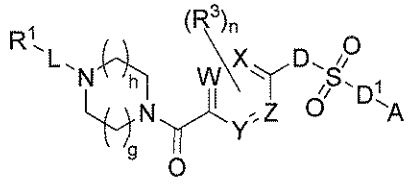
of FBP from PKM2 and conformational changes of PKM2 from an active, tetrameric form to an inactive form. Compounds that bind to PKM2 and lock the enzyme in the active confirmation will lead to the loss of allosteric control of PKM2 needed for shunting biochemical intermediates from glycolysis into biosynthesis of nucleotides and lipids. Thus, the activation of PKM2 (i.e., activators of PKM2) can also inhibit the growth and proliferation of cancer cells, activated immune cells, and fat cells.

There is a continuing need for novel treatments of diseases such as cancer, diabetes, obesity, autoimmune conditions, proliferation-dependent diseases (e.g., BPH), and other diseases related to the function of pyruvate kinase (e.g., PKM2).

## SUMMARY

Described herein are compounds that modulate pyruvate kinase M2 (PKM2) and pharmaceutically acceptable salts, solvates, and hydrates thereof, for example, compounds that activate 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., PKM2 function), including, e.g., cancer, diabetes, obesity, autoimmune disorders, and benign prostatic hyperplasia (BPH).

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



(I)

W, X, Y and Z are CH;

D is $NR^b$;

$D^1$ is a bond;

A is optionally substituted quinolinyl;

L is $-(CR^cR^c)_m-$;

$R^1$ is selected from alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl; each of which is substituted with 0-3 occurrences of $R^d$;

each $R^3$ is independently selected from halo, haloalkyl, alkyl, hydroxyl and -$OR^a$;

each $R^a$ is independently selected from alkyl, acyl, hydroxyalkyl and haloalkyl;

each $R^b$ is independently selected from hydrogen and alkyl;

each $R^c$ is independently selected from hydrogen, halo and alkyl;

each $R^d$ is independently selected from halo and alkyl;

n is 0 or 1;

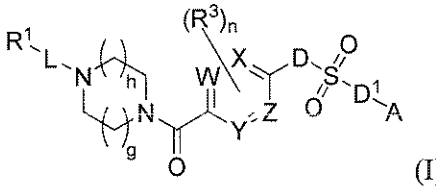
m is 1 or 2;

h is 1; and

g is 1.

In another aspect, there is provided a pharmaceutical composition comprising a compound of the present invention or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In one example, provided is a pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt of formula (I):




(I)

wherein:

W, X, Y and Z are each independently selected from CH or N;

D and $D^1$ are independently selected from a bond or $NR^b$;

A is optionally substituted aryl or optionally substituted heteroaryl;

L is a bond, -C(O)-, -$(CR^cR^c)_m$-, -OC(O)-, -$(CR^cR^c)_m$-OC(O)-, -$(CR^cR^c)_m$-C(O)-, -$NR^bC(S)$-, or -$NR^bC(O)$- (wherein the point of the attachment to $R^1$ is on the left-hand side);

$R^1$ is selected from alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl; each of which is substituted with 0-5 occurrences of $R^d$;

each $R^3$ is independently selected from halo, haloalkyl, alkyl, hydroxyl and $-OR^a$, or two adjacent $R^3$ taken together with the carbon atoms to which they are attached form an optionally substituted heterocyclyl;each $R^a$ is independently selected from alkyl, acyl, hydroxyalkyl and haloalkyl;

each $R^b$ is independently selected from hydrogen and alkyl;

each $R^c$ is independently selected from hydrogen, halo, alkyl, alkoxy and halo alkoxy or two $R^c$ taken together with the carbon atoms to which they are attached form an optionally substituted cycloalkyl;

each $R^d$ is independently selected from halo, haloalkyl, haloalkoxy, alkyl, alkynyl, nitro, cyano, hydroxyl, $-C(O)R^a$, $-OC(O)R^a$, $-C(O)OR^a$, $-SR^a$, $-NR^aR^b$ and $-OR^a$, or two $R^d$ taken together with the carbon atoms to which they are attached form an optionally substituted heterocyclyl;

n is 0, 1, or 2;

m is 1, 2 or 3;

h is 0, 1, 2; and

g is 0, 1 or 2.

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

In another example, provided is a method of modulating (e.g., increasing or decreasing) the level of PKM2 activity and/or glycolysis (e.g., modulating the endogenous ability of a cell in the patient to down regulate PKM2) 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 modulating (e.g., increasing or decreasing) the level of PKM2 activity and/or glycolysis in the patient. In some examples, a a compound or a composition described herein is used to maintain PKM2 in its active conformation or activate pyruvate kinase activity in

proliferating cells as a means to divert glucose metabolites into catabolic rather than anabolic processes in the patient.

In another example, provided is a method of inhibiting cell proliferation 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 inhibiting cell proliferation in the patient. E.g., this method can inhibiting growth of a transformed cell, e.g., a cancer cell, or generally inhibiting growth in a PKM2-dependent cell that undergoes aerobic glycolysis.

