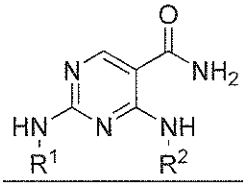
hepatic fibrosis [Kodama *et al.*, *Gastroenterology* 137:1467-1477 (2009)]. While both JNK1-/- and JNK2-/- mice developed steatosis, the JNK1-/- mice, but not JNK2-/- mice, were remarkably resistant to progression to hepatitis and fibrosis. Chimeric mice with JNK1-/- deletion restricted to bone marrow cells were similarly resistant to hepatitis and fibrosis implicating the activated Kupffer cell as a key trigger for disease progression beyond steatosis. Indeed, JNK1-/- macrophages do not express IL-1, IL-6, TNF and NO in response to LPS [Sanchez-Tillo *et al., J Biol Chem.* 282(17):12566-73 (2007)], and Kupffer cells derived from JNK1 -/- mice or from wild-type mice and treated with JNK inhibitor SP600125 display reduced TNF, IL-6, and IL-1 expression in response to LPS [Kodama *et al.*, *Gastroenterology* 137:1467-1477 (2009)].

[0006] The elucidation of the intricacy of protein kinase pathways and the complexity of the relationship and interaction among and between the various protein kinases and kinase pathways highlights the importance of developing pharmaceutical agents capable of acting as protein kinase modulators, regulators or inhibitors that have beneficial activity on multiple kinases or multiple kinase pathways. Accordingly, there remains a need for new kinase modulators, and in particular JNK modulators.

[0007] Citation or identification of any reference in Section 2 of this application is not to be construed as an admission that the reference is prior art to the present application.

## SUMMARY

[0007a] In one aspect, there is provided a compound of formula (I):




(I)

and pharmaceutically acceptable salts, tautomers, stereoisomers, enantiomers, and isotopologues thereof,

wherein:

$R^1$ is substituted or unsubstituted $C_{1-8}$ alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted alkylcycloalkyl, or substituted or unsubstituted alkylheterocyclyl, provided that $R^1$ is not 1-aminocyclohexyl;

$R^2$ is substituted or unsubstituted $C_{1-8}$ alkyl, substituted or unsubstituted saturated cycloalkyl, or substituted or unsubstituted non-aromatic heterocyclyl;

provided the compound is not

2-(2-aminoethylamino)-4-(methylamino)pyrimidine-5-carboxamide,

2-(2-aminopropylamino)-4-(cyclohexylamino)pyrimidine-5-carboxamide,

2-(2-amino-2-oxoethylamino)-4-(cyclohexylamino)pyrimidine-5-carboxamide,

2-(2-aminoethylamino)-4-(cyclohexylamino)pyrimidine-5-carboxamide,

(S)-2-(2-aminopropylamino)-4-(cyclobutylamino)pyrimidine-5-carboxamide,

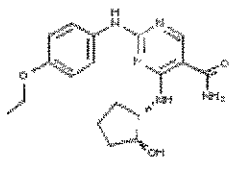
(R)-2-(1-amino-3-methyl-1-oxobutan-2-ylamino)-4-(cyclobutylamino)pyrimidine-5-carboxamide,

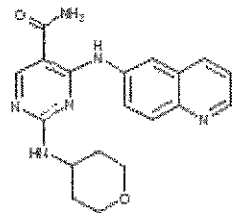
4-(cyclopentylamino)-2-(methylamino)pyrimidine-5-carboxamide, or

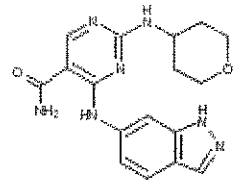
2-(1-acetylpiperidin-4-ylamino)-4-(cyclopropylamino)pyrimidine-5-carboxamide,

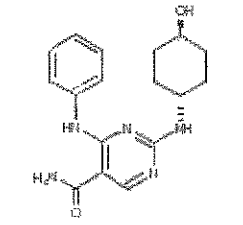
wherein when a $C_{1-8}$ alkyl group is substituted, the $C_{1-8}$ alkyl group is substituted with halogen, alkyl, hydroxyl, alkoxy, alkoxyalkyl, carboxy, nitro, cyano, thiol, thioether, imine, imide, amidine, guanidine, enamine, aminocarbonyl, acylamino, phosphonato, phosphine, thiocarbonyl, sulfonyl, sulfone, sulfonamide, ketone, aldehyde, ester, urea, urethane, oxime, hydroxyl amine, alkoxyamine, aralkoxyamine, N-oxide, hydrazine, hydrazide, hydrazone, azide, isocyanate, isothiocyanate, cyanate, thiocyanate, $B(OH)_2$, or O(alkyl)aminocarbonyl.

