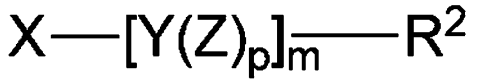
CLAIMS

1. A compound of Formula 1:



Formula 1

where:

X comprises an antigen, a tolerogenic portion thereof, or a mimetic thereof;

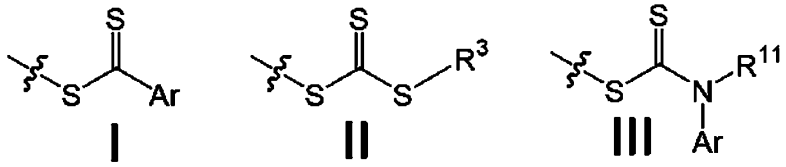
Y comprises a linker moiety;

Z comprises a moiety that specifically targets a mannose receptor;

p is an integer from 2 to 250;

m is an integer from 1 to 100;

R^2 is any of functional groups I-III:



where Ar is a substituted or unsubstituted aromatic group,

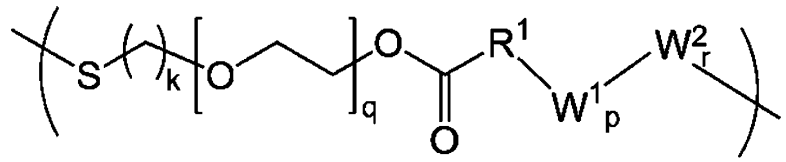
R^3 is any carbon-containing linear or heterocyclic moiety, and R^{11} is hydrogen or an alkyl group.

2. The compound of claim 1, wherein the moiety that specifically targets a mannose receptor is selected from the group consisting of α-linked mannose, β-linked mannose, substituted mannose, mannose-6-phosphate, N-acetyl mannosamine, and mannan having β(1-4), α(1-6), α(1-2), and/or α(1-3) linkages.

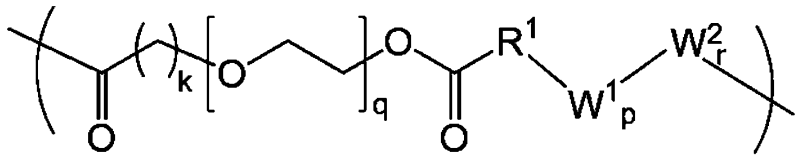
3. The compound of claim 1, wherein Y is a linker resulting from reaction of at least one of a N-hydroxysuccinamidyl linker, maleimide linker, PEG linker, vinylsulfone linker, pyridyl di-thiol-poly(ethylene glycol) linker, pyridyl di-thiol linker, n-nitrophenyl carbonate linker, NHS-ester linker, and nitrophenoxy poly(ethylene glycol)ester linker.

4. The compound of claim 3, wherein Y is covalently bound to X.

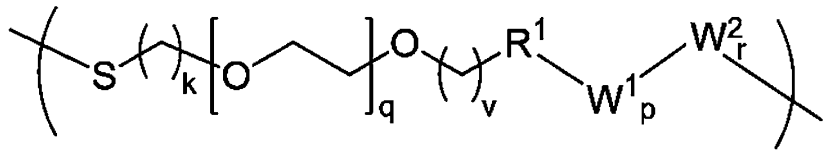
5. The compound of claim 1, wherein -[Y(Z)$_p$]- is represented by one of Formula Ya to Yr:



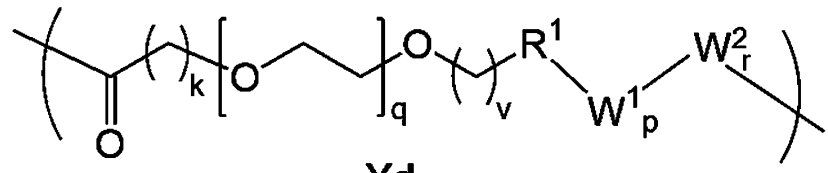
Ya



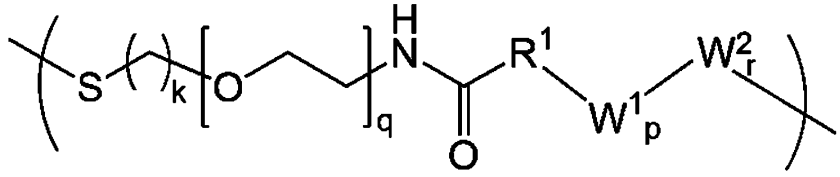
Yb



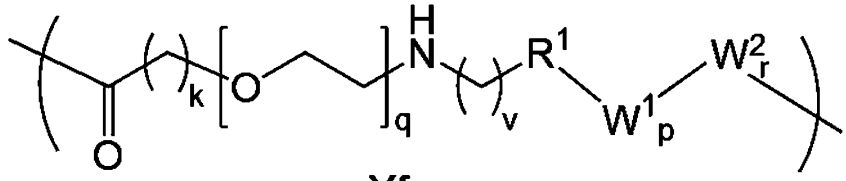
Yc



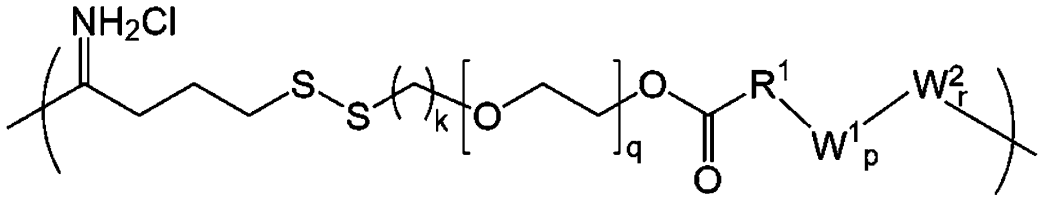
Yd



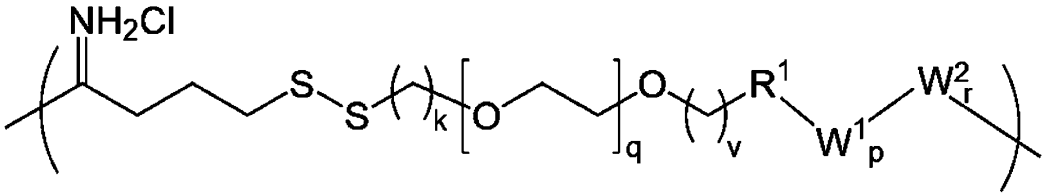
Ye



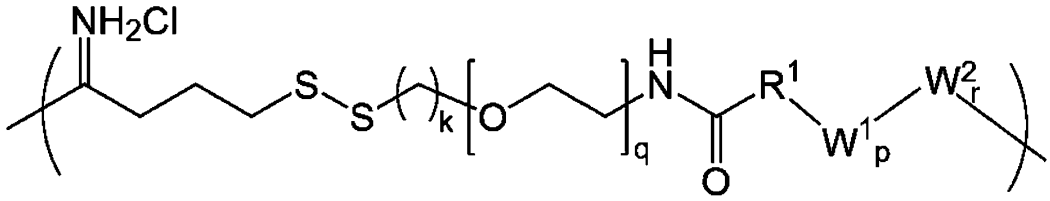
Yf



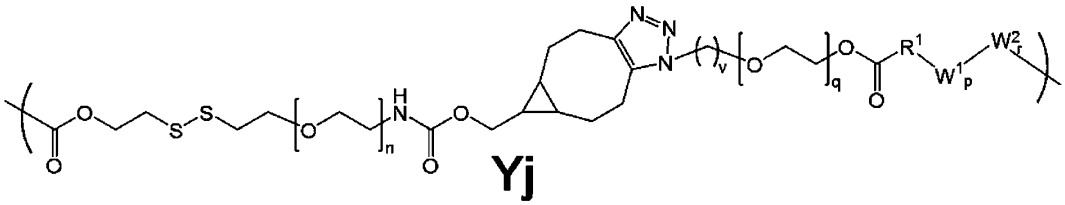
Yg



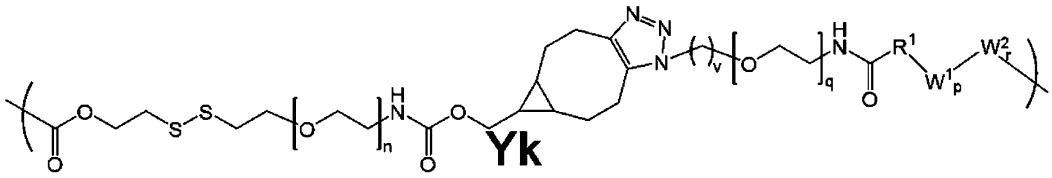
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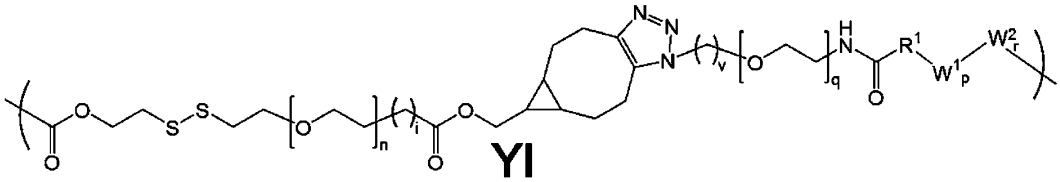
Yi



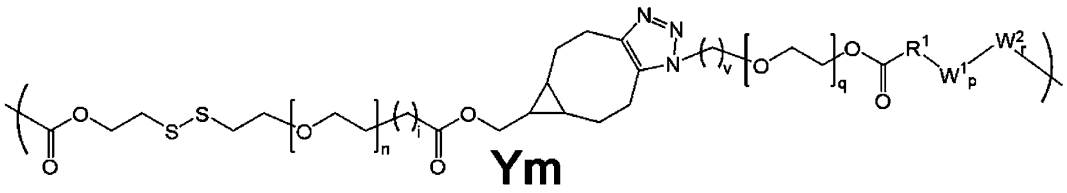
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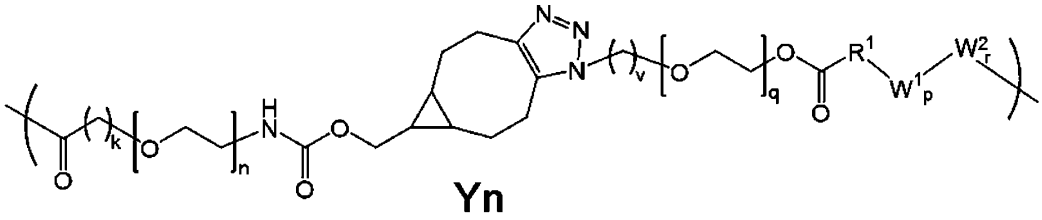
Yk



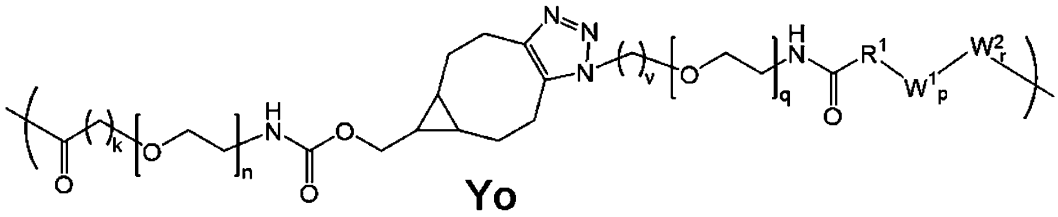
Yl



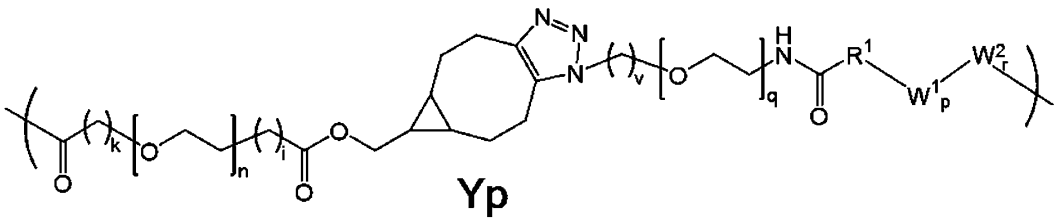
Ym



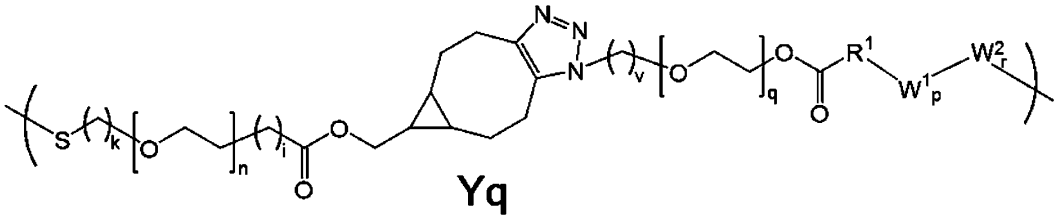
Yn



Yo

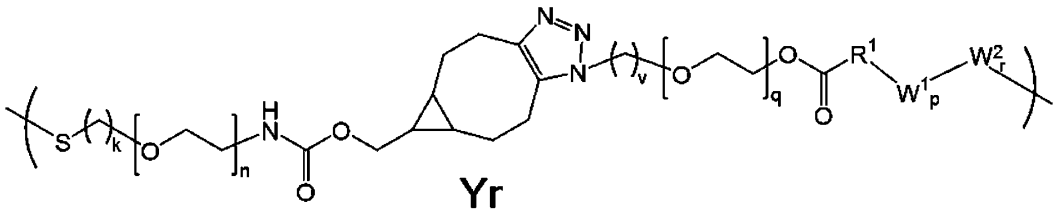


Yp



Yq

and



Yr

where

n is an integer from 1 to 100;

q is an integer from 1 to 44;

k is an integer from 1 to 12;

i is an integer from 0 to 20;

