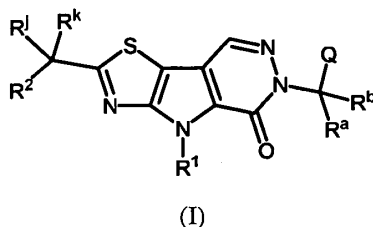


CLAIMS

1. A compound represented by the following structural formula:



- 5 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:
- 10 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
- 15 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:
- 20 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
- 25 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
- 30 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;

5 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

10 each instance of R^{j5} 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
15 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
20 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
25 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
30 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

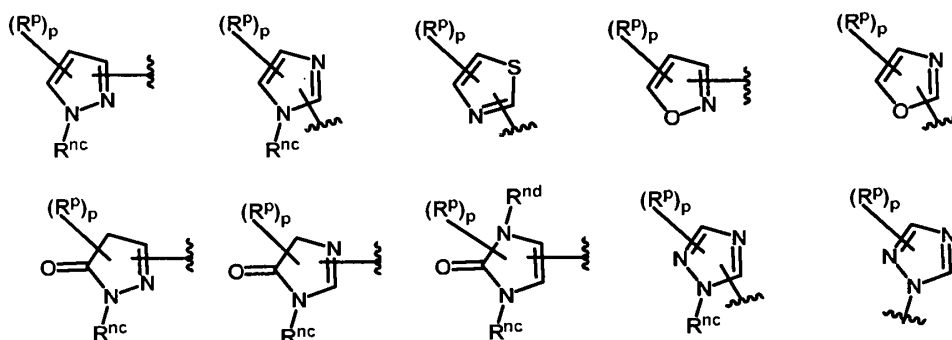
each instance of R^{c4} is an optionally substituted $-C_1-C_6$ alkyl;

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

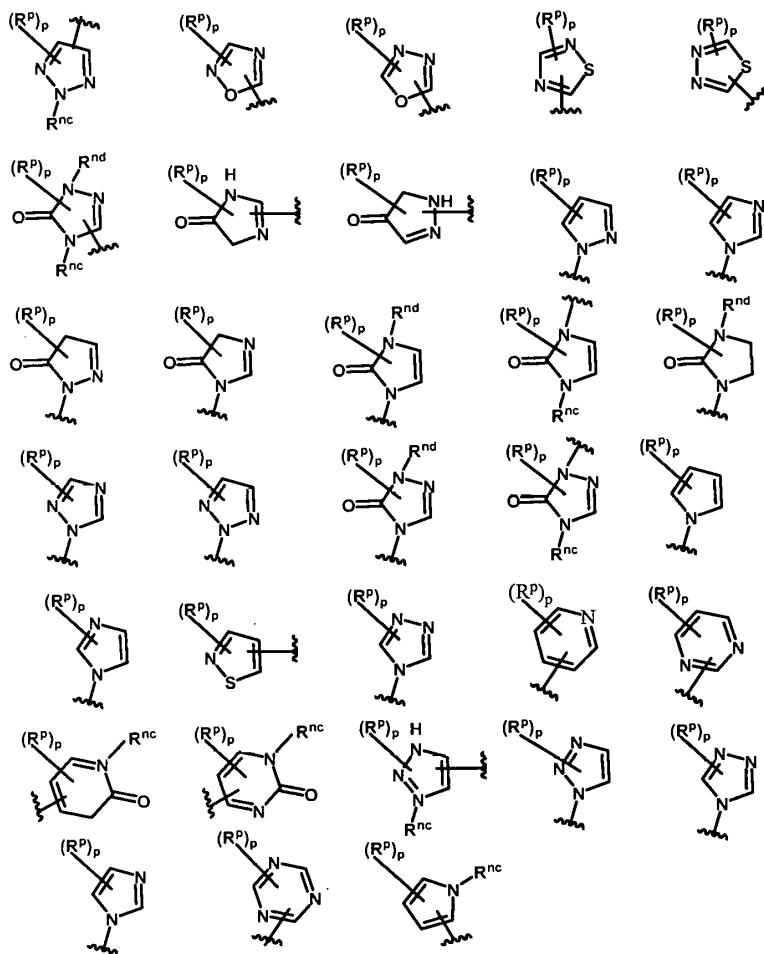
R^{n6} is hydrogen, an optionally substituted $-C_1-C_6$ alkyl, or a nitrogen protecting group.

