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(71) Applicant: **DIZAL (JIANGSU) PHARMACEUTICAL CO., LTD.** [CN/CN]; No.199 Liangjing Road, Zhangjiang Hi-Tech Park, Shanghai 201203 (CN).

(72) Inventors: **ZHOU, Quan**; No.199 Liangjing Road, Zhangjiang Hi-Tech Park, Shanghai 201203 (CN). **ZOU, Hao**; No.199 Liangjing Road, Zhangjiang Hi-Tech Park, Shanghai 201203 (CN). **ZHU, Wei**; No.199 Liangjing Road, Zhangjiang Hi-Tech Park, Shanghai 201203 (CN). **SHEN, Changmao**; No.199 Liangjing Road, Zhangjiang Hi-Tech Park, Shanghai 201203 (CN). **WANG, Rumin**; No.199 Liangjing Road, Zhangjiang Hi-Tech Park, Shanghai 201203 (CN). **LIU, Wengeng**; No.199 Liangjing Road, Zhangjiang Hi-Tech Park, Shanghai 201203 (CN). **CHEN, Xiang**; No.199 Liangjing Road, Zhangjiang Hi-Tech Park, Shanghai 201203 (CN). **TSUI, Honchung**; No.199 Liangjing Road, Zhangjiang Hi-Tech Park, Shanghai 201203 (CN). **YANG, Zhenfan**; No.199 Liangjing Road, Zhangjiang Hi-Tech Park, Shanghai 201203 (CN). **ZHANG, Xiaolin**; No.199 Liangjing Road, Zhangjiang Hi-Tech Park, Shanghai 201203 (CN).

(74) Agent: **JUN HE LAW OFFICES**; 20/F, China Resources Building 8 Jianguomenbei Avenue, Beijing 100005 (CN).

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(54) Title: SELECTIVE ESTROGEN RECEPTOR DOWNREGULATORS AND USES THEREOF

(57) Abstract: The invention relates to novel tetrahydroisoquinoline compounds that are selective estrogen receptor downregulators (SERDs). The present invention also relates to pharmaceutical compositions comprising one or more of the compounds as an active ingredient, and to the use of the compounds in the treatment of estrogen receptor (ER) mediated or dependent diseases or conditions, for example cancer such as breast cancer.

SELECTIVE ESTROGEN RECEPTOR DOWNREGULATORS AND USES THEREOF

FIELD OF THE DISCLOSURE

The present invention relates to novel tetrahydroisoquinoline compounds that are selective estrogen receptor downregulators (SERDs). The present invention also relates to pharmaceutical compositions comprising one or more of the compounds as an active ingredient, and to the use of the compounds in the treatment of estrogen receptor (ER) mediated or dependent diseases or conditions, for example cancer such as breast cancer.

BACKGROUND

The ER is a ligand-activated transcriptional regulatory protein that mediates induction of a variety of biological effects through its interaction with estrogens (e.g. endogeneous estrogens, such as estrone, estradiol, estriol, and estetrol; or synthetic estrogens, such as, ethinylestradiol, diethylstilbestrol etc.). ER has been found to have two isoforms, ER-α (alpha) and ER-β (beta). Both receptors are implicated in a number of diseases or conditions, such as cancer (e.g. breast cancer, ovarian cancer, endometrial cancer, uterine cancer, lung cancer, hepatocellular carcinoma, adrenocortical carcinoma, pancreatic cancer, bladder cancer, or gastric cancer etc.) as well as other diseases or conditions (e.g. menopause, obesity, and osteoporosis).

A large number of structurally distinct compounds have an effect at the ER. These can be divided into two different classes depending on their functional effects, the selective estrogen receptor modulators (SERMs) which are competitive binder of estrogens but possesses estrogenic or antiestrogenic activity in a tissue- and/or cell- selective manner; and the selective estrogen receptor degraders or downregulators (SERDs) which selectively bind to the ER and causing the ER to be degraded and thus downregulated. Examples of SERMs include but are not limited to: tamoxifen, raloxifene, toremifene, anordrin, bazedoxifene, clomifene, and ospemifene. Fulvestrant is an example of SERD and is capable of blocking estrogen activity by inducing rapid down-regulation of the ER via the proteosomal pathway.

Taking tamoxifen as an example of the tissue selectivity of a SERM, it is an ER antagonist in breast and therefore is useful in breast cancer treatment, but an ER agonist in

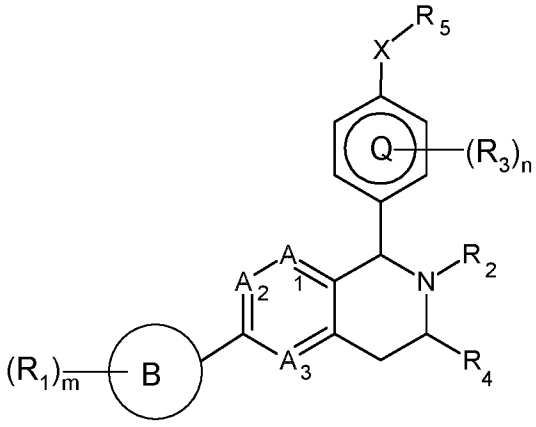
bone (thereby protecting against osteoporosis) and a partial agonist in the endometrium (increasing the potential risk of endometrial cancer). A SERD that does not possess the partial agonist activity of a SERM has several potential advantages, including the reduced endometrial cancer risk. Accordingly, there remains a need to develop novel SERDs with no partial agonist activity that have activity in treating estrogen receptor mediated or dependent diseases or conditions.

Certain tetrahydroisoquinoline derivatives have been disclosed previously. WO 2016/202161, WO 2017/107754 and WO 2017/174757 claim tetrahydroisoquinoline compounds. These compounds are described as SERMs with estrogen receptor modulation activity.

Disclosed herein are novel tetrahydroisoquinoline compounds that are SERDs and do not possess the partial agonist activity of SERMs. They therefore have a potentially improved safety and efficacy profile, in particular with respect to the risk of causing endometrial cancer. Furthermore, these compounds possess superior downregulation properties, and possess an improved pharmokinetic profile including in terms of lower plasma protein binding, longer half-life in the body, lower predicted human clearance and flatter free drug AUC coverage to increase the safety margin and /or may exhibit other advantageous physical properties (for example, lower lipophilicity, higher aqueous solubility, higher permeability, and/or greater chemical stability). They may also possess favourable toxicity profiles (for example a decreased activity at hERG), and/or favourable metabolic or pharmacokinetic profiles, in comparison with known ER modulators.

SUMMARY

In one aspect, the present disclosure provides a compound represented by Formula (I):



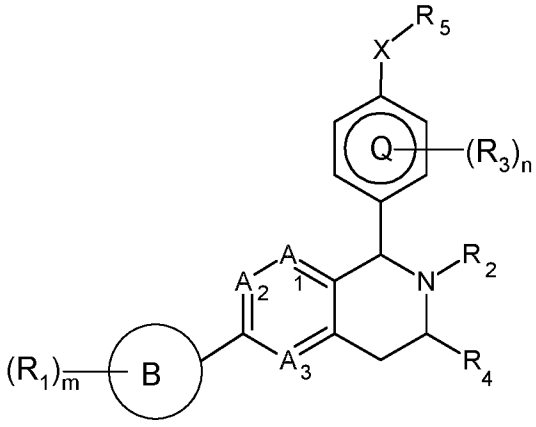
Formula (I)

wherein R_1, R_2, R_3, R_4, R_5, X, A_1, A_2, A_3, Ring B, Ring Q, m and n are as herein defined, or a pharmaceutically acceptable salt thereof.

In another aspect the present invention also relates to pharmaceutical compositions comprising one or more of the compounds, or a pharmaceutically acceptable salt thereof, as an active ingredient, and to the use of the compounds, or a pharmaceutically acceptable salt thereof, as a SERD in the treatment of ER mediated or dependent diseases or conditions, for example cancer such as breast cancer.

DETAILED DESCRIPTION

In one aspect, the present disclosure provides compounds of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof, wherein:

A_1, A_2, and A_3 are each independently $-C(R_6)=$ or $-N=$;

Ring Q is a 6 membered aromatic ring wherein the ring atoms are independently selected from carbon or nitrogen;

Ring B is a 5 or 6 membered unsaturated ring which may be carbon or nitrogen linked; wherein if said 5 or 6 membered unsaturated ring contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R_7;

X is -O-, -NR_8-, -$C(R_9)(R_{10})$-, or -S-;

R_1 and R_3 are substituents on carbon and are independently selected from hydroxyl, halogen, nitro, cyano, carboxyl, amino, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoroethyl, methoxy, ethoxy, trifluoromethoxy, trifluoroethoxy, methylamino, dimethylamino or ethylamino; or two R_1 groups on vicinal atoms form a five- or six-membered fused carbocyclyl or fused heterocyclyl ring; wherein said five- or six-membered fused carbocyclyl or fused heterocyclyl ring can be optionally substituted on carbon by R_{11}; and wherein if said five- or six-membered fused heterocyclyl ring contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R_{12};

R_2 and R_5 are independently selected from C_{1-12} alkyl, a 3-10 membered saturated or unsaturated carbocyclyl, or a 3-10 membered saturated or unsaturated heterocyclyl; wherein R_2 and R_5 can be optionally substituted on carbon by R_{13}; and wherein if said 3-10 membered saturated or unsaturated heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R_{14};

R_4 is C_{1-3} alkyl or C_{3-4} cycloalkyl; wherein R_4 may be optionally substituted by one or more hydroxyl, halogen or methoxy;

R_8 is hydrogen or C_{1-12} alkyl optionally substituted by one or more halo or hydroxy;

R_6, R_9 and R_{10} are each independently hydrogen, hydroxyl, halogen, nitro, cyano, carboxyl, amino, carbamoyl, mercapto, sulphamoyl, C_{1-12} alkyl or C_{1-12} alkoxyl; wherein said C_{1-12} alkyl or C_{1-12} alkoxyl can be independently optionally substituted by one or more halo or hydroxy;

R_{11} and R_{13} are substituents on carbon and are each independently selected from hydroxyl, halogen, nitro, cyano, carboxyl, trifluoromethoxy, amino, carbamoyl, mercapto, sulphamoyl, C_{1-12} alkyl, C_{1-12} alkoxyl, C_{1-12} alkanoyl, C_{1-12} alkanoyloxy, N-(C_{1-12} alkyl)amino, N,N-(C_{1-12} alkyl)$_2$amino, C_{1-12} alkanoylamino, N-(C_{1-12} alkyl)carbamoyl, N,N-(C_{1-12} alkyl)$_2$carbamoyl, C_{1-12} alkyl$S(O)_a$ wherein a is 0 to 2, C_{1-12} alkoxycarbonyl, N-(C_{1-12}

alkyl)sulphamoyl, N,N-(C_{1-12} alkyl)$_2$sulphamoyl, C_{1-12} alkylsulphonylamino, C_{1-12} alkyl-OH, C_{1-12} haloalkyl, -Si($R_aR_bR_c$), 3-10 membered saturated or unsaturated carbocyclyl, or 3-10 membered saturated or unsaturated heterocyclyl; wherein R_{11} and R_{13} independently of each other may be optionally substituted on carbon by one or more R_{15}; and wherein if said 3-10 membered saturated or unsaturated heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R_{16};

R_7, R_{12}, R_{14} and R_{16} are independently selected from C_{1-12} alkyl, C_{1-12} alkanoyl, C_{1-12} alkylsulphonyl, C_{1-12} alkoxycarbonyl, carbamoyl, N-(C_{1-12} alkyl)carbamoyl, N,N-(C_{1-12} alkyl)$_2$carbamoyl, 3-10 membered saturated or unsaturated carbocyclyl, 3-10 membered saturated or unsaturated heterocyclyl, 3-10 membered saturated or unsaturated carbocyclylC_{1-12} alkyl, 3-10 membered saturated or unsaturated heterocyclylC_{1-12} alkyl, benzyl, benzyloxycarbonyl, benzoyl or phenylsulphonyl; wherein R_7, R_{12}, R_{14} and R_{16} may be independently optionally substituted on carbon by R_{17};

R_{15} and R_{17} are each independently selected from hydroxyl, halogen, nitro, cyano, carboxyl, trifluoromethoxy, amino, carbamoyl, mercapto, sulphamoyl, C_{1-12} alkyl, C_{1-12} alkoxyl, C_{1-12} haloalkyl, N-(C_{1-12} alkyl)amino, N-(C_{1-12} haloalkyl)amino, or C_{1-12} alkyl-OH;

R_a, R_b and R_c are each independently selected from hydroxyl, C_{1-12} alkyl, or C_{1-12} alkyl-OH; and

m is 0, 1, 2, 3 or 4;

n is 0, 1 or 2.

In one aspect of the invention A_1, A_2, and A_3 are each independently -C(R_6)= or -N=; wherein R_6 are each independently hydrogen or halogen.

In one aspect of the invention A_1, A_2, and A_3 are each independently -C(R_6)= or -N=; wherein R_6 are each independently hydrogen or fluoro.

In one aspect of the invention A_1, A_2, and A_3 are each independently -C(R_6)=.

In one aspect of the invention A_1, A_2, and A_3 are each independently -C(R_6)=; wherein R_6 is hydrogen.

In one aspect of the invention A_1 is -N= and A_2, and A_3 are each independently -C(R_6)=.

In one aspect of the invention A_2 is -N= and A_1, and A_3 are each independently -C(R_6)=.

In one aspect of the invention A_3 is -N= and A_1, and A_2 are each independently -C(R_6)=.

In one aspect of the invention Ring Q is phenyl or pyridyl.

In one aspect of the invention Ring Q is pyridyl.

In one aspect of the invention Ring Q is phenyl.

In one aspect of the invention Ring B is a 5 or 6 membered unsaturated ring which may be carbon or nitrogen linked; wherein if said 5 or 6 membered unsaturated ring contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R_7; wherein

R_7 is selected from C_{1-12} alkyl or cyclopropyl; wherein R_7 may be independently optionally substituted on carbon by one or more R_{17}; and

R_{17} are each independently selected from halogen.

In one aspect of the invention Ring B is pyrazolyl, oxazolyl, 1,2,4-triazol-4-yl, 1,2,3-triazol-4-yl, 2,5-dihydrothiophen-4-yl1,1-dioxide, pyrimidinyl, pyridazinyl, pyridyl, pyrrolyl, tetrazolyl or imidazolyl; wherein if said pyrazolyl, 1,2,3-triazolyl, pyrrolyl, tetrazolyl, 1,2,4-triazolyl and imidazolyl contain an -NH- moiety that nitrogen may be optionally substituted by a group selected from R_7; wherein

R_7 is selected from methyl, ethyl or cyclopropyl; wherein R_7 may be independently optionally substituted on carbon by one or more R_{17}; and

R_{17} are each independently selected from fluoro.

In one aspect of the invention Ring B is 1H-pyrazol-1-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, oxazol-4-yl, 4H-1,2,4-triazol-4-yl, 2H-1,2,3-triazol-4-yl, 1H-1,2,4-triazol-3-yl, 2,5-dihydrothiophen-4-yl1,1-dioxide, pyrimidin-5-yl, pyridazin-4-yl, pyrid-3-yl, pyrid-4-yl, 1H-pyrrol-3-yl, 2H-tetrazol-5-yl or 1H-imidazol-2-yl; wherein said 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 2H-1,2,3-triazol-4-yl, 1H-pyrrol-3-yl, 2H-tetrazol-5-yl, 1H-1,2,4-triazol-3-yl and 1H-imidazol-2-yl may be optionally substituted on the -NH- moiety by a group selected from R_7; wherein

R_7 is selected from methyl, difluoromethyl, ethyl or cyclopropyl.

In one aspect of the invention Ring B is pyrazolyl, oxazolyl, 1,2,4-triazol-4-yl, 1,2,3-triazol-4-yl, 2,5-dihydrothiophen-4-yl1,1-dioxide, pyrimidinyl, pyridazinyl, pyridyl, pyrrolyl, tetrazolyl or imidazolyl; wherein if said pyrazolyl, 1,2,3-triazolyl, pyrrolyl, tetrazolyl, 1,2,4-triazolyl and imidazolyl contain an -NH- moiety that nitrogen may be

optionally substituted by a group selected from R_7.

In one aspect of the invention Ring B is 1H-pyrazol-1-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, oxazol-4-yl, 4H-1,2,4-triazol-4-yl, 2H-1,2,3-triazol-4-yl, 1H-1,2,4-triazol-3-yl, 2,5-dihydrothiophen-4-yl1,1-dioxide, pyrimidin-5-yl, pyridazin-4-yl, pyrid-3-yl, pyrid-4-yl, 1H-pyrrol-3-yl, 2H-tetrazol-5-yl or 1H-imidazol-2-yl; wherein said 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 2H-1,2,3-triazol-4-yl, 1H-pyrrol-3-yl, 2H-tetrazol-5-yl, 1H-1,2,4-triazol-3-yl and 1H-imidazol-2-yl may be optionally substituted on the -NH- moiety by a group selected from R_7.

In one aspect of the invention X is -O-.

In one aspect of the invention X is -NR_8-.

In one aspect of the invention X is -NR_8-; wherein R_8 is hydrogen.

In one aspect of the invention X is -$C(R_9)(R_{10})$-.

In one aspect of the invention X is -$C(R_9)(R_{10})$-; wherein R_9 and R_{10} are each independently hydrogen, hydroxyl or halogen.

In one aspect of the invention X is -S-.

In one aspect of the invention X is -O-, -NR_8- or -$C(R_9)(R_{10})$-; wherein

R_8 is hydrogen; and

R_9 and R_{10} are each independently hydrogen, hydroxyl or halogen.

In one aspect of the invention X is -O-, -NH-, -CH_2-, -CH(OH)- or -CH(F)-.

In one aspect of the invention R_1 is not hydroxyl.

In one aspect of the invention R_1 is a substituent on carbon and is independently selected from hydroxyl, halogen or methyl.

In one aspect of the invention R_1 is a substituent on carbon and is independently selected from halogen or methyl.

In one aspect of the invention R_1 is a substituent on carbon and is independently selected from hydroxyl, fluoro or methyl.

In one aspect of the invention R_1 is a substituent on carbon and is independently selected from fluoro or methyl.

In one aspect of the invention R_2 is selected from $C_{1\text{-}12}$ alkyl or a 5 membered saturated carbocyclyl; wherein R_2 can be optionally substituted on carbon by one or more R_{13}; wherein

R_{13} is a substituent on carbon and are each independently selected from hydroxyl, halogen or C_{1-12} alkyl.

In one aspect of the invention R_2 is selected from ethyl, propyl or bicyclo[1.1.1]pentan-1-yl; wherein R_2 can be optionally substituted on carbon by one or more R_{13}; wherein

R_{13} is a substituent on carbon and are each independently selected from hydroxyl, fluoro or methyl.

In one aspect of the invention R_2 is selected from C_{1-12} alkyl or a 5 membered saturated carbocyclyl.

In one aspect of the invention R_2 is selected from ethyl, propyl or bicyclo[1.1.1]pentan-1-yl; wherein R_2 can be optionally substituted on carbon by one or more R_{13}.

In one aspect of the invention R_3 is a substituent on carbon and is independently selected from halogen or methoxy.

In one aspect of the invention R_3 is a substituent on carbon and is independently selected from fluoro or methoxy.

In one aspect of the invention R_4 is C_{1-3} alkyl or C_{3-4} cycloalkyl; wherein R_4 may be optionally substituted by one or more halogen.

In one aspect of the invention R_4 is methyl, ethyl or cyclopropyl; wherein R_4 may be optionally substituted by one or more fluoro.

In one aspect of the invention R_4 is methyl, difluoromethyl, ethyl, 2,2-difluoroeth-2-yl or cyclopropyl.

In one aspect of the invention R_4 is methyl.

In one aspect of the invention R_5 is selected from C_{1-12} alkyl or a 4 or 5 membered saturated heterocyclyl; wherein R_5 can be optionally substituted on carbon by one or more R_{13}; and wherein if said 4 or 5 membered saturated heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R_{14}; wherein

R_{13} are substituents on carbon and are independently selected N-(C_{1-12} alkyl)amino; wherein R_{13} independently of each other may be optionally substituted on carbon by one or more R_{15};

R_{14} are independently selected from C_{1-12} alkyl; wherein R_{14} may be independently optionally substituted on carbon by one or more R_{17}; and

R_{15} and R_{17} are each independently selected from halogen.

In one aspect of the invention R_5 is selected from ethyl, azetidine-3-yl or pyrrolidine-3-yl; wherein R_5 can be optionally substituted on carbon by one or more R_{13}; and wherein said azetidine-3-yl or pyrrolidine-3-yl may be optionally substituted on the -NH- moiety by a group selected from R_{14}; wherein

R_{13} are substituents on carbon and are independently selected propylamino; wherein R_{13} independently of each other may be optionally substituted on carbon by one or more R_{15};

R_{14} are independently selected from propyl; wherein R_{14} may be independently optionally substituted on carbon by one or more R_{17}; and

R_{15} and R_{17} are each independently selected from fluoro.

In one aspect of the invention R_5 is selected from C_{1-12} alkyl or a 4 or 5 membered saturated heterocyclyl; wherein R_5 can be optionally substituted on carbon by one or more R_{13}; and wherein if said 4 or 5 membered saturated heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R_{14}.

In one aspect of the invention R_5 is selected from ethyl, azetidine-3-yl or pyrrolidine-3-yl; wherein R_5 can be optionally substituted on carbon by one or more R_{13}; and wherein said azetidine-3-yl or pyrrolidine-3-yl may be optionally substituted on the -NH- moiety by a group selected from R_{14}.

In one aspect of the invention R_5 is 1-(3-fluoropropyl)azetidine-3-yl.

In one aspect of the invention -X-R_5 is [1-(3-fluoropropyl)azetidine-3-yl]amino.

In one aspect of the invention R_6 are each independently hydrogen or halogen.

In one aspect of the invention R_6 are each independently hydrogen or fluoro.

In one aspect of the invention R_7 is selected from methyl, difluoromethyl, ethyl or cyclopropyl.

In one aspect of the invention R_8 is hydrogen.

In one aspect of the invention R_9 and R_{10} are each independently hydrogen, hydroxyl or halogen.

In one aspect of the invention R_{13} is a substituent on carbon and are each independently

selected from hydroxyl, halogen or C_{1-12} alkyl.

In one aspect of the invention R_{13} is a substituent on carbon and are each independently selected from hydroxyl, fluoro or methyl.

In one aspect of the invention R_{13} is a substituent on carbon and are each independently selected N-(C_{1-12} alkyl)amino; wherein R_{13} independently of each other may be optionally substituted on carbon by one or more R_{15}.

In one aspect of the invention R_{14} are independently selected from C_{1-12} alkyl; wherein R_{14} may be independently optionally substituted on carbon by one or more R_{17}.

In one aspect of the invention R_{15} and R_{17} are each independently selected from halogen.

m is 0.

m is 1.

m is 2.

m is 3.

m is 4.

m is 0 or 1.

n is 0.

n is 1.

n is 2.

In one aspect of the invention there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof wherein:

A_1, A_2, and A_3 are each independently -C(R_6)= or -N=; wherein R_6 are each independently hydrogen or halogen;

Ring Q is phenyl or pyridyl;

Ring B is a 5 or 6 membered unsaturated ring which may be carbon or nitrogen linked; wherein if said 5 or 6 membered unsaturated ring contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R_7; wherein R_7 is selected from C_{1-12} alkyl or cyclopropyl; wherein R_7 may be independently optionally substituted on carbon by one or more R_{17}; and R_{17} are each independently selected from halogen;

X is -O-, -NR_8- or -C(R_9)(R_{10})-; wherein R_8 is hydrogen; and R_9 and R_{10} are each

independently hydrogen, hydroxyl or halogen;

R_1 is a substituent on carbon and is independently selected from hydroxyl, halogen or methyl;

R_2 is selected from C_{1-12} alkyl or a 5 membered saturated carbocyclyl; wherein R_2 can be optionally substituted on carbon by one or more R_{13}; wherein R_{13} is a substituent on carbon and are each independently selected from hydroxyl, halogen or C_{1-12} alkyl;

R_3 is a substituent on carbon and is independently selected from halogen or methoxy;

R_4 is C_{1-3} alkyl or C_{3-4} cycloalkyl; wherein R_4 may be optionally substituted by one or more halogen;

R_5 is selected from C_{1-12} alkyl or a 4 or 5 membered saturated heterocyclyl; wherein R_5 can be optionally substituted on carbon by one or more R_{13}; and wherein if said 4 or 5 membered saturated heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R_{14}; wherein R_{13} are substituents on carbon and are independently selected N-(C_{1-12} alkyl)amino; wherein R_{13} independently of each other may be optionally substituted on carbon by one or more R_{15}; R_{14} are independently selected from C_{1-12} alkyl; wherein R_{14} may be independently optionally substituted on carbon by one or more R_{17}; and R_{15} and R_{17} are each independently selected from halogen;

m is 0 or 1; and

n is 0, 1, or 2.

In one aspect of the invention there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof wherein:

A_1, A_2, and A_3 are each independently -C(R_6)= or -N=; wherein R_6 are each independently hydrogen or fluoro;

Ring Q is phenyl or pyridyl;

Ring B is pyrazolyl, oxazolyl, 1,2,4-triazol-4-yl, 1,2,3-triazol-4-yl, 2,5-dihydrothiophen-4-yl1,1-dioxide, pyrimidinyl, pyridazinyl, pyridyl, pyrrolyl, tetrazolyl or imidazolyl; wherein if said pyrazolyl, 1,2,3-triazolyl, pyrrolyl, tetrazolyl, 1,2,4-triazolyl and imidazolyl contain an -NH- moiety that nitrogen may be optionally substituted by a group selected from R_7; wherein R_7 is selected from methyl, ethyl or cyclopropyl; wherein R_7 may be independently optionally substituted on carbon by one or more R_{17}; and R_{17} are each

independently selected from fluoro;

X is -O-, -NH-, -CH_2-, -CH(OH)- or -CH(F)-;

R_1 is a substituent on carbon and is independently selected from hydroxyl, fluoro or methyl;

R_2 is selected from ethyl, propyl or bicyclo[1.1.1]pentan-1-yl; wherein R_2 can be optionally substituted on carbon by one or more R_{13}; wherein R_{13} is a substituent on carbon and are each independently selected from hydroxyl, fluoro or methyl;

R_3 is a substituent on carbon and is independently selected from fluoro or methoxy;

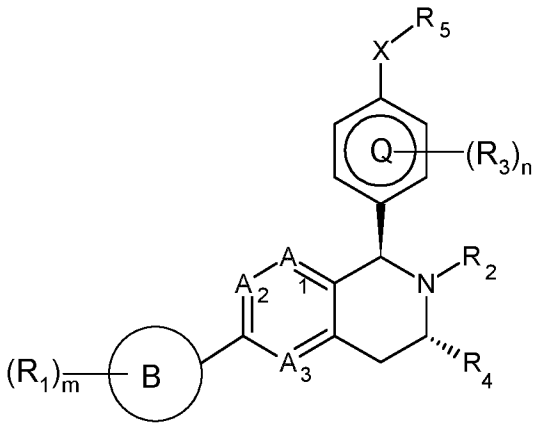
R_4 is methyl, ethyl or cyclopropyl; wherein R_4 may be optionally substituted by one or more fluoro;

R_5 is selected from ethyl, azetidine-3-yl or pyrrolidine-3-yl; wherein R_5 can be optionally substituted on carbon by one or more R_{13}; and wherein said azetidine-3-yl or pyrrolidine-3-yl may be optionally substituted on the -NH- moiety by a group selected from R_{14}; wherein R_{13} are substituents on carbon and are independently selected propylamino; wherein R_{13} independently of each other may be optionally substituted on carbon by one or more R_{15}; R_{14} are independently selected from propyl; wherein R_{14} may be independently optionally substituted on carbon by one or more R_{17}; and R_{15} and R_{17} are each independently selected from fluoro;

m is 0 or 1; and

n is 0, 1, or 2.

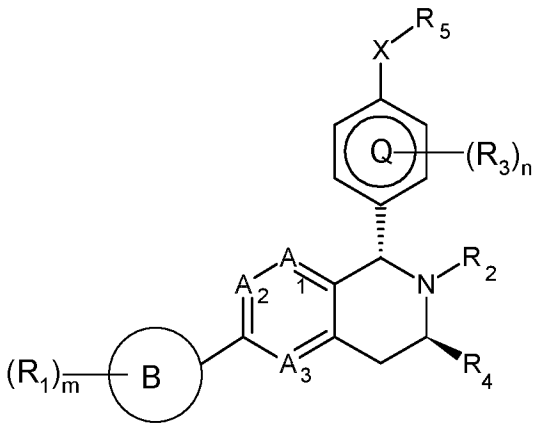
In a further aspect of the invention, there is provided a compound of formula (I) which is a compound of formula (Ia):



(Ia)

or a pharmaceutically acceptable salt thereof, wherein R_1, R_2, R_3, R_4, R_5, X, A_1, A_2, A_3, Ring B, Ring Q, m and n are as herein defined.

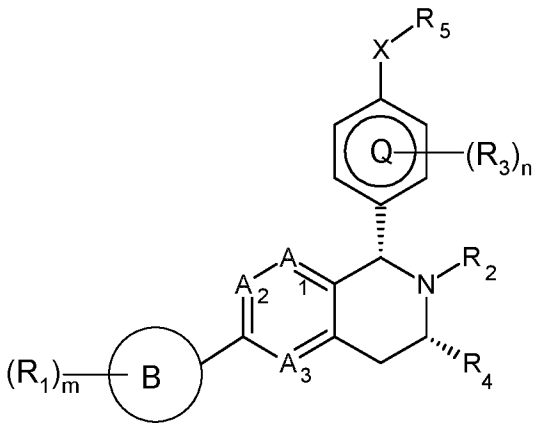
In a further aspect of the invention, there is provided a compound of formula (I) which is a compound of formula (Ib):



(Ib)

or a pharmaceutically acceptable salt thereof, wherein R_1, R_2, R_3, R_4, R_5, X, A_1, A_2, A_3, Ring B, Ring Q, m and n are as herein defined.

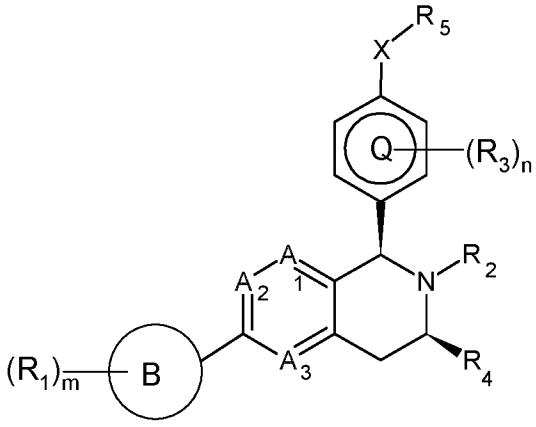
In a further aspect of the invention, there is provided a compound of formula (I) which is a compound of formula (Ic):



(Ic)

or a pharmaceutically acceptable salt thereof, wherein R_1, R_2, R_3, R_4, R_5, X, A_1, A_2, A_3, Ring B, Ring Q, m and n are as herein defined.

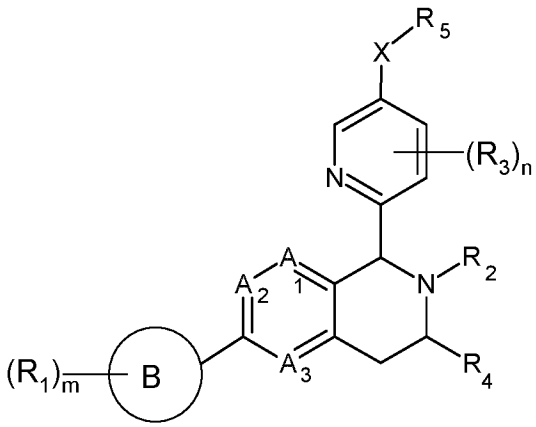
In a further aspect of the invention, there is provided a compound of formula (I) which is a compound of formula (Id):



(Id)

or a pharmaceutically acceptable salt thereof, wherein R_1, R_2, R_3, R_4, R_5, X, A_1, A_2, A_3, Ring B, Ring Q, m and n are as herein defined.

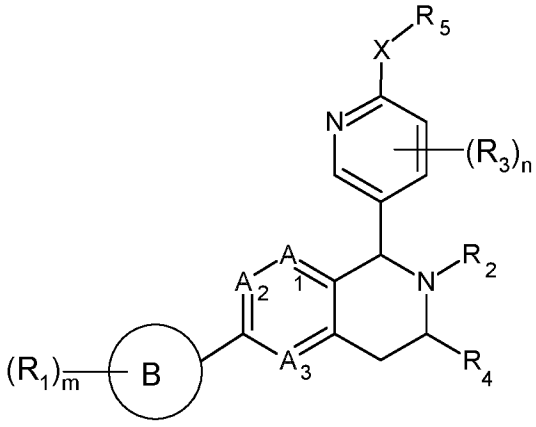
In a further aspect of the invention, there is provided a compound of formula (I) which is a compound of formula (Ie):



Formula (Ie)

or a pharmaceutically acceptable salt thereof, wherein R_1, R_2, R_3, R_4, R_5, X, A_1, A_2, A_3, Ring B, m and n are as herein defined.

In a further aspect of the invention, there is provided a compound of formula (I) which is a compound of formula (If):



Formula (If)

or a pharmaceutically acceptable salt thereof, wherein R_1, R_2, R_3, R_4, R_5, X, A_1, A_2, A_3, Ring B, m and n are as herein defined.

In one aspect, the present disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof selected from:

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3R)-3-methyl-6-(1-methyl-1H-pyrazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;

2,2-difluoro-3-((1S,3R)-1-(5-((1-(3-fluoropropyl)azetidin-3-yl)amino)pyridin-2-yl)-3-methyl-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroisoquinolin-2(1H)-yl)propan-1-ol;

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3R)-3-methyl-6-(1H-pyrazol-1-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3R)-3-methyl-6-(1H-pyrazol-3-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3R)-6-(isoxazol-4-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3R)-3-methyl-6-(1H-pyrazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;

6-((1S,3R)-6-(1-ethyl-1H-pyrazol-4-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-N-(1-(3-fluoropropyl)azetidin-3-yl)pyridin-3-amine;

6-((1S,3R)-6-(1-cyclopropyl-1H-pyrazol-4-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-N-(1-(3-fluoropropyl)azetidin-3-yl)pyridin-3-amine;

6-((1S,3R)-6-(1-(difluoromethyl)-1H-pyrazol-4-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-

tetrahydroisoquinolin-1-yl)-N-(1-(3-fluoropropyl)azetidin-3-yl)pyridin-3-amine;
N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3R)-3-methyl-6-(1-methyl-1H-pyrazol-3-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;
N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3R)-3-methyl-6-(4H-1,2,4-triazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine; and
N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3R)-3-methyl-6-(2H-1,2,3-triazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine.

In one aspect, the present disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof selected from:
N-(1-(3-fluoropropyl)azetidin-3-yl)-6-(3-methyl-6-(1-methyl-1H-pyrazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;
2,2-difluoro-3-(1-(5-((1-(3-fluoropropyl)azetidin-3-yl)amino)pyridin-2-yl)-3-methyl-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroisoquinolin-2(1H)-yl)propan-1-ol;
N-(1-(3-fluoropropyl)azetidin-3-yl)-6-(3-methyl-6-(1H-pyrazol-1-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;
N-(1-(3-fluoropropyl)azetidin-3-yl)-6-(3-methyl-6-(1H-pyrazol-3-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;
N-(1-(3-fluoropropyl)azetidin-3-yl)-6-(6-(isoxazol-4-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;
N-(1-(3-fluoropropyl)azetidin-3-yl)-6-(3-methyl-6-(1H-pyrazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;
6-(6-(1-ethyl-1H-pyrazol-4-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-N-(1-(3-fluoropropyl)azetidin-3-yl)pyridin-3-amine;
6-(6-(1-cyclopropyl-1H-pyrazol-4-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-N-(1-(3-fluoropropyl)azetidin-3-yl)pyridin-3-amine;
6-(6-(1-(difluoromethyl)-1H-pyrazol-4-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-N-(1-(3-fluoropropyl)azetidin-3-yl)pyridin-3-amine;
N-(1-(3-fluoropropyl)azetidin-3-yl)-6-(3-methyl-6-(1-methyl-1H-pyrazol-3-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;
N-(1-(3-fluoropropyl)azetidin-3-yl)-6-(3-methyl-6-(4H-1,2,4-triazol-4-yl)-2-(2,2,2-trifluoroet

hyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine; and
N-(1-(3-fluoropropyl)azetidin-3-yl)-6-(3-methyl-6-(2H-1,2,3-triazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine.

In one aspect, the present disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof selected from:
N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1R,3S)-3-methyl-6-(1-methyl-1H-pyrazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;
2,2-difluoro-3-((1R,3S)-1-(5-((1-(3-fluoropropyl)azetidin-3-yl)amino)pyridin-2-yl)-3-methyl-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroisoquinolin-2(1H)-yl)propan-1-ol;
N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1R,3S)-3-methyl-6-(1H-pyrazol-1-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;
N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1R,3S)-3-methyl-6-(1H-pyrazol-3-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;
N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1R,3S)-6-(isoxazol-4-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;
N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1R,3S)-3-methyl-6-(1H-pyrazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;
6-((1R,3S)-6-(1-ethyl-1H-pyrazol-4-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-N-(1-(3-fluoropropyl)azetidin-3-yl)pyridin-3-amine;
6-((1R,3S)-6-(1-cyclopropyl-1H-pyrazol-4-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-N-(1-(3-fluoropropyl)azetidin-3-yl)pyridin-3-amine;
6-((1R,3S)-6-(1-(difluoromethyl)-1H-pyrazol-4-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-N-(1-(3-fluoropropyl)azetidin-3-yl)pyridin-3-amine;
N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1R,3S)-3-methyl-6-(1-methyl-1H-pyrazol-3-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;
N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1R,3S)-3-methyl-6-(4H-1,2,4-triazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine; and
N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1R,3S)-3-methyl-6-(2H-1,2,3-triazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine.

In one aspect, the present disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof selected from:

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1R,3R)-3-methyl-6-(1-methyl-1H-pyrazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;

2,2-difluoro-3-((1R,3R)-1-(5-((1-(3-fluoropropyl)azetidin-3-yl)amino)pyridin-2-yl)-3-methyl-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroisoquinolin-2(1H)-yl)propan-1-ol;

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1R,3R)-3-methyl-6-(1H-pyrazol-1-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1R,3R)-3-methyl-6-(1H-pyrazol-3-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1R,3R)-6-(isoxazol-4-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1R,3R)-3-methyl-6-(1H-pyrazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;

6-((1R,3R)-6-(1-ethyl-1H-pyrazol-4-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-N-(1-(3-fluoropropyl)azetidin-3-yl)pyridin-3-amine;

6-((1R,3R)-6-(1-cyclopropyl-1H-pyrazol-4-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-N-(1-(3-fluoropropyl)azetidin-3-yl)pyridin-3-amine;

6-((1R,3R)-6-(1-(difluoromethyl)-1H-pyrazol-4-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-N-(1-(3-fluoropropyl)azetidin-3-yl)pyridin-3-amine;

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1R,3R)-3-methyl-6-(1-methyl-1H-pyrazol-3-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1R,3R)-3-methyl-6-(4H-1,2,4-triazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine; and

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1R,3R)-3-methyl-6-(2H-1,2,3-triazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine.

In one aspect, the present disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof selected from:

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3S)-3-methyl-6-(1-methyl-1H-pyrazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;

2,2-difluoro-3-((1S,3S)-1-(5-((1-(3-fluoropropyl)azetidin-3-yl)amino)pyridin-2-yl)-3-methyl-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroisoquinolin-2(1H)-yl)propan-1-ol;

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3S)-3-methyl-6-(1H-pyrazol-1-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3S)-3-methyl-6-(1H-pyrazol-3-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3S)-6-(isoxazol-4-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3S)-3-methyl-6-(1H-pyrazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;

6-((1S,3S)-6-(1-ethyl-1H-pyrazol-4-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-N-(1-(3-fluoropropyl)azetidin-3-yl)pyridin-3-amine;

6-((1S,3S)-6-(1-cyclopropyl-1H-pyrazol-4-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-N-(1-(3-fluoropropyl)azetidin-3-yl)pyridin-3-amine;

6-((1S,3S)-6-(1-(difluoromethyl)-1H-pyrazol-4-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-N-(1-(3-fluoropropyl)azetidin-3-yl)pyridin-3-amine;

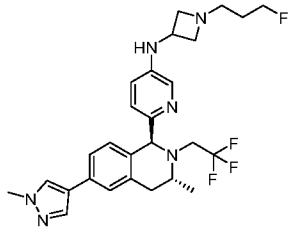
N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3S)-3-methyl-6-(1-methyl-1H-pyrazol-3-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;

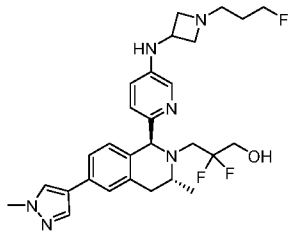
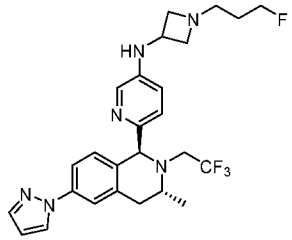
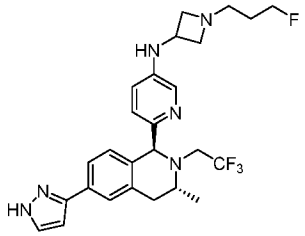
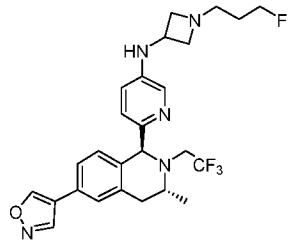
N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3S)-3-methyl-6-(4H-1,2,4-triazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine; and

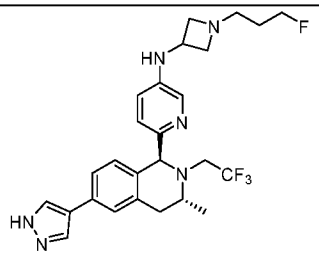
N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3S)-3-methyl-6-(2H-1,2,3-triazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine.

Exemplary compounds 1-54 of Formula (I) are set forth in Table 1 below.

Table 1. Exemplary Compounds 1-54

Cpd No.	Compound Structure and Name
1	

	N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3R)-3-methyl-6-(1-methyl-1H-pyrazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine
2	
	2,2-difluoro-3-((1S,3R)-1-(5-((1-(3-fluoropropyl)azetidin-3-yl)amino)pyridin-2-yl)-3-methyl-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroisoquinolin-2(1H)-yl)propan-1-ol
3	
	N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3R)-3-methyl-6-(1H-pyrazol-1-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine
4	
	N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3R)-3-methyl-6-(1H-pyrazol-3-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine
5	
	N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3R)-6-(isoxazol-4-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine

6	
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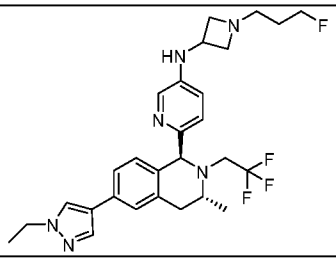
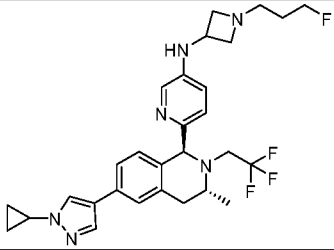
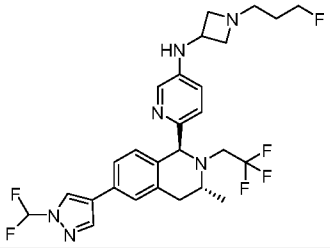
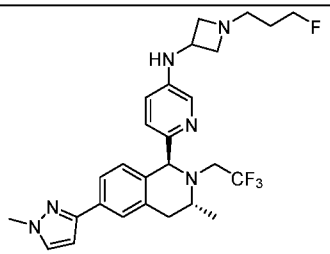
7	
	6-((1S,3R)-6-(1-ethyl-1H-pyrazol-4-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-N-(1-(3-fluoropropyl)azetidin-3-yl)pyridin-3-amine
8	
	6-((1S,3R)-6-(1-cyclopropyl-1H-pyrazol-4-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-N-(1-(3-fluoropropyl)azetidin-3-yl)pyridin-3-amine
9	
	6-((1S,3R)-6-(1-(difluoromethyl)-1H-pyrazol-4-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-N-(1-(3-fluoropropyl)azetidin-3-yl)pyridin-3-amine

10	
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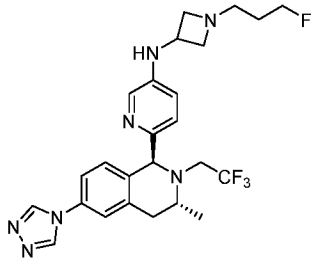
11	
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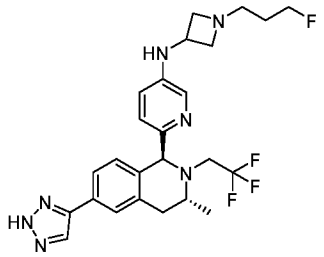
12	
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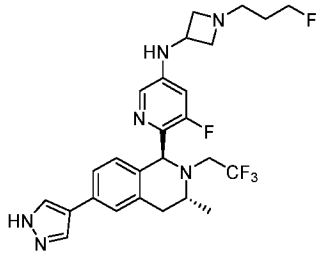
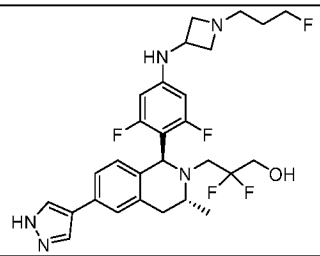
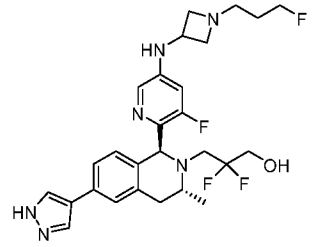
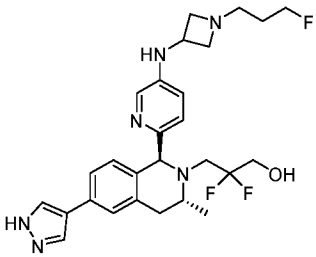
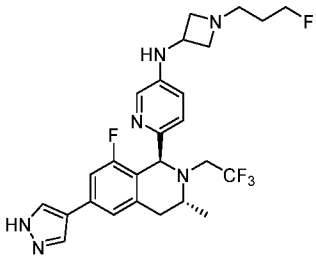
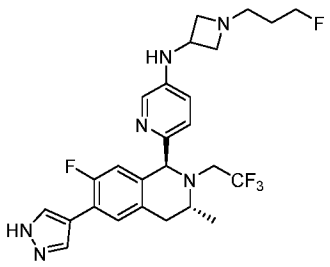
13	
	5-fluoro-N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3R)-3-methyl-6-(1H-pyrazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine

14	
	3-((1S,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-3-methyl-6-(1H-pyrazol-4-yl)-3,4-dihydroisoquinolin-2(1H)-yl)-2,2-difluoropropan-1-ol
15	
	2,2-difluoro-3-((1S,3R)-1-(3-fluoro-5-((1-(3-fluoropropyl)azetidin-3-yl)amino)pyridin-2-yl)-3-methyl-6-(1H-pyrazol-4-yl)-3,4-dihydroisoquinolin-2(1H)-yl)propan-1-ol
16	
	2,2-difluoro-3-((1S,3R)-1-(5-((1-(3-fluoropropyl)azetidin-3-yl)amino)pyridin-2-yl)-3-methyl-6-(1H-pyrazol-4-yl)-3,4-dihydroisoquinolin-2(1H)-yl)propan-1-ol
17	
	6-((1S,3R)-8-fluoro-3-methyl-6-(1H-pyrazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-N-(1-(3-fluoropropyl)azetidin-3-yl)pyridin-3-amine

18	
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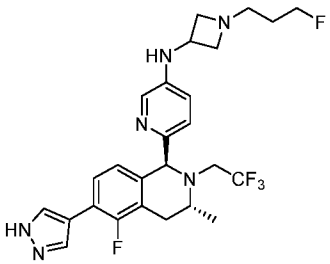
19	
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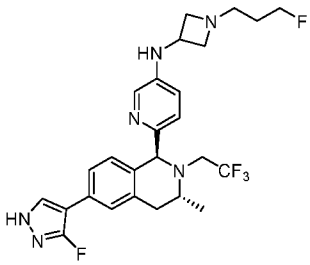
20	
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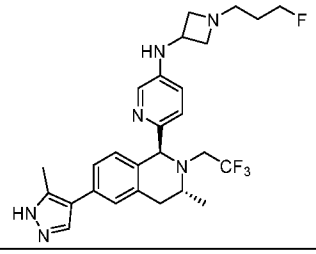
21	

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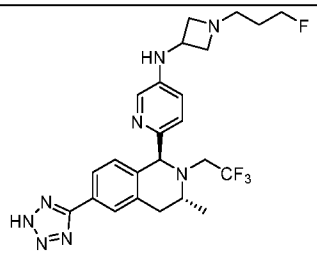
22	
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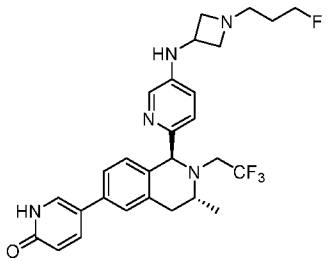
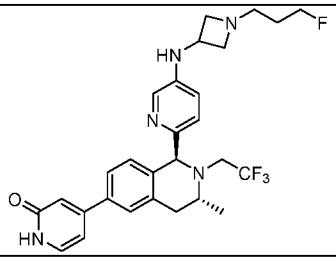
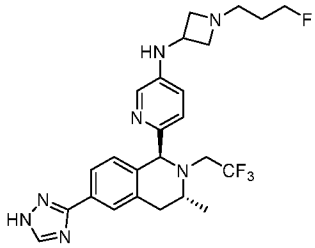
23	
	5-((1S,3R)-1-(5-((1-(3-fluoropropyl)azetidin-3-yl)amino)pyridin-2-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)pyridin-2(1H)-one
24	
	4-((1S,3R)-1-(5-((1-(3-fluoropropyl)azetidin-3-yl)amino)pyridin-2-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)pyridin-2(1H)-one
25	
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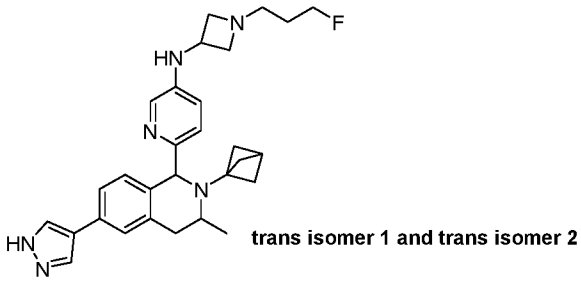
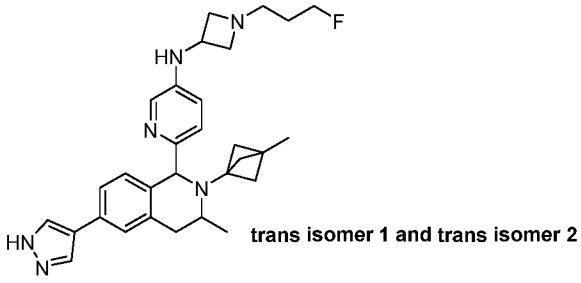
26	 trans isomer 1 and trans isomer 2
	6-(2-(bicyclo[1.1.1]pentan-1-yl)-3-methyl-6-(1H-pyrazol-4-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-N-(1-(3-fluoropropyl)azetidin-3-yl)pyridin-3-amine
27	 trans isomer 1 and trans isomer 2
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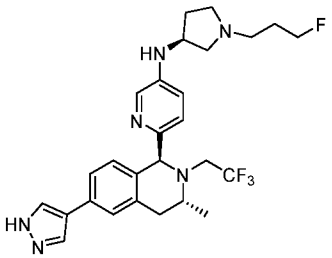
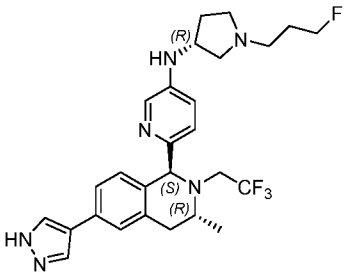
28	
	N-((S)-1-(3-fluoropropyl)pyrrolidin-3-yl)-6-((1S,3R)-3-methyl-6-(1H-pyrazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine
29	
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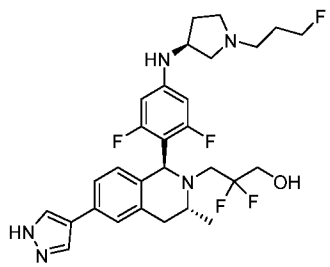
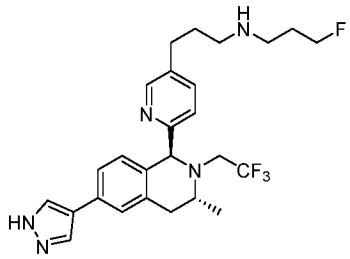
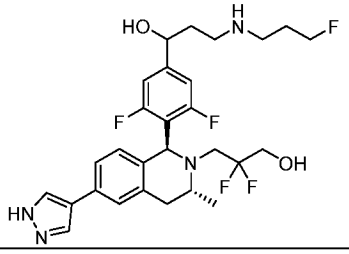
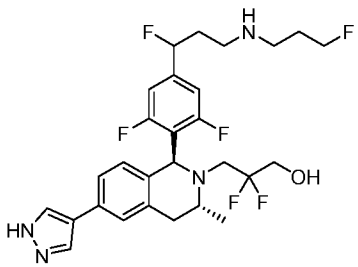
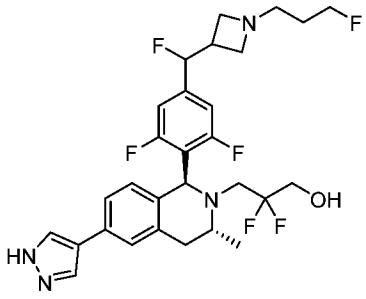
30	
	3-((1S,3R)-1-(2,6-difluoro-4-(((S)-1-(3-fluoropropyl)pyrrolidin-3-yl)amino)phenyl)-3-methyl-6-(1H-pyrazol-4-yl)-3,4-dihydroisoquinolin-2(1H)-yl)-2,2-difluoropropan-1-ol
31	
	3-fluoro-N-(3-(6-((1S,3R)-3-methyl-6-(1H-pyrazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-yl)propyl)propan-1-amine
32	
	3-((1S,3R)-1-(2,6-difluoro-4-(3-((3-fluoropropyl)amino)-1-hydroxypropyl)phenyl)-3-methyl-6-(1H-pyrazol-4-yl)-3,4-dihydroisoquinolin-2(1H)-yl)-2,2-difluoropropan-1-ol (isomer 1 and isomer 2)
33	
	3-((1S,3R)-1-(2,6-difluoro-4-(1-fluoro-3-((3-fluoropropyl)amino)propyl)phenyl)-3-methyl-6-(1H-pyrazol-4-yl)-3,4-dihydroisoquinolin-2(1H)-yl)-2,2-difluoropropan-1-ol (isomer 1 and isomer 2)

34	
	3-((1S,3R)-1-(2,6-difluoro-4-(fluoro(1-(3-fluoropropyl)azetidin-3-yl)methyl)phenyl)-3-methyl-6-(1H-pyrazol-4-yl)-3,4-dihydroisoquinolin-2(1H)-yl)-2,2-difluoropropan-1-ol (isomer 1 and isomer 2)

It is appreciated that certain features of the present disclosure, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the present disclosure, which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable sub combination.

At various places in the present disclosure, linking substituents are described. Where the structure clearly requires a linking group, the Markush variables listed for that group are understood to be linking groups. For example, if the structure requires a linking group and the Markush group definition for that variable lists "alkyl", then it is understood that the "alkyl" represents a linking alkylene group.

As used herein, the term "substituted", when refers to a chemical group, means the chemical group has one or more hydrogen atoms that is/are removed and replaced by substituents. As used herein, the term "substituent" has the ordinary meaning known in the art and refers to a chemical moiety that is covalently attached to, or if appropriate, fused to, a parent group. As used herein, the term "optionally substituted" or "optionally…substituted" means that the chemical group may have no substituents (i.e. unsubstituted) or may have one or more substituents (i.e. substituted). It is to be understood that substitution at a given atom is limited by valency.

As used herein, the term "C_{i-j}" indicates a range of the carbon atoms numbers, wherein i and j are integers and the range of the carbon atoms numbers includes the endpoints (i.e. i

and j) and each integer point in between, and wherein j is greater than i. For examples, C_{1-6} indicates a range of one to six carbon atoms, including one carbon atom, two carbon atoms, three carbon atoms, four carbon atoms, five carbon atoms and six carbon atoms. In some embodiments, the term "C_{1-12}" indicates 1 to 12, particularly 1 to 10, particularly 1 to 8, particularly 1 to 6, particularly 1 to 5, particularly 1 to 4, particularly 1 to 3 or particularly 1 to 2 carbon atoms.

As used herein, the term "alkyl", whether as part of another term or used independently, refers to a saturated or unsaturated hydrocarbon chain, while the latter may be further subdivided into hydrocarbon chain having at least one double or triple bonds (alkenyl or alkynyl). The hydrocarbon chain mentioned above may be straight-chain or branched-chain. The term "C_{i-j} alkyl" refers to an alkyl having i to j carbon atoms. Examples of saturated alkyl group include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, isobutyl, sec-butyl; higher homologs such as 2-methyl-1-butyl, n-pentyl, 3-pentyl, n-hexyl, 1,2,2-trimethylpropyl, and the like. Examples of unsaturated alkyl groups include, but are not limited to, ethenyl, n-propenyl, isopropenyl, n-butenyl, sec-butenyl, ethynyl, propyn-1-yl, propyn-2-yl, and the like. Examples of "C_{1-12} alkyl" are methyl, ethyl, propyl and butyl. Examples of "C_{1-3} alkyl" are methyl, ethyl, propyl and isopropyl.

As used herein the terms "halo" and "halogen" refer to an atom selected from fluorine, chlorine, bromine and iodine.

As used herein, the term "alkoxy", whether as part of another term or used independently, refers to a group of formula -O-alkyl. The term "C_{i-j} alkoxy" means that the alkyl moiety of the alkoxy group has i to j carbon atoms. Examples of alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy (e.g. n-propoxy and isopropoxy), t-butoxy, and the like. Examples of "C_{1-12} alkoxyl" are methoxy, ethoxy and propoxy.

As used herein, the term "C_{i-j} alky-OH", refers to a group of formula "-C_{1-12} alkyl-OH" wherein the alkyl moiety of the group has i to j carbon atoms, and one or more hydroxyl groups may be linked to any carbon atoms in the alkyl moiety. Examples of "C_{1-12} alkyl-OH" are hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and 1-hydroxyisopropyl.

As used herein, the term "C_{i-j} haloalkyl", refers to a halogen substituted (mono- or multi- substituted) C_{i-j} alkyl group. Examples of "C_{1-12} haloalkyl" are fluoromethyl,

trifluoromethyl, 2-chloroethyl and 1-bromoisopropyl. Examples of "N-(C_{1-12} haloalkyl)amino" are fluoromethylamino, trifluoromethylamino, 2-chloroethylamino and 1-bromoisopropylamino.

Examples of "C_{1-12} alkanoyl" are propionyl and acetyl. Examples of "C_{1-12} alkanoylamino" are formamido, acetamido and propionylamino. Examples of "C_{1-12} alkanoyloxy" are acetoxy. Examples of "C_{1-12} alkoxycarbonyl" are methoxycarbonyl, ethoxycarbonyl, *n*- and t-butoxycarbonyl. Examples of "C_{1-12} alkyl$S(O)_a$ wherein a is 0 to 2" are methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl. Examples of "C_{1-12} alkylsulphonyl" are mesyl, ethylsulphonyl and isopropylsulphonyl. Examples of "C_{1-12} alkylsulphonylamino" are mesylamino, ethylsulphonylamino and isopropylsulphonylamino. Examples of "N-(C_{1-12} alkyl)amino" are methylamino and ethylamino. Examples of "N-(C_{1-12} alkyl)carbamoyl" are methylaminocarbonyl and ethylaminocarbonyl. Examples of "N-(C_{1-12} alkyl)sulphamoyl" are N-(methyl)sulphamoyl and N-(ethyl)sulphamoyl. Examples of "N,N-(C_{1-12} alkyl)$_2$amino" are di-N-methylamino, di-(N-ethyl)amino and N-ethyl-N-methylamino. Examples of "N,N-(C_{1-12} alkyl)$_2$carbamoyl" are dimethylaminocarbonyl and methylethylaminocarbonyl. Examples of "N,N-(C_{1-12} alkyl)$_2$sulphamoyl" are N,N-(dimethyl)sulphamoyl and N-(methyl)-N(ethyl)-sulphamoyl. Examples of "trifluoroethoxy" are 2,2,2-trifluoroethoxy and 1,2,2-trifluoroethoxy. Examples of "trifluoroethyl" are 2,2,2-trifluoroethyl and 1,2,2-trifluoroethlyl.

As used herein, the term "carbocyclyl", whether as part of another term or used independently, refers to any ring, including mono- or poly-cyclic ring(s) (e.g. having 2 or 3 fused, bridged or spiro rings), in which all the ring atoms are carbon and which contains at least three ring forming carbon atoms. In some embodiments, the carbocyclyl may contain 3 to 10 ring forming carbon atoms, 3 to 9 ring forming carbon atoms or 4 to 8 ring forming carbon atoms. Carbocyclyl groups may be saturated, partially unsaturated or fully unsaturated. In some embodiments, the carbocyclyl group may be a saturated cyclic alkyl group. In some embodiments, the carbocyclyl group may be an unsaturated cyclic alkyl group that contains at least one double bond in its ring system. In some embodiments, an unsaturated carbocyclyl group may contains one or more aromatic rings. In some embodiments a ring -CH_2- group may be replaced by a ring -C(O)- group.

Examples of monocyclic carbocyclyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, and the like. As used herein, the term "spiro rings" refers to ring systems having two rings connected through one single common atom; the term "fused rings" refers to ring systems having two rings sharing two adjacent atoms; and the term "bridged rings" refers to ring systems with two rings sharing three or more atoms. Examples of spiro carbocyclyl include, but are not limited to, spiro[5.5]undecanyl, spiro-pentadienyl, spiro[3.6]-decanyl, and the like. Examples of fused carbocyclyl include, but are not limited to, naphthyl, benzopyrenyl, anthracenyl, acenaphthenyl, fluorenyl and the like. Examples of bridged carbocyclyl include, but are not limited to bicyclo[1,1,1]pentenyl, bicyclo[2,2,1]heptenyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo [3.3.1]nonanyl, bicyclo[3.3.3]undecanyl, and the like.

A "3-10 membered saturated or unsaturated carbocyclyl" is a saturated, partially unsaturated or fully unsaturated mono- or poly-cyclic ring system having 3 to 10 ring carbon atoms wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-.

A "5 membered saturated carbocyclyl" is a saturated mono-cyclic ring system having 5 ring carbon atoms wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-.

Where "two R_1 groups on vicinal atoms form a five- or six-membered fused carbocyclyl" that carbocyclyl is a saturated, partially unsaturated or fully unsaturated mono- cyclic ring system having 5 or 6 ring carbon atoms wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-.

Examples of "3-10 membered saturated or unsaturated carbocyclyl" are cyclopropyl, cyclohexyl, cyclohexenyl, phenyl, naphthyl and bicyclo[1.1.1]pentan-1-yl. Examples of "5 membered saturated carbocyclyl" are cyclopentyl.

Examples of "3-10 membered saturated or unsaturated carbocyclylC_{1-12} alkyl" are cyclopropylmethyl, cyclohexylethyl, 1-cyclohexenylprop-2-yl, benzyl, 1-napthylethyl and bicyclo[1.1.1]pentan-1-ylmethyl.

Examples of "C_{3-4} cycloalkyl" are cyclopropyl and cyclobutyl.

Examples of "two R_1 groups on vicinal atoms form a five- or six-membered fused carbocyclyl" are fused cyclohexenyl, fused phenyl are fused cyclopentyl.

As used herein, the term "heterocyclyl" refers to a carbocyclyl group wherein one or more (e.g. 1, 2 or 3) ring atoms are replaced by heteroatoms which include, but are not limited to, oxygen, sulfur, nitrogen, phosphorus, and the like. In some embodiments, the heterocyclyl is a saturated heterocyclyl. In some embodiments, the heterocyclyl is an unsaturated heterocyclyl having one or more double bonds in its ring system. In some embodiments, the heterocyclyl is a partially unsaturated heterocyclyl. In some embodiments, the heterocyclyl is a fully unsaturated heterocyclyl having one or more double bonds in its ring system. In some embodiments, an unsaturated heterocyclyl group may contain one or more aromatic rings. In some embodiments a ring sulphur atom may be optionally oxidised to form the S-oxides. In some embodiments the heterocycle is carbon linked. In some embodiments the heterocycle is nitrogen linked.

Exemplary monocyclic heterocyclyl groups include, but are not limited to, piperidyl, pyrrolidyl, tetrahydrofuryl, piperidyl, piperazinyl, morpholinyl, and the like. Examples of spiro heterocyclyl include, but are not limited to, spiropyranyl, spirooxazinyl, and the like. Examples of fused heterocyclyl include, but are not limited to, quinolinyl, isoquinolinyl, quinolizinyl, quinazolinyl, pteridinyl, chromenyl, isochromenyl, indolyl, isoindolyl, indolizinyl, indazolyl, purinyl, benzofuranyl, isobenzofuranyl, benzimidazolyl, benzothienyl, carbazolyl, phenazinyl, phenothiazinyl, phenanthridinyl groups, and the like. Examples of bridged heterocyclyl include, but are not limited to, morphanyl, hexamethylenetetraminyl, 8-aza-bicyclo[3.2.1]octane, 1-aza-bicyclo[2.2.2]octane, 1,4-diazabicyclo[2.2.2]octane (DABCO), and the like.

A "3-10 membered saturated or unsaturated heterocyclyl" is a saturated, partially unsaturated or fully unsaturated mono- or poly-cyclic ring system having 3 to 10 ring atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and a ring sulphur atom may be optionally oxidised to form the S-oxides.

A "4 or 5 membered saturated heterocyclyl" is a saturated mono- cyclic ring system having 4 or 5 ring atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a

-CH_2- group can optionally be replaced by a -C(O)- and a ring sulphur atom may be optionally oxidised to form the S-oxides.

A "5 or 6 membered unsaturated ring which may be carbon or nitrogen linked is a partially unsaturated or fully unsaturated mono-cyclic ring system having 5 or 6 ring atoms with ring atoms chosen from carbon, nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH_2- group can optionally be replaced by a -C(O)- and a ring sulphur atom may be optionally oxidised to form the S-oxides.

Where two R_1 groups on vicinal atoms form a five- or six-membered fused heterocyclyl ring that heterocyclyl ring is a saturated, partially unsaturated or fully unsaturated mono-cyclic ring system having 5 or 6 ring atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, wherein a -CH_2- group can optionally be replaced by a -C(O)- and a ring sulphur atom may be optionally oxidised to form the S-oxides.

Examples of "3-10 membered saturated or unsaturated heterocyclyl" are pyrrolyl, pyrazolyl, oxathiolanyl, isoxazolyl, pyrimidinyl and pyridazinyl.

Examples of "3-10 membered saturated or unsaturated heterocyclylC_{1-12} alkyl" are pyrrolylmethyl, 1-pyrazolylethyl, oxathiolanylmethyl, 1-isoxazolylprop-2-yl, pyrimidinylmethyl and pyridazinylbutyl.

Examples of a "4 or 5 membered saturated heterocyclyl" are azetidinyl and 1,3-dioxolanyl.

Examples of "5 or 6 membered unsaturated ring which may be carbon or nitrogen linked" are phenyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, 2-pyrrolinyl and 2-pyrazolinyl.

Examples of two R_1 groups on vicinal atoms form a five- or six-membered fused heterocyclyl ring are fused pyrimidinyl, fused pyridazinyl, fused furyl, fused isothiazolyl and fused triazolyl.

A "6 membered aromatic ring wherein the ring atoms are independently selected from carbon or nitrogen" refers to monocyclic carbocyclyl or heterocyclyl moiety having alternating double and single bonds between ring forming atoms. Exemplary "6 membered aromatic ring wherein the ring atoms are independently selected from carbon or nitrogen" are

phenyl, pyridyl, pyrazinyl, pyrimidinyl, triazinyl and pyridazinyl.

The "compound" of present disclosure is intended to encompass all stereoisomers, geometric isomers, and tautomers of the structures depicted unless otherwise specified.

The term "stereoisomer" refers to any of the various stereoisomeric configurations (e.g. enantiomers, diastereomers and racemates) of an asymmetric compound (e.g. those having one or more asymmetrically substituted carbon atoms or "asymmetric centers"). Compounds of the present disclosure that contain asymmetric centers can be isolated in optically active (enantiomers or diastereomers) or optically inactive (racemic) forms. The term "enantiomer" includes pairs of stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic mixture". The terms "diastereomers" or "diastereoisomers" include stereoisomers that have at least two asymmetric atoms, but which are not mirror images of each other. Certain compounds containing one or more asymmetric centers may give rise to enantiomers, diastereomers or other stereoisomeric forms that may be defined, in terms of absolute configuration, as (R)- or (S)- at each asymmetric center according to the Cahn-Ingold-Prelog R-S system. Resolved compounds whose absolute configuration is unknown can be designated using the term "or" at the asymmetric center. Methods on how to prepare optically active forms from racemic mixtures are known in the art, such as resolution by HPLC or stereoselective synthesis.

The terms "geometric isomers" or "cis and trans isomers" refer to compounds with same formula but their functional groups are rotated into a different orientation in three-dimensional space.

The term "tautomers" include prototropic tautomers that are isomeric protonation states of compounds having the same formula and total charge. Examples of prototropic tautomers include, but are not limited to, ketone-enol pairs, amide-imidic acid pairs, lactam-lactim pairs, enamine-imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, for example, 1H- and 3H-imidazole, 1H-, 2H- and 4H- 1,2,4-triazole, 1H- and 2H- isoindole, and 1H- and 2H- pyrazole. Tautomers can be in equilibrium or sterically locked into one form by appropriate substitution. Compounds of the present disclosure identified by name or structure as one particular tautomeric form are intended to include other tautomeric forms unless otherwise specified.

The "compound" of the present disclosure is also intended to encompass all isotopes of atoms in the compounds. Isotopes of an atom include atoms having the same atomic number but different mass numbers. For example, unless otherwise specified, hydrogen, carbon, nitrogen, oxygen, phosphorous, sulphur, fluorine, chlorine, bromide or iodine in the "compound" of present disclosure are meant to also include their isotopes such as but are not limited to: ^{1}H, ^{2}H, ^{3}H, ^{11}C, ^{12}C, ^{13}C, ^{14}C, ^{14}N, ^{15}N, ^{16}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{32}S, ^{33}S, ^{34}S, ^{36}S, ^{17}F, ^{19}F, ^{35}Cl, ^{37}Cl, ^{79}Br, ^{81}Br, ^{127}I and ^{131}I. In some embodiments, hydrogen includes protium, deuterium and tritium. In some embodiments, the term "substituted by deuterium" or "deuterium substituted" to replace the other isoform of hydrogen (e.g. protium) in the chemical group with deuterium. In some embodiments, carbon includes ^{12}C and ^{13}C.

