majority of "normal" cells in adult tissues utilize aerobic respiration. This fundamental difference in cellular metabolism between cancer cells and normal cells, termed the Warburg Effect, has been exploited for diagnostic purposes, but has not yet been exploited for therapeutic benefit.

Pyruvate kinase (PK) is a metabolic enzyme that converts phosphoenolpyruvate to pyruvate during glycolysis. Four PK isoforms exist in mammals: the L and R isoforms are expressed in liver and red blood cells, the M1 isoform is expressed in most adult tissues, and the M2 isoform is a splice variant of M1 expressed during embryonic development. All tumor cells exclusively express the embryonic M2 isoform. A well-known difference between the M1 and M2 isoforms of PK is that M2 is a low-activity enzyme that relies on allosteric activation by the upstream glycolytic intermediate, fructose-1,6-bisphosphate (FBP), whereas M1 is a constitutively active enzyme.

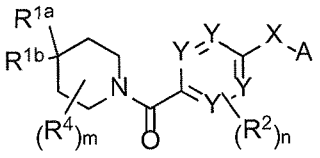
All tumor cells exclusively express the embryonic M2 isoform of pyruvate kinase, suggesting PKM2 as a potential target for cancer therapy. PKM2 is also expressed in adipose tissue and activated T-cells. Phosphotyrosine peptide binding to PKM2 leads to a dissociation of FBP from PKM2 and conformational changes of PKM2 from an active, tetrameric form to an inactive form. Compounds that bind to PKM2 and lock the enzyme in the active confirmation will lead to the loss of allosteric control of PKM2 needed for shunting biochemical intermediates from glycolysis into biosynthesis of nucleotides and lipids. Thus, the activation of PKM2 can inhibit the growth and proliferation of cancer cells, activated immune cells, and fat cells. Activation of PKM2 may therefore be effective in the treatment of cancer, obesity, diabetes, autoimmune conditions, and proliferation-dependent diseases, e.g., benign prostatic hyperplasia (BPH).

SUMMARY ~~OF INVENTION~~

Described herein are compounds that activate pyruvate kinase and pharmaceutically acceptable salts, solvates, and hydrates thereof, for example, compounds that activate PKR and/or PKM2.

Also provided are pharmaceutical compositions comprising a compound provided herewith and the use of such compositions in methods of treating diseases and conditions that are related to pyruvate kinase function, e.g., PKR function, and/or PKM2 function (including, e.g., cancer, diabetes, obesity, autoimmune disorders, and benign prostatic hyperplasia (BPH)).

In one ~~embodiment~~aspect, there is provided ~~herein is~~ a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein:



(I)~~, or a pharmaceutically acceptable salt thereof, wherein:~~

A is aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted, and the aryl or heteroaryl is optionally fused to an optionally substituted carbocyclyl or an optionally substituted heterocyclyl;

X is selected from –NH-$S(O)_2$-, -$S(O)_2$-NH-, -NH-$S(O)_2$-CH_2-, -CH_2-S(O)-NH-, -NH-S(O)-CH_2-, -NH-S(O)-, -S(O)-NH-, and~~or~~ –CH_2-$S(O)_2$-NH-;

Y is C(H) or N; provided that no more than two Y groups are N;

R^{1a} is selected from hydroxyl, -CH_2OH, –CHO, –CO_2H, -$N(R^{10a})_2$, –CO_2-C_{1-6} alkyl, -OP(=O)$(OH)_2$, and~~or~~ -OCO_2-CH_2-OP(=O)$(OH)_2$;

R^{1b} is selected from C_{1-8} alkyl optionally substituted with one to four R^5 groups; C_{1-8} alkenyl optionally substituted with one to four R^5 groups; cycloalkyl; heterocycle; aryl; heteroaryl; cycloalkylalkyl; cycloalkylalkenyl; heterocyclylalkyl; heterocyclylalkenyl; aralkyl; aralkenyl; heteroaralkyl; heteroaralkenyl; ~~or~~and –OH, with the proviso that when R^{1a} is OH, R^{1b} is not OH; wherein each cycloalkyl, heterocycle, aryl, heteroaryl, cycloalkylalkyl, cycloalkylalkenyl, heterocyclylalkyl, heterocyclylalkenyl, aralkyl, aralkenyl, heteroaralkyl, or heteroaralkenyl is optionally substituted;

each R^2 is independently selected from halo, alkyl, CN, OH, and alkoxy, wherein said alkyl or alkoxy is optionally substituted with one to four R^5 groups; or two adjacent R^2 groups are taken together with the ring atoms they are attached to form a 5- or 6-membered carbocyclic, aryl, heterocyclic or heteroaryl ring;

each R^4 is independently selected from halo, alkyl, alkoxy, haloalkyl, haloalkoxy and hydroxyl;

each R^5 is independently selected from halo, OH, C_{1-6} alkoxy, CN, NH_2, -SO_2-C_{1-6} alkyl, -NH(C_{1-6} alkyl), and –N(C_{1-6} alkyl)$_2$;

each R^{10a} is independently selected from hydrogen ~~or~~and C_{1-6} alkyl;

n is 0, 1, 2 or 3; and

m is 0, 1 or 2; provided that a compound of Formula (I) is not the following:

(1) 4-[[4-hydroxy-4-(4-methylphenyl)-1-piperidinyl]carbonyl]-N-2-thiazolyl-benzenesulfonamide;

(2) 4-[[4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl]carbonyl]-N-2-thiazolyl-benzenesulfonamide;

(3) 4-[[4-(3-fluorophenyl)-4-hydroxy-1-piperidinyl]carbonyl]-N-2-thiazolyl-benzenesulfonamide;

