PYRUVATE KINASE ACTIVATORS FOR USE IN TREATING BLOOD DISORDERS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority of U.S. Provisional Patent Application Nos. 62/673,526 and 62/673,533, both filed May 18, 2018. This application also claims the benefit of priority of International Patent Application No. PCT/CN2017/097496, filed August 15, 2017. Each of the aforementioned priority applications is incorporated herein by reference in its entirety.

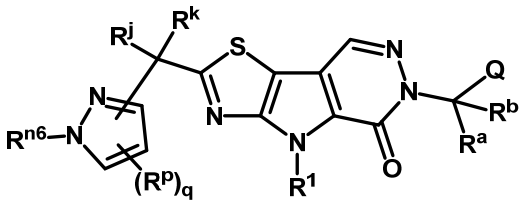
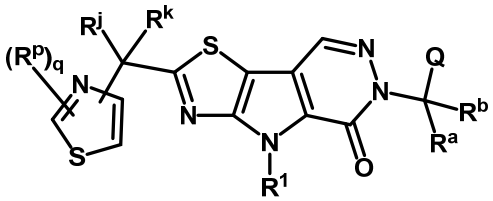
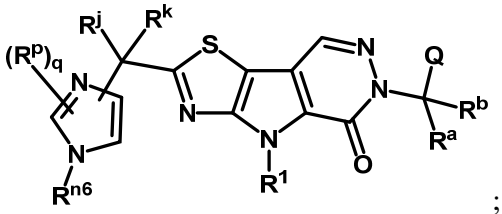
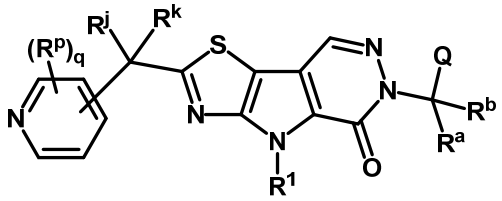
BACKGROUND

Pyruvate kinase deficiency (PKD) is a disease of the red blood cells caused by a deficiency of the pyruvate kinase R (PKR) enzyme due to recessive mutations of PKLR gene (Wijk et al. *Human Mutation*, **2008**, *30* (3) 446-453). PKR activators can be beneficial to treat PKD, thalassemia (*e.g.*, beta-thalessemia), hereditary elliptocytosis, abetalipoproteinemia or Bassen-Kornzweig syndrome, sickle cell disease, paroxysmal nocturnal hemoglobinuria, anemia (*e.g.*, congenital anemias (*e.g.*, enzymopathies), hemolytic anemia (e.g. hereditary and/or congenital hemolytic anemia, acquired hemolytic anemia, chronic hemolytic anemia caused by phosphoglycerate kinase deficiency, anemia of chronic diseases, non-spherocytic hemolytic anemia or hereditary spherocytosis).

SUMMARY

Described herein are compounds of Formulas (I), (II), (III), (IV), and (V) (collectively referred to herein as "Formulas (I)-(V)"), that activate pyruvate kinase R (PKR), wild type and/or mutant enzymes (such as those described herein), and pharmaceutically acceptable salts thereof.

In one aspect of the present disclosure, there is provided a compound represented by the following structural formula:


;

;

; ; or

;

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen, an optionally substituted alkyl, an optionally substituted haloalkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted heterocyclyl, an optionally substituted aryl, $–OR^{o1}$, $–C(=O)R^{c1}$, or a nitrogen protecting group; wherein:

R^{o1} is hydrogen, optionally substituted alkyl, or an oxygen protecting group;

R^{c1} is optionally substituted alkyl or $–N(R^{cn})_2$, wherein each instance of R^{cn} is independently hydrogen, $−C_{1-6}$ alkyl, or a nitrogen protecting group;

Q is an optionally substituted 6-membered monocyclic heteroaryl;

R^a and R^b are each independently hydrogen, a halogen, –CN, $–NO_2$, $–N_3$, an optionally substituted alkyl, $–OR^{o3}$, $–N(R^{n1})_2$, $–C(=O)N(R^{n1})_2$, or $–C(=O)R^{c2}$; wherein:

each instance of R^{n1} is independently hydrogen, an optionally substituted $−C_1$-C_6 alkyl, or a nitrogen protecting group;

R^{o3} is hydrogen, an optionally substituted $–C_1$-C_6 alkyl, or an oxygen protecting group; and

