the synthetic route in Example 1, the starting material **1c** in Step 2 was replaced with compound **27b**, to give the title compound **27c** (190 mg, yield: 76%).

MS m/z(ESI): 680.9 [M+1].

Step 3

3-Fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-5-((*Z*)-4,4,4-trifluoro-2-phenyl-1-(6-(((*S*)-piperidin-3-yl)oxy)pyridin-3-yl)but-1-en-1-yl)-1*H*-indazole **27d**

In accordance with the synthetic route in Example 1, the starting material **1f** in Step 3 was replaced with compound **27c**, to give the title compound **27d** (85 mg, yield: 100%).

Step 4

(*E*)-*N*,*N*-Dimethyl-4-((3*S*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **27e**

In accordance with the synthetic route in Example 1, the starting material **1g** in Step 4 was replaced with compound **27d**, and the starting material **1h** was replaced with compound **5d**, to give the title compound **27e** (65 mg, yield: 64%).

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Step 5

(*E*)-*N*,*N*-Dimethyl-4-((*S*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)but-2-enamide **27**

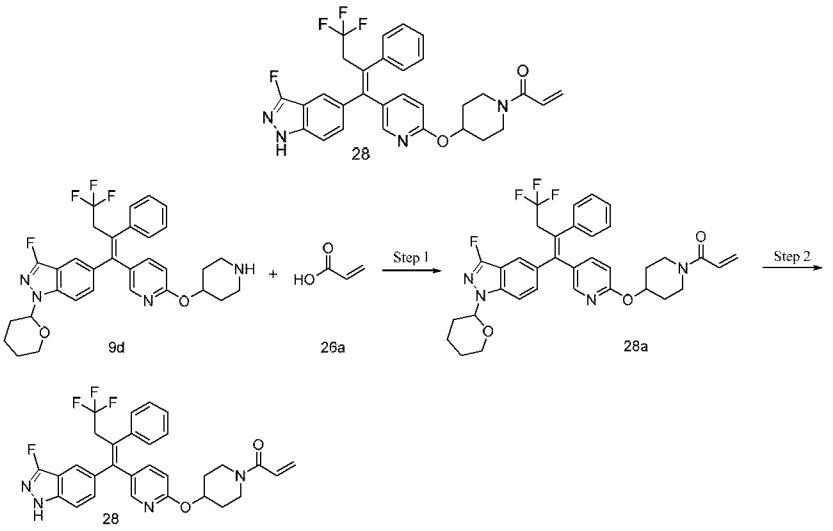
In accordance with the synthetic route in Example 1, the starting material **1i** in Step 5 was replaced with compound **27e**, to give the title compound **27** (15 mg, yield: 43%).

MS m/z(ESI): 607.9 [M+1].

^{1}H NMR (400 MHz, $CDCl_3$) 9.36 (s, 1H), 7.69-7.67 (m, 1H), 7.64-7.63 (d, 1H), 7.45-7.43 (m, 1H), 7.35-7.32 (d, 1H), 7.28-7.19 (m, 4H), 7.08-7.06 (d, 1H), 6.89-6.82 (m, 1H), 6.46-6.41 (m, 1H), 5.39-5.36 (m, 1H), 5.08-5.02 (br, 1H), 3.38-3.30 (m, 2H), 3.22-3.16 (m, 2H), 3.05 (s, 3H), 3.10 (s, 3H), 2.92-2.86 (m, 1H), 2.67-2.61 (m, 1H), 2.34-2.24 (m, 2H), 2.07-1.77 (m, 4H), 1.53-1.48 (m, 1H).

Example 28

(*Z*)-1-(4-((5-(4,4,4-Trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)prop-2-en-1-one **28**



Step 1

(*Z*)-1-(4-((5-(4,4,4-Trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)prop-2-en-1-one **28a**

In accordance with the synthetic route in Example 10, the starting material **10a** in Step 1 was replaced with compound **26a**, to give the title compound **28a** (50 mg, yield: 63%).

Step 2

(*Z*)-1-(4-((5-(4,4,4-Trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)piperidin-1-yl)prop-2-en-1-one **28**

In accordance with the synthetic route in Example 10, the starting material **10b** in Step 2 was replaced with compound **28a**, to give the title compound **28** (10 mg, yield: 23%).

MS m/z(ESI): 551.2 [M+1].

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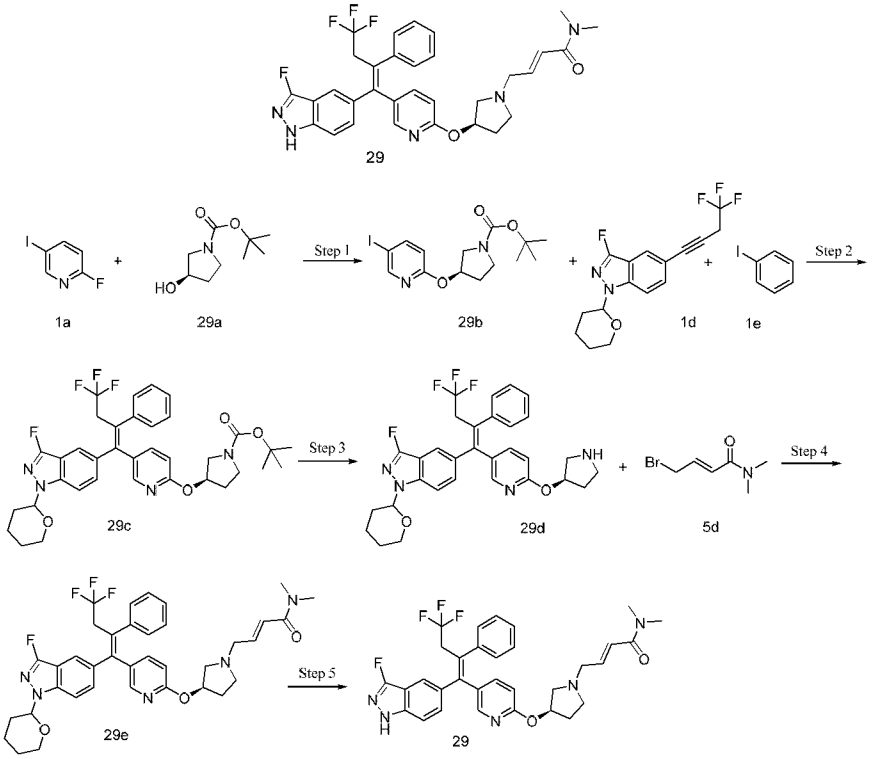
^{1}H NMR (400 MHz, $CDCl_3$) 9.47 (br, 1H), 7.60 (d, 2H), 7.35 (d, 1H), 7.28 (d, 1H), 7.26-7.19 (m, 5H), 6.59 (dd, 1H), 6.49 (d, 1H), 6.29 (d, 1H), 5.76 (d, 1H), 5.14 (m, 1H), 3.89-3.53 (m, 5H), 3.34 (t, 2H), 1.99-1.94 (m, 2H), 1.77-1.66 (m, 2H).

Example 29

(*E*)-*N*,*N*-Dimethyl-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)pyrrolidin-1-yl)but-2-enamide **29**



Step 1

Tert-butyl (*R*)-3-((5-iodopyridin-2-yl)oxy)pyrrolidine-1-carboxylate **29b**

In accordance with the synthetic route in Example 1, the starting material **1b** in Step 1 was replaced with *tert*-butyl (*R*)-3-hydroxypyrrolidine-1-carboxylate **29a**, to give the title compound **29b** (0.9 g, yield: 86%).

Step 2

Tert-butyl

(3*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)pyrrolidine-1-carboxylate **29c**

In accordance with the synthetic route in Example 1, the starting material **1c** in Step 2 was replaced with compound **29b**, to give the title compound **29c** (260 mg, yield: 37%).

Step 3

3-Fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-5-((*Z*)-4,4,4-trifluoro-2-phenyl-1-(6-(((*R*)-pyrrolidin-3-yl)oxy)pyridin-3-yl)but-1-en-1-yl)-1*H*-indazole **29d**

In accordance with the synthetic route in Example 1, the starting material **1f** in

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Step 3 was replaced with compound **29c**, to give the title compound **29d** (93 mg, yield: 99%).

Step 4

(*E*)-*N*,*N*-Dimethyl-4-((3*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)pyrrolidin-1-yl)but-2-enamide **29e**

In accordance with the synthetic route in Example 1, the starting material **1g** in Step 4 was replaced with compound **29d**, and the starting material **1h** was replaced with compound **5d**, to give the title compound **29e** (60 mg, yield: 54%).

MS m/z(ESI): 678.3 [M+1].

Step 5

(*E*)-*N*,*N*-Dimethyl-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)pyrrolidin-1-yl)but-2-enamide **29**

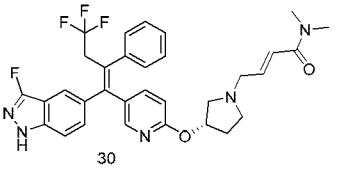
In accordance with the synthetic route in Example 1, the starting material **1i** in Step 5 was replaced with compound **29e**, to give the title compound **29** (15 mg, yield: 29%).

MS m/z(ESI): 594.3 [M+1].

^{1}H NMR (400 MHz, $CDCl_3$) 12.72 (s, 1H), 7.70-7.65 (m, 2H), 7.60-7.50 (d, 1H), 7.25-7.20 (m, 5H), 7.19-7.15 (m, 2H), 6.55-6.45 (m, 3H), 5.17-5.10 (m, 1H), 3.50-3.35 (m, 2H), 3.15-3.10 (m, 2H), 2.95 (s, 3H), 2.83 (s, 3H), 2.70-2.60 (m, 2H), 2.50-2.45 (m, 1H), 2.35-2.25 (m, 1H), 2.15-2.05 (m, 1H), 1.70-1.60 (m, 1H).

Example 30

(*E*)-*N*,*N*-Dimethyl-4-((*S*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)pyrrolidin-1-yl)but-2-enamide **30**



30

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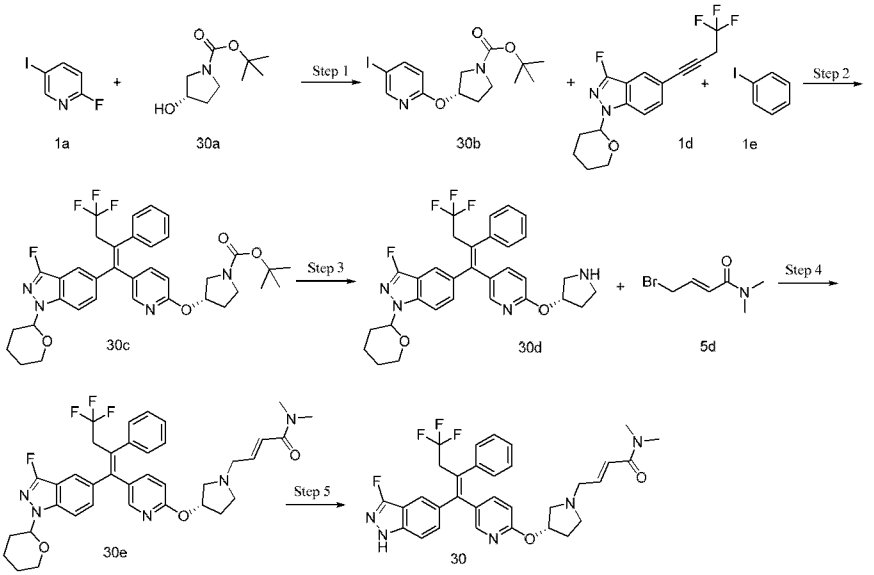

Step 1

Tert-butyl (*S*)-3-((5-iodopyridin-2-yl)oxy)pyrrolidine-1-carboxylate **30b**

In accordance with the synthetic route in Example 1, the starting material **1b** in Step 1 was replaced with *tert*-butyl (*S*)-3-hydroxypyrrolidine-1-carboxylate **30a**, to give the title compound **30b** (0.5 g, yield: 50%).

Step 2

Tert-butyl (3*S*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)pyrrolidine-1-carboxylate **30c**

In accordance with the synthetic route in Example 1, the starting material **1c** in Step 2 was replaced with compound **30b**, to give the title compound **30c** (260 mg, yield: 85%).

Step 3

3-Fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-5-((*Z*)-4,4,4-trifluoro-2-phenyl-1-(6-(((*S*)-pyrrolidin-3-yl)oxy)pyridin-3-yl)but-1-en-1-yl)-1*H*-indazole **30d**

In accordance with the synthetic route in Example 1, the starting material **1f** in Step 3 was replaced with compound **30c**, to give the title compound **30d** (100 mg, yield: 98%).

Step 4

(*E*)-*N*,*N*-Dimethyl-4-((3*S*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)pyrrolidin-1-yl)but-2-enamide **30e**

In accordance with the synthetic route in Example 1, the starting material **1g** in Step 4 was replaced with compound **30d**, and the starting material **1h** was replaced with compound **5d**, to give the title compound **30e** (70 mg, yield: 62%).

MS m/z(ESI): 678.3 [M+1].

Step 5

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(*E*)-*N*,*N*-Dimethyl-4-((*S*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)pyrrolidin-1-yl)but-2-enamide **30**

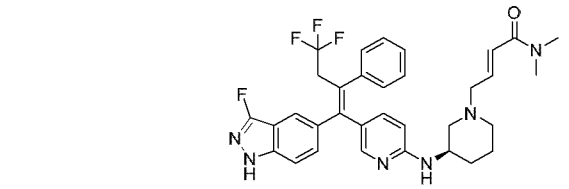
In accordance with the synthetic route in Example 1, the starting material **1i** in Step 5 was replaced with compound **30e**, to give the title compound **30** (10 mg, yield: 23%).

MS m/z(ESI): 593.9 [M+1].

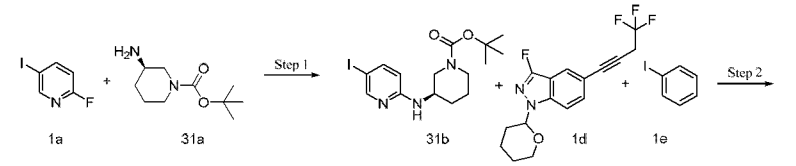
^{1}H NMR (400 MHz, $CDCl_3$) 9.58 (s, 1H), 7.67-7.65 (m, 2H), 7.46 (d, 1H), 7.34-7.30 (m, 2H), 7.27-7.16 (m, 4H), 6.87-6.77 (m, 2H), 6.59 (d, 1H), 5.53 (s, 1H), 4.14 (s, 1H), 3.93 (s, 3H), 3.39-3.31 (m, 2H), 3.29-3.03 (m, 7H), 2.41-2.28 (m, 4H).

