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(54) Title: ANTI-ANGIOGENIC COMPOUNDS

(57) Abstract: The present invention provides AA targeting compounds which comprise AA targeting agent-linker conjugates which are linked to a combining site of an antibody. Various uses of the compounds are provided, including methods to treat disorders connected to abnormal angiogenesis.

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ANTI-ANGIOGENIC COMPOUNDS

FIELD OF THE DISCLOSURE

The present invention relates to novel compounds that possess anti-angiogenic activity and methods of making and using these compounds.

BACKGROUND

Angiogenesis is the fundamental process by which new blood vessels are formed and is essential to a variety of normal body activities such as reproduction, development and wound repair. Although angiogenesis is a highly regulated process under normal conditions, many diseases (characterized as "angiogenic diseases") are caused or exacerbated by unregulated angiogenesis. For example, ocular neovascularization has been implicated as the most common cause of blindness. In certain existing conditions such as arthritis, newly formed capillary blood vessels invade the joints and destroy cartilage. In diabetes, new capillaries formed in the retina invade the vitreous, bleed, and cause blindness. Growth and metastasis of solid tumors are also angiogenesis-dependent (J. Folkman, Cancer Res., 46:467-473 (1986), J. Folkman, J. Natl. Cancer Inst., 82:4-6 (1989)). It has been shown, for example, that tumors which enlarge to greater than 2 mm obtain their own blood supply by inducing the growth of new capillary blood vessels. Once these new blood vessels become embedded in the tumor, they provide a means for tumor cells to enter the circulation and metastasize to distant sites such as the liver, lungs, and bones (N. Weidner, et. al., N. Engl. J. Med., 324:1-8 (1991)).

Various peptides have been identified that bind to the angiogenesis related factor angiopoietin-2 ("Ang-2") (Oliner, J. *et al.*, Cancer Cell, 204(6), 507-516 (2004)). The Ang-2 binding peptides have been shown to possess anti-angiogenic activity.

The reference to any art in this specification is not, and should not be taken as, an acknowledgement of any form or suggestion that the referenced art forms part of the common general knowledge.

BRIEF SUMMARY

The present invention provides anti-angiogenic targeting compounds (AA targeting compounds) based upon Ang-2 binding peptides with unique specificity and biological properties which are useful in many applications. The anti-angiogenic targeting compounds of the invention are formed by covalently linking a anti-angiogenic targeting agent to a combining site of an antibody. Pharmaceutical compositions comprising targeting compounds of the invention and a

pharmaceutically acceptable carrier are also provided. In some embodiments, the present invention provides a targeting agent comprising a peptide comprising a sequence substantially homologous to:

$x^1\ x^2\ x^3\ x^4\ x^5\ x^6$ **D** $x^8\ x^9\ x^{10}\ x^{11}\ x^{12}\ x^{13}\ x^{14}\ x^{15}\ x^{16}\ x^{17}\ x^{18}\ x^{19}\ x^{20}\ x^{21}\ x^{22}$ (SEQ ID NO:161)

wherein

x^1 may be any residue, x^2 may be any residue, x^3 may be any aromatic amino acid residue, x^4 may be any residue x^5 may be P, hP, dhP, or BnHP x^6 may be any residue, x^8 may be D or E, x^9 may be any residue comprising a nucleophilic or electrophilic side chain, x^{10} may be D or E, x^{11} may be any residue comprising a nucleophilic or electrophilic side chain, x^{12} may be any residue x^{13} may be selected from the group consisting of L, HL, Nva, I, HchA, HF, and ThA. x^{14} may be any aromatic amino acid residue, x^{15} may be D or E,

x^{16} may be any residue x^{17} may be any aromatic amino acid residue, x^{18} may be any residue x^{19} may be any residue x^{20} may be any residue, or may be absent when x^{22} and x^{21} are absent, x^{21} may be any residue, or may be absent when x^{22} is absent, x^{22} may be any residue, or absent.

x^1 may be Q. x^1 may be T. x^1 may be S. x^1 may be R. x^1 may be H. x^2 may be K. x^2 may be N. x^2 may be R. x^2 may be H. x^2 may be AcK. x^2 may be Nick. x^2 may be CbcK. In some embodiments, x^2 may be selected from the group consisting of K, N, R, H, AcK, Nick, or CbcK. X^2 may be selected from the group consisting of N, R, H, AcK, Nick, or CbcK. X^2 may be selected from the group consisting of R, H, AcK, Nick, or CbcK. X^2 may be selected from the group consisting of R, H, AcK, or CbcK. x^2 may be selected from the group consisting of R, H, or AcK. x^3 may be F. x^3 may be Y. x^3 may be W. x^3 may be BPA. x^3 may be CF. x^3 may be or NF. x^4 may be Q. x^4 may be M. x^4 may be E. x^4 may be K. x^5 may be P. x^5 may be HP. x^5 may be DHP. x^5 may be BnHP. x^6 may be M. x^6 may be L. x^6 may be I. x^8 may be E. x^8 may be D. x^9 may be L. x^9 may be I. x^9 may be TA. x^9 may be ThA. x^9 may be K. x^9 may be AcK. x^{10} may be E. x^{10} may be D. x^{11} may be Q. x^{11} may be N. x^{11} may be C. x^{11} may be K. x^{11} may be AcK. x^{11} may be Dab. X^{11} may be Dap. x^{12} may be T. x^{12} may be R. x^{12} may be K. x^{13} may be L. x^{13} may be HL. x^{13} may be Nva. x^{13} may be I. x^{13} may be HchA. x^{13} may be HF. x^{13} may be ThA. x^{13} may be K. In some embodiments, x^{13} may be selected from the group consisting of L, HL, Nva, I, HchA, HF, and ThA. In some embodiments, x^{13} may be selected from the group consisting of L, HL, and Nva. x^{14} may be F. x^{14} may be Y. x^{14} may be W. x^{14} may be BPA. x^{14} may be CF. x^{14} may be or NF. x^{15} may be D. x^{15} may be E. x^{16} may be Q. x^{16} may be N. x^{17} may be F. x^{17} may be Y. x^{17} may be W. x^{17} may be BPA. X^{17} may be CF. x^{17} may be NF. x^{18} may be M. x^{19} may be L. x^{19} may be I. x^{20} may be Q. x^{20} may be N. x^{21} may be Q. x^{21} may be N. x^{22} may be G.

In some embodiments, the present invention provides an anti-angiogenic (AA) targeting agent comprising a peptide comprising the sequence:

R^1-Q^1 $(A_cK)^2$ Y^3 Q^4 P^5 L^6 D^7 $E^8$$(A_cK)^9$ D^{10} K^{11} T^{12} L^{13} Y^{14} D^{15} Q^{16} F^{17} M^{18} L^{19} Q^{20} Q^{21} G^{22}-R^2 (SEQ ID NO: 43)

wherein

R^1 is CH_3, $C(O)CH_3$, $C(O)CH_3$, $C(O)CH_2CH_3$, $C(O)CH_2CH_2CH_3$, $C(O)CH(CH_3)CH_3$, $C(O)CH_2CH_2CH_2CH_3$, $C(O)CH(CH_3)CH_2CH_3$, $C(O)C_6H_5$, $C(O)CH_2CH_2(CH_2CH_2O)_{1\text{-}5}Me$, dichlorobenzoyl (DCB), difluorobenzoyl (DFB), pyridinyl carboxlate (PyC) or amido-2-PEG, an amino protecting group, a lipid fatty acid group or a carbohydrate; and

R^2 is OH, NH_2, $NH(CH_3)$, $NHCH_2CH_3$, $NHCH_2CH_2CH_3$, $NHCH(CH_3)CH_3$, $NHCH_2CH_2CH_2CH_3$, $NHCH(CH_3)CH_2CH_3$, NHC_6H_5, $NHCH_2CH_2OCH_3$, $NHOCH_3$, $NHOCH_2CH_3$, a carboxy protecting group, a lipid fatty acid group or a carbohydrate, and wherein

one of Q^1, E^8, $(A_cK)^9$, K^{11}, T^{12}, D^{15}, Q^{16}, M^{18}, L^{19} or G^{22} is substituted by a linking residue comprising a nucleophilic side chain covalently linkable to the combining site of an antibody directly or via an intermediate linker, the linking residue being selected from the group comprising K, Y, T, homologs of lysine, homocysteine, homoserine, Dap, and Dab, or the N-terminus or C-terminus.

In some embodiments, the present invention provides a compound having the formula:

L – [AA targeting agent] or

L' - [AA targeting agent]

wherein:

[AA targeting agent] is an AA targeting agent as claimed in any preceding claim, and

L is a linker moiety having the formula -X-Y-Z-, and L' is a linear or branched linker moiety having the formula -X-Y-Z', and wherein:

X is attached to the AA targeting agent via the amino terminus, carboxy terminus or side chain of the linking residue, and is a biologically compatible connecting chain including any atom selected from the group consisting of C, H, N, O, P, S, F, CL, Br, and I, and may comprise a polymer or block co-polymer,

Y is an optionally present recognition group comprising at least a ring structure; and

Z is a reactive group that is capable of forming a covalent bond with an amino acid side chain in a combining site of an antibody and

Z' is an attachment moiety comprising a covalent link to an amino acid side in a combining site of an antibody.

In some embodiments, the present invention provides a targeting agent comprising a peptide comprising a sequence substantially homologous to:

$x^1\ x^2\ x^3\ x^4\ x^5\ x^6$ **D E** x^9 **D** $x^{11}\ x^{12}\ x^{13}\ x^{14}$ **D** $x^{16}\ x^{17}\ x^{18}\ x^{19}\ x^{20}\ x^{21}\ x^{22}$ (SEQ ID NO:162)

wherein

each of $x^1, x^2, x^4, x^6, x^{12}, x^{16}, x^{18}, x^{19}$ may individually be any residue,

each of x^3 x^{14} and x^{17} may individually be any aromatic amino acid residue,

x^5 may be one of P, hP, dhP, or BnHP

each of x^9 and x^{11} may individually be any residue comprising a nucleophilic or electrophilic side chain,

x^{13} may be selected from the group consisting of L, HL, Nva, I, HchA, HF, and ThA.

x^{20} may be any residue, or may be absent when x^{22} and x^{21} are absent,

x^{21} may be any residue, or may be absent when x^{22} is absent,

x^{22} may be any residue, or absent.

x^1 may be Q. x^1 may be T. x^1 may be S. x^1 may be R. x^1 may be H. x^2 may be K. x^2 may be N. x^2 may be R. x^2 may be H. x^2 may be AcK. x^2 may be Nick. x^2 may be CbcK. In some embodiments, x^2 may be selected from the group consisting of K, N, R, H, AcK, Nick, or CbcK. x^2 may be selected from the group consisting of N, R, H, AcK, Nick, or CbcK. X^2 may be selected from the group consisting of R, H, AcK, Nick, or CbcK. x^2 may be selected from the group consisting of R, H, AcK, or CbcK. x^2 may be selected from the group consisting of R, H, or AcK. x^3 may be F. x^3 may be Y. x^3 may be W. x^3 may be BPA. x^3 may be CF. x^3 may be NF. x^4 may be Q. x^4 may be M. x^4 may be E. x^4 may be K. x^5 may be P. x^5 may be HP. x^5 may be DHP. x^5 may be BnHP. x^6 may be M. x^6 may be L. x^6 may be I. x^9 may be L. x^9 may be I. x^9 may be TA. x^9 may be ThA. x^9 may be K. x^9 may be AcK. x^{11} may be Q. x^{11} may be N. x^{11} may be C. X^{11} may be K. x^{11} may be AcK. x^{11} may be Dab. X^{11} may be Dap. x^{12} may be T. x^{12} may be R. x^{12} may be K. x^{13} may be L. x^{13} may be HL. x^{13} may be Nva. x^{13} may be I. x^{13} may be HchA. x^{13} may be HF. x^{13} may be ThA. In some embodiments, x^{13} may be selected from the group consisting of L, HL, Nva, I, HchA, HF, and ThA. In some embodiments, x^{13} may be selected from the group consisting of L, HL, and Nva. x^{14} may be F. x^{14} may be Y. $x1^4$ may be W. x^{14} may be BPA. x^{14} may be CF. x^{14} may be NF. x^{16} may be Q. x^{16} may be N. x^{17} may be F. x^{17} may be Y. x^{17} may be W. x^{17} may be BPA. x^{17} may be CF. x^{17} may be NF. x^{18} may be M. x^{19} may be L. x^{19} may be I. x^{20} may be Q. x^{20} may be N. x^{21} may be Q. x^{21} may be N. x^{22} may be G.

In some embodiments, the present invention provides a targeting agent comprising a peptide comprising a sequence substantially homologous to:

x^1 **AcK** $x^3 x^4 x^5 x^6$ **D E** x^9 **D** $x^{11} x^{12} x^{13} x^{14}$ **D** $x^{16} x^{17} x^{18} x^{19} x^{20} x^{21} x^{22}$ (SEQ ID NO:163)

wherein each of $x^1, x^4, x^6, x^{12}, x^{16}, x^{18}, x^{19}$ may individually be any residue, each of x^3 x^{14} and x^{17} may individually be any aromatic amino acid residue, x^5 may be P, hP, dhP, or BnHP.

each of x^9 and X^{11}may individually be any residue comprising a nucleophilic or electrophilic side chain, x^{13} may be selected from the group consisting of L, HL, Nva, I, HchA, HF, and ThA, x^{20} may be any residue, or may be absent when x^{22} and x^{21} are absent, x^{21} may be any residue, or may be absent when x^{22} is absent, x^{22} may be any residue, or absent. Compounds 22, 24, 29, 30, 31, 32, 33, 44, 45, 56, 57, 58, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 34, 35, and 42 in Table 7 exemplify aspects of the invention covered by this formula.

x^1 may be Q. x^1 may be T. x^1 may be S. x^1 may be R. x^1 may be H. x^3 may be F. x^3 may be Y. x^3 may be W. x^3 may be BPA. x^3 may be CF. x^3 may be or NF. x^4 may be Q. x^4 may be M. x^4 may be E. x^4 may be K. x^5 may be P. x^5 may be HP. x^5 may be DHP. x^5 may be BnHP. x^6 may be M. x^6 may be L. x^6 may be I.x^9 may be L. x^9 may be I. x^9 may be TA. x^9 may be ThA. x^9 may be K. x^9 may be AcK. x^{11} may be Q. x^{11} may be N. x^{11} may be C. x^{11} may be K. x^{11} may be AcK. x^{11} may be Dab. x^{11} may be Dap. x^{12} may be T. x^{12} may be R. x^{12} may be K. x^{13} may be L. x^{13} may be HL. x^{13} may be Nva. x^{13} may be I. x^{13} may be HchA. x^{13} may be HF. x^{13} may be ThA. In some embodiments, x^{13} may be selected from the group consisting of L, HL, Nva, I, HchA, HF, and ThA. In some embodiments, x^{13} may be selected from the group consisting of L, HL, and Nva. x^{14} may be F. x^{14} may be Y. $x1^4$ may be W. x^{14} may be BPA. x^{14} may be CF. x^{14} may be or NF. x^{16} may be Q. x^{16} may be N. x^{17} may be F. x^{17} may be Y. x^{17} may be W. x^{17} may be BPA. X^{17} may be CF. x^{17} may be or NF. x^{18} may be M. x^{19} may be L. x^{19} may be I. x^{20} may be Q. x^{20} may be N. x^{21} may be Q. x^{21} may be N. x^{22} may be G.

In some embodiments, the present invention provides a targeting agent comprising a peptide comprising a sequence substantially homologous to:

x^1 **N** x^3 x^4 x^5 x^6 **D E** x^9 **D** x^{11} x^{12} x^{13} x^{14} **D** x^{16} x^{17} x^{18} x^{19} x^{20} x^{21} x^{22} (SEQ ID NO:164)

wherein

each of x^1, x^4, x^6, x^{12}, x^{16}, x^{18}, x^{19} may individually be any residue, each of x^3 x^{14} and x^{17} may individually be any aromatic amino acid residue, x^5 may be P, hP, dhP, or BnHP, each of x^9 and x^{11}may individually be any residue comprising a nucleophilic or electrophilic side chain, x^{13} may be selected from the group consisting of L, HL, Nva, I, HchA, HF, and ThA, x^{20} may be any residue, or may be absent when x^{22} and x^{21} are absent, x^{21} may be any residue, or may be absent when x^{22} is absent, x^{22} may be any residue, or absent. Compounds 23, 25, 28, 56, 57, and 58 in Table 7 exemplify these aspects of the invention.

x^1 may be Q. x^1 may be T. x^1 may be S. x^1 may be R. x^1 may be H. x^3 may be F. x^3 may be Y. x^3 may be W. x^3 may be BPA. x^3 may be CF. x^3 may be or NF. x^4 may be Q. x^4 may be M. x^4 may be E. x^4 may be K. x^5 may be P. x^5 may be HP. x^5 may be DHP. x^5 may be BnHP. x^6 may be M. x^6 may be L. x^6

may be I. x^9 may be L. x^9 may be I. x^9 may be TA. x^9 may be ThA. x^9 may be K. x^9 may be AcK. x^{11} may be Q. x^{11} may be N. x^{11} may be C. x^{11} may be K. x^{11} may be AcK. x^{11} may be Dab. X^{11} may be Dap. x^{12} may be T. x^{12} may be R. x^{12} may be K. x^{13} may be L. x^{13} may be HL. x^{13} may be Nva. x^{13} may be I. x^{13} may be HchA. x^{13} may be HF. x^{13} may be ThA. In some embodiments, x^{13} may be selected from the group consisting of L, HL, Nva, I, HchA, HF, and ThA. In some embodiments, x^{13} may be selected from the group consisting of L, HL, and Nva. x^{14} may be F. x^{14} may be Y. $x1^4$ may be W. x^{14} may be BPA. X^{14} may be CF. x^{14} may be or NF. x^{16} may be Q. x^{16} may be N. x^{17} may be F. x^{17} may be Y. x^{17} may be W. x^{17} may be BPA. X^{17} may be CF. x^{17} may be or NF. x^{18} may be M. x^{19} may be L. x^{19} may be I. x^{20} may be Q. x^{20} may be N. x^{21} may be Q. x^{21} may be N. x^{22} may be G.

In some embodiments, the present invention provides a targeting agent comprising a peptide comprising a sequence substantially homologous to:

$x^1\ x^2\ x^3\ x^4\ x^5\ x^6$ **D E** x^9 **D K** $x^{12}\ x^{13}\ x^{14}$ **D** $x^{16}\ x^{17}\ x^{18}\ x^{19}\ x^{20}\ x^{21}\ x^{22}$ (SEQ ID NO:165)

wherein each of x^1, x^2, x^4, x^6, x^{12}, x^{16}, x^{18}, x^{19} may individually be any residue, each of x^3 x^{14} and x^{17} may individually be any aromatic amino acid residue, x^5 may be P, hP, dhP, or BnHP x^9 and may be any residue, and may be selected from the group L, I, K, ThA, and AcK, x^{13} may be selected from the group consisting of L, HL, Nva, I, HchA, HF, and ThA, x^{20} may be any residue, or may be absent when x^{22} and x^{21} are absent, x^{21} may be any residue, or may be absent when x^{22} is absent, x^{22} may be any residue, or absent.

x^1 may be Q. x^1 may be T. x^1 may be S. x^1 may be R. x^1 may be H. x^2 may be K. x^2 may be N. x^2 may be R. x^2 may be H. x^2 may be AcK. x^2 may be Nick. x^2 may be CbcK. In some embodiments, x^2 may be selected from the group consisting of K, N, R, H, AcK, Nick, or CbcK. X^2 may be selected from the group consisting of N, R, H, AcK, Nick, or CbcK. X^2 may be selected from the group consisting of R, H, AcK, Nick, or CbcK. X^2 may be selected from the group consisting of R, H, AcK, or CbcK. X^2 may be selected from the group consisting of R, H, or AcK. x^3 may be F. x^3 may be Y. x^3 may be W. x^3 may be BPA. x^3 may be CF. x^3 may be or NF. x^4 may be Q. x^4 may be M. x^4 may be E. x^4 may be K. x^5 may be P. x^5 may be HP. x^5 may be DHP. x^5 may be BnHP. x^6 may be M. x^6 may be L. x^6 may be I.x^9 may be L. x^9 may be I. x^9 may be TA. x^9 may be ThA. x^9 may be K. x^9 may be AcK. x^{12} may be T. x^{12} may be R. x^{12} may be K. x^{13} may be L. x^{13} may be HL. x^{13} may be Nva. x^{13} may be I. x^{13} may be HchA. x^{13} may be HF. x^{13} may be ThA. In some embodiments, x^{13} may be selected from the group consisting of L, HL, Nva, I, HchA, HF, and ThA. In some embodiments, x^{13} may be selected from the group consisting of L, HL, and Nva. x^{14} may be F. x^{14} may be Y. $x1^4$ may be W. x^{14} may be BPA. X^{14} may be CF. x^{14} may be or NF. x^{16} may be Q. x^{16} may be N. x^{17} may be F. x^{17} may be Y. x^{17}

may be W. x^{17} may be BPA. X^{17} may be CF. x^{17} may be or NF. x^{18} may be M. x^{19} may be L. x^{19} may be I. x^{20} may be Q. x^{20} may be N. x^{21} may be Q. x^{21} may be N. x^{22} may be G.

In some embodiments, the present invention provides a targeting agent comprising a peptide comprising a sequence substantially homologous to:

Q x^2 x^3 **Q** x^5 **L D E** x^9 **D** x^{11} **T** x^{13} x^{14} **D Q** x^{17} **M L Q Q G** (SEQ ID NO:166)

wherein

x^2 may be AcK, N, R, H, Nick, CbcK, each of x^3 x^{14} and x^{17} may individually be any aromatic amino acid residue, x^5 may be P, hP, dhP, or BnHP, x^9 may be any one of K, AcK, Ile, L or ThA, x^{11}may be any one of K, Dab, Dap,AcK, C, or R, x^{13} may be selected from the group consisting of L, HL, Nva, I, HchA, HF, and ThA.

x^2 may be K. x^2 may be N. x^2 may be R. x^2 may be H. x^2 may be AcK. x^2 may be Nick. x^2 may be CbcK. In some embodiments, x^2 may be selected from the group consisting of K, N, R, H, AcK, Nick, or CbcK. X^2 may be selected from the group consisting of N, R, H, AcK, Nick, or CbcK. X^2 may be selected from the group consisting of R, H, AcK, Nick, or CbcK. X^2 may be selected from the group consisting of R, H, AcK, or CbcK. X^2 may be selected from the group consisting of R, H, or AcK. x^3 may be F. x^3 may be Y. x^3 may be W. x^3 may be BPA. x^3 may be CF. x^3 may be NF. x^5 may be P. x^5 may be HP. x^5 may be DHP. x^5 may be BnHP.x^9 may be L. x^9 may be I. x^9 may be TA. x^9 may be ThA. x^9 may be K. x^9 may be AcK.x^{11} may be Q. x^{11} may be N. x^{11} may be C. x^{11} may be K. x^{11} may be AcK. x^{11} may be Dab.x^{13} may be L. x^{13} may be HL. x^{13} may be Nva. x^{13} may be I. x^{13} may be HchA. x^{13} may be HF. x^{13} may be ThA. In some embodiments, x^{13} may be selected from the group consisting of L, HL, Nva, I, HchA, HF, and ThA. In some embodiments, x^{13} may be selected from the group consisting of L, HL, and Nva. x^{14} may be F. x^{14} may be Y. $x1^4$ may be W. x^{14} may be BPA. X^{14} may be CF. x^{14} may be or NF. x^{17} may be F. x^{17} may be Y. x^{17} may be W. x^{17} may be BPA. X^{17} may be CF. x^{17} may be or NF.

In some embodiments, the present invention provides a targeting agent comprising a peptide comprising a sequence substantially homologous to:

Q x^2 x^3 **Q** x^5 **L D E** x^9 **D K T** x^{13} x^{14} **D Q** x^{17} **M L Q Q G** (SEQ ID NO:167)

wherein

x^2 may be any one of K, N, R, H, AcK, Nick, or CbcK. each of x^3 x^{14} and x^{17} may individually be any aromatic amino acid residue, x^5 may be P, hP, dhP, or BnHP x^9 may be any one of K, AcK, Ile, L or

ThA, x^{13} may be selected from the group consisting of L, HL, Nva, I, HchA, HF, and ThA. x^2 may be K. x^2 may be N. x^2 may be R. x^2 may be H. x^2 may be AcK. x^2 may be Nick. x^2 may be CbcK. In some embodiments, x^2 may be selected from the group consisting of K, N, R, H, AcK, Nick, or CbcK. X^2 may be selected from the group consisting of N, R, H, AcK, Nick, or CbcK. X^2 may be selected from the group consisting of R, H, AcK, Nick, or CbcK. X^2 may be selected from the group consisting of R, H, AcK, or CbcK. X^2 may be selected from the group consisting of R, H, or AcK.

x^3 may be F. x^3 may be Y. x^3 may be W. x^3 may be BPA. x^3 may be CF. x^3 may be or NF. x^5 may be P. x^5 may be HP. x^5 may be DHP. x^5 may be BnHP. x^9 may be L. x^9 may be I. x^9 may be TA. x^9 may be ThA. x^9 may be K. x^9 may be AcK.x^{13} may be L. x^{13} may be HL. x^{13} may be Nva. x^{13} may be I. x^{13} may be HchA. x^{13} may be HF. x^{13} may be ThA. In some embodiments, x^{13} may be selected from the group consisting of L, HL, Nva, I, HchA, HF, and ThA. In some embodiments, x^{13} may be selected from the group consisting of L, HL, and Nva.x^{14} may be F. x^{14} may be Y. $x1^4$ may be W. x^{14} may be BPA. X^{14} may be CF. x^{14} may be or NF. x^{17} may be F. x^{17} may be Y. x^{17} may be W. x^{17} may be BPA. X^{17} may be CF. x^{17} may be or NF.

In some embodiments, the present invention provides a targeting agent comprising a peptide comprising a sequence substantially homologous to:

Q AcK x^3 **Q** x^5 **L D E** x^9 **D K T** x^{13} x^{14} **D Q** x^{17} **M L Q Q G** (SEQ ID NO:168)

wherein

each of x^3 x^{14} and x^{17} may individually be any aromatic amino acid residue, x^5 may be P, hP, dhP, or BnHP x^9 may be any one of K, AcK, Ile, L or ThA, x^{13} may be selected from the group consisting of L, HL, Nva, I, HchA, HF, and ThA. x^3 may be F. x^3 may be Y. x^3 may be W. x^3 may be BPA. x^3 may be CF. x^3 may be or NF. x^5 may be P. x^5 may be HP. x^5 may be DHP. x^5 may be BnHP. x^9 may be L. x^9 may be I. x^9 may be TA. x^9 may be ThA. x^9 may be K. x^9 may be AcK. x^{13} may be L. x^{13} may be HL. x^{13} may be Nva. x^{13} may be I. x^{13} may be HchA. x^{13} may be HF. x^{13} may be ThA. In some embodiments, x^{13} may be selected from the group consisting of L, HL, Nva, I, HchA, HF, and ThA. In some embodiments, x^{13} may be selected from the group consisting of L, HL, and Nva. x^{14} may be F. x^{14} may be Y. $x1^4$ may be W. x^{14} may be BPA. X^{14} may be CF. x^{14} may be or NF. x^{17} may be F. x^{17} may be Y. x^{17} may be W. x^{17} may be BPA. X^{17} may be CF. x^{17} may be or NF.

In some embodiments, the present invention provides a targeting agent comprising a peptide comprising a sequence substantially homologous to:

Q N x^3 **Q** x^5 **L D E** x^9 **D K T** x^{13} x^{14} **D Q** x^{17} **M L Q Q G** (SEQ ID NO:169)

Wherein each of x^3 x^{14} and x^{17} may individually be any aromatic amino acid residue,

x^5 may be P, hP, dhP, or BnHP x^9 may be any one of K, AcK, Ile, L or ThA
x^{13} may be selected from the group consisting of L, HL, Nva, I, HchA, HF, and ThA.

In some embodiments, the present invention provides a targeting agent comprising a peptide comprising a sequence substantially homologous to:

$x^1\ x^2\ x^3\ x^4\ x^5\ x^6$ **D E** x^9 **D** $x^{11}\ x^{12}$ **L** x^{14} **D** $x^{16}\ x^{17}\ x^{18}\ x^{19}\ x^{20}\ x^{21}\ x^{22}$ (SEQ ID NO:170)

wherein
each of x^1, x^4, x^6, x^{12}, x^{16}, x^{18}, x^{19} may individually be any residue, x^2 may be AcK, N, R, H, Nick, CbcK, each of x^3 x^{14} and x^{17} may individually be any aromatic amino acid residue,
x^5 may be one of P, hP, dhP, or BnHP each of x^9 and x^{11}may individually be any residue comprising a nucleophilic or electrophilic side chain, x^{20} may be any residue, or may be absent when x^{22} and x^{21} are absent, x^{21} may be any residue, or may be absent when x^{22} is absent, x^{22} may be any residue, or absent.

In some embodiments, the present invention provides a targeting agent comprising a peptide comprising a sequence substantially homologous to:

x^1 **AcK** $x^3\ x^4\ x^5\ x^6$ **D E** x^9 **D** $x^{11}\ x^{12}$ **L** x^{14} **D** $x^{16}\ x^{17}\ x^{18}\ x^{19}\ x^{20}\ x^{21}\ x^{22}$ (SEQ ID NO:171)

wherein each of x^1, x^4, x^6, x^{12}, x^{16}, x^{18}, x^{19} may individually be any residue, each of x^3 x^{14} and x^{17} may individually be any aromatic amino acid residue, x^5 may be P, hP, dhP, or BnHP
each of x^9 and X^{11}may individually be any residue comprising a nucleophilic or electrophilic side chain, x^{20} may be any residue, or may be absent when x^{22} and x^{21} are absent, x^{21} may be any residue, or may be absent when x^{22} is absent, x^{22} may be any residue, or absent.
Compounds 22, 24, 29, 30, 33, 34, 35, 36, 37, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 54, 55, and 62 in Table 7 exemplify aspects of the invention covered by this formula.

In some embodiments, the present invention provides a targeting agent comprising a peptide comprising a sequence substantially homologous to:

x^1 **N** $x^3\ x^4\ x^5\ x^6$ **D E** x^9 **D** $x^{11}\ x^{12}$ **L** x^{14} **D** $x^{16}\ x^{17}\ x^{18}\ x^{19}\ x^{20}\ x^{21}\ x^{22}$ (SEQ ID NO:172)

wherein each of x^1, x^4, x^6, x^{12}, x^{16}, x^{18}, x^{19} may individually be any residue, each of x^3 x^{14} and x^{17} may individually be any aromatic amino acid residue, x^5 may be P, hP, dhP, or BnHP
each of x^9 and x^{11}may individually be any residue comprising a nucleophilic or electrophilic side chain, x^{20} may be any residue, or may be absent when x^{22} and x^{21} are absent, x^{21} may be any residue, or may be absent when x^{22} is absent, x^{22} may be any residue, or absent.
Compounds 23, 25, 28, 56, 57, and 58 in Table 7 exemplify aspects of the invention covered by this formula.

In some embodiments, the present invention provides a targeting agent comprising a peptide comprising a sequence substantially homologous to:

$x^1\ x^2\ x^3\ x^4\ x^5\ x^6$ **D E** x^9 **D K** x^{12} **L** x^{14} **D** $x^{16}\ x^{17}\ x^{18}\ x^{19}\ x^{20}\ x^{21}\ x^{22}$ (SEQ ID NO:173)

wherein each of x^1, x^4, x^6, x^{12}, x^{16}, x^{18}, x^{19} may individually be any residue, x^2 may be AcK, N, R, H, Nick, CbcK, each of x^3 x^{14} and x^{17} may individually be any aromatic amino acid residue, x^5 may be P, hP, dhP, or BnHP x^9 and may be any residue, and may be selected from the group L, I, K, ThA, and AcK, x^{20} may be any residue, or may be absent when x^{22} and x^{21} are absent, x^{21} may be any residue, or may be absent when x^{22} is absent, x^{22} may be any residue, or absent.

In some embodiments, the present invention provides a targeting agent comprising a peptide comprising a sequence substantially homologous to:

Q $x^2\ x^3$ **Q** x^5 **L D E** x^9 **D** x^{11} **T L** x^{14} **D Q** x^{17} **M L Q Q G** (SEQ ID NO:174)

Wherein x^2 may be AcK, N, R, H, Nick, CbcK, each of x^3 x^{14} and x^{17} may individually be any aromatic amino acid residue, x^5 may be P, hP, dhP, or BnHP, x^9 may be any one of K, AcK, Ile, L or ThA, x^{11} may be any one of K, Dab, AcK, C, or R,

In some embodiments, the present invention provides a targeting agent comprising a peptide comprising a sequence substantially homologous to:

Q $x^2\ x^3$ **Q** x^5 **L D E** x^9 **D K T L** x^{14} **D Q** x^{17} **M L Q Q G** (SEQ ID NO:175)

Wherein x^2 may be any one of K, N, R, H, AcK, Nick, or CbcK, each of x^3 x^{14} and x^{17} may individually be any aromatic amino acid residue, x^5 may be P, hP, dhP, or BnHP, x^9 may be any one of K, AcK, Ile, L or ThA,

In some embodiments, the present invention provides a targeting agent comprising a peptide comprising a sequence substantially homologous to:

Q AcK x^3 **Q** x^5 **L D E** x^9 **D K T L** x^{14} **D Q** x^{17} **M L Q Q G** (SEQ ID NO:176)

Wherein, each of x^3 x^{14} and x^{17} may individually be any aromatic amino acid residue, x^5 may be P, hP, dhP, or BnHP, x^9 may be any one of K, AcK, Ile, L or ThA,

In some embodiments, the present invention provides a targeting agent comprising a peptide comprising a sequence substantially homologous to:

Q N x^3 **Q** x^5 **L D E** x^9 **D K T L** x^{14} **D Q** x^{17} **M L Q Q G** (SEQ ID NO:177)

Wherein each of x^3 x^{14} and x^{17} may individually be any aromatic amino acid residue, x^5 may be P, hP, dhP, or BnHP, x^9 may be any one of K, AcK, Ile, L or ThA.

Compounds of the invention may comprise an amino-terminus (N-terminus) capping group or a carboxy-terminus (C-terminus) capping group. The N-terminus capping group may be "ac": $C(O)CH_3$) (e.g. compounds 21, 22, 23, 24, 25, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40,41, 42, 43, 44, 45, 46, 47, 48, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63 in Table 7). Compounds of the invention may comprise a DCB group as N-terminus capping group (e.g. compound 49 in Table 7). Compounds of the invention may comprise a DFB group as N-terminus capping group (e.g. compound 50 in Table 7). Compounds of the invention may comprise a PyC group as N-terminus capping group (e.g compound 51 in Table 7). Compounds of the invention may comprise a 2-PEG group as N-terminus capping group (e.g. compound 52 in Table 7). The C-terminus capping group may be "am": NH_2.

In some embodiments, the present invention provid an Angiopoietin receptor-antagonist (AA) targeting agent comprising a peptide comprising a sequence substantially homologous to:

Q^1 x^2 Y^3 Q^4 x^5 L^6 D^7 E^8 x^9 D^{10} x^{11} T^{12} x^{13} x^{14} x^{15} x^{16} F^{17} x^{18} x^{19} Q^{20} Q^{21} G^{22} (SEQ ID NO:178)
wherein
x^2 is selected from the group consisting of K, N, R, H, AcK, Nick, CbcK and a linking residue, and x^5 is selected from the group consisting of P, hP, dhP, or BnHP, and x^9 is selected from the group consisting of L, I, ThA, AcK and a linking residue, and x^{11} is selected from the group consisting of Q, N, C, K, AcK, Dab, Dap and a linking residue, and x^{13} is selected from the group consisting of L, HL, Nva, I, HchA, HF, ThA and a linking residue, and x^{14} is selected from the group consisting of aromatic residues and a linking residue, and x^{15} is selected from the group consisting of D and a linking residue, and x^{16} is selected from the group consisting of Q, N and a linking residue, and x^{18} is selected from the group consisting of M and a linking residue, and x^{19} is selected from the group consisting of L, I and a linking residue, and wherein one of Q^1, x^9, x^{11}, x^{13}, x^{15}, x^{16}, x^{18}, x^{19} and G^{22} is a linking residue comprising a nucleophilic side chain covalently linkable to the combining site of an antibody directly or via an intermediate linker, the linking residue being selected from the group comprising K, R, Y,C, T, and S, or the N-terminus or C-terminus.

In some embodiments, the present invention provid an Angiopoietin receptor-antagonist (AA) targeting agent comprising a peptide comprising a sequence substantially homologous to:

Q^1 x^2 Y^3 Q^4 x^5 L^6 D^7 x^8 x^9 D^{10} x^{11} x^{12} x^{13} x^{14} x^{15} x^{16} F^{17} x^{18} x^{19} Q^{20} Q^{21} G^{22} (SEQ ID NO:193)
wherein

x^2 is selected from the group consisting of K, N, R, H, AcK, Nick, CbcK and a linking residue, and x^5 is selected from the group consisting of P, hP, dhP, or BnHP, and x^8 is E or a linking residue, x^9 is selected from the group consisting of L, I, ThA, AcK and a linking residue, and x^{11} is selected from the group consisting of Q, N, C, K, AcK, Dab, Dap and a linking residue, and x^{12} is T or a linking residue, and x^{13} is selected from the group consisting of L, HL, Nva, I, HchA, HF, ThA, and x^{14} is selected from the group consisting of aromatic residues and a linking residue, and x^{15} is selected from the group consisting of D and a linking residue, and x^{16} is selected from the group consisting of Q, N and a linking residue, and x^{18} is selected from the group consisting of M and a linking residue, and x^{19} is selected from the group consisting of L, I and a linking residue, and wherein one of Q^1, x^9, x^8, x^{11}, x^{12}, x^{15}, x^{16}, x^{18}, x^{19} and G^{22} is a linking residue comprising a nucleophilic side chain covalently linkable to the combining site of an antibody directly or via an intermediate linker, the linking residue being selected from the group comprising K, R, Y,C, T, S, Dap, Dab, homologs of S, homologs of C, homologs of K, or the N-terminus or C-terminus.

The linking residue may be selected from the group consisting of K, Y, T, Dap, and Dab.The linking residue may be located at one of X^9, X^{11}, X^{12}, X^{15}, X^{16}, X^{18} and X^{19}. In some embodiments, X^{11} is the linking residue. TABLEs 7 and 8 provide examples of compounds of the invention covalently linked to the combining site of h38C2 at different linging residues.

x^2 may be selected from the group consisting of K, N, AcK. Exemplary compounds of the invention where x2 is N are 23, 25, 28, 56, 57 and 58. Exemplary compounds of the invention where x2 is AcK are 22, 24, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 43(a), 44, 45, 46, 47, 48, 49, 50, 51, 52, 54, 55, 62, 63, 64, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, and 91

x^5 may be selected from the group consisting of P, hP, and dhP. Exemplary compounds of the invention where x5 is P are 21, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 35, 36, 37, 38, 39, 40, 41, 42, 43, 43(a), 44, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, and 91.Exemplary compounds of the invention where x5 is HP are 35, 45, 46, and 47.Exemplary compounds of the invention where x5 is DHP is 34.

x^8 may be E.

x^{11} may be selected from the group consisting of K, AcK, Dab and Dap. Exemplary compounds of the invention where x^{11} is AcK are 30 and 32. Exemplary compounds of the invention where x^{11} is Dab are 54. Exemplary compounds of the invention where x^{11} is Dap are 55.

X^{12} may be T.

x^{13} may be selected from the group consisting of K, L, HL, Nva, and I. Exemplary compounds of the invention where $x^{13}$is K are 31 and 32 Exemplary compounds of the invention where x^{13} is HL are 42. Exemplary compounds of the invention where x^{13} is Nva are 41. Exemplary compounds of the invention where x^{13} is I are 36.

x^{14} may be selected from the group consisting of F, Y, W, BPA, CF, and NF. Exemplary compounds of the invention where x^{14} is F are 44. Exemplary compounds of the invention where x^{14} is BPA are 46 and 56. Exemplary compounds of the invention where x^{14} is CF are 47, 57 and 62. Exemplary compounds of the invention where x^{14} is NF are 45, 48 and 58.

AA targeting agents of the invention may comprise a peptide comprising a sequence substantially homologous to one or more compounds selected from the group consisting of: 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 43(a) 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, and 91

AA targeting agents of the invention may comprise a peptide comprising a sequence substantially homologous to one or more compounds selected from the group consisting of: 24, 25, 26, 27, 28, 29, 30, 34, 35, 37, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 54, 55, 56, 57, 58, 59, 60, 61, 62, 75, 76, 77, 78, and 79.

AA targeting agents of the invention may comprise a peptide comprising a sequence substantially homologous to one or more compounds selected from the group consisting of: 24, 25, 27, 28, 29, 30, 34, 35, 37, 41, 42, 43, 44, 45, 46, 47, 48, 56, 57, 58, 60, 62, 75, 76, 77, 78, and 79.

AA targeting agents of the invention may comprise a peptide comprising a sequence substantially homologous to one or more compounds selected from the group consisting of: 22, 34, 41, 43, 44, 48 and 91.

AA targeting agents of the invention may comprise a peptide comprising a sequence substantially homologous to one or more compounds selected from the group consisting of: 27, 28, 29, 43, 45, and 48.

The compounds of the invention are useful in targeting Ang2 and demonstrate advantageous properties over existing Ang2-targeting agents. In some aspects of the invention, advantageous agents and compounds of the invention provide an attractive balance between half-life and IC50 values.

In some embodiments of the invention at least one residue of x^9 and x^{11} is a linking residue comprising an amino acid whose side chain is capable covalently bonding to chemical groups comprising electrophiles or nucleophiles respectively.

The presence of the linking residue provides the targeting agents of the invention with great flexibility for linkages to scaffolds, macromolecules and other moieties. In particular, the compounds of the invention may be reliably, securely and efficiently covalently linked to scaffolds, such as an antibody. Surprisingly, it has been found that locating the linking residue at certain key positions in the peptide leads to increased stability and/or binding of the peptide.

The linking residue is an amino acid residue available for covalent bonding through the amino terminus, the carboxy terminus, or the side chain of the linking residue. The linking residue may be K. In other embodiments, the linking residue may be Y. In other embodiments, the linking residue may be T. The linking residue may be Dab. The linking residue may be Dap. In some embodiments, the linking residue is selected from the group consisting of K, Dab, Dap, Y, and T.

In other embodiments, the linking residue may be C. The linking residue may be R. The linking residue may be S. The linking residue may be N. The linking residue may be Q. The linking residue may be D. The linking residue may be E.

The linking residue may be any one residue. In some embodiments, the linking residue may be x^9. The linking residue may be x^{11}. In some embodiments, using the side chain of lysine and modified lysine residues as the linking residue has been found to provide certain advantages, including permitting specific, reliable, directional and efficient chemical covalent linkages at that location.

Refering to the foregoing formulae (SEQ ID NOs: 161-178, and SEQ ID NO: 193) and more generally:

x^1 may be Q. x^1 may be T. x^1 may be S. x^1 may be R. x^1 may be H. x^2 may be N. x^2 may be R. x^2 may be H. x^2 may be AcK. x^2 may be Nick. x^2 may be CbcK. In some embodiments, x^2 may be selected from the group consisting of K, N, R, H, AcK, Nick, or CbcK. X^2 may be selected from the group consisting of N, R, H, AcK, Nick, or CbcK. X^2 may be selected from the group consisting of R, H, AcK, Nick, or CbcK. X^2 may be selected from the group consisting of R, H, AcK, or CbcK. X^2 may be selected from the group consisting of R, H, or AcK. In some embodiments of the invention comprising linkers and antibodies, x^2 may be K.x^3 may be F. x^3 may be Y. x^3 may be W. x^3 may be BPA. x^3 may be CF. x^3 may be or NF. x^4 may be Q. x^4 may be M. x^4 may be E. x^4 may be K. x^6 may be M. x^6 may be L. x^6 may be I.x^8 may be E. x^8 may be D.X^9 may be L. x^9 may be I. X^9 may be TA. X^9 may be ThA. X^9 may be K. X^9 may be AcK. X^9 may be a linking residue.x^{10} may be E. x^{10} may be D.x^{11} may be Q. X^{11} may be N. X^{11} may be C. X^{11} may be K. X^{11} may be AcK. X^{11} may be Dab. X^{11}

may be Dap.X^{11} may be a linking residue.x^{12} may be T. x^{12} may be R. x^{12} may be K. x^{13} may be L. x^{13} may be HL. x^{13} may be Nva. x^{13} may be I. x^{13} may be HchA. x^{13} may be HF. x^{13} may be ThA. In some embodiments, x^{13} may be selected from the group consisting of L, HL, Nva, I, HchA, HF, and ThA. In some embodiments, x^{13} may be selected from the group consisting of L, HL, and Nva.x^{14} may be F. x^{14} may be Y. x^{14} may be W. x^{14} may be BPA. X^{14} may be CF. x^{14} may be or NF. x^{15} may be D. x^{15} may be E.x^{16} may be Q. x^{16} may be N. x^{17} may be F. x^{17} may be Y. x^{17} may be W. x^{17} may be BPA. X^{17} may be CF. x^{17} may be or NF. x^{18} may be M.x^{19} may be L. x^{19} may be I. x^{20} may be Q. x^{20} may be N. x^{21} may be Q. x^{21} may be N.x^{22} may be G.

In some aspects of the invention, AA targeting agents of the invention may comprise any Angiopoietin 2 antagonist.

In some aspects of the invention, AA targeting agents of the invention may comprise a peptide comprising a sequence substantially homologous to one or more sequences selected from the group consisting of: SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, SEQ ID NO:127, SEQ ID NO:128, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:131, SEQ ID NO:132, SEQ ID NO:133, SEQ ID NO:134, SEQ ID NO:135, SEQ ID NO:136, SEQ ID NO:137, SEQ ID NO:138, SEQ ID NO:139, SEQ ID NO:140, SEQ ID NO:141, SEQ ID NO:142, SEQ ID NO:143, SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146, SEQ ID NO:147, SEQ ID NO:148, SEQ ID NO:149, SEQ ID NO:150, SEQ ID NO:151, SEQ ID NO:152,

SEQ ID NO:153, SEQ ID NO:154, SEQ ID NO:155, SEQ ID NO:156, SEQ ID NO:157, SEQ ID NO:158, SEQ ID NO:159, SEQ ID NO:160, SEQ ID NO:161, SEQ ID NO:162, SEQ ID NO:163, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:166, SEQ ID NO:167, SEQ ID NO:168, SEQ ID NO:169, SEQ ID NO:170, SEQ ID NO:171, SEQ ID NO:172, SEQ ID NO:173, SEQ ID NO:174, SEQ ID NO:175, SEQ ID NO:176, SEQ ID NO:177, SEQ ID NO:178, SEQ ID NO:191, SEQ ID NO:192, and SEQ ID NO: 193.

In some aspects, the invention provides an AA targeting agent selected from the group consisting of:

R^1-Q(AcK)Y QPL DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:29)

R^1-QNY QPL DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:28)

R^1-Q(AcK)Y QPL DEK D(AcK)T LYD QFM LQQ G- R^2; (SEQ ID NO:30)

R^1-Q(AcK)Y QPL DEK DET LYD QFM LQQ G- R^2; (SEQ ID NO:33)

R^1-Q(AcK)Y Q(DHP)L DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:34)

R^1-Q(AcK)Y Q(HP)L DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:35)

R^1-Q(AcK)Y QPL DEL DKT IYD QFM LQQ G- R^2; (SEQ ID NO:36)

R^1-Q(AcK)Y QPL DEI DKT LYD QFM LQQ G- R^2; (SEQ ID NO:37)

R^1-Q(AcK)Y QPL DEL DKT (HChA)YD QFM LQQ G- R^2; (SEQ ID NO:38)

R^1-Q(AcK)Y QPL DEL DKT (HF)YD QFM LQQ G- R^2; (SEQ ID NO:39)

R^1-Q(AcK)Y QPL DEL DKT (ThA)YD QFM LQQ G- R^2; (SEQ ID NO:40)

R^1-Q(AcK)Y QPL DEL DKT (Nva)YD QFM LQQ G- R^2; (SEQ ID NO:41)

R^1-Q(AcK)Y QPL DEL DKT (HL)YD QFM LQQ G- R^2; (SEQ ID NO:42)

R^1-Q(AcK)Y QPL DE(AcK) DKT LYD QFM LQQ G- R^2; (SEQ ID NO:43)

R^1-Q(AcK)Y QPL DEL DKT LFD QFM LQQ G- R^2; (SEQ ID NO:44)

R^1-Q(AcK)Y Q(HP)L DE(ThA) DKT L(NO2F)D QFM LQQ G- R^2; (SEQ ID NO:45)

R^1-Q(AcK)Y Q(HP)L DE(ThA) DKT L(BPA)D QFM LQQ G- R^2; (SEQ ID NO:46)

R^1-Q(AcK)Y Q(HP)L DE(ThA) DKT L(CO2H)FD QFM LQQ G- R^2; (SEQ ID NO:47)

R^1-Q(AcK)Y QPL DE(AcK) DKT L(NO2F)D QFM LQQ G- R^2; (SEQ ID NO:48)

R^1-Q(AcK)Y QPL DE(AcK) DKT LFD QFM LQQ G- R^2 (SEQ ID NO:63)

DCB-Q(AcK)Y QPL DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:49)

DFB-Q(AcK)Y QPL DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:50)

PyC-Q(AcK)Y QPL DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:51)

Amido 2-PEG-Q(AcK)Y QPL DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:52)

R^1-Q(ClBnCarbamateK)Y QPL DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:53)

R^1-Q(AcK)Y QPL DEL D(Dab)T LYD QFM LQQ G- R^2; (SEQ ID NO:54)

R^1-Q(AcK)Y QPL DEL D(Dap)T LYD QFM LQQ G- R^2; (SEQ ID NO:55)

R^1-Q(AcK)Y QPL DEL DKT L(NO2F)D QFM LQQ G-R^2; (SEQ ID NO:91)

R^1-QNY QPL DEL DKT L(BPA)D QFM LQQ G-R^2; (SEQ ID NO:56)

R^1-QNY QPL DEL DKT L(CF)D QFM LQQ G-R^2; (SEQ ID NO:57)

R^1-Q(Nick)Y QPL DEL DKT LYD QFM LQQ G-R^2; (SEQ ID NO:61)

R^1-Q(AcK)Y QPL DE(AcK) DKT L(CF)D QFM LQQ G-R^2; (SEQ ID NO:62) and

R^1-Q(AcK)Y QPL DE(AcK) DKT LFD QFM LQQ G-R^2; (SEQ ID NO: 63)

wherein

R^1 is CH_3, $C(O)CH_3$, $C(O)CH_3$, $C(O)CH_2CH_3$, $C(O)CH_2CH_2CH_3$, $C(O)CH(CH_3)CH_3$, $C(O)CH_2CH_2CH_2CH_3$, $C(O)CH(CH_3)CH_2CH_3$, $C(O)C_6H_5$, $C(O)CH_2CH_2(CH_2CH_2O)_{1\text{-}5}Me$, dichlorobenzoyl (DCB), difluorobenzoyl (DFB), pyridinyl carboxlate (PyC) or amido-2-PEG, an amino protecting group, a lipid fatty acid group or a carbohydrate; and

R^2 is OH, NH_2, $NH(CH_3)$, $NHCH_2CH_3$, $NHCH_2CH_2CH_3$, $NHCH(CH_3)CH_3$, $NHCH_2CH_2CH_2CH_3$, $NHCH(CH_3)CH_2CH_3$, NHC_6H_5, $NHCH_2CH_2OCH_3$, $NHOCH_3$, $NHOCH_2CH_3$, a carboxy protecting group, a lipid fatty acid group or a carbohydrate.

In some aspects, the invention provides an AA targeting agent-linker conjugate having Formula I:

L – [AA targeting agent] (I)

wherein:

[AA targeting agent] is a peptide selected from the group consisting of:

R^1-QKY QPL DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:21)

R^1-Q(AcK)Y QPL DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:22)

R^1-QNY QPL DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:23)

R^1-Q(AcK)Y QPL DEK D(AcK)T LYD QFM LQQ G- R^2; (SEQ ID NO:30)

R^1-Q(AcK)Y QPL DEK DET LYD QFM LQQ G- R^2; (SEQ ID NO:33)

R^1-Q(AcK)Y Q(DHP)L DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:34)

R^1-Q(AcK)Y Q(HP)L DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:35)

R^1-Q(AcK)Y QPL DEL DKT IYD QFM LQQ G- R^2; (SEQ ID NO:36)

R^1-Q(AcK)Y QPL DEI DKT LYD QFM LQQ G- R^2; (SEQ ID NO:37)

R^1-Q(AcK)Y QPL DEL DKT (HChA)YD QFM LQQ G- R^2; (SEQ ID NO:38)

R^1-Q(AcK)Y QPL DEL DKT (HF)YD QFM LQQ G- R^2; (SEQ ID NO:39)

R^1-Q(AcK)Y QPL DEL DKT (ThA)YD QFM LQQ G- R^2; (SEQ ID NO:40)

R^1-Q(AcK)Y QPL DEL DKT (Nva)YD QFM LQQ G- R^2; (SEQ ID NO:41)

R^1-Q(AcK)Y QPL DEL DKT (HL)YD QFM LQQ G- R^2; (SEQ ID NO:42)

R^1-Q(AcK)Y QPL DE(AcK) DKT LYD QFM LQQ G- R^2; (SEQ ID NO:43)

R^1-Q(AcK)Y QPL DEL DKT LFD QFM LQQ G- R^2; (SEQ ID NO:44)

R^1-Q(AcK)Y Q(HP)L DE(ThA) DKT L(NO2F)D QFM LQQ G- R^2; (SEQ ID NO:45)

R^1-Q(AcK)Y Q(HP)L DE(ThA) DKT L(BPA)D QFM LQQ G- R^2; (SEQ ID NO:46)

R^1-Q(AcK)Y Q(HP)L DE(ThA) DKT L(CO2H)FD QFM LQQ G- R^2; (SEQ ID NO:47)

R^1-Q(AcK)Y QPL DE(AcK) DKT L(NO2F)D QFM LQQ G- R^2; (SEQ ID NO:48)

R^1-Q(AcK)Y QPL DE(AcK) DKT LFD QFM LQQ G- R^2; (SEQ ID NO:68)

DCB-Q(AcK)Y QPL DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:49)

DFB-Q(AcK)Y QPL DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:50)

PyC-Q(AcK)Y QPL DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:51)

Amido 2-PEG-Q(AcK)Y QPL DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:52)

R^1-Q(ClBnCarbamateK)Y QPL DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:53)

R^1-Q(AcK)Y QPL DEL D(Dab)T LYD QFM LQQ G- R^2; (SEQ ID NO:54)

R^1-Q(AcK)Y QPL DEL D(Dap)T LYD QFM LQQ G- R^2; (SEQ ID NO:55)

R^1-Q(AcK)Y QPL DEL DKT L(NO2F)D QFM LQQ G-R^2; (SEQ ID NO:91)

R^1-QNY QPL DEL DKT L(BPA)D QFM LQQ G-R^2; (SEQ ID NO:56)

R^1-QNY QPL DEL DKT L(CF)D QFM LQQ G-R^2; (SEQ ID NO:57)

R^1-QNY QPL DEL DKT LYD QFM LQQ G-R^2; (SEQ ID NO:58)

R^1-Q(Nick)Y QPL DEL DKT LYD QFM LQQ G-R^2; (SEQ ID NO:61)

R^1-Q(AcK)Y QPL DE(AcK) DKT L(CF)D QFM LQQ G-R^2; (SEQ ID NO:62) and

R^1-Q(AcK)Y QPL DE(AcK) DKT LFD QFM LQQ G-R^2; (SEQ ID NO:63) wherein

R^1 refers to the amino group portion of the amino terminus residue of a targeting agent and is NH_2, $NHC(O)CH_3$, $NHC(O)CH_2CH_3$, $NHC(O)CH_2CH_2CH_3$, $NHC(O)CH(CH_3)CH_3$, $NHC(O)CH_2CH_2CH_2CH_3$, $NHC(O)CH(CH_3)CH_2CH_3$, $NHC(O)C_6H_5$, $NH(CH_3)C(O)CH_2CH_2(CH_2CH_2O)_{1-5}Me$, an amino protecting group, a lipid fatty acid group or a carbohydrate;

R^2 refers to the carboxy terminus portion of the carboxy terminus residue of a targeting agent and is COOH, $C(O)NH_2$, $C(O)NH(CH_3)$, $C(O)NHCH_2CH_3$, $C(O)NHCH_2CH_2CH_3$, $C(O)NHCH(CH_3)CH_3$, $C(O)NHCH_2CH_2CH_2CH_3$, $C(O)NHCH(CH_3)CH_2CH_3$, $C(O)NHC_6H_5$, $C(O)NHCH_2CH_2OCH_3$,$C(O)NHOCH_3$, $C(O)NHOCH_2CH_3$, a carboxy protecting group, a lipid fatty acid group or a carbohydrate; and

L is a linker moiety having the formula -X-Y-Z, wherein:

X is optionally present, and is a biologically compatible polymer, block copolymer C, H, N, O, P, S, halogen (F, Cl, Br, I), or a salt thereof, alkyl, alkenyl, alkynyl, oxoalkyl, oxoalkenyl, oxoalkynyl, aminoalkyl, aminoalkenyl, aminoalkynyl, sulfoalkyl, sulfoalkenyl, sulfoalkynyl, phosphoalkyl, phosphoalkenyl, or phosphoalkynyl group, attached to one of the residues that comprises an AA targeting agent;

Y is an optionally present recognition group comprising at least a ring structure; and

Z is a reactive group that is capable of covalently linking to a side chain in a combining site of an antibody; and

pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, and prodrugs thereof.

In describing aspects of the invention as above, the initial NH group or R^1 is provided by the N-terminal amino-acid residue of the peptide in question: thus, $NHC(O)CH_3$ represents a $C(O)CH_3$ group covalently bonded to the N-terminus of the peptide, and may elsewhere throughout this specification and claims be written as $C(O)CH_3$, and so on. Accordingly, R^1 may be written as:

R^1 is CH_3, $C(O)CH_3$, $C(O)CH_3$, $C(O)CH_2CH_3$, $C(O)CH_2CH_2CH_3$, $C(O)CH(CH_3)CH_3$, $C(O)CH_2CH_2CH_2CH_3$, $C(O)CH(CH_3)CH_2CH_3$, $C(O)C_6H_5$, $C(O)CH_2CH_2(CH_2CH_2O)_{1-5}Me$, dichlorobenzoyl (DCB), difluorobenzoyl (DFB), pyridinyl carboxlate (PyC) or amido-2-PEG, an amino protecting group, a lipid fatty acid group or a carbohydrate; and

Similarily, in describing aspects of the invention as above, the initial C(O) group of R^2 is provided by the C-terminal amino-acid residue of the peptide in question: thus, $C(O)NH_2$represents a NH_2 group covalently bonded to the C-terminus of the peptide, and may elsewherwe be written as NH_2, and so on. Accordingly, R^2 may be written as:

R^2 is OH, NH_2, $NH(CH_3)$, $NHCH_2CH_3$, $NHCH_2CH_2CH_3$, $NHCH(CH_3)CH_3$, $NHCH_2CH_2CH_2CH_3$, $NHCH(CH_3)CH_2CH_3$, NHC_6H_5, $NHCH_2CH_2OCH_3$, $NHOCH_3$, $NHOCH_2CH_3$, a carboxy protecting group, a lipid fatty acid group or a carbohydrate.

In the listed peptide sequences, non-standard amino acid residues are enclosed within parentheses. In some cases, the amino terminus of a peptide is attached to one of the following capping groups: dichlorobenzoyl (DCB), difluorobenzoyl (DFB), pyridinyl carboxlate (PyC) or amido-2-PEG.

In other aspects, the invention provides compounds according to:

A compound having the formula selected from the group consisting of:

R^1-Q(AcK)Y QPL DEL DK(L)T LYD QFM LQQ G-R^2 (SEQ ID NO:132);

R^1-Q(AcK)Y QPL DEL DK(L)T L(NO2F)D QFM LQQ G- R^2; (SEQ ID NO:133)

R^1-Q(AcK)Y QPL DEK(L) DK(Ac)T LYD QFM LQQ G-R^2 (SEQ ID NO:134); and

R^1-Q(AcK)Y QPL DEK(Ac) DK(L)T LYD QFM LQQ G-R^2 (SEQ ID NO:135);

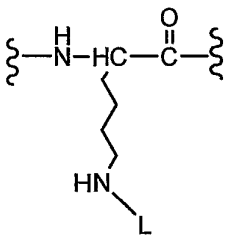
wherein

R^1 is CH_3, $C(O)CH_3$, $C(O)CH_3$, $C(O)CH_2CH_3$, $C(O)CH_2CH_2CH_3$, $C(O)CH(CH_3)CH_3$, $C(O)CH_2CH_2CH_2CH_3$, $C(O)CH(CH_3)CH_2CH_3$, $C(O)C_6H_5$, $C(O)CH_2CH_2(CH_2CH_2O)_{1-5}Me$, dichlorobenzoyl (DCB), difluorobenzoyl (DFB), pyridinyl carboxlate (PyC) or amido-2-PEG, an amino protecting group, a lipid fatty acid group or a carbohydrate; and

R^2 is OH, NH_2, $NH(CH_3)$, $NHCH_2CH_3$, $NHCH_2CH_2CH_3$, $NHCH(CH_3)CH_3$, $NHCH_2CH_2CH_2CH_3$, $NHCH(CH_3)CH_2CH_3$, NHC_6H_5, $NHCH_2CH_2OCH_3$, $NHOCH_3$, $NHOCH_2CH_3$, a carboxy protecting group, a lipid fatty acid group or a carbohydrate, and

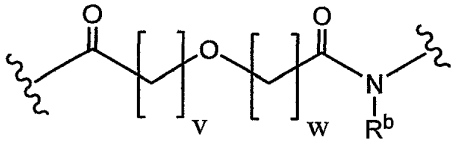
K(L) is a lysine reside attached to a linker L wherein L is capable of forming a covalent bond with an amino acid side chain in a combining site of an antibody.

In some embodiments, K(L) is



wherein L is a linker moiety having the formula -X-Y-Z-, wherein:

X is:

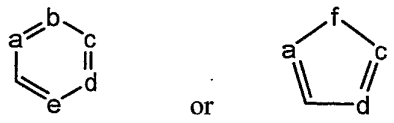


wherein v and w are selected such that the backbone length of X is 6-12 atoms;

Y is a recognition group comprising at least a ring structure; and

Z is a reactive group that is capable of forming a covalent bond with an amino acid side chain in a combining site of an aldolase antibody.

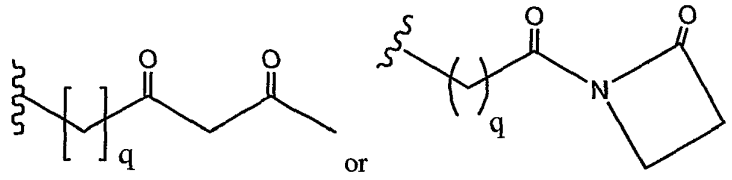
In some embodiments Y has the optionally substituted structure:



wherein a, b, c, d, and e are independently carbon or nitrogen; f is carbon, nitrogen, oxygen, or sulfur; Y is attached to X and Z independently at any two ring positions of sufficient valence; and no more than four of a, b, c, d, e, or f are simultaneously nitrogen.

In some embodiments, Z is selected from the group consisting of substituted 1,3-diketones or acyl beta-lactams.

In some embodiments Z has the structure:



wherein q=0, 1, 2, 3, 4, or 5. In other embodiments, q=1, 2, or 3.

In some embodiments of compounds of Formula I, X is:

$-R^{22}-P-R^{23}-$ or $-R^{22}-P-R^{21}-P'-R^{23}-$

wherein:

P and P' are independently selected from the group consisting of polyoxyalkylene oxides such as polyethylene oxide, polyethyloxazoline, poly-N-vinyl pyrrolidone, polyvinyl alcohol, polyhydroxyethyl acrylate, polyhydroxy ethylmethacrylate and polyacrylamide, polyamines having amine groups on either the polymer backbone or the polymer sidechains, such as polylysine, polyornithine, polyarginine, and polyhistidine, nonpeptide polyamines such as polyaminostyrene, polyaminoacrylate, poly(N-methyl aminoacrylate), poly(N-ethylaminoacrylate), poly(N,N-dimethyl aminoacrylate), poly(N,N-diethylaminoacrylate), poly(aminomethacrylate), poly(N-methyl amino-methacrylate), poly(N-ethyl aminomethacrylate), poly(N,N-dimethyl aminomethacrylate), poly(N,N-diethyl aminomethacrylate), poly(ethyleneimine), polymers of quaternary amines, such as poly(N,N,N-trimethylaminoacrylate chloride), poly(methyacrylamidopropyltrimethyl ammonium chloride), proteoglycans such as chondroitin sulfate-A (4-sulfate) chondroitin sulfate-C (6-sulfate) and chondroitin sulfate-B, polypeptides such as polyserine, polythreonine, polyglutamine, natural or synthetic polysaccharides such as chitosan, hydroxy ethyl cellulose, and lipids;

R^{21}, R^{22}, and R^{23} are each independently a covalent bond, -O-, -S-, $-NR^b-$, amide, substituted or unsubstituted straight or branched chain C_{1-50} alkylene, or substituted or unsubstituted straight or branched chain C_{1-50} heteroalkylene;

R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl; and

R^{21}, R^{22}, and R^{23} are selected such that the backbone length of X remains about 200 atoms or less.

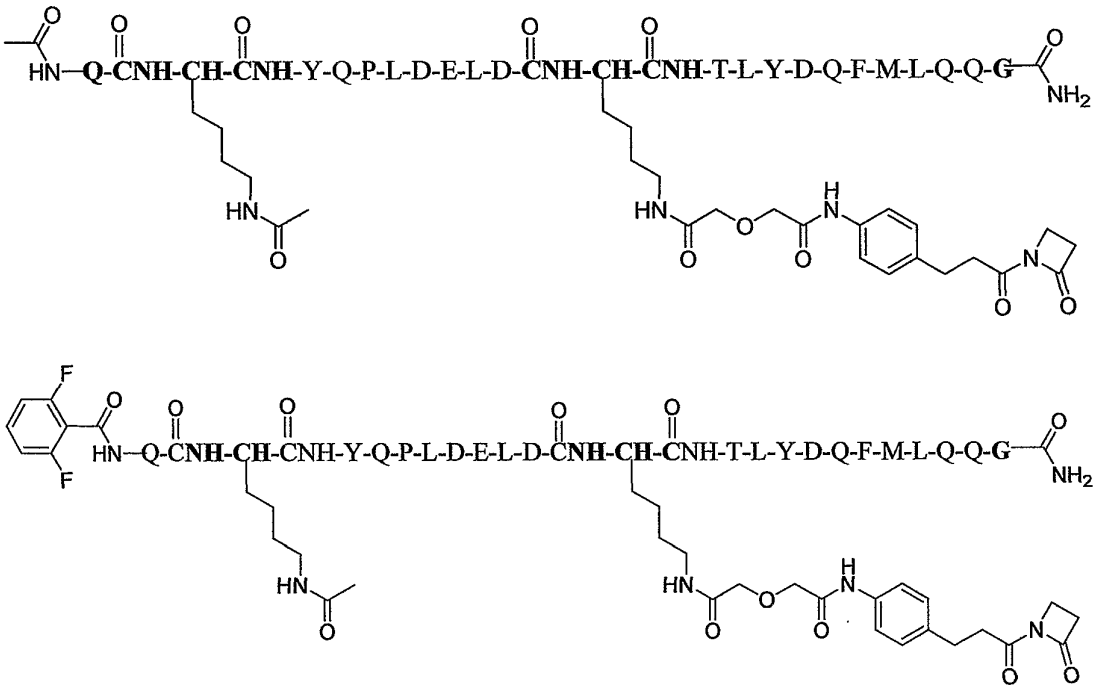
In some embodiments of compounds of Formula I, X is attached to an amino acid residue in [AA targeting agent], and is an optionally substituted -R^{22}-[CH_2-CH_2-O]$_t$-R^{23}-, -R^{22}-cycloalkyl-R^{23}-, -R^{22}-aryl-R^{23}-, or -R^{22}-heterocyclyl-R^{23}-, wherein t is 0 to 50.

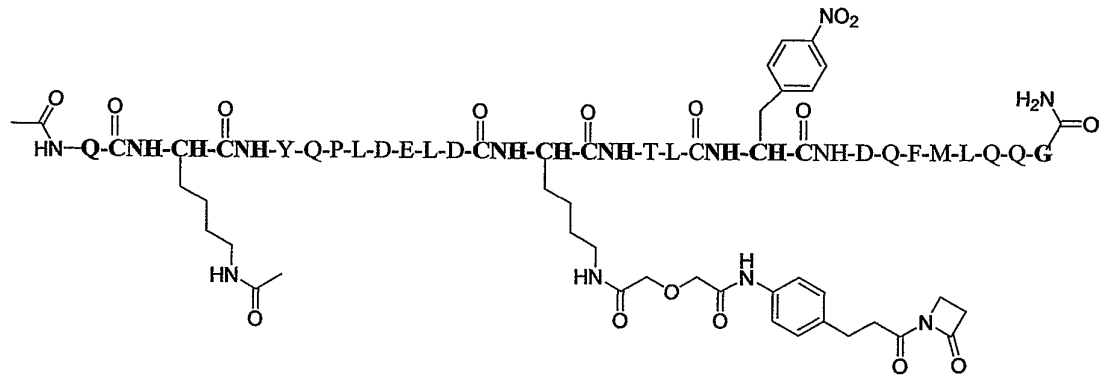
In some embodiments of compounds of Formula I, R^{22} is -$(CH_2)_v$-, -$(CH_2)_u$-C(O)-$(CH_2)_v$-, -$(CH_2)_u$-C(O)-O-$(CH_2)_v$-, -$(CH_2)_u$-C(S)-NR^b-$(CH_2)_v$-, -$(CH_2)_u$-C(O)-NR^b-$(CH_2)_v$-, -$(CH_2)_u$-NR^b-$(CH_2)_v$-, -$(CH_2)_u$-O-$(CH_2)_v$-, -$(CH_2)_u$-S(O)$_{0-2}$-$(CH_2)_v$-, -$(CH_2)_u$-S(O)$_{0-2}$-NR^b-$(CH_2)_v$-, or -$(CH_2)_u$-P(O)(OR^b)-O-$(CH_2)_v$-, wherein u and v are independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20.

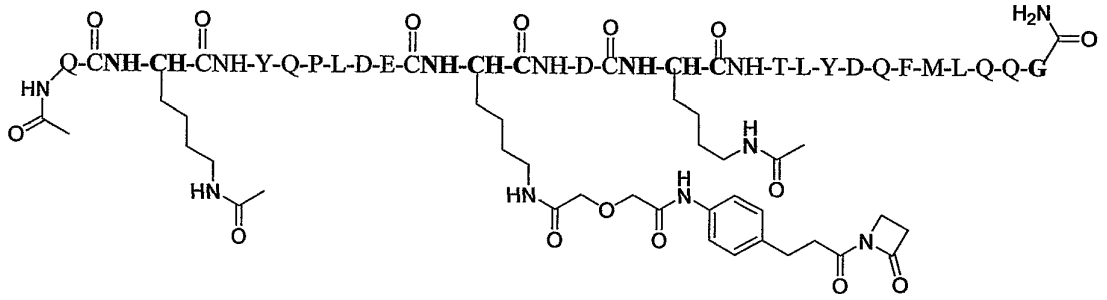
In some embodiments of compounds of Formula I, R^{21} and R^{23} are independently -$(CH_2)_s$-, -$(CH_2)_r$-C(O)-$(CH_2)_s$-, -$(CH_2)_r$-C(O)-O-$(CH_2)_v$-, -$(CH_2)_r$-C(S)-NR^b-$(CH_2)_s$-, -$(CH_2)_r$-C(O)-NR^b-$(CH_2)_s$-, -$(CH_2)_r$-NR^b-$(CH_2)_s$-, -$(CH_2)_r$-O-$(CH_2)_s$-, -$(CH_2)_r$-S(O)$_{0-2}$-$(CH_2)_s$-, -$(CH_2)_r$-S(O)$_{0-2}$-NR^b-$(CH_2)_s$-, or -$(CH_2)_r$-P(O)(OR^b)-O-$(CH_2)_s$-, wherein r, s, and v are independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20.

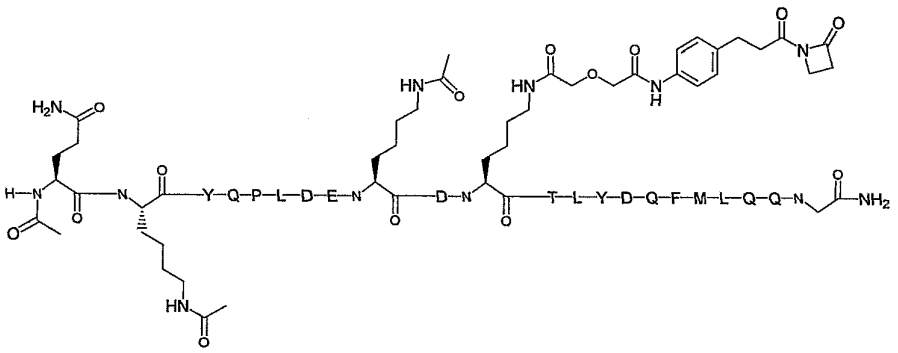
In some embodiments of Formula I, if t>1 or if X is -R^{22}-[CH_2-CH_2-O]$_t$-R^{23}-, -R^{22}-cycloalkyl-R^{23}-, -R^{22}-aryl-R^{23}-, or -R^{22}-heterocyclyl-R^{23}-, Y is present.

