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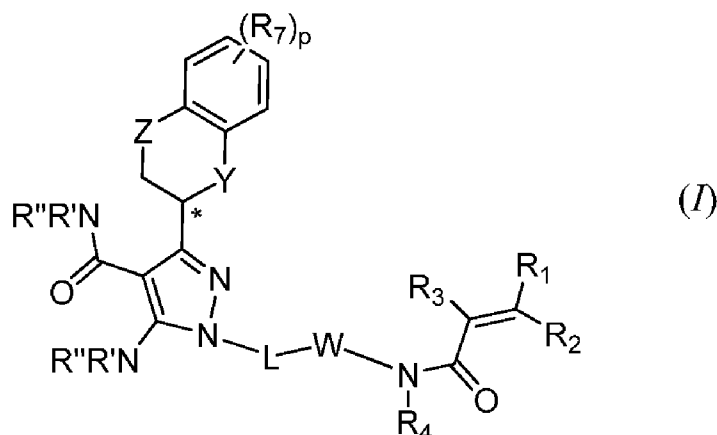
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(54) Title: 5-AMINO-4-CARBAMOYL-PYRAZOLE COMPOUNDS AS SELECTIVE AND IRREVERSIBLE T790M OVER WT-EGFR KINASE INHIBITORS AND USE THEREOF



(57) Abstract: Disclosed are compounds of Formula (I), pharmaceutical compositions comprising the same, processes for the preparation thereof, and the use thereof.

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5-AMINO-4-CARBAMOYL-PYRAZOLE COMPOUNDS AS SELECTIVE AND IRREVERSIBLE T790M OVER WT-EGFR KINASE INHIBITORS AND USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

- 5 **[0001]** This application claims the benefit of PCT application No. PCT/CN2014/082439 filed on July 18, 2014, the disclosure of which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

1. FIELD OF THE INVENTION

- 10 **[0002]** Disclosed herein are 5-amino-4-carbamoyl-pyrazole compounds, pharmaceutical compositions comprising the same, processes for the preparation thereof, and the use thereof in therapy. Disclosed herein are certain 5-amino-4-carbamoyl-pyrazole compounds that have good selectivity of T790M vs WT EGFR inhibition and are useful for treating disorders mediated thereby.

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2. DESCRIPTION OF RELATED ART

- [0003]** Lung cancer continues to be the leading cause of cancer-related mortality, demonstrating the limited efficacy of traditional cytotoxic chemotherapy in patients with this disease (Bedano PM, Hanna NH. *J Thorac Oncol.* 2006;1:582–587.; Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, et al. *CA Cancer J Clin.* 2006; 56:106–130.). The development of new and effective therapies for patients with advanced lung cancer remains a major health imperative, and targeted therapies may offer well-tolerated disease-modifying treatment options in patient populations defined by relevant oncogene mutation status. Members of the ERBB receptor tyrosine kinase family, including epidermal growth factor receptor (EGFR), HER2, HER3 and HER4, present an attractive option for targeted therapy in patients with NSCLC, due to observed patterns of oncogenic mutation of *EGFR* and *HER2* (Lynch TJ, Bell DW, Sordella R,
- 20
- 25

Gurubhagavatula S, Okimoto RA, Brannigan BW, et al. *N Engl J*

Med. 2004;350:2129–2139.; Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, et al.

Science. 2004;304:1497–1500.; Pao W, Miller V, Zakowski M, Doherty J, Politi K, Sarkaria I, et

al. *Proc Natl Acad Sci USA.* 2004; 101:13306 – 13311.; Stephens P, Hunter C, Bignell G, Edkins

5 S, Davies H, Teague J, et al. *Nature.* 2004;431:525–526.; Shigematsu H, Takahashi T, Nomura M,

Majmudar K, Suzuki M, Lee H, et al. *Cancer Res.* 2005;65:1642–1646.; Shimamura T, Ji H,

Minami Y, Thomas RK, Lowell AM, Shah K, et al. *Cancer Res.* 2006;66:6487–6491.; Wang SE,

Narasanna A, Perez-Torres M, Xiang B, Wu FY, Yang S, et al. *Cancer Cell.* 2006;10:25–38.).

[0004] First-generation small molecule EGFR tyrosine kinase inhibitors, such as gefitinib and

10 erlotinib, were shown to be effective against lung tumor cells harboring mutations in the kinase domain of EGFR, most commonly small in-frame deletions in exon 19 or the L858R missense mutation in exon 21 (Janne PA, Engelman JA, Johnson BE. *J Clin Oncol.* 2005;23:3227–3234.).

However, despite the initial response, patients almost invariably develop resistance to these inhibitors and relapse after several months (Riely GJ, Pao W, Pham D, Li AR, Rizvi N,

15 Venkatraman ES, et al. *Clin Cancer Res.* 2006;12:839–844.).

[0005] Non-small cell lung cancer (NSCLC) patients with activating EGFR mutations initially respond well to the EGFR tyrosine kinase inhibitors (TKIs) erlotinib and gefitinib. However, clinical efficacy is limited by the development of resistance. The most common mechanism of resistance is a second site mutation within exon 20 of EGFR (T790M), observed in ~50% of cases

20 (Kobayashi S, Ji H, Yuza Y, Meyerson M, Wong KK, Tenen DG, et al. *Cancer*

Res. 2005b;65:7096–7101.; Pao W, Miller VA, Politi KA, Riely GJ, Somwar R, Zakowski MF, et

al. *PLoS Med.* 2005a;2:e73.). T790M EGFR exhibits elevated enzymatic and transforming

activity, both alone and in combination with primary alterations in exon 19 or 21 (Mulloy R,

Ferrand A, Kim Y, Sordella R, Bell DW, Haber DA, et al. *Cancer Res.* 2007;67:2325–2330.;

25 Schiffer HH, Reding EC, Fuhs SR, Lu Q, Piu F, Wong S, et al. *Mol*

Pharmacol. 2007;71:508–518.; Vikis H, Sato M, James M, Wang D, Wang Y, Wang M, et al.

Cancer Res. 2007;67:4665–4670; Yuza Y, Glatt KA, Jiang J, Greulich H, Minami Y, Woo MS, et

al. *Cancer Biol Ther.* 2007;6:661–667.), indicating a need for increased therapeutic efficacy of the next generation of EGFR inhibitors.

[0006] Irreversible inhibitors that covalently modify EGFR exhibit increased efficacy against mutants resistant to gefitinib and erlotinib in cell-based assays (Greulich H, Chen TH, Feng W, Janne PA, Alvarez JV, Zappaterra M, et al. *PLoS Med.* 2005;2:e313.; Kwak EL, Sordella R, Bell DW, Godin-Heymann N, Okimoto RA, Brannigan BW, et al. *Proc Natl Acad Sci USA.* 2005;102:7665–7670.; Kobayashi S, Boggon TJ, Dayaram T, Janne PA, Kocher O, Meyerson M, et al. *N Engl J Med.* 2005a;352:786–792.; Kobayashi S, Ji H, Yuza Y, Meyerson M, Wong KK, Tenen DG, et al. *Cancer Res.* 2005b;65:7096–7101; Shimamura T, Ji H, Minami Y, Thomas RK, Lowell AM, Shah K, et al. *Cancer Res.* 2006;66:6487–6491.; Yuza Y, Glatt KA, Jiang J, Greulich H, Minami Y, Woo MS, et al. *Cancer Biol Ther.* 2007;6:661–667.). Preclinical and early clinical trials also suggest a potential efficacy of a new class of panHER inhibitor in overcome acquired resistance related to T790M. One such inhibitor, BIBW2992 or afatinib, is a new irreversible dual specificity EGFR/HER2 inhibitor derived from the anilino-quinazoline chemical series that was designed to covalently bind to Cys 773 of EGFR and Cys 805 of HER2. Although afatinib demonstrated clinical benefits and was recently approved for the treatment of metastatic non-small cell lung carcinoma (NSCLC). However, indirect comparison of phase III trials showed higher incidences of diarrhea, skin rash and stomatitis for afatinib respect to erlotinib or gefitinib (Mok TS, Wu YL, Thongprasert S, et al. *N Engl J Med* 2009;361:947-57; Rosell R, Carcereny E, Gervais R, et al. *Lancet Oncol* 2012;13:239-46; Han JY, Park K, Kim SW, et al. *J Clin Oncol* 2012;30:1122-8.). Taken into account, all these data suggested that toxicities of the second-generation covalent inhibitors are probably higher than those observed with first-generation compounds. Wild type EGFR inhibition is believed to drive the observed dose limiting toxicities (such as skin rash and diarrhea) for these first and second generation therapies in the clinic.

[0007] To further improve the efficacy and overcome the side effect of the second generation of EGFR inhibitors such as afatinib, dacomitinib and neratinib, the third generation of irreversible EGFR inhibitors have been reported and moved into clinical trials. These new type of EGFR

inhibitors have good selectivity of T790M vs WT EGFR inhibition. For examples, CO-1686 and AZD9291 are irreversible kinase inhibitors that target the mutant forms of EGFR by inhibiting the common activating mutations (L858R, delE746-A750) and the gatekeeper mutation (T790M) but not the wild-type receptor. Therefore, CO-1686 and AZD9291 have the potential to effectively treat first- and second-line NSCLC patients with EGFR mutations without causing the dose limiting toxicities associated with approved EGFR kinase inhibitors.

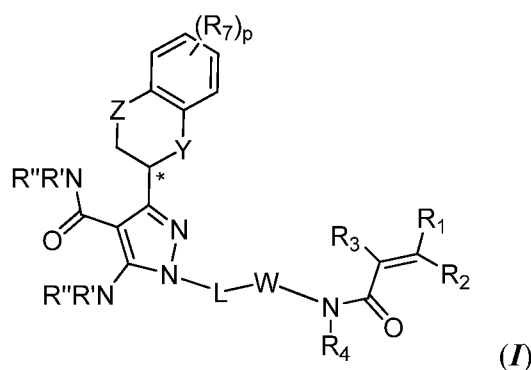
[0008] Certain other T790M EGFR kinase inhibitors have also been identified. International Patent Application Publication WO 2011/162515, International Patent Application Publication WO 2013/184757, International Patent Application Publication WO 2013/184766, International Patent Application Publication WO 2013/014448, International Patent Application Publication WO 2013/042006, International Patent Application Publication WO 2013/118817, International Patent Application Publication WO 2013/125709, International Patent Application Publication WO 2014/025486.

BRIEF SUMMARY OF THE INVENTION

[0009] The present invention aims to provide new 5-amino-4-carbamoyl-pyrazole compounds which inhibit mutant EGFR kinases.

[0010] Disclosed herein are 5-amino-4-carbamoyl-pyrazole compounds that can selectively inhibit T790M EGFR kinases over WT-EGFR kinases.

[0011] Provided is at least one 5-amino-4-carbamoyl-pyrazole compounds selected from compounds of Formula (I)



stereoisomers thereof, and pharmaceutically acceptable salts thereof,

wherein:

R_1 , R_2 and R_3 are independently selected from hydrogen, halo, C_{1-6} alkyl, and C_{1-6} haloalkyl;

R_4 is selected from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

L is a linking group selected from a bond, $-(CR_5R_6)_n-$, S, -O-, and $-NR_8-$, wherein n is an

5 integer of 1, 2, or 3;

W is selected from aryl or heteroaryl, said aryl or heteroaryl is optionally substituted by 1, 2, or 3 substituents selected from the group consisting of halogen, CN, NO_2 , OR_8 , $NR'R''$, $NR'COR''$, $NR'SO_2R''$, $CONR'R''$, $COOR'$, SO_2R' , C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, heterocyclyl, aryl, and heteroaryl; or

10 W and R_4 taken together with the nitrogen to which they are attached form a 4-, or 5-, or 6-membered heterocyclic ring optionally containing a further heteroatom selected from NR_8 , O and S, said heterocyclic ring is optionally substituted by 1, 2, or 3 substituents selected from the group consisting of halogen, CN, NO_2 , OR_8 , $NR'R''$, $NR'COR''$, $NR'SO_2R''$, $CONR'R''$, $COOR'$, SO_2R' , C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, heterocyclyl, aryl, and heteroaryl;

15 R_7 , at each occurrence, is independently selected from hydrogen, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy; and wherein p is an integer of 0, 1, 2, 3, or 4;

Y is selected from $-CR_5R_6-$ and -O-;

Z is selected from $-(CR_5R_6)_m-$, $-CR_5R_6-O-$, -O-, and $-NR'-$, wherein m is an integer of 1 or 2;

R_5 and R_6 are independently selected from hydrogen, halo, C_{1-6} alkyl, and C_{1-6} haloalkyl;

20 R_8 is selected from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

R' and R'' , at each occurrence, are independently selected from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; and

* is a chiral center.

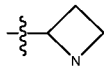
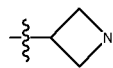
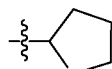
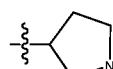
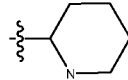
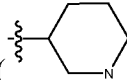
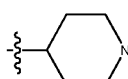
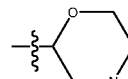
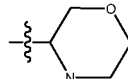
[0012] In some embodiments, R_1 , R_2 , and R_3 are hydrogen.

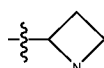
25 **[0013]** In some embodiments, R_4 is hydrogen.

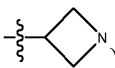
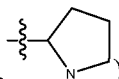
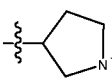
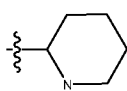
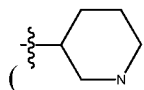
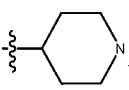
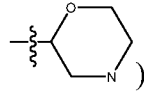
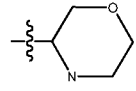
[0014] In some embodiments, L is a bond, and W is aryl or heteroaryl. In some further embodiments, L is a bond, and W is a phenyl or pyridyl group.

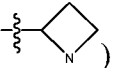
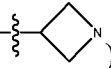
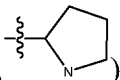
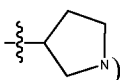
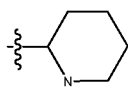
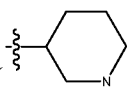
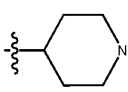
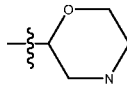
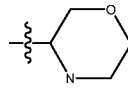
[0015] In some embodiments, L is $-(CR_5R_6)_n-$, and W is aryl or heteroaryl, wherein n is an integer of 1, 2, or 3, and R_5 and R_6 are independently selected from hydrogen, halo, C_{1-6} alkyl, and C_{1-6} haloalkyl. In some further embodiments, L is $-(CR_5R_6)_n-$, and W is a phenyl or pyridyl group, wherein n is an integer of 1, 2, or 3, and R_5 and R_6 are independently selected from hydrogen, halo, C_{1-6} alkyl, and C_{1-6} haloalkyl. In some further embodiments, L is $-CH_2-$, and W is a phenyl or pyridyl group.

[0016] In some embodiments, L is a bond or $-(CR_5R_6)_n-$, and W and R_4 taken together with the nitrogen to which they are attached form a 4-, or 5-, or 6-membered heterocyclic ring optionally containing a further heteroatom selected from NR₈, O and S, said heterocyclic ring is optionally substituted by 1, 2, or 3 substituents selected from the group consisting of halogen, CN, NO₂, OR₈, NR'R'', NR'COR'', NR'SO₂R'', CONR'R'', COOR', SO₂R', C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, heterocyclyl, aryl, and heteroaryl, wherein R_5 , R_6 , R_8 , R', R'' and n are defined as above. In some further embodiments, L is a bond or $-(CR_5R_6)_n-$, and W and R_4 taken together with the nitrogen to which they are attached form a 4-, or 5-, or 6-membered heterocyclic ring selected

from the group consisting of azetidiny (such as azetidin-2-yl (i.e., ) and azetidin-3-yl (i.e., )), pyrrolidiny (such as pyrrolidin-2-yl (i.e., ) and pyrrolidin-3-yl (i.e., )), piperidiny (such as piperidin-2-yl (i.e., ) and piperidin-3-yl (i.e., )), and piperidin-4-yl (i.e., )), and morpholinyl (such as morpholin-2-yl (i.e., )), and morpholin-3-yl (i.e., )), and wherein R_5 and R_6 are independently selected from

hydrogen, halo, C_{1-6} alkyl, and C_{1-6} haloalkyl; and n is an integer of 1, 2, or 3, and wherein the wavy lines represent points of attachment to the linking group L, and the acryloyl group on the nitrogen atom is omitted. In some further embodiments, L is a bond, and W and R_4 taken together with the nitrogen to which they are attached form a 4-, or 5-, or 6-membered heterocyclic ring selected from the group consisting of azetidiny (such as azetidin-2-yl (i.e., ) and

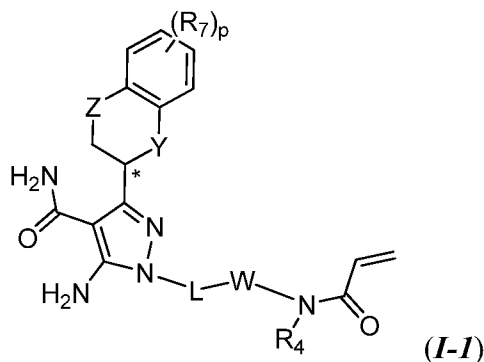
azetidin-3-yl (i.e., ) , pyrrolidinyl (such as pyrrolidin-2-yl (i.e., ) , and pyrrolidin-3-yl (i.e., ) , piperidinyl (such as piperidin-2-yl (i.e., ) , piperidin-3-yl () , and piperidin-4-yl (i.e., ) , and morpholinyl (such as morpholin-2-yl (i.e., ) , and morpholin-3-yl (i.e., ) , and wherein the wavy lines represent points of

5 attachment to the linking group L, and the acryloyl group on the nitrogen atom is omitted. In some further embodiments, L is -CH₂-, and W and R₄ taken together with the nitrogen to which they are attached form a 4-, or 5-, or 6-membered heterocyclic ring selected from the group consisting of azetidinyl (such as azetidin-2-yl (i.e., ) and azetidin-3-yl (i.e., ) , pyrrolidinyl (such as pyrrolidin-2-yl (i.e., ) , and pyrrolidin-3-yl (i.e., ) , piperidinyl (such as piperidin-2-yl (i.e., ) , piperidin-3-yl () , and piperidin-4-yl (i.e., ) , and morpholinyl (such as morpholin-2-yl (i.e., ) , and morpholin-3-yl (i.e., ) , and wherein the wavy lines represent points of attachment to the linking group L, and the acryloyl group on the nitrogen atom is omitted.

[0017] In some embodiments, Y is -O-, and Z is -O-. In some embodiments, Y is -O-, and Z is -NR'-, wherein R' is independently selected from hydrogen, C₁₋₆ alkyl, and C₁₋₆ haloalkyl. In some embodiments, Y is -CR₅R₆-, and Z is -NR'-, wherein R₅ and R₆ are independently selected from hydrogen, halo, C₁₋₆ alkyl, and C₁₋₆ haloalkyl ; and R' is independently selected from hydrogen, C₁₋₆ alkyl, and C₁₋₆ haloalkyl. In some embodiments, Y is -CR₅R₆-, and Z is -CR₅R₆-, wherein R₅ and R₆ are independently selected from hydrogen, halo, C₁₋₆ alkyl, and C₁₋₆ haloalkyl. In some embodiments, Y is -CR₅R₆-, and Z is -O-, wherein R₅ and R₆ are independently selected from hydrogen, halo, C₁₋₆ alkyl, and C₁₋₆ haloalkyl. In some embodiments, Y is -CR₅R₆-, Z is -(CR₅R₆)₂-, wherein R₅ and R₆ are independently selected from hydrogen, halo, C₁₋₆ alkyl, and

C₁₋₆ haloalkyl. In some embodiments, Y is -CR₅R₆-, and Z is -CR₅R₆O-, wherein R₅ and R₆ are independently selected from hydrogen, halo, C₁₋₆ alkyl, and C₁₋₆ haloalkyl.

[0018] Provided is at least one 5-amino-4-carbamoyl-pyrazole compounds according to Formula (I), which is Formula (I-1):



stereoisomers thereof, and pharmaceutically acceptable salts thereof,

wherein:

R₄ is selected from hydrogen, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

L is a linking group selected from a bond, or -CH₂-;

W is selected from phenyl or pyridyl; or

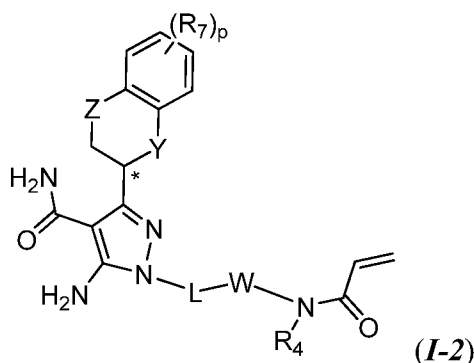
R₇, at each occurrence, is independently selected from hydrogen, halo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, and C₁₋₆ haloalkoxy; and wherein p is an integer of 0, 1, 2, 3, or 4;

Y is selected from -CH₂- and -O-;

Z is selected from -CH₂-, -CH₂CH₂-, -CH₂O-, -O-, and -NMe-; and

* is a chiral center.

[0019] Provided is at least one 5-amino-4-carbamoyl-pyrazole compounds according to Formula (I), which is Formula (I-2):



stereoisomers thereof, and pharmaceutically acceptable salts thereof,

wherein:

L is a bond or -CH₂-,

W and R₄ taken together with the nitrogen to which they are attached form a 4-, or 5-, or
 5 6-membered heterocyclic ring selected from the group consisting of azetidiny, pyrrolidinyl,
 piperidinyl, and morpholinyl, said heterocyclic ring is optionally substituted by 1, 2, or 3
 substituents selected from the group consisting of halogen, CN, NO₂, OR₈, NR'R'', NR'COR'',
 NR'SO₂R'', CONR'R'', COOR', SO₂R', C₁₋₆alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl,
 heterocyclyl, aryl, and heteroaryl;

10 R₇, at each occurrence, is independently selected from hydrogen, halo, C₁₋₆ alkyl,
 C₁₋₆ haloalkyl, C₁₋₆ alkoxy, and C₁₋₆ haloalkoxy; and wherein p is an integer of 0, 1, 2, 3, or 4; R₈ is
 selected from hydrogen, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

R₈ is selected from hydrogen, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

R' and R'', at each occurrence, are independently selected from hydrogen, C₁₋₆ alkyl, and
 15 C₁₋₆ haloalkyl;

Y is selected from -CH₂- and -O-;

Z is selected from -CH₂-, -CH₂CH₂-, -CH₂O-, -O-, and -NMe-; and

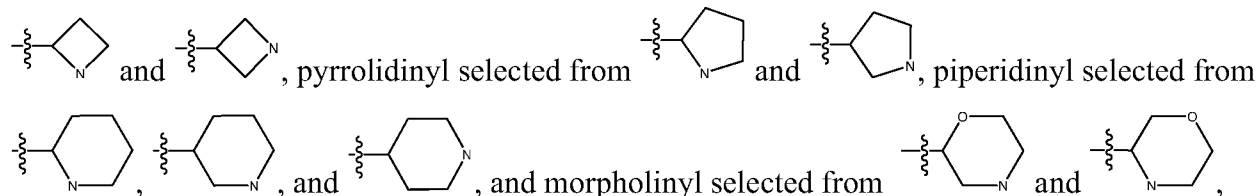
* is a chiral center.

[0020] In some embodiments, at least one 5-amino-4-carbamoyl-pyrazole compounds

20 according to Formula I-2, wherein

L is a bond or -CH₂-,

W and R₄ taken together with the nitrogen to which they are attached form a 4-, or 5-, or
 6-membered heterocyclic ring selected from the group consisting of azetidiny selected from



25 and wherein the wavy lines represent points of attachment to the linking group L, and the acryloyl
 group on the nitrogen atom is omitted,

R₇, at each occurrence, is independently selected from hydrogen, halo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, and C₁₋₆ haloalkoxy; and wherein p is an integer of 0, 1, 2, 3, or 4;

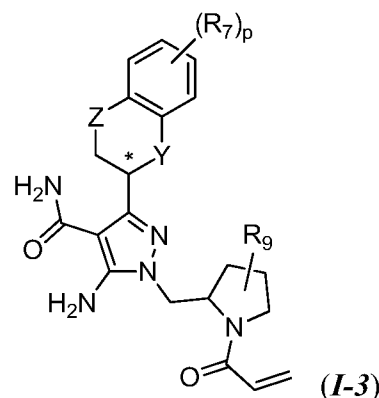
Y is selected from -CH₂- and -O-;

Z is selected from -CH₂-, -CH₂CH₂-, -CH₂O-, -O-, and -NMe-; and

5 * is a chiral center.

[0021] In some embodiments, at least one 5-amino-4-carbamoyl-pyrazole compounds according to Formula I-2, the carbon atom to which the linking group L is attached to the 4-, or 5-, or 6-membered heterocyclic ring formed by W and R₄ taken together with the nitrogen atom is (R) or (S) configuration.

10 **[0022]** Provided is at least one 5-amino-4-carbamoyl-pyrazole compounds according to
 Formula (I), which is Formula (I-3):



stereoisomers thereof, and pharmaceutically acceptable salts thereof,

wherein:

15 R₇, at each occurrence, is independently selected from hydrogen, halo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, and C₁₋₆ haloalkoxy; and wherein p is an integer of 0, 1, 2, 3, or 4;

Y is selected from -CH₂- and -O-;

Z is selected from -CH₂-, -CH₂CH₂-, -CH₂O-, -O-, and -NMe-; and

* is a chiral center.

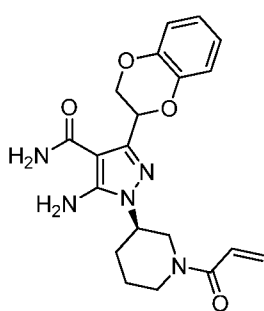
20 R₉ is selected from F, Cl, Br, OR₈, NR'R", O-(CH₂)_n-NR'R";

$$n = 1, 2, 3;$$

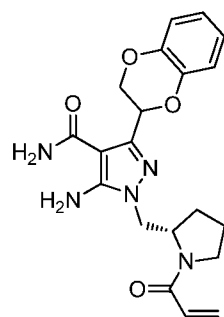
R₈ is selected from hydrogen, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

R' and R", at each occurrence, are independently selected from hydrogen, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

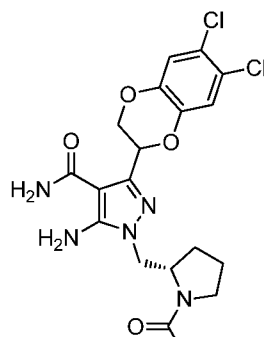
[0023] Also provided herein is at least one compound selected from the following compounds:



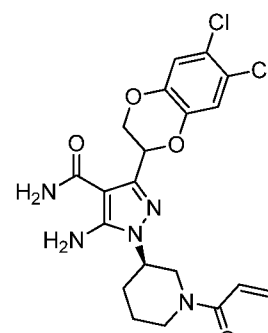
Compound 1.1



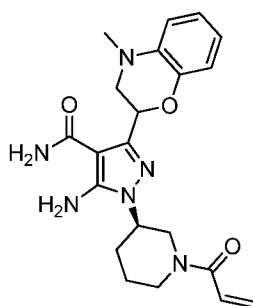
Compound 1.2



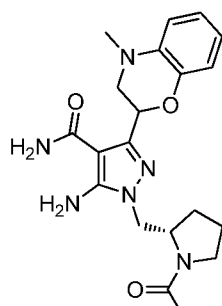
Compound 1.3



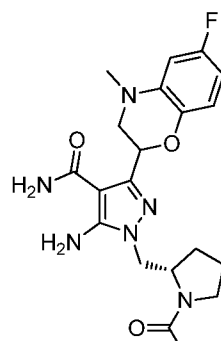
Compound 1.4



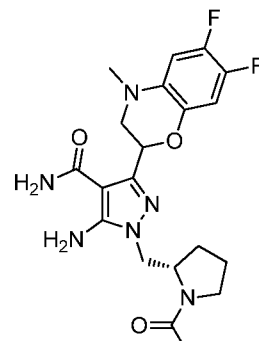
Compound 1.5



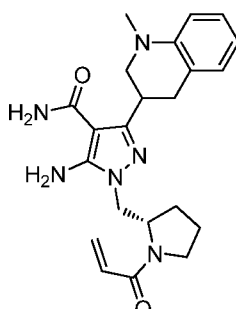
Compound 1.6



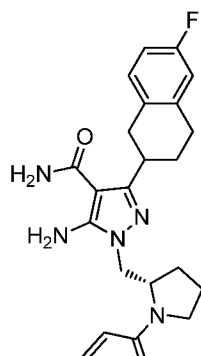
Compound 1.7



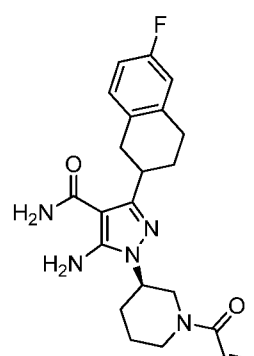
Compound 1.8



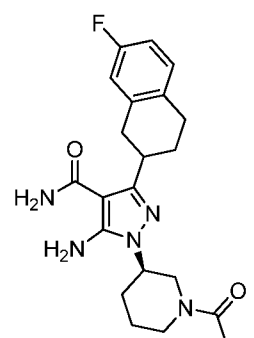
Compound 1.9



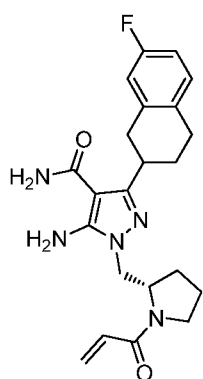
Compound 1.10



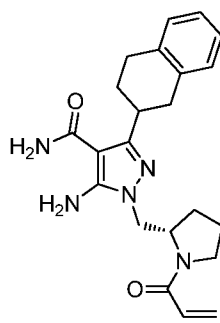
Compound 1.11



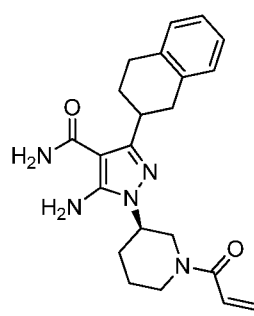
Compound 1.12



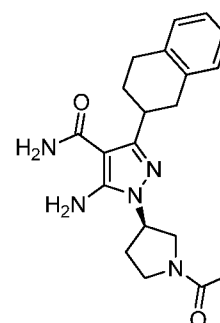
Compound 1.13



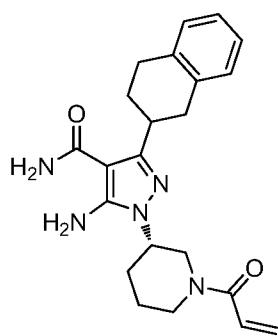
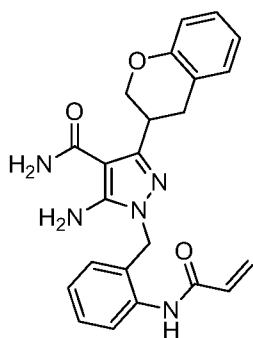
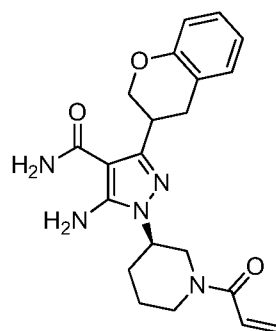
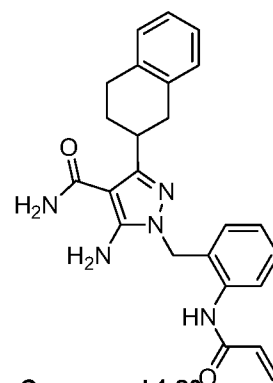
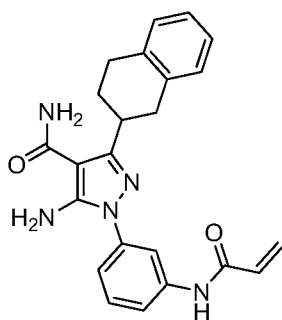
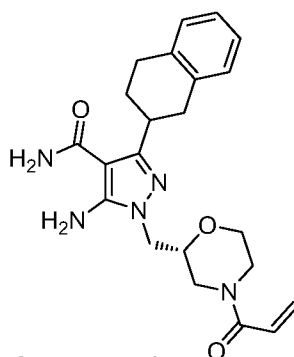
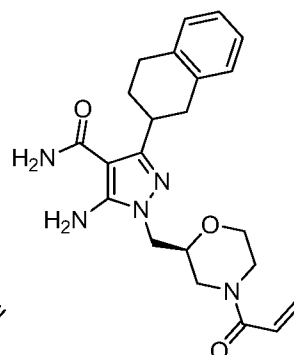
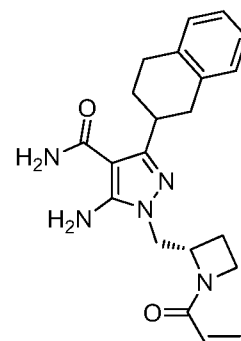
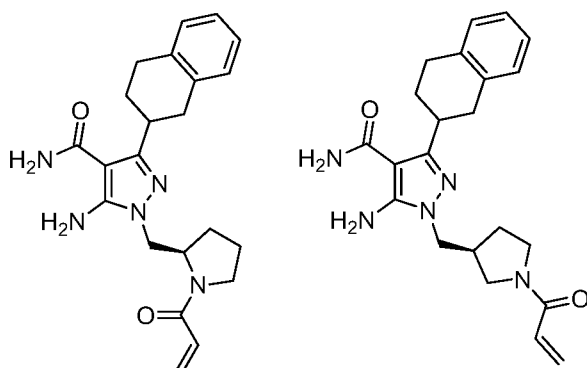
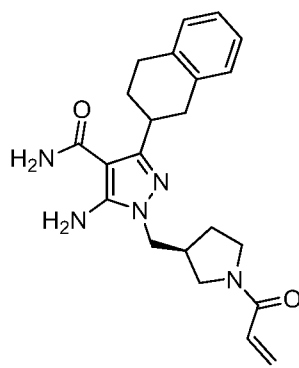
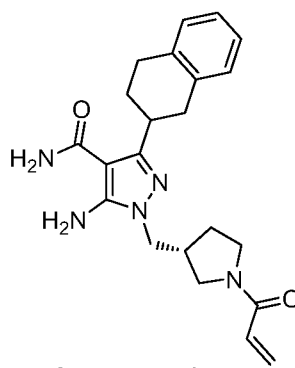
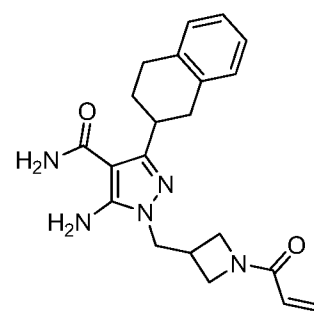
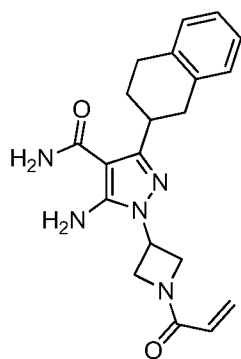
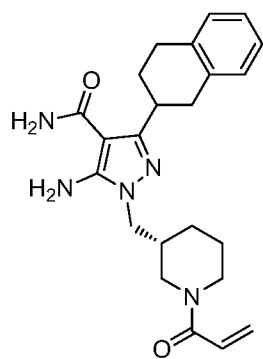
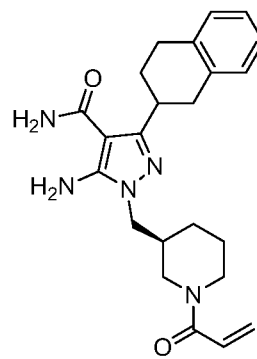
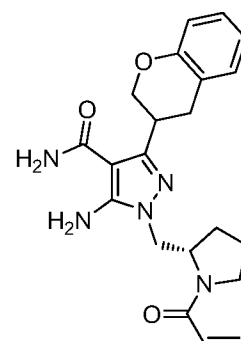
Compound 1.14

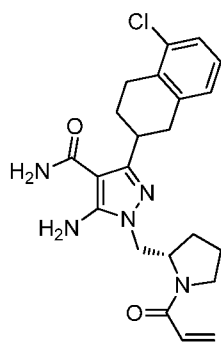


Compound 1.15

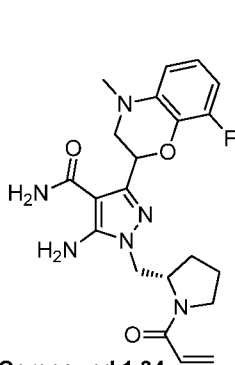


Compound 1.16

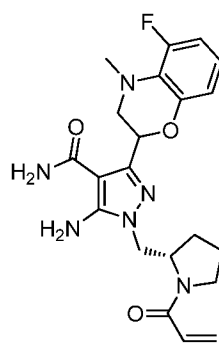
**Compound 1.17****Compound 1.18****Compound 1.19****Compound 1.20****Compound 1.21****Compound 1.22****Compound 1.23****Compound 1.24****Compound 1.25****Compound 1.26****Compound 1.27****Compound 1.28****Compound 1.29****Compound 1.30****Compound 1.31****Compound 1.32**



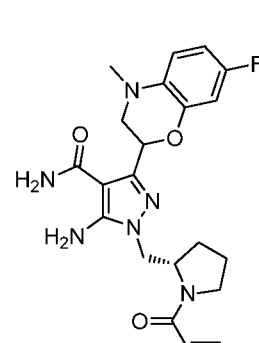
Compound 1.33



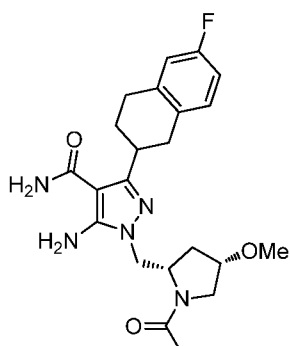
Compound 1.34



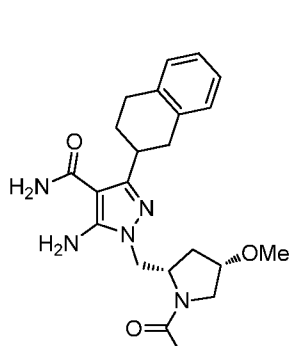
Compound 1.35



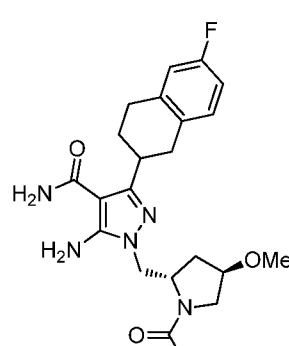
Compound 1.36



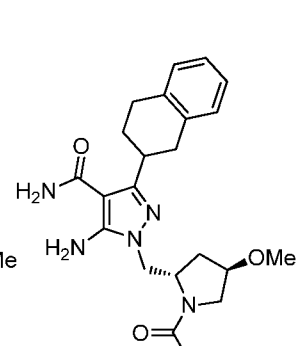
Compound 1.37



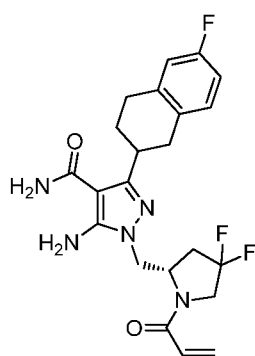
Compound 1.38



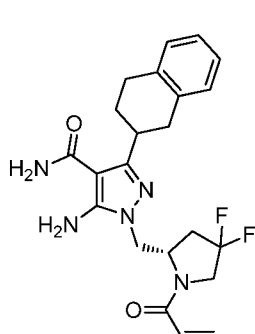
Compound 1.39



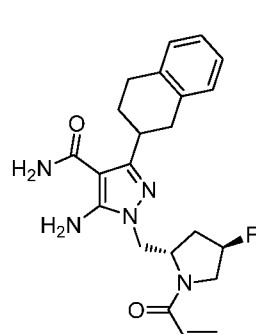
Compound 1.40



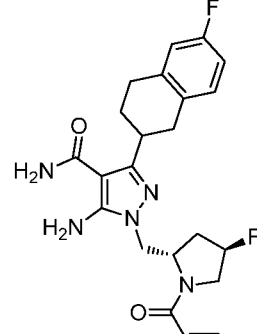
Compound 1.41



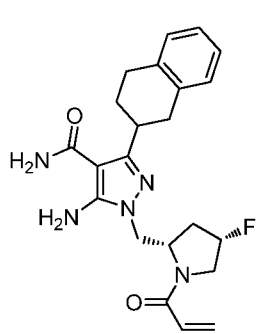
Compound 1.42



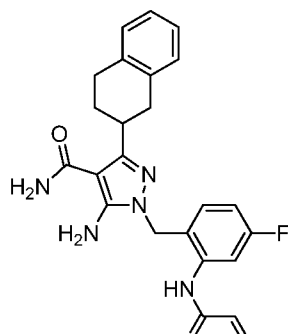
Compound 1.43



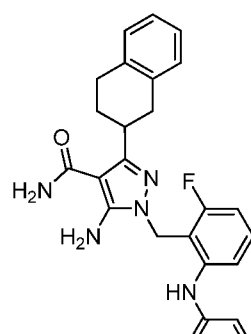
Compound 1.44



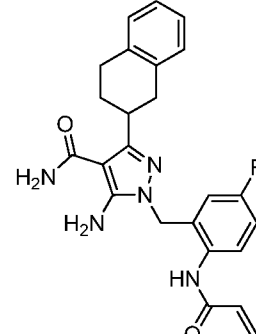
Compound 1.45



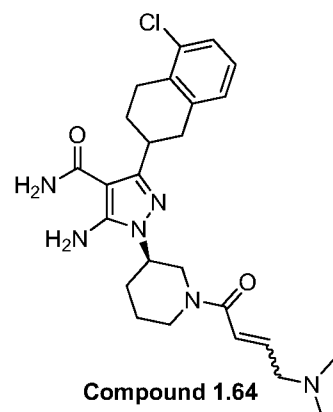
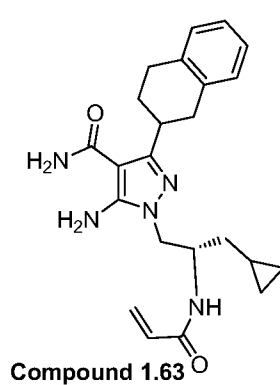
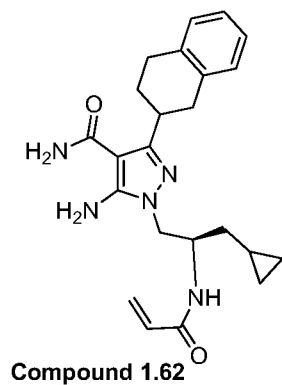
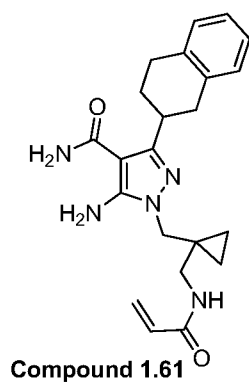
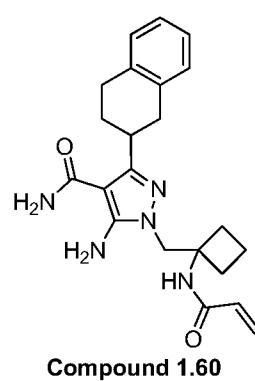
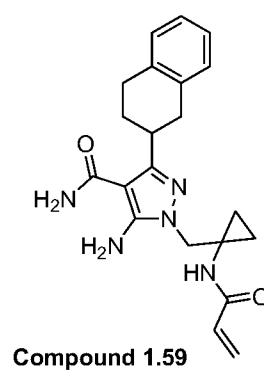
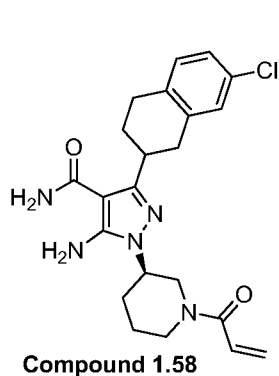
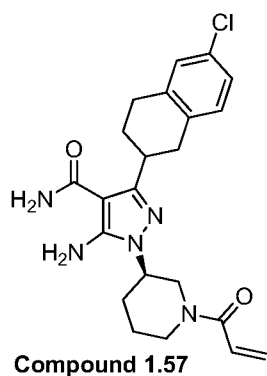
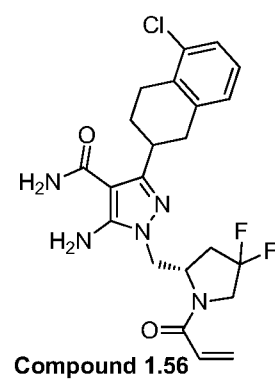
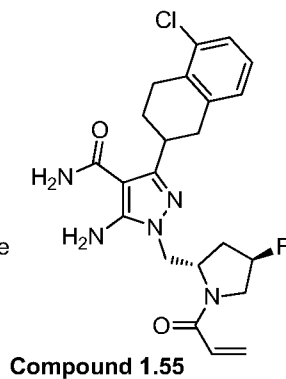
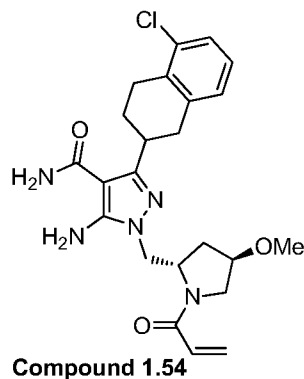
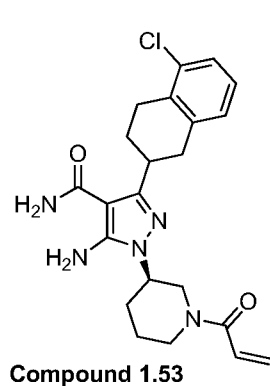
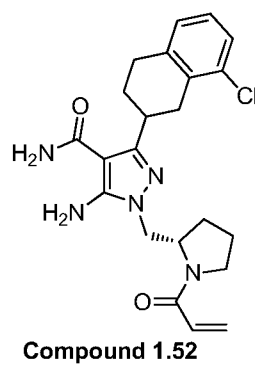
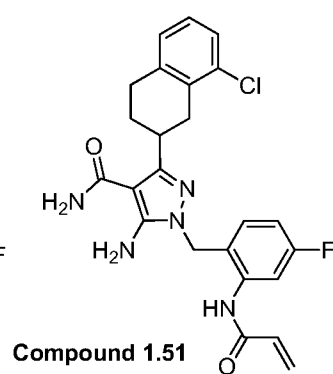
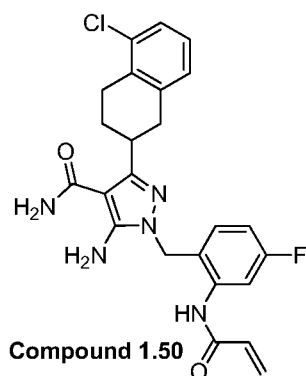
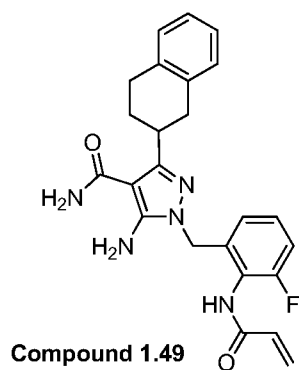
Compound 1.46

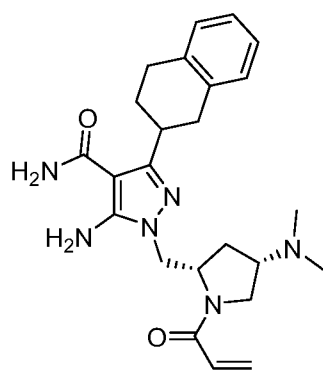
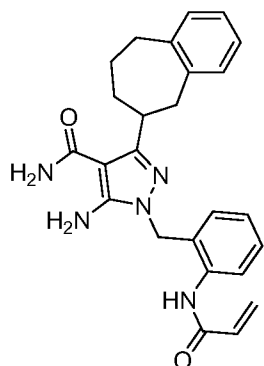
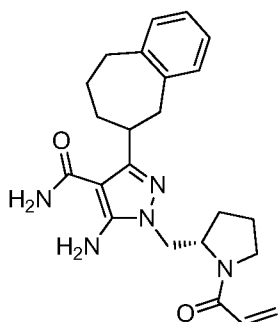
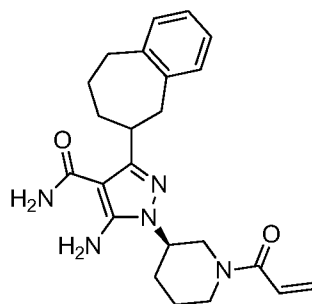
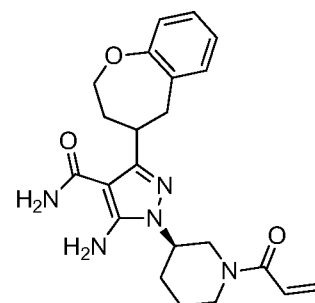
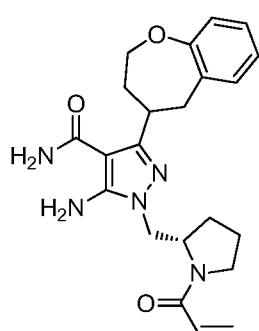
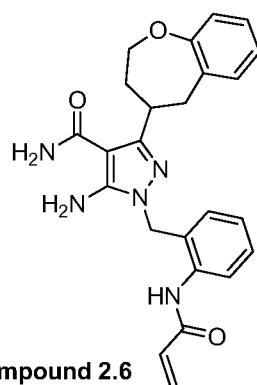
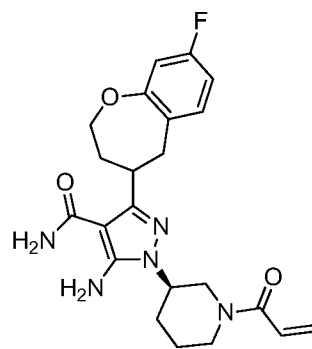
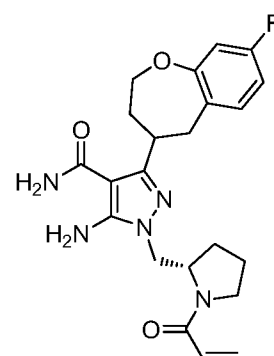
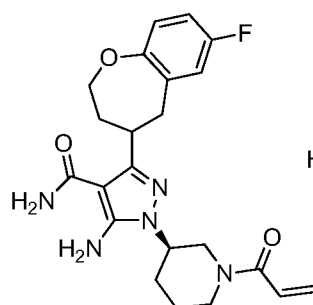
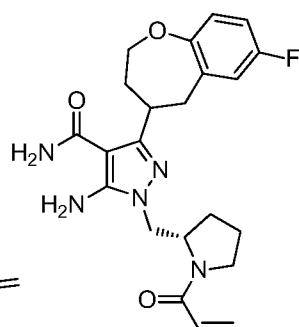
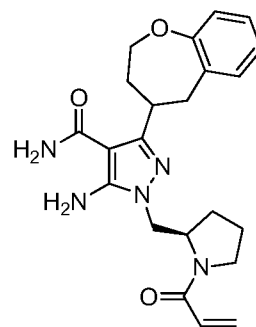


Compound 1.47



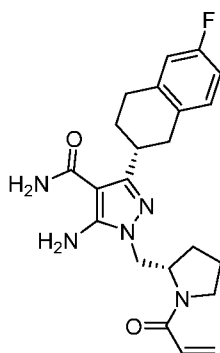
Compound 1.48



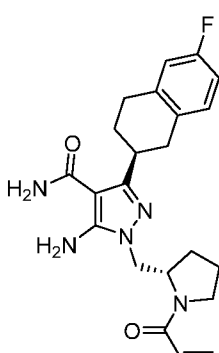
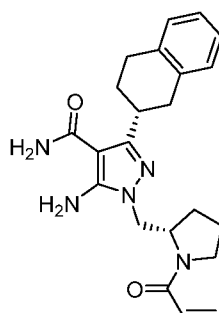
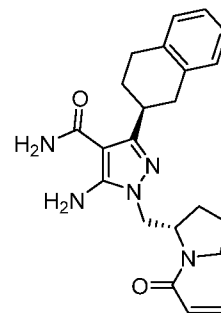
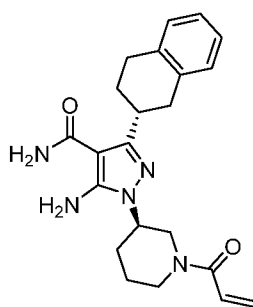
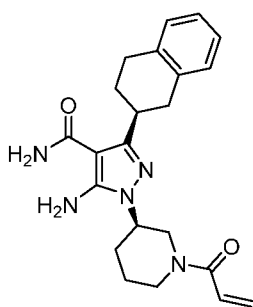
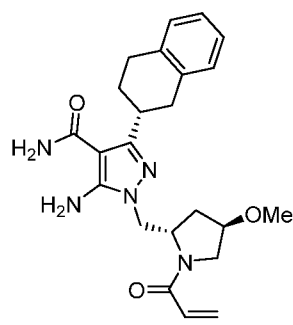
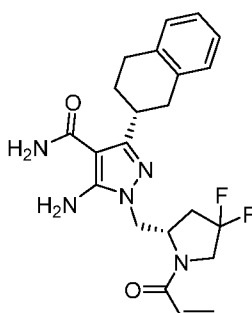
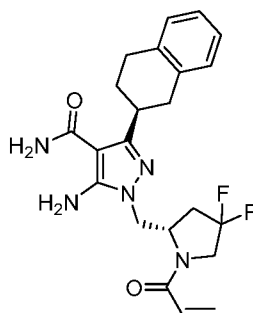
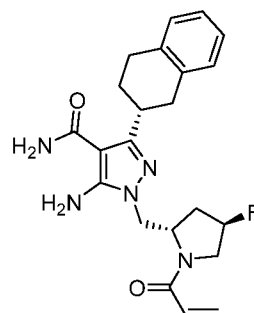
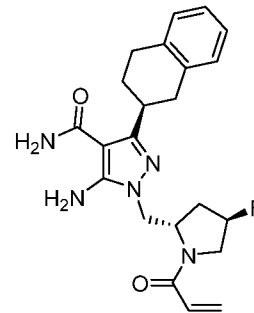
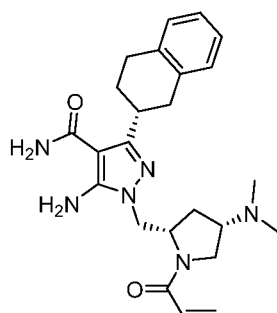
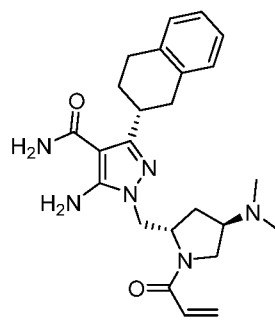
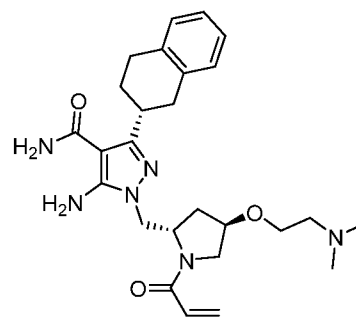
**Compound 1.65****Compound 2.1****Compound 2.2****Compound 2.3****Compound 2.4****Compound 2.5****Compound 2.6****Compound 2.7****Compound 2.8****Compound 2.9****Compound 2.10****Compound 2.11**

stereoisomers thereof, and pharmaceutically accept salts thereof described herein.

[0024] Also provided herein is at least one compound selected from the following compounds showing the following stereochemistry:



or

**Compound 1.10a or 1.10b****Compound 1.14a****Compound 1.14b****Compound 1.15a****Compound 1.15b****Compound 1.40a****Compound 1.42a****Compound 1.42b****Compound 1.43a****Compound 1.43b****Compound 1.65a****Compound 1.66a****Compound 1.67a**

[0025] Also provided is a pharmaceutical composition comprising at least one pharmaceutically acceptable carrier and at least one compound selected from compounds of Formula (I), Formula (I-1) or Formula (I-2).

[0026] Also provided is a use of at least one compound selected from compounds of Formula (I), Formula (I-1) or Formula (I-2), stereoisomers thereof, and pharmaceutically accept salts thereof described herein in manufacture of a medicament for inhibiting EGFR-T790M kinase.

[0027] Also provided is a use of at least one compound selected from compounds of Formula (I), stereoisomers thereof, and pharmaceutically accept salts thereof described herein in the manufacture of a medicament for treating cancer, including but not limited to ovarian cancer, cervical cancer, colorectal cancer, breast cancer, pancreatic cancer, glioma, glioblastoma, melanoma, prostate cancer, leukaemia, lymphoma, non- Hodgkins lymphoma, gastric cancer, lung cancer including non- small cell lung cancer, hepatocellular cancer, gastric cancer, gastrointestinal stromal tumour (GIST), thyroid cancer, bile duct cancer, endometrial cancer, renal cancer, anaplastic large cell lymphoma, acute myeloid leukaemia (AML), multiple myeloma, melanoma and mesothelioma.

DETAILED DESCRIPTION OF THE INVENTION

[0028] As used herein, the following words, phrases and symbols are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise. The following abbreviations and terms have the indicated meanings throughout:

[0029] The term "C₁₋₆alkyl" herein refers to a hydrocarbon group selected from linear and branched saturated hydrocarbon groups comprising from 1 to 6, carbon atoms. Examples of the alkyl group can be selected from methyl, ethyl, 1-propyl or n-propyl ("n-Pr"), 2-propyl or isopropyl ("i-Pr"), 1-butyl or n-butyl ("n-Bu"), 2-methyl-1-propyl or isobutyl ("i-Bu"), 1-methylpropyl or s-butyl ("s-Bu"), and 1,1-dimethylethyl or t-butyl ("t-Bu").

[0030] The term "C₂₋₆alkenyl" herein refers to a hydrocarbon group selected from linear and branched hydrocarbon groups comprising at least one C=C double bond and from 2 to 6, carbon

atoms. Examples of the alkenyl group may be selected from ethenyl or vinyl ($-\text{CH}=\text{CH}_2$), prop-1-enyl ($-\text{CH}=\text{CHCH}_3$), prop-2-enyl ($-\text{CH}_2\text{CH}=\text{CH}_2$), 2-methylprop-1-enyl, but-1-enyl, but-2-enyl, but-3-enyl, buta-1,3-dienyl, 2-methylbuta-1,3-diene, hex-1-enyl, hex-2-enyl, hex-3-enyl, hex-4-enyl, and hexa-1,3-dienyl groups.

- 5 **[0031]** The term " C_{2-6} alkynyl" herein refers to a hydrocarbon group selected from linear and branched hydrocarbon group, comprising at least one $\text{C}\equiv\text{C}$ triple bond and from 2 to 6, carbon atoms. Examples of the alkynyl group include ethynyl ($-\text{C}\equiv\text{CH}$), 1-propynyl ($-\text{C}\equiv\text{CCH}_3$), 2-propynyl (propargyl, $-\text{CH}_2\text{C}\equiv\text{CH}$), 1-butylnyl, 2-butylnyl, and 3-butylnyl groups.

- [0032]** The term " C_{3-8} cycloalkyl" herein refers to a hydrocarbon group selected from saturated
10 and partially unsaturated cyclic hydrocarbon groups, comprising monocyclic and polycyclic (e.g., bicyclic and tricyclic) groups, and comprise from 3 to 8, such as 3 to 6, 3 to 5, or 3 to 4 carbon atoms. Even further for example, the C_{3-8} cycloalkyl group may be selected from monocyclic group comprising from 3 to 8, such as 3 to 6 carbon atoms. Examples of the monocyclic cycloalkyl group include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl,
15 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, cyclohexadienyl, cycloheptyl, and cyclooctyl.

[0033] The term "Aryl" herein refers to a group selected from:

5- and 6-membered carbocyclic aromatic rings, for example, phenyl;

- bicyclic ring systems such as 7 to 12 membered bicyclic ring systems wherein at least one
20 ring is carbocyclic and aromatic, selected, for example, from naphthalene, indane, and 1,2,3,4-tetrahydroquinoline; and

tricyclic ring systems such as 10 to 15 membered tricyclic ring systems wherein at least one ring is carbocyclic and aromatic, for example, fluorene.

[0034] The term "halogen" or "halo" herein refers to F, Cl, Br or I.

- 25 **[0035]** The term "heteroaryl" herein refers to a group selected from:

5- to 7-membered aromatic, monocyclic rings comprising at least one heteroatom, for example, from 1 to 4, or, in some embodiments, from 1 to 3, heteroatoms, selected from N, O, and S, with the remaining ring atoms being carbon;

8- to 12-membered bicyclic rings comprising at least one heteroatom, for example, from 1 to 4, or, in some embodiments, from 1 to 3, or, in other embodiments, 1 or 2, heteroatoms, selected from N, O, and S, with the remaining ring atoms being carbon and wherein at least one ring is aromatic and at least one heteroatom is present in the aromatic ring; and

5 11- to 14-membered tricyclic rings comprising at least one heteroatom, for example, from 1 to 4, or in some embodiments, from 1 to 3, or, in other embodiments, 1 or 2, heteroatoms, selected from N, O, and S, with the remaining ring atoms being carbon and wherein at least one ring is aromatic and at least one heteroatom is present in an aromatic ring.

[0036] For example, the heteroaryl group includes a 5- to 7-membered heterocyclic aromatic ring fused to a 5- to 7-membered cycloalkyl ring. For such fused, bicyclic heteroaryl ring systems wherein only one of the rings comprises at least one heteroatom, the point of attachment may be at the heteroaromatic ring or at the cycloalkyl ring.

[0037] When the total number of S and O atoms in the heteroaryl group exceeds 1, those heteroatoms are not adjacent to one another. In some embodiments, the total number of S and O atoms in the heteroaryl group is not more than 2. In some embodiments, the total number of S and O atoms in the aromatic heterocycle is not more than 1.

[0038] Examples of the heteroaryl group include, but are not limited to, (as numbered from the linkage position assigned priority 1) pyridyl (such as 2-pyridyl, 3-pyridyl, or 4-pyridyl), cinnolinyl, pyrazinyl, 2,4-pyrimidinyl, 3,5-pyrimidinyl, 2,4-imidazolyl, imidazopyridinyl, isoxazolyl, oxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, tetrazolyl, thienyl, triazinyl, benzothienyl, furyl, benzofuryl, benzoimidazolyl, indolyl, isoindolyl, indolinyl, phthalazinyl, pyrazinyl, pyridazinyl, pyrrolyl, triazolyl, quinolinyl, isoquinolinyl, pyrazolyl, pyrrolopyridinyl (such as 1H-pyrrolo[2,3-b]pyridin-5-yl), pyrazolopyridinyl (such as 1H-pyrazolo[3,4-b]pyridin-5-yl), benzoxazolyl (such as benzo[d]oxazol-6-yl), pteridinyl, purinyl, 1-oxa-2,3-diazolyl, 1-oxa-2,4-diazolyl, 1-oxa-2,5-diazolyl, 1-oxa-3,4-diazolyl, 1-thia-2,3-diazolyl, 1-thia-2,4-diazolyl, 1-thia-2,5-diazolyl, 1-thia-3,4-diazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl,

naphthyridinyl, furopyridinyl, benzothiazolyl (such as benzo[d]thiazol-6-yl), indazolyl (such as 1H-indazol-5-yl) and 5,6,7,8-tetrahydroisoquinoline.

[0039] The term "heterocyclic" or "heterocycle" or "heterocyclyl" herein refers to a ring selected from 4- to 12-membered (such as 4-membered, 5-membered, or 6-membered)

5 monocyclic, bicyclic and tricyclic, saturated and partially unsaturated rings comprising at least one carbon atoms in addition to at least one heteroatom, such as from 1-4 heteroatoms, further such as from 1-3, or further such as 1 or 2 heteroatoms, selected from oxygen, sulfur, and nitrogen.

[0040] Examples of the heterocycle include, but not limited to, (as numbered from the linkage position assigned priority 1), 1-azetidiny, 2-azetidiny, 3-azetidiny, 1-pyrrolidinyl,

10 2-pyrrolidinyl, 3-pyrrolidinyl, 2,4-imidazolidinyl, 2,3-pyrazolidinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 2,5-piperazinyl, pyranyl, 2-morpholinyl, 3-morpholinyl, oxiranyl, aziridinyl, thiranyl, azetidiny, oxetanyl, thietanyl, 1,2-dithietanyl, 1,3-dithietanyl, dihydropyridinyl, tetrahydropyridinyl, thiomorpholinyl, thioxanyl, piperazinyl, homopiperazinyl, homopiperidinyl, azepanyl, oxepanyl, thiepanyl, 1,4-oxathianyl, 1,4-dioxepanyl,

15 1,4-oxathiepanyl, 1,4-oxaazepanyl, 1,4-dithiepanyl, 1,4-thiazepanyl and 1,4-diazepane 1,4-dithianyl, 1,4-azathianyl, oxazepinyl, diazepinyl, thiazepinyl, dihydrothienyl, dihydropyranyl, dihydrofuranyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1-pyrrolinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, 1,4-dioxanyl, 1,3-dioxolanyl, pyrazolinyl, pyrazolidinyl, dithianyl, dithiolanyl, pyrazolidinyl, imidazolinyl,

20 pyrimidinonyl, 1,1-dioxo-thiomorpholinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl and azabicyclo[2.2.2]hexanyl. A substituted heterocycle also includes a ring system substituted with one or more oxo moieties, such as piperidinyl N-oxide, morpholinyl-N-oxide, 1-oxo-1-thiomorpholinyl and 1,1-dioxo-1-thiomorpholinyl.

[0041] As used herein, "C₁₋₆haloalkyl" refers to an C₁₋₆alkyl group in which one or more of the

25 hydrogen atoms are replaced by a halogen (e.g., mono-haloalkyl, di-haloalkyl and tri- haloalkyl). Such groups include but are not limited to, chloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl and 1-chloro-2-fluoromethyl, 2-fluoroisobutyl. A C₁₋₆haloalkyl may be substituted or unsubstituted.

[0042] As used herein, "C₁₋₆alkoxy" refers to the formula -OR wherein R is an C₁₋₆alkyl. A non-limiting list of alkoxys are methoxy, ethoxy, n-propoxy, 1-methylethoxy (isopropoxy), n-butoxy, iso-butoxy, sec-butoxy and tert-butoxy. An C₁₋₆alkoxy may be substituted or unsubstituted.

[0043] As used herein, "C₁₋₆haloalkoxy" refers to an C₁₋₆alkoxy group in which one or more of the hydrogen atoms are replaced by a halogen (e.g., mono-haloalkoxy, di-haloalkoxy and tri-haloalkoxy). Such groups include but are not limited to, chloromethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy and 1-chloro-2-fluoromethoxy, 2-fluoroisobutoxy. A C₁₋₆haloalkoxy may be substituted or unsubstituted.

[0044] Compounds described herein may contain an asymmetric center and may thus exist as enantiomers. Where the compounds described herein possess two or more asymmetric centers, they may additionally exist as diastereomers. Enantiomers and diastereomers fall within the broader class of stereoisomers. All such possible stereoisomers as substantially pure resolved enantiomers, racemic mixtures thereof, as well as mixtures of diastereomers are intended to be included. All stereoisomers of the compounds disclosed herein and /or pharmaceutically acceptable salts thereof are intended to be included. Unless specifically mentioned otherwise, reference to one isomer applies to any of the possible isomers. Whenever the isomeric composition is unspecified, all possible isomers are included.

[0045] The term "substantially pure" as used herein means that the target stereoisomer contains no more than 35%, such as no more than 30%, further such as no more than 25%, even further such as no more than 20%, by weight of any other stereoisomer(s). In some embodiments, the term "substantially pure" means that the target stereoisomer contains no more than 10%, for example, no more than 5%, such as no more than 1%, by weight of any other stereoisomer(s).

[0046] It may be advantageous to separate reaction products from one another and /or from starting materials. The desired products of each step or series of steps is separated and /or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example: reverse-phase and normal phase; size exclusion; ion exchange;

high, medium and low pressure liquid chromatography methods and apparatus; small scale analytical; simulated moving bed ("SMB") and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography. One skilled in the art will apply techniques most likely to achieve the desired separation.

5 **[0047]** Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as by chromatography and /or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid
10 chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereoisomers to the corresponding pure enantiomers. Enantiomers can also be separated by use of a chiral HPLC column.

[0048] A single stereoisomer, e.g., a substantially pure enantiomer, may be obtained by resolution of the racemic mixture using a method such as formation of diastereomers using
15 optically active resolving agents (Eliel, E. and Wilen, S. Stereochemistry of Organic Compounds. New York: John Wiley & Sons, Inc., 1994; Lochmuller, C. H., et al. "Chromatographic resolution of enantiomers: Selective review." J. Chromatogr., 113(3) (1975): pp. 283-302). Racemic mixtures of chiral compounds of the invention can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and
20 separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions. See: Wainer, Irving W., Ed. Drug Stereochemistry: Analytical Methods and Pharmacology. New York: Marcel Dekker, Inc., 1993.

25 **[0049]** "Pharmaceutically acceptable salts" include, but are not limited to salts with inorganic acids, selected, for example, from hydrochlorates, phosphates, diphosphates, hydrobromates, sulfates, sulfinates, and nitrates; as well as salts with organic acids, selected, for example, from malates, maleates, fumarates, tartrates, succinates, citrates, lactates, methanesulfonates,

p-toluenesulfonates, 2-hydroxyethylsulfonates, benzoates, salicylates, stearates, alkanoates such as acetate, and salts with $\text{HOOC}-(\text{CH}_2)_n-\text{COOH}$, wherein n is selected from 0 to 4. Similarly, examples of pharmaceutically acceptable cations include, but are not limited to, sodium, potassium, calcium, aluminum, lithium, and ammonium.

5 **[0050]** In addition, if a compound disclosed herein is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, such as a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds.

10 Those skilled in the art will recognize various synthetic methodologies that may be used without undue experimentation to prepare non-toxic pharmaceutically acceptable addition salts.