It is also to be understood that the "compound" of present disclosure can exist in solvated as well as unsolvated forms, such as, for example, hydrated forms, solid forms, and the present disclosure is intended to encompass all such solvated and unsolvated forms.

It is further to be understood that the "compound" of present disclosure can exist in forms of pharmaceutically acceptable salts.

As used herein, the term "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. In some embodiments, compounds, materials, compositions, and/or dosage forms that are pharmaceutically acceptable refer to those approved by a regulatory agency (such as U.S. Food and Drug Administration, China Food and Drug Administration or European Medicines Agency) or listed in generally recognized pharmacopoeia (such as U.S. Pharmacopoeia, China Pharmacopoeia or European Pharmacopoeia) for use in animals, and more particularly in humans.

As used herein, "pharmaceutically acceptable salts" refers to derivatives of the compounds of present disclosure wherein the parent compound is modified by converting an existing acidic moiety (e.g. carboxyl and the like) or base moiety (e.g. amine, alkali and the like) to its salt form. In many cases, compounds of present disclosure are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups

similar thereto. And the pharmaceutically acceptable salts are acid and/or base salts that retain biological effectiveness and properties of the parent compound, which typically are not biologically or otherwise undesirable. Suitable pharmaceutically acceptable salts of a compound of the present disclosure includes, for example, an acid-addition salt, which can be derived from for example an inorganic acid (for example, hydrochloric, hydrobromic, sulfuric, nitric, phosphoric acid and the like) or organic acid (for example, formic, acetic, propionic, glycolic, oxalic, maleic, malonic, succinic, fumaric, tartaric, trimesic, citric, lactic, phenylacetic, benzoic, mandelic, methanesulfonic, napadisylic, ethanesulfonic, toluenesulfonic, trifluoroacetic, salicylic, sulfosalicylic acids and the like). In some embodiments, the pharmaceutically acceptable salt of the compound of the present disclosure is a formic acid salt. In some embodiments, the pharmaceutically acceptable salt of the compound of the present disclosure is a TFA salt.

Suitable pharmaceutically acceptable salts of a compound of the present disclosure also include, for example, an base-addition salt, which can be derived from for example an inorganic bases (for example, sodium, potassium, ammonium salts and hydroxide, carbonate, bicarbonate salts of metals from columns I to XII of the periodic table such as calcium, magnesium, iron, silver, zinc, copper and the like) or organic bases (for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like). Certain organic amines include but are not limited to isopropylamine, benzathine, cholinate, diethanolamine, diethylamine, lysine, meglumine, piperazine and tromethamine. The skilled person would appreciate that adding acids or bases for forming acid/base-addition salts other than those shown in the examples may also be possible. Lists of additional suitable salts can be found, *e.g.* in “Remington's Pharmaceutical Sciences”, 20th ed., Mack Publishing Company, Easton, Pa., (1985); and in “Handbook of Pharmaceutical Salts: Properties, Selection, and Use” by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

The present disclosure also includes active intermediates, active metabolites and prodrugs of the compounds of present disclosure. As used herein, an “active intermediate” refer to intermediate compound in the synthetic process, which exhibits the same or essentially the same biological activity as the final synthesized compound.

As used herein, an "active metabolite" refers to a break-down or end product of a compound of the present disclosure or its salt or prodrug produced through metabolism or biotransformation in the animal or human body, which exhibits the same or essentially the same biological activity as the specified compound. Such metabolites may result from, for example, oxidation, reduction, hydrolysis, amidation, deamidation, esterification, deesterification, enzymatic cleavage, and the like, of the administered compound or salt or prodrug.

As used herein, "prodrugs" refer to any compounds or conjugates which release the active parent drug when administered to an animal or human subject. Prodrugs can be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compounds. Prodrugs include compounds wherein hydroxyl, amino, sulfhydryl, or carboxyl group is bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, sulfhydryl, or carboxyl group respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the present disclosure. Preparation and use of prodrugs is discussed in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems", Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are hereby incorporated by reference in their entirety.

Synthetic Method

Synthesis of the compounds provided herein, including pharmaceutically acceptable salts thereof, are illustrated in the synthetic schemes in the examples. The compounds provided herein can be prepared using any known organic synthesis techniques and can be synthesized according to any of numerous possible synthetic routes, and thus these schemes are illustrative only and are not meant to limit other possible methods that can be used to prepare the compounds provided herein. Additionally, the steps in the Schemes are for better illustration and can be changed as appropriate. The embodiments of the compounds in examples were synthesized for the purposes of research and potentially submission to regulatory agencies.

The reactions for preparing compounds of the present disclosure can be carried out in suitable solvents, which can be readily selected by one skilled in the art of organic synthesis. Suitable solvents can be substantially non-reactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, e.g. temperatures that can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected by a skilled artisan.

Preparation of compounds of the present disclosure can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 3rd Ed., Wiley & Sons, Inc., New York (1999), which is incorporated herein by reference in its entirety.

Reactions can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g. ^{1}H or ^{13}C), infrared spectroscopy, spectrophotometry (e.g. UV-visible), mass spectrometry, or by chromatographic methods such as high performance liquid chromatography (HPLC), liquid chromatography-mass spectroscopy (LCMS), or thin layer chromatography (TLC). Compounds can be purified by those skilled in the art by a variety of methods, including high performance liquid chromatography (HPLC) ("Preparative LC-MS Purification: Improved Compound Specific Method Optimization" Karl F. Blom, Brian Glass, Richard Sparks, Andrew P. Combs J. Combi. Chem. 2004, 6(6), 874-883, which is incorporated herein by reference in its entirety), and normal phase silica chromatography.

The structures of the compounds in the examples are characterized by nuclear magnetic resonance (NMR) or/and liquid chromatography-mass spectrometry (LC-MS). NMR chemical shift (δ) is given in the unit of 10^{-6} (ppm). ^{1}H-NMR spectra is recorded in dimethyl sulfoxide-d_6 (DMSO-d_6) or $CDCl_3$ or CD_3OD or D_2O or Acetone_d6 or CD3CN (from Aldrich or Cambridge Isotope Lab., Inc.) on Bruker AVANCE NMR (400 MHz)

spectrometers using ICON-NMR (under TopSpin program control), or Varian 400MR NMR or Varian VNMR400 NMR (400 MHz) spectrometers (under VnmrJ program control) with tetramethylsilane as an internal standard.

MS measurement is carried out using Shimadzu 2010 Mass Spectrometer or Agilent 6110A MSD or 1969A TOF mass spectrometer using electrospray, chemical and electron impact ionization methods from a range of instruments.

High Performance Liquid Chromatography (HPLC) measurement is carried out on Shimadzu LC-20A systems or Shimadzu LC-2010HT series, or Agilent 1200 LC or Agilent 1100 series using Ultimate XB-C18 column (3.0*50mm, 3um or 3.0*150mm, 3um), or Xbridge shieldRP18 column (5um, 50mm*2.1mm), or Xtimate C18 column (3um, 2.1*30mm), or MERCK RP18 2.5-2 mm etc.

Thin layer chromatography is carried out using Yantai Huanghai HSGF254 silica gel or Anhui Liang Chen Gui Yuan plates. The silica gel plates used for thin layer chromatography (TLC) are 0.15mm~0.2mm. The silica gel plates used for separating and purifying products by TLC are 0.4mm~0.5mm.

Purified chromatographic column uses the silica gel as the carrier (100~200, 200~300 or 300~400 mesh, produced by Yantai Huanghai co., or Anhui Liang Chen Gui Yuan co., etc.), or flash column (silica-CS flash column 40-60 um, or reversed phase C18 column 20-35um, produced by Agela Technologies, etc.) or flash column silica-CS (40-60um) or C18 column (20-40um) by Agela Technologies in the Teledyne ISCO combi-flash or Biotage flash system. The size of columns are adjusted according to the amount of compounds.

The known starting materials of the present disclosure can be synthesized by using or according to the known methods in the art, or can be purchased from Alfa Aesar, TCI, Aldrich, Bepharm, and Scochem (or PharmaBlock, Bide, Amatek, Stru Chem, Firster Pharmaceutical, Titan (Adamas) etc.).

Unless otherwise specified, the reactions are all carried out under argon or nitrogen atmosphere. Argon or nitrogen atmosphere refers to that the reaction flask is connected to an argon or nitrogen balloon with a volume of about 1L. Hydrogenation is usually carried out under pressure. Unless otherwise specified, the reaction temperature in the examples is ambient temperature, which is 10°C~30°C.

The reaction progress are monitored by TLC or/and LC-MS. The eluent systems used for the reactions include dichloromethane-methanol system and petroleum ether-ethyl acetate system. The volume ratios of the solvents are adjusted according to the different polarities of compounds.

The elution system of column chromatography used for purifying compounds and eluent system of TLC include dichloromethane-methanol system and petroleum ether-ethyl acetate system. The volume ratios of the solvents are adjusted according to the different polarities of compounds. A small amount of alkaline or acidic agents (0.1%~1%) such as formic acid, or acetic acid, or TFA, or ammonia can be added for adjustment.

Abbreviations for chemicals used in the synthesis of the compounds provided herein are listed below:

BINAP	(±)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene
Brettphos Pd G3	(2-Dicyclohexylphosphino-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)palladium(II) methanesulfonate
Boc	*tert*-Butyloxycarbonyl
$CDCl_3$	Deuterated chloroform
CF_3CH_2OTf	2,2,2-Trifluoroethyl trifluoromethanesulfonate
CH_3CN	Acetonitrile
CuI	Copper iodide
DCE	1,2-Dichloroethane
DCM or CH_2Cl_2	Dichloromethane
DEA	Diethyl amine
DIEA	*N*,*N*,-Diisopropylethylamine
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
DMSO-d_6	Dimethyl sulfoxide-d6
D_2O	Deuterium oxide
EtOH	Ethanol

HCl	Hydrochloric acid
K_2CO_3	Potassium carbonate
MeOH	Methanol
MeOD or CD_3OD	Methanol-d4
Me_2S	Dimethyl sulfide
$NaHCO_3$	Sodium bicarbonate
Na_2CO_3	Sodium carbonate
NaH	Sodium hydride
NaOH	Sodium hydroxide
NaCl	Sodium chloride
Na_2SO_4	Sodium sulfate
$NaIO_4$	Sodium periodate
Pd/C	Palladium on carbon
$Pd(OAc)_2$	Palladium(II) acetate
$Pd(dppf)Cl_2$	[1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium (II)
$Pd_2(dba)_3$	tris(Dibenzylideneacetone)dipalladium(0)
PPh_3	Triphenylphosphine
$RuCl_3$	Ruthenium(III) chloride
$SOCl_2$	Thionyl chloride
TBAF	Tetrabutylammonium fluoride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
t-BuONa	Sodium *tert*-butoxide
$Yb(OTf)_3$	Ytterbium(III) Trifluoromethanesulfonate

Pharmaceutical Composition

The present disclosure provides pharmaceutical compositions comprising at least one compound of the present disclosure, or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises more than one compound of the

present disclosure, or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises one or more compounds of the present disclosure, , or a pharmaceutically acceptable salt thereof, and a pharmaceutical acceptable carrier.

In general, the pharmaceutically acceptable carriers are conventional medicinal carriers in the art which can be prepared in a manner well known in the pharmaceutical art. In some embodiments, the compounds of the present disclosure, or a pharmaceutically acceptable salt thereof, may be admixed with pharmaceutically acceptable carrier for the preparation of pharmaceutical composition.

The form of pharmaceutical compositions depends on a number of criteria, including, but not limited to, route of administration, extent of disease, or dose to be administered. The pharmaceutical compositions can be formulated for oral, nasal, rectal, percutaneous, intravenous, or intramuscular administration. In accordance to the desired route of administration, the pharmaceutical compositions can be formulated in the form of tablets, capsule, pill, powder, granule, sachets, cachets, lozenges, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), spray, ointment, paste, cream, lotion, gel, patch, inhalant, or suppository.

In certain embodiments, the pharmaceutical compositions comprise about 1 mg to about 500 mg of the compounds of the present disclosure, or a pharmaceutically acceptable salt thereof,, particularly 1 mg to about 50 mg.

In some embodiments, the pharmaceutical compositions comprise one or more compounds of the present disclosure, or a pharmaceutically acceptable salt thereof, as a first active ingredient, and further comprise a second active ingredient. The second active ingredient can be any anti tumour agent known in the art, for examples, chemotherapeutics, cell signal transduction inhibitors, cell signal transduction inhibitors, alkylating agents, topoisomerase inhibitors, immunotherapeutic agents, mitosis inhibitors, antihormonal agents, chemotherapy drugs, EGFR inhibitors, CTLA-4 inhibitors, CDK 4/6 inhibitors, MEK inhibitors, PD-L1 inhibitors; OX40 agonists, antiandrogen inhibitors, IgG4 isotype antibodies, tyrosine kinase inhibitors, DNA methyltransferase inhibitors, Hsp90 inhibitors, FGFR inhibitors, mTOR inhibitors, aromatase inhibitors, VEGF inhibitors, LHRH antagonists, PI3K inhibitors, AKT inhibitors, aurora kinase inhibitors, MEK inhibitors,

HDAC inhibitors, BET inhibitors, PIK3CA inhibitors, proteasome inhibitors, other SERDs, farnesyltransferase inhibitors, VEGF-A antibodies, ErbB3 (Her3) antibodies, proteasome inhibitors, protein kinase Cβ inhibitors, anti PD-L1 antibodies, anti-IGF-1R antibodies, anti-HER2 antibodies, SERMs, IGF inhibitors, anti-IgG antibodies and the like. Representative examples of the anti tumour agents for treating cancers or tumors may include, but are not limited to, sorafenib, neratinib, sunitinib, dasatinib, vorinostat, temsirolimus, everolimus, pazopanib, trastuzumab, ado-trastuzumab emtansine, pertuzumab, bevacizumab, cetuximab, ranibizumab, pegaptanib, panitumumab, tremelimumab, pembrolizumab, nivolumab, ipilimumab, atezolizumab, avelumab, durvalumab, crizotinib, ruxolitinib, paclitaxel, vincristine, vinblastine, cisplatin, carboplatin, gemcitabine, tamoxifen, raloxifene, cyclophosphamide, chromabucil, carmustine, methotrexate, fluorouracil, actinomycin, doxorubicin, epirubicin, anthracycline, bleomycin, mitomycin-C, irinotecan, topotecan, teniposide interleukin, interferon, palbociclib, abemaciclib, enzalutamide, dovitinib, lapatinib, erlotinib, CC-486, ganetespib, Debio 1347, erdafitinib, vitusertib, sapanisertib, GDC-0980, gedatolisib, anastrazole, cediranib, goserelin, alpelisib, BKM120, copanlisib, AZD8835, GDC-0941, taselisib, AZD5363, MK2206, alisertib, selumetinib, entinostat, GS-5829, GSK525762, G1T38, ribociclib, MLN9708, GDC-0810, docetaxel, AFP464, tipifarnib, seribantumab, bortezomib, enzastaurin, gefitinib, AVE1642, xentuzumab, dalotuzumab, tamoxifen, AMG 479, MCLA-128 and the like. In some embodiments, the second active agent is a CDK 4/6 inhibitor for example palbociclib or abemaciclib.

According to this aspect of the invention there is provided a combination suitable for use in the treatment of cancer comprising a compound of formula (I) as defined hereinbefore or a pharmaceutically acceptable salt thereof and any one of the anti tumour agents listed above.

Therefore in a further aspect of the invention there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof in combination with an antitumour agent selected from one listed above.

Herein, where the term "combination" is used it is to be understood that this refers to simultaneous, separate or sequential administration. In one aspect of the invention "combination" refers to simultaneous administration. In another aspect of the invention

"combination" refers to separate administration. In a further aspect of the invention "combination" refers to sequential administration. Where the administration is sequential or separate, the delay in administering the second component should not be such as to lose the beneficial effect of the combination.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof in combination with an anti-tumour agent selected from one listed above, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof in combination with an anti-tumour agent selected from one listed above, in association with a pharmaceutically acceptable diluent or carrier for use in producing an anti-cancer effect.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof in combination with an anti-tumour agent selected from one listed above, in association with a pharmaceutically acceptable diluent or carrier for use in treating breast cancer (etc.).

According to a further aspect of the present invention there is provided a kit comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof in combination with an anti-tumour agent selected from one listed above.

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula (I) or a pharmaceutically acceptable salt thereof in a first unit dosage form;

b) an anti-tumour agent selected from one listed above; in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

In addition to their use in therapeutic medicine, the compounds of formula (I), or a pharmaceutically acceptable salt thereof, are also useful as pharmacological tools in the development and standardisation of in vitro and in vivo test systems for the evaluation of the

effects SERD activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

Method for Treatment

The compounds of the present disclosure are selective estrogen receptor downregulators (SERDs). In some embodiments, the compounds, or pharmaceutically acceptable salts thereof, of the present disclosure possess potent anti-cancer activity in early stage, actively progressing, metastatic and/or drug-resistant cancers. In addition, the compounds of the present invention, or pharmaceutically acceptable salts thereof may be useful in the treatment of other diseases and conditions, for example aging (e.g. menopause), metabolic diseases (e.g. diabetes, osteoporosis), cardiovascular diseases, and other diseases, in particular osteoporosis, and in particular aging.

The present disclosure provides a method of treating a disease or condition by administering a selective ER downregulating compound or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure.

In particular, the cancer includes but is not limited to, breast cancer, ovarian cancer, endometrial cancer, uterine cancer, lung cancer, hepatocellular carcinoma, adrenocortical carcinoma, pancreatic cancer, bladder cancer, or gastric cancer.

In some embodiments, the cancer is breast cancer, uterine cancer, ovarian cancer, endometrial cancer, or lung cancer. In some embodiments, the cancer is breast cancer. In some embodiments the cancer is hormone receptor positive breast cancer. In some embodiments the cancer is hormone receptor positive breast cancer in postmenopausal women whose disease progressed after endocrine therapy. In some embodiments the cancer is early stage breast cancer. In some embodiments the cancer is locally advanced breast cancer. In some embodiments the cancer is locally advanced and/or metastatic breast cancer. In some embodiments the cancer is metastatic breast cancer. In some embodiments the cancer is invasive breast cancer. In some embodiments the cancer is tamoxifen resistant breast cancer. In some embodiments the cancer is HR-positive, HER2-negative advanced or

metastatic breast cancer. In some embodiment, the cancer is uterine cancer. In some embodiments, the cancer is metastatic breast/uterine cancer.

As used herein, the terms “treatment” and “treat” refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease or disorder, or one or more symptoms thereof, as described herein. In some embodiments, treatment may be conducted after one or more symptoms have developed. In other embodiments, treatment may be conducted in the absence of symptoms. For example, treatment may be conducted to a susceptible individual prior to the onset of symptoms (e.g. in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example to present or delay their recurrence.

The therapeutically effective amount of a compound or a pharmaceutically acceptable salts thereof as provided herein will depend on various factors known in the art, such as for example body weight, age, past medical history, present medications, state of health of the subject and potential for cross-reaction, allergies, sensitivities and adverse side-effects, as well as the administration route and extent of disease development. Dosages may be proportionally reduced or increased by one of ordinary skill in the art (e.g. physician or veterinarian) as indicated by these and other circumstances or requirements.

Use of Compounds

In certain embodiments, the present disclosure provides use of the compounds, pharmaceutically acceptable salts thereof, or pharmaceutical composition of the present disclosure in the manufacture of medicaments for the treatment of ER mediated or dependent diseases or conditions.

In such situation, the present disclosure also provides a method of screening patient suitable for treating with the compounds or pharmaceutical composition of the present disclosure alone or combined with other ingredients (e.g. a second active ingredient, e.g. anticancer agent). The method includes sequencing the tumor samples from patients and detecting the accumulation of ER.

According to another aspect of the invention, there is therefore provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore for use as a medicament.

According to a further aspect of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for the selective downregulation of estrogen receptors in a warm-blooded animal such as man.

According to a further aspect of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for the treatment of ER mediated or dependent diseases or conditions in a warm-blooded animal such as man.

According to this aspect of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for the production of an anti-cancer effect in a warm-blooded animal such as man.

According to a further feature of the invention, there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of breast cancer, ovarian cancer, endometrial cancer, uterine cancer, lung cancer, hepatocellular carcinoma, adrenocortical carcinoma, pancreatic cancer, bladder cancer, or gastric cancer.

According to a further feature of the invention, there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of breast cancer.

According to a further feature of this aspect of the invention there is provided a method of selectively downregulating estrogen receptors in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore.

According to a further feature of this aspect of the invention there is provided a method of treating ER mediated or dependent diseases or conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore.

According to a further feature of this aspect of the invention there is provided a method for producing an anti-cancer effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore.

According to a further feature of this aspect of the invention there is provided a method of producing an anti-cancer effect in a warm-blooded animal, such as man, in need of such treatment which comprises (1) determining whether or not the warm blooded animal has an ER positive cancer and (2) if so administering to said animal an effective amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore.

According to an additional feature of this aspect of the invention there is provided a method of treating breast cancer, ovarian cancer, endometrial cancer, uterine cancer, lung cancer, hepatocellular carcinoma, adrenocortical carcinoma, pancreatic cancer, bladder cancer, or gastric cancer, in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore.

According to an additional feature of this aspect of the invention there is provided a method of treating breast cancer, in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore for use in producing a selective ER degradation effect in a warm-blooded animal such as man.

According to a further aspect of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore for use in the treatment of ER mediated or dependent diseases or conditions in a warm-blooded animal such as man.

According to this aspect of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore for use in the production of an anti-cancer effect in a warm-blooded animal such as man.

According to a further feature of the invention, there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore for use in the treatment of breast cancer, ovarian cancer, endometrial cancer, uterine cancer, lung cancer, hepatocellular carcinoma, adrenocortical carcinoma, pancreatic cancer, bladder cancer, or gastric cancer.

According to a further feature of the invention, there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore for use in the treatment of breast cancer.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier for use in producing a selective ER degradation effect in a warm-blooded animal such as man.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier for use in the treatment of ER mediated or dependent diseases or conditions in a warm-blooded animal such as man.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier for use in the production of an anti-cancer effect in a warm-blooded animal such as man.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier for use in the treatment of breast cancer, ovarian cancer, endometrial cancer, uterine cancer, lung cancer, hepatocellular carcinoma, adrenocortical carcinoma, pancreatic cancer, bladder cancer, or gastric cancer in a warm-blooded animal such as man.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier for

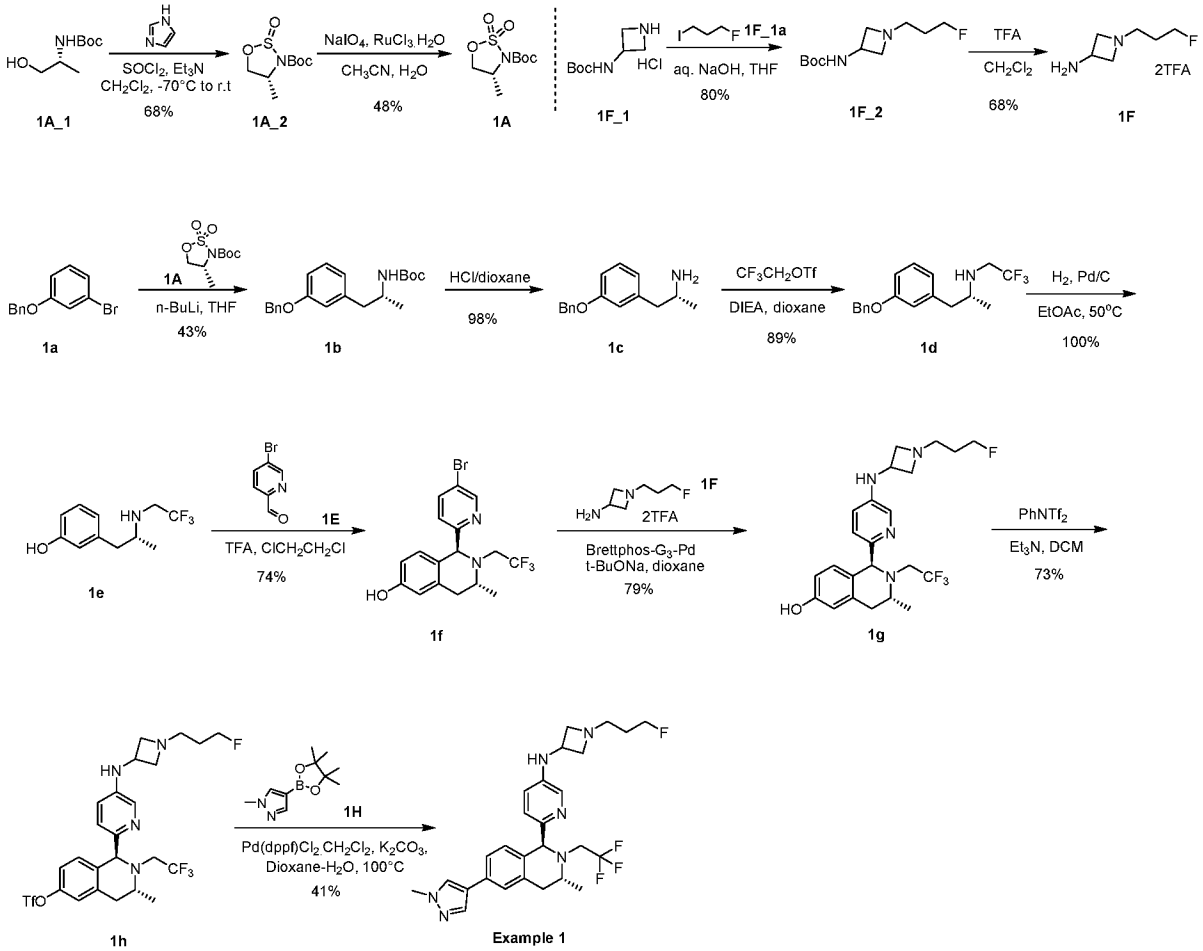
use in the treatment of breast cancer in a warm-blooded animal such as man.

EXAMPLES

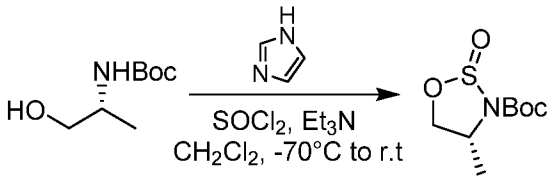
The followings further explain the general methods of the present disclosure. The compounds of the present disclosure may be prepared by the methods known in the art. The following illustrates the detailed preparation methods of the preferred compounds of the present disclosure. However, they are by no means limiting the preparation methods of the compounds of the present disclosure.

Example 1

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3R)-3-methyl-6-(1-methyl-1H-pyrazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine



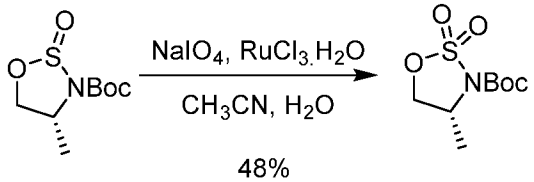
The procedure to prepare **1A**:



1A_1 1A_2

To a solution of imidazole (108.78 g, 1.6 mol) and triethylamine (120 mL, 878.87 mmol) in dichloromethane (1.3 L) was added $SOCl_2$ (32 mL, 439.43 mmol) at -70 °C dropwise. Then a solution of **1A_1** (70 g, 399.49 mmol) in dichloromethane (650 mL) was added to the reaction mixture dropwise at -70 °C over 3 hours. The resulting reaction mixture was stirred at -70 °C for 2 hours and then at 20 °C for 16 hours under nitrogen. Then the reaction mixture was washed with brine (300 mL × 2). The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give crude product. Another two batches of this reaction (60 g and 70 g scale of compound **1A_1**) were carried out with the same manner. The crude product of three batches (total 200 g of compound **1A_1**) was combined and purified by column chromatography on silica gel (petroleum ether/Ethyl acetate=10:1 to 9:1 to 8:1) to afford **1A_2** (190 g , 67.7% yield, 90% purity) as a yellow oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 4.78 (dd, *J* = 7.2 Hz, 9.2 Hz, 1H), 4.67 (t, *J* = 9.2 Hz, 1H), 4.09-3.98 (m, 1H), 1.55-1.45 (m, 12H).



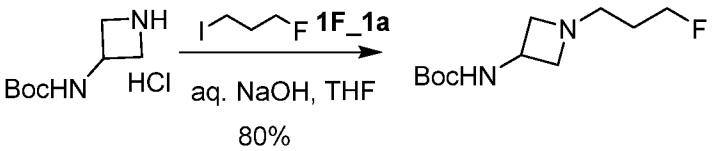
1A_2 1A

To a solution of **1A_2** (90 g, 406.7 mmol) in acetonitrile (900 mL) and water (420 mL) was added $RuCl_3 \cdot H_2O$ (917 mg, 2.51 mmol), followed by $NaIO_4$ (104.4 g, 488.08 mmol) in portions at room temperature (11-19 °C). The resulting mixture was stirred at 20 °C for 16 hours under nitrogen. The reaction mixture was filtered and the filtrate was extracted with ethyl acetate (300 mL × 3). The combined organic layers were washed with brine (300 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give crude product. Another batch with 100 g scale of compound **1A_2**

was carried out with same manner. The crude product of the two batches was combined and re-crystallized from petroleum ether/ethyl acetate (7:1, 800 mL) and then filtered. The cake was dried under vacuum to obtain **1A** (82.4 g pure product) as a white solid. The filtrate was concentrated under reduced pressure and then recrystallized again from petroleum ether/ethyl acetate (15:1, 640 mL). The cake was dried under reduced pressure to afford 17.5 g product (~90% purity) as a white solid. Totally the yield was about 48%.

^{1}H NMR (400MHz, $CDCl_3$): δ = 4.67 (dd, *J* = 5.6, 9.2 Hz, 1H), 4.51-4.36 (m, 1H), 4.20 (dd, *J* = 3.2, 9.2 Hz, 1H), 1.56 (s, 9H), 1.51 (d, *J* = 6.4 Hz, 3H).

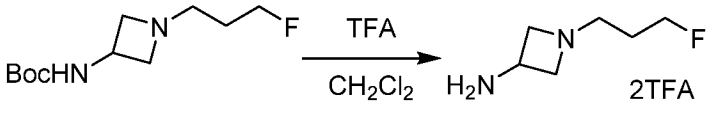
Procedure to prepare **1F**:



1F_1 **1F_2**

To a solution of compound **1F_1** (10 g, 47.9 mmol, 1.0 eq) in THF (100 mL) was added an aqueous solution of NaOH (28.7 mL, 143.7 mmol, 5M). The reaction mixture was stirred at 17 °C for one hour. Compound **1F_1a** (9.9 g, 52.7 mmol, 1.1 eq) in THF (50 mL) was added dropwise to the above reaction. After that, the reaction was stirred at 17 °C for 12h. The reaction was concentrated in vacuo, diluted with water (80 mL), extracted with dichloromethane (80 mL x 3) and washed with brine (100 mL). The organic layers were dried over anhydrous sodium sulfate, filtered, concentrated and purified by column chromatography (2% methanol in CH_2Cl_2) to afford product **1F_2** (8.85 g, 79.6% yield) as white solid.

^{1}H NMR (400MHz, $CDCl_3$) δ = 4.95 (br s, 1H), 4.46 (dt, *J* = 47.2 Hz, 6.0 Hz, 2H), 4.34-4.22 (m, 1H), 3.64-3.60 (m, 2H), 2.88-2.70 (m, 2H), 2.52 (t, *J* = 7.2 Hz, 2H), 1.78-1.64 (m, 2H), 1.42 (s, 9H).



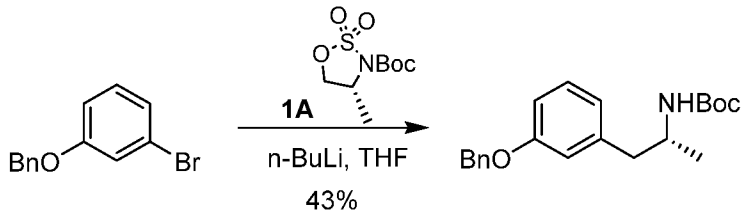
1F_2 68% **1F**

To a solution of compound **1F_2** (8.85 g, 38.09 mmol, 1.0 eq) in dichloromethane (100 mL)

was added TFA (34 mL) dropwise. The reaction was stirred at 16 °C for 3 hours. TLC showed the reaction was completed. The reaction was concentrated in vacuo and co-evaporated with dichloromethane to afford product **1F** (18.32 g TFA salt, purity: 67.8%) as light yellow oil.

^{1}H NMR (400MHz, $CDCl_3$) δ = 4.47 (t, *J* = 5.6 Hz, 1H), 4.44-4.32 (m, 3H), 4.30-4.18 (m, 3H), 3.34 (t, *J* = 7.4 Hz, 2H), 1.96-1.81 (m, 2H).

Procedure to prepare **Compound 1**:



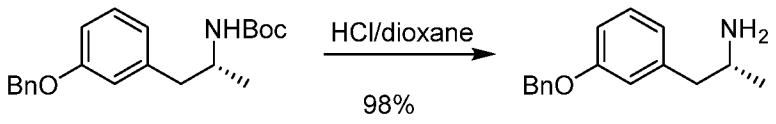
1a **1b**

To a solution of compound **1a** (10 g, 38.17 mmol) in THF (100 mL), n-BuLi (20 mL, 45.8mmol, 2.5 M in hexane) was added at -65 °C dropwise over 30 min. After stirred for one hour, a solution of compound **1A** (9.05 g, 38.17 mmol) in THF (50 mL) was added dropwise to the above reaction mixture dropwise and keep the temperature at -65 °C. Then the reaction mixture was stirred at -70 °C for another 2 hours and then slowly warmed to 3-12 °C for 5 hours. Then the reaction was quenched with 1N citric acid (30 mL) and then the mixture was stirred at 20 °C for 30 min. The resulting mixture was extracted with ethyl acetate (300 mL x 3). The combined organic layers were washed with brine (100 mL x 2), dried over anhydrous sodium sulfate and then filtered. The filtrate was evaporated under vacuum to give crude product, which was purified by column chromatography on silica gel (0-10% of ethyl acetate in petroleum ether) to give compound **1b** (5.6 g, 43% yield) as a white solid.

LCMS: t_R = 4.153 min in 10-80AB_7min_220&254_Shimadzu.lcm chromatography (Xtimate C18 2.1*30mm), MS (ESI) m/z 285.9 $[M-55+H]^+$.

^{1}H NMR ($CDCl_3$ 400MHz): δ = 7.47-7.43 (m, 2H), 7.40 (t, *J* = 7.2 Hz, 2H), 7.36-7.31 (m, 1H), 7.22 (t, *J* = 7.8 Hz, 1H), 6.89-6.77 (m, 3H), 5.06 (s, 2H), 4.39 (br s, 1H), 3.92 (br s, 1H), 2.84 (dd, *J* = 5.2, 13.2 Hz, 1H), 2.63 (dd, *J* = 7.2, 13.0 Hz, 1H), 1.44 (s, 9H), 1.08 (d, *J* = 6.4

Hz, 3H).

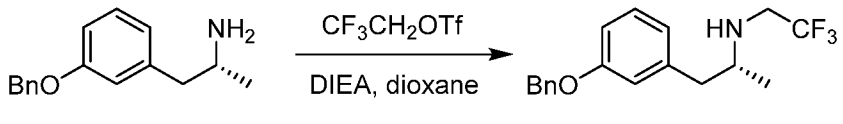


1b **1c**

To a solution of compound **1b** (5.6 g, 16.4 mmol) in 4 M HCl/1,4-dioxane (100 mL) was stirred at -1~8 °C for 16 hours. Then the reaction mixture was concentrated and the residue was basified with saturated aqueous $NaHCO_3$ to pH = 8. The aqueous layer was extracted with ethyl acetate (300 mL × 4). The combined organic layers were dried over anhydrous sodium sulfate and then filtered. The filtrate was concentrated under vacuum to give compound **1c** (3.9 g, 98% yield) as yellow oil.

LCMS: t_R = 0.801 min in 5-95AB_220&254 chromatography (Merck RP18 2.5-2mm), MS (ESI) m/z = 242.0 $[M+H]^+$.

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.47-7.30 (m, 5H), 7.23 (t, *J* = 7.6 Hz, 1H), 6.87-6.78 (m, 3H), 5.07 (s, 2H), 3.22-3.13 (m, 1H), 2.70 (dd, *J* = 5.2, 13.2 Hz, 1H), 2.50 (dd, *J* = 8.0, 13.2 Hz, 1H), 1.13 (d, *J* = 6.4 Hz, 3H).

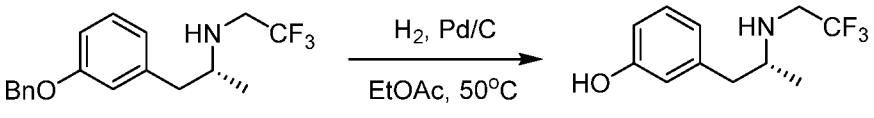


1c **1d**

To a solution of compound **1c** (3.9 g, 16.18 mmol) and DIEA (6.3 g, 48.54 mmol) in 1,4-dioxane (80 mL), CF_3CH_2OTf (3.8 g, 16.18 mmol) was added. After the reaction mixture was stirred at 80°C for 16 hours, the mixture was concentrated under vacuum and the residue was dissolved in ethyl acetate (100 mL). The resulting mixture was washed with brine (50 mL x 2), dried over anhydrous sodium sulfate and then filtered. The filtrate was concentrated under vacuum to obtain the crude product, which was purified by column chromatography on silica gel (0-10% of ethyl acetate in petroleum ether) to obtained compound **1d** (4.7 g, 89% yield) as oil.

LCMS: t_R = 1.070 min in 10-80AB_220&254 chromatography (Xtimate C18 2.1*30mm), MS (ESI) m/z = 324.0 $[M+H]^+$.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.47-7.31 (m, 5H), 7.23 (t, *J* = 8 Hz, 1H), 6.88-6.78 (m, 3H), 5.07 (s, 2H), 3.15 (q, *J* = 9.6 Hz, 2H), 3.07-2.99 (m, 1H), 2.73-2.58 (m, 2H), 1.08 (d, *J* = 6.4 Hz, 3H).

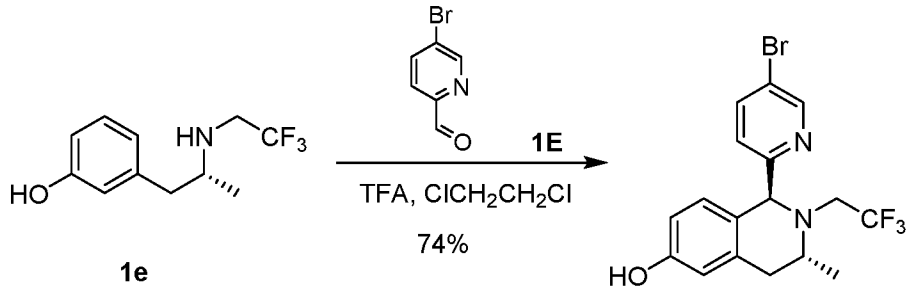


1d **1e**

To a mixture of compound **1d** (4.70 g, 14.54 mmol) in ethyl acetate (150 mL) was added 10% Pd/C (1.0 g, 50% water) at room temperature (4-9 °C). Then the reaction mixture was stirred at 50 °C under H_2 atmosphere (15 Psi, H_2 balloon) for 6 hours. Then the reaction mixture was filtered through celite and washed with ethyl acetate (15 mL x 3). The combined filtrate was concentrated under vacuum to afford compound **1e** (3.40 g, 100%) as a light brown gum.

LCMS: t_R = 0.254 min in 5-95AB_1.5min_220&254.lcm chromatography (Merck RP18 2.5-2mm), MS (ESI) m/z 234.0 $[M+H]^+$.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.18 (t, *J* = 7.6 Hz, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 6.71 (dd, *J* = 2.0, 8.0 Hz, 1H), 6.67 (s, 1H), 3.18 (q, *J* = 9.2 Hz, 2H), 3.12-2.99 (m, 1H), 2.73-2.55 (m, 2H), 1.11 (d, *J* = 6.4 Hz, 3H).



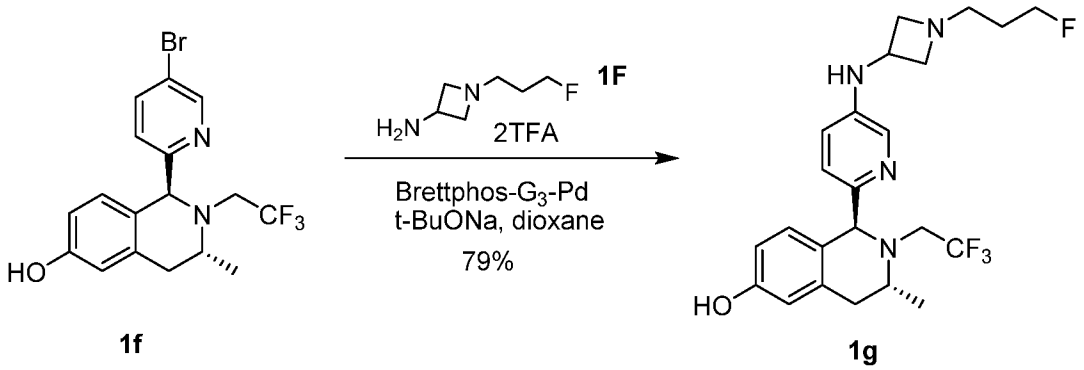
1e **1f**

To a solution of compound **1e** (3.40 g, 14.58 mmol) in 1,2-dichloroethane (300 mL) was added compound **1E** (4.07 g, 21.87 mmol), followed by TFA (3.26 mL, 43.73 mmol) at room temperature (4-9 °C). Then the reaction mixture was stirred at stirred at room temperature (4-9 °C) under nitrogen for 16 hours. Then the reaction mixture was poured into saturated aqueous $NaHCO_3$ (200 mL) under stirring. The resulting mixture was separated. The aqueous layer was extracted with dichloromethane (40 mL x 2). The combined organic layers were dried over anhydrous sodium sulfate and then filtered. The filtrate was concentrated under

vacuum to give crude product, which was purified by column chromatography on silica gel (0~20% ethyl acetate in petroleum ether) to afford an inseparable 4:1 diastereomers (4.3 g, 74%) as a light yellow solid. The major isomer compound **1f** was characterized below.

LCMS: t_R = 2.202 min in 30-90AB_7min_220&254.lcm chromatography (Xtimate C18 2.1*30mm), MS (ESI) m/z 402.9 $[M+H]^+$.

^{1}H NMR (400MHz, $CDCl_3$): δ = 8.56 (d, *J* = 2.0 Hz, 1H), 7.77 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 6.72 (d, *J* = 8.8 Hz, 1H), 6.55 (s, 1H), 6.52 (dd, *J* = 2.4, 8.4 Hz, 1H), 5.70 (s, 1H), 4.93 (s, 1H), 3.48-3.35 (m, 1H), 3.30-3.16 (m, 1H), 3.08 (dd, *J* = 4.8, 16.4 Hz, 1H), 3.00-2.85 (m, 1H), 2.54 (dd, *J* = 6.4, 16.8 Hz, 1H), 1.07 (d, *J* = 6.4 Hz, 3H).

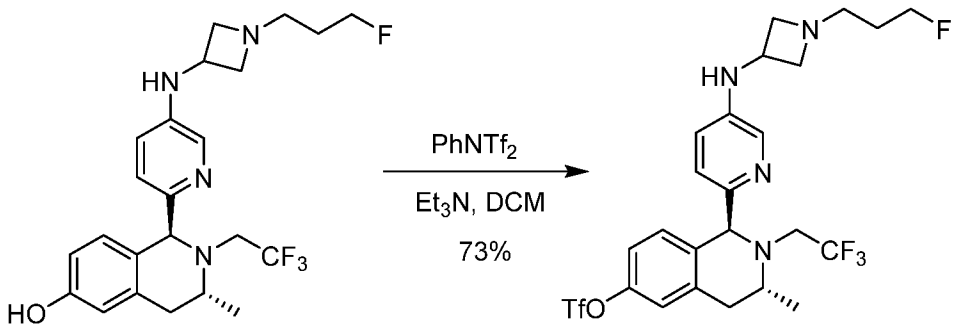


To a mixture of compound **1f** (3.80 g, 9.47 mmol), Brettphos Pd-G3 (1.29 g, 1.42 mmol) and *t*-BuONa (9.10 g, 94.71 mmol) in 1,4-dioxane (130 mL) was added a solution of **1F** (6.82 g, 12.84 mmol) in 1,4-dioxane (20 mL) under nitrogen. Then the reaction mixture was stirred at 80°C for 2 hours under nitrogen. Then the reaction mixture was combined with the pilot reaction batch (0.5 g scale of compound **1f**), extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (200 mL), dried over anhydrous sodium sulfate and then filtered, the filtrate was concentrated under vacuum to give crude product, which was purified by column chromatography on silica gel (0~10% methanol in dichloromethane) to afford compound **1g** (4.25 g in total with 78.8% average yield, 90% purity) as a yellow solid.

LCMS: t_R = 0.761 min in 5-95AB_1.5min_220&254.lcm chromatography (Merck RP18 2.5-2mm), MS (ESI) m/z 453.1 $[M+H]^+$.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.79 (d, *J* = 2.8 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 6.79 (dd,

J = 2.8, 8.4 Hz, 1H), 6.64 (d, J = 8.4 Hz, 1H), 6.50 (d, J = 2.4 Hz, 1H), 6.44 (dd, J = 2.4, 8.4 Hz, 1H), 4.85 (s, 1H), 4.49 (td, J = 6.0, 47.2 Hz, 2H), 4.14-4.00 (m, 2H), 3.78-3.69 (m, 2H), 3.50-3.40 (m, 1H), 3.23-3.13 (m, 1H), 3.06 (dd, J = 4.8, 11.6 Hz, 1H), 3.01-2.91 (m, 3H), 2.64 (t, J = 7.2 Hz, 2H), 2.49 (dd, J = 6.0, 16.4 Hz, 1H), 1.86-1.68 (m, 2H), 1.04 (d, J = 6.4 Hz, 3H).

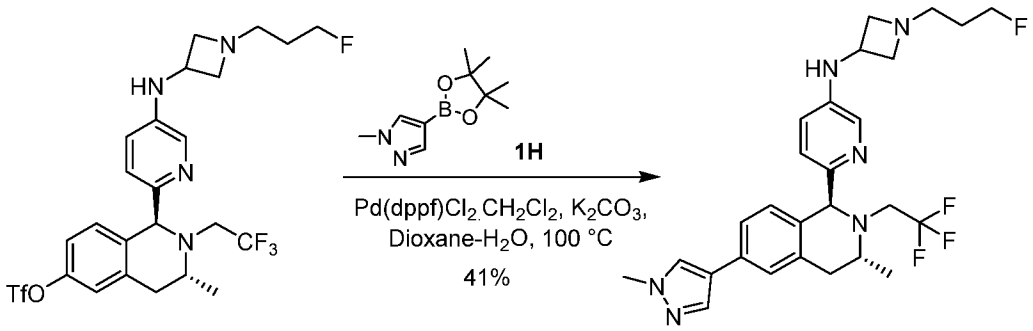


1g **1h**

To a mixture of compound **1g** (4.25 g, 9.39 mmol, 90% purity) in dichloromethane (190 mL) was added triethylamine (4.0 mL, 28.17 mmol), followed by $PhNTf_2$ (6.71 g, 18.78 mmol) at room temperature (4-14 °C). Then the reaction mixture was stirred at 25°C for 5 hours. Then the reaction mixture was concentrated under vacuum. The residue was diluted with ethyl acetate (50 mL) and water (50 mL) and then separated. The aqueous layer was extracted with ethyl acetate (20 mL x 2). The combined organic layers were washed with brine (150 mL x 3), dried over anhydrous sodium sulfate and then filtered. The filtrate was concentrated under vacuum to give crude product, which was purified by column chromatography on silica gel (0~5% methanol in dichloromethane) to afford compound **1h** (4.00 g, 72.8%) as a light yellow gum.

LCMS: t_R = 0.854 min in 5-95AB_1.5min_220&254.lcm chromatography (Merck RP18 2.5-2mm), MS (ESI) m/z 585.0 $[M+H]^+$.

^{1}H NMR ($CDCl_3$ 400MHz): δ = 7.83 (d, J = 2.4 Hz, 1H), 7.15 (d, J = 8.8 Hz, 1H), 7.03 (s, 1H), 6.98-6.92 (m, 2H), 6.80 (dd, J = 2.8, 8.4 Hz, 1H), 4.93 (s, 1H), 4.48 (dt, J = 47.2, 6.0 Hz, 2H), 4.17-4.07 (m, 2H), 3.83-3.73 (m, 2H), 3.59-3.48 (m, 1H), 3.30-3.12 (m, 2H), 3.04-2.96 (m, 3H), 2.70-2.57 (m, 3H), 1.86-1.69 (m, 2H), 1.08 (d, J = 6.4 Hz, 3H).



1h **Compound 1**

A mixture of compound **1h** (500 mg, 0.870 mmol), boronic ester **1H** (199 mg, 0.957 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (71 mg, 0.087 mmol) and K_2CO_3 (296 mg, 2.138 mmol) was purged with nitrogen. Then to the mixture was added a mixture solution of 1,4-dioxane and H_2O (v/v=10:1) (25 mL) under nitrogen. The resulting mixture was stirred at 100°C under nitrogen for 16 hours. Then the reaction mixture was diluted with water (40 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum to give crude product, which was purified by column chromatography on silica gel (0~5% methanol in dichloromethane) to afford chemical pure product (250 mg). Another batch of this reaction with the same scale was carried out with the same manner and 200 mg chemical pure product was obtained. The chemical pure product of these two batches was combined and further purified by chiral SFC [Column: DAIRALCEL OJ-H (250 mm * 30 mm, 5 um); Condition: 30% EtOH (0.1% NH_3H_2O) in CO_2; Flowrate: 60 mL/min] to afford **Compound 1** (330.5 mg in total, 100% chemical purity; 100% optical purity, 41% average yield) as a white solid.

LCMS: t_R = 1.837 min in 10-80AB_7min_220&254.lcm chromatography (Xtimate C18 2.1*30mm), MS (ESI) m/z 517.3 $[M+H]^+$.

HPLC: t_R = 2.29 min in 10-80_CD_1.2ml.met.chromatography (Ultimate C18 3.0um 3.0*50mm)

SFC: t_R = 2.330 min; 100% optical purity.

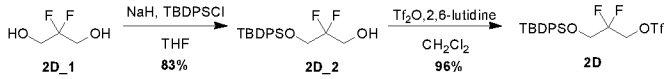
Method: Column: Chiralcel OJ-3 100×4.6mm I.D., 3um; Mobile phase: A: CO_2 B: ethanol (0.05% DEA)

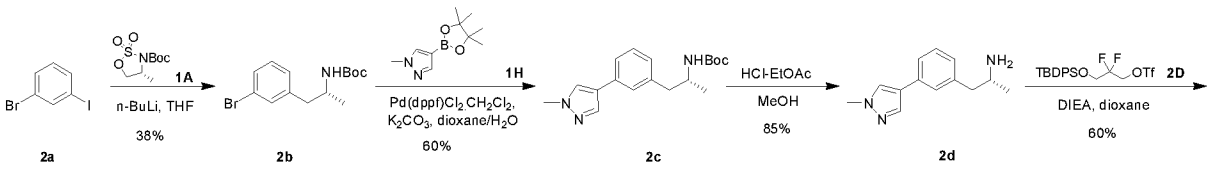
Gradient: from 5% to 40% of B in 4.5min and hold 40%; for 0.5 min, then 5% of B for 1 min; Flow rate: 2.8mL/min Column temperature:40 °C

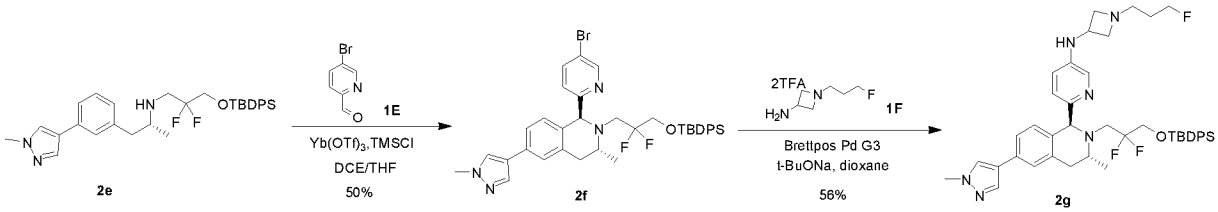
^{1}H NMR (400MHz, $CDCl_3$): δ = 7.85 (d, *J* = 2.8 Hz, 1H), 7.72 (s, 1H), 7.56 (s, 1H), 7.22 (s, 1H), 7.20-7.11 (m, 2H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.80 (dd, *J* = 2.8, 8.4 Hz, 1H), 4.91 (s, 1H), 4.50 (dt, *J* = 47.2, 6.0 Hz, 2H), 4.17-4.07 (m, 1H), 4.05-3.98 (m, 1H), 3.93 (s, 3H), 3.81-3.70 (m, 2H), 3.60-3.48 (m, 1H), 3.27-3.14 (m, 2H), 3.07-2.96 (m, 1H), 2.96-2.90 (m, 2H), 2.66-2.57 (m, 3H), 1.84-1.69 (m, 2H), 1.09 (d, *J* = 6.8 Hz, 3H).

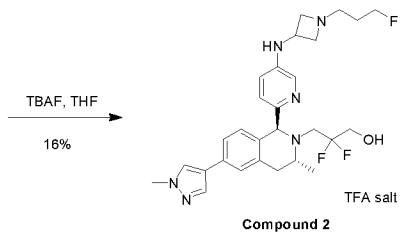
Example 2

2,2-difluoro-3-((1S,3R)-1-(5-((1-(3-fluoropropyl)azetidin-3-yl)amino)pyridin-2-yl)-3-methyl-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroisoquinolin-2(1H)-yl)propan-1-ol

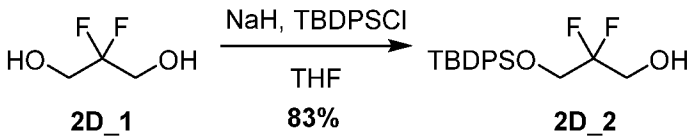








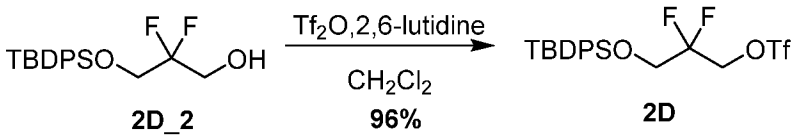
Procedure to prepare intermediate **2D**:



To a solution of compound **2D_1** (4.20 g, 37.47 mmol) in THF (85 mL) was added NaH

(1.50 g, 37.47 mmol, 60% purity) in portions slowly at 0°C. After the reaction mixture was stirred at 0°C for 30 min, TBDPSCl (10.3 g, 37.47 mmol) was added. During TBDPSCl was added, the reaction mixture turned to be gum and then to the mixture was added THF (100 mL). The reaction mixture was warmed to 20°C and then stirred at 20°C under nitrogen for 3 hours. Then the reaction mixture was poured into water (150 mL) under stirring. The resulting mixture was extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (200 mL), dried over anhydrous sodium sulfate and then filtered. The filtrate was concentrated under vacuum to give crude product, which was purified column chromatography on silica gel (0~4% ethyl acetate in petroleum ether) to afford **2D_2** (10.9 g, 83% purity) as a colorless oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.71-7.63 (m, 4H), 7.48-7.39 (m, 6H), 4.02-3.84 (m, 4H), 1.83 (t, *J* = 7.2 Hz, 1H), 1.08 (s, 9H).

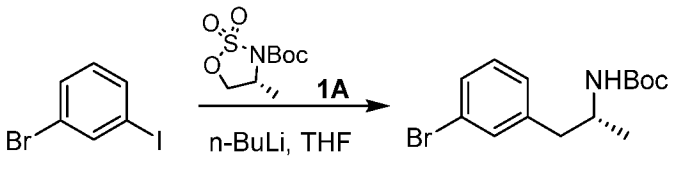


2D_2 **96%** **2D**

To a solution of compound **2D_2** (10.9 g, 31.10 mmol) and 2,6-lutidine (10.0 g, 93.30 mmol) in CH_2Cl_2 (220 mL) was added dropwise Tf_2O (10.4 mL, 62.20 mmol) at 0°C under nitrogen. Then the reaction mixture was stirred at 20°C under nitrogen for 3 hours. Then the reaction mixture was washed with HCl (1M) (150 mL × 2), saturated aqueous solution of $NaHCO_3$ (150 mL) and brine (150 mL). The resulting organic layer was dried over anhydrous sodium sulfate and then filtered. The filtrate was concentrated under vacuum to give crude product, which was purified column chromatography on silica gel (0~2% ethyl acetate in petroleum ether) to afford **2D** (14.4 g, 96% purity) as a colorless oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.76-7.56 (m, 4H), 7.54-7.35 (m, 6H), 4.76 (t, *J* = 11.2 Hz, 2H), 3.89 (t, *J* = 11.6 Hz, 2H), 1.09 (s, 9H).

Procedure to prepare **Compound 2**:

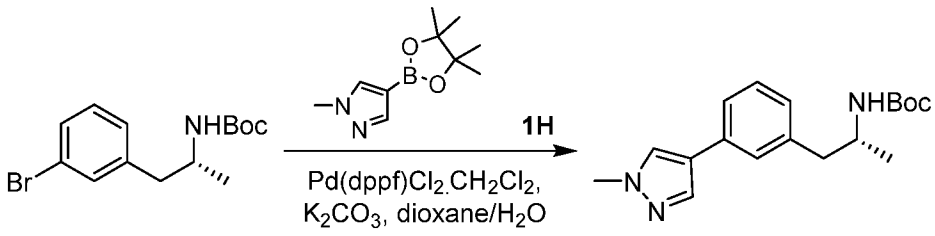


2a **2b**

To the mixture of compound **2a** (5.0 g, 17.7 mmol) in THF (60 mL) was added a solution of n-BuLi (7.8 mL, 19.5 mmol) at -70 °C under nitrogen over 5 min. The reaction mixture was stirred at this temperature for 5 min while a white suspension was observed, then stirred for another 30 min at -70 °C. A solution of compound **1A** (4.2 g, 17.7 mmol) in THF (20 mL) was added dropwise at -70 °C under nitrogen over 5 min. The resulting mixture was stirred at -70 °C for 3.5 hours. The reaction was quenched with citric acid (100 mL, 1 M) and extracted with ethyl acetate (300 mL × 2). The combined organic layer was washed with brine (200 mL), dried over anhydrous sodium sulfate and concentrated in vacuum to give the crude residue, which was purified by flash column chromatography on silica gel (ethyl acetate in petroleum ether from 0 to 10%) to afford the title product **2b** (2.1 g, 38% yield) as a white solid.

LCMS: t_R = 0.984 min in 5-95AB_220&254.lcm chromatography (Merck RP18 2.5-2mm), MS (ESI) m/z=259.8 $[M-56]^+$.

^{1}H NMR: (400MHz, $CDCl_3$) δ = 7.40-7.30 (m, 2H), 7.19-7.14 (m, 1H), 7.14-7.10 (m, 1H), 4.36 (br s, 1H), 3.89 (br s, 1H), 2.90-2.77 (m, 1H), 2.64 (dd, *J* = 7.6, 12.0 Hz, 1H), 1.44 (s, 9H), 1.10 (d, *J* = 6.0 Hz, 3H).



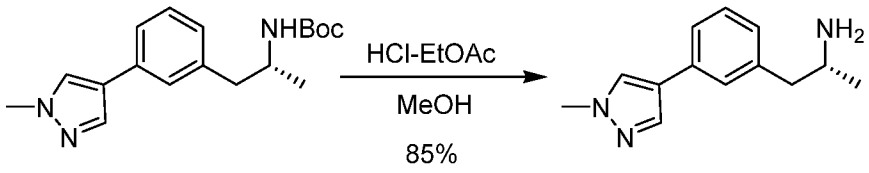
2b **2c**

To a solution of compound **2b** (1.5 g, 4.77 mmol), K_2CO_3 (1.06 g, 7.64 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (1.4 g, 2.385 mmol)) in 1,4-dioxane/H_2O (20 mL/2 mL) was added compound **1H** (1.09 g, 5.25 mmol) at 12-21°C. The mixture was stirred at 100°C under

nitrogen atmosphere for 15 hours. The reaction was combined with pilot batch and extracted with ethyl acetate (100 mL × 3). The combined organic layers was washed with brine (100 mL), dried over anhydrous sodium sulfate and then concentrated in vacuum to give the crude residue, which was purified by flash column chromatography on silica gel (Ethyl acetate/petroleum ether = 0-20%) to afford the title product **2c** (1.0 g, 60% yield) as a yellow oil.

LCMS: t_R = 0.858 min in 5-95AB_220&254.lcm chromatography (Agilent pursult5 C18 20*2mm), MS (ESI) m/z= 316.1 $[M+H]^+$.

^{1}H NMR: (400MHz, $CDCl_3$) δ = 7.76 (s, 1H), 7.62 (s, 1H), 7.35-7.31 (m, 1H), 7.31-7.28 (m, 2H), 7.05 (d, *J* = 7.6 Hz, 1H), 4.41 (br s, 1H), 4.00-3.90 (m, 1H), 3.95 (s, 3H), 2.88 (br d, *J* = 7.6 Hz, 1H), 2.67 (dd, *J* = 7.6, 13.2 Hz, 1H), 1.43 (s, 9H), 1.11 (d, *J* = 6.4 Hz, 3H).

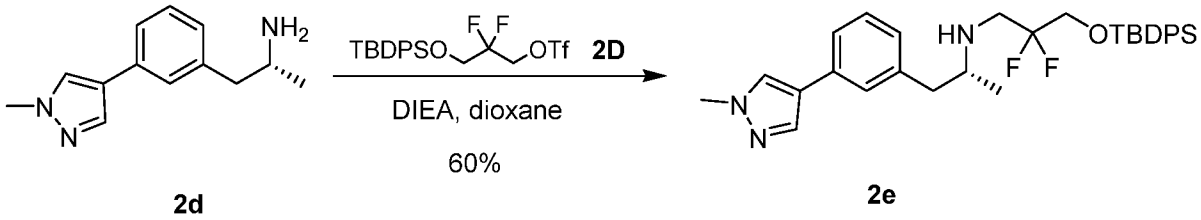


2c **2d**

To the mixture of compound **2c** (1.0 g, 3.17 mmol) in MeOH (3 mL) was added HCl/ethyl acetate (4 M, 6 mL), then stirred at 14-19°C for 3 hours. The mixture was concentrated in vacuum to remove most of the solvent and the residue was treated with saturated aqueous solution of $NaHCO_3$ to pH=8 and concentrated in vacuum again to give the crude, which was purified by flash column chromatography on silica gel (methanol/dichloromethane = 0-10%) to afford the title product **2d** (600 mg, 85% yield) as yellow oil.

LCMS: t_R = 0.589 min in 5-95AB_220&254.lcm chromatography (Agilent pursult5 C18 20*2mm), MS (ESI) m/z=215.7 $[M+H]^+$.

^{1}H NMR: (400MHz, $CDCl_3$) δ = 7.78 (s, 1H), 7.63 (s, 1H), 7.38-7.29 (m, 3H), 7.06 (d, *J* = 7.6 Hz, 1H), 3.92 (s, 3H), 3.46-3.39 (m, 1H), 2.95 (dd, *J* = 6.8, 13.2 Hz, 1H), 2.81 (dd, *J* = 7.6, 13.2 Hz, 1H), 1.30 (d, *J* = 6.4 Hz, 3H).

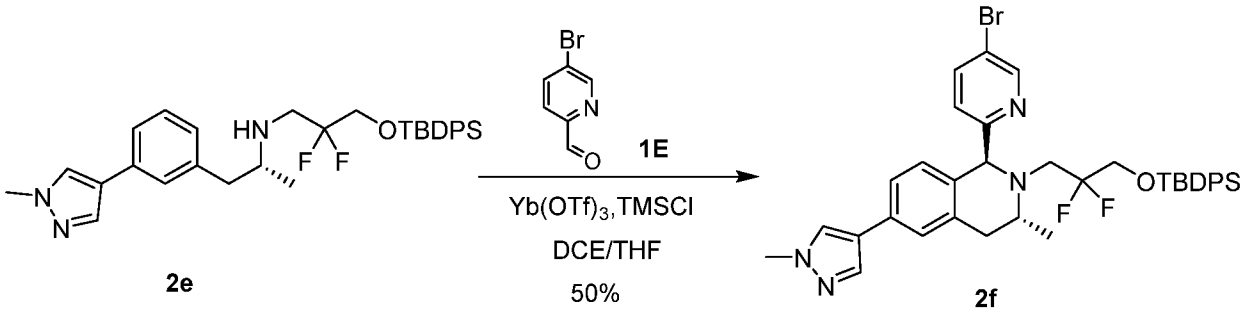


2d **2e**

To a solution of compound **2d** (600 mg, 2.79 mmol), DIEA (1.08 g, 8.37 mmol) in 1,4-dioxane (10 mL) was added compound **2D** (1.34 g, 2.79 mmol) at 7-21℃. The mixture was stirred at 80°C for 15 hours. The reaction was concentrated in vacuum to afford the residue, which was purified by flash column chromatography on silica gel (ethyl acetate/ petroleum ether = 0-30%) to give the title product **2e** (970 mg, 60% yield) as a yellow oil.

LCMS: t_R = 0.891 min in in 5-95AB_220&254.1cm chromatography (Agilent pursult5 C18 20*2mm), MS (ESI) m/z=548.4 $[M+H]^+$.

^{1}H NMR: (400MHz, $CDCl_3$) δ = 7.75 (s, 1H), 7.70-7.65 (m, 4H), 7.58 (s, 1H), 7.48-7.42 (m, 2H), 7.42-7.37 (m, 4H), 7.34-7.31 (m, 1H), 7.30-7.27 (m, 2H), 7.04 (d, *J* = 7.2 Hz, 1H), 3.94 (s, 3H), 3.87-3.80 (m, 2H), 3.26-3.09 (m, 2H), 3.08-2.97 (m, 1H), 2.79 (dd, *J* = 6.4, 13.2 Hz, 1H), 2.60 (dd, *J* = 6.4, 13.2 Hz, 1H), 1.08 (d, *J* = 6.4 Hz, 3H), 1.05 (s, 9H).



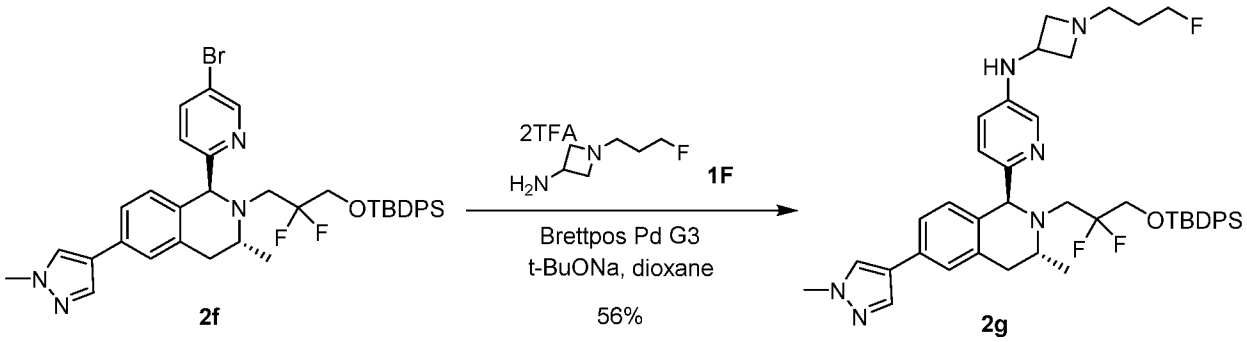
2e **2f**

To the mixture of compound **2e** (100 mg, 0.182 mmol) in DCE and THF (2 mL, 4/1) was added compound **1E** (41 mg, 0.220 mmol), TMSCl (21 mg, 0.182 mmol) and $Yb(OTf)_3$ (12 mg, 0.018 mmol), then the mixture was stirred at 70°C for 48 hours. The reaction was concentrated in vacuum to afford the residue, which was purified by flash column chromatography (ethyl acetate / petroleum ether =0-50%) to afford the title product **2f** (80 mg, 50% yield, the other diastereomer is not observed by ^{1}H NMR) as a yellow solid.

LCMS: t_R =1.101 min in 5-95AB_220&254.1cm chromatography (Merck RP18 2.5-2mm),

MS (ESI) m/z =717.3 $[M+H]^+$.

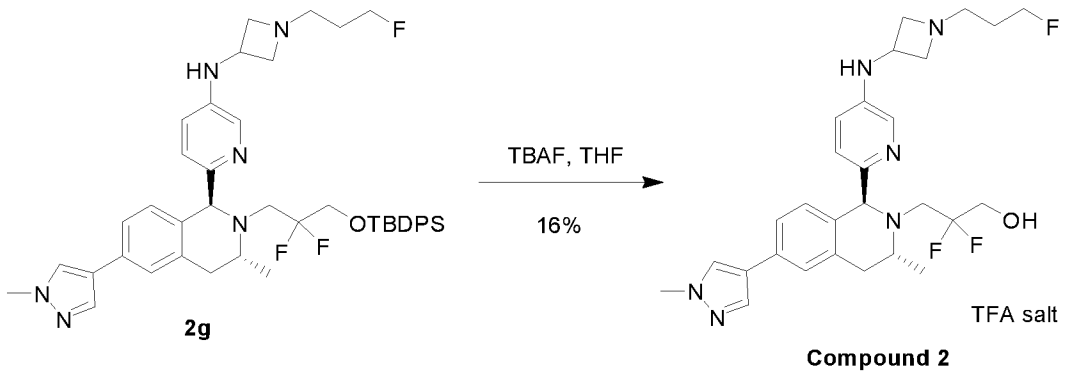
^{1}H NMR: (400MHz, $CDCl_3$) δ = 8.54 (d, *J* = 2.0 Hz, 1H), 7.74 (s, 1H), 7.64 (t, *J* = 6.4 Hz, 4H), 7.59-7.55 (m, 2H), 7.48-7.43 (m, 2H), 7.39 (q, *J* = 7.2 Hz, 4H), 7.24 (s, 1H), 7.18 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.0 Hz, 1H), 5.05 (s, 1H), 3.95 (s, 3H), 3.88-3.71 (m, 2H), 3.53-3.45 (m, 1H), 3.22 (q, *J* = 14.4 Hz, 1H), 3.01 (dd, *J* = 4.8, 16.4 Hz, 1H), 2.87 (q, *J* = 15.2 Hz, 1H), 2.63 (dd, *J* = 6.4, 16.0 Hz, 1H), 1.09 (d, *J* = 6.4 Hz, 3H), 1.03 (m, 9H).



To the mixture of compound **2f** (100 mg, 0.139 mmol) in 1,4-dioxane (3 mL) was added compound **1F** (66 mg, 0.182 mmol), Brettphos Pd-G3 (32 mg, 0.035 mmol) and t-BuONa (40 mg, 0.417 mmol), then the mixture was stirred at 80°C under nitrogen atmosphere for 3 hours. The reaction was concentrated in vacuum to give the crude, which was purified by flash column chromatography on silica gel ($MeOH/CH_2Cl_2$ =0-10%) to give the title product **2g** (60 mg, 56% yield) as a light-yellow oil.

LCMS: t_R =0.903 min in 5-95AB_220&254.lcm chromatography (Agilent pursult5 C18 20*2mm), MS (ESI) m/z = 767.5 $[M+H]^+$.

