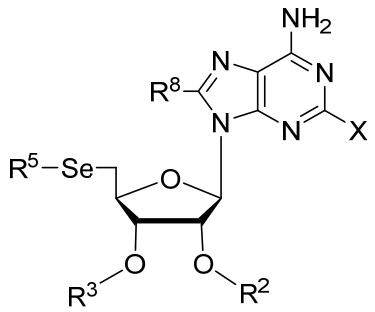
Claims:

1. A compound of formula (1):



(1)

or a pharmaceutically acceptable salt, ester, or isomer thereof, wherein

each of R^2 and R^3 is independently H or -C(O)-R, wherein each R is independently $C_{1\text{-}6}$alkyl or 3-8 membered carbocyclic or heterocyclic, wherein R^2 and R^3 cannot be both H;

or R^2 together with R^3 form -$(CH_2)_n$-C(O)-$(CH_2)_m$-, wherein each of n and m is independently 0-3, and n+m≤3;

R^5 is -$C_{1\text{-}6}$alkyl or -$C_{1\text{-}6}$alkyl-$CH(NH_2)COOH$;

R^8 is H or halogen; and

X is H or halogen,

wherein each of the carbocyclic, heterocyclic, -$(CH_2)_n$-, and -$(CH_2)_m$- moieties, independently, may optionally be substituted 1-3 times by -OH, halogen, NH_2, CN, or $C_{1\text{-}6}$alkyl; and

each $C_{1\text{-}6}$alkyl moiety, independently, may optionally be substituted 1-3 times by -OH, halogen, NH_2, or CN.

2. The compound of claim 1, wherein R^8 is H.

3. The compound of claim 1, wherein X is H.

4. The compound of claim 1, wherein R^5 is -$C_{1\text{-}6}$alkyl, which may optionally be substituted 1-3 times by -OH, halogen, NH_2, or CN.

5. The compound of claim 4, wherein R^5 is unsubstituted -C_{1-6}alkyl.

6. The compound of claim 5, wherein R^5 is methyl.

7. The compound of claim 1, wherein R^5 is -C_{1-6}alkyl-$CH(NH_2)COOH$, wherein C_{1-6}alkyl may optionally be substituted 1-3 times by -OH, halogen, NH_2, or CN.

8. The compound of claim 7, wherein R^5 is -C_{1-6}alkyl-$CH(NH_2)COOH$, wherein C_{1-6}alkyl is unsubstituted.

9. The compound of claim 8, wherein R^5 is -CH_2CH_2-$CH(NH_2)COOH$.

10. The compound of claim 1, wherein R^2 is H, and R^3 is -C(O)-R, wherein R is C_{1-6}alkyl or 3-8 membered carbocyclic or heterocyclic, wherein each of the carbocyclic and heterocyclic moieties, independently, may optionally be substituted 1-3 times by -OH, halogen, NH_2, CN, or C_{1-6}alkyl; and each C_{1-6}alkyl, independently, may optionally be substituted 1-3 times by -OH, halogen, NH_2, or CN.

11. The compound of claim 1, wherein R^3 is H, and R^2 is -C(O)-R, wherein R is C_{1-6}alkyl or 3-8 membered carbocyclic or heterocyclic, wherein each of the carbocyclic and heterocyclic moieties, independently, may optionally be substituted 1-3 times by -OH, halogen, NH_2, CN, or C_{1-6}alkyl; and each C_{1-6}alkyl, independently, may optionally be substituted 1-3 times by -OH, halogen, NH_2, or CN.

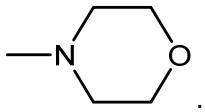
12. The compound of claim 1, wherein R is 3-8 membered carbocyclic or heterocyclic, wherein each of the carbocyclic and heterocyclic moieties, independently, may optionally be substituted 1-3 times by -OH, halogen, NH_2, CN, or C_{1-6}alkyl; and each C_{1-6}alkyl, independently, may optionally be substituted 1-3 times by -OH, halogen, NH_2, or CN.

