CLAIMS

We claim:

1. A conjugate comprising a drug and a ligand including a first saccharide; wherein the conjugate is characterized in that, when the conjugate is administered to a mammal, at least one pharmacokinetic or pharmacodynamic property of the conjugate is sensitive to serum concentration of a second saccharide.

2. The conjugate of claim 1, wherein the second saccharide is glucose.

3. The conjugate of claim 1, wherein the second saccharide is mannose.

4. The conjugate of claim 1, wherein the second saccharide is L-fucose.

5. The conjugate of claim 1, wherein the second saccharide is N-acetyl glucosamine.

6. The conjugate of claim 1, wherein the second saccharide is alpha-methyl mannose.

7. The conjugate of claim 1, wherein the molecular weight of the conjugate absent the drug is less than about 10,000 Da.

8. The conjugate of claim 1, wherein the molecular weight of the conjugate absent the drug is in the range of about 250 to about 5,000 Da.

9. The conjugate of claim 1, wherein the molecular weight of the conjugate absent the drug is in the range of about 900 to about 2,000 Da.

10. The conjugate of claim 1, wherein the molecular weight of the conjugate including the drug is less than about 20,000 Da.

11. The conjugate of claim 1, wherein the molecular weight of the conjugate including the drug is in the range of about 2,000 to about 18,000 Da.

12. The conjugate of claim 1, wherein the molecular weight of the conjugate including the drug is in the range of about 6,500 to about 8,000 Da.

13. The conjugate of claim 1, wherein the conjugate has a unique molecular weight.

14. The conjugate of claim 1, wherein the conjugate has a substantially different serum concentration curve under fasted and hyperglycemic conditions.

15. The conjugate of claim 14, wherein the hyperglycemic conditions are induced by concurrent administration of conjugate and glucose to the mammal.

16. The conjugate of claim 14, wherein the conjugate has a serum C_{max} that is higher under hyperglycemic conditions as compared to fasted conditions.

17. The conjugate of claim 14, wherein the conjugate has a serum AUC that is higher under hyperglycemic conditions as compared to fasted conditions.

18. The conjugate of claim 14, wherein the conjugate has a serum elimination rate that is slower under hyperglycemic conditions as compared to fasted conditions.

19. The conjugate of claim 14, wherein the conjugate has a serum concentration curve that can be fit using a two-compartment bi-exponential model with one short and one long half-life and the long half-life is longer under hyperglycemic conditions as compared to fasted conditions.

20. The conjugate of any one of claims 14-19, wherein the fasted conditions involve a serum glucose C_{max} of less than 100 mg/dL.

21. The conjugate of any one of claims 14-19, wherein the hyperglycemic conditions involve a serum glucose C_{max} in excess of 200 mg/dL.

22. The conjugate of claim 1, wherein the conjugate has a serum concentration curve that is substantially different at 100 and 300 mg/dL glucose.

23. The conjugate of claim 22, wherein the conjugate has a C_{max} that is higher at 300 mg/dL glucose than at 100 mg/dL glucose.

24. The conjugate of claim 23, wherein the C_{max} of the conjugate is at least 50% higher at 300 mg/dL glucose.

25. The conjugate of claim 22, wherein the conjugate has an AUC that is higher at 300 mg/dL glucose than at 100 mg/dL glucose.

26. The conjugate of claim 25, wherein the AUC of the conjugate is at least 50% higher at 300 mg/dL glucose.

27. The conjugate of claim 22, wherein the conjugate has a serum elimination rate that is faster at 100 mg/dL glucose than at 300 mg/dL glucose.

28. The conjugate of claim 27, wherein the serum elimination rate of the conjugate is at least 25% faster at 100 mg/dL glucose.

29. The conjugate of claim 22, wherein the serum concentration curve of the conjugate can be fit using a two-compartment bi-exponential model with one short and one long half-life and the long half-life is longer at 300 mg/dL.

30. The conjugate of claim 29, wherein the long half-life is at least 50% longer at 300 mg/dL glucose.

31. The conjugate of claim 1, wherein the conjugate and an unconjugated version of the drug have serum concentration curves that are substantially the same under hyperglycemic conditions.

32. The conjugate of claim 1, wherein the conjugate and an unconjugated version of the drug have serum concentration curves that are substantially different under fasted conditions.

33. The conjugate of claim 1, wherein the conjugate and an unconjugated version of the drug have serum concentration curves that are substantially the same under hyperglycemic conditions and substantially different under fasted conditions.

34. The conjugate of any one of claims 31-33, wherein the fasted conditions involve a serum glucose C_{max} of less than 100 mg/dL.

35. The conjugate of any one of claims 31-33, wherein the hyperglycemic conditions involve a serum glucose C_{max} in excess of 200 mg/dL.

36. The conjugate of claim 1, wherein the conjugate has lower bioactivity under fasted conditions as compared to hyperglycemic conditions.

37. The conjugate of claim 36, wherein the fasted conditions involve a serum glucose C_{max} of less than 100 mg/dL.

38. The conjugate of claim 36, wherein the hyperglycemic conditions involve a serum glucose C_{max} in excess of 200 mg/dL.

39. The conjugate of claim 1, wherein the conjugate has lower bioactivity at 100 mg/dL glucose than 300 mg/dL glucose.

40. The conjugate of claim 39, wherein the bioactivity of the conjugate is at least 25% higher at 300 mg/dL glucose.

41. The conjugate of any one of claims 1-40, wherein the mammal is a human, dog, cat, rat, or minipig.

42. The conjugate of any one of claims 1-40, wherein the mammal is a human.

43. The conjugate of claim 1, wherein the drug is an anti-diabetic drug.

44. The conjugate of claim 1, wherein the drug is an insulin sensitizer.

45. The conjugate of claim 1, wherein the drug is an insulin secretatogue.

46. The conjugate of claim 1, wherein the drug is insulin-type growth factor 1 (IGF-1).

47. The conjugate of claim 1, wherein the drug is an insulin molecule.

48. The conjugate of claim 47, wherein the insulin molecule is selected from the group consisting of human insulin, porcine insulin, and bovine insulin.

49. The conjugate of claim 47, wherein the insulin molecule is selected from the group consisting of insulin lispro, insulin aspart and insulin glulisine.

50. The conjugate of claim 47, wherein the insulin molecule is insulin glargine or insulin detemir.

51. The conjugate of claim 47, wherein the insulin molecule includes three disulfide bridges.

52. The conjugate of claim 47, wherein the insulin molecule is conjugated via the A1 amino acid residue.

53. The conjugate of claim 47, wherein the insulin molecule is conjugated via the B1 amino acid residue.

54. The conjugate of claim 47, wherein the insulin molecule is conjugated via the epsilon-amino group of Lys^{B29}.

55. The conjugate of claim 47, wherein the insulin molecule is insulin glulisine conjugated via the epsilon-amino group of Lys^{B3}.

56. The conjugate of claim 47, wherein the insulin molecule is truncated.

57. The conjugate of claim 56, wherein the insulin molecule is des(B30)-insulin, des(B28-B30)-insulin, des(B27)-insulin, des(B1)-insulin, or des(B1-B3)-insulin.

58. The conjugate of claim 47, wherein conjugation results in decreased insulin receptor affinity *in vitro* as compared to wild-type human insulin.

59. The conjugate of claim 47, wherein the insulin molecule is conjugated via the A3, A4, A5, A8, A9, or B30 amino acid residue.

60. The conjugate of claim 47, wherein the insulin molecule is conjugated via the A1 amino acid residue and the epsilon-amino group of Lys^{B29}.

61. The conjugate of claim 1, wherein the conjugate includes a single ligand.

62. The conjugate of claim 1, wherein the conjugate includes at least two separate ligands each of which includes a saccharide.

63. The conjugate of claim 1, wherein the conjugate includes two separate ligands each of which includes a saccharide.

64. The conjugate of claim 1, wherein the conjugate includes three separate ligands each of which includes a saccharide.

65. The conjugate of claim 1, wherein the conjugate includes four separate ligands each of which includes a saccharide.

66. The conjugate of claim 1, wherein the conjugate includes five separate ligands each of which includes a saccharide.

67. The conjugate of any one of claims 62-66, wherein the separate ligands are the same.

68. The conjugate of claim 62, wherein the at least two separate ligands are conjugated to the drug via different conjugation points.

69. The conjugate of claim 62, wherein the at least two separate ligands are conjugated to a single conjugate framework that is also conjugated to the drug.

70. The conjugate of claim 62, wherein the at least two separate ligands and drug are each located on a separate branch of a branched conjugate framework.

71. The conjugate of claim 70, wherein the at least two separate ligands and drug are each located on termini of separate branches of a branched conjugate framework.

72. The conjugate of claim 70, wherein the conjugate framework is hyperbranched.

73. The conjugate of claim 62, wherein the conjugate framework is non-polymeric.

74. The conjugate of claim 1, wherein the ligand includes a first saccharide selected from the group consisting of glucose, mannose and L-fucose.

75. The conjugate of claim 1, wherein the ligand includes a first saccharide selected from the group consisting of mannosamine and beta-linked N-acetyl mannosamine.

76. The conjugate of claim 1, wherein the ligand includes a first saccharide selected from the group consisting of methylglucose, methylmannose, ethylglucose, ethylmannose, propylglucose and propylmannose.

77. The conjugate of claim 1, wherein the ligand includes alpha-L-fucopyranoside.

78. The conjugate of claim 1, wherein the ligand includes a bimannose.

79. The conjugate of claim 1, wherein the ligand includes a trimannose.

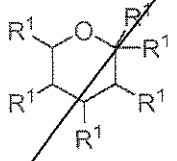
80. The conjugate of claim 1, wherein the ligand includes a linear trimannose.

81. The conjugate of claim 1, wherein the ligand includes a branched trimannose.

82. The conjugate of claim 1, wherein the ligand includes a first saccharide and an amine group.

83. The conjugate of claim 82, wherein the first saccharide and amine group are separated by a C_1-C_6 alkyl group.

84. The conjugate of claim 1, wherein the ligand is of formula (IIIa) or (IIIb):



IIIa



IIIb

wherein:

each R^1 is independently hydrogen, $-OR^y$, $-N(R^y)_2$, $-SR^y$, -O-Y, -G-Z, or $-CH_2R^x$;

each R^x is independently hydrogen, $-OR^y$, $-N(R^y)_2$, $-SR^y$, or -O-Y;

each R^y is independently $-R^2$, $-SO_2R^2$, $-S(O)R^2$, $-P(O)(OR^2)_2$, $-C(O)R^2$, $-CO_2R^2$, or $-C(O)N(R^2)_2$;

each Y is independently a monosaccharide, disaccharide, or trisaccharide;

each G is independently a covalent bond or an optionally substituted C_{1-9} alkylene, wherein one or more methylene units of G is optionally replaced by $-O-$, $-S-$, $-N(R^2)-$, $-C(O)-$, $-OC(O)-$, $-C(O)O-$, $-C(O)N(R^2)-$, $-N(R^2)C(O)-$, $-N(R^2)C(O)N(R^2)-$, $-SO_2-$, $-SO_2N(R^2)-$, $-N(R^2)SO_2-$, or $-N(R^2)SO_2N(R^2)-$;

each Z is independently halogen, $-N(R^2)_2$, $-OR^2$, $-SR^2$, $-N_3$, $-C{\equiv}CR^2$, $-CO_2R^2$, $-C(O)R^2$, or $-OSO_2R^2$; and

each R^2 is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered heterocyclic ring having 1-2 heteroatoms selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms selected from nitrogen, oxygen, or sulfur,

with the proviso that the ligand comprises no more than a total of four monosaccharide moieties.

85. The conjugate of claim 84, wherein R^1 is hydrogen, -OH, $-NHC(O)CH_3$, -O-Y, -G-Z, $-CH_2OH$, -CH2-O-Y, or $-NH_2$.

86. The conjugate of claim 84, wherein R^x is hydrogen, -OH, or -O-Y.

87. The conjugate of claim 84, wherein R^y is hydrogen, $-R^2$, $-C(O)R^2$, or acetyl.

88. The conjugate of claim 84, wherein Y is a monosaccharide.

89. The conjugate of claim 88, wherein Y is mannose, glucose, fructose, galactose, rhamnose, or xylopyranose.

90. The conjugate of claim 88, wherein Y is mannose.

91. The conjugate of claim 88, wherein Y is D-mannose.

92. The conjugate of claim 84, wherein Y is a disaccharide.

93. The conjugate of claim 92, wherein Y is sucrose, maltose, turanose, trehalose, cellobiose, or lactose.

94. The conjugate of claim 84, wherein G is a covalent bond.

95. The conjugate of claim 84, wherein G is $-O-C_{1-8}$ alkylene.

96. The conjugate of claim 95, wherein G is $-OCH_2CH_2-$.

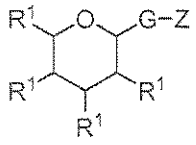
97. The conjugate of claim 84, wherein Z is $-N(R^2)_2$, $-OR^2$, or $-SR^2$.

98. The conjugate of claim 97, wherein Z is –SH.

99. The conjugate of claim 97, wherein Z is $-NH_2$.

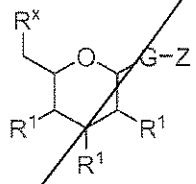
100. The conjugate of claim 84, wherein –G-Z is $-OCH_2CH_2NH_2$.

101. The conjugate of claim 84, wherein the ligand is of formula (IIIa-*i*):



IIIa-*i*

102. The conjugate of claim 84, wherein the ligand is of formula (IIIa-*ii*):



IIIa-*ii*

103. The conjugate of claim 1, wherein the ligand includes aminoethylglucose (AEG), aminoethylmannose (AEM), aminoethylbimannose (AEBM) or aminoethyltrimannose (AETM).

104. The conjugate of claim 1, wherein the ligand includes aminoethyltrimannose (AETM).

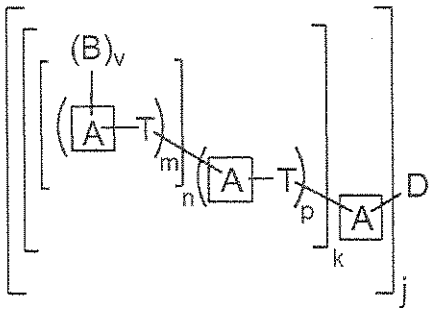
105. The conjugate of claim 1, wherein the conjugate includes two or three separate ligands each of which includes aminoethyltrimannose (AETM).

106. The conjugate of any one of the preceding claims, wherein the ligand includes a first saccharide that is conjugated via an anomeric carbon.

107. The conjugate of claim 106, wherein the anomeric carbon is an alpha anomer.

108. The conjugate of claim 106, wherein the saccharide is indirectly conjugated to the drug via a conjugate framework.

109. The conjugate of any one of the preceding claims, wherein the conjugate has the general formula (II):



II

wherein:

each occurrence of $\left[\left(\boxed{A}\text{—}T\right)\right]$ represents a potential branch within the conjugate;

each occurrence of $\left(\boxed{A}\text{—}T\right)$ represents a potential repeat within a branch of the conjugate;

each occurrence of $\boxed{A}$ is independently a covalent bond, a carbon atom, a heteroatom, or an optionally substituted group selected from the group consisting of acyl, aliphatic, heteroaliphatic, aryl, heteroaryl, and heterocyclic;

each occurrence of T is independently a covalent bond or a bivalent, straight or branched, saturated or unsaturated, optionally substituted C_{1-30} hydrocarbon chain wherein one or more methylene units of T are optionally and independently replaced by -O-, -S-, -N(R)-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)C(O)-, -C(O)N(R)-, -S(O)-, $-S(O)_2-$, $-N(R)SO_2-$, $-SO_2N(R)-$, a heterocyclic group, an aryl group, or a heteroaryl group;

each occurrence of R is independently hydrogen, a suitable protecting group, or an acyl moiety, arylalkyl moiety, aliphatic moiety, aryl moiety, heteroaryl moiety, or heteroaliphatic moiety;

–B is $–T–L^B–X$;

each occurrence of X is independently a ligand;

each occurrence of L^B is independently a covalent bond or a group derived from the covalent conjugation of a T with an X;

–D is $–T–L^D–W$;

each occurrence of W is independently a drug;

each occurrence of L^D is independently a covalent bond or a group derived from the covalent conjugation of a T with a W;

k is an integer from 1 to 12, inclusive;

j is an integer from 1 to 4, inclusive;

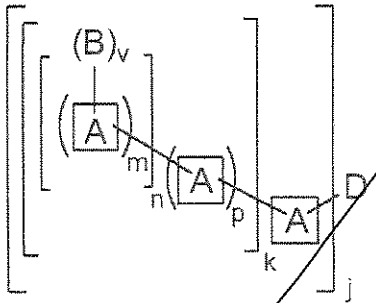
each occurrence of p is independently an integer from 1 to 5, inclusive; and

each occurrence of n is independently an integer from 0 to 5, inclusive; and

each occurrence of m is independently an integer from 1 to 5, inclusive; and

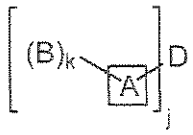
each occurrence of v is independently an integer from 0 to 5, inclusive, with the proviso that within each k-branch at least one occurrence of n is ≥ 1 and at least one occurrence of v is ≥ 1.

110. The conjugate of claim 109, wherein each occurrence of T outside groups B and D is a covalent bond and the conjugate is of the formula (V):



V

111. The conjugate of claim 109, wherein each occurrence of [A] except for the central [A] is a covalent bond, each occurrence of v = 1, and the conjugate is of the formula (VII):



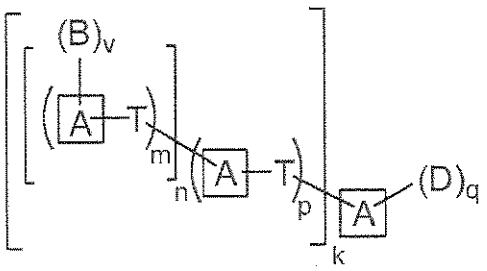
VII

112. The conjugate of claim 109, wherein k = 1 and j = 2.

113. The conjugate of claim 109, wherein k = 2 and j = 2.

114. The conjugate of claim 109, wherein k = 3 and j = 2.

115. The conjugate of any one of the preceding claims, wherein the conjugate has the general formula (I):



I

wherein:

each occurrence of $\left[\left(\boxed{A}-T\right)\right]$ represents a potential branch within the conjugate;

each occurrence of $\left(\boxed{A}-T\right)$ represents a potential repeat within a branch of the conjugate;

each occurrence of $\boxed{A}$ is independently a covalent bond, a carbon atom, a heteroatom, or an optionally substituted group selected from the group consisting of acyl, aliphatic, heteroaliphatic, aryl, heteroaryl, and heterocyclic;

each occurrence of T is independently a covalent bond or a bivalent, straight or branched, saturated or unsaturated, optionally substituted C_{1-30} hydrocarbon chain wherein one or more methylene units of T are optionally and independently replaced by -O-, -S-, -N(R)-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)C(O)-, -C(O)N(R)-, -S(O)-, $-S(O)_2-$, $-N(R)SO_2-$, $-SO_2N(R)-$, a heterocyclic group, an aryl group, or a heteroaryl group;

each occurrence of R is independently hydrogen, a suitable protecting group, or an acyl moiety, arylalkyl moiety, aliphatic moiety, aryl moiety, heteroaryl moiety, or heteroaliphatic moiety;

–B is $-T-L^B-X$;

each occurrence of X is independently a ligand;

each occurrence of L^B is independently a covalent bond or a group derived from the covalent conjugation of a T with an X;

–D is $-T-L^D-W$;

each occurrence of W is independently a drug;

each occurrence of L^D is independently a covalent bond or a group derived from the covalent conjugation of a T with a W;

k is an integer from 1 to 12, inclusive;

q is an integer from 1 to 4, inclusive;

each occurrence of p is independently an integer from 1 to 5, inclusive; and

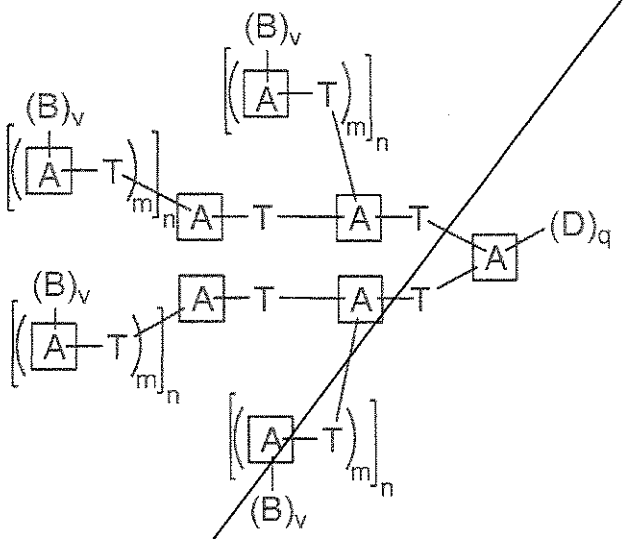
each occurrence of n is independently an integer from 0 to 5, inclusive; and

each occurrence of m is independently an integer from 1 to 5, inclusive; and

each occurrence of v is independently an integer from 0 to 5, inclusive, with the proviso that within each k-branch at least one occurrence of n is ≥ 1 and at least one occurrence of v is ≥ 1.