In another example, provided is a method of treating a patient suffering from or susceptible to a disease or disorder associated with the function of PKM2 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 example the modulator is provided in a pharmaceutical composition. In certain example, the method includes identifying or selecting a patient who would benefit from modulation (e.g., activation) of PKM2. E.g., the patient can be identified on the basis of the level of PKM2 activity in a cell of the patient for treatment of cancer associated with PKM2 function. In another example, the selected patient is a patient suffering from or susceptible to a disorder or disease identified herein, e.g., a disorder characterized by unwanted cell growth or proliferation, e.g., cancer, obesity, diabetes, atherosclerosis, restenosis, and autoimmune diseases.

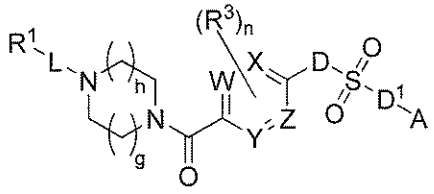
In another example, the compound described herein is administered at a dosage and frequency sufficient to increase lactate production or oxidative phosphorylation.

## BRIEF DESCRIPTION OF THE FIGURES

Figure 1 represents a table of exemplary compounds and the corresponding activity of the compound.

## CLAIMS

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



(I)

W, X, Y and Z are CH;

D is $NR^b$;

$D^1$ is a bond;

A is optionally substituted quinolinyl;

L is $-(CR^cR^c)_m-$;

$R^1$ is selected from alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl; each of which is substituted with 0-3 occurrences of $R^d$;

each $R^3$ is independently selected from halo, haloalkyl, alkyl, hydroxyl and $-OR^a$;

each $R^a$ is independently selected from alkyl, acyl, hydroxyalkyl and haloalkyl;

each $R^b$ is independently selected from hydrogen and alkyl;

each $R^c$ is independently selected from hydrogen, halo and alkyl;

each $R^d$ is independently selected from halo and alkyl;

n is 0 or 1;

m is 1 or 2;

h is 1; and

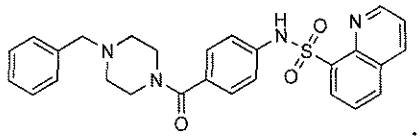
g is 1.

2. The compound of claim 1, wherein $R^1$ is heterocyclyl or cycloalkyl, each substituted with 0-5 occurrences of $R^d$.

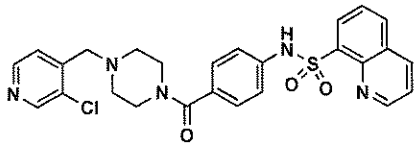
3. The compound of claim 1 or 2, wherein n is 0.

4. The compound of claim 1 or 2, wherein n is 1 and $R^3$ is $CH_3$, $CH_2CH_3$, $OCH_3$, $OCH_2CH_3$, OH, F, Cl, or $CF_3$.

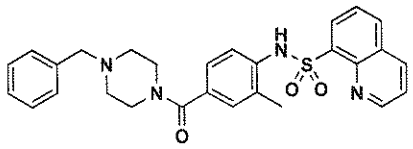
5. A compound of claim 1 or pharmaceutically acceptable salt thereof having the following structural formula:



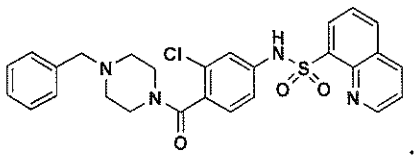
6. A compound of claim 1 or pharmaceutically acceptable salt thereof having the following structural formula:



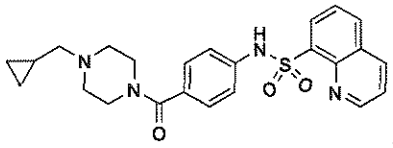
7. A compound of claim 1 or pharmaceutically acceptable salt thereof having the following structural formula:



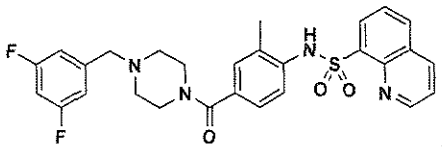
8. A compound of claim 1 or pharmaceutically acceptable salt thereof having the following structural formula:



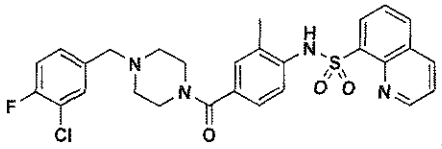
9. A compound of claim 1 or pharmaceutically acceptable salt thereof having the following structural formula:



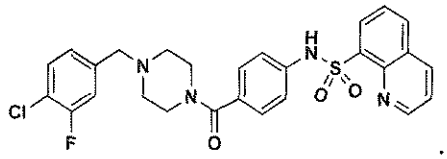
10. A compound of claim 1 or pharmaceutically acceptable salt thereof having the following structural formula:



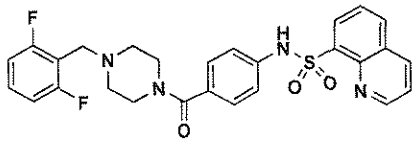
11. A compound of claim 1 or pharmaceutically acceptable salt thereof having the following structural formula:



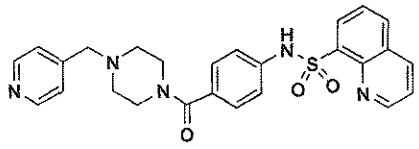
12. A compound of claim 1 or pharmaceutically acceptable salt thereof having the following structural formula:



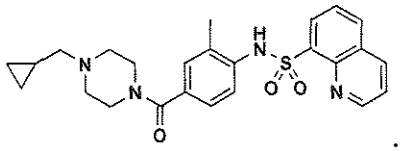
13. A compound of claim 1 or pharmaceutically acceptable salt thereof having the following structural formula:



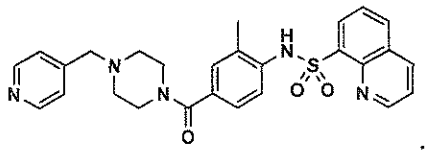
14. A compound of claim 1 or pharmaceutically acceptable salt thereof having the following structural formula:



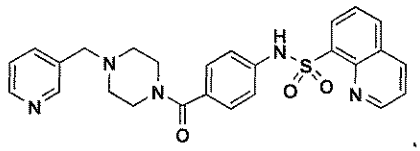
15. A compound of claim 1 or pharmaceutically acceptable salt thereof having the following structural formula:



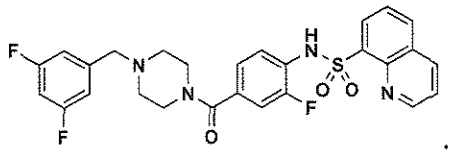
16. A compound of claim 1 or pharmaceutically acceptable salt thereof having the following structural formula:



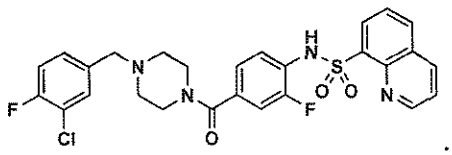
17. A compound of claim 1 or pharmaceutically acceptable salt thereof having the following structural formula:



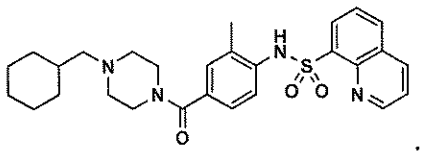
18. A compound of claim 1 or pharmaceutically acceptable salt thereof having the following structural formula:



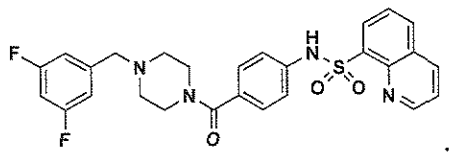
19. A compound of claim 1 or pharmaceutically acceptable salt thereof having the following structural formula:



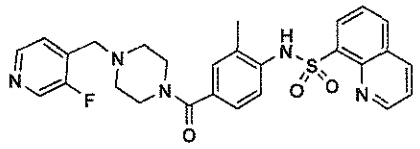
20. A compound of claim 1 or pharmaceutically acceptable salt thereof having the following structural formula:



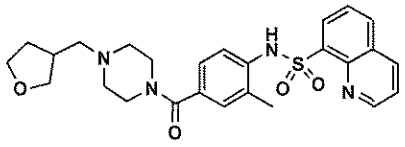
21. A compound of claim 1 or pharmaceutically acceptable salt thereof having the following structural formula:



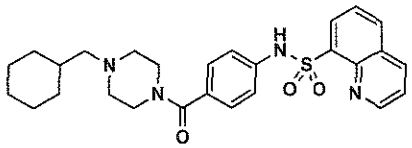
22. A compound of claim 1 or pharmaceutically acceptable salt thereof having the following structural formula:



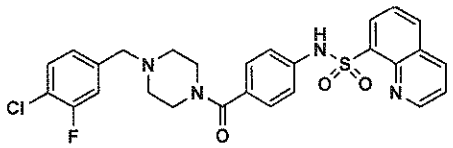
23. A compound of claim 1 or pharmaceutically acceptable salt thereof having the following structural formula:



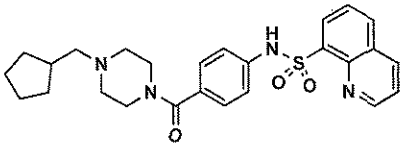
24. A compound of claim 1 or pharmaceutically acceptable salt thereof having the following structural formula:



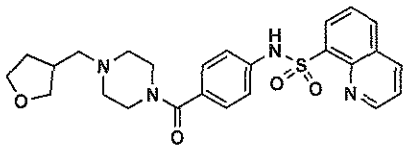
25. A compound of claim 1 or pharmaceutically acceptable salt thereof having the following structural formula:



26. A compound of claim 1 or pharmaceutically acceptable salt thereof having the following structural formula:



27. A compound of claim 1 or pharmaceutically acceptable salt thereof having the following structural formula:



28. A pharmaceutical composition comprising a compound of any one of claims 1 to 27 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.