Exemplary compounds in accordance with Formula I, wherein R^1 is either NHC(O)CH_3 or DFB, R^2 is C(O)NH_2, and the X portion of the linker moiety is "O" PEG, include:









Another aspect of the invention, illustrated in Formula II, is an AA targeting compound comprising an AA targeting agent covalently linked to a combining site of an Antibody via an intervening linker L'. The Antibody portion of an AA targeting compound can include whole (full length) antibody, unique antibody fragments, or any other forms of an antibody as this term is used herein. In one embodiment, the Antibody is a humanized version of a murine aldolase antibody comprising a constant region from a human IgG, IgA, IgM, IgD, or IgE antibody. In another embodiment, the Antibody is a chimeric antibody comprising the variable region from a murine aldolase antibody and a constant region from a human IgG, IgA, IgM, IgD, or IgE antibody. In a further embodiment, the Antibody is a fully human version of a murine aldolase antibody comprising a polypeptide sequence from natural or native human IgG, IgA, IgM, IgD, or IgE antibody

Antibody – L' – [AA targeting agent] (II)

wherein:

[AA targeting agent] is a peptide selected from the group consisting of:

R^1-QKY QPL DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:21)

R^1-Q(AcK)Y QPL DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:22)

R^1-QNY QPL DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:23)

R^1-Q(AcK)Y QPL DEK D(AcK)T LYD QFM LQQ G- R^2; (SEQ ID NO:30)

R^1-Q(AcK)Y QPL DEK DET LYD QFM LQQ G- R^2; (SEQ ID NO:33)

R^1-Q(AcK)Y Q(DHP)L DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:34)

R^1-Q(AcK)Y Q(HP)L DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:35)

R^1-Q(AcK)Y QPL DEL DKT IYD QFM LQQ G- R^2; (SEQ ID NO:36)

R^1-Q(AcK)Y QPL DEI DKT LYD QFM LQQ G- R^2; (SEQ ID NO:37)

R^1-Q(AcK)Y QPL DEL DKT (HChA)YD QFM LQQ G- R^2; (SEQ ID NO:38)

R^1-Q(AcK)Y QPL DEL DKT (HF)YD QFM LQQ G- R^2; (SEQ ID NO:39)

R^1-Q(AcK)Y QPL DEL DKT (ThA)YD QFM LQQ G- R^2; (SEQ ID NO:40)

R^1-Q(AcK)Y QPL DEL DKT (Nva)YD QFM LQQ G- R^2; (SEQ ID NO:41)

R^1-Q(AcK)Y QPL DEL DKT (HL)YD QFM LQQ G- R^2; (SEQ ID NO:42)

R^1-Q(AcK)Y QPL DE(AcK) DKT LYD QFM LQQ G- R^2; (SEQ ID NO:43)

R^1-Q(AcK)Y QPL DEL DKT LFD QFM LQQ G- R^2; (SEQ ID NO:44)

R^1-Q(AcK)Y Q(HP)L DE(ThA) DKT L(NO2F)D QFM LQQ G- R^2; (SEQ ID NO:45)

R^1-Q(AcK)Y Q(HP)L DE(ThA) DKT L(BPA)D QFM LQQ G- R^2; (SEQ ID NO:46)

R^1-Q(AcK)Y Q(HP)L DE(ThA) DKT L(CO2H)FD QFM LQQ G- R^2; (SEQ ID NO:47)

R^1-Q(AcK)Y QPL DE(AcK) DKT L(NO2F)D QFM LQQ G- R^2; (SEQ ID NO:48)

R^1-Q(AcK)Y QPL DE(AcK) DKT LFD QFM LQQ G- R^2; (SEQ ID NO:68)

DCB-Q(AcK)Y QPL DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:49)

DFB-Q(AcK)Y QPL DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:50)

PyC-Q(AcK)Y QPL DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:51)

Amido 2-PEG-Q(AcK)Y QPL DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:52)

R^1-Q(ClBnCarbamateK)Y QPL DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:53)

R^1-Q(AcK)Y QPL DEL D(Dab)T LYD QFM LQQ G- R^2; (SEQ ID NO:54)

R^1-Q(AcK)Y QPL DEL D(Dap)T LYD QFM LQQ G- R^2; (SEQ ID NO:55)

R^1-Q(AcK)Y QPL DEL DKT L(NO2F)D QFM LQQ G-R^2; (SEQ ID NO:91)

R^1-QNY QPL DEL DKT L(BPA)D QFM LQQ G-R^2; (SEQ ID NO:56)

R^1-QNY QPL DEL DKT L(CF)D QFM LQQ G-R^2; (SEQ ID NO:57)

R^1-QNY QPL DEL DKT LYD QFM LQQ G-R^2; (SEQ ID NO:58)

R^1-Q(Nick)Y QPL DEL DKT LYD QFM LQQ G-R^2; (SEQ ID NO:61)

R^1-Q(AcK)Y QPL DE(AcK) DKT L(CF)D QFM LQQ G-R^2; (SEQ ID NO:62) and

R^1-Q(AcK)Y QPL DE(AcK) DKT LFD QFM LQQ G-R^2; (SEQ ID NO:63) wherein

R^1 is CH_3, $C(O)CH_3$, $C(O)CH_3$, $C(O)CH_2CH_3$, $C(O)CH_2CH_2CH_3$, $C(O)CH(CH_3)CH_3$, $C(O)CH_2CH_2CH_2CH_3$, $C(O)CH(CH_3)CH_2CH_3$, $C(O)C_6H_5$, $C(O)CH_2CH_2(CH_2CH_2O)_{1\text{-}5}Me$, dichlorobenzoyl (DCB), difluorobenzoyl (DFB), pyridinyl carboxlate (PyC) or amido-2-PEG, an amino protecting group, a lipid fatty acid group or a carbohydrate; and

R^2 is OH, NH_2, $NH(CH_3)$, $NHCH_2CH_3$, $NHCH_2CH_2CH_3$, $NHCH(CH_3)CH_3$, $NHCH_2CH_2CH_2CH_3$, $NHCH(CH_3)CH_2CH_3$, NHC_6H_5, $NHCH_2CH_2OCH_3$, $NHOCH_3$, $NHOCH_2CH_3$, a carboxy protecting group, a lipid fatty acid group or a carbohydrate, and

L' is a linker moiety having the formula -X-Y-Z', wherein:

X is a biologically compatible polymer or block copolymer attached to one of the residues that comprises an AA targeting agent;

Y is an optionally present recognition group comprising at least a ring structure; and

Z is a group that is covalently linked to a side chain in a combining site of an antibody;

and pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, and prodrugs thereof.

In the listed peptide sequences, non-standard amino acid residues are enclosed within parentheses. In some cases, the amino terminus of a peptide is attached to one of the following capping groups: dichlorobenzoyl (DCB), difluorobenzoyl (DFB), pyridinyl carboxlate (PyC) or amido-2-PEG.

In some embodiments of compounds of Formula II, X is:

$-R^{22}-P-R^{23}-$ or $-R^{22}-P-R^{21}-P'-R^{23}-$

wherein:

P and P' are independently selected from the group consisting of polyoxyalkylene oxides such as polyethylene oxide, polyethyloxazoline, poly-N-vinyl pyrrolidone, polyvinyl alcohol, polyhydroxyethyl acrylate, polyhydroxy ethylmethacrylate and polyacrylamide, polyamines having amine groups on either the polymer backbone or the polymer side chains, such as polylysine, polyornithine, polyarginine, and polyhistidine, nonpeptide polyamines such as polyaminostyrene, polyaminoacrylate, poly(N-methyl aminoacrylate), poly(N-ethylaminoacrylate), poly(N,N-dimethyl aminoacrylate), poly(N,N-diethylaminoacrylate), poly(aminomethacrylate), poly(N-methyl amino-methacrylate), poly(N-ethyl aminomethacrylate), poly(N,N-dimethyl aminomethacrylate), poly(N,N-diethyl aminomethacrylate), poly(ethyleneimine), polymers of quaternary amines, such as poly(N,N,N-trimethylaminoacrylate chloride), poly(methyacrylamidopropyltrimethyl ammonium chloride), proteoglycans such as chondroitin sulfate-A (4-sulfate) chondroitin sulfate-C (6-sulfate) and chondroitin sulfate-B, polypeptides such as polyserine, polythreonine, polyglutamine, natural or synthetic polysaccharides such as chitosan, hydroxy ethyl cellulose, and lipids;

R^{21}, R^{22}, and R^{23} are each independently a covalent bond, -O-, -S-, $-NR^b-$, substituted or unsubstituted straight or branched chain C_{1-50} alkylene, or substituted or unsubstituted straight or branched chain C_{1-50} heteroalkylene;

R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl; and

R^{21}, R^{22}, and R^{23} are selected such that the backbone length of X remains about 200 atoms or less.

In some embodiments of compounds of Formula II, X is attached to an amino acid residue in [AA targeting agent], and is an optionally substituted $-R^{22}-[CH_2-CH_2-O]_t-R^{23}-$, $-R^{22}$-cycloalkyl-$R^{23}-$, $-R^{22}$-aryl-$R^{23}-$, or $-R^{22}$-heterocyclyl-$R^{23}-$, wherein t is 0 to 50.

In some embodiments of compounds of Formula II, R^{22} is $-(CH_2)_v-$, $-(CH_2)_u-C(O)-(CH_2)_v-$, $-(CH_2)_u-C(O)-O-(CH_2)_v-$, $-(CH_2)_u-C(S)-NR^b-(CH_2)_v-$, $-(CH_2)_u-C(O)-NR^b-(CH_2)_v-$, $-(CH_2)_u-NR^b-(CH_2)_v-$, $-(CH_2)_u-O-(CH_2)_v-$, $-(CH_2)_u-S(O)_{0-2}-(CH_2)_v-$, $-(CH_2)_u-S(O)_{0-2}-NR^b-(CH_2)_v-$, or

$-(CH_2)_u-P(O)(OR^b)-O-(CH_2)_v-$, wherein u and v are independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20.

In some embodiments of compounds of Formula II, R^{21} and R^{23} are independently $-(CH_2)_s-$, $-(CH_2)_r-C(O)-(CH_2)_s-$, $-(CH_2)_r-C(O)-O-(CH_2)_v-$, $-(CH_2)_r-C(S)-NR^b-(CH_2)_s-$, $-(CH_2)_r-C(O)-NR^b-(CH_2)_s-$, $-(CH_2)_r-NR^b-(CH_2)_s-$, $-(CH_2)_r-O-(CH_2)_s-$, $-(CH_2)_r-S(O)_{0-2}-(CH_2)_s-$, $-(CH_2)_r-S(O)_{0-2}-NR^b-(CH_2)_s-$, or $-(CH_2)_r-P(O)(OR^b)-O-(CH_2)_s-$, wherein r, s, and v are independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20.

Some aspects of the invention provide a compound selected from the groups consisting of:

R^1-Q(AcK)Y QPL DEL DK(L')T LYD QFM LQQ G-R^2; (SEQ ID NO: 136)

R^1-Q(AcK)Y QPL DEL DK(L')T L(NO2F)D QFM LQQ G- R^2; (SEQ ID NO: 137)

R^1-Q(AcK)Y QPL DEK(L') DK(Ac)T LYD QFM LQQ G-R^2; (SEQ ID NO: 138) and

R^1-Q(AcK)Y QPL DE(AcK) DK(L')T LYD QFM LQQ G-R^2; (SEQ ID NO: 139)

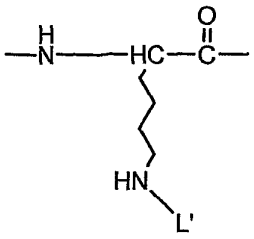
wherein

R^1 is CH_3, $C(O)CH_3$, $C(O)CH_3$, $C(O)CH_2CH_3$, $C(O)CH_2CH_2CH_3$, $C(O)CH(CH_3)CH_3$, $C(O)CH_2CH_2CH_2CH_3$, $C(O)CH(CH_3)CH_2CH_3$, $C(O)C_6H_5$, $C(O)CH_2CH_2(CH_2CH_2O)_{1-5}Me$, dichlorobenzoyl (DCB), difluorobenzoyl (DFB), pyridinyl carboxlate (PyC) or amido-2-PEG, an amino protecting group, a lipid fatty acid group or a carbohydrate; and

R^2 is OH, NH_2, $NH(CH_3)$, $NHCH_2CH_3$, $NHCH_2CH_2CH_3$, $NHCH(CH_3)CH_3$, $NHCH_2CH_2CH_2CH_3$, $NHCH(CH_3)CH_2CH_3$, NHC_6H_5, $NHCH_2CH_2OCH_3$, $NHOCH_3$, $NHOCH_2CH_3$, a carboxy protecting group, a lipid fatty acid group or a carbohydrate, and

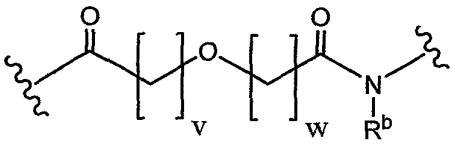
K(L') is a lysine reside attached to a linker L' wherein L is covalent bonded with an amino acid side chain in a combining site of an antibody.

In some embodiments K(L') is



L' is a linker moiety having the formula -X-Y-Z'-, wherein:

X is:

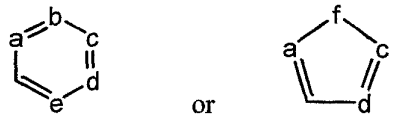


wherein v and w are selected such that the backbone length of X is 6-12 atoms;

Y is a recognition group comprising at least a ring structure; and

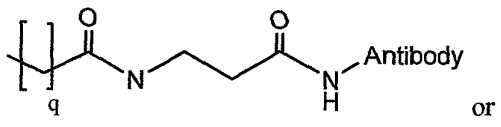
Z' is an attachment moiety comprising a covalent link to an amino acid side chain in a combining site of an antibody.

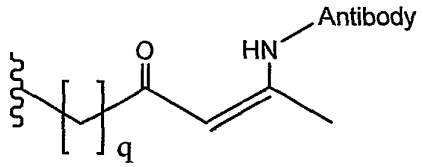
In some embodiments Y has the optionally substituted structure:



wherein a, b, c, d, and e are independently carbon or nitrogen; f is carbon, nitrogen, oxygen, or sulfur; Y is attached to X and Z' independently at any two ring positions of sufficient valence; and no more than four of a, b, c, d, e, or f are simultaneously nitrogen.

In some embodiments Z' has the structure:





Wherein q=0, 1, 2, 3, 4, or 5 and –N-Antibody refers to a covalent link to an amino acid side chain in a combining site of an antibody bearing an amino group. In other aspects, q=1, 2 or 3.

Another aspect of the invention, illustrated in Formula III, is an AA targeting compound in which two AA targeting agents, which may be the same or different, are each covalently linked to a combining site of an antibody. The Antibody portion of an AA targeting compound can include whole (full length) antibody, unique antibody fragments, or any other forms of an antibody as this term is used herein. In one embodiment, the Antibody is a humanized version of a murine aldolase antibody comprising a constant region from a human IgG, IgA, IgM, IgD, or IgE antibody. In another embodiment, the Antibody is a chimeric antibody comprising the variable region from a murine aldolase antibody and a constant region from a human IgG, IgA, IgM, IgD, or IgE antibody. In a further embodiment, the Antibody is a fully human version of a murine aldolase antibody comprising a polypeptide sequence from natural or native human IgG, IgA, IgM, IgD, or IgE antibody.

$$\text{Antibody}[\text{–L'–}[\text{AA targeting agent}]]_2 \qquad \text{(III)}$$

wherein:

[AA targeting agent], Antibody, and L' are as defined according to Formula II.

Also provided are methods of delivering or administering AA targeting compounds of the invention and methods of treatment using AA targeting compounds of the invention. For example, methods of treating (including preventing) a disease or condition associated with abnormal angiogenesis in a subject include administering a therapeutically effective amount of an AA targeting compound of the invention to the subject. Diseases and conditions that may be treated include cancer, arthritis, hypertension, kidney disease, psoriasis, angiogenesis of the eye associated with ocular disorder, infection or surgical intervention, macular degeneration, diabetic retinopathy, and the like.

Another aspect of the invention includes methods of using AA targeting compounds of the invention for diagnostic purposes. For example, the AA targeting compounds can be used for the diagnosis of a disease or condition associated with abnormal angiogenesis, including cancer, arthritis, psoriasis, angiogenesis of the eye associated with an ocular disorder, infection or surgical intervention, macular degeneration, diabetic retinopathy, and the like.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 illustrates one embodiment according to Formula II or Formula III.

FIGURE 2 illustrates one embodiment according to Formula II or Formula III.

FIGURE 3 illustrates one embodiment according to Formula II or Formula III.

FIGURES 4A and 4b each illustrate one embodiment according to Formula II or Formula III.

FIGURES 5A and 5b each illustrate one embodiment according to Formula II or Formula III.

FIGURES 6A and FIGURE 6B illustrate the solid phase synthesis of targeting agent-linker conjugates of the present invention.

FIGURE 7A illustrates the amino acid sequence alignment of the variable domains of m38c2, h38c2, and human germlines. Framework regions (FR) and complementarity determining regions (CDR) are defined according to Kabat *et al.* Asterisks mark differences between m38c2 and h38c2 or between h38c2 and the human germlines. FIGURE 7B illustrates the amino acid sequence of the light and heavy chains (SEQ ID NOs:189 and 190, respectively) of one embodiment of a humanized 38c2 IgG1.

FIGURE 8 shows various structures that may serve as linker reactive groups. Structures A-C form reversible covalent bonds with surface accessible reactive nucleophilic groups (e.g., lysine or cysteine side chain) of a combining site of an antibody. R'_1, R'_2, R'_3, and R_4 in structures A-C represent substituents which include, for example, C, H, N, O, P, S, halogen (F, Cl, Br, I) or a salt thereof. X is N, C, or any other heteroatom. These substituents may also include a group such as an alkyl, alkenyl, alkynyl, oxoalkyl, oxoalkenyl, oxoalkynyl, aminoalkyl, aminoalkenyl, aminoalkynyl, sulfoalkyl, sulfoalkenyl, or sulfoalkynyl group, phosphoalkyl, phosphoalkenyl, phosphoalkynyl group. R'_2 and R'_3 could be cyclic as exemplified in structures B and C while X could be a heteroatom. For example, structure A could form an irreversible covalent bond with a reactive nucleophile if X is N and if R'_1 and R_3 form part of a cyclic structure. Structures D-G may form nonreversible covalent bonds with reactive nucleophilic groups in a combining site of an antibody. In these structures, R''_1 and R''_2 represent C, O, N, halide or leaving groups such as mesyl or tosyl.

FIGURE 9 shows various electrophiles that are suitable for reactive modification with a reactive amino acid side chain in a combining site of an antibody and thus may serve as linker reactive groups. Key: (A) acyl beta-lactam; (B) simple diketone; (C) succinimide active ester; (D) maleimide; (E) haloacetamide with linker; (F) haloketone; (G) cyclohexyl diketone; and (H) aldehyde. The squiggle line indicates the point of attachment to the rest of the linker or targeting agent. X refers to a halogen.

FIGURE 10 shows the addition of a nucleophilic ("nu") side chain in an antibody combining site to compounds A-G in FIGURE 8. Antibody- Nu- refers to a covalent bond to an amino acid side chain bearing a nucleophile in a combining site of an antibody.

FIGURE 11 shows the addition of a nucleophilic side chain in an antibody combining to compounds A-H in FIGURE 9. Antibody- Nu- refers to a covalent bond to an amino acid side chain bearing a nucleophile in a combining site of an antibody.

FIGURE 12 shows a synthesis of:

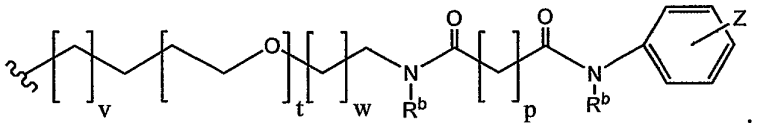


FIGURE 13 shows a synthesis of:

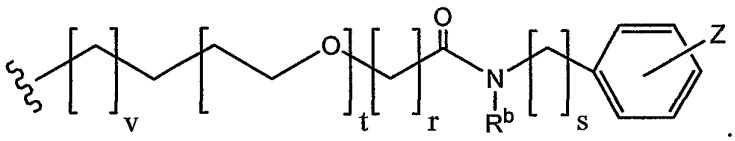


FIGURE 14 shows a synthesis of:

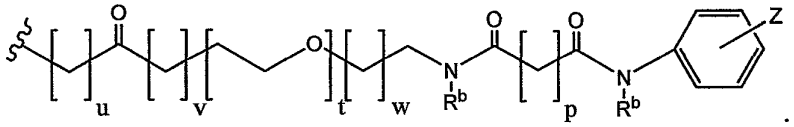


FIGURE 15 shows a synthesis of:

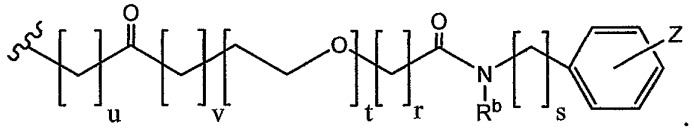


FIGURE 16 shows a synthesis of:

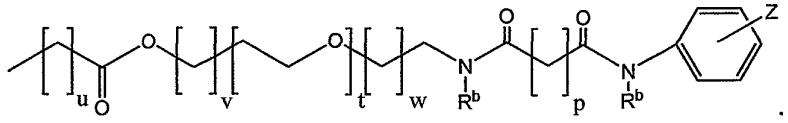


FIGURE 17 shows a synthesis of:

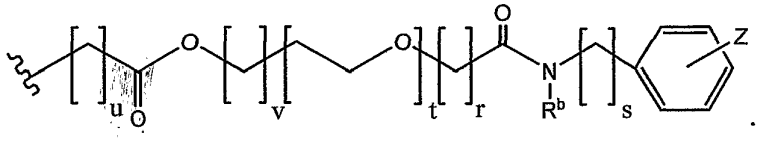
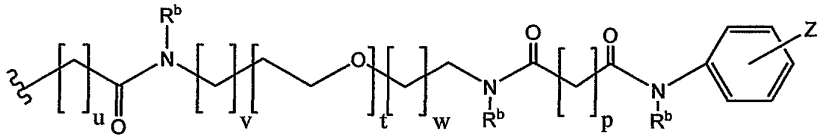


FIGURE 18 shows a synthesis of:



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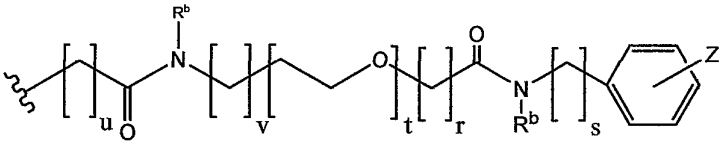


FIGURE 20 shows a synthesis of:

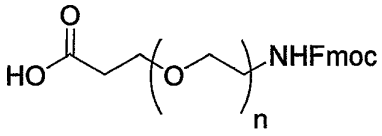


FIGURE 21 shows syntheses of:

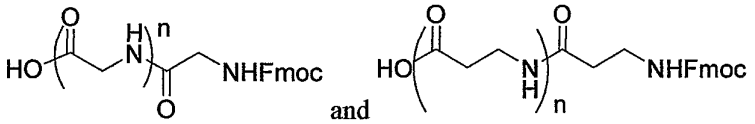
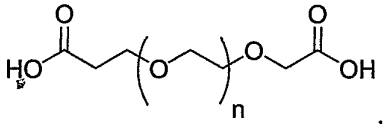


FIGURE 22 shows a synthesis of:



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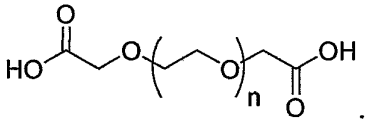
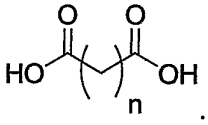


FIGURE 24 shows a synthesis of:



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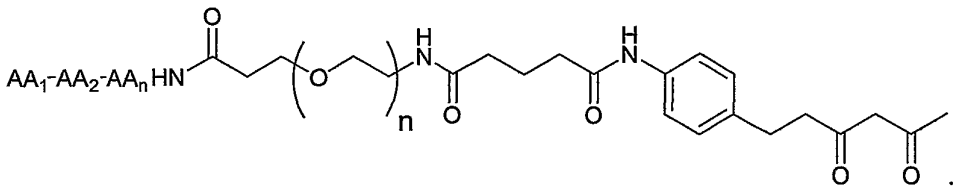


FIGURE 26 shows a synthesis of:

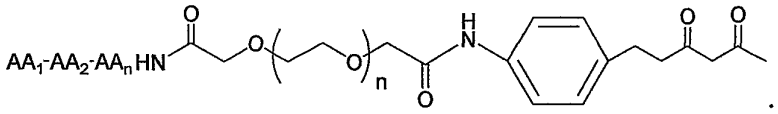


FIGURE 27 shows a synthesis of:

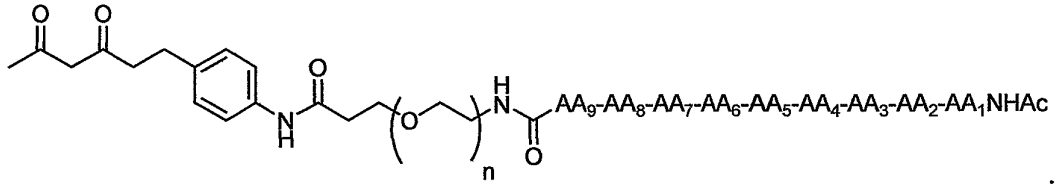


FIGURE 28 shows a synthesis of:

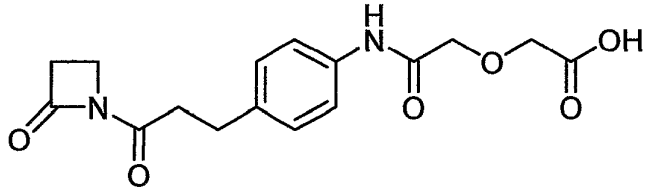


FIGURE 29 illustrates one embodiment of the invention.

FIGURE 30 illustrates one embodiment of the invention.

FIGURE 31 illustrates one embodiment of the invention.

FIGURE 32 illustrates one embodiment of the invention.

FIGURE 33 illustrates one embodiment of the invention.

FIGURE 34 illustrates one embodiment of the invention.

FIGURE 35 illustrates one embodiment of the invention.

FIGURE 36 illustrates one embodiment of the invention.

FIGURE 37 illustrates one embodiment of the invention.

FIGURE 38 illustrates one embodiment of the invention

FIGURE 39 illustrates one embodiment of the invention.

FIGURE 40 illustrates one embodiment of the invention.

FIGURE 41 illustrates one embodiment of the invention.

DETAILED DESCRIPTION

Definitions

The following abbreviations, terms and phrases are used herein as defined below.

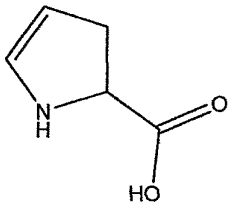
Table 1: Amino acid abbreviations

Amino acid	One letter abbreviation	Three letter or other abbreviation
Alanine	A	Ala
Arginine	R	Arg
Asparagine	N	Asn
Aspartic acid	D	Asp
Cysteine	C	Cys
Glutamic acid	E	Glu
Glutamine	Q	Gln
Glycine	G	Gly
Histidine	H	His
Isoleucine	I	Ile
Leucine	L	Leu
Lysine	K	Lys
Methionine	M	Met
Phenylalanine	F	Phe
Proline	P	Pro
Serine	S	Ser
Threonine	T	Thr
Tryptophan	W	Trp
Tyrosine	Y	Tyr
Valine	V	Val
Dehydroproline	--	DHP
Hydroxyproline	--	HP
Homocyclohexyl alanine	--	HChA
Homophenyl alanine		HF
Thiazolyl alanine		ThA

Norvaline	Nva
Homoleucine	HL
Epsilon acyl lysine	AcK
4-benzoyl phenylalanine	BPA
4-Carboxy phenylalanine	(CO2H)F: also: CF
Epsilon chloro benzyl carbamate lysine	(ClBnCarbamate)K: also: CbcK
Diaminobutyric acid	Dab
Diaminopropionic acid	Dap
4-Nitro phenylalanine	NO2F: also: NF
(2S,4R)-4-Hydroxyproline	BnHP
Nictinyl lysine	NicK
Thienyl Alanine	TA

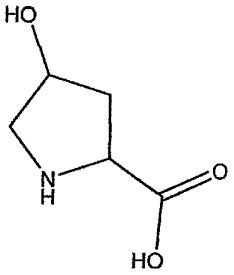
Every amino-bearing side chain of a targeting agent can be terminated by R^1 as defined herein. Every COOH/COO^--bearing side chain of a targeting agent can be terminated by R^2 as defined herein.

Dehydroproline or DHP refers to

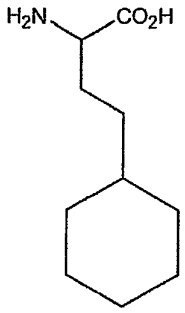


.

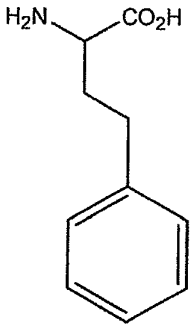
Hydroxyproline or HP refers to:



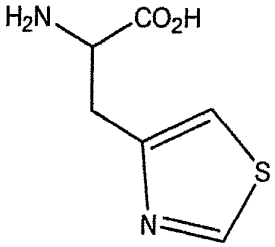
Homocyclohexyl alanine or HChA refers to:



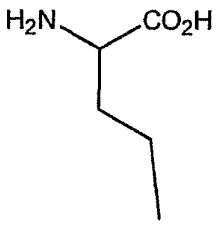
Homophenyl alanine or HF refers to:



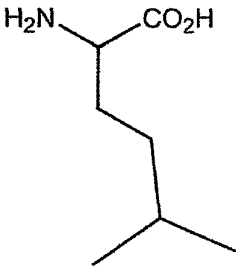
Thiazolyl alanine or ThA refers to:



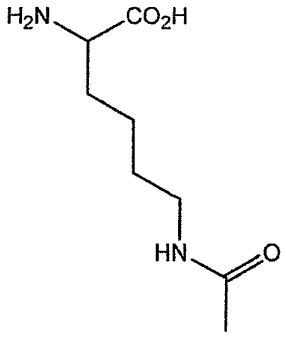
Norvaline or Nva refers to:



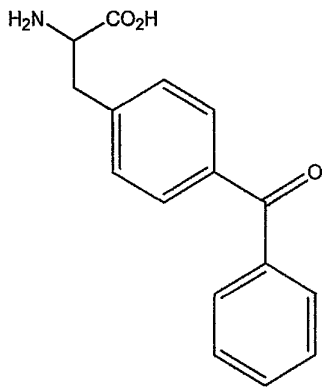
Homoleucine or HL refers to:



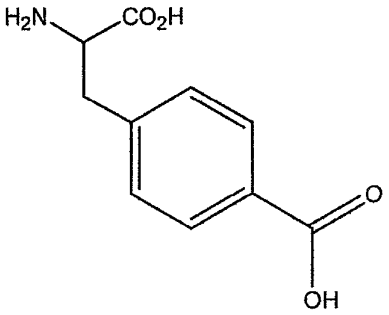
Epsilon acyl lysine or AcK refers to:



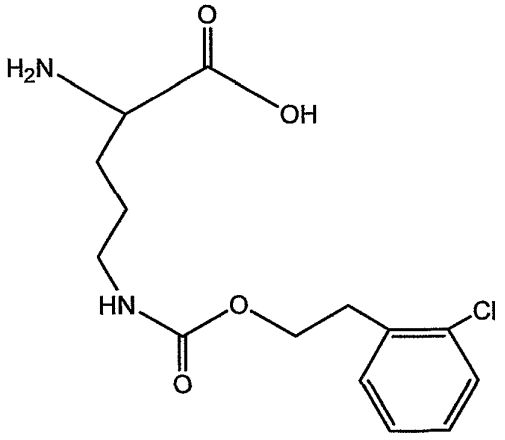
4-benzoyl phenylalanine or BPA refers to:



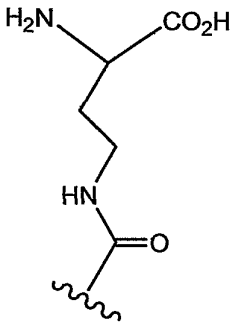
4-Carboxy phenylalanine or (CO2H)F or CF refers to:



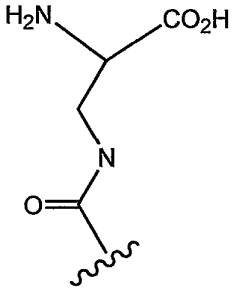
Epsilon chloro benzyl carbamate lysine or (ClBnCarbamate)K or CbcK refers to:



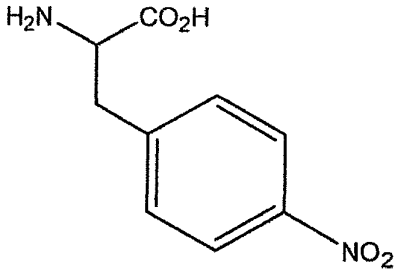
Diaminobutyric acid or Dab refers to:



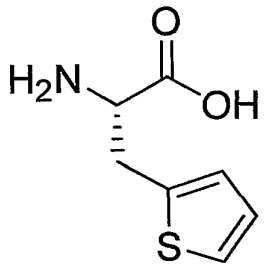
Diaminopropionic acid or Dap refers to:



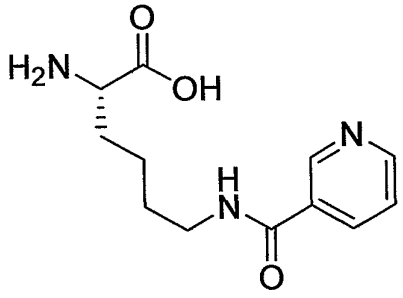
4-Nitro phenylalanine or NO2F or NF refers to:



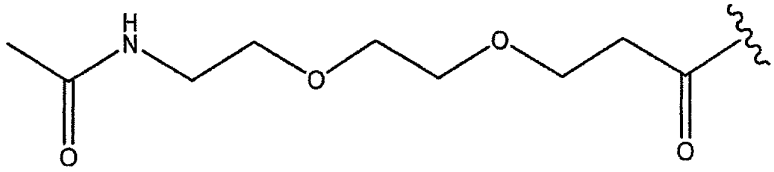
Thienyl Alanine or TA refers to



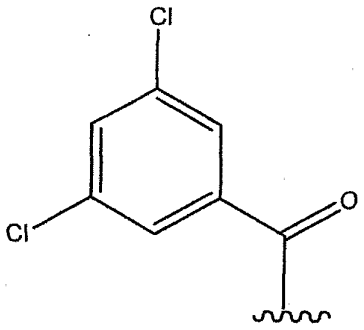
Nicotinyl Lysine (NicK) refers to:



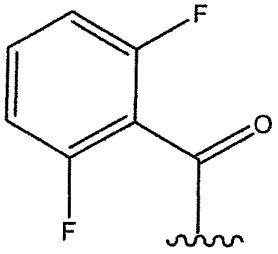
Amido 2-PEG refers to:



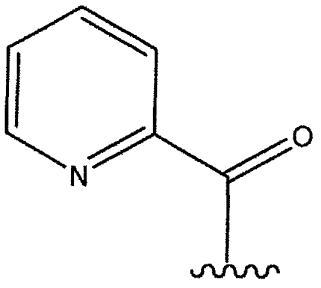
Dichlorobenzoyl or DCB refers to:



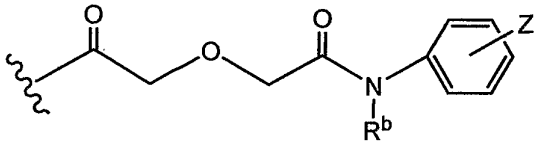
Difluorobenzoyl or DFB refers to:



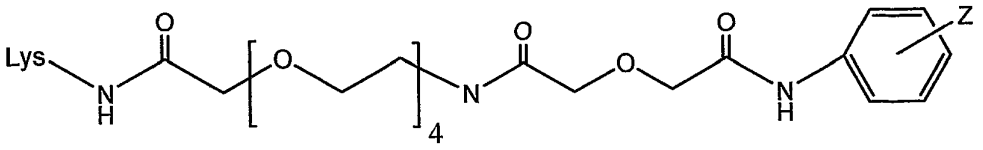
Pyridinyl carboxylate or PyC refers to:



"O" PEG or OP refers to:



"4" PEG or 4P refers to:



shown attached to a lysine residue.

Unless indicated otherwise by a "D" prefix, e.g., D-Ala or N-Me-D-Ile, the stereochemistry of the alpha-carbon of the amino acids and aminoacyl residues in peptides described in this specification and the appended claims is the natural or "L" configuration. The Cahn-Ingold-Prelog "R" and "S" designations are used to specify the stereochemistry of chiral centers in certain acyl substituents at the N-terminus of the peptides. The designation "R,S" is meant to indicate a racemic mixture of the two enantiomeric forms. This nomenclature follows that described in R. S. Cahn, *et al.*, Angew. Chem. Int. Ed. Engl., 5:385-415 (1966).

"Polypeptide," "peptide," and "protein" are used interchangeably to refer to a polymer of amino acid residues. As used herein, these terms apply to amino acid polymers in which one or more amino acid residues is an artificial chemical analog of a corresponding naturally occurring amino acid. These terms also apply to naturally occurring amino acid polymers. Amino acids can be in the L or D form as long as the binding function of the peptide is maintained. Peptides may be cyclic, having an intramolecular bond between two non-adjacent amino acids within the peptide, e.g., backbone to backbone, side-chain to backbone and side-chain to side-chain cyclization. Cyclic peptides can be prepared by methods well know in the art. See e.g., U.S. Patent No. 6,013,625.

All peptide sequences are written according to the generally accepted convention whereby the alpha-N-terminal amino acid residue is on the left and the alpha-C-terminal amino acid residue is on the right. As used herein, the term "N-terminus" refers to the free alpha-amino group of an amino acid in a peptide, and the term "C-terminus" refers to the free α-carboxylic acid terminus of an amino acid in a peptide. A peptide which is N-terminated with a group refers to a peptide bearing a group on the alpha-amino nitrogen of the N-terminal amino acid residue. An amino acid which is N-terminated with a group refers to an amino acid bearing a group on the alpha-amino nitrogen.

"Substantially homologous" means at least about 75% (preferably at least about 80%, and more preferably at least about 90% or most preferably at least about 95%, of the amino-acid residues match over the defined length of the peptide sequences. Substantially homologous sequences include sequences sharing at least 65% of the amino acid residues over their length, and at least 10% of the non-shared sequences being conservative subustitutions.Sequences that are substantially homologous

can be identified by comparing the sequences using standard software available in sequence data banks, such as BLAST programs available from the National Cancer Center for Biotechology Information at ncbi.nlm.nih.gov.

In general, "substituted" refers to a group as defined below in which one or more bonds to a hydrogen atom contained therein are replaced by a bond to non-hydrogen or non-carbon atoms such as, but not limited to, a halogen atom such as F, Cl, Br, and I; an oxygen atom in groups such as hydroxyl groups, alkoxy groups, aryloxy groups, and ester groups; a sulfur atom in groups such as thiol groups, alkyl and aryl sulfide groups, sulfone groups, sulfonyl groups, and sulfoxide groups; a nitrogen atom in groups such as amines, amides, alkylamines, dialkylamines, arylamines, alkylarylamines, diarylamines, N-oxides, imides, and enamines; a silicon atom in groups such as in trialkylsilyl groups, dialkylarylsilyl groups, alkyldiarylsilyl groups, and triarylsilyl groups; and other heteroatoms in various other groups. Substituted alkyl groups and also substituted cycloalkyl groups and others also include groups in which one or more bonds to a carbon(s) or hydrogen(s) atom is replaced by a bond to a heteroatom such as oxygen in carbonyl, carboxyl, and ester groups; nitrogen in groups such as imines, oximes, hydrazones, and nitriles. As employed herein, a group which is "optionally substituted" may be substituted or unsubstituted. Thus, e.g., "optionally substituted alkyl" refers to both substituted alkyl groups and unsubstituted alkyl groups.

The phrase "unsubstituted alkyl" refers to alkyl groups that do not contain heteroatoms. Thus, the phrase includes straight chain alkyl groups such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl and the like. The phrase also includes branched chain isomers of straight chain alkyl groups, including but not limited to, the following which are provided by way of example: $-CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-CH(CH_2CH_3)_2$, $-C(CH_3)_3$, $-C(CH_2CH_3)_3$, $-CH_2CH(CH_3)_2$, $-CH_2CH(CH_3)(CH_2CH_3)$, $-CH_2CH(CH_2CH_3)_2$, $-CH_2C(CH_3)_3$, $-CH_2C(CH_2CH_3)_3$, $-CH(CH_3)CH(CH_3)(CH_2CH_3)$, $-CH_2CH_2CH(CH_3)_2$, $-CH_2CH_2CH(CH_3)(CH_2CH_3)$, $-CH_2CH_2CH(CH_2CH_3)_2$, $-CH_2CH_2C(CH_3)_3$, $-CH_2CH_2C(CH_2CH_3)_3$, $-CH(CH_3)CH_2CH(CH_3)_2$, $-CH(CH_3)CH(CH_3)CH(CH_3)_2$, $-CH(CH_2CH_3)CH(CH_3)CH(CH_3)(CH_2CH_3)$, and others. The phrase does not include cycloalkyl groups. Thus, the phrase unsubstituted alkyl groups includes primary alkyl groups, secondary alkyl groups, and tertiary alkyl groups. Unsubstituted alkyl groups may be bonded to one or more carbon atom(s), oxygen atom(s), nitrogen atom(s), and/or sulfur atom(s) in the parent compound. Possible unsubstituted alkyl groups include straight and branched chain alkyl groups having 1 to 20 carbon atoms. Alternatively, such unsubstituted alkyl groups have from 1 to 10 carbon atoms or are lower alkyl groups having from 1 to about 6 carbon atoms. Other unsubstituted alkyl groups include straight and branched chain alkyl groups having from 1 to 3 carbon atoms and include methyl, ethyl, propyl, and $-CH(CH_3)_2$.

The phrase "substituted alkyl" refers to an alkyl group in which one or more bonds to a carbon(s) or hydrogen(s) are replaced by a bond to non-hydrogen and non-carbon atoms such as, but not limited to, a halogen atom in halides such as F, Cl, Br, and I; an oxygen atom in groups such as hydroxyl groups, alkoxy groups, aryloxy groups, and ester groups; a sulfur atom in groups such as thiol groups, alkyl and aryl sulfide groups, sulfone groups, sulfonyl groups, and sulfoxide groups; a nitrogen atom in groups such as amines, amides, alkylamines, dialkylamines, arylamines, alkylarylamines, diarylamines, N-oxides, imides, and enamines; a silicon atom in groups such as in trialkylsilyl groups, dialkylarylsilyl groups, alkyldiarylsilyl groups, and triarylsilyl groups; and other heteroatoms in various other groups. Substituted alkyl groups also include groups in which one or more bonds to a carbon(s) or hydrogen(s) atom is replaced by a bond to a heteroatom such as oxygen in carbonyl, carboxyl, and ester groups; nitrogen in groups such as imines, oximes, hydrazones, and nitriles. Substituted alkyl groups include, among others, alkyl groups in which one or more bonds to a carbon or hydrogen atom is/are replaced by one or more bonds to fluorine atoms. One example of a substituted alkyl group is the trifluoromethyl group and other alkyl groups that contain the trifluoromethyl group. Other alkyl groups include those in which one or more bonds to a carbon or hydrogen atom is replaced by a bond to an oxygen atom such that the substituted alkyl group contains a hydroxyl, alkoxy, aryloxy group, or heterocyclyloxy group. Still other alkyl groups include alkyl groups that have an amine, alkylamine, dialkylamine, arylamine, (alkyl)(aryl)amine, diarylamine, heterocyclylamine, (alkyl)(heterocyclyl)amine, (aryl)(heterocyclyl)amine, or diheterocyclylamine group.

The phrase "unsubstituted alkylene" refers to a divalent unsubstituted alkyl group as defined above. Thus methylene, ethylene, and propylene are each examples of unsubstituted alkylenes. The phrase "substituted alkylene" refers to a divalent substituted alkyl group as defined above. Substituted or unsubstituted lower alkylene groups have from 1 to about 6 carbons.

The phrase "unsubstituted cycloalkyl" refers to cyclic alkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl and such rings substituted with straight and branched chain alkyl groups as defined above. The phrase also includes polycyclic alkyl groups such as, but not limited to, adamantyl norbornyl, and bicyclo[2.2.2]octyl and the like, as well as such rings substituted with straight and branched chain alkyl groups as defined above. Thus, the phrase would include methylcylcohexyl groups among others. The phrase does not include cyclic alkyl groups containing heteroatoms. Unsubstituted cycloalkyl groups may be bonded to one or more carbon atom(s), oxygen atom(s), nitrogen atom(s), and/or sulfur atom(s) in the parent compound. In some embodiments unsubstituted cycloalkyl groups have from 3 to 20 carbon atoms. In other embodiments, such unsubstituted alkyl groups have from 3 to 8 carbon atoms while in others, such groups have from 3 to 7 carbon atoms.

The phrase "substituted cycloalkyl" " has the same meaning with respect to unsubstituted cycloalkyl groups that substituted alkyl groups have with respect to unsubstituted alkyl groups. Thus, the phrase includes, but is not limited to, oxocyclohexyl, chlorocyclohexyl, hydroxycyclopentyl, and chloromethylcyclohexyl groups.

The phrase "unsubstituted aryl" refers to aryl groups that do not contain heteroatoms. Thus the phrase includes, but is not limited to, groups such as phenyl, biphenyl, anthracenyl, and naphthenyl by way of example. Although the phrase "unsubstituted aryl" includes groups containing condensed rings such as naphthalene, it does not include aryl groups that have other groups such as alkyl or halo groups bonded to one of the ring members, as aryl groups such as tolyl are considered herein to be substituted aryl groups as described below. Typically, an unsubstituted aryl may be a lower aryl, having from 6 to about 10 carbon atoms. One unsubstituted aryl group is phenyl. Unsubstituted aryl groups may be bonded to one or more carbon atom(s), oxygen atom(s), nitrogen atom(s), and/or sulfur atom(s) in the parent compound, however.

The phrase "substituted aryl group" has the same meaning with respect to unsubstituted aryl groups that substituted alkyl groups have with respect to unsubstituted alkyl groups. However, a substituted aryl group also includes aryl groups in which one of the aromatic carbons is bonded to one of the non-carbon or non-hydrogen atoms described above and also includes aryl groups in which one or more aromatic carbons of the aryl group is bonded to a substituted and/or unsubstituted alkyl, alkenyl, or alkynyl group as defined herein. This includes bonding arrangements in which two carbon atoms of an aryl group are bonded to two atoms of an alkyl, alkenyl, or alkynyl group to define a fused ring system (e.g., dihydronaphthyl or tetrahydronaphthyl). Thus, the phrase "substituted aryl" includes, but is not limited to tolyl and hydroxyphenyl among others.

The phrase "unsubstituted alkenyl" refers to straight and branched chain and cyclic groups such as those described with respect to unsubstituted alkyl groups as defined above, except that at least one double bond exists between two carbon atoms. Examples include, but are not limited to vinyl, -$CH{=}C(H)(CH_3)$, -$CH{=}C(CH_3)_2$, -$C(CH_3){=}C(H)_2$, -$C(CH_3){=}C(H)(CH_3)$, -$C(CH_2CH_3){=}CH_2$, cyclohexenyl, cyclopentenyl, cyclohexadienyl, butadienyl, pentadienyl, and hexadienyl among others. Lower unsubstituted alkenyl groups have from 1 to about 6 carbons.

The phrase "substituted alkenyl" has the same meaning with respect to unsubstituted alkenyl groups that substituted alkyl groups have with respect to unsubstituted alkyl groups. A substituted alkenyl group includes alkenyl groups in which a non-carbon or non-hydrogen atom is bonded to a carbon double bonded to another carbon and those in which one of the non-carbon or non-hydrogen atoms is bonded to a carbon not involved in a double bond to another carbon. For example, -$CH{=}CH\text{-}OCH_3$

and –CH=CH-CH_2-OH are both substituted alkenyls. Oxoalkenyls wherein a CH_2 group is replaced by a carbonyl, such as –CH=CH-C(O)-CH_3, are also substituted alkenyls.

The phrase "unsubstituted alkenylene" refers to a divalent unsubstituted alkenyl group as defined above. For example, -CH=CH- is an exemplary unsubstituted alkenylene. The phrase "substituted alkenylene" refers to a divalent substituted alkenyl group as defined above.

The phrase "unsubstituted alkynyl" refers to straight and branched chain groups such as those described with respect to unsubstituted alkyl groups as defined above, except that at least one triple bond exists between two carbon atoms. Examples include, but are not limited to, -C≡C(H), -C≡C(CH_3), -C≡C(CH_2CH_3), -C(H_2)C≡C(H), -C(H)$_2$C≡C(CH_3), and –C(H)$_2$C≡C(CH_2CH_3) among others. Unsubstituted lower alkynyl groups have from 1 to about 6 carbons.

The phrase "substituted alkynyl" has the same meaning with respect to unsubstituted alkynyl groups that substituted alkyl groups have with respect to unsubstituted alkyl groups. A substituted alkynyl group includes alkynyl groups in which a non-carbon or non-hydrogen atom is bonded to a carbon triple bonded to another carbon and those in which a non-carbon or non-hydrogen atom is bonded to a carbon not involved in a triple bond to another carbon. Examples include, but are not limited to, oxoalkynyls wherein a CH_2 group is replaced by a carbonyl, such as –C(O)-CH≡CH-CH_3 and –C(O)-CH_2-CH≡CH.

The phrase "unsubstituted alkynylene" refers to a divalent unsubstituted alkynyl group as defined above. A –C≡C- is an example of an unsubstituted alkynylene. The phrase "substituted alkynylene" refers to a divalent substituted alkynyl group as defined above.

The phrase "unsubstituted aralkyl" refers to unsubstituted alkyl groups as defined above in which a hydrogen or carbon bond of the unsubstituted alkyl group is replaced with a bond to an aryl group as defined above. For example, methyl (-CH_3) is an unsubstituted alkyl group. If a hydrogen atom of the methyl group is replaced by a bond to a phenyl group, such as if the carbon of the methyl were bonded to a carbon of benzene, then the compound is an unsubstituted aralkyl group (*i.e.*, a benzyl group). Thus, the phrase includes, but is not limited to, groups such as benzyl, diphenylmethyl, and 1-phenylethyl (-CH(C_6H_5)(CH_3)).

The phrase "substituted aralkyl" has the same meaning with respect to unsubstituted aralkyl groups that substituted aryl groups have with respect to unsubstituted aryl groups. However, substituted aralkyls also include groups in which a carbon or hydrogen bond of the alkyl part of the group is replaced by a bond to a non-carbon or a non-hydrogen atom. Examples of substituted aralkyl groups include, but are not limited to, -CH_2C(=O)(C_6H_5), and –CH_2(2-methylphenyl).

The phrase "unsubstituted aralkenyl" refers to unsubstituted alkenyl groups as defined above in which a hydrogen or carbon bond of the unsubstituted alkenyl group is replaced with a bond to an aryl group as defined above. For example, vinyl is an unsubstituted alkenyl group. If a hydrogen atom of the vinyl group is replaced by a bond to a phenyl group, such as if a carbon of the vinyl were bonded to a carbon of benzene, then the compound is an unsubstituted aralkenyl group (i.e., a styryl group). Thus, the phrase includes, but is not limited to, groups such as styryl, diphenylvinyl, and 1-phenylethenyl (-$C(C_6H_5)(CH_2)$).

The phrase "substituted aralkenyl" has the same meaning with respect to unsubstituted aralkenyl groups that substituted aryl groups have with respect to unsubstituted aryl groups. A substituted aralkenyl group also includes groups in which a carbon or hydrogen bond of the alkenyl part of the group is replaced by a bond to a non-carbon or a non-hydrogen atom. Examples of substituted aralkenyl groups include, but are not limited to, -CH=C(Cl)(C_6H_5), and –CH=CH(2-methylphenyl).

The phrase "unsubstituted aralkynyl" refers to unsubstituted alkynyl groups as defined above in which a hydrogen or carbon bond of the unsubstituted alkynyl group is replaced with a bond to an aryl group as defined above. For example, acetylene is an unsubstituted alkynyl group. If a hydrogen atom of the acetylene group is replaced by a bond to a phenyl group, such as if a carbon of the acetylene were bonded to a carbon of benzene, then the compound is an unsubstituted aralkynyl group. Thus, the phrase includes, but is not limited to, groups such as –C≡C-phenyl and –CH_2-C≡C-phenyl.

The phrase "substituted aralkynyl" has the same meaning with respect to unsubstituted aralkynyl groups that substituted aryl groups have with respect to unsubstituted aryl groups. However, a substituted aralkynyl group also includes groups in which a carbon or hydrogen bond of the alkynyl part of the group is replaced by a bond to a non-carbon or a non-hydrogen atom. Examples of substituted aralkynyl groups include, but are not limited to, -C≡C-C(Br)(C_6H_5) and –C≡C(2-methylphenyl).

The phrase "unsubstituted heteroalkyl" refers to unsubstituted alkyl groups as defined above in which the carbon chain is interrupted by one or more heteroatoms chosen from N, O, and S. Unsubstituted heteroalkyls containing N may have NH or N(unsubstituted alkyl) in the carbon chain. For example, unsubstituted heteroalkyls include alkoxy, alkoxyalkyl, alkoxyalkoxy, thioether, alkylaminoalkyl, aminoalkyloxy, and other such groups. Typically, unsubstituted heteroalkyl groups contain 1-5 heteroatoms, and particularly 1-3 heteroatoms. In some embodiments unsubstituted heteroalkyls include, for example, alkoxyalkoxyalkoxy groups such as ethyloxyethyloxyethyloxy.

The phrase "substituted heteroalkyl" has the same meaning with respect to unsubstituted heteroalkyl groups that substituted alkyl groups have with respect to unsubstituted alkyl groups.

The phrase "unsubstituted heteroalkylene" refers to a divalent unsubstituted heteroalkyl group as defined above. For example, $-CH_2-O-CH_2-$ and $-CH_2-NH-CH_2CH_2-$ are both exemplary unsubstituted heteroalkylenes. The phrase "substituted heteroalkylene" refers to a divalent substituted heteroalkyl group As defined above.

The phrase "unsubstituted heteroalkenyl" refers to unsubstituted alkene groups as defined above in which the carbon chain is interrupted by one or more heteroatoms chosen from N, O, and S. Unsubstituted heteroalkenyls containing N may have NH or N(unsubstituted alkyl or alkene) in the carbon chain. The phrase "substituted heteroalkenyl" has the same meaning with respect to unsubstituted heteroalkenyl groups that substituted heteroalkyl groups have with respect to unsubstituted heteroalkyl groups.

The phrase "unsubstituted heteroalkenylene" refers to a divalent unsubstituted heteroalkenyl group as defined above. Thus $-CH_2-O-CH=CH-$ is an example of an unsubstituted heteroalkenylene. The phrase "substituted heteroalkenylene" refers to a divalent substituted heteroalkenyl group as defined above.

The phrase "unsubstituted heteroalkynyl" refers to unsubstituted alkynyl groups as defined above in which the carbon chain is interrupted by one or more heteroatoms chosen from N, O, and S. Unsubstituted heteroalkynyls containing N may have NH or N(unsubstituted alkyl, alkene, or alkyne) in the carbon chain. The phrase "substituted heteroalkynyl" has the same meaning with respect to unsubstituted heteroalkynyl groups that substituted heteroalkyl groups have with respect to unsubstituted heteroalkyl groups.

The phrase "unsubstituted heteroalkynylene" refers to a divalent unsubstituted heteroalkynyl group as defined above. Thus $-CH_2-O-CH_2-C\equiv C-$ is an example of an unsubstituted heteroalkynylene. The phrase "substituted heteroalkynylene" refers to a divalent substituted heteroalkynyl group as defined above.

The phrase "unsubstituted heterocyclyl" refers to both aromatic and nonaromatic ring compounds including monocyclic, bicyclic, and polycyclic ring compounds such as, but not limited to, quinuclidyl, containing 3 or more ring members of which one or more is a heteroatom such as, but not limited to, N, O, and S. Although the phrase "unsubstituted heterocyclyl" includes condensed heterocyclic rings such as benzimidazolyl, it does not include heterocyclyl groups that have other groups such as alkyl or halo groups bonded to one of the ring members as compounds such as 2-methylbenzimidazolyl are substituted heterocyclyl groups. Examples of heterocyclyl groups include, but are not limited to: unsaturated 3 to 8 membered rings containing 1 to 4 nitrogen atoms such as, but not limited to pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, dihydropyridyl, pyrimidyl,

pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl etc.), tetrazolyl, (e.g., 1H-tetrazolyl, 2H tetrazolyl, etc.); saturated 3 to 8 membered rings containing 1 to 4 nitrogen atoms such as, but not limited to, pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl; condensed unsaturated heterocyclic groups containing 1 to 4 nitrogen atoms such as, but not limited to, indolyl, isoindolyl, indolinyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl; unsaturated 3 to 8 membered rings containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms such as, but not limited to, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.); saturated 3 to 8 membered rings containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms such as, but not limited to, morpholinyl; unsaturated condensed heterocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, benzoxazolyl, benzoxadiazolyl, benzoxazinyl (e.g., 2H-1,4-benzoxazinyl, etc.); unsaturated 3 to 8 membered rings containing 1 to 3 sulfur atoms and 1 to 3 nitrogen atoms such as, but not limited to, thiazolyl, isothiazolyl, thiadiazolyl (e.g., 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.); saturated 3 to 8 membered rings containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms such as, but not limited to, thiazolodinyl; saturated and unsaturated 3 to 8 membered rings containing 1 to 2 sulfur atoms such as, but not limited to, thienyl, dihydrodithiinyl, dihydrodithionyl, tetrahydrothiophene, tetrahydrothiopyran; unsaturated condensed heterocyclic rings containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms such as, but not limited to, benzothiazolyl, benzothiadiazolyl, benzothiazinyl (e.g., 2H-1,4-benzothiazinyl, etc.), dihydrobenzothiazinyl (e.g., 2H-3,4-dihydrobenzothiazinyl, etc.), unsaturated 3 to 8 membered rings containing oxygen atoms such as, but not limited to furyl; unsaturated condensed heterocyclic rings containing 1 to 2 oxygen atoms such as benzodioxolyl (e.g., 1,3-benzodioxoyl, etc.); unsaturated 3 to 8 membered rings containing an oxygen atom and 1 to 2 sulfur atoms such as, but not limited to, dihydrooxathiinyl; saturated 3 to 8 membered rings containing 1 to 3 oxygen atoms and 1 to 2 sulfur atoms such as 1,4-oxathiane; unsaturated condensed rings containing 1 to 2 sulfur atoms such as benzothienyl, benzodithiinyl; and unsaturated condensed heterocyclic rings containing an oxygen atom and 1 to 3 oxygen atoms such as benzoxathiinyl. Heterocyclyl group also include those described above in which one or more S atoms in the ring is double-bonded to one or two oxygen atoms (sulfoxides and sulfones). For example, heterocyclyl groups include tetrahydrothiophene, tetrahydrothiophene oxide, and tetrahydrothiophene 1,1-dioxide. In some embodiments heterocyclyl groups contain 5 or 6 ring members. In other embodiments heterocyclyl groups include morpholine, piperazine, piperidine, pyrrolidine, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, thiomorpholine, thiomorpholine in which the S atom of the thiomorpholine is bonded to one or more O atoms, pyrrole, homopiperazine, oxazolidin-2-one, pyrrolidin-2-one, oxazole, quinuclidine, thiazole, isoxazole, furan, and tetrahydrofuran.

The phrase "substituted heterocyclyl" refers to an unsubstituted heterocyclyl group as defined above in which one of the ring members is bonded to a non-hydrogen atom such as described above with

respect to substituted alkyl groups and substituted aryl groups. Examples include, but are not limited to, 2-methylbenzimidazolyl, 5-methylbenzimidazolyl, 5-chlorobenzthiazolyl, 1-methyl piperazinyl, and 2-chloropyridyl.

The phrase "unsubstituted heteroaryl" refers to unsubstituted aromatic heterocyclyl groups as defined above. Thus, unsubstituted heteroaryl groups include but are not limited to furyl, imidazolyl, oxazolyl, isoxazolyl, pyridinyl, benzimidazolyl, and benzothiazolyl. The phrase "substituted heteroaryl" refers to substituted aromatic heterocyclyl groups as defined above.

The phrase "unsubstituted heterocyclylalkyl" refers to unsubstituted alkyl groups as defined above in which a hydrogen or carbon bond of the unsubstituted alkyl group is replaced with a bond to a heterocyclyl group as defined above. For example, methyl ($-CH_3$) is an unsubstituted alkyl group. If a hydrogen atom of the methyl group is replaced by a bond to a heterocyclyl group, such as if the carbon of the methyl were bonded to carbon 2 of pyridine (one of the carbons bonded to the N of the pyridine) or carbons 3 or 4 of the pyridine, then the compound is an unsubstituted heterocyclylalkyl group.

The phrase "substituted heterocyclylalkyl" has the same meaning with respect to unsubstituted heterocyclylalkyl groups that substituted aralkyl groups have with respect to unsubstituted aralkyl groups. A substituted heterocyclylalkyl group also includes groups in which a non-hydrogen atom is bonded to a heteroatom in the heterocyclyl group of the heterocyclylalkyl group such as, but not limited to, a nitrogen atom in the piperidine ring of a piperidinylalkyl group.

The phrase "unsubstituted heterocyclylalkenyl" refers to unsubstituted alkenyl groups as defined above in which a hydrogen or carbon bond of the unsubstituted alkenyl group is replaced with a bond to a heterocyclyl group as defined above. For example, vinyl is an unsubstituted alkenyl group. If a hydrogen atom of the vinyl group is replaced by a bond to a heterocyclyl group, such as if the carbon of the vinyl were bonded to carbon 2 of pyridine or carbons 3 or 4 of the pyridine, then the compound is an unsubstituted heterocyclylalkenyl group.

The phrase "substituted heterocyclylalkenyl" has the same meaning with respect to unsubstituted heterocyclylalkenyl groups that substituted aralkenyl groups have with respect to unsubstituted aralkenyl groups. However, a substituted heterocyclylalkenyl group also includes groups in which a non-hydrogen atom is bonded to a heteroatom in the heterocyclyl group of the heterocyclylalkenyl group such as, but not limited to, a nitrogen atom in the piperidine ring of a piperidinylalkenyl group.

The phrase "unsubstituted heterocyclylalkynyl" refers to unsubstituted alkynyl groups as defined above in which a hydrogen or carbon bond of the unsubstituted alkynyl group is replaced with a bond to a heterocyclyl group as defined above. For example, acetylene is an unsubstituted alkynyl group.

If a hydrogen atom of the acetylene group is replaced by a bond to a heterocyclyl group, such as if the carbon of the acetylene were bonded to carbon 2 of pyridine or carbons 3 or 4 of the pyridine, then the compound is an unsubstituted heterocyclylalkynyl group.

The phrase "substituted heterocyclylalkynyl" has the same meaning with respect to unsubstituted heterocyclylalkynyl groups that substituted aralkynyl groups have with respect to unsubstituted aralkynyl groups. A substituted heterocyclylalkynyl group also includes groups in which a non-hydrogen atom is bonded to a heteroatom in the heterocyclyl group of the heterocyclylalkynyl group such as, but not limited to, a nitrogen atom in the piperidine ring of a piperidinylalkynyl group.

The phrase "unsubstituted alkoxy" refers to a hydroxyl group (-OH) in which the bond to the hydrogen atom is replaced by a bond to a carbon atom of an otherwise unsubstituted alkyl group as defined above.

The phrase "substituted alkoxy" refers to a hydroxyl group (-OH) in which the bond to the hydrogen atom is replaced by a bond to a carbon atom of an otherwise substituted alkyl group as defined above.

A "pharmaceutically acceptable salt" includes a salt with an inorganic base, organic base, inorganic acid, organic acid, or basic or acidic amino acid. Salts of inorganic bases include, for example, alkali metals such as sodium or potassium; alkaline earth metals such as calcium and magnesium or aluminum; and ammonia. Salts of organic bases include, for example, trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, and triethanolamine. Salts of inorganic acids include for example, hydrochloric acid, hydroboric acid, nitric acid, sulfuric acid, and phosphoric acid. Salts of organic acids include for example, formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, and p-toluenesulfonic acid. Salts of basic amino acids include, for example, arginine, lysine and ornithine. Acidic amino acids include, for example, aspartic acid and glutamic acid.

"Tautomers" refers to isomeric forms of a compound that are in equilibrium with each other. The concentrations of the isomeric forms will depend on the environment the compound is found in and may be different depending upon, for example, whether the compound is a solid or is in an organic or aqueous solution. For example, in aqueous solution, ketones are typically in equilibrium with their enol forms. Thus, ketones and their enols are referred to as tautomers of each other. As readily understood by one skilled in the art, a wide variety of functional groups and other structures may exhibit tautomerism, and all tautomers of compounds of Formulas I, II, and III are within the scope of the present invention.

The compounds according to the invention may be solvated, especially hydrated. Hydration may occur during manufacturing of the compounds or compositions comprising the compounds, or the hydration may occur over time due to the hygroscopic nature of the compounds.

Certain embodiments are derivatives referred to as prodrugs. The expression "prodrug" denotes a derivative of a pharmaceutically or therapeutically active drug, e.g., esters and amides, wherein the derivative has an enhanced characteristic such as, for example, enhanced delivery and therapeutic value as compared to the drug and can be transformed into the drug by an enzymatic or chemical process. See, for example, R.E. Notari, Methods Enzymol. 112:309-323 (1985); N. Bodor, Drugs of the Future 6:165-182 (1981); H. Bundgaard, Chapter 1 in *Design of Prodrugs* (H. Bundgaard, ed.), Elsevier, New York (1985); and A. G. Gilman *et al.*, *Goodman And Gilman's The Pharmacological Basis of Therapeutics*, 8th ed., McGraw-Hill (1990). Thus, the prodrug may be designed to alter the metabolic stability or transport characteristics of a drug, mask side effects or toxicity of a drug, improve the flavor of a drug, or to alter other characteristics or properties of a drug.

Compounds of the present invention include enriched or resolved optical isomers at any or all asymmetric atoms as are apparent from the depictions. Both racemic and diastereomeric mixtures, as well as the individual optical isomers can be isolated or synthesized so as to be substantially free of their enantiomeric or diastereomeric partners. All such stereoisomers are within the scope of the invention.

The term "carboxy protecting group" as used herein refers to a carboxylic acid protecting ester group employed to block or protect the carboxylic acid functionality while the reactions involving other functional sites of the compound are carried out. Carboxy protecting groups are disclosed in, for example, Greene, *Protective Groups in Organic Synthesis*, pp. 152-186, John Wiley & Sons, New York (1981), which is hereby incorporated herein by reference. In addition, a carboxy protecting group can be used as a prodrug, whereby the carboxy protecting group can be readily cleaved *in vivo* by, for example, enzymatic hydrolysis to release the biologically active parent. T. Higuchi and V. Stella provide a discussion of the prodrug concept in "Pro-drugs as Novel Delivery Systems", Vol. 14 of the A.C.S. Symposium Series, American Chemical Society (1975), which is hereby incorporated herein by reference. Such carboxy protecting groups are well known to those skilled in the art, having been extensively used in the protection of carboxyl groups in the penicillin and cephalosporin fields, as described in U.S. Patent Nos. 3,840,556 and 3,719,667, S. Kukolja, J. Am. Chem. Soc. 93:6267-6269 (1971), and G.E. Gutowski, Tetrahedron Lett. 21:1779-1782 (1970), the disclosures of which are hereby incorporated herein by reference. Examples of esters useful as prodrugs for compounds containing carboxyl groups can be found, for example, at pp. 14-21 in *Bioreversible Carriers in Drug Design: Theory and Application* (E.B. Roche, ed.), Pergamon Press, New York (1987), which is hereby incorporated herein by reference. Representative carboxy protecting groups are C_1 to C_8 alkyl

(e.g., methyl, ethyl or tertiary butyl and the like); haloalkyl; alkenyl; cycloalkyl and substituted derivatives thereof such as cyclohexyl, cyclopentyl and the like; cycloalkylalkyl and substituted derivatives thereof such as cyclohexylmethyl, cyclopentylmethyl and the like; arylalkyl, for example, phenethyl or benzyl and substituted derivatives thereof such as alkoxybenzyl or nitrobenzyl groups and the like; arylalkenyl, for example, phenylethenyl and the like; aryl and substituted derivatives thereof, for example, 5-indanyl and the like; dialkylaminoalkyl (e.g., dimethylaminoethyl and the like); alkanoyloxyalkyl groups such as acetoxymethyl, butyryloxymethyl, valerytoxymethyl, isobutyryloxymethyl, isovaleryloxymethyl, 1-(propionyloxy)-1-ethyl, 1-(pivaloyloxyl)-1-ethyl, 1-methyl-1-(propionyloxy)-1-ethyl, pivaloyloxymethyl, propionyloxymethyl and the like; cycloalkanoyloxyalkyl groups such as cyclopropylcarbonyloxymethyl, cyclobutylcarbonyloxymethyl, cyclopentylcarbonyloxymethyl, cyclohexylcarbonyloxymethyl and the like; aroyloxyalkyl, such as benzoyloxymethyl, benzoyloxyethyl and the like; arylalkylcarbonyloxyalkyl, such as benzylcarbonyloxymethyl, 2-benzylcarbonyloxyethyl and the like; alkoxycarbonylalkyl, such as methoxycarbonylmethyl, cyclohexyloxycarbonylmethyl, 1-methoxycarbonyl-1-ethyl, and the like; alkoxycarbonyloxyalkyl, such as methoxycarbonyloxymethyl, t-butyloxycarbonyloxymethyl, 1-ethoxycarbonyloxy-1-ethyl, 1-cyclohexyloxycarbonyloxy-1-ethyl and the like; alkoxycarbonylaminoalkyl, such as t-butyloxycarbonylaminomethyl and the like; alkylaminocarbonylaminoalkyl, such as methylaminocarbonylaminomethyl and the like; alkanoylaminoalkyl, such as acetylaminomethyl and the like; heterocycliccarbonyloxyalkyl, such as 4-methylpiperazinylcarbonyloxymethyl and the like; dialkylaminocarbonylalkyl, such as dimethylaminocarbonylmethyl, diethylaminocarbonylmethyl and the like; (5-(alkyl)-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-t-butyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like; and (5-phenyl-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like.

The term "N-protecting group" or "N-protected" as used herein refers to those groups intended to protect the N-terminus of an amino acid or peptide or to protect an amino group against undesirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in, for example, Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York (1981), which is hereby incorporated by reference. For example, N-protecting groups can comprise acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, a-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl and the like; carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-

trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α,α-di methyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2,-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, phenylthiocarbonyl and the like; alkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. In some embodiments N-protecting groups are formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, benzyl, 9-fluorenylmethyloxycarbonyl (Fmoc), t-butyloxycarbonyl (Boc), and benzyloxycarbonyl (Cbz).

As used herein, "halo," "halogen" or "halide" refers to F, Cl, Br or I.

As used herein, the abbreviations for any protective groups, amino acids or other compounds, are, unless indicated otherwise, in accord with their common usage, recognized abbreviations, or the IUPAC-IUB Commission on Biochemical Nomenclature, Biochem. 11:942-944 (1972).

As used herein, "substantially pure" means sufficiently homogeneous to appear free of readily detectable impurities as determined by standard methods of analysis, such as thin layer chromatography (TLC), gel electrophoresis, and high performance liquid chromatography (HPLC), used by those of skill in the art to assess such purity, or sufficiently pure such that further purification would not detectably alter the physical and chemical properties, such as enzymatic and biological activities, of the substance. Substantially pure includes compositions in which the AA targeting agent or AA targeting compound forms the major component of the composition, such as constituting about 50%, about 60%, about 70%, about 80%, about 90%, or about 95% or more of the substances in the composition. Methods for purification of compounds to produce substantially chemically pure compounds are known to those of skill in the art. A substantially chemically pure compound may, however, be a mixture of stereoisomers. In such instances, further purification may increase the specific activity of the compound. However, AA targeting agents need not always be provided in a specific purified state. Partially purified compositions will have utility in certain embodiments and depending on the desired use. For example, purification methods that may yield a greater total recovery of AA-targeting agent may produce a lower degree of relative purification.

As used herein, "biological activity" refers to the *in vivo* activities of a compound, composition, or other mixture, or physiological responses that result upon *in vivo* administration of a compound, composition or other mixture. Biological activity thus encompasses therapeutic effects, diagnostic effects and pharmaceutical activity of such compounds, compositions, and mixtures. The term "biologically active" or "functional" when used as a modifier of invention AA targeting agent

containing polypeptides or compositions thereof refers to a polypeptide that exhibits at least one activity that is characteristic of or similar to an AA targeting agent.

