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(54) **ARYL HYDROCARBON RECEPTOR MODULATOR**

ARYL-KOHLENWASSERSTOFF-REZEPTOR-MODULATOR

MODULATEUR DE RÉCEPTEUR D'HYDROCARBURE ARYLE

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(73) Proprietor: **Ariagen, Inc.**
**Menlo Park, CA 94025 (US)**

(72) Inventors:
- **YANG, Luqing**
  **Shanghai 201203 (CN)**
- **LI, Guodong**
  **Shanghai 201203 (CN)**
- **ZHANG, Suoming**
  **Shanghai 201203 (CN)**

(74) Representative: **Cohausz & Florack**
**Patent- & Rechtsanwälte**
**Partnerschaftsgesellschaft mbB**
**Bleichstraße 14**
**40211 Düsseldorf (DE)**

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**WO-A1-2016/040553**
**WO-A2-2019/099977**
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**US-A- 3 946 029**
**US-A1- 2007 043 092**





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- **CLAUDIA CAVALLUZZO ET AL.: 'De Novo Design of Small Molecule Inhibitors Targeting the LEDGF/p75-HIV Integrase Interaction' RSC ADVANCES vol. 2, no. 3, 2012, ISSN 2046-2069 pages 974 - 984, XP055509714**
- **GIUSEPPE LA REGINA ET AL.: 'New Arylthioindoles and Related Bioisosteres at the Sulfur Bridging Group. 4. Synthesis, Tubulin Polymerization, Cell Growth Inhibition, and Molecular Modeling Studies' JOURNAL OF MEDICINAL CHEMISTRY vol. 52, no. 23, 14 July 2009, ISSN 0022-2623 pages 7512 - 7527, XP055460034**
- **ABBS FEN REJI T. F . ET AL.: 'Synthesis and Cytotoxicity Studies of Thiazole Analogs of the Anticancer Marine Alkaloid Dendrodoine' INDIAN JOURNAL OF CHEMISTRY, SECTION B: ORGANIC CHEMISTRY INCLUDING MEDICINAL CHEMISTRY vol. 47B, no. 7, 02 December 2011, ISSN 0376-4699 pages 1145 - 1150, XP055509736**


(52) Cooperative Patent Classification (CPC): (Cont.)
**C07D 413/06; C07D 417/10; C07D 417/14; C07D 419/14; C07H 19/044**

## Description

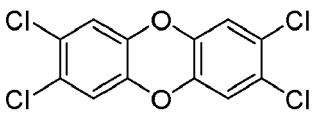
### FIELD OF THE INVENTION

**[0001]** The present invention belongs to the field of anti-tumor compounds, relates to a class of compounds which can modulate activity of aryl hydrocarbon receptor (AhR) and pharmaceutically acceptable salts thereof.

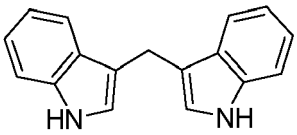
### BACKGROUND OF THE INVENTION

**[0002]** Due to changes of environment and lifestyle, incidence of cancer increases with each passing day. Coupled with its high fatality rate, cancer is a serious threat to human's health. Although there has been significant progress in medical treatment of certain cancers and targeted drugs and immune therapy have improved survival rate of patients greatly, in the past 20 years, the total of 5 year survival rate of all cancer patients increased only 10% monthly. And due to resistance or uncontrolled migration and rapid growth of malignant tumors, detection and treatment of cancer are extremely difficult.

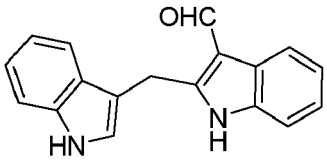
**[0003]** Aryl hydrocarbon receptor (AhR) is a kind of intracellular transcriptional regulatory factor which can sense stimulation of xenobiotic in external environment and mediate toxic reactions. AhR after activation can regulate expression of many genes in chromosome and promote decomposition of xenobiotic. Previous studies have shown that this signal is also involved in several important biological processes, such as signal transduction, cellular differentiation and apoptosis. Relationship between AhR and immune regulation has also been a hotspot of research. Previous research has shown that AhR can participate in differentiation and function of T cells, macrophages and DC. In addition, AhR also plays a key role in immune rejection reactions after organ transplantation. Study has found that to activate AhR in body of mice by use of dioxin can reduce their survival rate after viral infection and differentiation and proliferation rate of virus-specific COB8 T cells are also affected. For example, another compound of DIM and derivatives thereof have activity of inhibiting tumor (Breast Cancer Res. Treat. 2001, 66, 147). DIM is currently in phase II clinical trials for treatment of prostate cancer and cervical cancer. Natural products ICZ and FICZ are both AhR agonist, and can anti-asthmatic (Chem. Rev., 2002, 102, 4303; Chem. Rev., 2012, 112, 3193; J. Biol.chem. 2009, 284, 2690). Malassezin (Bioorg. Med. Chem. 2001, 9, 955). Aminoflavonone, developed by NCI, is in phase I clinical trials. 3-hydroxymethyl indole (indole-3-carbinol), in phase II clinical trials, is used as chemical protection agent and immune stimulant. Phortress is an AhR agonists developed by Pharminox Univ. of Nottingham, and is in phase I clinical trials for treatment of solid tumors (Br. J. Cancer, 2003, 88, 599; Mal.Cancer Ther. 2004, 3, 1565). Tanshinone I is a natural AhR ligand for antitumor chemoprotectant (Toxicol Appl Pharmacol. 2011 Apr 1; 252 (1): 18-27). 2-(indolylacetyl-3-yl) furan (Food Chem. 2011, 127, 1764-1772). ITE is a natural endogenous AhR agonist having effect of anti-liver cancer, prostate cancer, breast cancer and ovarian cancer (Proc. Natl. Acad. Sci. 2002, 99, 14694-9; CN102573470; WO2016040553).



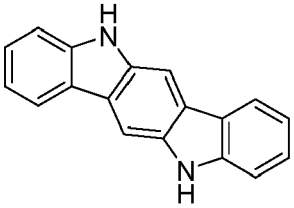

TCDD



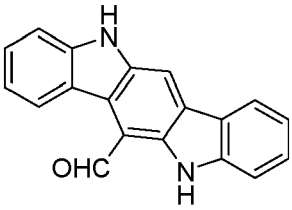

DIM



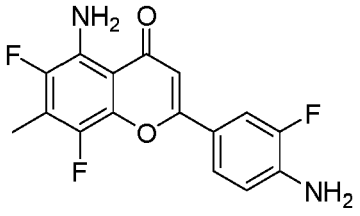

Malasserin



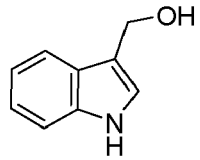

ICZ



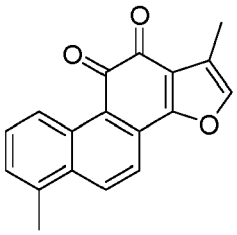

FICZ



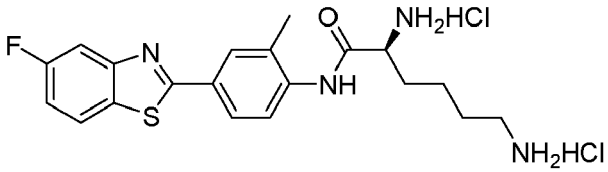

aminoflavonone



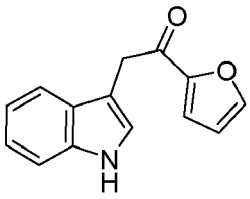

Indole-3-carbinol



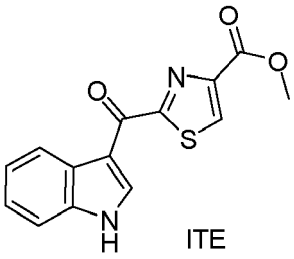

Tanshinone I



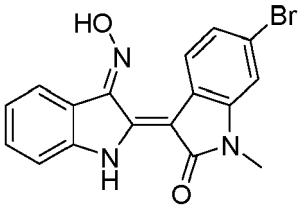

Phortress




Indolylfuran




ITE




MeBio

**[0004]** C. Cavalluzzo et al., RSC Advances, 2012, vol. 2, pages 974-984 describes a de novo design of small molecule inhibitors targeting the lens epithelium-derived growth factor LEDGF/p75-HIV integrase interaction.

**[0005]** G. La Regina et al., J. Med. Chem. 2009, vol. 52, no. 23, pages 7512-7527 describes new arylthioindoles and related bioisosteres at the sulfur bridging group: synthesis, tubulin polymerization, cell growth inhibition, and molecular modeling studies.

**[0006]** WO 02/064138 A1 describes preparations and use of an AH receptor ligand, 2-(1'H-indole-3'-carbonyl)-thiazole-4-carboxylic acid methyl ester.

**[0007]** CN 102573470 A describes a method of cancer intervention or eradication by administering an effective amount of an endogenous ligand for the aryl hydrocarbon receptor (AhR) named ITE or one of its analogs (the active ingredient) to a subject with cancer.

**[0008]** US 2007/0043092 A1 describes a method of treating angiogenesis-implicated disorders by selecting a subject predisposed to an angiogenesis-implicated disorder and then administering an effective amount of an endogenous aryl hydrocarbon receptor ligand or its analogs.

**[0009]** WO 2016/040553 A1 describes methods of synthesizing 2-(1'H-indole-3'-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE) and structural analogs thereof. The methods include condensation reactions or condensation and oxidation reactions to form the thiazoline or thiazole moiety of ITE or its structural analogs.

**[0010]** WO 2013/116182 A1 describes heterocyclic compounds as inhibitors of leukotriene production and pharmaceutical compositions comprising these compounds, methods of using these compounds in the treatment of various diseases and disorders, processes for preparing these compounds and intermediates useful in these processes.

**[0011]** WO 03/105847 A1 describes the use of potent potassium channel blockers or a formulation thereof in the treatment of glaucoma and other conditions which leads to elevated intraocular pressure in the eye of a patient as well as the use of such compounds to provide a neuroprotective effect to the eye of mammalian species, particularly humans.

**[0012]** US 3,946,029 describes novel 3-indolyl pyridyl ketone derivatives having pharmacological activity, pharmaceutical and veterinary compositions containing them and a method of preparing the said derivatives.

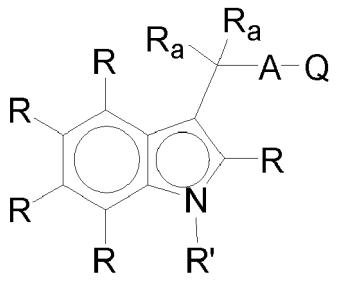
**[0013]** GB 1,318,300 describes indole derivatives having pharmacological activity and pharmaceutical and veterinary compositions containing them.

**[0014]** WO 03/068742 A1 describes a synthesis of indole thiazole compounds as ligands for the aryl hydrocarbon receptor (AhR).

**[0015]** T. F. Abbs Fen Reji et al., Indian Journal of Chemistry, vol. 47B, 2008, pages 1145-1150 describes a synthesis and cytotoxicity studies of thiazole analogs of the anticancer marine alkaloid dendrodoine.

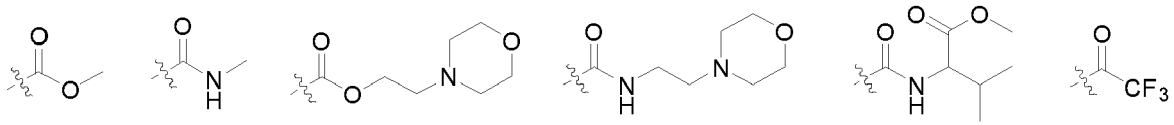
## SUMMARY OF THE INVENTION

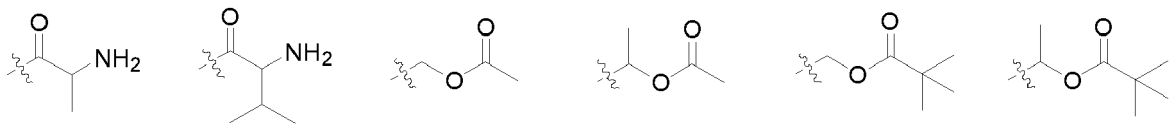
**[0016]** Objective of the present invention is to provide a new kind of aryl hydrocarbon receptor modulators of formula (I) having AhR activity, and pharmaceutically acceptable salts thereof,

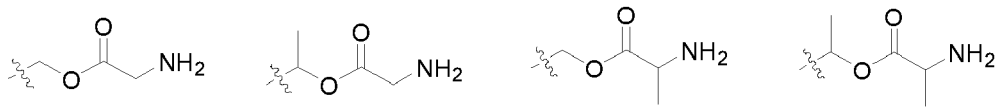


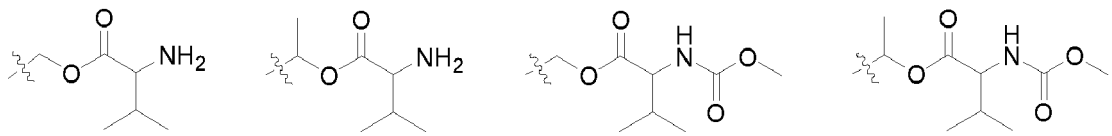

(I)

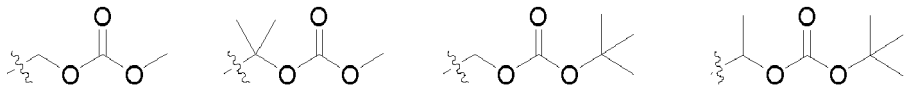
R' is selected from the following substituents: H,

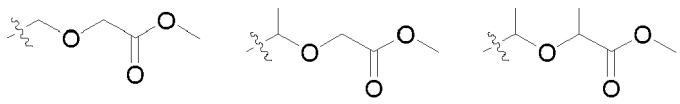


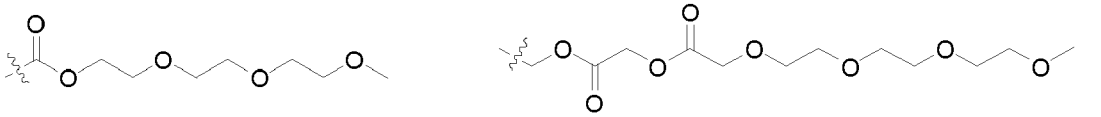







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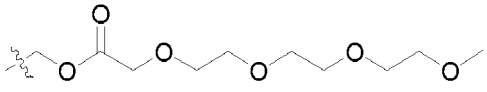
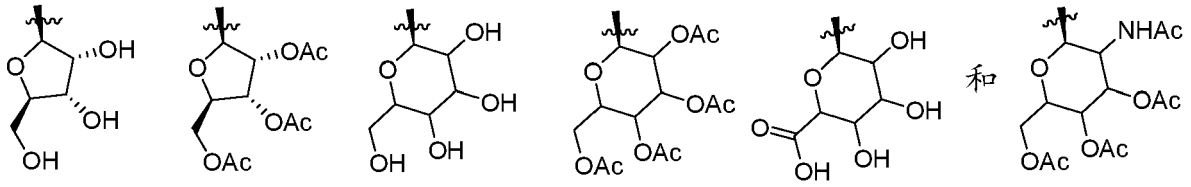




two $R_a$ is independently H, or two $R_a$ together form =O, =N-CN or =N-$W_3$-$R_1$; when $W_3$ is O or NH, $R_1$ is H, $C_mH_{2m+1}$, $C_mH_{2m+1}C(O)$, $C_mH_{2m+1}OC(O)$ or $C_mH_{2m}{}_{+1}S(O)_{1\sim2}$;

A is $C_2$ to $C_{10}$ heteroaromatic ring containing 1 to 5 heteroatoms selected from N, O and S, or 4 to 7 membered non-aromatic heterocyclic ring containing 1 to 3 heteroatoms selected from N, O and S and containing C=N, which are with no substituent or substituted by 1 to 3 R;

Q is R or a 3 to 10 membered, preferably 4 to 7 membered, more preferably 5 to 6 membered heterocyclic ring, preferably heteroaryl ring with no substituent or substituted by 1 to 3 R, which contains 1 to 5, preferably 1 to 3, more preferably 2 to 3 heteroatoms selected from N, O and S;

R is $R_c$ connected with C or $R_N$ connected with N, wherein each $R_c$ is independently R", -Y-NR"$_2$, -Y-NR"C(O)R", -Y-NR"C(O)NR"$_2$, -Y-OC(O)NR"$_2$, -Y-NR"C(O)OR", -Y-$S(O)_{1\sim2}$R", -Y-$S(O)_{1\text{-}2}$NR"$_2$ or -Y-NR"$S(O)_{1\sim2}$R"; each $R_N$ is independently CN, R", -Y-OR", -Y-C(O)R", -Y-OC(O)R", -Y-C(O)OR", -Y-OC(O)OR", -Y-NR"$_2$, -Y-C(O)NR"$_2$, -Y-NR"C(O)R", -Y-NR"C(O)NR"$_2$ , -Y-OC(O)NR"$_2$, -Y-NR"C(O)OR", -Y-$S(O)_{1\sim2}$R", -Y-$S(O)_{1\sim2}$NR"$_2$ or -Y-NR"$S(O)_{1\sim2}$R";

R" is H, D, $C_mH_{2m+1}$, $C_nH_{2n-1}$, $C_nH_{2n-3}$, $C_mH_{2m+1-r}X_r$, $C_nH_{2n-1-s}X_s$ or $C_nH_{2n-3-t}X_t$;

Y is bond, -$C_mH_{2m}$-, -$C_nH_{2n-2}$-, -$C_nH_{2n-4}$-, -$C_mH_{2m-i}X_i$-, -$C_nH_{2n-2-j}X_j$- or -$C_nH_{2n-4-k}X_k$-;

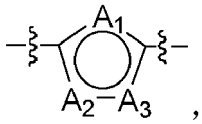
*m* is 1 to 3, *n* is 2 to 4, *u* is 1 to 3, $r\leq 2m+1$, $s\leq 2n-1$, $t\leq 2n-3$, $i\leq 2m$, $j\leq 2n-2$, $k\leq 2n-4$;

X is F, Cl or Br.

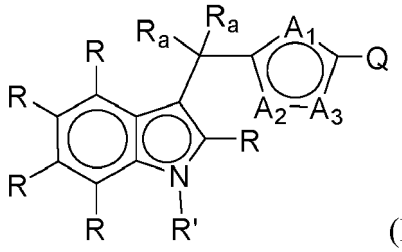
**[0017]** Wherein, the term "cyclic $C_4H_8NO$" in (cyclic $C_4H_8NO)C_mH_{2m}$ is a 6 membered ring in which atoms of N and O are arranged by meta or para arrangements, preferably morpholine substituted at N position.

**[0018]** $C_mH_{2m+1}$, $C_mH_{2m+1-r}X_r$, -$C_mH_{2m}$- and -$C_mH_{2m-i}X_i$- can be a straight-chain or branch-chain alkyl. $C_nH_{2n-1}$, $C_nH_{2n-1-s}X_s$, -$C_nH_{2n-2}$- and -$C_nH_{2n-2-j}X_j$- can be a straight-chain or branch-chain alkenyl. $C_nH_{2n-3}$, $C_nH_{2n-3-t}X_t$, -$C_nH_{2n-4}$- and -$C_nH_{2n-4-k}X_k$ can be a straight-chain or branch-chain alkynyl.

**[0019]** When n is 3 or 4, $C_nH_{2n-1}$, $C_nH_{2n-1-s}X_s$, -$C_nH_{2n-2}$- and -$C_nH_{2n-2-j}X_j$- can also be naphthenic group. In some preferable embodiments of the invention, when A is



formula (I) turns into formula (I1),



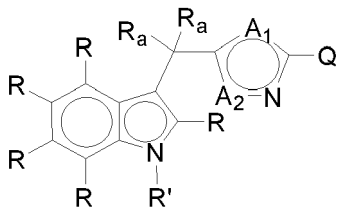
(I1)

in formula (I1), one of $A_1$, $A_2$ and $A_3$ is O, S or N(R), the rest two are each independently C(R) or N.

**[0020]** To be specific, it can be divided three classes, if $A_1$ is O, S or N(R), $A_2$ and $A_3$ is independently C(R) or N respectively; if $A_2$ is O, S or N(R), $A_1$ and $A_3$ is independently C(R) or N respectively; if $A_3$ is O, S or N(R), $A_1$ and $A_1$ is independently C(R) or N respectively.

**[0021]** On the base of formula (I1) of the invention, more preferably, one of $A_1$, $A_2$ and $A_3$ is O, S or N(R); the rest two ones are each independently N.

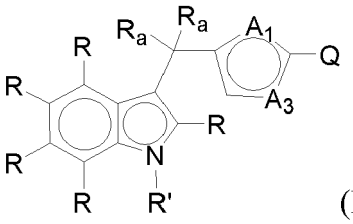
**[0022]** At this moment, all of $A_1$, $A_2$ and $A_3$ are heteroatom. More preferably on the base of this, when $A_3$ is fixed to be N, the formula (I1) turns into formula (Ia)



(Ia)

in formula (Ia), $A_1$ is O, S or N(R), $A_2$ is N; or $A_2$ is O, S and N(R), $A_1$ is N.

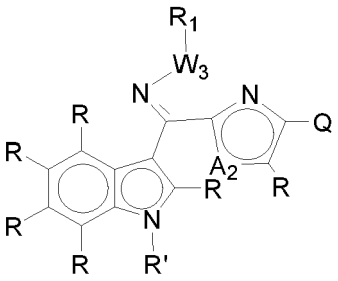
**[0023]** On the base of formula (I1) of the invention, more preferably, when $A_2$ is CH, formula (I1) turns into formula (Ib),



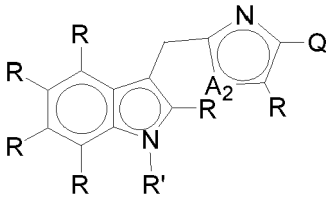
(Ib)

in formula (Ib), $A_1$ is N or C(R), $A_3$ is O, S or N(R); or $A_1$ is O, S or N(R), $A_3$ is N or C(R).

**[0024]** On the base of formula (I1) of the invention, more preferably, when $A_1$ is N, $A_3$ is C(R) and two $R_a$ together form =N-$W_3$-$R_1$ or H independently, at this moment, formula (I1) turns into formula (Ic) or formula (Id) ;



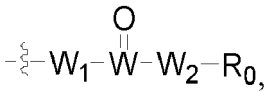
(Ic)



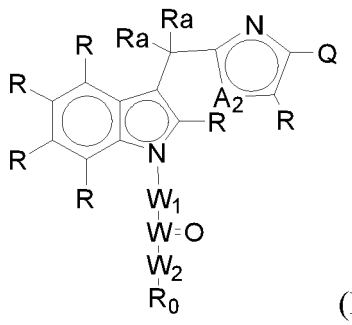
(Id)

in formula (Ic) and formula (Id), $A_2$ is O, S or N(R).

**[0025]** On the base of formula (I1) of the disclosure, more preferably, when $A_1$ is N, $A_3$ is C(R) and R' is



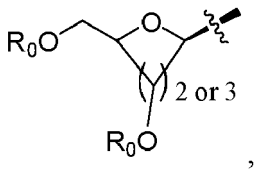
at this moment, formula (I1) turns into formula (Ie),



(Ie)

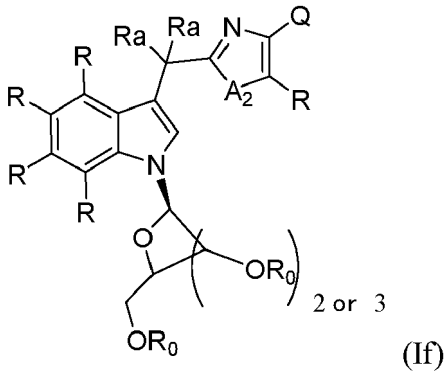
in formula (Ie), $A_2$ is O, S or N(R).

**[0026]** On the base of formula (I1) of the disclosure, more preferably, when $A_1$ is N, $A_3$ is C(R) and R' is



,

at this moment, formula (I1) turns into formula (If),

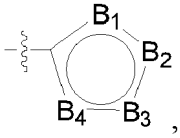


(If)

in formula (If), $A_2$ is O, S or N(R), each Ro is independently H or Ac.

**[0027]** In some preferable embodiments of the invention,

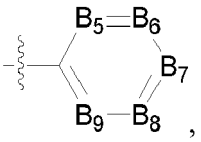
Q is



,

one of $B_1$, $B_2$, $B_3$ and $B_4$ is O, S or N(R), the rest three ones are each independently C(R) or N; that is to say,
when $B_1$ is O, S or N(R), $B_2$, $B_3$ and $B_4$ are independently C(R) or N;
or when $B_2$ is O, S or N(R), $B_1$, $B_3$ and $B_4$ are independently C(R) or N;
or when $B_3$ is O, S or N(R), $B_1$, $B_2$ and $B_4$ are independently C(R) or N;
or when $B_4$ is O, S or N(R), $B_1$, $B_2$ and $B_3$ are independently C(R) or N.

**[0028]** In some preferable embodiments of the invention, when Q is

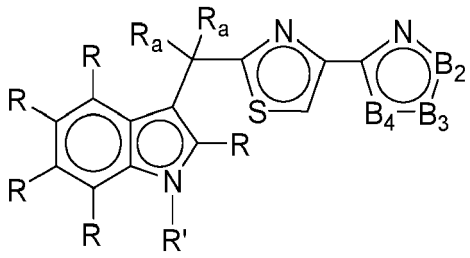


,

$B_5$ to $B_9$ are C(R), i.e. Q is a benzene ring; or one or two of $B_5$ to $B_9$ is N, the rest three ones are independently C(R), that is to say,

Q can be a pyridine ring, at this moment, if $B_5$ is N, $B_6$ to $B_9$ are independently C(R); or if $B_6$ is N, $B_5$, $B_7$ to $B_9$ are independently C(R); or if $B_7$ is N, $B_5$, $B_6$, $B_8$ and $B_9$ are independently C(R);
Q can be a pyridazine ring, at this moment, if $B_5$ and $B_6$ are N respectively, $B_7$ to $B_9$ are independently C(R); or if $B_6$ and $B_7$ are N respectively, $B_5$, $B_8$ and $B_9$ are independently C(R);
Q can be a pyrimidine ring, at this moment, if $B_5$ and $B_7$ are N respectively, $B_6$, $B_8$ and $B_9$ are independently C(R);
Q can be a pyrazine ring, at this moment, if $B_5$ and $B_8$ are N respectively, $B_6$, $B_7$ and $B_9$ are independently C(R).

**[0029]** On the base of formula (I1) of the invention, more preferably, when $A_1$ is N, $A_2$ is S, $A_3$ is CH and Q is a 5 membered heteroaromatic ring, formula (I1) turns into formula (Ig),

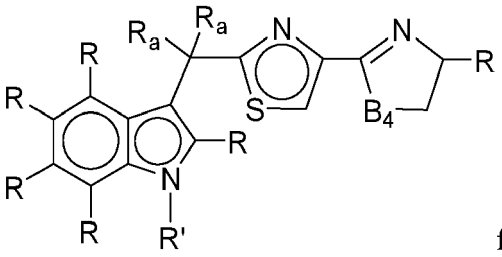


formula (Ig)

wherein one of $B_2$, $B_3$ and $B_4$ is O, S or N(R), the rest ones are each independently C(R) or N, that is to say,

if $B_2$ is O, S or N(R), $B_3$ and $B_4$ are each independently C(R) or N;
if $B_3$ is O, S or N(R), $B_2$ and $B_4$ are each independently C(R) or N;
if $B_4$ is O, S or N(R), $B_2$ and $B_3$ are each independently C(R) or N.

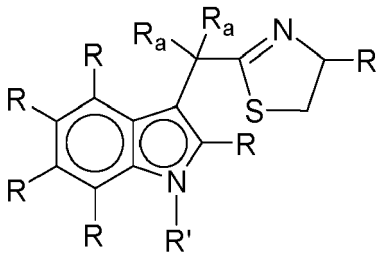
**[0030]** On the base of formula (I1) of the invention, more preferably, when $A_1$ is N, $A_2$ is S, $A_3$ is CH and Q is a 5 membered non-aromatic heterocycle containing C=N, at this moment, formula (I1) turns into formula (Ih),



formula (Ih)

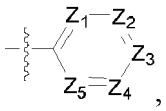
$B_4$ is O, S or N(R).

**[0031]** In some preferable embodiments of the invention, when A is a non-aromatic heterocyclic ring with N and S heteroatom and Q is R, formula (I) turns into formula (I2),

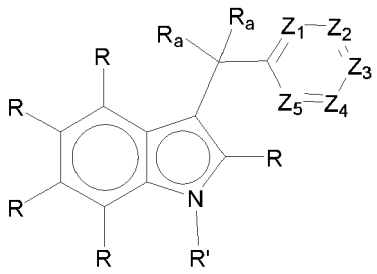


formula (I2).

**[0032]** In some preferable embodiments of the invention, when A is



formula (I) turns into formula (I3),



(I3)

in formula (I3), one or two of $Z_1$ to $Z_5$ are N, the rest ones are independently C(Q), i.e.

**[0033]** A can be a pyridine ring, at this moment, if $Z_1$ is N, $Z_2$ to $Z_5$ are independently C(Q); or if $Z_2$ is N, $Z_1$, $Z_3$ to $Z_5$ are independently C(Q); or if $Z_3$ is N, $Z_1$, $Z_2$, $Z_4$ and $Z_5$ are independently C(Q);

**[0034]** A can be a pyridazine ring, at this moment, if $Z_1$ and $Z_2$ are N respectively, $Z_3$ to $Z_5$ are independently C(Q); or if $Z_2$ and $Z_3$ are N respectively, $Z_1$, $Z_4$ and $Z_5$ are independently C(R);

**[0035]** A can be a pyrimidine ring, at this moment, $Z_1$ and $Z_3$ are N respectively, $Z_2$, $Z_4$ and $Z_5$ are independently C(Q);

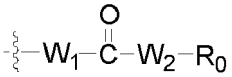
**[0036]** A can be a pyrazine ring, at this moment, $Z_1$ and $Z_4$ are N respectively, $Z_2$, $Z_3$ and $Z_5$ are independently C(Q);

or, the two ones of $Z_1$ to $Z_5$ adjacent to each other is C(Q) and forms together a 5 to 6 membered carbocyclic ring or a 5 to 6 membered heterocyclic ring containing 1 to 3 heteroatom selected from N, O and S, the rest three ones each are independently C(Q) , or two of the rest three ones are each independently C(Q), the last ones is N; or one of the rest three ones is C(Q), the rest two are independently N. According to position forming a ring, two kinds of situations can be classified:

when $Z_1$ and $Z_2$ is C(Q) and form a 5 to 6 carbon ring or a 5 to 6 heterocycle containing 1 to 3 heteroatom selected from N, O and S, $Z_3$ to $Z_5$ are independently C(Q), or $Z_3$ and $Z_4$ are independently C(Q) and $Z_5$ is N; or $Z_3$ and $Z_5$ are independently C(Q) and $Z_4$ is N; or $Z_4$ and $Z_5$ are independently C(Q) and $Z_3$ is N; or $Z_3$ is C(Q) and $Z_4$ and $Z_5$ are N independently; or $Z_4$ is C(Q) and $Z_3$ and $Z_5$ are N independently; or $Z_5$ is C(Q) and $Z_3$ and $Z_4$ are N independently;

when $Z_2$ and $Z_3$ is C(Q) and form a 5 to 6 carbon ring or a 5 to 6 heterocycle containing 1 to 3 heteroatom selected from N, O and S, $Z_1$, $Z_4$ and $Z_5$ are independently C(Q), or $Z_1$ and $Z_4$ are independently C(Q) and $Z_5$ is N; or $Z_1$ and $Z_5$ are independently C(Q) and $Z_4$ is N; or $Z_4$ and $Z_5$ are independently C(Q) and $Z_1$ is N; or $Z_1$ is C(Q) and $Z_4$ and $Z_5$ are N independently; or $Z_4$ is C(Q) and $Z_1$ and $Z_5$ are N independently; or $Z_5$ is C(Q) and $Z_1$ and $Z_4$ are N independently.

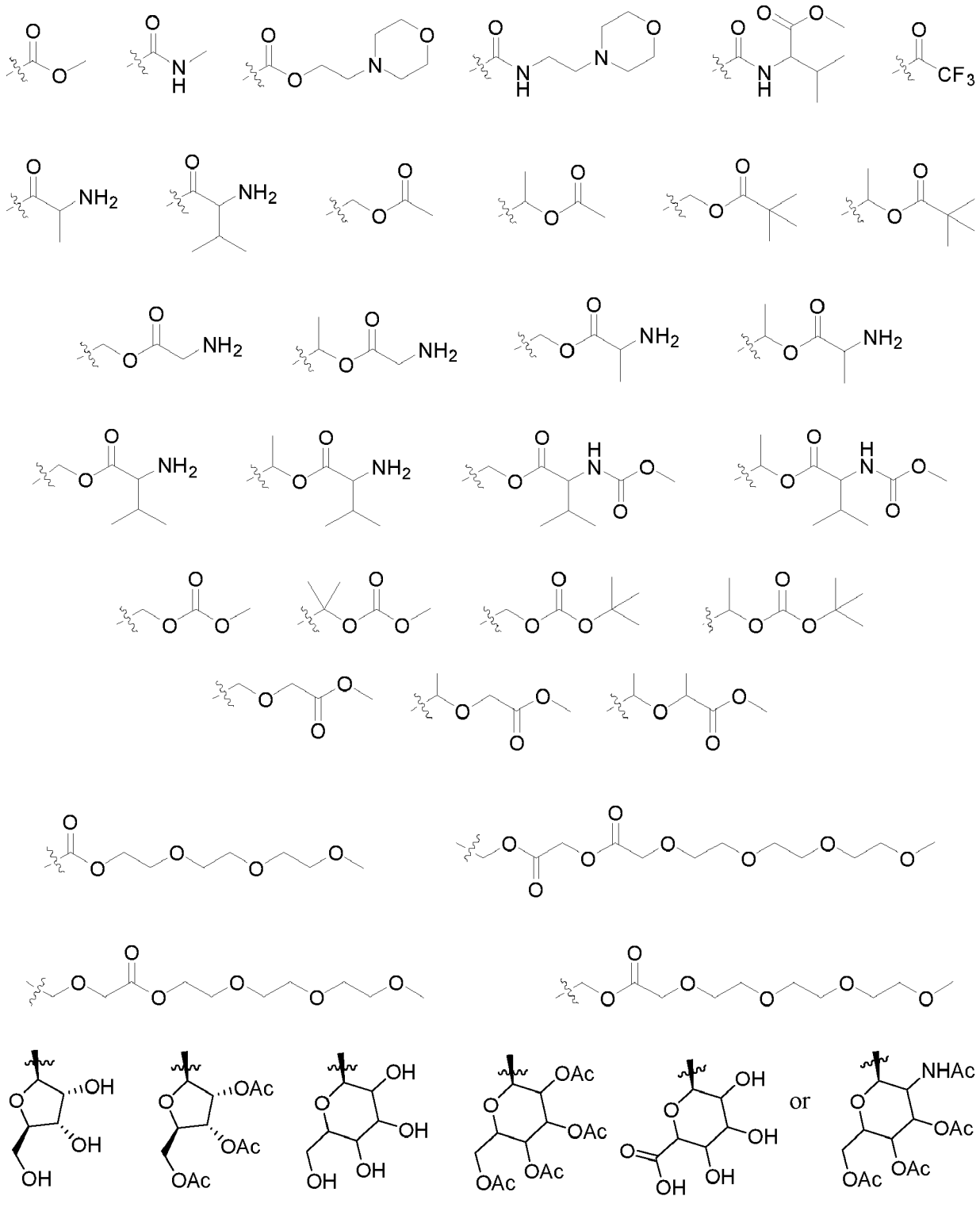
**[0037]** Further disclosed is R' being



, $W_1$ is bond, $C(R_0)_2O$ or $C(R_0)_2OC(R_0)_2$; $W_2$ is O or $CH(N(R_0)_2)R_0$.