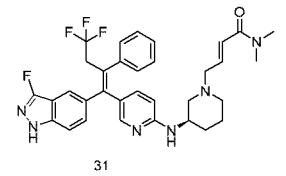
Example 31

(*E*)-*N*,*N*-Dimethyl-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)amino)piperidin-1-yl)but-2-enamide **31**



31





31

Step 1

Tert-butyl (*R*)-3-((5-iodopyridin-2-yl)amino)piperidine-1-carboxylate **31b**

In accordance with the synthetic route in Example 1, the starting material **1b** in Step 1 was replaced with *tert*-butyl (*R*)-3-aminopiperidine-1-carboxylate **31a**, to give the title compound **31b** (0.8 g, yield: 57%).

Step 2

Tert-butyl

(3*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)amino)piperidine-1-carboxylate **31c**

In accordance with the synthetic route in Example 1, the starting material **1c** in Step 2 was replaced with compound **31b**, to give the title compound **31c** (210 mg, yield:

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75%).

Step 3

(*R*,*Z*)-*N*-(Piperidin-3-yl)-5-(4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-amine **31d**

In accordance with the synthetic route in Example 1, the starting material **1f** in Step 3 was replaced with compound **31c**, to give the title compound **31d** (42 mg, yield: 92%).

Step 4

(*E*)-*N*,*N*-Dimethyl-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)amino)piperidin-1-yl)but-2-enamide **31**

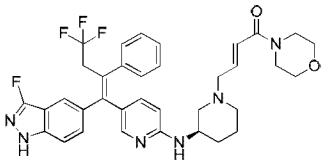
In accordance with the synthetic route in Example 1, the starting material **1g** in Step 4 was replaced with compound **31d**, and the starting material **1h** was replaced with compound **5d**, to give the title compound **31** (20 mg, yield: 39%).

MS m/z(ESI): 607.3 [M+1].

^{1}H NMR (400 MHz, $CDCl_3$) 9.26 (s, 1H), 7.68 (s, 1H), 7.55-7.54 (m, 1H), 7.44-7.41 (m, 1H), 7.36-7.31 (m, 1H), 7.28-7.23 (m, 4H), 6.92-6.80 (m, 2H), 6.45-6.41 (m, 1H), 6.15-6.13 (m, 1H), 5.39-5.37 (m, 1H), 3.35-3.28 (m, 2H), 3.17-3.15 (m, 2H), 3.07 (s, 3H), 3.02 (s, 3H), 2.70-2.68 (m, 1H), 2.47-2.45 (m, 1H), 2.47-2.45 (m, 1H), 2.06-2.04 (m, 2H), 1.34-1.29 (m, 4H).

Example 32

(*E*)-1-Morpholino-4-((*R*)-3-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)amino)piperidin-1-yl)but-2-en-1-one **32**



32

In accordance with the synthetic route in Example 31, the starting material **5d** in Step 4 was replaced with compound **1h**, to give the title compound **32** (8 mg, yield: 19%).

MS m/z(ESI): 649.2 [M+1].

^{1}H NMR (400 MHz, $CDCl_3$) 9.25 (s, 1H), 7.68 (s, 1H), 7.56-7.52 (m, 1H), 7.45-7.40 (m, 1H), 7.36-7.32 (m, 1H), 7.28-7.21 (m, 4H), 6.94-6.82 (m, 2H), 6.44-6.37 (m, 1H), 6.15-6.07 (m, 1H), 5.39-5.35 (m, 1H), 3.76-3.46 (m, 8H), 3.36-3.26 (m, 2H), 3.17-3.05 (m, 2H), 2.99-2.92 (m, 1H), 2.65-2.03 (m, 7H), 0.95-0.87 (m, 1H).

Example 33

(*E*)-*N*,*N*-Dimethyl-4-(4-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)amino)piperidin-1-yl)but-2-enamide **33**

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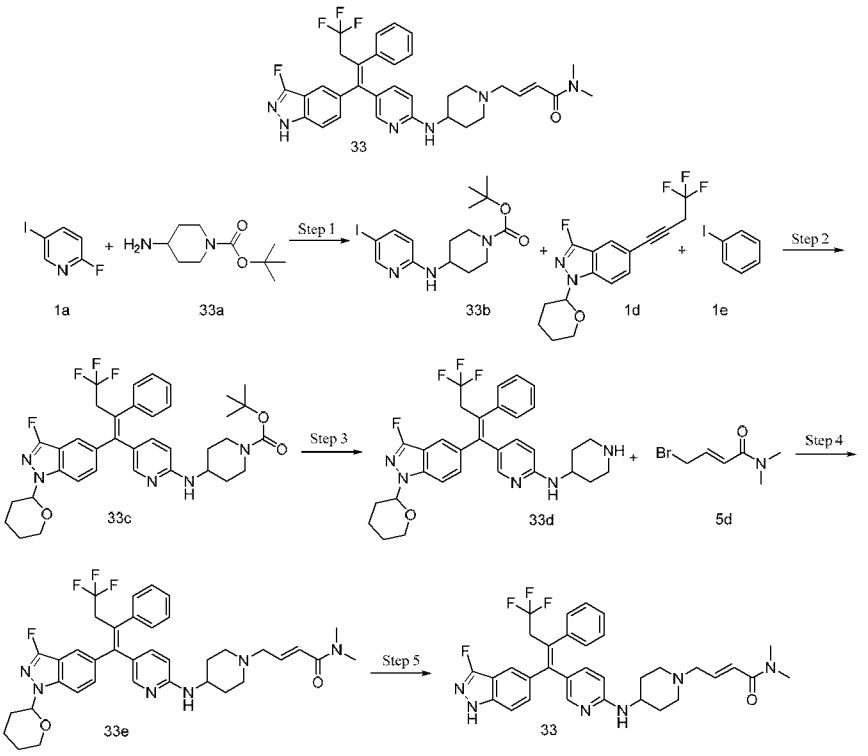

Step 1

Tert-butyl 4-((5-iodopyridin-2-yl)amino)piperidine-1-carboxylate **33b**

In accordance with the synthetic route in Example 1, the starting material **1b** in Step 1 was replaced with *tert*-butyl 4-aminopiperidine-1-carboxylate **33a**, to give the title compound **33b** (0.2 g, yield: 20%).

Step 2

Tert-butyl (*Z*)-4-((5-(4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)amino)piperidine-1-carboxylate **33c**

In accordance with the synthetic route in Example 1, the starting material **1c** in Step 2 was replaced with compound **33b**, to give the title compound **33c** (80 mg, yield: 64%).

MS m/z(ESI): 680.3 [M+1].

Step 3

(*Z*)-*N*-(Piperidin-4-yl)-5-(4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-amine **33d**

In accordance with the synthetic route in Example 1, the starting material **1f** in Step 3 was replaced with compound **33c**, to give the title compound **33d** (68 mg, yield: 100%).

Step 4

(*E*)-*N*,*N*-Dimethyl-4-(4-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)amino)piperidin-1-yl)but-2-enamide **33e**

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In accordance with the synthetic route in Example 1, the starting material **1g** in Step 4 was replaced with compound **33d**, and the starting material **1h** was replaced with compound **5d**, to give the title compound **33e** (70 mg, yield: 86%).

Step 5

(*E*)-*N*,*N*-Dimethyl-4-(4-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)amino)piperidin-1-yl)but-2-enamide **33**

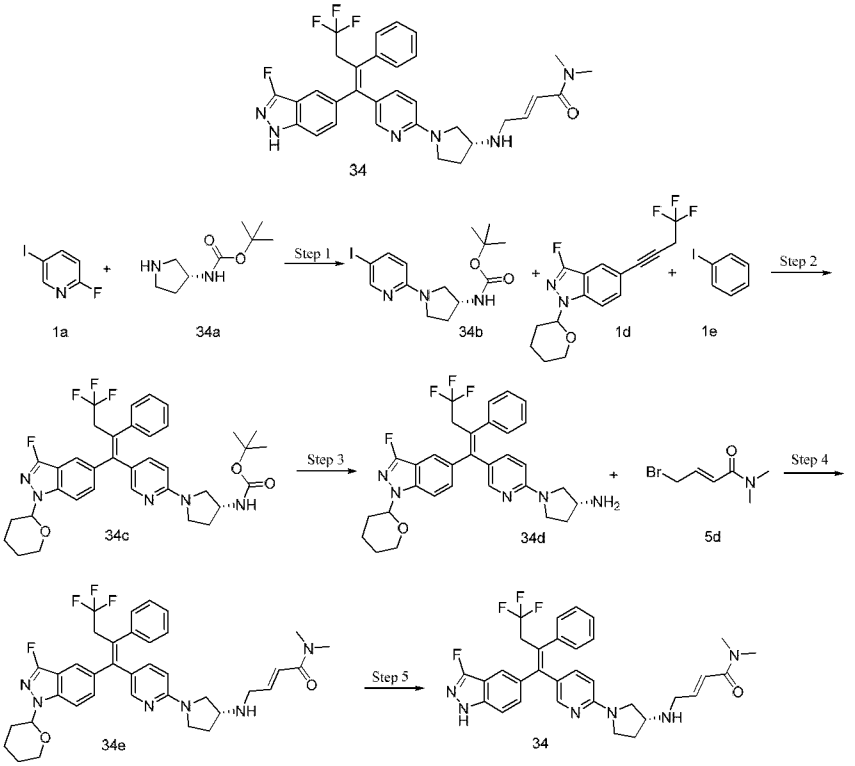
In accordance with the synthetic route in Example 1, the starting material **1i** in Step 5 was replaced with compound **33e**, to give the title compound **33** (15 mg, yield: 24%).

MS m/z(ESI): 607.7 [M+1].

^{1}H NMR (400 MHz, $CDCl_3$) 7.63 (s, 1H), 7.59 (s, 1H), 7.38-7.32 (m, 4H), 7.24 (d, 2H), 7.23-7.02 (m, 2H), 6.77 (s, 2H), 6.47 (d, 1H), 5.36 (s, 1H), 3.93 (s, 1H), 3.83 (s, 2H), 3.39-3.29 (m, 6H), 3.12 (s, 3H), 3.09 (s, 3H), 2.42 (m, 2H), 2.07 (s, 2H).

Example 34

(*E*)-*N*,*N*-Dimethyl-4-(((*R*)-1-(5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)pyrrolidin-3-yl)amino)but-2-enamide **34**



Step 1

Tert-butyl (*R*)-(1-(5-iodopyridin-2-yl)pyrrolidin-3-yl)carbamate **34b**

In accordance with the synthetic route in Example 1, the starting material **1b** in Step 1 was replaced with *tert*-butyl (*R*)-pyrrolidin-3-ylcarbamate **34a**, to give the title compound **34b** (0.8 g, yield: 70%).

Step 2

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Tert-butyl ((3*R*)-1-(5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)pyrrolidin-3-yl)carbamate **34c**

In accordance with the synthetic route in Example 1, the starting material **1c** in Step 2 was replaced with compound **34b**, to give the title compound **34c** (85 mg, yield: 83%).

MS m/z(ESI): 665.9 [M+1].

Step 3

(3*R*)-1-(5-((*Z*)-4,4,4-Trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)pyrrolidin-3-amine **34d**

In accordance with the synthetic route in Example 1, the starting material **1f** in Step 3 was replaced with compound **34c**, to give the title compound **34d** (60 mg, yield: 82%).

Step 4

(*E*)-*N*,*N*-Dimethyl-4-(((3*R*)-1-(5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)pyrrolidin-3-yl)amino)but-2-enamide **34e**

In accordance with the synthetic route in Example 1, the starting material **1g** in Step 4 was replaced with compound **34d**, and the starting material **1h** was replaced with compound **5d**, to give the title compound **34e** (45 mg, yield: 63%).

Step 5

(*E*)-*N*,*N*-Dimethyl-4-(((*R*)-1-(5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)pyrrolidin-3-yl)amino)but-2-enamide **34**

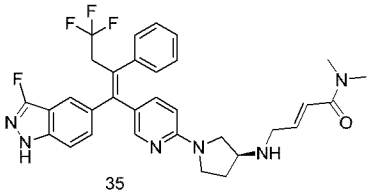
In accordance with the synthetic route in Example 1, the starting material **1i** in Step 5 was replaced with compound **34e**, to give the title compound **34** (9 mg, yield: 23%).

MS m/z(ESI): 592.9 [M+1].

^{1}H NMR (400 MHz, $CDCl_3$) 9.53 (s, 1H), 7.67 (s, 2H), 7.38 (d, 1H), 7.30-7.22 (m, 6H), 6.95-6.87 (m, 2H), 6.45 (d, 1H), 6.07(d, 1H), 3.63-3.59 (m, 1H), 3.54-3.48 (m, 3H), 3.41-3.28 (m, 3H), 3.23-3.19 (m, 1H), 3.06 (d, 6H), 2.27-2.14 (m, 2H), 1.89-1.81 (m, 2H).

Example 35

(*E*)-*N*,*N*-Dimethyl-4-(((*S*)-1-(5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)pyrrolidin-3-yl)amino)but-2-enamide **35**



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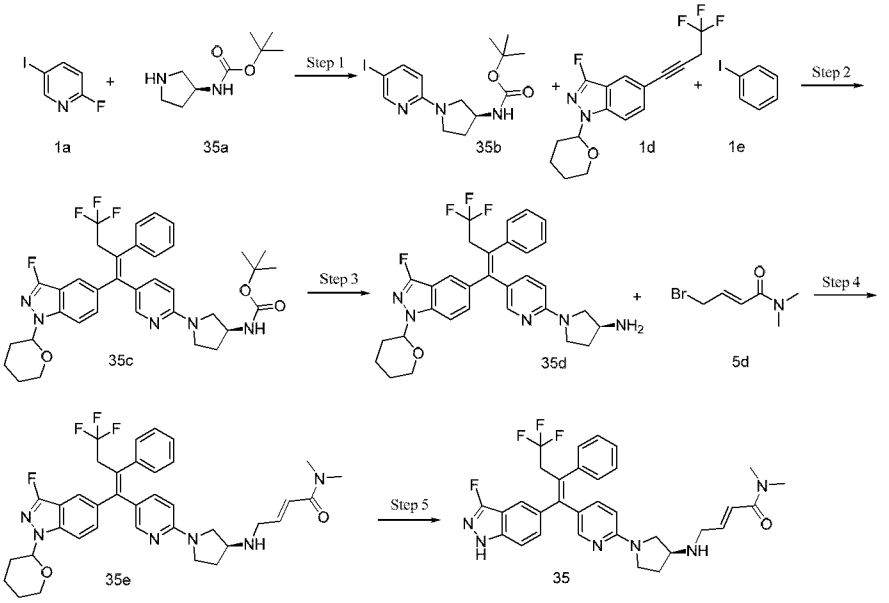

Step 1

Tert-butyl (*S*)-(1-(5-iodopyridin-2-yl)pyrrolidin-3-yl)carbamate **35b**

In accordance with the synthetic route in Example 1, the starting material **1b** in Step 1 was replaced with *Tert*-butyl (*S*)-pyrrolidin-3-ylcarbamate **35a**, to give the title compound **35b** (0.8 g, yield: 69%).