13. The compound of claim 12, wherein R is 3-8 membered unsubstituted carbocyclic or unsubstituted heterocyclic.

14. The compound of claim 13, wherein R is 6 membered unsubstituted carbocyclic or unsubstituted heterocyclic.

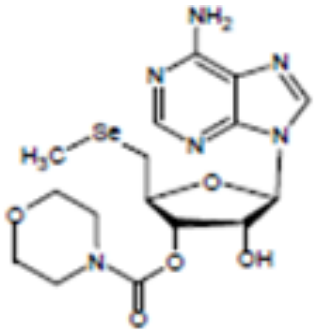
15. The compound of claim 14, wherein R is unsubstituted heterocyclic.

16. The compound of claim 15, wherein R is

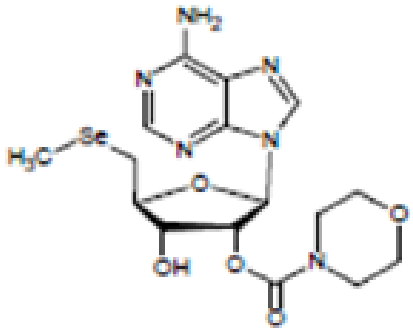


.

17. The compound of claim 16, wherein the compound is of formula:



, or



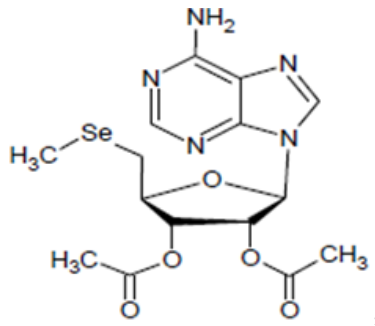
.

18. The compound of claim 1, wherein each of R^2 and R^3 is independently C(O)-R, wherein each R is independently C_{1-6}alkyl or 3-8 membered carbocyclic or heterocyclic, wherein each of the carbocyclic and heterocyclic moieties, independently, may optionally be substituted 1-3 times by -OH, halogen, NH_2, CN, or C_{1-6}alkyl; and each C_{1-6}alkyl, independently, may optionally be substituted 1-3 times by -OH, halogen, NH_2, or CN.

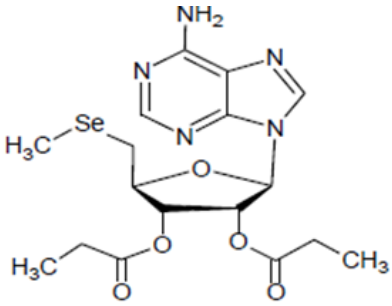
19. The compound of claim 18, wherein each R is independently C_{1-6}alkyl, which may optionally be substituted 1-3 times by -OH, halogen, NH_2, or CN.

20. The compound of claim 19, wherein each R is independently unsubstituted C_{1-6}alkyl.

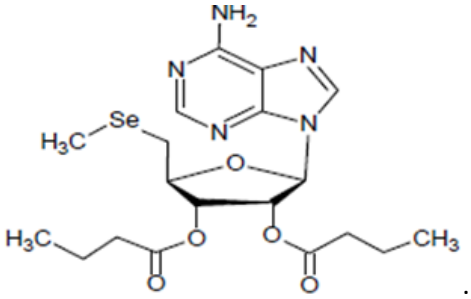
21. The compound of claim 20, wherein the compound is of the formula:



,



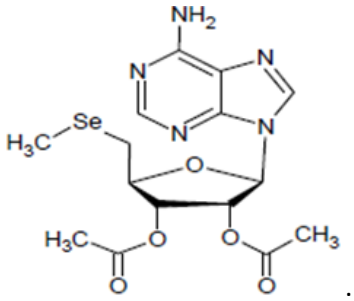
, or



.