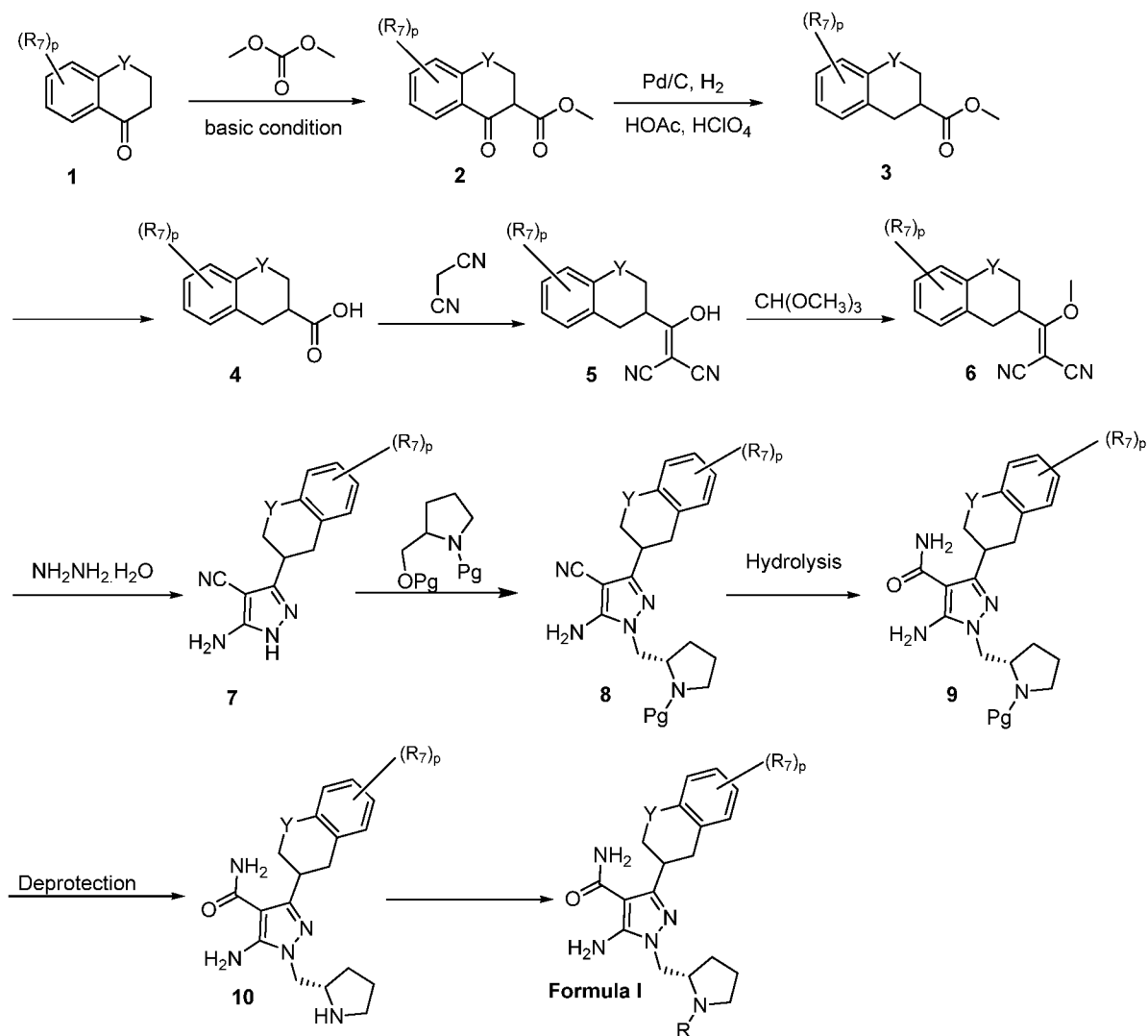
[0051] As defined herein, "pharmaceutically acceptable salts thereof" include salts of at least one compound of Formulae I, and salts of the stereoisomers of at least one compound of Formulae I and II, such as salts of enantiomers, and /or salts of diastereomers.

15 **[0052]** "Treating," "treat," or "treatment" or "alleviation" refers to administering at least one compound and /or at least one stereoisomer thereof, and /or at least one pharmaceutically acceptable salt thereof disclosed herein to a subject in recognized need thereof that has, for example, cancer.

20 **[0053]** The term "effective amount" refers to an amount of at least one compound and /or at least one stereoisomer thereof, and /or at least one pharmaceutically acceptable salt thereof disclosed herein effective to "treat," as defined above, a disease or disorder in a subject.

[0054] The compounds disclosed herein, and /or the pharmaceutically acceptable salts thereof, can be synthesized from commercially available starting materials taken together with the disclosure herein. The following scheme illustrates methods for preparation of some of the
25 compounds disclosed herein.

Scheme I



R = different wareheads

Pg = protecting group such as t-Boc

5 R₇, p, Y are defined as above.

[0055] In this scheme, a commercially available starting material **1** (3,4-Dihydro-1(2H)-naphthalenone or 6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one) is reacted with dimethyl carbonate under basic condition to form formula **2**, which is reduced in the presence of acidic condition to give ester **3**. Then the ester **3** is hydrolyzed to get the acid **4**, which is coupled with malononitrile and reacted with trimethoxymethane to obtain formula **6**. Then the ring is closed by using hydrazine hydrate to afford the key pyrazole **7**. A compound of formula **7** is alkylated using protected chiral prolinol, then the cyano group is hydrolyzed under acidic condition to form amide **9**. The compound of formula **9** is deprotected (for example, the BOC protecting group may be

removed by treating with trifluoroacetic acid). The amine **10** is reacted with different warheads to afford a compound of Formula I.

[0056] Also provided herein is a method of treating cancer responsive to inhibition of EGFR kinase comprising administering to a subject, such as a mammal or human, in need of treating for the cancer an effective amount of at least one compound selected from compounds of Formula (I), stereoisomers thereof, and pharmaceutically acceptable salts thereof described herein.

[0057] The at least one compound selected from compounds of Formula (I), stereoisomers thereof, and pharmaceutically acceptable salts thereof may be employed alone or in combination with at least one other therapeutic agent for treatment. In some embodiments, the at least one compound selected from compounds of Formula (I), stereoisomers thereof, and pharmaceutically acceptable salts thereof can be used in combination with at least one additional therapeutic agent. The at least one additional therapeutic agent can be, for example, selected from anti-hyperproliferative, anti-cancer, and chemotherapeutic agents. The at least one compound and/or at least one pharmaceutically acceptable salt disclosed herein may be administered with the at least one other therapeutic agent in a single dosage form or as a separate dosage form. When administered as a separate dosage form, the at least one other therapeutic agent may be administered prior to, at the same time as, or following administration of the at least one compound and/or at least one pharmaceutically acceptable salt disclosed herein. A "chemotherapeutic agent" is a chemical compound useful in the treatment of cancer, regardless of mechanism of action.

Chemotherapeutic agents include compounds used in "targeted therapy" and conventional chemotherapy. Suitable chemotherapeutic agents can be, for example, selected from: agents that induce apoptosis; polynucleotides (e.g., ribozymes); polypeptides (e.g., enzymes); drugs; biological mimetics; alkaloids; alkylating agents; antitumor antibiotics; antimetabolites; hormones; platinum compounds; monoclonal antibodies conjugated with anticancer drugs, toxins, and/or radionuclides; biological response modifiers (e.g., interferons, such as IFN- α and interleukins, such as IL-2); adoptive immunotherapy agents; hematopoietic growth factors; agents that induce tumor cell differentiation (e.g., all-trans-retinoic acid); gene therapy reagents; antisense therapy reagents and nucleotides; tumor vaccines; and inhibitors of angiogenesis.

[0058] Examples of chemotherapeutic agents include Erlotinib (TARCEVA®, Genentech/OSI Pharm.); Bortezomib (VELCADE®, Millennium Pharm.); Fulvestrant (FASLODEX®, AstraZeneca); Sunitinib (SUTENT®, Pfizer); Letrozole (FEMARA®, Novartis); Imatinib mesylate (GLEEVEC®, Novartis); PTK787/ZK 222584 (Novartis); Oxaliplatin (Eloxatin®, Sanofi); 5-FU (5-fluorouracil); Leucovorin; Rapamycin (Sirolimus, RAPAMUNE®, Wyeth); Lapatinib (TYKERB®, GSK572016, Glaxo Smith Kline); Lonafermib (SCH 66336); Sorafenib (NEXAVAR®, Bayer); Irinotecan (CAMPTOSAR®, Pfizer) and Gefitinib (IRESSA®, AstraZeneca); AG1478, AG1571 (SU 5271, Sugen); alkylating agents such as thiotepea and CYTOXAN® cyclophosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines such as altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and trimethylomelamine; acetogenins (such as bullatacin and bullatacinone); a camptothecin (such as the synthetic analog topotecan); bryostatin; callistatin; CC-1065 and its adozelesin, carzelesin and bizelesin synthetic analogs; cryptophycins (such as cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin and the synthetic analogs thereof, such as KW-2189 and CB1-TM1; eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, chlorophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, such as calicheamicin gammaII and calicheamicin omegaII (Angew Chem. Intl. Ed. Engl. (1994) 33:183-186); dynemicin, such as dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores, aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabycin, caminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, ADRIAMYCIN® (doxorubicin), morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin,

marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, porfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogs such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; and rogens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminogluthethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminol evulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, Oreg.); razoxane; rhizoxin; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes (such as T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxoids, e.g., TAXOL® (paclitaxel; Bristol-Myers Squibb Oncology, Princeton, N.J.), ABRAXANE® (Cremophor-free), albumin-engineered nanoparticle formulations of paclitaxel (American Pharmaceutical Partners, Schaumburg, Ill.), and TAXOTERE® (doxetaxel; Rhone-Poulenc Rorer, Antony, France); chloranmbucil; GEMZAR® (gemcitabine); 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; NAVELBINE® (vinorelbine); novantrone; teniposide; edatrexate; daunomycin; aminopterin; capecitabine (XELODA®); ib and ronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; and pharmaceutically acceptable salts, acids and derivatives of any of the above.

[0059] The "chemotherapeutic agent" can also be selected, for example, from: (i) anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens and selective estrogen receptor modulators (SERMs), including, for example, tamoxifen (including NOLVADEX®; tamoxifen citrate), raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and FARESTON® (toremifine citrate); (ii) aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production in the adrenal glands, such as, for example, 4(5)-imidazoles, aminoglutethimide, MEGASE® (megestrol acetate), AROMASIN® (exemestane; Pfizer), formestane, fadrozole, RIVISOR® (vorozole), FEMARA® (letrozole; Novartis), and ARIMIDEX® (anastrozole; AstraZeneca); (iii) anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; as well as troxacitabine (a 1,3-dioxolane nucleoside cytosine analog); (iv) protein kinase inhibitors; (v) lipid kinase inhibitors; (vi) antisense oligonucleotides, such as those which inhibit expression of genes in signaling pathways implicated in aberrant cell proliferation, such as, for example, PKC- α , Ralf and H-Ras; (vii) ribozymes such as VEGF expression inhibitors (e.g., ANGIOZYME®) and HER² expression inhibitors; (viii) vaccines such as gene therapy vaccines, for example, ALLOVECTIN®, LEUVECTIN®, and VAXID®; PROLEUKIN® rIL-2; a topoisomerase 1 inhibitor such as LURTOTECAN®; ABARELIX® rmRH; (ix) anti-angiogenic agents such as bevacizumab (AVASTIN®, Genentech); and (x) pharmaceutically acceptable salts, acids and derivatives of any of the above.

[0060] The "chemotherapeutic agent" can also be selected, for example, from therapeutic antibodies such as alemtuzumab (Campath), bevacizumab (AVASTIN®, Genentech); cetuximab (ERBITUX®, Imclone); panitumumab (VECTIBIX®, Amgen), rituximab (RITUXAN®, Genentech/Biogen Idec), pertuzumab (OMNITARG®, 2C4, Genentech), trastuzumab (HERCEPTIN®, Genentech), tositumomab (Bexxar, Corixa), and the antibody drug conjugate, gemtuzumab ozogamicin (MYLOTARG®, Wyeth).

[0061] Humanized monoclonal antibodies with therapeutic potential as chemotherapeutic agents in combination with the at least one compound selected from compounds of Formula (I) (such as Formulae (II)), stereoisomers thereof, and pharmaceutically acceptable salt thereof may,

for example, be selected from: alemtuzumab, apolizumab, aselizumab, atlizumab, bapineuzumab, bevacizumab, bivatuzumab mertansine, cantuzumab mertansine, cedelizumab, certolizumab pegol, cidfusituzumab, cidtuzumab, daclizumab, eculizumab, efalizumab, epratuzumab, erlizumab, felvizumab, fontolizumab, gentuzumab ozogamicin, inotuzumab ozogamicin, 5 ipilimumab, labetuzumab, lintuzumab, matuzumab, mepolizumab, motavizumab, motovizumab, natalizumab, nimotuzumab, nolovizumab, numavizumab, ocrelizumab, omalizumab, palivizumab, pascolizumab, pecfusituzumab, pectuzumab, pertuzumab, pexelizumab, ralivizumab, ranibizumab, reslivizumab, reslizumab, resyvizumab, rovelizumab, ruplizumab, sibrotuzumab, sipilizumab, sontuzumab, tacatuzumab tetraxetan, tadocizumab, talizumab, 10 tefibazumab, tocilizumab, toralizumab, trastuzumab, tucotuzumab celmoleukin, tucosituzumab, umavizumab, urtoxazumab, visilizumab, Nivolumab and Lambrolizumab.

[0062] Also provided herein is a composition comprising at least one compound selected from compounds of Formula (I), stereoisomers thereof, and pharmaceutically acceptable salts thereof, and at least one pharmaceutically acceptable carrier.

15 **[0063]** The composition comprising at least one compound selected from compounds of Formula (I), stereoisomers thereof, and pharmaceutically acceptable salts thereof can be administered in various known manners, such as orally, topically, rectally, parenterally, by inhalation spray, or via an implanted reservoir, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active 20 ingredient is being administered. The term "parenteral" as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques. The compositions disclosed herein may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art.

25 **[0064]** The at least one compound selected from Formula (I), stereoisomers thereof, and pharmaceutically acceptable salts thereof can be administered orally in solid dosage forms, such as capsules, tablets, troches, dragées, granules and powders, or in liquid dosage forms, such as elixirs, syrups, emulsions, dispersions, and suspensions. The at least one compound selected from

compounds of Formula (I), stereoisomers thereof, and pharmaceutically acceptable salts thereof disclosed herein can also be administered parenterally, in sterile liquid dosage forms, such as dispersions, suspensions or solutions. Other dosages forms that can also be used to administer the at least one compound selected from Formula (I), stereoisomers thereof, and pharmaceutically acceptable salts thereof disclosed herein as an ointment, cream, drops, transdermal patch or powder for topical administration, as an ophthalmic solution or suspension formation, i.e., eye drops, for ocular administration, as an aerosol spray or powder composition for inhalation or intranasal administration, or as a cream, ointment, spray or suppository for rectal or vaginal administration.

[0065] Gelatin capsules containing the at least one compound and /or the at least one pharmaceutically acceptable salt thereof disclosed herein and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like, can also be used. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of time. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

[0066] Liquid dosage forms for oral administration can further comprise at least one agent selected from coloring and flavoring agents to increase patient acceptance.

[0067] In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols can be examples of suitable carriers for parenteral solutions. Solutions for parenteral administration may comprise a water soluble salt of the at least one compound describe herein, at least one suitable stabilizing agent, and if necessary, at least one buffer substance. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, can be examples of suitable stabilizing agents. Citric acid and its salts and sodium EDTA can also be used as examples of suitable stabilizing agents. In addition, parenteral solutions can further comprise at least one preservative, selected, for example, from benzalkonium chloride, methyl- and propylparaben, and chlorobutanol.

[0068] A pharmaceutically acceptable carrier is, for example, selected from carriers that are compatible with active ingredients of the composition (and in some embodiments, capable of stabilizing the active ingredients) and not deleterious to the subject to be treated. For example, solubilizing agents, such as cyclodextrins (which can form specific, more soluble complexes with the at least one compound and /or at least one pharmaceutically acceptable salt disclosed herein), can be utilized as pharmaceutical excipients for delivery of the active ingredients. Examples of other carriers include colloidal silicon dioxide, magnesium stearate, cellulose, sodium lauryl sulfate, and pigments such as D&C Yellow # 10. Suitable pharmaceutically acceptable carriers are described in Remington's Pharmaceutical Sciences, A. Osol, a standard reference text in the art.

[0069] The at least one compound selected from compounds of Formula (I), stereoisomers thereof, and pharmaceutically acceptable salts thereof disclosed herein can further be examined for efficacy in treating cancer by in vivo assays. For example, the at least one compound and /or the at least one pharmaceutically acceptable salts thereof disclosed herein can be administered to an animal (e.g., a mouse model) having cancer and its therapeutic effects can be accessed. Positive results in one or more of such tests are sufficient to increase the scientific storehouse of knowledge and hence sufficient to demonstrate practical utility of the compounds and /or salts tested. Based on the results, an appropriate dosage range and administration route for animals, such as humans, can also be determined.

[0070] For administration by inhalation, the at least one compound selected from compounds of Formula (I), stereoisomers thereof, and pharmaceutically acceptable salts thereof disclosed herein may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or nebulisers. The at least one compound selected from compounds of Formula (I), stereoisomers thereof, and pharmaceutically acceptable salts thereof disclosed herein may also be delivered as powders, which may be formulated and the powder composition may be inhaled with the aid of an insufflation powder inhaler device. One exemplary delivery system for inhalation can be a metered dose inhalation (MDI) aerosol, which may be formulated as a suspension or solution of at least one compound selected from compounds of Formula (I), stereoisomers thereof, and pharmaceutically

acceptable salts thereof disclosed herein in at least one suitable propellant, selected, for example, from fluorocarbons and hydrocarbons.

[0071] For ocular administration, an ophthalmic preparation may be formulated with an appropriate weight percentage of a solution or suspension of the at least one compound selected from compounds of Formula (I), stereoisomers thereof, and pharmaceutically acceptable salts thereof disclosed herein in an appropriate ophthalmic vehicle, such that the at least one compound selected from compounds of Formula (I), stereoisomers thereof, and at least one pharmaceutically acceptable salts thereof disclosed herein is maintained in contact with the ocular surface for a sufficient time period to allow the compound to penetrate the corneal and internal regions of the eye.

[0072] Useful pharmaceutical dosage-forms for administration of the at least one compound selected from compounds of Formula (I), stereoisomers thereof, and pharmaceutically acceptable salts thereof disclosed herein include, but are not limited to, hard and soft gelatin capsules, tablets, parenteral injectables, and oral suspensions.

[0073] The dosage administered will be dependent on factors, such as the age, health and weight of the recipient, the extent of disease, type of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired. In general, a daily dosage of the active ingredient can vary, for example, from 0.1 to 2000 milligrams per day. For example, 10- 500 milligrams once or multiple times per day may be effective to obtain the desired results.

[0074] In some embodiments, a large number of unit capsules can be prepared by filling standard two-piece hard gelatin capsules each with, for example, 100 milligrams of the at least one compound selected from compounds of Formula (I), stereoisomers thereof, and pharmaceutically acceptable salt thereof disclosed herein in powder, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

[0075] In some embodiments, a mixture of the at least one compound selected from compounds of Formula (I), stereoisomers thereof, and pharmaceutically acceptable salts thereof a digestible oil such as soybean oil, cottonseed oil or olive oil can be prepared and injected by means of a

positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules are washed and dried.

[0076] In some embodiments, a large number of tablets can be prepared by conventional procedures so that the dosage unit comprises, for example, 100 milligrams of the at least one compound selected from compounds of Formula (I), stereoisomers thereof, and pharmaceutically acceptable salts thereof, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

[0077] In some embodiments, a parenteral composition suitable for administration by injection can be prepared by stirring 1.5% by weight of the at least one compound and /or at least an enantiomer, a diastereomer, or pharmaceutically acceptable salt thereof disclosed herein in 10% by volume propylene glycol. The solution is made to the expected volume with water for injection and sterilized.

[0078] In some embodiment, an aqueous suspension can be prepared for oral administration.

For example, each 5 milliliters of an aqueous suspension comprising 100 milligrams of finely divided at least one compound selected from compounds of Formula (I), stereoisomers thereof, and pharmaceutically acceptable salts thereof, 100 milligrams of sodium carboxymethyl cellulose, 5 milligrams of sodium benzoate, 1.0 grams of sorbitol solution, U.S.P., and 0.025 milliliters of vanillin can be used.

[0079] The same dosage forms can generally be used when the at least one compound selected from compounds of Formula (I), stereoisomers thereof, and pharmaceutically acceptable salts thereof are administered stepwise or in conjunction with at least one other therapeutic agent.

When drugs are administered in physical combination, the dosage form and administration route should be selected depending on the compatibility of the combined drugs. Thus the term

"coadministration" is understood to include the administration of at least two agents concomitantly or sequentially, or alternatively as a fixed dose combination of the at least two active components.

[0080] The at least one compound selected from compounds of Formula (I), stereoisomers thereof, and pharmaceutically acceptable salt thereof disclosed herein can be administered as the

sole active ingredient or in combination with at least one second active ingredient, selected, for example, from other active ingredients known to be useful for treating cancers in a patient.

[0081] The examples below are intended to be purely exemplary and should not be considered to be limiting in any way. Efforts have been made to ensure accuracy with respect to numbers used (for example, amounts, temperature, etc.), but some experimental errors and deviations should be accounted for. Unless indicated otherwise, temperature is in degrees Centigrade. Reagents were purchased from commercial suppliers such as Sigma-Aldrich, Alfa Aesar, or TCI, and were used without further purification unless otherwise indicated.

[0082] Unless otherwise indicated, the reactions set forth below were performed under a positive pressure of nitrogen or argon or with a drying tube in anhydrous solvents; the reaction flasks were fitted with rubber septa for the introduction of substrates and reagents via syringe; and glassware was oven dried and /or heat dried.

[0083] Unless otherwise indicated, column chromatography purification was conducted on a Biotage system (Manufacturer: Dyax Corporation) having a silica gel column or on a silica SepPak cartridge (Waters), or was conducted on a Teledyne Isco Combiflash purification system using prepacked silica gel cartridges.

[0084] ¹H NMR spectra were recorded on a Varian instrument operating at 400 MHz. ¹H-NMR spectra were obtained using CDCl₃, CD₂Cl₂, CD₃OD, D₂O, *d*₆-DMSO, *d*₆-acetone or (CD₃)₂CO as solvent and tetramethylsilane (0.00 ppm) or residual solvent (CDCl₃: 7.25 ppm; CD₃OD: 3.31 ppm; D₂O: 4.79 ppm; *d*₆-DMSO: 2.50 ppm; *d*₆-acetone: 2.05; (CD₃)₂CO: 2.05) as the reference standard. When peak multiplicities are reported, the following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), qn (quintuplet), sx (sextuplet), m (multiplet), br (broadened), dd (doublet of doublets), dt (doublet of triplets). Coupling constants, when given, are reported in Hertz (Hz). All compound names except the reagents were generated by ChemDraw version 12.0.

[0085] In the following examples, the abbreviations below are used:

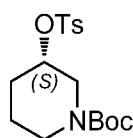
AcOH	Acetic acid
Aq	Aqueous
Brine	Saturated aqueous sodium chloride solution
Bn	Benzyl

BnBr	Benzyl Bromide
CH ₂ Cl ₂	Dichloromethane
DMF	N,N-Dimethylformamide
Dppf	1,1''-bis(diphenylphosphino)ferrocene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIEA or DIPEA	N,N-diisopropylethylamine
DMAP	4-N,N-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	Dimethyl sulfoxide
EtOAc	Ethyl acetate
EtOH	Ethanol
Et ₂ O or ether	Diethyl ether
G	grams
h or hr	hour
HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HCl	Hydrochloric acid
HPLC	High-performance liquid chromatography
IPA	2-propanol
i-PrOH	Isopropyl alcohol
Mg	milligrams
mL	milliliters
Mmol	millimole
MeCN	Acetonitrile
MeOH	Methanol
Min	minutes
ms or MS	Mass spectrum
Na ₂ SO ₄	Sodium sulfate
PE	petroleum ether
PPA	Polyphosphoric acid
Rt	Retention time
Rt or rt	Room temperature
TBAF	Tetra-butyl ammonium fluoride

TBSCl	tert-Butyldimethylsilyl chloride
TFA	Trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
μL	microliters

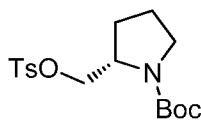
Example 1: Synthesis of Compounds **1.1-1.67**

BL-1: (S)-Tert-butyl 3-(tosyloxy)piperidine-1-carboxylate



- 5 **[0086]** To a solution of (S)-tert-butyl 3-hydroxypiperidine-1-carboxylate (168 g, 0.836 mol, 1.0eq) in pyridine (1000 mL) was added tosyl chloride (TsCl, 176 g, 0.92 mol, 1.1 eq) slowly; the reaction mixture was stirred overnight at room temperature. The mixture was concentrated *in vacuo* to remove pyridine; the residue was dissolved in ethyl alcohol /H₂O 1000 ml/600 ml, stirred for 30 min, the separated. EA layer was washed with water (500 ml x3), brine (500 ml x2), dried
- 10 over Na₂SO₄, concentrated to remove about 800 ml EA. PE (1.5 L) was added and stirred overnight, the white solid was collected and dried in air to give the desired product (228 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.79-8.81 (d, *J*=8.0Hz, 2H), 7.48-7.50 (d, *J*=8.0Hz, 2H), 4.47 (s, 1H), 3.38-3.65 (m, 2H), 2.93-3.06 (m, 1H), 2.42 (s, 3H), 1.50-1.76 (m, 3H), 1.35 (s, 11 H)

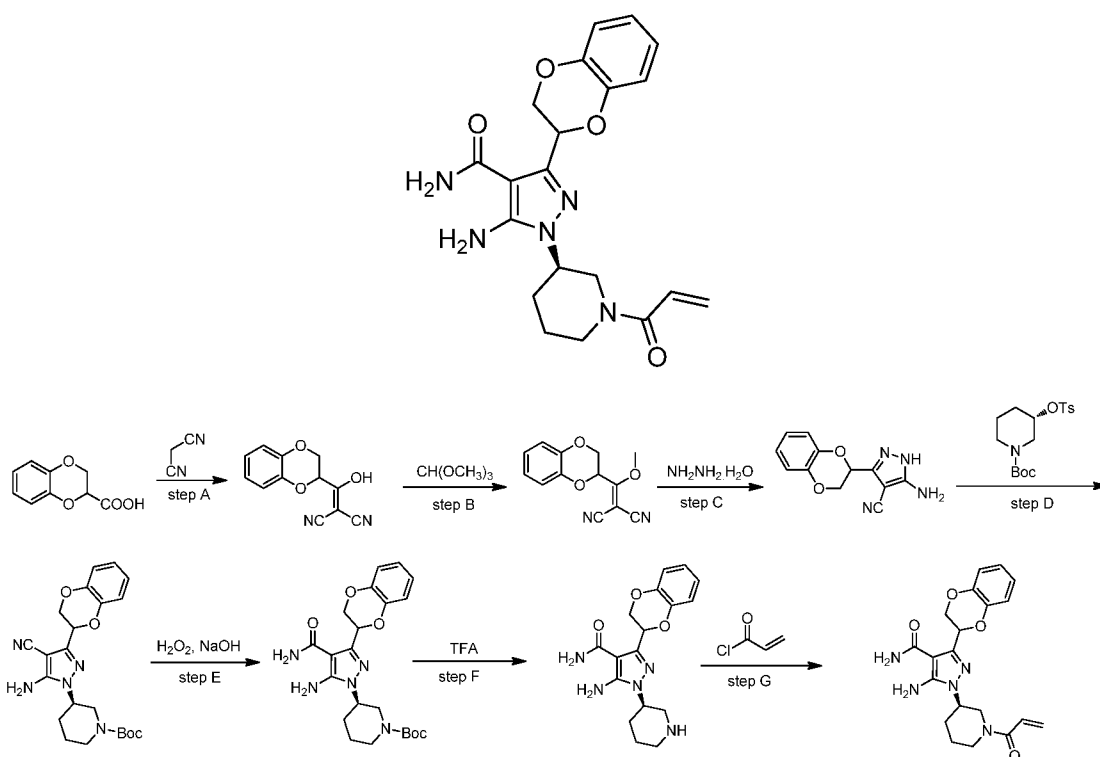
- 15 **BL-2:** (S)-tert-butyl 2-((tosyloxy)methyl)pyrrolidine-1-carboxylate



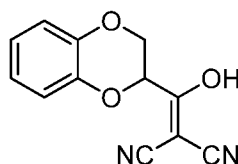
- [0087]** To a stirred solution of (S)-tert-butyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate (20 g, 99.2 mmol) in CH₂Cl₂ (200 mL) was added Et₃N (20 g, 0.198 mol), DMAP (1.23 g, 9.92 mmol), then the reaction mixture was cooled to 0°C and Tosyl chloride (TsCl, 28.4 g, 0.149 mol) was
- 20 added. After the addition, the reaction was stirred overnight. The reaction mixture was acidified to pH=4~5 with *aq.*HCl (1.0 M), then extracted with brine, dried over Na₂SO₄, concentrated and

purified by column chromatography (silica gel weight: 30 g, petroleum ether/EtOAc=10:1~2:1) to give target compound (33 g, 93.7%) as yellow syrup, which was solidified after one day. ¹H NMR (400 MHz, CDCl₃) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 4.11 – 4.05 (m, 1H), 3.94 (br.s, 2H), 3.29 (dd, *J* = 13.2, 6.0 Hz, 2H), 2.45 (s, 3H), 2.02 – 1.74 (m, 4H), 1.41 (s, 9H). MS: *M/e* 356 (M+1)⁺

Compound 1.1: 1-((R)-1-acryloylpiperidin-3-yl)-5-amino-3-(2,3-dihydrobenzo[*b*][1,4]dioxin-2-yl)-1H-pyrazole-4-carboxamide



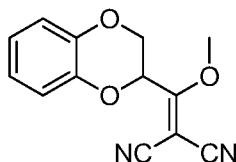
Step A: 2-((2,3-dihydrobenzo[*b*][1,4]dioxin-2-yl)(hydroxy)methylene)malononitrile



[0088] To a solution of 2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxylic acid (20.0 g, 111 mmol) in DCM (200 mL) was added oxalyl dichloride (30.0 g, 238 mmol) at 0 °C, followed by 0.5 ml of DMF. The solution was stirred at 0 °C for 1 hour, and at ambient temperature for 2h, and then concentrated to dryness. The resulting oil was diluted in THF (200 mL). Malononitrile (11.0 g, 167

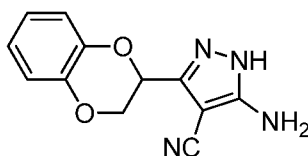
mmol) was added at 0 °C and followed by TEA (24.6 g, 167 mmol). The final solution was stirred at ambient temperature for 16 h. The reaction mixture was filtered through a celite pad and the filtrate was added 200 mL of H₂O, extracted with EA (200mL x 3). The combined extracts were washed with brine (200mL x 3), dried over sodium sulfate anhydrous and concentrated to get crude product (25.5 g) as brown oil, which was used in next step directly. MS: M/e 229 (M+1)⁺

Step B: 2-((2,3-dihydrobenzo[b][1,4]dioxin-2-yl)(methoxy)methylene)malononitrile



[0089] A solution of the product of Step A (25.5 g, 111 mmol) in EA (200 mL) was added aqueous HCl (15%, 100 mL) and the mixture was stirred at ambient temperature for 10 min. The layers were separated and the organics was dried over Na₂SO₄, concentrated and the resulted oil was dissolved with trimethoxymethane (200 mL) and heated at 100 °C for 2 hrs. The mixture was concentrated and the residue was purified by column chromatography to give the title product (17.1 g, 63% for 2 steps) as a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.02 – 6.87 (m, 4H), 5.47 (dd, *J* = 7.6, 2.8 Hz, 1H), 4.64 (dd, *J* = 12.0, 2.8 Hz, 1H), 4.32 (s, 3H), 4.10 (dd, *J* = 12.0, 7.6 Hz, 1H).

Step C: 5-amino-3-(2,3-dihydrobenzo[b][1,4]dioxin-2-yl)-1H-pyrazole-4-carbonitrile

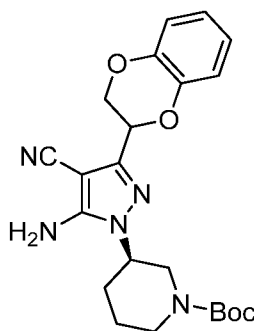


[0090] To a stirred solution of the product of Step B (17.0 g, 70.2 mmol) in EtOH (10 mL) was added hydrazine hydrate (4.5 g, 90 mmol) in drops at 0 °C over 10 min and the mixture was stirred at rt for 1 h. The mixture was concentrated and the residue was diluted with EA (200 mL), washed with brine (100mL x 3), dried over sodium sulfate anhydrous and concentrated. The resulting solid was purified by column chromatography to get the title product (14.5 g, 85%) as a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.79 (s, 1H), 6.97 – 6.82 (m, 4H), 6.44 (s, 2H), 5.17 (dd,

$J = 8.0, 2.4 \text{ Hz, 1H}$), 4.47 (dd, $J = 11.6, 2.4 \text{ Hz, 1H}$), 4.27 (dd, $J = 11.6, 8.0 \text{ Hz, 1H}$). MS: M/e 243 ($M+1$)⁺.

Step D: (3R)-tert-butyl 3-(5-amino-4-cyano-3-(2,3-dihydrobenzo[b][1,4]dioxin-2-yl)

5 -1H-pyrazol-1-yl)piperidine-1-carboxylate



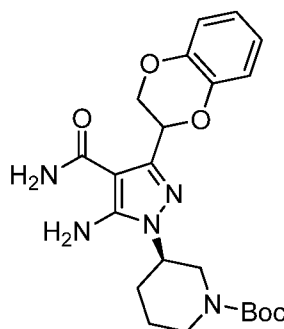
[0091] A mixture of the product of Step C (500 mg, 2.05 mmol), (*S*)-tert-butyl

3-(tosyloxy)piperidine-1-carboxylate (BL-1, 944 mg, 2.66 mmol) and Cs₂CO₃ (1.34 g, 4.1 mmol)

in DMF (10 mL) was stirred at 70 °C for 24 hrs. The resulting solution was concentrated. The

10 residue was washed by water, extracted with EA (10 mL x 3). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous, concentrated and purified by column chromatography eluting with PE:EA=1:1 to get the desired product (700 mg, 36%) as a yellow solid. MS: M/e 426 ($M+1$)⁺

15 Step E: (3R)-tert-butyl 3-(5-amino-4-carbamoyl-3-(2,3-dihydrobenzo[b][1,4]dioxin-2-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate



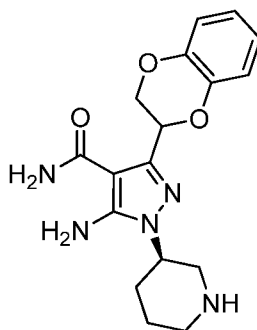
[0092] To a solution of the product of step D (600 mg, 1.41 mmol) in EtOH (5 mL) was added DMSO (2 mL), 5N NaOH aqueous solution (2 mL) and followed by H₂O₂ (1 mL). The solution

20 was stirred at 70 °C for 1 h. The resulting solution was concentrated. The residue was washed by

water, extracted with EA (10 mL x 3). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated and purified by silica gel column chromatography eluting with PE:EA=1:1 to get the desired product (400 mg, 64%) as yellow oil. MS: M/e 444 (M+1)⁺

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Step F: 5-amino-3-(2,3-dihydrobenzo[b][1,4]dioxin-2-yl)-1-((R)-piperidin-3-yl)-1H-pyrazole-4-carboxamide

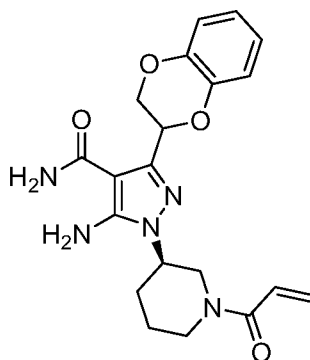


[0093] To the solution of the product of step E (400 mg, 0.90 mmol) in DCM (2 mL) was added TFA (2 mL). The solution was stirred at rt for 1 h. The resulting solution was concentrated to get the crude product (310 mg, 100%) as yellow oil, which was used in next step directly. MS: M/e 344 (M+1)⁺

10

Step G: 1-((R)-1-acryloylpiperidin-3-yl)-5-amino-3-(2,3-dihydrobenzo[b][1,4]dioxin-2-yl)-1H-pyrazole-4-carboxamide

15

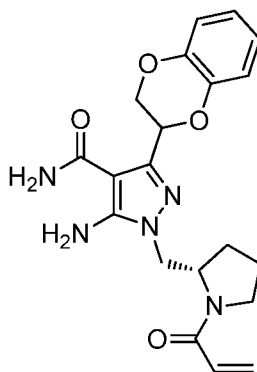


[0094] A mixture of the product of step F (310 mg, 0.90 mmol) and NaHCO₃ (454 mg, 5.40 mmol) in CH₃CN/H₂O (7 mL/7 mL) was stirred at 0 °C for 5 min. Acryloyl chloride (81 mg, 0.90 mmol) was added dropwise at 0 °C. The final solution was stirred at 0 °C for 5 min and quenched

by water, then extracted with EA (10 mL x 3). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous, concentrated and purified by silica gel column chromatography eluting with DCM:MeOH=20:1 to get the desired product (250 mg, 70%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆, 80 °C) δ 7.00 – 6.79 (m, 4H), 6.77 – 6.54 (m, 3H), 6.35 (s, 2H), 6.05 (d, *J* = 17.2 Hz, 1H), 5.63 (d, *J* = 9.2 Hz, 1H), 5.35 (d, *J* = 8.0 Hz, 1H), 4.53 (d, *J* = 11.2 Hz, 1H), 4.41-4.32 (m, 1H), 4.31-3.87 (m, 3H), 3.28-3.18 (m, 1H), 3.02-3.01 (m, 1H), 2.04-1.77 (m, 3H), 1.60-1.40 (m, 1H) ppm. MS: M/e 398 (M+1)⁺

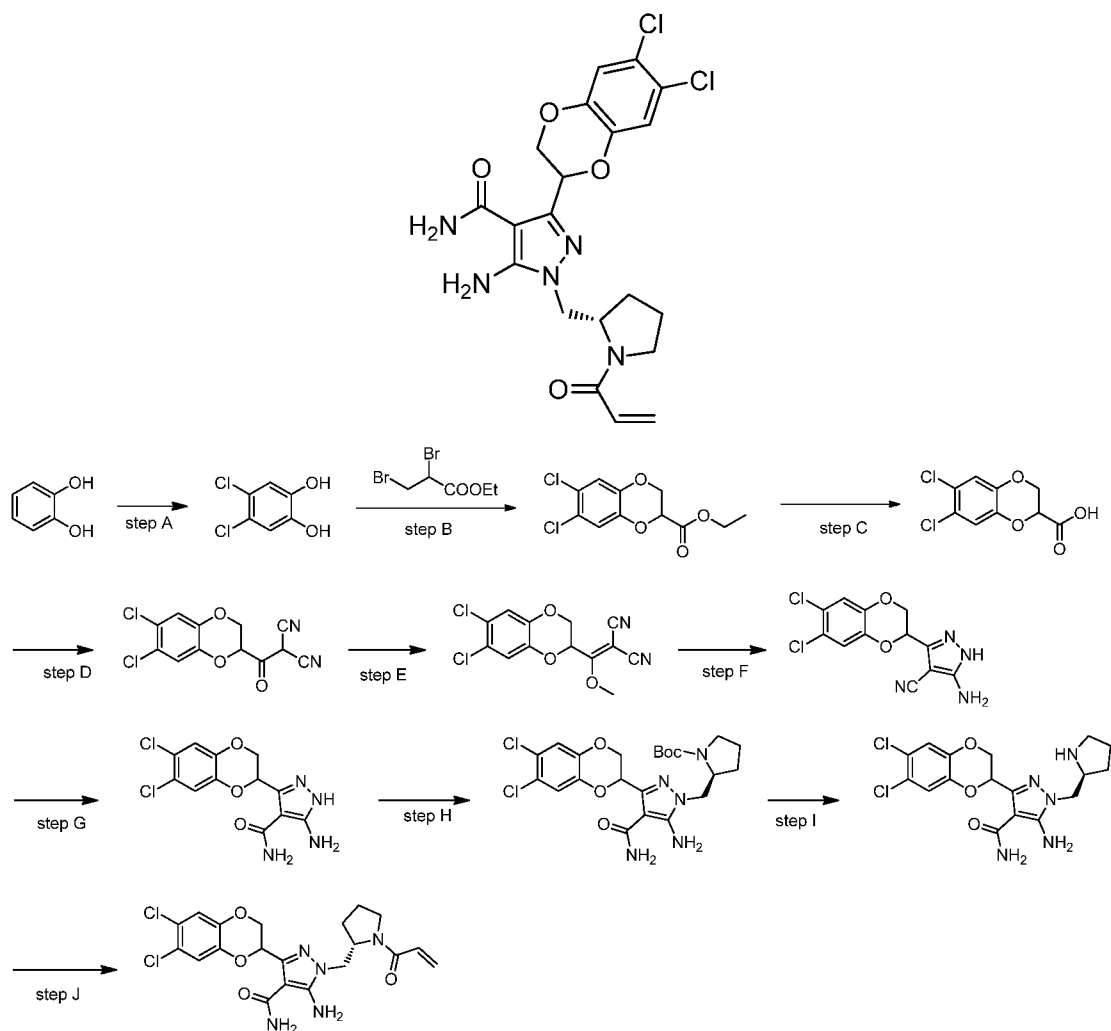
Compound 1.2: 1-(((S)-1-acryloylpyrrolidin-2-yl)methyl)-5-amino-3-(2,3-dihydrobenzo[b][1,4]dioxin-2-yl)-1H-pyrazole-4-carboxamide

[0095] **Compound 1.2** was prepared according to the procedures described for **Compound 1.1** under appropriate conditions that could be recognized by one skilled in the art.

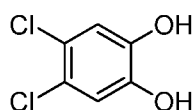


[0096] ¹H NMR (400 MHz, DMSO-*d*₆, 80 °C) δ 6.98 – 6.78 (m, 4H), 6.65 (s, 2H), 6.61 – 6.46 (m, 1H), 6.25 (s, 2H), 6.22 – 5.95 (m, 1H), 5.75-5.68 (m, 1H), 5.37 (d, *J* = 8 Hz, 1H), 4.52 (d, *J* = 11.6 Hz, 1H), 4.44 – 4.31 (m, 1H), 4.31 – 4.17 (m, 1H), 4.15 – 4.02 (m, 1H), 4.01 – 3.83 (m, 1H), 3.61 – 3.30 (m, 2H), 2.06 – 1.61 (m, 4H) ppm. MS: M/e 398 (M+1)⁺

Compound 1.3: 1-(((S)-1-acryloylpyrrolidin-2-yl)methyl)-5-amino-3-(6,7-dichloro-2,3-dihydrobenzo[b][1,4]dioxin-2-yl)-1H-pyrazole-4-carboxamide

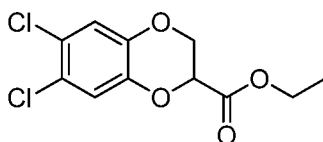


Step A: 4,5-dichlorobenzene-1,2-diol



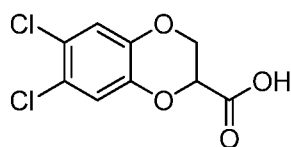
[0097] SO_2Cl_2 (27.2 g, 0.2 mmol) was added dropwise to a stirred solution of pyrocatechol (10 g, 91 mmol) in Et_2O (100 mL) at 0°C under N_2 . After the addition, the reaction was stirred for 3 hours. The reaction mixture was concentrated to give the residue, which was treated with petroleum ether and then filtered. The cake was collected to give target compound (11.6 g, 71.2%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 6.98 (s, 2H), 5.13 (s, 2H) ppm.

Step B: ethyl 6,7-dichloro-2,3-dihydrobenzo[b][1,4]dioxine-2-carboxylate



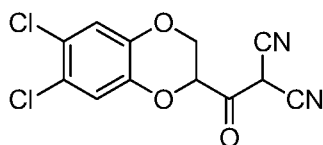
[0098] To a stirred solution of product of Step A (11.6 g, 61.4 mmol) in acetone (100 mL) was added K_2CO_3 (19.8 g, 0.14 mol) and ethyl 2,3-dibromopropanoate (19 g, 73.6 mmol). After the addition, the reaction mixture was stirred at 60°C for 5 hours. The reaction mixture was filtered and the cake was washed with EtOAc (100 mL). Then the filtrate was concentrated to give the residue, which was purified by column chromatography (petroleum ether/EtOAc=3:1) to give target compound (13.8 g, 81.1%) as colorless oil, which was solidified after an hour. MS: M/e 277 ($M+1$)⁺

10 Step C: 6,7-dichloro-2,3-dihydrobenzo[b][1,4]dioxine-2-carboxylic acid



[0099] To a stirred mixture of the product of Step B (13.8 g, 49.8 mmol) in THF/H₂O (50 mL/20 mL) was added LiOH·H₂O (4.2 g, 99.6 mmol). After the addition, the reaction mixture was stirred overnight. Most THF was removed *in vacuo*, the aqueous layer was acidified to pH=4~5 with aq.HCl, then extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated to give target compound (10 g, 80.6%) as a light yellow solid. MS: M/e 248 ($M-1$)⁻

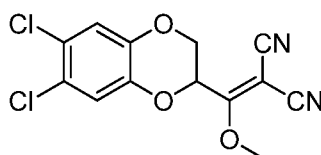
Step D: 2-(6,7-dichloro-2,3-dihydrobenzo[b][1,4]dioxine-2-carbonyl)malononitrile



[0100] To a stirred solution of the product of Step C (5.0 g, 20.1 mmol) in CH₂Cl₂ (50 mL) was added HOBt (3.2 g, 24 mmol) and Et₃N (4.0 g, 40 mmol), then EDCI (4.6 g, 24 mmol) and malononitrile (1.3 g, 20.1 mmol). After the addition, the reaction was stirred for 3 hours. The

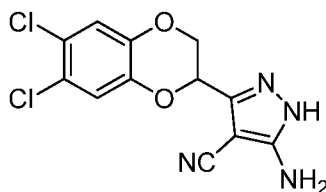
reaction mixture was poured into H₂O (200 mL), then extracted with CH₂Cl₂ (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated to give the residue, which was dissolved in EtOAc (150 mL) and stirred with *aq.* HCl (6.0 M, 50 mL) for 2 hours, then separated. The EtOAc layer was washed with brine, dried over Na₂SO₄ and concentrated to give desired compound, which was directly used to the next step. MS: M/e 297 (M+1)⁺

Step E: 2-((6,7-dichloro-2,3-dihydrobenzo[b][1,4]dioxin-2-yl)(methoxy)methylene) malononitrile



[0101] A solution of the product of step D (5.97 g, 20.1 mmol) in trimethoxymethane (50 mL) was stirred at 90°C for 6 hrs. The resulting solution was concentrated to give the residue, which was washed by water, extracted with EA (50 mL x 3). The combined organic layer was washed by brine, dried over anhydrous sodium sulfate then concentrated and purified by silica gel column chromatography eluting with petroleum ether/EtOAc=5:1~2:1 to get the desired product (2.2 g, 35.2%) as a white solid. MS: M/e 311 (M+1)⁺

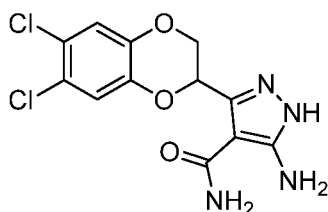
Step F: 5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carbonitrile



[0102] A solution of the product of step E (2.2 g, 7.07 mmol) and hydrazine hydrate (5 mL) in EtOH (20 mL) was stirred at rt for 30 min. The resulting solution was concentrated. The residue was washed by water, extracted with EA (20 mL x 3). The combined organic layer was washed by brine, dried over anhydrous sodium sulfate then concentrated and purified by silica gel column chromatography eluting with petroleum ether/EtOAc=3:1~1:1 to get the desired product (1.5 g,

68.2%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.15 (s, 1H), 7.23 (d, $J = 6.8$ Hz, 2H), 6.51 (s, 2H), 5.28 (d, $J = 5.2$ Hz, 1H), 4.52 (dd, $J = 11.6, 2.4$ Hz, 1H), 4.34 (dd, $J = 9.2, 5.2$ Hz, 1H)ppm. MS: M/e 311 ($M+1$)⁺

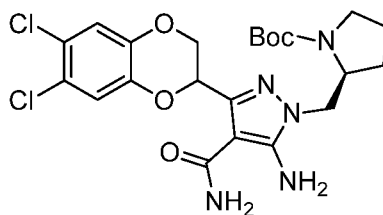
5 **Step G:** 5-amino-3-(6,7-dichloro-2,3-dihydrobenzo[b][1,4]dioxin-2-yl)-1H-pyrazole-4-carboxamide



[0103] A mixture of the product of step F (300 mg, 0.964 mmol) in MsOH (3 mL) was stirred at 70°C for 2 hours. The reaction mixture was poured into H_2O (30 mL) and basified to $\text{pH}=9\sim 10$ with *aq.* NaOH , then extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , concentrated *invacuo* to give target compound (307 mg, 96.8%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.94 (s, 1H), 7.24 (d, $J = 4.4$ Hz, 2H), 6.72 (br.s, 2H), 6.04 (s, 2H), 5.54 (s, 1H), 4.60 (dd, $J = 11.6, 2.4$ Hz, 1H), 4.46 – 4.32 (m, 1H)ppm. MS: M/e 329 ($M+1$)⁺

15

Step H: (2S)-tert-butyl 2-((5-amino-4-carbamoyl-3-(6,7-dichloro-2,3-dihydrobenzo[b][1,4]dioxin-2-yl)-1H-pyrazol-1-yl)methyl)pyrrolidine-1-carboxylate

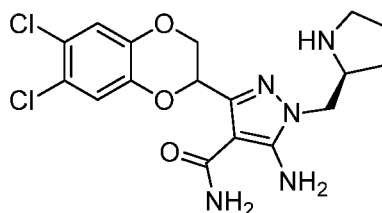


[0104] A mixture of the product of step H (100 mg, 0.304 mmol), (S)-tert-butyl 2-((tosyloxy)methyl)pyrrolidine-1-carboxylate (**BL-2**, 129 mg, 0.364 mmol) and Cs_2CO_3 (198 mg, 0.608 mmol) in DMF (3 mL) was stirred for 2 hours at 70°C. The reaction mixture was poured into H_2O (20 mL) and extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , concentrated and purified by column chromatography

20

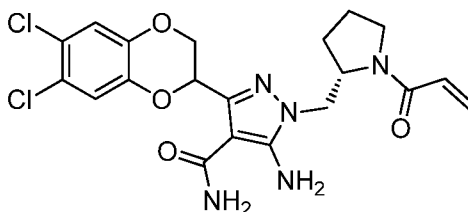
(petroleum ether/EtOAc=1:1) to give target compound (90 mg, 57.8%) as a white solid. MS: M/e 512 (M+1)⁺

Step I: 5-amino-3-(6,7-dichloro-2,3-dihydrobenzo[b][1,4]dioxin-2-yl)-1-((S)-pyrrolidin-2-ylmethyl)-1H-pyrazole-4-carboxamide



[0105] To the solution of the product of step H (90 mg, 0.176 mmol) in DCM (2 mL) was added TFA (1 mL). The solution was stirred at rt overnight. The resulting solution was concentrated to get the crude product as yellow oil, which was used in next step directly. MS: M/e 412 (M+1)⁺

Step J: 1-(((S)-1-acryloylpyrrolidin-2-yl)methyl)-5-amino-3-(6,7-dichloro-2,3-dihydrobenzo[b][1,4]dioxin-2-yl)-1H-pyrazole-4-carboxamide

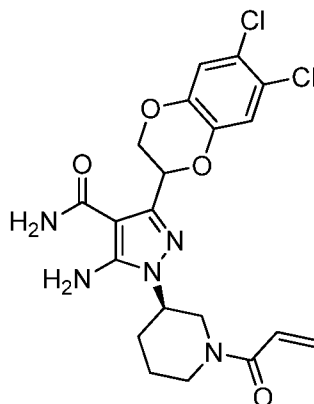


[0106] A mixture of the product of step I (0.176 mmol) and NaHCO₃ (29 mg, 0.352 mmol) in CH₃CN/H₂O (3 mL/3 mL) was stirred at 0°C for 5 min. Acryloyl chloride (15.9 mg, 0.176 mmol) was added dropwise at 0°C. The final solution was stirred at 0°C for 5 min and quenched by water, then extracted with EA (10 mL x 3). The combined organic layer was washed by brine, dried over anhydrous sodium sulfate then concentrated and purified by *prep*-HPLC to get the desired product (20 mg, 22%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.25 – 7.15 (m, 2H), 6.73 (br.s, 2H), 6.55 (m, 1H), 6.33 (br.s, 1H), 6.20 – 5.93 (m, 2H), 5.68 (dd, *J* = 10.4 Hz, 1H), 5.53 – 5.43 (m, 1H), 4.53 (t, *J* = 12.8 Hz, 1H), 4.35 (dd, *J* = 11.5, 8.4 Hz, 1H), 4.15 (s, 1H), 4.05 (d, *J* = 14.2 Hz, 1H), 3.96 – 3.82 (m, 2H), 1.81 (m, 5H) ppm. MS: M/e 466 (M+1)⁺

Compound 1.4: 1-((R)-1-acryloylpiperidin-3-yl)-5-amino-3-(6,7-dichloro-2,3-dihydro benzo[b][1,4]dioxin-2-yl)-1H-pyrazole-4-carboxamide

[0107] **Compound 1.4** was prepared according to the procedures described for **Compound 1.3**

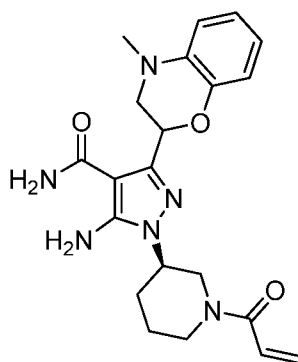
5 under appropriate conditions that could be recognized by one skilled in the art.

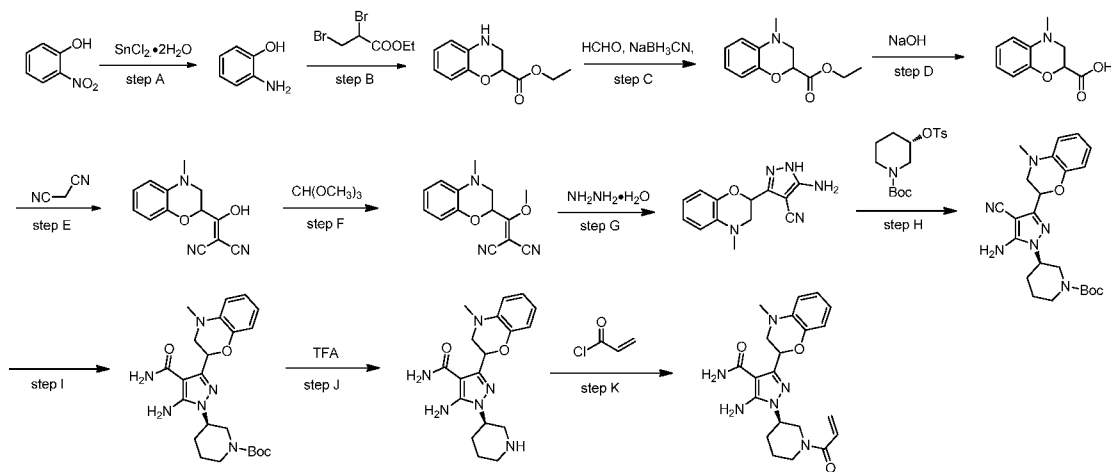


[0108] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.30 – 7.22 (m, 2H), 6.94 – 6.33 (m, 5H), 6.18 – 6.03 (m, 1H), 5.69 – 5.56 (m, 1H), 5.49 (d, $J = 6.4$ Hz, 1H), 4.64 – 4.53 (m, 1H), 4.46 – 4.34 (m, 1H), 4.29 – 4.12 (m, 2H), 4.09 – 3.96 (m, 1H), 3.16 – 2.95 (m, 1H), 2.07 – 1.73 (m, 4H), 1.57 – 1.36 (m,

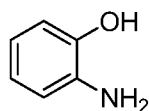
10 1H) ppm. MS: M/e 466 ($M+1$) $^+$

Compound 1.5: 1-((R)-1-acryloylpiperidin-3-yl)-5-amino-3-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)-1H-pyrazole-4-carboxamide



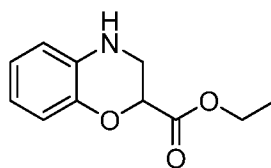


Step A: 2-aminophenol



- 5 **[0109]** The mixture of 2-nitrophenol (20 g, 215.66 mmol) and Tin(II) chloride dihydrate (223 g, 1.08 mol) in EtOH (500 mL) was stirred at 85 °C for 12 hrs. The resulting solution was concentrated. The residue was poured into ice water (500 mL), basified by 5N NaOH aqueous solution till pH=8, then extracted with EA (200 mL). The suspension was filtered through a celite pad. The filtrate was extracted with EA (200 mL x 3). The combined organic layer was washed by
- 10 brine, dried over sodium sulfate anhydrous then concentrated to get the desired compound (20 g, 85%) as a black solid. MS: M/e 110 (M+1)⁺

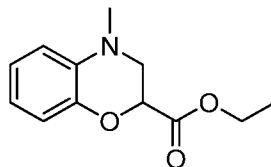
Step B: ethyl 3,4-dihydro-2H-benzo[b][1,4]oxazine-2-carboxylate



- 15 **[0110]** A mixture of the product of Step A (20 g, 183.24 mmol), ethyl 2,3-dibromopropionate (57.16 g, 219.92 mmol) and K₂CO₃ (70.80 g, 513.08 mmol) in acetone (80 mL) was stirred at reflux for 5 hrs. The resulting solution was concentrated. The residue was washed by water, extracted with EA (50 mL x 3). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated and purified by silica gel column chromatography

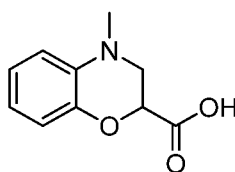
eluting with PE:EA=5:1 to get the desired product (26 g, 68%) as red-brown oil. MS: M/e 208 (M+1)⁺

Step C: ethyl 4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazine-2-carboxylate



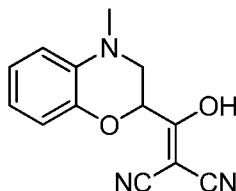
[0111] To a solution of the product of Step B (26 g, 125.46 mmol) in HOAc (100 mL) was added 60% HCHO aqueous solution (25.10 g, 501.84 mmol). The reaction mixture was stirred at rt for 10 min. Then the mixture was cooled to 0 °C, Sodium cyanoborohydride (15.77 g, 250.92 mmol) was added several portions for 15 min at 0 °C. The final solution was stirred at rt for 30 min. The resulting mixture was poured into ice water (100 mL), neutralized by 5N NaOH aqueous solution till pH=7, then extracted with EA (200 mL x 3). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated and purified by silica gel column chromatography eluting with PE:EA=5:1 to get the desired product (19.7 g, 71%) as yellow oil. MS: M/e 222 (M+1)⁺

Step D: 4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazine-2-carboxylic acid



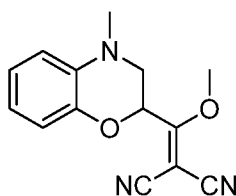
[0112] To a solution of the product of Step C (19.7 g, 89.04 mmol) in EtOH (40 mL) was added 6N NaOH (17.8 g, 445.20 mmol) aqueous solution at 0 °C. The solution was stirred at rt for 1 h. The resulting solution was neutralized by 2N HCl aqueous solution till pH = 6. The white solid was formed and filtered to get the desired product (17.20 g, 100%) as a white solid, which was used in next step directly. ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.83 – 6.52 (m, 4H), 4.78 (t, *J* = 4.0 Hz, 1H), 3.32 (d, *J* = 4.0 Hz, 2H), 2.78 (s, 3H) ppm. MS: M/e 194 (M+1)⁺

Step E: 2-(hydroxy(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methylene) malononitrile



[0113] To a solution of the product of step D (17.20 g, 89.02 mmol) in DCM (50 mL) was added
 5 HOBT (14.42 g, 106.83 mmol), Et₃N (25.69 mL, 178.04 mmol) followed by EDCI (20.48 g, 106.83 mmol). The solution was stirred at rt for 30 min. The malononitrile (7.06 g, 106.83 mmol) was added. The final solution was stirred at rt for 2-3 hrs. The resulting solution was concentrated, the residue was diluted in EA (100 mL), washed by saturated NaHCO₃ aqueous solution followed by saturated NH₄Cl aqueous solution. The organic layer was washed by 6 N HCl aqueous
 10 solution. The organic layer was separated and concentrated to get crude product (21.48 g, 100%) as yellow oil, which was used in next step directly. MS: M/e 242 (M+1)⁺

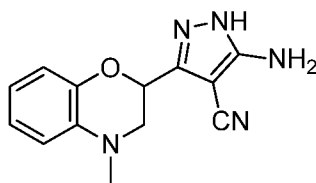
Step F: 2-(methoxy(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methylene) malononitrile



15 [0114] A solution of the product of step E (21.48 g, 89.04 mmol) in trimethoxymethane (30 mL) was stirred at 90 °C for 2 hrs. The resulting solution was concentrated and purified by silica gel column chromatography eluting with PE:EA=5:1 to get the desired product (5 g, 22%) as yellow oil. MS: M/e 256 (M+1)⁺

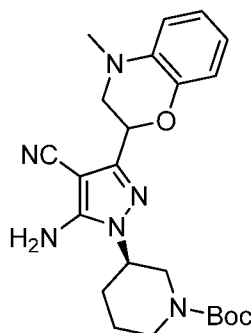
20

Step G: 5-amino-3-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)-1H-pyrazole-4-carbonitrile



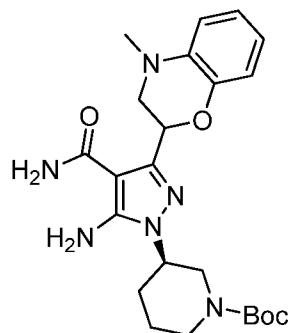
[0115] A solution of the product of step F (5 g, 19.59 mmol) and hydrazine hydrate (2 mL) in EtOH (4 mL) was stirred at rt for 10 min. The resulting solution was concentrated. The residue was washed by water, extracted with EA (20 mL x 3). The combined organic layer was washed by
 5 brine, dried over sodium sulfate anhydrous then concentrated and purified by silica gel column chromatography eluting with DCM:MeOH=40:1-20:1 to get the desired product (4 g, 80%) as a yellow solid. MS: M/e 256 (M+1)⁺

Step **H**: (3R)-tert-butyl 3-(5-amino-4-cyano-3-(4-methyl-3,4-dihydro-2H-benzo [b][1,4]
 10 oxazin-2-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate



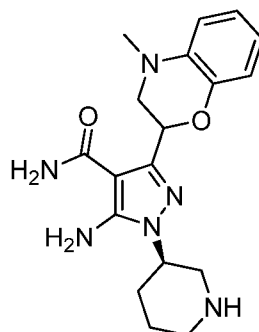
[0116] A mixture of the product of step G (581 mg, 2.28 mmol), (S)-Tert-butyl 3-(tosyloxy)piperidine-1-carboxylate (**BL-1**, 970 mg, 2.73 mmol) and Cs₂CO₃ (1.49 g, 4.56 mmol) in DMF (10 mL) was stirred at 70 °C for 24 hrs. The resulting solution was concentrated. The
 15 residue was washed by water, extracted with EA (10 mL x 3). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated and purified by silica gel column chromatography eluting with PE:EA=1:1 to get the desired product (654 mg, 65%) as yellow oil. MS: M/e 439 (M+1)⁺

Step **I**: (3R)-tert-butyl 3-(5-amino-4-carbamoyl-3-(4-methyl-3,4-dihydro-2H-benzo
 20 [b][1,4]oxazin-2-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate



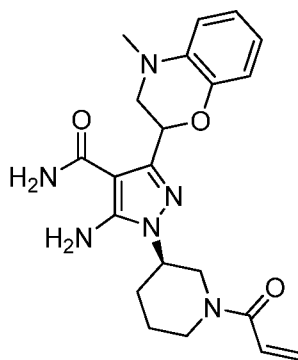
[0117] To a solution of the product of step H (654 mg, 1.49 mmol) in EtOH (5 mL) was added DMSO (2 mL), 5N NaOH aqueous solution (2 mL) followed by H₂O₂ (1 mL). The solution was stirred at 70 °C for 1 h. The resulting solution was concentrated. The residue was washed by water, extracted with EA (10 mL x 3). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated and purified by silica gel column chromatography eluting with PE:EA=1:4 to get the desired product (305 mg, 45%) as yellow oil. MS: M/e 457 (M+1)⁺

Step J: 5-amino-3-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)-1-((R)-piperidin-3-yl)-1H-pyrazole-4-carboxamide



[0118] To the solution of the product of step I (305 mg, 0.67 mmol) in DCM (3 mL) was added TFA (1 mL). The solution was stirred at rt for 1 hrs. The resulting solution was concentrated to get the crude product (238mg, 100%) as yellow oil, which was used in next step directly. MS: M/e 357 (M+1)⁺

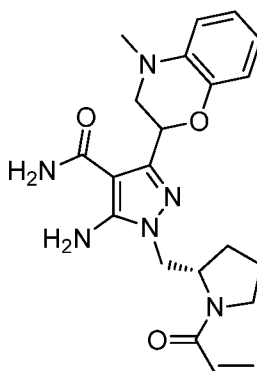
Step K: 1-((R)-1-acryloylpiperidin-3-yl)-5-amino-3-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)-1H-pyrazole-4-carboxamide



[0119] A mixture of the product of step J (238 mg, 0.67 mmol) and NaHCO₃ (337 mg, 4.02 mmol) in CH₃CN/H₂O (5 mL/5 mL) was stirred at 0 °C for 5 min. Acryloyl chloride (60 mg, 0.67 mmol) was added drop wise at 0 °C. The final solution was stirred at 0 °C for 5 min and quenched
 5 by water, then extracted with EA (10 mL x 3). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated and purified by silica gel column chromatography eluting with DCM:MeOH=20:1 to get the desired product (90 mg, 32%) as white solid. ¹H NMR (400 MHz, DMSO-*d*₆, 80°C) δ 6.84 (t, *J* = 7.6 Hz, 1H), 6.79 – 6.71 (m, 3H), 6.69 (s, 2H), 6.57 (t, *J* = 7.6 Hz, 1H), 6.34 (s, 2H), 6.12 – 5.99 (m, 1H), 5.69 – 5.57 (m, 1H), 5.23 (dd, *J* =
 10 8.8, 2.6 Hz, 1H), 4.28 – 3.98 (m, 3H), 3.64 – 3.54 (m, 1H), 3.53 – 3.43 (m, 1H), 3.33 – 3.23 (m, 1H), 3.16 – 3.03 (m, 1H), 2.89 (s, 3H), 2.06 – 1.78 (m, 3H), 1.60 – 1.40 (m, 1H) ppm. MS: *M/e* 411 (M+1)⁺

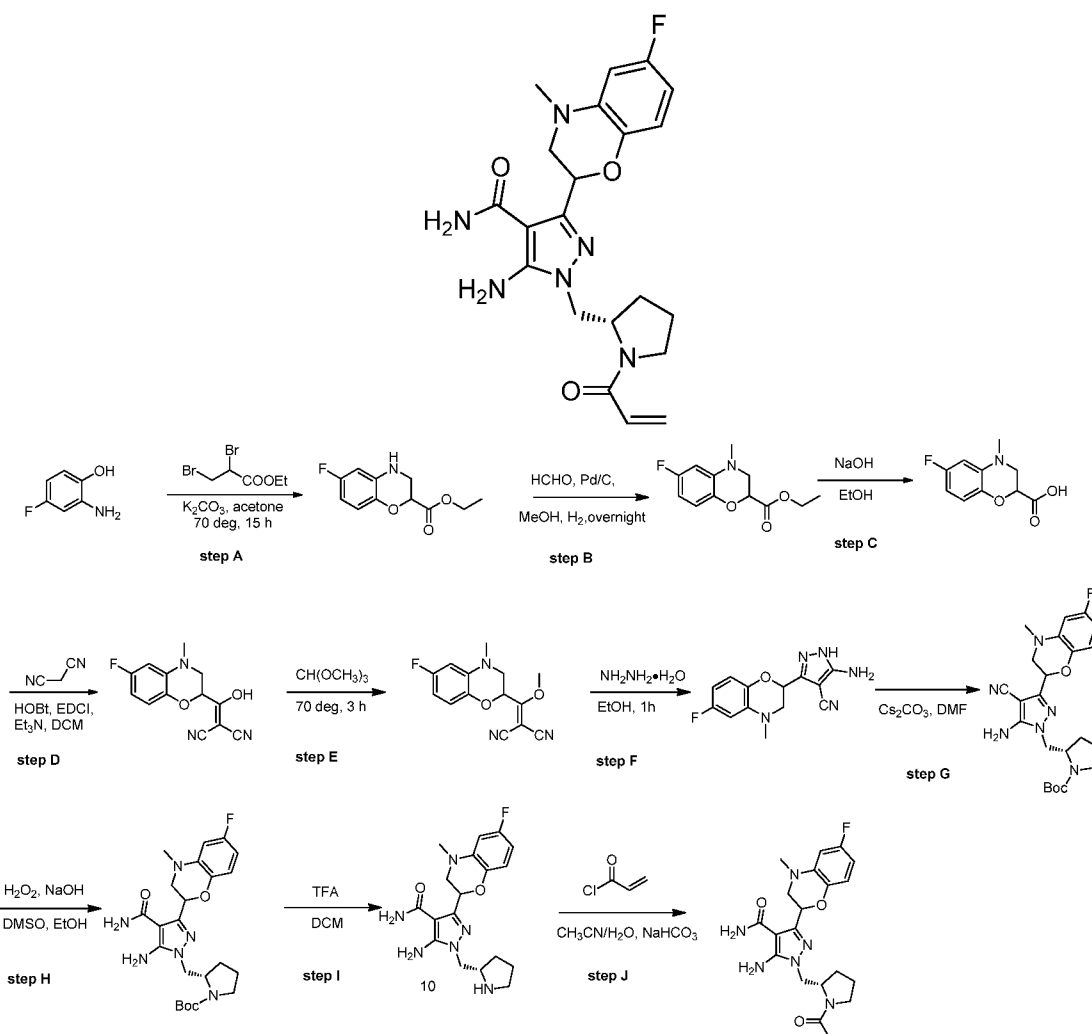
[0120] **Compound 1.6** was prepared according to the procedures described for **Compound 1.5** under appropriate conditions that could be recognized by one skilled in the art.

Compound 1.6: 1-(((S)-1-acryloylpyrrolidin-2-yl)methyl)-5-amino-3-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)-1H-pyrazole-4-carboxamide

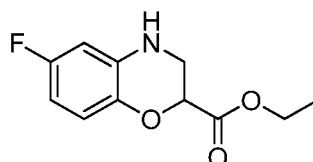


[0121] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.00 – 6.79 (m, 2H), 6.81 – 6.72 (m, 2H), 6.67 – 6.55 (m, 2H), 6.30 – 5.98 (m, 1H), 5.79 – 5.42 (m, 1H), 5.33 – 5.21 (m, 1H), 4.45 – 4.16 (m, 1H), 4.13 – 3.88 (m, 2H), 3.65 – 3.34 (m, 4H), 2.89 (s, 3H), 1.98 – 1.71 (m, 4H). MS: M/e 411 ($M+1$)⁺

5 **Compound 1.7:** 1-(((S)-1-acryloylpyrrolidin-2-yl)methyl)-5-amino-3-(6-fluoro-4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)-1H-pyrazole-4-carboxamide



Step A: ethyl 6-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine-2-carboxylate



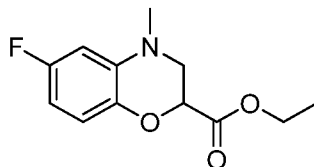
10

[0122] To a suspension of 2-amino-4-fluorophenol (12.7 g, 100 mmol) and K_2CO_3 (34 g, 250 mmol) in acetone (200 mL) was added ethyl 2,3-dibromopropanoate (28.6 g, 110 mmol). The resulting mixture was stirred at reflux for 4 hrs. The mixture was cooled to room temperature and

concentrated. The residue was washed by water, extracted with EA (50 mL x 4). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated and purified by silica gel column chromatography eluting with PE:EA=5:1 to give brown oil. PE/EA (30/1, 60 mL) was added to the oil and the mixture was stirred at room temperature for 30 min.