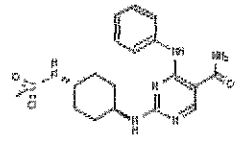
[0007b] In another aspect, there is provided a compound selected from

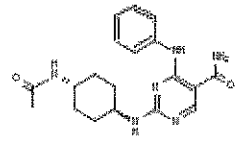


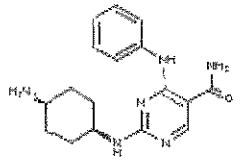


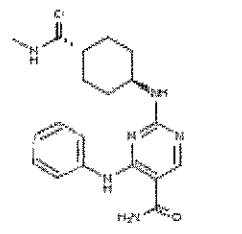


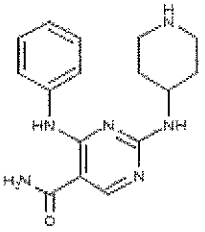


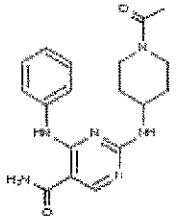


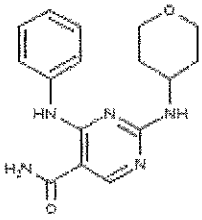


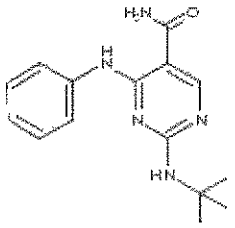


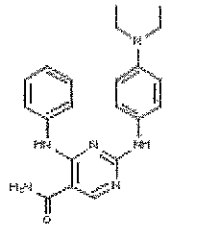


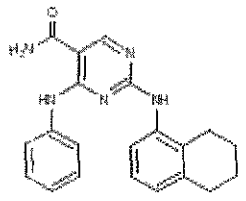


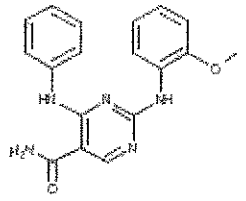


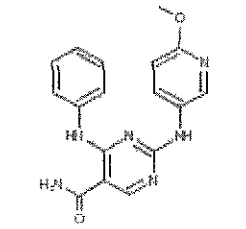


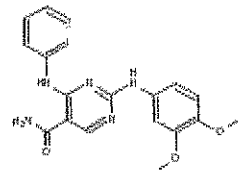


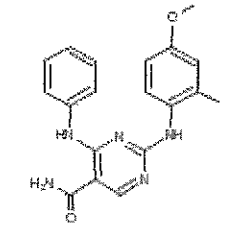


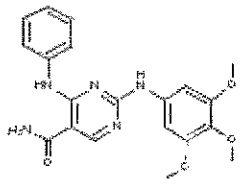


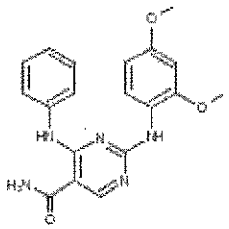


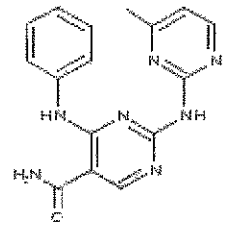


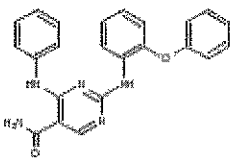


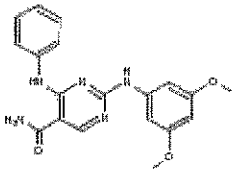


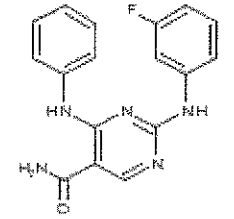


