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.

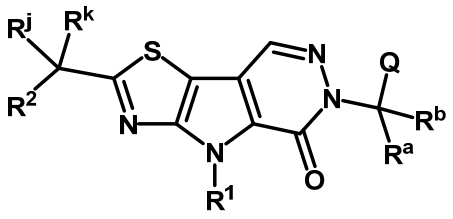
BACKGROUND

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, the present disclosure refers to a compound represented by the following structural formula:



(I)

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;

R^2 and Q are each independently an optionally substituted 5- or 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 $–C(=O)R^{c2}$; or alternatively R^a and R^b can be taken together with the carbon atom to which they are attached to form an optionally substituted cycloalkyl or an optionally substituted heterocyclyl; 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, an optionally substituted C_1-C_6 monocyclic cycloalkyl ring, or an optionally substituted C_3-C_6 monocyclic heterocyclyl ring; 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.

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 according to claim 31 for the manufacture of a medicament for increasing the lifetime of red blood cells (RBCs).

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 according to claim 31 for the manufacture of a medicament for regulating 2,3-diphosphoglycerate levels in blood.

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.

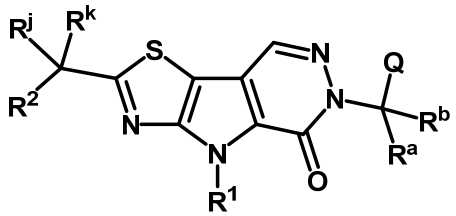
In another aspect, the present disclosure refers to a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof; or the pharmaceutical composition disclosed herein for the manufacture of a medicament for treating hemolytic anemia in a subject.

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)

wherein R^1, R^2, R^a, R^b, R^j, R^k, and Q are as defined herein.

In one example, the compound or pharmaceutically acceptable salt thereof is selected from the compounds of Table 1 or Figure 1.

Also provided are pharmaceutical compositions comprising a compound of Formulas (I)-(V), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The present disclosure further provides a method of treating anemia in a subject comprising administering to the subject an effective amount of (1) a compound described herein or a pharmaceutically acceptable salt thereof; (2) a pharmaceutically acceptable composition comprising a compound described herein or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In certain examples, the anemia is a dyserythropoietic anemia such as congenital dyserythropoietic anemia type I, II, III, or IV.

The present disclosure further provides a method for treating sickle cell disease in a subject comprising administering to the subject an effective amount of (1) a compound disclosed herein or a pharmaceutically acceptable salt thereof; (2) a pharmaceutical composition comprising a compound disclosed herein or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The present disclosure further provides a method for treating hemolytic anemia (*e.g.*, chronic hemolytic anemia caused by phosphoglycerate kinase deficiency, Blood Cells Mol Dis, 2011; 46(3):206) in a subject comprising administering to the subject an effective amount of (1) a compound disclosed herein or a pharmaceutically acceptable salt thereof; (2) a pharmaceutical composition comprising a compound disclosed herein or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In certain examples, the hemolytic anemia is hereditary and/or congenital hemolytic anemia, acquired hemolytic anemia, or anemia as part of a multi-system disease. In certain examples, the hemolytic anemia is congenital anemia. In certain examples, the hemolytic anemia is hereditary (*e.g.* non-spherocytic hemolytic anemia or hereditary spherocytosis).

The present disclosure further provides a method for treating thalassemia (*e.g.*, beta-thalassemia), hereditary spherocytosis, hereditary elliptocytosis, abetalipoproteinemia (or Bassen-Kornzweig syndrome), paroxysmal nocturnal hemoglobinuria, acquired hemolytic anemia (*e.g.*, congenital anemias (*e.g.*, enzymopathies)), sickle cell disease, or anemia of chronic diseases in a subject comprising administering to the subject an effective amount of (1) a compound disclosed herein or a pharmaceutically acceptable salt thereof; (2) a pharmaceutical composition comprising a compound disclosed herein or a pharmaceutically

acceptable salt thereof, and a pharmaceutically acceptable carrier. In one example, the acquired hemolytic anemia comprises congenital anemias. In certain examples, the provided method is to treat thalassemia. In certain examples, the thalassemia is beta-thalassemia.