22. The compound of claim 20, wherein R is CH_3.

23. The compound of claim 22, wherein the compound is of the formula:

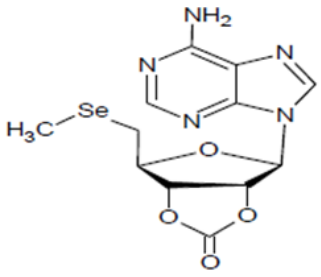


24. The compound of claim 1, wherein R^2 together with R^3 form -$(CH_2)_n$-C(O)-$(CH_2)_m$-, wherein each of n and m is independently 0-3, and n+m≤3, wherein each of the -$(CH_2)_n$- and -$(CH_2)_m$- moieties, independently, may optionally be substituted 1-3 times by -OH, halogen, NH_2, CN, or C_{1-6}alkyl; and each C_{1-6}alkyl, independently, may optionally be substituted 1-3 times by -OH, halogen, NH_2, or CN.

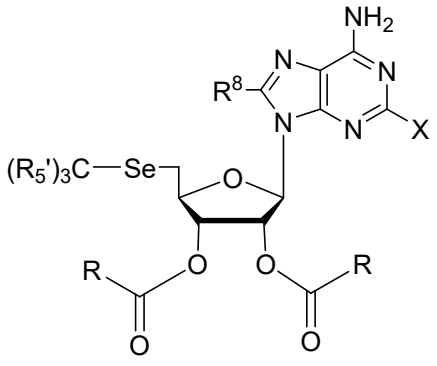
25. The compound of claim 24, wherein the -$(CH_2)_n$- and -$(CH_2)_m$- moieties are unsubstituted.

26. The compound of claim 24, wherein n=m=0.

27. The compound of claim 26, wherein the compound is of the formula:



28. The compound of claim 1, or a pharmaceutically acceptable salt, ester, or isomer thereof, wherein the compound is of formula (2):



(2),

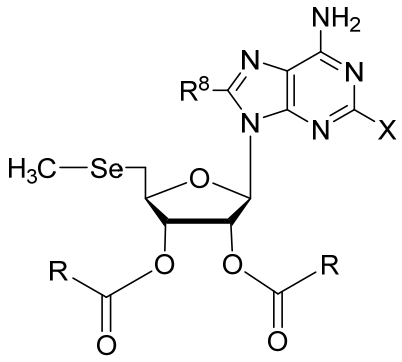
wherein R_8 is H or halogen;

X is H or halogen;

each R_5' is independently H or halogen; and

each R is independently $C_{1\text{-}6}$alkyl, each of which, independently, may optionally be substituted 1-3 times by halogen.

29. The compound of claim 28, wherein the compound is of formula (2'):



(2').

30. The compound of claim 28, wherein R^8 is H.

31. The compound of claim 28, wherein X is H.

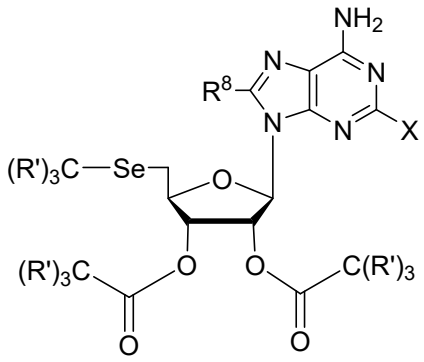
32. The compound of claim 28, wherein each R is independently unsubstituted $C_{1\text{-}6}$alkyl.

33. The compound of claim 28, wherein each R is independently $C_{1\text{-}3}$alkyl, each of which, independently, may optionally be substituted 1-3 times by halogen.

34. The compound of claim 28, wherein each R is independently unsubstituted $C_{1\text{-}3}$alkyl.

35. The compound of claim 34, wherein each R is independently $-CH_3$, $-CH_2CH_3$, or $-CH_2CH_2CH_3$.

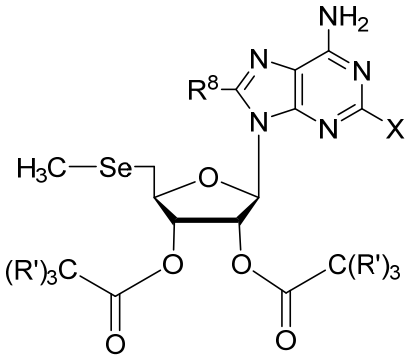
36. The compound of claim 1, or a pharmaceutically acceptable salt, ester, or isomer thereof, wherein the compound is of formula (3):



(3),

wherein R^8 is H or halogen;
X is H or halogen; and
each R' is independently H or halogen.