Step 2

Tert-butyl ((3*S*)-1-(5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)pyrrolidin-3-yl)carbamate **35c**

In accordance with the synthetic route in Example 1, the starting material **1c** in Step 2 was replaced with compound **35b**, to give the title compound **35c** (86 mg, yield: 84%).

MS m/z(ESI): 666.3 [M+1].

Step 3

(3*S*)-1-(5-((*Z*)-4,4,4-Trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)pyrrolidin-3-amine **35d**

In accordance with the synthetic route in Example 1, the starting material **1f** in Step 3 was replaced with compound **35c**, to give the title compound **35d** (55 mg, yield: 80%).

Step 4

(*E*)-*N*,*N*-Dimethyl-4-(((3*S*)-1-(5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)pyrrolidin-3-yl)amino)but-2-enamide **35e**

In accordance with the synthetic route in Example 1, the starting material **1g** in Step 4 was replaced with compound **35d**, and the starting material **1h** was replaced with compound **5d**, to give the title compound **35e** (40 mg, yield: 61%).

Step 5

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(*E*)-*N*,*N*-Dimethyl-4-(((*S*)-1-(5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)pyrrolidin-3-yl)amino)but-2-enamide **35**

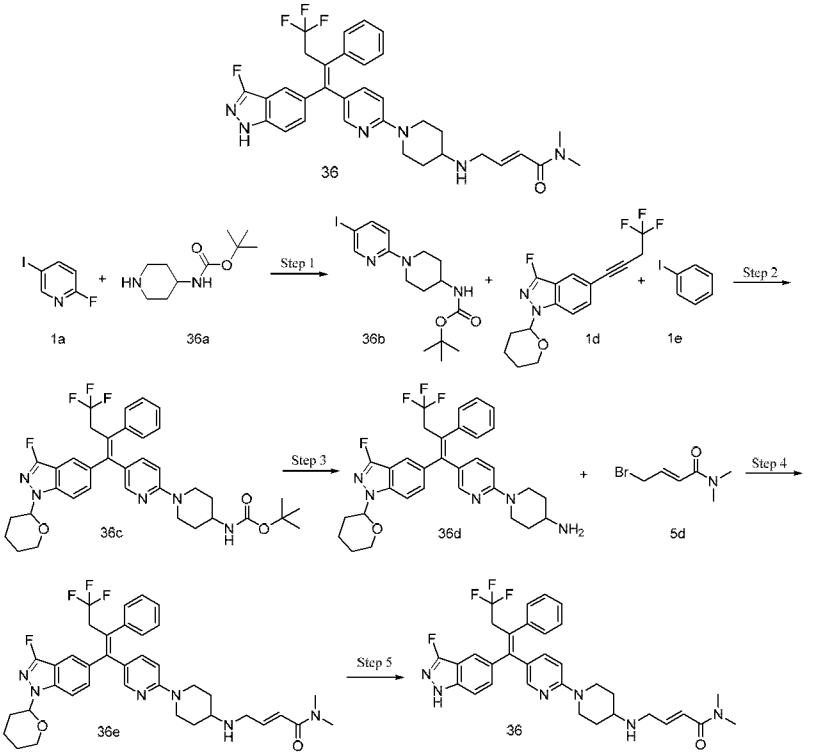
In accordance with the synthetic route in Example 1, the starting material **1i** in Step 5 was replaced with compound **35e**, to give the title compound **35** (8 mg, yield: 23%).

MS m/z(ESI): 592.9 [M+1].

^{1}H NMR (400 MHz, $CDCl_3$) 9.47 (s, 1H), 7.67 (s, 2H), 7.39 (dd, 1H), 7.34 (dd, 1H),7.28-7.22 (m, 5H), 6.96-6.87 (m, 2H), 6.45 (dd, 1H), 6.07 (dd, 1H), 3.63-3.59 (m, 1H), 3.54-3.46 (m, 3H), 3.41-3.28(m, 3H), 3.22-3.19 (m, 1H), 3.07 (d, 6H), 2.20-2.15 (m, 2H),1.88-1.81 (m, 2H).

Example 36

(*E*)-*N*,*N*-Dimethyl-4-((1-(5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)piperidin-4-yl)amino)but-2-enamide **36**



Step 1

Tert-butyl (1-(5-iodopyridin-2-yl)piperidin-4-yl)carbamate **36b**

In accordance with the synthetic route in Example 1, the starting material **1b** in Step 1 was replaced with *tert*-butyl piperidin-4-ylcarbamate **36a**, to give the title compound **36b** (0.3 g, yield: 28%).

Step 2

Tert-butyl

(*Z*)-(1-(5-(4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)piperidin-4-yl)carbamate **36c**

In accordance with the synthetic route in Example 1, the starting material **1c** in

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Step 2 was replaced with compound **36b**, to give the title compound **36c** (120 mg, yield: 74%).

MS m/z(ESI): 679.9 [M+1].

Step 3

(*Z*)-1-(5-(4,4,4-Trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)piperidin-4-amine **36d**

In accordance with the synthetic route in Example 1, the starting material **1f** in Step 3 was replaced with compound **36c**, to give the title compound **36d** (68 mg, yield: 100%).

Step 4

(*E*)-*N*,*N*-Dimethyl-4-((1-(5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)piperidin-4-yl)amino)but-2-enamide **36e**

In accordance with the synthetic route in Example 1, the starting material **1g** in Step 4 was replaced with compound **36d**, and the starting material **1h** was replaced with compound **5d**, to give the title compound **36e** (70 mg, yield: 86%).

Step 5

(*E*)-*N*,*N*-Dimethyl-4-((1-(5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)piperidin-4-yl)amino)but-2-enamide **36**

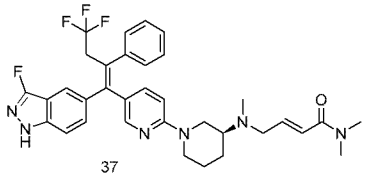
In accordance with the synthetic route in Example 1, the starting material **1i** in Step 5 was replaced with compound **36e**, to give the title compound **36** (15 mg, yield: 24%).

MS m/z(ESI): 607.7 [M+1].

^{1}H NMR (400 MHz, CD_3OD) 7.70 (s, 1H), 7.56-7.53 (m, 1H), 7.48-7.42 (m, 1H), 7.35-7.32 (m, 1H), 7.30-7.26 (m, 6H), 7.00-6.98 (d, 1H), 6.92-6.89 (m, 1H), 6.72-6.64 (m, 1H), 4.25-4.21 (d, 2H), 3.92-3.90 (d, 2H), 3.57-3.39 (m, 4H), 3.17-3.11 (m, 4H), 3.01 (s, 3H), 2.24-2.22 (m, 2H), 1.67-1.67 (m, 2H).

Example 37

(*E*)-*N*,*N*-Dimethyl-4-(methyl((*S*)-1-(5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)piperidin-3-yl)amino)but-2-enamide **37**



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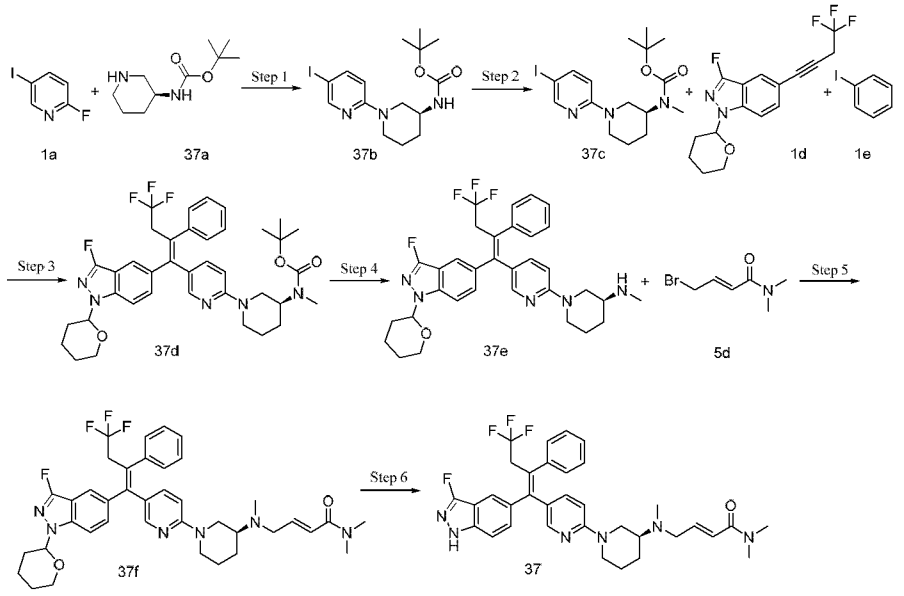

Step 1

Tert-butyl (*S*)-(1-(5-iodopyridin-2-yl)piperidin-3-yl)carbamate **37b**

Potassium carbonate (1.5 g, 20.5 mmol) was dissolved in *N*,*N*-dimethylformamide (10 mL), followed by the addition of *tert*-butyl (*S*)-piperidin-3-ylcarbamate **37a** (2.0 g, 10.0 mmol) at room temperature. After completion of the addition, compound **1a** (2.2 g, 10.0 mmol) was slowly added. The reaction was heated to 100°C, and stirred for 4 hours. The reaction solution was concentrated under reduced pressure, and the resulting residues were purified by thin layer chromatography with developing system B to obtain the title product **37b** (3.5 g, yield: 87%).

Step 2

Tert-butyl (*S*)-(1-(5-iodopyridin-2-yl)piperidin-3-yl)(methyl)carbamate **37c**

Sodium hydride (12 mg, 0.5 mmol) was dissolved in *N*,*N*-dimethylformamide (10 mL), followed by the addition of compound **37b** (100 mg, 0.2 mmol) at room temperature. After completion of the addition, iodomethane (28 mg, 0.2 mmol) was slowly added. The reaction was stirred at room temperature for 2 hours. The reaction solution was concentrated under reduced pressure, and the resulting residues were purified by thin layer chromatography with developing system B to obtain the title product **37c** (95 mg, yield: 92%).

MS m/z(ESI): 418.1 [M+1].

Step 3

Tert-butyl

methyl((3*S*)-1-(5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)piperidin-3-yl)carbamate **37d**

In accordance with the synthetic route in Example 1, the starting material **1c** in Step 2 was replaced with compound **37c**, to give the title compound **37d** (150 mg, yield: 71%).

MS m/z(ESI): 694.4 [M+1].

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Step 4

(3*S*)-*N*-Methyl-1-(5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)piperidin-3-amine **37e**

In accordance with the synthetic route in Example 1, the starting material **1f** in Step 3 was replaced with compound **37d**, to give the title compound **37e** (80 mg, yield: 93%).

Step 5

(*E*)-*N*,*N*-Dimethyl-4-(methyl((3*S*)-1-(5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)piperidin-3-yl)amino) but-2-enamide **37f**

In accordance with the synthetic route in Example 1, the starting material **1g** in Step 4 was replaced with compound **37e**, and the starting material **1h** was replaced with compound **5d**, to give the title compound **37f** (75 mg, yield: 79%).

Step 6

(*E*)-*N*,*N*-Dimethyl-4-(methyl((*S*)-1-(5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)piperidin-3-yl)amino)but-2-enamide **37**

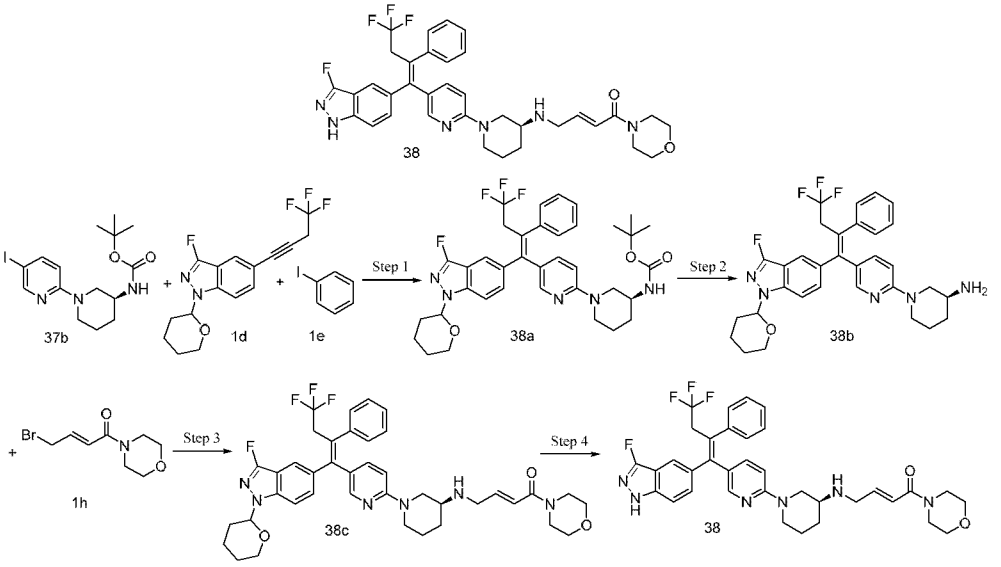
In accordance with the synthetic route in Example 1, the starting material **1i** in Step 5 was replaced with compound **37f**, to give the title compound **37** (22 mg, yield: 25%).

MS m/z(ESI): 621.2 [M+1].

^{1}H NMR (400 MHz, $CDCl_3$) 10.51 (s, 1H), 7.71 (s, 1H), 7.62 (s, 1H), 7.74-7.31 (m, 4H), 7.29-7.21 (m, 4H), 6.80 (s, 2H), 6.65 (dd, 1H), 4.71 (dd, 1H), 4.04 (d, 2H), 3.87 (d, 2H), 3.41 (d, 2H), 3.35-3.31 (m, 2H), 3.06 (d, 6H), 2.84 (s, 3H), 2.29 (d, 1H), 2.02-1.92 (m, 2H), 1.69 (d, 1H).

Example 38

(*E*)-1-Morpholino-4-(((*S*)-1-(5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)piperidin-3-yl)amino)but-2-en-1-one **38**



Step 1

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Tert-butyl ((3*S*)-1-(5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)piperidin-3-yl)carbamate **38a**

In accordance with the synthetic route in Example 1, the starting material **1c** in Step 2 was replaced with compound **37b**, to give the title compound **38a** (100 mg, yield: 80%).

MS m/z(ESI): 680.4 [M+1].

Step 2

(3*S*)-1-(5-((*Z*)-4,4,4-Trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)piperidin-3-amine **38b**

In accordance with the synthetic route in Example 1, the starting material **1f** in Step 3 was replaced with compound **38a**, to give the title compound **38b** (35 mg, yield: 82%).

Step 3

(*E*)-1-Morpholino-4-(((3*S*)-1-(5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)piperidin-3-yl)amino)but-2-en-1-one **38c**

In accordance with the synthetic route in Example 1, the starting material **1g** in Step 4 was replaced with compound **38b**, to give the title compound **38c** (75 mg, yield: 79%).

