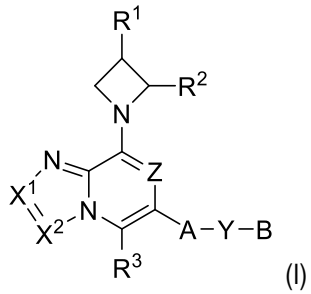
[0005] Attempts to inhibit KHK have thus far stalled in preclinical or clinical development, with only modest inhibition of fructose uptake and metabolism demonstrated by the furthest-developed compound, PF-06835919, in phase 1 and phase 2 clinical studies. While this molecule demonstrated potent inhibition of the isolated KHK-C enzyme, its potency was reduced approximately 10-fold in a cell-based assay of KHK activity, translating to the need for twice-daily 300mg doses in the phase 2 clinical study. Even with these high doses, only modest effects on liver fat and markers of liver injury were observed. As a carboxylic acid, PF-06835919 is a substrate of organic anion transporter protein, leading to increased accumulation in liver relative to other tissues and organs. While KHK-C is preferentially expressed in liver, it is also highly expressed in kidney, intestine and some brain centers, other sites of fructose metabolism to F1P, which may drive metabolic dysregulation, endothelial dysfunction, metabolic disease or craving disorders. Further, PF-06835919 is a KHK-C-biased inhibitor, with much weaker inhibition of KHK-A. PF-06835919 is disclosed in US 2017/0183328 A1. See also, J. Med. Chem. 2020, 63, 13546-13560. In addition, U.S. patent no. 11,124,500 discloses certain disubstituted pyrazole KHK inhibitor compounds. Also, Durham et. al. J. Med Chem. 2023, 66, 15960-15976 *"Identification of LY3522348: A Highly Selective and Orally Efficacious Ketohexokinase Inhibitor",* discloses ketohexokinase inhibitors. While KHK-C drives fructose metabolism in several tissues at physiological fructose concentrations, as fructose concentrations rise (due to diet, metabolic disease, or inhibition of KHK-C), the contribution of KHK-A metabolism of fructose to F1P becomes more substantial.

[0006] Therefore, there is significant need to develop a KHK inhibitor that is potent both in enzyme assays and in cell-based assays; provides balanced inhibition of KHK-C and KHK-A to minimize escape flux to F1P through KHK-A or compensation by KHK-A; and is systemically distributed to inhibit KHK-C and KHK-A in not just liver, but also kidney, intestine, and all other tissues.

SUMMARY

[0007] The present disclosure generally relates to methods of inhibiting ketohexokinase (KHK), to methods of treating or preventing diseases or disorders in a subject (e.g., wherein the diseases or disorders are associated with KHK dysregulation or fructose metabolism, including secondary to excessive consumption of fructose and/or alcohol), and to compounds and compositions that can be employed for such methods.

[0008] The disclosure, in an aspect, provides compounds of Formula (I), and pharmaceutically acceptable salts thereof:



(I)

wherein

each of X^1 and X^2 is independently N or CR^4; Z is N or CR^5; R^1 is H or OH; R^2 is C_{1-6}alkyl or C_{1-6}haloalkyl; R^3 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, or C_{1-6}alkoxy; R^4 is H, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, or C_{3-10} cycloalkyl; R^5 is H, halo, C_{1-6}alkyl, or C_{1-}

$_{6}$haloalkyl; Y is a bond or C_{1-6}alkylene-C(O); A is 5- or 6-membered heteroaryl having 1 to 3 ring nitrogen atoms, wherein the heteroaryl is optionally substituted with 1 or 2 R^6; B is 4- to 8-membered heterocycloalkyl having 1 or 2 ring nitrogen atoms, and is optionally substituted with 1 or 2 R^6; each R^6 independently is OH, halo, CN, -N(R^a)(R^b), C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, or C_{1-6}alkoxy; and R^a and R^b are independently H or C_{1-3}alkyl.

[0008a] The disclosure, in another aspect, provides a compound as recited in Table A, or a pharmaceutically acceptable salt thereof.