^{1}H NMR: (400MHz, $CDCl_3$) δ = 7.81 (d, *J* = 2.6 Hz, 1H), 7.73 (s, 1H), 7.67-7.63 (m, 4H), 7.57 (s, 1H), 7.45-7.37 (m, 6H), 7.21 (s, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.61 (dd, *J* = 2.8, 8.4 Hz, 1H), 4.96 (s, 1H), 4.50 (dt, *J* = 47.2, 6.0 Hz, 2H), 4.05 (br d, *J* = 6.0 Hz, 1H), 3.94 (s, 3H), 3.90-3.83 (m, 1H), 3.80-3.67 (m, 4H), 3.55-3.47 (m, 1H), 3.22-3.11 (m, 1H), 3.03-2.85 (m, 4H), 2.62-2.55 (m, 2H), 1.75-1.72 (m, 2H), 1.07 (d, *J* = 6.4 Hz, 3H), 1.03 (s, 9H).



2g Compound 2

To the mixture of compound **2g** (60 mg, 0.078 mmol) in THF (3 mL) was added TBAF(85 mg, 0.234 mmol), the mixture was stirred at 12-21°C for 16 hours. The reaction was concentrated in vacuum to give the crude reside, which was purified by prep-TLC (methanol/dichloromethane=1/10) followed by acidic prep-HPLC in TFA system [Waters Xbridge 150*25 5u Condition: 13-43%B (A: water (0.1% TFA) B: CH_3CN); Flow rate: 25 ml/min] to give the title product **Compound 2** (7.0 mg TFA salt, 16% yield) as a brown solid.

LCMS: t_R = 1.129 min in 10-80AB_3min_220&254 chromatography (A: Xtimate C18, 2.1*30mm, 3um), MS (ESI) m/z=529.3 $[M+H]^+$.

HPLC: t_R =3.14 min in 10-80_CD_1.2ml. met, XBridge Shield RP 18 2.1*50mm 5um

Chiral SFC: 93% purity.

Column: Chiralcel OJ-3 100×4.6mm I.D., 3um

Mobile phase: A: CO2 B: ethanol (0.05% DEA)

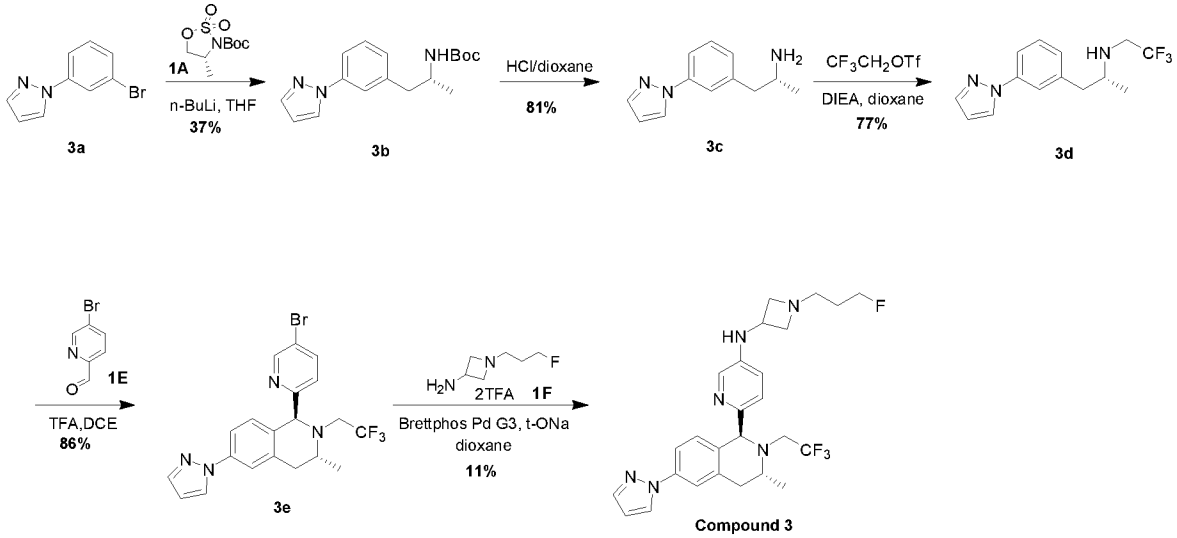
Gradient: from 5% to 40% of B in 4.5min and hold 40% for 2.5 min, then 5% of B for 1 min

Flow rate: 2.8mL/min; Column temperature: 40°C

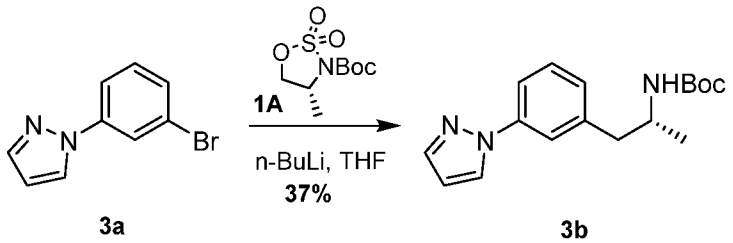
^{1}H NMR: (400MHz, MeOD) δ = 7.96 (s, 2H), 7.81 (s, 1H), 7.65 (d, *J* = 8.8 Hz, 1H), 7.56 (s, 1H), 7.45 (s, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 5.26 (s, 1H), 4.63 (t, *J* = 5.6 Hz, 4H), 4.51 (t, *J* = 5.6 Hz, 2H), 4.39-3.99 (m, 2H), 3.92 (s, 3H), 3.74 (td, *J* = 9.6, 15.6Hz, 2H), 3.54 (d, *J* = 5.6 Hz, 1H), 3.48-3.36 (m, 3H), 2.97-2.71 (m, 2H), 2.12-1.95 (m, 2H), 1.17 (d, *J* = 6.4 Hz, 3H).

Example 3

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3R)-3-methyl-6-(1H-pyrazol-1-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine

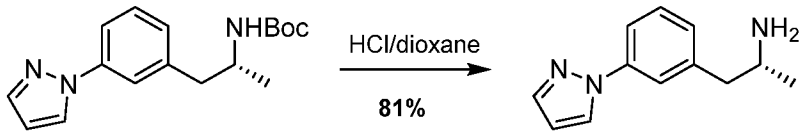


Procedure to prepare **Compound 3**:



To a solution of compound **3a** (2.8 g, 12.6 mmol) in THF (25 mL) at -78°C was added a solution of n-BuLi (6 mL, 15.1 mmol, 2.5M in hexane), the mixture was stirred for 30 min at -78°C. A solution of compound **1A** (2.98 g, 12.6 mmol) in THF (5 mL) was added to above solution at -78°C. The reaction mixture was stirred at -78°C for 4 hours. The reaction mixture was diluted with ethyl acetate (50 mL) and saturated aqueous ammonium chloride (50 mL), then separated. The aqueous layer was extracted with ethyl acetate (50 mL x 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated, purified by flash column (Petroleum: ether Ethyl acetate: 30/1 to 10/1) to give compound **3b** (1.4 g, 37% yield) as yellow oil.

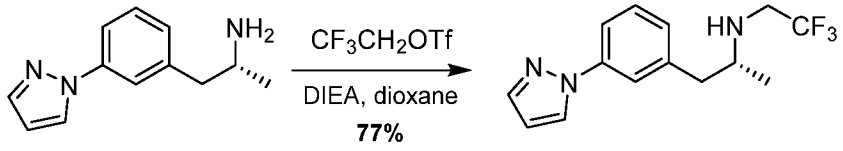
^{1}H NMR (400MHz, $CDCl_3$) δ = 7.62 (d, *J* = 1.6 Hz, 1H), 7.45-7.52 (m, 2H), 7.35-7.44 (m, 3H), 6.30 (d, *J* = 1.6 Hz, 1H), 4.31 (br s, 1H), 3.93 (br s, 1H), 2.75-2.93 (m, 2H), 1.42 (s, 9H), 1.03 (d, *J* = 6.4 Hz, 3H).



3b 3c

A solution of compound **3b** (1.4 g, 4.65 mmol) in 4M HCl/1,4-dioxane (20 mL) and dichloromethane (20 mL) was stirred for 15 hours at 6-10°C. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in water (45 mL), basified with aqueous $NaHCO_3$ till pH = 8 and extracted with dichloromethane/methanol (v/v: 3/1, 50 mL×2). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give compound **3c** (760 mg, 81% yield) as yellow oil.

LCMS: t_R = 0.195 min in 5-95AB_220&254 chromatography (Merck RP18 2.5-2mm), MS (ESI) m/z = 202.1 $[M+H]^+$.

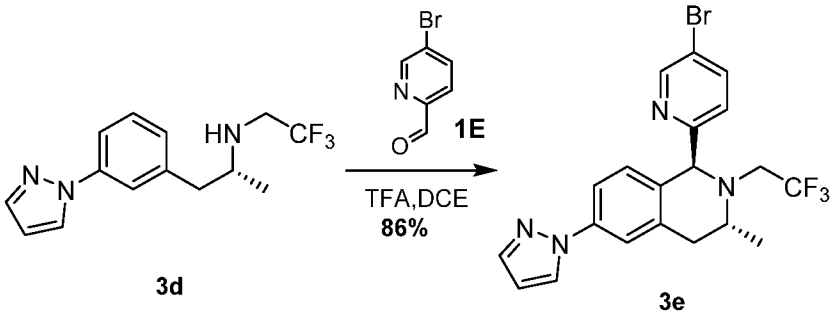


3c 3d

To a solution of compound **3c** (750 mg, 3.73 mmol) and DIEA (1.4 g, 11.2 mmol) in 1,4-dioxane (20 mL) was added CF_3CH_2OTf (952 mg, 4.1 mmol), the resulting mixture was stirred at 80°C for 15 hours. The reaction mixture was diluted with ethyl acetate (20 mL) and water (20 mL), then separated. The aqueous layer was extracted with ethyl acetate (20 mL x 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated, purified by flash column (Petroleum ether:Ethyl acetate: 30/1 to 15/1) to give compound **3d** (810 mg, 77% yield) as yellow oil.

LCMS: t_R = 0.544 min in 10-80AB_220&254 chromatography (Merck RP18 2.5-2mm), MS (ESI) m/z = 284.1 $[M+H]^+$.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.62 (d, *J* = 1.6 Hz, 1H), 7.45-7.52 (m, 2H), 7.39-7.45 (m, 3H), 6.28 (d, *J* = 1.6 Hz, 1H), 3.04 (q, *J* = 9.2 Hz, 2H), 2.91-2.99 (m, 1H), 2.81 (dd, *J* = 6.8 Hz, 14.8 Hz, 1H), 2.71 (dd, *J* = 6.8 Hz, 14.8 Hz, 1H), 1.02 (d, *J* = 6.0 Hz, 3H).



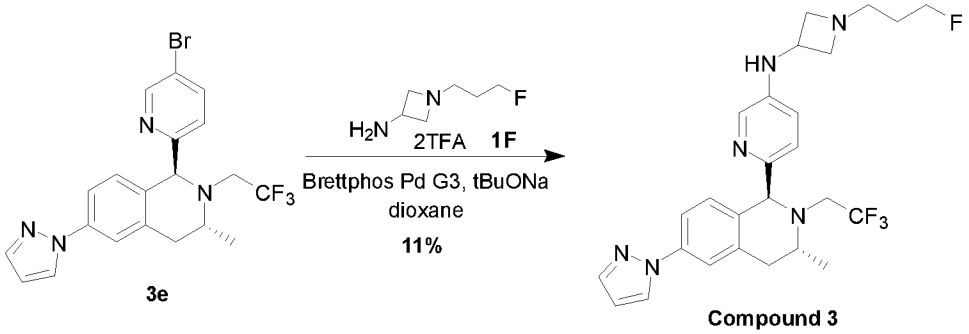
3d 3e

To a solution of compound **3d** (810 mg, 2.85 mmol) in DCE (40 mL) was added compound **1E** (796 mg, 4.3 mmol) and TFA (830 mg, 7.28 mmol). The resulting mixture was stirred at 3-9 °C for 2 hours. The reaction mixture was diluted with dichloromethane (20 mL) and water (20 mL), adjust pH = 8 with Na_2CO_3 aqueous solution, separated. The aqueous layer was extracted with dichloromethane (20 mL x 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated, purified by flash column (0-30% ethyl acetate in petroleum ether) to give compound **3e** (1.1 g, 86% yield, the other diastereomer is not observed by ^{1}H NMR) as yellow oil.

Note: The structure was not confirmed by 2D NMR.

LCMS: t_R = 0.896 min in 10-80AB_220&254 chromatography (Merck RP18 2.5-2mm), MS (ESI) m/z = 451.1 and 453.1 $[M+H]^+$.

^{1}H NMR (400MHz, $CDCl_3$) δ 8.62 (d, *J* = 2.0 Hz, 1H), 7.80 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.44-7.58 (m, 6H), 7.34 (t, *J* = 7.6 Hz, 1H), 4.97 (s, 1H), 3.44-3.35 (m, 1H), 3.32-3.21 (m, 1H), 3.11-3.01 (m, 2H), 2.64 (dd, *J* = 16.0, 6.4 Hz, 1H), 1.19 (d, *J* = 6.8 Hz, 3H).



3e Compound 3

A mixture of compound **3e** (200 mg, 0.44 mmoL), t-BuONa (348 mg, 3.5 mmol), Brettphos Pd G3 (40 mg, 0.044 mmol) and compound **1F** (289 mg, 0.54 mmol, 67.8% purity) in 1,4-dioxane (6 mL) under nitrogen was stirred at 80°C for 15 hours. The reaction mixture was diluted with ethyl acetate (20 mL) and water (20 mL), separated. The aqueous layer was extracted with ethyl acetate (20 mL x 2). The combined organic layers were wash with brine

(10 mL), dried over anhydrous sodium sulfate, filtered and concentrated, purified by flash column (Dichloromethane: methanol = 30/1 to 20/1) to give **Compound 3** (24.5 mg) as a yellow solid, yield 11%.

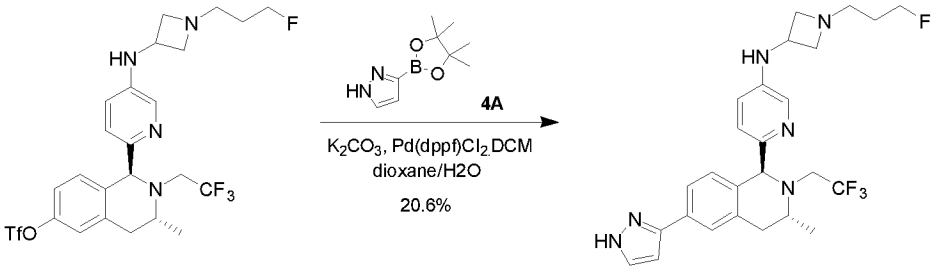
LCMS: t_R = 2.849 min in 0-60AB_7min_220&254_Shimadzu.lcm (Xtimate C18 2.1*30mm), MS (ESI) m/z = 503.2 $[M+H]^+$.

HPLC: t_R = 3.46 min in 0-60_AB_1.2ml METHOD (Ultimate C18 3*50mm 3um)

^{1}H NMR (400MHz, $CDCl_3$) δ 7.89 (d, *J* = 2.8 Hz, 1H), 7.54 (d, *J* = 7.6 Hz, 2H), 7.47 (t, *J* = 8.0 Hz, 2H), 7.37 (s, 1H), 7.29-7.36 (m, 2H), 6.84 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.87 (s, 1H), 4.51 (dt, *J* = 47.2 Hz, 6.0 Hz, 2H), 4.19-4.06 (m, 2H), 3.84-3.74 (m, 2H), 3.53-3.44 (m, 1H), 3.21-2.92 (m, 5H), 2.69-2.56 (m, 3H), 1.86-1.71 (m, 2H), 1.14 (d, *J* = 6.4 Hz, 3H).

Example 4

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3R)-3-methyl-6-(1H-pyrazol-3-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine



1h Compound 4

The mixture of compound **1h** (prepared in **Example 1**, 150 mg, 0.256 mmol) and boronic ester **4A** (55 mg, 0.28 mmol) in 1,4-dioxane/H_2O (5 mL/0.5 mL), K_2CO_3 (89 mg, 0.64 mmol, 2.5 eq.) and Pd(dppf)Cl_2·DCM (21 mg, 0.0256 mmol) were added. The resulting mixture was stirred at 100°C for 16 hours under nitrogen. The mixture was combined with another batch of 45 mg of compound **1h** and purified by flash column chromatography on silica gel (0-10% of methanol in dichloromethane) to obtain 50 mg pure product, which was further separated by chiral SFC [Column: Phenomenex-Amylose-1 (250mm*30mm, 5um), Condition: 40% ETOH (0.1% NH_3H_2O) in CO_2, Flow Rate (ml/min): 50] to afford **Compound 4** (35.3 mg, 20.6% yield) as a brown solid.

LCMS: t_R = 0.698 min in 5-95AB_1.5min_220&254 chromatography (Xtimate C18 2.1*30mm), MS (ESI) m/z = 503.1 $[M+H]^+$.

HPLC: t_R = 3.871 min in 10-80_CD_1.2ml chromatography (XBridge Shield RP 18 2.1*50mm 5um)

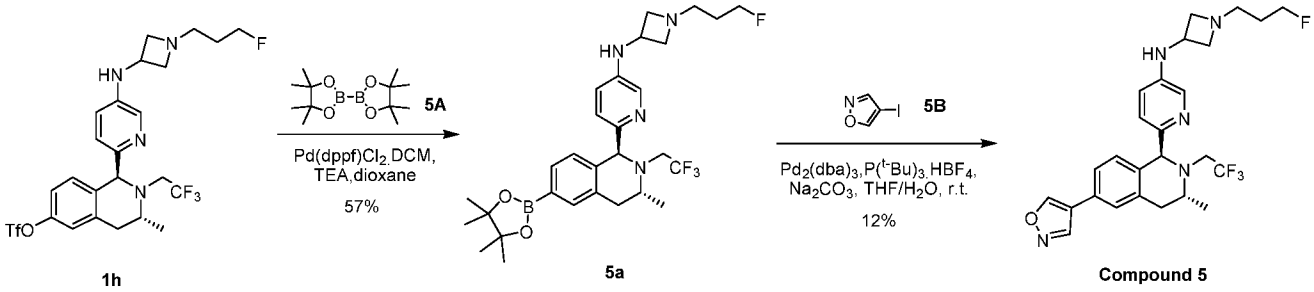
^{1}H NMR (400MHz, $CDCl_3$) δ 10.74 (br s, 1H), 7.84 (d, *J* = 2 Hz, 1H), 7.59 (d, *J* = 1.6 Hz, 1H), 7.55-7.36 (m, 2H), 7.14 (d, *J* = 8.8 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.79 (dd, *J* = 2 Hz, 8.4 Hz, 1H), 6.56 (s, 1H), 4.94 (s, 1H), 4.50 (dt, *J* = 47.2 Hz, 6.0 Hz, 2H), 4.22 (d, *J* = 6.8 Hz, 1H), 4.16-4.07 (m, 1H), 3.73 (q, *J* = 6 Hz, 2H), 3.59-3.50 (m, 1H), 3.29-3.14 (m, 2H), 3.05-2.91 (m, 3H), 2.69-2.59 (m, 3H), 1.82-1.72 (m, 2H), 1.08 (d, *J* = 6.4 Hz, 3H).

SFC: t_R = 4.303 min

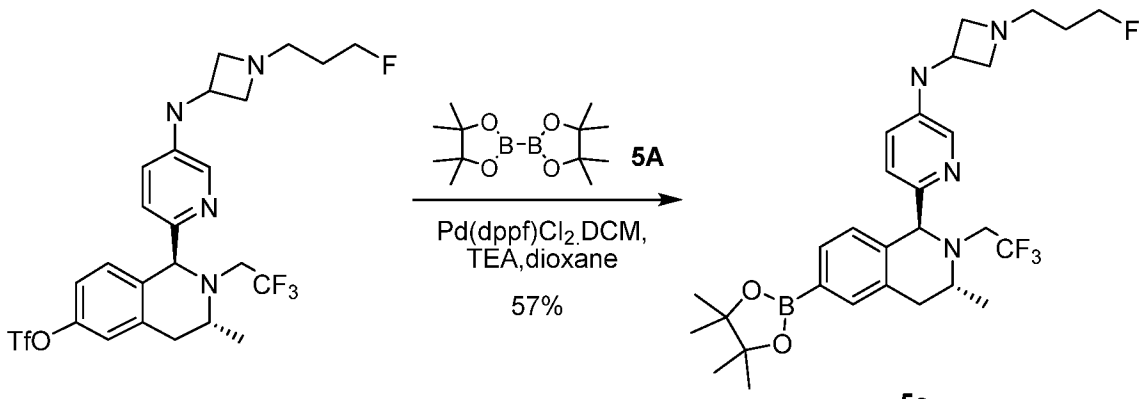
Method: Column: Chiralcel OD-3 100×4.6mm I.D., 3um Mobile phase: A:CO_2 B:ethanol (0.05% DEA) Gradient: from 5% to 40% of B in 4.5min and hold 40% for 2.5min, then 5% of B for 1min Flow rate: 2.8 mL/min Column temperature: 40°C

Example 5

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3R)-6-(isoxazol-4-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine



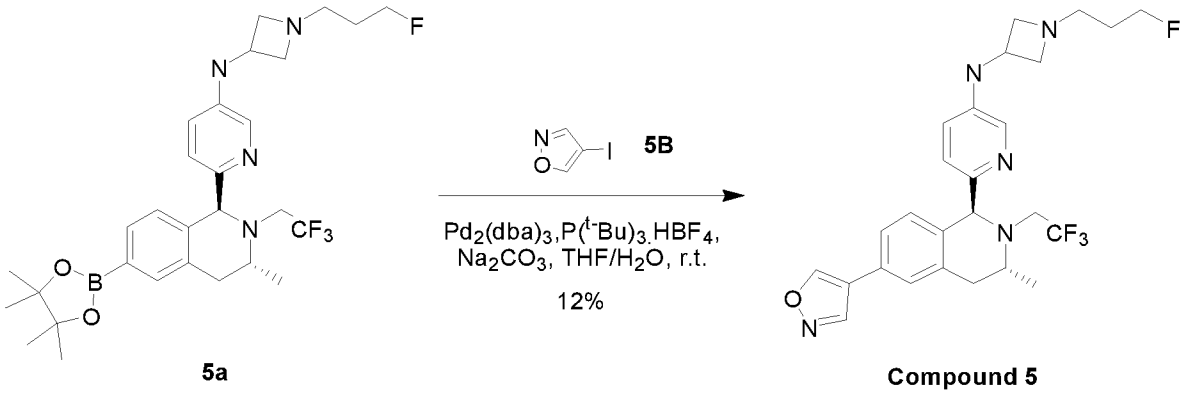
Procedure to prepare Compound 5:



1h **5a**

A mixture of compound **1h** (prepared in **Example 1**, 150 mg, 0.25 mmol) and diborate ester **5A** (195 mg, 0.77 mmol) in 1,4-dioxane (3 mL), triethylamine (152 mg, 1.5 mmol) and Pd(dppf)Cl_2·DCM (20 mg, 0.025 mmol) were added. The resulting mixture was stirred at 95 °C for 1.5 hours under nitrogen. The mixture was combined with another batch of 30 mg of compound **1h**, concentrated and purified by flash column chromatography on silica gel (0-8% methanol in dichloromethane) to obtain compound **5a** (100 mg, 57% yield) as brown oil.

LCMS: t_R = 0.909 min in 5-95AB_1.5 min_220&254 chromatography (Merck RP18 2.5-2mm), MS (ESI) m/z = 562.9 $[M+H]^+$.



5a **Compound 5**

A mixture of compound **5a** (80 mg, 0.14 mmol) and compound **5B** (23 mg, 0.11 mmol) in THF/H_2O (1 mL/1 mL), Na_2CO_3 (44 mg, 0.42 mmol), $Pd_2(dba)_3$ (4 mg, 0.007 mmol) and P(t-Bu)$_3$.HBF_4 (2 mg, 0.015 mmol) were added. The resulting mixture was stirred at 8-10 °C for one hour under nitrogen. The mixture was combined with another batch of 20 mg of compound **5a**. The mixture was concentrated in vacuum and purified by flash column chromatography on silica gel (0-6% of methanol in dichloromethane) to obtain 25 mg of

product, which was further separated by chiral SFC [YMC CHIRAL Amylose-C (250mm*30mm, 10um, Condition: 30% EtOH (0.1% $NH_3.H_2O$) in CO_2, Flow Rate (ml/min): 70] to afford **Compound 5** (10.3 mg, 11.5% yield) as a pink solid.

LCMS: t_R = 0.685 min in 5-95AB_1.5min_220&254 chromatography (Merck RP18 2.5-2mm), MS (ESI) m/z = 504.2 $[M+H]^+$.

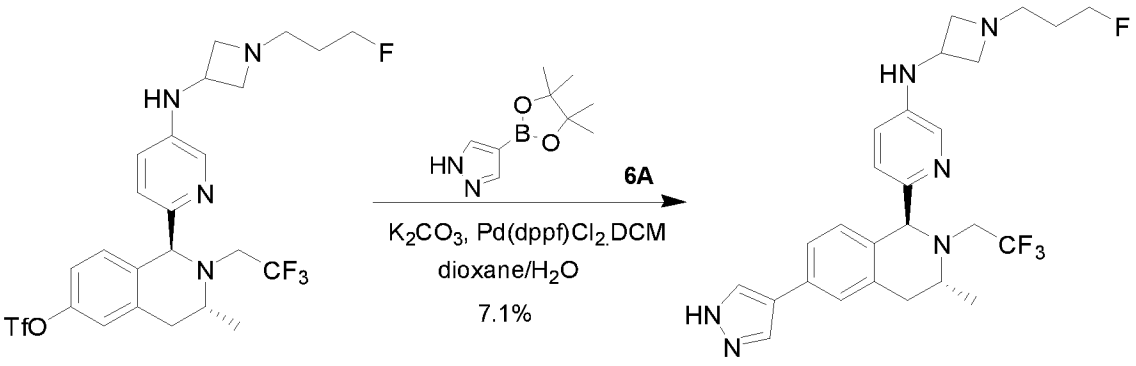
HPLC: t_R = 4.04 min in 10-80_cd_1.2ML.MET chromatography (XBridge Shield RP 18 2.1*50mm 5um)

^{1}H NMR (400MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.52 (s, 1H), 7.85 (d, *J* = 2.8 Hz, 1H), 7.23 (s, 1H), 7.18 (t, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 8 Hz, 1H), 6.82 (dd, *J* = 2.8 Hz, 8.4 Hz, 1H), 4.94 (s, 1H), 4.51 (dt, *J* = 47.2 Hz, 6 Hz, 2H), 4.24-4.13 (m, 2H), 3.83 (brs, 2H), 3.58-3.51 (m, 1H), 3.27-3.18 (m, 2H), 3.09 (brs, 2H), 3.03-2.92 (m, 1H), 2.71 (t, *J* = 7.2 Hz, 2H), 2.64 (dd, *J* = 5.2 Hz, 16 Hz, 1H), 1.86-1.79 (m, 2H), 1.10 (d, *J* = 6.4 Hz, 3H).

SFC: t_R = 1.526 min Column: Chiralpak AD-3 50×3mm I.D., 3um Mobile phase: A: CO_2 B:ethanol (0.05% DEA) Gradient: from 5% to 40% of B in 2.5 min and hold 40% for 0.35 min, then from 40% to 5% of B for 0.15 min Flow rate: 2.5mL/min Column temperature:40°C

Example 6

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3R)-3-methyl-6-(1H-pyrazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine



1h **Compound 6**

To the mixture of compound **1h** (prepared in **Example 1**, 200 mg, 0.34 mmol) and boronic ester **6A** (73 mg, 0.37 mmol) in 1,4-dioxane/H_2O (5 mL/0.5 mL) was added K_2CO_3 (118 mg,

0.85 mmol) and Pd(dppf)Cl_2·DCM (28 mg, 0.034 mmol). The resulting mixture was stirred at 95°C for 6 hours under nitrogen. The mixture was concentrated and purified by flash column chromatography on silica gel (0-10% of methanol in dichloromethane) to obtain 80 mg of product, which was combined with another batch of 20 mg product and further separated by chiral SFC [DAICEL CHIRALPAK AD-H (250mm*30mm, 5um), Condition: 35% IPA (0.1% NH_3H_2O) in CO_2, Flow Rate (ml/min): 50] to afford **Compound 6** (44.7 mg, 7.1% yield) as a white solid.

LCMS: t_R = 0.829 min in 5-95AB_1.5min_220&254 chromatography (Merck RP18 2.5-2mm), MS (ESI) m/z = 503.3 $[M+H]^+$.

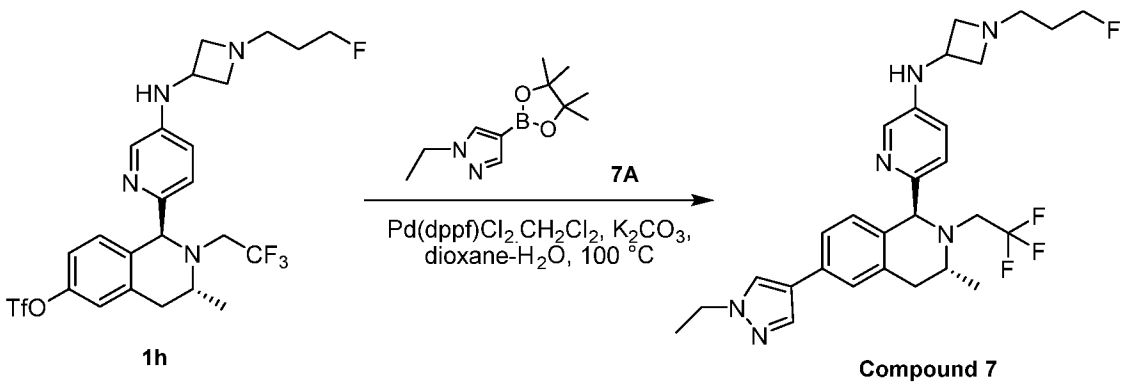
HPLC: t_R = 4.79 min in 10-80_1.5ML_LONG.MET chromatography (YMC-C18 4.6*150mm 5um_long column)

^{1}H NMR (400MHz, $CDCl_3$) δ 7.85 (d, *J* = 2.4 Hz, 1H), 7.76 (s, 2H), 7.25-7.16 (m, 3H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.81 (dd, *J* = 2.8 Hz, 8.8 Hz, 1H), 4.93 (s, 1H), 4.50 (dt, *J* = 47.2 Hz, 6 Hz, 2H), 4.17-4.07 (m, 2H), 3.78-3.71 (m, 2H), 3.58-3.49 (m, 1H), 3.28-3.15 (m, 2H), 3.06-2.92 (m, 3H), 2.66-2.58 (m, 3H), 1.85-1.70 (m, 2H), 1.10 (d, *J* = 6.8 Hz, 3H).

SFC: t_R = 1.880 min Column: Chiralpak AD-3 50×3mm I.D., 3um Mobile phase: A: CO_2 B:iso-propanol (0.05% DEA) Gradient: from 5% to 40% of B in 2.5 min and hold 40% for 0.35 min, then from 40% to 5% of B for 0.15 min Flow rate: 2.5mL/min Column temperature: 40°C

Example 7

6-((1S,3R)-6-(1-ethyl-1H-pyrazol-4-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-N-(1-(3-fluoropropyl)azetidin-3-yl)pyridin-3-amine



To a solution of compound **1h** (prepared in **Example 1**, 100 mg, 0.171 mmol), K_2CO_3 (36 mg, 0.256 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (50 mg, 0.0855 mmol) in 1,4-dioxane/H_2O (3 mL/0.3 mL) was added boronic ester **7A** (45 mg, 0.205 mmol) at 11-21°C. The resulting mixture was stirred at 100°C for 2 hours. Then the reaction mixture was diluted with water and then extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and then filtered, the filtrate was concentrated under vacuum to give the crude residue, which was purified by column chromatography on silica gel (0-20% ethyl acetate in petroleum ether) to afford the title product **Example 7** (36.3 mg, 97% purity, 39% yield) as a yellow solid.

LCMS: t_R = 1.283 min in 10-80AB_3min_220&254 chromatography (A: Xtimate C18, 2.1*30mm, 3um; B: XBrige Shield RP18 2.1*50mm), MS (ESI) m/z= 531.3 $[M+H]^+$.

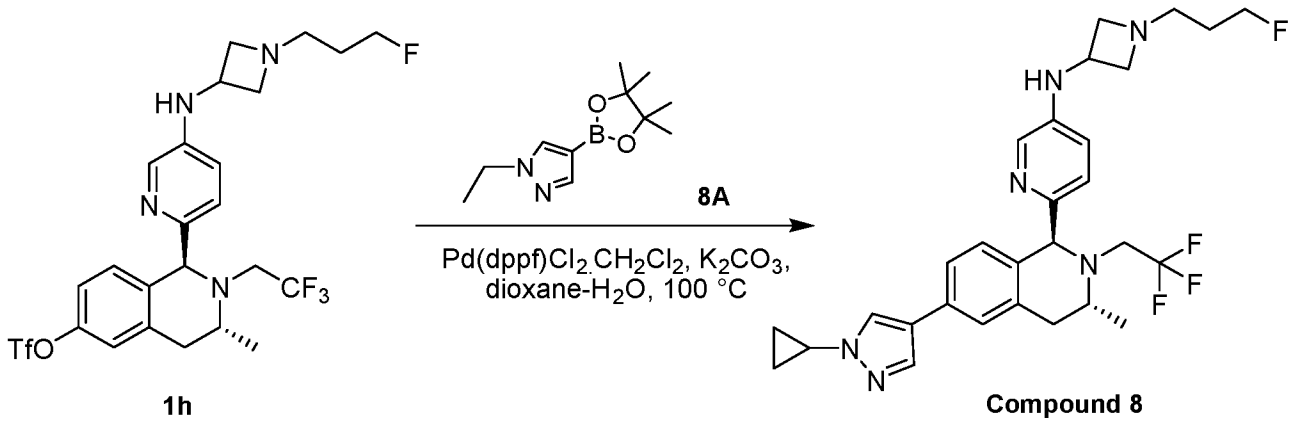
HPLC: t_R = 3.95 min in 10-80_CD_1.2ml. met XBridge Shield RP 18 2.1*50mm 5um

SFC method: t_R = 1.707 min; 100% optical purity; Column: Chiralpak AD-3 50×3mm I.D., 3um Mobile phase: A: CO2 B:ethanol (0.05% DEA) Gradient:from 5% to 40% of B in 2.5 min and hold 40% for 0.35 min, then from 40% to 5% of B for 0.15 min Flow rate: 2.5mL/min Column temperature:40 °C

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.84 (s, 1H), 7.72 (s, 1H), 7.59 (s, 1H), 7.22 (s, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 7.6 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 4.90 (s, 1H), 4.49 (dt, *J* = 46.8 Hz, 6.0 Hz, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 4.14-4.04 (m, 2H), 3.79-3.70 (m, 2H), 3.57-3.47 (m, 1H), 3.27-3.13 (m, 2H), 3.05-2.89 (m, 3H), 2.68-2.56 (m, 3H), 1.83-1.70 (m, 2H), 1.50 (t, *J* = 7.2 Hz, 3H), 1.07 (d, *J* = 6.4 Hz, 3H).

Example 8

6-((1S,3R)-6-(1-cyclopropyl-1H-pyrazol-4-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-N-(1-(3-fluoropropyl)azetidin-3-yl)pyridin-3-amine



To a solution of compound **1h** (prepared in **Example 1**, 100 mg, 0.171 mmol), K_2CO_3 (36 mg, 0.256 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (50 mg, 0.0855 mmol) in 1,4-dioxane/H_2O (3 mL/0.3 mL) was added boronic ester **8A** (45 mg, 0.205 mmol) at 11-21°C. The resulting mixture was stirred at 100°C for 2 hours. Then the reaction mixture was diluted with water and then extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and then filtered, the filtrate was concentrated under vacuum to give the crude residue, which was purified by column chromatography on silica gel (0-20% ethyl acetate in petroleum ether) to afford the title product **Compound 8** (29.2 mg, 97.3% purity, 30.6% yield) as an off-white solid.

LCMS: t_R =1.736min in 10-80AB_4min_220&254.lcm chromatography (A:Xtimate C18,2.1*30mm,3um B:XBrige Shield RP18 2.1*50mm), MS (ESI) m/z =543.3 $[M+H]^+$.

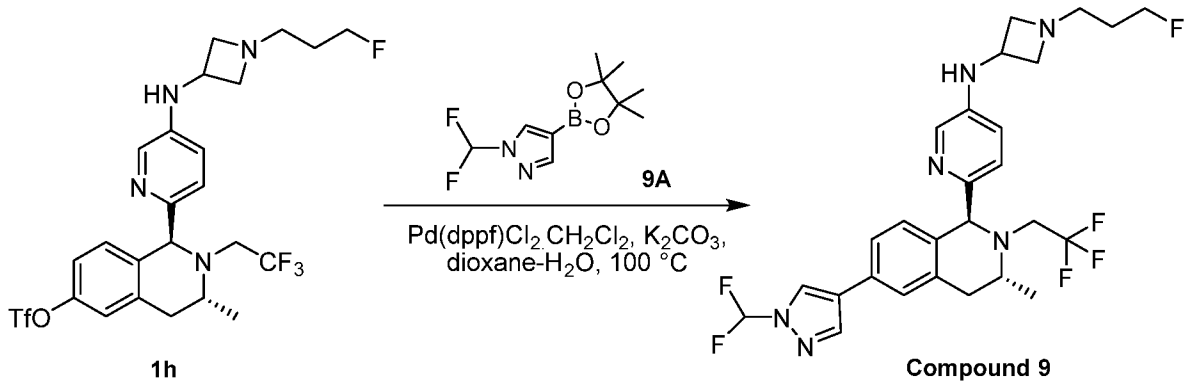
HPLC: t_R = 2.59 min in 10-80_AB_1.2ml.met. HPLC-AUltimate C18 3*50mm 3um

SFC method: t_R =1.928 min; Column: Chiralpak AD-3 50×3mm I.D., 3um; Mobile phase: A: CO2 B:ethanol (0.05% DEA); Gradient: from 5% to 40% of B in 2.5 min and hold 40% for 0.35 min, then from 40% to 5% of B for 0.15 min. Flow rate: 2.5mL/min Column temperature:40 °C

^{1}H NMR (400 MHz, CD_3OD) δ = 7.98 (s, 1H), 7.78 (d, *J* = 2.8 Hz, 1H), 7.76 (s, 1H), 7.33 (s, 1H), 7.23-7.18 (m, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 6.94 (dd, *J* = 2.4, 8.4 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 4.85 (s, 1H), 4.48 (dt, *J* = 47.2 Hz, 6.0 Hz, 2H), 4.23-4.11 (m, 1H), 3.94 (br s, 2H), 3.72-3.60 (m, 1H), 3.57-3.46 (m, 1H), 3.39-3.32 (m, 1H), 3.29-3.23 (m, 1H), 3.18 (br s, 2H), 2.97-2.91 (m, 1H), 2.80 (t, *J*=7.2 Hz, 2H), 2.68 (dd, *J* = 4.4, 16.0 Hz, 1H), 1.91-1.66 (m, 2H), 1.13-1.03 (m, 7H).

Example 9

6-((1S,3R)-6-(1-(difluoromethyl)-1H-pyrazol-4-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-N-(1-(3-fluoropropyl)azetidin-3-yl)pyridin-3-amine



1h **Compound 9**

To a solution of compound **1h** (prepared in **Example 1**, 100 mg, 0.171 mmol), K_2CO_3 (36 mg, 0.256 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (50 mg, 0.0855 mmol) in 1,4-dioxane/H_2O (3 mL/0.3 mL) was added boronic ester **9A** (45 mg, 0.205 mmol) at 11-21°C. The resulting mixture was stirred at 100°C for 2 hours. Then the reaction mixture was diluted with water and then extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and then filtered, the filtrate was concentrated under vacuum to give the crude residue, which was purified by column chromatography on silica gel (0-20% ethyl acetate in petroleum ether) to afford the title product **Compound 9** (36.5 mg, 96% purity, 38.61% yield) as a grey solid.

LCMS: t_R = 1.569 min in 10-80AB_3min_220&254 chromatography (Xtimate C18 2.1*30mm), MS (ESI) m/z = 553.2 $[M+H]^+$.

HPLC: t_R = 3.32 min in 10-80_AB_1.2ml chromatography (Ultimate C18 3*50mm 3um)

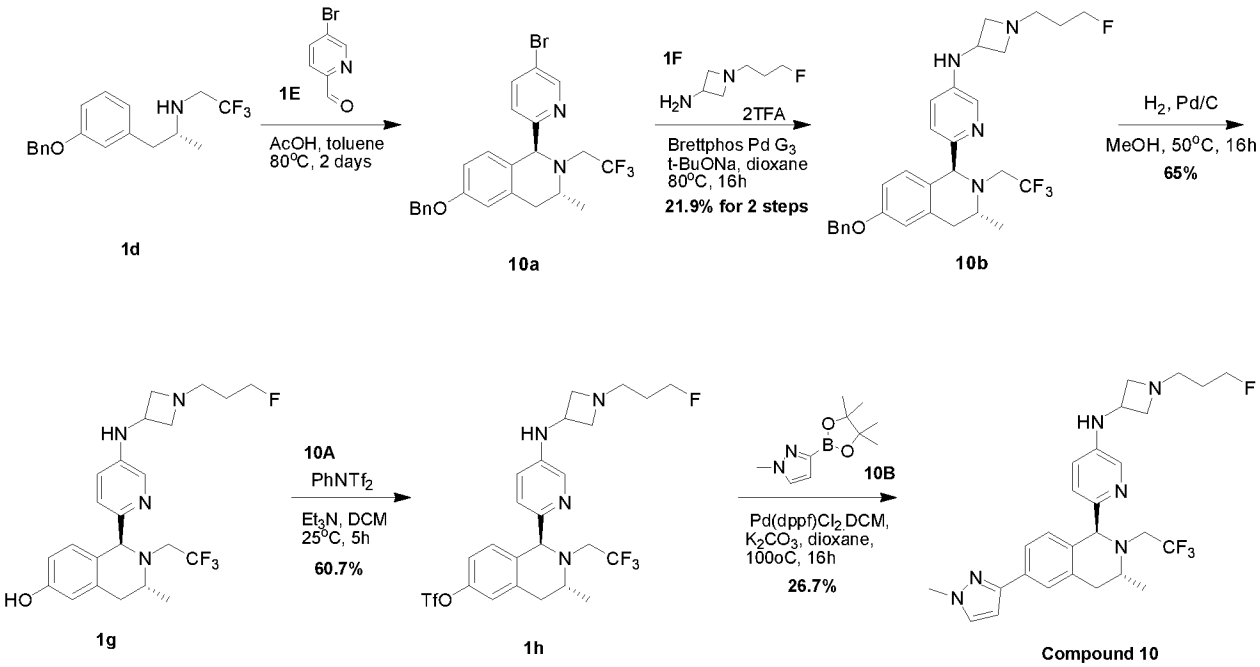
SFC Method: t_R = 1.736 min; Column: Chiralcel OJ-3 100×4.6mm I.D., 3μm; Mobile phase: A: CO_2 B:ethanol (0.05%DEA); Gradient: from 5% to 40% of B in 4.5min and hold 40% for 2.5 min, then 5% of B for 1min, Flow rate: 2.8mL/min Column temperature: 40 °C

^{1}H NMR (400 MHz, CD_3OD) δ = 8.36 (s, 1H), 8.05 (s, 1H), 7.78 (d, *J* = 2.8 Hz, 1H), 7.47 (t, *J* = 59.6 Hz, 1H), 7.42 (s, 1H), 7.29 (dd, *J* = 2.0 Hz, 8.0 Hz, 1H), 7.13 (d, *J* = 8.8 Hz, 1H), 6.95 (dd, *J* = 2.8, 8.8 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 4.82 (s, 1H), 4.47 (dt, *J* = 47.2 Hz, 6.0 Hz, 2H), 4.18-4.08 (m, 1H), 3.93-3.85 (m, 2H), 3.60-3.50 (m, 1H), 3.40-3.33 (m, 1H), 3.30-3.26 (m, 1H), 3.14-3.07 (m, 2H), 3.00-2.89 (m, 1H), 2.78-2.66 (m, 3H), 1.86-1.73 (m, 2H), 1.09 (d, *J* = 6.4 Hz, 3H).

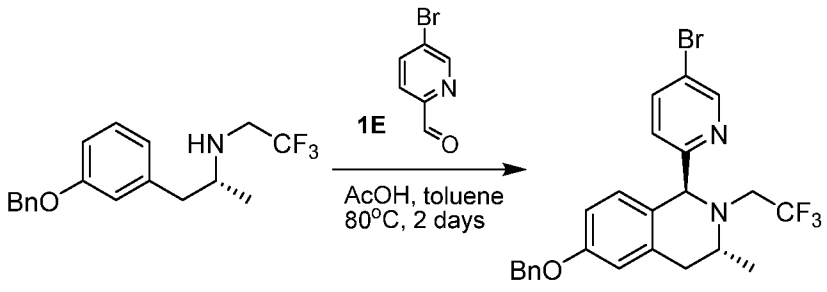
Example 10

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3R)-3-methyl-6-(1-methyl-1H-pyrazol-3-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine

Method one:



Procedure to prepare **Compound 10**:

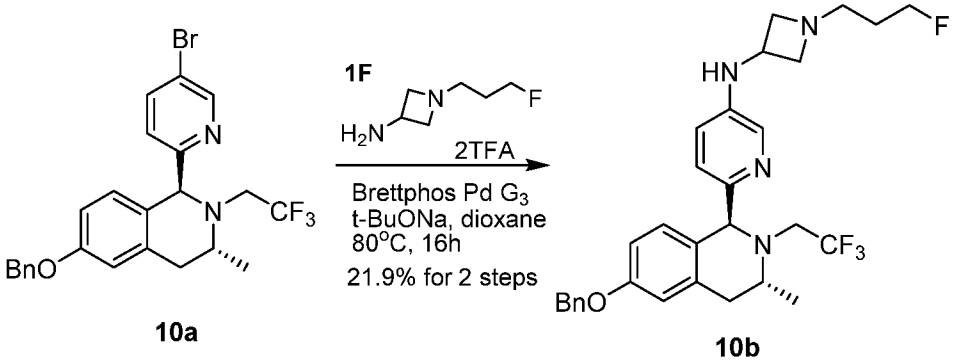


1d **10a**

To a solution of compound **1d** (1.9 g, 5.87 mmol) in toluene (50 mL) and acetic acid (0.8 mL), compound **1E** (1.09 g, 5.87 mmol) was added. The mixture was stirred at 80°C for 2 days. The mixture was concentrated and the residue was dissolved in dichloromethane (30 mL) and washed with saturated sodium bicarbonate aqueous (30 mL), the aqueous layer was extracted with dichloromethane (30 mL x 3). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to obtained the crude product, which was purified by flash column (0-30% of ethyl acetate in petroleum ether) to obtained compound **10a** (1.7 g, contained 1.5 equivalent of compound **1E**) as oil and 0.8 g of compound **1d** was recycled. The mixture containing **10a** was used directly without further purification. Only one dominant isomer was observed by H NMR and characterized as below.

LCMS: t_R = 1.033 min in 5-95AB_220&254 chromatography (Merck RP18 2.5-2mm), MS (ESI) m/z = 491.0 and 493.0 $[M+H]^+$.

^{1}H NMR (400MHz, $CDCl_3$) δ = 8.55 (d, *J* = 2 Hz, 1H), 7.72 (dd, *J* = 2.4 Hz, 8.8 Hz, 1H), 7.43-7.32 (m, 6H), 6.80 (d, *J* = 8.4 Hz, 1H), 6.74-6.71 (m, 2H), 5.02 (s, 2H), 4.93 (s, 1H), 3.50-3.42 (m, 1H), 3.29-3.18 (m, 1H), 3.15 (dd, *J* = 4.4 Hz, 16.4 Hz, 1H), 3.00-2.88 (m, 1H), 2.58 (dd, *J* = 5.6 Hz, 16 Hz, 1H), 1.08 (d, *J* = 6.8 Hz, 3H).



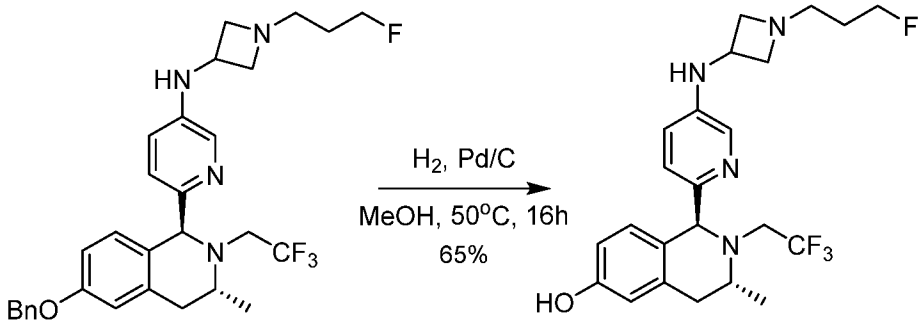
10a **10b**

A mixture of compound **10a** (1.7 g, 3.46 mmol) and compound **1F** (2.25 g, 4.64 mmol, 67%

purity) in 1,4-dioxane (60 mL), t-BuONa (2.7 g, 27.68 mmol) and Brettphos Pd G3 (313 mg, 0.34 mmol) were added. The resulting mixture was stirred at 80°C for 16 hours under nitrogen. The mixture was concentrated. Water (30 mL) was added and extracted with ethyl acetate (30 mL x 4). The combined organic layer was washed with brine (50 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated to obtained the crude product, which was purified by prep-TLC (petroleum ether/ethyl acetate = 25/1 for 4 times and petroleum ether/ethyl acetate = 20/1 for 4 times) followed by column chromatography (0-50% of ethyl acetate in petroleum ether to 0-10% of methanol in dichloromethane) to afford product **10b** (700 mg, 21.9% yield for two steps) as a yellow oil.

LCMS: t_R = 0.761 min in 5-95AB_1.5 min_220&254 chromatography (Merck RP18 2.5-2mm), MS (ESI) m/z = 543.2 $[M+H]^+$.

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.84 (d, *J* = 2.8 Hz, 1H), 7.44-7.30 (m, 5H), 7.15 (d, *J* = 8.4 Hz, 1H), 6.81-6.76 (m, 2H), 6.74-6.69 (m, 2H), 5.01 (s, 2H), 4.87 (s, 1H), 4.50 (dt, *J* = 47.2 Hz, 6.0 Hz, 2H), 3.97 (brs, 1H), 3.78-3.71 (m, 2H), 3.53-3.47 (m, 1H), 3.23-3.12 (m, 2H), 3.04-2.87 (m, 3H), 2.63-2.57 (m, 3H), 1.83-1.69 (m, 2H), 1.07 (d, *J* = 6.8 Hz, 3H).

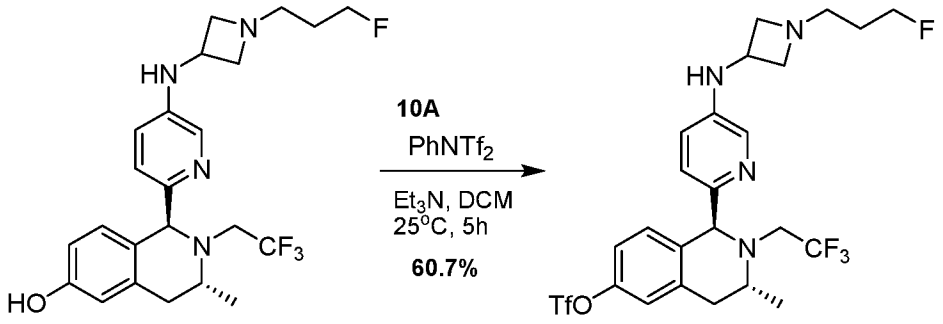


10b **1g**

To a mixture of compound **10b** (0.7 g, 1.29 mmol) in methanol (30 mL), 10% Pd/C (100 mg) was added. The resulting mixture was stirred at 50°C for 16 hours under hydrogen atmosphere (50psi). The mixture was filtered through a Celite Pad and the filtrate was concentrated to afford the crude product, which was purified by column chromatography (0-10% of methanol in dichloromethane) to afford compound **1g** (380 mg, 65% yield) as oil.

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.81 (d, *J* = 2.8 Hz, 1H), 7.18 (d, *J* = 8.8 Hz, 1H), 6.79 (dd, *J* = 2.4 Hz, 8.4 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 6.54 (d, *J* = 2.4 Hz, 1H), 6.48 (dd, *J* = 2.4 Hz, 8.4 Hz, 1H), 4.85 (s, 1H), 4.50 (dt, *J* = 47.2 Hz, 5.6 Hz, 2H), 4.13-4.02 (m, 2H),

3.78-3.74 (m, 2H), 3.51-3.41 (m, 1H), 3.22-3.05 (m, 2H), 3.02-2.94 (m, 3H), 2.65 (t, J = 7.2 Hz, 2H), 2.51 (dd, J = 6 Hz, 16.4 Hz, 1H), 1.86-1.71 (m, 3H), 1.06 (d, J = 6.8 Hz, 3H).

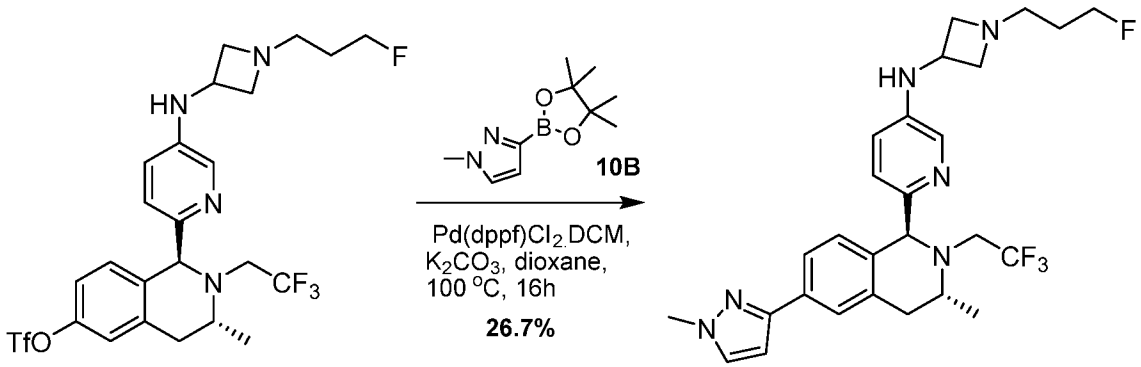


1g **1h**

The mixture of compound **1g** (335 mg, 0.74 mmol), triethylamine (224 mg, 2.22 mmol) in dichloromethane (15 mL), compound **10A** (555 mg, 1.48 mmol) was added. The resulting mixture was stirred at 25°C for 5 hours. The mixture was quenched with water (20 mL), extracted with dichloromethane (30 mL x 4). The aqueous layer also contained the product, so the organic layer and the aqueous layer were concentrated separately. The organic layer was purified by column chromatography (0-10% of methanol in dichloromethane) to afford compound **1h** (198 mg) as a yellow solid. The aqueous layer was purified by column chromatography (0-10% of methanol in dichloromethane) to afford compound **1h** (100 mg) as a yellow solid, 60.7% yield total.

LCMS: t_R = 0.761 min in 5-95AB_1.5 min_220&254 chromatography (Merck RP18 2.5-2mm), MS (ESI) m/z = 585.1 $[M+H]^+$.

^{1}H NMR (400MHz, $CDCl_3$) δ = 11.30 (brs, 1H), 8.05-7.90 (m, 1H), 7.51 (brs, 2H), 7.38 (s, 1H), 7.31-7.22 (m, 1H), 7.10-7.04 (m, 1H), 5.36 (brs, 1H), 4.65-4.43 (m, 5H), 4.28 (brs, 1H), 4.09 (brs, 1H), 3.96-3.87 (m, 2H), 3.60 (dd, J = 9.6 Hz, 15.6 Hz, 1H), 3.45-3.38 (m, 1H), 3.24-3.16 (m, 1H), 3.07-3.01 (m, 2H), 2.75 (dd, J = 4.4 Hz, 16.4 Hz, 1H), 2.00-1.90 (m, 2H), 1.01 (d, J = 6.4 Hz, 3H).



1h **Compound 10**

A mixture of compound **1h** (140 mg, 0.24 mmol) and compound **10B** (55 mg, 0.26 mmol) in 1,4-dioxane / water (10 mL/1 mL), potassium carbonate (83 mg, 0.60 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (20 mg, 0.024 mmol) were added. The resulting mixture was stirred at 100 °C for 16 hours under nitrogen. The mixture was concentrated and purified by column chromatography (0-10% of methanol in dichloromethane) followed by prep-TLC (dichloromethane / methanol =15/1 for 2 times) to afford 52 mg product which was combined with a pilot reaction at the scale of 18 mg **1h**. The chiral HPLC spectrum showed the optical purity is 85%. The product was further separated by chiral SFC [Column: DAICEL CHIRALCEL OJ-H (250 mm*30 mm,5 um), Condition: 40% ETOH (0.1% $NH_3.H_2O$), Flow Rate (mL/min): 70] to afford **Compound 10** (46.7 mg, 26.7% yield) as a yellow solid. The stereochemistry of final compound was confirmed by 2D NMR.

LCMS: t_R = 0.710 min in 5-95AB_1.5 min_220&254 chromatography (Merck RP18 2.5-2mm), MS (ESI) m/z = 517.1 $[M+H]^+$.

LCMS: t_R = 0.700 min in 5-95AB_1.5min_220&254 chromatography (Xtimate C18 2.1*30mm), MS (ESI) m/z = 517.1 $[M+H]^+$.

HPLC: t_R = 4.04 min in 10-80_CD_1.2ml chromatography (Ultimate C18 2.1*50mm 5um)

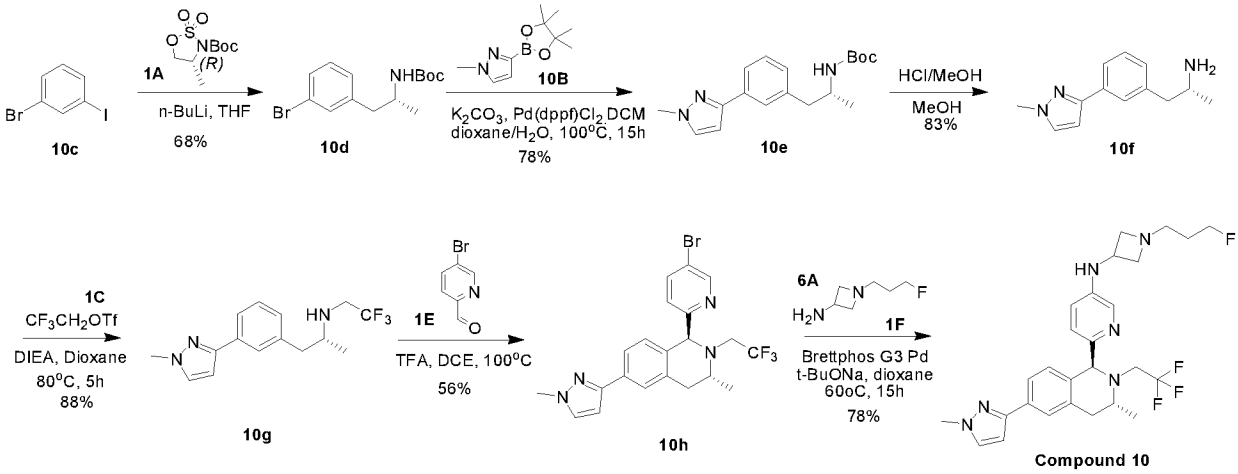
^{1}H NMR (400MHz, $CDCl_3$) δ 7.85 (d, *J* = 2.8 Hz, 1H), 7.58 (s, 1H), 7.43 (dd, *J* = 1.2 Hz, 8 Hz, 1H), 7.35 (d, *J* = 2.4 Hz, 1H), 7.13 (d, *J* = 8.8 Hz, 1H), 6.87 (d, *J* = 8 Hz, 1H), 6.78 (dd, *J* = 2.8 Hz, 8.4 Hz, 1H), 6.48 (d, *J* = 2.4 Hz, 1H), 4.92 (s, 1H), 4.50 (dt, *J* = 47.2 Hz, 6 Hz, 2H), 4.16-4.07 (m, 1H), 4.01 (brd, *J* = 7.6 Hz, 1H), 3.94 (s, 3H), 3.75 (q, *J* = 6 Hz, 2H), 3.57-3.50 (m, 1H), 3.30-3.14 (m, 2H), 3.07-2.97 (m, 1H), 2.95-2.89 (m, 2H), 2.70-2.59 (m, 3H),

1.83-1.70 (m, 2H), 1.08 (d, J = 6.4 Hz, 3H).

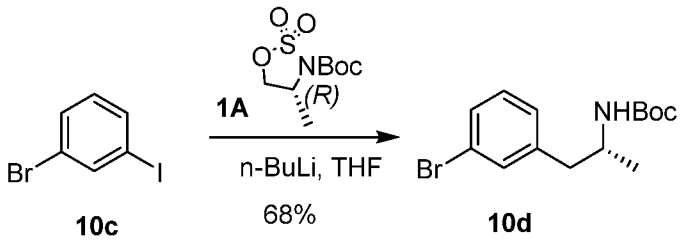
SFC: t_R = 1.853 min

Method Column: Chiralpak AD-3 50×3mm I.D., 3um Mobile phase: A:CO_2 B: IPA (0.05% DEA) Gradient: from 5% to 40% of B in 2.5min and hold 40% for 0.35min, then from 40% to 5% of B for 0.15 min Flow rate: 2.5mL/min Column temperature: 40 °C

Method two:



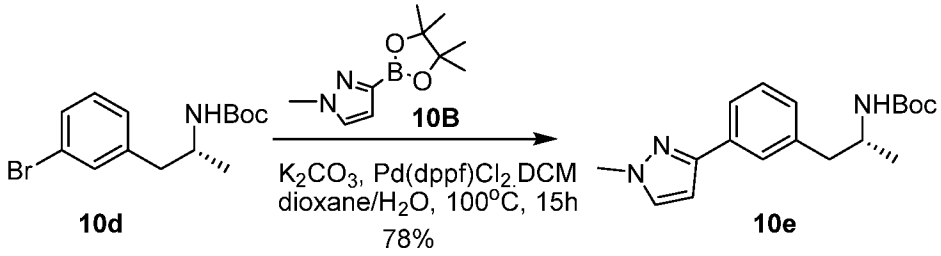
Procedure to prepare **Compound 10**:



To a solution of compound **10c** (14.0 g, 49.38 mmol) in THF (160 mL) was added a solution of n-BuLi 921.7 ml, 54.32 mmol, 2.5M in hexane) dropwise at -65°C~-70°C under nitrogen. A yellow solution was appeared. After addition, a solution of compound **1A** (10 g, 42.15 mmol) in THF (50 mL) was added dropwise at -65°C~-70°C. The reaction mixture was stirred at this temperature for 2 hours. Then 1M citric acid solution (100 mL) was added to this above mixture at -65°C~-70°C and a white suspension appeared. The mixture was allowed to warm to room temperature, diluted with water (200 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layer was washed with brine (300 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified

by column chromatography on silica gel (0~5% ethyl acetate in petroleum ether) to afford pure compound **10d** (8.10 g) and impure product (1.90 g, 50% purity) as white solid. Yield: 68%.

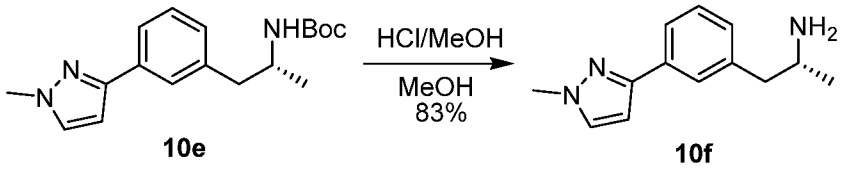
^{1}H NMR (400MHz, $CDCl_3$): δ = 7.40-7.32 (m, 2H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 4.37 (br s, 1H), 3.89 (br s, 1H), 2.91-2.77 (m, 1H), 2.64 (dd, *J* = 7.2, 13.2 Hz, 1H), 1.43 (s, 9H), 1.09 (d, *J* = 6.4 Hz, 3H).



The mixture of compound **10d** (4.2 g, 13.4 mmol), compound **10B** (3.07 g, 14.7 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (1.1 g, 1.34 mmol) and potassium carbonate (4.6 g, 33.5 mmol) in 1,4-dioxane/water (60/6 mL) was stirred at 100°C for 15 hours under nitrogen atmosphere. The reaction was quenched with water (50 mL) and extracted with ethyl acetate (300 mL × 2). The combined organic layer was washed with brine (200 mL), dried over anhydrous sodium sulfate and then concentrated in vacuum to give the crude residue, which was purified by column chromatography on silica gel (ethyl acetate/petroleum ether = 0-20%) to afford the title product **10e** (3.3 g, 78% yield) as a brown oil.

LCMS: t_R = 0.856 min in 5-95AB_220&254.lcm chromatography (Merck RP18 2.5-2mm), MS (ESI) m/z= 338.0 $[M+Na]^+$.

^{1}H NMR: (400MHz, $CDCl_3$) δ = 7.64 (d, *J* = 7.6 Hz, 1H), 7.62 (s, 1H), 7.38 (d, *J* = 2.0 Hz, 1H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 6.54 (d, *J* = 2.0 Hz, 1H), 4.41 (brs, 1H), 4.01-3.91 (m, 1H), 3.96 (s, 3H), 2.90 (dd, *J* = 5.6 Hz and 12.8 Hz, 1H), 2.70 (dd, *J* = 7.2 and 13.6 Hz, 1H), 1.43 (s, 9H), 1.11 (d, *J* = 6.4 Hz, 3H).

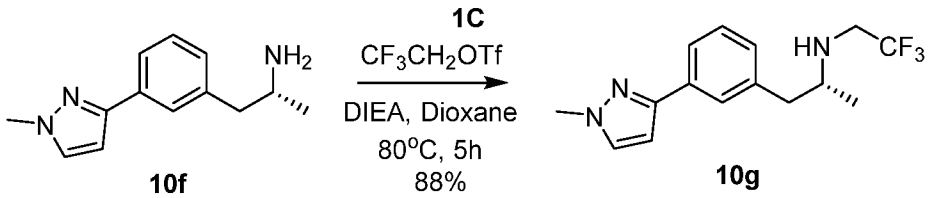


The mixture of **10e** (3.0 g, 9.5 mmol) and HCl/methanol (40 mL, 4 M) in methanol (20 mL)

was stirred 10 °C for 2 hours. The reaction was concentrated in vacuo to remove most of the solvent and the residue was treated with solution of sodium hydroxide (1.0 mL, 15%), ethyl acetate (50 mL) and methanol (4 mL). The mixture was stirred for 10 min and filtered. The filtrated was concentrated in vacuo to afford the crude product. The crude and the filter cake was respectively purified by flash column chromatography on silica gel (eluting with A/B = 5% ~ 20%, A: the mixture solvent of 2% $NH_3.H_2O$/MeOH, B: CH_2Cl_2) and combined the elution to afford product **10f** (1.7 g, 83% yield) as a yellow solid.

LCMS: t_R = 0.724 min in 5-95AB_220&254.lcm chromatography (Merck RP18 2.5-2mm), MS (ESI) m/z=216.0 $[M+H]^+$.

^{1}H NMR: (400MHz, $CDCl_3$) δ = 7.68-7.63 (m, 2H), 7.62 (d, *J* = 2.0 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 6.63 (d, *J* = 2.8 Hz, 1H), 3.95 (s, 3H), 3.37-3.33 (m, 1H), 2.86-2.71 (m, 2H), 1.18 (d, *J* = 6.4 Hz, 3H).

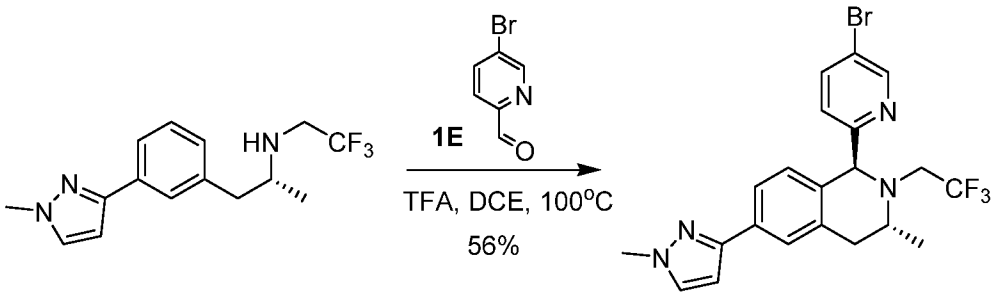


10f **10g**

A mixture of **4f** (1.4 g, 6.5 mmol) and CF_3CH_2OTf (1.82 g, 7.8 mmol) and DIEA (1.67 g, 13.0mmol in 1,4-dioxane (20 mL) was stirred at 80°C for 5 hours. The reaction mixture was concentrated in vacuo to give the crude which was purified by column chromatography (eluting with 0~20% ethyl acetate in petroleum ether) to afford product **10g** (1.7 g, 88% yield) as a colorless oil.

LCMS: t_R = 0.674 min in 5-95AB_220&254.lcm chromatography (Agilent pursult5 C18 20*2mm), MS (ESI) m/z=298.0 $[M+H]^+$.

^{1}H NMR: (400MHz, $CDCl_3$) δ = 7.69-7.61 (m, 2H), 7.39 (d, *J* = 2.4 Hz, 1H), 7.34 (t, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 6.55 (d, *J* = 2.4 Hz, 1H), 3.97 (s, 3H), 3.18 (q, *J* = 9.6 Hz, 2H), 3.13-3.04 (m, 1H), 2.78 (dd, *J* = 6.8 Hz and 13.6 Hz, 1H), 2.67 (dd, *J* = 6.4 Hz and 13.6 Hz, 1H), 1.10 (d, *J* = 6.0 Hz, 3H).

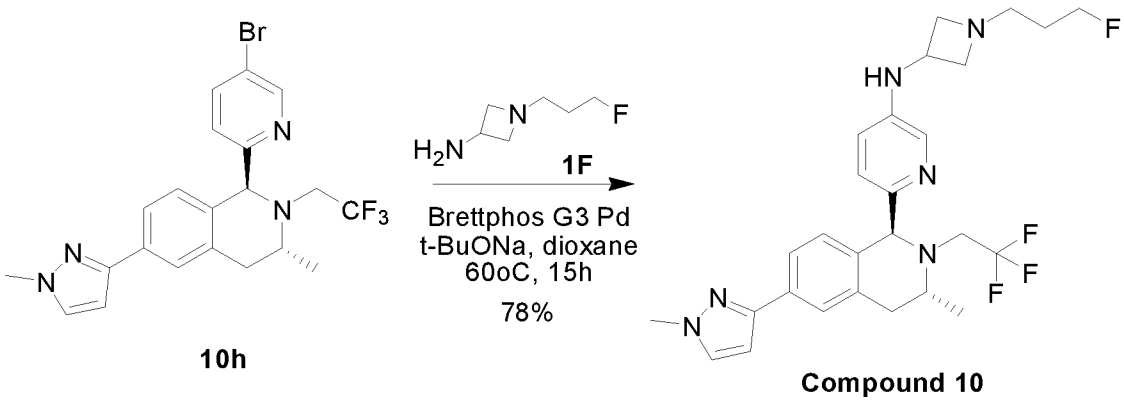


10g **10h**

To the mixture of compound **10g** (400 mg, 1.35 mmol) and compound **1E** (300 mg, 1.61 mmol) in dichloroethane (6 mL) was added trifluoroacetic acid (462 mg, 4.05 mmol) and the mixture was stirred at 100 °C for 10 hours under nitrogen. The reaction mixture was combined with other three parallel batches with same scale (total 1.6 g of compound **10g**). To the combined mixture was added saturated aqueous sodium bicarbonate (50 mL) and extracted with ethyl acetate (100 ml × 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluting with 0~20% ethyl acetate in petroleum ether) to afford product **10h** (1.4 g, 56% yield) as a brown oil and while recycled the staring material **10g** (400 mg) as a brown oil. The obtained compound **10h** was an inseparable mixture and the ratio is about 8.3: 1 according to H NMR spectrum. The dominant isomer was characterized as below.