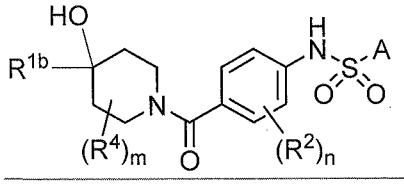
(4) 4-[[4-(2-fluoro-5-methylphenyl)-4-hydroxy-1-piperidinyl]carbonyl]-N-2-thiazolyl- benzenesulfonamide;

(5) 4-phenyl-1-[4-[(phenylamino)sulfonyl]benzoyl]-4-piperidinecarboxylic acid methyl ester;

(6) 1-[4-[[(2-methylphenyl)amino]sulfonyl]benzoyl]-4-phenyl-4-piperidinecarboxylic acid methyl ester; or

(7) N-(4-fluorophenyl)-4-[[4-hydroxy-4-(methoxymethyl)-1-piperidinyl]carbonyl]-benzenesulfonamide.

In one aspect, there is provided a compound of Formula (Ib) or a pharmaceutically acceptable salt thereof, wherein:



(Ib),

A is aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted, and the aryl or heteroaryl is fused to an optionally substituted carbocyclyl or an optionally substituted heterocyclyl;

R^{1b} is selected from C_{1-8} alkyl optionally substituted with one to four R^5 groups; C_{1-8} alkenyl optionally substituted with one to four R^5 groups; cycloalkyl; heterocycle; aryl; heteroaryl; cycloalkylalkyl; cycloalkylalkenyl; heterocyclylalkyl;

heterocyclylalkenyl; aralkyl; aralkenyl; heteroaralkyl; heteroaralkenyl; and –OH, with the proviso that when R^{1a} is OH, R^{1b} is not OH; wherein each cycloalkyl, heterocycle, aryl, heteroaryl, cycloalkylalkyl, cycloalkylalkenyl, heterocyclylalkyl, heterocyclylalkenyl, aralkyl, aralkenyl, heteroaralkyl, or heteroaralkenyl is optionally substituted;

each R^2 is independently selected from halo, alkyl, CN, OH, and alkoxy, wherein said alkyl or alkoxy is optionally substituted with one to four R^5 groups; or

two adjacent R^2 groups are taken together with the ring atoms they are attached to form a 5- or 6-membered carbocyclic, aryl, heterocyclic or heteroaryl ring;

each R^4 is independently selected from halo, alkyl, alkoxy, haloalkyl, haloalkoxy and hydroxyl;

each R^5 is independently selected from halo, OH, C_{1-6} alkoxy, CN, NH_2, $-SO_2-C_{1-6}$ alkyl, $-NH(C_{1-6}$ alkyl), and $-N(C_{1-6}$ alkyl$)_2$;

n is 0, 1, 2 or 3; and

m is 0, 1 or 2.

In one aspect, there is provided a pharmaceutical composition comprising a compound as defined herein or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

In another embodiment, provided is a method for treating or preventing (e.g., treating) a disease, condition or disorder as described herein comprising administering a compound provided herein, a pharmaceutically acceptable salt, solvate or hydrate thereof, or pharmaceutical composition thereof.

In one aspect, there is provided the use of (1) a compound as defined herein or a pharmaceutically acceptable salt thereof; or (2) a pharmaceutical composition as defined herein in the manufacture of a medicament for increasing the lifetime of red blood cells (RBCs) in need thereof.

In another embodiment, provided is a method for increasing lifetime of the red blood cells (RBCs) in need thereof comprising contacting blood with an effective amount of (1) a compound disclosed herein or a pharmaceutically acceptable salt, solvate or hydrate thereof; (2) a composition comprising a compound disclosed herein or a salt, solvate or hydrate thereof and a carrier; or (3) a pharmaceutical composition comprising a compound disclosed herein or a pharmaceutically acceptable salt, solvate or hydrate thereof, and a pharmaceutically acceptable carrier.

In one aspect, there is provided the use of (1) a compound as defined herein or a pharmaceutically acceptable salt thereof; or (2) a pharmaceutical composition as defined herein in the manufacture of a medicament for regulating 2,3-diphosphoglycerate levels in blood in need thereof.

In another embodiment, provided is a method for regulating 2,3-diphosphoglycerate levels in blood in need thereof comprising contacting blood with an effective amount of (1) a compound disclosed herein or a pharmaceutically acceptable salt, solvate or hydrate thereof; (2) a composition comprising a compound disclosed herein or a salt, solvate or hydrate thereof and a carrier; or (3) a pharmaceutical composition comprising a compound disclosed herein or a pharmaceutically acceptable salt, solvate or hydrate thereof, and a pharmaceutically acceptable carrier.

In one aspect, there is provided the use of (1) a compound as defined herein or a pharmaceutically acceptable salt thereof; or (2) a pharmaceutical composition as defined herein in the manufacture of a medicament for treating hemolytic anemia.

In another embodiment, provided is a method for treating hereditary non-spherocytic haemolytic anemia comprising administering to a subject in need thereof a therapeutically effective amount of (1) a compound disclosed herein or a pharmaceutically acceptable salt, solvate or hydrate thereof; (2) a pharmaceutical composition comprising a compound disclosed herein or a pharmaceutically acceptable salt, solvate or hydrate thereof, and a pharmaceutically acceptable carrier.

In one aspect, there is provided the use of (1) a compound as defined herein or a pharmaceutically acceptable salt thereof; or (2) a pharmaceutical composition as defined herein in the manufacture of a medicament for treating sickle cell anemia.

