

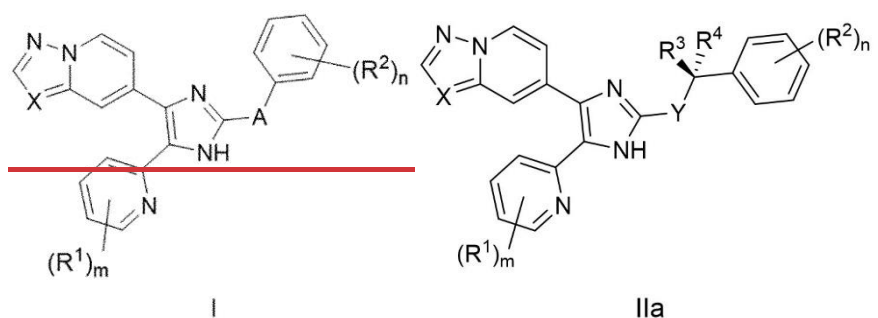
composition is useful for treating pulmonary fibrosis, obesity, diabetes, cancers and other inflammation.

[50] In other aspects, the present invention is directed to a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or prodrug thereof. In some embodiments, the pharmaceutical composition is in a form suitable for oral administration. In further or additional embodiments, the pharmaceutical composition is in the form of a tablet, capsule, pill, powder, sustained release formulation, solution and suspension. In some embodiments, the pharmaceutical composition is in a form suitable for parenteral injection, such as a sterile solution, suspension or emulsion; for topical administration as an ointment or cream or for rectal administration as a suppository. In further or additional embodiments, the pharmaceutical composition is in unit dosage forms suitable for single administration of precise dosages. In further or additional embodiments, the amount of compound of formula I is in the range of about 0.001 to about 1000 mg/kg body weight/day. In further or additional embodiments, the amount of compound of formula I is in the range of about 0.5 to about 50 mg/kg body weight/day.

[51] In other aspects, the present invention is directed to a process for preparing a compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or prodrug thereof.

Summary

[51a] In one aspect, there is provided a compound of ~~formula~~ Formula IIa, or a pharmaceutically acceptable salt, solvate, polymorph, ester or tautomer thereof,



wherein;

each R^1 is independently selected from the group consisting of hydrogen, halogen,

CF₃, acyl, amino, substituted amino, C₁-C₆alkyl, substituted C₁-C₆alkyl, C₁-C₆haloalkyl, C₃-C₇cycloalkyl, alkylcarboxy, cyano, nitro, and alkoxy;

each R² is independently selected from the group consisting of hydrogen, halogen, CF₃, acyl, amino, substituted amino, ~~C₁-C₆alkyl~~, substituted C₁-C₆alkyl, C₁-C₆haloalkyl, cyano, nitro, alkoxy, acyloxy, and aryloxy;

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

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

X is CH or N;

~~A is CH₂Y, CHR³Y, CR³R⁴Y, C(O)Y, YCH₂, YCHR³, YCR³R⁴, or YC(O)-;~~

Y is NH, NR⁵, O, S, S(O) or S(O)₂;

R³ is selected from the group consisting of F, CF₃, C₁-C₆alkyl, substituted C₁-C₆alkyl, and cyano;

or R³ and R⁴ together with the atom to which they are attached form a 3 to 7 membered carbocyclic or heterocyclic ring;

R⁴ is F, CF₃, or C₁-C₆ alkyl; and

R⁵ is C₁-C₆alkyl, C₁-C₆fluoroalkyl, C₁-C₆difluoroalkyl, or C₁-C₆trifluoroalkyl.

[51b] In another aspect, there is provided a pharmaceutical composition comprising a pharmaceutically effective amount of a compound as defined herein or a pharmaceutically acceptable salt, solvate, polymorph, ester, or tautomer ~~or prodrug~~ thereof, and a pharmaceutically acceptable carrier.

~~[51c]—In another aspect, there is provided use of a compound as defined herein or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or prodrug thereof in the preparation of a pharmaceutical composition for inhibiting ALK enzyme.~~

[51d] In another aspect, there is provided use of a compound as defined herein or a pharmaceutically acceptable salt, solvate, polymorph, ester, or tautomer ~~or prodrug~~ thereof in the preparation of a pharmaceutical composition for the treatment or prophylaxis of ~~an ALK-kinase-mediated disease or condition, wherein the disease or condition is~~ papillary thyroid carcinoma, pancreatic cancer, lung cancer, colon cancer, breast carcinoma, neuroblastoma, pain, cachexia, dermatitis or asthma.