5

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:



10

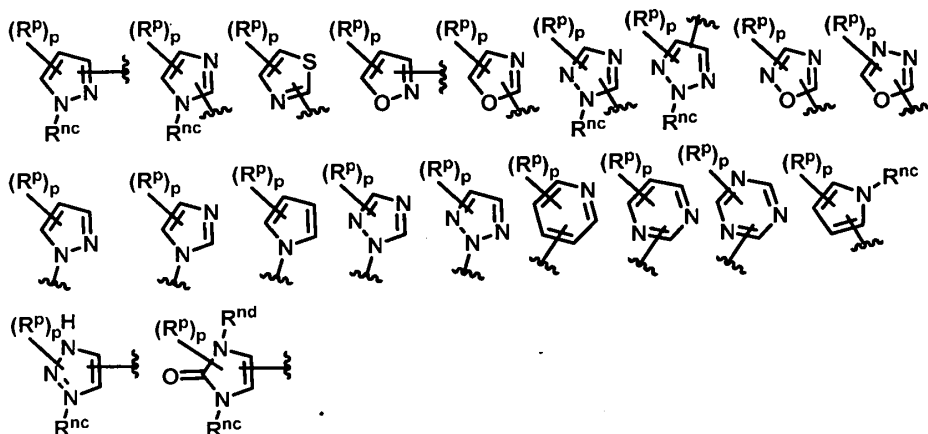


wherein:

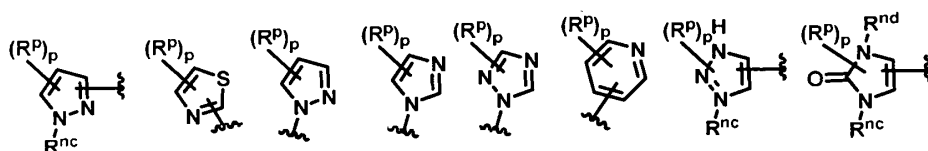
each instance of R^{nc} and R^{nd} is independently hydrogen, optionally substituted $-C_1-C_6$ alkyl, or a nitrogen protecting group; and

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

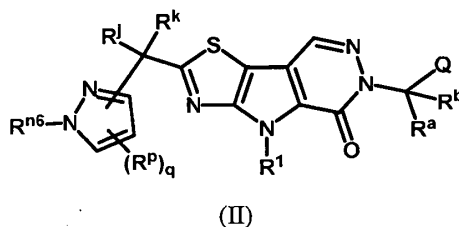
4. The compound according to any one of claims 1-3 or a pharmaceutically acceptable salt thereof, wherein the 5- or 6-membered monocyclic heteroaryl represented by R^2 is selected from one of the following:



5. The compound according to any one of claims 1-4 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:

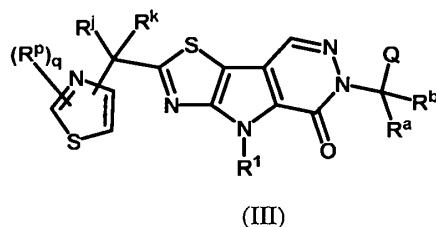


6. The compound according to any one of claims 1-5, wherein the compound is represented by the following structural formula:



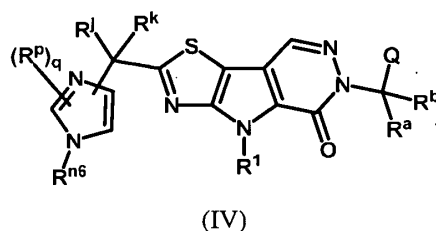
or a pharmaceutically acceptable salt thereof, wherein q is 0, 1, 2, or 3.