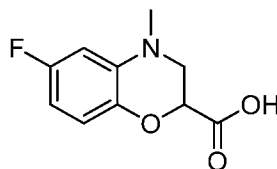
- 5 The solid was formed, filtered and dried to give the desired product (3.6 g, 16%) as a brown solid. ^1H NMR (400 MHz, DMSO- d_6) δ 6.71 (dd, $J = 8.8, 5.6$ Hz, 1H), 6.36 (dd, $J = 10.8, 3.2$ Hz, 1H), 6.31 – 6.26 (m, 1H), 6.15 (s, 1H), 4.90 (t, $J = 4.0$ Hz, 1H), 4.12 (q, $J = 7.2$ Hz, 2H), 4.41 – 3.39 (m, 2H), 1.17 (t, $J = 6.8$ Hz, 3H). ppm. MS: M/e 226 (M+1) $^+$

- 10 Step B: ethyl 6-fluoro-4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazine-2-carboxylate



- [0123] To a solution of the product of Step A (3.6 g, 16 mmol) in EtOH (40 mL) was added 40% HCHO aqueous solution (25 mL) and Pd/C (0.5 g). The reaction mixture was stirred at rt under H₂ atmosphere (balloon) for 16 hrs. Then the mixture was filtered through a pad of celite, washed with
15 EtOH (40 mL). The filtrate was concentrated to give the desired product (5 g, crude) as black oil which used directly for next step without further purification. MS: M/e 240 (M+1) $^+$

Step C: 6-fluoro-4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazine-2-carboxylic acid

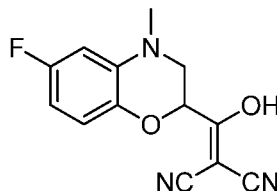


- 20 [0124] To a solution of the product of Step B (5 g, crude) in EtOH (50 mL) was added a solution of sodium hydroxide (2.56 g, 64 mmol) in water (20 mL). The solution was stirred at rt for 3 h. The mixture was concentrated. The resulting residue was neutralized by 2N HCl aqueous solution till pH = 6. A solid was formed and filtered to get the desired product (1.3 g, 38.5% for two steps) as an off-white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 6.60 (dd, $J = 8.4, 5.6$ Hz, 1H), 6.41 (dd, $J =$

12, 3.2 Hz, 1H), 6.28- 6.23 (m, 1H), 4.14- 4.11 (m, 1H), 3.45- 3.39 (m, 1H), 3.14- 3.09 (m, 1H), 2.78 (s, 3H) ppm. MS: M/e 212 (M+1)⁺

Step D: 2-((6-fluoro-4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(hydroxy)

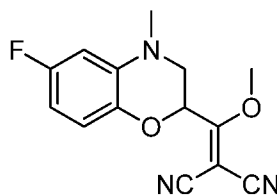
5 methylene)malononitrile



[0125] To a solution of the product of Step C (1.3 g, 6.16 mmol) in DCM (20 mL) was added HOBT (1 g, 7.39 mmol), Et₃N (1.26 g, 12.5 mmol) followed by EDCI (1.4 g, 7.39 mmol). The solution was stirred at rt for 30 min. The malononitrile (0.4 g, 6.16 mmol) was added. The final
10 solution was stirred at rt for 16 hrs. The resulting solution was concentrated, the residue was diluted in EA (100 mL), washed by saturated NaHCO₃ aqueous solution followed by saturated NH₄Cl aqueous solution. The organic layer was washed by 10% H₂SO₄ aqueous solution. The organic layer was separated and concentrated to get crude product (1.5 g, 93%) as a solid, which was used in next step directly. ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.66 – 6.64 (m, 1H), 6.50 (dd, *J* =
15 11.6, 3.2 Hz, 1H), 6.34- 6.29 (m, 1H), 4.67 (dd, *J* = 7.6, 2.8 Hz, 1H), 3.29- 3.26 (m, 1H), 3.20- 3.15 (m, 1H), 2.82 (s, 3H) ppm. MS: M/e 260 (M+1)⁺

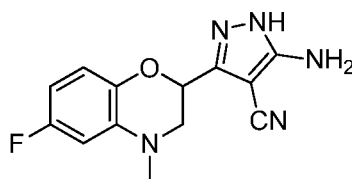
Step E: 2-((6-fluoro-4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(methoxy)

methylene)malononitrile



20 [0126] A solution of the product of step D (1.5 g, 5.8 mmol) in trimethoxymethane (30 mL) was stirred at 70 °C for 3 hrs. The resulting solution was concentrated and purified by silica gel column chromatography eluting with PE:EA=5:1 to get the desired product (0.25 g, 16%) as brown oil. MS: M/e 274 (M+1)⁺

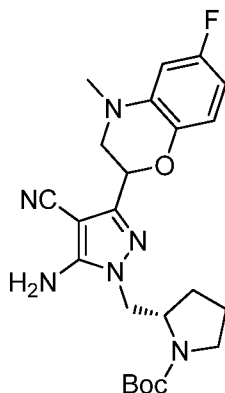
Step F: 5-amino-3-(6-fluoro-4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)-1H-pyrazole-4-carbonitrile



- 5 **[0127]** A solution of the product of step E (0.25 g, 0.91 mmol) and hydrazine hydrate (2 mL) in EtOH (6 mL) was stirred at rt for 2 h. The resulting solution was concentrated. The residue was washed by water, extracted with EA (30 mL x 3). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated to give the desired product (0.245 g, 100%) as yellow foam. MS: M/e 274 (M+1)⁺

10

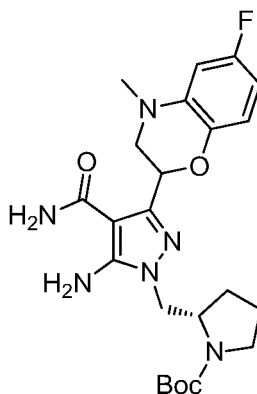
Step G: (2S)-tert-butyl 2-((5-amino-4-cyano-3-(6-fluoro-4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)-1H-pyrazol-1-yl)methyl)pyrrolidine-1-carboxylate



- 15 **[0128]** A mixture of the product of step F (245 mg, 0.9 mmol), (S)-tert-butyl 2-((tosyloxy)methyl)pyrrolidine-1-carboxylate (**BL-2**, 383 mg, 1.08 mmol) and Cs₂CO₃ (585 mg, 1.8 mmol) in DMF (5 mL) was stirred at 70 °C for 5 hrs. The resulting solution was concentrated. The residue was washed by water, extracted with EA (30 mL x 3). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated to give the desired product (400 mg, crude) as yellow oil. MS: M/e 457 (M+1)⁺

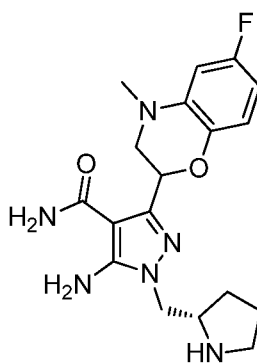
20

Step H: (2S)-tert-butyl 2-((5-amino-4-carbamoyl-3-(6-fluoro-4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)-1H-pyrazol-1-yl)methyl)pyrrolidine-1-carboxylate



[0129] To a solution of the product of step G (400 mg, crude) in EtOH (5 mL) was added
 5 DMSO (2 mL), 5N NaOH aqueous solution (2 mL) followed by H₂O₂ (2 mL). The solution was
 stirred at 50 °C for 2 h. The resulting solution was concentrated. The residue was washed by water,
 extracted with EA (60 mL). The combined organic layer was washed by brine, dried over sodium
 sulfate anhydrous then concentrated and purified by silica gel column chromatography eluting
 with PE:EA=1:1 to get the desired product (130 mg, 30% for three steps) as yellow oil. MS: M/e
 10 475 (M+1)⁺

Step I: 5-amino-3-(6-fluoro-4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)-
 1-((S)-pyrrolidin-2-ylmethyl)-1H-pyrazole-4-carboxamide

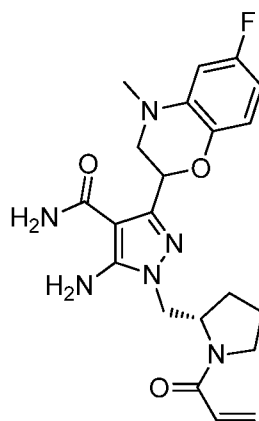


15 [0130] To the solution of the product of step H (130 mg, 0.274 mmol) in DCM (3 mL) was
 added TFA (1 mL). The solution was stirred at rt for 3 hrs. The resulting solution was treated with
 saturated Na₂CO₃ aqueous solution to pH = 8, extracted with DCM (30 mL x 2). The combined
 organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated to get

the crude product (100mg, 98%) as yellow oil, which was used in next step directly. MS: M/e 375 (M+1)⁺

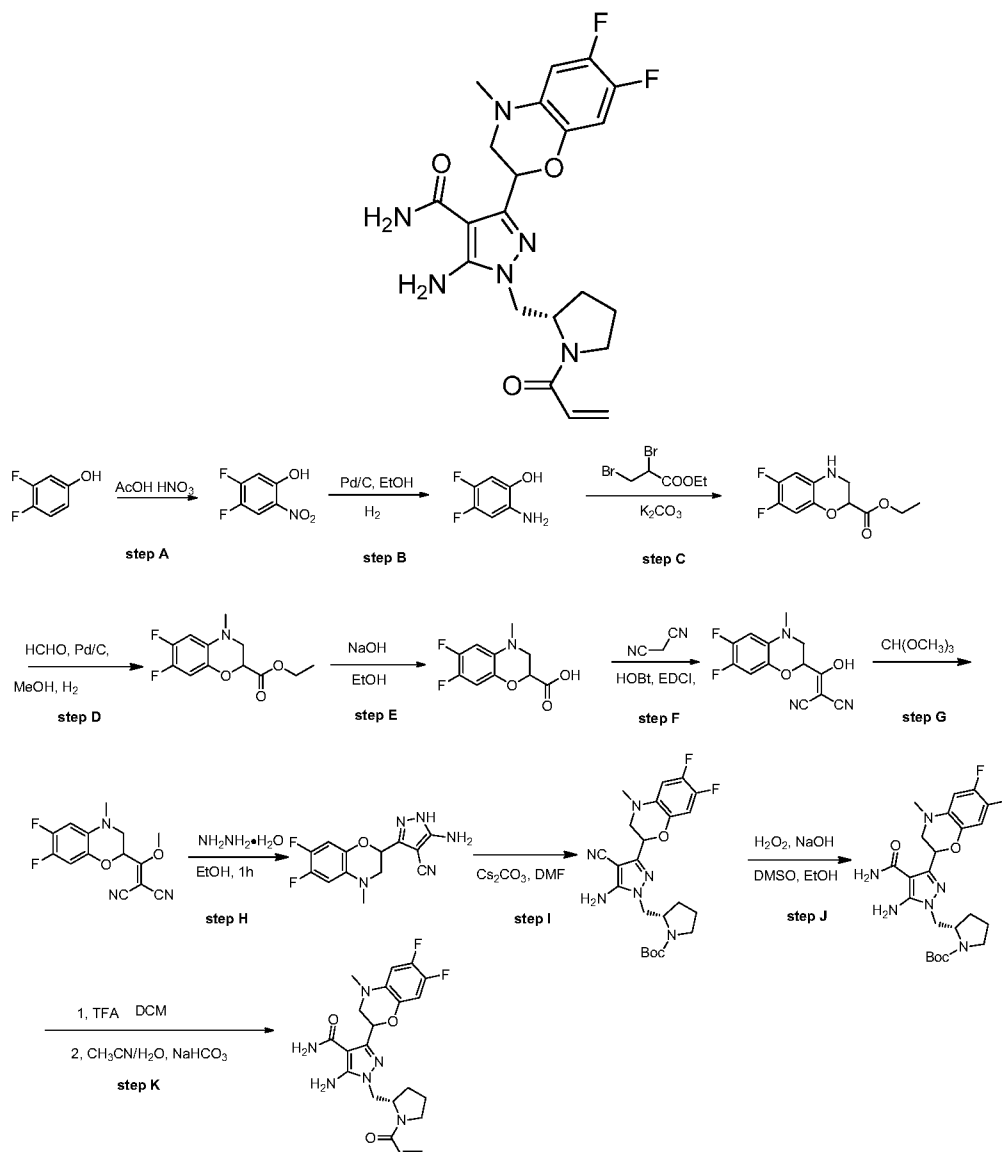
Step J: 1-(((S)-1-acryloylpyrrolidin-2-yl)methyl)-5-amino-3-(6-fluoro-4-methyl-

5 3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)-1H-pyrazole-4-carboxamide

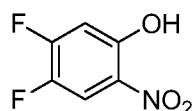


[0131] To a mixture of the product of step I (100 mg, 0.267 mmol) in CH₃CN (4 mL) was added saturated NaHCO₃ aqueous solution (1 mL). The resulting solution was cooled to 0 °C and a solution of acryloyl chloride (24 mg, 0.267 mmol) in CH₃CN (1 mL) was added dropwise. The final solution was stirred at 0 °C for 5 min and quenched by water, then extracted with EA (30 mL x 2). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated and purified by *prep*-TLC (DCM:MeOH=20:1) to give the desired product (53 mg, 46%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.83 (br.s, 2H), 6.74- 6.70 (m, 1H), 6.64 – 6.51 (m, 2H), 6.45 – 6.40 (m, 2H), 6.35 – 6.30 (m, 1H), 6.24 – 6.18 (m, 1H), 6.05– 5.71 (m, 1H), 5.25 – 5.21 (m, 1H), 4.21 – 3.90 (m, 3H), 3.65 – 3.40 (m, 4H), 2.90 (s, 3H), 2.00 – 1.74 (m, 4H), ppm. MS: M/e 429 (M+1)⁺

Compound 1.8: 1-(((S)-1-acryloylpyrrolidin-2-yl)methyl)-5-amino-3-(6,7-difluoro-4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)-1H-pyrazole-4-carboxamide



Step A: 4,5-difluoro-2-nitrophenol

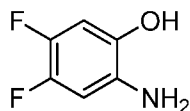


5

[0132] To a solution of 3,4-difluorophenol (37 g, 0.28 mol) in AcOH (200 mL) was added a solution of fuming HNO_3 (10 mL) in AcOH (80 mL) dropwise to keep the temperature below 40°C over about 2 hours. The mixture was slowly poured to ice water (300 mL). A red solid was formed, filtered, and washed with water (1.8 L). The solid was dried to give the desired product (36 g, 72%) as a red solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.46 (s, 1H), 8.19 – 8.12 (m, 1H), 7.19 – 7.13 (m, 1H). ppm.

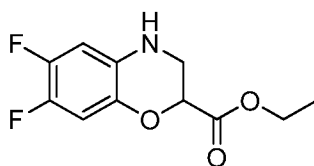
10

Step B: 2-amino-4,5-difluorophenol



[0133] To a solution of the product of Step A (40 g, 228 mmol) in EtOH (200 mL) was added
5 Pd/C (4 g). The reaction mixture was stirred at rt under H₂ atmosphere (balloon) for 3 days. Then
the mixture was filtered through a pad of Celite, washed with EtOH (100 mL). The filtrate was
concentrated and the residue was treated with PE/EA (10/1, 300mL). The suspension was stirred at
rt for 0.5 hour. The solid was filtered, washed with PE, dried to give the desired product (30 g,
90%) as a black solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.39 (br.s, 1H), 6.62 – 6.42 (m, 2H), 4.68
10 (br.s, 2H). ppm. MS: M/e 146 (M+1)⁺

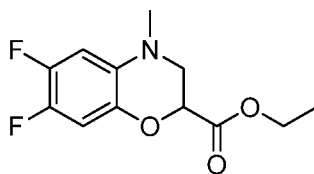
Step C: ethyl 6,7-difluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine-2-carboxylate



[0134] To a suspension of 2-amino-4-fluorophenol (10 g, 69 mmol) and K₂CO₃ (23.6 g, 172.5
15 mmol) in acetone (80 mL) was added ethyl 2,3-dibromopropanoate (19.7 g, 76 mmol). The
resulting mixture was stirred at reflux overnight. The mixture was cooled to room temperature and
concentrated. The residue was washed by water, extracted with EA (50 mL x 4). The combined
organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated and
purified by silica gel column chromatography eluting with PE:EA=5:1 to give black oil. PE/EA
20 (30/1, 60 mL) was added to the oil and the mixture was stirred at room temperature for 30 min.
The solid was formed, filtered and dried to give the desired product (4.5 g, 26.8%) as a brown
solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.87 (dd, *J* = 8.4, 3.6 Hz, 1H), 6.56 (dd, *J* = 8.4, 3.6 Hz,
1H), 5.99 (s, 1H), 4.96 (t, *J* = 3.6 Hz, 1H), 4.13(q, *J* = 7.2 Hz, 2H), 4.40 – 3.34 (m, 2H), 1.17 (t, *J* =
6.8 Hz, 3H). ppm. MS: M/e 244 (M+1)⁺

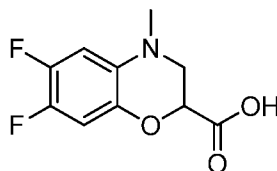
25

Step D: ethyl 6,7-difluoro-4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazine-2- carboxylate



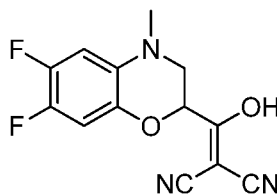
[0135] To a solution of the product of Step C (4.5 g, 18.5 mmol) in EtOH (40 mL) was added 40% HCHO aqueous solution (20 mL) and Pd/C (0.5 g). The reaction mixture was stirred at rt under H₂ atmosphere (balloon) for 36 hrs. Then the mixture was filtered through a pad of Celite, washed with EtOH (40 mL). The filtrate was concentrated to give the desired product (8 g, crude) as black oil which used directly for next step without further purification. MS: M/e 258 (M+1)⁺

Step E: 6,7-difluoro-4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazine-2-carboxylic acid



[0136] To a solution of the product of step D (8 g, crude) in EtOH (50 mL) was added 2N NaOH (25 mL). The solution was stirred at rt for 4 h. The mixture was concentrated. The resulting residue was neutralized by 2N HCl aqueous solution till pH = 6. The solid was formed and filtered to get the desired product (2 g) as a brown solid. The filtrate was extracted with EA (30 mL x 2), washed with brine, dried over Na₂SO₄, filtered and concentrated to give a red solid (0.6 g). 2.6 g of product was obtained in total (63% for two steps). ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.87 (dd, *J* = 8.0, 3.6 Hz, 1H), 6.76 (dd, *J* = 8.0, 5.2 Hz, 1H), 4.96 (t, *J* = 3.2 Hz, 1H), 3.42 – 3.27 (m, 2H), 2.78 (s, 3H). ppm. MS: M/e 230 (M+1)⁺

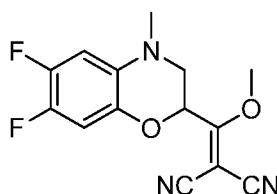
Step F: 2-((6,7-difluoro-4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(hydroxy)methylene)malononitrile



[0137] To a solution of the product of step E (2.6 g, 11.35 mmol) in DCM (40 mL) was added HOBT (1.83 g, 13.6 mmol), Et₃N (2.3 g, 22.7 mmol) followed by EDCI (2.6 g, 13.6 mmol). The solution was stirred at rt for 30 min. The malononitrile (0.74 g, 11.35 mmol) was added. The final

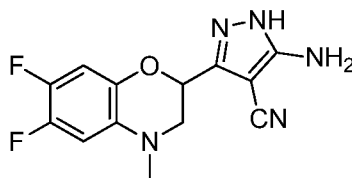
solution was stirred at rt for 3 hrs. The resulting solution was concentrated, the residue was diluted in EA (100 mL), washed by saturated NaHCO_3 aqueous solution followed by saturated NH_4Cl aqueous solution. The organic layer was washed by 10% H_2SO_4 aqueous solution and brine. The organic layer was separated and concentrated to get crude product (3 g, 95%) as a brown solid, which was used in next step directly. MS: M/e 278 ($M+1$)⁺

Step G: 2-((6,7-difluoro-4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(methoxy)methylene)malononitrile



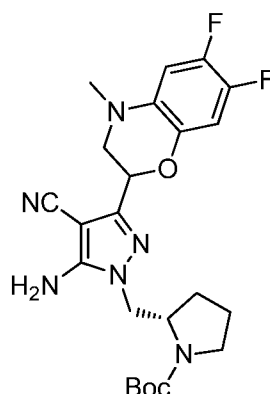
A solution of the product of step F (3 g, 10.8 mmol) in trimethoxymethane (50 mL) was stirred at 70 °C for 3 hrs. The resulting solution was concentrated and purified by silica gel column chromatography eluting with PE:EA=5:1 to get the desired product (0.5g, 16%) as brown oil. MS: M/e 292($M+1$)⁺

Step H: 5-amino-3-(6,7-difluoro-4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)-1H-pyrazole-4-carbonitrile



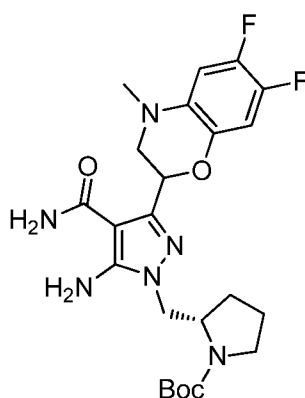
A solution of the product of step G (0.5 g, 1.7 mmol) and hydrazine hydrate (2 mL) in EtOH (5 mL) was stirred at rt for 1 h. The resulting solution was concentrated. DCM (4 mL) was added to the residue and the solid was formed. The solid was filtered and dried to give the product (0.3 g, 60%) as a yellow solid. MS: M/e 292 ($M+1$)⁺

Step I: (2S)-tert-butyl 2-((5-amino-4-cyano-3-(6,7-difluoro-4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)-1H-pyrazol-1-yl)methyl)pyrrolidine-1-carboxylate



[0140] A mixture of the product of step H (0.3 g, 1 mmol), (S)-tert-butyl 2-((tosyloxy)methyl)pyrrolidine-1-carboxylate (**BL-2**, 426 mg, 1.2 mmol) and Cs₂CO₃ (650 mg, 2 mmol) in DMF (5 mL) was stirred at 70 °C for 6 hrs. The resulting solution was concentrated. The residue was washed by water, extracted with EA (30 mL x 3). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated to give the desired product (600 mg, crude) as yellow oil. MS: M/e 475 (M+1)⁺

Step J: (2S)-tert-butyl 2-((5-amino-4-carbamoyl-3-(6,7-difluoro-4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)-1H-pyrazol-1-yl)methyl)pyrrolidine-1-carboxylate



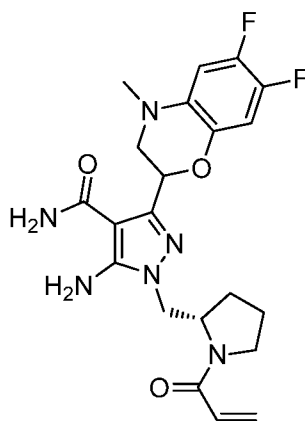
[0141] To a solution of the product of step I (600 mg, crude) in EtOH (6 mL) was added DMSO (2 mL), 5N NaOH aqueous solution (2 mL) followed by H₂O₂ (2 mL). The solution was stirred at 50 °C for 3 hrs. The resulting solution was concentrated. The residue was washed by water, extracted with EA (30 mL x 2). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated and purified by silica gel column chromatography

eluting with PE:EA=1:1 to get the desired product (230 mg, 46% for two steps) as a white solid.

MS: M/e 493 (M+1)⁺

Step K: 1-(((S)-1-acryloylpyrrolidin-2-yl)methyl)-5-amino-3-(6,7-difluoro-4-

5 methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)-1H-pyrazole-4-carboxamide

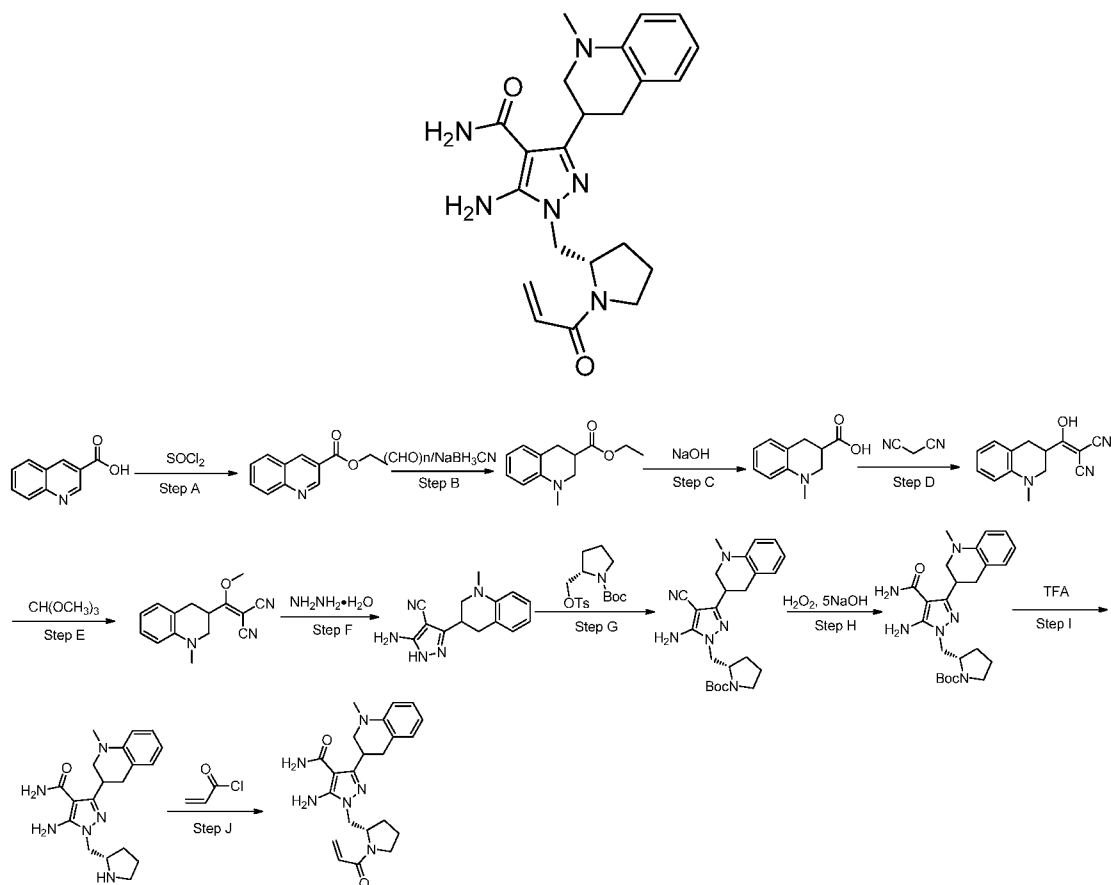


[0142] To the solution of the product of step H (230 mg, 0.274 mmol) in DCM (5 mL) was added TFA (1 mL). The solution was stirred at rt for 4 hrs. The resulting solution was concentrated to dryness and the residue was dissolved in CH₃CN (5 mL). After cooling to 0 °C, saturated

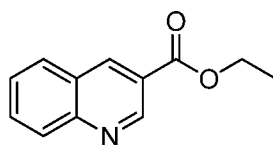
10 NaHCO₃ aqueous solution (2 mL) was added. Then a solution of acryloyl chloride (24 mg, 0.267 mmol) in CH₃CN (1 mL) was added drop wise. The final solution was stirred at 0 °C for 30 min and quenched by water, then extracted with EA (40 mL). The organic layer was washed by brine, dried over anhydrous sodium sulfate then concentrated and purified by *prep*-TLC (DCM:MeOH=20:1) to give the desired product (60 mg, 28%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.90 (t, *J* = 10.0 Hz, 1H), 6.84 – 6.68 (m, 3H), 6.66 – 6.54 (m, 1H), 6.37 (s, 2H), 6.20 (dd, *J* = 16.8, 2.4 Hz, 1H), 5.72 (dd, *J* = 10.4, 2.4 Hz, 1H), 5.36 – 5.28 (m, 1H), 4.40 – 4.20 (m, 1H), 4.09 – 3.85 (m, 2H), 3.65 – 3.38 (m, 4H), 2.87 (s, 3H), 2.00 – 1.70 (m, 4H), ppm. MS: M/e 447 (M+1)⁺

Compound 1.9: 1-(((S)-1-acryloylpyrrolidin-2-yl)methyl)-5-amino-3-(1-methyl-1,2,3,4-

20 -tetrahydroquinolin-3-yl)-1H-pyrazole-4-carboxamide



Step A: ethyl quinoline-3-carboxylate

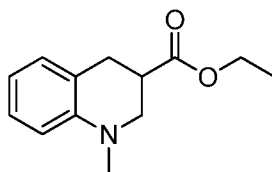


5

[0143] To a stirred solution of quinoline-3-carboxylic acid (20 g, 0.12 mol) in EtOH (500 mL) was added sulfurous dichloride (25.6 mL, 0.36 mol) at room temperature. The mixture was stirred at 80 °C for 4 hours. The reaction was concentrated under reduced pressure. The residue was dissolved into EA (500 mL). The organic phase was washed with saturated NaHCO₃ aqueous solution and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue (yellow solid, 22g, 96%) was used into next step directly. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.32 (s, 1H), 8.99 (s, 1H), 8.22 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.94 (t, *J* = 7.6 Hz, 1H), 7.74 (t, *J* = 7.6 Hz, 1H), 4.44 (q, *J* = 7.2 Hz, 2H), 1.41 (t, *J* = 7.2 Hz, 3H)ppm. MS: M/e 202 (M+1)⁺

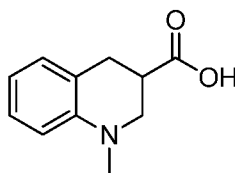
15

Step B: ethyl 1-methyl-1,2,3,4-tetrahydroquinoline-3-carboxylate



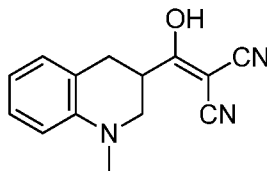
[0144] To a stirred solution of the product of Step A (10 g, 0.05 mol) and paraformaldehyde (14.9 g, 0.5 mol) in acetic acid (200 mL) was added Sodium cyanoborohydride (15.7 g, 0.25 mol) carefully at room temperature. The reaction was concentrated under reduced pressure. The residue was diluted with saturated NaHCO₃ aqueous solution and extracted with EA (100 mL x 2). The combined organic phase was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue (yellow solid, 7.5 g, 69%) was used into next step directly. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.00 (t, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 7.2 Hz, 1H), 6.62 – 6.52 (m, 2H), 4.09 (q, *J* = 7.2 Hz, 2H), 3.45 – 3.30 (m, 1H), 3.29 – 3.17 (m, 1H), 3.00 – 2.86 (m, 3H), 2.82 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H) ppm. MS: M/e 220 (M+1)⁺

Step C: 1-methyl-1,2,3,4-tetrahydroquinoline-3-carboxylic acid



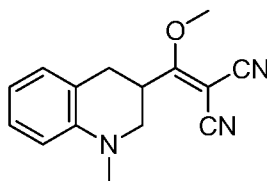
[0145] To a solution of the product of Step B (7.5 g, 0.03 mol) in MeOH (150 mL) was added 2N NaOH (50 mL) aqueous solution at room temperature. The solution was stirred at 60 °C for 2 hours. The reaction was concentrated under reduced pressure. The residue was diluted with water (100 mL). The resulting solution was neutralized by 2N HCl aqueous solution till pH = 6. The white solid was precipitated from the mixture. The mixture was filtered and the solid was dried in the infrared oven at 60 °C. The solid (4.8 g, 72.7%) was used into next step directly. MS: M/e 192 (M+1)⁺

Step D: 2-(hydroxy(1-methyl-1,2,3,4-tetrahydroquinolin-3-yl)methylene)malononitrile



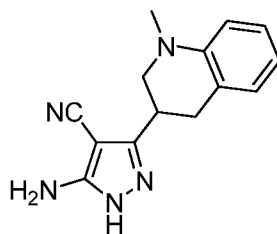
[0146] To a stirred solution of the product of Step C (4.8 g, 25 mmol) and HOBT (3.1 g, 30mmol) in DCM (40 mL) was added triethylamine (5.1 g, 50 mmol) at room temperature. The EDCI (5.8 g, 30 mmol) and malononitrile (1.7 g, 26 mmol) was added at room temperature. The mixture was stirred at room temperature for 2 hours. Water (40 mL) was added to quench the reaction. The mixture was extracted with DCM (40 mL x 2). The combined organic phase was washed with brine, dried over anhydrate sodium sulfate and concentrated under reduced pressure. The residue was diluted with HCl/EA (6 N). The mixture was stirred at room temperature for 0.5 hour. The mixture was concentrated under reduced pressure. The residue (crude product) was used into next step directly. MS: M/e 240 (M+1)⁺

Step E: 2-(methoxy(1-methyl-1,2,3,4-tetrahydroquinolin-3-yl)methylene)malononitrile



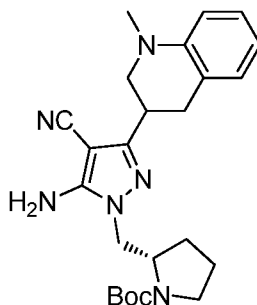
[0147] A solution of the product of step D (4.5 g, 18.8 mmol) in trimethoxymethane (100 mL) was stirred at 100 °C for 2 hours. The resulting solution was concentrated under reduced pressure. The residue was diluted with water (100 mL) and extracted with EA (100 mL x 2). The combined organic phase was washed by brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with EA (100%) to afford the desired product (280 mg, 5.9%) as a yellow solid. MS: M/e 254 (M+1)⁺

Step F: 5-amino-3-(1-methyl-1,2,3,4-tetrahydroquinolin-3-yl)-1H-pyrazole-4-carbo nitrile



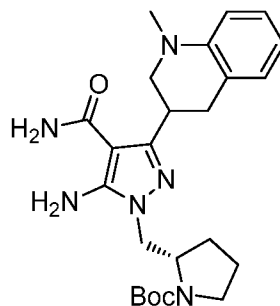
[0148] A solution of the product of step E (280 mg, 1.1 mmol) and hydrazine hydrate (1 mL) in EtOH (5 mL) was stirred at room temperature for 30 min. The resulting solution was concentrated under reduced pressure. The residue was diluted with water (10 mL) and extracted with EA (10 mL x 2). The combined organic phase was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with MeOH/DCM 1:20) to obtain the desired product (250 mg, 89.3%) as a yellow solid. MS: M/e 254 (M+1)⁺

Step G: (2S)-tert-butyl 2-((5-amino-4-cyano-3-(1-methyl-1,2,3,4-tetrahydroquinolin-3-yl)-1H-pyrazol-1-yl)methyl)pyrrolidine-1-carboxylate



[0149] A mixture of the product of step F (250 mg, 0.1 mmol), (S)-tert-butyl 2-((tosyloxy)methyl)pyrrolidine-1-carboxylate (**BL-2**, 421 mg, 0.12 mmol) and Cs₂CO₃ (644 mg, 0.2 mmol) in DMF (10 mL) was stirred at 70 °C overnight. The resulting solution was concentrated under reduced pressure. The residue was diluted with water (20 mL) and extracted with EA (20 mL x 2). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The yellow oil (200 mg, 45.9%) was used into next step directly. MS: M/e 437 (M+1)⁺

Step H: (2S)-tert-butyl 2-((5-amino-4-carbamoyl-3-(1-methyl-1,2,3,4-tetrahydroquinolin-3-yl)-1H-pyrazol-1-yl)methyl)pyrrolidine-1-carboxylate

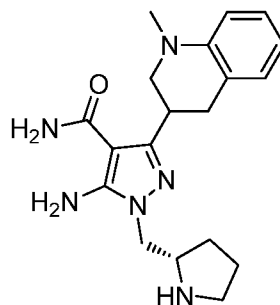


[0150] To a solution of the product of step G (200 mg, 0.46 mmol) in EtOH (3 mL) was added DMSO (0.5 mL), 5N NaOH aqueous solution (0.5 mL) followed by H₂O₂ (0.5 mL). The solution was stirred at 60 °C for 2 hours. The resulting solution was concentrated under reduced pressure.

5 The residue was diluted with water (5 mL) and extracted with EA (10 mL x 2). The combined organic phase was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with EA 100% to obtain the desired product (190 mg, 91%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.00 (t, *J* = 7.6 Hz, 1H), 6.92 (d, *J* = 7.2 Hz, 1H), 6.68 – 6.57 (m, 3H), 6.53 (t, *J* = 7.2
10 Hz, 1H), 6.02 (s, 2H), 3.98 – 3.88 (m, 2H), 3.66 – 3.52 (m, 1H), 3.42 – 3.35 (m, 1H), 3.25 – 3.10 (m, 3H), 2.91 (d, *J* = 8.1 Hz, 2H), 2.85 (s, 3H), 2.54 (s, 2H), 1.82 – 1.64 (m, 3H), 1.42 (s, 9H). MS: M/e 455 (M+1)⁺

Step I: 5-amino-3-(1-methyl-1,2,3,4-tetrahydroquinolin-3-yl)-1-((S)-pyrrolidin-2-yl

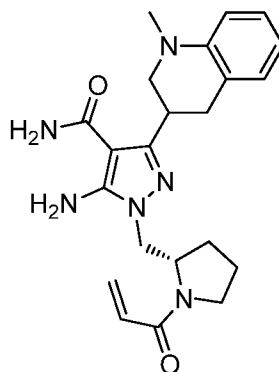
15 methyl)-1H-pyrazole-4-carboxamide



[0151] To the solution of the product of step H (190 mg, 0.42 mmol) in DCM (5 mL) was added TFA (0.5 mL). The solution was stirred at room temperature for 1 hour. The resulting solution was concentrated to get the crude product (146 mg, 100%) as yellow oil, which was used in next step

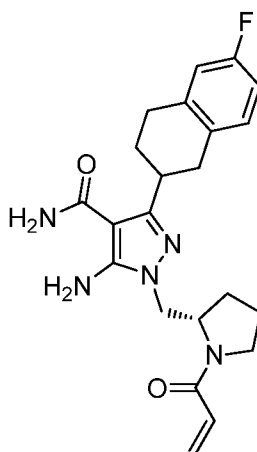
20 directly. MS: M/e 355 (M+1)⁺

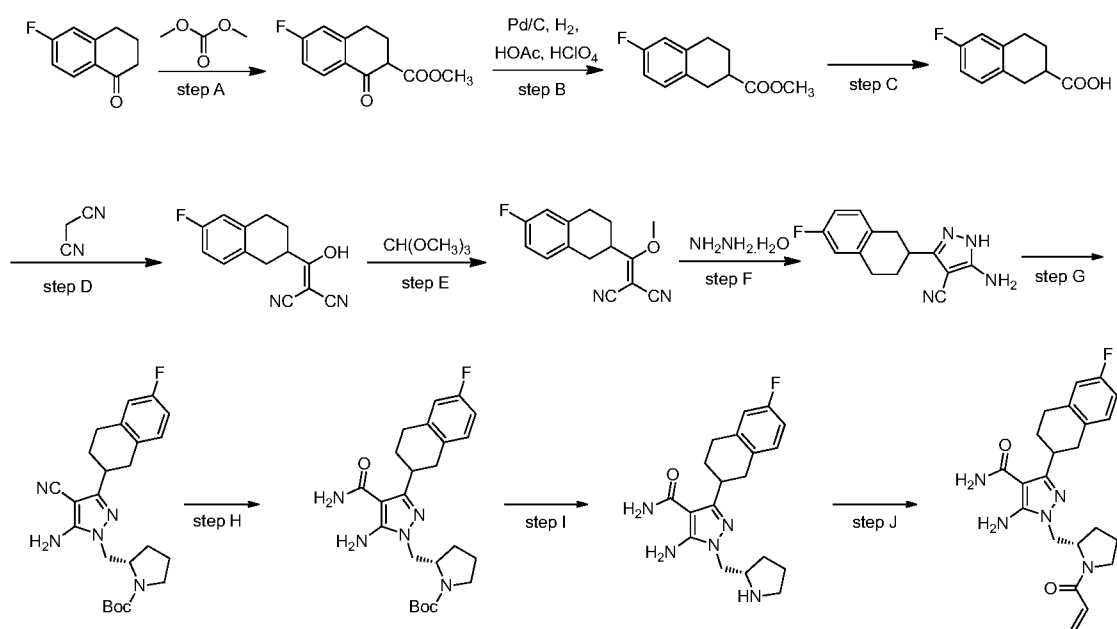
Step J: 1-(((S)-1-acryloylpyrrolidin-2-yl)methyl)-5-amino-3-(1-methyl-1,2,3,4-tetrahydroquinolin-3-yl)-1H-pyrazole-4-carboxamide



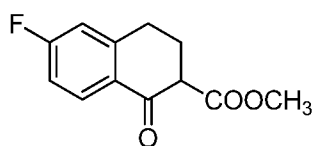
[0152] A mixture of the product of step I (146 mg, 0.42 mmol) and saturated NaHCO₃ aqueous solution (5 mL) in CH₃CN (5 mL) was stirred at 0 °C for 5 min. Acryloyl chloride (37 mg, 0.41 mmol) was added dropwise at 0 °C. The final solution was stirred at 0 °C for 5 min and quenched by water, then extracted with EA (10 mL x 2). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by *prep*-TLC to obtain the desired product (50 mg, 29%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.00 (t, *J* = 7.6 Hz, 1H), 6.96 – 6.90 (m, *J* = 7.2 Hz, 1H), 6.70 – 6.48 (m, 5H), 6.26 – 6.16 (m, 1H), 6.15 – 5.98 (m, 2H), 5.76 – 5.44 (m, 1H), 4.43 – 4.14 (m, 1H), 4.07 – 3.87 (m, 2H), 3.64 – 3.36 (m, 4H), 3.24 – 3.10 (m, 1H), 2.95 – 2.87 (m, 2H), 2.85 (t, *J* = 3.2 Hz, 3H), 1.95 – 1.68 (m, 4H). MS: M/e 409 (M+1)⁺

Compound 1.10: 1-(((S)-1-acryloylpyrrolidin-2-yl)methyl)-5-amino-3-(6-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



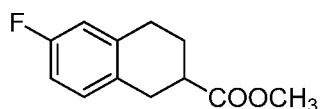


Step A: methyl 6-fluoro-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate



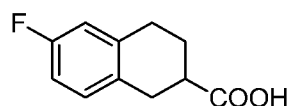
- 5 **[0153]** To a solution of NaH (2.7 g, 67 mmol) in dimethyl carbonate (25mL) was added the solution of 6-fluoro-3,4-dihydronaphthalen-1(2H)-one (5 g, 30.45 mmol) in dimethyl carbonate (25 mL). The mixture was stirred at rt for 30 min then at 90 °C for 1 h. The reaction mixture was turned from the suspension to the solid state. The reaction was quenched by ice water (100 mL), extracted with EA (100 mL x 3). The combined organic layer was washed by brine (100 mL), dried over anhydrous sodium sulfate then concentrated to get the crude product (6.8g, 100%) as yellow oil, which was used in next step directly. ¹H NMR (400 MHz, CDCl₃) δ 8.15 – 7.70 (m, 1H), 7.10 – 6.77 (m, 2H), 3.76(s, 3H), 3.59 (dd, *J* = 10.0, 4.8 Hz, 1H), 3.11 – 2.90 (m, 1H), 2.78 (t, *J* = 7.8 Hz, 1H), 2.78 – 2.52 (m, 1H), 2.52 – 2.30 (m, 1H). MS: M/e 223 (M+1)⁺

- 15 **Step B:** methyl 6-fluoro-1,2,3,4-tetrahydronaphthalene-2-carboxylate



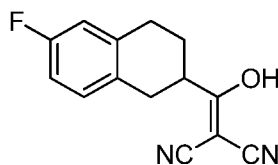
[0154] A mixture of the product of Step A (6.8g, 30.5 mmol), HClO₄ (0.5 mL) and Pd/C (1.0 g) in HOAc (30 mL) was stirred at rt under hydrogen atmosphere for 24 hrs. The mixture suspension was filtered through a celite pad. The filtrate was concentrated. The residue was diluted with EA (150 mL), washed by brine (50 mL), dried over anhydrous sodium sulfate and then concentrated to get the crude product (6.2 g, 100%) as yellow oil, which was used in next step directly. MS: M/e 209 (M+1)⁺

Step C: 6-fluoro-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid



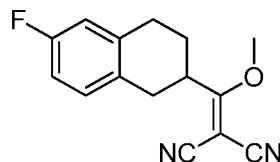
[0155] A solution of the product of Step B (6.5 g, 30.5 mmol) and NaOH (4.9 g, 122 mmol) in MeOH (20 mL) and H₂O was stirred at rt for 1 h. The mixture was concentrated. The residue was diluted with H₂O (20 mL) and adjusted to pH=5-6 by 2N HCl. The precipitate was collected and filtered to get the desired product (6.0 g, 100%) as a white solid, which was used in next step directly. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.19 – 7.04 (m, 1H), 6.97 – 6.80 (m, 2H), 2.96 – 2.64 (m, 4H), 2.60 – 2.51 (m, 1H), 2.09 – 1.98 (m, 1H), 1.74 – 1.56 (m, 1H). MS: M/e 195 (M+1)⁺

Step D: 2-((6-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)(hydroxy)methylene)malononitrile



[0156] To a solution of the product of Step C (3.9 g, 20 mmol) in DCM (20 mL) was added oxalyl dichloride (4 mL), followed by 2 drops of DMF at 0 °C. The solution was stirred at rt for 2h, and then concentrated. The residue was diluted in THF (20 mL). The malononitrile (2.0 g, 30 mmol) was added. Cooled to 0 °C, TEA (6 mL, 40 mmol) was added drop wise. The final solution was stirred at 0 °C for 1 h. The resulting solution was washed by water (30 mL), extracted with EA (50mL x 3). The organic layer was washed by 6N HCl aqueous solution (50mL x 2) and brine (50mL), dried over anhydrous sodium sulfate and concentrated to get crude product (5.0 g) as yellow oil, which was used in next step directly. MS: M/e 243 (M+1)⁺

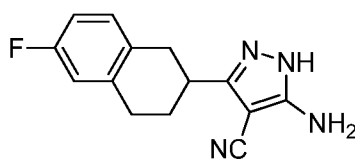
Step E: 2-((6-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)(methoxy)methylene)malononitrile



[0157] A solution of the product of step D (5 g, 20.60 mmol) in trimethoxymethane (15 mL)

5 was stirred at 70 °C for 5 hrs. The resulting solution was concentrated. The residue was diluted with EA (100 mL), washed by brine (50 mL), dried over anhydrous sodium sulfate then concentrated and purified by silica gel column chromatography eluting with PE:EA=5:1 to get the desired product (2.2 g, 43 % for 2 steps) as a yellow oil. MS: M/e 257 (M+1)⁺

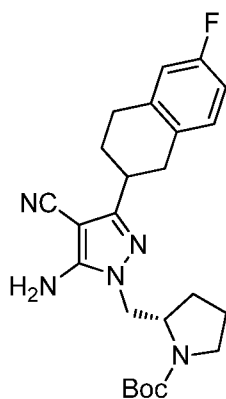
10 Step F: 5-amino-3-(6-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carbonitrile



[0158] A solution of the product of step E (2.2 g, 8.6 mmol) and hydrazine hydrate (2 mL) in EtOH (10 mL) was stirred at rt for 10 min. The resulting solution was concentrated. The residue

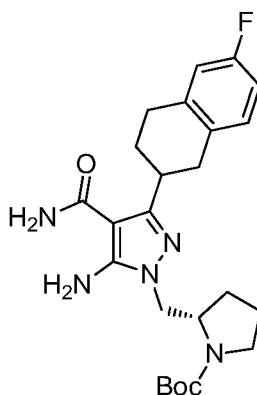
15 then concentrated to get crude product (2.0 g, 91%) as a yellow solid, which was used in next step directly. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.66 (s, 1H), 7.19 – 7.05 (m, 1H), 7.03 – 6.80 (m, 2H), 6.27 (s, 2H), 3.10 – 2.61 (m, 5H), 2.16 – 2.02 (m, 1H), 1.93 – 1.76 (m, 1H). MS: M/e 257 (M+1)⁺

20 Step G: (2S)-tert-butyl 2-((5-amino-4-cyano-3-(6-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazol-1-yl)methyl)pyrrolidine-1-carboxylate



[0159] A mixture of the product of step **F** (1.0 g, 3.9 mmol), (R)-tert-butyl 2-(tosyloxy)pyrrolidine-1-carboxylate (BL-2, 1.5 g, 4.2 mmol) and Cs₂CO₃ (2.5 g, 7.6 mmol) in DMF (10 mL) was stirred at 70 °C for 5 hrs. The mixture was diluted with EA(50 mL), washed with brine (20mL x 3), dried, concentrated and purified by column chromatography eluting with CH₂Cl₂/MeOH (100:1 ~ 40:1) to afford the desired product (1.02 g, 58%) as yellow oil. MS: M/e 440 (M+1)⁺.

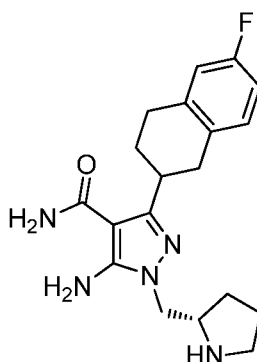
Step **H**: (2S)-tert-butyl 2-((5-amino-4-carbamoyl-3-(6-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazol-1-yl)methyl)pyrrolidine-1-carboxylate



[0160] To a solution of the product of step **G** (1.02 g, 2.3 mmol) in EtOH (20 mL) and DMSO (1 mL) was added 5N NaOH aqueous solution (1 mL), followed by H₂O₂ (1 mL) at rt. The mixture was stirred at 50 °C for 30 min. After removing EtOH, the residue was diluted with EA (500 mL), washed with NaHSO₃ (10 mL) and brine (20 mL x 3), dried over anhydrous sodium sulfate, concentrated and purified by silica gel column chromatography eluting with CH₂Cl₂/MeOH (100:1 ~ 40:1) to get the desired product (950 mg, 90%) as brown oil.

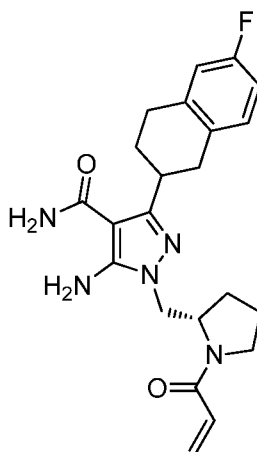
[0161] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.17 – 7.06 (m, 1H), 6.98 – 6.86 (m, 2H), 6.59 (s, 2H), 6.05 (br.s, 2H), 4.07 – 3.86 (m, 3H), 3.51 – 3.31 (m, 2H), 3.27 – 3.13 (m, 2H), 2.98 – 2.75 (m, 4H), 2.17 – 2.04 (m, 1H), 1.88 – 1.55 (m, 5H), 1.41 (s, 9H). MS: M/e 458 (M+1)⁺.

5 **Step I:** 5-amino-3-(6-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-1-((S)-pyrrolidin-2-ylmethyl)-1H-pyrazole-4-carboxamide



[0162] To the solution of the product of step H (950 mg, 2.08 mmol) in DCM (20 mL) was added TFA (5 mL) at r^t and the solution was stirred for 16 hrs. The mixture was concentrated to get
10 the crude product (880 mg) as brown oil, which was used in next step directly. MS: M/e 358 (M+1)⁺.

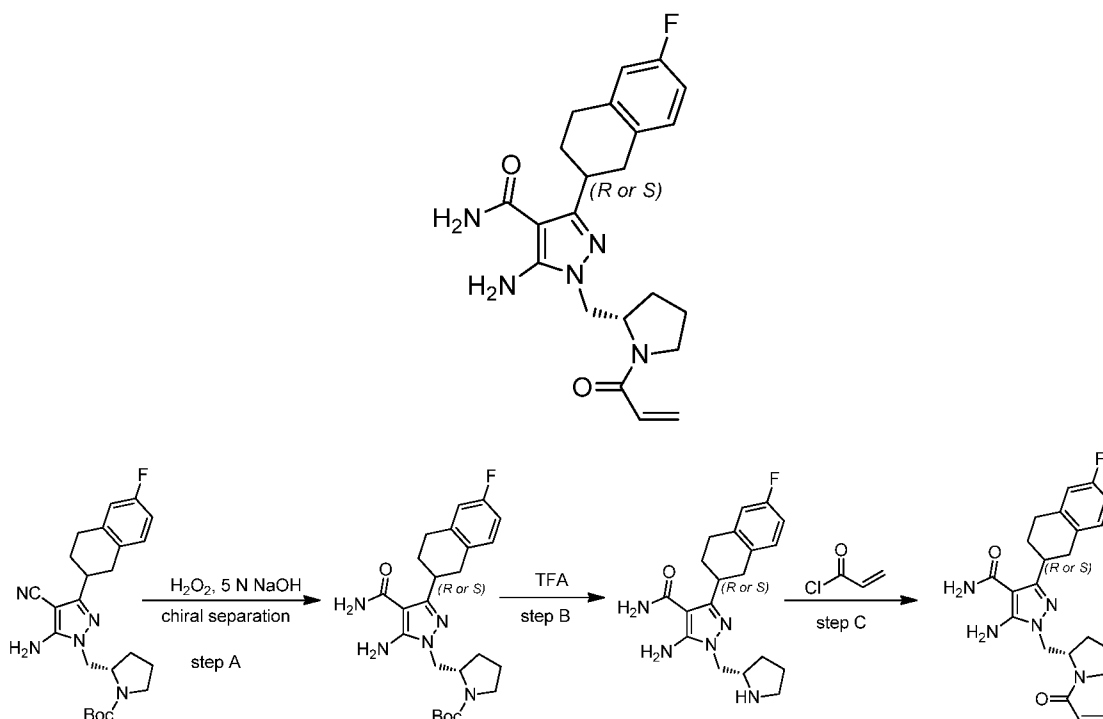
Step J: 1-(((S)-1-acryloylpyrrolidin-2-yl)methyl)-5-amino-3-(6-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



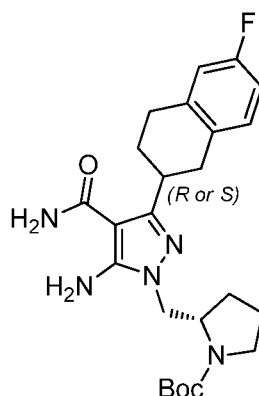
15 **[0163]** To a mixture of the product of step I (880 mg, crude) and NaHCO_3 (400 mg, 4.76 mmol) in MeCN/ H_2O (10 mL/10 mL) was added dropwise a solution of acryloyl chloride (160 mg, 1.78

mmol) in MeCN(1 mL) at rt and the mixture was stirred for 1 h. The resulting mixture was extracted with EA (10 mL x 3). The combined extracts were washed with brine (20 mL x 2), dried over anhydrous sodium sulfate, concentrated and purified by silica gel column chromatography eluting with EA to give crude product (560 mg), which was recrystallized in PE/EA (2:1, 40 mL) to give the desired product (425 mg, 50% for 2 steps) as a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆, 80 °C) δ 7.13 – 7.04 (m, 1H), 6.91 – 6.80 (m, 2H), 6.54 (br.s, 1H), 6.36 (s, 2H), 6.16 (d, *J* = 16.4 Hz, 1H), 5.99 (s, 2H), 5.75 – 5.35 (m, 1H), 4.45 – 4.12 (m, 1H), 4.11 – 3.81 (m, 2H), 3.47 (br.s, 2H), 3.39 – 3.26 (m, 1H), 3.01 – 2.75 (m, 4H), 2.18 – 2.03 (m, 1H), 1.91 – 1.65 (m, 5H). MS: *M/e* 412 (*M*+1)⁺.

Compound 1.10a or 1.10b: (*R* or *S*) 1-(((*S*)-1-acryloylpyrrolidin-2-yl)methyl)-5-amino-3-(6-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



Step A: (*R* or *S*) (2*S*)-tert-butyl 2-(((5-amino-4-carbamoyl-3-(6-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazol-1-yl)methyl)pyrrolidine-1-carboxylate



[0164] To a stirred solution of the product of step G in synthesis of **Compound 1.10** (20 g, 46 mmol) in EtOH (200 mL) was added DMSO (20 mL), and aq.NaOH (5.0 N, 20 mL), followed by H₂O₂ (20 mL) at rt. After the addition, the reaction was stirred at 50°C for 30 min. The reaction mixture was concentrated to give the residue, which was diluted with EtOAc (500 mL), washed with brine (200 mL x 3), dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography (petroleum ether/EtOAc=2:1) to give desired product (13 g, 62%) as a yellow solid, which was separated by chiral HPLC to give peak 1 (5.20 g) and peak 2 (6.35 g).

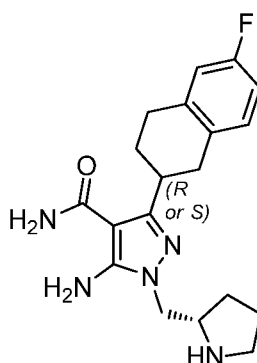
Peak 1: ¹H NMR (400 MHz, DMSO-*d*₆) 7.10 (s, 1H), 6.97 – 6.85 (m, 2H), 6.59 (s, 2H), 6.04 (s, 2H), 4.10-3.80 (m, 3H), 3.40 – 3.34 (m, 1H), 3.23 – 3.12 (m, 2H), 3.02 – 2.75 (m, 4H), 2.10 (d, *J* = 12.0 Hz, 1H), 1.81 – 1.55 (m, 5H), 1.40 (s, 9H) ppm. **Peak 2:** ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.17 – 7.05 (m, 1H), 6.98 – 6.85 (m, 2H), 6.59 (s, 2H), 6.06 (s, 2H), 4.09 – 3.78 (m, 3H), 3.40 – 3.35 (m, 1H), 3.23 – 3.11 (m, 2H), 3.0 – 2.78 (m, 4H), 2.11 (d, *J* = 10.6 Hz, 1H), 1.81 – 1.54 (m, 5H), 1.41 (s, 9H) ppm. MS: *M/e* 458 (*M*+1)⁺

[0165] The chiral separation conditions are shown below:

Column	CHIRALPAK IC
Column size	0.46 cm I.D. × 15 cm L
Injection	5ul
Mobile phase	EtOH
Flow rate	1.0 ml/min
Wave length	UV 214nm

Temperatu	35 °C
re	

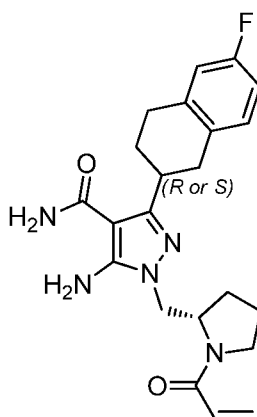
Step B: (**R or S**) 5-amino-1-((S)-pyrrolidin-2-ylmethyl)-3-(6-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



- 5 **[0166]** To the solution of the product of Step A (1.0 mg, 2.2 mmol) in DCM (10 mL) was added TFA (5 mL) at 0°C and the solution was stirred at rt for 2 hrs. The mixture was concentrated to get the crude product (1 g) as brown oil, which was used in next step directly. MS: M/e 358 (M+1)⁺

Step C: (**R or S**) 1-(((S)-1-acryloylpyrrolidin-2-yl)methyl)-5-amino-3-(6-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide

10



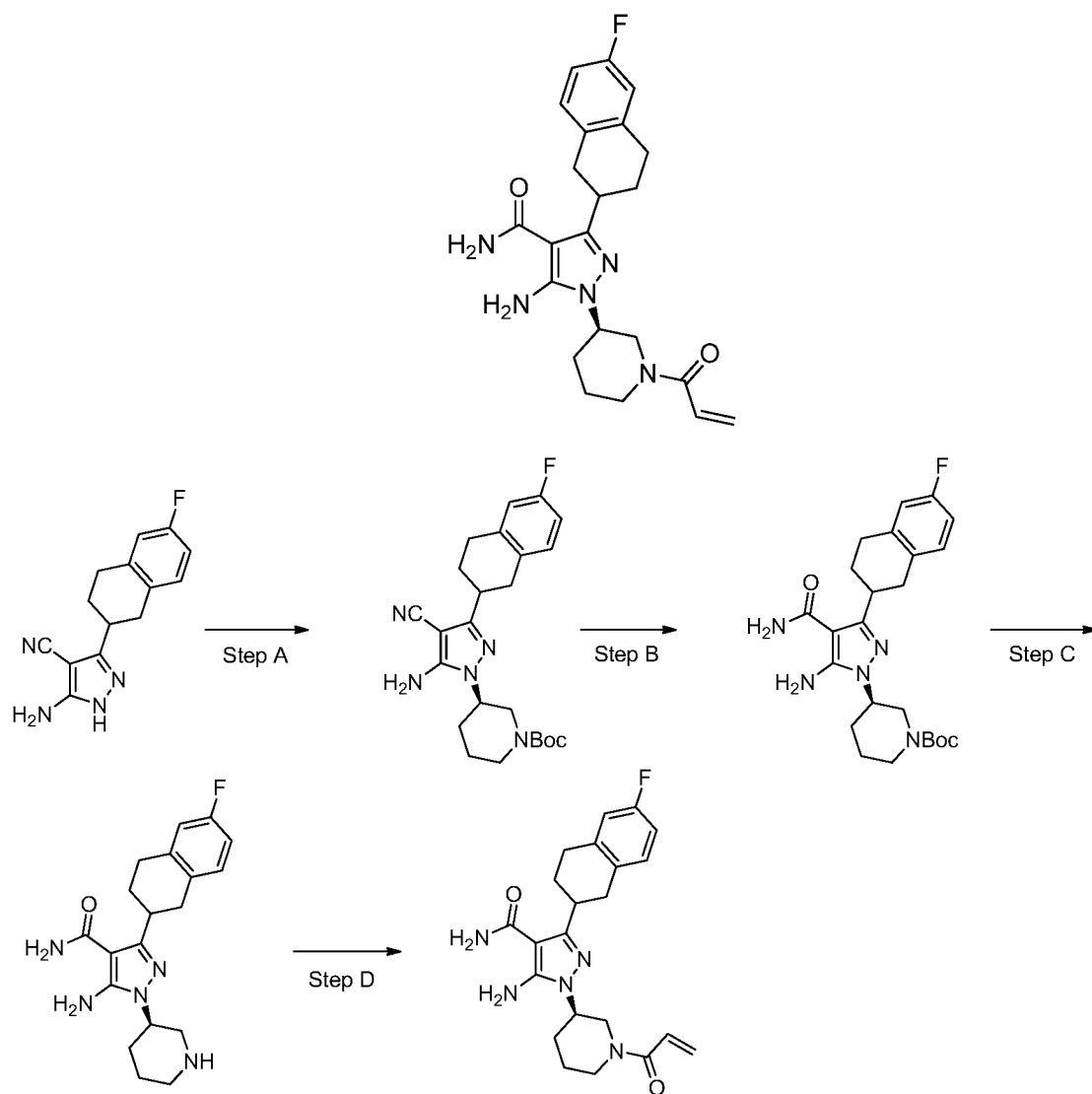
- [0167]** To a mixture of the product of Step B (1 g, crude, 2.2 mmol) and NaHCO₃ (739 mg, 8.8 mmol) in MeCN/H₂O (25 mL/25 mL) was added dropwise a solution of acryloyl chloride (200 mg, 2.2 mmol) in MeCN (2 mL) at 0°C and the mixture was stirred at 0°C for 10 min. The resulting mixture was extracted with EA (100 mL), washed with brine (30 mL x 2), dried over anhydrous sodium sulfate, concentrated and purified by silica gel column chromatography eluting with
- 15

DCM/MeOH (30:1) to give the desired product (650 mg, 79% for 2 steps) as a white solid. Peak 1 (**Compound 1.10a**, retention time: 5.219 min): ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.19 – 7.08 (m, $J = 8.9$ Hz, 1H), 6.99 – 6.85 (m, $J = 8.0$ Hz, 2H), 6.72 – 6.52 (m, 2H), 6.28 – 5.98 (m, 3H), 5.78 – 5.42 (m, 1H), 4.41 – 4.13 (m, 1H), 4.07 – 3.84 (m, 2H), 3.60 – 3.35 (m, 3H), 3.06 – 2.74 (m, 4H), 2.13 – 2.04 (m, 1H), 1.96 – 1.62 (m, 5H) ppm. Peak 2 (**Compound 1.10b**, retention time: 6.182 min): ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.19 – 7.06 (m, 1H), 6.98 – 6.85 (m, 2H), 6.68 – 6.47 (m, 2H), 6.30 – 6.00 (m, 3H), 5.79 – 5.44 (m, 1H), 4.42 – 4.15 (m, 1H), 4.09 – 3.82 (m, 2H), 3.59 – 3.36 (m, 3H), 3.02 – 2.75 (m, 4H), 2.11 (d, $J = 11.2$ Hz, 1H), 1.93 – 1.62 (m, 5H) ppm. MS: M/e 412 ($M+1$)⁺

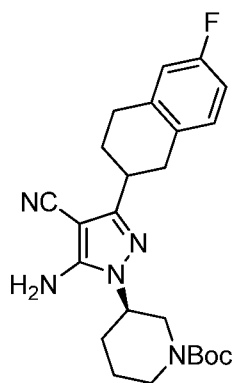
10 **[0168]** The chiral analysis conditions are shown below:

Column	CHIRALPAK AD-H
Column size	0.46 cm I.D.× 15 cm L, 5 μm
Injection	2 μl
Mobile phase	n-Hexane/EtOH (0.1% triethyl amine)=50/50 (v/v)
Flow rate	1.0 ml/min
Wave length	UV 254nm
Temperature	35 $^{\circ}\text{C}$

Compound 1.11: 1-((R)-1-acryloylpiperidin-3-yl)-5-amino-3-(6-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



Step A: (3R)-tert-butyl 3-(5-amino-4-cyano-3-(6-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate



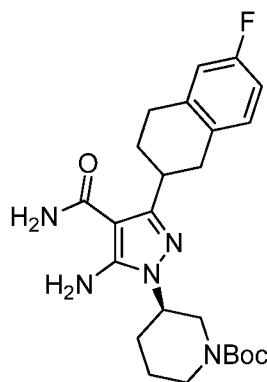
5

[0169] A mixture of 5-amino-3-(7-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carbonitrile (the product of step F in synthesis of **Compound 1.10**, 1.0 g, 4 mmol), (S)-tert-butyl 3-(tosyloxy)piperidine-1-carboxylate (**BL-1**, 2.1 g, 6 mmol) and Cs_2CO_3 (2.6 g, 8

mmol) in DMF (20 mL) was stirred at 70 °C for 24 hrs. The resulting solution was concentrated. The residue was diluted with EA (100 mL), washed by brine (50 mL x 2), dried over sodium sulfate, concentrated and purified by silica gel column chromatography eluting with PE:EA=4:1 to afford the crude product (700 mg) which was directly used in the next step. MS: M/e 440 ($M+1$)⁺

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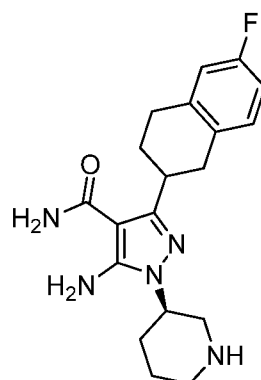
Step B: (3R)-tert-butyl 3-(5-amino-4-carbamoyl-3-(6-fluoro-1,2,3,4-tetrahydro naphthalen-2-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate



[0170] To a solution of the product of Step A (700 mg, crude, 1.6 mmol) in EtOH (10 mL) and DMSO (2 mL) was added 6N NaOH aqueous solution (2 mL), followed by H₂O₂ (2 mL) at rt. The mixture was stirred at 50 °C for 30 min. Removing EtOH, the residue was diluted with EA (100 mL), washed with brine (50 mL x 2), dried over anhydrous sodium sulfate, concentrated and purified by silica gel column chromatography eluting with PE:EA 1: 2 get the crude product (130 mg, 8% for 2 steps) as a yellow solid.

15

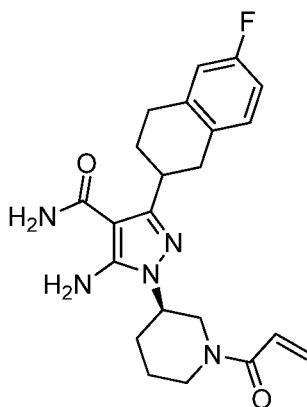
Step C: 5-amino-3-(6-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-1-((R)-piperidin-3-yl)-1H-pyrazole-4-carboxamide



[0171] To the solution of the product of Step B (130 mg, 0.3 mmol) in DCM (5 mL) was added TFA (2 mL) at 0 °C. The solution was stirred at 0 °C for 0.5 hrs. The resulting solution was concentrated to get the crude product (150 mg, 100%) as yellow oil, which was used in next step directly. MS: M/e 358 (M+1)⁺

5

Step D: 1-((R)-1-acryloylpiperidin-3-yl)-5-amino-3-(6-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



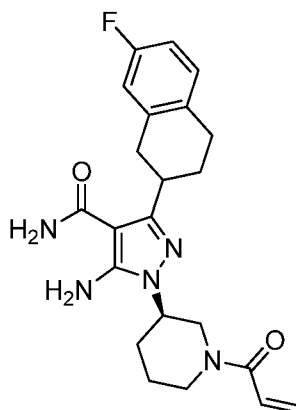
[0172] To a mixture of the product of step I (150 mg, 0.28 mmol) and NaHCO₃ (94 mg, 1.4 mmol) in CH₃CN/H₂O (10 mL/10mL) was added acryloyl chloride (25 mg, 0.28mmol) dropwise at 0 °C. The mixture was stirred at 0 °C for 10 min. The resulting mixture was diluted with EA (80 mL), washed with brine (30 mL), dried over anhydrous sodium sulfate, concentrated and purified by *prep*-TLC DCM:MeOH=12:1 to get the desired product (40 mg, 35%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.18 – 7.06 (m, 1H), 6.98 – 6.72 (m, 3H), 6.59 (s, 2H), 6.34 – 6.16 (m, 2H), 6.16 – 6.01 (m, 1H), 5.76 – 5.59 (m, 1H), 4.45 – 3.94 (m, 3H), 3.50 – 3.30 (m, 2H), 3.15 – 2.76 (m, 5H), 2.18 – 2.04 (m, 1H), 1.99 – 1.76 (m, 3H), 1.75 – 1.59 (m, 1H), 1.55 – 1.39 (m, 1H). MS: M/e 412 (M+1)⁺

15

[0173] **Compounds 1.12 and 1.13** were prepared according to the procedures described for **Compound 1.11** under appropriate conditions that could be recognized by one skilled in the art.

