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(56) Related Art
US 20140005221 A1
WO 2011150156 A2
WO 2009137404 A1
NITYA G. KUNDU ET AL: "Cyclopenta[f]isoquinoline derivatives designed to bind specifically to native deoxyribonucleic acid . . . , JOURNAL OF MEDICINAL CHEMISTRY, vol. 18, no. 4, 1975-04-01, pages 395-399
US 20130115190 A1
WO 2007089557 A2
WO 2004103998 A1
CA 2880178 A1

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

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根据细则 4.17 的声明:
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— 发明人资格(细则 4.17(iv))

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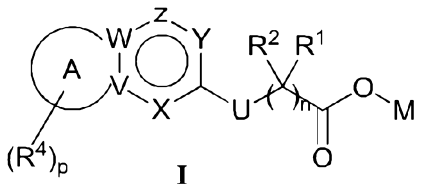
— 包括国际检索报告(条约第 21 条(3))。

(54) Title: CONDENSED RING DERIVATIVE, AND PREPARATION METHOD, INTERMEDIATE, PHARMACEUTICAL COMPOSITION AND USE THEREOF

(54) 发明名称 : 稠环衍生物、其制备方法、中间体、药物组合物及应用



I

(57) Abstract: Disclosed are a condensed ring derivative, and a preparation method, an intermediate, a pharmaceutical composition and a use thereof. The condensed ring derivative of the present invention has a significant inhibitive effect on URAT1, which can effectively alleviate or treat hyperuricemia and other related diseases.

(57) 摘要: 本发明公开了一种稠环衍生物、其制备方法、中间体、药物组合物及应用。本发明的稠环衍生物对 URAT1 具有明显抑制作用，能够有效缓解或治疗高尿酸血症等相关疾病。

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Condensed Ring Derivative, and Preparation Method, Intermediate, Pharmaceutical Composition and Use Thereof

The International Application claims priority of Chinese Patent Application CN201510131828.5, filed on March 24, 2015, the contents of which are incorporated herein by reference in their entireties.

Field of invention

The present invention relates to a condensed ring derivative, and preparation method, intermediate, pharmaceutical composition and use thereof.

Prior arts

Hyperuricemia (HUA) is related to many diseases such as gout, hypertension, diabetes, hypertriglyceridemia, metabolic syndrome, coronary heart disease and renal damage etc. (Puig JG, et al. *CurrOpin Rheumatol*, **2008**, *20*, 187-191; Edwards NL, et al. *Cleve Clin J Med*, **2008**, *75*(*Suppl 5*), 13-16), which has been a metabolic disease threatening human's health, and was recognized as one of the twenty stubborn and chronic diseases in the 21st century by the United Nations.

Uric acid is the final product metabolized from the purine *in vivo*, which goes through glomerular filtration mainly in its origin form, and reabsorption, re-secretion by renal tubule, finally excreted with urine, and very few of them can enter enteric cavity through the secreting of the mesenteric cells. (Hediger M A, et al. *Physiology* **2005**, *20(2)*, 125-133). S1 section of the proximal convoluted tubule is the position where the uric acid is reabsorbed, and 98%-100% filtered uric acid enters the epithelium through urate transporter 1 (URAT1) upon the brush border membrane of the tubular epithelial cells. Inhibiting the activity of the URAT1 can reduce the reabsorption of the uric acid, which allows the uric acid excreted with urine thereby lowering the level of the uric acid in the blood and relieving or treating hyperuricemia and various related diseases.

Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present disclosure as it existed before the priority date of each of the appended claims.

Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

Content of the present invention

The technical problem to be solved in the present invention is to provide a condensed ring derivative totally different from the prior art, and preparation method,

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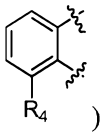
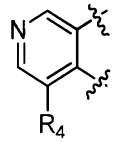
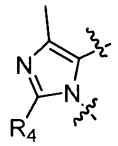
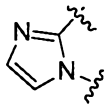
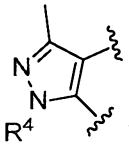
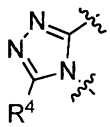
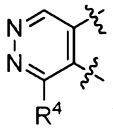
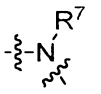
intermediate, pharmaceutical composition and use thereof. The condensed ring derivative of the present invention has obvious inhibitory activity against URAT1, which can effectively relieve or treat hyperuricemia and various related diseases.

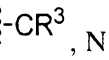
The present invention provides a condensed ring derivative having a structure of formula I, a tautomer, a mesomer, a racemate, an enantiomer, a diastereoisomer, or a pharmaceutically acceptable salt, a metabolite, a metabolic precursor or a pro-drug thereof,

Wherein ring A is an aryl (preferably a C_{6-10} aryl, more preferably a phenyl (e.g. ) or a heteroaryl (preferably a C_{2-5} heteroaryl having 1-3 heteroatoms selected from N or S, more preferably pyridinyl (e.g. ), imidazolyl (e.g.  or ), pyrazolyl (e.g. ), triazolyl (e.g. ) or pyridazinyl (e.g. );

M is a hydrogen, a deuterium or a pharmaceutically acceptable cation (preferably a sodium ion, a potassium ion or a calcium ion);

U is a chemical bond (preferably a single bond or a double bond),  , ,  or  ;

V and W are independently C or N, provided that V and W are not N simultaneously;

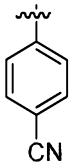
X is  , N or S;

Y is a chemical bond (preferably a single bond or a double bond),  or N;

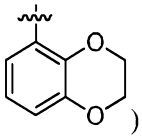
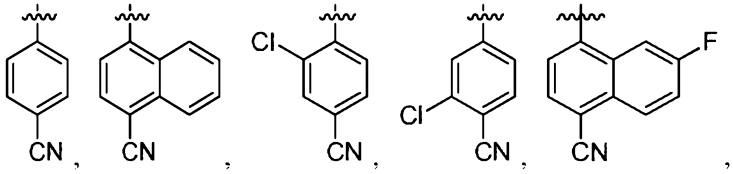
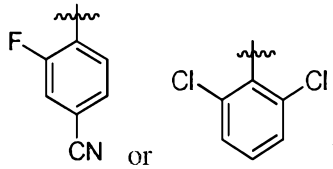
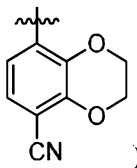
Z is  or S;

R^1 and R^2 are independently H, D, a halogen (preferably F, Cl, Br or I, more

preferably F), an alkyl (preferably a C_{1-4} alkyl), CN, an alkoxy (preferably a C_{1-4} alkoxy), a cycloalkyl (preferably a C_{3-6} cycloalkyl), an alkenyl (preferably a C_{2-4} alkenyl), a alkynyl (preferably a C_{2-4} alkynyl) or a heterocycloalkyl (preferably a C_{2-10} heterocycloalkyl having 1-2 heteroatoms selected from O, S or N; the C_{2-10} heterocycloalkyl is preferably a C_{2-5} heterocycloalkyl); or, R^1, R^2 together with the carbon atom attached form a cycloalkyl (preferably a C_{3-6} cycloalkyl, more preferably cyclobutyl) or a heterocyclic group (preferably a C_{2-5} heterocyclic group having 1-2 heteroatoms selected from O or S); the alkyl, the alkoxy, the cycloalkyl, the alkenyl, the alkynyl, the heterocycloalkyl, the cycloalkyl formed by R^1, R^2 and the carbon atom attached, or the heteroalkyl formed by R^1, R^2 and the carbon atom attached can further be substituted by a substituent selected from the group consisting of D (e.g. ), a halogen (e.g. F, Cl, Br or I, preferably Cl), CN, an alkyl (preferably a C_{1-4} alkyl), an alkoxy (preferably a C_{1-4} alkoxy), a cycloalkyl (preferably a C_{3-6} cycloalkyl), an alkenyl (preferably a C_{2-4} alkenyl), an alkynyl (preferably a C_{2-4} alkynyl), a heterocycloalkyl (preferably a C_{2-10} heterocycloalkyl having 1-2 heteroatoms selected from O, S or N; the C_{2-10} heterocycloalkyl is preferably a C_{2-5} heterocycloalkyl) or an aryl (preferably a C_{6-10} aryl);

R^3 is H, D, a halogen (preferably F, Cl, Br or I, more preferably F), an alkyl (preferably a C_{1-4} alkyl), an alkoxy (preferably a C_{1-4} alkoxy), an aryl (preferably a C_{6-10} aryl, more preferably a phenyl), a heteroaryl (preferably a C_{2-5} heteroaryl having 1-3 heteroatoms selected from N, O or S; the C_{2-10} heterocycloalkyl is preferably a C_{2-5} heterocycloalkyl) or an amino (); wherein the alkyl, the alkoxy, the aryl, the heteroaryl, the heterocycloalkyl or the amino can be further substituted by a substituent selected from the group consisting of D, a halogen (e.g. F, Cl, Br or I, preferably Cl), CN (e.g. ), an alkyl (preferably a C_{1-4} alkyl), an aryl (preferably a C_{6-10} aryl, more preferably phenyl), an aryl substituted by halogen(s) (preferably 2,6-dichlorophenyl), a benzyl, a benzyl substituted by halogen(s) on the benzene ring (preferably 2,6-dichlorobenzyl), a benzoyl or a benzoyl substituted by a halogen on the benzene ring (preferably 2,6-dichlorobenzoyl); when the number of the substituents is more than one, the substituents are the same or different;

R^4 is H, D, a halogen (e.g. F, Cl, Br or I, preferably F or Cl), CN, NH_2, OH, an alkyl (preferably a C_{1-4} alkyl), an alkoxy (preferably a C_{1-4} alkoxy), a cycloalkyl (preferably a C_{3-6} cycloalkyl), an alkenyl (preferably a C_{2-4} alkenyl), an alkynyl (preferably a C_{2-4} alkynyl), a heterocycloalkyl (preferably a C_{2-10} heterocycloalkyl having 1-3 heteroatoms selected from N, S or O; the C_{2-10} heterocycloalkyl is preferably a C_{2-5} heterocycloalkyl), an aryl (preferably a C_{6-10} aryl, more preferably a phenyl or a naphthyl) or a heteroaryl (preferably a C_{2-10} heteroaryl having 1-2 heteroatoms

selected from O, more preferably ); wherein the NH_2, the OH, the alkyl, the alkoxy, the cycloalkyl, the alkenyl, the alkynyl, the heterocycloalkyl, the aryl or the heteroaryl can further be substituted by a substituent selected from the group consisting of D, a halogen (e.g. F, Cl, Br or I, preferably F or Cl), CN, an alkyl (preferably a C_{1-4} alkyl), an alkoxy (preferably a C_{1-4} alkoxy), a cycloalkyl (preferably a C_{3-6} cycloalkyl), an alkenyl (preferably a C_{2-4} alkenyl), an alkynyl (preferably a C_{2-4} alkynyl), a heterocycloalkyl (preferably a C_{2-10} heterocycloalkyl having 1-2 heteroatoms selected from O, S or N; the C_{2-10} heterocycloalkyl is preferably a C_{2-5} heterocycloalkyl), an aryl (preferably a C_{6-10} aryl), an aryl substituted by a halogen and/or CN (e.g.  , ), a heteroaryl (preferably a C_{2-10} heteroaryl having 1-2 heteroatoms selected from O) or a heteroaryl substituted by CN (e.g. );

each of R^5 and R^6 is independently H, D, OH, a halogen (e.g. F, Cl, Br or I, preferably F), an alkyl (preferably a C_{1-4} alkyl), CN, an alkoxy (preferably a C_{1-4} alkoxy), a cycloalkyl (preferably a C_{3-6} cycloalkyl), an alkenyl (preferably a C_{2-4} alkenyl), an alkynyl (preferably a C_{2-4} alkynyl) or a heterocycloalkyl (preferably a C_{2-10} heterocycloalkyl having 1-2 heteroatoms selected from O, S or N; the C_{2-10} heterocycloalkyl is preferably a C_{2-5} heterocycloalkyl); or R^5, R^6 together with the carbon atom attached form a cycloalkyl (preferably a C_{3-6} cycloalkyl) or a heterocyclic group (preferably a C_{2-5} heterocyclic group having 1-2 heteroatoms selected from O or S); the alkyl, the alkoxy, the cycloalkyl, the alkenyl, the alkynyl, the heterocycloalkyl, the cycloalkyl formed by R^5, R^6 together with the carbon atom attached or the heteroalkyl formed by R^5, R^6 together with the carbon atom attached can further be substituted by a substituent selected from the group consisting of D, a halogen (e.g. F, Cl, Br or I, preferably Cl), CN, an alkyl (preferably a C_{1-4} alkyl), an alkoxy (preferably a C_{1-4} alkoxy), a cycloalkyl (preferably a C_{3-6} cycloalkyl), an alkenyl (preferably a C_{2-4} alkenyl), an alkynyl (preferably a C_{2-4} alkynyl), a heterocycloalkyl (preferably a C_{2-10} heterocycloalkyl having 1-2 heteroatoms selected from O, S or N; the C_{2-10} heterocycloalkyl is preferably a C_{2-5} heterocycloalkyl) or an

aryl (preferably a C_{6-10} aryl); R^7 is H or an alkyl (preferably a C_{1-4} alkyl);

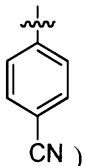
n is 0, 1 or 2;

p is 1, 2, 3 or 4.

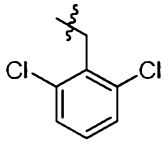
Each of the letter and the substituent in the condensed ring derivative having a structure of formula I is preferably as follows:

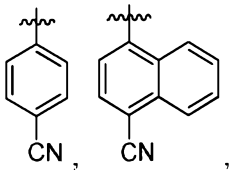
M is H or a pharmaceutically acceptable cation;

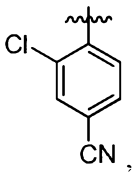
each of R^1 and R^2 is H, a halogen (e.g. F, Cl, Br or I, preferably F) or an alkyl (preferably a C_{1-4} alkyl); or R^1, R^2 together with the carbon atom attached form a cycloalkyl (preferably a C_{3-6} cycloalkyl, more preferably a cyclobutyl);

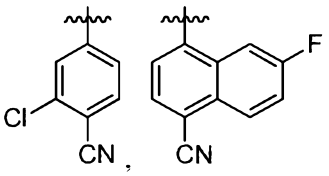
R^3 is H, a halogen (preferably F, Cl, Br or I, more preferably F), an alkyl (preferably a C_{1-4} alkyl) or an aryl (preferably a C_{6-10} aryl, more preferably a phenyl, wherein the C_{6-10} aryl can be further substituted by one or more than one CN(s), e.g. 

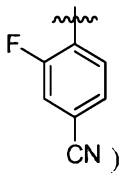
);

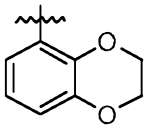
R^4 is H, a halogen (preferably F, Cl, Br or I, more preferably F), an alkyl (preferably a C_{1-4} alkyl, wherein the C_{1-4} alkyl can be further substituted by an aryl substituted by halogen(s), e.g. 

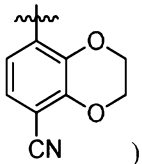
), an aryl (preferably a C_{6-10} aryl, more preferably a phenyl or a naphthyl, wherein the C_{6-10} aryl can be further substituted by one or more than one CN(s) and/or halogen(s) (preferably F, Cl, Br or I, more preferably F or Cl), e.g. 

, 

, 

or 

) or a heteroaryl (preferably a C_{2-10} heteroaryl having 1-2 heteroatoms selected from O, more preferably 

; wherein the C_{2-10} heteroaryl can be further substituted by one or more than one CN(s), e.g. 

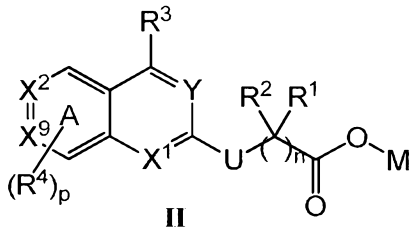
);

each of R^5 and R^6 is independently H, a halogen (e.g. F, Cl, Br or I, preferably F), an

alkyl (preferably a C_{1-4} alkyl) or OH;

p is 1.

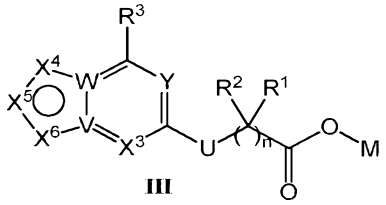
The condensed ring derivative I in the present invention, is more preferably a compound having a structure of formula II,



II

wherein each of X^1 and X^2 is independently CH or N; X^9 is CH or N; Y is CH or N; R^1, R^2, R^3, R^4, U, M, n and p are defined as above.

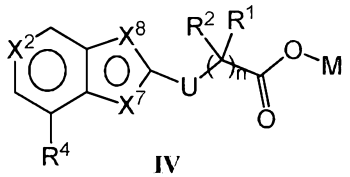
The condensed ring derivative I in the present invention, is more preferably a compound having a structure of formula III,



III

wherein X^3 is $-CR^3$ or N; X^4 is $-CR^4$, N or S; X^5 is $-CR^4$ or N; X^6 is $-CR^4$, N or S; Y is CH or N; R^1, R^2, R^3, R^4, W, V, U, M and n are defined as above.

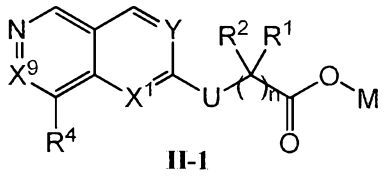
The condensed ring derivative I in the present invention, is more preferably a compound having a structure of formula IV,



IV

wherein X^2 is CH or N; each of X^7 and X^8 is independently CH or S; R^1, R^2, R^4, U, M and n are defined as above.

The compound having a structure of formula II in the present invention preferably has a structure of formula II-1,



II-1

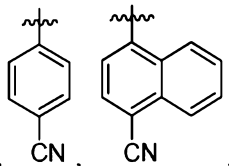
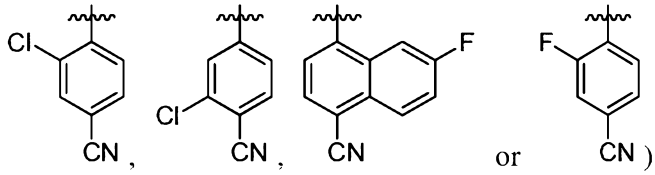
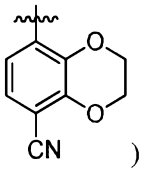
wherein X^1, X^9, Y, R^1, R^2, R^4, U, M and n are defined as above.

In a preferred embodiment of the present invention, in the compound having a structure of formula II-1,

X^1 and Y are C; X^9 is C or N;

each of R^1 and R^2 is independently H or an alkyl (preferably a C_{1-4} alkyl); or R^1, R^2 together with the carbon atom attached form a cycloalkyl (preferably a C_{3-6} cycloalkyl, more preferably a cyclobutyl);

M is H;

R^4 is an aryl (preferably a C_{6-10} aryl, more preferably a phenyl or a naphthyl, wherein the C_{6-10} aryl can be further substituted by one or more than one CN(s) and/or halogen(s) (preferably F, Cl, Br or I, more preferably F or Cl), e.g.  , ) or a heteroaryl (preferably a C_{2-10} heteroaryl having 1-2 heteroatoms selected from O, wherein the C_{2-10} heteroatom can be further substituted by one or more than one CN(s), e.g. );

U is  or  ;

each of R^5 and R^6 is independently H or an alkyl (preferably a C_{1-4} alkyl);

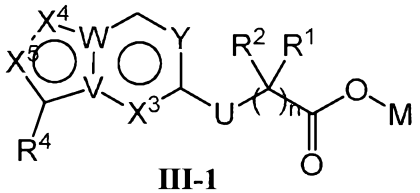
n is 1.

Preferably, in the compound having a structure of formula II-1,

where U is  and both of R^5 and R^6 are hydrogen, R^1 and R^2 are not H at the same time;

where X^9 is N, U is  .

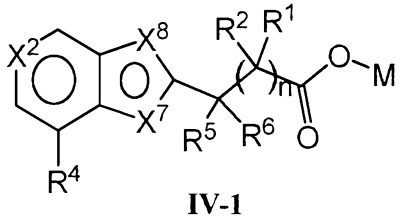
The compound having a structure of formula III in the present invention preferably has a structure of formula III-1,



III-1

wherein X^3, X^4, X^5, Y, R^1, R^2, R^3, R^4, W, V, U, M and n are defined as above.

The compound having a structure of formula IV in the present invention preferably has a structure of formula IV-1,



IV-1

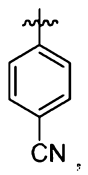
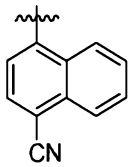
wherein X^2, X^7, X^8, R^1, R^2, R^4, R^5, R^6, M and n are defined as above.

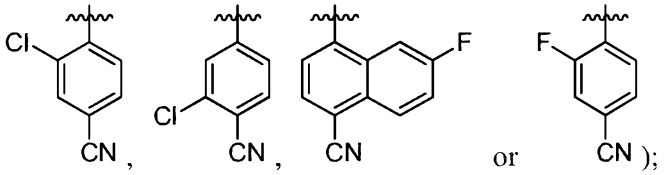
In a preferred embodiment of the present invention, in the compound having a structure of formula IV-1,

X^2 is N;

each of X^7 and X^8 is independently CH or S;

each of R^1 and R^2 is independently H or an alkyl (preferably a C_{1-4} alkyl);

R4 is an aryl (preferably a C_{6-10} aryl, more preferably a phenyl or a naphthyl, wherein the C_{6-10} aryl can be further substituted by one or more than one CN(s) and/or halogen(s) (preferably F, Cl, Br or I, more preferably F or Cl), e.g.  ,  ,



each of R^5 and R^6 is independently H or an alkyl (preferably a C_{1-4} alkyl);

n is 0 or 1.

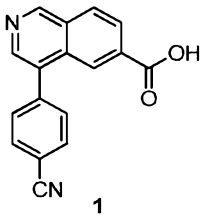
Preferably, X^2 is N; X^7 is CH; X^8 is S.

Preferably, in the compound having a structure of formula IV-1, M is H.

Preferably, in the compound having a structure of formula IV-1, where R^1 and/or R^2 is an alkyl, R^5 and R^6 are H; where R^5 and/or R^6 is an alkyl, R^1 and R^2 are H.

Preferably, in the compound having a structure of formula IV-1, where X^7 is S, X^8 is CH, R^1 and R^2 are alkyl, and R^5 and R^6 are H, R^4 is a phenyl.

The condensed ring derivative having a structure of formula I in the present invention is preferably selected from the compound consisting of



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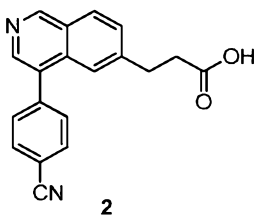

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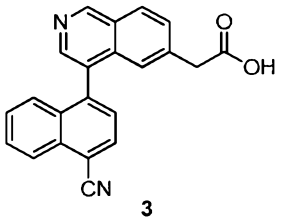

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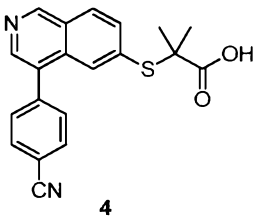

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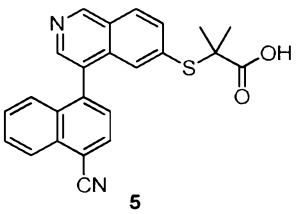

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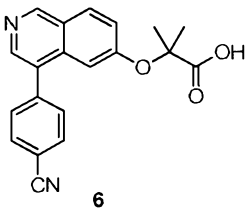

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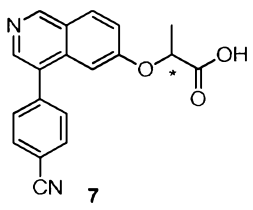

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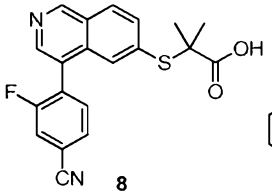

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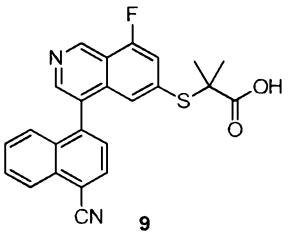

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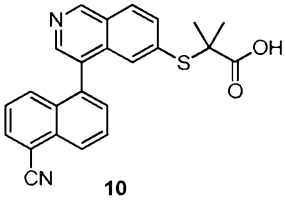

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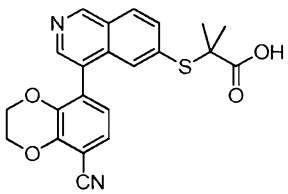

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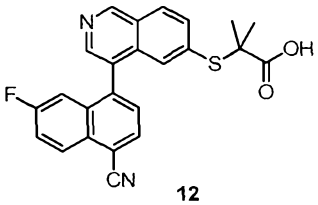
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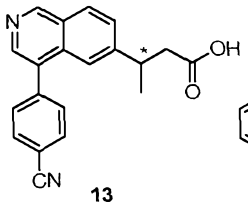
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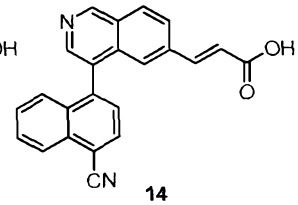
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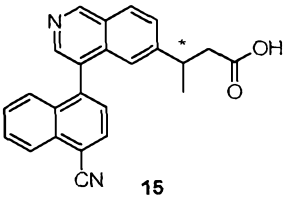
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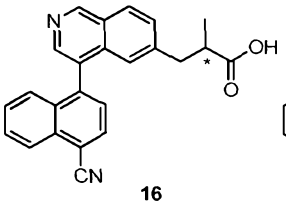
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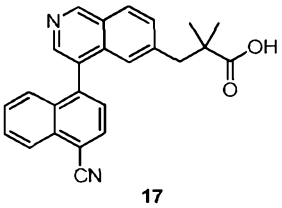
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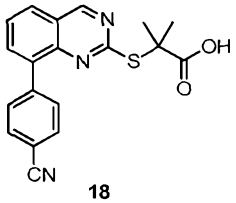
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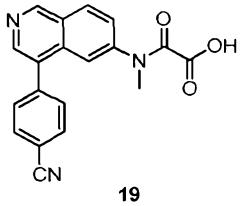
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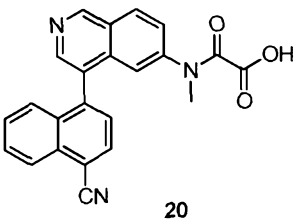
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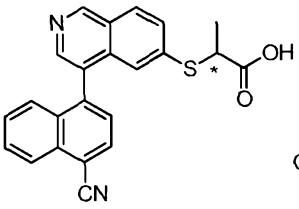
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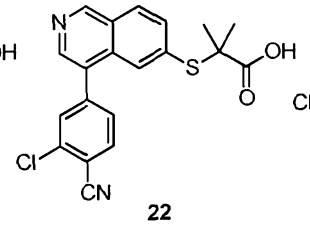
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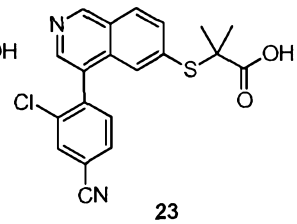
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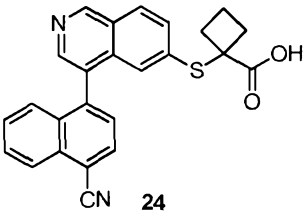
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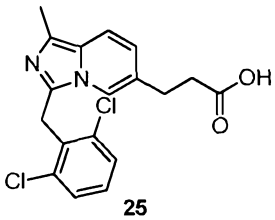
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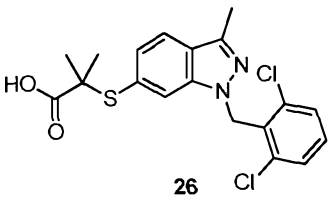
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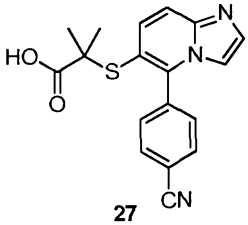
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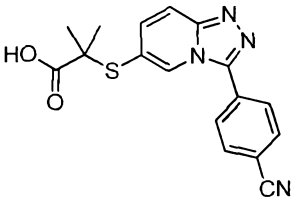
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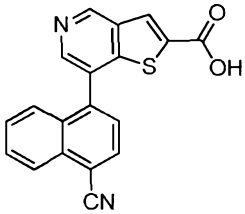
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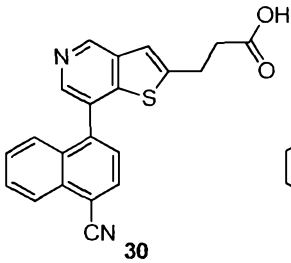
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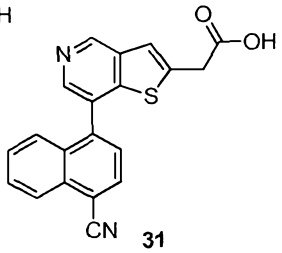
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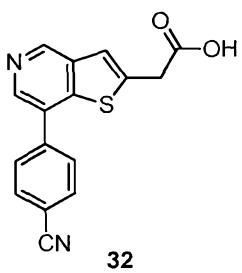
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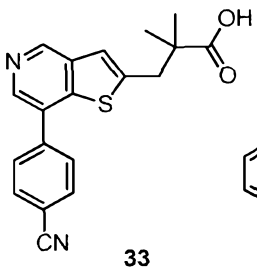
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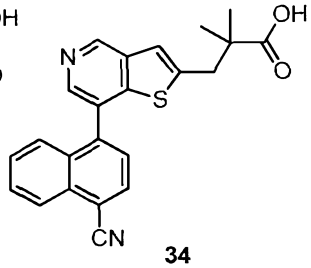
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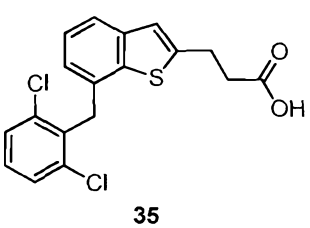
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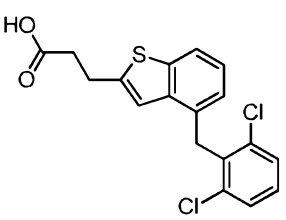
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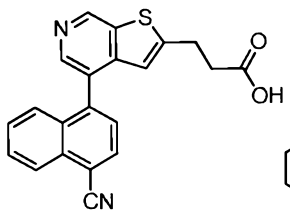
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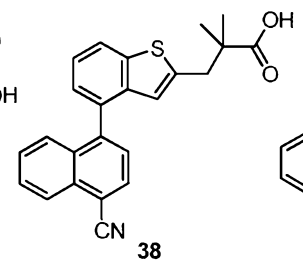
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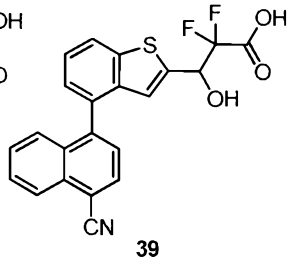
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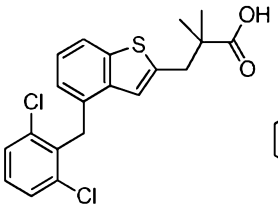
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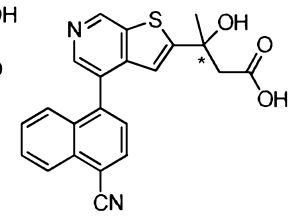
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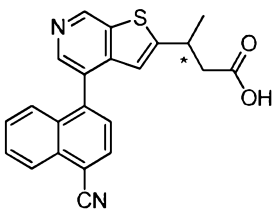
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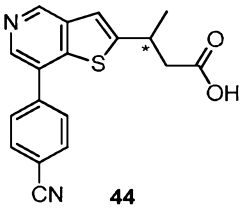
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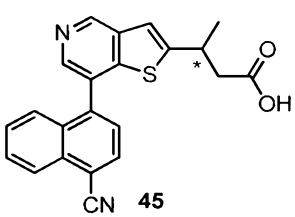
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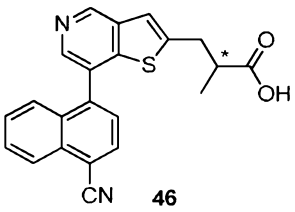
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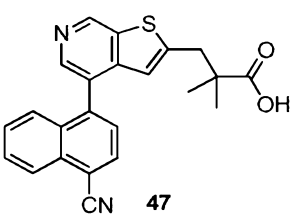
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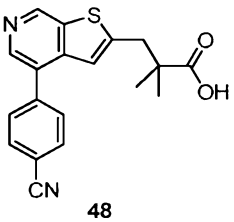
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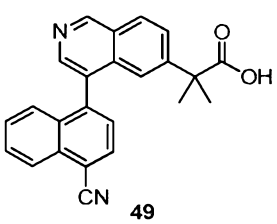
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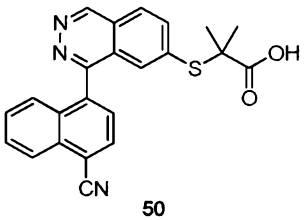
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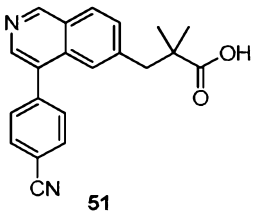
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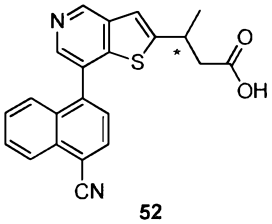
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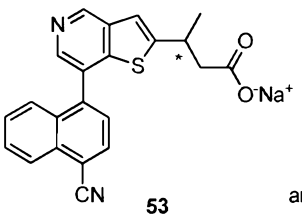
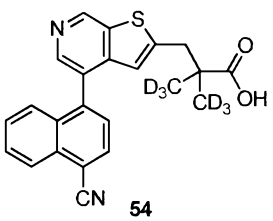

53

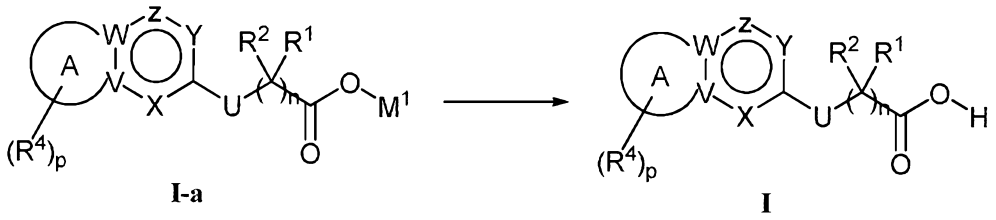
and


54

In the above compounds, the carbon marked with * is a chiral carbon or a non-chiral carbon; where it is a chiral carbon, it has S configuration or R configuration, where it is a non-chiral carbon, it is racemic.

The present invention also provides a process for preparing the condensed ring derivative having a structure of formula I, the tautomer, the mesomer, the racemate, the enantiomer, the diastereoisomer, or the pharmaceutically acceptable salt, the

metabolite, the metabolic precursor or the pro-drug thereof, which can be synthesized according to the method known in the art with commercially available raw materials. In the present invention, the process for preparing the condensed ring derivative having a structure of formula I preferably comprises that in a solvent, in the presence of a base, carrying out a hydrolysis reaction on the compound having a structure of formula I-a to give the compound having a structure of formula I;



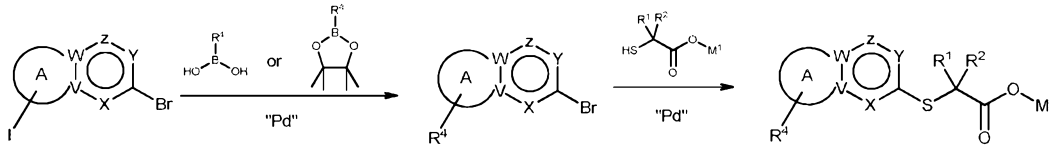
I-a I

in formula I-a and I, ring A, R^1, R^2, R^4, W, V, Z, Y, X, U, n and p are defined as above, in the compound having a structure of formula I-a, M^1 is an alkyl (preferably a C_{1-4} alkyl). The method and condition of the hydrolysis reaction are common method and condition in the art, therefore, in the hydrolysis reaction, the solvent used and the amount thereof, the base used and the amount thereof, the temperature and time of the hydrolysis reaction, and the post treatment after the hydrolysis reaction can all be selected according to the common processes and conditions in the art. For example, the solvent can be a mixed solution of alcohols (e.g. methanol), ethers (e.g. THF) and water, or a mixed solution of alcohols (e.g. methanol) and water. The base can be alkalis hydroxide (e.g. LiOH and/or NaOH). Where a base is used, the base can be in the form of its aqueous solution (the molar concentration of the base aqueous solution can be 1mol/L). The hydrolysis reaction can be carried out at room temperature. The process of the hydrolysis reaction can be monitored by the common method in the art (e.g. TLC, GC, HPLC or NMR etc.). The post treatment can comprise that mixing the reaction solution obtained after the hydrolysis reaction with the hydrochloric acid aqueous solution (e.g. 2mol/L hydrochloric acid aqueous solution) and water (solid precipitated), filtering, washing the filtrate cake with water, drying under reduced pressure.

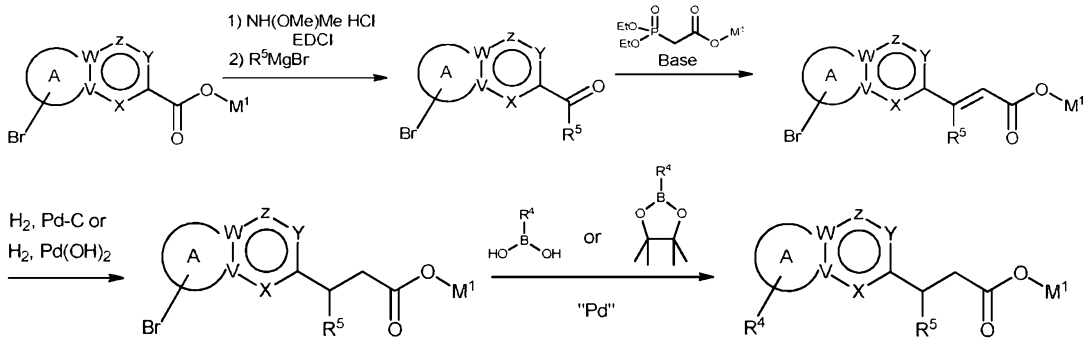
When M is a pharmaceutically acceptable cation, the compound having a structure of formula (I) wherein M is H can be neutralized by a hydroxide containing a pharmaceutically acceptable cation (e.g. sodium hydroxide). The conditions used in the process of a neutralizing reaction are common conditions used in the neutralizing reaction in the organic synthesis field.

The compound having a structure of formula I can be prepared according to the following process, comprising

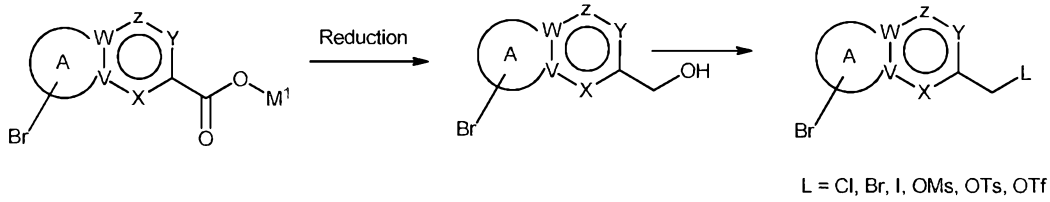
where U is  , the compound having a structure of formula I can be prepared according to route I, which comprises



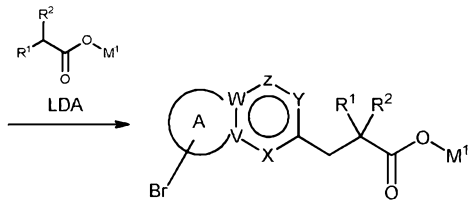
where U is  , R^6 is H and n is 1, the compound having a structure of formula I can be prepared according to route II, which comprises



where U is  , both R^5 and R^6 are H and n is 1, the compound having a structure of formula I can be prepared according to route III, which comprises

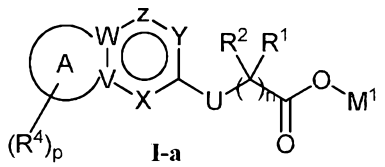


L = Cl, Br, I, OMs, OTs, OTf



In the above three routes, each letter or group involved is defined as above. Meanwhile, the conditions and steps used in the chemical reactions involved in the above three routes can refer to the common conditions and steps used in the art, and the compound obtained according to the above process can further be modified in the peripheral region, thereby obtaining other target compound of the present invention.

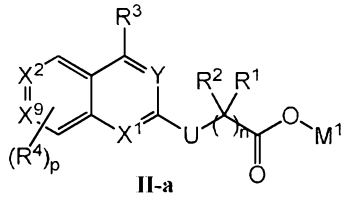
The present invention also provides a compound having a structure of formula I-a:



I-a

wherein, ring A, R^1, R^2, R^4, W, V, Z, Y, X, U, n and p are defined as above; M^1 is an alkyl (preferably a C_{1-4} alkyl).

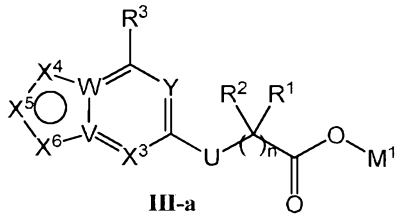
The intermediate having a structure of formula I-a, further preferably has a structure of formula II-a:



II-a

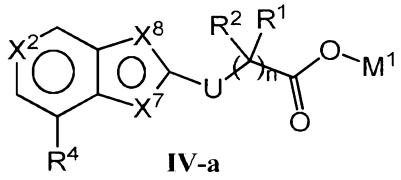
wherein, X^1 and X^2 are independently CH or N; X^9 is CH or N; Y is CH or N; R^1, R^2, R^3, R^4, U, M^1, n and p are defined as above.

In the present invention, the intermediate having a structure of formula I-a, preferably has a structure of formula III-a:



III-a

wherein, X^3 is $-\overset{}{\underset{}{\text{CR}^3}}$ or N; X^4 is $\overset{}{\underset{}{\text{CR}^4}}$, N or S; X^5 is $\overset{}{\underset{}{\text{CR}^4}}$ or N; X^6 is $\overset{}{\underset{}{\text{CR}^4}}$, N or S; Y is CH or N; R^1, R^2, R^3, R^4, W, V, U, M^1 and n are defined as above.

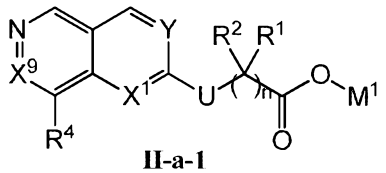


IV-a

wherein, X^2 is CH or N; X^7 and X^8 are independently CH or S; R^1, R^2, R^4, U, M^1 and n are defined as above.

In the present invention, the compound having a structure of formula II-a, preferably

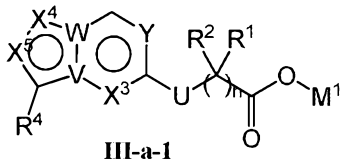
has a structure of formula II-a-1:



II-a-1

wherein, X^1, X^9, Y, R^1, R^2, R^4, U, M^1 and n are defined as above.

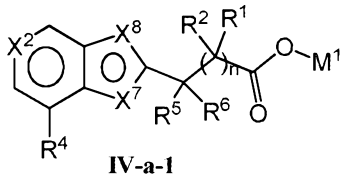
In the present invention, the compound having a structure of formula III-a, preferably has a structure of formula III-a-1:



III-a-1

wherein, X^3, X^4, X^5, Y, R^1, R^2, R^4, W, V, U, M^1 and n are defined as above.

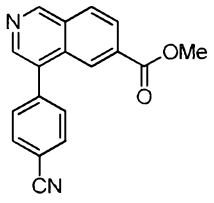
In the present invention, the compound having a structure of formula IV-a, preferably has a structure of formula IV-a-1:



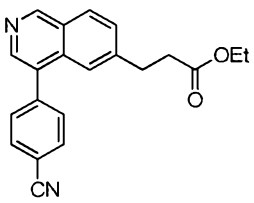
IV-a-1

wherein, X^2, X^7, X^8, R^1, R^2, R^4, R^5, R^6, M^1 and n are defined as above.