As used herein, "pharmacokinetics" refers to the concentration of an administered compound in the serum over time. Pharmacodynamics refers to the concentration of an administered compound in target and nontarget tissues over time and the effects on the target tissue (e.g., efficacy) and the non-target tissue (e.g., toxicity). Improvements in, for example, pharmacokinetics or pharmacodynamics can be designed for a particular targeting agent or biological agent, such as by using labile linkages or by modifying the chemical nature of any linker (e.g., changing solubility, charge, and the like).

As employed herein, the phrases "an effective amount" and "therapeutically effective amount" refer to an amount of an AA targeting agent or compound comprising an AA targeting agent that is useful or able to support an observable change in the level of one or more biological activity characteristic of an AA targeting agent, or a dose sufficient to impart a beneficial effect, e.g., an amelioration of a symptom on the recipient thereof. The specific therapeutically effective dose level for any particular subject will depend upon a variety of factors including the symptom or disorder being treated, the severity of the symptom or disorder, the activity of the specific compound, the route of administration, the rate of clearance of the compound, the duration of treatment, the drugs used in combination or coincident with the compound, the age, body weight, sex, diet, and general health of the subject, and like, as well as other factors well known in the medical arts and sciences. A therapeutically effective amount can be an amount of AA targeting compound sufficient to produce a measurable inhibition of angiogenesis in the tissue being treated, i.e., an angiogenesis-inhibiting amount. Inhibition of angiogenesis can be measured in situ by immunohistochemistry, or by other methods known to one skilled in the art. Various general considerations taken into account in determining the "therapeutically effective amount" are known to those of skill in the art and are described, e.g., in Gilman, A.G., *et al.*, *Goodman And Gilman's The Pharmacological Basis of Therapeutics*, 8th ed., McGraw-Hill (1990); and *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Co., Easton, PA (1990).

In one aspect, the present invention provides various targeting compounds in which AA targeting agents are covalently linked to a combining site of an antibody.

In another aspect, the present invention includes methods of altering at least one physical or biological characteristic of an AA targeting agent. The methods include covalently linking an AA targeting agent to a combining site of an antibody, either directly or though a linker. Characteristics of an AA targeting agent that may be modified include, but are not limited to, binding affinity, susceptibility to degradation (e.g., by proteases), pharmacokinetics, pharmacodynamics, immunogenicity, solubility, lipophilicity, hydrophilicity, hydrophobicity, stability (either more or less stable, as well as planned

degradation), rigidity, flexibility, modulation of antibody binding, and the like. Also, the biological potency of a particular AA targeting agent may be increased by the addition of the effector function(s) provided by the antibody. For example, an antibody provides effector functions such as complement mediated effector functions. Without wishing to be bound by any theory, the antibody portion of an AA targeting compound may generally extend the half-life of a smaller sized AA targeting agent *in vivo*. Thus, in one aspect, the invention provides a method for increasing the effective circulating half-life of an AA targeting agent.

In another aspect, the present invention provides methods for modulating the binding activity of an antibody by covalently attaching an AA targeting agent to a combining site of the antibody. Although not wishing to be bound by any theory, substantially reduced antibody binding to an antigen may result from the linked AA targeting agent(s) sterically hindering the antigen from contacting the antibody combining site. Alternatively, substantially reduced antigen binding may result if the amino acid side chain of the antibody combining site modified by covalent linkage is important for binding to the antigen. By contrast, substantially increased antibody binding to an antigen may result when a linked AA targeting agent(s) does not sterically hinder the antigen from contacting the antibody combining site and/or when the amino acid side chain of the antibody combining site modified by covalent linkage is not important for binding to the antigen.

In another aspect, the present invention includes methods of modifying a combining site of an antibody to generate binding specificity for Ang-2. Such methods include covalently linking a reactive amino acid side chain in a combining site of the antibody to a chemical moiety on a linker of an AA targeting agent-linker compound as described herein where an AA targeting agent is based upon an Ang-2 binding peptide. The chemical moiety of the linker is sufficiently distanced from the AA targeting agent so that an AA targeting agent can bind its cognate when an AA targeting agent-linker compound is covalently linked to an antibody combining site. Typically, the antibody will not be considered specific for the target molecule. In certain embodiments, an antibody prior to covalent linking would have an affinity for Ang-2 of less than about 1×10^{-5} moles/liter. However, after the antibody is covalently linked to the AA targeting agent-linker compound, the modified antibody preferably has an affinity for the target molecule of at least about 1×10^{-6} moles/liter, alternatively, at least about 1×10^{-7} moles/liter, alternatively, at least 1×10^{-8} moles/liter, alternatively at least 1×10^{-9} moles/liter, or alternatively, at least about 1×10^{-10} moles/liter.

AA Targeting Agents

An AA targeting agent is a peptide selected from the group consisting of:

R^1-Q(AcK)Y QPL DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:29)

R^1-QNY QPL DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:28)

R^1-Q(AcK)Y QPL DEK D(AcK)T LYD QFM LQQ G- R^2; (SEQ ID NO:30)

R^1-Q(AcK)Y QPL DEK DET LYD QFM LQQ G- R^2; (SEQ ID NO:33)

R^1-Q(AcK)Y Q(DHP)L DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:34)

R^1-Q(AcK)Y Q(HP)L DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:35)

R^1-Q(AcK)Y QPL DEL DKT IYD QFM LQQ G- R^2; (SEQ ID NO:36)

R^1-Q(AcK)Y QPL DEI DKT LYD QFM LQQ G- R^2; (SEQ ID NO:37)

R^1-Q(AcK)Y QPL DEL DKT (HChA)YD QFM LQQ G- R^2; (SEQ ID NO:38)

R^1-Q(AcK)Y QPL DEL DKT (HF)YD QFM LQQ G- R^2; (SEQ ID NO:39)

R^1-Q(AcK)Y QPL DEL DKT (ThA)YD QFM LQQ G- R^2; (SEQ ID NO:40)

R^1-Q(AcK)Y QPL DEL DKT (Nva)YD QFM LQQ G- R^2; (SEQ ID NO:41)

R^1-Q(AcK)Y QPL DEL DKT (HL)YD QFM LQQ G- R^2; (SEQ ID NO:42)

R^1-Q(AcK)Y QPL DE(AcK) DKT LYD QFM LQQ G- R^2; (SEQ ID NO:43)

R^1-Q(AcK)Y QPL DEL DKT LFD QFM LQQ G- R^2; (SEQ ID NO:44)

R^1-Q(AcK)Y Q(HP)L DE(ThA) DKT L(NO2F)D QFM LQQ G- R^2; (SEQ ID NO:45)

R^1-Q(AcK)Y Q(HP)L DE(ThA) DKT L(BPA)D QFM LQQ G- R^2; (SEQ ID NO:46)

R^1-Q(AcK)Y Q(HP)L DE(ThA) DKT L(CO2H)FD QFM LQQ G- R^2; (SEQ ID NO:47)

R^1-Q(AcK)Y QPL DE(AcK) DKT L(NO2F)D QFM LQQ G- R^2; (SEQ ID NO:48)

R^1-Q(AcK)Y QPL DE(AcK) DKT LFD QFM LQQ G- R^2 (SEQ ID NO:63)

DCB-Q(AcK)Y QPL DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:49)

DFB-Q(AcK)Y QPL DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:50)

PyC-Q(AcK)Y QPL DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:51)

Amido 2-PEG-Q(AcK)Y QPL DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:52)

R^1-Q(ClBnCarbamateK)Y QPL DEL DKT LYD QFM LQQ G- R^2; (SEQ ID NO:53)

R^1-Q(AcK)Y QPL DEL D(Dab)T LYD QFM LQQ G- R^2; (SEQ ID NO:54)

R^1-Q(AcK)Y QPL DEL D(Dap)T LYD QFM LQQ G- R^2; (SEQ ID NO:55)

R^1-Q(AcK)Y QPL DEL DKT L(NO2F)D QFM LQQ G-R^2; (SEQ ID NO:91)

R^1-QNY QPL DEL DKT L(BPA)D QFM LQQ G-R^2; (SEQ ID NO:56)

R^1-QNY QPL DEL DKT L(CF)D QFM LQQ G-R^2; (SEQ ID NO:57)

R^1-Q(Nick)Y QPL DEL DKT LYD QFM LQQ G-R^2; (SEQ ID NO:61)

R^1-Q(AcK)Y QPL DE(AcK) DKT L(CF)D QFM LQQ G-R^2; (SEQ ID NO:62) and

R^1-Q(AcK)Y QPL DE(AcK) DKT LFD QFM LQQ G-R^2; (SEQ ID NO: 63)

wherein

R^1 is CH_3, $C(O)CH_3$, $C(O)CH_3$, $C(O)CH_2CH_3$, $C(O)CH_2CH_2CH_3$, $C(O)CH(CH_3)CH_3$, $C(O)CH_2CH_2CH_2CH_3$, $C(O)CH(CH_3)CH_2CH_3$, $C(O)C_6H_5$, $C(O)CH_2CH_2(CH_2CH_2O)_{1\text{-}5}Me$, dichlorobenzoyl (DCB), difluorobenzoyl (DFB), pyridinyl carboxlate (PyC) or amido-2-PEG, an amino protecting group, a lipid fatty acid group or a carbohydrate; and

R^2 is OH, NH_2, $NH(CH_3)$, $NHCH_2CH_3$, $NHCH_2CH_2CH_3$, $NHCH(CH_3)CH_3$, $NHCH_2CH_2CH_2CH_3$, $NHCH(CH_3)CH_2CH_3$, NHC_6H_5, $NHCH_2CH_2OCH_3$, $NHOCH_3$, $NHOCH_2CH_3$, a carboxy protecting group, a lipid fatty acid group or a carbohydrate, and

An AA targeting compound can be prepared using techniques well known in the art. Typically, synthesis of the peptidyl AA targeting agent is the first step and is carried out as described herein. The targeting agent is then derivatized for linkage to a connecting component (the linker), which is then combined with the antibody. One of skill in the art will readily appreciate that the specific synthetic steps used depend upon the exact nature of the three components. Thus, AA targeting agent – linker conjugates and AA targeting compounds described herein can be readily synthesized.

AA targeting agent peptides may be synthesized by many techniques that are known to those skilled in the art. For solid phase peptide synthesis, a summary of exemplary techniques may be found in *Chemical Approaches to the Synthesis of Peptides and Proteins* (Williams *et al.*, eds.), CRC Press, Boca Raton, FL (1997).

Typically, the desired peptidic AA targeting agent is synthesized sequentially on solid phase according to procedures well known in the art. See, e.g., U.S. Patent Application No. 2003/0045477). The linker may be attached to the peptide in part or in full on the solid phase, or may be added using solution phase techniques after the removal of the peptide from the resin (see FIGURES 6A and 6B). For example, an N-protected amino and carboxylic acid-containing linking moiety may be attached to a resin such as 4-hydroxymethyl-phenoxymethyl-poly(styrene-1% divinylbenzene). The N-protecting group may be removed by the appropriate acid (e.g., TFA for Boc) or base (e.g., piperidine for Fmoc), and the peptide sequence developed in the normal C-terminus to N-terminus fashion (see FIGURE 6A). Alternatively, the peptide sequence may be synthesized first and the linker added to the N-

terminal amino acid residue last (see FIGURE 6B). Yet another method entails deprotecting an appropriate side chain during synthesis and derivatizing with a suitably reactive linker. For example, a lysine side chain may be deprotected and reacted with a linker having an active ester. Alternatively, an amino acid derivative with a suitably protected linker moiety already attached to the side chain (see FIGURE 6B) or, in some cases, the alpha-amino nitrogen, may be added as part of the growing peptide sequence.

At the end of the solid phase synthesis, the targeting agent-linker conjugate is removed from the resin and deprotected, either in succession or in a single operation. Removal of the targeting agent-linker conjugate and deprotection can be accomplished in a single operation by treating the resin-bound peptide-linker conjugate with a cleavage reagent, for example, trifluoroacetic acid containing scavengers such as thianisole, water, or ethanedithiol. After deprotection and release of the targeting agent, further derivatization of the targeting agent peptide may be carried out.

The fully deprotected targeting agent-linker conjugate is purified by a sequence of chromatographic steps employing any or all of the following types: ion exchange on a weakly basic resin in the acetate form; hydrophobic adsorption chromatography on underivatized polystyrene-divinylbenzene (e.g., AMBERLITE XAD); silica gel adsorption chromatography; ion exchange chromatography on carboxymethylcellulose; partition chromatography, e.g., on SEPHADEX G-25, LH-20 or countercurrent distribution; high performance liquid chromatography (HPLC), especially reverse-phase HPLC on octyl- or octadecylsilyl-silica bonded phase column packing.

Antibodies

"Antibody" as used herein includes polypeptide molecules comprising heavy and/or light chains which have immunoreactive activity. Antibodies include immunoglobulins which are the product of B cells and variants thereof, as well as the T cell receptor (TcR) which is the product of T cells and variants thereof. An immunoglobulin is a protein comprising one or more polypeptides substantially encoded by the immunoglobulin kappa and lambda, alpha, gamma, delta, epsilon and mu constant region genes, as well as myriad immunoglobulin variable region genes. Light chains are classified as either kappa or lambda. Heavy chains are classified as gamma, mu, alpha, delta, or epsilon, which in turn define the immunoglobulin classes, IgG, IgM, IgA, IgD, and IgE, respectively. Subclasses of heavy chains are also known. For example, IgG heavy chains in humans can be any of IgG1, IgG2, IgG3, and IgG4 subclasses.

A typical immunoglobulin structural unit is known to comprise a tetramer. Each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kD) and one "heavy" chain (about 50-70 kD). The N-terminus of each chain defines a variable region of about

100 to 110 or more amino acids primarily responsible for antigen recognition. The terms variable light chain (V_L) and variable heavy chain (V_H) refer to these light and heavy chains respectively. The amino acids of an antibody may be naturally or nonnaturally occurring.

Antibodies that contain two combining sites are bivalent in that they have two complementarity or antigen recognition sites. A typical natural bivalent antibody is an IgG. Although vertebrate antibodies generally comprise two heavy chains and two light chains, heavy chain only antibodies are also known. See Muyldermans *et al.*, TRENDS in Biochem. Sci. 26(4):230-235 (1991). Such antibodies are bivalent and are formed by the pairing of heavy chains. Antibodies may also be multi-valent, as in the case of dimeric forms of IgA and the pentameric IgM molecule. Antibodies also include hybrid antibodies wherein the antibody chains are separately homologous with referenced mammalian antibody chains. One pair of heavy and light chain has a combining site specific to one antigen and the other pair of heavy and light chains has a combining site specific to a different antigen. Such antibodies are referred to as bi-specific because they are able to bind two different antigens at the same time. Antibodies may also be univalent, such as, for example, in the case of Fab or Fab' fragments.

Antibodies exist as full length intact antibodies or as a number of well-characterized fragments produced by digestion with various peptidases or chemicals. Thus, for example, pepsin digests an antibody below the disulfide linkages in the hinge region to produce $F(ab')_2$, a dimer of Fab which itself is a light chain joined to V_H-CH_1 by a disulfide bond. $F(ab')_2$ may be reduced under mild conditions to break the disulfide linkage in the hinge region, thereby converting the $F(ab')_2$ dimer into a Fab' monomer. The Fab' monomer is essentially a Fab fragment with part of the hinge region (see, e.g., *Fundamental Immunology* (W. E. Paul, ed.), Raven Press, N.Y. (1993) for a more detailed description of other antibody fragments). As another example, partial digestion with papain can yield a monovalent Fab/c fragment. See M.J. Glennie *et al.*, Nature 295:712-714 (1982). While various antibody fragments are defined in terms of the digestion of an intact antibody, one of skill in the art will appreciate that any of a variety of antibody fragments may be synthesized *de novo* either chemically or by utilizing recombinant DNA methodology. Thus, the term antibody as used herein also includes antibody fragments produced by the modification of whole antibodies, synthesized *de novo*, or obtained from recombinant DNA methodologies. One skilled in the art will recognize that there are circumstances in which it is advantageous to use antibody fragments rather than whole antibodies. For example, the smaller size of the antibody fragments allows for rapid clearance and may lead to improved access to solid tumors.

Recombinant antibodies may be conventional full length antibodies, hybrid antibodies, heavy chain antibodies, antibody fragments known from proteolytic digestion, antibody fragments such as Fv or single chain Fv (scFv), single domain fragments such as V_H or V_L, diabodies, domain deleted

antibodies, minibodies, and the like. An Fv antibody is about 50 kD in size and comprises the variable regions of the light and heavy chain. The light and heavy chains may be expressed in bacteria where they assemble into an Fv fragment. Alternatively, the two chains can be engineered to form an interchain disulfide bond to give a dsFv. A single chain Fv ("scFv") is a single polypeptide comprising V_H and V_L sequence domains linked by an intervening linker sequence, such that when the polypeptide folds the resulting tertiary structure mimics the structure of the antigen binding site. See J.S. Huston *et al.*, Proc. Nat. Acad. Sci. U.S.A. 85:5879-5883 (1988). One skilled in the art will recognize that depending on the particular expression method and/or antibody molecule desired, appropriate processing of the recombinant antibodies may be performed to obtain a desired reconstituted or reassembled antibody. See, e.g., Vallejo and Rinas, Biomed Central., available at world wide web URL microbialcellfactories.com/content/3/1/11.

Single domain antibodies are the smallest functional binding units of antibodies (approximately 13 kD in size), corresponding to the variable regions of either the heavy V_H or light V_L chains. See U.S. Patent No. 6,696,245, WO04/058821, WO04/003019 and WO03/002609. Single domain antibodies are well expressed in bacteria, yeast, and other lower eukaryotic expression systems. Domain deleted antibodies have a domain, such as CH2, deleted relative to the full length antibody. In many cases such domain deleted antibodies, particularly CH2 deleted antibodies, offer improved clearance relative to their full length counterparts. Diabodies are formed by the association of a first fusion protein comprising two V_H domains with a second fusion protein comprising two V_L domains. Diabodies, like full length antibodies, are bivalent and may be bi-specific. Minibodies are fusion proteins comprising a V_H, V_L, or scFv linked to CH3, either directly or via an intervening IgG hinge. See T. Olafsen *et al.*, Protein Eng. Des. Sel. 17:315-323 (2004). Minibodies, like domain deleted antibodies, are engineered to preserve the binding specificity of full-length antibodies but with improved clearance due to their smaller molecular weight.

The T cell receptor (TcR) is a disulfide linked heterodimer composed of two chains. The two chains are generally disulfide-bonded just outside the T cell plasma membrane in a short extended stretch of amino acids resembling the antibody hinge region. Each TcR chain is composed of one antibody-like variable domain and one constant domain. The full TcR has a molecular mass of about 95 kD, with the individual chains varying in size from 35 to 47 kD. Also encompassed within the meaning of TcR are portions of the receptor, such as, for example, the variable region, which can be produced as a soluble protein using methods well known in the art. For example, U.S. Patent No. 6,080,840 and A.E. Slanetz and A.L. Bothwell, Eur. J. Immunol. 21:179-183 (1991) describe a soluble T cell receptor prepared by splicing the extracellular domains of a TcR to the glycosyl phosphatidylinositol (GPI) membrane anchor sequences of Thy-1. The molecule is expressed in the absence of CD3 on the cell surface, and can be cleaved from the membrane by treatment with phosphatidylinositol specific

phospholipase C (PI-PLC). The soluble TcR also may be prepared by coupling the TcR variable domains to an antibody heavy chain CH_2 or CH_3 domain, essentially as described in U.S. Patent No. 5,216,132 and G.S. Basi *et al.*, J. Immunol. Methods 155:175-191 (1992), or as soluble TcR single chains, as described by E.V. Shusta *et al.*, Nat. Biotechnol. 18:754-759 (2000) or P.D. Holler *et al.*, Proc. Natl. Acad. Sci. U.S.A. 97:5387-5392 (2000). Certain embodiments of the invention use TcR "antibodies" as a soluble antibody. The combining site of the TcR can be identified by reference to CDR regions and other framework residues using the same methods discussed above for antibodies.

The combining site refers to the part of an antibody molecule that participates in antigen binding. The antigen binding site is formed by amino acid residues of the N-terminal variable ("V") regions of the heavy ("H") and light ("L") chains. The antibody variable regions comprise three highly divergent stretches referred to as "hypervariable regions" or "complementarity determining regions" (CDRs), which are interposed between more conserved flanking stretches known as "framework regions" (FRs). The three hypervariable regions of a light chain (LCDR1, LCDR2, and LCDR3) and the three hypervariable regions of a heavy chain (HCDR1, HCDR2, and HCDR3) are disposed relative to each other in three dimensional space to form an antigen binding surface or pocket. In heavy-chain antibodies or V_H domains, the antigen binding site is formed by the three hypervariable regions of the heavy chains. In V_L domains, the antigen binding site is formed by the three hypervariable regions of the light chain.

The identity of the amino acid residues in a particular antibody that make up a combining site can be determined using methods well known in the art. For example, antibody CDRs may be identified as the hypervariable regions originally defined by Kabat *et al.* See E.A. Kabat *et al.*, *Sequences of Proteins of Immunological Interest*, 5th ed., Public Health Service, NIH, Washington D.C. (1992). The positions of the CDRs may also be identified as the structural loop structures originally described by Chothia and others. See, e.g., C. Chothia and A.M. Lesk, J. Mol. Biol. 196:901-917 (1987); C. Chothia *et al.*, Nature 342:877-883 (1989); and A. Tramontano *et al.*, J. Mol. Biol. 215:175-182 (1990). Other methods include the "AbM definition," which is a compromise between Kabat and Chothia and is derived using Oxford Molecular's AbM antibody modeling software (now Accelrys), or the "contact definition" of CDRs set forth in R.M. MacCallum *et al.*, J. Mol. Biol. 262:732-745 (1996). Table 2 identifies CDRs based upon various known definitions:

Table 2: CDR definitions

CDR	Kabat	AbM	Chothia	Contact
L1	L24-L34	L24-L34	L24-L34	L30-L36
L2	L50-L56	L50-L56	L50-L56	L46-L55
L3	L89-L97	L89-L97	L89-L97	L89-L96

H1 (Kabat numbering)	H31-H35B	H26-H35B	H26-H32..H34	H30-H35B
H1 (Chothia numbering)	H31-H35	H26-H35	H26-H32	H30-H35
H2	H50-H56	H50-H58	H52-H56	H47-H58
H3	H95-H102	H95-H102	H95-H102	H93-H101

General guidelines by which one may identify the CDRs in an antibody from sequence alone are as follows:

LCDR1:

Start – Approximately residue 24.

Residue before is always a Cys.

Residue after is always a Trp, typically followed by Tyr-Gln, but also followed by Leu-Gln, Phe-Gln, or Tyr-Leu.

Length is 10 to 17 residues.

LCDR2:

Start – 16 residues after the end of L1.

Sequence before is generally Ile-Tyr, but also may be Val-Tyr, Ile-Lys, or Ile-Phe.

Length is generally 7 residues.

LCDR3:

Start – 33 residues after end of L2.

Residue before is a Cys.

Sequence after is Phe-Gly-X-Gly.

Length is 7 to 11 residues.

HCDR1:

Start – approximately residue 26, four residues after a Cys under Chothia/AbM definitions; start is 5 residues later under Kabat definition.

Sequence before is Cys-X-X-X.

Residue after is a Trp, typically followed by Val, but also followed by Ile or Ala.

Length is 10 to 12 residues under AbM definition; Chothia definition excludes the last 4 residues.

HCDR2:

Start –15 residues after the end of Kabat /AbM definition of CDR-H1.

Sequence before is typically Leu-Glu-Trp-Ile-Gly, but a number of variations are possible.

Sequence after is Lys/Arg-Leu/Ile/Val/Phe/Thr/Ala-Thr/Ser/Ile/Ala.

Length is 16 to 19 residues under Kabat definition; AbM definition excludes the last 7 residues.

HCDR3:

Start –33 residues after end of CDR-H2 (two residues after a Cys).

Sequence before is Cys-X-X (typically Cys-Ala-Arg).

Sequence after is Trp-Gly-X-Gly.

Length is 3 to 25 residues.

The identity of the amino acid residues in a particular antibody that are outside the CDRs, but nonetheless make up part of the combining site by having a side chain that is part of the lining of the combining site (i.e., that is available to linkage through the combining site), can be determined using methods well known in the art, such as molecular modeling and X-ray crystallography. See, e.g., L. Riechmann *et al.*, Nature 332:323-327 (1988).

As discussed, antibodies that can be used in preparing antibody-based AA targeting compounds require a reactive side chain in the antibody combining site. A reactive side chain may be present naturally or may be placed in an antibody by mutation. The reactive residue of the antibody combining site may be associated with the antibody, such as when the residue is encoded by nucleic acid present in the lymphoid cell first identified to make the antibody. Alternatively, the amino acid residue may arise by purposely mutating the DNA so as to encode the particular residue (see, e.g., WO 01/22922 to Meares *et al.*). The reactive residue may be a non-natural residue arising, for example, by biosynthetic incorporation using a unique codon, tRNA, and aminoacyl-tRNA as discussed herein. In another approach, the amino acid residue or its reactive functional groups (e.g., a nucleophilic amino group or sulfhydryl group) may be attached to an amino acid residue in the antibody combining site. Thus, covalent linkage with the antibody occurring "through an amino acid residue in a combining site of an antibody" as used herein means that linkage can be directly to an amino acid residue of an antibody combining site or through a chemical moiety that is linked to a side chain of an amino acid residue of an antibody combining site.

Catalytic antibodies are one source of antibodies with combining sites that comprise one or more reactive amino acid side chains. Such antibodies include aldolase antibodies, beta lactamase antibodies, esterase antibodies, amidase antibodies, and the like.

One embodiment comprises an aldolase antibody such as the mouse monoclonal antibody mAb 38C2 or mAb 33F12, as well as suitably humanized and chimeric versions of such antibodies. Mouse mAb 38C2 has a reactive lysine near to but outside HCDR3, and is the prototype of a new class of catalytic antibodies that were generated by reactive immunization and mechanistically mimic natural aldolase enzymes. See C.F. Barbas 3rd *et al.*, Science 278:2085-2092 (1997)). Other aldolase catalytic

antibodies that may be used include the antibodies produced by the hybridoma 85A2, having ATCC accession number PTA-1015; hybridoma 85C7, having ATCC accession number PTA-1014; hybridoma 92F9, having ATCC accession number PTA-1017; hybridoma 93F3, having ATCC accession number PTA-823; hybridoma 84G3, having ATCC accession number PTA-824; hybridoma 84G11, having ATCC accession number PTA-1018; hybridoma 84H9, having ATCC accession number PTA-1019; hybridoma 85H6, having ATCC accession number PTA-825; hybridoma 90G8, having ATCC accession number PTA-1016. Through a reactive lysine, these antibodies catalyze aldol and retro-aldol reactions using the enamine mechanism of natural aldolases. See, e.g., J. Wagner *et al.*, Science 270:1797-1800 (1995); C.F. Barbas 3rd *et al.*, Science 278:2085-2092 (1997); G. Zhong *et al.*, Angew. Chem. Int. Ed. Engl. 38:3738-3741 (1999); A. Karlstrom *et al.*, Proc. Natl. Acad. Sci. U.S.A., 97:3878-3883 (2000). Aldolase antibodies and methods of generating aldolase antibodies are disclosed in U.S. Patents Nos. 6,210,938, 6,368,839, 6,326,176, 6,589,766, 5,985,626, and 5,733,757.

AA targeting compounds may also be formed by linking an AA targeting agent to a reactive cysteine, such as those found in the combining sites of thioesterase and esterase catalytic antibodies. Suitable thioesterase catalytic antibodies are described by K.D. Janda *et al.*, Proc. Natl. Acad. Sci. U.S.A. 91:2532-2536 (1994). Suitable esterase antibodies are described by P. Wirsching *et al.*, Science 270:1775-1782 (1995). Reactive amino acid-containing antibodies may be prepared by means well known in the art, including mutating an antibody combining site residue to encode for the reactive amino acid or chemically derivatizing an amino acid side chain in an antibody combining site with a linker that contains the reactive group.

Antibodies suitable for use herein may be obtained by conventional immunization, reactive immunization *in vivo*, or by reactive selection *in vitro*, such as with phage display. Antibodies may also be obtained by hybridoma or cell fusion methods or *in vitro* host cells expression system. Antibodies may be produced in humans or in other animal species. Antibodies from one species of animal may be modified to reflect another species of animal. For example, human chimeric antibodies are those in which at least one region of the antibody is from a human immunoglobulin. A human chimeric antibody is typically understood to have variable region amino acid sequences homologous to a non-human animal, e.g., a rodent, with the constant region having amino acid sequence homologous to a human immunoglobulin. In contrast, a humanized antibody uses CDR sequences from a non-human antibody with most or all of the variable framework region sequence and all the constant region sequence from a human immunoglobulin. Chimeric and humanized antibodies may be prepared by methods well known in the art including CDR grafting approaches (see, e.g., N. Hardman *et al.*, Int. J. Cancer 44:424-433 (1989); C. Queen *et al.*, Proc. Natl. Acad. Sci. U.S.A. 86:10029-10033 (1989)), chain shuffling strategies (see, e.g., Rader *et al.*, Proc. Natl. Acad.

Sci. U.S.A. 95:8910-8915 (1998), genetic engineering molecular modeling strategies (see, e.g., M.A. Roguska *et al.*, Proc. Natl. Acad. Sci. U.S.A. 91:969-973 (1994)), and the like.

Methods for humanizing non-human antibodies have been described in the art. Preferably, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the methods of Winter and colleagues (see, e.g., P.T. Jones *et al.*, Nature 321:522-525 (1986); L. Riechmann *et al.*, Nature 332:323-327 (1988); M. Verhoeyen *et al.*, Science 239:1534-1536 (1988)) by substituting hypervariable region sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some hypervariable region residues and possibly some framework (FR) residues are substituted by residues from analogous sites in rodent antibodies.

The choice of human variable domains, both light and heavy, to be used in making humanized antibodies is very important to reduce antigenicity and human anti-mouse antibody (HAMA) response when the antibody is intended for human therapeutic use. According to the so-called "best-fit" method, the human variable domain utilized for humanization is selected from a library of known domains based on a high degree of homology with the rodent variable region of interest (M.J. Sims *et al.*, J. Immunol., 151:2296-2308 (1993); M. Chothia and A.M. Lesk, J. Mol. Biol. 196:901-917 (1987)). Another method uses a framework region derived from the consensus sequence of all human antibodies of a particular subgroup of light or heavy chains. The same framework may be used for several different humanized antibodies (see, e.g., P. Carter *et al.*, Proc. Natl. Acad. Sci. U.S.A. 89:4285-4289 (1992); L.G. Presta *et al.*, J. Immunol., 151:2623-2632 (1993)).

It is further important that antibodies be humanized with retention of high linking affinity for the Z group. To achieve this goal, according to one method, humanized antibodies are prepared by analysis of the parental sequences and various conceptual humanized products using three-dimensional models of the parental and humanized sequences. Three-dimensional immunoglobulin models are commonly available and are familiar to those skilled in the art. Computer programs are available which illustrate and display probable three-dimensional conformational structures of selected candidate immunoglobulin sequences. Inspection of these displays permits analysis of the likely role of the residues in the functioning of the candidate immunoglobulin sequence with respect to linking to the Z group. In this way, FR residues can be selected and combined from the recipient and import sequences so that the desired antibody characteristic, such as increased affinity for the target antigen(s), is achieved.

Various forms of humanized murine aldolase antibodies are contemplated. One embodiment uses the humanized aldolase catalytic antibody h38c2 IgG1 or h38c2 Fab with human constant domains $C_{\square}$ and $C_{\square 1}1$. C. Rader *et al.*, J. Mol. Bio. 332:889-899 (2003) discloses the gene sequences and vectors that may be used to produce h38c2 Fab and h38c2 IgG1. Human germline V_k gene DPK-9 and human J_k gene JK4 were used as frameworks for the humanization of the kappa light chain variable domain of m38c2, and human germline gene DP-47 and human J_H gene JH4 were used as frameworks for the humanization of the heavy chain variable domain of m38c2. FIGURE 7A illustrates a sequence alignment between the variable light and heavy chains in m38c2, h38c2, and human germlines. h38c2 may utilize IgG1, IgG2, IgG3, or IgG4 constant domains, including any of the allotypes thereof. FIGURE 7B illustrates one embodiment of h38c2 IgG1 using the G1m(f) allotype, where the light and heavy chain amino acid sequences of this h38c2 IgG1 are set forth in the figure. In certain embodiments of AA targeting compounds of formula II or III wherein Antibody is h38c2 IgG1 with the G1m(f) allotype, Z binds to the side chain of the lysine residue at position 99 of the heavy chain. This residue is denoted by bold print in FIGURE 7B. Another embodiment uses a chimeric antibody comprising the variable domains (V_L and V_H) of h38c2 and the constant domains from an IgG1, IgG2, IgG3, or IgG4.

Various forms of humanized aldolase antibody fragments are also contemplated. One embodiment uses h38c2 $F(ab')_2$. h38c2 $F(ab')_2$ may be produced by the proteolytic digestion of h38c2 IgG1. Another embodiment uses an h38c2 scFv comprising the V_L and V_H domains from h38c2 which are optionally connected by the intervening linker $(Gly_4Ser)_3$.

As an alternative to humanization, human antibodies can be generated. For example, it is now possible to produce transgenic animals (e.g., mice) that are capable, upon immunization (or reactive immunization in the case of catalytic antibodies) of producing a full repertoire of human antibodies in the absence of endogenous immunoglobulin production. For example, it has been described that the homozygous deletion of the antibody heavy-chain joining region (J_H) gene in chimeric and germ-line immunoglobulin gene array into such germ-line mutant mice will result in the production of human antibodies upon antigen challenge. See, e.g., B.D. Cohen *et al*, Clin. Cancer Res. 11:2063-2073 (2005); J.L. Teeling *et al.*, Blood 104:1793-1800 (2004); N. Lonberg *et al.*, Nature 368:856-859 (1994); A. Jakobovits *et al.*, Proc. Natl. Acad. Sci. U.S.A. 90:2551-2555 (1993); A. Jakobovits *et al.*, Nature 362:255-258 (1993); M. Bruggemann *et al.*, Year Immunol. 7:33-40 (1993); L.D. Taylor, *et al.* Nucleic Acids Res. 20:6287-6295 (1992); M. Bruggemann *et al.*, Proc. Natl. Acad. Sci. U.S.A. 86:6709-6713 (1989)); and WO 97/17852.

Alternatively, phage display technology (see, e.g., J. McCafferty *et al.*, Nature 348:552-553 (1990); H.J. de Haard *et al.*, J Biol Chem 274, 18218-18230 (1999); and A.Kanppik *et al.*, J Mol Biol, 296, 57-86 (2000)) can be used to produce human antibodies and antibody fragments *in vitro* using

immunoglobulin variable (V) domain gene repertoires from unimmunized donors. According to this technique, antibody V domain genes are cloned in-frame into either a major or minor coat protein gene of a filamentous bacteriophage, such as M13 or fd, and displayed as functional antibody fragments on the surface of the phage particle. Because the filamentous particle contains a single-stranded DNA copy of the phage genome, selections based on the functional properties of the antibody also result in selection of the gene encoding the antibody exhibiting those properties. Thus, the phage mimics some of the properties of the B-cell. Phage display can be performed in a variety of formats, and is reviewed in, e.g., K.S. Johnson and D.J. Chiswell, Curr. Opin. Struct. Biol. 3:564-571 (1993). Several sources of V-gene segments can be used for phage display. T. Clackson *et al.*, Nature, 352:624-628 (1991) isolated a diverse array of anti-oxazolone antibodies from a small random combinatorial library of V genes derived from the spleens of immunized mice. A repertoire of V genes from unimmunized human donors can be constructed and antibodies to a diverse array of antigens (including self-antigens) can be isolated essentially following the techniques described by J.D. Marks *et al.*, J. Mol. Biol. 222:581-597 (1991) or A.D. Griffiths *et al.*, EMBO J. 12:725-734 (1993). See also U.S. Pat. Nos. 5,565,332 and 5,573,905; and L.S. Jespers *et al.*, Biotechnology 12:899-903 (1994).

As indicated above, human antibodies may also be generated by *in vitro* activated B cells. See, e.g., U.S. Patent Nos. 5,567,610 and 5,229,275; and C.A.K. Borrebaeck *et al.*, Proc. Natl. Acad. Sci. U.S.A. 85:3995-3999 (1988).

Amino acid sequence modification(s) of the antibodies described herein are contemplated. For example, it may be desirable to improve the binding affinity and/or other biological properties of the antibody. Amino acid sequence variants of an antibody are prepared by introducing appropriate nucleotide changes into the antibody nucleic acid, or by peptide synthesis. Such modifications include, for example, deletions from, insertions into, and/or substitutions of residues within the amino acid sequences of the antibody. Any combination of deletion, insertion, and substitution is made to arrive at the final construct, provided that the final construct possesses the desired characteristics. The amino acid changes also may alter post-translational processes of the antibody, such as changing the number or position of glycosylation sites.

A useful method for identification of certain residues or regions of an antibody that are preferred locations for mutagenesis is called "alanine scanning mutagenesis," as described in B.C. Cunningham and J.A. Wells, Science 244:1081-1085 (1989). Here, a residue or group of target residues are identified (e.g., charged residues such as Arg, Asp, His, Lys, and Glu) and replaced by a neutral or negatively charged amino acid (most preferably Ala or Polyalanine) to affect the interaction of the amino acids with the Z group of the linker. Those amino acid locations demonstrating functional sensitivity to the substitutions are then refined by introducing further or other variants at, or for, the

sites of substitution. Thus, while the site for introducing an amino acid sequence variation is predetermined, the nature of the mutation per se need not be predetermined. For example, to analyze the performance of a mutation at a given site, alanine scanning or random mutagenesis is conducted at the target codon or region and the expressed antibody variants are screened for the ability to form a covalent bond with Z.

Amino acid sequence insertions include amino- and/or carboxyl-terminal fusions ranging in length from one residue to polypeptides containing a hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Examples of terminal insertions include an antibody with an N-terminal methionyl residue or the antibody fused to a cytotoxic polypeptide. Other insertional variants of an antibody molecule include the fusion to the N- or C-terminus of an anti-antibody to an enzyme or a polypeptide which increases the serum half-life of the antibody.

Another type of variant is an amino acid substitution variant. These variants have at least one amino acid residue in an antibody molecule replaced by a different residue. The sites of greatest interest for substitutional mutagenesis include the hypervariable regions, but FR alterations are also contemplated. Conservative substitutions are shown in Table 3 below under the heading of "preferred substitutions." If such substitutions result in a change in biological activity, then more substantial changes, denominated "exemplary substitutions" as further described below in reference to amino acid classes, may be introduced and the products screened.

Substantial modifications in the biological properties of the antibody are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side-chain properties:

(1) hydrophobic: Nle, Met, Ala, Val, Leu, Ile;
(2) neutral hydrophilic: Cys, Ser, Thr;
(3) acidic: Asp, Glu;
(4) basic: Asn, Gln, His, Lys, Arg;
(5) residues that influence chain orientation: Gly, Pro; and
(6) aromatic: Trp, Tyr, Phe.

Non-conservative substitutions will entail exchanging a member of one of these classes for a member of another class.

Any cysteine residue not involved in maintaining the proper conformation of the antibody may be substituted, generally with serine, to improve the oxidative stability of the molecule and prevent

aberrant crosslinking. Conversely, cysteine bond(s) may be added to the antibody to improve its stability (particularly where the antibody is an antibody fragment such as an Fv fragment).

One type of substitutional variant involves substituting one or more hypervariable region residues of a parent antibody (e.g., a humanized or human antibody). Generally, the resulting variant(s) selected for further development will have improved biological properties relative to the parent antibody from which they are generated. A convenient way for generating such substitutional variants involves affinity maturation using phage display. Briefly, several hypervariable region sites (e.g., 6-7 sites) are mutated to generate all possible amino substitutions at each site. The antibody variants thus generated are displayed in a monovalent fashion from filamentous phage particles as fusions to the gene III product of M13 packaged within each particle. The phage-displayed variants are then screened for their biological activity (e.g., binding affinity) as herein disclosed. In order to identify candidate hypervariable region sites for modification, alanine scanning mutagenesis can be performed to identify hypervariable region residues contributing significantly to antigen binding. Alternatively, or additionally, it may be beneficial to analyze a structure of the antibody conjugate complex to identify contact points between the antibody and the Z group. Such contact residues and neighboring residues are candidates for substitution according to the techniques elaborated herein. Once such variants are generated, the panel of variants is subjected to screening as described herein and antibodies with superior properties in one or more relevant assays may be selected for further development.

Another type of amino acid variant of the antibody alters the original glycosylation pattern of the antibody by deleting one or more carbohydrate moieties found in the antibody and/or adding one or more glycosylation sites that are not present in the antibody.

Glycosylation of antibodies is typically either N-linked or O-linked. N-linked refers to the attachment of the carbohydrate moiety to the side chain of an asparagine residue. The tripeptide sequences Asn-X''-Ser and Asn-X''-Thr, where X'' is any amino acid except proline, are generally the recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the presence of either of these tripeptide sequences in a polypeptide creates a potential glycosylation site. O-linked glycosylation refers to the attachment of one of the sugars N-acetylgalactosamine, galactose, or xylose to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine may also be used.

Addition of glycosylation sites to the antibody is conveniently accomplished by altering the amino acid sequence such that it contains one or more of the above-described tripeptide sequences (for N-linked glycosylation sites). The alteration may also be made by the addition of or substitution by one or more serine or threonine residues to the sequence of the original antibody (for O-linked glycosylation sites).

It may be desirable to modify an antibody with respect to effector function, for example to enhance antigen-dependent cell-mediated cytotoxicity (ADCC) and/or complement dependent cytotoxicity (CDC) of the antibody. This may be achieved by introducing one or more amino acid substitutions in an Fc region of the antibody. Alternatively, an antibody can be engineered which has dual Fc regions and may thereby have enhanced complement lysis and ADCC capabilities. See G.T. Stevenson *et al.*, Anticancer Drug Des. 3:219-230 (1989).

To increase the serum half life of an antibody, one may incorporate a salvage receptor binding epitope into the antibody (especially an antibody fragment) as described in U.S. Pat. No. 5,739,277, for example. As used herein, the term "salvage receptor binding epitope" refers to an epitope of the Fc region of an IgG molecule (e.g., IgG_1, IgG_2, IgG_3, or IgG_4) that is responsible for increasing the *in vivo* serum half-life of the IgG molecule.

Table 3: Amino acid substitutions

Original Residue	Exemplary Substitutions	Preferred Substitutions
Ala (A)	Val; Leu; Ile	Val
Arg I	Lys; Gln; Asn	Lys
Asn (N)	Gln; His; Asp; Lys; Arg	Gln
Asp (D)	Glu; Asn	Glu
CI(C)	Ser; Ala	Ser
Gln (Q)	Asn; Glu	Asn
Glu (E)	Asp; Gln	Asp
Gly (G)	Ala	Ala
His (H)	Asn; Gln; Lys; Arg	Arg
Ile (I)	Leu; Val; Met; Ala; Phe; Nle	Leu
Leu (L)	Nle; Ile; Val; Met; Ala; Phe	Ile
Lys (K)	Arg; Gln; Asn	Arg
Met (M)	Leu; Phe; Ile	Leu
Phe (F)	Leu; Val; Ile; Ala; Tyr	Tyr
Pro (P)	Ala	Ala
Ser (S)	Thr	Thr
Thr (T)	Ser	Ser
Trp (W)	Tyr; Phe	Tyr
Tyr (Y)	Trp; Phe; Thr; Ser	Phe
Val (V)	Ile; Leu; Met; Phe; Ala; Nle	Leu

Various techniques have been developed for the production of whole antibodies and antibody fragments. Traditionally, antibody fragments were derived via proteolytic digestion of intact antibodies (see, e.g., K. Morimoto and K. Inouye, J. Biochem. Biophys. Methods 24:107-117 (1992); M. Brennan *et al.*, Science 229:81-83 (1985)). However, these fragments can now be produced directly by recombinant host cells. Fab, Fv, V_H, V_L, and scFv antibody fragments can all be expressed in and secreted from *E. coli* as is detailed below, thus allowing the facile production of large amounts

of these fragments. Antibody fragments can be isolated from the antibody phage libraries discussed above. Alternatively, Fab'-SH fragments can be directly recovered from *E. coli* and chemically coupled to form $F(ab')_2$ fragments (P. Carter *et al.*, Biotechnology 10:163-167 (1992)). According to another approach, $F(ab')_2$ fragments can be isolated directly from recombinant host cell culture.

A variety of expression vector/host systems may be utilized to express antibodies. These systems include but are not limited to microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with virus expression vectors (e.g., baculovirus); plant cell systems transfected with virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with bacterial expression vectors (e.g., Ti or pBR322 plasmid); or animal cell systems.

Mammalian cells that are useful in recombinant antibody expression include but are not limited to VERO cells, HeLa cells, Chinese hamster ovary (CHO) cell lines, COS cells (such as COS-7), W138, BHK, HepG2, 3T3, RIN, MDCK, A549, PC12, K562 and 293 cells, as well as hybridoma cell lines as described herein. Mammalian cells are preferred for preparation of those antibodies that are typically glycosylated and require proper refolding for activity. Preferred mammalian cells include CHO cells, hybridoma cells, and myeloid cells.

Some exemplary protocols for the recombinant expression of antibodies are described herein below.

The term "expression vector" or "vector" refers to a plasmid, phage, virus or vector, for expressing a polypeptide from a DNA (RNA) sequence. An expression vector may comprise a transcriptional unit comprising (1) one or more regulatory sequences controlling gene expression, for example, promoters or enhancers, (2) one or more sequences that encode one or more polypeptides, and (3) appropriate transcription initiation and termination sequences. Expression vectors intended for use in yeast or eukaryotic expression systems preferably include a leader sequence enabling extracellular secretion of translated protein by a host cell. Alternatively, where an antibody polypeptide(s) is expressed without a leader or transport sequence, it may include an amino terminal methionine residue. This residue may or may not be subsequently cleaved from the expressed recombinant protein to provide a final antibody product.

Antibodies, specifically antibody fragments, may be expressed in prokaryotic systems such as *E. coli*. In another example, the DNA sequence encoding the specific binding agent peptide can be amplified by PCR and cloned into an appropriate vector, such as for example pGEX-3x (Pharmacia). The pGEX vector is designed to produce a fusion protein comprising glutathione-S-transferase (GST), encoded by the vector, and a peptide encoded by a DNA fragment inserted into the vector's cloning site. The

primers for PCR can be generated to include for example, an appropriate cleavage site. The pGEX-3x antibody peptide construct is transformed into *E. coli* XL-1 Blue cells (Stratagene, La Jolla Calif.), and individual transformants are isolated and grown. The expressed peptide fusion protein may then be cleaved from the GST portion of the fusion protein.

Expression of polynucleotides encoding antibodies using the recombinant systems described above may result in production of antibodies or fragments thereof that must be "re-folded" (to properly create various disulphide bridges) in order to be biologically active.

Antibodies, specifically antibody fragments, made in bacterial cells may be produced as an insoluble inclusion body in the bacteria. Such antibodies can be purified as follows. Host cells can be sacrificed by centrifugation; washed in 0.15 M NaCl, 10 mM Tris, pH 8, 1 mM EDTA; and treated with 0.1 mg/ml lysozyme (Sigma, St. Louis, Mo.) for 15 minutes at room temperature. The lysate can be cleared by sonication, and cell debris can be pelleted by centrifugation for 10 minutes at 12,000 x g. The antibody containing pellet can be resuspended in 50 mM Tris, pH 8, and 10 mM EDTA, layered over 50% glycerol, and centrifuged for 30 min. at 6000 x g. The pellet can be resuspended in standard phosphate buffered saline solution (PBS) free of Mg and Ca ions. The antibody can be further purified by fractionating the resuspended pellet in a denaturing SDS polyacrylamide gel (Sambrook *et al.*, supra). The gel can be soaked in 0.4 M KCl to visualize the protein, which can be excised and electroeluted in gel-running buffer lacking SDS.

Mammalian host systems for the expression of antibodies are well known to those of skill in the art. Host cell strains can be chosen for a particular ability to process the expressed protein or produce certain post-translation modifications that will be useful in providing protein activity. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation and acylation. Different host cells such as CHO, HeLa, MDCK, 293, W138, as well as hybridoma cell lines, and the like have specific cellular machinery and characteristic mechanisms for such post-translational activities and can be chosen to ensure the correct modification and processing of the introduced, foreign protein.

A number of selection systems can be used to recover the cells that have been transformed for recombinant antibody production. Such selection systems include, but are not limited to, HSV thymidine kinase, hypoxanthine-guanine phosphoribosyltransferase and adenine phosphoribosyltransferase genes, in tk-, hgprt- or aprt-cells, respectively. Also, anti-metabolite resistance can be used as the basis of selection for DHFR which confers resistance to methotrexate; gpt which confers resistance to mycophenolic acid; neo which confers resistance to the aminoglycoside G418 and confers resistance to chlorsulfuron; and hygro which that confers resistance to hygromycin. Additional selectable genes that may be useful include trpB, which allows cells to

utilize indole in place of tryptophan, or hisD, which allows cells to utilize histinol in place of histidine. Markers that give a visual indication for identification of transformants include anthocyanins, beta.-glucuronidase and its substrate, GUS, and luciferase and its substrate, luciferin.

In some cases, antibodies produced using procedures described above may need to be "refolded" and oxidized into a proper tertiary structure and allowed to generate disulfide linkages in order to be biologically active. Refolding can be accomplished using a number of procedures well known in the art. Such methods include, for example, exposing the solubilized polypeptide agent to a pH usually above 7 in the presence of a chaotropic agent. The selection of chaotrope is similar to the choices used for inclusion body solubilization. However a chaotrope is typically used at a lower concentration. An exemplary chaotropic agent is guanidine. In most cases, the refolding/oxidation solution will also contain a reducing agent plus its oxidized form in a specific ratio to generate a particular redox potential which allows for disulfide shuffling to occur for the formation of cysteine bridges. Some commonly used redox couples include cysteine/cystamine, glutathione/dithiobisGSH, cupric chloride, dithiothreitol DTT/dithiane DTT, and 2-mercaptoethanol (bME)/dithio-bME. In many instances, a co-solvent may be used to increase the efficiency of the refolding. Commonly used cosolvents include glycerol, polyethylene glycol of various molecular weights, and arginine.

Linkers and Linked Compounds

An AA targeting agent may be covalently linked to a combining site in an antibody either directly or via a linker. An appropriate linker can be chosen to provide sufficient distance between the targeting agent and the antibody The general design of an embodiment of a linker for use in preparing AA targeting compounds is represented by the formula: -X-Y-Z, wherein X is a connecting chain, Y is a recognition group and Z is a reactive group. The linker may be linear or branched, and optionally includes one or more carbocyclic or heterocyclic groups. Linker length may be viewed in terms of the number of linear atoms, with cyclic moieties such as aromatic rings and the like to be counted by taking the shortest route around the ring. In some embodiments, the linker has a linear stretch of between 5-15 atoms, in other embodiments 15-30 atoms, in still other embodiments 30-50 atoms, in still other embodiments 50-100 atoms, and in still other embodiments 100-200 atoms. Other linker considerations include the effect on physical or pharmacokinetic properties of the resulting AA targeting compound or AA targeting agent-linker, such as solubility, lipophilicity, hydrophilicity, hydrophobicity, stability (more or less stable as well as planned degradation), rigidity, flexibility, immunogenicity, modulation of antibody binding, the ability to be incorporated into a micelle or liposome, and the like.

The connecting chain X of the linker includes any atom from the group C, H, N, O, P, S, halogen (F, Cl, Br, I), or a salt thereof. X also may include a group such as an alkyl, alkenyl, alkynyl, oxoalkyl,

oxoalkenyl, oxoalkynyl, aminoalkyl, aminoalkenyl, aminoalkynyl, sulfoalkyl, sulfoalkenyl, sulfoalkynyl, phosphoalkyl, phosphoalkenyl, or phosphoalkynyl group. In some embodiments, X may include one or more ring structures. In some embodiments, the linker is a repeating polymer such as polyethylene glycol comprising 2-100 units.

The recognition group Y of the linker is optional, and if present is located between the reactive group and the connecting chain. In some embodiments, Y is located from 1-20 atoms from Z. Although not wishing to be bound by any theory, it is believed that the recognition group acts to properly position the reactive group into the antibody combining site so that it may react with a reactive amino acid side chain. Exemplary recognition groups include carbocyclic and heterocyclic rings, preferably having five or six atoms. However, larger ring structures also may be used. In some embodiments, an AA targeting agent is linked directly to Y without the use of an intervening linker.

Z is capable of forming a covalent bond with a reactive side chain in an antibody combining site. In some embodiments, Z includes one or more C=O groups arranged to form a diketone, an acyl beta-lactam, an active ester, a haloketone, a cyclohexyl diketone group, an aldehyde, a maleimide, an activated alkene, an activated alkyne or, in general, a molecule comprising a leaving group susceptible to nucleophilic or electrophilic displacement. Other groups may include a lactone, an anhydride, an alpha-haloacetamide, an imine, a hydrazide, or an epoxide. Exemplary linker electrophilic reactive groups that can covalently bond to a reactive nucleophilic group (e.g., a lysine or cysteine side chain) in a combining site of antibody include acyl beta-lactam, simple diketone, succinimide active ester, maleimide, haloacetamide with linker, haloketone, cyclohexyl diketone, aldehyde, amidine, guanidine, imine, eneamine, phosphate, phosphonate, epoxide, aziridine, thioepoxide, a masked or protected diketone (a ketal for example), lactam, sulfonate, and the like, masked C=O groups such as imines, ketals, acetals, and any other known electrophilic group. In certain embodiments, the reactive group includes one or more C=O groups arranged to form an acyl beta-lactam, simple diketone, succinimide active ester, maleimide, haloacetamide with linker, haloketone, cyclohexyl diketone, or aldehyde.

The linker reactive group or similar such reactive group is chosen for use with a reactive residue in a particular combining site. For example, a chemical moiety for modification by an aldolase antibody may be a ketone, diketone, beta lactam, active ester haloketone, lactone, anhydride, maleimide, alpha-haloacetamide, cyclohexyl diketone, epoxide, aldehyde, amidine, guanidine, imine, eneamine, phosphate, phosphonate, epoxide, aziridine, thioepoxide, masked or protected diketone (ketal for example), lactam, haloketone, aldehyde, and the like.

A linker reactive group chemical moiety suitable for covalent modification by a reactive sulfhydryl group in an antibody may be a disulfide, aryl halide, maleimide, alpha-haloacetamide, isocyanate,

epoxide, thioester, active ester, amidine, guanidine, imine, eneamine, phosphate, phosphonate, epoxide, aziridine, thioepoxide, masked or protected diketone (ketal for example), lactam, haloketone, aldehyde, and the like.

One of skill in the art will readily appreciate that reactive amino acid side chains in antibody combining sites may possess an electrophilic group that reacts with a nucleophilic group on an AA targeting agent or its linker, whereas in other embodiments a reactive nucleophilic group in an amino acid side chain reacts with an electrophilic group in an AA targeting agent or linker.

An AA targeting compound may be prepared by several approaches. In one approach, an AA targeting agent-linker compound is synthesized with a linker that includes one or more reactive groups designed for covalent reaction with a side chain of an amino acid in a combining site of an antibody. The targeting agent-linker compound and antibody are combined under conditions where the linker reactive group forms a covalent bond with the amino acid side chain.

In another approach, linking can be achieved by synthesizing an antibody-linker compound comprising an antibody and a linker wherein the linker includes one or more reactive groups designed for covalent reaction with an appropriate chemical moiety of an AA targeting agent. An AA targeting agent may need to be modified to provide the appropriate moiety for reaction with the linker reactive group. The antibody-linker and AA targeting agent are combined under conditions where the linker reactive group covalently links to the targeting and/or biological agent.

A further approach for forming an antibody-AA targeting compound uses a dual linker design. In certain embodiments, an AA targeting agent-linker compound is synthesized which comprises an AA targeting agent and a linker with a reactive group. An antibody-linker compound is synthesized which comprises an antibody and a linker with a chemical group susceptible to reactivity with the reactive group of the AA targeting agent-linker of the first step. These two linker containing compounds are then combined under conditions whereby the linkers covalently link, forming the antibody-AA-targeting compound.

Exemplary functional groups that can be involved in the linkage include, for example, esters, amides, ethers, phosphates, amino, keto, amidine, guanidine, imines, eneamines, phosphates, phosphonates, epoxides, aziridines, thioepoxides, masked or protected diketones (ketals for example), lactams, haloketones, aldehydes, thiocarbamate, thioamide, thioester, sulfide, disulfide, phosphoramide, sulfonamide, urea, thioruea, carbamate, carbonate, hydroxamide, and the like.

The linker includes any atom from the group C, H, N, O, P, S, halogen (F, Cl, Br, I), or a salt thereof. The linker also may include a group such as an alkyl, alkenyl, alkynyl, oxoalkyl, oxoalkenyl, oxoalkynyl, aminoalkyl, aminoalkenyl, aminoalkynyl, sulfoalkyl, sulfoalkenyl, sulfoalkynyl group,

phosphoalkyl, phosphoalkenyl, or phosphoalkynyl group. The linker also may include one or more ring structures. As used herein, a "ring structure" includes saturated, unsaturated, and aromatic carbocyclic rings and saturated, unsaturated, and aromatic heterocyclic rings. The ring structures may be mono-, bi-, or polycyclic, and include fused or unfused rings. Further, the ring structures are optionally substituted with functional groups well known in the art, including but not limited to halogen, oxo, -OH, -CHO, -COOH, $-NO_2$, -CN, $-NH_2$, $-C(O)NH_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} oxoalkyl, oxoalkenyl, oxoalkynyl, aminoalkyl, aminoalkenyl, aminoalkynyl, sulfoalkyl, sulfoalkenyl, sulfoalkynyl, phosphoalkyl, phosphoalkenyl, or phosphoalkynyl group. Combinations of the above groups and rings may also be present in the linkers of AA targeting compounds.

One aspect of the invention is an AA targeting agent-linker conjugate having Formula I:

L – [AA targeting agent] (I)

wherein [AA targeting agent] is an AA targeting agent peptide.

The linker moiety L in compounds of Formula I may be attached to the amino terminus, carboxy terminus or any amino acid side chain of an AA targeting agent. In certain embodiments, L is linked to the carboxy terminus of an AA targeting agent. In certain other embodiments, L is linked to the amino terminus of an AA targeting agent. In still other embodiments, L is linked to either a nucleophilic or electrophilic side chain. For the case of linking to an electrophilic side chain, L should possess a nucleophilic group susceptible to covalent reaction with the electrophilic side chain. Exemplary electrophilic side chains are Asp and Glu. Exemplary nucleophilic side chains are Cys, Lys, Ser, Thr, and Tyr. For the case of linking to a nucleophilic side chain, L should comprise an electrophilic group susceptible to covalent reaction with the nucleophilic side chain. In another embodiment, a nucleophilic amino acid is added to either the carboxy terminus or the amino terminus of an AA targeting agent and the linker L is covalently attached to the side chain of this additional amino acid. In certain embodiments, Lys is added to the amino terminus of an AA targeting agent. In certain other embodiments, Lys is added to the carboxy terminus of an AA targeting agent.

Thus, in those embodiments comprising R^1-QKY QPL DEL DKT LYD QFM LQQ G-R^2 based AA targeting agents, exemplary compounds of Formula I formed by linking to either i) the side chains of D, E, K, T, and Y or ii) the amino or carboxy termini, include the following, where (Li) following an amino acid residue indicates linking to that residue:

Q(Li)KY QPL DEL DKT LYD QFM LQQ G-R^2 (SEQ ID NO:140)
R^1-QK(Li)Y QPL DEL DKT LYD QFM LQQ G-R^2 (SEQ ID NO:141)
R^1-QKY(Li) QPL DEL DKT LYD QFM LQQ G-R^2 (SEQ ID NO:142)

R^1-QKY QPL D(Li)EL DKT LYD QFM LQQ G-R^2 (SEQ ID NO:13)
R^1-QKY QPL DE(Li)L DKT LYD QFM LQQ G-R^2 (SEQ ID NO:144)
R^1-QKY QPL DEL D(Li)KT LYD QFM LQQ G-R^2 (SEQ ID NO:145)
R^1-QKY QPL DEL DK(Li)T LYD QFM LQQ G-R^2 (SEQ ID NO:146)
R^1-QKY QPL DEL DKT(Li) LYD QFM LQQ G-R^2 (SEQ ID NO:147)
R^1-QKY QPL DEL DKT LY(Li)D QFM LQQ G-R^2 (SEQ ID NO:148)
R^1-QKY QPL DEL DKT LYD(Li) QFM LQQ G-R^2 (SEQ ID NO:149)
R^1-QKY QPL DEL DKT LYD QFM LQQ G(Li) (SEQ ID NO:150)

Similarly, in those embodiments comprising R^1-Q-[ACK]-Y QPL DEL DKT LYD QFM LQQ G-R^2 based AA targeting agents, exemplary compounds of Formula I formed by linking to either i) the side chains of D, E, K, T, and Y or ii) the amino or carboxy termini, include:

Q(Li)-[AcK]Y QPL DEL DKT LYD QFM LQQ G-R^2 (SEQ ID NO:151)
R^1-Q-[AcK]-Y(Li) QPL DEL DKT LYD QFM LQQ G-R^2 (SEQ ID NO:152)
R^1-Q-[AcK]-Y QPL D(Li)EL DKT LYD QFM LQQ G-R^2 (SEQ ID NO:153)
R^1-Q-[AcK]-Y QPL DE(Li)L DKT LYD QFM LQQ G-R^2 (SEQ ID NO:154)
R^1-Q-[AcK]-Y QPL DEL D(Li)KT LYD QFM LQQ G-R^2 (SEQ ID NO:155)
R^1-Q-[AcK]-Y QPL DEL DK(Li)T LYD QFM LQQ G-R^2 (SEQ ID NO:156)
R^1-Q-[AcK]-Y QPL DEL DKT(Li) LYD QFM LQQ G-R^2 (SEQ ID NO:157)
R^1-Q-[AcK]-Y QPL DEL DKT LY(Li)D QFM LQQ G-R^2 (SEQ ID NO:158)
R^1-Q-[AcK]-Y QPL DEL DKT LYD(Li) QFM LQQ G-R^2 (SEQ ID NO:159)
R^1-Q-[AcK]-Y QPL DEL DKT LYD QFM LQQ G(Li) (SEQ ID NO:160)

In compounds of Formula I, L is a linker moiety having the formula -X-Y-Z, wherein:

X is an optionally present biologically compatible polymer or block copolymer attached to one of the residues that comprises an AA targeting agent;

Y is an optionally present recognition group comprising at least a ring structure; and

Z is a reactive group that is capable of covalently linking to a side chain in a combining site of an antibody.

In some embodiments of compounds in Formula I, X is:

-R^{22}-P- R^{2-}- or -R^{22}-P-R^{21}-P'-R^{23}-

wherein:

P and P'are independently selected from the group consisting of polyoxyalkylene oxides such as polyethylene oxide, polyethyloxazoline, poly-N-vinyl pyrrolidone, polyvinyl alcohol, polyhydroxyethyl acrylate, polyhydroxy ethylmethacrylate and polyacrylamide, polyamines having amine groups on either the polymer backbone or the polymer sidechains, such as polylysine, polyornithine, polyarginine, and polyhistidine, nonpeptide polyamines such as polyaminostyrene, polyaminoacrylate, poly(N-methyl aminoacrylate), poly(N-ethylaminoacrylate), poly(N,N-dimethyl aminoacrylate), poly(N,N-diethylaminoacrylate), poly(aminomethacrylate), poly(N-methyl amino-methacrylate), poly(N-ethyl aminomethacrylate), poly(N,N-dimethyl aminomethacrylate), poly(N,N-diethyl aminomethacrylate), poly(ethyleneimine), polymers of quaternary amines, such as poly(N,N,N-trimethylaminoacrylate chloride), poly(methyacrylamidopropyltrimethyl ammonium chloride), proteoglycans such as chondroitin sulfate-A (4-sulfate) chondroitin sulfate-C (6-sulfate) and chondroitin sulfate-B, polypeptides such as polyserine, polythreonine, polyglutamine, natural or synthetic polysaccharides such as chitosan, hydroxy ethyl cellulose, and lipids;

R^{21}, R^{22}, and R^{23} are each independently a covalent bond, -O-, -S-, -NR^b-, substituted or unsubstituted straight or branched chain C_{1-50} alkylene, or substituted or unsubstituted straight or branched chain C_{1-50} heteroalkylene;

R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl; and

R^{21}, R^{22}, and R^{23} are selected such that the backbone length of X remains about 200 atoms or less.

In some embodiments of compounds of Formula I, R^{22} is —$(CH_2)_v$-, -$(CH_2)_u$-C(O)-$(CH_2)_v$-, -$(CH_2)_u$-C(O)-O-$(CH_2)_v$-, -$(CH_2)_u$-C(S)-NR^b-$(CH_2)_v$-, -$(CH_2)_u$-C(O)-NR^b-$(CH_2)_v$-, -$(CH_2)_u$-NR^b-$(CH_2)_v$-, -$(CH_2)_u$-O-$(CH_2)_v$-, -$(CH_2)_u$-S(O)$_{0-2}$-$(CH_2)_v$-, -$(CH_2)_u$-S(O)$_{0-2}$-NR^b-$(CH_2)_v$—, or -$(CH_2)_u$-P(O)(OR^b)-O-$(CH_2)_v$-, wherein u and v are each independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20.

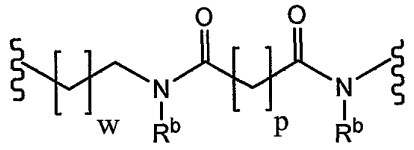
In yet other embodiments of compounds of Formula I, R^{22} is -$(CH_2)_v$-, -$(CH_2)_u$-C(O)-$(CH_2)_v$-, -$(CH_2)_u$-C(O)-O-$(CH_2)_v$-, -$(CH_2)_u$-C(O)-NR^b-$(CH_2)_v$—, or -$(CH_2)_u$-NR^b-$(CH_2)_v$. In still other embodiments, R^{-2} is -$(CH_2)_u$-C(O)-NR^b-$(CH_2)_v$-.

In some embodiments of compounds of Formula I, R^{21} and R^{23} are each independently -$(CH_2)_s$-, -$(CH_2)_r$-C(O)-$(CH_2)_s$-, -$(CH_2)_r$-C(O)-O-$(CH_2)_v$-, -$(CH_2)_r$-C(S)-NR^b-$(CH_2)_s$-, -$(CH_2)_r$-C(O)-NR^b-$(CH_2)_s$-, -$(CH_2)_r$-NR^b-$(CH_2)_s$-, -$(CH_2)_r$-O-$(CH_2)_s$-, -$(CH_2)_r$-S(O)$_{0-2}$-$(CH_2)_s$-,

$-(CH_2)_r-S(O)_{0-2}-NR^b-(CH_2)_s-$, or $-(CH_2)_r-P(O)(OR^b)-O-(CH_2)_s-$, wherein r, s, and v are each independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20.

In yet other embodiments, R^{21} and R^{23} are each independently $-(CH_2)_s-$, $-(CH_2)_r-C(O)-(CH_2)_s-$, $-(CH_2)_r-C(O)-O-(CH_2)_s-$, $-(CH_2)_r-C(O)-NR^b-(CH_2)_s-$, or $-(CH_2)_r-NR^b-(CH_2)_s$, and $-(CH_2)_r-C(O)-NR^b-(CH_2)_s-$.

In still other embodiments, R^{21} and R^{23} each independently have the structure:



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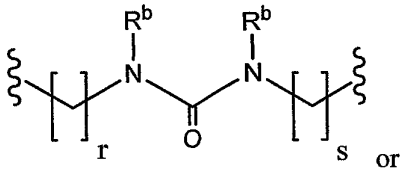

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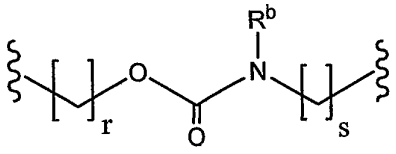

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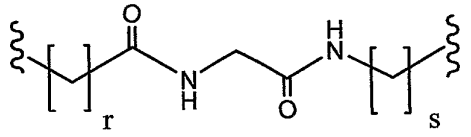

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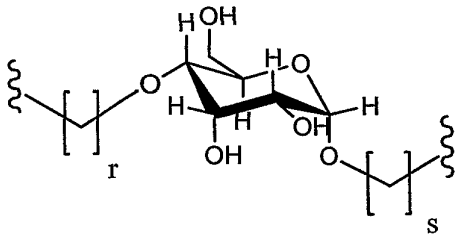
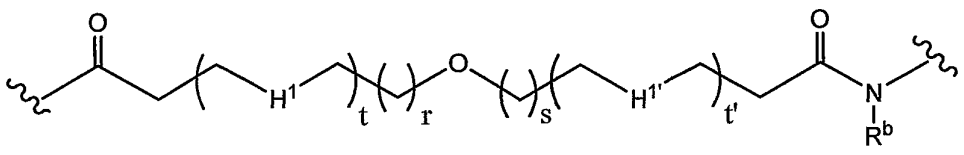


wherein p is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33,34, 35, 36, 37, 38, 39, 40, 41, 32, 43, 44, or 45; w, r, and s are each independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl.

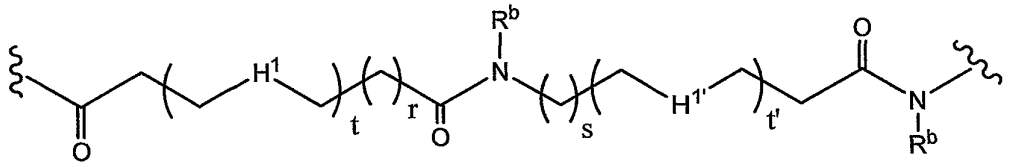
In certain embodiments of compounds of Formula I, X has the structure:



wherein H^1 and $H^{1'}$ at each occurrence are independently N, O, S, or CH_2; r and s are each independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20; t and t' are each independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25,

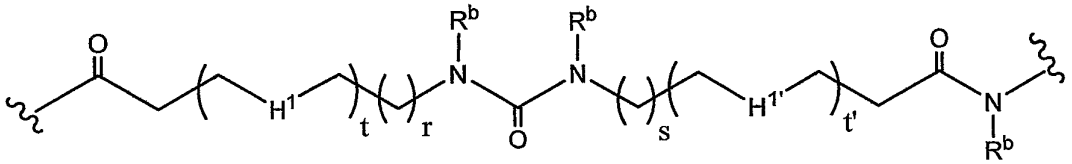
26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 32, 43, 44, 45, 46, 47, 48, 49 or 50; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl.

In certain embodiments of compounds of Formula I, X has the structure:



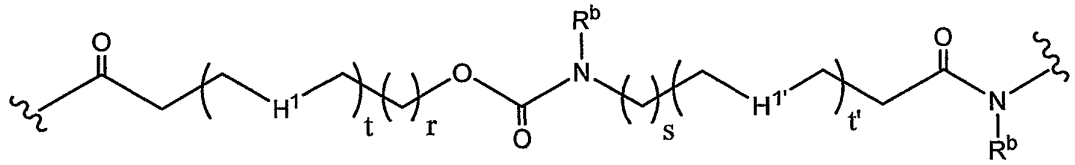
wherein H^1 and $H^{1'}$ at each occurrence are independently N, O, S, or CH_2; r and s are each independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20; t and t' are each independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 32, 43, 44, 45, 46, 47, 48, 49 or 50; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl.

In certain embodiments of compounds of Formula I, X has the structure:



wherein H^1 and $H^{1'}$ at each occurrence are independently N, O, S, or CH_2; r and s are each independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20; t and t' are each independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 32, 43, 44, 45, 46, 47, 48, 49 or 50; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl.

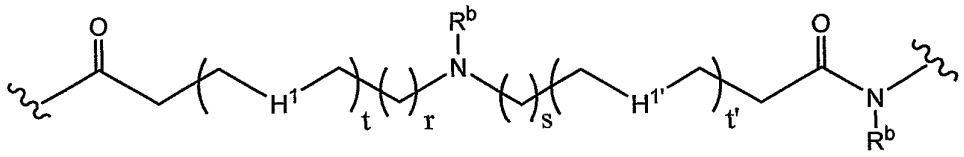
In certain embodiments of compounds of Formula I, X has the structure:



wherein H^1 and $H^{1'}$ at each occurrence are independently N, O, S, or CH_2; r and s are each independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20; t and t' are each

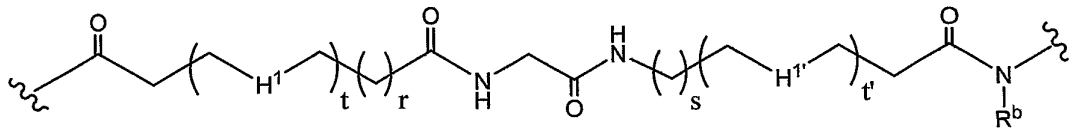
independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 32, 43, 44, 45, 46, 47, 48, 49 or 50; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl.