In another embodiment, provided is a method for treating sickle cell anemia comprising administering to a subject in need thereof a therapeutically effective amount of (1) a compound disclosed herein or a pharmaceutically acceptable salt, solvate or hydrate thereof; (2) a pharmaceutical composition comprising a compound disclosed herein or a pharmaceutically acceptable salt, solvate or hydrate thereof, and a pharmaceutically acceptable carrier.

In another embodiment, provided is a method for treating hemolytic anemia (e.g., chronic hemolytic anemia caused by phosphoglycerate kinase deficiency, Blood Cells Mol Dis, 2011; 46(3):206) comprising administering to a subject in need thereof a therapeutically effective amount of (1) a compound disclosed herein or a pharmaceutically acceptable salt, solvate or hydrate thereof; (2) a pharmaceutical composition comprising a compound disclosed herein or a pharmaceutically acceptable salt, solvate or hydrate thereof, and a pharmaceutically acceptable carrier.

In another embodiment, provided is a method for treating diseases or conditions that are associated with increased 2,3-diphosphoglycerate levels (e.g., liver diseases (Am J Gastroenterol, 1987;82(12):1283) and Parkinson's (J. Neurol, Neurosurg, and Psychiatry 1976,39:952) comprising administering to a subject in

need thereof a therapeutically effective amount of (1) a compound disclosed herein or a pharmaceutically acceptable salt, solvate or hydrate thereof; (2) a pharmaceutical composition comprising a compound disclosed herein or a pharmaceutically acceptable salt, solvate or hydrate thereof, and a pharmaceutically acceptable carrier.

In one aspect, there is provided the use of (1) a compound as defined herein or a pharmaceutically acceptable salt thereof; or (2) a pharmaceutical composition as defined herein in the manufacture of a medicament for treating thalassemia; hereditary spherocytosis; hereditary elliptocytosis; abetalipoproteinemia or Bassen-Kornzweig syndrome; paroxysmal nocturnal hemoglobinuria; acquired hemolytic anemia; or anemia of chronic diseases.

In another embodiment, provided is 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)), or anemia of chronic diseases comprising administering to a subject in need thereof a therapeutically effective amount of (1) a compound disclosed herein or a pharmaceutically acceptable salt, solvate or hydrate thereof; (2) a pharmaceutical composition comprising a compound disclosed herein or a pharmaceutically acceptable salt, solvate or hydrate thereof, and a pharmaceutically acceptable carrier.

In another embodiment, provided is a method for treating diseases or conditions that are associated with increased 2,3-diphosphoglycerate levels (e.g., liver diseases (Am J Gastroenterol, 1987;82(12):1283) and Parkinson's (J. Neurol, Neurosurg, and Psychiatry 1976,39:952) comprising administering to a subject in need thereof a therapeutically effective amount of (1) a compound disclosed herein or a pharmaceutically acceptable salt, solvate or hydrate thereof; (2) a pharmaceutical composition comprising a compound disclosed herein or a pharmaceutically acceptable salt, solvate or hydrate thereof, and a pharmaceutically acceptable carrier.

Compounds and compositions described herein are activators of PKR mutants having lower activities compared to the wild type, thus are useful for methods of the present invention. Such mutations in PKR can affect enzyme activity (catalytic efficiency), regulatory properties (modulation by fructose bisphosphate (FBP)/ATP), and/or thermostability of the emzyme. 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, G37E, R479H, R479K, R486W, R532W, R510Q, and R490W. Without being bound by theory, compounds described herein affect the activities of PKR mutants by activating FBP non-responsive PKR mutants, restoring thermostability to mutants with decreased stability,

amount of a compound described herein to the patient in need thereof, thereby inhibiting cell proliferation in the patient. In one ~~aspect~~embodiment this method can inhibit growth of a transformed cell, more specifically a cancer cell. In another ~~aspect~~embodiment the method generally inhibits growth of a PKM2-dependent cell that undergoes aerobic glycolysis.

In another embodiment, provided is a method of treating a patient suffering from or susceptible to a disease or disorder associated with reduced PKM2 activity or reduced glycolysis in a patient in need thereof. The method comprises the step of administering an effective amount of a compound described herein to the patient in need thereof, thereby treating, preventing or ameliorating the disease or disorder in the patient. In certain embodiment the compound described herein is provided in a pharmaceutical composition. In certain embodiments, the method includes the step of identifying or selecting a patient who would benefit from activation of PKM2 prior to treatment. Identifying or selecting such a patient can be on the basis of the level of PKM2 activity in a cell of the patient. In one embodiment~~aspect~~, the selected patient is suffering from or susceptible to unwanted cell growth or proliferation, e.g., cancer, obesity, diabetes, atherosclerosis, restenosis, and autoimmune diseases. In another ~~aspect~~embodiment, the selected patient is suffering from a cancer associated with PKM2 function.

In one aspect, there is provided the use of (1) a compound as defined herein or a pharmaceutically acceptable salt thereof; or (2) a pharmaceutical composition as defined herein in the manufacture of a medicament for treating pyruvate kinase deficiency (PKD).

In another embodiment, the compound described herein is administered at a dosage and frequency sufficient to increase lactate production or oxidative phosphorylation.

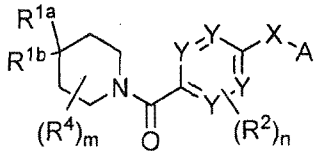
DETAILED DESCRIPTION

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. Also, the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The use of "including," "comprising," or "having," "containing", "involving", and variations thereof herein, is meant to encompass the items listed thereafter and equivalents thereof as well as additional items.