Step 4

(*E*)-1-Morpholino-4-(((*S*)-1-(5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)piperidin-3-yl)amino)but-2-en-1-one **38**

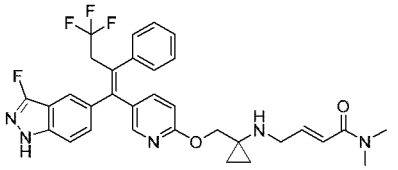
In accordance with the synthetic route in Example 1, the starting material **1i** in Step 5 was replaced with compound **38c**, to give the title compound **38** (9 mg, yield: 25%).

MS m/z(ESI): 649.3 [M+1].

^{1}H NMR (400 MHz, $CDCl_3$) 9.92 (s, 1H), 7.65 (s, 2H), 7.37 (d, 1H), 7.30-7.22 (m, 6H), 6.95-6.88 (m, 2H), 6.40 (d, 2H), 4.15 (d, 1H), 3.76-3.49 (m, 7H), 3.53-3.49 (m, 4H), 3.32-3.29 (m, 2H), 3.00-2.95 (m, 1H), 2.86-2.81 (m, 1H), 2.73-2.69 (m, 1H), 1.99-1.94 (m, 1H), 1.78-1.72 (m, 1H), 1.58-1.48 (m, 1H), 1.33-1.27 (m, 2H).

Example 39

(*E*)-*N*,*N*-Dimethyl-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-enamide **39**



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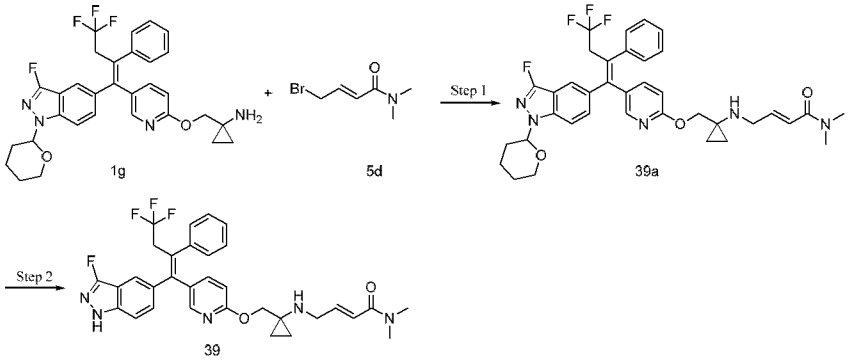


1g 5d 39a 39

Step 1

(*E*)-*N*,*N*-Dimethyl-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-enamide **39a**

In accordance with the synthetic route in Example 1, the starting material **1h** in Step 4 was replaced with compound **5d**, to give the title compound **39a** (53 mg, yield: 65%).

Step 2

(*E*)-*N*,*N*-Dimethyl-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-enamide **39**

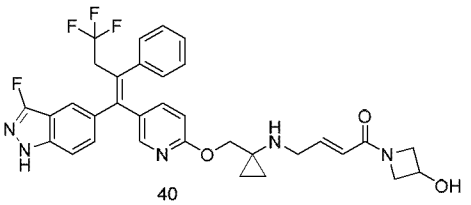
In accordance with the synthetic route in Example 1, the starting material **1i** in Step 5 was replaced with compound **39a**, to give the title compound **39** (24 mg, yield: 62%).

MS m/z(ESI): 593.9 [M+1].

^{1}H NMR (400 MHz, CD_3OD) 7.63 (d, 2H), 7.41-7.08 (m, 8H), 6.83-6.76 (m, 1H), 6.48-6.36 (m, 2H), 4.12 (s, 2H), 3.49-3.48 (m, 2H), 3.36-3.31 (m, 2H), 3.09 (s, 3H), 3.03 (s, 3H), 0.67-0.55 (m, 4H).

Example 40

(*E*)-1-(3-Hydroxyazetidin-1-yl)-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-en-1-one **40**



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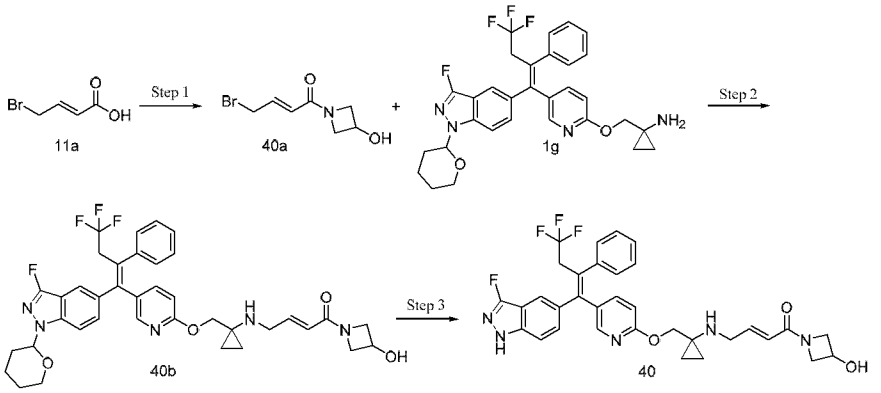

Step 1

(*E*)-4-Bromo-1-(3-hydroxyazetidin-1-yl)but-2-en-1-one **40a**

Compound **11a** (0.5 g, 3.0 mmol) was dissolved in dichloromethane (5 mL), followed by the addition of triethylamine (0.3 g, 3.3 mmol), 3-hydroxyazetidine (0.2 g, 3.3 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.6 g, 3.3 mmol) and 1-hydroxybenzotriazole (0.4 g, 3.3 mmol) at room temperature. The reaction solution was stirred for 12 hours. The reaction solution was cooled. Saturated sodium bicarbonate solution (15 mL) was added, and the solution was extracted with ethyl acetate (20 mL×2). The organic phases were combined, washed with saturated sodium chloride solution (20 mL×4), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the resulting residues were purified by thin layer chromatography with developing system A to obtain the title product **40a** (0.5 g, yield: 72%).

Step 2

(*E*)-1-(3-Hydroxyazetidin-1-yl)-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-en-1-one **40b**

In accordance with the synthetic route in Example 1, the starting material **1h** in Step 4 was replaced with compound **40a**, to give the title compound **40b** (43 mg, yield: 51%).

Step 3

(*E*)-1-(3-Hydroxyazetidin-1-yl)-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-en-1-one **40**

In accordance with the synthetic route in Example 1, the starting material **1i** in Step 5 was replaced with compound **40b**, to give the title compound **40** (27 mg, yield: 67%).

MS m/z(ESI): 622.1 [M+1].

^{1}H NMR (400 MHz, CD_3OD) 7.71-7.66 (m, 2H), 7.53-7.51 (m, 1H), 7.35-7.21 (m, 8H), 6.71-6.65 (m, 2H), 4.63-4.48 (m, 2H), 4.43 (s, 2H), 4.29-4.25 (m, 1H), 4.05-4.00 (m, 3H), 3.85-3.81 (m, 1H), 3.48-3.33 (m, 2H), 1.17-1.11 (m, 4H).

Example 41

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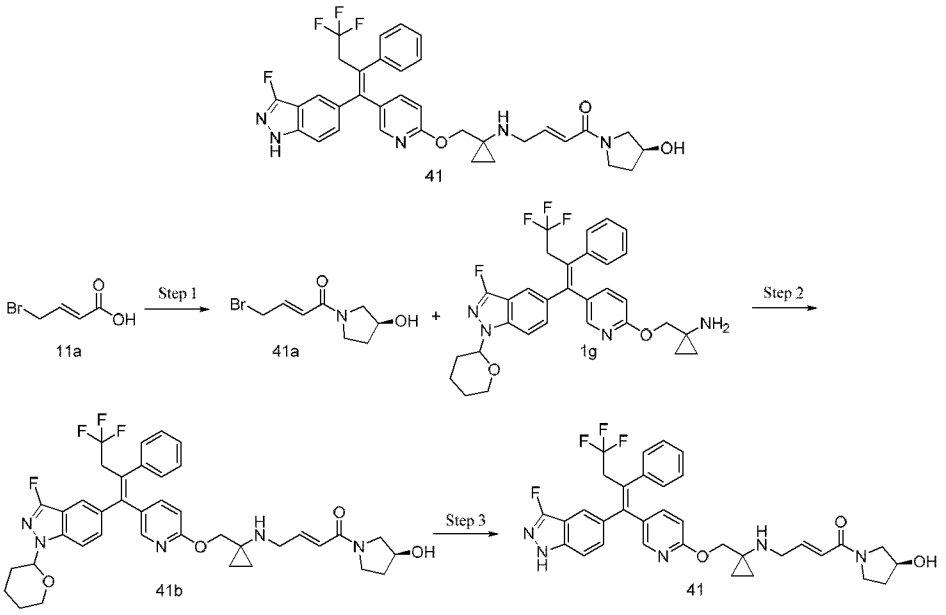
(*E*)-1-((*S*)-3-Hydroxypyrrolidin-1-yl)-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-en-1-one **41**



Step 1

(*S*,*E*)-4-Bromo-1-(3-hydroxypyrrolidin-1-yl)but-2-en-1-one **41a**

Compound **11a** (0.5 g, 3.0 mmol) was dissolved in dichloromethane (5 mL), followed by the addition of triethylamine (0.3 g, 3.3 mmol), (*S*)-3-hydroxypyrrolidine (0.2 g, 3.3 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.6 g, 3.3 mmol) and 1-hydroxybenzotriazole (0.4 g, 3.3 mmol) at room temperature. The reaction solution was stirred for 12 hours. The reaction solution was cooled. Saturated sodium bicarbonate solution (15 mL) was added, and the solution was extracted with ethyl acetate (20 mL×2). The organic phases were combined, washed with saturated sodium chloride solution (20 mL×4), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the resulting residues were purified by thin layer chromatography with developing system A to obtain the title product **41a** (0.5 g, yield: 73%).

Step 2

(*E*)-1-((*S*)-3-Hydroxypyrrolidin-1-yl)-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-en-1-one **41b**

In accordance with the synthetic route in Example 1, the starting material **1h** in Step 4 was replaced with compound **41a**, to give the title compound **41b** (41 mg, yield: 57%).

Step 3

(*E*)-1-((*S*)-3-Hydroxypyrrolidin-1-yl)-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-en-1

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-one **41**

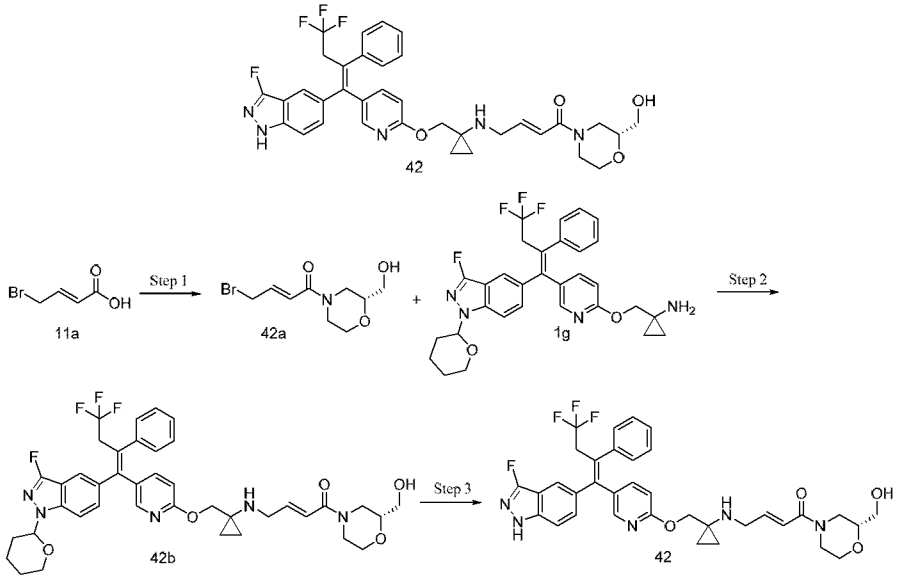
In accordance with the synthetic route in Example 1, the starting material **1i** in Step 5 was replaced with compound **41b**, to give the title compound **41** (37 mg, yield: 69%).

MS m/z(ESI): 636.2 [M+1].

^{1}H NMR (400 MHz, CD_3OD) 7.71-7.66 (m, 2H), 7.53-7.51 (m, 1H), 7.35-7.22 (m, 8H), 6.71-6.66 (m, 2H), 4.44 (s, 2H), 4.07-4.00 (m, 2H), 3.74-3.67 (m, 2H), 3.55-3.51 (m, 5H), 2.21-2.19 (m, 2H), 1.19-1.13 (m, 4H).

Example 42

(*E*)-1-((*R*)-2-(Hydroxymethyl)morpholino)-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-en-1-one **42**



Step 1

(*R*,*E*)-4-Bromo-1-(2-(hydroxymethyl)morpholino)but-2-en-1-one **42a**

Compound **11a** (0.5 g, 3.0 mmol) was dissolved in dichloromethane (5 mL), followed by the addition of triethylamine (0.3 g, 3.3 mmol), (*R*)-morpholin-2-ylmethanol (0.4 g, 3.3 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.6 g, 3.3 mmol) and 1-hydroxybenzotriazole (0.4 g, 3.3 mmol) at room temperature. The reaction solution was stirred for 12 hours. The reaction solution was cooled. Saturated sodium bicarbonate solution (15 mL) was added, and the solution was extracted with ethyl acetate (20 mL×2). The organic phases were combined, washed with saturated sodium chloride solution (20 mL×4), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the resulting residues were purified by thin layer chromatography with developing system A to obtain the title product **42a** (0.5 g, yield: 63%).

Step 2

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(*E*)-1-((*R*)-2-(Hydroxymethyl)morpholino)-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-en-1-one **42b**

In accordance with the synthetic route in Example 1, the starting material **1h** in Step 4 was replaced with compound **42a**, to give the title compound **42b** (31 mg, yield: 47%).

Step 3

(*E*)-1-((*R*)-2-(Hydroxymethyl)morpholino)-4-((1-(((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)methyl)cyclopropyl)amino)but-2-en-1-one **42**

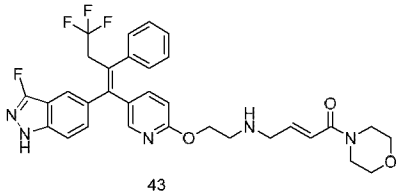
In accordance with the synthetic route in Example 1, the starting material **1i** in Step 5 was replaced with compound **42b**, to give the title compound **42** (27 mg, yield: 59%).

MS m/z(ESI): 666.1 [M+1].