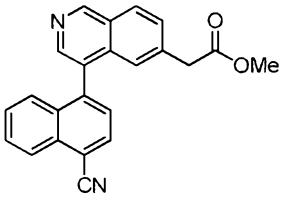
The intermediate having a structure of formula I-a, preferably is selected from the compound consisting of



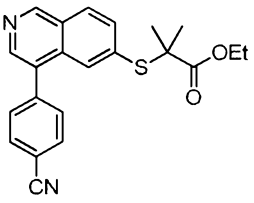
1-a



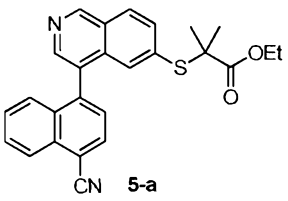
2-a



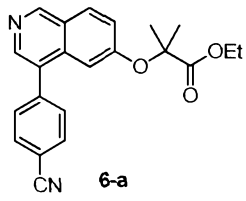
3-a



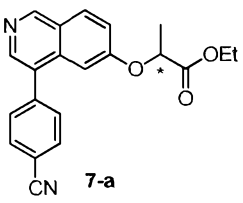
4-a



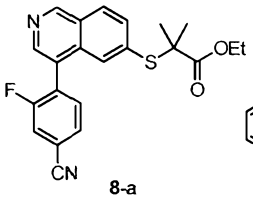
5-a



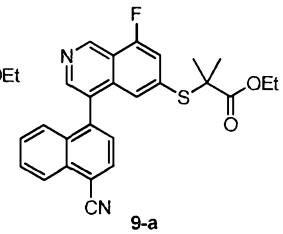
6-a



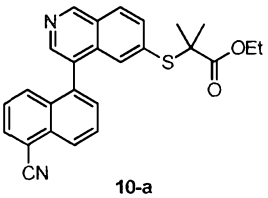
7-a



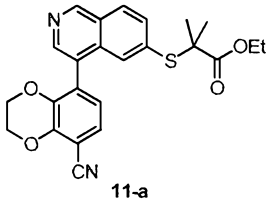
8-a



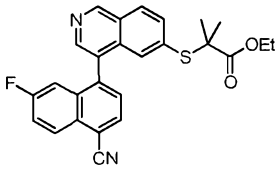
9-a



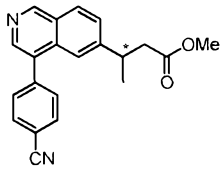
10-a



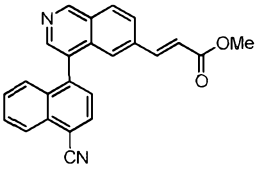
11-a



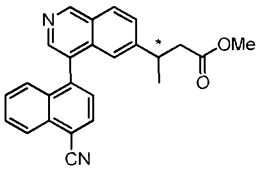
12-a



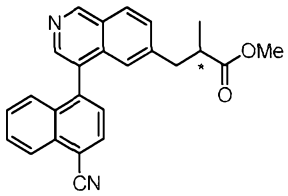
13-a



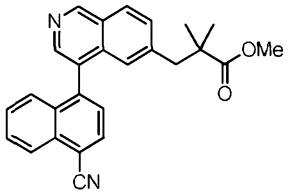
14-a



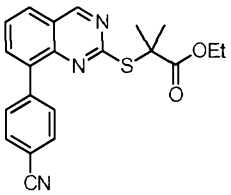
15-a



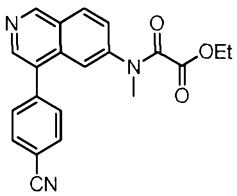
16-a



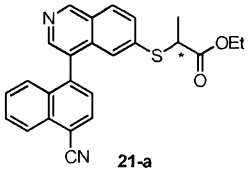
17-a



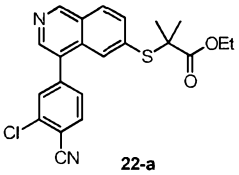
18-a



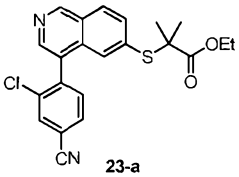
19-a



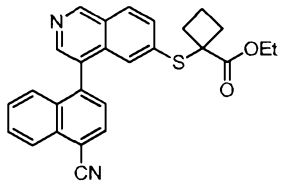
21-a



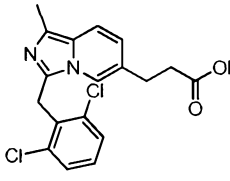
22-a



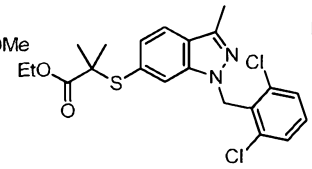
23-a



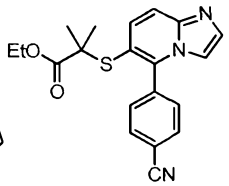
24-a



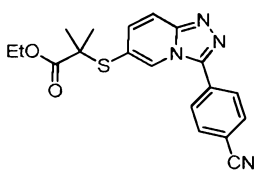
25-a



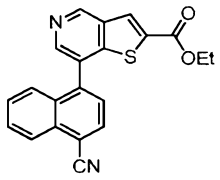
26-a



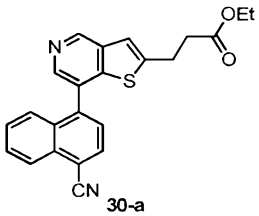
27-a



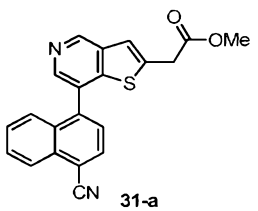
28-a



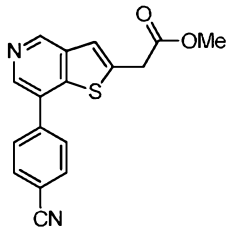
29-a



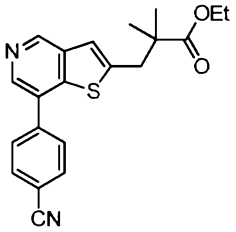
30-a



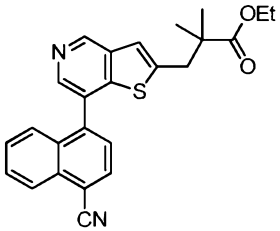
31-a



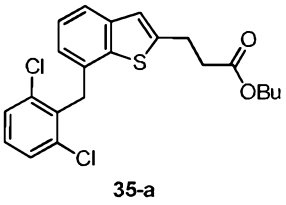
32-a



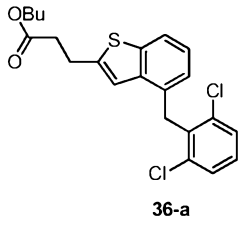
33-a



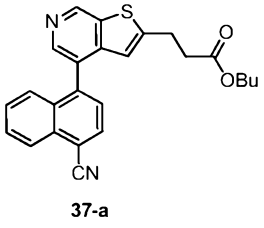
34-a



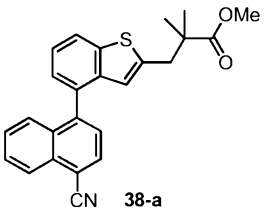
35-a



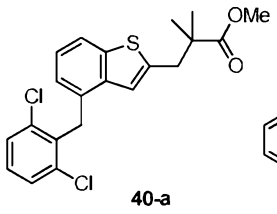
36-a



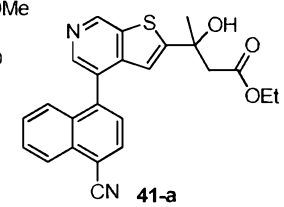
37-a



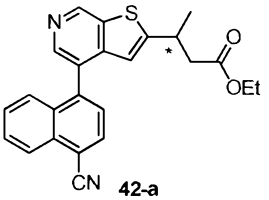
38-a



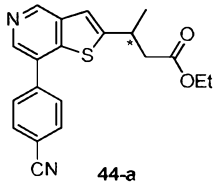
40-a



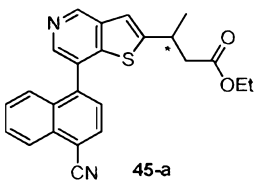
41-a



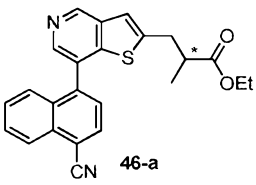
42-a



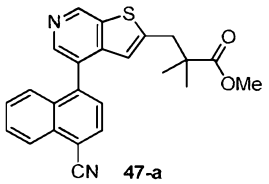
44-a



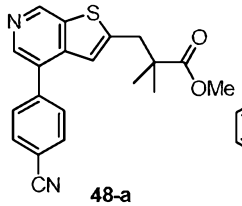
45-a



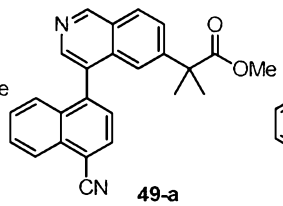
46-a



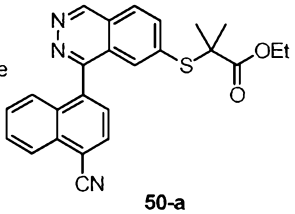
47-a



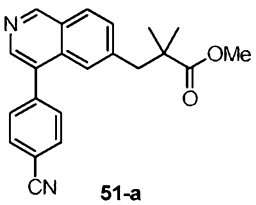
48-a



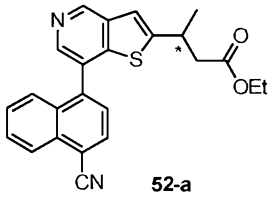
49-a



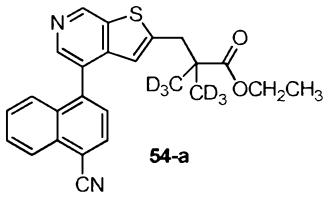
50-a



51-a



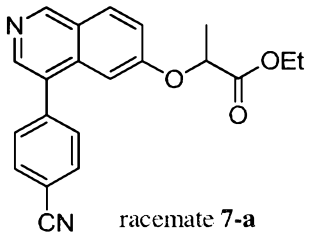
52-a



54-a

In above compounds, the carbon marked with * is a chiral carbon or a non-chiral carbon; where it is a chiral carbon, it has S configuration or R configuration, where it is a non-chiral carbon, it is racemic.

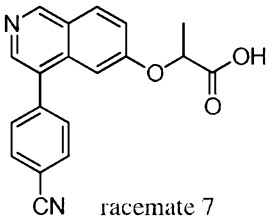
The present invention also provides one of enantiomers contained in the racemic compound 7-a, which is given by separating the racemic compound 7-a by an enantiomeric chromatographic column:



racemate **7-a**

wherein the chromatograph is preferably Gilson 281, the preparative column is preferably r, r-Whelk-O1 (20×250 mm, 5 μm), the mobile phase is preferably Hexane : EtOH : DEA = 70 : 30 : 0.1 (v/v/v); when the retaining time is 9.0 min, one enantiomer 7A-a is given; when the retaining time is 11.0 min, the other enantiomer 7B-a is given.

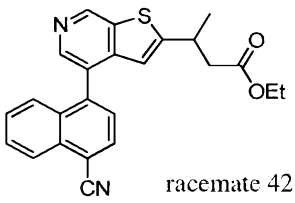
The present invention also provides one of enantiomers contained in the racemate 7:



racemate 7

wherein the process for preparing one enantiomer preferably comprises that in an organic solvent, in the presence of a base, carrying out a hydrolysis reaction on the enantiomer 7A-a; the process for preparing the other enantiomer preferably comprises that in an organic solvent, in the presence of a base, carrying out a hydrolysis reaction on the enantiomer 7B-a.

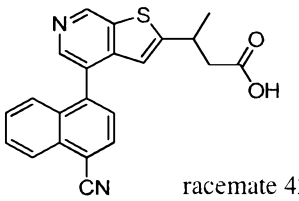
The present invention also provides one of the enantiomers contained in the racemate 42-a, which is given by separating the racemate 42-a by an enantiomeric chromatographic column:



racemate 42-a

wherein the chromatograph is preferably SFC-80 (Thar, Waters), the preparative column is preferably AD 30×250mm, 5μm (Decial), the mobile phase is preferably *n*-Hexane-0.1% DEA : EtOH-0.1%DEA = 80 : 20 (v/v); when the retaining time is 18.0 min, one enantiomer 43A-a is given; when the retaining time is 20.0 min, the other enantiomer 43B-a is given.

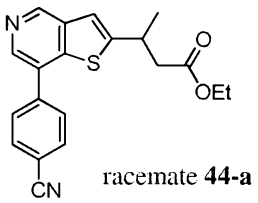
The present invention also provides one of the enantiomers contained in the racemate 42:



racemate 42

wherein the process for preparing one enantiomer preferably comprises that in an organic solvent, in the presence of a base, carrying out a hydrolysis reaction on the enantiomer 43A-a; the process for preparing the other enantiomer preferably comprises that in an organic solvent, in the presence of a base, carrying out a hydrolysis reaction on the antimer 43B-a.

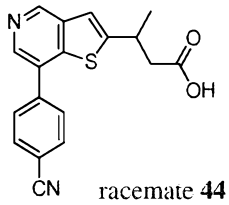
The present invention also provides one of the enantiomers contained in the racemate 44-a, which is given by separating the racemate 44-a by an enantiomeric chromatographic column:



racemate **44-a**

wherein the chromatograph is preferably Gilson 281, the preparative column is preferably r, r-Whelk-O1 (20×250 mm, 5 μm), the mobile phase is preferably *n*-Hexane : EtOH : DEA = 70 : 30 : 0.1 (v/v/v); when the retaining time is 6.0 min, one enantiomer 44A-a is given; when the retaining time is 7.0 min, the other enantiomer 44B-a is given.

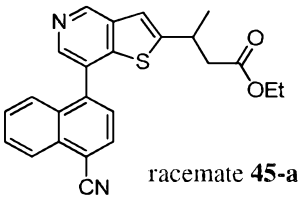
The present invention provides one of the enantiomers contained in the racemate 44:



racemate **44**

wherein the process for preparing one enantiomer preferably comprises that in an organic solvent, in the presence of a base, carrying out a hydrolysis reaction on the antimer 44A-a; the process for preparing the other enantiomer preferably comprises that in an organic solvent, in the presence of a base, carrying out a hydrolysis reaction on the antimer 44B-a.

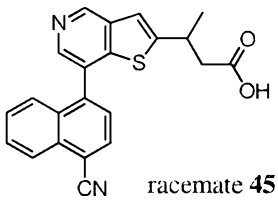
The present invention provides one of the enantiomers contained in the racemate 45-a, which is given by separating the racemate 45-a by an enantiomeric chromatographic column:



racemate **45-a**

wherein the chromatograph is preferably SFC-80 (Thar, Waters), the preparative column is preferably AD 30×250mm, 5μm (Decial), the mobile phase is preferably CO_2 : (Methanol-0.1%NH_4OH) = 65 : 35 (v/v); when the retaining time is 8.5 min, one enantiomer 45A-a is given; when the retaining time is 10.5 min, the other enantiomer 45B-a is given.

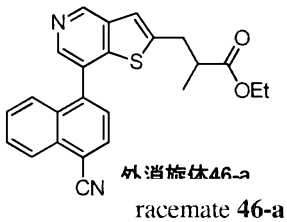
The present invention provides one of the enantiomers contained in the racemate 45:



racemate **45**

wherein the process for preparing one enantiomer preferably comprises that in an organic solvent, in the presence of a base, carrying out a hydrolysis reaction on the antimer 45A-a; the process for preparing the other enantiomer preferably comprises that in an organic solvent, in the presence of a base, carrying out a hydrolysis reaction on the enantiomer 45B-a.

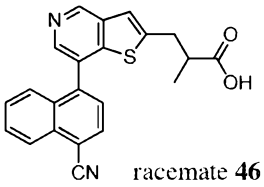
The present invention provides one of the enantiomers contained in the racemate 46-a, which is given by separating the racemate 46-a by an enantiomeric chromatographic column:



racemate **46-a**

wherein the chromatograph is preferably Gilson 281, the preparative column is preferably r, r-Whelk-O1 (20×250 mm, 5 μm), the mobile phase is preferably Hexane : EtOH : DEA = 80 : 20 : 0.1 (v/v/v); when the retaining time is 14.0 min, one enantiomer 46A-a is given; when the retaining time is 18.0 min, the other antimer 46B-a is given.

The present invention provides one of the enantiomers contained in the racemate 46:



racemate **46**

wherein the process for preparing one enantiomer preferably comprises that in an organic solvent, in the presence of a base, carrying out a hydrolysis reaction on the enantiomer 46A-a; the process for preparing the other enantiomer preferably comprises that in an organic solvent, in the presence of a base, carrying out a hydrolysis reaction on the enantiomer 46B-a.

The present invention also provides one of the enantiomers included in the racemate 53, the process for preparing one enantiomer preferably comprises, in water, neutralizing the enantiomer 45A by NaOH.

The present invention also provides a use of the condensed ring derivative having a structure of formula I, the tautomer, the mesomer, the racemate, the enantiomer, the diastereoisomer, or the pharmaceutically acceptable salt, the metabolite, the metabolic precursor or the pro-drug thereof in manufacturing a medicament for preventing and/or treating hyperuricemia or its related diseases. The hyperuricemia related diseases generally include gout, hypertension, diabetes, hypertriglyceridemia, metabolic syndrome, coronary heart disease and renal damage and so on.

The present invention also provides a pharmaceutical composition, which comprises therapeutically effective amount of the condensed ring derivative having a structure of formula I, the tautomer, the mesomer, the racemate, the enantiomer, the diastereoisomer, or the pharmaceutically acceptable salt, the metabolite, the metabolic precursor or the pro-drug thereof, and one or more than one pharmaceutically acceptable carrier and/or diluter.

In the present invention, the pharmaceutical composition can be in the form of an oral administration, as well as a sterile injectable aqueous solution, which can be prepared

according to any known process for preparing pharmaceutical composition in the art.

The pharmaceutical composition can be used alone, as well as in combination with other medicament having activity on lowering uric acid. The medicament having activity on lowering uric acid is selected from the group consisting of uric acid transporter 1 inhibitor, Xanthine oxidase inhibitor, Xanthine oxidoreductase and Xanthine dehydrogenase inhibitor, preferably Allopurinol and/or Febuxostat.

The present invention also provides a method for preventing and/or treating hyperuricemia or its related diseases, the method comprises administrating proactively effective amount and/or therapeutically effective amount of the condensed ring derivative having a structure of formula I, the tautomer, the mesomer, the racemate, the enantiomer, the diastereoisomer, or the pharmaceutically acceptable salt, the metabolite, the metabolic precursor or the pro-drug thereof to the subject, or administrating proactively effective amount and/or therapeutically effective amount of the pharmaceutical composition of the present invention to the subject.

Unless otherwise specified, the terms involved in the description and the claims of the present invention have following definitions:

"Alkyl" used herein (including used alone and contained in other groups) refers to a saturated linear and branched aliphatic hydrocarbyl containing 1-20 carbon atoms, preferably containing 1-10 carbon atoms, more preferably containing 1-8 carbon atoms, such as methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *tert*-butyl, *iso*-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, 4,4-dimethylpentyl, 2,2,4-trimethylpentyl, undecyl, dodecyl, and isomers thereof; as well as the alkyl containing 1-4 substituents (with no further substitutions) selected from the group consisting of D, a halogen (preferably F, Br, Cl or I), an alkyl, an alkoxy, an aryl, an aryloxy, an aryl or diaryl substituted by an aryl, an aralkyl, an aralkoxy, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, a cycloalkyl alkyl, a cycloalkyl alkoxy, an optionally substituted amino, a hydroxyl, a hydroxyl alkyl, an acyl, an aldehyde group, a heteroaryl, a heteroaryloxy, a heterocycloalkyl, a heterocycloalkoxy, an aryl heteroaryl, an arylalkoxycarbonyl, a heteroarylalkyl, a heteroarylalkoxy, an aryloxyalkyl, an aryloxyaryl, an alkylamino, an amido, an arylcarbonylamino, a nitro, a nitrile group, a sulphydryl, a haloalkyl, a trihaloalkyl and/or an alkylthio. In the present invention, "C_{x1}-C_{y1}" alkyl (x1 and y1 are integers) having indicated number of carbon atoms, such as "C_{1-4} alkyl", has the same definition of the "alkyl" described in this paragraph, except for the number of carbon atoms.

"Alkylidene" used herein (including used alone and contained in other groups) refers to a sub-saturated linear and branched aliphatic hydrocarbyl containing 1-20 carbon atoms, preferably containing 1-10 carbon atoms, more preferably containing 1-8 carbon atoms, such as methylene, ethylidene, propylidene, *iso*-propylidene, *n*-butylidene, *tert*-butylidene, *iso*-butylidene, pentylidene, hexylidene, heptylidene, octylidene, nonylidene, decylidene, bis(4,4-dimethylpentyl), bis(2,2,4-trimethylpentyl), undecylidene, dodecylidene, and the isomers thereof;

including the alkylidene containing 1-4 substituents (without further substituents) selected from the group consisting of D, a halogen (preferably F, Br, Cl or I), an alkyl, an alkoxy, an aryl, an aryloxy, an aryl or diaryl substituted by an aryl, an aralkyl, an aralkoxy, an alkenyl, an alkynyl, an cycloalkyl, an cycloalkenyl, an cycloalkylalkyl, an cycloalkylalkoxy, an optionally substituted amino, an hydroxyl, an hydroxyalkyl, an acyl, an aldehyde group, an heteroaryl, an heteroaryloxy, an heterocycloalkyl, an heterocycloalkoxy, an arylheteroaryl, an arylalkoxycarbonyl, an heteroarylalkyl, an heteroarylalkoxy, an aryloxyalkyl, an aryloxyaryl, an alkylamino, an amido, an arylcarbonylamino, a nitro, a nitrile group, a sulphydryl, a haloalkyl, a trihaloalkyl and/or an alkylthio; one or more than one substituents together with the alkylidene can form a ring, thereby forming a fused ring or a spiro ring.

The term "aliphatic ring" or "cycloalkyl" (including used alone and contained in other groups) includes saturated or partially unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon group containing 1-3 rings, including monocycloalkyl, bicycloalkyl and tricycloalkyl which contains 3-20 carbon atoms which can form a ring, preferably contains 3-10 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl; the cycloalkyl can be substituted by any of 1-4 substituents (without further substitutions) selected from the group consisting of D, a halogen, an alkyl, an alkoxy, a hydroxyl, an aryl, an aryloxy, an aralkyl, a cycloalkyl, an alkylamino, an amido, an oxo, an acyl, an arylcarbonylamino, an amino, a nitro, a nitrile group, a sulphydryl and/or an alkylthio and/or any alkyl group.

The term "alkoxy" refers to a cyclic or non-cyclic alkyl having indicated number of carbon atoms linked by an oxygen bridge. Therefore, "alkoxy" includes the definitions of the alkyl and the cycloalkyl.

The term "alkenyl" refers to a linear, branched or cyclic non-aryl hydrocarbyl having indicated carbon atoms and at least one carbon-carbon double bond. Preferably, it has one carbon-carbon double bond and can exist up to four non-aryl carbon-carbon double bonds. Therefore, "C_{2-12} alkenyl" refers to an alkenyl having 2-12 carbon atoms. "C_{2-6} alkenyl" refers to an alkenyl having 2-6 carbon atoms, including vinyl, propenyl, butenyl, 2-methyl butenyl and cyclohexenyl. The linear, branched and cyclic part of the alkenyl can contain a double bond, and if it is a substituted alkenyl, the alkenyl can be substituted (but the substituent with no further substitution).

The term "alkynyl" refers to a linear, branched or cyclic hydrocarbyl having indicated carbon atoms and at least one carbon-carbon triple bond. It can have up to three carbon-carbon triple bonds. Therefore, "C_{2-12} alkynyl" refers to an alkynyl having 2-12 carbon atoms. "C_{2-6} alkynyl" refers to an alkynyl having 2-6 carbon atoms, including ethynyl, propynyl, butynyl and 3-methyl butynyl etc.

The term "aryl" used herein refers to any stable monocyclic or bicyclic carbon rings which can have up to 7 atoms in each ring, and at least one of the rings is an aromatic ring. The typical aryl unit includes phenyl, naphthyl, tetrahydronaphthyl, 2,

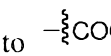
3-dihydroindenyl, biphenyl, phenanthryl, anthryl or acenaphthyl. It can be understood that where the aryl is a bicyclic group and one of the ring is a non-aromatic ring, the linkage is through the aromatic ring. The aryl also includes any of 1-4 substituents (without further substitutions) selected from the group consisting of D, a halogen (F, Br Cl or I), an alkyl, an alkoxy, an aryl, an aryloxy, an aryl or diaryl substituted by an aryl, an aralkyl, an aralkoxy, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, a cycloalkylalkyl, a cycloalkylalkoxy, an optionally substituted amino, a hydroxyl, a hydroxyalkyl, an acyl, an aldehyde group, a heteroaryl, a heteroaryloxy, a heterocycloalkyl, a heterocycloalkoxy, an arylheteroaryl, an arylalkoxycarbonyl, a heteroarylalkyl, a heteroarylalkoxy, an aryloxyalkyl, an aryloxyaryl, an alkylamino, an acylamino, an arylcarbonylamino, a nitro, a nitrile group, a sulphydryl, a haloalkyl, a trihaloalkyl and/or an alkylthio.

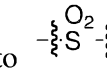
The term "halogen" refers to F, Cl, Br, I or At.

The term "hydroxyl" refers to  .

The term "amino" refers to  .

The term "cyano" refers to  .

The term "carboxyl" refers to  .

The term "sulfonyl" refers to  .

The term "acyl" refers to  , a univalence group derived from an organic or inorganic oxygenic acid cleaving a hydroxyl off.

The term "haloalkyl" refers to an alkyl substituted by halogen at any position. Therefore, "haloalkyl" includes the definitions of the halogen and the alkyl.

The term "haloalkoxy" refers to an alkoxy substituted by halogen at any position. Therefore, "haloalkoxy" includes the definitions of the halogen and the alkoxy.

The term "aryloxy" refers to an aryl having indicated number of carbon atoms linked by an oxygen bridge. Therefore, "aryloxy" includes the definition of the aryl.

The term "aromatic hetero group" or "heteroaryl" used herein refers to a stable monocycle or bicycle which can have up to 7 atoms in each ring, and at least one of the rings is an aromatic ring containing 1-4 heteroatoms selected from O, N and S. The heteroaryl defined herein includes but not limited to acridinyl, carbazolyl, cinnolinyl, quinoxalinyl, pyrazolyl, indolyl, benzotriazolyl, furanyl, thienyl,

benzothienyl, benzofuranyl, quinolinyl, isoquinolyl, oxazolyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridyl, pyrimidyl, pyrryl, tetrahydroquinoline. As defined in the heterocyclo, "heteroaryl" can also be understood including the N-Oxide derivative of any N-containing heteroaryl. Where the heteroaryl is a bicyclic group and one of the rings is a non-aromatic ring or without any heteroatom, it can be understood, the linkage is through the aryl or the ring containing the heteroatom. The heteroaryl can be substituted by any of 1-4 substituents selected from the group consisting of D, a halogen, an alkyl, an alkoxy, a hydroxyl, an aryl, an aryloxy, an aralkyl, a cycloalkyl, an alkylamino, an acylamino, an acyl, an arylcarbonylamino, an amino, a nitro, a nitrile group, a sulphydryl and/or an alkylthio and/or any of alkyl group.

The term "heterocyclo" or "heterocyclic group" used herein refers to a 5-10 membered aromatic or non-aromatic heterocycle having 1-4 heteroatoms selected from O, N and S, including bicyclic group. Therefore, "heterocyclic group" includes the aryl and the dihydro- or tetrahydro- analogues thereof. The embodiments of the "heterocyclic group" include but not limited to benzimidazolyl, benzofuranyl, benzofurazinyl, benzopyrazolyl, benzotriazolyl, benzothienyl, benzoxazolyl, carbazyl, carbazolyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indazolyl, isobenzofuranyl, pseudoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthalene pyrimidinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, oxycyclobutyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridyl, pyridazinyl, pyridyl, pyrimidyl, pyrryl, quinazolyl, quinolyl, quinoxalinyl, tetrahydropyranyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzimidazolyl, dihydrobenzofuranyl, dihydrobenzothienyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisoxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridyl, dihydropyrimidinyl, dihydropyryl, dihydroquinolyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydro-azetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, tetrahydrothienyl and N-Oxide thereof. The heterocyclo (without further substitution) can link with other groups by its carbon atom or heteroatom.

The term "cycloheteroaliphatic" or "heterocycloalkyl" used herein alone or contained in other groups refers to a saturated or partially unsaturated 4-12 membered ring having 1-4 heteroatoms (e.g. N, O and/or S). The heterocycloalkyl can contain 1-4 substituents (without further substitution), such as an alkyl, a halogen, an oxo and/or any of alkyl list above. Besides, any heterocycloalkyl can fuse to a cycloalkyl, an aryl, a heteroaryl or a heterocycloalkyl. The heterocycloalkyl can link to other groups through its carbon atom or heteroatom.

The term "aromatic ring" used herein refers to any stable monocyclic or bicyclic carbon rings which can have up to 7 atoms in each ring and at least one of the ring is an aromatic ring. The embodiments of the aromatic unit include phenyl, naphthyl, tetrahydronaphthyl, 2, 3-dihydroindenyl, biphenyl, phenanthryl, anthryl or

acenaphthyl. It can be understood that when the aryl is a bicyclic group and one of the ring is a non-aromatic ring, the linkage is through "aromatic ring". The aromatic ring includes any of 1-4 substituents (without further substitution) selected from the group consisting of D, a halogen (F, Br, Cl or I), an alkyl, an alkoxy, an aryl, an aryloxy, an aryl or biaryl substituted with an aryl, an aralkyl, an aralkoxy, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, a cycloalkylalkyl, a cycloalkylalkoxy, an amino, a hydroxyl, a hydroxyalkyl, an acyl, an aldehyde group, a heteroaryl, a heteroaryloxy, a heterocycloalkyl, a heterocycloalkoxy, an arylheteroaryl, an arylalkoxycarbonyl, a heteroarylalkyl, a heteroarylalkoxy, an aryloxyalkyl, an aryloxyaryl, an alkylamino, an acylamino, an arylcarbonylamino, a nitro, a nitrile group, a sulphydryl, a haloalkyl, a trihaloalkyl and/or an alkylthio.

The term "heteroaryl" or "aromatic heterocyclo" used herein refers to a stable monocyclic or bicyclic group which can have up to 7 atoms in each ring and at least one of the ring is an aromatic ring having 1-4 heteroatoms selected from O, N and S. In this definition, the heteroaryl includes but not limited to acridine, carbazole, cinnoline, carboline, quinoxaline, imidazole, pyrazole, pyrrole, indole, indoline, benzotriazole, benzimidazole, furan, thiophen, isothiazole, benzothiophene, dihydrobenzothiophene, benzofuran, isobenzofuran, benzoxazole, benzofuraxan, benzopyrazole, quinoline, isoindoline, isoquinoline, oxazole, oxadiazole, isoxazole, indole, pyrazine, pyridopyridine, tetrazolopyridine, pyridazine, pyridine, naphthalene pyrimidine, pyrimidine, pyrrole, tetrazole, thiadiazole, thiazole, thiophene, triazole, quinazoline, tetrahydroquinoline, dihydrobenzimidazole, dihydrobenzofuran, dihydrobenzoxazole, dihydroquinoline. As defined in the definition of heterocycle, "heteroaryl" is also understood to include N-Oxide derivatives of any N-containing heteroaryl. Where the heteroaryl is a bicyclic group and one of the ring is a non-aromatic ring or without any heteroatom, it can be understood that the linkage is through the aryl or the heteroatom contained in the ring. The heteroaryl can be substituted by any of 1-4 substituents (without further substitutions) selected from the group consisting of D, a halogen, an alkyl, an alkoxy, a hydroxyl, an aryl, an aryloxy, an aralkyl, a cycloalkyl, an alkylamino, an acylamino, an acyl, an arylcarbonylamino, an amino, a nitro, a nitrile group, a sulphydryl and/or an alkylthio and/or any alkyl defined in the present invention.

"Proactively effective amount and/or therapeutically effective amount" refers to an amount of the compound administered to a subject sufficient to prevent and/or treat the diseases involved in the present invention. Though the proactively effective amount and/or therapeutically effective amount of the compound depends on the compound, the condition and its severity, and the age of the subject to be treated, it can be determined by the person skilled in the art according to the common method.

As used in the present invention, when the specific salt, pharmaceutical composition, composition, excipient are mentioned to be "pharmaceutically acceptable", it means that the salt, pharmaceutical composition, composition, excipient are generally non-toxic, safe and suitable to be administered to the subject; the subject is preferably a mammal, more preferably human.

The term "pharmaceutically acceptable salt" as used herein refers to a pharmaceutically acceptable organic or inorganic salt of the compound of the present invention. Typical embodiments are include but not limited to sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methylsulfonate, ethylsulfonate, benzene sulfonate, tosilate, embonate (i.e. 1-1-methylene-bis(2-hydroxyl-3-naphthoate)).

As used herein, unless otherwise specified, the term "prodrug" refers to a derivative of a compound containing biological reactive functional groups, which can be cleaved from the compound or react in other ways to provide the compound under biological condition (*in vivo* or *in vitro*). Generally, the prodrug does not have activity, or have less activity than the compound itself, this makes the compound exhibit effects until the biological reactive functional group cleaved from the compound. The biological reactive functional group can hydrolyze or oxidize under biological condition to provide the compound. For example, the prodrug can include biologically hydrolysable groups. The biologically hydrolysable groups include but not limited to biologically hydrolysable phosphate, biologically hydrolysable ester, biologically hydrolysable amide, biologically hydrolysable carbonate, biologically hydrolysable carbamate and biologically hydrolysable uride.

The compound of the present invention can contain one or more than one asymmetric centers ("stereoisomers"). As used herein, the term "stereoisomers" refers to *Cis*- and *Trans*- isomer, R- and S- antimer and diastereomer. These stereoisomers can be prepared by asymmetric synthesis or chiral separation (e.g. isolating, crystallizing, TLC, column chromatography, gas chromatography, HPLC). These stereoisomers can also derive from the diastereomer obtained from reacting a mixture of the enantiomers or racemate with a proper chiral compound, followed by crystallizing or conducting any other proper common method.

As used herein, the term "subject" refers to any animal to be administered or have been administered with the compound or the pharmaceutical composition according to the embodiment of the present invention, preferably a mammal, most preferably human. As used herein, the term "mammal" includes any mammal. Typical mammal includes but not limited to cattle, horse, sheep, pig, cat, dog, mouse, rat, rabbit, Guinea pig, monkey, human and so on, human is the most preferable.

In one embodiment, "treat" or "treating" refers to an improvement, prevention or reversion of a disease or a condition or at least one distinguished symptom thereof. In another embodiment, "treat" or "treating" refers to an improvement, prevention or reversion of at least one of measurable body parameters of a disease or a condition which is being treated, which may not been distinguished in a mammal. However, in another embodiment, "treat" or "treating" refers to slowing the development of a disease or a condition, or refers to stabilizing in body, such as a recognizable

symptom, or refers to stabilizing in physiology, such as body parameters, or refers to both. In another embodiment, treat" or "treating" refers to slowing the initiation of a disease or a condition.

In certain embodiments, the claimed compound is administered for prevention. As used herein, "prevent" or "preventing" refers to lowering a risk of having a disease or a condition. In a preferred embodiment, administering an indicated compound to a subject for a preventive purpose, such as the subject having a tendency to catch or having a family history of cancer or autoimmune diseases.

In the present invention, abbr. "Abs" refers to the absolute configuration of the chiral carbon atom contained in the compound is unknown, indicating S-configuration or R-configuration.

In the present invention, 0.1% DEA refers to that DEA volume accounts for 0.1% volume of the mixture solution containing DEA, for example, in Hexane-0.1% DEA, 0.1% DEA refers to that DEA volume accounts for 0.1% total volume of Hexane and DEA. Additionally, the definition of 0.1% NH_4OH is the same as that of 0.1% DEA.

In the present invention, room temperature refers to ambient temperature, generally refers to 10-30℃.

Without departing from the common knowledge in the art, the optimized embodiments can be obtained by optionally combining the preferred conditions above.

The reagents and raw materials are commercially available.

The positive effects achieved by the present invention lie in that:

the present invention provides a condensed ring derivative which is totally distinguished from the prior art, the preparation method, the intermediate, the pharmaceutical composition and the use thereof. The condensed ring derivative of the present invention has distinct inhibitory effects against URAT1, which can relieve or treat hyperuricemia etc. and related diseases.

Detailed description of the preferred embodiment

The structure of the compound is determined by NMR or MS, NMR is obtained by Bruker Avance-500 apparatus, d_6-DMSO, $CDCl_3$ and CD_3OD etc. as a solvent, TMS as an interior label. MS is obtained by LC-MS Agilent Technologies 6110, ESI as an ion source.

Microwave reaction is conducted in Explorer full automatic microwave irradiation equipment supplied by CEM, US Corporation, magnetron frequency is 2450MHz, continuous microwave output power is 300W.

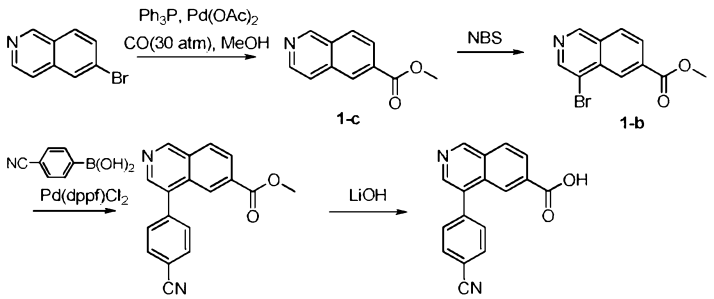
HPLC is Gilson 281, the preparative column is Xbridge, 21.2×250mm C18, 10μm.

Process I for separating enantiomers: the apparatus is Gilson 281, the preparative

column is r,r-Whelk-O1 (20×250mm, 5μm); process II: the apparatus is SFC-80 (Thar, Waters), the preparative column is AD 30×250mm, 5μm (Decial).

Embodiment 1

4-(4-cyanophenyl)isoquinoline-6-carboxylic acid (Compound **1**)



Synthesis of compound **1-c**

Under CO atmosphere (30 atm), 6-bromoisoquinoline (10.0g, 48mmol), sodium acetate (5.0g, 61mmol), triphenylphosphine (3.8g, 14mmol) and palladium acetate (2.8g, 12mmol) were dissolved in DMF (40mL) and methanol (40mL), the mixture was reacted at 100℃ for 24hrs. The mixture was then cooled to room temperature, evaporated to remove methanol, the residue was filtered through celite, the filtrate cake was washed with EA (200mL). The filtrate was washed in turn with water (100 mL×3) and saturated brine (100 mL), dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure. The residue was purified with silica column chromatography (PE: EA = 10:1) to give white solid **1-c** (7g, yield: 78%). LC-MS (ESI): m/z = 188 $[M+H]^+$

Synthesis of compound **1-b**

Compound **1-c** (1.88g, 10mmol) and N-bromosuccinimide (2.7g, 15mmol) were dissolved in acetic acid (40mL), the mixture was cooled to room temperature after reacting at 80℃ for 24hrs. Part of acetic acid was removed under reduced pressure, the residue was filtered through celite, the filtrate cake was washed with DCM (200mL). The filtrate was in turn washed with saturated sodium sulfite solution (200mL), dried over anhydrous sodium sulfate, filtered, evaporated under reduced pressure. The residue was purified with silica column chromatography (PE:EA = 50:1) to give colorless solid **1-b** (2.5g, yield 94%). LC-MS (ESI): m/z = 266 $[M+H]^+$.

Synthesis of compound **1-a**

Under N_2 atmosphere, compound **1-b** (133mg, 0.5mmol), 4-cyanophenylboronic acid (75mg, 0.5mmol) and sodium carbonate (60mg, 0.6mmol) were suspended in a mixed solution of dioxane (4mL) and water (1mL), [1,1'-bis(diphenylphosphine)ferrocene] palladium dichloride (25mg, 0.03mmol) was added. The mixture was stirred at 80℃

for 3hrs, then cooled to room temperature. The mixture was filtered through celite, the filtrate cake was washed with EA (50mL). The filtrate was in turn washed with water (20mL×3) and saturated brine (10mL), dried over anhydrous sodium sulfate, filtered, evaporated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 1:1) to give compound **1-a** (126mg, yield 83%). LC-MS (ESI): m/z = 289 $[M+H]^+$.

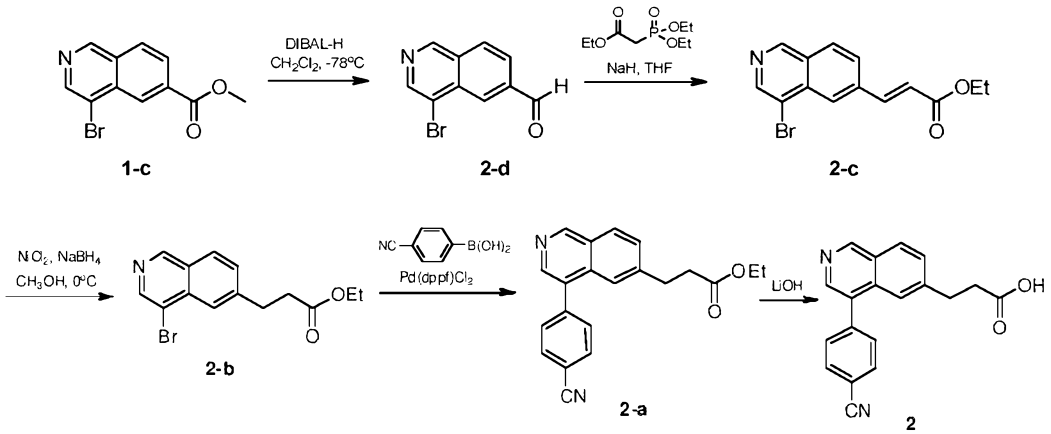
Synthesis of compound **1**

At room temperature, LiOH (42mg, 1.0mmol) was added to a solution of compound **1-a** (120mg, 0.42mmol) in a mixed solution of methanol (1mL), THF (4mL) and water (1mL). The mixture was stirred at room temperature for 1h, followed by adding 2M HCl aqueous solution (1mL) and water (20mL), solid was precipitated and filtered out. The solid was washed with water (10mL), dried under vacuum to give white solid **1** (91mg, yield 79%). LC-MS (ESI): m/z = 295 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 13.55 (s, 1H), 9.53 (s, 1H), 8.60 (s, 1H), 8.34 (m, 2H), 8.21 (m, 1H), 8.10 (d, J=8.0 Hz, 1H), 7.82 (d, J=8.0 Hz, 1H) ppm.

Embodiment 2

3-[4-(4-Cyanophenyl)isoquinolin-6-yl]propionic acid (Compound **2**)



Synthesis of compound **2-d**

A solution of compound **1-c** (1.33g, 5mmol) in DCM (50mL) was cooled to -78℃, 1.0M diisobutylaluminum hydride in DCM (20mL, 20mmol) was slowly added dropwise, the mixture was further stirred for 1h. The mixture was warmed to room temperature, saturated aqueous solution of NH_4Cl (300mL) was added, organic phase was seperated, aqueous phase was extracted with DCM (50mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, evaporated under reduced pressure. The residue was purified with silica column chromatography (PE:EA = 3:1) to give light yellow solid **2-d** (900 mg, yield 76%). LC-MS (ESI): m/z =236 $[M+H]^+$.

Synthesis of compound **2-c**

At 0℃, triethyl phosphonoacetate (1.4mL, 5mmol) and sodium hydride (240mg, 6mmol) were added into a solution of compound **2-d** (470mg, 2mmol) in THF (10mL), the mixture was further stirred for 1h. The mixture was warmed to room temperature, followed by adding saturated aqueous solution of NH_4Cl (300mL), extracted with EA (50mL×3). The organic phases were combined, washed in turn with water (10mL×3) and saturated brine (10mL), dried over anhydrous sodium sulfate, filtered, evaporated under reduced pressure. The residue was purified with silica column chromatography (PE:EA = 5:1) to give light yellow solid **2-c** (380mg, yield 62%). LC-MS (ESI): m/z =306 $[M+H]^+$.

Synthesis of compound **2-b**

At 0℃, $NaBH_4$ (40mg, 1mmol) was added slowly into a solution of compound **2-c** (310mg, 1mmol) and $NiCl_2$ (13mg, 0.1mmol) in methanol (5mL), the mixture was further stirred for 3hrs. The mixture was warmed to room temperature, followed by adding saturated aqueous solution of NH_4Cl (30mL), being extracted with EA (10mL×3). The organic phases were combined, washed in turn with water (5mL×3) and saturated brine (5mL), dried over anhydrous sodium sulfate, filtered, evaporated under reduced pressure. The residue was purified with silica column chromatography (PE:EA = 4:1) to give light yellow solid **2-b** (280mg, yield 91%). LC-MS (ESI): m/z =308 $[M+H]^+$.

Synthesis of compound **2-a**

Under N_2 atmosphere, compound **2-b** (155mg, 0.5mmol), 4-cyanophenylboronic acid (75mg, 0.5mmol) and sodium carbonate (106mg, 1mmol) were suspended in a mixture of dioxane (4mL) and water (1mL), [1,1'-bis (diphenylphosphine)ferrocene]palladium dichloride (40mg, 0.05mmol) was added. The mixture was stirred at 80℃ for 3hrs, then cooled to room temperature. The mixture was filtered through celite, the filtrate cake was washed with EA (50mL). The filtrate was in turn washed with water (20mL×3) and saturated brine (10mL), dried over anhydrous magnesium sulfate, filtered, evaporated under reduced pressure. The residue was purified with silica column chromatography (PE:EA = 1:1) to give compound **2-a** (100mg, yield 61%). LC-MS (ESI): m/z = 331 $[M+H]^+$.