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



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

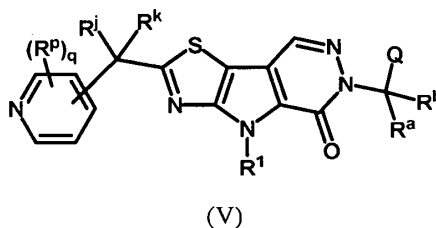
8. The compound according to any one of claims 1-5, wherein the compound is represented by the following structural formula:



10

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

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



15

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

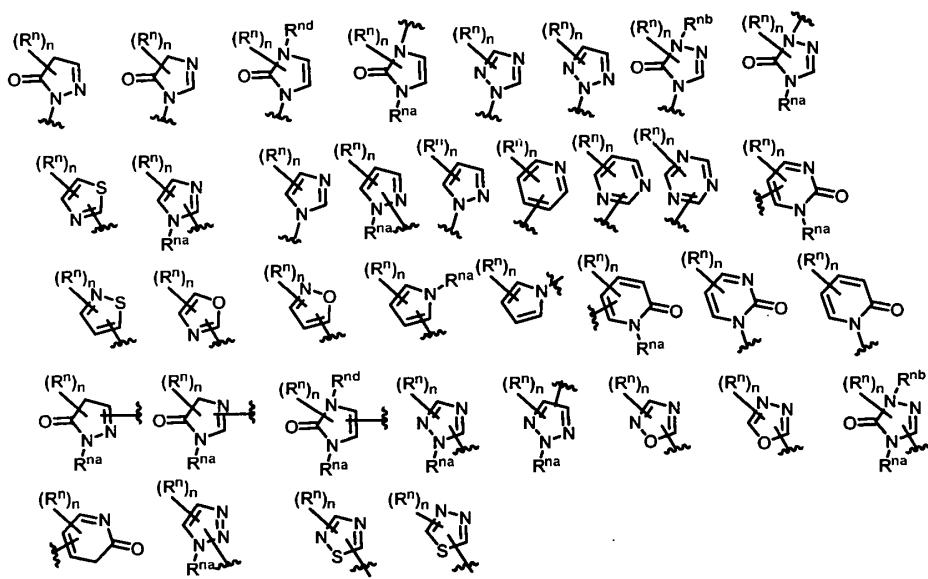
10. The compound according to any one of claims 2-9 or a pharmaceutically acceptable salt thereof, wherein Rⁿ⁶ is hydrogen or a -C₁₋₄ alkyl.

20

11. 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 $-C(=O)OR^{o4}$.

5

12. The compound according to any one of claims 1-11 or a pharmaceutically acceptable salt thereof, wherein the 5- or 6-membered monocyclic heteroaryl represented by Q is selected from the following:



10 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

15

20

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;

5 each instance of R^{n4} is independently hydrogen, an optionally substituted $-C_1-C_6$ alkyl, or an oxygen protecting group;

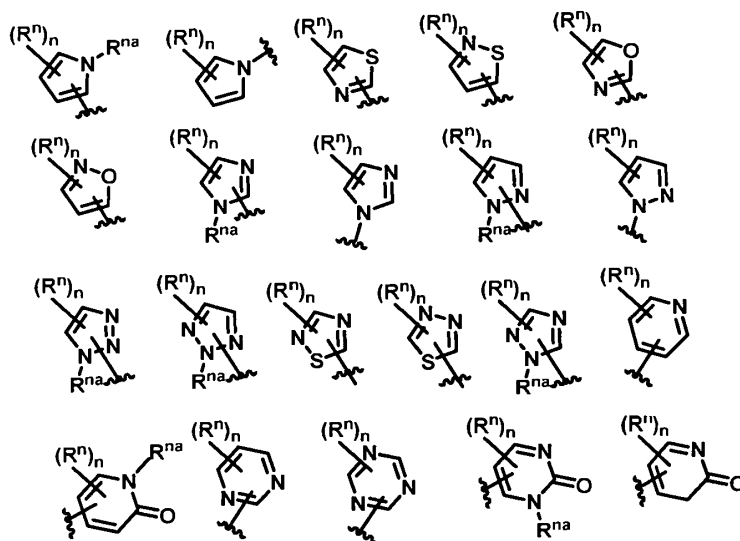
each instance of R^{n3} is independently an optionally substituted $-C_1-C_6$ alkyl;

