hematopoietic growth factor and IL-2). Therefore, TYK2 inhibitors can avoid adverse reactions associated with currently marketed JAK inhibitors by not acting on other subtypes.

Common small molecule JAK inhibitors are active site-directed inhibitors that bind to adenosine triphosphate (ATP) sites of the catalytic domains (JH1) of JAK proteins. Due to the high homology of the ATP sites of JAK family kinases and the similarity to the ATP-binding regions of the human kinase group, there generally exists an issue of low selectivity.

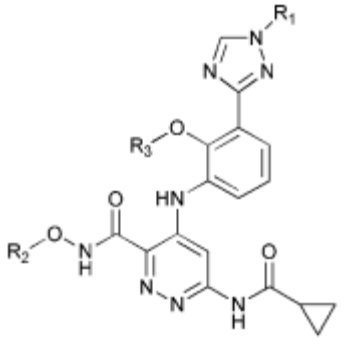
Studies have shown that the pseudokinase domain (JH2) in the JAK family, which exhibits significant catalytic activity, can provide an ideal allosteric site for the discovery of TYK2 selective inhibitors. Compound BMS-986165 is a currently known compound that can selectively bind to the JH2 of TYK2 and inhibit TYK2 kinase functions through an allosteric effect.

There is currently a need for drugs with improved activity in selectively inhibiting TYK2 by binding to JH2, thereby providing therapeutic benefits in the treatment of diseases.

SUMMARY

In view of the foregoing, the present disclosure provides a substituted pyridazine-3-carboxamide compound, which has excellent activity for selective inhibition of TYK2 and can treat a variety of TYK2-mediated diseases.

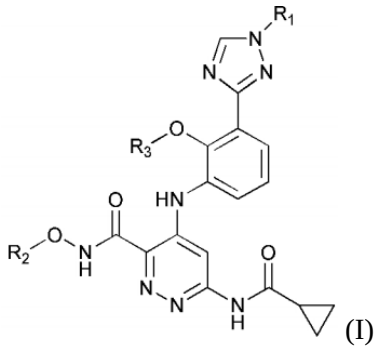
The present disclosure provides a compound represented by general formula (I), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, and a mixture thereof:



(I)

wherein each substituent is as defined in the present disclosure.

An aspect of the present disclosure provides a compound represented by general formula (I), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, and a mixture thereof:


(I)

wherein

R_1 is selected from H, a C_{1-6} haloalkyl, a C_{1-6} alkylene-OR_a, a C_{1-6} alkylene-SR_a, a C_{1-6} alkylene-NR_bR_c, a C_{1-6} alkylene-$C(O)R_a$, a C_{1-6} alkylene-$C(O)OR_a$, a C_{1-6} alkylene-$C(O)NR_bR_c$, a C_{1-6} alkylene-$OC(O)R_a$, a C_{1-6} alkylene-$NR_bC(O)R_a$, a C_{1-6} alkylene-$S(O)_mR_a$, a C_{1-6} alkylene-$S(O)_mNR_bR_c$ or a C_{1-6} alkylene-$NR_bS(O)_mR_a$, and the group is optionally substituted with one or more deuteriums until fully deuterated;

R_2 is selected from a C_{1-6} alkyl, a C_{1-6} haloalkyl, a C_{2-6} alkenyl, a C_{2-6} alkynyl, a C_{3-7} cycloalkyl, a 3- to 7-membered heterocyclyl, a C_{6-10} aryl or a 5- to 10-membered heteroaryl, and the group is optionally substituted with one or more deuteriums until fully deuterated;

R_3 is selected from H, a C_{1-6} alkyl or a C_{1-6} haloalkyl, and the group is optionally substituted with one or more deuteriums until fully deuterated;

each group of R_1, R_2 and R_3 is optionally substituted with 1, 2, 3 or 4 R;

wherein R_a, R_b and R_c are independently selected from H, a C_{1-6} alkyl, a C_{1-6} haloalkyl, a C_{2-6} alkenyl, a C_{2-6} alkynyl, a C_{3-7} cycloalkyl, a 3- to 7-membered heterocyclyl, a C_{6-10} aryl or a 5- to 10-membered heteroaryl;

m is 1 or 2; and

R is selected from H, D, a halogen, CN, a C_{1-6} alkyl or a C_{1-6} haloalkyl.