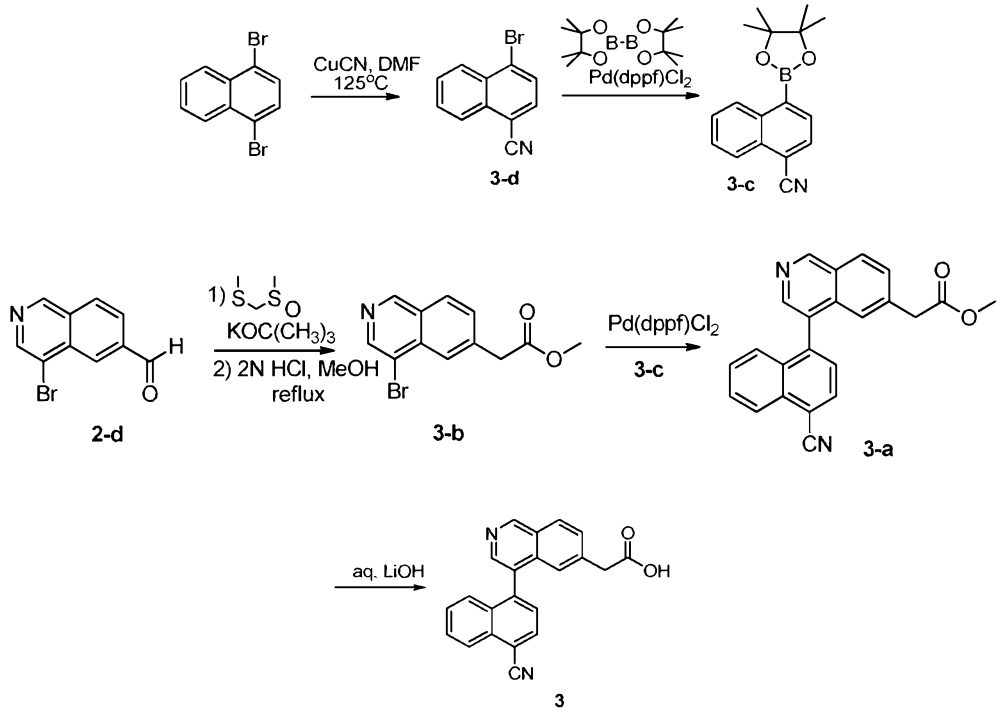
Synthesis of compound **2**

At room temperature, LiOH (42mg, 1.0mmol) was added to a mixed solution of compound **2-a** (100mg, 0.3mmol) in methanol (1mL), THF (4mL) and water (1mL), the mixture was further stirred for 1h, 2M HCl aqueous solution (1mL) and water (20mL) were added, solid was precipitated and filtered out. The solid was washed with water (10mL), dried under vacuum to give white solid **2** (61mg, yield 67%). LC-MS (ESI): m/z = 303 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 12.18 (s, 1H), 9.34 (s, 1H), 8.44 (s, 1H), 8.18 (d, J=8.0 Hz, 1H), 8.04 (d, J=8.0 Hz, 2H), 7.77 (d, J=8.0 Hz, 2H), 7.68 (d, J=8.0 Hz, 1H), 2.99 (t, J=8.0 Hz, 2H), 2.59 (t, J=8.0 Hz, 1H) ppm.

Embodiment 3

2-[4-(4-Cyanonaphthalen-1-yl)isoquinolin-6-yl]acetic acid (Compound **3**)



Synthesis of compound **3-d**

CuCN (5.0g, 56.3mmol) was added to a solution of 1,4-dibromonaphthalene (20g, 70.4mmol) in DMF (250mL), the mixture was reacted for 16hrs at 125℃, evaporated under reduced pressure. Aqueous ammonia (200mL) and EA (200mL) were added to the residue, the mixture was stirred for 1h and organic phase was seperated. The organic phase was in turn washed with water (100mL×3) and saturated brine (100mL), dried over anhydrous magnesium sulfate, filtered, evaporated under reduced pressure. The residue was purified with silica chromatography (PE:EA = 10:1) to give compound **3-d** (5.1g, yield 31%). LC-MS (ESI): m/z = 232 $[M+H]^+$.

Synthesis of compound **3-c**

Under N_2 atmosphere, bis(pinacolato)diboron (8.4g, 33mmol), potassium acetate (6.5g, 66mmol) and [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (1.2g, 1.76mmol) were respectively added to a solution of compound **3-d** (5.1g, 22mmol) in dioxane (150mL), the mixture was stirred at 80℃ for 6hrs. The mixture was evaporated under reduced pressure, the residue was filtered through celite, the filtrate cake was washed with dioxane (50mL), the filtrate was evaporated under reduced pressure. The residue was purified with silica column chromatography (PE:EA = 10:1) to give compound **3-c** (6 g, yield 97%). LC-MS (ESI): m/z = 280 $[M+H]^+$.

Synthesis of compound **3-b**

At 0℃, under N_2 atmosphere, potassium *tert*-butanolate (71mg, 0.63mmol) was added to a solution of methyl(methylthiomethyl)sulfoxide (78mg, 0.63mmol) in anhydrous THF (5mL). The mixture was stirred for 30mins, followed by adding compound **2-d** (100mg, 0.42mmol), stirred for 1h at room temperature, then evaporated under reduced pressure. 2M HCl in methanol (5mL) was added to the residue, the mixture was refluxed for 3hrs, then concentrated under reduced pressure. The residue was purified with silica column chromatography (PE:EA = 5:1) to give compound **3-b** (70 mg, yield 60%). LC-MS (ESI): m/z = 281 $[M+H]^+$.

Synthesis of compound **3-a**

Under N_2 atmosphere, compound **3-c** (40mg, 0.14mmol), sodium carbonate (46mg, 0.43mmol) and [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (30mg, 0.036mmol) were respectively added to a mixed solution of compound **3-b** (40mg, 0.14mmol) in ethylene glycol dimethyl ether (150mL) and water (1mL). The mixture was stirred at 75℃ for 16hrs, and then concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 2:1) to give compound **3-a** (27 mg, yield 53%). LC-MS (ESI): m/z = 353 $[M+H]^+$.

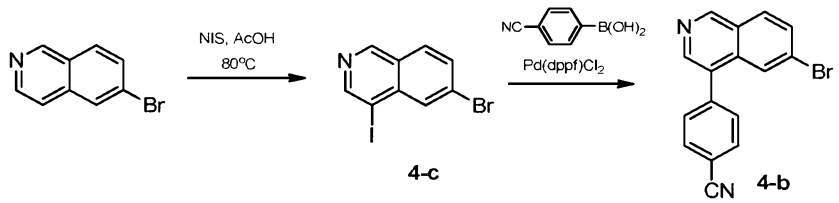
Synthesis of compound **3**

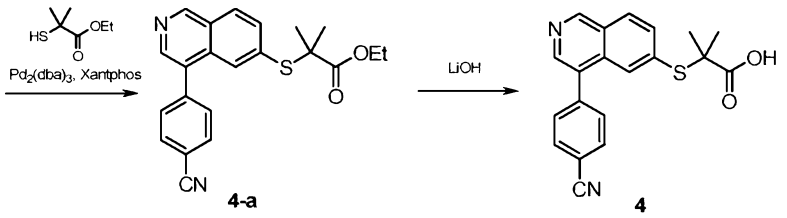
At room temperature, 1M LiOH aqueous solution (1.0mL) was added to a mixed solution of compound **3-a** (27mg, 0.076mmol) in methanol (5mL) and THF (5mL), the mixture was stirred for 16hrs, and evaporated under reduced pressure. The residue was dissolved with water (6mL), adjusted to pH=3 with 1M citric acid aqueous solution, solid was precipitated and filtered out. The solid was washed with water (5mL), dried under vacuum to give white solid **3** (20mg, yield 77%). LC-MS (ESI): m/z = 339 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 12.34 (s, br., 1H), 9.47 (s, 1H), 8.45 (s, 1H), 8.35 (d, J=8.0 Hz, 1H), 8.27 (d, J=8.0 Hz, 1H), 8.24 (d, J=8.0 Hz, 1H), 7.85 (t, J=8.0 Hz, 1H), 7.73 (d, J=8.0 Hz, 2H), 7.64 (d, J=8.0 Hz, 1H), 7.59 (t, J=8.0 Hz, 1H), 7.41 (d, J=8.0 Hz, 1H), 7.14 (s, 1H), 3.63 (s, 2H) ppm.

Embodiment 4

2{[4-(4-Cyanophenyl)isoquinolin-6-yl]thio-2-methylpropionic acid (Compound **4**)





Synthesis of compound **4-c**

6-Bromoisoquinoline (10.4g, 50mmol) and N-iodosuccinimide (13.5g, 60mmol) were dissolved in acetic acid (100mL), the mixture was reacted for 8hrs at 80℃. The mixture was cooled to room temperature, followed by concentrating under reduced pressure to remove half of acetic acid, the residue was filtered through celite, the filtrate cake was washed with DCM (200mL), the organic phase was in turn washed with saturated sodium sulfite solution (200mL) and water (100mL), dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure. The residue was purified with silica column chromatography (PE:EA = 5:1) to give compound **4-c** (11.6g, yield 70%). LC-MS (ESI): m/z = 334 $[M+H]^+$.

Synthesis of compound **4-b**

Under N_2 atmosphere, compound **4-c** (2.33g, 10mmol), 4-cyanobenzene boronic acid (1.5g, 10mmol) and sodium carbonate (2.12g, 20mmol) were suspended in dioxane (40mL) and water (10mL), [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (0.55g, 1mmol) was added. The mixture was stirred at 80℃ for 3hrs, and then cooled to room temperature. The mixture was filtered through celite, the filtrate cake was washed with EA (50mL). The filtrate was in turn washed with water (100mL×3) and saturated brine (100mL), dried over magnesium sulfate, filtered, concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 3:1) to give compound **4-b** (1.6g, yield 52%). LC-MS (ESI): m/z = 309 $[M+H]^+$.

Synthesis of compound **4-a**

Under N_2 atmosphere, tris(dibenzylidene indene acetone)dipalladium (0.29g, 0.5mmol) and 4,5-bis(diphenylphosphine)-9,9-dimethyloxacanthracene (0.46mg, 0.5mmol) were added to a solution of compound **4-b** (1.5g, 5mmol), ethyl 2-methyl-2-mercaptopropionate (0.75g, 5mmol) and diisopropylethylamine (1.29g, 1mmol) in dioxane (8mL), the mixture was reacted in microwave at 110℃ for 30mins. The mixture was cooled to room temperature, concentrated under reduced pressure to remove dioxane. The residue was filtered through celite, the filtrate cake was washed with EA (200mL). The filtrate was in turn washed with water (100mL×3) and saturated brine (100mL), dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 3:1) to give compound **4-a** (1.39g, yield 74%). LC-MS (ESI): m/z = 377 $[M+H]^+$.

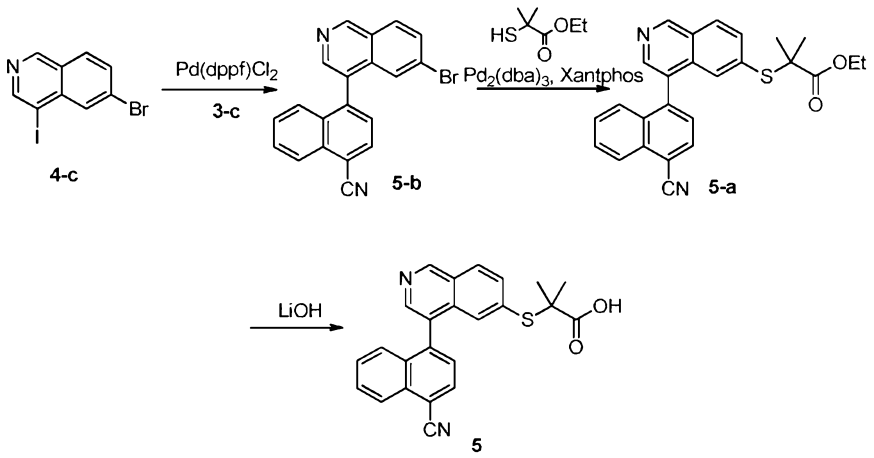
Synthesis of compound **4**

At room temperature, LiOH (0.178g, 0.74mmol) was added to a mixed solution of compound **4-a** (1.39g, 0.37mmol) in methanol (5mL), THF (20mL) and water (5mL), the mixture was stirred at room temperature for 1h, 2M HCl aqueous solution (2mL) and water (20mL) were added, solid was precipitated and filtered out. The solid was washed with water (10mL), dried under vacuum to give white solid **4** (1.1g, yield 85%). LC-MS (ESI): m/z = 349 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 12.78 (s, 1H), 9.41 (s, 1H), 8.53 (s, 1H), 8.23 (d, J=8.0 Hz, 1H), 8.06 (d, J=8.0 Hz, 2H), 7.73 (m, 4H), 1.44 (s, 6H) ppm.

Embodiment 5

2{[4-(4-Cyanonaphthalen)isoquinolin-6-yl]thio}-2-methylpropionic acid (Compound **5**)



Synthesis of compound **5-b**

Under N_2 atmosphere, compound **4-c** (0.66g, 2mmol), compound **3-c** (0.56g, 2mmol) and sodium carbonate (0.42g, 0.4mmol) were suspended in dioxane (4mL) and water (1mL), [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (0.12g, 0.2mmol) was added. The mixture was stirred at 80℃ for 3hrs, and then cooled to room temperature, filtered through celite, washed with EA (20mL). The filtrate was in turn washed with water (10mL×3) and saturated brine (10mL), dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 3:1) to give compound **5-b** (0.46g, yield 64%). LC-MS (ESI): m/z = 359 $[M+H]^+$.

Synthesis of compound **5-a**

Under N_2 atmosphere, tris(dibenzylidene indene acetone)dipalladium (0.06g, 0.1mmol) and 4,5-bis(diphenylphosphine)-9,9-dimethyloxacanthracene (0.1g, 0.1mmol) were added to a solution of compound **5-b** (0.36g, 1mmol), ethyl 2-methyl-2-mercaptopropionate (0.15g, 1mmol) and diisopropylethylamine (0.26g,

2mmol) in dioxane (8mL), the mixture was reacted in a microwave at 110℃ for 30mins. The mixture was cooled to room temperature, and then concentrated under reduced pressure to remove dioxane, the residue was filtered through celite, the filtrate cake was washed with EA (50mL). The filtrate was in turn washed with water (50mL×3) and saturated brine (50mL), dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 3:1) to give compound **5-a** (0.37g, yield 87%). LC-MS (ESI): m/z = 427 $[M+H]^+$.

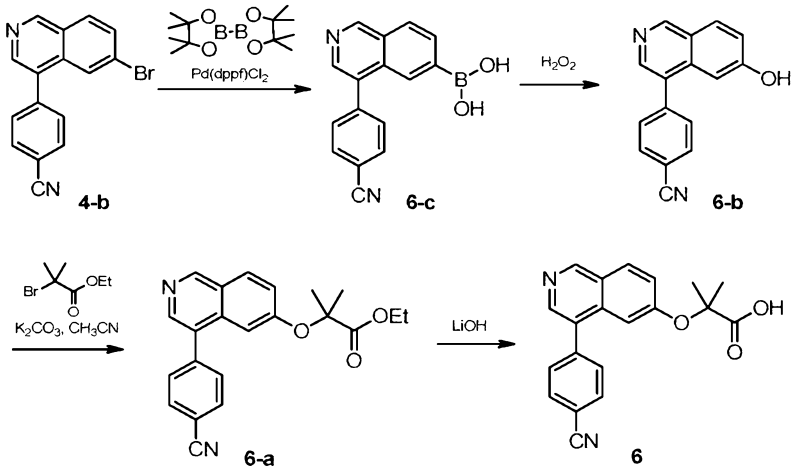
Synthesis of compound **5**

At room temperature, LiOH (42mg, 1mmol) was added to a mixed solution of compound **5-a** (370mg, 0.86mmol) in methanol (1mL), THF (4mL) and water (1mL), the mixture was stirred for 1h, and then 2M HCl aqueous solution (2mL) and water (20mL) were added, solid was precipitated and filtered out. The solid was washed with water (10mL), dried under vacuum to give white solid **5** (280mg, yield 82%). LC-MS (ESI): m/z = 399 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 12.67 (s, 1H), 9.51 (s, 1H), 8.57 (s, 1H), 8.35 (d, J=7.6 Hz, 1H), 8.27(m, 2H), 7.85 (t, J=7.6 Hz, 1H), 7.75 (d, J=7.6 Hz, 1H), 7.66 (d, J=8.0 Hz, 1H), 7.60 (t, J=8.0 Hz, 2H), 7.41 (d, J=8.0 Hz, 1H), 7.26 (s, 1H), 1.27 (s, 3H), 1.24 (s, 3H) ppm.

Embodiment 6

2{[4-(4-Cyanophenyl)isoquinolin-6-yl]oxy}-2-methylpropionic acid (Compound **6**)



Synthesis of compound **6-c**

Under N_2 atmosphere, bis(pinacolato)diboron (3.1g, 12mmol), potassium acetate (2.0g, 20mmol) and [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (0.56g, 1mmol) were respectively added to a solution of compound **4-b** (3.1g, 10mmol) in dioxane (15mL), the mixture was stirred at 80℃ for 8hrs. The mixture was cooled to room temperature, filtered through celite, the filtrate cake was washed

with EA (50mL). The filtrate was in turn washed with water (50mL×3) and saturated brine (50mL), dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure. The residue was purified with silica column chromatography (PE:EA = 1:1) to give white solid **6-c** (1.76 g, yield 63%). LC-MS (ESI): m/z = 275 $[M+H]^+$.

Synthesis of compound **6-b**

At 0℃, 30% H_2O_2 solution (2mL) was added to a solution of compound **6-c** (1.1g, 4mmol) in THF (20mL), the mixture was stirred for 4hrs before water (100mL) was added. The mixture was extracted with EA (100mL×3), the combined organic phases were washed in turn with water (50mL×3) and saturated brine (50mL), dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 1:1) to give white solid **6-b** (0.5g, yield 50%). LC-MS (ESI): m/z = 247 $[M+H]^+$.

Synthesis of compound **6-a**

Under N_2 atmosphere, ethyl 2-bromoisobutyrate (190mg, 1mmol) and potassium carbonate (138mg, 1mmol) were added to a solution of compound **6-b** (75mg, 0.3mmol) in acetonitrile (4mL), the mixture was reacted for 3hrs at 80℃. The mixture was cooled to room temperature, concentrated under reduced pressure. The residue was filtered through celite, the filtrate cake was washed with EA (50mL). The filtrate was in turn washed with water (8mL×3) and saturated brine (10mL), dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 3:1) to give yellow liquid **6-a** (56 mg, yield 52%). LC-MS (ESI): m/z = 361 $[M+H]^+$.

Synthesis of compound **6**

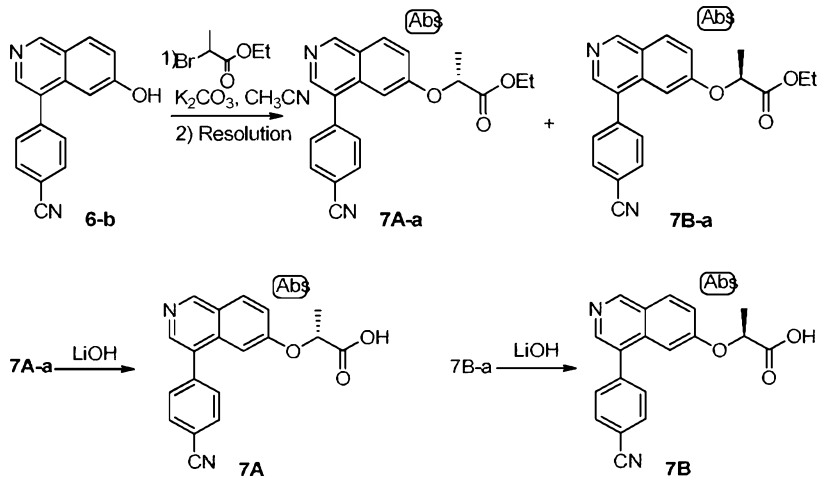
At room temperature, LiOH (42mg, 1mmol) was added to a mixed solution of compound **6-a** (56mg, 0.156mmol) in methanol (1mL), THF (2mL) and water (1mL), the mixture was stirred for 1h, followed by adding 2M HCl aqueous solution (2mL) and water (1mL), solid was precipitated and filtered. The solid was washed with water (5mL), dried under vacuum to give white solid **6** (32mg, yield 62%). LC-MS (ESI): m/z = 333 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 13.27 (s, 1H), 9.24 (s, 1H), 8.39 (s, 1H), 8.16 (d, J=8.0 Hz, 1H), 8.02 (d, J=8.0Hz, 1H), 7.72 (d, J=8.0 Hz, 2H), 7.30 (d, J=8.0 Hz, 2H), 7.26 (s, 1H), 6.94 (s, 1H), 1.55 (s, 6H) ppm.

Embodiment 7

Compound **7A**

Compound **7B**



Synthesis of compound **7A-a** and **7B-a**

Under N_2 atmosphere, ethyl 2-bromopropionate (540mg, 3mmol) and potassium carbonate (560mg, 4mmol) were added to a solution of compound **6-b** (500mg, 2mmol) in acetonitrile (20mL), the mixture was reacted for 6hrs at 80℃. The mixture was cooled to room temperature, concentrated under reduced pressure, the residue was filtered through celite, the filtrate cake was washed with EA (200mL). The filtrate was washed with water (50mL×3) and saturated brine (50mL), dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 3:1) to give yellow liquid, followed by separating with enantiomeric chromatographic column (process I, mobile phase: Hexane: EtOH: DEA =70:30:0.1) to give enantiomer **7A-a** which is obtained firstly (80 mg, yield 11.5%; LC-MS (ESI): m/z = 347 $[M+H]^+$) (T_r = 9.0 min) and enantiomer **7B-a** which is obtained later (90 mg, yield 13%; LC-MS (ESI): m/z = 347 $[M+H]^+$) (T_r = 11.0 min). The absolute configuration of **7A-a** and **7B-a** is unknown.

Synthesis of compound **7A**

At room temperature, LiOH (42mg, 1mmol) was added to a mixed solution of compound **7A-a** (70mg, 0.2mmol) in methanol (1mL), THF (2mL) and water (1mL), the mixture was stirred for 1h, followed by adding 2M HCl aqueous solution (2mL) and water (2mL), solid was precipitated and filtered out. The solid was washed with water (5mL), dried under vacuum to give white solid **7A** (51mg, yield 80%). LC-MS (ESI): m/z = 319 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 13.15 (s, 1H), 9.24 (s, 1H), 8.40 (s, 1H), 8.19 (d, J=8.0 Hz, 1H), 8.01 (d, J=8.0Hz, 1H), 7.73 (d, J=8.0 Hz, 2H), 7.40 (d, J=8.0 Hz, 2H), 7.26 (s, 1H), 6.94 (s, 1H), 4.89 (m, 1H), 1.53 (d, J=8.0 Hz, 3H) ppm.

Synthesis of compound **7B**

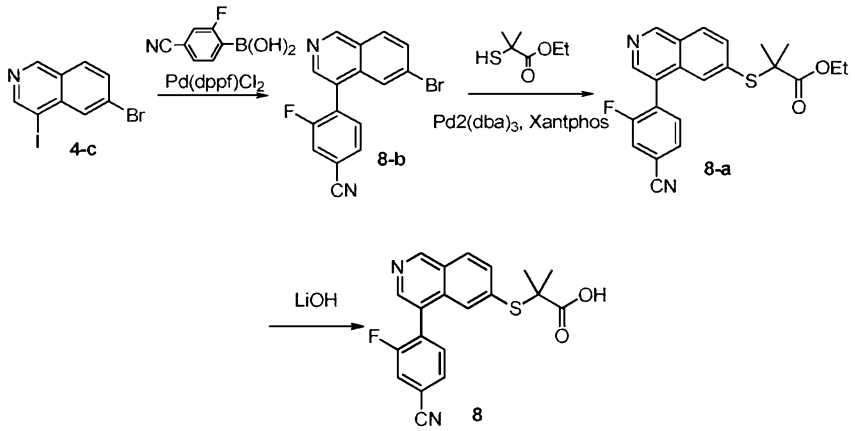
At room temperature, LiOH (42mg, 1mmol) was added to a mixed solution of compound **7B-a** (70mg, 0.2mmol) in methanol (1mL), THF (2mL) and water (1mL),

the mixture was stirred for 1h, followed by adding 2M HCl aqueous solution (2mL) and water (2mL), solid was precipitated and filtered out. The solid was washed with water (5mL), dried under vacuum to give white solid **7B** (46mg, yield 72%). LC-MS (ESI): m/z = 319 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 13.15 (s, 1H), 9.24 (s, 1H), 8.40 (s, 1H), 8.19 (d, J=8.0 Hz, 1H), 8.01 (d, J=8.0Hz, 1H), 7.73 (d, J=8.0 Hz, 2H), 7.40 (d, J=8.0 Hz, 2H), 7.26 (s, 1H), 6.94 (s, 1H), 4.89 (m, 1H), 1.53 (d, J=8.0 Hz, 3H) ppm.

Embodiment 8

2{[4-(4-Cyano-2-fluorophenyl)isoquinolin-6-yl]thio}-2-methylpropionic acid (Compound **8**)



Synthesis of compound **8-b**

Under N_2 atmosphere, compound **4-c** (330mg, 1mmol), 2-fluoro-4-cyanophenylboronic acid (165mg, 1mmol) and sodium carbonate (212mg, 0.2mmol) were suspended in a mixed solution of dioxane (4mL) and water (1mL), [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (56mg, 0.1mmol) was added. The mixture was stirred at 80℃ for 3hrs, cooled to room temperature, filtered through celite, the filtrate cake was washed with EA (20mL). The filtrate was in turn washed with water (10mL×3) and saturated brine (10mL), dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 3:1) to give compound **8-b** (63mg, yield 19%). LC-MS (ESI): m/z = 387 $[M+H]^+$.

Synthesis of compound **8-a**

Under N_2 atmosphere, tris(dibenzylidene indene acetone)dipalladium (12mg, 0.02mmol) and 4,5- bis(diphenylphosphine)-9,9-dimethyloxacanthracene (20mg, 0.02mmol) were added to a solution of compound **8-b** (63mg, 0.2mmol), ethyl 2-methyl-2-mercaptopropionate (30mg, 0.2mmol) and diisopropylethylamine (52mg, 0.4mmol) in dioxane (8mL), the mixture was reacted in a microwave at 110℃ for 30mins. The mixture was cooled to room temperature, followed by evaporating

dioxane under reduced pressure, the residue was filtered through celite, the filtrate cake was washed with EA (50mL). The filtrate was in turn washed with water (10mL×3) and saturated brine (10mL), dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 3:1) to give compound **8-a** (72mg, yield 91.3%). LC-MS (ESI): m/z = 395 $[M+H]^+$.

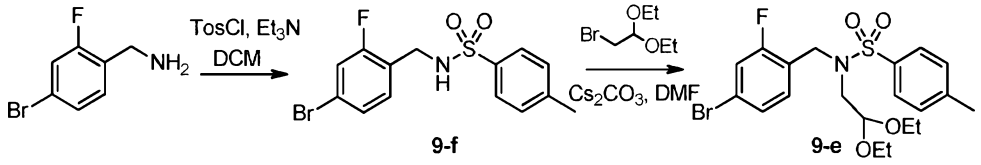
Synthesis of compound **8**

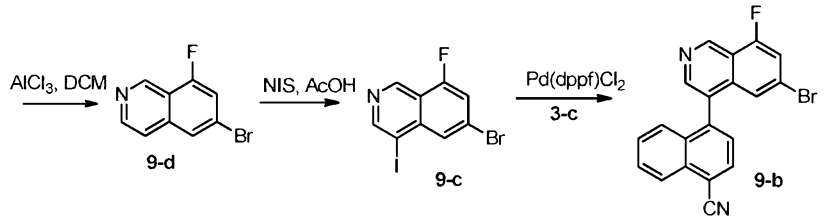
At room temperature, LiOH (42mg, 1mmol) was added to a mixed solution of compound **8-a** (72mg, 0.18mmol) in methanol (1mL), THF (2mL) and water (1mL). The mixture was stirred for 1h, followed by adding 2M HCl aqueous solution (2mL) and water (2mL), solid was precipitated and filtered out. The solid was washed with water (5mL), dried under vacuum to give white solid **8** (16mg, yield 24%). LC-MS (ESI): m/z = 367 $[M+H]^+$.

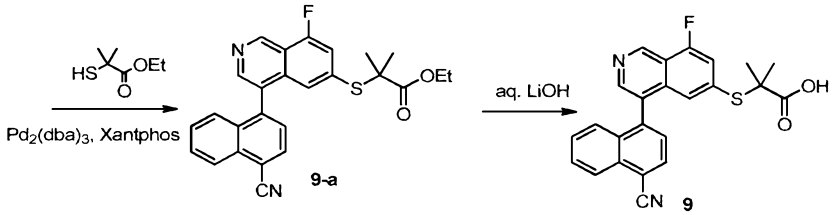
^{1}H-NMR (400MHz, DMSO-d6) δ: 12.8 (s, 1H), 9.44 (s, 1H), 8.54 (s, 1H), 8.23 (d, J=7.6 Hz, 1H), 8.10 (d, J=7.6 Hz, 1H), 7.92 (d, J=7.6 Hz, 1H), 7.78 (t, J=7.6 Hz, 1H), 7.70 (d, J=7.6 Hz, 1H), 7.59 (s, 1H), 1.44 (s, 6H) ppm.

Embodiment 9

2{[4-(4-Cyanonaphthalen-1-yl)-8-fluoroisoquinolin-6-yl]thio}-2-methylpropionic acid (Compound **9**)







Synthesis of compound **9-f**

At 0℃, *p*-toluenesulfonyl chloride (4.00g, 21mmol) was added in portion to a solution of 5-bromo-2-fluorobenzylamine (4.08g, 20mmol) and triethylamine (4.04g,

40mmol) in DCM (60mL). The mixture was reacted at 0℃ for 30mins, followed by removing the ice bath, further reacting at room temperature for 16hrs, then being concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 5:1) to give compound **9-f** (5.30g, yield 74%). LC-MS (ESI): m/z = 358 $[M+H]^+$.

Synthesis of compound **9-e**

At room temperature, 2-bromo-1,1-diethoxyethane (3.0g, 15mmol), cesium carbonate (6.5g, 20mmol) were added to a solution of compound **9-f** (3.57g, 10mmol) in DMF (15mL). The mixture was reacted for 16hrs at 80℃, concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA = 8:1) to give compound **9-e** (3.80g, 80%).

Synthesis of compound **9-d**

At -5℃, compound **9-e** (1.50mg, 3.18mmol) was added to a mixture of $AlCl_3$ (2.0g, 15mmol) in DCM (20mL). The mixture was reacted for 16hrs at room temperature, followed by adding 2M HCl aqueous solution (20mL), extracted with DCM (30mL×3). The organic phases were combined, washed in turn with water (10mL×3) and saturated brine (20mL), dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 7:1) to give compound **9-d** (220mg, yield 31%). LC-MS (ESI): m/z = 226 $[M+H]^+$.

Synthesis of compound **9-c**

Compound **9-d** (200mg, 0.89mmol) and N-iodosuccinimide (300mg, 1.33mmol) were dissolved in acetic acid (10mL) and trifluoroacetic acid (2mL), the mixture was reacted for 6hrs at 80℃. The mixture was cooled to room temperature, concentrated under reduced pressure to remove the solvent. The residue was purified by silica column chromatography (PE:EA = 8:1) to give compound **9-c** (200mg, yield 64%). LC-MS (ESI): m/z = 352 $[M+H]^+$.

Synthesis of compound **9-b**

Under N_2 atmosphere, compound **9-c** (144mg, 0.4mmol), compound **3-c** (111mg, 0.4mmol) and sodium carbonate (170mg, 1.6mmol) were suspended in ethylene glycol dimethyl ether (10mL) and water (1mL), [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (43mg, 0.05mmol) was added. The mixture was reacted for 4hrs at 50℃, cooled to room temperature, concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 3:1) to give compound **9-b** (100mg, yield 66%). LC-MS (ESI): m/z = 377 $[M+H]^+$.

Synthesis of compound **9-a**

Under N_2 atmosphere, tris(dibenzylidene indene acetone)dipalladium (30mg, 0.033mmol) and 4,5-bis(diphenylphosphine))-9,9-dimethyloxacanthracene (38mg,

0.066mmol) were added to a solution of compound **9-b** (110mg, 0.29mmol), ethyl 2-methyl-2-mercaptopropionate (64mg, 0.44mmol) and diisopropylethylamine (187mg, 1.45mmol) in dioxane (10mL). The mixture was reacted for 5hrs at 100℃, followed by cooling to room temperature, concentrating under reduced pressure to remove dioxane. The residue was purified by silica column chromatography (PE:EA = 4:1) to give compound **9-a** (120mg, yield 93%). LC-MS (ESI): m/z = 445 $[M+H]^+$.

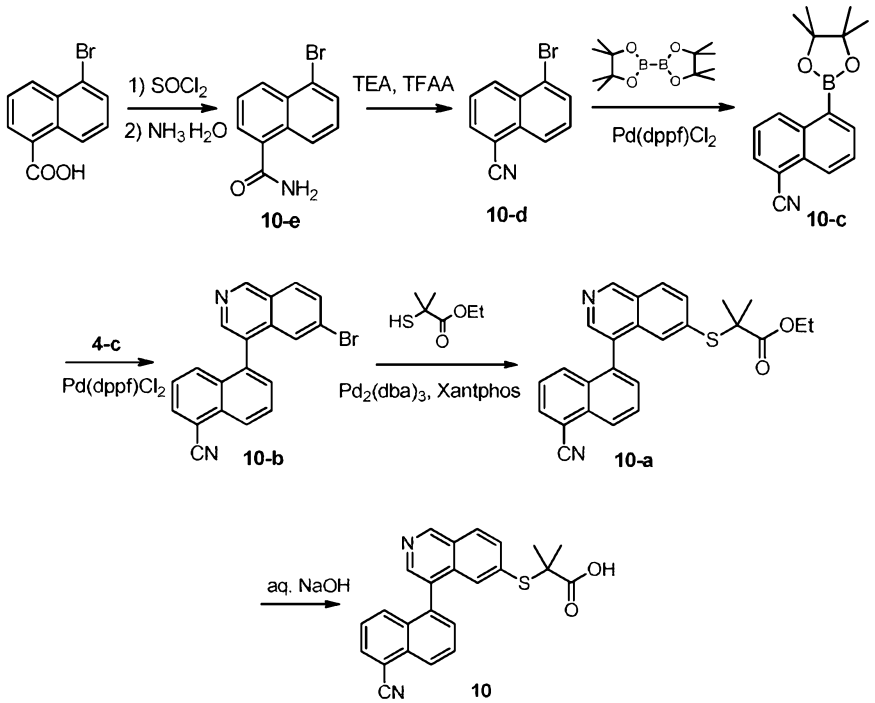
Synthesis of compound **9**

At room temperature, 1M LiOH aqueous solution (2.0mL) was added to a mixed solution of compound **9-a** (100mg, 0.22mmol) in methanol (8mL) and THF (8mL). The mixture was stirred at room temperature for 16hrs, followed by being concentrated under reduced pressure. The residue was dissolved with water (10mL), adjusted to pH=3 with 1M citric acid aqueous solution, solid was precipitated and filtered out. The solid was washed with water (10mL), dried under vacuum to give white solid **9** (70 mg, yield 76%). LC-MS (ESI): m/z = 417 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 12.79 (s, br., 1H), 9.61 (s, 1H), 8.68 (s, 1H), 8.35 (d, J=8.0 Hz, 1H), 8.28 (d, J=8.0 Hz, 1H), 7.86 (d, J=7.2 Hz, 1H), 7.75 (d, J=8.0 Hz, 1H), 7.60 (t, J=8.0 Hz, 1H), 7.51 (d, J=10.4 Hz, 1H), 7.42 (d, J=11.2 Hz, 1H), 7.07 (s, 1H), 1.29 (s, 3H), 1.22 (s, 3H) ppm.

Embodiment 10

2{[4-(5-Cyanonaphthalen-1-yl)isoquinolin-6-yl]thio}-2-methylpropionic acid (Compound **10**)



Synthesis of compound **10-e**

5-Bromo-1-naphthoic acid (980mg, 3.92mmol) was added to thionyl chloride (5mL). The mixture was stirred at 85℃ for 2hrs, concentrated under reduced pressure. The residue was dissolved in anhydrous THF (10mL), the solution was added dropwise into 25%-28% aqueous ammonia (20mL) at 0℃. The mixture was warmed to room temperature and further stirred for 2hrs, followed by being extracted with EA (60mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give white solid **10-e** (950mg, yield 97%). The product was used directly for the next step without further purification. LC-MS (ESI): m/z = 250 $[M+H]^+$.

Synthesis of compound **10-d**

At 0℃, trifluoroacetic anhydride (3.2g, 15.1mmol) was added dropwise to a solution of compound **10-e** (0.94g, 3.78mmol) and triethylamine (1.53g, 15.1mmol) in THF (8mL). The mixture was slowly warmed to room temperature and further reacted for 3hrs, and then concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 10:1) to give compound **10-d** (0.85g, yield 97%). LC-MS (ESI): m/z = 232 $[M+H]^+$.

Synthesis of compound **10-c**

Under N_2 atmosphere, bis(pinacolato)diboron (1.32g, 5.2mmol), potassium acetate (1.0g, 10.38mmol) and [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (0.253 g, 0.346 mmol) were added respectively to a solution of compound **10-d** (0.8g, 3.46mmol) in dioxane (15mL). The mixture was stirred at 80 ℃ for 6hrs, concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 10:1) to give compound **10-c** (0.85g, yield 88%). LC-MS (ESI): m/z = 280 $[M+H]^+$.

Synthesis of compound **10-b**

Under N_2 atmosphere, compound **10-c** (200mg, 0.72mmol), compound **4-c** (200mg, 0.6mmol) and sodium carbonate (130mg, 1.2mmol) were suspended in dioxane (20mL) and water (2mL), [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (50mg, 0.06mmol) was added. The mixture was reacted for 2hrs at 80℃, cooled to room temperature, filtered through celite, the filtrate cake was washed with EA (20mL), the filtrate was concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 3:1) to give compound **10-b** (50mg, yield 81%). LC-MS (ESI): m/z = 359 $[M+H]^+$.

Synthesis of compound **10-a**

Under N_2 atmosphere, tris(dibenzylidene indene acetone)dipalladium (16mg, 0.015mmol) and 4,5-bis(bis(diphenylphosphine)-9,9-dimethyloxacanthracene (17mg, 0.03mmol) were added to a solution of compound **10-b** (53mg, 0.15mmol), ethyl 2-methyl-2-mercaptopropionate (28mg, 0.19mmol) and diisopropylethylamine (38mg,

0.29mmol) in dioxane (5mL). The mixture was reacted for 6hrs at 100℃, cooled to room temperature, followed by being concentrated under reduced pressure to remove dioxane. The residue was purified by silica column chromatography (PE:EA = 2:1) to give compound **10-a** (45mg, yield 71%). LC-MS (ESI): m/z = 427 $[M+H]^+$.

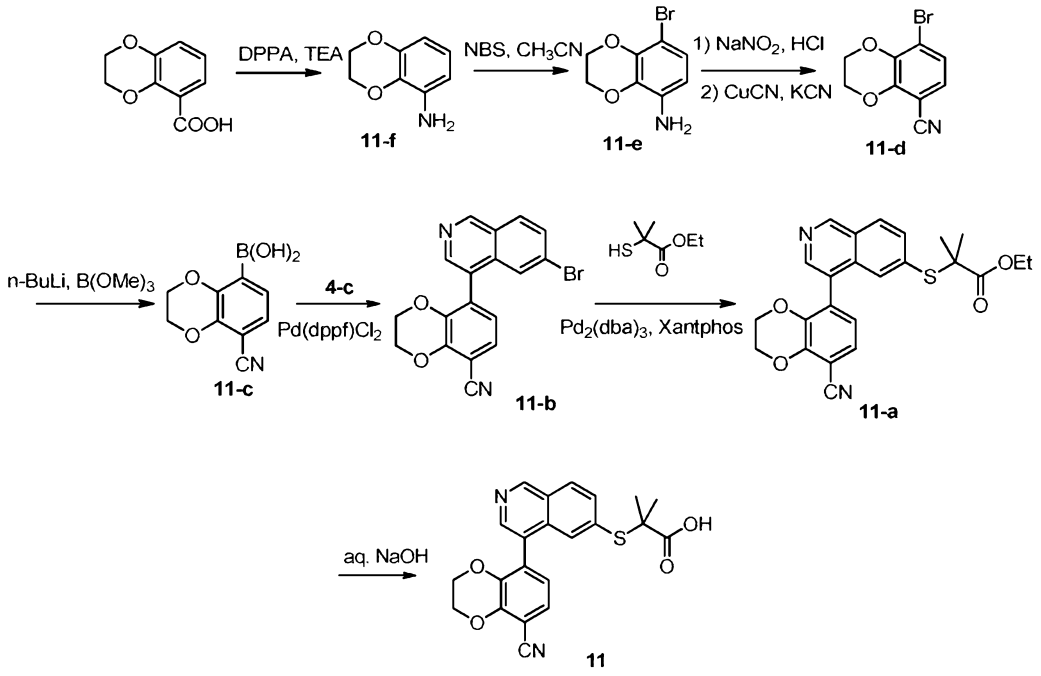
Synthesis of compound **10**

At room temperature, 1M NaOH aqueous solution (2.5mL) was added to a solution of compound **10-a** (59mg, 0.14mmol) in methanol (5mL), the mixture was stirred for 5hrs, followed by adding 1M HCl aqueous solution to adjust pH=6, being concentrated under reduced pressure to remove methanol, solid was precipitated and filtered out. The solid was washed with water (5mL), dried under vacuum to give white solid **10** (43mg, yield 78%). LC-MS (ESI): m/z = 399 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 12.63 (s, 1H), 9.50 (s, 1H), 8.56 (s, 1H), 8.28 (m, 3H), 7.99 (m, 1H), 7.78 (d, J=6.3 Hz, 1H), 7.61 (m, 3H), 7.26 (s, 1H), 1.29 (s, 3H), 1.23 (s, 3H) ppm.

Embodiment 11

2-{[4-(8-Cyano-2,3-dihydro-1,4-benzodioxan-5-yl)isoquinolin-6-yl]thio}-2-methylpropionic acid (Compound **11**)



Synthesis of compound **11-f**

At room temperature, diphenyl phosphoryl azide (8.02g, 29mmol) and triethyl amine (4.2g, 42mmol) were added to a solution of 2,3-dihydro-1,4-benzodioxane-5-carboxylic acid (5.0g, 28mmol) in anhydrous THF (110mL). The mixture was stirred for 2hrs, followed by adding water (30mL),

heating to 70℃ and further reacting for 3hrs, then cooling to room temperature, being extracted with EA (100mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 5:1) to give compound **11-f** (1.58g, yield 37%). LC-MS (ESI): m/z = 152 $[M+H]^+$.

Synthesis of compound **11-e**

At 0℃, a solution of N-bromosuccinimide (1.73g, 9.73mmol) in acetonitrile (5mL) was added to a solution of compound **11-f** (1.4g, 9.27mmol) in acetonitrile (35mL). The mixture was warmed to room temperature and reacted for 3hrs, evaporated under reduced pressure to remove the solvent. The residue was purified by silica column chromatography (PE:EA = 10:1 to 5:1) to give compound **11-e** (1.63g, yield 77%). LC-MS (ESI): m/z = 230 $[M+H]^+$.

Synthesis of compound **11-d**

At 0℃, sodium nitrite (0.5g, 7.2mmol) was slowly added to a suspension of compound **11-e** (1.5g, 6.55mmol) in 3M HCl aqueous solution (12mL), reacted for 30mins, sodium bicarbonate solid was added to adjust the reaction mixture to pH=7. The mixture was heated to 60℃, a solution of CuCN (0.7g, 7.86mmol) and KCN (1.06g, 16.37mmol) in water (20mL) was added dropwise, and further stirred for 30mins. The reaction solution was cooled to room temperature, extracted with DCM (60mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE: EA = 10:1) to give compound **11-d** (1.2g, yield 77%). LC-MS (ESI): m/z = 240 $[M+H]^+$.

Synthesis of compound **11-c**

At -78℃, a solution of 2.5M *n*-butyl lithium in *n*-hexane (1.7mL, 4.2mmol) was added dropwise to a solution of compound **11-d** (910mg, 3.8mmol) in anhydrous THF (20mL), the mixture was stirred for 1h, followed by adding trimethyl borate (594mg, 5.7mmol) to the reaction solution. The reaction solution was slowly warmed to room temperature, further stirred for 16hrs, saturated NaCl aq. solution (20mL) was added. Organic phase was seperated, the aqueous phase was extracted with EA (60mL×3). The combined organic phases were dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure to give yellow solid **11-c** (700mg, yield 90%). The product was directly used for the next step without further purification. LC-MS (ESI): m/z = 206 $[M+H]^+$.

Synthesis of compound **11-b**

Under N_2 atmosphere, compound **11-c** (130mg, 0.63mmol), compound **4-c** (200mg, 0.6mmol) and cesium carbonate (390mg, 1.2mmol) were suspended to a mixture of dioxane (10mL) and water (1mL), [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (43mg, 0.06mmol) was added. The mixture was reacted for 10hrs at 80℃, cooled to room temperature, filtered through celite, the filtrate cake was washed with

EA (20mL), the filtrate was concentrated under reduced pressure. The residue was purified by silica preparative plate chromatography (PE:EA = 3:1) to give compound **11-b** (146mg, yield 66%). LC-MS (ESI): m/z = 367 $[M+H]^+$.

Synthesis of compound **11-a**

Under N_2 atmosphere, tris(dibenzylidene indene acetone)dipalladium (36mg, 0.04mmol) and 4,5- bis(diphenylphosphine)9,9-dimethyloxacanthracene (46mg, 0.08mmol) were added to a solution of compound **11-b** (146mg, 0.52mmol), ethyl 2-methyl-2-mercaptopropionate (77mg, 0.52mmol) and diisopropylethylamine (103mg, 0.8mmol) in dioxane (8mL). The mixture was stirred for 6hrs at 100℃, cooled to room temperature, concentrated under reduced pressure to remove dioxane. The residue was purified by silica preparative plate chromatography (PE:EA = 1:2) to give compound **11-a** (147mg, yield 85%). LC-MS (ESI): m/z = 435 $[M+H]^+$.