The present disclosure further provides a method for treating pyruvate kinase deficiency (PKD) in a subject, the method comprising administering to the subject an effective amount of (1) a compound disclosed herein or a pharmaceutically acceptable salt thereof; (2) a pharmaceutical composition comprising a compound disclosed herein or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In certain examples, the PKD is a deficiency of PKR. In certain examples, the deficiency of PKR is associated with a pyruvate kinase R mutation.

Compounds and pharmaceutical compositions described herein are activators of PKR having lower activities compared to the wild type, thus are useful for methods of the present disclosure. In certain examples, the PKR is a wild type. In certain examples, the PKR is a mutant. Such mutations in PKR can affect enzyme activity (catalytic efficiency), regulatory properties (modulation by fructose bisphosphate (FBP)/ATP), and/or thermostability of the enzyme. Examples of such mutations are described in Valentini et al, JBC 2002. Some examples of the mutants that are activated by the compounds described herein include G332S, G364D, T384M, R479H, R479K, R486W, R532W, K410E, R510Q, and R490W. Without being bound by theory, in certain examples, the compounds described herein affect the activities of PKR mutants by activating FBP non-responsive PKR mutants, restoring thermostability to mutants with decreased stability, or restoring catalytic efficiency to impaired mutants. The activating activity of the present compounds against PKR mutants may be tested following a method described in the Examples. In certain examples, the compounds described herein are also activators of wild type PKR.

In an example, the disclosure provides a method for activating PKR in red blood cells in a subject in need thereof comprising administering to the subject an effective amount of (1) a compound disclosed herein or a pharmaceutically acceptable salt thereof; (2) a pharmaceutical composition comprising a compound disclosed herein or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In certain examples, the PKR is a wild type. In certain examples, the PKR is a mutant.

In an example, the mutant PKR is selected from G332S, G364D, T384M, K410E, R479H, R479K, R486W, R532W, R510Q, and R490W. In certain examples, the mutant PKR is selected from A468V, A495V, I90N, T408I, and Q421K, and R498H. In certain examples, the mutant PKR is R532W, K410E, or R510Q.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a listing of the structures of exemplary compounds of the invention.

Figure 2 shows synthesis of exemplary intermeidates used in Examples 1-10.

DETAILED DESCRIPTION OF THE INVENTION

The details of construction and the arrangement of components set forth in the following description or illustrated in the drawings are not meant to be limiting. Embodiments can be practiced or carried out in various ways. The phraseology and terminology used herein is for purpose of description and shouldn't be regarded as limiting.

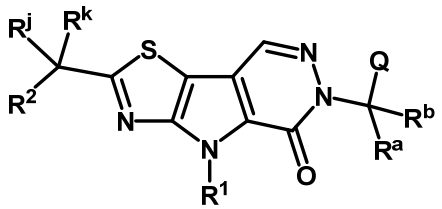
Definitions

Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various stereoisomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques et al., Enantiomers, Racemates and Resolutions (Wiley Interscience, New York, 1981); Wilen et al., Tetrahedron 33:2725 (1977); Eliel, E.L. Stereochemistry of Carbon Compounds (McGraw-Hill, NY, 1962); and Wilen, S.H. Tables of Resolving Agents and Optical Resolutions p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972).

The compounds described herein may also be represented in multiple tautomeric forms, in such instances, expressly includes all tautomeric forms of the compounds described herein, even though only a single tautomeric form may be represented (*e.g.*, alkylation of a ring system may result in alkylation at multiple sites; all such reaction products are expressly included). All such isomeric forms of such compounds are expressly included. If a tautomer of a compound is aromatic, this compound is aromatic. Similarly, if a tautomer of a substitutent is a heteroaryl, this substituent is heteroaryl.