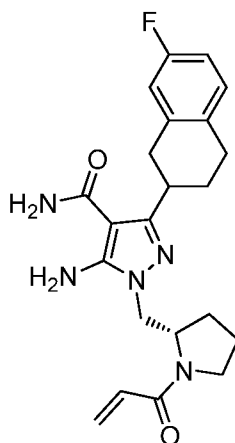
20

Compound 1.12: 1-((R)-1-acryloylpiperidin-3-yl)-5-amino-3-(7-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



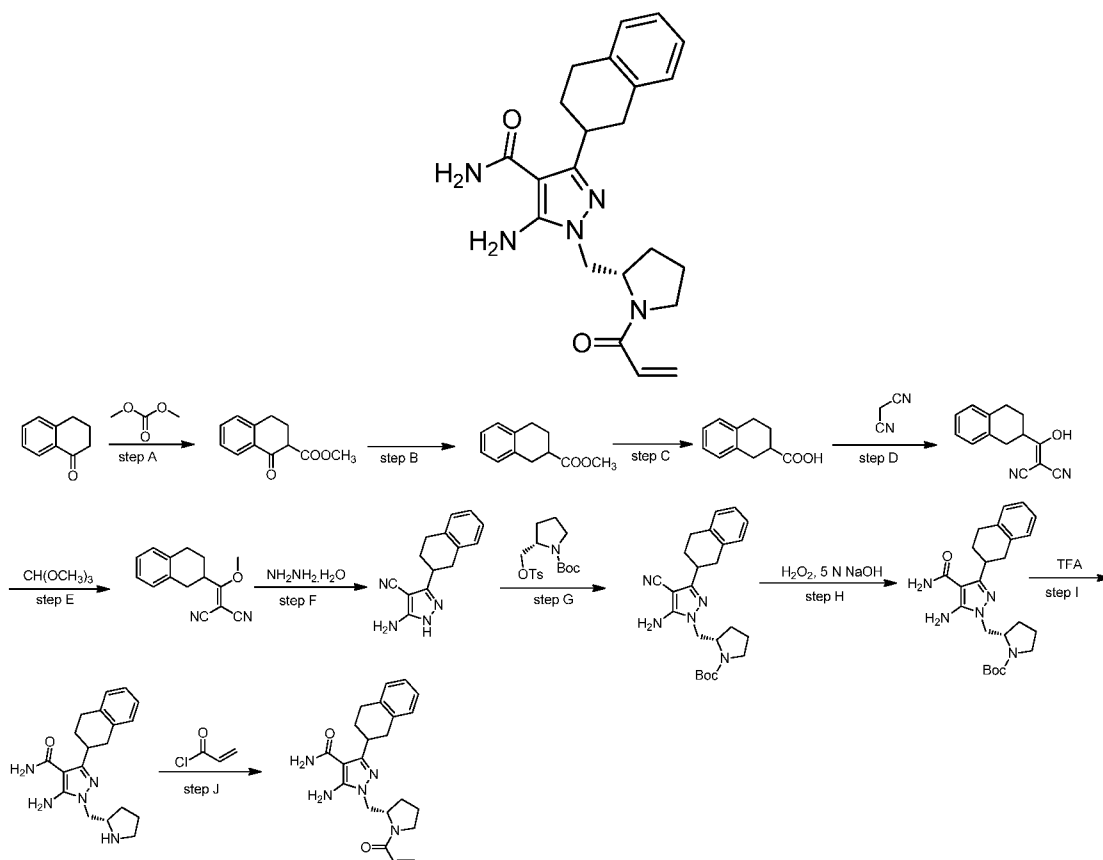
[0174] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.14 – 7.02 (m, 1H), 6.92 – 6.81 (m, $J = 8.4$ Hz, 2H), 6.77 – 6.64 (m, 1H), 6.45 – 6.29 (m, 2H), 6.15 – 5.96 (m, 3H), 5.68 – 5.59 (m, 1H), 4.22 – 3.93 (m, 3H), 3.40 – 3.25 (m, 2H), 3.01 – 2.91 (m, 3H), 2.86 – 2.76 (m, 2H), 2.17 – 2.05 (m, 1H), 1.98 – 1.77 (m, 3H), 1.78 – 1.66 (m, 1H), 1.56 – 1.38 (m, 1H). MS: M/e 412 ($M+1$)⁺

Compound 1.13: 1-(((S)-1-acryloylpyrrolidin-2-yl)methyl)-5-amino-3-(7-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide

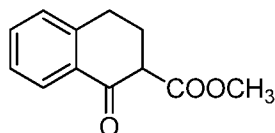


[0175] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.12 – 7.05 (m, 1H), 6.92 – 6.80 (m, 2H), 6.61 – 6.46 (m, 1H), 6.43 – 6.26 (m, 2H), 6.21 – 5.90 (m, 3H), 5.74 – 5.43 (m, 1H), 4.41 – 4.16 (m, 1H), 4.11 – 3.84 (m, 2H), 3.54 – 3.30 (m, 3H), 3.00 – 2.94 (m, 2H), 2.85 – 2.77 (m, 2H), 2.18 – 2.05 (m, 1H), 1.90 – 1.70 (m, 5H). MS: M/e 412 ($M+1$)⁺

Compound 1.14: 1-(((S)-1-acryloylpyrrolidin-2-yl)methyl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



Step A: methyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate

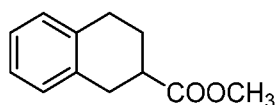


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[0176] To a solution of NaH (6.0 g, 150.68 mmol) in dimethyl carbonate (50 mL) was added the solution of 3,4-dihydronaphthalen-1(2H)-one (10 g, 68.50 mmol) in dimethyl carbonate (25 mL). The mixture was stirred at rt for 30 min then at 85 °C for 2 h. The reaction mixture was turned from the suspension to solid state. The reaction was quenched by water (100 mL), extracted with EA (100 mL x 2). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated to get the crude product (13.23g, 95%) as yellow oil, which was used in next step directly. MS: M/e 205 (M+1)⁺

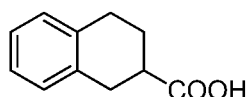
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Step B: methyl 1,2,3,4-tetrahydronaphthalene-2-carboxylate



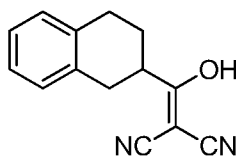
[0177] A mixture of the product of Step A (13.23 g, 64.78 mmol), HClO₄ (1 mL) and Pd/C (1.3 g, 0.1 eq) in HOAc (50 mL) was stirred at rt under 4 atm hydrogen atmosphere for 24 hrs. The mixture suspension was filtered through a celite pad. The filtrate was concentrated. The residue was washed by water, extracted with EA (50 mL x 3). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated to get the crude product (10 g, 81%) as yellow oil, which was used in next step directly. MS: M/e 191 (M+1)⁺

Step C: 1,2,3,4-tetrahydronaphthalene-2-carboxylic acid



[0178] To a solution of the product of Step B (10 g, 52.57 mmol) in MeOH (50 mL) was added 6N NaOH (10.51 g, 262.83 mmol) aqueous solution at 0 °C. The solution was stirred at rt for 2 h. The resulting solution was neutralized by 2N HCl aqueous solution till pH = 6. The white solid was formed and filtered to get the desired product (8.3 g, 90%) as a white solid, which was used in next step directly. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.13 – 7.01 (m, 4H), 2.98 – 2.82 (m, 2H), 2.81 – 2.73 (m, 2H), 2.70 – 2.59 (m, 1H), 2.13 – 2.03 (m, 1H), 1.79 – 1.67 (m, 1H) ppm. MS: M/e 177 (M+1)⁺

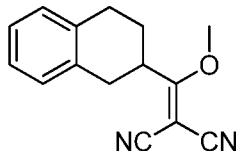
Step D: 2-(hydroxy(1,2,3,4-tetrahydronaphthalen-2-yl)methylene)malononitrile



[0179] To a solution of the product of Step C (18 g, 102.15 mmol) in DCM (40 mL) was added oxalyl dichloride (18 mL) followed by 5 drops DMF at 0 °C. The solution was stirred at rt for 30 min, then concentrated. The residue was diluted in THF (50 mL). The malononitrile (10.11 g, 153.22 mmol) was added. Cooled to 0 °C, the solution was added TEA (29 mL, 204.30 mmol) drop wise. The final solution was stirred at 0 °C for 1 h. The resulting solution was washed by water,

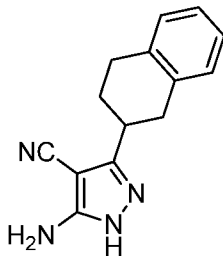
extracted with EA (50 mL x 3). The organic layer was washed by 6N HCl aqueous solution. The organic layer was separated and concentrated to get crude product (22.80 g, 100%) as black oil, which was used in next step directly. MS: M/e 225 (M+1)⁺

5 Step E: 2-(methoxy(1,2,3,4-tetrahydronaphthalen-2-yl)methylene)malononitrile



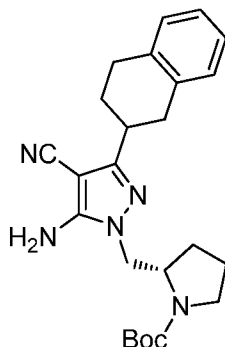
[0180] A solution of the product of step D (22.8 g, 101.66 mmol) in trimethoxymethane (40 mL) was stirred at 70 °C for 4-5 hrs. The resulting solution was concentrated. The residue was washed by water, extracted with EA (50 mL x 3). The combined organic layer was washed by
10 brine, dried over sodium sulfate anhydrous then concentrated and purified by silica gel column chromatography eluting with PE:EA=10:1 to get the desired product (16 g, 66%) as a yellow solid. MS: M/e 239 (M+1)⁺

Step F: 5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carbonitrile



15 [0181] A solution of the product of step E (13 g, 54.56 mmol) and hydrazine hydrate (2 mL) in EtOH (10 mL) was stirred at rt for 30 min. The resulting solution was concentrated. The residue was washed by water, extracted with EA (20 mL x 3). The combined organic layer was washed by
20 brine, dried over sodium sulfate anhydrous then concentrated and purified by silica gel column chromatography eluting with PE:EA=1:1 to get the desired product (7 g, 54%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.64 (br.s, 1H), 7.09-7.02 (m, 4H), 6.27 (br.s, 2H), 3.03 – 2.90 (m, 3H), 2.88 – 2.79 (m, 2H), 2.15 – 2.04 (m, 1H), 1.86 (s, 1H) ppm. MS: M/e 239 (M+1)⁺

Step **G**: (2S)-tert-butyl 2-((5-amino-4-cyano-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazol-1-yl)methyl)pyrrolidine-1-carboxylate

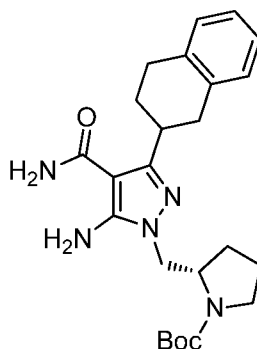


[0182] A mixture of the product of step F (200 mg, 0.84 mmol), (S)-tert-butyl

5 2-((tosyloxy)methyl)pyrrolidine-1-carboxylate (**BL-2**, 328 mg, 0.92 mmol) and Cs_2CO_3 (548 mg, 1.68 mmol) in DMF (15 mL) was stirred at 70 °C for 2 h. The resulting solution was concentrated. The residue was washed by water, extracted with EA (10 mL x 3). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated to get the crude product (354 mg, 100%) as yellow oil, which was used in next step directly. MS: M/e 422 ($M+1$)⁺

10

Step **H**: (2S)-tert-butyl 2-((5-amino-4-carbamoyl-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazol-1-yl)methyl)pyrrolidine-1-carboxylate

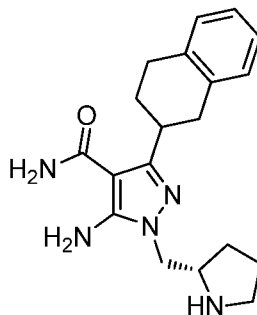


[0183] To a solution of the product of step G (354 mg, 0.84 mmol) in EtOH (5 mL) was added
15 DMSO (2 mL), 5N NaOH aqueous solution (2 mL) followed by H_2O_2 (1 mL). The solution was stirred at 60 °C for 2 h. The resulting solution was concentrated. The residue was washed by water, extracted with EA (10 mL x 3). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated and purified by silica gel column chromatography

eluting with PE:EA=1:1 to get the desired product (254 mg, 69%) as a yellow solid. MS: M/e 440 (M+1)⁺

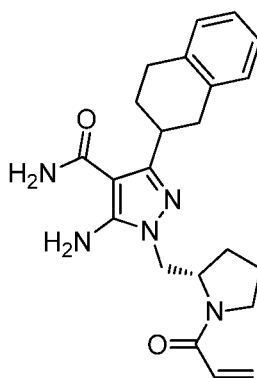
Step I: 5-amino-1-((S)-pyrrolidin-2-ylmethyl)-3-(1,2,3,4-tetrahydronaphthalen-2-yl)

5 -1H-pyrazole-4-carboxamide



[0184] To the solution of the product of step H (254 mg, 0.58 mmol) in DCM (2 mL) was added TFA (1 mL). The solution was stirred at rt for 1 h. The resulting solution was concentrated to get the crude product (196 mg, 100%) as yellow oil, which was used in next step directly. MS: M/e 340 (M+1)⁺

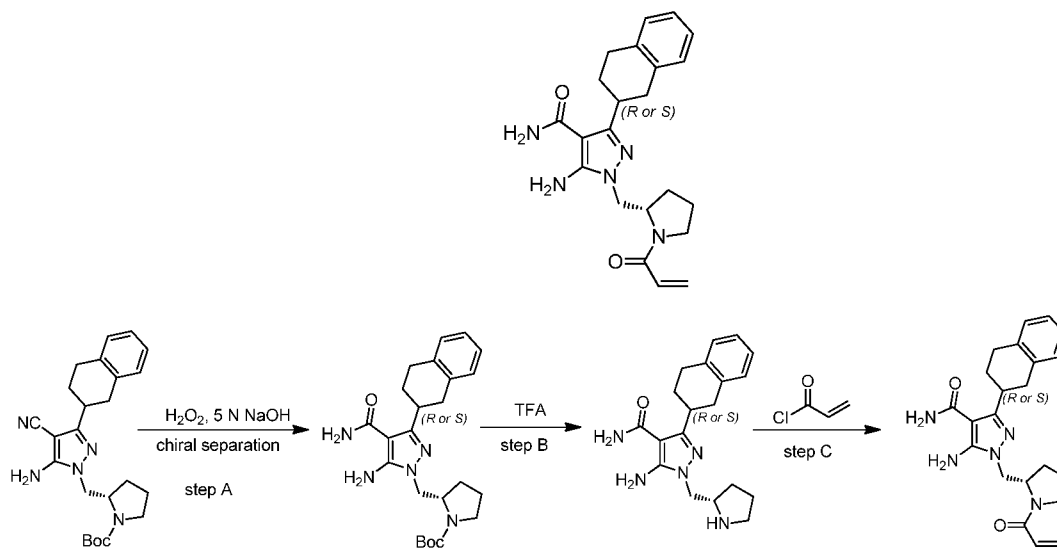
Step J: 1-(((S)-1-acryloylpyrrolidin-2-yl)methyl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



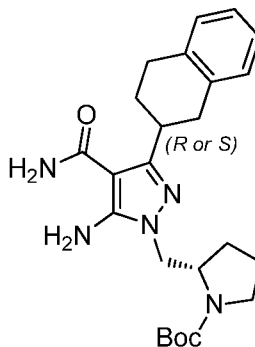
15 [0185] A mixture of the product of step I (196 mg, 0.58 mmol) and NaHCO₃ (291 mg, 3.47 mmol) in CH₃CN/H₂O (5 mL/5 mL) was stirred at 0 °C for 5 min. Acryloyl chloride (51 mg, 0.58 mmol) was added dropwise at 0 °C. The final solution was stirred at 0 °C for 5 min and quenched by water, then extracted with EA (10 mL x 3). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated and purified by silica gel column

chromatography eluting with DCM:MeOH=20:1 to get the desired product (60 mg, 26%) as white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$, 80°C) δ 7.07-7.05 (m, 4H), 6.66-6.52 (m, 1H), 6.34 (s, 2H), 6.18-6.14 (m, 1H), 5.99 (s, 2H), 5.57-5.30 (m, 1H), 4.40-4.22 (m, 1H), 4.06-4.04 (m, 1H), 3.95-3.81 (m, 1H), 3.54-3.40 (m, 2H), 3.35-3.25 (m, 1H), 3.02 – 2.71 (m, 4H), 2.20-2.00 (m, 1H), 1.90-1.75 (m, 5H) ppm. MS: M/e 394 ($M+1$)⁺

Compound 1.14a or 1.14b: (*R* or *S*) 1-(((*S*)-1-acryloylpyrrolidin-2-yl)methyl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



Step A: (*R* or *S*)(2*S*)-tert-butyl 2-((5-amino-4-carbamoyl-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazol-1-yl)methyl)pyrrolidine-1-carboxylate



[0186] To a stirred solution of the product of step G in synthesis of **Compound 1.14** (2.0 g, 4.46 mmol) in EtOH (50 mL) was added H_2O_2 (2 mL), aq. NaOH (5.0 N, 2 mL), DMSO (2 mL). After the addition, the reaction was stirred at 50°C for 2 hours. The reaction mixture was concentrated to

give the residue, which was treated with EtOAc/brine, extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated and purified by column chromatography (petroleum ether/EtOAc=5:1~1:1) to give desired product (2.23 g, 100%) as a yellow solid, which was separated by chiral HPLC to give **peak 1** (0.93 g,

5 earlier peak) and **peak 2** (0.89 g, later peak). The chiral separation conditions are shown below:

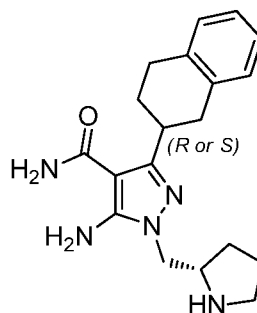
Column	CHIRALPAK IC
Column	0.46 cm I.D. ×15 cm L
size	
Injection	3ul
Mobile	
phase	EtOH
Flow rate	0.6 ml/min
Wave	
length	UV 254nm
Temperatu	
re	Room Temperature

[0187] Peak1: ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.07 (s, 4H), 6.58 (s, 2H), 6.04 (s, 2H), 4.57 – 3.80 (m, 4H), 3.17 (s, 2H), 3.03 – 2.75 (m, 4H), 2.12 (d, *J* = 14.4 Hz, 1H), 1.82 - 1.58 (m, 5H), 1.40 (s, 9H)ppm.

10 **[0188] Peak 2:** ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.07 (s, 4H), 6.58 (s, 2H), 6.06 (s, 2H), 4.51 – 3.81 (m, 4H), 3.18 (s, 2H), 3.01 – 2.75 (m, 4H), 2.13 (d, *J* = 11.6 Hz, 1H), 1.81 – 1.53 (m, 5H), 1.41 (s, 9H)ppm. MS: M/e 440.5 (M+1)⁺

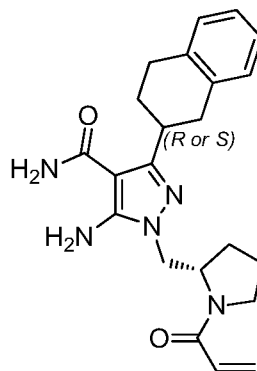
Step B: (**R or S**) 5-amino-1-((S)-pyrrolidin-2-ylmethyl)-3-(1,2,3,4-tetrahydro

15 naphthalen-2-yl)-1H-pyrazole-4-carboxamide



[0189] The product of Step A (0.93 g, 2.12 mmol) was added to CH₂Cl₂ (10 mL), then TFA (2 mL) was added. After the addition, the reaction mixture was stirred overnight. Most solvent was removed to give the residue, which was basified to pH=9~10 with *aq.*NaOH and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated to give target compound (538 mg, 74.8%) as a white solid. MS: M/e 340.5 (M+1)⁺

Step C: (R or S) 1-(((S)-1-acryloylpyrrolidin-2-yl)methyl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



[0190] NaHCO₃ (267 mg, 3.18 mmol) was added to a stirred mixture of the product of Step B (538 mg, 1.59 mmol) in CH₃CN/H₂O (10 mL/10 mL). Then the mixture was cooled to 0°C and a solution of acryloyl chloride (143.6 mg, 1.59 mmol) in CH₃CN (3 mL) was added dropwise. After the addition, the reaction was stirred for 10min. The reaction mixture was extracted with EtOAc (40 mL x 2). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated to give the residue, which was purified by column chromatography (petroleum ether/EtOAc=3:1~100%EtOAc) to give target compound (440 mg, 70.4%) as a light yellow solid.

[0191] Peak1(**Compound 1.14a**, retention time: 4.756 min): ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 7.07 (s, 4H), 6.74 – 6.44 (m, 2H), 6.28 – 5.97 (m, 4H), 5.82 – 5.36 (m, 1H), 4.45 – 4.11 (m, 1H), 4.09 – 3.83 (m, 2H), 3.60 – 3.35 (m, 3H), 3.08 – 2.70 (m, 4H), 2.10 (d, $J = 11.2$ Hz, 1H), 2.02 – 1.61 (m, 5H)ppm.

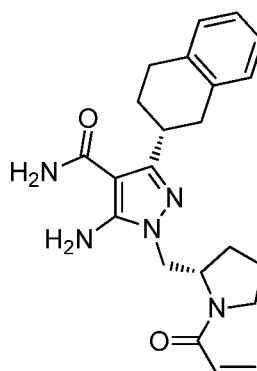
5 **[0192]** Peak 2 (**Compound 1.14b**, retention time: 5.347 min): ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 7.07 (s, 4H), 6.67 – 6.49 (m, 2H), 6.28 – 5.97 (m, 4H), 5.76 – 5.43 (m, 1H), 4.42 – 4.14 (m, 1H), 4.11 – 3.82 (m, 2H), 3.59 – 3.36 (m, 3H), 3.05 – 2.72 (m, 4H), 2.13 (d, $J = 12.0$ Hz, 1H), 1.95 – 1.64 (m, 5H)ppm.. MS: M/e 394.5 ($M+1$) $^+$

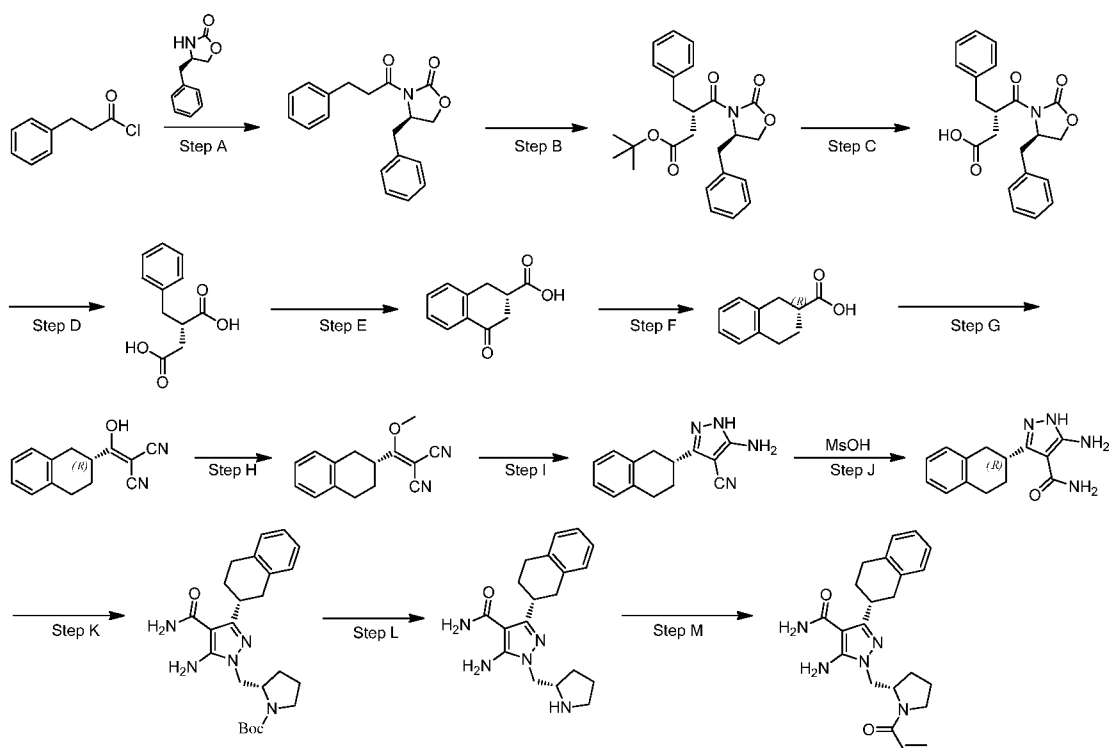
[0193] The chiral analysis conditions are shown below.

Column	CHIRALPAK AS-H
Column size	0.46 cm I.D. $\times$ 15 cm L
Injection	3ul
Mobile phase	n-Hexane/EtOH (0.1% triethyl amine)=80/20 (v/v)
Flow rate	1.0 ml/min
Wave length	UV 254nm
Temperature	35oC

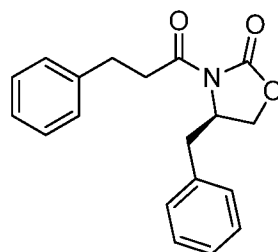
10

Chiral synthesis of **Compound 1.14a**: 1-(((S)-1-acryloylpyrrolidin-2-yl)methyl)-5-amino-3-((R)-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide





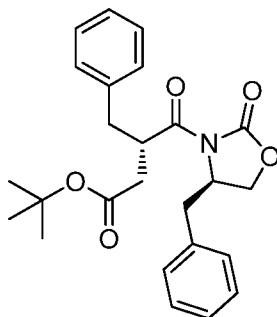
Step A: (R)-4-benzyl-3-(3-phenylpropanoyl)oxazolidin-2-one



5

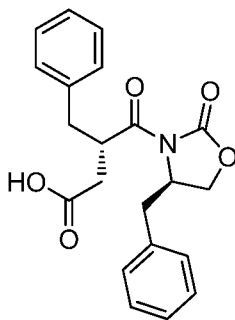
[0194] To a stirred solution of (R)-4-benzyl-2-oxooxazolidin-3-yl isocyanate (16.7 g, 94.3 mmol), Et₃N (19 g, 0.188 mol) and DMAP (1.1 g, 9.43 mmol) in CH₂Cl₂ (200 mL) was added dropwise a solution of 3-phenylpropanoyl chloride (17.4 g, 10.3 mmol) in CH₂Cl₂ (50 mL) at 0°C. After the addition, the reaction was stirred for 2 hours. The reaction mixture was washed with H₂O (200 mL), aq.HCl (2.0 M, 200 mL), aq.NaHCO₃ and brine, then dried over Na₂SO₄, concentrated to give the residue, which was washed with THF/Hexane (100 mL/100 mL) and filtered. The cake was collected, dried to give target compound (24 g, 82.3%) as a white solid. MS: M/e 310 (M+)⁺

Step B: (S)-tert-butyl 3-benzyl-4-((R)-4-benzyl-2-oxooxazolidin-3-yl)-4-oxobutanoate



[0195] To a stirred solution of the product of Step A (24 g, 77.7 mmol) in dry THF (200 mL) was added dropwise Lithium diisopropylamide (LDA, 2.0 M, 46.6 mL, 93.24 mmol) at -70°C, then a solution of tert-butyl 2-bromoacetate (16.7 g, 85.4 mmol) in THF (20 mL) was added dropwise. After the addition, the reaction was stirred for an hour at room temperature. The reaction was quenched with *aq.*NH₄Cl, and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated to give the residue, which was stirred at -5°C with IPA/Hexane (50 mL/50 mL) and filtered. The cake was collected to give target compound (16 g, 48.6%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.38 – 7.17 (m, 10H), 4.65 – 4.52 (m, 1H), 4.32 – 4.18 (m, 2H), 4.14 (dd, *J* = 8.8, 2.4 Hz, 1H), 2.97 (dd, *J* = 13.2, 4.0 Hz, 2H), 2.89 (dd, *J* = 13.6, 7.6 Hz, 1H), 2.69 (dd, *J* = 16.8, 10.8 Hz, 1H), 2.57 (dd, *J* = 13.2, 9.2 Hz, 1H), 2.25 (dd, *J* = 16.8, 4.0 Hz, 1H)ppm. MS: M/e 368 (M-*t*-Bu+1)⁺

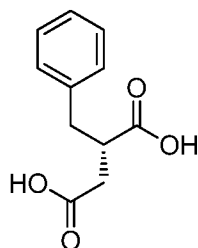
Step C: (S)-3-benzyl-4-((R)-4-benzyl-2-oxooxazolidin-3-yl)-4-oxobutanoic acid



[0196] To a stirred solution of the product of Step B (16 g, 37.8 mmol) in CH₂Cl₂ (200 mL) was added TFA (20 mL). After the addition, the reaction mixture was stirred for two days. The reaction mixture was concentrated to give the residue, which was treated with *aq.*NH₄Cl (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried

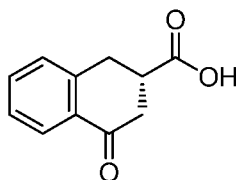
over Na₂SO₄ and concentrated to give target compound (12.9 g, 92.4%) as a white solid. MS: M/e 368 (M + 1)⁺

Step D: (S)-2-benzylsuccinic acid



[0197] To a stirred solution of the product of Step C (12.9 g, 34.96 mmol) in THF (50 mL) was added dropwise *aq.*H₂O₂ (30%, 15 mL) at 0°C, followed by a solution of LiOH (2.5 g, 104 mmol) in H₂O (20 mL). After the addition, the reaction was stirred overnight. The reaction mixture was quenched with *aq.*Na₂SO₃ (50 mL), most THF was removed to give the aqueous layer, then extracted with EtOAc (50 mL x 3). The aqueous layer was acidified to pH=3~4 with *aq.*HCl (2.0 M), and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated to give the target compound (7 g, 100%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.22 (s, 2H), 7.35 – 7.13 (m, 5H), 2.98 – 2.84 (m, 2H), 2.81 – 2.67 (m, 1H), 2.42 (dd, *J* = 16.8, 8.8 Hz, 1H), 2.24 (dd, *J* = 16.8, 4.4 Hz, 1H)ppm. MS: M/e 207 (M - 1)⁻

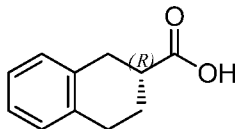
Step E: (S)-4-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid



[0198] A mixture of the product of step D (7 g, 33.6 mmol) in *conc.*H₂SO₄ (20 mL) was stirred at 60°C for 20 min. The reaction mixture was poured into ice-H₂O (150 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brined, dried over Na₂SO₄ and concentrated to give the target compound (6.3 g, 100%) as a white solid, which was directly used to the next step. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.48 (s, 1H), 7.85 (dd, *J* = 7.6, 1.2 Hz,

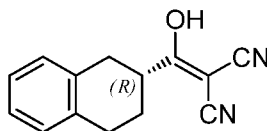
1H), 7.60 – 7.53 (m, 1H), 7.37 (dd, $J = 16.0, 8.0$ Hz, 2H), 3.28 – 3.12 (m, 3H), 2.79 (d, $J = 8.8$ Hz, 2H) ppm. MS: M/e 191 ($M + 1$)⁺

Step F: (R)-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid



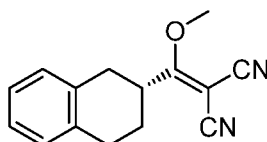
5 [0199] The product of step E (6.3 g, 33.6 mmol) was dissolved in AcOH (40 mL), HClO₄ (0.5 mL) and Pd/C (500 mg) were added. Then the reaction mixture was stirred overnight under H₂ (1 atm). The reaction mixture was filtered and the filtrate was concentrated to give the residue, which was stirred with H₂O (50 mL) for half an hour and filtered. The cake was collected, dried to give
10 target compound (3 g, 50.7%) as a white solid. MS: M/e 177 ($M + 1$)⁺

Step G: (R)-2-(hydroxy(1,2,3,4-tetrahydronaphthalen-2-yl)methylene)malononitrile



15 [0200] To a solution of the product of step F (3 g, 17 mmol) in CH₂Cl₂ (30 mL) was added HOBT (2.7 g, 20.4 mmol) and Et₃N (4.4 g, 34 mmol) followed by EDCI (3.9 g, 20.4 mmol). After stirred for 20 min, malononitrile (1.12 g, 17 mmol) was added. Then the reaction mixture was stirred for 2 hours. The mixture was washed with H₂O (30 mL), brine, dried over Na₂SO₄ and concentrated to give the residue, which was dissolved in EtOAc (50 mL) and washed with
20 aq. H₂SO₄ (4 M, 40 mL), brine, dried over Na₂SO₄ and concentrated to give target compound (3.8 g, 99.7%) as a tan solid. MS: M/e 225 ($M + 1$)⁺

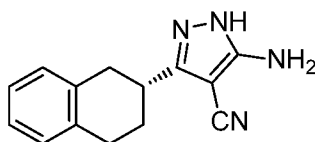
Step H: (R)-2-(methoxy(1,2,3,4-tetrahydronaphthalen-2-yl)methylene)malononitrile



[0201] A solution of the product of step G (3.8 g, 16.96 mmol) in trimethoxymethane (20 mL) was stirred at 70°C for 4-5 hrs. The resulting solution was concentrated. The residue was washed with EtOH/Hexane (5 mL/10 mL) and filtered. The cake was collected to give target compound (2.2 g, 54.5%) as a white solid. MS: M/e 239 (M+1)⁺

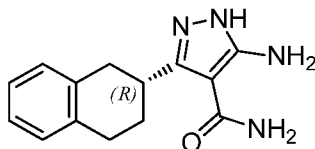
5

Step I: (R)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carbonitrile



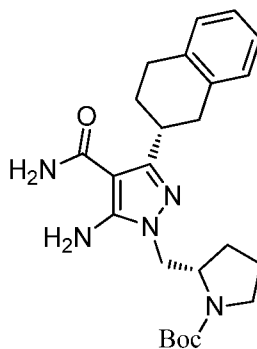
[0202] A solution of the product of step H (2.2 g, 9.24 mmol) and hydrazine hydrate (2 mL) in EtOH (10 mL) was stirred at rt for 30 min. The resulting solution was concentrated. The residue was washed by water, extracted with EA (20 mL x 3). The combined organic layer was washed by brine, dried over Na₂SO₄ and concentrated to give target compound (2.3 g, 100%) as a white solid. MS: M/e 239 (M+1)⁺

Step J: (R)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



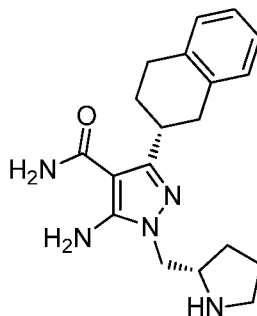
[0203] A mixture of the product of step I (1.0 g, 4.2 mmol) in MsOH (5 mL) was stirred at 70°C for 3 hours. The reaction mixture was poured into H₂O (20 mL) and basified to pH=8~9 with aq. NaOH, then extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated to give target compound (770 mg, 71.6%) as a white solid. MS: M/e 257 (M+1)⁺

Step K: (S)-tert-butyl 2-((5-amino-4-carbamoyl-3-((R)-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazol-1-yl)methyl)pyrrolidine-1-carboxylate



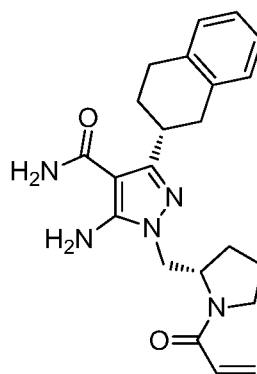
[0204] A mixture of the product of step J (100 mg, 0.39 mmol), **BL-2** (166 mg, 0.47 mmol) and Cs_2CO_3 (254 mg, 0.78 mmol) in DMF (5 mL) was stirred at 70°C for 24 h. The resulting solution was poured into H_2O (20 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , concentrated and purified by column chromatography (petroleum ether/EtOAc=4:1~EtOAc) to give the target compound (45 mg, 26%) as a yellow solid. MS: M/e 440 ($M+1$)⁺

Step **L**: 5-amino-1-((S)-pyrrolidin-2-ylmethyl)-3-((R)-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



[0205] To a stirred solution of the product of step K (45 mg, 0.102 mmol) in CH_2Cl_2 (5 mL) was added TFA (1 mL). After the addition, the reaction mixture was stirred for 2 hours. The reaction mixture was concentrated to give the residue, which was directly used to the next step without further purification. MS: M/e 340 ($M+1$)⁺

Step **M**: 1-(((S)-1-acryloylpyrrolidin-2-yl)methyl)-5-amino-3-((R)-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide

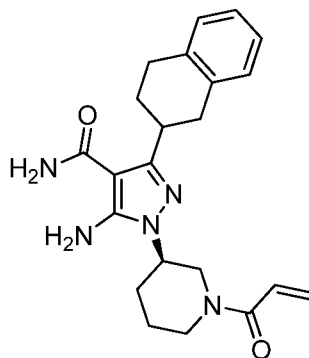


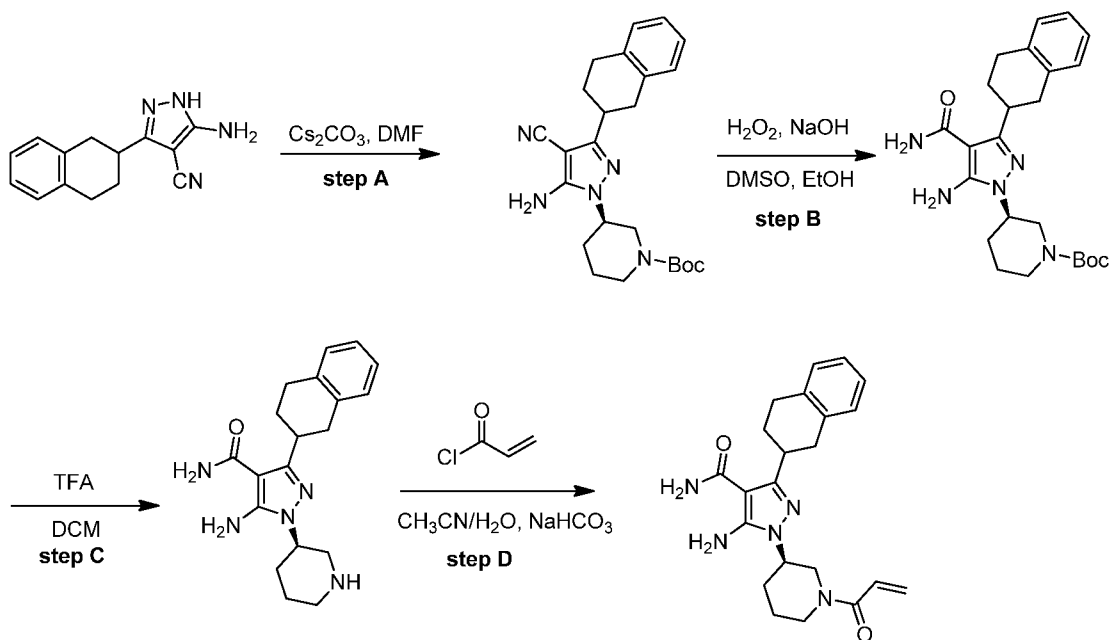
[0206] To a stirred solution of the product of step L (0.102 mmol) in CH₃CN/H₂O (3 mL/3 mL) was added NaHCO₃ (17.1 mg, 0.204 mmol), then a solution of acryloyl chloride (9.28 mg, 0.102 mmol) in CH₃CN (1 mL) was added dropwise at 0°C. The reaction mixture was extracted with

5 EtOAc (5 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated and purified by *Prep*-HPLC to give target compound (12 mg, 29.7 %) in the form of TFA salt. ¹H NMR (400 MHz, DMSO-*d*₆+D₂O) δ 7.08 (s, 4H), 6.59 (dd, *J* = 16.8, 10.4 Hz, 1H), 6.26 – 6.12 (m, 1H), 5.79 – 5.40 (m, 1H), 4.43 – 4.14 (m, 1H), 4.08 – 3.86 (m, 2H), 3.49 – 3.31 (m, 3H), 3.05 – 2.73 (m, 4H), 2.10 (d, *J* = 11.6 Hz, 1H), 1.98 – 1.61 (m, 5H)ppm. MS: M/e 394 (M+1)⁺

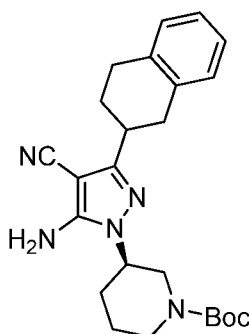
10

Compound 1.15: 1-((R)-1-acryloylpiperidin-3-yl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide





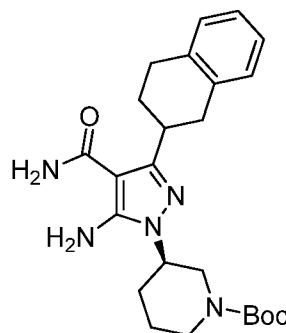
Step A: (3R)-tert-butyl 3-(5-amino-4-cyano-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate



5

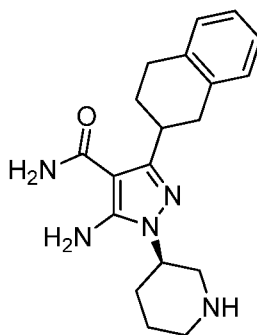
[0207] A mixture of the product of step F in synthesis of **Compound 1.14** (714 mg, 3 mmol), (S)-Tert-butyl 3-(tosyloxy)piperidine-1-carboxylate (**BL-1**, 1.6 g, 4.5 mmol) and Cs_2CO_3 (1.95 g, 6 mmol) in DMF (6 mL) was stirred at 70 °C for 24 hrs. Then another portion of **BL-1** (1.6 g, 4.5 mmol) was added and the resulting mixture was heated at 70 °C for 24 hrs. The resulting solution was concentrated. The residue was washed by water, extracted with EA (40 mL x 2). The combined organic layer was washed by brine, dried over anhydrous sodium sulfate then concentrated and purified by silica gel column chromatography eluting with PE:EA=1:5 to get the desired product (650 mg, crude) as a yellow solid. MS: M/e 422 ($M+1$)⁺

Step B: (3R)-tert-butyl 3-(5-amino-4-carbamoyl-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate



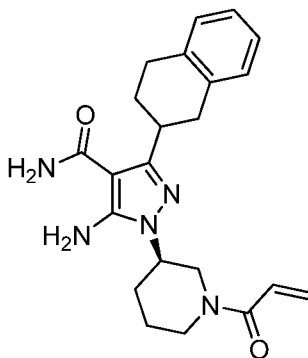
[0208] To a solution of the product of Step A (650 mg, crude) in EtOH (5 mL) was added
 5 DMSO (2 mL), 5N NaOH aqueous solution (2 mL) followed by H₂O₂ (2 mL). The solution was stirred at 50 °C for 2 hrs. The resulting solution was concentrated. The residue was washed by water, extracted with EA (30 mL x 2). The combined organic layer was washed by brine, dried over anhydrous sodium sulfate then concentrated and purified by silica gel column chromatography eluting with PE:EA=1:1 to get the desired product (300 mg, 23% for two steps) as
 10 a yellow solid. MS: M/e 440 (M+1)⁺

Step C: 5-amino-1-((R)-piperidin-3-yl)-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



15 [0209] To the solution of the product of Step B (300 mg, 0.68 mmol) in DCM (5 mL) was added TFA (2 mL). The solution was stirred at rt for 2 hrs. The resulting solution was treated with saturated Na₂CO₃ aqueous solution to pH = 8, extracted with DCM (30 mL x 2). The combined organic layer was washed by brine, dried over anhydrous sodium sulfate then concentrated to get the crude product (190mg, 83%) as yellow foam, which was used in next step directly. MS: M/e
 20 340 (M+1)⁺

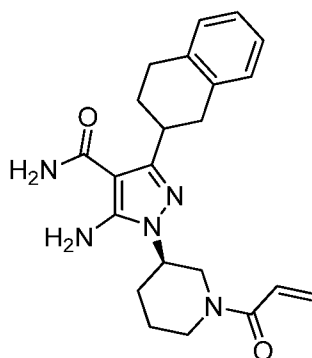
Step D: 1-((R)-1-acryloylpiperidin-3-yl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide

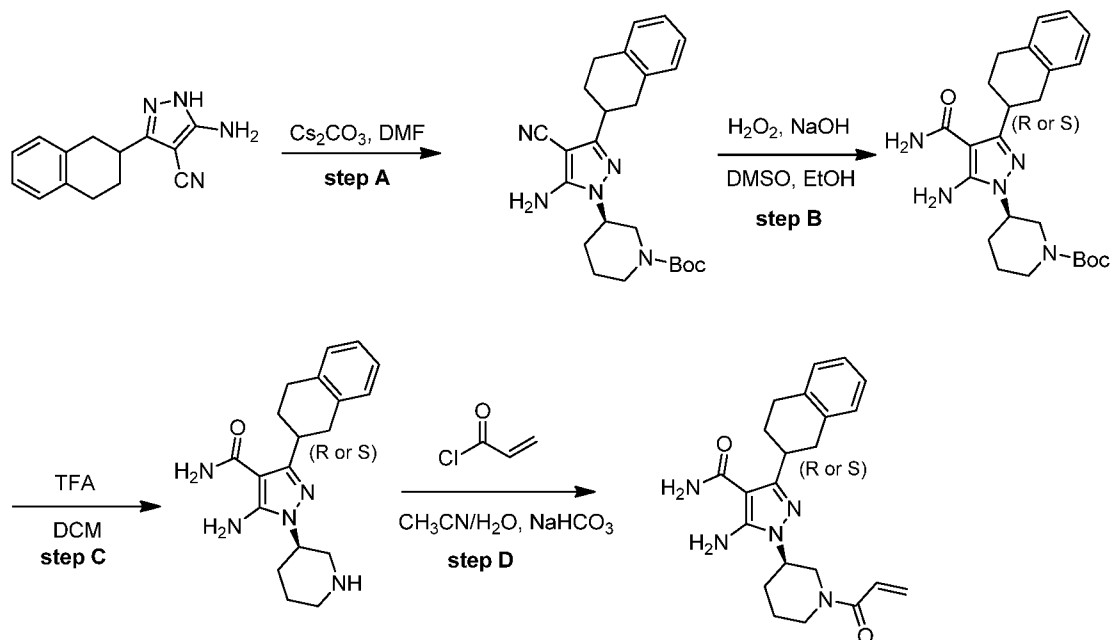


5 [0210] To a mixture of the product of Step C (160 mg, 0.47 mmol) in CH₃CN (5 mL) was added saturated NaHCO₃ aqueous solution (1 mL). The resulting solution was cooled to 0 °C and a solution of acryloyl chloride (43 mg, 0.47 mmol) in CH₃CN (1 mL) was added dropwise. The final solution was stirred at 0 °C for 5 min and quenched by water, then extracted with EA (30 mL x 2). The combined organic layer was washed by brine, dried over anhydrous sodium sulfate then
10 concentrated and purified by *prep*-TLC (DCM:MeOH=20:1) to give the desired product (68 mg, 37%) as a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.06 – 7.02 (m, 4H), 6.90 – 6.75 (m, 1H), 6.60 (s, 2H), 6.23 (s, 2H), 6.10 – 5.99 (m, 1H), 5.72 – 5.58 (m, 1H), 4.44 – 3.90 (m, 3H), 3.50 – 3.38 (m, 1H), 3.15 – 2.76 (m, 6H), 2.18 – 2.08 (m, 1H), 2.00 – 1.79 (m, 3H), 1.78 – 1.62 (m, 1H), 1.55 – 1.35 (m, 1H) ppm. MS: M/e 394 (M+1)⁺

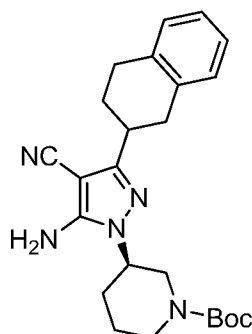
15

Compound 1.15a or 1.15b: (R or S) 1-((R)-1-acryloylpiperidin-3-yl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide





Step A: (R or S) (3R)-tert-butyl 3-(5-amino-4-cyano-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate



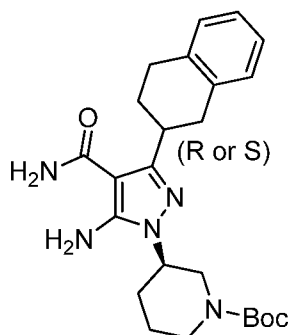
5

[0211] A mixture of the product of step F in synthesis of **Compound 1.14** (4.7 g, 20 mmol), **BL-1** (8.52 g, 24 mmol) and Cs_2CO_3 (13 g, 40 mmol) in DMF (50 mL) was stirred at 70 °C for 80 hrs. Another two portions of **BL-1** (2 g, 5.6 mmol) were added in this period time. The resulting solution was concentrated. The residue was washed by water, extracted with EA (100 mL x 2). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate then concentrated and purified by silica gel column chromatography eluting with PE:EA=1:5 to get the desired product (2.1 g, 25%) as a yellow solid. MS: M/e 422 ($M+1$)⁺

10

Step B: (R or S) (3R)-tert-butyl 3-(5-amino-4-carbamoyl-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate

15

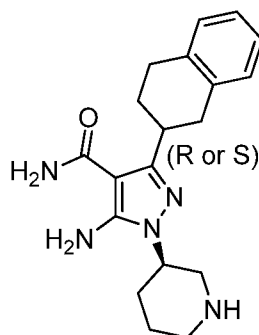


[0212] To a solution of the product of Step A (2.1 g, 5 mmol) in EtOH (20 mL) was added DMSO (5 mL), 5N NaOH aqueous solution (5 mL) followed by H₂O₂ (5 mL). The solution was stirred at 50 °C for 4 hrs. The resulting solution was concentrated. The residue was washed by water, extracted with EA (40 mL x 3). The combined organic layer was washed by brine, dried over anhydrous sodium sulfate then concentrated and purified by silica gel column chromatography eluting with PE:EA=1:1 to get the desired product (1.55 g, 70%) as a yellow solid. MS: M/e 440 (M+1)⁺. The product was separated by chiral *prep*-HPLC to give **peak 1** and **peak 2**. The chiral separation conditions are shown below:

10

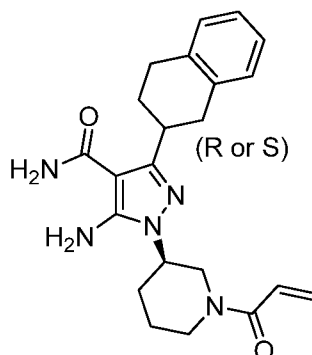
Column	CHIRALPAK OJH
Column size	0.46 cm I.D. ×25 cm L
Injection	10 ul
Mobile phase	CO ₂ /MeOH=75/25(V/V)
Flow rate	2.0 ml/min
Wave length	UV 220nm
Temperature	35°C

Step C: (R or S) 5-amino-1-((R)-piperidin-3-yl)-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



[0213] To the solution of the product of Step B (820 mg, 1.86 mmol) in DCM (10 mL) was added TFA (3 mL). The solution was stirred at rt overnight. The resulting solution was concentrated to get the crude product which was used in next step directly. MS: M/e 340 (M+1)⁺

5 Step D: (R or S)1-((R)-1-acryloylpiperidin-3-yl)-5-amino-3-(1,2,3,4-tetrahydro naphthalen-2-yl)-1H-pyrazole-4-carboxamide



[0214] To a mixture of the product of Step C in CH₃CN (15 mL) and H₂O (3 mL) was added NaHCO₃ (1 g, 12 mmol). The resulting solution was cooled to 0 °C and a solution of acryloyl chloride (300 mg, 1.86 mmol) in CH₃CN (2 mL) was added dropwise. The final solution was stirred at 0 °C for 5 min and quenched by water, then extracted with EA (30 mL x 2). The combined organic layer was washed by brine, dried over anhydrous sodium sulfate then concentrated and purified by *prep*-HPLC. Most of CH₃CN from collection was removed by concentration. The resulting solution was treated with saturated NaHCO₃ solution to PH 8,
10 extracted with DCM (50 mL x 3). The combined organic layer was washed by brine, dried over anhydrous sodium sulfate, filtered then concentrated to give the desired product (300 mg, 41% for 2 steps) as a white solid.

[0215] Peak1(Compound 1.15a, retention time: 5.85 min): ¹H NMR (400 MHz, DMSO-*d*₆) δ
20 7.12 – 7.04 (m, 4H), 6.90 – 6.71 (m, 1H), 6.59 (s, 2H), 6.22 (s, 2H), 6.15 – 6.02 (m, 1H), 5.75 – 5.58 (m, 1H), 4.44 – 3.94 (m, 3H), 3.50 – 3.38 (m, 1H), 3.15 – 2.75 (m, 6H), 2.16 – 2.08 (m, 1H), 2.00 – 1.79 (m, 3H), 1.78 – 1.62 (m, 1H), 1.55 – 1.35 (m, 1H) ppm. MS: M/e 394 (M+1)⁺

[0216] Peak2(Compound 1.15b, retention time: 6.944 min): ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 7.12 – 7.04 (m, 4H), 6.90 – 6.71 (m, 1H), 6.58 (s, 2H), 6.21 (s, 2H), 6.15 – 6.02 (m, 1H), 5.75 – 5.58 (m, 1H), 4.45 – 3.94 (m, 3H), 3.50 – 3.36 (m, 1H), 3.15 – 2.75 (m, 6H), 2.18 – 2.06 (m, 1H), 2.00 – 1.80 (m, 3H), 1.76 – 1.62 (m, 1H), 1.55 – 1.35 (m, 1H) ppm. MS: M/e 394 ($M+1$)⁺

5

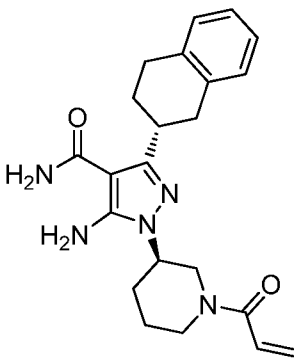
[0217] The chiral analysis conditions are shown below.

Column	CHIRALPAK AD-H
Column size	0.46 cm I.D. 15 cm $\times$ L, 5 μ m
Injection	2 μ l
Mobile phase	n-Hexane/EtOH (0.1% triethyl amine)=50/50 (v/v)
Flow rate	1.0 ml/min
Wave length	UV 254nm
Temperature	35°C

[0218] Compound 1.15a was prepared according to the procedures described for chiral synthesis of **Compound 1.14a** under appropriate conditions that could be recognized by one skilled in the art.

10

Compound 1.15a: 1-((R)-1-acryloylpiperidin-3-yl)-5-amino-3-((R)-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide in the form of CF_3COOH salt



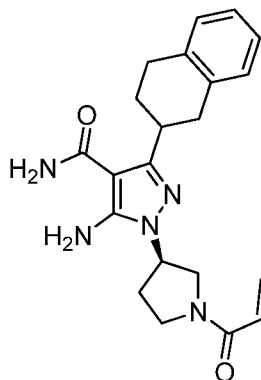
[0219] ^1H NMR(400 MHz, $\text{DMSO-}d_6$) δ 7.07 (s, 4H), 6.93-6.70 (m, 1H), 6.59 (s, 2H), 6.38-5.97 (m, 2H), 5.66 (dd, $J=28.8, 10.4$ Hz, 1H), 4.48-3.91 (m, 3H), 3.60-3.48 (m, 1H), 3.15-2.75 (m, 6H), 2.22-2.06 (m, 1H), 2.05-1.79 (m, 3H), 1.68 (s, 1H), 1.45 (s, 1H) ppm. MS: M/e 394 ($M+1$)⁺

15

[0220] **Compounds 1.16 - 1.17** were prepared according to the procedures described for **Compound 1.15** under appropriate conditions that could be recognized by one skilled in the art.

Compound 1.16: 1-((R)-1-acryloylpyrrolidin-3-yl)-5-amino-3-(1,2,3,4-

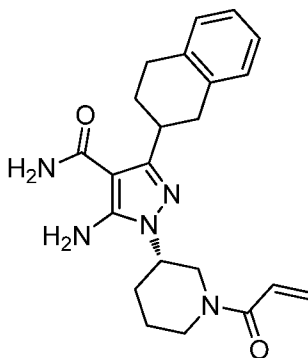
5 tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



[0221] ^1H NMR (400 MHz, DMSO- d_6 , 80°C) δ 7.06 – 7.02 (m, 4H), 6.54 – 6.20 (m, 3H), 6.12 – 6.07 (m, 1H), 5.25 – 5.15 (m, 2H), 5.62 (d, J = 9.6 Hz, 1H), 4.87 – 4.80 (m, 1H), 3.95 – 3.29 (m, 5H), 3.01 – 2.65 (m, 4H), 2.35 – 2.05 (m, 3H), 1.80 – 1.69 (m, 1H) ppm. MS: M/e 380 ($M+1$) $^+$

10

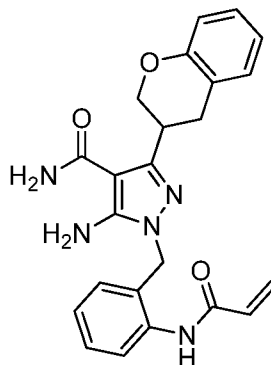
Compound 1.17: 1-((S)-1-acryloylpiperidin-3-yl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



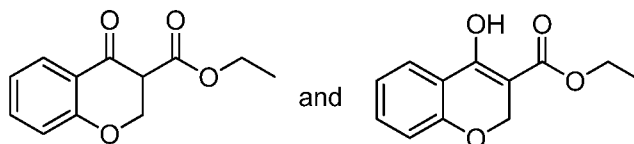
[0222] ^1H NMR (400 MHz, DMSO- d_6 , 80°C) δ 7.06 – 7.02 (m, 4H), 6.80 – 6.65 (m, 1H), 6.34 (s, 2H), 6.10 – 5.97 (m, 1H), 5.68 – 5.57 (m, 1H), 4.30 – 3.90 (m, 3H), 3.38 – 3.28 (m, 1H), 3.06 – 2.75 (m, 6H), 2.18 – 2.06 (m, 1H), 2.00 – 1.65 (m, 4H), 1.56 – 1.40 (m, 1H) ppm. MS: M/e 394 ($M+1$) $^+$

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Compound 1.18: 1-(2-acrylamidobenzyl)-5-amino-3-(chroman-3-yl)-1H-pyrazole-4-carboxamide



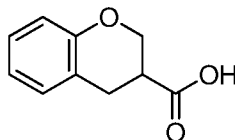
5 Step A: Ethyl 4-oxochroman-3-carboxylate and ethyl 4-hydroxy-2H-chromene-3-carboxylate



[0223] To a solution of chroman-4-one (8.8 g, 60 mmol) in dry THF (200 mL) was added LiHMDS (1 M, 72 mL, 72 mmol) at -78°C. After stirring for 40 min, ethyl carbonocyanidate (4.5 g, 90 mmol) was added dropwise and the resulting mixture was stirred from -78°C to room temperature for two hours. Saturated aqueous of NH₄Cl (200 mL) was added, extracted with EA (200 mL × 3), combined the organic layers, dried over Na₂SO₄, evaporated the solvent and the residue was purified by column chromatography (PE/EA=100:5) to give 9.0 g ethyl 4-oxochroman-3-carboxylate in 68% yield as a mixture of tautomer.

15

Step B: Chroman-3-carboxylic acid

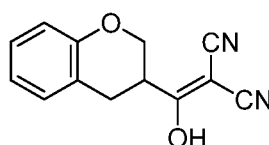


[0224] To a slution of ethyl 4-oxochroman-3-carboxylate (7.7g, 35 mmol) in AcOH (40 mL) and HClO₄ (2 mL) was added Pd/C (770 mg) and the resulting mixture was stirred at room temperature under H₂ (0.4 MPa) for 6 hours. Filtered to remove Pd/C, the filtrate was evaporated,

20

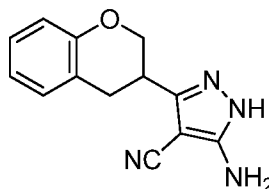
washed with water and brine (100 mL $\times$ 2) to give crude ethyl chroman-3-carboxylate. Then hydrolyzed with LiOH (1.5 g, 36 mmol) in a solution of THF/H₂O/MeOH (30 mL/30 mL/30 mL) at room temperature stirring for 1 hour, then evaporated the solvent and water (20 mL) was added to the residue, acidification with HCl (1 N) to pH=1-2, the white precipitate was collected by
5 filtration, dried *in vacuo* to give 4.5 g in 73% yield for two steps. ¹H NMR (400 MHz, CD₃OD) δ 7.00-7.06 (m, 2 H), 6.80 (t, *J* = 7.6 Hz, 1 H), 6.72 (d, *J* = 8.0 Hz, 1 H), 4.35 (dd, *J* = 10.8 Hz, 1.6 Hz, 1H), 4.08-4.13 (m, 1 H), 2.94-3.01 (m, 3 H). MS (ESI) *m/e* [M-1]+177.

Step C: 2-(Chroman-3-yl(hydroxy)methylene)malononitrile



[0225] A solution of chroman-3-carboxylic acid (1.5 g, 8.4 mmol) in AcOEt (75 mL) was added Et₃N (1.02 g, 10.1 mmol), HOBT (1.37 g, 10.1 mmol), EDCI (1.935 g, 10.1 mmol) and the mixture was stirred at room temperature for 0.5 h, then malononitrile (0.665 g, 10.1 mmol) was added to the mixture and the resulting mixture was stirred at room temperature for 2 hours. Water (100 mL)
15 was added, the organic layer was isolated, and washed with brine, dried over Na₂SO₄. Filtered to remove Na₂SO₄, the solvent was evaporated and the residue was dissolved in AcOEt (100 mL), H₂SO₄ (1 N, 20 mL) was added and the mixture was stirred for 0.5 h before isolated the organic layer, evaporated the solvent to give crude product and used for next step without further purification. MS (ESI) *m/e* [M+1]+227.0.

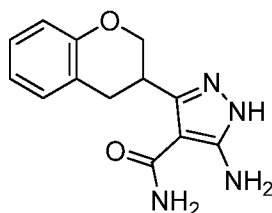
Step D: 5-Amino-3-(chroman-3-yl)-1*H*-pyrazole-4-carbonitrile



[0226] A solution of crude 2-(chroman-3-yl(hydroxy)methylene)malononitrile (8.4 mmol) in trimethoxymethane (50 mL) was heated at 100°C for 1.5 hour. Then the solvent was evaporated

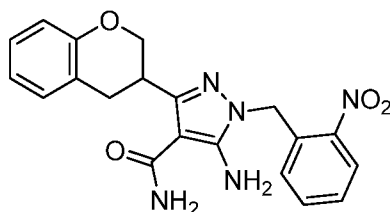
and the residue was dissolved in EtOH (20 mL), followed by addition of hydrazine hydrate (1.5 mL) at 0°C and the mixture was stirred for 0.5 h. Then the solvent evaporated and the residue was used for next step without further purification. MS (ESI) m/e [M+1]+241.0.

5 Step E: 5-Amino-3-(chroman-3-yl)-1H-pyrazole-4-carboxamide



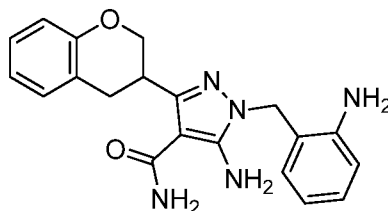
[0227] A solution of crude 5-amino-3-(chroman-3-yl)-1H-pyrazole-4-carbonitrile (8.4 mmol) in conc.H₃PO₄ (20 mL) was heated at 130°C for 20 min. Then the mixture was cooled to room temperature and added dropwise to water (40 mL) with vigorous stirring, followed adjust pH to 7-8 with NaHCO₃, extracted with EA (20 mL × 3), combined the organic layer, washed with brine (50 mL × 2), dried over Na₂SO₄, filtered to remove Na₂SO₄ and the filtrate was evaporated to give 550 mg crude product and this was used for next step without further purification. MS (ESI) m/e [M+1]+259.0.

15 Step F: 5-Amino-3-(chroman-3-yl)-1-(2-nitrobenzyl)-1H-pyrazole-4-carboxamide



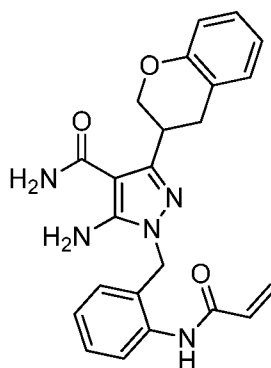
[0228] A mixture of 5-amino-3-(chroman-3-yl)-1H-pyrazole-4-carboxamide (380 mg, 1.47 mmol) and 1-(bromomethyl)-2-nitrobenzene (382 mg, 1.77 mmol) in DMF (10 mL) was stirred at room temperature for 1 hour. Water (50 mL) was added to the resulting mixture, followed by addition of NaCl (solid) with stirring and the brown precipitate was collected by filtration and the filter cake was washed with H₂O, and then dried *in vacuo*, the crude product was used for next step without further purification. MS (ESI) m/e [M+1]+393.9

Step G: 5-amino-1-(2-aminobenzyl)-3-(chroman-3-yl)-1H-pyrazole-4-carboxamide



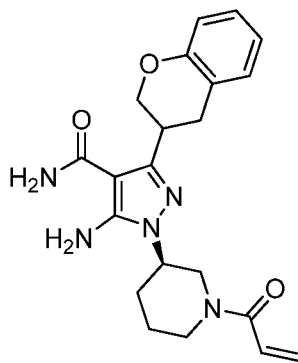
[0229] To a solution of crude 5-amino-3-(chroman-3-yl)-1-(2-nitrobenzyl)-1H-pyrazole-4-carboxamide (1.0 mmol) in MeOH (50 mL) was added Pd/C (100 mg) at room temperature and stirred overnight under an air balloon of H₂. Filtered to remove Pd/C, evaporated the solvent and the crude yellow solid was used for next step without further purification. MS (ESI) m/e [M+1]⁺364.0.

Step H: 1-(2-acrylamidobenzyl)-5-amino-3-(chroman-3-yl)-1H-pyrazole-4-carboxamide

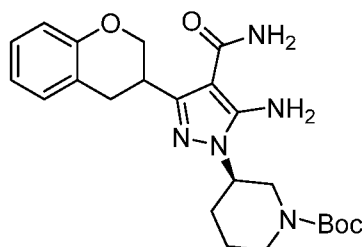


[0230] To a solution of 5-amino-1-(2-aminobenzyl)-3-(chroman-3-yl)-1H-pyrazole-4-carboxamide (135 mg, 0.37 mmol) in CH₃CN (10 mL) and H₂O (2 mL) was added NaHCO₃ (62 mg, 0.74 mmol), followed by addition of acryloyl chloride (34 mg, 0.37 mmol) at 0°C and the resulting mixture was stirred for 15 minutes. The product (29 mg) was obtained by purification with *prep*-HPLC. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.01 (s, 1 H), 7.63 (d *J* = 7.6 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.05-7.13 (m, 3 H), 6.94 (d, *J* = 7.2 Hz, 1H), 6.76-6.84 (m, 4 H). 6.49-6.56 (m, 1H), 6.29 (t, *J* = 8.0 Hz, 2 H), 5.79 (d, *J* = 10.8 Hz, 1H), 5.13 (s, 2 H), 4.41 (dd, *J* = 10.4, 2.4 Hz, 1H), 3.90 (t, *J* = 10.4 Hz, 1H), 3.68-3.76 (m, 1 H), 2.99 (d, *J* = 8.0 Hz, 2H). MS (ESI) m/e [M+1]⁺417.9.

Compound 1.19: 1-((R)-1-acryloylpiperidin-3-yl)-5-amino-3-(chroman-3-yl)-1H-pyrazole-4-carboxamide

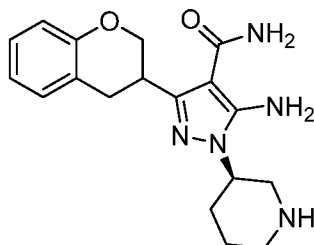


Step A: (3*R*)-*tert*-Butyl 3-(5-amino-4-carbamoyl-3-(chroman-3-yl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate



- 5 **[0231]** A mixture of (5-amino-3-(chroman-3-yl)-1*H*-pyrazole-4-carboxamide (the product of step E in synthesis of **Compound 1.18**, 0.50 g, 1.93 mmol), (*S*)-*tert*-butyl 3-(tosyloxy)piperidine-1-carboxylate (**BL-1**, 0.897 g, 2.52 mmol), cesium carbonate (0.943 g, 2.90 mmol), DMF (10 mL) was stirred at 70°C for 16 hours, cooled. (*S*)-*tert*-butyl 3-(tosyloxy)piperidine-1-carboxylate (0.897 g, 2.52 mmol), cesium carbonate (0.943 g, 2.90 mmol) was added and heated to 70°C for 4 hours, cooled. Ethyl acetate (100 mL) was added, combined with another batch of the same Step A and similar procedure (5-amino-3-(chroman-3-yl)-1*H*-pyrazole-4-carboxamide (0.107 g, 0.416 mmol)), filtered. The filtrate was washed with water (10 mL), brine (20 mL x2), dried over Na₂SO₄ and concentrated, purified by silica gel column (silica gel:30 g, ethyl acetate: petroleum ether =2:3, then
- 15 dichloromethane : methanol =40:1) to give (3*R*)-*tert*-butyl 3-(5-amino-4-carbamoyl-3-(chroman-3-yl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate (0.238 g, 28%) as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.05-7.12 (m, 2H), 6.73-6.85 (m, 4H), 6.20-6.21 (m, 2H), 4.39-4.42 (m, 1H), 3.62-4.04 (m, 5H), 3.34-3.40 (m, 1H), 2.97-3.01 (m, 3H), 2.75-2.85 (m, 1H), 1.79-1.91 (m, 3H), 1.39 (s, 9H). MS (ESI) *m/e* [M+1]⁺ 442.

Step B: 5-Amino-3-(chroman-3-yl)-1-((*R*)-piperidin-3-yl)-1*H*-pyrazole-4- carboxamide



[0232] (*3R*)-*tert*-butyl 3-(5-amino-4-carbamoyl-3-(chroman-3-yl)-1*H*-pyrazol-1-yl)

piperidine-1-carboxylate (0.238 g, 0.54 mmol) was dissolved in dichloromethane (9 mL),

5 trifluoroacetic acid (1.5 mL) was added, the reaction mixture was stirred at room temperature for 4

hours, concentrated to give 5-amino-3-(chroman-3-yl)-1-((*R*)-piperidin-3-yl)-1*H*-pyrazole-4-

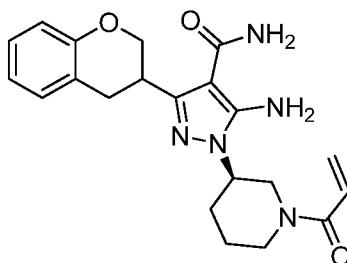
carboxamide in the form of trifluoroacetic acid salt as a brown semi-solid (0.452 g, 417%, crude,

0.54 mmol). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.74-8.75 (m, 2H), 8.47-8.50 (m, 1H), 8.31-8.32

(m, 1H), 7.09-7.13 (m, 2H), 6.77-6.84 (m, 4H), 4.36-4.39 (m, 2H), 4.04-4.06 (m, 1H), 3.69-3.73

10 (m, 1H), 3.32-3.37 (m, 2H), 2.89-3.10 (m, 4H), 1.65-1.91 (m, 4H). MS (ESI) *m/e* [M+1]⁺ 342.

Step C: 1-((*R*)-1-acryloylpiperidin-3-yl)-5-amino-3-(chroman-3-yl)-1*H*-pyrazole-4- carboxamide



15 [0233] A mixture of 5-amino-3-(chroman-3-yl)-1-((*R*)-piperidin-3-yl)-1*H*-

pyrazole-4-carboxamide (0.452 g, crude, 0.54 mmol), acetonitrile (3 mL), water (1.5 mL),

NaHCO₃ (solid, 0.36 g, 4.31 mmol) was cooled to 0°C, a solution of acryloyl chloride (73 mg, 0.81

mmol) was added. The reaction mixture was stirred at 0°C for 30 minutes, concentrated, and water

(10 mL) was added, extracted with ethyl acetate (10 mL). The organic phase was separated and

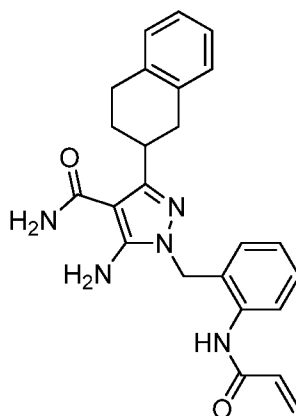
20 washed with brine (10 mL x2), dried over Na₂SO₄ and concentrated, purified by prep-HPLC

(Instrument:gilson-281; Column: 21.2×150×5uM, gemini-new; Flow rate: 20ML/MIN; UV:

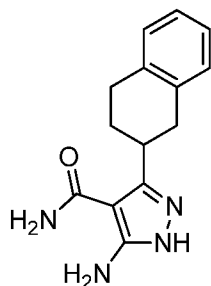
254nm; method: 0.1% FA in water and in CH₃CN, CH₃CN from 35 to 45 in 11 min, then from 45

to 90 in 3 min, 90 hold 3 min, then balance 2 min. Total run time 20 min. Single gradient method) to afford 1-((*R*)-1-acryloylpiperidin-3-yl)-5-amino-3-(chroman-3-yl)-1*H*-pyrazole-4-carboxamide (61 mg, 29%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆, 80°C) δ 7.03-7.09 (m, 2H), 6.68-6.83 (m, 3H), 6.49 (s, 2H), 6.01-6.06 (m, 3H), 5.60-5.63 (m, 1H), 4.38-4.41 (m, 1H), 3.87-4.16 (m, 4H), 3.62-3.64 (m, 1H), 2.97-3.02 (m, 4H), 1.84-1.97 (m, 3H), 1.47-1.50 (m, 1H). MS (ESI) *m/e* [M+1]⁺ 396.