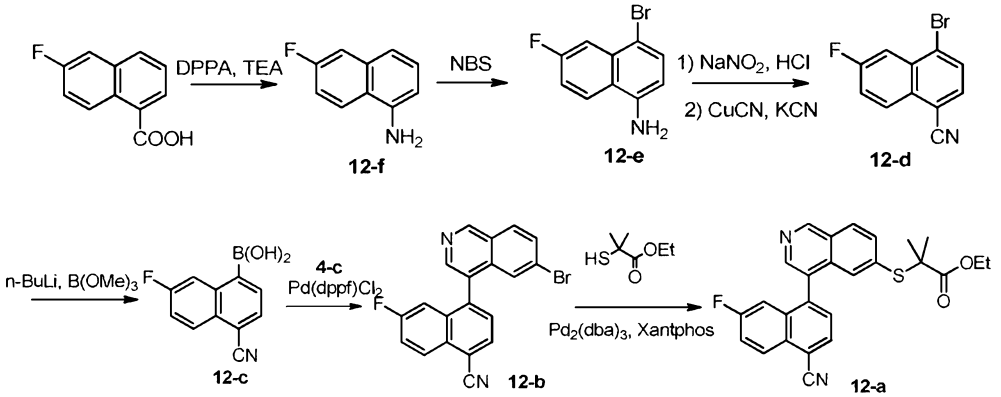
Synthesis of compound **11**

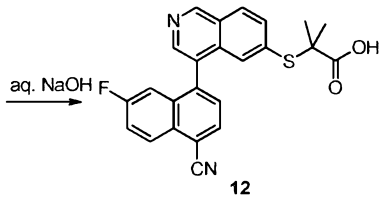
At room temperature, 1M NaOH aq. solution (2.5mL) was added to a solution of compound **11-a** (146mg, 0.34mmol) in methanol (5mL), the mixture was stirred for 5hrs. The mixture was adjusted to pH=6 with 1M HCl aq. solution, concentrated under reduced pressure to remove methanol, solid was precipitated and filtered out. The solid was washed with water (5mL), dried under vacuum to give white solid **11** (95 mg, yield 69%). LC-MS (ESI): m/z = 407 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 12.79 (s, 1H), 9.36 (s, 1H), 8.56 (s, 1H), 8.42 (s, 1H), 8.17 (d, J=8.0 Hz, 1H), 7.63 (m, 2H), 7.46 (d, J=8.0 Hz, 1H), 7.04 (d, J=8.0 Hz, 1H), 4.47 (m, 2H), 4.23 (m, 2H), 1.47 (s, 3H), 1.44 (s, 3H) ppm.

Embodiment 12

2-{[4-(4-Cyano-7-fluoronaphthalen-1-yl)isoquinolin-6-yl]thio}-2-methyl propionic acid (Compound **12**)





12

Synthesis of compound **12-f**

At room temperature, diphenyl phosphoryl azide (7.6g, 27.6mmol) and triethyl amine (4.0g, 54mmol) were added to a solution of 6-fluoronaphthalene-1-carboxylic acid (5.0g, 26.3mmol) in anhydrous THF (60mL). The mixture was stirred for 2hrs, followed by adding water (30mL), heating to 70℃ and further stirring for 3hrs. The reaction solution was cooled to room temperature, extracted with EA (150mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA=15:1) to give compound **12-f** (1.0g, yield 16%). LC-MS (ESI): m/z = 162 $[M+H]^+$.

Synthesis of compound **12-e**

At 0℃, a solution of N-bromosuccinimide (1.55g, 8.7mmol) in DCM (5mL) was added dropwise to a solution of compound **12-f** (1.4g, 8.7mmol) in DCM (50mL). The reaction solution was stirred for 30mins, concentrated under reduced pressure to remove the solvent. The residue was purified by silica column chromatography (PE:EA = 15:1) to give compound **12-e** (1.45g, yield 70%). LC-MS (ESI): m/z = 240 $[M+H]^+$.

Synthesis of compound **12-d**

At 0℃, sodium nitrite (0.5g, 7.2mmol) was slowly added to a suspension of compound **12-e** (800mg, 3.3mmol) in 3M HCl aqueous solution (12mL), the mixture was reacted for 30mins, sodium bicarbonate solid was added to adjust the reaction solution to pH=7. At 60℃, the mixture was added to a solution of CuCN (357mg, 4.0mmol) and KCN (536mg, 8.25mmol) in water (20mL), the mixture was further reacted for 30mins. The reaction solution was cooled to room temperature, extracted with DCM (60mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 5:1) to give compound **12-d** (420mg, yield 50%). LC-MS (ESI): m/z = 250 $[M+H]^+$.

Synthesis of compound **12-c**

At -78℃, a solution of 2.5M *n*-butyl lithium in *n*-hexane (0.5mL, 1.17mmol) was added dropwise to a solution of compound **12-d** (226mg, 0.9mmol) in anhydrous THF (10mL). The mixture was stirred for 1h, followed by adding trimethyl borate (142mg, 1.36mmol) dropwise, then slowly warming to room temperature, and further stirring for 16hrs, 1M HCl aqueous solution (5mL) was added. The organic phase

was seperated, the aqueous phase was extracted with EA (30mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give yellow solid **12-c** (200mg, yield 100%). The product was directly used for the next step without further purification. LC-MS (ESI): m/z = 216 $[M+H]^+$.

Synthesis of compound **12-b**

Under N_2 atmosphere, compound **12-c** (120mg, 0.93mmol), compound **4-c** (223mg, 1.11mmol) and cesium carbonate (363mg, 1.11mmol) were suspended in a mixture of dioxane (8mL) and water (0.8mL), [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (41mg, 0.056mmol) was added. The mixture was reacted for 5hrs at 80℃, cooled to room temperature, filtered through celite, the filtrate cake was washed with EA (20mL). The filtrate was concentrated under reduced pressure, the residue was purified by silica preparative plate chromatography (PE:EA = 1:1) to give compound **12-b** (90mg, yield 43%). LC-MS (ESI): m/z = 377 $[M+H]^+$.

Synthesis of compound **12-a**

Under N_2 atmosphere, tris(dibenzylidene indene acetone)dipalladium (22mg, 0.02mmol) and 4,5-bis(diphenylphosphine)-9,9-dimethyloxacanthracene (28mg, 0.05mmol) were added to a solution of compound **12-b** (90mg, 0.24mmol), ethyl 2-methyl-2-mercaptopropionate (46mg, 0.3mmol) and diisopropylethylamine (62mg, 0.48mmol) in dioxane (8mL). The mixture was stirred for 6hrs at 100℃, cooled to room temperature, concentrated under reduced pressure to remove dioxane. The residue was purified by silica preparative plate chromatography (PE:EA = 1:1) to give compound **12-a** (100mg, yield 94%). LC-MS (ESI): m/z = 445 $[M+H]^+$.

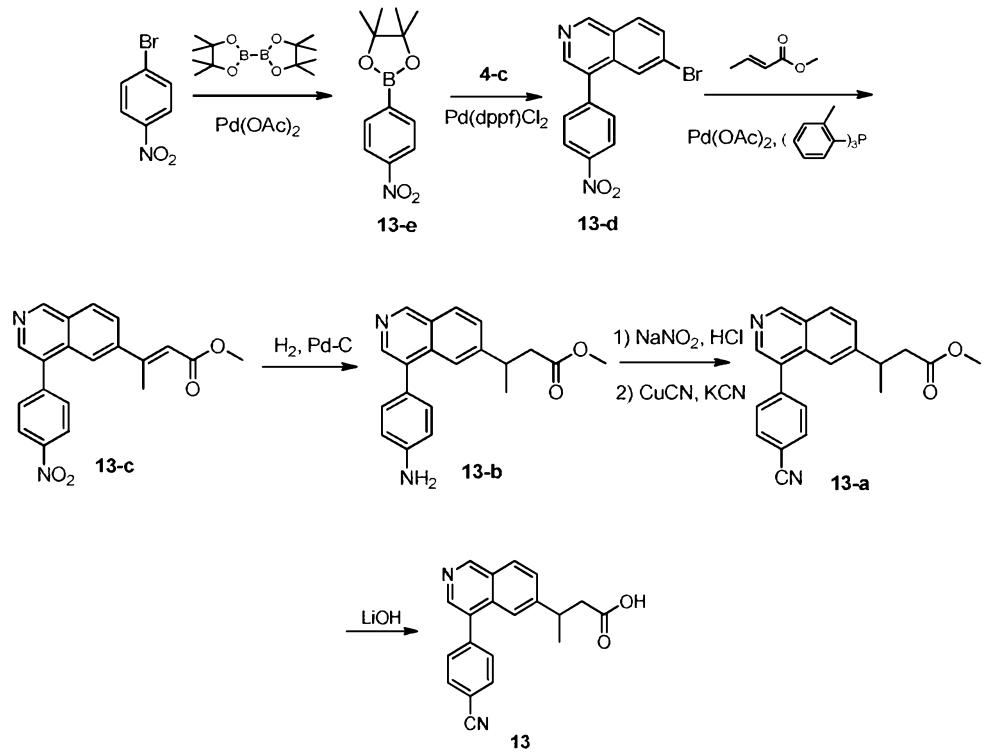
Synthesis of compound **12**

At room temperature, 1M NaOH aq. solution (2.5mL) was added to a solution of compound **12-a** (100mg, 0.22mmol) in methanol (5mL), the mixture was stirred for 10hrs. The mixture was adjusted to pH=6 with 1M HCl aq. solution, concentrated under reduced pressure to remove methanol, solid was precipitated and filtered out. The solid was washed with water (5mL), dried under vacuum to give white solid **12** (70 mg, yield 75%). LC-MS (ESI): m/z = 417 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 12.69 (s, 1H), 9.51 (s, 1H), 8.68 (s, 1H), 8.47 (d, J=8.5 Hz, 1H), 8.29 (m, 2H), 8.12 (m, 1H), 7.83 (m, 2H), 7.73 (d, J=8.5 Hz, 1H), 7.61 (s, 1H), 1.41 (s, 3H), 1.40 (s, 3H) ppm.

Embodiment 13

3-[4-(4-Cyanophenyl)isoquinolin-6-yl]butyric acid (Compound **13**)



Synthesis of compound **13-e**

Under N_2 atmosphere, bis(pinacolato)diboron (4.53g, 17.82mmol), potassium acetate (4.37g, 44.55mmol) and palladium acetate (0.17g, 0.74mmol) were added respectively to a solution of 1-bromo-4-nitrobenzene (3.0g, 14.85mmol) in DMF (10mL). The mixture was stirred at 80℃ for 2hrs, followed by adding water (20mL) and EA (20mL), the organic phase was in turn washed with water (10mL×3) and saturated brine (10mL), dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 10:1) to give compound **13-e** (2g, yield 54%). LC-MS (ESI): m/z = 250 $[M+H]^+$.

Synthesis of compound **13-d**

Under N_2 atmosphere, compound **4-c** (1.0g, 3mmol), compound **13-e** (0.82g, 3.3mmol) and sodium carbonate (0.95g, 8.98mmol) were suspended in DMF (10mL) and water (5mL), [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (0.245g, 0.3mmol) was added. The mixture was stirred at 80℃ for 2hrs, cooled to room temperature, followed by adding water (15mL), being extracted with EA (30mL×3). The organic phase was in turn washed with water (20mL×3) and saturated brine (20mL), dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 2:1) to give compound **13-d** (0.9g, yield 90%). LC-MS (ESI): m/z = 329 $[M+H]^+$.

Synthesis of compound **13-c**

Under N_2 atmosphere, methyl crotonate (0.29mL, 2.7mmol), palladium acetate (41mg, 0.18mmol), tri-*o*-methylphenylphosphine (111mg, 0.36mmol) and triethyl amine (0.5mL, 3.6mmol) were added to a solution of compound **13-d** (600mg, 1.8mmol) in DMF (5mL). The mixture was stirred for 16hrs at 80℃, cooled to room temperature, followed by adding water (15mL) and being extracted with EA (30mL×3). The organic phase was washed with water (20mL×3) and saturated brine (20mL), dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 1:1) to give compound **13-c** (360mg, yield 57%). LC-MS (ESI): m/z = 349 $[M+H]^+$.

Synthesis of compound **13-b**

Under H_2 atmosphere (1 atm.), Pd-C (100mg) was added to a solution of compound **13-c** (180mg, 0.51mmol) in ethanol (20mL). The mixture was stirred for 16hrs at room temperature, filtered, concentrated under reduced pressure. The residue was purified by silica chromatography (PE:EA = 1:1) to give compound **13-b** (360 mg, yield 57%). LC-MS (ESI): m/z = 321 $[M+H]^+$.

Synthesis of compound **13-a**

At 0℃, sodium nitrite (14.2mg, 0.2mmol) was slowly added to a suspension of compound **13-b** (60mg, 0.18mmol) in concentrated HCl aqueous solution (1mL), the mixture was stirred for 30mins, sodium bicarbonate solid was added to adjust the reaction solution to pH=7. The mixture was heated to 60℃, then was added to a solution of CuCN (20.1mg, 0.22mmol) and KCN (30.5mg, 0.46mmol) in water (3mL), further reacted for 30mins. The reaction solution was cooled to room temperature, extracted with DCM (20mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 5:1) to give compound **13-a** (30mg, yield 48%). LC-MS (ESI): m/z = 331 $[M+H]^+$.

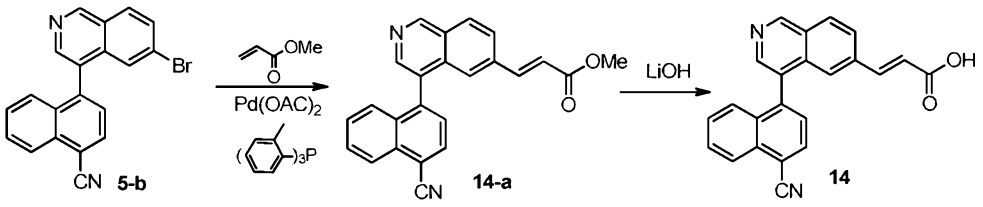
Synthesis of compound **13**

At room temperature, LiOH (50mg, 2mmol) was added to a mixed solution of compound **13-a** (30mg, 0.09mmol) in methanol (2mL), THF (2mL) and water (4mL). The mixture was stirred for 2hrs, followed by being adjusted to pH=7 with 2M HCl aq. solution and then extracted with EA (10 mL×3). The organic phases were combined, washed in turn with water (10mL×3) and saturated brine (10mL), dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure to give compound **13** (10mg, yield 35%). LC-MS (ESI): m/z = 317 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 12.10 (s, 1H), 9.34 (s, 1H), 8.44 (s, 1H), 8.20 (d, J=8.8 Hz, 1H), 8.05 (d, J=8.0Hz, 2H), 7.77 (d, J=8.0 Hz, 2H), 7.74 (d, J=8.8 Hz, 2H), 7.62 (s, 1H), 3.30 (m, 1H), 2.57 (d, J=7.6 Hz, 2H), 1.26 (d, J=8.8 Hz, 3H) ppm.

Embodiment 14

(2E)-3-[4-(4-Cyanonaphthalen-1-yl)isoquinolin-6-yl]acrylic acid (Compound **14**)



Synthesis of compound **14-a**

Under N_2 atmosphere, methyl acrylate (0.189mL, 2.09mmol), palladium acetate (31.2mg, 0.14mmol), tri-*o*-methylphenylphosphine (85mg, 0.27mmol) and triethyl amine (0.39mL, 2.78mmol) were added to a solution of compound **5-b** (500mg, 1.39mmol) in DMF (5mL). The mixture was stirred at 80℃ for 16hrs, cooled to room temperature, followed by adding water (15mL), being extracted with EA (30mL×3). The organic phases were combined, washed in turn with water (20mL×3) and saturated brine (20mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified with silica column chromatography (PE:EA = 1:1) to give compound **14-a** (400mg, yield 79%). LC-MS (ESI): m/z = 379 $[M+H]^+$.

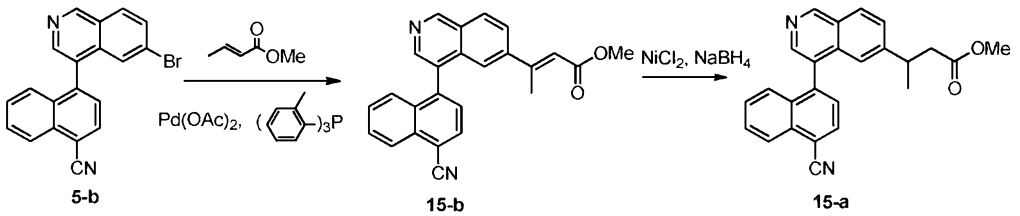
Synthesis of compound **14**

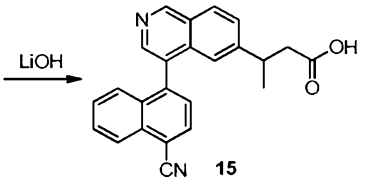
At room temperature, LiOH (52.6mg, 2.19mmol) was added to a mixed solution of compound **14-a** (80mg, 0.22mmol) in methanol (2mL), THF (2mL) and water (4mL). The mixture was stirred for 2hrs, adjusted to pH=7 with 2M HCl aq. solution, extracted with EA (20mL×3). The organic phases were combined, washed in turn with water (10mL×3) and saturated brine (10mL), dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure to give compound **14** (68mg, yield 88%). LC-MS (ESI): m/z = 351 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 12.60 (s, 1H), 9.51 (s, 1H), 8.55 (s, 1H), 8.24 (m, 3H), 8.13 (d, J=8.4 Hz, 1H), 7.85 (t, J=7.6 Hz, 1H), 7.75 (d, J=7.6 Hz, 1H), 7.51 (m, 4H), 6.61 (d, J=15.6 Hz, 1H) ppm.

Embodiment 15

3-[4-(4-Cyanonaphthalen-1-yl)isoquinolin-6-yl]butyric acid (Compound **15**)





15

Synthesis of compound **15-b**

Under N_2 atmosphere, methyl crotonate (72mg, 0.56mmol), palladium acetate (12.5mg, 0.05mmol), tri-*o*-methylphenylphosphine (34mg, 0.11mmol) and triethyl amine (0.15mL, 1.11mmol) were added to a solution of compound **5-b** (200mg, 0.56mmol) in DMF (5mL). The mixture was stirred at 80℃ for 16hrs, cooled to room temperature, followed by adding water (10mL), being extracted with EA (20mL×3). The organic phases were combined, washed in turn with water (10mL×3) and saturated brine (10mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 1:1) to give compound **15-b** (120mg, yield 59%). LC-MS (ESI): m/z = 379 $[M+H]^+$.

Synthesis of compound **15-a**

At 0℃, $NaBH_4$ (120mg, 3.17mmol) was slowly added to a solution of compound **15-b** (120mg, 0.31mmol) and $NiCl_2$ (102mg, 0.79mmol) in methanol (150mL). The mixture was stirred at 0℃ for 4.5hrs, warmed to room temperature, and concentrated under reduced pressure, followed by adding water (20mL) to the residue, being extracted with EA (50mL×3). The organic phases were combined, washed in turn with water (50mL×3) and saturated brine (50mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified with silica column chromatography (PE:EA = 2:1) to give compound **15-a** (45mg, yield 37%). LC-MS (ESI): m/z =381 $[M+H]^+$.

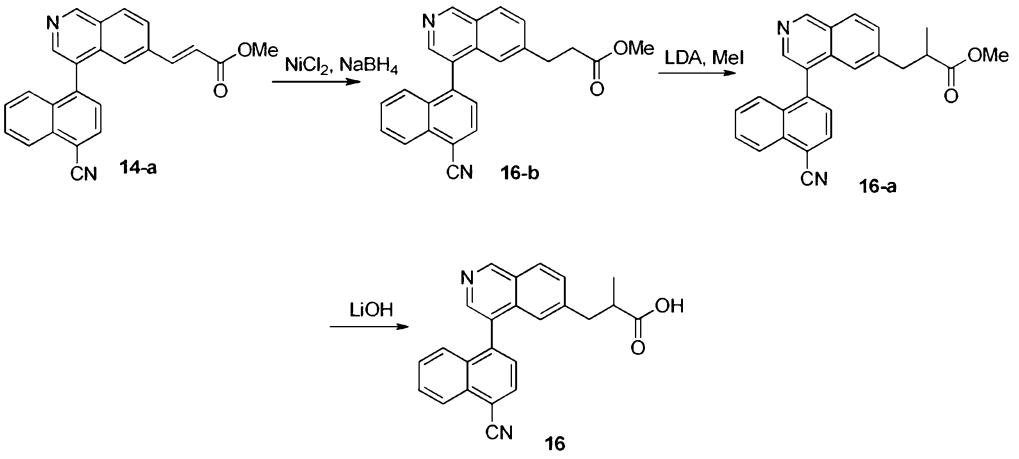
Synthesis of compound **15**

At room temperature, LiOH (28.3mg, 1.18mmol) was added to a mixed solution of compound **15-a** (45mg, 0.11mmol) in methanol (2mL), THF (2mL) and water (4mL). The mixture was stirred for 2hrs, and then adjusted to pH=7 with 2M HCl aq. solution, extracted with EA (20mL×3). The organic phases were combined, washed in turn with water (10mL×3) and saturated brine (10mL), dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure to give compound **15** (18mg, yield 42%). LC-MS (ESI): m/z = 367 $[M+H]^+$.

^{1}H-NMR (400MHz, CD_3OD) δ: 9.25 (s, 1H), 8.31 (s, 1H), 8.25 (d, J=8.4 Hz, 1H), 8.12 (d, J=4.4 Hz, 1H), 8.09 (d, J=7.2 Hz, 1H), 7.70 (t, J=7.2 Hz, 1H), 7.59 (m, 2H), 7.44 (m, 1H), 7.35 (t, J=8.8 Hz, 1H), 7.04 (d, J=10 Hz, 1H), 3.12 (m, 1H), 2.36 (m, 1H), 1.07 (m,3H) ppm.

Embodiment 16

3-[4-(4-Cyanonaphthalen-1-yl)isoquinolin-6-yl]-2-methyl propionic acid (Compound **16**)



Synthesis of compound **16-b**

At 0℃, $NaBH_4$ (145mg, 3.84mmol) was slowly added to a solution of compound **14-a** (350mg, 0.96mmol) and $NiCl_2$ (62.2mg, 0.48mmol) in methanol (150mL). The mixture was stirred at 0℃ for 4.5hrs, warmed to room temperature, and concentrated under reduced pressure, followed by adding water (20mL) to the residue, being extracted with EA (50mL×3). The organic phases were combined, washed in turn with water (50mL×3) and saturated brine (50mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified with silica column chromatography (PE:EA = 2:1) to give compound **16-b** (200mg, yield 57%). LC-MS (ESI): m/z =367 $[M+H]^+$.

Synthesis of compound **16-a**

Under N_2 atmosphere, at -78℃, a solution of 2.5M *n*-butyl lithium in *n*-hexane (0.87mL, 2.18mmol) was added dropwise in a solution of diisopropylamine (0.11mL, 2.18mmol) in anhydrous THF (10mL). The mixture was stirred for 30mins, a solution of compound **16-b** (200mg, 0.55mmol) in anhydrous THF (5mL) was added dropwise, and the mixture was further stirred for 30mins, a solution of CH_3I (139.5mg, 0.98mmol) in anhydrous THF (5mL) was added dropwise, the mixture was slowly warmed to room temperature and further stirred for 2hrs, saturated NH_4Cl aq. solution (10mL) was added, the mixture was extracted with EA (20mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 2:1) to give compound **16-a** (20mg, yield 19%). LC-MS (ESI): m/z =381 $[M+H]^+$.

Synthesis of compound **16**

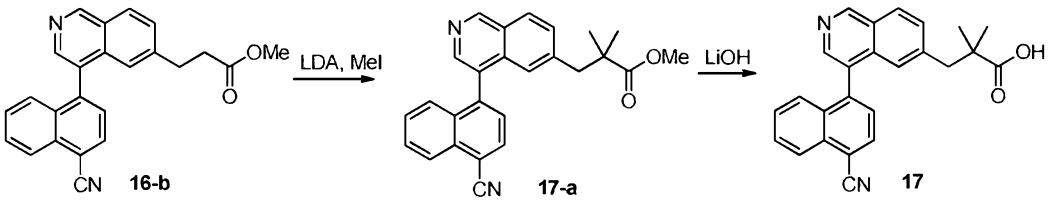
At room temperature, LiOH (25mg, 1.05mmol) was added to a mixed solution of compound **16-a** (20mg, 0.05mmol) in methanol (2mL), THF (2mL) and water (4mL).

The mixture was stirred for 2hrs, adjusted to pH=7 with 2M HCl aq. solution, extracted with EA (20mL×3). The organic phases were combined, washed in turn with water (10mL×3) and saturated brine (10mL), dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure to give compound **16** (10mg, yield 52%). LC-MS (ESI): m/z = 367 $[M+H]^+$.

^{1}H-NMR (400MHz, CD_3OD) δ: 9.37 (s, 1H), 8.42 (d, J=2.4 Hz, 1H), 8.36 (d, J=8.4 Hz, 1H), 8.21 (m, 2H), 7.81 (t, J=7.6 Hz, 1H), 7.69 (d, J=7.6 Hz, 1H), 7.66 (d, J=8.4 Hz, 1H), 7.50 (m, 2H), 7.13 (d, J=7.6 Hz, 1H), 2.97 (m, 1H), 2.65 (m, 2H), 1.02 (m,3H) ppm.

Embodiment 17

3-[4-(4-Cyanonaphthalen-1-yl)isoquinolin-6-yl]-2,2-dimethyl propionic acid (Compound **17**)



Synthesis of compound **17-a**

Under N_2 atmosphere, at -78℃, a solution of 2.5M *n*-butyl lithium in *n*-hexane (0.87mL, 2.18mmol) was slowly added to a solution of diisopropylamine (0.11mL, 2.18mmol) in anhydrous THF (10mL) dropwise. The mixture was stirred for 30mins, followed by adding a solution of compound **16-b** (200mg, 0.55mmol) in anhydrous THF (5mL) dropwise, further stirred for 30mins, followed by adding a solution of CH_3I (139.5mg, 0.98mmol) in anhydrous THF (5mL). The mixture was slowly warmed to room temperature, further stirred for 2hrs, followed by adding saturated NH_4Cl aq. solution (10mL) and being extracted with EA (20mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 2:1) to give compound **17-a** (20mg, yield 18.5%). LC-MS (ESI): m/z =395 $[M+H]^+$.

Synthesis of compound **17**

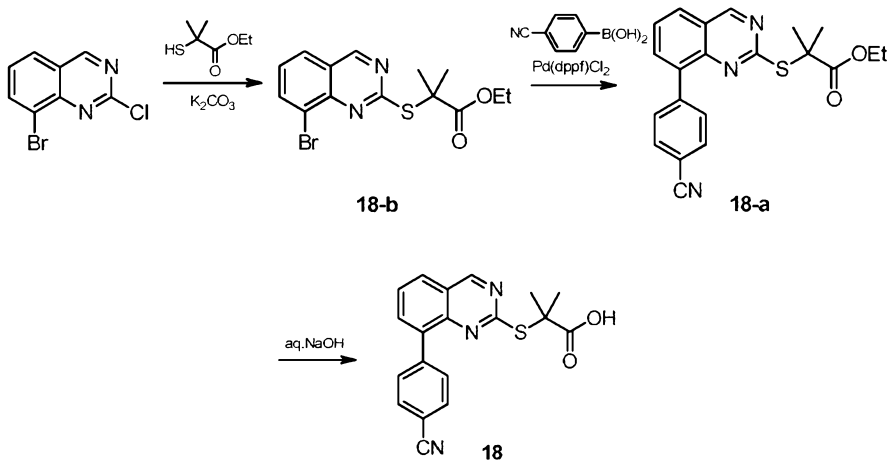
At room temperature, LiOH (24mg, 1.01mmol) was added to a mixed solution of compound **17-a** (20mg, 0.05mmol) in methanol (2mL), THF (2mL) and water (4mL). The mixture was stirred for 2hrs, followed by adding 2M HCl aq. solution to adjust pH=7, and then extracted with EA (20mL×3). The organic phases were combined, washed in turn with water (10mL×3) and saturated brine (10mL), dried over magnesium sulfate, filtered, concentrated under reduced pressure to give compound **17** (5mg, yield 26%). LC-MS (ESI): m/z = 381 $[M+H]^+$.

^{1}H-NMR (400MHz, CD_3OD) δ: 9.37 (s, 1H), 8.42 (s, 1H), 8.37 (d, J=8.8 Hz, 1H),

8.21 (d, J=7.6 Hz, 1H), 7.81 (m, 1H), 7.55 (m, 5H), 7.11 (s, 1H), 2.97 (m, 1H), 2.89 (m, 2H), 1.02 (s, 3H), 0.97 (s, 3H) ppm.

Embodiment 18

2-{[8-(4-Cyanophenyl)isoquinolin-2-yl]thio}-2-methyl propionic acid (Compound **18**)



Synthesis of compound **18-b**

8-Bromo-2-chloroquinazoline (110mg, 0.45mmol) was added to a suspension of ethyl 2-methyl-2-mercaptopropionate (80mg, 0.54mmol), potassium carbonate (124mg, 0.9mmol) in DMF (3mL). The mixture was stirred for 3hrs at 130℃, cooled to room temperature, followed by adding water (20mL), being extracted with EA (30mL×3). The organic phases were combined, washed in turn with water (20mL×3) and saturated brine (20mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 6:1) to give colorless oil **18-b** (108mg, yield 67.5%). LC-MS (ESI): m/z =355 $[M+H]^+$.

Synthesis of compound **18-a**

Under N_2 atmosphere, compound **18-b** (108mg, 0.3mmol), 4-cyanophenyl boronic acid (54mg, 0.36mmol) and cesium carbonate (196mg, 0.6mmol) were suspended in dioxane (10mL) and water (1mL), [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (40mg, 0.05mmol) was added. The mixture was stirred at 90℃ for 16hrs, followed by cooling to room temperature, being concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 5:1) to give colorless oil **18-a** (83mg, yield 72%). LC-MS (ESI): m/z = 378 $[M+H]^+$.

Synthesis of compound **18**

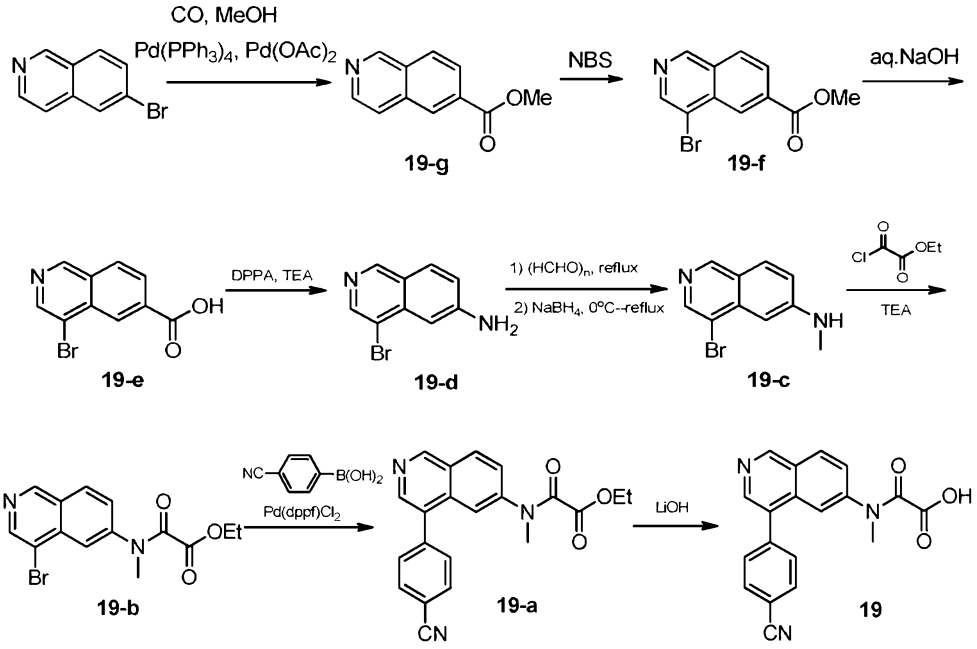
At room temperature, 1M NaOH aq. solution (2.0mL) was added to a solution of compound **18-a** (83mg, 0.22mmol) in methanol (5mL). The mixture was stirred for 2hrs, followed by adding 1M HCl aq. solution to adjust pH=5-6, being extracted with

EA (20mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by HPLC (mobile phase: 10mM NH_4HCO_3 aq. solution: acetonitrile = 25%-55%) to give yellow solid **18** (7mg, yield 9%). LC-MS (ESI): m/z = 350 $[M+H]^+$.

^{1}H-NMR (400MHz, CD_3OD) δ: 9.31 (s, 1H), 8.07 (dd, J=8.0 Hz, 1.6 Hz, 1H), 7.98 (dd, J=7.6 Hz, 2.4 Hz, 1H), 7.84 (d, J=7.6 Hz, 2H), 7.77 (d, J=7.6 Hz, 2H), 7.71 (dd, J=7.8 Hz, 3.6 Hz, 1H), 1.68 (s, 6H) ppm.

Embodiment 19

{[4-(4-Cyanophenyl)isoquinolin-6-yl](methyl)carbamoyl}formic acid (Compound **19**)



Synthesis of compound **19-g**

Under CO atmosphere (10 atm.), a mixture of 6-bromoisoquinoline (5.0g, 24mmol), sodium acetate (2.56g, 31mmol), tetrakis(triphenylphosphine)palladium (2.77g, 2.4mmol), palladium acetate (1.1g, 4.8mmol), DMF (50mL) and DCM (50mL) was heated to 100℃, stirred for 16hrs and then cooled to room temperature, concentrated under reduced pressure to remove methanol. Water (100mL) was added to the residue, EA (200mL×2) was used for extract. The organic phases were combined, washed in turn with water (100mL×3) and saturated brine (100mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 5:1) to give white solid **19-g** (4.34g, yield 96%). LC-MS (ESI): m/z =188 $[M+H]^+$.

Synthesis of compound **19-f**

N-Bromosuccinimide (6.19g, 34.8mmol), compound **19-g** (4.34g, 23.2mmol) and

acetic acid (25mL) were added to 80℃ and stirred for 16hrs, the mixture was cooled to room temperature, concentrated under reduced pressure. Saturated sodium bicarbonate solution was added to the residue (30mL), the mixture was extracted with EA (50mL×2). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica chromatography (PE:EA = 5:1) to give compound **19-f** (3.59g, yield 58%). LC-MS (ESI): m/z = 268 $[M+H]^+$.

Synthesis of compound **19-e**

At room temperature, 2M NaOH aq. solution (10mL) was added to a solution of compound **19-f** (3.59g, 13.5mmol) in methanol (30mL). The mixture was stirred for 16hrs, followed by adding 1M HCl aq. solution to adjust pH=5-6, solid was precipitated and filtered out. The solid was washed with water (10mL), dried under vacuum to give yellow solid **19-e** (3.29g, yield 96.8%). LC-MS (ESI): m/z = 254 $[M+H]^+$.

Synthesis of compound **19-d**

At room temperature, diphenyl phosphoryl azide (5.2g, 25.2mmol) and triethyl amine (2.5g, 25.2mmol) were added to a solution of compound **19-e** (3.17g, 12.6mmol) in anhydrous THF (30mL). The mixture was stirred for 3hrs, followed by adding water (10mL), refluxing for 12hrs, then cooling to room temperature, being concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 1:1) to give yellow solid **19-g** (0.2g, yield 7%). LC-MS (ESI): m/z = 225 $[M+H]^+$.

Synthesis of compound **19-c**

Sodium methoxide (218mg, 4.03mmol) and polyformaldehyde (121mg, 4.03mmol) were added to a solution of compound **19-d** (180mg, 0.81mmol) in methanol (6mL). The mixture was refluxed for 1.5hrs, cooled to 0℃, $NaBH_4$ (185mg, 4.86mmol) was added in portions. The mixture was refluxed again for 1.5hrs, then cooled to room temperature, saturated $NaHCO_3$ (30mL) was added, the mixture was extracted with DCM (20mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure to give yellow solid **19-c** (175mg, yield 91.6%), the product was directly used for the next step without further purification. LC-MS (ESI): m/z = 237 $[M+H]^+$.

Synthesis of compound **19-b**

At room temperature, ethyl oxalyl monochloride (151mg, 1.11mmol) was added to a solution of compound **19-c** (175mg, 0.74mmol) and triethyl amine (150mg, 1.48mmol) in DCM (10mL). The mixture was stirred for 1h, followed by adding water (10mL), being extracted with DCM (20mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure to give yellow oil **19-b** (249mg, yield 99%), the product was directly used for the next step without further purification. LC-MS (ESI): m/z = 339 $[M+H]^+$.

Synthesis of compound **19-a**

Under N_2 atmosphere, compound **19-b** (249mg, 0.74mmol), 4-cyanophenylboronic acid (163mg, 1.11mmol) and sodium carbonate (157mg, 1.48mmol) were suspended in dioxane (15mL) and water (2mL), [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (54mg, 0.07mmol) was added. The mixture was stirred at 90℃ for 12hrs, followed by cooling to room temperature, being concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 3:1-1:1) to give compound **19-a** (90 mg, yield 34%). LC-MS (ESI): m/z = 360 $[M+H]^+$.

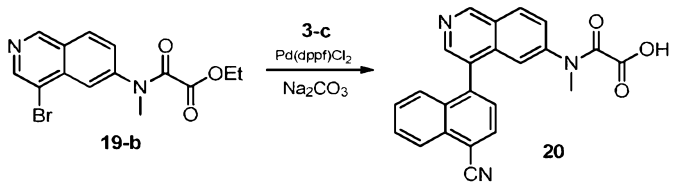
Synthesis of compound **19**

At room temperature, LiOH (2.0mL) was added to a solution of compound **19-a** (90mg, 0.25mmol) in methanol (5mL), THF (3mL) and water (1mL). The reaction solution was stirred for 2hrs, and then concentrated under reduced pressure. The residue was adjusted to pH=5-6 with 1M HCl aq. solution, then extracted with EA (20mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, concentrated under reduce pressure. The residue underwent HPLC preparation (mobile phase: 10mM NH_4HCO_3 aq. solution: acetonitrile = 25%-55%) to give white solid **19** (5mg, yield 7%). LC-MS (ESI): m/z = 332 $[M+H]^+$.

^{1}H-NMR (400MHz, CD_3OD) δ: 9.34 (s, 1H), 8.47 (s, 1H), 8.31 (d, J=8.6 Hz, 1H), 7.96 (d, J=8.6 Hz, 1H), 7.80 (m, 4H), 3.39 (s, 3H) ppm.

Embodiment 20

{[4-(4-Cyanonaphthalen-1-yl)isoquinolin-6-yl](methyl)carbamoyl}formic acid (Compound **20**)



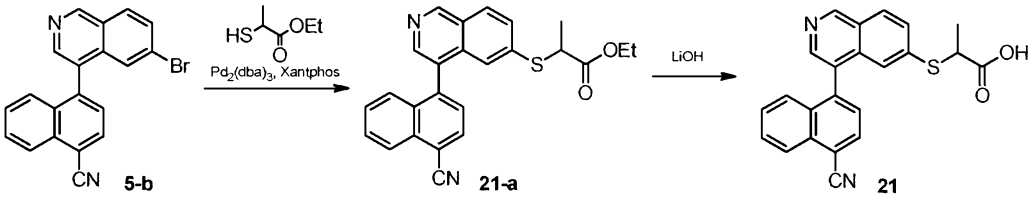
Synthesis of compound **20**

Under N_2 atmosphere, compound **19-b** (260mg, 0.77mmol), compound **3-c** (258mg, 0.93mmol) and sodium carbonate (163mg, 1.54mmol) were suspended in dioxane (8mL) and water (1mL), [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (56mg, 0.07mmol) was added. The mixture was stirred at 90℃ for 12hrs, followed by cooling to room temperature, being concentrated under reduced pressure. The residue underwent HPLC preparation (mobile phase: 10mM NH_4HCO_3 aq. solution: acetonitrile = 25%-45%) to give yellow solid **20** (40mg, yield 13.6%). LC-MS (ESI): m/z = 382 $[M+H]^+$.

^{1}H-NMR (400MHz, CD_3OD) δ: 9.42 (s, 1H), 8.47 (s, 1H), 8.33 (d, J=8.7 Hz, 2H), 8.20 (d, J=7.3 Hz, 1H), 7.79 (dd, J=8.6 Hz, 4.8 Hz, 1H), 7.71 (d, J=7.3 Hz, 1H), 7.56 (m, 2H), 7.33 (d, J=1.4 Hz, 2H), 3.24 (s, 3H) ppm.

Embodiment 21

2-{[4-(4-Cyanonaphthalen-1-yl)isoquinolin-6-yl]thio}propionic acid (Compound **21**)



Synthesis of compound **21-a**

Under N_2 atmosphere, tris(dibenzylidene indene acetone)dipalladium (24mg, 0.05mmol) and 4,5-bis(diphenylphosphine)-9,9-dimethyloxacanthracene (30mg, 0.05mmol) were added to a solution of compound **5-b** (185mg, 0.51mmol), ethyl 2-mercaptopropionate (83mg, 0.61mmol) and diisopropylethylamine (133mg, 1.03mmol) in dioxane (6mL). The mixture was reacted in a microwave at 110℃ for 1h, cooled to room temperature, and then concentrated under reduced pressure to remove dioxane. The residue was purified by silica column chromatography (PE:EA = 3:2) to give yellow solid **21-a** (163mg, yield 77%). LC-MS (ESI): m/z = 413 $[M+H]^+$.

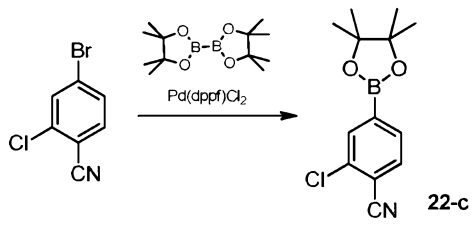
Synthesis of compound **21**

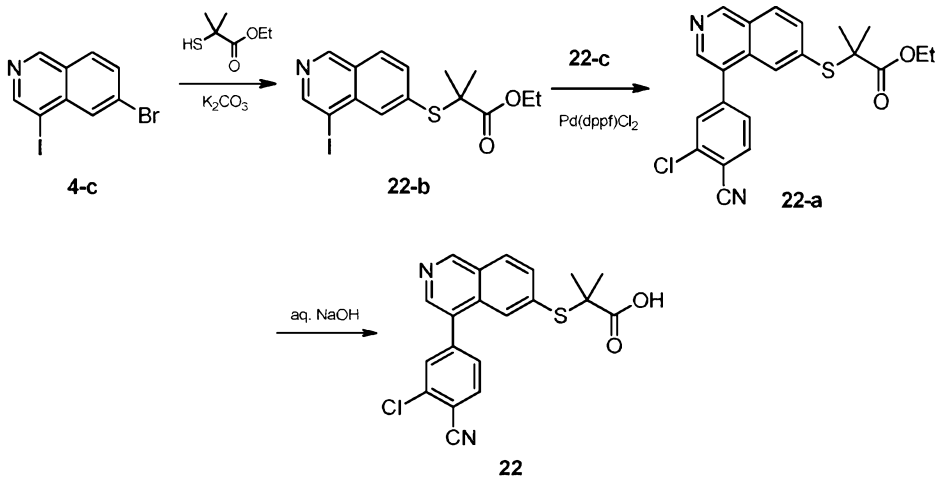
At room temperature, LiOH (12mg, 0.29mmol) was added to a solution of compound **21-a** (30mg, 0.07mmol) in methanol (1mL), THF (4mL) and water (1mL). The mixture was stirred for 1h, followed by adding 1M HCl aq. solution to adjust pH=5-6, the mixture was extracted with EA (15mL×2). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure to give white solid **21** (16mg, yield 57%). LC-MS (ESI): m/z = 385 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 9.43 (s, 1H), 8.50 (s, 1H), 8.27 (m, 3H), 7.85 (s, 1H), 7.72 (dd, J=11.7 Hz, 7.5 Hz, 2H), 7.59 (d, J=7.2 Hz, 1H), 7.45 (d, J=9.0 Hz, 1H), 7.15 (d, J=10.1 Hz, 1H), 1.35 (s, 1H), 1.24 (m, 3H) ppm.

Embodiment 22

2-{[4-(3-Chloro-4-cyanophenyl)isoquinolin-6-yl]thio}-2-methyl propionic acid (Compound **22**)





Synthesis of compound **22-c**

Under N_2 atmosphere, bis(pinacolato)diboron (391mg, 1.54mmol), potassium acetate (412mg, 4.2mmol) and [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (102mg, 0.14mmol) were respectively added to a solution of 2-chloro-4-bromobenzonitrile (300mg, 1.4mmol) in dioxane (15mL). The mixture was stirred at 115℃ for 12hrs, cooled to room temperature, filtered through celite, washed with EA (50mL). The filtrate was evaporated under reduced pressure to give compound **22-c** (620mg, yield 100%). The product was directly used for the next step without further purification. LC-MS (ESI): m/z = 182 $[M+H]^+$.