CLAIMS

1. A compound represented by the following structural formula:



(I)

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;

R^2 and Q are each independently an optionally substituted 5- or 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 $–C(=O)R^{c2}$; or alternatively R^a and R^b can be taken together with the carbon atom to which they are attached to form an optionally substituted cycloalkyl or an optionally substituted heterocyclyl; 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, an optionally substituted C_1-C_6 monocyclic cycloalkyl ring, or an optionally substituted C_3-C_6 monocyclic heterocyclyl ring; 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.

2. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein the 5- or 6-membered monocyclic heteroaryl represented by R^2 is optionally substituted at each substitutable ring carbon atom by R^p and optionally substituted at each substitutable ring nitrogen atom by R^{n6}; wherein:

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;

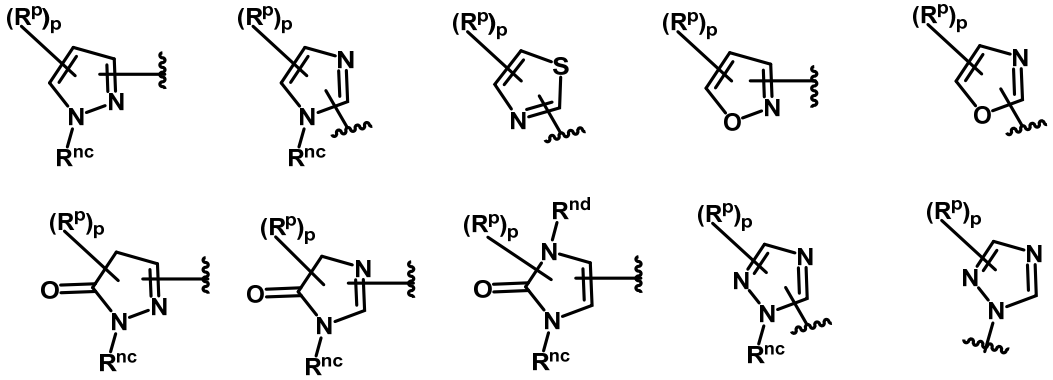
each instance of R^{o6} is independently hydrogen, an optionally substituted $–C_1$-C_6 alkyl, or an oxygen protecting group; and

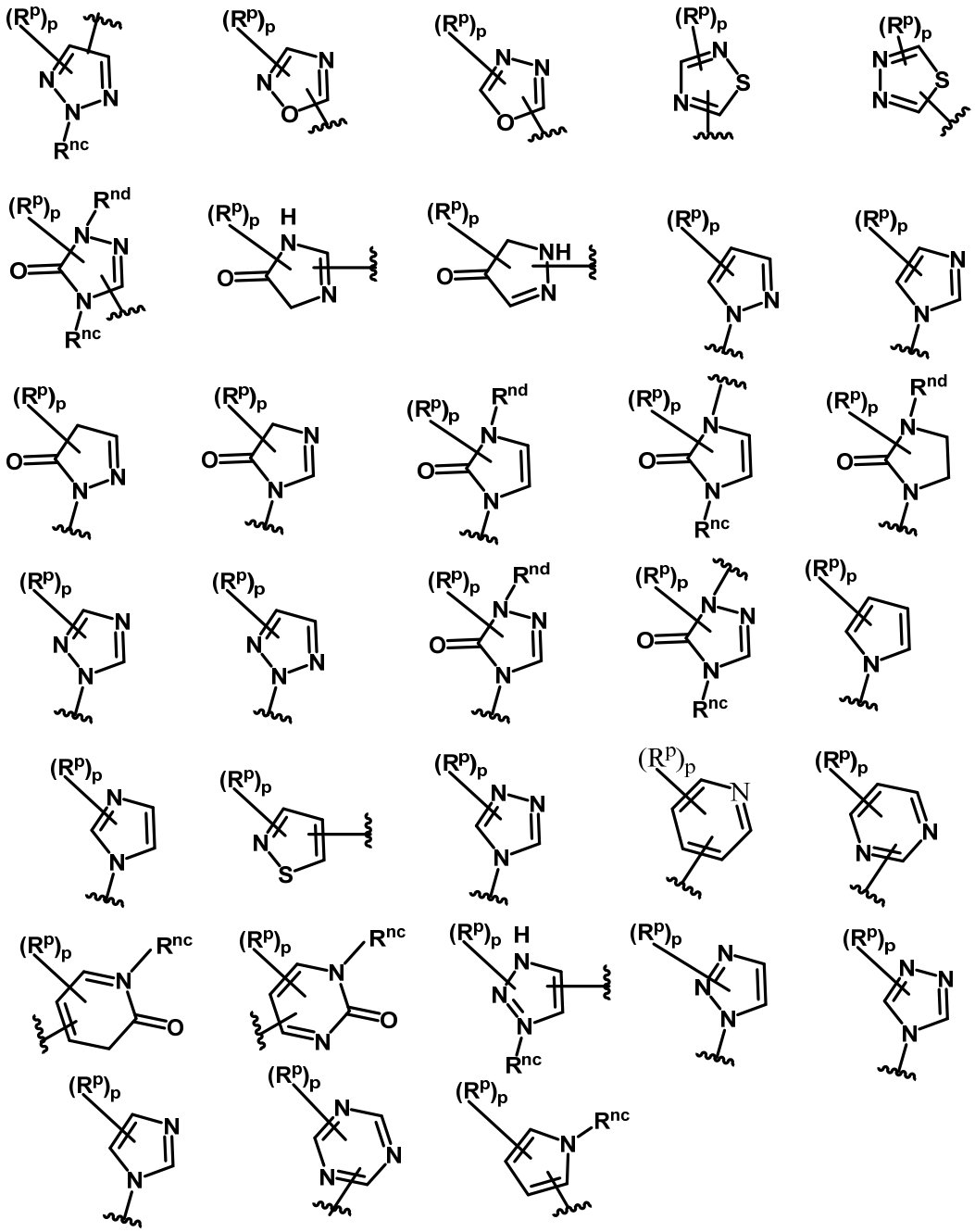
each instance of R^{c4} is an optionally substituted $–C_1$-C_6 alkyl;