[0008b] The disclosure, in a further aspect, provides a compound selected from (2S,3R)-1-{3-chloro-5-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-1,3a,6-triaza-7-indenyl}-2-methyl-3-azetidinol (A18);

7-[(R)-2-(trifluoromethyl)-1-azetidinyl]-4-methyl-5-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-1,3a,6-triazaindene (A11);

7-[(S)-2-methyl-1-azetidinyl]-4-methyl-5-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-1,3a,6-triazaindene (A9);

7-[(R)-2-(trifluoromethyl)-1-azetidinyl]-3-methyl-5-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-1,3a,6-triazaindene (A21);

2-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidinyl]-3-chloro-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone (A29);

7-[(S)-2-methyl-1-azetidinyl]-3-methyl-5-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-1,3a,6-triazaindene (A49);

2-(4-{7-[(S)-2-methyl-1-azetidinyl]-3-chloro-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone (A60); and

7-[(R)-2-(trifluoromethyl)-1-azetidinyl]-4-methyl-5-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-1,3,3a,6-tetraazaindene (A89), or a pharmaceutically acceptable salt thereof.

[0009] Further provided are methods of administering to a biological sample or patient a safe and effective amount of a compound as disclosed herein, e.g., as represented by Formula (I) or a compound of Table A.

[0010] Also provided herein are methods of inhibiting ketohexokinase (KHK) in a biological sample or in a patient (e.g., in a cell) by administering to said biological sample or patient an effective amount of a compound as disclosed herein, e.g., as represented by Formula (I) or a compound of Table A.

[0011] Further provided are methods of treating or preventing diseases or disorders in a subject (e.g., wherein the diseases or disorders are associated with KHK dysregulation or fructose metabolism, including secondary to excessive consumption of fructose and/or alcohol), comprising administering to said subject an effective amount of a compound as disclosed herein, e.g., as represented by Formula (I) or a compound of Table A.

[0012] Also provided are pharmaceutical compositions comprising a compound as disclosed herein, e.g., as represented by Formula (I) or a compound of Table A, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, carrier, adjuvant or vehicle.

[00012a] The disclosure, in another aspect, provides a pharmaceutical composition comprising the compound or salt as disclosed herein and a pharmaceutically acceptable excipient.

[0013] Also provided are uses of a compound described herein for inhibiting ketohexokinase (KHK), e.g., in a cell, and for treating or preventing diseases or disorders in a subject (e.g., wherein the diseases or disorders are associated with KHK dysregulation or fructose metabolism, including secondary to excessive consumption of fructose and/or alcohol).

[0014] Further provided herein are uses of a compound described herein for the manufacture of a medicament for inhibiting ketohexokinase (KHK), and for treating or preventing diseases or disorders in a subject (e.g., wherein the diseases or disorders are associated with KHK dysregulation or fructose metabolism, including via excessive consumption of fructose and/or alcohol).

[0014a] The disclosure, in a further aspect, provides an in vitro method for inhibiting ketohexokinase (KHK) in a cell comprising contacting the cell with the compound or salt as disclosed herein or the pharmaceutical composition as disclosed herein.

[0014b] The disclosure, in another aspect, provides use of a compound or salt as disclosed herein, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating or preventing a disease or disorder associated with aberrant ketohexohinase (KHK) activity in a subject.

[0014c] The disclosure, in another aspect, provides a compound or salt as disclosed herein, or a pharmaceutical composition as disclosed herein, for use in therapy.

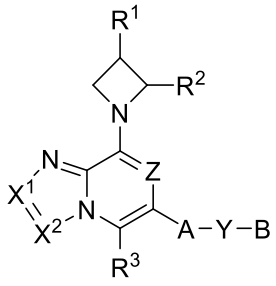
DETAILED DESCRIPTION

[0015] Provided herein are compounds, and their use in inhibiting ketohexokinase (KHK), e.g., in a cell, and for treating or preventing diseases or disorders in a subject (e.g., wherein the diseases or disorders are associated with KHK dysregulation or fructose metabolism, including secondary to excessive consumption of fructose and/or alcohol). Also provided are uses of the compounds described herein, or pharmaceutically acceptable salts thereof, or pharmaceutically acceptable compositions comprising such a compound or a pharmaceutically acceptable salt thereof, for inhibiting ketohexokinase (KHK), e.g., in a cell, and for treating or preventing diseases or disorders in a subject (e.g., wherein the diseases or disorders are associated with KHK dysregulation).

