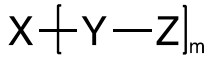
WHAT IS CLAIMED IS

1. A compound of Formula 1:



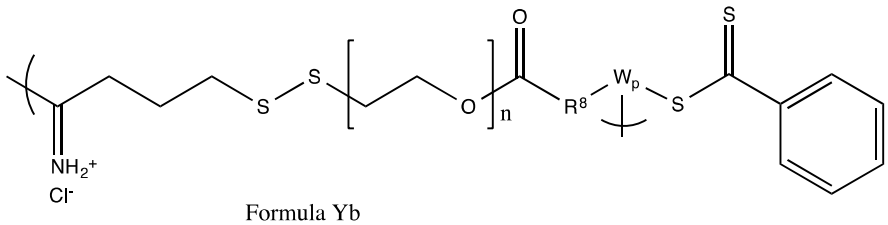
Formula 1

wherein:

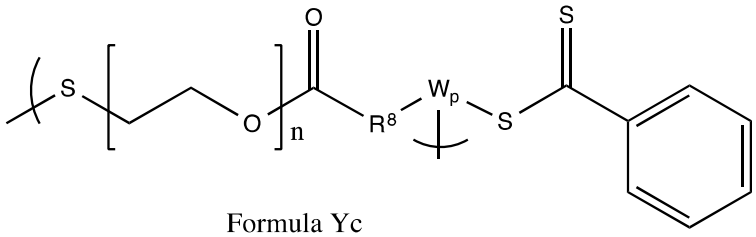
m is an integer from 1 to 10;

X comprises an antigen against which a patient develops an unwanted immune response;

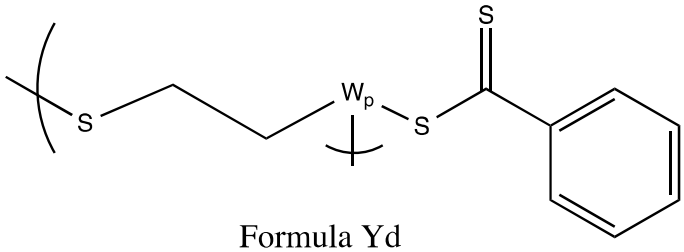
Y is of a linker moiety comprising one or more of a disulfanyl ethyl ester, a sulfur of a dithiol bond, and/or having a formula selected from the group consisting of:



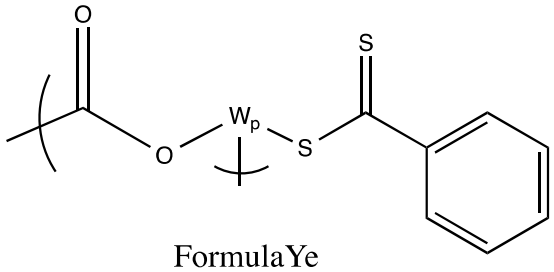
Formula Yb



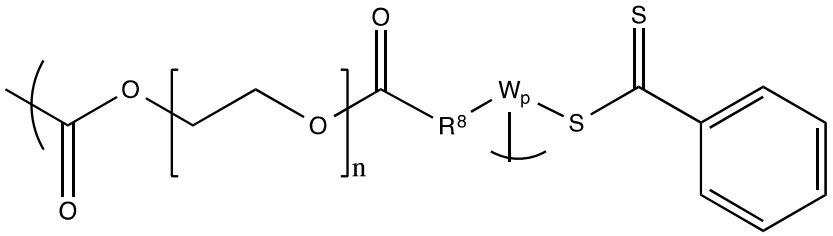
Formula Yc



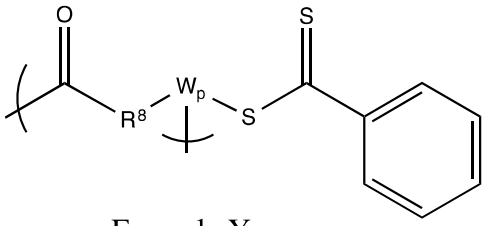
Formula Yd



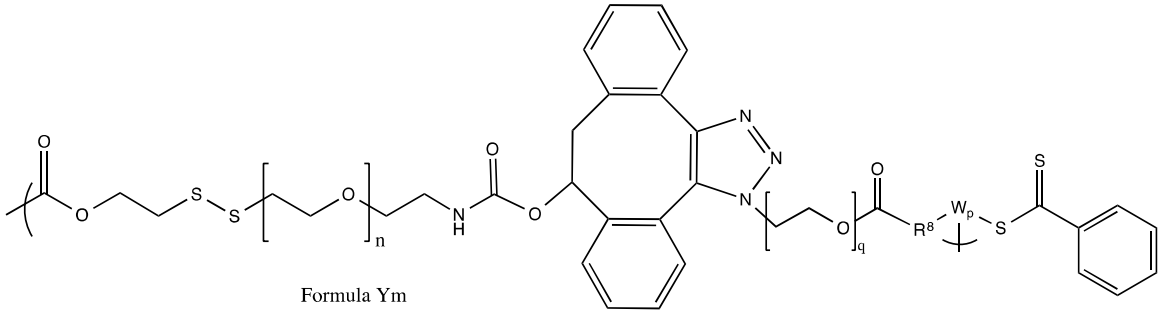
FormulaYe



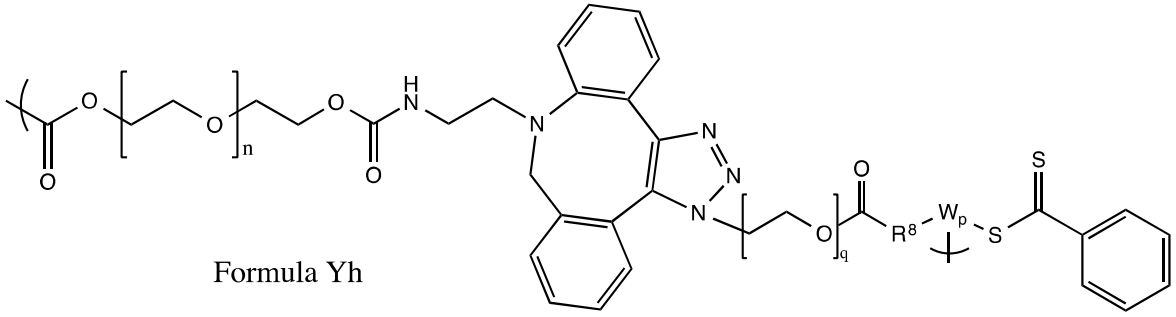
Formula Yf



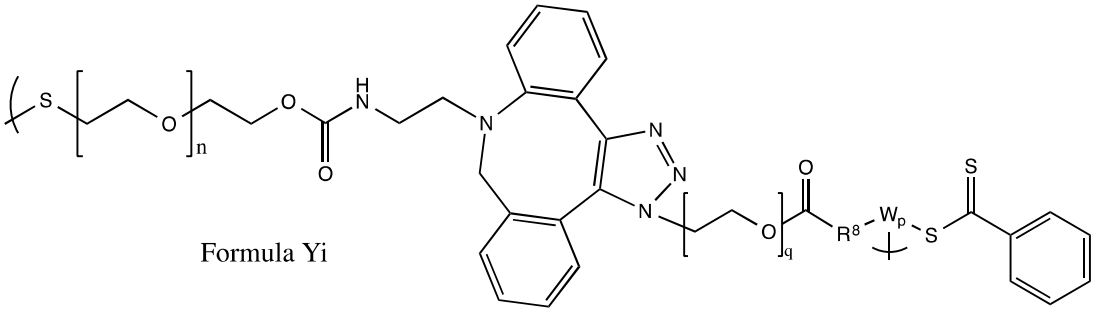
Formula Yg



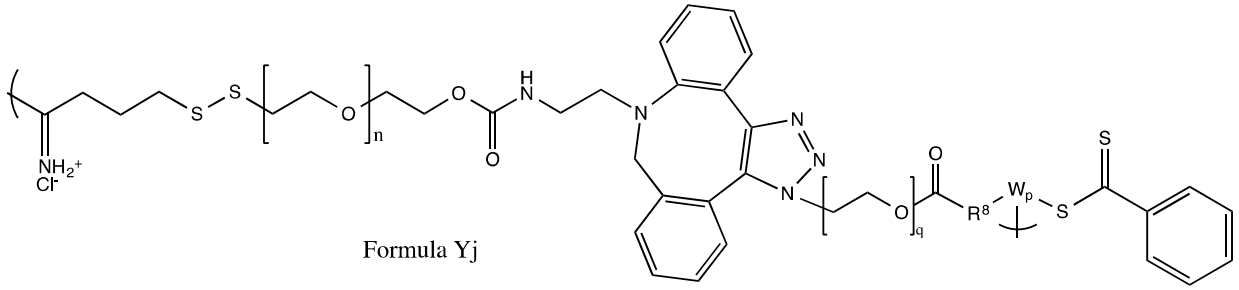
Formula Ym



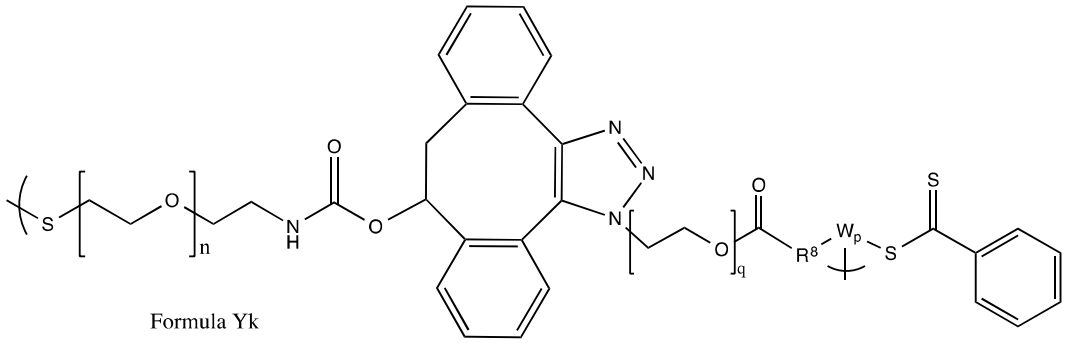
Formula Yh



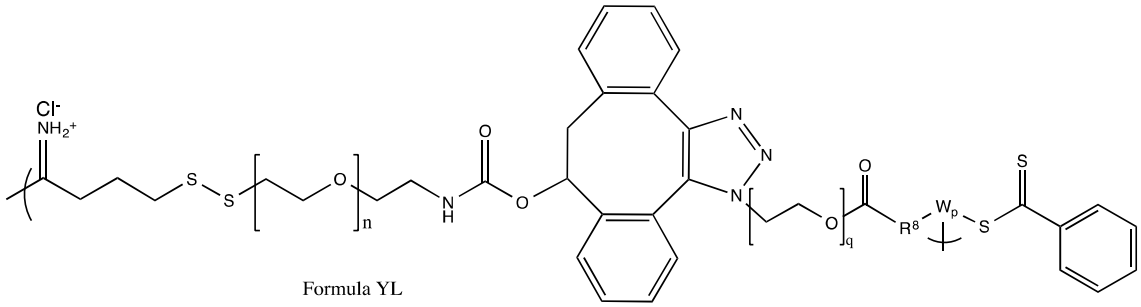
Formula Yi



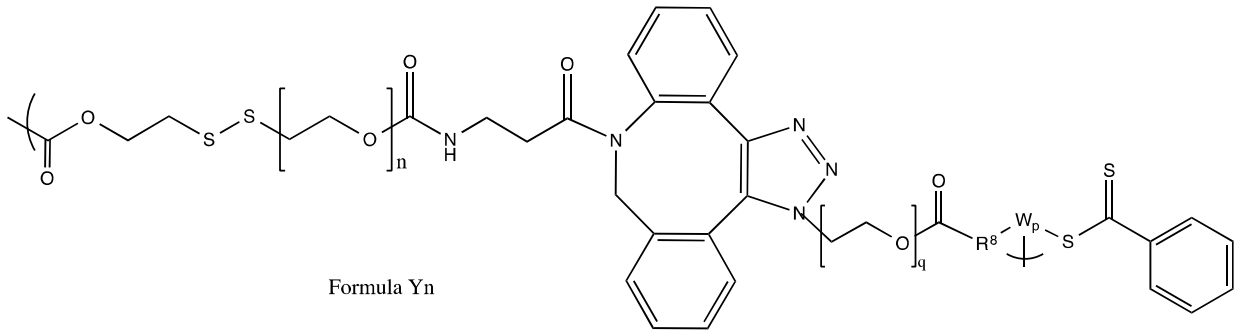
Formula Yj



Formula Yk

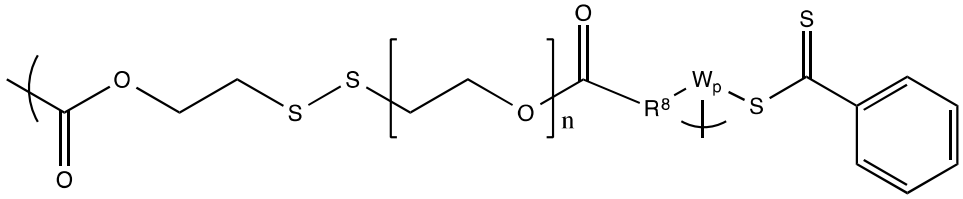


Formula YL



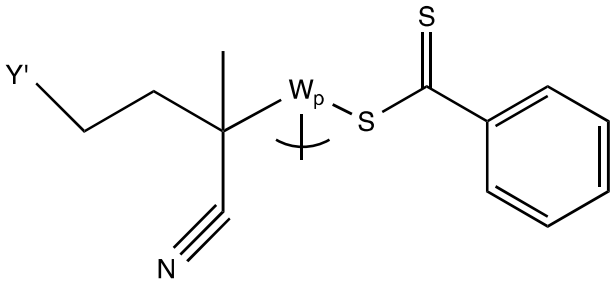
Formula Yn

and



Formula Yp

or Y has a portion represented by Formula Y'-CMP:



Formula Y'-CMP

where:

the left bracket "(" indicates the bond between X and Y;

the right or bottom bracket and ")" indicates the bond between Y and Z;

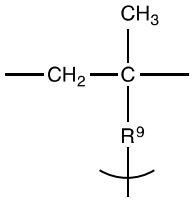
n is an integer from 1 to 100;

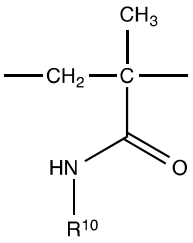
q is an integer from 1 to 44;

R^8 is $–CH_2–$ or $–CH_2-CH_2-C(CH_3)(CN)–$;

Y' represents the remaining portion of Y; and

W is a copolymer or a random copolymer of the same or different W^1 and W^2 groups, where:

W^1 = 

and W^2 = 

where:

p is an integer from 2 to 50;

R^9 is a direct bond, $–CH_2-CH_2-$–NH–C(O)–, or $-CH_2-CH_2-(O-CH_2-CH_2)_t-NH-C(O)-$;

t is an integer from 1 to 5; and

R^{10} is an aliphatic group, an alcohol or an aliphatic alcohol; and

Z comprises a liver targeting moiety selected from glucose, glucosamine, and N-acetylglucosamine.

2. The compound of Claim 1, wherein:

n is 40 to 80;

q is 3 to 20;

R^8 is $–CH_2-CH_2-C(CH_3)(CN)–$;

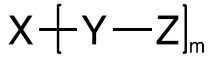
when R^9 is $–CH_2-CH_2-$–NH–C(O)–; and

when W is a copolymer, R^{10} is 2-hydroxypropyl.

3. The compound of Claim 1 or 2, wherein Y comprises Formula Yc.

4. The composition of any one of Claims 1 to 3, wherein Y comprises Formula Ya, Formula Yb, Formula Ym or Formula Yn.

5. A compound of Formula 1:



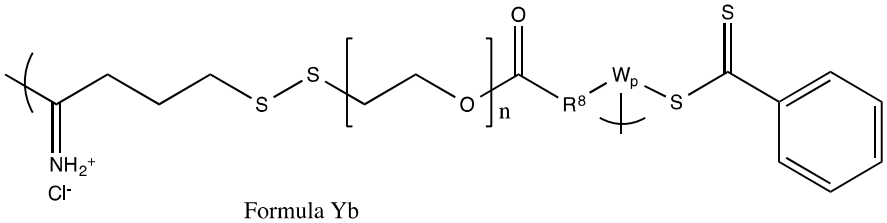
Formula 1

wherein:

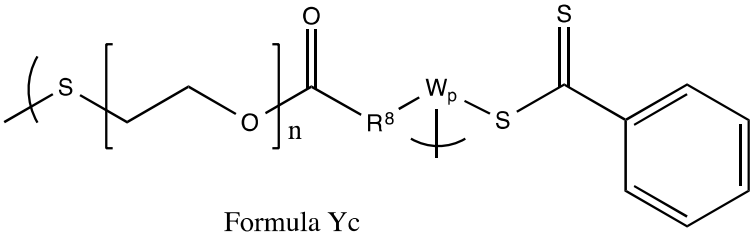
m is an integer from 1 to 10;

X comprises an antigen against which a patient develops an unwanted immune response;

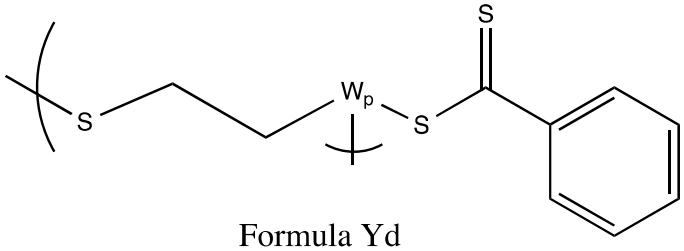
Y is of a linker moiety comprising one or more of a disulfanyl ethyl ester, a sulfur of a dithiol bond, and/or having a formula selected from the group consisting of:



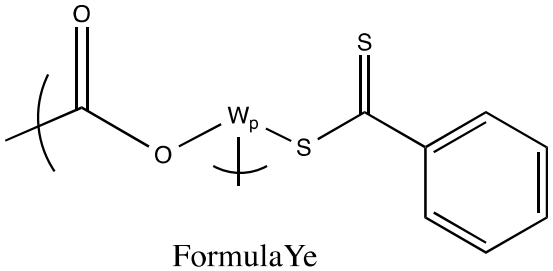
Formula Yb



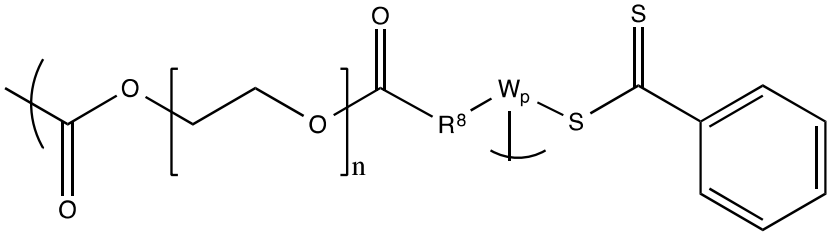
Formula Yc



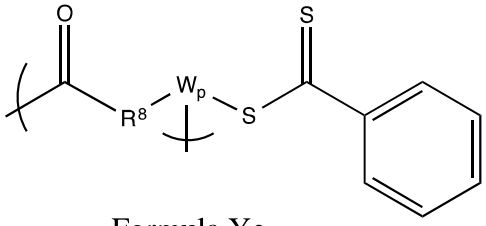
Formula Yd



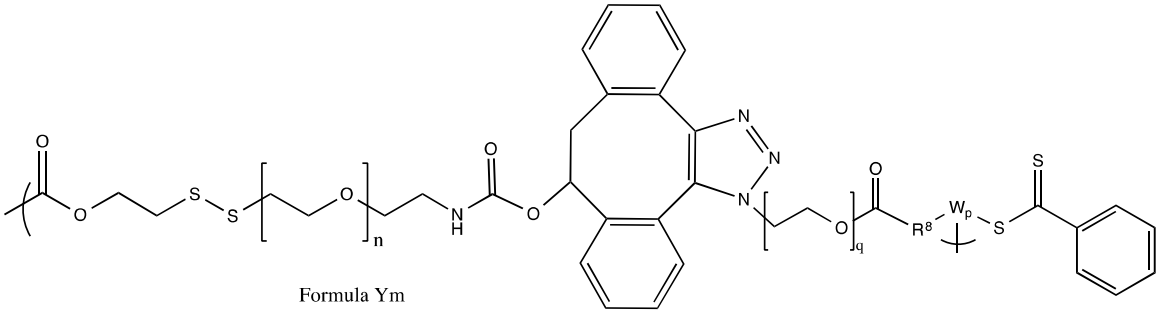
FormulaYe



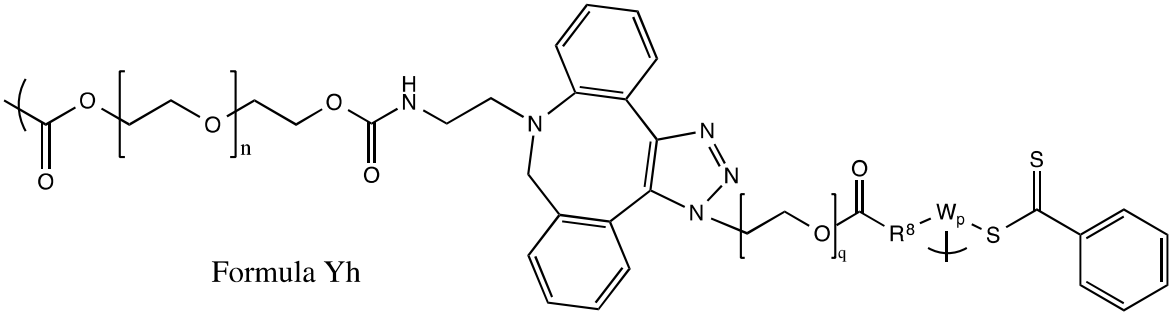
Formula Yf



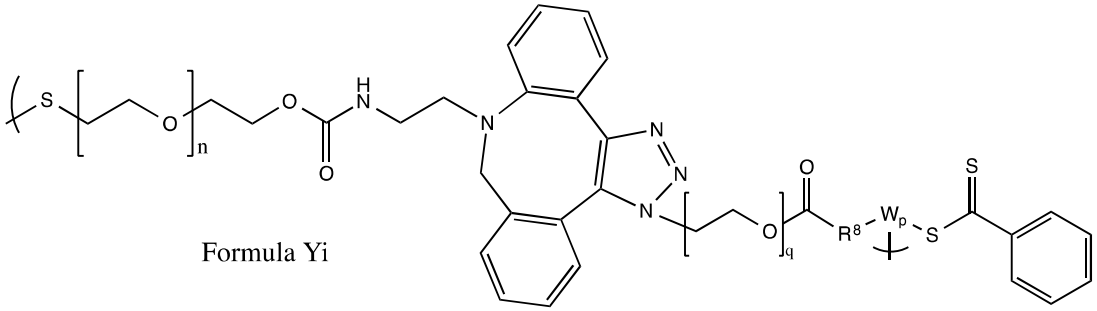
Formula Yg



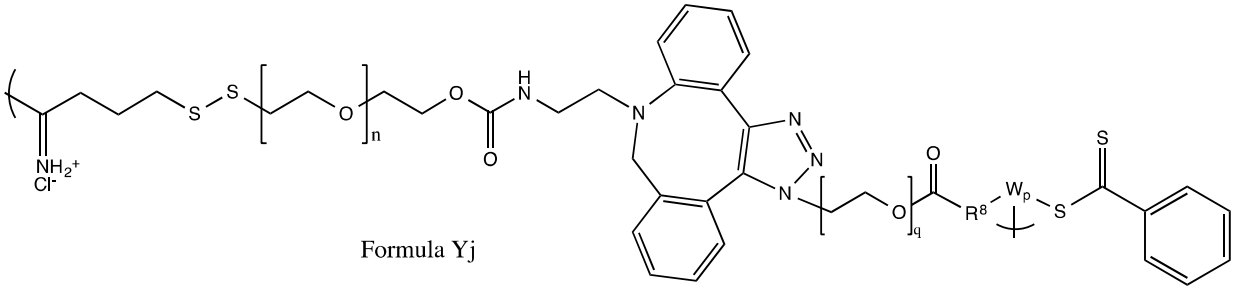