116. The conjugate of claim 115, wherein each occurrence of [A] in a p-bracketed moiety is substituted by a number of n-bracketed moieties corresponding to a value of n ≥ 1.

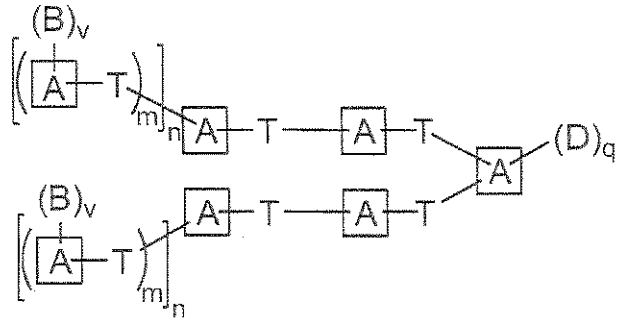
117. The conjugate of claim 116, wherein k = 2 and p = 2 in both k-branches and the conjugate is of the formula (Ia):



Ia

118. The conjugate of claim 115, wherein only terminal occurrences of [A] in a p-bracketed moiety are substituted by a number of n-bracketed moieties corresponding to a value of n ≥ 1.

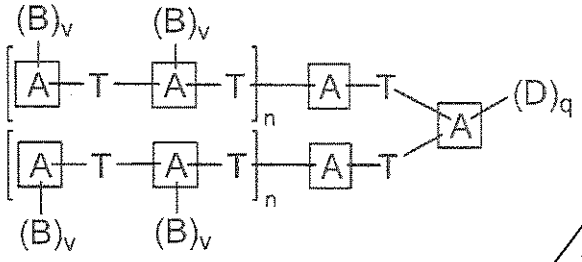
119. The conjugate of claim 118, wherein k = 2 and p = 2 in both k-branches, n = 0 for the first p-bracketed moiety in both k-branches and the conjugate is of the formula (Ib):



Ib

120. The conjugate of claim 115, wherein each occurrence of [A] in an m-bracketed moiety is substituted by a number of B moieties corresponding to the value of $v \geq 1$.

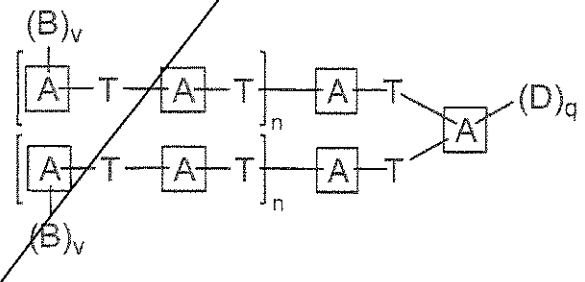
121. The conjugate of claim 120, wherein k = 2, each occurrence of p = 1, and each occurrence of m = 2 and the conjugate is of the formula (Ic):



Ic

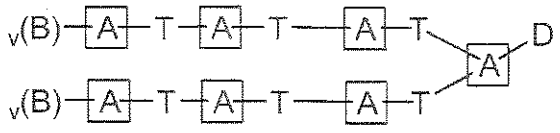
122. The conjugate of claim 115, wherein only terminal occurrences of [A] in an m-bracketed moiety are substituted by a number of B moieties corresponding to a value of $v \geq 1$.

123. The conjugate of claim 122, wherein k = 2, each occurrence of p = 1, each occurrence of m = 2, v = 0 for the first m-bracketed moeity in each n-branch and the conjugate is of the formula (Id):



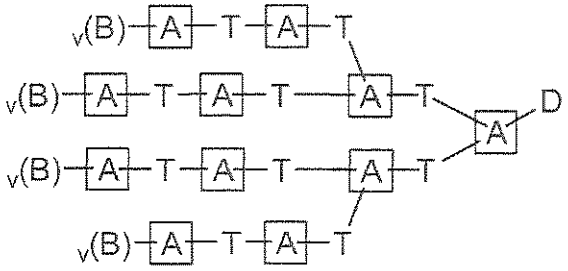
Id

124. The conjugate of claim 123, wherein q =1 and n = 1 in both k-branches and the conjugate is of the formula (Ie):



Ie

125. The conjugate of claim 123, wherein q =1 and n = 2 in both k-branches and the conjugate is of the formula (If):



If

126. The conjugate of claim 115, wherein each occurrence of [A] is an optionally substituted group selected from the group consisting of acyl, aliphatic, heteroaliphatic, aryl, heteroaryl, and heterocyclic.

127. The conjugate of claim 115, wherein each occurrence of [A] is the same.

128. The conjugate of claim 115, wherein the central [A] is different from all other occurrences of [A].

129. The conjugate of claim 128, wherein all occurrences of [A] are the same except for the central [A].

130. The conjugate of claim 115, wherein [A] is an optionally substituted aryl or heteroaryl group.

131. The conjugate of claim 130, wherein [A] is 6-membered aryl.

132. The conjugate of claim 131, wherein [A] is phenyl.

133. The conjugate of claim 115, wherein [A] is a heteroatom selected from N, O, or S.

134. The conjugate of claim 115, wherein [A] is a nitrogen atom.

135. The conjugate of claim 115, wherein A is a carbon atom.

136. The conjugate of claim 115, wherein each occurrence of T is independently a bivalent, straight or branched, saturated or unsaturated, optionally substituted C_{1-20} hydrocarbon chain wherein one or more methylene units of T are optionally and independently replaced by –O–, –S–, –N(R)–, –C(O)–, –C(O)O–, –OC(O)–, –N(R)C(O)–, –C(O)N(R)–, –S(O)–, –S(O)$_2$–, –N(R)SO$_2$–, –SO$_2$N(R)–, a heterocyclic group, an aryl group, or a heteroaryl group.

137. The conjugate of claim 136, wherein one, two, three, four, or five methylene units of T are optionally and independently replaced.

138. The conjugate of claim 136, wherein T is constructed from a C_{1-10} hydrocarbon chain wherein one or more methylene units of T are optionally and independently replaced by –O–, –S–, –N(R)–, –C(O)–, –C(O)O–, –OC(O)–, –N(R)C(O)–, –C(O)N(R)–, –S(O)–, –S(O)$_2$–, –N(R)SO$_2$–, –SO$_2$N(R)–, a heterocyclic group, an aryl group, or a heteroaryl group.

139. The conjugate of claim 136, wherein one or more methylene units of T is replaced by a heterocyclic group.

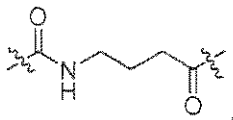
140. The conjugate of claim 136, wherein one or more methylene units of T is replaced by a triazole moiety.

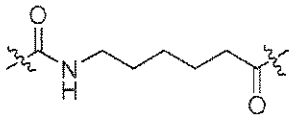
141. The conjugate of claim 136, wherein one or more methylene units of T is replaced by –C(O)–.

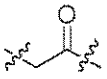
142. The conjugate of claim 136, wherein one or more methylene units of T is replaced by –C(O)N(R)–.

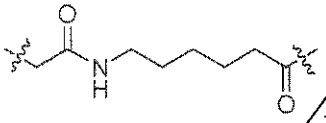
143. The conjugate of claim 136, wherein one or more methylene units of T is replaced by –O–.

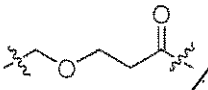
144. The conjugate of claim 136, wherein T is .

145. The conjugate of claim 136, wherein T is .

146. The conjugate of claim 136, wherein T is .

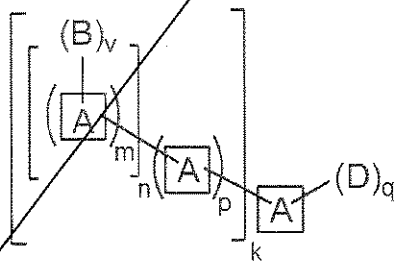
147. The conjugate of claim 136, wherein T is .

148. The conjugate of claim 136, wherein T is .

149. The conjugate of claim 136 wherein T is .

150. The conjugate of claim 136, wherein each occurrence of T is the same.

151. The conjugate of claim 136, wherein each occurrence of T outside groups B and D is a covalent bond and the conjugate is of the formula (IV):



IV

152. The conjugate of claim 151, wherein each occurrence of  except for the central is a covalent bond, each occurrence of v = 1, and the conjugate is of the formula (VI):



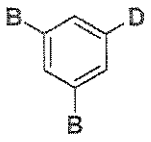
VI

153. The conjugate of claim 152, wherein k = 1 and q = 1.

154. The conjugate of claim 152, wherein k = 2 and q = 1.

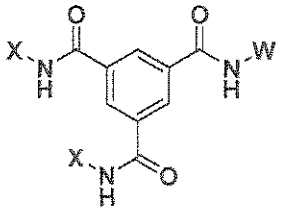
155. The conjugate of claim 152, wherein k = 3 and q = 1.

156. The conjugate of claim 154, wherein the conjugate is of the formula (VIa):



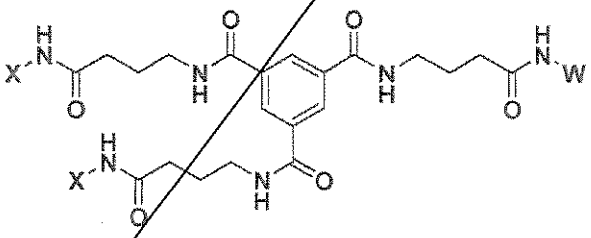
VIa

157. The conjugate of claim 156, wherein the conjugate is of the formula (VIa-1):



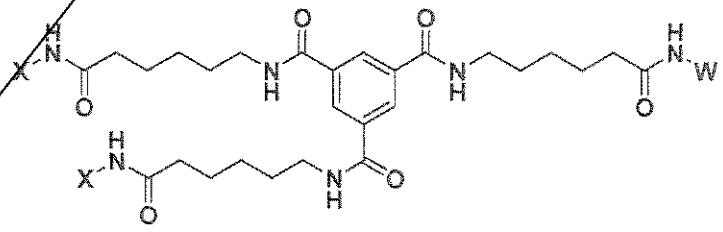
VIa-1

158. The conjugate of claim 156, wherein the conjugate is of the formula (VIa-2):



VIa-2

159. The conjugate of claim 156, wherein the conjugate is of the formula (VIa-3):



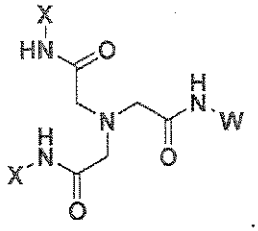
VIa-3

160. The conjugate of claim 154, wherein the conjugate is of the formula (VIb):



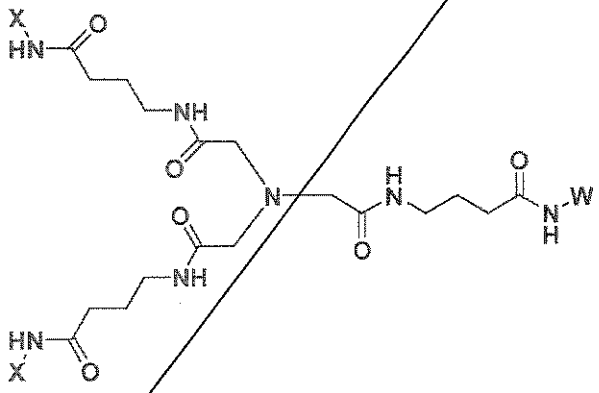
VIb

161. The conjugate of claim 160, wherein the conjugate is of the formula (VIb-1):



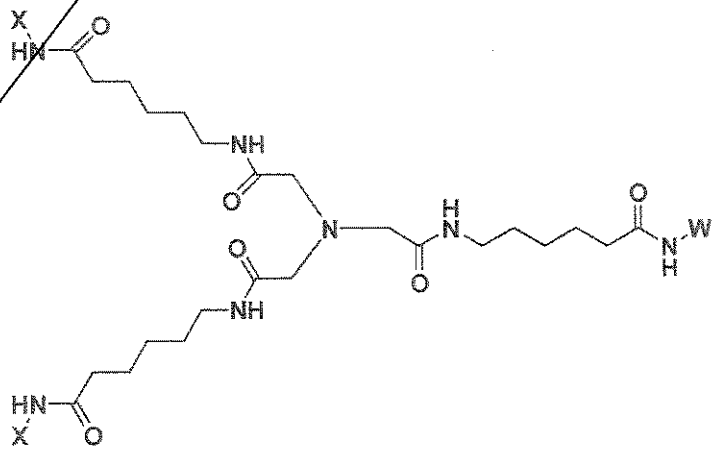
VIb-1

162. The conjugate of claim 160, wherein the conjugate is of the formula (VIb-2):



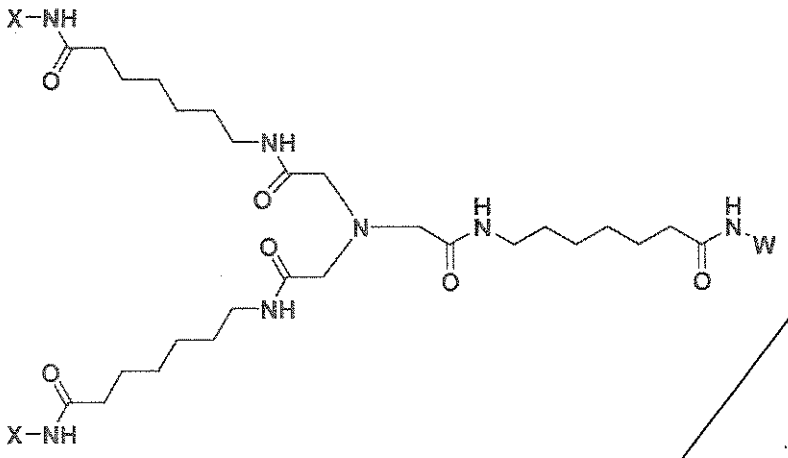
VIb-2

163. The conjugate of claim 160, wherein the conjugate is of the formula (VIb-3):



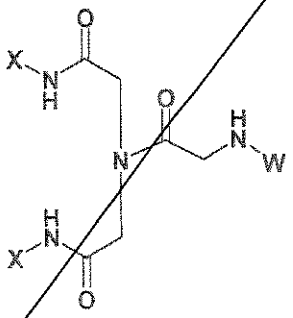
VIb-3

164. The conjugate of claim 160, wherein the conjugate is of the formula (VIb-4):



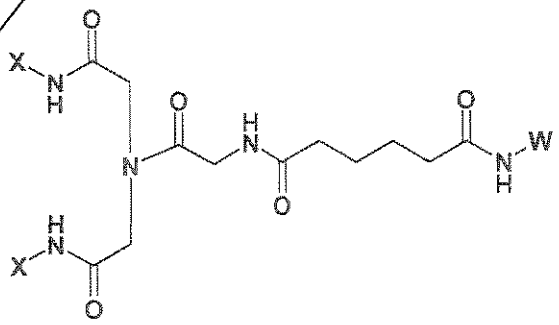
VIb-4

165. The conjugate of claim 160, wherein the conjugate is of the formula (VIb-5):



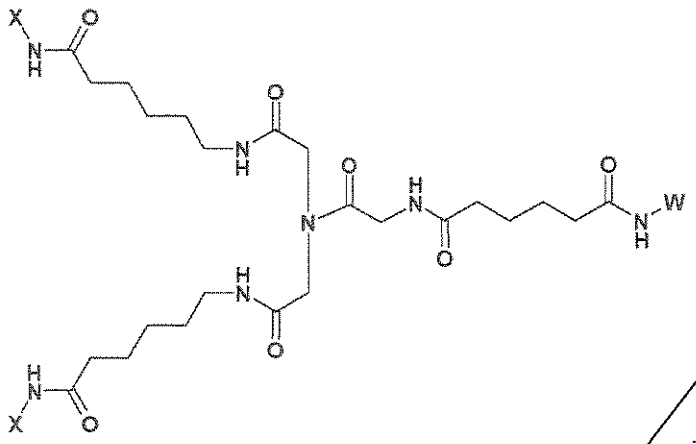
VIb-5

166. The conjugate of claim 160, wherein the conjugate is of the formula (VIb-6):



VIb-6

167. The conjugate of claim 160, wherein the conjugate is of the formula (VIb-7):



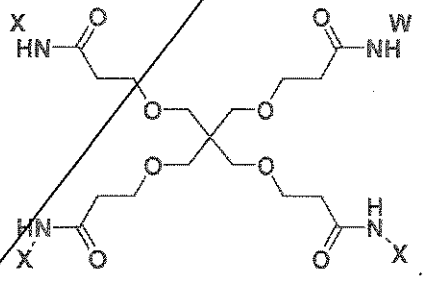
VIb-7

168. The conjugate of claim 155, wherein the conjugate is of the formula (VIc):



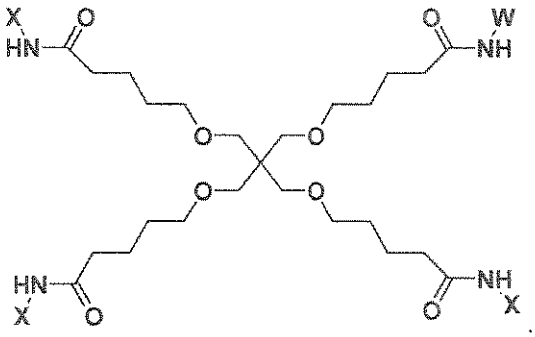
VIc

169. The conjugate of claim 168, wherein the conjugate is of the formula (VIc-1):



VIc-1

170. The conjugate of claim 168, wherein the conjugate is of the formula (VIc-2):



VIc-2

171. The conjugate of claim 115, wherein at least one of L^B and L^D is a covalent bond.

172. The conjugate of claim 115, wherein at least one of L^B and L^D is an optionally substituted moiety derived from conjugating an optionally substituted carbonyl-reactive, thiol-reactive, amine-reactive, or hydroxyl-reactive moiety of T with a carboxyl, thiol, amine, or hydroxyl group of X or W.

173. The conjugate of claim 115, wherein at least one of L^B and L^D is an optionally substituted moiety derived from conjugating an optionally substituted carboxyl-reactive, thiol-reactive, amine-reactive, or hydroxyl-reactive moiety of X or W with a carboxyl, thiol, amine, or hydroxyl group of T.

174. The conjugate of claim 172, wherein at least one of L^B and L^D is .

175. The conjugate of claim 172, wherein at least one of L^B and L^D is a succinimide moiety.

176. The conjugate of claim 115, wherein k + q is an integer from 2 to 6, inclusive.

177. The conjugate of claim 176, wherein k + q is 2, 3 or 4.

178. The conjugate of claim 115, wherein each occurrence of p is 1, 2 or 3.

179. The conjugate of claim 115, wherein each occurrence of p is 1.

180. The conjugate of claim 115, wherein each occurrence of p is the same.

181. The conjugate of claim 115, wherein each occurrence of m is 1, 2 or 3.

182. The conjugate of claim 115, wherein each occurrence of m is 1.

183. The conjugate of claim 115, wherein each occurrence of m is the same.

184. The conjugate of any one of claims 109-183, wherein each occurrence of X is a ligand that includes aminoethylglucose (AEG), aminoethylmannose (AEM), aminoethylbimannose (AEBM) or aminoethyltrimannose (AETM).

185. The conjugate of any one of claims 109-183, wherein each occurrence of X is a ligand that includes aminoethyltrimannose (AETM).