[0016] Unless otherwise indicated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, cis-trans, conformational, and rotational) forms of the structure. For example, the R and S

What is claimed is:

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



(I)

wherein

each of X^1 and X^2 is independently N or CR^4;

Z is N or CR^5;

R^1 is H or OH;

R^2 is C_{1-6}alkyl or C_{1-6}haloalkyl;

R^3 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, or C_{1-6}alkoxy;

R^4 is H, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, or C_{3-10} cycloalkyl;

R^5 is H, halo, C_{1-6}alkyl, or C_{1-6}haloalkyl;

Y is a bond or C_{1-6}alkylene-C(O);

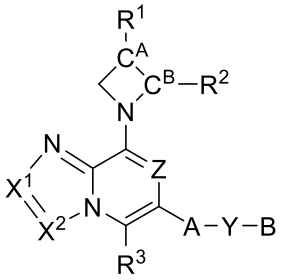
A is 5- or 6-membered heteroaryl having 1 to 3 ring nitrogen atoms, wherein the heteroaryl is optionally substituted with 1 or 2 R^6;

B is 4- to 8-membered heterocycloalkyl having 1 or 2 ring nitrogen atoms, wherein the heterocycloalkyl is optionally substituted with 1 or 2 R^6;

each R^6 independently is OH, halo, CN, $-N(R^a)(R^b)$, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, or C_{1-6}alkoxy; and

R^a and R^b are independently H or C_{1-3}alkyl.

2. The compound or salt of claim 1, having the structure of Formula II:



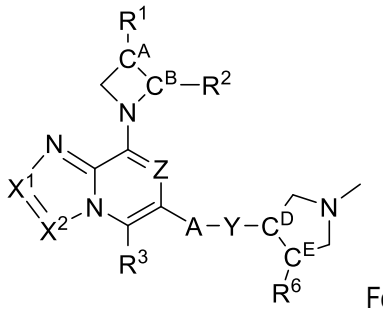
Formula II,

wherein C^A and C^B each represent a carbon stereocenter.

3. The compound or salt of claim 2, wherein C^A is a carbon in the R configuration and C^B is a carbon in the R configuration.

4. The compound or salt of claim 2, wherein C^A is a carbon in the R configuration and C^B is a carbon in the S configuration.

5. The compound or salt of claim 1, having the structure of Formula III:



Formula III

wherein C^A, C^B, C^D and C^E each represent a carbon stereocenter.

6. The compound or salt of claim 5, wherein C^A is a carbon in the R configuration, C^B is a carbon in the R configuration and C^D and C^E are carbons in the R configuration,

7. The compound or salt of claim 5, wherein C^A is a carbon in the R configuration, C^B is a carbon in the R configuration and C^D and C^E are carbons in the S configuration.

8. The compound or salt of claim 5, wherein C^A is a carbon in the R configuration, C^B is a carbon in the R configuration, C^D is a carbon in the R configuration and C^E is a carbon in the S configuration.

9. The compound or salt of claim 5, wherein C^A is a carbon in the R configuration, C^B is a carbon in the R configuration, C^D is a carbon in the S configuration and C^E is a carbon in the R configuration.

10. The compound or salt of claim 5, wherein C^A is a carbon in the R configuration, C^B is a carbon in the S configuration and C^D and C^E are carbons in the R configuration,

11. The compound or salt of claim 5, wherein C^A is a carbon in the R configuration, C^B is a carbon in the S configuration and C^D and C^E are carbons in the S configuration.

12. The compound or salt of claim 5, wherein C^A is a carbon in the R configuration, C^B is a carbon in the S configuration, C^D is a carbon in the R configuration and C^E is a carbon in the S configuration.

13. The compound or salt of claim 5, wherein C^A is a carbon in the R configuration, C^B is a carbon in the S configuration, C^D is a carbon in the S configuration and C^E is a carbon in the R configuration.

14. The compound or salt of any one of claims 1 to 13, wherein one of X^1 and X^2 is N and the other is CR^4.

15. The compound or salt of claim 14, wherein X^1 is N and X^2 is CR^4.

16. The compound or salt of claim 14, wherein X^1 is CR^4 and X^2 is N.

17. The compound or salt of any one of claims 1 to 16, wherein R^4 is H, halo, $C_{1\text{-}6}$alkyl, or $C_{1\text{-}6}$haloalkyl.