R^{c2} is an optionally substituted $–C_1$-C_6 alkyl; and

R^j and R^k are each independently hydrogen, a halogen, –CN, $–OR^{o7}$, $–N(R^{n5})_2$, $–N(R^{n5})C(=O)$ R^{c5}, $–C(=O)N(R^{n5})_2$, $–C(=O)R^{c5}$, $–C(=O)OR^{o7}$, $–SR^{js}$, $–S(=O)_2R^{js}$,

–S(=O)R^{js}, or an optionally substituted −C_1-C_6 alkyl; or alternatively R^j and R^k can be taken together with the carbon atom to which they are attached to form C=O; wherein:

each instance of R^{n5} is independently hydrogen, an optionally substituted –C_1-C_6 alkyl, –OR^{o8}, or a nitrogen protecting group, wherein R^{o8} is hydrogen, an optionally substituted –C_1-C_6 alkyl, or an oxygen protecting group;

each instance of R^{o7} is independently hydrogen, an optionally substituted –C_1-C_6 alkyl, or an oxygen protecting group;

each instance of R^{c5} is independently an optionally substituted –C_1-C_6 alkyl; and

each instance of R^{js} is independently an optionally substituted –C_1-C_6 alkyl, an optionally substituted C_{6-12} aryl, an optionally substituted heteroaryl, or a sulfur protecting group;

each instance of R^p is independently hydrogen, a halogen, –CN, –NO_2, –N_3, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted aryl, an optionally substituted heterocyclyl, an optionally substituted heteroaryl, –OR^{o6}, –SR^{s2}, –$N(R^{n3})_2$, –$C(=O)N(R^{n3})_2$, –$N(R^{n3})C(=O)R^{c4}$, –$C(=O)R^{c4}$, –$C(=O)OR^{o6}$, –$OC(=O)R^{c4}$, –$S(=O)R^{s2}$, –$S(=O)_2R^{s2}$, –$S(=O)OR^{o6}$, –$OS(=O)R^{c4}$, –$S(=O)_2OR^{o6}$, –$OS(=O)_2R^{c4}$, –$S(=O)N(R^{n3})_2$, –$S(=O)_2N(R^{n3})_2$, –$N(R^{n3})S(=O)R^{s2}$, –$N(R^{n3})S(=O)_2R^{s2}$, –$N(R^{n3})C(=O)OR^{o6}$, –$OC(=O)N(R^{n3})_2$, –$N(R^{n3})C(=O)N(R^{n3})_2$, –$N(R^{n3})S(=O)N(R^{n3})_2$, –$N(R^{n3})S(=O)_2N(R^{n3})_2$, –$N(R^{n3})S(=O)OR^{o6}$, –$N(R^{n3})S(=O)_2OR^{o6}$, –$OS(=O)N(R^{n3})_2$, or –$OS(=O)_2N(R^{n3})_2$; or alternatively two instances of R^p attached to the same or adjacent carbon atoms, can be taken together with the carbon atom(s) to which they are attached to form an optionally substituted cycloalkyl or a heterocycloalkyl; wherein:

each instance of R^{n3} is independently hydrogen, an optionally substituted –C_1-C_6 alkyl, or a nitrogen protecting group;

each instance of R^{o6} is independently hydrogen, an optionally substituted –C_1-C_6 alkyl, or an oxygen protecting group; and

each instance of R^{c4} is an optionally substituted –C_1-C_6 alkyl;

each instance of R^{s2} is independently an optionally substituted –C_1-C_6 alkyl or a sulfur protecting group; and

R^{n6} is hydrogen, an optionally substituted –C_1-C_6 alkyl, or a nitrogen protecting group; and

q is 0, 1, 2, or 3.

In another aspect, the present disclosure refers to a pharmaceutical composition comprising an effective amount of the compound disclosed herein or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In a further aspect, the present disclosure refers to a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof; or the pharmaceutical composition disclosed herein for the manufacture of a medicament for treating anemia in a subject.

In another aspect, the present disclosure refers to a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof; or the pharmaceutical composition disclosed herein for the manufacture of a medicament for treating hemolytic anemia in a subject.