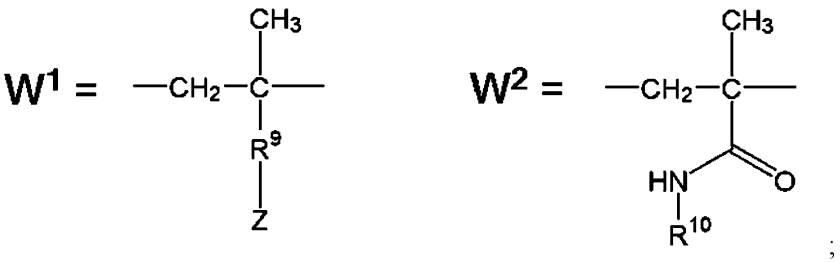
v is an integer from 1 to 4;

p is an integer from 2 to 250;

r is an integer from 0 to 250;

R_1 is $-CH_2-$, $-(CH_2)_2-C(CH_3)(CN)-$, $-(CH_2)_2-C(CH_3)(CH_3)-$, $-(CH_2)_2-CH(CH_3)-$ or $-CH(CH_3)-$;

W^1 and W^2 are as defined below:



;

R^9 is a direct bond, -(CH2)2-NH-C(O)- (an ethylaceetamido group or "EtAcN") or -(CH2)2-(O-CH2-CH2)t-NH-C(O)- (a pegylated ethylacetamido group or "Et-PEGt-AcN")

t is an integer from 1 to 5;

Z is mannose or a mannose receptor-targeting moiety; and

R^{10} is an aliphatic group, an alcohol, an aliphatic amine-containing group, or an aliphatic alcohol.

6. The compound of claim 1, wherein Y is an antibody, antibody fragment, peptide or other ligand that binds to X.

7. The compound of claim 1, wherein X is an antigen against which a patient may develop or has developed an unwanted immune response.

8. The compound of claim 7, wherein the antigen is a foreign transplant antigen, an alloantigen, an autoimmune antigen, a food antigen, an animal antigen, a plant antigen, an

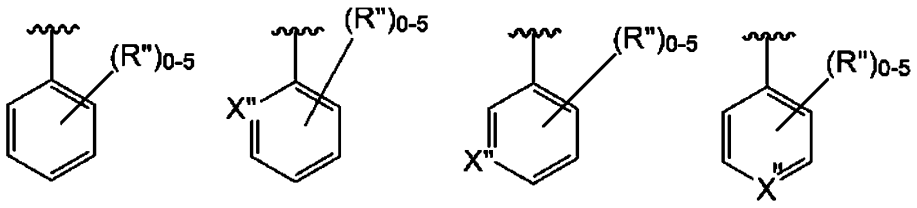
environmental antigen, a therapeutic antigen, a synthetic self-antigen, or a tolerogenic portion thereof.

9. The compound of claim 8, wherein X is an asparaginase antigen or an ovalbumin antigen.

10. The compound of claim 1, wherein the mannose receptor is mannose-6-phosphate receptor.

11. The compound of claim 1, wherein Y and X are connected through a bond configured to cleave when the compound reaches a target area.

12. The compound of claim 1, wherein Ar is selected from:



;

where each instance of R", where present, is independently selected from an optionally substituted C_{1-6}-alkyl, optionally substituted C_{1-6} alkoxy, optionally substituted amino, OH, or halogen and wherein, X" is a heteroatom.

13. The compound of claim 12 wherein X" is N.

14. The compound of claim 1, wherein R^{11} is C_{1-6}-alkyl.

15. The compound of claim 1, wherein R^{11} is $-CH_3$.

16. The compound of claim 1, wherein R^3 is C_{1-6}-alkyl.

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

18. Use of the compound of any one of claims 1 to 16, for inducing tolerance to the antigen, the tolerogenic portion thereof, or the mimetic thereof.

19. A method of inducing immunological tolerance to an antigen target comprising administering to a subject a composition Formula 1:

$$X—[Y(Z)_p]_m—R^2$$

Formula 1

where:

X comprises an antigen, a tolerogenic portion thereof, or a mimetic thereof;

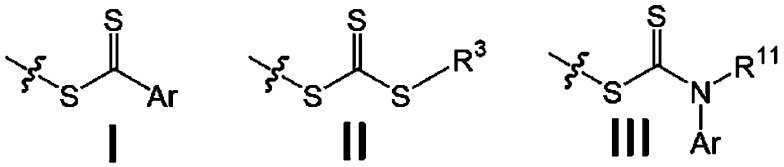
Y comprises a linker moiety;

Z comprises a moiety that specifically targets a mannose receptor;

p is an integer from 2 to 250;

m is an integer from 1 to 100;

R^2 is any of functional groups I-III:



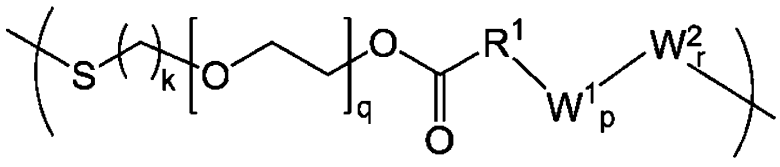
where Ar is a substituted or unsubstituted aromatic group, R^3 is any carbon-containing linear or heterocyclic moiety, and R^{11} is hydrogen or an alkyl group.

20. The method of claim 19, wherein the moiety that specifically targets a mannose receptor is selected from the group consisting of α-linked mannose, β-linked mannose, substituted mannose, mannose-6-phosphate, N-acetyl mannosamine, and mannan having β(1-4), α(1-6), α(1-2), and/or α(1-3) linkages.

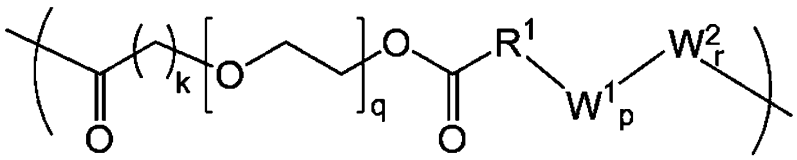
21. The method of claim 19 or 20, wherein Y is a linker resulting from reaction of at least one of a N-hydroxysuccinamidyl linker, PEG linker, maleimide linker, vinylsulfone linker, pyridyl di-thiol-poly(ethylene glycol) linker, pyridyl di-thiol linker, n-nitrophenyl carbonate linker, NHS-ester linker, and nitrophenoxy poly(ethylene glycol)ester linker.

