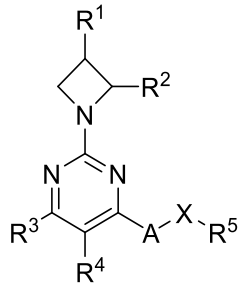
[0005] Attempts to inhibit KHK have thus far stalled in preclinical or clinical development, with only modest inhibition of fructose uptake and metabolism demonstrated by the furthest-developed compound, PF-06835919, in phase 1 and phase 2 clinical studies. While this molecule demonstrated potent inhibition 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.

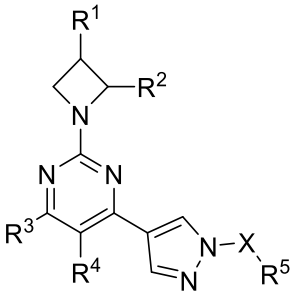
[0008] The disclosure, in an aspect, provides compounds of Formula I, and pharmaceutically acceptable salts thereof:



(I)

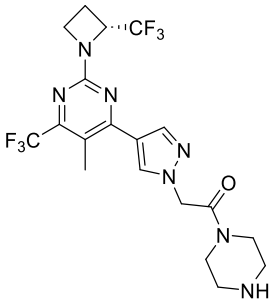
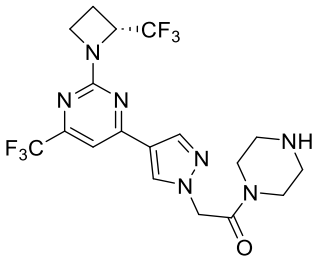
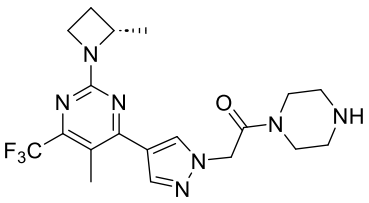
wherein R^1 is H or OH; R^2 is C_{1-6}alkyl or C_{1-6}haloalkyl; R^3 is C_{1-6}alkyl or C_{1-6}haloalkyl; R^4 is H, halo, CN, C_{1-6}alkyl, C_{1-6}alkoxy, or C_{3-5}cycloalkyl; A is a 5-membered heteroaryl comprising 2-3 nitrogen ring atoms; X is a bond or C_{1-6}alkylene-C(O); and R^5 is 4- to 6-membered heterocycloalkyl having 1 or 2 ring nitrogen atoms, wherein the heterocycloalkyl is

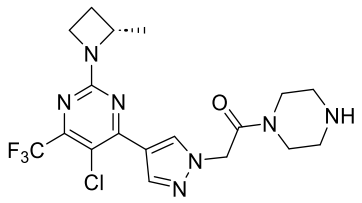
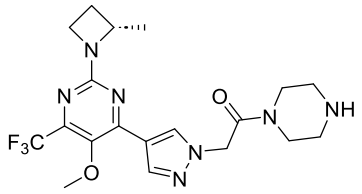
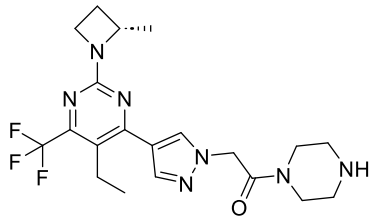
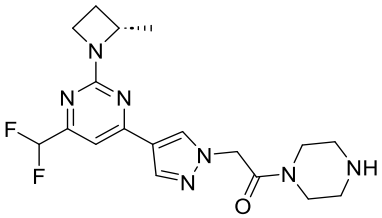
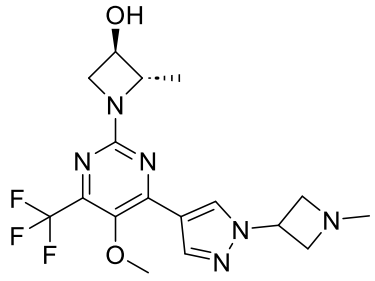
optionally substituted with 1 or 2 C_{1-6}alkyl, with the proviso that when R^4 is H, compounds where both R^2 is methyl and R^3 is trifluoromethyl are excluded. In examples, A is pyrazolyl. In examples, the compounds have the structure of Formula Ix:

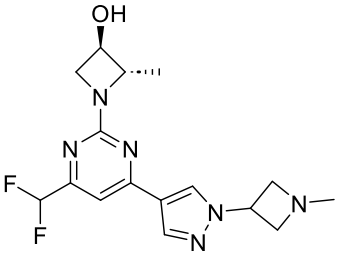
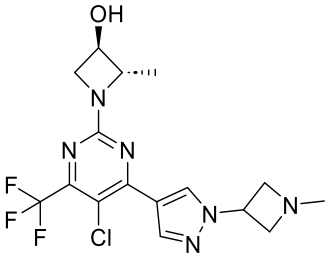
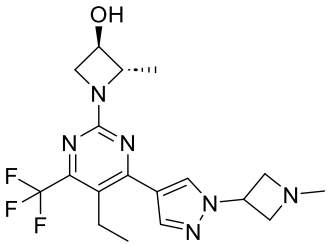
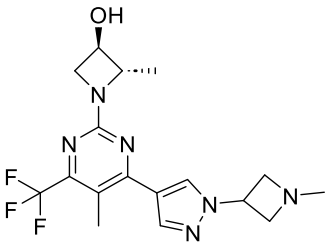
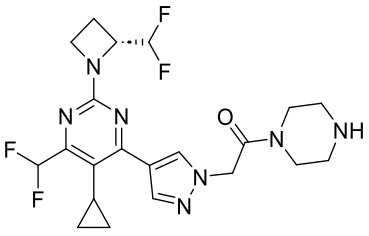

(Ix).