CLAIMS

What is claimed is:

1. A compound of Formula (I):



(I), or a pharmaceutically acceptable salt thereof, wherein:

A is aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted, and the aryl or heteroaryl is optionally fused to an optionally substituted carbocyclyl or an optionally substituted heterocyclyl;

X is selected from –NH-$S(O)_2$-, -$S(O)_2$-NH-, -NH-$S(O)_2$-CH_2-, -CH_2-S(O)-NH-, -NH-S(O)-CH_2-, -NH-S(O)-, -S(O)-NH-, or –CH_2-$S(O)_2$-NH-;

Y is C(H) or N; provided that no more than two Y groups are N;

R^{1a} is hydroxyl, -CH_2OH, –CHO, –CO_2H, -$N(R^{10a})_2$, –CO_2-C_{1-6} alkyl, -$OP(=O)(OH)_2$, or -OCO_2-CH_2-$OP(=O)(OH)_2$;

R^{1b} is C_{1-8} alkyl optionally substituted with one to four R^5 groups; C_{1-8} alkenyl optionally substituted with one to four R^5 groups; cycloalkyl; heterocycle; aryl; heteroaryl; cycloalkylalkyl; cycloalkylalkenyl; heterocyclylalkyl; heterocyclylalkenyl; aralkyl; aralkenyl; heteroaralkyl; heteroaralkenyl; or –OH, with the proviso that when R^{1a} is OH, R^{1b} is not OH; wherein each cycloalkyl, heterocycle, aryl, heteroaryl, cycloalkylalkyl, cycloalkylalkenyl, heterocyclylalkyl, heterocyclylalkenyl, aralkyl, aralkenyl, heteroaralkyl, or heteroaralkenyl is optionally substituted;

each R^2 is independently selected from halo, alkyl, CN, OH, and alkoxy, wherein said alkyl or alkoxy is optionally substituted with one to four R^5 groups; or

two adjacent R^2 groups are taken together with the ring atoms they are attached to form a 5- or 6-membered carbocyclic, aryl, heterocyclic or heteroaryl ring;

each R^4 is independently selected from halo, alkyl, alkoxy, haloalkyl, haloalkoxy and hydroxyl;

each R^5 is independently selected from halo, OH, C_{1-6} alkoxy, CN, NH_2, -SO_2-C_{1-6} alkyl, -NH(C_{1-6} alkyl), and –N(C_{1-6} alkyl)$_2$;

each R^{10a} is independently selected from hydrogen or C_{1-6} alkyl;

n is 0, 1, 2 or 3; and

m is 0, 1 or 2; provided that a compound of Formula (I) is not the following:

(1) 4-[[4-hydroxy-4-(4-methylphenyl)-1-piperidinyl]carbonyl]-N-2-thiazolyl-benzenesulfonamide;

(2) 4-[[4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl]carbonyl]-N-2-thiazolyl-benzenesulfonamide;

(3) 4-[[4-(3-fluorophenyl)-4-hydroxy-1-piperidinyl]carbonyl]-N-2-thiazolyl-benzenesulfonamide;

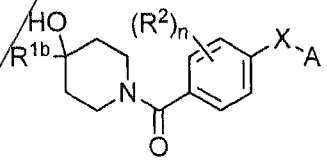
(4) 4-[[4-(2-fluoro-5-methylphenyl)-4-hydroxy-1-piperidinyl]carbonyl]-N-2-thiazolyl- benzenesulfonamide;

(5) 4-phenyl-1-[4-[(phenylamino)sulfonyl]benzoyl]-4-piperidinecarboxylic acid methyl ester;

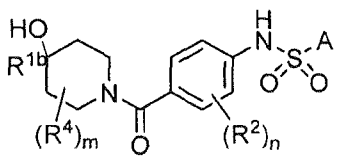
(6) 1-[4-[[(2-methylphenyl)amino]sulfonyl]benzoyl]-4-phenyl-4-piperidinecarboxylic acid methyl ester; or

(7) N-(4-fluorophenyl)-4-[[4-hydroxy-4-(methoxymethyl)-1-piperidinyl]carbonyl]-benzenesulfonamide.

2. The compound of claim 1, wherein the compound is a compound of Formula (Ia):



3. A compound of Formula (Ib):



(Ib),

or a pharmaceutically acceptable salt thereof,wherein:

A is aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted, and the aryl or heteroaryl is fused to an optionally substituted carbocyclyl or an optionally substituted heterocyclyl;

R^{1b} is C_{1-8} alkyl optionally substituted with one to four R^5 groups; C_{1-8} alkenyl optionally substituted with one to four R^5 groups; cycloalkyl; heterocycle; aryl; heteroaryl; cycloalkylalkyl; cycloalkylalkenyl; heterocyclylalkyl; heterocyclylalkenyl; aralkyl; aralkenyl; heteroaralkyl; heteroaralkenyl; or –OH, with the proviso that when R^{1a} is OH, R^{1b} is not OH; wherein each cycloalkyl, heterocycle, aryl, heteroaryl, cycloalkylalkyl, cycloalkylalkenyl, heterocyclylalkyl, heterocyclylalkenyl, aralkyl, aralkenyl, heteroaralkyl, or heteroaralkenyl is optionally substituted;

each R^2 is independently selected from halo, alkyl, CN, OH, and alkoxy, wherein said alkyl or alkoxy is optionally substituted with one to four R^5 groups; or

two adjacent R^2 groups are taken together with the ring atoms they are attached to form a 5- or 6-membered carbocyclic, aryl, heterocyclic or heteroaryl ring;

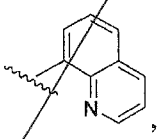
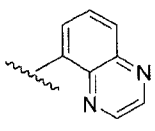
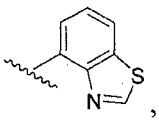
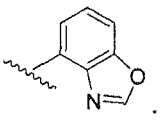
each R^4 is independently selected from halo, alkyl, alkoxy, haloalkyl, haloalkoxy and hydroxyl;

each R^5 is independently selected from halo, OH, C_{1-6} alkoxy, CN, NH_2, $-SO_2-C_{1-6}$ alkyl, $-NH(C_{1-6}$ alkyl), and $-N(C_{1-6}$ alkyl$)_2$;

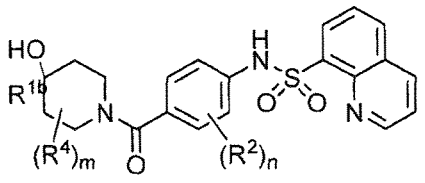
n is 0, 1, 2 or 3; and

m is 0, 1 or 2.