LCMS: t_R =1.101 min in 5-95AB_220&254.lcm chromatography (Merck RP18 2.5-2mm), MS (ESI) m/z =464.8 and 466.8 $[M+H]^+$.

^{1}H NMR: (400MHz, $CDCl_3$) δ = 8.58 (d, *J* = 2.4 Hz, 1H), 7.73 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.61 (s, 1H), 7.46 (dd, *J* = 1.6 Hz and 8.4 Hz, 1H), 7.36 (d, *J* = 2.0 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.49 (d, *J* = 2.0 Hz, 1H), 5.00 (s, 1H), 3.95 (s, 3H), 3.57-3.48 (m, 1H), 3.32-3.20 (m, 2H), 3.03-2.93 (m, 1H), 2.69 (dd, *J* = 5.2, 16.0 Hz, 1H), 1.09 (d, *J* = 6.4 Hz, 3H).



A mixture of compound **10h** (400 mg, 0.86 mmol), compound **1F** (148 mg, 1.12 mmol), Brettphos Pd G_3 (195 mg, 0.215 mmol) and t-BuONa (232 mg, 2.4 mmol) in 1,4-dioxane (5 mL) was stirred at 60°C for 15 hours under nitrogen. The reaction was combined with the other three parallel batches (total 1.6 g of compound **10h**) and the combined mixture was concentrated in vacuo. The residue was suspended in 70 mL of the mixture solvents (dichloromethane/methanol=55 mL/15 mL). The mixture was stirred for 30 min and filtered, concentrated in vacuo to give the crude which was directly purified by column chromatography (eluting with 0~5% methanol in dichloromethane) to afford product **Compound 10** (1.4 g, 89% optical purity, 78% yield) as a brown oil. The dominant isomer was characterized as below.

LCMS: t_R =0.723 min in 5-95AB_1.5min_shimadzu.lcm chromatography (Xtimate C18 2.1*30mm), MS (ESI) m/z = 517.1 $[M+H]^+$.

Chiral SFC: 89% optical purity.

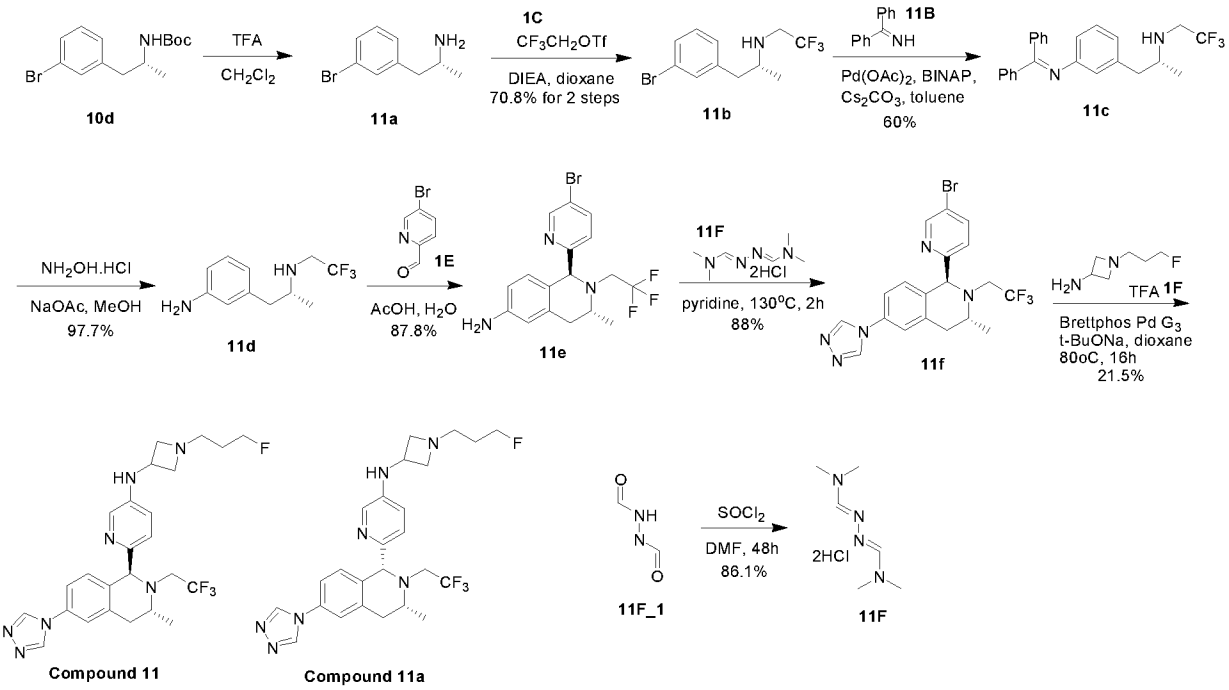
Column: Chiralpak AD-3 50 ×3 mm I. D., 3um OJ-3 100×4.6mm I.D., 3um; Mobile phase: A: CO_2 B: iso-propanol (0.05% DEA);Gradient: from 5% to 40% of B in 2.5 min and hold 40% for 0.35 min, then from 40% to 5% of B for 0.15 min; Flow rate: 2.5mL/min; Column temperature: 40 °C

^{1}H NMR: (400MHz, $CDCl_3$) δ = 7.85 (d, *J* = 2.4 Hz, 1H), 7.58 (s, 1H), 7.43 (dd, *J* = 1.6 Hz and 8.0 Hz, 1H), 7.35 (d, *J* = 2.4 Hz, 1H), 7.13 (d, *J* = 8.8 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.78 (dd, *J* = 2.8, 8.8 Hz, 1H), 6.48 (d, *J* = 2.4 Hz, 1H), 4.92 (s, 1H), 4.50 (dt, *J* = 47.2 Hz and 6.0 Hz, 2H), 4.11-4.07 (m, 1H), 3.94 (s, 3H), 4.00-3.90 (m, 1H), 3.74 (q, *J* = 5.6 Hz, 2H), 3.57-3.51 (m, 1H), 3.31-3.18 (m, 2H), 3.07-2.95 (m, 1H), 2.92-2.87 (m, 2H), 2.66 (dd, *J* =

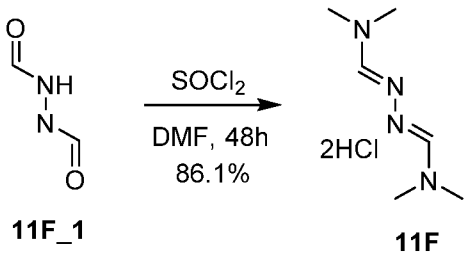
4.8, 16.0 Hz, 1H), 2.60 (t, *J* = 7.2 Hz, 2H), 1.82-1.77 (m, 1H), 1.76-1.71 (m, 1H), 1.08 (d, *J* = 6.8 Hz, 3H).

Example 11

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3R)-3-methyl-6-(4H-1,2,4-triazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine



Procedure to prepare **11F**:

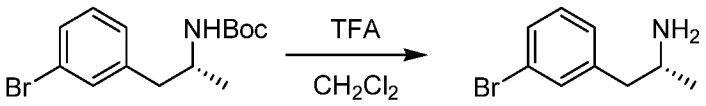


To a solution of compound **11F_1** (13.7 g, 157.4 mmol) in DMF (150 mL) was added thionyl chloride (46.4 g, 393.6 mmol). Then the mixture was stirred at 12°C for 48 hours. The precipitate was filtered and washed with DMF (10 mL) followed by methyl tert-butyl ether (10 mL). After drying under a vacuum, the product (29 g, 86.1%yield) was obtained as a white solid.

LCMS: t_R = 0.123 min in 5-95AB_220&254 _Shimadzu.lcm (Agilent pursult5 C18 20*2mm), MS (ESI) m/z = 142.8 $[M+H]^+$.

^{1}H NMR (400MHz, D_2O): δ = 8.33 (s, 2H), 3.21 (br s, 12H).

Procedure to prepare **Compound 11**:

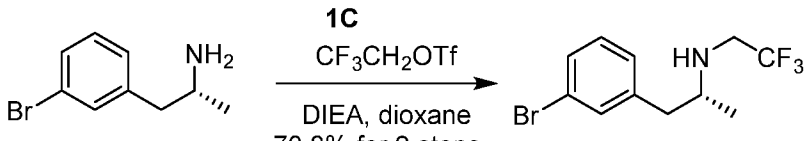


10d **11a**

To a solution of compound **10d** (prepared in **Example 10**, 5.60 g, 17.82 mmol) in dichloromethane (90 mL) was added trifluoroacetic acid (30 mL), the reaction mixture was stirred for 0.5 hour at 12~26°C. The mixture was poured into saturated aqueous solution of sodium bicarbonate (400 mL) under stirring and basified to pH = 8~9 with potassium carbonate solid. The mixture was extract ethyl acetate (200 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give crude compound **11a** (4.20 g, 90% purity, 100% yield) as colorless oil.

LCMS: t_R = 0.555 min in 5-95AB_1.5min_220&254.lcm chromatography (Merck RP18 2.5-2mm), MS (ESI) m/z 213.9 and 215.9 $[M+H]^+$.

^{1}H NMR (400MHz, CD_3OD): δ = 7.46-7.34 (m, 2H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 3.20-3.04 (m, 1H), 2.71-2.57 (m, 2H), 1.09 (d, *J* = 6.4 Hz, 3H).



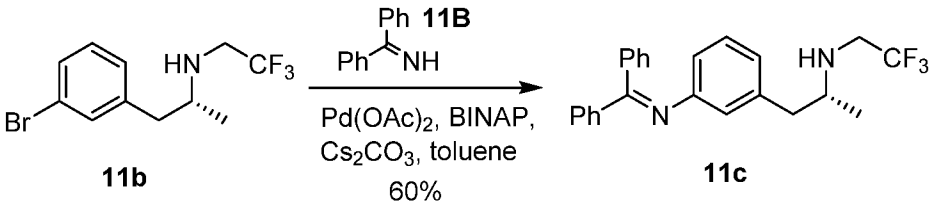
11a **11b**

To a solution of compound **11a** (4.20 g, 17.65 mmol, 90% purity) in 1,4-dioxane (80 mL) was added N,N-di-isopropyl ethylamine (6.2 mL, 35.30 mmol) followed by compound **1C** (4.10 g, 17.65 mmol). The reaction mixture was stirred for 16 hours at 80 °C under nitrogen. The mixture was diluted with water (100 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine (150 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by column

chromatography on silica gel (0~5% ethyl acetate in petroleum ether) to afford compound **11b** (3.70 g, 70.8% yield) as colorless oil.

LCMS: t_R = 0.656 min in 5-95AB_1.5min_220&254.lcm chromatography (Merck RP18 2.5-2mm), MS (ESI) m/z 295.9 and 297.9 $[M+H]^+$.

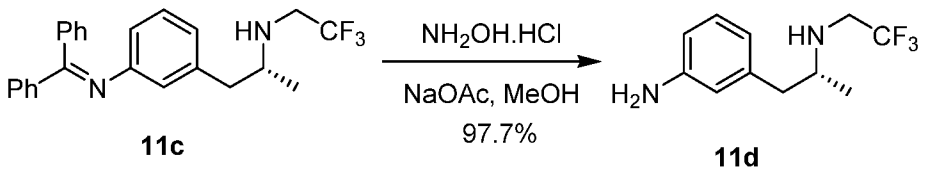
^{1}H NMR (CD_3OD 400MHz): δ = 7.39 (s, 1H), 7.35 (dt, *J* = 7.2, 2.0 Hz, 1H), 7.23-7.15 (m, 2H), 3.29-3.15 (m, 2H), 3.03-2.90 (m, 1H), 2.81 (dd, *J* = 5.6, 13.2 Hz, 1H), 2.50 (dd, *J* = 7.6, 13.2 Hz, 1H), 1.01 (d, *J* = 6.4 Hz, 3H).



11b **11c**

To a mixture of $Pd(OAc)_2$ (561 mg, 2.498 mmol), BINAP (3.19 g, 4.996 mmol) and cesium carbonate (12.21 g, 37.47 mmol) was added a solution of compound **11b** (3.70 g, 12.49 mmol) in toluene (60 mL) and a solution of compound **11B** (3.75 g, 20.69 mmol) in toluene (10 mL) under nitrogen. The reaction mixture was stirred for 16 hours under nitrogen at 100°C. The mixture was diluted with water (150 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (0~5% ethyl acetate in petroleum ether) to afford compound **11c** (3.70 g, 80% purity, 59.8% yield) as yellow oil.

LCMS: t_R = 0.788 min in 5-95AB_1.5min_220&254.lcm chromatography (Merck RP18 2.5-2mm), MS (ESI) m/z 397.2 $[M+H]^+$.



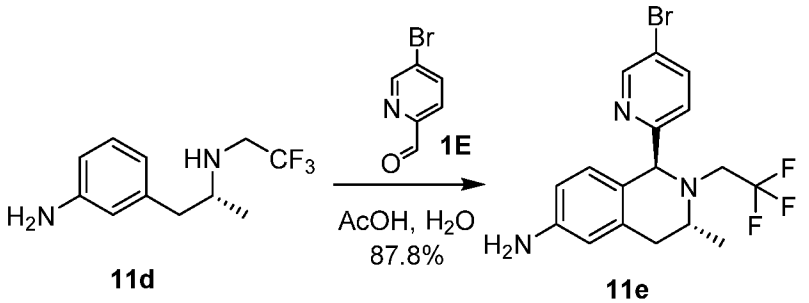
11c **11d**

A mixture of compound **11c** (3.70 g, 80% purity, 7.47 mmol), hydroxylamine hydrochloride (1.04 g, 14.94 mmol) and sodium acetate (1.59 g, 19.42 mmol) in methanol (370 mL) was

stirred at 16~24°C for one hour. The mixture was concentrated in vacuo, the residue was treated with saturated aqueous solution of sodium bicarbonate (100 mL) and ethyl acetate (30 mL) and then separated. The aqueous layer was extracted with ethyl acetate (20 mL x 2). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (0~10% ethyl acetate in petroleum ether) to afford compound **11d** (1.90 g, 90% purity, 97.7% yield) as yellow gum.

LCMS: t_R = 0.126 min in 5-95AB_1.5min_220&254.lcm chromatography (Merck RP18 2.5-2mm), MS (ESI) m/z 233.0 $[M+H]^+$.

^{1}H NMR (400MHz, CD_3OD): δ = 7.07-6.96 (m, 1H), 6.63-6.56 (m, 2H), 6.54 (d, *J* = 7.2 Hz, 1H), 3.22 (q, *J* = 9.6 Hz, 2H), 3.01-2.89 (m, 1H), 2.69 (dd, *J* = 6.4, 13.2 Hz, 1H), 2.44 (dd, *J* = 7.6, 13.2 Hz, 1H), 1.03 (d, *J* = 6.4 Hz, 3H).



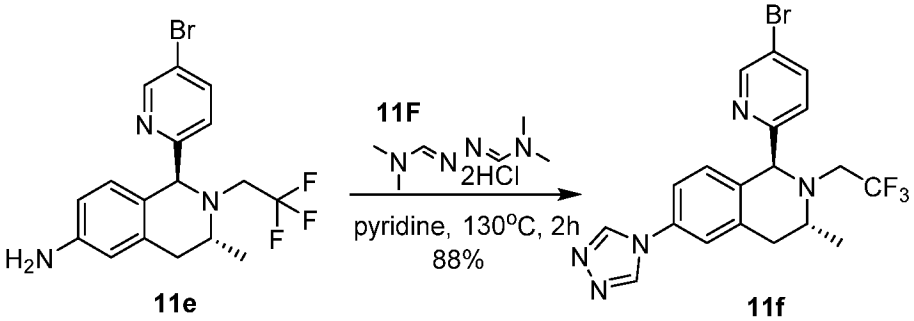
11d 11e

A mixture of compound **11d** (1.90 g, 7.36 mmol, 90% purity), **1E** (1.37 g, 7.36 mmol) and water (662 mg, 36.8 mmol) in acetic acid (20 ml) was stirred at 80°C for one hour under nitrogen. The mixture was poured into saturated aqueous solution of sodium bicarbonate (300 mL) under stirring conditions, basified to pH = 8~9 with potassium carbonate solid and extracted with ethyl acetate (50 mL x 2). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (0~10% ethyl acetate in petroleum ether) to afford compound **11e** (2.87 g, 90% purity, 87.8% yield) as orange gum. The product is inseparable diastereomers and the ratio is about 4:1 according to H NMR spectrum. The dominant isomer is characterized as below:

LCMS: t_R = 0.745 min in 5-95AB_1.5min_220&254.lcm chromatography (Merck RP18

2.5-2mm), MS (ESI) m/z 400.1 and 402.1 $[M+H]^+$.

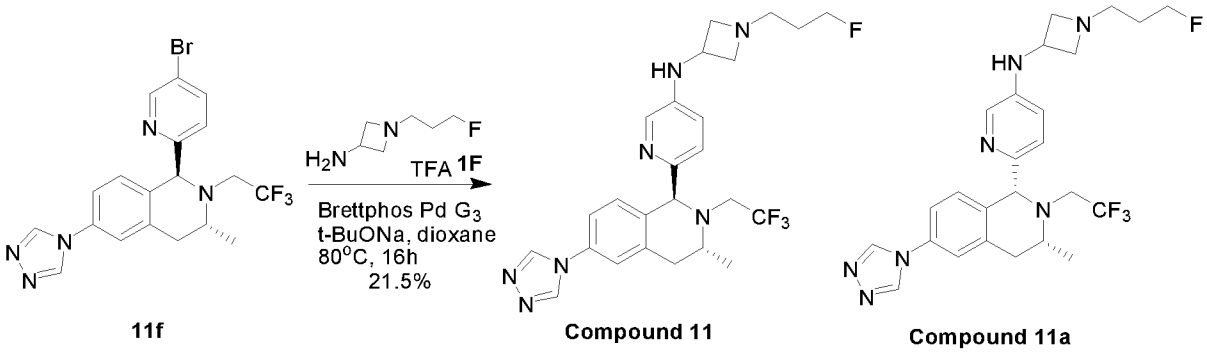
^{1}H NMR (400MHz, CD_3OD): δ = 8.51 (d, *J* = 2.4 Hz, 1H), 7.86 (dd, *J* = 2.8, 8.8 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 1H), 6.57-6.49 (m, 2H), 6.46 (dd, *J* = 2.4, 8.4 Hz, 1H), 4.85 (s, 1H), 3.48-3.33 (m, 2H), 3.11 (dd, *J* = 4.8, 16.0 Hz, 1H), 3.00-2.83 (m, 1H), 2.55 (dd, *J* = 4.8, 16.0 Hz, 1H), 1.06 (d, *J* = 6.4 Hz, 3H).



To a solution of compound **11e** (200 mg, 0.5 mmol) in pyridine (5 mL) was added compound **11F** (362.5 mg, 1.5 mmol) at 12°C. Then the mixture was stirred at 130°C for 2 hours. The reaction mixture was concentrated under reduced pressure to give crude product, which was purified by flash column (0-15% of methanol in ethyl acetate) to give **11f** (200 mg, 88%yield) as colorless oil.

LCMS: t_R = 0.885 min in 5-95AB_220&254_Shimadzu.lcm (Agilent pursult5 C18 20*2mm), MS (ESI) m/z = 452.0 and 454.0 $[M+H]^+$.

^{1}H NMR (400MHz, $CDCl_3$): δ = 8.57 (d, *J* = 2.4 Hz, 1H), 8.45 (s, 2H), 7.79 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.17 (s, 1H), 7.14-7.10 (m, 2H), 5.06 (s, 1H), 3.55-3.49 (m, 1H), 3.35-3.19 (m, 2H), 3.02-2.89 (m, 1H), 2.69 (dd, *J* = 6.0, 16.8 Hz, 1H), 1.12 (d, *J* = 6.8 Hz, 3H).



To a mixture of **11f** (150 mg, 0.33 mmol), **1F** (231.0 mg, 0.43 mmol, 67% purity) and

t-BuONa (319.6 mg, 3.3 mmol)) in 1,4-dioxane (3 mL) was added Brettphos-Pd G_3 (45.9 mg, 0.05 mmol) under nitrogen. Then the reaction was heated to 80 °C and stirred at 80 °C for 16 hours. The mixture was diluted with ethyl acetate (100 mL) and water (30 mL). After separation, the aqueous layer was extracted with ethyl acetate (300 mL x 2). The combined organic layers were washed with brine (30 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product which was purified by flash column (0-5% of ethyl acetate in petroleum ether) followed by chiral SFC (Column: DAICEL CHIRALPAK IC (250mm*30mm, 10um); Condition: 55% B (A: CO_2, B: EtOH (0.1% $NH_3.H_2O$)); Flow Rate: 70 ml/min) to afford **Compound 11** (27.8 mg, 16.6% yield, t_R: 2.647min) as a white solid and the stereochemistry was confirmed by 2D NMR. The other isomer **Compound 11a** was obtained also (8.2 mg, 4.9% yield) as a white solid.

Chiral SFC analytical method: t_R = 2.153min, 85.81% optical purity

Method: Column: Chiralpak IC 100*4.6mm I.D., 3um; Mobile phase: 40% of methanol (0.05% DEA) in CO2; Flow rate: 3mL/min; Column temp: 40 °C

Compound 11:

LCMS: t_R = 0.676 min in 5-95AB_220&254 _Shimadzu.lcm (Agilent pursult5 C18 20*2mm), MS (ESI) m/z = 504.3 $[M+H]^+$.

HPLC: t_R = 2.31 min in 10-80_AB_1.2ml.met (Ultimate C18 3*50mm 3um).

SFC: t_R = 2.647 min in IC_3_40_3ML_8min_10CM.M (Column: Chiralpak IC 100*4.6mm I.D., 3um; Mobile phase: 40% of methanol (0.05% DEA) in CO_2; Flow rate: 3mL/min; Column temp: 40°C).

^{1}H NMR (400MHz, $CDCl_3$): δ = 8.44 (s, 2H), 7.85 (d, *J* = 2.8 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 1H), 7.14 (s, 1H), 7.10-7.05 (m, 2H), 6.85 (dd, *J* = 2.8, 8.4 Hz, 1H), 4.99 (s, 1H), 4.51 (dt, *J* = 47.2 Hz and 6.0 Hz, 2H), 4.34 (br s, 1H), 4.22-4.13 (m, 1H), 3.85 (t, *J* = 7.2 Hz, 2H), 3.61-3.51 (m, 1H), 3.31-3.18 (m, 2H), 3.18-3.08 (m, 2H), 3.05-2.91 (m, 1H), 2.74 (t, *J* = 7.2 Hz, 2H), 2.67 (dd, *J* = 5.6 Hz and 16.8 Hz, 1H), 1.81-1.73 (m, 2H), 1.11 (d, *J* = 6.4 Hz, 3H).

Compound 11a:

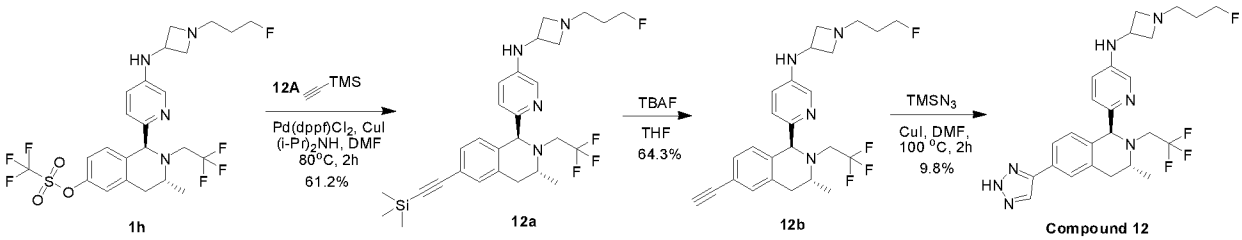
LCMS: t_R = 0.712 min in 5-95AB_220&254 _Shimadzu.lcm (Xtimate C18 2.1*30mm), MS (ESI) m/z = 504.3 $[M+H]^+$.

HPLC: t_R = 2.33 min in 10-80_AB_1.2ml.met (Ultimate C18 3*50mm 3um).

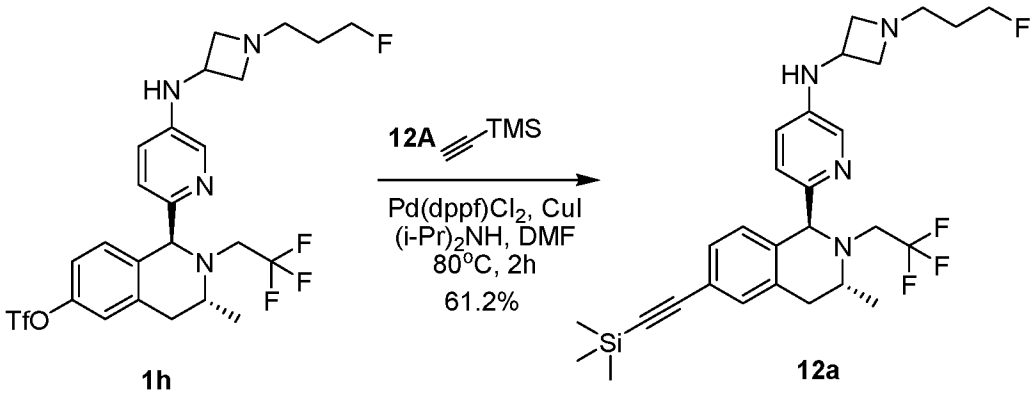
^{1}H NMR (400MHz, $CDCl_3$)**:** δ = 8.43 (s, 2H), 7.91 (s, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.12-7.07 (m, 3H), 6.91 (d, *J* = 7.2 Hz, 1H), 5.21 (s, 1H), 4.92 (br s, 1H), 4.53 (dt, *J* = 46.8 Hz and 5.6 Hz, 2H), 4.36-4.26 (m, 1H), 4.09-3.99 (m, 2H), 3.61-3.39 (m, 3H), 3.34-3.18 (m, 2H), 3.01-2.92 (m, 2H), 2.83 (d, *J* = 6.4 Hz, 2H), 2.07-1.88 (m, 2H), 1.35 (d, *J* = 6.0 Hz, 3H).

Example 12

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3R)-3-methyl-6-(2H-1,2,3-triazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine



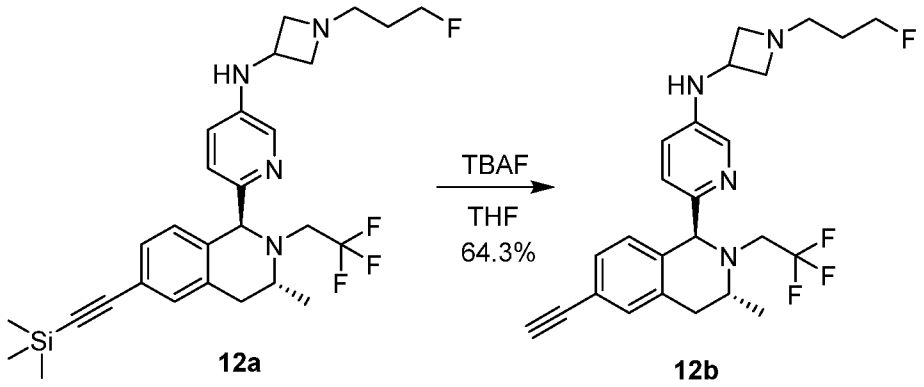
Procedure to prepare **Compound 12**:



To a mixture of compound **1h** (prepared in **Example 1**, 500 mg, 0.855 mmol), CuI (16 mg, 0.0856 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(ii) (31 mg, 0.0428 mmol) in N,N-dimethylformamide (5 mL) was added diisopropylamine (173 mg, 1.71 mmol), followed by compound **12A** (168 mg, 1.71 mmol) and then the mixture was stirred at 80 °C for 2 hour under nitrogen. The mixture was diluted with water (50 mL) and extracted with ethyl acetate (30 mL * 3). The combined organic layers were concentrated

under reduced pressure to give crude product, which was purified by column chromatography on silica gel eluted with 0~3% methanol in dichloromethane to afford compound **12a** (300 mg, 61.2% yield, 90% purity) as a brown gum.

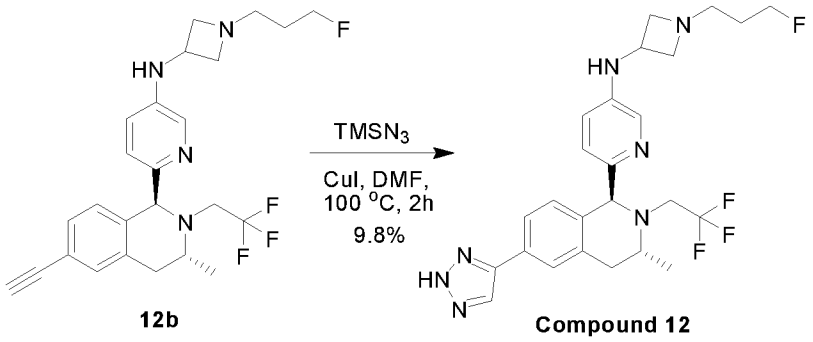
LCMS: t_R = 0.795 min in 5-95AB_220&254_Shimadzu.lcm (Merck RP18 2.5-2mm), MS (ESI) m/z = 533.4 $[M+H]^+$.



To a solution of compound **12a** (300 mg, 0.507 mmol, 90% purity) in tetrahydrofuran (3 mL) was added tetrabutylammonium fluoride (1.0 mL, 1.014 mmol, 1M in tetrahydrofuran) at room temperature (4-20 °C). Then the reaction mixture was stirred at room temperature (4-20 °C) for 1 hour. The resulting reaction mixture was diluted with saturated sodium bicarbonate (30 mL) and then extracted with ethyl acetate (10 mL * 3). The combined organic layers were washed with saturated sodium bicarbonate (40 mL * 2), dried over anhydrous sodium sulfate and then filtered. The filtrate was concentrated under vacuum to give crude product, which was purified by column chromatography on silica gel (0~10% methanol in dichloromethane) to afford compound **12b** (150 mg, 64.3 % yield) as a purple solid.

LCMS: t_R = 0.760 min in 5-95AB_220&254_Shimadzu.lcm (Agilent pursult5 C18 20*2mm), MS (ESI) m/z = 461.3 $[M+H]^+$.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.77 (d, *J* = 2.4 Hz, 1H), 7.26 (s, 1H), 7.17-7.06 (m, 2H), 6.94 (dd, *J* = 2.8, 8.8 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 4.86 (s, 1H), 4.46 (dt, *J* = 47.6, 5.6 Hz, 2H), 4.17-1.04 (m, 1H), 3.82 (t, *J* = 7.2 Hz, 2H), 3.58 - 3.46 (m, 1H), 3.41 (s, 1H), 3.36-3.32 (m, 1H), 3.28-3.17 (m, 1H), 3.01 (br s, 2H), 2.97-2.86 (m, 1H), 2.73-2.56 (m, 3H), 1.87-1.69 (m, 2H), 1.07 (d, *J* = 6.4 Hz, 3H).



12b Compound 12

A mixture of compound **12b** (120 mg, 0.261 mmol), azidotrimethylsilane (285 mg, 2.476 mmol) and copper(I) iodide (12.4 mg, 0.0653 mmol) in N,N-dimethylformamide (9.6 mL) was stirred at 100°C for 2 hours. Then the reaction mixture was concentrated under vacuum to give crude product, which was purified by reversed phase column chromatography on silica gel (0-100% methanol in water (0.1% ammonia hydroxide)) and then further purified by prep-TLC (dichloromethane / methanol = 6:1 (0.1% ammonia hydroxide)) to afford chemical pure product (25 mg) as a colorless gum. Then the chemical pure product was purified by chiral SFC [Column: Phenomenex-Amylose-1 (250 mm * 30 mm, 5 um); Condition: 35% ethanol (0.1% ammonia hydroxide) in carbon dioxide; Flow Rate: 50 mL/min] to afford **Compound 12** (12.8 mg, 94.90% chemical purity, 99.48% optical purity, 9.8% yield) as a white solid.

LCMS: t_R = 3.134 min in 10-80CD_7min_220&254.lcm chromatography (A:Xtimate C18, 2.1*30mm, 3um B: XBrige Shield RP18 2.1*50mm), MS (ESI) m/z 504.3$[M+H]^+$.

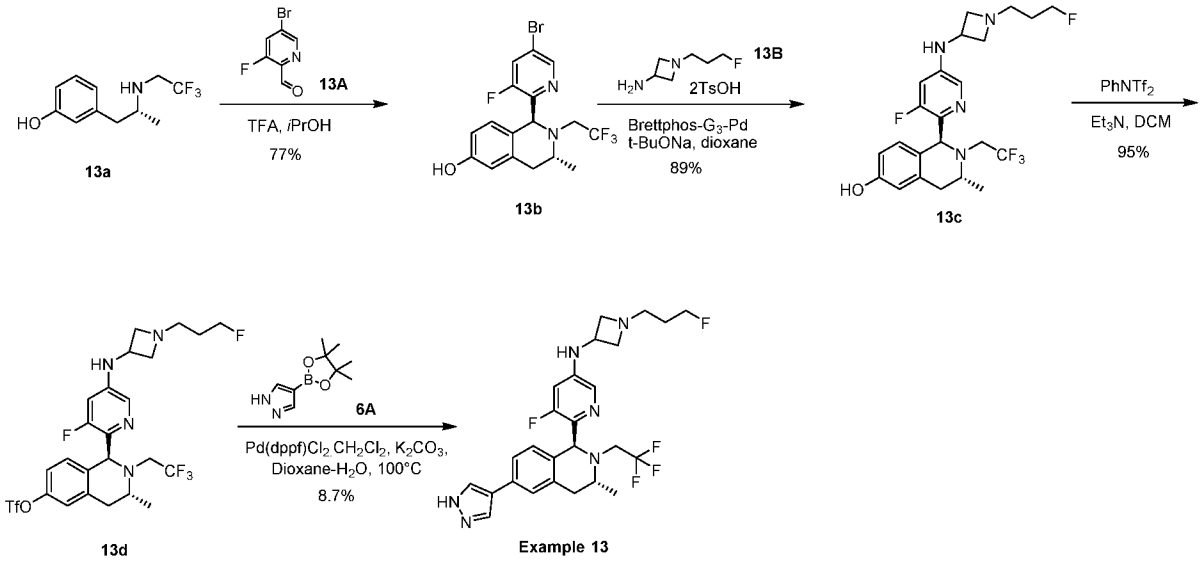
HPLC: t_R = 2.92 min in 10-80_CD_1.2ml.met.chromatography (XBridge Shield RP 18 2.1*50mm 5um).

SFC: t_R = 3.577 min; Column: Chiralcel OD-3 100×4.6mm I.D.,3um; Mobile phase: A:CO_2 B:methanol (0.05% DEA); Gradient: from 5% to 40% of B in 4.5min and hold 40% for 2.5 min, then 5% of B for 1 min; Flow rate: 2.8 mL/min Column temperature:40 °C.

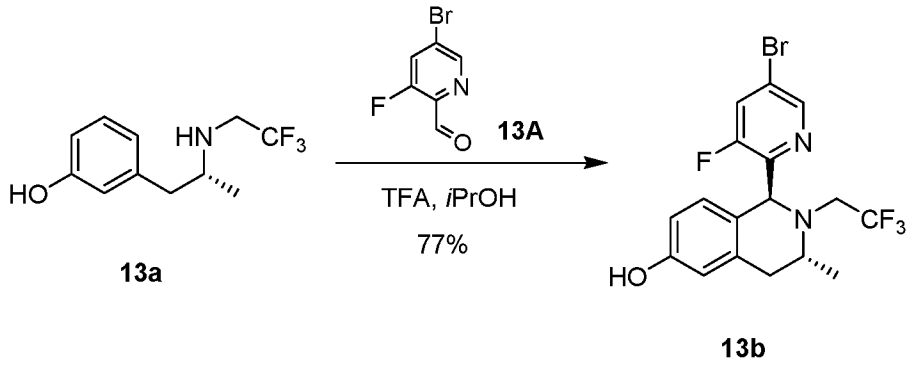
^{1}H NMR (400MHz, CD_3OD): δ = 8.10 (s, 1H), 7.78 (d, *J* = 2.8 Hz, 1H), 7.63 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 8.8 Hz, 1H), 6.95 (dd, *J* = 2.8, 8.4 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 4.91 (s, 1H), 4.47 (dt, *J* = 47.2, 6.0 Hz, 2H), 4.19-4.05 (m, 1H), 3.92-3.78 (m, 2H), 3.61-3.49 (m, 1H), 3.41-3.33 (m, 1H), 3.30-3.26 (m, 1H), 3.12-3.02 (m, 2H), 3.02-2.87 (m, 1H), 2.78-2.65 (m, 3H), 1.88-1.70 (m, 2H), 1.10 (d, *J* = 6.4 Hz, 3H).

Example 13

5-fluoro-N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3R)-3-methyl-6-(1H-pyrazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine



Procedure to prepare **Example 13**:



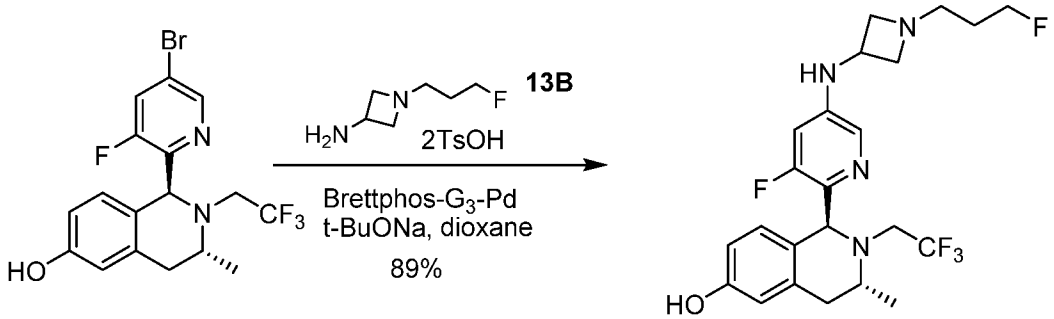
To a solution of compound **13a** (400 mg, 1.72 mmol) and compound **13A** (526.3 mg, 2.58 mmol) in *i*-PrOH (20 mL) was added TFA (0.4 mL, 5.16 mmol). The mixture was stirred at 25°C for 16 hours under nitrogen. The reaction was poured into a mixture solution of $NaHCO_3$ aqueous solution (10 mL) and brine (50 mL) and extracted with ethyl acetate (150 mL × 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, concentrated. The crude was purified by column chromatography on silica gel (0-10% ethyl acetate in petroleum ether) to an inseparable 13:1 diastereomers (550 mg, 76.6% yield) as a yellow solid. The major trans isomer **13b** was confirmed by 2D NMR (NOE).

LCMS: t_R = 0.917 min in 5-95AB_ 1.5min_220&254_Shimadzu.lcm (Agilent pursult5 C18 20*2mm), MS (ESI) m/z = 419.0 $[M+H]^+$.

SFC (Method 1): t_R = 3.326 min; 90.35% purity. Method: Column: Chiralpak AD-3 150× 4.6mm I.D., 3um; Mobile phase: A: CO_2 B: Ethanol (0.05% DEA); Gradient: from 5% to 40% of B in 5 min and hold 40% for 2.5 min, then 5% of B for 2.5min; Flow rate: 2.5mL/min; Column temp.: 35°C.

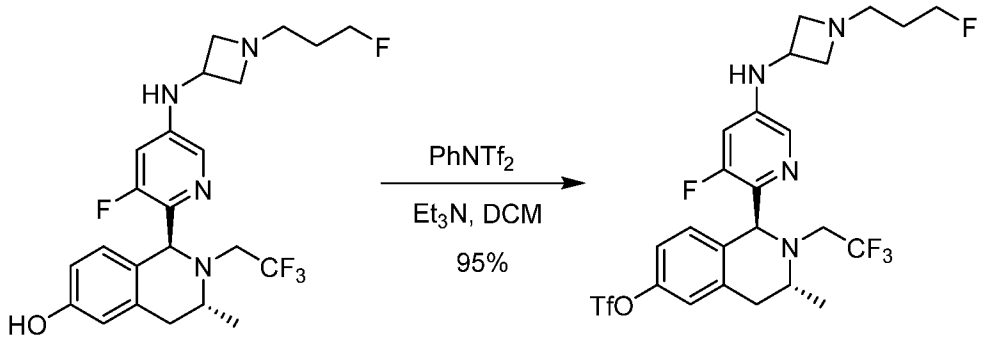
SFC (Method 2): t_R = 3.255 min; 90.38% purity. Method: Column: Chiralcel OD-3 150×4.6mm I.D., 3um; Mobile phase: A: CO_2 B: ethanol (0.05% DEA) Gradient: from 5% to 40% of B in 5 min and hold 40%; for 2.5 min, then 5% of B for 2.5 min; Flow rate: 2.5mL/min; Column temperature: 35°C.

^{1}H NMR (400MHz, $CDCl_3$) δ = 8.30 (d, *J* = 1.6 Hz, 1H), 7.49 (dd, *J* = 8.8, 1.6 Hz, 1H), 6.57 (d, *J* = 8.8 Hz, 1H), 6.53 (d, *J* = 2.0 Hz, 1H), 6.45 (dd, *J* = 8.0, 2.4 Hz, 1H), 5.15 (s, 1H), 3.53-3.45 (m, 1H), 3.20-3.10 (m, 1H), 2.97 (dd, *J* = 16.4, 4.8 Hz, 1H), 2.93-2.86 (m, 1H), 2.47 (dd, *J* = 16.8, 7.2 Hz, 1H), 0.99 (d, *J* = 6.4 Hz, 3H).



To a solution of compound **13b** (500 mg, 1.2 mmol) and compound **13B** (857 mg, 1.8 mmol) in 1,4-dioxane (20 mL) was added t-BuONa (634 mg, 6.6 mmol), followed by Brettphos-Pd-G3 (54 mg, 0.06 mmol) at 24-31°C under nitrogen. The reaction mixture was stirred for 16 hours at 80°C under nitrogen. Then the mixture was diluted with H_2O (100 mL) and extracted with ethyl acetate (100 mL x 3), washed with brine (30 mL x 2), dried over anhydrous sodium sulfate, filtered and evaporated to give crude product. The crude was purified by column chromatography on silica gel (0-5% of methanol in dichloromethane) to obtained compound **13c** (500 mg, 89.1% yield) as a yellow solid.

LCMS: t_R = 0.739 min in 5-95AB_ 1.5min_220&254_Shimadzu.lcm (Agilent pursult5 C18 20*2mm), MS (ESI) m/z = 471.2 $[M+H]^+$.

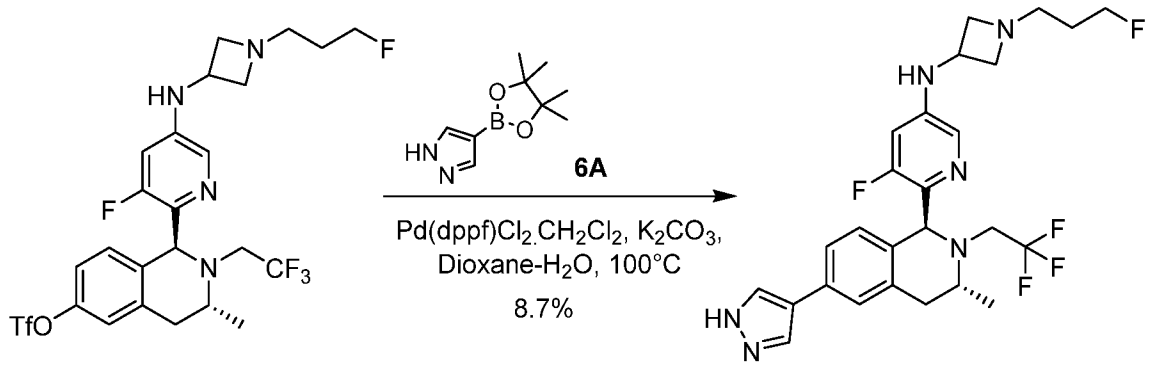


13c **13d**

To a solution of compound **13c** (450 mg, 0.96 mmol) and $PhNTf_2$ (985.9 mg, 1.92 mmol) in dichloromethane (20 mL) was added triethylamine (291.4 mg, 2.88 mmol) at 28°C. The reaction mixture was stirred for 5 hours at 80°C under nitrogen. Then the mixture was diluted with water (100 mL) and extracted with dichloromethane (100 mL x 3), washed with brine (30 mL x 2), dried over anhydrous sodium sulfate, filtered and evaporated to give crude product. The crude was purified by column chromatography on silica gel (0-10% methanol in dichloromethane) to obtained compound **13d** (550 mg, 95.5% yield) as a yellow solid which contained some Et_3N.

LCMS: t_R = 0.860 min in 5-95AB_1.5min_220&254_Shimadzu.lcm (Agilent pursult5 C18 20*2mm), MS (ESI) m/z = 603.3 $[M+H]^+$.

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.69 (d, *J* = 2.0 Hz, 1H), 7.05 (d, *J* = 2.4 Hz, 1H), 6.97 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.57 (dd, *J* = 11.6, 2.0 Hz, 1H), 5.21 (s, 1H), 5.05 (d, *J* = 6.4 Hz, 1H), 4.51 (dt, *J* = 46.8, 5.6 Hz, 2H), 4.34-4.28 (m, 1H), 4.11 (br s, 2H), 3.68-3.63 (m, 1H), 3.53 (br s, 2H), 3.03-2.99 (m, 3H), 2.61 (br dd, *J* = 16.8, 6.8 Hz, 1H), 1.94-1.82 (m, 2H), 1.08 (d, *J* = 6.8 Hz, 3H).



13d **Example 13**

To a mixture of **13d** (150 mg, 0.25 mmol), **6A** (97 mg, 0.50 mmol), potassium carbonate (103.4 mg, 0.75 mmol)) in 1,4-dioxane (3 mL) and water (0.3 mL) was added $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (40.8 mg, 0.05 mmol) under nitrogen. Then the reaction was heated up to 100°C and stirred at 100°C for 16 hours under nitrogen. Then the mixture was diluted with water (50 mL) and extracted with dichloromethane (150 mL x 3), washed with brine (50 mL x 2), dried over anhydrous sodium sulfate, filtered and evaporated to give crude product, which was purified by column chromatography on silica gel (0-10% methanol in dichloromethane) to obtained crude product. The crude product was separated by chiral SFC (92.59% purity, Column: DAICEL CHIRALCEL OJ-H (250mm*30mm, 5um)); Condition: 35%B (A: CO_2, B: 0.1% NH_3H_2O /EtOH); Flow rate: 60 mL/min) to give **Example 13** (11.3 mg, 8.7% yield) as a yellow solid.

LCMS: t_R = 0.743 min in 5-95AB_1.5min_220&254_Shimadzu.lcm (Agilent pursult5 C18 20*2mm), MS (ESI) m/z = 521.4 $[M+H]^+$.

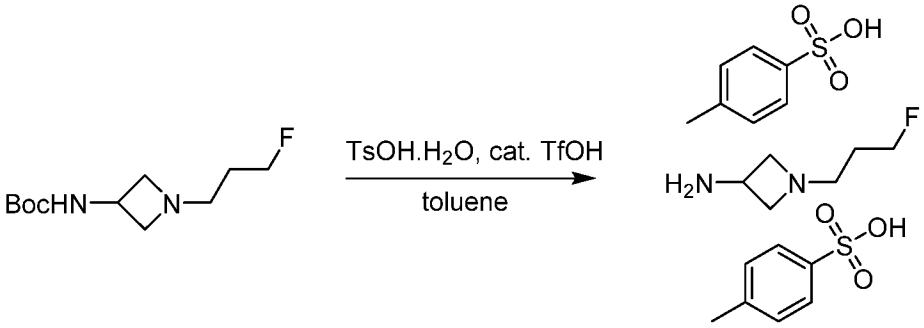
HPLC: t_R = 3.44 min in 10-80_AB_1.2ml.met.chromatography (Ultimate C18 3.0um 3.0*50mm).

SFC: t_R = 2.289 min; 100% purity. Method: Column: Chiralcel OJ-3 100×4.6mm I.D., 3um; Mobile phase: A: CO_2 B: ethanol (0.1% ethanolamine); Gradient: from 5% to 40% of B in 4.5 min, then 5% of B for 1 min; Flow rate: 2.8 mL/min; Column temperature: 40°C.

^{1}H NMR (400MHz, CD_3OD) δ = 7.89 (br s, 2H), 7.63 (d, *J* = 2.0 Hz, 1H), 7.34 (s, 1H), 7.24 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.70 (s, 1H), 6.69-6.66 (m, 1H), 5.11 (s, 1H), 4.46 (dt, *J* = 47.2, 5.6 Hz, 2H), 4.15-4.11 (m, 1H), 3.91 (br t, *J* = 6.8 Hz, 2H), 3.61-3.54 (m, 1H), 3.31-3.30 (m, 1H), 3.24-3.08 (m, 3H), 3.00-2.87 (m, 1H), 2.77 (t, *J* = 7.6 Hz, 2H), 2.65 (dd, *J* = 16.0, 5.2 Hz,

1H), 1.87-1.71 (m, 2H), 1.07 (d, *J* = 6.4 Hz, 3H).

The procedure to synthesize intermediate **13B**:



1F_2 **13B**

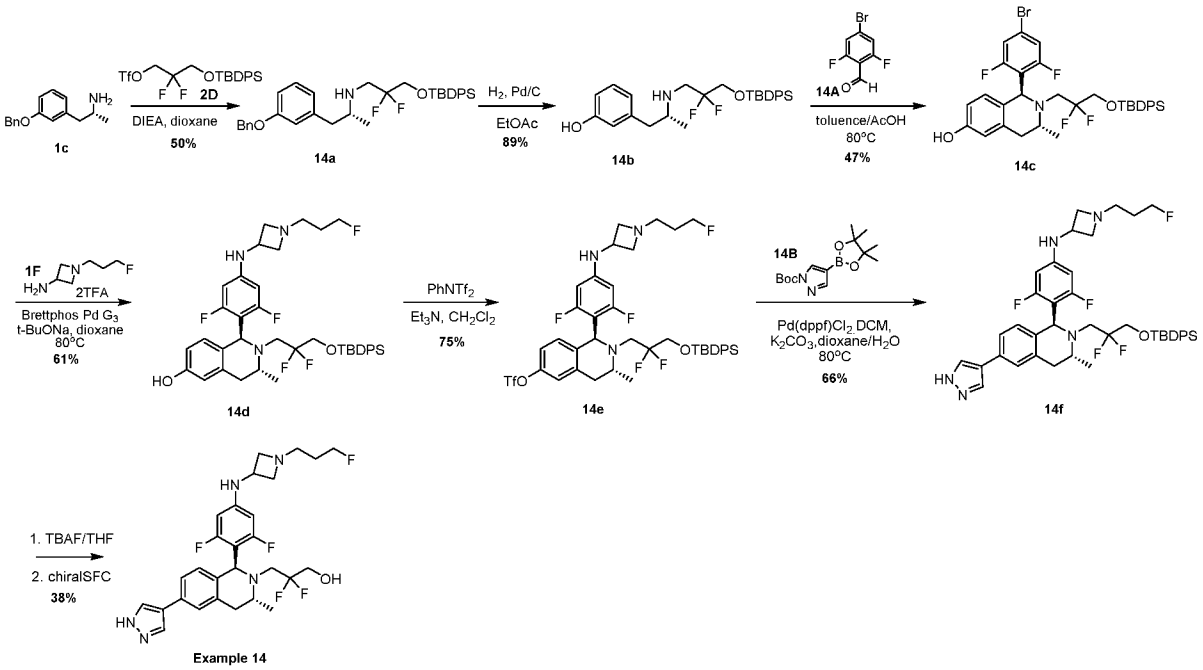
To a solution of compound **1F_2** (23 g, 99.01 mmol) in toluene (150 mL) was added TsOH·H_2O (37.7 g, 198.02 mmol) and TfOH (575 mg, 3.83 mmol). The resulting mixture was stirred at 50°C for 2 hours. The reaction mixture was diluted with ethyl acetate (150 mL) and the solid was collected by filtration quickly. The filtered cake was washed with ethyl acetate (150 mL) and dried under high vacuum to give compound **13B** (47 g TsOH salt, 99% yield) as white solid.

LCMS: t_R = 0.099 min in 0-60AB_2min_E_50_Agilent.M chromatography (Xtimate C18, 2.1*30mm, 3um), MS (ESI) m/z = 133.1 $[M+H]^+$.

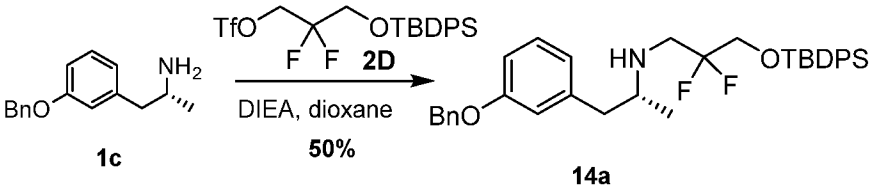
^{1}H NMR (400MHz, MeOD): δ = 7.73 (d, *J* = 8.0 Hz, 4H), 7.27 (d, *J* = 8.0 Hz, 4H), 4.70-4.20 (m, 7H), 3.50 (br t, *J* = 6.8 Hz, 2H), 2.39 (s, 6H), 2.09-2.01 (m, 1H), 2.00-1.92 (m, 1H).

Example 14

3-((1S,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-3-methyl-6-(1H-pyrazol-4-yl)-3,4-dihydroisoquinolin-2(1H)-yl)-2,2-difluoropropan-1-ol



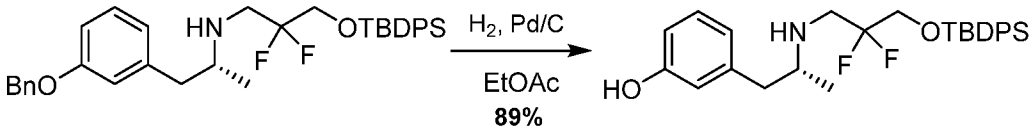
Procedure to prepare **Example 14**:



To a mixture of compound **2D** (1.60 g, 6.63 mmol) in 1,4-dioxane (30 mL) was added DIEA (3.5 mL, 19.89 mmol), followed by compound **1c** (3.20g, 6.63 mmol) in 1,4-dioxane (2 mL) at room temperature (0-6°C). Then the reaction mixture was stirred at 80°C under nitrogen for 24 hours. Then the reaction mixture was diluted with water (40 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (80 mL x 3), dried over anhydrous sodium sulfate, filtered and then concentrated under vacuum to give crude product, which was purified by column chromatography on silica gel (0~5% ethyl acetate in petroleum ether) to afford compound **14a** (1.9 g, 50% Yield) as colorless gum.

LCMS: t_R = 0.996 min in 5-95AB_1.5 min_220&254 chromatography (Merck RP18 2.5-2mm), MS (ESI) m/z = 574.1 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73-7.63 (m, 4H), 7.48-7.30 (m, 11H), 7.20 (t, J = 8.0 Hz, 1H), 6.87-6.81 (m, 2H), 6.79 (d, J = 7.6 Hz, 1H), 5.05 (s, 2H), 3.94-3.74 (m, 2H), 3.26-3.04 (m, 2H), 3.04-2.93 (m, 1H), 2.75 (dd, J = 13.2, 6.4 Hz, 1H), 2.57 (dd, J = 13.6, 7.2 Hz, 1H), 1.10-1.03 (m, 9H).

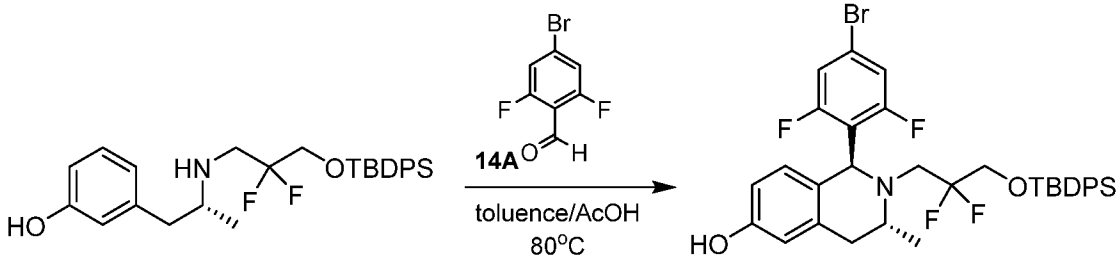


14a **14b**

To a solution of compound **14a** (400 mg, 0.697 mmol) in ethyl acetate (30 mL) was added 10% Pd/C (80 mg, 50w% water). Then the reaction mixture was stirred at 40°C under hydrogen atmosphere (15 Psi, H_2 balloon) for 16 hours. Then the reaction mixture was filtered through celite. To the filtrate was added 10% Pd/C (80 mg, 50w% water). The resulting mixture was stirred at 50°C under H_2 atmosphere (15 Psi, H_2 balloon) for 5 hours. Then the reaction mixture was filtered through celite. The filtrate was concentrated under vacuum to give crude product, which was purified by column chromatography on silica gel (0~10% ethyl acetate in petroleum ether) to afford compound **14b** (300 mg, 89% Yield) as colorless gum.

LCMS: t_R = 0.936 min in 5-95AB_1.5 min_220&254 chromatography (Merck RP18 2.5-2mm), MS (ESI) m/z = 484.1 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76-7.63 (m, 4H), 7.52-7.36 (m, 6H), 7.14 (t, J = 8.0 Hz, 1H), 6.74 (d, J = 7.2 Hz, 1H), 6.68 (dd, J = 8.4, 2.4Hz, 1H), 6.64 (s, 1H), 3.91-3.72 (m, 2H), 3.25-3.05 (m, 2H), 3.05-2.97 (m, 1H), 2.71 (dd, J = 13.6, 6.8Hz, 1H), 2.57 (dd, J = 13.6, 6.4Hz, 1H), 1.09 (d, J = 6.4 Hz, 3H), 1.07 (s, 9H).

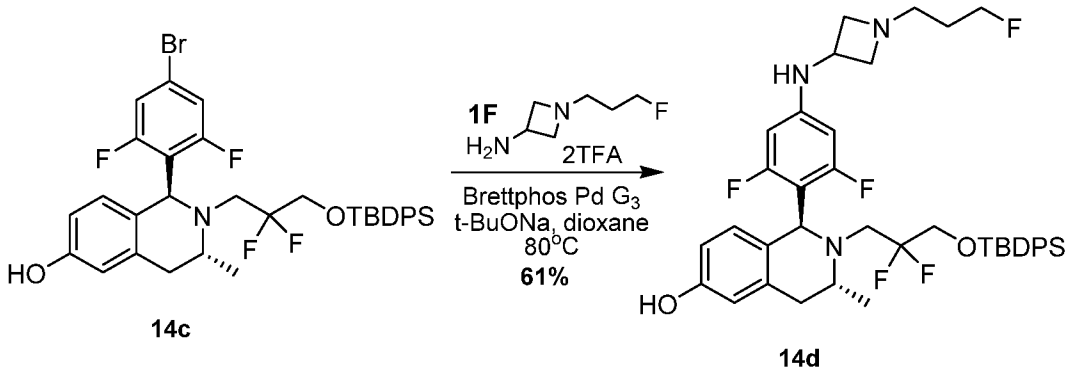


14b **14c**

To a solution of compound **14b** (600 mg, 1.24 mmol)) in toluene (27 mL) was added acetic acid (3 mL) and **14A** (300 mg, 1.36 mmol) at room temperature (15-23°C). Then the reaction mixture was stirred 80°C for 20 hours. Then the reaction mixture was concentrated under vacuum. The residue was treated with ethyl acetate (20 mL) and water (20 mL), then separated. The water layer was extracted with ethyl acetate (20 mL*3). The combined

organic layers were washed with saturated $NaHCO_3$ solution (20 mL*3), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum and purified by column chromatography on silica gel (0~20% ethyl acetate in petroleum ether) to afford a 9:1 inseparable diastereomers as a yellow oil (400 mg, 46.7%). Compound **14c** is the major diastereomer.

LCMS: t_R = 1.120 min in 5-95AB_220&254 chromatography (Merck RP18 2.5-2mm), MS (ESI) m/z = 688.3 $[M+2+H]^+$.



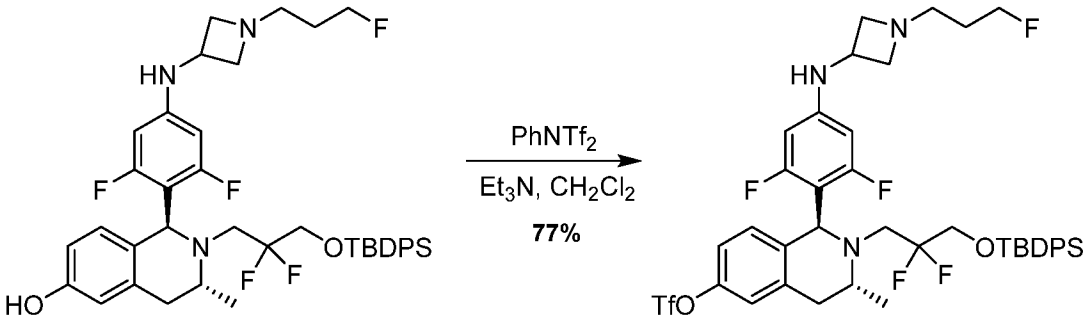
14c **14d**

To a mixture of Brettphos Pd G3 (69.7 mg, 0.077 mmol) and t-BuONa (440.6 mg, 4.59 mmol) was added a solution of **14c** (350 mg, 0.510 mmol) and **1F** (367.4 mg, 1.02 mmol) in 1,4-dioxane (9 mL) at room temperature (13-25°C). Then the reaction mixture was stirred at 80°C for 3 hours. Then the reaction mixture was filtered and the filtrate was concentrated under vacuum. The residue was treated with ethyl acetate (20 mL) and water (20 mL), and then separated. The water layer was extracted with ethyl acetate (20 mL*3). The combined organic layers were washed with brine (20 mL*3), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum and purified by column on silica gel (0~10% MeOH in CH_2Cl_2) to afford **5** (230 mg, 61.1%) as a yellow oil.

LCMS: t_R = 0.887 min in 5-95AB_220&254 chromatography (Merck RP18 2.5-2mm), MS (ESI) m/z = 738.4 $[M+H]^+$.

^{1}H NMR (400 MHz, MeOD): δ = 7.63-7.57 (m, 4H), 7.50-7.33 (m, 6H), 6.52-6.39 (m, 3H), 5.89 (d, J = 11.6 Hz, 2H), 4.96 (s, 1H), 4.46 (dt, J = 47.2, 6.0 Hz, 2H), 4.01-3.82 (m, 2H), 3.78-3.67 (m, 2H), 3.59-3.35 (m, 2H), 3.06 (br dd, J = 15.2, 4.8 Hz, 2H), 2.90 (t, J = 7.2 Hz, 2H), 2.64 (br t, J = 7.2 Hz, 3H), 2.40 (dd, J = 15.2, 2.4 Hz, 1H), 1.85-1.65 (m, 2H), 1.07-0.95

(m, 12H).

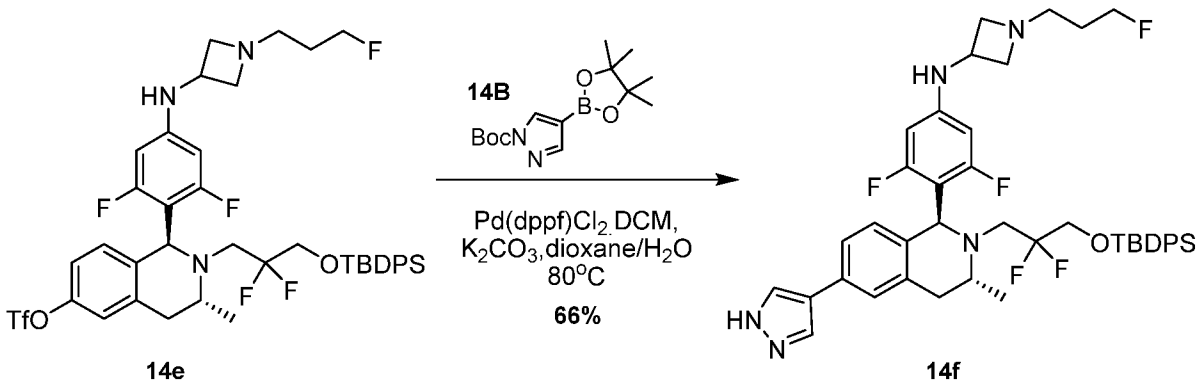


14d **14e**

To a solution of compound **14d** (230 mg, 0.312 mmol) in dichloromethane (7 mL) was added Et_3N (94.7 mg, 0.936 mmol), followed by $PhNTf_2$ (223 mg, 0.624 mmol) at room temperature (16-28°C). Then the reaction mixture was stirred at room temperature (16-28°C) for 16 hours. Then the reaction mixture was concentrated under vacuum. The residue was treated with ethyl acetate (20 mL) and water (20 mL), and then separated. The water layer was extracted with ethyl acetate (20 mL*3). The combined organic layers were washed with brine (20 mL*3), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum and purified by column chromatography on silica gel (0~10% methanol in dichloromethane) to afford compound **14e** (220 mg, 76.9%) as an off-blue solid.

LCMS: t_R = 1.018 min in 5-95AB_220&254 chromatography (Merck RP18 2.5-2mm), MS (ESI) m/z = 870.5 $[M+H]^+$.

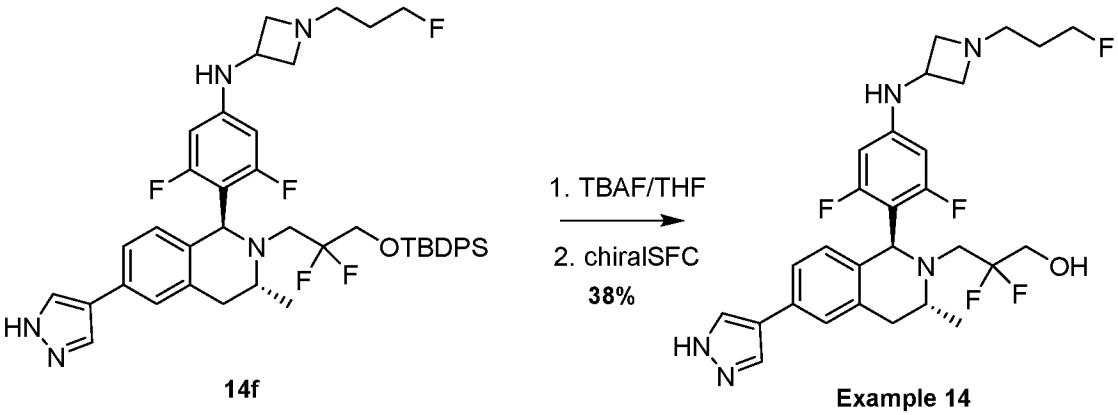
^{1}H NMR (400 MHz, MeOD): δ = 7.65-7.56 (m, 4H), 7.50-7.36 (m, 6H), 7.09 (d, J = 2.4 Hz, 1H), 7.00 (dd, J = 8.4, 2.4Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 5.94 (br d, J = 11.6 Hz, 2H), 5.10 (s, 1H), 4.46 (dt, J = 47.2, 6.0 Hz, 2H), 3.96-3.86 (m, 2H), 3.79 (br s, 2H), 3.57 (br s, 1H), 3.50-3.39 (m, 1H), 3.20-3.05 (m, 2H), 3.04-2.92 (m, 2H), 2.80-2.65 (m, 3H), 2.60 (dd, J = 16.0, 3.2 Hz, 1H), 1.85-1.68 (m, 2H), 1.06-0.94 (m, 12H).



To a mixture of compound **14B** (25 mg, 0.086 mmol), $Pd(dppf)Cl_2.CH_2Cl_2$ (9.3 mg, 0.015 mmol) and K_2CO_3 (23.6 mg, 0.171 mmol) was added a solution of compound **14e** (50 mg, 0.057 mmol) in 1,4-dioxane/H_2O (5 mL (v/v = 10:1)) at room temperature (8-17°C). Then the reaction mixture was stirred at 100°C for 20 hours. Then the reaction mixture was combined with a previous pilot batch (10 mg of compound **14e**) which was carried out with same manner. The reaction mixture was filtered and the filtrate was concentrated under vacuum. The residue was treated with ethyl acetate (10 mL) and water (10 mL), and then separated. Then the water layer was extracted with ethyl acetate (10 mL x 3) and the combined organic layers were washed with brine (10 mL x 3), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum and purified by column chromatography on silica gel (0-10% methanol in CH_2Cl_2) to obtain compound **14f** (60 mg, 65.5%) as an off-blue solid.

LCMS: t_R = 1.046 min in 5-95AB_220&254 chromatography (Xtimate C18 2.1*30mm), MS (ESI) m/z = 788.6 $[M+H]^+$.

^{1}H NMR (400 MHz, MeOD): δ = 7.88 (s, 2H), 7.67-7.55 (m, 4H), 7.50-7.33 (m, 6H), 7.27 (s, 1H), 7.20 (br d, J = 8.0 Hz, 1H), 6.67 (d, J = 8.0 Hz, 1H), 5.92 (d, J = 11.6 Hz, 2H), 5.04 (s, 1H), 4.45 (dt, J = 47.2, 6.0 Hz, 2H), 4.03-3.85 (m, 2H), 3.76 (br t, J = 7.2 Hz, 2H), 3.59 (br d, J = 7.2 Hz, 1H), 3.49-3.35 (m, 1H), 3.22-3.05 (m, 2H), 2.96 (br t, J = 6.8 Hz, 2H), 2.86-2.71 (m, 1H), 2.67 (t, J = 7.2 Hz, 2H), 2.55 (br dd, J = 2.8, 15.6 Hz, 1H), 1.86-1.66 (m, 2H), 1.04-0.96 (m, 12H).



14f Example 14

To a solution of compound **14f** (40 mg, 0.063 mmol) in THF (5 mL) was added TBAF (0.189 mL, 0.189 mmol, 1M in THF) at room temperature (8-24°C). Then the reaction mixture was stirred at room temperature (8-24°C) for 3 hours. The reaction mixture was diluted with saturated $NaHCO_3$ solution (10 mL) and the water layer was extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (10 mL*3), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum and purified by pre-TLC (CH_2Cl_2/methanol = 9:1) to afford the crude product. Then the crude product was further purified by chiral SFC (Column: Column: Lux Cellulose-2 150×4.6mm I.D., 3um; Gradient: 40% of Methanol (0.05% DEA) in CO_2; Flow rate: 2.5mL/min; Column temperature: 40°C) to give **Example 14** (13.6 mg, 38.2%) as an off-white solid.

LCMS: t_R = 1.623 min in 10-80AB_4min_220&254.lcm chromatography (Xtimate C18 2.1*30mm), MS (ESI) m/z =550.1H]$^+$.