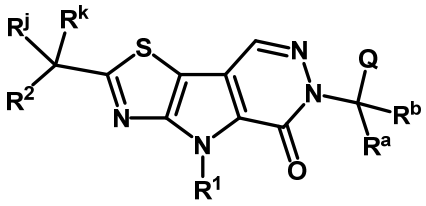
In a further aspect, the present disclosure refers to a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof; or the pharmaceutical composition disclosed herein for the manufacture of a medicament for treating sickle cell disease in a subject.

In another aspect, the present disclosure refers to a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof; or the pharmaceutical composition disclosed herein for the manufacture of a medicament for treating pyruvate kinase deficiency (PKD) in a subject.

In another aspect, the present disclosure refers to a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof; or the pharmaceutical composition disclosed herein for the manufacture of a medicament treating thalassemia, hereditary spherocytosis, hereditary elliptocytosis, abetalipoproteinemia or Bassen-Kornzweig

syndrome, sickle cell disease, paroxysmal nocturnal hemoglobinuria, acquired hemolytic anemia, or anemia of chronic diseases in a subject.

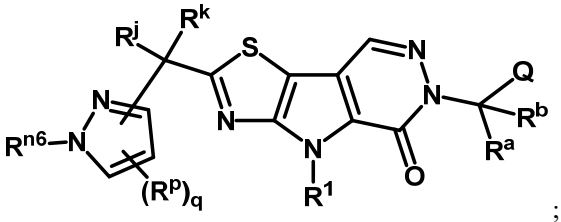
In one example, the present disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof:



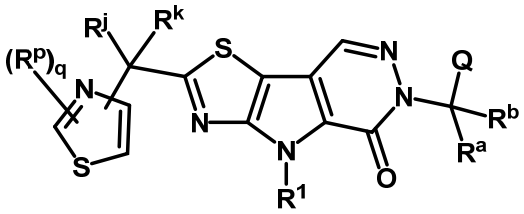
(I)

CLAIMS

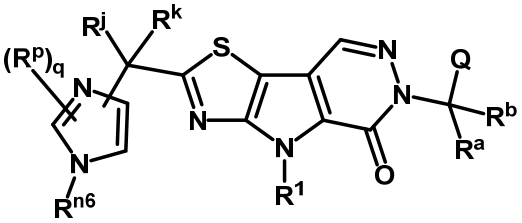
1. A compound represented by the following structural formula:



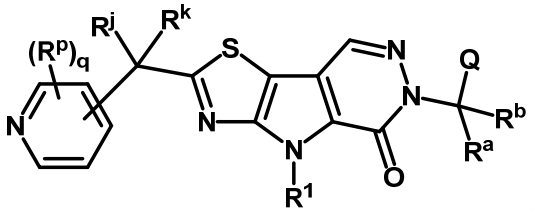
;



;



; or



;

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen, an optionally substituted alkyl, an optionally substituted haloalkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted heterocyclyl, an optionally substituted aryl, $–OR^{o1}$, $–C(=O)R^{c1}$, or a nitrogen protecting group; wherein:

R^{o1} is hydrogen, optionally substituted alkyl, or an oxygen protecting group;

R^{c1} is optionally substituted alkyl or $–N(R^{cn})_2$, wherein each instance of R^{cn} is independently hydrogen, $-C_{1-6}$ alkyl, or a nitrogen protecting group;

Q is an optionally substituted 6-membered monocyclic heteroaryl;

R^a and R^b are each independently hydrogen, a halogen, –CN, $–NO_2$, $–N_3$, an optionally substituted alkyl, $–OR^{o3}$, $–N(R^{n1})_2$, $–C(=O)N(R^{n1})_2$, or $–C(=O)R^{c2}$; wherein:

each instance of R^{n1} is independently hydrogen, an optionally substituted $-C_1$-C_6 alkyl, or a nitrogen protecting group;

R^{o3} is hydrogen, an optionally substituted $–C_1$-C_6 alkyl, or an oxygen protecting group; and