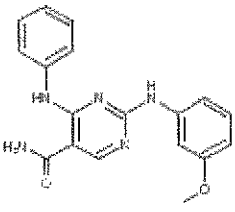


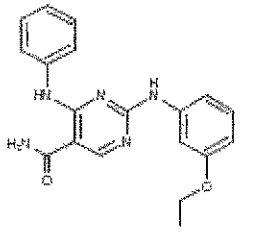


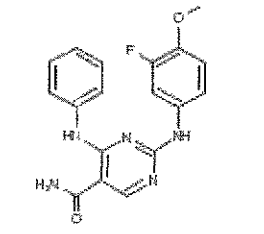


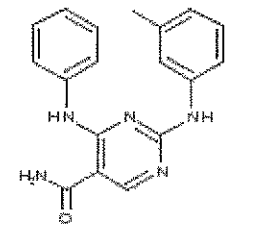


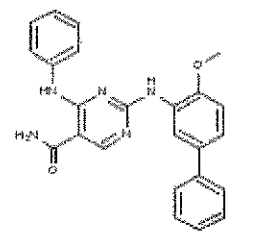


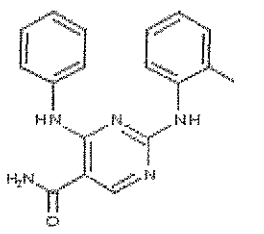


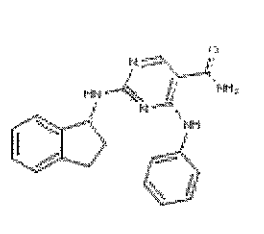


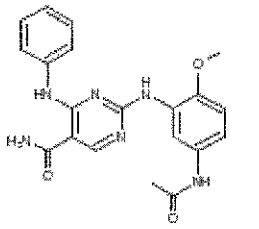


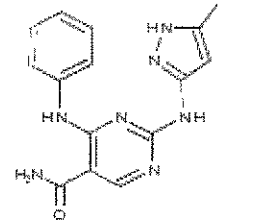


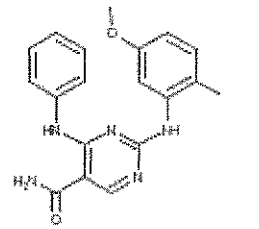


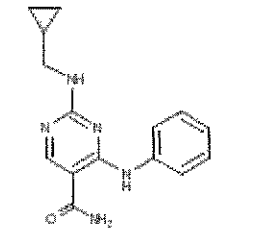


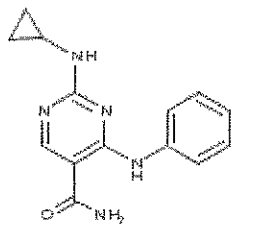


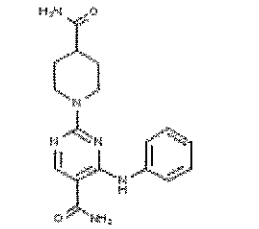


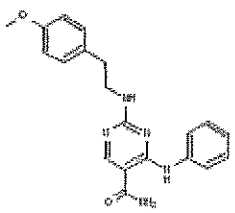


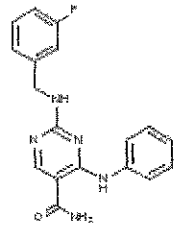


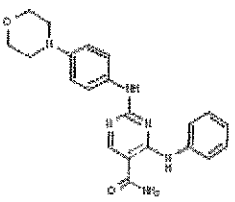


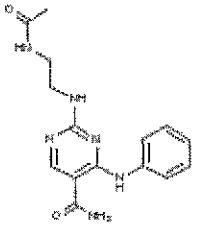


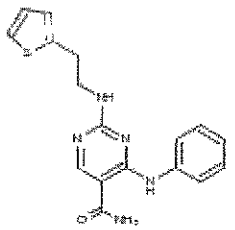


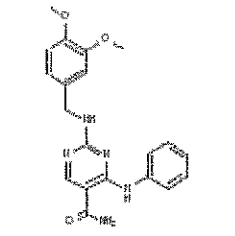












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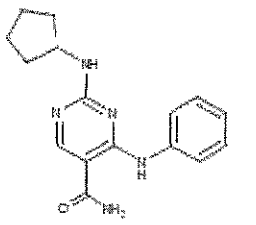