[51~~ed~~^{fe}] In another aspect, there is provided use of a compound as defined herein or a pharmaceutically acceptable salt, solvate, polymorph, ester, or tautomer ~~or prodrug~~ thereof in the preparation of a pharmaceutical composition for the treatment or prophylaxis of proliferative disorders.

[51~~ed~~^{fe}] In another aspect, there is provided an in vitro method for inhibiting an ALK enzyme comprising the step of contacting the ALK enzyme with an amount sufficient to inhibit the enzyme of a compound as defined herein or a pharmaceutically acceptable salt, solvate, polymorph, ester, or tautomer ~~or prodrug~~ thereof.

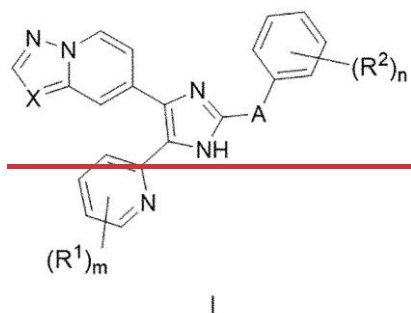
Advantageous Effects of Invention

[52] In the present invention, novel compounds are provided to inhibit ALK4/5. In this regard, the present invention can be used for preventing and/or treating various diseases associated with TGF- β , in particular ALK5 and/or ALK4.

Best Mode for Carrying out the Invention

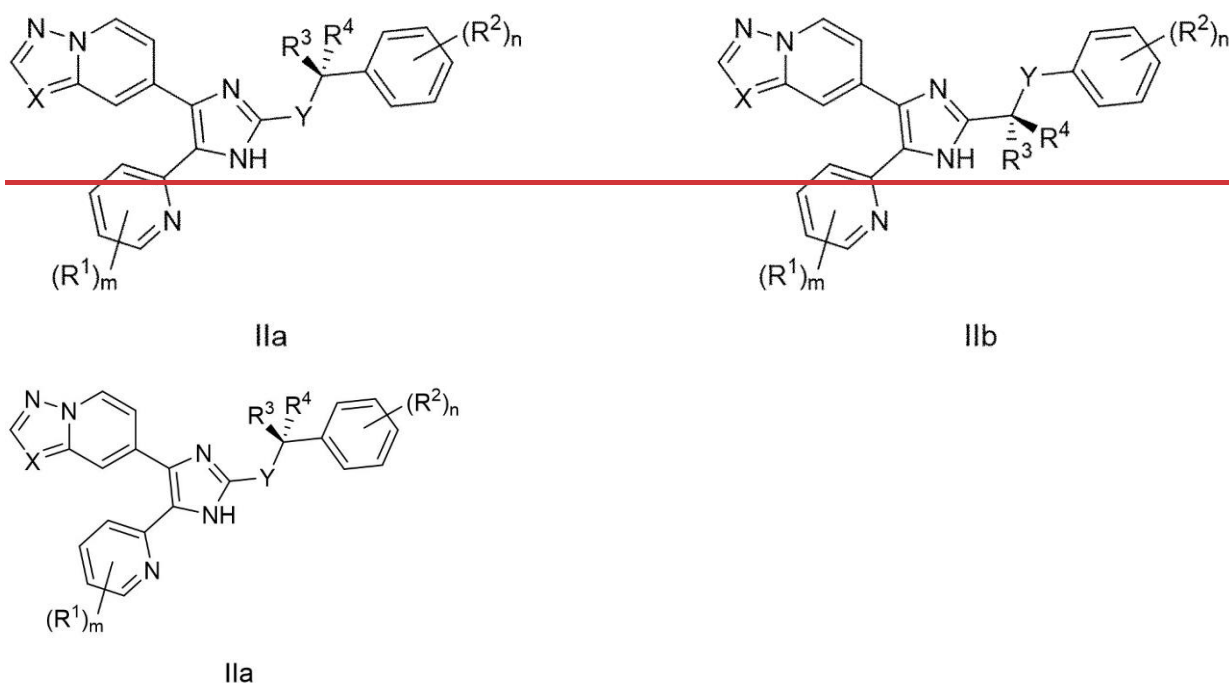
[53] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized. While preferred embodiments of the present invention have been shown and described herein such embodiments are provided by way of example only. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. Those ordinary skilled in the art will appreciate that numerous variations, changes, and substitutions are possible without departing from the invention. It is intended that the following claims define the scope of aspects of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter

~~A compound of formula I~~



R⁵ is C₁-C₆alkyl, C₁-C₆fluoroalkyl, C₁-C₆difluoroalkyl, or C₁-C₆trifluoroalkyl.