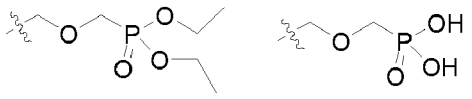
**[0038]** In the embodiments, each functional group or radical can be selected optionally and combined in the scope of description, for example

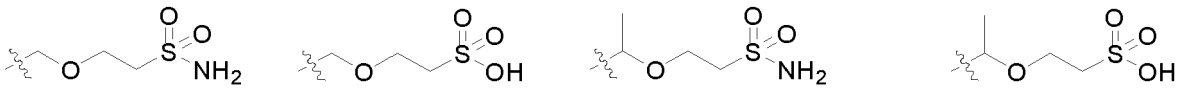
in formula (I), R' can be one selected from the following substituent:



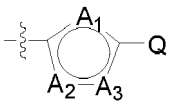
.

**[0039]** Further disclosed herein, in formula (I), R' is selected from the following substituents :

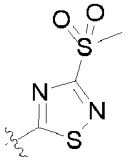


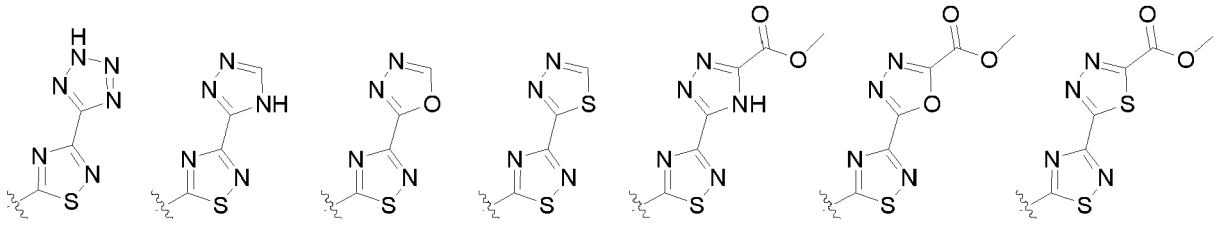


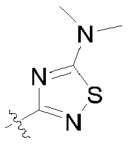
**[0040]** In the embodiments, in formula (I1),

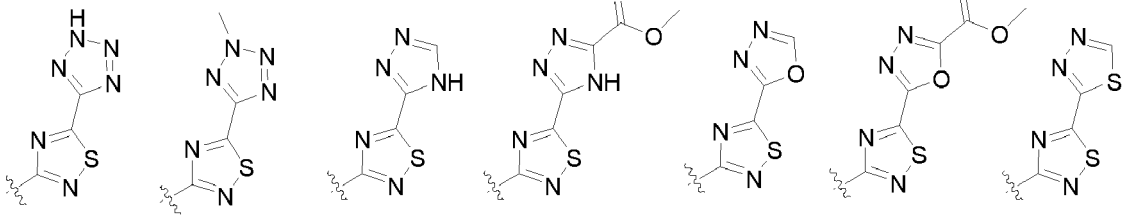


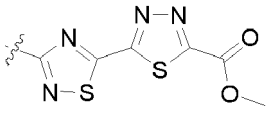
can be one selected from the following substituents :

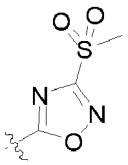


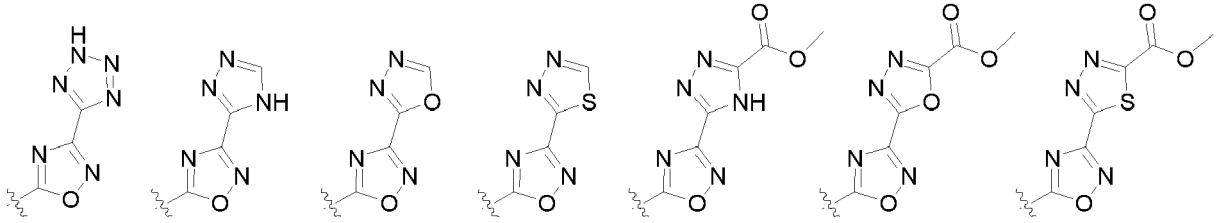


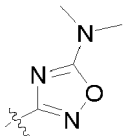


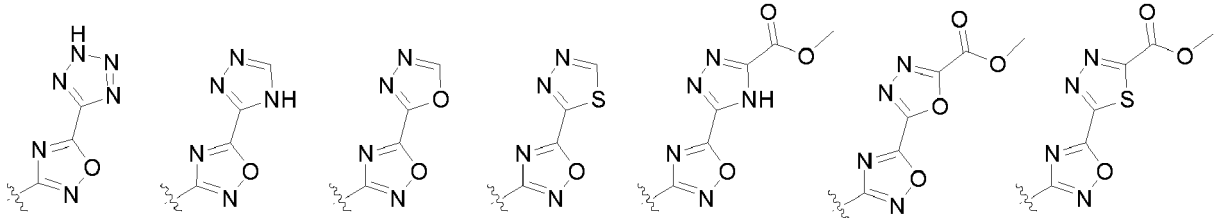


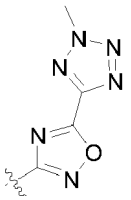




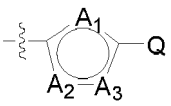




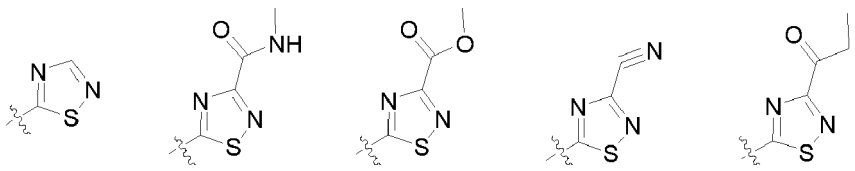


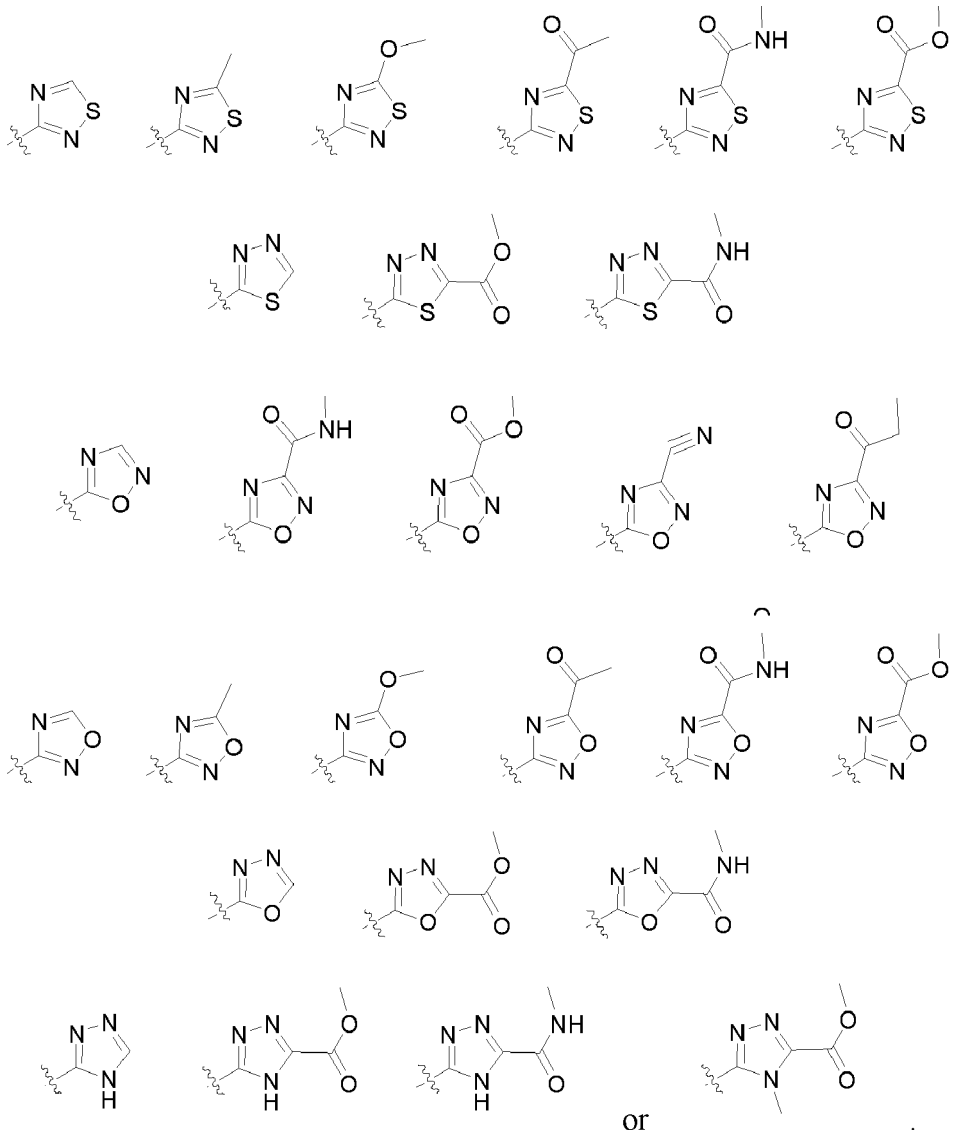


**[0041]** Further disclosed herein, in formula (I1), substituents :

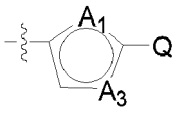


is selected from the following

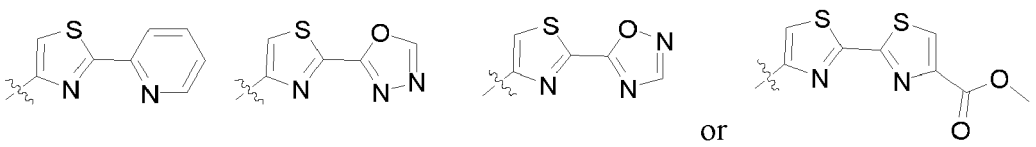




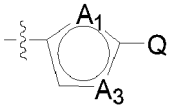
**[0042]** In one embodiment, in formula (Ib),



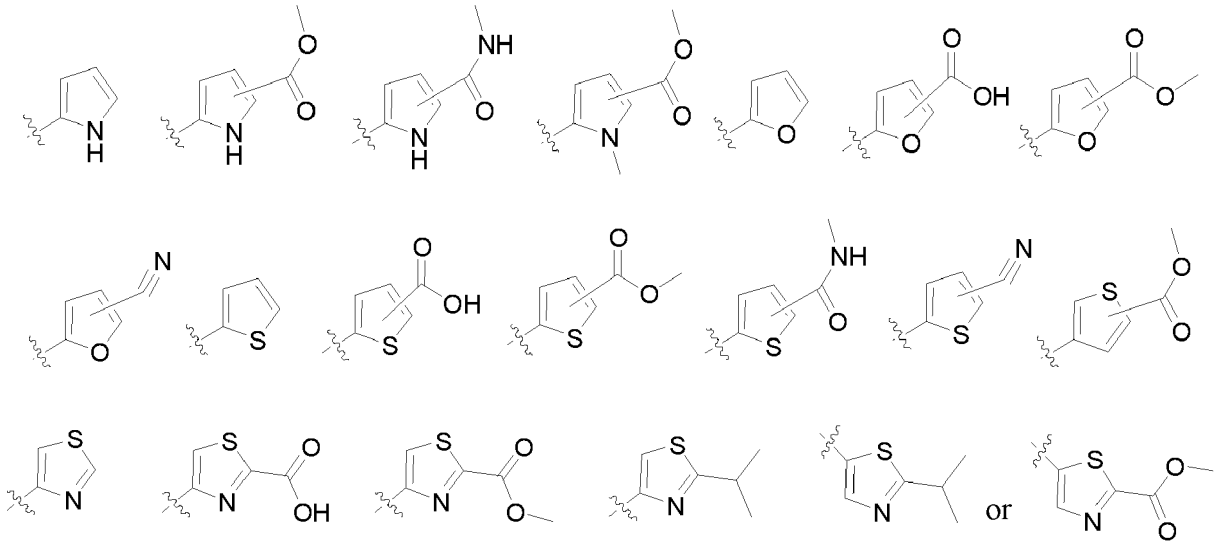
can be one selected from the following substituents :



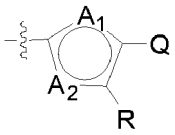
**[0043]** Further disclosed herein, in formula (Ib),



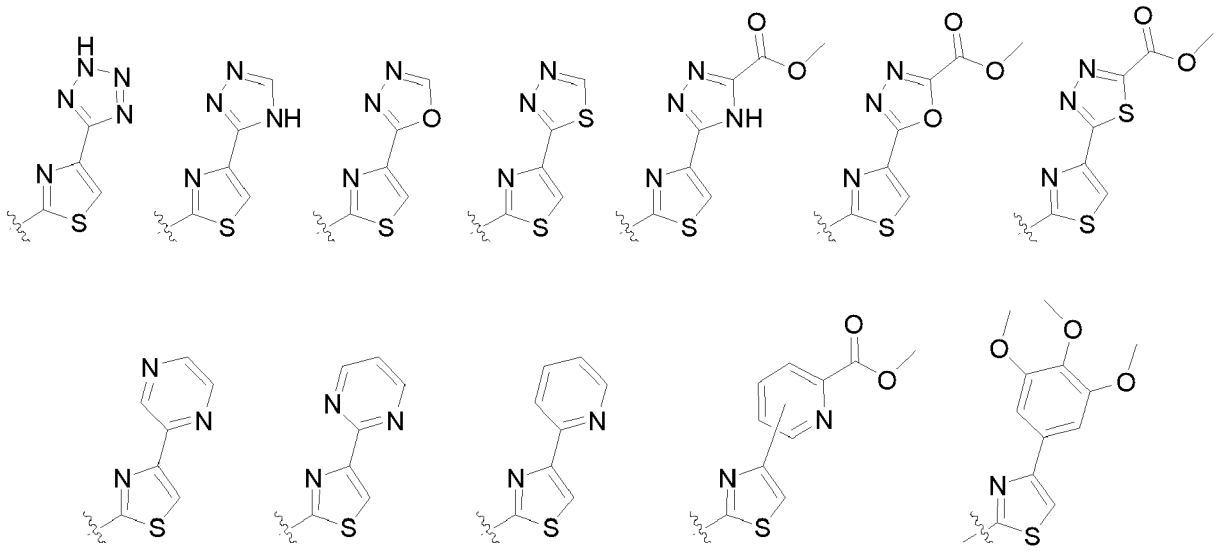
is selected from the following substituents :



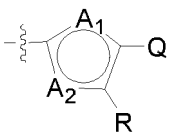
**[0044]** In one embodiment, in formula (Ic) to formula (If), following substituents:



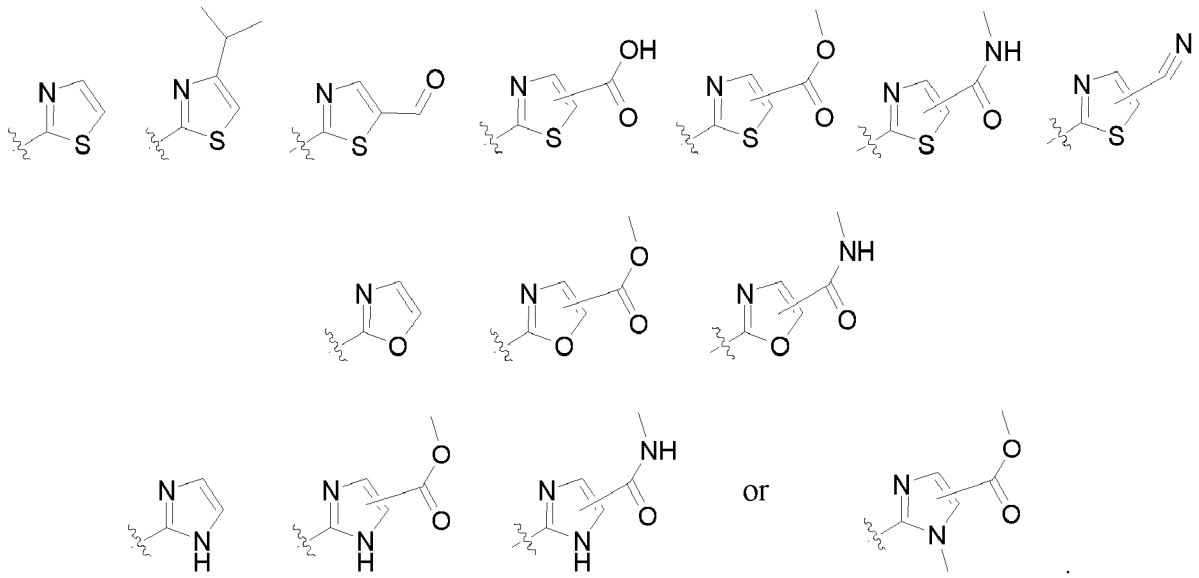
can be one selected from the



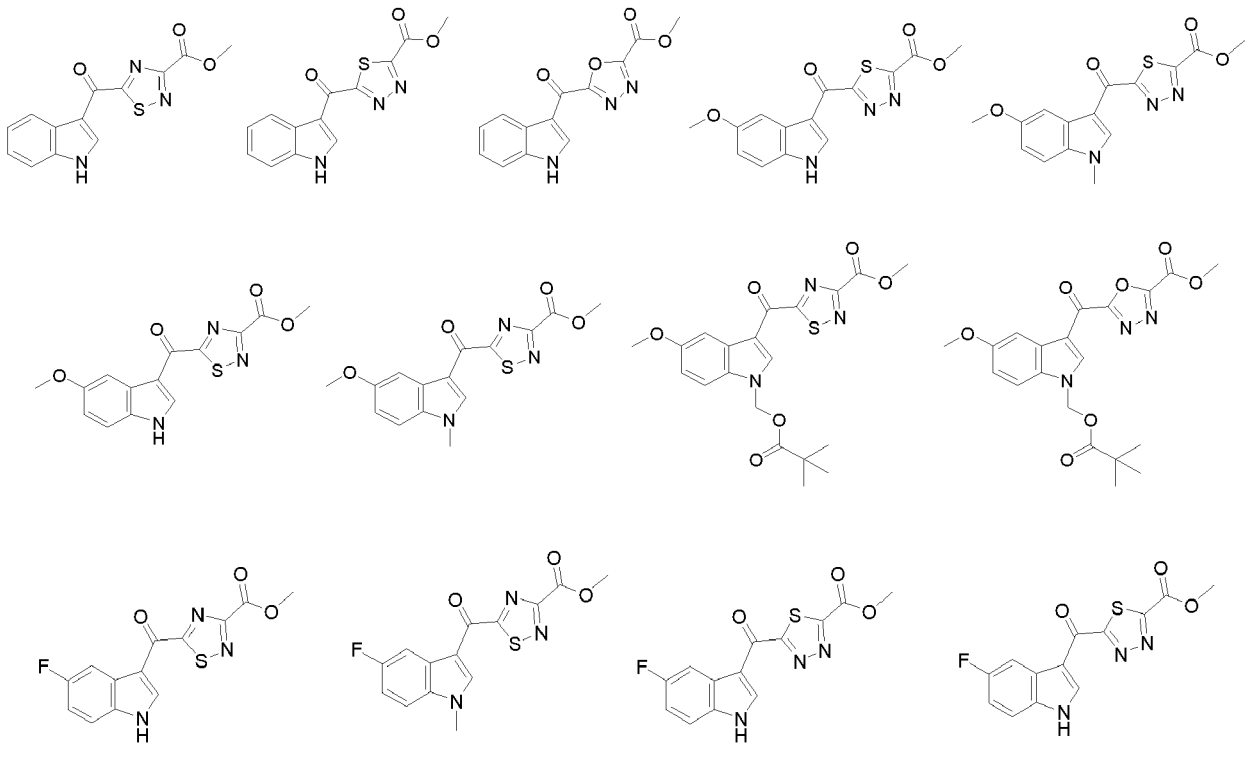
**[0045]** Further disclosed herein, in formula (Ic) to formula (If),

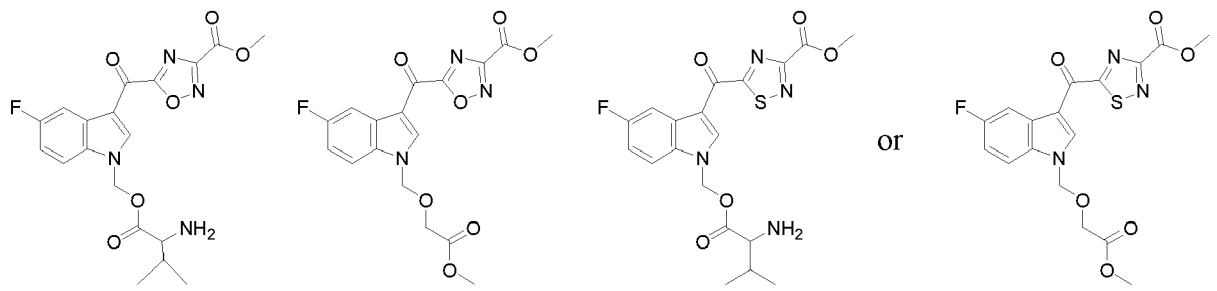


can be one selected from the following substituents:

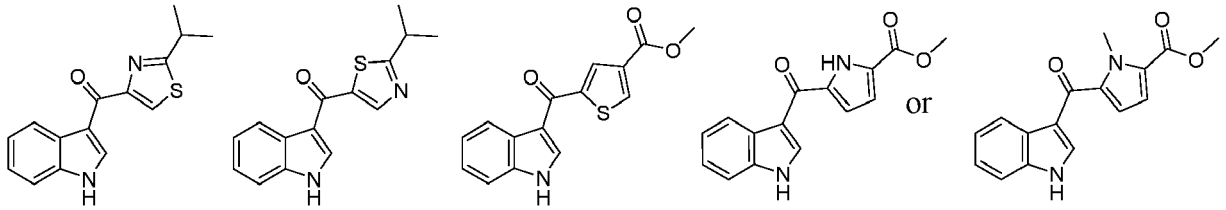


**[0046]** Disclosed herein as compound of formula (Ia) is:

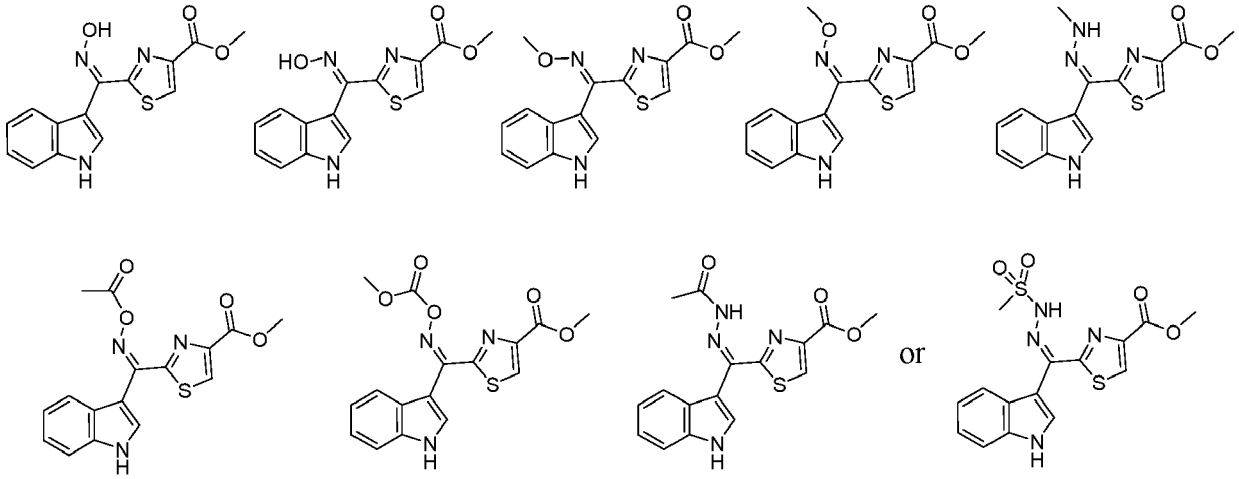




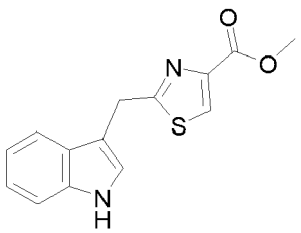
**[0047]** Disclosed herein as compound of formula (Ib) is



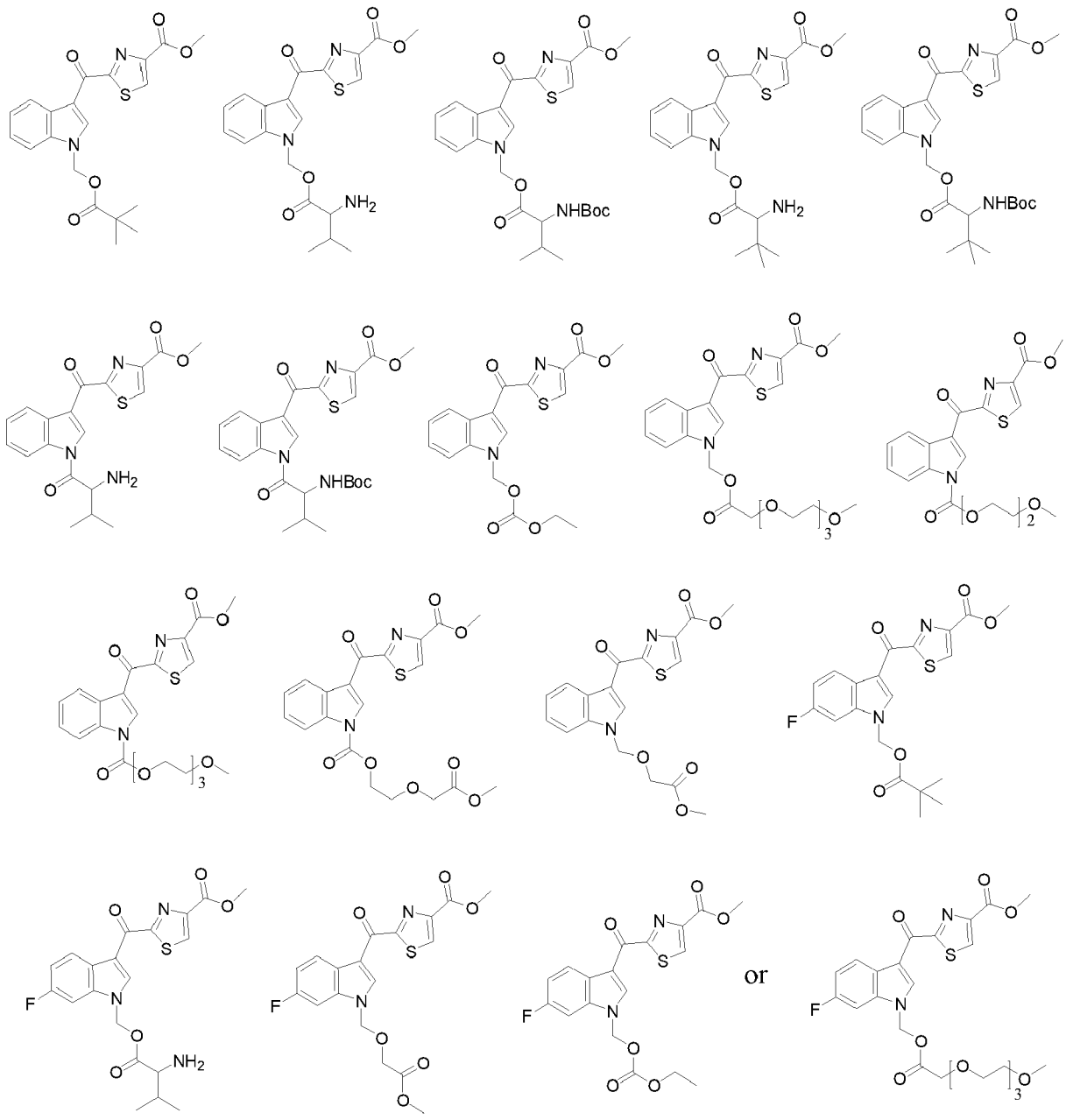
**[0048]** Disclosed herein as compound of formula (Ic) is



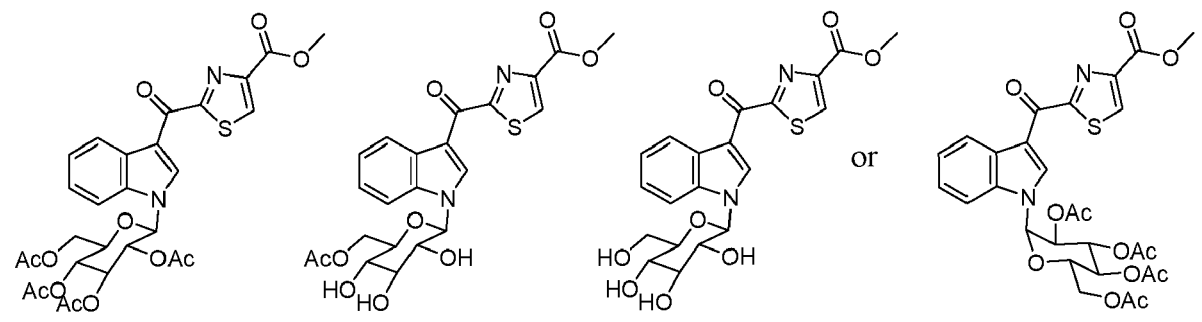
**[0049]** Disclosed herein as compound of formula (Id) is



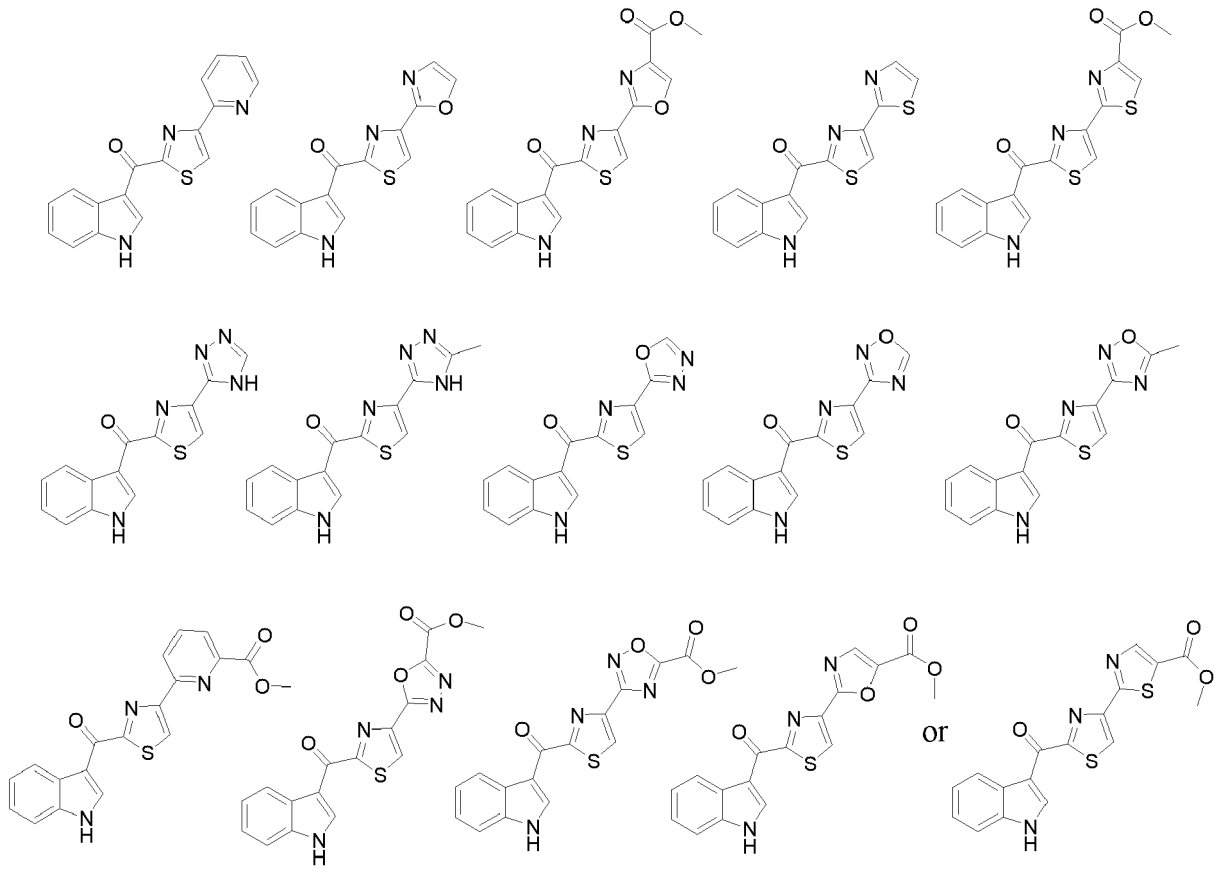
**[0050]** Disclosed herein as compound of formula (Ie) is



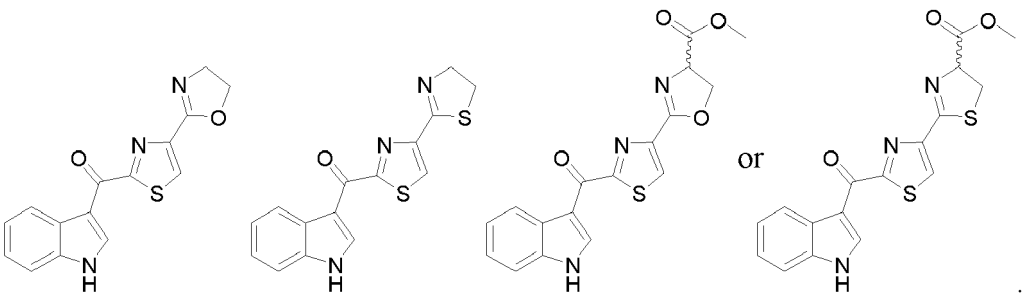
**[0051]** Disclosed herein as compound of formula (If) is



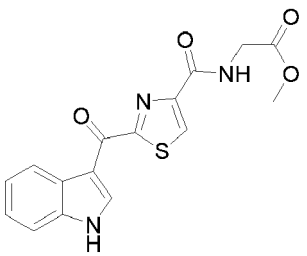
**[0052]** In one embodiment, compound of formula (Ig) can be selected from