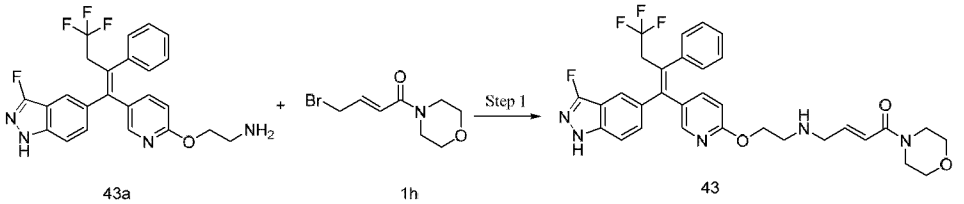
^{1}H NMR (400 MHz, CD_3OD) 7.67-7.65 (m, 2H), 7.52-7.50 (m, 1H), 7.31-7.26 (m, 7H), 6.81-6.77 (m, 1H), 6.61-6.59 (m, 2H), 4.45-4.42 (m, 1H), 4.30 (s, 2H), 3.99-3.93 (m, 2H), 3.61-3.42 (m, 9H), 3.03-3.00 (m, 1H), 0.81-0.72 (m, 4H).

Example 43

(*E*)-1-Morpholino-4-((2-((5-((*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)ethyl)amino)but-2-en-1-one **43**



43



43a 1h 43

In accordance with the synthetic route in Example 1, the starting material **1g** in Step 4 was replaced with **43a** (prepared according to the method disclosed in Example 1 on page 77 of the description of the patent application WO2018098305), to give the title compound **43** (21 mg, yield: 42%).

MS m/z(ESI): 610.2 [M+1].

^{1}H NMR (400 MHz, CD_3OD) 7.69-7.67 (m, 2H), 7.53-7.50 (m, 1H), 7.32-7.20 (m, 7H), 6.80-6.59 (m, 3H), 4.36-4.34 (m, 2H), 3.66-3.58 (m, 10H), 3.48-3.40 (m, 3H), 3.13-3.10 (m, 2H).

Biological Assay

The present disclosure will be further described with reference to the following test

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examples, but the examples should not be considered as limiting the scope of the present disclosure.

Test Example 1. Inhibitory effect of the compounds of the present disclosure on the activity of the estrogen receptor reporter gene

1. Experimental purpose

The purpose of the experiment is to determine the inhibitory effect of the compounds of the present disclosure on the activity of the estrogen receptor reporter gene, and evaluate the *in vitro* activity of the compounds according to IC_{50}.

2. Experimental method

MCF7 cells MCF7/ERE-luc (ATCC, HTB-22) expressing the luciferase reporter gene ERE-luc (synthesized by GENEWIZ, Inc.) controlled by the estrogen receptor response element were cultured in MEM (GE Healthcare, SH30024.01) medium containing 10% fetal bovine serum and 500 μg/ml G418. On the first day of the experiment, MCF7/ERE-luc cells were seeded in a 96-well plate with incomplete MEM medium containing 10% fetal bovine serum treated with activated charcoal (BioSun, BS-0004-500) at a density of 30,000 cells/well (100 μl of cell suspension per well), and the plate was incubated in a cell incubator at 37°C and 5% CO_2 overnight. On the second day, 10 μl of β-estradiol (SIGMA, E2758-250MG) solution formulated with the above incomplete medium or test compound solution of different concentrations formulated with the above incomplete medium was added to each well, wherein the final concentration of β-estradiol was 0.1 nM, and the final concentrations of the compound were nine concentration points obtained by a 10-fold gradient dilution starting from 10 μM, a blank control containing 0.5% DMSO was set, and the plate was incubated in a cell incubator at 37°C and 5% CO_2 for 20 hours. On the third day, the 96-well plate was taken out, and 100 μl of ONE-Glo™ Luciferase Assay system (Promega, E6110) was added to each well to determine the activity of luciferase. The plate was left to stand at at room temperature for 3 minutes until the cells were fully lysed, and the luminescence signal values were measured using a multi-label microplate reader (PerkinElmer, VICTOR 3). The IC_{50} values of the inhibitory activity of the compounds were calculated using Graphpad Prism software based on the concentrations and luminescence signal values of the compounds.

3. Experimental results

The inhibitory effect of the compounds of the present disclosure on the activity of the estrogen receptor reporter gene was determined by the above test. A graph of the chemiluminescence signal values versus the logarithmic concentrations of the compound was made using Graghpad Prism. The resulting IC_{50} values are shown in Table 1 below.

Table 1 IC_{50} of inhibitory activity of the compounds of the present disclosure on the activity of the estrogen receptor reporter gene

Example No.	IC_{50} (nM)

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1	1
2	3
3	4
4	4
5	3
6	0.5
7	38
8	3
9	2
10	8
11	3
12	2
13	3
14	2
15	3
16	5
17	6
18	6
19	4
22	24
23	13
24	9
25	3
26	3
27	7
28	4
29	3
30	3
31	6
32	28
33	3
34	3
35	4
36	5
37	8
38	5
39	2
40	2
41	3

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42	0.7

Conclusion: The compounds of the present disclosure have a significant inhibitory effect on the estrogen receptor reporter gene.

Test Example 2. Inhibitory effect of the compounds of the present disclosure on the proliferation of MCF7 cell

1. Experimental purpose

The purpose of the experiment is to determine the inhibitory activity of the compounds of the present disclosure on the proliferation of MCF7 cell, and evaluate the *in vitro* activity of the compounds according to IC_{50}.

2. Experimental method

MCF7 cells (ATCC, HTB-22) were cultured in MEM (GE Healthcare, SH30024.01) complete medium containing 10% fetal bovine serum. On the first day of the experiment, MCF7 cells were seeded in a 96-well plate with the complete medium at a density of 3,000 cells/well (100 μl of cell suspension per well), and the plate was incubated in a cell incubator at 37°C and 5% CO_2 overnight. On the second day, the medium in each well was replaced with 135 μl of MEM incomplete medium containing 2% fetal bovine serum. 15 μl of test compound solution of different concentrations formulated with the incomplete medium was added to each well, wherein the final concentrations of the compound were nine concentration points obtained by a 4-fold gradient dilution starting from 100 nM. A blank control containing 0.5% DMSO was set. The plate was incubated in a cell incubator at 37°C and 5% CO_2 for 144 hours. On the eighth day, the 96-well plate was taken out, and 150 μl of CellTiter-Glo® Luminescent Cell Viability Assay (Promega, G7573) was added to each well. The plate was left to stand at at room temperature for 10 minutes, and the luminescence signal values were measured using a multi-label microplate reader (PerkinElmer, VICTOR 3). The IC_{50} values of the inhibitory activity of the compounds were calculated based on the concentrations and luminescence signal values of the compounds using Graphpad Prism software.

3. Data analysis

A graph of the chemiluminescence signal values versus the logarithmic concentrations of the compound was made using Graghpad Prism to obtain the IC_{50} values of the compound. The results are shown in Table 2.

Table 2 IC_{50} of the inhibitory effect IC_{50} of the compounds of the present disclosure on the proliferation of MCF7 cell

Example No.	IC_{50} (nM)	Maximum inhibition (%)
1	0.5	100
2	0.6	112
3	2	101

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4	1.5	113
5	0.1	96
6	0.15	94
7	2	102
8	0.1	113
9	0.1	110
10	0.3	104
11	0.5	110
12	0.4	108
13	0.6	88
14	0.8	108
15	0.2	107
16	0.8	102
17	0.6	96
18	1	100
19	0.4	97
21	45	90
22	4	103
23	1	97
24	1	98
25	0.5	109
26	0.3	103
27	0.3	86
28	0.1	90
29	0.4	93
30	0.2	93
31	0.7	97
32	5	100
33	0.3	105
34	0.2	103
35	1.1	105
36	0.5	104
37	0.8	98
38	0.8	96
39	0.2	113
40	0.1	115
41	0.1	115
42	0.03	105

Conclusion: The compounds of the present disclosure have a significant inhibitory

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effect on the proliferation of MCF7 cell.

Test Example 3. Inhibitory effect of the compounds of the present disclosure on the proliferation of MCF7 cell expressing ERα mutant

1. Experimental purpose

The purpose of the experiment is to determine the inhibitory activity of the compounds of the present disclosure on the proliferation of MCF7 cell expressing ERα mutant.

2. Experimental method

Site-directed mutagenesis and cell line construction

The mutants ERα Y537S and ERα D538G of human estrogen receptor α (ERα) protein were obtained by site-directed mutagenesis using the cDNA of wild-type ESR1 gene (Accession No. NM000125) as a template according to double-primer PCR. The primer sequences used for mutagenesis are as follows (the nucleotides underlined are the sites of mutagenesis):

No.	Primer name	Primer sequence
SEQ ID NO：1	Y537S-F	AAG AAC GTG GTG CCC CTC TCT GAC CTG CTG CTG GAG ATG
SEQ ID NO：2	Y537S-R	CAT CTC CAG CAG CAG GTC AGA GAG GGG CAC CAC GTT CTT
SEQ ID NO：3	D538G-F	AAC GTG GTG CCC CTC TAT GGC CTG CTG CTG GAG ATG CTG
SEQ ID NO：4	D538G-R	CAG CAT CTC CAG CAG CAG GCC ATA GAG GGG CAC CAC GTT

The cDNA of mutant ESR1 was cloned into the target lentiviral vector pCDH-CMV-MCS-EF1-Puro (SBI, CD510B-1). The lentiviral plasmid with the mutant ESR1 gene sequence and the lentiviral packaging plasmids pVSV-G and pCMV-dR8.91 (SBI, LV500A-1) were transfected into HEK-293T cells (ATCC, CRL-3216) by Lipofectamine 3000 Transfection Reagent (ThermoFisher Scientific, Cat# L3000075). 48 hours after the transfection, the supernatant of the virus-containing DMEM high-glycemic medium (GE Healthcare, SH30243.01) containing 10% FBS was filtered, and ultracentrifuged to obtain the virus pellet. The virus pellet was resuspended in an appropriate amount of MEM medium (GE Healthcare, SH30024.01) containing 10% FBS, non-essential amino acids (SIGMA, M7145-100ML) and sodium pyruvate (SIGMA, S8636-100ML), and the resulting suspension was added to MCF7 cells (ATCC, HTB-22). Polybrene (SIGMA, H9268-5G) at a final concentration of 8 μg/ml was added, and the cells were incubated overnight. Two days after the transfection, 1 μg/ml puromycin (invitrogen, A11138-03) was added to the cell culture medium for resistance screening. After about two weeks, the MCF7 cell line capable of stably expressing ERαY537S and ERα D538G mutants was obtained.

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Cell proliferation inhibition test

MCF7 cells expressing ERα mutant were cultured in MEM (GE Healthcare, SH30024.01) complete medium containing 10% fetal bovine serum. On the first day of the experiment, the cells were seeded in a 96-well plate with the complete medium at a density of 3,000 cells/well (100 μl of cell suspension per well), and the plate was incubated in a cell incubator at 37°C and 5% CO_2 overnight. On the second day, the medium in each well was replaced with 135 μl of MEM incomplete medium containing 2% fetal bovine serum. 15 μl of test compound solution of different concentrations formulated with the incomplete medium was added to each well, wherein the final concentrations of the compound were nine concentration points obtained by a 4-fold gradient dilution starting from 100 nM. A blank control containing 0.5% DMSO was set. The plate was incubated in a cell incubator at 37°C and 5% CO_2 for 144 hours. On the eighth day, the 96-well plate was taken out, and 150 μl of CellTiter-Glo® Luminescent Cell Viability Assay (Promega, G7573) was added to each well. The plate was left to stand at at room temperature for 10 minutes, and the luminescence signal values were measured using a multi-label microplate reader (PerkinElmer, VICTOR 3). The IC_{50} values of the inhibitory activity of the compounds were calculated based on the concentrations and luminescence signal values of the compounds using Graphpad Prism software.

Table 3 IC_{50} of inhibitory effect of the compounds of the present disclosure on the proliferation of MCF7 cell expressing ERα mutant

Example No.	MCF7 D538G		MCF7 ERαY537S	
	IC_{50} (nM)	Maximum inhibition (%)	IC_{50} (nM)	Maximum inhibition (%)
1	2	100	3	100
2	2	104	3	107
3	9	96	9	93
4	10	105	11	101
5	0.2	98	0.3	107
6	0.5	98	1	102
7	12	84	12	88
8	1	103	2	107
9	0.8	108	2	94
10	4	104	7	86
11	1	100	2	107
12	1	96	2	104
13	3	107	5	104
14	3	107	6	97
15	1	105	2	102
16	2	110	4	88

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17	3	104	3	102
18	5	104	8	92
19	2	97	2	106
22	15	93	15	97
23	7	101	5	94
24	8	94	8	102
25	1	112	1	107
26	1	111	2	104
29	3	93	2	93
31	2	101	3	105
32	11	95	19	84
33	1	106	2	105
34	1	101	1	105
35	3	104	6	97
36	2	99	3	100
37	2	101	3	86
38	2	108	4	102
39	0.6	105	1	112
40	0.2	106	0.5	112
41	0.2	106	0.6	111
42	0.1	105	0.2	107

Conclusion: The compounds of the present disclosure have a significant inhibitory effect on the proliferation of MCF7 cell expressing ERα mutant.

Test Example 4. Determination of the inhibitory activity of the compounds of the present invention on $Na_V1.5$

The purpose of the experiment is to investigate the effect of the compounds on $Na_V1.5$ ion channel in an *ex-vivo* experiment. $Na_V1.5$ ion channel is stably expressed on HEK293 cell. After the $Na_V1.5$ current becomes stable, the $Na_V1.5$ currents before and after the administration of the compound are compared so as to obtain the effect of the compound on the $Na_V1.5$ ion channel.

1. Experimental materials and instruments

1) Patch clamp amplifier: patch clamp PC-505B (WARNER instruments)

2) Digital-to-analog converter: Digidata 1440A (Axon CNS)

3) Micro-manipulator: MP-225 (SUTTER instrument)

4) Inverted microscope: TL4 (Olympus)

5) Glass microelectrode puller: PC-10 (NARISHIGE)

6) Microelectrode glass capillary: B12024F (Wuhan Weitan Scientific Instrument Co., Ltd.)

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7) Dimethyl sulfoxide (DMSO): D2650 (Sigma-Aldrich)

2. Experimental procedures

2.1 Formulation of the compounds

Except for NaOH and KOH used for acid titration and base titration, all the agents used for formulating the extracellular fluid and intracellular fluid were purchased from Sigma (St. Louis, MO).

Extracellular fluid: NaCl, 137 mM; KCl, 4 mM; $CaCl_2$, 1.8 mM; $MgCl_2$, 1 mM; HEPES, 10; glucose, 10 mM; pH 7.4 (NaOH titration).

Intracellular fluid: aspartic acid, 140 mM; $MgCl_2$, 2 mM; EGTA, 11 mM; HEPES, 10 mM; pH 7.2 (CsOH titration).

The test compound was dissolved in dimethyl sulfoxide (DMSO) at a stock concentration of 9 mM. The stock solution of the test compound was dissolved in the extracellular fluid on the day of the test and formulated into the required concentration.

2.2 Test process of the manual patch clamp

1) The compound was formulated into solutions with specified concentrations. The solutions were added to the pipelines respectively in order from high to low concentration, and the pipelines were marked.