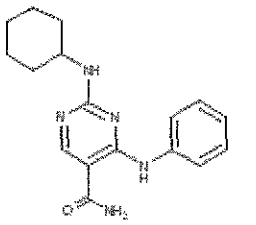

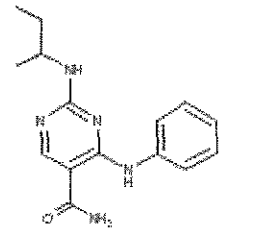

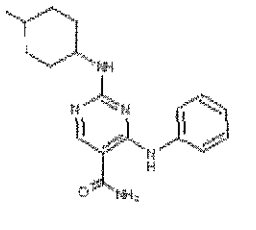

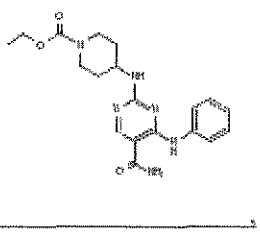

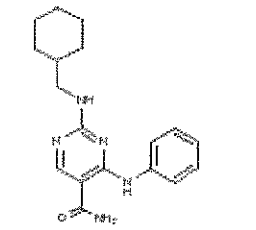

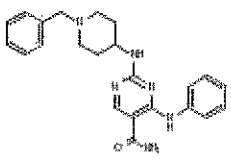

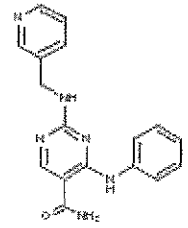

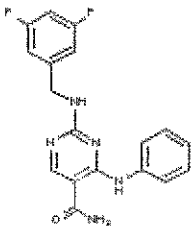

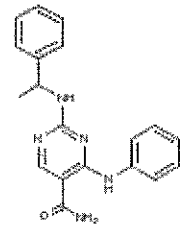

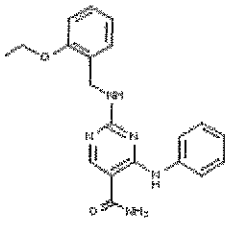

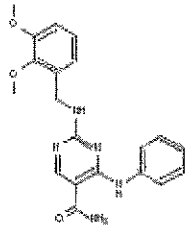

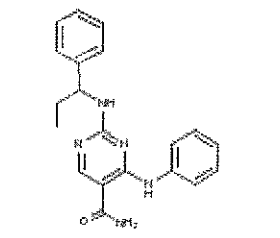

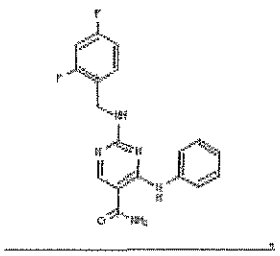

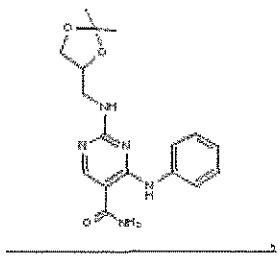

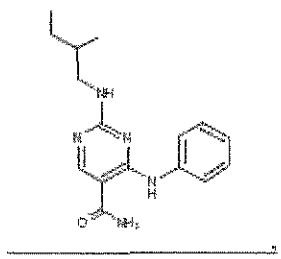

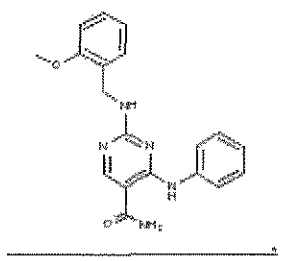

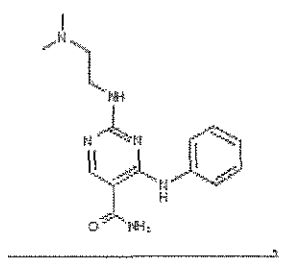

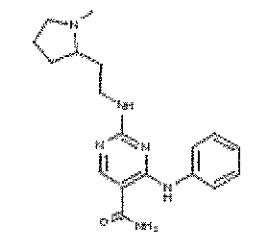

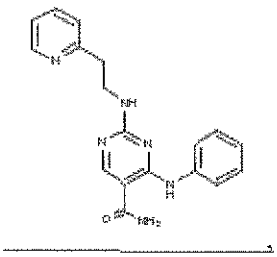

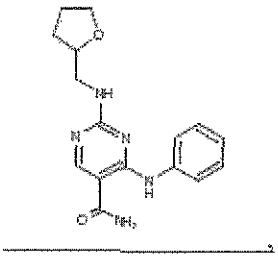

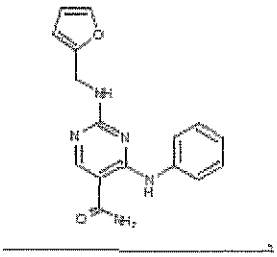

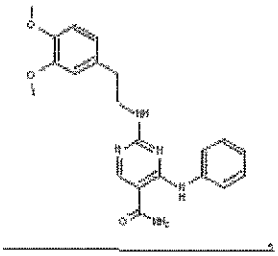