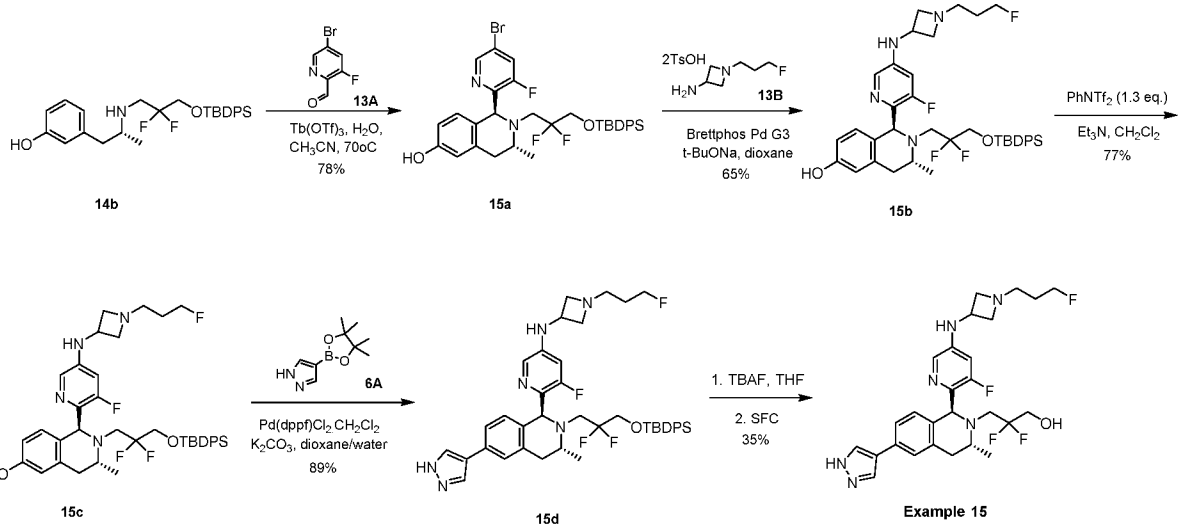
HPLC: t_R = 1.91min in 10-80_AB_1.2ml.met. HPLC-A Ultimate C18 3*50mm 3um.

SFC: t_R = 2.788 min, purity: 100%, Column: Lux Cellulose-2 150×4.6mm I.D., 3um Gradient: 40% of Methanol (0.05% DEA) in CO_2 Flow rate: 2.5mL/min; Column temperature: 40°C.

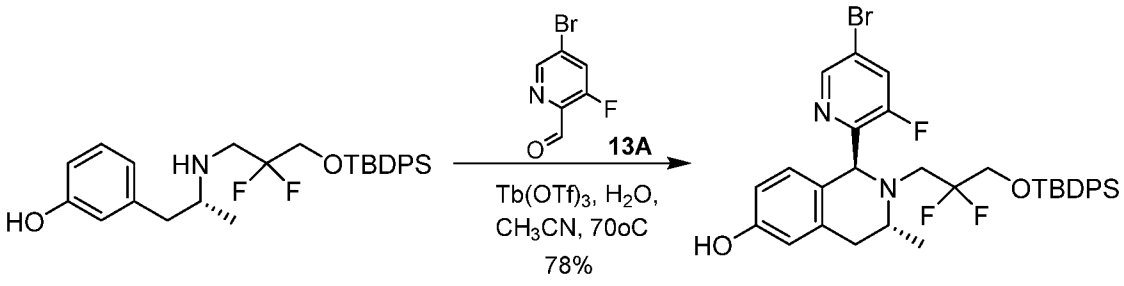
^{1}H NMR (400 MHz, MeOD): δ = 7.91 (br s, 2H), 7.30 (s, 1H), 7.23 (d, J = 8.0 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 6.10 (d, J = 11.2 Hz, 2H), 5.07 (s, 1H), 4.45 (dt, J = 47.2, 6.0 Hz, 2H), 4.11 (br t, J = 6.4 Hz, 1H), 3.91 (br d, J = 4.8 Hz, 2H), 3.82-3.66 (m, 1H), 3.59 (br s, 1H), 3.43-3.32 (m, 1H), 3.24 (br d, J = 4.4 Hz, 1H), 3.20-3.04 (m, 3H), 2.82-2.75 (m, 2H), 2.75-2.67 (m, 1H), 2.64 (dd, J = 3.2, 15.6 Hz, 1H), 1.89-1.70 (m, 2H), 1.05 (d, J = 6.4 Hz, 3H).

Example 15

2,2-difluoro-3-((1S,3R)-1-(3-fluoro-5-((1-(3-fluoropropyl)azetidin-3-yl)amino)pyridin-2-yl)-3-methyl-6-(1H-pyrazol-4-yl)-3,4-dihydroisoquinolin-2(1H)-yl)propan-1-ol



Procedure to prepare **Example 15**:

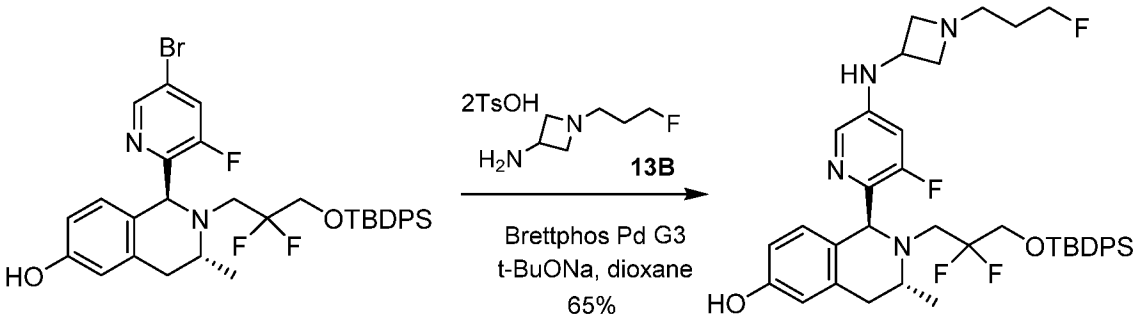


14b **15a**

To a solution of compound **14b** (200 mg, 0.414 mmol), Compound **13A** (101.4 mg, 0.497 mmol) and $Yb(OTf)_3$ (10.3 mg, 0.0166 mmol) in MeCN (6 mL) was added water (37.3 uL, 2.07 mmol). After that, the reaction was stirred at 70°C for 12 hours under nitrogen. The mixture was concentrated to give crude product, which was purified by column chromatography on silica gel (0~18% ethyl acetate in petroleum ether) to afford a 10:1 inseparable diastereomers as a yellow oil (215.8 mg, 78.0% yield). Compound **15a** is the major diastereomer.

LCMS: t_R = 1.133 min in 5-95AB_1.5min_220&254.lcm chromatography (Agilent Pursult 5 C18 20*2.0mm), MS (ESI) m/z = 671.4 $[M+H+2]^+$.

^{1}H NMR (400MHz, $CDCl_3$): δ = 8.33 (d, *J* = 1.2 Hz, 1H), 7.66-7.61 (m, 4H), 7.49-7.36 (m, 7H), 6.65-6.60 (m, 2H), 6.57-6.53 (m, 1H), 4.86 (s, 1H), 3.99-3.87 (m, 1H), 3.77-3.69 (m, 1H),3.63-3.55 (m, 1H), 3.32-3.19 (m, 1H), 2.99 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.87-2.77(m, 1H), 2.53 (dd, *J* = 16.4, 6.8 Hz, 1H), 1.07-1.03 (m, 12H).

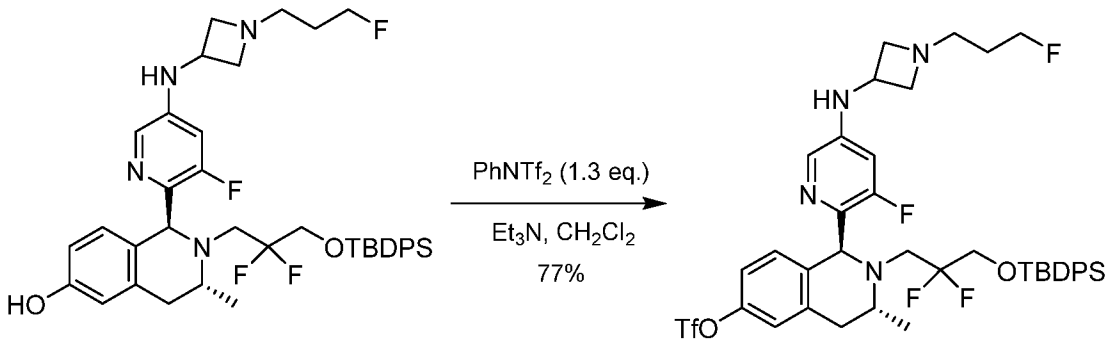


15a **15b**

To a mixture of compound **15a** (195.8 mg, 0.293 mmol), **13B** (209.0 mg, 0.439 mmol) in 1,4-dioxane (8 mL) were added Brettphos Pd-G_3 (26.5 mg, 0.0293 mmol) and t-BuONa (154.7 mg, 1.612 mmol) under nitrogen. Then the reaction mixture was stirred at 80°C for 12 hours under nitrogen. The mixture was combined with the parallel batches (90 mg of compound **14b**) which was carried out with same manner. The reaction mixture was concentrated *in vacuo* and purified by column chromatography on silica gel (0~10% methanol in dichloromethane) to afford compound **15b** (201.6 mg, 65.3% average yield) as yellow oil.

LCMS: t_R = 0.862 min in 5-95AB_1.5min_220&254.lcm chromatography (Agilent Pursult 5 C18 20*2.0mm), MS (ESI) m/z = 721.6 $[M+H]^+$.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.67-7.59 (m, 5H), 7.45-7.35 (m, 6H), 6.59-6.52 (m, 2H), 6.44-6.34 (m, 2H), 5.17 (s, 1H), 4.48 (dt, *J* = 47.2, 6.0 Hz, 2H), 4.46 (s, 1H), 4.05-3.92 (m, 2H), 3.73-3.66 (m, 3H), 3.59-3.53 (m, 1H), 3.18 (q, *J* = 14.8 Hz, 1H), 3.06-2.98 (m, 2H), 2.92 (dd, *J* = 16.4, 4.4 Hz, 1H), 2.78 (q, *J* = 14.8 Hz, 1H), 2.66 (t, *J* = 7.2 Hz, 2H), 2.49 (dd, *J* = 16.4, 7.6 Hz, 1H), 1.83-1.72 (m, 2H), 1.07-1.01 (m, 12H).

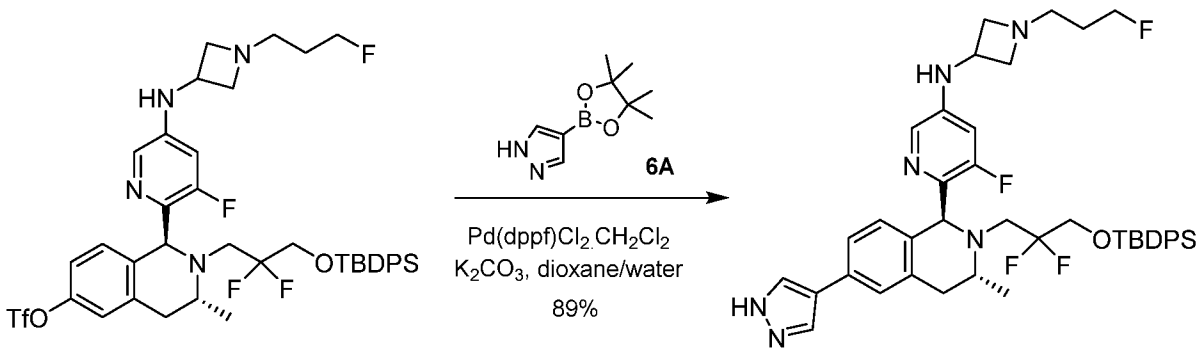


15b **15c**

To a mixture of compound **15b** (201.6 mg, 0.280 mmol) in dichloromethane (5 mL) was added triethylamine (188.5 uL, 1.12 mmol), followed by $PhNTf_2$ (150.0 mg, 0.420 mmol). Then the reaction mixture was stirred at room temperature (24-35°C) for 12 hours. The mixture was combined with another batch (48.3 mg of compound **15b**). Then the mixture was concentrated under vacuum to give crude product, which was purified by column chromatography on silica gel (0~8% methanol in dichloromethane) to afford compound **15c** (227.1 mg, 76.8% yield) as yellow oil.

LCMS: t_R = 1.035 min in 5-95AB_1.5min_220&254.lcm chromatography (Agilent Pursult 5 C18 20*2.0mm), MS (ESI) m/z = 853.6 $[M+H]^+$.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.67-7.60 (m, 5H), 7.49-7.35 (m, 6H), 7.04 (d, *J* = 2.4 Hz, 1H), 6.95 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 1H), 6.39 (dd, *J* = 12.0, 2.0 Hz, 1H), 5.24 (s, 1H), 4.59-4.52 (br s, 1H), 4.50 (dt, *J* = 47.2, 5.6 Hz, 2H), 4.16-4.05 (m, 1H), 4.00-3.90 (m, 1H), 3.90-3.82 (m, 2H), 3.73-3.61 (m, 2H), 3.25-3.17 (m, 3H), 3.02 (dd, *J* = 16.4, 4.4 Hz, 1H), 2.87-2.76 (m, 3H), 2.59 (dd, *J* = 16.4, 6.4 Hz, 1H), 1.87-1.76 (m, 2H), 1.10-1.00 (m, 12H).

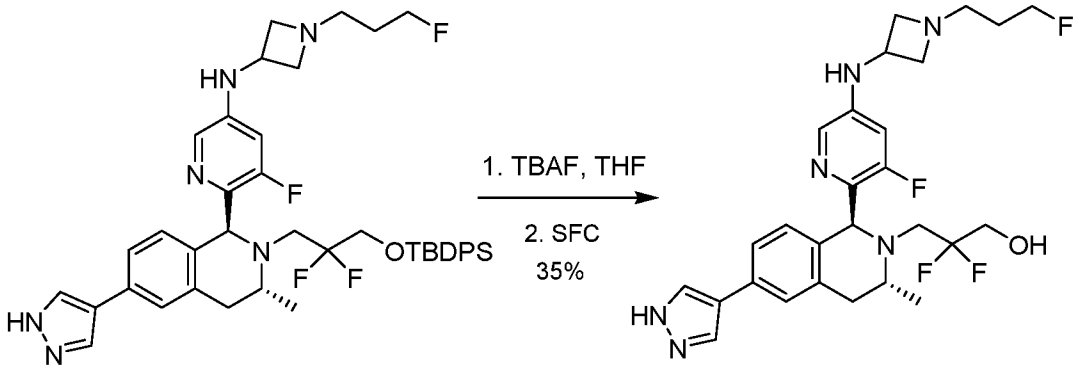


15c **15d**

To a mixture of compound **15c** (227.1 mg, 0.267 mmol), compound **6A** (117.9 mg, 0.401 mmol), Pd(dppf)Cl_2.dichloromethane (43.6 mg, 0.0534 mmol) and K_2CO_3 (92.3 mg, 0.668 mmol) was purged with nitrogen. Then to the mixture was added a mixture solution of 1, 4-dioxane and H_2O (v/v=4:1) (7.5 mL) under nitrogen. The resulting mixture was stirred at 100°C under nitrogen for 3 hours. The mixture was filtered and concentrated under vacuum to give crude product, which was purified by column chromatography on silica gel (0~10% methanol in dichloromethane) to afford compound **15d** (182.7 mg in total, 88.8% yield) as a brown solid.

LCMS: t_R = 0.918 min in 5-95AB_1.5min_220&254.lcm chromatography (Agilent Pursult 5 C18 20*2.0mm), MS (ESI) m/z = 771.3 $[M+H]^+$.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.76 (s, 2H), 7.64-7.57 (m, 5H), 7.45-7.34 (m, 6H), 7.23 (s, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 7.6 Hz, 1H), 6.38 (d, *J* = 11.6 Hz, 1H), 5.23 (s, 1H), 4.74-4.58 (br s, 1H), 4.46 (dt, *J* = 46.8, 5.2 Hz, 2H), 4.12-4.04 (m, 1H), 4.00-3.84 (m, 3H), 3.74-3.60 (m, 2H), 3.25-3.12 (m, 3H), 3.01 (d, *J* = 13.2 Hz, 1H), 2.86-2.73 (m, 3H), 2.58 (dd, *J* = 16.4, 7.2 Hz, 1H), 1.85-1.71 (m, 2H), 1.08-1.00 (m, 12H).



15d **Example 15**

To a mixture of compound **15d** (182.7 mg, 0.237 mmol) in tetrahydrofuran (5 mL), a solution of TBAF (356 uL, 0.356 mmol, 1M in THF) was added. The resulting mixture was stirred at 60°C under nitrogen for 12 hours. The mixture was adjusted to pH ~8 with saturated $NaHCO_3$ solution. The mixture was extracted with ethyl acetate (20

mL*3) ,washed with brine (20 mL*2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. The mixture was purified by column chromatography silica gel (0-10% of methanol in dichloromethane) to afford 80.9 mg of 10:1 inseparable diastereomers, which was further purified by chiral SFC (Column: DAICEL CHIRALCEL OJ-H (250mm*30mm, 5um); Condition: (0.1% NH_3H_2O) MeOH; Flow rate: 60 mL/min) to afford compound **Example 15** (43.5 mg, 34.5% yield) as a white solid.

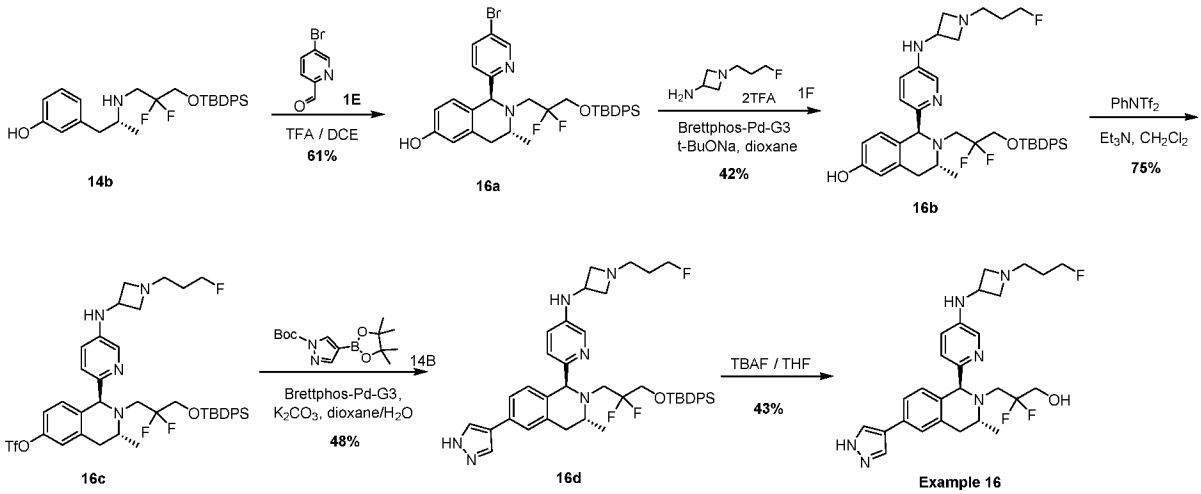
HPLC: t_R = 3.29 min in 0-60_AB_1.2ml.met.chromatography (Ultimate C18 3*50mm 3um).

SFC: t_R = 2.479 min; 99.84% purity. Method: Column: Chiralcel OJ-3 100×4.6mm I.D., 3um; Mobile phase: A: CO_2 B: Methanol (0.1% ethanolamine); Gradient: from 5% to 40% of B in 4.5 min; then5% of B for 1 min; Flow rate: 2.8 mL/min; Column temp.: 40°C.

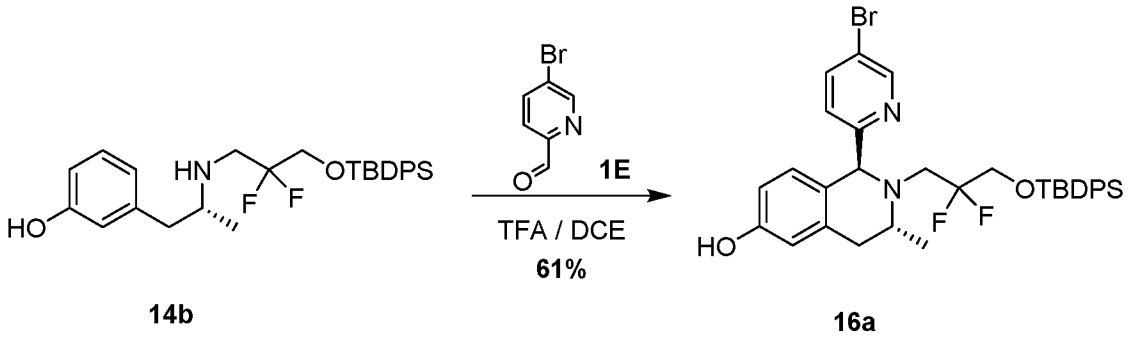
^{1}H NMR (400MHz, $CDCl_3$): δ = 7.80 (s, 2H), 7.75 (d, *J* = 1.6 Hz, 1H), 7.27-7.25 (m, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 1H), 6.55 (dd, *J* = 11.6, 2.4 Hz, 1H), 5.18 (s, 1H), 4.50 (dt, *J* = 46.8, 5.6 Hz, 2H), 4.38 (d, *J* = 6.8 Hz, 1H), 4.11-4.03 (m, 1H), 3.95-3.79 (m, 1H), 3.72 (q, *J* = 6.0 Hz, 2H), 3.76-3.67 (m, 1H), 3.62-3.51 (m, 1H), 3.29 (dd, *J* = 16.0, 4.8 Hz, 1H), 3.23-3.13 (m, 1H), 3.00-2.91 (m, 2H), 2.90-2.76 (m, 1H), 2.69-2.58 (m, 3H), 1.82-1.77 (m, 2H),1.12 (d, *J* = 6.4 Hz, 3H).

Example 16

2,2-difluoro-3-((1S,3R)-1-(5-((1-(3-fluoropropyl)azetidin-3-yl)amino)pyridin-2-yl)-3-methyl-6-(1H-pyrazol-4-yl)-3,4-dihydroisoquinolin-2(1H)-yl)propan-1-ol



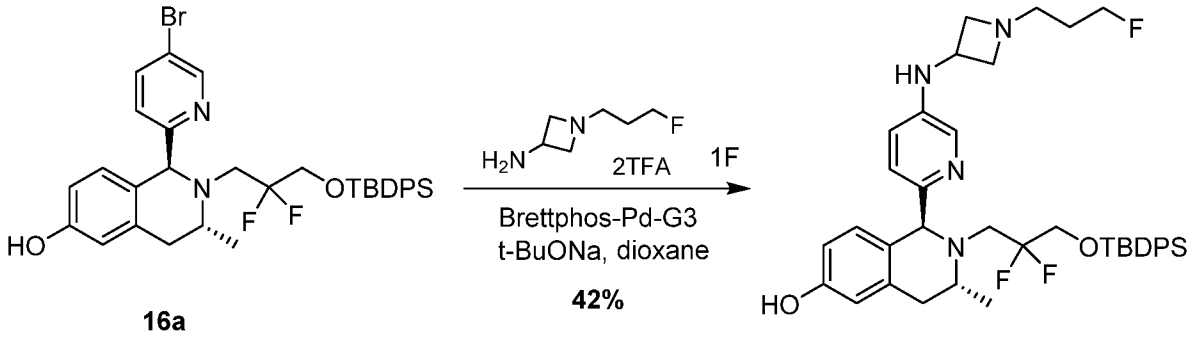
Procedure to prepare **Example 16**:



To the mixture of compound **14b** (1.2 g, 2.48 mmol) in DCE (10 mL) was added compound **1E** (560 mg, 2.98 mmol) and TFA (0.554 mL, 7.44 mmol), the resulting mixture was stirred at 12-18°C for 16 hours. The reaction was basified with saturated aqueous solution of $NaHCO_3$ to adjust pH = 8, then extracted with ethyl acetate (200 mL × 3). The combined organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate and filtered, the filtrate was concentrated in vacuum to give the crude product, which was purified by prep-HPLC [Boston Green ODS, 40*150mm, 10um, 120A Condition: 90-100%B (A: water (0.1% TFA) B: CH_3CN); Flow rate: 25 mL/min]. Fractions containing the desired compound were basified with saturated aqueous solution of $NaHCO_3$ to adjust pH = 8 and extracted with ethyl acetate (200 mL × 3). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate and filtered, the filtrate was concentrated in vacuum to afford compound **16a** (1.0 g, 61% yield) as a yellow solid.

LCMS: t_R = 1.116 min in 5-95AB_220&254.lcm chromatography (Agilent Pursult 5 C18 20*2.0mm), MS (ESI) m/z = 653.3 $[M+H+2]^+$.

^{1}H NMR (400MHz, $CDCl_3$): δ = 8.51 (d, *J* = 2.0 Hz, 1H), 7.62 (br t, *J* = 6.4 Hz, 4H), 7.56 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.47-7.42 (m, 2H), 7.38 (t, *J* = 7.6 Hz, 4H), 7.15 (d, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.60-6.52 (m, 2H), 4.98 (s, 1H), 4.82 (br s, 1H), 3.91-3.69 (m, 2H), 3.45-3.37 (m, 1H), 3.25-3.10 (m, 1H), 2.97-2.75 (m, 2H), 2.54 (dd, *J* = *16.4*, 6.4 Hz, 1H), 1.05 (d, *J* = 6.4 Hz, 3H), 1.01 (s, 9H).



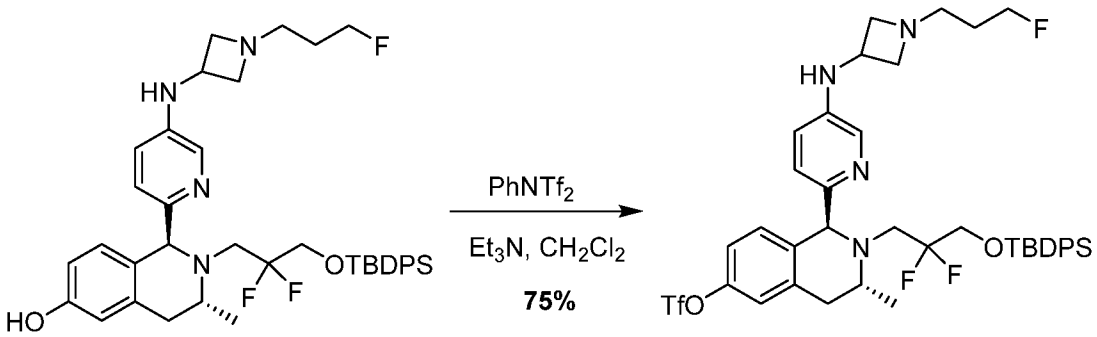
16a **16b**

To the mixture of compound **16a** (0.9 g, 1.38 mmol) in 1,4-dioxane (10 mL) was added compound **1F** (0.995 g, 2.76 mmol), Brettphos Pd G3 (313 mg, 0.345 mmol), t-BuONa (1.19 g, 12.42 mmol) under nitrogen. The resulting mixture was stirred at 80°C for 4 hours under nitrogen. The reaction mixture was combined with that of parallel batch (100 mg of compound **16a**) and filtered, the filtrate was concentrated in vacuum to give the residue, which was diluted with ethyl acetate (200 mL) and water (150 mL), the organic layer was extracted with ethyl acetate (200 mL × 3), the combined organic layers was washed with brine (50 mL), dried over anhydrous sodium sulfate and filtered, the filtrate was concentrated in vacuum to give the crude product, which was purified by column chromatography on silica gel (methanol/dichloromethane = 0-10%) to afford compound **16b** (450 mg, 42% yield) as a brown solid.

LCMS: t_R = 0.837 min in in 5-95AB_220&254.lcm chromatography (Agilent pursult5 C18 20*2mm), MS (ESI) m/z = 703.5 $[M+H]^+$.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.77 (d, *J* = 2.8 Hz, 1H), 7.66-7.60 (m, 4H), 7.47-7.40 (m, 2H), 7.40-7.33 (m, 4H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 6.61 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.53 (d, *J* = 2.4 Hz, 1H), 6.44 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.90 (s, 1H), 4.48 (dt, *J* = 47.2 , 6.0 Hz, 2H), 4.06-3.97 (m, 1H), 3.94-3.82 (m, 2H), 3.77-3.66 (m, 3H), 3.46-3.38 (m, 1H), 3.13 (q, *J* = 14.4 Hz, 1H), 2.91-2.83 (m, 3H), 2.60 (t, *J* = 7.2 Hz, 2H), 2.49 (dd, *J* = 16.4,

7.6 Hz, 1H), 1.82-169 (m, 2H), 1.05-1.01 (m, 12H).

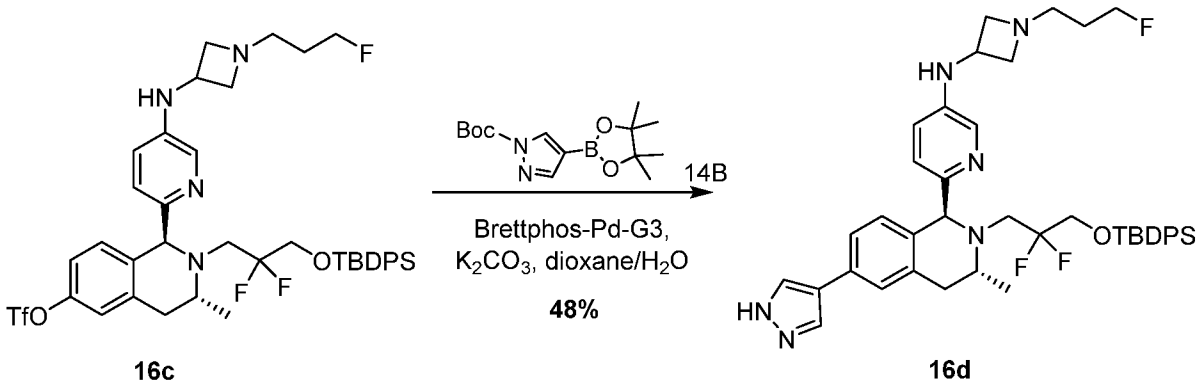


16b **16c**

To the mixture of compound **16b** (380 mg, 0.54 mmol) in dichloromethane (6 mL) was added Et_3N (0.194 mL, 1.32 mmol) followed by $PhNTf_2$ (387 mg, 1.08 mmol). The resulting mixture was stirred at 13-23°C for 16 hours. The reaction mixture was combined with that of parallel batch (70 mg of compound **16b**) and concentrated in vacuum to give the residue, which was diluted with dichloromethane (200 mL) and water (150 mL). The organic layer was extracted with dichloromethane (200 mL × 3), and the combined organic layers was washed with brine (50 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuum to give the crude product, which was purified by column chromatography on silica gel (methanol/dichloromethane = 0-10%) and further concentration in high vacuum to give the compound **16c** (450 mg, 75% yield) as a yellow solid.

LCMS: t_R = 0.949 min in 5-95AB_220&254.lcm chromatography (Agilent pursult5 C18 20*2mm), MS (ESI) m/z = 835.5 $[M+H]^+$.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.76 (d, *J* = 2.4 Hz, 1H), 7.64-7.60 (m, 4H), 7.49-7.33 (m, 6H), 7.24-7.18 (m, 2H), 7.02 (s, 1H), 6.94 (s, 1H), 6.64 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.97 (s, 1H), 4.45 (dt, *J* = 47.2, 6.0 Hz, 2H), 4.11 (br s, 2H), 3.91-3.80 (m, 3H), 3.71 (q, *J* = 12.0 Hz, 1H), 3.54-3.44 (m, 1H), 3.14-3.12 (m, 3H), 2.97 (br dd, *J* = 16.4, 4.0 Hz, 1H), 2.87-2.77 (m, 1H), 2.72 (t, *J* = 7.2 Hz, 2H), 2.58 (br dd, *J* = 16.4, 6.8 Hz, 1H), 1.84-1.70 (m, 2H), 1.07-0.96 (m, 12H).

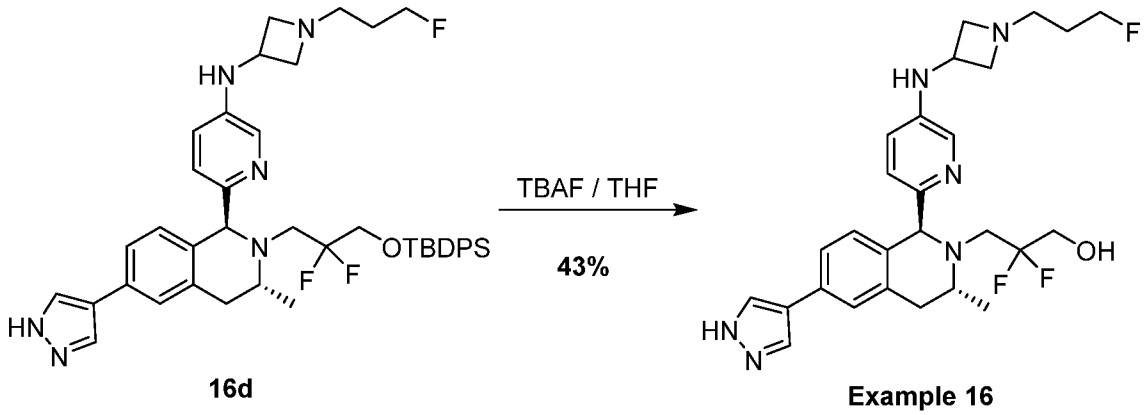


16c **16d**

To a solution of compound **16c** (150 mg, 0.179 mmol), K_2CO_3 (75 mg, 0.539 mmol) and Brettphos Pd G3 (25 mg, 0.0239 mmol) in 1,4-dioxane/H_2O (5.5 mL, 10/1 v/v) was added compound **14B** (106 mg, 0.359 mmol) under nitrogen at 16-25℃. The mixture was stirred at 100°C for 16 hours under nitrogen. The reaction was concentrated in vacuum to give the residue, diluted with ethyl acetate (100 mL) and water (80 mL), and separated. The aqueous layer was extracted with ethyl acetate (100 mL × 3), the combined organic layers was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to afford the crude, which was purified by prep-TLC (methanol/dichloromethane = 1/10) to afford compound **16d** (65 mg, 48% yield) as a yellow solid.

LCMS: t_R =0.861 min in 5-95AB_220&254.lcm chromatography (Agilent pursult5 C18 20*2mm), MS (ESI) m/z = 753.6 $[M+H]^+$.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.82-7.77 (m, 3H), 7.67-7.61 (m, 4H), 7.48-7.41 (m, 2H), 7.40-7.35 (m, 4H), 7.24 (s, 1H), 7.18 (br d, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.60 (dd, *J* = 8.4, 3.2 Hz, 1H), 4.97 (s, 1H), 4.48 (dt, *J* = 47.2, 6.0 Hz, 2H), 4.05-3.98 (m, 1H), 3.97-3.82 (m, 2H), 3.73 (s, 1H), 3.72-3.68 (m, 2H), 3.55-3.45 (m, 1H), 3.17 (q, *J* = 14.0 Hz, 1H), 3.00 (br dd, *J* =16.0, 4.0 Hz, 1H), 2.92-2.83 (m, 3H), 2.64-2.56 (m, 3H), 1.78-1.72 (m, 2H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.02 (s, 9H).



16d Example 16

To the mixture of compound **16d** (60 mg, 0.079 mmol) in THF (3 mL) was added a solution of TBAF (0.24 mL, 0.237 mmol, 1M in THF), the mixture was stirred for 4 hours at room temperature (12-21°C). The reaction was basified with saturated aqueous solution of $NaHCO_3$ to adjust pH = 8 and extracted with ethyl acetate (100 mL × 3). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuum to afford the crude, which was purified by prep-TLC (methanol/dichloromethane = 1/10) to give the product as a light-yellow oil and then lyophilized to afford the desired product of **Example 16** (18.0 mg, 43% yield) as a yellow solid.

LCMS: t_R = 0.988 min in 10-80AB_3min_220&254_Agilent, XBrige Shield RP18 2.1*50mm, MS (ESI) m/z = 515.3 $[M+H]^+$.

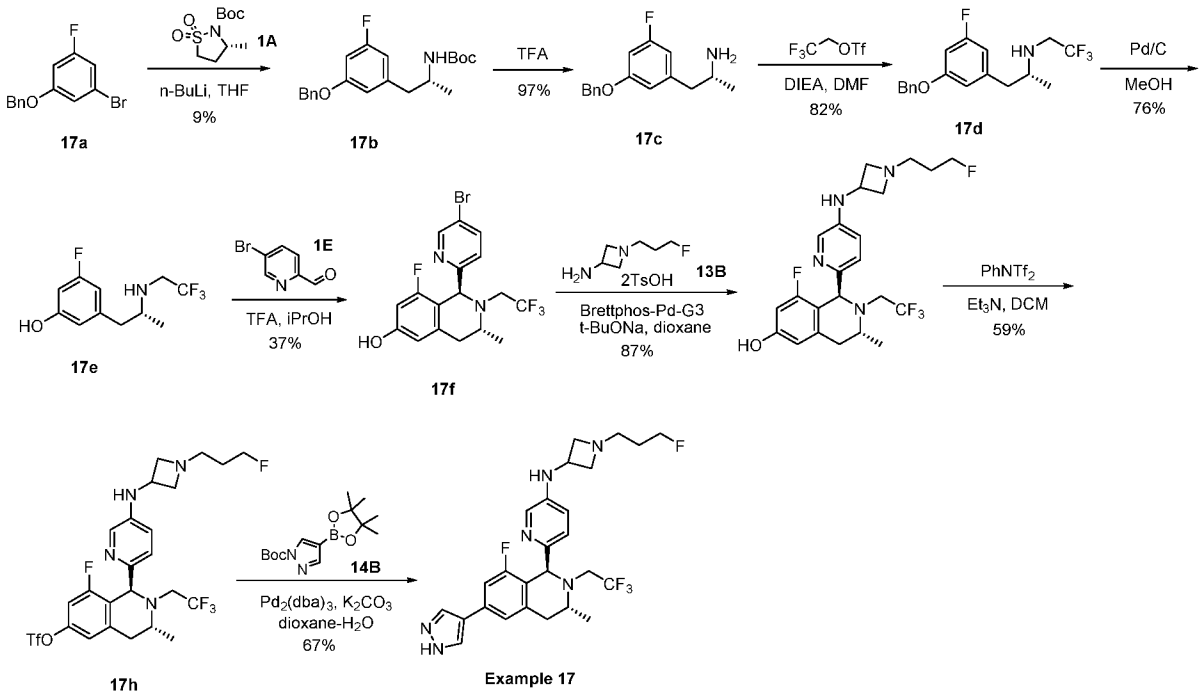
^{1}H NMR (400MHz, CD_3OD): δ = 7.91 (br s, 2H), 7.79 (d, *J* = 2.4 Hz, 1H), 7.37 (s, 1H), 7.26 (br d, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.92 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 4.83 (s, 1H), 4.47 (dt, *J* = 47.2, 6.0 Hz, 2H), 4.16-4.07 (m, 1H), 3.86 (br t, *J* = 7.2 Hz, 2H), 3.71 (q, *J* = 13.2 Hz, 1H), 3.59-3.48 (m, 2H), 3.20-3.12 (m, 2H), 3.07 (br s, 2H), 2.82-2.64 (m, 4H), 1.85-1.71 (m, 2H), 1.07 (d, *J* = 6.4 Hz, 3H).

HPLC: t_R = 3.02 min in 10-80_CD_1.2ml.met, chromatography (XBridge Shield RP 18 2.1*50mm 5um).

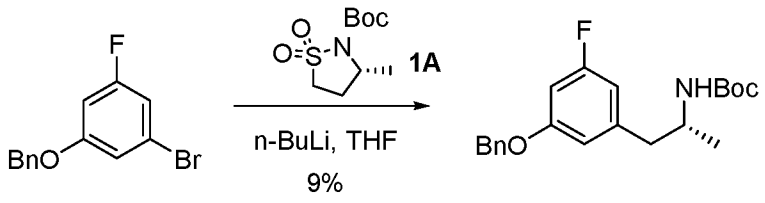
SFC: t_R = 4.451 min. Method: Column: Chiralcel OD-3 100×4.6mm I.D., 3um; Mobile phase: A: CO_2 B: ethanol (0.05% DEA); Gradient: from 5% to 40% of B in 4.5min and hold 40% for 2.5 min, then 5% of B for 1min; Flow rate: 2.8 mL/min; Column temperature: 40°C.

Example 17

6-((1S,3R)-8-fluoro-3-methyl-6-(1H-pyrazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-N-(1-(3-fluoropropyl)azetidin-3-yl)pyridin-3-amine



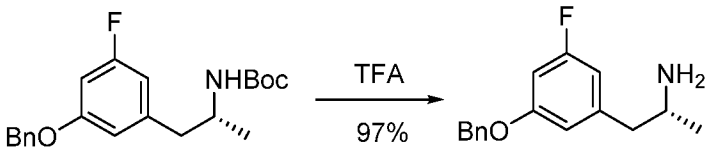
Procedure to prepare **Example 17**:



To a solution of compound **17a** (4.0 g, 14 mmol) in THF (20 mL), n-BuLi (6.8 mL, 17 mmol, 2.5 M in hexane) was added at -70 °C dropwsie over 10 min. After stirred for 30 min, a solution of compound **1A** (3.3 g, 14 mmol) in THF (20 mL) was added dropwise at -70 °C. The resulting mixture was stirred at -70 °C for 2 hours. Then the reaction was quenched with 1N citric acid (30 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and then filtered. The filtrate was evaporated under vacuum and the residue was purified by C18-flash chromatography, elution gradient 40% to 90% MeCN in water (0.02% FA). Pure fractions were evaporated to dryness to afford compound **17b** (480 mg, 9.4 % yield) as a white solid.

LCMS: t_R = 1.95 min in 3 min chromatography (3min-5-95% MeCN in water (0.02% FA),

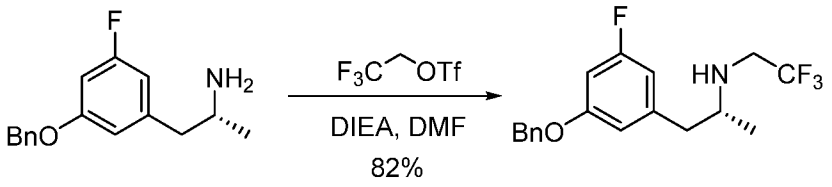
Warters Acquity UPLC BEH C18 1.7um, 2.1*50 mm, 40°C), MS (ESI) m/z 360.4 $[M+H]^+$.



17b **17c**

A solution of compound **17b** (460 mg, 1.3 mmol) in TFA (2 mL) was stirred at 20 °C for 1 hour. Then the reaction mixture was concentrated and the residue was purified by C18-flash chromatography, elution gradient 5% to 40% MeCN in water (0.02% FA). Pure fractions were evaporated to dryness to afford compound **17c** (380 mg, 97 % yield) as a white solid.

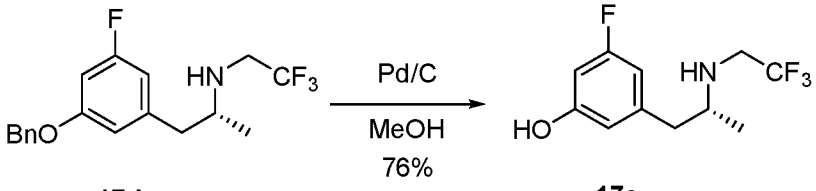
LCMS: t_R = 1.32 min in 3 min chromatography (3min-5-95% MeCN in water (0.02% FA), Warters Acquity UPLC BEH C18 1.7um, 2.1*50 mm, 40°C), MS (ESI) m/z 260.2 $[M+H]^+$.



17c **17d**

To a solution of compound **17c** (350 mg, 1.1 mmol) and DIEA (290 mg, 2.2 mmol) in 1,4-dioxane (5 mL) was added CF3CH2OTf (520 mg, 2.2 mmol). The resulting mixture was stirred at 80 °C for 5 hours. The mixture was concentrated under vacuum and the residue was purified by C18-flash chromatography, elution gradient 5% to 60% MeCN in water (0.02% FA). Pure fractions were evaporated to dryness to afford compound **17d** (320 mg, 82 % yield) as a white solid.

LCMS: t_R = 1.44 min in 3 min chromatography (3min-5-95% MeCN in water (0.02% FA), Warters Acquity UPLC BEH C18 1.7um, 2.1*50 mm, 40°C), MS (ESI) m/z 342.4 $[M+H]^+$.

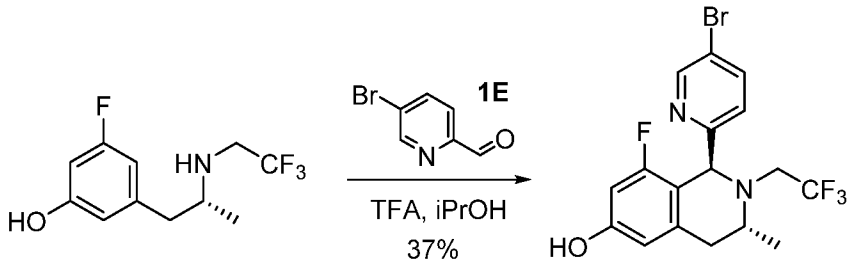


17d **17e**

To a solution of compound **17d** (320 mg, 0.94 mmol) in methanol (5 mL) was added Pd/C (64 mg, 10% w.t.). The resulting mixture was stirred at 20 °C for 16 hours. Then the mixture

was filtered and the filtrate was concentrated under vacuum. The residue was purified by C18-flash chromatography, elution gradient 5% to 60% MeCN in water (0.02% FA). Pure fractions were evaporated to dryness to afford compound **17e** (180 mg, 76%) as a white solid.

LCMS: t_R = 0.96 min in 3 min chromatography (3min-5-95% MeCN in water (0.02% FA), Warters Acquity UPLC BEH C18 1.7um, 2.1*50 mm, 40°C), MS (ESI) m/z 252.2 $[M+H]^+$.

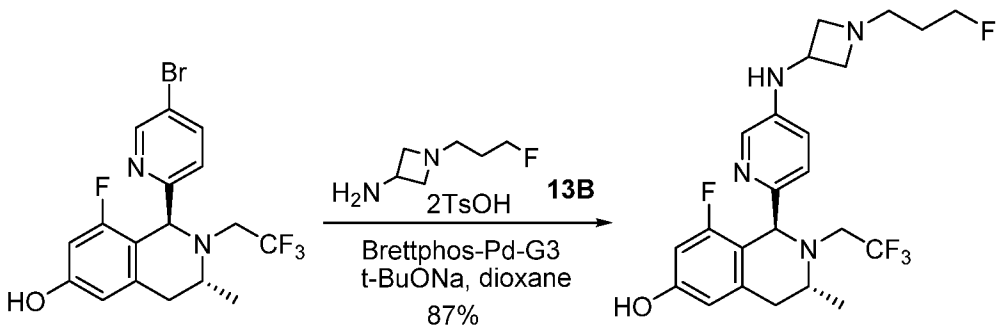


17e **17f**

To a solution of compound **17e** (180 mg, 0.72 mmol) in isopropanol (5 mL) were added compound **1E** (270 mg, 2.2 mmol) and TFA (245 mg, 2.2 mmol). The resulting mixture was stirred at 20 °C for 2 hours, then the mixture was concentrated under vacuum and the residue was purified by C18-flash chromatography, elution gradient 5% to 70% MeCN in water (0.02% FA). Pure fractions were evaporated to dryness to afford compound compound **17f** (110 mg, 37%) as a white solid.

LCMS: t_R = 1.81 min in 3 min chromatography (3min-5-95% MeCN in water (0.02% FA), Warters Acquity UPLC BEH C18 1.7um, 2.1*50 mm, 40°C), MS (ESI) m/z 419.2, 421.2 $[M+H]^+$.

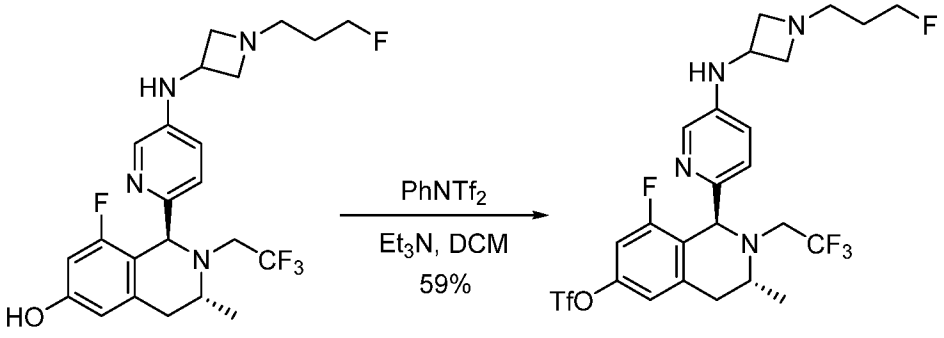
1H NMR (500 MHz, DMSO-d6): δ 9.88 – 9.59 (s, 1H), 8.54 – 8.53 (d, J = 2.4 Hz, 1H), 8.06 – 8.03 (dd, J = 2.4, 8.4 Hz, 1H), 7.42 – 7.37 (d, J = 8.5 Hz, 1H), 6.42 – 6.41 (d, J = 2.2 Hz, 1H), 6.37 – 6.33 (dd, J = 2.3, 11.3 Hz, 1H), 5.04 – 5.02 (s, 1H), 3.60 – 3.51 (m, 1H), 3.09 – 3.01 (m, 2H), 2.59 – 2.55 (m, 2H), 1.02 – 0.99 (d, J = 6.6 Hz, 3H).



17f **17g**

To a mixture of compound **17f** (187 mg, 0.39 mmol) and Brettphos-Pd-G3 (24 mg, 0.026 mmol) in 1,4-dioxane (4 mL) was added sodium tert-butoxide (150 mg, 1.6 mmol). The resulting mixture was stirred at 70 °C for 1 hour under nitrogen. Then the mixture was directly purified by C18-flash chromatography, elution gradient 5% to 60% MeCN in water (0.02% TFA). Pure fractions were evaporated to dryness to afford compound **17g** (120 mg, 87 % yield) as a yellow solid.

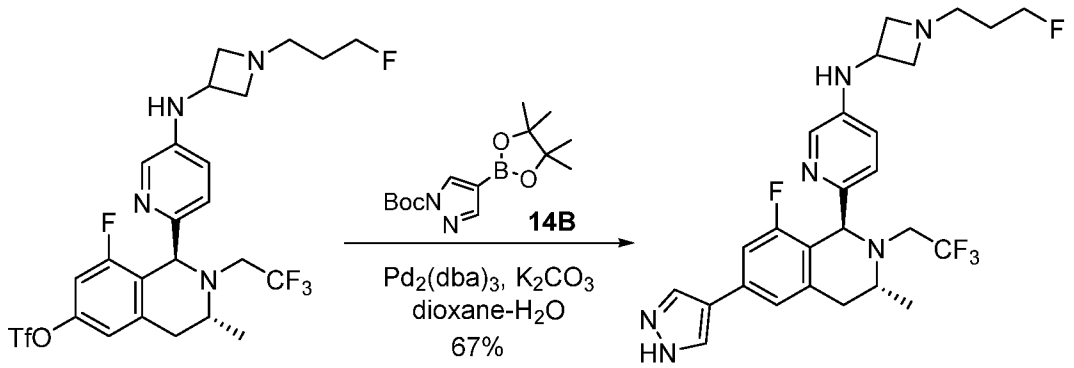
LCMS: t_R = 1.14 min in 3 min chromatography (3min-5-95% MeCN in water (0.02% FA), Warters Acquity UPLC BEH C18 1.7um, 2.1*50 mm, 40°C), MS (ESI) m/z 471.5 $[M+H]^+$.



17g **17h**

To a solution of compound **17g** (120 mg, 0.21 mmol) and triethylamine (62 mg, 0.62 mmol) in DCM (5 mL) was added $PhNTf_2$ (147 mg, 0.41 mmol). The resulting mixture was stirred at 25 °C for 16 hours. Then the mixture was concentrated under vacuum and the residue was purified by C18-flash chromatography, elution gradient 5% to 80% MeCN in water (0.02% TFA). Pure fractions were evaporated to dryness to afford compound **17h** (90 mg, 59 % yield) as a white solid.

LCMS: t_R = 1.49 min in 3 min chromatography (3min-5-95% MeCN in water (0.02% FA), Warters Acquity UPLC BEH C18 1.7um, 2.1*50 mm, 40°C), MS (ESI) m/z 603.5 $[M+H]^+$.



17h **Example 17**

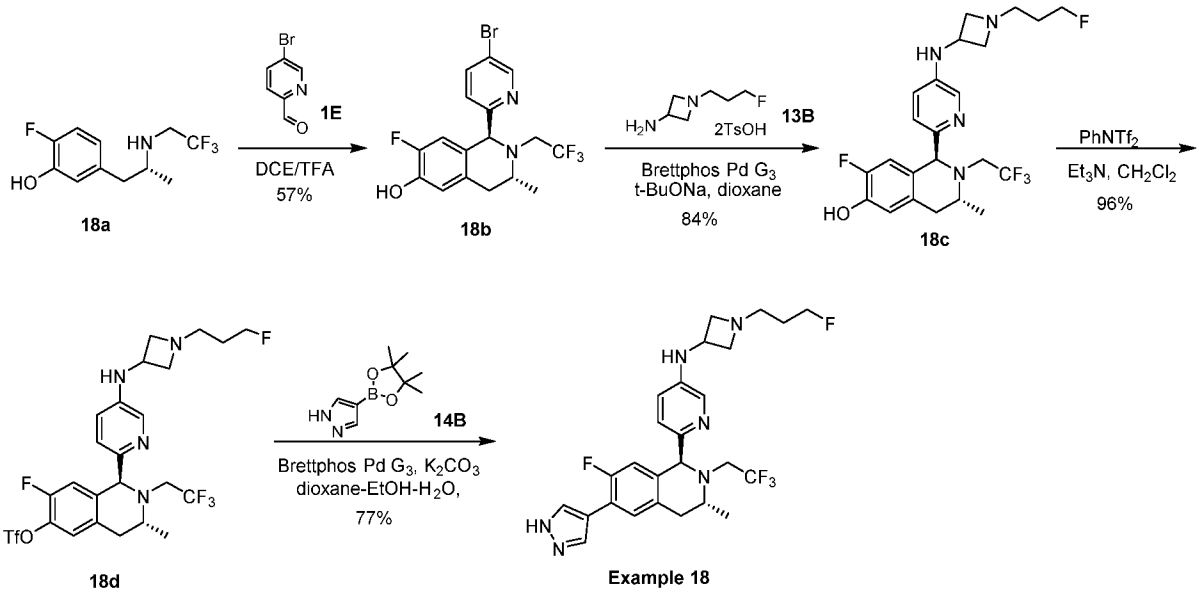
To a mixture of compound **17h** (90 mg, 0.15 mmol), compound **14B** (88 mg, 0.30 mmol), Pd2(dba)3 (7 mg, 0.0075 mmol), 1,3,5,7-Tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane (4 mg, 0.015 mmol) in 1,4-dioxane (3 mL) and water (1 mL) was added potassium carbonate (62 mg, 0.45 mmol). The resulting mixture was heated at 120 °C for 15 min in microwave. Then the mixture was directly purified by C18-flash chromatography, elution gradient 5% to 60% MeCN in water (0.02% TFA). Pure fractions were evaporated to dryness to afford compound **Example 17** (52 mg, 67 % yield) as a yellow solid.

LCMS: t_R = 1.14 min in 3 min chromatography (3min-5-95% MeCN in water (0.02% FA), Warters Acquity UPLC BEH C18 1.7um, 2.1*50 mm, 40°C), MS (ESI) m/z 521.5 $[M+H]^+$.

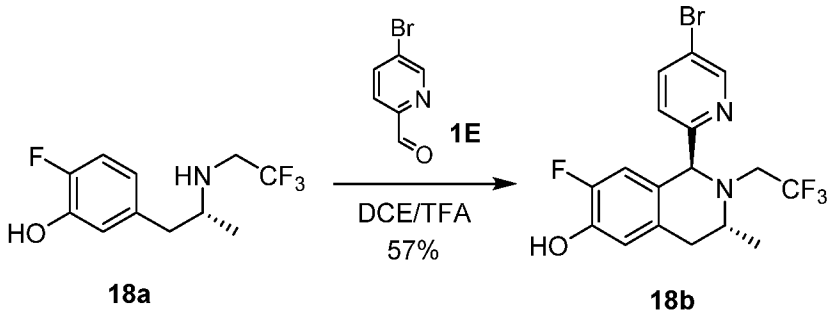
1H NMR (500 MHz, DMSO-d6): δ10.23 – 9.95 (d, J = 58.8 Hz, 1H), 8.16 – 8.01 (s, 2H), 7.84 – 7.71 (dd, J = 2.8, 23.6 Hz, 1H), 7.32 – 7.28 (d, J = 8.6 Hz, 1H), 7.28 – 7.26 (s, 1H), 7.24 – 7.18 (d, J = 10.9 Hz, 1H), 7.16 – 7.05 (m, 1H), 6.98 – 6.58 (s, 1H), 5.11 – 5.08 (s, 1H), 4.59 – 4.55 (m, 2H), 4.49 – 4.46 (m, 1H), 4.35 – 4.30 (m, 2H), 4.09 – 4.07 (m, 1H), 3.90 – 3.87 (m, 1H), 3.63 – 3.56 (m, 1H), 3.37 – 3.28 (m, 2H), 3.23 – 3.15 (m, 1H), 3.10 – 3.01 (m, 1H), 2.79 – 2.60 (m, 2H), 1.96 – 1.84 (m, 2H), 1.06 – 0.98 (d, J = 6.7 Hz, 3H).

Example 18

6-((1S,3R)-7-fluoro-3-methyl-6-(1H-pyrazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-N-(1-(3-fluoropropyl)azetidin-3-yl)pyridin-3-amine



Procedure to prepare **Example 18** is analogous to the procedure to prepare **Example 17**. Key steps as below:

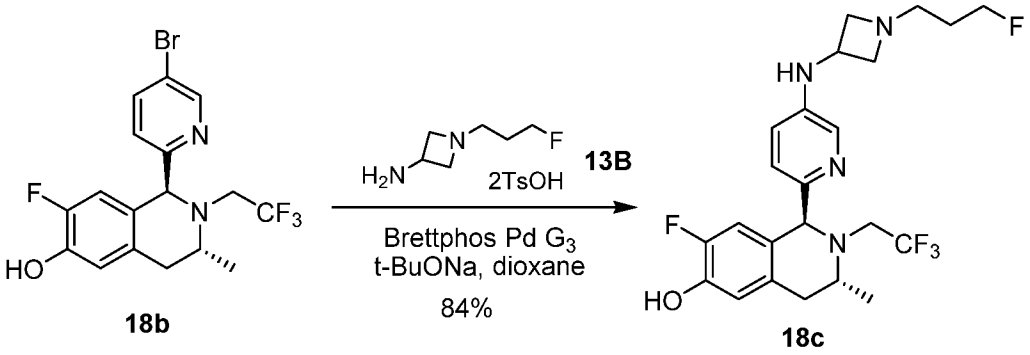


To the mixture of compound **18a** (240 mg, 0.955 mmol) in DCE (5 mL) was added compound **1E** (213 mg, 1.15 mmol), followed with TFA (327 mg, 2.87 mmol), the resulting mixture was stirred at 90 °C under nitrogen for 12 hours. The reaction was basified with saturated aqueous solution of $NaHCO_3$ to adjust pH = 8, then extracted with ethyl acetate (100 mL × 3). The combined organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate and filtered, the filtrate was concentrated in vacuum to give the crude product, which was purified by column chromatography on silica gel (ethyl acetate/petroleum ether = 0-20%) to give compound **18b** (240 mg, 57% yield) as a yellow solid.

LCMS: t_R = 2.395 min in 10-80AB_3min_220&254 chromatography (Xtimate C18 2.1*30mm), MS (ESI) m/z = 418.9 $[M+H]^+$.

^{1}H NMR (400MHz, $CDCl_3$): δ = 8.58-8.55 (m, 1H), 7.79 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.40 (d, *J*

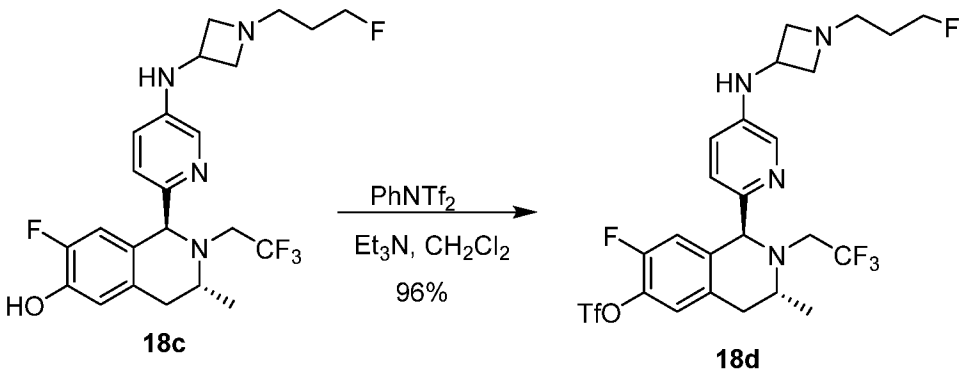
= 8.4 Hz, 1H), 6.74-6.71 (m, 1H), 6.63 (d, *J* = 11.6 Hz, 1H), 4.91 (s, 1H), 3.45-3.36 (m, 1H), 3.31-3.12 (m, 2H), 3.08-2.97 (m, 1H), 2.52 (dd, *J* = 16.4, 6.4 Hz, 1H), 1.08 (d, *J* = 6.8 Hz, 3H).



To the mixture of compound **18b** (240 mg, 0.572 mmol) in 1,4-dioxane (5 mL) was added compound **13B** (545 mg, 1.144 mmol), Brettphos-Pd-G3 (52 mg, 0.0572 mmol) and t-BuONa (495 mg, 5.148 mmol), the resulting mixture was stirred at 80°C for 4 hours under nitrogen. The reaction mixture was combined with that of parallel batch (300 mg of compound **18b**) and filtered, the filtrate was concentrated in vacuum to give the residue, which was diluted with dichloromethane (100 mL) and water (50 mL), the organic layer was extracted with dichloromethane (50 mL × 3), the combined organic layers was washed with brine (50 mL), dried over anhydrous sodium sulfate and filtered, the filtrate was concentrated in vacuum to give the crude product, which was purified by column chromatography on silica gel (methanol/dichloromethane = 0-10%) to afford the compound **18c** (510 mg, 84% yield) as a light-yellow oil. The ratio of trans/cis is about 3/1 based on H NMR.

LCMS: t_R = 0.797 min in 10-80AB_2.0min_220&254 chromatography (Xtimate C18 2.1*30mm), MS (ESI) m/z = 471.1 $[M+H]^+$.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.79 (d, *J* = 2.8 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 6.81 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.61 (d, *J* = 8.8 Hz, 1H), 6.51 (d, *J* = 12.0 Hz, 1H), 4.80 (s, 1H), 4.49 (dt, *J* = 47.2, 5.6 Hz, 2H), 4.16-4.11 (m, 2H), 3.81-3.68 (m, 2H), 3.47-3.38 (m, 1H), 3.19-3.13 (m, 1H), 3.05-2.87 (m, 4H), 2.70-2.59 (m, 2H), 2.45 (dd, *J* =16.0, 6.4 Hz, 1H), 1.83-1.72 (m, 2H), 1.04 (d, *J* = 6.4 Hz, 3H).

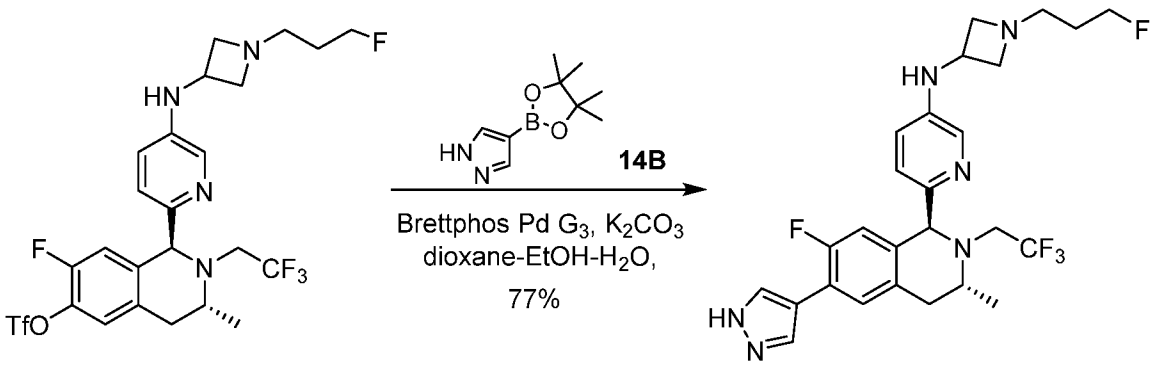


18c 18d

To the mixture of compound **18c** (300 mg, 0.637 mmol) in dichloromethane (5 mL) was added Et_3N (195 mg, 1.911 mmol), follow by $PhNTf_2$ (456 mg, 1.28 mmol), the mixture was stirred at 26-33°C for 4 hours. The reaction was concentrated in vacuum to give the residue, which was diluted with dichloromethane (100 mL) and water (50 mL), the organic layer was extracted with dichloromethane (30 mL × 3), the combined organic layers was washed with brine (50 mL), dried over anhydrous sodium sulfate and filtered, the filtrate was concentrated in vacuum to give the crude product, which was purified by column chromatography on silica gel (methanol/dichloromethane = 0-10%) to give compound **18d** (370 mg , 96% yield) as a yellow oil.

LCMS: t_R =1.066 min in 10-80AB_2min_220&254.lcm chromatography (Xtimate C18 2.1*30mm), MS (ESI) m/z = 603.1 $[M+H]^+$.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.83 (d, *J* = 2.8 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.07 (d, *J* = 7.2 Hz, 1H), 6.83-6.79 (m, 2H), 4.89 (s, 1H), 4.49 (dt, *J* = 47.2, 5.6 Hz, 2H), 4.24-4.08 (m, 2H), 3.83-3.73 (m, 2H), 3.56-3.47 (m, 1H), 3.30-3.09 (m, 2H), 3.02-2.90 (m, 3H), 2.65 (t, *J* = 7.2 Hz, 2H), 2.58 (br dd, *J* = 16.4, 5.6 Hz, 1H), 1.86-1.67 (m, 2H), 1.08 (d, *J* = 6.8 Hz, 3H).



18d Example 18

To a solution of compound **18d** (300 mg, 0.498 mmol), K_2CO_3 (207 mg, 1.49 mmol) and Brettphos-Pd-G3 (45 mg, 0.0498 mmol)) in dioxane-EtOH-H_2O (5 mL, 5/2/1 v/v/v) was added compound **14B** (193 mg, 0.995 mmol) at 27-36 ℃. The mixture was stirred at 100°C for 12 hours under nitrogen. The reaction was concentrated in vacuum to give the residue, which was dissolved with ethyl acetate (100 mL) and water (50 mL), the aqueous layer was separated and extracted with ethyl acetate (50 mL × 3). The combined organic layers was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to afford the crude, which was purified by column chromatography on silica gel (methanol/dichloromethane = 0-10%) to give crude product (200 mg, 77% yield) as a yellow solid. The crude proruct was separated by chiral SFC [column: DAICEL CHIRALPAK AD-H (250mm*30mm, 5um), condition: (0.1% $NH_3 \cdot H_2O$) EtOH; Begin B: 30%, End B: 30%; Flow rate: 50 mL/min] and further purified by acidic prep-HPLC in TFA system [Boston Green ODS 150*30 5u; Condition: 24-54% B (A: water (0.075% TFA) B: CH_3CN); Flow rate: 25 mL/min] to give the title product of **Example 18** (51.8 mg TFA salt, 72% yield) as a yellow solid.

LCMS: t_R = 0.858 min in 10-80AB_2min_220&254 chromatography (Xtimate C18, 2.1*30mm, 3um), MS (ESI) m/z = 521.1 $[M+H]^+$.

^{1}H NMR (400MHz, D_2O): δ = 8.11 (s, 2H), 7.97-7.87 (m, 1H), 7.70-7.60 (m, 2H), 7.56 (br d, *J* = 7.6 Hz, 1H), 6.88 (br d, *J* = 11.2 Hz, 1H), 5.30 (s, 1H), 4.70-4.59 (m, 3H), 4.55 (br t, *J* = 5.6 Hz, 1H), 4.52-4.44 (m, 1H), 4.41-4.26 (m, 1H), 4.12-4.04 (m, 1H), 3.64-3.45 (m, 3H), 3.27 (br d, *J* = 5.2 Hz, 1H), 3.15-2.97 (m, 2H), 2.68 (dd, *J* = 16.4, 7.6 Hz, 1H), 2.16-1.97 (m, 2H), 1.13 (d, *J* = 6.0 Hz, 3H).

HPLC: t_R = 3.64 min in 10-80_CD_1.2ml. met, XBridge Shield RP 18 2.1*50mm 5um.

SFC: t_R = 4.710 min. Method: Column; Chiralcel AD-3 150×4.6mm I.D., 3um; Mobile phase: A: CO_2 B: ethanol (0.05% DEA); Gradient: from 5% to 40% of B in 5.5 min, then 5% of B for 1.5 min; Flow rate: 2.5 mL/min.

Example 19

6-((1S,3R)-5-fluoro-3-methyl-6-(1H-pyrazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-N-(1-(3-fluoropropyl)azetidin-3-yl)pyridin-3-amine

The preparation of **Example 19** is analogous to the preparation of **Example 18**. The analytical data of **Example 19** are shown below:

LCMS: t_R = 1.593 min in 10-80AB_4min_220&254_Shimadzu chromatography (Xtimate C18 2.1*30mm), MS (ESI) m/z = 521.2 $[M+H]^+$.

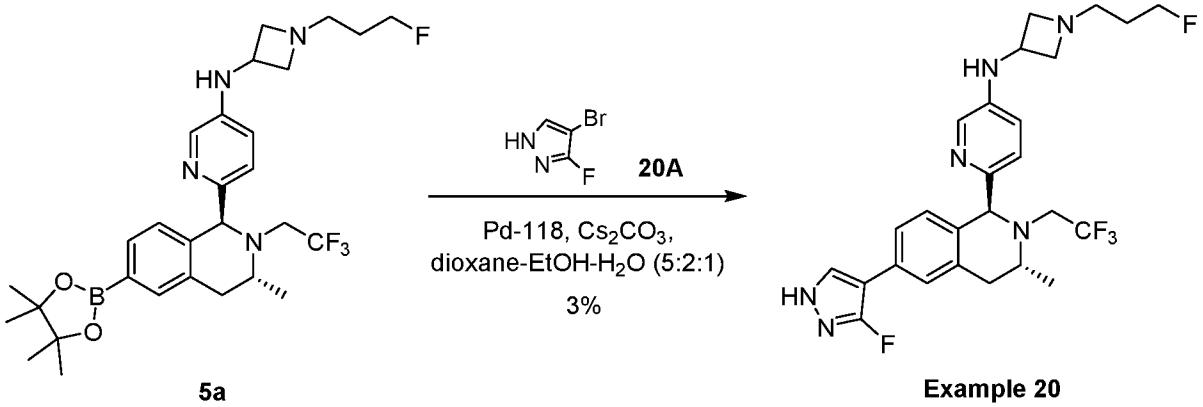
HPLC: t_R = 2.85 min in 10-80_AB_1.2ml.met.chromatography (Ultimate C18 3*50mm 3um).