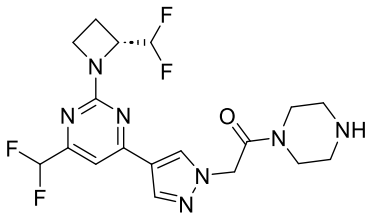
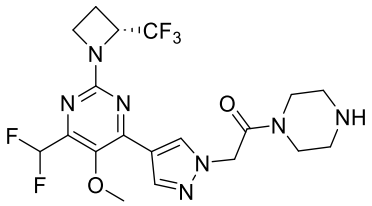
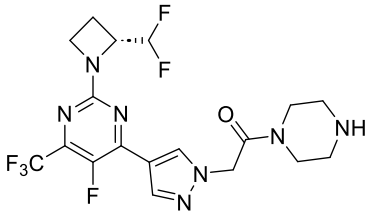
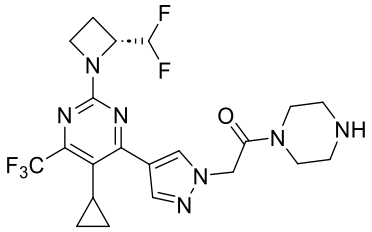
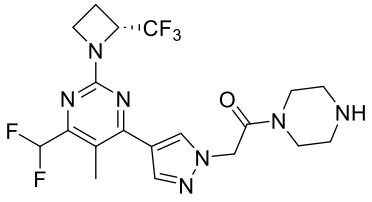
[0008a] In another aspect of the present disclosure, there is provided a compound as recited in Table A, or a pharmaceutically acceptable salt thereof:

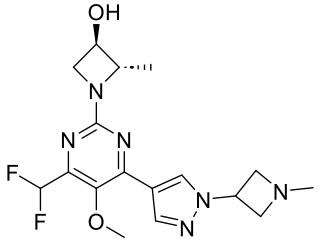
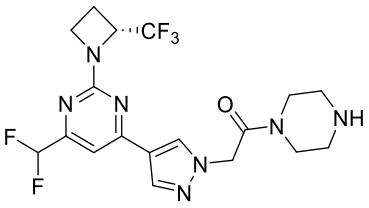
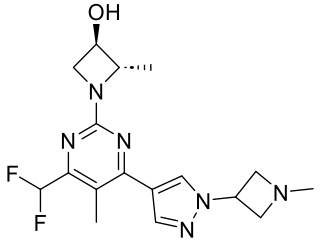
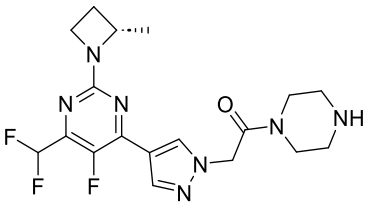
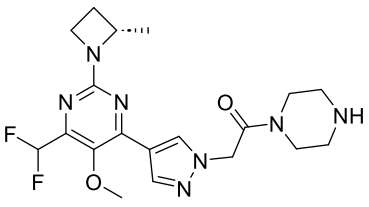
TABLE A

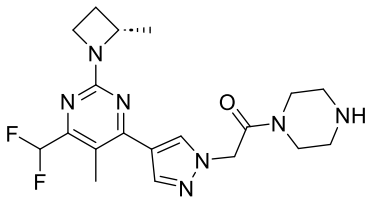
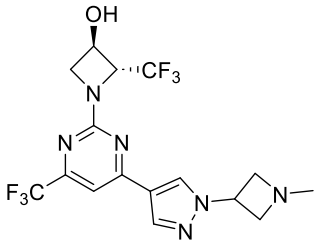
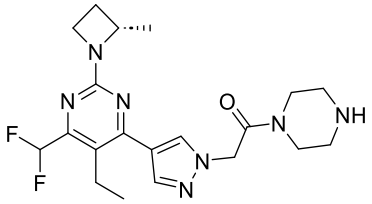
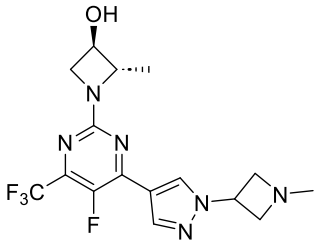
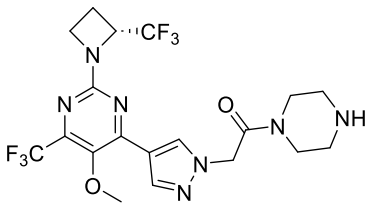
	Name	Structure
A1	2-(4-{2-[(R)-2-(trifluoromethyl)-1-azetidinyl]-5-methyl-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A2	2-(4-{2-[(R)-2-(trifluoromethyl)-1-azetidinyl]-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A3	2-(4-{2-[(S)-2-methyl-1-azetidinyl]-5-methyl-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	

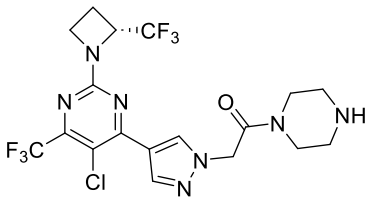
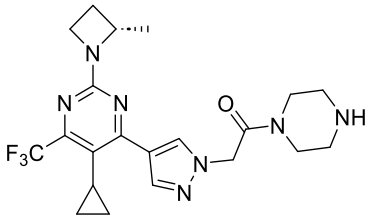
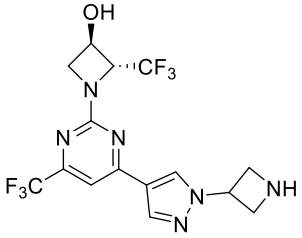
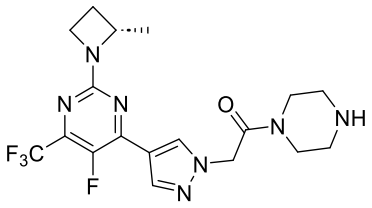
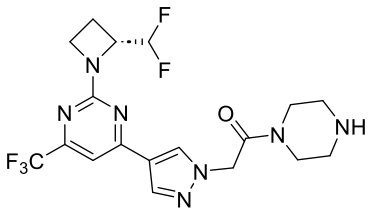
A4	2-(4-{2-[(S)-2-methyl-1-azetidinyl]-5-chloro-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A5	2-(4-{2-[(S)-2-methyl-1-azetidinyl]-5-methoxy-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A6	2-(4-{2-[(S)-2-methyl-1-azetidinyl]-5-ethyl-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A7	2-(4-{2-[(S)-2-methyl-1-azetidinyl]-6-(difluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A8	(2S,3R)-1-{5-methoxy-4-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-6-(trifluoromethyl)-2-pyrimidinyl}-2-methyl-3-azetidinol	