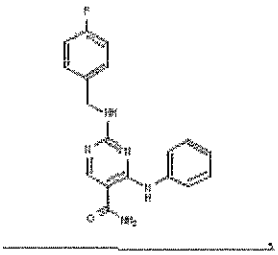

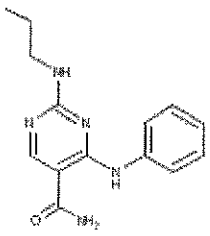

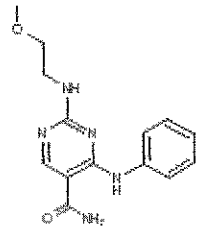

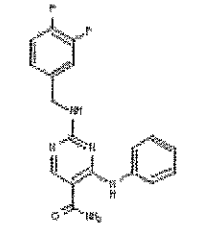

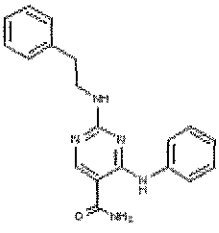

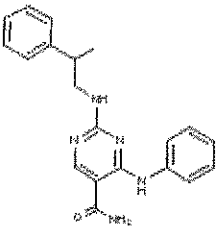

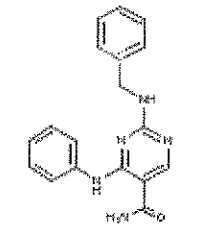

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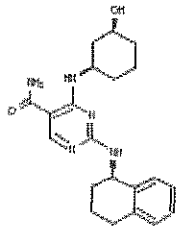

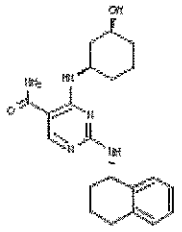

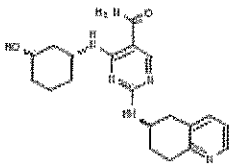

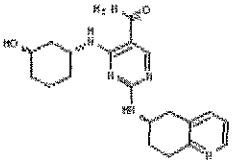

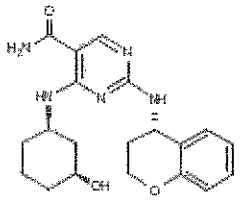

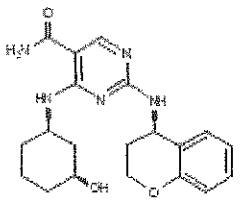

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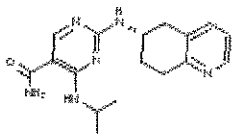
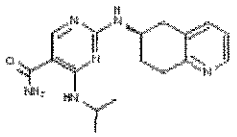
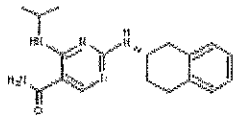
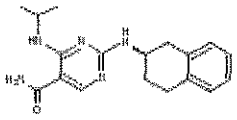
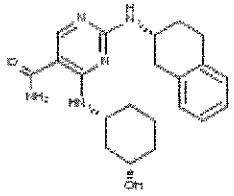
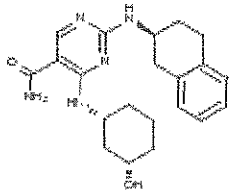