22. The method of any of claims 19 to 21, wherein Y is covalently bound to X.

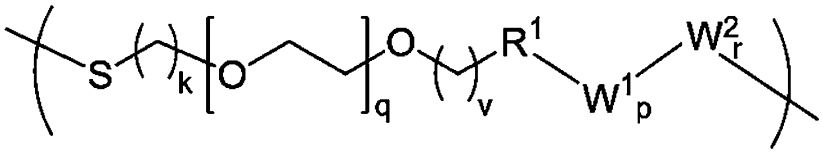
23. The method of any of claims 19 to 22, wherein -[$Y(Z)_p$]- is represented by one of Formula Ya to Yr:



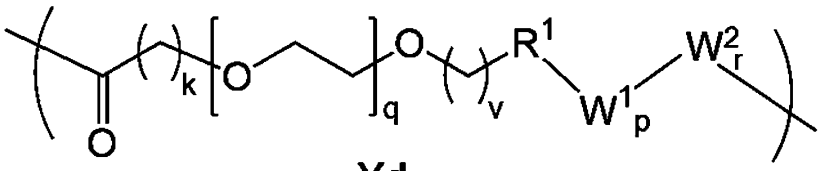
Ya



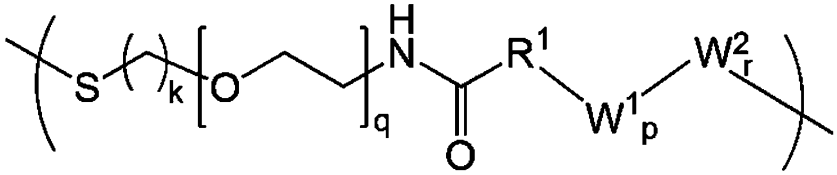
Yb



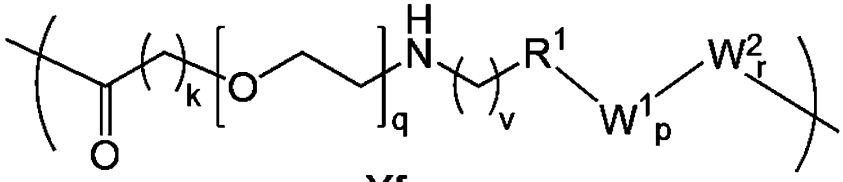
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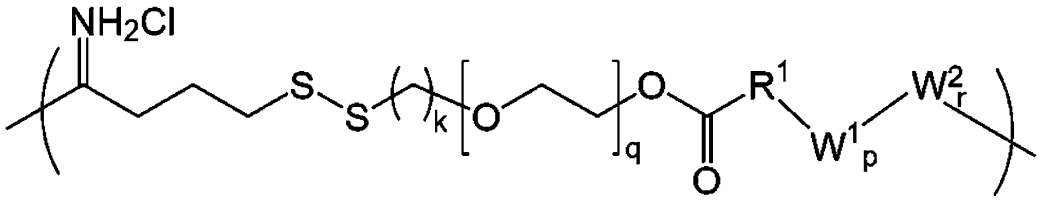
Yd



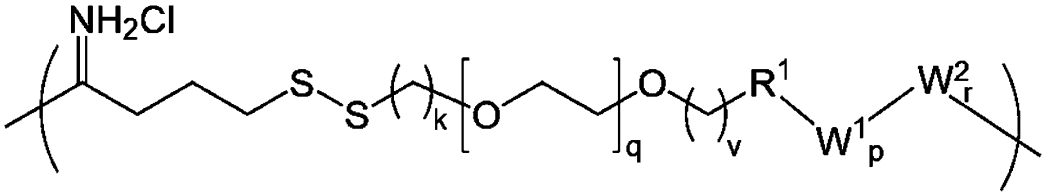
Ye



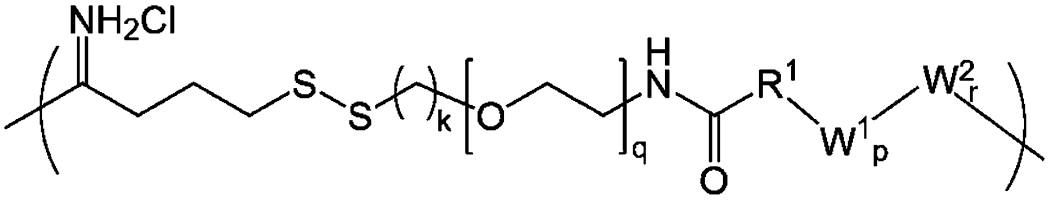
Yf



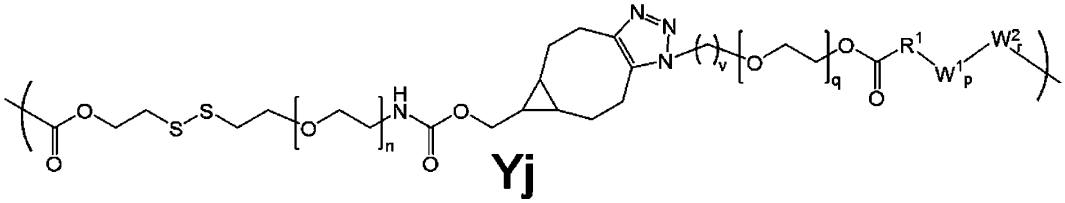
Yg



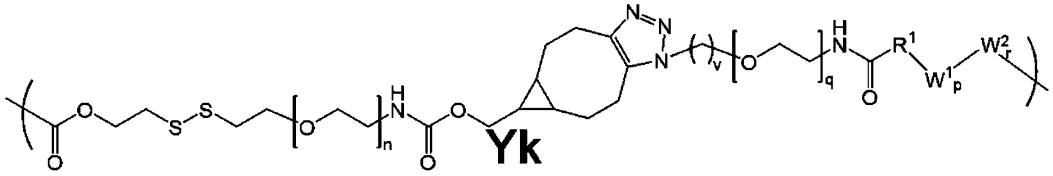
Yh



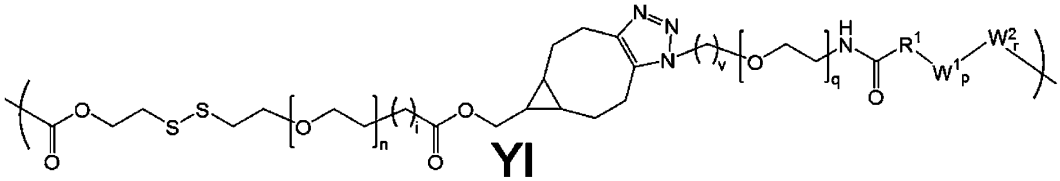
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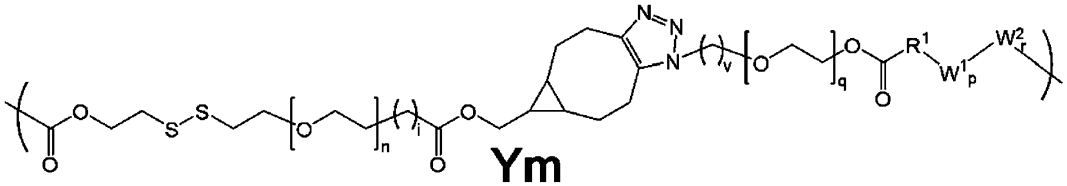
Yj