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.

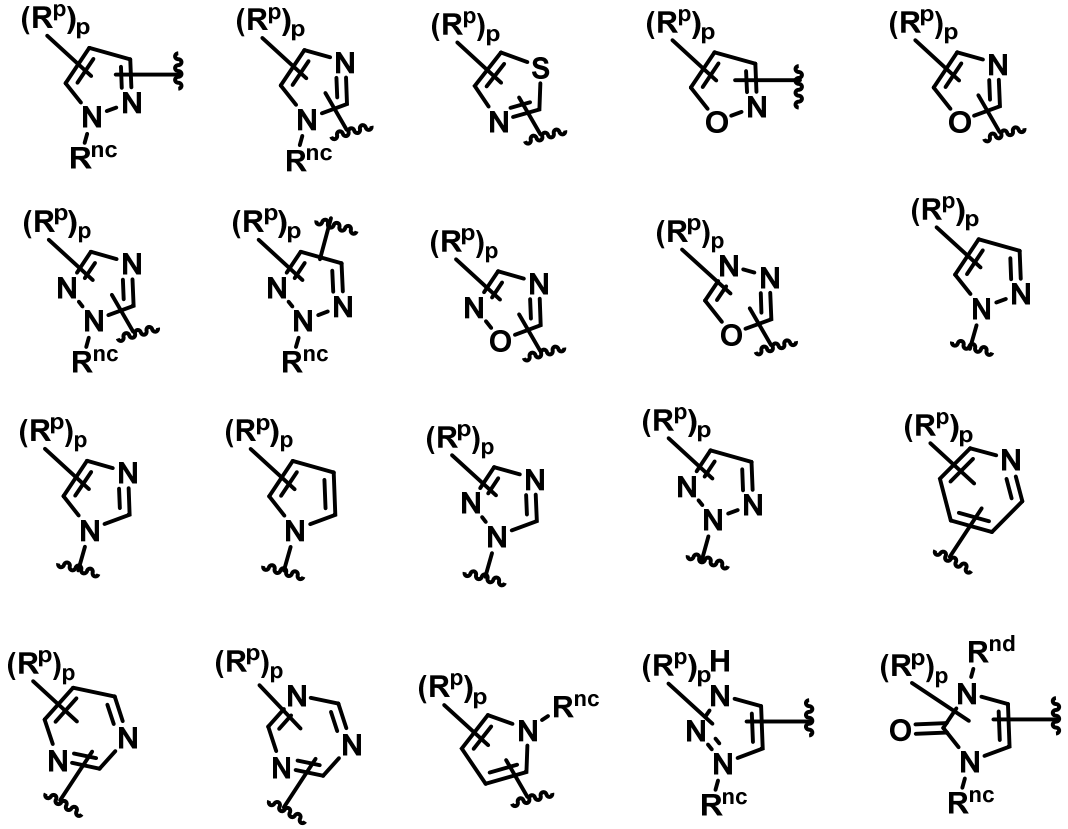
3. The compound according to any one of claims 1 and 2 or a pharmaceutically acceptable salt thereof, wherein the 5- or 6-membered monocyclic heteroaryl represented by R^2 is selected from one of the following:





;

alternatively, wherein the 5- or 6-membered monocyclic heteroaryl represented by R^2 is selected from one of the following:



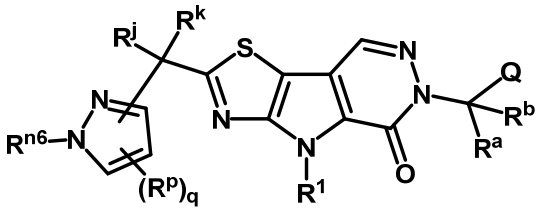
;

wherein:

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

p is 0, 1, 2, 3, or 4, as valency permits.

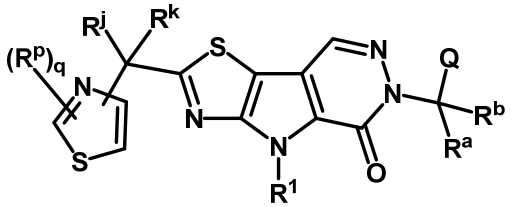
4. The compound according to any one of claims 1-3, wherein the compound is represented by the following structural formula:



(II)

or a pharmaceutically acceptable salt thereof, wherein q is 0, 1, 2, or 3.

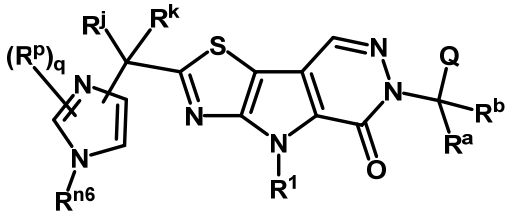
5. The compound according to any one of claims 1-3, wherein the compound is represented by the following structural formula:



(III)

or a pharmaceutically acceptable salt thereof, wherein q is 0, 1, 2, or 3.

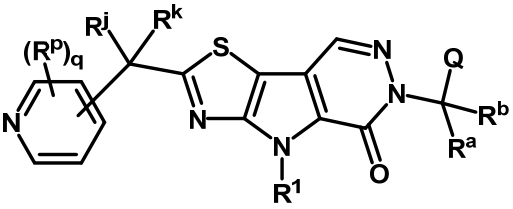
6. The compound according to any one of claims 1-3, wherein the compound is represented by the following structural formula:



(IV)

or a pharmaceutically acceptable salt thereof, wherein q is 0, 1, 2, or 3.

7. The compound according to any one of claims 1-3, wherein the compound is represented by the following structural formula:

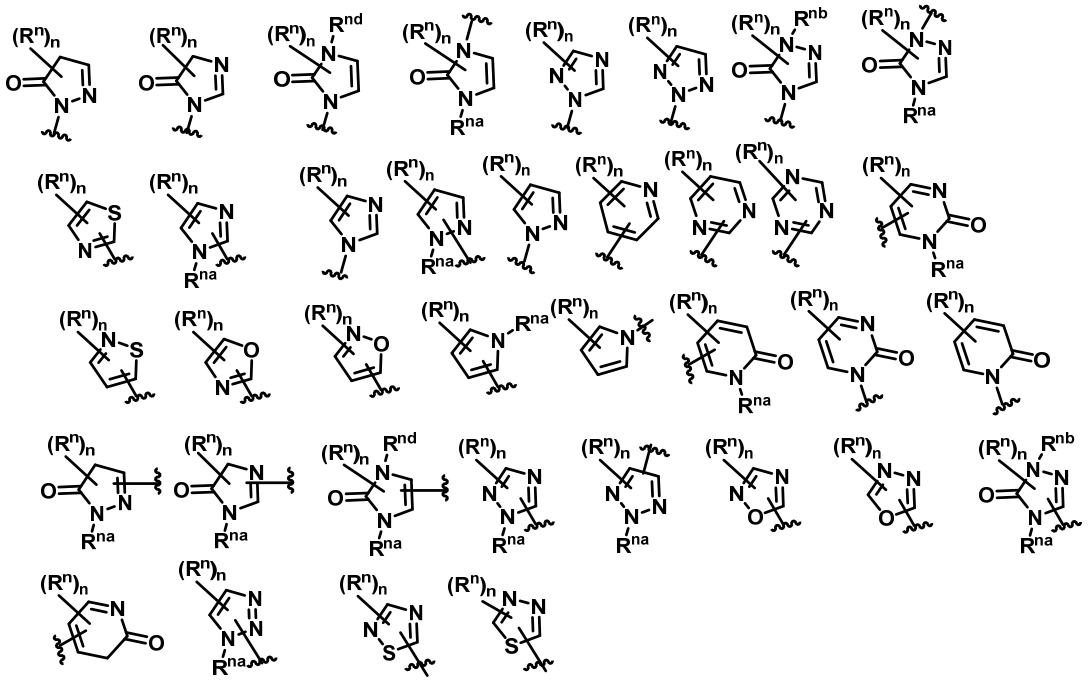


(V)

or a pharmaceutically acceptable salt thereof, wherein q is 0, 1, 2, or 3.

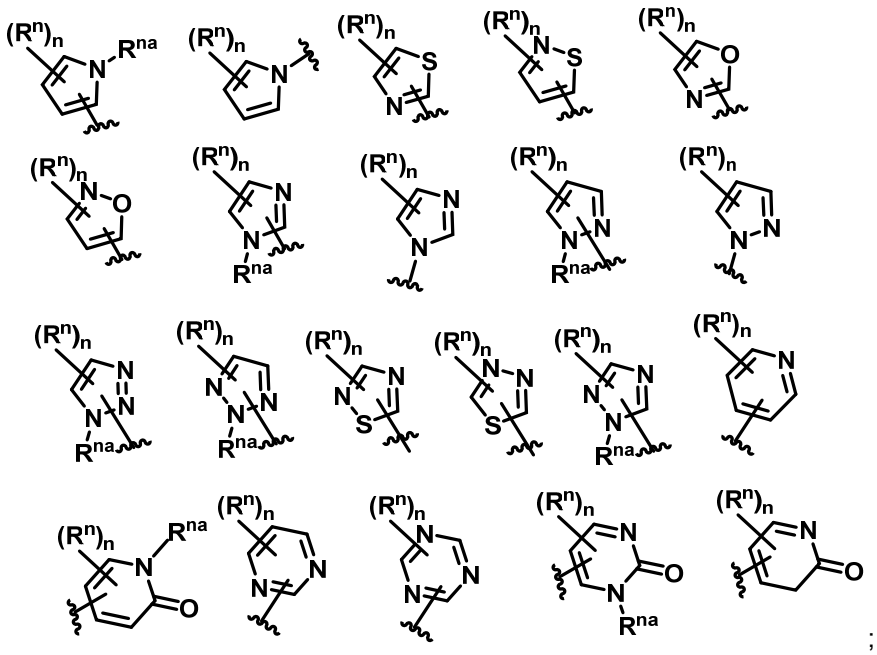
8. The compound according to any one of claims 2-7 or a pharmaceutically acceptable salt thereof, wherein each instance of R^p is independently hydrogen, halogen, optionally substituted C_{1-4} alkyl, −CN,−NO_2,−N_3, –OR^{o4}, –$N(R^{n2})_2$, –$C(=O)N(R^{n2})_2$, –$C(=O)R^{c3}$, or –$C(=O)OR^{o4}$.