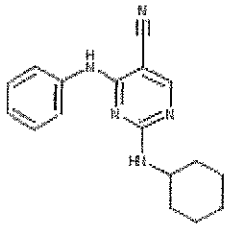


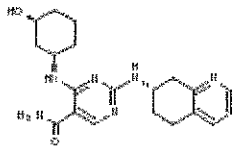


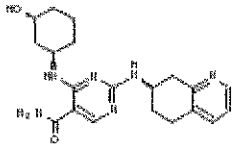


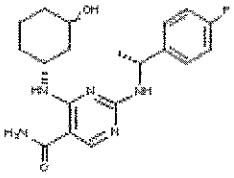


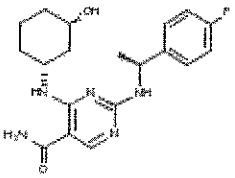


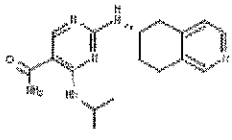


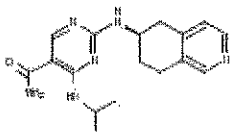


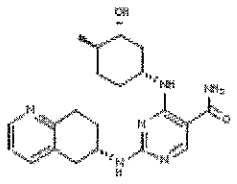


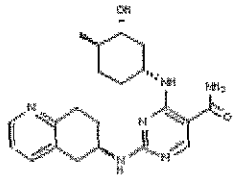


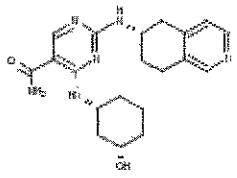


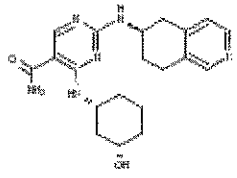


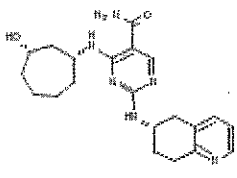


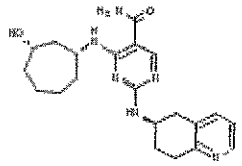


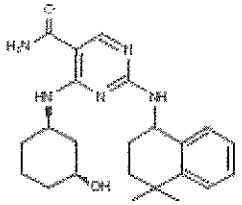


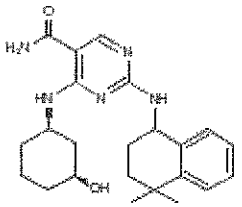


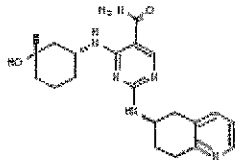


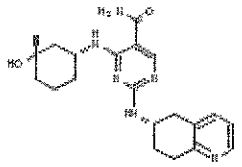






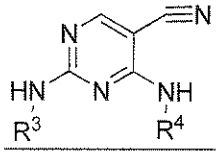






or a pharmaceutically acceptable salt, tautomer, stereoisomer, or enantiomer thereof.

[0007c] In yet another aspect, there is provided a compound of formula (IB):



**(IB)**

and pharmaceutically acceptable salts, tautomers, stereoisomers, enantiomers, and isotopologues thereof,

wherein:

$R^3$ is substituted or unsubstituted $C_{1-8}$ alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted alkylcycloalkyl, or substituted or unsubstituted alkyl-(non-aromatic heterocyclyl);

$R^4$ is substituted or unsubstituted $C_{1-8}$ alkyl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted non-aromatic heterocyclyl;

provided the compound is not

4-(isopentylamino)-2-(3-(2-methylpiperidin-1-yl)propylamino)pyrimidine-5-carbonitrile;

(2S,2'S)-dimethyl 2,2'-(5-cyanopyrimidine-2,4-diyl)bis(azanediyl)bis(4-methylpentanoate);

(2S,2'S)-diethyl 2,2'-(5-cyanopyrimidine-2,4-diyl)bis(azanediyl)bis(3-methylbutanoate);

4-(cycloheptylamino)-2-(3-(2-methylpiperidin-1-yl)propylamino)pyrimidine-5-carbonitrile;

4-(4-methylcyclohexylamino)-2-(3-(2-methylpiperidin-1-yl)propylamino)pyrimidine-5-carbonitrile; or

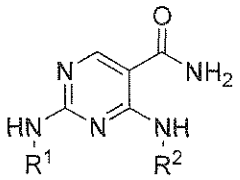
2-(3-(diethylamino)propylamino)-4-(4-methylcyclohexylamino)pyrimidine-5-carbonitrile,

wherein when a $C_{1-8}$ alkyl group is substituted, the $C_{1-8}$ alkyl group is substituted with halogen, alkyl, hydroxyl, alkoxy, alkoxyalkyl, alkylamino, carboxy, nitro, cyano, thiol, thioether, imine, imide, amidine, guanidine, enamine, aminocarbonyl, acylamino, phosphonato, phosphine, thiocarbonyl, sulfonyl, sulfone, sulfonamide, ketone, aldehyde, ester, urea, urethane, oxime, hydroxyl amine, alkoxyamine, aralkoxyamine, N-oxide, hydrazine, hydrazide, hydrazone, azide, isocyanate, isothiocyanate, cyanate, thiocyanate, $B(OH)_2$, or O(alkyl)aminocarbonyl.

[0007d] In a further aspect, there is provided a pharmaceutical composition comprising an effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, tautomer, isotopologue, or stereoisomer thereof, and a pharmaceutically acceptable carrier, excipient or vehicle.

[0007e] In yet a further aspect, there is provided the use of a compound of the present invention in the manufacture of a medicament for treatment or prevention of liver fibrotic disorders, or diabetes or metabolic syndrome leading to liver fibrotic disorders.

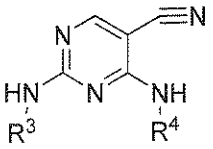
[0008] Provided herein are compounds having the following formula (I):



**(I)**

and pharmaceutically acceptable salts, tautomers, isotopologues, stereoisomers and prodrugs thereof, wherein $R^1$, and $R^2$ are as defined herein.

[0009] Provided herein are compounds having the following formula (IB):



**(IB)**

and pharmaceutically acceptable salts, tautomers, isotopologues, stereoisomers and prodrugs thereof, wherein $R^3$, and $R^4$ are as defined herein.