R^{c2} is an optionally substituted $–C_1$-C_6 alkyl; and

R^j and R^k are each independently hydrogen, a halogen, –CN, $–OR^{o7}$, $–N(R^{n5})_2$, $–N(R^{n5})C(=O)\ R^{c5}$, $–C(=O)N(R^{n5})_2$, $–C(=O)R^{c5}$, $–C(=O)OR^{o7}$, $–SR^{js}$, $–S(=O)_2R^{js}$, $–S(=O)R^{js}$, or an optionally substituted $-C_1$-C_6 alkyl; or alternatively R^j and R^k can be taken together with the carbon atom to which they are attached to form C=O; wherein:

each instance of R^{n5} is independently hydrogen, an optionally substituted $–C_1$-C_6 alkyl, $–OR^{o8}$, or a nitrogen protecting group, wherein R^{o8} is hydrogen, an optionally substituted $–C_1$-C_6 alkyl, or an oxygen protecting group;

each instance of R^{o7} is independently hydrogen, an optionally substituted $–C_1$-C_6 alkyl, or an oxygen protecting group;

each instance of R^{c5} is independently an optionally substituted $–C_1$-C_6 alkyl; and

each instance of R^{js} is independently an optionally substituted $–C_1$-C_6 alkyl, an optionally substituted $C_{6\text{-}12}$ aryl, an optionally substituted heteroaryl, or a sulfur protecting group;

each instance of R^p is independently hydrogen, a halogen, –CN, $–NO_2$, $–N_3$, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted aryl, an optionally substituted heterocyclyl, an optionally substituted heteroaryl, $–OR^{o6}$, $–SR^{s2}$, $–N(R^{n3})_2$, $–C(=O)N(R^{n3})_2$, $–N(R^{n3})C(=O)R^{c4}$, $–C(=O)R^{c4}$, $–C(=O)OR^{o6}$, $–OC(=O)R^{c4}$, $–S(=O)R^{s2}$, $–S(=O)_2R^{s2}$, $–S(=O)OR^{o6}$, $–OS(=O)R^{c4}$, $–S(=O)_2OR^{o6}$, $–OS(=O)_2R^{c4}$, $–S(=O)N(R^{n3})_2$, $–S(=O)_2N(R^{n3})_2$, $–N(R^{n3})S(=O)R^{s2}$, $–N(R^{n3})S(=O)_2R^{s2}$, $–N(R^{n3})C(=O)OR^{o6}$, $–OC(=O)N(R^{n3})_2$, $–N(R^{n3})C(=O)N(R^{n3})_2$, $–N(R^{n3})S(=O)N(R^{n3})_2$, $–N(R^{n3})S(=O)_2N(R^{n3})_2$, $–N(R^{n3})S(=O)OR^{o6}$, $–N(R^{n3})S(=O)_2OR^{o6}$, $–OS(=O)N(R^{n3})_2$, or $–OS(=O)_2N(R^{n3})_2$; or alternatively two instances of R^p attached to the same or adjacent carbon atoms, can be taken together with the carbon atom(s) to which they are attached to form an optionally substituted cycloalkyl or a heterocycloalkyl; wherein:

each instance of R^{n3} is independently hydrogen, an optionally substituted $–C_1$-C_6 alkyl, or a nitrogen protecting group;

each instance of R^{o6} is independently hydrogen, an optionally substituted $–C_1$-C_6 alkyl, or an oxygen protecting group; and

each instance of R^{c4} is an optionally substituted $–C_1$-C_6 alkyl;

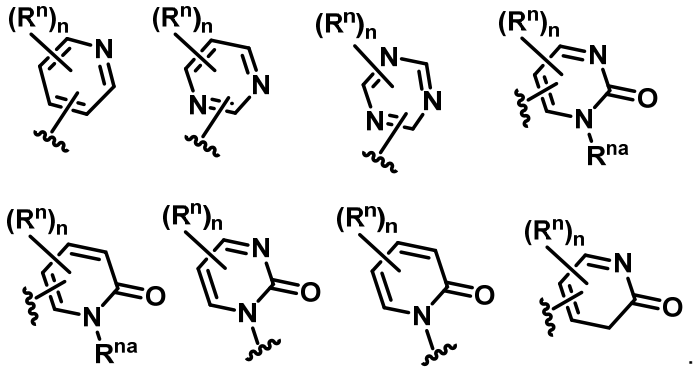
each instance of R^{s2} is independently an optionally substituted $–C_1$-C_6 alkyl or a sulfur protecting group; and

R^{n6} is hydrogen, an optionally substituted $–C_1$-C_6 alkyl, or a nitrogen protecting group; and

q is 0, 1, 2, or 3.