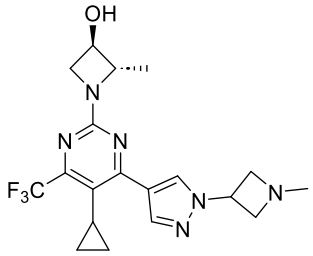
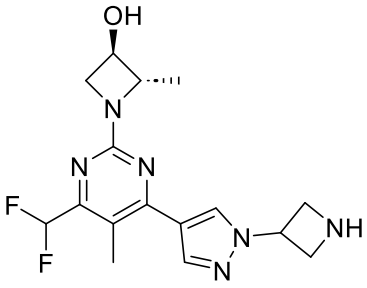
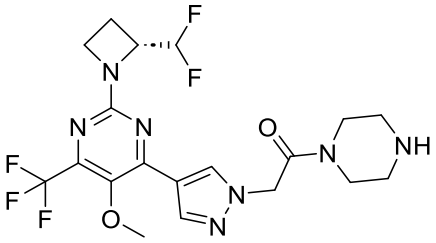
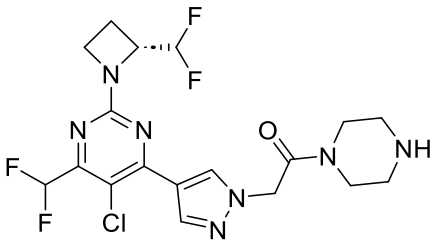
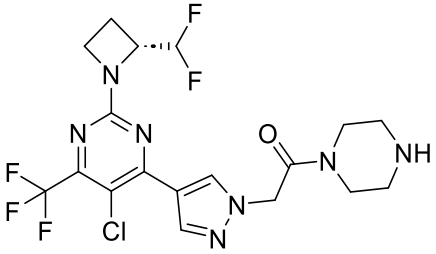
A9	(2S,3R)-1-{6-(difluoromethyl)-4-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-2-pyrimidinyl}-2-methyl-3-azetidinol	
A10	(2S,3R)-1-{5-chloro-4-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-6-(trifluoromethyl)-2-pyrimidinyl}-2-methyl-3-azetidinol	
A11	(2S,3R)-1-{5-ethyl-4-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-6-(trifluoromethyl)-2-pyrimidinyl}-2-methyl-3-azetidinol	
A12	(2S,3R)-2-methyl-1-{5-methyl-4-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-6-(trifluoromethyl)-2-pyrimidinyl}-3-azetidinol	
A13	2-(4-{2-[(R)-2-(difluoromethyl)-1-azetidinyl]-5-cyclopropyl-6-(difluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	

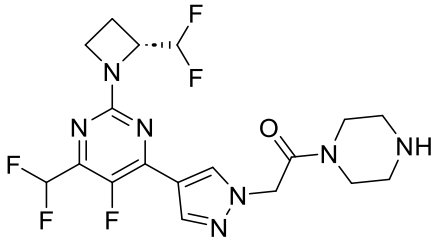
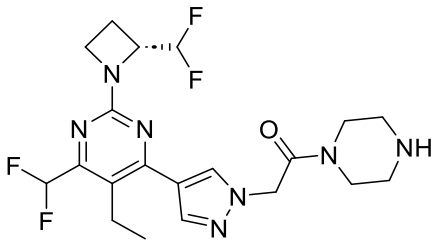
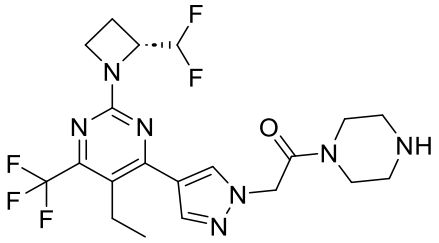
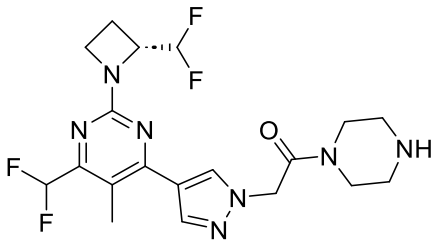
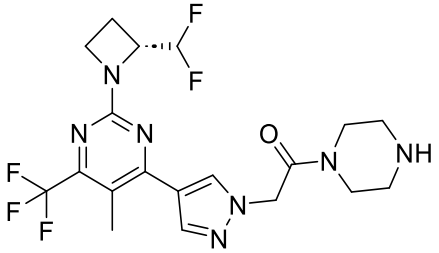
A14	2-(4-{2-[(R)-2-(difluoromethyl)-1-azetidinyl]-6-(difluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A15	2-(4-{2-[(R)-2-(trifluoromethyl)-1-azetidinyl]-6-(difluoromethyl)-5-methoxy-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A16	2-(4-{2-[(R)-2-(difluoromethyl)-1-azetidinyl]-5-fluoro-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A17	2-(4-{2-[(R)-2-(difluoromethyl)-1-azetidinyl]-5-cyclopropyl-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A18	2-(4-{2-[(R)-2-(trifluoromethyl)-1-azetidinyl]-6-(difluoromethyl)-5-methyl-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	