In certain embodiments of compounds of Formula I, X has the structure:



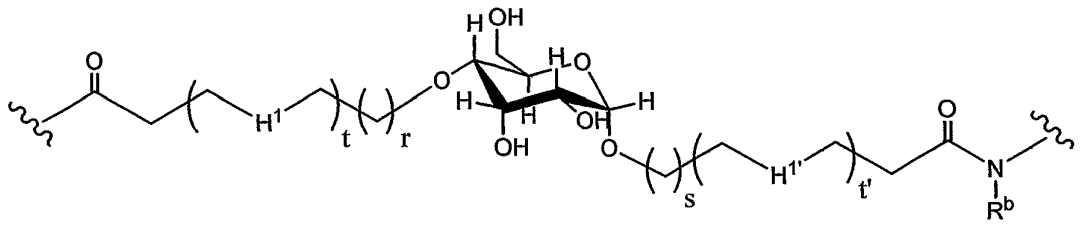
wherein H^1 and $H^{1'}$ at each occurrence are independently N, O, S, or CH_2; r and s are each independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20; t and t' are each independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 32, 43, 44, 45, 46, 47, 48, 49 or 50; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl.

In certain embodiments of compounds of Formula I, X has the structure:



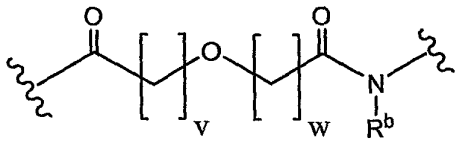
wherein H^1 and $H^{1'}$ at each occurrence are independently N, O, S, or CH_2; r and s are each independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20; t and t' are each independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 32, 43, 44, 45, 46, 47, 48, 49 or 50; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl.

In certain embodiments of compounds of Formula I, X has the structure:



wherein H^1 and $H^{1'}$ at each occurrence are independently N, O, S, or CH_2; r and s are each independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20; t and t' are each independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 32, 43, 44, 45, 46, 47, 48, 49 or 50; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl.

In certain embodiments of compounds of Formula I, X has the structure:



wherein v and w are each independently 1, 2, 3, 4, or 5 and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain of these embodiments, v is 1, 2 or 3, w is 1, 2, or 3, and R^b is hydrogen.

In certain embodiments of Formula I, L is a linker moiety having the formula -X-Y-Z, wherein:

X is attached to one of the residues that comprises an AA targeting agent, and is an optionally substituted -R^{22}-$[CH_2$-CH_2-$O]_t$-R^{23}-, -R^{22}-cycloalkyl-R^{23}-, -R^{22}-aryl-R^{23}-, or –R^{22}-heterocyclyl-R^{23}-, wherein;

R^{22} and R^{23} are each independently a covalent bond, -O-, -S-, -NR^b-, substituted or unsubstituted straight or branched chain C_{1-50} alkylene, substituted or unsubstituted straight or branched chain C_{1-50} heteroalkylene, substituted or unsubstituted straight or branched chain C_{2-50} alkenylene, or substituted or unsubstituted C_{2-50} heteroalkenylene;

R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl;

t is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 32, 43, 44, 45, 46, 47, 48, 49 or 50;

and the size of R^{22} and R^{23} are such that the backbone length of X remains about 200 atoms or less;

Y is an optionally present recognition group comprising at least a ring structure; and

Z is a reactive group that is capable of covalently linking to a side chain in a combining site of an antibody. In some embodiments of compounds of Formula I, if $t > 1$ or if–X is $-R^{22}$-cycloalkyl-R^{23}-, $-R^{22}$-aryl-R^{23}-, or $-R^{22}$-heterocyclyl-R^{23}-, Y is present.

In some embodiments of compounds of Formula I, X is:

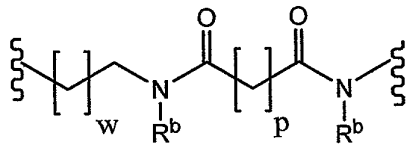
$-R^{22}-[CH_2-CH_2-O]_t-R^{23}-$,

wherein:

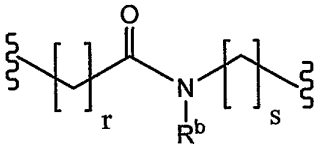
R^{22} is $-(CH_2)_v-$, $-(CH_2)_u-C(O)-(CH_2)_v-$, $-(CH_2)_u-C(O)-O-(CH_2)_v-$, $-(CH_2)_u-C(O)-NR^b-(CH_2)_v-$, $-(CH_2)_u-C(S)-NR^b-(CH_2)_v-$, $-(CH_2)_u-NR^b-(CH_2)_v-$, $-(CH_2)_u-O-(CH_2)_v-$, $-(CH_2)_u-S(O)_{0-2}-(CH_2)_v-$, $-(CH_2)_u-S(O)_{0-2}-NR^b-(CH_2)_v-$, or $-(CH_2)_u-P(O)(OR^b)-O-(CH_2)_v-$;

u and v are each independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 and t is 0 to 50.

R^{23} has the structure:



or



wherein:

p is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33,34, 35, 36, 37, 38, 39, 40, 41, 32, 43, 44, or 45;

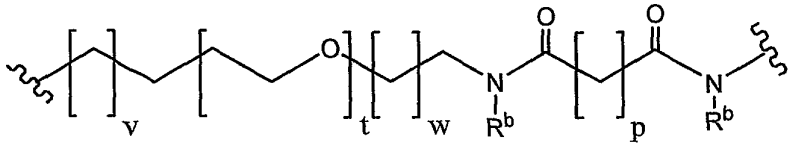
w and r are each independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20;

s is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20; and

R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl;

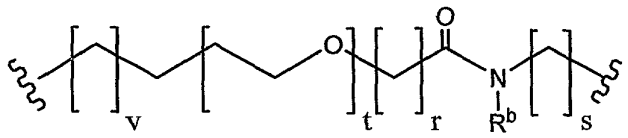
and the values of t, u, w, p, v, r and s are such that the backbone length of X remains about 200 atoms or less.

In certain embodiments of compounds of Formula I, X has the formula:



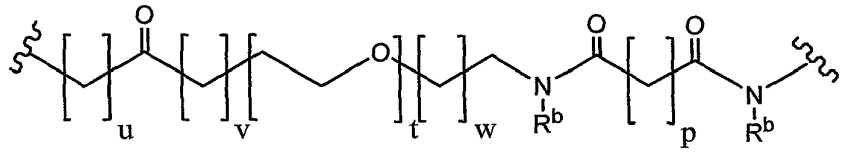
wherein the values of v, t, w, and p are selected such that the backbone length of X is less than 200 atoms, alternatively is less than 100 atoms, alternatively is less than 75 atoms, alternatively is less than 50 atoms, alternatively is less than 25 atoms, or alternatively is less than 15 atoms.

In certain embodiments of compounds of Formula I, X has the structure:



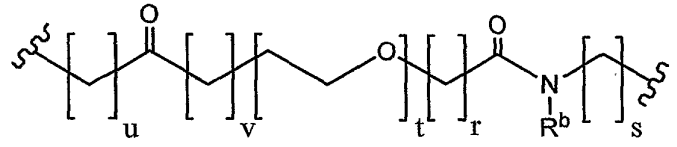
wherein the values of v, t, r, and s are selected such that the backbone length of X is less than 200 atoms, alternatively is less than 100 atoms, alternatively is less than 75 atoms, alternatively is less than 50 atoms, alternatively is less than 25 atoms, or alternatively is less than 15 atoms.

In certain embodiments of compounds of Formula I, X has the structure:



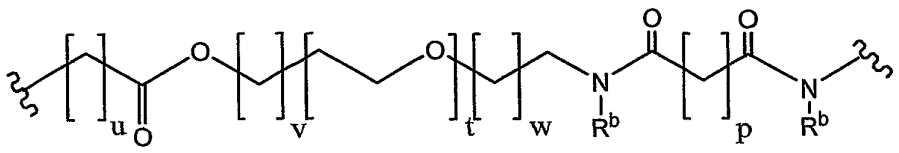
wherein the values of u, v, t, w, and p are selected such that the backbone length of X is less than 200 atoms, alternatively is less than 100 atoms, alternatively is less than 75 atoms, alternatively is less than 50 atoms, alternatively is less than 25 atoms, or alternatively is less than 15 atoms..

In certain embodiments of compounds of Formula I, X has the structure:



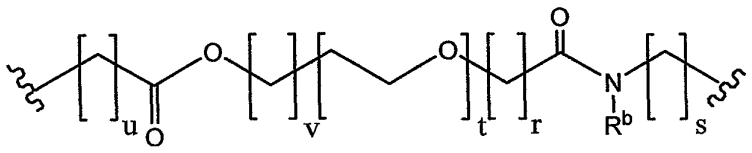
wherein the values of u, v, t, r, and s are selected such that the backbone length of X is less than 200 atoms, alternatively is less than 100 atoms, alternatively is less than 75 atoms, alternatively is less than 50 atoms, alternatively is less than 25 atoms, or alternatively is less than 15 atoms.

In certain embodiments of compounds of Formula I, X has the structure:



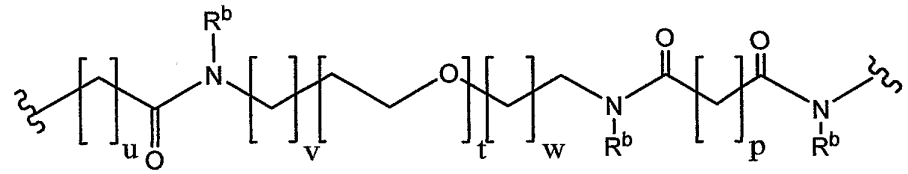
wherein the values of u, v, t, w, and p are selected such that the backbone length of X is less than 200 atoms, alternatively is less than 100 atoms, alternatively is less than 75 atoms, alternatively is less than 50 atoms, alternatively is less than 25 atoms, or alternatively is less than 15 atoms.

In certain embodiments of compounds of Formula I, X has the structure:



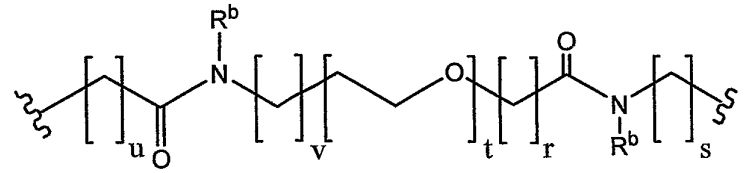
wherein the values of u, v, t, r, and s are selected such that the backbone length of X is less than 200 atoms, alternatively is less than 100 atoms, alternatively is less than 75 atoms, alternatively is less than 50 atoms, alternatively is less than 25 atoms, or alternatively is less than 15 atoms.

In certain embodiments of compounds of Formula I, X has the structure:



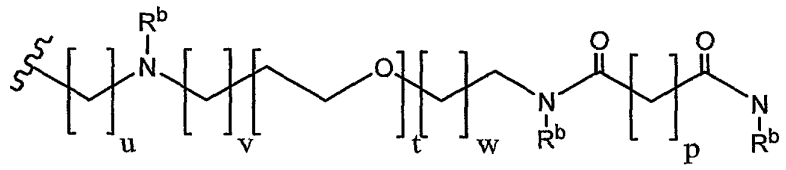
wherein the values of u, v, t, w, and p are selected such that the backbone length of X is less than 200 atoms, alternatively is less than 100 atoms, alternatively is less than 75 atoms, alternatively is less than 50 atoms, alternatively is less than 25 atoms, or alternatively is less than 15 atoms.

In certain embodiments of compounds of Formula I, X has the structure:



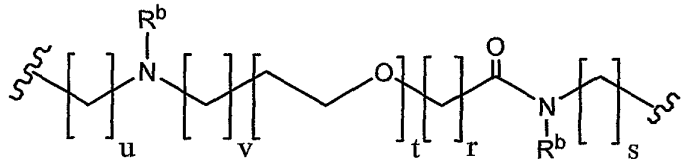
wherein the values of u, v, t, r, and s are selected such that the backbone length of X is less than 200 atoms, alternatively is less than 100 atoms, alternatively is less than 75 atoms, alternatively is less than 50 atoms, alternatively is less than 25 atoms, or alternatively is less than 15 atoms.

In certain embodiments of compounds of Formula I, X has the structure:



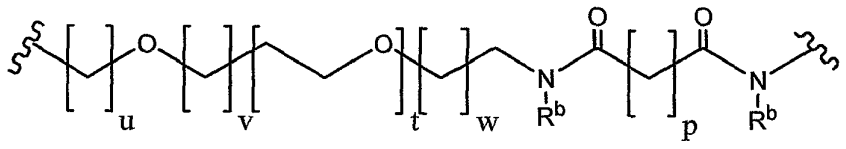
wherein the values of u, v, t, w, and p are selected such that the backbone length of X is less than 200 atoms, alternatively is less than 100 atoms, alternatively is less than 75 atoms, alternatively is less than 50 atoms, alternatively is less than 25 atoms, or alternatively is less than 15 atoms.

In certain embodiments of compounds of Formula I, X has the structure:



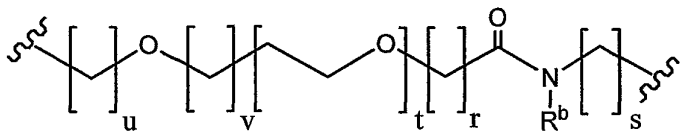
wherein the values of u, v, t, r, and s are selected such that the backbone length of X is less than 200 atoms, alternatively is less than 100 atoms, alternatively is less than 75 atoms, alternatively is less than 50 atoms, alternatively is less than 25 atoms, or alternatively is less than 15 atoms.

In certain embodiments of compounds of Formula I, X has the structure:



wherein the values of u, v, t, w, and p are selected such that the backbone length of X is less than 200 atoms, alternatively is less than 100 atoms, alternatively is less than 75 atoms, alternatively is less than 50 atoms, alternatively is less than 25 atoms, or alternatively is less than 15 atoms.

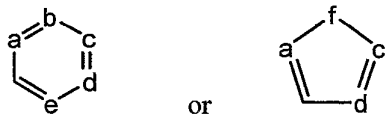
In certain embodiments of compounds of Formula I, X has the structure:



wherein the values of u, v, t, r, and s are selected such that the backbone length of X is less than 200 atoms, alternatively is less than 100 atoms, alternatively is less than 75 atoms, alternatively is less than 50 atoms, alternatively is less than 25 atoms, or alternatively is less than 15 atoms.

In compounds having Formula I wherein L has the formula –X-Y-Z, the ring structure of Y includes saturated, unsaturated, and aromatic carbocyclic rings and saturated, unsaturated, and aromatic heterocyclic rings. The ring structure(s) may be mono-, bi-, or polycyclic, and include fused or unfused rings. Further, the ring structure(s) is optionally substituted with functional groups well known in the art including, but not limited to halogen, oxo, -OH, -CHO, -COOH, $-NO_2$, -CN, $-NH_2$, amidine, guanidine, hydroxylamine, $-C(O)NH_2$, secondary and tertiary amides, sulfonamides, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, oxoalkyl, oxoalkenyl, oxoalkynyl, aminoalkyl, aminoalkenyl, aminoalkynyl, sulfoalkyl, sulfoalkenyl, sulfoalkynyl, phosphoalkyl, phosphoalkenyl, and phosphoalkynyl groups.

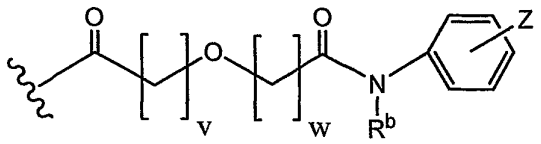
In some embodiments of compounds having Formula I, the ring structure of Y has the optionally substituted structure:



wherein a, b, c, d, and e are each independently carbon or nitrogen; f is carbon, nitrogen, oxygen, or sulfur; Y is attached to X and Z independently at any two ring positions of sufficient valence; and no more than four of a, b, c, d, e, or f are simultaneously nitrogen.

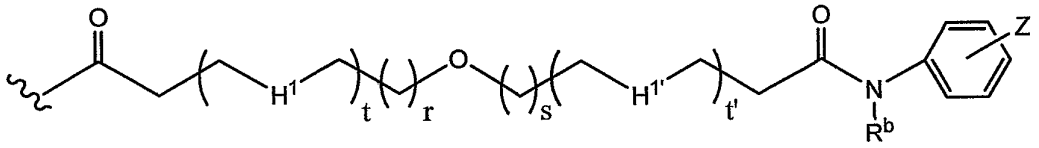
Any open valences remaining on atoms constituting the ring structure may be filled by hydrogen or other substituents, or by the covalent attachments to X and Z. For example, if b is carbon, its valence may be filled by hydrogen, a substituent such as halogen, a covalent attachment to X, or a covalent attachment to Z. In some embodiments, a, b, c, d, and e are each carbon, while in others, a, c, d and f are each carbon. In other embodiments, at least one of a, b, c, d, or e is nitrogen, and in still others, f is oxygen or sulfur. In yet another embodiment, the ring structure of Y is unsubstituted. In certain embodiments, Y is phenyl.

In certain embodiments of compounds of Formula I, X-Y has the structure:



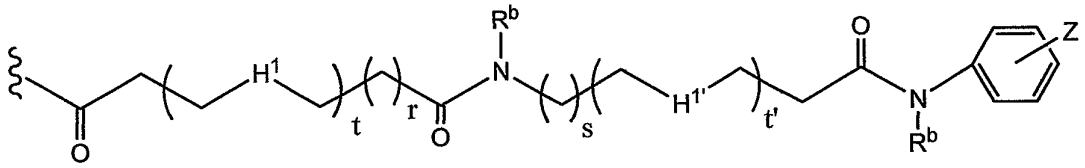
In certain of these embodiments, v is 1, 2, 3, 4, or 5; w is 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain other embodiments, v is 1, 2 or 3 and w is 1, 2, or 3. In still other embodiments, v is 1 or 2 and w is 1 or 2.

In certain embodiments of compounds of Formula I, X has the structure:



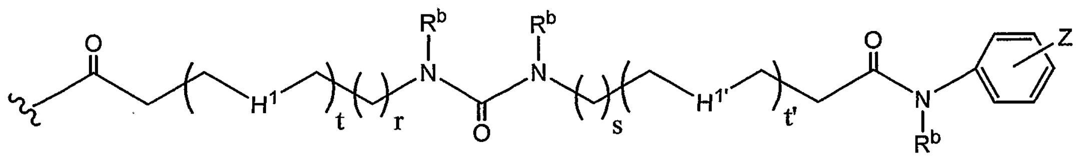
wherein H^1 and $H^{1'}$ are each independently N, O, S, or CH_2; r and s are each independently 1, 2, 3, 4, or 5; and t and t' are each independently 0, 1, 2, 3, 4, or 5. In certain of these embodiments, H^1 and $H^{1'}$ are each independently O or CH_2; r and s are each independently 1 or 2; and t and t' are each independently 0 or 1.

In certain embodiments of compounds of Formula I, X has the structure:



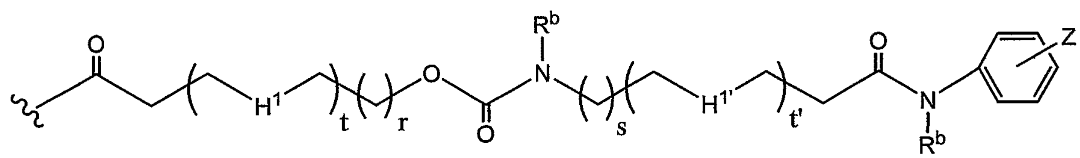
wherein H^1 and $H^{1'}$ are each independently N, O, S, or CH_2; r and s are each independently 1, 2, 3, 4, or 5; t and t' are each independently 0, 1, 2, 3, 4, or 5, and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain of these embodiments, H^1 and $H^{1'}$ are each independently O or CH_2; r and s are each independently 1 or 2; and t and t' are each independently 0 or 1.

In certain embodiments of compounds of Formula I, X has the structure:



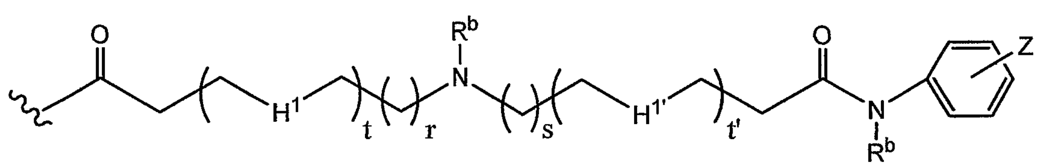
wherein H^1 and $H^{1'}$ are each independently N, O, S, or CH_2; r and s are each independently 1, 2, 3, 4, or 5; t and t' are each independently 0, 1, 2, 3, 4, or 5, and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain of these embodiments, H^1 and $H^{1'}$ are each independently O or CH_2; r and s are each independently 1 or 2; and t and t' are each independently 0 or 1.

In certain embodiments of compounds of Formula I, X has the structure:



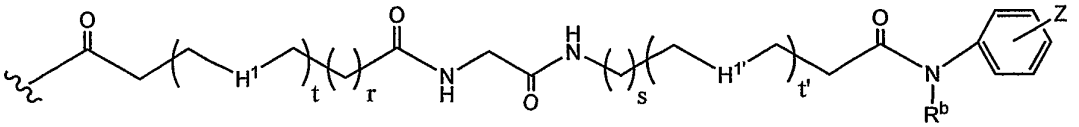
wherein H^1 and $H^{1'}$ are each independently N, O, S, or CH_2; r and s are each independently 1, 2, 3, 4, or 5; t and t' are each independently 0, 1, 2, 3, 4, or 5, and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain of these embodiments, H^1 and $H^{1'}$ are each independently O or CH_2; r and s are each independently 1 or 2; and t and t' are each independently 0 or 1.

In certain embodiments of compounds of Formula I, X has the structure:



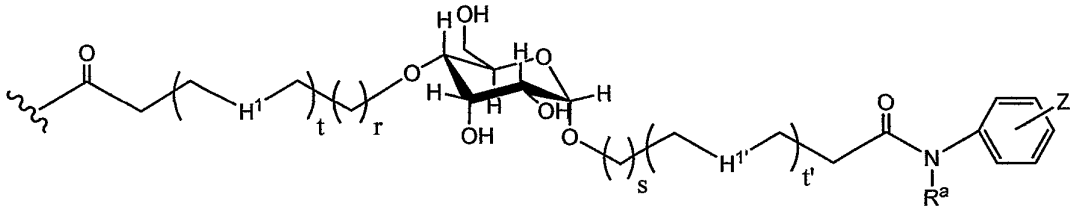
wherein H^1 and $H^{1'}$ are each independently N, O, S, or CH_2; r and s are each independently 1, 2, 3, 4, or 5; t and t' are each independently 0, 1, 2, 3, 4, or 5, and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain of these embodiments, H^1 and $H^{1'}$ are each independently O or CH_2; r and s are each independently 1 or 2; and t and t' are each independently 0 or 1.

In certain embodiments of compounds of Formula I, X has the structure:



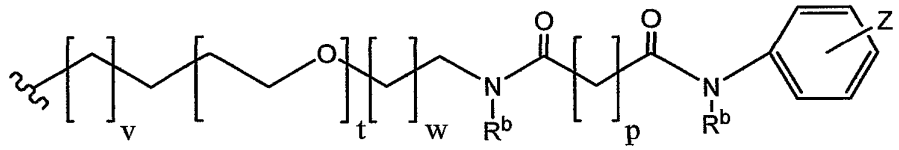
wherein H^1 and $H^{1'}$ are each independently N, O, S, or CH_2; r and s are each independently 1, 2, 3, 4, or 5; t and t' are each independently 0, 1, 2, 3, 4, or 5, and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain of these embodiments, H^1 and $H^{1'}$ are each independently O or CH_2; r and s are each independently 1 or 2; and t and t' are each independently 0 or 1.

In certain embodiments of compounds of Formula I, X has the structure:



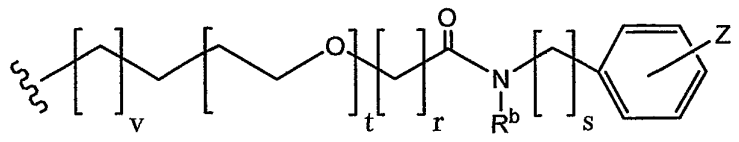
wherein H^1 and $H^{1'}$ are each independently N, O, S, or CH_2; r and s are each independently 1, 2, 3, 4, or 5; and t and t' are each independently 0, 1, 2, 3, 4, or 5. In certain of these embodiments, H^1 and $H^{1'}$ are each independently O or CH_2; r and s are each independently 1 or 2; and t and t' are each independently 0 or 1.

In certain of these embodiments of compounds of Formula I, X-Y has the structure:



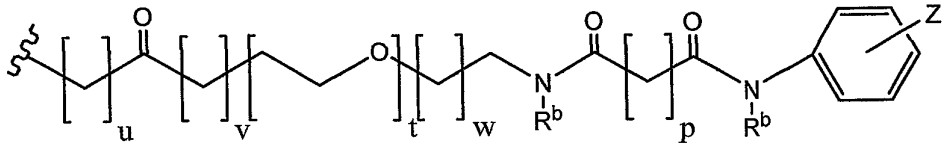
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5, and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; and p is 3. In some embodiments, v is 0; t is 1, 2, or 3, w is 1; and p is 1 or 2.

In certain embodiments of compounds of Formula I, X-Y has the structure:



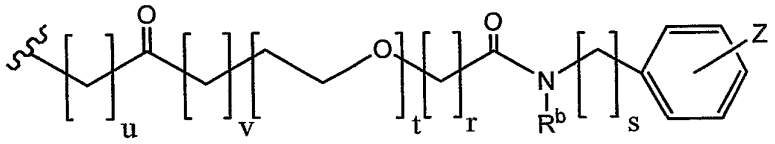
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; and s is 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; and s is 1 or 2.

In certain embodiments of compounds of Formula I, X-Y has the structure:



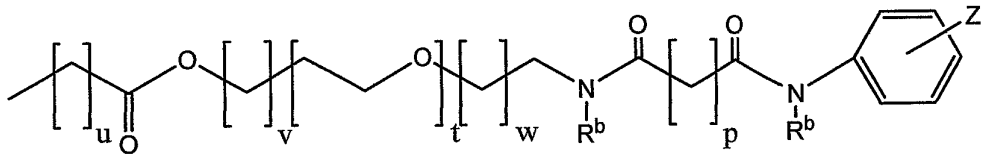
In certain of these embodiments, u is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; and p is 3. In some embodiments, u is 0 or 1; v is 0; t is 1 or 2; w is 1; and p is 1 or 2.

In certain embodiments of compounds of Formula I, X-Y has the structure:



In certain of these embodiments, u is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; and s is 3. In some embodiments, u is 0 or 1; v is 0; t is 1, 2, or 3; r is 1; and s is 1 or 2.

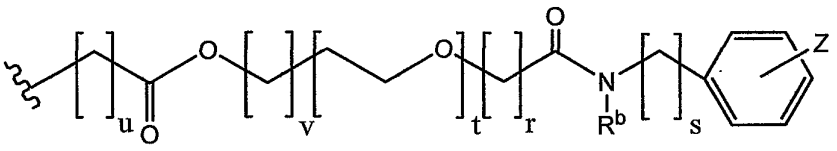
In certain embodiments of compounds of Formula I, X-Y has the structure:



In certain of these embodiments, u is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted

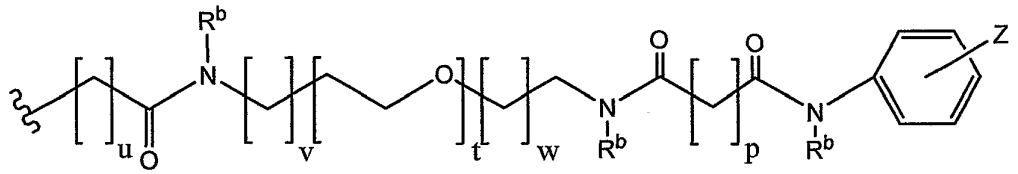
or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; and p is 3. In some embodiments, u is 0 or 1; v is 0; t is 1 or 2; w is 1; and p is 1 or 2.

In certain embodiments of compounds of Formula I, X-Y has the structure:



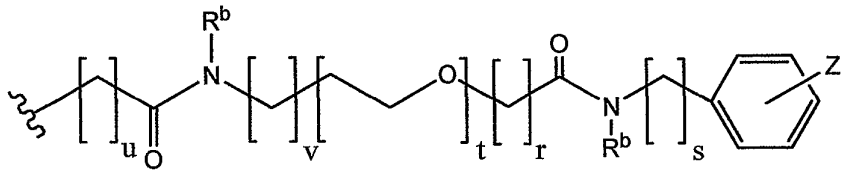
In certain of these embodiments, u is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; and s is 3. In some embodiments, u is 0 or 1; v is 0; t is 1, 2, or 3, r is 1; and s is 1 or 2.

In certain embodiments of compounds of Formula I, X-Y has the structure:



In certain of these embodiments, u is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; and p is 3. In some embodiments, u is 0 or 1; v is 0; t is 1 or 2; w is 1; and p is 1 or 2.

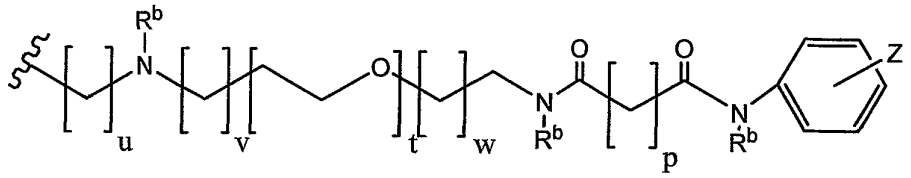
In certain embodiments of compounds of Formula I, X-Y has the structure:



In certain of these embodiments, u is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or

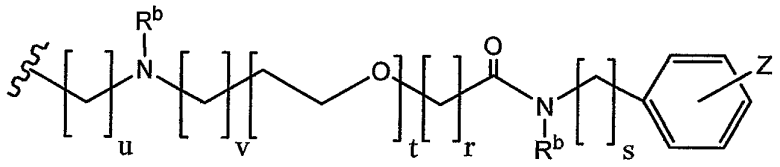
unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; and s is 3. In some embodiments, u is 0 or 1; v is 0; t is 1, 2, or 3, r is 1; and s is 1 or 2.

In certain embodiments of compounds of Formula I, X-Y has the structure:



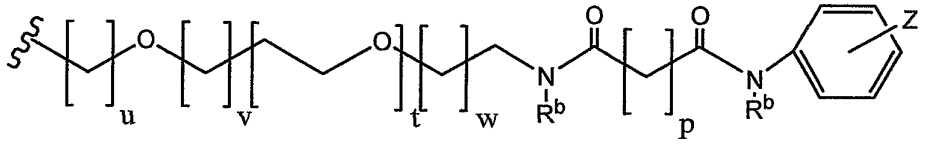
In certain of these embodiments, u is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; and p is 3. In some embodiments, u is 0 or 1; v is 0; t is 1 or 2; w is 1; and p is 1 or 2.

In certain embodiments of compounds of Formula I, X-Y has the structure:



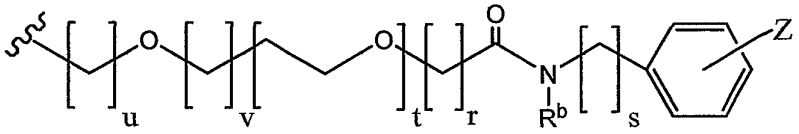
In certain of these embodiments, u is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; and s is 3. In some embodiments, u is 0 or 1; v is 0; t is 1, 2, or 3, r is 1; and s is 1 or 2.

In certain embodiments of compounds of Formula I, X-Y has the structure:



In certain of these embodiments, u is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; and p is 3. In some embodiments, u is 0 or 1; v is 0; t is 1 or 2; w is 1; and p is 1 or 2.

In certain embodiments of compounds of Formula I, X-Y has the structure:



In certain of these embodiments, u is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiment, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; and s is 3. In some embodiments, u is 0 or 1; v is 0; t is 1, 2, or 3, r is 1; and s is 1 or 2.

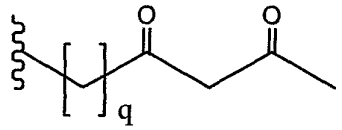
In compounds having Formula I wherein L has the formula –X-Y-Z, the reactive group Z contains a moiety capable of forming a covalent linkage with an amino acid in a combining site of an antibody. For example, Z may be substituted alkyl, substituted cycloalkyl, substituted aryl, substituted arylalkyl, substituted heterocyclyl, or substituted heterocyclylalkyl, wherein at least one substituent is a 1,3-diketone moiety, an acyl beta-lactam, an active ester, an alpha-haloketone, an aldehyde, a maleimide, a lactone, an anhydride, an alpha-haloacetamide, an amine, a hydrazide, or an epoxide. In some such embodiments, Z is substituted alkyl.

Z may be a group that forms a reversible or irreversible covalent bond. In some embodiments, reversible covalent bonds may be formed using diketone Z groups such as those shown in FIGURE 8. Thus, structures A-C may form reversible covalent bonds with reactive nucleophilic groups (e.g. lysine or cysteine side chain) in a combining site of an antibody. R'_1, R'_2, R'_3, and R_4 in structures A-C of FIGURE 8 represent substituents which can be C, H, N, O, P, S, halogen (F, Cl, Br, I) or a salt thereof. These substituents also may include a group such as an alkyl, alkenyl, alkynyl, oxoalkyl, oxoalkenyl, oxoalkynyl, aminoalkyl, aminoalkenyl, aminoalkynyl, sulfoalkyl, sulfoalkenyl, or sulfoalkynyl group, phosphoalkyl, phosphoalkenyl, phosphoalkynyl group. R'_2 and R'_3 also could from a ring structure as exemplified in structures B and C. X in FIGURE 8 could be a heteroatom. Other Z groups that form reversible covalent bonds include the amidine, imine, and other reactive groups encompassed by structure G of FIGURE 8. FIGURE 9 includes the structures of other linker reactive groups that form reversible covalent bonds, e.g., structures B, G, H, and, where X is not a leaving group, E and F.

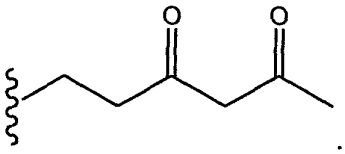
Z reactive groups that form an irreversible covalent bond with a combining site of an antibody include structures D-G in FIGURE 8 (e.g., when G is an imidate) and structures A, C and D of FIGURE 9. When X is a leaving group, structures E and F of FIGURE 9 may also form irreversible covalent

bonds. Such structures are useful for irreversibly attaching a targeting agent-linker to a reactive nucleophilic group to a combining site of an antibody.

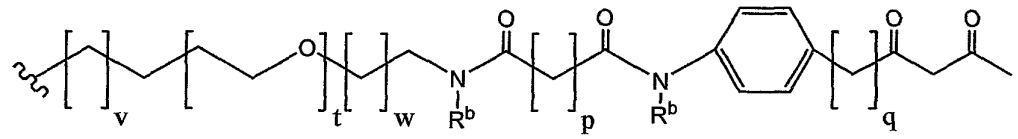
In other such embodiments, Z is a 1,3-diketone moiety. In still other such embodiments, Z is alkyl substituted by a 1,3-diketone moiety. In certain embodiments, Z has the structure:



wherein q = 0-5. In certain other embodiments, Z has the structure:

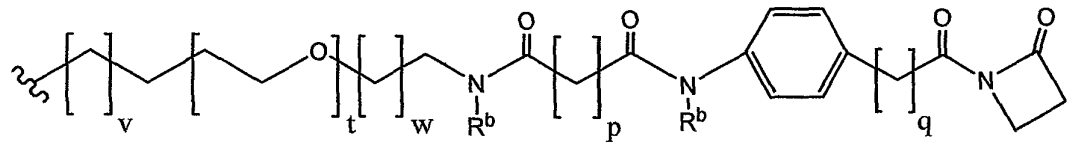


One linker for use in AA targeting compounds and for preparing AA targeting agent-linker compounds includes a 1,3-diketone reactive group as Z. In certain embodiments of Formula I, L has the structure:



In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

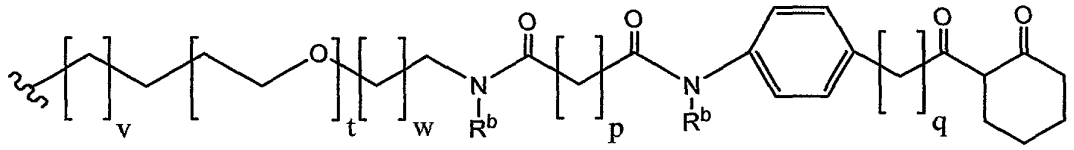
In certain embodiments of Formula I, L has the structure:



In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or

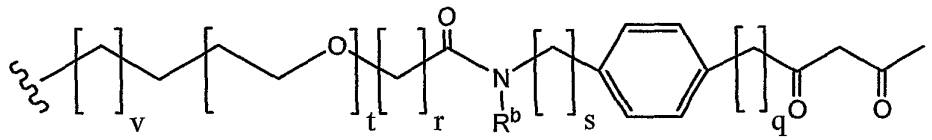
unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 2 or 3.

In certain embodiments of Formula I, L has the structure:



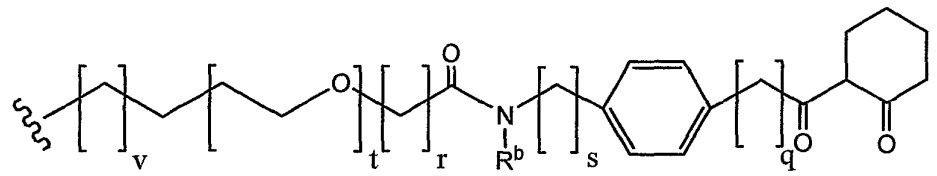
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

In certain embodiments of Formula I, L has the structure:



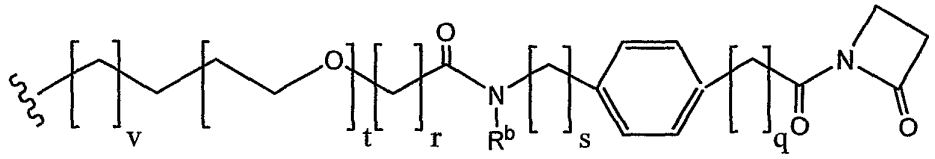
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

In certain embodiments of Formula I, L has the structure:



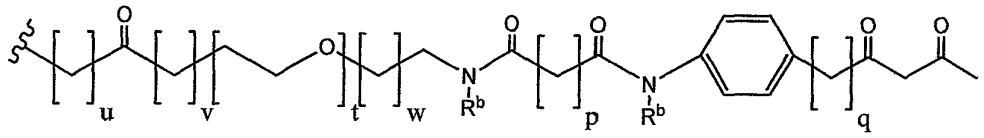
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

In certain embodiments of Formula I, L has the structure:



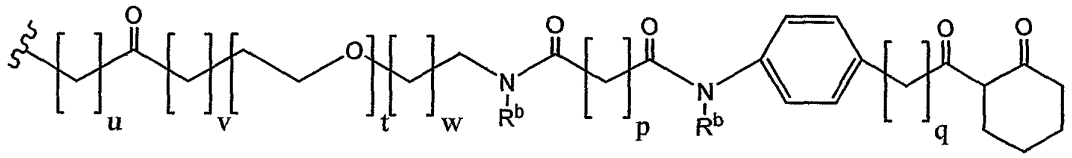
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 2 or 3.

In certain embodiments of Formula I, L has the structure:



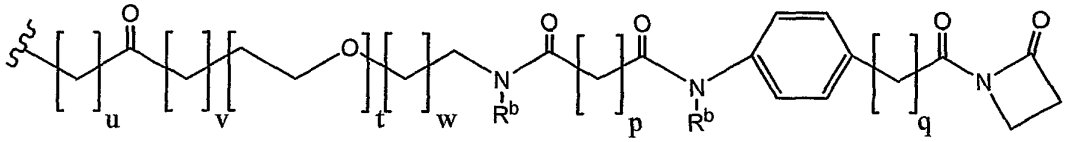
In certain of these embodiments, u is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, u is 0 or 1; v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

In certain embodiments of Formula I, L has the structure:



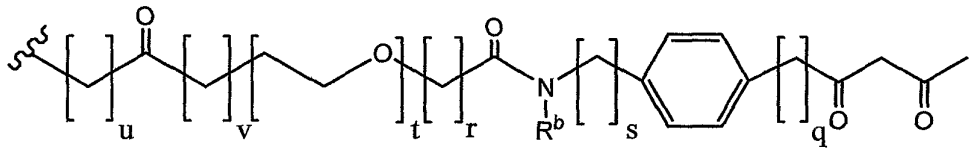
In certain of these embodiments, u is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5;q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

In certain embodiments of Formula I, L has the structure:



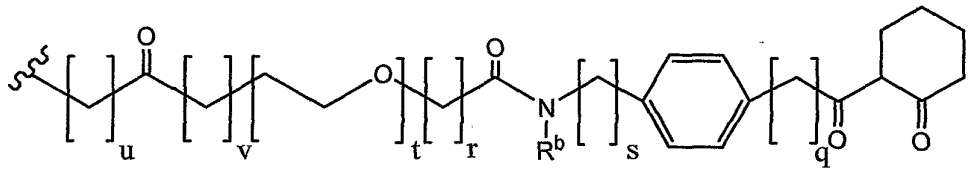
In certain of these embodiments, u is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 2 or 3.

In certain embodiments of Formula I, L has the structure:



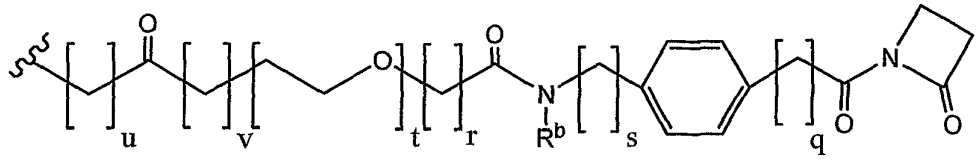
In certain of these embodiments, u is 0, 1, 2, 3, 5, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, u is 0 or 1; v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

In certain embodiments of Formula I, L has the structure:



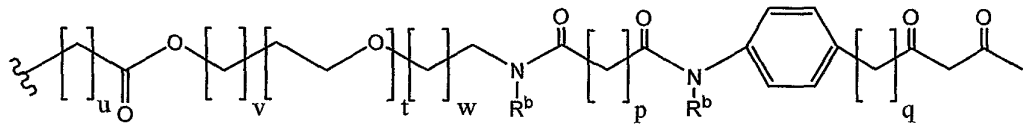
In certain of these embodiments u is 0, 1, 2, 3, 5, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, u is 0 or 1; v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

In certain embodiments of Formula I, L has the structure:



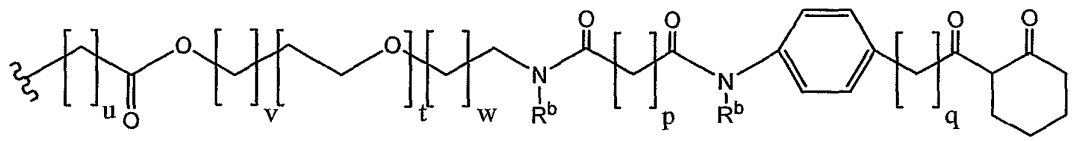
In certain of these embodiments, u is 0, 1, 2, 3, 5, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, u is 0 or 1; v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 2 or 3.

In certain embodiments of Formula I, L has the structure:



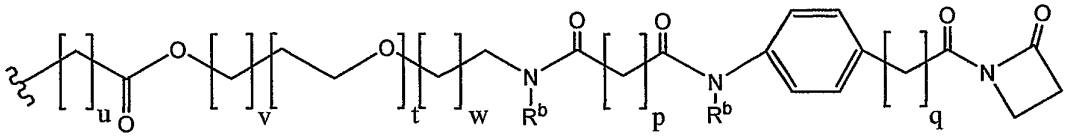
In certain of these embodiments, u is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, u is 0 or 1; v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

In certain embodiments of Formula I, L has the structure:



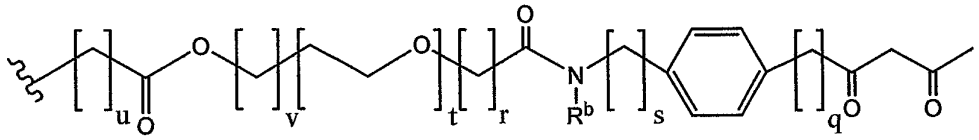
In certain of these embodiments, u is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, u is 0 or 1; v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

In certain embodiments of Formula I, L has the structure:



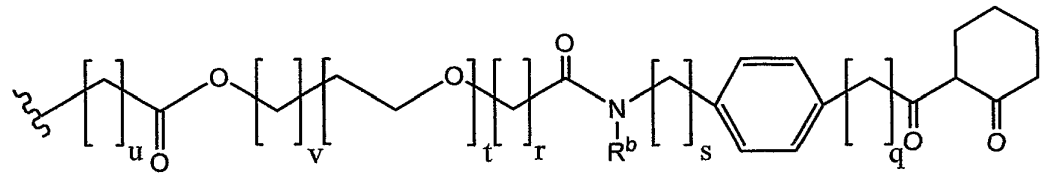
In certain of these embodiments, u is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, u is 0 or 1; v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 2 or 3.

In certain embodiments of Formula I, L has the structure:



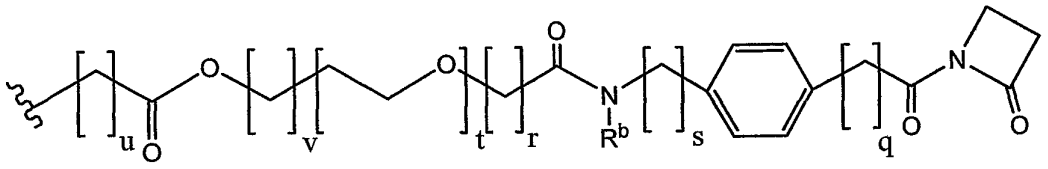
In certain of these embodiments, u is 0, 1, 2, 3, 5, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, u is 0 or 1; v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

In certain embodiments of Formula I, L has the structure:



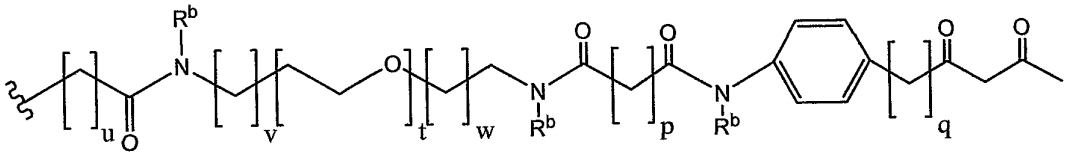
In certain of these embodiments, u is 0, 1, 2, 3, 5, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, u is 0 or 1; v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

In certain embodiments of Formula I, L has the structure:



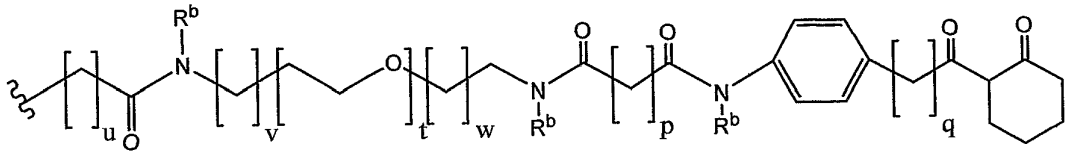
In certain of these embodiments, u is 0, 1, 2, 3, 5, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, u is 0 or 1; v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 2 or 3.

In certain embodiments of Formula I, L has the structure:



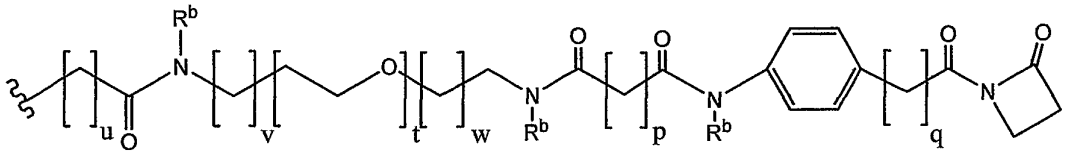
In certain of these embodiments, u is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, u is 0 or 1; v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

In certain embodiments of Formula I, L has the structure:



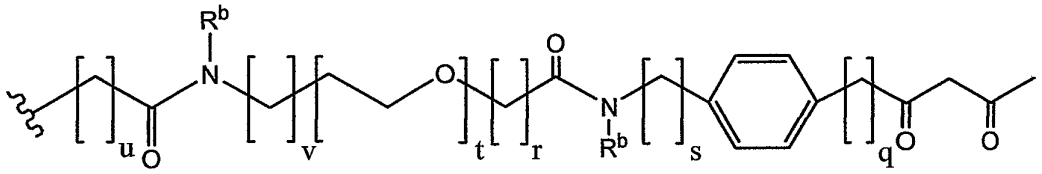
In certain of these embodiments, u is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, u is 0 or 1; v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

In certain embodiments of Formula I, L has the structure:



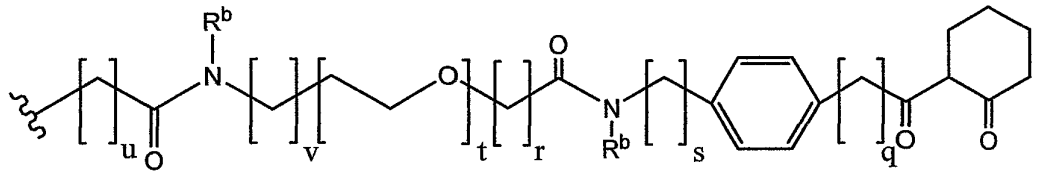
In certain of these embodiments, u is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, u is 0 or 1; v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 2 or 3.

In certain embodiments of Formula I, L has the structure:



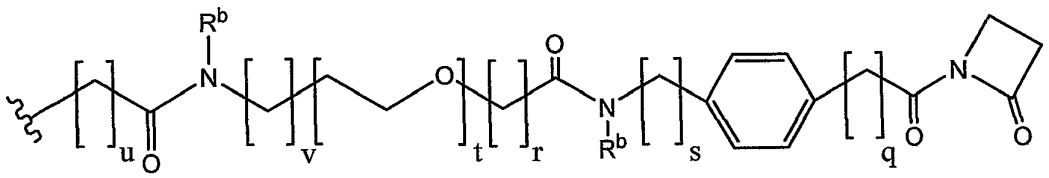
In certain of these embodiments, u is 0, 1, 2, 3, 5, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, u is 0 or 1; v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

In certain embodiments of Formula I, L has the structure:



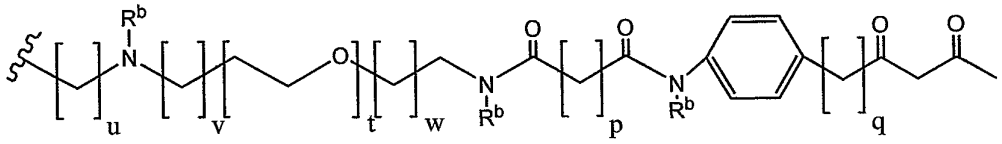
In certain of these embodiments, u is 0, 1, 2, 3, 5, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, u is 0 or 1; v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

In certain embodiments of Formula I, L has the structure:



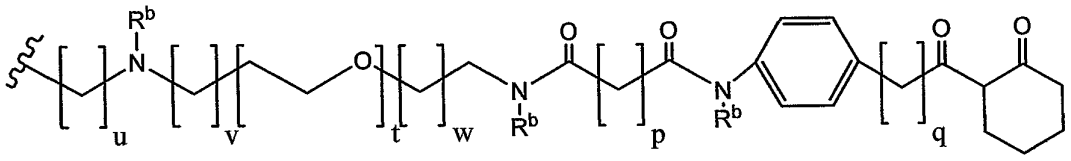
In certain of these embodiments, u is 0, 1, 2, 3, 5, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, u is 0 or 1; v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 2 or 3.

In certain embodiments of Formula I, L has the structure:



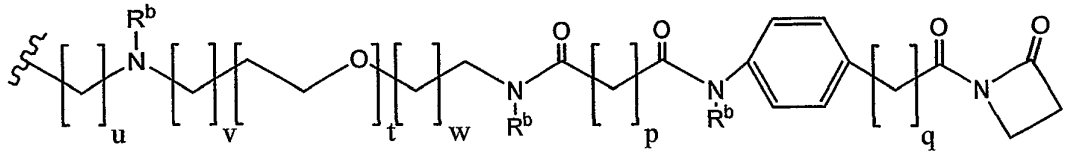
In certain of these embodiments, u is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In still some embodiments, u is 0 or 1; v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

In certain embodiments of Formula I, L has the structure:



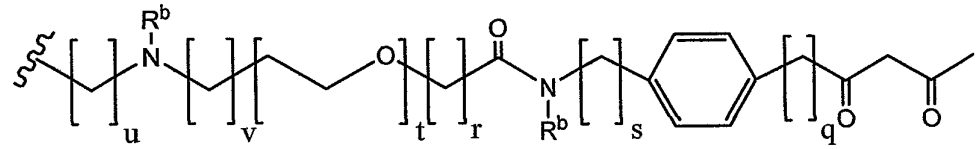
In certain of these embodiments, u is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, u is 0 or 1; v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

In certain embodiments of Formula I, L has the structure:



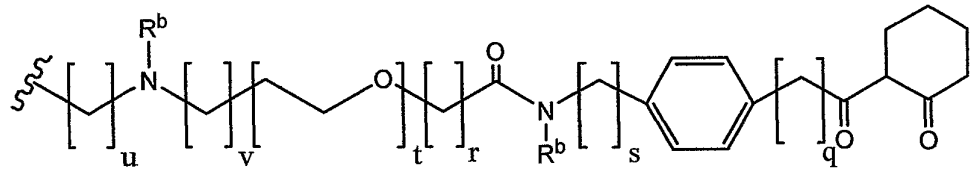
In certain of these embodiments, u is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, u is 0 or 1; v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 2 or 3.

In certain embodiments of Formula I, L has the structure:



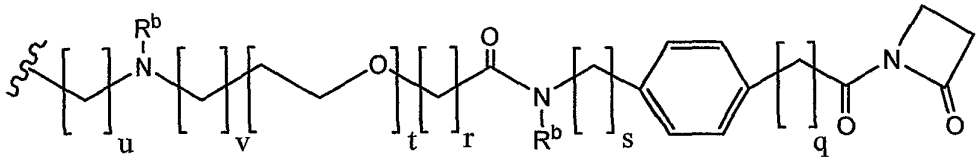
In certain of these embodiments, u is 0, 1, 2, 3, 5, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, u is 0 or 1; v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

In certain embodiments of Formula I, L has the structure:



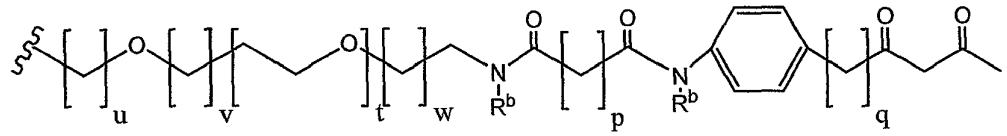
In certain of these embodiments, u is 0, 1, 2, 3, 5, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, u is 0 or 1; v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

In certain embodiments of Formula I, L has the structure:



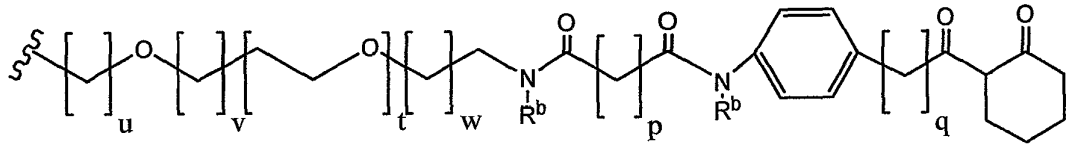
In certain of these embodiments, u is 0, 1, 2, 3, 5, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, u is 0 or 1; v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 2 or 3.

In certain embodiments of Formula I, L has the structure:



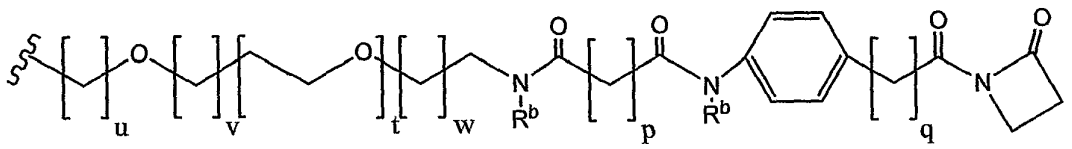
In certain of these embodiments, u is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In still other embodiments, u is 0 or 1; v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

In certain embodiments of Formula I, L has the structure:



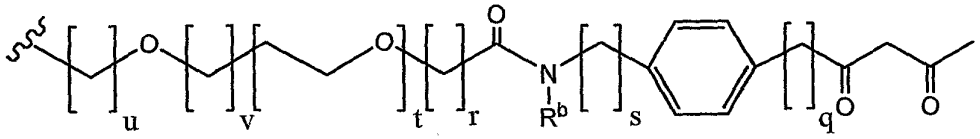
In certain of these embodiments, u is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, u is 0 or 1; v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

In certain embodiments of Formula I, L has the structure:



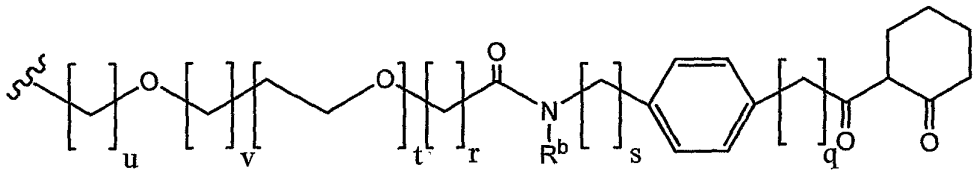
In certain of these embodiments, u is 0, 1, 2, 3, 4, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, u is 0 or 1; v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 2 or 3.

In certain embodiments of Formula I, L has the structure:



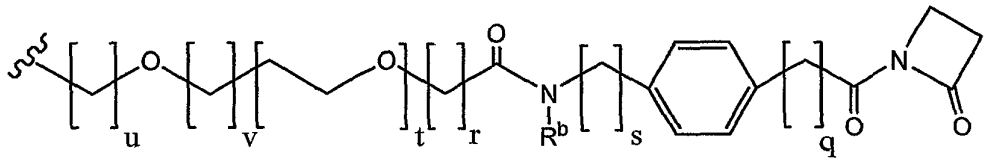
In certain of these embodiments, u is 0, 1, 2, 3, 5, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, u is 0 or 1; v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

In certain embodiments of Formula I, L has the structure:



In certain of these embodiments, u is 0, 1, 2, 3, 5, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, u is 0 or 1; v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

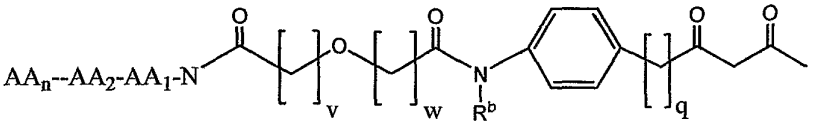
In certain embodiments of Formula I, L has the structure:



In certain of these embodiments, u is 0, 1, 2, 3, 5, or 5; v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, u is 0; v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, u is 0 or 1; v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 2 or 3.

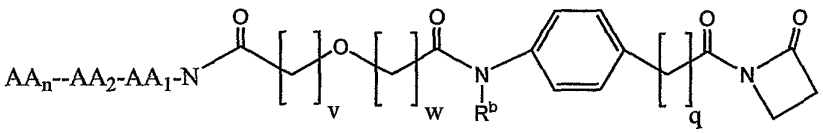
As used herein, "AA_1-AA_2—AA_n" refers to an AA targeting agent wherein "AA_1" is the first amino acid in the AA targeting agent sequence, as measured from the N-terminus, "AA_2" is the second amino acid in the AA targeting agent sequence, as measured from the N-terminus, and "AA_n" is the n^{th} amino acid in the AA targeting agent sequence, as measured from the N-terminus.

Certain embodiments in accordance with Formula I have the structure:



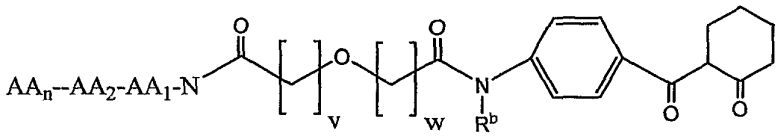
In certain of these embodiments, v is 1, 2, 3, 4, or 5; w is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 1, 2, or 3; w is 1, 2, or 3; and q is 0, 1, 2, or 3. In some embodiments, v is 1 or 2; w is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula I have the structure:



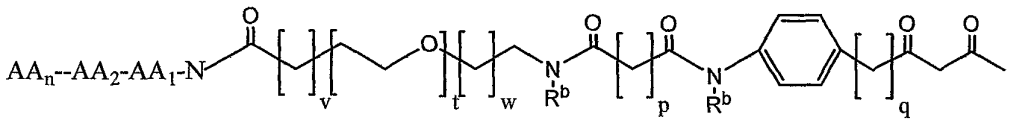
In certain of these embodiments, v is 1, 2, 3, 4, or 5; w is 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 1, 2, or 3; w is 1, 2, or 3; and q is 0, 1, 2, 3. In some embodiments, v is 1 or 2; w is 1 or 2; and q is 2 or 3.

Certain embodiments in accordance with Formula I have the structure:



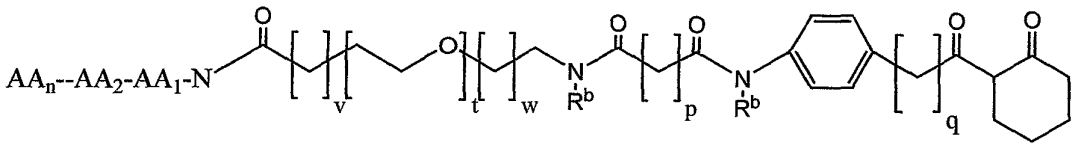
In certain of these embodiments, v is 1, 2, 3, 4, or 5; w is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 1, 2, or 3; w is 1, 2, or 3; and q is 0, 1, 2, 3. In some embodiments, v is 1 or 2; w is 1 or 2; and q is 2 or 3.

Certain embodiments in accordance with Formula I have the structure:



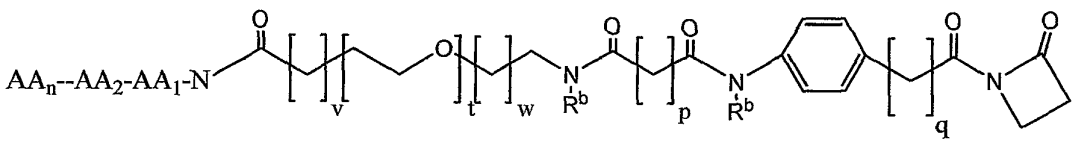
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula I have the structure:



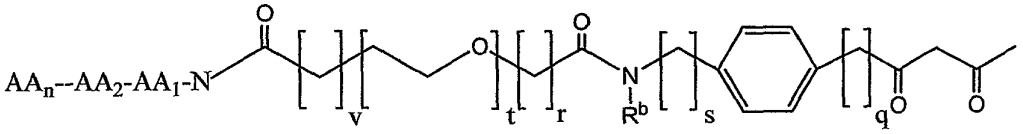
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula I have the structure:



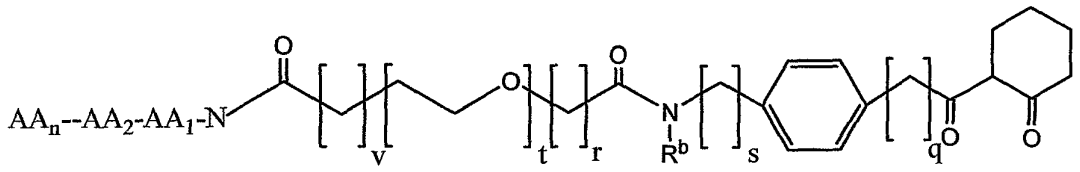
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; and q is 0, 1, 2, or 3. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; and p is 3, and in some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 2 or 3.

Certain embodiments in accordance with Formula I have the structure:



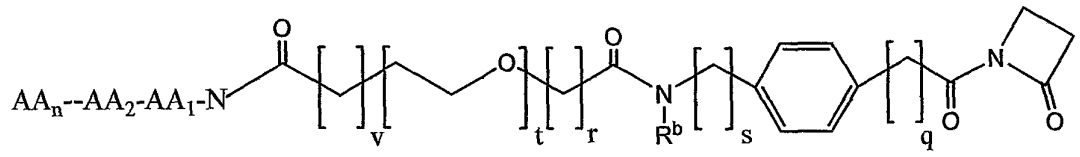
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula I have the structure:



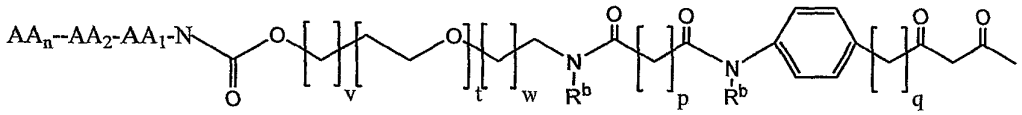
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula I have the structrue:



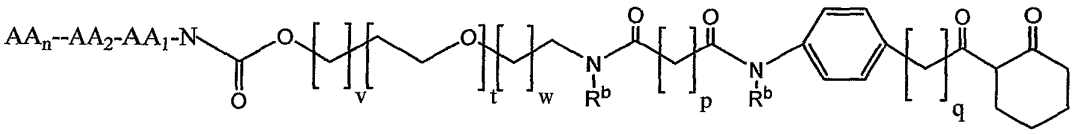
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 2 or 3.

Certain embodiments in accordance with Formula I have the structure:



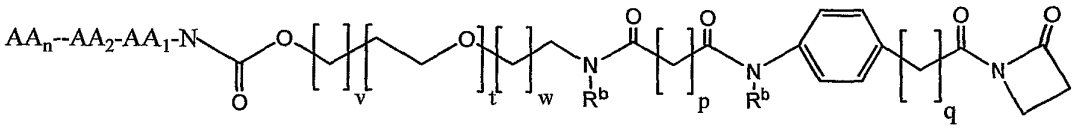
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula I have the structure:



In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

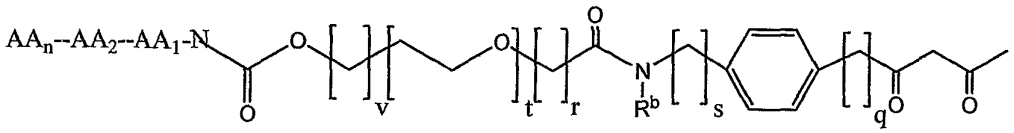
Certain embodiments in accordance with Formula I have the structure:



In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or

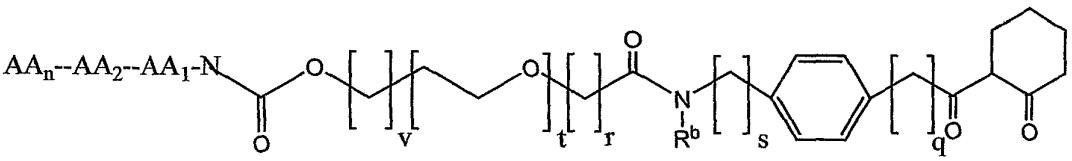
unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 2 or 3.

Certain embodiments in accordance with Formula I have the structure:



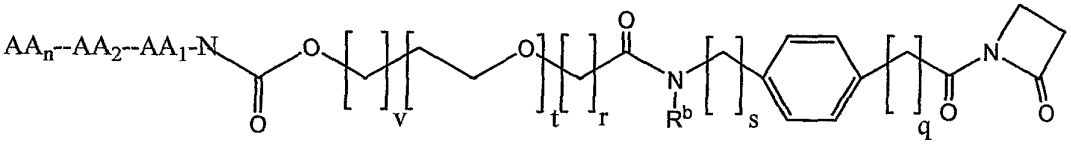
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula I have the structure:



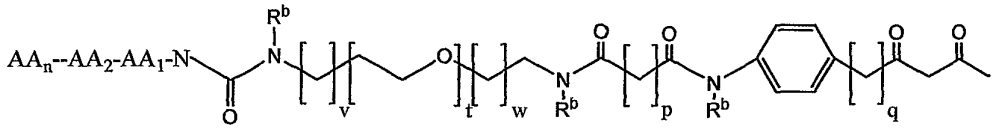
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula I have the structure:



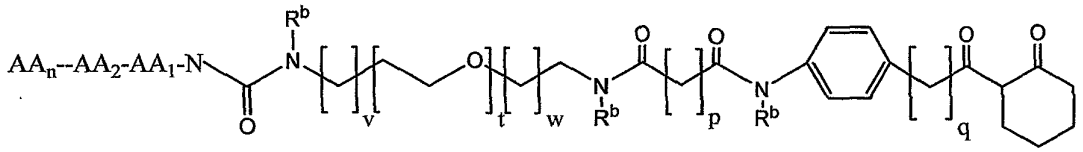
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 2 or 3.

Certain embodiments in accordance with Formula I have the structure:



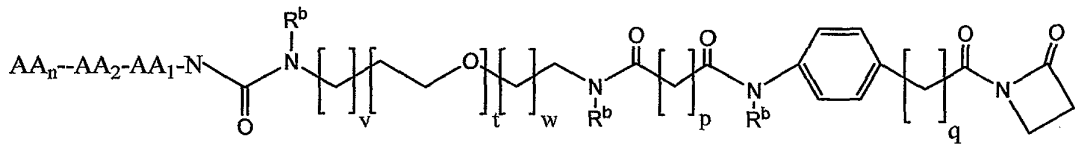
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula I have the structure:



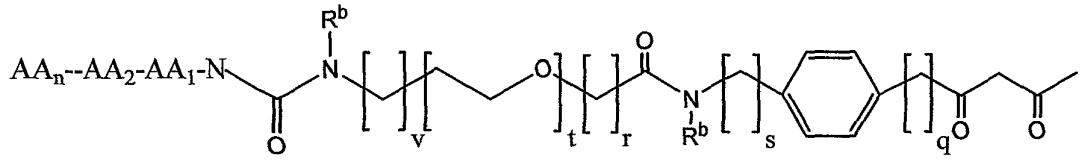
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula I have the structure:



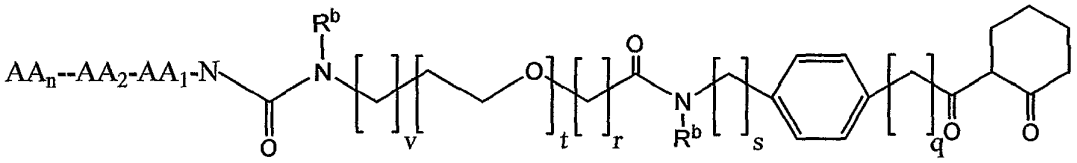
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 2 or 3.

Certain embodiments in accordance with Formula I have the structure:



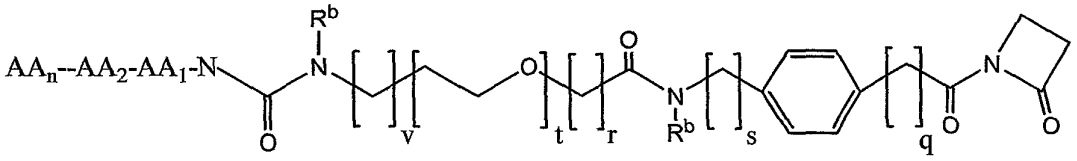
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula I have the structure:



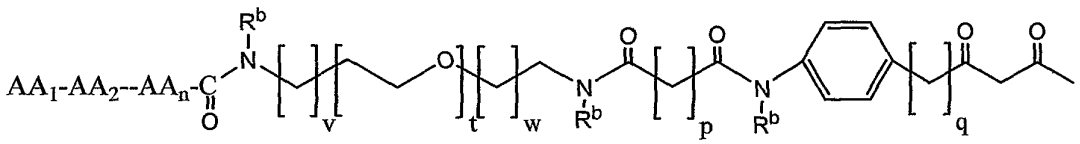
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula I have the structure:



In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 2 or 3.

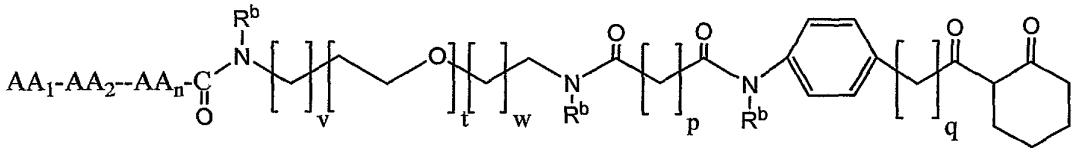
Certain embodiments in accordance with Formula I have the structure:



In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted

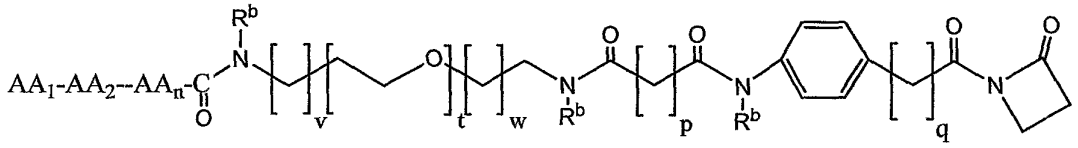
or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula I have the structure:



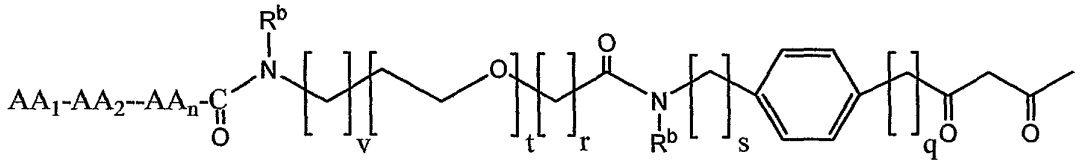
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula I have the structure:



In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 2 or 3.