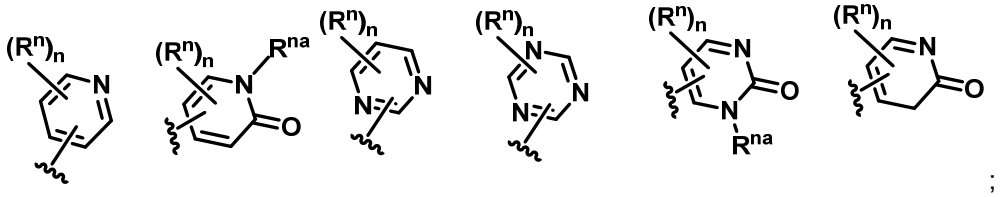
2. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein each instance of R^p is independently hydrogen, halogen, optionally substituted C_{1-4} alkyl, –CN, $–NO_2$, $–N_3$, $–OR^{o4}$, $–N(R^{n2})_2$, $–C(=O)N(R^{n2})_2$, $–C(=O)R^{c3}$, or $–C(=O)OR^{o4}$.

3. The compound according to claim 1 or 2 or a pharmaceutically acceptable salt thereof, wherein the 6-membered monocyclic heteroaryl represented by Q is selected from the following:



;

alternatively, wherein the 6-membered monocyclic heteroaryl represented by Q is selected from the following:



;

wherein:

each instance of R^n is independently hydrogen, a halogen, –CN, $–NO_2$, $–N_3$, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted aryl, an optionally substituted heterocyclyl, an optionally substituted heteroaryl, $–OR^{o4}$, $–SR^{s1}$, $–N(R^{n2})_2$, $–C(=O)N(R^{n2})_2$, $–N(R^{n2})C(=O)R^{c3}$, $–C(=O)R^{c3}$, $–C(=O)OR^{o4}$, $–OC(=O)R^{c3}$, $–S(=O)R^{s1}$, $–S(=O)_2R^{s1}$, $–S(=O)OR^{o4}$, $–OS(=O)R^{c3}$, $–S(=O)_2OR^{o4}$, $–OS(=O)_2R^{c3}$, $–S(=O)N(R^{n2})_2$, $–S(=O)_2N(R^{n2})_2$, $–N(R^{n2})S(=O)R^{s1}$, $–N(R^{n2})S(=O)_2R^{s1}$, $–N(R^{n2})C(=O)OR^{o4}$, $–OC(=O)N(R^{n2})_2$, $–N(R^{n2})C(=O)N(R^{n2})_2$, $–N(R^{n2})S(=O)N(R^{n2})_2$, $–N(R^{n2})S(=O)_2N(R^{n2})_2$, $–N(R^{n2})S(=O)OR^{o4}$, $–N(R^{n2})S(=O)_2OR^{o4}$, $–OS(=O)N(R^{n2})_2$, or $–OS(=O)_2N(R^{n2})_2$; or two instances of R^n attached to the same or adjacent carbon atoms, taken together with the

carbon atoms to which they are attached to form an optionally substituted cycloalkyl or a heterocycloalkyl; wherein:

each instance of R^{n2} is independently hydrogen, an optionally substituted $-C_1$-C_6 alkyl, or a nitrogen protecting group;

each instance of R^{o4} is independently hydrogen, an optionally substituted $-C_1$-C_6 alkyl, or an oxygen protecting group;

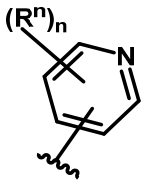
each instance of R^{c3} is independently an optionally substituted $-C_1$-C_6 alkyl;

each instance of R^{s1} is independently an optionally substituted $-C_1$-C_6 alkyl or a sulfur protecting group;

n is 0, 1, 2, or 3, as valency permits; and

each of R^{na}, R^{nb}, and R^{nd} is independently hydrogen, an optionally substituted $-C_1$-C_6 alkyl, or a nitrogen protecting group.

4. The compound according to any one of claims 1-3 or a pharmaceutically acceptable salt thereof, wherein the 5- or 6-membered monocyclic heteroaryl represented by Q is



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5. The compound according to claim 3 or 4 or a pharmaceutically acceptable salt thereof, wherein each instance of R^n is independently hydrogen, halogen, optionally substituted C_{1-4} alkyl, $-CN$, $-NO_2$, $-N_3$, $-OR^{o4}$, $-N(R^{n2})_2$, $-C(=O)N(R^{n2})_2$, $-C(=O)R^{c3}$, or $-C(=O)OR^{o4}$.