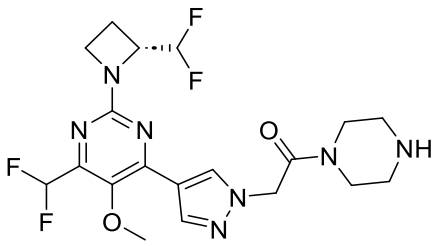
A19	(2S,3R)-1-{6-(difluoromethyl)-5-methoxy-4-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-2-pyrimidinyl}-2-methyl-3-azetidinol	
A20	2-(4-{2-[(R)-2-(trifluoromethyl)-1-azetidinyl]-6-(difluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A21	(2S,3R)-1-{6-(difluoromethyl)-5-methyl-4-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-2-pyrimidinyl}-2-methyl-3-azetidinol	
A22	2-(4-{2-[(S)-2-methyl-1-azetidinyl]-6-(difluoromethyl)-5-fluoro-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A23	2-(4-{2-[(S)-2-methyl-1-azetidinyl]-6-(difluoromethyl)-5-methoxy-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	

A24	2-(4-{2-[(S)-2-methyl-1-azetidinyl]-6-(difluoromethyl)-5-methyl-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A25	(2R,3R)-1-{4-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-6-(trifluoromethyl)-2-pyrimidinyl}-2-(trifluoromethyl)-3-azetidinol	
A26	2-(4-{2-[(S)-2-methyl-1-azetidinyl]-6-(difluoromethyl)-5-ethyl-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A27	(2S,3R)-1-{5-fluoro-4-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-6-(trifluoromethyl)-2-pyrimidinyl}-2-methyl-3-azetidinol	
A28	2-(4-{2-[(R)-2-(trifluoromethyl)-1-azetidinyl]-5-methoxy-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	

A29	2-(4-{2-[(R)-2-(trifluoromethyl)-1-azetidinyl]-5-chloro-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A30	2-(4-{2-[(S)-2-methyl-1-azetidinyl]-5-cyclopropyl-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A31	(2R,3R)-1-{4-[1-(3-azetidinyl)-4-pyrazolyl]-6-(trifluoromethyl)-2-pyrimidinyl}-2-(trifluoromethyl)-3-azetidinol	
A32	2-(4-{2-[(S)-2-methyl-1-azetidinyl]-5-fluoro-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A33	2-(4-{2-[(R)-2-(difluoromethyl)-1-azetidinyl]-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	

A34	(2S,3R)-1-{5-cyclopropyl-4-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-6-(trifluoromethyl)-2-pyrimidinyl}-2-methyl-3-azetidinol	
A35	(2S,3R)-1-{4-[1-(3-azetidinyl)-4-pyrazolyl]-6-(difluoromethyl)-5-methyl-2-pyrimidinyl}-2-methyl-3-azetidinol	
A36	2-(4-{2-[(R)-2-(difluoromethyl)-1-azetidinyl]-5-methoxy-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A37	2-(4-{2-[(R)-2-(difluoromethyl)-1-azetidinyl]-5-chloro-6-(difluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A38	2-(4-{2-[(R)-2-(difluoromethyl)-1-azetidinyl]-5-chloro-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	

A39	2-(4-{2-[(R)-2-(difluoromethyl)-1-azetidinyl]-6-(difluoromethyl)-5-fluoro-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A40	2-(4-{2-[(R)-2-(difluoromethyl)-1-azetidinyl]-6-(difluoromethyl)-5-ethyl-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A41	2-(4-{2-[(R)-2-(difluoromethyl)-1-azetidinyl]-5-ethyl-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A42	2-(4-{2-[(R)-2-(difluoromethyl)-1-azetidinyl]-6-(difluoromethyl)-5-methyl-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A43	2-(4-{2-[(R)-2-(difluoromethyl)-1-azetidinyl]-5-methyl-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	

A44	2-(4-{2-[(R)-2-(difluoromethyl)-1-azetidinyl]-6-(difluoromethyl)-5-methoxy-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	

.

[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.

[0012a] In another aspect of the present disclosure, there is provided 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).

[0013a] In another aspect of the present disclosure, there is provided a compound or salt as disclosed herein, or a pharmaceutical composition as disclosed herein, for use in inhibiting ketohexokinase (KHK) in a cell.

[0013b] In a further aspect of the present disclosure, there is provided a compound or salt as disclosed herein, or a pharmaceutical composition as disclosed herein, for use in treating or preventing a disease or disorder in a subject.

[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] In another aspect of the present disclosure, there is provided a use of a compound or salt as disclosed herein, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating a disease or disorder in a subject, 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.

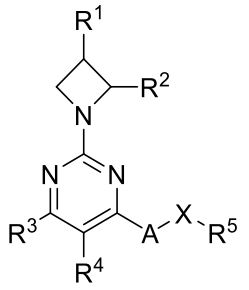
BRIEF DESCRIPTION OF THE DRAWINGS

[0015] FIG 1 shows an XPRD diffractogram comparison between A21 Free Base (top trace) and A21 HCl salt (bottom trace).

[0016] FIG 2 shows an ^{1}H NMR spectrum comparison between A21 Free Base and HCl salt (DMSO- d6).

What is claimed is:

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



(I)

wherein

R^1 is H or OH;

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

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

R^4 is H, halo, CN, C_{1-6}alkyl, C_{1-6}alkoxy, or C_{3-5}cycloalkyl;

A is a 5-membered heteroaryl comprising 2-3 nitrogen ring atoms;

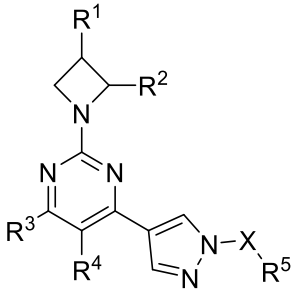
X is a bond or C_{1-6}alkylene-C(O); and

R^5 is 4- to 6-membered heterocycloalkyl having 1 or 2 ring nitrogen atoms, wherein the heterocycloalkyl is optionally substituted with 1 or 2 C_{1-6}alkyl;

with the proviso that when R^4 is H, compounds where both R^2 is methyl and R^3 is trifluoromethyl are excluded.