18. The compound or salt of claim 17, wherein R^4 is H, $C_{1\text{-}6}$alkyl, or $C_{1\text{-}6}$haloalkyl.

19. The compound or salt of claim 17 or 18, wherein R^4 is H, methyl, or CF_3.

20. The compound or salt of claim 17, wherein R^4 is halo.

21. The compound or salt of claim 20, wherein R^4 is fluoro.

22. The compound or salt of any one of claims 1 to 16, wherein R^4 is C_{3-10} cycloalkyl.

23. The compound or salt of claim 22, wherein R^4 is cyclopropyl.

24. The compound or salt of any one of claims 1 to 23, wherein Z is N.

25. The compound or salt of any one of claims 1 to 23, wherein Z is CR^5.

26. The compound or salt of any one of claims 1 or 14 to 25, wherein R^1 is H.

27. The compound or salt of any one of claims 1 to 25, wherein R^1 is OH.

28. The compound or salt of any one of claims 1 to 27, wherein R^2 is C_{1-6}alkyl.

29. The compound or salt of claim 28, wherein R^2 is methyl.

30. The compound or salt of any one of claims 1 to 27, wherein R^2 is C_{1-6}haloalkyl.

31. The compound or salt of claim 30, wherein R^2 is CHF_2 or CF_3.

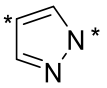
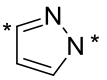
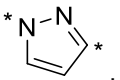
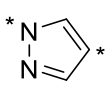
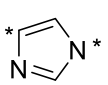
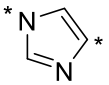
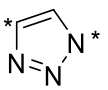
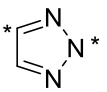
32. The compound or salt of any one of claims 1 to 31, wherein R^3 is H or C_{1-6}alkyl.

33. The compound or salt of claim 32, wherein R^3 is H or methyl.

34. The compound or salt of any one of claims 1 to 33, wherein A is a 5-membered heteroaryl having 1 to 3 ring nitrogen atoms, and is optionally substituted with 1 or 2 R^6.

35. The compound or salt of claim 34, wherein A is pyrazolyl, imidazolyl, or triazolyl, and is optionally substituted with 1 or 2 R^6.

36. The compound or salt of claim 34 or 35, wherein A is unsubstituted.

37. The compound or salt of any one of claims 34 to 36, wherein A is , , , , , , , or , each * indicates a point of attachment to the rest of the compound, and A is optionally substituted with 1 or 2 R^6.

38. The compound or salt of any one of claims 1 to 37, wherein Y is a bond.

39. The compound or salt of any one of claims 1 to 37, wherein Y is C_{1-6}alkylene-C(O).

40. The compound or salt of claim 39, wherein Y is C_1alkylene-C(O).

41. The compound or salt of any one of claims 1 to 40, wherein B is a 4- to 8-membered heterocycloalkyl having 1 or 2 ring nitrogen atoms, and is optionally substituted with 1 or 2 R^6.

42. The compound or salt of any one of claims 1 to 4 or 14 to 41, wherein B is a 4- or 6-membered heterocycloalkyl having 1 or 2 ring nitrogen atoms, and is optionally substituted with 1 or 2 R^6.

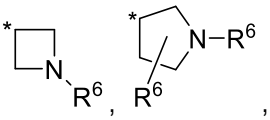
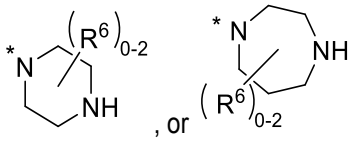
43. The compound or salt of claim 42, wherein B is azetidinyl, pyrrolidinyl, piperazinyl, or diazepinyl, and is optionally substituted with 1 or 2 R^6.

44. The compound or salt of claim 43, wherein B is azetidinyl or piperazinyl, and is optionally substituted with 1 or 2 R^6.

45. The compound or salt of any one of claims 1 to 4 and 14 to 44, wherein B is unsubstituted.

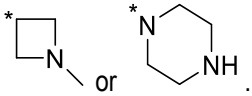
46. The compound or salt of any one of claims 1 to 44, wherein B is substituted with one R^6.

47. The compound or salt of any one of claims 1 to 44, wherein B is substituted with two R^6.

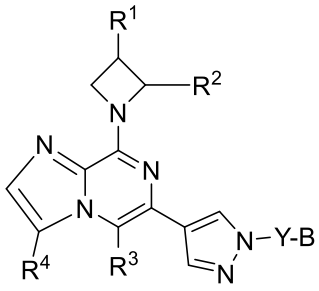
48. The compound or salt of any one of claims 1 to 4 or 14 to 41, wherein B is , , or , and * indicates a point of attachment to the rest of the compound.

49. The compound or salt of any one of claims 46 to 48, wherein at least one R^6 is $C_{1\text{-}6}$alkyl.

50. The compound or salt of claim 49, wherein at least one R^6 is methyl.

51. The compound or salt of claim 48, wherein B is .

52. The compound or salt of any one of claims 1-4, 26, and 27, having a structure of Formula (IV):


(IV)

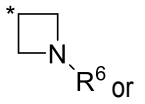
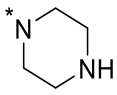
wherein

R^4 is H, chloro, fluoro or $C_{1\text{-}2}$alkyl,

R^2 is trifluoromethyl or $C_{1\text{-}2}$alkyl,

R^3 is H or $C_{1\text{-}2}$alkyl,

Y is a bond or C_1alkylene-C(O),

B is  or , and

R^6 is $C_{1\text{-}2}$alkyl.