4. The compound of claim 3, wherein A is:

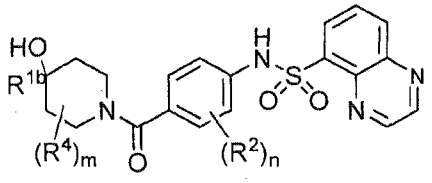

, 
, 
, or 
.

5. The compound of claim 3, wherein the compound is a compound of Formula (II):



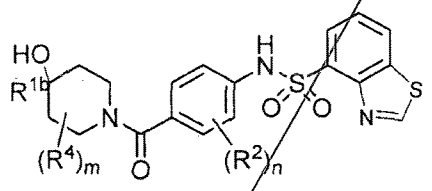
(II).

6. The compound of claim 3, wherein the compound is a compound of Formula (III):



(III).

7. The compound of claim 3, wherein the compound is a compound of Formula (IV):



(IV).

8. The compound of claim 3, wherein R^{1b} is C_{1-8} alkyl optionally substituted with one to four R^5 groups; aryl; heteroaryl; aralkyl; or heteroaralkyl; wherein each aryl; heteroaryl; aralkyl; or heteroaralkyl; is optionally substituted.

9. The compound of claim 8, wherein each aryl; heteroaryl; aralkyl; or heteroaralkyl is optionally substituted with halo, C_{1-6} alkyl, -OH, C_{1-6} alkoxy, -CN, -NH_2, -SO_2-C_{1-6} alkyl, -NH(C_{1-6} alkyl), –N(C_{1-6} alkyl)$_2$, aryl, haloalkyl, or haloalkoxy.

10. The compound of claim 3, wherein R^{1b} is C_{1-8} alkyl optionally substituted with one to four R^5 groups.

11. The compound of claim 3, wherein R^5 is fluoro, -OH, or -SO_2-CH_3.

12. The compound of claim 3, wherein R^{1b} is phenyl, optionally substituted with chloro, fluoro, bromo, methyl, ethyl,-CN, difluoromethyl, trifluoromethyl, $-OCF_3$, $-SO_2-CH_3$, or $-OCH_3$.

13. The compound of claim 1, wherein the compound of Formula (I) is selected from Compounds 100-529 of Table 1.

14. A pharmaceutical composition comprising a compound of claim 1 or a pharmaceutical acceptable salt thereof and a pharmaceutically acceptable carrier.

15. A method of modulating PKM2 activity in a subject in need thereof, the method comprising administering to said subject a pharmaceutical composition of claim 14.

16. A method of treating a cancer associated with PKM2 activity in a subject in need thereof, the method comprising administering to the subject a pharmaceutical composition of claim 14.

17. Use of a pharmaceutical composition of claim 14 in the manufacture of a medicament for modulating PKM2 activity.

18. Use of a pharmaceutical composition of claim 14 in the manufacture of a medicament for treating a cancer associated with PKM2 activity.

19. A method for increasing the lifetime of the red blood cells (RBCs) in need thereof comprising contacting blood with an effective amount of (1) a compound of claim 1 or a pharmaceutically acceptable salt thereof; or (2) a composition of claim 14.

20. The method of claim 19, wherein the compound is added directly to whole blood or packed cells extracorporeally.

21. The method of claim 19, wherein the pharmaceutical composition is administered to a subject in need thereof.

22. A method for regulating 2,3-diphosphoglycerate levels in blood in need thereof comprising contacting blood an effective amount of (1) a compound of claim 1; or (2) a composition of claim 14.

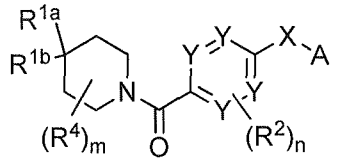
23. A method for treating hereditary non-spherocytic haemolytic anemia comprising administering to a subject in need thereof a therapeutically effective amount of an effective amount of (1) a compound of claim 1; or (2) a pharmaceutically acceptable composition of claim 14.

24. A method for treating sickle cell anemia comprising administering to a subject in need thereof a therapeutically effective amount of an effective amount of (1) a compound of claim 1; or (2) a pharmaceutically acceptable composition of claim 14.