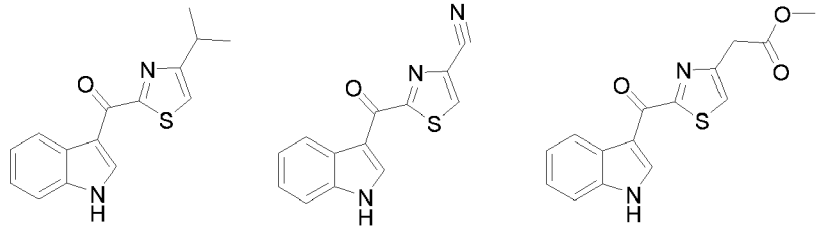
**[0053]** In one embodiment, compound of formula (Ih) can be selected from

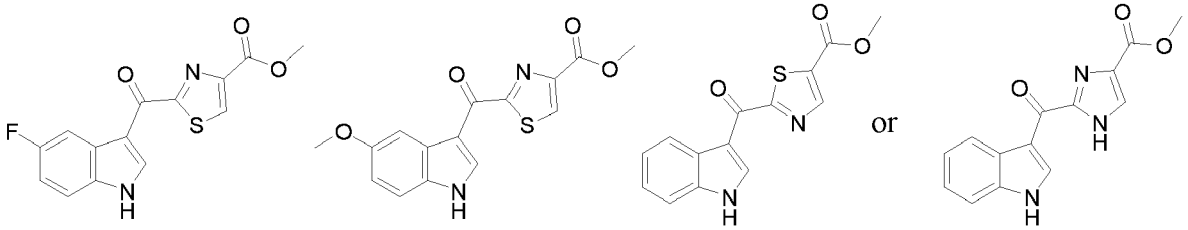


**[0054]** In one embodiment, compound of formula (I1) can be

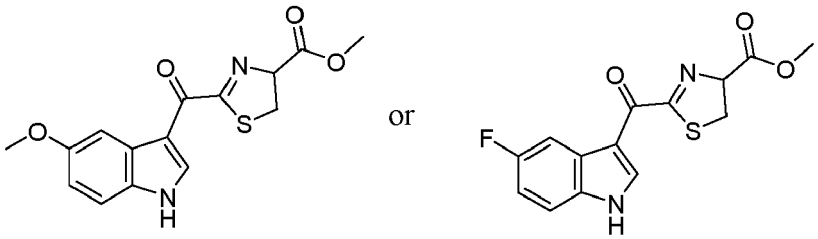


**[0055]** Disclosed herein as compound of formula (I1) is

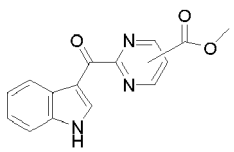




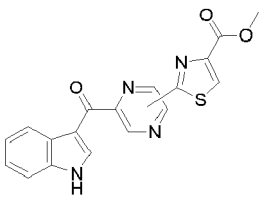
**[0056]** Disclosed as compound of formula (I2) is



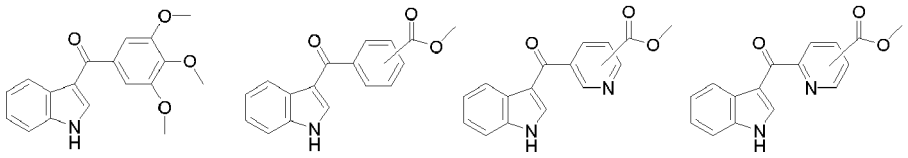
**[0057]** In one embodiment, compound of formula (I3) can be selected from



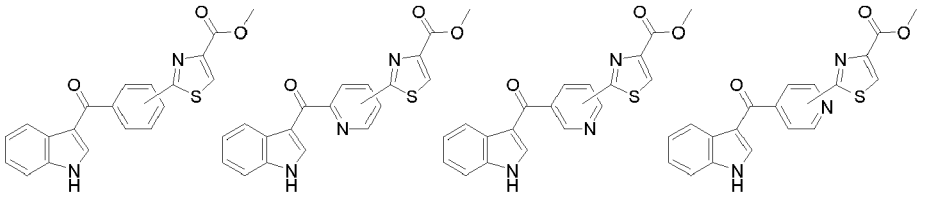
or



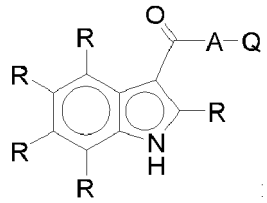
**[0058]** Disclosed herein as compound of formula (I3) is



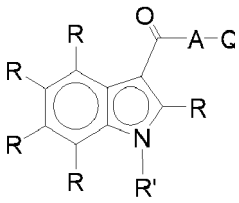
or



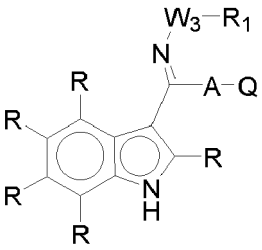
**[0059]** Aryl hydrocarbon receptor modulators shown in formula (I) of the invention can be classified into 5 categories of compound as follows:



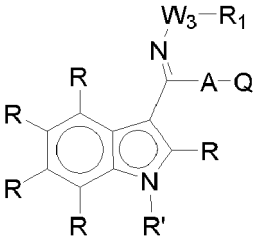
formula ($I_A$)(when R' is H)



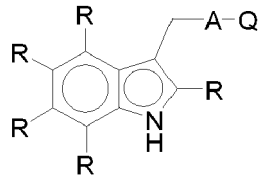
formula ($I_B$)(when R' isn't H)



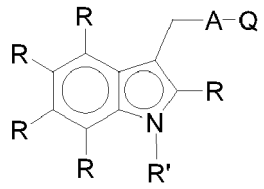
formula ($I_C$)(when R' is H),



formula ($I_D$)(when R' isn't H),

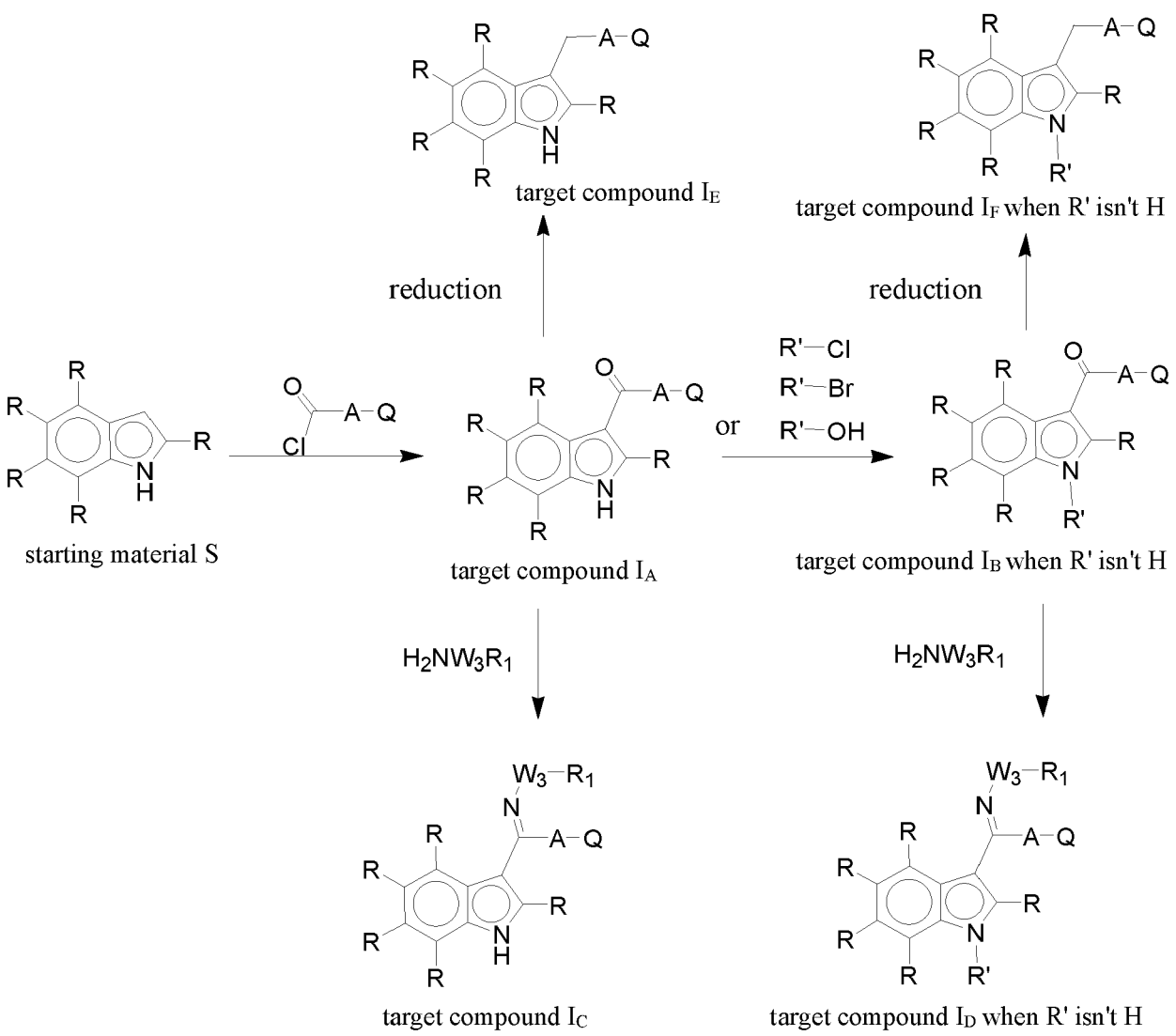


formula ($I_E$) (when R' is H)



formula ($I_F$)(when R' isn't H)

**[0060]** Wherein, synthesis route of formula ($I_A$) to formula ($I_F$) is as follows




Step 1, starting material S (indole or indole derivative) reacts with acyl halides compound (ClC(O)AQ) , alcoholic compound, or olefinic compound by the Friedel-Craft to give target compound $I_A$ of 3-substituted indole;
Step 2, target compound $I_A$ reacts with R'X or R'OH to give target compound $I_B$;

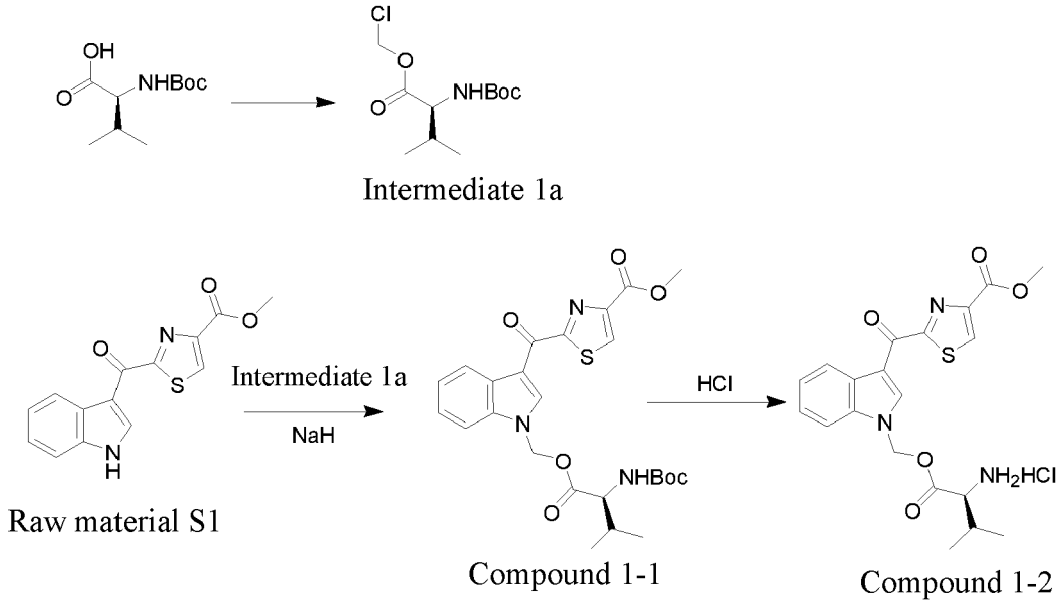
Step 3, target compound $I_A$ or target compound $I_B$ reacts with $H_2NW_3R_1$ to give target compound $I_C$ or target compound $I_D$;
Step 4, target compound $I_A$ or target compound $I_B$ are reduced to give target compound $I_E$ or target compound $I_F$ by reduction reaction.

**[0061]** Positive effect of the present invention is that compounds shown in formula (I) of the present invention can coupled to AhR to regulate those functions and signal paths controlled by AhR, thereby to affect growth and proliferation of cancer cells and invasiveness of tumor cells. Pharmaceutical composition containing compound shown in Formula (I) can be used as AhR inhibitor or non-constitutive AhR agonists (non-constitutive AhR agonists) to inhibit cancer cell growth and to inhibit metastasis and invasion of tumor cells.

DETAIL DESCRIPTION OF PREFERRED EMBODIMENTS

Example 1 Compound 1-1 and Compound 1-2

**[0062]**




Synthesis of Intermediate 1a

**[0063]** Sodium bicarbonate (1.546g, 16.411mmol) and tetrabutylammonium bromide (0.237g, 0.736mmol) were added into a suspension of Boc-L-Valine (0.8g, 3.66mmol) in dichloromethane and water (12mL/12mL) under stirring. Then reaction mixture was cooled to below 0°C, into which chloromethyl chlorosulfonate (0.91g, 5.52mmol) was slowly added dropwise, and then stirred overnight. Reaction solution was extracted with dichloromethane twice. Organic phase was washed by water and saturated aqueous sodium chloride solution once respectively, then dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (PE/EA= 20/1) to give an oily Intermediate 1a (0.97g, yield 99%).

Synthesis of Compound 1-1

**[0064]** Sodium hydride (0.165g, 4.139mmol) was added in batches into a solution of Raw material S1 (1g, 3.763mmol) in dimethyl formamide (DMF) (10mL) under stirring. Then reaction system was heated up to 40°C to react for 1 hour and cooled to room temperature, into which a solution of Intermediate 1a (0.97g, 3.6mmol) in DMF (2mL) was slowly added dropwise, lastly stirred at room temperature overnight. Reaction solution was poured into 60mL of ice water and filtered to give a crude product. The crude product was purified by silica gel column chromatography (PE/EA= 20/1 to 10/1) to give Compound 1-1 (0.5g, yield 28%). MS (ESI) *m/z:* 516 [M + 1] +.

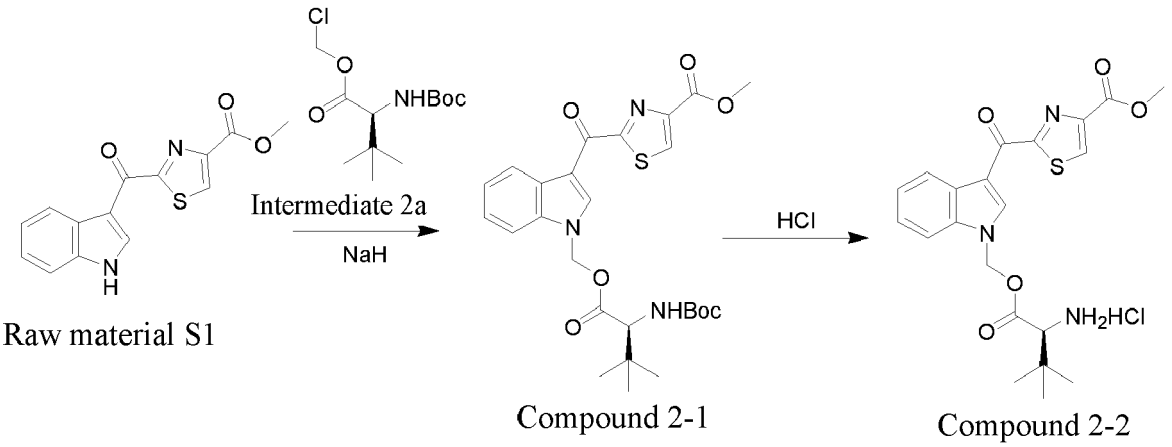
Synthesis of Compound 1-2

**[0065]** Compound 1-1 (0.5g, 0.97mmol) was dissolved in dioxane (2mL), into which a solution of hydrogen chloride in dioxane (5mL) was added dropwise. Reaction system was kept at room temperature overnight. Then the reaction solution was filtered to give Compound 1-2 (0.24g, yield 55%).

**[0066]** $^1$H NMR(400MHz, $CDCl_3$): δ 9.24(s, 1H), 8.94(s, 1H), 8.41(brs, 3H), 8.35(d, *J*=7.6Hz, 1H), 7.81(d, *J*=7.6Hz, 1H), 7.39~7.47(m, 2H), 6.63(d, *J*=10.8Hz, 1H), 6.58(d, *J*=10.8Hz, 1H), 4.02(d, *J*=7.6Hz, 1H), 3.94 (s, 3H), 2.07~2.12(m, 1H), 0.84(d, *J*=7.2Hz, 1H), 0.80(d, *J*=7.2Hz, 1H). MS(ESI) *m/z:*416 $[M+1]^+$

Example 2 Compound 2-1 and Compound 2-2

**[0067]**




Synthesis of Intermediate 2a

**[0068]** Synthesis method of Intermediate 2a was the same as that of Intermediate 1a, an oily Intermediate 2a (2.3g, Yield 95%) was synthesized from Boc-L-Tert-leucine (2g, 8.647mmol).

Synthesis of Compound 2-1

**[0069]** Synthesis method of Compound 2-1 was the same as that of Compound 1-1. Compound 2-1(1.4g, yield 74%) was synthesized from Intermediate 2a (1g, 3.6mmol).

**[0070]** $^1$H NMR(400MHz, $CDCl_3$): δ 9.24(s, 1H), 8.50~8.52(m, 1H), 8.46(s, 1H), 7.57~7.60(m, 1H), 7.39~7.43(m, 1H), 6.42(d, *J*=11.2Hz, 1H), 6.17(d, *J*=11.2Hz, 1H), 5.05(d, *J*=9.2Hz, 1H), 4.10(d, *J*=8.4Hz, 1H), 4.04(s, 3H), 1.42(s, 9H), 0.83(s, 9H). MS(ESI) *m/z:*530 $[M+ 1]^+$.

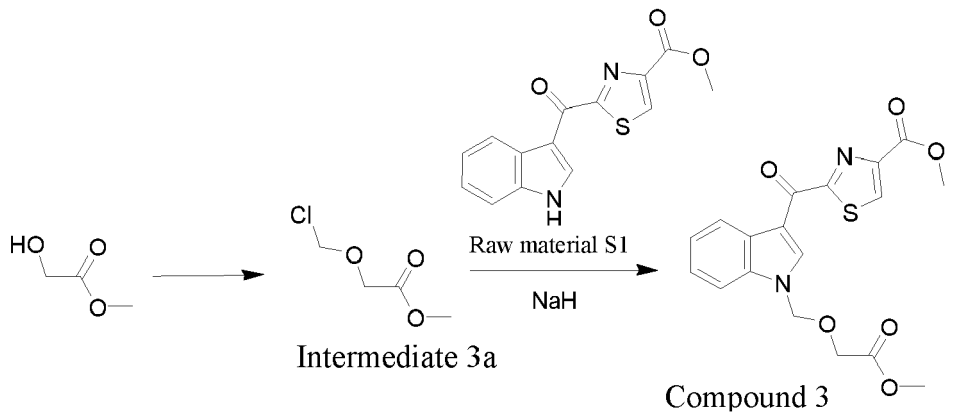
Synthesis of Compound 2-2

**[0071]** Synthesis method of Compound 2-2 was the same as that of Compound 1-2. Compound 2-2 (0.85g, yield 70%) was synthesized from Compound 2-1 (1.4g, 2.6mmol).

**[0072]** $^1$H NMR(400MHz, $CDCl_3$): δ 9.24(s, 1H), 8.94(s, 1H), 8.36(d, *J*=7.2Hz, 1H), 8.27(brs, 3H), 7.82(d, *J*=7.6Hz, 1H), 7.39~7.47(m, 2H), 6.61(s, 1H), 3.93(s, 3H), 3.86(s, 3H), 0.89(s, 9H). MS(ESI)*m/z*: 430$[M+1]^+$.

Example 3 Compound 3

**[0073]**




Synthesis of Intermediate 3a

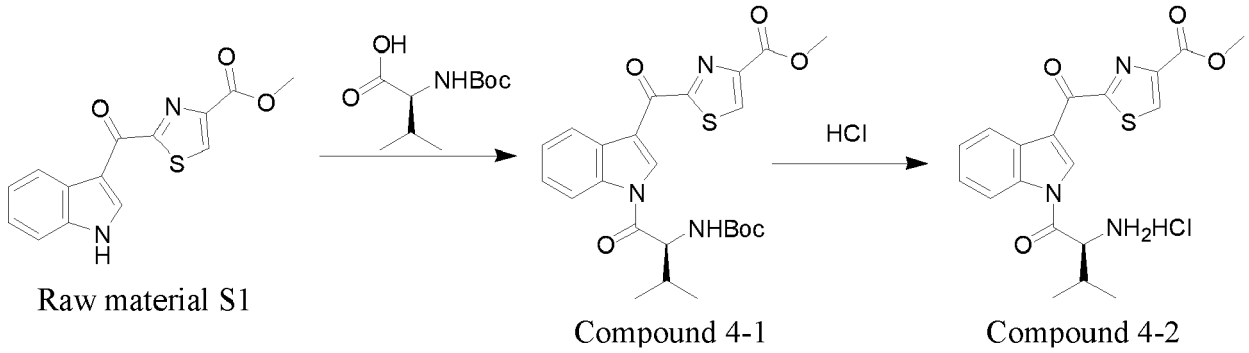
**[0074]** Dichloromethane (50mL) and paraformaldehyde (1.3g, 43.3mmol) were added to methyl glycolate weighed (3g, 33.3mmol). Reaction system was cooled to below -20°C, through which hydrogen chloride gas prepared at real time was continuously aerated, and kept to react for 30 minutes at -20°C. After that, hydrogen chloride gas was removed. Reaction solution was added with anhydrous magnesium sulfate and anhydrous sodium sulfate, further incubated for 1 hour, then kept overnight at room temperature, then filtered to remove the solid. Mother liquor was concentrated to dryness at room temperature and purified by silica gel column chromatography to give Intermediate 3a(1.2g, yield 26%).

Synthesis of Compound 3

**[0075]** Synthesis method of Compound 3 was the same as that of Compound 1-1. A pale yellow solid of Compound 3 (280mg, yield 74%) was synthesized from Raw material S1 (286mg, 1mmol) and Intermediates 3a (500mg, 3.6mmol).

**[0076]** $^1$H NMR(400MHz, $CDCl_3$): δ 9.19(s, 1H), 8.55~8.56(m, 1H), 8.45(s, 1H), 7.63~7.65 (m,1H), 7.41~7.45(m, 2H), 5.82(s, 2H), 4.12(s, 2H), 4.03(s, 3H), 3.77(s, 3H). MS (ESI) *m/z:* 389 $[M+1]^+$.

**[0077]** Example 4 Compound 4-1 and Compound 4-2




Synthesis of Compound 4-1

**[0078]** Raw material S1 (2.86g, 10mmol) was added to a solution of Boc-L-valine (2.17g, 10mmol) in DMF (20mL), then into which HATU (4.56g, 12mmol) and DIEA (2.6g, 20mmol) were added under stirring. Reaction system was stirred overnight. Reaction solution was poured into water and extracted with ethyl acetate twice. Organic phase was washed with water and saturated brine each once, then dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (PE/ EA= 4/1) to give Compound 4-1 (3.01g, yield 62%).

**[0079]** $^1$H NMR(400MHz, $CDCl_3$): δ 9.75(s, 1H), 8.48~8.55(m, 3H), 7.47~7.52(m, 2H), 5.44(d, *J*= 8.8Hz, 1H), 5.27(dd, *J*=4.0, 8.8Hz, 1H), 4.05(s, 3H), 2.37~2.42(m, 1H), 1.48(s, 9H), 1.25(d, *J*=6.8Hz, 3H), 1.01(d, *J*=6.4Hz, 3H). MS (ESI) *m/z:* 508 $[M+23]^+$.

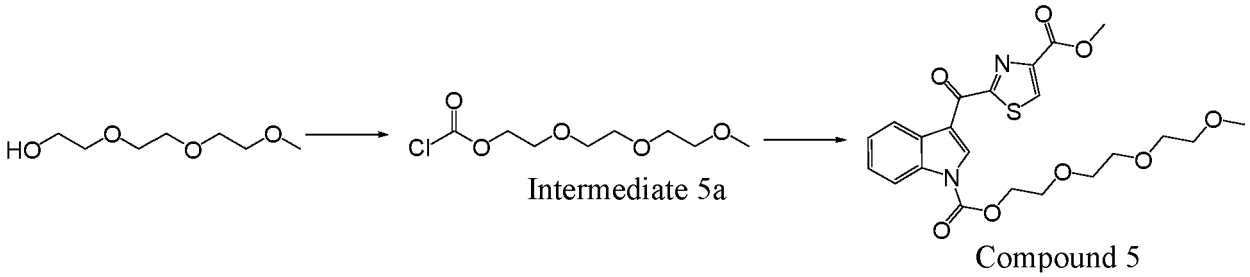
Synthesis of Compound 4-2

**[0080]** Synthesis method of Compound 4-2 was same as that of Compound 1-2. Compound 4-2 (348mg, yield 77%) was synthesized from Compound 4-1 (486mg, 1mmol).

**[0081]** $^1$H NMR(400MHz, $CDCl_3$): δ 9.56(s, 1H), 9.04(s, 1H), 8.81(brs, 3H), 8.46~8.48(m, 1H), 8.35~8.37(s,1H), 7.54~7.60(m, 2H), 5.01(d, *J*=4.8Hz, 1H), 3.99(s, 3H), 2.42~2.47(m, 1H), 1.17(d, *J*=6.8Hz, 3H), 1.07(d, *J*=6.8Hz, 3H). MS (ESI) *m/z:* 386 $[M+1]^+$.

Example 5 Compound 5

**[0082]**




Synthesis of Intermediate 5a

**[0083]** Triethylene glycol monomethyl ether (2.0g, 12.2 mmol) was dissolved in tetrahydrofuran (20mL), into which triphosgene (1.8g, 6.1mmol) was added under stirring. Reaction system was cooled to 0°C by ice bath, into which pyridine (1.5g, 19.0mmol ) was slowly added dropwise, kept to react at room temperature for 1 hour and then filtered. Mother liquor was concentrated under reduced pressure to give a colourless liquid of Intermediate 5a (2.1g, yield 75.9%).

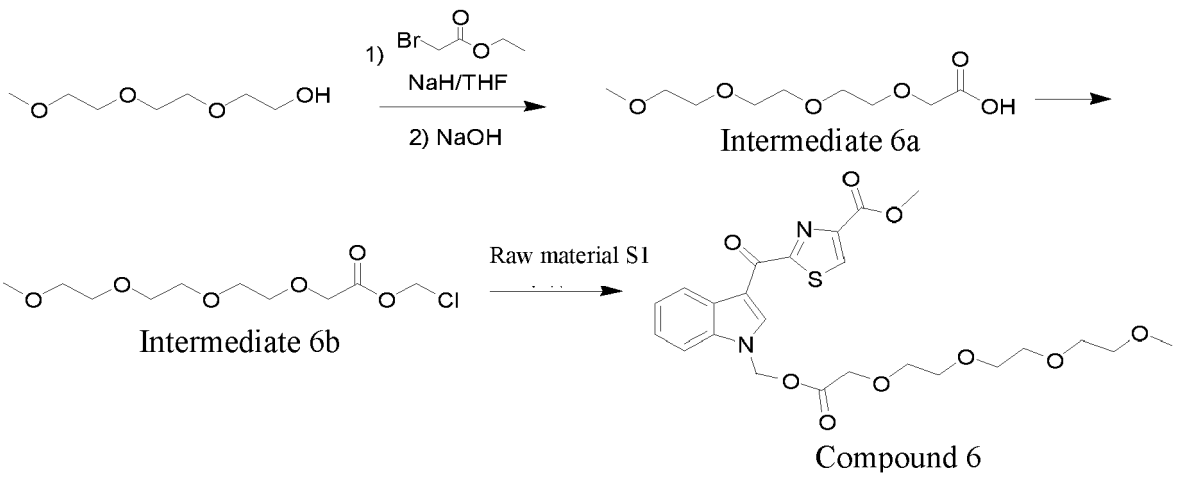
Synthesis of Compound 5

**[0084]** Raw material S-1 (2.0g, 7.0mmol) was dissolved in tetrahydrofuran (80mL), then into which triethylamine(1.5g, 14.9 mmol) was added dropwise. Reaction system was cooled to 0°C by ice bath, then into which a solution of Intermediate 5-1 (2.1g, 9.3mmol) in dichloromethane (20mL) was added dropwise. Reaction system was kept for 1 hour at room temperature, then poured into ice water and extracted with dichloromethane. Organic phase was washed with saturated brine and dried over anhydrous sodium sulfate, and then concentrated to dryness under reduced pressure. Crude product was purified by silica gel column chromatography (PE/ EA= 3/1) to give a white solid of Compound 5 (2.5g, yield 75.8%) .

**[0085]** $^1$H NMR (400 MHz, $CDCl_3$): δ 9.56 (s, 1H), 8.49 (s, 2H), 8.33~8.24 (m, 1H), 7.51~7.39 (m, 2H), 4.75~4.67 (m, 2H), 4.03 (s, 3H), 4.01~3.94 (m, 2H), 3.80 (dd, *J*=5.9, 3.4 Hz, 2H), 3.74~3.69 (m, 2H), 3.67~3.62 (m, 2H), 3.53~3.48 (m,2H),3.35(s, 3H). LCMS(ESI) m/z:477.2[M+1]+.

Example 6 Compound 6

**[0086]**




Synthesis of Intermediate 6a

**[0087]** Triethylene glycol monomethyl ether (10g, 60.9mmol) was dissolved in tetrahydrofuran (100mL), into which sodium hydride (3.2g, 60% content, 79.17mmol) was added in batches at 0°C. After addition, reaction system was stirred at room temperature for 1 hour, then into which ethyl bromoacetate (20.1 g, 122mmol) was added dropwise, and kept to react at room temperature for 3 hours. Reaction solution was added directly with water (100mL) and then extracted with dichloromethane. Organic phase was dried over anhydrous sodium sulphate, concentrated to dryness under reduced pressure, then into which water (100mL) and sodium hydroxide of solid (3g, 73mmol) were added, stirred at room temperature for 1hour and extracted with ethyl acetate twice. Aqueous phase was adjusted with dilute hydrochloric acid to pH = 2 to 3 and then extracted with mixed solvent of dichloromethane / isopropanol ( V / V = 10: 1) for 5 times. Organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude product. Crude product was purified by silica gel column chromatography (DCM: $CH_3OH$= 100: 1 - 20: 1) to give Compound 6a (10g, yield 74%).

Synthesis of Intermediate 6b

**[0088]** Compound 6a (2g, 8.99mmol) was dissolved in dichloromethane (20mL), then into which sodium bicarbonate (3.1g, 36mmol), tetrabutylammonium bromide (289mg, 0.699mmol) and water (20mL) were added. Reaction system was cooled to 0°C, hereinafter, into which a solution of chloromethyl chlorosulfonate (1.48g, 8.99mmol) in dichloromethane (10mL) solution was added dropwise, and was stirred overnight at room temperature, then kept statically for stratification. Aqueous phase was extracted with dichloromethane twice. Organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (DCM: $CH_3OH$ = 50: 1) to give an oily liquid of Intermediate 6b (300mg, yield 12.3%). LCMS (ESI) m/z: 271 [M + 1] +.

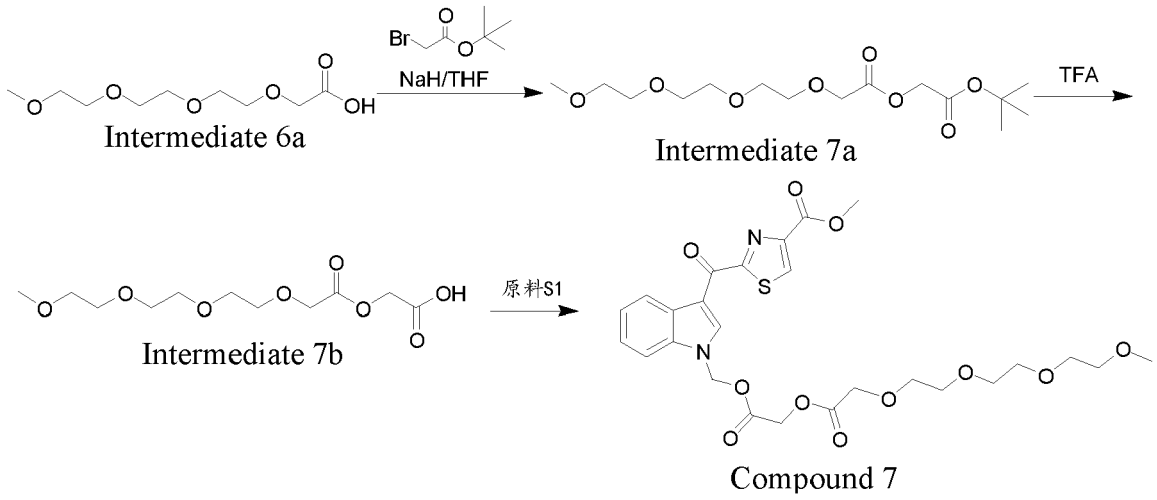
Synthesis of Compound 6

**[0089]** Raw material S1 (1g, 3.49mmol) was dissolved in DMF (15mL), into which sodium hydride (153mg, content of 60%, 3.84mmol) was added at 0°C. After addition, reaction system was stirred for 10 minutes, then heated to 50°C, stirred for 1 hour and then cooled to room temperature, into which Compound 6b (0.944mg, 3.49mmol) was added, then kept to react for 4h at room temperature, then into which water and dichloromethane were added and extracted with dichloromethane for 3 times. Organic phase was dried over anhydrous sulphate sodium and concentrated under reduced pressure to obtain a crude product. The crude product was purified by silica gel column chromatography ($CH_3OH$: DCM = 0-2%) to give Compound 6 (650mg, yield 35.8%) .

**[0090]** $^1H$ NMR(400MHz, $CDCl_3$): $\delta$ 9.25(s, 1H), 8.52~8.54(m, 1H), 8.46(s, 1H), 7.59~7.61(m, 1H), 7.41~7.44(m, 2H), 6.32(s, 2H), 4.21(s, 2H), 4.04(s, 3H), 3.70~3.72(m, 2H), 3.65~3.68(m, 2H), 3.60~3.64(m, 6H), 3.52~3.54(m, 2H), 3.37(s, 3H). LCMS (ESI) *m/z:* 521 $[M+1]^+$.

Example 7 Compound 7

**[0091]**




Synthesis of Intermediate 7a

**[0092]** Synthesis method of Intermediate 7a was the same as that of Compound 6a. Starting material was Intermediate 6a. Yield was 75%. LCMS (ESI) m Iz: 337.2 [M + 1] $^{+}$.

Synthesis of Intermediate 7b

**[0093]** Intermediate 7a (3.4g, 10mmol) was dissolved in dichloromethane (5mL), then into which trifluoroacetic acid (5mL) was added. Reaction system was stirred at room temperature overnight and concentrated to dryness under reduced pressure. Crude product was purified by silica gel column chromatography ($CH_3OH$:DCM = 0-2%) to give an oil of Intermediate 7b (2.6g, yield 76%). LCMS (ESI) m/z: 281.2 $[M+1]^+$.