Compound 1.20: 1-(2-acrylamidobenzyl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1*H*-pyrazole-4-carboxamide



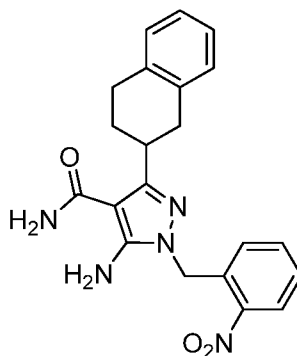
Step A: 5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1*H*-pyrazole-4-carboxamide



[0234] A mixture of 5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1*H*-pyrazole-4-carbonitrile (the product of step F in synthesis of **Compound 1.14**, 1.5 g, 6.3 mmol) in

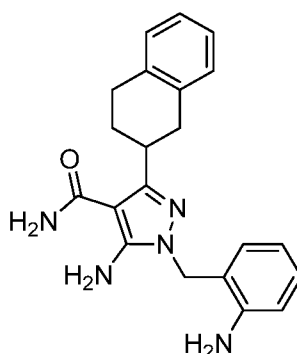
methanesulfonic acid (5 mL) was stirred at 110 °C for 1 h, then it was poured into ice-water and the mixture was neutralized with K₂CO₃ to pH 7-8. The mixture was extracted with EtOAc, then the organic layer was washed with brine, dried over Na₂SO₄, concentrated under vacuum to give the desired product (1.2 g, 75%) as a yellow solid, which was used for the next step without further purification. MS (ESI) *m/e* [M+1]⁺ 257.0

Step B: 5-amino-1-(2-nitrobenzyl)-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



- 5 **[0235]** A reaction mixture of 5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide (1.2 g, 4.68 mmol), 1-(bromomethyl)-2-nitrobenzene (1.01 g, 4.68 mmol) and K_2CO_3 (1.3 g, 9.36 mmol) in DMF (10 mL) was stirred at room temperature for 16h, then it was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 , concentrated under vacuum. The residue was purified by silica gel
- 10 chromatography (elution with hexane/ethyl acetate 1:2 to MeOH/DCM 1:50) to the desired product (1 g, 55%) as a yellow solid. MS (ESI) m/e $[M+1]^+$ 392

Step C: 5-amino-1-(2-aminobenzyl)-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide

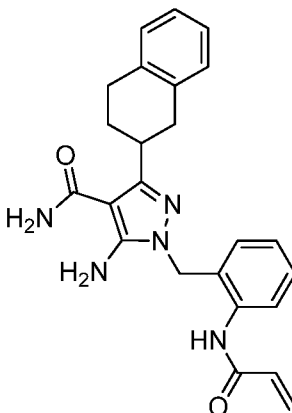


- 15 **[0236]** A reaction mixture of 5-amino-1-(2-nitrobenzyl)-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide (1 g, 2.55 mmol), Fe powder (0.86 g, 15.3 mmol), MH_4Cl (95 mg, 1.785 mmol) in EtOH (45 mL) and H_2O (15 mL) was stirred at 80 °C for 3 h, then it was

poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 , concentrated under vacuum. The residue was purified by silica gel chromatography (elution with hexane/ethyl acetate 1:2 to MeOH/DCM 1:50) to give the desired product (0.41 g, 45%) as a yellow solid. MS (ESI) m/e $[\text{M}+1]^+$ 362.0

5

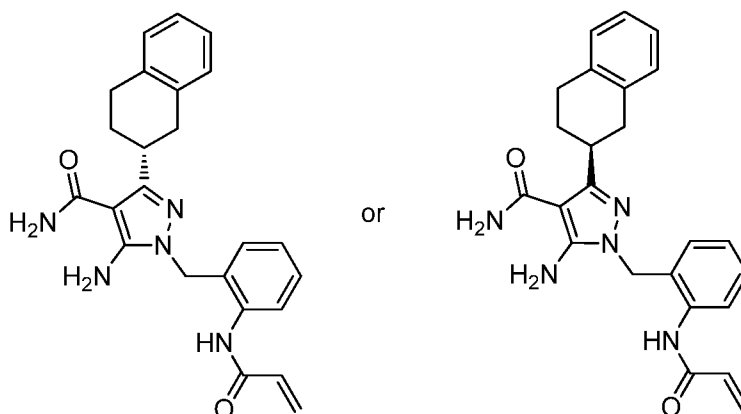
Step D: 1-(2-acrylamidobenzyl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



[0237] To a mixture of 5-amino-1-(2-aminobenzyl)-3-(1,2,3,4-tetrahydronaphthalen

10 -2-yl)-1H-pyrazole-4-carboxamide (0.41 g, 1.13 mmol), NaHCO_3 (0.19 g, 2.26 mmol) in CH_3CN (18 mL) and H_2O (4 mL) was added a solution of acryloyl chloride (0.113 g, 1.25 mmol) in CH_3CN (2 mL), then the reaction mixture was stirred at room temperature for 1 h. The solvent was removed under vacuum and the residue was partitioned between water and DCM. The organic layer was washed with brine, dried over Na_2SO_4 , concentrated under vacuum. The residue was
15 purified by *prep*-HPLC to afford the desired product (0.34 g, 72%) as a white solid. ^1H NMR ($\text{DMSO}-d_6$) δ 10.20 (s, 1H), 7.70 (d, 1H, $J=8$ Hz), 7.30 (t, 1H, $J=7.6$ Hz), 7.13 (t, 1H, $J=7.6$ Hz), 7.07 (s, 5H), 6.66 (s, 2H), 6.54-6.47 (dd, 1H, $J=10.4$ Hz), 6.35 (s, 2H), 6.28-6.32 (dd, 1H, $J=1.6$ Hz), 5.77-5.80 (dd, 1H, $J=1.6$ Hz), 5.13 (s, 2H), 3.42 (m, 1H), 2.77-3.04 (m, 4H), 2.13-2.16 (m, 1H) and 1.69-1.73 (m, 1H). MS (ESI) m/e $[\text{M}+1]^+$ 416. The separation conditions are shown
20 below: instrument: Gilson-281, column size: 21.2 $\times$ 150 5 μm Gemini-new, flow rate: 20 mL/min, UV: 214 nm. Method: 0.1% TFA in water, CH_3CN from 42 to 50, in 11 min, then from 50 to 90 in 3 min, 90 hold on 3 min, then balance 2 min. Total run time: 20 min. Single gradient method.

[0238] Compound **1.20** was separated into two enantiomeric stereoisomers compound **1.20a** (peak 1, R or S, earlier peak, retention time at 6.59 min in chiral analysis), and compound **1.20b** (peak 2, S or R, later peak, retention time at 10.46 min in chiral analysis) by chiral *prep*-HPLC.



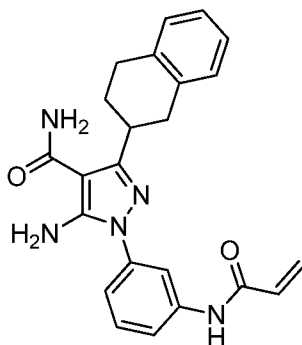
5 [0239] The chiral separation conditions are shown below.

Column	CHIRALPAK OJH
Column size	2 cm × 25 cm
Injection	2.1 mL
Mobile phase	CO ₂ /MeOH = 70/30
Flow rate	13 mL/min
Wave length	UV 254 nm
Temperature	35 °C
Sample solution	20 mg/mL in mobile phase
Prep-SFC equipment	BJ-DAICEL-SFC

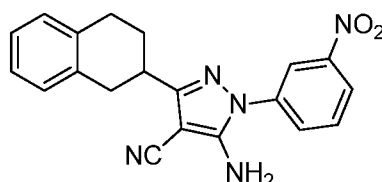
[0240] The chiral analysis conditions are shown below.

Column	CHIRALPAK AD-H
Column size	0.46 cm I.D. × 25 cm L
Injection	10 µL
Mobile phase	CO ₂ /MeOH = 60/40
Flow rate	2.0 mL/min
Wave length	UV 254 nm
Temperature	35 °C

Compound 1.21: 1-(3-acrylamidophenyl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



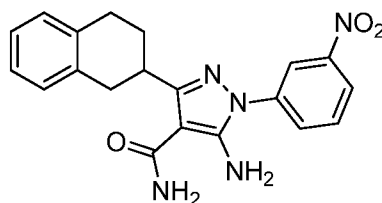
5 Step A: 5-Amino-1-(3-nitrophenyl)-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carbonitrile



[0241] To a solution of

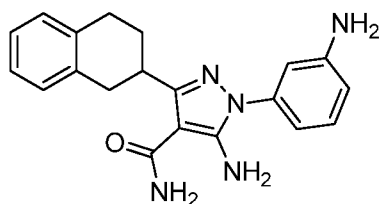
2-(methoxy(1,2,3,4-tetrahydronaphthalen-2-yl)methylene)malononitrile (the product of step E in
 10 synthesis of **Compound 1.14**, 10g, 42mmol) in EtOH (50 ml) was added (3-nitrophenyl)hydrazine
 hydrochloride(9.6 g, 50.4 mmol) and Et₃N(13g, 126mmol). The mixture was stirred at 90°C for 6h
 under N₂. After cooling to RT, the solvent was removed *in vacuo*. Then dissolved in H₂O (50 ml),
 extracted with EtOAc (50 ml × 3), dried over with Na₂SO₄, filtered and concentrated to give crude
 product which was further purified by chromatography column on silica (200g), eluting with
 15 EtOAc:PE:Et₃N=1:4:0.001 to give the product(2.8g, 19%) as a brown solid. MS (ESI) m/e
 [M+1]⁺360.

Step B: 5-Amino-1-(3-nitrophenyl)-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



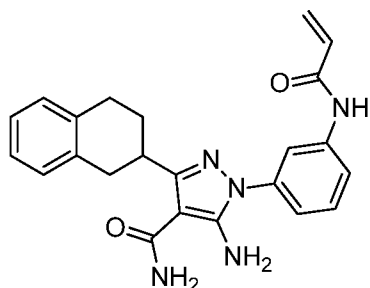
[0242] A solution of 5-amino-1-(3-nitrophenyl)-3-(1,2,3,4-tetrahydronaphthalen-2-yl)- 1H-pyrazole-4-carboxamide (2.8 g, 7.8 mmol) in MeSO₃H (50 ml) was stirred at 85°C for 40 mins under N₂. LC/MS showed the reaction was completed. Then mixture was poured into ice-water, basified by NaOH to pH=10 and extracted with EtOAc (100 ml × 3). The organic layer was dried over with Na₂SO₄, filtered and concentrated to give the product (2g, 69%) as brown oil, which was used next step without further purification. MS (ESI) m/e [M+1]⁺ 378.

Step C: 5-amino-1-(3-aminophenyl)-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



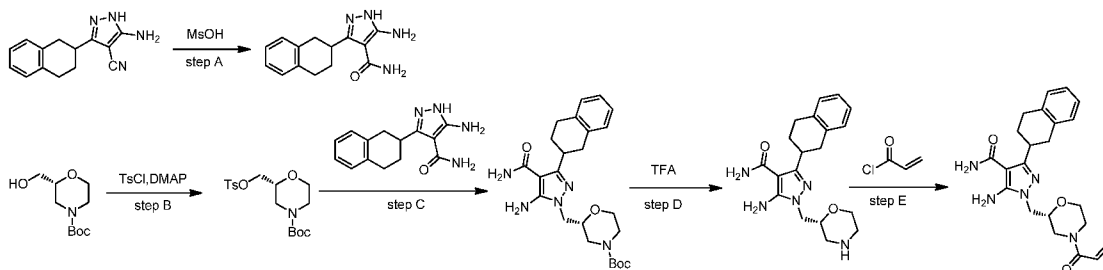
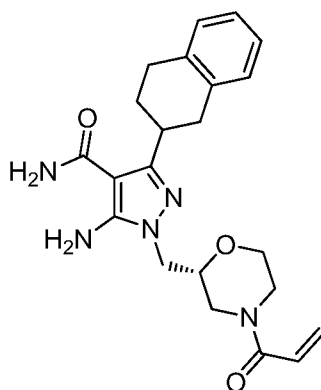
[0243] To a solution of 5-amino-1-(3-nitrophenyl)-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide (2g, 5.3 mmol) in EtOH (50 ml) and H₂O (10 ml) was added iron powder (1.5g, 26.5 mmol) and NH₄Cl (843 mg, 15.9 mmol). The mixture was stirred at 90°C for 1h. The solid was filtered and the filtrate was concentrated to give crude product. To the crude product extracted with H₂O (50 ml) and EtOAc (50 ml × 3). The organic layer was dried over with Na₂SO₄, filtered and concentrated to give the crude product (1.5g, 83%) as a brown solid, which was used next step without further purification. MS (ESI) m/e [M+1]⁺ 348.

Step D: 1-(3-acrylamidophenyl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide

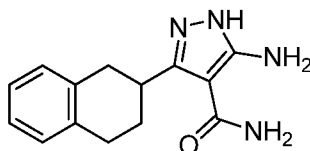


[0244] To a solution of 5-amino-1-(3-aminophenyl)-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide (1.5 g, 4.3 mmol) in CH₃CN(20 ml) and H₂O(5 ml) was added NaHCO₃(1.1 g, 12.9 mmol) and acryloyl chloride (391 mg, 4.3 mmol) at 0°C. The mixture was stirred for 10mins at 0°C and was quenched with water (20 mL), extracted with EtOAc (20 ml × 3). The organic layers were dried over with Na₂SO₄, filtered and concentrated to give the crude product which was further purified by *prep*-HPLC to give the product (781.02 mg, 45%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.37(s, 1H), 7.87-7.79 (m, 1H), 7.69-7.73 (m, 1H), 7.43-7.48 (m, 1H), 7.24-7.28 (m, 1H), 7.06-7.12 (m, 3H), 6.79 (s, 2H), 6.26-6.49 (m, 4H), 5.77-5.81(m, 1H), 3.43- 3.49 (m, 1H), 2.81-3.08 (m, 4H), 2.20 -2.24 (m, 1H) and 1.73-1.78 (m, 1H). MS (ESI) *m/e* [M+1]⁺402.

Compound 1.22: 1-(((R)-4-acryloylmorpholin-2-yl)methyl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide

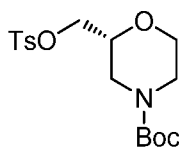


Step A: 5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



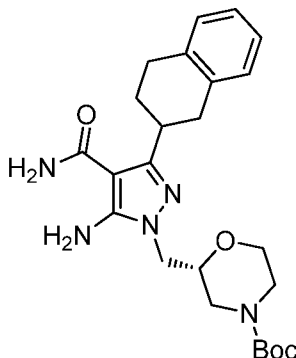
[0245] A solution of the product of step F in synthesis of **Compound 1.14** (2.3g, 8.8 mmol) in
5 MsOH (10 mL) was stirred at 70 °C for 6 hrs. The resulting solution was poured into water,
neutralized by 5N NaOH aqueous solution till pH = 8, then extracted with EA (50 mL x 3). The
combined organic layer was washed by brine, dried over anhydrous sodium sulfate then
concentrated to get the crude product (3.3 g) as a white solid. The solid was recrystallized by DCM
(10 mL) to get desired product (2.3 g, 100%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ
10 11.60 (br.s, 1H), 7.27 – 6.97 (m, 4H), 6.71 (br.s, 2H), 5.48 (br.s, 2H), 3.450-3.40 (m, 1H), 3.13 -
2.70 (m, 4H), 2.15-2.00 (m, 1H), 1.90-1.70 (m, 1H) ppm. MS: M/e 257 (M+1)⁺

Step B: (R)-tert-butyl 2-((tosyloxy)methyl)morpholine-4-carboxylate



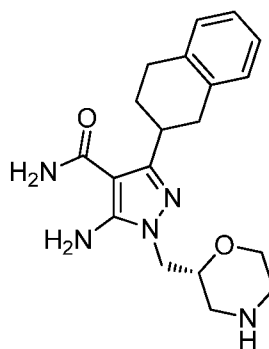
15 [0246] A mixture of the (R)-tert-butyl 2-(hydroxymethyl)morpholine-4-carboxylate (2.0 g,
9.21 mmol), DMAP (114 mg, 0.92 mmol), Tosyl chloride (TsCl, 1.93 g, 10.13 mmol) and Et₃N
(2.65 mL, 18.42 mmol) in DCM (20 mL) was stirred at rt for 2 h. The resulting solution was
washed by water, extracted with DCM (10 mL x 3). The combined organic layer was washed by
brine, dried over anhydrous sodium sulfate then concentrated and purified by silica gel column
20 chromatography eluting with PE:EA=2:1 to get the desired product (2.62g, 77%) as a white solid.
¹H NMR (400 MHz, CDCl₃) δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 4.10 – 3.94 (m,
2H), 3.94 – 3.72 (m, 3H), 3.65-3.55 (m, 1H), 3.53 – 3.38 (m, 1H), 3.01 – 2.80 (m, 1H), 2.69-2.61
(m, 1H), 2.45 (s, 3H), 1.45 (s, 9H) ppm. MS: M/e 372 (M+1)⁺

Step C: (2R)-tert-butyl 2-((5-amino-4-carbamoyl-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazol-1-yl)methyl)morpholine-4-carboxylate



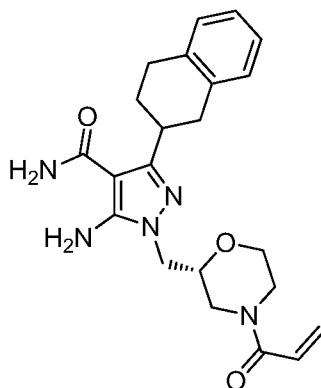
[0247] A mixture of the product of Step A (200 mg, 0.78 mmol), the product of Step B (348 mg, 0.94 mmol) and Cs_2CO_3 (509 mg, 1.56 mmol) in DMF (10 mL) was stirred at 70 °C for 4 h. The resulting solution was concentrated. The residue was washed by water, extracted with EA (10 mL x 3). The combined organic layer was washed by brine, dried over anhydrous sodium sulfate then concentrated and purified by silica gel column chromatography eluting with EA to get the desired product (219 mg, 62%) as yellow oil. MS: M/e 456 ($M+1$)⁺

Step D: 5-amino-1-((R)-morpholin-2-ylmethyl)-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



[0248] To the solution of the product of Step C (219 mg, 0.48 mmol) in DCM (2 mL) was added TFA (2 mL). The solution was stirred at rt for 1 h. The resulting solution was concentrated to get the crude product (171 mg, 100%) as yellow oil, which was used in next step directly. MS: M/e 356 ($M+1$)⁺

Step E: 1-(((R)-4-acryloylmorpholin-2-yl)methyl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide

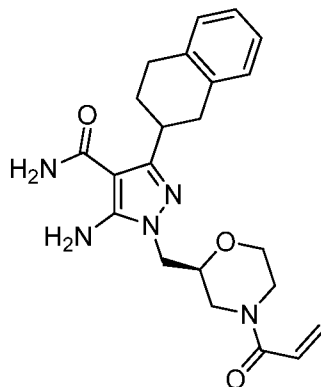


- 5 **[0249]** A mixture of the product of step D (171 mg, 0.48 mmol) and NaHCO₃ (242 mg, 32.88 mmol) in CH₃CN/H₂O (4 mL/4 mL) was stirred at 0 °C for 5 min. Acryloyl chloride (43 mg, 0.48 mmol) was added dropwise at 0 °C. The final solution was stirred at 0 °C for 5 min and quenched by water, then extracted with EA (10 mL x 3). The combined organic layer was washed by brine, dried over anhydrous sodium sulfate then concentrated and purified by silica gel column
- 10 chromatography eluting with DCM:MeOH=20:1 to get the desired product (51 mg, 26%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆, 80 °C) δ 7.10-7.00 (m, 4H), 6.66 (dd, *J* = 16.8, 10.6 Hz, 1H), 6.37 (s, 2H), 6.07 (dd, *J* = 16.8, 2.0 Hz, 1H), 5.94 (br.s, 2H), 5.64 (dd, *J* = 10.6, 2.0 Hz, 1H), 4.20-3.85 (m, 5H), 3.75-3.65 (m, 1H), 3.48 – 3.27 (m, 2H), 3.04 – 2.71 (m, 6H), 2.20-2.05 (m, 1H), 1.81-1.75 (m, 1H) ppm. MS: *M/e* 410 (*M*+1)⁺

15

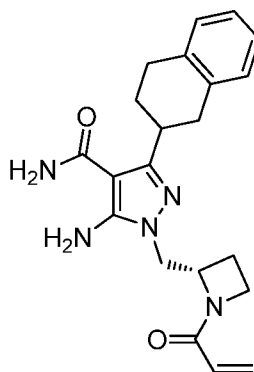
[0250] **Compounds 1.23-1.31** were prepared according to the procedures described for **Compound 1.22** under appropriate conditions that could be recognized by one skilled in the art.

Compound 1.23: 1-(((S)-4-acryloylmorpholin-2-yl)methyl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



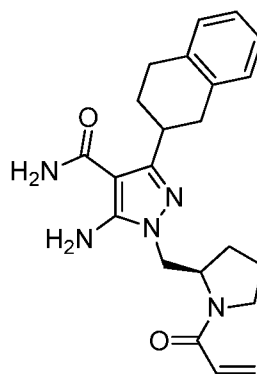
[0251] ^1H NMR (400 MHz, $\text{DMSO}-d_6$, 80 $^\circ\text{C}$) δ 7.12 – 6.99 (m, 4H), 6.66 (dd, J = 16.8, 10.6 Hz, 1H), 6.37 (s, 2H), 6.07 (dd, J = 16.8, 2.2 Hz, 1H), 5.93 (s, 2H), 5.64 (dd, J = 10.6, 2.2 Hz, 1H), 4.22 – 3.80 (m, 5H), 3.77 – 3.64 (m, 1H), 3.47 – 3.29 (m, 2H), 3.01 – 2.70 (m, 6H), 2.20 – 2.07 (m, 1H), 1.85 – 1.68 (m, 1H) ppm. MS: M/e 410 ($M+1$) $^+$

Compound 1.24: 1-(((S)-1-acryloylazetidin-2-yl)methyl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



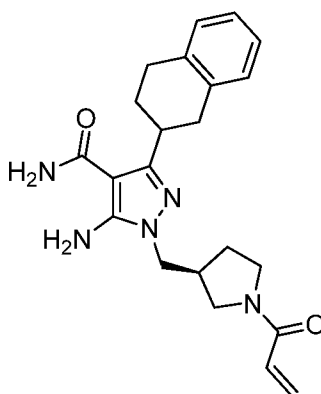
10 [0252] ^1H NMR (400 MHz, $\text{DMSO}-d_6$, 80 $^\circ\text{C}$) δ 7.15 – 6.93 (m, 4H), 6.37 (s, 2H), 6.17 – 5.79 (m, 4H), 5.69 – 5.41 (m, 1H), 4.81 – 4.52 (m, 1H), 4.37 – 4.12 (m, 2H), 4.05 – 3.69 (m, 2H), 3.47 – 3.24 (m, 1H), 3.02 – 2.70 (m, 4H), 2.41 – 2.21 (m, 1H), 2.19 – 1.95 (m, 2H), 1.87 – 1.64 (m, 1H) ppm. MS: M/e 380 ($M+1$) $^+$

15 **Compound 1.25:** 1-(((R)-1-acryloylpyrrolidin-2-yl)methyl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



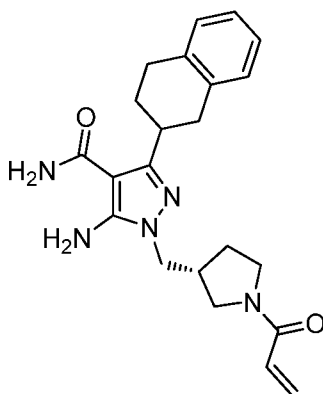
[0253] ^1H NMR (400 MHz, $\text{DMSO}-d_6$, 80°C) δ 7.17 – 6.93 (m, 4H), 6.66 – 6.42 (m, 1H), 6.35 (s, 2H), 6.16 (d, $J = 17.2$ Hz, 1H), 5.99 (s, 2H), 5.78 – 5.35 (m, 1H), 4.48 – 4.14 (m, 1H), 4.14 – 3.97 (m, 1H), 3.99 – 3.78 (m, 1H), 3.64 – 3.24 (m, 3H), 3.04 – 2.71 (m, 4H), 2.23 – 2.02 (m, 1H), 1.98 – 1.64 (m, 5H) ppm. MS: M/e 394 ($M+1$)⁺

Compound 1.26: 1-(((S)-1-acryloylpyrrolidin-3-yl)methyl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



[0254] ^1H NMR (400 MHz, $\text{DMSO}-d_6$, 80°C) δ 7.18 – 6.93 (m, 4H), 6.60 – 6.40 (m, 1H), 6.34 (s, 2H), 6.08 – 6.03 (m, 3H), 5.62 (d, $J = 10.0$ Hz, 1H), 3.95 – 3.79 (m, 2H), 3.67 – 3.08 (m, 5H), 3.04 – 2.52 (m, 5H), 2.21 – 2.05 (m, 1H), 2.01 – 1.40 (m, 3H) ppm. MS: M/e 394 ($M+1$)⁺

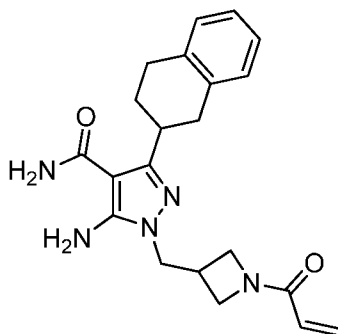
Compound 1.27: 1-(((R)-1-acryloylpyrrolidin-3-yl)methyl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



[0255] ^1H NMR (400 MHz, $\text{DMSO}-d_6$, 80°C) δ 7.18 – 6.93 (m, 4H), 6.60 – 6.40 (m, 1H), 6.34 (s, 2H), 6.10 – 6.03 (s, 2H), 5.60 (d, $J = 10.0$ Hz, 1H), 3.95 – 3.74 (m, 2H), 3.67 – 3.08 (m, 5H), 3.04 – 2.50 (m, 5H), 2.28 – 2.05 (m, 1H), 2.01 – 1.50 (m, 3H) ppm. MS: M/e 394 ($M+1$) $^+$

5

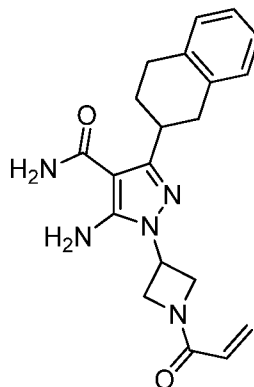
Compound 1.28: 1-((1-acryloylazetidin-3-yl)methyl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



[0256] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.15 – 6.98 (m, 4H), 6.35 (s, 2H), 6.29 – 6.16 (m, 1H), 6.13 – 5.97 (m, 3H), 5.60 (d, $J = 10.4$ Hz, 1H), 4.31 – 3.63 (m, 6H), 3.42 – 3.27 (m, 1H), 3.05 – 2.68 (m, 5H), 2.17 – 2.03 (m, 1H), 1.86 – 1.67 (m, 1H) ppm. MS: M/e 380 ($M+1$) $^+$

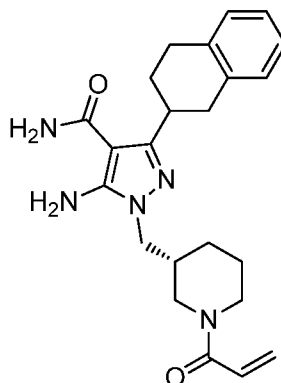
10

Compound 1.29: 1-(1-acryloylazetidin-3-yl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



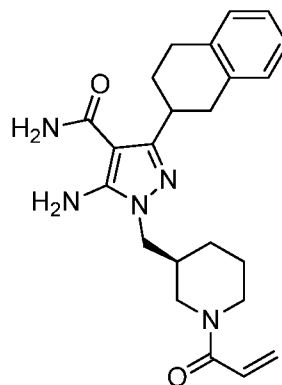
[0257] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.20 – 6.99 (m, 4H), 6.72 (s, 2H), 6.47 – 6.31 (m, 1H), 6.26 (s, 2H), 6.13 (d, $J = 16.8$ Hz, 1H), 5.69 (d, $J = 10.4$ Hz, 1H), 5.25 – 5.06 (m, 1H), 4.59–4.55 (m, 1H), 4.50–4.40 (m, 1H), 4.37 – 4.12 (m, 2H), 3.50 – 3.35 (m, 1H), 3.11 – 2.68 (m, 4H), 2.25 – 2.07 (m, 1H), 1.86 – 1.62 (m, 1H) ppm. MS: M/e 366 ($M+1$)⁺

Compound 1.30: 1-(((R)-1-acryloylpiperidin-3-yl)methyl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



[0258] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.07 (s, 4H), 6.85 – 6.51 (m, 3H), 6.20 (s, 2H), 6.10 – 5.98 (m, 1H), 5.60 (dd, $J = 27.6, 10.0$ Hz, 1H), 4.29 – 4.02 (m, 1H), 3.95 – 3.72 (m, 3H), 3.47 – 3.35 (m, 2H), 3.04 – 2.73 (m, 5H), 2.13 (d, $J = 11.8$ Hz, 1H), 2.00 – 1.59 (m, 4H), 1.40 – 1.08 (m, 2H) ppm. MS: M/e 408 ($M+1$)⁺

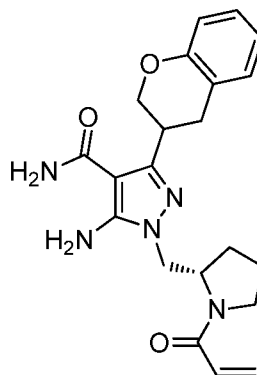
Compound 1.31: 1-(((S)-1-acryloylpiperidin-3-yl)methyl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



[0259] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.07 (s, 4H), 6.89 – 6.47 (m, 3H), 6.20 (s, 2H), 6.03 (d, $J = 16.4$ Hz, 1H), 5.60 (dd, $J = 27.6, 10.8$ Hz, 1H), 4.30 – 4.02 (m, 1H), 3.95 – 3.68 (m, 3H), 3.45 – 3.34 (m, 2H), 3.06 – 2.72 (m, 5H), 2.17-2.07 (m, 1H), 1.99 – 1.56 (m, 4H), 1.39 – 1.08 (m, 2H) ppm. MS: M/e 408 ($M+1$)⁺

Compound 1.32: 1-(((S)-1-acryloylpyrrolidin-2-yl)methyl)-5-amino-3-(chroman-3-yl)-1H-pyrazole-4-carboxamide

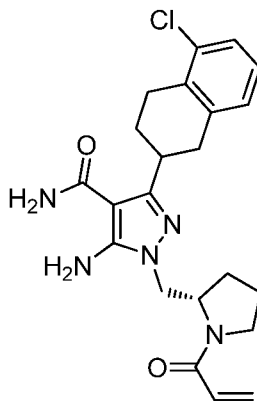
[0260] **Compound 1.32** was prepared according to the procedures described for **Compound 1.19** under appropriate conditions that could be recognized by one skilled in the art.



[0261] ^1H NMR (400 MHz, $\text{DMSO}-d_6$, 80°C) δ 7.05-7.08 (m, 2H), 6.74-6.83 (m, 2H), 6.48-6.50 (m, 3H), 5.96-6.18 (m, 3H), 5.48-5.68 (m, 1H), 4.37-4.41 (m, 1H), 3.90-4.21 (m, 4H), 3.47-3.66 (m, 3H), 2.98-3.02 (m, 2H), 1.81-1.82 (m, 4H). MS (ESI) m/e [$M+1$]⁺ 396.

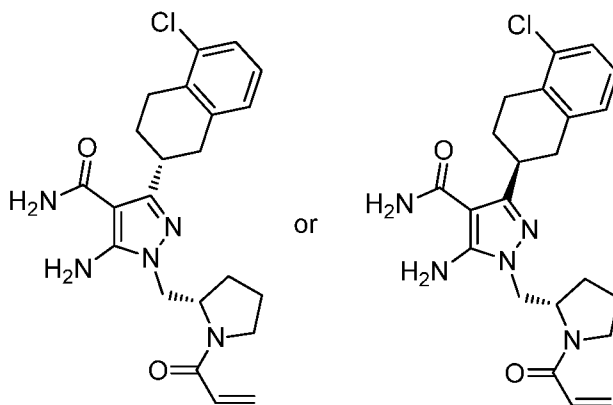
Compound 1.33: 1-(((S)-1-acryloylpyrrolidin-2-yl)methyl)-5-amino-3-(8-chloro-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide

[0262] **Compound 1.33** was prepared according to the procedures described for **Compound 1.10** under appropriate conditions that could be recognized by one skilled in the art.



[0263] ^1H NMR (400 MHz, $\text{DMSO}-d_6$, 80 °C) δ 7.19-7.21 (dd, $J=2.0$ Hz, 1H), 7.05-7.12 (m, 2H), 6.25-6.61 (m, 3H), 6.07-6.14 (m, 1H), 5.99 (s, 2H), 5.44-5.67 (m, 1H), 4.16-4.36 (m, 1H), 3.85-4.08 (m, 2H), 3.31-3.47 (m, 3H), 2.97-3.05 (m, 2H), 2.85-2.90 (m, 1H), 2.75-2.80 (m, 1H), 2.17-2.20 (m, 1H), 1.74-1.86 (m, 5H). MS (ESI) m/e $[\text{M}+1]^+$ 428.

[0264] **Compound 1.33** was separated into two enantiomeric stereoisomers compound **1.33a** (peak 1, R or S, earlier peak, retention time at 4.68 min in chiral analysis), and compound **1.33b** (peak 2, S or R, later peak, retention time at 5.30 min in chiral analysis) by chiral *prep*-HPLC.



[0265] The separation conditions are shown below:

Column	CHIRALPAK OJH
Column size	3 cm $\times$ 25 cm
Injection	3 mL

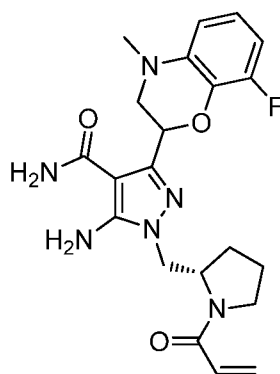
Mobile phase	CO ₂ /MeOH = 84/16
Flow rate	60 mL/min
Wave length	UV 220 nm
Temperature	35 °C
Sample solution	4 mg/mL in mobile phase
Prep-SFC equipment	BJ-DAICEL-SFC

[0266] The chiral analysis conditions are shown below.

Column	CHIRALPAK AD-H
Column size	0.46 cm I.D. × 25 cm L
Injection	10 uL
Mobile phase	CO ₂ /MeOH = 80/20
Flow rate	2.0 mL/min
Wave length	UV 220 nm
Temperature	35 °C

5 **[0267]** **Compounds 1.34 -1.36** were prepared according to the procedures described for **Compound 1.7** under appropriate conditions that could be recognized by one skilled in the art.

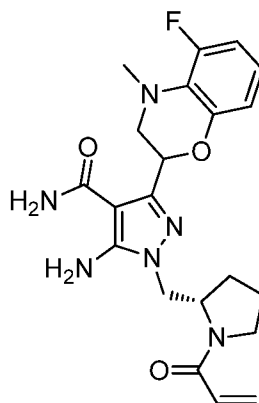
Compound 1.34



[0268] ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.90 (br.s, 2H), 6.83 – 6.76 (m, 1H), 6.64 – 6.48 (m, 4H), 6.30– 6.16 (m, 2H), 5.75 – 5.71 (m, 1H), 5.35 – 5.31 (m, 1H), 4.26 – 4.20 (m, 1H), 4.11 – 4.05

(m, 1H), 3.97 – 3.92 (m, 1H), 3.70 – 3.38 (m, 4H), 2.96 – 2.91 (m, 3H), 1.96 – 1.75 (m, 4H)ppm. MS: M/e 429 (M+1)⁺

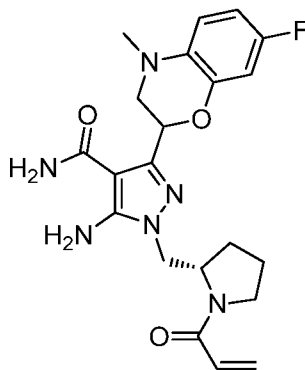
Compound 1.35



5

[0269] ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.90- 6.56 (m, 7H), 6.31 – 6.16 (m, 2H), 5.75– 5.71 (m, 1H), 5.20 – 5.16 (m, 1H), 4.28 – 4.18 (m, 1H), 4.12 – 3.90 (m, 2H), 3.65 – 3.28 (m, 4H), 2.91 (s, 3H), 2.01 – 1.75 (m, 4H)ppm. MS: M/e 429 (M+1)⁺

10 Compound 1.36

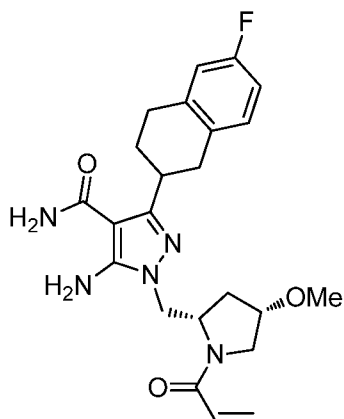


[0270] ¹H NMR (400 MHz, DMSO-*d*₆, 80°C) δ 6.80 – 5.89 (m, 9H), 5.80 – 5.40 (s, 1H), 5.34 (dd, *J* = 8.0, 2.8 Hz, 1H), 4.50 – 3.80 (m, 3H), 3.65 – 3.30 (m, 4H), 2.87 (s, 3H), 1.95 – 1.75 (m, 4H), ppm. MS: M/e 429 (M+1)⁺.

15

[0271] **Compounds 1.37 -1.45** were prepared according to the procedures described for **Compound 1.10** under appropriate conditions that could be recognized by one skilled in the art.

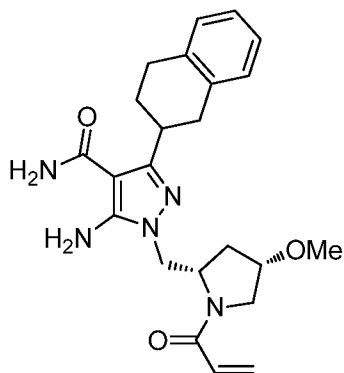
Compound 1.37



[0272] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.17 – 7.05 (m, 1H), 6.97 – 6.84 (m, 2H), 6.70 – 6.54 (m, 3H), 6.27 – 5.95 (m, 3H), 5.79 – 5.41 (m, 1H), 4.42 – 3.87 (m, 4H), 3.84 – 3.75 -3.62 (m, 2H), 3.51 – 3.23 (m, 4H), 3.04 – 2.72 (m, 4H), 2.19 – 1.98 (m, 2H), 1.96 – 1.62 (m, 2H). MS: M/e 442

5 $(M+1)^+$

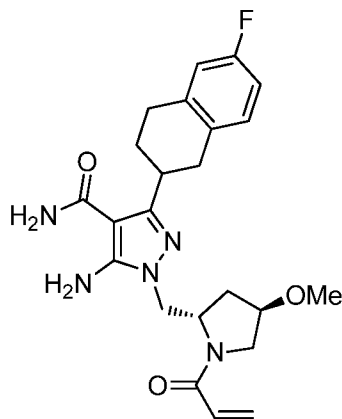
Compound 1.38



[0273] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.15 – 7.02 (m, , 4H), 6.71 – 6.53 (m, 2H), 6.28 – 5.98 (m, 3H), 5.79 – 5.42 (m, 1H), 4.44 – 3.87 (m, 4H), 3.81 – 3.65 (m, 2H), 3.48 – 3.40 – 3.35 (m, 1H), 3.30 – 3.25 (m, 3H), 3.05 – 2.73 (m, 4H), 2.20 – 1.97 (m, 2H), 1.96 – 1.62 (m, 2H). MS: M/e 424

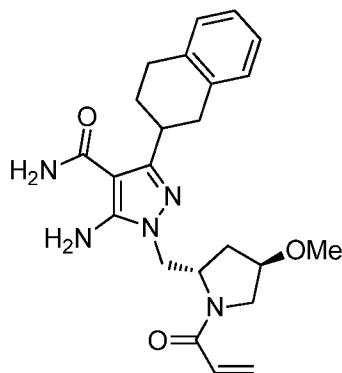
10 $(M+1)^+$

Compound 1.39



[0274] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.19 – 7.06 (m, 1H), 6.99 – 6.87 (m, 2H), 6.69 – 6.50 (m, 3H), 6.27 – 5.98 (m, 3H), 5.77 – 5.43 (m, 1H), 4.48 – 4.20 (m, 1H), 4.16 – 3.85 (m, 2H), 3.79 – 3.60 (m, 1H), 3.57 – 3.38 (m, 3H), 3.23 – 3.12 (m, 3H), 3.04 – 2.75 (m, 4H), 2.14 – 2.04 (m, 1H),
 5 1.98 – 1.90 (m, 1H), 1.90 – 1.63 (m, 2H). MS: M/e 442 ($M+1$) $^+$

Compound 1.40

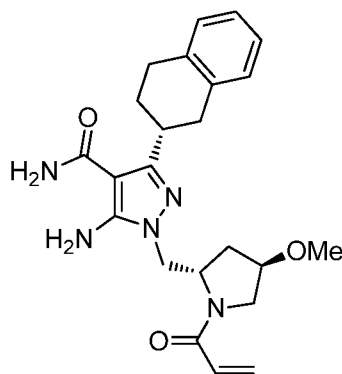


[0275] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.07 (s, 4H), 6.74 – 6.45 (m, 3H), 6.25 – 5.98 (m, 3H),
 10 5.78 – 5.41 (m, 1H), 4.52 – 4.22 (m, 1H), 4.15 – 3.85 (m, 2H), 3.79 – 3.60 (m, 1H), 3.58 – 3.36 (m, 3H), 3.22 – 3.14 (m, 3H), 3.06 – 2.74 (m, 4H), 2.17 – 2.03 (m, 1H), 2.01 – 1.82 (m, 2H), 1.78 – 1.63 (m, 1H). MS: M/e 424 ($M+1$) $^+$

Compound 1.40a: 1-(((2S,4R)-1-acryloyl-4-methoxypyrrolidin-2-yl)methyl)-5-amino

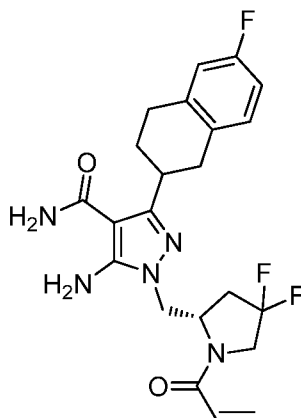
15 -3-((R)-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide

[0276] **Compound 1.40a** was prepared according to the procedures described for chiral synthesis of **Compound 1.14a** under appropriate conditions that could be recognized by one skilled in the art.



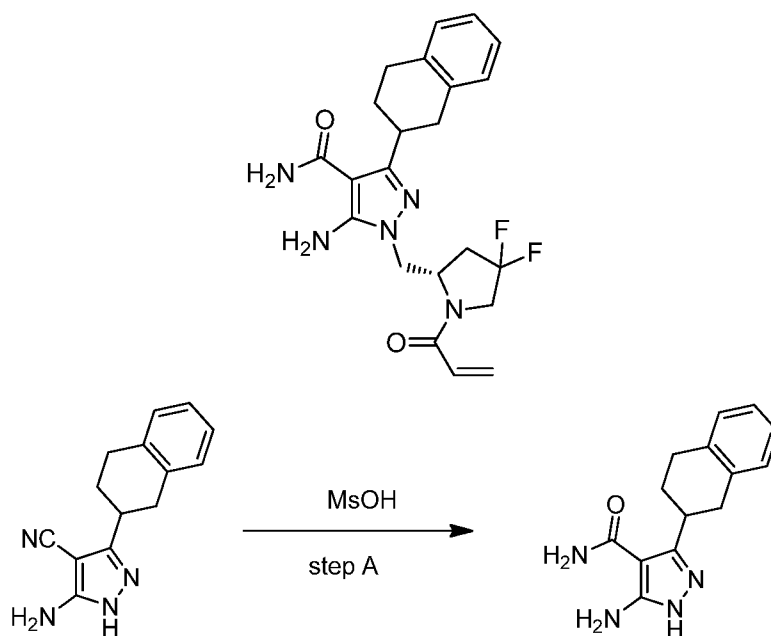
[0277] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.07 (s, 4H), 6.66 – 6.49 (m, 3H), 6.25 – 5.98 (m, 3H), 5.75 – 5.43 (m, 1H), 4.48 – 4.21 (m, 1H), 4.13 – 3.85 (m, 2H), 3.80 – 3.60 (m, 1H), 3.58 – 3.35 (m, 3H), 3.22 – 3.14 (m, 3H), 3.06 – 2.74 (m, 4H), 2.16 – 2.04 (m, 1H), 2.02 – 1.83 (m, 2H), 1.78 – 1.66 (m, 1H). MS: M/e 424($M+1$)⁺

Compound 1.41

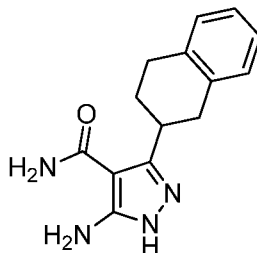


[0278] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.09 (d, J = 6.0 Hz, 1H), 6.95 – 6.75 (m, 2H), 6.60 – 6.25 (m, 3H), 6.25 – 6.04 (m, 1H), 5.90 (s, 2H), 5.79 – 5.43 (m, 1H), 4.76 – 4.40 (m, 1H), 4.23 – 3.95 (m, 3H), 3.78 (s, 1H), 3.46 – 3.23 (m, 1H), 3.02 – 2.54 (m, 5H), 2.47 – 2.29 (m, 1H), 2.18 – 1.99 (m, 1H), 1.86 – 1.65 (m, 1H) ppm. MS: M/e 448 ($M+1$)⁺

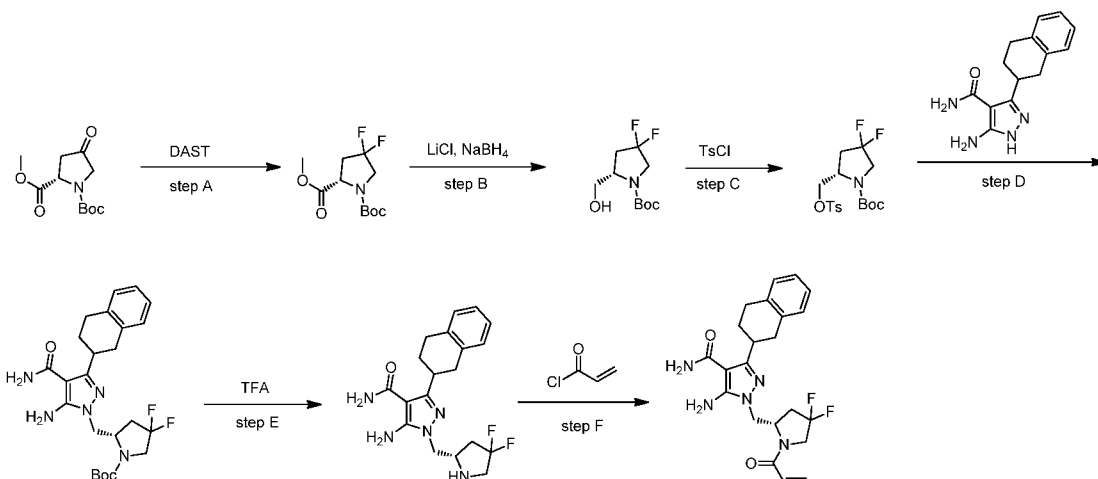
Compound 1.42: 1-(((S)-1-acryloyl-4,4-difluoropyrrolidin-2-yl)methyl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



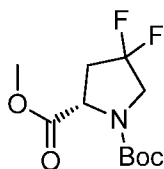
5 Step A: 5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



[0279] A solution of 5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carbonitrile (2.1 g, 8.8 mmol) in methanesulfonic acid (10 mL) was stirred at 70 °C for 4 hrs. The resulting solution was poured into water, neutralized by 5N NaOH aqueous solution till pH = 8, then extracted with EA (50 mL x 3). The combined organic layers were dried over sodium sulfate anhydrous and concentrated to get 3.3 g white solid, which was recrystallized by DCM to get desired product (2.3g, 99%) as a white solid. MS: M/e 257 (M+1)⁺

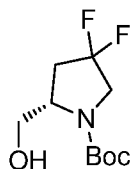


Step A: (S)-1-tert-butyl 2-methyl 4,4-difluoropyrrolidine-1,2-dicarboxylate



- 5 **[0280]** To a stirred solution of (S)-1-tert-butyl 2-methyl 4,4-difluoropyrrolidine-1,2-dicarboxylate (5 g, 20.55 mmol) in dry DCM (100 mL) at -78°C was added diethylaminosulfur trifluoride (DAST, 8.5 mL, 61.66 mol) dropwise over a period of 30 minutes under nitrogen atmosphere. The reaction mixture was stirred at this temperature for 1 h then at room temperature for 16 h. The reaction mixture was poured into the mixture of crushed ice and saturated NaHCO_3 aqueous solution till pH = 8. The two layers were separated and the aqueous layer was extracted with DCM (20 mL $\times$ 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 then concentrated to get crude product (4.7 g, yellow oil) which was used in next step directly. MS: M/e 210 ($M-55$) $^{+}$.

- 15 **Step B:** (S)-tert-butyl 4,4-difluoro-2-(hydroxymethyl)pyrrolidine-1-carboxylate

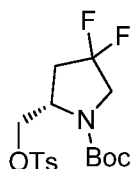


- [0281]** To the solution of the product of Step A (4.7 g, 17.72 mmol) in THF (20 mL) was added NaBH_4 (1.88 g, 44.30 mmol) followed by LiCl (1.48 g, 38.98 mmol). The mixture solution was cooled to 0°C , EtOH (30 mL) was added dropwise. The final solution was stirred at rt for 15 hrs.

And then the solution was cooled to 0 °C, neutralized by 4N HCl till pH = 4, then concentrated. The residue was washed by water, extracted with DCM (50 mL×3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated to get crude product (3.7 g, 88%) as yellow oil, which was used in next step directly. MS: M/e 182 (M-55)⁺.

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Step C: (S)-tert-butyl 4,4-difluoro-2-((tosyloxy)methyl)pyrrolidine-1-carboxylate

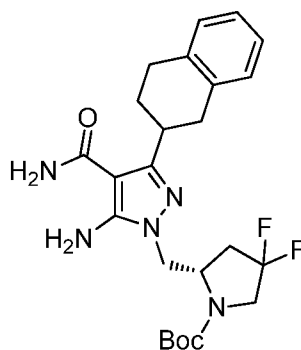


[0282] A mixture of the product of Step B (3.7 g, 15.6 mmol), TsCl (3.27 g, 17.2 mmol), DMAP (193 mg, 1.56 mmol) and Et₃N (4.5 mL, 31.2 mmol) in DCM (15 mL) was stirred at RT for 4 hrs.

10 The resulting solution was washed by water, extracted with DCM (20 mL×3). The combined organic layers were dried over Na₂SO₄, concentrated and purified by silica gel column chromatography eluting with PE:EA=5:1 to get the desired product (5.2 g, 85%) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.77 (d, *J* = 7.8 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 2H), 4.33 – 3.92 (m, 3H), 3.89 – 3.67 (m, 1H), 3.64 – 3.41 (m, 1H), 2.58 – 2.24 (m, 5H), 1.47 (s, 9H) ppm. MS: M/e 292

15 (M-100+1)⁺

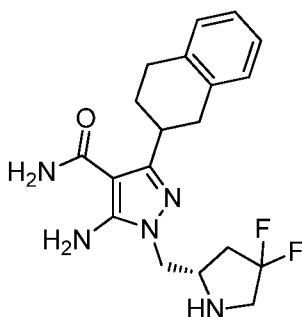
Step D: (2S)-tert-butyl 2-((5-amino-4-carbamoyl-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazol-1-yl)methyl)-4,4-difluoropyrrolidine-1-carboxylate



20 [0283] A mixture of the product of Step C (4.58 g, 11.7 mmol), 5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide (2.0 g, 7.8 mmol) and Cs₂CO₃ (5.08 g, 15.6 mmol) in DMF (20 mL) was stirred at 70 °C for 15 hrs. The resulting solution was

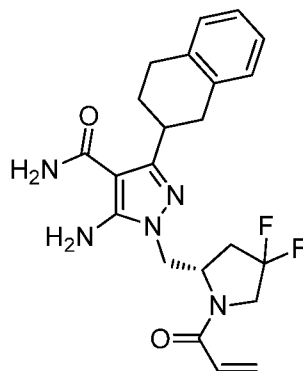
concentrated. The residue was washed by water, extracted with EA (20 mL x 3). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated and purified by silica gel column chromatography eluting with EA to get the desired product (1.8 g, 49%) as yellow oil. ^1H NMR (400 MHz, DMSO- d_6) δ 7.17 – 6.98 (m, 4H), 6.61 (s, 2H), 6.10 (s, 2H), 4.41 – 4.18 (m, 1H), 4.13 – 3.95 (m, 2H), 3.89 – 3.65 (m, 1H), 3.55 – 3.34 (m, 2H), 3.09 – 2.70 (m, 4H), 2.43 – 2.24 (m, 1H), 2.20 – 2.05 (m, 1H), 1.81 – 1.59 (m, 1H), 1.40 (s, 9H) ppm. MS: M/e 476(M+1)⁺

Step E: 5-amino-1-(((S)-4,4-difluoropyrrolidin-2-yl)methyl)-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



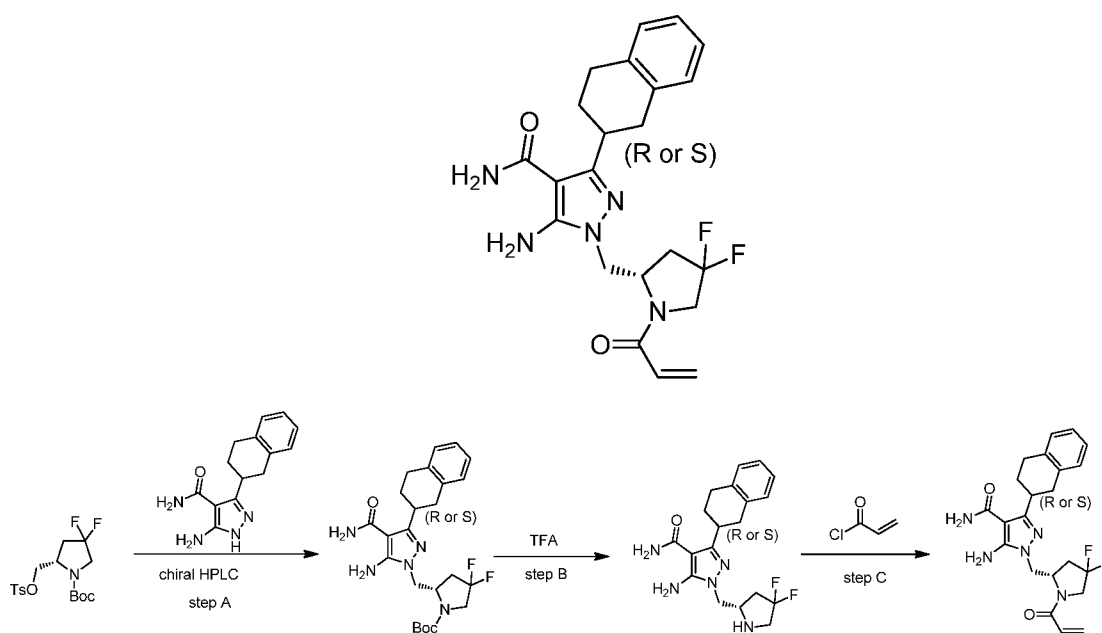
[0284] To the solution of the product of step D (414 mg, 0.87 mmol) in DCM (3 mL) was added TFA (2 mL). The solution was stirred at rt for 1 h. The resulting solution was concentrated to get the crude product (326 mg, 100%) as yellow oil, which was used in next step directly. MS: M/e 376 (M+1)⁺

Step F: 1-(((S)-1-acryloyl-4,4-difluoropyrrolidin-2-yl)methyl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide

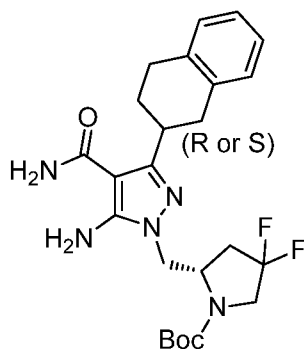


[0285] A mixture of the product of step E (326 mg, 0.86 mmol) and NaHCO₃ (289 mg, 3.44 mmol) in CH₃CN/H₂O (8 mL/8 mL) was stirred at 0 °C for 5 min. Acryloyl chloride (78 mg, 0.86 mmol) in CH₃CN (1 mL) was added dropwise at 0 °C. The final solution was stirred at 0 °C for 5 min and quenched by water, then extracted with EA (20 mL x 3). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated and purified by silica gel column chromatography eluting with PE/EA = 1/1 to get the desired product (200 mg, 54%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.17 – 6.89 (m, 4H), 6.52 – 6.27 (m, 3H), 6.25 – 6.04 (m, 1H), 5.95 (s, 2H), 5.78 – 5.46 (m, 1H), 4.71 – 4.41 (m, 1H), 4.24 – 3.91 (m, 3H), 3.89 – 3.62 (m, 1H), 3.44 – 3.23 (m, 1H), 3.01 – 2.70 (m, 4H), 2.70 – 2.52 (m, 1H), 2.44 – 2.28 (m, 1H), 2.21 – 2.01 (m, 1H), 1.87 – 1.65 (m, 1H) ppm. MS: M/e 430 (M+1)⁺

Compound 1.42a or 1.42b: (*R or S*) 1-(((*S*)-1-acryloyl-4,4-difluoropyrrolidin -2-yl)methyl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4- carbox amide



Step A: (*R or S*) (2*S*)-tert-butyl 2-((5-amino-4-carbamoyl-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazol-1-yl)methyl)-4,4-difluoropyrrolidine-1-carboxylate

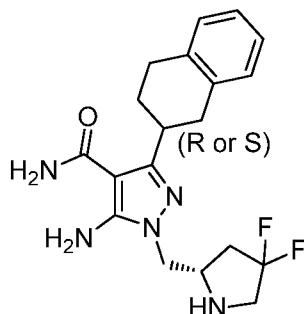


[0286] A mixture of the (S)-tert-butyl 4,4-difluoro-2-((tosyloxy)methyl)pyrrolidine-1-carboxylate (4.58 g, 11.7 mmol), 5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide (2.0 g, 7.8 mmol) and Cs₂CO₃ (5.08 g, 15.6 mmol) in DMF (20 mL) was stirred at 70 °C for 15 hrs. The resulting solution was concentrated. The residue was washed by water, extracted with EA (20 mL x 3). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated and purified by silica gel column chromatography eluting with EA to get the desired product (1.4 g, 38%) as yellow oil, which was separated by chiral HPLC to give **peak 1** (600 mg, earlier peak) and **peak 2** (600 mg, later peak).

[0287] The chiral separation conditions are shown below:

Column	CHIRALPAK IC
Column size	0.46 cm I.D. × 15 cm L
Injection	10ul
Mobile phase	MeOH=100
Flow rate	0.5 ml/min
Wave length	UV 220nm
Temperature	30 °C

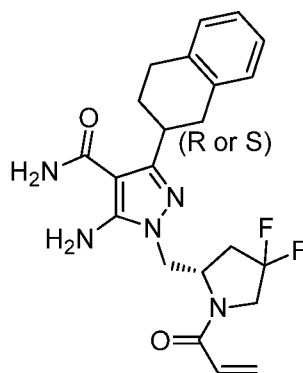
Step B: (*R or S*) 5-amino-1-(((S)-4,4-difluoropyrrolidin-2-yl)methyl)-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



[0288] To the solution of the product of Step A (600 mg, 1.26 mmol) in DCM (5 mL) was added TFA (5 mL). The solution was stirred at rt for 1 h. The resulting solution was concentrated to get the crude product (473 mg, 100%) as yellow oil, which was used in next step directly. MS: M/e 376 (M+1)⁺

5

Step C: (*R or S*) 1-(((*S*)-1-acryloyl-4,4-difluoropyrrolidin-2-yl)methyl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide

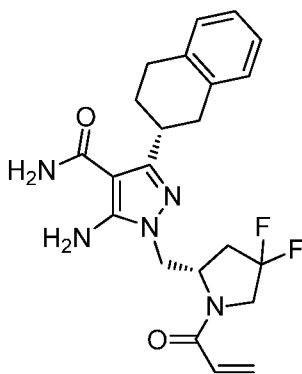


[0289] A mixture of the product of Step B (473 mg, 1.26 mmol) and NaHCO₃ (423 mg, 5.04 mmol) in CH₃CN/H₂O (12 mL/12 mL) was stirred at 0 °C for 5 min. Acryloyl chloride (113 mg, 1.26 mmol) in CH₃CN (1 mL) was added drop wise at 0 °C. The final solution was stirred at 0 °C for 5 min and quenched by water, then extracted with EA (10 mL x 3). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated and purified by silica gel column chromatography eluting with PE/EA = 1/1 to get the desired product (372 mg, 69%) as a white solid. Peak 1(**Compound 1.42a**, retention time: 5.391 min): ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.18 – 6.96 (m, 4H), 6.58 – 6.27 (m, 3H), 6.26 – 6.07 (m, 1H), 5.97 (s, 2H), 5.82 – 5.46 (m, 1H), 4.73 – 4.44 (m, 1H), 4.22 – 3.96 (m, 3H), 3.90 – 3.64 (m, 1H), 3.47 – 3.25 (m, 1H), 3.00 – 2.73 (m, 4H), 2.68 – 2.54 (m, 1H), 2.45 – 2.35 (m, 1H), 2.19 – 2.01 (m, 1H), 1.86 – 1.67 (m, 1H) ppm. MS: M/e 430 (M+1)⁺ ee: 100%. Peak 2(**Compound 1.42b**, retention time: 6.044 min): ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.20 – 6.93 (m, 4H), 6.55 – 6.29 (m, 3H), 6.25 – 6.05 (m, 1H), 5.97 (s, 2H), 5.76 – 5.31 (m, 1H), 4.80 – 4.38 (m, 1H), 4.23 – 3.92 (m, 3H), 3.91 – 3.61 (m, 1H), 3.47 – 3.22 (m, 1H), 3.01 – 2.70 (m, 4H), 2.64 – 2.53 (m, 1H), 2.43 – 2.27 (m, 1H), 2.23 – 2.00 (m, 1H), 1.91 – 1.67 (m, 1H) ppm. MS: M/e 430 (M+1)⁺ . ee: 100%.

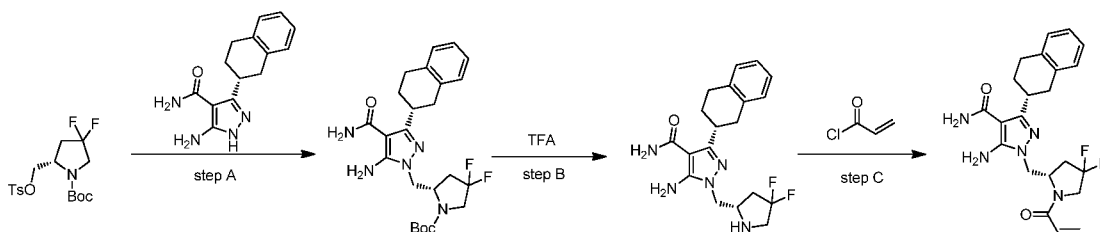
[0290] The chiral analysis conditions are shown below.

Column	CHIRALPAK As-H
Column size	0.46 cm I.D. ×15 cm L
Injection	1.5 ul
Mobile phase	n-Hex :EtOH(0.1% TEA OH ⁺) = 95 :5
Flow rate	1 ml/min
Wave length	UV 254nm, UV 280nm
Temperature	35 °C

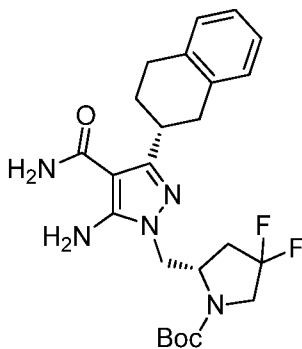
Compound 1.42a: 1-(((S)-1-acryloyl-4,4-difluoropyrrolidin-2-yl)methyl)-5-amino-3-((R)-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



5



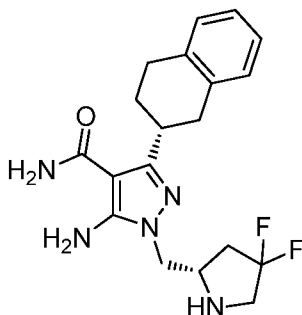
Step A: (S)-tert-butyl 2-(((5-amino-4-carbamoyl-3-((R)-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazol-1-yl)methyl)-4,4-difluoropyrrolidine-1-carboxylate



10

[0291] A mixture of (S)-tert-butyl 4,4-difluoro-2-((tosyloxy)methyl)pyrrolidine -1-carboxylate (229 mg, 0.58 mmol), (R)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide (100 mg, 0.39 mmol) and Cs₂CO₃ (254 mg, 0.78 mmol) in DMF (10 mL) was stirred at 70 °C for 15 hrs. The resulting solution was concentrated. The residue was washed by water, extracted with EA (20 mL x 3). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated and purified by silica gel column chromatography eluting with EA to get the desired product (100 mg, 54%) as yellow oil. MS: M/e 476 (M+1)⁺

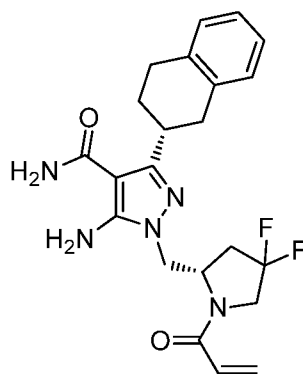
10 Step **B:** 5-amino-1-(((S)-4,4-difluoropyrrolidin-2-yl)methyl)-3-((R)-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



[0292] To the solution of the product of Step A (100 mg, 0.21 mmol) in DCM (2 mL) was added TFA (2 mL). The solution was stirred at rt for 1 h. The resulting solution was concentrated to get the crude product (79 mg, 100%) as yellow oil, which was used in next step directly. MS: M/e 376 (M+1)⁺

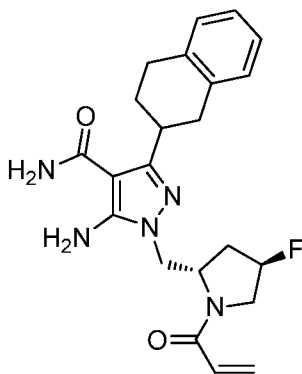
15

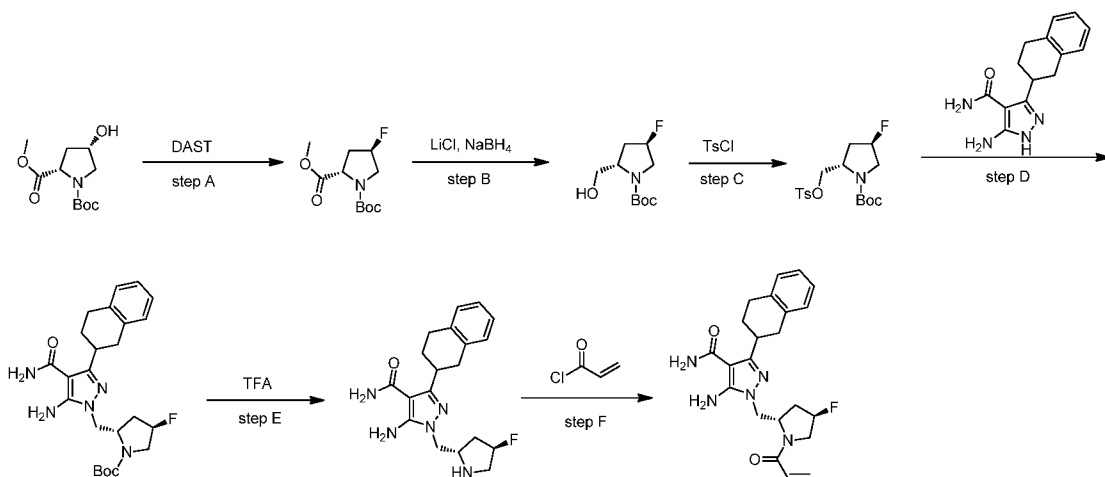
Step **C:** 1-(((S)-1-acryloyl-4,4-difluoropyrrolidin-2-yl)methyl)-5-amino-3-((R)-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



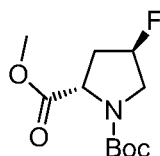
[0293] A mixture of the product of Step **B** (79 mg, 0.21 mmol) and NaHCO₃ (70 mg, 0.84 mmol) in CH₃CN/H₂O (2 mL/2 mL) was stirred at 0 °C for 5 min. Acryloyl chloride (19 mg, 0.21 mmol) was added drop wise at 0 °C. The final solution was stirred at 0 °C for 5 min and quenched
 5 by water, then extracted with EA (10 mL x 3). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated and purified by silica gel column chromatography eluting with PE/EA = 1/1 to get the desired product (45 mg, 50%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.18 – 6.96 (m, 4H), 6.58 – 6.27 (m, 3H), 6.26 – 6.07 (m, 1H), 5.97 (s, 2H), 5.82 – 5.46 (m, 1H), 4.73 – 4.44 (m, 1H), 4.22 – 3.96 (m, 3H), 3.90 – 3.64 (m,
 10 1H), 3.47 – 3.25 (m, 1H), 3.00 – 2.73 (m, 4H), 2.68 – 2.54 (m, 1H), 2.45 – 2.35 (m, 1H), 2.19 – 2.01 (m, 1H), 1.86 – 1.67 (m, 1H) ppm. MS: M/e 430 (M+1)⁺. ee: 100%.

Compound 1.43: 1-(((2S,4R)-1-acryloyl-4-fluoropyrrolidin-2-yl)methyl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



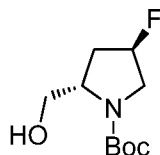


Step A: (2S,4R)-1-tert-butyl 2-methyl 4-fluoropyrrolidine-1,2-dicarboxylate



- 5 **[0294]** To a stirred solution of (2S,4S)-1-tert-butyl 2-methyl 4-hydroxypyrrolidine-1,2-dicarboxylate (10 g, 40.77 mmol) in dry DCM (100 mL) cooled to -78 °C was added diethylaminosulfur trifluoride (9.5 mL, 77.47 mol) dropwise over a period of 30 minutes. The reaction mixture was stirred at this temperature for 1 h then at room temperature for 16 h. The reaction mixture was poured into the mixture of crushed ice and saturated NaHCO₃ aqueous solution till pH = 8. The two layers were separated and the aqueous layer was extracted with DCM (50 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ then concentrated to get crude product (10 g, yellow oil) which was used in next step directly. MS: M/e 148 (M-100+1)⁺.