[0010] A compound of formula (I) or formula (IB) or a pharmaceutically acceptable salt, tautomer, isotopologue, stereoisomer or prodrug thereof (each being referred to herein as an "Diaminopyrimidine Compound") is useful for treating or preventing liver fibrotic disorders, or diabetes and/or metabolic syndrome leading to liver fibrotic disorders, as described herein. In another ~~aspect~~example, a Diaminopyrimidine Compound is useful for treating or preventing a condition treatable or preventable by inhibition of a JNK pathway, as described herein.

[0011] In one ~~aspect~~example, provided herein are Diaminopyrimidine Compounds as described in the instant disclosure, such as, for example, in Tables 1, 2 and 3.

[0012] In one ~~aspect~~example, provided herein are pharmaceutical compositions comprising an effective amount of a Diaminopyrimidine Compound as described herein, and a pharmaceutically acceptable carrier, excipient or vehicle. In some ~~embodiments~~examples the pharmaceutical composition is suitable for oral, parenteral, mucosal, transdermal or topical administration.

[0013] In one ~~aspect~~example, provided herein are methods for treating or preventing liver fibrotic disorders, such as non-alcoholic steatohepatitis, steatosis, cirrhosis, primary sclerosing cholangitis, primary biliary cirrhosis, hepatitis, hepatocellular carcinoma, and liver fibrosis coincident with chronic or repeated alcohol ingestion, with infection, with liver transplant, or with drug induced liver injury, comprising administering to a subject in need thereof an effective amount of a Diaminopyrimidine Compound as described herein; and a pharmaceutically acceptable carrier, excipient or vehicle. In another ~~aspect~~example, provided herein are methods for treating or preventing diabetes or metabolic syndrome leading to liver fibrotic disorders, such as non-alcoholic steatohepatitis, steatosis, hepatitis, or cirrhosis, comprising administering to a subject in need thereof an effective amount of a Diaminopyrimidine Compound. Also provided herein are methods for treating or

preventing a condition treatable or preventable by inhibition of a JNK pathway, comprising administering to a subject in need thereof an effective amount of a Diaminopyrimidine Compound as described herein; and a pharmaceutically acceptable carrier, excipient or vehicle.

[0014] In one ~~aspect~~example, provided herein are methods for inhibiting a kinase, for example JNK1, JNK2 or both, in a cell expressing said kinase, comprising contacting said cell with an effective amount of a Diaminopyrimidine Compound as described herein.

[0015] In another ~~aspect~~example provided herein are methods for preparing Diaminopyrimidine Compounds as described herein.

[0016] The present embodiments can be understood more fully by reference to the detailed description and examples, which are intended to exemplify non-limiting embodiments.

## DETAILED DESCRIPTION

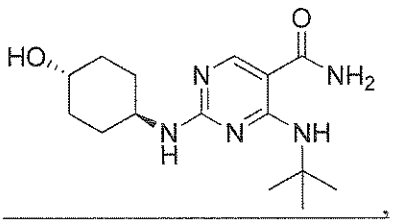
### DEFINITIONS

[0017] An "alkyl" group is a saturated, partially saturated, or unsaturated straight chain or branched non-cyclic hydrocarbon having from 1 to 10 carbon atoms, typically from 1 to 8 carbons or, in some embodiments, from 1 to 6, 1 to 4, or 2 to 6 or carbon atoms. Representative alkyl groups include -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl and -n-hexyl; while saturated branched alkyls include -isopropyl, -*sec*-butyl, -isobutyl, -*tert*-butyl, -isopentyl, -neopentyl, *tert*-pentyl, -2-methylpentyl, -3-methylpentyl, -4-methylpentyl, -2,3-dimethylbutyl and the like. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, allyl, $-CH{=}CH(CH_3)$, $-CH{=}C(CH_3)_2$, $-C(CH_3){=}CH_2$, $-C(CH_3){=}CH(CH_3)$, $-C(CH_2CH_3){=}CH_2$, $-C{\equiv}CH$, $-C{\equiv}C(CH_3)$, $-C{\equiv}C(CH_2CH_3)$, $-CH_2C{\equiv}CH$, $-CH_2C{\equiv}C(CH_3)$ and $-CH_2C{\equiv}C(CH_7CH_3)$, among others. An alkyl group can be substituted or unsubstituted. When the alkyl groups described herein are said to be "substituted," they may be substituted with any substituent or substituents as those found in the exemplary compounds and embodiments disclosed herein, as well as halogen (chloro, iodo, bromo, or fluoro); alkyl; hydroxyl; alkoxy; alkoxyalkyl; amino; alkylamino; carboxy; nitro; cyano; thiol; thioether; imine; imide; amidine; guanidine; enamine; aminocarbonyl; acylamino; phosphonato; phosphine; thiocarbonyl; sulfonyl; sulfone;

53. The use of claim 52, wherein the liver fibrotic disorder is non-alcoholic steatohepatitis, steatosis, cirrhosis, primary sclerosing cholangitis, primary biliary cirrhosis, hepatitis, hepatocellular carcinoma, or liver fibrosis coincident with chronic or repeated alcohol ingestion, with infection, with liver transplant, or with drug induced liver injury.