Another aspect of the present disclosure provides a pharmaceutical composition comprising the compound, or the pharmaceutically acceptable salt, enantiomer, diastereomer,

racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, and the mixture thereof as defined herein, and a pharmaceutically acceptable excipient; wherein preferably, the pharmaceutical composition further comprises other therapeutic agents.

A further aspect of the present disclosure provides a use of the compound or the pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, and the mixture thereof, or the pharmaceutical composition comprising the same as defined herein in the preparation of a medicament for treating and/or preventing a TYK2-mediated disease.

Another aspect of the present disclosure provides a compound or the pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, and the mixture thereof as defined herein, or the pharmaceutical composition as defined herein, for use in treating and/or preventing a TYK2 kinase-mediated disease.

The present disclosure also provides a use of the compound or the pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, and the mixture thereof, or the pharmaceutical composition comprising the compound as defined herein in the treatment and/or prevention of a TYK2 kinase-mediated disease.

The present disclosure further provides a method for treating and/or preventing a TYK2 kinase-mediated disease in a subject by using the compound as defined herein, the method comprising administering to the subject the compound or the pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, and the mixture thereof, or the pharmaceutical composition comprising the same.

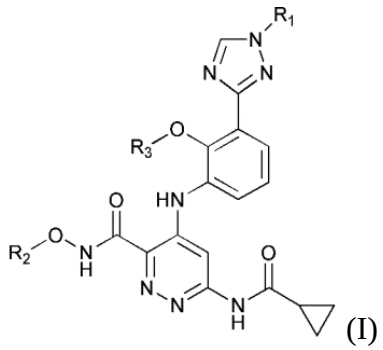
A further aspect of the present disclosure provides a compound or the pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, and the mixture thereof as defined herein, or the pharmaceutical composition as defined herein, for use in therapy.

The TYK2 kinase-mediated disease recited in the present disclosure is selected from an autoimmune disease, a skin disease, an allergic disease, organ rejection, cancer, dry eye disease, myelofibrosis and polycythemia vera. Further, the autoimmune disease is lupus, multiple sclerosis, rheumatoid arthritis, juvenile arthritis, psoriasis, ulcerative colitis, Crohn's disease or autoimmune thyroid disease; the skin disease is psoriasis, a rash or atopic dermatitis; the allergic disease is asthma or rhinitis; the organ transplant rejection is allograft rejection or graft-versus-host disease; and the cancer is renal cancer, liver cancer, pancreatic cancer, gastric cancer, breast cancer, prostate cancer, head and neck cancer, thyroid cancer, lung cancer, glioblastoma, melanoma, lymphoma or leukemia.

In some examples, the TYK2 kinase-mediated disease relating to the method is selected from rheumatoid arthritis, psoriasis, ulcerative colitis and Crohn's disease.

CLAIMS

1. A compound represented by general formula (I), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, and a mixture thereof:


(I)

wherein

R_1 is selected from H, a C_{1-6} haloalkyl, a C_{1-6} alkylene-OR_a, a C_{1-6} alkylene-SR_a, a C_{1-6} alkylene-NR_bR_c, a C_{1-6} alkylene-$C(O)R_a$, a C_{1-6} alkylene-$C(O)OR_a$, a C_{1-6} alkylene-$C(O)NR_bR_c$, a C_{1-6} alkylene-$OC(O)R_a$, a C_{1-6} alkylene-$NR_bC(O)R_a$, a C_{1-6} alkylene-$S(O)_mR_a$, a C_{1-6} alkylene-$S(O)_mNR_bR_c$ or a C_{1-6} alkylene-$NR_bS(O)_mR_a$, and the group is optionally substituted with one or more deuteriums until fully deuterated;

R_2 is selected from a C_{1-6} alkyl, a C_{1-6} haloalkyl, a C_{2-6} alkenyl, a C_{2-6} alkynyl, a C_{3-7} cycloalkyl, a 3- to 7-membered heterocyclyl, a C_{6-10} aryl or a 5- to 10-membered heteroaryl, and the group is optionally substituted with one or more deuteriums until fully deuterated;