10 each instance of R^{n1} 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

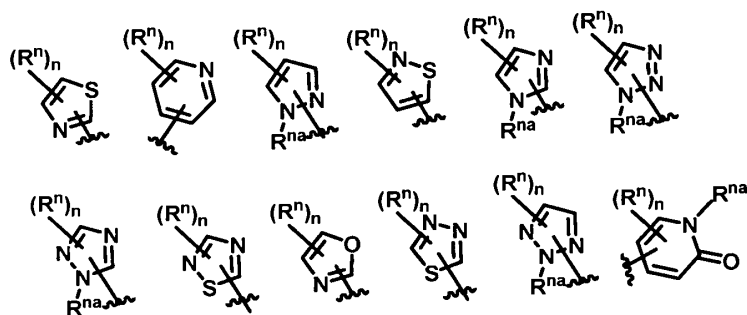
each of R^{na} , R^{nb} , and R^{nd} is independently hydrogen, an optionally substituted $-C_1-C_6$ alkyl, or a nitrogen protecting group.

15 13. The compound according to any one of claims 1-12 or a pharmaceutically acceptable salt thereof, wherein the 5- or 6-membered monocyclic heteroaryl represented by Q is selected from the following:



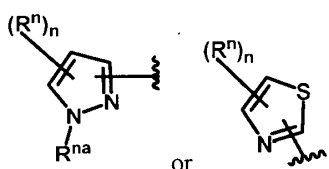
20

14. The compound according to any one of claims 1-13 or a pharmaceutically acceptable salt thereof, wherein the 5- or 6-membered monocyclic heteroaryl represented by Q is selected from the following:

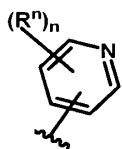


5

15. The compound according to any one of claims 1-14 or a pharmaceutically acceptable salt thereof, wherein the 5- or 6-membered monocyclic heteroaryl represented by Q is



10 16. The compound according to any one of claims 1-14 or a pharmaceutically acceptable salt thereof, wherein the 5- or 6-membered monocyclic heteroaryl represented by Q is



17. The compound according to any one of claims 12-15 or a pharmaceutically acceptable salt thereof, wherein R^{na} is hydrogen or $-C_{1-4}$ alkyl.

18. The compound according to any one of claims 12-17 or a pharmaceutically acceptable salt thereof, wherein each instance of R^n is independently hydrogen, halogen, optionally substituted C_{1-4} alkyl, $-CN$, $-NO_2$, $-N_3$, $-OR^{o4}$, $-N(R^{n2})_2$,
 20 $-C(=O)N(R^{n2})_2$, $-C(=O)R^{c3}$, or $-C(=O)OR^{o4}$.