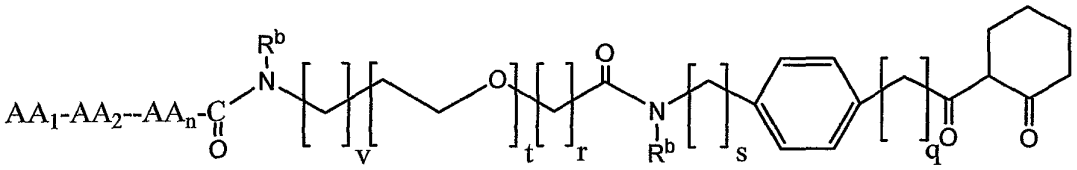
Certain embodiments in accordance with Formula I have the structure:



In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or

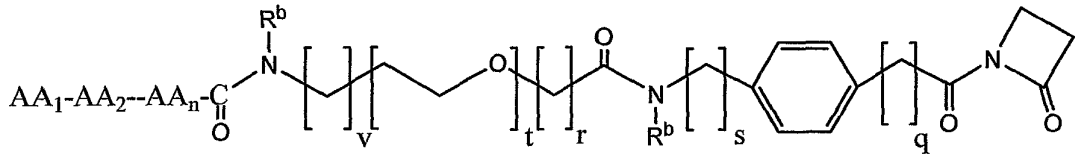
unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula I have the structure:



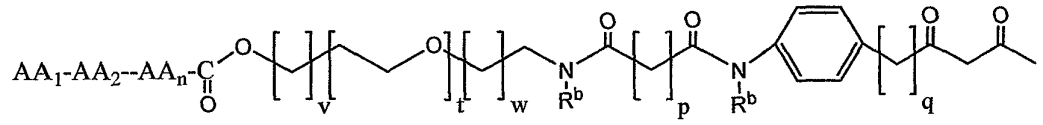
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula I have the structure:



In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 2 or 3.

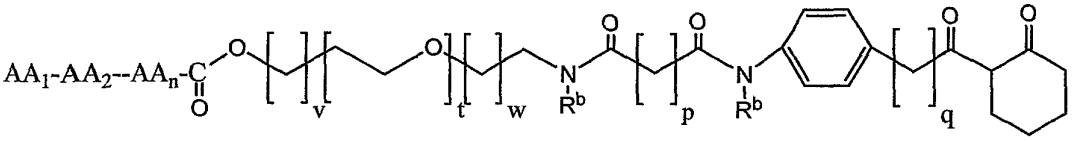
Certain embodiments in accordance with Formula I have the structure:



In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or

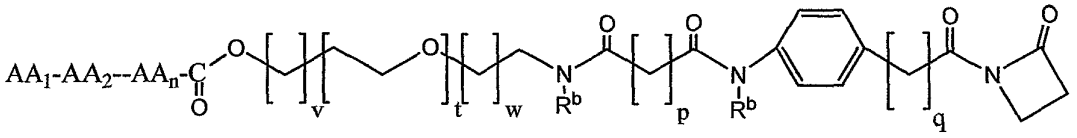
unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula I have the structure:



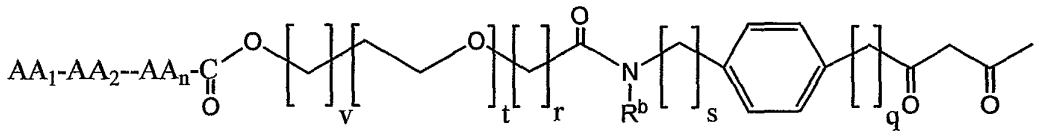
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula I have the structure:



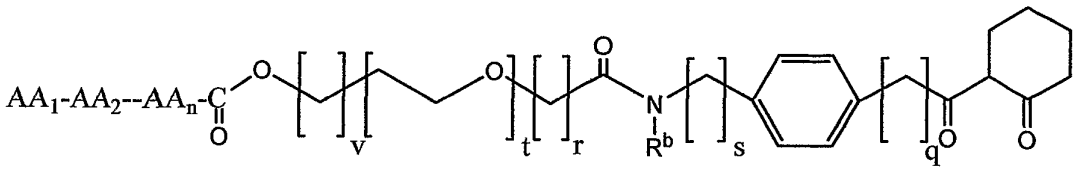
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 2 or 3.

Certain embodiments in accordance with Formula I have the structure:



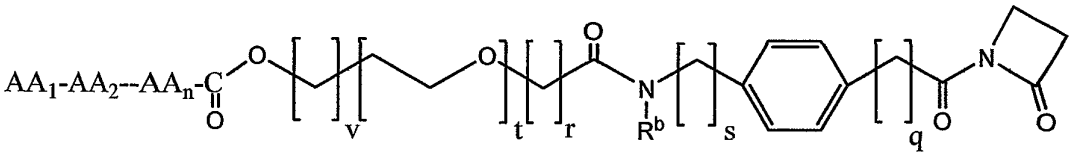
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula I have the structure:

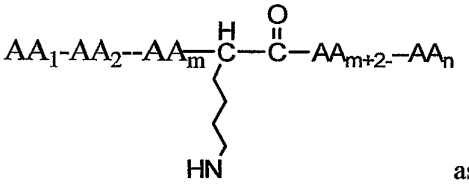


In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula I have the structure:

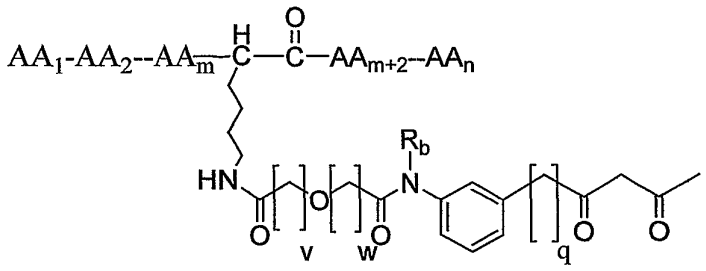


In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 2 or 3.



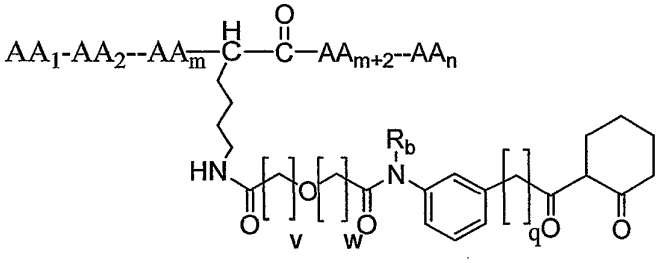
as used herein refers to an AA targeting agent wherein "AA_1" is the first amino acid in an AA targeting agent sequence as measured from the N-terminus, "AA_2" is the second amino acid in an AA targeting agent sequence as measured from the N-terminus, and "AA_n" is the n^{th} amino acid in an AA targeting agent sequence as measured from the N-terminus. The targeting agent further comprises a Lys residue at arbitrary position m+1 as measured from the N-terminus. It will be appreciated that in addition to linking to a Lys side chain in the body of an AA targeting agent, it is also possible to link to a Lys side chain on the N-terminus or C-terminus of an AA targeting agent.

Certain embodiments in accordance with Formula I have the structure:



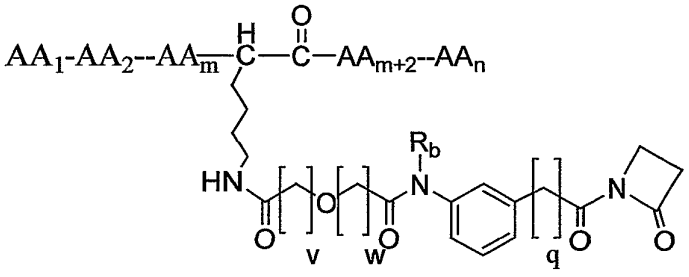
In certain of these embodiments, v is 1, 2, 3, 4, or 5; w is 1, 2, 3, 4, 5, or 6; q is 1, 2, 3, 4, or 5; and R_b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 1, 2 or 3; w is 1, 2 or 3; and q is 1, 2, or 3. In some embodiments, v is 1 or 2; w is 1 or 2; and q is 2, or 3.

Certain embodiments in accordance with Formula I have the structure:



In certain of these embodiments, v is 1, 2, 3, 4, or 5; w is 1, 2, 3, 4, 5, or 6; q is 1, 2, 3, 4, or 5; and R_b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 1, 2 or 3; w is 1, 2 or 3; and q is 1, 2, or 3. In some embodiments, v is 1 or 2; w is 1 or 2; and q is 2, or 3.

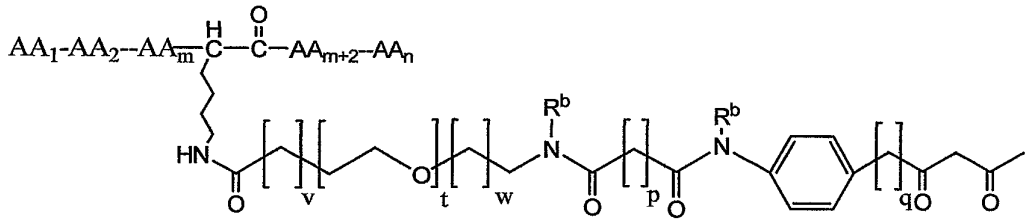
Certain embodiments in accordance with Formula I have the structure:



In certain of these embodiments, v is 1, 2, 3, 4, or 5; w is 1, 2, 3, 4, 5, or 6; q is 1, 2, 3, 4, or 5; and R_b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain

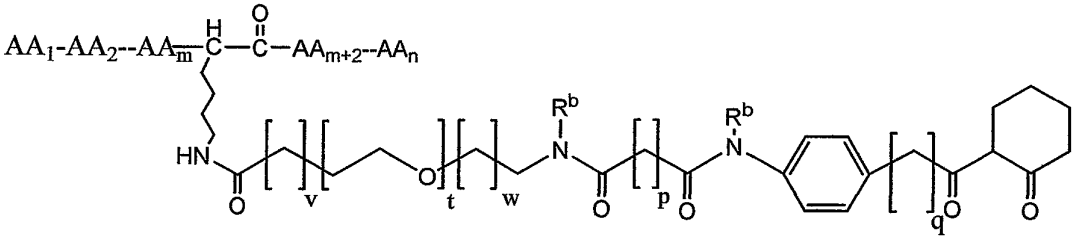
embodiments, v is 1, 2 or 3; w is 1, 2 or 3; and q is 1, 2, or 3. In some embodiments, v is 1 or 2; w is 1 or 2; and q is 2, or 3.

Certain embodiments in accordance with Formula I have the structure:



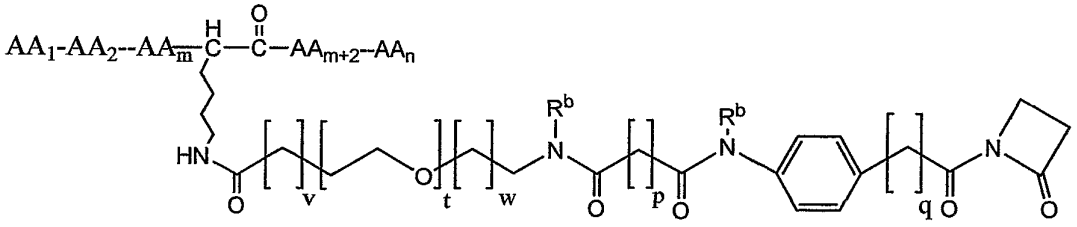
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula I have the structure:



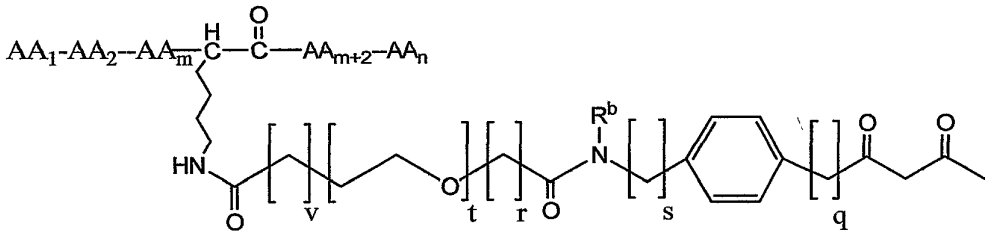
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula I have the structure:



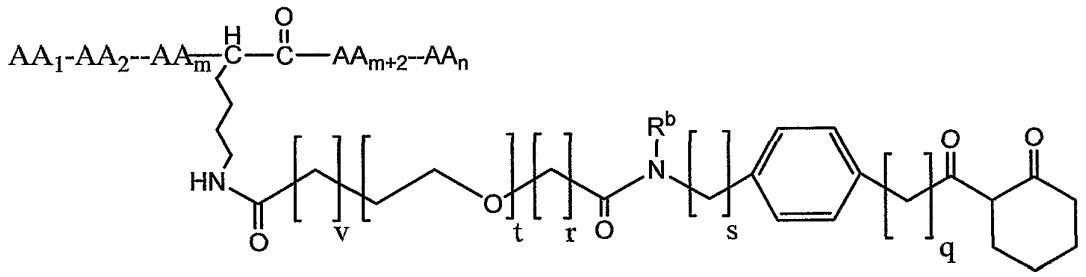
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 2 or 3.

Certain embodiments in accordance with Formula I have the structure:



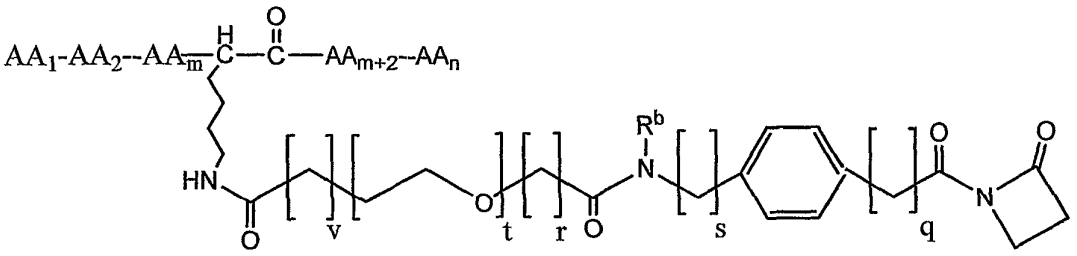
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula I have the structure:



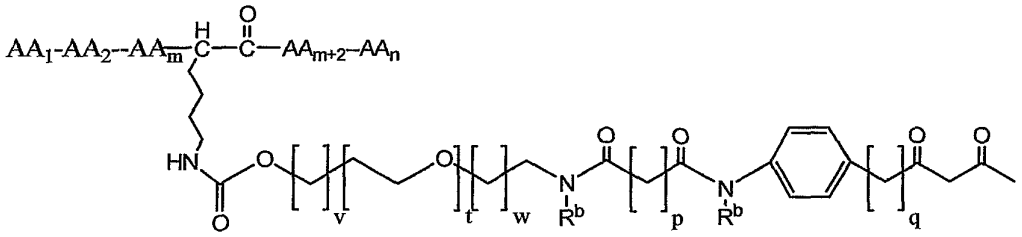
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula I have the structure:



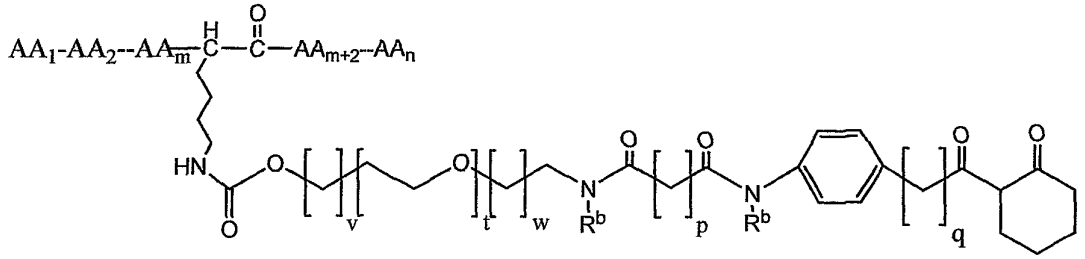
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 2 or 3.

Certain embodiments in accordance with Formula I have the structure:



In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

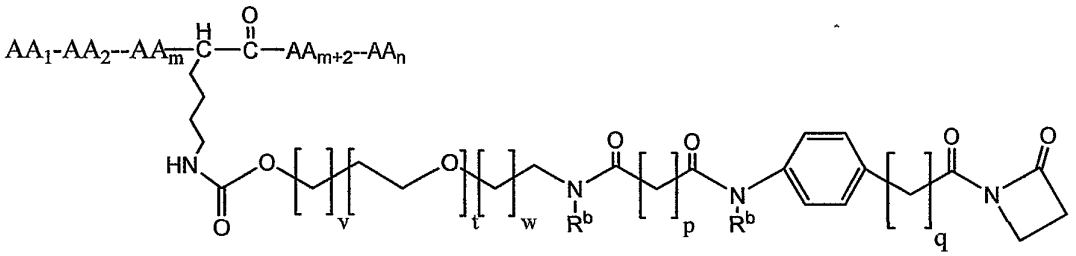
Certain embodiments in accordance with Formula I have the structure:



In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or

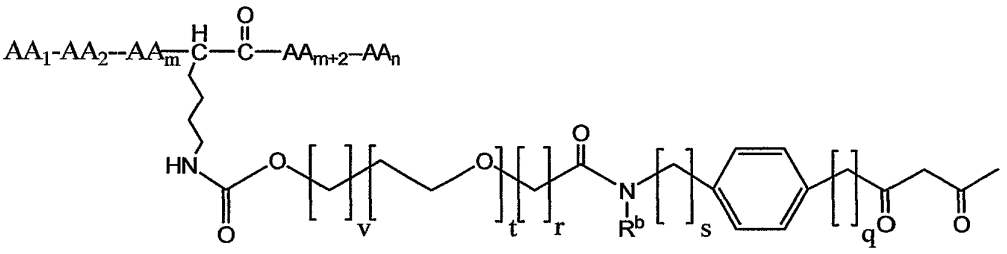
unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula I have the structure:



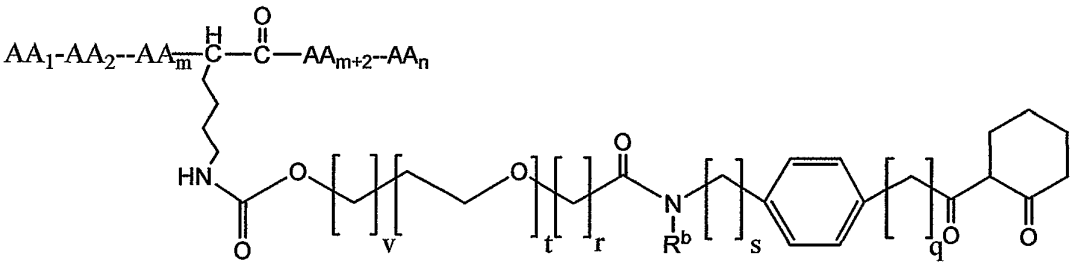
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 2 or 3.

Certain embodiments in accordance with Formula I have the structure:



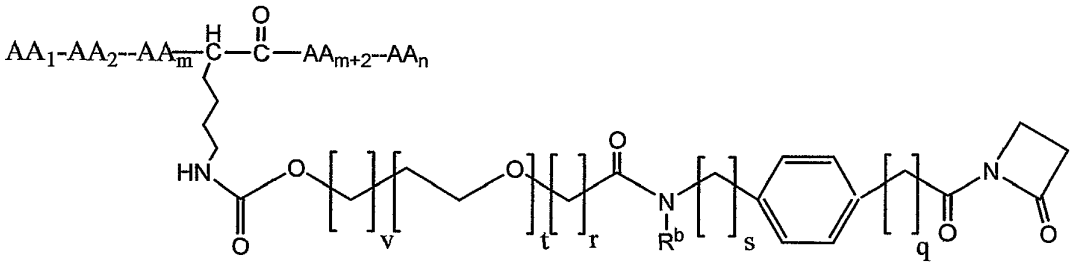
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula I have the structure:



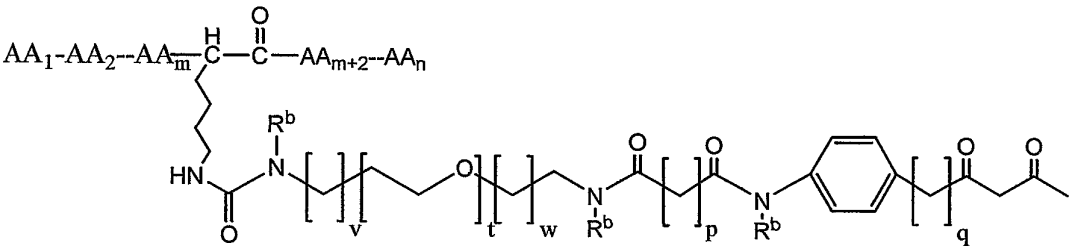
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula I have the structure:



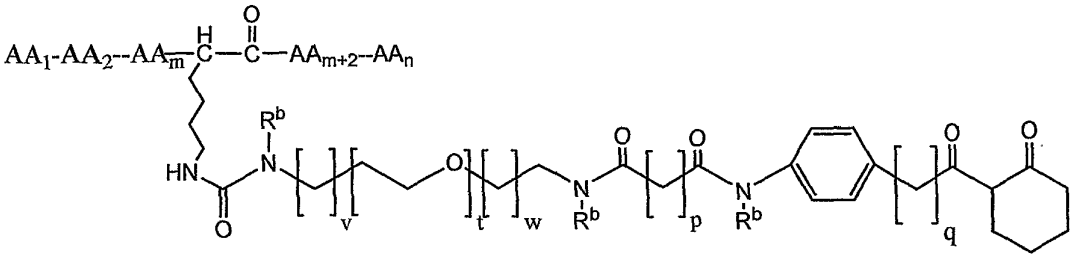
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 2 or 3.

Certain embodiments in accordance with Formula I have the structure:



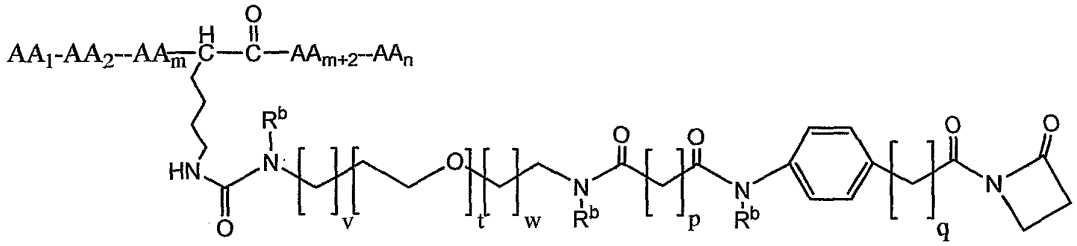
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula I have the structure:



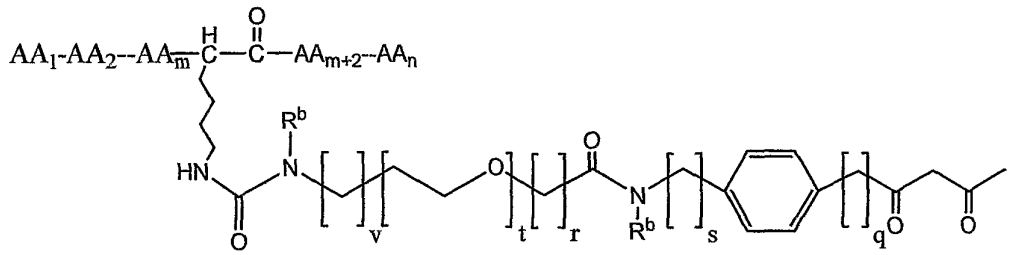
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiment v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula I have the structure:



In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 2 or 3.

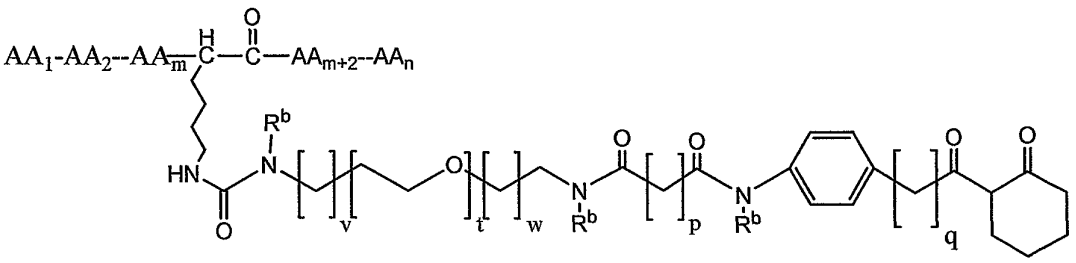
Certain embodiments in accordance with Formula I have the structure:



In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or

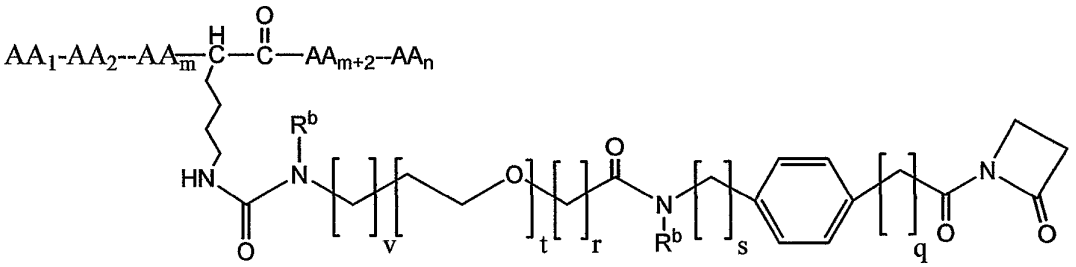
unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula I have the structure:



In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula I have the structure:



In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 2 or 3.

The administration of an AA targeting compound to an immunocompetent individual may result in the production of antibodies against the conjugate. Such antibodies may be directed to the variable region, including the antibody idiotype, as well as to the targeting agent or any linker used to conjugate the targeting agent to the antibody. Reducing the immunogenicity of an AA targeting compound can be accomplished by methods well known in the art, such as by attaching long chain polyethylene glycol (PEG)-based spacers and the like to the AA targeting compound. Long chain PEG and other polymers are known for their ability to mask foreign epitopes, resulting in the reduced

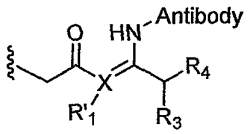
immunogenicity of therapeutic proteins that display foreign epitopes (N.V. Katre, J. Immunol. 144:209-213 (1990); G.E. Francis *et al.*, Int. J. Hematol. 68:1-18 (1998). Alternatively, or in addition, the individual administered the antibody-AA targeting agent conjugate may be administered an immunosuppressant such as cyclosporin A, anti-CD3 antibody, and the like.

In one embodiment, an AA targeting compound is as shown by Formula II, and includes stereoisomers, tautomers, solvates, prodrugs, and pharmaceutically acceptable salts thereof.

Antibody – L' – [AA targeting agent] (II)

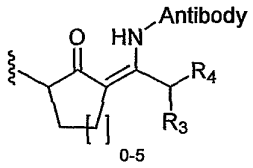
In compounds of Formula II, [AA targeting agent] is defined as in Formula I. L' is a linker moiety linking an antibody to the targeting agent and having the formula –X-Y-Z'-. In compounds of Formula II, X and Y are defined as in Formula I, and Antibody is an antibody as defined herein. FIGURES 10 and 11, respectively, illustrate the addition mechanism of a reactive, nucleophilic side chain in a combining site of an antibody to the Z moieties illustrated in FIGURES 8 and 9.

In certain embodiments, wherein Antibody is an aldolase catalytic antibody, Z'- Antibody has the structure:



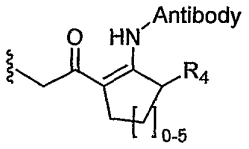
wherein HN-Antibody refers to an arbitrary side chain in the combining site of an antibody bearing an amino group.

In certain embodiments, wherein Antibody is an aldolase catalytic antibody, Z'- Antibody has the structure:



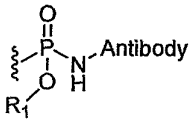
wherein HN-Antibody refers to an arbitrary side chain in the combining site of an antibody bearing an amino group.

In certain embodiments, wherein Antibody is an aldolase catalytic antibody, Z'- Antibody has the structure:



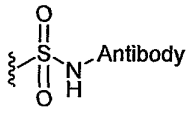
wherein HN-Antibody refers to an arbitrary side chain in the combining site of an antibody bearing an amino group.

In certain embodiments, wherein Antibody is an aldolase catalytic antibody, Z'- Antibody has the structure:



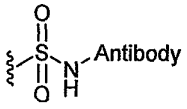
wherein HN-Antibody refers to an arbitrary side chain in the combining site of an antibody bearing an amino group.

In certain embodiments, wherein Antibody is an aldolase catalytic antibody, Z'- Antibody has the structure:



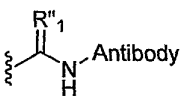
wherein HN-Antibody refers to an arbitrary side chain in the combining site of an antibody bearing an amino group.

In certain embodiments, wherein Antibody is an aldolase catalytic antibody, Z'- Antibody has the structure:



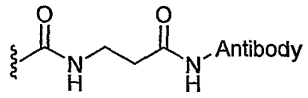
wherein HN-Antibody refers to an arbitrary side chain in the combining site of an antibody bearing an amino group.

In certain embodiments, wherein Antibody is an aldolase catalytic antibody, Z'- Antibody has the structure:



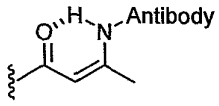
wherein HN-Antibody refers to an arbitrary side chain in the combining site of an antibody bearing an amino group.

In certain embodiments, wherein Antibody is an aldolase catalytic antibody, Z'- Antibody has the structure:



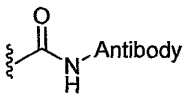
wherein HN-Antibody refers to an arbitrary side chain in the combining site of an antibody bearing an amino group.

In certain embodiments, wherein Antibody is an aldolase catalytic antibody, Z'- Antibody has the structure:



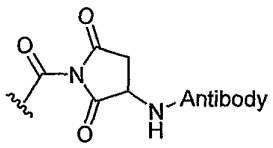
wherein HN-Antibody refers to an arbitrary side chain in the combining site of an antibody bearing an amino group.

In certain embodiments, wherein Antibody is an aldolase catalytic antibody, Z'- Antibody has the structure:



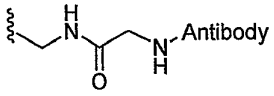
wherein HN-Antibody refers to an arbitrary side chain in the combining site of an antibody bearing an amino group.

In certain embodiments, wherein Antibody is an aldolase catalytic antibody, Z'- Antibody has the structure:



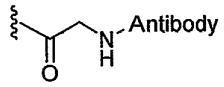
wherein HN-Antibody refers to an arbitrary side chain in the combining site of an antibody bearing an amino group.

In certain embodiments, wherein Antibody is an aldolase catalytic antibody, Z'- Antibody has the structure:



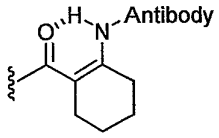
wherein HN-Antibody refers to an arbitrary side chain in the combining site of an antibody bearing an amino group.

In certain embodiments, wherein Antibody is an aldolase catalytic antibody, Z'- Antibody has the structure:



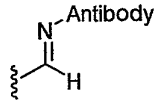
wherein HN-Antibody refers to an arbitrary side chain in the combining site of an antibody bearing an amino group.

In certain embodiments, wherein Antibody is an aldolase catalytic antibody, Z'- Antibody has the structure:



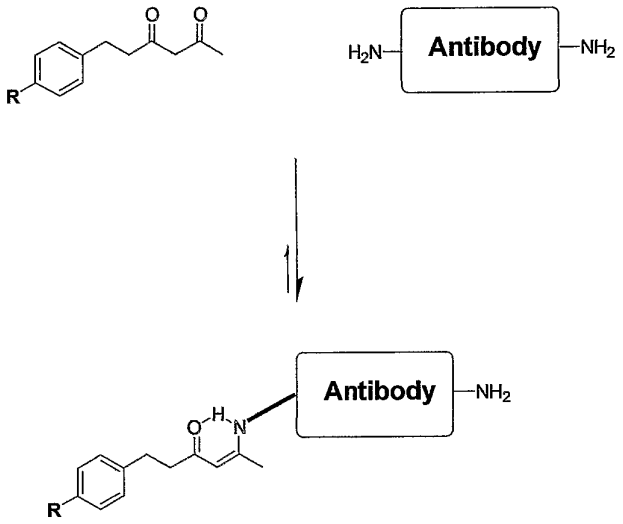
wherein HN-Antibody refers to an arbitrary side chain in the combining site of an antibody bearing an amino group.

In certain embodiments, wherein Antibody is an aldolase catalytic antibody, Z'- Antibody has the structure:

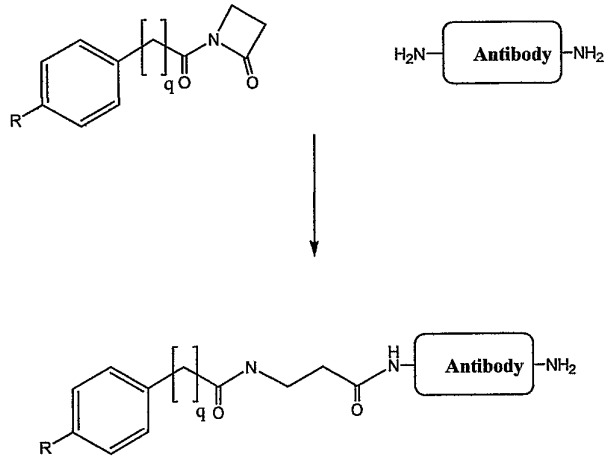


wherein HN-Antibody refers to an arbitrary side chain in the combining site of an antibody bearing an amino group.

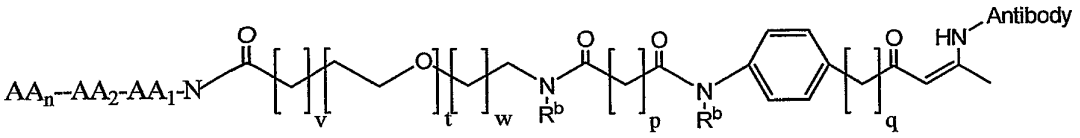
In compounds having Formula II, Z' is an attachment moiety comprising a covalent bond and 0-20 carbon atoms to which the Antibody is attached. This is shown below for the case where the linker has a diketone moiety as the reactive group and linkage occurs with the side chain amino group of a lysine residue in the antibody combining site. The Antibody is shown schematically as bivalent with a reactive amino acid side chain for each combining site indicated.



Another embodiment shown below is for the case where the linker has a beta lactam moiety as the reactive group and linkage occurs with the side chain amino group of a lysine residue in the antibody combining site. The Antibody is shown schematically as bivalent with a reactive amino acid side chain for each combining site indicated.

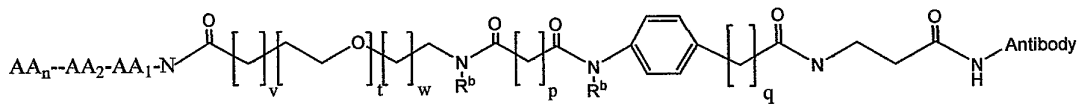


Certain embodiments in accordance with Formula II have the structure:



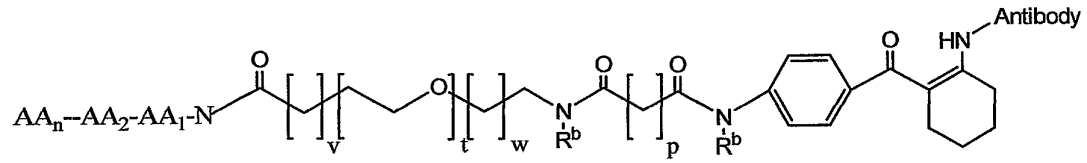
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 2 or 3.

Certain embodiments in accordance with Formula II have the structure:



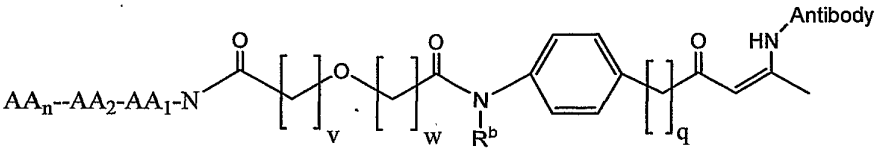
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula II have the structure:



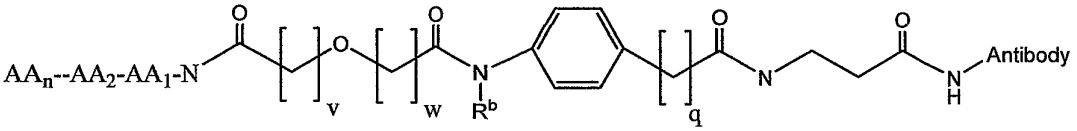
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; and p is 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; and p is 3. In some embodiments, v is 0; t is 1 or 2; w is 1; and p is 1 or 2.

Certain embodiments in accordance with Formula II have the structure:



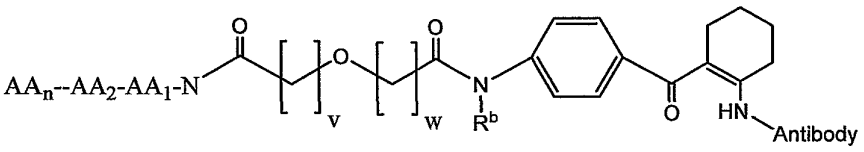
In certain of these embodiments, v is 1, 2, 3, 4, or 5; w is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 1, 2, or 3; w is 1, 2, or 3; and q is 0, 1, 2, 3. In some embodiments, v is 1 or 2; w is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula II have the structure:



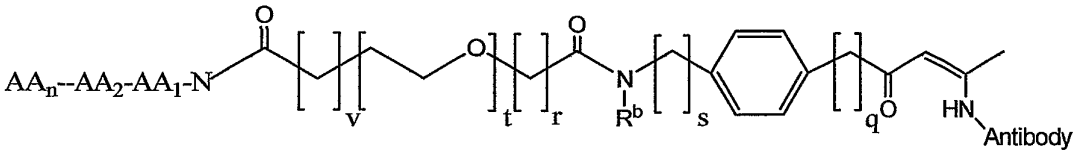
In certain of these embodiments, v is 1, 2, 3, 4, or 5; w is 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 1, 2, or 3; w is 1, 2, or 3; and q is 0, 1, 2, 3. some embodiments, v is 1 or 2; w is 1 or 2; and q is 2 or 3.

Certain embodiments in accordance with Formula II have the structure:



In certain of these embodiments, v is 1, 2, 3, 4, or 5; w is 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 1, 2, or 3; and w is 1, 2, or 3. In some embodiments, v is 1 or 2 and w is 1 or 2.

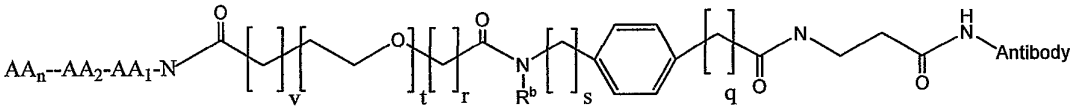
Certain embodiments in accordance with Formula II have the structure:



In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl,

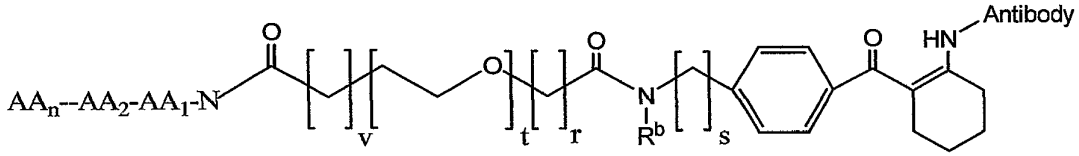
substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3 and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula II have the structure:



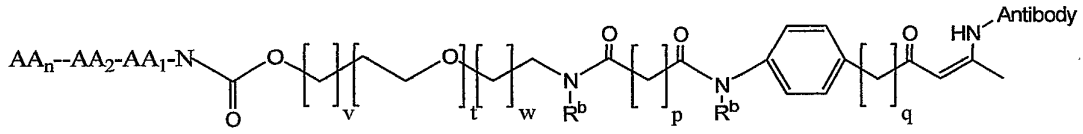
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3 and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 2 or 3.

Certain embodiments in accordance with Formula II have the structure:



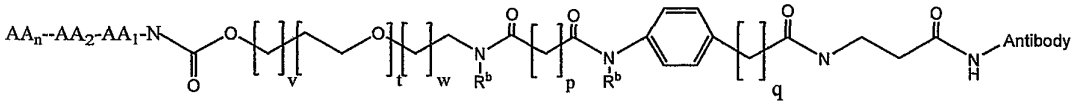
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; and s is 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; and s is 1 or 2.

Certain embodiments in accordance with Formula II have the structure:



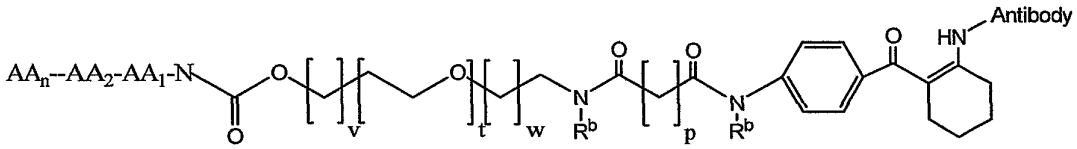
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula II have the structure:



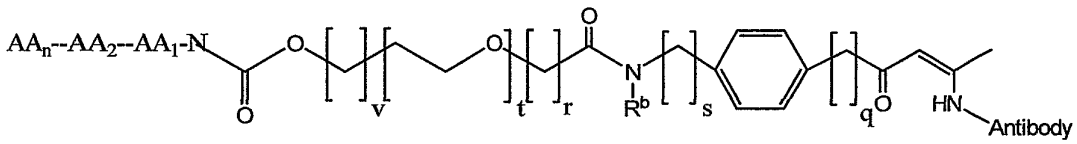
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 2 or 3.

Certain embodiments in accordance with Formula II have the structure:



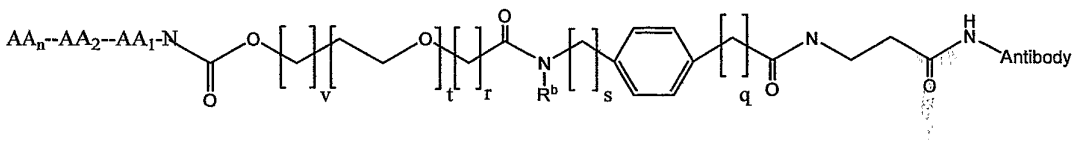
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; and p is 3. In some embodiments, v is 0; t is 1 or 2; w is 1; and p is 1 or 2.

Certain embodiments in accordance with Formula II have the structure:



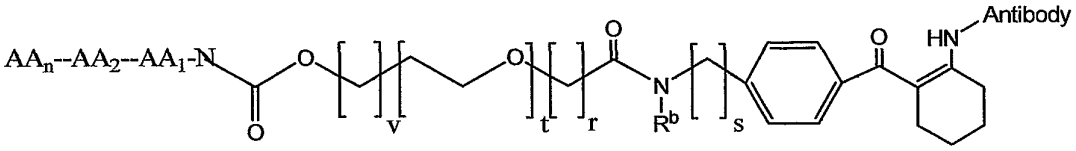
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3 and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula II have the structure:



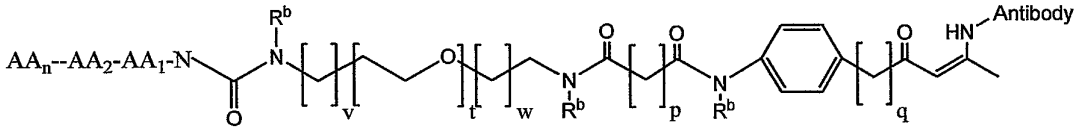
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3 and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 2 or 3.

Certain embodiments in accordance with Formula II have the structure:



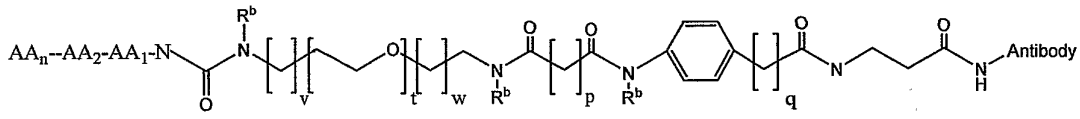
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; and s is 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; and s is 1 or 2.

Certain embodiments in accordance with Formula II have the structure:



In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

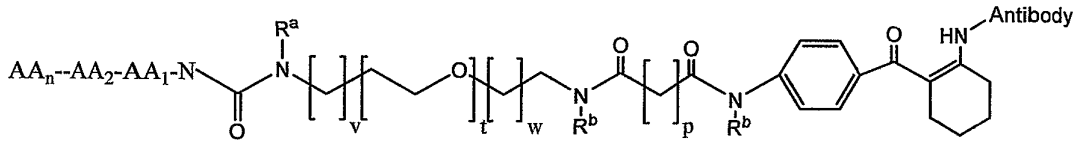
Certain embodiments in accordance with Formula II have the structure:



In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or

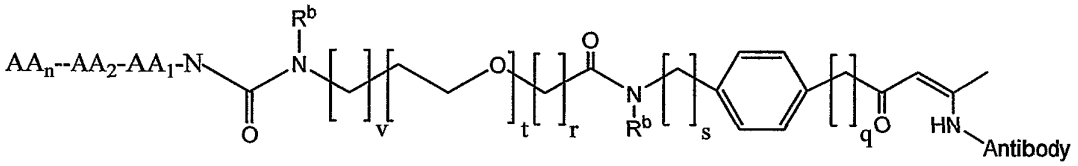
unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 2 or 3.

Certain embodiments in accordance with Formula II have the structure:



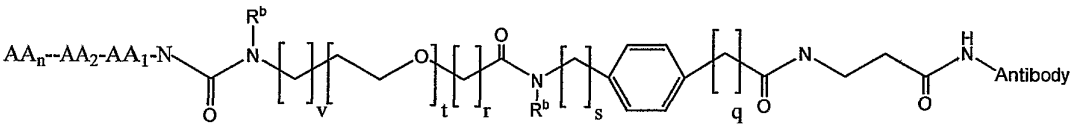
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; and R^b at each occurrence are independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; and p is 3. In some embodiments, v is 0; t is 1 or 2; w is 1; and p is 1 or 2.

Certain embodiments in accordance with Formula II have the structure:



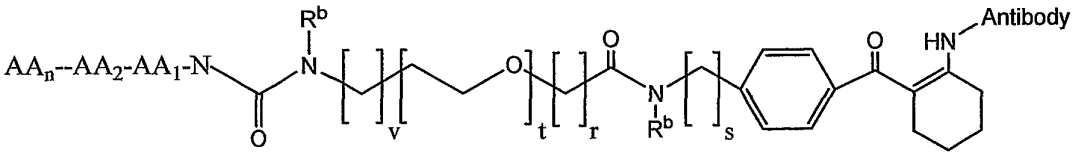
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3 and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula II have the structure:



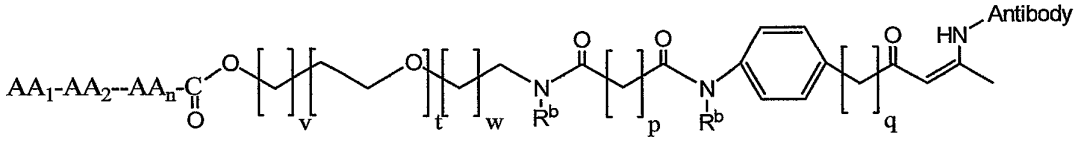
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3 and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 2 or 3.

Certain embodiments in accordance with Formula II have the structure:



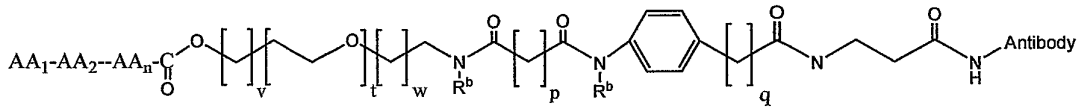
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; and s is 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; and s is 1 or 2.

Certain embodiments in accordance with Formula II have the structure:



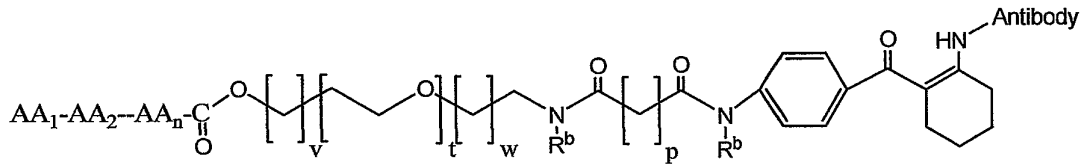
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula II have the structure:



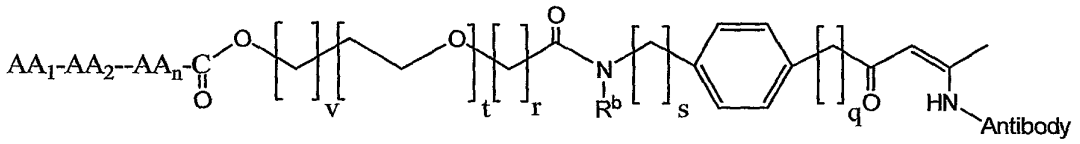
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 2 or 3.

Certain embodiments in accordance with Formula II have the structure:



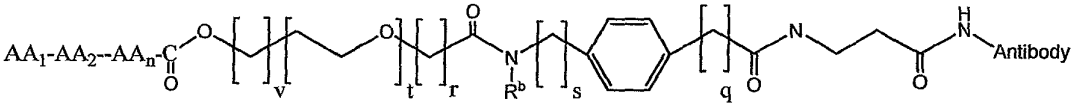
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; and p is 3. In some embodiments, v is 0; t is 1 or 2; w is 1; and p is 1 or 2.

Certain embodiments in accordance with Formula II have the structure:



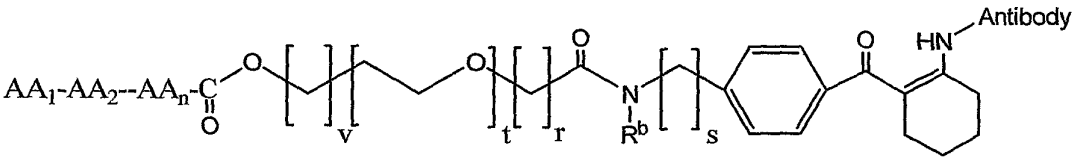
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3 and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula II have the structure:



In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3 and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 2 or 3.

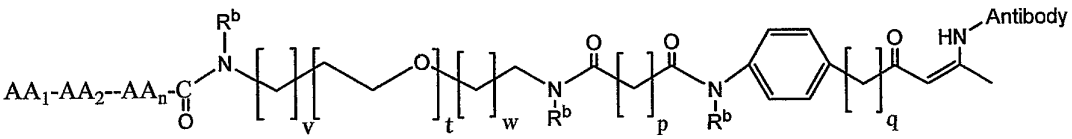
Certain embodiments in accordance with Formula II have the structure:



In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain

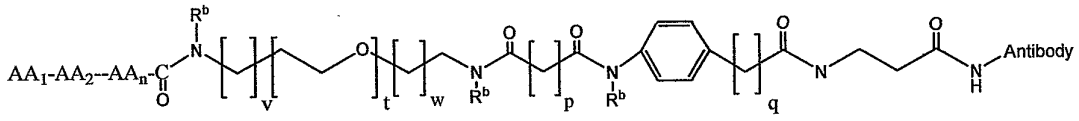
embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; and s is 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; and s is 1 or 2.

Certain embodiments in accordance with Formula II have the structure:



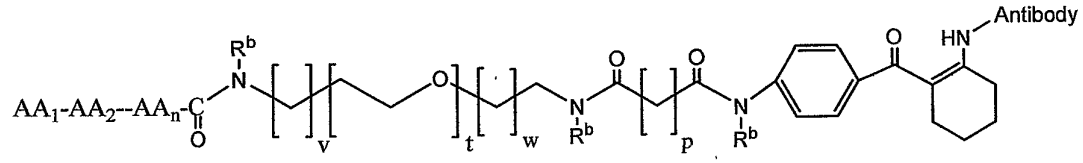
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula II have the structure:



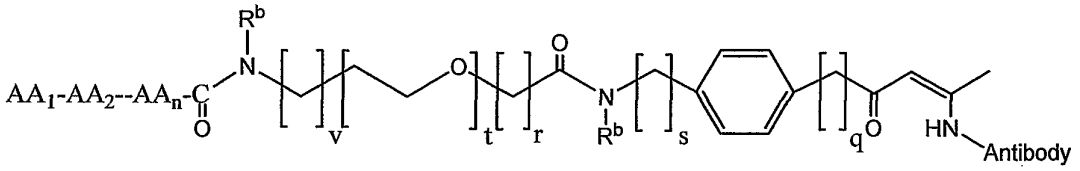
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 2 or 3.

Certain embodiments in accordance with Formula II have the structure:



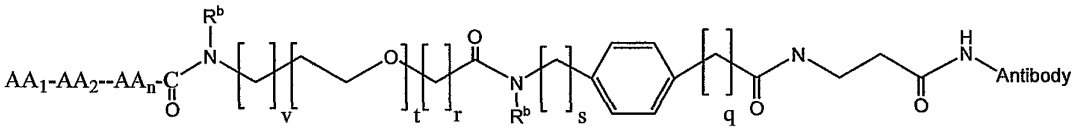
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; and p is 3. In some embodiments, v is 0; t is 1 or 2; w is 1; and p is 1 or 2.

Certain embodiments in accordance with Formula II have the structure:



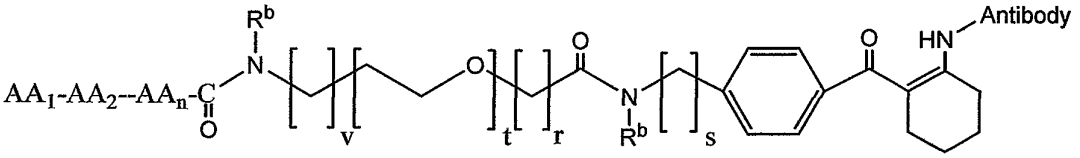
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3 and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula II have the structure:



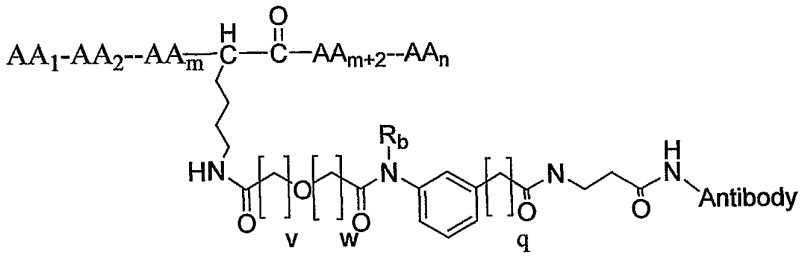
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3 and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 2 or 3.

Certain embodiments in accordance with Formula II have the structure:



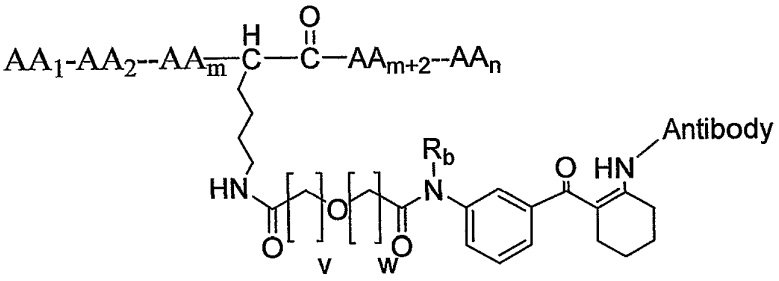
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; and s is 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; and s is 1 or 2.

Certain embodiments in accordance with Formula II have the structure:



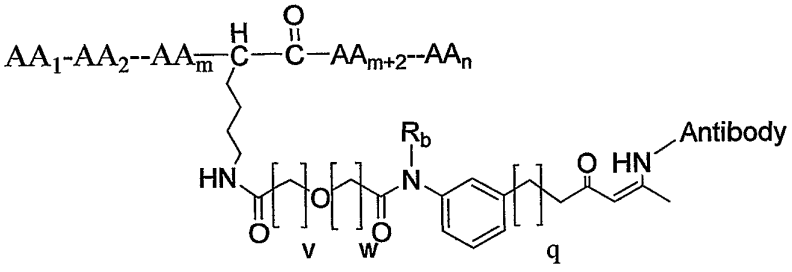
In certain of these embodiments, v is 1, 2, 3, 4, or 5; w is 1, 2, 3, 4, 5, or 6; q is 1, 2, 3, 4, or 5; and R_b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 1, 2 or 3; w is 1, 2 or 3; and q is 1, 2, or 3. In some embodiments, v is 1 or 2; w is 1 or 2; and q is 2, or 3.

Certain embodiments in accordance with Formula II have the structure:



In certain of these embodiments, v is 1, 2, 3, 4, or 5; and w is 1, 2, 3, 4, 5; and R_b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 1, 2 or 3; and w is 1, 2 or 3. In some embodiments, v is 1 or 2;and w is 1 or 2.

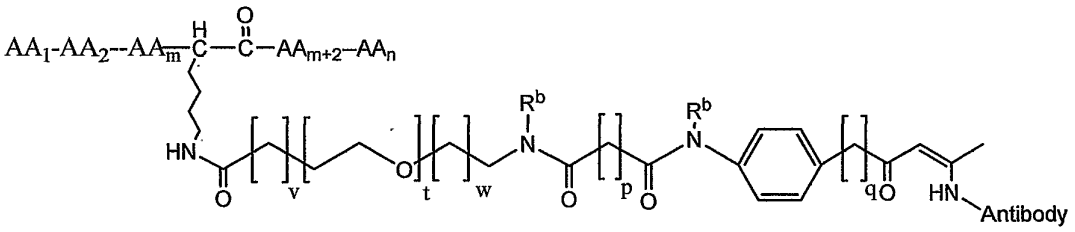
Certain embodiments in accordance with Formula II have the structure:



In In certain of these embodiments, v is 1, 2, 3, 4, or 5; w is 1, 2, 3, 4, 5, or 6; q is 1, 2, 3, 4, or 5; and R_b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain

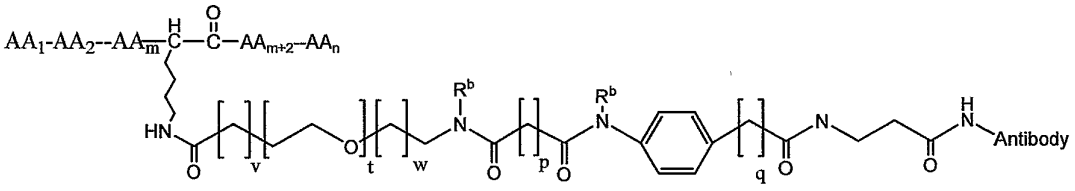
embodiments, v is 1, 2 or 3; w is 1, 2 or 3; and q is 1, 2, or 3. In some embodiments, v is 1 or 2; w is 1 or 2; and q is 2, or 3.

Certain embodiments in accordance with Formula II have the structure:



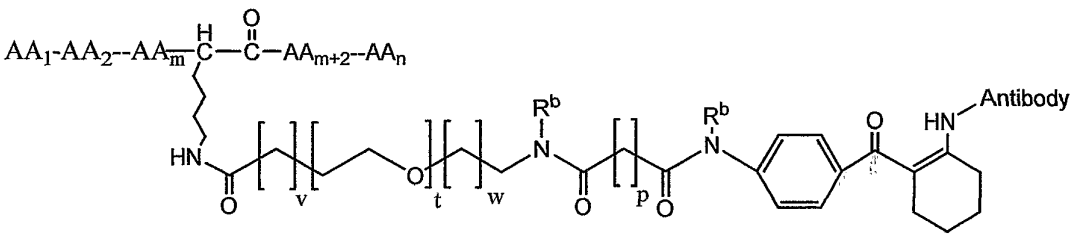
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula II have the structure:



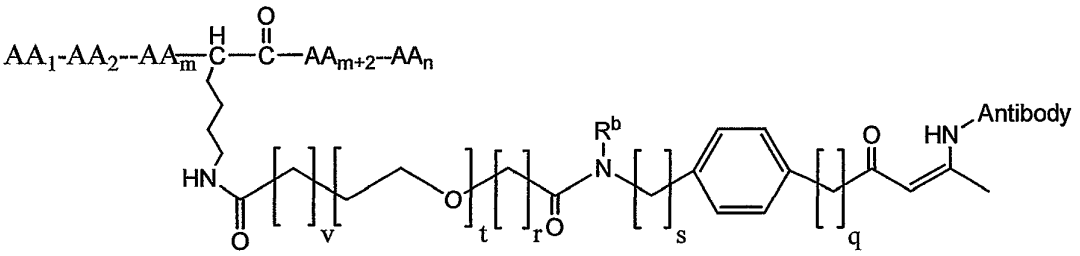
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 2 or 3.

Certain embodiments in accordance with Formula II have the structure:



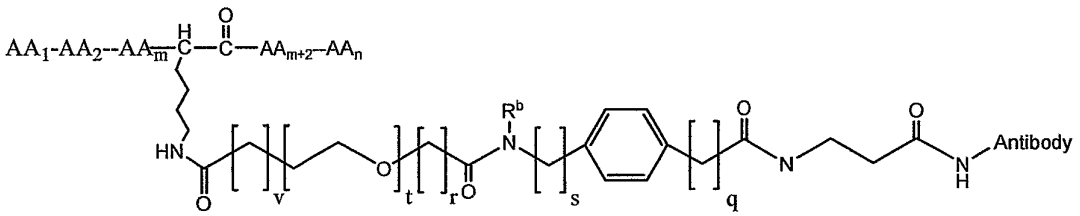
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; and p is 3. In some embodiments, v is 0; t is 1 or 2; w is 1; and p is 1 or 2.

Certain embodiments in accordance with Formula II have the structure:



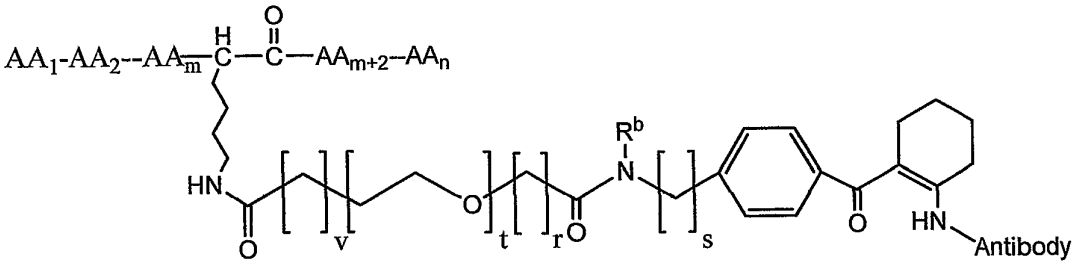
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula II have the structure:



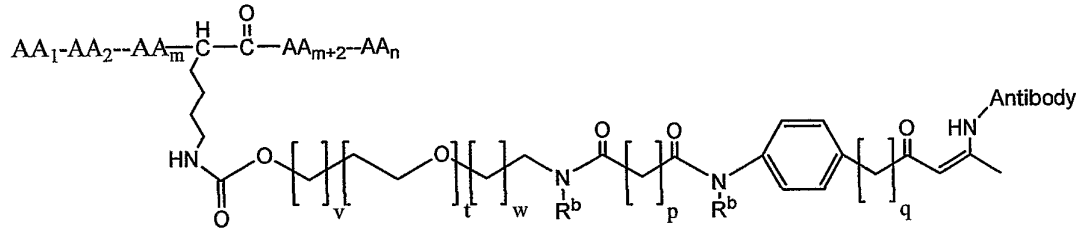
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 2 or 3.

Certain embodiments in accordance with Formula II have the structure:



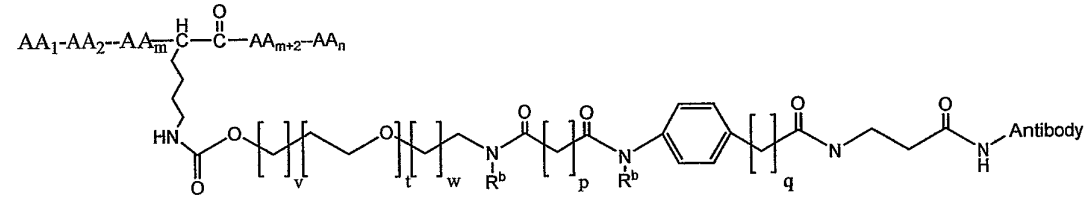
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; and s is 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; and s is 1 or 2.

Certain embodiments in accordance with Formula II have the structure:



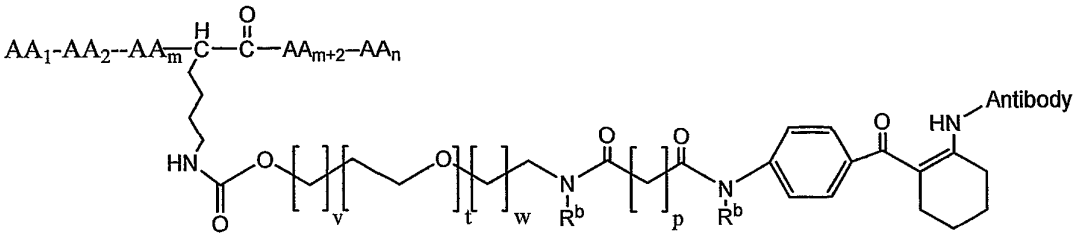
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula II have the structure:



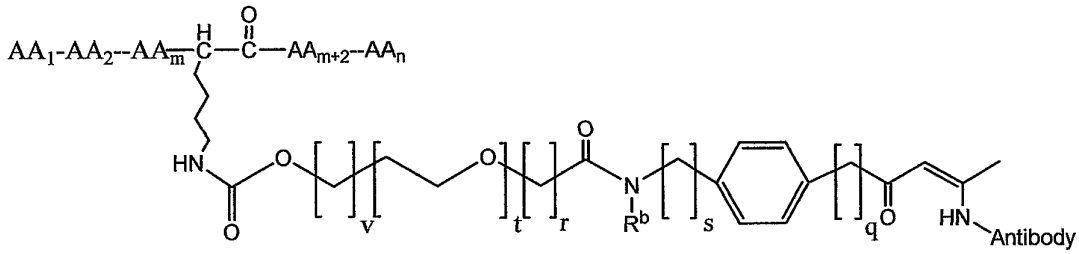
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 2 or 3.

Certain embodiments in accordance with Formula II have the structure:



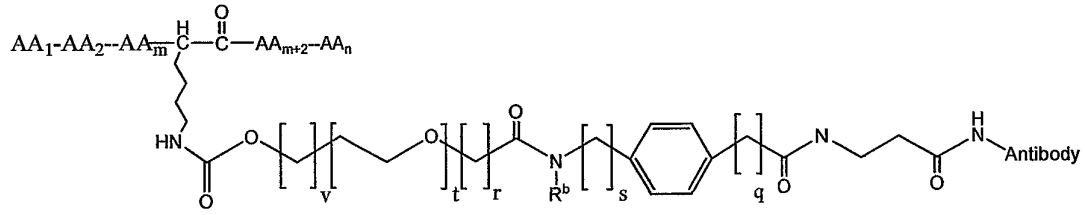
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; and p is 3. In some embodiments, v is 0; t is 1 or 2; w is 1; and p is 1 or 2.

Certain embodiments in accordance with Formula II have the structure:



In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

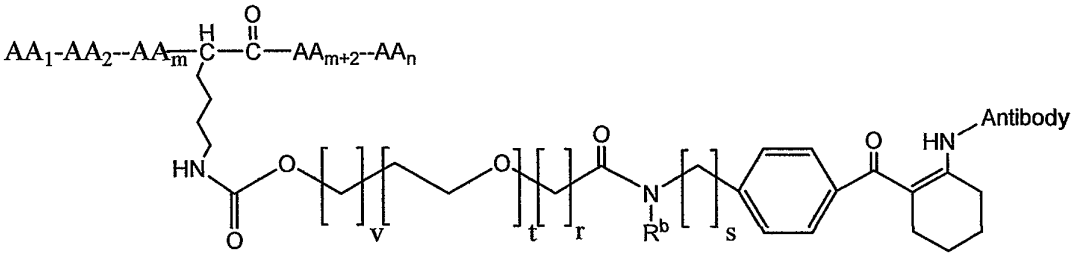
Certain embodiments in accordance with Formula II have the structure:



In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl.

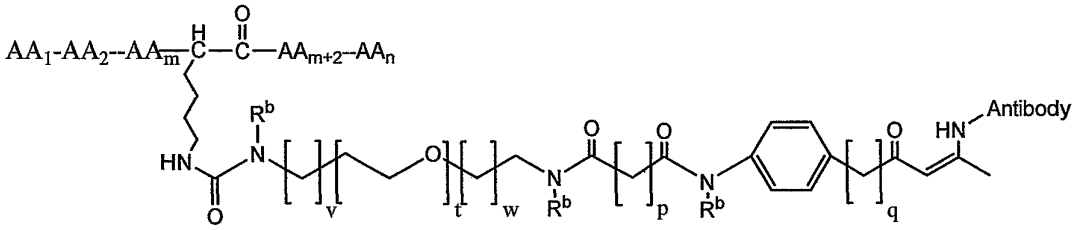
In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 2 or 3.

Certain embodiments in accordance with Formula II have the structure:



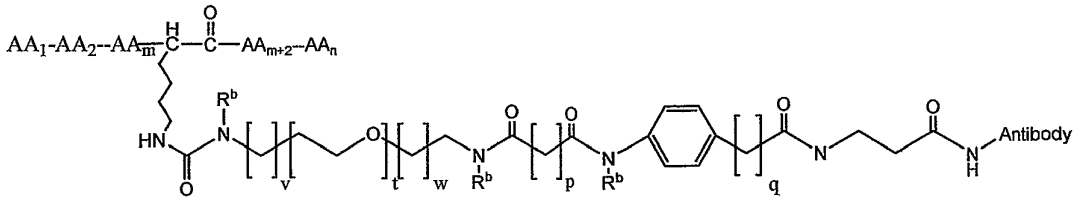
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; and R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; and s is 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; and s is 1 or 2.

Certain embodiments in accordance with Formula II have the structure:



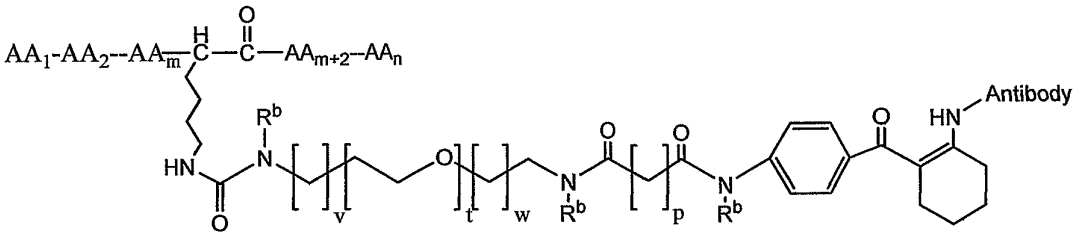
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula II have the structure:



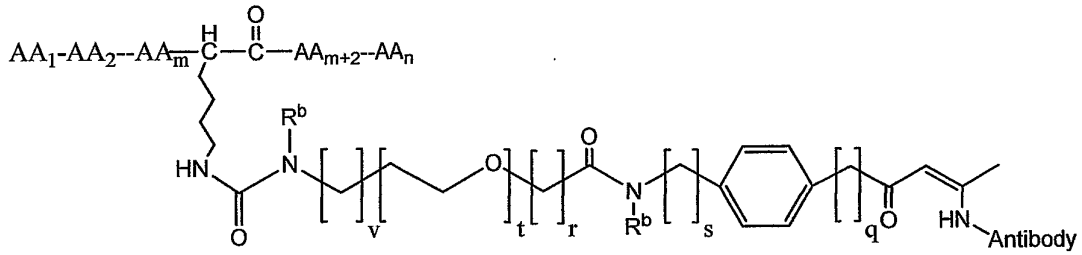
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; p is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1 or 2; w is 1; p is 1 or 2; and q is 2 or 3.