186. The conjugate of claim 185, wherein W is an insulin molecule.

187. The conjugate of claim 186, wherein the insulin molecule is conjugated via the A1 amino acid residue.

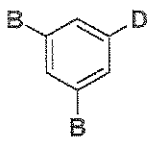
188. The conjugate of claim 186, wherein the insulin molecule is conjugated via the B1 amino acid residue.

189. The conjugate of claim 186, wherein the insulin molecule is conjugated via the epsilon-amino group of Lys^{B29}.

190. The conjugate of claim 186, wherein the insulin molecule is insulin glulisine conjugated via the epsilon-amino group of Lys^{B3}.

191. The conjugate of claim 115, wherein each occurrence of X is aminoethyltrimannose (AETM) conjugated to the conjugate framework via an alpha anomeric carbon; and W is an insulin molecule conjugated to the conjugate framework via the epsilon-amino group of Lys^{B29}.

192. A conjugate of formula (VIa):



VIa

wherein:

–B is $-T-L^B-X$;

each occurrence of X is independently a ligand that includes a saccharide;

each occurrence of L^B is independently a covalent bond or a group derived from the covalent conjugation of a T with an X;

–D is $-T-L^D-W$;

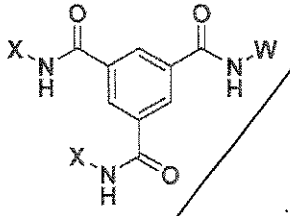
W is a drug;

each occurrence of L^D is independently a covalent bond or a group derived from the covalent conjugation of a T with a W;

each occurrence of T is independently a covalent bond or a bivalent, straight or branched, saturated or unsaturated, optionally substituted C_{1-30} hydrocarbon chain wherein one or more methylene units of T are optionally and independently replaced by -O-, -S-, -N(R)-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)C(O)-, -C(O)N(R)-, -S(O)-, $-S(O)_2-$, $-N(R)SO_2-$, $-SO_2N(R)-$, a heterocyclic group, an aryl group, or a heteroaryl group; and

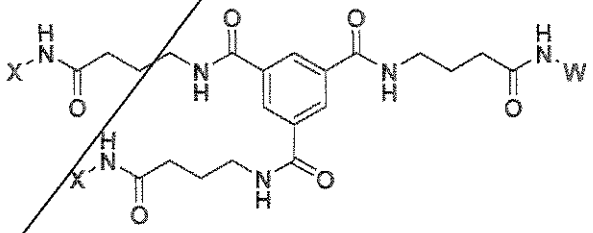
each occurrence of R is independently hydrogen, a suitable protecting group, or an acyl moiety, arylalkyl moiety, aliphatic moiety, aryl moiety, heteroaryl moiety, or heteroaliphatic moiety.

193. The conjugate of claim 192, wherein the conjugate is of the formula (VIa-1):



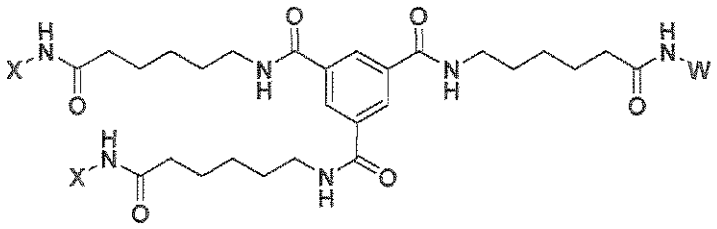
VIa-1

194. The conjugate of claim 192, wherein the conjugate is of the formula (VIa-2):



VIa-2

195. The conjugate of claim 192, wherein the conjugate is of the formula (VIa-3):



VIa-3

196. A conjugate of formula (VIb):



VIb

wherein:

–B is –T–L^B–X;

each occurrence of X is independently a ligand that includes a saccharide;

each occurrence of L^B is independently a covalent bond or a group derived from the covalent conjugation of a T with an X;

–D is –T–L^D–W;

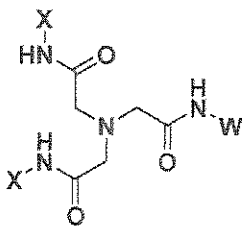
W is a drug;

each occurrence of L^D is independently a covalent bond or a group derived from the covalent conjugation of a T with a W;

each occurrence of T is independently a covalent bond or a bivalent, straight or branched, saturated or unsaturated, optionally substituted C_{1-10} hydrocarbon chain wherein one or more methylene units of T are optionally and independently replaced by -O-, -S-, -N(R)-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)C(O)-, -C(O)N(R)-, -S(O)-, -$S(O)_2$-, -N(R)SO_2-, -SO_2N(R)-, a heterocyclic group, an aryl group, or a heteroaryl group; and

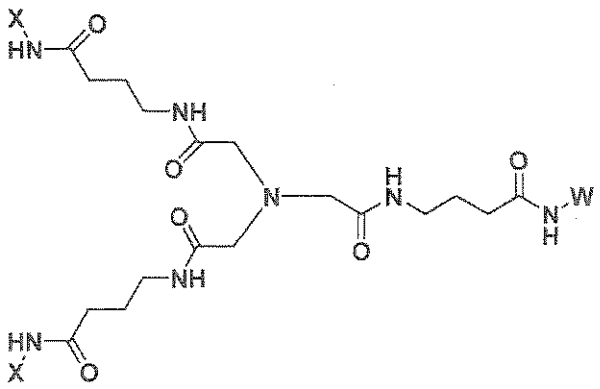
each occurrence of R is independently hydrogen, a suitable protecting group, or an acyl moiety, arylalkyl moiety, aliphatic moiety, aryl moiety, heteroaryl moiety, or heteroaliphatic moiety.

197. The conjugate of claim 196, wherein the conjugate is of the formula (VIb-1):



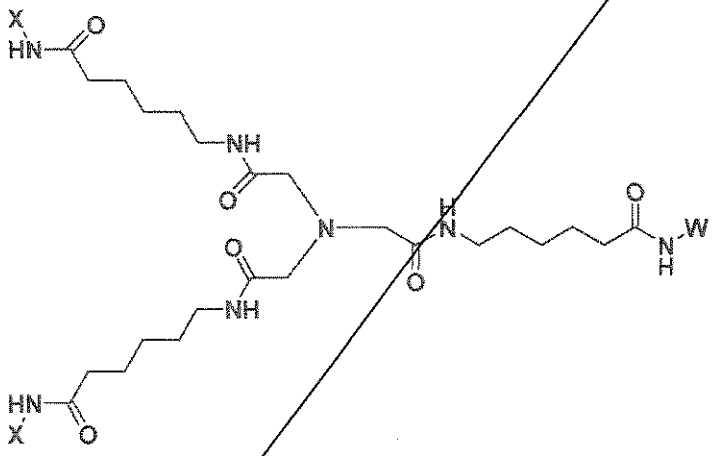
VIb-1

198. The conjugate of claim 196, wherein the conjugate is of the formula (VIb-2):



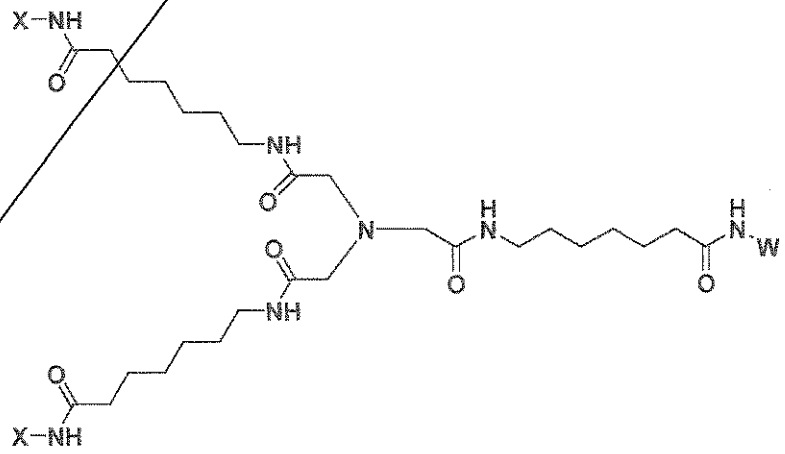
VIb-2

199. The conjugate of claim 196, wherein the conjugate is of the formula (VIb-3):



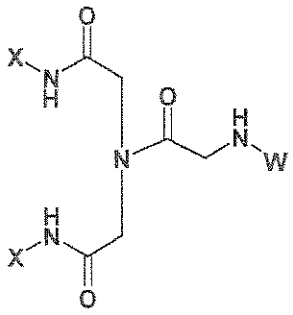
VIb-3

200. The conjugate of claim 196, wherein the conjugate is of the formula (VIb-4):



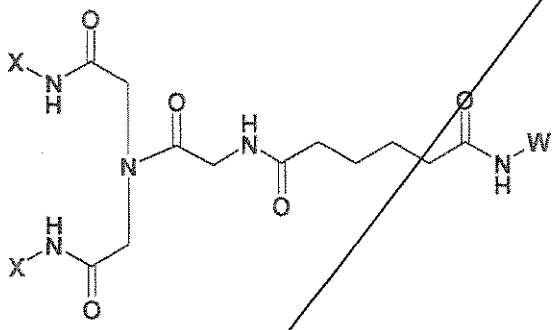
VIb-4

201. The conjugate of claim 196, wherein the conjugate is of the formula (VIb-5):



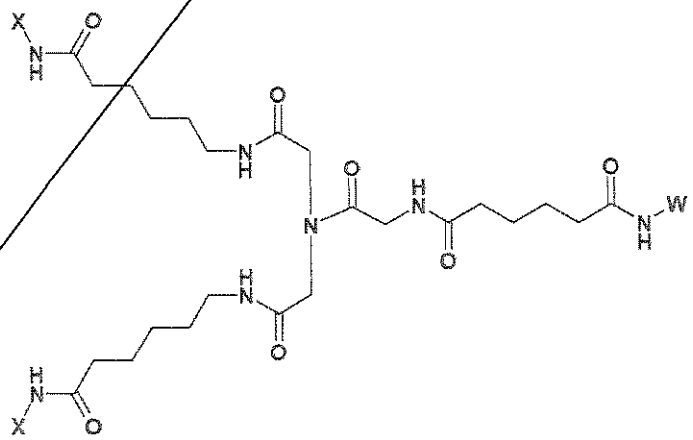
VIb-5

202. The conjugate of claim 196, wherein the conjugate is of the formula (VIb-6):



VIb-6

203. The conjugate of claim 196, wherein the conjugate is of the formula (VIb-7):



VIb-7

204. A conjugate of formula (VIc):



VIc

wherein:

–B is –T–L^B–X;

each occurrence of X is independently a ligand that includes a saccharide;

each occurrence of L^B is independently a covalent bond or a group derived from the covalent conjugation of a T with an X;

–D is –T–L^D–W;

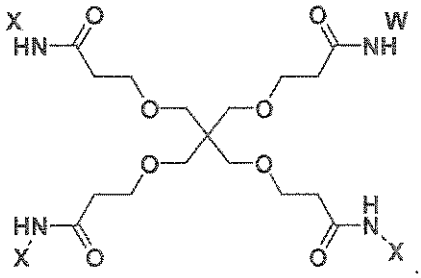
W is a drug;

each occurrence of L^D is independently a covalent bond or a group derived from the covalent conjugation of a T with a W;

each occurrence of T is independently a covalent bond or a bivalent, straight or branched, saturated or unsaturated, optionally substituted C_{1-30} hydrocarbon chain wherein one or more methylene units of T are optionally and independently replaced by -O-, -S-, -N(R)-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)C(O)-, -C(O)N(R)-, -S(O)-, -$S(O)_2$-, -N(R)SO_2-, -SO_2N(R)-, a heterocyclic group, an aryl group, or a heteroaryl group; and

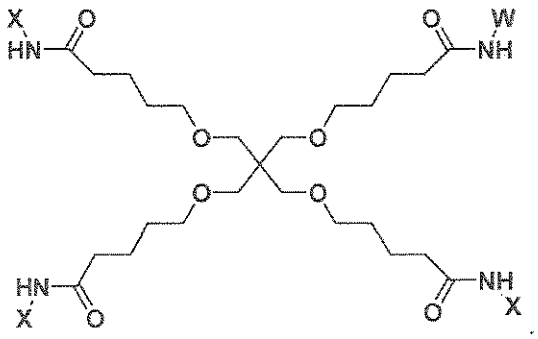
each occurrence of R is independently hydrogen, a suitable protecting group, or an acyl moiety, arylalkyl moiety, aliphatic moiety, aryl moiety, heteroaryl moiety, or heteroaliphatic moiety.

205. The conjugate of claim 204, wherein the conjugate is of the formula (VIc-1):



VIc-1

206. The conjugate of claim 204, wherein the conjugate is of the formula (VIc-2):



VIc-2

207. The conjugate of claim 192, 196 or 204, wherein each occurrence of T is independently a bivalent, straight or branched, saturated or unsaturated, optionally substituted C_{1-20} hydrocarbon chain wherein one or more methylene units of T are optionally and independently replaced by –O–, –S–, –N(R)–, –C(O)–, –C(O)O–, –OC(O)–, –N(R)C(O)–, –C(O)N(R)–, –S(O)–, –$S(O)_2$–, –N(R)SO_2–, –SO_2N(R)–, a heterocyclic group, an aryl group, or a heteroaryl group.

208. The conjugate of claim 207, wherein one, two, three, four, or five methylene units of T are optionally and independently replaced.

209. The conjugate of claim 207, wherein T is constructed from a C_{1-10} hydrocarbon chain wherein one or more methylene units of T are optionally and independently replaced by –O–, –S–, –N(R)–, –C(O)–, –C(O)O–, –OC(O)–, –N(R)C(O)–, –C(O)N(R)–, –S(O)–, –$S(O)_2$–, –N(R)SO_2–, –SO_2N(R)–, a heterocyclic group, an aryl group, or a heteroaryl group.

210. The conjugate of claim 207, wherein one or more methylene units of T is replaced by a heterocyclic group.

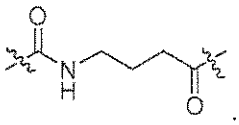
211. The conjugate of claim 207, wherein one or more methylene units of T is replaced by a triazole moiety.

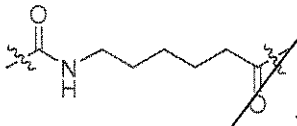
212. The conjugate of claim 207, wherein one or more methylene units of T is replaced by –C(O)–.

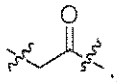
213. The conjugate of claim 207, wherein one or more methylene units of T is replaced by –C(O)N(R)–.

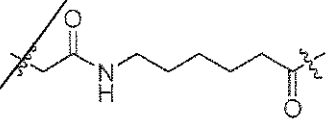
214. The conjugate of claim 207, wherein one or more methylene units of T is replaced by –O–.

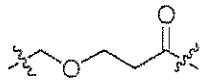
215. The conjugate of claim 207, wherein T is .

216. The conjugate of claim 207, wherein T is .

217. The conjugate of claim 207, wherein T is .

218. The conjugate of claim 207, wherein T is .

219. The conjugate of claim 207, wherein T is .

220. The conjugate of claim 207, wherein T is .

221. The conjugate of claim 207, wherein each occurrence of T is the same.

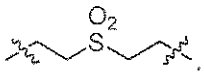
222. The conjugate of claim 192, 196 or 204, wherein at least one of L^B and L^D is a covalent bond.

223. The conjugate of claim 192, 196 or 204, wherein at least one of L^B and L^D is an optionally substituted moiety derived from conjugating an optionally substituted carbonyl-reactive, thiol-reactive, amine-reactive, or hydroxyl-reactive moiety of T with a carboxyl, thiol, amine, or hydroxyl group of X or W.

224. The conjugate of claim 192, 196 or 204, wherein at least one of L^B and L^D is an optionally substituted moiety derived from conjugating an optionally substituted carboxyl-

reactive, thiol-reactive, amine-reactive, or hydroxyl-reactive moiety of X or W with a carboxyl, thiol, amine, or hydroxyl group of T.

225. The conjugate of claim 192, 196 or 204, wherein at least one of L^B and L^D is



226. The conjugate of claim 192, 196 or 204, wherein at least one of L^B and L^D is a succinimide moiety.

227. The conjugate of any one of claims 192-226, wherein the drug is an anti-diabetic drug.

228. The conjugate of any one of claims 192-226, wherein the drug is an insulin sensitizer.

229. The conjugate of any one of claims 192-226, wherein the drug is an insulin secretatogue.

230. The conjugate of any one of claims 192-226, wherein the drug is an insulin molecule.

231. The conjugate of claim 230, wherein the insulin molecule is selected from the group consisting of human insulin, porcine insulin, and bovine insulin.

232. The conjugate of claim 230, wherein the insulin molecule is selected from the group consisting of insulin lispro, insulin aspart and insulin glulisine.

233. The conjugate of claim 230, wherein the insulin molecule is insulin glargine or insulin detemir.

234. The conjugate of claim 230, wherein the insulin molecule includes three disulfide bridges.

235. The conjugate of claim 230, wherein the insulin molecule is conjugated via the A1 amino acid residue.

236. The conjugate of claim 230, wherein the insulin molecule is conjugated via the B1 amino acid residue.

237. The conjugate of claim 230, wherein the insulin molecule is conjugated via the epsilon-amino group of Lys^{B29}.

238. The conjugate of claim 230, wherein the insulin molecule is insulin glulisine conjugated via the epsilon-amino group of Lys^{B3}.

239. The conjugate of any one of claims 192-226, wherein each occurrence of X is independently a ligand that includes a saccharide selected from the group consisting of glucose, mannose and L-fucose.

240. The conjugate of claim 239, wherein each occurrence of X is independently a ligand that includes a saccharide selected from the group consisting of mannosamine and beta-linked N-acetyl mannosamine.

241. The conjugate of claim 239, wherein each occurrence of X is independently a ligand that includes a saccharide selected from the group consisting of methylglucose, methylmannose, ethylglucose, ethylmannose, propylglucose and propylmannose.

242. The conjugate of claim 239, wherein each occurrence of X is a ligand that includes alpha-L-fucopyranoside.

243. The conjugate of claim 239, wherein each occurrence of X is a ligand that includes a bimannose.

244. The conjugate of claim 239, wherein each occurrence of X is a ligand that includes a trimannose.

245. The conjugate of claim 239, wherein each occurrence of X is a ligand that includes a linear trimannose.

246. The conjugate of claim 239, wherein each occurrence of X is a ligand that includes a branched trimannose.

247. The conjugate of claim 239, wherein each occurrence of X is a ligand that includes a saccharide and an amine group.

248. The conjugate of claim 247, wherein the saccharide and amine group are separated by a C_1-C_6 alkyl group.

249. The conjugate of claim 248, wherein each occurrence of X is independently a ligand that includes aminoethylglucose (AEG), aminoethylmannose (AEM), aminoethylbimannose (AEBM) or aminoethyltrimannose (AETM).

250. The conjugate of claim 249, wherein each occurrence of X is a ligand that includes aminoethyltrimannose (AETM).

251. The conjugate of claim 250, wherein the conjugate includes two or three occurrences where X is a ligand that includes aminoethyltrimannose (AETM).

252. The conjugate of any one of claims 192-226, wherein each occurrence of X is a ligand that includes a saccharide that is conjugated via an anomeric carbon.

253. The conjugate of claim 252, wherein the anomeric carbon is an alpha anomer.

254. The conjugate of any one of claims 192-226, wherein each occurrence of X is aminoethyltrimannose (AETM) conjugated to the conjugate framework via an alpha anomeric carbon; and W is an insulin molecule conjugated to the conjugate framework via the epsilon-amino group of Lys^{B29}.

255. A sustained release formulation comprising a conjugate of any one of the preceding claims.

256. The formulation of claim 255, wherein the formulation exhibits a zero-order release of the conjugate when administered to a mammal under fasting conditions.

257. The formulation of claim 255, wherein the formulation exhibits a zero-order release of the conjugate when administered subcutaneously to a mammal under fasting conditions.

258. The formulation of claim 255, wherein the drug is an insulin molecule and the formulation comprises protamine and zinc.

259. The formulation of claim 258, wherein the insulin molecule is selected from the group consisting of human insulin, porcine insulin, and bovine insulin.

260. The formulation of claim 258, wherein the insulin molecule is insulin glargine or insulin detemir.

261. The formulation of claim 258, wherein the insulin molecule includes three disulfide bridges.

262. The formulation of claim 258, wherein the formulation includes from about 0.05 to about 10 mg protamine/mg conjugate.