Formula Ym



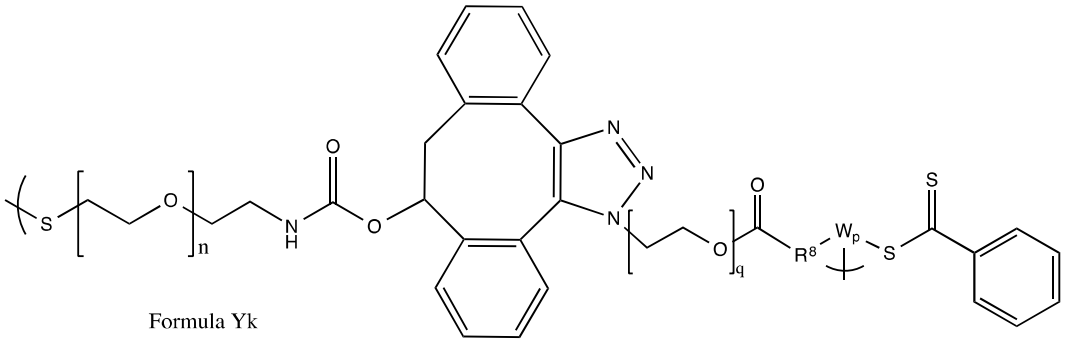
Formula Yh



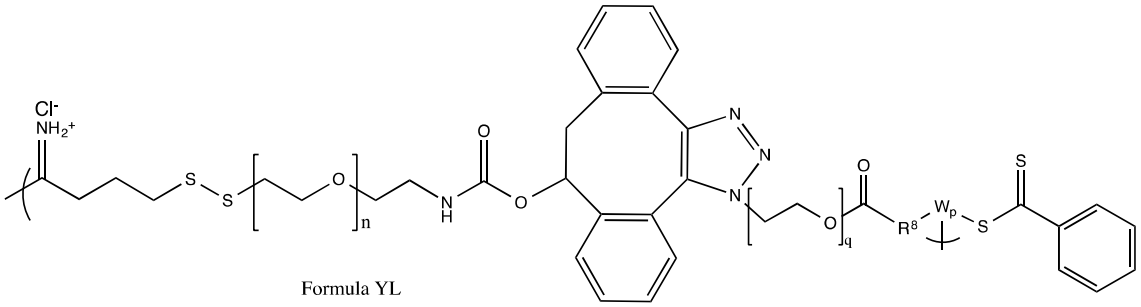
Formula Yi



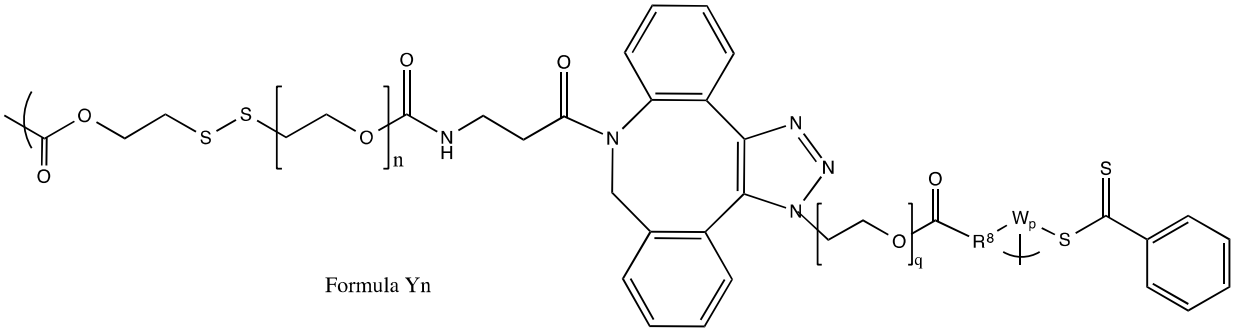
Formula Yj



Formula Yk

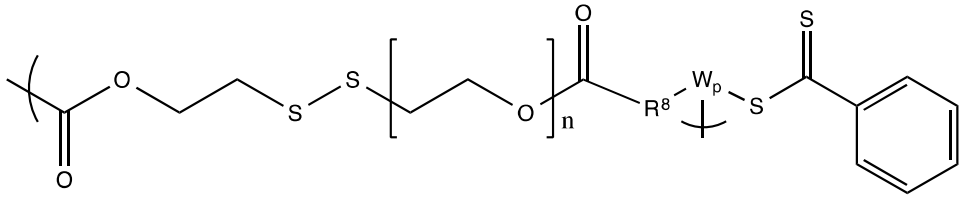


Formula YL



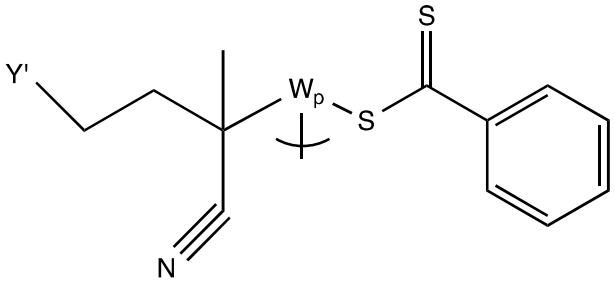
Formula Yn

and



Formula Yp

or Y has a portion represented by Formula Y'-CMP:



Formula Y'-CMP

where:

the left bracket "(" indicates the bond between X and Y;

the right or bottom bracket and ")" indicates the bond between Y and Z;

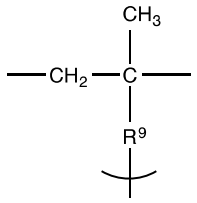
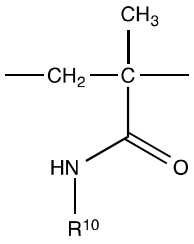
n is an integer from 1 to 100;

q is an integer from 1 to 44;

R^8 is $–CH_2–$ or $–CH_2-CH_2-C(CH_3)(CN)–$;

Y' represents the remaining portion of Y; and

W is a copolymer or a random copolymer of the same or different W^1 and W^2 groups, where:

W^1 =  and W^2 = 

where:

p is an integer from 2 to 150;

R^9 is a direct bond, $–CH_2-CH_2-–NH–C(O)–$, or $-CH_2-CH_2-(O-CH_2-CH_2)_t-NH-C(O)-$;

t is an integer from 1 to 5; and

R^{10} is an aliphatic group, an alcohol or an aliphatic alcohol; and

Z comprises a liver targeting moiety, wherein the liver targeting moiety comprises one or more of a glucosylating moiety and a galactosylating moiety.

6. The compound of any one of Claims 1 to 5, wherein X comprises:

a foreign transplant antigen against which transplant recipients develop an unwanted immune response;

a foreign food, animal, plant or environmental antigen against which patients develop an unwanted immune response;

a foreign therapeutic agent against which patients develop an unwanted immune response; or

a synthetic self-antigen against the endogenous version of which patients develop an unwanted immune response,

or a tolerogenic portion thereof.

7. The compound of any one of claims 1 to 6, wherein Z is the beta anomer.

8. The compound of any one of claims 1 to 7, wherein Z is conjugated at its C1, C2 or C6 to Y.

9. The compound of any one of claims 1 to 8, wherein Y is prepared using a linker precursor selected from N-hydroxysuccinamidyl-based linkers, malaemide-based linkers, vinylsulfone-based linkers, pyridyl di-thiol-poly(ethylene glycol) -based linkers, pyridyl di-thiol-based linkers, n-nitrophenyl carbonate-based linkers, NHS-ester-based linkers, and nitrophenoxy poly(ethylene glycol)ester-based linkers.

10. The compound of any one of claims 1 to 9, wherein X comprises a food antigen, wherein the food antigen is selected from the group consisting of conarachin (Ara h 1), allergen II (Ara h 2), arachis agglutinin, conglutin (Ara

h 6), 31 kda major allergen/disease resistance protein homolog (Mal d 2), lipid transfer protein precursor (Mal d 3), major allergen Mal d 1.03D (Mal d 1), a-lactalbumin (ALA), lactotransferrin, actinidin (Act c 1, Act d 1), phytocystatin, thaumatin-like protein (Act d 2), kiwellin (Act d 5), ovomucoid, ovalbumin, ovotransferrin, and lysozyme, livetin, apovitillin, vosvetin, 2S albumin (Sin a 1), 1 IS globulin (Sin a 2), lipid transfer protein (Sin a 3), profilin (Sin a 4), profilin (Api g 4), high molecular weight glycoprotein (Api g 5), Pen a 1 allergen (Pen a 1), allergen Pen m 2 (Pen m 2), tropomyosin fast isoform, high molecular weight glutenin, low molecular weight glutenin, alpha-, gamma- and omega-gliadin, hordein, secalin, avenin, major strawberry allergy Fra a 1-E (Fra a 1), profilin (Mus xp 1), a portion of any of said antigens, and a mimetic of any of said antigens.

11. The compound of claim 10, wherein the food antigen is selected from the group consisting of high molecular weight glutenin, low molecular weight glutenin, alpha-, gamma- and omega-gliadin, hordein, secalin, avenin, a portion of any of said antigens, and a mimetic of any of said antigens.

12. The compound of any one of claims 1 to 9, wherein X comprises a self-antigen, wherein the self-antigen is selected from insulin, proinsulin, preproinsulin, glutamic acid decarboxylase-65 (GAD-65), GAD-67, insulinomaassociated protein 2 (IA-2), and insulinoma-associated protein 2β (IA-2β), ICA69, ICA12 (SOX-13), carboxypeptidase H, Imogen 38, GLIMA 38, chromogranin- A, HSP-60, caboxypeptidase E, peripherin, glucose transporter 2, hepatocarcinoma-intestinepancreas/pancreatic associated protein, S100β, glial fibrillary acidic protein, regenerating gene II, pancreatic duodenal homeobox 1, dystrophia myotonica kinase, islet-specific glucose-6- phosphatase catalytic subunit-related protein, SST G-protein coupled receptors 1-5, and a portion of any of said antigens, and a mimetic of any of said antigens.

13.The compound of claim 12, wherein X comprises a self-antigen, wherein the self-antigen is selected from myelin basic protein, myelin oligodendrocyte glycoprotein and proteolipid protein, a portion of any of said antigens, and a mimetic of any of said antigens.

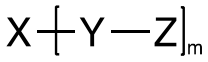
14. The compound of any one of claims 1 to 9, wherein X comprises a therapeutic agent, wherein the therapeutic agent is selected from Abciximab, Adalimumab, Agalsidase alfa, Agalsidase beta, Aldeslukin, Alglucosidase alfa, Factor VIII, Factor IX, Infliximab, L-asparaginase, Laronidase, Natalizumab, Octreotide, Phenylalanine ammonia-lyase (PAL), or Rasburicase (uricase), a portion of any of said antigens, and a mimetic of any of said antigens.

15. The compound of any one of claims 1 to 9, wherein X comprises a human allograft transplant antigen, wherein the transplant antigen is selected from the group consisting of subunits of the MHC class I and MHC class II haplotype proteins, and minor blood group antigens RhCE, Kell, Kidd, Duffy and Ss.