9. The compound according to any one of claims 1-8 or a pharmaceutically acceptable salt thereof, wherein the 5- or 6-membered monocyclic heteroaryl represented by Q is selected from the following:



;

alternatively, wherein the 5- or 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;

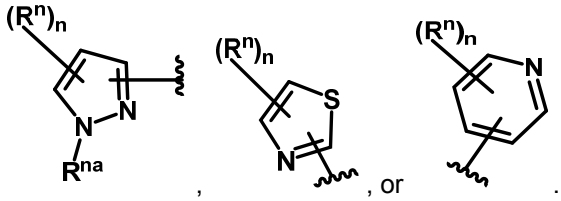
each instance of R^{c3} is independently an optionally substituted $-C_1$-C_6 alkyl;

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.

10. The compound according to any one of claims 1-9 or a pharmaceutically acceptable salt thereof, wherein the 5- or 6-membered monocyclic heteroaryl represented by Q is



, , or .

11. The compound according to claim 9 or 10 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 –$C(=O)OR^{o4}$.

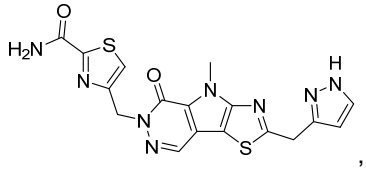
12. The compound according to any one of claims 1-11 or a pharmaceutically acceptable salt thereof, wherein R^1 is hydrogen or a $-C_1$-C_4 alkyl.

13. The compound according to any one of claims 1-12 or a pharmaceutically acceptable salt thereof, wherein R^j and R^k are each hydrogen.

14. The compound according to any one of claims 1-13 or a pharmaceutically acceptable salt thereof, wherein R^a and R^b are each hydrogen.

15. The compound according to any one of claims 3-14, wherein q is 0 or 1, and n is 0 or 1.

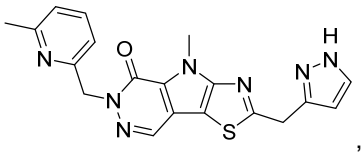
16. The compound according to claim 1, wherein the compound is:



,

or a pharmaceutically acceptable salt thereof.

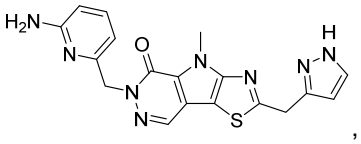
17. The compound according to claim 1, wherein the compound is:



,

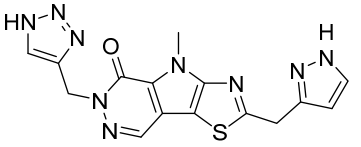
or a pharmaceutically acceptable salt thereof.

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


,

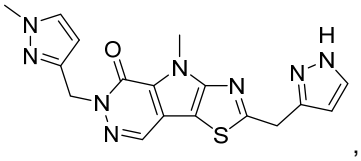
or a pharmaceutically acceptable salt thereof.

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


,

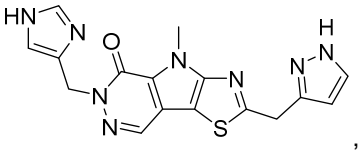
or a pharmaceutically acceptable salt thereof.

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


,

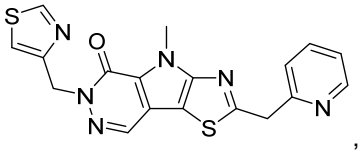
or a pharmaceutically acceptable salt thereof.

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


,

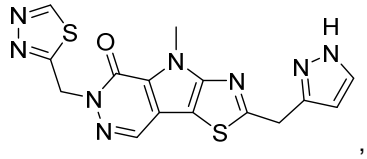
or a pharmaceutically acceptable salt thereof.

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


,

or a pharmaceutically acceptable salt thereof.