263. The formulation of claim 258, wherein the formulation includes from about 1 to about 5 mg protamine/mg conjugate

264. The formulation of claim 258, wherein the formulation includes from about 0.006 to about 0.5 mg zinc/mg conjugate.

265. The formulation of claim 258, wherein the formulation includes from about 0.1 to about 0.25 mg zinc/mg conjugate.

266. The formulation of claim 258, wherein the formulation includes protamine and zinc in a ratio (w/w) in the range of about 100:1 to about 5:1.

267. The formulation of claim 258, wherein the formulation includes protamine and zinc in a ratio (w/w) in the range of about 40:1 to about 10:1.

268. The formulation of any one of claims 258-267, wherein the formulation further comprises an antimicrobial preservative.

269. The formulation of claim 268, wherein the antimicrobial preservative is selected from the group consisting of m-cresol, phenol, methylparaben, and propylparaben.

270. The formulation of claim 268, wherein the antimicrobial preservative is m-cresol.

271. The formulation of claim 270, wherein the formulation comprises from about 0.1 to about 1.0% v/v m-cresol.

272. The formulation of claim 270, wherein the formulation comprises from about 0.15 to about 0.35% v/v m-cresol.

273. The formulation of any one of claims 258-267, wherein the formulation further comprises an isotonic agent.

274. The formulation of claim 273, wherein the isotonic agent is a polyol.

275. The formulation of claim 274, wherein the isotonic agent is selected from the group consisting of mannitol, propylene glycol and glycerol.

276. The formulation of claim 275, wherein the isotonic agent is glycerol.

277. The formulation of claim 273, wherein the isotonic agent is a salt.

278. The formulation of claim 277, wherein the salt is NaCl.

279. The formulation of claim 278, wherein the formulation comprises from about 0.05 to about 0.5 M NaCl.

280. The formulation of claim 278, wherein the formulation comprises from about 0.1 to about 0.2 M NaCl.

281. The formulation of any one of claims 258-267, wherein the formulation further comprises an amount of unconjugated insulin molecule.

282. The formulation of claim 281, wherein the formulation comprises a molar ratio of conjugated insulin molecule to unconjugated insulin molecule in the range of about 100:1 to about 1:1.

283. The formulation of claim 281, wherein the formulation comprises a molar ratio of conjugated insulin molecule to unconjugated insulin molecule in the range of about 25:1 to about 2:1.

284. The formulation of any one of claims 255-283, wherein the conjugate is as defined in any one of claims 327-350.

285. A pump delivery system comprising a conjugate of any one of claims 1-254, wherein the pump delivery system operates by infusing the conjugate into a mammal.

286. The pump of claim 285, wherein the pump operates by infusing the conjugate intravenously, subcutaneously, or intraperitoneally.

287. The pump of claim 285, wherein the conjugate is as defined in any one of claims 327-350.

288. A method of treating hyperglycemia comprising administering a formulation of any one of claims 255-284 to a mammalian patient in need thereof.

289. The method of claim 288, wherein the patient is diabetic.

290. The method of claim 288, wherein the patient has an infection associated with impaired glycemic control.

291. The method of claim 288, wherein the formulation does not include a lectin.

292. The method of claim 288, wherein the formulation is administered by subcutaneous injection.

293. The method of claim 288, wherein the patient is a human.

294. The method of claim 288, wherein the drug is an anti-diabetic drug.

295. The method of claim 288, wherein the drug is an insulin sensitizer.

296. The method of claim 288, wherein the drug is an insulin secretatogue.

297. The method of claim 288, wherein the drug is an insulin molecule.

298. The method of claim 297, wherein the conjugate is administered such that the average daily dose of the insulin molecule is in the range of 10 to 200 U.

299. The method of claim 298, wherein the conjugate is administered daily.

300. The method of claim 298, wherein the conjugate is administered weekly.

301. The method of claim 298, wherein the conjugate is administered monthly.

302. The method of claim 298, wherein the patient is also receiving an insulin sensitizer.

303. The method of claim 298, wherein the patient is also receiving an insulin secretagogue.

304. The method of any one of claims 288-303, wherein the formulation does not include a lectin.

305. The method of any one of claims 288-304, wherein the conjugate is as defined in any one of claims 327-350.

306. A method comprising administering a conjugate of any one of claims 1-254 to a mammalian patient in need thereof.

307. The method of claim 306, wherein the drug is an insulin molecule.

308. The method of claim 307, wherein the conjugate induces less hypoglycemia than an unconjugated version of the insulin molecule.

309. The method of claim 307 or 308, wherein the conjugate is as defined in any one of claims 327-350.

310. A method comprising administering a formulation of any one of claims 255-283 to a mammalian patient in need thereof.

311. The method of claim 310, wherein the drug is an insulin molecule.

312. The method of claim 311, wherein the formulation induces less hypoglycemia than a formulation comprising an unconjugated version of the insulin molecule.

313. The method of claim 311, wherein the formulation induces a lower HbA1c than a formulation comprising an unconjugated version of the insulin molecule.

314. The method of any one of claims 311-313, wherein the conjugate is as defined in any one of claims 327-350.

315. The method of any one of claims 306-314, further comprising administering a triggering amount of an exogenous saccharide to the patient.

316. The method of claim 315, wherein the exogenous saccharide is mannose.

317. The method of claim 315, wherein the exogenous saccharide is L-fucose.

318. The method of claim 315, wherein the exogenous saccharide is N-acetyl glucosamine.

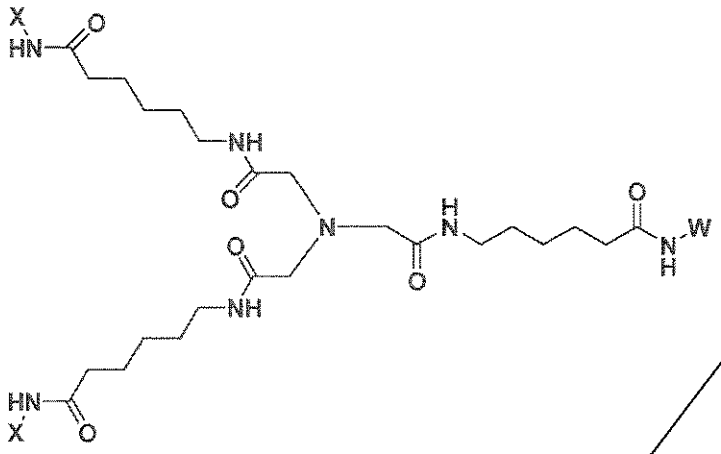
319. The method of claim 315, wherein the exogenous saccharide is alpha-methyl mannose.

320. The method of claim 315, wherein the conjugate or formulation and the exogenous saccharide are administered to the mammal via different routes.

321. The method of claim 320, wherein the conjugate or formulation is administered subcutaneously and the exogenous saccharide is administered orally.

322. The method of claim 320, wherein the conjugate or formulation is administered subcutaneously and the exogenous saccharide is administered intravenously.

323. A conjugate of formula (VIb-3):

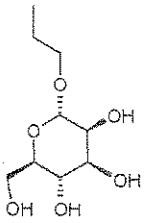


VIb-3

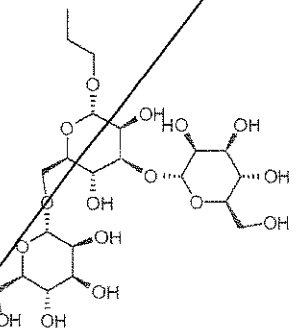
wherein:

W is an insulin molecule; and

each occurrence of -X is



or



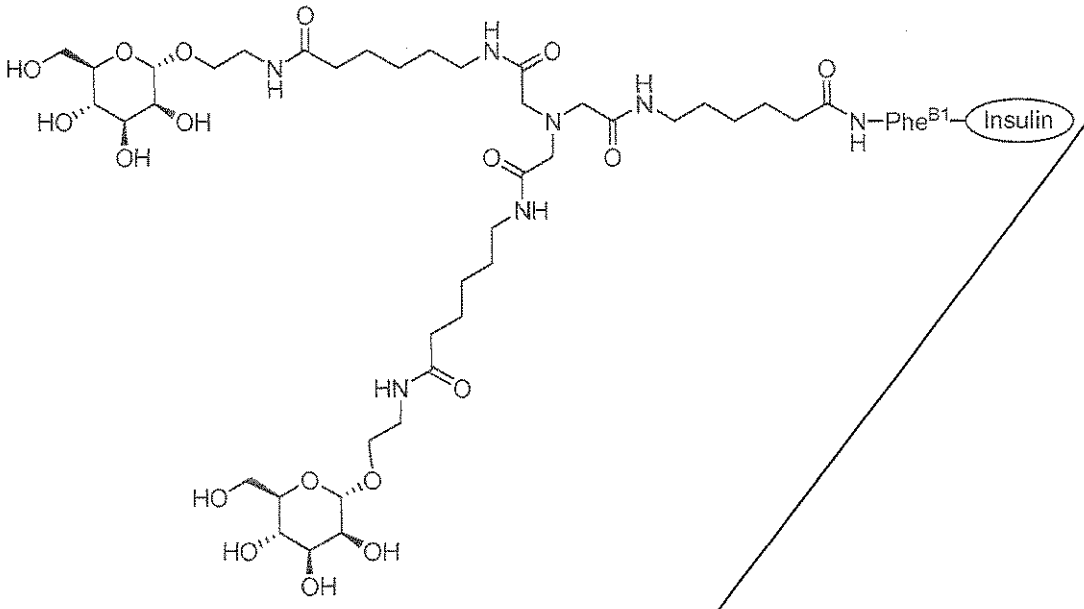
.

324. The conjugate of claim 323, wherein the insulin molecule is selected from the group consisting of human insulin, porcine insulin, and bovine insulin.

325. The conjugate of claim 323, wherein the insulin molecule is insulin glargine or insulin detemir.

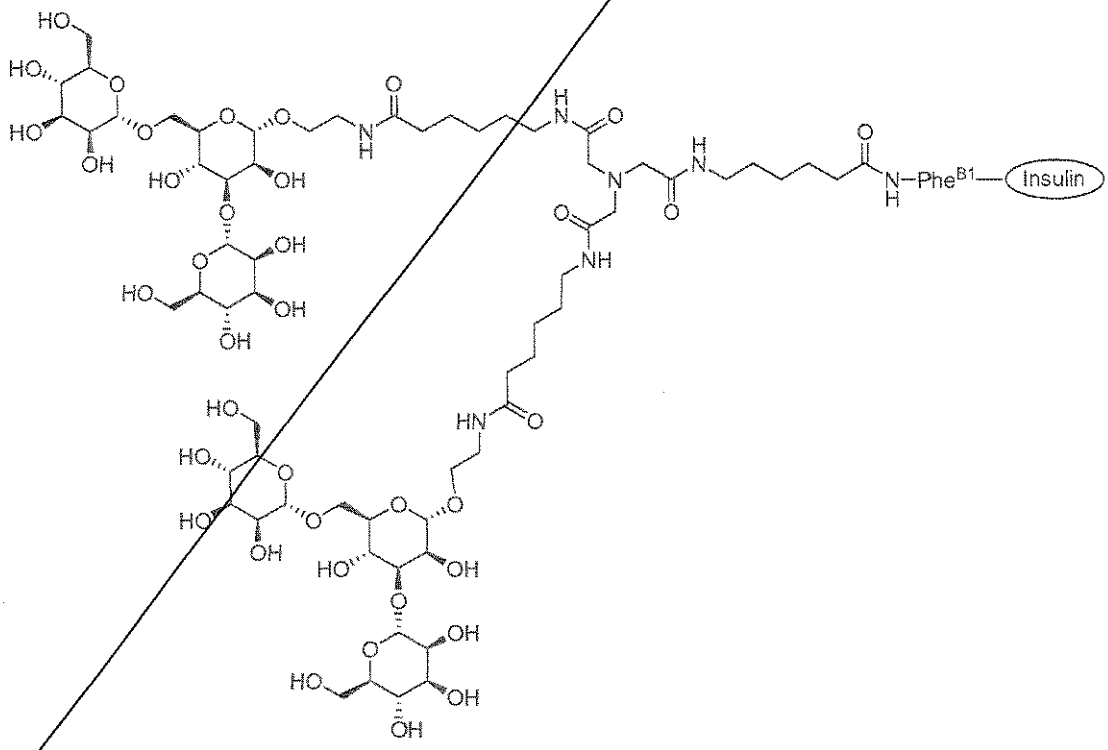
326. The conjugate of claim 323, wherein the insulin molecule includes three disulfide bridges.