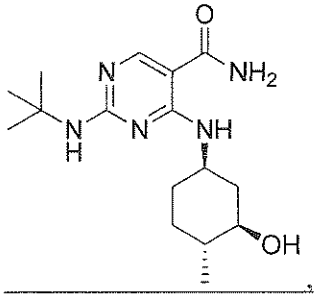
54. The use of claim 52, wherein the liver fibrotic disorder is non-alcoholic steatohepatitis, steatosis, hepatitis, or cirrhosis.

55. The compound of claim 29, wherein the compound is



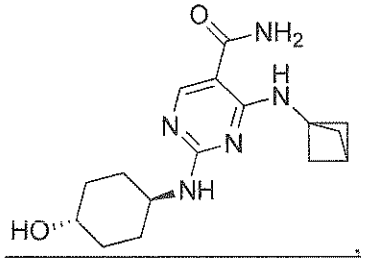
or a pharmaceutically acceptable salt thereof.

56. The compound of claim 29, wherein the compound is



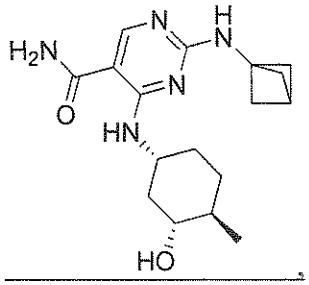
or a pharmaceutically acceptable salt thereof.

57. The compound of claim 29, wherein the compound is



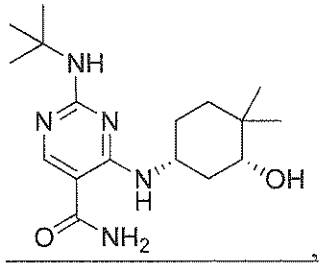
or a pharmaceutically acceptable salt thereof.

58. The compound of claim 29, wherein the compound is



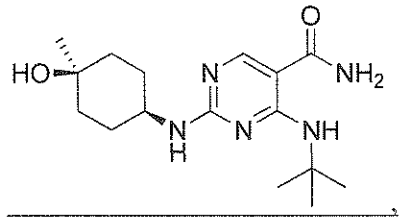
or a pharmaceutically acceptable salt thereof.

59. The compound of claim 29, wherein the compound is



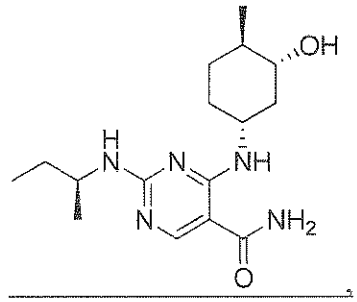
or a pharmaceutically acceptable salt thereof.

60. The compound of claim 29, wherein the compound is



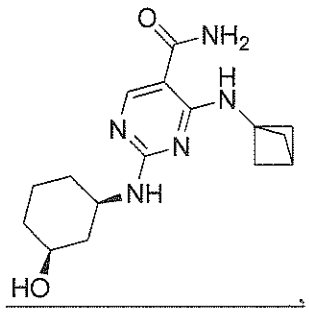
or a pharmaceutically acceptable salt thereof.

61. The compound of claim 29, wherein the compound is



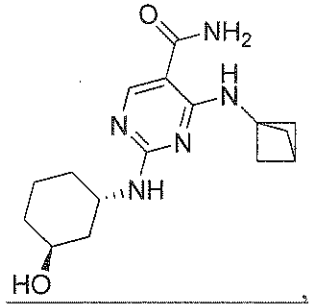
or a pharmaceutically acceptable salt thereof.

62. The compound of claim 29, wherein the compound is



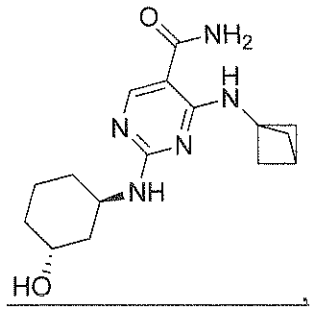
or a pharmaceutically acceptable salt thereof.

63. The compound of claim 29, wherein the compound is



or a pharmaceutically acceptable salt thereof.

64. The compound of claim 29, wherein the compound is



or a pharmaceutically acceptable salt thereof.