Synthesis of compound **22-b**

Compound **4-c** (80mg, 0.24mmol) was added to a suspension of ethyl 2-methyl-2-mercaptopropionate (71mg, 0.48mmol) and potassium carbonate (100mg, 0.72mmol) in DMF (2mL). The mixture was stirred at 130 for 2hrs, cooled to room temperature, followed by adding water (20mL), being extracted with EA (20mL×3). The organic phases were combined, washed in turn with water (20mL×3) and saturated brine (20mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified with silica preparative plate (PE:EA = 3:1) to give yellow oil **22-b** (75mg, yield 78%). LC-MS (ESI): m/z = 402 $[M+H]^+$.

Synthesis of compound **22-a**

Under N_2 atmosphere, compound **22-b** (60mg, 0.15mmol), compound **22-c** (120mg, 0.23mmol) and cesium carbonate (98mg, 0.3mmol) were suspended in dioxane (3mL) and water (0.3mL), [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (11mg, 0.02mmol) was added. The mixture was stirred at 100 for 12hrs, cooled to room temperature, followed by adding water (10mL), being extracted with EA (10mL×3). The organic phases were combined, washed in turn with water (10mL×3) and saturated brine (10mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified with silica

preparative plate (DCM: methanol = 20:1) to give brown solid **22-a** (43mg, yield 70%).

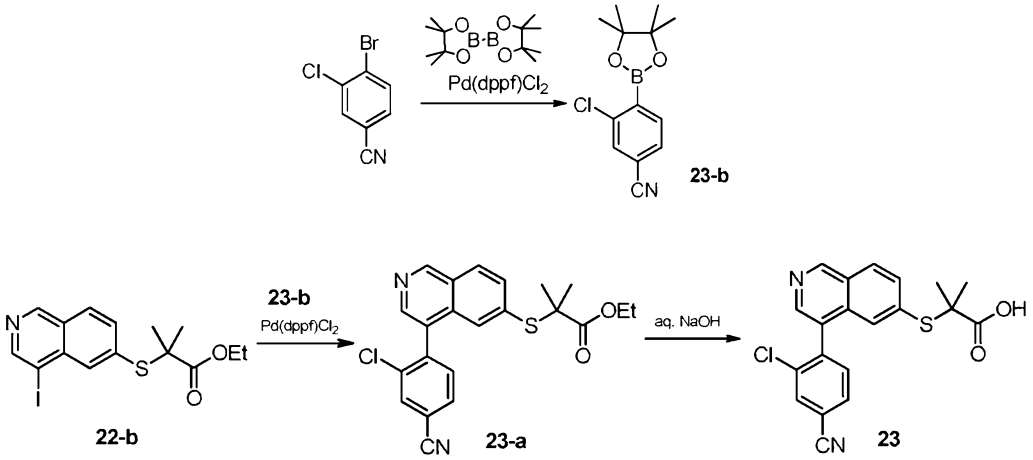
Synthesis of compound **22**

At room temperature, 1M NaOH aq. solution (1mL) was added to a solution of compound **22-a** (43mg, 0.1mmol) in methanol (1mL) and THF (1mL). The mixture was stirred for 4hrs, followed by evaporating under reduced pressure to remove methanol. The residue was adjusted to pH=5-6 with 1M HCl aq. solution, followed by being extracted with DCM (10mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica preparative plate (DCM: methanol = 10:1) to give yellow solid **22** (21mg, yield 53%). LC-MS (ESI): m/z = 383 $[M+H]^+$.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 9.21 (s, 1H), 8.38 (s, 1H), 7.98 (d, J=8.4 Hz, 1H), 7.95 (s, 2H), 7.78 (d, J=8.8 Hz, 1H), 7.73 (d, J=8.0 Hz, 1H), 7.63 (s, 1H), 7.50 (d, J=8.0 Hz, 1H), 1.61 (s, 6H) ppm.

Embodiment 23

2-{[4-(2-Chloro-4-cyanophenyl)isoquinolin-6-yl]thio}-2-methyl propionic acid (Compound **23**)



Synthesis of compound **23-b**

Under N_2 atmosphere, bis(pinacolato)diboron (391mg, 1.54mmol), potassium acetate (412mg, 4.5mmol) and [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (102mg, 0.14mmol) were respectively added to a solution of 2-chloro-4-bromobenzonitrile (300mg, 1.4mmol) in dioxane (15mL). The mixture was stirred at 80℃ for 12hrs, cooled to room temperature, filtered through celite, washed with EA (50mL). The filtrate was evaporated under reduced pressure, and the residue was purified by silica preparative plate to give white solid **23-b** (73mg, yield 20%).

^{1}H-NMR (400MHz, $CDCl_3$) δ: 7.78 (d, J=7.6 Hz, 1H), 7.62 (d, J=1.2 Hz, 1H), 7.52

(dd, J=7.6 Hz, 1.2 Hz, 1H), 1.37 (s, 12H) ppm.

Synthesis of compound **23-a**

Under N_2 atmosphere, compound **22-b** (100mg, 0.15mmol), compound **23-b** (73mg, 0.27mmol) and cesium carbonate (163mg, 0.5mmol) were suspended in dioxane (3mL) and water (0.3mL), [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (19mg, 0.03mmol) was added. The mixture was stirred at 100 ℃ for 12hrs, cooled to room temperature, followed by adding water (10mL), being extracted with EA (10mL×3). The organic phases were combined, washed in turn with water (10mL×3) and saturated brine (10mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica preparative plate (DCM: methanol = 20:1) to give white solid **23-a** (72mg, yield 71%). LC-MS (ESI): m/z = 411 $[M+H]^+$.

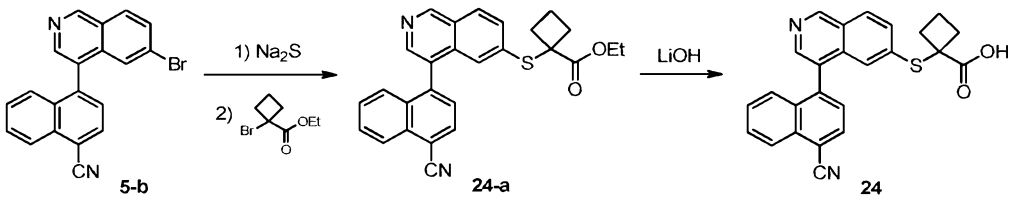
Synthesis of compound **23**

At room temperature, 1M NaOH aq. solution (1mL) was added to a solution of compound **23-a** (72mg, 0.18mmol) in methanol (1mL) and THF (1mL). The mixture was stirred for 2hrs, followed by evaporating under reduced pressure to remove methanol. The residue was adjusted to pH=5-6 with 1M HCl aq. solution, followed by being extracted with DCM (10mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified with silica preparative plate (DCM: methanol = 10:1) to give white solid **23** (31mg, yield 46%). LC-MS (ESI): m/z = 383 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 9.42 (s, 1H), 8.44 (s, 1H), 8.31 (d, J=1.6 Hz, 1H), 8.21 (d, J=8.4 Hz, 1H), 8.03 (dd, J=8.0 Hz, 1.2 Hz, 1H), 7.73 (d, J=8.0 Hz, 1H), 7.39 (s, 1H), 1.42 (s, 3H), 1.41 (s, 3H) ppm.

Embodiment 24

1-{[4-(4-cyanonaphthalen-1-yl)isoquinolin-6-yl]thio}cyclobutane-1-carboxylic acid (Compound **24**)



Synthesis of compound **24-a**

$Na_2S•9H_2O$ (182mg, 0.75mmol) was added to a solution of compound **5-b** (180mg, 0.5mmol) in DMF (2mL). The mixture was reacted in a microwave at 130 ℃ for 1h, cooled to room temperature, 1-bromo-cyclobutanoic acid ethyl ester (155mg, 0.75mmol) was added, the mixture was stirred at 50 ℃ for 2hrs. The mixture was

cooled to room temperature, followed by adding ice water (20mL), being extracted with EA (50mL). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica preparative plate (PE:EA = 1:1) to give white solid **24-a** (89 mg, yield 40%). LC-MS (ESI): m/z = 439 $[M+H]^+$.

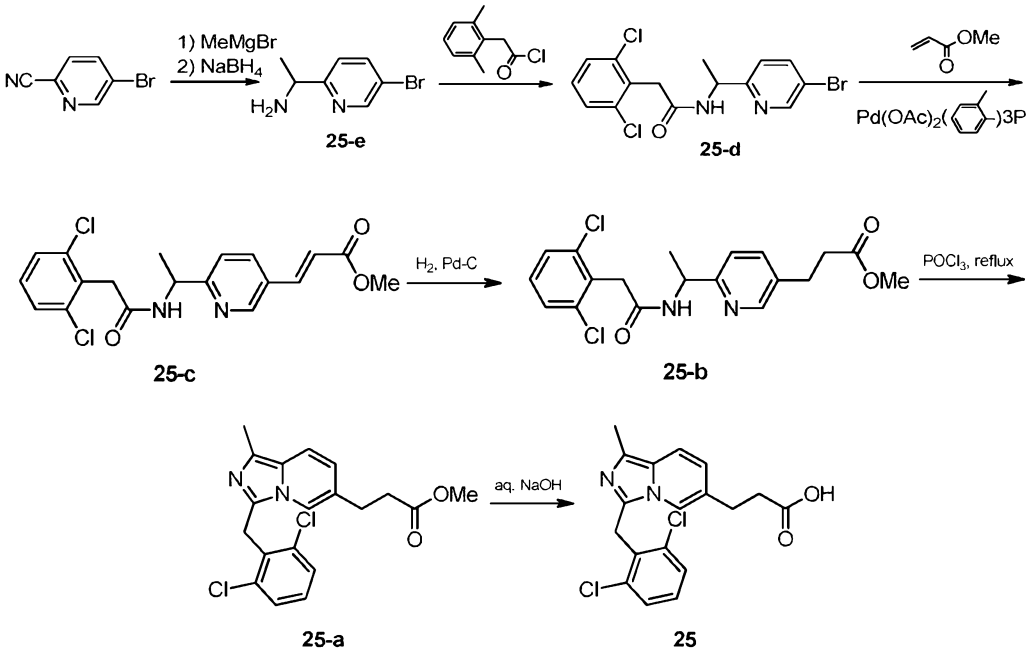
Synthesis of compound **24**

At room temperature, $LiOH•H_2O$ (26mg, 0.61mmol) was added to a mixed solution of compound **24-a** (89mg, 0.20mmol) in methanol (1mL), THF (1mL) and water (1mL). The mixture was stirred for 4hrs, concentrated under reduced pressure, followed by adding water (10mL) and EA (20mL). The aqueous phase was adjusted to pH=5-6 with 0.5M HCl aq. solution, solid turned out, the mixture was further stirred for 30mins and filtered. The solid was washed with water (10mL), dried under vacuum to give white solid **24** (65 mg, yield 78%). LC-MS (ESI): m/z = 411 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 12.69 (s, 1H), 9.41 (s, 1H), 8.52 (s, 1H), 8.33 (d, J=8.0 Hz, 1H), 8.31 (d, J=8.0 Hz, 1H), 8.19 (d, J=8.0 Hz, 1H), 7.83 (m, 1H), 7.69 (d, J=8.0 Hz, 1H), 7.57 (m, 1H), 7.51 (d, J=8.0 Hz, 1H), 7.39 (d, J=8.0 Hz, 1H), 2.51 (m, 1H), 2.01 (m, 3H), 1.71 (m, 2H) ppm.

Embodiment 25

3-{3-[(2, 6-dichlorophenyl)methyl]-1-methylimidazole[1,5-a]pyridine-6-yl}propionic acid (Compound **25**)



Synthesis of compound **25-e**

At 0□, a solution of 3M methyl magnesium bromide in THF (2.09mL, 6.28mmol) was added into a solution of 5-bromo-2-cyanopyridine (1.0g, 5.46mmol) in anhydrous

THF (10mL). The mixture was warmed to room temperature slowly, further stirred for 30mins, and followed by adding methanol (20mL), adding $NaBH_4$ (410mg, 10.93mmol) in portions. The mixture was further stirred for 10hrs, followed by adding water (10mL) and 2M NaOH aq. solution (10mL) in turn, being extracted with EA (50mL×3). The organic phases were combined, washed in turn with water (20mL×3) and saturated brine (20mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica preparative plate (PE:EA = 1:1) to give white solid **25-e** (1.0g, yield 91%). LC-MS (ESI): m/z = 201 $[M+H]^+$.

Synthesis of compound **25-d**

At room temperature, oxalyl chloride (0.69g, 5.47mmol) and DMF (0.1mL) were added to a solution of 2,6-dichlorophenylacetic acid (1.02g, 4.97mmol) in DCM (10mL), the mixture was stirred for 2hrs and concentrated under reduced pressure. The residue was dissolved in DCM (10mL) again, at 0□, the above solution was slowly added to a solution of compound **25-e** (1.0g, 4.97mmol) and triethyl amine (1.39mL, 9.95mmol) in DCM (10mL). The mixture was warmed to room temperature and further stirred for 2hrs, followed by adding water (20mL), and being extracted with DCM (50mL×3). The organic phases were combined, washed in turn with water (20mL×3) and saturated brine (20mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified (PE:EA = 5:1) to give light yellow solid **25-d** (0.9g, yield 46%). LC-MS (ESI): m/z = 387 $[M+H]^+$.

Synthesis of compound **25-c**

Under N_2 atmosphere, methyl acrylate (0.186mL, 2.06mmol), palladium acetate (23.1mg, 0.1mmol), tris(*o*-methylphenyl)phosphine (62.7mg, 0.2mmol) and triethyl amine (0.28mL, 2mmol) were added to a solution of compound **25-d** (400mg, 1.03mmol) in DMF (5mL). The mixture was reacted in a microwave at 120□ for 10mins, cooled to room temperature, followed by adding water (15mL), being extracted with EA (30mL×3). The organic phase was washed in turn with water (20mL×3) and saturated brine (20mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 1:1) to give compound **25-c** (400mg, yield 98%). LC-MS (ESI): m/z = 393 $[M+H]^+$.

Synthesis of compound **25-b**

Under H_2 atmosphere (1 atm.), the Pd-C (50mg) was added to a solution of compound **25-c** (400mg, 1.02mmol) in ethanol (10mL). The mixture was stirred for 12hrs, filtered, and concentrated under reduced pressure to give compound **25-b** (350mg, yield 87%). The product was used directly for the next step without further purification. LC-MS (ESI): m/z = 393 $[M+H]^+$.

Synthesis of compound **25-a**

Compound **25-b** (350mg, 0.89mmol) was dissolved in phosphorus oxychloride (8mL), stirred at 110□ for 5hrs. The mixture was cooled to room temperature, added to ice water (20mL), followed by adding sodium carbonate solid to adjust pH=8, and then extracted with EA (30mL×3). The organic phases were in turn washed with water (20mL) and saturated brine (20mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 2:1) to give yellow oil **25-a** (150mg, yield 45%). LC-MS (ESI): m/z = 377 $[M+H]^+$.

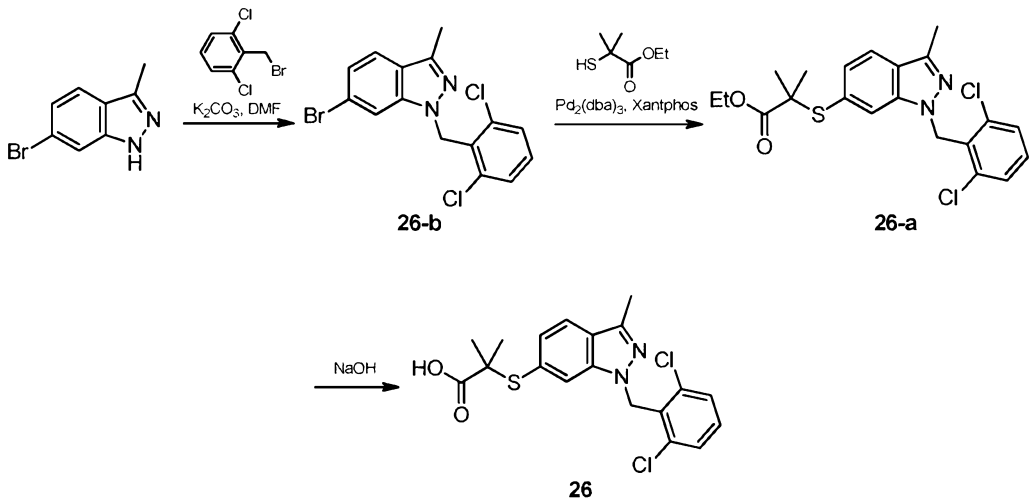
Synthesis of compound **25**

At room temperature, 20% NaOH aq. solution (2mL) was added to a solution of compound **25-a** (120mg, 0.32mmol) in methanol (2mL). The reaction solution was stirred for 2hrs, concentrated under reduced pressure to remove methanol, 6M HCl aq. solution was added to adjust pH=7, solid was precipitated and filtered out. The solid was washed with water (10mL), dried under vacuum to give white solid **25** (65mg, yield 56%). LC-MS (ESI): m/z = 363 $[M+H]^+$.

^{1}H-NMR (400MHz, CD_3OD) δ: 7.91 (s, 1H), 7.30-7.46 (m, 4H), 6.67 (d, J=9.6 Hz, 1H), 4.60 (s, 2H), 2.89 (t, J=7.6 Hz, 1H), 2.67 (t, J=7.6 Hz, 2H), 2.38 (s, 3H) ppm.

Embodiment 26

2-({1-[(2,6-dichlorophenyl)methyl]-3-methyl-1H-indazol-6-yl}thio)-2-methyl propionic acid (Compound **26**)



Synthesis of compound **26-b**

At room temperature, potassium carbonate (490mg, 3.55mmol) was added to a solution of 6-bromo-3-methyl-1H-indazole (500mg, 2.37mmol) and 2,6-dichlorobenzyl bromide (680mg, 2.84mmol) in DMF (5mL). The mixture was stirred for 12hrs, followed by adding water (10mL), being extracted with EA (20mL×3). The organic phases were combined, washed in turn with water (10mL)

and saturated brine (10mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 10:1) to give yellow oil **26-b** (400mg, yield 45%). LC-MS (ESI): m/z = 369 $[M+H]^+$.

Synthesis of compound **26-a**

Under N_2 atmosphere, tris(dibenzylidene indene acetone)dipalladium (25.5mg, 0.02mmol), 4,5-bis(diphenylphosphine)-9,9-dimethyloxacanthracene (31mg, 0.05mmol) and CuI (5.1mg, 0.02mmol) were added to a solution of compound **26-b** (100mg, 0.27mmol), ethyl 2-methyl-2-mercaptopropionate (0.04mL, 0.27mmol) and diisopropylethylamine (0.14mL, 0.81mmol) in dioxane (2mL). The mixture was reacted in a microwave at 125℃ for 1h, cooled to room temperature, concentrated under reduced pressure to remove dioxane. The residue was purified by silica preparative plate chromatography (PE:EA = 1:1) to give compound **26-a** (80mg, yield 67%). LC-MS (ESI): m/z = 437 $[M+H]^+$.

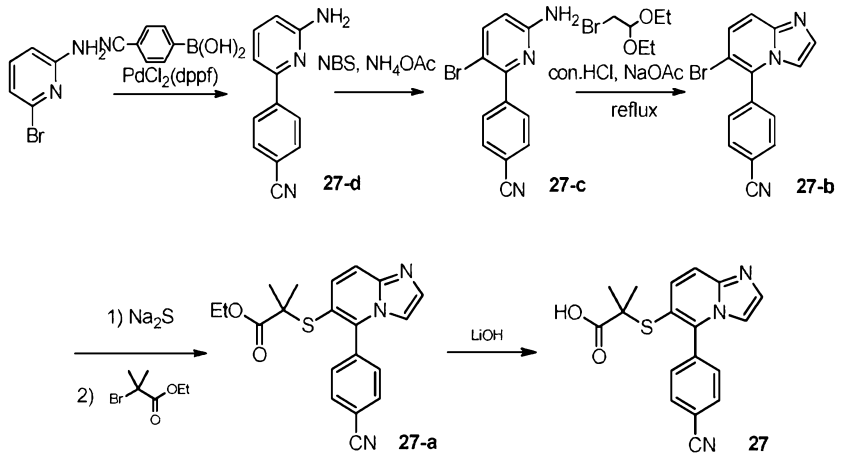
Synthesis of compound **26**

At room temperature, NaOH (72mg, 1.8mmol) was added to a mixed solution of compound **26-a** (80mg, 0.18mmol) in methanol (2mL), THF (2mL) and water (2mL). The mixture was stirred for 2hrs, adjusted to pH=7 by 2M HCl aq. solution, extracted with EA (20mL×3). The organic phases were washed in turn with water (10mL) and saturated brine (10mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give compound **26** (20mg, yield 27%). LC-MS (ESI): m/z = 409 $[M+H]^+$.

^{1}H-NMR (400MHz, CD_3OD) δ: 7.60 (s, 1H), 7.52 (d, J=8.0 Hz, 1H), 7.34 (m, 2H), 7.24 (m, 1H), 7.13 (d, J=8.0 Hz, 1H), 5.64 (s, 1H), 2.37 (s, 3H), 1.35 (s, 6H) ppm.

Embodiment 27

2-{[5-(4-Cyanophenyl)imidazo[1,2-a]pyridin-6-yl]thio}-2-methyl propionic acid (Compound **27**)



Synthesis of compound **27-d**

Under N_2 atmosphere, 2-amino-6-bromopyridine (500mg, 2.89mmol), 4-cyanophenylboronic acid (510mg, 3.47mmol) and sodium carbonate (920mg, 8.67mmol) were suspended in DMF (10mL) and water (5mL), [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (240mg, 0.29mmol) was added. The mixture was stirred at 80℃ for 2hrs, cooled to room temperature, followed by adding water (15mL), being extracted with EA (30mL×3). The organic phase was washed in turn with water (20mL) and saturated brine (20mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA=2:1) to give compound **27-d** (400mg, yield 71%). LC-MS (ESI): m/z = 196 $[M+H]^+$.

Synthesis of compound **27-c**

At 0℃, N-bromosuccinimide (360mg, 2.05mmol) was added to a solution of compound **27-d** (400mg, 2.05mmol) and ammonium acetate (160mg, 2.05mmol) in CH_3CN (10mL). The reaction solution was warmed to room temperature and stirred for 12hrs, and concentrated under reduced pressure to remove solvent. The residue was purified by silica column chromatography (PE:EA=2:1) to give compound **27-c** (500mg, yield 89%). LC-MS (ESI): m/z = 274 $[M+H]^+$.

Synthesis of compound **27-b**

A solution of sodium acetate (42mg, 0.78mmol) and 2-bromo-1,1-diethoxyethane (0.28mL, 1.8mmol) in conc. HCl aqueous solution (0.1mL) and water (0.6mL) was heated to 110℃ and refluxed for 10mins. The reaction solution was cooled to 60℃, the solution was added to a solution of compound **27-b** (250mg, 0.91mmol) and sodium acetate (83mg, 1.55mmol) in 60% ethanol aqueous solution (10mL). The mixture was heated to 100℃ and refluxed for 2.5hrs, cooled to room temperature, and concentrated under reduced pressure. The residue was added to ice water (5mL), adjusted to pH=7 with saturated sodium bicarbonate solution, extracted with EA (30mL×3). The organic phase was washed in turn with water (20mL) and saturated brine (20mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified with silica column chromatography (PE:EA = 1:1) to give compound **27-b** (150mg, yield 55%). LC-MS (ESI): m/z = 298 $[M+H]^+$.

Synthesis of compound **27-a**

$Na_2S \cdot 9H_2O$ (182mg, 0.75mmol) was added to a solution of compound **27-b** (180mg, 0.5mmol) in N-methyl pyrrolidone (2mL). The reaction solution was reacted in a microwave at 150℃ for 1h, cooled to room temperature, followed by adding ethyl 2-bromo-2-methylpropionate (100mg, 0.67mmol) and potassium carbonate (90mg, 0.67mmol). The mixture was stirred at 50 for 2hrs, cooled to room temperature, followed by adding water (5mL), being extracted with EA (10mL). The organic phase was washed in turn with water (10mL) and saturated brine (10mL), dried over

anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 1:1) to give compound **27-a** (10mg, yield 8%). LC-MS (ESI): m/z = 366 $[M+H]^+$.

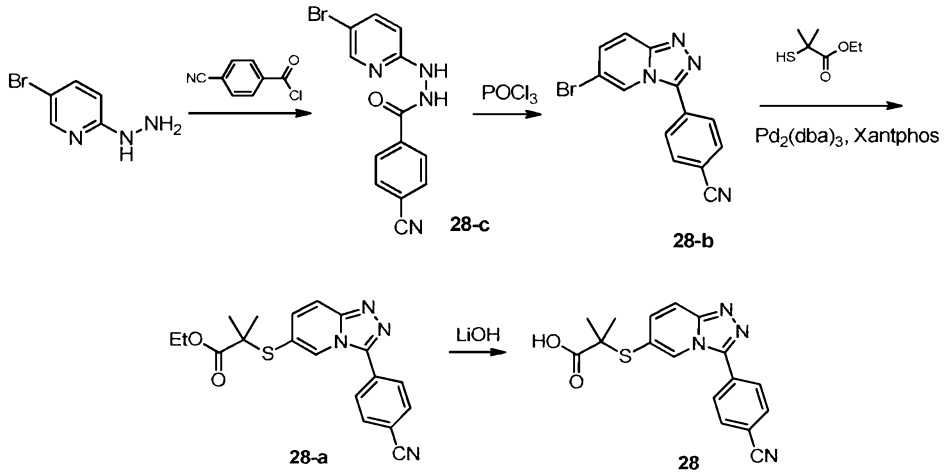
Synthesis of compound **27**

At room temperature, LiOH (13.1mg, 0.55mmol) was added to a solution of compound **27-a** (10mg, 0.02mmol) in methanol (2mL), THF (2mL) and water (4mL). The mixture was stirred for 2hrs, adjusted to pH=7 with 2M HCl aq. solution, extracted with EA (20mL×3). The organic phase was in turn washed with water (10mL) and saturated brine (10mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give compound **27** (5mg, yield 54%). LC-MS (ESI): m/z = 338 $[M+H]^+$.

^{1}H-NMR (400MHz, CD_3OD) δ: 7.97 (d, J=8.0 Hz, 1H), 7.59-7.70 (m, 5H), 7.26 (s, 1H), 1.38 (s, 6H) ppm.

Embodiment 28

2-{[3-(4-Cyanophenyl)-[1,2,4]triazo[4,3-a]pyridin-6-yl]thio}-2-methyl propionic acid (Compound **28**)



Synthesis of compound **28-c**

At room temperature, a mixture of 2-hydrazino-5-bromopyridine (1.0g, 5.3mmol), 4-cyanobenzoyl chloride (0.97g, 5.85mmol), triethyl amine (0.64g, 0.88mmol) and DCM (15mL) was stirred for 12hrs, and filtered. The solid was washed with DCM (5mL), dried under vacuum to give yellow solid **28-c** (1.13g, yield 67%). The produce was used directly for the next step without further purification. LC-MS (ESI): m/z = 319 $[M+H]^+$.

Synthesis of compound **28-b**

Compound **28-c** (1.03g, 3.25mmol) was added to $POCl_3$ (10mL). The mixture was stirred at 100℃ for 12hrs, cooled to room temperature, and concentrated under

reduced pressure. Saturated $NaHCO_3$ aq. solution was added to the residue to adjust pH=7, the mixture was extracted with EA (50mL×2). The organic phase was in turn washed with water (30mL) and saturated $NaHCO_3$ aq. solution (30mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give compound **28-b** (0.85g, yield 80%). The product was used directly for the next step without further purification. LC-MS (ESI): m/z = 301 $[M+H]^+$.

Synthesis of compound **28-a**

Under N_2 atmosphere, tris(dibenzylidene indene acetone)dipalladium (54mg, 0.05mmol) and 4,5-bis(diphenylphosphine)-9,9-dimethyloxacanthracene (68mg, 0.11mmol) were added to a solution of compound **28-b** (350mg, 1.17mmol), ethyl 2-methyl-2-mercaptopropionate (208mg, 1.4mmol) and diisopropylethylamine (302mg, 2.34mmol) in dioxane (10mL). The mixture was reacted in a microwave at 110℃ for 1h, cooled to room temperature, concentrated under reduced pressure to remove dioxane. The residue was purified by silica preparative plate chromatography (PE:EA = 3:1-1:1) to give compound **28-a** (268mg, yield 55%). LC-MS (ESI): m/z = 367 $[M+H]^+$.

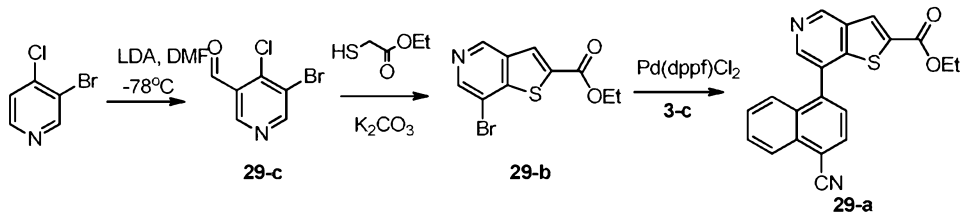
Synthesis of compound **28**

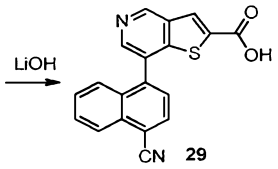
At room temperature, LiOH (51mg, 1.22mmol) was added to a solution of compound **28-a** (223mg, 0.61mmol) in methanol (2mL), THF (6mL) and water (2mL). The mixture was stirred for 3hrs, concentrated under reduced pressure, followed by adding water (10mL), being extracted with EA (30mL×2), the aqueous phase was adjusted to pH=5-6 with 2M HCl aq. solution and extracted with EA (30mL×2). The organic phases were combined, washed in turn with water (10mL) and saturated brine (10mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was recrystallized in EA (15mL) and PE (10mL) to give yellow solid **28** (108mg, yield 52%). LC-MS (ESI): m/z = 339 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 12.92 (s, 1H), 8.56 (s, 1H), 8.12 (m, 4H), 7.92 (d, J=9.8 Hz, 1H), 7.45 (d, J=9.4 Hz, 1H), 1.44 (s, 6H) ppm.

Embodiment 29

7-(4-Cyanonaphthalen-1-yl)thieno[3,2-c]pyridin-2-formic acid (Compound **29**)





29

Synthesis of compound **29-c**

Under N_2 atmosphere, at -78℃, a solution of 2.5M *n*-butyl lithium in *n*-hexane (24mL, 60mmol) was slowly added to a solution of diisopropylamine (6.1g, 60mmol) in anhydrous THF (100mL). The mixture was stirred for 15mins, followed by adding a solution of 3-bromo-4-chloropyridine (9.6g, 50mmol) in anhydrous THF (100mL), further stirred for 1h, followed by adding anhydrous DMF (10mL) and stirred for 30mins. The mixture was slowly warmed to room temperature, followed by adding saturated NH_4Cl aq. solution (300mL), the mixture was extracted with EA (300mL×3). The organic phases were combined, washed in turn with water (100mL) and saturated brine (100mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica preparative plate chromatography (PE:EA = 2:1-1:1) to give light yellow solid **29-c** (5.9g, yield 54%).

^{1}H-NMR (400MHz, $CDCl_3$) δ: 10.44 (s, 1H), 8.80 (s, 1H), 7.67 (s, 1H) ppm.

Synthesis of compound **29-b**

Ethyl mercaptoacetate (2.4g, 20mmol) and potassium carbonate (3.0g, 24mmol) were added to a solution of compound **29-c** (4.4g, 20mmol) in DMF (40mL). The mixture was heated to 45℃ and stirred for 12hrs, cooled to room temperature, followed by adding ice water (200mL), solid was precipitated and filtered out. The solid was washed with water (100mL×3) and dried under vacuum to give white solid **29-b** (5.1g, yield 89.5%). The product was used directly for the next step without further purification. LC-MS (ESI): m/z = 286 $[M+H]^+$.

Synthesis of compound **29-a**

Under N_2 atmosphere, compound **29-b** (285mg, 1mmol), compound **3-c** (279mg, 1mmol) and sodium carbonate (212mg, 2mmol) were suspended in dioxane (6mL) and water (2mL), [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (73mg, 0.1mmol) was added. The mixture was stirred at 80℃ for 3hrs, cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica preparative plate (PE:EA = 2:1) to give compound **29-a** (190mg, yield 53%). LC-MS (ESI): m/z = 359 $[M+H]^+$.

Synthesis of compound **29**

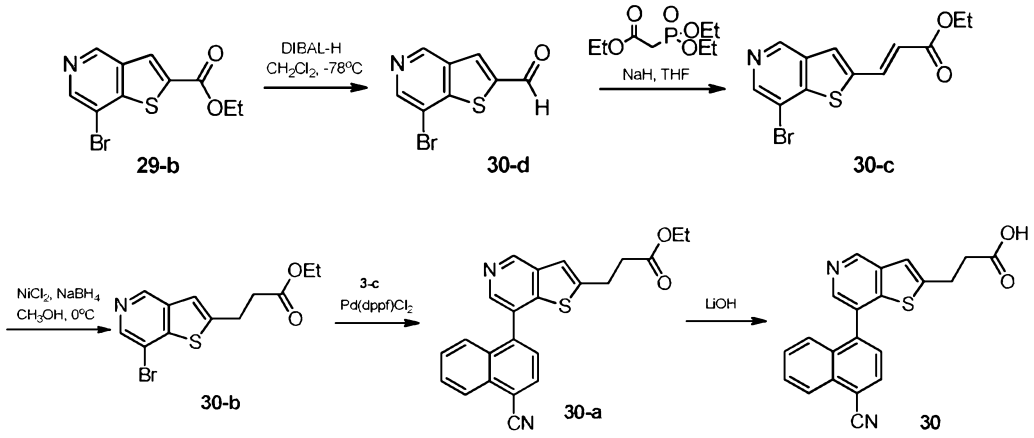
At room temperature, LiOH (41mg, 1mmol) was added to a solution of compound **29-a** (190mg, 0.53mmol) in methanol (3mL), THF (3mL) and water (3mL). The mixture was stirred for 1h, adjusted to pH=5-6 with 2M HCl aq. solution, solid was precipitated and filtered out. The solid was washed with water (10mL), dried under

vacuum to give light yellow solid **29** (130mg, yield 74%). LC-MS (ESI): m/z = 331 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 9.42 (s, 1H), 8.64 (s, 1H), 8.40 (s, 1H), 8.35 (d, J=8.0 Hz, 1H), 8.29 (d, J=8.0 Hz, 1H), 7.90 (m, 2H), 7.66 (s, 2H) ppm.

Embodiment 30

3-[7-(4-Cyanonaphthalen-1-yl)thieno[3,2-c]pyridin-2-yl]propionic acid (Compound **30**)



Synthesis of compound **30-d**

At -78℃, a solution of 1.0M diisobutylaluminum hydride in DCM (58mL, 58mmol) was slowly added to a solution of compound **29-b** (5.7g, 20mmol) in DCM (50mL). The mixture was stirred for 1h, warmed to room temperature, followed by adding saturated NH_4Cl aq. solution (300mL). The organic phase was seperated, the aqueous phase was extracted with DCM (50mL×3). The organic phases were combined, washed in turn with water (50mL) and saturated brine (50mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 3:1) to give light yellow solid **30-d** (4g, yield 83%). LC-MS (ESI): m/z = 242 $[M+H]^+$.

Synthesis of compound **30-c**

At 0℃, triethyl phosphonoacetate (2.82mL, 10mmol) and sodium hydride (0.48g, 12mmol) were respectively added to a solution of compound **30-d** (2.42g, 10mmol) in THF (50mL). The mixture was further stirred for 1h, warmed to room temperature, followed by adding saturated NH_4Cl aq. solution (300mL), the mixture was extracted with EA (50mL×3). The organic phases were combined, washed in turn with water (30mL×3) and saturated brine (30mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 5:1) to give light yellow solid **30-c** (2g, yield 64%). LC-MS (ESI): m/z =312 $[M+H]^+$.

Synthesis of compound **30-b**

At 0℃, $NaBH_4$ (0.25g, 6.4mmol) was slowly added to a solution of compound **30-c** (2.0g, 6.4mmol) and NiCl (0.82g, 6.4mmol) in methanol (50mL). The mixture was stirred for 3hrs, warmed to room temperature, followed by adding NH_4Cl aq. solution (300mL), the mixture was extracted with EA (100mL×3). The organic phases were combined, washed in turn with water (50mL×3) and saturated brine (50mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 4:1) to give light yellow solid **30-b** (1.6g, yield 80%). LC-MS (ESI): m/z =314 $[M+H]^+$.

Synthesis of compound **30-a**

Under N_2 atmosphere, compound **30-b** (155mg, 0.5mmol), compound **3-c** (140mg, 0.5mmol) and sodium carbonate (106mg, 1mmol) were suspended in dioxane (4mL) and water (1mL), [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (40mg, 0.05mmol) was added. The mixture was stirred at 80℃ for 3hrs, cooled to room temperature and concentrated under reduced pressure. The residue was filtered through celite, the filtrate cake was washed with EA (30mL). The filtrate was washed in turn with water (10mL×3) and saturated brine (10mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 1:1) to give compound **30-b** (120mg, yield 62%). LC-MS (ESI): m/z = 387 $[M+H]^+$.

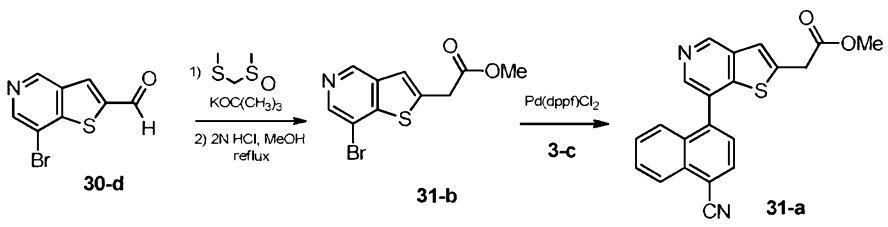
Synthesis of compound **30**

At room temperature, LiOH (42mg, 1mmol) was added to a solution of compound **30-a** (120mg, 0.31mmol) in methanol (1mL), THF (4mL) and water (1mL). The mixture was stirred for 1h, adjusted to pH=5-6 by 2M HCl aq. solution, solid was precipitated and filtered out. The solid was washed with water (10mL), dried under vacuum to give white solid **30** (93mg, yield 84%). LC-MS (ESI): m/z = 359 $[M+H]^+$.

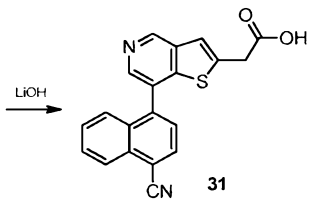
^{1}H-NMR (400MHz, DMSO-d6) δ: 9.15 (s, 1H), 8.42 (s, 1H), 8.32 (d, J=8.0 Hz, 1H), 8.27 (d, J=8.0 Hz, 1H), 7.90 (m, 1H), 7.81 (m, 1H), 7.68 (m, 2H), 3.10 (t, J=8.0 Hz, 2H), 3.07 (d, J=8.0 Hz, 2H) ppm.

Embodiment 31

2-[7-(4-Cyanonaphthalen-1-yl)thieno[3,2-c]pyridin-2-yl]acetic acid (Compound **31**)



30-d 31-b 31-a



31

Synthesis of compound **31-b**

NaOH (40mg, 1mmol) was added to a solution of methyl(methylthiomethyl)sulfoxide (18mg, 1.5mmol) and compound **30-d** (240mg, 1mmol) in THF (6mL). The mixture was heated to 80℃ and stirred for 4hrs, cooled to room temperature, concentrated under reduced pressure to remove the solvent. The residue was added to a solution of 2M HCl in methanol (10mL), refluxed for 1h, concentrated under reduced pressure. The residue was added to saturated $NaHCO_3$ aq. solution (10mL), extracted with EA (10mL×3). The organic phases were combined, washed in turn with water (10mL×3) and saturated brine (10mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 4:1) to give compound **31-b** (0.15g, yield 88%). LC-MS (ESI): m/z =285 $[M+H]^+$.

Synthesis of compound **31-a**

Under N_2 atmosphere, compound **31-b** (87mg, 0.3mmol), compound **3-c** (84mg, 0.3mmol) and sodium carbonate (60mg, 0.6mmol) were suspended in dioxane (4mL) and water (1mL), [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (25mg, 0.03mmol) was added. The mixture was stirred at 80℃ for 3hrs, cooled to room temperature and concentrated under reduced pressure. The residue was filtered through celite, the filtrate cake was washed with EA (30mL). The filtrate was washed in turn with water (20mL×3) and saturated brine (10mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 1:1) to give compound **31-a** (76mg, yield 71%). LC-MS (ESI): m/z = 359 $[M+H]^+$.

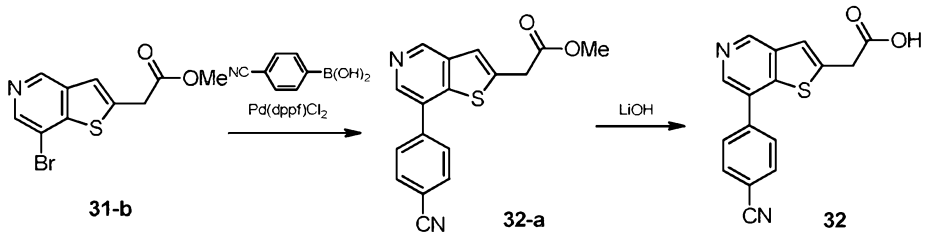
Synthesis of compound **31**

At room temperature, LiOH (42mg, 1mmol) was added to a solution of compound **31-a** (120mg, 0.31mmol) in methanol (1mL), THF (4mL) and water (1mL). The mixture was stirred for 1h, followed by adding 2M HCl aq. solution to adjust pH=5-6, solid was precipitated and filtered out. The solid was washed with water (10mL), dried under vacuum to give white solid **31** (44mg, yield 64%). LC-MS (ESI): m/z = 345 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 9.30 (s, 1H), 8.55 (s, 1H), 8.36 (d, J=7.6 Hz, 1H), 8.29 (d, J=7.6 Hz, 1H), 7.90 (m, 2H), 7.72 (m, 3H), 4.04 (s, 2H) ppm.

Embodiment 32

2-[7-(4-Cyanophenyl)thieno[3,2-c]pyridin-2-yl]acetic acid (Compound **32**)



Synthesis of compound **32-a**

Under N_2 atmosphere, compound **31-b** (140mg, 0.5mmol), 4-cyanophenyl boronic acid (75mg, 0.5mmol) and sodium carbonate (60mg, 0.6mmol) were suspended in dioxane (4mL) and water (10mL), [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (25mg, 0.03mmol) was added. The mixture was stirred at 80℃ for 3hrs, cooled to room temperature and concentrated under reduced pressure. The residue was filtered through celite, the filtrate cake was washed with EA (30mL). The filtrate was in turn washed with water (20mL×3) and saturated brine (10mL), dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 1:1) to give compound **32-b** (86mg, yield 56%). LC-MS (ESI): m/z = 309 $[M+H]^+$.

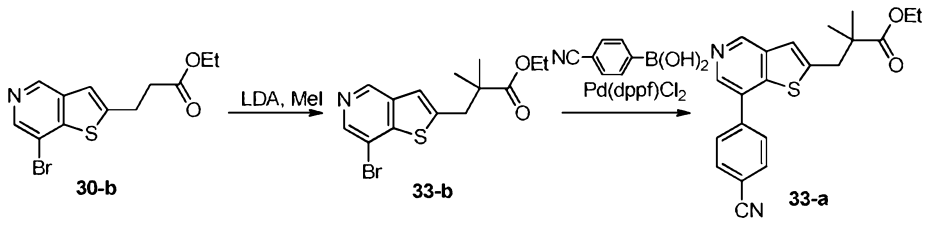
Synthesis of compound **32**

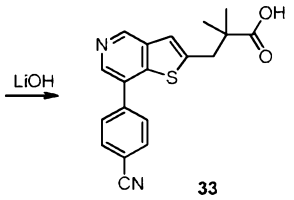
At room temperature, LiOH (42mg, 1mmol) was added to a solution of compound **32-a** (86mg, 0.28mmol) in methanol (1mL), THF (4mL) and water (1mL). The mixture was stirred for 1h, followed by adding 2M HCl aq. solution (2mL), solid was precipitated and filtered out. The solid was washed with water (10mL), dried under vacuum to give white solid **32** (28mg, yield 34%). LC-MS (ESI): m/z = 295 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 12.87 (s, 1H), 9.11 (s, 1H), 8.64 (s, 1H), 8.06 (d, J=7.6 Hz, 1H), 7.91 (d, J=7.6 Hz, 1H), 7.57 (s, 1H), 4.06 (s, 2H) ppm.

Embodiment 33

3-[7-(4-Cyanophenyl)thieno[3,2-c]pyridin-2-yl]-2,2-dimethylpropionic acid (Compound **33**)





33

Synthesis of compound **33-b**

Under N_2 atmosphere, at -78℃, a solution of 2.5M *n*-butyl lithium in *n*-hexane (2.0mL, 5mmol) was slowly added to a solution of diisopropylamine (505mg, 5mmol) in anhydrous THF (10mL). The mixture was stirred for 15mins, added dropwise to a solution of compound **30-b** (630mg, 2mmol) in anhydrous THF (10mL), stirred for 2hrs, followed by adding CH_3I (720mg, 5mmol) and the mixture was further stirred for 3hrs. The mixture was slowly warmed to room temperature, then added to saturated NH_4Cl aq. solution (30mL), extracted with EA (30mL×3). The organic phases were combined, washed in turn with water (10mL) and saturated brine (10mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica preparative plate chromatography (PE:EA = 2:1-1:1) to give light yellow liquid **33-b** (310mg, yield 45%).

