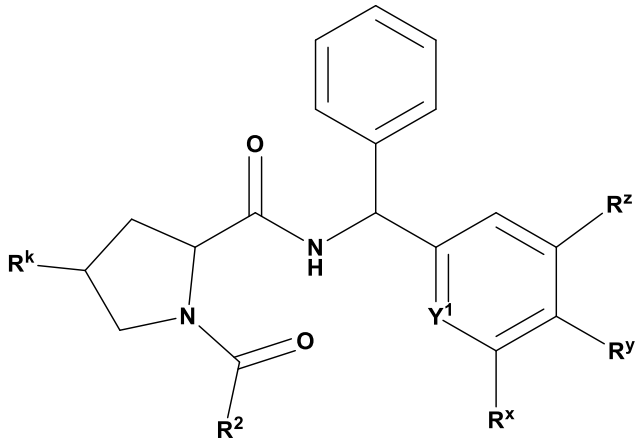
[0005] The reliance on high levels of glycogen by clear cell cancers has recently emerged as a novel therapeutic target. Ewing sarcoma (ES), clear cell renal cell carcinoma (ccRCC), glycogen rich clear cell carcinoma breast cancer (GRCC), acute myeloid leukemia (AML), and nonsmall-cell lung carcinoma (NSCLC) are all examples of cancers histopathologically defined by PAS+ abnormally high levels of cellular glycogen. Elevated transcriptional levels of GYS1 have been significantly correlated with poor disease outcomes in NSCLC (Giatromanolaki A, et al. Expression of enzymes related to glucose metabolism in non-small cell lung cancer and prognosis. Experimental Lung Research, vol. 43, no. 4-5, 2017) and AML (Falantes JF, et al. Overexpression of GYS1, MIF, and MYC is associated with adverse outcome and poor response to azacitidine in myelodysplastic syndromes and acute myeloid leukemia. Clinical Lymphoma, Myeloma & Leukemia, vol. 15, no. 4, 2015). Lentiviral knockdown of GYS1 in cultured myeloid leukemia cells potently inhibited in vitro cancer cell growth and in vivo tumorigenesis (Bhanot H, et al. Pathological glycogenesis through glycogen synthase I and suppression of excessive AMP kinase activity in myeloid leukemia cells. Leukemia, vol. 29, no. 7, 2015). Genetic knock-down of GYS1 in ccRCC cell models both suppresses tumor growth in vivo and increases the synthetic lethality of sunitinub (Chen S, et al. GYS1 induces glycogen accumulation and promotes tumor progression via the NF-kB pathway in clear cell renal carcinoma. Theranostics, vol. 10, no. 20, 2020).

[0006] Reduction of GYS1 enzyme activity and reduced cellular stores of glycogen in preclinical models of Pompe disease, APBD, LD, AML, ccRCC, and NSCLC all provide compelling evidence of the potential therapeutic benefit of inhibiting glycogen synthesis. It is the aim of this invention to inhibit glycogen synthase enzyme activity resulting in reduction of tissue glycogen stores with therapeutic benefit to patients suffering the consequences of accumulated cellular glycogen.

BRIEF SUMMARY

[0006a] In an aspect of the present disclosure, there is provided a compound of formula (I-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing:



(I-A),

wherein

Y^1 is CH or N;

R^x and R^z are independently H, halo, $C_{1\text{-}6}$alkyl, or -NH_2, wherein, when Y^1 is CH, the $C_{1\text{-}6}$alkyl of R^x or R^z may be optionally substituted with one or more halo;

R^y is (i) $C_{1\text{-}6}$alkyl, or (ii) $C_{3\text{-}10}$cycloalkyl, wherein the $C_{3\text{-}10}$cycloalkyl is optionally substituted with one or more halo or $C_{1\text{-}6}$alkyl;

R^k is H, halo, -OH, -NH_2, or -NH-C(O)$C_{1\text{-}6}$alkyl;

R^2 is $C_{1\text{-}6}$alkyl, wherein the $C_{1\text{-}6}$alkyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^a is optionally substituted with one or more R^b; and
R^b is halo, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, -NH_2, -NH($C_{1\text{-}6}$alkyl), -N($C_{1\text{-}6}$alkyl)$_2$, $C_{3\text{-}10}$cycloalkyl, 3-15 membered heterocyclyl, or -C(O)-$C_{1\text{-}6}$alkoxy, wherein the $C_{1\text{-}6}$alkyl of R^b is optionally substituted with one or more halo, -NH_2, -NH($C_{1\text{-}6}$alkyl), -N($C_{1\text{-}6}$alkyl)$_2$, -NH-C(O)$C_{1\text{-}6}$alkyl, or -NH-C(O)-$C_{1\text{-}6}$alkoxy, and the 3-15-membered heterocyclyl of R^b is optionally substituted with one or more halo or -C(O)-$C_{1\text{-}6}$alkoxy.

[0006b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising (i) a compound disclosed herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and (ii) one or more pharmaceutically acceptable excipients.

[0006c] In another aspect of the present disclosure, there is provided a kit, comprising (i) a compound disclosed herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition disclosed herein, and (ii) instructions for use in treating an GYS1-mediated disease, disorder, or condition in an individual in need thereof, wherein the disease, disorder, or condition is selected from Pompe disease, Cori disease (GSD III), adult polyglucosan body disease (APBD), and Lafora disease.

[0006d] In a further aspect of the present disclosure, there is provided use of a compound disclosed herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating or delaying the development of a disease, disorder, or condition selected from: (a) a glycogen storage disorder (GSD), optionally selected from the group consisting of Pompe disease, Cori disease (GSD III), adult polyglucosan body disease (APBD), and Lafora disease, optionally wherein the disease, disorder, or condition is Pompe disease; and (b) cancer, optionally selected from the group consisting of Ewing sarcoma (ES), clear cell renal cell carcinoma (ccRCC), glycogen rich clear cell carcinoma (GRCC) breast cancer, non-small-cell lung carcinoma (NSCLC), and acute myeloid leukemia (AML), optionally wherein the individual has a GAA mutation, such as a loss-of-function mutation.