CLAIMS

What is claimed is:

1. A compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein:



(I),

A is aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted, and the aryl or heteroaryl is optionally fused to an optionally substituted carbocyclyl or an optionally substituted heterocyclyl;

X is selected from –NH-$S(O)_2$-, -$S(O)_2$-NH-, -NH-$S(O)_2$-CH_2-, -CH_2-S(O)-NH-, -NH-S(O)-CH_2-, -NH-S(O)-, -S(O)-NH-, and –CH_2-$S(O)_2$-NH-;

Y is C(H) or N; provided that no more than two Y groups are N;

R^{1a} is selected from hydroxyl, -CH_2OH, –CHO, –CO_2H, -$N(R^{10a})_2$, –CO_2-C_{1-6} alkyl, -OP(=O)$(OH)_2$, and -OCO_2-CH_2-OP(=O)$(OH)_2$;

R^{1b} is selected from C_{1-8} alkyl optionally substituted with one to four R^5 groups; C_{1-8} alkenyl optionally substituted with one to four R^5 groups; cycloalkyl; heterocycle; aryl; heteroaryl; cycloalkylalkyl; cycloalkylalkenyl; heterocyclylalkyl; heterocyclylalkenyl; aralkyl; aralkenyl; heteroaralkyl; heteroaralkenyl; and –OH, with the proviso that when R^{1a} is OH, R^{1b} is not OH; wherein each cycloalkyl, heterocycle, aryl, heteroaryl, cycloalkylalkyl, cycloalkylalkenyl, heterocyclylalkyl, heterocyclylalkenyl, aralkyl, aralkenyl, heteroaralkyl, or heteroaralkenyl is optionally substituted;

each R^2 is independently selected from halo, alkyl, CN, OH, and alkoxy, wherein said alkyl or alkoxy is optionally substituted with one to four R^5 groups; or

two adjacent R^2 groups are taken together with the ring atoms they are attached to form a 5- or 6-membered carbocyclic, aryl, heterocyclic or heteroaryl ring;

each R^4 is independently selected from halo, alkyl, alkoxy, haloalkyl, haloalkoxy and hydroxyl;

each R^5 is independently selected from halo, OH, C_{1-6} alkoxy, CN, NH_2, -SO_2-C_{1-6} alkyl, -NH(C_{1-6} alkyl), and –N(C_{1-6} alkyl)$_2$;

each R^{10a} is independently selected from hydrogen and C_{1-6} alkyl;

n is 0, 1, 2 or 3; and

m is 0, 1 or 2; provided that a compound of Formula (I) is not the following:

(1) 4-[[4-hydroxy-4-(4-methylphenyl)-1-piperidinyl]carbonyl]-N-2-thiazolyl-benzenesulfonamide;

(2) 4-[[4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl]carbonyl]-N-2-thiazolyl-benzenesulfonamide;

(3) 4-[[4-(3-fluorophenyl)-4-hydroxy-1-piperidinyl]carbonyl]-N-2-thiazolyl-benzenesulfonamide;

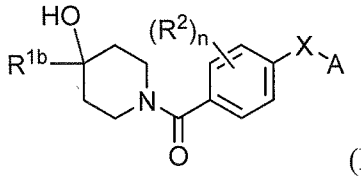
(4) 4-[[4-(2-fluoro-5-methylphenyl)-4-hydroxy-1-piperidinyl]carbonyl]-N-2-thiazolyl- benzenesulfonamide;

(5) 4-phenyl-1-[4-[(phenylamino)sulfonyl]benzoyl]-4-piperidinecarboxylic acid methyl ester;

(6) 1-[4-[[(2-methylphenyl)amino]sulfonyl]benzoyl]-4-phenyl-4-piperidinecarboxylic acid methyl ester; or

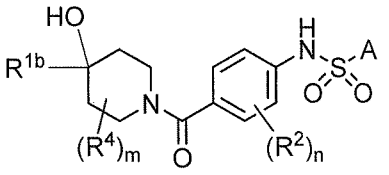
(7) N-(4-fluorophenyl)-4-[[4-hydroxy-4-(methoxymethyl)-1-piperidinyl]carbonyl]-benzenesulfonamide.

2. The compound of claim 1, wherein the compound is a compound of Formula (Ia):



(Ia).

3. A compound of Formula (Ib) or a pharmaceutically acceptable salt thereof, wherein:



(Ib),

A is aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted, and the aryl or heteroaryl is fused to an optionally substituted carbocyclyl or an optionally substituted heterocyclyl;

R^{1b} is selected from C_{1-8} alkyl optionally substituted with one to four R^5 groups; C_{1-8} alkenyl optionally substituted with one to four R^5 groups; cycloalkyl; heterocycle; aryl; heteroaryl; cycloalkylalkyl; cycloalkylalkenyl; heterocyclylalkyl; heterocyclylalkenyl; aralkyl; aralkenyl; heteroaralkyl; heteroaralkenyl; and –OH, with the proviso that when R^{1a} is OH, R^{1b} is not OH; wherein each cycloalkyl, heterocycle, aryl, heteroaryl, cycloalkylalkyl, cycloalkylalkenyl, heterocyclylalkyl, heterocyclylalkenyl, aralkyl, aralkenyl, heteroaralkyl, or heteroaralkenyl is optionally substituted;

each R^2 is independently selected from halo, alkyl, CN, OH, and alkoxy, wherein said alkyl or alkoxy is optionally substituted with one to four R^5 groups; or

two adjacent R^2 groups are taken together with the ring atoms they are attached to form a 5- or 6-membered carbocyclic, aryl, heterocyclic or heteroaryl ring;

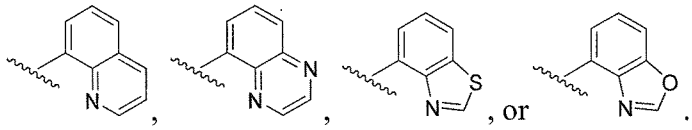
each R^4 is independently selected from halo, alkyl, alkoxy, haloalkyl, haloalkoxy and hydroxyl;

each R^5 is independently selected from halo, OH, C_{1-6} alkoxy, CN, NH_2, $-SO_2-C_{1-6}$ alkyl, $-NH(C_{1-6}$ alkyl), and $-N(C_{1-6}$ alkyl$)_2$;

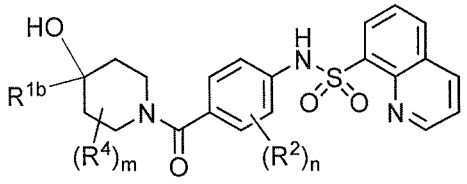
n is 0, 1, 2 or 3; and

m is 0, 1 or 2.