37. The compound of claim 36, wherein the compound is of formula (3'):



(3').

38. The compound of claim 36, wherein R^8 is H.

39. The compound of claim 36, wherein X is H.

40. The compound of claim 36, wherein each $C(R')_3$ is independently CF_3, CHF_2, or

CH_2F, or CH_3.

41. The compound of claim 40, wherein each $C(R')_3$ is CH_3.

42. The compound of any one of claims 1 to 41 for use in therapy.

43. Use of a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt, ester, or isomer thereof, in the preparation of a medicament for the treatment of an insulin resistance disorder.

44. The use of claim 43, wherein the disorder is hyperglycemia, retinopathy, neuropathy, nephropathy, hyperinsulinemia, polycystic ovarian syndrome (PCOS), or a type II diabetes related vascular disorder.

45. The use of claim 43, wherein the medicament comprises a composition that comprises and/or delivers the compound, according to a regimen that achieves administration of the therapeutically effective amount.

46. The use of claim 45, wherein the composition is a pharmaceutical composition comprising an active pharmaceutical ingredient and one or more carriers or excipients, wherein the active pharmaceutical ingredient comprises or consists of the compound of formula I.

47. The use of claim 45, wherein the active pharmaceutical ingredient consists of the compound.

48. Use of a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt, ester, or isomer thereof, in the preparation of a medicament for the treatment of diabetes.

49. The use of claim 48, wherein the diabetes is type I diabetes or type II diabetes.

50. Use of a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt, ester, or isomer thereof, in the preparation of a medicament

for the treatment of a degenerative disease selected from the group consisting of Alzheimer's disease, Parkinson's diseases, and sarcopenia.

51. Use of a compound of claim 1, or a pharmaceutically acceptable salt, ester, or isomer thereof, in the preparation of a medicament for inhibiting glucose production.

52. Use of a compound of claim 1, or a pharmaceutically acceptable salt, ester, or isomer thereof, in the preparation of a medicament for reducing serum HbA1c level.

53. Use of a compound of claim 1, or a pharmaceutically acceptable salt, ester, or isomer thereof, in the preparation of a medicament for increasing glucose tolerance.

54. Use of a compound of claim 1, or a pharmaceutically acceptable salt, ester, or isomer thereof, in the preparation of a medicament for inhibiting G6pc expression.

55. Use of a compound of claim 1, or a pharmaceutically acceptable salt, ester, or isomer thereof, in the preparation of a medicament for enhancing phosphorylation of Pdk1, Akt, AS160, and Foxo1 in the liver and/or in the skeletal muscle.

56. Use of a compound of claim 1, or a pharmaceutically acceptable salt, ester, or isomer thereof, in the preparation of a medicament for increasing Glut4 expression.

57. Use of a compound of claim 1, or a pharmaceutically acceptable salt, ester, or isomer thereof, in the preparation of a medicament for activating and/or restoring insulin signaling in a subject in insulin-resistant state.

58. The use of claim 57, wherein the subject is characterized by significant levels of circulating insulin.

59. The use of claim 57, wherein the insulin-resistant state is characterized by a reduction in correctly or appropriate phosphorylated insulin receptor in the subject.

60. The use of claim 57, wherein the subject has diabetes, and/or diabetes associated disease, disorders, or conditions.

61. Use of a compound of claim 1, or a pharmaceutically acceptable salt, ester, or isomer thereof, in the preparation of a medicament for enhancing glucose uptake into cells in a subject.

62. The use of claim 61, wherein the cells are skeletal muscle cells and liver cells.

63. Use of a compound of claim 1, or a pharmaceutically acceptable salt, ester, or isomer thereof in the preparation of a medicament for enhancing translocation of glucose transporter proteins (GLUTs) from cytosolic vesicles to plasma membrane for glucose uptake.