- 15 **Step B:** (2S,4R)-tert-butyl 4-fluoro-2-(hydroxymethyl)pyrrolidine-1-carboxylate

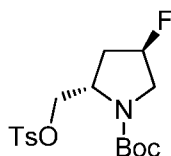


[0295] To the solution of the product of Step A (10 g, 40.44 mmol) in THF (100 mL) was added NaBH₄ (4.3 g, 101.10 mmol) followed by LiCl (3.3 g, 88.98 mmol). The mixture solution was cooled to 0 °C, EtOH (100 mL) was added dropwise. The final solution was stirred at rt for 15 hrs.

And then the solution was cooled to 0 °C, neutralized by 4N HCl till pH = 4, then concentrated. The residue was washed by water, extracted with DCM (50 mL×3). The combined organic layers were dried over anhydrous Na₂SO₄ was concentrated to get crude product (8.86 g, yellow oil) which was used in next step directly. MS: M/e 164 (M-55)⁺.

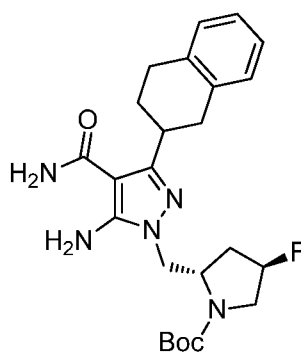
5

Step C: (2S,4R)-tert-butyl 4-fluoro-2-((tosyloxy) methyl)pyrrolidine-1-carboxylate



[0296] A mixture of the product of Step B (8.86 g, 40.44 mmol), TsCl (8.48 g, 44.50 mmol), DMAP (496 mg, 4 mmol) and Et₃N (8.7 mL, 60.67 mmol) in DCM (40 mL) was stirred at RT for 4 hrs. The resulting solution was washed by water, extracted with DCM (20 mL×3). The combined organic layers were dried over Na₂SO₄, concentrated and purified by silica gel column chromatography eluting with PE:EA=5:1 to get the desired product (6.0 g, 40% of three steps) as yellow oil. MS: M/e 274 (M-100+1)⁺

15 Step D: (2S,4R)-tert-butyl 2-((5-amino-4-carbamoyl-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazol-1-yl)methyl)-4-fluoropyrrolidine-1-carboxylate



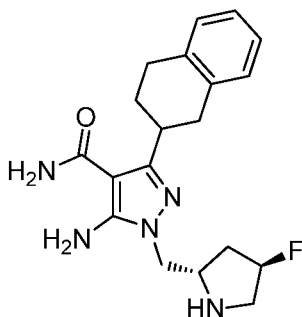
[0297] A mixture of the product of Step C (3.26 g, 8.74 mmol), 5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide (1.6 g, 6.24 mmol) and Cs₂CO₃ (4.0 g, 12.48 mmol) in DMF (20 mL) was stirred at 70 °C for 15 hrs. The resulting solution was concentrated. The residue was washed by water, extracted with EA (20 mL x 3). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated and

20

purified by silica gel column chromatography eluting with EA to get the desired product (800 mg, 28%) as yellow oil. MS: M/e 458 (M+1)⁺

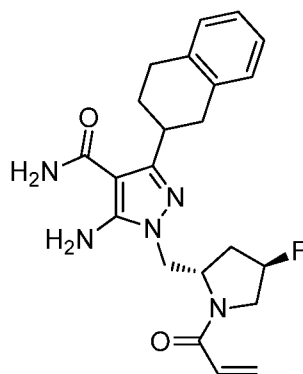
Step E: 5-amino-1-(((2S,4R)-4-fluoropyrrolidin-2-yl)methyl)-3-(1,2,3,4-tetrahydro

5 naphthalen-2-yl)-1H-pyrazole-4-carboxamide



[0298] To the solution of the product of step D (525 mg, 1.14 mmol) in DCM (3 mL) was added TFA (2 mL). The solution was stirred at rt for 1 h. The resulting solution was concentrated to get the crude product (410mg, 100%) as yellow oil, which was used in next step directly. MS: M/e 358 (M+1)⁺

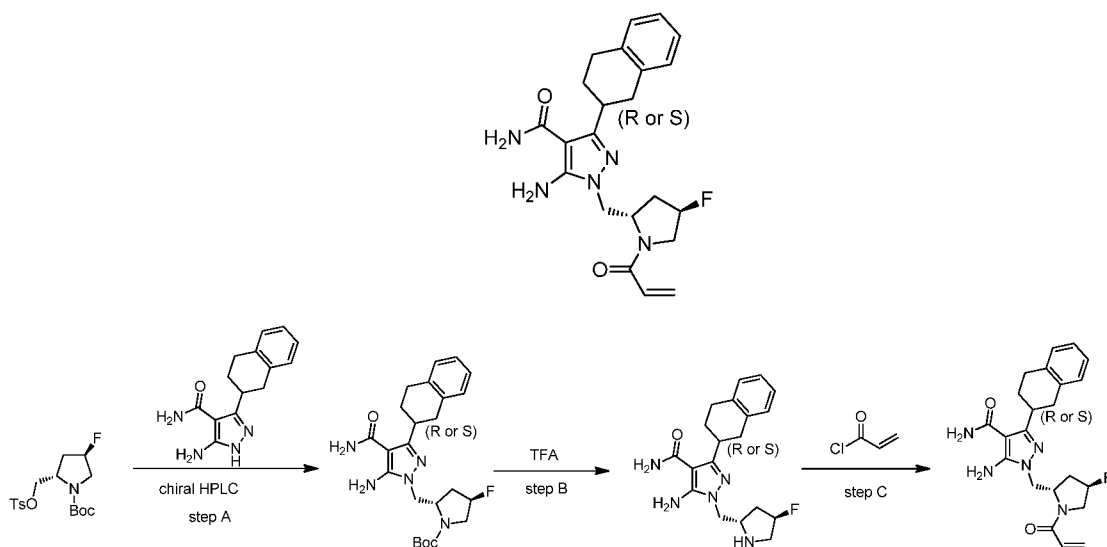
Step F: 1-(((2S,4R)-1-acryloyl-4-fluoropyrrolidin-2-yl)methyl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



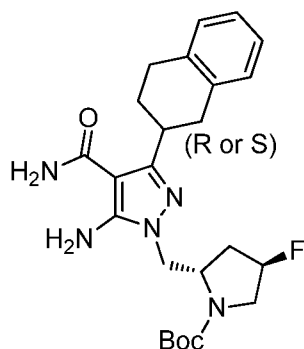
15 [0299] A mixture of the product of step E (410 mg, 1.15 mmol) and NaHCO₃ (386 mg, 4.6 mmol) in CH₃CN/H₂O (10 mL/10 mL) was stirred at 0 °C for 5 min. Acryloyl chloride (103 mg, 1.15 mmol) was added drop wise at 0 °C. The final solution was stirred at 0 °C for 5 min and quenched by water, then extracted with EA (20 mL x 3). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated and purified by silica gel column

chromatography eluting with PE/EA = 1/1 to get the desired product (240 mg, 51%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.13 – 6.98 (m, 4H), 6.60 – 6.42 (m, 1H), 6.36 (s, 2H), 6.25 – 6.04 (m, 1H), 5.93 (s, 2H), 5.79 – 5.40 (m, 1H), 5.32 – 4.97 (m, 1H), 4.58 – 4.30 (m, 1H), 4.30 – 3.65 (m, 3H), 3.60 – 3.24 (m, 2H), 3.01 – 2.62 (m, 4H), 2.29 – 1.99 (m, 3H), 1.87 – 1.68 (m, 1H) ppm. MS: M/e 412 ($M+1$)⁺

Compound 1.43a or 1.43b: (*R* or *S*) 1-(((2*S*,4*R*)-1-acryloyl-4-fluoropyrrolidin-2-yl)methyl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1*H*-pyrazole-4-carboxamide



Step A: (*R* or *S*) (2*S*,4*R*)-tert-butyl 2-((5-amino-4-carbamoyl-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1*H*-pyrazol-1-yl)methyl)-4-fluoropyrrolidine-1-carboxylate



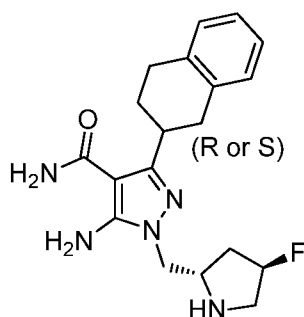
[0300] A mixture of (2*S*,4*R*)-tert-butyl 4-fluoro-2-((tosyloxy)methyl)pyrrolidine-1-carboxylate (3.26 g, 8.74 mmol), 5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-

1H-pyrazole-4-carboxamide (1.6 g, 6.24 mmol) and Cs₂CO₃ (4.0 g, 12.48 mmol) in DMF (20 mL) was stirred at 70 °C for 15 hrs. The resulting solution was concentrated. The residue was washed by water, extracted with EA (20 mL x 3). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated and purified by silica gel column

- 5 chromatography eluting with EA to get the desired product (1.2 g, 42%) as yellow oil, which was separated by chiral HPLC to give **peak 1** (0.37 g, earlier peak) and **peak 2** (0.37 g, later peak). The chiral separation conditions are shown below:

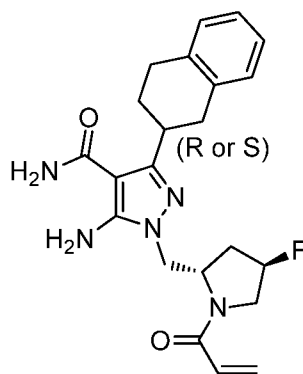
Column	CHIRALPAK IC
Column size	0.46 cm I.D. ×15 cm L
Injection	10ul
Mobile phase	MeOH=100
Flow rate	0.5 ml/min
Wave length	UV 220nm
Temperature	30 °C

- Step **B**: (*R or S*) 5-amino-1-(((2*S*,4*R*)-4-fluoropyrrolidin-2-yl)methyl)-3- ((*R*)-1,2,3,4-
10 tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



- [0301] To the solution of the product of Step **B** (370 mg, 0.81 mmol) in DCM (5 mL) was added TFA (5 mL). The solution was stirred at rt for 1 h. The resulting solution was concentrated to get the crude product (291 mg, 100%) as yellow oil, which was used in next step directly. MS: M/e
15 358 (M+1)⁺

Step **C**: (*R or S*) 1-(((2*S*,4*R*)-1-acryloyl-4-fluoropyrrolidin-2-yl)methyl)-5-amino-3-((*R*)-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide

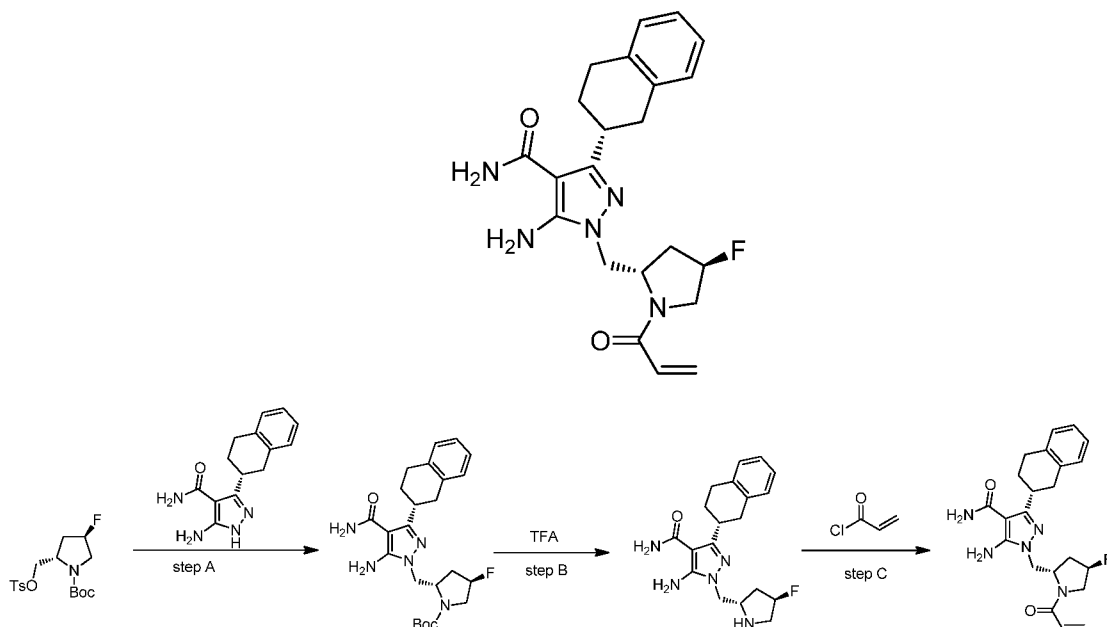


[0302] A mixture of the product of Step **B** (291 mg, 0.81 mmol) and NaHCO₃ (272 mg, 3.24 mmol) in CH₃CN/H₂O (7 mL/7 mL) was stirred at 0 °C for 5 min. Acryloyl chloride (73 mg, 0.81 mmol) was added drop wise at 0 °C. The final solution was stirred at 0 °C for 5 min and quenched by water, then extracted with EA (10 mL x 3). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated and purified by silica gel column chromatography eluting with PE/EA = 1/1 to get the desired product (213 mg, 64%) as a white solid. Peak 1 (**Compound 1.43a**, retention time: 5.456 min): ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.22 – 6.94 (m, 4H), 6.64 – 6.44 (m, 1H), 6.36 (s, 2H), 6.22 – 6.06 (m, 1H), 5.91 (s, 2H), 5.79 – 5.44 (m, 1H), 5.35 – 4.90 (m, 1H), 4.64 – 4.31 (m, 1H), 4.20 – 3.71 (m, 3H), 3.54 – 3.26 (m, 2H), 3.02 – 2.67 (m, 4H), 2.34 – 1.97 (m, 3H), 1.89 – 1.69 (m, 1H) ppm. MS: M/e 412 (M+1)⁺. ee: 100%. Peak 2 (**Compound 1.43b**, retention time: 6.985 min): ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.13 – 6.97 (m, 4H), 6.59 – 6.43 (m, 1H), 6.36 (s, 2H), 6.23 – 6.05 (m, 1H), 5.93 (s, 2H), 5.77 – 5.46 (m, 1H), 5.32 – 4.99 (m, 1H), 4.63 – 4.31 (m, 1H), 4.28 – 3.66 (m, 3H), 3.58 – 3.22 (m, 2H), 3.00 – 2.69 (m, 4H), 2.26 – 1.96 (m, 3H), 1.89 – 1.69 (m, 1H) ppm. MS: M/e 412 (M+1)⁺. ee: 100%.

[0303] The chiral analysis conditions are shown below.

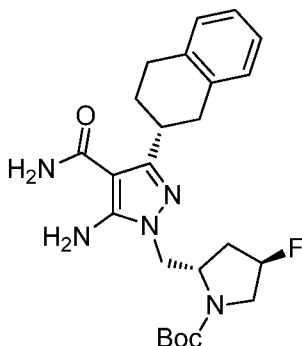
Column	CHIRALPAK As-H
Column size	0.46 cm I.D. × 15 cm L
Injection	1.5 ul
Mobile phase	n-Hex :EtOH(0.1% TEA OH ⁻) = 80 :20
Flow rate	1 ml/min
Wave length	UV 254nm, UV 280nm
Temperature	35 °C

Compound 1.43a: 1-(((2S,4R)-1-acryloyl-4-fluoropyrrolidin-2-yl)methyl)-5-amino-3-((R)-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



5

Step A: (2S,4R)-tert-butyl 2-(((5-amino-4-carbamoyl-3-((R)-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazol-1-yl)methyl)-4-fluoropyrrolidine-1-carboxylate

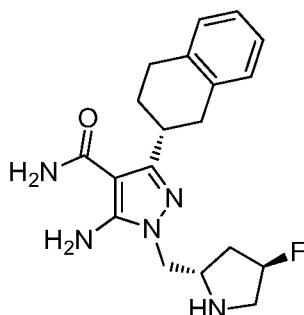


[0304] A mixture of (2S,4R)-tert-butyl 4-fluoro-2-((tosyloxy)methyl)pyrrolidine

10 -1-carboxylate (219 mg, 0.58 mmol), (R)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide (100 mg, 0.39 mmol) and Cs_2CO_3 (254 mg, 0.78 mmol) in DMF (10 mL) was stirred at 70 °C for 15 hrs. The resulting solution was concentrated. The residue was washed by water, extracted with EA (20 mL x 3). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated and purified by silica gel column

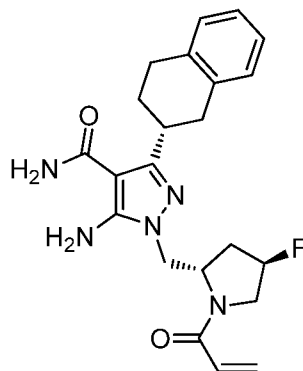
15 chromatography eluting with EA to get the desired product (90 mg, 51%) as yellow oil. MS: M/e 458 ($M+1$)⁺

Step **B:** 5-amino-1-(((2S,4R)-4-fluoropyrrolidin-2-yl)methyl)-3-((R)-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



5 **[0305]** To the solution of the product of Step **B** (90 mg, 0.20 mmol) in DCM (2 mL) was added TFA (2 mL). The solution was stirred at rt for 1 h. The resulting solution was concentrated to get the crude product (70mg, 100%) as yellow oil, which was used in next step directly. MS: M/e 358 (M+1)⁺

10 Step **C:** 1-(((2S,4R)-1-acryloyl-4-fluoropyrrolidin-2-yl)methyl)-5-amino-3-((R)-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide

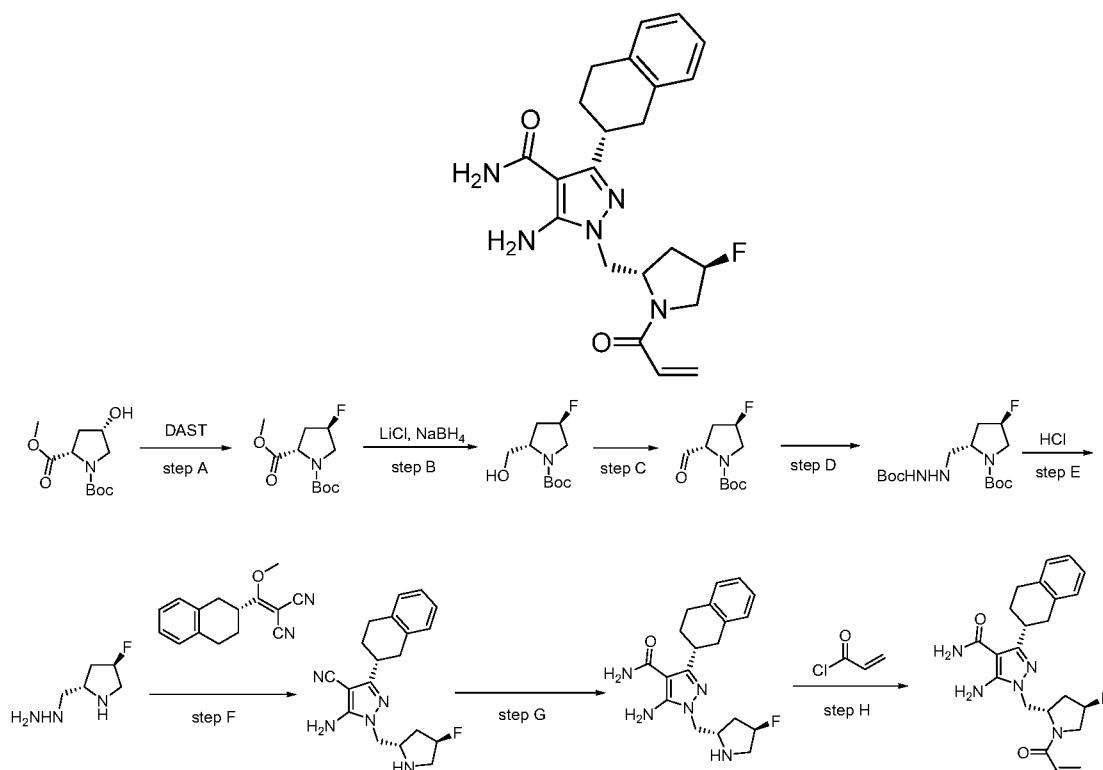


15 **[0306]** A mixture of the product of Step **B** (70 mg, 0.20 mmol) and NaHCO₃ (67 mg, 0.80 mmol) in CH₃CN/H₂O (2 mL/2 mL) was stirred at 0 °C for 5 min. Acryloyl chloride (18 mg, 0.20 mmol) was added drop wise at 0 °C. The final solution was stirred at 0 °C for 5 min and quenched by water, then extracted with EA (10 mL x 3). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated and purified by silica gel column chromatography eluting with PE/EA = 1/1 to get the desired product (30 mg, 37%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆, 80°C) δ 7.13 – 6.95 (m, 4H), 6.62 – 6.43 (m, 1H), 6.35 (s,

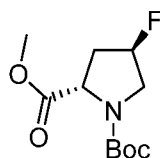
2H), 6.22 – 6.06 (m, 1H), 5.92 (s, 2H), 5.78 – 5.39 (m, 1H), 5.32 – 4.94 (m, 1H), 4.61 – 4.32 (m, 1H), 4.26 – 3.70 (m, 3H), 3.57 – 3.22 (m, 2H), 3.00 – 2.70 (m, 4H), 2.27 – 1.97 (m, 3H), 1.88 – 1.66 (m, 1H) ppm. MS: M/e 412 ($M+1$)⁺. ee: 100%.

[0307] The alternative route of Compound 1.43a: 1-(((2S,4R)-1-acryloyl

5 -4-fluoropyrrolidin-2-yl)methyl)-5- amino-3-((R)-1,2,3,4-tetrahydronaphthalen -2-yl)-1H-pyrazole-4-carboxamide



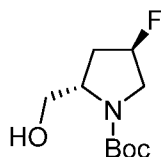
10 Step A: 1-(tert-butyl) 2-methyl (2S,4R)-4-fluoropyrrolidine-1,2-dicarboxylate



[0308] The solution of 1-(tert-butyl) 2-methyl (2S,4S)-4-hydroxypyrrolidine-1,2-dicarboxylate (10 g, 40.77 mmol) in DCM (100 mL) was cooled to -78 °C and stirred for 5 mins. Then DAST (9.5 mL, 77.47 mmol) was added dropwise for about 10 mins. The final solution was stirred at -78 °C to rt for 48 h. The resulting solution was poured into ice-water with 2 g NaHCO₃ and stirred for 15 mins, then extracted with DCM (50 mL x 3). The combined organic layer was washed by brine,

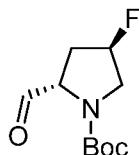
dried over sodium sulfate anhydrous then concentrated to get the crude product (10 g) as yellow oil which was used in the next step directly. MS: M/e 248 $(M+1)^+$

Step B: tert-butyl (2S,4R)-4-fluoro-2-(hydroxymethyl)pyrrolidine-1-carboxylate



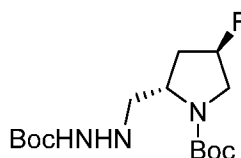
[0309] To the solution of the crude product of Step A (10 g, 40 mmol) in THF (100 mL) was added NaBH_4 (4.3 g, 100 mmol) followed by LiCl (3.3 g, 88 mmol). The solution was cooled to 0°C and EtOH (100 mL) was added dropwise. The final solution was stirred at 0°C to rt for 15 hrs. The resulting solution was cooled to 0°C , 4 N HCl was added till pH = 4, then concentrated. The residue was washed by water, extracted with DCM (50 mL x 3). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated to get the crude product (8.86 g, 100%) as yellow oil, which was used in next step directly. MS: M/e 220 $(M+1)^+$

Step C: tert-butyl (2S,4R)-4-fluoro-2-formylpyrrolidine-1-carboxylate



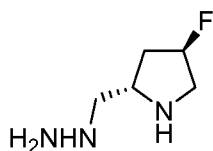
[0310] A solution of oxalyl chloride (4 mL, 47.43 mmol) in dry DCM (100 mL) was cooled to -78°C . To the solution, DMSO (3.6 mL, 51.07 mmol) in DCM (10 mL) was added dropwise for about 30 min at -78°C followed by the solution of the crude product of Step B (8 g, 36.48 mmol) in DCM (25 mL), then triethylamine (20 mL, 145.92 mmol) was added. The final solution was stirred at -78°C for 30 min, then at 0°C for 1 h. The resulting solution was washed by water, extracted with DCM (50 mL x 3). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated to get the crude product (8 g, 100%) as yellow oil, which was used in next step directly. MS: M/e 218 $(M+1)^+$

Step D: tert-butyl (2S,4R)-2-((2-(tert-butoxycarbonyl)hydrazinyl)methyl)-4-fluoropyrrolidine-1-carboxylate



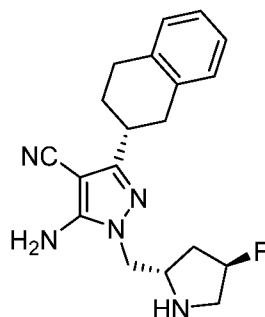
[0311] A mixture of the crude product of Step C (8 g, 36.82 mmol) and tert-butyl
 5 hydrazinecarboxylate (4.86 g, 36.82 mmol) in MeOH (10 mL) was stirred at rt for 2 hrs. Then the solution was cooled to 0 °C, HOAc (10 mL) was added followed by NaBH₃CN (2.36 g, 36.82 mmol). The solution was stirred at 0 °C for another 1 h. The resulting solution was concentrated. The residue was dissolved in DCM (50 mL), basified by 5N NaOH solution to pH = 8, then washed by water, extracted with DCM (50 mL x 3). The combined organic layer was washed by
 10 brine, dried over sodium sulfate anhydrous then concentrated to get the crude product (8.5 g, 69%) as yellow oil, which was used in next step directly. MS: M/e 334 (M+1)⁺

Step E: (2S,4R)-4-fluoro-2-(hydrazinylmethyl)pyrrolidine



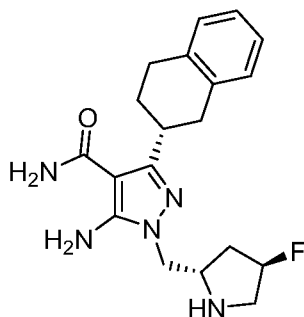
15 [0312] To the solution of the crude product of step D (8.5 g, 25.49 mmol) in DCM (20 mL) was added TFA (10 mL). The solution was stirred at rt for 2 h. The resulting solution was concentrated. The residue was dissolved in the mixed solvent of MeOH/DCM=1/20. To the solution was added K₂CO₃ till pH = 8. The mixture solution was stirred for 30 min, filtered. The filtrate was concentrated to get the crude product (3.39g, 100%) as yellow oil, which was used in next step
 20 directly. MS: M/e 134 (M+1)⁺

Step F: 5-amino-1-(((2S,4R)-4-fluoropyrrolidin-2-yl)methyl)-3-((R)-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carbonitrile



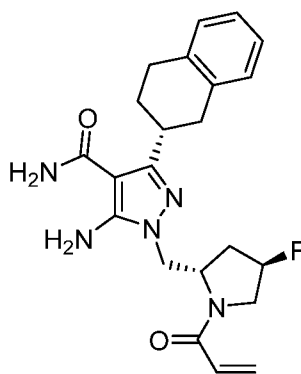
[0313] A mixture of the crude product of step E (3.39 g, 25.45 mmol) and (R)-2-(methoxy(1,2,3,4-tetrahydronaphthalen-2-yl)methylene)malononitrile (3 g, 12.72 mmol) in EtOH (5 mL) was stirred at rt for 4 hrs. The resulting solution was concentrated. The residue was washed by water, extracted with EA (20 mL x 3). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated and purified by silica gel column chromatography eluting with EA to get the desired product (3.4 g, 79%) as yellow oil. MS: M/e 340 (M+1)⁺.

Step G: 5-amino-1-(((2S,4R)-4-fluoropyrrolidin-2-yl)methyl)-3-((R)-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



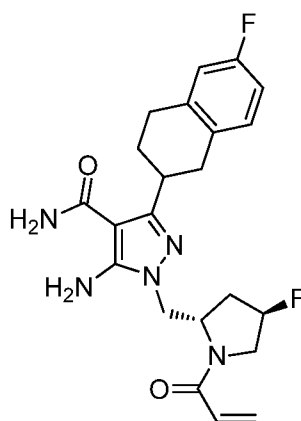
[0314] The solution of the product of step F (3.4 g, 10 mmol) in MsOH (15 mL) was stirred at 70 °C for 4 hrs. The resulting solution was cooled to rt, neutralized by 5 N NaOH aqueous solution till pH = 8, then extracted with DCM (20 mL x 3). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated to get crude product (2.8 g, 80%) as yellow oil, which was used in next step directly. MS: M/e 358 (M+1)⁺

Step H: 1-(((2S,4R)-1-acryloyl-4-fluoropyrrolidin-2-yl)methyl)-5-amino-3-((R)-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide

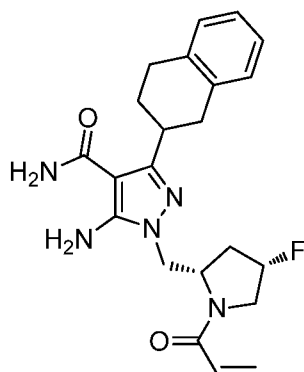


[0315] A mixture of the crude product of step G (2.8 g, 7.83 mmol) and NaHCO₃ (1.3 g, 15.66 mmol) in CH₃CN/H₂O (20 mL/20 mL) was stirred at 0 °C for 5 min. Acryloyl chloride (705 mg, 7.83 mmol) was added drop wise at 0 °C. The final solution was stirred at 0 °C for 5 min and
 5 quenched by water, then extracted with EA (10 mL x 3). The combined organic layer was washed by brine, dried over sodium sulfate anhydrous then concentrated and purified by silica gel column chromatography eluting with PE/EA = 1/1 to get the desired product (1.8 g, 56%) as a white solid.
¹H NMR (400 MHz, DMSO-*d*₆, 80°C) δ 7.13 – 6.95 (m, 4H), 6.62 – 6.43 (m, 1H), 6.35 (s, 2H), 6.22 – 6.06 (m, 1H), 5.92 (s, 2H), 5.78 – 5.39 (m, 1H), 5.32 – 4.94 (m, 1H), 4.61 – 4.32 (m, 1H),
 10 4.26 – 3.70 (m, 3H), 3.57 – 3.22 (m, 2H), 3.00 – 2.70 (m, 4H), 2.27 – 1.97 (m, 3H), 1.88 – 1.66 (m, 1H) ppm. MS: M/e 412 (M+1)⁺. ee: 100%.

Compound 1.44



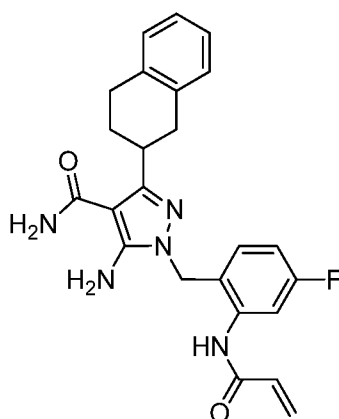
15 **[0316]** ¹H NMR (400 MHz, DMSO-*d*₆, 80°C) δ 7.17 – 7.02 (m, 1H), 6.95 – 6.77 (m, 2H), 6.67 – 6.23 (m, 3H), 6.21 – 5.80 (m, 3H), 5.75 – 5.40 (m, 1H), 5.30 – 4.98 (m, 1H), 4.67 – 4.32 (m, 1H), 4.27 – 3.68 (m, 3H), 3.62 – 3.25 (m, 2H), 3.01 – 2.70 (m, 4H), 2.29 – 1.95 (m, 3H), 1.87 – 1.57 (m, 1H) ppm. MS: M/e 430 (M+1)⁺

Compound 1.45

[0317] ^1H NMR (400 MHz, DMSO- d_6 , 80°C) δ 7.13 – 6.86 (m, 4H), 6.72 – 6.27 (m, 3H), 6.26 – 5.59 (m, 4H), 5.52 – 5.14 (m, 1H), 4.73 – 3.46 (m, 5H), 3.41 – 3.24 (m, 1H), 3.04 – 2.68 (m, 4H), 2.38 – 1.97 (m, 3H), 1.91 – 1.66 (m, 1H) ppm. MS: M/e 412 (M+1) $^+$

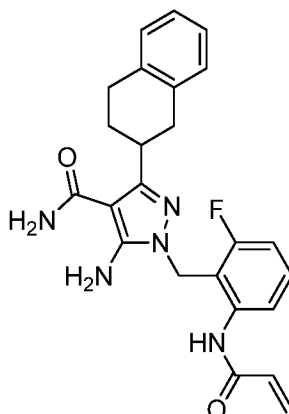
[0318] **Compounds 1.46 -1.49** were prepared according to the procedures described for **Compound 1.20** under appropriate conditions that could be recognized by one skilled in the art.

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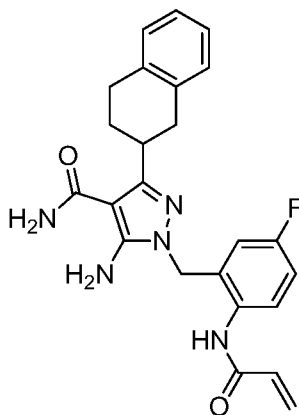
Compound 1.46

[0319] ^1H NMR (400 MHz, DMSO- d_6) δ 10.37 (s, 1H), 7.70-7.73 (dd, J = 2.0, 11.2 Hz, 1H), 7.21-7.25 (dd, J = 7.2, 8.8 Hz, 1H), 7.06-7.09 (m, 4H), 6.99-7.02 (m, 1H), 6.68 (s, 2H), 6.49-6.55 (m, 1H), 6.40 (s, 2H), 6.30-6.35 (m, 1H), 5.80-5.83 (m, 1H), 5.14 (s, 2H), 3.39-3.45 (m, 1H), 2.98-3.03 (m, 1H), 2.85-2.94 (m, 2H), 2.77-2.82 (m, 1H), 2.13-2.16 (m, 1H), 1.67-1.76 (m, 1H). MS (ESI) m/e [M+1] $^+$ 434.

15

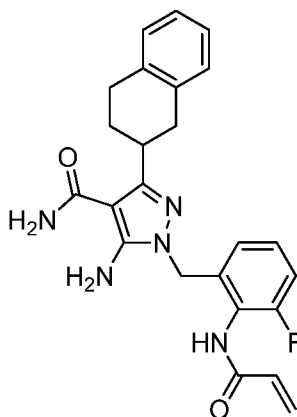
Compound 1.47

[0320] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.56 (s, 1H), 7.74 (d, $J = 8.4$ Hz, 1H), 7.38 (dd, $J = 14.8, 8.2$ Hz, 1H), 7.16 - 6.94 (m, 5H), 6.69 (s, 2H), 6.51 - 6.45 (m, 1H), 6.39 - 6.17 (m, 3H), 5.81 (d, $J = 11.4$ Hz, 1H), 5.19 (t, $J = 16.8$ Hz, 2H), 3.42 - 3.40 (m, 1H), 2.99 (dd, $J = 16.4, 4.0$ Hz, 1H), 2.94 - 2.68 (m, 3H), 2.12 (d, $J = 10.6$ Hz, 1H), 1.70 - 1.63 (m, 1H). (ESI) m/e $[\text{M}+1]^+$ 434.

Compound 1.48

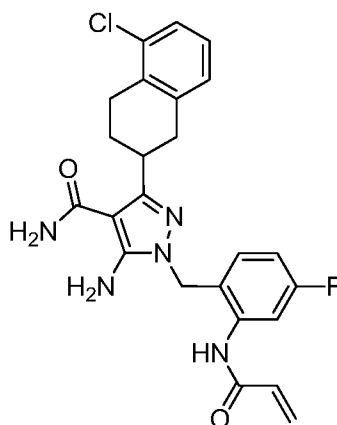
[0321] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.12 (s, 1H), 7.67 (dd, $J = 8.8, 5.5$ Hz, 1H), 7.15 (td, $J = 8.6, 3.0$ Hz, 1H), 7.07 (s, 4H), 6.76 (dd, $J = 9.6, 2.9$ Hz, 1H), 6.69 (s, 2H), 6.49 (dd, $J = 17.0, 10.2$ Hz, 1H), 6.36 (s, 2H), 6.30 (dd, $J = 17.0, 1.7$ Hz, 1H), 5.80 (dd, $J = 10.2, 1.6$ Hz, 1H), 5.12 (s, 2H), 3.51 - 3.38 (m, 1H), 3.02 (dd, $J = 16.5, 3.9$ Hz, 1H), 2.97 - 2.84 (m, 2H), 2.81 (dd, $J = 9.6, 6.8$ Hz, 1H), 2.14 (d, $J = 10.9$ Hz, 1H), 1.71 - 1.66 (m, 1H). (ESI) m/e $[\text{M}+1]^+$ 434.

Compound 1.49



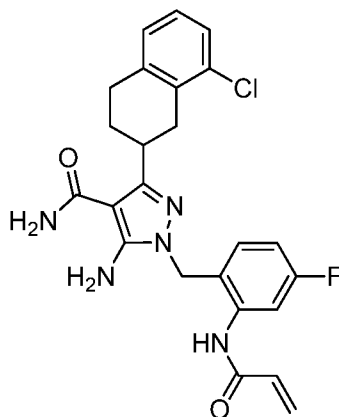
[0322] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.96 (s, 1H), 7.32 – 7.15 (m, 2H), 7.07 (s, 4H), 6.65 (s, 2H), 6.58 (d, $J = 7.6$ Hz, 1H), 6.51 (dd, $J = 17.0, 10.2$ Hz, 1H), 6.31 (s, 1H), 6.26 (s, 2H), 5.81 (d, $J = 11.1$ Hz, 1H), 5.07 (s, 2H), 3.40 (d, $J = 11.9$ Hz, 1H), 3.01 (dd, $J = 16.6, 4.3$ Hz, 1H), 2.96 – 2.68 (m, 3H), 2.14 (d, $J = 11.2$ Hz, 1H), 1.72 – 1.66 (m, 1H). (ESI) m/e $[\text{M}+1]^+$ 434.

Compound 1.50

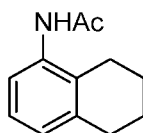


[0323] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.29 (s, 1H), 7.68-7.70 (d, $J = 11.2$ Hz, 1H), 7.24-7.26 (d, $J = 7.6$ Hz, 1H), 7.07-7.19 (m, 3H), 6.96-7.01 (m, 1H), 6.68 (s, 2H), 6.49-6.56 (m, 1H), 6.40 (s, 2H), 6.30-6.35 (m, 1H), 5.82-5.85 (m, 1H), 5.13 (s, 2H), 3.37-3.45 (m, 1H), 3.01-3.06 (m, 1H), 2.86-2.94 (m, 2H), 2.67-2.79 (m, 1H), 2.20-2.23 (m, 1H), 1.70-1.75 (m, 1H). MS (ESI) m/e $[\text{M}+1]^+$ 468.

Compound 1.51: 1-(2-acrylamido-4-fluorobenzyl)-5-amino-3-(8-chloro-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide

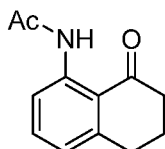


Step A: N-(5,6,7,8-tetrahydronaphthalen-1-yl)acetamide



[0324] A solution of 5,6,7,8-tetrahydronaphthalen-1-amine (12.7 g, 86.2 mmol) in EtOH (40 mL) was added dropwise to a solution of acetic anhydride (17.6 g, 172.4 mmol) in anhydrous EtOH (200 mL) at 0 °C for 16 h. The solvent was removed under vacuum on a rotary evaporator to give N-(5,6,7,8-tetrahydronaphthalen-1-yl)acetamide (16.3 g, 100%) as a white solid and the crude was used for the next step without further purification. MS (ESI) m/e [M+1]⁺ 190

Step B: N-(8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide

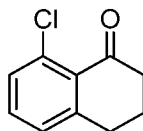


[0325] A solution of 15 % MgSO₄ (1.68 g in 10 mL of H₂O) was added to a suspension of N-(5,6,7,8-tetrahydronaphthalen-1-yl)acetamide (1.9 g, 10 mmol) in acetone (30 mL), then KMnO₄ (4.74 g, 30 mmol) was added in several batches. The reaction mixture was stirred at room temperature for 2 h, filtered through celite and the solid was washed with DCM and water. The organic layer was separated and washed with brine, dried over Na₂SO₄, concentrated under vacuum. The residue was purified by silica gel chromatography (elution with hexane/ethyl acetate

1:5) to give N-(8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide (1.2 g, 60%) as a yellow solid.

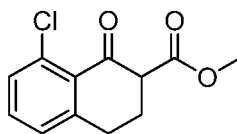
MS (ESI) m/e $[M+1]^+ 204$

Step C: 8-chloro-3,4-dihydronaphthalen-1(2H)-one



[0326] A mixture of CuCl_2 and tert-butyl nitrile (495 mg, 4.8 mmol) in CH_3CN (15 mL) was treated with N-(8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide (484 mg, 3 mmol) in CH_3CN (5 mL) at 65 °C. After 10 min, the mixture was cooled to room temperature and the solvent was removed under vacuum. The residue was partitioned between water and EtOAc, the organic layer was washed with brine, dried over Na_2SO_4 , concentrated under vacuum. The residue was purified by silica gel chromatography (elution with hexane/ethyl acetate 1:10) to give 8-chloro-3,4-dihydronaphthalen-1(2H)-one (0.36 g, 67%) as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.32-7.33 (m, 2H), 7.16 (t, $J=5.2$ Hz, 1H), 2.97 (t, $J=6.4$ Hz, 2H), 2.69 (t, $J=6.4$ Hz, 2H), 2.07-2.13 (m, 1H). MS (ESI) m/e $[M+1]^+ 181$.

Step D: methyl 8-chloro-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate

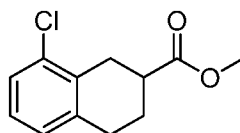


[0327] NaH (176 mg, 4.4 mmol) was added to methyl orthoformate (5 mL), then a solution of 8-chloro-3,4-dihydronaphthalen-1(2H)-one (0.36 g, 2 mmol) in methyl orthoformate (5 mL) was added thereto. The mixture was stirred at 100 °C for 1 h, cooled to room temperature, poured into water, extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 , concentrated under vacuum. The residue was purified by silica gel chromatography (elution with hexane/ethyl acetate 1:15) to give methyl

8-chloro-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (0.28 g, 59%) as a yellow oil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.94 (s, 1H), 7.29-7.31 (dd, $J = 1.2, 8$ Hz, 1H), 7.20 (t, $J = 7.6$ Hz, 1H), 7.08-7.10 (dd, $J = 1.2, 7.2$ Hz, 1H), 3.83 (s, 3H), 2.73-2.77 (m, 2H), 2.46-2.50 (m, 2H). MS (ESI) m/e $[\text{M}+1]^+ 239$.

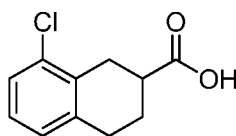
5

Step E: methyl 8-chloro-1,2,3,4-tetrahydronaphthalene-2-carboxylate



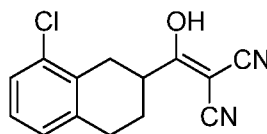
[0328] Triethylsilane (2 mL) was added to a solution of methyl 8-chloro-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (0.28 g, 1.17 mmol) in trifluoroacetic acid (5 mL), then the reaction mixture was stirred at room temperature for 16 h. The solvent was removed under vacuum, the residue was concentrated with toluene azeotrope to give methyl 8-chloro-1,2,3,4-tetrahydronaphthalene-2-carboxylate (0.31 g, >100%) as a yellow oil. The crude was used for the next step without further purification. MS (ESI) m/e $[\text{M}+1]^+ 225$.

15 Step F: 8-chloro-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid



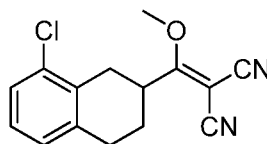
[0329] A solution of NaOH (0.28 g, 6.9 mmol) in H_2O (5 mL) was added to a solution of 8-chloro-1,2,3,4-tetrahydronaphthalene-2-carboxylate (0.31 g, 1.38 mmol) in MeOH (10 mL), then the reaction mixture was stirred at room temperature for 1 h. The organics were removed under vacuum; the residual aqueous layer was acidified with aq HCl to pH 2-3. The solid was collected by filtered, dried under vacuum to give 8-chloro-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (200 mg, 69%) as a beige solid. The solid was used for the next step without further purification. MS (ESI) m/e $[\text{M}-1]^+ 209$.

Step **G**: 2-((8-chloro-1,2,3,4-tetrahydronaphthalen-2-yl)(hydroxy)methylene) malononitrile



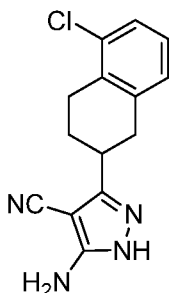
[0330] To a solution of 8-chloro-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (200 mg, 0.95 mmol) in DCM (10 mL) was added HOBT (154 mg, 1.14 mmol), EDCI (220 mg, 1.14 mmol) and Et₃N (192 mg, 1.9 mmol), after stirring at room temperature for 10 min, malononitrile (63 mg, 0.95 mmol) was added thereto. The reaction mixture was stirred at room temperature for 16 h. The solvent was removed under vacuum, the residue was partitioned between EtOAc and saturated aq NaHCO₃. The organic layer was washed with aq NH₄Cl, 1.25 N H₂SO₄, brine, dried over Na₂SO₄, concentrated under vacuum to give 2-((8-chloro-1,2,3,4-tetrahydronaphthalen-2-yl)(hydroxy)methylene)malononitrile (200 mg, 81%) as a yellow solid. MS (ESI) m/e [M-1]⁺257.

Step **H**: 2-((8-chloro-1,2,3,4-tetrahydronaphthalen-2-yl)(methoxy)methylene) malononitrile



[0331] A reaction mixture of 2-((8-chloro-1,2,3,4-tetrahydronaphthalen-2-yl)(hydroxy)methylene)malononitrile (200 mg, 0.77 mmol) in trimethyl Orthoformate (5 mL) was stirred at 100 °C for 1 h, then it was cooled to room temperature and the solvent was removed under vacuum. The crude was recrystallized with MeOH to give 2-((8-chloro-1,2,3,4-tetrahydronaphthalen-2-yl)(methoxy)methylene)malononitrile (120 mg, 57%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.22 (d, *J*=7.6 Hz, 1H), 7.09 (t, *J*=7.2 Hz, 1H), 7.01 (d, *J*=7.6 Hz, 1H), 4.43 (s, 3H), 3.24-3.29 (m, 1H), 3.05-3.11 (m, 1H), 2.90-2.93 (m, 2H), 2.73-2.80 (m, 1H), 2.01-2.04 (m, 1H), 1.81-1.87 (m, 1H).

Step I: 5-amino-3-(8-chloro-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4- carbonitrile

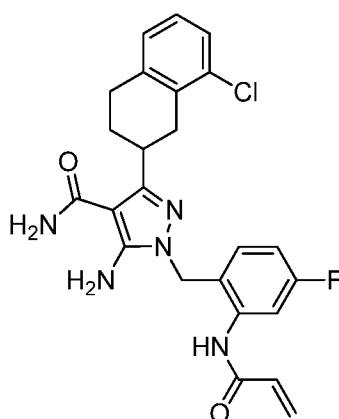


[0332] Hydrazine hydrate (0.84 g, 16.8 mmol) was added to a suspension of

- 5 2-((8-chloro-1,2,3,4-tetrahydronaphthalen-2-yl)(methoxy)methylene)malononitrile (2.3 g, 8.4 mmol) in EtOH (20 mL), then the reaction mixture was stirred at room temperature for 16 h. The solvent was removed under vacuum, the residue was recrystallized with MeOH to give 5-amino-3-(8-chloro-1,2,3,4-tetra hydronaphthalen-2-yl)-1H-pyrazole-4-carbonitrile (2 g, 87%) as a white solid. MS (ESI) m/e [M+1]⁺273.

10

[0333] **Compound 1.51** was prepared according to the procedures described for **Compound 1.20** using the product of Step I under appropriate conditions that could be recognized by one skilled in the art.

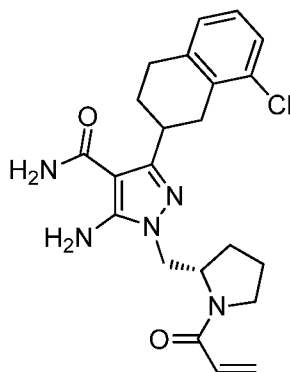


- 15 [0334] ¹H NMR (400 MHz, DMSO-*d*₆) δ10.27 (s, 1H), 7.67-7.71 (dd, *J*=2.4, 11.6 Hz, 1H), 7.19-7.25 (m, 2H), 7.09-7.16 (m, 2H), 6.97-7.02 (m, 1H), 6.72 (s, 2H), 6.46-6.53 (m, 1H), 6.33 (s, 2H), 6.28-6.33 (m, 1H), 5.75-5.78 (m, 1H), 5.15 (s, 2H), 3.44-3.50 (m, 1H), 3.14-3.19 (m, 1H),

2.80-2.95 (m, 2H), 2.67-2.74 (m, 1H), 2.08-2.12 (m, 1H), 1.65-1.72 (m, 1H). MS (ESI) m/e [M+1]⁺468.

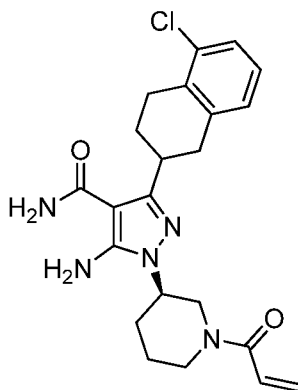
[0335] **Compound 1.52** was prepared according to the procedures described for **Compound**

5 **1.10** under appropriate conditions that could be recognized by one skilled in the art.



[0336] ¹H NMR (400 MHz, DMSO-*d*₆) δ7.23-7.25 (d, *J*=7.6 Hz, 1H), 7.08-7.15 (m, 2H), 6.52-6.64 (m, 3H), 6.00-6.23 (m, 3H), 5.44-5.72 (m, 1H), 4.18-4.36 (m, 1H), 3.89-4.06 (m, 2H), 3.39-3.55 (m, 3H), 3.07-3.15 (m, 1H), 2.67-2.94 (m, 3H), 2.07 (m, 1H), 1.66-1.94 (m, 5H). MS (ESI) m/e [M+1]⁺ 428.

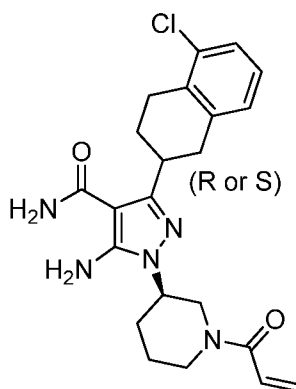
[0337] **Compound 1.53** was prepared according to the procedures described for **Compound** 1.11 under appropriate conditions that could be recognized by one skilled in the art.



[0338] ¹H NMR (400 MHz, DMSO-*d*₆) δ7.22-7.25 (m, 1H), 7.11-7.15 (m, 2H), 6.73-6.88 (m, 1H), 6.60(s, 2H), 6.24 (s, 2H), 6.04-6.14 (m, 1H), 5.61-5.71 (m, 1H), 4.24-4.42 (m, 1H), 3.96-4.05

(m, 2H), 2.71-3.11 (m, 5H), 2.19-2.22 (m, 1H), 1.69-1.92 (m, 5H), 1.42-1.47 (m, 1H), 1.23-1.25 (m, 1H). MS (ESI) m/e $[M+1]^+$ 428.

[0339] Compound **1.53** was separated into two enantiomeric stereoisomers **compound 1.53a** (peak 1, R or S, earlier peak), and **compound 1.53b** (peak 2, S or R, later peak) by chiral *prep*-HPLC.



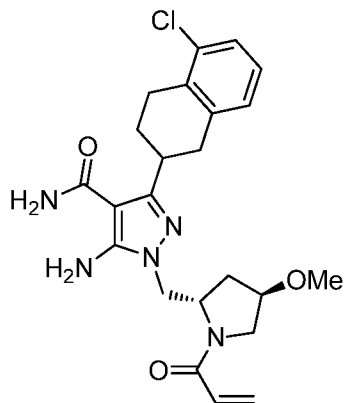
[0340] Compound **1.53a**: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.23-7.25 (dd, $J=2.8, 6.4\text{Hz}$, 1H), 7.10-7.15 (m, 2H), 6.73-6.88 (m, 1H), 6.60 (s, 2H), 6.24 (s, 2H), 6.04-6.14 (m, 1H), 5.61-5.71 (m, 1H), 4.16-4.42 (m, 1H), 3.96-4.05 (m, 2H), 3.37-3.44 (m, 1H), 2.71-3.07 (m, 6H), 2.20 (m, 1H), 1.42-1.92 (m, 5H). MS (ESI) m/e $[M+1]^+$ 428.

[0341] Compound **1.53b**: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.23-7.25 (dd, $J=2.0, 7.6\text{Hz}$, 1H), 7.10-7.15 (m, 2H), 6.73-6.88 (m, 1H), 6.60 (s, 2H), 6.24 (s, 2H), 6.04-6.10 (m, 1H), 5.62-5.71 (m, 1H), 4.16-4.42 (m, 1H), 3.96-4.05 (m, 2H), 3.37-3.44 (m, 1H), 2.71-3.07 (m, 6H), 2.20 (m, 1H), 1.42-1.92 (m, 5H). MS (ESI) m/e $[M+1]^+$ 428.

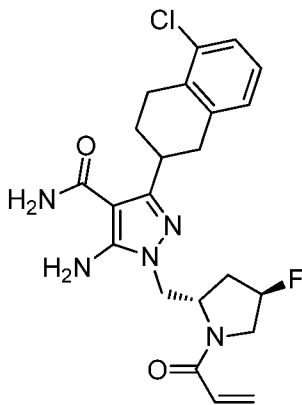
[0342] The separation conditions are shown below.

Column	CHIRALPAK OJH
Column size	3 cm $\times$ 25 cm
Injection	3 mL
Mobile phase	$\text{CO}_2/\text{MeOH} = 70/30$
Flow rate	54 mL/min
Wave length	UV 220 nm

[0343] Compounds **1.54 -1.60** were prepared according to the procedures described for Compound **1.14** under appropriate conditions that could be recognized by one skilled in the art.

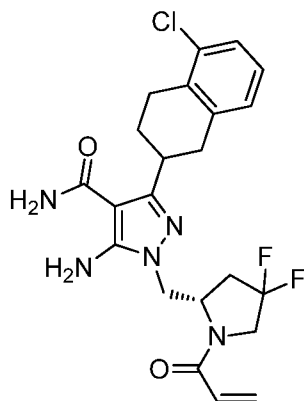
Compound 1.54

[0344] ^1H NMR (400 MHz, DMSO- d_6) δ 7.23-7.25 (d, $J=7.2$ Hz, 1H), 7.08-7.15 (m, 2H), 6.51-6.63 (m, 2H), 6.01-6.20 (m, 3H), 5.47-5.72 (m, 1H), 4.23-4.43 (m, 1H), 3.88-4.14 (m, 2H), 3.38-3.78 (m, 4H), 3.16-3.19 (m, 3H), 2.67-3.05 (m, 4H), 1.75-2.23 (m, 4H). MS (ESI) m/e $[\text{M}+1]^+$ 458.

Compound 1.55

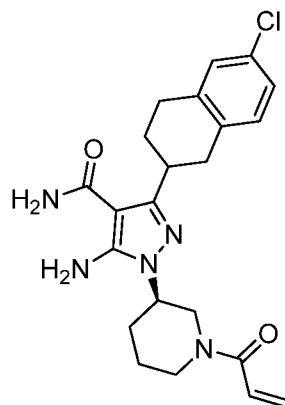
[0345] ^1H NMR (400 MHz, DMSO- d_6) δ 7.23-7.25 (d, $J=6.4$ Hz, 1H), 7.08-7.15 (m, 2H), 6.51-6.62 (m, 2H), 6.03-6.21 (m, 3H), 5.49-5.74 (m, 1H), 5.08-5.33 (m, 1H), 4.34-4.59 (m, 1H), 3.82-4.21 (m, 3H), 3.35-3.47 (m, 3H), 2.67-3.04 (m, 4H), 1.71-2.20 (m, 4H). MS (ESI) m/e $[\text{M}+1]^+$ 446.

Compound 1.56



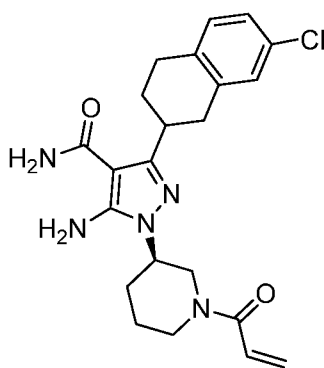
[0346] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.23-7.25 (d, $J=6.8$ Hz, 1H), 7.08-7.15 (m, 2H), 6.43-6.63 (m, 2H), 6.21-6.25 (m, 1H), 6.12 (s, 1H), 6.03-6.08 (s, 1H), 5.47-5.79 (m, 1H), 4.49-4.67 (m, 1H), 3.73-4.17 (m, 4H), 3.35-3.42 (m, 1H), 2.66-3.05 (m, 5H), 2.32-2.49 (m, 1H), 2.17-2.29 (m, 1H), 1.68-1.77 (m, 1H). MS (ESI) m/e $[\text{M}+1]^+$ 464.

Compound 1.57



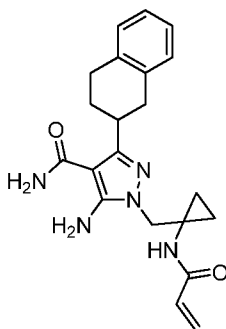
[0347] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.20 – 7.07 (m, 3H), 6.81 (m, 1H), 6.59 (s, 2H), 6.21 (s, 2H), 6.18 – 5.97 (m, 1H), 5.77 – 5.54 (m, 1H), 4.50 – 3.90 (m, 3H), 3.43 (s, 1H), 3.15 – 2.71 (m, 6H), 2.17 – 2.01 (m, 1H), 1.99 – 1.77 (m, 3H), 1.77 – 1.59 (m, 1H), 1.44 (s, 1H). MS (ESI) m/e $[\text{M}+1]^+$ 428.

Compound 1.58



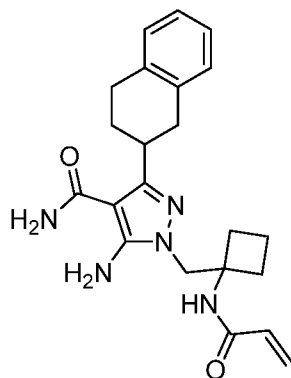
[0348] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.21 – 7.05 (m, 3H), 6.82 (m, 1H), 6.59 (s, 2H), 6.21 (s, 2H), 6.17 – 5.98 (m, 1H), 5.74 – 5.53 (m, 1H), 4.46 – 3.89 (m, 3H), 3.48 – 3.33 (m, 1H), 3.14 – 2.73 (m, 6H), 2.19 – 2.03 (m, 1H), 2.01 – 1.79 (m, 3H), 1.79 – 1.62 (m, 1H), 1.44 (s, 1H). MS (ESI) m/e $[\text{M}+1]^+$ 428.

Compound 1.59



[0349] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.38 (s, 1H), 7.18 – 6.92 (m, 4H), 6.57 (s, 2H), 6.23 – 5.93 (m, 3H), 5.57 (dd, $J = 8.8, 3.6$ Hz, 1H), 4.22 – 4.02 (m, 2H), 3.34 – 3.26 (m, 1H), 3.06 – 2.68 (m, 4H), 2.12 (d, $J = 13.2$ Hz, 1H), 1.69 (m, 1H), 0.74 (m, 2H), 0.65 – 0.55 (m, 2H). MS (ESI) m/e $[\text{M}+1]^+$ 380.

Compound 1.60

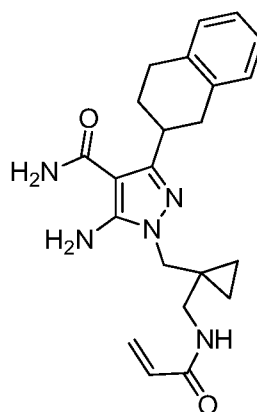


[0350] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.23 (s, 1H), 7.07 (s, 4H), 6.58 (s, 2H), 6.24-6.05 (m, 2H), 5.91 (s, 2H), 5.57 (dd, $J = 10.0, 2.3$ Hz, 1H), 4.21 (s, 2H), 3.38-3.36 (m, 1H), 3.02-2.77 (m, 4H), 2.28-2.26 (m, 2H), 2.19 – 1.99 (m, 3H), 1.91 – 1.52 (m, 3H). MS (ESI) m/e $[\text{M}+1]^+$ 394.

5

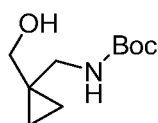
Compound 1.61:

1-((1-(acrylamidomethyl)cyclopropyl)methyl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



10

Step 1: tert-butyl (1-(hydroxymethyl)cyclopropyl)methylcarbamate

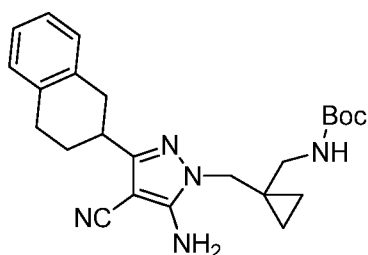


[0351] To a solution of ethyl 1-cyanocyclopropanecarboxylate (200 mg, 1.4 mmol) in THF (10 ml) was added Lithium aluminum hydride (273 mg, 7.2 mmol) at 0 °C. The reaction mixture was heated to 65 °C for 4h and cooled to 0 °C. Water (10 ml) was added, filtered and washed with THF, (Boc)₂O (1.1eq) was added, stirred at rt for 2h. It was purified by *prep*-TLC (P/E=2:1) to give a

15

white solid (50 mg). ^1H NMR (400 MHz, CDCl_3) δ 5.11 (s, 1H), 3.50 (s, 1H), 3.38 (s, 2H), 3.11 (d, $J = 6.4$ Hz, 2H), 1.44 (d, $J = 8.7$ Hz, 9H), 0.44 (d, $J = 6.0$ Hz, 4H).

Step 2: tert-butyl ((1-((5-amino-4-cyano-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazol-1-yl)methyl)cyclopropyl)methyl)carbamate

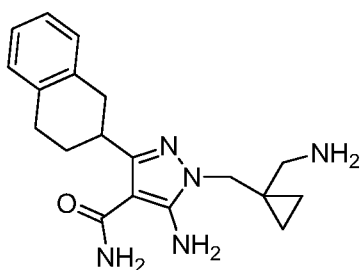


[0352] To a solution of tert-butyl (1-(hydroxymethyl)cyclopropyl)methylcarbamate (200 mg, 1.01 mmol) in DCM (10 ml) was added TEA (0.3 ml, 2.0 mmol) and MsCl (126 mg, 1.1 mmol) at 0°C for 1h. 10 ml of NaHCO_3 was added and extracted with EA (10 ml), dried over Na_2SO_4 , evaporated in vacuum to give a colorless oil which was used directly in the next step. The crude product was dissolved in DMF (5 ml) and

5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carbonitrile (190 mg, 0.8 mmol) was added at 60°C , then the mixture was stirred at 60°C for 1h. TLC showed the starting material (SM) was consumed completely. 25 ml of water was added and extracted with EA (20 ml),

combined organic layer was washed with brine (20 ml), dried over Na_2SO_4 , evaporated under vacuum to give colorless oil (400 mg), which was purified by *prep*-TLC (P/E=1:1) to give a white solid (290 mg). MS (ESI) m/e $[\text{M}+1]^+$ 422. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.11 (m, 4H), 6.80 (s, 1H), 6.56 (s, 1H), 3.87 (s, 2H), 3.05 - 2.90 (m, 5H), 2.84 (dd, $J = 9.1, 5.4$ Hz, 2H), 2.10 (d, $J = 13.9$ Hz, 1H), 1.84 (dd, $J = 12.9, 8.6$ Hz, 1H), 1.37 (m, 9H), 1.31 (s, 2H), 0.43 (dd, $J = 23.2, 3.6$ Hz, 4H).

Step 3: 5-amino-1-((1-(aminomethyl)cyclopropyl)methyl)-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



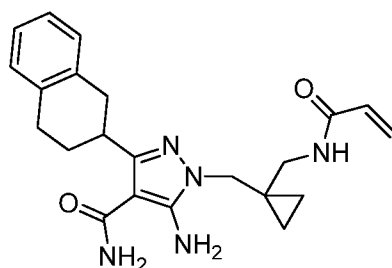
[0353] tert-butyl

((1-((5-amino-4-cyano-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazol-1-yl)

methyl)cyclopropyl)methyl)carbamate (290 mg) was dissolved in $\text{CH}_3\text{SO}_3\text{H}$ (6 ml). The reaction

5 mixture was heated to 110 °C for 40 min. LC-MS showed SM was consumed completely. The mixture was cooled to 5 °C and NaHCO_3 was added to adjust to pH 7~8, extracted with EA (10 ml), combined organic layer was dried over Na_2SO_4 , evaporated under vacuum to give a yellow solid (280 mg). MS (ESI) m/e $[\text{M}+1]^+$ 340.

10 Step 4: 1-((1-(acrylamidomethyl)cyclopropyl)methyl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



[0354] To a solution of 5-amino-1-((1-(aminomethyl)cyclopropyl)methyl)-3-

(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide (280 mg, 0.83 mmol) in CH_3CN

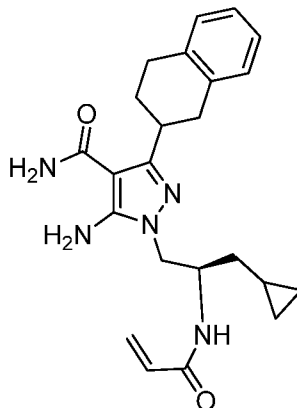
15 (10 ml) and water (10 ml) was added NaHCO_3 (208 mg, 2.48 mmol) and acryloyl chloride (89 mg, 0.99 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 20 min. 10ml of water was added extracted with EA (10 ml), dried over Na_2SO_4 , and evaporated under vacuum. The residue was purified by *prep*-TLC (DCM/MeOH=8:1) to give a white solid (37 mg). MS (ESI) m/e $[\text{M}+1]^+$ 394. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.12 (d, J = 5.1 Hz, 1H), 7.07 (s, 2H), 6.61 (s, 2H), 6.27 (dd, J = 17.0, 10.0 Hz, 1H), 6.09 (d, J = 17.0 Hz, 1H), 5.61 (d, J = 10.2 Hz, 1H), 3.89 (s, 2H), 3.38

20

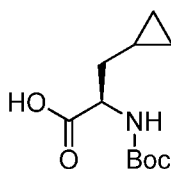
(s, 1H), 3.17 (d, $J = 4.6$ Hz, 2H), 3.04 – 2.72 (m, 4H), 2.12 (d, $J = 13.7$ Hz, 1H), 1.81 – 1.66 (m, 1H), 0.53 (s, 2H), 0.40 (s, 2H).

Compound 1.62: 1-((R)-2-acrylamido-3-cyclopropylpropyl)-5-amino-3-(1,2,3,4-

5 tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide

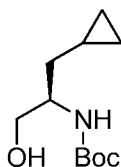


Step 1: (R)-2-(tert-butoxycarbonylamino)-3-cyclopropylpropanoic acid



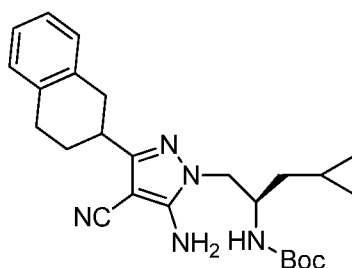
[0355] (R)-2-amino-3-cyclopropylpropanoic acid (0.5g, 3.9 mmol) was suspended in ethanol (8 ml) and water (4 ml), then 1N NaOH (5 ml) was added. The reaction mixture was cooled to 10 °C, (Boc)₂O (950 mg, 4.3 mmol) in THF (4 ml) was added and stirred at rt overnight. 15 ml of water was added and washed with tert-Butyl methyl ether (MTBE, 10 ml), water layer was acidified by 3M HCl to adjust to pH 4, extracted with EA (15 ml). Combined organic layer was dried over Na₂SO₄, evaporated under vacuum to give colorless oil (640 mg).

Step 2: (R)-tert-butyl 1-cyclopropyl-3-hydroxypropan-2-ylcarbamate



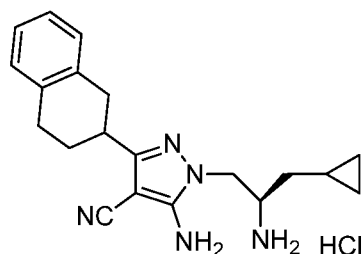
[0356] To a solution of (R)-2-(tert-butoxycarbonylamino)-3-cyclopropylpropanoic acid (780 mg, 3.4 mmol) in THF (15 ml) was added TEA (0.6 ml, 4.1 mmol) and isopropyl carbonochloridate (513 mg) at 0 °C. The reaction mixture was stirred at rt for 0.5 h, filtered and washed with THF, and cooled to 0 °C, NaBH₄ (260 mg, 6.8 mmol) in water (1.5 ml) was added. The reaction mixture was stirred at rt for 2h. 20 ml of water was added and extracted with EA (20 ml), combined organic layer was washed with brine (20 ml), dried over Na₂SO₄, evaporated under vacuum to give a white solid (809 mg).

Step 3: tert-butyl (R)-1-(5-amino-4-cyano-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazol-1-yl)-3-cyclopropylpropan-2-ylcarbamate



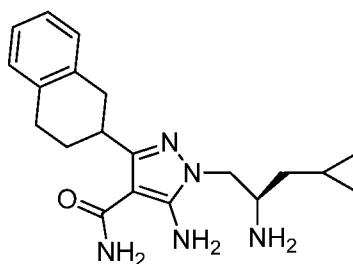
[0357] To a solution of (R)-tert-butyl 1-cyclopropyl-3-hydroxypropan-2-ylcarbamate (809 mg, 3.8 mmol) in DCM (20 ml) was added TEA (1.0 ml, 7.5 mmol) and MsCl (0.32 ml, 4.1 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1h. NaHCO₃ (20 ml) was added and extracted with DCM (20 ml), dried over Na₂SO₄, which was used directly in the next step. The crude product was dissolved in DMF (6 ml), then Cs₂CO₃ (1.8 g, 7.5 mmol) and 5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carbonitrile (716 mg, 3.0 mmol) were added. The reaction mixture was heated to 60 °C for 2h. The residue was purified by *prep*-TLC (P/E=1:1) to give a white solid (33 mg). MS (ESI) m/e [M+1]⁺ 436.

Step 4: 5-amino-1-((R)-2-amino-3-cyclopropylpropyl)-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carbonitrile hydrochloride



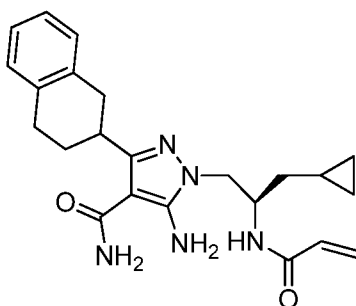
[0358] (R)-1-(5-amino-4-cyano-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazol-1-yl)-3-cyclopropylpropan-2-ylcarbamate (500 mg) was dissolved in HCl/dioxane (5 ml). The reaction mixture was stirred at rt for 2h. TLC showed SM was consumed completely. Solvent was removed under vacuum to give a white solid (460 mg). MS (ESI) m/e [M+1]⁺ 336.