Certain embodiments in accordance with Formula II have the structure:



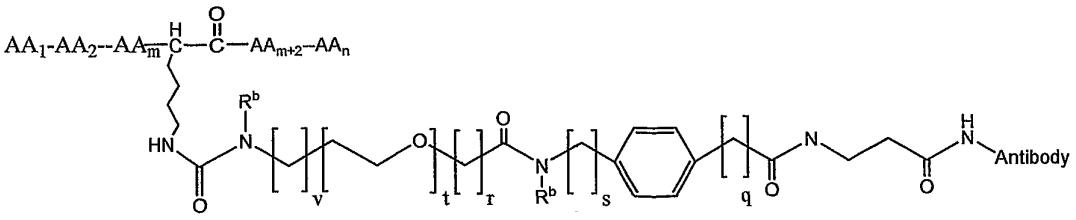
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; w is 1, 2, 3, 4, or 5; p is 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; w is 1; and p is 3. In some embodiments, v is 0; t is 1 or 2; w is 1; and p is 1 or 2.

Certain embodiments in accordance with Formula II have the structure:



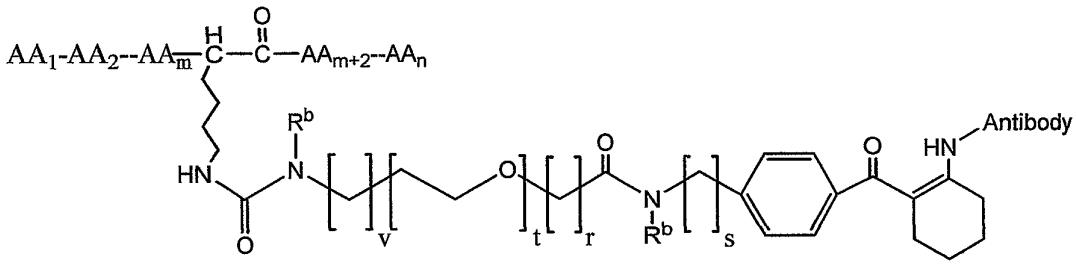
In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 1 or 2.

Certain embodiments in accordance with Formula II have the structure:



In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; s is 3; and q is 0, 1, 2, or 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; s is 1 or 2; and q is 2 or 3.

Certain embodiments in accordance with Formula II have the structure:



In certain of these embodiments, v is 0, 1, 2, 3, 4, or 5; t is 1, 2, 3, 4, 5, or 6; r is 1, 2, 3, 4, or 5; s is 0, 1, 2, 3, 4, or 5; and R^b at each occurrence is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{3-7} cycloalkyl-C_{0-6} alkyl, or substituted or unsubstituted aryl-C_{0-6} alkyl. In certain embodiments, v is 0; t is 1, 2, 3, 4, 5, or 6; r is 1 or 2; and s is 3. In some embodiments, v is 0; t is 1, 2, or 3, r is 1; and s is 1 or 2.

Alternatively, the linker may have an amine or hydrazide as the reactive group and the Antibody may be engineered to have a diketone moiety. An unnatural diketone-containing amino acid may be readily incorporated into an antibody combining site using techniques well known in the art; proteins containing unnatural amino acids have been produced in yeast and bacteria. See, e.g., J.W. Chin *et al.*, Science 301:964-966 (2003); L. Wang *et al.*, Science 292:498-500 (2001); J.W. Chin *et al.*, J. Am. Chem. Soc. 124:9026-9027 (2002); L. Wang, *et al.*, J. Am. Chem. Soc. 124:1836-1837 (2002); J.W. Chin and P.G. Schultz, Chembiochem. 3:1135-1137 (2002); J.W. Chin *et al.*, Proc. Natl. Acad. Sci. U.S.A. 99:11020-11024 (2002); L. Wang and P.G. Schultz, Chem. Commun. (1):1-11 (2002); Z. Zhang *et al.*, Angew. Chem. Int. Ed. Engl. 41:2840-2842 (2002); L. Wang, Proc. Natl. Acad. Sci. U.S.A. 100:56-61 (2003). Thus, for example, to insert an unnatural amino acid containing a diketone moiety into the yeast *Saccharomyces cerevisiae* requires the addition of new components to the protein biosynthetic machinery including a unique codon, tRNA, and aminoacyl-tRNA synthetase (aa RS). For example, the amber suppressor tyrosyl-tRNA synthetase (TyrRS)-$tRNA_{CUA}$ pair from *E. coli* may be used as reported for eukaryotes in J.W. Chin *et al.*, Science 301:964-966 (2003). The amber codon is used to code for the unnatural amino acid of interest. Libraries of mutant TyrRS and $tRNA_{CUA}$ may then be produced and selected for those aaRS-$tRNA_{CUA}$ pairs in which the TyrRS charges the $tRNA_{CUA}$ with the unnatural amino acid of interest, e.g., the diketone-containing amino acid.

Subsequently, antibodies incorporating the diketone-containing amino acid may be produced by cloning and expressing a gene containing the amber codon at one or more antibody combining sites.

In some embodiments of compounds of Formula II, the Antibody is a full length antibody. In other embodiments, the Antibody is Fab, Fab' $F(ab')_2$, Fv, V_H, V_L, or scFv. In certain embodiments, the Antibody is a human antibody, humanized antibody or chimeric human antibody. In certain embodiments, the Antibody is a catalytic antibody. In one embodiment, the Antibody is a humanized version of a murine 38c2 comprising a constant region from a human IgG, IgA, IgM, IgD, or IgE antibody. In another embodiment, Antibody is a chimeric antibody comprising the variable region from murine 38c2 and a constant region from a human IgG, IgA, IgM, IgD, or IgE antibody.

In some cases, two or more AA targeting agents may be linked to a single full length bivalent Antibody. This is shown below as Formula III:

$$\text{Antibody}[\text{–L'–}[\text{AA targeting agent}]]_2 \qquad \text{(III)}$$

Also provided are stereoisomers, tautomers, solvates, prodrugs, and pharmaceutically acceptable salts thereof.

In compounds of Formula III, [AA targeting agent], L' and Antibody are each defined as in Formula II.

Targeting compounds such as those of Formula II may also be readily synthesized by covalently linking a targeting agent-linker compound as described herein to a combining site of a multivalent antibody. For example, an AA targeting-agent linker conjugate, where the linker includes a diketone reactive moiety, can be incubated with 0.5 equivalents of an aldolase antibody, such as h38C2 IgG1 to produce an AA targeting compound. Alternatively, an AA targeting compound such as those of Formula III may be produced by covalently linking an AA targeting agent-linker compound as described herein to each combining site of a bivalent antibody.

Methods of use for AA targeting compounds

One aspect of the invention provides methods for modulating Ang-2 activity *in vivo* comprising administering an effective amount of an AA targeting compound as described herein to a subject. There are further provided methods for treating abnormal angiogenesis or an angiogenesis-mediated condition in a subject. Such methods include administering to the subject a therapeutically effective amount of an AA targeting compound as described herein. As used herein, an angiogenesis-mediated condition is a condition that is caused by abnormal angiogenesis activity or one in which compounds that modulate angiogenesis activity have therapeutic use. Diseases and conditions that may be treated include cancer, arthritis, psoriasis, angiogenesis of the eye associated with infection or surgical intervention, macular degeneration or diabetic retinopathy. In particular, methods of treating cancer include carcinomas of the breast, colon, rectum, lung, oropharynx, hypopharynx, esophagus, stomach, pancreas, liver, gallbladder and bile ducts, small intestine, urinary tract, female genital tract, male, genital tract, endocrine glands, and skin; hemangiomas; melanomas; sarcomas; tumors of the brain, nerves, eyes, and meninges; leukemia; or lymphoma.

Pharmaceutical Compositions and Methods of Administration

Another aspect of the invention provides pharmaceutical compositions of the AA targeting compounds. The AA targeting compounds can be mixed with pharmaceutically-acceptable carriers to form a pharmaceutical composition for administration to a cell or subject, either alone, or in combination with one or more other modalities of therapy.

A pharmaceutical composition is generally formulated to be compatible with its intended route of administration. Those skilled in the art will know that the choice of the pharmaceutical medium and the appropriate preparation of the composition will depend on the intended use and mode of administration. Examples of routes of administration include parenteral (e.g. intravenous, intramuscular, intramedullary, intradermal, subcutaneous), oral (e.g. inhalation, ingestion), intranasal, transdermal (e.g. topical), transmucosal, and rectal administration. Administration routes of AA targeting compounds may also include intrathecal, direct intraventricular and intraperitoneal delivery. The AA targeting compounds may be administered through any of the parenteral routes either by direct injection of the formulation or by infusion of a mixture of the targeting AA compound formulation with an infusion matrix such as normal saline, D5W, lactated Ringers solution or other commonly used infusion media.

The AA targeting compounds may be administered using techniques well known to those in the art. Preferably, agents are formulated and administered systemically. Techniques for formulation and administration may be found in "Remington's Pharmaceutical Sciences," 18th Ed., 1990, Mack Publishing Co., Easton, PA. For injection, AA targeting compounds may be formulated in aqueous solutions, emulsions or suspensions. AA targeting compounds are preferably formulated in aqueous solutions containing physiologically compatible buffers such as citrate, acetate, histidine or phosphate. Where necessary, such formulations may also contain various tonicity adjusting agents, solubilizing agents and/or stabilizing agents (e.g. salts such as sodium chloride or sugars such as sucrose, mannitol, and trehalose, or proteins such as albumin or amino acids such as glycine and histidine or surfactants such as polysorbates (Tweens) or cosolvents such as ethanol, polyethylene glycol and propylene glycol.

The pharmaceutical composition may contain formulation materials for modifying, maintaining or preserving, for example, the pH, osmolarity, viscosity, clarity, color, isotonicity, odor, sterility, stability, rate of dissolution or release, adsorption or penetration of the composition. Suitable formulation materials include, but are not limited to, amino acids (such as glycine, glutamine, asparagine, arginine or lysine); antimicrobials; antioxidants (such as ascorbic acid, sodium sulfite or sodium hydrogen-sulfite); buffers (such as borate, bicarbonate, Tris-HCl, citrates, phosphates, other organic acids, chelating agents [such as ethylenediamine tetraacetic acid (EDTA)]; solvents (such as glycerin, propylene glycol or polyethylene glycol); sugar alcohols (such as mannitol or sorbitol); suspending agents; surfactants or wetting agents (such as pluronics, PEG, sorbitan esters, polysorbates such as polysorbate 20, polysorbate 80, triton, tromethamine, lecithin, cholesterol, tyloxapal); stability enhancing agents (sucrose or sorbitol); tonicity enhancing agents (such as alkali metal halides (preferably sodium or potassium chloride, mannitol sorbitol); delivery vehicles; diluents; excipients and/or pharmaceutical adjuvants. (Remington's Pharmaceutical Sciences, 18th Edition, A. R. Gennaro, ed., Mack Publishing Company, 1990).

When parenteral administration is contemplated, the therapeutic compositions may be in the form of a pyrogen-free, parenterally acceptable aqueous solution comprising an AA targeting compound in a pharmaceutically acceptable vehicle. One vehicle for parenteral injection is sterile distilled water in which an AA targeting compound is formulated as a sterile, isotonic solution. Yet another formulation can involve the formulation an AA targeting compound with an agent, such as injectable microspheres, bio-degradable particles, polymeric compounds (polylactic acid, polyglycolic acid), beads, or liposomes, that provides for the controlled or sustained release of the product which may then be delivered via a depot injection. Hyaluronic acid may also be used, and this may have the effect of promoting sustained duration in the circulation. Other suitable means for the introduction of the desired molecule include implantable drug delivery devices.

In another aspect, pharmaceutical formulations suitable for parenteral administration may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or a physiologically buffered saline. Aqueous injection suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Suitable lipophilic solvents or vehicles include fatty oils, such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate, triglycerides, or liposomes. Non-lipid polycationic amino

polymers may also be used for delivery. Optionally, the suspension may also contain suitable stabilizers or agents to increase the solubility of the compounds and allow for the preparation of highly concentrated solutions.

The pharmaceutical composition to be used for *in vivo* administration typically must be sterile. This may be accomplished by filtration through sterile filtration membranes. Where the composition is lyophilized, sterilization using this method may be conducted either prior to or following lyophilization and reconstitution. The composition for parenteral administration may be stored in lyophilized form or in solution. In addition, parenteral compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Once the pharmaceutical composition has been formulated, it may be stored in sterile vials as a solution, suspension, gel, emulsion, solid, or a dehydrated or lyophilized powder. Such formulations may be stored either in a ready-to-use form or in a form (e.g., lyophilized) requiring reconstitution prior to administration.

One embodiment is directed to kits for producing a single-dose administration unit. The kits may each contain both a first container having an AA targeting compound and a second container having an aqueous formulation. Also included within the scope of this invention are kits containing single and multi-chambered pre-filled syringes.

In treating mammals, including humans, having a disorder with an angiogenic component to the disorder, a therapeutically effective amount of an AA targeting compound or a pharmaceutically acceptable derivative is administered. The frequency of dosing will depend upon the pharmacokinetic parameters of the AA targeting compound in the formulation used. Typically, a composition is administered until a dosage is reached that achieves the desired effect. The composition may therefore be administered as a single dose, or as multiple doses (at the same or different concentrations/dosages) over time, or as a continuous infusion. Routes and frequency of administration of a composition as well as dosage may vary from individual to individual and may be readily established using standard techniques. Further refinement of the appropriate dosage is routinely made. Appropriate dosages may be developed by one skilled in the art through the use of appropriate dose-response data.

An appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (e.g. reduced number of blood vessels in a target area, decreased tumor size or volume) in treated patients as compared to non-treated patients. Typically, a suitable dose is an amount of a compound that, when administered as described herein, is capable of promoting an anti-angiogenesis response, and/or is at least 10-50% above the basal or untreated level.

In some embodiments, the most effective mode of administration and dosage regimen for the invention compositions depends upon the severity and course of the disease, the patient's health and response to treatment, and the judgment of the treating physician. Accordingly, the dosages of the invention compositions should be titrated to the individual patient. An effective dose of the compounds is in the range of from about 0.1 ug to about 40 mg per kilogram per day. An AA targeting compound may be administered as a daily intravenous infusion from about 0.1 mg/kg body weight to about 15 mg/kg body weight. Accordingly, one embodiment provides a dose of about 0.5 mg/kg body weight. Another embodiment provides a dose of about 0.75 mg/kg body weight. Another embodiment provides a dose of about 1.0 mg/kg body weight. Another embodiment provides a dose of about 2.5 mg/kg body weight. Another embodiment provides a dose of about 5 mg/kg body weight. Another embodiment provides a dose of about 10.0 mg/kg body weight. Another embodiment provides a dose of about 15.0 mg/kg body weight. Doses of an AA targeting compound or a pharmaceutically acceptable derivative should be administered in intervals of from about once per day to 2 times per week, or alternatively, from about once every week to once per month. In one embodiment, a dose is administered to achieve peak plasma concentrations of an AA targeting

compound or a pharmaceutically acceptable derivative thereof from about .002 mg/ml to 30 mg/ml. This may be achieved by the sterile injection of a solution of the administered ingredients in an appropriate formulation (any suitable formulation solutions known to those skilled in the art of chemistry may be used). Desirable blood levels may be maintained by a continuous infusion of an AA targeting compound as ascertained by plasma levels measured by a validated analytical methodology.

One method for administering an AA targeting compound to an individual comprises administering an AA targeting agent – linker conjugate to the individual and allowing it to form a covalent compound with a combining site of an appropriate antibody *in vivo*. The antibody portion of an AA targeting compound that forms *in vivo* may be administered to the individual before, at the same time, or after administration of the targeting agent – linker conjugate. As already discussed, an AA targeting agent may include a linker/reactive moiety, or the antibody combining site may be suitably modified to covalently link to the targeting agent. Alternatively, or in addition, an antibody may be present in the circulation of the individual following immunization with an appropriate immunogen. For example, catalytic antibodies may be generated by immunizing with a reactive intermediate of the substrate conjugated to a carrier protein. See R.A. Lerner and C.F. Barbas 3rd, Acta Chem. Scand. 50:672-678 (1996). In particular, aldolase catalytic antibodies may be generated by administering with keyhole limpet hemocyanin linked to a diketone moiety as described by P. Wirsching *et al.*, Science 270:1775-1782 (1995) (commenting on J. Wagner *et al.*, Science 270:1797-1800 (1995)).

The invention also provides a method of visualizing or localizing Ang-2 or anti-angiogenesis target (i.e. AA-targeting agent receptor) in tissues and cells. In one embodiment, biopsied tissues may be examined for presence of AA-targeting agent receptor. In another embodiment, neovascularization in a subject may be imaged by administering to the subject an AA targeting agent or compound including a detectable label. As used herein, the term "detectable label" refers to any molecule which can be administered *in vivo* and subsequently detected. Exemplary detectable labels include radiolabels and fluorescent molecules. Exemplary radionuclides include indium-111, technetium-99, carbon-11, and carbon-13. Fluorescent molecules include, without limitation, fluorescein, allophycocyanin, phycoerythrin, rhodamine, and Texas red.

Combination Therapies

The vasculature within a tumor generally undergoes active angiogenesis, resulting in the continual formation of new blood vessels to support the growing tumor. Such angiogenic blood vessels are distinguishable from mature vasculature in that angiogenic vasculature expresses unique endothelial cell surface markers, including the $\forall_v\exists_3$ integrin. (Brooks, Cell 79:1157-1164 (1994); WO 95/14714, Int. Filing Date Nov. 22, 1994) and receptors for angiogenic growth factors (Mustonen and Alitalo, J. Cell Biol. 129:895-898 (1995); Lappi, Semin. Cancer Biol. 6:279-288 (1995)).

The invention also includes administration of one or more AA targeting agents in combination with one or more oncology therapeutics, each being administered according to a regimen suitable for that therapeutic. The components of the combination therapy may be administered concurrently or non-concurrently. As used herein, the terms "concurrently administered" and "concurrent administration" encompass substantially simultaneous administration of one or more AA targeting compounds and one other oncology therapeutic.

As used herein, the term, "non-concurrent" administration encompasses administering one or more AA targeting compounds at different times, in any order, whether overlapping or not. This includes, but is not limited to, sequential treatment (such as pretreatment, post-treatment, or overlapping treatment) with the components of the combination, as well as regimens in which the drugs are alternated, or wherein one component is administered long-term and the other(s) are administered intermittently. Components may be administered in the same or in separate compositions, and by the same or different routes of administration.

Suitable oncology therapeutics and combinations that may be used in combination with an AA targeting compound are listed in Tables 4-6.

Table 4: Approved oncology drugs and indications

Generic	Trade Name	Indication	Company
Aldesleukin	Proleukin	Proleukin is indicated for the treatment of adults with metastatic renal cell carcinoma (metastatic RCC) and for the treatment of adults with metastatic melanoma.	Chiron Corp
Alemtuzumab	Campath	Campath is indicated for the treatment of B-cell chronic lymphocytic leukemia (B-CLL) in patients who have been treated with alkylating agents and who have failed fludarabine therapy.	Millennium and ILEX Partners, LP
Alitretinoin	Panretin	Topical treatment of cutaneous lesions in patients with AIDS-related Kaposi's sarcoma.	Ligand Pharmaceuticals
Allopurinol	Zyloprim	Patients with leukemia, lymphoma and solid tumor malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels and who cannot tolerate oral therapy.	GlaxoSmithKline
Palonosetron	Aloxi	For the treatment of nausea	MGI Pharmaceuticals
Altretamine	Hexalen	Single agent palliative treatment of patients with persistent or recurrent ovarian cancer following first-line therapy with a cisplatin and/or alkylating agent based combination.	US Bioscience
Amifostine	Ethyol	To reduce the cumulative renal toxicity associated with repeated administration of cisplatin in patients with advanced ovarian cancer	US Bioscience
Amifostine	Ethyol	Reduces platinum toxicity in non-small cell lung cancer	US Bioscience
Amifostine	Ethyol	To reduce post-radiation xerostomia for head and neck cancer where the radiation port includes a substantial portion of the parotid glands.	US Bioscience
Anastrozole	Arimidex	Adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer	AstraZeneca
Anastrozole	Arimidex	Treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy.	AstraZeneca Pharmaceuticals
Anastrozole	Arimidex	For first-line treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer.	AstraZeneca Pharmaceuticals
Nelarabine	Arranon	For the treatement of T cell acute lymphoblatic leukemia	GlaxoSmithKline
Arsenic trioxide	Trisenox	Second line treatment of relapsed or refractory APL following ATRA plus an anthracycline.	Cell Therapeutic
Asparaginase	Elspar	ELSPAR is indicated in the therapy of patients with acute lymphocytic leukemia. This agent is useful primarily in combination with other chemotherapeutic agents in the induction of remissions of the disease in	Merck & Co, Inc

		pediatric patients.	
Bevacizumab	Avastin	For the treatment of metastatic colorectal cancer	Genentech
Bexarotene capsules	Targretin	For the treatment by oral capsule of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy.	Ligand Pharmaceuticals
Bexarotene gel	Targretin	For the topical treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy.	Ligand Pharmaceuticals
Bleomycin	Blenoxane	Palliative agent for the management of the following neoplasms: Squamous Cell Carcinoma (head and neck including mouth, tongue, tonsil, nasopharynx, oropharynx, sinus, palate, lip, buccal mucosa, gingivae, epiglottis, skin, larynx, penis, cervix, and vulva. Lymphomas (Hodgkin's Disease, non-Hodgkin's lymphoma). Testicular Carcinoma (Embryonal cell, choriocarcinoma, and teratocarcinoma).	Bristol-Myers Squibb
Bleomycin	Blenoxane	Sclerosing agent for the treatment of malignant pleural effusion (MPE) and prevention of recurrent pleural effusions.	Bristol-Myers Squibb
Busulfan intravenous	Busulfex	Use in combination with cyclophoshamide as conditioning regimen prior to allogeneic hematopoietic progenitor cell transplantation for chronic myelogenous leukemia.	Orphan Medical, Inc.
Busulfan oral	Myleran	Palliative therapy for Chronic Myelogenous Leukemia –	GlaxoSmithKline
Calusterone	Methosarb	Synthetic androgen for the treatment of androgen sensitive cancers	Pharmacia & Upjohn Company
Capecitabine	Xeloda	Treatment of metastatic breast cancer resistant to both paclitaxel and an anthracycline containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy may be contraindicated, e.g., patients who have received cumulative doses of 400 mg/m2 of doxorubicin or doxorubicin equivalents	Roche
Capecitabine	Xeloda	Initial therapy of patients with metastatic colorectal carcinoma when treatment with fluoropyrimidine therapy alone is preferred. Combination chemotherapy has shown a survival benefit compared to 5-FU/LV alone. A survival benefit over 5_FU/LV has not been demonstrated with Xeloda monotherapy.	Roche
Capecitabine	Xeloda	Treatment in combination with docetaxel of patients with metastatic breast cancer after failure of prior anthracycline containing chemotherapy	Roche
Carboplatin	Paraplatin	Palliative treatment of patients with ovarian carcinoma recurrent after prior chemotherapy, including patients who have been previously treated with cisplatin.	Bristol-Myers Squibb
Carboplatin	Paraplatin	Initial chemotherapy of advanced ovarian carcinoma in combination with other	Bristol-Myers Squibb

		approved chemotherapeutic agents.	
Carmustine	BCNU, BiCNU	Palliative therapy as a single agent or in established combination therapy with other approved chemotherapeutic agents in the following: Brain tumors (glioblastoma, brainstem glioma, medulloblastoma, astrocytoma, ependymoma, and metastatic brain tumors); Multiple myeloma; Hodgkin's Disease; and Non-Hodgkin's lymphomas.	Bristol-Myers Squibb
Carmustine with Polifeprosan 20 Implant	Giladel Wafer	For use in addition to surgery to prolong survival in patients with recurrent glioblastoma multiforme who qualify for surgery.	Guilford Pharmaceuticals Inc.
Celecoxib	Celebrex	Reduction of polyp number in patients with the rare genetic disorder of familial adenomatous polyposis.	Searle
Cetuximab	Erbitux	For the treatement of EGFR expressing metastatic colorectal cancer	
Chlorambucil	Leukeran	Chronic Lymphocytic Leukemia- palliative therapy	GlaxoSmithKline
Chlorambucil	Leukeran	Treatment for CLL or indolent NHL.	GlaxoSmithKline
Cinacalchet	Sensipar	For the treatment of secondary hypparathyroidism	Amgen
Cisplatin	Platinol	Metastatic testicular-in established combination therapy with other approved chemotherapeutic agents in patients with metastatic testicular tumors whoc have already received appropriate surgical and/or radiotherapeutic procedures. An established combination therapy consists of Platinol, Blenoxane and Velbam.	Bristol-Myers Squibb
Cisplatin	Platinol	Metastatic ovarian tumors - in established combination therapy with other approved chemotherapeutic agents: Ovarian-in established combination therapy with other approved chemotherapeutic agents in patients with metastatic ovarian tumors who have already received appropriate surgical and/or radiotherapeutic procedures. An established combination consists of Platinol and Adriamycin. Platinol, as a single agent, is indicated as secondary therapy in patients with metastatic ovarian tumors refractory to standard chemotherapy who have not previously received Platinol therapy.	Bristol-Myers Squibb
Cisplatin	Platinol	Transitional cell bladder cancer which is no longer amenable to local treatments such as surgery and/or radiotherapy.	Bristol-Myers Squibb
Cladribine	Leustatin, 2-CdA	Treatment of active hairy cell leukemia.	R.W. Johnson Pharmaceutical Research Institute
Clofarabine	Clolar	Treatment for acute lymphblastic leukemia	Genzyme
Cyclophospha mide	Cytoxan, Neosar	Treatment for ovary, breast, bladder and CLL.	Bristol-Myers Squibb
Cytarabine	Cytosar-U	Treatment for AML	Pharmacia & Upjohn Company
Cytarabine Liposomal	DepoCyt	Intrathecal therapy of lymphomatous meningitis	Skye Pharmaceuticals

Dacarbazine	DTIC-Dome	Treatment for melanoma and Hodgkins lymphoma	Bayer
Dactinomycin, actinomycin D	Cosmegan	Treatment for pediatric leukemias	Merck
Darbepoetin alfa	Aranesp	Treatment of anemia associated with chronic renal failure.	Amgen, Inc.
Darbepoetin alfa	Aranesp	Aranesp is indicated for the treatment of anemia in patients with non- myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy.	Amgen, Inc.
Daunorubicin liposomal	DanuoXome	First line cytotoxic therapy for advanced, HIV related Kaposi's sarcoma.	Nexstar, Inc.
Daunorubicin, daunomycin	Daunorubicin	Leukemia/myelogenous/monocytic/erythroid of adults/remission induction in acute lymphocytic leukemia of children and adults.	Bedford Labs'
Daunorubicin, daunomycin	Cerubidine	In combination with approved anticancer drugs for induction of remission in adult ALL.	Wyeth Ayerst
Danileukin diftitox	Ontak	Treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor	Seragen, Inc.
Dexrazoxane	Zinecard	Prevention of cardiomyopathy associated with doxorubicin administration	Pharmacia & Upjohn Company
Dexrazoxane	Zinecard	Used for reducing the incidence and severity of cardiomyopathy associated with doxorubicin administration in women with metastatic breast cancer who have received a cumulative doxorubicin dose of 300 mg/m2 and who will continue to receive doxorubicin therapy to maintain tumor control.	Pharmacia & Upjohn Company
Docetaxel	Taxotere	Treatment of patients with locally advanced or metastatic breast cancer who have progressed during anthracycline-based therapy or have relapsed during anthracycline-based adjuvant therapy.	Aventis Pharmaceutical
Docetaxel	Taxotere	For the treatment of locally advanced or metastatic breast cancer which has progressed during anthracycline-based treatment or relapsed during anthracycline-based adjuvant therapy.	Aventis Pharmaceutical
Docetaxel	Taxotera	For locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy.	Aventis Pharmaceutical
Docetaxel	Taxotere		Aventis Pharmaceutical
Docetaxel	Taxotere	Used in combination with cisplatin for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for this condition.	Aventis Pharmaceutical
Doxorubicin	Adriamycin PFS Injection intravenous injection	Antibiotic, antitumor agent.	Pharmacia & Upjohn Company
Doxorubicin	Doxil	Treatment of AIDS-related Kaposi's	Sequus

liposomal		sarcoma in patients with disease that has progressed on prior combination chemotherapy or in patients who are intolerant to such therapy.	Pharmaceuticals, Inc.
Doxorubicin liposomal	Doxil	Treatment of metastatic carcinoma of the ovary in patient with disease that is refractory to both paclitaxel and platinum based regimens	Sequus Pharmaceuticals, Inc.
Dromostanolone Propionate	Dromostanolone	Sythetic androgen for use in androgen sensitve cancers	Eli Lilly
Elliott's B Solution	Elliott's B Solution	Diluent for the intrathecal administration of methotrexate sodium and cytarabine for the prevention or treatment of meningeal leukemia or lymphocytic lymphoma.	Orphan Medical, Inc.
Epoetin alfa/beta	Epogen	EPOGEN is indicated for the treatment of anemia.	Amgen, Inc.
Erlotinib	Tarceva	For the treatment of advanced metatstaic non-small cell lung cancer	OSI Pharmaceuticals
Estramustine	Emcyt	Palliation of prostate cancer	Pharmacia & Upjohn Company
Etoposide phosphate	Etopophos	Management of refractory testicular tumors, in combination with other approved chemotherapeutic agents.	Bristol-Myers Squibb
Etoposide phosphate	Etopophos	Management of small cell lung cancer, first-line, in combination with other approved chemotherapeutic agents.	Bristol-Myers Squibb
Etoposide phosphate	Etopophos	Management of refractory testicular tumors and small cell lung cancer.	Bristol-Myers Squibb
Etoposide, VP-16	Vepesid	Refractory testicular tumors-in combination therapy with other approved chemotherapeutic agents in patients with refractory testicular tumors who have already received appropriate surgical, chemotherapeutic and radiotherapeutic therapy.	Bristol-Myers Squibb
etoposide, VP-16	VePesid	In combination with other approved chemotherapeutic agents as first line treatment in patients with small cell lung cancer.	Bristol-Myers Squibb
Etoposide, VP-16	Vepesid	In combination with other approved chemotherapeutic agents as first line treatment in patients with small cell lung cancer.	Bristol-Myers Squibb
Exemestane	Aromasin	Treatment of advance breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy.	Pharmacia & Upjohn Company
Filgrastim	Neupogen	NEUPOGEN is indicated for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation hemotherapy treatment of adults with AML.	Amgen, Inc.
Floxuridine (intraarterial)	FUDR	An analog for 5-flurouracil. FUDR has been approved in the directed treatment of liver metastases using hepatic arterial infusion.	Roche
Fludarabine	Fludara	Palliative treatment of patients with B-cell lymphocytic leukemia (CLL) who have not responded or have progressed during treatment with at least one standard	Berlex Laboratories Inc.

		alkylating agent containing regimen.	
Fluorouracil, 5-FU	Adrucil	Prolong survival in combination with leucovorin	ICN Puerto Rico
Fulvestrant	Faslodex	the treatment of hormone receptor-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy	IPR
Gemcitabine	Gemzar	Treatment of patients with locally advanced (nonresectable stage II or III) or metastatic (stage IV) adenocarcinoma of the pancreas. Indicated for first-line treatment and for patients previously treated with a 5-fluorouracil-containing regimen.	Eli Lilly
Gemcitabine	Gemzar	For use in combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced (Stage IIIA or IIIB) or metastatic (Stage IV) non-small cell lung cancer.	Eli Lilly
Gemtuzumab ozogamicin	Mylotarg	Treatment of CD33 positive acute myeloid leukemia in patients in first relapse who are 60 years of age or older and who are not considered candidates for cytotoxic chemotherapy.	Wyeth Ayerst
Goserelin acetate	Zoladex implant	Palliative treatment of advanced breast cancer in pre- and perimenopausal women.	AstraZeneca Pharmaceuticals
Goserelin acetate	Zoladex	Used for treatement of prostate cancer	AstraZeneca Pharmaceuticals
Hydroxyurea	Hydrea	Decrease need for transfusions in sickle cell anemia	Bristol-Myers Squibb
Ibritumomab tiuxetan	Zevalin	Treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma, including patients with Rituximab refractory follicular non-Hodgkin's lymphoma.	IDEC Pharmaceuticals Corp.
Idarubicin	Idamycin	For use in combination with other approved antileukemic drugs for the treatment of acute myeloid leukemia (AML) in adults.	Adria Laboratories
Idarubicin	Idamycin	In combination with other approved antileukemic drugs for the treatment of acute non-lymphocytic leukemia in adults.	Pharmacia & Upjohn Company
Ifosfamide	IFEX	Third line chemotherapy of germ cell testicular cancer when used in combination with certain other approved antineoplastic agents.	Bristol-Myers Squibb
Imatinib mesylate	Gleevec	Initial therapy of chronic myelogenous leukemia	Novartis
Imatrinib mesylate	Gleevac	Treatment of metastatic or unresectable malignant gastrointestinal stromal tumors	Novartis
Imatinib mesylate	Gleevec	Initial treatment of newly diagnosed Ph+ chronic myelogenous leukemia (CML).	Novartis
Interferon alfa-2a	Roferon-A	Treatment of chronic hepatitis C, hairy cell leukemia and AIDS-related Kaposi's sarcoma in adult patients and for chronic phase, Philadelphia chromosome (Ph) positive chronic myelogenous leukemia (CML) patients who are minimally pretreated (within 1 year of	Hoffmann-La Roche Inc.

		diagnosis).	
Interferon alfa-2b	Intron A	Interferon alfa-2b, recombinant for injection is indicated as adjuvant to surgical treatment in patients 18 years of age or older with malignant melanoma who are free of disease but at high risk for systemic recurrence within 56 days of surgery. Interferon alfa-2b, recombinant for Injection is indicated for the initial treatment of clinically aggressive follicular Non-Hodgkin's Lymphoma in conjunction with anthracycline-containing combination chemotherapy in patients 18 years of age or older. Interferon alfa-2b, recombinant for Injection is indicated for intralesional treatment of selected patients 18 years of age or older with condylomata acuminata involving external surfaces of the genital and perianal areas. Interferon alfa-2b, recombinant for Injection is indicated for the treatment of patients 18 years of age or older with hairy cell leukemia. Interferon alfa-2b, recombinant for Injection is indicated for the treatment of selected patients 18 years of age or older with AIDS-Related Kaposi's Sarcoma. The likelihood of response to INTRON A therapy is greater in patients who are without systemic symptoms, who have limited lymphadenopathy and who have a relatively intact immune system as indicated by total CD4 count.	Schering Corp.
Irinotecan	Camptosar	Treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU-based therapy.	Pharmacia & Upjohn Company
Letrozole	Femara	First-line treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer.	Novartis
Letrozole	Femara	Used for treatment of post-menopausal women with early stage breast cancer	Novartis
Leucovorin	Wellcovorin, Leucovorin	Leucovorin calcium is indicated fro use in combination with 5-fluorouracil to prolong survival in the palliative treatment of patients with advanced colorectal cancer.	Immunex Corporation
Leucovorin	Leucovorin	In combination with fluorouracil to prolong survival in the palliative treatment of patients with advanced colorectal cancer.	Lederle laboratories
Levamisole	Ergamisol	Adjuvant treatment in combination with 5-fluorouracil after surgical resection in patients with Dukes' Stage C colon cancer.	Janssen Research Foundation
Lomustine,	CeeNu	An alkylating agent used for the treatment of	Bristol-Myers

CCNU		brain cancer and NHL.	Squibb
Meclorethamine, nitrogen mustard	Mustargen	A nitrogen mustard used in the treatment of lymphoma.	Merck
Megestrol acetate	Megace	A synthetic progesterone used for the treatment of estrogen sensitive cancers.	Bristol-Myers Squibb
Melphalan, L-PAM	Alkeran	Systemic administration for palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.	GlaxoSmithKline
Mercaptopurine, 6-MP	Purinethol	Purinethol is indicated for remission induction and maintenance therapy of acute lymphatic leukemia.	GlaxoSmithKline
Mesna	Mesnex	Prevention of ifosfamide-induced hemorrhagic cystitis	Asta Medica
Methotrexate	Methotrexate	Is used to treat cancer of the breast, head and neck, lung, blood, bone, and lymph, and tumors in the uterus.	Laderle Laboratories
Methoxsalen	Uvadex	For the use of UVADEX with the UVAR Photopheresis System in the palliative treatment of the skin manifestations of cutaneous T-cell lymphoma (CTCL) that is unresponsive to other forms of treatment.	Therakos
Mitromycin C	Mitozytrex	Therapy of disseminated adenocarcinoma of the stomach or pancreas in proven combinations with other approved chemotherapeutic agents and as palliative treatment when other modalities have failed.	Supergen
Mitotane	Lysodren	Used for the treatment of adrenal cancers.	Bristol-Myers Squibb
Mitoxantrone	Novantrone	For use in combination with corticosteroids as initial chemotherapy for the treatment of patients with pain related to advanced hormone-refractory prostate cancer.	Immunex Corporation
Mitoxantrone	Novantrone	For use with other approved drugs in the initial therapy for acute nonlymphocytic leukemia (ANLL) in adults.	Laderle Laboratories
Nandrolone phenpropionate	Durabolin-509	It is indicated as a treatment for palliation of inoperable metastatic breast cancer in postmenopausal women.	Organon
Nofetumomab	Verluma	Verluma is a monoclonal antibody Fab fragment linked to ^{99m}Tc. Verluma identifies advanced-stage disease in patients with small-cell lung cancer (SCLC).	Boehringer Ingelheim Pharma KG (formerly Dr. Karl Thomae GmbH)
Oprelvekin	Neumega	Neumega is indicated for the prevention of severe thrombocytopenia and the reduction of the need for platelet transfusions following myelosuppressive chemotherapy in adult patients with nonmyeloid malignancies who are at high risk of severe thrombocytopenia.	Genetics Institute, Inc.
Oxaliplatin	Eloxatin	Used) in combination with infusional 5-FU/LV, is indicated for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed during or within 6 months of completion of first line therapy with the combination of bolus 5-FU/LV and	Sanofi Synthelabo

		irinotecan.	
Paclitaxel	Paxene	Treatment of advanced AIDS-related Kaposi's sarcoma after failure of first line or subsequent systemic chemotherapy	Baker Norton Pharmaceuticals, Inc.
Paclitaxel	Taxol	Treatment of patients with metastatic carcinoma of the ovary after failure of first-line or subsequent chemotherapy. Treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated. New dosing regimen for patients who have failed initial or subsequent chemotherapy for metastatic carcinoma of the ovary Second line therapy for AIDS related Kaposi's sarcoma. For first-line therapy for the treatment of advanced carcinoma of the ovary in combination with cisplatin. For use in combination with cisplatin, for the first-line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy. For the adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin-containing combination therapy. First line ovarian cancer with 3 hour infusion.	Bristol-Myers Squibb
Pamidronate	Aredia	Treatment of osteolytic bone metastases of breast cancer in conjunction with standard antineoplastic therapy.	Novartis
Pegademase	Adagen (Pegademase Bovine)	Enzyme replacement therapy for patients with severe combined immunodeficiency asa result of adenosine deaminase deficiency.	Enzon
Pegaspargase	Oncaspar	PEG asparginase used in the treatment of ALL.	Enzon, Inc.
Pegfilgrastim	Neulasta	Neulasta is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.	Amgen, Inc.
Pemetrexed	Alimta	Treatment of malignant pleural mesothelioma	Eli Lilly
Pentostatin	Nipent	Single agent treatment for adult patients with alpha interferon refractory hairy cell leukemia.	Parke-Davis Pharmaceutical Co.
Pipobroman	Vercyte	Used in the treatment of CRC.	Abbott Labs
Plicamycin,	Mithracin	Used in the treatment of testicular cancer.	Pfizer Labs

mithramycin			
Porfimer sodium	Photofrin	For use in photodynamic therapy (PDT) for palliation of patients with completely obstructing esophageal cancer, or patients with partially obstructing esophageal cancer who cannot be satisfactorily treated with ND-YAG laser therapy. For use in photodynamic therapy for treatment of microinvasive endobronchial nonsmall cell lung cancer in patients for whom surgery and radiotherapy are not indicated. For use in photodynamic therapy (PDT) for reduction of obstruction and palliation of symptoms in patients with completely or partially obstructing endobroncial nonsmall cell lung cancer (NSCLC).	QLT Phototherapeutics Inc.
Procarbazine	Matulane	One component of the MOPP regime.	Sigma Tau Pharms
Rasburicase	Elitek	ELITEK is indicated for the initial management of plasma uric acid levels in pediatric patients with leukemia, lymphoma, and solid tumor malignancies who are receiving anti-cancer therapy expected to result in tumor lysis and subsequent elevation of plasma uric acid.	Sanofi-Synthelabo, Inc.
Rituximab	Rituxan	Used in the treatment NHL.	Genentech, Inc.
Sargramostim	Prokine	GM-CSF used in the treatment of NHL, Hodgkins Leukemia and acute lymphoblastic leukemia.	Immunex Corp.
Sorafenib	Nexavar	Treatment of RCC	Bayer/Onyx
Streptozocin	Zanosar	Antineoplastic agent.	Pharmacia & Upjohn Company
Talc	Slerosol	For the prevention of the recurrence of malignant pleural effusion in symptomatic patients.	Bryan
Tamoxifen	Nolvadex	As a single agent to delay breast cancer recurrence following total mastectomy and axillary dissection in postmenopausal women with breast cancer (T1-3, N1, M0). For use in premenopausal women with metastatic breast cancer as an alternative to oophorectomy or ovarian irradiation. For use in women with axillary node-negative breast cancer adjuvant therapy. Metastatic breast cancer in men.	AstraZeneca Pharmaceuticals
Temozolomide	Temodar	For treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients at first relapse with disease progression on a nitrosourea and	Scherine

		procarbazine containing regimen	
Teniposide, VM-26	Vumon	In combination with other approved anticancer agents for induction therapy in patients with refractory childhood acute lymphoblastic leukemia (all).	Bristol-Myers Squibb
Testolactone	Teslac	Used in the treatment of breast cancer.	Bristol-Myers Squibb
Thioguanine, 6-TG	Thioguanine	Antimetabolite used in the treatment of AML, CML, CLL.	GlaxoSmithKline
Thiotepa	Thioplex	Thiotepa is a cytotoxic agent of the polyfunctional type, related chemically and pharmacologically to nitrogen mustard. Thiotepa has been tried with varying results in the palliation of a wide variety of neoplastic diseases. However, the most consistent results have been seen in the following tumors: 1. Adenocarcinoma of the breast. 2. Adenocarcinoma of the ovary. 3. For controlling intracavitary effusions secondary to diffuse or localized neoplastic diseases of various serosal cavities. 4. For the treatment of superficial papillary carcinoma of the urinary bladder. While now largely superseded by other treatments, thiotepa has been effective against other lymphomas, such as lymphosarcoma and Hodgkin's disease.	Immunex Corporation
Topotecan	Hycamtin	Treatment of patients with metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy. Treatment of small cell lung cancer sensitive disease after failure of first-line chemotherapy.	GlaxoSmithKline
Toremifene	Fareston	Treatment of advanced breast cancer in postmenopausal women.	Chiron Corp.
Tositumomab	Bexxar	Accel. Approv. (clinical benefit not established) Treatment of patients with CD20 positive, follicular, non-Hodgkin's lymphoma, with and without transformation, whose disease is refractory to Rituximab and has relapsed following chemotherapy	Corixa Corporation
Trastuzumab	Herceptin	HERCEPTIN as a single agent is indicated for the treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease. Herceptin in combination with paclitaxel is indicated for treatment of patients with metastatic breast cancer whose tumors overexpress the HER-2 protein and had not received chemotherapy for their metastatic disease	Genentech, Inc.

Tretinoin, ATRA	Vesanoid	Induction of remission in patients with acute promyelocytic leukemia (APL) who are refractory to or unable to tolerate anthracycline based cytotoxic chemotherapeutic regimens.	Roche
Uracil Mustard	Uracil Mustard Capsules	Used in the treatment of CML, NHL and CLL.	Roberts Labs
Valrubicin	Valstar	For intravesical therapy of BCG-refractory carcinoma in situ (CIS) of the urinary bladder in patients for whom immediate cystectomy would be associated with unacceptable morbidity or mortality.	Anthra → Medeva
Vinblastine	Velban	Vinca alkyloid used in the treatment of many types of cancer.	Eli Lilly
Vincristine	Oncovin	Vinca alkyloid used in the treatment of many types of cancer.	Eli Lilly
Vinorelbine	Navelbine	Single agent or in combination with cisplatin for the first-line treatment of ambulatory patients with unresectable, advanced non-small cell lung cancer (NSCLC).	GlaxoSmithKline
Vinorelbine	Navelbine	Navelbine is indicated as a single agent or in combination with cisplatin for the first-line treatment of ambulatory patients with unreseactable, advanced non-small cell lung cancer (NSCLC). In patients with Stage IV NSCLC, Navelbine is indicated as a single agent or in combination with cisplatin. In Stage III NSCLC, Navelbine is indicated in combination with cisplatin.	GlaxoSmithKline
Zoledronate	Zometa	Used in the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy	Novartis

Table 5: Advanced antiangiogenic compounds in the clinic

Product	Mechanism of Action	Clinical Phase	Marketing Co.
Sorafenib	Inhibits VEGFR2, VEGFR3, Raf Kinase and PDGFRa	Pre-registration	Bayer/Onyx
Sutent	Inhibits VEGFR1, VEGFR2, VEGFR3, PDGFR, CSF-1, Fit-3, and C-Kit	Pre-registration	Pfizer
Thalomid	Antiangiogenic compound of unknown mechanism of action	III	Celgene
Revlimid	Antiangiogenic compound of unknown mechanism of action	III	Celgene
Vatalanib	Inhibits VEGFR1, VEGFR2, VEGFR3, PDGFR, and C-Kit	III	Novartis/Schering
ZD-6474	Inhibits VEGFR2, and EGFR	III	AstraZeneca

Neovastat	Liquid extract derived from Shark cartilage that blocks VEGFR2 and inhibits MMP-1, MMP-9 and MMP-12	III	AEterna
GSK-786024	Inihibits VEGFR1, VEGFR2 and VEGFR3	II	GlaxoSmithKline
AEE-788	Inhibits EGFR, HER2 and VEGFR	II	Novartis
AG-13736	Inihibits VEGFR1, VEGFR2 and PDGF	II	Pfizer
AMG706	Inhibits VEGFR1, VEGFR2, VEGFR3, PDGFR, Ret, and C-Kit	II	Amgen
AZD-2171	Inhibits VEGFR1, VEGFR2, VEGFR3, and EGFR	II	AstraZeneca
BIBF-1120	Inhibits VEGFR, FGFR, and PDGFR	II	Boehringer Ingelheim
CP-547,632	Inhibits VEGFR1 and VEGFR2	II	Pfizer/OSI Pharma
Midostaurin	Inhibits FLT3 Kinase, VEGFR2, and various PKC kinases	II	Novartis
SU-6668	Inhibits VEGFR1, PDGF and FGFR	II	Pfizer/Taiho
CDP-791	Inhibits VEFR2	II	UCB/Imclone Systems
PI-88	Inhibits heparinase, binds to VEGF, FGF1, FGF2 and stimulates the release of TFP1	II	Progen
PCK-3145	Binds to laminin receptor and VEGFR2, and downregulates MMP9 expression	II	Procyon Biopharma
Atiprimod	Inhibits IL6 and VEGF secretion	II	Callisto Pharmaceuticals
A6	Eight amino acid, uPA derived peptide that inhibits the activity of uPAR	II	Angstrom Pharmaceuticals
Angiostatin	Peptidic angiostatin inhibitor that is a fragment of the clotting factor plasminogen	II	Alchemgen Therapeutics
Cilengitide	Cyclic Peptide that is an alpha-v integrin antagonist	II	Merck
Enodstatin	Peptidic angiogenesis inhibitor based Collagen XVIII fragment	II	Alchemgen Therapeutics
rPF4	Recombinant form of Platlet Factor 4	II	Repligen Clinical Partners
Vitakin	Antibody antagonist of alpha-v-beta-3 ingrins	II	MedImmune
Volociximab	Antibody antagonist of alpha-v-beta-3 ingrins	II	Biogen Idec/Protein Design Labs
2-methoxyestradiol	Estrogen metabolite that inhibits HIF1a translation	II	EntreMed
AP-23573	Inhibits mTOR	II	Ariad Pharmaceuticals
Cancertinib	TKI that inhibits EGFR	II	Pfizer

Actimid	Thalomid derivative	II	Celgene
Combretastatin A4 prodrug	Tubulin destabilizing agent	II	Oxigene
Endo Tag 1	Antineovasculature agent, formation of paclitaxel encapsulated in positively charged liposomes	II	Medigene
Enzastaurin	Protein kinase C-beta inhibitor	II	Eli Lilly
Ceflatonin	Induces apoptosis	II	ChemGenex Pharmaceuticals
Silipide	A complex of silybin and phosphatidiylcholine	II	Indena
INGN-241	Gene therapy based upon the mda-7 gene coding for IL-24	II	Introgen Therapeutics
OSI-461	Inhibits cGMP phospodiesterase	II	OSI Pharmaceuticals
Patupilone	A non-taxane microtubule stabilizing agent	II	Novartis
Squalamine	Blocks multiple angiogenic cofactors	II	Genaera
Tacedinaline	Cystostatic histone deacetylation inhibitor	II	Pfizer
UCN-01	Inhibitor of serine-threonine kinases, including protein kinase C	II	NCI
UK-356202	Urokinase-like plasminogen activator	II	Pfizer

Table 6: Combination therapies for use in oncology

ABVD	Doxorubcin, Bleomycin, Vinblastine, and Dacarbazine
AC	Doxorubicin and Cyclophosphamide
BEP	Bleomycin, Etoposide and Cisplatin
CAF	Cyclosphosphamide, Doxorubicin and 5-Fluorouracil (5FU)
CAV	Cyclophosphamide, Doxorubicin, Vincristine
Carboplatin-Etoposide	Carboplatin and Etoposide
ChlVPP	Chlorambucil, Vinblastine, Procarbazine, and Prednisolone
CHOP	Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone
CHOP-R	Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone, and Rituximab
CMF	Cyclophosphamide, Methotrexate and 5FU
CVAMP	Cyclophosphamide, Doxorubicin, Vincristine, and Methyl-prednisolone
De Gramont	5FU and leucovorin
DHAP	Dexamethasone, Cytarabine, and Cisplatin
DAHP-R	Dexamethasone, Cytarabine, Cisplatin and Rituximab
Doxorubicin-Ifostamide	Doxorubicin and Ifostamide
EC	Epirubicin and Cyclophosphamide
ECF	Epirubicin, Cyclophosphamide, and 5FU
ECMF	Epirubicin, Cyclophosphamide, Methotrexate, and 5FU

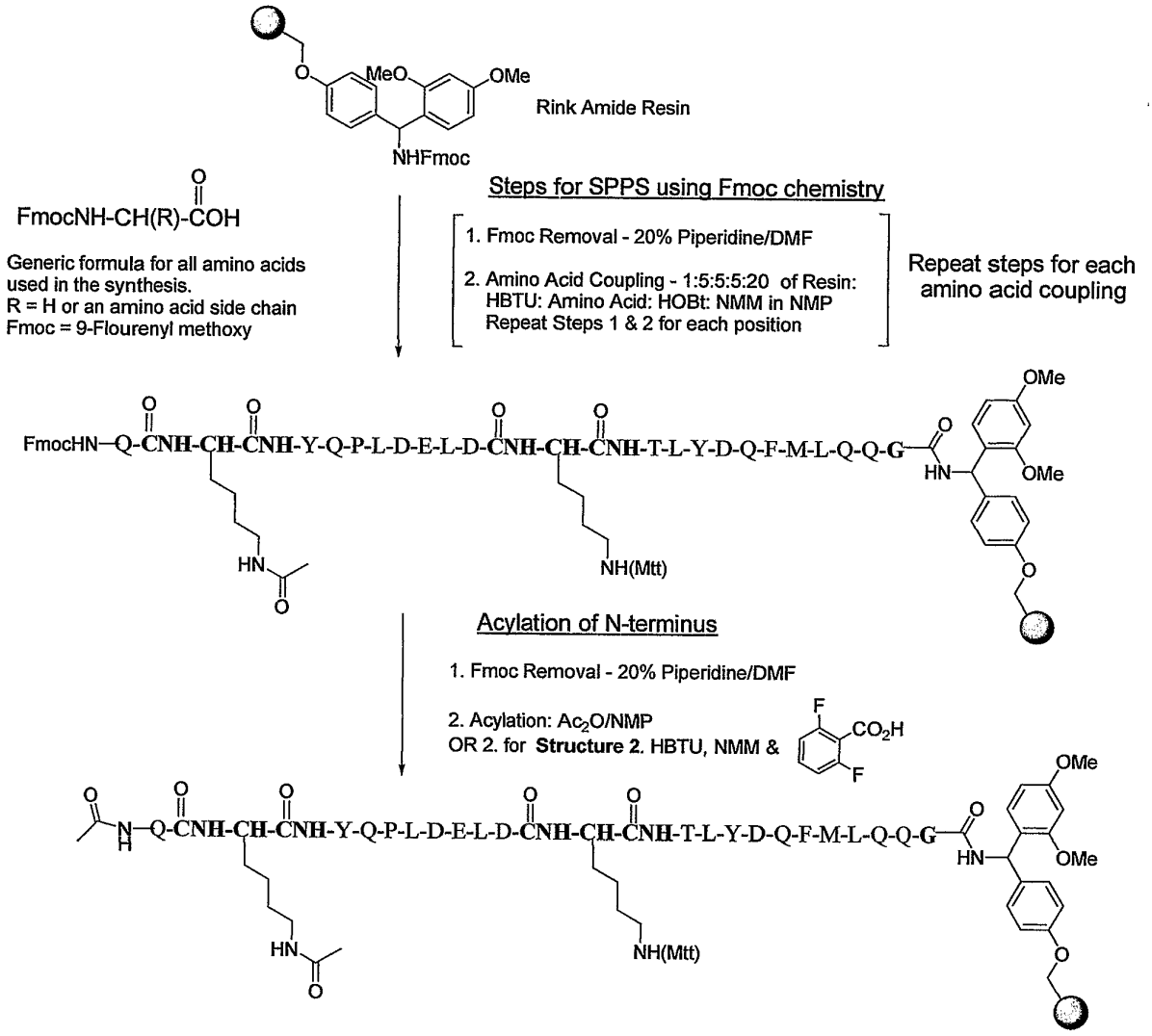
EEX	Epirubicin, Oxaliplatin, and Capecitabine
ECX	Epirubicin, Cisplatin, and Capecitabine
ESHAP	Etoposide, Methyl-prednisolone, Cytarabine and Cisplatin
FEC	5FU, Epirubicin, and Cyclophosphamide
Gemcarbo	Gemcitabine and Carboplatin
Gemcitabine-Cisplatin	Gemcitabine and Cisplatin
Irinotecan-De Gramont	Irinotecan, 5FU and Leucovorin
MIC	Mitomycin, Ifosamide and Cisplatine
MM	Methotrexate and Mitoxantrone
MMM	Methotrexate, Mitomycin, and Mitoxantrone
MVP	Mitomycin, Vinblastine and Cisplatin
FOLFOX	5FU, Oxilaplatin and Leucovorin
FOLFIRI	5FU, Leucovorin and Irinotecan
Paclitaxel-Carboplatin	Paclitaxel and Carboplatin
PmitCebo	Prednisolone, Mitoxantrone, Cyclophosphamide, Etoposide, Bleomycin and Vincristine
VAD	Vincristine, Doxorubicin, and Dexamethasone
VAPEC-B	Vincristine, Doxorubicin, Prednisolone, Etoposide, Cyclosphosphamide, and Bleomycin
Vinorelabine-Cisplatin	Vinorelabine and Cisplatin

The versatility of the invention is illustrated by the following Examples, which illustrate typical embodiments of the invention and are not limiting of the claims or specification in any way.

EXAMPLES

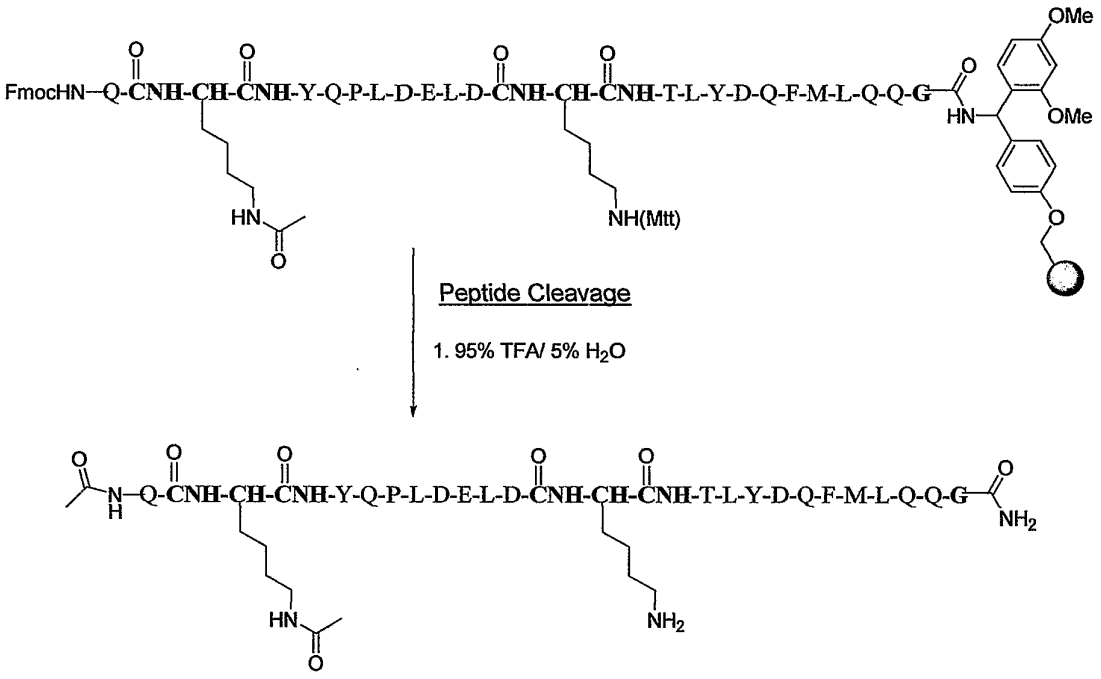
EXAMPLE 1: Synthesis of exemplary compounds:

Scheme 1. Solid phase synthesis of a peptide chain using Fmoc chemistry



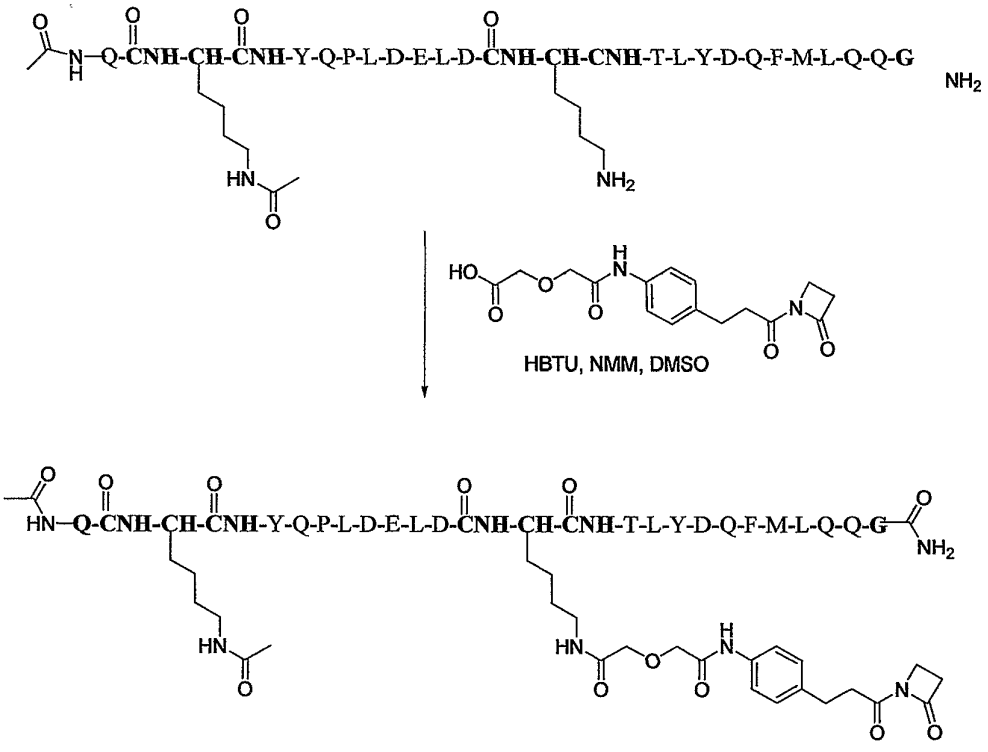
EXAMPLE 2: Cleavage from resin of the peptide prepared as in EXAMPLE 1.

Cleavage of peptide from resin

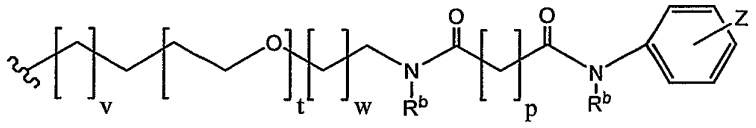


EXAMPLE 3: Coupling to linker of the compound prepared as in EXAMPLE 2.

Coupling of linker

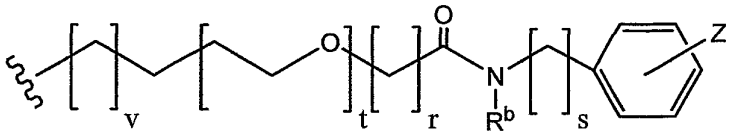


EXAMPLE 4: Synthesis of:



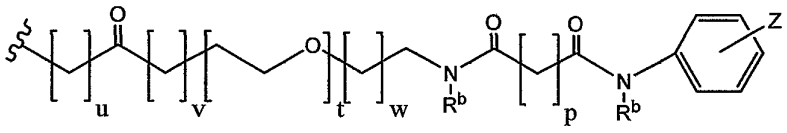
is provided in FIGURE 12.

EXAMPLE 5: Synthesis of:



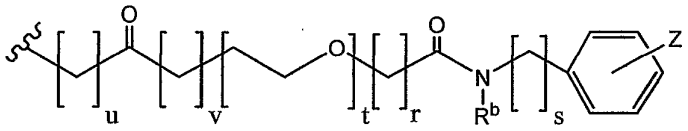
is provided in FIGURE 13.

EXAMPLE 6: Synthesis of:



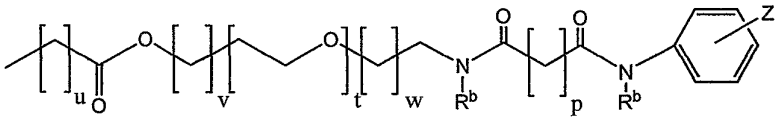
is provided in FIGURE 14.

EXAMPLE 7: Synthesis of



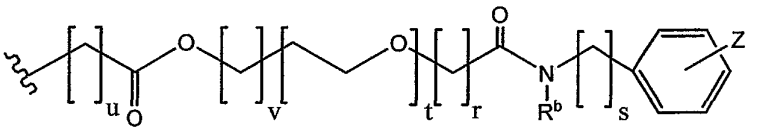
is provided in FIGURE 15.

EXAMPLE 8: Synthesis of:



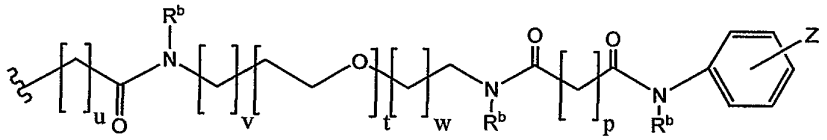
is provided in FIGURE 16.

EXAMPLE 9: Synthesis of:



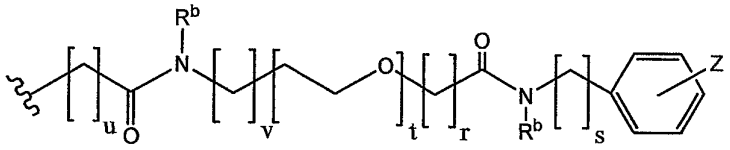
is provided in FIGURE 17.

EXAMPLE 10: Synthesis of:



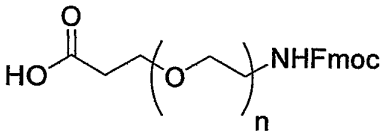
is provided in FIGURE 18.

EXAMPLE 11: Synthesis of:



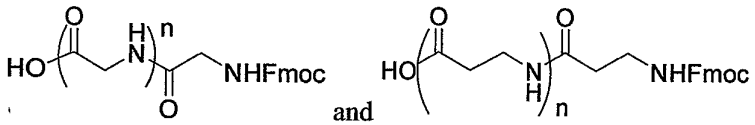
is provided in FIGURE 19.

EXAMPLE 12: Synthesis of:



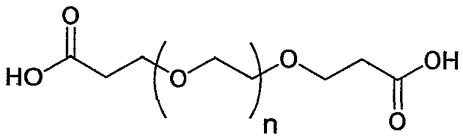
is provided in FIGURE 20.

EXAMPLE 13: Synthesis of:



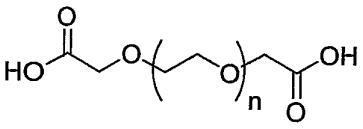
is provided in FIGURE 21.

EXAMPLE 14: Synthesis of:



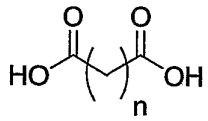
is provided in FIGURE 22.

EXAMPLE 15: Synthesis of:



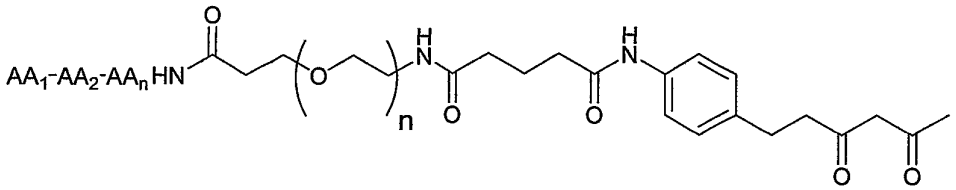
is provided in FIGURE 23.

EXAMPLE 16: Synthesis of:



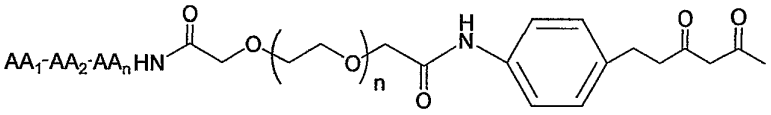
is provided in FIGURE 24.

EXAMPLE 17: Synthesis of:



is provided in FIGURE 25. While this EXAMPLE uses the compound of EXAMPLE 12, it could also sufficiently employ the compounds of EXAMPLE 13. Further, while this EXAMPLE shows linking to the N-terminus, the free acid on the left side of the compounds of EXAMPLES 12 and 13 may also be linked to any nucleophilic side chain on a peptide, such as the C, K, S, T or Y side chains. As is also shown in this EXAMPLE, the Fmoc protected amino group on the right side of the compounds of EXAMPLES 12 and 13 is used to link to the recognition group, Y, via an amide bond.

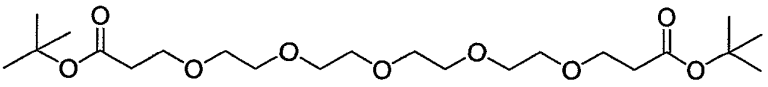
EXAMPLE 18: Synthesis of:



is provided in FIGURE 26. While this EXAMPLE uses the compound of EXAMPLE 15, it could also sufficiently employ the compounds of EXAMPLES 14 and 16. Further, while this EXAMPLE shows linking to the N-terminus, the free acid on the left side of the compounds of EXAMPLES 14-16 may also be linked to any nucleophilic side chain on a peptide, such as the C, K, S, T or Y side chains. As is also shown in this EXAMPLE, the free acid on the right side of the compounds of EXAMPLES 14-16 is used to link to the antibody recognition group, Y, via an amide bond.

EXAMPLE 19: Synthesis of:

3-{2-[2-(2-{2-[2-(2-tert-Butoxycarbonyl-ethoxy)-ethoxy]-ethoxy}-ethoxy)-ethoxy]ethoxy}-propionic acid tert-butyl ester

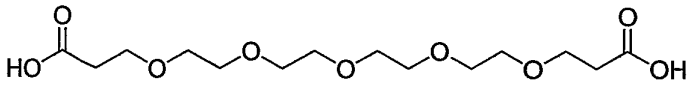


The title compound was prepared using a reported method (O. Seitz and H. Kunz, J. Org. Chem. 62:813-826 (1997)). A small piece of sodium metal was added to a solution of tetra(ethylene glycol) (47.5 g, 244 mmol) in THF (200 ml) and stirred until the sodium was dissolved completely. ^{t}Butyl acrylate (94 g, 730mmol) was then added and stirring continued for 2 days at RT. Another batch of ^{t}Butyl acrylate (94 g, 730mmol) was added and stirring continued for another 2 days. The reaction mixture was neutralized with a few drops of 1N HCl and concentrated under reduced pressure. The residue was

suspended in water and extracted with ethyl acetate (3 X 150 ml). Combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of volatiles over reduced pressure provided the crude product as colorless liquid which was purified using a silica gel column (42 g, 51%).

EXAMPLE 20: Synthesis of:

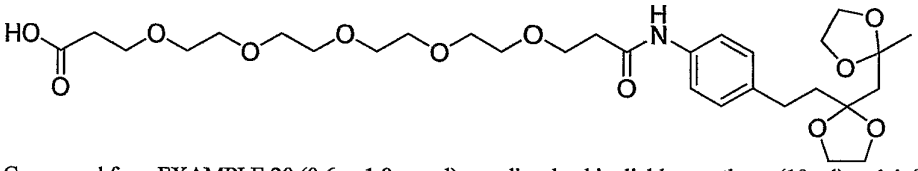
3-{2-[2-(2-{2-[2-(2-Carboxy-ethoxy)-ethoxy]-ethoxy}-ethoxy)-ethoxy]-ethoxy}-propionic acid



A solution of 3-{2-[2-(2-{2-[2-(2-tert-Butoxycarbonyl-ethoxy)-ethoxy]-ethoxy}-ethoxy)-ethoxy]-ethoxy}-propionic acid tert-butyl ester (6 g, 18.6mmol) in anisole (20 ml) was cooled in an ice bath and trifluroacetic acid (65 g) was added. After 3 hrs at RT volatiles were removed under reduced pressure and the residue was partitioned between ethyl acetate (50 ml) and 5% sodium bicarbonate solution. The aqueous layer was acidified with 1 N HCl, saturated with NaCl and then extracted with ethyl acetate (3 X 50 ml). Combined organic layers were washed with brine and dried over sodium sulfate. Removal of volatiles under the reduced pressure provided the product as colorless liquid which solidified upon refrigeration (3.8 g, 82%).

EXAMPLE 21: Synthesis of:

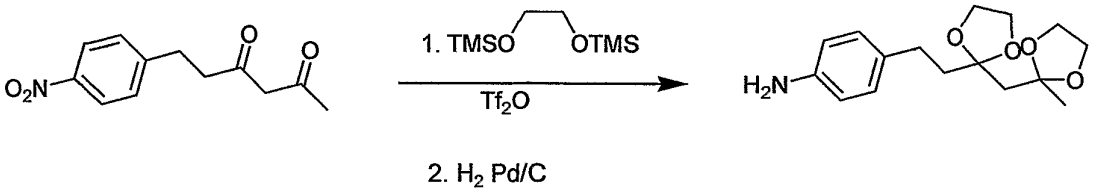
3-(2-{2-[2-(2-{2-[2-(4-{2-[2-(2-Methyl-[1,3]dioxolan-2-ylmethyl)-[1,3]dioxolan-2-yl]-ethyl}-phenylcarbamoyl)-ethoxy]-ethoxy}-ethoxy)-ethoxy]-ethoxy}-ethoxy)-propionic acid



Compound from EXAMPLE 20 (0.6 g, 1.8 mmol) was dissolved in dichloromethane (10 ml) and 4-{2-[2-(2-Methyl-[1,3]dioxolan-2-ylmethyl)-[1,3]dioxolan-2-yl]-ethyl}-phenylamine (0.3 g, 1.4 mmol) followed by EDCI (0.28 g, 1.8 mmol) was added at RT. After 1 hr at RT the RM was washed with water and dried over sodium sulfate. Evaporation of volatiles and purification over silica gel column with 1 to 15% methanol in dichloromethane provided title compound as gum (0.47 g, 32%).

EXAMPLE 22: Synthesis of:

4-{2-[2-(2-Methyl-[1,3]dioxolan-2-ylmethyl)-[1,3]dioxolan-2-yl]-ethyl}-phenylamine

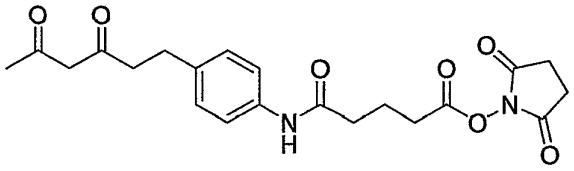


A clean oven dried flask was charged with the 6-(4-nitro-phenyl)-hexane-2,4-dione (3.7g, 15.72 mmol), dry CH_2Cl_2 (20 ml) followed by bisTMS ethylene glycol (38.5 ml, 157.3 ml) were added to the flask and the resulting solution was cooled to -5°C with stirring under argon. TMSOTf (300µl) was added to the reaction mixture and the solution was stirred at -5°C for 6h. Reaction was quenched with pyridine (10 ml) and poured into sat. $NaHCO_3$. The mixture was extracted with EtOAc and

the organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated to give a yellow solid. The solid was triturated with hexanes to give a free flowing pale yellow solid (3.5g, 72%) which was dissolved in EtOAc (50 ml) and hydrogenated on a Parr shaker starting with 50 psi of hydrogen pressure. After two hours the reaction was filtered through a pad of celite, the celite was washed thoroughly with CH_2Cl_2/MeOH and combined organics were concentrated to give title compound (1.46 g, 100%) as an oil that solidifies upon standing.