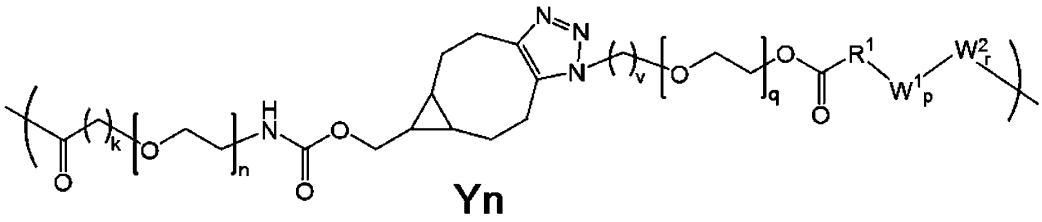
Yk



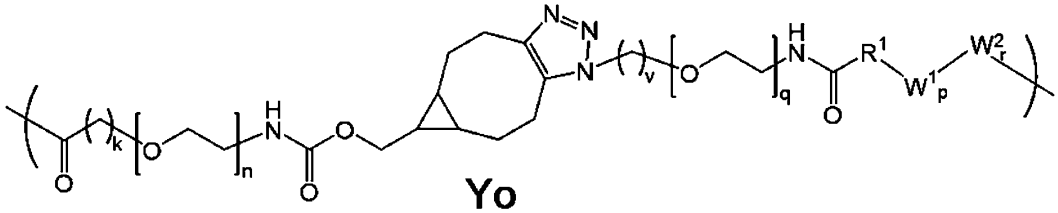
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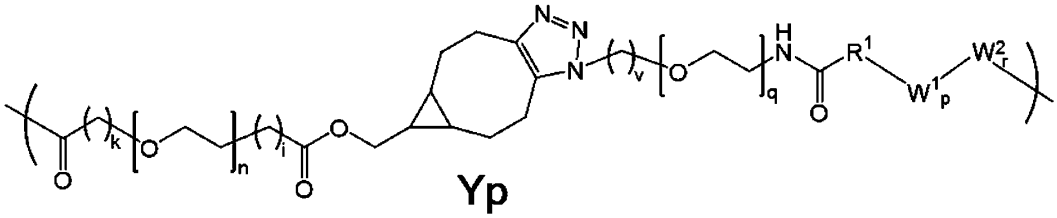
Ym



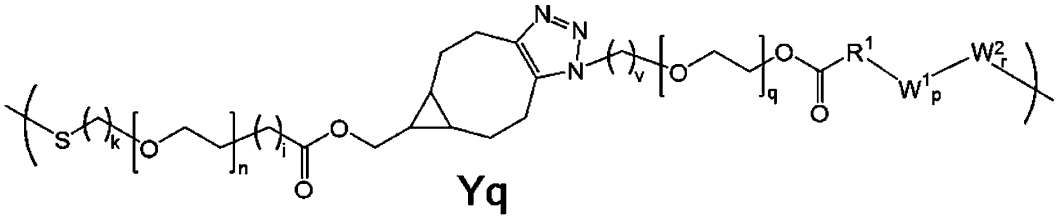
Yn



Yo

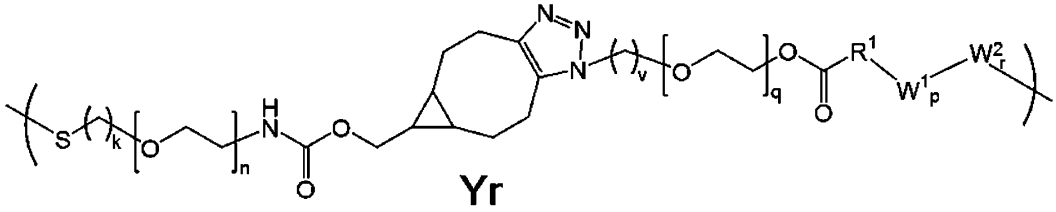


Yp



Yq

and



Yr

where

n is an integer from 1 to 100;

q is an integer from 1 to 44;

k is an integer from 1 to 12;

i is an integer from 0 to 20;

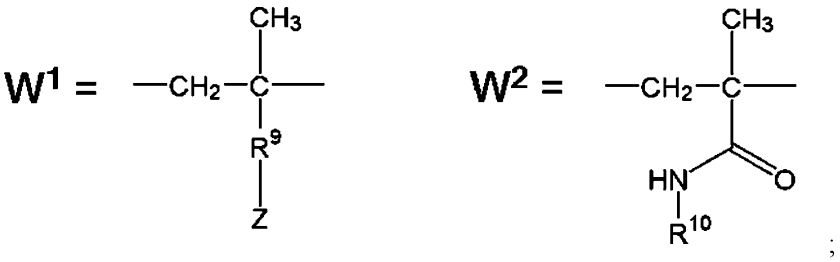
v is an integer from 1 to 4;

p is an integer from 2 to 250;

r is an integer from 0 to 250;

R_1 is $-CH_2-$, $-(CH_2)_2-C(CH_3)(CN)-$, $-(CH_2)_2-C(CH_3)(CH_3)-$, $-(CH_2)_2-CH(CH_3)-$ or $-CH(CH_3)-$;

W^1 and W^2 are as defined below:



;

R^9 is a direct bond, $-(CH_2)_2-NH-C(O)-$ (an ethylaceetamido group or "EtAcN") or $-(CH_2)_2-(O-CH_2-CH_2)_t-NH-C(O)-$ (a pegylated ethylacetamido group or "Et-PEG$_t$-AcN")

t is an integer from 1 to 5;

Z is mannose or a mannose receptor-targeting moiety; and

R^{10} is an aliphatic group, an alcohol, an aliphatic amine-containing group, or an aliphatic alcohol.

24. The method of claim 19 or 20, wherein Y is an antibody, antibody fragment, peptide or other ligand that binds to X.

25. The method of any of claims 19 to 24, wherein X is an antigen against which a patient may develop or has developed an unwanted immune response.

26. The method of any of claims 19 to 25, wherein the antigen is a foreign transplant antigen, an alloantigen, an autoimmune antigen, a food antigen, an animal antigen, a plant antigen, an environmental antigen, a therapeutic agent, a synthetic self-antigen, or a tolerogenic portion thereof.

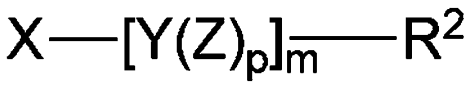
27. The method of any one of claims 19 to 26, wherein the antigen is comprised in a vesicle, cell fragment, or cell.

28. The method of any of claims 19 to 27, wherein X is an asparaginase antigen or an ovalbumin antigen.

29. The method of any of claims 19 to 28, wherein the mannose receptor is mannose-6-phosphate receptor.

30. The method of any of claims 19 to 29, wherein the bond between X and Y is configured to cleave at a target site in the subject.