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.97-7.73 (m, 3H), 7.27-7.16 (m, 2H), 6.83 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 4.97 (s, 1H), 4.49 (dt, *J* = 47.2, 6.0 Hz, 2H), 4.32 (d, *J* = 7.2 Hz, 1H), 4.16-4.04 (m, 1H), 3.71 (t, *J* = 7.2 Hz, 2H), 3.55-3.43 (m, 1H), 3.29-3.14 (m, 1H), 3.05-2.88 (m, 4H), 2.68-2.57 (m, 3H), 1.85-1.66 (m, 2H), 1.11 (d, *J* = 6.8 Hz, 3H).

SFC: t_R = 1.434 min; 100% purity. Method: Column: Chiralpak IC-3 150×4.6mm I.D., 3um; Mobile phase: 40% of ethanol (0.05% DEA) in CO_2; Flow rate: 2.5 mL/min Column temperature: 35°C; ABPR: 1500psi.

Example 20

6-((1S,3R)-6-(3-fluoro-1H-pyrazol-4-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-N-(1-(3-fluoropropyl)azetidin-3-yl)pyridin-3-amine



5a **Example 20**

The procedure to prepare **Example 20**:

A stirred mixture of compound **5a** (102.5 mg, 0.18 mmol) and compound **20A** (45.0 mg, 0.28 mmol) with Cs_2CO_3 (176 mg, 0.54 mmol) in mixed solvents of 1,4-dioxane/EtOH/H_2O (5.0 mL/ 2.0 mL/ 1.0 mL, 5/2/1 v/v/v) was degassed and purged with nitrogen for three times, Pd-118 (11.7 mg, 0.018 mmol) was added quickly, the resulting mixture was degassed and purged with nitrogen again, then stirred at 100°C under nitrogen atmosphere for 12 hours. The reaction mixture was filtered, and the filtrate was concentrated in vacuum to give crude product (120 mg) as brown oil, which was purified by prep-TLC (dichloromethane: methanol = 8:1) to give impure product (50 mg). The impure product was further purified by prep-HPLC [Column: Boston Prime C18 150*30mm 5um, Condition: 50-80% (A: water/0.05% $NH_3.H_2O$, B: CH_3CN), flow rate: 25 mL/min]. Fractions containing the desired compound were lyophilized to afford **Example 20** (3.0 mg, 3% yield) as a white solid.

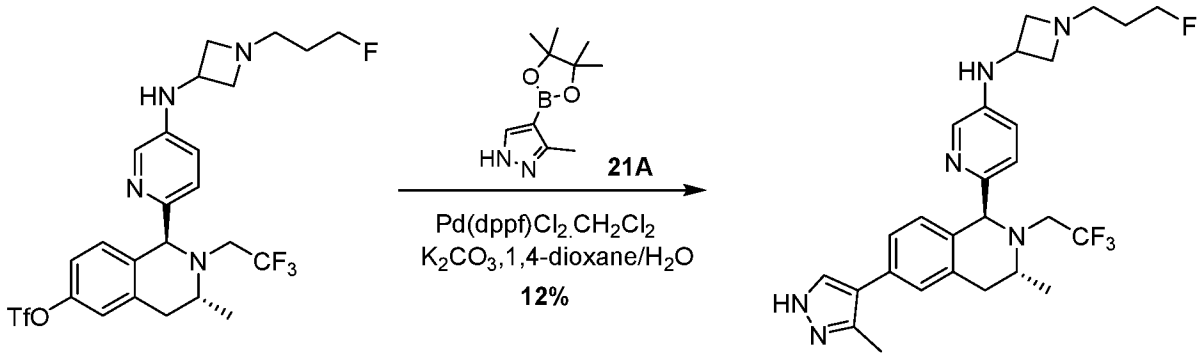
LCMS: t_R = 1.616 min in 10-80AB_4min_220&254_Shimadzu (Xtimate C18 2.1*30 mm), MS (ESI) m/z = 521.2 $[M+H]^+$.

HPLC: t_R = 2.94 min in 10-80AB_1.2ml.met; chromatography (Ultimate C18 3*50mm 3um).

^{1}H NMR: (400MHz, $CDCl_3$) δ = 10.58 (br s, 1H), 7.83 (d, *J* = 2.4 Hz, 1H), 7.34 (d, *J* = 2.0 Hz, 1H), 7.29 (s, 1H), 7.24 (s, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 1H), 6.84 (dd, *J* = 8.8, 3.2 Hz, 1H), 4.96 (s, 1H), 4.50 (dt, *J* = 47.2, 6.0 Hz, 2H), 4.18-4.08 (m, 2H), 3.78-3.73 (m, 2H), 3.55-3.45 (m, 1H), 3.30-3.07 (m, 2H), 3.03-2.89 (m, 3H), 2.66-2.56 (m, 3H), 1.85-1.74 (m, 2H), 1.10 (d, *J* = 6.8 Hz, 3H).

Example 21

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3R)-3-methyl-6-(5-methyl-1H-pyrazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine



1h **Example 21**

Procedure to prepare **Example 21**:

To a mixture of compound **1h** (200 mg, 0.34 mmol), potassium carbonate (140 mg 1.02 mmol), $Pd(dppf)Cl_2.CH_2Cl_2$ (27.7 mg, 0.034 mmol) and compound **21A** (107 mg, 0.51 mmol) was added a mixed solvents of 1,4-dioxane (10 mL) and water (1 mL) under N_2. The resulting mixture was stirred at 100°C for 5 hours. The reaction mixture was concentrated under reduced pressure to give the crude residue, which was diluted with CH_2Cl_2 (30 mL) and water (30 mL), the organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (20 mL x 2). The combined organic layers was dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to give the crude product, which was purified by column chromatography on silica gel (0~5% methanol in dichloromethane) to give 80 mg impure product, it was further purified by chiral SFC (Column: DAICEL CHIRALCEL OJ-H (250mm*30mm, 5um), Condition: 35% EtOH (0.1% $NH_3.H_2O$), Flow rate: 50 mL/min) to afford **Example 21** (21.2 mg, 12% yield) as a yellow solid.

LCMS: t_R =2.800 min in 0-60AB_7min_220&254_1500_Shimadzu.lcm chromatography (Xtimate C18 2.1*30mm), MS (ESI) m/z = 517.3 $[M+H]^+$.

HPLC: t_R = 2.03 min in 10-80_AB_1.2ml.method (Ultimate C18 3*50mm 3um).

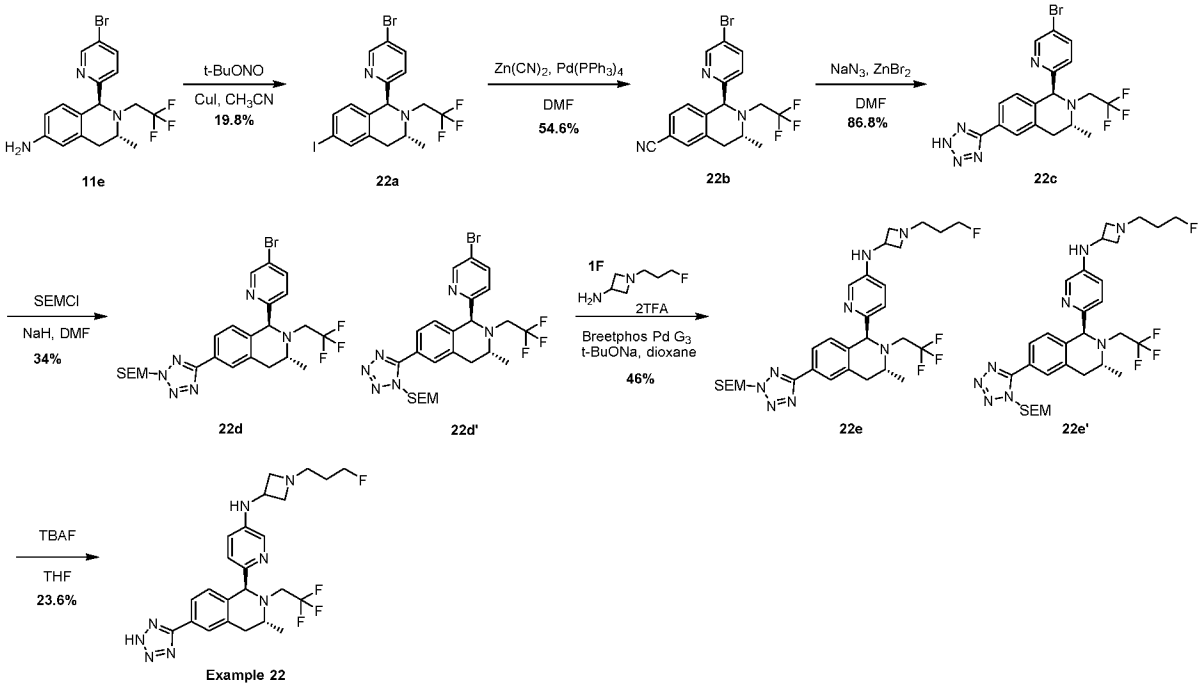
SFC: t_R = 1.812 min, 99.69% purity. Column: Chiralpak AD-3 50×3mm I.D., 3um; Mobile phase: A: CO_2 B: iso-propanol (0.05% DEA); Gradient: from 5% to 40% of B in 2.5 min and hold 40% for 0.35 min, then from 40% to 5% of B for 0.15 min; Flow rate: 2.5 mL/min; Column temperature: 40°C.

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.86 (d, *J* = 2.4 Hz, 1H), 7.67 (br s, 1H), 7.20 (d, *J* = 8.8 Hz, 1H), 7.15 (s, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.82 (dd, *J* = 8.4, 2.8 Hz,

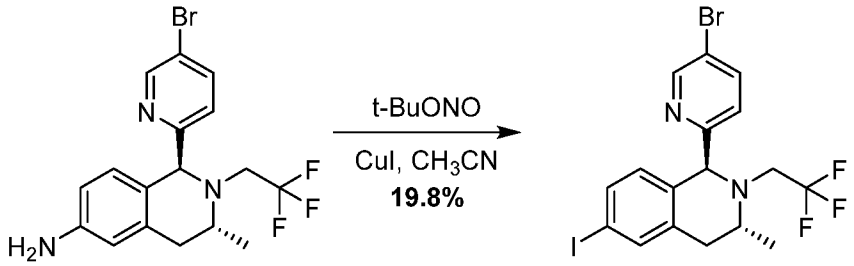
1H), 4.94 (s, 1H), 4.51 (dt, J = 47.2, 6.0 Hz, 2H), 4.12 (br s, 2H), 3.78 (br s, 2H), 3.59-3.50 (m, 1H), 3.29-3.14 (m, 2H), 3.08-2.94 (m, 3H), 2.72-2.59 (m, 3H), 2.43 (s, 3H), 1.84-1.77 (m, 2H), 1.10 (d, J = 6.8 Hz, 3H).

Example 22

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3R)-3-methyl-6-(2H-tetrazol-5-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine



The procedure to prepare **Example 22**:



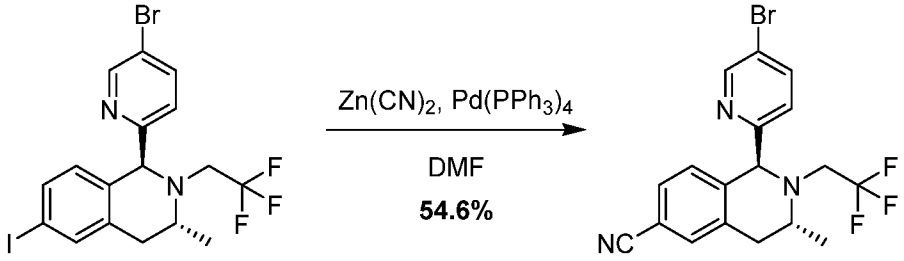
11e **22a**

To a mixture of compound **11e** (1.80 g, 4.498 mmol) and CuI (1.03 g, 5.397 mmol) in acetonitrile (27 mL) was added dropwise t-BuONO (809 uL, 6.747 mmol) slowly at room temperature (14-23 °C). Then the reaction mixture was stirred at 50 °C under nitrogen for 16 hours. The reaction mixture was cooled to room temperature and diluted with water (50 mL). The resulting mixture was extracted with ethyl acetate (10 mL x 3). The combined

organic layers were dried over anhydrous sodium sulfate, filtered and then concentrated under vacuum to give crude product, which was purified by column chromatography on silica gel (0~5% ethyl acetate in petroleum ether) to afford compound **22a** (570 mg, 80% purity on LCMS, 19.8% Yield) as brown gum.

LCMS: t_R = 1.101 min in 5-95AB_1.5 min_220&254 chromatography (Merck RP18 2.5-2mm), MS (ESI) m/z = 512.9 $[M+2+H]^+$.

^{1}H NMR (400 MHz, Methanol-*d*4): δ = 8.52 (d, *J* = 2.0 Hz, 1H), 7.90 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.54 (s, 1H), 7.43-7.34 (m, 2H), 6.63 (d, *J* = 8.0 Hz, 1H), 4.97 (s, 1H), 3.50-3.35 (m, 2H), 3.09 (dd, *J* = 16.4, 4.8 Hz, 1H), 3.02-2.89 (m, 1H), 2.64 (dd, *J* = 16.8, 6.0 Hz, 1H), 1.08 (d, *J* = 6.8 Hz, 3H).

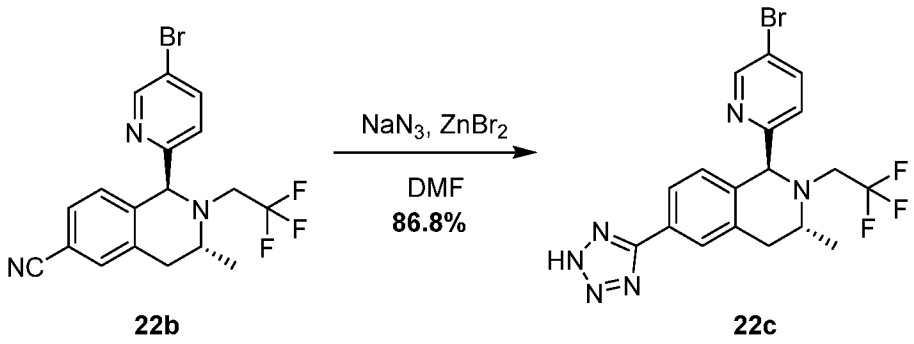


22a **22b**

A mixture of compound **22a** (570 mg, 0.892 mmol, 80% purity), $Zn(CN)_2$ (79 mg, 0.669 mmol) and $Pd(PPh_3)_4$ (129 mg, 0.112 mmol) in DMF (14 mL) was stirred at 80°C under nitrogen atmosphere for 2 hours. The reaction mixture was diluted with water (30 mL) and then extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (50 mL x 2), dried over anhydrous sodium sulfate, filtered and then concentrated under vacuum to give crude product, which was purified by column chromatography on silica gel (0~5% ethyl acetate in petroleum ether) to afford compound **22b** (200 mg, 54.6% Yield) as colorless gum.

LCMS: t_R = 0.988 min in 5-95AB_1.5 min_220&254 chromatography (Merck RP18 2.5-2mm), MS (ESI) m/z = 410.1 $[M+H]^+$.

^{1}H NMR (400 MHz, Methanol-d_4): δ = 8.53 (d, *J* = 2.4 Hz, 1H), 7.94 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.56 (s, 1H), 7.47-7.38 (m, 2H), 7.09 (d, *J* = 8.4 Hz, 1H), 5.13 (s, 1H), 3.54-3.40 (m, 2H), 3.13 (dd, *J* = 16.8, 4.4 Hz, 1H), 3.06-2.92 (m, 1H), 2.75 (dd, *J* = 16.8, 6.8 Hz, 1H), 1.10 (d, *J* = 6.4 Hz, 3H).

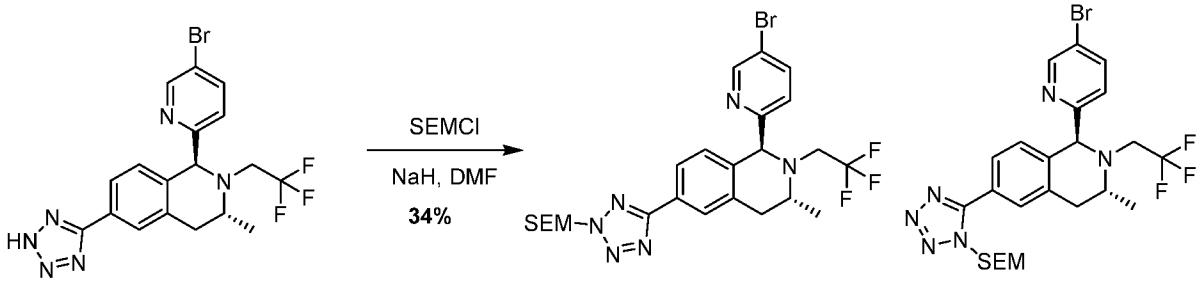


22b **22c**

$ZnBr_2$ was pre-dried under vacuum and heating. Then a mixture of compound **22b** (200 mg, 0.488 mmol), NaN_3 (200 mg, 0.488 mmol) and $ZnBr_2$ (220 mg, 0.976 mmol) in DMF (4 mL) was stirred at 130°C under nitrogen for 16 hours. The reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (0~20% MeOH (0.1% ammonia hydroxide) in CH_2Cl_2 (0.1% ammonia hydroxide)) to afford compound **22c** (240 mg, 80% purity on ^1H NMR, 86.8% Yield) as yellow solid.

LCMS: t_R = 0.898 min in 5-95AB_1.5 min_220&254 chromatography (Merck RP18 2.5-2mm), MS (ESI) m/z = 455.0 $[M+2+H]^+$.

^1H NMR (400 MHz, Methanol-d_4): δ = 8.55 (d, J = 2.4 Hz, 1H), 7.94 (dd, J = 8.4, 2.4 Hz, 1H), 7.86 (s, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 5.13 (s, 1H), 3.57-3.41 (m, 2H), 3.24 (dd, J = 16.4, 4.4 Hz, 1H), 3.08-3.00 (m, 1H), 2.81 (dd, J = 16.4, 6.0 Hz, 1H), 1.13 (d, J = 6.4 Hz, 3H).

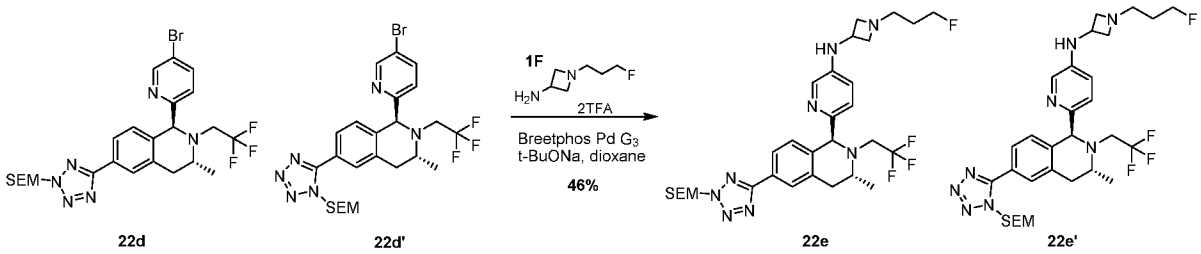


22c **22d** **22d'**

To a mixture of sodium hydride (17 mg, 0.424 mmol, 60% purity) in DMF (1.2 mL) was added dropwise a solution of compound **22c** (120 mg, 0.212 mmol, 80% purity) in DMF (1.2 mL) at room temperature (16-21°C). After the reaction mixture was stirred at room temperature (16-21°C) under nitrogen for 0.5 hour, a solution of SEMCl (53 mg, 0.318 mmol) in DMF (0.5 mL) was added dropwise at room temperature (16-21°C) under nitrogen. Then the reaction mixture was stirred at 50°C under nitrogen for 2 hours to give a yellow

suspension. The reaction mixture was poured into water (20 mL) under stirring. The resulting mixture was combined with the pilot reaction (50 mg of compound **22c**). The combined mixture was extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (50 mL x 2), dried over anhydrous sodium sulfate, filtered and then concentrated under vacuum to give crude product, which was purified by prep-TLC (petroleum ether/ethyl acetate = 4:1) to afford a mixture product of compound **22d** and **22d'** (60 mg) as colorless gum totally. The average yield was about 34%.

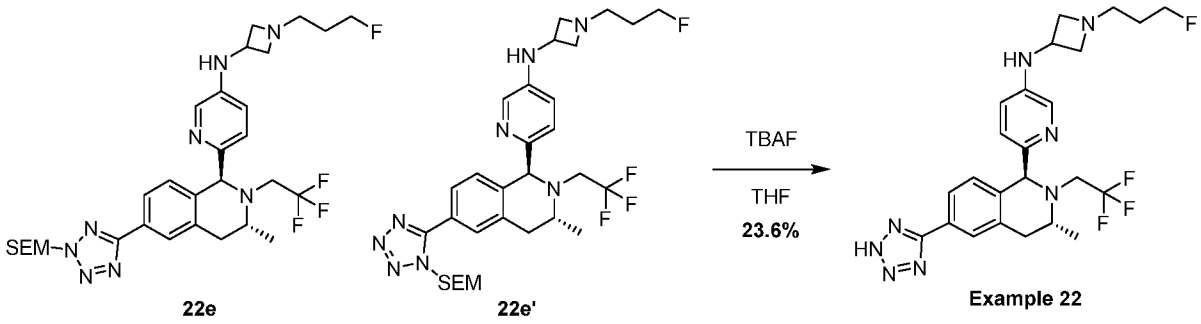
LCMS: t_R = 1.100 & 1.146 min in 5-95AB_1.5 min_220&254 chromatography (Agilent Pursult 5 C18 20*2.0mm), MS (ESI) m/z = 583.3 $[M+H]^+$.



22d 22d' 22e 22e'

To a mixture of compound **22d** and **22d'** (70 mg, 0.120 mmol), Brettphos Pd G3 (16.3 mg, 0.018 mmol) and *t*-BuONa (115 mg, 1.20 mmol) was added a solution of compound **1F** (86 mg, 0.144 mmol, 60% purity) in 1,4-dioxane (3.5 mL) under nitrogen. Then the reaction mixture was stirred at 80°C under nitrogen for 2 hours. The reaction mixture was combined with the pilot reaction (10 mg of compound **22d** and **22d'**). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to give crude product, which was purified by prep-TLC (CH_2Cl_2/MeOH=10:1) to afford a mixture product of compound **22e** and **22e'** (40 mg) as light yellow gum totally. The average yield was about 46%.

LCMS: t_R = 0.868 min in 5-95AB_1.5 min_220&254 chromatography (Agilent Pursult 5 C18 20*2.0mm), MS (ESI) m/z = 635.4 $[M+H]^+$.



To a solution of compound **22e** and **22e'** (35 mg, 0.055 mmol) in THF (2.1 mL) was added TBAF (1.4 mL, 1M in THF) at room temperature (22-29°C). Then the reaction mixture was stirred at 40°C under nitrogen for 2 hours. Then the reaction mixture was combined with the pilot reaction (5 mg of compound **22e** and **22e'**). The combined mixture was diluted with saturated $NaHCO_3$ (30 mL) and then extracted with ethyl acetate (10 mL x 4). The combined organic layers were dried over anhydrous sodium sulfate, filtered and then concentrated under vacuum to give crude product, which was purified by prep-TLC (CH_2Cl_2 / MeOH = 5:1, (0.1% ammonia hydroxide)) to give 15 mg of impure product. Then the product was further purified by chiral SFC [Column: DAICEL CHIRALPAK AS-H (250 mm * 30 mm, 5 um); Condition: 30% EtOH (0.1% ammonia hydroxide) in CO_2; Flow rate: 65 mL/min] to afford **Example 22** (7.6 mg, 23.9% yield) as light yellow solid.

LCMS: t_R = 2.585 min in 0-60AB_7 min_220&254 chromatography (Xtimate C18 2.1*30mm), MS (ESI) m/z = 505.1 $[M+H]^+$.

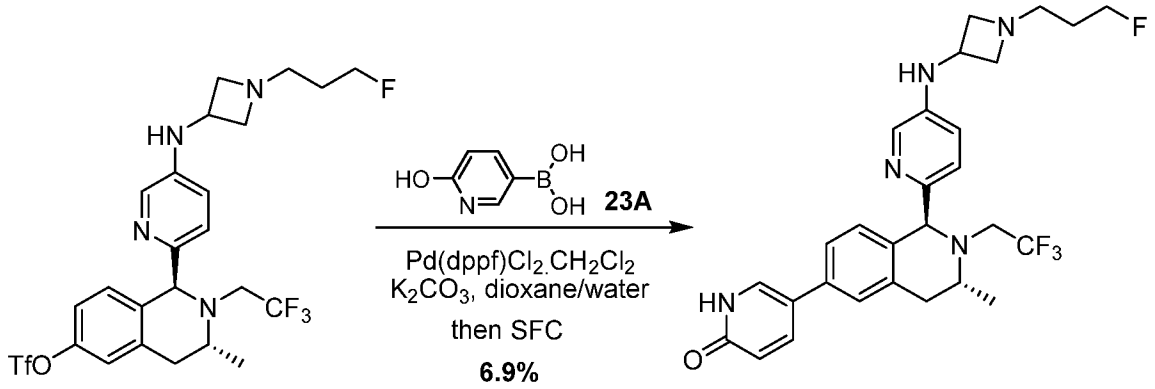
HPLC: t_R = 3.69 min in 0-60AB_1.2ml. met; Column: Ultimate C18 3*50mm 3um.

SFC method: t_R = 3.003 min; 99.004% purity; Column: Chiralpak AS-3 100×4.6mm I.D., 3um; Mobile phase: A: CO_2 B:ethanol (0.1% ethanolamine), Gradient: from 5% to 40% of B in 4.5min and hold 40% for 0.5min, then 5% of B for 1 min, Flow rate: 2.8 mL/min; Column temperature: 40°C.

^{1}H NMR (400 MHz, Methanol-d_4): δ = 7.88-7.80 (m, 2H), 7.68 (d, J = 8.0 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 7.00 (dd, J = 8.4, 2.4 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 4.93 (s, 1H), 4.64-4.42 (m, 5H), 4.02-3.88 (m, 2H), 3.63-3.50 (m, 1H), 3.43-3.32 (m, 4H), 3.04-2.87 (m, 1H), 2.76 (dd, J = 16.4, 4.4 Hz, 1H), 2.09-1.91 (m, 2H), 1.11 (d, J = 6.4 Hz, 3H).

Example 23

5-((1S,3R)-1-(5-((1-(3-fluoropropyl)azetidin-3-yl)amino)pyridin-2-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)pyridin-2(1H)-one



1h

The procedure to prepare **Example 23**:

A mixture of compound **1h** (180 mg, 0.308 mmol), compound **23A** (51 mg, 0.369 mmol), Pd(dppf)Cl_2. CH_2Cl_2 (25 mg, 0.0308 mmol) and potassium carbonate (107 mg, 0.77 mmol) was purged with nitrogen, then added with a mixed solvents of 1,4-dioxane and water (5.5 mL, v/v = 10:1) under nitrogen. The resulting mixture was stirred at 95°C under nitrogen for 2 hours. The mixture was combined with the pilot batch (30 mg compound **1**) which was carried out with same manner and concentrated under vacuum to give the crude product, which was purified by column chromatography on silica gel (0~10% methanol in dichloromethane) to afford 100mg of the crude product. It was further purified by chiral SFC (Column: DAICEL CHIRALPAK AD-H (250mm*30mm,5um); Condition: 35% IPA (0.1% ammonia) in CO_2; Flow rate: 50 mL/min) to afford **Example 23** (peak 1, 27.4 mg, 100% chemical purity; 99.07% optical purity, 6.9% yield) as a white solid, along with the cis-isomer of **Example 23** (peak 2, 5 mg, 100% chemical purity) as a yellow solid.

Spectra for Example 23 (peak 1):

LCMS: t_R = 2.644 min in 0-60AB_7min_220&254_Shimadzu.lcm chromatography (Xtimate C18 2.1*30mm), MS (ESI) m/z = 530.2 $[M+H]^+$.

HPLC: t_R = 3.80 min in 0-60_AB_1.2ml.met, chromatography (Ultimate C18 3.0um

3.0*50mm).

SFC: t_R = 2.108 min; 99.07% purity. Method: Column: Chiralpak AD-3 50×3mm I.D., 3um; Mobile phase: A: CO_2 B:iso-propanol (0.05% DEA); Gradient: from 5% to 40% of B in 2.5 min and hold 40% for 0.35 min, then from 40% to 5% of B for 0.15 min; Flow rate: 2.5 mL/min; Column temperature: 40°C.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.85 (d, *J* = 2.4 Hz, 1H), 7.75 (dd, *J* = 9.6, 2.8 Hz, 1H), 7.54 (d, *J* = 2.0 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 7.16 (s, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 8 Hz, 1H), 6.81 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.66 (d, *J* = 9.6 Hz, 1H), 4.95 (s, 1H), 4.49 (dt, *J* = 47.2, 5.6 Hz, 2H), 4.16-4.10 (m, 2H), 3.78-3.71 (m, 2H), 3.59-3.50 (m, 1H), 3.27-3.15 (m, 2H), 3.06-2.92 (m, 3H), 2.67-2.59 (m, 3H), 1.82-1.69 (m, 2H), 1.10 (d, *J* = 6.8 Hz, 3H).

Spectra for isomer of the cis-isomer of Example 23 (peak 2)

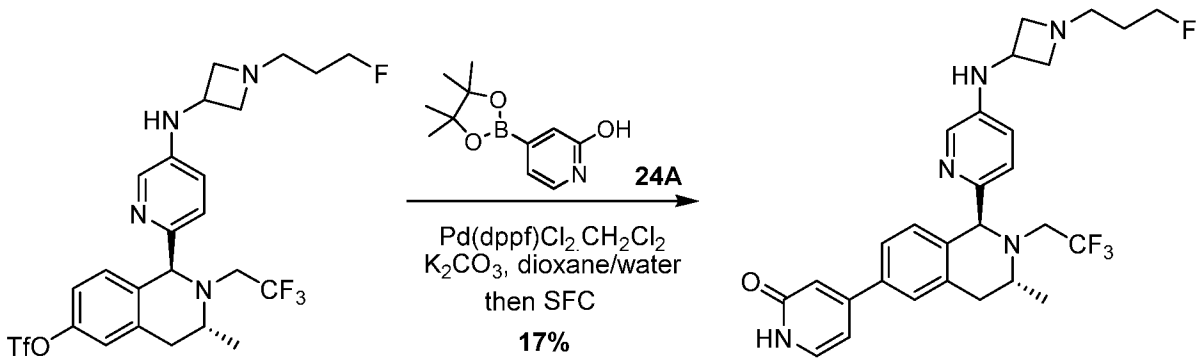
LCMS: t_R = 2.653 min in 0-60AB_7.0min_220&254_Shimadzu.lcm chromatography (Xtimate C18 2.1*30mm), MS (ESI) m/z = 530.1 $[M+H]^+$.

HPLC: t_R = 3.83 min in 0-60_AB_1.2ml.met.chromatography (Ultimate C18 3.0um 3.0*50mm).

^{1}H NMR (400MHz, MeOD): δ = 7.91 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.84 (d, *J* = 2.4 Hz, 1H), 7.65 (d, *J* = 2.8 Hz, 1H), 7.36 (d, *J* = 8.8 Hz, 1H), 7.29 (d, *J* = 1.2 Hz, 1H), 7.20 (dd, *J* = 8, 1.2 Hz, 1H), 7.04 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 6.62 (d, *J* = 9.6 Hz, 1H), 5.10 (s, 1H), 4.65-4.45 (m, 6H), 4.00 (brs, 2H), 3.46-3.37 (m, 3H), 3.23-3.18 (m, 1H), 2.92-2.78 (m, 2H), 2.09-2.03 (m, 1H), 2.00-1.94 (m, 1H), 1.31 (d, *J* = 6.0 Hz, 3H).

Example 24

4-((1S,3R)-1-(5-((1-(3-fluoropropyl)azetidin-3-yl)amino)pyridin-2-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)pyridin-2(1H)-one



1 Example 24

The procedure to prepare **Example 24** is analogous to that to prepare **Example 23**.

Spectra for Example 24 (peak 1)

LCMS: t_R = 2.717 min in 0-60AB_7min_220&254_Shimadzu.lcm chromatography (Xtimate C18 2.1*30mm), MS (ESI) m/z = 530.1 $[M+H]^+$.

HPLC: t_R = 3.77 min in 0-60_AB_1.2ml.met, chromatography (Ultimate C18 3.0um 3.0*50mm).

SFC: t_R = 2.083 min; 100% purity. Method: Column: Chiralpak AD-3 50×3mm I.D., 3um; Mobile phase: A: CO_2 B:iso-propanol (0.05% DEA); Gradient: from 5% to 40% of B in 2.5 min and hold 40% for 0.35 min, then from 40% to 5% of B for 0.15 min; Flow rate: 2.5 mL/min; Column temperature: 40°C.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.85 (d, *J* = 2.8 Hz, 1H), 7.39 (d, *J* = 7.2 Hz, 1H), 7.35 (s, 1H), 7.31-7.28 (m, 1H), 7.20 (d, *J* = 8.8 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.82 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.76 (d, *J* = 1.2 Hz, 1H), 6.53 (dd, *J* = 6.8, 1.6 Hz, 1H), 4.97 (s, 1H), 4.50 (dt, *J* = 46.8, 5.6 Hz, 2H), 4.18-4.08 (m, 2H), 3.79-3.72 (m, 2H), 3.60-3.53 (m, 1H), 3.29-3.18 (m, 2H), 3.05-2.94 (m, 3H), 2.71-2.60 (m, 3H), 1.84-1.70 (m, 2H), 1.10 (d, *J* = 6.8 Hz, 3H).

Spectra for isomer of the cis-isomer of Example 24 (peak 2)

LCMS: t_R = 2.757 min in 0-60AB_7.0min_220&254_Shimadzu.lcm chromatography (Xtimate C18 2.1*30mm), MS (ESI) m/z = 530.1 $[M+H]^+$.

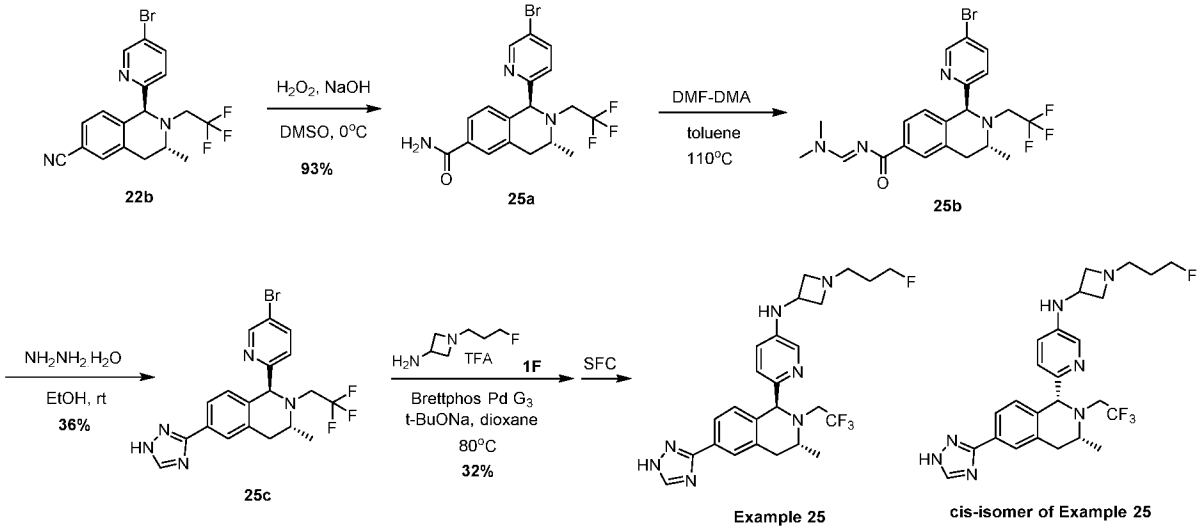
HPLC: t_R = 3.78 min in 0-60_AB_1.2ml.met.chromatography (Ultimate C18 3.0um

3.0*50mm).

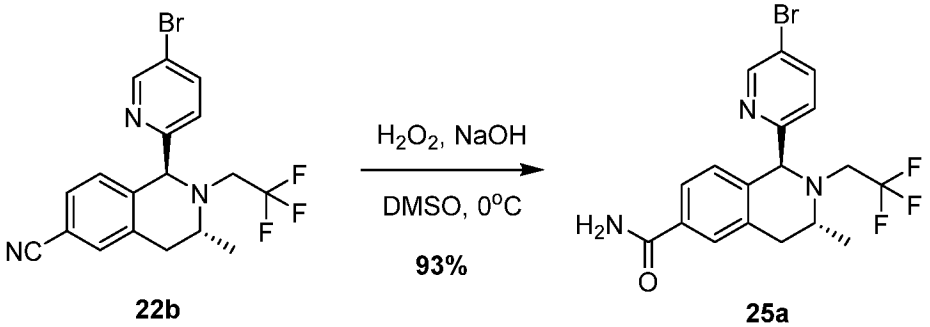
^{1}H NMR (400MHz, MeOD): δ = 7.81 (d, *J* = 2.8 Hz, 1H), 7.50-7.45 (m, 2H), 7.37 (d, *J* = 10 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 1H), 6.99 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.90 (d, *J* = 8 Hz, 1H), 6.75-6.70 (m, 2H), 5.12 (s, 1H), 4.62 (brs, 3H), 4.48 (dt, *J* = 46.8, 5.6 Hz, 2H), 4.18-4.11 (m, 1H), 3.92-3.84 (m, 2H), 3.50-3.41 (m, 1H), 3.12-3.03 (m, 2H), 2.97-2.85 (m, 2H), 2.73 (brt, *J* = 7.2 Hz, 2H), 1.86-1.72 (m, 2H), 1.33 (d, *J* = 6.0 Hz, 3H).

Example 25

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3R)-3-methyl-6-(1H-1,2,4-triazol-3-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine



The procedure to prepare **Example 25**:

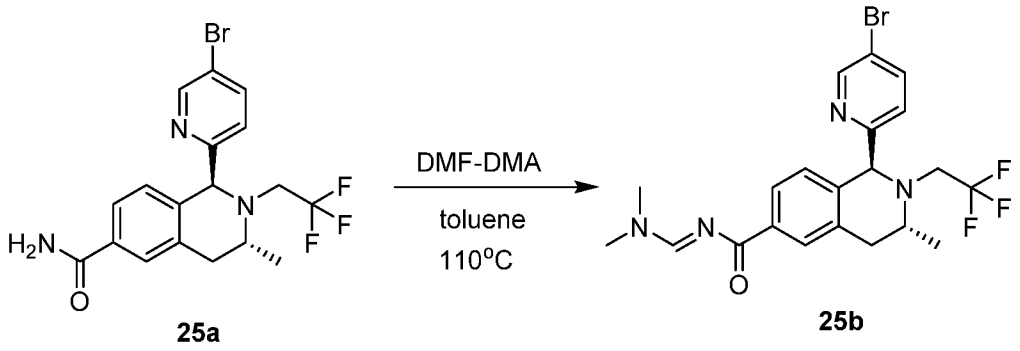


A mixture of compound **22b** (240 mg, 0.585 mmol) in DMSO (6 mL) was added aqueous solution of H_2O_2 (0.88 mL, 8.78 mmol, 30%) at 0 °C, then aqueous solution of NaOH (2.94 mL, 2.93 mmol, 1 M) was added drop-wise at 0 °C. The resulting mixture was stirred at 0 °C for 1 hour to give a colorless solution. The mixture was quenched with saturated

aqueous solution of Na_2SO_3 (50 mL) at 0-10 °C, extracted with ethyl acetate (50 ml × 3). The combined organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate and concentrated in vacuo to give the crude product, which was purified by column chromatography on silica gel (0-60% ethyl acetate in petroleum ether) to afford compound **25a** (270 mg, 93% purity, 100% yield) as yellow oil.

LCMS: t_R = 0.862 min in 5-95AB_220&254 chromatography (Agilent Pursult 5 C18 20*2.0mm), MS (ESI) m/z = 430.0 $[M+2+H]^+$.

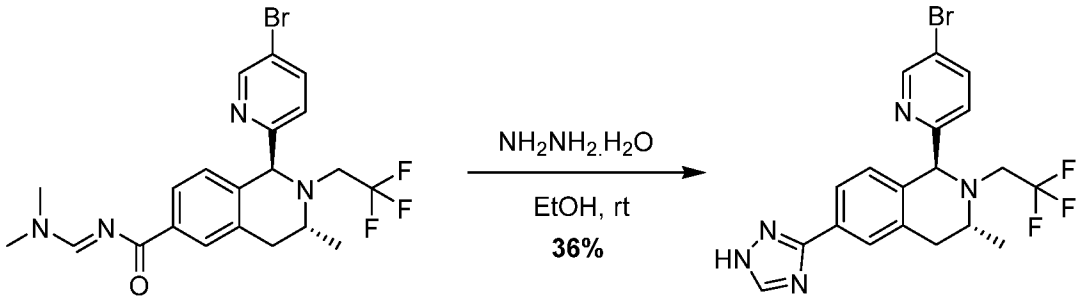
^{1}H NMR (400MHz, CD_3OD) δ = 8.54 (d, *J* = 2.4 Hz, 1H), 7.93 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.70 (d, *J* = 1.6 Hz, 1H), 7.57 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 5.09 (s, 1H), 3.56-3.40 (m, 2H), 3.22 (dd, *J* = 16.4, 4.8 Hz, 1H), 3.00-2.92 (m, 1H), 2.76 (dd, *J* = 16.4, 6.0 Hz, 1H), 1.10 (d, *J* = 6.8 Hz, 3H).



25a **25b**

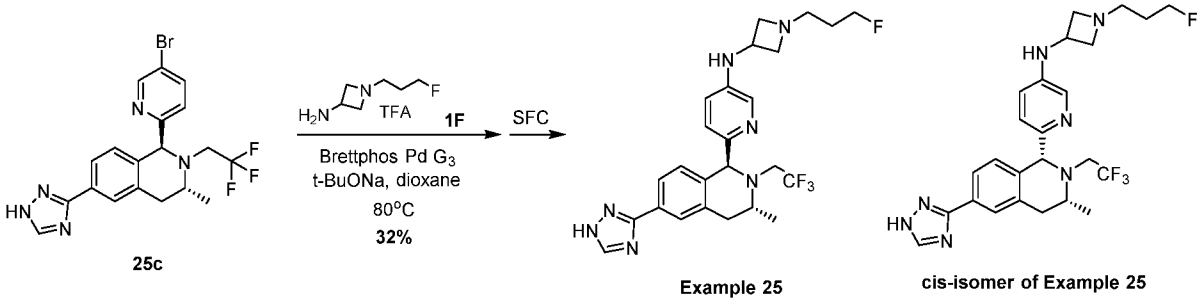
A mixture of compound **25a** (230 mg, 0.497 mmol, 92.6% purity) in toluene (5.8 mL) was added DMF-DMA (330 uL, 2.49 mmol) at 20-32 °C. The mixture was degassed and purged with nitrogen for 3 times, then stirred at 110 °C for 1 hour under nitrogen to give a yellow solution. The mixture was concentrated in vacuo directly to give compound **25b** (240.3 mg, 100% yield), which was used in the next step directly without further purification.

LCMS: t_R = 0.811 min in 5-95AB_220&254 chromatography (Agilent Pursult 5 C18 20*2.0mm), MS (ESI) m/z = 483.1 $[M+H]^+$.



A mixture of compound **25b** (240.3 mg, 0.497 mmol) in ethanol (5.8 mL) was added $NH_2NH_2.H_2O$ (173 uL, 3.48 mmol, 98%) at 20-32 °C. The mixture was degassed and purged with nitrogen for 3 times, then stirred at 20-32°C for 1 hour under nitrogen to give a yellow solution. The reaction was combined with the pilot batch (41.8 mg of compound **25b**) which was carried out with same manner and diluted with ethyl acetate (100 mL). The organic phase was washed with brine (30 mL × 3) and dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give the residue, which was purified by prep-TLC (dichloromethane: methanol =20:1) twice to give compound **25c** (95 mg, 36.0% average yield) as a yellow solid.

LCMS: t_R = 0.870 min in 5-95AB_220&254 chromatography (Agilent Pursult 5 C18 20*2.0mm), MS (ESI) m/z = 454.1 $[M+2+H]^+$.



To a mixture of compound **25c** (70 mg, 0.155 mmol), compound **1F** (119.5 mg, 0.232 mmol, 70% purity) and *t*-BuONa (148.7 mg, 1.55 mmol) in dioxane (3.5 mL) was added Brettphos-Pd-G_3 (28.1 mg, 0.031 mmol). The mixture was purged with N_2, sealed and stirred at 80°C for 2 hours under nitrogen to give a black brown solution. The mixture was filtered and concentrated in vacuo to give a residue, which was purified by prep-TLC (dichloromethane: methanol =12:1, with 1% ammonia) to give the product (45 mg), it was

further separated by chiral SFC (Column: DAICEL CHIRALCEL OD-H (250 mm * 30 mm,5 um); Condition: 30% EtOH (0.1% ammonia) in CO_2; Flow rate: 60 mL/min) to give title product of **Example 25** (peak 2, 25.1 mg, 98.81% purity, 32% yield) as a white solid, along with isomer of **Example 25** (peak 1, 2.5 mg, 98.88% chemical purity) as a yellow solid.

Spectrum for Example 25 (peak 2):

LCMS: t_R = 1.714 min in 0-60AB_3min_220&254.lcm chromatography (Xtimate C18 2.1*30mm), MS (ESI) m/z = 504.2 $[M+H]^+$.

HPLC: t_R = 2.40 min in 10-80_AB_1.2ml.met.chromatography (Ultimate C18 3.0um 3.0*50mm).

SFC: t_R = 4.565 min; 98.81% purity. Method: Column: ChiralCel OD-3 150×4.6mm I.D., 3um; Mobile phase: A: CO_2 B: Ethanol (0.05% DEA); Gradient: from 5% to 40% of B in 5.5min and hold 40% for 3 min, then 5% of B for 1.5 min; Flow rate: 2.5 mL/min; Column temperature: 40°C.

^{1}H NMR (400MHz, $CDCl_3$): δ = 8.04 (s, 1H), 7.78 (d, *J* = 2.4 Hz, 1H), 7.68 (s, 1H), 7.46 (br d, *J* = 7.2 Hz, 1H), 7.29 (s, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.85 (dd, *J* = 8.8, 2.8 Hz, 1H), 4.98 (s, 1H), 4.54 (t, *J* = 6.0 Hz, 1H), 4.48-4.36 (m, 2H), 4.20-4.05 (m, 1H), 3.74 (q, *J* = 6.0 Hz, 2H), 3.61-3.45 (m, 1H), 3.30-3.13 (m, 1H), 3.08-2.88 (m, 4H), 2.66 (t, *J* = 7.2 Hz, 2H), 2.56 (dd, *J* = 16.8, 7.2 Hz, 1H), 1.87-1.68 (m, 2H), 1.07 (d, *J* = 6.4 Hz, 3H).

Spectrum for isomer of Example 25 (peak 1):

LCMS: t_R = 1.984 min in 0-60AB_220&254 chromatography (Xtimate C18 2.1*30mm), MS (ESI) m/z = 504.3 $[M+H]^+$.

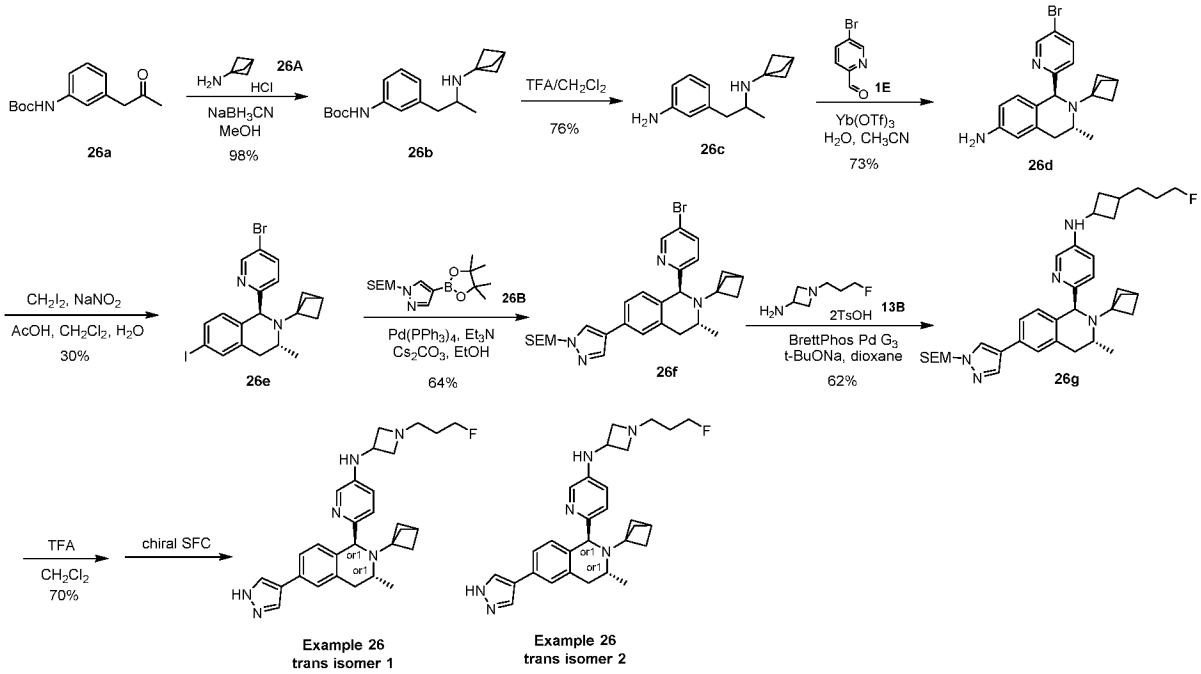
HPLC: t_R = 2.43 min in 10-80_AB_1.2ml.met (Ultimate C18 3*50mm 3um).

^{1}H NMR (400MHz, $CDCl_3$)**:** δ = 8.15 (s, 1H), 7.89 (d, *J* = 2.4 Hz, 1H), 7.76 (s, 1H), 7.68-7.64 (m, 1H), 7.26 (s, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.82 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.18 (s, 1H), 4.50 (dt, *J* = 47.2, 6.0 Hz, 2H), 4.19-4.06 (m, 2H), 3.79-3.71 (m, 2H), 3.48-3.36 (m, 1H), 3.31-3.21 (m, 2H), 3.01-2.93 (m, 2H), 2.84-2.79 (m, 2H), 2.63 (t, *J* = 7.2 Hz, 2H),

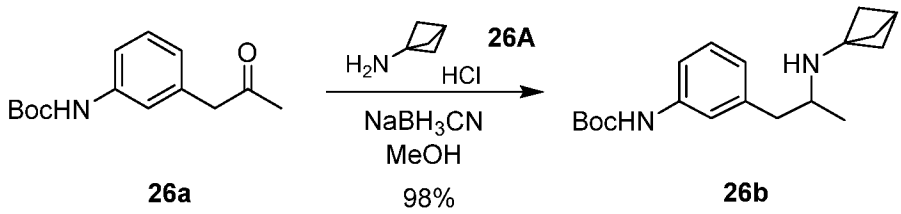
1.85-1.71 (m, 2H), 1.31 (d, J = 6.0 Hz, 3H).

Example 26

6-(2-(bicyclo[1.1.1]pentan-1-yl)-3-methyl-6-(1H-pyrazol-4-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-N-(1-(3-fluoropropyl)azetidin-3-yl)pyridin-3-amine



The procedure to prepare **Example 26 trans isomer 1** and **Example 26 trans isomer 2**:

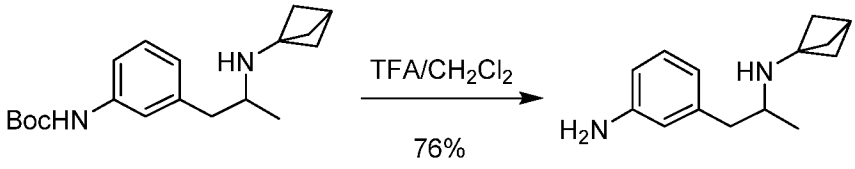


The mixture of compound **26A** (1.146 , 9.6 mmol) and Et_3N (0.970 g, 9.6 mmol) in methanol (26 mL) was stirred at 50°C for 30 min, then added a solution of compound **26a** (2.0 g, 8.0 mmol) in methanol (4 mL) and adjusted to pH = 6 with AcOH. The resulting mixture was stirred at 50°C for 2 hours. To the mixture was added $NaBH_3CN$ (0.992 g, 16 mmol) at 0°C, and the mixture was stirred at 50°C for 2.5 hours (as white suspension). The reaction was cooled to 20°C and quenched with saturated aqueous solution of $NaHCO_3$ (50 mL) and extracted with ethyl acetate (200 mL×3), the combined organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate and filtered, the filtrate was concentrated *in*

vacuo to give the crude product, which was purified by column chromatography on silica gel (ethyl acetate/petroleum ether = 0-30%) to afford the compound **26b** (2.5 g, 98% yield) as a white solid.

LCMS: t_R = 0.737 min in 5-95AB_220&254.lcm chromatography (Agilent pursult5 C18 20*2mm), MS (ESI) m/z = 317.6 $[M+H]^+$.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.26-7.19 (m, 2H), 7.16 (s, 1H), 6.86 (d, *J* = 7.2 Hz, 1H), 6.45 (br s, 1H), 3.06-3.02 (m, 1H), 2.73 (dd, *J* = 13.2, 6.4 Hz, 1H), 2.53 (dd, *J* = 13.2, 7.2 Hz, 1H), 2.37 (s, 1H), 1.85-1.75 (m, 6H), 1.53 (s, 9H), 1.05 (d, *J* = 6.4 Hz, 3H).

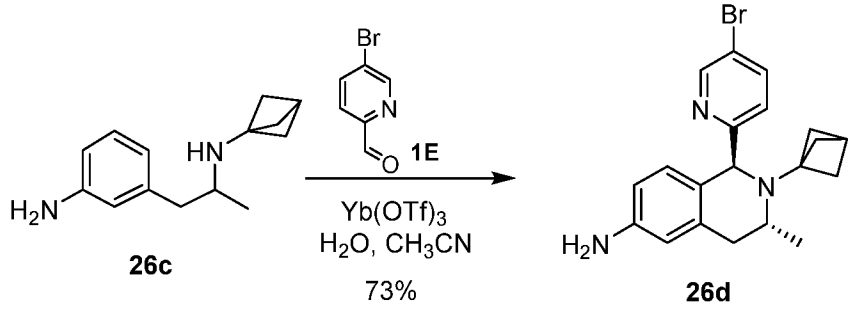


26b **26c**

To the compound **26b** (2.5 g, 7.9 mmol) in dichloromethane (30 mL) was added TFA (6 mL) at 14-24°C and the mixture was stirred at 14-24°C for 4 hours. The reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ (50 mL) and extracted with ethyl acetate (100 mL × 2). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate and filtered, the filtrate was concentrated *in vacuo* to give the crude product, which was purified by column chromatography on silica gel (eluting with 0~50% ethyl acetate in petroleum ether) to afford product **26c** (1.3 g, 76%) as a brown oil

LCMS: t_R = 1.673 min in 10-80CD_220&254.lcm chromatography (A: Xtimate C18, 2.1 * 30 mm, 3 um, B: XBrige Shield RP18 2.1 * 50 mm), MS (ESI) m/z = 217.1 $[M+H]^+$.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.08 (t, *J* = 7.6 Hz, 1H), 6.61-6.54 (m, 2H), 6.52 (s, 1H), 3.63 (br s, 2H), 3.01 (m, 1H), 2.66 (dd, *J* = 13.2, 6.8 Hz, 1H), 2.48 (dd, *J* = 13.2, 6.8 Hz, 1H), 2.37 (s, 1H), 1.81 (dq, *J* = 9.6, 1.6 Hz, 6H), 1.06 (d, *J* = 6.0 Hz, 3H).

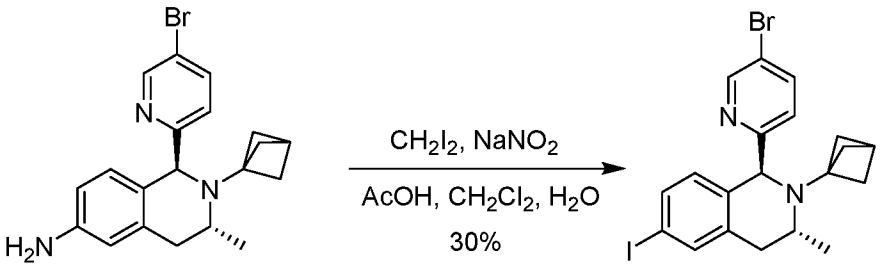


26c **26d**

To the mixture of compound **26c** (300 mg, 1.39 mmol), compound **1E** (284 mg, 1.53 mmol) in CH_3CN (9 mL) and water (125.1 mg, 6.95 mmol) was added $Yb(OTf)_3$ (17.5 mg, 0.0278 mmol) at 15-23°C with sealed tube. The mixture was stirred at 70°C for 2 hours (as brown solution). The reaction mixture was combined with that of four parallel batches (300 mg each of compound **26c**) and quenched with water (50 mL). The aqueous layer was extracted with ethyl acetate (100 mL × 3). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate and filtered, the filtrate was concentrated *in vacuo* to give the crude product, which was purified by flash column chromatography on silica gel (eluting with 0~10% ethyl acetate in petroleum ether) to afford compound **26d** (1.9 g, trans/cis = 3.5/1 based on H NMR, 73% average yield) as a brown solid

LCMS: t_R = 1.146 min in 10-80AB_220&254.lcm chromatography (Xtimate C18 2.1 * 30 mm), MS (ESI) m/z = 383.9 $[M+H]^+$.

^{1}H NMR: (400MHz, $CDCl_3$): δ = 8.56 (d, *J* = 2.0 Hz, 1H), 7.62 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 6.72 (d, *J* = 8.4 Hz, 1H), 6.41 (s, 1H), 6.40-6.35 (m, 1H), 4.95 (s, 1H), 3.65-3.59 (m, 1H), 3.53 (br s, 2H), 3.29 (dd, *J* = 15.2, 4.8 Hz, 1H), 2.47 (d, *J* = 17.2 Hz, 1H), 2.23 (s, 1H), 1.76 (dd, *J* = 9.6, 1.2 Hz, 3H), 1.48 (dd, *J* = *9.2,* 1.6 Hz, 3H), 1.03 (d, *J* = 6.4 Hz, 3H).



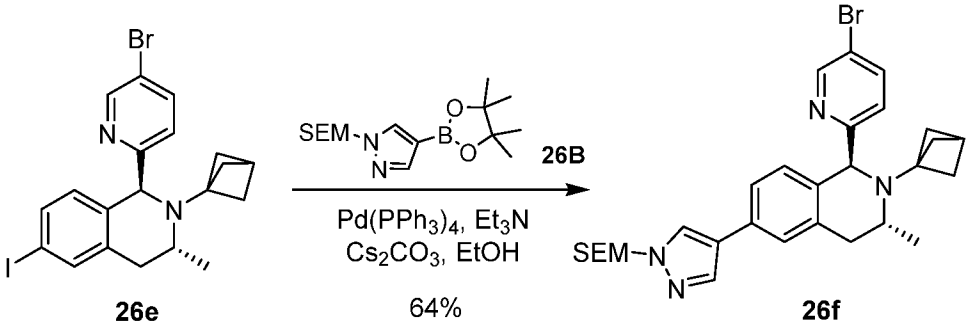
26d **26e**

To the stirred mixture of compound **26d** (700 mg, 1.82 mmol) in dichloromethane (8.4 mL) and water (7.0 mL) was added CH_2I_2 (976 mg, 3.6 mmol), a solution of $NaNO_2$ (628 mg, 9.1 mmol) in water (1.4 mL) and AcOH (2184 mg, 36.4 mmol) successively at 5°C under nitrogen. The resulting mixture was stirred at 20-25°C for 5 min while turned from the light brown solution to black solution. After stirred for another 1 hour at 20-25°C, the reaction was combined with that of parallel batch (700 mg of compound **26d**) and diluted with ethyl acetate (20 mL), then treated with saturated aqueous solution of $NaHCO_3$ to adjust pH = 9.

The mixture was filtered and the filtrate was extracted with ethyl acetate (100 mL × 2). The combined organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate and filtered, the filtrate was concentrated *in vacuum* at 30°C to give the crude product, which was purified by prep-TLC (petroleum ether/ethyl acetate = 4/1) to afford compound **26e** (540 mg, 30%) as a brown solid.

LCMS: t_R = 0.880 min in 5-95AB_220&254.lcm chromatography (Agilent pursult5 C18 20*2mm), MS (ESI) m/z = 495.1 $[M+H]^+$.

^{1}H NMR (400MHz, $CDCl_3$): δ = 8.57 (d, *J* = 2.0 Hz, 1H), 7.64 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.45 (s, 1H), 7.33 (br d, *J* = 8.4 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 6.72 (d, *J* = 8.4 Hz, 1H), 4.99 (s, 1H), 3.69-3.60 (m, 1H), 3.32 (dd, *J* = 15.6, 4.4 Hz, 1H), 2.54 (dd, *J* = 15.6, 2.0 Hz, 1H), 2.24 (s, 1H), 1.75 (dd, *J* = 9.6, 1.6 Hz, 3H), 1.48 (dd, *J* = 9.2, 1.6 Hz, 3H), 1.02 (d, *J* = 6.4 Hz, 3H).

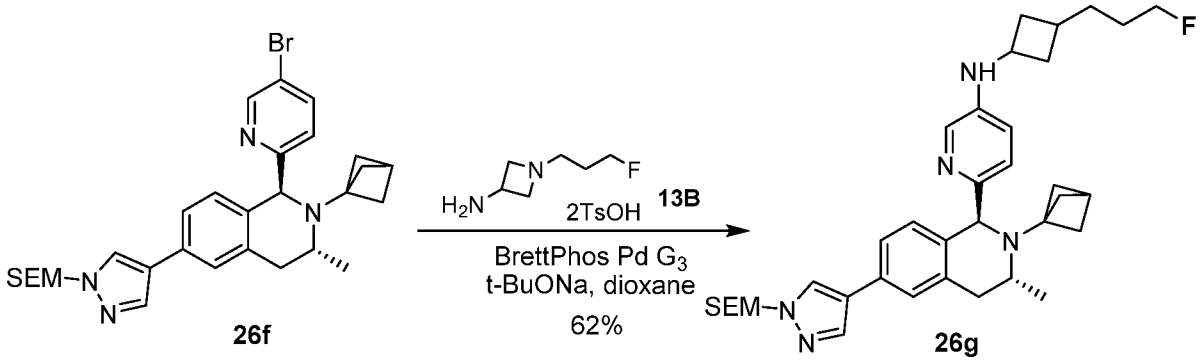


26e **26f**

The mixture of compound **26e** (270 mg, 0.545 mmol), compound **26B** (211 mg, 0.708 mmol), $Pd(PPh_3)_4$ (63 mg, 0.0545 mmol), Cs_2CO_3 (357 mg, 1.09 mmol) and Et_3N (110 mg, 1.09 mmol) in EtOH (5 mL) and water (1.1 mL) was stirred at 40°C for 15 hours under nitrogen (as brown solution). The reaction was diluted with ethyl acetate (10 mL) and water (5 mL). The mixture was concentrated *in vacuo* and the residue was extracted with ethyl acetate (50 mL×3). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate and filtered, the filtrate was concentrated *in vacuo* to give the crude product, which was purified by flash column chromatography on silica gel (eluting with 0~15% ethyl acetate in petroleum ether) to afford the product **26f** (200 mg, 64% yield) as a brown oil.

LCMS: t_R = 0.901 min in 5-95AB_220&254.lcm chromatography (Agilent pursult5 C18 20*2mm), MS (ESI) m/z = 567.2 $[M+H+2]^+$.

^{1}H NMR (400MHz, $CDCl_3$): δ = 8.62 (d, *J* = 2.4 Hz, 1H), 7.76 (s, 1H), 7.75 (s, 1H), 7.67 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.26 (s, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 5.46 (s, 2H), 5.09 (s, 1H), 3.73-3.68 (m, 1H), 3.56 (t, *J* = 8.0 Hz, 2H), 3.42 (dd, *J* = 15.2, 4.8 Hz, 1H), 2.65 (d, *J* = 15.2 Hz, 1H), 2.28 (s, 1H), 1.81 (dd, *J* = 9.2, 1.2 Hz, 3H), 1.53 (dd, *J* = 9.2, 1.2 Hz, 3H), 1.08 (d, *J* = 6.4 Hz, 3H), 0.91 (t, *J* = 8.0 Hz, 2H), 0.00 (s, 9H).

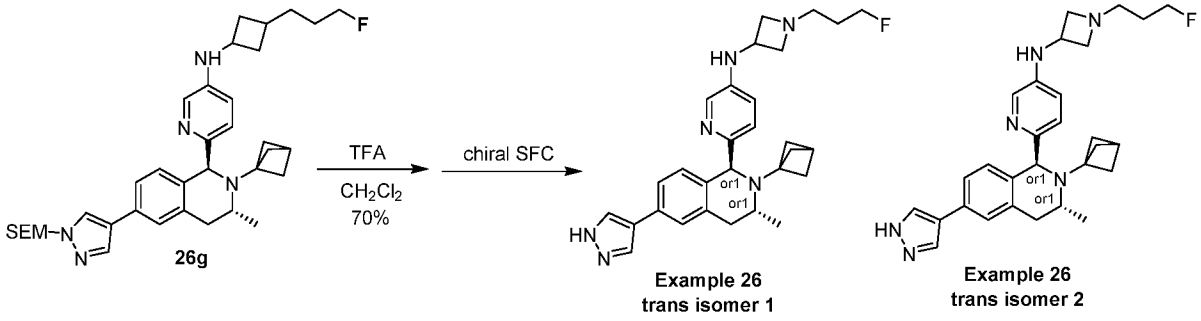


The mixture of compound **26f** (200 mg, 0.355 mmol), compound **13B** (253mg, 0.53 mmol), BrettPhos-Pd-G_3 (64 mg, 0.071 mmol), t-BuONa (187mg, 1.95 mmol) in 1,4-dioxane (5 mL) was stirred at 100°C for 4 hours under nitrogen (as black solution). The reaction was diluted with saturated aqueous solution of NH_4Cl (15 mL) and extracted with ethyl acetate (50 mL × 3), the combined organic layers was washed with brine (50 mL), dried over anhydrous sodium sulfate and filtered, the filtrate was concentrated *in vacuo* to give the crude product, which was purified by column chromatography on silica gel (eluting with 0~15% methanol in dichloromethane) to afford the product **26g** (136 mg, 62% yield) as a brown solid.

LCMS: t_R = 1.747 min in 10-80AB_220&254.lcm chromatography (Xtimate C18 2.1 * 30 mm), MS (ESI) m/z = 617.4 $[M+H]^+$.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.88 (d, *J* = 2.8 Hz, 1H), 7.76 (s, 1H), 7.74 (s, 1H), 7.21 (s, 1H), 7.14 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.73 (dd, *J* = 8.4, 2.8 Hz, 1H), 5.43 (s, 2H), 4.98 (s, 1H), 4.50 (dt, *J* = 46.8, 6.0 Hz, 2H), 4.12-4.06 (m, 1H), 3.97-3.93 (m, 1H), 3.78-3.71 (m, 2H), 3.68-3.65 (m, 1H), 3.55 (t, *J* = 8.0 Hz, 2H), 3.39 (dd, *J* = 4.8, 15.2 Hz, 1H), 2.95-2.88 (m, 2H), 2.66-2.54 (m, 3H), 2.22 (s, 1H), 1.83-1.71 (m, 5H), 1.50 (d, *J* = 8.8

Hz, 3H), 1.06 (d, J = 6.4 Hz, 3H), 0.90 (t, J = 8.0 Hz, 2H), -0.02 (s, 9H).



The mixture of compound **26g** (116 mg, 0.188 mmol) and TFA (2.0 mL) in dichloromethane (5.0 mL) was stirred at 21-25°C for 2.5 hours. The reaction was combined with of the pilot batch (10 mg of compound **26g**) which was carried out with same manner and adjusted to pH = 9 with saturated aqueous solution of $NaHCO_3$, extracted with dichloromethane (50 mL × 3). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate and filtered, the filtrate was concentrated *in vacuo* to give the crude product, which was purified by column chromatography on silica gel (eluting with 0~15% methanol in dichloromethane) to afford the 1:1 mixture of **Example 26 trans isomer 1** and **Example 26 trans isomer 2** (70 mg, 70% yield) as a brown solid.

LCMS: t_R = 0.640 min in 5-95AB_220&254.lcm chromatography (Agilent pursult5 C18 20*2mm), MS (ESI) m/z = 487.3 $[M+H]^+$.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.88 (d, J = 2.4 Hz, 1H), 7.79 (s, 2H), 7.22 (s, 1H), 7.18-7.13 (m, 2H), 6.94 (d, J = 8.0 Hz, 1H), 6.76 (dd, J = 8.4, 2.8 Hz, 1H), 4.99 (s, 1H), 4.50 (dt, J = 47.2, 5.6 Hz, 2H), 4.38-4.23 (m, 1H), 4.21-4.15 (m, 1H), 3.88-3.80 (m, 2H), 3.70-3.63 (m, 1H), 3.38 (dd, J = 15.8, 4.8 Hz, 1H), 3.26-3.15 (m, 2H), 2.74 (t, J = 7.2 Hz, 2H), 2.60 (d, J = 15.2 Hz, 1H), 2.22 (s, 1H), 1.89-1.83 (m, 2H), 1.80-1.77 (m, 3H), 1.50 (dd, J = 9.2, 1.2 Hz, 3H), 1.07 (d, J = 6.4 Hz, 3H).

SFC for mixture: t_R = 4.115 min and 5.539 min. Method: Column: Chiralcel OD-3 100×4.6mm I.D., 3um; Mobile phase: A: CO_2 B: ethanol (0.05% DEA); Gradient: from 5% to 40% of B in 4.5min and hold 40% for 2.5min, then 5% of B for 1min; Flow rate: 2.8 mL/min; Column temperature: 40°C.

The obtained mixture (70 mg, 0.14 mmol) was separated by chiral SFC [Phenomenex-Amylose(250mm*30mm,5um); Condition: EtOH (0.1% NH_3H_2O) in CO_2;

Flow rate: 50 mL/min] to afford **Example 26 trans isomer 1** (19.2 mg, 27% yield, peak 1) as a yellow solid and **Example 26 trans isomer 2** (19.4 mg, 27% yield, peak 2) as a yellow solid.

Spectra for Example 26 trans isomer 1:

LCMS: t_R = 1.796 min in 0-60AB_4min_220&254.lcm chromatography (Xtimate C18 2.1 * 30 mm), MS (ESI) m/z = 487.2 $[M+H]^+$.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.88 (d, *J* = 2.4 Hz, 1H), 7.78 (s, 2H), 7.21 (s, 1H), 7.15 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.73 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.98 (s, 1H), 4.49 (dt, *J* = 47.2, 6.0 Hz, 2H), 4.17-3.98 (m, 2H), 3.73 (q, *J* = 6.8 Hz, 2H), 3.69-3.63 (m, 1H), 3.44-3.32 (m, 1H), 2.95-2.88 (m, 2H), 2.63-2.57 (m, 3H), 2.22 (s, 1H), 1.80-1.72 (m, 5H), 1.50 (d, *J* = 9.2 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H).

HPLC: t_R = 3.43 min in 0-60_AB_1.2ml.met, chromatography (Ultimate C18 3 * 50 mm 3um).

SFC: t_R = 4.111 min. Method: Column: Chiralcel OD-3 100×4.6mm I.D., 3um; Mobile phase: A: CO_2 B: ethanol (0.05% DEA); Gradient: from 5% to 40% of B in 4.5min and hold 40% for 2.5min, then 5% of B for 1min; Flow rate: 2.8 mL/min; Column temperature: 40°C.