EXAMPLE 23: Synthesis of:

Synthesis of 4-[4-(3,5-Dioxo-hexyl)-phenylcarbamoyl]-butyric acid 2,5-dioxo pyrrolidin-1-yl ester (10)



Step 1: 6-(4-Nitro-phenyl)-hexane-2,4-dione (11)

To a reaction vessel (heat and vacuum dried and equipped with a magnetic spin bar) was added tetrahydrofuran and lithium diisopropylamide (2M heptane / ethylbenzene / tetrahydrofuran; 69.4 mL, 138.9 mmol). The solution cooled to -78°C. Pentane-2,4-dione (7.13 mL, 69.4 mmol) was added dropwise and the solution stirred 30 minutes at -78°C. 4-nitrobenzyl bromide (15.0 g, 69.4 mmol) was added in one portion. The solution was removed from the dry-ice/acetone bath, allowed to warm to room temperature and stirred 16 hours. The solution was cooled to approximately 0°C and the reaction quenched with 1M HCl. Tetrahydrofuran was removed under reduced pressure. The crude material was taken up into dichloromethane and washed with 1M HCl and brine. The aqueous layers were again washed with dichloromethane. The combined dichloromethane layers were dried (Na_2SO_4) and removed under reduced pressure. Gradient flash column chromatography (FCC) was performed using 5% to 15% ethyl acetate/hexanes to afford title compound (8.5 g, 52%; yellow solid). ^{1}H NMR ($CDCl_3$): δ 8.14 (d, J = 9.0 Hz, 2 H), δ 7.43 (d, J = 8.4 Hz, 2 H), δ 5.45 (s, 1 H), δ 3.06 (t, J = 7.5 Hz, 2 H), δ 2.64 (t, J = 7.8 Hz, 2 H), δ 2.04 (s, 3 H).

Step 2: 4-[4-(3,5-Dioxo-hexyl)-phenylcarbamoyl]-butyric acid (12)

200 mL tetrahydrofuran, 6-(4-nitro-phenyl)-hexane-2,4-dione (8.0 g, 34.0 mmol) and dihydro-pyran-2,6-dione (3.88 g, 34.0 mmol) were added to a reaction vessel. The reaction vessel was purged three times with argon. Approximately 200 mg palladium (10 wt % on activated carbon) was added. The reaction vessel was purged again with argon and excess hydrogen introduced via a balloon. Solution stirred 16 hours at room temperature. Hydrogen removed under reduced pressure and catalyst removed by filtration through celite. Tetrahydrofuran removed under reduced pressure to afford title compound (10.5 g, 97%, yellow solid).

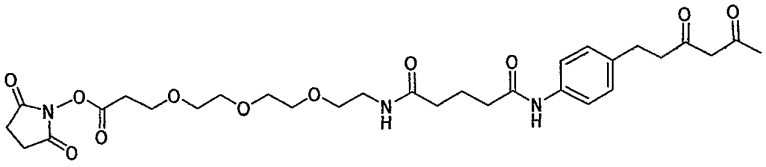
Step 3: 4-[4-(3,5-Dioxo-hexyl)-phenylcarbamoyl]-butyric acid 2,5-dioxo pyrrolidin-1-yl ester (10)

To a reaction vessel (heat and vacuum dried and equipped with a magnetic spin bar) was added 4-[4-(3,5-dioxo-hexyl)-phenylcarbamoyl]-butyric acid (10.53 g, 33.0 mmol), N-hydroxysuccinimide (3.8 g, 33.0 mmol) and 1-[3-(dimethylamino) propyl]-3-ethylcarbodiimide hydrochloride (6.3 g, 33.0 mmol) and dichloromethane (250 mL). The solution was stirred

under nitrogen at room temperature for 16 hours then washed with 10% citric acid, brine and dried (Na_2SO_4). Dichloromethane was removed under reduced pressure. FCC with 70% ethyl acetate / hexanes gave title compound (7.4 g, yellow solid, 54%). ^1H NMR ($CDCl_3$): δ 7.87 (s, 1 H), δ 7.43 (d, J = 8.4 Hz, 2 H), δ 7.12 (d, J = 8.4 Hz, 2 H), δ 5.46 (s, 1 H), δ 2.89 (t (& m), J = 8.1 Hz (for the t), 7 H), δ 2.73 (t, J = 6.0 Hz, 2 H), δ 2.56 (t, J = 7.2 Hz, 2 H), δ 2.47 (t, J = 6.9 Hz, 2 H), δ 2.21 (p, J = 6.6 Hz, 2 H), δ 2.04 (s, 3 H).

EXAMPLE 24: Synthesis of:

Synthesis of 3-{2-[2-(2-{4-[4-(3,5-Dioxo-hexyl)-phenylcarbamoyl]-butyrylamino}-ethoxy)-ethoxy]-ethoxy}-propionic acid 2,5-dioxo-pyrrolidin-1-yl ester, (20)



Step 1: 3-{2-[2-(2-Hydroxy-ethoxy)-ethoxy]-ethoxy}-propionic acid tert-butyl ester

Na metal (catalytic) was added to a stirring solution of acrylic acid tert-butyl ester (6.7 mL, 46 mmol), and 2-[2-(2-hydroxy-ethoxy)-ethoxy]-ethanol (20.7 g, 138 mmol) in THF (100 mL) at 0 °C and the mixture was stirred overnight. Solvent was removed and the remaining oil dissolved in EtOAc (100 mL). The organic layer was washed with water (3 × 50 mL), and dried over Na_2SO_4 and the solvent removed in vacuo to give an oil which corresponds to the title compound that would be used as is for the next step. (M + 1) = 279.

Step 2: 3-{2-[2-(2-Tosylsulfonyloxy-ethoxy)-ethoxy]-ethoxy}-propionic acid tert-butyl ester

Tosyl chloride (22.3 g, 117 mmol) was added in portions to a stirring solution of 3-{2-[2-(2-hydroxy-ethoxy)-ethoxy]-ethoxy}-propionic acid tert-butyl ester (16.3 g, 58.6 mmol) and pyridine 60 mL in (240 mL) and the mixture was stirred overnight. The reaction was quenched with water (300 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layer was washed with HCl (1N, 100 mL), water (100 mL), and dried over Na_2SO_4 and the solvent was removed in vacuo to give an oil which corresponds to the title compound that would be used as is for the next step. (M + 1) = 433.

Step 3: 3-{2-[2-(2-Amino-ethoxy)-ethoxy]-ethoxy}-propionic acid tert-butyl ester

NaN_3 (35g, 538 mmol) was added to a stirring solution of 3-{2-[2-(2-tosylsulfonyloxy-ethoxy)-ethoxy]-ethoxy}-propionic acid tert-butyl ester (20g, 46 mmol) in DMF (150 mL) and the reaction was stirred overnight. Reaction was diluted with water (200 mL) and extracted with EtOAc (4 × 100 mL). The organic layer was washed with water (100 mL) and brine (100 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to give an oil. Column chromatography EtOAc/Hex (1:4) gave an oil which corresponds to the 3-{2-[2-(2-azido-ethoxy)-ethoxy]-ethoxy}-propionic acid tert-butyl ester, (M + 1) = 304. This oil was hydrogenated using Pd (5% on carbon) in EtOAc under hydrogen (1 atm.) over 3 days. The catalyst was removed by filtration and solvent removed in vacuo to give an oil corresponding to the title compound, (M + 1) = 278.

Step 4: 3-{2-[2-(2-{4-[4-(3,5-Dioxo-hexyl)-phenylcarbamoyl]-butyrylamino}-ethoxy)-ethoxy]-ethoxy}-propionic acid tert-butyl ester

A solution of 4-[4-(3,5-dioxo-hexyl)-phenylcarbamoyl]-butyric acid 2,5-dioxo-pyrrolidin-1-yl ester (1.5 g, 3.6 mmol), 3-{2-[2-(2-amino-ethoxy)-ethoxy]-ethoxy}-propionic acid tert-butyl ester (1.0 g, 3.6 mmol) and DIEA (1.3 µL, 7.2 mmol) in CH_2Cl_2 (10 mL) was stirred at rt overnight. The solvent was removed in vacuo and the residual oil purified using column chromatography EtOAc/MeOH (95:5) to give the title compound as a transparent oil, (M + 1) = 579.

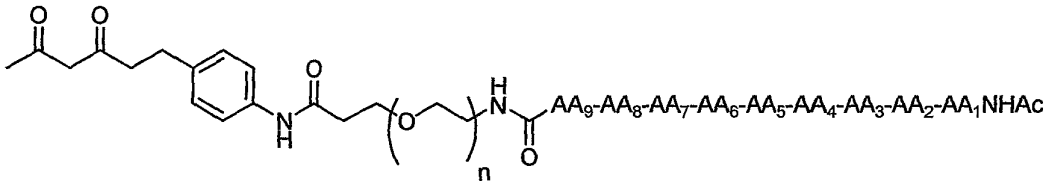
Step 5: 3-{2-[2-(2-{4-[4-(3,5-Dioxo-hexyl)-phenylcarbamoyl]-butyrylamino}-ethoxy)-ethoxy]-ethoxy}-propionic acid 2,5-dioxo-pyrrolidin-1-yl ester

3-{2-[2-(2-{4-[4-(3,5-Dioxo-hexyl)-phenylcarbamoyl]-butyrylamino}-ethoxy)-ethoxy]-ethoxy}-propionic acid tert-butyl ester (400 mg, 0.692 mmol) was dissolved in TFA/CH_2Cl_2 (1:1, 3 mL) and the mixture stirred overnight. The solvent was removed to give an oil as the acid intermediate. This oil was dissolved in CH_2Cl_2 (4 mL) containing DIEA (569 µL, 3.09 mmol), N-hydroxysuccinimide (119 mg, 1.03 mmol) and EDC (197 mg, 1.0 mmol) and the mixture stirred over the night. The solvent was removed and the residual oil was purified using column chromatography EtOAc/MeOH (95:5) to give an oil as the title compound, (M + 1) = 620.

EXAMPLE 25: Synthesis of AA targeting compound

Compound of EXAMPLES 17 or 18 can be linked to antibody 38C2 by the following procedure: One mL antibody 38C2 in phosphate buffered saline (10 mg/mL) is added to 12 µL of a 10 mg/mL stock solution of AA targeting agent and the resulting mixture maintained at room temperature for 2 hours prior to use.

EXAMPLE 26: Synthesis of:



is provided in FIGURE 27. While this EXAMPLE uses the compound of EXAMPLE 12, it could also sufficiently employ the compounds of EXAMPLE 13.

EXAMPLE 27:

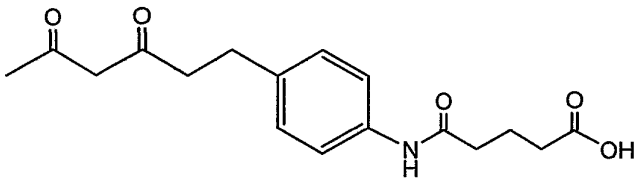
C. Rader, *et al.*, J. Mol. Biol. 332:889-899 (2003) details one method of making h38c2. The following details the results, materials and methods in this reference.

Humanization Human Vκ gene DPK-9 and human Jκ gene JK4 were used as frameworks for the humanization of the kappa light chain variable domain, and human VH gene DP-47 and human J_H gene J_H4 are used as frameworks for the humanization of the heavy chain variable domain of m38C2. All complementarity determining region (CDR) residues as defined by Kabat *et al.*, as well as defined framework residues in both light chain and heavy chain variable domain, were grafted from m38C2 onto the human framework. The selection of grafted framework residues may be based on the crystal structure of mouse mAb 33F12 Fab (PDB 1AXT). mAb 33F12 Fab shares a 92% sequence homology with m38c2 in the variable domains and identical CDR lengths. Furthermore, both 33F12 and m38C2 have similar catalytic activity. Framework residues consisted of five residues in the light chain and seven residues in the heavy chain (Figure 7A) and encompassed the residues that are likely to participate directly or indirectly in the catalytic activity of m38C2. These include

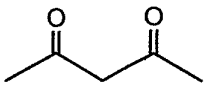
the reactive lysine of m38C2, Lys^{H93}, which is positioned in framework region 3 (FR3) of the heavy chain. Six residues, Ser^{H35}, Val^{H37}, Trp^{H47}, Trp^{H103}, and Phe^{L98}, which are conserved between mouse mAbs 33F12 and 38C2, are within a 5-Å radius of the ε amino group of Lys^{H93}. These residues were also conserved in the humanization. Lys^{H93} lies at the bottom of a highly hydrophobic substrate binding sites of mouse mAbs 33F12 and 38C2. In addition to CDR residues, a number of framework residues line this pocket. Among these, Leu^{L37}, Gln^{L42}, Ser^{L43}, Val^{L85}, Phe^{L87}, Val^{H5}, Ser^{H40}, Glu^{H42}, Gly^{H88}, Ile^{H89}, and Thr^{H94} were grafted onto the human framework.

Expression By fusing the humanized variable domains to human constant domains C_κ and $C_{\gamma 1}1$, h38C2 was initially generated as Fab expressed in *E. coli*. Next, h38c2 IgG was formed from h38c2 Fab using the PIGG vector engineered for human IgG1 expression in mammalian cells. Supernatants from transiently transfected human 293T cells were subjected to affinity chromatography on recombinant protein A, yielding approximately 1 mg/L h38C2 IgG1. Purity was established by SDS-PAGE followed by Coomassie blue staining.

β-Diketone Compounds –



1



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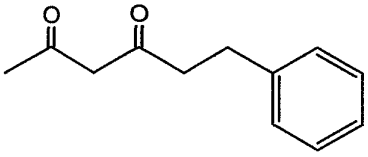

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The enaminone formed by the covalent addition of a β-diketone with m38c2 has a characteristic UV absorbance at λ_{max} = 318 nm. Like m38C2 IgG, h38C2 IgG showed the characteristic enaminone absorbance after incubation with β-diketone. As a negative control, recombinant human anti-HIV-1 gp120 mAb b12 with the same IgG1 isotype as h38C2 but without reactive lysine, did not reveal enaminone absorbance after incubation with β-diketone **2**. For a quantitative comparison of the binding of β-diketones to m38C2 and h38C2, the authors used a competition ELISA. The antibodies were incubated with increasing concentrations of β-diketones **2** and **3** and assayed against immobilized BSA-conjugated β-diketone **1**. The apparent equilibrium dissociation constants were 38 μM (m38C2) and 7.6 μM (h38C2) for β-diketone **2** and 0.43 μM (m38C2) and 1.0 μM (h38C2) for β-

diketone **3**, revealing similar β-diketone binding properties for mouse and humanized antibody (Fig. 6).

Molecular modeling – A molecular model of h38C2 Fab was constructed by homology modeling using the crystal structure of a related aldolase antibody, mouse 33F12 Fab (Protein Data Bank ID: 1AXT), as a template. The crystal structure of mouse 33F12 Fab was previously determined at a resolution of 2.15 Å.[4] Alignment of mouse 33F12 and 38C2 amino acid sequences using the HOMOLOGY module within INSIGHT II software (Accelrys) confirmed that both sequences are highly homologous. They differ from each other by 19 out of 226 amino acids in the two variable domains, and their CDRs share the same lengths. In addition to the high sequence homology, both structures exhibit considerable structural similarity, as observed by a low-resolution crystal structure of 38C2. Residues in the model were mutated to conform to the h38C2 amino acid sequence and sidechains were placed based on standard rotamers. This model was then minimized with the DISCOVER module in INSIGHT II using 100 steps each of steepest descent minimization followed by conjugate gradient minimization.

Construction of h38C2 Fab – The sequences of the variable light and heavy chain domains of m38C2 (SEQ ID NOs:15 and 16, respectively) as well as the sequences of human germline sequences DPK-9 (SEQ ID NO:17), JK4 (SEQ ID NO:18), DP-47 (SEQ ID NO:19), and JH4 (SEQ ID NOs:20, 187 and 188) (V BASE; http://vbase.mrc-cpe.cam.ac.uk/) were used to design overlapping oligonucleotides for the synthetic assembly of humanized V_κ and and V_H, respectively. N-glycosylation sites with the sequence NXS/T as well as internal restriction sites *HindIII*, *XbaI*, *SacI*, *ApaI*, and *SfiI* were avoided. PCR was carried out by using the Expand High Fidelity PCR System (Roche Molecular Systems). The humanized V_κ oligonucleotides were: L flank sense (Rader, C., Ritter, G., Nathan, S., Elia, M., Gout, I., Junbluth, A.A., J. Biol. Chem. 275: 13668-13676 (2000)) (sense 5'-GAGGAGGAGGAGGAGGGCCCAGGCGGCCGAGCTCCAGATGACCCAGTCTCTCCA-3' SEQ ID NO:179); h38C2L1 (sense; 5'-GAGCTCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGTGACCGCGTCACCATCACTTG-3') (SEQ ID NO:1); h38C2L2 (antisense; 5'-ATTCAGATATGGGCTGCCATAAGTGTGCAGGAGGCTCTGACTGGAGCGGCAAGTGATGGTGACGCGGTC-3') (SEQ ID NO:2); h38C2L3 (sense; 5'-TATGGCAGCCCATATCTGAATTGGTATCTCCAGAAACCAGGCCAGTCTCCTAAGCTCCTGATCTAT-3') (SEQ ID NO:3); h38C2L4 (antisense; 5'-CTGAAACGTGATGGGACACCACTGAAACGATTGGACACTTTATAGATCAGGAGCTTAGGAGACTG-3') (SEQ ID NO:4); h38C2L5 (sense; 5'-AGTGGTGTCCCATCACGTTTCAGTGGCAGTGGTTCTGGCACAGATTTCACTCTCACCATCAGCAGTCTGCAACC TGAAGATTTTGCAGTG-3') (SEQ ID NO:5); h38C2L6 (antisense; 5'-GATCTCCACCTTGGTCCCTCCGCCGAAAGTATAAGGGAGGTGGGTGCCCTGACTACAGAAGTACACTGCAAAA TCTTCAGGTTGCAG-3') (SEQ ID NO:6); L antisense flank (C. Rader *et al.*, J. Biol. Chem. 275:13668-13676 (2000)) (antisense5'-GACAGATGGTGCAGCCACAGTTCGTTTGATCTCCACCTTGGTCCCTCC-3' SEQ ID NO:180). The humanized V_H oligonucleotides were: H flank sense (C. Rader *et al.*, J. Biol. Chem. 275:13668-13676 (2000))(sense 5'-GCTGCCCAACCAGCCATGGCCGAGGTGCAGCTGGTGGAGTCTGGGGGA-3' SEQ ID NO:181); h38C2H1 (sense; 5'-GAGGTGCAGCTGGTGGAGTCTGGCGGTGGCTTGGTACAGCCTGGCGGTTCCCTGCGCCTCTCCTGTGCAGCCT CTGGCT-3') (SEQ ID NO:7); h38C2H2 (antisense; 5'-CTCCAGGCCCTTCTCTGGAGACTGGCGGACCCAGCTCATCCAATAGTTGCTAAAGGTGAAGCCAGAGGCTGCA CAGGAGAG-3') (SEQ ID NO:8); h38C2H3 (sense; 5'-TCTCCAGAGAAGGGCCTGGAGTGGGTCTCAGAGATTCGTCTGCGCAGTGACAACTACGCCACGCACTATGCAG

AGTCTGTC-3') (SEQ ID NO:9); h38C2H4 (antisense; 5'-CAGATACAGCGTGTTCTTGGAATTGTCACGGGAGATGGTGAAGCGGCCCTTGACAGACTCTGCATAGTGCGTG-3') (SEQ ID NO:10); h38C2H5 (sense; 5'-CAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGCGCCGAGGACACGGGCATTTATTACTGTAAAACG-3') (SEQ ID NO:11); h38C2H6 (antisense; 5'-TGAGGAGACGGTGACCAGGGTGCCCTGGCCCCAGTAGCTGAAACTGTAGAAGTACGTTTTACAGTAATAAATGCCCGTG-3') (SEQ ID NO:12); H flank antisense (C. Rader *et al.*, J. Biol. Chem. 275:13668-13676 (2000))(antisense 5'-GACCGATGGGCCCTTGGTGGAGGCTGAGGAGACGGTGACCAGGGTGCC-3' SEQ ID NO:182). Following assembly, humanized V_κ and V_H were fused to human C_κ and $C_\gamma 1$, respectively, and the resulting light chain and heavy chain fragment were fused and *SfiI*-cloned into phagemid vector pComb3X as described (C. Rader *et al*, J. Biol. Chem. 275:13668-13676 (2000); C.F. Barbas 3rd *et al.*, *Phage Display: A laboratory manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor N.Y. (2001)). To enrich for clones with the correct h38C2 sequence, Fab were displayed on phage and selected by one round of panning against the immobilized β-diketone 1 (JW) conjugated to BSA. Soluble Fab were produced from single clones and tested for binding to immobilized JW-BSA by ELISA using donkey anti-human $F(ab')_2$ polyclonal antibodies conjugated to horseradish peroxidase (Jackson ImmunoResearch Laboratories) as secondary antibody. Light chain and heavy chain encoding sequences of positive clones were analyzed by DNA sequencing using the primers OMPSEQ (5'-AAGACAGCTATCGCGATTGCAG-3' SEQ ID NO:183) and PELSEQ (5'-CTATTGCCTACGGCAGCCGCTG-3' SEQ ID NO:184) (C.F. Barbas 3rd *et al.*, *Phage Display: A laboratory manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor N.Y., (2001)), respectively, to confirm the assembled V_κ and V_H sequences of h38C2.

Construction, production, and purification of h38C2 IgG1 – The recently described vector PIGG (C. Rader *et al*, FASEB J., 16:2000-2002 (2002)) was used for mammalian expression of h38C2 IgG1. The mammalian expression vector PIGG-h38c2 is illustrated in FIGURE 23. The 9kb vector comprises heavy chain γ1 and light chain κ expression cassettes driven by a bidirectional CM promoter construct. Using primers PIGG-h38C2H (sense; 5'-GAGGAGGAGGAGGAGGAGCTCACTCCGAGGTGCAGCTGGTGGAGTCTG-3') (SEQ ID NO:13) and GBACK (5'-GCCCCCTTATTAGCGTTTGCCATC-3' SEQ ID NO:185) (C.F. Barbas 3rd *et al*, *Phage Display: A laboratory manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor N.Y. (2001)), the VH coding sequence from h38C2 Fab in phagemid vector pComb3X was amplified, digested with *SacI* and *ApaI*, and cloned into the appropriately digested vector PIGG. Using primers PIGG-h38C2L (sense: 5'-GAGGAGGAGGAGGAGAAGCTTGTTGCTCTGGATCTCTGGTGCCTACGGGGAGCTCCAGATGACCCAGTCTCC-3') (SEQ ID NO:14) and LEADB (5'-GCCATGGCTGGTTGGGCAGC-3' SEQ ID NO:186) ((C.F. Barbas 3rd *et al*, *Phage Display: A laboratory manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor N.Y. (2001)) the light chain coding sequence from h38C2 Fab in phagemid vector pComb3X was amplified, digested with *HindIII* and *XbaI*, and cloned into the appropriately digested vector PIGG that already contained the h38C2 heavy chain. Intermediate and final PIGG vector constructs were amplified in *E. coli* strain SURE (Stratagene) and prepared with the QIAGEN Plasmid Maxi Kit. h38C2 IgG1 were produced from the prepared final PIGG vector construct by transient transfection of human 293T cells using Lipofectamine 2000 (Invitrogen). Transfected cells were maintained in GIBCO 10% ultra-low IgG (<0.1%) FCS (Invitrogen) in RPMI 1640 (Hyclone) for 2 weeks. During this time, the medium was collected and replaced three times. The collected medium was subjected to affinity chromatography on a recombinant Protein A HiTrap column (Amersham Biosciences). This purification step yielded 2.45 mg h38C2 IgG1 from 2,300 mL collected medium as determined by measuring the optical density at 280 nm using an Eppendorf BioPhotometer. Following dialysis against PBS in a Slide-A-Lyzer 10K dialysis cassette (Pierce), the antibody was concentrated to 760 μg/mL using an Ultrafree-15 Centrifugal Filter Device (UFV2BTK40; Millipore), and sterile filtered through a 0.2-μm Acrodisc 13MM S-200 Syringe Filter (Pall). The

final yield was 2.13 mg (87 %). Purified h38C2 IgG1 was confirmed by nonreducing SDS-PAGE followed by Coomassie Blue staining.

Enaminone formation – Antibody (h38C2 IgG1 or b12 IgG1) was added to β-diketone 2 to a final concentration of 25 μM antibody binding site and 125 μM β-diketone. This mixture was incubated at room temperature for 10 minutes before a UV spectrum was acquired on a SpectraMax Plus 384 UV plate reader (Molecular Devices) using SOFTmax Pro software (version 3.1.2).

Binding assays – Unless noted otherwise, all solutions were phosphate buffered saline (pH 7.4). A 2 x solution of either β-diketone 2 or 3 (50 μL) was added to 50 μL of the antibody (either h38C2 or m38C2) and allowed to incubate at 37°C for 1 hr. Solutions were mixed by pipetting. Final concentrations of antibody were 0.4 to 8 nM antibody binding site, and final concentrations of β-diketones 2 and 3 were 10^{-9} to 10^{-2} M and 10^{-10} to 10^{-4} M, respectively. Each well of a Costar 3690 96-well plate (Corning) was coated with 100 ng of the BSA conjugate of β-diketone 1 in TBS. Wells were then blocked with 3% (w/v) BSA in TBS. Then, 50 μL of the antibody/β-diketone mixture was added, followed by 50 μL of a 1:1,000 dilution of either goat anti-human Fc IgG polyclonal antibodies (Pierce) or rabbit anti-mouse Fc IgG polyclonal antibodies (Jackson ImmunoResearch Laboratories) conjugated to horseradish peroxidase. This was followed by 50 μL ABTS substrate solution. Between each addition, the plate was covered, incubated at 37°C for 1 hr, and then washed five times with deionized H_2O. The absorbance at 405 nm was monitored as described above until the reaction with no β-diketone reached an appropriate value ($0.5 < A_{405} < 1.0$). For each well, the fractional inhibition of ELISA signal (v_i) was calculated using equation i:

$$v_i=(A_o - A_i)/(A_o) \qquad \text{(i)}$$

where A_o is the ELISA absorbance obtained in the absence of β-diketone and A_i is the absorbance obtained in the presence of β-diketone. For monovalent binding proteins, the fraction of antibody bound to soluble β-diketone (f) is equal to v_i. However, the IgG antibody is bivalent, and the ELISA signal is inhibited only by the presence of doubly liganded antibody and not by monovalent binding. Therefore, the Stevens correction for a bivalent antibody was used:

$$f_i = (v_i)^{1/2} \qquad \text{(ii)}$$

The following relationship was used to determine the apparent equilibrium dissociation constant (modified from [ref. 37]):

$$f_i = f_{min} + (f_{max} - f_{min})(1 + K_D/a_0)^{-1} \qquad \text{(iii)}$$

where a_0 corresponds to the total β-diketone concentration, K_D is the equilibrium dissociation constant, and f_{min} and f_{max} represent the experimentally determined values when the antibody binding sites are unoccupied or saturated, respectively. Because this equation is only valid when the K_D values are at least 10 x higher than the antibody concentration, it was verified that the K_D values determined from equation iii met this criterion. Data were fit using a nonlinear least-squares fitting procedure of KaleidaGraph (version 3.0.5, Abelbeck software) with K_D, f_{max}, and f_{min} as the adjustable parameters and normalized using equation iv:

$$f_{norm} = (f_i - f_{min}) / (f_{max} - f_{min}) \qquad \text{(iv)}$$

EXAMPLE 28:

The ability of Ang-2 binding compounds to interact with Ang-2 was measured by competition with Tie-2.

For competitive ELISA, human angiopoietin-2 protein and Tie-2-Fc (R&D Systems) were reconstituted without carrier protein. Mouse anti-human Tie-2 (Pharmingen) was used as the primary antibody and goat anti-mouse-IgG1-HRP (Pierce) was used as the secondary antibody. TMB substrate from Pierce was used.

High-binding half-well plates were coated with Ang-2 (100 ng/well) in 50 µl PBS and incubated at 4°C overnight. Plates were washed three times with washing buffer (0.1% Tween 20, PBS, pH 7.4) and blocked with Superblock (Scytek), 100 µl/well at room temperature ("RT") for 1 hour. After removing the blocking solution, 50 µl of an Ang-2 binding peptide compound (1 uM and 5x serial dilution) in the presence of 0.25 nM hTie-2-Fc using Superblock as diluent was added and incubated at RT for 2 hours. Plates were washed 3 times with washing buffer. Then, 50 ul of 0.1 ug/ml mouse anti-human Tie-2 diluted in Superblock added and incubated at RT for 1 hour. Following incubation, 50 ul of 1:5,000 dilution of goat anti-mouse IgG-HRP in Superblock was then added and incubated at RT for one hour. After washing 3 times, 50 µl (25 µl TMB + 25 µl H_2O_2) was added, and incubated for 3-5 minutes. Color development was monitored and stopped with 25 µl of 2 M H_2SO_4. OD450 nm with a correction wavelength of 540 nm was measured. IC50 values (50% inhibition of Ang-2-Tie-2 binding) were calculated using non-linear Sigmoidal dose-response curve fitting function in the Prism 4 software (GraphPad).

For reverse competition ELISA, human Tie-2-Fc, angiopoietin-2 protein, biotinylated anti-human Ang-2 antibody, and streptavidin HRP (R&D Systems) and TMB substrate from Pierce were used.

High-binding half-well plates were coated with Tie-2-Fc (50 ng/well) in 50 µl PBS and incubated at 4°C overnight. Plates were washed three times with washing buffer (0.1% Tween 20, PBS, pH 7.4) and blocked with Superblock, 150 µl/well at RT for 1 hour. Plates were washed three times. Following washing, 50 µl of an Ang-2 binding peptide compound (50 nM, 5x serial dilution) in the presence of 50 ng/ml (0.83 nM) Ang-2 in Superblock were added and incubated at RT for 1 hour. Plates were washed 3 times, 50 µl of 1 µg/ml biotinylated anti-Ang-2 detection antibody in Superblock was added and incubated at RT for 2 hours. Plates were washed 3 times, and 50 µl of streptavidin HRP (1:200 dilution in Superblock) was added at RT for 20 minutes. Plates were washed 3 times, and 50 µl (25 µl TMB + 25 µl H_2O_2) substrate solution was added and incubated for 20-30 minutes. Color development was stopped with 25 µl of 2 M H_2SO_4. OD450 nm with a correction wavelength of 540 nm was measured. IC50 values (50% inhibition of Ang-2-Tie-2 binding) were calculated using non-linear Sigmoidal dose-response curve fitting function in the Prism 4 software.

IC50 values for exemplary Ang-2 binding peptide compounds as determined by competitive ELISA are presented in Table 7. IC50 values are provided for the targeting peptide plus linker (as shown in FIGURE 3, or FIGURE 2 for compounds 24 and 25) (T) and the targeting peptide linked to an antibody (P) via the linker of FIGURE 3, unless otherwise specified. In Table 7, compounds of SEQ ID NOs: 21-23 are Ang-2 binding peptides alone, not conjugated to either a linker or linker-antibody; compounds of SEQ ID NOs:65 and 66 are Ang-2 binding peptides conjugated to a linker-antibody, where the linker is 4P ("4" PEG) and has the structure of the linker shown in FIGURE 2; and compounds 26-63 are Ang-2 binding peptides conjugated to a linker-antibody, where the linker is OP ("O" PEG) and has the structure of the linker shown in FIGURE 3. Compounds 24-63 were conjugated to humanized aldolase antibody h38c2 and the linker structures shown in FIGURE 2 (4P) and FIGURE 3 (OP) when obtainng the data shown below, except where otherwise indicated. All compounds of the invention shown in the Tables were capped with an acyl group at the N-terminus and an amino group at the C-terminus, except where otherwise indicated (e.g. compounds 26, 49, 50, 51 and 52).

In Table 7, amino acid sequences of peptide compounds are shown with the position of linker OP or 4P indicated in parentheses following the internal amino acid residue to which the linker is attached. For compound of SEQ ID NO:67, the N-terminal "OP" linker is indicated at the beginning of the peptide sequence.

For example, compound 24 in Table 7 has the following sequence: QAcKY QPL DEL DK(4P)T LYD QFM LQQ G (SEQ ID NO:65). In this example, the second amino acid residue is epsilon acyl lysine, followed by tyrosine, and the linking position (in this case a 4P linker) is the lysine residue 11, followed by threonine. Also, compound 52 has the following sequence: (Amido 2-PEG)QAcKY QPL DEL DK(0P)T LYD QFMLQQ G (SEQ ID NO:93). In this case, the N-terminal glutamine residue is capped by an amido-2-PEG group, the second amino acid residue is epsilon acyl lysine, and the OP linker is attached to lysine residue 11.

Tables 7 and 8 also show half-life (T ½) and "screening" half life (results in parentheses): this is essentially an alternative method of determining T ½, based on a shorter test period. For "Screening" T ½, test compounds were intravenously administered into male Swiss Webster mice. Blood samples were taken from 4 mice per time point via retroorbital sinus bleed at the following time points: 0.08, 5, and 32 hours. Blood level of test compounds were determined by ELISA. The data were reported as the percentage of test compounds at 32 hours versus 5 min. Normal T ½ was calculated in a similar fashion, after undergoing additional data analysis using WinNonlin version 4.1 (Pharsight Corporation). The data was fit to a model based upon the shape of the curve (i.e. a bi-exponential decline will be fit to a two compartment model, etc.) The criteria for best fit (i.e. lowest %CV) was based on iterative re-weighted least squares.

TABLE 7

Compound	Sequence	Ang-2 T IC50 nM	Ang-2 P IC50 nM	$T^1/_2$ (Sc) hours
21	QKY QPL DEL DKT LYD QFM LQQ G (SEQ ID NO:21)	25.81		
22	Q(AcK)Y QPL DEL DKT LYD QFM LQQ G (SEQ ID NO:22)	41.9		
23	QNY QPL DEL DKT LYD QFM LQQ G (SEQ ID NO:23)	27.83		
24	Q(AcK)Y QPL DEL DK(4P)T LYD QFM LQQ G (SEQ ID NO:65)	206.7	17.4	104 (27)
25	QNY QPL DEL DK(4P)T LYD QFM LQQ G (SEQ ID NO:66)	300.3	40.456	
26	(0P)QKY QPL DEL DKT LYD QFM LQQ G (SEQ ID NO:67)	32.3	58.77	(7)
27	QKY QPL DEL DK(0P)T LYD QFM LQQ G (SEQ ID NO:68)	29	55.876	117 (32)
28	QNY QPL DEL DK(0P)T LYD QFM LQQ G (SEQ ID NO:69)	175	28.63	100 (57)
29	Q(AcK)Y QPL DEL DK(0P)T LYD QFM LQQ G (SEQ ID NO:70)	83.3	13.195	77 (33)
30	Q(AcK)Y QPL DEK(0P) D(AcK)T LYD QFM LQQ G (SEQ ID NO:71)	279	65.4	(17)
31	Q(AcK)Y QPL DEL DET K(0P)YD QFM LQQ G (SEQ ID NO:72)	>5K	>1000	

32	Q(AcK)Y QPL DEL D(AcK)T K(0P)YD QFM LQQ G (SEQ ID NO:73)	>5K	>1000	
33	Q(AcK)Y QPL DEK(0P) DET LYD QFM LQQ G (SEQ ID NO:74)	369.6	88.81	
34	Q(AcK)Y QD(HP)L DEL DK(0P)T LYD QFM LQQ G (SEQ ID NO:75)	224.5	19.75	(31)
35	Q(AcK)Y Q(HP)L DEL DK(0P)T LYD QFM LQQ G (SEQ ID NO:76)	121	16.68	
36	Q(AcK)Y QPL DEL DK(0P)T IYD QFM LQQ G (SEQ ID NO:77)	2410	152.9	
37	Q(AcK)Y QPL DEI DK(0P)T LYD QFM LQQ G (SEQ ID NO:78)	1273	80.05	
38	Q(AcK)Y QPL DEL DK(0P)T(HChA)YD QFM LQQ G (SEQ ID NO:79)	>5K	702.6	
39	Q(AcK)Y QPL DEL DK(0P)T(HF)YD QFM LQQ G (SEQ ID NO:80)	4894	258.1	
40	Q(AcK)Y QPL DEL DK(0P)T(ThA)YD QFM LQQ G (SEQ ID NO:81)	>5K	357.8	
41	Q(AcK)Y QPL DEL DK(0P)T(Nva)YD QFM LQQ G (SEQ ID NO:82)	1339	23.32	(36)
42	Q(AcK)Y QPL DEL DK(0P)T(HL)YD QFM LQQ G (SEQ ID NO:83)	1342	38.15	(42)
43	Q(AcK)Y QPL DE(AcK) DK(0P)T LYD QFM LQQ G (SEQ ID NO:84)	240	14.515	110 (38)
44	Q(AcK)Y QPL DEL DK(0P)T LFD QFM LQQ G (SEQ ID NO:85)	36.9	11.68	58 (31)
45	Q(AcK)Y Q(HP)L DE(ThA) DK(0P)T L(NO2F)D QFM LQQ G (SEQ ID NO:86)	24.7	12.7	68 (30)
46	Q(AcK)Y QHPL DEThA DK(0P)T L(BPA)D QFM LQQ G (SEQ ID NO:87)	82.7	25.21	(32)
47	Q(AcK)Y Q(HP)L DE(ThA) DK(0P)T L(CO2H)FD QFM LQQ G (SEQ ID NO:88)	43.3	20.65	(47)
48	Q(AcK)Y QPL DE(AcK) DK(0P)T L(NO2F)D QFM LQQ G (SEQ ID NO:89)	82.4	15.75	64 (35)
49	(DCB)Q(AcK)Y QPL DEL DK(0P)T LYD QFMLQQ G (SEQ ID NO:90)	28.4	12.45	(24)
50	(DFB)Q(AcK)Y QPL DEL DK(0P)T LYD QFMLQQ G (SEQ ID NO:91)	33	13.56	(23)
51	(PyC)Q(AcK)Y QPL DEL DK(0P)T LYD QFMLQQ G (SEQ ID NO:92)	14.3	19.38	(18)
52	(Amido 2-PEG)Q(AcK)Y QPL DEL DK(0P)T LYDQFMLQQ G (SEQ ID NO:93)	133.8	18.14	(31)
53	Q(ClBnCarbamate)KY QPL DEL DK(0P)T LYD QFM LQQ G (SEQ ID NO:94)	146.9		
54	Q(AcK)Y QPL DEL D(Dab)(0P)T LYD QFM LQQ G (SEQ ID NO:95)	291.7	22	
55	Q(AcK)Y QPL DEL D(Dap)(0P)T LYD QFM LQQ G (SEQ ID NO:96)	598	34.54	
56	QNY QPL DEL DK(0P)T L(BPA)D QFM LQQ G (SEQ ID NO:97)	92.2	17.2	(29)
57	QNY QPL DEL DK(0P)T L(CF)D QFM LQQ G (SEQ ID NO:98)	110	15.3	(11)
58	QNY QPL DEL DK(0P)T LYD QFM LQQ G (SEQ ID NO:99)	36.9	12.9	(24)

59	QRY QPL DEL DK(0P)T LYD QFM LQQ G (SEQ ID NO:100)	176.8	16.1
60	QHY QPL DEL DK(0P)T LYD QFM LQQ G (SEQ ID NO:101)	214	14.4
61	Q(Nick)Y QPL DEL DK(0P)T LYD QFM LQQ G (SEQ ID NO:102)	83.9	
62	Q(AcK)Y QPL DE(AcK) DK(0P)T L(CF)D QFM LQQ G (SEQ ID NO:103)	499	41.3
63	Q(AcK)Y QPL DE(AcK) DK(0P)T LFD QFM LQQ G (SEQ ID NO:104)		

IC50 values for exemplary Ang-2 binding peptide compounds as determined by reverse competitive ELISA are presented in Table 8. IC50 values are provided for the targeting peptide plus linker (as shown in FIGURE 3) and the targeting peptide linked to an antibody (P) via the linker of FIGURE 3, unless otherwise specified. In Table 8, compounds are conjugated to humanized aldolase antibody h38c2 and the linker structures shown in FIGURE 3 (OP).

TABLE 8

Compound No.	**Sequence**	**Ang-2 P IC50 nM**	**Ang-2 T ½ Hours**
21	QKY QPL DEL DKT LYD QFM LQQ G (SEQ ID NO:21)	36.39	
22	Q(AcK)Y QPL DEL DKT LYD QFM LQQ G (SEQ ID NO:22)	14.41	
27	QKY QPL DEL DK(0P)T LYD QFM LQQ G (SEQ ID NO:68)	0.59	
28	QNY QPL DEL DK(0P)T LYD QFM LQQ G (SEQ ID NO:69)	0.15	
29	Q(AcK)Y QPL DEL DK(0P)T LYD QFM LQQ G (SEQ ID NO:70)	0.41	
30	Q(AcK)Y QPL DEK(0P) D(AcK)T LYD QFM LQQ G (SEQ ID NO:71)	1.27	72
32	Q(AcK)Y QPL DEL D(AcK)T K(0P)YD QFM LQQ G (SEQ ID NO:73)	>100	
43	Q(AcK)Y QPL DE(AcK) DK(0P)T LYD QFM LQQ G (SEQ ID NO:84)	0.92	
44	Q(AcK)Y QPL DEL DK(0P)T LFD QFM LQQ G (SEQ ID NO:85)	0.41	
48	Q(AcK)Y QPL DE(AcK) DK(0P)T L(NO2F)D QFM LQQ G (SEQ ID NO:89)	0.33	
54	Q(AcK)Y QPL DEL D(Dab)(0P)T LYD QFM LQQ G (SEQ ID NO:95)	0.09	
55	Q(AcK)Y QPL DEL D(Dap)(0P)T LYD QFM LQQ G (SEQ ID NO:96)	1.61	
64	K(0P)(AcK)Y QPL DEL D(AcK)T LYD QFM LQQ G (SEQ ID NO:105)	1.92	24

65	QK(0P)Y QPL DEL D(AcK)T LYD QFM LQQ G (SEQ ID NO:106)	0.31	12
66	Q(AcK)K(0P) QPL DEL D(AcK)T LYD QFM LQQ G (SEQ ID NO:107)	0.23	17
67	Q(AcK)Y K(0P)PL DEL D(AcK)T LYD QFM LQQ G (SEQ ID NO:108)	N.I.	
68	Q(AcK)Y QK(0P)L DEL D(AcK)T LYD QFM LQQ G (SEQ ID NO:109)	44.21	
69	Q(AcK)Y QPK(0P) DEL D(AcK)T LYD QFM LQQ G (SEQ ID NO:110)	N.I	
70	Q(AcK)Y QPL K(0P)EL D(AcK)T LYD QFM LQQ G (SEQ ID NO:111)	N.I.	
71	Q(AcK)Y QPL DK(0P)L D(AcK)T LYD QFM LQQ G (SEQ ID NO:112)	0.288	35
72	Q(AcK)Y QPL DEL K(0P)(AcK)T LYD QFM LQQ G (SEQ ID NO:113)	N.I	
73	Q(AcK)Y QPL DEL D(AcK)K(0P) LYD QFM LQQ G (SEQ ID NO:114)	0.11	56
74	Q(AcK)Y QPL DEL D(AcK)T LK(0P)D QFM LQQ G (SEQ ID NO:115)	32.82	
75	Q(AcK)Y QPL DEL D(AcK)T LYK(0P) QFM LQQ G (SEQ ID NO:116)	0.19	65
76	Q(AcK)Y QPL DEL D(AcK)T LYD K(0P)FM LQQ G (SEQ ID NO:117)	0.27	94
77	Q(AcK)Y QPL DEL D(AcK)T LYD QK(0P)M LQQ G (SEQ ID NO:118)	19.53	
78	Q(AcK)Y QPL DEL D(AcK)T LYD QFK(0P) LQQ G (SEQ ID NO:119)	0.74	72
79	Q(AcK)Y QPL DEL D(AcK)T LYD QFM K(0P)QQ G (SEQ ID NO:120)	0.077	65
80	Q(AcK)Y QPL DEL D(AcK)T LYD QFM LK(0P)Q G (SEQ ID NO:121)	0.11	35
81	Q(AcK)Y QPL DEL D(AcK)T LYD QFM LQK(0P) G (SEQ ID NO:122)	0.27	27
82	Q(AcK)Y QPL DEL D(AcK)T LYD QFM LQQ K(0P) (SEQ ID NO:123)	0.21	20

TRUNCATION STUDY

Recombinant human Ang-2 was coated on microtiter plates at 0.5 µg/mL in 100 µL, overnight at 2-8°C. Plates were washed between all steps and all subsequent incubations occurred at room temperature. Plates were blocked with 250 µL per well of SuperBlock for 1-3 hours. Test compounds were pre-mixed with compound 43 linked to linker (as shown in FIGURE 3) and h38c2 at 10ng/mL. Peptide mixtures in 100 µL were then added at the listed final concentrations, the plates sealed, and incubated for 1-2 hours. Bound compound 43 was detected with 100 µL of a 1:20,000 dilution of HRP-labeled anti-human IgG reagent for 1-2 hours. Finally, 100 µL TMB substrate was added for 10 minutes and the reaction stopped with 100 µL of 2 N H_2SO_4 stop solution. The plate was then read at 450 nm with correction at 650 nm (IC50 values shown in TABLE 9).

TABLE 9

Compound No.	Sequence	Ang-2 T IC50 nM
43(a)	ac-Q(AcK)Y QPL DE(AcK) DK(0P)T LYD QFM LQQ G-am (SEQ ID NO:191)	139
83	ac-Q(AcK)Y QPL DE(AcK) DK(0P)T LYD QFM LQQ-am (SEQ ID NO:124)	111
84	ac-Q(AcK)Y QPL DE(AcK) DK(0P)T LYD QFM LQ-am (SEQ ID NO:125)	190
85	ac-Q(AcK)Y QPL DE(AcK) DK(0P)T LYD QFM L-am (SEQ ID NO:126)	444
86	ac-Q(AcK)Y QPL DE(AcK) DK(0P)T LYD QFM-am (SEQ ID NO:127)	847
87	ac-(AcK)Y QPL DE(AcK) DK(0P)T LYD QFM LQQ G-am (SEQ ID NO:128)	>4000
88	ac- Y QPL DE(AcK) DK(0P)T LYD QFM LQQ G-am (SEQ ID NO:129)	>4000
89	ac- QPL DE(AcK) DK(0P)T LYD QFM LQQ G-am (SEQ ID NO:130)	>4000
90	ac- PL DE(AcK) DK(0P)T LYD QFM LQQ G-am (SEQ ID NO:131)	>4000

XENOGRAFT STUDIES

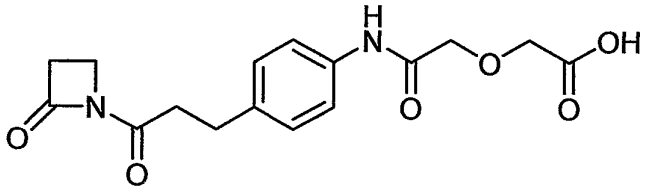
Colo205 cells were cultured with 10% FBS RPMI medium and 3 $x10^6$ cells in 0.1 ml Hank's balanced salt solution (HBSS) were injected subcutaneously into the upper right flank of nude mice. After 7-9 days, animals were randomized into appropriate number of groups with average tumor size of 200-300 mm^3. Mice were then treated with the requisite amount of compounds of the invention and tumor volumes were measured twice a week. Animals were terminated once their average tumor volume reached 2000 mm^3. Upon termination, tumors were weighed and saved for further histological studies. Treatment efficacy was evaluated by measuring the difference in the tumor volumes of treated versus control groups. Results are reported as % T/C, where % T/C was calculated as: % T/C = (Vt-V0)/(Ct-C0)X100, where, V0 and Vt were the average tumor volumes of treated groups at the beginning and termination of the group. C0 and Ct were the average tumor volumes of the control group at the beginning and termination of the group (Table 10).

TABLE 10:

Compound	Sequence	%TC 10 mg/kg 1x/wk	%TC 3 mg/kg 1x/wk	%TC 1 mg/kg 1x/wk
27	QKY QPL DEL DK(0P)T LYD QFM LQQ G (SEQ ID NO:68)	52		

28	QNY QPL DEL DK(0P)T LYD QFM LQQ G (SEQ ID NO:69)	38	34	
29	Q(AcK)Y QPL DEL DK(0P)T LYD QFM LQQ G (SEQ ID NO:70)	60	28	9
43	Q(AcK)Y QPL DE(AcK) DK(0P)T LYD QFM LQQ G (SEQ ID NO:84)	53	27	34
44	Q(AcK)Y QPL DEL DK(0P)T LFD QFM LQQ G (SEQ ID NO:85)	40	22	
45	Q(AcK)Y Q(HP)L DE(ThA) DK(0P)T L(NO2F)D QFM LQQ G (SEQ ID NO:86)	47		
48	Q(AcK)Y QPL DE(AcK) DK(0P)T L(NO2F)D QFM LQQ G (SEQ ID NO:89)	45		
58	QNY QPL DEL DK(0P)T LYD QFM LQQ G (SEQ ID NO:99)	51		
92	PL DEL DK(0P)T LYD QFM LQQ G (SEQ ID NO:192)	60		

EXAMPLE 29: Synthesis of:



is provided in FIGURE 28.

The invention thus has been disclosed broadly and illustrated in reference to representative embodiments described above. Those skilled in the art will recognize that various modifications can be made to the present invention without departing from the spirit and scope thereof. All publications, patent applications, and issued patents, are herein incorporated by reference to the same extent as if each individual publication, patent application or issued patent were specifically and individually indicated to be incorporated by reference in its entirety. Definitions that are contained in text incorporated by reference are excluded to the extent that they contradict definitions in this disclosure.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable sub-combination.

It is specifically contemplated that any limitation discussed with respect to one embodiment of the invention may apply to any other embodiment of the invention. Furthermore, any composition of the invention may be used in any method of the invention, and any method of the invention may be used to produce or to utilize any composition of the invention. In particular, any aspect of the invention described in the claims, alone or in combination owth one or more additional claims and/or aspects of the description, is to be understood as being combinable with other aspects of the invention set out elsewhere in the claims and/or description.

The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternative are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and "and/or."

As used herein the specification, "a" or "an" may mean one or more, unless clearly indicated otherwise. As used herein in the claim (s), when used in conjunction with the word "comprising, "the words "a" or "an" may mean one or more than one. As used herein "another" may mean at least a second or more.

The words “comprises/comprising” and the words “having/including” when used herein with reference to the present invention are used to specify the presence of stated features, integers, steps or components but does not preclude the presence or addition of one or more other features, integers, steps, components or groups thereof.

The claims defining the invention are as follows:

1. An anti-angiogenic (AA) targeting agent comprising a peptide comprising the sequence:

R^1-Q^1 $(A_cK)^2$ Y^3 Q^4 P^5 L^6 D^7 $E^8$$(A_cK)^9$ D^{10} K^{11} T^{12} L^{13} Y^{14} D^{15} Q^{16} F^{17} M^{18} L^{19} Q^{20} Q^{21} G^{22}-R^2

(SEQ ID NO: 43)

wherein

R^1 is CH_3, $C(O)CH_3$, $C(O)CH_3$, $C(O)CH_2CH_3$, $C(O)CH_2CH_2CH_3$, $C(O)CH(CH_3)CH_3$, $C(O)CH_2CH_2CH_2CH_3$, $C(O)CH(CH_3)CH_2CH_3$, $C(O)C_6H_5$, $C(O)CH_2CH_2(CH_2CH_2O)_{1-5}Me$, dichlorobenzoyl (DCB), difluorobenzoyl (DFB), pyridinyl carboxlate (PyC) or amido-2-PEG, an amino protecting group, a lipid fatty acid group or a carbohydrate; and

R^2 is OH, NH_2, $NH(CH_3)$, $NHCH_2CH_3$, $NHCH_2CH_2CH_3$, $NHCH(CH_3)CH_3$, $NHCH_2CH_2CH_2CH_3$, $NHCH(CH_3)CH_2CH_3$, NHC_6H_5, $NHCH_2CH_2OCH_3$, $NHOCH_3$, $NHOCH_2CH_3$, a carboxy protecting group, a lipid fatty acid group or a carbohydrate, and wherein one of Q^1, E^8, $(A_cK)^9$, K^{11}, T^{12}, D^{15}, Q^{16}, M^{18}, L^{19} or G^{22} is substituted by a linking residue comprising a nucleophilic side chain covalently linkable to the combining site of an antibody directly or via an intermediate linker, the linking residue being selected from the group comprising K, Y, T, homologs of lysine, homocysteine, homoserine, Dap, and Dab, or the N-terminus or C-terminus.

2. An AA targeting agent as claimed in claim 1, wherein one of $(A_cK)^9$, and K^{11} is substituted by the linking residue, and preferably K^{11} is substituted by the linking residue.

3. An AA targeting agent as claimed in any preceding claim, wherein the linking residue is K.

4. An AA targeting agent as claimed in any preceding claim, wherein R^1 is $C(O)CH_3$.

5. An AA targeting agent as claimed in any preceding claim, wherein R^2 is NH_2.

6. A compound having the formula:

L – [AA targeting agent] or

L' - [AA targeting agent]

wherein:

[AA targeting agent] is an AA targeting agent as claimed in any preceding claim, and

L is a linker moiety having the formula -X-Y-Z-, and L' is a linear or branched linker moiety having the formula -X-Y-Z', and wherein:

X is attached to the AA targeting agent via the amino terminus, carboxy terminus or side chain of the linking residue, and is a biologically compatible connecting chain including any

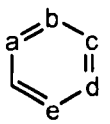
atom selected from the group consisting of C, H, N, O, P, S, F, CL, Br, and I, and may comprise a polymer or block co-polymer,

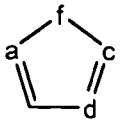
Y is an optionally present recognition group comprising at least a ring structure; and

Z is a reactive group that is capable of forming a covalent bond with an amino acid side chain in a combining site of an antibody and

Z' is an attachment moiety comprising a covalent link to an amino acid side in a combining site of an antibody.

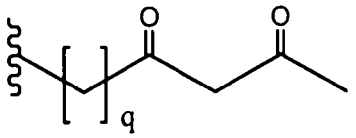
7. The compound according to claim 6, wherein the ring structure Y has the optionally substituted structure:

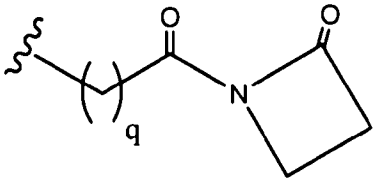


or


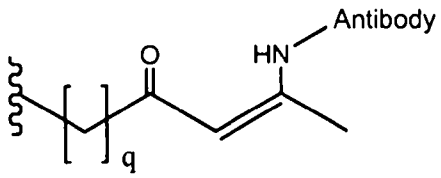
wherein a, b, c, d, and e are independently carbon or nitrogen; f is carbon, nitrogen, oxygen, or sulfur; Y is attached to X and Z independently at any two ring positions of sufficient valence; and no more than four of a, b, c, d, e, or f are simultaneously nitrogen and preferably a, b, c, d, and e in the ring structure are each carbon, and Y may be phenyl.

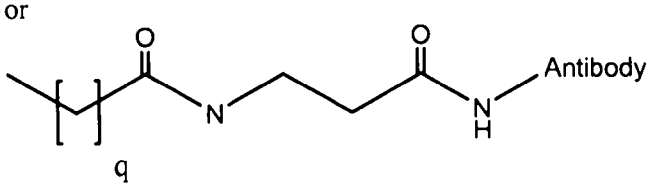
8. The compound according to any one of claims 6-7, wherein Z or Z' if present is substituted alkyl, substituted cycloalkyl, substituted aryl, substituted arylalkyl, substituted heterocyclyl, or substituted heterocyclylalkyl, wherein at least one substituent is a 1,3-diketone moiety, an acyl beta-lactam, an active ester, an alpha-haloketone, an aldehyde, a maleimide, a lactone, an anhydride, an alpha-haloacetamide, an amine, a hydrazide, or an epoxide---, and wherein Z if present may have the structure:



or


and wherein Z' if present may have the structure:



or


wherein q=0-5 and Antibody-N- if present is a covalent bond to a side chain in a combining site of an antibody.

9. A compound as claimed in any one of claims 6-8, wherein

X is attached to the linking residue, is substituted or unsubstituted and is selected from -R^{22} - $[CH_2\text{-}CH_2\text{-}O]_t$ - R^{23}-, -R^{22}-cycloalkyl- R^{23}-, -R^{22}-aryl- R^{23}-, or -R^{22}-heterocyclyl-R^{23}-, wherein:

R^{22} and R^{23} are independently a covalent bond, -O-, -S-, -NR^b-, substituted or unsubstituted straight or branched chain $C_{1\text{-}50}$ alkylene, substituted or unsubstituted straight or branched chain $C_{1\text{-}50}$ heteroalkylene, substituted or unsubstituted straight or branched chain $C_{2\text{-}50}$ alkenylene, or substituted or unsubstituted $C_{2\text{-}50}$ heteroalkenylene;

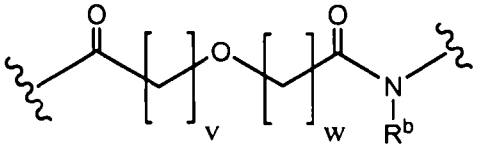
R^b, at each occurrence, is independently hydrogen, substituted or unsubstituted $C_{1\text{-}10}$ alkyl, substituted or unsubstituted $C_{3\text{-}7}$ cycloalkyl-$C_{0\text{-}6}$ alkyl, or substituted or unsubstituted aryl-$C_{0\text{-}6}$ alkyl;

t = 2-50;

and the size of R^{22} and R^{23} are such that the backbone length of X remains about 200 atoms or less;

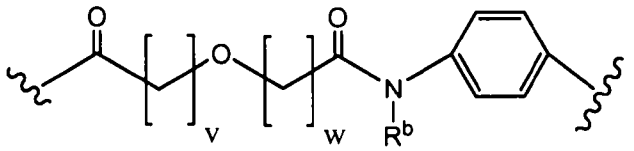
10. A compound as claimed in any one of claims 6-9, wherein:

X is:



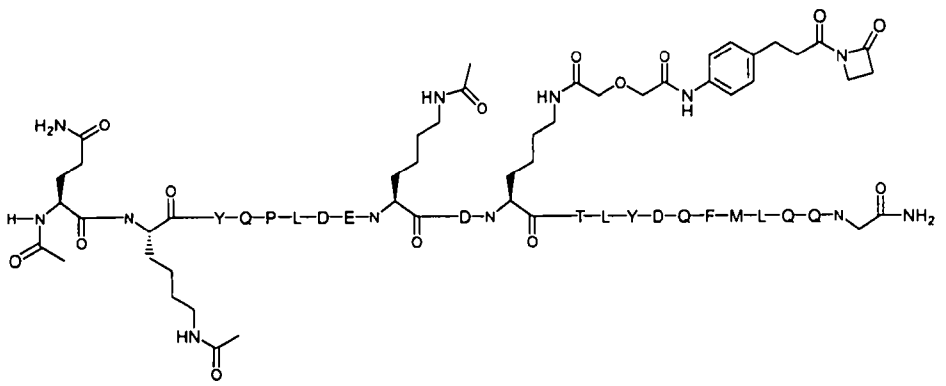
wherein R^b is hydrogen, substituted or unsubstituted $C_{1\text{-}10}$ alkyl, substituted or unsubstituted $C_{3\text{-}7}$ cycloalkyl-$C_{0\text{-}6}$ alkyl, or substituted or unsubstituted aryl-$C_{0\text{-}6}$ alkyl, and v and w are selected such that the backbone length of X is 6-12 atoms;

11. A compound as claimed in claim 10, wherein X-Y is:



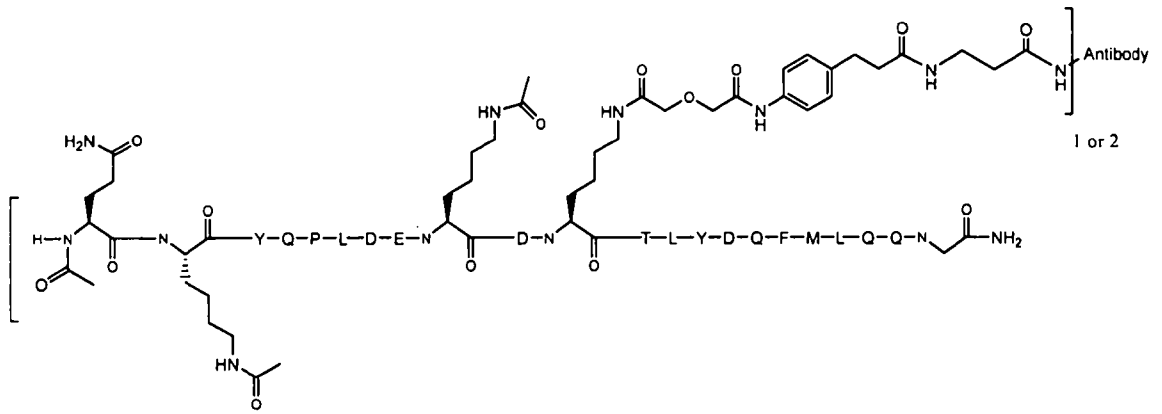
v=1 or 2; w=1 or 2; R^b is hydrogen.

12. A compound as claimed in any one of claims 6-11, having the formula



13. A compound as claimed in any one of claims 6-12, wherein the Z group is covalently linked to the combining site of an Antibody.

14. A compound as claimed in claim 13, having a structure:



15. A compound as claimed in any one of claims 13-14, wherein the Antibody is a catalytic antibody, and is preferably an aldolase catalytic antibody.

16. The compound according to any one of claims 13-15, wherein said Antibody is a full length antibody, Fab, Fab', $F(ab')_2$, F_v, dsF_v, scF_v, V_H, diabody, or minibody comprising V_H and V_L domains from h38c2, or is an antibody comprising the V_H and V_L domains from h38c2 and a constant domain selected from the group consisting of IgG1, IgG2, IgG3, and IgG4, or is an antibody comprising SEQ ID NO:189 and SEQ ID NO:190

17. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of claims 6-16 or an AA targeting agent as claimed in any one of claims 1-5.

18. The pharmaceutical composition of claim 17, further comprising a therapeutically effective amount of one or more chemotherapeutic agent, the chemotherapeutic agent preferably being a compound selected from the group consisting of 5-Flurouracil, irinotecan, oxilaplatin, bevacizumab, and cetuximab.

19. Use of an AA targeting agent as claimed in any one of claims 1-5 or a compound as claimed in any one of claims 6-16, or a pharmaceutical composition as claimed in any one of claims 17-18, in a method of inhibiting or reducing angiogenesis or for treating or preventing a disease or symptom associated with an angiogenic disorder, particularly abnormal angiogenesis or an angiogenesis-mediated condition in a subject, including arthritis, psoriasis, angiogenesis of the eye associated with infection or surgical intervention, macular degeneration , diabetic retinopathy, and cancer; including carcinomas of the breast, colon, rectum, lung, oropharynx, hypopharynx, esophagus, stomach, pancreas, liver, gallbladder and bile ducts, small intestine, urinary tract, female genital tract, male genital tract, endocrine glands, and skin; hemangiomas; melanomas; sarcomas; tumors of the brain, nerves, eyes, and meninges; leukemia; or lymphoma.

20. An Anti-Antigenic compound as claimed in any one of claims 1-5, a compound as claimed in any one of claims 6-16, a pharmaceutical composition as claimed in any one of claims 17-18, or a use as claimed in any one of claims 28-29, substantially as described herein with reference to the accompanying figures, description and sequence listing.