R_3 is selected from H, a C_{1-6} alkyl or a C_{1-6} haloalkyl, and the group is optionally substituted with one or more deuteriums until fully deuterated;

each group of R_1, R_2 and R_3 is optionally substituted with 1, 2, 3 or 4 R;

wherein R_a, R_b and R_c are independently selected from H, a C_{1-6} alkyl, a C_{1-6} haloalkyl, a C_{2-6} alkenyl, a C_{2-6} alkynyl, a C_{3-7} cycloalkyl, a 3- to 7-membered heterocyclyl, a C_{6-10} aryl or a 5- to 10-membered heteroaryl;

m is 1 or 2; and

R is selected from H, D, a halogen, CN, a C_{1-6} alkyl or a C_{1-6} haloalkyl.

2. The compound, or the pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, and the mixture thereof according to claim 1, wherein R_1 is selected from H, a C_{1-6} haloalkyl, a C_{1-6} alkylene-OR_a, a C_{1-6} alkylene-SR_a, a C_{1-6} alkylene-NR_bR_c, a C_{1-6} alkylene-$C(O)R_a$, a C_{1-6} alkylene-$C(O)OR_a$, a C_{1-6} alkylene-$C(O)NR_bR_c$, a C_{1-6} alkylene-$OC(O)R_a$ or a C_{1-6} alkylene-$NR_bC(O)R_a$, and the group is optionally substituted with one or more deuteriums until fully deuterated; preferably, R_1 is selected from H, a C_{1-6} haloalkyl, a C_{1-6} alkylene-OR_a, a C_{1-6} alkylene-SR_a, a C_{1-6} alkylene-NR_bR_c, a C_{1-6} alkylene-$C(O)OR_a$ or a C_{1-6} alkylene-$C(O)NR_bR_c$, and the group is optionally substituted with one or more deuteriums until fully deuterated; preferably, R_1 is selected from H, a C_{1-6} haloalkyl, a C_{1-6} alkylene-OH, a C_{1-6} alkylene-SH, a C_{1-6} alkylene-NH_2, a C_{1-6} alkylene-C(O)OH or a C_{1-6} alkylene-$C(O)NH_2$, and the group is optionally substituted with one or more deuteriums until fully deuterated; preferably, R_1 is selected from H or a C_{1-6} haloalkyl, and the group is optionally substituted with one or more deuteriums until fully deuterated; and preferably, R_1 is a C_{1-6} alkylene-OR_a, wherein R_a is selected from a C_{1-6} alkyl or a C_{1-6} haloalkyl.

3. The compound, or the pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, and the mixture thereof according to claim 1 or 2, wherein R_2 is selected from a C_{1-6} alkyl, a C_{1-6} haloalkyl, a C_{2-6} alkenyl, a C_{2-6} alkynyl, a C_{3-7} cycloalkyl or a 3- to 7-membered heterocyclyl, and the group is optionally substituted with one or more deuteriums until fully deuterated; preferably, R_2 is selected from a C_{1-6} alkyl, a C_{1-6} haloalkyl, a C_{3-7} cycloalkyl or a 3- to 7-membered heterocyclyl, and the group is optionally substituted with one or more deuteriums until fully deuterated; and preferably, R_2 is selected from a C_{1-6} alkyl or a C_{3-7} cycloalkyl, and the group is optionally substituted with one or more deuteriums until fully deuterated.

4. The compound, or the pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, and the mixture thereof according to any one of claims 1 to 3, wherein R_3 is selected from a C_{1-6} alkyl or a C_{1-6} haloalkyl, and the group is optionally substituted with one or more deuteriums until fully deuterated; and preferably, R_3 is methyl, which is optionally substituted with one or more deuteriums until fully deuterated.

5. The compound, or the pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, and the mixture thereof according to claim 1, wherein

R_1 is selected from H, a C_{1-6} haloalkyl, a C_{1-6} alkylene-OR_a, a C_{1-6} alkylene-SR_a or a C_{1-6} alkylene-C(O)OR_a, and the group is optionally substituted with one or more deuteriums until fully deuterated;

R_2 is selected from a C_{1-6} alkyl, a C_{1-6} haloalkyl, a C_{3-7} cycloalkyl or a 3- to 7-membered heterocyclyl, and the group is optionally substituted with one or more deuteriums until fully deuterated;

R_3 is selected from H, a C_{1-6} alkyl or a C_{1-6} haloalkyl, and the group is optionally substituted with one or more deuteriums until fully deuterated;

each group of R_1, R_2 and R_3 is optionally substituted with 1, 2, 3 or 4 R;

wherein R_a is selected from H, a C_{1-6} alkyl or a C_{1-6} haloalkyl; and

R is selected from H, D, a halogen, CN, a C_{1-6} alkyl or a C_{1-6} haloalkyl.