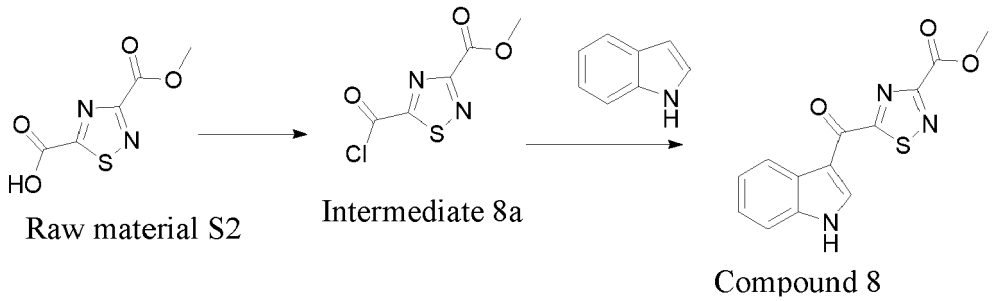
Compound 7

**[0094]** Synthesis method of Compound 7 was the same as that of compound 6. Yield was 55%.

**[0095]** $^1$H NMR(400MHz, $CDCl_3$): $\delta$ 9.20(s, 1H), 8.50~8.52(m, 1H), 8.44(s, 1H), 7.53~7.56(m, 1H), 7.40~7.42(m, 2H), 6.31(s, 2H), 4.70(s, 2), 4.25(s, 2H), 4.02(s, 3H), 3.63~3.71(m, 10H), 3.53~3.55(m, 2H), 3.37(s, 3H). LCMS (ESI) m/z: 579.2 [M+1]+

Example 8 Compound 8

**[0096]**




Synthesis of Intermediate 8a

**[0097]** Raw material S2 (188mg, 1mmol) was dissolved in dichloromethane (20mL), into which one drop of DMF was added. Reaction system was then cooled to 0 to 5°C, then into which oxalyl chloride (151mg, 1.2mmol) was added dropwise. Then ice bath was removed. Reaction system was stirred at room temperature for 1 hour, then concentrated to dryness under reduced pressure, into which dichloromethane (20mL) was used for dissolution, concentrated to dryness under reduced pressure to give Intermediate 8a which was used directly for the next step.

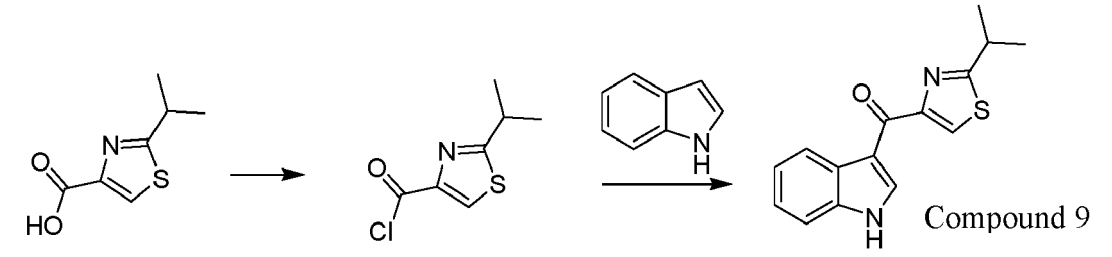
Synthesis of Compound 8

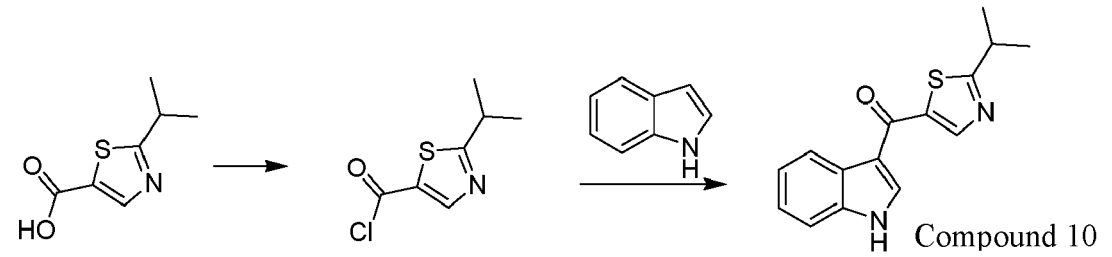
**[0098]** A solution of Intermediate 8a (1mmol) in dichloromethane (30mL) was added dropwise to a suspension of anhydrous aluminium trichloride (164mg, 1.2mmol) in dichloromethane (30mL). Reaction system was stirred for 2 hours, into which a solution of indole (143mg, 1.2mmol) in dichloromethane (30mL) was slowly added dropwise and then reacted overnight. After that, reaction system was washed with saturated sodium bicarbonate solution. Organic phase was washed with saturated brine, then dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (PE/EA=4/1) to obtain a pale yellow solid of Compound 8 (120mg, yield 42%).

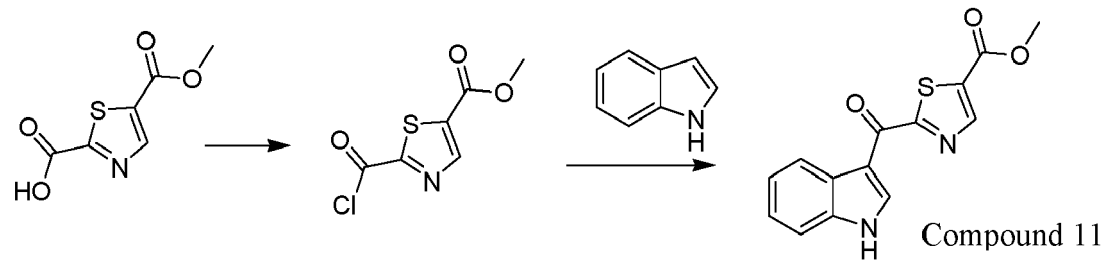
**[0099]** $^1$H NMR(400MHz, DMSO-$d_6$): $\delta$ 12.4(brs, 1H), 9.05(s, 1H), 8.28~8.30(m, 1H), 7.62~7.64(m, 1H), 7.32~7.37 (m, 2H), 4.00(s, 3H). MS (ESI) *m/z:* 288.0 $[M+1]^+$.

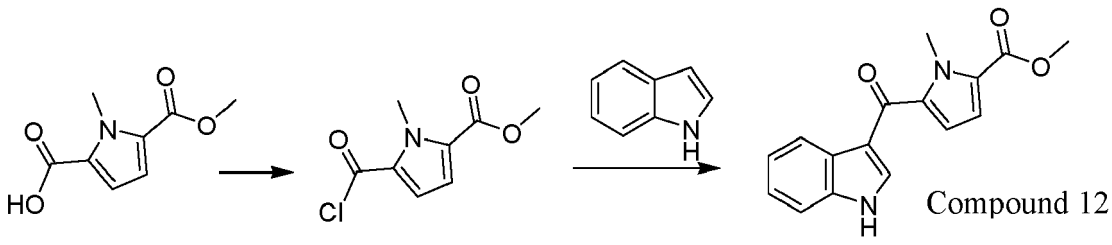
Example 9 to 18 Compound 9 to 18

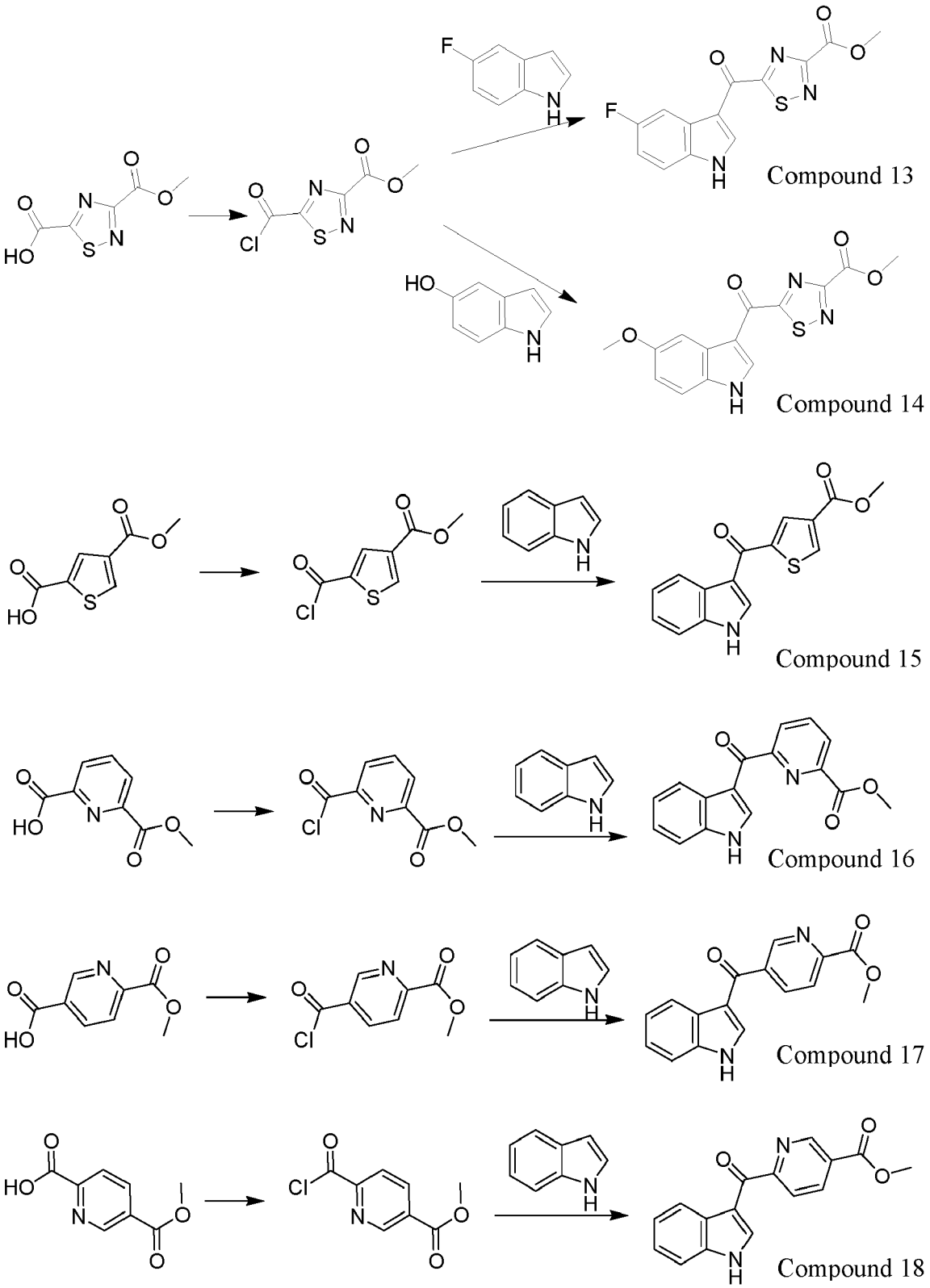
**[0100]**






**[0101]** Methods of preparing Compound 9 to 18 were the same as that of Example 8. The difference was that corresponding acid was used in place of Raw material S-2. Other materials were the same as that of Example 8.

**[0102]** Compound 9: MS (ESI) m/z: 271.1 $[M+1]^+$

**[0103]** Compound 10: $^1$H NMR (400MHz, $CDCl_3$): δ 8.79 (brs, 1H), 8.41~8.43 (m, 1H),8.24(s,1H), 7.98 (d, *J*= 2.8Hz, 1H), 7.48~7.50 (m, 1H), 7.31~7.37 (m, 2H), 3.37~3.43 (m, 1H), 1.49 (d, *J* = 6.8Hz, 6H).

**[0104]** Compound 11: $^1$H NMR(400MHz, DMSO-$d_6$): δ 12.49(brs, 1H),9.09(s, 1H), 8.70(s,1H), 8.29~ 8.34 (m, 1H),

7.58~7.60 (m, 1H), 7.29~7.34 (m, 2H), 3.98(s, 3H).

**[0105]** Compound 12: $^1$H NMR(400MHz, $CDCl_3$): δ 8.73 (brs, 1H), 8.50~8.35 (m, 1H), 7.83 (d, *J*= 3.1 Hz, 1H), 7.55~7.41 (m, 1H), 7.43~7.31 (m, 2H), 6.96 (d, *J*=4.1 Hz, 1H), 6.69 (d, *J*=4.2 Hz, 1H), 4.25 (s, 3H), 3.90 (s,3H).

**[0106]** Compound 13: $^1$H NMR(400MHz, DMSO-$d_6$): δ 12.56(brs, 1H), 9.06(s, 1H), 7.94(dd, *J* =2.8, 9.6Hz, 1H), 7.65(dd, *J*=4.8, 8.8Hz, 1H), 7.20 (dt, *J*=2.8, 9.6Hz, 1H), 4.00(s, 3H). MS (ESI) *m/z:* 306.0 $[M+1]^+$.

**[0107]** Compound 14: $^1$H NMR(400MHz, DMSO-$d_6$): δ 12.43(brs, 1H), 8.97(s, 1H), 7.9(d, *J*=2.4Hz, 1H), 7.52(d, *J*=8.8Hz, 1H), 6.97(dd, *J*=2.4, 8.8Hz, 1H), 3.99(s, 3H), 3.83(s, 3H). MS (ESI) *m/z:* 318.0 $[M+1]^+$.

**[0108]** Compound 15: $^1$H NMR(400MHz, $CDCl_3$): δ 9.07(brs,1H), 8.41~8.44(m,1H), 8.37(s, 1H), 8.11(s,1H), 7.95(d, *J*=2.0Hz, 1H), 7.48~7.50(m, 1H), 7.34~7.37(m,2H), 3.94(s, 3H). MS (ESI) *m/z:* 286.0 $[M+1]^+$.

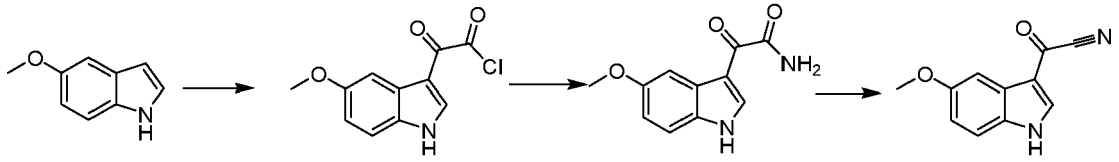
**[0109]** Compound 16: $^1$H NMR(400MHz, DMSO-$d_6$): δ 12.22(brs,1H),9.10(s,1H), 8.39~8.42(m,1H), 8.20~8.30(m, 3H),7.53~7.57(m,1), 7.26~7.30(m, 2H),3.97(s, 3H). MS (ESI) *m/z:* 281.0 $[M+1]^+$.

**[0110]** Compound 17: $^1$H NMR(400MHz, $CDCl_3$): δ 9.17(brs,1H), 8.43~8.47(m,1H), 8.30(brs, 2H), 7.70(s,1H), 7.54~7.56(m, 2H), 7.38~7.40(m, 2H), 4.09(s, 3H). MS (ESI) *m/z:* 286.0 $[M+1]^+$.

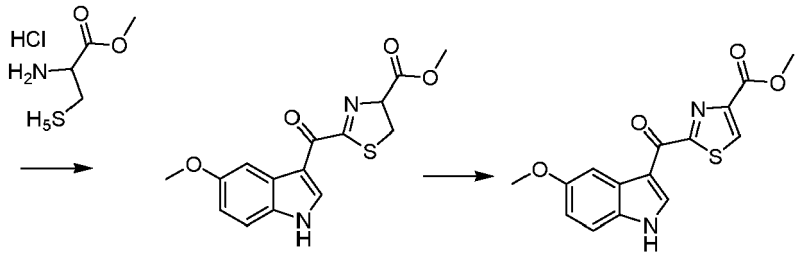
**[0111]** Compound 18: $^1$H NMR (400MHz, DMSO): δ 12.20(brs, 1H), 9.23~9.24(m, 1H), 8.76(s, 1H), 8.51(dd, *J*=8.0, *J*=2.0, 1H), 8.35~8.52(m, 1H), 8.14(dd, *J*=8.4, *J*=0.8, 1H), 7.53~7.56(m, 1H), 7.25~7.31(m,2H), 3.95(s, 3H). MS(ESI) *m/z:* 281$[M+1]^+$.

Example 19 Compound 19-1, 19-2

**[0112]**



Intermediate 19a Intermediate 19b Intermediate 19c



Compound 19-1 Compound 19-2

Synthesis Intermediate 19a

**[0113]** 5-Methoxy indole (10g, 68mmol) was added into 250mL of three-necked flask, then into which methyl tertiary butyl ether (75mL) was added for dissolution. Reaction system was cooled to -10°C, then into which oxalyl chloride (9.5g, 74mmol) was dropped slowly. During this course of dropping, temperature of reaction system was controlled below -5°C. After dropping, reaction system was stirred for 1h at low temperature. Then ice bath was removed. Reaction system was stirred for 30 minutes at room temperature, then into which petroleum ether (100mL) was added, stirred for 30 minutes and filtered. Filter cake was washed with a mixture of petroleum ether and methyl tertiary butyl ether, then dried to give Intermediate 19a (15.5g, yield 97%). LCMS (ESI) m/z: 234 $[M+1]^+$ (the product was diluted with methanol, the acyl chloride was transferred to methyl ester).

Synthesis of Intermediate 19b

**[0114]** Intermediate 19a (15.5g) was added in batches into a mixture of 52.3g concentrated ammonia (25%) and 100mL ethanol at 0°C. After addition, reaction system was kept to react for 2h at 10°C. Reaction mixture was poured into 100mL ice water, then stirred for 30 minutes and filtered. Filter cake was dried to give a pale gray solid, i.e. Intermediate 19b (10.5g). LCMS (ESI) m/z: 219 $[M + 1)^+$.

Synthesis of Intermediate 19c

**[0115]** Intermediate 19b (10g, 45.8mmol) was suspended in 150mL ethyl acetate, then into which pyridine ( 10.87g, 137.5mmol) was added. Reaction system was cooled to below 10°C, into which, trifluoroacetic anhydride (14.439, 68.7mmol) was slowly added dropwise for approximately 30 minutes. After addition, reaction continued for 2h at 10°C. Reaction solution was poured into 100mL ice water and extracted with ethyl acetate twice. Organic phase after being combined was washed with saturated sodium bicarbonate twice, and with 0.5N diluted hydrochloric acid twice, then dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude solid of 8.8g. The crude solid was washed with a mixed solvent of ethyl acetate: dichloromethane = 5: 1, then filtered to give Intermediate 19c (7.2g, yield 78%).

**[0116]** $^1$H NMR (400MHz, $CDCl_3$): δ 12.76(bis, 1H), 8.53(s, 1H), 7.48~7.51(m, 2H), 6.99(dd, *J*=8.8 Hz, *J*=2.4 Hz, 1H),3.80(s, 3H).MS (ESI) *m/z:* 201.0 [M+1]

Synthesis of Compound 19-1

**[0117]** Intermediate 19c (2g, 10mmol) was dissolved in N,N'-dimethylformamide (15mL), then into which L- cysteine methyl ester hydrochloride (1.72g, 10mmol) and DBU (152mg, 1mmol) were added. Reaction system was heated to 40°C for reacting for 3h, then cooled to room temperature and dropped into 80mL ice-dilute hydrochloric acid (containing 0.1 mmol HCl), stirred for 20 minutes and filtered. Filter cake was pressed to dryness and washed with a little dichloromethane and dried to give Intermediate 19-1 (3.1g, yield 97%).

**[0118]** $^1$H NMR(400MHz, $CDCl_3$):δ 8.78(brs, 1H), 8.71(d, *J*=2.8 Hz, 1H), 7.97(d, *J*=2.8 Hz, 1H), 7.33(d, *J*=8.8 Hz, 1H), 6.97(dd, *J*=8.8 Hz, *J* =2.8 Hz, 1H), 5.48(t, *J*=8.8 Hz ,1H), 3.92(s, 3H), 3.89(t, 3H), 3.61 (d, *J*=9.6Hz, 2H).MS (ESI) *m/z:* 319.0 $[M+1]^+$.

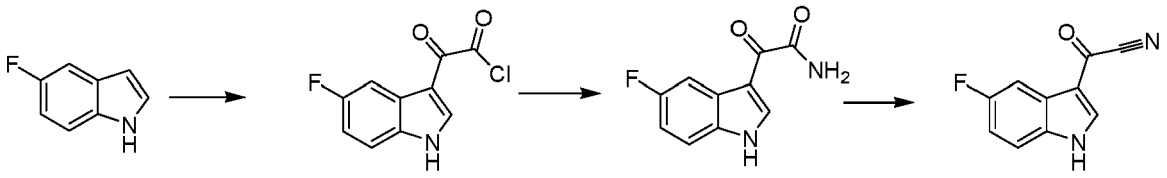
Synthesis of Compound 19-2

**[0119]** Compound 19-1 (2.6g, 6.16mmol) was dissolved in N,N-dimethylformamide (30mL). Reaction system was kept to react at 80 °C by bubbling air for 12h. Reaction solution was dropped into ice water, then stirred for 20 minutes and filtered. Filter cake was washed with water and dried to give Compound 19-2 (2.5g, yield 96%).

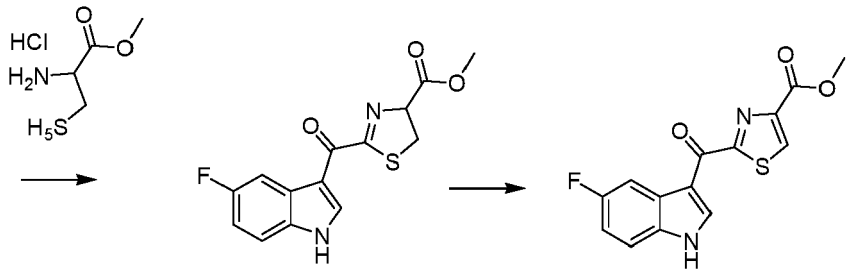
**[0120]** $^1$H NMR(400MHz, $CDCl_3$): δ 9.23(d, *J*=3.6 Hz, 1H),9.02(brs, 1H), 8.44(s, 1H), 8.05(d, *J*=2.4 Hz, 1H), 7.37(d, *J*=8.8 Hz, 1H), 6.99 (dd, *J*=8.8Hz, *J*=2.4Hz, 1H), 4.03(s, 3H), 3.95(s, 3H).MS (ESI) *m/z:* 317.0 $[M+1]^+$.

Example 20 Compound 20-1, 20-2

**[0121]**




Intermediate 20a Intermediate 20b Intermediate 20c




Compound 20-1 Compound 20-2

**[0122]** Synthetic route of Compound 20-1 and compound 20-2 were the same as that of Example 19. The difference was that 5-fluoro indole was used as starting raw materials to replace of 5-methoxy indole. Identification data of related

structures were as follows,

**[0123]** Intermediate 20b: MS(ESI) *m/z:* 207.2[M+1] $^{+}$.

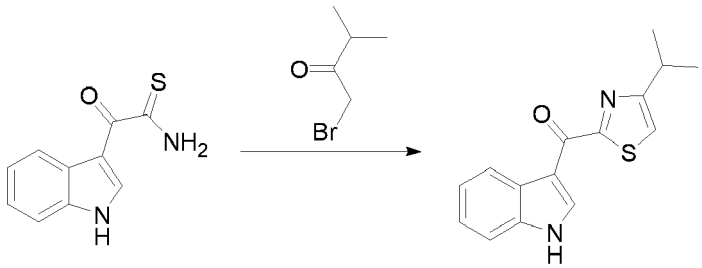
**[0124]** Intermediate 20c: $^{1}$H NMR (400MHz, DMSO-$d_6$): δ 12.94(brs, 1H), 8.68(s, 1H), 7.70(dd, *J*= 2.4, 9.2Hz, 1H), 7.62(dd, *J*=4.4, 8.8 Hz, 1H), 7.24(dt, *J*=2.4, 9.2 Hz, 1H). MS(ESI) *m/z:* 189[M+1] $^{+}$.

**[0125]** Compound 20-1: $^{1}$H NMR (400MHz, DMSO-$d_6$): δ 12.42(brs, 1H), 8.69(d, *J*=3.2 Hz , 1H), 7.87(dd, *J*=2.4, 8.8 Hz, 1H), 7.59(dd, *J*=4.4, 8.8 Hz, 1H), 7.16(dt, *J*=2.4, 9.2 Hz, 1H), 5.67(dd, *J*=8.4, 10.0 Hz, 1H), 3.92(s, 3H), 3.68(dd, *J*=11.2, 10.0 Hz, 1H), 3.55(dd, *J*=8.4, 11.2 Hz, 1H).MS(ESI) *m/z:* 307[M+1] $^{+}$.

**[0126]** Compound 20-2: $^{1}$H NMR (400MHz, DMSO-$d_6$): δ 12.48(brs, 1H), 9.13(s, 1H), 8.89(s, 1H), 7.97(dd, *J*=2.4, 9.6 Hz, 1H), 7.62(dd, *J*=4.4, 8.8 Hz, 1H), 7.17(dt, *J*=2.4, 9.2 Hz, 1H), 3.92(s, 3H). MS(ESI) *m/z:* 305[M+1] $^{+}$

Example 21 Compound 21

**[0127]**




Raw material S3 Compound 21

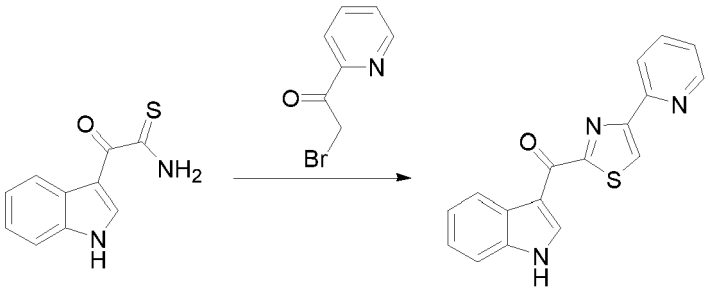
Synthesis of Compound 21

**[0128]** 1-bromine-3-methyl-2-butanone (0.8g, 4.89mmol) was dissolved in ethanol (25mL), into which Raw material S3 (1.0g, 4.89mmol) was added under stirring. Reaction system was heated to 80°C and kept to react for 2h, then cooled to room temperature, filtered and washed with ethanol to give Compound 21 (0.6g, yield 45%).

**[0129]** $^{1}$H NMR(400MHz, DMSO-$d_6$): δ 12.22(brs, 1H), 9.10(d, *J*=3.2Hz,1H), 8.31~8.33(m, 1H), 7.77(s,1H), 7.57~7.59(m,1H), 7.25~7.31(m, 2H), 3.16~3.23(m,1H), 1.36(d, *J*=6.8Hz, 6H)

Example 22 Compound 22

**[0130]**



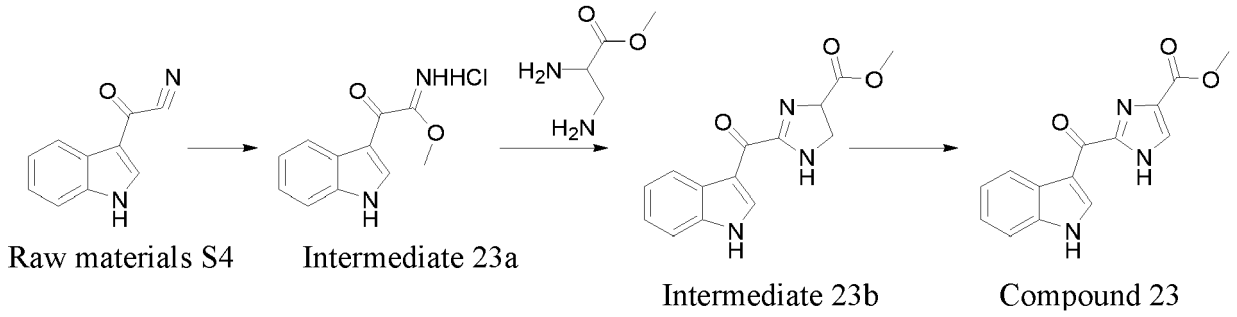

Raw materials S3 Compound 22

**[0131]** Synthesis of Compound 22 was the same as that of compound 21. Raw material S3 (1.0g, 4.89mmol) was used to synthesize Compound 22 (1.2g, yield 80%).

**[0132]** $^{1}$H NMR (400MHz, DMSO-$d_6$): δ 12.30(brs, 1H), 9.30(s, 1H), 8.69(dd, *J*=1.2, 4.2Hz,1H), 8.65 (s, 1H), 8.34~8.36(m, 1H), 8.32(d, *J*=1.2Hz, 1H), 8.01(dt, *J*=2.0, 7.2Hz, 1H), 7.60~7.62 (m, 1H), 7.44~7.47(m, 1H), 7.30~7.34(m, 2H).

Example 23 Compound 23

**[0133]**




Synthesis of Intermediate 23a

**[0134]** Raw material S4 (4.0g, 23.5mmol) was dissolved in methanol (50mL). Reaction system was cooled to below 0°C and kept to react for 8 hours, into which dry hydrogen chloride gas continuously aerated. After stopping aeration, reaction system was sealed and stirred overnight, then filtered to give 5.4g yellow solid, i.e. Intermediate 23a, which was used directly in subsequent reaction.

Synthesis of Intermediate 23b

**[0135]** Intermediate 23a (5.4g, 19.6mmol) was dissolved in acetonitrile (15mL), into which 2,3-diamino propionic acid methyl ester hydrochloride (3.7g, 19.6mmol) was added, and then triethylamine (10g, 98mmol) was added dropwise. Reaction mixture was refluxed for 5h, then from which solvent was removed under reduced pressure, and into which dichloromethane and water were added for dissolution and layer. Aqueous phase was extracted with dichloromethane twice. Organic phase after being combined was washed with saturated brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography to obtain Intermediate 23b (2.4g, yield 45%).

**[0136]** $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.19(s, 1H), 8.91(d, *J*=2.8Hz, 1H), 8.44(dd, *J*=6.8Hz, *J*=1.6Hz, 1H), 7.41~7.43(m, 1H), 7.30~7.36 (m, 2H), 4.67(brs, 1H), 4.18(d, *J*=7.6Hz, 2H), 3.82(s, 3H), 1.87(brs, 1H).MS (ESI) *m/z:* 272 $[M+1]^+$.

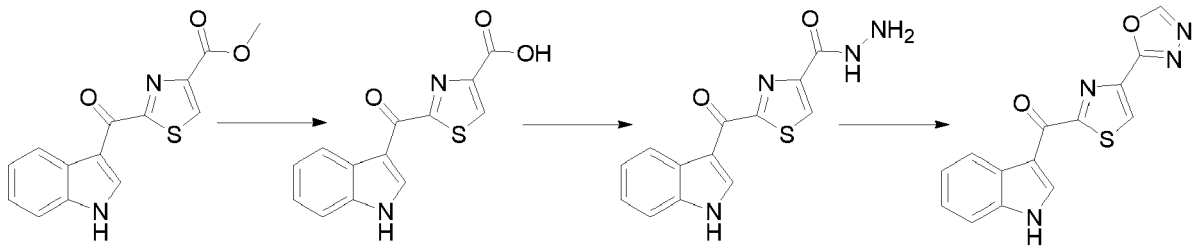
Synthesis of Compound 23

**[0137]** Intermediate 23b (1.2g, 4.42mmol) was dissolved in DMF (20mL), into which sodium hydroxide (530mg, 13.3mmol) was added. Reaction system was stirred to react for 3 hours with aeration of air at 60 °C, then cooled and poured into ice water, extracted with ethyl acetate for three times. Organic phase was washed with saturated brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude product. The crude product was washed with a mixed solvent of PE: EA= 2: 1 to give Compound 23 (960mg, yield 81%).

**[0138]** $^1$H NMR (400 MHz, DMSO): $\delta$ 13.69(brs, 1H), 12.20(s, 1H), 9.15(s, 1H), 8.32~8.36(m, 1H), 8.03(s, 1H), 7.55~7.59(m, 1H), 7.24~7.30 (m,2H), 3.83(s, 3H).MS(ESI) *m/z:* 270$[M+ 1]^+$.

Example 24 Compound 24

**[0139]**




Synthesis of Intermediates 24a

**[0140]** Raw material S1 (2.86g, 10mmol) was dissolved in a mixed solvent of THF / MeOH /$H_2O$(16/15/15mL). Reaction system was stirred overnight at room temperature. Reaction solution was adjusted to pH= 4-5 with 4N hydrochloric acid and then filtered. Filter cake was washed with water and dried in vacuo to give Intermediate 24a (2.6g, yield 96%). MS(ESI) m/z: 271$[M-1]^-$.

Synthesis of Intermediate 24b

**[0141]** Intermediate 24a (1.36g, 5mmol) was dissolved in THF (20mL), into which 2 drops of DMF was added and oxalyl chloride (755mg, 6mmol) was added dropwise. Reaction system was kept at room temperature for 2h, then concentrated to dryness under reduced pressure and then dissolved in THF (20mL), then which was added dropwise into 80% hydrazine hydrate (2mL, 57mmol) and stirred overnight. Reaction solution was concentrated to 5mL under reduced pressure and filtered. Filter cake was washed with THF and dried to give Intermediate 24b (1.38g, yield 97%).

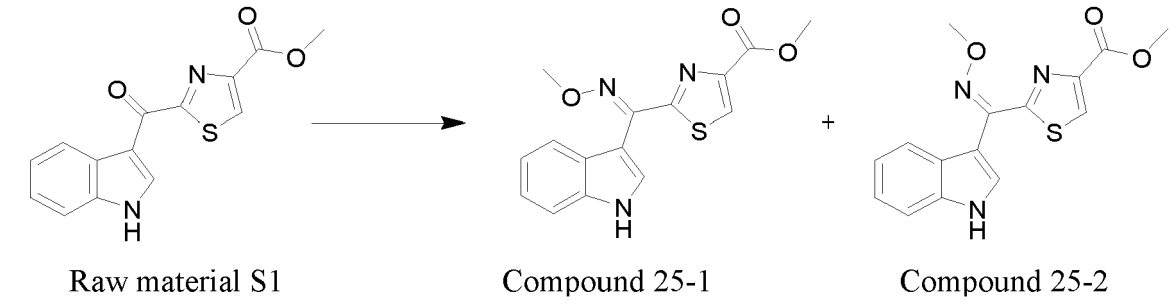
Synthesis of Compound 24

**[0142]** Mixture of Intermediate 24b (1.0g, 3.5mmol), p-toluenesulfonic acid monohydrate (20mg) and trimethyl orthoformate (5mL) was heated to 80°C and stirred overnight. Reaction solution was poured into ice water and filtered. Filter cake was washed with ethyl acetate and dried to give Compound 24 (280mg, yield 27%).

**[0143]** $^1$H NMR (400 MHz, DMSO-$d_6$): δ 12.45(brs, 1H), 9.43(s, 1H), 9.15(s, 1H), 8.95(s, 1H), 8.32(m, 1H), 7.61(m, 1H), 7.32(m, 2H). MS(ESI) *m/z:* 297$[M+1]^+$.

Example 25 Compound 25-1, 25-2

**[0144]**




Synthesis of Compound 25-1 and Compound 25-2

**[0145]** Raw material S1 (1.0g, 3.5mmol) was dissolved in pyridine (15mL), into which methoxylamine hydrochloride (1.75g, 21mmol) was added. Reaction system was heated to 90 °C and kept to react for 24h, then cooled to room temperature and diluted with water and extracted with ethyl acetate twice. Organic phase was washed with IN hydrochloric acid twice, then washed with saturated brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 20: 1 to 5: 17) to give Compound 25-1 (410mg) and Compound 25-2 (300mg). Yield was 64.3%.