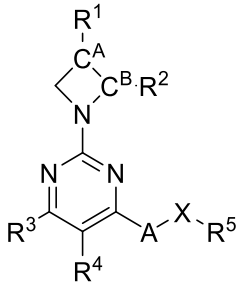
2. The compound or salt of claim 1, wherein A is pyrazolyl.

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



(Ix).

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



(II), wherein C^A and C^B represent carbon stereocenters having the same or opposite stereochemistry.

5. 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.

6. The compound or salt of claim 4 or 5, wherein A is pyrazolyl.

7. The compound or salt of any one of claims 1 to 6, wherein:

   (i) R^5 is 4-membered heterocycloalkyl having 1 ring nitrogen atom, wherein the heterocycloalkyl is optionally substituted with 1 or 2 C_{1-6}alkyl; or

   (ii) R^5 is 6-membered heterocycloalkyl having 2 ring nitrogen atoms, wherein the heterocycloalkyl is optionally substituted with 1 or 2 C_{1-6}alkyl.

8. The compound or salt of claim 7, wherein R^5 is unsubstituted.

9. The compound or salt of claim 7, wherein R^5 is substituted with 1 C_{1-6}alkyl.

10. The compound or salt of any one of claims 1 to 9, wherein R^2 is methyl.

11. The compound or salt of any one of claims 1 to 9, wherein R^2 is CHF_2 or CF_3.

12. The compound or salt of any one of claims 1 to 11, wherein R^3 is CHF_2 or CF_3.

13. The compound or salt of any one of claims 1 to 12, wherein R^4 is H.

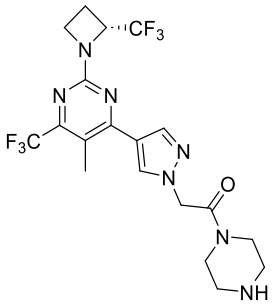
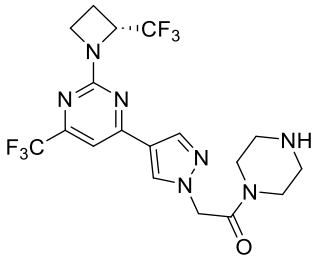
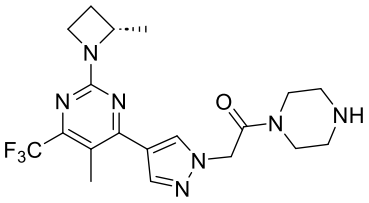
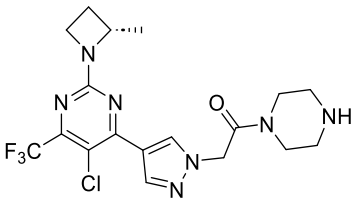
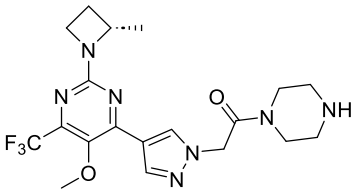
14. The compound or salt of any one of claims 1 to 13, wherein R^3 is CHF_2 and R^4 is methyl.

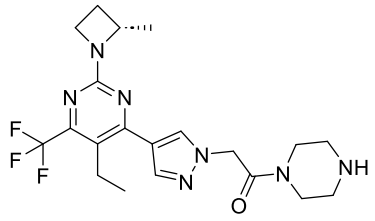
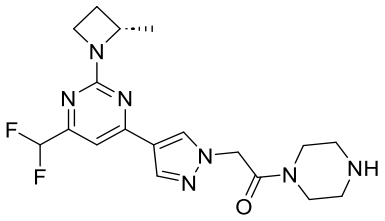
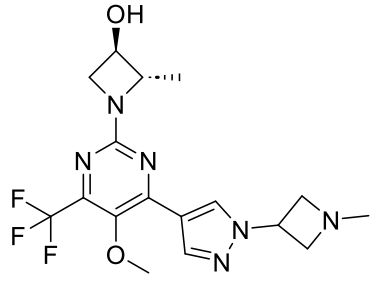
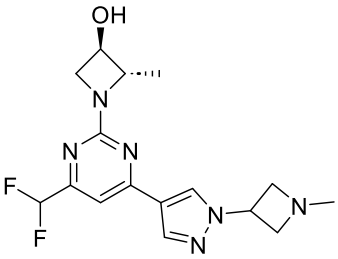
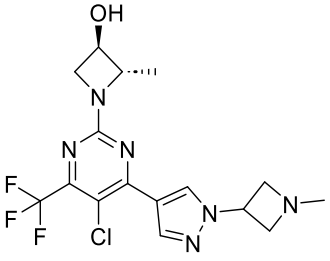
15. The compound of claim 5 wherein R^1 is H or hydroxy, R^2 is methyl, R^3 is CHF_2, R^4 is methyl, X is a bond and R^5 is a 4- to 6-membered heterocycloalkyl having 1 ring nitrogen atom, wherein the heterocycloalkyl is optionally substituted with C_{1-2}alkyl.