327. A conjugate of formula:



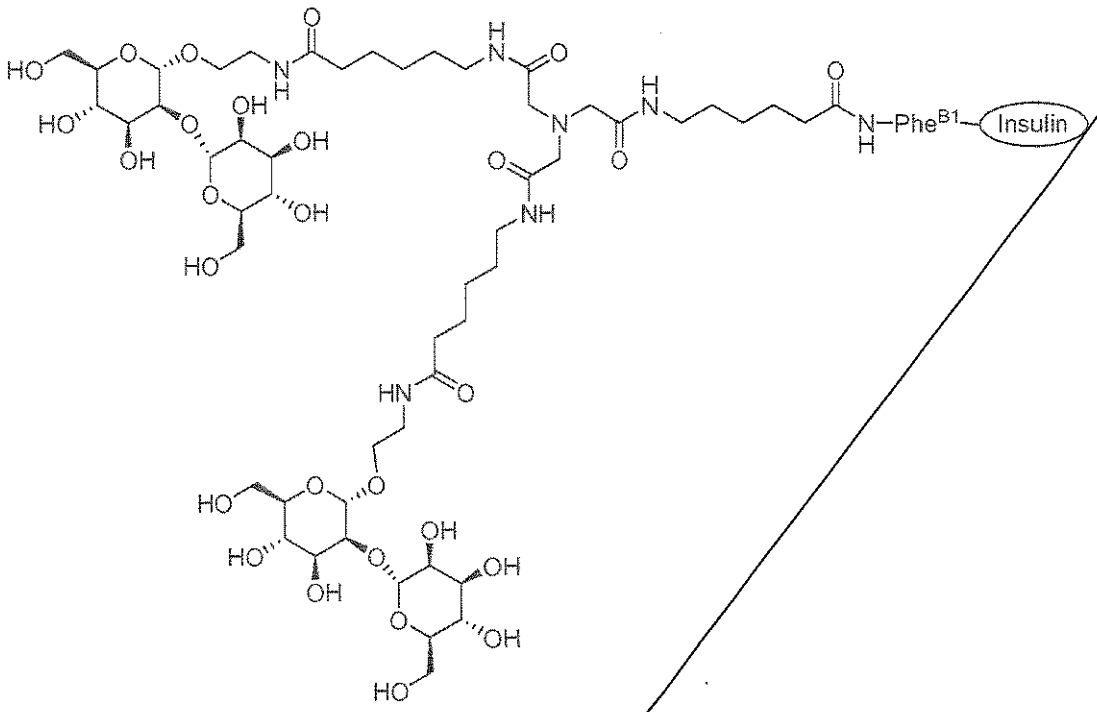
I-1

328. A conjugate of formula:



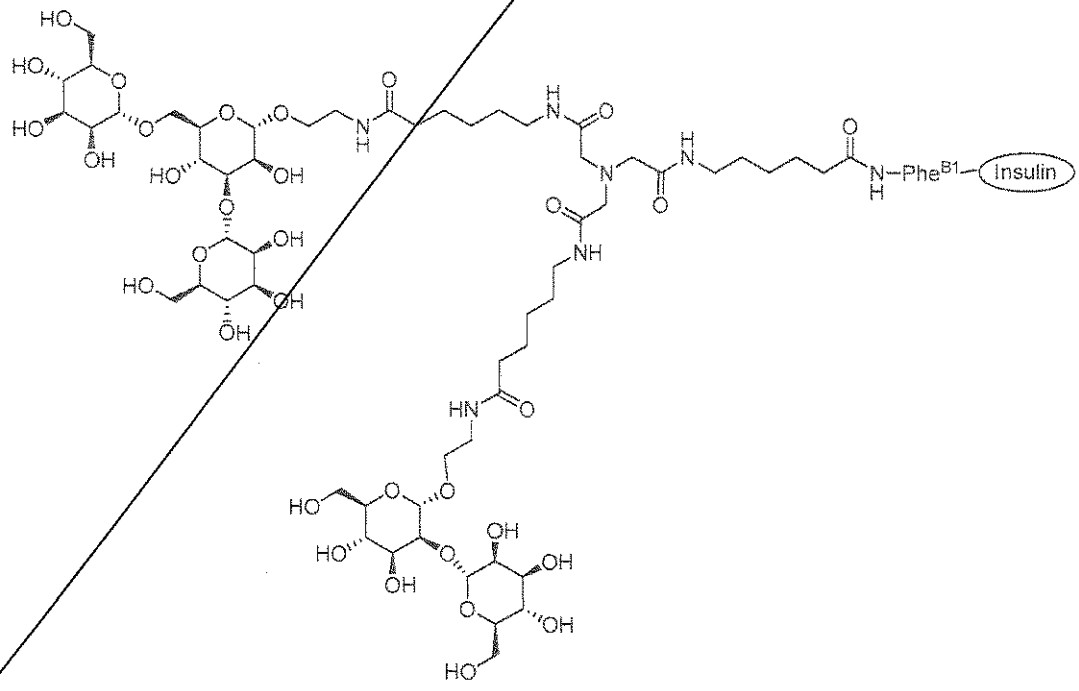
I-2

329. A conjugate of formula:



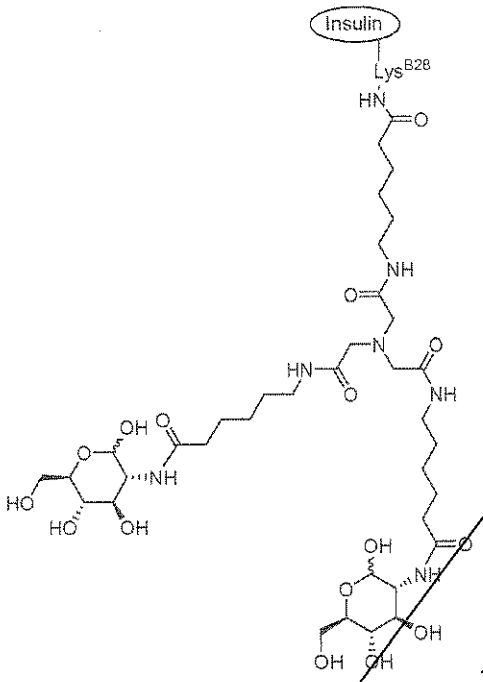
I-3

330. A conjugate of formula:



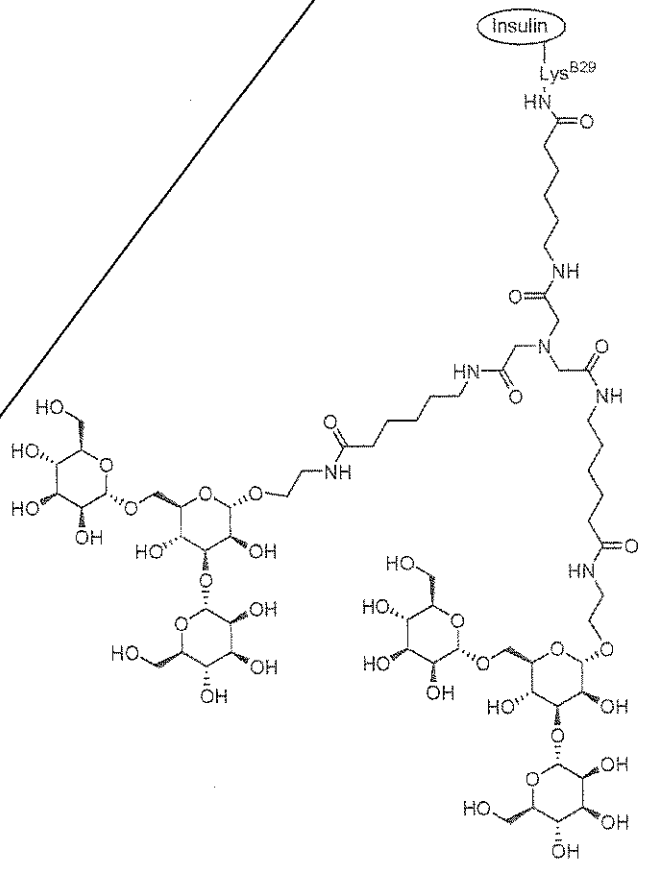
I-4

331. A conjugate of formula:



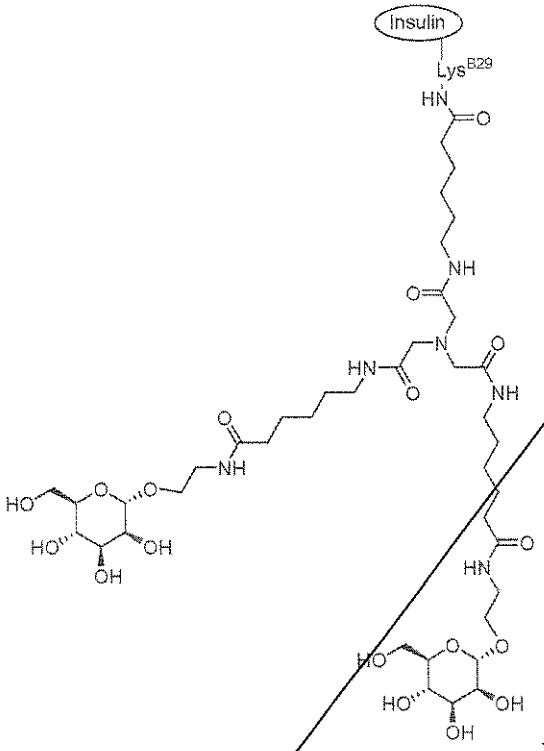
I-5

332. A conjugate of formula:



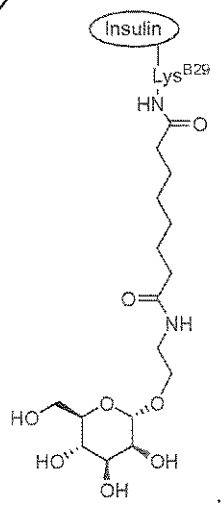
I-6

333. A conjugate of formula:



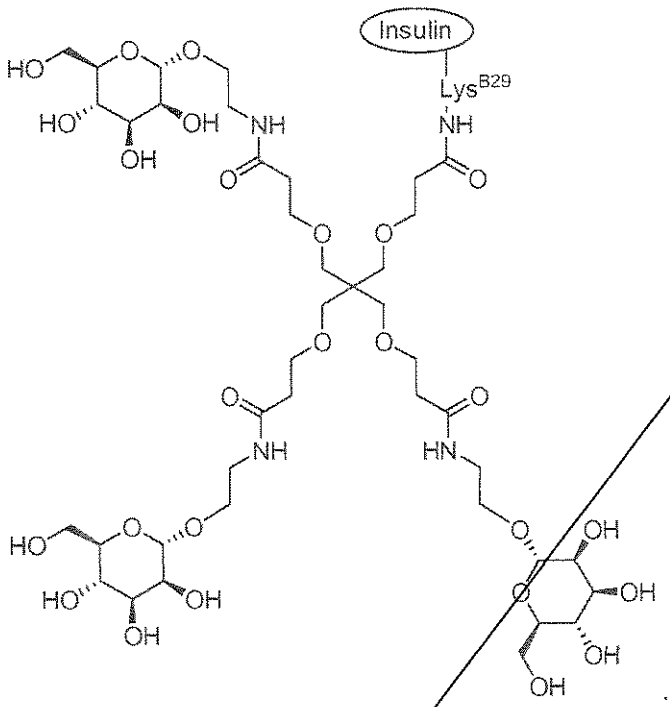
I-7

334. A conjugate of formula:



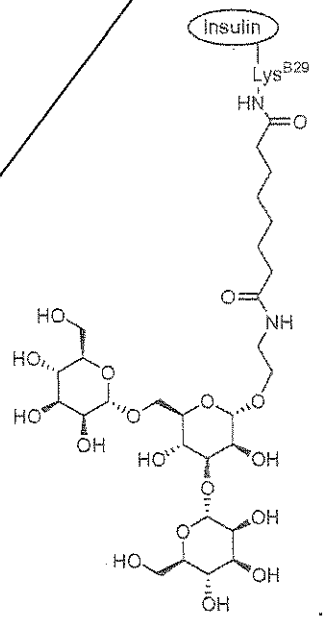
I-8

335. A conjugate of formula:



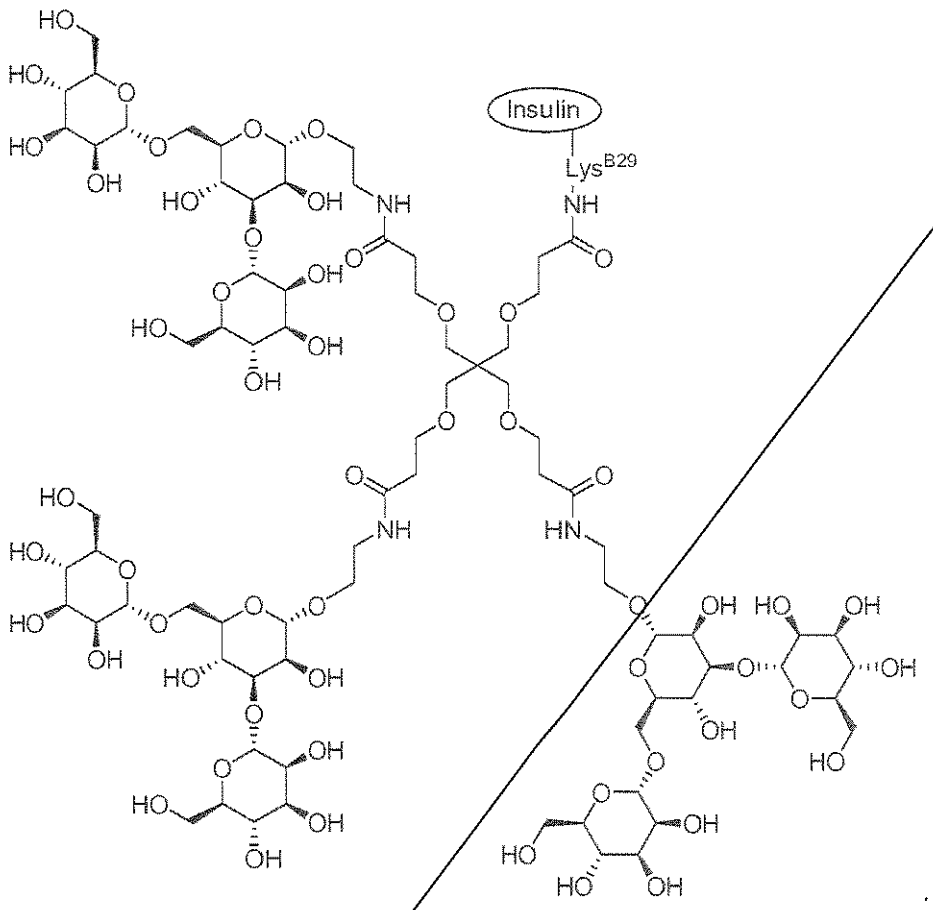
I-9

336. A conjugate of formula:



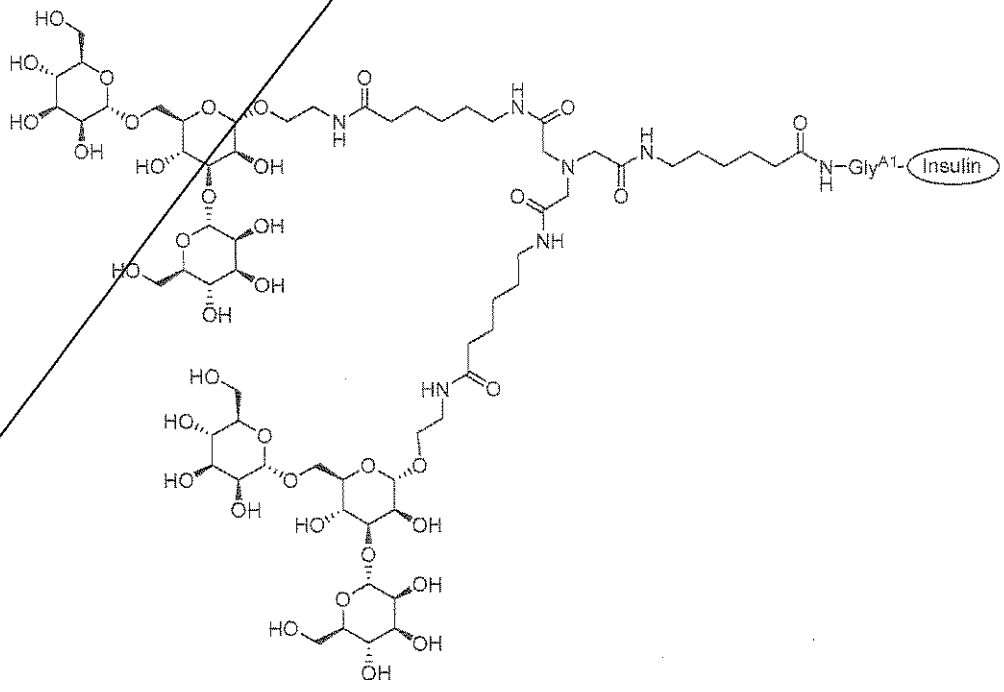
I-10

337. A conjugate of formula:



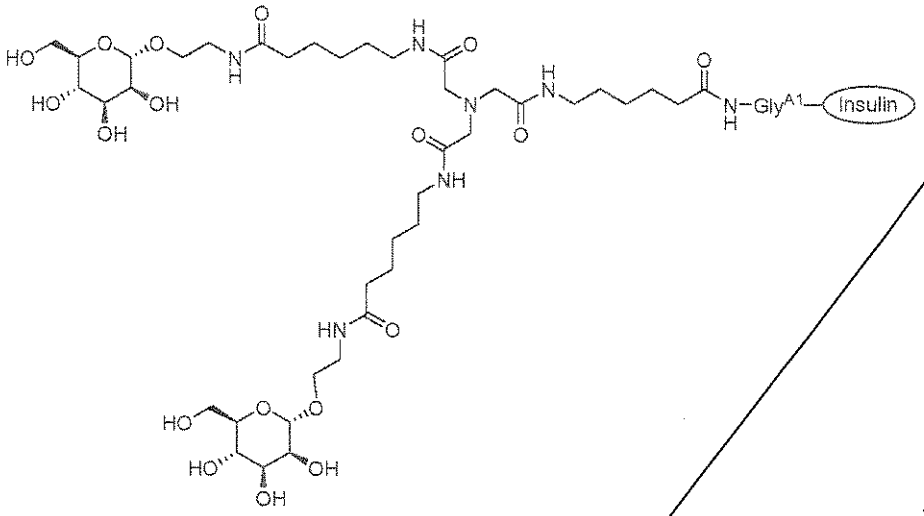
I-11

338. A conjugate of formula:



I-12

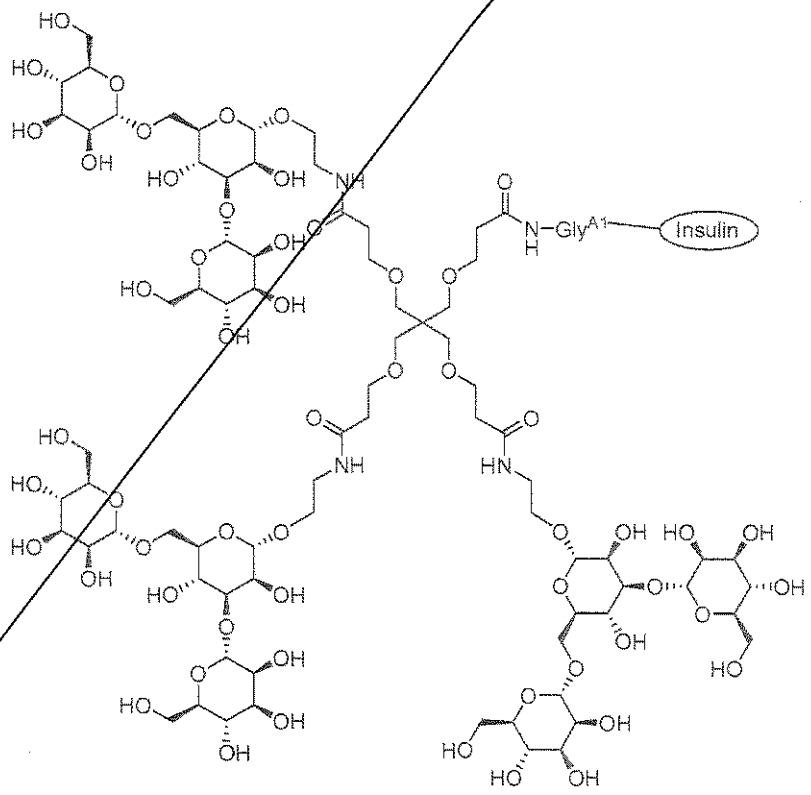
339. A conjugate of formula:



I-13

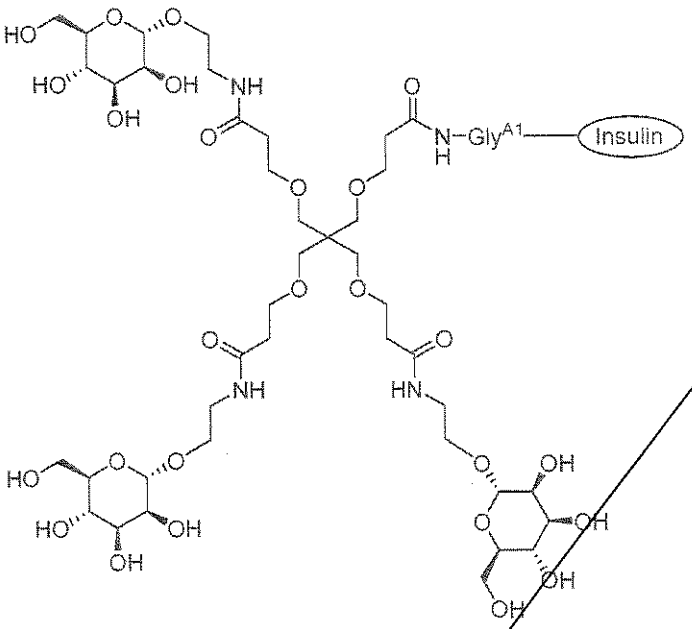
5

340. A conjugate of formula:



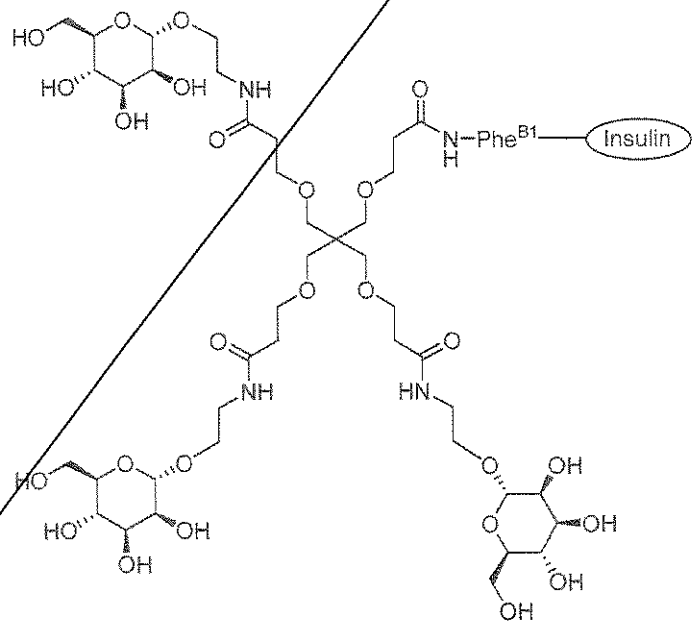
I-14

341. A conjugate of formula:



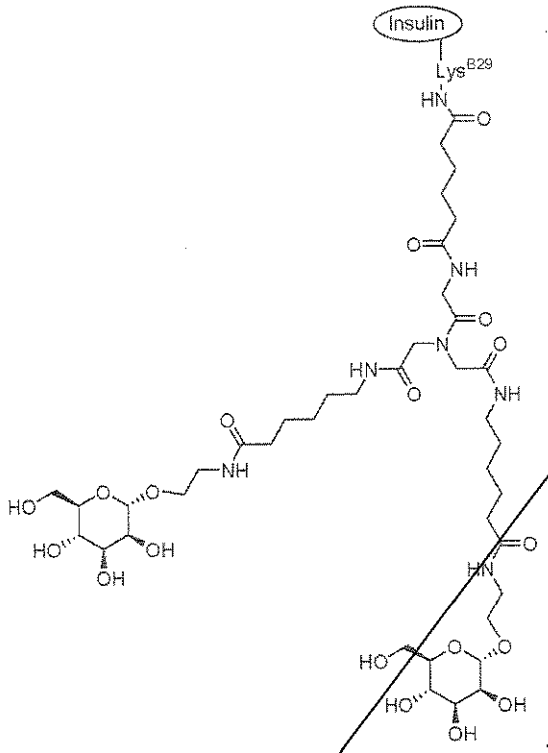
I-15

342. A conjugate of formula:



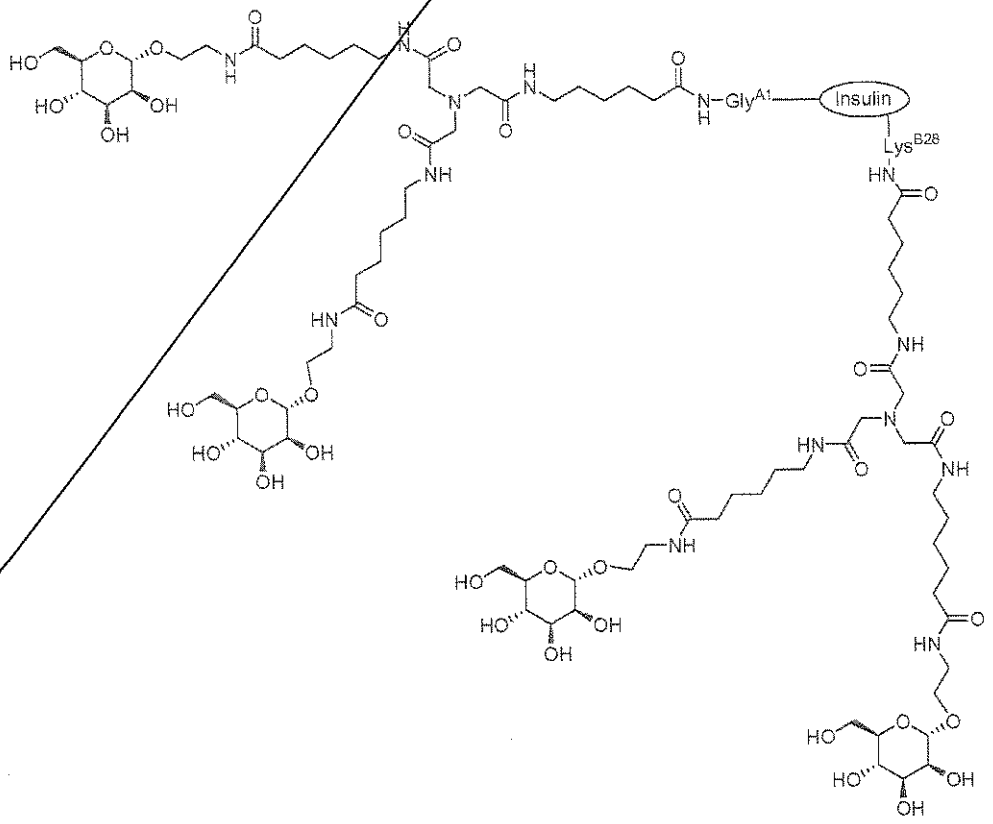
I-16

343. A conjugate of formula:



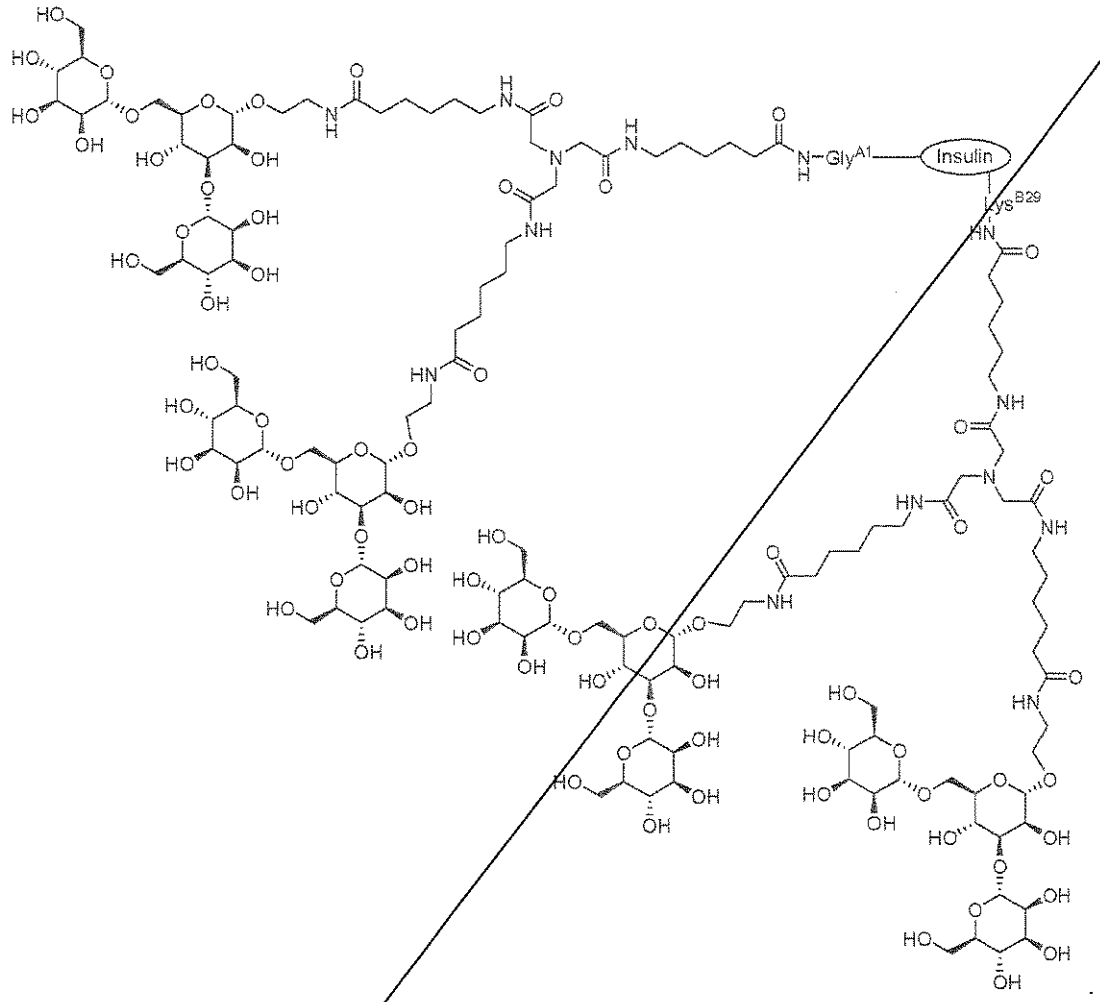
I-17

344. A conjugate of formula:



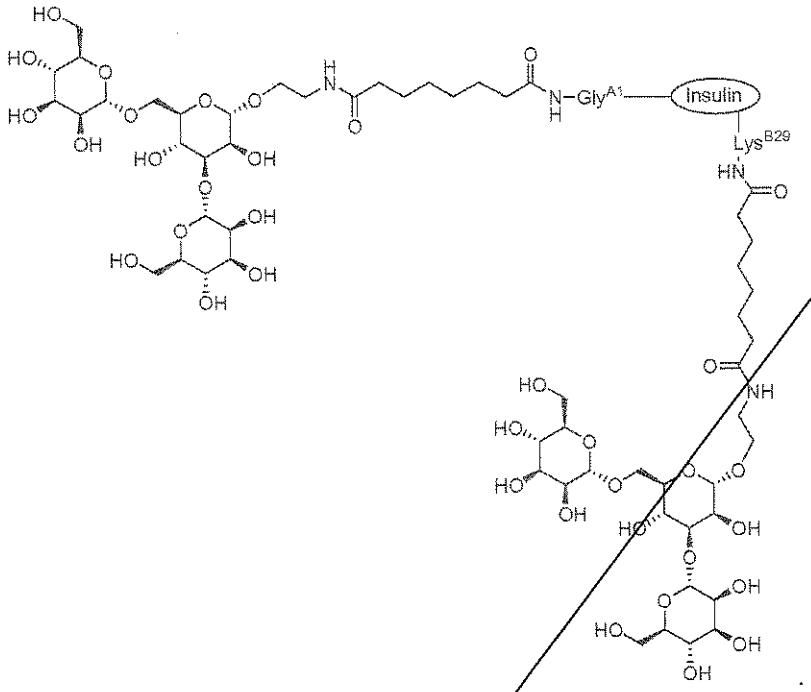
II-1

345. A conjugate of formula:



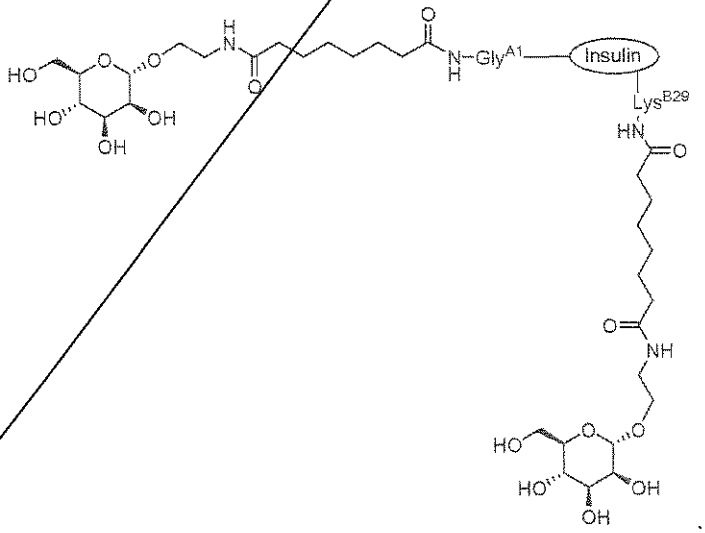
II-2

346. A conjugate of formula:



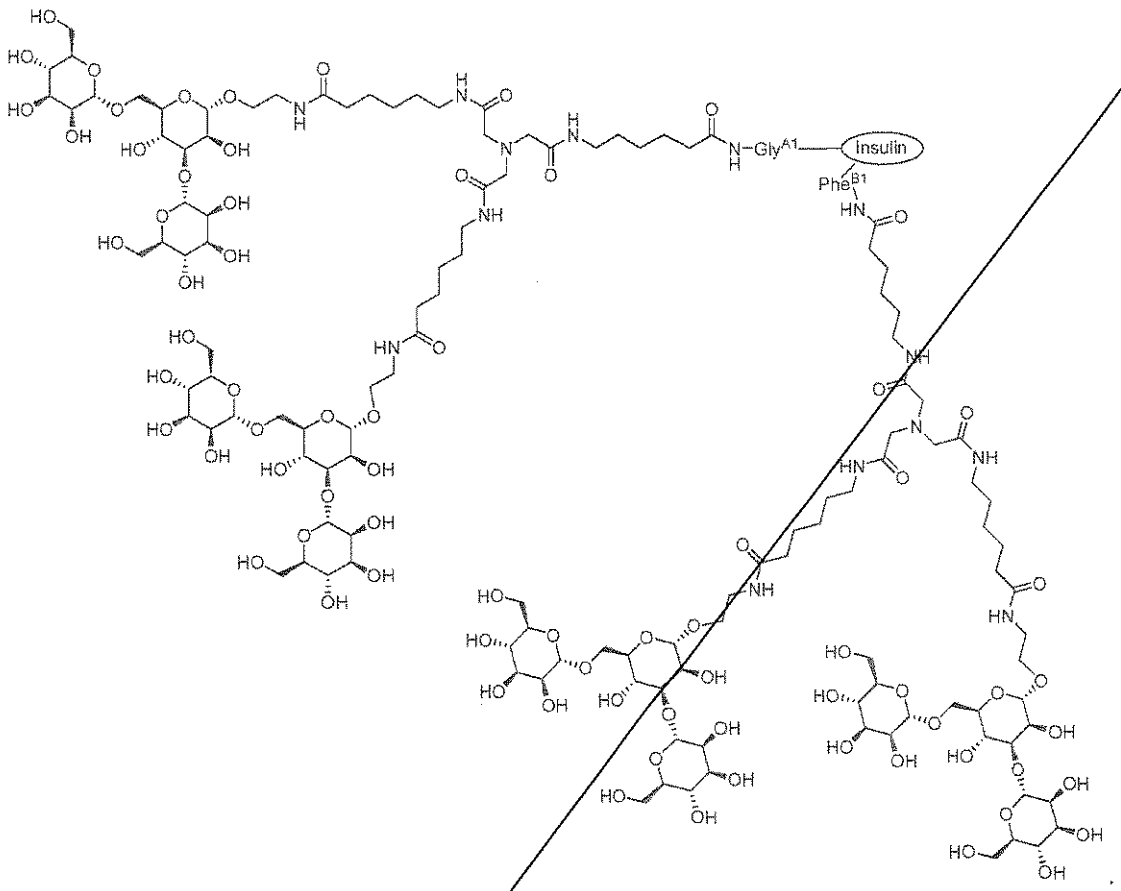
II-3

347. A conjugate of formula:



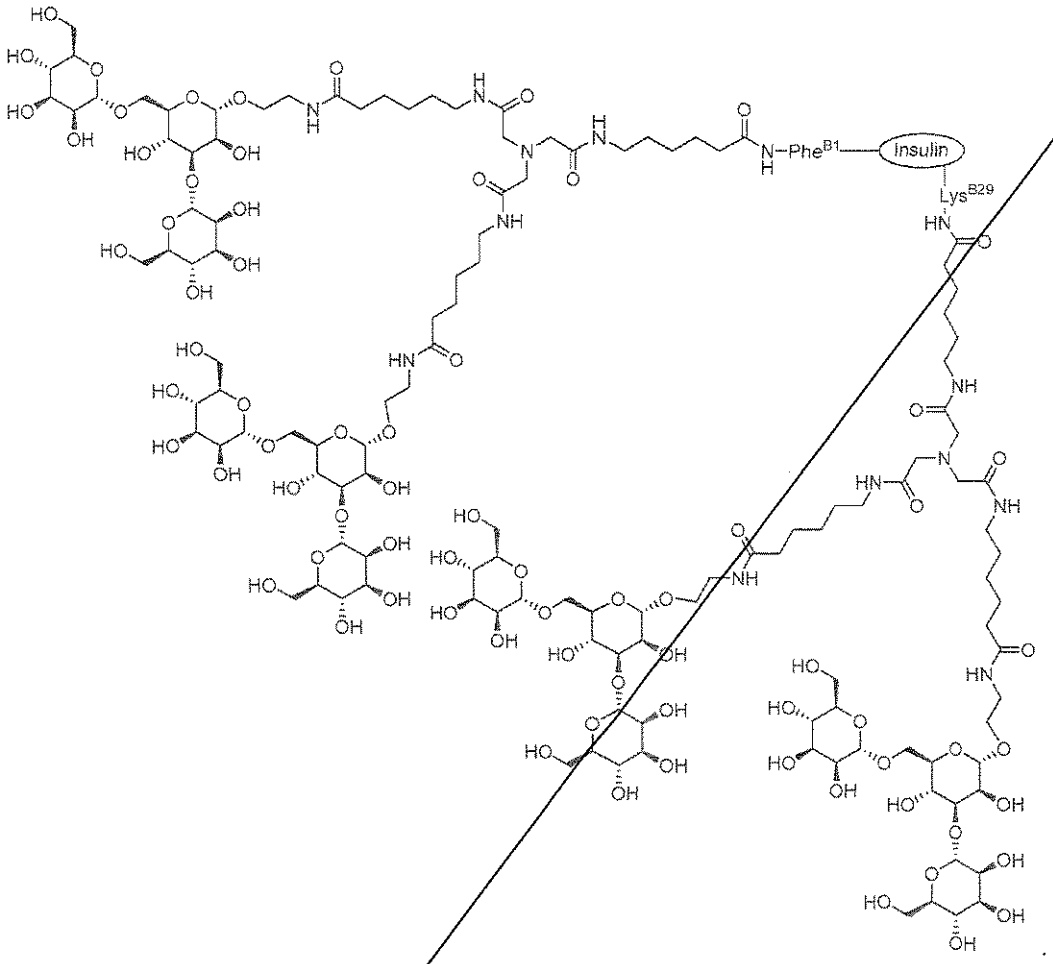
II-4

348. A conjugate of formula:



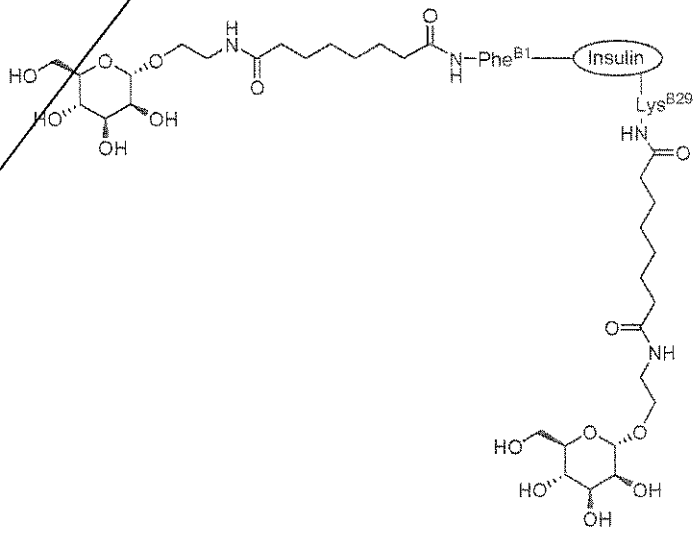
II-5

349. A conjugate of formula:



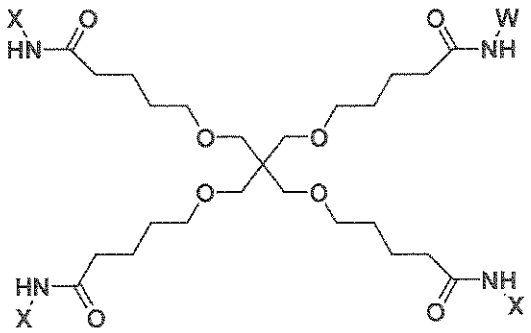
II-6

350. A conjugate of formula:



II-7

351. A conjugate of formula (VIc-2):

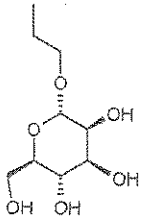


VIc-2

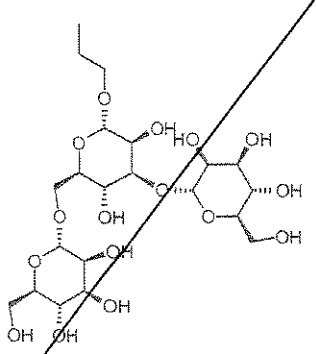
wherein:

W is an insulin molecule; and

each occurrence of -X is



or

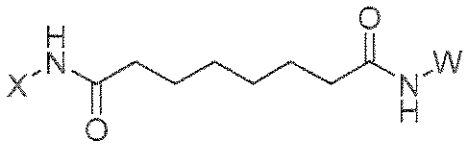


352. The conjugate of claim 351, wherein the insulin molecule is selected from the group consisting of human insulin, porcine insulin, and bovine insulin.

353. The conjugate of claim 351, wherein the insulin molecule is insulin glargine or insulin detemir.

354. The conjugate of claim 351, wherein the insulin molecule includes three disulfide bridges.

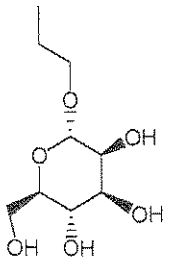
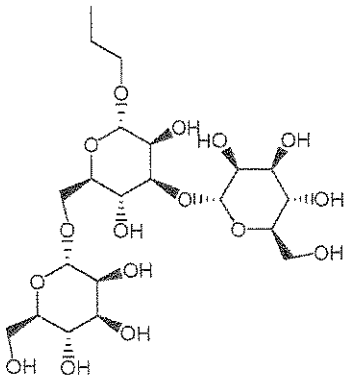
355. A conjugate of formula (VId-1):



VId-1

wherein:

W is an insulin molecule; and

-X is  or .

356. The conjugate of claim 355, wherein the insulin molecule is selected from the group consisting of human insulin, porcine insulin, and bovine insulin.

357. The conjugate of claim 355, wherein the insulin molecule is insulin glargine or insulin detemir.

358. The conjugate of claim 355, wherein the insulin molecule includes three disulfide bridges.

359. A sustained release formulation comprising the conjugate of any one of claims 327-350, wherein the formulation comprises protamine and zinc.

360. The formulation of claim 359, wherein the formulation includes:
from about 1 to about 5 mg protamine/mg conjugate; and
from about 0.1 to about 0.25 mg zinc/mg conjugate.

361. The formulation of claim 359, wherein the formulation includes protamine and zinc in a ratio (w/w) in the range of about 40:1 to about 10:1.

362. The formulation of any one of claims 359-361, wherein the formulation further comprises an amount of unconjugated insulin molecule.

363. The formulation of claim 362, wherein the formulation comprises a molar ratio of conjugated insulin molecule to unconjugated insulin molecule in the range of about 25:1 to about 2:1.

364. The formulation of any one of claims 359-363, wherein the formulation further comprises an antimicrobial preservative.

365. The formulation of claim 364, wherein the antimicrobial preservative is m-cresol.

366. The formulation of claim 365, wherein the formulation comprises from about 0.15 to about 0.35% v/v m-cresol.

367. The formulation of any one of claims 359-366, wherein the formulation further comprises an isotonic agent.

368. The formulation of claim 367, wherein the isotonic agent is glycerol.

369. The formulation of claim 367, wherein the isotonic agent is NaCl.

370. The formulation of claim 369, wherein the formulation comprises from about 0.1 to about 0.2 M NaCl.

371. The formulation of claim 359, wherein the formulation further comprises an amount of unconjugated insulin molecule.

372. The formulation of claim 371, wherein the formulation comprises a molar ratio of conjugated insulin molecule to unconjugated insulin molecule in the range of about 25:1 to about 2:1.

373. The formulation of claim 372, wherein the formulation further comprises an antimicrobial preservative.

374. The formulation of claim 373, wherein the antimicrobial preservative is m-cresol.

375. The formulation of claim 374, wherein the formulation comprises from about 0.15 to about 0.35% v/v m-cresol.

376. The formulation of claim 375, wherein the formulation further comprises an isotonic agent.

377. The formulation of claim 376, wherein the isotonic agent is glycerol.

378. The formulation of claim 376, wherein the isotonic agent is NaCl.

379. The formulation of claim 378, wherein the formulation comprises from about 0.1 to about 0.2 M NaCl.

380. A sustained release formulation comprising the conjugate of any one of claims 327-350, wherein the formulation comprises:

about 3.6 mg protamine/mg conjugate; and

about 0.2 mg zinc/mg conjugate.

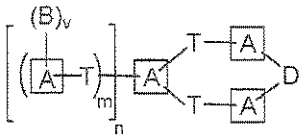
381. The formulation of claim 380, wherein the formulation further comprises an amount of unconjugated insulin molecule, and the molar ratio of conjugated insulin molecule to unconjugated insulin molecule is about 5:1.

382. The formulation of claim 381, wherein the formulation further comprises about 0.2% v/v m-cresol.

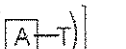
383. The formulation of claim 382, wherein the formulation further comprises glycerol.