31. A method of treating or preventing an unwanted immune response against an antigen comprising administering a composition comprising a compound of Formula 1:



Formula 1

where:

X comprises an antigen, a tolerogenic portion thereof, or a mimetic thereof;

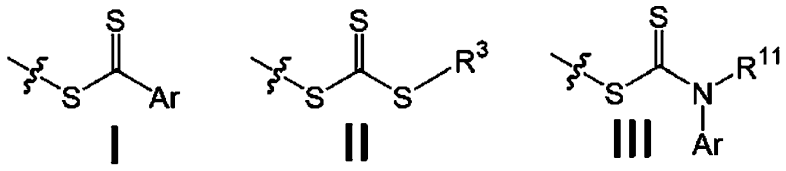
Y comprisees a linker moiety;

Z comprises a moiety that specifically targets a mannose receptor;

p is an integer from 2 to 250;

m is an integer from 1 to 100;

R^2 is any of functional groups I-III:



where Ar is a substituted or unsubstituted aromatic group, R^3 is any carbon-containing linear or heterocyclic moiety, and R^{11} is hydrogen or an alkyl group;

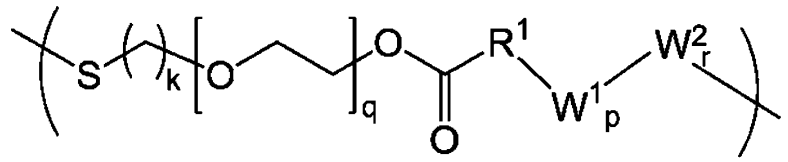
to a subject in need of suppression of an immune response to the antigen.

32. The method of claim 31, wherein the moiety that specifically targets a mannose receptor is selected from the group consisting of α-linked mannose, β-linked mannose, substituted mannose, mannose-6-phosphate, N-acetyl mannosamine, and mannan having β(1-4), α(1-6), α(1-2), and/or α(1-3) linkages.

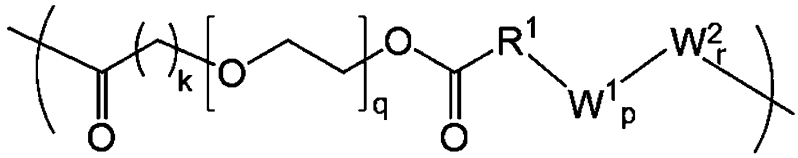
33. The method of claim 31 or 32, wherein Y is a linker resulting from reaction of at least one of a N-hydroxysuccinamidyl linker, PEG linker, maleimide linker, vinylsulfone linker, pyridyl di-thiol-poly(ethylene glycol) linker, pyridyl di-thiol linker, n-nitrophenyl carbonate linker, NHS-ester linker, and nitrophenoxy poly(ethylene glycol)ester linker.

34. The method of any of claims 31 to 33, wherein Y is covalently bound to X.

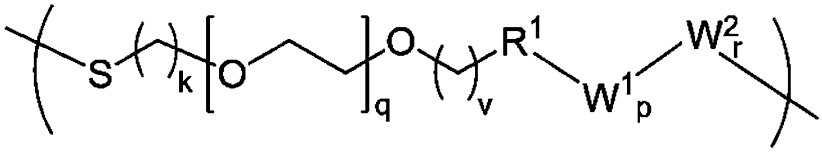
35. The composition of any of claims 31 to 34, wherein -[Y(Z)$_p$]- is represented by one of Formula Ya to Yr:



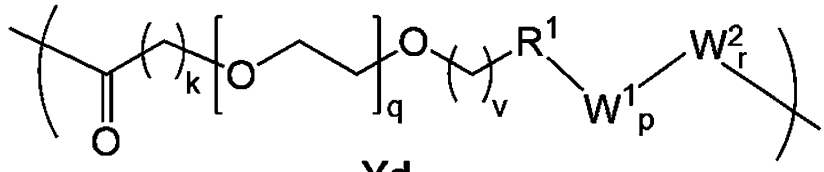
Ya



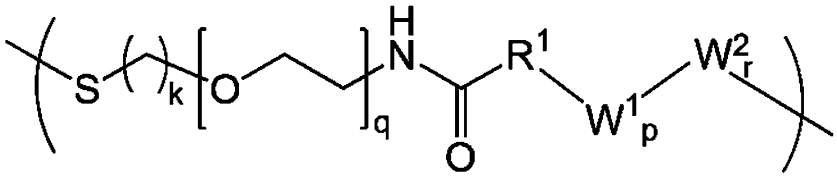
Yb



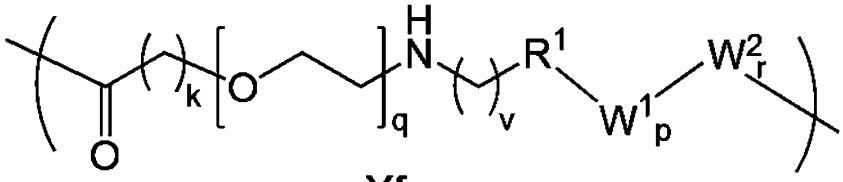
Yc



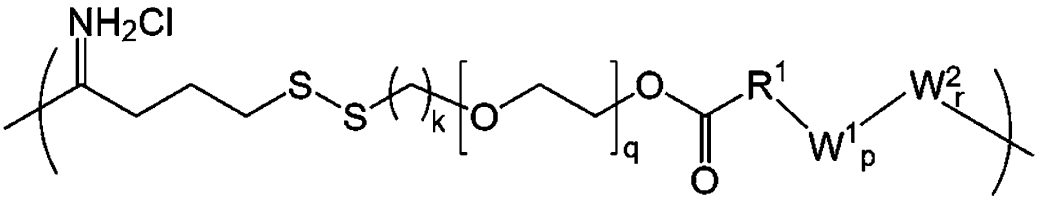
Yd



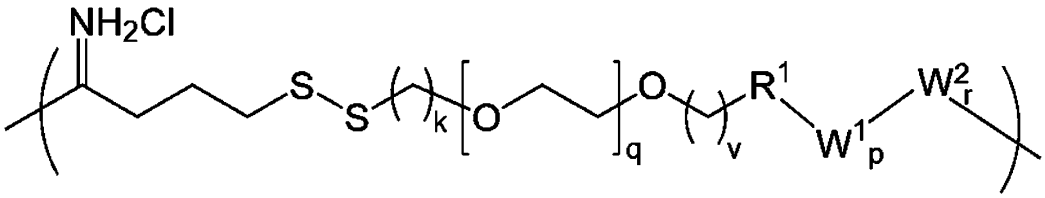
Ye



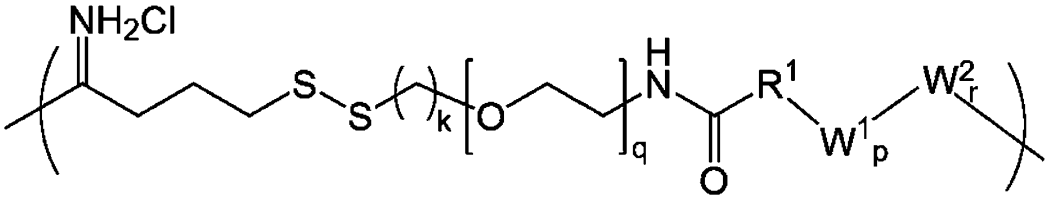
Yf



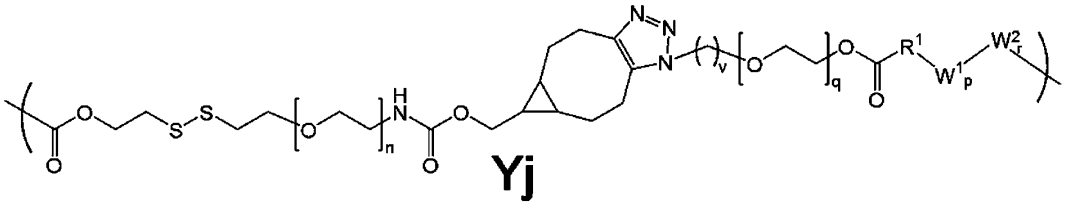
Yg



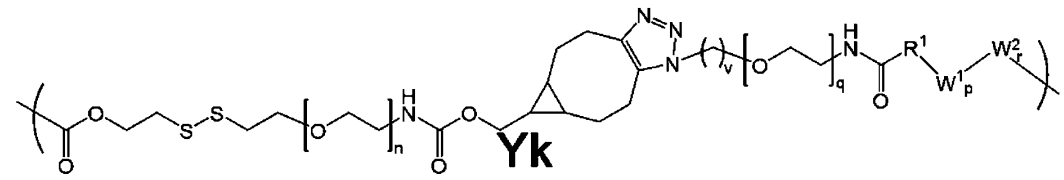
Yh



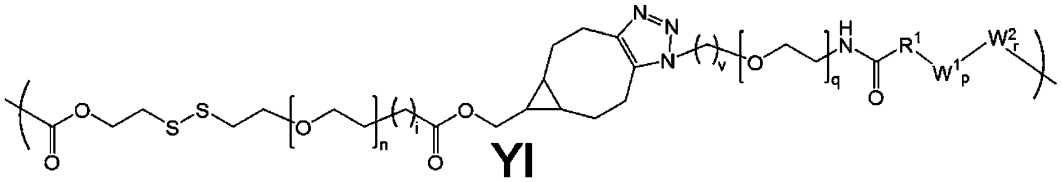
Yi



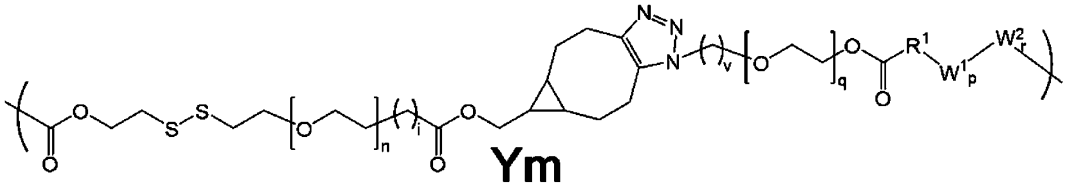
Yj



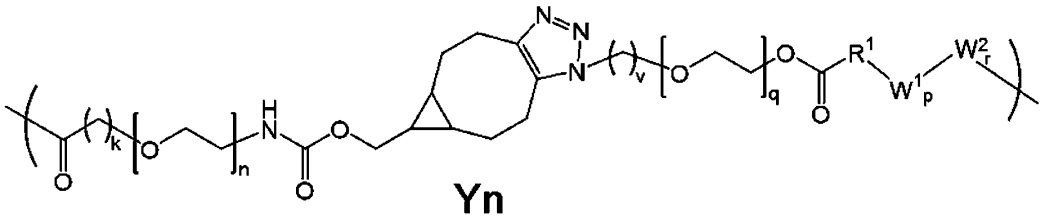
Yk



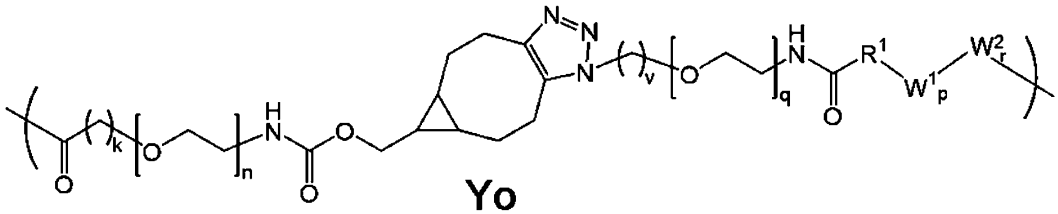
Yl



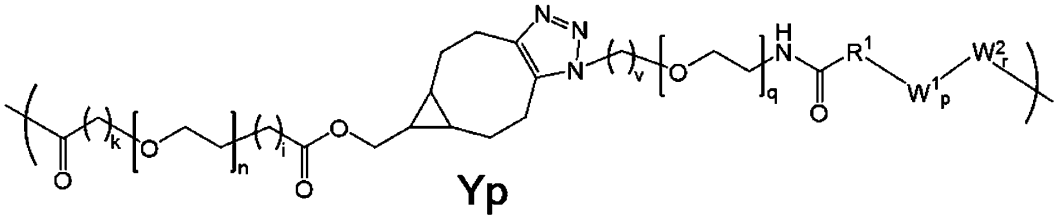
Ym



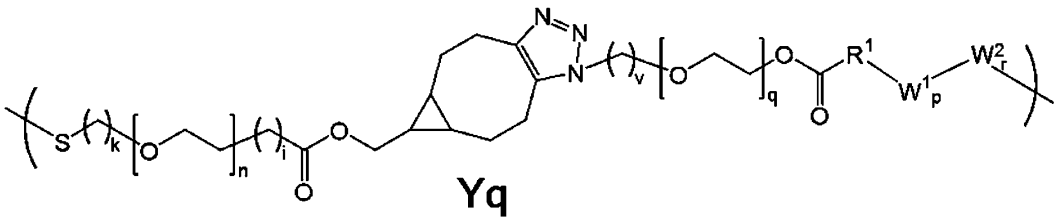
Yn



Yo

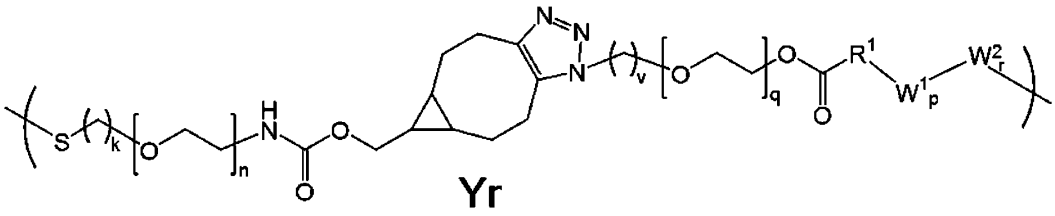


Yp



Yq

and



where

n is an integer from 1 to 100;

q is an integer from 1 to 44;

k is an integer from 1 to 12;

i is an integer from 0 to 20;