Synthesis of compound **33-a**

Under N_2 atmosphere, compound **33-b** (310mg, 0.91mmol), 4-cyanophenyl boronic acid (140mg, 0.91mmol) and sodium carbonate (212mg, 2mmol) were suspended in dioxane (4mL) and water (1mL), [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (40mg, 0.05mmol) was added. The mixture was stirred at 80℃ for 3hrs, and then cooled to room temperature, concentrated under reduced pressure to remove the solvent. The residue was filtered through celite, the filtrate cake was washed with EA (30mL). The filtrate was in turn washed with water (20mL×3) and saturated brine (10mL), dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 1:1) to give yellow liquid **33-a** (76mg, yield 23%). LC-MS (ESI): m/z = 365 $[M+H]^+$.

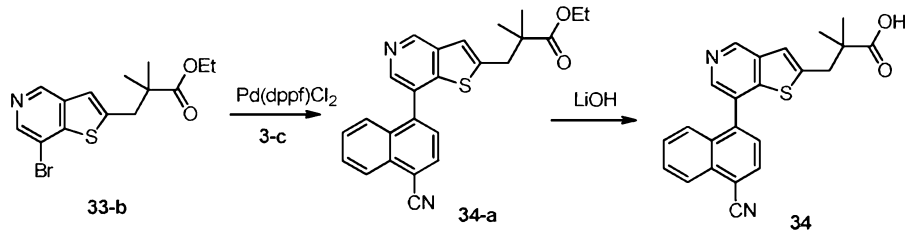
Synthesis of compound **33**

At room temperature, LiOH (42mg, 1mmol) was added to a solution of compound **33-a** (73mg, 0.19mmol) in methanol (1mL), THF (4mL) and water (1mL). The mixture was stirred for 1h, followed by adding 2M HCl aq. solution (2mL) and water (1mL), solid was precipitated and filtered out. The solid was washed with water (5mL), dried under vacuum to give white solid **33** (39mg, yield 61%). LC-MS (ESI): m/z = 337 $[M+H]^+$.

^{1}H-NMR (400MHz, CD_3OD) δ: 9.34 (s, 1H), 8.64 (s, 1H), 8.02 (s, 4H), 7.71 (s, 1H), 7.57 (s, 1H), 3.34 (s, 2H), 1.26 (s, 6H) ppm.

Embodiment 34

3-[7-(4-Cyanonaphthalen-1-yl)thieno[3,2-c]pyridin-2-yl]-2,2-dimethylpropionic acid (Compound **34**)



Synthesis of compound **34-a**

Under N_2 atmosphere, compound **33-b** (230mg, 0.7mmol), compound **3-c** (280mg, 0.5mmol) and sodium carbonate (150mg, 1.4mmol) were suspended in dioxane (4mL) and water (1mL), [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (40mg, 0.05mmol) was added. The mixture was stirred at 80℃ for 3hrs, cooled to room temperature and concentrated under reduced pressure. The residue was filtered through celite, the filtrate cake was washed with EA (30mL). The filtrate was in turn washed with water (20mL×3) and saturated brine (10mL), dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure. The residue was prepared by HPLC (mobile phase: 10mM NH_4HCO_3 aq. solution: acetonitrile =35%-45%) to give compound **34-a** (53mg, yield 18%). LC-MS (ESI): m/z = 401 $[M+H]^+$.

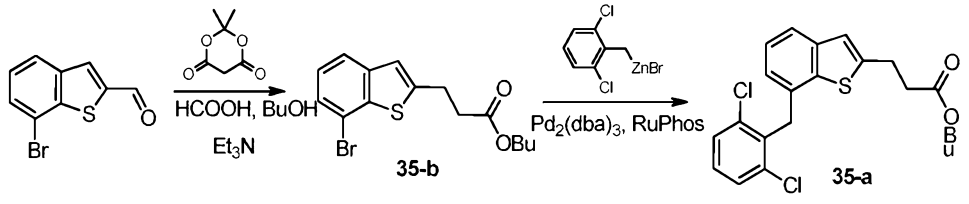
Synthesis of compound **34**

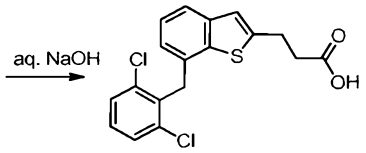
At room temperature, LiOH (42mg, 1mmol) was added to a solution of compound **34-a** (41mg, 0.1mmol) in methanol (1mL), THF (4mL) and water (1mL). The mixture was stirred for 1h, followed by adding 2M HCl aq. solution (2mL) and water (1mL), solid was precipitated and filtered out. The solid was washed with water (5mL), dried under vacuum to give white solid **34** (16mg, yield 41%). LC-MS (ESI): m/z = 387 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 12.41 (s, 1H), 9.19 (s, 1H), 8.43 (s, 1H), 8.32 (d, J=7.6 Hz, 1H), 8.27 (d, J=7.6 Hz, 1H), 7.88 (m, 2H), 7.65 (m, 2H), 7.47 (s, 1H), 3.14 (s, 2H), 1.12 (s, 6H) ppm.

Embodiment 35

3-{7-[(2,6-Dichlorophenyl)methyl]-1-benzothiophene-2-yl}propionic acid (Compound **35**)





35

Synthesis of compound **35-b**

At 0℃, triethyl amine (3.6mL) was slowly added to a mixture of *n*-butanol (10mL) and formic acid (1mL). The mixture was stirred for 10mins, followed by adding 7-bromo-1-benzothiophene-2-carbaldehyde (241mg, 1mmol) and 2,2-dimethyl-1,3-dioxane-4,6-dione (216mg, 1.5mmol). The mixture was heated to reflux for 8hrs, cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 15:1) to give compound **35-b** (200mg, yield 59%). LC-MS (ESI): m/z = 341 $[M+H]^+$.

Synthesis of compound **35-a**

Under N_2 atmosphere, tris(dibenzylidene indene acetone)dipalladium (54mg, 0.05mmol) and 4,5-bis(diphenylphosphine)-9,9-dimethyloxacanthracene (94mg, 0.02mmol) and a solution of 0.4M 2,6-dichlorobenzyl zinc bromide in THF solution (2.5mL, 1mmol) were added to a solution of compound **35-b** (170mg, 0.5mmol) in anhydrous THF (10mL). The mixture was reacted at 60℃ for 16hrs, cooled to room temperature, concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 10:1) to give compound **35-a** (170mg, yield 80%). LC-MS (ESI): m/z = 421 $[M+H]^+$.

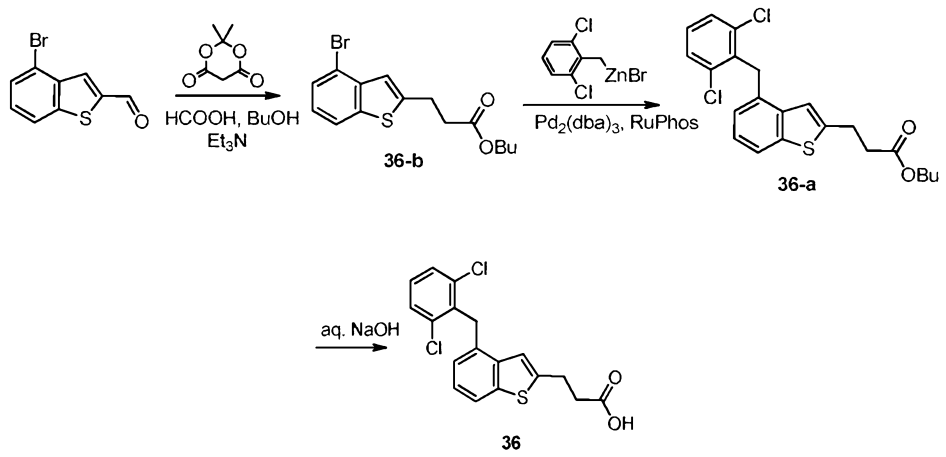
Synthesis of compound **35**

At room temperature, 1.0M NaOH aq. solution (3mL) was added to a solution of compound **35-a** (84mg, 0.2mmol) in methanol (4mL) and THF (8mL). The mixture was stirred for 16hrs, and concentrated under reduced pressure. The residue was adjusted to pH=3 with 1M HCl aq. solution, solid was precipitated and filtered out. The solid was washed with water (5mL), dried under vacuum to give white solid **35** (60mg, yield 82%). LC-MS (ESI): m/z = 365 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 12.35 (s, br. 1H), 7.61 (d, J=8.0 Hz, 1H), 7.58 (d, J=8.0 Hz, 2H), 7.42 (t, J=8.0 Hz, 1H), 7.25 (s, 1H), 7.21 (t, J=8.0 Hz, 1H), 6.47 (d, J=7.2 Hz, 1H), 4.35 (s, 2H), 3.16 (t, J=7.2 Hz, 2H), 2.71 (t, J=7.2 Hz, 2H) ppm.

Embodiment 36

3-{4-[(2,6-Dichlorophenyl)methyl]-1-benzothiophene-2-yl}propionic acid (Compound **36**)



Synthesis of compound **36-b**

At 0℃, triethyl amine (3.6mL) was slowly added to a mixture of *n*-butanol (10mL) and formic acid (1mL). The mixture was stirred for 10mins, followed by adding 4-bromo-1-benzothiophene-2-carbaldehyde (241mg, 1mmol) and 2,2-dimethyl-1,3-dioxane-4,6-dione (216mg, 1.5mmol). The mixture was heated to reflux for 8hrs, cooled to room temperature, concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 15:1) to give compound **36-b** (221mg, yield 65%). LC-MS (ESI): m/z = 341 $[M+H]^+$.

Synthesis of compound **36-a**

Under N_2 atmosphere, tris(dibenzylidene indene acetone)dipalladium (47mg, 0.05mmol) and 2-dicyclohexylphospho-2',6'-diisopropoxy-1,1'-biphenyl (94mg, 0.02mmol) and a solution of 0.4M 2,6-dichlorobenzyl zinc bromide in THF solution (2.5mL, 1mmol) were added to a solution of compound **36-b** (170mg, 0.5mmol) in anhydrous THF (10mL). The mixture was reacted at 60℃ for 16hrs, cooled to room temperature, concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 10:1) to give compound **36-a** (180mg, yield 86%). LC-MS (ESI): m/z = 421 $[M+H]^+$.

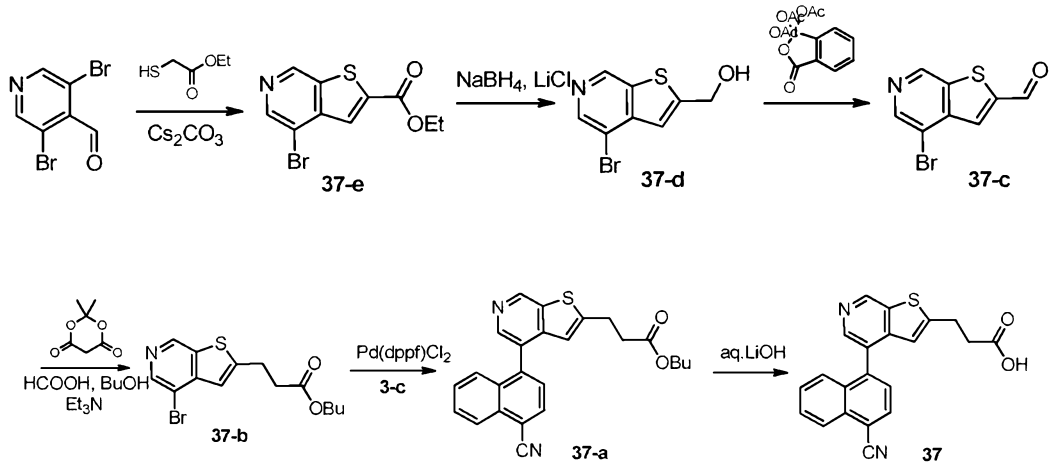
Synthesis of compound **36**

At room temperature, a solution of 1.0M NaOH aq. solution (3mL) was added to a solution of compound **36-a** (84mg, 0.2mmol) in methanol (4mL) and THF (8mL). The mixture was stirred for 16hrs, and concentrated under reduced pressure. The residue was adjusted to pH=3 with 1M HCl aq. solution, solid was precipitated and filtered out. The solid was washed with water (5mL), dried under vacuum to give white solid **36** (70mg, yield 95%). LC-MS (ESI): m/z = 365 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 12.30 (s, br. 1H), 7.73 (d, J=8.0 Hz, 1H), 7.57 (d, J=8.0 Hz, 2H), 7.51 (s, 1H), 7.41 (t, J=8.0 Hz, 1H), 7.13 (t, J=8.0 Hz, 1H), 6.41 (d, J=7.2 Hz, 1H), 4.54 (s, 2H), 3.18 (t, J=7.2 Hz, 2H), 2.72 (t, J=7.2 Hz, 2H) ppm.

Embodiment 37

3-[4-[(4-Cyanonaphthalen-1-yl)thieno[2,3-c]pyridine-2-yl]propionic acid (Compound **37**)



Synthesis of compound **37-e**

Ethyl mercaptoacetate (1.81g, 15.1mmol) and cesium carbonate (6.0g, 18.6mmol) were added to a solution of 3,5-dibromo-4-pyridinecarboxaldehyde (4.0g, 15.1mmol) in THF (100mL). The mixture was stirred at 60℃ for 3hrs, cooled to room temperature, concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 15:1) to give compound **37-e** (3.7g, yield 85%). LC-MS (ESI): m/z = 286 $[M+H]^+$.

Synthesis of compound **37-d**

At 0℃, $NaBH_4$ (530mg, 13.9mmol) was added into a solution of compound **37-e** (1.0g, 3.48mmol), LiCl (590mg, 13.9mmol) in THF (40mL) and methanol (20mL). The mixture was warmed to room temperature and stirred for 4hrs, concentrated under reduced pressure. Water (40mL) and DCM (40mL) were added to the residue, the organic phase was seperated, aqueous phase was extracted with DCM (20mL×3). The organic phases were combined, washed in turn with water (20mL×3) and saturated brine (10mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give compound **37-d** (750mg, yield 89%). The product was used directly for the next step without further purification. LC-MS (ESI): m/z = 244 $[M+H]^+$.

Synthesis of compound **37-c**

At 0 ℃ , (1,1,1-triacetoxy)-1,1-dihydro-1,2-benzoiodooxol-3(1H)-one (1.39g, 3.27mmol) was added to a solution of compound **37-d** (750mg, 2.18mmol) in DCM (30mL). The reaction solution was warmed to room temperature and further stirred for 2hrs, followed by adding saturated sodium bicarbonate aq. solution (10mL) and saturated sodium thiosulfate aq. solution (10mL). The mixture was stirred for

10mins, organic phase was seperated. The organic phase was in turn washed with water (20mL×3) and saturated brine (20mL), dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 10:1) to give compound **37-c** (680mg, yield 91%). LC-MS (ESI): m/z = 342 $[M+H]^+$.

Synthesis of compound **37-b**

At 0℃, triethyl amine (3.6mL) was slowly added to a mixture of *n*-butanol (10mL) and formic acid (1mL). The mixture was stirred for 10mins, followed by adding compound **37-c** (300mg, 1.24mmol) and 2,2-dimethyl-1,3-dioxane-4,6-dione (300mg, 2.08mmol), refluxing for 8hrs. The mixture was cooled to room temperature, concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 12:1) to give compound **37-b** (280mg, yield 66%). LC-MS (ESI): m/z = 342 $[M+H]^+$.

Synthesis of compound **37-a**

Under N_2 atmosphere, compound **37-b** (120mg, 0.35mmol), compound **3-c** (110mg, 0.39mmol) and sodium carbonate (150mg, 1.4mmol) were suspended in ethylene glycol dimethyl ether (10mL) and water (1mL), [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (40mg, 0.05mmol) was added. The mixture was stirred at 75℃ for 16hrs, cooled to room temperature, and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 8:1) to give compound **37-a** (90mg, yield 62%). LC-MS (ESI): m/z = 415 $[M+H]^+$.

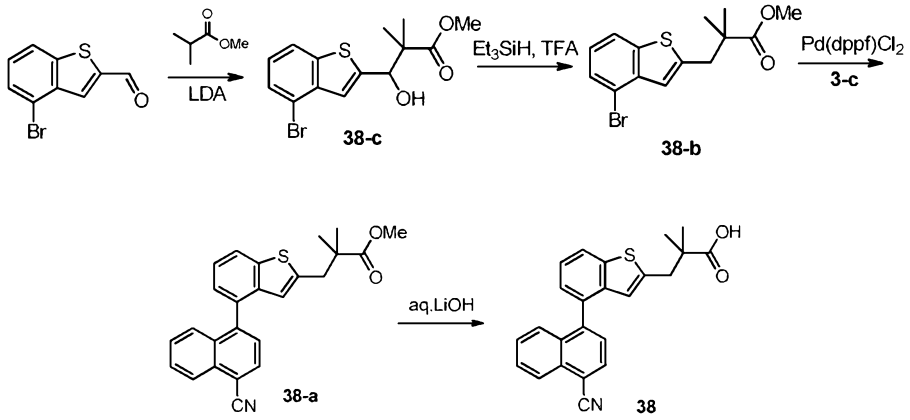
Synthesis of compound **37**

At room temperature, a solution of 1.0M LiOH aq. solution (2mL) was added to a solution of compound **37-a** (100mg, 0.25mmol) in methanol (10mL) and THF (10mL). The mixture was stirred for 16hrs, concentrated under reduced pressure. The residue was dissolved in water (10mL), adjusted to pH=3 with 1M citric acid aq. solution, solid was precipitated and filtered out. The solid was washed with water (5mL), dried under vacuum to give white solid **37** (50 mg, yield 55%). LC-MS (ESI): m/z = 359 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 12.30 (s, br. 1H), 9.30 (s, 1H), 8.44 (s, 1H), 8.32 (d, J=8.0 Hz, 1H), 8.26 (d, J=8.0 Hz, 1H), 7.87 (t, J=8.8 Hz, 1H), 7.73 (d, J=7.2 Hz, 1H), 7.68 (t, J=7.2 Hz, 1H), 7.57 (d, J=8.8 Hz, 1H), 6.74 (s, 1H), 3.10 (t, J=7.2 Hz, 2H), 2.59 (t, J=7.2 Hz, 2H) ppm.

Embodiment 38

3-[4-(4-Cyanonaphthalen-1-yl)-1-benzothiophen-2-yl]-2,2-dimethyl propionic acid (Compound **38**)



Synthesis of compound **38-c**

At -78℃, a solution of 1M lithium diisopropylamide in THF (3mL, 3mmol) was added slowly to a solution of methyl isobutyrate (714mg, 7.1mmol) in anhydrous THF (5mL). The mixture was stirred for 1h, followed by adding 4-bromo-1-benzothiophene-2-carbaldehyde (500mg, 2.38mmol). The mixture was slowly warmed to room temperature, followed by adding NH_4Cl aq. solution (20mL), being extracted with EA (30mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 10:1) to give compound **38-c** (700mg, yield 86%). LC-MS (ESI): m/z = 365 $[M+Na]^+$.

Synthesis of compound **38-b**

At 0℃, trifluoroacetic acid (2mL) was added to a solution of compound **38-c** (170mg, 0.5mmol) and triethylsilane (392mg, 4mmol) in DCM (10mL). The mixture was warmed to room temperature and further stirred for 16hrs, and then concentrated under reduced pressure. DCM (30mL) was added to the residue. The mixture was in turn washed with saturated sodium bicarbonate solution (10mL) and saturated brine (10mL), dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 10:1) to give compound **38-b** (150mg, yield 92%). LC-MS (ESI): m/z = 349 $[M+Na]^+$.

Synthesis of compound **38-a**

Under N_2 atmosphere, compound **38-b** (150mg, 0.46mmol), compound **3-c** (150mg, 0.54mmol) and sodium carbonate (300mg, 2.8mmol) were suspended in ethylene glycol dimethyl ether (12mL) and water (1mL), [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (50mg, 0.06mmol) was added. The mixture was stirred at 75℃ for 16hrs, cooled to room temperature, concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA = 4:1) to give compound **38-a** (105mg, yield 57%). LC-MS (ESI): m/z = 400 $[M+H]^+$.

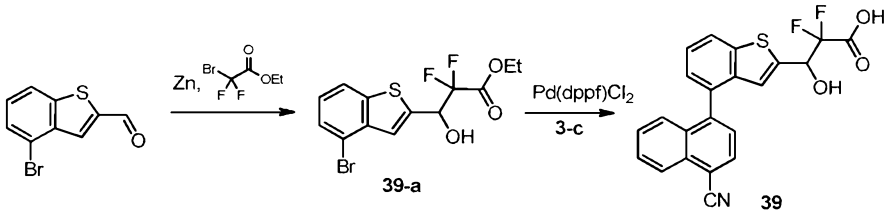
Synthesis of compound **38**

At room temperature, 1.0M LiOH aq. solution (2.5mL) was added to a solution of compound **38-a** (100mg, 0.25mmol) in methanol (10mL) and THF (10mL). The mixture was stirred for 16hrs, concentrated under reduced pressure. Water (10mL) was added to the residue. The mixture was adjusted to pH=3 with 1M citric acid aq. solution, solid was precipitated and filtered out. The solid was washed with water (5mL), dried under vacuum to give white solid **37** (80 mg, yield 83%). LC-MS (ESI): m/z = 408 $[M+Na]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 12.37 (s, br. 1H), 8.29 (d, J=8.0 Hz, 1H), 8.24 (d, J=8.0 Hz, 1H), 8.06 (d, J=8.0 Hz, 1H), 7.85 (t, J=8.0 Hz, 1H), 7.67 (d, J=8.0 Hz, 1H), 7.58 -7.62 (m, 2H), 7.49 (t, J=7.2 Hz, 2H), 7.36 (d, J=7.2 Hz, 1H), 2.99 (s, 2H), 1.06 (s, 6H) ppm.

Embodiment 39

3-[4-(4-Cyanonaphthalen-1-yl)-1-benzothiophen-2-yl]-2,2-difluoro-3-hydroxyl propionic acid (Compound **39**)



Synthesis of compound **39-a**

Under N_2 atmosphere, Zn powder (130mg, 2mmol) was added to a solution of 4-bromo-1-benzothiophene-2-carbaldehyde (500mg, 2.38mmol) and ethyl difluorobromoacetate (808mg, 4mmol) in anhydrous THF (10mL). The mixture was heated to 45 ℃ and further stirred for 16hrs, cooled to room temperature, followed by adding saturated NH_4Cl aq. solution (20mL), being extracted with EA (30mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 10:1) to give compound **39-a** (253mg, yield 71%). LC-MS (ESI): m/z = 388 $[M+Na]^+$.

Synthesis of compound **39**

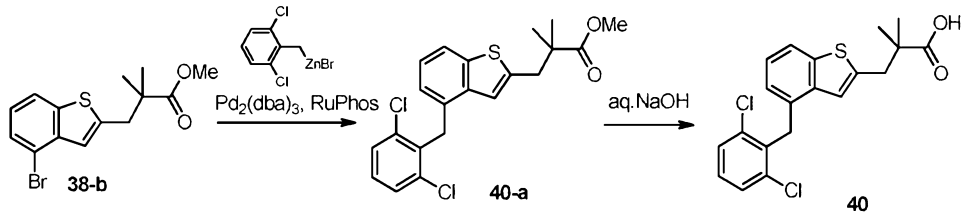
Under N_2 atmosphere, compound **39-a** (190mg, 0.5mmol), compound **3-c** (140mg, 0.5mmol) and sodium carbonate (106mg, 1mmol) were suspended in ethylene glycol dimethyl ether (20mL) and water (2mL), [1,1'-bis(diphenylphosphine)ferrocene] palladium dichloride (50mg, 0.06mmol) was added. The mixture was stirred at 75 ℃ for 16hrs, cooled to room temperature, concentrated under reduced pressure. Water (20mL) was added to the residue, the mixture was extracted with EA (30mL×3). The aqueous phase was adjusted to pH=3 with 1M HCl aqueous solution, solid was precipitated and filtered out. The solid was washed with water (5mL), dried under vacuum to give white solid **39** (120mg, yield 58%). LC-MS (ESI): m/z = 432

$[M+Na]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 8.30 (d, J=7.2 Hz, 1H), 8.25 (d, J=8.0 Hz, 1H), 8.14 (d, J=8.0 Hz, 1H), 7.85 (t, J=7.0 Hz, 1H), 7.65-7.68 (m, 1H), 7.60 -7.63 (m, 1H), 7.55 (t, J=8.0 Hz, 2H), 7.39-7.42 (m, 1H), 6.82 (d, J=16.8 Hz, 1H), 5.23-5.30 (m, 1H) ppm.

Embodiment 40

3-{4-[(2,6-Dichlorophenyl)methyl]-1-benzothiophen-2-yl]-2,2-dimethyl propionic acid (Compound **40**)



Synthesis of compound **40-a**

Under N_2 atmosphere, tris(dibenzylidene indene acetone)dipalladium (47mg, 0.05mmol) and 2-dicyclohexylphospho-2',6'-diisopropoxy-1,1'-biphenyl (94mg, 0.02mmol) and a solution of 0.4M 2,6-dichlorobenzyl zinc bromide in THF solution (2.5mL, 1mmol) were added to a solution of compound **38-b** (130mg, 0.4mmol) in anhydrous THF (10mL). The mixture was reacted at 60℃ for 16hrs, cooled to room temperature, concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 8:1) to give compound **40-a** (150mg, yield 72%). LC-MS (ESI): m/z = 407 $[M+H]^+$.

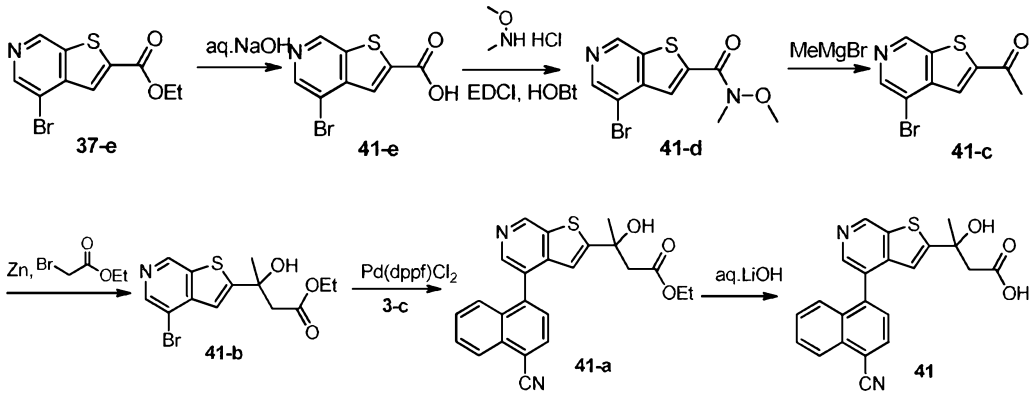
Synthesis of compound **40**

At room temperature, 1.0M NaOH aq. solution (1mL) was added to a solution of compound **40-a** (84mg, 0.2mmol) in methanol (5mL) and THF (5mL). The mixture was stirred for 16hrs, concentrated under reduced pressure. Water (10mL) was added to the residue, 1M HCl aq. solution was added to adjust pH=3, solid was precipitated and filtered out. The solid was washed with water (5mL), dried under vacuum to give white solid **40** (40mg, yield 50%). LC-MS (ESI): m/z = 393 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 12.49 (s, br. 1H), 7.73(d, J=8.0 Hz, 1H), 7.56 (d, J=8.0 Hz, 1H), 7.45 (s, 1H), 7.41 (t, J=8.0 Hz, 2H), 6.45 (d, J=10.4 Hz, 1H), 4.54 (s, 2H), 3.16 (s, 3H), 1.20 (s, 6H) ppm.

Embodiment 41

3-[4-(4-Cyanonaphthalen-1-yl)thieno[2,3-c]pyridin-2-yl]-3-hydroxyl butyric acid (Compound **41**)



Synthesis of compound **41-e**

At room temperature, 7.0M NaOH aq. solution (2mL) was added to a solution of compound **37-e** (1.0g, 3.5mmol) in methanol (4mL) and THF (10mL). The mixture was stirred for 2hrs, concentrated under reduced pressure. Water (30mL) was added to the residue, 1M citric acid aq. solution was added to adjust pH=3, solid was precipitated and filtered out. The solid was washed with water (5mL), dried under vacuum to give compound **41-e** (740mg, yield 82%).

Synthesis of compound **41-d**

At room temperature, N,O-dimethylhydroxylamine hydrochloride (546mg, 5.6mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.08g, 5.6mmol), 1-hydroxybenzotriazole (378mg, 2.8mmol) and triethyl amine (1.13g, 11.2mmol) were added to a solution of compound **41-e** (720mg, 2.8mmol) in DMF (10mL) and DCM (30mL). The mixture was stirred for 24hrs, concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 3:1) to give compound **41-d** (740mg, yield 82%). LC-MS (ESI): m/z = 301 $[M+H]^+$.

Synthesis of compound **41-c**

At -78 ℃, 3M methyl magnesium bromide in ether (1mL, 3mmol) was added to a solution of compound **41-d** (604mg, 2mmol) in anhydrous THF (20mL). The mixture was slowly warmed to room temperature and further stirred for 20mins, followed by adding saturated NH_4Cl aq. solution (5mL), water (20mL) and EA (30mL) in turn. The organic phase was seperated, the aqueous phase was extracted with EA (20mL×2). The organic phases were combined, concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA=8:1) to give compound **41-c** (740mg, yield 82%). LC-MS (ESI): m/z = 256 $[M+H]^+$.

Synthesis of compound **41-b**

Under N_2 atmosphere, Zn powder (65mg, 1mmol) was added to a solution of compound **41-c** (257mg, 1mmol) and ethyl bromoacetate (217mg, 1.3mmol) in anhydrous THF (10mL). The mixture was heated to 50 ℃ and further stirred for 16hrs, cooled to room temperature, followed by adding saturated NH_4Cl aq. solution

(5mL) and water (20mL) in turn. The mixture was extracted with EA (30mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA=4:1) to give compound **41-b** (281mg, yield 82%). LC-MS (ESI): m/z = 344 $[M+H]^+$.

Synthesis of compound **41-a**

Under N_2 atmosphere, compound **41-b** (137mg, 1mmol), compound **3-c** (140mg, 0.5mmol) and sodium carbonate (106mg, 1mmol) were suspended in ethylene glycol dimethyl ether (15mL) and water (1mL), [1,1'-bis(diphenylphosphine)ferrocene] palladium dichloride (50mg, 0.06mmol) was added. The mixture was stirred at 75 for 16hrs, cooled to room temperature, concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 3:1) to give compound **41-a** (160mg, yield 96%). LC-MS (ESI): m/z = 417 $[M+H]^+$.

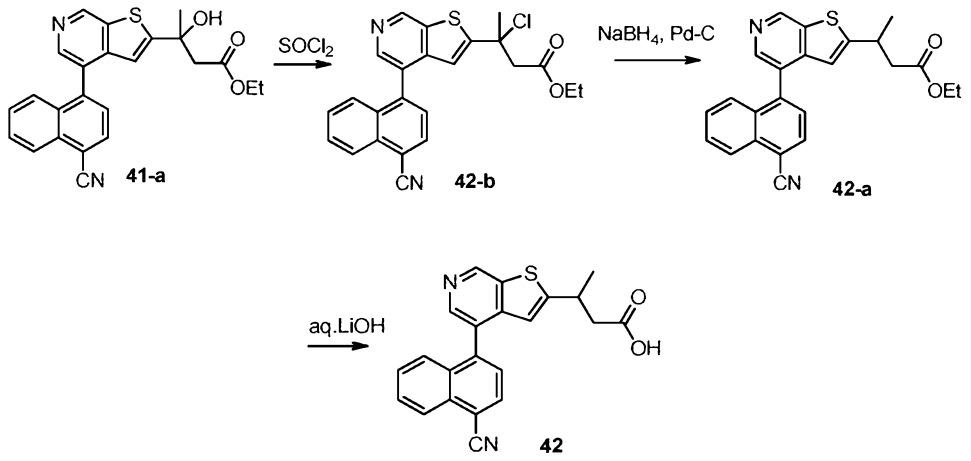
Synthesis of compound **41**

At room temperature, 1.0M LiOH aq. solution (5mL) was added to a solution of compound **41-a** (42mg, 0.1mmol) in methanol (5mL) and THF (5mL). The mixture was stirred for 16hrs, concentrated under reduced pressure. Water (10mL) was added to the residue, 1M citric acid aq. solution was added to adjust pH=3, solid was precipitated and filtered out. The solid was washed with water (5mL), dried under vacuum to give white solid **41** (30mg, yield 77%). LC-MS (ESI): m/z = 389 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 12.08 (s, br. 1H), 9.31 (s, 1H), 8.44 (s, 1H), 8.32 (d, J=7.2 Hz, 1H), 8.27 (d, J=8.0 Hz, 1H), 7.87 (t, J=8.0 Hz, 1H), 7.73 (t, J=7.2 Hz, 1H), 7.62 -7.67 (m, 1H), 7.59 (d, J=8.0 Hz, 1H), 6.79 (d, J=10.0 Hz, 1H), 2.65-2.76 (m, 2H), 1.56 (d, J=6.0 Hz, 3H) ppm.

Embodiment 42

3-[4-(4-Cyanonaphthalen-1-yl)thieno[2,3-c]pyridin-2-yl] butyric acid (Compound **42**)



Synthesis of compound **42-b**

At 20℃, thionyl chloride (2mL) was added to a solution of compound **41-a** (160mg, 0.4mmol) in DCM (10mL). The mixture was stirred for 16hrs, concentrated under reduced pressure to give compound **42-b**. The product was used directly for the next step without further purification.

Synthesis of compound **42-a**

At 0℃, $NaBH_4$ (114mg, 3mmol) was added to a solution of compound **42-b**, 10% Pd-C (30mg) and ethanol (10mL) in portions. The mixture was warmed to room temperature and stirred for 16hrs, filtered through celite. Water (10mL) was added to the filtrate, the mixture was extracted with DCM (10mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 10:1) to give compound **42-a** (62mg, yield 42%). LC-MS (ESI): m/z = 401 $[M+H]^+$.

Synthesis of compound **42**

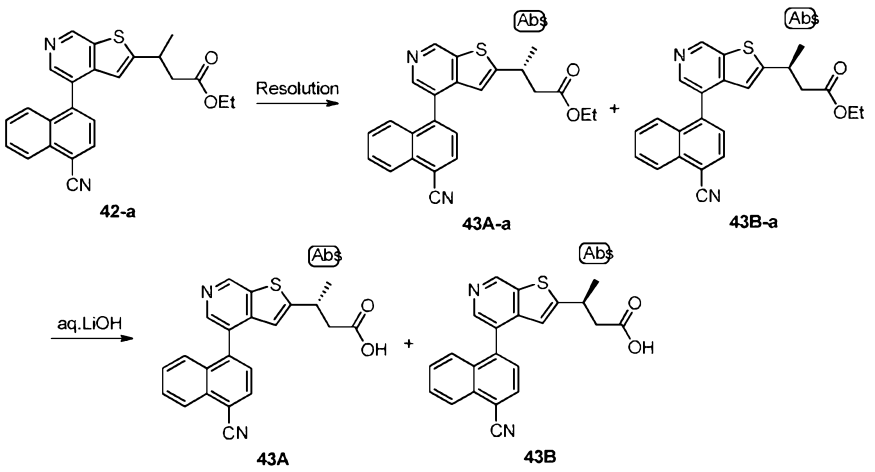
At room temperature, 1M LiOH aq. solution (5mL) was added to a solution of compound **42-a** (40mg, 0.1mmol) in methanol (5mL) and THF (5mL). The mixture was stirred for 16hrs, and concentrated under reduced pressure. Water (10mL) was added to the residue, 1M citric acid aq. solution was added to adjust pH=3, solid was precipitated and filtered out. The solid was washed with water (5mL), dried under vacuum to give white solid **42** (20mg, yield 53%). LC-MS (ESI): m/z = 373 $[M+H]^+$.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 9.12 (s, 1H), 8.43 (s, 1H), 8.36 (d, J=8.8 Hz, 1H), 8.01 (t, J=8.0 Hz, 1H), 7.69-7.74 (m, 1H), 7.61 (d, J=8.8 Hz, 1H), 7.47 -7.55 (m, 2H), 6.67 (d, J=4.4 Hz, 1H), 3.59-3.64 (m, 1H), 2.58-2.74 (m, 2H), 1.24 (d, J=9.0 Hz, 3H) ppm.

Embodiment 43

Compound **43A**

Compound **43B**



Synthesis of compound **43A**

Compound **42-a** (170mg) underwent enantiomeric chromatographic column (process II, mobile phase: n-Hexane (0.1% DEA): EtOH (0.1% DEA) = 80:20), compound **43A-a** (59mg) (T_r = 18.0min) was eluted firstly and compound **43B-a** (46mg) (T_r = 20.0min) was eluted later, the absolute configuration of **43A-a** and **43B-a** remains unknown. At room temperature, 1M LiOH aq. solution (2.5mL) was added to a solution of **43A-a** (59mg, 0.14mmol) in methanol (5mL). The mixture was stirred for 4hrs, concentrated under reduced pressure to remove the solvent. Water (10mL) was added to the residue, 1M citric acid aq. solution was added to adjust pH=6, solid was precipitated and filtered out. The solid was washed with water (5mL), dried under vacuum to give white solid **43A** (38mg, yield 69%). LC-MS (ESI): m/z = 373 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 12.20 (s, 1H), 9.31 (s, 1H), 8.43 (s, 1H), 8.45 (s, 1H), 8.30 (dd, J=20.3 Hz, 7.9 Hz, 1H), 7.87 (t, J=7.4 Hz, 1H), 7.81 -7.52 (m, 3H), 6.67 (d, J=5.7 Hz, 1H), 3.50 (dd, J=13.4 Hz, 6.4 Hz, 1H), 2.57 (dd, J=9.7 Hz, 6.30 Hz, 1H), 1.28 (d, J=9.0 Hz, 3H) ppm.

Synthesis of compound **43B**

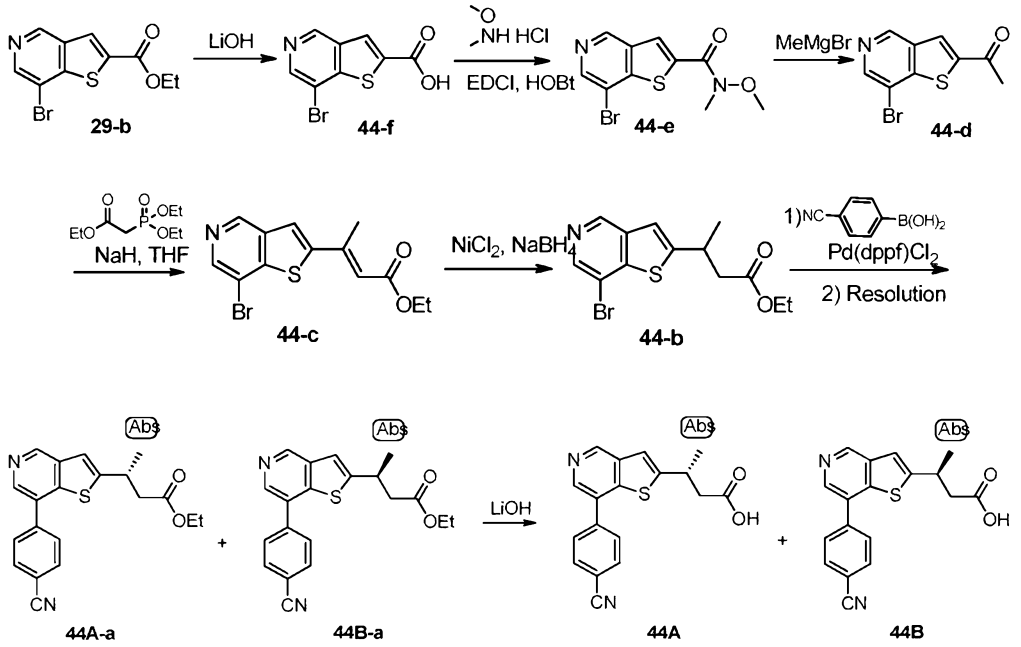
At room temperature, 1M LiOH aq. solution (2.5mL) was added to a solution of **43B-a** (46mg, 0.11mmol) in methanol (5mL). The mixture was stirred for 4hrs, concentrated under reduced pressure to remove the solvent. Water (10mL) was added to the residue, 1M citric acid aq. solution was added to adjust pH=6, solid was precipitated and filtered out. The solid was washed with water (5mL), dried under vacuum to give white solid **43B** (25mg, yield 58%). LC-MS (ESI): m/z = 373 $[M+H]^+$.

^{1}H-NMR (400MHz, CD_3OD) δ: 9.19 (s, 1H), 8.47-8.28 (m, 2H), 8.18 (d, J=7.4 Hz, 1H), 7.93-7.78 (m, 1H), 7.70 (d, J=7.4 Hz, 1H), 7.63 (t, J=3.7 Hz, 1H), 6.75 (d, J=8.6 Hz, 1H), 3.61 (dd, J=13.6 Hz, 6.9 Hz, 1H), 2.73-2.56 (m, 2H), 1.40 (d, J=9.0 Hz, 3H) ppm.

Embodiment 44

Compound **44A**

Compound **44B**



Synthesis of compound **44-f**

At room temperature, LiOH (1.68g, 40mmol) was added to a solution of compound **29-b** (5.7g, 20mmol) in methanol (10mL), THF (40mL) and water (10mL). The mixture was stirred for 1h, followed by adding 2M HCl (20mL) and water (20mL), solid was precipitated and filtered out. The solid was washed with water (50mL), dried under vacuum to give compound **44-f** (4.5g, yield 100%). LC-MS (ESI): m/z = 258 $[M+H]^+$.

Synthesis of compound **44-e**

At room temperature, N,O-dimethylhydroxylamine hydrochloride (1.6g, 3mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (5.6g, 3mmol), 1-hydroxybenzotriazole (4.04g, 3mmol) and diisopropylethylamine (3.9g, 3mmol) were added to a solution of compound **44-f** (4.9g, 3mmol) in DCM (100mL). The mixture was stirred for 8hrs, followed by adding 2M HCl (50mL) and water (20mL), being extracted with DCM (80mL×3). The organic phases were combined, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 1:1) to give compound **44-e** (6g, yield 100%). LC-MS (ESI): m/z = 301 $[M+H]^+$.

Synthesis of compound **44-d**

At -78℃, a solution of 1.5M methyl magnesium bromide in ether (20mL, 30mmol)

was added dropwise to a solution of compound **44-e** (6.0g, 20mmol) in anhydrous THF (100mL). The mixture was slowly warmed to room temperature and further stirred for 20mins, saturated NH_4Cl aq. solution (30mL) was added, the mixture was extracted with EA (30mL×3). The organic phases were combined, concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 2:1-1:1) to give compound **44-d** (4.8g, yield 94%). LC-MS (ESI): m/z = 256 $[M+H]^+$.

Synthesis of compound **44-c**

At 0℃, triethyl phosphonoacetate (5.6mL, 20mmol) and sodium hydride (1.6g, 20mmol) were added to a solution of compound **44-d** (4.8g, 18.9mmol) in THF (100mL) respectively. The mixture was stirred for 1h, warmed to room temperature, followed by adding NH_4Cl aq. solution (100mL), being extracted with EA (100mL×3). The organic phases were combined, washed in turn with water (100mL×3) and saturated brine (100mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 5:1) to give light yellow solid **44-c** (5.2g, yield 89%). LC-MS (ESI): m/z =326 $[M+H]^+$.

Synthesis of compound **44-b**

At 0℃, $NaBH_4$ (0.38g, 10mmol) was added into a solution of compound **44-c** (5.2g, 16mmol) and $NiCl_2$ (1.3g, 10mmol) in methanol (50mL). The mixture was stirred for 3hrs, warmed to room temperature, followed by adding saturated NH_4Cl aqueous solution (100mL), being extracted with EA (10mL×3). The organic phases were combined, washed in turn with water (50mL×3) and saturated brine (50mL), dried over anhydride sodium sulfate, filtered, and evaporated under reduced pressure. The residue was purified with silica column chromatography (PE:EA = 4:1) to give light yellow solid **44-b** (2.24g, yield 43%). LC-MS (ESI): m/z =328 $[M+H]^+$.

Synthesis of compound **44A-a** and **44B-a**

Under N_2 atmosphere, compound **44-b** (327mg, 1mmol), 4-cyanophenyl boronic acid (150mg, 1mmol) and sodium carbonate (212mg, 2mmol) were suspended in dioxane (8mL) and water (2mL), [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (60mg, 0.1mmol) was added. The mixture was stirred at 80℃ for 3hrs, and then cooled to room temperature, filtered through celite, the filtrate cake was washed with EA (50mL). The filtrate was in turn washed with water (20mL×3) and saturated brine (10mL), dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 1:1) to give racemic compound, followed by separating by enantiomeric chromatographic column (process I, mobile phase: Hexane:EtOH:DEA =70:30:0.1), compound **44A-a** (80mg, yield 22.8%; LC-MS (ESI): m/z = 351 $[M+H]^+$) (T_r = 6.0min) was diluted firstly and compound **44B-a** (90mg, yield 25.6%; LC-MS (ESI): m/z = 351 $[M+H]^+$) (T_r = 7.0 min) was diluted later. Absolute configuration of **44A-a** and **44B-a** remains unknown.