Step 5: 5-amino-1-((R)-2-amino-3-cyclopropylpropyl)-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



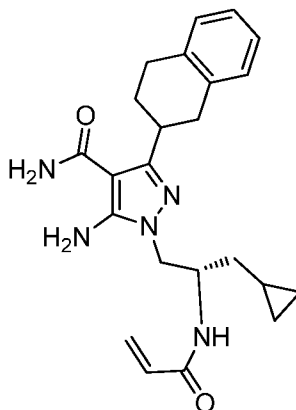
[0359] To a solution of 5-amino-1-((R)-2-amino-3-cyclopropylpropyl)-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carbonitrile hydrochloride (460 mg) in methanol (15 ml) was added 5M NaOH (5 ml). The reaction mixture was cooled to 10 °C and added DMSO (1 ml) and 30% H₂O₂ (2 ml). The mixture was heated to 50 °C for 2h. TLC showed SM was consumed completely. Solvent was removed under vacuum and diluted with water (10 ml), filtered and washed with water, dried under vacuum to give a yellow solid (270 mg). MS (ESI) m/e [M+1]⁺ 354.

Step 6: 1-((R)-2-acrylamido-3-cyclopropylpropyl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



[0360] To a solution of 5-amino-1-((R)-2-amino-3-cyclopropylpropyl)-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide (170 mg, 0.48 mmol) in CH₃CN (10 ml) and water (8 ml) was added NaHCO₃ (81 mg, 0.96 mmol) and acryloyl chloride (48 mg, 0.53 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min. 10 ml of water was added, filtered and washed with water, to give a white solid, which was purified by prep-TLC (DCM/MeOH=8:1) to give a white solid (80 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.21 – 8.09 (m, 1H), 7.16 (d, *J* = 2.8 Hz, 4H), 6.65 (s, 2H), 6.37 – 6.10 (m, 4H), 5.67 (dd, *J* = 10.1, 2.2 Hz, 1H), 4.25 (dd, *J* = 8.5, 4.7 Hz, 1H), 4.00 – 3.91 (m, 2H), 3.49 – 3.42 (m, 1H), 3.10 – 2.80 (m, 4H), 2.19 (d, *J* = 10.4 Hz, 1H), 1.89 – 1.70 (m, 1H), 1.54 – 1.30 (m, 2H), 0.78 (d, *J* = 6.5 Hz, 1H), 0.51 – 0.37 (m, 2H), 0.21 – 0.13 (m, 1H), 0.01 (dt, *J* = 8.7, 4.8 Hz, 1H). MS (ESI) *m/e* [M+1]⁺ 408.

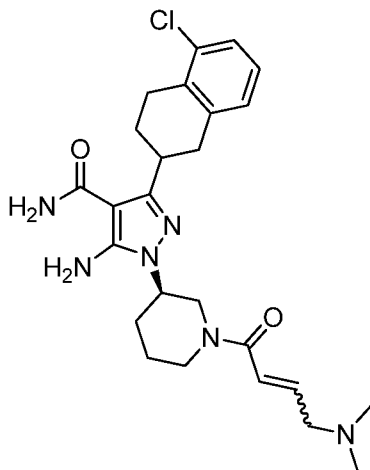
[0361] **Compound 1.63** was prepared according to the procedures described for synthesis of **Compound 1.62** under appropriate conditions that could be recognized by one skilled in the art.



[0362] ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.10 (dd, *J* = 8.3, 4.3 Hz, 1H), 7.16 (d, *J* = 2.9 Hz, 4H), 6.65 (s, 2H), 6.34 – 6.11 (m, 4H), 5.67 (dd, *J* = 10.1, 2.2 Hz, 1H), 4.30 – 4.20 (m, 1H), 3.96 (d, *J* = 6.1 Hz, 2H), 3.50 – 3.43 (m, 1H), 3.10 – 2.81 (m, 4H), 2.19 (d, *J* = 13.1 Hz, 1H), 1.88 – 1.71 (m,

1H), 1.54 – 1.30 (m, 2H), 0.79 (s, 1H), 0.51 – 0.38 (m, 2H), 0.22 - 0.12 (m, 1H), 0.05 -0.04 (m, 1H). MS (ESI) m/e [M+1]⁺ 408.

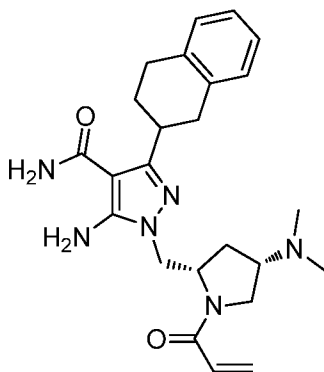
[0363] **Compound 64** was prepared according to the procedures described for synthesis of **Compound 1.11** under appropriate conditions that could be recognized by one skilled in the art.

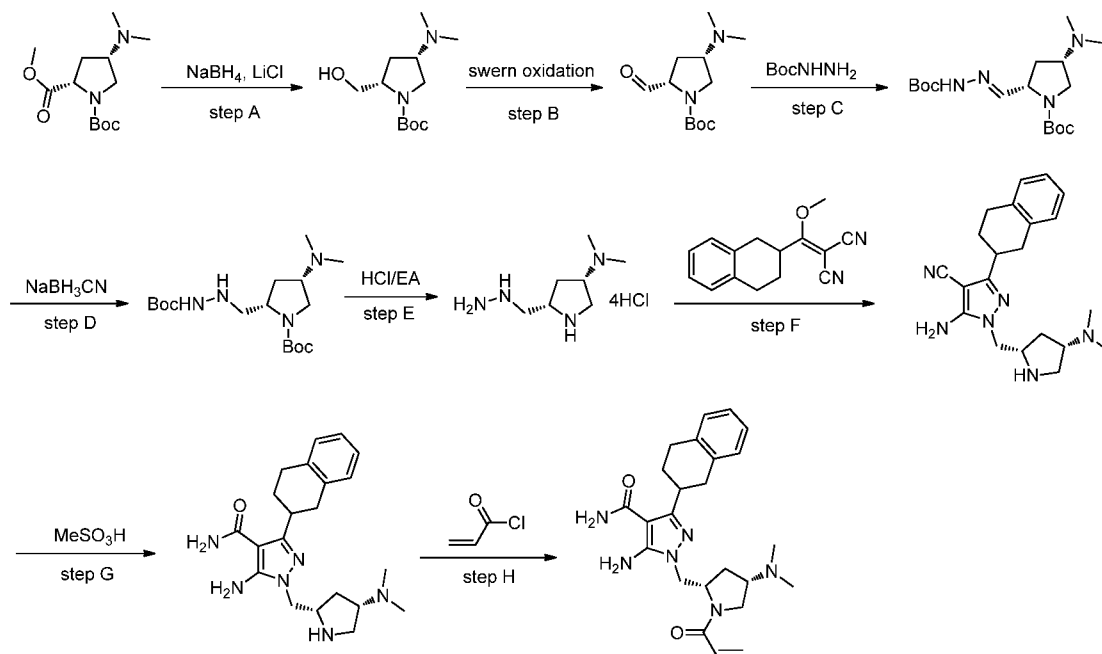


[0364] ¹H NMR (400 MHz, DMSO-*d*₆) δ7.23-7.25 (d, *J*=7.2Hz, 1H), 7.08-7.15 (m, 2H), 6.59-6.68 (m, 4H), 6.23 (s, 2H), 3.94-4.39 (m, 3H), 3.32-3.51 (m, 2H), 2.71-3.19 (m, 8H), 2.21 (s, 6H), 1.45-1.91 (m, 5H). MS (ESI) m/e [M+1]⁺ 485.

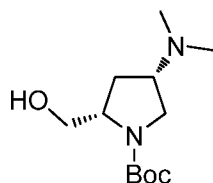
10

[0365] **Compound 1.65**: 1-(((2S,4S)-1-acryloyl-4-(dimethylamino)pyrrolidin-2-yl)methyl)-5-amino-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



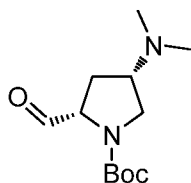


Step A: (2S,4S)-tert-butyl 4-(dimethylamino)-2-(hydroxymethyl)pyrrolidine-1-carboxylate



- 5 **[0366]** To a stirred solution of (2S,4S)-1-tert-butyl 2-methyl 4-(dimethylamino)pyrrolidine-1,2-dicarboxylate (4.9 g, 18 mmol) in THF was added NaBH₄ (1.7 g, 45 mmol) and LiCl (1.67 g, 40 mmol) at 0 °C and followed by the addition of EtOH in drops. After the addition, the mixture was stirred at room temperature for 16 hrs. The mixture was concentrated and added 50 mL of aqueous NaHCO₃, extracted with CH₂Cl₂ (50 mL x 3). The
- 10 combined extracts were washed with brine (50 mL x 2), dried over Na₂SO₄, concentrated to give 2.9 g of crude product. 1.6 g of which was purified by column chromatography eluting with CH₂Cl₂/MeOH (100:1 ~ 40:1) to obtain the title product (810 mg, yield: 32%) as a light yellow solid. MS: M/e 245 (M+1)⁺.

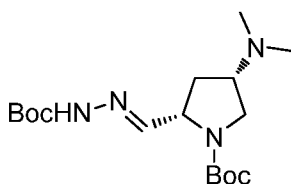
- 15 **Step B:** (2S,4S)-tert-butyl 4-(dimethylamino)-2-formylpyrrolidine-1-carboxylate



[0367] A solution of DMSO (400 mg, 5.1 mmol) in 2 mL of CH₂Cl₂ was added into a solution of oxalyl dichloride (510 mg, 4 mmol) in 2 mL of CH₂Cl₂ in drops at -78 °C under N₂. After stirring for 10 min, a solution of the product of Step A (250 mg, 1 mmol) in 2 mL of CH₂Cl₂ was added slowly below -60 °C. The mixture was stirring for 4 hrs. A solution of Et₃N (800 mg, 8 mmol) in 2 mL of CH₂Cl₂ was injected, and the mixture was allowed warm to room temperature and stirred for another 1 hour. The mixture was diluted with 20 mL of CH₂Cl₂, washed with brine (20 mL x 3), dried, concentrated to dryness to give crude product (280 mg) as light yellow oil which was used for the next step directly. MS: M/e 243 (M+1)⁺.

Step C: (2S,4S)-tert-butyl

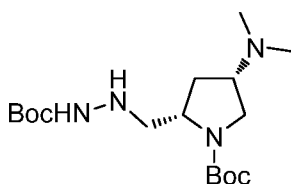
2-((E)-(2-(tert-butoxycarbonyl)hydrazono)methyl)-4-(dimethylamino)pyrrolidine-1-carboxylate



[0368] A mixture of the product of Step B (280 mg, crude) and tert-butyl hydrazinecarboxylate (160 mg, 1.2 mmol) in MeOH (5 mL) was stirred at room temperature for 5 hrs. The mixture was concentrated to dryness to give the title product (380 mg, crude) as light yellow oil which was used for the next step directly. MS: M/e 357 (M+1)⁺.

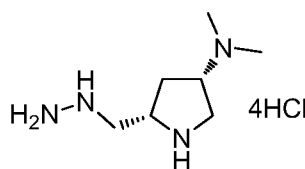
Step D: (2S,4S)-tert-butyl

2-((2-(tert-butoxycarbonyl)hydrazinyl)methyl)-4-(dimethylamino)pyrrolidine-1-carboxylate



[0369] To a stirred solution of the product of Step C (380 mg, crude) in a mixed solvent AcOH/H₂O (1:1, 5 mL) was added NaBH₃CN (160 mg, 2.6 mmol) at room temperature and the mixture was stirred for 5 hrs. The mixture was concentrated, and added 10 mL of aqueous NaOH (2M), extracted with CH₂Cl₂ (10 mL x 5). The combined extracts were washed brine (10 mL x 3), dried over Na₂SO₄, and concentrated to dryness and purified by column chromatography eluting with CH₂Cl₂/MeOH (50:1 ~ 30:1, 0.3% of NH₃/MeOH) to obtain the title product (105 mg, yield: 29% for 3 steps) as colorless oil. MS: M/e 359 (M+1)⁺.

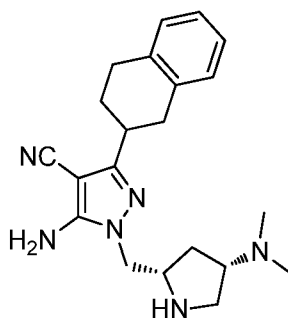
Step E: (3S,5S)-5-(hydrazinylmethyl)-N,N-dimethylpyrrolidin-3-amine



[0370] To a stirred solution of the product of step D (105 mg, 0.29 mmol) in EA (1 mL) was added HCl/EA (5 mL, 5 M) at room temperature and the mixture was stirred for 5 hrs. The mixture was concentrated to dryness and 20 mL of EA was added and the mixture was concentrated again to remove the residual of HCl to give the title product (86 mg, yield: 96%) as a white solid. MS: M/e 159 (M+1)⁺.

Step F:

5-amino-1-(((2S,4S)-4-(dimethylamino)pyrrolidin-2-yl)methyl)-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carbonitrile

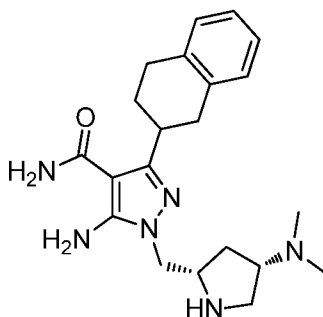


[0371] A mixture of the product of step E (86 mg, 0.28 mmol), and 2-(methoxy(1,2,3,4-tetrahydronaphthalen-2-yl)methylene)malononitrile (68 mg, 0.29 mmol) in

EtOH (2 mL) was added Et₃N (200 mg, 2 mmol) at room temperature and the mixture was stirred for 3 hrs. The mixture was concentrated to dryness to give the title product (158 mg, crude) as a dark brown solid which was used for the next step directly. MS: M/e 365 (M+1)⁺.

5 Step G:

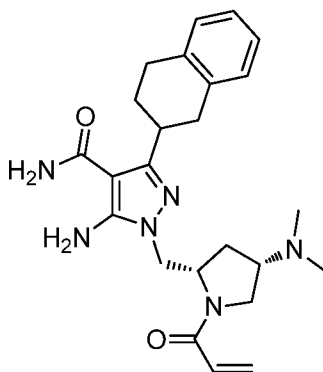
5-amino-1-(((2S,4S)-4-(dimethylamino)pyrrolidin-2-yl)methyl)-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



10 [0372] A solution of the product of step F (158 mg, crude) in MeSO₃H (5 mL) was heated at 70 °C for 3 hrs. The mixture was cooled to room temperature and was added an aqueous NaOH in drops to pH~9. The mixture was extracted with CH₂Cl₂ (20 mL x 5). The combined extracts was washed with brine (20 mL x 3), dried, concentrated to dryness to give crude product (145 mg) as brown oil which was used for the next step directly. MS: M/e 383 (M+1)⁺.

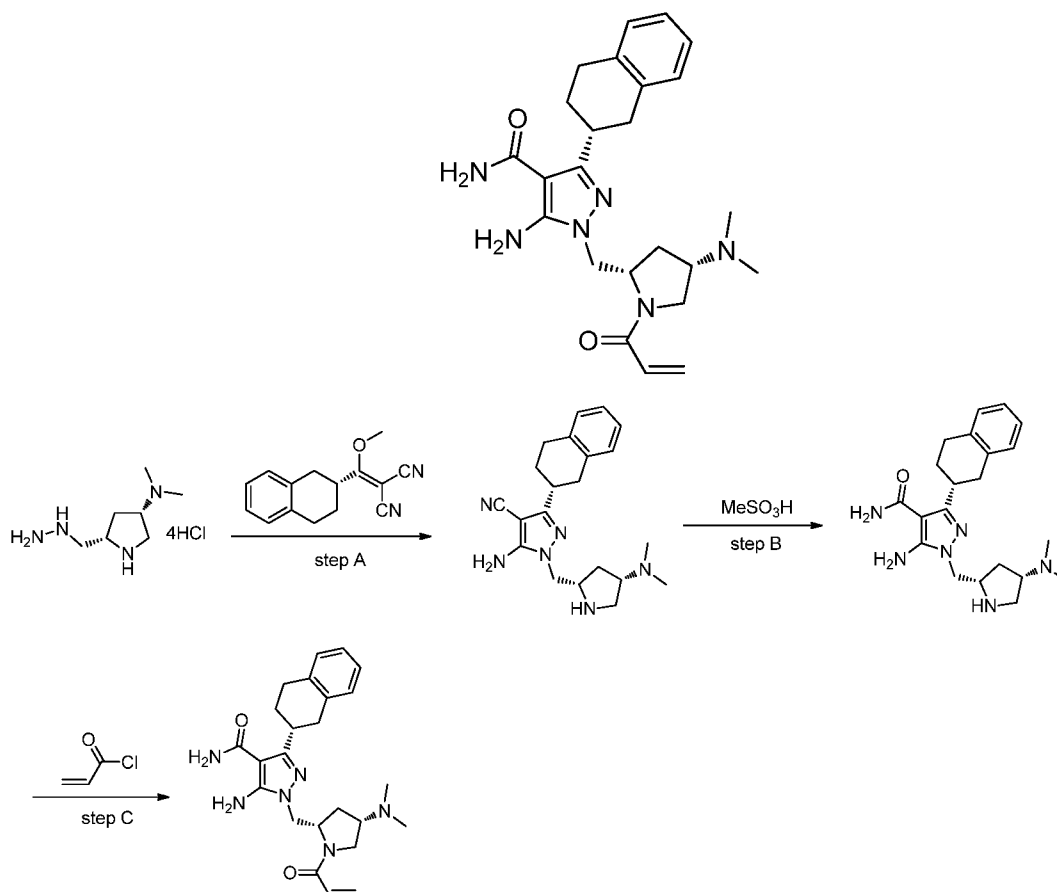
15 Step H:

1-(((2S,4S)-1-acryloyl-4-(dimethylamino)pyrrolidin-2-yl)methyl)-5-amino-3-(1,2,3,4-tetrahydro naphthalen-2-yl)-1H-pyrazole-4-carboxamide

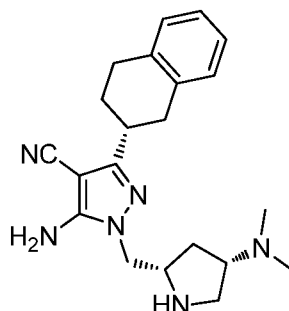


[0373] To a mixture of the product of step G (145 mg, crude) and NaHCO_3 (100 mg, 1.2 mmol) in a mixed solvent MeCN/ H_2O (1:1, 4 mL) was added a solution of acryloyl chloride (25 mg, 0.28 mmol) in MeCN (1 mL) in drops at room temperature. The mixture was stirred for 2 hrs. EA (10 mL) was added and the mixture was washed with brine (5 mL x 3), dried, concentrated to dryness and the resulted residue was purified by *prep*-TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}=12:1$, 0.5% of NH_3/MeOH), and *prep*-HPLC to give the title product (18 mg, yield: 15% for 3 steps) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$, 80°C) δ 7.10 – 6.98 (m, 4H), 6.65 – 6.25 (m, 3H), 6.20 – 6.02 (m, 1H), 5.92 (s, 2H), 5.65 (s, 1H), 4.34 – 3.69 (m, 4H), 3.41 – 3.25 (m, 1H), 3.01 – 2.72 (m, 5H), 2.65 – 2.52 (m, 1H), 2.15 (s, 6H), 2.13 – 1.90 (m, 2H), 1.83 – 1.71 (m, 2H). MS: M/e 437 ($M+1$) $^+$.

Compound 1.65a: 1-(((2S,4S)-1-acryloyl-4-(dimethylamino)pyrrolidin-2-yl)methyl)-5-amino-3-((R)-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide

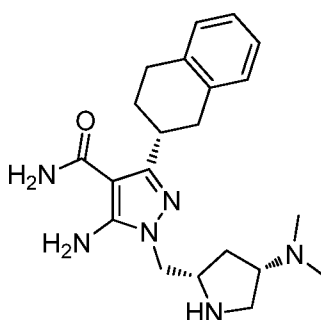


Step A: 5-amino-1-(((2S,4S)-4-(dimethylamino)pyrrolidin-2-yl)methyl)-3-((R)-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carbonitrile



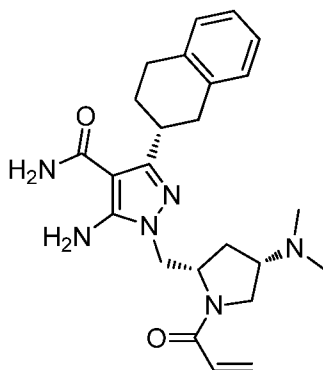
[0374] A mixture of (3S,5S)-5-(hydrazinylmethyl)-N,N-dimethylpyrrolidin-3-amine (190 mg, 0.63 mmol), and (R)-2-(methoxy(1,2,3,4-tetrahydronaphthalen-2-yl)methylene) malononitrile (165 mg, 0.69 mmol) in EtOH (5 mL) was added Et₃N (600 mg, 2 mmol) at room temperature and the mixture was stirred for 3 hrs. The mixture was concentrated. The residue was diluted with 10 mL of CH₂Cl₂ and washed with brine (50 mL x 3), dried over Na₂SO₄ and concentrated to give the title product (280 mg, crude) as a dark brown solid which was used for the next step directly. MS: M/e 365 (M+1)⁺.

Step B: 5-amino-1-(((2S,4S)-4-(dimethylamino)pyrrolidin-2-yl)methyl)-3-((R)-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



[0375] A solution of the product of Step A (280 mg, crude) in MeSO₃H (5 mL) was heated at 70 °C for 3 hrs. The mixture was cooled to room temperature and was added an aqueous NaOH in drops to pH~9. The mixture was extracted with CH₂Cl₂ (20 mL x 5). The combined extracts were washed with brine (20 mL x 3), dried and concentrated to give crude product (170 mg) as a brown oil which was used for the next step directly. MS: M/e 383 (M+1)⁺.

Step C: 1-(((2S,4S)-1-acryloyl-4-(dimethylamino)pyrrolidin-2-yl)methyl)-5-amino-3-((R)-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide

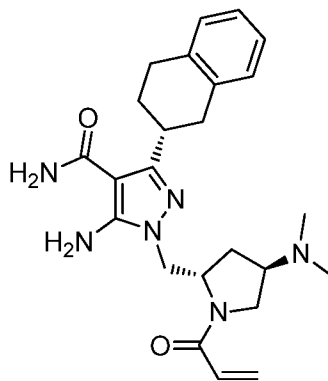


[0376] To a mixture of the product of Step B (170 mg, crude) and NaHCO₃ (180 mg, 1.2 mmol) in a mixed solvent MeCN/H₂O (1:1, 5 mL) was added a solution of acryloyl chloride (40 mg, 0.45 mmol) in MeCN (1 mL) in drops at room temperature. The mixture was stirred for 2 hrs. EA (20 mL) was added and the mixture was washed with brine (10 mL x 3), dried and concentrated. The resulted residue was purified by *prep*-HPLC to give the title product (45 mg, yield: 16% for 3 steps) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆, 80°C) δ 7.05 (s, 4H), 6.75 - 6.25 (m, 3H), 6.20 - 6.02 (m, 1H), 5.92 (s, 2H), 5.75 - 5.45 (m, 1H), 4.45 - 3.69 (m, 4H), 3.45 - 3.25 (m, 1H), 3.01 - 2.72 (m, 5H), 2.66 - 2.50 (m, 1H), 2.15 (s, 6H), 2.13 - 1.90 (m, 2H), 1.83 - 1.71 (m, 2H). MS: M/e 437 (M+1)⁺. ee: 100%, retention time: 9.662 min.

[0377] The chiral analysis conditions are shown below.

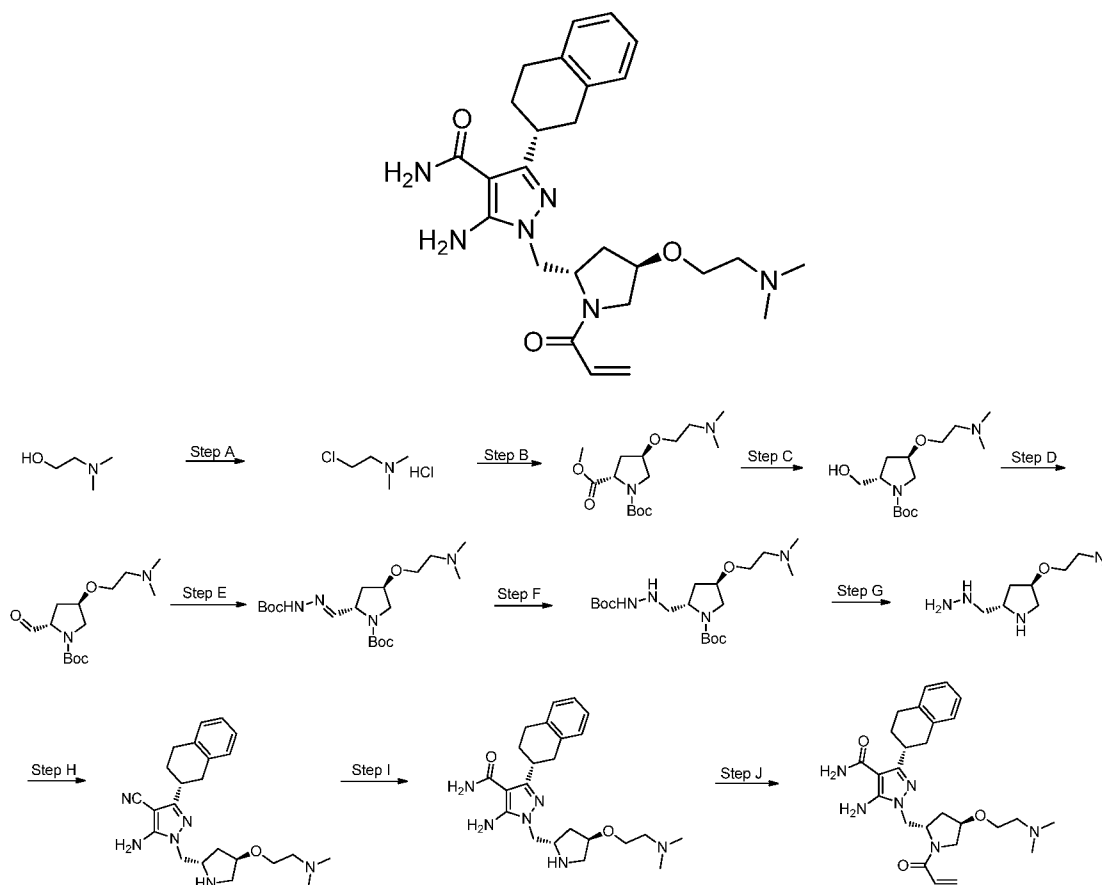
Column	CHIRALCEL AS-H
Column size	0.46 cm I.D. ×15 cm L
Injection	2.0 ul
Mobile phase	n-Hexane/EtOH (0.1%TEA)=90/10
Flow rate	1 ml/min
Wave length	UV 254nm, UV 280nm
Temperature	35 °C

[0378] Compound 1.66a was prepared according to the procedures described for the synthesis of Compound 1.65a under appropriate conditions that could be recognized by one skilled in the art.

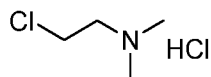


[0379] $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ 7.07 (s, 4H), 6.70 – 6.50 (m, 3H), 6.27 – 5.98 (m, 3H), 5.81 – 5.40 (m, 1H), 4.47 – 4.20 (m, 1H), 4.06 – 3.84 (m, 2H), 3.80 – 3.49 (m, 1H), 3.31 – 3.15 (m, 2H), 3.08 – 2.72 (m, 4H), 2.61 – 2.52 (m, 1H), 2.19 – 2.06 (m, 7H), 2.04 – 1.93 (m, 1H), 1.84 – 1.63 (m, 2H)ppm. MS: M/e 437 ($M+1$) $^+$.

Compound 1.67a: 1-(((2S,4R)-1-acryloyl-4-(2-(dimethylamino)ethoxy)pyrrolidin-2-yl)methyl)-5-amino-3-((R)-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide

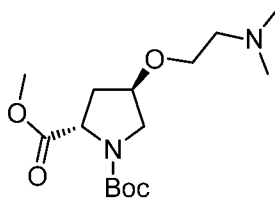


Step A: 2-chloro-N,N-dimethylethanamine hydrochloride



[0380] To a solution of 2-(dimethylamino)ethanol (2.0 g, 22.5 mmol) in DCM (20 mL) was added dropwise thionyl chloride (3.5 g, 29.3 mmol) at 0 °C. Then the reaction was stirred at rt overnight. Removing solvent, the residue was suspended with PE:EA 10:1 (50 mL). The mixture was filtered, and the solid was collected and dried to afford the product (3.2 g, yield: 100%)

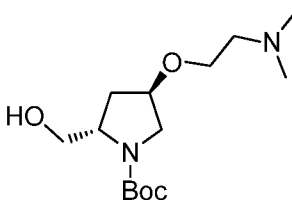
Step B: (2S,4R)-1-tert-butyl 2-methyl 4-(2-(dimethylamino)ethoxy)pyrrolidine-1,2-dicarboxylate



[0381] To a solution of (2S,4R)-1-tert-butyl 2-methyl 4-hydroxypyrrolidine-1,2-dicarboxylate (4.3 g, 17.5 mmol) in DMF (50 mL) was added NaH (1.75 g, 43.8 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min. Then the product of Step A (3.0 g, 21 mmol) was added at 0 °C. Allowed to warm to rt, the reaction was stirred at rt overnight. The reaction was quenched with H₂O (20 mL) at 0 °C. The mixture was diluted with H₂O (50 mL) and extracted with DCM (50 mL x 3). The combined extracts were washed with brine (50 mL x 2), dried over Na₂SO₄, concentrated to give the product which was purified by column chromatography eluting with CH₂Cl₂/MeOH (10:1) to obtain the title product (650 mg, yield: 12%) as a light yellow solid. MS: M/e 317 (M+1)⁺.

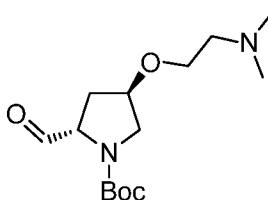
Step C: (2S,4R)-tert-butyl

4-(2-(dimethylamino)ethoxy)-2-(hydroxymethyl)pyrrolidine-1-carboxylate



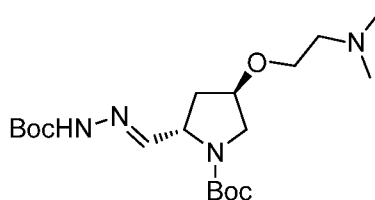
[0382] To a stirred solution of the product of Step B (650 mg, 2.0 mmol) in THF (6mL) was added NaBH₄ (190 g, 5.0 mmol) and LiCl (187 g, 4.4 mmol) at 0 °C, followed by the addition of EtOH (4 mL) in drops. After the addition, the mixture was stirred at room temperature for 2 days. The mixture was concentrated and the mixture was suspended with DCM (50 mL). The mixture was filtered, and the filtrates was concentrated to afford the crude product which was purified by column chromatography eluting with CH₂Cl₂/MeOH (20:1) to obtain the title product (300 mg, yield: 50%) as yellow oil. MS: M/e 289 (M+1)⁺.

Step D:(2S,4R)-tert-butyl 4-(2-(dimethylamino)ethoxy)-2-formylpyrrolidine-1-carboxylate



[0383] To a solution of oxalyl dichloride (635 mg, 5 mmol) in 2 mL of CH₂Cl₂ was added a solution of DMSO (468 mg, 6 mmol) in 2 mL of CH₂Cl₂ in drops at -78 °C under N₂. After stirring for 10 min, a solution of the product of Step C (300 mg, 1 mmol) in 2 mL of CH₂Cl₂ was added slowly below -60 °C. The mixture was stirring for 2 hrs. A solution of Et₃N (800 mg, 8 mmol) in 2 mL of CH₂Cl₂ was injected, and the mixture was allowed warm to room temperature and stirred for another 1 hour. The mixture was diluted with 10 mL of H₂O, extracted with DCM (15 mL x 5), dried, concentrated to dryness to give crude product (410 mg) as yellow oil which was used for the next step directly. MS: M/e 287 (M+1)⁺.

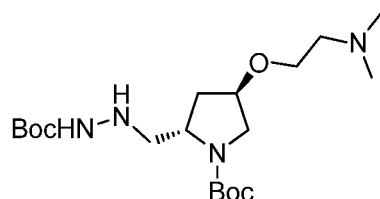
Step E:(2S,4R)-tert-butyl 2-((E)-(2-(tert-butoxycarbonyl)hydrazono)methyl)-4-(2-(dimethylamino)ethoxy)pyrrolidine-1-carboxylate



[0384] A mixture of the product of step D (410 mg, crude) and tert-butyl hydrazinecarboxylate (132mg, 1.0 mmol) in MeOH (5 mL) was stirred at room temperature for 5 overnight. The mixture

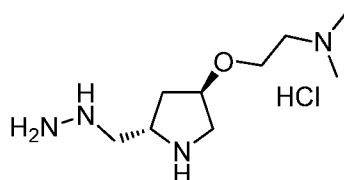
was concentrated to dryness to give the title product (500 mg, crude) as yellow oil which was used for the next step directly. MS: M/e 401 (M+1)⁺.

Step F: (2S,4R)-tert-butyl 2-((2-(tert-butoxycarbonyl)hydrazinyl)methyl)-4-(2-(dimethylamino)ethoxy)pyrrolidine-1-carboxylate



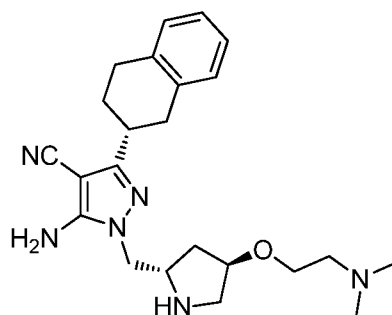
[0385] To a stirred solution of the product of step E (500 mg, crude) in a mixed solvent AcOH/H₂O (1:1, 4 mL) was added NaBH₃CN (95 mg, 1.5 mmol) at room temperature and the mixture was stirred for 3 hrs. The mixture was concentrated, and the residue was adjusted to pH=8-9 with aqueous NaOH (2M). Then the mixture was extracted with CH₂Cl₂ (10 mL x 5). The combined extracts were washed brine (10 mL), dried over Na₂SO₄, and concentrated to dryness and purified by column chromatography eluting with CH₂Cl₂/MeOH (25:1, 0.3% of NH₃/MeOH) to obtain the title product (260 mg, yield: 65% for 3 steps) as colorless oil. MS: M/e 403 (M+1)⁺.

Step G: 2-(((3R,5S)-5-(hydrazinylmethyl)pyrrolidin-3-yl)oxy)-N,N-dimethylethanamine hydrochloride



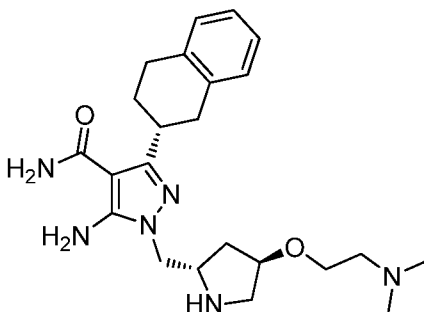
[0386] To a stirred solution of the product of step D (260 mg, 0.65 mmol) in EA (1 mL) was added HCl/EA (5 mL, 5 M) at room temperature and the mixture was stirred for 2 hrs. The mixture was concentrated to dryness to give the title product (360 mg, yield: 100%) as a white solid. MS: M/e 203 (M+1)⁺.

Step H: 5-amino-1-(((2S,4R)-4-(2-(dimethylamino)ethoxy)pyrrolidin-2-yl)methyl)-3-((R)-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carbonitrile



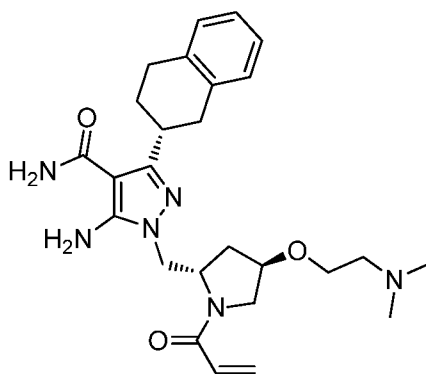
[0387] A mixture of the product of step E (360 mg, 0.65 mmol), and (R)-2-(methoxy(1,2,3,4-tetrahydronaphthalen-2-yl)methylene)malononitrile (155 mg, 0.65 mmol) in EtOH (5 mL) was added Et₃N (0.5) at room temperature and the mixture was stirred for 1h. The mixture was concentrated to dryness and purified by column chromatography eluting with CH₂Cl₂/MeOH (10:1, 0.3% of NH₃/MeOH) to obtain the title product (150 mg, crude) as yellow solid. MS: M/e 409 (M+1)⁺.

Step I: 5-amino-1-(((2S,4R)-4-(2-(dimethylamino)ethoxy)pyrrolidin-2-yl)methyl)-3-((R)-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide



[0388] A solution of the product of step H (150 mg, crude) in MeSO₃H (5 mL) was heated at 70 °C for 3 hrs. The mixture was cooled to room temperature and was adjusted to pH~8 with an aqueous NaOH (2N) in drops at 0 °C. The mixture was extracted with CH₂Cl₂ (15 mL x 5). The combined extracts were washed with brine (10 mL), dried, concentrated to dryness to give crude product (110 mg, crude) as brown oil which was used for the next step directly. MS: M/e 427 (M+1)⁺.

Step J: 1-(((2S,4R)-1-acryloyl-4-(2-(dimethylamino)ethoxy)pyrrolidin-2-yl)methyl)-5-amino-3-((R)-1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazole-4-carboxamide

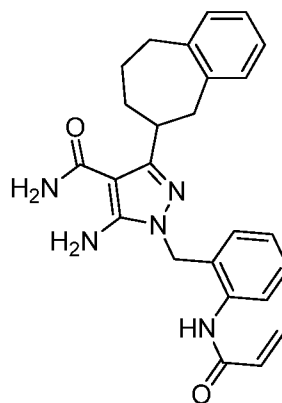


[0389] To a mixture of the product of step I (110 mg, crude) and NaHCO_3 (87 mg, 1.0 mmol) in a mixed solvent MeCN/ H_2O (1:1, 4 mL) was added a solution of acryloyl chloride (24 mg, 0.26 mmol) in MeCN (1 mL) in drops at 0 °C. The mixture was stirred for 10 min. EA (50 mL) was added and the mixture was washed with brine (10 mL), dried, concentrated to dryness and the resulted residue was purified *prep*-HPLC to give the title product (5 mg, yield: 2% for 3 steps) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.07 (s, 4H), 6.71 – 6.50 (m, 2H), 6.26 – 5.99 (m, 3H), 5.76 – 5.42 (m, 1H), 4.51 – 4.22 (m, 1H), 4.13 – 4.02 (m, 1H), 3.98 – 3.82 (m, 1H), 3.64 – 3.49 (m, 1H), 3.46 – 3.37 (m, 3H), 3.04 – 2.76 (m, 4H), 2.39 – 2.28 (m, 2H), 2.15 – 1.65 (m, 12H). MS: M/e 481 ($M+1$) $^+$.

Example 2: Synthesis of Compounds 2.1-2.11

Compound 2.1: 1-(2-acrylamidobenzyl)-5-amino-3-(6,7,8,9-tetrahydro-5H-benzo[7] annulen-6-yl)-1H-pyrazole-4-carboxamide

[0390] **Compound 2.1** was prepared according to the procedures described for **Compound 1.20** under appropriate conditions that could be recognized by one skilled in the art.

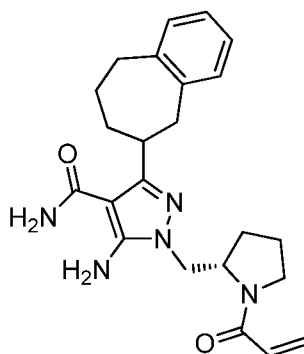


[0391] ^1H NMR (400 MHz, DMSO- d_6) δ 10.41 (br.s, 1H), 7.62 (d, $J = 7.8$ Hz, 1H), 7.45 (d, $J = 7.2$ Hz, 1H), 7.25 (t, $J = 7.8$ Hz, 1H), 7.19 – 7.02 (m, 6H), 6.78 – 6.50 (m, 3H), 6.29 (d, $J = 18.4$ Hz, 1H), 5.79 (d, $J = 10.4$ Hz, 1H), 4.31 (s, 2H), 3.18 (d, $J = 9.2$ Hz, 2H), 2.88 – 2.71 (m, 3H), 2.17 – 1.78 (m, 3H), 1.40 (d, $J = 14.0$ Hz, 1H)ppm. MS: M/e 430 (M+1) $^+$

5

Compound 2.2: 1-(((S)-1-acryloylpyrrolidin-2-yl)methyl)-5-amino-3-(6,7,8,9-tetrahydro-5H-benzo[7]annulen-6-yl)-1H-pyrazole-4-carboxamide

[0392] **Compound 2.2** was prepared according to the procedures described for **Compound 1.14** under appropriate conditions that could be recognized by one skilled in the art.

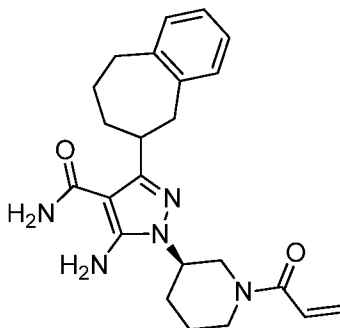


10

[0393] ^1H NMR (400 MHz, DMSO- d_6) δ 7.16 – 7.00 (m, 4H), 6.56 (br.s, 1H), 6.43 – 5.95 (m, 3H), 5.80 – 5.38 (m, 2H), 4.45 – 4.18 (m, 1H), 4.12 – 3.85 (m, 2H), 3.49 (br.s, 2H), 3.16 – 2.68 (m, 5H), 2.13 – 2.01 (m, 2H), 1.84 (s, 5H), 1.53 – 1.33 (m, 1H)ppm. MS: M/e 408 (M+1) $^+$

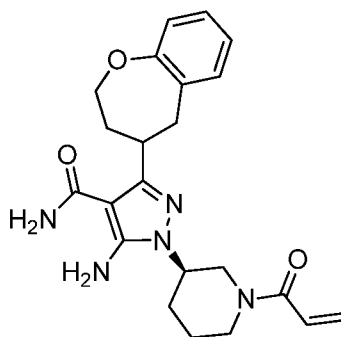
15 **Compound 2.3:** 1-(((R)-1-acryloylpiperidin-3-yl)-5-amino-3-(6,7,8,9-tetrahydro-5H-benzo[7]annulen-6-yl)-1H-pyrazole-4-carboxamide

[0394] **Compound 2.3** was prepared according to the procedures described for **Compound 1.15** under appropriate conditions that could be recognized by one skilled in the art.

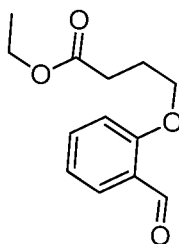


[0395] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.23 - 7.00 (m, 4H), 6.95 - 6.72 (m, 1H), 6.48 (br.s, 2H), 6.21 - 6.01 (m, 1H), 5.77 - 5.60 (m, 1H), 4.41 - 3.97 (m, 3H), 3.44 - 2.67 (m, 7H), 2.16 (d, $J = 12.4$ Hz, 1H), 2.06 - 1.72 (m, 5H), 1.45 - 1.36 (m, 2H)ppm. MS: M/e 408 ($M+1$)⁺

5 **Compound 2.4:** 1-((R)-1-acryloylpiperidin-3-yl)-5-amino-3-(2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)-1H-pyrazole-4-carboxamide

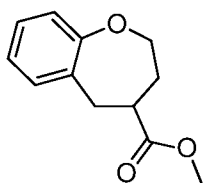


Step A: Ethyl 4-(2-formylphenoxy)butanoate



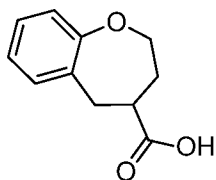
10 **[0396]** To a solution of 2-hydroxybenzaldehyde(122g, 1.0mol) and ethyl 4-bromobutanoate (195g, 1.0mol) in DMF(500mL) was added Cs_2CO_3 (325g, 1.0mol) at room temperature, the reaction mixture was stirred at room temperature for 3 hours. The mixtures was quenched with H_2O (1500mL), EA(1500mL) was added, the organic layer was washed with brine (500mL) , dried
15 over Na_2SO_4 and concentrated to give yellow oil (W=224g, Y=95%) which was used to the next step without further purification. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.37 (s, 1H), 7.62-7.70(m, 2H), 7.22 (d, 1H, $J=8.4$ Hz), 7.07 (t, 1H, $J=7.2$ Hz), 4.16 (t, 2H, $J=6.0$ Hz), 4.05 (q, 2H, $J=7.2$ Hz), 2.50-2.51 (m, 2H), 1.99-2.08 (m, 2H) and 1.15-1.19 (q, 3H, $J=7.2$ Hz).MS (ESI) m/e [$M+1$]⁺237

20 **Step B:** Methyl 2,3,4,5-tetrahydrobenzo[b]oxepine-4-carboxylate



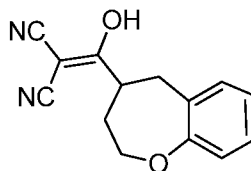
[0397] Ethyl 4-(2-formylphenoxy) butanoate (32g, 135mmol) in dimethyl carbonate (600mL) was dropwised CH_3ONa (5.4 M in MeOH) (30mL, 162mmol) at 50°C , it was stirred for another 2 hours at 50°C . The mixture was quenched with H_2O (600mL), EA (600mL) was added; the organic layer was washed with brine (200mL), dried over Na_2SO_4 and concentrated. The residue was dissolved in EA/MeOH (100mL/100mL), and then 10% Palladium on carbon (50% water wet, 5.0g) was added, the reaction mixture was hydrogenated with H_2 at 1.5Mpa overnight. The catalyst was removed by filtrating, the filtrate was concentrated. The residue was purified by chromatography on silica gel using PE/EA(1:5-1:10) as eluting solvent to give 19.0 g (Y=68%) product as yellow oil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.13-7.22(m, 2H), 6.92-7.01 (m, 2H), 4.18 -4.23(m, 1H), 3.74-3.79(m,2H), 3.61(s, 3H), 2.96-2.97(m, 2H) , and 1.99-2.13 (m, 2H).MS (ESI) m/e $[\text{M}+1]^+$ 207

Step C: 2,3,4,5-tetrahydrobenzo[b]oxepine-4-carboxylic acid



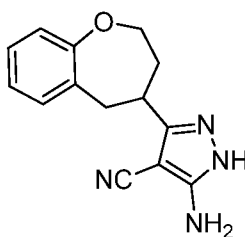
[0398] To a solution of methyl 2,3,4,5-tetrahydrobenzo[b]oxepine-4-carboxylate (19.0g , 92.2mmol) in MeOH/ H_2O (150mL/ 50mL) was added lithium hydroxide(13.8g, 276.6mmol) at 5°C - 10°C , the mixture was stirred at room temperature for 5 hours. Then the solvent was removed by reduce pressure. The residue was acidized with 1N HCl adjust to pH=3-4, the precipitate was filtered to give a white solid which was dried over infrared box (W=17.0g, Y=96%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.36 (s, 1H), 7.12-7.22 (m, 2H), 6.92-7.00 (m, 2H), 4.14 -4.24 (m, 1H), 3.73-3.78 (m, 2H), 2.90-2.99 (m, 2H) and 1.99-2.13 (m, 2H).MS (ESI) m/e $[\text{M}+1]^+$ 193

Step D: 2-(Hydroxy(2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)methylene)malononitrile



[0399] 2,3,4,5-Tetrahydrobenzo[b]oxepine-4-carboxylic acid (24.6g, 128mmol) was suspended in EA(200mL), then HOBt (19.0g, 141mmol) was added, the mixture was stirred at RT for 0.5 hour, then Et₃N(38.8g, 384mmol) was added, the reaction mixture was stirred for another 0.5 hour, then EDCI(27.09g, 141mmol) was added, then the mixture was stirred for another 0.5 hour, then malononitrile (9.3g, 141mmol) was dropwised. The reaction mixture was stirred at RT for overnight. The reaction mixture was quenched with H₂O, EA (200mL) was added, washed with aq NaHCO₃ (500mL), then the organic layer was stirred with aq H₂SO₄ (25g/200mL H₂O) for 3 hours, which was then directly concentrated to give yellow oil as crude product (w=27.0 g, Y=88%). MS (ESI) m/e [M+1]⁺241.

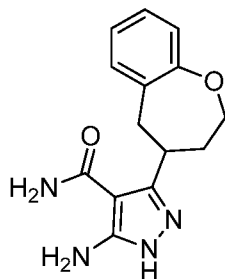
Step E: 5-Amino-3-(2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)-1H-pyrazole-4- carbo nitrile



[0400] 2-(Hydroxy(2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)methylene)malononitrile (27.0g, 112.5 mmol) was dissolved in trimethoxymethane (600mL), the reaction mixture was heated to 100°C for 5 hours. The solvent was removed by reduced pressure to give crude product, which was dissolved in EtOH(100mL), then hydrazine hydrate (6.12g, 123.75mmol) was added at 5°C-10 °C for 0.1 hour. The reaction mixture was stirred at RT overnight, and then solvent was removed by reduced pressure. The residue was purified by chromatography on silica gel usingEA (V=1.0L) as eluting solvent to give21.0 g (Y=73%) product as yellow oil.¹H NMR (400 MHz, DMSO-*d*₆) δ

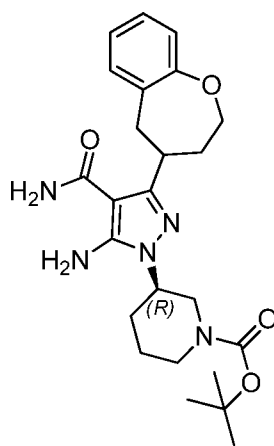
11.66 (s,1H),7.14-7.20 (m, 2H), 6.94-7.01 (m, 2H), 6.30 (s, 2H), 4.37-4.40 (m, 1H), 3.66-3.71 (m, 1H), 3.35 (m, 1H), 2.85-2.89 (m, 2H) and 2.06-2.23 (m, 2H).

Step F: 5-Amino-3-(2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)-1H-pyrazole-4-carboxamide



[0401] A solution of 5-amino-3-(2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)-1H-pyrazole -4-carbonitrile (4.7g, 18.5 mmol) and in H₃PO₄(60mL) was stirred for 1h at 130°C. LC/MS showed it was completed. The mixture was poured into ice-water and adjusted pH>8 with aq. NaOH. The mixture was extracted with EtOAc (100mL× 3) and dried over with Na₂SO₄, filtered and concentrated to give crude product, which was purified by chromatography column on silica(150 g) using EtOAc(3L) as eluting to give the product (2g, 40%) as a brown solid. MS (ESI) m/e [M+1]⁺273.

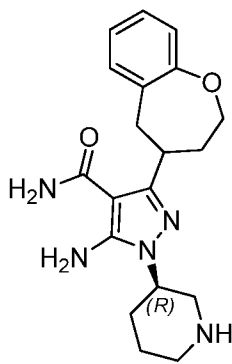
Step G: (3R)-tert-butyl 3-(5-amino-4-carbamoyl-3-(2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate



[0402] To a solution of 5-amino-3-(2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)- 1H-pyrazole-4-carboxamide(600mg, 2.21 mmol) in DMF (30mL) was added (*S*)-tert-butyl

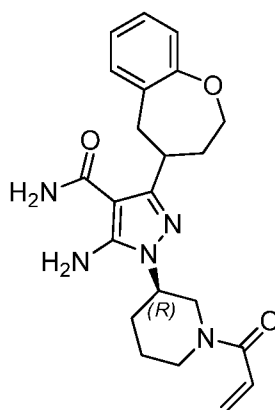
3-(tosyloxy)piperidine-1-carboxylate (**BL-1**, 1.6g, 4.42 mmol) and Cs_2CO_3 (1.44 g, 4.42 mmol). The mixture was stirred overnight at 70°C. After cooling to RT, the solution was removed *in vacuo*. H_2O (50 mL) was added to the residue, extracted with EtOAc (50 mL $\times$ 3). The organic layer was purified with chromatography column on silica (50 g) eluting with EtOAc (1L) to give the product (200mg, 20%) as a brown solid. MS (ESI) m/e $[\text{M}+1]^+$ 456.

Step H: 5-Amino-1-((R)-piperidin-3-yl)-3-(2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)-1H-pyrazole-4-carboxamide



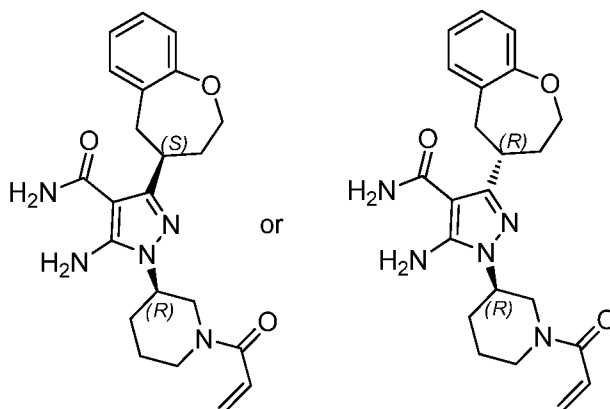
[0403] To a solution of (3R)-tert-butyl 3-(5-amino-4-carbamoyl-3-(2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)-1H-pyrazol-1-yl) piperidine-1-carboxylate (200 mg, 0.44 mmol) in DCM (20 mL) was added $\text{CF}_3\text{CO}_2\text{H}$ (2 mL) and stirred for 30 min. TLC showed the reaction was completed. The mixture was adjusted pH > 8 with saturated NaHCO_3 . The aqueous layer was extracted with DCM (20mL), dried over with Na_2SO_4 , filtered and concentrated to give the product (390mg, 250%) as brown oil, which was used to the next step without further purification.

Step I: 1-((R)-1-acryloylpiperidin-3-yl)-5-amino-3-(2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)-1H-pyrazole-4-carboxamide



[0404] To a solution of 5-amino-1-((R)-piperidin-3-yl)-3-(2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)-1H-pyrazole-4-carboxamide (390 mg, 1.1 mmol) and Et₃N (2 ml) in DCM was slowly dropwise added acryloyl chloride (99 mg, 1.1 mmol) at 0°C. The mixture was stirred for 2 mins at 0°C and was quenched with H₂O (30 ml), extracted with DCM (30 ml × 2), dried with Na₂SO₄, filtered and concentrated to give the crude product, which was further purified by prepare-HPLC to give the product (46.32 mg, 10%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.11-7.18 (m, 2H), 6.92-6.99 (m, 2H), 6.73-6.89 (m, 1H), 6.56 (s, 2H), 6.20 (s, 2H), 6.04-6.15 (m, 1H), 5.61-5.71 (m, 1H), 4.35-4.40 (m, 1H), 3.94-4.27 (m, 2H), 3.69-3.74 (m, 1H), 3.27-3.45 (m, 2H), 2.80-3.12 (m, 4H), 1.83-2.12 (m, 5H), 1.34-1.47 (m, 1H). MS (ESI) *m/e* [M+1]⁺ 410.

[0405] **Compound 2.4** was separated into two stereoisomers (**Compound 2.4a**, earlier peak, and **Compound 2.4b**, later peak) by chiral *prep*-HPLC. The chiral separation conditions are shown below:



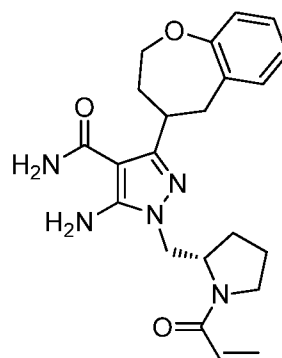
Column	CHIRALPAK OJH ODH
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Column size	0.46 cm I.D. ×25 cm L
Injection	20ul
Mobile phase	CO ₂ /MeOH=75/25(V/V)
Flow rate	2.0 ml/min
Wave length	UV 220nm
Temperature	35 °C

Compound 2.5: 1-(((S)-1-acryloylpyrrolidin-2-yl)methyl)-5-amino-3-(2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)-1H-pyrazole-4-carboxamide

[0406] **Compound 2.5** was prepared according to the procedures described for **Compound 2.4**

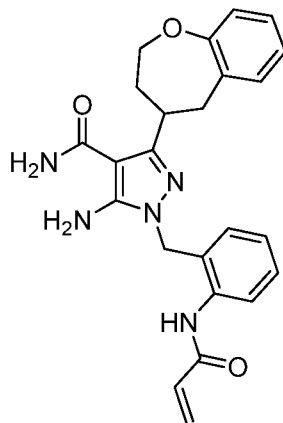
5 under appropriate conditions that could be recognized by one skilled in the art.



[0407] ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.11-7.16 (m, 2H), 6.92-6.99 (m, 2H), 6.55-6.93 (m, 1H), 6.36 (s, 2H), 6.17-6.19 (m, 1H), 6.96 (s, 2H), 5.64-5.69 (m, 1H), 4.36-4.41 (m, 1H), 4.21-4.23 (m, 1H), 4.04-4.07 (m, 1H), 3.89-3.94 (m, 1H), 3.72-3.79 (m, 1H), 3.45-3.47 (m, 2H),
 10 3.24-3.29 (m, 1H), 2.87-2.93 (m, 1H), 2.12-2.15 (m, 1H) and 1.76-1.83 (m, 4H). MS (ESI) m/e [M+1]⁺410.

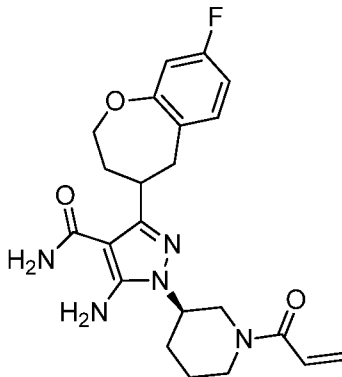
Compound 2.6: 1-(2-acrylamidobenzyl)-5-amino-3-(2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)-1H-pyrazole-4-carboxamide

15 **[0408]** **Compound 2.6** was prepared according to the procedures described for **Compound 1.20** under appropriate conditions that could be recognized by one skilled in the art.

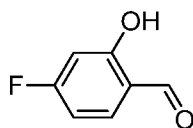


[0409] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.16 (s, 1H), 7.69 (d, $J = 8.0$ Hz, 1H), 7.29 (t, $J = 7.6$ Hz, 1H), 7.11-7.17 (m, 3H), 6.93-7.00 (m, 3H), 6.49-6.64 (m, 3H), 6.29-6.34 (m, 3H), 5.81 (d, $J = 10.0$ Hz, 1H), 5.13 (s, 2H), 4.36-4.40 (m, 1H), 3.69-3.75 (m, 1H), 3.29-3.32 (m, 1H), 2.89-3.07 (m, 2H), 2.06-2.15 (m, 2H). MS (ESI) m/e $[\text{M}+1]^+ 432$.

Compound 2.7: 1-((R)-1-acryloylpiperidin-3-yl)-5-amino-3-(8-fluoro-2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)-1H-pyrazole-4-carboxamide



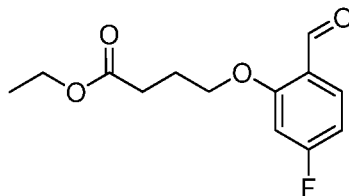
Step A: 4-Fluoro-2-hydroxybenzaldehyde



[0410] To the mixture of 3-fluorophenol (5 mL, 51 mmol), anhydrous magnesium chloride (14.1 g, 372 mmol) in 250 mL of acetonitrile was added triethylamine (34 mL, 190 mmol) and paraformaldehyde (11 g, 372 mmol). The mixture was then heated to reflux for 5 hours. After cooling to room temperature, 250 mL of 5% HCl.aq was added, extracted with EA (100 mL $\times$ 2). The combined organic layer was washed with 5% HCl.aq (100 mL $\times$ 2), brine, and dried over

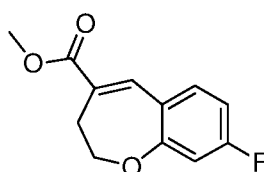
Na₂SO₄, concentrated, purified by chromatography column to give the desired product (2.7 g). ¹H NMR (400 MHz, CDCl₃) δ 11.36 (s, 1H), 9.84 (s, 1H), 7.54-7.58 (m, 1H), 6.65-6.75 (m, 2H)

Step B: Ethyl 4-(5-fluoro-2-formylphenoxy)butanoate



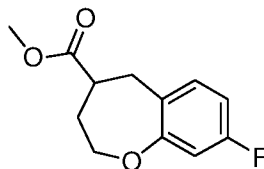
[0411] A mixture of 4-fluoro-2-hydroxybenzaldehyde (2.7 g, 19.3 mmol), ethyl 4-bromobutanoate (4.0 g, 20.5 mmol) and K₂CO₃ (3.5 g, 25.4 mmol) in DMF (30 mL) was heated to 80°C for 2 hours, after cooling to room temperature, the mixture was poured into water (200 mL), extracted with EA (100 mL×2), the combined organic layer was washed with brine, dried over Na₂SO₄, concentrated and purified by column chromatography to give the product (4.8 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.26 (s, 1H), 7.76 (dd, *J* = 8.8, 7.2 Hz, 1H), 7.15 (dd, *J* = 11.6, 2.4 Hz, 1H), 6.91 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.17 (t, *J* = 6.4 Hz, 2H), 4.06 (q, *J* = 7.2 Hz, 2H), 2.49-2.51 (m, 2H), 2.04-2.06 (m, 2H), 1.17 (t, *J* = 7.2 Hz, 3H). MS (ESI) *m/e* [M+1]⁺255.

Step C: (E)-methyl 8-fluoro-2,3-dihydrobenzo[b]oxepine-4-carboxylate



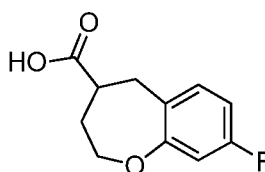
[0412] Ethyl 4-(5-fluoro-2-formylphenoxy)butanoate (3.81g, 15mmol) in dimethyl carbonate (30mL) was added CH₃ONa(5.4 M in MeOH) (3.0mL, 15mmol) at 50°C. The reaction mixture was stirred at 50°C for 3 hours. After cooling to room temperature, the mixture was quenched with EA (100mL) and H₂O (100mL), the organic layer was washed with brine (100mL), dried over Na₂SO₄ and concentrated to give yellow oil as the crude product (w=3.0 g, Y=90%). MS (ESI) *m/e* [M+1]⁺223.

Step D: Methyl 8-fluoro-2,3,4,5-tetrahydrobenzo[b]oxepine-4-carboxylate



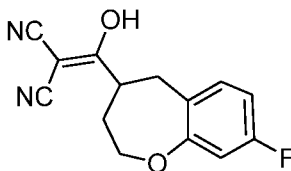
[0413] (E)-methyl 8-fluoro-2,3-dihydrobenzo[b]oxepine-4-carboxylate (3.0g, 13.5mmol) was dissolved in MeOH (30mL), then 10% Palladium on carbon (50% water wet, 5.0g) was added, the reaction mixture was hydrogenated with H₂ gas at 1.5Mpa overnight. The catalyst was removed, the filtrate was concentrated to give yellow oil as the crude product (w=2.8 g, Y=93%). MS (ESI) m/e [M+1]⁺225.

Step E: 8-Fluoro-2,3,4,5-tetrahydrobenzo[b]oxepine-4-carboxylic acid



[0414] To a solution of methyl 8-fluoro-2,3,4,5-tetrahydrobenzo[b]oxepine-4-carboxylate (2.8g, 12.5mmol) in MeOH/ H₂O (20mL/ 20mL) was added lithium hydroxide (1.76g, 62.5mmol) at 5°C-10 °C, the mixture was stirred at room temperature for 3 hours. Then the solvent was removed by reduced pressure. The residue was acidized with 1N HCl adjust to pH=2-4, the precipitate was collected to give a white solid which was dried over infrared box (W=1.8g, Y=69%). MS (ESI) m/e [M+1]⁺211.

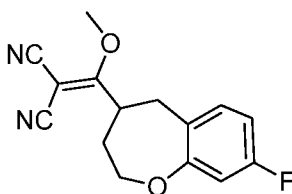
Step F: 2-((8-Fluoro-2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)(hydroxy)methylene)malononitrile



[0415] 8-Fluoro-2,3,4,5-tetrahydrobenzo[b]oxepine-4-carboxylic acid (1.8g, 8.6mmol) was suspended in EA (50mL), then HOBt (1.16g, 8.6mmol) was added, the mixture was stirred at RT

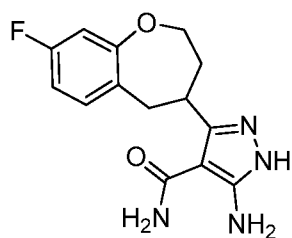
for 0.5 hour, then Et_3N (1.74g, 17.2mmol) was added, the reaction mixture was stirred for another 0.5 hour, then EDCI (1.65g, 8.6mmol) was added. After the mixture was stirred for another 0.5 hour, malononitrile (577mg, 8.6mmol) was added. The reaction mixture was stirred at RT overnight. The reaction mixture was quenched with EA (150mL), washed with H_2O (100mL), then the organic layer was stirred with aq H_2SO_4 (10g/100mL H_2O) for 3 hours then directly concentrated to give yellow oil as the crude product (w=2.7 g, Y=100%) MS (ESI) m/e $[\text{M}+1]^+ 259$.

Step G: 2-((8-Fluoro-2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)(methoxy)methylene)malononitrile



[0416] 2-((8-Fluoro-2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)(hydroxy)methylene)malononitrile (2.70g, 10.5 mmol) was dissolved in trimethoxymethane (30mL), the reaction mixture heated to 100°C for 3 hours under N_2 atmosphere. The solvent was removed by reduced pressure. The residue was purified by chromatography on silica gel using EA/PE (1:5-1:2) as eluting solvent to give the product (1.5g, Y=53%) as yellow oil. MS (ESI) m/e $[\text{M}+1]^+ 273$.

Step H: 5-Amino-3-(8-fluoro-2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)-1H-pyrazole-4-carboxamide

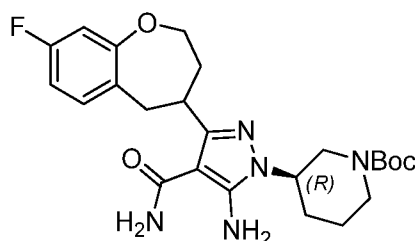


[0417] 2-((8-Fluoro-2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)(methoxy)methylene)malononitrile (1.5g, 5.5mmol) was dissolved in EtOH (10mL), then hydrazine hydrate (1.38g, 27.5mmol) was added at 5°C - 10°C for 0.1 hour. The reaction mixture was stirred at RT for 4 hours. The solvent was removed by reduced pressure to give the crude product, which was then suspended in

methanesulfonic acid (10mL), the reaction mixture was heated to 85°C for 0.5 hour and quenched with ice/H₂O (100mL), then neutralized with aq NaOH adjust to pH=7-9, extracted with EA (50mL×2), then washed with brine (100mL), dried over Na₂SO₄ and concentrated to give the product as a white solid(800 mg, Y=50%). MS (ESI) m/e [M+1]⁺291.

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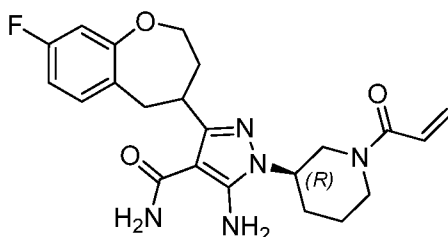
Step I: (3R)-tert-butyl 3-(5-amino-4-carbamoyl-3-(8-fluoro-2,3,4,5-tetrahydrobenzo [b]oxepin-4-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate:



[0418] 5-Amino-3-(8-fluoro-2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)-1H-pyrazole-4

10 –carboxamide (290mg, 1mmol), (S)-tert-butyl 3-(tosyloxy)piperidine-1-carboxylate (710mg, 2mmol) and Cs₂CO₃ (650mg, 2mmol) were suspended in DMF(10mL) then the reaction mixture was heated to 70°C overnight. After cooling to RT, the reaction mixture was quenched with EA (100mL)/H₂O (50mL), the organic layer was washed with brine (50mL), dried over Na₂SO₄ and concentrated. The residue was purified by chromatography on silica gel using EA as eluting
15 solvent to give the desired product (200mg, Y=42%) as a white solid. MS (ESI) m/e [M+1]⁺474.

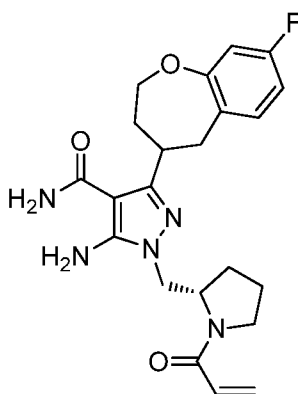
Step J: 1-((R)-1-acryloylpiperidin-3-yl)-5-amino-3-(8-fluoro-2,3,4,5-tetrahydrobenzo [b]oxepin-4-yl)-1H-pyrazole-4-carboxamide



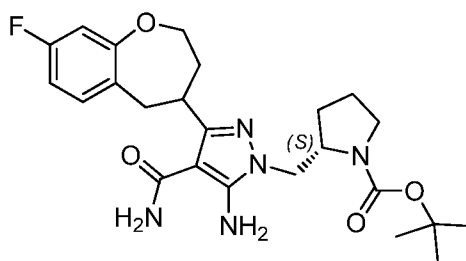
20 **[0419]** (3R)-tert-butyl 3-(5-amino-4-carbamoyl-3-(8-fluoro-2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (200mg, 0.42mmol) was suspended in DCM/TFA (3mL/1mL), the reaction mixture was stirred at RT for 2 hours and the solvent was

removed by reduced pressure. The residue was dissolved in CH₃CN/H₂O, then NaHCO₃ (84mg, 1.26mmol) and acryloyl chloride (38mg, 0.42mmol) was added. The reaction mixture was stirred at RT for 3 hours, then quenched with EA (50mL)/H₂O (50mL), the organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by *prep*-HPLC to give a white solid (w=30mg, Y=17%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.16-7.20 (m, 1H), 6.78-6.83 (m, 3H), 6.60 (s, 2H), 6.05-6.10 (m, 3H), 5.63-5.71 (m, 1H), 4.38 -4.41 (m, 1H), 3.74-4.06 (m, 3H), 3.27-3.29 (m, 1H), 2.67-2.83 (m, 4H), 1.83-2.11 (m, 5H) and 1.23 (m, 1H). MS (ESI) *m/e* [M+1]⁺428.

Compound 2.8: 1-(((S)-1-acryloylpyrrolidin-2-yl)methyl)-5-amino-3-(8-fluoro-2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)-1H-pyrazole-4-carboxamide



Step A: (2S)-tert-butyl 2-((5-amino-4-carbamoyl-3-(8-fluoro-2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)-1H-pyrazol-1-yl)methyl)pyrrolidine-1-carboxylate



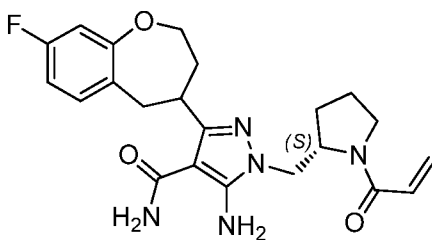
[0420] 5-Amino-3-(8-fluoro-2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)-1H-pyrazole-4-carboxamide (the product of step H in synthesis of **Compound 2.7**, 500mg, 1.72mmol),

(S)-tert-butyl 2-(tosyloxymethyl)pyrrolidine-1-carboxylate (**BL-2**, 1.22g, 3.44mmol) and Cs₂CO₃ (1.22g, 2mmol) were suspended in DMF(10mL), then the reaction mixture was heated to 70°C overnight. After cooling to RT, the reaction mixture was quenched with EA (100mL)/H₂O (50mL), the organic layer was washed with brine (50mL), dried over Na₂SO₄ and concentrated.