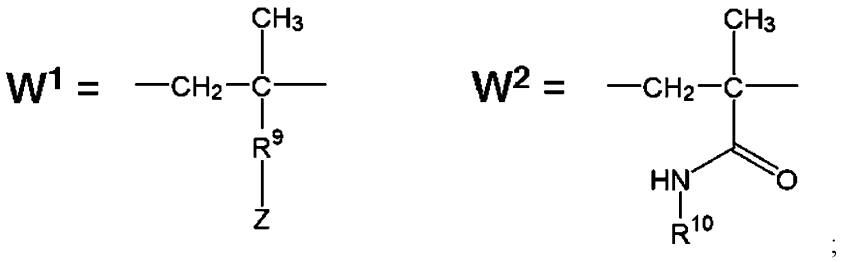
v is an integer from 1 to 4;

p is an integer from 2 to 250;

r is an integer from 0 to 250;

R_1 is $-CH_2-$, $-(CH_2)_2-C(CH_3)(CN)-$, $-(CH_2)_2-C(CH_3)(CH_3)-$, $-(CH_2)_2-CH(CH_3)-$ or $-CH(CH_3)-$;

W^1 and W^2 are as defined below:



;

R^9 is a direct bond, -(CH2)2-NH-C(O)- (an ethylaceetamido group or "EtAcN") or -(CH2)2-(O-CH2-CH2)t-NH-C(O)- (a pegylated ethylacetamido group or "Et-PEGt-AcN")

t is an integer from 1 to 5;

Z is mannose or a mannose receptor-targeting moiety; and

R10 is an aliphatic group, an alcohol, an aliphatic amine-containing group, or an aliphatic alcohol.

36. The method of claim 31 to 35, wherein Y is an antibody, antibody fragment, peptide or other ligand that binds to X.

37. The method of any of claims 31 to 36, wherein X is an antigen against which a patient may develop or has developed an unwanted immune response.

38. The method of claim 31 to 37, wherein the antigen is a foreign transplant antigen, an alloantigen, an autoimmune antigen, a food antigen, an animal antigen, a plant antigen, an environmental antigen, a therapeutic agent, a synthetic self-antigen, or a tolerogenic portion thereof.

39. The method of any one of claims 31 to 38, wherein the antigen is comprised in a vesicle, cell fragment, or cell.

40. The method of any of claims 31 to 39, wherein X is an asparaginase antigen or an ovalbumin antigen.

41. The method of any of claims 31 to 40, wherein the mannose receptor is mannose-6-phosphate receptor.

42. The method of any of claims 31 to 41, wherein Y and X are connected through a bond configured to cleave when the compound reaches a target area.

43. The compound according to any one of Claims 1 to 8 and 10 to 16, wherein the antigen comprises at least one autoimmune antigen or tolerogenic portion thereof.

44. The compound of Claim 43, wherein the at least one autoimmune antigen comprises at least one of an immunogenic fragment or fragments of myelin basic protein (MPB), an immunogenic fragment or fragments of myelin oligodendrocyte glycoprotein (MOG), an immunogenic fragment or fragments of myelin proteolipid protein (PLP), MBP, MOG, or PLP.

45. The compound of Claim 44, wherein the at least one autoimmune antigen comprises at least one of SEQ ID Nos. 23-47.

46. The compound of Claim 44, wherein the at least one autoimmune antigen comprises at least one of SEQ ID Nos. 24, 25, 27, 28, 31, 32, 33, 34, 35, 36, 43, 44, 45, 46, and 47.

47. The compound of Claim 46, further comprising at least one of SEQ ID NOs: 29, 38, 39, 40, 41, and 42.

48. The compound of any one of Claims 43-47, for use in the treatment of multiple sclerosis.

49. A method for treating or preventing multiple sclerosis comprising, administering to a subject having, or predicted to have, multiple sclerosis, a composition comprising the compound according to any one of Claims 43-47.

50. The compound of Claim 43, wherein the at least one autoimmune antigen comprises at least one of insulin, proinsulin, preproinsulin, glutamic acid decarboxylase-65 (GAD-65 or glutamate decarboxylase 2), GAD-67, glucose-6 phosphatase 2, islet-specific glucose 6 phosphatase catalytic subunit related protein (IGRP), insulinoma-associated protein 2 (IA-2), insulinoma-associated protein 2β (IA-2β), ICA69, ICA12 (SOX-13), carboxypeptidase H, Imogen 38, GLIMA 38, chromogranin-A, HSP-60, carboxypeptidase E, peripherin, glucose transporter 2, hepatocarcinoma-intestine-pancreas/pancreatic associated protein, S100β, glial fibrillary acidic protein, regenerating gene II, pancreatic duodenal homeobox 1, dystrophia myotonica kinase, and SST G-protein coupled receptors 1-5, or an immunogenic fragment of any of these antigens.

51. The compound of Claim 50, wherein the at least one autoimmune antigen comprises at least one of SEQ ID NOs: 1-19, or an immunogenic fragment of any of SEQ ID NOs: 1-19.

52. The compound of Claim 50, wherein the at least one autoimmune antigen comprises at least one of SEQ ID NOs: 4-19.

53. The compound of any one of Claims 50-52, for use in the treatment of Type 1 Diabetes.

54. A method for treating or preventing Type 1 Diabetes comprising, administering to a subject having, or predicted to have, Type 1 Diabetes, a composition comprising the compound according to any one of Claims 50-52.

55. The compound according to any one of Claims 1 to 8 and 10 to 16, wherein the antigen comprises a food antigen, or a tolerogenic portion thereof.

56. The compound of Claim 55, wherein the antigen comprises at least one of tissue transglutaminase, high molecular weight glutenin, low molecular weight glutenin, gluten, alpha-gliadin, gamma-gliadin, omega-gliadin, hordein, secalin, avenin, and deamidated forms thereof.

57. The compound of Claim 55, wherein the antigen comprises a tolerogenic portion of at least one of tissue transglutaminase, high molecular weight glutenin, low molecular weight glutenin, gluten, alpha-gliadin, gamma-gliadin, omega-gliadin, hordein, secalin, avenin, and deamidated forms thereof.

58. The compound of Claim 57, wherein the antigen comprises at least one of SEQ ID NOs. 54-61.

59. The compound of any one of Claims 55-58, for use in the treatment of Celiac disease.

60. A method for treating or preventing celiac disease comprising, administering to a subject having, or predicted to have, celiac disease, a composition comprising the compound according to any one of Claims 55-58.