Synthesis of compound **44A**

At room temperature, LiOH (42mg, 1mmol) was added to a solution of compound **44A-a** (70mg, 0.2mmol) in methanol (1mL), THF (2mL) and water (1mL). The mixture was stirred for 1h, followed by adding 1M HCl aq. solution (1mL) and water (2mL), solid was precipitated and filtered out. The solid was washed with water (5mL), dried under vacuum to give compound **44A** (53mg, yield 82%). LC-MS (ESI): m/z = 323 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 12.30 (s, 1H), 9.07 (s, 1H), 8.52 (s, 1H), 8.06 (d, J=8.0 Hz, 2H), 7.97 (d, J=8.0 Hz, 2H), 7.51 (s, 1H), 3.58 (m, 1H), 2.66 (t, J=8.0 Hz, 2H), 1.37 (d, J=8.0 Hz, 3H) ppm.

Synthesis of compound **44B**

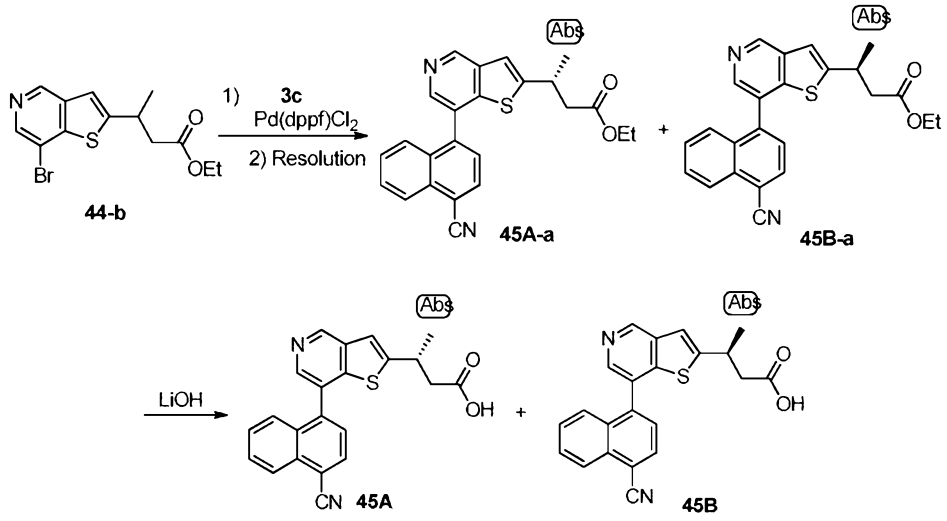
At room temperature, LiOH (42mg, 1mmol) was added to a solution of compound **44B-a** (70mg, 0.2mmol) in methanol (1mL), THF (2mL) and water (1mL). The mixture was stirred for 1h, followed by adding 1M HCl aq. solution (1mL) and water (2mL), solid was precipitated and filtered out. The solid was washed with water (5mL), dried under vacuum to give compound **44B** (39mg, yield 60.6%). LC-MS (ESI): m/z = 323 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 12.30 (s, 1H), 9.07 (s, 1H), 8.52 (s, 1H), 8.06 (d, J=8.0 Hz, 2H), 7.97 (d, J=8.0 Hz, 2H), 7.51 (s, 1H), 3.58 (m, 1H), 2.66 (t, J=8.0 Hz, 2H), 1.37 (d, J=8.0 Hz, 3H) ppm.

Embodiment 45

Compound **45A**

Compound **45B**



Synthesis of compound **45A-a** and **45B-a**

Under N_2 atmosphere, compound **44-b** (800mg, 2.5mmol), compound **3-c** (750mg, 2.5mmol) and sodium carbonate (510mg, 5mmol) were suspended in dioxane (8mL) and water (2mL), [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (140mg, 0.25mmol) was added. The mixture was stirred for 3hrs at 80℃, cooled to room temperature, filtered through celite, the filtrate cake was washed with EA (50mL). The filtrate was washed in turn with water (20mL×3) and saturated brine (10mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA=1:1) to give racemic compound, followed by separating by enantiomeric chromatographic column (process II, mobile phase: CO_2:Methanol (0.1% NH_4OH) = 65:35), compound **45A-a** was diluted firstly (260 mg, yield 26%; LC-MS (ESI): m/z = 401 $[M+H]^+$) (T_r = 8.5min), and compound **45B-a** (230mg, yield 23%; LC-MS (ESI): m/z = 401 $[M+H]^+$) (T_r = 10.5min) was diluted later. Absolute configuration of **45A-a** and **45B-a** remains unknown.

Synthesis of compound **45A**

At room temperature, LiOH (42mg, 1mmol) was added to a solution of compound **45A-a** (80mg, 0.2mmol) in methanol (1mL), THF (2mL) and water (1mL). The mixture was stirred for 1h, followed by adding 1M HCl aq. solution (1mL) and water (2mL), solid was precipitated and filtered out. The solid was washed with water (5mL), dried under vacuum to give compound **45A** (61mg, yield 82%). $[\alpha]^{25}_D$ = +26.248 (c=1.1018 MeOH), LC-MS (ESI): m/z = 373 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 12.27 (s, 1H), 9.17 (s, 1H), 8.43 (s, 1H), 8.33 (d, J=7.2 Hz, 1H), 8.27 (d, J=8.4 Hz, 1H), 7.90 (dd, J=7.2 Hz, 5.6 Hz, 1H), 7.83 (d, J=7.2 Hz, 1H), 7.68 (dd, J=6.8 Hz, 6.0 Hz, 1H), 7.64 (d, J=8.4 Hz, 1H), 7.52 (s, 1H), 3.50 (m, 1H), 2.60 (m, 2H), 1.31 (dd, J=7.6 Hz, 6.8 Hz, 3H) ppm.

Synthesis of compound **45B**

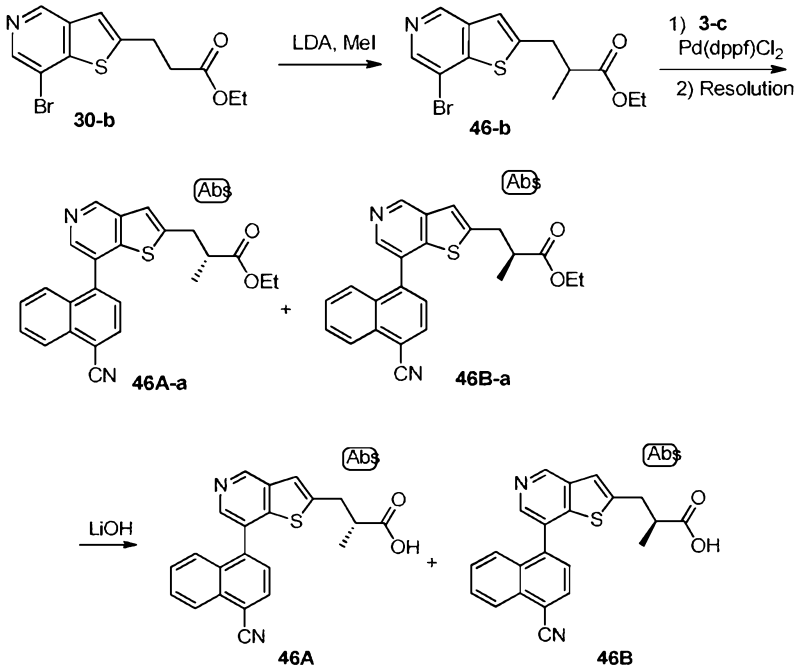
At room temperature, LiOH (42mg, 1mmol) was added to a solution of compound **45B-a** (80mg, 0.2mmol) in methanol (1mL), THF (2mL) and water (1mL). The mixture was stirred for 1h, followed by adding 1M HCl aq. solution (1mL) and water (2mL), solid was precipitated and filtered out. The solid was washed with water (5mL), dried under vacuum to give compound **45B** (56mg, yield 75%). $[\alpha]^{25}_D$ = -25.594 (c=1.002 MeOH), LC-MS (ESI): m/z = 373 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 12.27 (s, 1H), 9.17 (s, 1H), 8.43 (s, 1H), 8.33 (d, J=7.2 Hz, 1H), 8.27 (d, J=8.4 Hz, 1H), 7.90 (dd, J=7.2 Hz, 5.6 Hz, 1H), 7.83 (d, J=7.2 Hz, 1H), 7.68 (dd, J=6.8 Hz, 6.0 Hz, 1H), 7.64 (d, J=8.4 Hz, 1H), 7.52 (s, 1H), 3.50 (m, 1H), 2.60 (m, 2H), 1.31 (dd, J=7.6 Hz, 6.8 Hz, 3H) ppm.

Embodiment 46

Compound **46A**

Compound **46B**



Synthesis of compound **46-b**

Under N2 atmosphere, at -78℃, 2.5M *n*-butyl lithium in *n*-hexane (2.0mL, 5mmol) was slowly added to a solution of diisopropylamine (505mg, 5mmol) in anhydrous THF (10mL) dropwise. The mixture was stirred for 15mins, followed by adding a solution of compound **30-b** (630mg, 2mmol) in anhydrous THF (10mL) dropwise, the mixture was stirred for 2hrs, followed by adding CH_3I (720mg, 5mmol) and the mixture was further stirred for 3hrs. The mixture was slowly warmed to room temperature, followed by adding saturated NH_4Cl aq. solution (30mL), being extracted with EA (30mL×3). The organic phases were combined, washed in turn with water (10mL) and saturated brine (10mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica preparative plate chromatography (PE:EA = 2:1-1:1) to give compound **46-b** (170mg, yield 26%). LC-MS (ESI): m/z = 328 $[M+H]^+$.

Synthesis of compound **46A-a** and **46B-a**

Under N_2 atmosphere, compound **46-b** (170mg, 0.52mmol), compound **3-c** (145mg, 0.52mmol) and sodium carbonate (120mg, 1.13mmol) were suspended in dioxane (4mL) and water (1mL), [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (43mg, 0.05mmol) was added. The mixture was stirred at 80℃ for 3hrs, cooled to room temperature, concentrated under reduced pressure. The residue was filtered through celite, the filtrate cake was washed with EA (30mL). The filtrate was washed in turn with water (20mL×3) and saturated brine (10mL), dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 1:1) to give racemic compound, followed by separating by enantiomeric chromatographic column (process

I, mobile phase: Hexane : EtOH:DEA = 80:20:0.1), compound **46A-a** was eluted firstly (66mg, yield 31%; LC-MS (ESI): m/z = 401 $[M+H]^+$) (T_r = 14.0min) and compound **46B-a** was eluted later (61mg, yield 29%; LC-MS (ESI): m/z = 401 $[M+H]^+$) (T_r = 18.0min). Absolute configuration of **46A-a** and **46B-a** remains unknown.

Synthesis of compound **46A**

At room temperature, LiOH (42mg, 1mmol) was added to a solution of compound **46A-a** (60mg, 0.15mmol) in methanol (1mL), THF (4mL) and water (1mL). The mixture was stirred for 1h, followed by adding 1M HCl aq. solution (1mL) and water (10mL), solid was precipitated and filtered out. The solid was washed with water (5mL), dried under vacuum to give compound **46A** (26mg, yield 46%). LC-MS (ESI): m/z = 373 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d_6) δ: 12.31 (s, 1H), 9.17 (s, 1H), 8.44 (s, 1H), 8.33 (d, J=8.0 Hz, 1H), 8.27 (d, J=8.0 Hz, 1H), 7.88 (m, 2H), 7.66 (m, 2H), 7.49 (s, 1H), 3.16 (m, 1H), 3.02 (m, 1H), 2.68 (m, 1H), 1.23 (d, J=6.8 Hz, 1H) ppm.

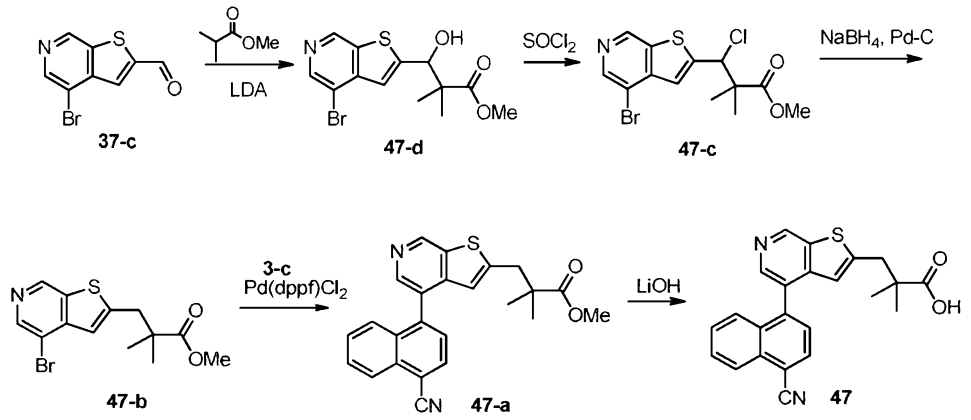
Synthesis of compound **46B**

At room temperature, LiOH (42mg, 1mmol) was added to a solution of compound **46B-a** (60mg, 0.15mmol) in methanol (1mL), THF (4mL) and water (1mL). The mixture was stirred for 1h, followed by adding 1M HCl aq. solution (1mL) and water (10mL), solid was precipitated and filtered out. The solid was washed with water (5mL), dried under vacuum to give compound **46B** (26mg, yield 46%). LC-MS (ESI): m/z = 373 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d_6) δ: 12.31 (s, 1H), 9.17 (s, 1H), 8.44 (s, 1H), 8.33 (d, J=8.0 Hz, 1H), 8.27 (d, J=8.0 Hz, 1H), 7.88 (m, 2H), 7.66 (m, 2H), 7.49 (s, 1H), 3.16 (m, 1H), 3.02 (m, 1H), 2.68 (m, 1H), 1.23 (d, J=6.8 Hz, 1H) ppm.

Embodiment 47

3-[4-(4-Cyanonaphthalen-1-yl)thieno[2,3-c]pyridin-2-yl]-2,2-dimethyl propionic acid (Compound **47**)



Synthesis of compound **47-d**

At -78℃, 1M Lithium diisopropylamide in THF (3mL, 3mmol) was slowly added to a solution of methyl isobutyrate (306mg, 3mmol) in anhydrous THF (4mL). The mixture was stirred for 1h, followed by adding compound **37-c** (242mg, 1mmol), the mixture was further stirred for 1h. The mixture was slowly warmed to room temperature, followed by adding saturated $NaHCO_3$ aq. solution (20mL), being extracted with EA (20mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give compound **47-d** (425mg). The product was used directly for the next step without further purification. LC-MS (ESI): m/z = 344 $[M+H]^+$.

Synthesis of compound **47-c**

Thionyl chloride (6mL) was added to a solution of compound **47-d** (425mg) in DCM (10mL). The mixture was heated to 40℃, stirred for 16hrs and concentrated under reduced pressure to remove the solvent. Water (15mL) was added to the residue, the mixture was extracted with EA (15mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give compound **47-c** (487mg). The product was used directly for the next step without further purification. LC-MS (ESI): m/z = 364 $[M+H]^+$.

Synthesis of compound **47-b**

At room temperature, $NaBH_4$ (204mg, 5.37mmol) was added to a mixture of compound **47-c** (487mg), 10% Pd-C (50mg) and ethanol (20mL) in portions, the mixture was stirred for 16hrs. The mixture was filtered through celite, the filtrate cake was washed with ethanol (10mL×3). The filtrate was concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 5:1) to give compound **47-b** (135 mg, yield 31%). LC-MS (ESI): m/z = 328 $[M+H]^+$.

Synthesis of compound **47-a**

Under N_2 atmosphere, compound **47-b** (135mg, 0.41mmol), compound **3-c** (121mg, 0.43mmol) and sodium sulfate (106mg, 1mmol) were suspended in dioxane (8mL) and water (1mL), [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (30mg, 0.04mmol) was added. The mixture was stirred at 90℃ for 16hrs, cooled to room temperature, and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA=3:1) to give compound **47-a** (130mg, yield 79%). LC-MS (ESI): m/z = 401 $[M+H]^+$.

Synthesis of compound **47**

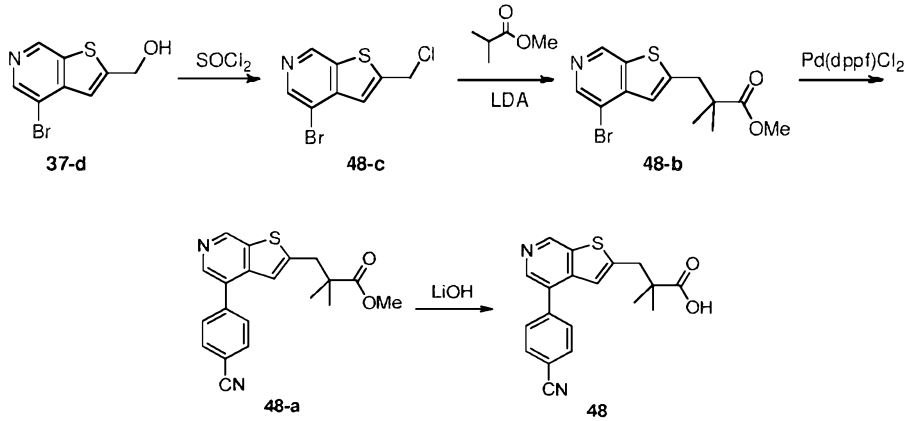
At room temperature, LiOH (55mg, 1.3mmol) was added to a solution of compound **47-a** (130mg, 0.32mmol) in methanol (1mL), THF (5mL) and water (1mL). The mixture was stirred for 1h, followed by adding 1M HCl aq. solution to adjust pH=5-6, being extracted with EA (15mL×3). The organic phases were combined, dried over

anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was prepared by HPLC (mobile phase: 10mM NH_4HCO_3 aq. solution: acetonitrile =35%-45%) to give white solid **47** (13mg, yield 10.5%). LC-MS (ESI): m/z = 387 $[M+H]^+$.

^{1}H-NMR (400MHz, CD_3OD) δ: 9.22 (s, 1H), 8.39 (s, 1H), 8.22 (d, J=8.1 Hz, 1H), 8.10-8.01 (m, 1H), 7.71 (dd, J=7.9 Hz, 3.7 Hz, 1H), 7.60 (d, J=7.1 Hz, 1H), 7.50 (s, 2H), 6.68 (s, 1H), 3.13-3.02 (m, 2H), 1.19 (s, 3H), 1.18 (s, 3H) ppm.

Embodiment 48

3-[4-(4-Cyanophenyl)thieno[2,3-c]pyridin-2-yl]-2,2-dimethyl propionic acid (Compound **48**)



Synthesis of compound **48-c**

Thionyl chloride (5mL) was added to a solution of compound **37-d** (200mg, 0.82mmol) in DCM (10mL). The mixture was heated to 30℃, stirred for 16hrs, and concentrated under reduced pressure to give compound **48-c** (236mg). The product was used directly for the next step without further purification. LC-MS (ESI): m/z = 264 $[M+H]^+$.

Synthesis of compound **48-b**

Under N_2 atmosphere, at -78℃, a solution of 2.5M *n*-butyl lithium in *n*-hexane (1.37mL, 3.43mmol) was slowly added to a solution of diisopropylamine (347mg, 3.43mmol) in anhydrous THF (10mL). The mixture was warmed to 0℃ and further stirred for 1h, then cooled again to -78℃, methyl isobutyrate (350mg, 3.43mmol) was added, the mixture was stirred for 1h, followed by adding compound **48-c** (180mg, 0.69mmol) and further stirred for 1h. The mixture was slowly warmed to room temperature, stirred for 2hrs, followed by adding saturated NH_4Cl aq. solution (20mL), being extracted with EA (50mL×2). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 3:1) to give compound **48-b** (280mg, yield 97%). LC-MS (ESI): m/z = 329 $[M+H]^+$.

Synthesis of compound **48-a**

Under N_2 atmosphere, compound **48-b** (280mg, 0.85mmol), 4-cyanophenylboronic acid (138mg, 0.94mmol) and sodium sulfate (180mg, 1.7mmol) were suspended in dioxane (15mL) and water (2mL), [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (62mg, 0.08mmol) was added. The mixture was added at 90℃ for 16hrs, cooled to room temperature, concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 3:1) to give compound **48-a** (135mg, yield 45%). LC-MS (ESI): m/z = 351 $[M+H]^+$.

Synthesis of compound **48**

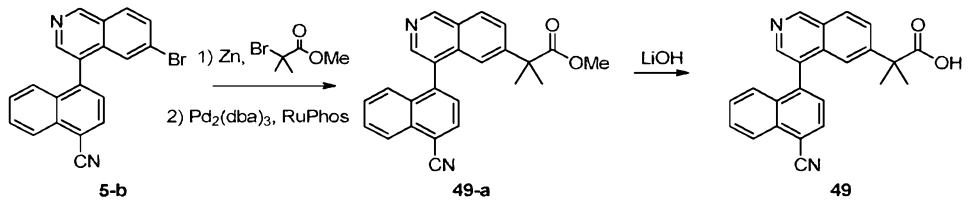
At room temperature, LiOH (65mg, 1.54mmol) was added to a solution of compound **48-a** (135mg, 0.38mmol) in methanol (1mL), THF (5mL) and water (1mL). The mixture was stirred for 6hrs, 1M HCl aq. solution was added to adjust pH=5-6, and concentrated under reduced pressure. The residue was adjusted to pH=7-8 with 2M NaOH aq. solution, and then extracted with EA (10mL) to remove the impurities. The aqueous phase was adjusted to pH=5-6 with 1M HCl aq. solution, extracted with EA (15mL×2). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give yellow solid **48** (75 mg, yield 58%). LC-MS (ESI): m/z = 337 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 12.52 (s, 1H), 9.21 (s, 1H), 8.48 (s, 1H), 8.03 (d, J=8.2 Hz, 2H), 7.84 (d, J=8.2 Hz, 2H), 7.30 (s, 1H), 3.21 (s, 2H), 1.16 (s, 6H) ppm.

Embodiment 49

2-[4-(4-Cyanonaphthalen-1-yl)isoquinolin-6-yl]-2-methyl propionic acid (Compound **49**)

Synthetic route



5-b **49-a** **49**

Synthesis of compound **49-a**

Under N_2 atmosphere, trimethylchlorosilane (11mg, 0.1mmol) was added dropwise to a solution of Zn powder (130mg, 2mmol) and THF (4mL). The mixture was stirred for 15mins at room temperature, heated to 40℃, followed by adding a solution of methyl 2-bromoisobutyrate (181mg, 1mmol) in THF (2mL). The mixture was further stirred at 40℃ for 30mins, added to a mixture of compound **5-b** (90mg, 0.25mmol), LiCl (11mg, 0.25mmol), tris(dibenzylidene indene acetone)dipalladium (23mg, 0.025mmol), 2-dicyclohexylphospho-2',6'-diisopropoxy-1,1'-biphenyl (12mg,

0.025mmol) and THF (4mL). The mixture was heated to 80℃ and further stirred for 1h, and then cooled to room temperature, and concentrated under reduced pressure to remove the solvent. The residue was dissolved in DCM (50mL), washed in turn with water (20mL×3) and saturated brine (10mL), dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure. The residue was purified by silica preparative plate chromatography (DCM: methanol = 20:1) to give compound **49-a** (40mg, yield 42%). LC-MS (ESI): m/z = 381 $[M+H]^+$.

Synthesis of compound **49**

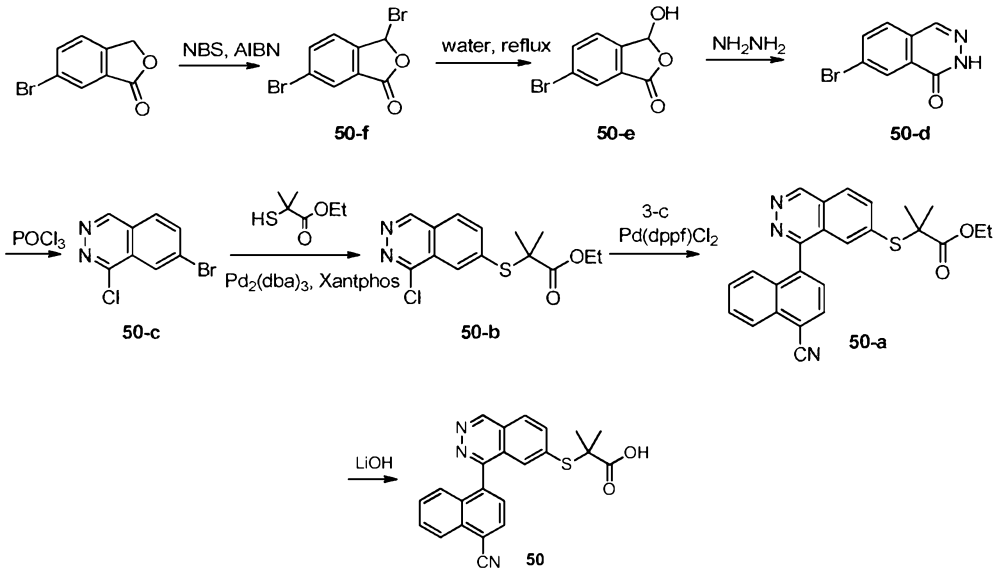
At room temperature, LiOH (22mg, 0.5mmol) was added to a solution of compound **49-a** (40mg, 0.1mmol) in methanol (1mL) and THF (3mL). The mixture was stirred for 16hrs, evaporated to remove the solvent, followed by adding water (5mL), being extracted with EA (10mL×3). 1M HCl aq. solution was added to the aqueous phase to adjust pH=5-6, extracted with EA (15mL×3), the organic phases were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was prepared by HPLC (mobile phase: water (0.05% trifluoroacetic acid): nitrile =25%-40%) to give compound **49** (15mg, yield 39%). LC-MS (ESI): m/z = 367 $[M+H]^+$.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 9.39 (s, 1H), 8.50 (s, 1H), 8.36 (d, J=8.4 Hz, 1H), 8.13 (d, J=8.4 Hz, 1H), 7.77 (d, J=8.4 Hz, 1H), 7.72-7.67 (m, 1H), 7.58 (d, J=7.2 Hz, 1H), 7.48-7.46 (m, 2H), 7.34 (s, 1H), 1.45 (s, 6H) ppm.

Embodiment 50

2-{[4-(4-Cyanonaphthalen-1-yl)phthalazin-6-yl]thio}-2-methyl propionic acid (Compound **50**)

Synthetic route



Synthesis of compound **50-f**

6-Bromo-phthalide (2.30g, 10.9mmol) was added to a solution of N-bromosuccinimide (2.1g, 11.8mmol), azobisisobutyronitrile (0.1g, 0.06mmol) in 1,2-dichloroethane (60mL). The mixture was heated to reflux for 2hrs, cooled to room temperature, and concentrated under reduced pressure. The residue was washed with water (10mL×3) to give compound **50-f**. The product was used directly for the next step without further purification.

Synthesis of compound **50-e**

A mixture of compound **50-f** and water (40mL) was heated to reflux for 2hrs, cooled to room temperature, white solid was precipitated and filtered out. Solid was washed with water (20mL×3), dried under vacuum to give compound **50-e** (1.6g, yield 64%). The product was used directly for the next step without further purification.

Synthesis of compound **50-d**

85% Hydrazine hydrate (2mL) was added to a solution of compound **50-e** (1.60g, 7mmol) in isopropyl alcohol (40mL). The mixture was heated to reflux for 2hrs, cooled to room temperature, white solid was precipitated and filtered out. The solid was washed with water (20mL×3), dried under vacuum to give compound **50-d** (1.2g, yield 76%). The product was used directly for the next step without further purification.

Synthesis of compound **50-c**

A mixture of compound **50-d** (600mg, 2.67mmol) and $POCl_3$ (8mL) was heated to reflux for 1.5h, cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in DCM (40mL), washed in turn with saturated sodium bicarbonate (40mL) and saturated brine (10mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 3:1) to give compound **50-c** (500mg, yield 75%). LC-MS (ESI): m/z = 243 $[M+H]^+$.

Synthesis of compound **50-b**

Under N_2 atmosphere, tris(dibenzylidene indene acetone)dipalladium (30mg, 0.03mmol) and 4,5-bis(diphenylphosphine)-9,9-dimethyloxacanthracene (38mg, 0.06mmol) were added to a solution of compound **50-c** (131mg, 0.5mmol), ethyl 2-methyl-2-mercaptopropionate (73mg, 0.5mmol) and diisopropylethylamine (193mg, 1.5mmol) in dioxane (10mL). The mixture was stirred at 100℃ for 16hrs, cooled to room temperature, concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 3:1) to give compound **50-b** (120mg, yield 77%). LC-MS (ESI): m/z = 311 $[M+H]^+$.

Synthesis of compound **50-a**

Under N_2 atmosphere, compound **50-b** (120mg, 0.38mmol), compound **3-c** (111mg, 0.4mmol) and sodium carbonate (170mg, 2.8mmol) were suspended in ethylene glycol dimethyl ether (10mL) and water (1mL), [1,1'-bis(diphenylphosphine)ferrocene]

palladium dichloride (43mg, 0.05mmol) was added. The mixture was stirred at 80℃ for 4hrs, cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 2:1) to give compound **50-a** (96mg, yield 60%). LC-MS (ESI): m/z = 428 $[M+H]^+$.

Synthesis of compound **50**

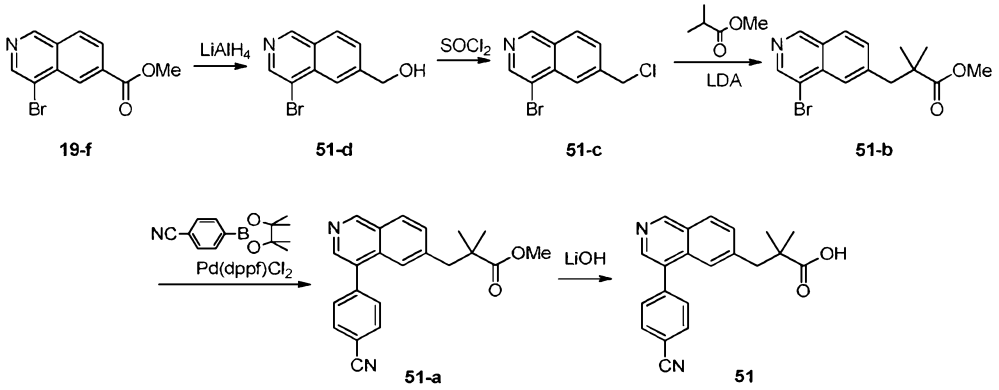
At room temperature, 1M LiOH aq. solution (3.0mL) was added to a solution of compound **50-a** (86mg, 0.2mmol) in methanol (4mL) and THF (8mL). The mixture was stirred for 16hrs and concentrated under reduced pressure. The residue was dissolved in water (10mL), adjusted to pH=3 with 1M HCl aq. solution, solid was precipitated and filtered out. The solid was washed with water (5mL), dried under vacuum to give white solid **50** (60mg, yield 75%). LC-MS (ESI): m/z = 400 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 12.77 (s, br. 1H,), 9.87 (s, 1H), 8.39 (d, J=8.0 Hz, 1H), 8.30 (d, J=8.0 Hz, 2H), 7.98-8.00 (m, 1H), 7.85-7.90 (m, 2H), 7.62 (t, J=8.0 Hz, 1H), 7.47 (d, J=8.8 Hz, 1H), 7.42 (s, 1H), 1.32 (s, 3H), 1.26 (s, 3H) ppm.

Embodiment 51

3-[4-(4-Cyanophenyl)isoquinolin-6-yl]-2,2-dimethyl propionic acid (Compound **51**)

Synthetic route



Synthesis of compound **51-d**

At 0℃, lithium aluminum hydride (214mg, 5.64mmol) was suspended in anhydrous THF (100mL), a solution of compound **19-f** (1.5g, 5.64mmol) in THF (10mL) was slowly added. The mixture was stirred for 10mins, $Na_2SO_4 \cdot 10H_2O$ (2.0g) was added in portions, then the mixture was warmed to room temperature and further stirred for 30mins. The mixture was filtered, the filtrate cake was washed with EA (20mL). The filtrate was concentrated under reduced pressure, the residue was purified by silica column chromatography (PE:EA = 3:1) to give compound **51-d** (600mg, yield 44%). LC-MS (ESI): m/z = 238 $[M+H]^+$.

Synthesis of compound **51-c**

Thionyl chloride (1.84mL) was added to a solution of compound **51-d** (600mg, 2.52mmol) in DCM (25mL). The mixture was heated to 30℃, stirred for 16hrs and concentrated under reduced pressure to give compound **51-c** (720mg). The product was used directly for the next step without further purification. LC-MS (ESI): m/z = 256 $[M+H]^+$.

Synthesis of compound **51-b**

Under N_2 atmosphere, at -78℃, a solution of 2.5M *n*-butyl lithium in *n*-hexane (2.05mL, 5.1mmol) was added to a solution of diisopropylamine (0.72mL, 5.1mmol) in anhydrous THF (20mL). The mixture was warmed to room temperature, stirred for 1h, cooled again to -78℃. The mixture was added to methyl isobutyrate (0.59mL, 5.1mmol), stirred for 1h, followed by adding compound **51-c** (300mg, 1.02mmol) and further stirred for 1h. The mixture was slowly warmed to room temperature, stirred for 2hrs, followed by adding saturated NH_4Cl aq. solution (20mL), being extracted with EA (50mL×2). The organic phases were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 3:1) to give yellow oil **51-b** (300mg, yield 91%). LC-MS (ESI): m/z = 322 $[M+H]^+$.

Synthesis of compound **51-a**

Under N_2 atmosphere, compound **51-b** (300mg, 0.93mmol), 4-cyanophenylboronic acid (215mg, 0.93mmol) and sodium carbonate (296mg, 2.79mmol) were suspended in DMF (10mL) and water (5mL), [1,1'-bis(diphenylphosphine)ferrocene] palladium dichloride (76mg, 0.09mmol) was added. The mixture was stirred at 80℃ for 16hrs, cooled to room temperature, and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 3:1-2:1) to give compound **51-a** (250mg, yield 78%). LC-MS (ESI): m/z = 345 $[M+H]^+$.

Synthesis of compound **51**

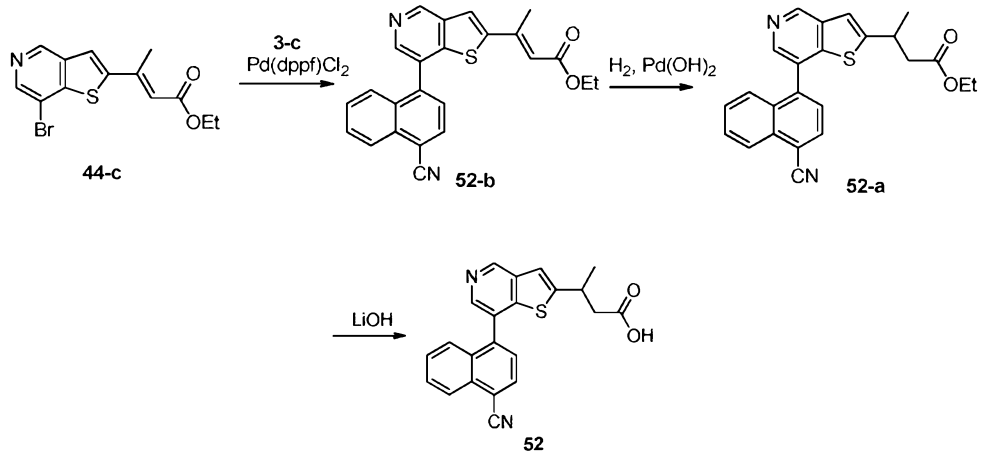
At room temperature, LiOH (152mg, 3.6mmol) was added to a solution of compound **51-a** (250mg, 0.72mmol) in methanol (1mL), THF (5mL) and water (2mL). The mixture was stirred for 6hrs, 1M HCl aq. solution was added to adjust pH=5-6, the mixture was concentrated under reduced pressure, extracted with EA (20mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was prepared by HPLC (mobile phase: water (0.01% NH_3+10 mm NH_4HCO_3) : nitrile = 45%-75%) to give compound **51** (33mg, yield 14%). LC-MS (ESI): m/z = 331 $[M+H]^+$.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 9.19 (s, 1H), 8.36 (s, 1H), 7.94 (m, 1H), 7.51-7.65 (m, 6H), 3.06 (s, 2H), 1.27 (s, 6H) ppm.

Embodiment 52

3-[7-(4-Cyanonaphthalen-1-yl)thieno[3,2-c]pyridine-2-yl]-butyric acid (Compound **52**)

Synthetic route



Synthesis of compound **52-b**

Under N_2 atmosphere, compound **44-c** (9.0g, 27.6mmol), compound **3-c** (15.4g, 55.2mmol) and sodium carbonate (5.85g, 55.2mmol) were suspended in dioxane (240mL) and water (40mL), [1,1'-bis(diphenylphosphine)ferrocene] palladium dichloride (1.0g, 1.38mmol) was added. The mixture was stirred at 80℃ for 16hrs, cooled to room temperature, and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 10:1) to give yellow solid **52-b** (9.1g, yield 82.8%). LC-MS (ESI): m/z = 399 $[M+H]^+$.

Synthesis of compound **52-a**

Under H_2 (1atm.) atmosphere, palladium hydroxide (3.0g) was added to a solution of compound **52-b** (9.1g, 22.8mmol) in THF (100mL) and methanol (280mL). The mixture was stirred for 16hrs, filtered, and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE:EA = 1:1) to give yellow oil **52-a** (8.0g, yield 87.5%). LC-MS (ESI): m/z = 401 $[M+H]^+$.

Synthesis of compound **52**

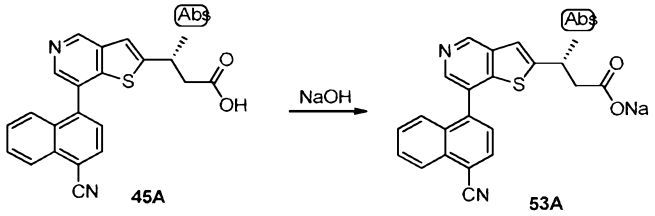
At room temperature, LiOH (1.51g, 36mmol) was added to a solution of compound **52-a** (8.0g, 20mmol) in methanol (15mL), THF (30mL) and water (5mL). The mixture was stirred for 8hrs, followed by adding 1M HCl aq. solution to adjust pH=5-6, solid was precipitated and filtered out. The solid was washed with water (20mL×3), dried under vacuum to give white solid **52** (6.18g, yield 83%). LC-MS (ESI): m/z = 373 $[M+H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 12.27 (s, 1H), 9.17 (s, 1H), 8.43 (s, 1H), 8.33 (d, J=7.2 Hz, 1H), 8.27 (d, J=8.4 Hz, 1H), 7.90 (dd, J=7.2 Hz, 5.6 Hz, 1H), 7.83 (d, J=7.2 Hz, 1H), 7.68 (dd, J=6.8 Hz, 6.0 Hz, 1H), 7.64 (d, J=8.4 Hz, 1H), 7.52 (s, 1H), 3.50 (m, 1H), 2.60 (m, 2H), 1.31 (dd, J=7.6 Hz, 6.8 Hz, 3H) ppm.

Embodiment 53

Compound 53A

Synthetic route



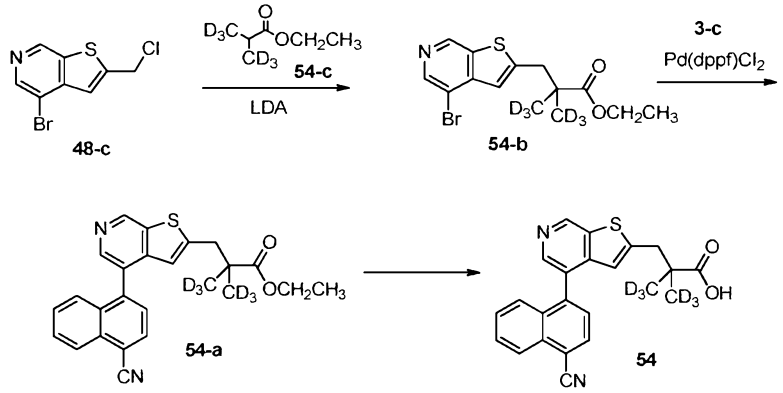
Synthesis of compound **53A**

At room temperature, NaOH (8mg, 0.02mmol) was added to a solution of compound **45A** (74mg, 0.02mmol) in water (1mL). The mixture was stirred for 2hrs, freeze-dried to give white solid **53A** (79mg, yield 100%). LC-MS (ESI): m/z = 373 $[M-Na+2H]^+$.

^{1}H-NMR (400MHz, DMSO-d6) δ: 9.11 (s, 1H), 8.38 (s, 1H), 8.32 (d, J=7.2 Hz, 1H), 8.27 (d, J=8.0 Hz, 1H), 7.88 (t, J=6.4 Hz, 1H), 7.82 (d, J=7.2 Hz, 1H), 7.65 (m, 2H), 7.42 (s, 1H), 3.47 (m, 1H), 2.23 (m, 1H), 2.11 (m, 1H), 1.25 (dd, J=7.2 Hz, 6.8 Hz, 3H) ppm.

Embodiment 54

3-[4-(4-Cyanonaphthalen-1-yl)thieno[3,2-c]pyridine-2-yl]-2,2-bis(triadecylmethyl) propionic acid (Compound **54**)



Synthesis of compound **54-b**

According to the process for preparing compound **48-b**, compound **54-b** (1000mg, 46%) was prepared by using commercially available compound **54-c**. LC-MS (ESI): m/z = 349 $[M+H]^+$.

According to the process for preparing compound **47-a**, compound **54-a** (500mg, 72%) was prepared by using compound **54-b**. LC-MS (ESI): m/z = 421 $[M+H]^+$.

Synthesis of compound **54**

According to the process for preparing compound **47**, white solid compound **54** (63mg, 32%) was prepared by compound **47-a**. LC-MS (ESI): m/z = 394 $[M+H]^+$. ^{1}H-NMR (400MHz, DMSO-d6) δ: 12.46(s, 1H), 9.30 (s, 1H), 8.45(s, 1H), 8.32(d, J=8Hz, 1H), 8.26(d, J=8Hz, 1H), 7.89(d, J=8Hz, 1H), 7.74(d, J=8Hz, 1H) , 7.65 (m, 1H) , 7.59 (m, 1H), 6.67(s, 1H), 3.09(s, 2H) ppm

Effect Example Biological assessment

Example 1: the inhibitory activity against URAT1 of the compound of the present invention

Human embryonic kidney cells (HEK293) was incubated in DMEM tissue culture medium, at 37℃, under 5% CO_2 and 95% air atmosphere. TransIT-293 transfection agent (MIRUS BIO, Cat. No. MIR2706) and model URAT1 were used to construct transfected HEK293 cells. Transfected HEK293/hURAT1 cells were used to the test for ^{14}C-uric acid transport activity.

HEK293/hURAT1 cells were seeded in a 96-well plate (BD, Cat. No. 356461) fully coating with poly-D-lysine at a density of 6×10^4 cells per well. Cells were incubated at 37℃ for at least 12hrs in the calorstat, and then washed with pre-heated washing buffer (125mM sodium gluconate, 10mM HEPES pH=7.4) at an amount of 200μL per well to wash out the culture medium. The uric acid [8-14C] (ARC, Cat. No. ARC0513-250UCI) containing or not containing the compound was added to 50μL HBSS buffer which was free of chloric ion each well (HBSS buffer: 125mM sodium gluconate, 4.8mM potassium gluconate, 1.3mM calcium gluconate, 1.2mM potassium dihydrogen phosphate, 1.2mM magnesium sulfate, 5.6mM glucose, 25mM HEPES pH=7.4) to make the specific concentration of the uric acid 1μCi per well. The incubating solution was removed after 10mins incubation, followed by adding 100μL cold washing buffer, after washing with this buffer for 3 times, the buffer was completely removed from the well. 50μL Lysis buffer (0.1mM NaOH) was added to each well, and transferred to a 96-well plate (PERKIN ELMER, Cat. No. 6005040) containing scintillation fluid after 5mins, and counted by MicroBeta Trilux (PerkinElmer) to give IC_{50} value eventually.

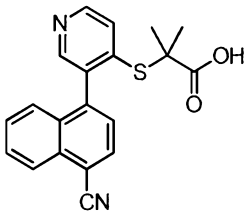
The inhibitory activity of the compound of the present invention against hURAT1 was tested according to the assessment above, the results were listed below (Table 1):

Table 1 IC_{50} value of partial compounds of the present invention against hURAT1

Compound	IC_{50} (μM)	Compound	IC_{50} (μM)
Verinurad (RDEA3170)	0.113	30	0.087
1	2.534	31	3.418
2	0.161	32	5.405
3	0.327	33	0.042
4	0.015	34	0.139
5	0.008	35	2.408
6	0.214	36	0.542

7A	5.524	37	0.035
7B	2.687	38	0.209
8	0.057	40	3.467
9	0.127	41	0.934
10	0.019	42	0.024
11	0.062	43A	0.011
12	0.071	43B	0.037
13	0.189	44A	0.038
14	0.385	44B	1.858
15	0.024	45A	0.580
16	0.015	45B	0.010
17	0.012	46A	0.148
21	0.100	46B	0.051
22	0.055	47	0.018
23	0.018	48	0.012
24	0.018	49	0.116
25	0.289	50	0.971
26	0.119	51	0.019
27	1.731	52	0.037
29	2.858	/	/

Compound Verinurad (RDEA3170, CAS No.:1352792-74-5) was a known hURAT1 inhibitor having a structure shown as below:



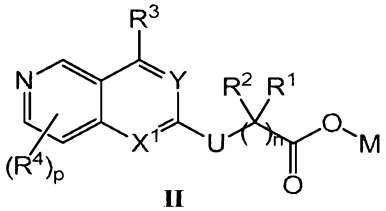
Verinurad (RDEA3170)

What can be concluded from Table 1 was that compounds of the present invention are of significantly inhibitory effects against hURAT1.