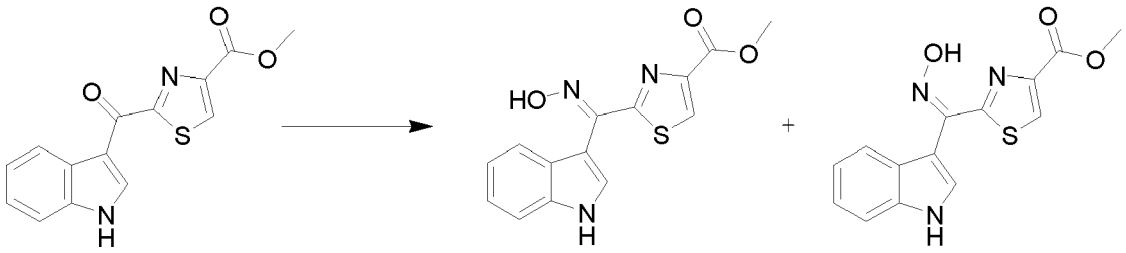
**[0146]** Compound 25-1: $^1$H NMR (400 MHz, $CDCl_3$): δ 8.54(d, *J*=3.2 Hz, 1H), 8.51 (brs, 1H), 8.42(s, 1H), 8.37~8.39(m,

1H), 7.41~7.43(m, 1H), 7.25~7.29(m, 2H), 4.32(s, 3H), 4.00(s, 3H). MS(ESI) *m/z:* 316[M+1]$^+$.

**[0147]** Compound 25-2: $^1$H NMR (400 MHz, CDC13): δ 8.94(bis, 1H), 8.24(s, 1H), 7.80(d, *J*=2.8 Hz, 1H), 7.40(d, *J*=7.6 Hz, 1H), 7.29~7.31(m, 1H), 7.14~7.18(m, 1H), 7.09~7.13(m, 1H), 4.16 (s, 3H), 3.92 (s, 3H). MS(ESI) *m/z:* 316[M+1] $^+$.

Example 26 Compound 26-1, 26-2

**[0148]**




Synthesis of Compound 26-1 and Compound 26-2

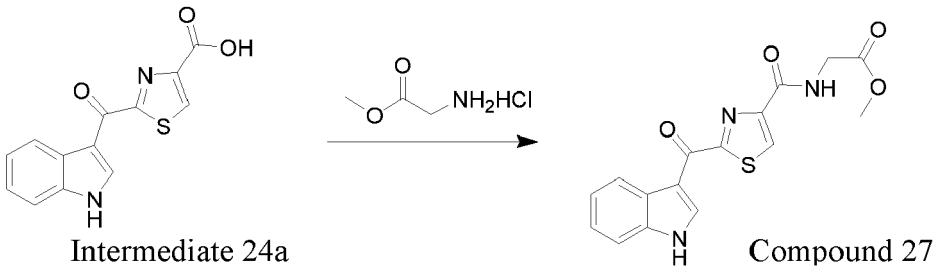
**[0149]** Synthesis of Compound 26-1 and Compound 26-2 was the same as that of Compound 25-1 and Compound 25-2. Raw material S1 (324mg, 1.13mmol) and hydroxylamine hydrochloride (696mg, 10mmol) were used to synthesize Compound 26-1 and Compound 26-2 (149mg, yield 44%).

**[0150]** Compound 26-1: $^1$H NMR (400 MHz, $CDCl_3$): δ 9.00(s, 1H), 8.26(s, 1H), 8.19 (d, *J*=8.0 Hz, 1H), 7.80(d, *J*=2.8 Hz, 1H), 7.47(d, *J*=8.0 Hz, 1H), 7.09~7.19(m,2H), 3.93(s, 3H).MS(ESI) *m/z:* 302[M+1]$^+$.

**[0151]** Compound 26-2: $^1$H NMR (400 MHz, $CDCl_3$): δ 8.58(s, 1H), 8.45(s, 1H), 8.27(d, *J*=3.2 Hz, 1H), 7.40 (dd, *J*=7.2 Hz, *J*=1.6 Hz, 1H), 7.33(d, *J*=8.0 Hz, 1H), 7.20~7.28(m , 2H), 4.01(s, 3H).MS(ESI) *m/z:* 302[M+1]$^+$.

Example 27 Compound 27

**[0152]**

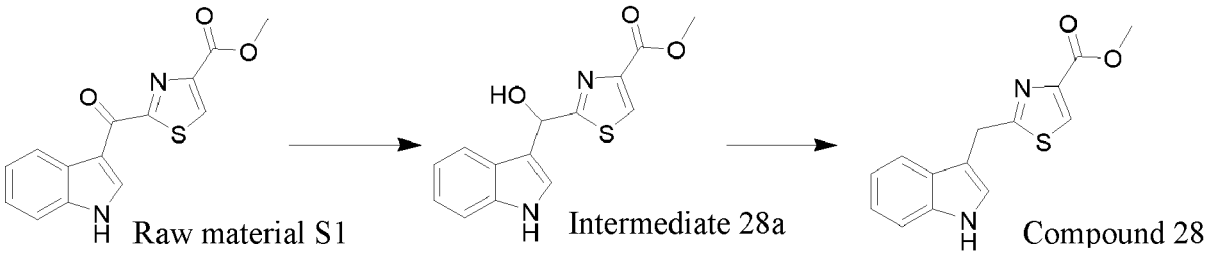



**[0153]** Glycine methyl ester hydrochloride (753mg, 6mmol), HATU (2.26g, 6mmol) and DIEA(2.3g, 10mmol) were added into a solution of Intermediate 24a (1.36g, 5mmol) in DMF (20mL). Reaction system was stirred at room temperature for 2h. Reaction mixture was poured into 100mL ice water and filtered. Filter cake was washed with ethyl acetate and dried to give Compound 27 (1.45g, yield 84.5%).

**[0154]** $^1$H NMR (400MHz, DMSO-$d_6$): δ 12.40(d, *J*=2.0Hz, 1H), 9.43(d, *J*=3.2Hz, 1H), 9.29(t, *J*=2.4Hz, 1H), 8.66(s, 1H), 8.32~8.35(m, 1H), 7.58~7.60(m, 1H), 7.27~7.34(m, 2H), 4.13(d, *J*=6.4Hz, 2H), 3.70(s, 3H)

Example 28 Compound 28

**[0155]**




Synthesis of Intermediate 28a

**[0156]** Raw material S1 (7g, 24mmol) was dissolved in a mixed solvent of THF (42mL) and methanol (168mL). Mixture was cooled to 0°C by ice-salt bath. Then sodium borohydride was slowly added (4.6 g, 122.mmol) in batches to the mixture. Then the ice-salt bath was removed. Reaction system was raised to room temperature to react for 1 hour. Reaction solution was poured into ice water and filtered. Filter cake was washed with methanol to give Intermediate 28a (6.8g, yield 98%).

**[0157]** $^1$H NMR(400MHz,DMSO-$d_6$): δ 11.07(s,1H), 8.46(s,1H), 7.48(d, *J*=8.0Hz, 1H), 7.37(d, *J*=8.0Hz, 1H), 7.34(d, *J*=2.4Hz, 1H), 7.07(dt, *J*=0.8, 8.0Hz, 1H), 6.96 (dt, *J*=0.8, 8.0Hz, 1H), 6.68(d, *J*=4.0Hz, 1H), 6.18(d, *J*=4.0Hz, 1H), 3.77(s, 3H).MS (ESI) *m/z:* 291.0 [M+ 1]$^+$.

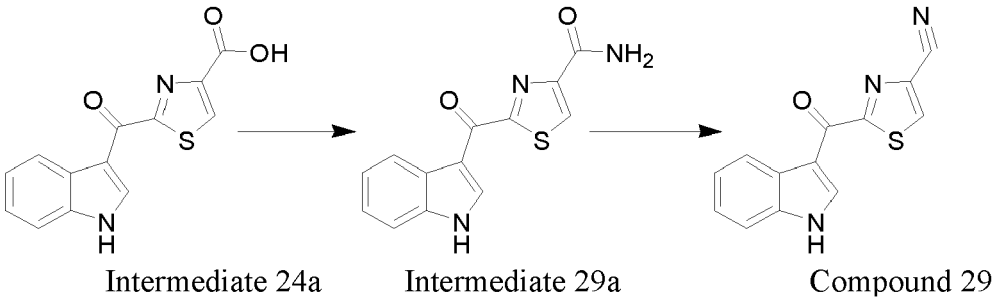
Synthesis of Compound 28

**[0158]** Intermediate 28a (3g, 10.4mmol) was dissolved in methanol (25mL), into which zinc powder (2g,31.2mmol) was added under stirring. Reaction system was refluxed for 1h at 100°C under protection of nitrogen gas. Reaction solution was dropped to ice water and filtered to give 1.8g of crude product. Crude product (200mg) was purified by silica gel column chromatography (PE/ EA= 4/1to 2/1) to give Compound 28 (20mg).

**[0159]** $^1$H NMR(400MHz, DMSO-$d_6$): δ 11.06(s,1H), 8.32(s,1H), 7.39~7.44(m,3H), 7.10(dt, *J*=1.1, 8.0Hz, 1H), 6.98(dt, *J*=1.1, 8.0Hz, 1H), 4.05(s,2H), 3.81(s, 3H).MS (ESI) *m/z:* 275.0 [M+1]$^+$.

Example 29 Compound 29

**[0160]**




Synthesis of Intermediate 29a

**[0161]** Intermediate 24a (1.36g, 5mmol) was dissolved in THF (20mL), into which 2 drop of DMF was added and oxalyl chloride (755mg, 6mmol) were added dropwise. Reaction system was kept to react for 2h at room temperature, then concentrated under reduced pressure to dryness, and then dissolved in THF (20mL), which was added dropwise into concentrated ammonia (10mL). Reaction solution was stirred overnight and concentrated to 5mL under reduced pressure and filtered. Filter cake was washed with THF and dried to give Intermediate 29a (1.3g, yield 95%) .

**[0162]** $^1$H NMR(400MHz, DMSO-$d_6$): δ12.27(s,1H), 9.52(s,1H), 8.61(s,1H), 8.31~8.35(m, 1H), 7.57~7.60 (m,1H), 8.28(s, 1H), 7.81(s, 1H), 7.26~7.34 (m, 2H). MS (ESI) *m/z*: 272.0[M+1]$^+$.

Synthesis of Compound 29

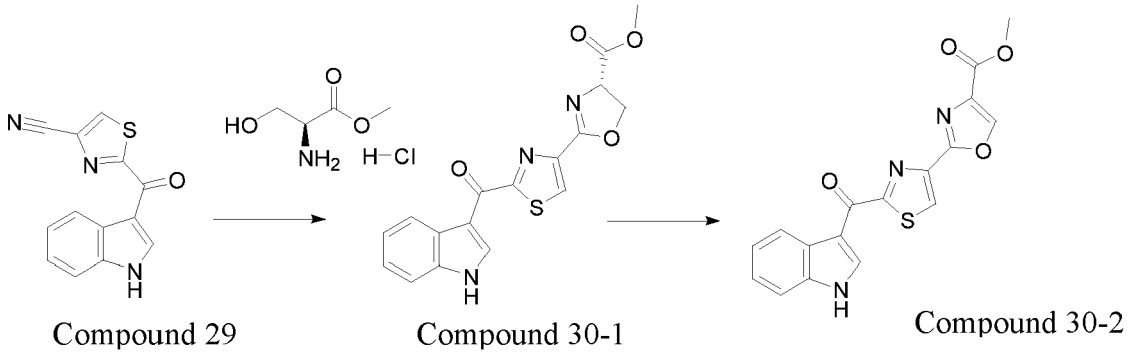
**[0163]** Intermediate 29a (17g, 62.66mmol) was dissolved in ethyl acetate (250mL), into which pyridine 14.87g (187.9

mmol) was added, and trifluoroacetic anhydride (19.7g, 93.99mmol) was added dropwise at room temperature. Reaction system was stirred at room temperature for 4h, concentrated to dryness under reduced pressure and then recrystallized with ethyl acetate to give Compound 29 (14g, yield 88%).

**[0164]** $^1$H NMR(400MHz, DMSO-$d_6$): δ 12.44(s,1H), 9.15(s,1H), 9.03(d, *J*=3.6Hz,1H), 8.28~8.31(m, 1H), 7.57~7.62 (m, 1H), 7.29~7.34 (m, 2H).MS (ESI) *m/z:* 254.0[M+1]$^+$.

Example 30 Compound 30-1, 30-2

**[0165]**




Synthesis of Compound 30-1

**[0166]** Compound 29 (1g, 3.9mmol) was dissolved in methanol (100mL), which was replaced with nitrogen gas for three times, into which a solution of sodium methoxide (sodium 0.23g, 10mmol; methanol 50mL) was added dropwise. Reaction system was stirred at room temperature for 4h, then into which a solution of L-serine methyl ester hydrochloride (1.8g, 11.6mmol) in methanol (50mL) was added dropwise. Reaction system was heated to 55°C and stirred for 2h. Reaction solution was poured into ice water and filtered to give a crude product. The crude product was purified by silica gel column chromatography (PE: EA= 1:1) to give Compound 30-1 (0.4g, yield 29%).

**[0167]** $^1$H NMR (400 MHz, DMSO-$d_6$): δ 12.33 (s, 1H), 9.10 (d, *J*=2.9 Hz, 1H), 8.73 (s, 1H), 8.44~8.21 (m,1H), 7.69~7.49 (m, 1H), 7.40~7.21 (m, 2H), 5.06 (dd, *J*=10.0, 8.0 Hz, 1H), 4.76~4.57 (m, 2H), 3.74 (s, 3H). MS (ESI) *m/z:* 356.0[M+1]$^+$.

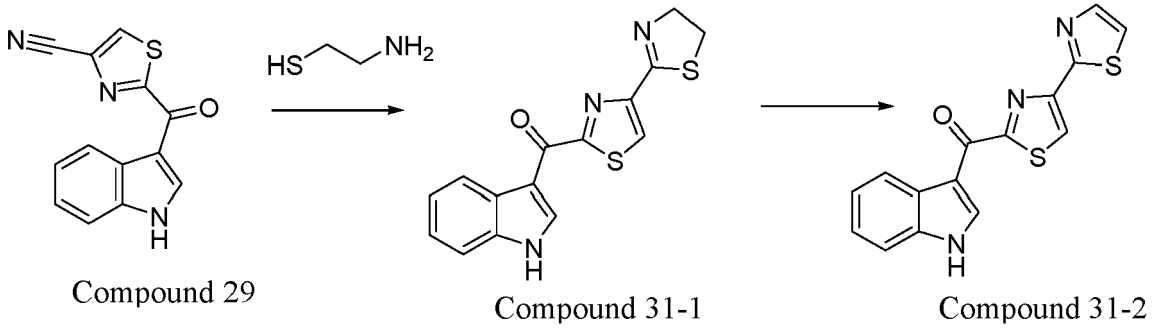
Synthesis of Compound 30-2

**[0168]** Compound 30-1 (200mg, 0.56mmol) was dissolved in tetrahydrofuran (50mL), into which manganese dioxide (1000mg, 11 .56mmol) was added. Reaction system was refluxed overnight, cooled and filtered. Filtrate was concentrated to dryness under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (PE: EA= 2:1) to give Compound 30-2 (25mg, yield 12%).

**[0169]** $^1$H NMR (400 MHz, DMSO-$d_6$): δ 12.37 (s, 1H), 9.17 (d, *J*=2.7 Hz, 1H), 9.09 (s, 1H), 8.90 (s, 1H), 8.37~8.29 (m, 1H), 7.66~7.59 (m, 1H), 7.38~7.26 (m, 2H), 3.89 (s, 3H)。MS (ESI) *m/z:* 354[M+1]$^+$.

Example 31 Compound 31-1, 31-2

**[0170]**



Synthesis of Compound 31-1:

Synthesis method of Compound 31-1 was the same as that of Compound 30-1.

**[0171]** $^1$H NMR (400 MHz, DMSO-$d_6$): δ 12.41 (s, 1H), 9.08 (d, *J*=3.1 Hz, 1H), 8.63 (s, 1H), 8.42~8.24 (m, 1H), 7.68~7.49 (m, 1H), 7.31 (m, 2H), 4.47 (t, *J* = 8.5 Hz, 2H), 3.48 (t, *J* = 8.5 Hz, 2H).MS (ESI) *m/z:* 314.0 $[M+1]^+$.

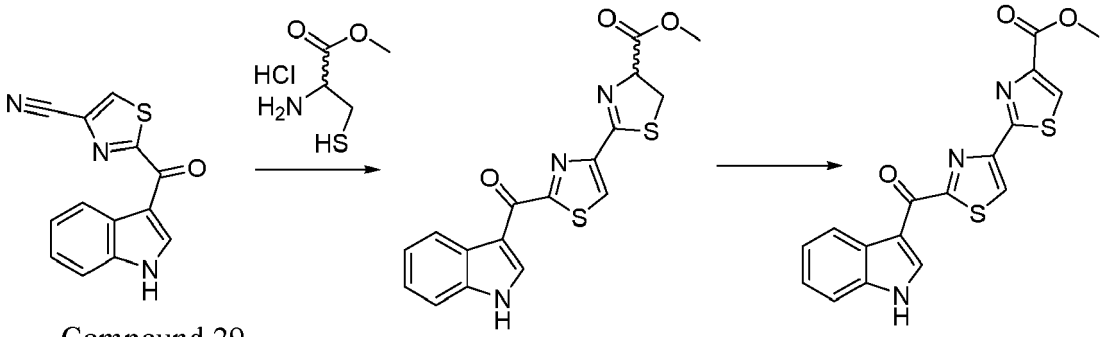
Synthesis of Compound 31-2:

Synthesis method of Compound 31-2 was the same as that of compound 30-2.

**[0172]** $^1$H NMR (400 MHz, DMSO-$d_6$): δ 12.41 (s, 1H), 9.13 (d, *J*=3.2 Hz, 1H), 8.64 (s, 1H), 8.37~8.30 (m,1H), 8.01 (d, *J*=3.2 Hz, 1H), 7.91 (d, *J*=3.2 Hz, 1H), 7.65~7.57 (m, 1H), 7.35~7.27 (m, 2H). MS (ESI) *m/z*: 312.0 $[M+1]^+$.

Example 32 Compound 32-1, 32-2

**[0173]**




Compound 32-1:

Synthesis method of Compound 32-1 was the same as that of Compound 30-1.

**[0174]** $^1$H NMR(400MHz,DMSO-$d_6$): δ 12.43(s,1H), 9.04(s,1H), 8.70(s,1H), 8.29~8.344(m, 1H), 7.57~7.60(m,1H), 7.21~7.34 (m, 2H), 5.48(dd, *J*=9.2, 8.4Hz, 1H), 3.78(dd, *J*=6.0,11.6Hz,1H), 3.75(s,3H), 3.67(dd, *J*=11.6, 8.4Hz, 1H).MS (ESI) *m/z*: 372.0$[M+1]^+$.

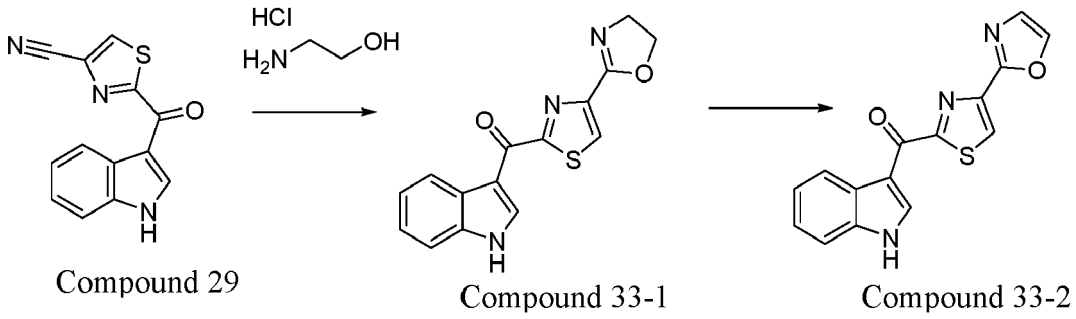
Compound 32-2:

Synthesis method of Compound 32-2 was the same as that of compound 30-2.

**[0175]** MS (ESI) *m/z*: 370.0$[M+1]^+$.

Example 33 Compound 33-1, 33-2

**[0176]**




Compound 33-1:

Synthesis method of Compound 33-1 was the same as that of Compound 30-1.

**[0177]** MS (ESI) *m*/*z*: 298.0[M+1]$^+$.

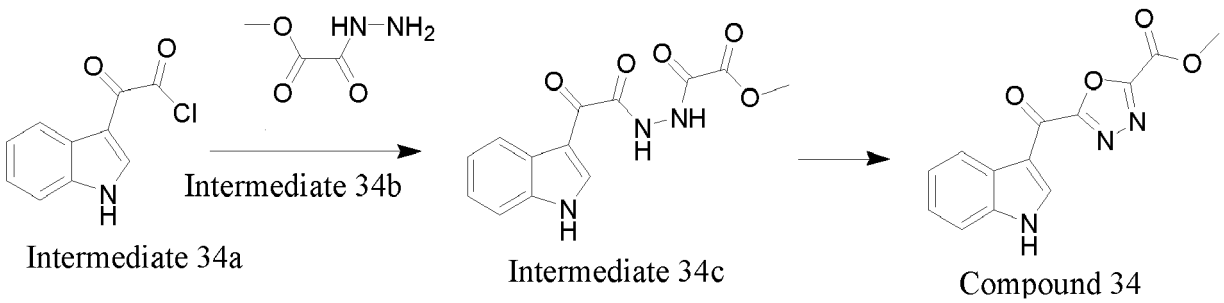
Compound 33-2:

Synthesis method of Compound 33-2 was the same as that of compound 30-2.

**[0178]** $^1$H NMR (400 MHz, DMSO-$d_6$): δ 12.41 (s, 1H), 9.13 (d, *J*=3.2 Hz, 1H), 8.64 (s, 1H), 8.37~8.30 (m,1H), 7.65~7.57 (m, 1H), 7.52 (brs, 1H), 7.35~7.27 (m, 2H), 7.11(brs, 1H).MS (ESI) *m*/*z*: 296.0[M+1]$^+$.

Example 34 Compound 34

**[0179]**




**[0180]** For synthesis of Intermediate 34a, please refer to J. Am. Chem. Soc., 2002, 124(44), 13179-13184.
**[0181]** For synthesis of Intermediate 34b, please refer to J. Med. Chem., 1961, 4, 259-296.

Synthesis of Intermediate 34c

**[0182]** Compound 34b (1.18g, 10mmol) and triethylamine (3.03g, 30mmol) were dissolved in dichloromethane (15mL), then into which a solution of Compound 34a (2.07g, 10mmol) in dichloromethane (10mL) was added dropwise at 0°C. Reaction mixture was stirred overnight at room temperature, then diluted with 30mL water and extracted with dichloromethane for 3 times. Organic phase after being combined was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give Intermediate 34c (2.8g, yield 97%).
**[0183]** MS (ESI) *m*/*z:* 290.0 [M+1]$^+$.

Synthesis of Compound 34

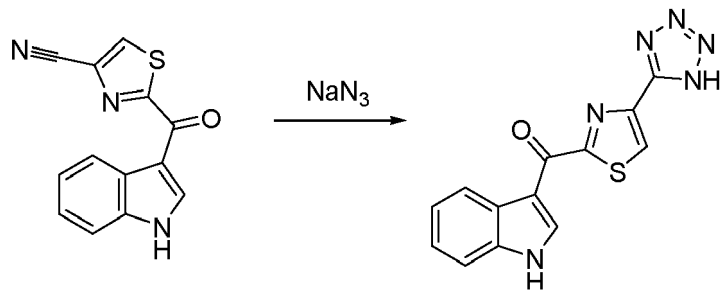
**[0184]** Intermediate 34c (5g, 17.286mmol) was dissolved in DMF (200mL), into which triethylamine (5.2g, 51.86mmol) was added under stirring, then THF (100mL) was added and p-toluenesulfonyl chloride (9.88g, 51.86mmol) dissolved in dichloromethane (50mL) was slowly added dropwise for 1 hour under protection of nitrogen gas. Reaction system was kept at room temperature overnight, then concentrated under reduced pressure to remove dichloromethane and

THF, and then added dropwise to ice water and stirred and filtered to give a crude product. The crude product was purified by silica gel column chromatography (dichloromethane/ methanol =50/1~10/1) to give Compound 34 (0.5g, yield 10%).

**[0185]** $^1$H NMR(400MHz, DMSO-$d_6$): δ 12.53(brs, 1H), 8.90(s,1H), 8.27~8.29(m,1H), 7.60~7.62(m,1H), 7.32-7.37(m,2H), 4.02(s, 3H).MS (ESI) *m/z:* 272.1 $[M+1]^+$.

Example 35 Compound 35

**[0186]**



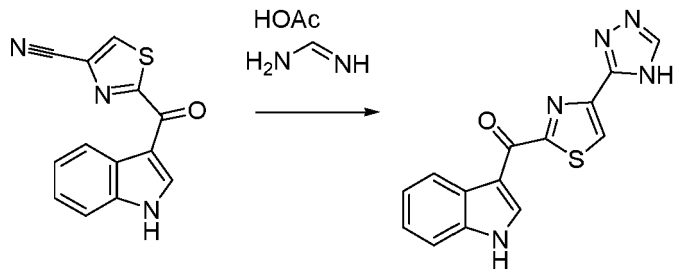

Compound 29 Compound 35

**[0187]** Compound 29 (2g, 7.9mmol) was added to a sealed reaction vessel, into which DMF (30mL) was added and stirred, then ammonium chloride (0.49g, 9.2mmol) was added and sodium azide(0.6g, 9.2mmol) was added. Then the reaction vessel was sealed and kept to react overnight at 120°C by oil bath. Reaction solution was cooled to room temperature, then added dropwise to 200mL of ice water and extracted with ethyl acetate (150mL). The pH of aqueous phase was adjusted to be acidic by 2N hydrochloric acid to precipitate solid, then filtered, washed with water and dried to give Compound 35 (1.8g, 77%).

**[0188]** $^1$H NMR (400 MHz, DMSO-$d_6$): δ 12.50 (s, 1H), 9.48(d, *J*=3.6Hz, 1H), 8.88 (s, 1H), 8.36~8.34 (m, 1H), 7.62~7.60 (m, 1H), 7.34~7.31 (m, 2H).MS (ESI) *m/z:* 297.0 $[M+1]^+$.

Example 36 Compound 36

**[0189]**



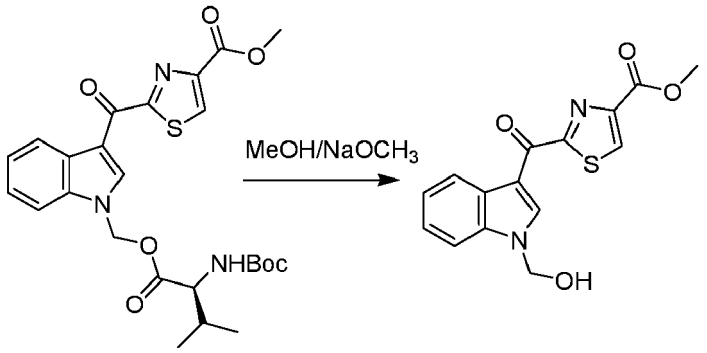

Compound 29 Compound 36

**[0190]** Compound 29 (0.5g, 1.7mmol) was suspended in 10mL ethylene glycol methyl ether, into which 2mL acetic acid and formamidine acetate (0.215g, 2.07mmol) were added. Reaction system was reflux for 24 hours by an oil bath under protection of nitrogen gas, then distilled under reduced pressure. Crude product was purified by silica gel column chromatography (DCM/methanol=200/1~20/1) to give Compound 35 (0.32 g, yield 55%).

**[0191]** $^1$H NMR (400MHz, DMSO-$d_6$): δ 12.41 (s, 1H), 10.6(s, 1H), 10.05(s, 1H), 9.55(s, 1H), 8.72 (s, 1H), 8.32~8.34 (m, 1H), 7.58 ~7.59 (m, 1H), 7.28~7.33 (m, 2H). MS (ESI) *m/z*: 296.0 $[M+1]^+$.

Example 37 Compound 37

**[0192]**



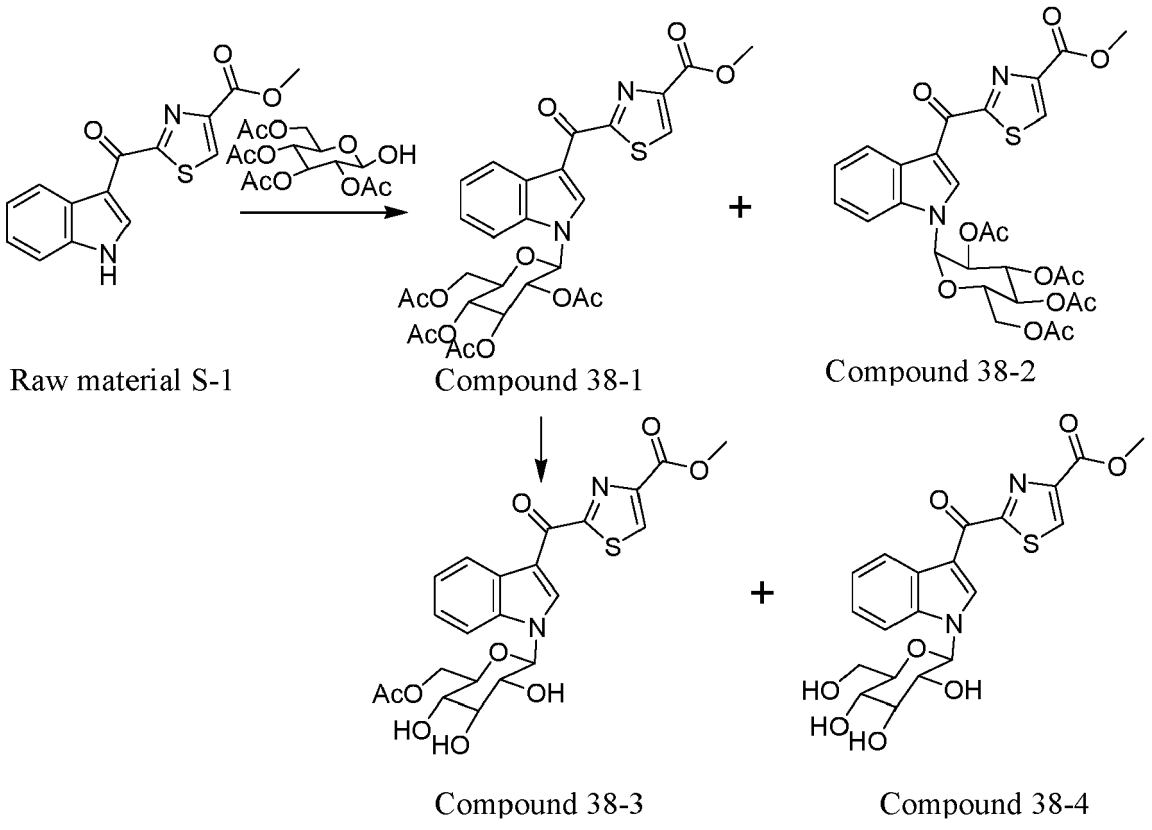

Compound 1-1 Compound 33

**[0193]** Compound 1-1 (500mg, 0.97mmol) was dissolved in methanol (2mL), into which 0.1N sodium methoxide solution (2mL) was added dropwise. Reaction system was kept at room temperature overnight and then filtered. Solid was washed with methanol and dried to give Compound 37 (153mg, yield 50%).

**[0194]** $^1$H NMR (400MHz, $CDCl_3$): δ 9.25(s, 1H), 8.93(s, 1H), 8.35(d, *J*=7.6Hz, 1H), 7.81(d, *J*=7.6Hz, 1H), 7.39~7.47(m, 2H), 6.92(t, 1H), 5.6(d, 2H), 3.94 (s, 3H). MS(ESI) *m*/*z*:317 $[M+1]^+$.

Example 38 Compound 38-1 to Compound 38-4

**[0195]**




Raw material S-1 Compound 38-1 Compound 38-2

Compound 38-3 Compound 38-4

Synthesis of Compound 38-1, 38-2

**[0196]** Raw material S-1 (1.07g, 3.78mmol) was dissolved in THF (50mL), into which 2, 3, 4, 6-tetraacetyl glucose (2.6g, 7.55mmol ) was added, and then triphenylphosphine (2g, 7.55mmol) was added under protection of nitrogen gas. Reaction system was cooled to -15°C , then into which diisopropyl azodicarboxylate (1.53g, 7.55mmol) was added dropwise. Reaction solution was poured into ice water, extracted with ethyl acetate (100mL × 2 ), dried over anhydrous

sodium sulfate, concentrated to dryness under reduced pressure and purified by silica gel column chromatography (petroleum ether/ ethyl acetate: 10 / 1-2 / 1 ) to give Compound 38-1 (650mg) and Compound 38-2 ( 600mg) (yield 54%).

**[0197]** Compound 38-1: $^1$H NMR (400 MHz, $CDCl_3$): $^1$H NMR (400 MHz, $CDCl_3$): δ 9.18 (s, 1H), 8.52~8.54 (m, 1H), 8.44 (s, 1H), 7.60 ~7.63 (m, 1H), 7.38~7.42 (m, 2H), 5.72 (d, *J*=9.2 Hz, 1H), 5.64 (t, *J*=9.2 Hz, 1H), 5.50 (t, *J*=9.6 Hz, 1H), 5.40 (d, *J*=9.6 Hz, 2H), 4.35 (dd, *J*=4.8 , 12.4 Hz , 2H), 4.27 ( dd, *J*=2.4 , 12.4 Hz, 1H ) , 4.07 (s, 3H), 4.05~4.10(m,1H), 2.16 (s, 3H), 2.13(s, 3H), 2.05(s, 3H), 1.74(s,3H);MS (ESI) m/z: 617.14 $[M+1]^+$.

**[0198]** Compound 38-2: δ 9.20 (s, 1H), 8.56~8.49 (m, 1H), 8.45 (s, 1H), 7.87~7.80 (m, 1H), 7.44~7.35 (m, 2H), 5.92 (d, *J*=5.2 Hz, 1H), 5.35 (t, *J*=2.3 Hz, 1H), 4.99 (dt, *J*=9.4, 1.7 Hz, 1H), 4.38~4.25 (m, 2H), 4.21~4.12 (m, 2H), 4.04 (s, 3H), 2.21 (s, 3H), 2.18 (s, 3H), 2.16(s,3H), 2.07 (s, 3H); MS (ESI) m/z: 617.14 $[M+1]^+$.