6. The compound, or the pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, and the mixture thereof according to claim 1, wherein

R_1 is selected from H, a C_{1-4} haloalkyl, a C_{1-4} alkylene-OR_a or a C_{1-4} alkylene-C(O)OH, and the group is optionally substituted with one or more deuteriums until fully deuterated;

R_2 is selected from a C_{1-4} alkyl, a C_{1-4} haloalkyl or a C_{3-7} cycloalkyl, and the group is optionally substituted with one or more deuteriums until fully deuterated; and

R_3 is selected from a C_{1-4} alkyl or a C_{1-4} haloalkyl, and the group is optionally substituted with one or more deuteriums until fully deuterated;

wherein R_a is selected from H, a C_{1-4} alkyl or a C_{1-4} haloalkyl.

7. The compound, or the pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, and the mixture thereof according to claim 1, wherein

R_1 is a C_{1-4} alkylene-OR_a, which is optionally substituted with one or more deuteriums until fully deuterated;

R_2 is selected from a C_{1-4} alkyl, a C_{1-4} haloalkyl or a C_{3-7} cycloalkyl, and the group is optionally substituted with one or more deuteriums until fully deuterated; preferably a C_{1-4} alkyl, which is optionally substituted with one or more deuteriums until fully deuterated; and

R_3 is selected from a C_{1-4} alkyl or a C_{1-4} haloalkyl, and the group is optionally substituted with one or more deuteriums until fully deuterated;

wherein R_a is selected from a C_{1-4} alkyl or a C_{1-4} haloalkyl.

8. The compound, or the pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, and the mixture thereof according to claim 1, wherein

R_1 is selected from H, a C_{1-4} haloalkyl, a C_{1-4} alkylene-OH or a C_{1-4} alkylene-C(O)OH, and the group is optionally substituted with one or more deuteriums until fully deuterated;

R_2 is selected from a C_{1-4} alkyl, a C_{1-4} haloalkyl or a C_{3-7} cycloalkyl, and the group is optionally substituted with one or more deuteriums until fully deuterated; preferably a C_{1-4} alkyl, which is optionally substituted with one or more deuteriums until fully deuterated; and

R_3 is selected from a C_{1-4} alkyl or a C_{1-4} haloalkyl, and the group is optionally substituted with one or more deuteriums until fully deuterated.

9. The compound, or the pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, and the mixture thereof according to claim 1, wherein

R_1 is selected from H, a C_{1-6} alkylene-OR_a and a C_{1-6} alkylene-SR_a, and the group is optionally substituted with one or more deuteriums until fully deuterated;

R_2 is selected from a C_{1-6} alkyl and a C_{1-6} haloalkyl, and the group is optionally substituted with one or more deuteriums until fully deuterated;

R_3 is selected from H, a C_{1-6} alkyl or a C_{1-6} haloalkyl, and the group is optionally substituted with one or more deuteriums until fully deuterated;

each group of R_1, R_2 and R_3 is optionally substituted with 1, 2, 3 or 4 R;

wherein R_a is selected from H, a C_{1-6} alkyl and a C_{1-6} haloalkyl; and

R is selected from H, D, a halogen, CN, a C_{1-6} alkyl or a C_{1-6} haloalkyl.

10. The compound, or the pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, and the mixture thereof according to claim 1, wherein

R_1 is selected from H and a C_{1-6} alkylene-OR_a, and the group is optionally substituted with one or more deuterium groups until fully deuterated;

R_2 is selected from a C_{1-6} alkyl and a C_{1-6} haloalkyl; and

R_3 is a C_{1-6} alkyl, and the group is optionally substituted with one or more deuteriums until fully deuterated;

wherein R_a is selected from H and a C_{1-6} alkyl.