- 5 The residue was purified by chromatography on silica gel using EA:PE (1:1-50:1) as eluting solvent to give product (250mg, Y=31%) as white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.16-7.20 (br.s, 1H), 6.78-6.83 (m, 2H), 6.56 (s, 2H), 6.04 (s, 2H), 4.3 -4.42 (m, 1H), 3.74-3.95 (m, 3H), 3.27-3.29 (m, 2H), 2.94-3.18 (m, 4H), 2.10 (m, 2H), 1.72 (m, 3H) and 1.23(m, 9H). MS (ESI) m/e [M+1]⁺474.

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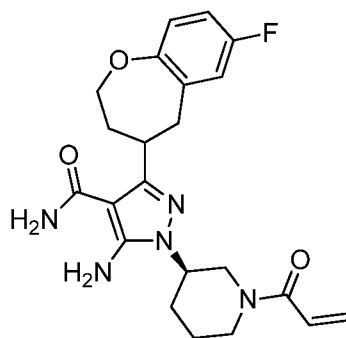
Step B: 1-(((S)-1-acryloylpyrrolidin-2-yl)methyl)-5-amino-3-(8-fluoro-2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)-1H-pyrazole-4-carboxamide



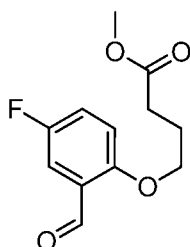
- [0421] (2S)-tert-butyl 2-((5-amino-4-carbamoyl-3-(8-fluoro-2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)-1H-pyrazol-1-yl)methyl)pyrrolidine-1-carboxylate (250mg, 0.53mmol) was suspended in DCM/TFA(3mL/1mL), the reaction mixture was stirred at RT for 2 hours. Then the solvent was removed by reduced pressure. The residue was dissolved in CH₃CN/H₂O, NaHCO₃ (89mg, 1.06mmol) and acryloyl chloride (48mg, 0.53mmol) were added. The reaction mixture was stirred at RT for 2 hours, and quenched with EA (50mL)/H₂O (50mL), the organic layer was washed with brine (50mL), dried over Na₂SO₄ and concentrated. The residue was purified by *prep*-HPLC to give the product (w=80mg, Y=35%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.15-7.18 (m, 1H), 6.70-6.83 (m, 2H), 6.51-6.62 (m, 3H), 6.05-6.22 (m, 3H), 5.48-5.74 (m, 1H), 4.38-4.41 (m, 1H), 3.77-4.17 (m, 4H), 3.31-3.49 (m, 3H), 2.95-3.01 (m, 2H), 2.08-2.11 (m, 2H) and 1.78-1.79 (m, 4H). MS (ESI) m/e [M+1]⁺428.

25

Compound 2.9: 1-((R)-1-acryloylpiperidin-3-yl)-5-amino-3-(7-fluoro-2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)-1H-pyrazole-4-carboxamide

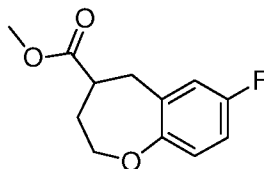


5 Step A: methyl 4-(4-fluoro-2-formylphenoxy)butanoate



[0422] To a solution of 5-fluoro-2-hydroxybenzaldehyde (42g, 0.3mol) and ethyl 4-bromobutanoate (58.5g, 0.3mol) in DMF(500mL) were added Cs_2CO_3 (117g, 0.36mol) at room temperature for 1 hour, the reaction mixture was stirred at room temperature for 3 hours. The
10 reaction mixtures was quenched with EA(600mL) and H_2O (1500mL), the organic layer was washed with brine (500mL $\times$ 2), dried over Na_2SO_4 and concentrated to give product as yellow oil (W=75g, Y=98%), which was used to the next step without further purification. MS (ESI) m/e $[\text{M}+1]^+$ 241.

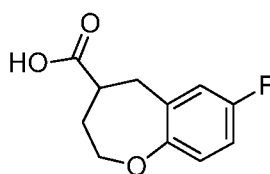
15 Step B: methyl 7-fluoro-2,3,4,5-tetrahydrobenzo[b]oxepine-4-carboxylate



[0423] To a solution of methyl 4-(4-fluoro-2-formylphenoxy) butanoate (75g, 135mmol) in dimethyl carbonate (1000mL) was added CH_3ONa (5.4 M in MeOH) (60mL, 325mmol) at 50°C. The reaction mixture was stirred at 50°C for 2 hours. The mixture was quenched with EA (500mL)

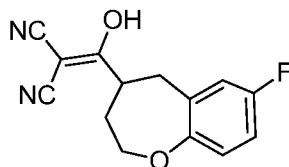
and H₂O (500mL), the organic layer was washed with brine (500mL) and concentrated. The residue was dissolved with MeOH (500 mL), 10% Palladium on carbon (50% water wet, 6.5g) was added. The reaction mixture was hydrogenated with H₂ gas at 1.5Mpa overnight. The catalyst was removed, the filtrate was concentrated to give the product (50.0g, Y=68%) as yellow oil, which was used to the next step without further purification. MS (ESI) m/e [M+1]⁺225.

Step C: 7-fluoro-2,3,4,5-tetrahydrobenzo[b]oxepine-4-carboxylic acid



[0424] To a solution of methyl 7-fluoro-2,3,4,5-tetrahydrobenzo[b]oxepine-4-carboxylate (50g, 223mmol) in MeOH/ H₂O(500mL/ 100mL) was added lithium hydroxide (17.86g, 446mmol) at 5°C-10 °C, the mixture was stirred at room temperature overnight. Then the solvent was removed by reduced pressure. The residue was acidized with 6N HCl adjust to pH=3-4, extracted with EA(500mL×2), the organic layer was washed with brine (500mL), dried over Na₂SO₄ and concentrated to give the crude product(W=31g, Y=67%) as a white solid. MS (ESI) m/e [M+1]⁺211.

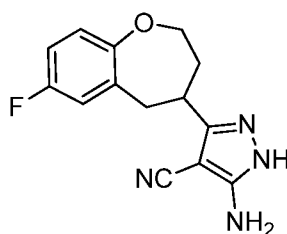
Step D: 2-((7-Fluoro-2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)(hydroxy)methylene)malononitrile



[0425] 7-fluoro-2,3,4,5-tetrahydrobenzo[b]oxepine-4-carboxylic acid (31g, 147.6mmol) was suspended in EA(200mL), then HOBt (19.9g, 147.6mmol) was added. The mixture was stirred at RT for 0.5 hour, then Et₃N (44.7g, 443mmol) was added. The reaction mixture was stirred for another 0.5 hour, then EDCI (28.3g, 147.6mmol) was added. After the mixture was stirred for another 0.5 hour, malononitrile (9.74g, 147.6mmol) was added. The reaction mixture was stirred at RT overnight. The reaction mixture was quenched with EA (200mL), washed with H₂O

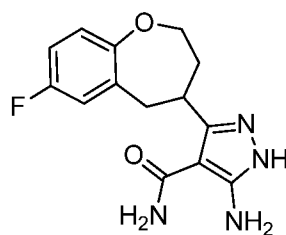
(100mL), and the organic layer was stirred with aq H₂SO₄ (40g/400mL H₂O) for 3 hours then directly concentrated to give the crude product (w=21 g, Y=55%) as yellow oil. MS (ESI) m/e [M+1]⁺259.

5 **Step E:** 5-amino-3-(7-fluoro-2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)-1H-pyrazole-4-carboxamide



10 **[0426]** 2-((7-Fluoro-2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)(hydroxy)methylene)malononitrile (21g, 81.4 mmol) was dissolved in trimethoxymethane (150mL), the reaction mixture was heated to 100°C for 4 hours under N₂ atmosphere. After cooling to RT, the solvent was removed by reduced pressure. The residue was purified by chromatography on silica gel using EA:PE (1:5-1:2) as eluting solvent to give intermediate compound (18g, Y=82%) as a white solid. Then the compound was dissolved in EtOH (100mL), hydrazine hydrate (8.14g, 162.8mmol) was added at 5°C-10 °C for 0.1 hour. The reaction mixture was stirred at RT for 4 hours. The solvent was removed by reduced pressure to give the product (16g, two steps Y=73%) as a yellow solid. MS (ESI) m/e [M+1]⁺273.

15 **Step F:** 5-Amino-3-(7-fluoro-2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)-1H-pyrazole-4-carboxamide



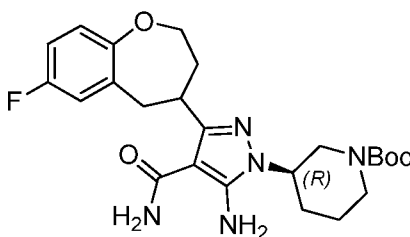
20 **[0427]** 5-Amino-3-(7-fluoro-2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)-1H-pyrazole-4-carboxamide (16g, 59mmol) was suspended in methanesulfonic acid (60mL), the reaction mixture

was heated to 85°C for 0.5 hour. After cooling to RT, the reaction mixture was quenched with ice/H₂O (500mL), then neutralized with aq NaOH adjust to pH=7-9, extracted with

EA(250mL×2), then washed with brine (200mL), dried over Na₂SO₄ and concentrated. The residue was purified by chromatography on silica gel using EA:MeOH (100:1-50:1) as eluting

5 solvent to give product (9.0g, Y=57%) as white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.59 (br.s, 1H), 6.91-7.04 (m, 3H), 6.60 (s, 2H), 5.49 (br.s, 2H), 4.36-4.39 (m, 1H), 3.60-3.65 (m, 1H), 3.04-3.10 (m, 1H), 2.80-2.91 (m, 1H), 2.06-2.16 (m, 2H) and 0.82-0.85 (m, 1H). MS (ESI) m/e [M+1]⁺291.

10 **Step G:** (3R)-tert-butyl 3-(5-amino-4-carbamoyl-3-(7-fluoro-2,3,4,5-tetrahydrobenzo [b]oxepin-4-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate:



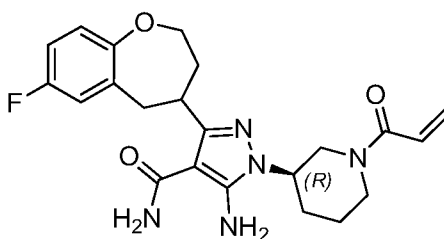
[0428] 5-Amino-3-(7-fluoro-2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)-1H-pyrazole-4-carboxamide (1.5g, 5.17mmol), (s)-tert-butyl 3-(tosyloxy) piperidine-1-carboxylate (**BL-1**, 3.67g,

15 10.34mmol) and Cs₂CO₃ (3.38g, 10.34mmol) were suspended in DMF(20mL). The reaction mixture was heated to 80°C overnight under N₂ atmosphere. After cooling to RT, the mixture was quenched with EA (100mL)/H₂O (100mL), the organic layer was washed with brine (100mL), dried over Na₂SO₄ and concentrated. The residue was purified by chromatography on silica gel using EA:MeOH(100:1-50:1) as eluting solvent to give the product (800mg, Y=33%) as white

20 solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.94-7.00 (m, 3H), 6.58 (s, 2H), 6.21 (s, 2H), 4.32-4.35 (m, 1H), 4.04-4.08 (m, 1H), 3.70-3.89 (m, 3H), 3.30-3.34 (m, 1H), 2.67-3.03 (m, 3H), 1.83-2.11 (m, 5H), and 1.36-1.39 (m, 11H). MS (ESI) m/e [M+1]⁺474.

Step H: 1-((R)-1-acryloylpiperidin-3-yl)-5-amino-3-(7-fluoro-2,3,4,5-tetrahydro benzo[b]oxepin-4-yl)-1H-pyrazole-4-carboxamide

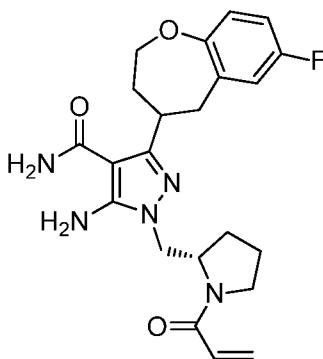
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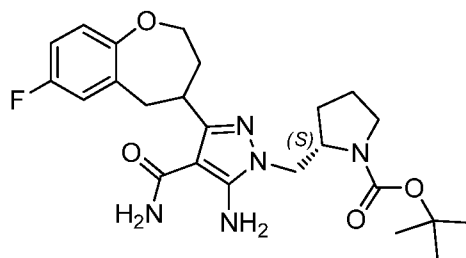
[0429] (3R)-tert-butyl 3-(5-amino-4-carbamoyl-3-(7-fluoro-2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (800mg, 1.69mmol) was suspended in DCM/TFA (3mL/1mL), the reaction mixture was stirred at RT for 2 hours. The solvent was removed by reduced pressure. The residue was dissolved in CH₃CN/H₂O (12mL/12mL), then NaHCO₃ (286mg, 3.4mmol) and acryloyl chloride (183mg, 2.02mmol) was added. The reaction mixture was stirred at RT for 3 hours, then quenched with EA (50mL)/H₂O (50mL), the organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by *prep*-HPLC to give a white solid (w=200mg, Y=28%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.73-7.03 (m, 4H), 6.59 (s, 2H), 6.05-6.21 (m, 3H), 5.61-5.71 (m, 1H), 3.95-4.36 (m, 3H), 3.68-3.70 (m, 1H), 3.27-3.42 (m, 2H), 2.82-3.11 (m, 4H), 1.83-2.09 (m, 5H) and 1.23 (m, 1H). MS (ESI) *m/e* [M+1]⁺428

Compound 2.10: 1-(((S)-1-acryloylpyrrolidin-2-yl)methyl)-5-amino-3-

(7-fluoro-2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)-1H-pyrazole-4-carboxamide



Step A: (2S)-tert-butyl 2-((5-amino-4-carbamoyl-3-(7-fluoro-2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)-1H-pyrazol-1-yl)methyl)pyrrolidine-1-carboxylate



[0430] 5-Amino-3-(7-fluoro-2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)-1H-pyrazole-4-

-carboxamide (the product of step F in synthesis of **Compound 2.9**, 1.5g, 5.17mmol),

(s)-tert-butyl 2-(tosyloxymethyl) pyrrolidine-1-carboxylate (3.67g, 10.34mmol) and Cs₂CO₃

(3.36g, 10.34mmol) were suspended in DMF(20mL), the reaction mixture was heated to 70°C for

overnight. The reaction mixture was quenched with EA (100mL)/H₂O (50mL), the organic layer

was washed with brine (50mL), dried over Na₂SO₄ and concentrated. The residue was purified by

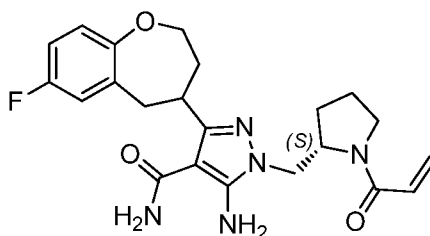
chromatography on silica using EA:Pet (1:1-50:1) as eluting to give product (900mg, Y=37%) as

white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.93-6.95 (m, 3H), 6.58 (s, 2H), 6.03 (s, 2H), 4.34

-4.46 (m, 2H), 3.71-3.86 (m, 3H), 2.89-3.07 (m, 5H), 1.71-1.93(m, 6H) and 1.23(m, 9H). MS

(ESI) m/e [M+1]⁺474.

Step B: 1-(((S)-1-acryloylpyrrolidin-2-yl)methyl)-5-amino-3-(7-fluoro-2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)-1H-pyrazole-4-carboxamide



[0431] (2S)-tert-butyl-2-((5-amino-4-carbamoyl-3-(7-fluoro-2,3,4,5-tetrahydrobenzo [b]

oxepin-4-yl)-1H-pyrazol-1-yl)methyl)pyrrolidine-1-carboxylate (900mg, 1.9mmol) was

suspended on DCM/TFA(5mL/2mL), the reaction mixture was stirred at RT for 2 hours. The

solvent was removed by reduced pressure. The residue was dissolved in CH₃CN/H₂O

(12mL/12mL), then NaHCO₃ (319mg, 3.8mmol) and acryloyl chloride (206mg, 2.28mmol) were

added. The reaction mixture was stirred at RT for 2 hours, then quenched with EA (50mL)/H₂O

(50mL), the organic layer was washed with brine (50mL), dried over Na₂SO₄ and concentrated.

The residue was purified by *prep*-HPLC to give the product (w=300mg, Y=37%) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 6.91-7.01(m, 3H), 6.50-6.70(m, 3H), 6.02-6.23 (m, 3H), 5.49-5.74 (m, 1H), 4.33 -4.39 (m, 2H), 3.27-3.91 (m, 6H), 2.87-3.04 (m, 2H), 2.08-2.11 (m, 2H) and 1.78-1.79 (m, 4H). MS (ESI) m/e $[\text{M}+1]^+$ 428.

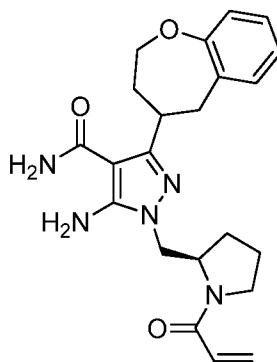
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Compound 2.11:

1-(((R)-1-acryloylpyrrolidin-2-yl)methyl)-5-amino-3-(2,3,4,5-tetrahydrobenzo[b]oxepin-4-yl)-1H-pyrazole-4-carboxamide

[0432] Compound 2.11 was prepared according to the procedures described for **Compound 2.5**

10 under appropriate conditions that could be recognized by one skilled in the art.



[0433] ^1H NMR (400 MHz, DMSO- d_6) δ 7.11-7.16 (m, 2H), 6.92-6.99 (m, 2H), 6.57-6.60 (m, 3H), 6.14-6.23 (m, 3H), 5.65-5.74 (m, 1H), 4.37-4.41 (m, 1H), 4.17- 4.18 (m, 1H), 3.89-4.03 (m, 2H), 3.71 -3.74 (m, 1H), 3.26-3.43 (m, 3H), 2.89-3.02 (m, 2H), 2.10-2.13 (m, 2H) and 1.79 -1.83 (m, 4H). MS (ESI) m/e $[\text{M}+1]^+$ 410

15

EGFR enzymatic assay

[0434] Compounds of the present invention were tested against WT EGFR kinase domain (aa.669-1210, Carna Biosciences, 08-115), EGFR T790M/L858R kinase domain

20 (aa.669-1210, Carna Biosciences, 08-510) and EGFR L858R kinase domain (aa.669-1210, Carna Biosciences, 08-502) in assays based on time-resolved fluorescence-resonance energy transfer methodology. The assay was carried out in 384-well low volume black plate in a reaction mixture containing EGFR kinases, 20 μ MATP for EGFR WT and T790M/L858R, and 125 μ M

for EGFR L858R, biotin-TK substrate and 0-0.5 μ M compounds in buffer containing 50 mM HEPES pH7.5, 10 mM MgCl₂, 1 mM EGTA, 0.01% Brij-35, 2.5 mM DTT, 0.1% BSA.

The kinase was incubated with compounds of the present invention at room temperature for 120 minutes and the reaction was initiated by the addition of ATP and biotin-TK substrate. After

5 reaction at room temperature for 40 minutes, an equal volume of stop/detection solution was added according to the manufacture's instruction (CisBio Bioassays). The stop/detection solution contained TK-Antibody-Cryptate and Streptavidin-XL665 in buffer containing 25 mM Tris pH7.4, 400 mM KF, 50 mM EDTA, 0.01% BSA, 0.01% Triton X-100. Plates were sealed and incubated at room temperature for 1 hour, and the TR-FRET signals were read on

10 BMG PHERAstar FS instrument. The IC₅₀ of an inhibitor was derived from fitting the %inhibition data at each compound concentration to the four-parameter logistic equation by Graphpad Prism software.

[0435] Compounds 1.1-1.67 and 2.1-2.11 inhibit EGFR kinases with IC₅₀ values ranging from 15 0.01 nM to 1 μ M.

[0436] Table 1: the IC₅₀ values (nM) of the compounds of the present invention for inhibiting EGFR kinases

Compound No.	WT EGFR	L858R EGFR	T790M/L858REG FR
1.1	0.56	0.23	0.17
1.2	2.7	1.6	0.49
1.3	10	8.0	45
1.4	4.5	2.1	7.0
1.5	0.16	0.057	0.054
1.6	0.68	0.38	0.28
1.7	2.3	1.1	0.30
1.8	3.7	1.4	1.7
1.9	0.90	0.31	0.23
1.10	4.4	1.7	0.55
1.10a	2.5	1.1	0.28
1.10b	22	11	12
1.11	60	8.3	3.7
1.12	1.1	0.56	0.43

1.13	8.8	4.4	1.4
1.14	2.0	0.49	0.10
1.14a	0.84	0.43	0.13
1.14b	19	5.1	3.0
1.15	0.12	0.070	0.037
1.16	0.52	0.26	0.19
1.17	10	5.3	2.7
1.18	2.9	0.57	0.20
1.19	0.38	0.12	0.079
1.20	0.41	0.22	0.059
1.20a	0.15	0.068	0.021
1.20b	3.2	0.77	2.1
1.21	0.71	0.28	0.11
1.22	89	46	21
1.23	63	22	11
1.24	0.68	0.51	0.17
1.25	28	13	5.3
1.26	54	19	17
1.27	>500	>56	>56
1.28	65	18	17
1.29	22	13	7.7
1.30	90	35	19
1.31	25	25	6.9
1.32	7.7	1.7	0.70
1.33	27	4.2	0.85
1.33a	15	2.6	0.28
1.33b	21	1.8	2.8
1.34	4.1	0.78	0.62
1.35	37	6.1	1.5
1.36	5.8	1.2	1.3
1.37	11	1.0	0.58
1.38	5.2	1.1	0.37
1.39	3.2	0.35	0.15
1.40	0.58	0.18	0.072
1.40a	0.25	0.16	0.093
1.41	1.2	0.20	0.076
1.42	0.45	0.095	0.031
1.42a	0.31	0.067	0.023
1.42b	1.9	0.38	0.53

1.43	0.41	0.092	0.025
1.43a	0.28	0.057	0.024
1.43b	3.2	0.64	0.43
1.44	33	6.1	1.5
1.45	5.7	0.96	0.26
1.46	1.2	0.19	0.075
1.47	1.1	0.17	0.053
1.48	0.34	0.058	0.041
1.49	0.51	0.12	0.054
1.50	27	3.5	1.3
1.51	7.1	1.3	0.33
1.52	7.4	1.8	0.42
1.53	8.9	1.3	0.16
1.53a	4.4	0.68	0.10
1.53b	36	2.6	9.5
1.54	7.8	1.7	0.61
1.55	2.1	0.92	0.37
1.56	5.4	0.75	0.23
1.57	3.0	0.76	0.36
1.58	35	2.8	8.4
1.59	7.5	2.2	0.38
1.60	7.7	2.1	0.37
1.61	41	13	1.7
1.62	478	>56	24
1.63	20	3.1	1.2
1.64	144	35	8.9
1.65	1.4	0.28	0.16
1.65a	1.1	0.25	0.090
1.66a	4.1	1.1	0.33
1.67a	1.9	1.4	0.54
2.1	58	53	>56
2.2	6.2	4.1	2.5
2.3	0.087	0.034	0.070
2.4	0.53	0.22	0.18
2.4a	0.23	0.089	0.096
2.4b	6.1	2.5	2.4
2.5	19	8.8	2.7
2.6	2.7	0.87	0.33
2.7	0.66	0.39	0.22

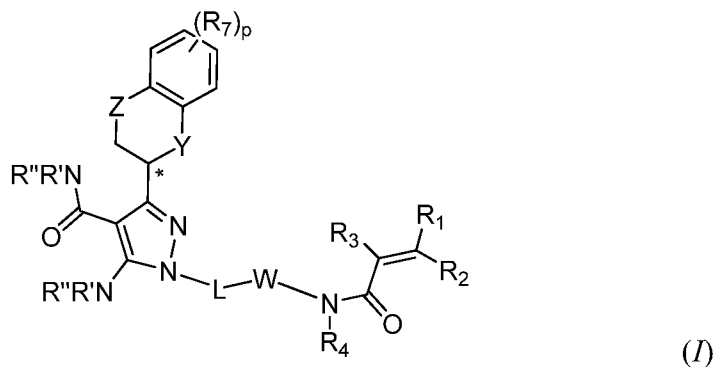
2.8	35	17	5.7
2.9	0.88	0.47	0.57
2.10	32	20	15
2.11	537	>56	27

[0437] The foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding. It will be obvious to one of skill in the art that changes and modifications may be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

[0438] All patents, patent applications and publications cited in this application are hereby incorporated by reference in their entirety for all purposes to the same extent as if each individual patent, patent application or publication were so individually denoted.

WHAT IS CLAIMED IS:

1. At least one compound selected from compounds of Formula (I)



stereoisomers thereof, and pharmaceutically acceptable salts thereof,

5 wherein:

R₁, R₂ and R₃ are independently selected from hydrogen, halo, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

R₄ is selected from hydrogen, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

L is a linking group selected from a bond, -(CR₅R₆)_n-, S, -O-, and -NR₈-, wherein n is an integer of 1, 2, or 3;

10 W is selected from aryl or heteroaryl, said aryl or heteroaryl is optionally substituted by 1, 2, or 3 substituents selected from the group consisting of halogen, CN, NO₂, OR₈, NR'R'', NR'COR'', NR'SO₂R'', CONR'R'', COOR', SO₂R', C₁₋₆alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, heterocyclyl, aryl, and heteroaryl; or

15 W and R₄ taken together with the nitrogen to which they are attached form a 4-, or 5-, or 6-membered heterocyclic ring optionally containing a further heteroatom selected from NR₈, O and S, said heterocyclic ring is optionally substituted by 1, 2, or 3 substituents selected from the group consisting of halogen, CN, NO₂, OR₈, NR'R'', NR'COR'', NR'SO₂R'', CONR'R'', COOR', SO₂R', C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, heterocyclyl, aryl, and heteroaryl;

20 R₇, at each occurrence, is independently selected from hydrogen, halo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, and C₁₋₆ haloalkoxy; and wherein p is an integer of 0, 1, 2, 3, or 4;

Y is selected from -CR₅R₆- and -O-;

Z is selected from -(CR₅R₆)_m-, -CR₅R₆-O-, -O-, and -NR'-, wherein m is an integer of 1 or 2;

R₅ and R₆ are independently selected from hydrogen, halo, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

R₈ is selected from hydrogen, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

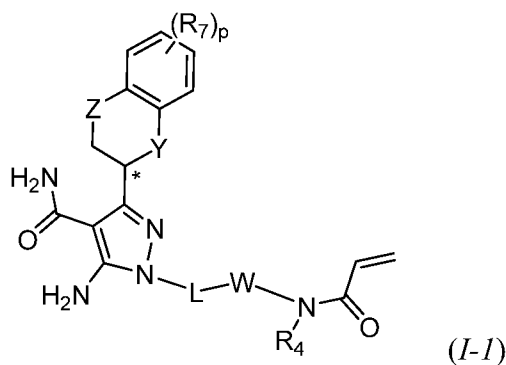
R' and R'', at each occurrence, are independently selected from hydrogen, C₁₋₆ alkyl, and C₁₋₆ haloalkyl; and

* is a chiral center.

- 5 **2.** The compound according to Claim 1, wherein R₁, R₂, and R₃ are hydrogen.
- 3.** The compound according to Claim 1, wherein R₄ is hydrogen.
- 4.** The compound according to Claim 1, wherein L is a bond, and W is aryl or heteroaryl.
- 5.** The compound according to Claim 4, wherein L is a bond, and W is a phenyl or pyridyl group.
- 10 **6.** The compound according to Claim 1, wherein L is -(CR₅R₆)_n-, and W is aryl or heteroaryl, wherein n is an integer of 1, 2, or 3, and R₅ and R₆ are independently selected from hydrogen, halo, C₁₋₆ alkyl, and C₁₋₆ haloalkyl.
- 7.** The compound according to Claim 6, wherein L is -(CR₅R₆)_n-, and W is a phenyl or pyridyl group, wherein n is an integer of 1, 2, or 3, and R₅ and R₆ are independently selected from
- 15 hydrogen, halo, C₁₋₆ alkyl, and C₁₋₆ haloalkyl.
- 8.** The compound according to Claim 7, wherein L is -CH₂-, and W is a phenyl or pyridyl group.
- 9.** The compound according to Claim 1, wherein L is a bond or -(CR₅R₆)_n-, and W and R₄ taken together with the nitrogen to which they are attached form a 4-, or 5-, or 6-membered
- 20 heterocyclic ring optionally containing a further heteroatom selected from NR₈, O and S, said heterocyclic ring is optionally substituted by 1, 2, or 3 substituents selected from the group consisting of halogen, CN, NO₂, OR₈, NR'R'', NR'COR'', NR'SO₂R'', CONR'R'', COOR', SO₂R', C₁₋₆alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, heterocyclyl, aryl, and heteroaryl, wherein R₅, R₆, R₈, R', R'' and n are defined as above.
- 25 **10.** The compound according to Claim 9, wherein L is a bond or -(CR₅R₆)_n-, and W and R₄ taken together with the nitrogen to which they are attached form a 4-, or 5-, or 6-membered heterocyclic ring selected from the group consisting of azetidiny, pyrrolidiny, piperidiny, and

morpholinyl, and wherein R_5 and R_6 are independently selected from hydrogen, halo, C_{1-6} alkyl, and C_{1-6} haloalkyl; and n is an integer of 1, 2, or 3.

11. The compound according to Claim 9, wherein L is a bond, and W and R_4 taken together with the nitrogen to which they are attached form a 4-, or 5-, or 6-membered heterocyclic ring selected from the group consisting of azetidiny, pyrrolidinyl, piperidinyl, and morpholinyl.
12. The compound according to Claim 9, wherein L is $-CH_2-$, and W and R_4 taken together with the nitrogen to which they are attached form a 4-, or 5-, or 6-membered heterocyclic ring selected from the group consisting of azetidiny, pyrrolidinyl, piperidinyl, and morpholinyl.
13. The compound according to Claim 1, wherein Y is $-O-$, and Z is $-O-$.
- 10 14. The compound according to Claim 1, wherein Y is $-O-$, and Z is $-NR'-$, wherein R' is independently selected from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl.
15. The compound according to Claim 1, wherein Y is $-CR_5R_6-$, and Z is $-NR'-$, wherein R_5 and R_6 are independently selected from hydrogen, halo, C_{1-6} alkyl, and C_{1-6} haloalkyl; and R' is independently selected from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl.
- 15 16. The compound according to Claim 1, wherein Y is $-CR_5R_6-$, and Z is $-CR_5R_6-$, wherein R_5 and R_6 are independently selected from hydrogen, halo, C_{1-6} alkyl, and C_{1-6} haloalkyl.
17. The compound according to Claim 1, wherein Y is $-CR_5R_6-$, and Z is $-O-$, wherein R_5 and R_6 are independently selected from hydrogen, halo, C_{1-6} alkyl, and C_{1-6} haloalkyl.
18. The compound according to Claim 1, wherein Y is $-CR_5R_6-$, Z is $-(CR_5R_6)_2-$, wherein R_5 and R_6 are independently selected from hydrogen, halo, C_{1-6} alkyl, and C_{1-6} haloalkyl.
- 20 19. The compound according to Claim 1, wherein Y is $-CR_5R_6-$, and Z is $-CR_5R_6O-$, wherein R_5 and R_6 are independently selected from hydrogen, halo, C_{1-6} alkyl, and C_{1-6} haloalkyl.
20. The compound according to Claim 1, which is a compound of Formula (I-I):



stereoisomers thereof, and pharmaceutically acceptable salts thereof,

wherein:

R_4 is selected from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

5 L is a linking group selected from a bond, or $-CH_2-$;

W is selected from phenyl or pyridyl; or

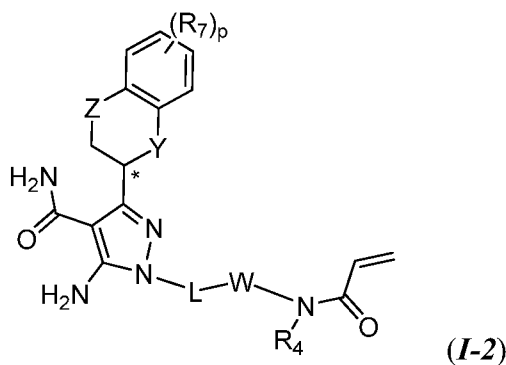
R_7 , at each occurrence, is independently selected from hydrogen, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy; and wherein p is an integer of 0, 1, 2, 3, or 4;

Y is selected from $-CH_2-$ and $-O-$;

10 Z is selected from $-CH_2-$, $-CH_2CH_2-$, $-CH_2O-$, $-O-$, and $-NMe-$; and

* is a chiral center.

21. The compound according to Claim 1, which is a compound of Formula (I-2):



stereoisomers thereof, and pharmaceutically acceptable salts thereof,

15 wherein:

L is a bond or $-CH_2-$,

W and R_4 taken together with the nitrogen to which they are attached form a 4-, or 5-, or 6-membered heterocyclic ring selected from the group consisting of azetidiny, pyrrolidinyl,

piperidinyl, and morpholinyl, said heterocyclic ring is optionally substituted by 1, 2, or 3 substituents selected from the group consisting of halogen, CN, NO₂, OR₈, NR'R'', NR'COR'', NR'SO₂R'', CONR'R'', COOR', SO₂R', C₁₋₆alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, heterocyclyl, aryl, and heteroaryl;

- 5 R₇, at each occurrence, is independently selected from hydrogen, halo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, and C₁₋₆ haloalkoxy; and wherein p is an integer of 0, 1, 2, 3, or 4; R₈ is selected from hydrogen, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

R₈ is selected from hydrogen, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

- R' and R'', at each occurrence, are independently selected from hydrogen, C₁₋₆ alkyl, and
10 C₁₋₆ haloalkyl;

Y is selected from -CH₂- and -O-;

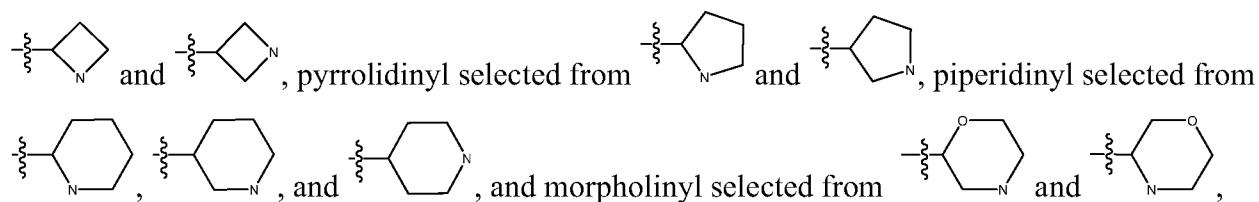
Z is selected from -CH₂-, -CH₂CH₂-, -CH₂O-, -O-, and -NMe-; and

* is a chiral center.

22. The compound according to Claim 21, wherein:

- 15 L is a bond or -CH₂-,

W and R₄ taken together with the nitrogen to which they are attached form a 4-, or 5-, or 6-membered heterocyclic ring selected from the group consisting of azetidiny selected from



- 20 and wherein the wavy lines represent points of attachment to the linking group L, and the acryloyl group on the nitrogen atom is omitted,

R₇, at each occurrence, is independently selected from hydrogen, halo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, and C₁₋₆ haloalkoxy; and wherein p is an integer of 0, 1, 2, 3, or 4;

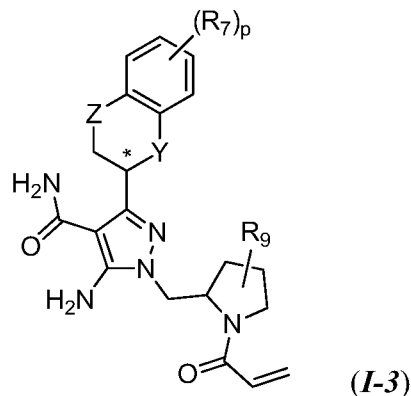
Y is selected from -CH₂- and -O-;

- 25 Z is selected from -CH₂-, -CH₂CH₂-, -CH₂O-, -O-, and -NMe-; and

* is a chiral center.

23. The compound according to Claim 21, wherein the carbon atom to which the linking group L is attached to the 4-, or 5-, or 6-membered heterocyclic ring formed by W and R₄ taken together with the nitrogen atom is (R) or (S) configuration.

24. The compound according to Claim 1, which is a compound of Formula (I-3):



stereoisomers thereof, and pharmaceutically acceptable salts thereof,

wherein:

R₇, at each occurrence, is independently selected from hydrogen, halo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, and C₁₋₆ haloalkoxy; and wherein p is an integer of 0, 1, 2, 3, or 4;

Y is selected from -CH₂- and -O-;

Z is selected from -CH₂-, -CH₂CH₂-, -CH₂O-, -O-, and -NMe-; and

* is a chiral center.

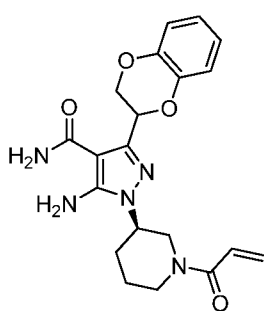
R₉ is selected from F, Cl, Br, OR₈, NR'R'', O-(CH₂)_n-NR'R'';

n = 1, 2, 3;

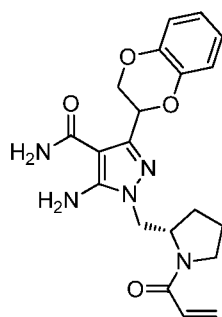
R₈ is selected from hydrogen, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

R' and R'', at each occurrence, are independently selected from hydrogen, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

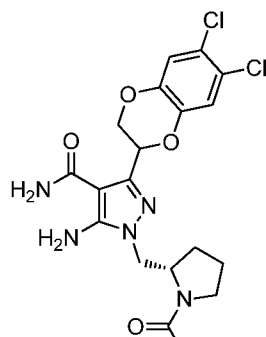
25. The compound according to Claim 1, which is selected from the following compounds:



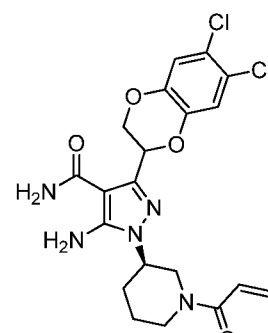
Compound 1.1



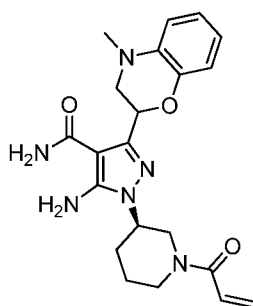
Compound 1.2



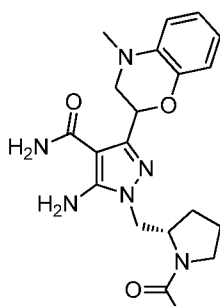
Compound 1.3



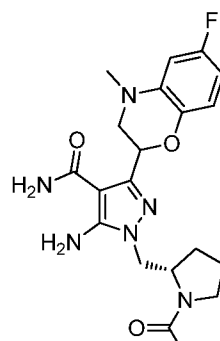
Compound 1.4



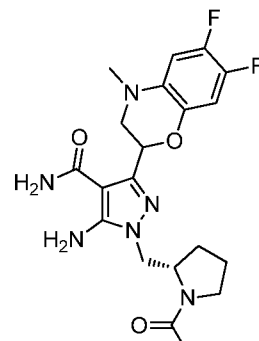
Compound 1.5



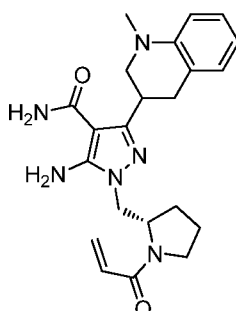
Compound 1.6



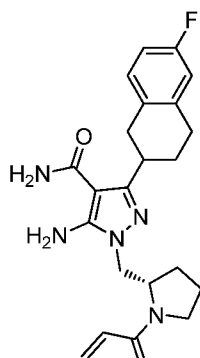
Compound 1.7



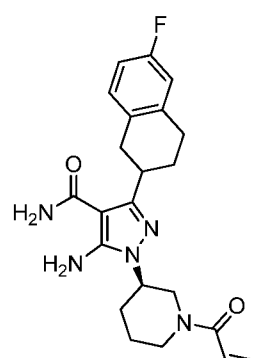
Compound 1.8



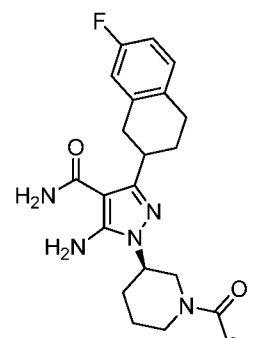
Compound 1.9



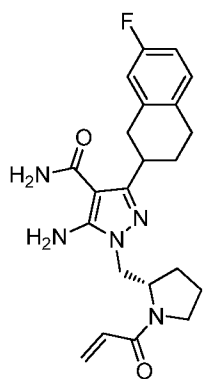
Compound 1.10



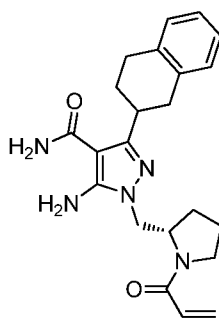
Compound 1.11



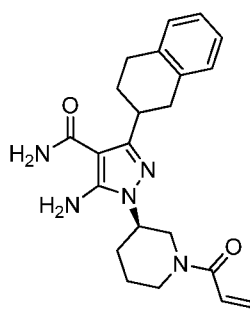
Compound 1.12



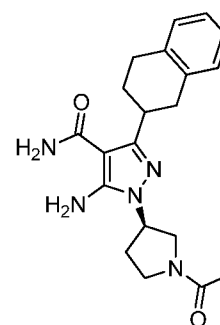
Compound 1.13



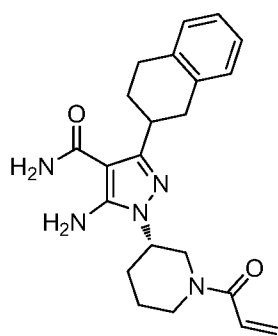
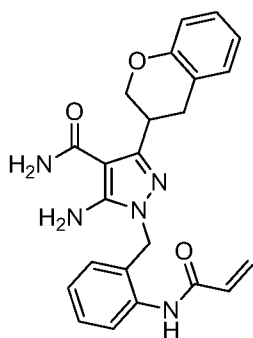
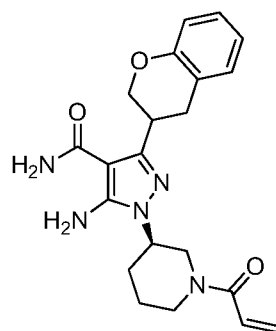
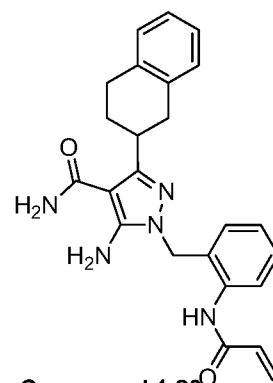
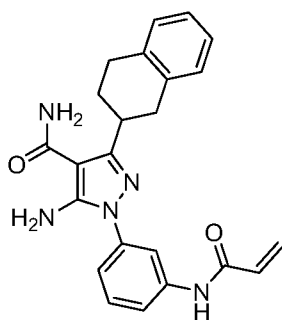
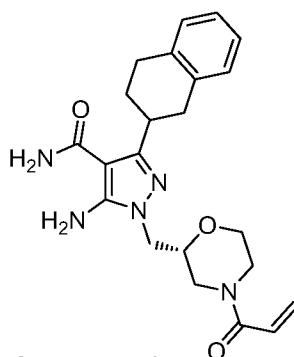
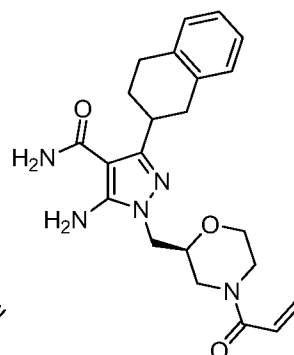
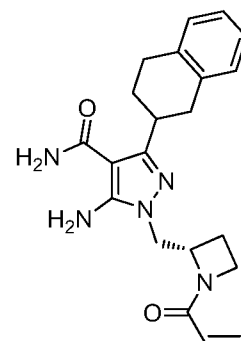
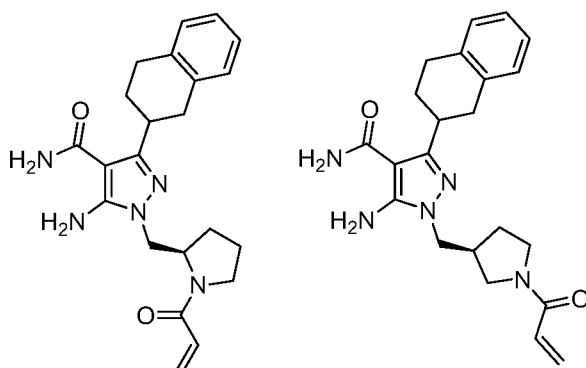
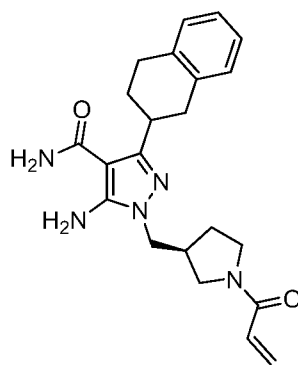
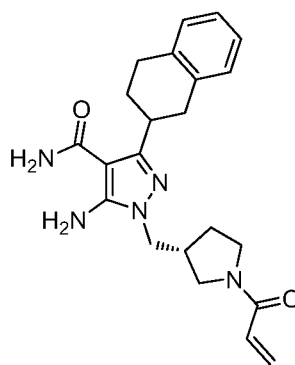
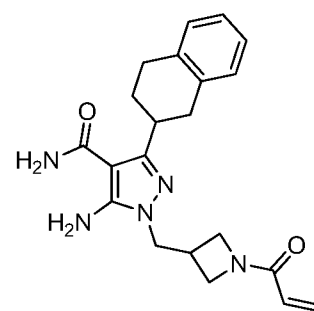
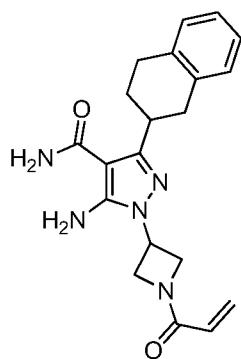
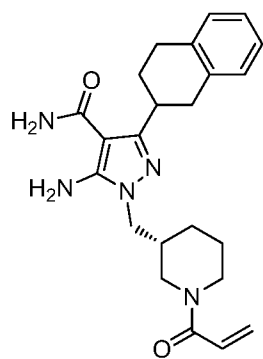
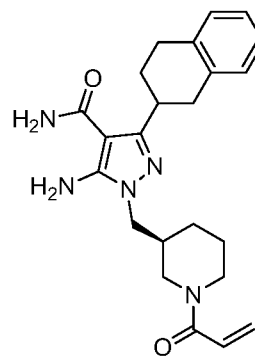
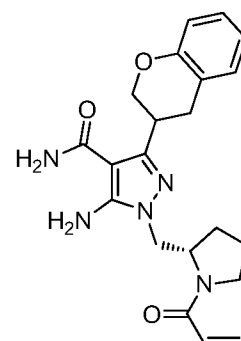
Compound 1.14

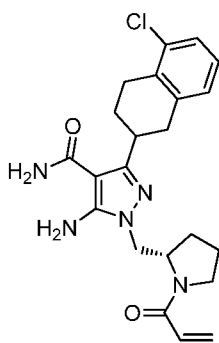


Compound 1.15

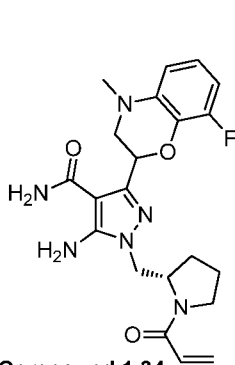


Compound 1.16

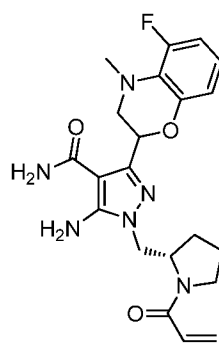
**Compound 1.17****Compound 1.18****Compound 1.19****Compound 1.20****Compound 1.21****Compound 1.22****Compound 1.23****Compound 1.24****Compound 1.25****Compound 1.26****Compound 1.27****Compound 1.28****Compound 1.29****Compound 1.30****Compound 1.31****Compound 1.32**



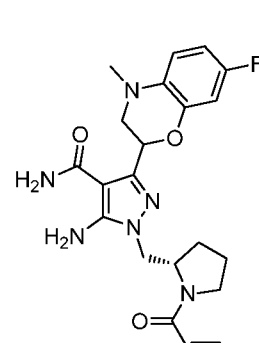
Compound 1.33



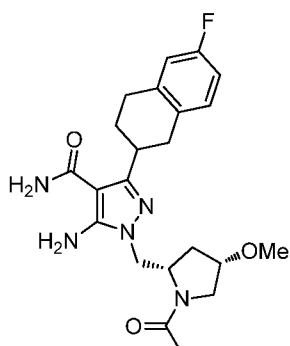
Compound 1.34



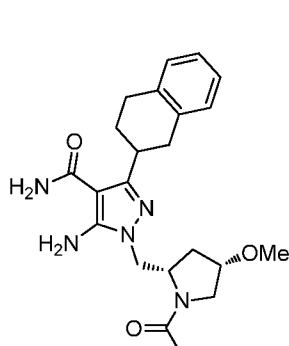
Compound 1.35



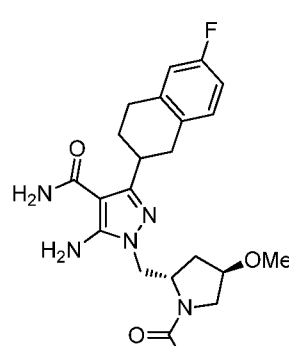
Compound 1.36



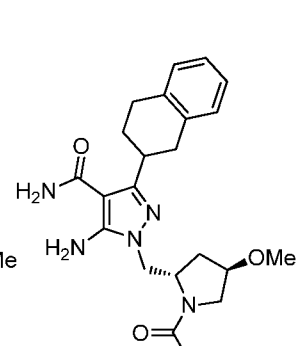
Compound 1.37



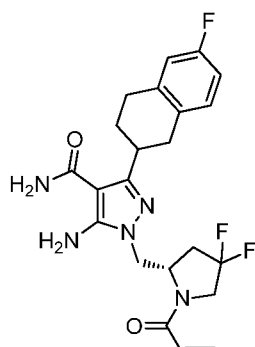
Compound 1.38



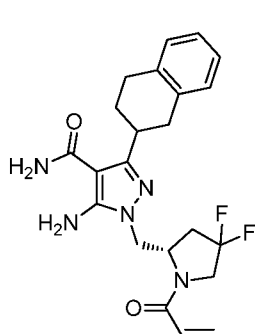
Compound 1.39



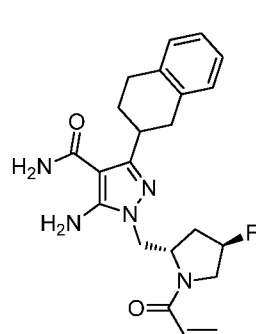
Compound 1.40



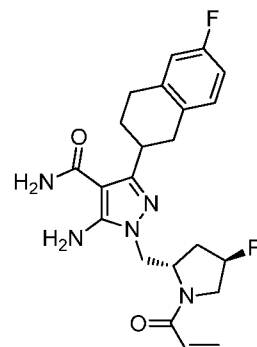
Compound 1.41



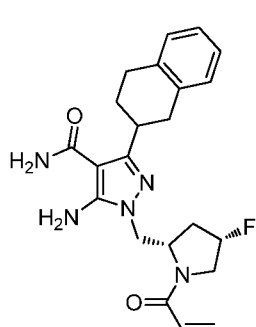
Compound 1.42



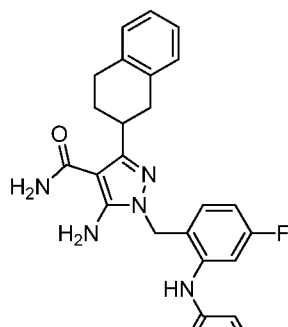
Compound 1.43



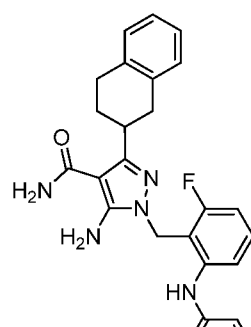
Compound 1.44



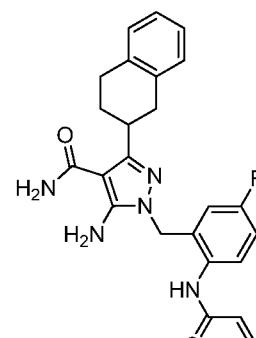
Compound 1.45



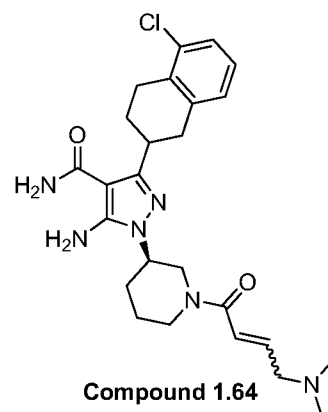
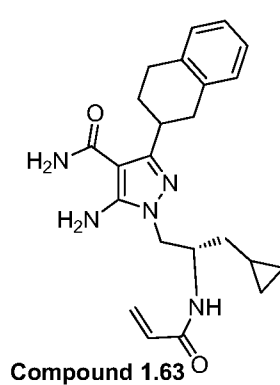
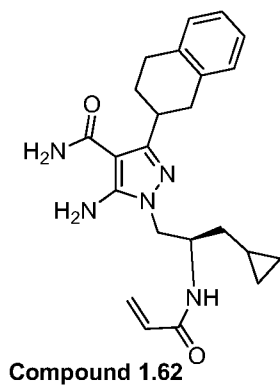
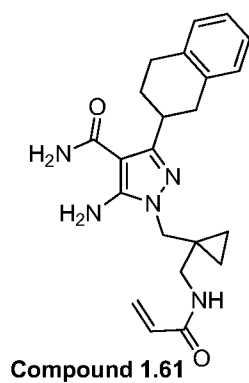
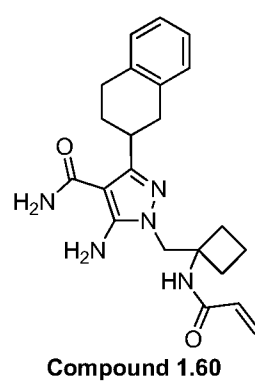
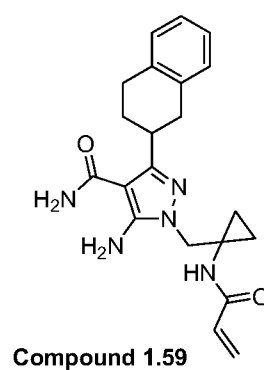
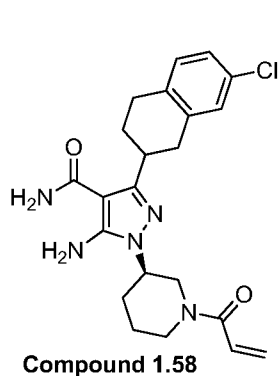
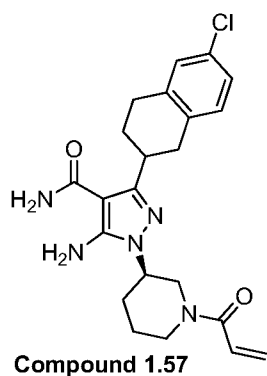
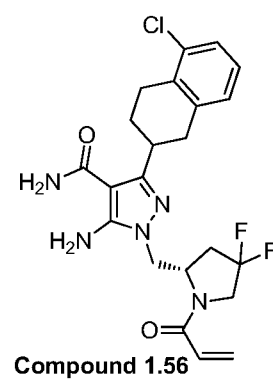
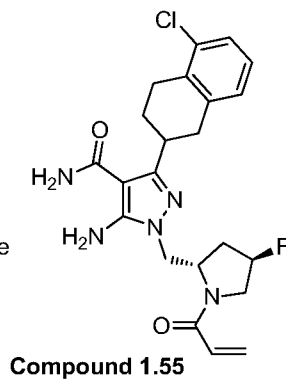
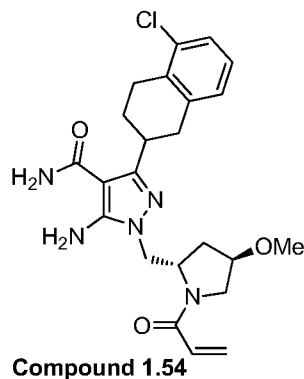
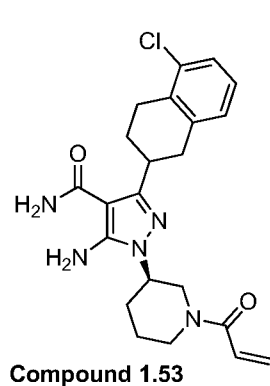
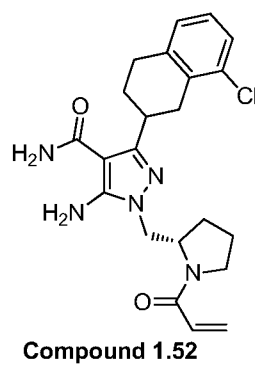
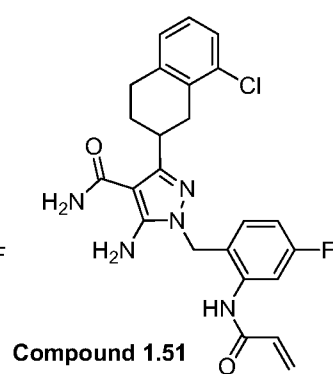
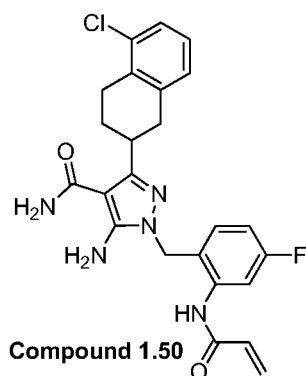
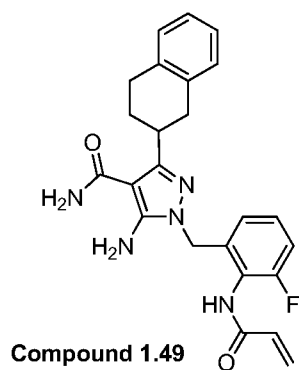
Compound 1.46

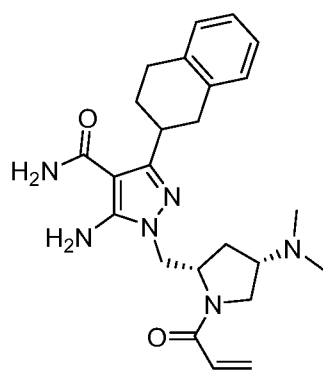
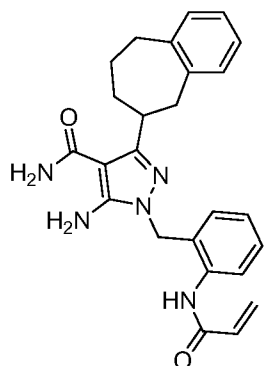
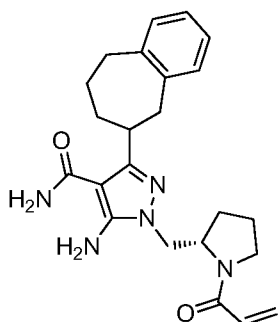
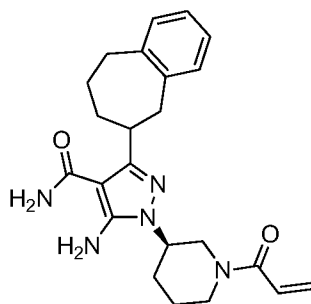
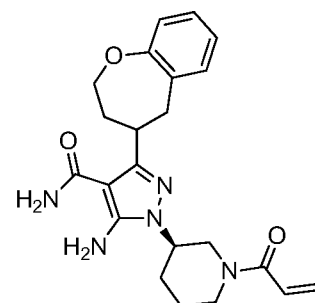
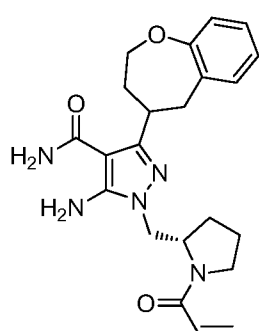
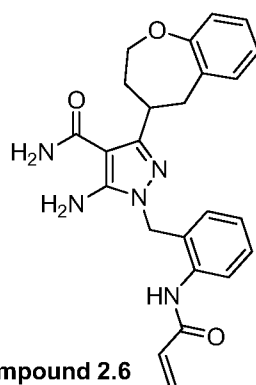
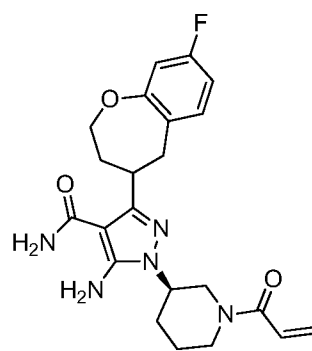
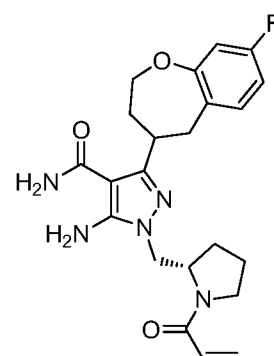
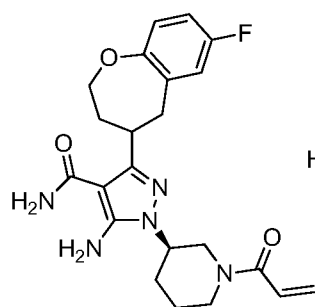
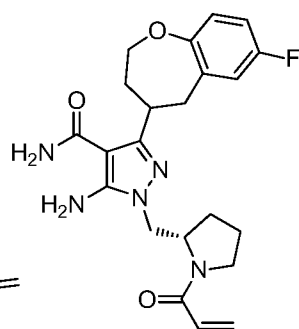
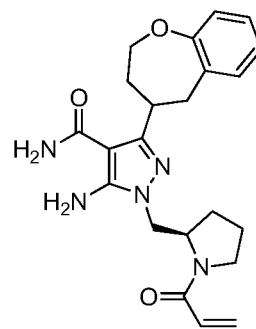


Compound 1.47



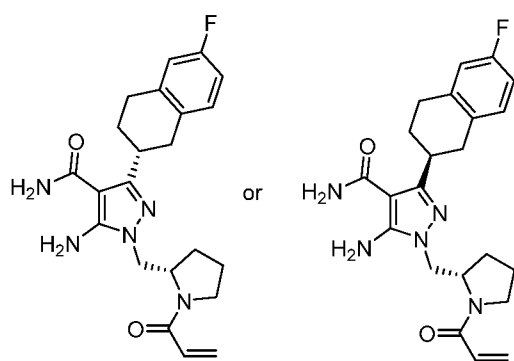
Compound 1.48



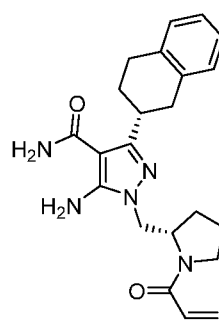
**Compound 1.65****Compound 2.1****Compound 2.2****Compound 2.3****Compound 2.4****Compound 2.5****Compound 2.6****Compound 2.7****Compound 2.8****Compound 2.9****Compound 2.10****Compound 2.11**

stereoisomers thereof, and pharmaceutically accept salts thereof.

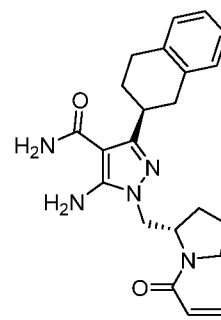
26. The compound according to Claim 1, which is selected from the following compounds:



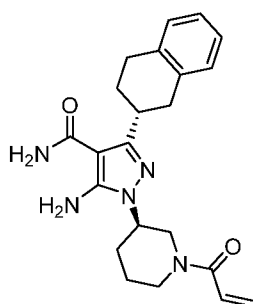
Compound 1.10a or 1.10b



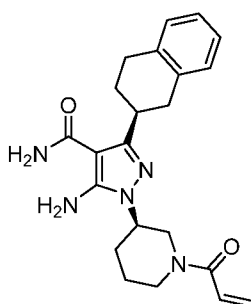
Compound 1.14a



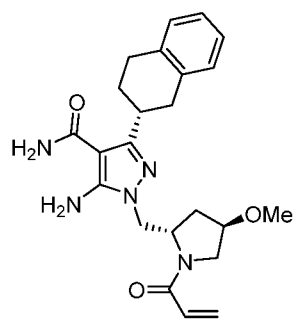
Compound 1.14b



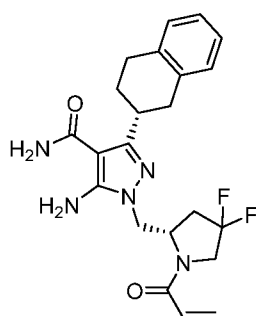
Compound 1.15a



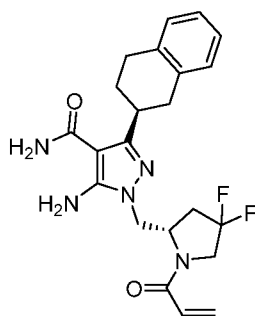
Compound 1.15b



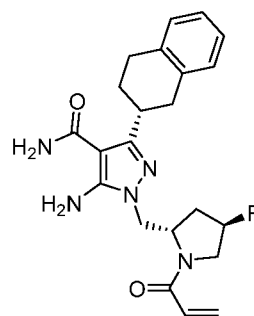
Compound 1.40a



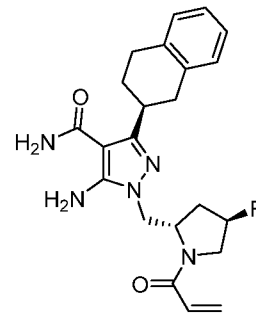
Compound 1.42a



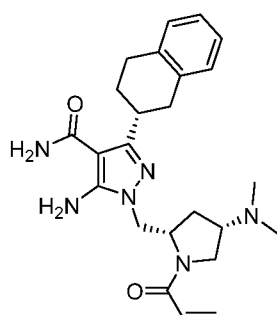
Compound 1.42b



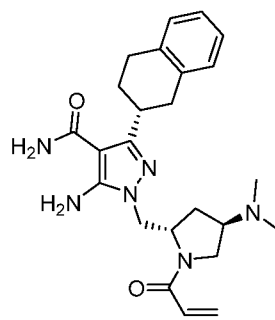
Compound 1.43a



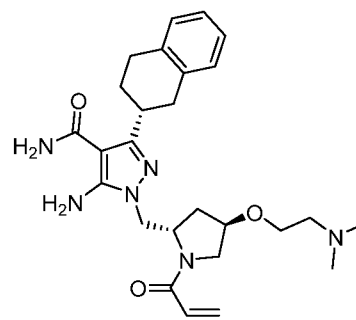
Compound 1.43b



Compound 1.65a



Compound 1.66a



Compound 1.67a

stereoisomers thereof, and pharmaceutically accept salts thereof.

27. A pharmaceutical composition comprising at least one pharmaceutically acceptable carrier and at least one compound according to any one of Claims 1-26, or stereoisomers thereof, or pharmaceutically accept salts thereof.

28. A use of at least one compound according to any one of Claims 1-26 or stereoisomers thereof, or pharmaceutically accept salts thereof in manufacture of a medicament for inhibiting EGFR-T790M kinase.

29. A use of at least one compound according to any one of Claims 1-26 or stereoisomers thereof, or pharmaceutically accept salts thereof in the manufacture of a medicament for treating cancer selecting from the group consisting of ovarian cancer, cervical cancer, colorectal cancer, breast cancer, pancreatic cancer, glioma, glioblastoma, melanoma, prostate cancer, leukaemia, lymphoma, non- Hodgkins lymphoma, gastric cancer, lung cancer including non- small cell lung cancer, hepatocellular cancer, gastric cancer, gastrointestinal stromal tumour (GIST), thyroid cancer, bile duct cancer, endometrial cancer, renal cancer, anaplastic large cell lymphoma, acute myeloid leukaemia (AML), multiple myeloma, melanoma and mesothelioma.

30. A method of treating cancer responsive to inhibition of T790M-EGFR kinase comprising administering to a subject in recognized need thereof a therapeutically effective amount of at least one compound of any one of Claims 1-26 or stereoisomers thereof, or pharmaceutically accept salts thereof.

31. A method of treating cancer responsive to inhibition of T790M-EGFR kinase comprising administering to a subject in recognized need thereof a therapeutically effective amount of at least one compound of any one of Claims 1-26 or stereoisomers thereof, or pharmaceutically accept salts thereof, wherein the cancer is selected from the group consisting of ovarian cancer, cervical cancer, colorectal cancer, breast cancer, pancreatic cancer, glioma, glioblastoma, melanoma, prostate cancer, leukaemia, lymphoma, non- Hodgkins lymphoma, gastric cancer, lung cancer including non- small cell lung cancer, hepatocellular cancer, gastric cancer, gastrointestinal stromal tumour (GIST), thyroid cancer, bile duct cancer, endometrial cancer, renal cancer, anaplastic large cell lymphoma, acute myeloid leukaemia (AML), multiple myeloma, melanoma and mesothelioma.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2015/084082

A. CLASSIFICATION OF SUBJECT MATTER

C07D 231/20(2006.01)i; C07D 319/20(2006.01)i; C07D 471/00(2006.01)i; C07D 498/00(2006.01)i; A61K 31/52(2006.01)i; A61K 31/4155(2006.01)i; A61K 31/357(2006.01)i; A61K 31/44(2006.01)i; A61P 35/00(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)

C07D231/-; C07D319/-; C07D471/-; C07D498/-; A61K31/-; A61P35/-

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)

WPI, EPODOC, CNPAT, CNKI, REGISTRY, CAPLUS: cancer, carbamoyl pyrazole, EGFR, leukaemia, lymphoma

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	US 2015005277 A1 (BEIGENE LTD) 01 January 2015 (2015-01-01) See table 1 of discription	1-31
X	WO 2014082598 A1 (CENTAURUS BIOPHARMA CO. LTD) 05 June 2014 (2014-06-05) See claim 20, paragraphs [009]-[013], [0309], [0310] and [0314]	1-31
X	WO 2014068527 A1 (PFIZER INC.) 08 May 2014 (2014-05-08) See claim 20	1-31



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

28 July 2015

Date of mailing of the international search report

30 September 2015

Name and mailing address of the ISA/CN

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Telephone No. (86-10)61648380

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2015/084082

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.: **30,31**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claims 30 and 31 are directed to a method of treating cancer, which is a method for treatment of the human body (PCT Rule 39.1(iv)), but the search report has been carried out and based on the use of a compound of any of claims 1-26 for the manufacture of treating cancer.
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/CN2015/084082

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
US	2015005277	A1	01 January 2015	None			
WO	2014082598	A1	05 June 2014	CA	2892924	A1	05 June 2014
				CN	103848810	A	11 June 2014
WO	2014068527	A1	08 May 2014	TW	201431851	A	16 August 2014
				AP	201508381	D0	30 April 2015
				AU	2013340345	A1	30 April 2015
				CA	2888960	A1	08 May 2014