Synthesis of Compound 38-3, 38-4

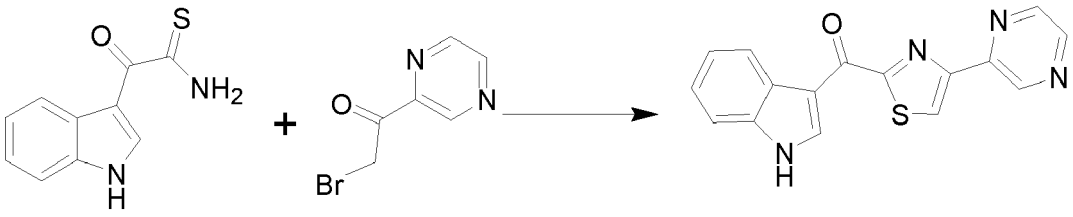
**[0199]** Compound 38-1 (200mg, 0.325mmol) was dissolved in methanol (10mL), into which sodium methoxide (190mg 3.57mmol) was added. Reaction system was stirred at room temperature for 5h, then poured into saturated aqueous sodium chloride, then into which 50mL ethyl acetate was added, and adjusted pH to neutral by use of citric acid. Organic phase was separated and aqueous phase was extracted once with ethyl acetate. Organic phase after being combined was dried over anhydrous sodium sulfate, filtered, concentrated to dryness under reduced pressure and purified by silica gel column chromatography (methanol/ dichloromethane: 5%-10%) to give Compound 38-3 ( 40mg) and Compound 38-4 ( 5mg ).

**[0200]** Compound 38-3: MS (ESI) *m/z:* 491.1 $[M+1]^+$.

**[0201]** Compound 38-4: MS (ESI) *m/z:* 449.1 $[M+1]^+$.

Example 39 Compound 39

**[0202]**



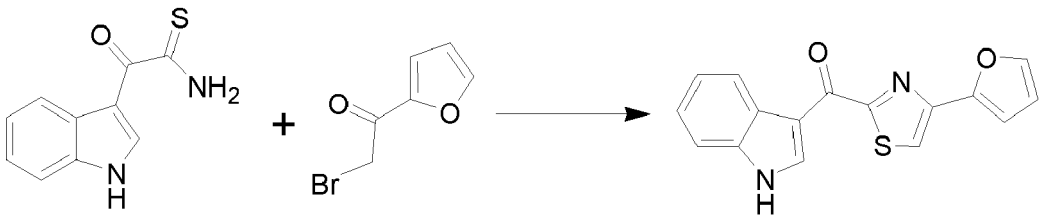
Raw material S3 Compound 39

**[0203]** Synthesis method of compound 39 was the same as that in Example 21 to give Compound 39 (yield 65%).

**[0204]** $^1$H NMR (400MHz, DMSO-$d_6$): δ 12.25 (s, 1H), 9.58(d, *J* =0.8Hz, 1H), 9.38(d, *J* = 3.2Hz, 1H), 8.79( s, 1H), 8.76 (d, *J* =1.2Hz, 1H), 8.72 (d, *J* =2.4Hz, 1H), 8.34~8.36(m, 1H), 7.60~7.63(m, 1H) , 7.28~7.33(m, 2H).MS(ESI) *m/z:* 307$[M+1]^+$.

Example 40 Compound 40

**[0205]**



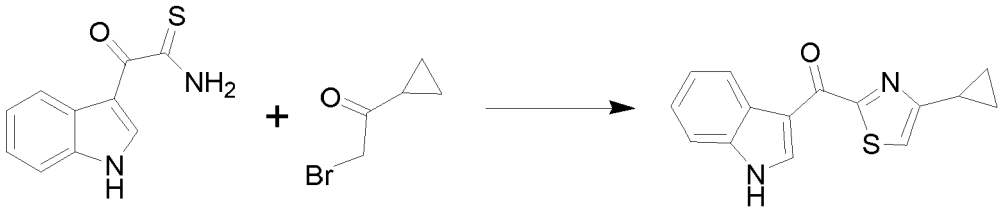
Raw material S3 Compound 40

**[0206]** Synthesis method of compound 40 was the same as that in Example 21 to give Compound 40 (yield 58%).

**[0207]** $^1$H NMR (400MHz, DMSO-$d_6$): δ 12.29 (s, 1H), 9.23(d, *J* = 3.2Hz, 1H), 8.33~8.36(m, 1H),8.21(s, 1H), 7.85(d, *J* = 0.8, 1H), 7.59~7.61(m, 1H) , 7.27~7.33(m, 2H) , 7.13( d, J= 2.8Hz, 1H), 6.69~6.71(m, 1H).MS(ESI) *m/z:* 295[M+1] $^+$.

Example 41 Compound 41

**[0208]**



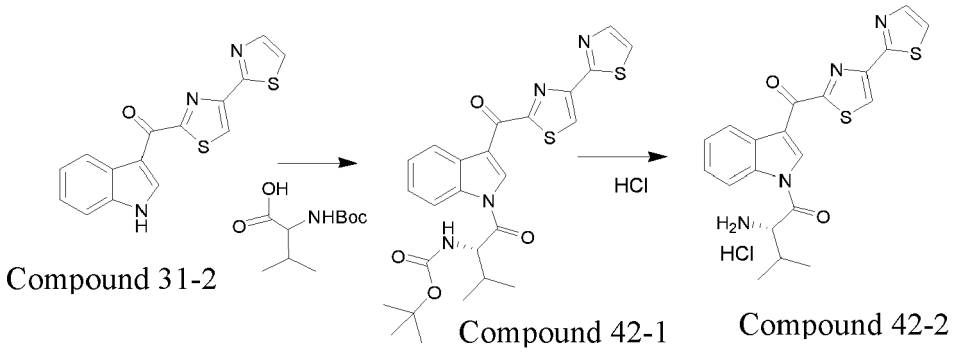
Raw material S3 Compound 41

**[0209]** Synthesis method of compound 41 was the same as that in Example 21 to give Compound 41 (yield 58%).

**[0210]** $^1$H NMR(400MHz, DMSO-$d_6$): δ 12.19(s, 1H), 8.99(d, *J*=3.2Hz,1H), 8.30(m, 1H), 7.71(s,1H), 7.60(m,1H), 7.27(m, 2H), 2.24(m,1H), 1.01(d, *J*=6.8Hz, 4H).MS(ESI) *m/z*: 269[M+1] $^+$.

Example 42 Compound 42-1 to Compound 42-2

**[0211]**



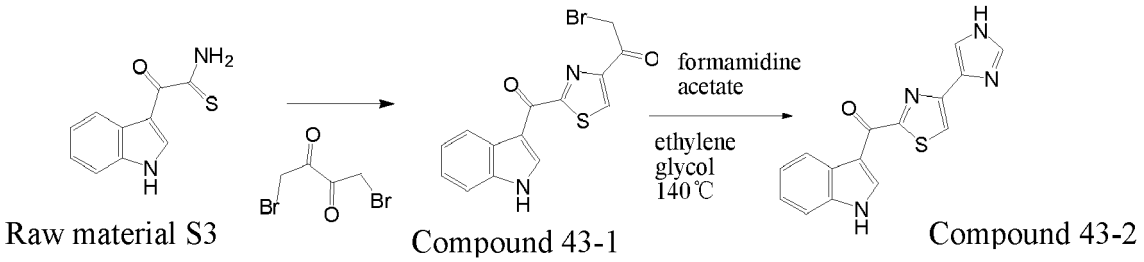
Compound 31-2 Compound 42-1 Compound 42-2

**[0212]** Synthesis method of compound 42-1 was the same as that in Example 4 to give Compound 42-1 (yield 83%). MS(ESI) *m/z:* 511.1[M+1]$^+$.

**[0213]** Compound 42-2 (yield 90%), $^1$H NMR(400MHz, $CDCl_3$): δ 9.58(s, 1H), 9.04(s, 1H), 8.89(brs, 3H), 8.78(m, 1H), 8.46~8.51(m,1H), 8.35~8.38 (m, 1H) , 8.03 ( d, *J*=3.2Hz, 1H) , 7.96 (d, *J*=3.2Hz, 1H) , 7.54~7.62(m, 2H), 5.13(m, 1H), 2.54~2.59(m, 1H), 1.15(d, *J*=7.2Hz, 3H), 1.07(d, *J*=7.2Hz, 3H).MS(ESI) *m/z*: 411.1[M+1]$^+$.

Example 43 Compound 43-1 to Compound 43-2

**[0214]**



Raw material S3 Compound 43-1 Compound 43-2

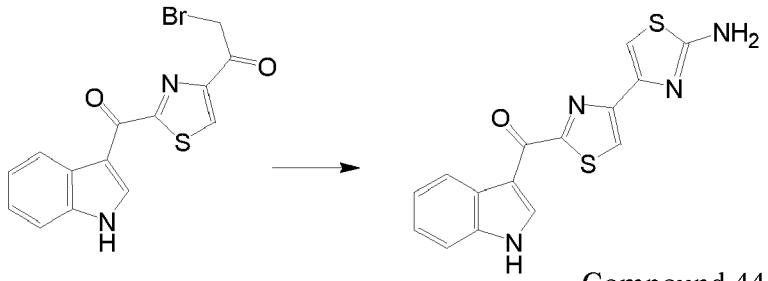
**[0215]** Synthesis method of Compound 43-1 was the same as that in Example 21. Yield was 78%, MS(ESI) *m/z:*349[M+1]$^+$.

**[0216]** Compound 43-1 (1.8g, 5.15mmol) was added to ethylene glycol (35mL), then into which formamidine acetate (2.68g, 25.77mmol) was added. Reaction system was kept at 140 °C (external temperature) for 2 hours under protection of $N_2$, then cooled and added into ice water, then into which an aqueous solution of sodium hydroxide was added to adjust pH = 9 to 10, and extracted with EA. Organic phases were combined, dried, distilled under reduced pressure to remove solvent. Solid was washed with mixture of EA and a small amount of ethanol and filtered. Crude product was dissolved in THF, filtered by silica gel, washed with THF, concentrated and then washed with mixture of THF / petroleum ether, then filtered to give 380mg of Compound 43-2.

**[0217]** $^1$H NMR (400 MHz, DMSO) $\delta$ =12.37(s, 1H), 12.45(s, 1H), 9.38(s, 1H), 8.338~.38(m, 1H), 8.04(s,1H), 7.79(s, 2H), 7.58~7.63(m,1H), 7.26~7.33(m,2H). MS(ESI) *m/z:* 295[M+1]$^+$.

Example 44 Compound 44

**[0218]**




Compound 43-1 Compound 44

**[0219]** Compound 43-1 (1.5g, 4.3mmol) was dissolved in ethanol (25mL), into which thiourea (327mg, 4.3mmol) was added. Reaction system was kept at 80°C for 3h. After completion of reaction, reaction solution was cooled, filtered, washed with aqueous sodium bicarbonate, dried, dissolved with THF, filtered through silica gel. Filtrate was concentrated and washed with EA to give1.2 g of Compound 44 (yield 85.6%).

**[0220]** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ =12.26 (d, *J* =2.4Hz, 1H), 9.27(d, *J* =3.2Hz, 1H), 8.32~8.36( m, 1H), 7.99(s, 1H), 7.58~7.61(m, 1H), 7.26~7.32(m, 3H), 7.21(s, 2H). MS(ESI) *m/z:* 327[M+1]$^+$.

Effect Example 1

**[0221]** AhR agonist assay (please refer to activity assay of MeBio agonist: Oncogene (2004) 23, 4400-4412)

**[0222]** Experimental material (plasmids): cells of reporter gene expressing natural (Human Hepatoma Huh-7) AhR receptor, in which reporter vector comprises a functional firefly luciferase gene connecting to an upstream receptor specific genetic response element (GRE). AhR agonist test includes following three steps:

1, Implanting into cells: a suspension of reporter cell of AhR receptor was prepared in cell recovery medium (CRM; containing 10 % charcoal-treated FBS). Then the suspension (100μL) was assigned to wells in a white culture plate with 96 wells.

2, Before the experiment was about to begin, Master Stocks was diluted to be a processing medium of "concentration of 2X" by use of appropriate compound screening assay medium (CSM: containing 10% charcoal-treated FBS). Test compounds were diluted with gradient method by use of CSM medium containing 0.2% DMSO to make the final concentration of DMSO in each well of each treatment group being 0.1 %. The processing medium was added to culture plate (100μL/ well) on which cells containing reporter gene had been laid in advance in wells by means of double duplicate. The culture plate was placed in an incubator of 37°C for 24 hours.

3, Fluorescence detection and analysis: after incubation, the processing medium was discarded and luciferase detection reagent was added 100μL/well. *Ave RLU* (mean relative fluorescence intensity) of each well and coefficient of variation for each set of experiments were detected. Ratio of *Ave RLU*$^{\text{Test Cmpd}}$ of treatment groups with test compound of different concentrations to Ave RLU$^{\text{Vehicle}}$ of blank control group can determine activity quantitatively of AhR receptor under influence of test compound of different concentrations and activating multiples as well as $EC_{50}$.

$$\text{Coefficient of variation } (\%\text{CV}) = 100 \times \frac{SD}{Ave\,RLU};$$

$$\text{Activating multiples} = \frac{\text{Ave RLU}^{\text{Test Cmpd}}}{\text{Ave RLU}^{\text{Vehicle}}}.$$

**[0223]** Processing method of data may refer to J. Biomol. Screen, 1999, 4(2), 67-73.

**[0224]** $EC_{50}$ of each compound was shown in Table 1, wherein A indicates 0.001μM< $EC_{50}$≤1.0μW; B indicates 1.0μM<$EC_{50}$≤10.0μM; C indicates 10.0μM<$EC_{50}$≤100μM.

Table 1 $EC_{50}$ of each test compound

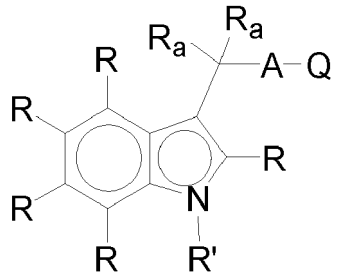
| Test compound | $EC_{50}$(nM) | Test compound | $EC_{50}$(nM) |
|---|---|---|---|
| 1-2 | A | 26-1 | B |
| 2-2 | A | 26-2 | B |
| 3 | A | 27 | A |
| 4-2 | A | 28 | C |
| 5 | A | 29 | A |
| 6 | A | 30-1 | A |
| 7 | A | 30-2 | A |
| 8 | B | 31-1 | A |
| 9 | A | 31-2 | A |
| 10 | C | 32-1 | A |
| 11 | C | 32-2 | A |
| 12 | A | 33-1 | A |
| 13 | B | 33-2 | A |
| 14 | B | 34 | B |
| 15 | C | 35 | B |
| 16 | A | 36 | A |
| 17 | C | 37 | A |
| 18 | B | 38-1 | A |
| 19-1 | A | 38-2 | A |
| 19-2 | A | 38-3 | A |
| 20-1 | A | 38-4 | A |
| 20-2 | A | 39 | A |
| 21 | A | 40 | A |
| 22 | A | 41 | A |
| 23 | A | 42-2 | A |
| 24 | A | 43-2 | A |
| 25-1 | B | 44 | A |
| 25-2 | B | 42-1 | A |

**[0225]** It can be found in Table 1 that each of test compound above may be coupled to AhR and regulate those functions and signal pathways controlled by AhR, further affect growth and proliferation of cancer cells and invasiveness of tumor cell. Thus pharmaceutical composition of compounds shown in formula (I) in the present invention can be used as AhR inhibitor or non-constitutive AhR agonists (non-constitutive AhR agonists) for inhibiting growth of cancer cell and inhibiting metastasis and invasion of tumor cells.

## Industrial Applicability

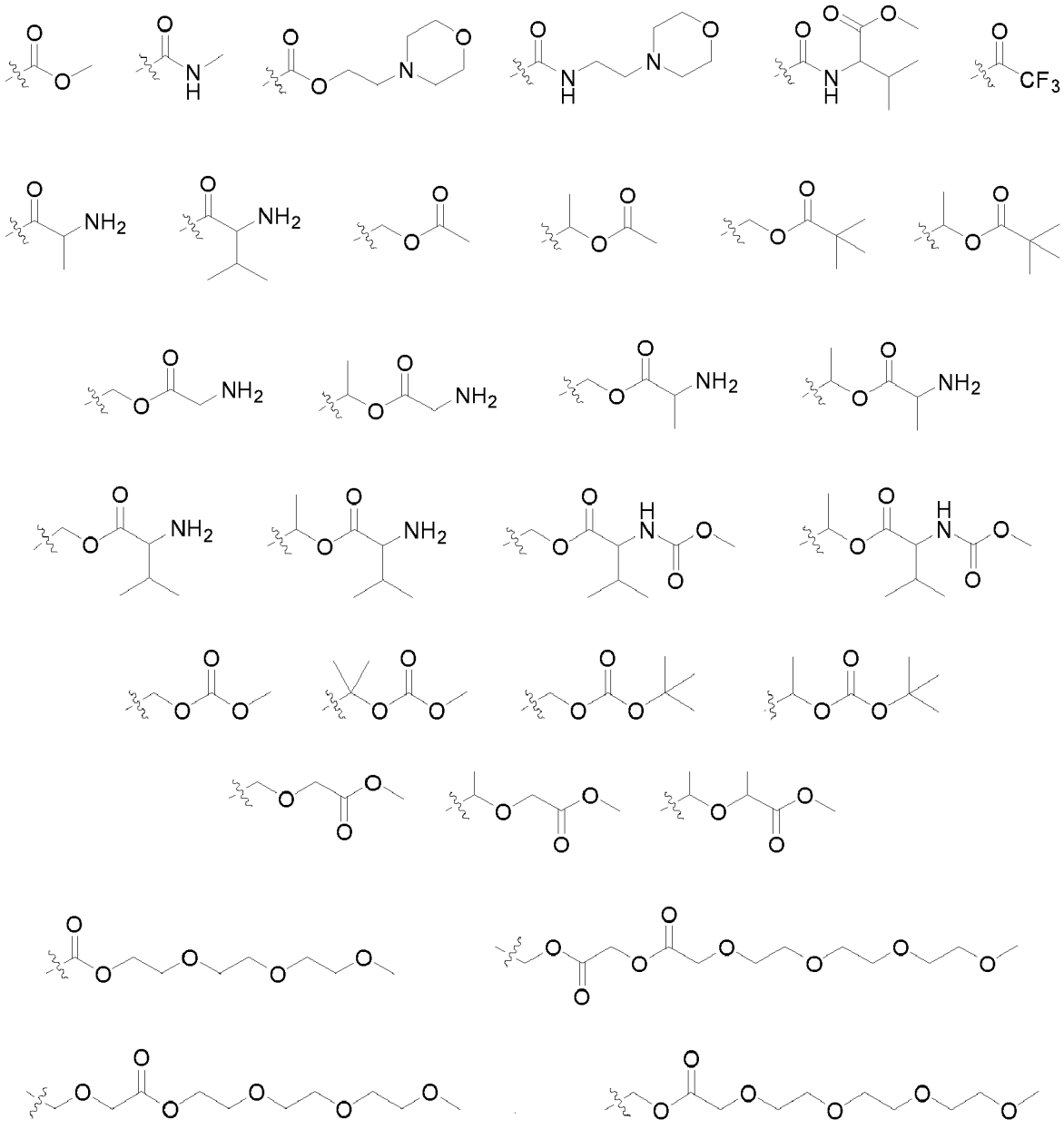
**[0226]** The invention discloses an aryl hydrocarbon receptor modulators of formula (I), and pharmaceutically acceptable

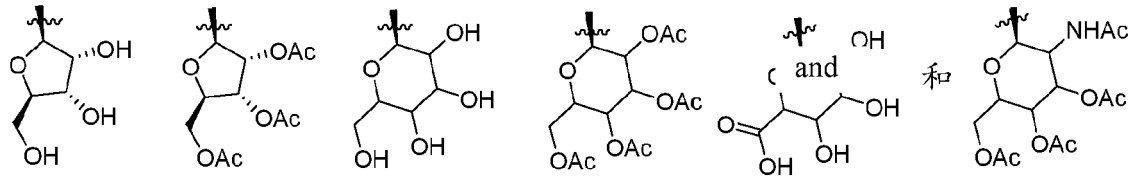
salts thereof,



(I)

R' is selected from the following substituents: H,





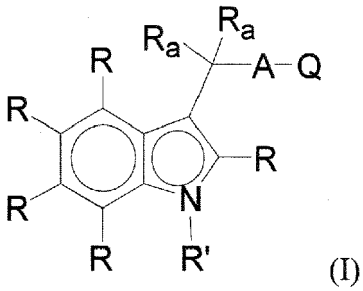
;

Two $R_a$ is independently H, or two $R_a$ together form =O, =N-CN or =N-$W_3$-$R_1$; when $W_3$ is O or NH, $R_1$ is H, $C_mH_{2m+1}$, $C_mH_{2m+1}C(O)$, $C_mH_{2m+1}OC(O)$ or $C_mH_{2m+1}S(O)_{1\sim2}$;
A is $C_2$ to $C_{10}$ heteroaromatic ring containing 1 to 5 heteroatoms selected from N, O and S, or 4 to 7 membered non-aromatic heterocyclic ring containing 1 to 3 heteroatoms selected from N, O and S and containing C=N, which are with no substituent or substituted by 1 to 3 R;
Q is R or a 3 to 10 membered, preferably 4 to 7 membered, more preferably 5 to 6 membered heterocyclic ring, preferably heteroaryl ring with no substituent or substituted by 1 to 3 R, which contains 1 to 5, preferably 1 to 3, more preferably 2 to 3 heteroatoms selected from N, O and S;
R is $R_c$ connected with C or $R_N$ connected with N.

**[0227]** Compounds of this invention of formula (I) can modulate activity of AhR for inhibiting growth of cancer cell and inhibiting migration and invasion of tumor cell.

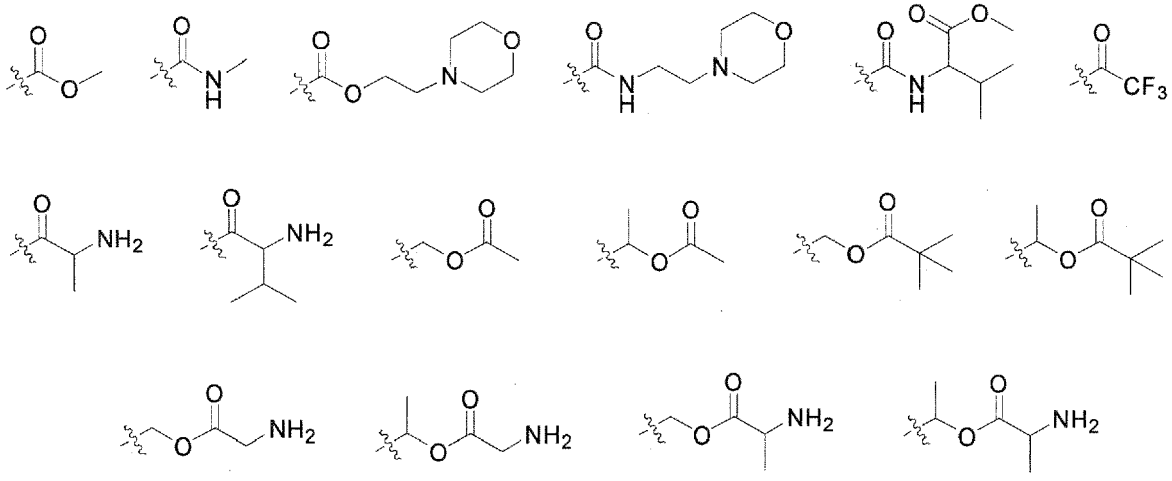
## Claims

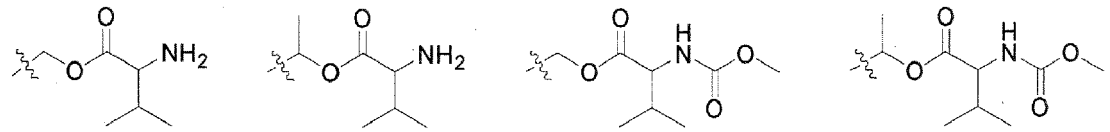
**1.** Aryl hydrocarbon receptor modulators of formula (I), and pharmaceutically acceptable salts thereof,

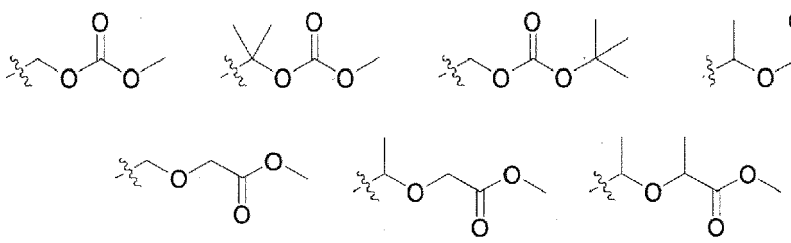


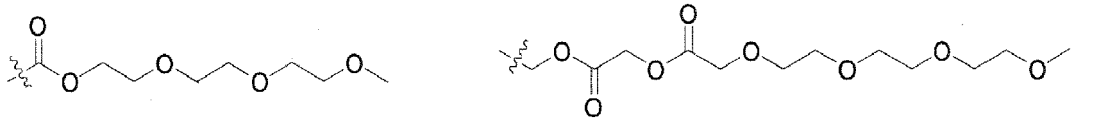
(I)

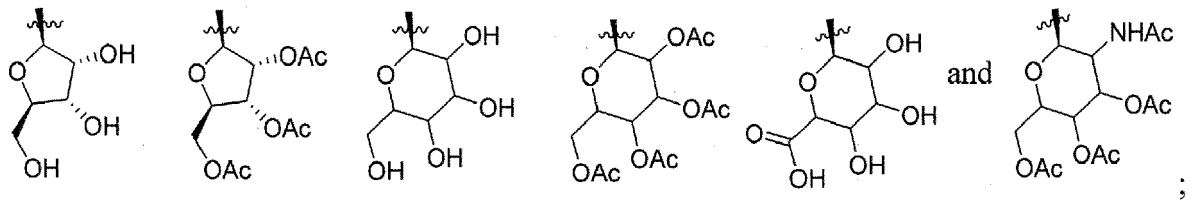
R' is selected from the following substituents: H,











two $R_a$ is independently H, or two $R_a$ together form =O, =N-CN or =N-$W_3$-$R_1$; when $W_3$ is O or NH, $R_1$ is H, $C_mH_{2m+1}$, $C_mH_{2m+1}C(O)$, $C_mH_{2m+1}OC(O)$ or $C_mH_{2m+1}S(O)_{1\sim2}$;

A is $C_2$ to $C_{10}$ heteroaromatic ring containing 1 to 5 heteroatoms selected from N, O and S, or 4 to 7 membered non-aromatic heterocyclic ring containing 1 to 3 heteroatoms selected from N, O and S and containing C=N, which are with no substituent or substituted by 1 to 3 R;

Q is R or a 3 to 10 membered, preferably 4 to 7 membered, more preferably 5 to 6 membered heterocyclic ring, preferably heteroaryl ring with no substituent or substituted by 1 to 3 R, which contains 1 to 5, preferably 1 to 3, more preferably 2 to 3 heteroatoms selected from N, O and S;

R is $R_c$ connected with C or $R_N$ connected with N, wherein each $R_c$ is independently R", -Y-NR"$_2$, -Y-NR"C(O)R", -Y-NR"C(O)NR"$_2$, -Y-OC(O)NR"$_2$, -Y-NR"C(O)OR", -Y-$S(O)_{1\sim2}$R", -Y-$S(O)_{1\sim2}$NR"$_2$ or -Y-NR"$S(O)_{1\sim2}$R"; each $R_N$ is independently CN, R", -Y-OR", -Y-C(O)R", -Y-OC(O)R", -Y-C(O)OR", -Y-OC(O)OR", -Y-NR"$_2$, -Y-C(O)NR"$_2$, -Y-NR"C(O)R", -Y-NR"C(O)NR"$_2$ -Y-OC(O)NR"$_2$, -Y-NR"C(O)OR", -Y-$S(O)_{1\sim2}$R", -Y-$S(O)_{1\sim2}$NR"$_2$ or -Y-NR"$S(O)_{1\sim2}$R";

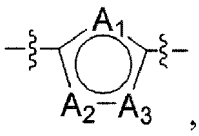
R" is H, D, $C_mH_{2m+1}$, $C_nH_{2n-1}$, $C_nH_{2n-3}$, $C_mH_{2m+1-r}X_r$, $C_nH_{2n-1-s}X_s$ or $C_nH_{2n-3-t}X_t$;

Y is bond, -$C_mH_{2m}$-, -$C_nH_{2n-2}$-, -$C_nH_{2n-4}$-, -$C_mH_{2m-i}X_i$-, -$C_nH_{2n-2-j}X_j$- or -$C_nH_{2n-4-k}X_k$;

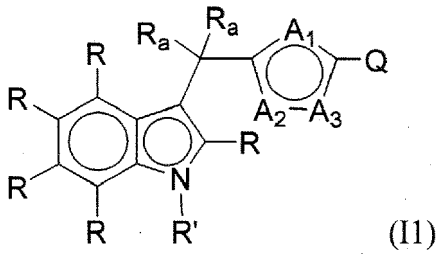
*m* is 1 to 3, *n* is 2 to 4, *u* is 1 to 3, $r\leq 2m+1$, $s\leq 2n-1$, $t\leq 2n-3$, $i\leq$2m, $j\leq 2n-2$, $k\leq 2n-4$;

X is F, Cl or Br.

**2.** Aryl hydrocarbon receptor modulator as claimed in claim 1 **characterized in that** when A is



formula (I) turns into formula (I1),

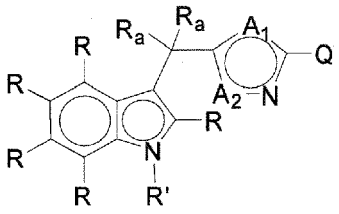


(I1)

in formula (I1), one of $A_1$, $A_2$ and $A_3$ is O, S or N(R), the rest two are each independently C(R) or N.

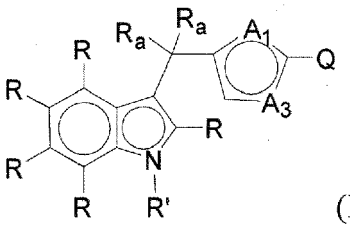
**3.** Aryl hydrocarbon receptor modulator as claimed in claim 2 **characterized in that** one of $A_1$, $A_2$ and $A_3$ is O, S or N(R), the rest two are each independently N.

**4.** Aryl hydrocarbon receptor modulator as claimed in claim 2 **characterized in that** when $A_3$ is N, formula (I1) turns into formula (Ia),



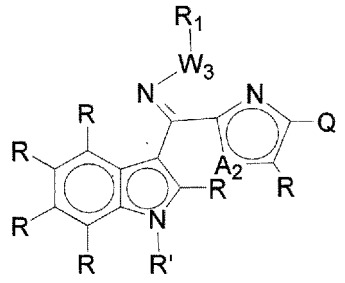
(Ia);

in formula (Ia), $A_1$ is O, S or N(R), $A_2$ is N; or $A_2$ is O, S or N(R), $A_1$ is N; or when $A_2$ is CH, formula (I1) turns into formula (Ib),



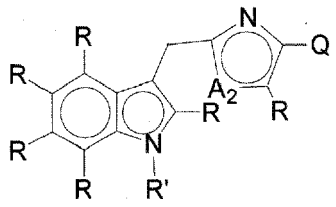
(Ib);

in formula (Ib), $A_1$ is N or C(R), $A_3$ is O, S or N(R); or $A_1$ is O, S or N(R), $A_3$ is N or C(R);
or when $A_1$ is N, $A_3$ is C(R) and two $R_a$ together form =N-$W_3$-$R_1$, formula (I1) turns into formula (Ic),



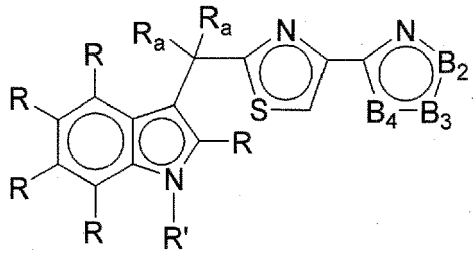
(Ic);

in formula (Ic), $A_2$ is O, S or N(R);
or when $A_1$ is N, $A_3$ is C(R) and two $R_a$ is H respectively, formula (I1) turns into formula (Id),



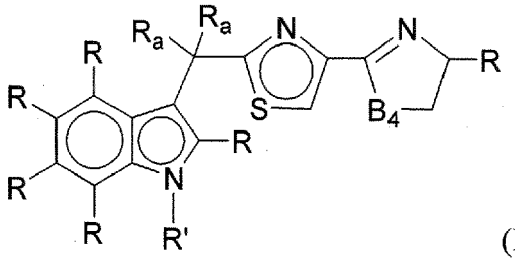
(Id)

in formula (Id), $A_2$ is O, S or N(R);
or when $A_1$ is N, $A_2$ is S, $A_3$ is CH and Q is a 5 membered heteroaromatic ring, formula (I1) turns into formula (Ig),



formula (Ig)

wherein one of $B_2$, $B_3$ and $B_4$ is O, S or N(R), the rest ones are each independently C(R) or N.
or when $A_1$ is N, $A_2$ is S, $A_3$ is CH and Q is a 5 membered non-aromatic heterocycle containing C=N, formula (I1) turns into formula (Ih),

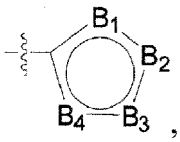


(Ih)

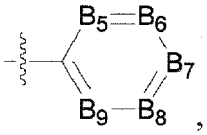
$B_4$ is O, S or N(R).

**5.** Aryl hydrocarbon receptor modulator as claimed in claim 1 **characterized in that**

Q is

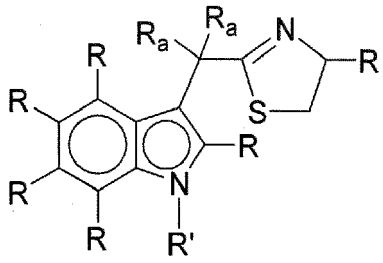


one of $B_1$, $B_2$, $B_3$ and $B_4$ is O, S or N(R), the rest three are each independently C(R) or N;
or, Q is



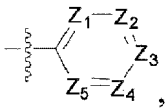
$B_5$ to $B_9$ is C(R); or one or two of $B_5$ to $B_9$ is N, the rest ones are each independently C(R).

**6.** Aryl hydrocarbon receptor modulator as claimed in claim 1 **characterized in that** when A is a non-aromatic heterocyclic ring with N and S heteroatom and Q is R, formula (I) turns into formula (I2),

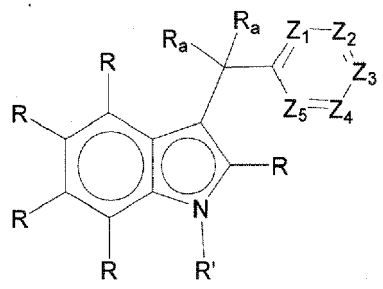


(I2).