Spectra for Example 26 trans isomer 2:

LCMS: t_R = 1.798 min in 0-60AB_4min_220&254.lcm chromatography (Xtimate C18 2.1 * 30 mm), MS (ESI) m/z = 487.2 $[M+H]^+$.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.88 (d, *J* = 2.4 Hz, 1H), 7.79 (s, 2H), 7.22 (s, 1H), 7.15 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.74 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.99 (s, 1H), 4.50 (dt, *J* = 47.2, 6.0 Hz, 2H), 4.15-4.09 (m, 1H), 4.05-3.99 (m, 1H), 3.79-3.71 (m, 2H), 3.70-6.65 (m, 1H), 3.42-3.33 (m, 1H), 2.99-2.92 (m, 2H), 2.65-2.57 (m, 3H), 2.22 (s, 1H), 1.78-1.75 (m, 5H), 1.50 (d, *J* = 9.5 Hz, 3H), 1.07 (d, *J* = 6.4 Hz, 3H).

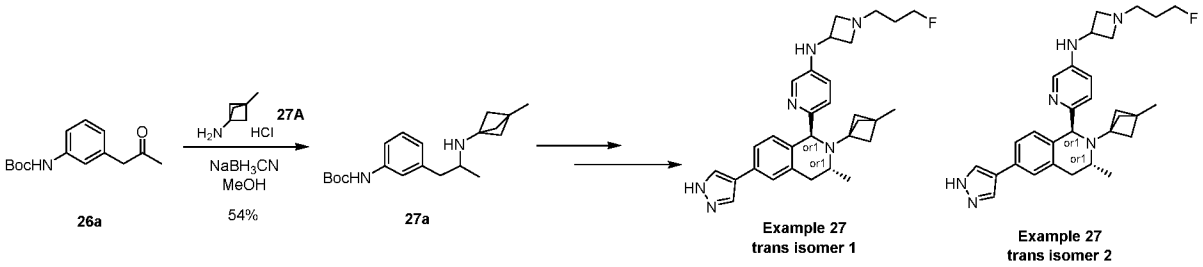
HPLC: t_R = 3.44 min in 0-60_AB_1.2ml.met, chromatography (Ultimate C18 3 * 50 mm 3um).

SFC: t_R = 5.500 min. Method: Column: Chiralcel OD-3 100×4.6mm I.D., 3um; Mobile phase: A: CO_2 B: ethanol (0.05% DEA); Gradient: from 5% to 40% of B in 4.5min and hold

40% for 2.5min, then 5% of B for 1min; Flow rate: 2.8 mL/min; Column temperature: 40°C.

Example 27

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-(3-methyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)-6-(1H-pyrazol-4-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine



The procedure to prepare **Example 27 trans isomer 1** and **Example 27 trans isomer 2** is analogous to that of preparation of **Example 26**:

The trans mixture of **Example 27** (100 mg, 0.199 mmol) was separated by chiral SFC [Column: DAICEL CHIRALCEL OD (250mm*30mm, 5um); Condition: (0.1% $NH_3.H_2O$) IPA in CO_2; Flow rate: 50 mL/min] to afford **Example 27 trans isomer 1** (30.9 mg, 30%, peak 1) as a yellow solid and **Example 27 trans isomer 2** (32.8 mg, peak 2).

Spectra for Example 27 trans isomer 1:

LCMS: t_R = 1.960 min in 0-60AB_4min_220&254.lcm chromatography (Xtimate C18 2.1*30mm), MS (ESI) m/z = 501.2 $[M+H]^+$.

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.89 (d, *J* = 2.8 Hz, 1H), 7.79 (s, 2H), 7.21 (s, 1H), 7.14 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.73 (dd, *J* = 8.4, 2.8 Hz, 1H), 4.95 (s, 1H), 4.50 (dt, *J* = 47.2, 6.0 Hz, 2H), 4.16-4.07 (m, 1H), 4.03-4.00 (m, 1H), 3.75 (q, *J* = 6.4 Hz, 2H), 3.67-3.63 (m, 1H), 3.38 (dd, *J* = 15.2, 4.8 Hz, 1H), 2.99-2.91 (m, 2H), 2.66-2.56 (m, 3H), 1.81-1.73 (m, 2H), 1.63 (d, *J* = 9.6 Hz, 3H), 1.35 (d, *J* = 9.2 Hz, 3H), 1.09 (s, 3H), 1.05 (d, *J* = 6.4 Hz, 3H).

HPLC: t_R = 3.67 min in 0-60_AB_1.2ml.met, chromatography (Ultimate C18 38 50 mm 3um).

SFC: t_R = 2.494 min. Method: Column: ChiralPak IC-3 150×4.6mm I.D., 3um; Mobile phase: A: CO_2 B: IPA (0.1% Ethanolamine); Isocratic: 40% of B; Flow rate: 2.5 mL/min; Column

temperature: 40°C.

Spectra for Example 27 trans isomer 2:

LCMS: t_R = 1.871 min in 10-80CDAB_3.0min_220&254.lcm chromatography (A: Xtimate C18, 2.1*30 mm, 3um, B: XBrige Shield RP18 2.1*50mm), MS (ESI) m/z = 501.3 $[M+H]^+$.

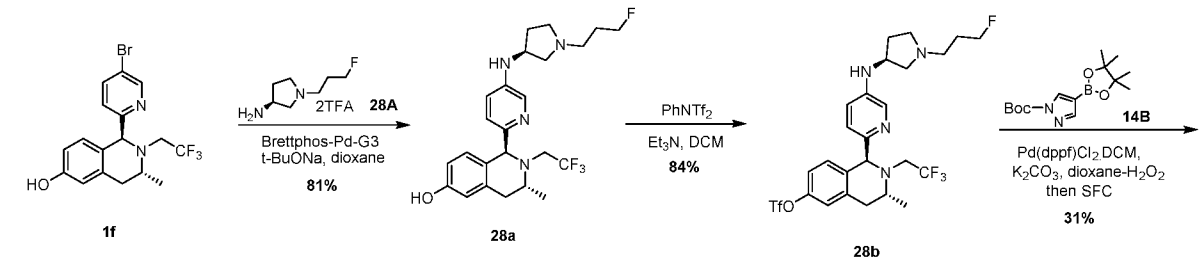
^{1}H NMR (400MHz, $CDCl_3$) δ = 7.89 (d, *J* = 2.4 Hz, 1H), 7.79 (s, 2H), 7.21 (s, 1H), 7.15 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.73 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.95 (s, 1H), 4.50 (dt, *J* = 47.2, 6.0 Hz, 2H), 4.18-4.08 (m, 1H), 4.06-4.00 (m, 1H), 3.77 (q, *J* = 6.8 Hz, 2H), 3.65-3.63 (m, 1H), 3.39 (dd, *J* = 15.2, 4.4 Hz, 1H), 2.98-2.97 (m, 2H), 2.68-2.55 (m, 3H), 1.82-1.73 (m, 2H), 1.64 (d, *J* = 9.6 Hz, 3H), 1.35 (d, *J* = 9.2 Hz, 3H), 1.09 (s, 3H), 1.05 (d, *J* = 6.4 Hz, 3H).

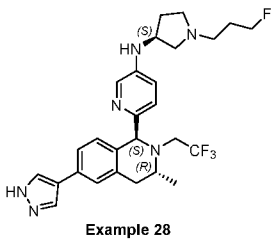
HPLC: t_R = 3.67 min in 0-60_AB_1.2ml.met, chromatography (Ultimate C18 38 50 mm 3um).

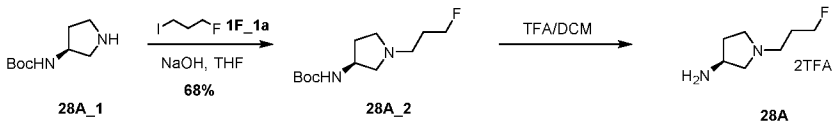
SFC: t_R = 3.609 min. Method: Column: ChiralPak IC-3 150×4.6mm I.D., 3um; Mobile phase: A: CO_2 B: IPA (0.1% Ethanolamine); Isocratic: 40% of B; Flow rate: 2.5 mL/min; Column temperature: 40°C.

Example 28

N-((S)-1-(3-fluoropropyl)pyrrolidin-3-yl)-6-((1S,3R)-3-methyl-6-(1H-pyrazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine







The procedure to prepare **28A**:

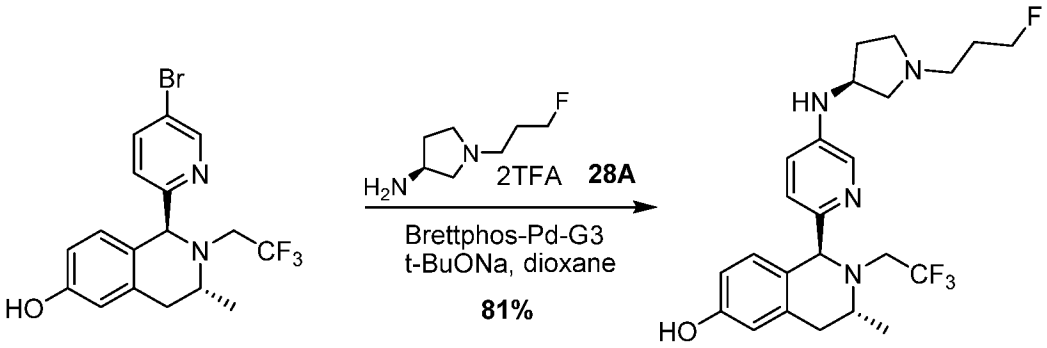
To a solution of compound **28A_1** (0.3 g, 1.6 mmol) in THF (5 mL) was added an aqueous solution of NaOH (0.64 mL, 3.2 mmol, 5 M), followed with compound **1F_1a** (184 uL, 1.7 mmol) in THF (1 mL). The resulting mixture was stirred at 20-28°C for 16 hours. The mixture was diluted with ethyl acetate (15 mL), washed with saturated aqueous solution of NH_4Cl (15 mL), the aqueous layer was extracted with ethyl acetate (15 mL x 2). The organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to give the crude product, which was purified by column chromatography on silica gel (dichloromethane/methanol = 97/3) to afford product **28A_2** (0.27 g, 68% yield) as yellow oil.

^{1}H NMR (400MHz, $CDCl_3$) δ = 4.90 (br s, 1H), 4.52 (dt, *J* = 47.2, 5.6 Hz, 2H), 4.19 (br s, 1H), 2.90 (brs, 1H), 2.68-2.57 (m, 4H), 2.41-2.21 (m, 2H), 2.00-1.82 (m, 3H), 1.44 (s, 9H).

To a solution of compound **28A_2** (0.27 g, 1.09 mmol) in dichloromethane (4 mL) was added TFA (1 mL) drop-wise. The reaction mixture was stirred at 21-28°C for 1 hour. The reaction was concentrated in vacuo to afford product **28A** (0.66 g TFA salts, purity: 61.7%) as yellow oil, which was used in the next step directly without further purification.

^{1}H NMR (400MHz, MeOD) δ = 4.58 (dt, *J* = 47.2, 5.2 Hz, 2H), 4.21-4.07 (m, 1H), 3.93-3.40 (m, 6H), 2.69-2.56 (m, 1H), 2.28-2.09 (m, 3H).

The procedure to prepare **Example 28**:

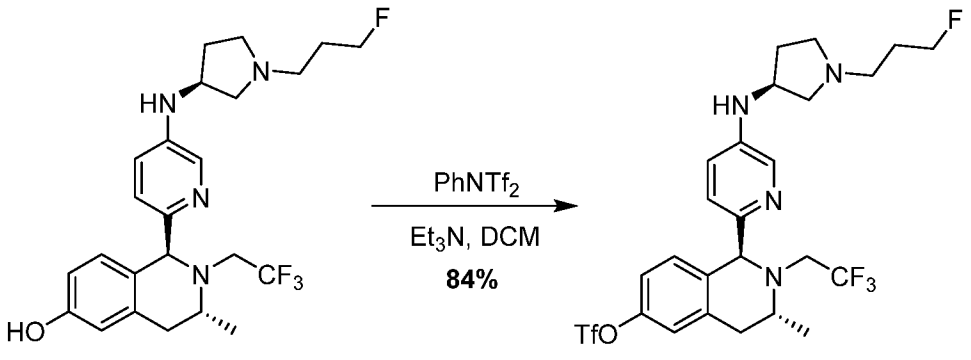


1f **28a**

To a mixture of compound **1f** (350 mg, 0.87 mmol), **28A** (593 mg, 0.97 mmol, 61.7% purity) in 1,4-dioxane (13 mL) were added Brettphos-Pd-G_3 (80 mg, 0.087 mmol) and t-BuONa (835 mg, 8.7 mmol) under nitrogen. The resulting mixture was stirred at 80°C for 2 hours under nitrogen. The mixture was combined with the pilot batch (40 mg of compound **1f**) which was carried out with same manner and filtered through a Celite Pad, the filtrate was concentrated in vacuum to give the crude product, which was purified by column chromatography on silica gel (0~6% methanol in dichloromethane) to afford compound **28a** (370 mg, 81% yield) as yellow oil.

LCMS: t_R = 0.647 min in 5-95AB_1.5min_220&254.1cm chromatography (Agilent pursult5 C18 20*2mm), MS (ESI) m/z = 467.4 $[M+H]^+$.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.82 (d, *J* = 2.4 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 6.79 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 6.51 (d, *J* = 2.0 Hz, 1H), 6.47 (dd, *J* = 8.0, 2.0 Hz, 1H), 4.85 (s, 1H), 4.52 (dt, *J* = 47.2, 5.6 Hz, 2H), 4.05 (brs, 1H), 3.49-3.42 (m, 1H), 3.23-2.90 (m, 4H), 2.84-2.66 (m, 4H), 2.55-2.44 (m, 2H), 2.41-2.32 (m, 1H), 2.03-1.88 (m, 2H), 1.82-1.73 (m, 1H), 1.05 (d, *J* = 6.8 Hz, 3H).

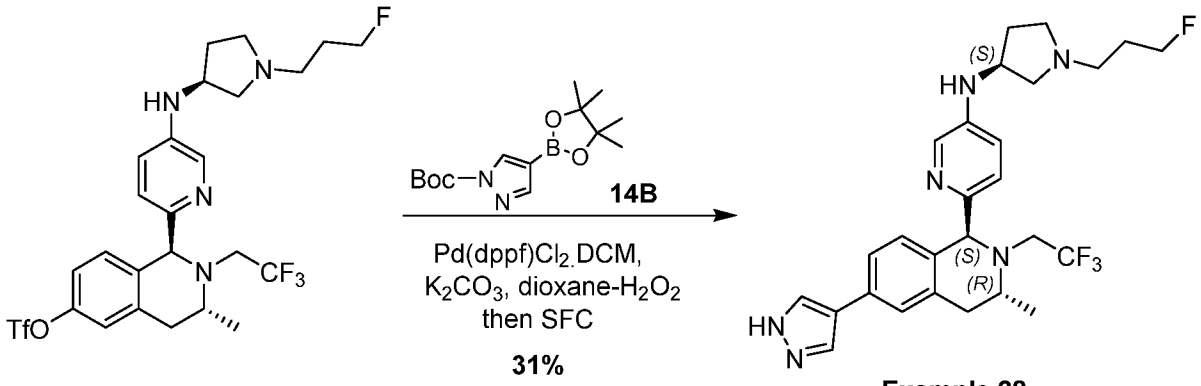


28a **28b**

To a mixture of compound **28a** (320 mg, 0.687 mmol) in dichloromethane (9 mL) was added triethylamine (277 mg, 2.75 mmol), followed by $PhNTf_2$ (368 mg, 1.03 mmol) at room temperature (21-27°C). Then the reaction mixture was stirred at 21-27°C for 16 hours. The mixture was combined with the pilot batch (50 mg of compound **28a**) which was carried out with same manner and diluted with dichloromethane (10 mL), the organic layer was washed with brine (15 mL x 2), dried over anhydrous sodium sulfate and then filtered, the filtrate was concentrated in vacuum to give the crude product, which was purified by column chromatography on silica gel (0~5% methanol in dichloromethane) to afford compound **28b** (0.4 g, 84% yield, contain little Et_3N based on NMR) as yellow oil.

LCMS: t_R = 0.848 min in 5-95AB_1.5min_220&254.lcm chromatography (Agilent Pursult 5 C18 20*2.0mm), MS (ESI) m/z = 599.4 $[M+H]^+$.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.87 (d, *J* = 2.8 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 7.03 (s, 1H), 6.98-6.95 (m, 2H), 6.86 (dd, *J* = 8.4, 2.8 Hz, 1H), 4.93 (s, 1H), 4.53 (dt, *J* = 47.2, 5.6 Hz, 2H), 4.09-4.00 (m, 1H), 3.58-3.50 (m, 1H), 3.26-3.18 (m, 2H), 3.05-2.92 (m, 2H), 2.85-2.49 (m, 6H), 2.43-2.32 (m, 1H), 2.02-1.88 (m, 2H), 1.81-1.74 (m, 1H), 1.08 (d, *J* = 6.8 Hz, 3H).



28b **Example 28**

A mixture of compound **28b** (170 mg, 0.283 mmol), compound **14B** (125 mg, 0.426 mmol), Pd(dppf)Cl_2. CH_2Cl_2 (23 mg, 0.0283 mmol) and potassium carbonate (98 mg, 0.707 mmol) was purged with nitrogen, then mixed solvents of 1, 4-dioxane and H_2O (5 mL, v/v = 4:1) was added under nitrogen. The resulting mixture was stirred at 95°C under nitrogen for 4 hours. The mixture was combined with the pilot batch (30 mg of compound **28b**) which was carried out with same manner and concentrated under vacuum to give crude product, which was purified by column chromatography on silica gel (0~7% methanol in dichloromethane) to afford 100 mg of chemical pure product. It was further purified by chiral SFC (DAICEL CHIRALCEL OD-H (250mm*30mm, 5um); Condition: 30% EtOH (0.1% ammonia) in CO_2; Flow rate: 60 mL/min] to afford **Example 28** (53.9 mg, 31% average yield) as a white solid.

LCMS: t_R = 2.698 min in 0-60AB_7min_220&254.lcm chromatography (Xtimate C18 2.1*30mm), MS (ESI) m/z = 517.1 $[M+H]^+$.

HPLC: t_R = 3.91 min in 0-60_AB_1.2ml.met.chromatography (Ultimate C18 3*50mm 3um).

SFC (Method 1): t_R = 3.494 min; 98.58% purity. Method: Column: Chiralpak AS-3 150×4.6mm I.D., 3um; Mobile phase: A: CO_2 B: ethanol (0.05% DEA); Gradient: from 5% to 40% of B in 5 min and from 40% to 5% of B in 0.5 min, hold 5% of B for 1.5 min; Flow rate: 2.5mL/min; Column temperature: 35°C.

SFC (Method 2): t_R = 3.073 min; 97.51% purity. Method: Column: Chiralcel OJ-3 150×4.6mm I.D., 3um; Mobile phase: A: CO_2 B:ethanol (0.05% DEA); Gradient: from 5% to 40% of B in 5 min and from 40% to 5% of B in 0.5 min, hold 5% of B for 1.5 min; Flow rate:

2.5 mL/min; Column temperature: 35°C.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.89 (d, *J* = 2.8 Hz, 1H), 7.78 (s, 2H), 7.24 (s, 1H), 7.19 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.85 (dd, *J* = 8.8, 2.8 Hz, 1H), 4.93 (s, 1H), 4.52 (dt, *J* = 46.8, 5.6 Hz, 2H), 4.11-3.95 (m, 2H), 3.59-3.49 (m, 1H), 3.28-3.14 (m, 2H), 3.08-2.87 (m, 2H), 2.76-2.55 (m, 5H), 2.49-2.41 (m, 1H), 2.40-2.29 (m, 1H), 2.00-1.85 (m, 2H), 1.77-1.68 (m, 1H), 1.10 (d, *J* = 6.8 Hz, 3H).

Example 29

N-((R)-1-(3-fluoropropyl)pyrrolidin-3-yl)-6-((1S,3R)-3-methyl-6-(1H-pyrazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine

The synthesis of **Example 29** is analogous to the synthesis of **Example 28**. The spectra for **Example 29** are:

LCMS: t_R = 2.687 min in 0-60AB_7min_220&254.lcm chromatography (Xtimate C18 2.1*30mm), MS (ESI) m/z = 517.2 $[M+H]^+$.

HPLC: t_R = 3.90 min in 0-60_AB_1.2ml.met.chromatography (Ultimate C18 3*50mm 3um).

SFC: t_R = 3.408 min; 93.26% purity. Method: Column: Chiralpak AS-3 150×4.6mm I.D., 3um Mobile phase: A: CO_2 B: ethanol (0.05% DEA) Gradient: from 5% to 40% of B in 5 min and from 40% to 5% of B in 0.5min, hold 5% of B for 1.5 min Flow rate: 2.5mL/min Column temp.: 35℃.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.89 (d, *J* = 2.8 Hz, 1H), 7.78 (s, 2H), 7.25 (s, 1H), 7.22-7.16 (m, 2H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.85 (dd, *J* = 8.4, 2.8 Hz, 1H), 4.93 (s, 1H), 4.53 (dt, *J* = 47.6, 6.0 Hz, 2H), 4.11-3.95 (m, 2H), 3.59-3.49 (m, 1H), 3.28-3.14 (m, 2H), 3.08-2.97 (m, 2H), 2.95-2.86 (m, 1H), 2.76-2.58 (m, 5H), 2.47-2.40 (m, 1H), 2.40-2.29 (m, 1H), 2.00-1.85 (m, 2H), 1.77-1.68 (m, 2H), 1.10 (d, *J* = 6.8 Hz, 3H).

Example 30

3-((1S,3R)-1-(2,6-difluoro-4-(((S)-1-(3-fluoropropyl)pyrrolidin-3-yl)amino)phenyl)-3-me

thyl-6-(1H-pyrazol-4-yl)-3,4-dihydroisoquinolin-2(1H)-yl)-2,2-difluoropropan-1-ol

The synthesis of **Example 30** is analogous to the synthesis of **Example 28**. The spectra for **Example 30** are:

LCMS: t_R = 1.831 min in 10-80CD_3min_220&254_Agilent.lcm chromatography (A: Xtimate C18 2.1*30mm, 3um; B: XBrige Shield RP18 2.1*50mm), MS (ESI) m/z = 564.3 $[M+H]^+$.

HPLC: t_R = 4.49 min in 10-80_AB_15MIN.met.chromatography (YMCpack-ODS AQ 150*4.6MM 5um).

SFC: t_R = 2.920 min; 100% purity.

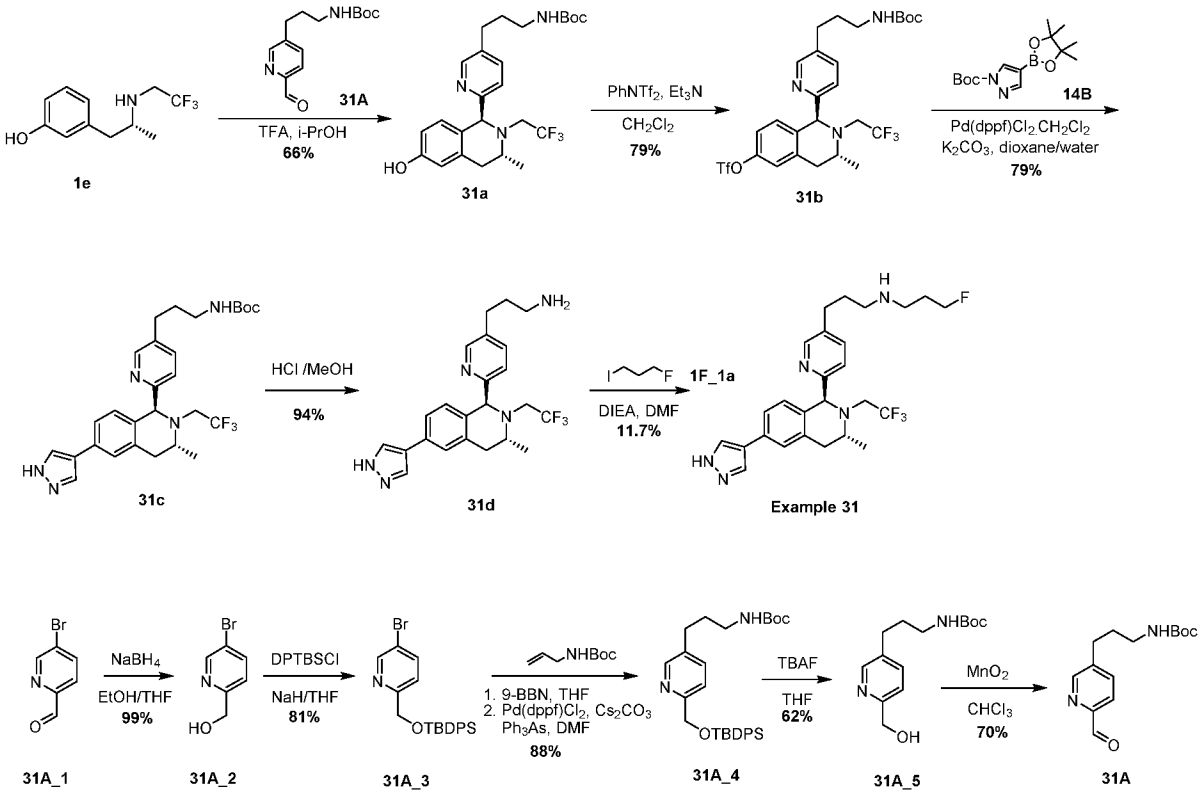
Method : Column: Chiralcel OJ-3 100×4.6mm I.D., 3um; Mobile phase: A: CO_2 B: ethanol (0.05% DEA); Gradient: from 5% to 40% of B in 4.5min and hold 40% for 2.5 min, then 5% of B for 1 min;

Flow rate: 2.8 mL/min; Column temperature: 40°C.

^{1}H NMR (400MHz, CD_3OD): δ = 7.89 (s, 2H), 7.35-7.26 (m, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.13 (d, *J* = 12.4 Hz, 2H), 5.07 (s, 1H), 4.48 (dt, *J* = 47.2, 6.0 Hz, 2H), 3.99-3.88 (m, 1H), 3.84-3.67 (m, 1H), 3.66-3.54 (m, 1H), 3.43-3.32 (m, 1H), 3.30-3.21 (1H), 3.19-3.04 (m, 1H), 2.92 (dd, *J* = 10.0, 7.2 Hz, 1H), 2.82-2.68 (m, 2H), 2.68-2.54 (m, 4H), 2.49 (dd, *J*= 9.6, 4.4 Hz, 1H), 2.37-2.23 (m, 1H), 1.99-1.81 (m, 2H), 1.75-1.62 (m, 1H), 1.05 (d, *J* = 6.4 Hz, 3H).

Example 31

3-fluoro-N-(3-(6-((1S,3R)-3-methyl-6-(1H-pyrazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-yl)propyl)propan-1-amine



The procedure to prepare **31A**:

To a solution of compound **31A_1** (5 g, 26.9 mmol) in a mixture solvent of EtOH (60 mL) and THF (20 mL) was added $NaBH_4$ (406 mg, 10.7 mmol). The reaction mixture was stirred for 45 minutes at 1-7°C and 2.5 mL water was added. TLC showed the desired product was observed. The reaction mixture was diluted with DCM (50 mL) and water (50 mL), separated. The aqueous layer was extracted with DCM (50 mL x 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered, concentrated in vacuo and purified by column chromatography on silica gel (0-10% of ethyl acetate in petroleum ether) to give compound **31A_2** (5 g, 99% yield) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$) : δ = 8.63 (d, *J* = 2.0 Hz, 1H), 7.82 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 4.74 (d, *J* = 3.6 Hz, 2H), 3.34 (br s, *J* = 5.2 Hz, 1H).

To a solution of compound **31A_2** (5 g, 26.6 mmol) in THF (90 mL) was added sodium hydride (1.6 g, 39.9 mmol) in 0°C. The mixture was stirred at 2-9°C for 30 minutes. Then DPTBSCl (8 g, 29.3 mmol) was added and the resulting mixture was stirred at 2-9°C for 2 hours. TLC showed the desired product was observed. The

reaction was diluted with ethyl acetate (80 mL) and water (50 mL), separated. The aqueous layer was extracted with ethyl acetate (80 mL x 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered, concentrated in vacuo and purified by column chromatography on silica gel (0-10% of ethyl acetate in petroleum ether) to give compound **31A_3** (9 g, 81% yield) as a colorless oil.

^{1}H NMR (400MHz, $CDCl_3$) : δ = 8.54 (d, *J* = 2.0 Hz, 1H), 7.87 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 4H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.46-7.37 (m, 6H), 4.83 (s, 2H), 1.14 (s, 9H).

To a solution of compound **31A_3** (1.66 g, 10.5 mmol) in THF (70 mL) was added 9-BBN (21 ml, 10.5 mmol, 0.5M in THF), the resulting mixture was stirred at room temperature 21-25°C for 2 hours. To the mixture was added 0.6 mL water. A 250 mL three-necked round bottom flask equipped with mechanical stirrer, added *tert*-butyl allylcarbamate (3 g, 7.0 mmol), Cs_2CO_3 (6.9 g, 21.0 mmol), $Pd(dppf)Cl_2$ (258 mg, 0.35 mmol) and Ph_3As (117 mg, 0.35 mmol) in DMF (70 mL) under nitrogen. The above reaction solution was added and stirred at 60°C for 15 hours. The reaction was diluted with ethyl acetate (100 mL) and water (100 mL), then separated. The aqueous layer was extracted with ethyl acetate (50 mL x 2). The combined organic layers were wash with brine (50 mL), dried over anhydrous sodium sulfate, filtered, concentrated in vacuo and purified by column chromatography on silica gel (0-65% of ethyl acetate in petroleum ether) to give compound **31A_4** (3.1 g, 88% yield) as a yellow oil.

LCMS: t_R = 0.938 min in 5-95AB_220&254 Shimadzu (Agilent Pursult 5 C18 20*2.0mm), MS (ESI) m/z = 505.8 $[M+H]^+$.

^{1}H NMR (400MHz, $CDCl_3$): δ = 8.31 (d, *J* = 1.6 Hz, 1H), 7.69 (dd, *J* = 8.0, 1.6 Hz, 4H), 7.63-7.53 (m, 2H), 7.47-7.33 (m, 6H), 4.86 (s, 2H), 3.20-3.10 (m, 2H), 2.64 (t, *J* = 8.0 Hz, 2H), 1.83-1.76 (m, 2H), 1.46 (s, 9H), 1.13 (s, 9H).

To a solution of compound **31A_4** (3.1 g, 6.15 mmol) in THF (30 mL) was added a solution of TBAF (12.3 mL, 12.3 mmol, 1M in THF). The reaction mixture was stirred for 15 hours at 19-26°C. The reaction was diluted with ethyl acetate (20 mL)

and water (20 mL), and then separated. The aqueous layer was extracted with ethyl acetate (20 mL x 2), dried over anhydrous sodium sulfate, filtered, concentrated and purified by column chromatography on silica gel (0-30% of ethyl acetate in petroleum ether) to give compound **31A_5** (1 g, 62% yield) as yellow oil.

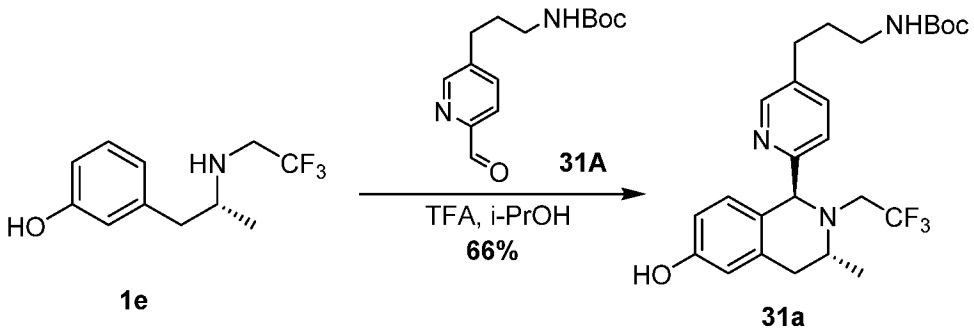
LCMS: t_R = 0.608 min in 5-95AB_220&254 Shimadzu (Agilent Pursult 5 C18 20*2.0mm), MS (ESI) m/z = 267.2 $[M+H]^+$.

To a solution of compound **31A_5** (1 g, 3.76 mmol) in DCM (20 mL) was added MnO_2 (3.9 g, 45.12 mmol). The mixture was stirred at 18-28°C for 4 hours. The reaction was filtered, the filtration was concentrated, and purified by column chromatography on silica gel (0-50% of ethyl acetate in petroleum ether) to give compound **31A** (700 mg, 70% yield) as yellow oil.

LCMS: t_R = 0.753 min in 5-95AB_220&254 Shimadzu (Agilent Pursult 5 C18 20*2.0mm), MS (ESI) m/z = 265.2 $[M+H]^+$.

^{1}H NMR (400MHz, CDCl3) : δ = 10.06 (s, 1H), 8.63 (d, *J* = 1.6 Hz, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.70 (dd, *J* = 7.6, 1.6 Hz, 1H), 3.20 (q, *J* = 6.4 Hz, 2H), 2.76 (t, *J* = 7.6 Hz, 2H), 1.91-1.83 (m, 2H), 1.45 (s, 9H).

The procedure to prepare **31A**:



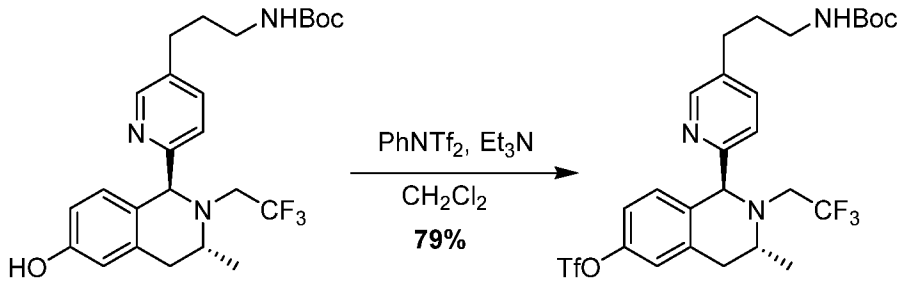
1e **31a**

To a solution of compound **31A** (626 mg, 2.68 mmol) in *i*-PrOH (31 mL) was added compound **1e** (780 mg, 2.95 mmol) and TFA (916 mg, 8.04 mmol). The resulting mixture was stirred at 21-28°C for 3 hours. The reaction was diluted with DCM (30 mL) and saturated $NaHCO_3$ solution (30 mL), separated. The aqueous layer was extracted with DCM (30 mL x 2). The combined organic layers were dried over

anhydrous sodium sulfate, filtered, concentrated and purified by column chromatography on silica gel (0-50% of ethyl acetate in petroleum ether) to give compound **31a** (850 mg, 66% yield) as yellow oil.

LCMS: t_R = 0.823 min in 5-95AB_220&254 Shimadzu (Agilent Pursult 5 C18 20*2.0mm), MS (ESI) m/z = 480.7 $[M+H]^+$.

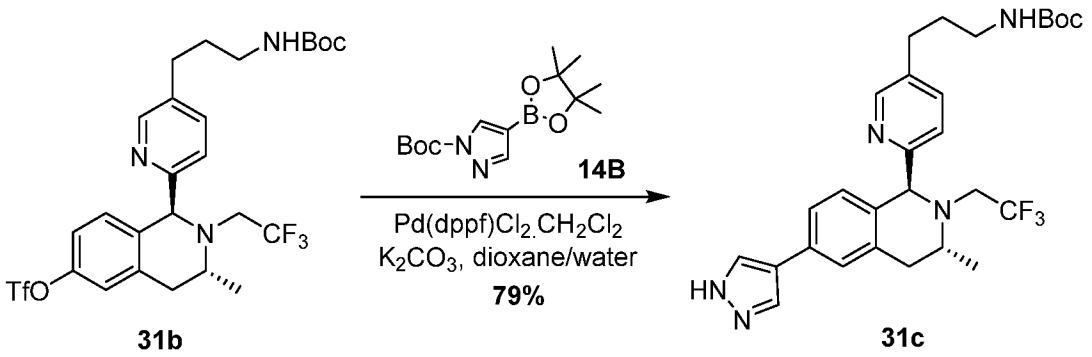
^{1}H NMR (400MHz, $CDCl_3$) δ = 8.30 (s, 1H), 7.47 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 6.52 (s, 1H), 6.49-6.43 (m, 1H), 4.94 (s, 1H), 4.61 (s, 1H), 3.50-3.34 (m, 1H), 3.27-3.11 (m, 3H), 3.06 (dd, *J* = 16.4, 4.4 Hz, 1H), 3.01-2.85 (m, 1H), 2.61 (t, *J* = 7.6 Hz, 2H), 2.51 (dd, *J* = 16.4, 6.4 Hz, 1H), 1.87-1.77 (m, 2H), 1.45 (s, 10H), 1.05 (d, *J* = 6.4 Hz, 3H).



31a **31b**

To a solution of compound **31a** (550 mg, 1.15 mmol) in DCM (11 mL) was added Et_3N (232 mg, 2.3 mmol) and $PhNTf_2$ (492 mg, 1.38 mmol). The resulting mixture was stirred at 22-29°C for 15 hours. The reaction was diluted with DCM (30 mL) and water (25 mL), separated. The aqueous layer was extracted with DCM (30 mL x 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered, concentrated and purified by column chromatography on silica gel (0-20% of ethyl acetate in petroleum ether) to give compound **31b** (560 mg, 79% yield) as yellow oil.

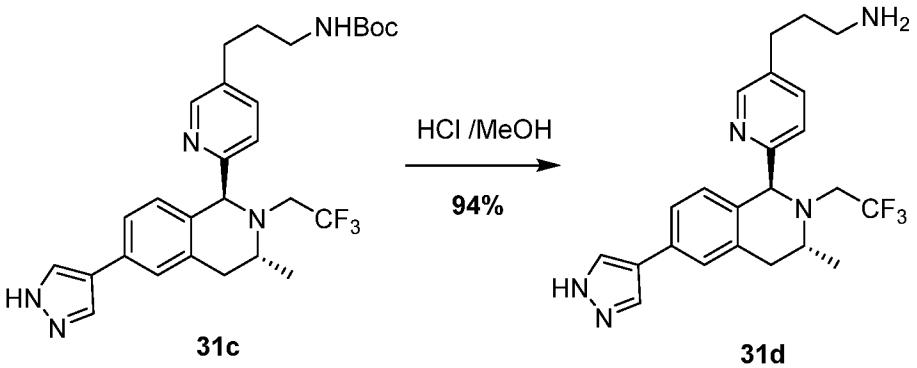
LCMS: t_R = 0.933 min in 5-95AB_220&254 Shimadzu (Agilent Pursult 5 C18 20*2.0mm), MS (ESI) m/z = 612.4 $[M+H]^+$.



A solution of compound **31b** (560 mg, 0.9 mmoL), potassium carbonate (397 mg 1.35 mmol) $Pd(dppf)Cl_2.CH_2Cl_2$ (73 mg, 0.09 mmol) and compound **14B** (397 mg, 1.35 mmol) in 1,4-dioxane (12 mL) and water (1.2 mL) under nitrogen was stirred at 100°C for 15 hours. The reaction was diluted with DCM (30 mL) and water (20 mL), separated. The aqueous layer was extracted with DCM (30 mL x 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered, concentrated and purified by column chromatography on silica gel (0-50% of ethyl acetate in petroleum ether) to give compound **31c** (380 mg, 79% yield) as yellow oil.

LCMS: t_R = 0.803 min in 5-95AB_220&254 Shimadzu (Agilent Pursult 5 C18 20*2.0mm), MS (ESI) m/z = 530.4 $[M+H]^+$.

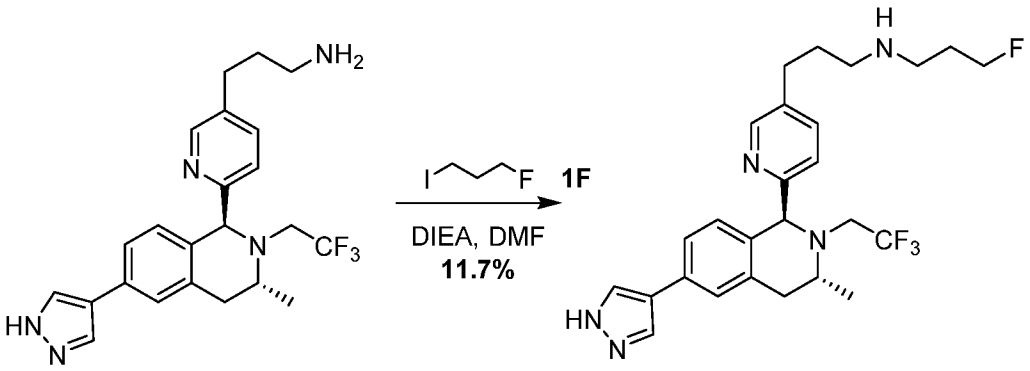
^{1}H NMR (400MHz, $CDCl_3$) δ = 8.27 (d, *J* = 1.6 Hz, 1H), 7.71 (s, 2H), 7.42-7.38 (m, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.18 (s, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 4.95 (s, 1H), 4.52 (s, 1H), 3.54-3.40 (m, 1H), 3.25-3.15 (m, 1H), 3.20-3.13 (m, 3H), 2.99-2.85 (m, 1H), 2.62-2.52 (m, 3H), 1.77-1.69 (*m*, 2H), 1.37 (s, 9H), 1.03 (d, *J* = 6.4 Hz, 3H)



To a solution of **31c** (380 mg, 0.718 mmol) in DCM (4 mL) was added HCl/MeOH (4 mL, 4M), then the mixture was stirred at room temperature 22-24°C for 2 hours. The mixture was adjusted to pH=9 with saturated Na_2CO_3 solution, then the mixture was extracted with DCM (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give compound **31d** (290 mg, 94% yield) as brown oil.

LCMS: t_R = 0.658 min in 5-95AB_220&254 Shimadzu (Agilent Pursult 5 C18 20*2.0mm), MS (ESI) m/z = 430.3 $[M+H]^+$.

^{1}H NMR (400MHz, MeOD) δ = 8.31 (d, *J* = 1.6 Hz, 1H), 7.91 (s, 2H), 7.63 (dd, *J*= 8.0, 2.0 Hz, 1H), 7.39 (s, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.25 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 1H), 4.97 (s, 1H), 3.58-3.50 (m, 1H), 3.44-3.35 (m, 1H), 3.30-3.26 (m, 1H), 3.01-2.88 (m, 1H), 2.74-2.62 (m, 5H), 1.82-1.74 (*m*, 2H), 1.10 (d, *J* = 6.8 Hz, 3H)



31d **Example 31**

To a solution of compound **31d** (320 mg, 0.745 mmoL) in DMF (10 mL) was added DIEA (192 mg, 1.488 mmol) and compound **1F_1a** (140 mg, 0.745 mmol). The resulting mixture was stirred at 20-28°C for 15 hours. The reaction was diluted with DCM (20 mL) and water (20 mL), separated. The aqueous layer was extracted with DCM (10 mL x 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered, concentrated and purified by column chromatography on silica gel (0-10% of methanol in dichloromethane) to give 120 mg impure product which was further purified by SFC (Column: Phenomenex-Amylose-1 (250mm*30mm,5um), Condition: 40% EtOH (0.1% NH_3H_2O), Flow rate: 50 mL/min) to afford **Example 31**

(4.67 min, 38.6 mg) as a yellow solid and **cis isomer of Example 31** (5.17 min, 4.2 mg) as a yellow solid.

Spectra of Example 31:

LCMS: t_R = 0.688 min in 5-95AB_220&254 Shimadzu (Agilent Pursult 5 C18 20*2.0mm), MS (ESI) m/z = 490.4 $[M+H]^+$.

SFC: t_R = 4.679 min; 97.34% purity. Method: Column: Chiralpak AD-3 150×4.6mm I.D., 3um Mobile phase: A: CO_2 B:ethanol (0.05% DEA); Gradient: from 5% to 40% of B in 5 min and hold 40% for 2.5 min, then 5% of B for 2.5 min; Flow rate: 2.5 mL/min; Column temp.: 35°C.

HPLC: t_R = 2.77 min in 10-80_AB_1.2ml METHOD (Ultimate C18 3*50mm 3um).

^{1}H NMR (400MHz, MEOD) δ = 8.32 (d, *J* = 1.2 Hz, 1H), 7.91 (s, 2H), 7.64 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.39 (s, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.26 (d, *J* = 9.2 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 4.97 (s, 1H), 4.50 (dt, *J* = 47.2, 6.0 Hz, 2H), 3.64-3.49 (m, 1H), 3.48-3.35 (m, 1H), 3.30-3.24 (m, 1H), 2.87-3.07 (m, 1H), 2.74-2.61 (m, 7H), 1.96-1.88 (m, 1H), 1.88-1.78 (m, 3H), 1.10 (d, *J* = 6.8 Hz, 3H).

Spectra of the cis isomer of Example 31:

LCMS: t_R = 0.683 min in 5-95AB_220&254 Shimadzu (Agilent Pursult 5 C18 20*2.0mm), MS (ESI) m/z = 490.4 $[M+H]^+$.

SFC: t_R = 5.179 min; 90.59% purity. Method: Column: Chiralpak AD-3 150×4.6mm I.D., 3um, Mobile phase: A: CO_2 B:ethanol (0.05% DEA); Gradient: from 5% to 40% of B in 5 min and hold 40% for 2.5 min, then 5% of B for 2.5 min; Flow rate: 2.5 mL/min; Column temp.: 35°C.

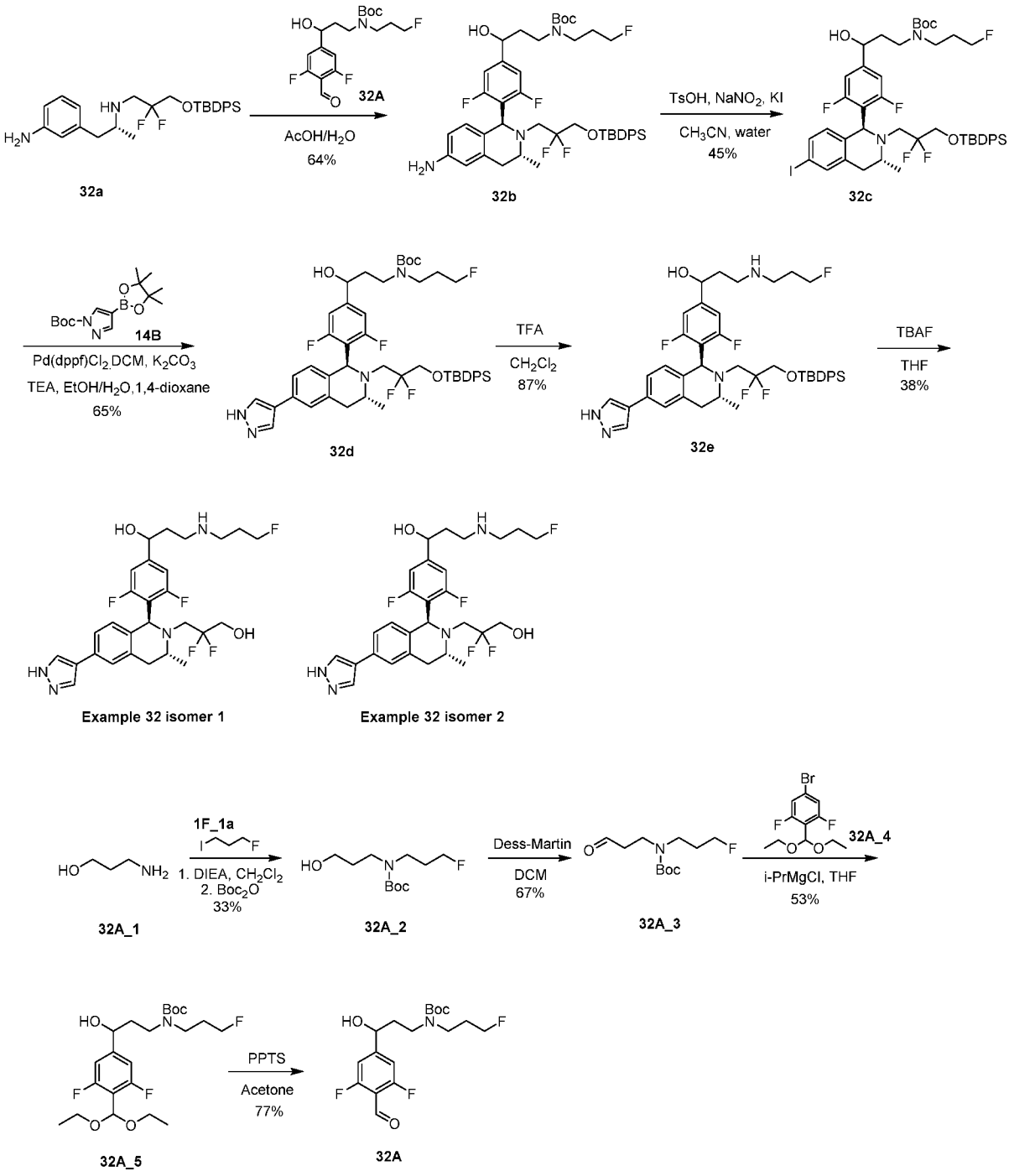
HPLC: t_R = 2.69 min in 10-80_AB_1.2ml METHOD (Ultimate C18 3*50mm 3um).

^{1}H NMR (400MHz, MeOD) δ = 8.33 (d, *J* = 2.0 Hz, 1H), 7.90 (s, 2H), 7.68 (dd, *J* = 8.0, 2.4 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.35 (s, 1H), 7.27 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 5.15 (s, 1H), 4.51 (dt, *J* = 47.6, 6.0 Hz, 2H), 3.48-3.36 (m, 2H), 3.25-5.17 (m, 1H),

2.89-2.70 (m, 8H), 2.01-1.84 (m, 4H), 1.33 (d, J = 6.0 Hz, 3H).

Example 32

3-((1S,3R)-1-(2,6-difluoro-4-(3-((3-fluoropropyl)amino)-1-hydroxypropyl)phenyl)-3-methyl-6-(1H-pyrazol-4-yl)-3,4-dihydroisoquinolin-2(1H)-yl)-2,2-difluoropropan-1-ol



The procedure to prepare **32A**:

To a solution of compound **32A_1** (10 g, 133 mmol) in DMF (70 mL) was added DIEA (34.3 g, 266 mmol) and compound **1F_1a** (27.6 g, 146 mmol). The mixture was stirred at room temperature (24-32°C) for 15 hours. Then DIEA (17.1 g, 133 mmol) and Boc_2O (29 g, 133 mmol) were added to above mixture and stirred at room temperature (24-32°C) for another 15 hours. The reaction was diluted with ethyl acetate (100 mL) and water (100 mL), separated. The aqueous layer was extracted with ethyl acetate (100 mL x 2). The combined organic layers were wash with brine (100 mL), dried over anhydrous sodium sulfate, filtered, concentrated in vacuo and purified by column chromatography on silica gel (0-10% of ethyl acetate in petroleum ether) to give compound **32A_2** (10.5 g, 33% yield) as a yellow oil.

^{1}H NMR (400MHz, $CDCl_3$) δ = 4.46 (dt, *J* = 47.2, 6.0 Hz, 2H), 3.81 (s, 1H), 3.53 (br s, 2H), 3.40-3.30 (m, 4H), 3.26 (t, *J* = 6.0 Hz, 1H), 1.98-1.77 (m, 2H), 1.73-1.60 (m, 2H), 1.43 (s, 9H).

To a solution of compound **32A_2** (10.5 g, 44.6 mmol) in dichloromethane (100 mL) was added Dess-Martin reagent (28.4 g, 67.0 mmol) at 0°C. The mixture was stirred at room temperature (24-29°C) for 2 hours. The reaction was diluted with dichloromethane (50 mL) and a mixture saturated solution of $NaHCO_3$ and Na_2SO_3 (v/v: 3/1, 100 mL), separated. The aqueous layer was extracted with dichloromethane (100 mL x 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered, concentrated in vacuo and purified by column chromatography on silica gel (0-10% of ethyl acetate in petroleum ether) to give compound **32A_3** (7 g, 67% yield) as a colorless oil.

^{1}H NMR (400MHz, $CDCl_3$) δ = 9.78 (t, *J* = 1.6 Hz, 1H), 4.46 (dt, *J* = 47.2, 6.0 Hz, 2H), 3.52 (d, *J* = 6.4 Hz, 2H), 3.32 (t, *J* = 6.8 Hz, 2H), 2.70 (t, *J* = 6.0 Hz, 2H), 2.01-1.79 (m, 2H), 1.43 (s, 9H).

To a solution of compound **32A_4** (3.58 g, 12.1 mmol) in THF (20 mL) was added a solution of *i*-PrMgCl (7.3 mL, 14.5 mmol, 2 M in THF) drop wise at 0°C under nitrogen. The reaction was stirred at room temperature (27-32°C) for 1 hour. Then compound **32A_3** (3.39 g, 14.5 mmol) was added drop wise to the above reaction at 0°C. After that, the reaction was stirred at room temperature (27-32°C) for 2 hours

under nitrogen. The mixture was quenched with saturated aqueous solution of NH_4Cl to pH = 7. The resulting mixture was extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (50 mL) and dried over anhydrous sodium sulfate, filtered, concentrated *in vacuo* and purified by column chromatography on silica gel (10~30% of ethyl acetate in petroleum ether) to give compound **32A_5** (2.88 g, 53% yield) as a colorless oil.

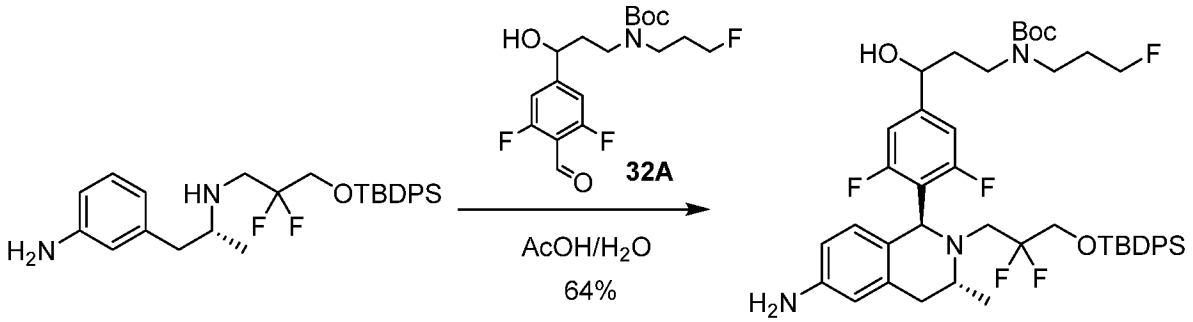
^{1}H NMR (400MHz, $CDCl_3$): δ = 6.91 (d, *J* = 9.2 Hz, 2H), 5.71 (s, 1H), 4.49 (dt, *J* = 47.2, 5.6 Hz, 2H), 4.52-4.45 (m, 1H), 3.82-3.70 (m, 2H), 3.66-3.55 (m, 2H), 3.50-3.26 (m, 4H), 2.03-1.88 (m, 4H), 1.48 (s, 9H), 1.25 (t, *J* = 6.8 Hz, 6H).

A solution of compound **32A_5** (3.5 g, 7.79 mmol) and PPTS (783 mg, 3.89 mmol) in acetone (90 mL) and water (9 mL) was heated at 60°C under nitrogen for 16 hours. The reaction mixture was concentrated *in vacuo* to give the residue. The residue was diluted with water (90 mL) and ethyl acetate (100 mL). After separated, the aqueous layer was extracted with ethyl acetate (100 mL x 2). The combined organic layers were washed with brine (100 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, concentrated and purified by column chromatography on silica gel (10~20% of ethyl acetate in petroleum ether) to give compound **32A** (2.26 g, 77% yield) as a brown solid.

LCMS: t_R = 0.863 min in 5-95AB_220&254 Shimadzu (Agilent Pursult 5 C18 20*2.0mm), MS (ESI) m/z = 276.1 $[M+H-100]^+$.

^{1}H NMR (400MHz, $CDCl_3$): δ = 10.31 (s, 1H), 7.03 (d, *J* = 10.0 Hz, 2H), 4.67-4.36 (m, 4H), 3.57-3.02 (m, 4H), 2.03-1.86 (m, 4H), 1.48 (s, 9H).

The procedure to prepare **Example 32 isomer 1** and **example 32 isomer 2**:

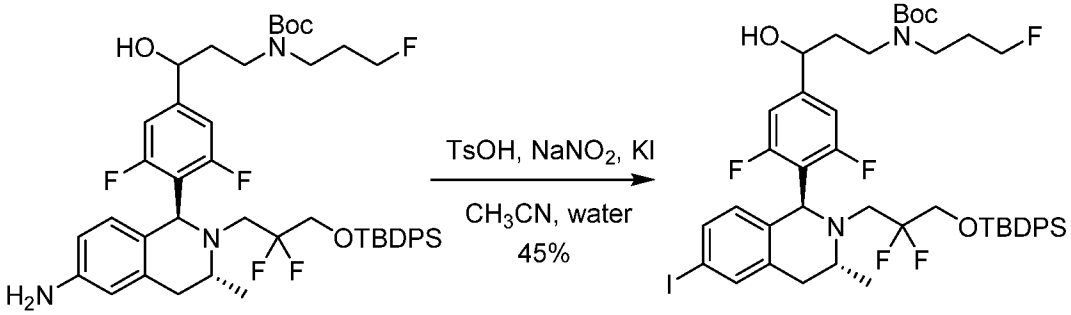


32a **32b**

To a solution of compound **32a** (800 mg, 1.66 mmol) and compound **32A** (624 mg, 1.66 mmol) in AcOH (6 mL) was added water (149 mg, 8.29 mmol), the resulting mixture was stirred at 80°C for one hour under nitrogen. The reaction was poured into a mixture of saturated aqueous solution of $NaHCO_3$ (20 mL) and brine (25 mL), extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, concentrated purified by column chromatography on silica gel (10-50% of ethyl acetate in petroleum ether) to give compound **32b** (900 mg, 64% yield) as yellow oil.

LCMS: t_R = 1.043 min in 5-95AB_220&254 Shimadzu (Agilent Pursult 5 C18 20*2.0mm), MS (ESI) m/z = 840.7 $[M+H]^+$.

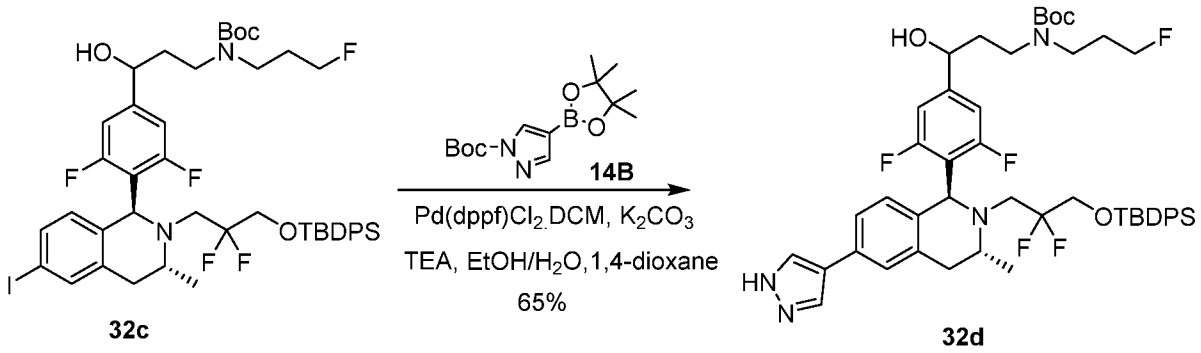
^{1}H NMR (400MHz, $CDCl_3$) δ = 7.66-7.59 (m, 4H), 7.45-7.38 (m, 6H), 6.75-6.65 (m, 2H), 6.49 (dd, *J* = 7.6, 0.8 Hz, 1H), 6.43 (d, *J* = 2.0 Hz, 1H), 6.38-6.35 (m, 1H), 5.14 (s, 1H), 4.48 (dt, *J* = 47.2, 5.6 Hz 2H), 4.46-4.42 (m, 1H), 4.00-3.86 (m, 1H), 3.84-3.80 (m, 1H), 3.56-3.36 (m, 4H), 3.19-3.06 (m, 3H), 2.77-2.65 (m, 1H), 2.42 (dd, *J* = 15.6, 3.6 Hz, 1H), 2.01-1.75 (m, 4H), 1.47 (s, 9H), 1.03 (s, 9H), 1.02 (d, *J* = 6.0 Hz, 3H).



32b **32c**

To a stirred mixture of compound **32b** (1.7 g, 2.02 mmol), TsOH (1.04 g, 6.06 mmol) in CH_3CN (50 mL) was added a solution of $NaNO_2$ (279 mg, 4.04 mmol) and KI (838 mg, 5.05 mmol) in water (10 mL) at 0°C. The mixture was stirred at room temperature (27-36°C) for 3 hours under nitrogen to give a brown solution. The mixture was quenched with saturated aqueous solution of $NaHCO_3$ (30 mL) and extracted with ethyl acetate (30 ml × 3). The combined organic layer was washed with brine (35 mL), dried over anhydrous sodium sulfate, filtered, concentrated and purified by column chromatography on silica gel (0-20% of ethyl acetate in petroleum ether) to give compound **32c** (860 mg, 45% yield) as yellow solid.

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.65-7.57 (m, 4H), 7.48-7.34 (m, 8H), 6.80-6.65 (m, 2H), 6.46 (d, *J* = 8.0 Hz, 1H), 5.17 (s, 1H),4.48 (dt, *J* = 47.2, 5.6 Hz, 2H), 4.47-4.42 (m, 1H),3.98-3.74 (m, 2H), 3.65-3.34 (m, 3H), 3.27-2.97 (m, 4H), 2.86-2.59 (m, 1H), 2.48 (dd, *J* = 14.0,4.0 Hz, 1H), 2.05-1.64 (m, 4H), 1.47 (s, 9H), 1.04-0.99 (m, 12H).

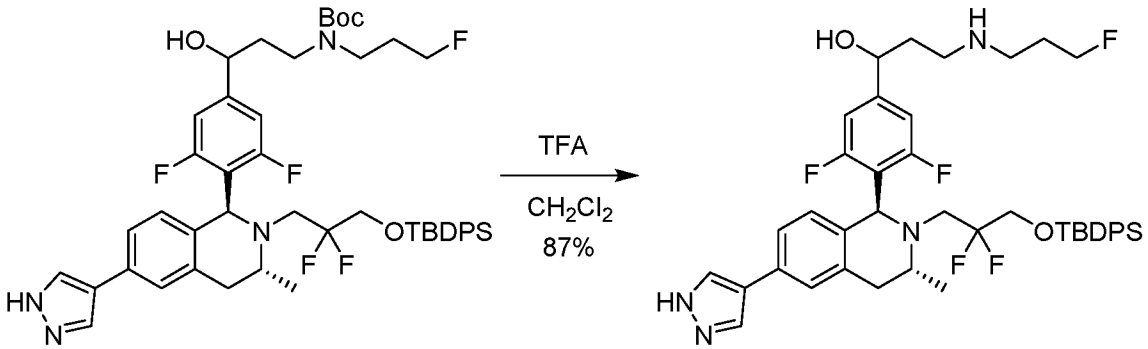


32c **32d**

To a solution of compound **32c** (360 mg, 0.053 mmol) and compound **14B** (223 mg, 0.758 mmol) in 1,4-dioxane (3.5 mL) was added K_2CO_3 (209 mg,1.516 mmol), followed by water (0.7 mL) and EtOH (1.4 mL) at room temperature (27-37°C), then $Pd(dppf)Cl_2.CH_2Cl_2$ (46 mg, 0.057 mmol) was added quickly. After degassed and purged with nitrogen for three times, the resulting mixture was stirred at 70°C for 16 hours under nitrogen. The reaction mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (30 mL x 2). The combined organic layers were washed with brine (25 mL), dried over anhydrous sodium sulfate, filtered, concentrated purified by column chromatography on silica gel (0~50% of ethyl acetate in petroleum ether) to give compound **32d** (220 mg, 65% yield) as yellow solid.

LCMS: t_R = 1.153 min in 5-95AB_220&254 Shimadzu (Agilent Pursult 5 C18 20*2.0mm), MS (ESI) m/z = 891.8 $[M+H]^+$.

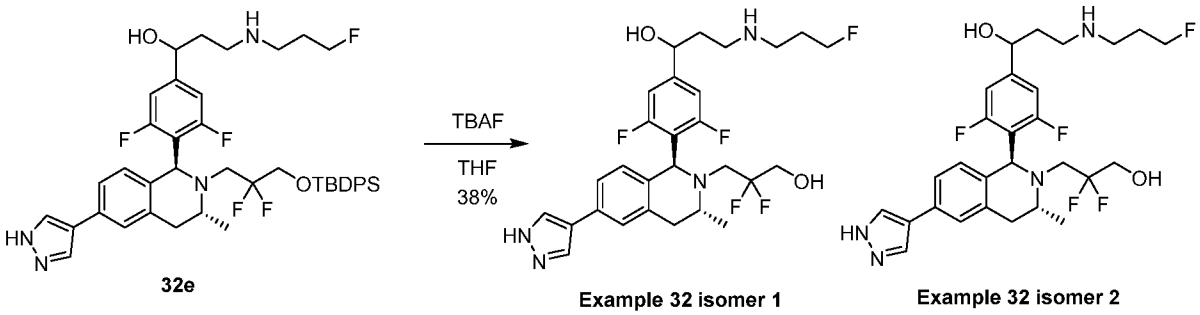
^{1}H NMR (400MHz, $CDCl_3$) δ = 7.82 (s, 2H), 7.68-7.58 (m, 4H), 7.48-7.35 (m, 6H), 7.24 (d, *J* = 0.8 Hz 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 6.80-6.70 (m, 3H), 5.25 (s, 1H), 4.48 (dt, *J* = 47.2, 6.0 Hz, 2H), 4.48-4.42 (m, 1H), 4.03-3.78 (m, 2H), 3.67-3.39 (m, 3H), 3.32-2.96 (m, 4H), 2.83-2.66 (m, 1H), 2.57 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.02-1.79 (m, 4H), 1.47 (s, 9H), 1.09-0.99 (m, 12H).



32d **32e**

A solution of compound **32d** (220 mg, 0.247 mmol) in TFA (1 mL) and dichloromethane (3 mL) was stirred at room temperature (26-34°C) for one hour under nitrogen. The mixture was neutralized with saturated aqueous solution of Na_2CO_3 (20 mL) and extracted with dichloromethane (30 mL x 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated to give compound **32e** (170 mg, 87% yield) as yellow solid.

LCMS: t_R = 0.968 min in 5-95AB_220&254 Shimadzu (Agilent Pursult 5 C18 20*2.0mm), MS (ESI) m/z = 791.6 $[M+H]^+$.



32e **Example 32 isomer 1** **Example 32 isomer 2**

To a solution of compound **32e** (150 mg, 0.189 mmol) in THF (3 mL) was added TBAF (0.38 mL, 0.379 mmol, 1M in THF) under nitrogen, the resulting mixture was stirred for 2 hours at room temperature (27-34°C). The reaction was diluted with dichloromethane (20 mL) and water (20 mL), separated. The aqueous layer was extracted with dichloromethane (10 mL x 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered, concentrated and purified by column chromatography on silica gel (0~10% of methanol in dichloromethane) to give 100 mg crude product which was further purified by chiral SFC (Column: Phenomenex-Amylose-1 (250mm*30mm, 5um), Condition: 30% EtOH (0.1% $NH_3.H_2O$), Flow rate: 50 mL/min) to afford **Example 32 isomer 1** (15.5 mg) as a white solid and **Example 32 isomer 2** (22.4 mg) as a yellow solid. The total yield was 39%.

Spectra for Example 32 isomer 1:

LCMS: t_R = 0.733 min in 5-95AB_220&254 Shimadzu (Agilent Pursult 5 C18 20*2.0mm), MS (ESI) m/z = 553.4 $[M+H]^+$.

SFC: t_R = 4.752 min; 92.42% purity. Method: Column: Chiralpak AD-3 150×4.6mm I.D., 3um; Mobile phase: A: CO_2 B: ethanol (0.1% Ethanolamine); Gradient: from 5% to 40% of B in 5.5min, then 5% of B for 1.5 min; Flow rate: 2.5 mL/min; Column temp.: 35°C.

HPLC: t_R = 3.02 min in 10-80_AB_1.2ml METHOD (Ultimate C18 3*50mm 3um).

^{1}H NMR (400MHz, CD_3OD) δ = 7.90 (s, 2H), 7.34 (s, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 10.0 Hz, 2H), 6.69 (d, *J* = 8.0 Hz, 1H), 5.25 (s, 1H), 4.75 (d, *J* = 4.8 Hz, 1h), 4.59-4.56 (m, 1H), 4.45 (t, *J* = 5.6 Hz, 1H), 3.80-3.56 (m, 2H), 3.45-3.35 (m, 2H), 3.24-3.08 (m, 1H), 2.84-2.74 (m, 4H), 2.68 (dd, *J* = 15.6, 4.0 Hz, 2H), 2.02-1.81 (m, 4H), 1.40-1.28 (m, 1H), 1.07 (d, *J* = 6.4 Hz, 3H).

Spectra for Example 32 isomer 2:

LCMS: t_R = 0.738 min in 5-95AB_220&254 Shimadzu (Agilent Pursult 5 C18 20*2.0mm), MS (ESI) m/z = 553.4 $[M+H]^+$.

SFC: t_R = 4.941 min; 83.59% purity. Method: Column: Chiralpak AD-3 150×4.6mm I.D.,

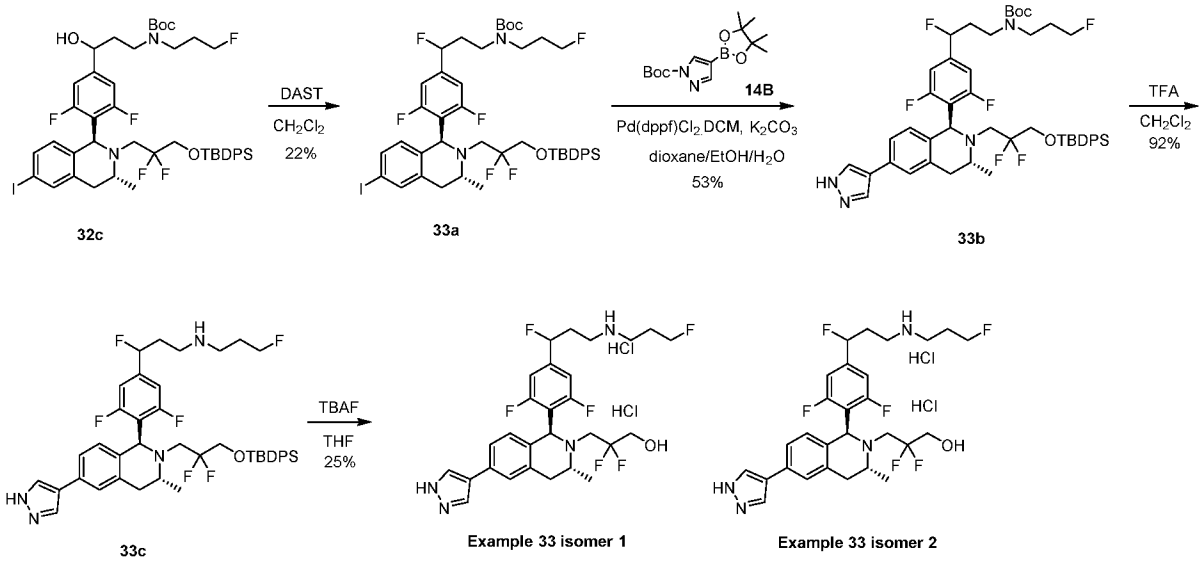
3um, Mobile phase: A: CO_2 B: ethanol (0.1% Ethanolamine); Gradient: from 5% to 40% of B in 5.5min, then 5% of B for 1.5 min; Flow rate: 2.5 mL/min; Column temp.: 35°C.