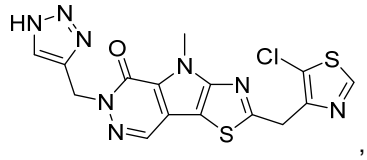
23. The compound according to claim 1, wherein the compound is:



,

or a pharmaceutically acceptable salt thereof.

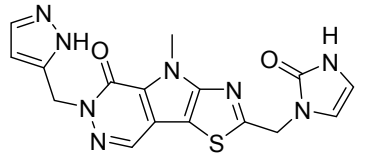
24. The compound according to claim 1, wherein the compound is:



,

or a pharmaceutically acceptable salt thereof.

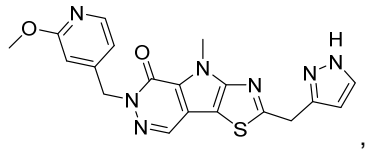
25. The compound according to claim 1, wherein the compound is:



,

or a pharmaceutically acceptable salt thereof.

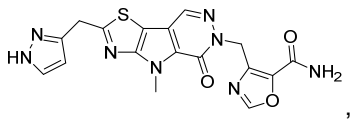
26. The compound according to claim 1, wherein the compound is:



,

or a pharmaceutically acceptable salt thereof.

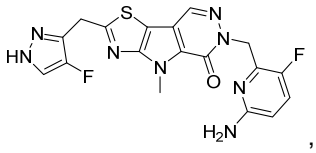
27. The compound according to claim 1, wherein the compound is:



,

or a pharmaceutically acceptable salt thereof.

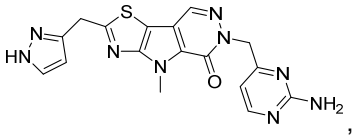
28. The compound according to claim 1, wherein the compound is:



,

or a pharmaceutically acceptable salt thereof.

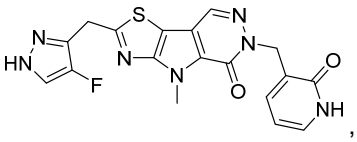
29. The compound according to claim 1, wherein the compound is:



,

or a pharmaceutically acceptable salt thereof.

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



,

or a pharmaceutically acceptable salt thereof.

31. A pharmaceutical composition comprising an effective amount of the compound according to any one of claims 1-30 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

32. Use of a compound according to any one of claims 1-30, or a pharmaceutically acceptable salt thereof; or the pharmaceutical composition according to claim 31 for the manufacture of a medicament for increasing the lifetime of red blood cells (RBCs).

33. Use of a compound according to any one of claims 1-30, or a pharmaceutically acceptable salt thereof; or the pharmaceutical composition according to claim 31 for the manufacture of a medicament for regulating 2,3-diphosphoglycerate levels in blood.

34. Use of a compound according to any one of claims 1-30, or a pharmaceutically acceptable salt thereof; or the pharmaceutical composition according to claim 31 for the manufacture of a medicament for treating anemia in a subject.

35. The use of claim 34, wherein the anemia is dyserythropoietic anemia.

36. Use of a compound according to any one of claims 1-30, or a pharmaceutically acceptable salt thereof; or the pharmaceutical composition according to claim 31 for the manufacture of a medicament for treating hemolytic anemia in a subject.

37. The use of claim 36, wherein the hemolytic anemia is hereditary and/or congenital hemolytic anemia, acquired hemolytic anemia, or anemia as part of a multi-system disease.

38. Use of a compound according to any one of claims 1-30, or a pharmaceutically acceptable salt thereof; or the pharmaceutical composition according to claim 31 for the manufacture of a medicament for treating sickle cell disease in a subject.

39. Use of a compound according to any one of claims 1-30, or a pharmaceutically acceptable salt thereof; or the pharmaceutical composition according to claim 31 for the manufacture of a medicament for treating pyruvate kinase deficiency (PKD) in a subject.

40. Use of a compound according to any one of claims 1-30, or a pharmaceutically acceptable salt thereof; or the pharmaceutical composition according to claim 31 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.

41. The use of claim 40, wherein the thalassemia is beta-thalassemia.