384. The formulation of claim 382, wherein the formulation further comprises about 0.15 M NaCl.

385. A conjugate of formula (VIII):



VIII

each occurrence of  represents a potential branch within the conjugate;

each occurrence of  represents a potential repeat within a branch of the conjugate;

each occurrence of [A] is independently a covalent bond, a carbon atom, a heteroatom, or an optionally substituted group selected from the group consisting of acyl, aliphatic, heteroaliphatic, aryl, heteroaryl, and heterocyclic;

each occurrence of T is independently a covalent bond or a bivalent, straight or branched, saturated or unsaturated, optionally substituted C_{1-30} hydrocarbon chain wherein one or more methylene units of T are optionally and independently replaced by -O-, -S-, -N(R)-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)C(O)-, -C(O)N(R)-, -S(O)-, $-S(O)_2-$, $-N(R)SO_2-$, $-SO_2N(R)-$, a heterocyclic group, an aryl group, or a heteroaryl group;

each occurrence of R is independently hydrogen, a suitable protecting group, or an acyl moiety, arylalkyl moiety, aliphatic moiety, aryl moiety, heteroaryl moiety, or heteroaliphatic moiety;

–B is $–T–L^B–X$;

each occurrence of X is independently a ligand that includes a saccharide;

each occurrence of L^B is independently a covalent bond or a group derived from the covalent conjugation of a T with an X;

–D is $–T–L^D–W$;

each occurrence of W is independently a drug;

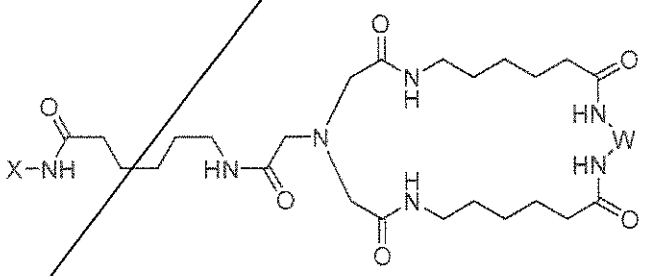
each occurrence of L^D is independently a covalent bond or a group derived from the covalent conjugation of a T with a W;

each occurrence of n is independently an integer from 0 to 5, inclusive;

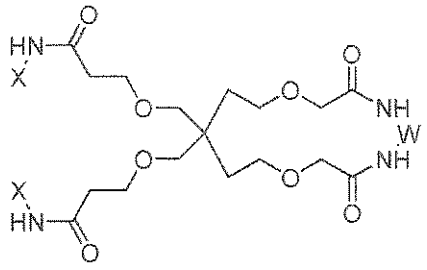
each occurrence of m is independently an integer from 1 to 5, inclusive; and

each occurrence of v is independently an integer from 0 to 5, inclusive, with the proviso that at least one occurrence of n is ≥ 1 and at least one occurrence of v is ≥ 1.

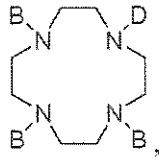
386. The conjugate of claim 385, wherein the conjugate is of formula:



or



387. A conjugate of formula (IX):



IX

wherein:

–B is –T–L^B–X;

each occurrence of T is independently a covalent bond or a bivalent, straight or branched, saturated or unsaturated, optionally substituted C_{1-30} hydrocarbon chain wherein one or more methylene units of T are optionally and independently replaced by -O-, -S-, -N(R)-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)C(O)-, -C(O)N(R)-, -S(O)-, $-S(O)_2-$, $-N(R)SO_2-$, $-SO_2N(R)-$, a heterocyclic group, an aryl group, or a heteroaryl group;

each occurrence of R is independently hydrogen, a suitable protecting group, or an acyl moiety, arylalkyl moiety, aliphatic moiety, aryl moiety, heteroaryl moiety, or heteroaliphatic moiety;

each occurrence of X is independently a ligand that includes a saccharide;

each occurrence of L^B is independently a covalent bond or a group derived from the covalent conjugation of a T with an X;

–D is –T–L^D–W;

each occurrence of W is independently a drug; and

each occurrence of L^D is independently a covalent bond or a group derived from the covalent conjugation of a T with a W.

388. A conjugate comprising an insulin molecule conjugated to one or more ligands that are independently selected from the group consisting of aminoethylglucose (AEG), aminoethylmannose (AEM), aminoethylbimannose (AEBM), aminoethyltrimannose (AETM), β-aminoethyl-N-acetylglucosamine (AEGA), and aminoethylfucose (AEF).

389. The conjugate of claim 388, wherein the insulin molecule is conjugated via the A1 amino acid residue.

390. The conjugate of claim 388, wherein the insulin molecule is conjugated via the B1 amino acid residue.

391. The conjugate of claim 388, wherein the insulin molecule is conjugated via the epsilon-amino group of Lys^{B29}.

392. The conjugate of claim 388, wherein the insulin molecule is insulin glulisine conjugated via the epsilon-amino group of Lys^{B3}.

393. The conjugate of any one of claim 389-392, wherein the one or more ligands are aminoethylglucose (AEG).

394. The conjugate of any one of claim 389-392, wherein the one or more ligands are aminoethylmannose (AEM).

395. The conjugate of any one of claim 389-392, wherein the one or more ligands are aminoethylbimannose (AEBM).

396. The conjugate of any one of claim 389-392, wherein the one or more ligands are aminoethyltrimannose (AETM).

397. The conjugate of any one of claim 389-392, wherein the one or more ligands are β-aminoethyl-N-acetylglucosamine (AEGA).

398. The conjugate of any one of claim 389-392, wherein the one or more ligands are aminoethylfucose (AEF).

399. The conjugate of claim 388, wherein the insulin molecule is conjugated to two or more separate ligands.

400. The conjugate of claim 399, wherein the insulin molecule is conjugated to two separate ligands.

401. The conjugate of claim 399, wherein the insulin molecule is conjugated to three separate ligands.

402. The conjugate of claim 399, wherein the insulin molecule is conjugated to four separate ligands.

403. The conjugate of claim 399, wherein the two or more separate ligands are conjugated to a single conjugate framework that is also conjugated to the insulin molecule.

404. The conjugate of claim 399, wherein the two or more separate ligands and insulin molecule are each located on a separate branch of a single branched conjugate framework.

405. The conjugate of claim 404, wherein the two or more separate ligands and insulin molecule are each located on termini of separate branches of a single branched conjugate framework.

406. The conjugate of claim 399, wherein the two or more separate ligands are conjugated to the insulin molecule via two or more different conjugation points.

407. The conjugate of claim 406, wherein the insulin molecule is conjugated via the A1 amino acid residue and the epsilon-amino group of Lys^{B29}.

408. The conjugate of claim 407, wherein the insulin molecule is conjugated to two separate conjugate frameworks that are each conjugated to one or more separate ligands.

409. The conjugate of claim 407, wherein the insulin molecule is conjugated to two separate conjugate frameworks that are each conjugated to one ligand.

410. The conjugate of claim 407, wherein the insulin molecule is conjugated to two separate branched conjugate frameworks that are each conjugated to two ligands.

411. The conjugate of claim 410, wherein the ligands are located on separate branches of the branched conjugate frameworks.

412. The conjugate of claim 411, wherein the ligands are located on termini of separate branches of the branched conjugate frameworks.

413. The conjugate of any one of claims 399-412, wherein the two or more separate ligands are aminoethylglucose (AEG).

414. The conjugate of any one of claims 399-412, wherein the two or more separate ligands are aminoethylmannose (AEM).

415. The conjugate of any one of claims 399-412, wherein the two or more separate ligands are aminoethylbimannose (AEBM).

416. The conjugate of any one of claims 399-412, wherein the two or more separate ligands are aminoethyltrimannose (AETM).

417. The conjugate of any one of claims 399-412, wherein the two or more separate ligands are β-aminoethyl-N-acetylglucosamine (AEGA).

418. The conjugate of any one of claims 399-412, wherein the two or more separate ligands are aminoethylfucose (AEF).

419. A conjugate comprising an insulin molecule conjugated to aminoethylglucose (AEG).

420. A conjugate comprising an insulin molecule conjugated to aminoethylmannose (AEM).

421. A conjugate comprising an insulin molecule conjugated to aminoethylbimannose (AEBM).

422. A conjugate comprising an insulin molecule conjugated to aminoethyltrimannose (AETM).

423. A conjugate comprising an insulin molecule conjugated to β-aminoethyl-N-acetylglucosamine (AEGA).

424. A conjugate comprising an insulin molecule conjugated to aminoethylfucose (AEF).

425. The conjugate of any one of claims 419-424, wherein the insulin molecule is conjugated via the A1 amino acid residue.

426. The conjugate of any one of claims 419-424, wherein the insulin molecule is conjugated via the B1 amino acid residue.

427. The conjugate of any one of claims 419-424, wherein the insulin molecule is conjugated via the epsilon-amino group of Lys^{B29}.

428. The conjugate of any one of claims 419-424, wherein the insulin molecule is insulin glulisine conjugated via the epsilon-amino group of Lys^{B3}.

429. The conjugate of any one of claims 419-424, wherein the insulin molecule is conjugated via the A1 amino acid residue and the epsilon-amino group of Lys^{B29}.

CLAIMS

We claim:

1. A conjugate comprising an insulin molecule conjugated to one or more ligands wherein at least one ligand is aminoethyltrimannose (AETM) or aminoethylfucose (AEF); wherein the conjugate is characterized in that, when the conjugate is administered to a mammal in the absence of an exogenous multivalent saccharide-binding molecule, at least one pharmacokinetic or pharmacodynamic property of the conjugate is sensitive to serum concentration of a saccharide.

2. The conjugate of claim 1, wherein the saccharide is glucose or alpha-methyl mannose.

3. The conjugate of claim 2, wherein the insulin molecule is conjugated via the A1 amino acid residue, via the B1 amino acid residue, or via the epsilon-amino group of Lys^{B29}.

4. The conjugate of claim 2, wherein the insulin molecule is truncated.

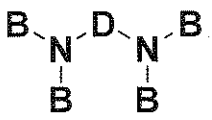
5. The conjugate of claim 1, wherein the conjugate includes two or more separate ligands each of which includes a saccharide.

6. The conjugate of claim 1, wherein the ligand further includes a saccharide selected from the group consisting of glucose, mannose and L-fucose.

7. The conjugate of claim 6, wherein the conjugate is of the formula:



VIb or



VIIb-*i*

Wherein B is –T–L^B–X;

each occurrence of X is independently a ligand wherein atleast one ligand is aminoethyltrimannose (AETM) or aminoethylfucose (AEF);

each occurrence of L^B is independently a covalent bond or a group derived from the covalent conjugation of a T with an X;

D is –T–L^D–W;

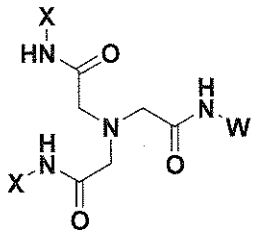
each occurrence of W is independently an insulin molecule;

each occurrence of L^D is independently a covalent bond or a group derived from the covalent conjugation of a T with a W;

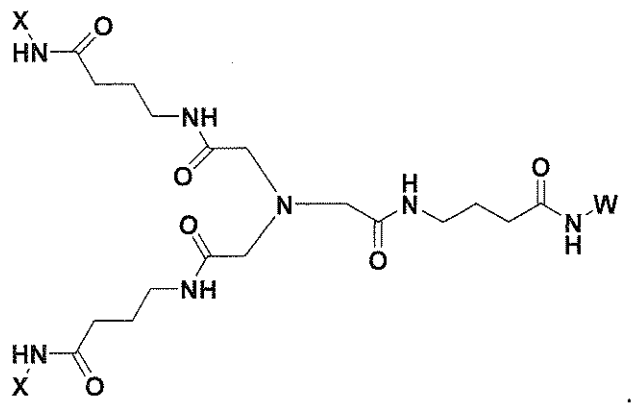
each occurrence of T is independently a covalent bond or a bivalent, straight or branched, saturated or unsaturated, optionally substituted C_{1-30} hydrocarbon chain wherein one or more methylene units of T are optionally and independently replaced by -O-, -S-, -N(R)-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)C(O)-, -C(O)N(R)-, -S(O)-, -$S(O)_2$-, -N(R)SO_2- , -SO_2N(R)-, a heterocyclic group, an aryl group, or a heteroaryl group; and

each occurrence of R is independently hydrogen, a suitable protecting group, or an acyl moiety, arylalkyl moiety, aliphatic moiety, aryl moiety, heteroaryl moiety, or heteroaliphatic moiety.

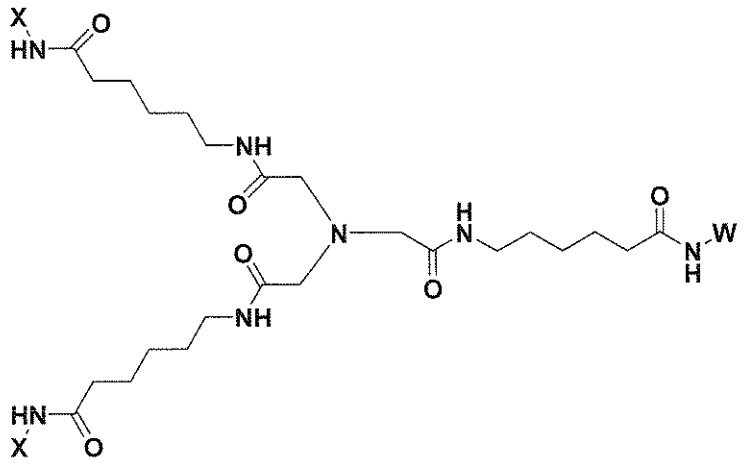
8. The conjugate of claim 7, wherein the conjugate is of the formula (VIb-1):



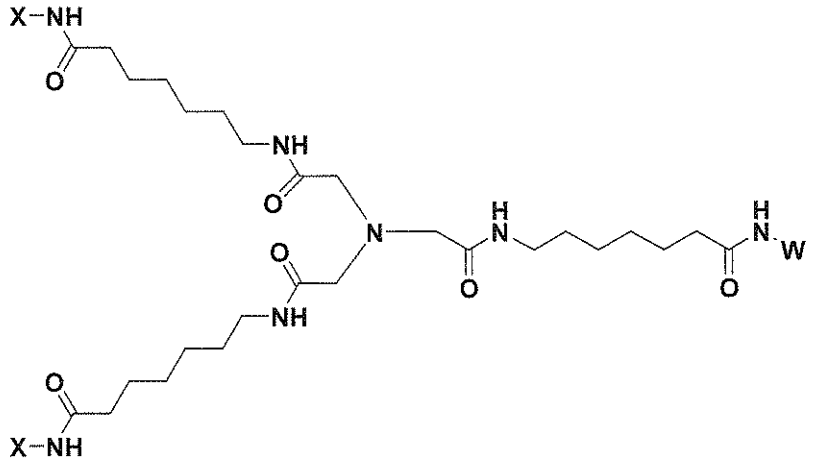
VIb-1 ,



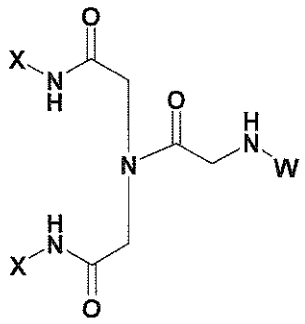
VIb-2,



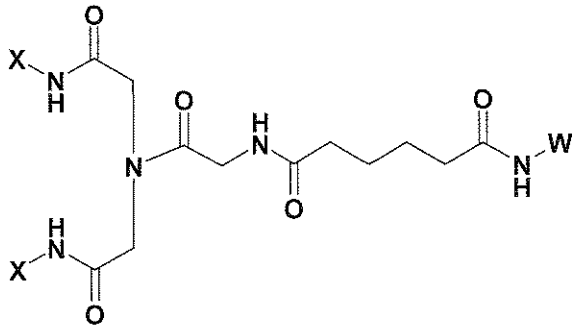
VIb-3



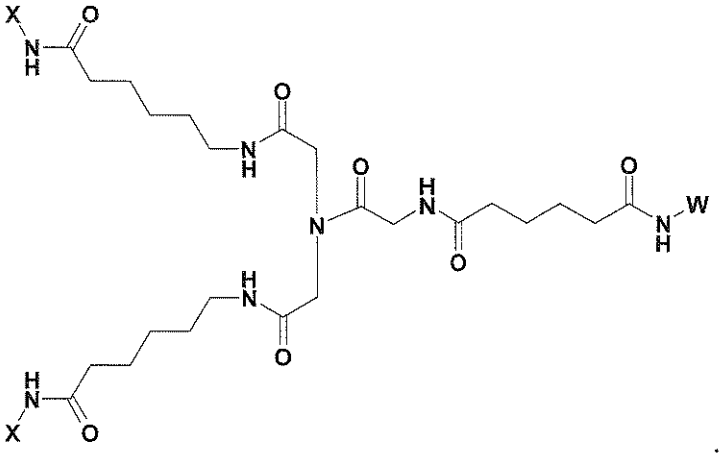
VIb-4,



VIb-5,



VIb-6, or



VIb-7.

9. A sustained release formulation comprising a conjugate of any one of the preceding claims.

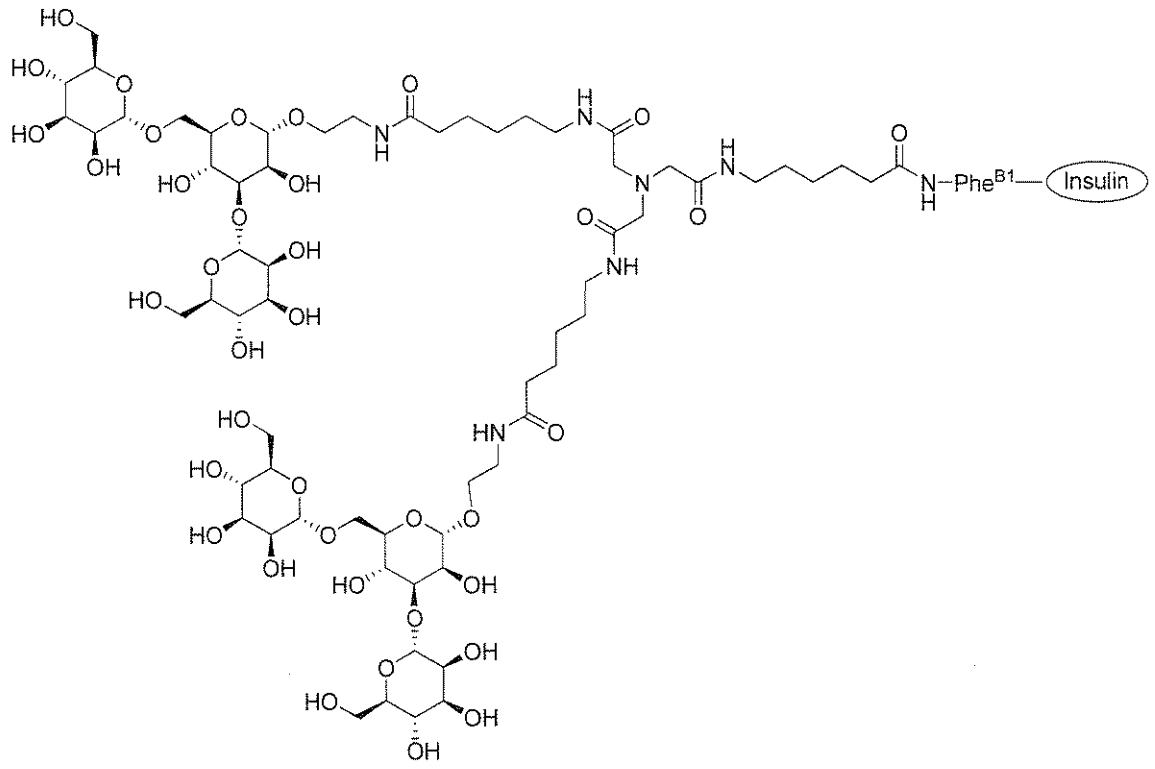
10. The formulation of claim 9, wherein the drug is an insulin molecule and the formulation comprises protamine and zinc.

11. A pump delivery system comprising a conjugate of any one of claims 1-8, wherein the pump delivery system operates by infusing the conjugate into a mammal.