16. A composition comprising the compound of any one of claims 1 to 15.

17. The use of the compound or composition of any one of claims 1 to 16, for the manufacture of a medicament for the treatment of an unwanted immune response.

18. A compound for inducing tolerance to an antigen to which a subject develops an unwanted immune response, the compound comprising a compound of Formula 1:



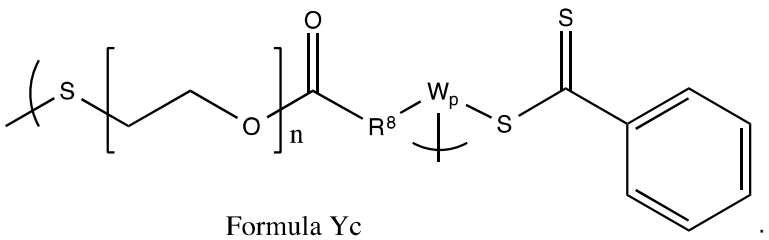
Formula 1

where:

m is an integer from 1 to 10;

X comprises an antigen to which patients develop an unwanted immune response, wherein the antigen is a food antigen, a therapeutic agent, or a self-antigen;

Y is :



Formula Yc ;

wherein:

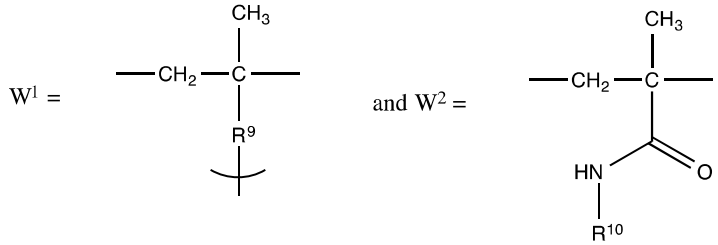
the left bracket "(" indicates a bond to X;

the bottom bracket and ")" indicates the bond between Y and Z;

n is an integer from 1 to 100;

where present R^8 $–CH_2-CH_2-C(CH_3)(CN)–$;

W represents a copolymer or a random copolymer of the same or different W^1 and W^2 groups, where:



where:

p is an integer from 2 to 150;

where present R^9 is a direct bond, $–CH_2-CH_2–NH–C(O)–$, or $-CH_2-CH_2-(O-CH_2-CH_2)_t-NH-C(O)-$ -;

t is an integer from 1 to 5; and

R^{10} is an aliphatic group, an alcohol, or an aliphatic alcohol; and

Z is a liver targeting moiety, wherein the liver targeting moiety comprises one or more of a glucosylating moiety and a galactosylating moiety.

19. The compound of claim 18, wherein Z comprises one or more of galactose, galactosamine, N-acetylgalactosamine, glucose, glucosamine, or N-acetyl glucosamine.

20. The compound of claim 19, wherein Z is the beta anomer.

21. The compound of any one of claims 18 to 20, where Z conjugated at its C1, C2 or C6 to Y.

22. The compound of any one of claims 18 to 21, wherein X comprises:

a foreign transplant antigen against which transplant recipients develop an unwanted immune response;

a foreign food, animal, plant or environmental antigen against which patients develop an unwanted immune response;

a foreign therapeutic agent against which patients develop an unwanted immune response; or

a synthetic self-antigen against the endogenous version of which patients develop an unwanted immune response,

or a tolerogenic portion thereof.

23. The compound of any one of claims 18 to 21, wherein X is a self-antigen and the unwanted immune response is an autoimmune response.

24. The compound of any one of claims 18 to 21, wherein X is selected from the group consisting of myelin oligodendrocyte glycoprotein, myelin proteolipid protein, and myelin basic protein and wherein the unwanted immune response is associated with multiple sclerosis.

25. The compound of any one of claims 18 to 21, wherein X is a is a food antigen selected from the group consisting of: conarachin (Ara h 1), allergen II (Ara h 2), arachis agglutinin, conglutin (Ara h 6), a-lactalbumin (ALA), lactotransferrin, Pen a 1 allergen (Pen a 1), allergen Pen m 2 (Pen m 2), tropomyosin fast isoform, high

molecular weight glutenin, low molecular weight glutenin, alpha- gliadin, gamma-gliadin, omega-gliadin, hordein, secalin, and avenin.

26. The compound of any one of claims 18 to 21, wherein X is a therapeutic agent selected from Abciximab, Adalimumab, Agalsidase alfa, Agalsidase beta, Aldeslukin, Alglucosidase alfa, Factor VIII, Factor IX, Infliximab, L-asparaginase, Laronidase, Natalizumab, Octreotide, Phenylalanine ammonia-lyase (PAL), or Rasburicase (uricase), a portion of any of said antigens, and a mimetic of any of said antigens

27. The compound of any one of claims 18 to 21, wherein X is selected from the group consisting of insulin, proinsulin, and preproinsulin and wherein the unwanted immune response is associated with type 1 diabetes mellitus.

28. A composition for the induction of antigen-specific immune tolerance in a subject, the composition comprising:

an antigen to which tolerance is desired;

wherein the antigen to which tolerance is desired is capable of inducing an unwanted immune response in the subject;

a polymeric linker comprising:

a copolymer or a random copolymer, wherein the copolymer or random copolymer comprises a first methacrylic unit and a second methacrylic unit, the first methacrylic unit comprising a first ethylacetamido functionality and the second methacrylic unit comprising a second ethylacetamido functionality;

wherein the second ethylacetamido functionality is conjugated to an aliphatic group, an alcohol, or an aliphatic alcohol;

wherein the polymeric linker is bonded to the antigen to which tolerance is desired via a dithiol bond or a disulfanyl ethyl ester,

wherein the dithiol bond or the disulfanyl ethyl ester are each configured to cleave after administration of the composition to the subject and to release the antigen to which tolerance is desired from the polymeric linker; and

a liver-targeting moiety;

wherein the liver-targeting moiety comprises a galactosylating or glucosylating moiety;

wherein the liver-targeting moiety is bonded to the polymeric linker through the first ethylacetamido functionality.