~~The A compound of claim 1, wherein formula I further includes the absolute configuration compounds of Formula IIa, or a pharmaceutically acceptable salt, solvate, polymorph, ester or tautomer thereof, and IIb:~~



~~or salt thereof~~, wherein;

each R^1 is independently selected from the group consisting of hydrogen, halogen, CF_3 , acyl, amino, substituted amino, C_1 - C_6 alkyl, substituted C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_3 - C_7 cycloalkyl, alkylcarboxy, cyano, nitro, and alkoxy;

each R^2 is independently selected from the group consisting of hydrogen, halogen, CF_3 , acyl, amino, substituted amino, ~~C_1 - C_6 alkyl~~, substituted C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, cyano, nitro, alkoxy, acyloxy, and aryloxy;

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

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

X is CH or N;

Y is NH, NR^5 , O, S, $S(O)$ or $S(O)_2$;

R^3 is selected from the group consisting of F, CF_3 , C_1 - C_6 alkyl, substituted C_1 - C_6 alkyl, and cyano;

or R^3 and R^4 together with the atom to which they are attached form a 3 to 7 membered carbocyclic or heterocyclic ring;

R^4 is F, CF_3 , or C_1 - C_6 alkyl; and

~~Y is NH, NR^5 , O, S, $S(O)$ or $S(O)_2$;~~

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

~~n is 0, 1, 2, 3, 4 or 5; and~~

R^5 is C_1 - C_6 alkyl, C_1 - C_6 fluoroalkyl, C_1 - C_6 difluoroalkyl, or C_1 - C_6 trifluoroalkyl.

【Claim ~~3~~2】

A pharmaceutical composition comprising a pharmaceutically effective amount of a compound of claim 1 ~~or 2~~ or a pharmaceutically acceptable salt, solvate, polymorph, ester, ~~or~~ tautomer ~~or prodrug~~ thereof, and a pharmaceutically acceptable carrier.

~~【Claim 4】~~

~~Use of a compound of claim 1 or 2 or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or prodrug thereof in the preparation of a pharmaceutical composition for inhibiting ALK enzyme.~~

【Claim ~~5~~3】

Use of a compound of claim 1 ~~or 2~~ or a pharmaceutically acceptable salt, solvate, polymorph, ester, ~~or~~ tautomer ~~or prodrug~~ thereof in the preparation of a pharmaceutical composition for the treatment or prophylaxis of ~~an ALK kinase-mediated disease or condition, wherein the disease or condition is~~ papillary thyroid carcinoma, pancreatic cancer, lung cancer, colon cancer, breast carcinoma, neuroblastoma, pain, cachexia, dermatitis or asthma.

【Claim ~~6~~4】

Use of a compound of claim 1 ~~or 2~~ or a pharmaceutically acceptable salt, solvate, polymorph, ester, ~~or~~ tautomer ~~or prodrug~~ thereof in the preparation of a pharmaceutical composition for the treatment or prophylaxis of proliferative disorders.

~~【Claim 7】~~

~~The use of claim 6, wherein the proliferative disorders are selected from the group consisting of pain, cancer, inflammation, neurodegenerative disease and certain infectious diseases.~~

【Claim ~~8~~5】

An in vitro method for inhibiting an ALK enzyme comprising the step of contacting the ALK enzyme with an amount sufficient to inhibit the enzyme of a compound of any of claim 1 ~~or 2~~ or a pharmaceutically acceptable salt, solvate, polymorph, ester, ~~or~~ tautomer ~~or prodrug~~ thereof.

~~【Claim 9】~~

~~The use of claim 6, wherein the proliferative disorders are selected from the group consisting of inflammatory diseases and cancers.~~