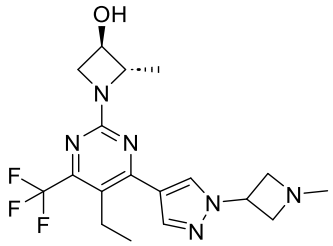
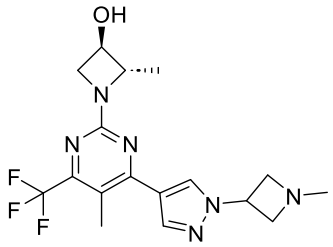
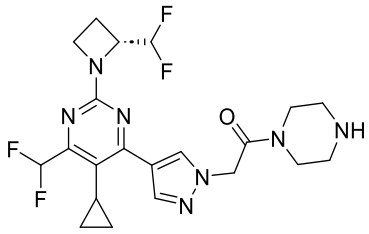
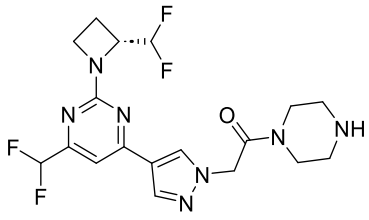
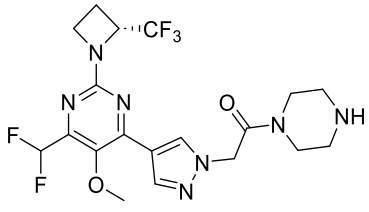
16. The compound of claim 5 wherein X is C_{1-6}alkylene-C(O), R^5 is azetidinyl optionally substituted with 1 or 2 C_{1-6}alkyl, R^1 is H or hydroxy, R^2 is C_{1-3}alkyl, R^3 is CHF_2, and R^4 is methyl.

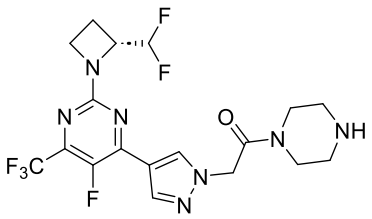
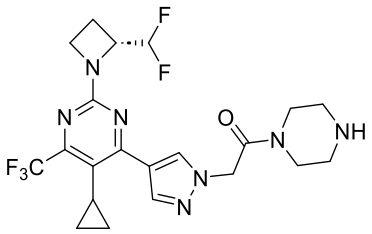
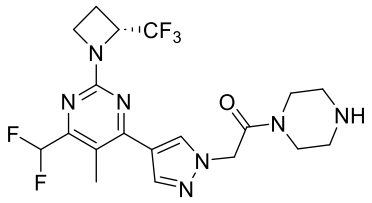
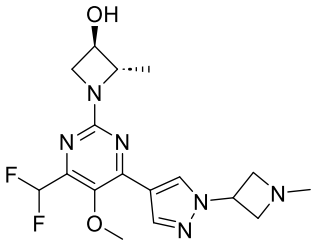
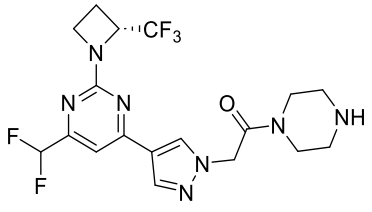
17. A compound as recited in Table A, or a pharmaceutically acceptable salt thereof:

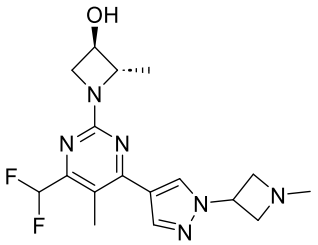
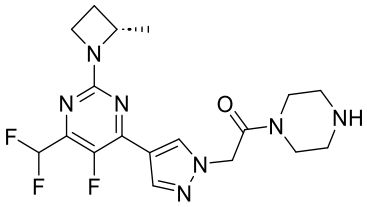
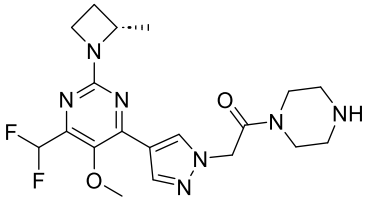
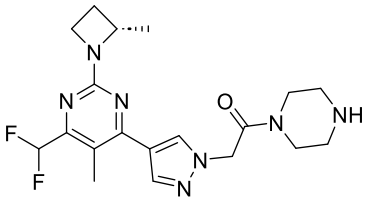
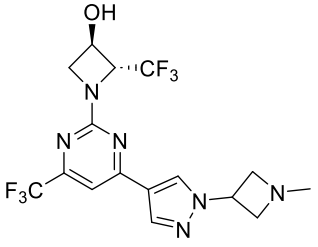
TABLE A

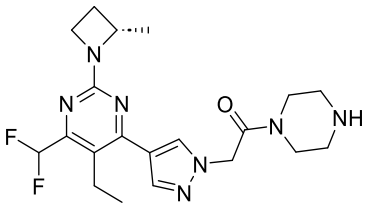
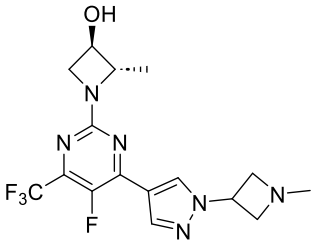
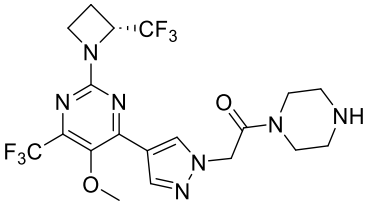
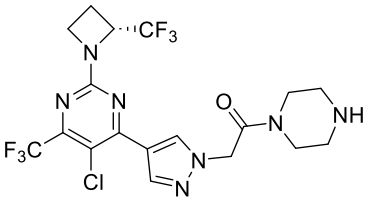
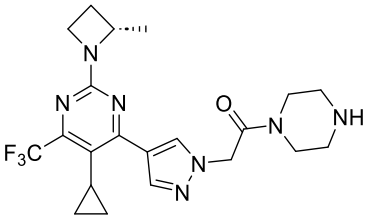
	Name	Structure
A1	2-(4-{2-[(R)-2-(trifluoromethyl)-1-azetidinyl]-5-methyl-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A2	2-(4-{2-[(R)-2-(trifluoromethyl)-1-azetidinyl]-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A3	2-(4-{2-[(S)-2-methyl-1-azetidinyl]-5-methyl-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A4	2-(4-{2-[(S)-2-methyl-1-azetidinyl]-5-chloro-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A5	2-(4-{2-[(S)-2-methyl-1-azetidinyl]-5-methoxy-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	

