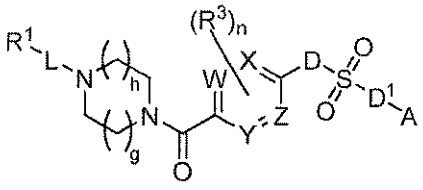
of FBP from PKM2 and conformational changes of PKM2 from an active, tetrameric form to an inactive form. Compounds that bind to PKM2 and lock the enzyme in the active confirmation will lead to the loss of allosteric control of PKM2 needed for shunting biochemical intermediates from glycolysis into biosynthesis 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 ~~OF INVENTION~~

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 embodiment, 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;

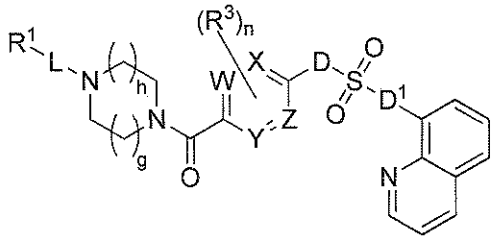
n is 0, 1, or 2;

m is 1, 2 or 3;

h is 0, 1, 2; and

g is 0, 1 or 2.

In one aspect, provided is a compound of formula II or a pharmaceutically acceptable salt thereof, wherein:




(II)

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

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

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;

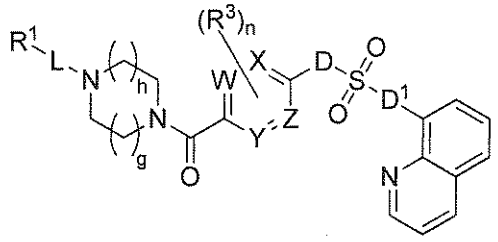
n is 0, 1, or 2;

m is 1, 2 or 3;

h is 1; and

g is 1.

In another aspect, provided is a pharmaceutical composition comprising a compound formula II or a pharmaceutically acceptable salt thereof, wherein:



(II)

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

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

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 1; and

g is 1.

In yet other aspects, provided are pharmaceutical compositions comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof.

In another embodiment, 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 embodiments, 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 embodiments, a a compound or a composition described herein is used to maintain PKM2 in its active conformation or activate pyruvate kinase activity in