HPLC: t_R = 3.02 min in 10-80_AB_1.2ml METHOD (Ultimate C18 3*50mm 3um).

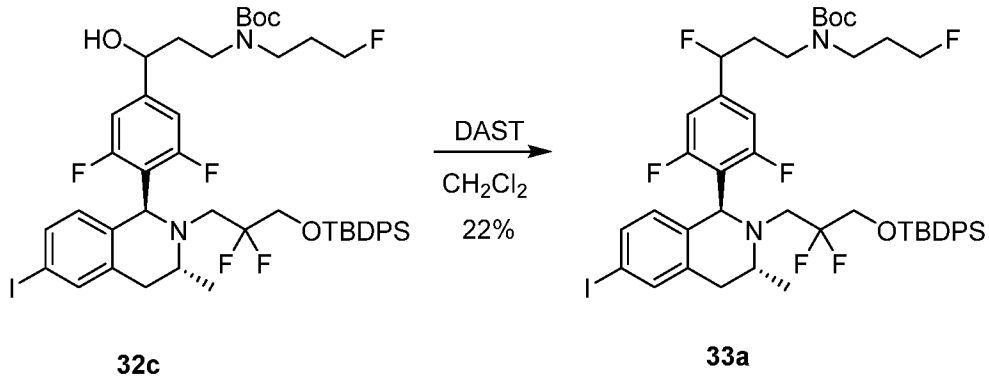
^{1}H NMR (400MHz, CD_3OD) δ = 7.89 (s, 2H), 7.34 (s, 1H), 7.23 (d, *J* = 6.8 Hz, 1H), 6.98 (d, *J* = 10.0 Hz, 2H), 6.68 (d, *J* = 8.0 Hz, 1H), 5.26 (s, 1H), 4.90 (s, 1H), 4.58 (dt, *J* = 47.2, 5.6 Hz, 2H), 3.78-3.56 (m, 2H), 3.47-3.32 (m, 2H), 3.22-3.06 (m, 5H), 2.78-2.62 (m, 2H), 2.17-1.93 (m, 4H), 1.07 (d, *J* = 6.4 Hz, 3H).

Example 33

3-((1S,3R)-1-(2,6-difluoro-4-(1-fluoro-3-((3-fluoropropyl)amino)propyl)phenyl)-3-methyl-6-(1H-pyrazol-4-yl)-3,4-dihydroisoquinolin-2(1H)-yl)-2,2-difluoropropan-1-ol



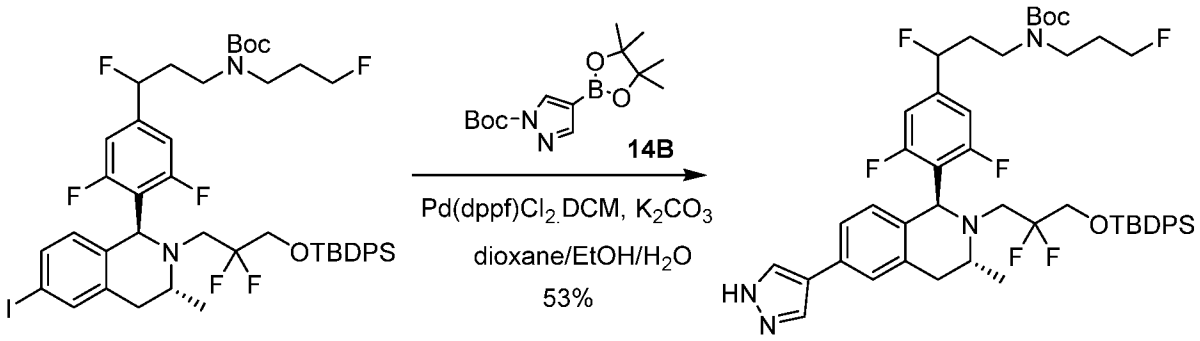
The procedure to prepare **Example 33 isomer 1** and **Example 33 isomer 2**:



To a solution of compound **32c** (500 mg, 0.526 mmol) in dichloromethane (15 mL) was added DAST (593 mg, 3.682 mmol) at 0 °C. The mixture was stirred at room temperature (26-31°C) for 2 hours. The reaction mixture was diluted with saturated aqueous solution of $NaHCO_3$ (20 mL) and dichloromethane (20 mL x 2), and then separated. The combined organic layers were washed with brine (25 mL), dried over anhydrous sodium sulfate, filtered, concentrated in vacuo and purified by column chromatography on silica gel (10-50% of ethyl acetate in petroleum ether) to give compound **33a** (110 mg, 22% yield) as yellow solid.

LCMS: t_R = 1.357 min in 5-95AB_220&254 Shimadzu (Agilent Pursult 5 C18 20*2.0mm), MS (ESI) m/z = 953.6 $[M+H]^+$.

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.65-7.57 (m, 4H), 7.51-7.31 (m, 8H), 6.69 (t, *J* = 9.2 Hz, 2H), 6.46 (d, *J* = 8.0 Hz, 1H), 5.45-5.30 (m, 1H), 5.20 (s, 1H), 4.46(dt, *J* = 47.6, 5.6 Hz, 2H), 3.99-3.80 (m, 1H), 3.65-3.43 (m, 2H), 3.40-3.11 (m, 6H), 2.80-2.62 (m, 1H), 2.48 (dd, *J* = 16.4, 4.0 Hz, 1H), 2.05-1.80 (m, 4H), 1.45 (s, 9H), 1.08-0.98 (m, 12H).

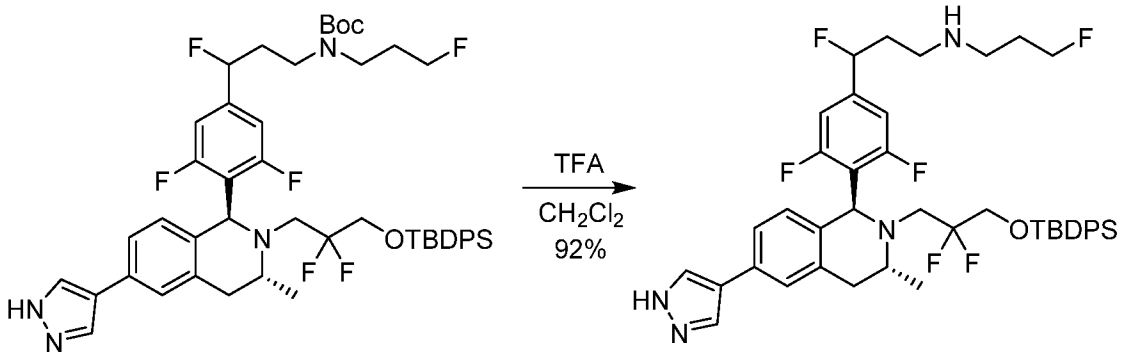


33a **33b**

To a stirred solution of compound **33a** (220 mg, 0.231 mmol) and compound **14B** (136 mg, 0.46 mmol) in 1,4-dioxane (3 mL) was added K_2CO_3 (127 mg,1.0 mmol), followed by water (0.6 mL) and EtOH (1.2 mL) at room temperature (23-31°C), then $Pd(dppf)Cl_2.CH_2Cl_2$ (28 mg, 0.0345 mmol) was added quickly. After degassed and purged with nitrogen for three times, the resulting mixture was stirred at 70°C for 16 hours under nitrogen. The reaction mixture was diluted with water (20 mL) and extracted with dichloromethane (30 mL x 2). The combined organic layers were

washed with brine (25 mL), dried over anhydrous sodium sulfate, filtered, concentrated and purified by column chromatography on silica gel (0-50% of ethyl acetate in petroleum ether) to give compound **33b** (110 mg, 53% yield) as yellow solid.

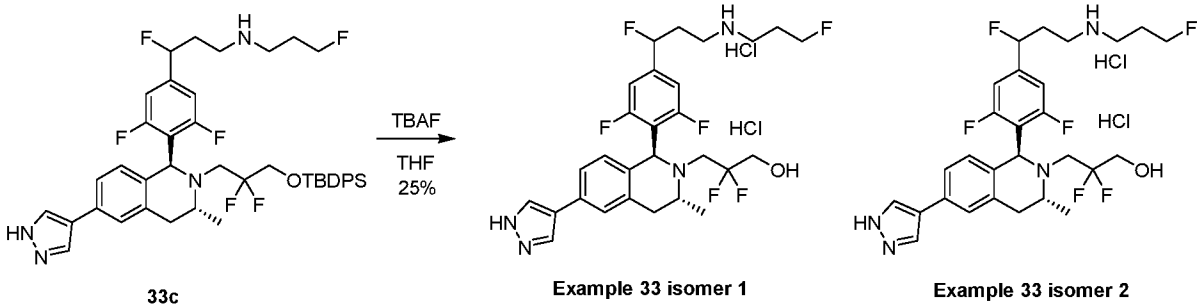
LCMS: t_R = 1.194 min in 5-95AB_220&254 Shimadzu (Agilent Pursult 5 C18 20*2.0mm), MS (ESI) m/z = 893.7 $[M+H]^+$.



33b **33c**

To a solution of compound **33b** (110 mg, 0.123 mmol) in dichloromethane (1.5 mL) was added TFA (0.5 mL) at room temperature (24-31°C). The mixture was stirred at room temperature (24-31°C) for 2 hours. The mixture was quenched to pH >7 with saturated aqueous solution of Na_2CO_3 (20 mL) and extracted with dichloromethane (30 mL x 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated to give compound **33c** (90 mg, 92% yield) as yellow solid.

LCMS: t_R = 1.000 min in 5-95AB_220&254 Shimadzu (Agilent Pursult 5 C18 20*2.0mm), MS (ESI) m/z = 793.3 $[M+H]^+$.



33c **Example 33 isomer 1** **Example 33 isomer 2**

To a solution of compound **33c** (90 mg, 0.113 mmol) in THF (2 mL) was added TBAF (0.23 mL, 0.227 mmol) under nitrogen at room temperature (24-31°C). The

resulting mixture was stirred for 2 hours at room temperature (24-31°C). The reaction was diluted with dichloromethane (20 mL) and water (20 mL), separated. The aqueous layer was extracted with dichloromethane (20 mL x 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered, concentrated and purified by column chromatography on silica gel (0-10% of methane in dichloromethane) to give 120 mg of product which was further separated by chiral SFC (Column: DAICEL CHIRALPAK AD-H(250mm*30mm, 5um), Condition: 20% EtOH (0.1% $NH_3.H_2O$) in CO_2, Flow rate: 50 mL/min) followed by prep-HPLC (column: Venusil ASB Phenyl 250*50mm 10um, Condition: 38-68% B (A: water 0.05% HCl), B: CH_3CN), flow rate: 25 mL/min) to give **Example 33 isomer 1** (7.8 mg) as a white solid and **Example 33 isomer 2** (8.1 mg) as a yellow solid. The total yield was 25%.

Spectra for Example 33 isomer 1:

LCMS: t_R = 0.771 min in 5-95AB_220&254 Shimadzu (Merck RP18e 25*3.0mm), MS (ESI) m/z = 555.5 $[M+H]^+$.

SFC: t_R = 4.696 min; 95.10% purity. Method: Column: Chiralpak AD-3 150×4.6mm I.D., 3um; Mobile phase: A: CO_2 B: ethanol (0.05% DEA); Gradient: from 5% to 40% of B in 5.5min and hold 40% for 3 min, then 5% of B for 1.5 min; Flow rate: 2.5 mL/min; Column temp.: 40°C.

HPLC: t_R = 3.49 min in 10-80_AB_1.2mL METHOD (Ultimate C18 3*50mm 3um).

^{1}H NMR (400MHz, CD_3OD) δ = 8.12 (s, 2H), 7.50 (s, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.10 (d, *J* = 10.0 Hz, 2H), 6.90 (d, *J* = 7.6 Hz, 1H), 5.88-5.62 (m, 2H), 4.58 (dt, *J* = 47.2, 5.6 Hz, 2H), 3.88 (br s, 1H), 3.82-3.70 (m, 1H), 3.68-3.52 (m, 2H), 3.50-3.35 (m, 2H), 3.26-3.16 (m, 4H), 2.92 (d, *J* = 13.6 Hz, 1H), 2.45-2.23 (m, 2H), 2.19-1.98 (m, 2H), 1.30 (d, *J* = 6.4 Hz, 3H).

Spectra for Example 33 isomer 2:

LCMS: t_R = 0.767 min in 5-95AB_220&254 Shimadzu (Merck RP18e 25*3.0mm), MS (ESI) m/z = 577.4 $[M+Na]^+$.

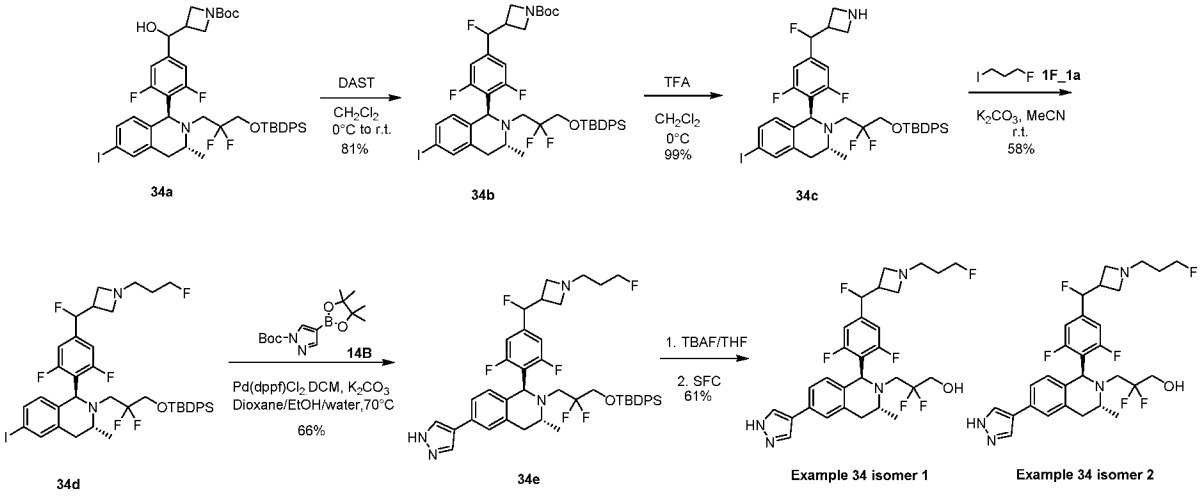
SFC: t_R = 4.995 min; 94.43% purity. Method: Column: Chiralpak AD-3 150×4.6mm I.D., 3um, Mobile phase: A: CO_2 B: ethanol (0.05% DEA); Gradient: from 5% to 40% of B in 5.5min and hold 40% for 3min, then 5% of B for 1.5 min; Flow rate: 2.5 mL/min; Column temp.: 40°C.

HPLC: t_R = 3.49 min in 10-80_AB_1.2mL METHOD (Ultimate C18 3*50mm 3um).

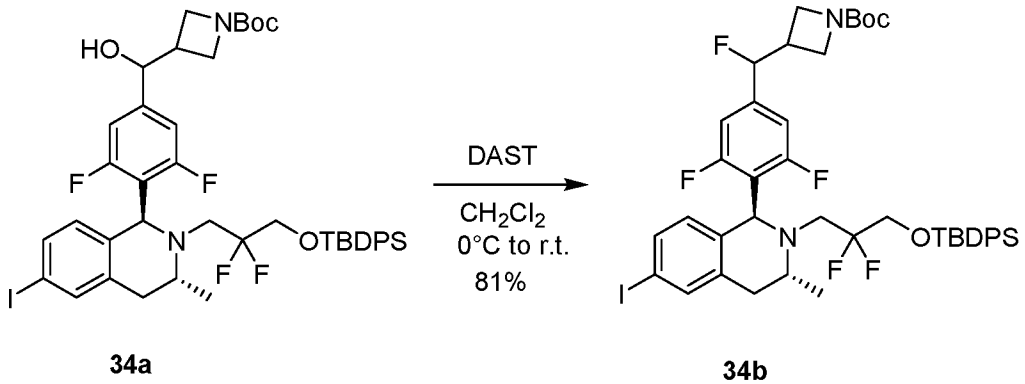
^{1}H NMR (400MHz, CD_3OD) δ = 8.11 (s, 2H), 7.59 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 10.0 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.13 (s, 1H), 5.89-5.68 (m, 1H), 4.62 (dt, *J* = 46.8, 5.2 Hz, 2H), 4.21-4.06 (m, 1H), 4.03-3.77 (m, 3H), 3.63-3.39 (m, 2H), 3.30-3.17 (m, 4H), 3.15-3.03 (m, 1H), 2.43-2.24 (m, 2H), 2.22-2.04 (m, 2H), 1.46 (d, *J* = 6.4 Hz, 3H).

Example 34

3-((1S,3R)-1-(2,6-difluoro-4-(fluoro(1-(3-fluoropropyl)azetidin-3-yl)methyl)phenyl)-3-methyl-6-(1H-pyrazol-4-yl)-3,4-dihydroisoquinolin-2(1H)-yl)-2,2-difluoropropan-1-ol



The procedure to prepare **Example 34 isomer 1** and **Example 34 isomer 2**:

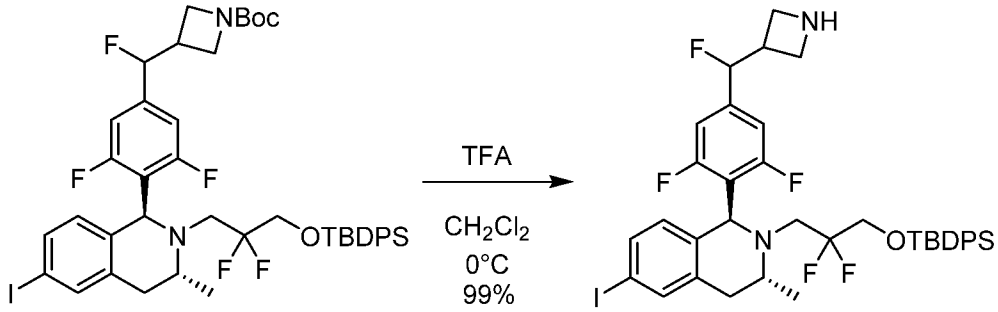


34a **34b**

To a solution of compound **34a** (430.0 mg, 0.476 mmol) in dichloromethane (13 mL) was added DAST (537 mg, 3.33 mmol) at 0 °C. The mixture was stirred at room temperature (26-34 °C) for 2 hours to give a red solution. The mixture was combined with pilot batch (100 mg of compound **34a**) which was carried out with same manner, quenched with saturated aqueous solution of $NaHCO_3$ (60 mL) to pH = 8 and then extracted with dichloromethane (100 mL × 3). The organic phases were combined and washed with brine (50 mL) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give the residue which was purified by column chromatography on silica gel (0~10% ethyl acetate in petroleum ether) to afford compound **34b** (430 mg, 81% average yield) as yellow oil.

LCMS: t_R = 1.322 min in 5-95AB_1.5min_220&254.lcm chromatography (Agilent pursult5 C18 20*2 mm), MS (ESI) m/z = 927.5 $[M+Na]^+$.

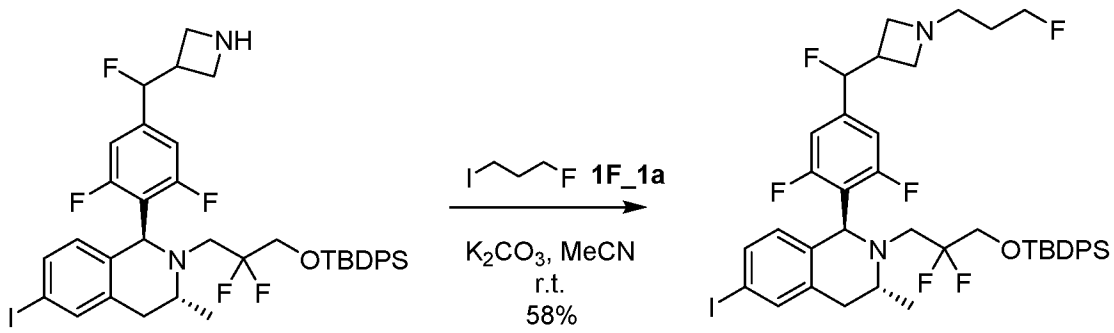
^{1}H NMR ($CDCl_3$ 400MHz): δ = 7.66-7.59 (m, 4H), 7.50-7.33 (m, 8H), 6.71-6.64 (m, 2H), 6.46 (d, *J* = 8.4 Hz, 1H), 5.46-5.28 (m, 1H), 5.21 (s, 1H), 3.95-3.81 (m, 4H), 3.78-3.71 (m, 1H), 3.62-3.43 (m, 2H), 3.30-3.12 (m, 2H), 2.90-2.61 (m, 2H), 2.49 (dd, *J* = 16.0, 3.6 Hz, 1H), 1.46-1.42 (m, 9H), 1.06-0.99 (m, 12H).



34b **34c**

A mixture of compound **34b** (430 mg, 0.475 mmol) in dichloromethane (6.5 mL) was added trifluoroacetic acid (2.2 mL) dropwise at 0°C. The mixture was stirred at 0°C for 1 hour to give a yellow solution. The mixture was adjusted to pH = 8 by addition of saturated aqueous solution of $NaHCO_3$ (50 mL) at 0°C, and extracted with dichloromethane (80 ml × 3). The organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate. The organic layer was filtered and concentrated *in vacuo* to give compound **34c** (378 mg, 99% yield) as a yellow solid.

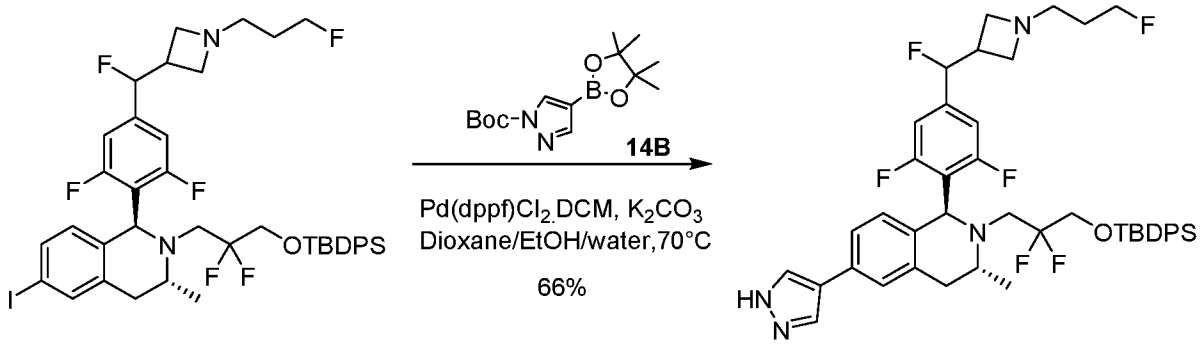
LCMS: t_R = 1.080 min in 5-95AB_1.5min_220&254.lcm chromatography (Agilent pursult5 C18 20*2mm), MS (ESI) m/z = 805.1 $[M+H]^+$.



34c **34d**

A mixture of compound **34c** (378 mg, 0.470 mmol), compound **1F_1a** (102 mg, 0.540 mmol) and K_2CO_3 (325 mg, 2.35 mmol) in acetonitrile (7 mL) was stirred at room temperature (26-34°C) for 16 hours to give a yellow suspension. The mixture was diluted with ethyl acetate (100 mL). The combined organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate. The organic layer was filtered and concentrated *in vacuo* to give the residue which was purified by column chromatography on silica gel (0~1% methanol (0.1% ammonia) in dichloromethane) to afford compound **34d** (235 mg, 58% yield) as yellow oil.

LCMS: t_R = 1.104 min in 5-95AB_1.5min_220&254.lcm chromatography (Agilent pursult5 C18 20*2mm), MS (ESI) m/z =865.5 $[M+H]^+$.



34d **34e**

A mixture of compound **34d** (185 mg, 0.214 mmol), compound **14B** (126 mg, 0.428 mmol) and K_2CO_3 (118 mg, 0.856 mmol) in 1,4-dioxane (1.9 mL), ethanol (0.7 mL) and water (0.4 mL) was degassed and purged with nitrogen for 3 times. Then $Pd(dppf)Cl_2.DCM$ (26 mg, 0.032 mmol) was added and degassed and purged with nitrogen for 3 times. The mixture

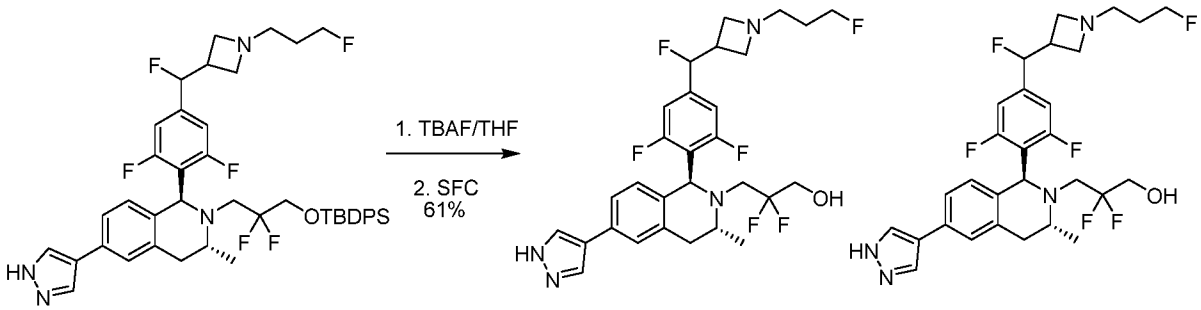
was stirred at 70°C for 16 hours under nitrogen to give a brown solution. The mixture was combined with pilot batch (50 mg of compound **34d**) which was carried out with same manner, diluted with ethyl acetate (200 mL). The combined organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate. The organic layer was filtered and concentrated *in vacuo* to give the residue which was purified by column chromatography on silica gel (0~1% methanol (0.1% ammonia) in dichloromethane) to afford compound **34e** (145 mg, 66% average yield) as a mixture of diastereomers which can be separated based on SFC.

SFC: t_R = 3.114 min and 4.135 min (Method: Column: Lux Cellulose-2 150×4.6mm I.D., 3μm; Mobile phase: 40% of methanol (0.05% DEA) in CO_2, flow rate: 2.5 mL / min; Column temperature: 40°C.).

Method: Column: Lux Cellulose-2 150×4.6mm I.D., 3μm; Mobile phase: 40% of methanol (0.05% DEA) in CO_2, flow rate: 2.5 mL / min; Column temperature: 40°C.

LCMS: t_R = 1.024 min in 5-95AB_1.5min_220&254.lcm chromatography (Agilent pursult5 C18 20*2mm), MS (ESI) m/z = 805.3 $[M+H]^+$.

^{1}H NMR ($CDCl_3$ 400MHz): δ = 7.83 (s, 2H), 7.68-7.59 (m, 4H), 7.48-7.36 (m, 6H), 7.26-7.24 (m, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 6.76-6.63 (m, 3H), 5.45-5.32 (m, 1H), 5.28 (br s, 1H), 4.46 (dt, *J* = 47.2, 6.0 Hz, 2H), 3.99-3.85 (m, 1H), 3.68-3.59 (m, 1H), 3.57-3.45 (m, 1H), 3.33-3.20 (m, 4H), 3.17-3.10 (m, 1H), 2.98-2.91 (m, 1H), 2.88-2.65 (m, 2H), 2.62-2.50 (m, 3H), 1.79-1.65 (m, 2H), 1.10-1.00 (m, 12H).



34e **Example 34 isomer 1** **Example 34 isomer 2**

A solution of compound **34e** (125.0 mg, 0.155 mmol) in tetrahydrofuran (3 mL) was added

TBAF (0.233 mL, 0.233 mmol, 1 M in THF). The mixture was stirred at room temperature (26-35 °C) for 2 hours to give a yellow solution. The mixture was diluted with ethyl acetate (100 mL). The combined organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate. The organic layer was filtered and concentrated *in vacuo* to give the residue which was purified by prep-TLC (dichloromethane: methanol = 20:1) to afford the product (86 mg) as yellow oil. Total 100 mg of this compound was separated by chiral SFC (Column: Phenomenex-Cellulose-2 (250mm*30mm, 5um), Condition: (0.1% $NH_3.H_2O$) methanol in CO_2, Begin B 45%, End B 45%, Flow rate: 50 mL/min) to give **Example 34 isomer 1** (29.9 mg, t_R = 2.579 min, peak 1, 100% purity, 29% yield) as a yellow solid and **Example 34 isomer 2** (32.9 mg, t_R = 3.476 min, peak 2, 100% purity, 32% yield) as a yellow solid.

SFC for racemic: t_R = 2.473 min and 3.274 min. Method: Column: Lux Cellulose-2 150×4.6mm I.D., 3μm; Mobile phase: 40% of Methanol (0.05% DEA) in CO_2; Flow rate: 2.5 mL/min; Column temperature: 40 °C.

Spectra for Example 34 isomer 1:

LCMS: t_R = 1.919 min in 10-80AB_4min_220&254.lcm chromatography (Xtimate C18 2.1*30mm), MS (ESI) m/z = 567.2 $[M+H]^+$.

HPLC: t_R = 3.29 min in 10-80_AB_1.2ml.met.chromatography (Ultimate C18 3.0um 3.0*50mm).

SFC: t_R = 2.579 min; 99.71% purity.

Method: Column: Lux Cellulose-2 150×4.6 mm I.D., 3μm; Mobile phase: 40% of Methanol (0.05% DEA) in CO_2, Flow rate: 2.5 mL/min, Column temperature: 40°C.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.83 (s, 2H), 7.28 (s, 1H), 7.20 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.88-6.82 (m, 2H), 6.72 (d, *J* = 8.0 Hz, 2H), 5.52 (dd, *J* = 47.6, 6.0 Hz, 1H), 5.22 (s, 1H), 4.48 (dt, *J* = 47.2, 6.0 Hz, 2H), 3.74-3.52 (m, 3H), 3.50-3.40 (m, 2H), 3.36 (dd, *J* = 16.0, 4.4 Hz, 1H), 3.30-3.21 (m, 2H), 3.20-3.12 (m, 1H), 3.03-2.91 (m, 1H), 2.87-2.75 (m, 1H), 2.72-2.61 (m, 3H), 1.84-1.71 (m, 2H), 1.10 (d, *J* = 6.4 Hz, 3H).

Spectra for Example 34 isomer 2:

LCMS: t_R = 1.898 min in 10-80AB_4min_220&254.lcm chromatography (Xtimate C18 2.1*30mm), MS (ESI) m/z = 567.2 $[M+H]^+$.

HPLC: t_R = 3.32 min in 10-80_AB_1.2ml.met.chromatography (Ultimate C18 3.0um 3.0*50mm).

SFC: t_R = 3.476min; 98.65% purity.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.83 (s, 2H), 7.28 (s, 1H), 7.21 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.87-6.81 (m, 2H), 6.72 (d, *J* = 8.0 Hz, 1H), 5.52 (dd, *J* = 48.0, 6.4 Hz, 1H), 5.23 (s, 1H), 4.48 (dt, *J* = 47.2, 6.0 Hz, 2H), 3.74-3.51 (m, 3H), 3.50-3.41 (m, 2H), 3.36 (dd, *J* = 15.6, 4.8 Hz, 1H), 3.30-3.13 (m, 3H), 3.04-2.91 (m, 1H), 2.88-2.75 (m, 1H), 2.72-2.60 (m, 3H), 1.84-1.71 (m, 2H), 1.10 (d, *J* = 6.4 Hz, 3H).

Example 35

TR-FRET ER-α Ligand Binding Domain Binding Assay

This example relates to the binding analysis of the test compound to ER-α Ligand Binding Domain.

Test compounds are prepared at 10μM in DMSO and serially diluted at 2-fold titration to obtain a total 22 points in Low-volume Non-binding polystyrene black 384-well plates (Geiner cat # 784900).

The ER-α ligand binding domain/Tb-anti-GST Ab complex screening buffer is freshly prepared on the day of experiment, by mixing 10 ml Nuclear Receptor Buffer, 50 μl of 1 M DTT to a final concentration of 5 mM, 10 μl of 20000 nM ER-α ligand binding domain Recombinant Protein to a final concentration of 20 nM, and 22.8 μl Tb-Anti-GST Antibody (Lantha screen TR-FRET Estrogen alpha receptor competitive binding kit, Thermofisher,Cat No. A15887) to a final concentration of 4 nM. The complex screening buffer is mixed gently several times by inversion, and then incubated on ice for 30 minutes before use.

Reaction plates are prepared by first dispense 100 nl of each prepared compound dilution (typically at least twelve different concentrations are used for each compound to obtain a dose response curve), as well as blanks (DMSO) and positive control samples (e.g. fulvestrant or a fulvestrant containing drug) in designated wells. 5 μl of the complex

screening buffer is also dispensed into each of the sample/control/blank well, and the reaction plates are covered and incubated on ice for 30 min.

In the meantime, the Fluoromone ES2 screening buffer is prepared by mixing 3 ml Nuclear Receptor Buffer, 15 µl of 1 M DTT to a final concentration of 5 mM, 12µl of 10% Tween-20 to a final concentration of 0.02%, and 40 µl of 1800 nM Fluoromone ES2 to a final concentration of 24 nM, the prepared buffer is vortexed. Upon completion of the 30min incubation of the test compounds and the complex screening buffer, 5 µl of the Fluoromone ES2 screening buffer is then dispensed into each of the sample/control/blank well, and the reaction plates are covered and incubated on ice for another 60 min.

Measurements of the fluorescent emission signal of each well are made using a Tecan Spark 20M at Ex337nm and Em490nm/520nm. Percentage inhibition values are calculated relative to blanks and Fulvestrant controls. Curve fitting and IC_{50} calculations are carried out using GraphPad Prism 7 software.

Example 36

Breast Cancer Cell ER-α Degradation Assay

This example relates to degradation analysis of the test compounds to the ER-α receptors expressed on the cell surface of breast cancer cells, e.g. MCF7 cells. This assay identifies compounds with ER α degradation properties.

Day 1-MCF7 breast cancer cells are seeded at a density of 12,000 cells per well in 100 µl phenol-free L-Glutamine containing RPMI (Gibco, Cat No. 11835-030) with 10% charcoal stripped FBS (BioSun, Cat No. BS-004-500) in 96 well poly-lysine coated tissue culture plate (Greiner # T-3101-4) and incubate overnight. The culture plates are incubate overnight at 37°C, 5% CO_2.

Day 2-Compound stock solutions are prepared in DMSO serially (33 µM, 11 µM, 3.3 µM, 1.1 µM, 0.3 µM, 0.1 µM, 0.03 µM, 0.01 µM, 0.001 µM), then 1:33 diluted in cell culture medium to obtain 9 working concentrations (1 µM, 333 nM, 100 nM, 33 nM, 10 nM, 3.3 nM, 1 nM, 0.3 nM, 0.03 nM) using Freedom Evo liquid Handling Workstation (TECAN).

11µl of each compound dilutions, control compounds (1 µM fulvestrant work solution diluted by cell culture medium) and blank controls (DMSO) are dispensed into pre-designated well in the cell culture plates using Freedom Evo liquid Handling Workstation (TECAN), obtaining a final concentration of 100 nM, 33.3 nM, 10 nM, 3 nM, 1 nM, 0.3 nM, 0.1 nM, 0.03 nM, 0.003 nM for each compound, 100 nM Fulvestrant as min control and 0.3% DMSO as max control. The cell culture plates are incubated at 37°C

overnight.

Day 3-Fixation and permeabilization are carried out as follows：

1) After 24hr compound treatment, remove the tissue culture growth media.

2) The cells are washed by adding 100 μL 1XPBS to each well. Swirl or tap the plate gently for about 20 seconds, then thoroughly remove all fluid by aspiration.

3) Fix cells by adding 100 μL Cell Fixation Buffer to each sample well. Incubate for at least 7 minutes at room temperature. Mix by gently swirling or tapping the plate.

4) Remove fixation solution and discard.

5) Wash each sample well 3 times with 250 μL 1X PBS, as described above.

6) Add 100 μL Cell Permeabilization Buffer to each sample well and mix by gently swirling or tapping the plate. Incubate at room temperature for 8 minutes.

7) Remove Cell Permeabilization Solution and discard.

8) Wash each well 3 times with 250 μL 1X PBS, as described above.

9) Add 100 μL blocking buffer to each sample well and incubate at room temperature for 1hr. The blocking buffer is prepared as 1X PBST (0.05% Tween-20) with 3% BSA.

10) Remove the blocking buffer and add 100 μL diluted primary antibody (1:10000 diluted in Antibody #1 Dilute) to each sample well, mix by gently swirling or tapping the plate and incubate at 4°C overnight.

Day 4-Secondary antibody incubation and reading-out of the ELISA are carried out as follows：

1) Remove primary antibody and wash the sample wells 3 times with 250 μL 1X Wash Buffer. After the last wash, invert the plate and gently tap the plate on paper towels to remove residual fluid. (Proceed immediately to the next step. Do not allow the plate to air dry between steps.)

2) Preparation of 1X HRP-Conjugated anti-rabbit IgG Antibody #2 (1:100 diluted in Antibody #2 Diluent), add 100 μL secondary antibody mix by gently swirling or tapping the plate and incubate at room temperature for 1 hour.

3) Wash the plate 3 times with 250 μL 1X Wash Solution. After the last wash, invert the plate and gently tap the plate on paper towels to remove residual fluid. (Proceed immediately to the next step. Do not allow the plate to dry before adding the TMB substrate.)

4) Add 100 μL TMB substrate and cover the reaction plate. Begin timing the reaction immediately after adding the TMB substrate. Gently rock the plate manually for 1

minute to thoroughly mix the reaction.

5) Incubate for 5–45 minutes at room temperature, and then add 100 µL Stop Buffer to stop the enzyme reaction.

6) Read the plate on the Multiscan Spectrum reader set to 450 nm wavelengths soon as possible after adding the Stop Buffer (the program "OD450-OD540").

Curve fitting and IC_{50} calculations are carried out using GraphPad Prism 7 software.

% ER degradation = 1 - (Compound treated – 100 nM Fulvestrant treated) / (0.3% DMSO treated - 100 nM fulvestrant treated) * 100

Example 37

PR Antagonist Assay

This example relates to antagonist analysis which indirectly identifies antagonists of estradiol stimulated ER α by measuring the effect on the Progesterone receptor which is downstream of the ER α.

Day 1-MCF7 breast cancer cells are seeded at a density of 12,000 cells per well in 100µl phenol-free L-Glutamine containing RPMI (Gibco, Cat No. 11835-030) with 10% charcoal stripped FBS (BioSun, Cat No. BS-004-500) in 96 well poly-lysine coated tissue culture plate (Greiner # T-3101-4) and incubate overnight. The culture plates are incubate overnight at 37°C, 5% CO_2.

Day 2-Compounds stock solutions are prepared in DMSO serially (33 µM, 11 µM, 3.3 µM, 1.1 µM, 0.3 µM, 0.1 µM, 0.03 µM, 0.01 µM, 0.001 µM) and then 1:33 diluted in cell culture medium to obtain 9 working concentrations (1 µM, 333 nM, 100 nM, 33 nM, 10 nM, 3.3 nM, 1 nM, 0.3 nM, 0.03 nM) using Freedom Evo liquid Handling Workstation (TECAN).

For pre-dosing, 11µl of 1 nM E2 working stock (diluted in cell culture medium) is dispensed in each well to obtain a final concentration at 0.1 nM and incubated for 30 min in the CO_2 incubator. Then 11µl of each compound dilutions and blank controls (DMSO) are dispensed into pre-designated well in the cell culture plates using Freedom Evo liquid Handling Workstation (TECAN), obtaining a final concentration of 100 nM, 33.3 nM, 10 nM, 3 nM, 1 nM, 0.3 nM, 0.1 nM, 0.03 nM, 0.003 nM for each compound, 0.1 nM E2 as max control and 0.3% DMSO as min control. The cell culture plates are incubated at 37°C overnight.

Day 3-Fixation and permeabilization are carried out as follows:

1) After 24hr compound treatment, remove the tissue culture growth media.

2) The cells are washed by adding 100µL 1XPBS to each well. Swirl or tap the plate

gently for about 20 seconds, then thoroughly remove all fluid by aspiration.

3) Fix cells by adding 100 µL Cell Fixation Buffer to each sample well. Incubate for at least 7 minutes at room temperature. Mix by gently swirling or tapping the plate.

4) Remove fixation solution and discard.

5) Wash each sample well 3 times with 250 µL 1X PBS, as described above.

6) Add 100 µL Cell Permeabilization Buffer to each sample well and mix by gently swirling or tapping the plate. Incubate at room temperature for 8 minutes.

7) Remove Cell Permeabilization Solution and discard.

8) Wash each well 3 times with 250 µL 1X PBS, as described above.

9) Add 100 µL diluted primary antibody (1:10000 diluted in Antibody #1 Dilute) to each sample well, mix by gently swirling or tapping the plate and incubate at 4°C overnight.

Day 4-Secondary antibody incubation and reading-out of the ELISA are carried out as follows：

1) Remove primary antibody and wash the sample wells 3 times with 250 µL 1X Wash Buffer. After the last wash, invert the plate and gently tap the plate on paper towels to remove residual fluid. (Proceed immediately to the next step. Do not allow the plate to air dry between steps.)

2) Preparation of 1X HRP-Conjugated anti-mouse IgG Antibody #2 (1:100 diluted in Antibody #2 Diluent), add 100 µL secondary antibody mix by gently swirling or tapping the plate and incubate at room temperature for 1 hour.

3) Wash the plate 3 times with 250 µL 1X Wash Solution. After the last wash, invert the plate and gently tap the plate on paper towels to remove residual fluid. (Proceed immediately to the next step. Do not allow the plate to dry before adding the TMB substrate.)

4) Add 100 µL TMB substrate and cover the reaction plate. Begin timing the reaction immediately after adding the TMB substrate. Gently rock the plate manually for 1 minute to thoroughly mix the reaction.

5) Incubate for 5–45 minutes at room temperature, and then add 100 µL Stop Buffer to stop the enzyme reaction.

6) Read the plate on the Multiscan Spectrum reader set to 450 nm wavelengths soon as possible after adding the Stop Buffer (the program “OD450-OD540”).

Curve fitting and IC_{50} calculations are carried out using GraphPad Prism 7 software.

% PR antagonism = 1- (Compound plus 0.1 nM E2 treated – 0.3% DMSO treated) / (0.1

nM E2 treated - 0.3% DMSO treated) * 100

Results of ER-α ligand binding domain binding, Breast Cancer Cell ER-α degradation, and PR antagonist assays for the exemplary compounds 1-12 are listed in table 2 below.

Table 2: Exemplary results obtained in Example 1-12

Compound Number	ER-α ligand binding domain Binding IC_{50} (nM)	MCF7 PR suppression IC_{50} (nM)	MCF7 ER degradation ER_{50} (nM)
1	1.73	1.51	1.91
2	2.46	0.75	1.65
3	1402.9	NA	NA
4	7.66	11.41	13.27
5	16.38	NA	NA
6	1.16	0.33	0.42
7	1.88	2.35	4.28
8	2.29	3.39	5.25
9	1.72	2.84	1.83
10	6.64	14.12	19.06
11	2332.0	NA	NA
12	1.77	<0.003	0.82
13	4.23	NA	1.88
14	0.79	0.22	0.17
15	2.03	NA	0.30
16	1.40	NA	0.80
17	87.8	NA	NA
18	1.28	NA	0.61
19	0.35	NA	0.29
20	2.40	NA	2.68
21	2.21	>100	>100

22	3313	NA	NA
23	53.4	NA	NA
24	50.3	NA	NA
25	38.8	NA	NA
26 isomer 1	314	NA	NA
26 isomer 2	2.02	NA	1.24
27 isomer 1	0.52	NA	0.85
27 isomer 2	87.6	NA	NA
28	1.15	NA	0.72
29	6.42	NA	>100
30	0.68	NA	0.28
31	0.93	NA	>100
32 isomer 1	0.55	NA	>100
32 isomer 2	1.48	NA	>100
33 isomer 1	1.61	NA	>100
33 isomer 2	1.13	NA	>100
34 isomer 1	0.92	NA	0.25
34 isomer 2	1.09	NA	0.21

Example 38

In Vitro Rat/Human Hepatocytes Clearance Assay

The protocol for rat/human hepatocytes metabolic stability assay is employed to determine the clearance of the compounds of the present disclosure in vitro.

Rat hepatocytes in male gender and human hepatocytes in mixed gender were obtained from commercial vendors (e.g., BioreclamationIVT) and stored at -150°C prior to use. 10 mM stock solutions of tested compounds were prepared in DMSO. Thawing medium and supplement incubation medium (serum-free) were placed in a 37°C water bath for at least 15 minutes prior to use. Stock solutions were diluted to 100 μM by combining 198 μL acetonitrile and 2 μL of 10 mM stock solution.

Vials of cryopreserved hepatocytes were removed from storage, ensured that vials remain at cryogenic temperatures. The vials were thawed in a 37°C water bath with gently shaking. Vials were kept in water bath until all ice crystals had dissolved and were no longer visible. Vials were sprayed with 70% ethanol before being transferred to a biosafety cabinet. And then the contents were poured into the 50 mL thawing medium conical tube. Vials were centrifuged at 100 g for 10 minutes at room temperature. Thawing medium was aspirated and hepatocytes were resuspended with serum-free incubation medium to yield ~1.5×10^6 cells/mL.

Cell viability and density were counted using a Trypan Blue exclusion, and then cells were diluted with serum-free incubation medium to a working cell density of 1×10^6 viable cells/ml. A portion of the hepatocytes at 1×10^6 viable cells/mL was boiled for 10 min prior to adding to the plate as negative control to eliminate the enzymatic activity so that little or no substrate turnover should be observed. The inactivated hepatocytes were used to prepare negative samples, which were used to exclude the misleading factor that resulted from instability of chemical itself.

Aliquots of 247.5 μL hepatocytes were dispensed into each well of a 96-well non-coated plate. The plate was placed in the incubator on an orbital shaker for approximately 10 minutes. Aliquots of 2.5 μL of the 100 μM test compounds were added into respective wells of the non-coated 96-well plate to start the reaction. This assay was performed in duplicate. The plate was incubated in the incubator on an orbital shaker for the designed time points. 20 μL of contents were transferred and mixed with 6 volumes (120 μL) of cold acetonitrile with internal standard to terminate the reaction at time points of 5, 15, 30,45, 60, 80 and 100 minutes. Samples were centrifuges for 20 minutes at 4000 g and aliquots of 100 μL of the supernatants were used for LC-MS/MS analysis for measurement of test compounds.

In vitro hepatocyte clearance was estimated based on determination of elimination half-life ($T_{1/2}$) of compounds disappearance from their initial concentrations. Peak area ratios of each compound (test or control) to IS was calculated. Ln (%Control) versus Incubation Time (min) curve was plotted, and the slope of a linear fitting line was calculated. Drug elimination rate constant k (min-1), $T_{1/2}$ (min), and in vitro intrinsic clearance CL_{int} (μL/min/E6) was calculated according to the following equations:

$k = -$ slope

$T_{1/2} = 0.693/k$

$CL_{int} = k/C_{hep}$

Where C_{hep} (cells×μL^{-1}) is the cell concentration in the incubation system.

Example 39

Procedure for Log D Determination

10 μL of working solution of each cassette is placed in order into respective 96-well rack position (Log D plate). Add 500 μL of saturated octanol into each vial of the above cap-less Log D plate followed by the addition of 500 μL of saturated phosphate buffer. Seal with a moulded PTDE/SIL 96-Well Plate Cover.

The Log D plate is transferred to the Eppendorf Thermomixer Comfort plateshaker and shaken at 25°C, 2,000 rpm for 2 hours.

The samples are centrifuged at 4,000 rpm at 25°C for 30 minutes to separate the phases. Pipette and syringe are used to pipette about 100 μL from the octanol and buffer phases to a new 96-well plate, respectively.

5 μL of octanol sample is transferred to a new 96-well plate, followed by addition of 495 μL of a mixture of H_2O and acetonitrile containing internal standard (1:1) as 100 fold octanol samples. Vortex for 5 minutes at 1,000 rpm.

50 μL of 100 fold samples are transferred to new 96-well plate, followed by addition of 450 μL of a mixture of H_2O and acetonitrile containing internal standard (1:1) as 1,000 fold octanol samples. Vortex for 5 minutes at 1,000 rpm.

The 1,000 folds octanol samples are serially diluted into 10,000, 100,000 and 1,000,000 folds with a mixture of H_2O and acetonitrile containing internal standard (1:1).

50 μL of buffer samples are transferred to new 96-well plate, followed by addition of 450 μL of a mixture of H_2O and acetonitrile containing internal standard (1:1) as 10 folds buffer samples. Vortex for 5 minutes at 1,000 rpm.

The 10 folds buffer samples are serially diluted into 100, 1,000 and 10,000 folds with a mixture of H_2O and acetonitrile containing internal standard (1:1). The samples are evaluated by LC/MS/MS analysis. All compounds are tested in singlicate.

All calculations are carried out using Microsoft Excel. The concentrations of test compound in octanol/buffer solution are evaluated by LC/MS/MS. Calculate the Log D value of the test compound as follows:

$$\text{Log D} = \frac{1}{n} * \sum(\text{Log}\,[(\text{Area Ratio Oct} \times \text{DF Oct}) / (\text{Area Ratio Buf} \times \text{DF Buf})])$$

DF means the dilution factor.

Example 40

Procedure for Protein Binding Measurements in Human Plasma by Using Equilibrium Dialysis

Add 597 μL of blank plasma into each vial of a new plastic plate or separate plastic tube by addition of 3 μL of the working solution of each cassette, vortex at 1,000 rpm for 5 minutes. The final percent volume of organic solvent is 0.5% and the final concentration for test compound is 5 μM. Immediately transfer 50 μL of the spiked plasma suspension to a 96-well plate to act as T=0 control sample. The samples are treated the same as the samples after incubation. Place all remaining spiked plasma in the incubator for the duration of the study.

Place inserts open end up into the wells of the base plate. Add 500 μL of phosphate buffer (pH 7.4) to the buffer chamber, which is indicated by the white ring. Add 300 μL of spiked plasma sample into the sample chamber, which is indicated by the red ring. Cover the unit with gas permeable lid and incubate for 18 hours at 37°C at 300 rpm with 5% CO2 on an orbital shaker in the CO2 incubator. At the end of incubation, remove lid and pipette 50 μL of post-dialysis samples from both buffer and plasma chambers into separated 96-well plate for analysis, respectively.

At the same time, the remaining spiked plasma sample in the plastic plate or separate plastic tube is incubated for 18 hours at 37°C with 5% CO2 in the CO2 incubator. At T=18 hours, transfer 50 μL of the original spiked plasma suspension to the 96-well plate for analysis.

Add 50 μL of Human plasma to the buffer samples, and an equal volume of PBS to the collected plasma samples. Votex the plate at 1,000 rpm for 2 minutes and add 400 μL of acetonitrile containing an appropriate internal standard (IS) to precipitate protein and release compound. Vortex at 1,000 rpm for 10 minutes. Centrifuge for 30 minutes at 4,000 rpm. Transfer 250 μL of the supernatant to new 96-well plates and centrifuge again (4,000 rpm, 30 minutes). Then transfer 100 μL of the supernatant to new 96-well plates for analysis. Add 100 μL of distilled water to each sample and vortex for 5 minutes at 1,000 rpm for analysis by LC-MS/MS. All compounds are tested in singlicate at 5 μM in human plasma.

All calculations are carried out using Microsoft Excel.

Calculate the percentage of unbound, percentage of bound and recovery of test compound as follows:

$$\%\ \text{Unbound} = (\text{Conc.}_{\text{buffer chamber}} / \text{Conc.}_{\text{plasma chamber}}) \times 100\%$$

$$\%\ \text{Bound} = 100\% - \%\ \text{Free}$$

$$\%\ \text{Recovery} = (500 \times \text{Conc.}_{\text{buffer chamber}} + 300 \times \text{Conc.}_{\text{plasma chamber}}) / (300 \times \text{Conc.}_{\text{Total sample}}) \times 100$$

$$LogK = Log\left(\frac{\%\ \text{Bound}}{100 - \%\ \text{Bound}}\right)$$

$$\text{Remaining}\% = \text{Conc.}_{18hr} / \text{Conc.}_{0hr} \times 100\%$$

Exemplary data are shown in below Table 3.

Table 3: PK results for the exemplary compounds 1-12

Compound Number	logD	Hu Mic Clint (μL/min/mg)	Rat Hep Clint (μL/min/10^6 cells)	hPPB (fu%)	DMSO solubility (μM)
1	3.48	14.6	118	1.53	77.1
2	2.59	27.8	134	16.4	228
3	3.02	13.9	4.64	20.2	420
4	3.42	16.3	17.7	1.28	579
5	>4.00	50.4	42.1	7.54	272
6	3.26	17.0	55.3	1.49	334
7	>4.00	22.8	37.4	1.28	9.18
8	3.52	14.5	13.3	1.33	10.7
9	3.82	19.0	10.3	2.16	938
10	3.40	6.18	30.1	2.15	141
11	1.58	5.35	3.59	51.6	>1000
12	2.99	<3	23.8	4.20	345
13	3.00	17.3	30.1	1.36	208
14	3.65	65.6	61.8	0.83	63.1

15	2.55	36.9	65.8	7.18	591
16	2.46	25.9	41.3	7.52	659
17	3.27	11.2	19.8	5.92	166
18	3.79	16.7	35.0	0.89	119
19	3.89	35.3	67.7	0.66	97.0
20	4.13	5.85	76.5	0.37	74.7
21	3.61	21.5	112	2.67	228
22	0.18	<3	<1	6.78	981
23	2.78	14.7	30.9	3.07	830
24	2.79	<3	22.1	11.6	574
25	2.66	7.9	19.9	6.48	927
26 isomer 1	3.23	70.5	129	8.77	302
26 isomer 2	3.1	36.1	22.8	1.89	202
27 isomer 1	3.93	22.3	11.0	0.42	134
27 isomer 2	3.70	121	210	3.19	121
28	3.52	31.9	34.2	2.71	204
29	3.29	27.5	49.6	1.61	418
30	3.57	156	130	0.98	5.28
31	2.16	16.8	10.6	2.0	293
32 isomer 1	1.98	24.1	9.31	10.7	25.9
32 isomer 2	2.00	40.0	8.23	8.00	49.8
33 isomer 1	3.19	21.8	7.27	NA	130.5
33 isomer 2	3.00	31.4	6.38	2.15	17.7
34 isomer 1	3.85	73.8	47.7	1.44	33.9
34 isomer 2	3.84	160	46.6	NA	38.1

Example 41

Immature Uterine Wet Weight Assay

Immature Uterine Wet Weight Assay

The study was conducted in sexually immature female SD rats aged between 17-19 days. The rats were randomised on body weight into following matched groups: vehicles (arachis oil), 17-β-Estradiol, fulvestrant alone or plus 17-β-Estradiol, tamoxifen alone or plus 17-β-Estradiol, test compounds alone or plus 17-β-Estradiol, respectively. Arachis oil vehicle, 1 ug/rat of 17-β-Estradiol, 0.2 mg/kg fulvestrant and all test compounds were administered via the subcutaneous route in a total volume of 0.2 ml per injection per day, while tamoxifen was dosed at 1 mg/kg once daily by oral gavage. The test compounds were dosed at two doses of 10 μg and 100 μg.

All animals were dosed daily for three days. 24 hours after the last dosing, plasma was collected for pharmacokinetic analysis, and immediately following plasma collection, the animals were euthanized and the uterus removed and weighed.

The uterotrophic and anti- uterotrophic activity is calculated with uterus weight as

$$\%\ \text{Agonism} = \frac{\text{Compound treated - Vehicle control}}{\text{Estrogen treated - Vehicle control}} \times 100$$

$$\%\ \text{Antagonism} = 1 - \frac{\text{Estrogen + compound treated - Vehicle control}}{\text{Estrogen treated - Vehicle control}} \times 100$$

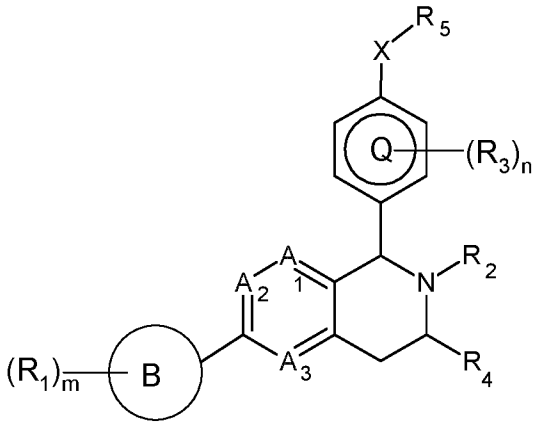
.

Dose/Route	Agents alone	Agents + Estradiol
	% Agonism (Mean ± SD)	% Antagonism (Mean ± SD)
Example 1 10ug, sc. qd	-15±4.3	62±15
Example 1 100ug, sc. qd	-15±7.1	107±2.0
Example 4 10ug, sc. qd	1.6±13	-16±29
Example 4 100ug, sc. qd	-18±10	87±6.0
Example 6 10ug, sc. qd	-14±8.1	85±9.9
Example 6 100ug, sc. qd	-16±7.7	112±7.4
Example 10 10ug, sc. qd	0.7±10	5.1±25

Example 10 100ug, sc. qd	-23±4.7	79±6.9
Tamoxifen 1mg/kg (Mean ± SEM) n=3	77±5.4	17±5.3
Faslodex, 0.2mg/kg (Mean ± SEM) n=3	-17±5.8	71±2.1

WHAT IS CLAIMED IS:

1. A compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof, wherein,

A_1, A_2, and A_3 are each independently -C(R_6)= or -N=;

Ring Q is a 6 membered aromatic ring wherein the ring atoms are independently selected from carbon or nitrogen;

Ring B is a 5 or 6 membered unsaturated ring which may be carbon or nitrogen linked; wherein if said 5 or 6 membered unsaturated ring contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R_7;

X is -O-, -NR_8-, -C(R_9)(R_{10})-, or -S-;

R_1 and R_3 are substituents on carbon and are independently selected from hydroxyl, halogen, nitro, cyano, carboxyl, amino, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoroethyl, methoxy, ethoxy, trifluoromethoxy, trifluoroethoxy, methylamino, dimethylamino or ethylamino; or two R_1 groups on vicinal atoms form a five- or six-membered fused carbocyclyl or fused heterocyclyl ring; wherein said five- or six-membered fused carbocyclyl or fused heterocyclyl ring can be optionally substituted on carbon by R_{11}; and wherein if said five- or six-membered fused heterocyclyl ring contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R_{12};

R_2 and R_5 are independently selected from $C_{1\text{-}12}$ alkyl, a 3-10 membered saturated or

unsaturated carbocyclyl, or a 3-10 membered saturated or unsaturated heterocyclyl; wherein R_2 and R_5 can be optionally substituted on carbon by R_{13}; and wherein if said 3-10 membered saturated or unsaturated heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R_{14};

R_4 is C_{1-3} alkyl or C_{3-4} cycloalkyl; wherein R_4 may be optionally substituted by one or more hydroxyl, halogen or methoxy;

R_8 is hydrogen or C_{1-12} alkyl optionally substituted by one or more halo or hydroxy;

R_6, R_9 and R_{10} are each independently hydrogen, hydroxyl, halogen, nitro, cyano, carboxyl, amino, carbamoyl, mercapto, sulphamoyl, C_{1-12} alkyl or C_{1-12} alkoxyl; wherein said C_{1-12} alkyl or C_{1-12} alkoxyl can be independently optionally substituted by one or more halo or hydroxy;

R_{11} and R_{13} are substituents on carbon and are each independently selected from hydroxyl, halogen, nitro, cyano, carboxyl, trifluoromethoxy, amino, carbamoyl, mercapto, sulphamoyl, C_{1-12} alkyl, C_{1-12} alkoxyl, C_{1-12} alkanoyl, C_{1-12} alkanoyloxy, N-(C_{1-12} alkyl)amino, N,N-(C_{1-12} alkyl)$_2$amino, C_{1-12} alkanoylamino, N-(C_{1-12} alkyl)carbamoyl, N,N-(C_{1-12} alkyl)$_2$carbamoyl, C_{1-12} alkyl$S(O)_a$ wherein a is 0 to 2, C_{1-12} alkoxycarbonyl, N-(C_{1-12} alkyl)sulphamoyl, N,N-(C_{1-12} alkyl)$_2$sulphamoyl, C_{1-12} alkylsulphonylamino, C_{1-12} alkyl-OH, C_{1-12} haloalkyl, -$Si(R_aR_bR_c)$, 3-10 membered saturated or unsaturated carbocyclyl, or 3-10 membered saturated or unsaturated heterocyclyl; wherein R_{11} and R_{13} independently of each other may be optionally substituted on carbon by one or more R_{15}; and wherein if said 3-10 membered saturated or unsaturated heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R_{16};

R_7, R_{12}, R_{14} and R_{16} are independently selected from C_{1-12} alkyl, C_{1-12} alkanoyl, C_{1-12} alkylsulphonyl, C_{1-12} alkoxycarbonyl, carbamoyl, N-(C_{1-12} alkyl)carbamoyl, N,N-(C_{1-12} alkyl)$_2$carbamoyl, 3-10 membered saturated or unsaturated carbocyclyl, 3-10 membered saturated or unsaturated heterocyclyl, 3-10 membered saturated or unsaturated carbocyclylC_{1-12} alkyl, 3-10 membered saturated or unsaturated heterocyclylC_{1-12} alkyl, benzyl, benzyloxycarbonyl, benzoyl or phenylsulphonyl; wherein R_7, R_{12}, R_{14} and R_{16} may be independently optionally substituted on carbon by R_{17};

R_{15} and R_{17} are each independently selected from hydroxyl, halogen, nitro, cyano,

carboxyl, trifluoromethoxy, amino, carbamoyl, mercapto, sulphamoyl, C_{1-12} alkyl, C_{1-12} alkoxyl, C_{1-12} haloalkyl, N-(C_{1-12} alkyl)amino, N-(C_{1-12} haloalkyl)amino, or C_{1-12} alkyl-OH;

R_a, R_b and R_c are each independently selected from hydroxyl, C_{1-12} alkyl, or C_{1-12} alkyl-OH; and

m is 0, 1, 2, 3 or 4;

n is 0, 1 or 2.

2. A compound of formula (I), or a pharmaceutically acceptable salt thereof ,as claimed in claim 1 wherein A_1, A_2, and A_3 are each independently -C(R_6)= or -N=; wherein R_6 are each independently hydrogen or halogen.

3. A compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in either claim 1 or claim 2 wherein Ring Q is phenyl or pyridyl.

4. A compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1-3 wherein Ring B is a 5 or 6 membered unsaturated ring which may be carbon or nitrogen linked; wherein if said 5 or 6 membered unsaturated ring contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R_7; wherein

R_7 is selected from C_{1-12} alkyl or cyclopropyl; wherein R_7 may be independently optionally substituted on carbon by one or more R_{17}; and

R_{17} are each independently selected from halogen.

5. A compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1-4 wherein X is -O-, -NR_8- or -C(R_9)(R_{10})-; wherein

R_8 is hydrogen; and

R_9 and R_{10} are each independently hydrogen, hydroxyl or halogen.

6. A compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1-5 wherein R_1 is a substituent on carbon and is independently selected

from hydroxyl, halogen or methyl.

7. A compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1-6 wherein R_2 is selected from C_{1-12} alkyl or a 5 membered saturated carbocyclyl; wherein R_2 can be optionally substituted on carbon by one or more R_{13}; wherein

R_{13} is a substituent on carbon and are each independently selected from hydroxyl, halogen or C_{1-12} alkyl.

8. A compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1-7 wherein R_3 is a substituent on carbon and is independently selected from halogen or methoxy.

9. A compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1-8 wherein R_4 is C_{1-3} alkyl or C_{3-4} cycloalkyl; wherein R_4 may be optionally substituted by one or more halogen.

10. A compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1-9 wherein R_5 is selected from C_{1-12} alkyl or a 4 or 5 membered saturated heterocyclyl; wherein R_5 can be optionally substituted on carbon by one or more R_{13}; and wherein if said 4 or 5 membered saturated heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R_{14}; wherein

R_{13} are substituents on carbon and are independently selected N-(C_{1-12} alkyl)amino; wherein R_{13} independently of each other may be optionally substituted on carbon by one or more R_{15};

R_{14} are independently selected from C_{1-12} alkyl; wherein R_{14} may be independently optionally substituted on carbon by one or more R_{17}; and

R_{15} and R_{17} are each independently selected from halogen.

11. A compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1-10 wherein m is 0 or 1.

12. A compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1-11 wherein:

A_1, A_2, and A_3 are each independently -C(R_6)= or -N=; wherein R_6 are each independently hydrogen or fluoro;

Ring Q is phenyl or pyridyl;

Ring B is pyrazolyl, oxazolyl, 1,2,4-triazol-4-yl, 1,2,3-triazol-4-yl, 2,5-dihydrothiophen-4-yl1,1-dioxide, pyrimidinyl, pyridazinyl, pyridyl, pyrrolyl, tetrazolyl or imidazolyl; wherein if said pyrazolyl, 1,2,3-triazolyl, pyrrolyl, tetrazolyl, 1,2,4-triazolyl and imidazolyl contain an -NH- moiety that nitrogen may be optionally substituted by a group selected from R_7; wherein R_7 is selected from methyl, ethyl or cyclopropyl; wherein R_7 may be independently optionally substituted on carbon by one or more R_{17}; and R_{17} are each independently selected from fluoro;

X is -O-, -NH-, -CH_2-, -CH(OH)- or -CH(F)-;

R_1 is a substituent on carbon and is independently selected from hydroxyl, fluoro or methyl;

R_2 is selected from ethyl, propyl or bicyclo[1.1.1]pentan-1-yl; wherein R_2 can be optionally substituted on carbon by one or more R_{13}; wherein R_{13} is a substituent on carbon and are each independently selected from hydroxyl, fluoro or methyl;

R_3 is a substituent on carbon and is independently selected from fluoro or methoxy;

R_4 is methyl, ethyl or cyclopropyl; wherein R_4 may be optionally substituted by one or more fluoro;

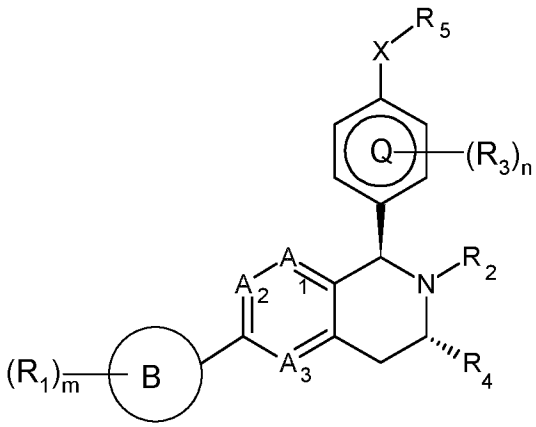
R_5 is selected from ethyl, azetidine-3-yl or pyrrolidine-3-yl; wherein R_5 can be optionally substituted on carbon by one or more R_{13}; and wherein said azetidine-3-yl or pyrrolidine-3-yl may be optionally substituted on the -NH- moiety by a group selected from R_{14}; wherein R_{13} are substituents on carbon and are independently selected propylamino; wherein R_{13} independently of each other may be optionally substituted on carbon by one or more R_{15}; R_{14} are independently selected from propyl; wherein R_{14} may be independently optionally substituted on carbon by one or more R_{17}; and R_{15} and R_{17} are each independently

selected from fluoro;

m is 0 or 1; and

n is 0, 1, or 2.

13. A compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1-12 wherein the compound of formula (I) is a compound of formula (Ia):



(Ia)

14. A compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1-13 selected from:

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3R)-3-methyl-6-(1-methyl-1H-pyrazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;

2,2-difluoro-3-((1S,3R)-1-(5-((1-(3-fluoropropyl)azetidin-3-yl)amino)pyridin-2-yl)-3-methyl-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroisoquinolin-2(1H)-yl)propan-1-ol;

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3R)-3-methyl-6-(1H-pyrazol-1-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3R)-3-methyl-6-(1H-pyrazol-3-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3R)-6-(isoxazol-4-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;

N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3R)-3-methyl-6-(1H-pyrazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;

6-((1S,3R)-6-(1-ethyl-1H-pyrazol-4-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-N-(1-(3-fluoropropyl)azetidin-3-yl)pyridin-3-amine;
6-((1S,3R)-6-(1-cyclopropyl-1H-pyrazol-4-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-N-(1-(3-fluoropropyl)azetidin-3-yl)pyridin-3-amine;
6-((1S,3R)-6-(1-(difluoromethyl)-1H-pyrazol-4-yl)-3-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-N-(1-(3-fluoropropyl)azetidin-3-yl)pyridin-3-amine;
N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3R)-3-methyl-6-(1-methyl-1H-pyrazol-3-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine;
N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3R)-3-methyl-6-(4H-1,2,4-triazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine; and
N-(1-(3-fluoropropyl)azetidin-3-yl)-6-((1S,3R)-3-methyl-6-(2H-1,2,3-triazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)pyridin-3-amine.

15. A pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-14, in association with a pharmaceutically acceptable diluent or carrier.

16. A compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-14, for use as a medicament.

17. The use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-14 in the manufacture of a medicament for the selective downregulation of estrogen receptors in a warm-blooded animal such as man.

18. A method of treating ER mediated or dependent diseases or conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-14.

19. A compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in

any one of claims 1-14, for use in the production of an anti-cancer effect in a warm-blooded animal such as man.

20. A pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-14, in association with a pharmaceutically-acceptable diluent or carrier for use in the treatment of breast cancer in a warm-blooded animal such as man.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2019/089215

A. CLASSIFICATION OF SUBJECT MATTER

C07D 401/04(2006.01)i; C07D 217/14(2006.01)i; C07D 405/12(2006.01)i; C07D 417/04(2006.01)i; C07D 471/04(2006.01)i; A61P 35/00(2006.01)i; A61K 31/4353(2006.01)i

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D401; C07D217; C07D405; C07D417; C07D174; A61P35; A61K31

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

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

CNKI,CNABS,VEN,STN(REG,CAPLUS), estrogen receptor downregulators,SERDs,estrogen receptor, ER, tetrahydroisoquinoline,the structure

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016202161 A1 (JIANGSU HENGRUI MEDICINE COET AL.) 22 December 2016 (2016-12-22) the abstract, examples 3,10-29,46-69	1-17, 19-20
A	CN 105229004 A (ASTRAZENECA AB) 06 January 2016 (2016-01-06) the whole document	1-17, 19-20

☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:

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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 August 2019	**04 September 2019**

Name and mailing address of the ISA/CN	Authorized officer
National Intellectual Property Administration, PRC **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088** **China**	**XING,Weiwei**
Facsimile No. **(86-10)62019451**	Telephone No. **62086316**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2019/089215

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: **18**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claim 18 is directed to a method of treatment which belongs to Rule 39.1(iv) PCT and is not need to be searched.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2019/089215

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		CN 105229004 B	03 May 2017
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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2019/089215

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
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