53. A compound as recited in Table A, or a pharmaceutically acceptable salt thereof.

54. A compound selected from (2S,3R)-1-{3-chloro-5-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-1,3a,6-triaza-7-indenyl}-2-methyl-3-azetidinol (A18);

    7-[(R)-2-(trifluoromethyl)-1-azetidinyl]-4-methyl-5-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-1,3a,6-triazaindene (A11);

    7-[(S)-2-methyl-1-azetidinyl]-4-methyl-5-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-1,3a,6-triazaindene (A9);

    7-[(R)-2-(trifluoromethyl)-1-azetidinyl]-3-methyl-5-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-1,3a,6-triazaindene (A21);

    2-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidinyl]-3-chloro-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone (A29);

    7-[(S)-2-methyl-1-azetidinyl]-3-methyl-5-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-1,3a,6-triazaindene (A49);

    2-(4-{7-[(S)-2-methyl-1-azetidinyl]-3-chloro-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone (A60); and

    7-[(R)-2-(trifluoromethyl)-1-azetidinyl]-4-methyl-5-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-1,3,3a,6-tetraazaindene (A89), or a pharmaceutically acceptable salt thereof.

55. A pharmaceutical composition comprising the compound or salt of any one of claims 1 to 54 and a pharmaceutically acceptable excipient.

56. An in vitro method for inhibiting ketohexokinase (KHK) in a cell comprising contacting the cell with the compound or salt of any one of claims 1 to 54 or the pharmaceutical composition of claim 55.

57. Use of a compound or salt of any one of claims 1 to 54, or a pharmaceutical composition of claim 55, in the manufacture of a medicament for treating or preventing a disease or disorder associated with aberrant ketohexohinase (KHK) activity in a subject.

58. The use of claim 57, wherein the disease or disorder is associated with KHK dysregulation.

59. The use of claim 57 or 58, wherein the disease or disorder is metabolic syndrome, hypertriglyceridemia, hypercholesterolemia, non-alcoholic fatty liver disease (NAFLD), metabolic dysfunction-associated steatotic liver disease (MASLD), MASLD with increased alcohol intake (MetALD), non-alcoholic steatohepatitis (NASH), metabolic dysfunction-associated steatohepatitis (MASH), type 2 diabetes mellitus (T2D), diabetic kidney disease (DKD), alcoholic steatohepatitis (ASH), alcohol-associated liver disease (ALD), liver fibrosis or

cirrhosis, liver disease caused by hepatocellular stress, hereditary fructose intolerance, hyperuricemia, gout, addictive craving, a neurodegenerative disease, or cancer.

60. The use of claim 59, wherein the disease or disorder is NASH or MASH.

61. The use of any one of claims 56 to 60, wherein an additional therapeutic agent is to be further administered to the subject.

62. The use of claim 61, wherein the additional therapeutic agent comprises metformin, a fructose transporter inhibitor, an aldose reductase inhibitor, a xanthine oxidase inhibitor, a thyroid hormone beta-receptor agonist, an incretin hormone receptor agonist or modulator, or a sodium/glucose transporter inhibitor.

63. The use of claim 62, wherein the incretin hormone receptor agonist or modulator is semaglutide, dulaglutide, liraglutide, tirzepatide, survodutide, retatrutide, pemvidutide, VK2735, orforglipron, cagrilintide/semaglutide, danuglipron, maridebart cafraglutide, RGT-075, PF-0695422, NN9487, NN9541, CT-388, CT-868, CT-996, efinopegdutide, efocipegtrutide, AZD9550, DR10624, NLY01, ECC5004, mazdutide, exenatide, TERN-601, ecnoglutide, or XW-004.

64. The use of claim 63, wherein the fructose transporter inhibitor is an inhibitor of GLUT2, GLUT5, or both.

65. The use of claim 63, wherein the aldose reductase inhibitor is AT-001, AT-003, gavorestat, ranirestat, epalrestat, fidarestat, imirestat, tolrestat, or risarestat.

66. A compound or salt of any one of claims 1 to 54, or a pharmaceutical composition of claim 55, for use in therapy.