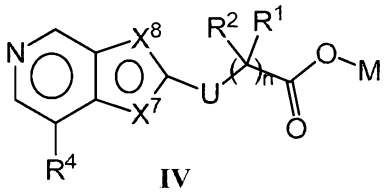
It is to be understood that the foregoing description of two preferred embodiments is intended to be purely illustrative of the principles of the invention, rather than exhaustive thereof, and that changes and variations will be apparent to those skilled in the art, and that the present invention is not intended to be limited other than expressly set forth in the following claims.

CLAIMS:

1. A condensed ring derivative having a structure of formula II or IV, a tautomer, a mesomer, a racemate, an enantiomer, a diastereoisomer, or a pharmaceutically acceptable salt or a pro-drug thereof,



II



IV

M is H, D or a pharmaceutically acceptable cation;

U is  ,  ,  ;

X^1 is CH or N,

Y is  or N;

each of X^7 and X^8 is independently CH or S;

each of R^1 and R^2 is independently H, D, a halogen, CN, an alkyl, an alkoxy, a cycloalkyl, an alkenyl, a alkynyl or a heterocycloalkyl; or, R^1, R^2 together with the carbon atom attached form a cycloalkyl or a heterocyclic group; the alkyl, the alkoxy, the cycloalkyl, the alkenyl, the alkynyl, the heterocycloalkyl, the cycloalkyl formed by R^1, R^2 and the carbon atom attached, or the heteroalkyl formed by R^1, R^2 and the carbon atom attached can further be substituted by a substituent selected from the group consisting of D, a halogen, CN, an alkyl, an alkoxy, a cycloalkyl, an alkenyl, an alkynyl, a heterocycloalkyl or an aryl;

R^3 is H, D, a halogen, an alkyl, an alkoxy, an aryl, a heteroaryl, a heterocycloalkyl or an amino; wherein the alkyl, the alkoxy, the aryl, the heteroaryl, the heterocycloalkyl or the amino can be further substituted by a substituent selected from the group consisting of D, a halogen, CN, an alkyl, an aryl, an aryl substituted by halogen, a benzyl, a benzyl which is substituted by halogen in the phenyl, a benzoyl or a benzoyl which is substituted by halogen in the phenyl; when the substituents are more than one, the substituents are the same or different;

R^4 is an alkyl, an aryl or a heteroaryl; wherein the alkyl is further substituted by a substituent selected from the group consisting of an aryl, an aryl substituted by a halogen and/or CN, a heteroaryl or a heteroaryl substituted by CN; and the aryl or the heteroaryl can further be substituted by a substituent selected from the group consisting of D, a halogen, CN, an alkyl, an alkoxy, a cycloalkyl, an alkenyl, an alkynyl, a heterocycloalkyl, an aryl, an aryl substituted by a halogen and/or CN, a heteroaryl or a heteroaryl substituted by CN;

each of R^5 and R^6 is independently H, D, OH, a halogen, CN, an alkyl, an alkoxy, a cycloalkyl, an alkenyl, an alkynyl or a heterocycloalkyl; or R^5, R^6 together with the carbon atom attached form a cycloalkyl or a heterocyclic group; the alkyl, the alkoxy, the cycloalkyl, the alkenyl, the alkynyl, the heterocycloalkyl, the cycloalkyl formed by R^5, R^6 together with the carbon atom attached or the heterocyclic group formed by R^5, R^6 together with the carbon atom attached can further be substituted by a substituent selected from the group consisting of D, a

halogen, CN, an alkyl, an alkoxy, a cycloalkyl, an alkenyl, an alkynyl, a heterocycloalkyl or an aryl;

n is 0, 1 or 2;

p is 1, 2 or 3; and

wherein the alkyl is selected from a saturated linear and branched aliphatic hydrocarbyl containing 1-20 carbon atoms;

the cycloalkyl is selected from a saturated or partially unsaturated cyclic hydrocarbon group containing 1-3 rings, including monocycloalkyl, bicycloalkyl and tricycloalkyl which contains 3-20 carbon atoms which can form a ring;

the alkoxy is selected from a cyclic or non-cyclic alkyl having indicated number of carbon atoms linked by an oxygen bridge, the alkoxy includes the definitions of the alkyl and the cycloalkyl;

the alkenyl is selected from a linear, branched or cyclic non-aryl hydrocarbyl having indicated carbon atoms and at least one carbon-carbon double bond;

the alkynyl is selected from a linear, branched or cyclic hydrocarbyl having indicated carbon atoms and at least one carbon-carbon triple bond;

the heterocycloalkyl is selected from a saturated or partially unsaturated 4-12 membered ring having 1-4 heteroatoms, the heteroatom is selected from N, O and S;

the heterocyclic group is selected from a 5-10 membered aromatic or non-aromatic heterocycle having 1-4 heteroatoms selected from O, N and S, including bicyclic group;

the aryl is selected from any stable monocyclic or bicyclic carbon rings which can have up to 7 atoms in each ring, and at least one of the rings is an aromatic ring;

the heteroaryl is selected from a stable monocycle or bicycle which can have up to 7 atoms in each ring, and at least one of the rings is an aromatic ring containing 1-4 heteroatoms selected from O, N and S; and

the amino is $-\overset{\S}{\S}NH_2$.

2. The condensed ring derivative having a structure of formula II or IV, the tautomer, the mesomer, the racemate, the enantiomer, the diastereoisomer, or the pharmaceutically acceptable salt or the pro-drug thereof according to claim 1, wherein,

M is H or a pharmaceutically acceptable cation;

each of R^1 and R^2 is independently H, D or an alkyl; or R^1 and R^2, together with the carbon atom attached form a cycloalkyl;

R^3 is H, a halogen, an alkyl or an aryl;

each of R^5 and R^6 is independently H, OH, a halogen or an alkyl;

p is 1.

3. The condensed ring derivative having a structure of formula II or IV, the tautomer, the mesomer, the racemate, the enantiomer, the diastereoisomer, or the pharmaceutically acceptable salt or the pro-drug thereof according to claim 1, wherein,

M is Na ion, K ion or Ca ion;

and/or, each of R^1 and R^2 is independently F, Cl, Br or I, C_{1-4} alkyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a C_{2-10} heterocycloalkyl having 1-2 heteroatom(s)

selected from O, S or N, or R^1 and R^2 together with the carbon atom attached form a C_{3-6} cycloalkyl, or, R^1 and R^2 together with the carbon atom attached form a C_{2-5} heterocyclic group having 1-2 heteroatom(s) selected from O or S;

and/or, R^3 is F, Cl, Br or I, C_{1-4} alkyl, C_{1-4} alkoxy, C_{6-10} aryl, or, a C_{2-5} heteroaryl having 1-3 heteroatom(s) selected from N, or, a C_{2-10} heterocycloalkyl having 1-3 heteroatom(s) selected from N, O or S;

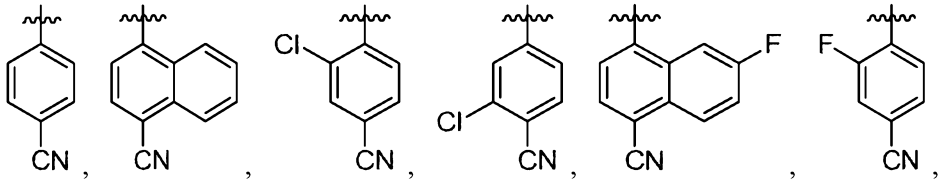
and/or, each of R^5 and R^6 is independently F, Cl, Br or I, a C_{1-4} alkyl, C_{1-4} alkoxy, a C_{3-6} cycloalkyl, a C_{2-4} alkenyl, a C_{2-4} alkynyl, or a C_{2-10} heterocycloalkyl having 1-2 heteroatom(s) selected from O, S or N, or, R^5 and R^6 together with the carbon atom form a C_{3-6} cycloalkyl, or, R^5, R^6 together with the carbon atom attached form a C_{2-10} heterocycloalkyl having 1-2 heteroatom(s) selected from O or S.

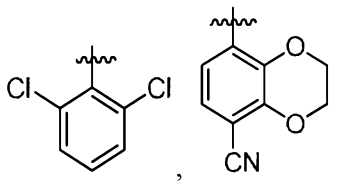
4. The condensed ring derivative having a structure of formula II or IV, the tautomer, the mesomer, the racemate, the enantiomer, the diastereoisomer, or the pharmaceutically acceptable salt or the pro-drug thereof according to claim 1, wherein,

the cycloalkyl formed by R^1 and R^2 together with the carbon atom attached, or the heterocyclic group formed by R^1, R^2 together with the carbon atom attached, is substituted by a substituent select from the group consisting of F, Cl, Br, I, a C_{1-4} alkyl, a C_{1-4} alkoxy, a C_{3-6} cycloalkyl, a C_{2-4} alkenyl, a C_{2-4} alkynyl, a C_{6-10} aryl, a C_{2-10} heterocycloalkyl having 1-2 heteroatom(s) selected from O, S or N;

and/or, the cycloalkyl formed by R^5, R^6 together with the carbon atom attached or the heterocyclic group formed by R^5, R^6 together with the carbon atom attached is substituted by a substituent selected from the group consisting of F, Cl, Br, I, a C_{1-4} alkyl, a C_{1-4} alkoxy, a C_{3-6} cycloalkyl, a C_{2-4} alkenyl, a C_{2-4} alkynyl, a C_{6-10} aryl, a C_{2-10} heterocycloalkyl having 1-2 heteroatom(s) selected from O, S or N;

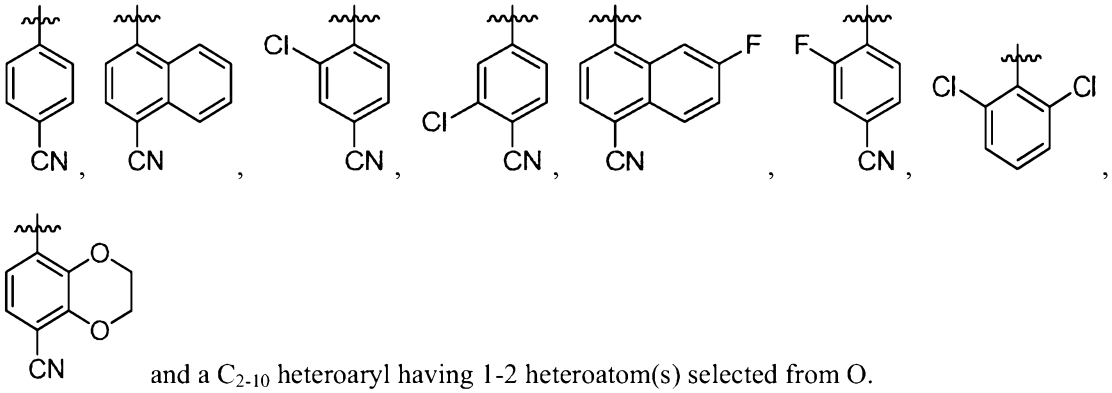
and/or, the alkyl, the alkoxy, the aryl, the heteroaryl, the heterocycloalkyl or the amino defined in R^3 is substituted by a substituent selected from the group consisting of F, Cl, Br, I, a C_{1-4} alkyl, a C_{6-10} aryl, 2,6-dichlorophenyl, 2,6-dichlorobenzyl and 2,6-dichlorobenzoyl;

and/or, the alkyl defined in R^4 is substituted by a substituent selected from the group consisting of 

, 

and a C_{2-10} heteroaryl having 1-2 heteroatom(s) selected from O,

and/or the aryl or the heteroaryl defined in R^4 is substituted by a substituent selected from the group consisting of F, Cl, Br, I, a C_{1-4} alkyl, a C_{1-4} alkoxy, a C_{3-6} cycloalkyl, a C_{2-4} alkenyl, a C_{2-4} alkynyl, a C_{6-10} aryl, a C_{2-10} heterocycloalkyl having 1-2 heteroatom(s) selected from O, S or N,



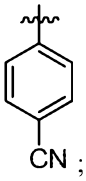
and a C_{2-10} heteroaryl having 1-2 heteroatom(s) selected from O.

5. The condensed ring derivative having a structure of formula II or IV, the tautomer, the mesomer, the racemate, the enantiomer, the diastereoisomer, or the pharmaceutically acceptable salt or the pro-drug thereof according to claim 3, wherein,

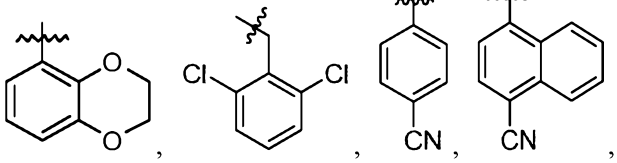
each of R^1 and R^2 is independently methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl or *tert*-butyl;

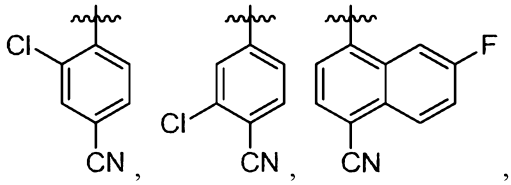
or, R^1 and R^2 together with the carbon atom attached form a cyclobutyl;

and/or, R^3 is methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *tert*-butyl, a phenyl, a



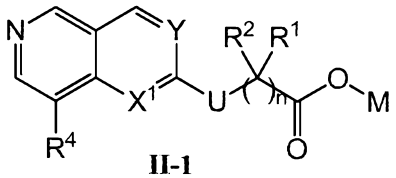
pyridyl or ;

and/or, R^4 is a phenyl, a naphthyl, 



and/or, each of R^5 and R^6 is independently methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl or *tert*-butyl.

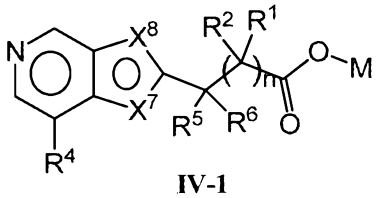
6. The condensed ring derivative having a structure of formula II or IV, the tautomer, the mesomer, the racemate, the enantiomer, the diastereoisomer, or the pharmaceutically acceptable salt or the pro-drug thereof according to any one of claim 1-5, wherein, the compound having a structure of formula II has a structure of formula II-1:



II-1

in the formula II-1, the definitions of X^1, Y, R^1, R^2, R^4, U, M and n refer to those in any one of claims 1-5;

the compound having a structure of formula IV has a structure of formula IV-1:



IV-1

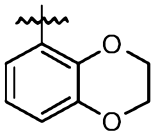
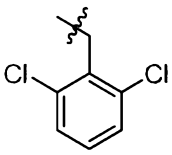
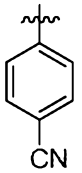
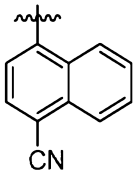
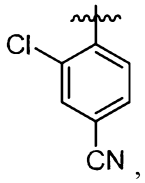
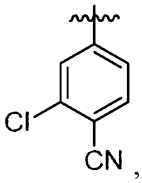
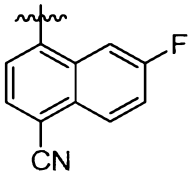
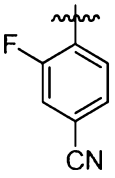
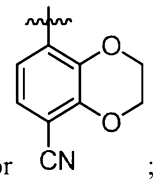
wherein, the definitions of X^7, X^8, R^1, R^2, R^4, R^5, R^6, M and n refer to those in any one of claims 1-5.

7. The condensed ring derivative having a structure of formula II or IV, the tautomer, the mesomer, the racemate, the enantiomer, the diastereoisomer, or the pharmaceutically acceptable salt or the pro-drug thereof according to claim 6, wherein,

in the compound of general formula II-1,

each of R^1 and R^2 is independently H, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl or tert-butyl; or R^1, R^2 together with the carbon atom attached form a cyclobutyl;

M is H;

R^4 is a phenyl, a naphthyl,  ,  ,  ,  ,  ,  ,  ,  or  ;

U is  or  ;

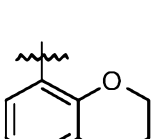
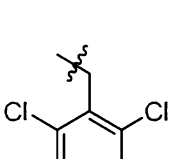
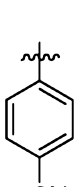
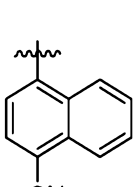
each of R^5 and R^6 is independently H, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl or tert-butyl;

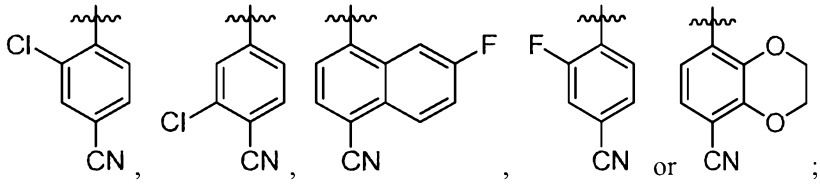
n is 1;

in the compound of formula IV-1,

each of X^7 and X^8 is independently CH or S;

each of R^1 and R^2 is independently H, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl or tert-butyl;

R^4 is a phenyl, a naphthyl,  ,  ,  ,  ,



each of R^5 and R^6 is independently H, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl or tert-butyl;

n is 0 or 1.

8. The condensed ring derivative having a structure of formula II or IV, the tautomer, the mesomer, the racemate, the enantiomer, the diastereoisomer or the pharmaceutically acceptable salt or the pro-drug thereof according to claim 7, wherein,

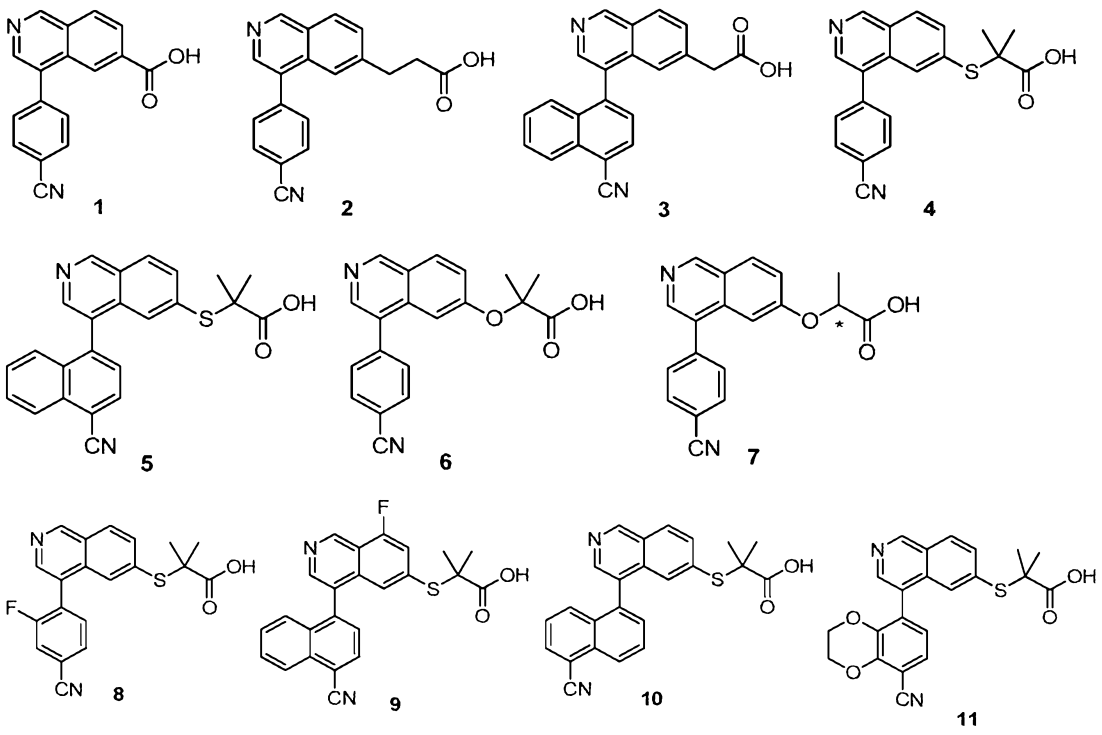
in the compound of formula II-1, where U is  and R^5 and R^6 are H, R^1 and R^2 are not H at the same time;

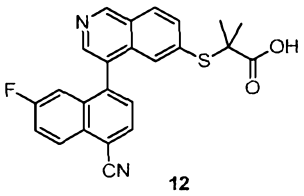
in the compound of formula IV-1,

X^7 is CH; X^8 is S;

where R^1 and/or R^2 is an alkyl, R^5 and R^6 are H; where R^5 and/or R^6 is an alkyl, R^1 and R^2 are H; where X^7 is S, X^8 is CH, R^1 and R^2 are alkyl, R^5 and R^6 are H, R^4 is a phenyl.

9. A condensed ring derivative, the tautomer, the mesomer, the racemate, the enantiomer, the diastereoisomer, or the pharmaceutically acceptable salt or the pro-drug thereof,

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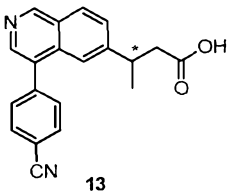
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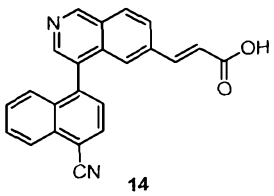
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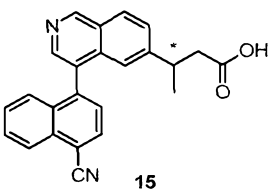
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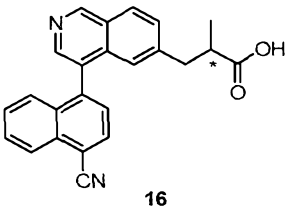
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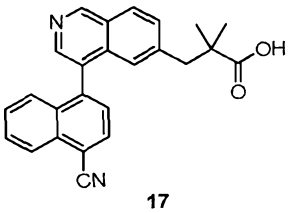
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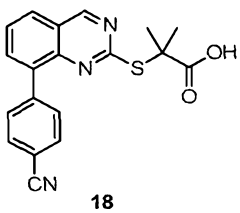
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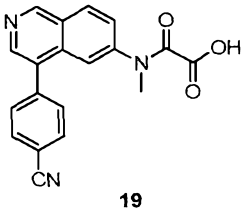
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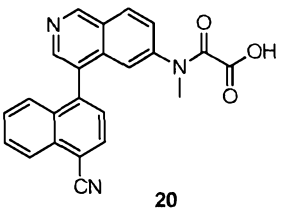
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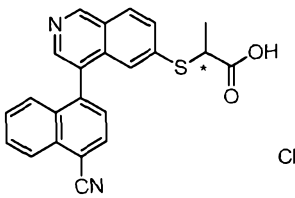
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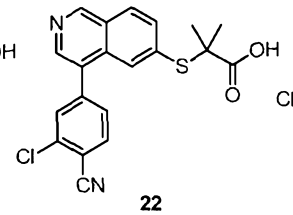
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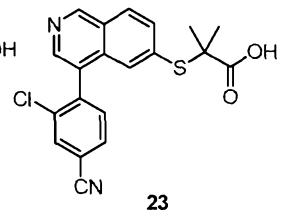
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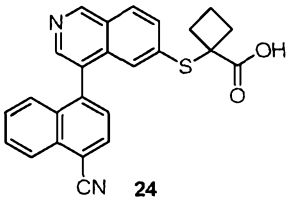
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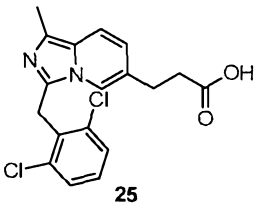
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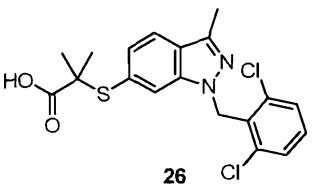
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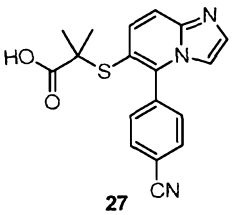
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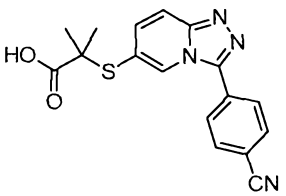
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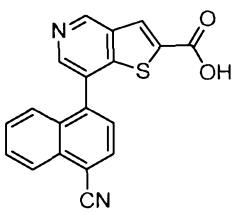
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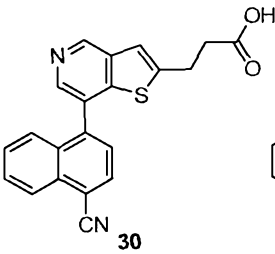
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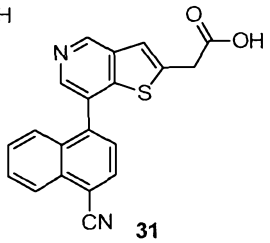
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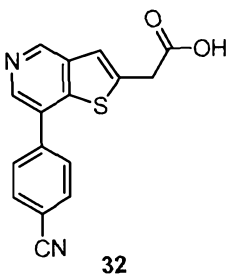
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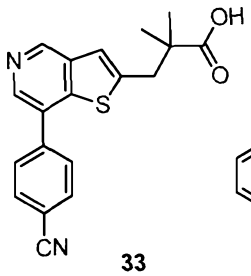
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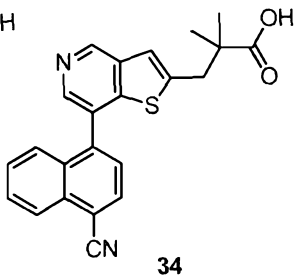
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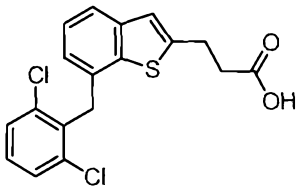
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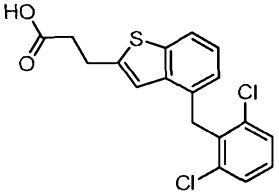
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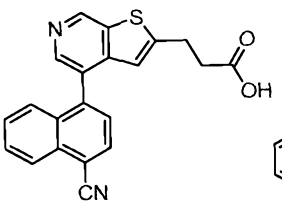
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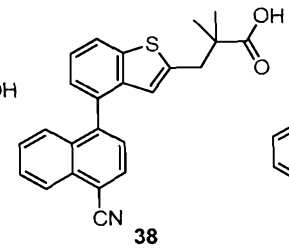
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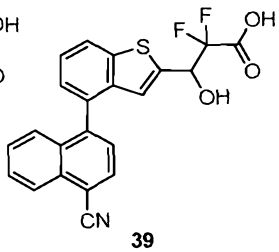
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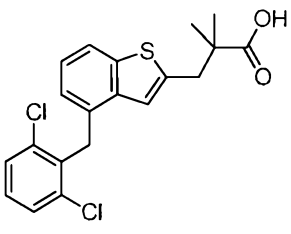
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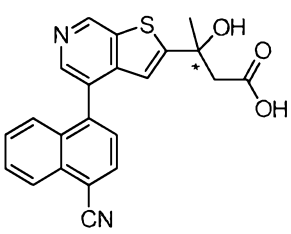
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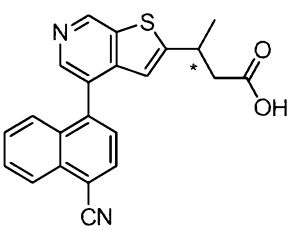
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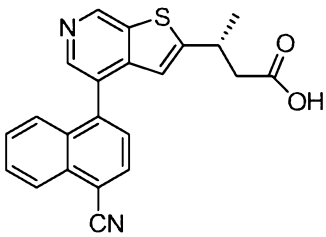
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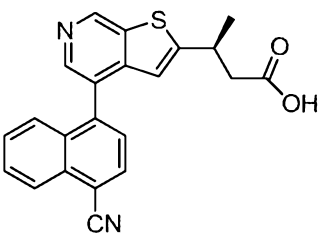
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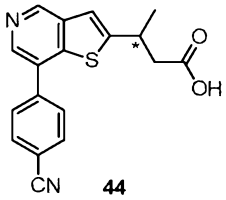
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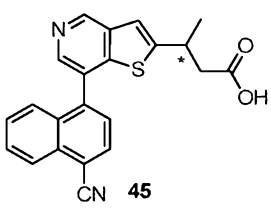
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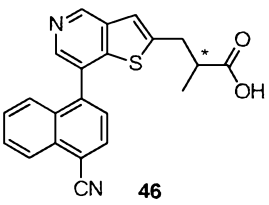
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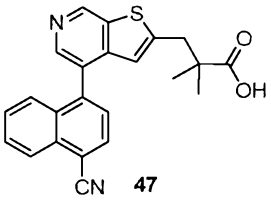
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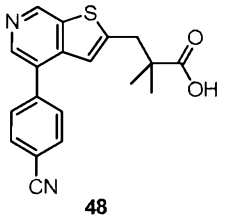
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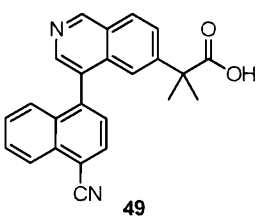
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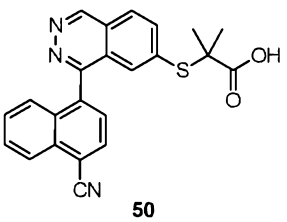
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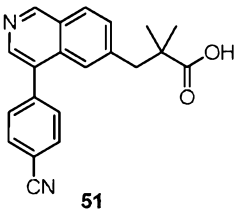
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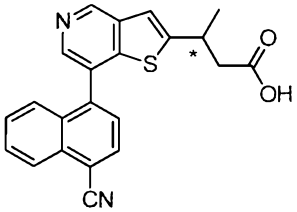
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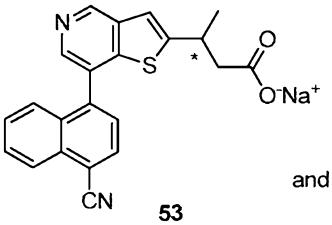
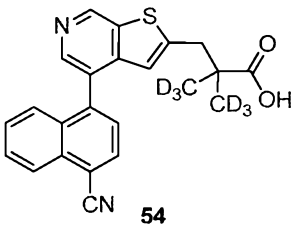
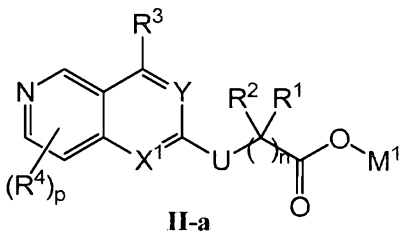

53

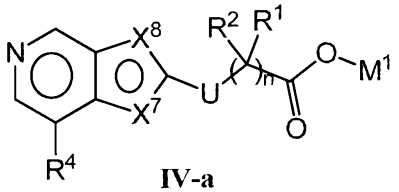
and


54

in the above compounds, the carbon atom marked with * refers to a chiral carbon atom or a non-chiral carbon atom, when it is a chiral carbon atom, it is of S-configuration or R-configuration, when it is a non-chiral carbon atom, it refers to racemate.

10. The compound of formula II-a or IV-a:


II-a



IV-a

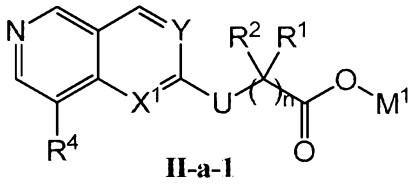
M^1 is an alkyl;

in the compound of formula II-a, X^1 is CH or N; Y is CH or N; the definitions of R^1, R^2, R^3, R^4, U, n and p refers to those in any one of claims 1-9;

in the compound of formula IV-a, each of X^7 and X^8 is independently CH or S; the definitions of R^1, R^2, R^4, U and n refer to those in any one of claims 1-9.

11. The compound of formula II-a or IV-a according to claim 10, wherein,

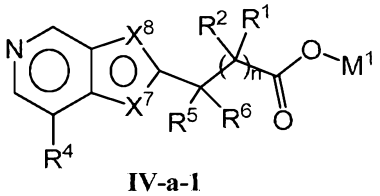
the compound of formula II-a has a structure of formula II-a-1:



II-a-1

wherein, the definitions of X^1, Y, R^1, R^2, R^4, U, M^1 and n refer to those in claim 10;

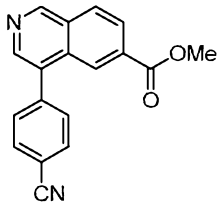
the compound of formula IV-a has a structure of formula IV-a-1:



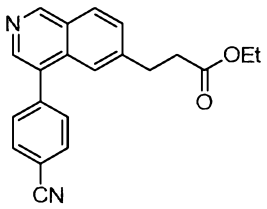
IV-a-1

wherein, the definitions of X^7, X^8, R^1, R^2, R^4, R^5, R^6, M^1 and n refer to those in claim 10.

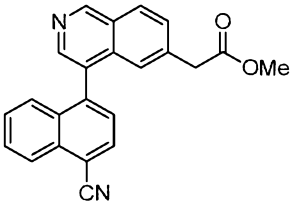
12. A compound which is selected from the group consisting of



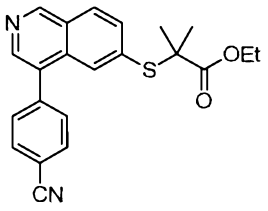
1-a



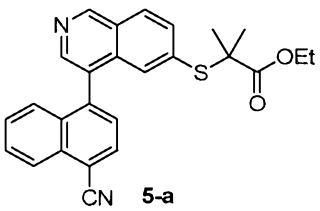
2-a



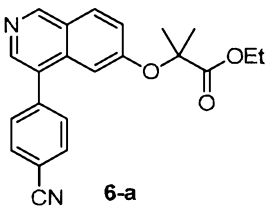
3-a



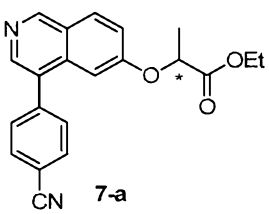
4-a



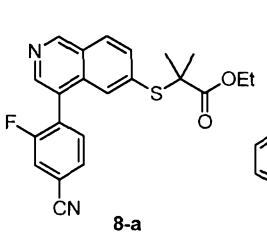
5-a

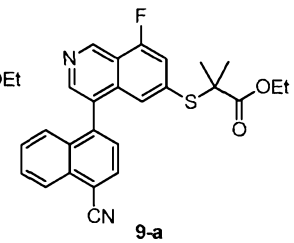


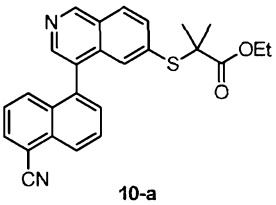
6-a

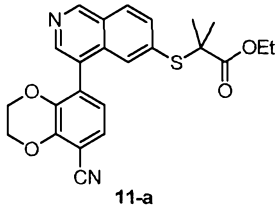


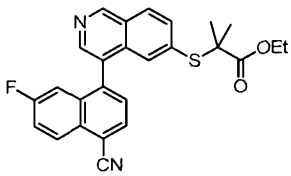
7-a

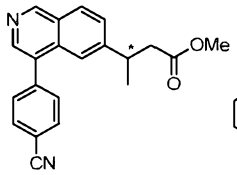

8-a

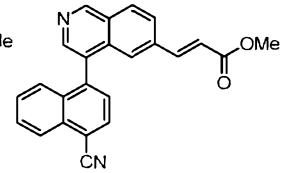

9-a

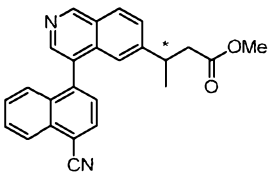

10-a

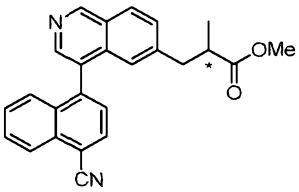

11-a

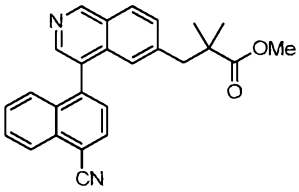

12-a

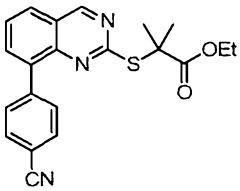

13-a

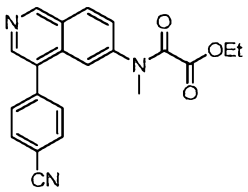

14-a

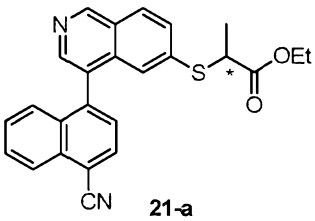

15-a

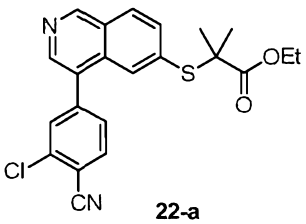

16-a


17-a


18-a


19-a


21-a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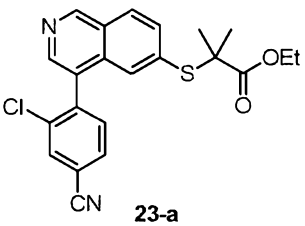
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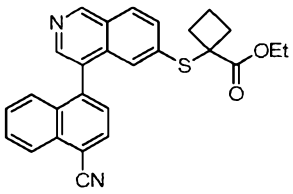
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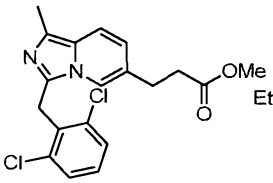
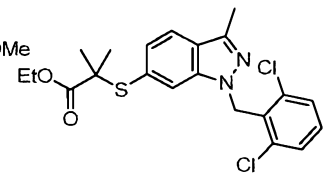
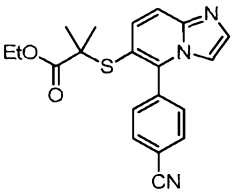
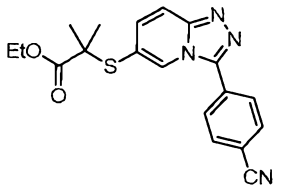

25-a


26-a


27-a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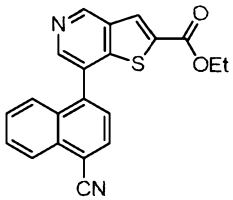
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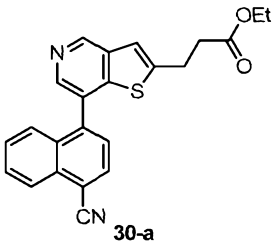
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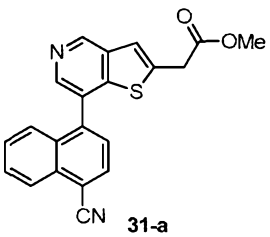
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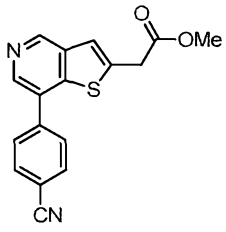
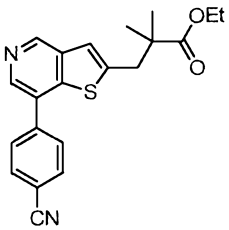

32-a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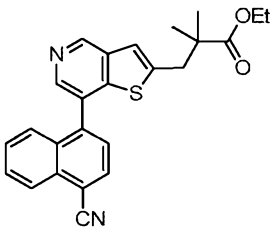
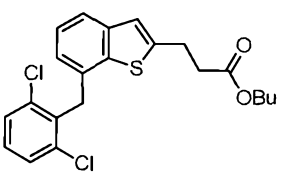
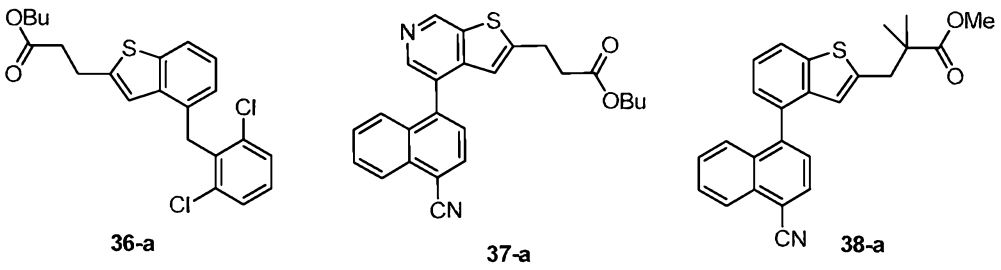
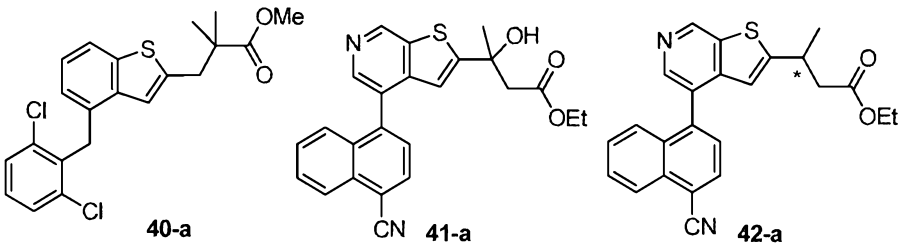
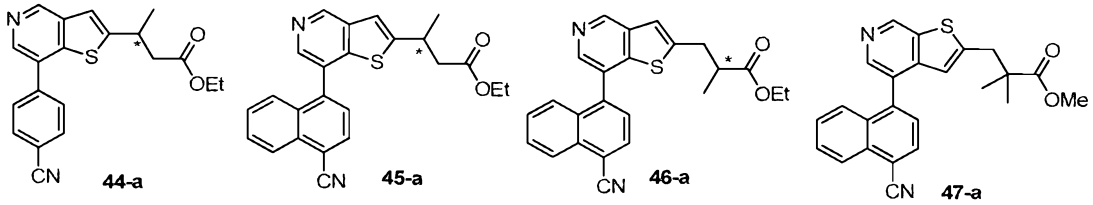
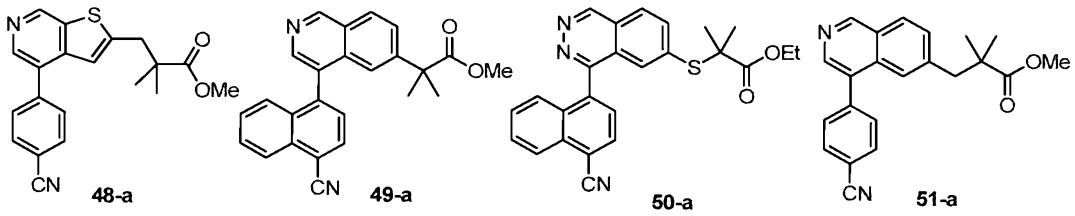

34-a

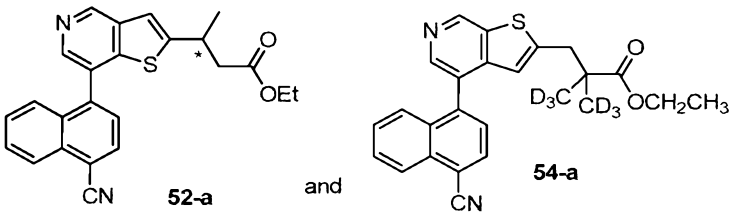

35-a











in the above compounds, the carbon atom marked with * is a chiral carbon atom or a non-chiral carbon atom, when it is a chiral carbon atom, it is of S-configuration or R-configuration, when it is a non-chiral carbon atom, it refers to racemate.

13. Use of the condensed ring derivative having a structure of formula II or IV, the tautomer, the mesomer, the racemate, the enantiomer, the diastereoisomer, or the pharmaceutically acceptable salt or the pro-drug thereof according to at least one of claims 1-9 in manufacturing a medicament in preventing and/or treating hyperuricemia or the disease related to hyperuricemia.

14. Use of the condensed ring derivative having a structure of formula II or IV, the tautomer, the mesomer, the racemate, the enantiomer, the diastereoisomer, or the pharmaceutically acceptable salt or the pro-drug thereof in the manufacture of a medicament according to claim 13, wherein, the disease related to hyperuricemia is selected from the group consisting of gout,

hypertension, diabetes, hypertriglyceridemia, metabolic syndrome, coronary heart disease and kidney damage.

15. A pharmaceutical composition, which contains a pharmaceutically effective amount of the condensed ring derivative having a structure of formula II or IV, the tautomer, the mesomer, the racemate, the enantiomer, the diastereoisomer, or the pharmaceutically acceptable salt or the pro-drug thereof according to at least one of claims 1-9, and one or more than one pharmaceutically acceptable carrier and/or diluent.

16. The pharmaceutical composition according to claim 15, wherein, the composition further contains other uric acid-lowering drugs; the uric acid-lowering drugs is selected from the group consisting of uric acid transporter 1 inhibitor, xanthine oxidase inhibitor, xanthine oxidoreductase and xanthine dehydrogenase inhibitor.

17. The pharmaceutical composition according to claim 16, wherein, the composition further contains purine alcohol and/or Febuxostat.

18. A method of treatment of hyperuricemia or a disease related to hyperuricemia, comprising administering to a subject in need thereof an effective amount of the condensed ring derivative having a structure of formula II or IV, the tautomer, the mesomer, the racemate, the enantiomer, the diastereoisomer, or the pharmaceutically acceptable salt or the pro-drug thereof according to at least one of claims 1-9.

19. A method of treatment of hyperuricemia or a disease related to hyperuricemia according to claim 18, wherein the disease related to hyperuricemia is selected from the group consisting of gout, hypertension, diabetes, hypertriglyceridemia, metabolic syndrome, coronary heart disease and kidney damage.