11. The compound, or the pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, and the mixture thereof according to claim 1, wherein

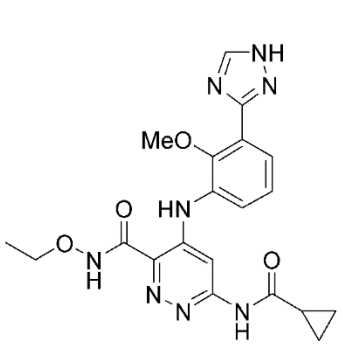
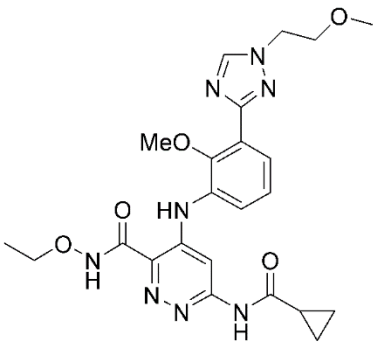
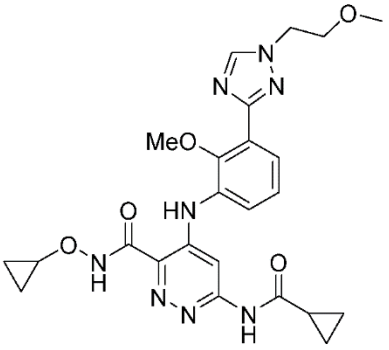
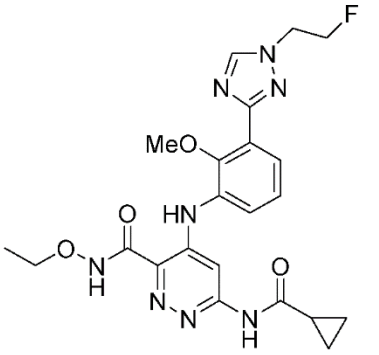
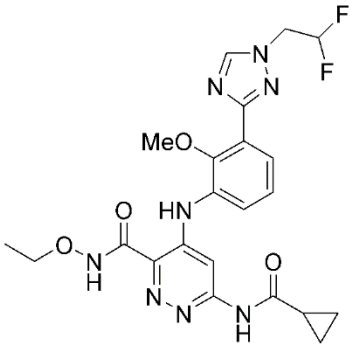
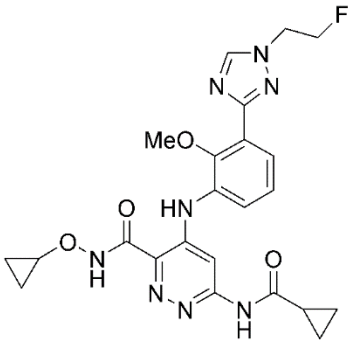
R_1 is selected from H and a C_{1-4} alkylene-OR_a, and the group is optionally substituted with one or more deuterium groups until fully deuterated;