2) The cell was transferred to the perfusion tank, and perfused with the extracellular fluid. The intracellular fluid was stored in small batches in a -80°C refrigerator, and melted on the day of the experiment. The electrode was pulled with PC-10 (Narishige, Japan). Recording was carried out with the whole-cell patch clamp, and the noise was filtered at one-fifth of the sampling frequency.

3) All compounds were perfused with a perfusion system that uses its own gravity. Each concentration was tested in at least two cells. After the current stabilized (or after 5 minutes), the blocking effect of the compound was calculated by comparing the changes in the current before and after the administration of the compound.

4) The perfusion tank was cleaned. The perfusion tank was rinsed with the drug solutions in order from high to low concentration, and the rinse duration for each concentration of drug solution was 20 seconds. The perfusion tank was finally rinsed with the extracellular fluid for 1 mintue.

2.3 Test voltage equation (resting) and results

The cell was clamped at -80 mV. The cell was depolarized to Vhalf with a square wave lasting 8 milliseconds, hyperpolarized to -120 mV with a square wave lasting 20 milliseconds, and depolarized to -10 mV with a square wave lasting 20 milliseconds to obtain the $Na_V1.5$ current. This procedure was repeated every 15 seconds. The maximum current caused by the -10 mV square wave was measured. After the current became stable, the test compound was perfused. After the response became stable, the blocking intensity was calculated.

3. Data analysis

The data was stored in the computer system for analysis. Data collection and analysis were carried out by pCLAMP 10 (Molecular Devices, Union City, CA). Stable

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current means that the absolute average value of the peak current of four consecutive scans exceeds 200 pA and the CV value is less than 10%, or the average value of the peak current of four consecutive scans is between 200 pA and 50 pA and the CV value is less than 30%. The average value of the last four current peaks after the current stabilized was used to calculate the effect of the compound at the concentration.

The inhibitory activity of the compounds of the present invention on $Na_V1.5$ was determined by the above test, and the resulting IC_{50} values are shown in Table 4 below.

Table 4 IC_{50} of the compounds of the present invention on inhibiting the $Na_V1.5$ channel activity

Example No.	IC_{50} (uM)
1	>10
39	8.2
40	11.5
41	5.3
43	2.7

Conclusion: The inhibitory effect of compounds 1 and 39 to 41 of the present invention on $Na_V1.5$ channel is weaker than that of the compound of Example 43. It can be seen that the risk of cardiotoxicity of these compounds is significantly lower than that of the compound of Example 43.

Pharmacokinetics Evaluation

Test Example 5. Pharmacokinetics assay of the compounds of the Examples of the present disclosure in BALB/C nude mice

1. Abstract

BALB/C nude mice were used as test animals. The drug concentration in plasma at different time points was determined by LC/MS/MS method after intragastric administration of the compounds of the present disclosure to BALB/C nude mice. The pharmacokinetic behavior and characteristics of the compounds of the present disclosure was studied and evaluated in BALB/C nude mice.

2. Test protocol

2.1 Test compounds and instruments

Compounds of Example 1, Example 14, Example 15 and Examples 39 to 42.

LC/MS/MS instruments: LC/MS/MS API4000 triple quadrupole tandem mass spectrometer (No.3, Applied Biosystems, USA), Shimadzu LC-30AD ultra high performance liquid chromatography system (Shimadzu, Japan).

2.2 Test animals

Sixty-three BALB/C nude mice (female, equally divided into seven groups, nine mice per group) were purchased from Jiesijie Laboratory Animal Co., LTD. (Certificate No.: SCXK(Shanghai)2013-0006).

2.3 Preparation of the test compound

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For the compound of Example 14, an appropriate amount of the compound was weighed, followed by the addition of 5% of DMSO, 5% of tween 80 and 90% of normal saline by volume to obtain a colorless, clear and transparent solution (0.1 mg/mL).

For the compounds of Examples 1, 15 and 39 to 42, an appropriate amount of the compound was weighed, followed by the addition of 9% of PEG400, 0.5% of tween 80 and 90.5% of 0.5%CMC-Na by volume to obtain a colorless, clear and transparent solution (1.5 mg/mL).

2.4 Administration

After an overnight fast, the test compounds were intragastrically administered at an administration volume of 0.2ml/10g respectively. The administration dose of the compound of Example 14 was 2 mg/kg, and the administration dose of the compounds of Examples 1, 15 and 39 to 42 was 30 mg/kg.

3. Process

After an overnight fast, sixty-three female BALB/C nude mice were intragastrically administered the test compounds.

For the compounds of Examples 1 and 39, 0.1 ml of blood was taken at 0.25, 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, 11.0 and 24.0 hours after the administration (from three animals per time point). The samples were stored in blood collection tubes treated with heparin (Sinopharm Chemical Reagent Co., Ltd.), and centrifuged for 10 minutes at 3500 rpm to separate the blood plasma. The blood plasma was stored at -20°C. The content of the test compound in the plasma of nude mouse after intragastrical administration of the test compound was determined. 25 μL of nude mouse plasma at each time point after the administration was taken, followed by the addition of 30 μL of the internal standard camptothecin solution (National Institutes for Food and Drug Control) (100 ng/mL) and 225 μL of acetonitrile. The resulting solution was vortex-mixed for 5 minutes, and centrifuged for 10 minutes (3700 to 4000 rpm). 0.1 to 0.5 μL of the supernatant was taken from the plasma samples for LC/MS/MS analysis.

For the compounds of Examples 14 and 15, 0.1 ml of blood was taken at 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, 11.0 and 24.0 hours after the administration (from three animals per time point). The samples were stored in heparinized tubes, and centrifuged for 10 minutes at 3500 rpm to separate the blood plasma. The blood plasma was stored at -20°C. The content of the test compound in the plasma of nude mouse after intragastrical administration of the test compound was determined. 25 μL of nude mouse plasma at each time point after the administration was taken, followed by the addition of 30 μL of the internal standard camptothecin solution (100 ng/mL) and 200 μL of acetonitrile. The resulting solution was vortex-mixed for 5 minutes, and centrifuged for 10 minutes (3700 rpm). 0.25 to 1 μL of the supernatant was taken from the plasma samples for LC/MS/MS analysis.

For the compounds of Examples 40 to 42, 0.1 ml of blood was taken at 0.25, 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, 11.0 and 24.0 hours after the administration (from three animals per time point). The samples were stored in tubes anticoagulated with EDTA-K2

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(Shanghai Titan Scientific Co., Ltd.), and centrifuged for 1 minute at 10000 rpm and 4°C. The blood plasma was separated within one hour, and stored at -20°C. The process from blood collection to centrifugation was operated under an ice bath condition. The content of the test compound in the plasma of nude mouse after intragastrical administration of the test compound was determined. 25 μL of nude mouse plasma at each time point after the administration was taken, followed by the addition of 50 μL of the internal standard camptothecin solution (100 ng/mL) and 200 μL of acetonitrile. The resulting solution was vortex-mixed for 5 minutes, and centrifuged for 10 minutes (3700 rpm). 1 μL of the supernatant was taken from the plasma samples for LC/MS/MS analysis.

4. Results of pharmacokinetic parameters in BALB/C nude mice

The pharmacokinetic parameters of the compounds of the Examples of the present disclosure are shown in Table 5 below.

Table 5 Pharmacokinetic parameters of the compounds of the Examples of the present disclosure in BALB/C nude mice

Example No.	Compound dose	Plasma concentration	Area under curve	Half-life	Residence time	Clearance rate	Apparent volume of distribution	Bioavailability
		Cmax (ng/mL)	AUC (ng/mL*h)	$t_{1/2}$ (h)	MRT (h)	CL/F (ml/min/kg)	Vz/F (ml/kg)	F(%)
1	30 mg/kg	4276	9849	1.99	1.6	50.8	8760	-
14	2 mg/kg	87	205	1.01	1.9	163	14214	24.8
15	30 mg/kg	4573	6564	0.89	1.41	76	5871	-
39	30 mg/kg	6597	16486	0.94	1.57	30.3	2468	-
40	30 mg/kg	3565	11867	1.26	2.3	42.1	4587	-
41	30 mg/kg	2889	5019	1.67	2.26	99.6	14392	-
42	30 mg/kg	2567	4512	1.2	1.56	111	11502	-

"-" refers to not determined.

Conclusion: The compounds of the present disclosure are well absorbed, and have a significant pharmacokinetic absorption effect.

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Test Example 6. Biological evaluation of the covalent modification of estrogen receptor ERα wild-type and ERα Y537S mutant-type

1. Experimental purpose

The purpose of the experiment is to determine the covalent modification effect of the compounds of the present disclosure on estrogen receptor ERα wild-type and ERα Y537S mutant-type.

2. Experimental method

The ligand binding domain (LBD, aa296-554) of estrogen receptor ERα wild-type and ERα Y537S mutant-type was expressed in *E. coli* and purified. 2 μM ERα wild-type or ERα Y537S mutant-type protein and 10 μM compound were added to a buffer solution containing 50 mM Tris-HCl, pH7.5, 150 mM NaCl, 1 mM TCEP and 5% glycerol and mixed well. The solution was incubated at 4°C for 24 hours, followed by high-resolution mass spectrometry (Agilent Technologies, Agilent Q-tof 6530) assay. Alternatively, 1 μM ERα wild-type or ERα Y537S mutant-type protein and 3 μM compound were added to a buffer solution containing 50 mM Tris-HCl, pH7.5, 150 mM NaCl, 1 mM TCEP and 5% glycerol and mixed well. The solution was incubated at 37°C for 15 minutes, followed by high-resolution mass spectrometry assay. In the mass spectrometry assay results, the peak whose molecular weight is the sum of the molecular weight of the protein and compound is the product of covalent modification. The percentage of covalent modification is obtained by calculating the ratio of unbound protein to total protein. The results are shown in Table 6 below.

Table 6 Percentage of covalent modification of the estrogen receptor ERα wild-type and ERα Y537S mutant-type after 24 hours of covalent modification by the compounds of the present disclosure

Example No.	Covalent modification effect on the estrogen receptor ERα wild-type (%)	Covalent modification effect on the estrogen receptor ERα Y537S mutant-type (%)
1	97	97
2	87	90
8	96	97
12	85	83
14	93	94
15	95	96
18	98	99
19	94	97
22	95	100
23	95	99
24	90	99
31	80	83
32	94	95
38	95	96
39	97	98

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40	96	98
41	93	95
42	-	97

Conclusion: The tested compounds have excellent covalent modification effect on the ERα wild-type or ERα Y537S mutant-type protein.

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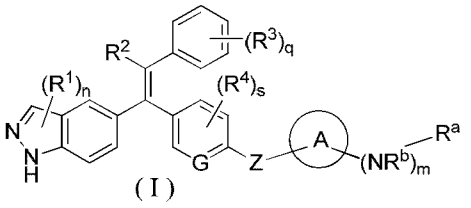
WHAT IS CLAIMED IS:

1. A compound of formula (I) or a tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or a pharmaceutically acceptable salt thereof:



(I)

wherein:

G is CH or N;

Z is selected from the group consisting of a bond, CR^5R^6, -O-$(CH_2)_t$- and -NR^7-$(CH_2)_t$-;

ring A is selected from the group consisting of cycloalkyl and heterocyclyl;

R^a is selected from the group consisting of -CH_2CH=$CHC(O)NR^8R^9$, -$C(O)CH$=$CR^{10}R^{11}$ and -$C(O)C$≡CR^{12};

R^b is selected from the group consisting of hydrogen atom and alkyl;

each R^1 is identical or different and each is independently selected from the group consisting of hydrogen atom, halogen, alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R^2 is selected from the group consisting of hydrogen atom, halogen, alkyl, haloalkyl, alkoxy, amino, cyano, nitro, carboxy, formyl, hydroxy, hydroxyalkyl, cycloalkyl, aryl and heteroaryl;

each R^3 is identical or different and each is independently selected from the group consisting of hydrogen atom, halogen, alkyl, haloalkyl, alkoxy, cyano, amino, nitro, carboxy, formyl, hydroxy, hydroxyalkyl, $NR^{13}C(O)R^{14}$, $C(O)NR^{13}R^{14}$, SO_2R^{15}, cycloalkyl, heterocyclyl, aryl and heteroaryl;

each R^4 is identical or different and each is independently selected from the group consisting of hydrogen atom, halogen, alkyl, haloalkyl, alkoxy, cyano, amino, nitro, carboxy, formyl, hydroxy, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R^5 and R^6 are identical or different and are each independently selected from the group consisting of hydrogen atom, halogen, alkyl, haloalkyl, alkoxy, cyano, amino, nitro, carboxy, formyl, hydroxy, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R^7 is selected from the group consisting of hydrogen atom, alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R^8 and R^9 are identical or different and are each independently selected from the group consisting of hydrogen atom, alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

or, R^8 and R^9 together with the nitrogen atom to which they are attached form a heterocyclyl, wherein the heterocyclyl optionally contains in addition to one nitrogen

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atom, one to two identical or different heteroatoms selected from the group consisting of N, O and S , and the heterocyclyl is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halogen, amino, cyano, nitro, hydroxy, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R^{10} and R^{11} are identical or different and are each independently selected from the group consisting of hydrogen atom, halogen, alkyl, haloalkyl, alkoxy, cyano, amino, nitro, carboxy, formyl, hydroxy, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R^{12} is selected from the group consisting of hydrogen atom, alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R^{13} and R^{14} are identical or different and are each independently selected from the group consisting of hydrogen atom, halogen, alkyl, haloalkyl, alkoxy, cyano, amino, nitro, carboxy, formyl, hydroxy, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R^{15} is selected from the group consisting of hydrogen atom, alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

m is 0 or 1;

n is 0, 1, 2 or 3;

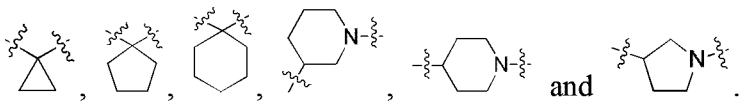
q is 0, 1, 2, 3, 4 or 5;

s is 0, 1, 2 or 3; and

t is 0, 1, 2, 3, 4, 5 or 6.

2. The compound of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to claim 1, wherein ring A is selected from the group consisting of C_3-C_6 cycloalkyl and 3 to 6 membered heterocyclyl; the heterocyclyl contains one to three heteroatoms selected from the group consisting of N, O and S; preferably, ring A is selected from the group consisting of cyclopropyl, cyclopentyl, cyclohexyl, tetrahydropyrrolyl and piperidinyl.

3. The compound of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein ring A is selected from the group consisting of



and .