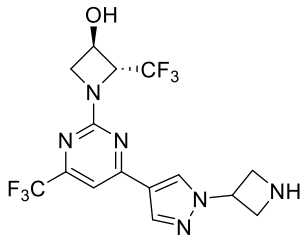
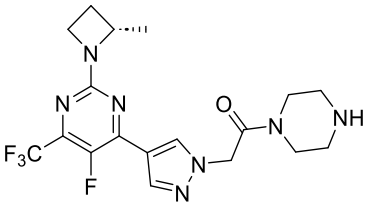
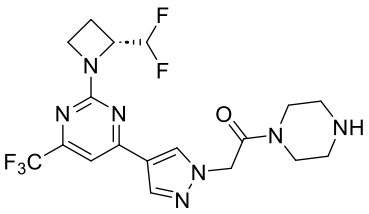
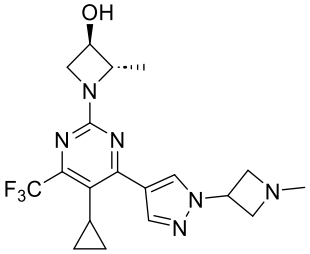
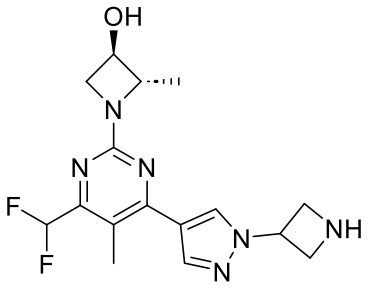
	Name	Structure
A6	2-(4-{2-[(S)-2-methyl-1-azetidinyl]-5-ethyl-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A7	2-(4-{2-[(S)-2-methyl-1-azetidinyl]-6-(difluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A8	(2S,3R)-1-{5-methoxy-4-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-6-(trifluoromethyl)-2-pyrimidinyl}-2-methyl-3-azetidinol	
A9	(2S,3R)-1-{6-(difluoromethyl)-4-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-2-pyrimidinyl}-2-methyl-3-azetidinol	
A10	(2S,3R)-1-{5-chloro-4-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-6-(trifluoromethyl)-2-pyrimidinyl}-2-methyl-3-azetidinol	

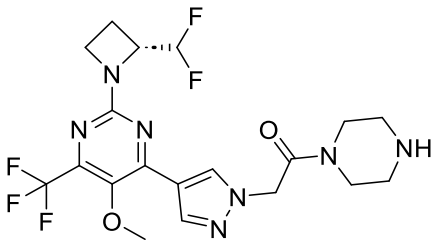
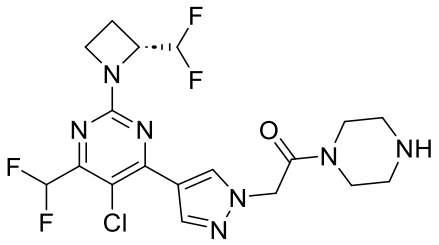
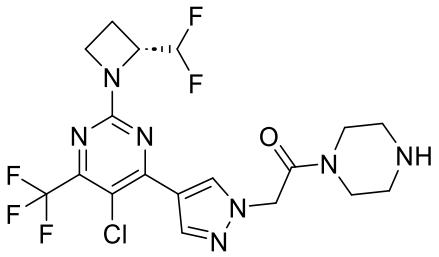
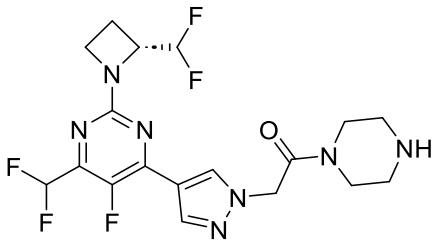
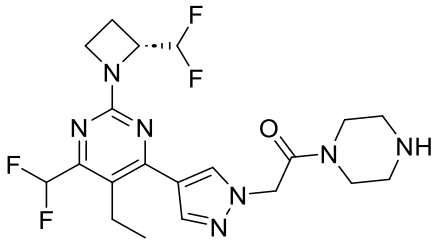
	Name	Structure
A11	(2S,3R)-1-{5-ethyl-4-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-6-(trifluoromethyl)-2-pyrimidinyl}-2-methyl-3-azetidinol	
A12	(2S,3R)-2-methyl-1-{5-methyl-4-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-6-(trifluoromethyl)-2-pyrimidinyl}-3-azetidinol	
A13	2-(4-{2-[(R)-2-(difluoromethyl)-1-azetidinyl]-5-cyclopropyl-6-(difluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A14	2-(4-{2-[(R)-2-(difluoromethyl)-1-azetidinyl]-6-(difluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A15	2-(4-{2-[(R)-2-(trifluoromethyl)-1-azetidinyl]-6-(difluoromethyl)-5-methoxy-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	