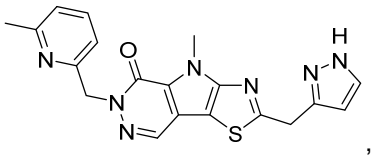
6. The compound according to any one of claims 1-5 or a pharmaceutically acceptable salt thereof, wherein R^1 is hydrogen or a $-C_1$-C_4 alkyl.

7. The compound according to any one of claims 1-6 or a pharmaceutically acceptable salt thereof, wherein R^j and R^k are each hydrogen.

8. The compound according to any one of claims 1-7 or a pharmaceutically acceptable salt thereof, wherein R^a and R^b are each hydrogen.

9. The compound according to any one of claims 2-8, or a pharmaceutically acceptable salt thereof, wherein q is 0 or 1, and n is 0 or 1.

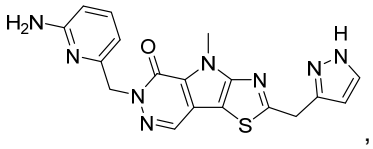
10. The compound according to claim 1, wherein the compound is:



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or a pharmaceutically acceptable salt thereof.

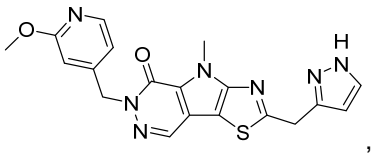
11. The compound according to claim 1, wherein the compound is:



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or a pharmaceutically acceptable salt thereof.

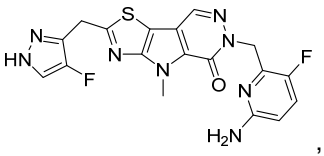
12. The compound according to claim 1, wherein the compound is:



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or a pharmaceutically acceptable salt thereof.

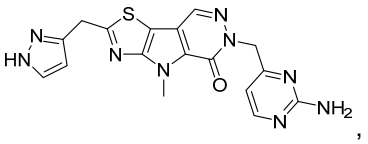
13. The compound according to claim 1, wherein the compound is:



,

or a pharmaceutically acceptable salt thereof.

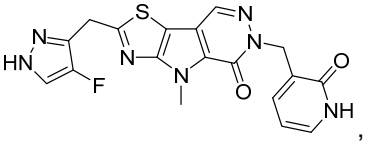
14. The compound according to claim 1, wherein the compound is:



,

or a pharmaceutically acceptable salt thereof.

15. The compound according to claim 1, wherein the compound is:



,

or a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition comprising an effective amount of the compound according to any one of claims 1-15 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

17. Use of a compound according to any one of claims 1-15, or a pharmaceutically acceptable salt thereof; or the pharmaceutical composition according to claim 16 for the manufacture of a medicament for treating anemia in a subject.

18. The use of claim 17, wherein the anemia is dyserythropoietic anemia.

19. Use of a compound according to any one of claims 1-15, or a pharmaceutically acceptable salt thereof; or the pharmaceutical composition according to claim 16 for the manufacture of a medicament for treating hemolytic anemia in a subject.

20. The use of claim 19, wherein the hemolytic anemia is hereditary and/or congenital hemolytic anemia, acquired hemolytic anemia, or anemia as part of a multi-system disease.

21. Use of a compound according to any one of claims 1-15, or a pharmaceutically acceptable salt thereof; or the pharmaceutical composition according to claim 16 for the manufacture of a medicament for treating sickle cell disease in a subject.

22. Use of a compound according to any one of claims 1-15, or a pharmaceutically acceptable salt thereof; or the pharmaceutical composition according to claim 16 for the manufacture of a medicament for treating pyruvate kinase deficiency (PKD) in a subject.

23. Use of a compound according to any one of claims 1-15, or a pharmaceutically acceptable salt thereof; or the pharmaceutical composition according to claim 16 for the manufacture of a medicament treating thalassemia, hereditary spherocytosis, hereditary elliptocytosis, abetalipoproteinemia or Bassen-Kornzweig syndrome, sickle cell disease, paroxysmal nocturnal hemoglobinuria, acquired hemolytic anemia, or anemia of chronic diseases in a subject.

24. The use of claim 23, wherein the thalassemia is beta-thalassemia.