29. A composition for the induction of antigen-specific immune tolerance in a subject, the composition comprising:

an antigen to which tolerance is desired;

wherein the antigen to which tolerance is desired is capable of inducing an unwanted immune response in the subject;

a liver-targeting moiety;

wherein the liver-targeting moiety comprises a galactosylating or glucosylating moiety;

a polymeric linker comprising:

a copolymer or a random copolymer, wherein the copolymer or random copolymer comprises a first unit and a second unit, the first unit comprising a first functionality that bonds the first unit to the liver-targeting moiety and the second unit comprising a second functionality conjugated to an aliphatic group, an alcohol, or an aliphatic alcohol;

wherein the polymeric linker is bonded to the antigen to which tolerance is desired via a dithiol bond or a disulfanyl ethyl ester,

wherein the dithiol bond or the disulfanyl ethyl ester are each configured to cleave after administration of the composition to the subject and to release the antigen to which tolerance is desired from the polymeric linker.

30. The composition of claim 28 or 29, wherein the liver targeting moiety is a beta anomer,
wherein the liver targeting moiety comprises N acetylgalactosamine, wherein the N acetylgalactosamine is conjugated at its C1, C2 or C6 carbon to the polymeric linker.

31. The composition of any one of claims 28 to 30, wherein the antigen comprises:

a foreign transplant antigen against which transplant recipients develop an unwanted immune response;

a foreign food, animal, plant or environmental antigen against which patients develop an unwanted immune response;

a foreign therapeutic agent against which patients develop an unwanted immune response; or

a synthetic self-antigen against the endogenous version of which patients develop an unwanted immune response,

or a tolerogenic portion thereof.

32. The composition of any one of claims 28 to 30, wherein the antigen is associated with multiple sclerosis or Type I Diabetes.

33. The composition of any one of claims 28 to 30, wherein the antigen to which tolerance is

desired is a self-antigen.

34. The composition of any one of claims 28 to 30, wherein the antigen which tolerance is desired is associated with multiple sclerosis.

35. The composition of any one of claims 28 to 30, wherein the antigen comprises one or more of SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 8, or SEQ ID NO. 9.

36. The composition of any one of claims 28 to 30, wherein the antigen comprises one or more of SEQ ID NO. 11 or SEQ ID NO. 12.

37. The composition of any one of claims 28 to 30, wherein the antigen to which tolerance is desired is associated with celiac disease.

38. The composition of any one of claims 28 to 30, wherein the antigen comprises one or more of SEQ ID NO: 21 or SEQ ID NO. 20.

39. The composition of any one of claims 28 to 30, wherein the antigen to which tolerance is desired is associated with Type I diabetes.

40. The composition of any one of claims 28 to 30, wherein the antigen comprises a portion of SEQ. ID. NO. 1

41. The composition of claim 40, wherein the antigen further comprises an immunogenic portion of one or more of SEQ ID NO. 2 and SEQ ID NO.3.

42. The composition of any one of claims 28 to 41, further comprising one or more additional antigens.

43. The composition of any one of claims 28 to 30, wherein composition further comprises an additional antigen to which tolerance is desired, wherein the additional antigen is derived from insulinoma-associated protein 2 (IA-2).

44. The composition of any one of claims 28 to 30, wherein the antigen to which tolerance is desired comprises one or more of myelin oligodendrocyte glycoprotein, myelin basic protein, proteolipid protein, and a tolerogenic portion of any of said antigens.

45. The composition of any one of claims 28 to 30, wherein the antigen to which tolerance is desired comprises at least one tolerogenic myelin oligodendrocyte glycoprotein.

46. The composition of any one of claims 28 to 30, wherein the antigen to which tolerance is desired comprises an amino acid sequence comprising a portion of SEQ. ID. NO. 1 and one or more of IA-2, and a tolerogenic fragment thereof.

47. A composition for the induction of antigen-specific immune tolerance in a subject, the composition comprising:

one or more antigens to which tolerance is desired,

wherein the one or more antigens to which tolerance is desired is capable of inducing an unwanted immune response in the subject;

wherein the one or more antigens to which tolerance is desired comprises:

one or more antigens associated with multiple sclerosis, or

one or more antigens associated with Type I Diabetes;

a liver targeting moiety, wherein the liver targeting moiety comprises N-acetylgalactosamine;

a polymeric linker:

wherein the polymeric linker comprises a copolymer or a random copolymer, wherein the copolymer or random copolymer comprises a first unit and a second unit, the first unit comprising a first functionality that bonds the first unit to the liver-targeting moiety and the second unit comprising a second functionality conjugated to an aliphatic group, an alcohol, or an aliphatic alcohol;

wherein the polymeric linker is bonded to the one or more antigens via a dithiol bond or a disulfanyl ethyl ester,

wherein the dithiol bond or the disulfanyl ethyl ester are each configured to cleave after administration of the composition to the subject and to release the one or more antigens from the polymeric linker.

48. The composition of Claim 47, wherein the one or more antigens to which tolerance is desired is associated with Type I diabetes and comprises a portion of SEQ. ID. NO. 1.

49. The composition of claim 48, wherein the antigen further comprises an immunogenic portion of one or more of SEQ ID NO. 2 and SEQ ID NO.3.

50. The composition of Claim 48 or 49, further comprising one or more of IA-2 and a tolerogenic fragment thereof.

51. The composition of Claim 47, wherein the one or more antigens is associated with multiple sclerosis and comprises one or more amino acid sequences of SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 8, or SEQ ID NO. 9.

52. The composition of any one of claims 28 to 30, wherein the one or more antigens is associated with multiple sclerosis and comprises one or more of SEQ ID NO. 11 or SEQ ID NO. 12.

53. The composition of Claim 51 or 52, further comprising one or more of proteolipid protein (PLP) and a tolerogenic fragment thereof.

54. The compound of any one of claims 47 to 53, wherein N-acetylgalactosamine is the beta anomer.

55. The compound of any one of claims 47 to 54, wherein N-acetylgalactosamine conjugated at its C1, C2 or C6 to Y.

56. The use of the composition of any one of claims 28 to 55, for the manufacture of a medicament for the treatment of an unwanted immune response.