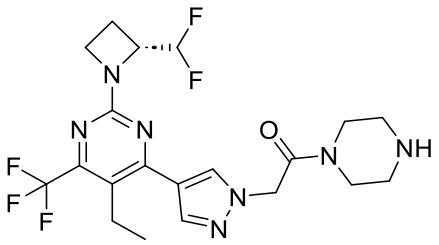
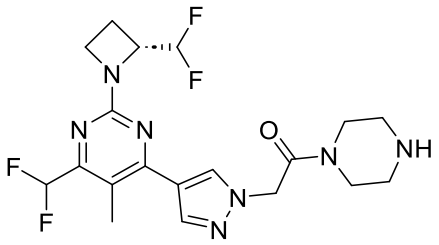
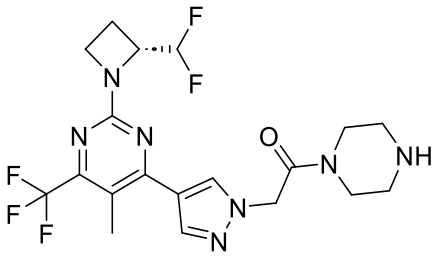
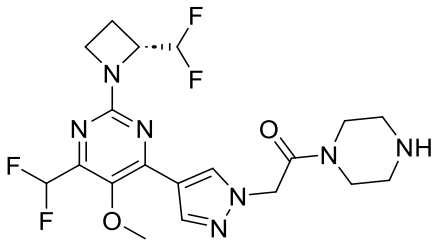
	Name	Structure
A16	2-(4-{2-[(R)-2-(difluoromethyl)-1-azetidinyl]-5-fluoro-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A17	2-(4-{2-[(R)-2-(difluoromethyl)-1-azetidinyl]-5-cyclopropyl-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A18	2-(4-{2-[(R)-2-(trifluoromethyl)-1-azetidinyl]-6-(difluoromethyl)-5-methyl-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A19	(2S,3R)-1-{6-(difluoromethyl)-5-methoxy-4-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-2-pyrimidinyl}-2-methyl-3-azetidinol	
A20	2-(4-{2-[(R)-2-(trifluoromethyl)-1-azetidinyl]-6-(difluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	

	Name	Structure
A21	(2S,3R)-1-{6-(difluoromethyl)-5-methyl-4-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-2-pyrimidinyl}-2-methyl-3-azetidinol	
A22	2-(4-{2-[(S)-2-methyl-1-azetidinyl]-6-(difluoromethyl)-5-fluoro-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A23	2-(4-{2-[(S)-2-methyl-1-azetidinyl]-6-(difluoromethyl)-5-methoxy-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A24	2-(4-{2-[(S)-2-methyl-1-azetidinyl]-6-(difluoromethyl)-5-methyl-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A25	(2R,3R)-1-{4-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-6-(trifluoromethyl)-2-pyrimidinyl}-2-(trifluoromethyl)-3-azetidinol	

	Name	Structure
A26	2-(4-{2-[(S)-2-methyl-1-azetidinyl]-6-(difluoromethyl)-5-ethyl-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A27	(2S,3R)-1-{5-fluoro-4-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-6-(trifluoromethyl)-2-pyrimidinyl}-2-methyl-3-azetidinol	
A28	2-(4-{2-[(R)-2-(trifluoromethyl)-1-azetidinyl]-5-methoxy-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A29	2-(4-{2-[(R)-2-(trifluoromethyl)-1-azetidinyl]-5-chloro-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A30	2-(4-{2-[(S)-2-methyl-1-azetidinyl]-5-cyclopropyl-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	

	Name	Structure
A31	(2R,3R)-1-{4-[1-(3-azetidinyl)-4-pyrazolyl]-6-(trifluoromethyl)-2-pyrimidinyl}-2-(trifluoromethyl)-3-azetidinol	
A32	2-(4-{2-[(S)-2-methyl-1-azetidinyl]-5-fluoro-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A33	2-(4-{2-[(R)-2-(difluoromethyl)-1-azetidinyl]-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A34	(2S,3R)-1-{5-cyclopropyl-4-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-6-(trifluoromethyl)-2-pyrimidinyl}-2-methyl-3-azetidinol	
A35	(2S,3R)-1-{4-[1-(3-azetidinyl)-4-pyrazolyl]-6-(difluoromethyl)-5-methyl-2-pyrimidinyl}-2-methyl-3-azetidinol	

	Name	Structure
A36	2-(4-{2-[(R)-2-(difluoromethyl)-1-azetidinyl]-5-methoxy-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A37	2-(4-{2-[(R)-2-(difluoromethyl)-1-azetidinyl]-5-chloro-6-(difluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A38	2-(4-{2-[(R)-2-(difluoromethyl)-1-azetidinyl]-5-chloro-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A39	2-(4-{2-[(R)-2-(difluoromethyl)-1-azetidinyl]-6-(difluoromethyl)-5-fluoro-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A40	2-(4-{2-[(R)-2-(difluoromethyl)-1-azetidinyl]-6-(difluoromethyl)-5-ethyl-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	

	Name	Structure
A41	2-(4-{2-[(R)-2-(difluoromethyl)-1-azetidinyl]-5-ethyl-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A42	2-(4-{2-[(R)-2-(difluoromethyl)-1-azetidinyl]-6-(difluoromethyl)-5-methyl-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A43	2-(4-{2-[(R)-2-(difluoromethyl)-1-azetidinyl]-5-methyl-6-(trifluoromethyl)-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A44	2-(4-{2-[(R)-2-(difluoromethyl)-1-azetidinyl]-6-(difluoromethyl)-5-methoxy-4-pyrimidinyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	

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18. A pharmaceutical composition comprising the compound or salt of any one of claims 1 to 17 and a pharmaceutically acceptable excipient.

19. A compound or salt of any one of claims 1 to 17, or a pharmaceutical composition of claim 18, for use in inhibiting ketohexokinase (KHK) in a cell.

20. A compound or salt of any one of claims 1 to 17, or a pharmaceutical composition of claim 18, for use in treating or preventing a disease or disorder in a subject.

21. Use of a compound or salt of any one of claims 1 to 17, or a pharmaceutical composition of claim 18, in the manufacture of a medicament for treating a disease or disorder in a subject, 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.