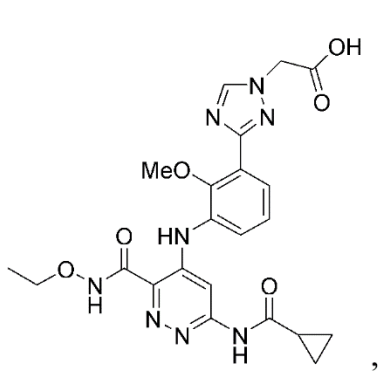
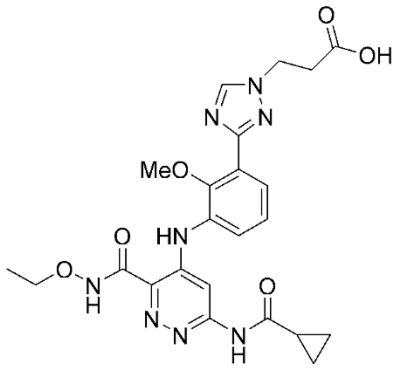
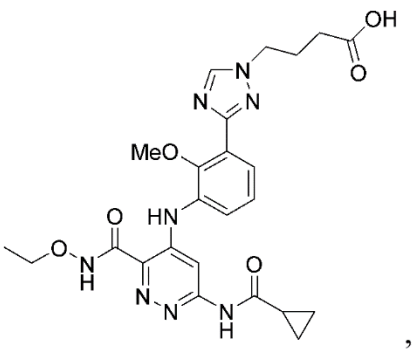
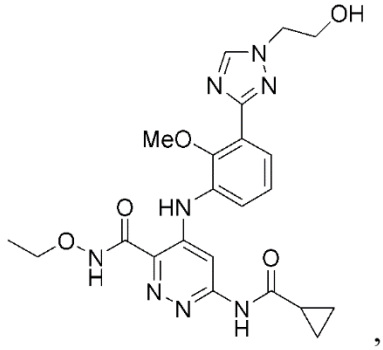
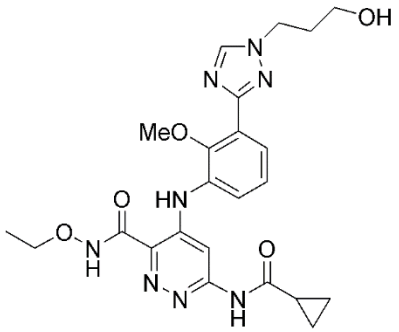
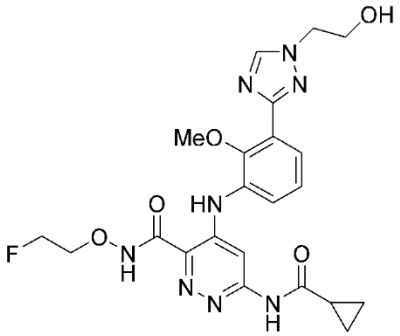
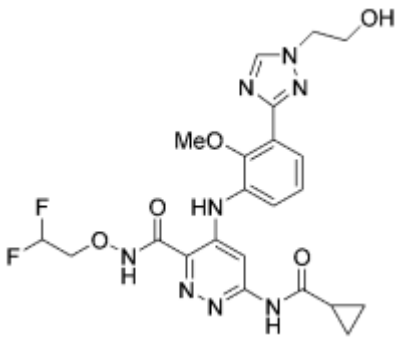
R_2 is a C_{1-4} alkyl, and the group is optionally substituted with one or more deuteriums until fully deuterated; and

R_3 is a C_{1-4} alkyl, and the group is optionally substituted with one or more deuteriums until fully deuterated;

wherein R_a is a C_{1-4} alkyl.

12. The compound, or the pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, and the mixture thereof according to claim 1, wherein the compound is selected from:


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or

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13. A pharmaceutical composition, comprising the compound, or the pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, and the mixture thereof according to any one of claims 1 to 12, and a pharmaceutically acceptable excipient; wherein preferably, the pharmaceutical composition further comprises other therapeutic agents.

14. A use of the compound or the pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, and the mixture thereof

according to any one of claims 1 to 12 in the preparation of a medicament for treating and/or preventing a TYK2 kinase-mediated disease.

15. A compound or the pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, and the mixture thereof according to any one of claims 1 to 12, or the pharmaceutical composition according to claim 13, for use in treating and/or preventing a TYK2 kinase-mediated disease.

16. The use according to claim 14, or the compound or pharmaceutical composition for use according to claim 15, wherein the TYK2 kinase-mediated disease is selected from an autoimmune disease, a skin disease, an allergic disease, organ rejection, cancer, dry eye disease, myelofibrosis and polycythemia vera; preferably, the autoimmune disease is lupus, multiple sclerosis, rheumatoid arthritis, juvenile arthritis, psoriasis, ulcerative colitis, Crohn's disease or autoimmune thyroid disease; the skin disease is psoriasis, a rash or atopic dermatitis; the allergic disease is asthma or rhinitis; the organ transplant rejection is allograft rejection or graft-versus-host disease; and the cancer is renal cancer, liver cancer, pancreatic cancer, gastric cancer, breast cancer, prostate cancer, head and neck cancer, thyroid cancer, lung cancer, glioblastoma, melanoma, lymphoma or leukemia.

17. The use according to claim 14, or the compound or pharmaceutical composition for use according to claim 15, wherein the TYK2 kinase-mediated disease is selected from rheumatoid arthritis, psoriasis, ulcerative colitis and Crohn's disease.

18. A compound or the pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, and the mixture thereof according to any one of claims 1 to 12, or the pharmaceutical composition according to claim 13, for use in therapy.