Dated 21 January, 2011
CovX Technologies Ireland Limited
Patent Attorneys for the Applicant/Nominated Person
SPRUSON & FERGUSON

FIGURE 1

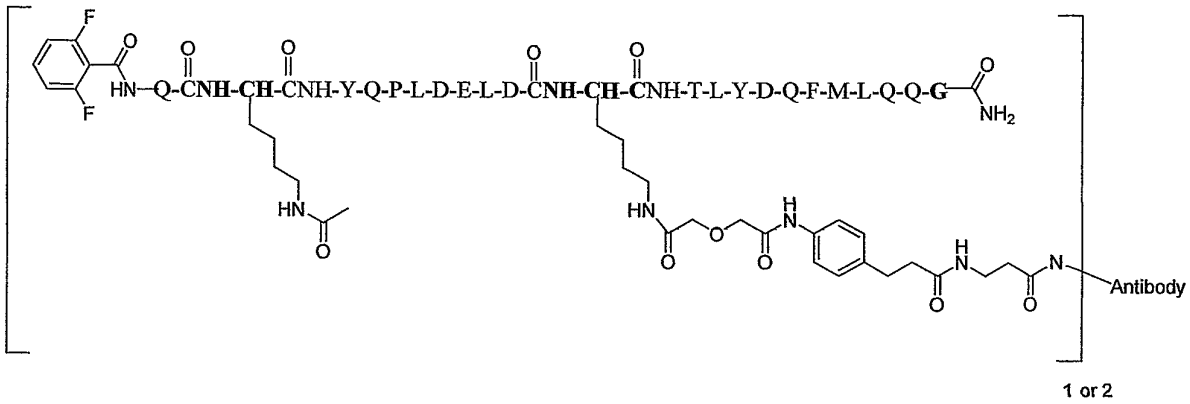

F
F
HN—Q-CNH-CH-CNH-Y-Q-P-L-D-E-L-D-CNH-CH-CNH-T-L-Y-D-Q-F-M-L-Q-Q-G
NH2
HN
HN
Antibody
1 or 2

FIGURE 2

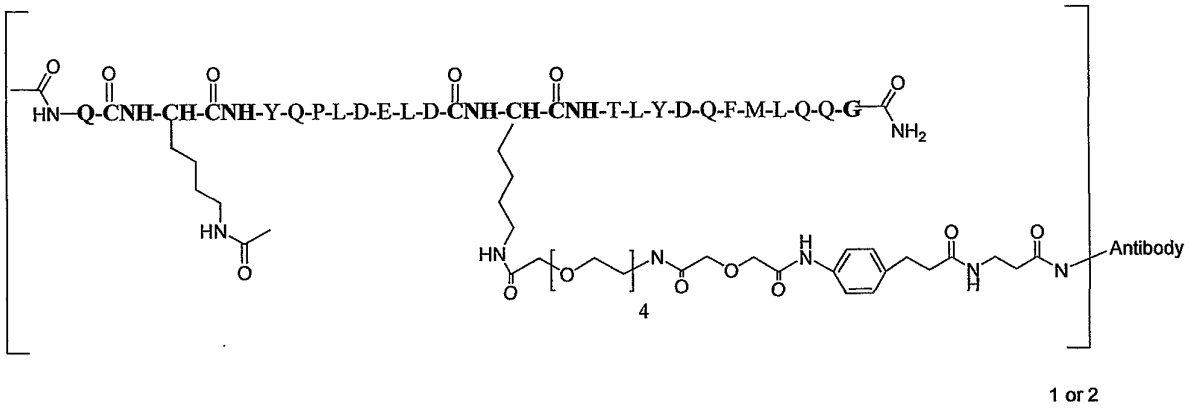

HN—Q-CNH-CH-CNH-Y-Q-P-L-D-E-L-D-CNH-CH-CNH-T-L-Y-D-Q-F-M-L-Q-Q-G
NH2
HN
HN
4
Antibody
1 or 2

FIGURE 3

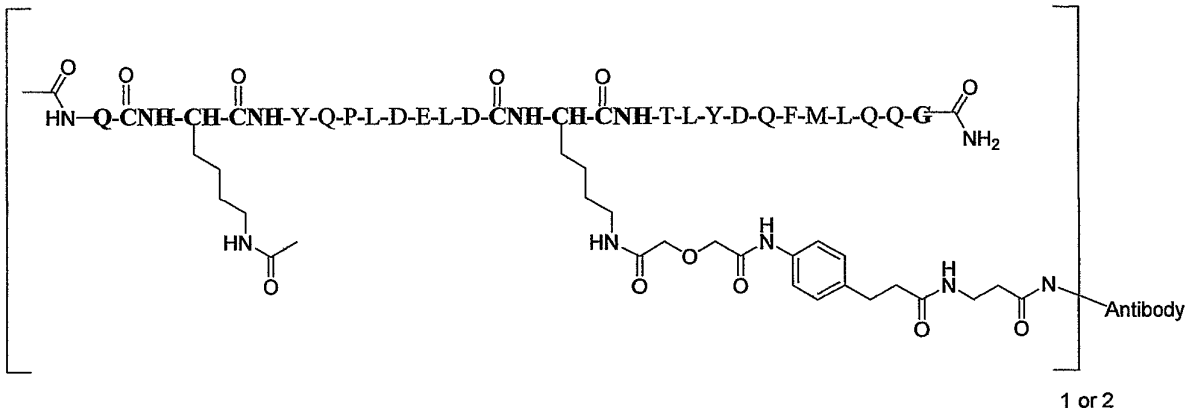

HN-Q-CNH-CH-CNH-Y-Q-P-L-D-E-L-D-CNH-CH-CNH-T-L-Y-D-Q-F-M-L-Q-Q-G
NH2
HN
HN
Antibody
1 or 2

FIGURE 4A

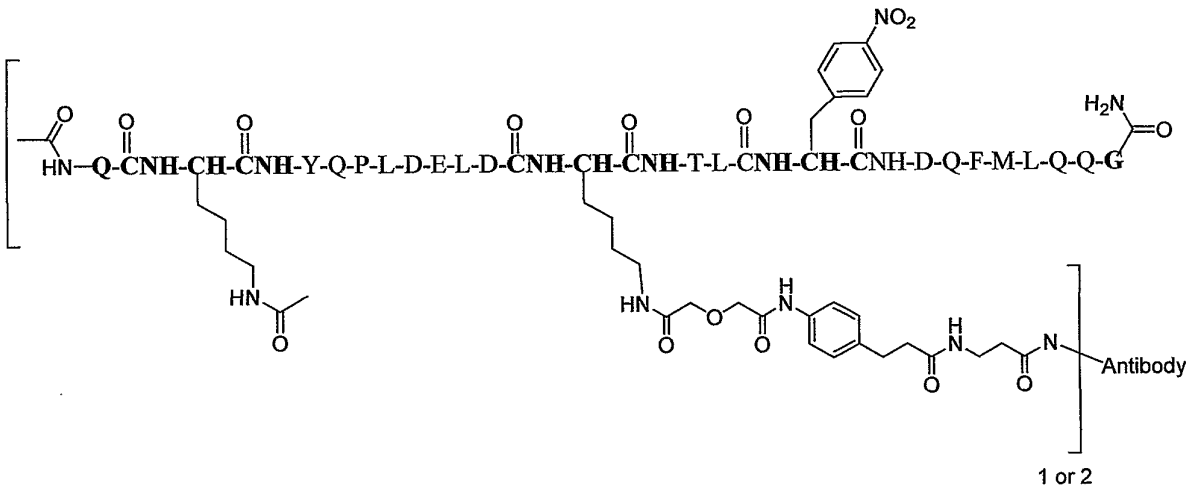


FIGURE 4B

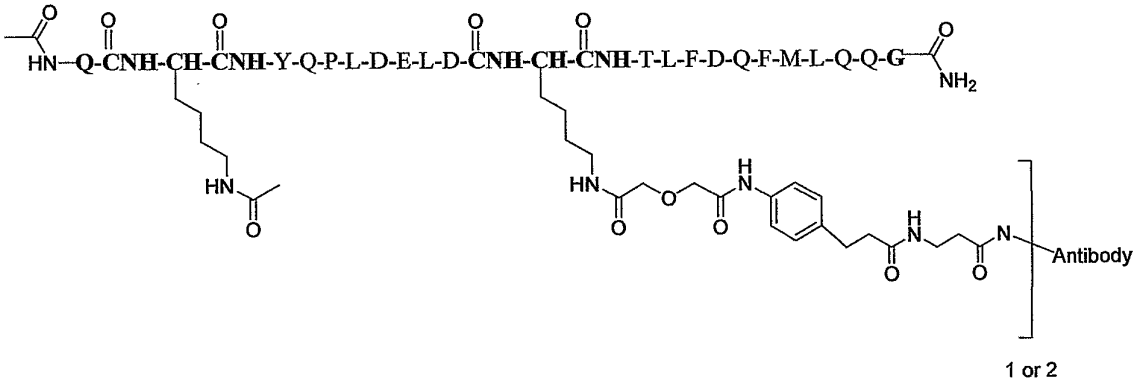


FIGURE 5A

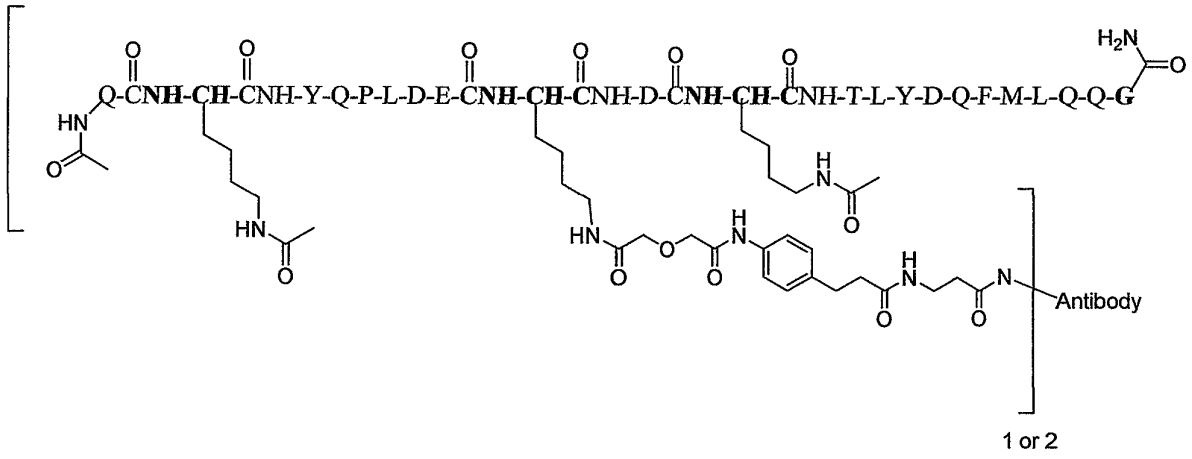


FIGURE 5B

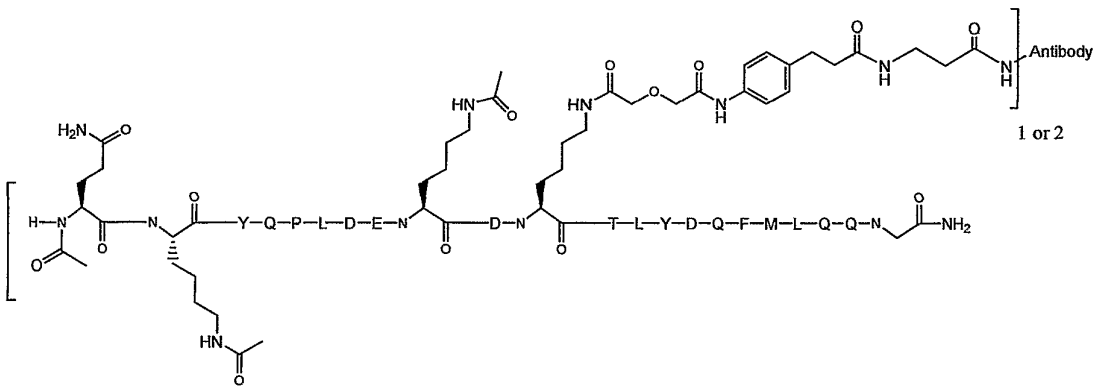


FIGURE 6A

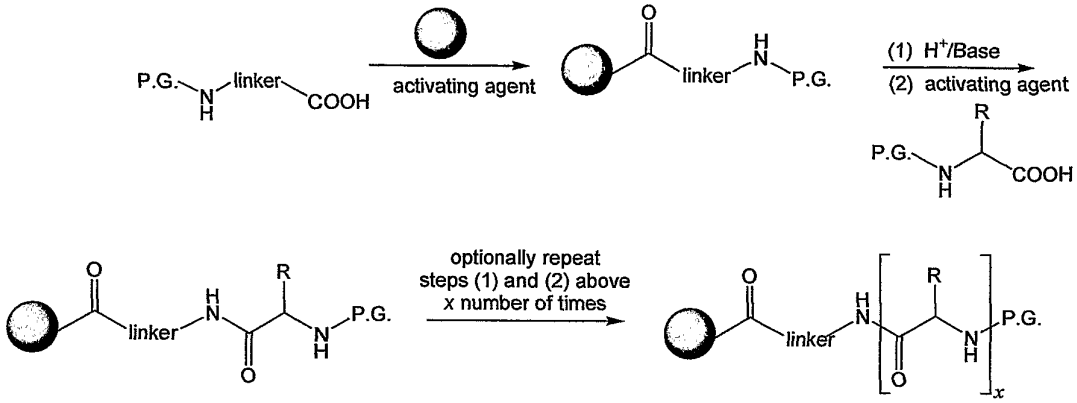


FIGURE 6B

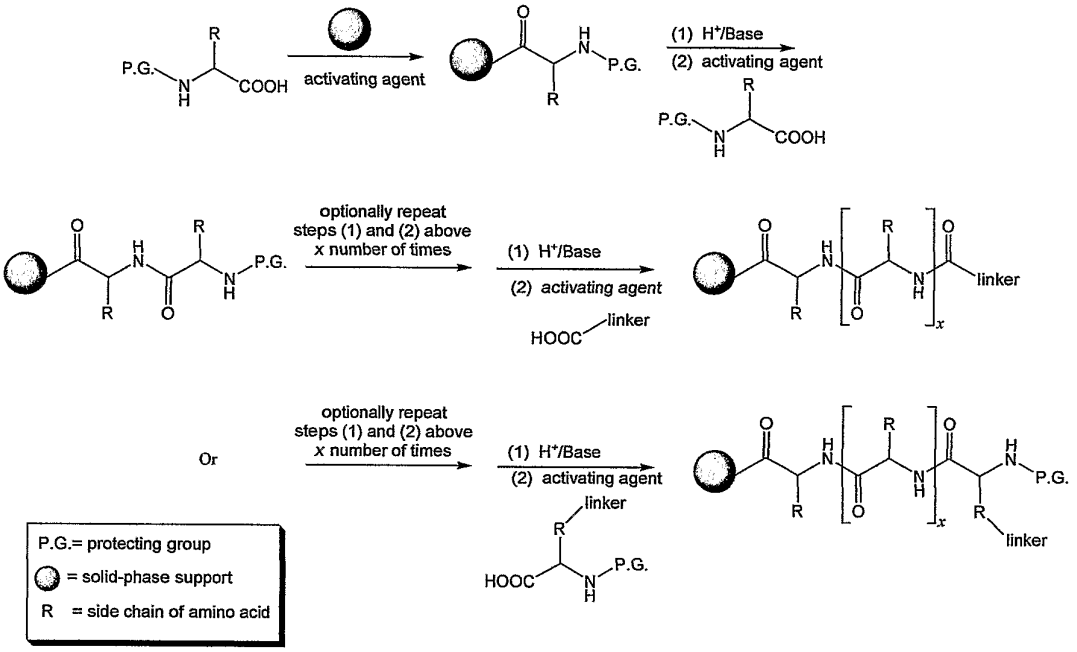


FIGURE 7A

```
VL
               FR1                   CDR1          FR2       CDR2             FR3                 CDR3    FR4
                                                                                                             1
               1         2         3                4          5      6         7         8         9         0
      12345678901234567890123 45678901abcde234 567890123456789 0123456 78901234567890123456789012345678 901234567 8901234567

m38C2 DVVMTQTPLSLPVRLGDQASISC RSSQSLLHTYGSPYLN WYLQKPGQSPKLLIY KVSNRFS GVPDRFSGSGSGTDFTLRISRVEAEDLGVYFC SQGTHLPYT FGGGTKLEIK
      ***   * *  ****  *** *                                         *             *  ****  **                    *
h38C2 ELQMTQSPSSLSASVGDRVTITC RSSQSLLHTYGSPYLN WYLQKPGQSPKLLIY KVSNRFS GVPSRFSGSGSGTDFTLTISSLQPEDFAVYFC SQGTHLPYT FGGGTKVEIK
      **                        *   ********      *    **     ** ***                             * *  * **** *

DPK-9 DIQMTQSPSSLSASVGDRVTITC RASQSISS-----YLN WYQQKPGKAPKLLIY AASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQSYSTP
JK4                                                                                                        LT FGGGTKVEIK


VH
                 FR1                   CDR1    FR2            CDR2                      FR3                   CDR3   FR4
                                                                                                                1      1
               1         2         3          4          5             6         7         8             9        0      1
      123456789012345678901234567890 1ab2345 678901234567890 012abc3456789012345 6789012345678901 2abc345678901234 56789012 34567890123
m38C2 EVKLVESGGGLVQPGGTMKLSCEISGLTFR N--YWMS WVRQSPEKGLEWVA EIRLRSDNYATHYAESVKG KFTISRDDSKSRLYLQMNSLRTEDTGIYYCKT YFY-SFSY WGQGTLVTVSA
        *            ***   **  *  *                   *                        *     *  **          *                        *
h38C2 EVOLVESGGGLVQPGGSLRLSCAASGFTFS N--YWMS WVRQSPEKGLEWVS EIRLRSDNYATHYAESVKG RFTISRDNSKNTLYLQMNSLRAEDTGIYYCKT YFY-SFSY WGQGTLVTVSS
          *                         *   *      * *       * **  **** *  *                            **   **      * *

DP-47 EVQLLESGGGLVQPGGSLRLSCAASGFTFS S--YAMS WVRQAPGKGLEWVS AISG--SGGSTYYADSVKG RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK
JH4                                                                                                              YFDY WGQGTLVTVSS
```

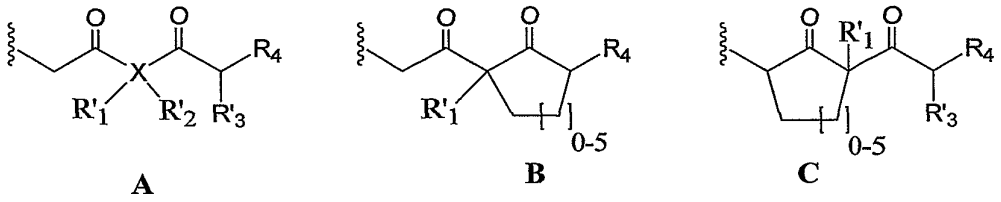
FIGURE 7B

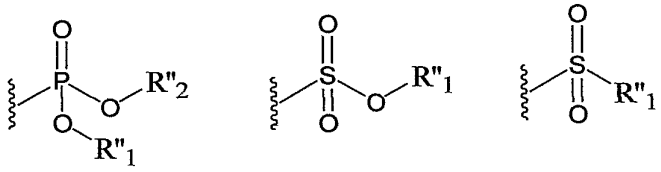
Light Chain (219 amino acids):
ELQMTQSPSSLSASVGDRVTITCRSSQSLLHTYGSPYLNWYLQKPGQSPKLLIYKVSNRFSGV
PSRFSGSGSGTDFTLTISSLQPEDFAVYFCSQGTHLPYTFGGGTKVEIKRTVAAPSVFIFPPSDE
QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA
DYEKHKVYACEVTHQGLSSPVTKSFNRGEC

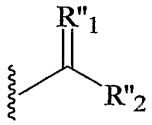
Heavy chain (448 amino acids):
EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMSWVRQSPEKGLEWVSEIRLRSDNYATH
YAESVKGRFTISRDNSKNTLYLQMNSLRAEDTGIYYCKTYFYSFSYWGQGTLVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKG
FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH
NHYTQKSLSLSPGK

FIGURE 8

Linker Reactive Groups

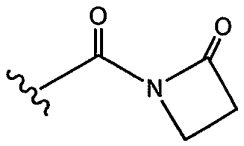




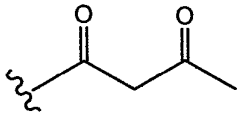


G

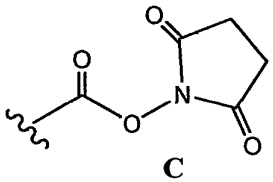
FIGURE 9



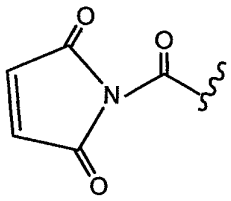
A



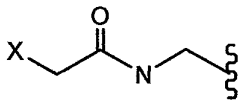
B



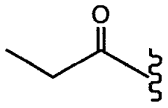
C



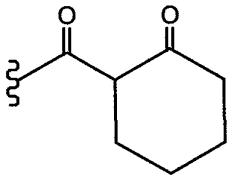
D



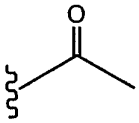
E



F



G



H

FIGURE 10

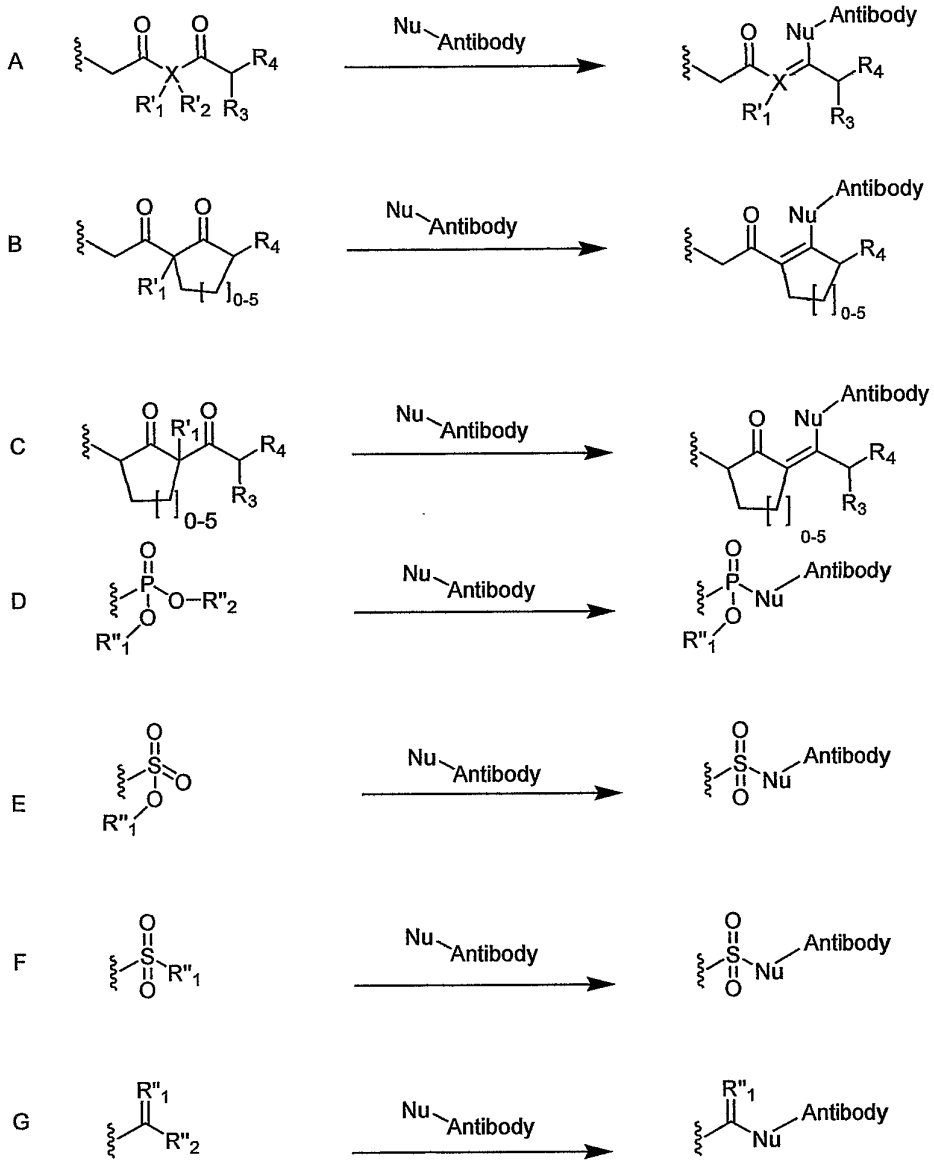


FIGURE 11

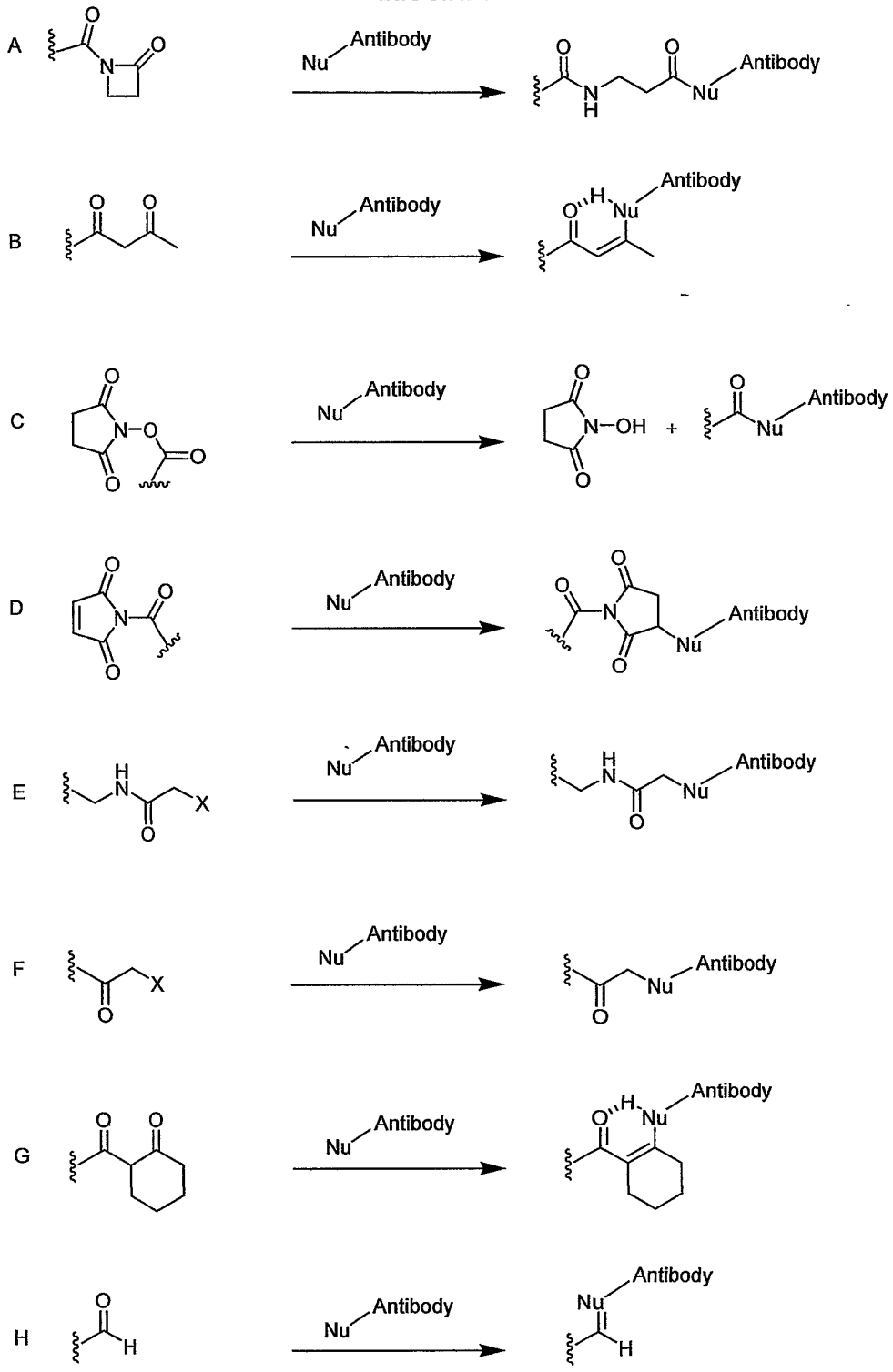


FIGURE 12

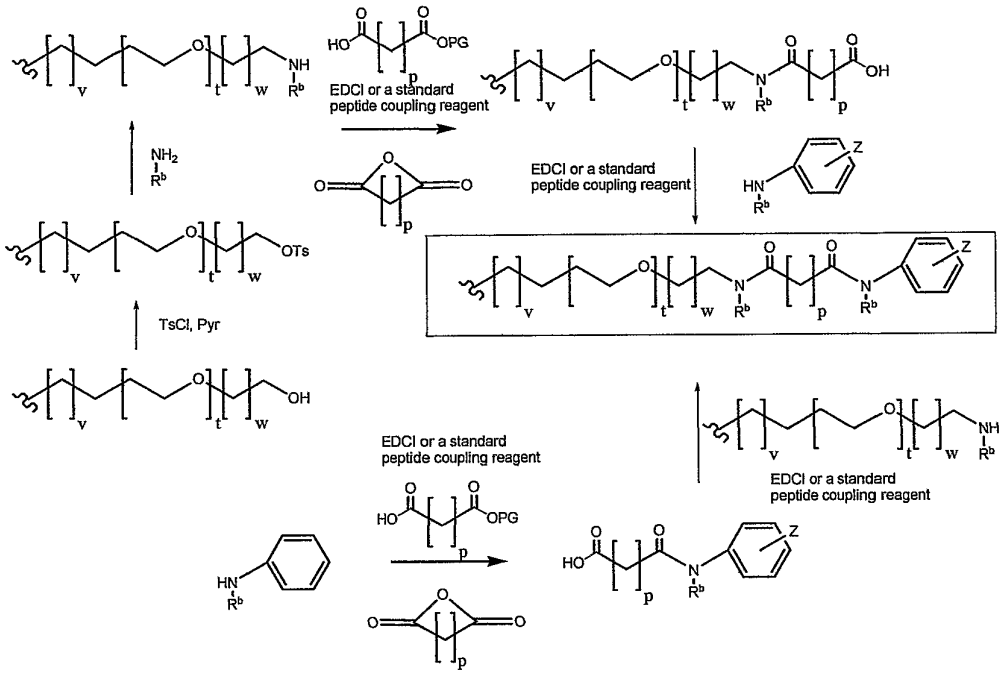

EDCI or a standard peptide coupling reagent
EDCI or a standard peptide coupling reagent
EDCI or a standard peptide coupling reagent
EDCI or a standard peptide coupling reagent
TsCl, Pyr

FIGURE 13

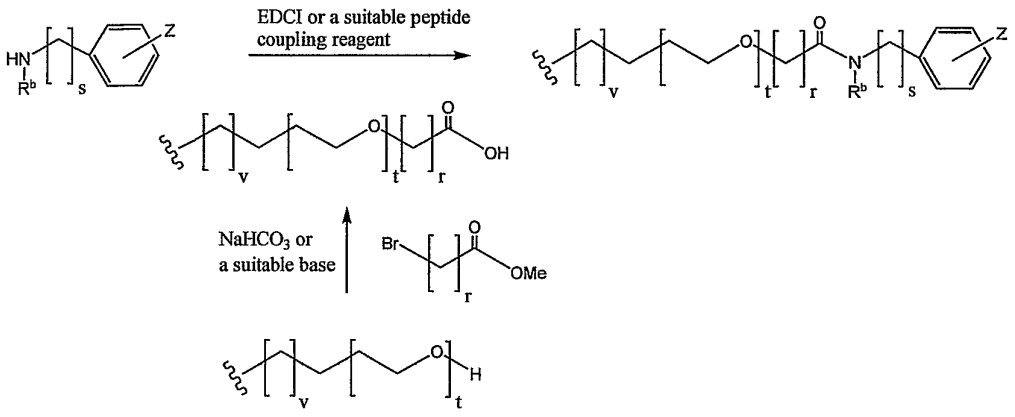

EDCI or a suitable peptide coupling reagent
NaHCO3 or a suitable base

FIGURE 14

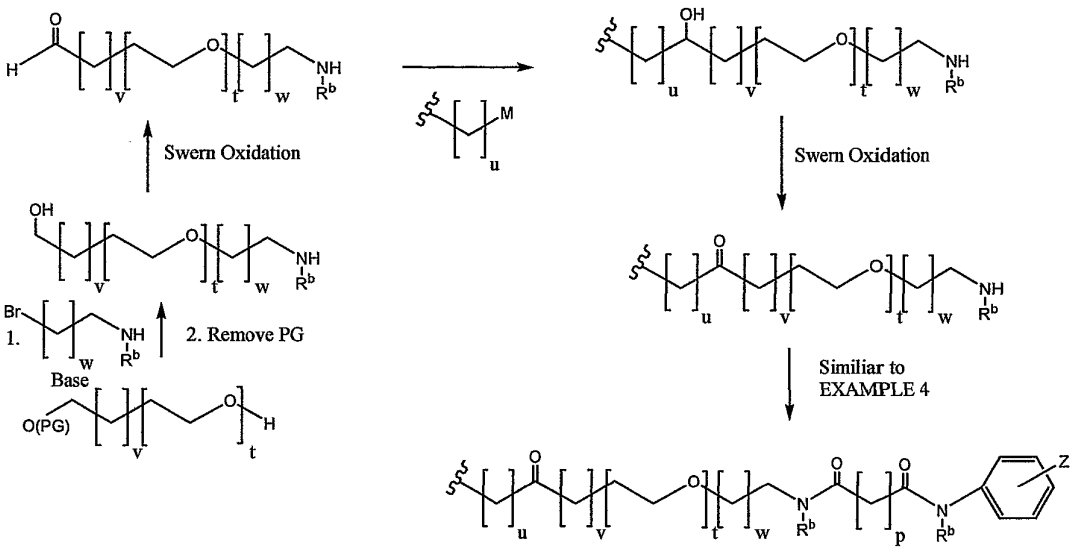

Swern Oxidation
Swern Oxidation
1.
2. Remove PG
Base
Similiar to
EXAMPLE 4

FIGURE 15

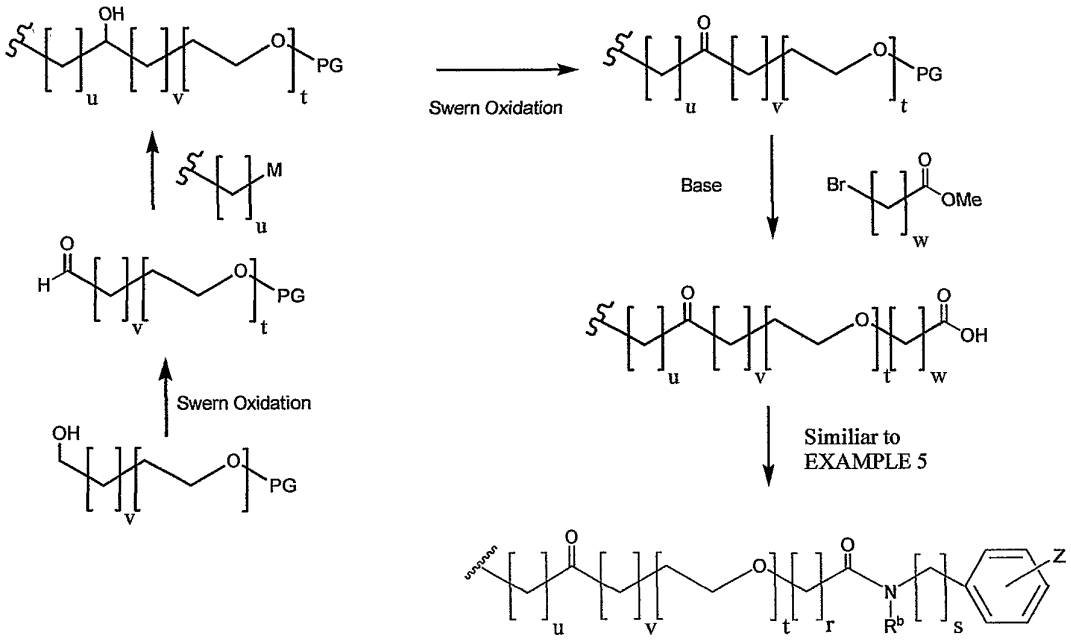

OH
PG
u
v
t
Swern Oxidation
M
H
O
Base
Br
OMe
w
OH
Similiar to
EXAMPLE 5
Z
N
Rb
s
r

FIGURE 16

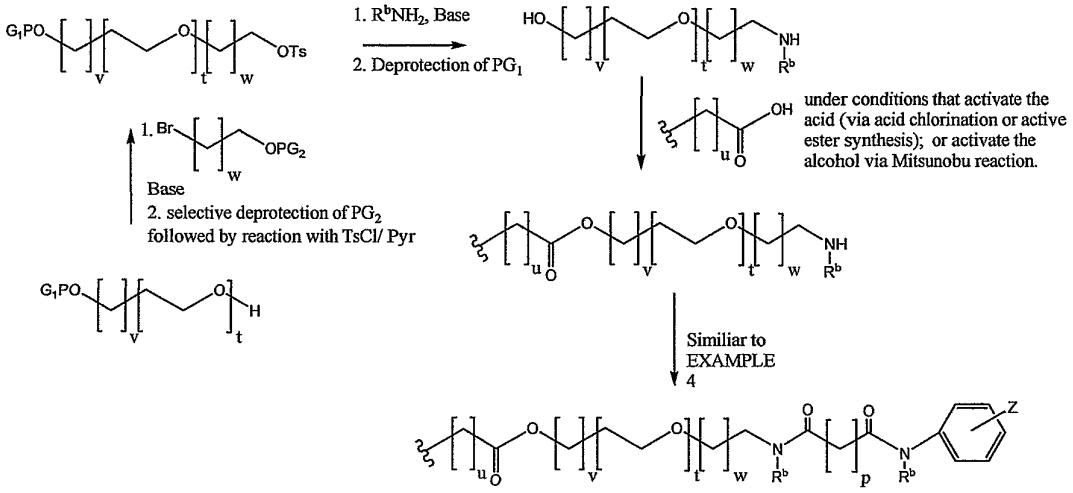

1. R^bNH_2, Base
2. Deprotection of PG_1
under conditions that activate the acid (via acid chlorination or active ester synthesis); or activate the alcohol via Mitsunobu reaction.
1. Br
Base
2. selective deprotection of PG_2 followed by reaction with TsCl/ Pyr
Similiar to EXAMPLE 4

FIGURE 17

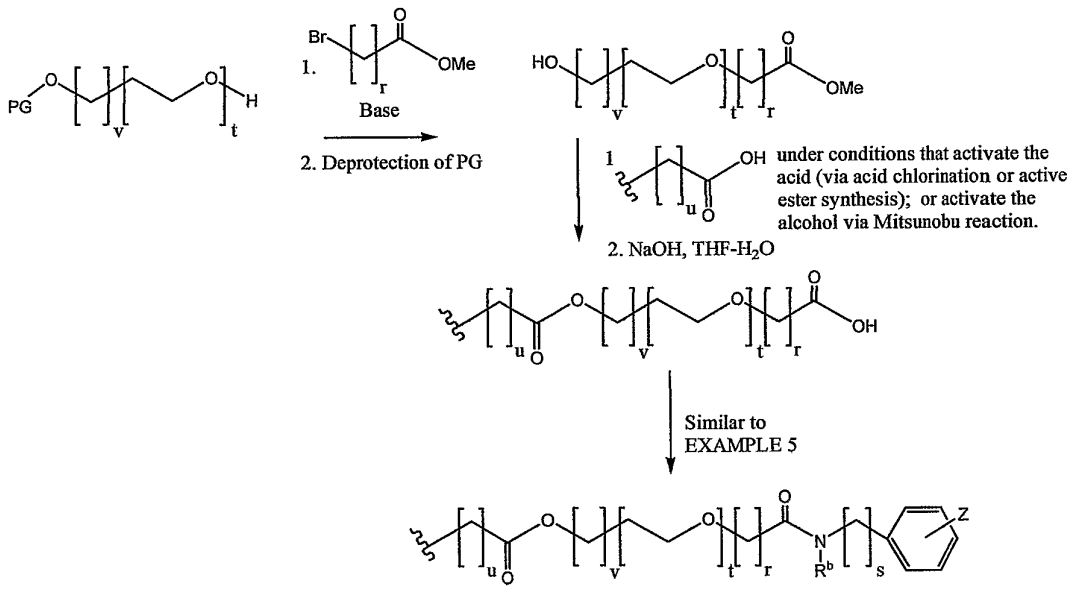

PG
H
Br
OMe
1.
Base
2. Deprotection of PG
HO
OMe
OH
under conditions that activate the acid (via acid chlorination or active ester synthesis); or activate the alcohol via Mitsunobu reaction.
2. NaOH, THF-H2O
OH
Similar to EXAMPLE 5
Z

FIGURE 18

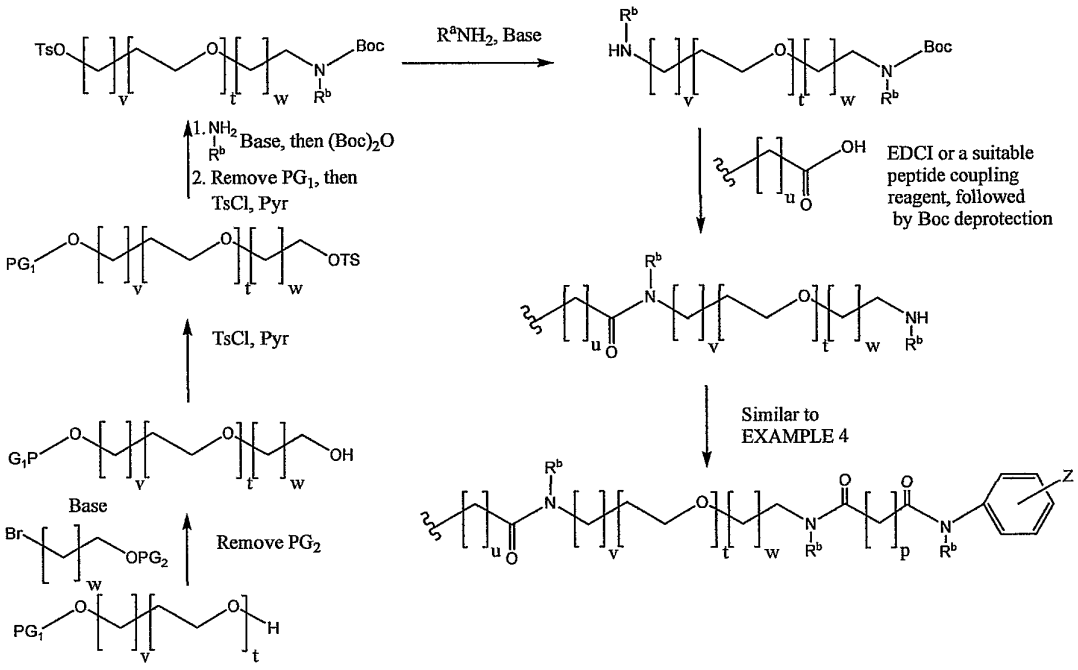

TsO
Boc
R^aNH_2, Base
1. NH_2R^b Base, then $(Boc)_2O$
2. Remove PG_1, then TsCl, Pyr
PG_1
OTS
TsCl, Pyr
G_1P
OH
Base
Br
OPG_2
Remove PG_2
PG_1
H
OH
EDCI or a suitable peptide coupling reagent, followed by Boc deprotection
NH
Similar to EXAMPLE 4
Z

FIGURE 19

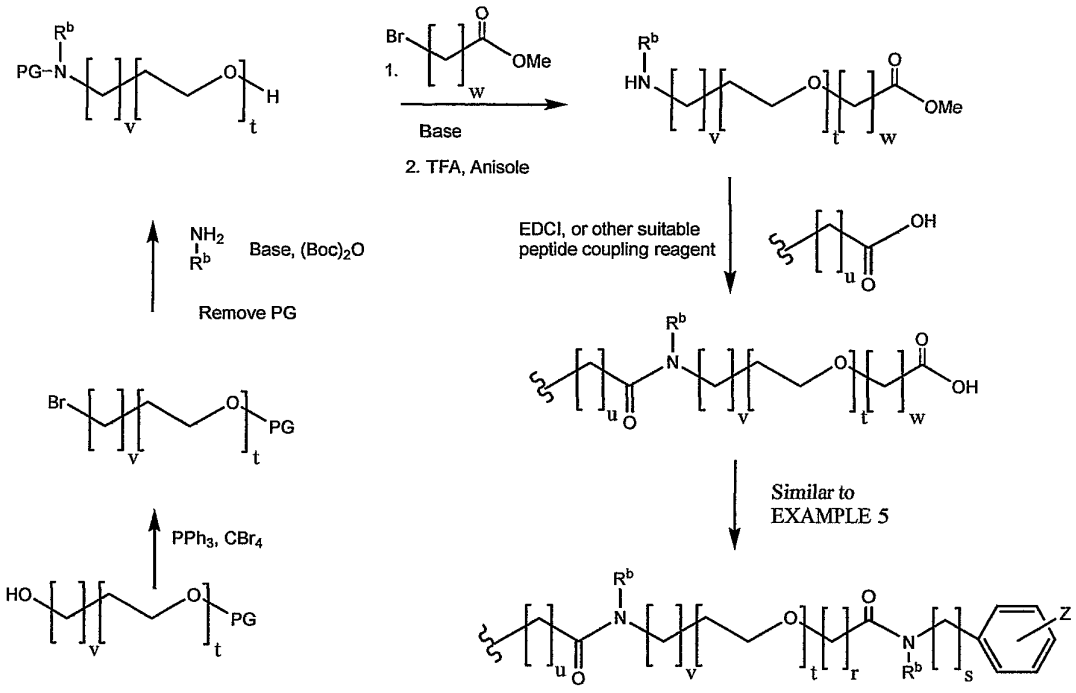

1.
Base
2. TFA, Anisole
EDCI, or other suitable peptide coupling reagent
Base, (Boc)2O
Remove PG
PPh3, CBr4
Similar to EXAMPLE 5

FIGURE 20

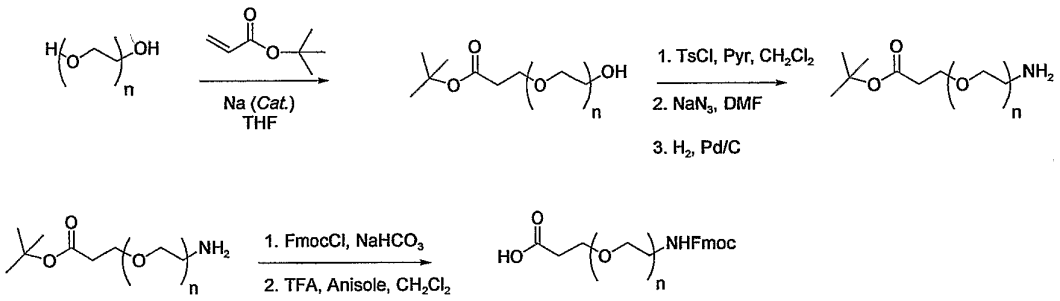

Na (Cat.)
THF
1. TsCl, Pyr, CH2Cl2
2. NaN3, DMF
3. H2, Pd/C
1. FmocCl, NaHCO3
2. TFA, Anisole, CH2Cl2

FIGURE 21

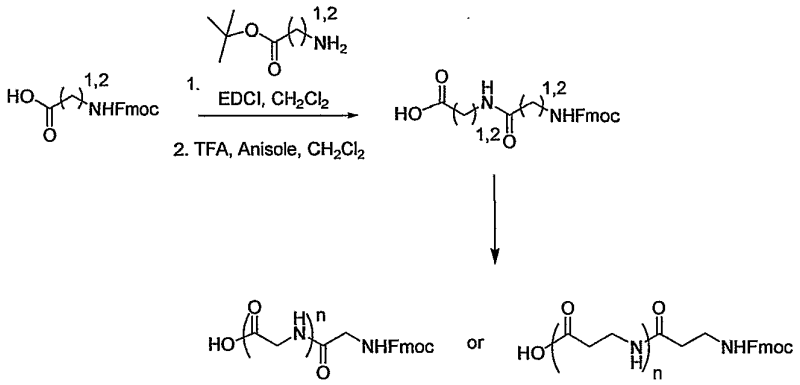

1,2
NH2
HO
1,2
NHFmoc
1.
EDCI, CH2Cl2
2. TFA, Anisole, CH2Cl2
HO
1,2
NHFmoc
HO
n
NHFmoc
or
HO
n
NHFmoc

FIGURE 22

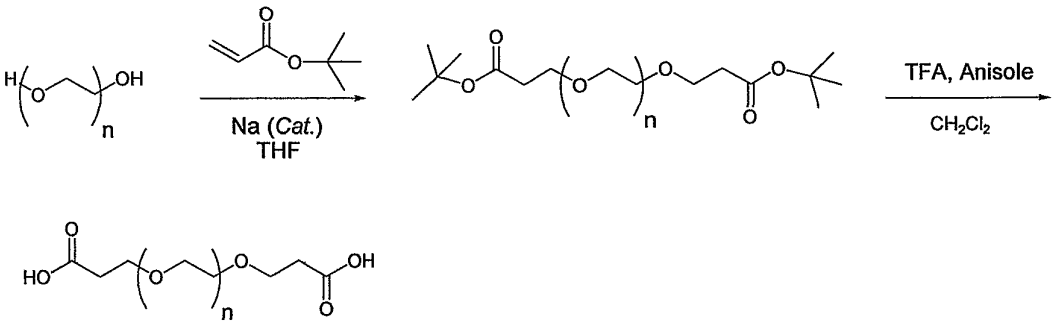


FIGURE 23

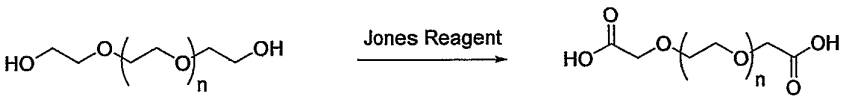


FIGURE 24

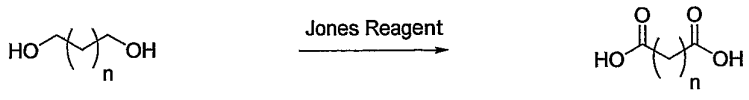


FIGURE 25

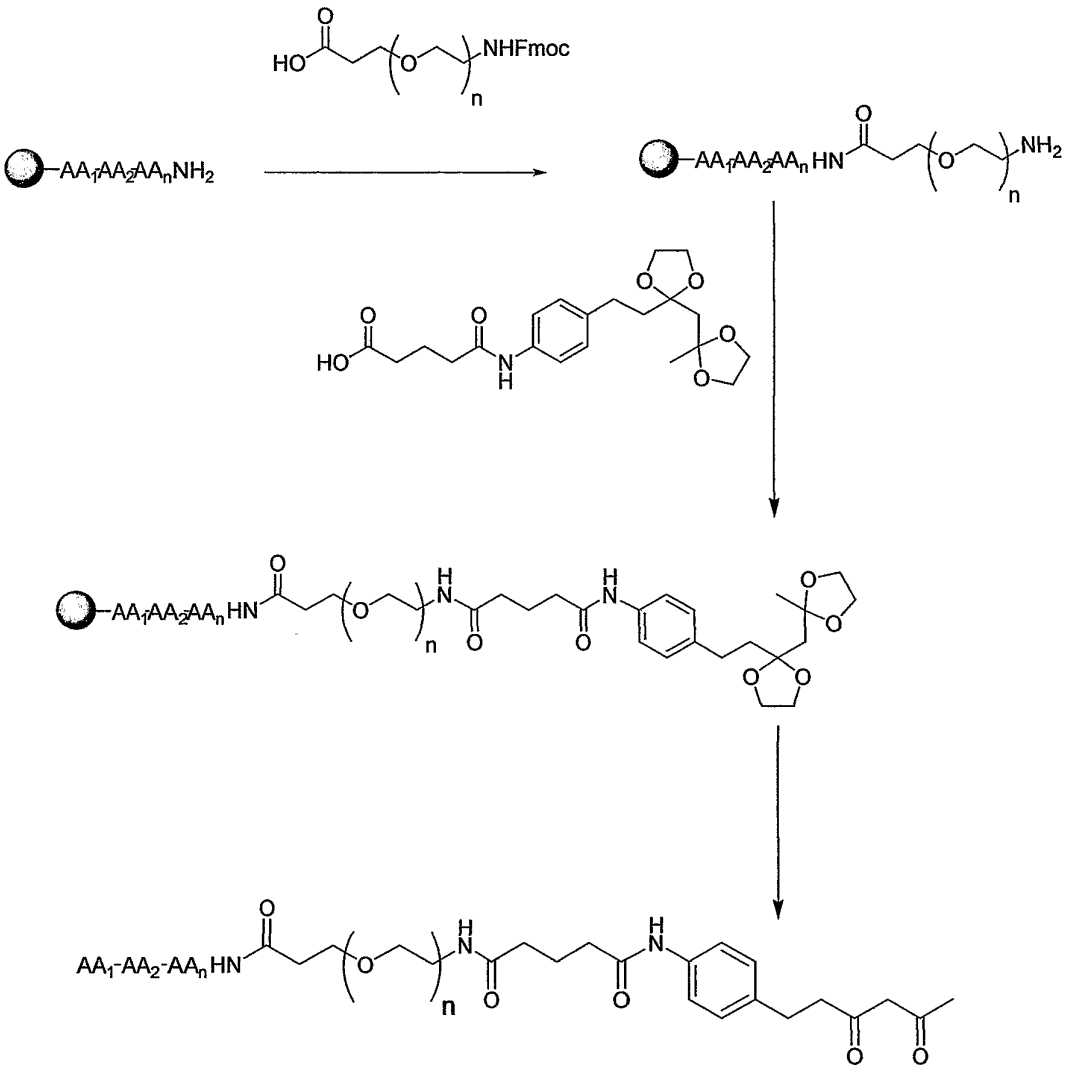

HO
O
NHFmoc
n
AA1AA2AAnNH2
AA1AA2AAn HN
NH2
HO
N
H
AA1AA2AAn HN
AA1-AA2-AAn HN

FIGURE 26

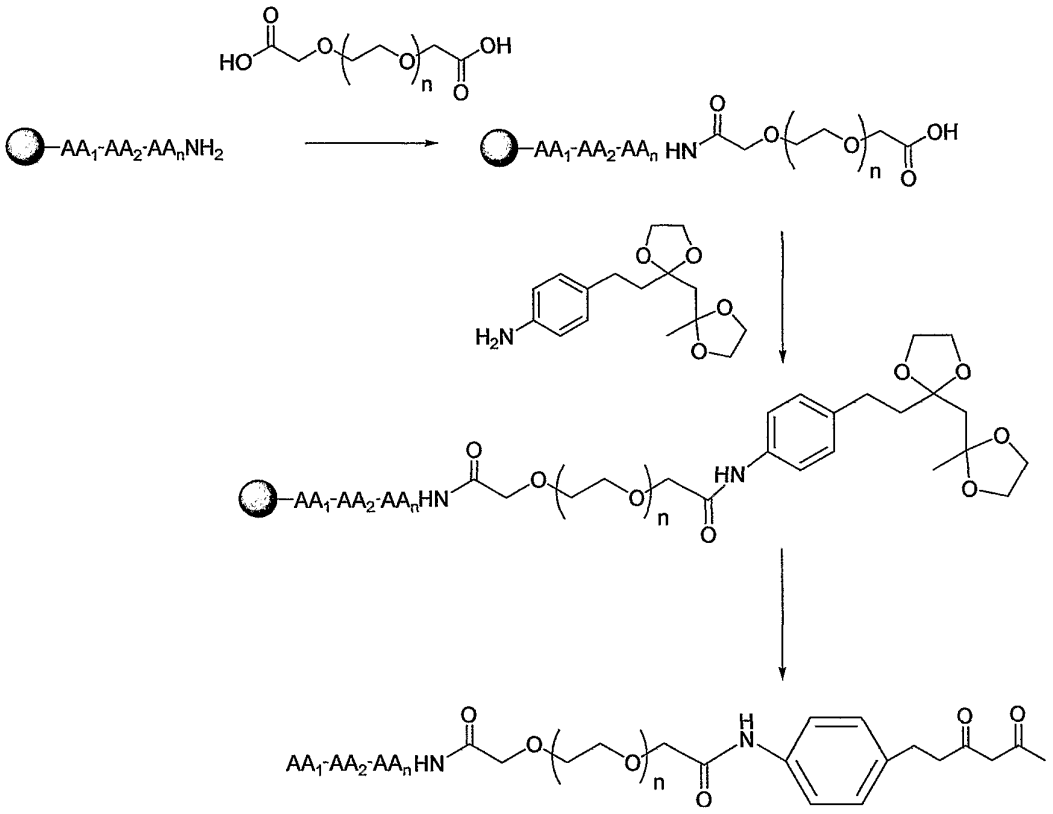

HO
OH
n
AA1-AA2-AAnNH2
AA1-AA2-AAn HN
H2N
AA1-AA2-AAnHN
HN
AA1-AA2-AAnHN
H
N

FIGURE 27

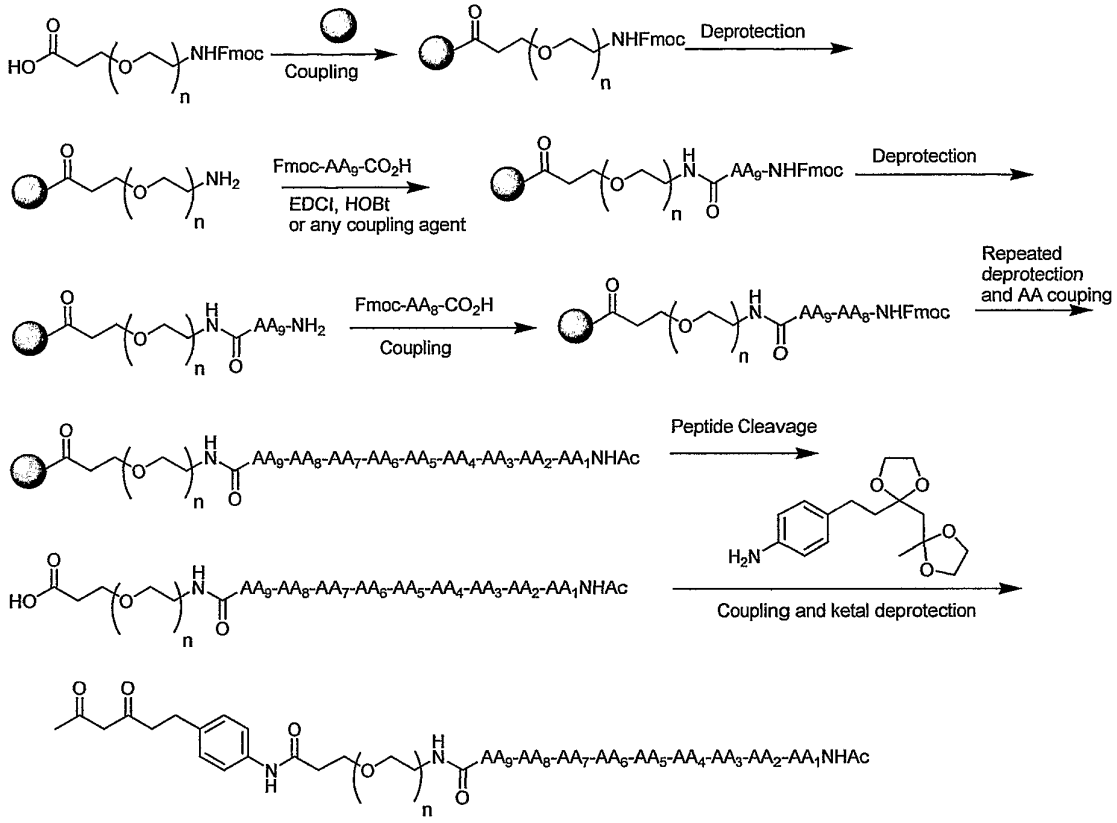

NHFmoc
Coupling
NHFmoc
Deprotection
NH2
Fmoc-AA9-CO2H
EDCI, HOBt
or any coupling agent
AA9-NHFmoc
Deprotection
AA9-NH2
Fmoc-AA8-CO2H
Coupling
AA9-AA8-NHFmoc
Repeated
deprotection
and AA couping
AA9-AA8-AA7-AA6-AA5-AA4-AA3-AA2-AA1NHAc
Peptide Cleavage
H2N
AA9-AA8-AA7-AA6-AA5-AA4-AA3-AA2-AA1NHAc
Coupling and ketal deprotection
AA9-AA8-AA7-AA6-AA5-AA4-AA3-AA2-AA1NHAc

FIGURE 28

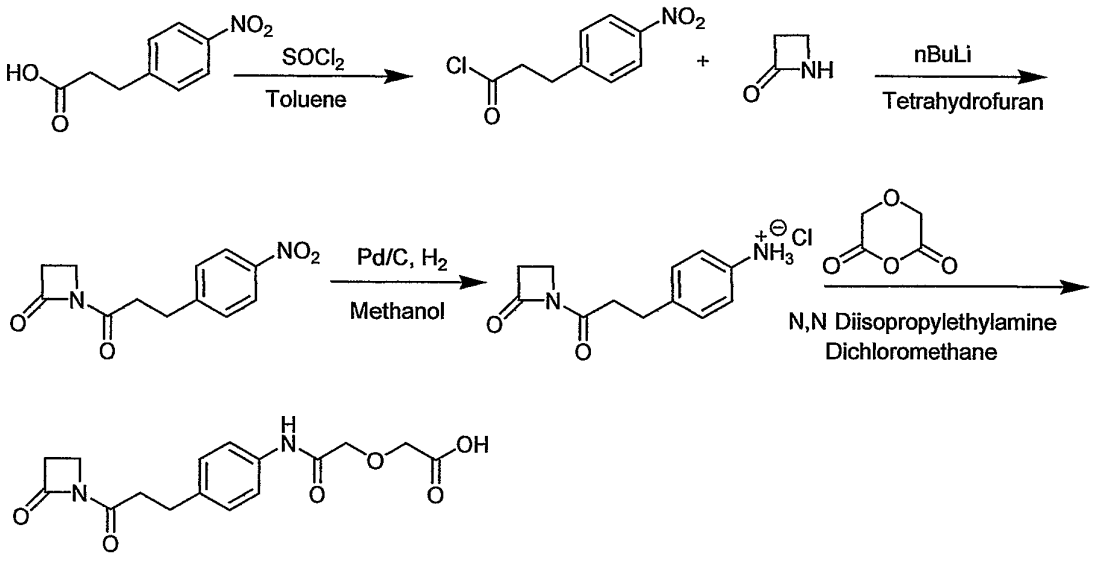

NO2
HO
O
SOCl2
Toluene
NO2
Cl
O
+
NH
O
nBuLi
Tetrahydrofuran
NO2
N
O
O
Pd/C, H2
Methanol
+NH3 Cl⊖
N
O
O
O
O
O
N,N Diisopropylethylamine
Dichloromethane
H
N
O
O
OH
N
O
O

FIGURE 29

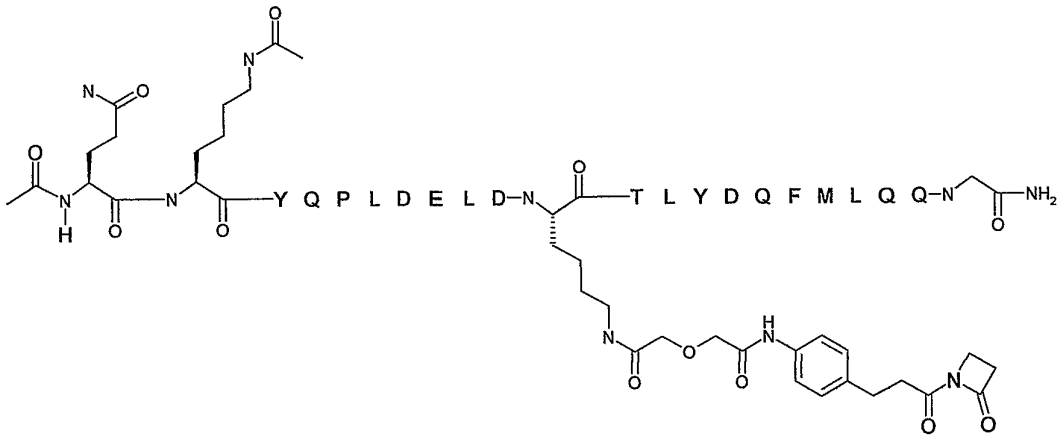


FIGURE 30

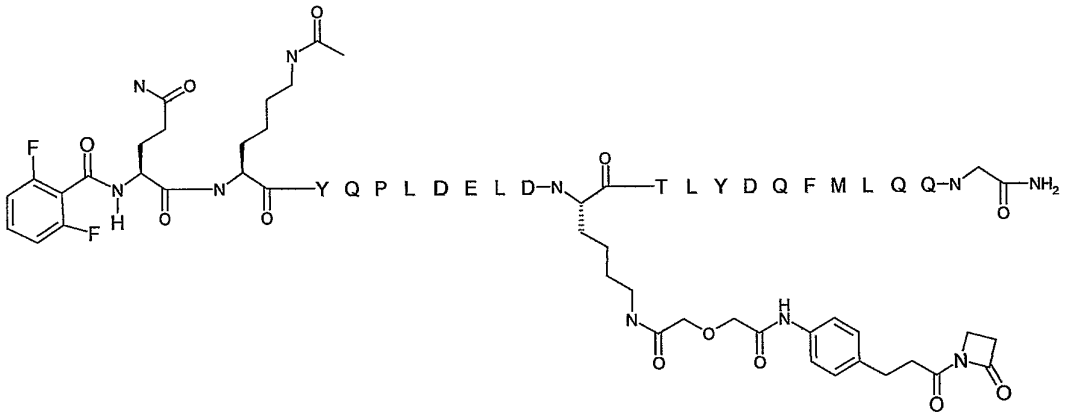


FIGURE31

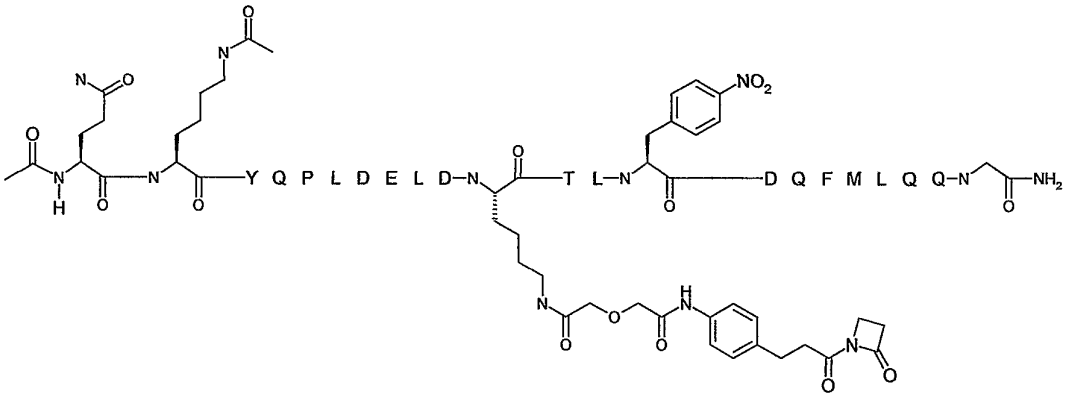


FIGURE 32

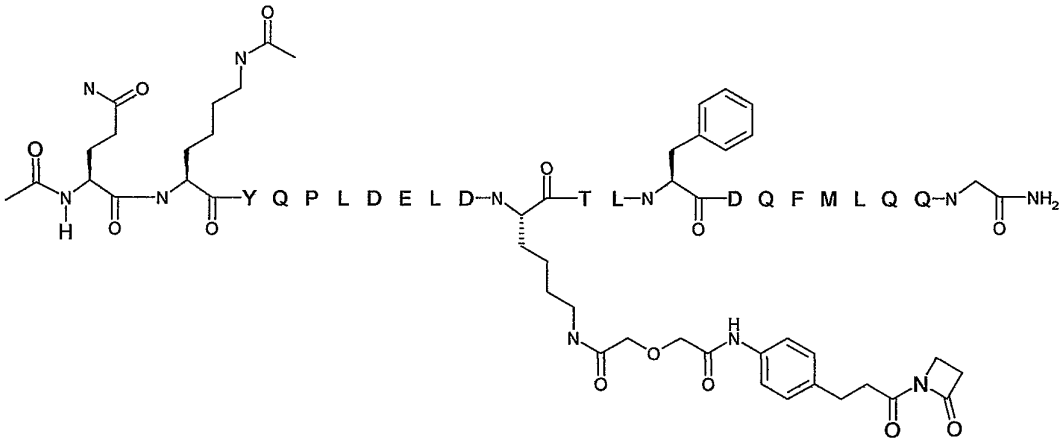


FIGURE 33

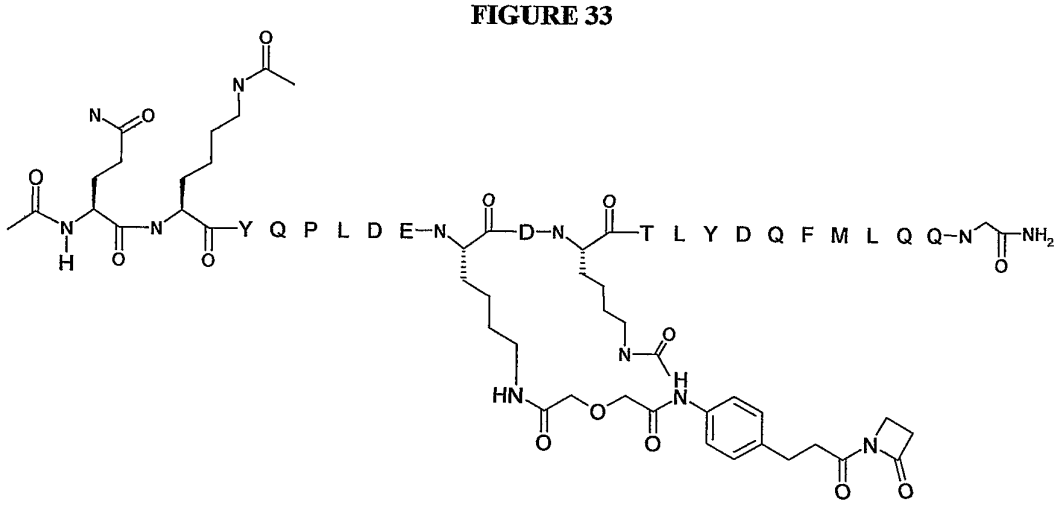


FIGURE 34

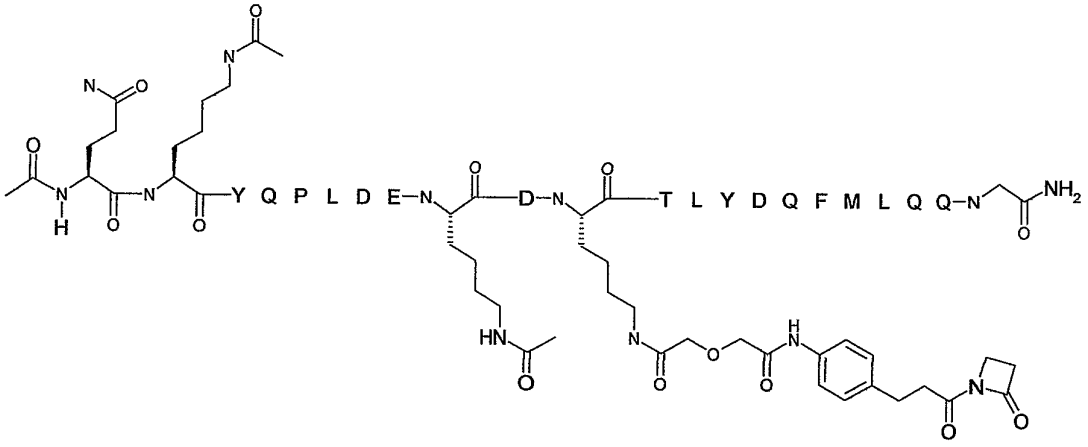


Figure 35

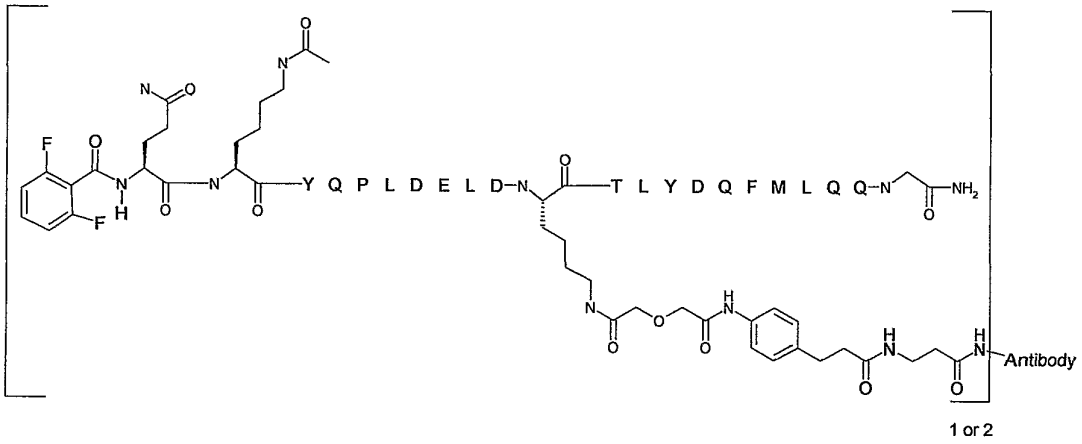


Figure 36

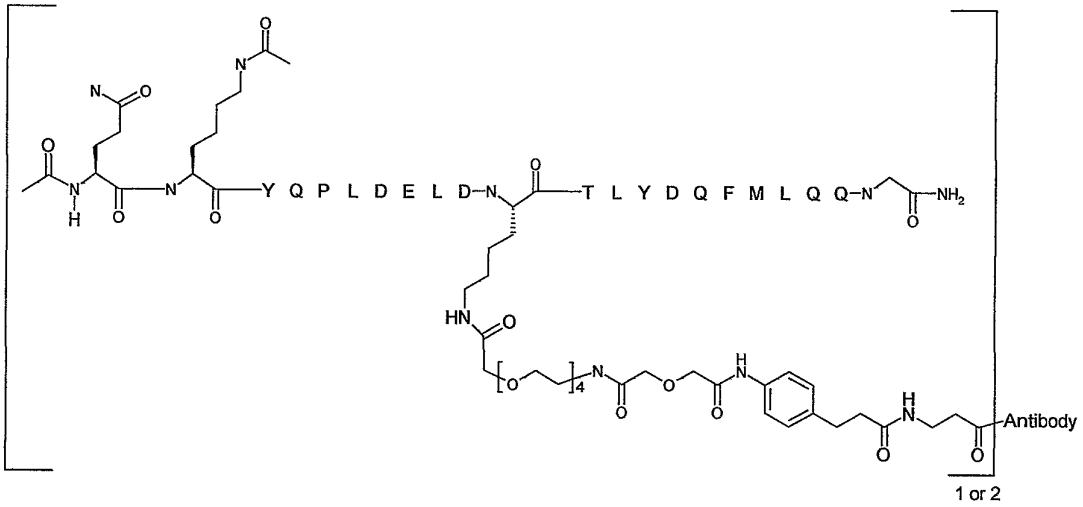


Figure 37

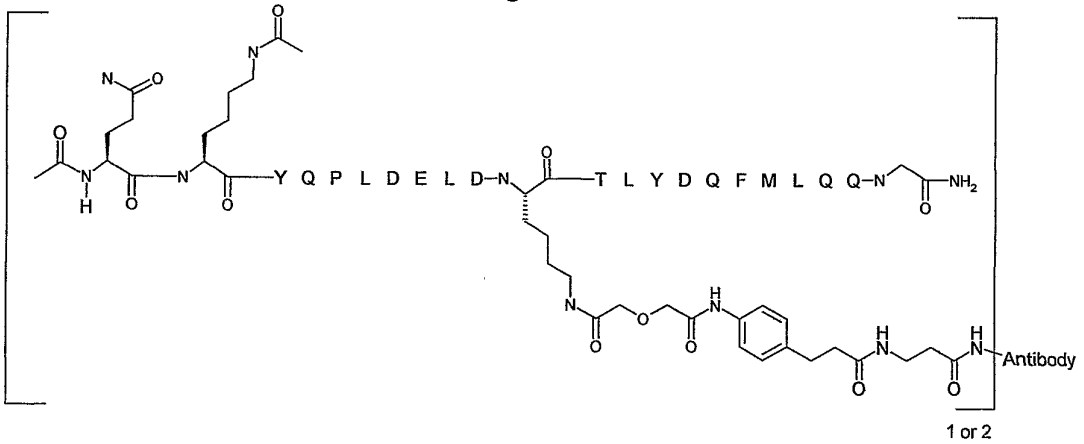


Figure 38

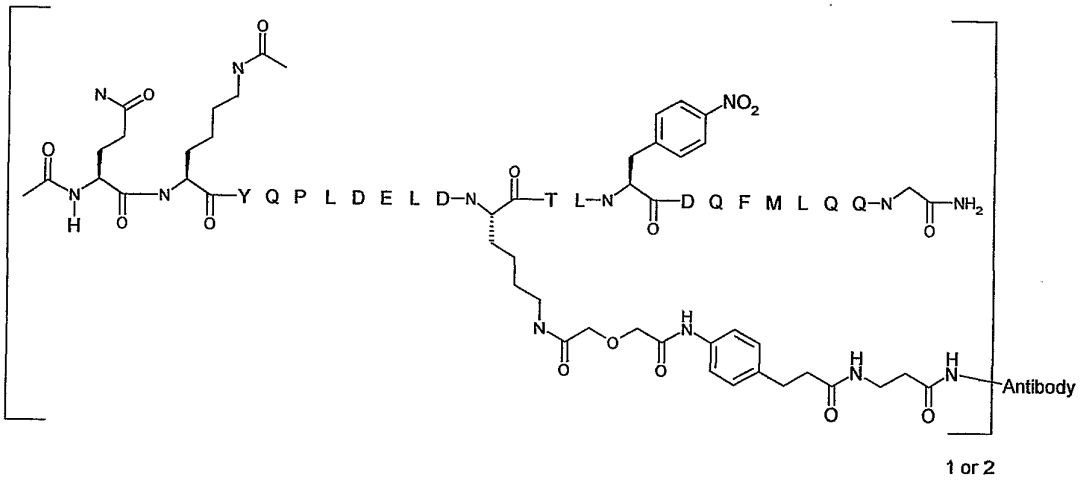


Figure 39

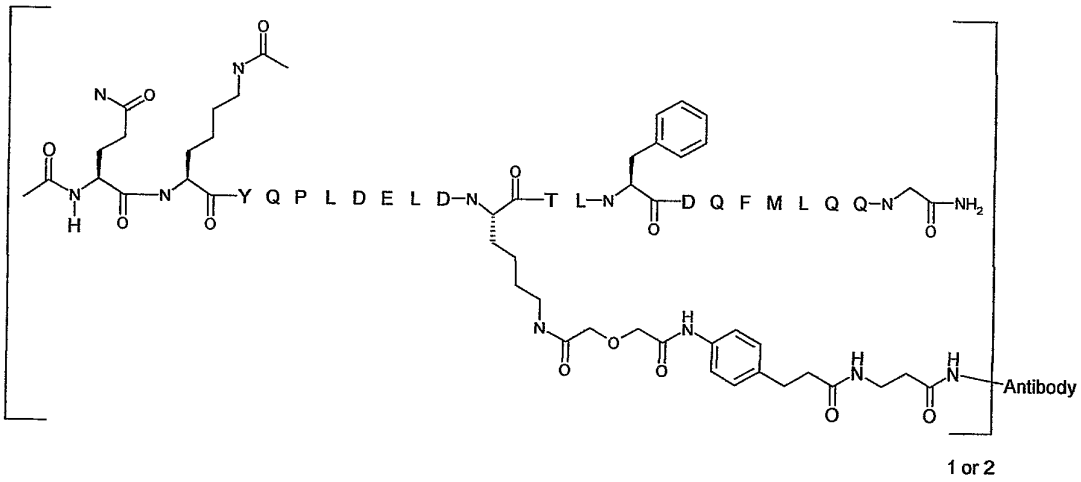


Figure 40

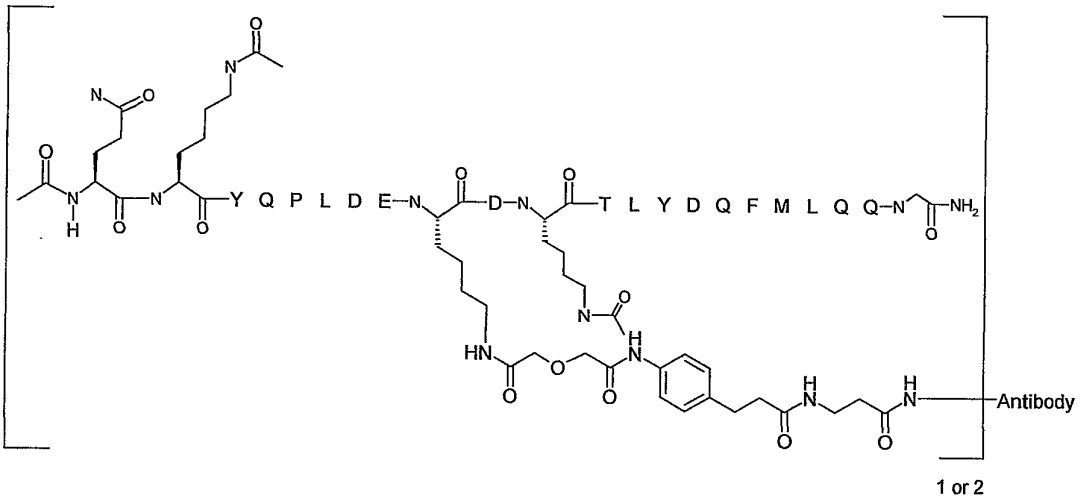


Figure 41