4. The compound of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to claim 1 or 2, being a compound of formula (II) or a tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or a pharmaceutically

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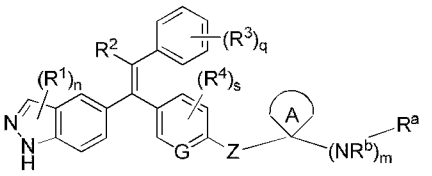
acceptable salt thereof:

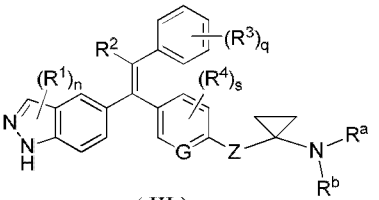


(II)

wherein

ring A, G, Z, R^1, R^2, R^3, R^4, R^a, R^b, n, m, s and q are as defined in claim 1.

5. The compound of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 4, being a compound of formula (III) or a tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or a pharmaceutically acceptable salt thereof:



(III)

wherein: G, Z, R^1, R^2, R^3, R^4, R^a, R^b, n, s and q are as defined in claim 1.

6. The compound of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 5, wherein G is an N atom.

7. The compound of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 6, wherein R^1 is selected from the group consisting of halogen and hydrogen atom.

8. The compound of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 7, wherein R^2 is a haloalkyl, preferably C_1-C_6 haloalkyl, and more preferably -CH_2CF_3.

9. The compound of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 8, wherein R^3 is selected from the group consisting of hydrogen atom, cyano, halogen, alkyl, haloalkyl, $NR^{13}C(O)R^{14}$, $C(O)NR^{13}R^{14}$ and SO_2R^{15}; R^{13} and R^{14} are identical or different and are each independently selected from

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the group consisting of hydrogen atom and alkyl; and R^{15} is selected from the group consisting of hydrogen atom and alkyl.

10. The compound of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 9, wherein each R^4 is identical or different and each is independently selected from the group consisting of hydrogen atom, halogen, alkyl and alkoxy, and preferably hydrogen atom.

11. The compound of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 10, wherein Z is selected from the group consisting of a bond, -O-, -O-CH_2- and -NH-.

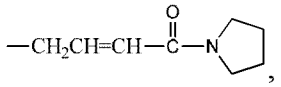
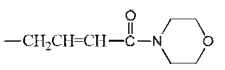
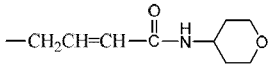
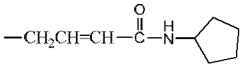
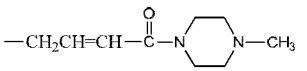
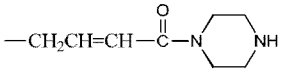
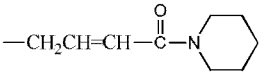
12. The compound of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 11, wherein R^a is selected from the group consisting of -CH_2CH=$CHC(O)NR^8R^9$, -$C(O)CH$=$CR^{10}R^{11}$ and -$C(O)C$≡CR^{12};

R^8 and R^9 are identical or different and are each independently selected from the group consisting of hydrogen atom, alkyl, cycloalkyl and heterocyclyl;

or, R^8 and R^9 together with the nitrogen atom to which they are attached form a heterocyclyl, wherein the heterocyclyl optionally contains in addition to one nitrogen atom, one to two identical or different heteroatoms selected from the group consisting of N, O and S , and the heterocyclyl is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halogen, amino, cyano, nitro, hydroxy, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R^{10} and R^{11} are identical or different and are each independently selected from the group consisting of hydrogen atom and alkyl;

R^{12} is selected from the group consisting of hydrogen atom and alkyl.

13. The compound of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 12, wherein R^a is selected from the group consisting of -CH_2CH=$CHC(O)N(CH_3)_2$, -CH_2CH=$CHC(O)NH(CH_3)$, -CH_2CH=$CHC(O)NHC(CH_3)_3$, -$C(O)CH$=CH_2, -$C(O)C$≡CCH_3,  ,  ,  ,  ,  ,  ,  ,

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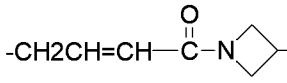
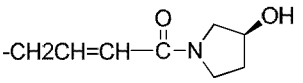
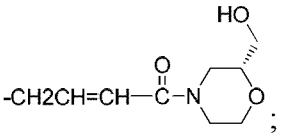

, 
and 
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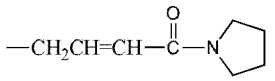
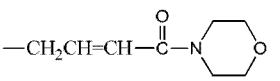
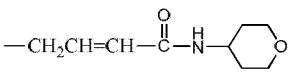
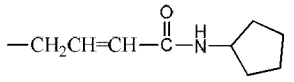
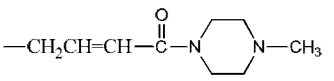
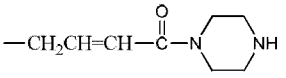
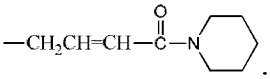
preferably, R^a is selected from the group consisting of $-CH_2CH=CHC(O)N(CH_3)_2$, $-CH_2CH=CHC(O)NH(CH_3)$, $-CH_2CH=CHC(O)NHC(CH_3)_3$, $-C(O)CH=CH_2$, $-C(O)C\equiv CCH_3$, 
, 
, 
, 
, 
, 
and 
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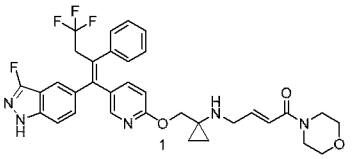
14. The compound of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 13, selected from the group consisting of: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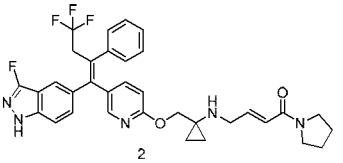
, 
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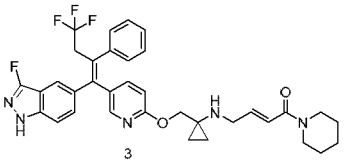
, 
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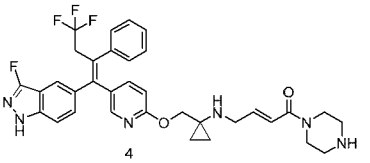
, 
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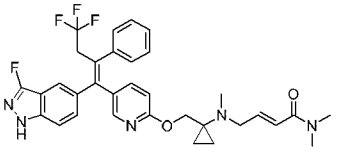
, 
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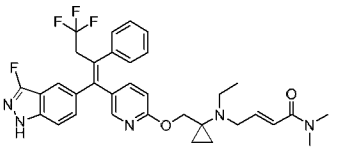
, 
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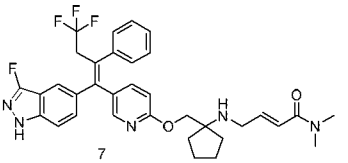
, 
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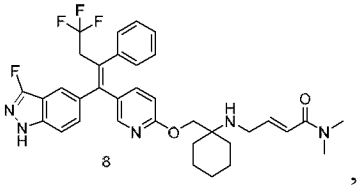
, 
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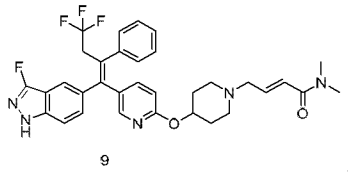
, 
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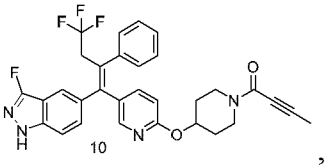
, 
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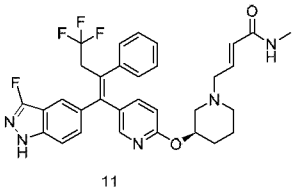
, 
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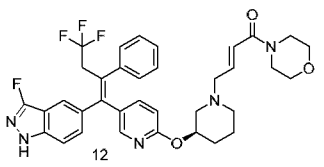
, 
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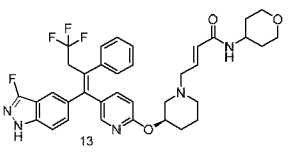
, 
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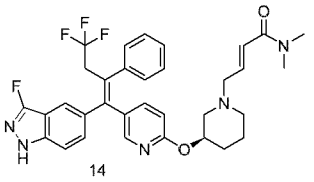
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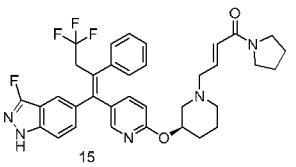
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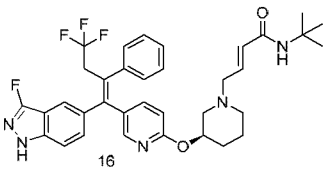
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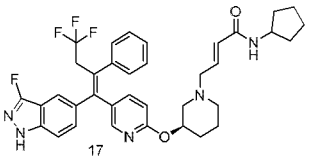
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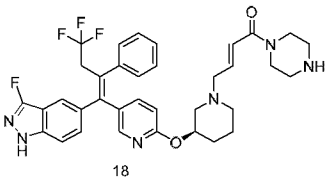
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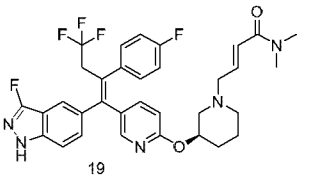
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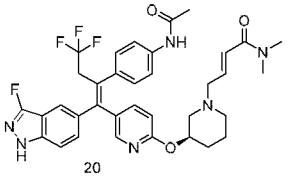
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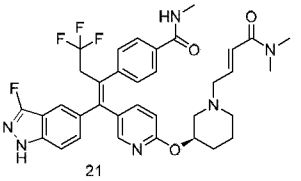
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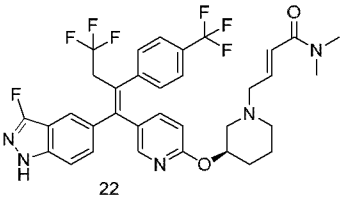
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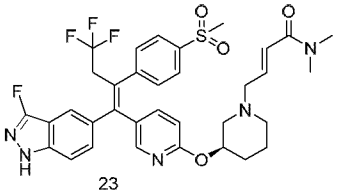
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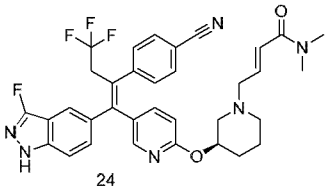
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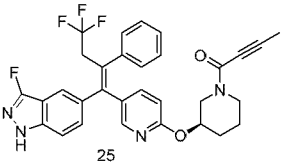
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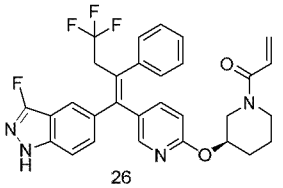
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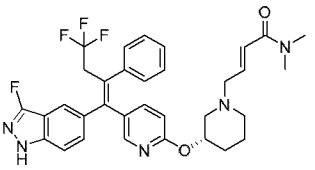
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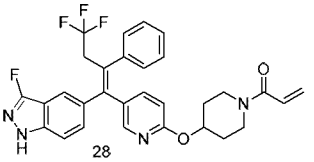
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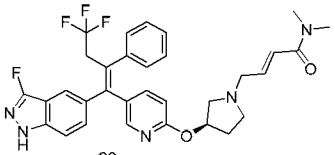
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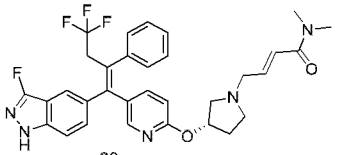
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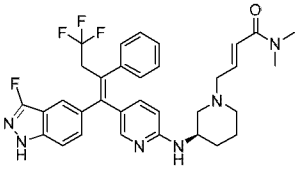
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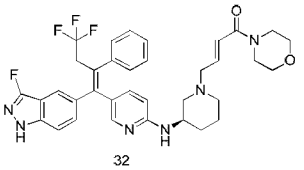
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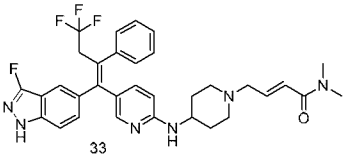
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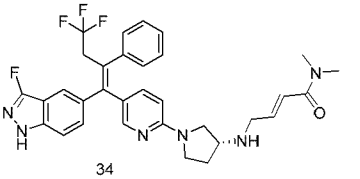
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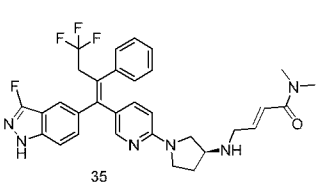
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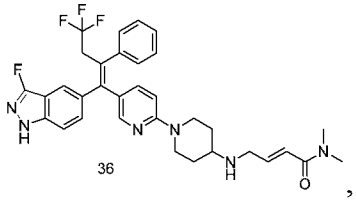
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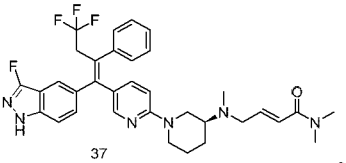
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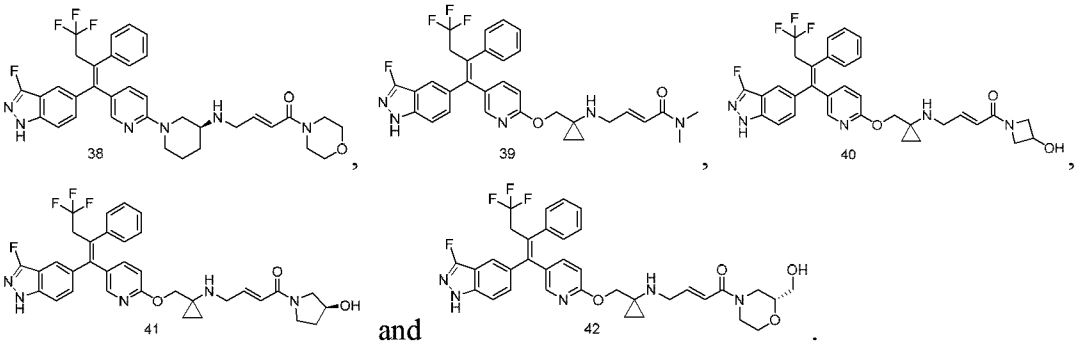
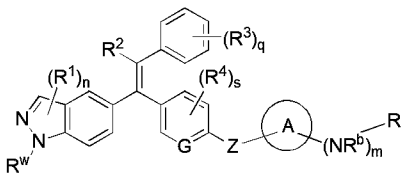


and .

15. A compound of formula (IA) or a tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or a pharmaceutically acceptable salt thereof,



(IA)

wherein:

R^w is an amino protecting group, and preferably tetrahydropyranyl;

R is selected from the group consisting of $-CH_2CH=CHC(O)NR^8R^9$, $-C(O)CH=CR^{10}R^{11}$ and $-C(O)C\equiv CR^{12}$;

R^8 and R^9 are identical or different and are each independently selected from the group consisting of hydrogen atom, alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

or, R^8 and R^9 together with the nitrogen atom to which they are attached form a heterocyclyl, wherein the heterocyclyl optionally contains in addition to one nitrogen atom, one to two identical or different heteroatoms selected from the group consisting of N, O and S , and the heterocyclyl is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halogen, amino, cyano, nitro, hydroxy, hydroxyalkyl, $-COOR^{16}$-, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R^{10} and R^{11} are identical or different and are each independently selected from the group consisting of hydrogen atom, halogen, alkyl, haloalkyl, alkoxy, cyano, amino, nitro, carboxy, formyl, hydroxy, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R^{12} is selected from the group consisting of hydrogen atom, alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R^{16} is selected from the group consisting of hydrogen atom, alkyl, haloalkyl and hydroxyalkyl;

ring A, G, Z, R^1, R^2, R^3, R^4, R^b, n, m, s and q are as defined in claim 1.