4. The compound of claim 3, wherein A is:

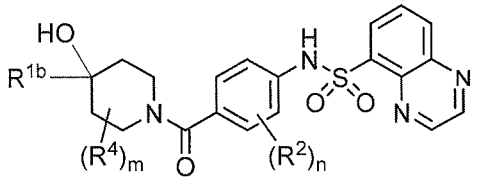


5. The compound of claim 3, wherein the compound is a compound of Formula (II):



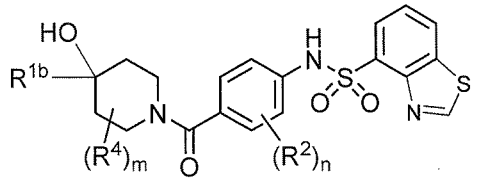
(II).

6. The compound of claim 3, wherein the compound is a compound of Formula (III):



(III).

7. The compound of claim 3, wherein the compound is a compound of Formula (IV):



(IV).

8. The compound of any one of claims 1 to 7, wherein R^{1b} is C_{1-8} alkyl optionally substituted with one to four R^5 groups; aryl; heteroaryl; aralkyl; or heteroaralkyl; wherein each aryl; heteroaryl; aralkyl; or heteroaralkyl; is optionally substituted.

9. The compound of claim 8, wherein each aryl; heteroaryl; aralkyl; or heteroaralkyl is optionally substituted with halo, C_{1-6} alkyl, -OH, C_{1-6} alkoxy, -CN, $-NH_2$, $-SO_2-C_{1-6}$ alkyl, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl$)_2$, aryl, haloalkyl, or haloalkoxy.

10. The compound of any one of claims 1 to 8, wherein R^{1b} is C_{1-8} alkyl optionally substituted with one to four R^5 groups.

11. The compound of any one of claims 1 to 10, wherein R^5 is fluoro, -OH, or $-SO_2-CH_3$.

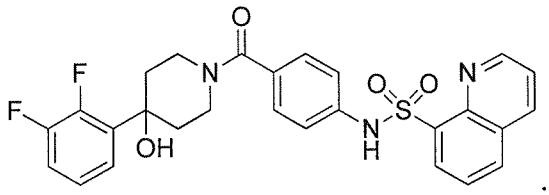
12. The compound of any one of claims 1 to 7, wherein R^{1b} is phenyl, optionally substituted with chloro, fluoro, bromo, methyl, ethyl,-CN, difluoromethyl, trifluoromethyl, $-OCF_3$, $-SO_2-CH_3$, or $-OCH_3$.

13. The compound of any one of claims 1 to 10, wherein R^{1b} is selected from methyl, ethyl, n-propyl, isopropyl, t-butyl, isobutyl, n-butyl, t-pentyl, 2-hydroxyethyl, 1-hydroxyethyl, 3-hydroxypropyl, 2-hydroxy-2-methylpropyl, 3-hydroxy-3-methylbutyl, 3,3,3-trifluoropropyl, 2-methoxyethyl, 3,3-difluoropropyl, ethoxymethyl, N,N-dimethylmethyl, pyrrollomethyl and 2-hydroxypropyl.

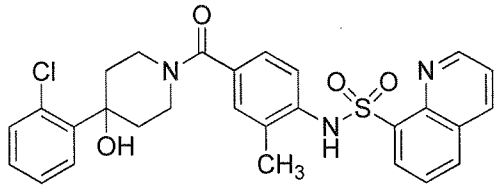
14. The compound of any one of claims 1 to 10, wherein R^{1b} is selected from methyl, ethyl, n-propyl, isopropyl, t-butyl, isobutyl, n-butyl, and t-pentyl.

15. The compound of claim 1, wherein the compound of Formula (I) is selected from Compounds 100-529 of Table 1.

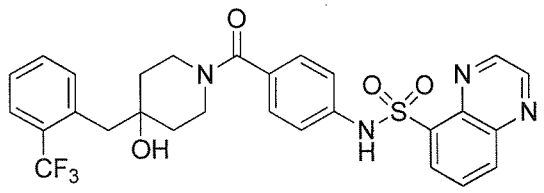
16. The compound of claim 1 having the following structure:



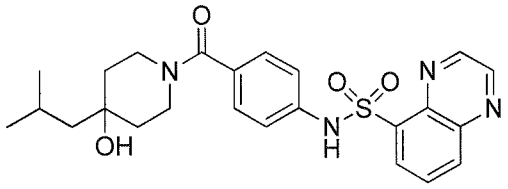
17. The compound of claim 1 having the following structure:



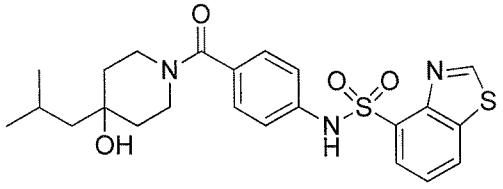
18. The compound of claim 1 having the following structure:



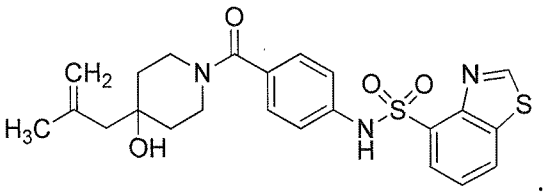
19. The compound of claim 1 having the following structure:



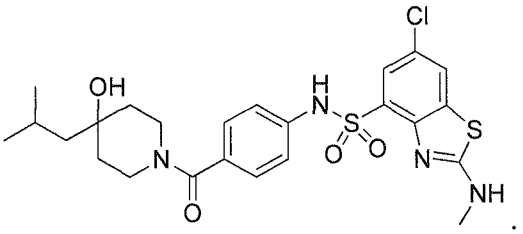
20. The compound of claim 1 having the following structure:



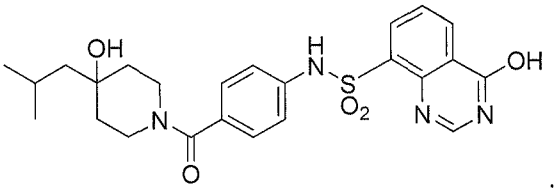
21. The compound of claim 1 having the following structure:



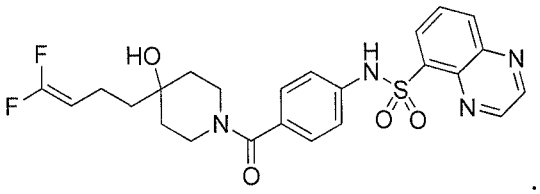
22. The compound of claim 1 having the following structure:



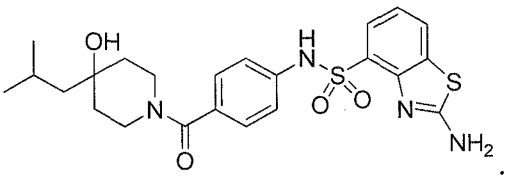
23. The compound of claim 1 having the following structure:



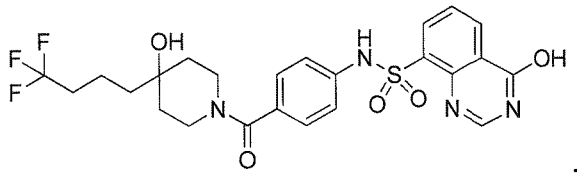
24. The compound of claim 1 having the following structure:



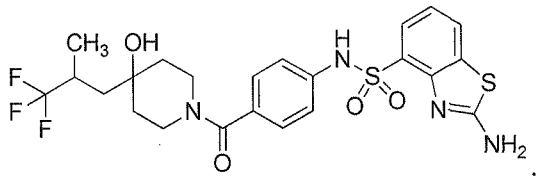
25. The compound of claim 1 having the following structure:



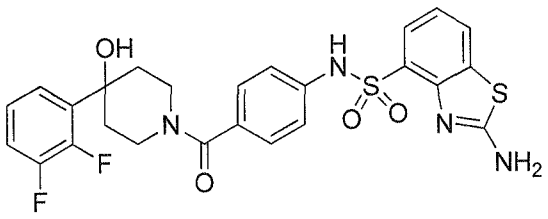
26. The compound of claim 1 having the following structure:



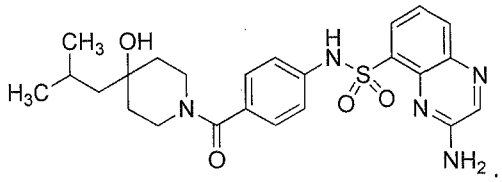
27. The compound of claim 1 having the following structure:



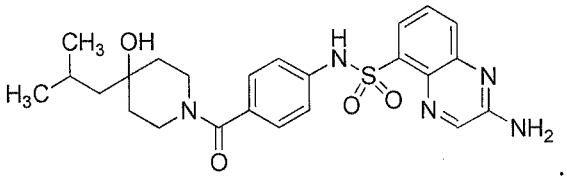
28. The compound of claim 1 having the following structure:



29. The compound of claim 1 having the following structure:



30. The compound of claim 1 having the following structure:



31. A pharmaceutical composition comprising a compound of any one of claims 1 to 30 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

32. Use of (1) a compound of any one of claims 1 to 30 or a pharmaceutically acceptable salt thereof; or (2) a pharmaceutical composition of claim 31 in the manufacture of a medicament for increasing the lifetime of red blood cells (RBCs) in need thereof.

33. The use of claim 32, wherein the medicament is to be added directly to whole blood or packed cells extracorporeally.

34. The use of claim 32, wherein the medicament is to be administered to a subject in need thereof.

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

36. Use of (1) a compound of any one of claims 1 to 30 or a pharmaceutically acceptable salt thereof; or (2) a pharmaceutical composition of claim 31 in the manufacture of a medicament for treating hemolytic anemia.

37. The use of claim 36, wherein the hemolytic anemia is hereditary non-spherocytic hemolytic anemia.

38. Use of (1) a compound of any one of claims 1 to 30 or a pharmaceutically acceptable salt thereof; or (2) a pharmaceutical composition of claim 31 in the manufacture of a medicament for treating sickle cell anemia.

39. Use of (1) a compound of any one of claims 1 to 30 or a pharmaceutically acceptable salt thereof; or (2) a pharmaceutical composition of claim 31 in the manufacture of a medicament for treating thalassemia; hereditary spherocytosis; hereditary elliptocytosis; abetalipoproteinemia or Bassen-Kornzweig syndrome; paroxysmal nocturnal hemoglobinuria; acquired hemolytic anemia; or anemia of chronic diseases.

40. The use of claim 39, wherein the thalassemia is beta-thalassemia.

41. The use of claim 39, wherein the acquired hemolytic anemia is a congenital anemia.

42. The use of claim 39, wherein the congenital anemia is an enzymopathy.

43. Use of (1) a compound of any one of claims 1 to 30 or a pharmaceutically acceptable salt thereof; or (2) a pharmaceutical composition of claim 31 in the manufacture of a medicament for treating pyruvate kinase deficiency (PKD).