19. The compound according to any one of claims 1-18 or a pharmaceutically acceptable salt thereof, wherein R¹ is hydrogen or a -C₁-C₄ alkyl.
20. The compound according to any one of claims 1-19 or a pharmaceutically acceptable salt thereof, wherein R¹ is methyl.
21. The compound according to any one of claims 1-20 or a pharmaceutically acceptable salt thereof, wherein R^j and R^k are each independently hydrogen, a halogen, -OR^{o7}, or a -C₁-C₄ alkyl, or R^j and R^k are joined together to form =O.
22. The compound according to any one of claims 1-21 or a pharmaceutically acceptable salt thereof, wherein R^j and R^k are each hydrogen.
23. The compound according to any one of claims 1-22 or a pharmaceutically acceptable salt thereof, wherein R^a and R^b are each hydrogen.
24. The compound according to any one of claims 5-23, wherein q is 0 or 1.
25. The compound according to any one of claims 12-24, wherein n is 0 or 1.
26. A pharmaceutical composition comprising an effective amount of the compound according to any one of claims 1-25 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
27. A method for increasing the lifetime of red blood cells (RBCs) comprising contacting the red blood cells with an effective amount of (1) the compound according to any one of claims 1-25 or a pharmaceutically acceptable salt thereof; or (2) the pharmaceutical composition according to claim 26.
28. The method of claim 27, wherein the compound or the pharmaceutical composition is added directly to whole blood comprising the red blood cells or packed red blood cells comprising the red blood cells extracorporeally.

29. The method of claim 28, wherein the compound or the pharmaceutical composition is administered to a subject comprising the red blood cells.

30. A method for regulating 2,3-diphosphoglycerate levels in blood comprising
5 contacting the blood with an effective amount of (1) the compound according to any one of claims 1-25 or a pharmaceutically acceptable salt thereof; or (2) the pharmaceutical composition according to claim 26.

31. A method for treating anemia in a subject comprising administering to the subject an
10 effective amount of (1) the compound according to any one of claims 1-25 or a pharmaceutically acceptable salt thereof; or (2) the pharmaceutical composition according to claim 26.

32. The method of claim 31, wherein the anemia is dyserythropoietic anemia.
15

33. A method for treating hemolytic anemia in a subject comprising administering to the subject an effective amount of (1) the compound according to any one of claims 1-25 or a pharmaceutically acceptable salt thereof; or (2) the pharmaceutical composition according to claim 26.
20

34. The method of claim 33, wherein the hemolytic anemia is hereditary and/or congenital hemolytic anemia, acquired hemolytic anemia, or anemia as part of a multi-system disease.

25 35. A method for treating sickle cell disease in a subject comprising administering to the subject an effective amount of (1) the compound according to any one of claims 1-25 or a pharmaceutically acceptable salt thereof; or (2) the pharmaceutical composition according to claim 26.

30 36. A method of treating pyruvate kinase deficiency (PKD) in a subject comprising administering to the subject an effective amount of (1) the compound according to any one of claims 1-25 or a pharmaceutically acceptable salt thereof; or (2) the pharmaceutical composition according to claim 26.

37. A method of 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 comprising administering to the subject an effective amount of (1) the compound
5 according to any one of claims 1-25 or a pharmaceutically acceptable salt thereof; or (2) the pharmaceutical composition according to claim 26.
38. A method of treating thalassemia in a subject comprising administering to the subject an effective amount of (1) the compound according to any one of claims 1-25 or a
10 pharmaceutically acceptable salt thereof; or (2) the pharmaceutical composition according to claim 26.
39. The method of claim 38, wherein the thalassemia is beta-thalassemia.
- 15 40. A method for activating mutant pyruvate kinase R (PKR) in red blood cells in a subject in need thereof comprising administering to the subject an effective amount of (1) the compound according to any one of claims 1-25 or a pharmaceutically acceptable salt thereof; or (2) the pharmaceutical composition according to claim 26.
- 20 41. A method for activating wild-type pyruvate kinase R (PKR) in red blood cells in a subject in need thereof comprising administering to the subject an effective amount of (1) the compound according to any one of claims 1-25 or a pharmaceutically acceptable salt thereof; or (2) the pharmaceutical composition according to claim 26.
- 25 42. A method of increasing amount of hemoglobin in a subject in need thereof comprising administering to the subject an effective amount of (1) the compound according to any one of claims 1-25 or a pharmaceutically acceptable salt thereof; or (2) the pharmaceutical composition according to claim 26.

30