16. The compound of formula (IA) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable

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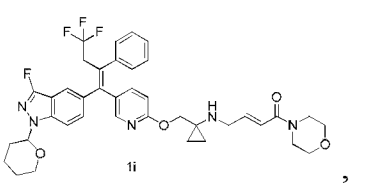
salt thereof according to claim 15, selected from the group consisting of: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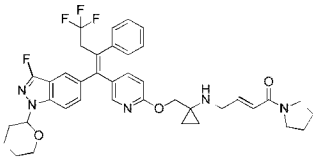
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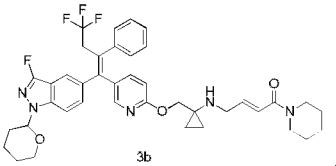
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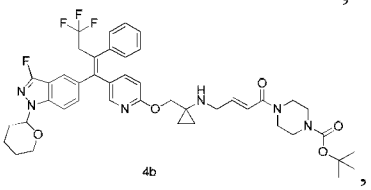
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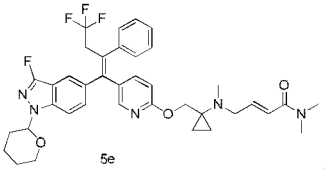
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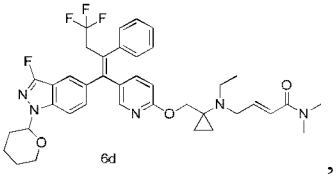
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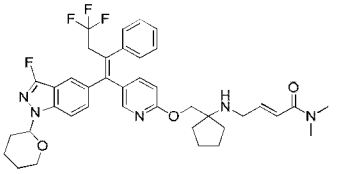
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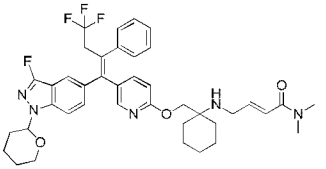
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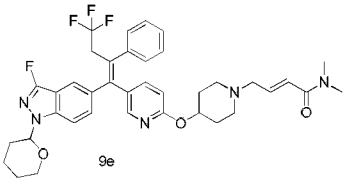
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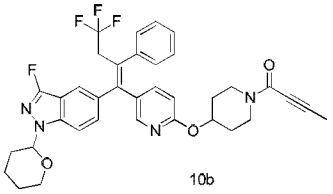
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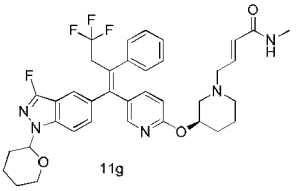
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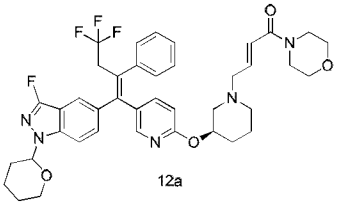
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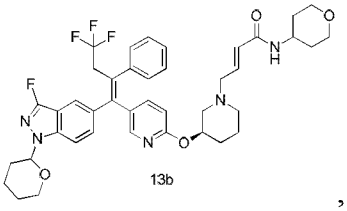
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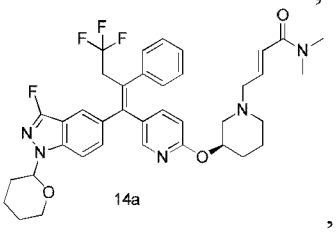
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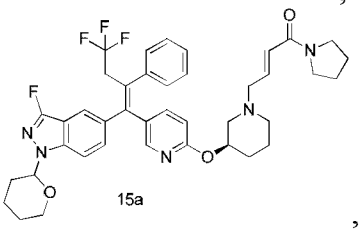
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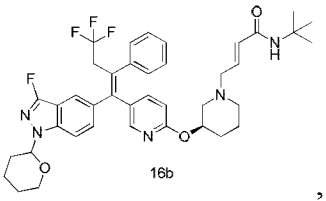
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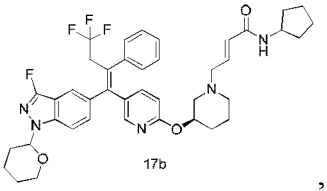
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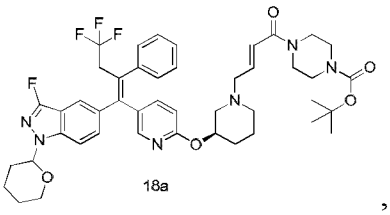
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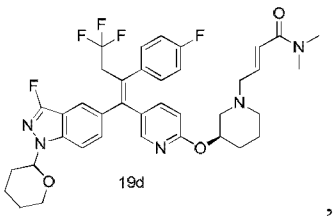
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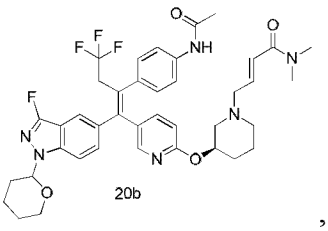
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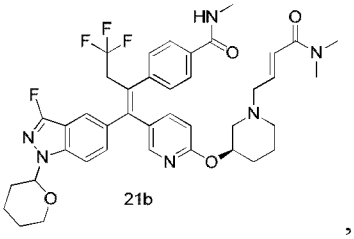
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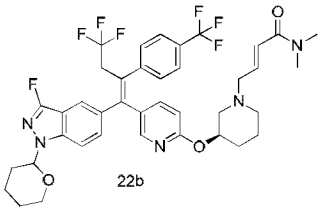
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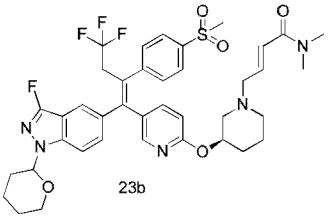
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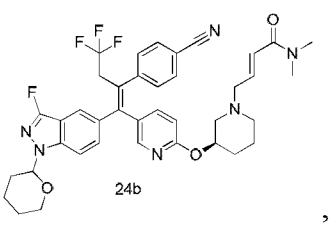
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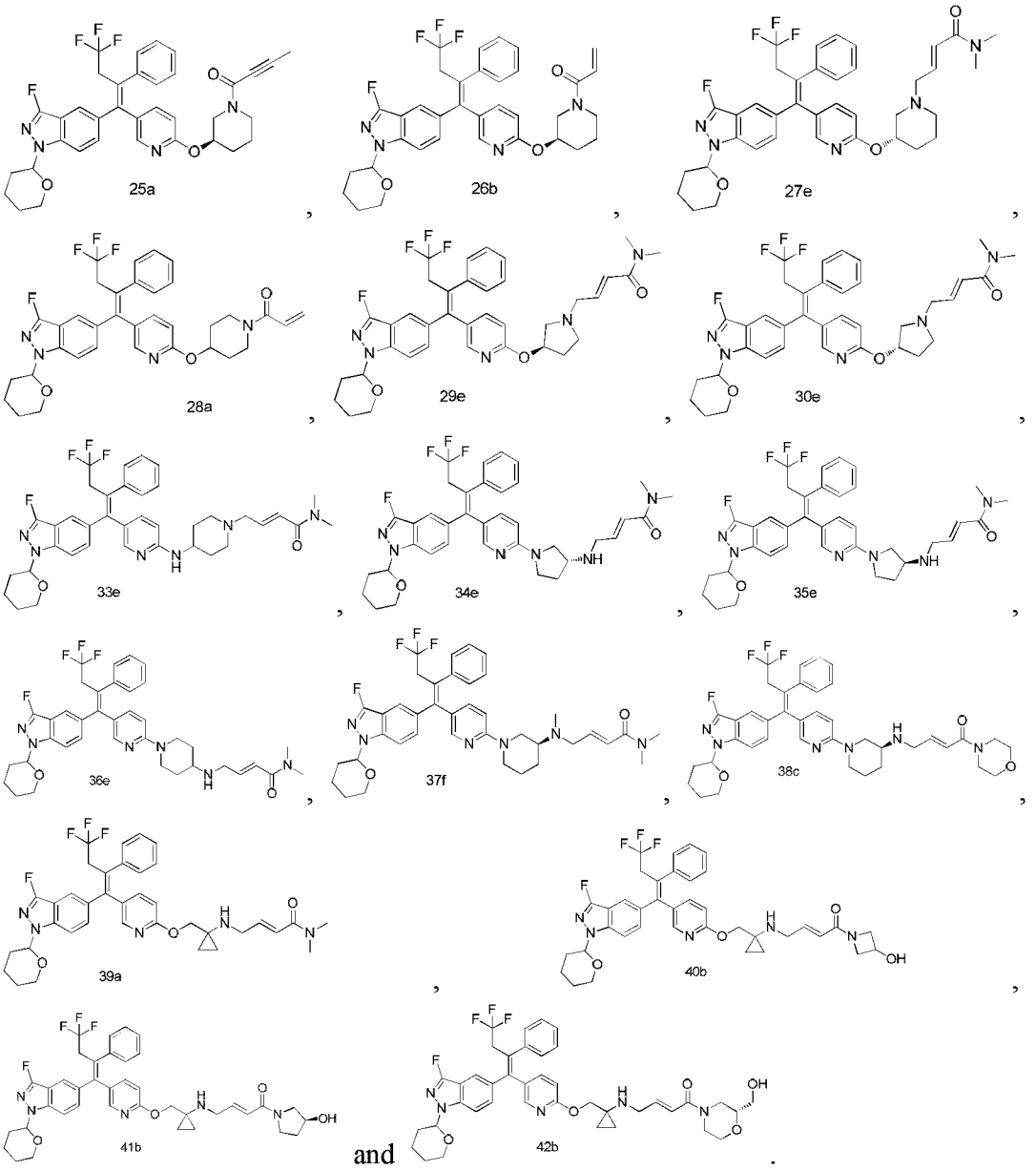
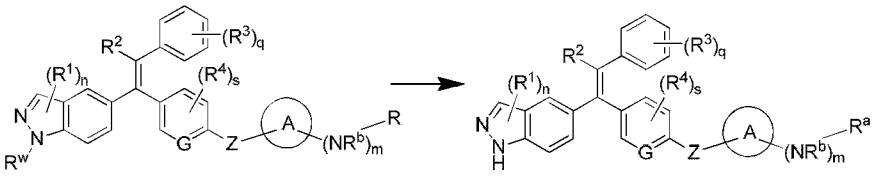


and .

17. A method for preparing the compound of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 14, comprising a step of:



(IA) (I)

subjecting the compound of formula (IA) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof to a deprotection reaction under an acidic condition to obtain the compound

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of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof;

wherein:

R^w is an amino protecting group, and preferably tetrahydropyranyl;

R is as defined in claim 15;

ring A, G, Z, R^1, R^2, R^3, R^4, R^a , R^b, n, m, s and q are as defined in claim 1.

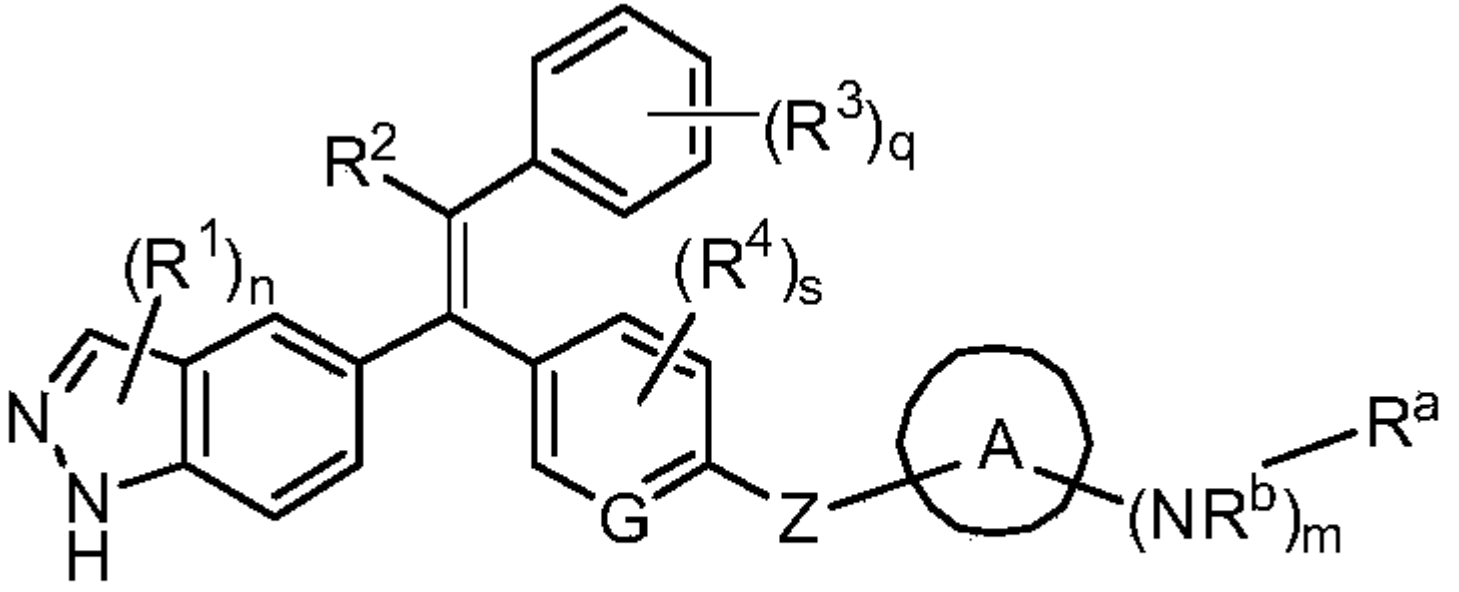
18. A pharmaceutical composition, comprising a therapeutically effective amount of the compound of formula (I) or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 14, and one or more pharmaceutically acceptable carriers, diluents or excipients.

19. Use of the compound of formula (I), or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 14, or the pharmaceutical composition according to claim 18 in the preparation of an estrogen receptor modulator.

20. Use of the compound of formula (I), or the tautomer, mesomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 14, or the pharmaceutical composition according to claim 18 in the preparation of a medicament for preventing and/or treating estrogen receptor-mediated or estrogen receptor-dependent disease or disorder.

21. The use according to claim 20, wherein the estrogen receptor-mediated or estrogen receptor-dependent disease or disorder is a cancer, preferably breast cancer, ovarian cancer, endometrial cancer, prostate cancer or uterine cancer, and more preferably breast cancer.

Date reçue / Date received 2021-12-14



(I)