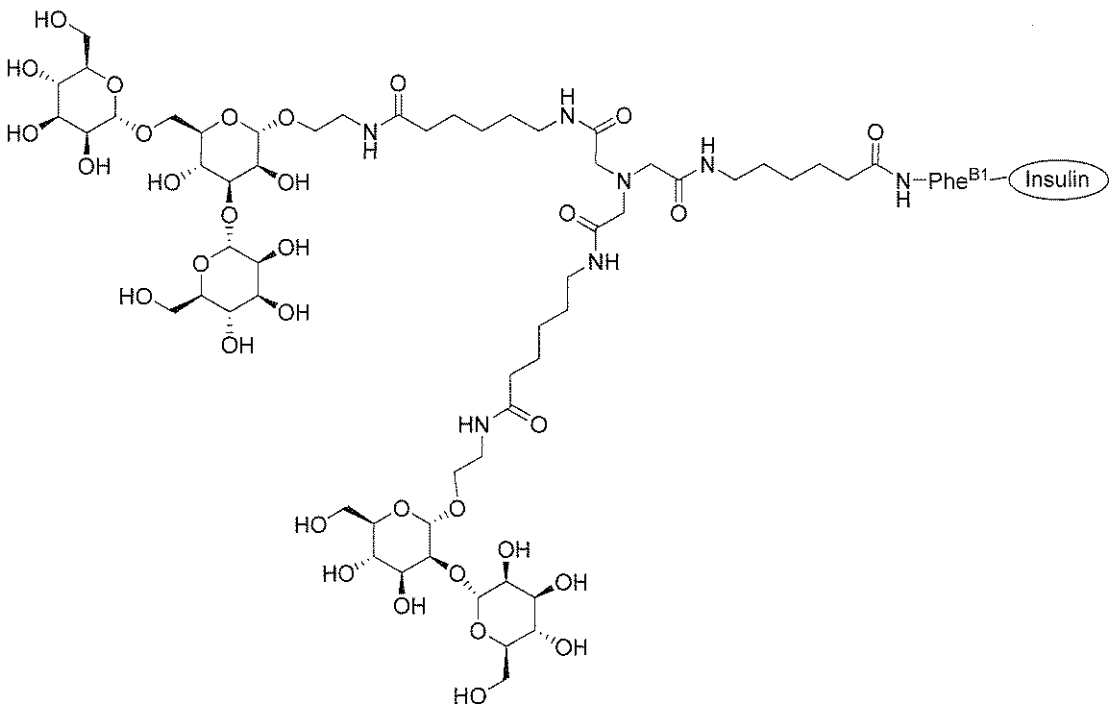
12. A formulation of any one of claims 9-10 for the treatment of hyperglycemia.

13. A conjugate of any one of claims 1-8 for the treatment of diabetes.

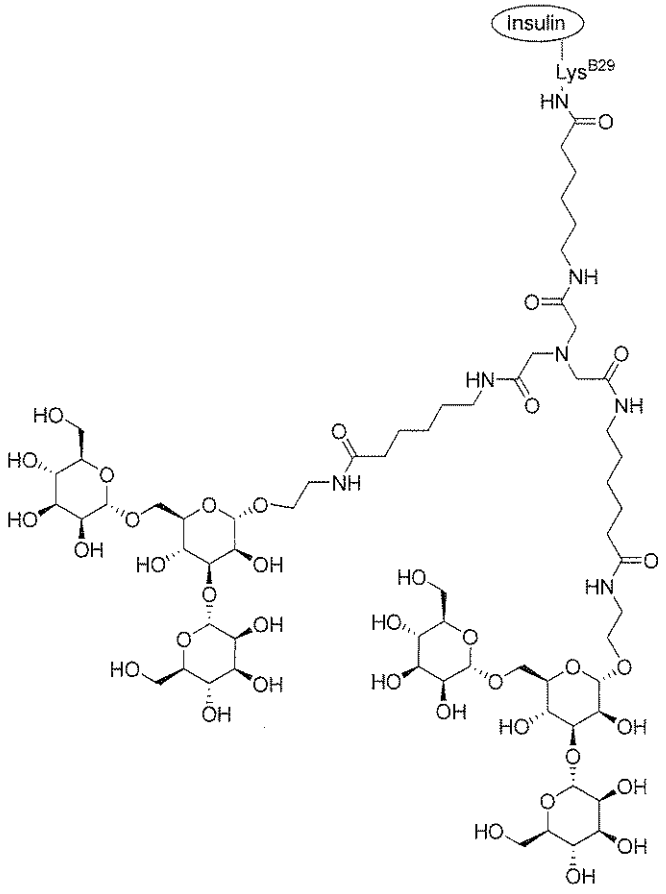
14. A conjugate comprising a formula selected form the group consisting of:



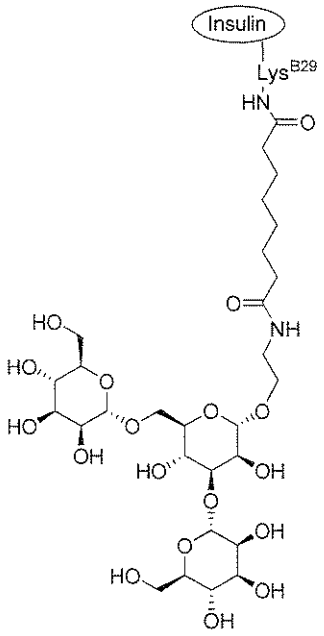
I-2,



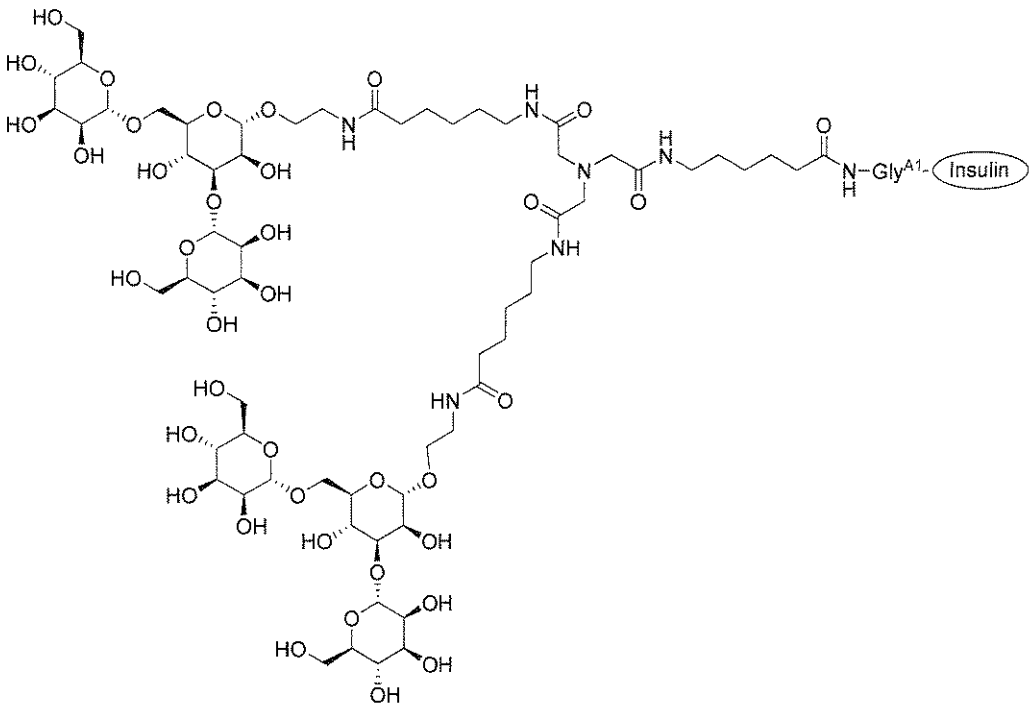
I-4,



I-6,

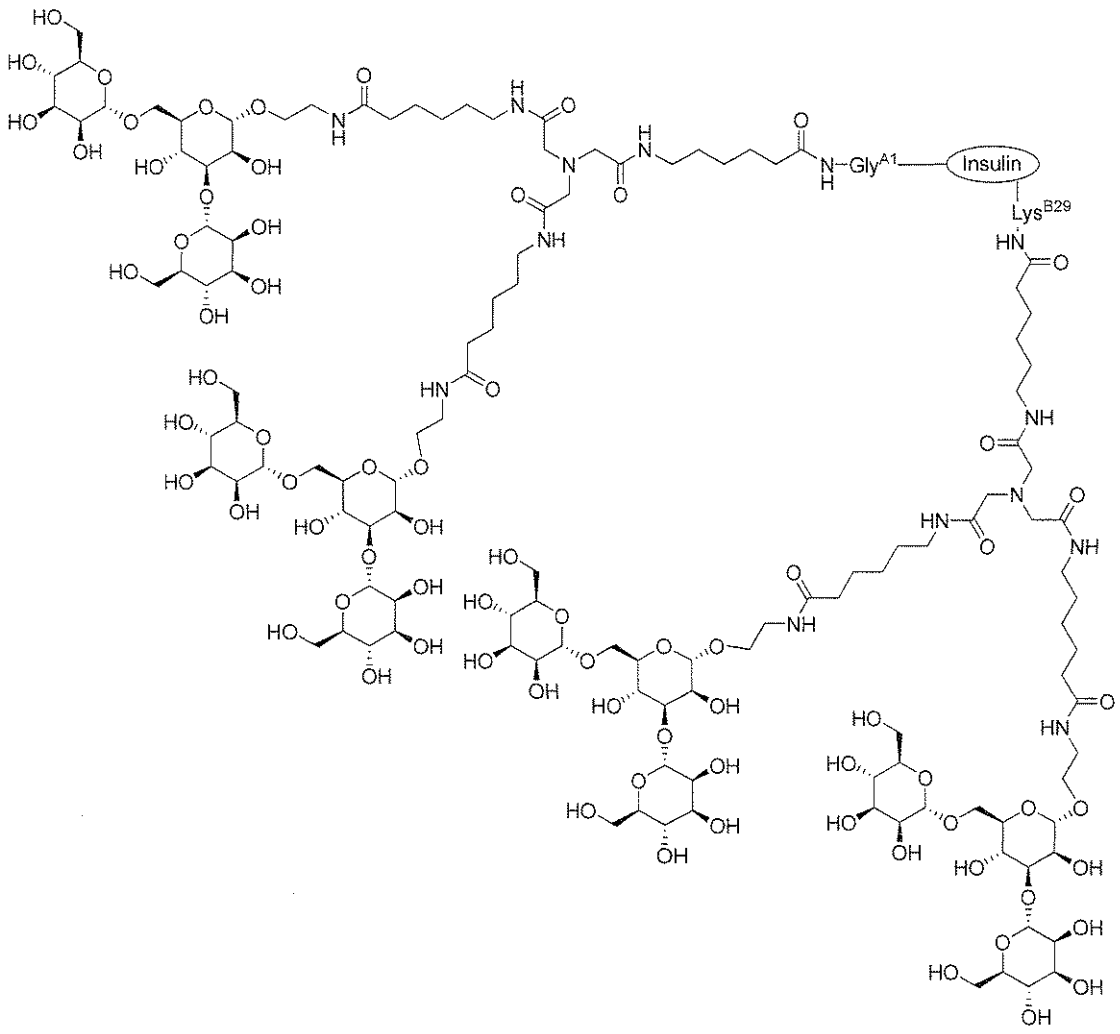


I-10,

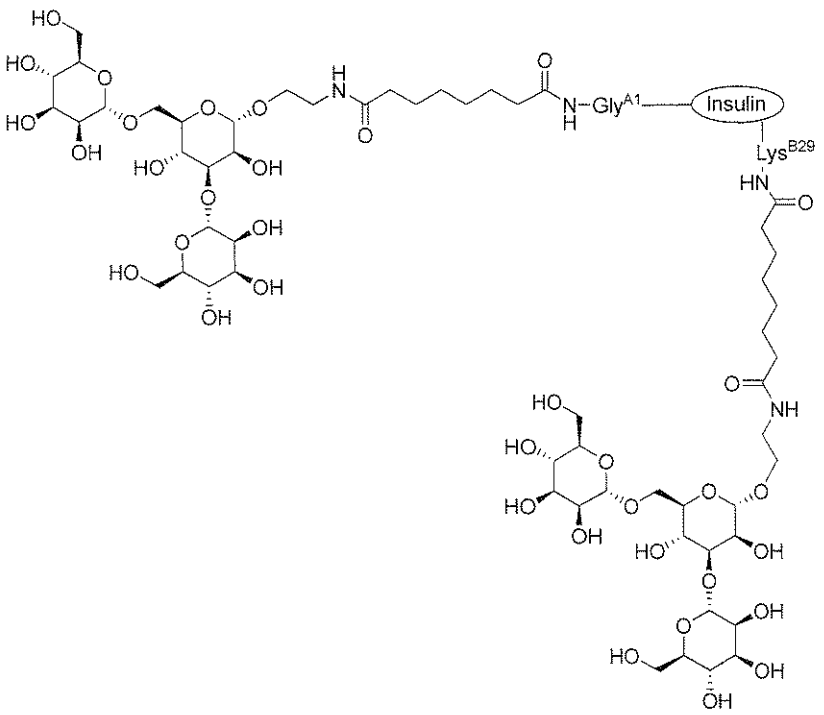

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I-12,

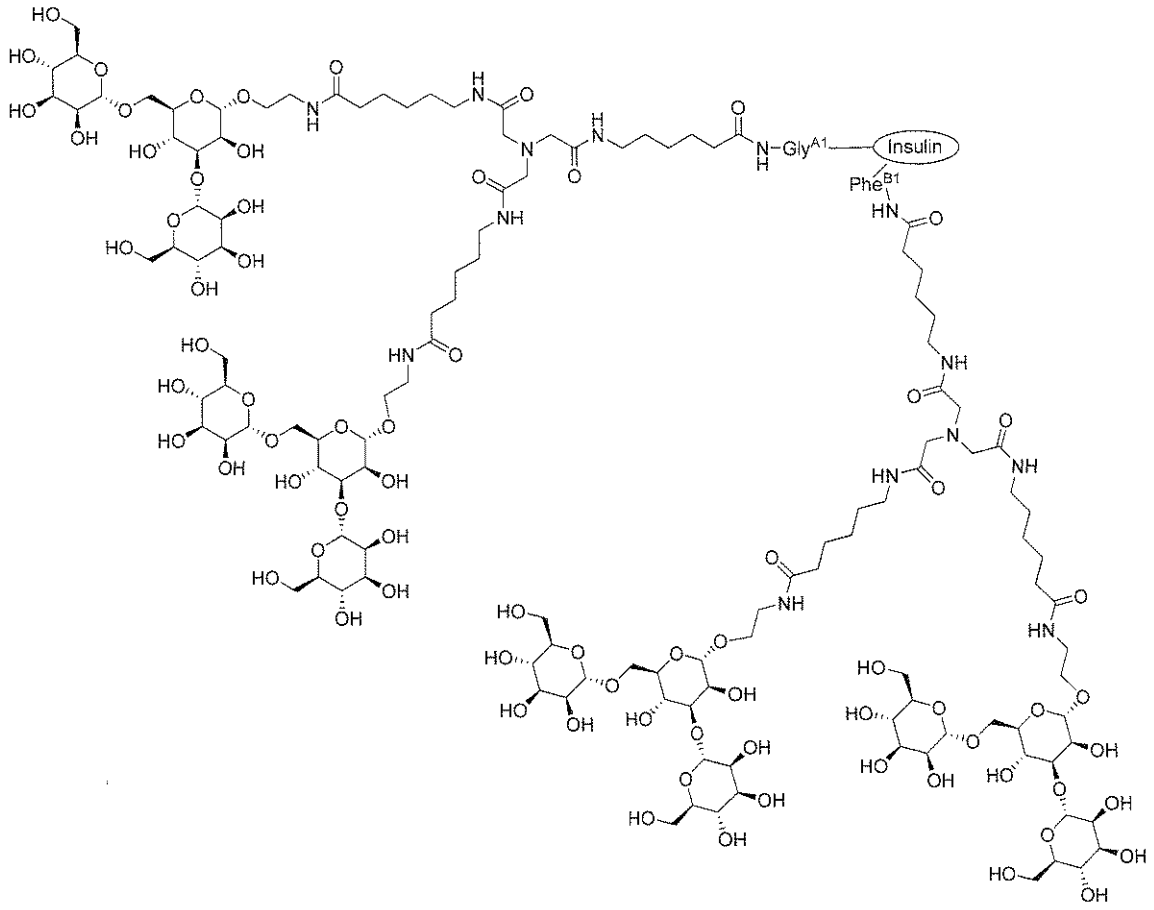
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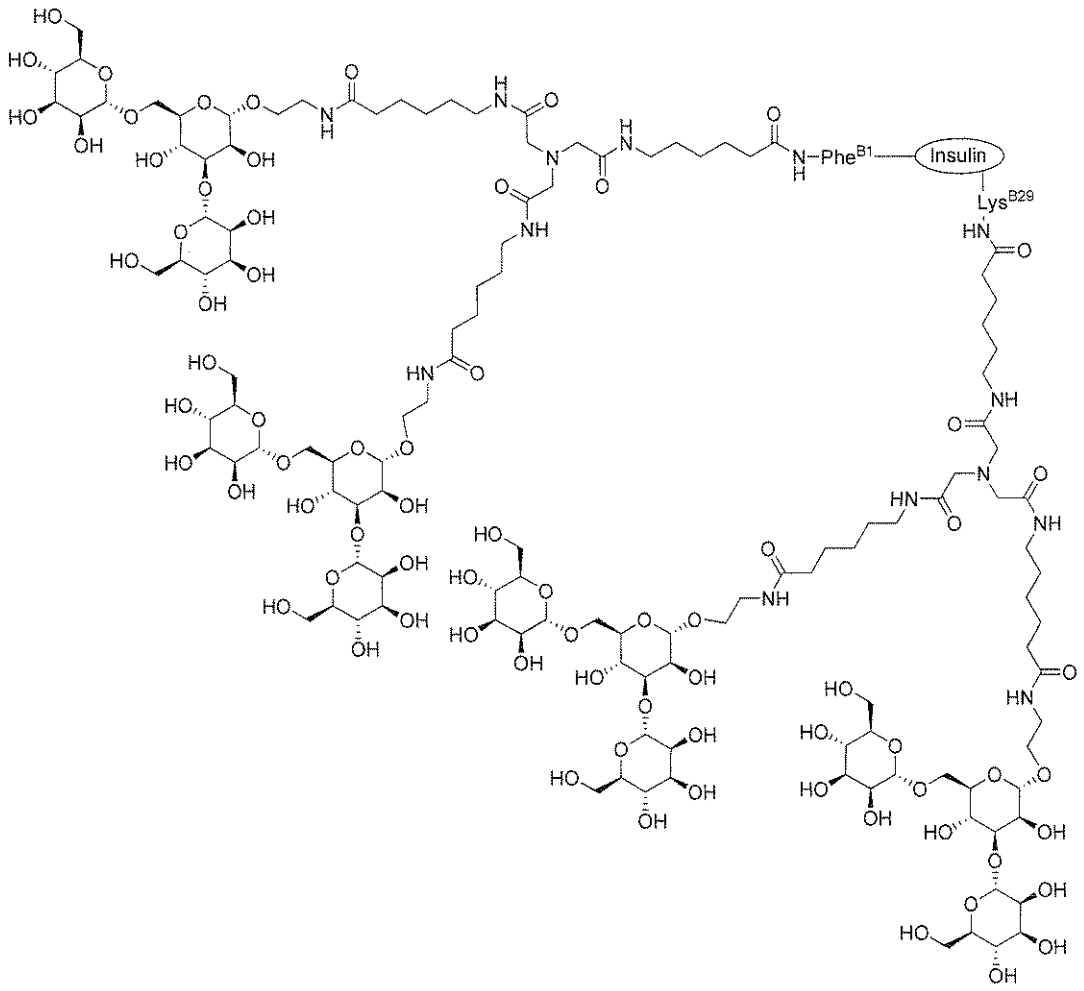
II-2,


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II-3,



II-5,



II-6.

15. A conjugate comprising an insulin molecule conjugated to one or more ligands that are independently selected from the group consisting of aminoethylglucose (AEG), aminoethylmannose (AEM), aminoethylbimannose (AEBM), aminoethyltrimannose (AETM), β-aminoethyl-N-acetylglucosamine (AEGA), and aminoethylfucose (AEF) wherein at least one ligand is aminoethytrimannose (AETM) or aminoethylfucose (AEF).

16. The conjugate of claim 15, wherein the insulin molecule is conjugated via the A1 amino acid residue, via the B1 amino acid residue, or via the epsilon-amino group of Lys^{B29}.

17. The conjugate of claim 15, wherein the insulin molecule is conjugated to two or more separate ligands.