**7.** Aryl hydrocarbon receptor modulator as claimed in claim 1 **characterized in that** when A is



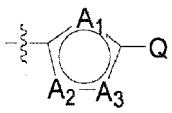
formula (I) turns into formula (I3),



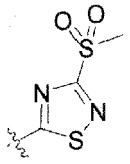
(I3)

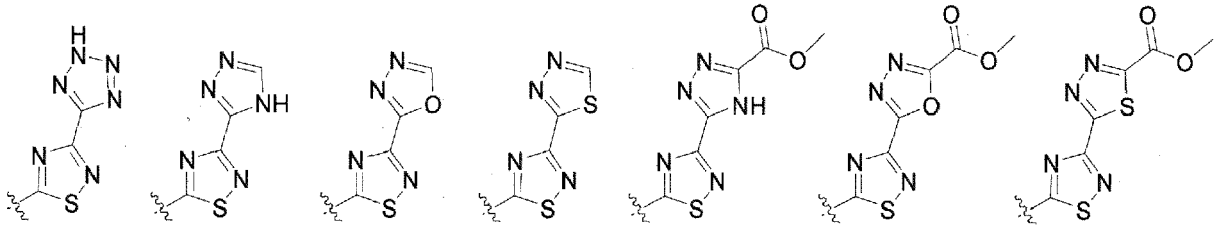
in formula (I3), one or two of $Z_1$ to $Z_5$ is N, the rest ones are each independently C(Q); or, the two ones of $Z_1$ to $Z_5$ adjacent to each other are C(Q) and forms together a 5 to 6 membered carbocyclic ring or a 5 to 6 membered heterocyclic ring containing 1 to 3 heteroatom selected from N, O and S, the rest three ones each are independently C(Q) , or two of the rest three ones are each independently C(Q), the last ones is N; or one of the rest three ones is C(Q), the rest two are independently N.

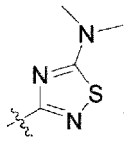
**8.** Aryl hydrocarbon receptor modulator as claimed in claim 3 **characterized in that** in formula (I1),

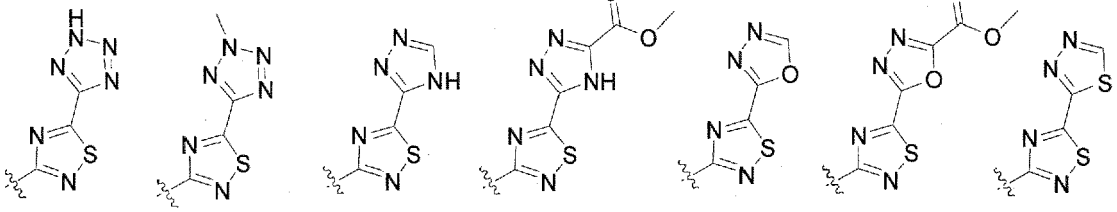


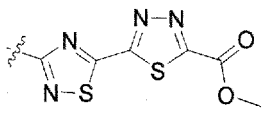
is selected from the following substituents:

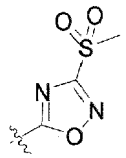


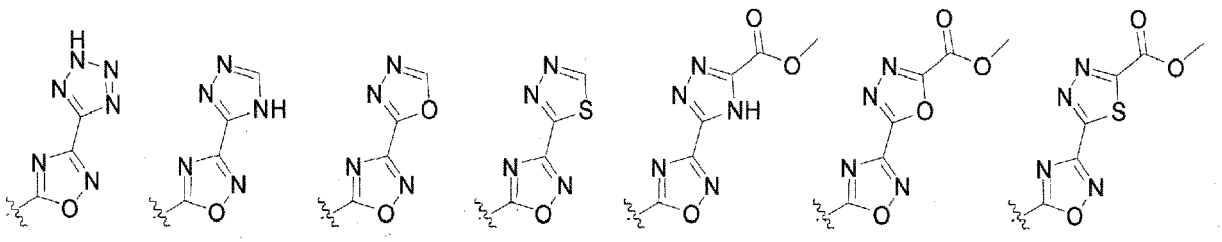


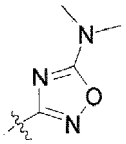


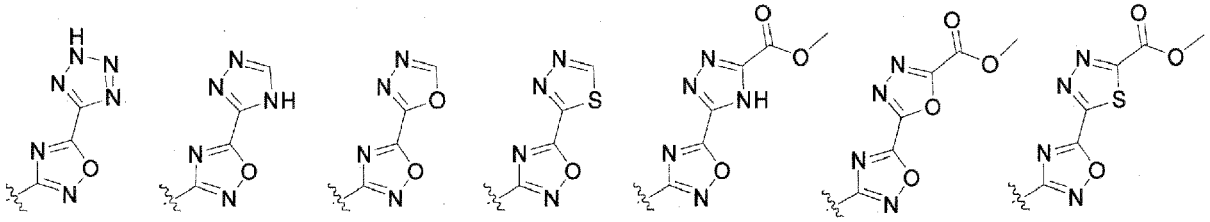


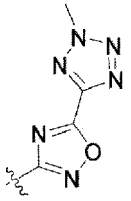




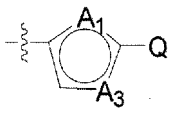




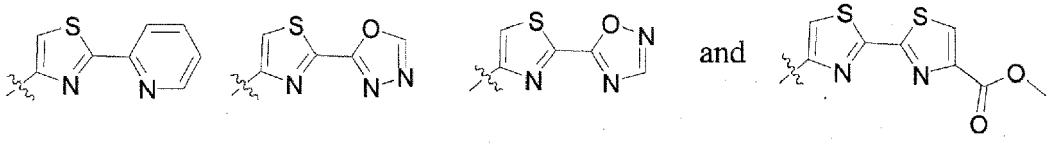




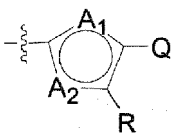
**9.** Aryl hydrocarbon receptor modulator as claimed in claim 4 **characterized in that** in formula (Ib),



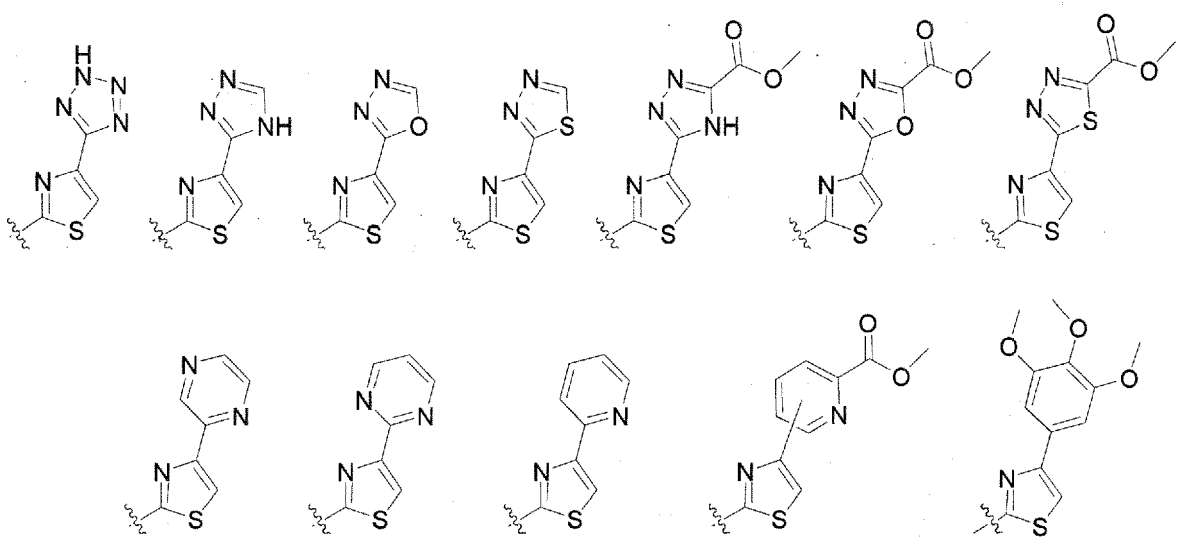
is selected from the following substituents:



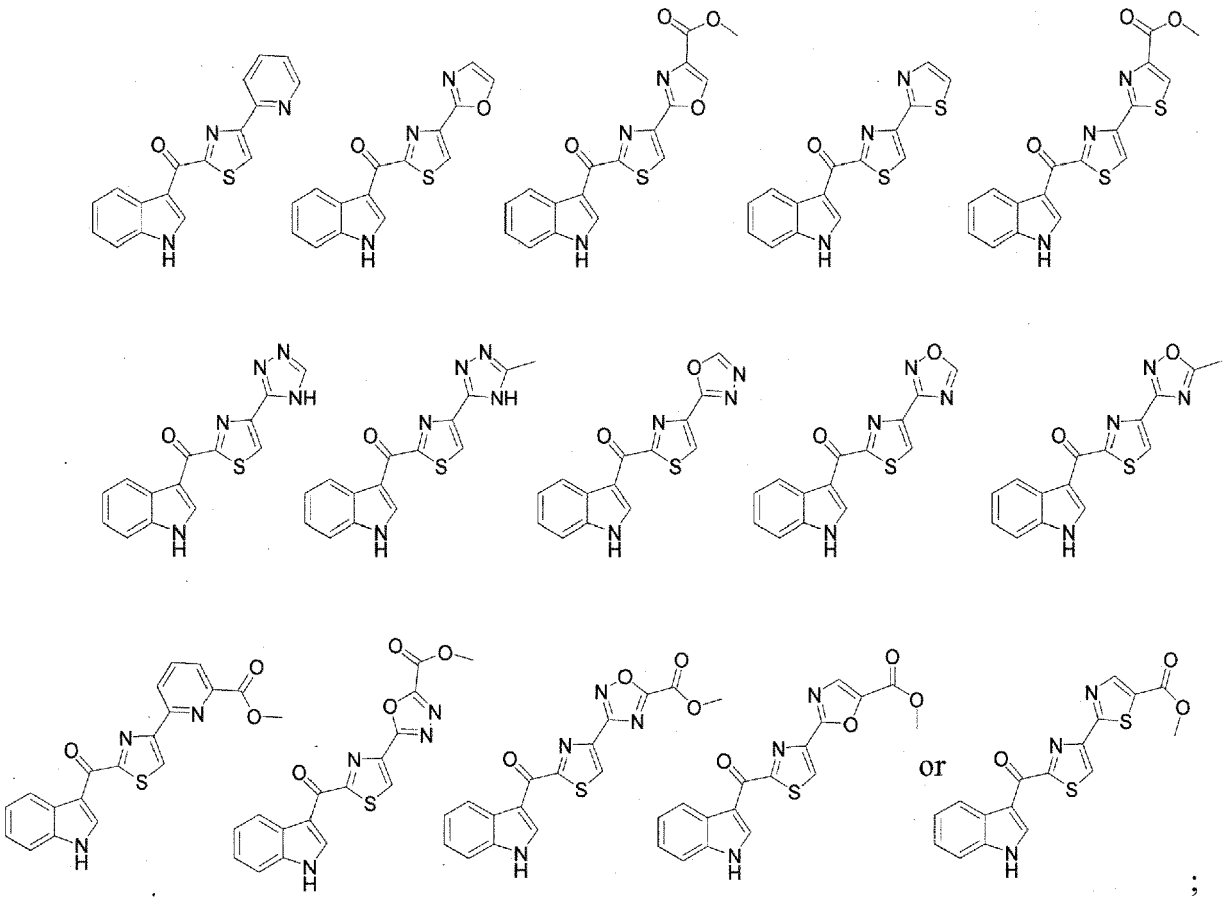
**10.** Aryl hydrocarbon receptor modulator as claimed in claim 4 **characterized in that** in formula (Ic) and formula (Id),



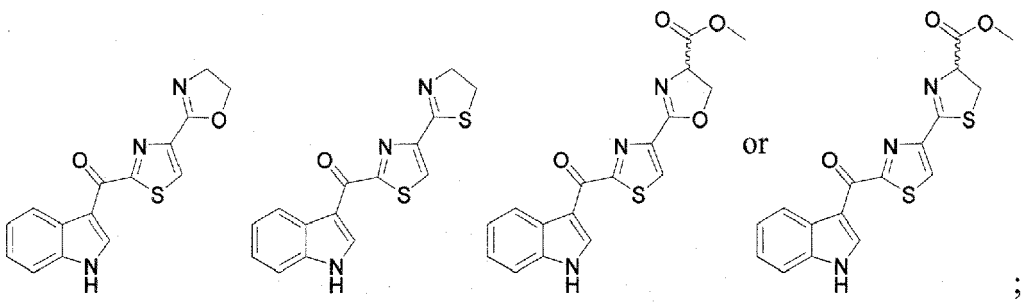
is selected from the following substituents:



**11.** Aryl hydrocarbon receptor modulator as claimed in claim 1 **characterized in that** the aryl hydrocarbon receptor modulator is selected from

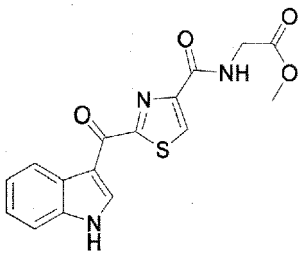


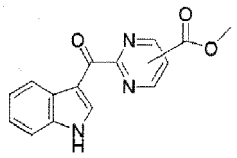
or

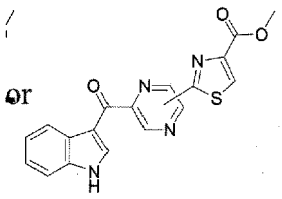



;

or





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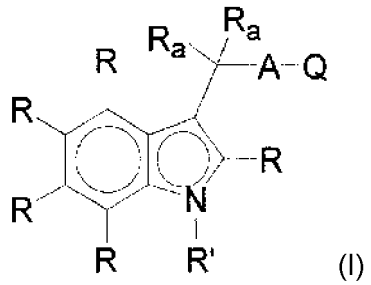
**12.** Use of aryl hydrocarbon receptor modulators claimed in any one of claim 1 to 11 for preparation of antitumor drugs.

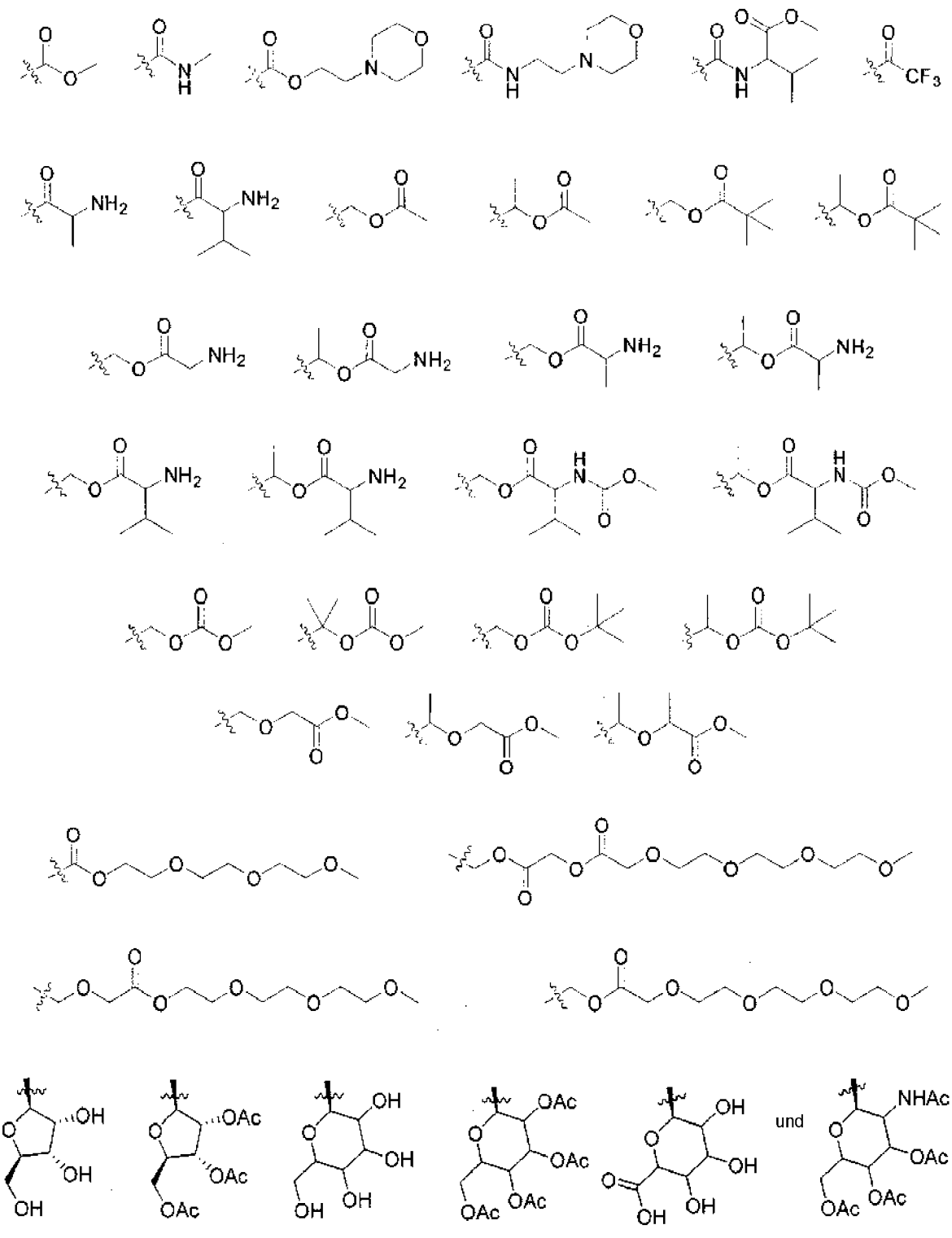
**Patentansprüche**

**1.** Aryl-Hydrocarbon-Rezeptor-Modulator der Formel (I) und pharmazeutisch verträgliche Salze davon,



(I)

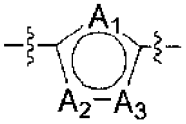
wobei R' aus den folgenden Substituenten ausgewählt ist: H,



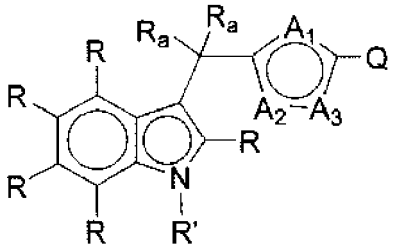
zwei $R_a$ unabhängig H sind oder zwei $R_a$ zusammen =O, =N-CN or =N-$W_3$-$R_1$ bilden; wenn $W_3$O oder NH ist, $R_1$ H, $C_mH_{2m+1}$, $C_mH_{2m+1}C(O)$, $C_mH_{2m+1}OC(O)$ oder $C_mH_{2m+1}S(O)_{1\sim2}$ ist;
A ein heteroaromatischer $C_2$- bis $C_{10}$-Ring, der 1 bis 5 Heteroatome enthält, die aus N, O und S ausgewählt sind, oder ein 4- bis 7-gliedriger nichtaromatischer heterocyclischer Ring ist, der 1 bis 3 Heteroatome enthält, die aus N, O und S ausgewählt sind, und der C=N enthält, die ohne Substituenten oder mit 1 bis 3 R substituiert sind;
Q R oder ein 3- bis 10-gliedriger, bevorzugt 4- bis 7-gliedriger, weiter bevorzugt 5-bis 6-gliedriger heterocyclischer Ring ist, bevorzugt ein Heteroarylring, der ohne Substituenten oder mit 1 bis 3 R substituiert ist, der 1 bis 5,

bevorzugt 1 bis 3, weiter bevorzugt 2 bis 3 Heteroatome enthält, die aus N, O und S ausgewählt sind;
R $R_c$, das mit C verbunden ist, oder $R_N$ ist, das mit N verbunden ist, wobei jedes $R_c$ unabhängig R", -Y-NR"$_2$, -Y-NR"C(O)R", -Y-NR"C(O)NR"$_2$, -Y-OC(O)NR"$_2$, -Y-NR"C(O)OR", -Y-S(O)$_{1\sim2}$R", -Y-S(O)$_{1\sim2}$NR"$_2$ or -Y-NR"S(O)$_{1\sim2}$R" ist; jedes $R_N$ unabhängig CN, R", -Y-OR", -Y-C(O)R", -Y-OC(O)R", -Y-C(O)OR", -Y-OC(O)OR", -Y-NR"$_2$, -Y-C(O)NR"$_2$, -Y-NR"C(O)R", -Y-NR"C(O)NR"$_2$ -Y-OC(O)NR"$_2$, -Y-NR"C(O)OR", -Y-S(O)$_{1\sim2}$R", -Y-S(O)$_{1\sim2}$NR"$_2$ or -Y-NR"S(O)$_{1\sim2}$R" ist;
R" H, D, $C_mH_{2m+1}$, $C_nH_{2n-1}$, $C_nH_{2n-3}$, $C_mH_{2m+1-r}X_r$, $C_nH_{2n-1-s}X_s$ or $C_nH_{2n-3-t}X_t$ ist;
Y eine Bindung, -$C_mH_{2m}$-, -$C_nH_{2n-2}$-, -$C_nH_{2n-4}$-, -$C_mH_{2m-i}X_i$)-, -$C_nH_{2n-2-j}X_j$- or -$C_nH_{2n-4-k}X_k$- ist;
*m* 1 bis 3 ist, *n* 2 bis 4 ist, *u* 1 bis 3 ist, $r\leq 2m+1$, $s\leq 2n-1$, $t\leq 2n-3$, $i\leq 2m$, $j\leq 2n-2$, $k\leq 2n-4$;
X F, Cl oder Br ist.

**2.** Aryl-Hydrocarbon-Rezeptor-Modulator nach Anspruch 1, **dadurch gekennzeichnet, dass** wenn A



ist, Formel (I) zu Formel (I1) wird,

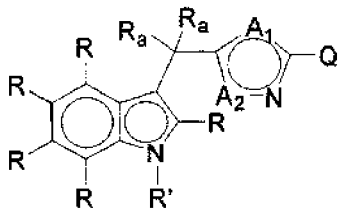


(I1)

in Formel (I1) eins von $A_1$, $A_2$ oder $A_3$ O, S oder N(R) ist, die restlichen zwei jeweils unabhängig voneinander C(R) oder N sind.

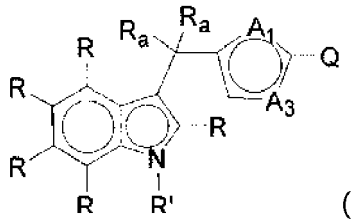
**3.** Aryl-Hydrocarbon-Rezeptor-Modulator nach Anspruch 2, **dadurch gekennzeichnet, dass** eins von $A_1$, $A_2$ oder $A_3$ O, S oder N(R) ist, die restlichen zwei jeweils unabhängig voneinander N sind.

**4.** Aryl-Hydrocarbon-Rezeptor-Modulator nach Anspruch 2, **dadurch gekennzeichnet, dass**, wenn $A_3$ N ist, Formel (I1) zu Formel (Ia) wird,



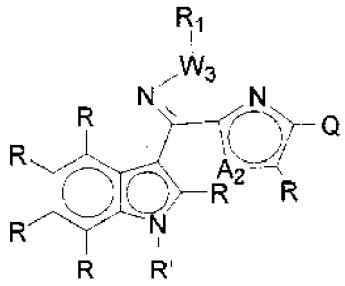
(Ia);

in Formel (Ia) $A_1$ O, S oder N(R) ist, $A_2$ N ist; oder $A_2$ O, S oder N(R) ist, $A_1$ N ist;
oder wenn $A_2$ CH ist, Formel (I1) zu Formel (Ib) wird,



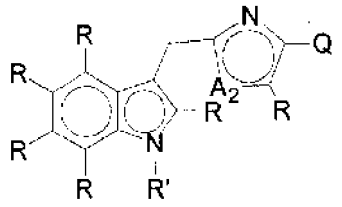
(Ib);

in Formel (Ib) $A_1$ N oder C(R) ist, $A_3$ O, S oder N(R) ist; oder $A_1$ O, S oder N(R) ist, $A_3$ N oder C(R) ist; oder wenn $A_1$ N ist, $A_3$ C(R) ist und zwei $R_a$ zusammen =N-$W_3$-$R_1$ bilden Formel (I1) zu Formel (Ic) wird,



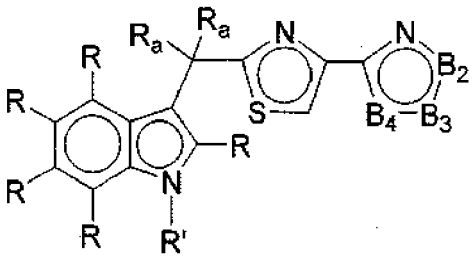
(Ic);

in Formel (Ic) $A_2$ O, S oder N(R) ist;
oder wenn $A_1$ N ist, $A_3$ C(R) ist und zwei $R_a$ H sind Formel (I1) zu Formel (Id) wird,



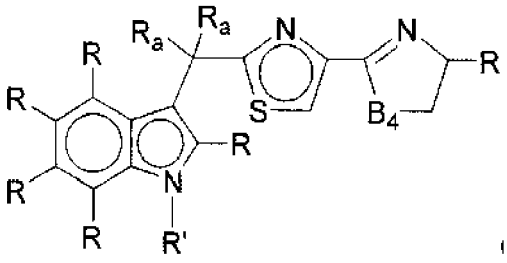
(Id)

in Formel (Id) $A_2$ O, S oder N(R) ist;
oder wenn $A_1$ N ist, $A_2$ S ist, $A_3$ CH ist und Q ein 5-gliedriger heteroaromatischer Ring ist, Formel (I1) zu Formel (Ig) wird,



Formel (Ig)

wobei eins von $B_2$, $B_3$ und $B_4$ O, S oder N(R) ist, die restlichen jeweils unabhängig voneinander C(R) oder N sind.
oder wenn $A_1$ N ist, $A_2$ S ist, $A_3$ CH ist und Q ein 5-gliedriger nichtaromatischer Heterocyclus ist, der C=N enthält, Formel (I1) zu Formel (Ih) wird,

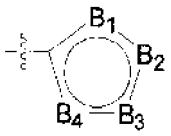


(Ih)

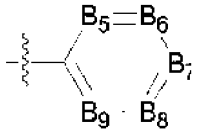
$B_4$ O, S oder N(R) ist.

**5.** Aryl-Hydrocarbon-Rezeptor-Modulator nach Anspruch 1, **dadurch gekennzeichnet, dass**

Q

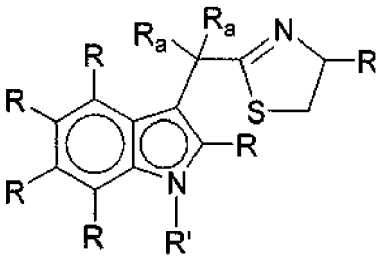


ist, eins von $B_1$, $B_2$, $B_3$ und $B_4$ O, S oder N(R) ist, die restlichen drei jeweils unabhängig voneinander C(R) oder N sind;
oder Q



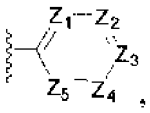
ist, $B_5$ bis $B_9$ C(R) sind; oder eines oder zwei von $B_5$ bis $B_9$ N sind, die restlichen jeweils unabhängig voneinander C(R) sind.

**6.** Aryl-Hydrocarbon-Rezeptor-Modulator nach Anspruch 1, **dadurch gekennzeichnet, dass**, wenn A ein nichtaromatischer heterocyclischer Ring mit N- und S-Heteroatom ist und Q R ist, Formel (I) zu Formel (I2) wird,

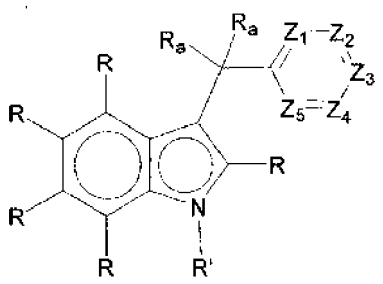


(I2).

**7.** Aryl-Hydrocarbon-Rezeptor-Modulator nach Anspruch 1, **dadurch gekennzeichnet, dass** wenn A



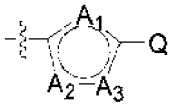
ist, Formel (I) zu Formel (I3) wird,



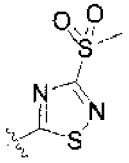
(I3)

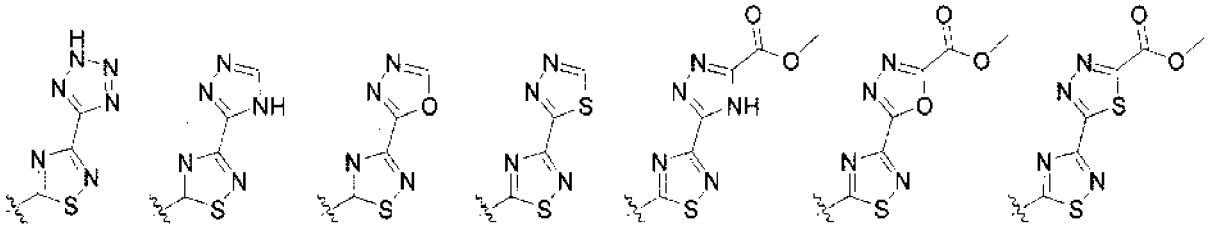
wobei in Formel (I3) ein oder zwei von $Z_1$ bis $Z_5$ N sind, die restlichen jeweils unabhängig voneinander C(Q) sind; oder die zwei von $Z_1$ bis $Z_5$, die aneinander angrenzen, C(Q) sind und zusammen einen 5- bis 6-gliedrigen carbocyclischen Ring oder einen 5- bis 6-gliedrigen heterocyclischen Ring bilden, der 1 bis 3 Heteroatome enthält, die aus N, O und S ausgewählt sind, die restlichen drei jeweils unabhängig voneinander C(Q) sind, oder zwei der restlichen drei jeweils unabhängig voneinander C(Q) sind, die letzten N sind; oder eine der restlichen drei C(Q) ist, die restlichen zwei unabhängig N voneinander sind.

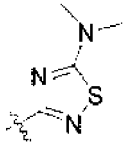
**8.** Aryl-Hydrocarbon-Rezeptor-Modulator nach Anspruch 3, **dadurch gekennzeichnet, dass** in Formel (I1)

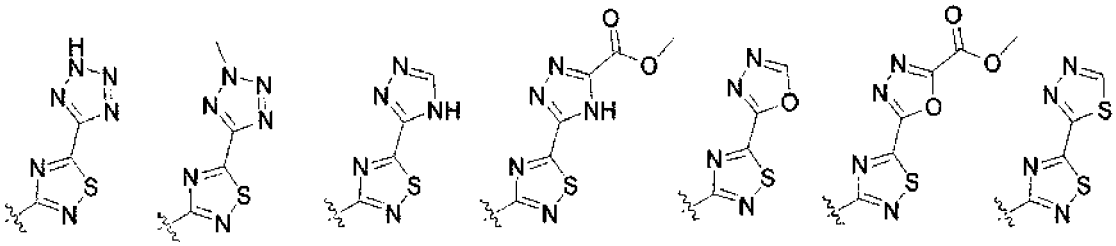


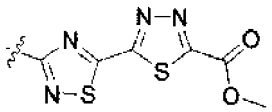
aus den folgenden Substituenten ausgewählt ist:

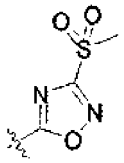


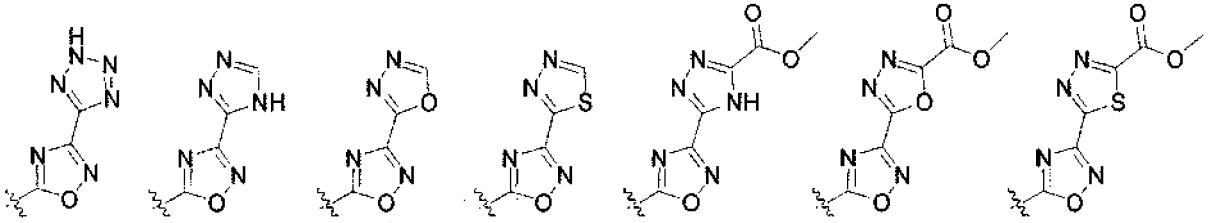


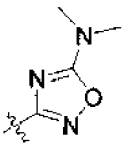


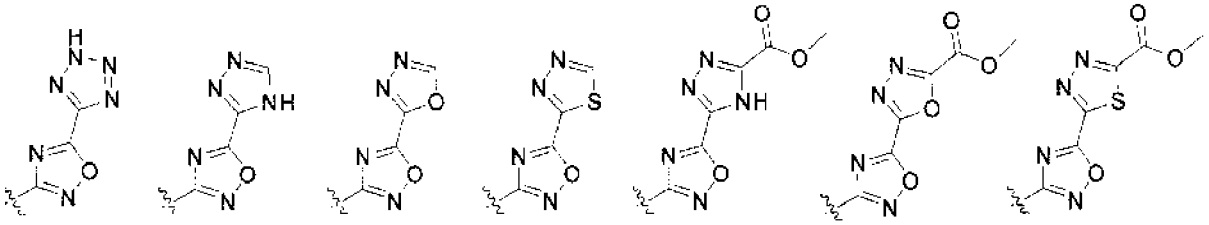


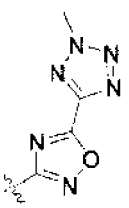




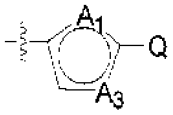




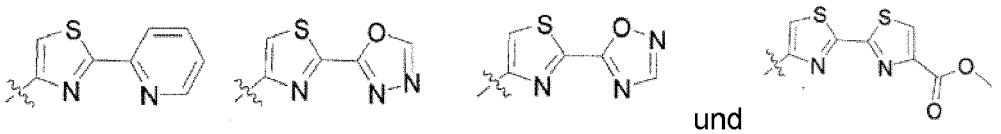




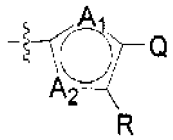
**9.** Aryl-Hydrocarbon-Rezeptor-Modulator nach Anspruch 4, **dadurch gekennzeichnet, dass** in Formel (Ib)



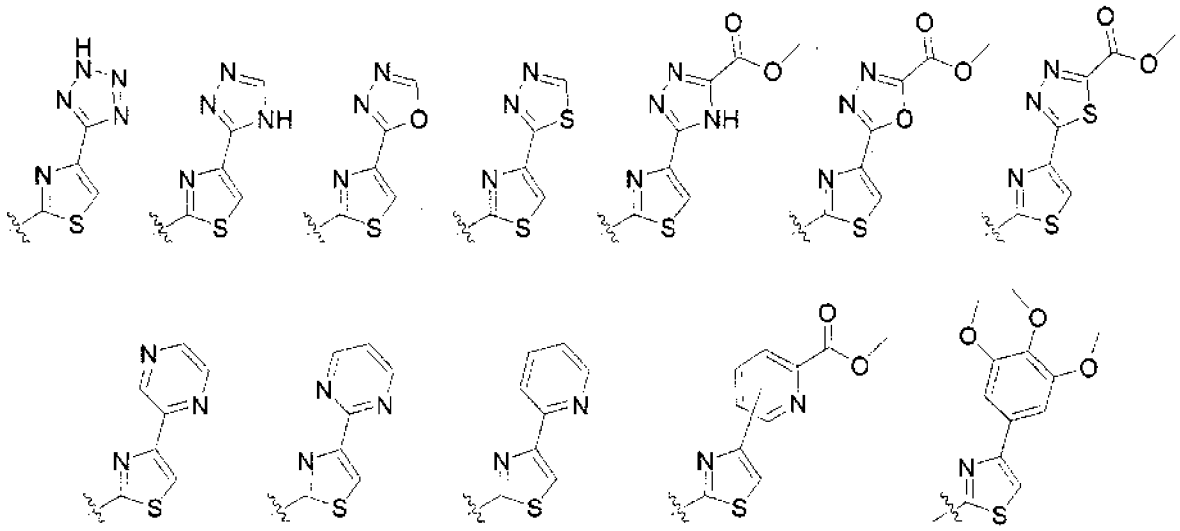
aus den folgenden Substituenten ausgewählt ist:



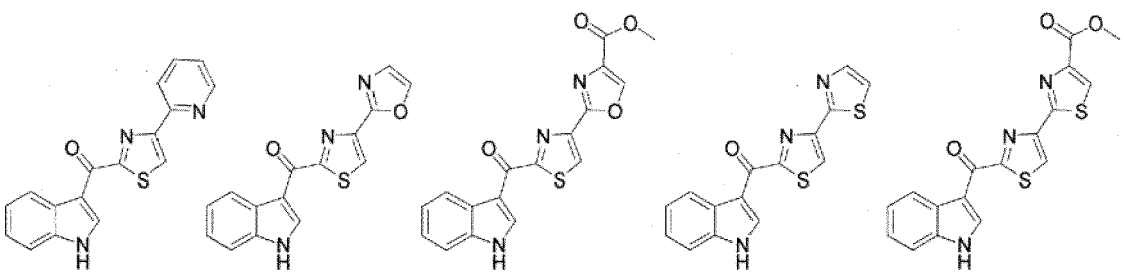
**10.** Aryl-Hydrocarbon-Rezeptor-Modulator nach Anspruch 4, **dadurch gekennzeichnet, dass** in Formel (Ic) und Formel (Id)

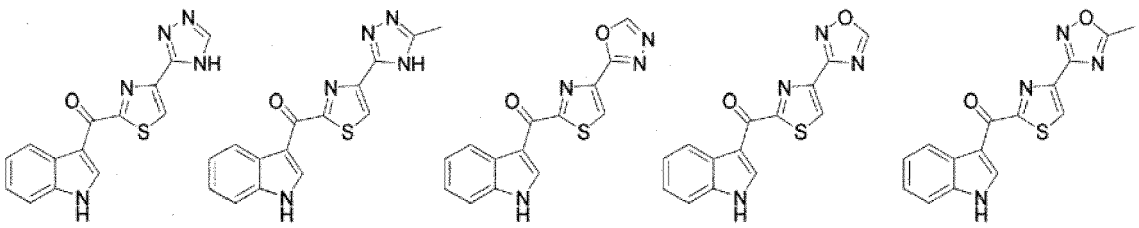


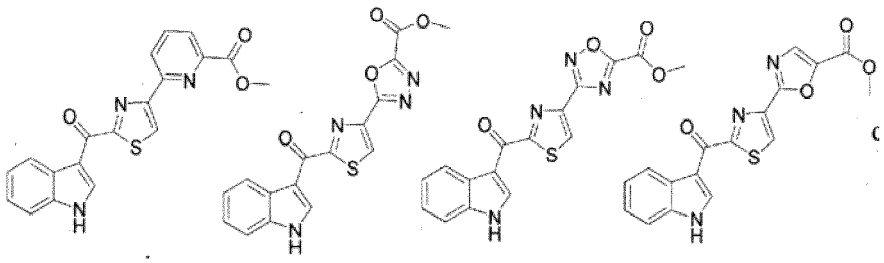
aus den folgenden Substituenten ausgewählt ist:



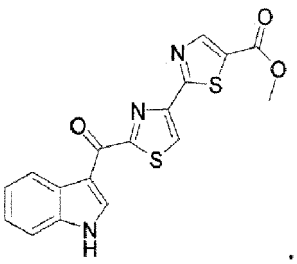
**11.** Aryl-Hydrocarbon-Rezeptor-Modulator nach Anspruch 1, **dadurch gekennzeichnet, dass** der Arylkohlenwasserstoffrezeptormodulator ausgewählt ist aus





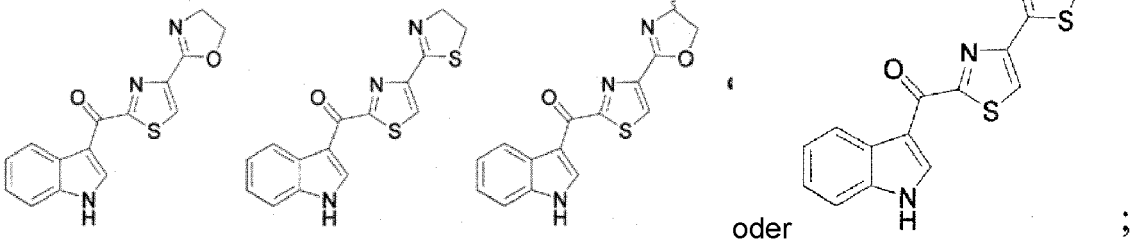


oder

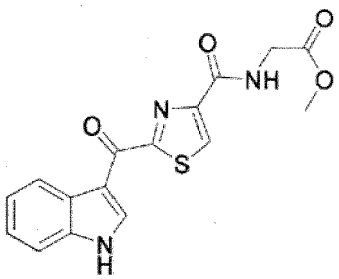


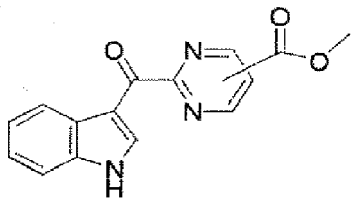
;

oder

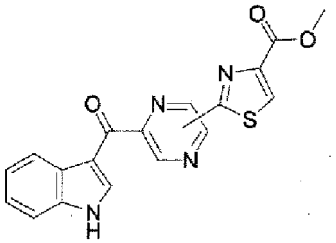


oder





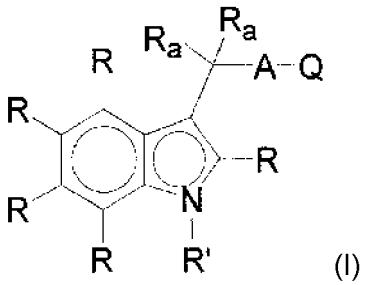
oder



**12.** Verwendung von Aryl-Hydrocarbon-Rezeptor-Modulatoren nach einem der Ansprüche 1 bis 11 für eine Herstellung von Antitumor-Arzneimitteln.

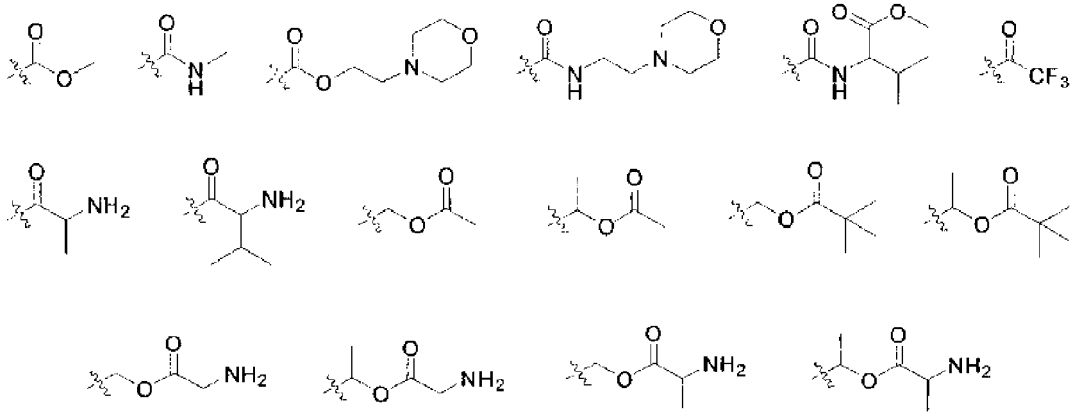
## Revendications

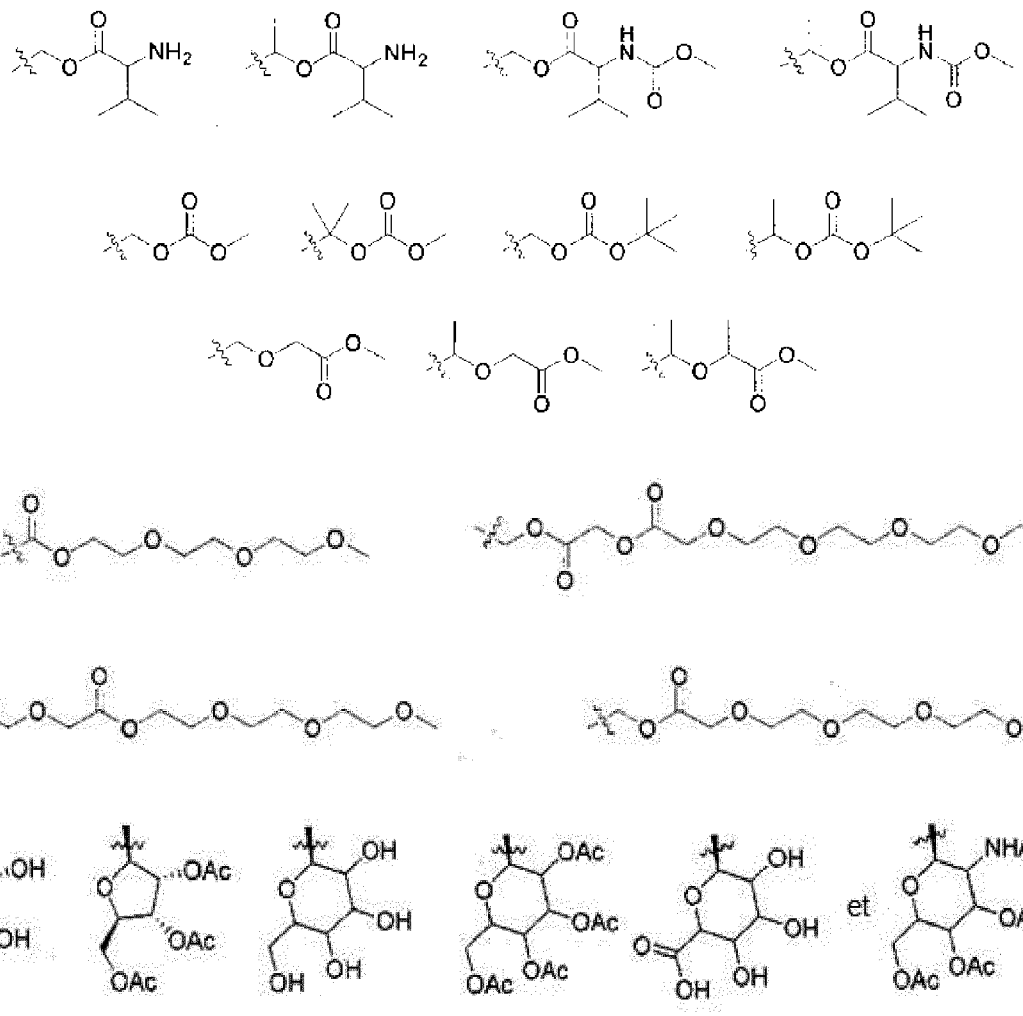
**1.** Modulateurs du récepteur d'aryl hydrocarbone de formule (I), et leurs sels pharmaceutiquement acceptables,



(I)

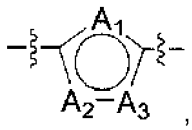
R' est choisi parmi les substituants suivants : H,





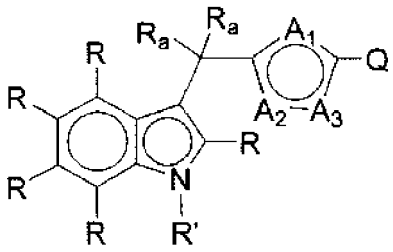
deux $R_a$ sont indépendamment H, ou deux $R_a$ ensemble forment =O, =N-CN ou =N-$W_3$-$R_1$ ; lorsque $W_3$ est O ou NH, $R_1$ est H, $C_mH_{2m+1}$, $C_mH_{2m+1}C(O)$, $C_mH_{2m+1}OC(O)$ ou $C_mH_{2m+1}S(O)_{1\sim2}$ ;
A est un cycle hétéroaromatique en $C_2$ à $C_{10}$ contenant 1 à 5 hétéroatomes choisis parmi N, O et S, ou un cycle hétérocyclique non aromatique à 4 à 7 chaînons contenant 1 à 3 hétéroatomes choisis parmi N, O et S et contenant C=N, qui sont sans substituant ou substitués par 1 à 3 R ;
Q est R ou un cycle hétérocyclique à 3 à 10 chaînons, de préférence à 4 à 7 chaînons, plus préférablement à 5 à 6 chaînons, de préférence un cycle hétéroaryle sans substituant ou substitué par 1 à 3 R, qui contient 1 à 5, de préférence 1 à 3, plus préférablement 2 à 3 hétéroatomes choisis parmi N, O et S ;
R est $R_c$ relié à C ou $R_N$ relié à N, chaque $R_c$ étant indépendamment R", -Y-$NR"_2$,-Y-NR"C(O)R", -Y-NR"C(O)$NR"_2$, -Y-OC(O)$NR"_2$, -Y-NR"C(O)OR", -Y-$S(O)_{1\sim2}$R", -Y-$S(O)_{1\sim2}NR"_2$ ou -Y-NR"$S(O)_{1\sim2}$R" ; chaque $R_N$ étant indépendamment CN, R", -Y-OR", -Y-C(O)R", -Y-OC(O)R", -Y-C(O)OR", -Y-OC(O)OR", -Y-$NR"_2$, -Y-C(O)$NR"_2$, -Y-NR"C(O)R",-Y-NR"C(O)$NR"_2$, -Y-OC(O)$NR"_2$, -Y-NR"C(O)OR", -Y-$S(O)_{1\sim2}$R", -Y-$S(O)_{1\sim2}NR"_2$ ou -Y-NR"$S(O)_{1\sim2}$R" ;
R" est H, D, $C_mH_{2m+1}$, $C_nH_{2n-1}$, $C_nH_{2n-3}$, $C_mH_{2m+1-r}X_r$, $C_nH_{2n-1-s}X_s$ ou $C_nH_{2n-3-t}X_t$ ;
Y est une liaison, -$C_mH_{2m}$-, -$C_nH_{2n-2}$-, -$C_nH_{2n-4}$-, -$C_mH_{2m-i}X_i$-, -$C_nH_{2n-2-j}X_j$- ou -$C_nH_{2n-4-k}X_k$- ;
m vaut de 1 à 3, *n* vaut de 2 à 4, *u* vaut de 1 à 3, $r \leq 2m+1$, $s \leq 2n-1$, $t \leq 2n-3$, $i \leq 2m$, $j \leq 2n-2$, $k \leq 2n-4$ ;
X est F, Cl ou Br.

**2.** Modulateur du récepteur d'aryl hydrocarbone selon la revendication 1, **caractérisé en ce que**, lorsque A est



,

la formule (I) se transforme en formule (I1),

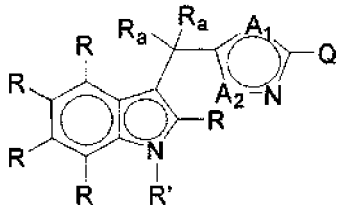


(I1)

dans la formule (I1), l'un de $A_1$, $A_2$ et $A_3$ est O, S ou N(R), les deux autres sont chacun indépendamment C(R) ou N.

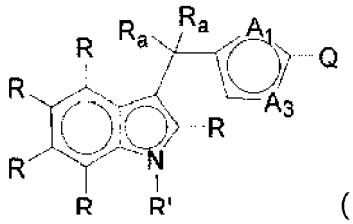
**3.** Modulateur du récepteur d'aryl hydrocarbone selon la revendication 2, **caractérisé en ce que** l'un de $A_1$, $A_2$ et $A_3$ est O, S ou N(R), les deux autres sont chacun indépendamment N.

**4.** Modulateur du récepteur d'aryl hydrocarbone selon la revendication 2, **caractérisé en ce que**, lorsque $A_3$ est N, la formule (I1) se transforme en formule (Ia),



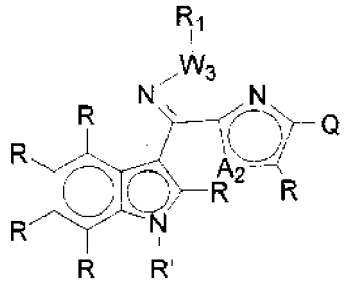
(Ia) ;

dans la formule (Ia), $A_1$ est O, S ou N(R), $A_2$ est N ; ou $A_2$ est O, S ou N(R), $A_1$ est N ;
ou lorsque $A_2$ est CH, la formule (I1) se transforme en formule (Ib),



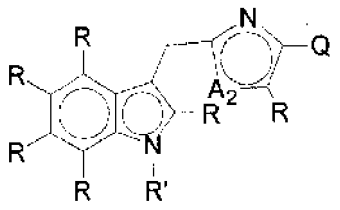
(Ib) ;

dans la formule (Ib), $A_1$ est N ou C(R), $A_3$ est O, S ou N(R) ; ou $A_1$ est O, S ou N(R), $A_3$ est N ou C(R) ;
ou lorsque $A_1$ est N, $A_3$ est C(R) et deux $R_a$ ensemble forment =N-$W_3$-$R_1$, la formule (I1) se transforme en formule (Ic),



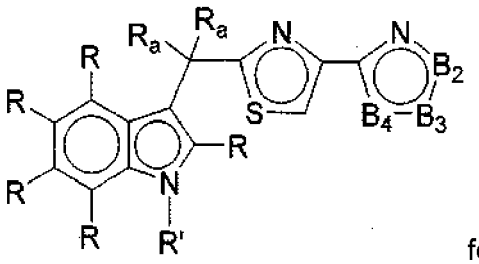
(Ic) ;

dans la formule (Ic), $A_2$ est O, S ou N(R) ;
ou lorsque $A_1$ est N, $A_3$ est C(R) et deux $R_a$ sont H respectivement, la formule (I1) se transforme en formule (Id),



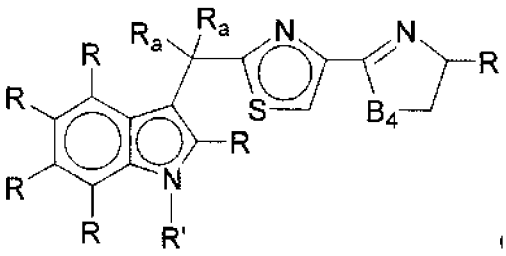
(Id)

dans la formule (Id), $A_2$ est O, S ou N(R) ;
ou lorsque $A_1$ est N, $A_2$ est S, $A_3$ est CH et Q est un cycle hétéroaromatique à 5 chaînons, la formule (I1) se transforme en formule (Ig),



formule (Ig)

dans laquelle l'un de $B_2$, $B_3$ et $B_4$ est O, S ou N(R), les autres sont chacun indépendamment C(R) ou N.
ou lorsque $A_1$ est N, $A_2$ est S, $A_3$ est CH et Q est un hétérocycle non aromatique à 5 chaînons contenant C=N, la formule (I1) se transforme en formule (Ih),

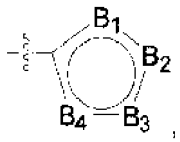


(Ih)

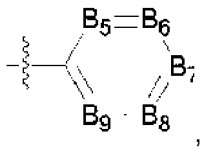
$B_4$ est O, S ou N(R).

**5.** Modulateur du récepteur d'aryl hydrocarbone selon la revendication 1, **caractérisé en ce que**

Q est

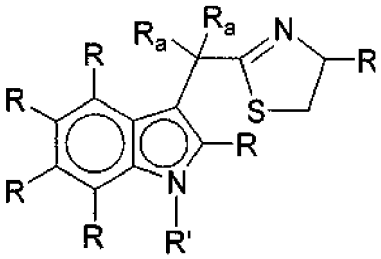


l'un de $B_1$, $B_2$, $B_3$ et $B_4$ est O, S ou N(R), les trois autres sont chacun indépendamment C(R) ou N ; ou, Q est



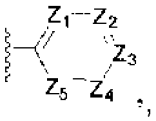
$B_5$ à $B_9$ est C(R) ; ou un ou deux de $B_5$ à $B_9$ est N, les autres sont chacun indépendamment C(R).

**6.** Modulateur du récepteur d'aryl hydrocarbone selon la revendication 1, **caractérisé en ce que**, lorsque A est un cycle hétérocyclique non aromatique avec un hétéroatome N et S et Q est R, la formule (I) se transforme en formule (I2),

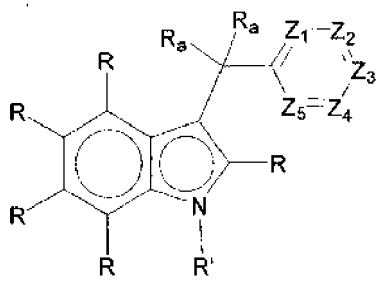


(I2).

**7.** Modulateur du récepteur d'aryl hydrocarbone selon la revendication 1, **caractérisé en ce que**, lorsque A est



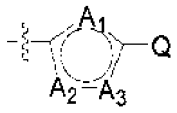
la formule (I) se transforme en formule (I3),



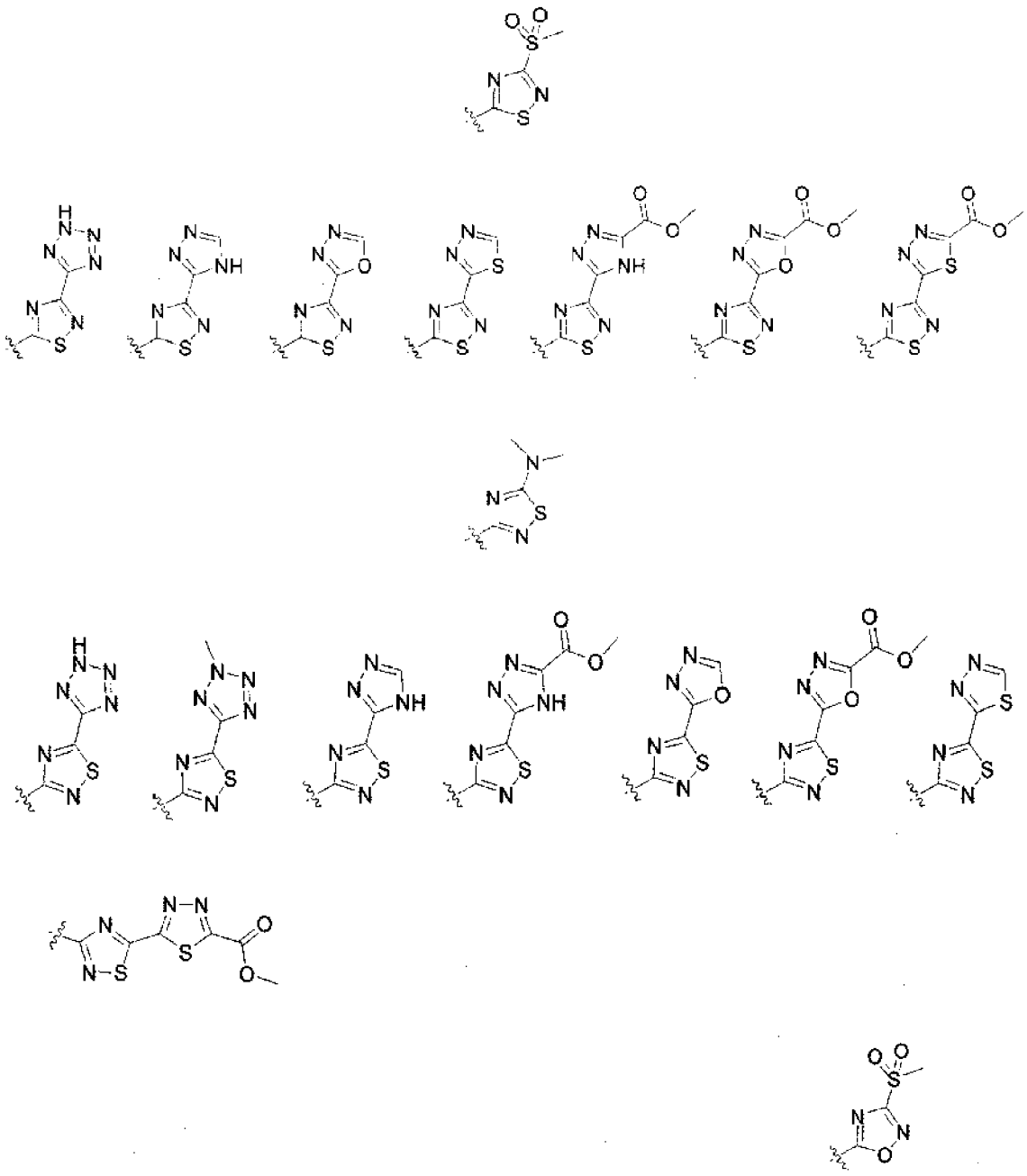
(I3)

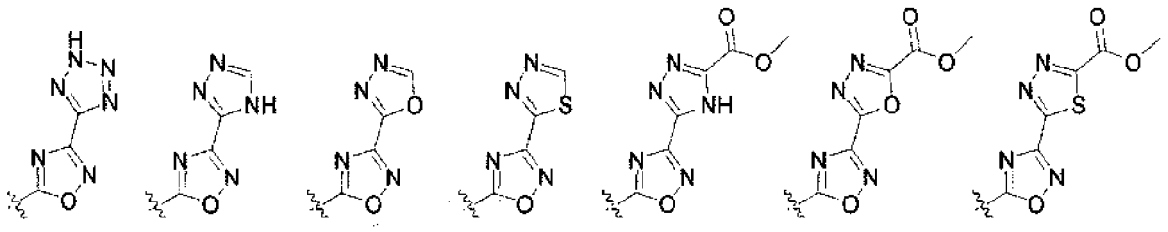
dans la formule (I3), un ou deux de $Z_1$ à $Z_5$ est N, les autres sont chacun indépendamment C(Q) ; ou, les deux de $Z_1$ à $Z_5$ adjacents l'un à l'autre sont C(Q) et forment ensemble un cycle carbocyclique à 5 à 6 chaînons ou un cycle hétérocyclique à 5 à 6 chaînons contenant 1 à 3 hétéroatomes choisis parmi N, O et S, les trois autres sont chacun indépendamment C(Q), ou deux des trois autres sont chacun indépendamment C(Q), le dernier est N ; ou l'un des trois autres est C(Q), les deux autres sont indépendamment N.

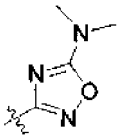
**8.** Modulateur du récepteur d'aryl hydrocarbone selon la revendication 3, **caractérisé en ce que**, dans la formule (I1),

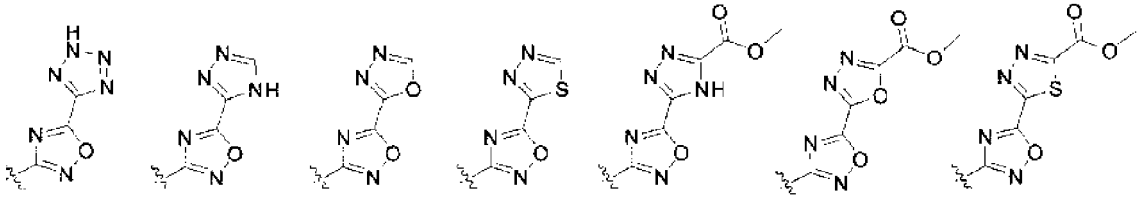


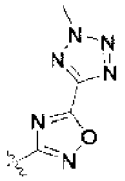
est choisi parmi les substituants suivants :



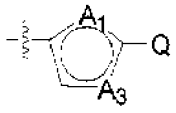




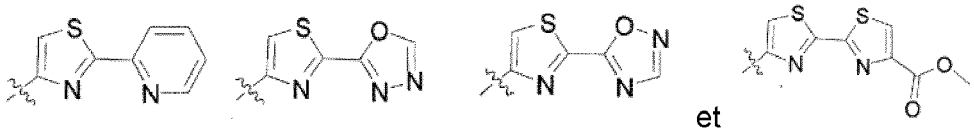




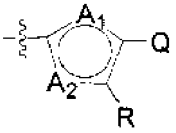
**9.** Modulateur du récepteur d'aryl hydrocarbone selon la revendication 4, **caractérisé en ce que**, dans la formule (Ib),



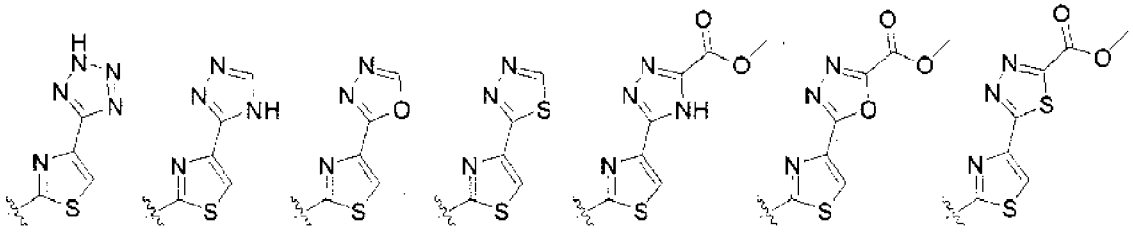
est choisi parmi les substituants suivants :

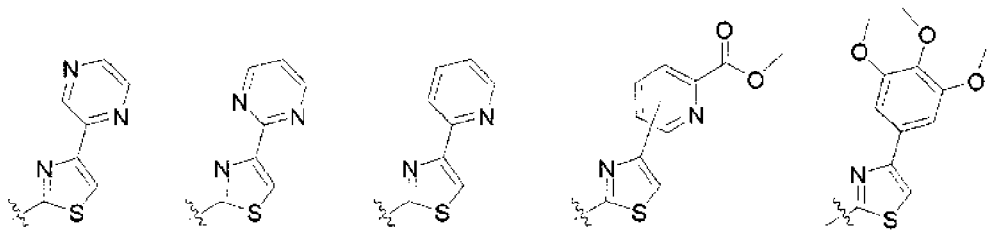


**10.** Modulateur du récepteur d'aryl hydrocarbone selon la revendication 4, **caractérisé en ce que**, dans la formule (Ic) et la formule (Id),

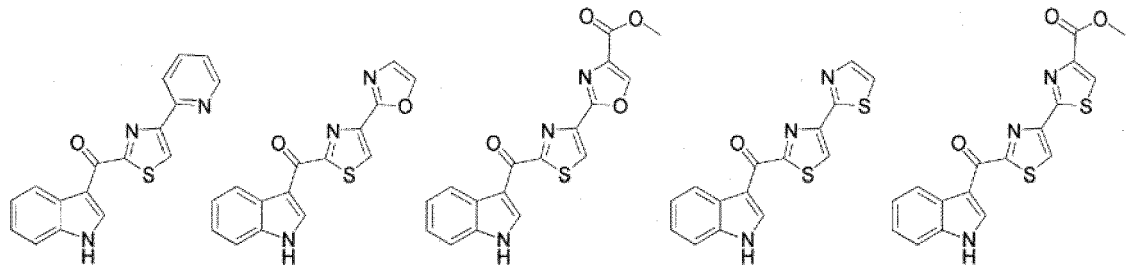


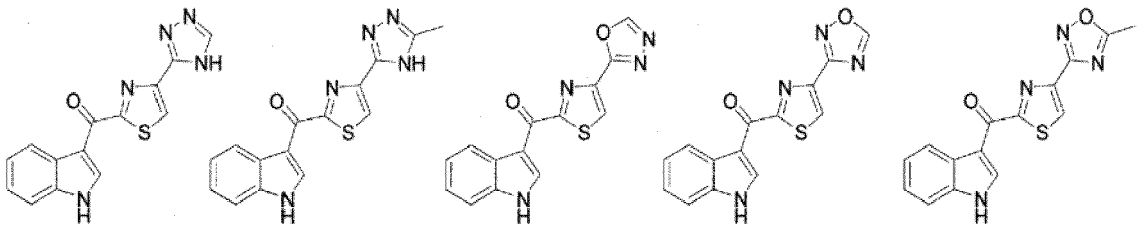
est choisi parmi les substituants suivants :

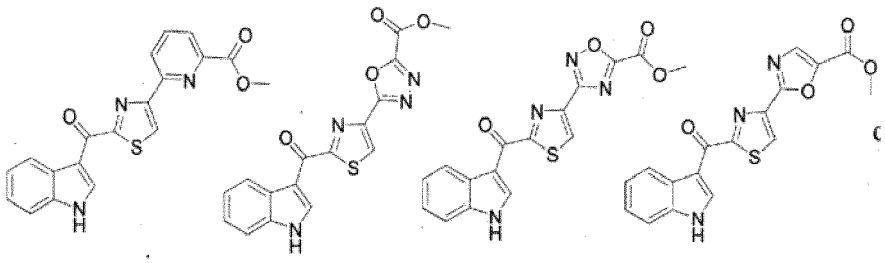




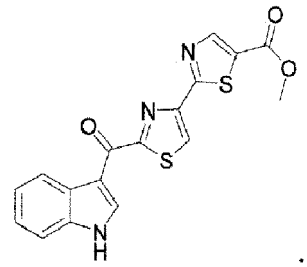
**11.** Modulateur du récepteur d'aryl hydrocarbone selon la revendication 1, **caractérisé en ce que** le modulateur du récepteur d'aryl hydrocarbone est choisi parmi





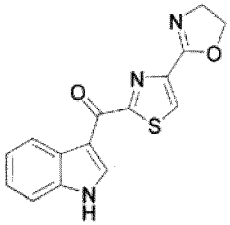
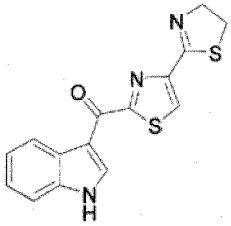
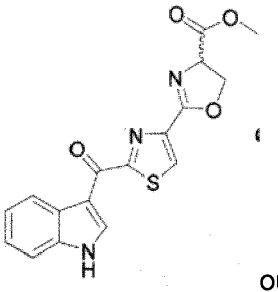


ou

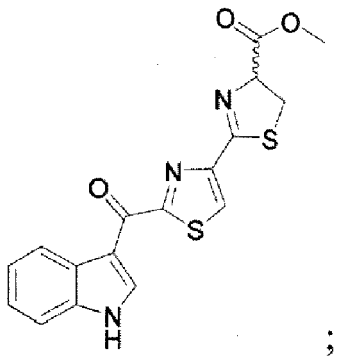


;

ou

ou



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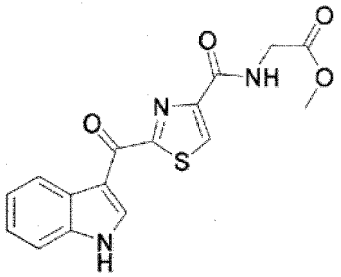
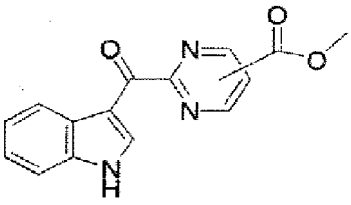
ou

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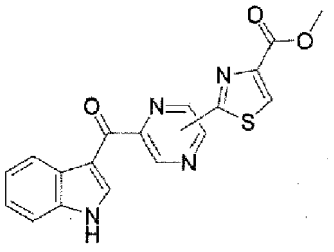

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**12.** Utilisation de modulateurs du récepteur d'aryl hydrocarbone selon l'une quelconque des revendications 1 à 11 pour la préparation de médicaments antitumoraux.

## REFERENCES CITED IN THE DESCRIPTION

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