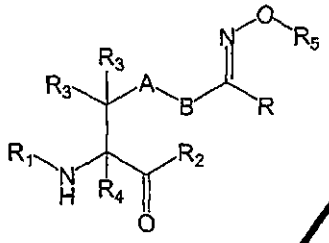
CLAIMS

1. The use of human growth hormone (hGH), having at least one non-natural amino acid in the B-C loop, the A-B loop, the C-D loop, proximal to helix A, or distal to the final helix of human growth hormone (hGH),

wherein the at least one non-natural amino acid has the structure:



(XI)

wherein:

A is phenylene;

B is a bond;

R is alkyl;

R_3 and R_4 are H;

R_1 is H, an amino protecting group, or at least one amino acid of human growth hormone (hGH); and

R_2 is OH, an ester protecting group, or at least one amino acid of human growth hormone (hGH);

R_5 is L-X, where

X is a polyalkylene glycol; and

L is optional, and when present is a linker selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, -O-(alkylene or substituted alkylene)-, -S-(alkylene or substituted alkylene)-, $-S(O)_k$(alkylene or substituted alkylene)-, -C(O)-, -C(O)-(alkylene or substituted alkylene)-, -C(S)-,

-C(S)-(alkylene or substituted alkylene)-, -NR'-(alkylene or substituted alkylene)-, -C(O)N(R')-, -CON(R')-(alkylene or substituted alkylene)-, -CSN(R')-, -CSN(R')-(alkylene or substituted alkylene)-, -N(R')CO-(alkylene or substituted alkylene)-, -(alkylene or substituted alkylene)-O-N=CR'-, -(alkylene or substituted alkylene)-C(O)NR'-(alkylene or substituted alkylene)-, -(alkylene or substituted alkylene)-$S(O)_k$-(alkylene or substituted alkylene)-S-, -(alkylene or substituted alkylene)-S-S-, -C(R')=N-, -C(R')=N-N(R')-, -C(R')=N-N=, -$C(R')_2$-N=N-, and -$C(R')_2$-N(R')-N(R')-, where each R' is independently H, alkyl, or substituted alkyl; and k is 1 or 2,

in the manufacture of a medicament for treating a growth hormone deficiency.

2. The use of claim 1, wherein X is a polyethylene glycol.

3. The use of claim 1, wherein L is absent.

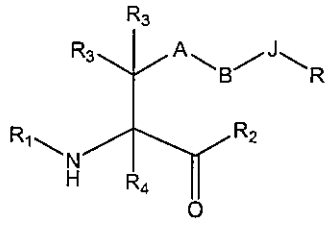
4. The use of claim 1, wherein the substituents on the phenylene group are oriented para to each other.

5. The use of claim 4, wherein L is absent.

6. The use of claim 5, wherein X is a polyethylene glycol.

CLAIMS

1. A method for derivatizing an antibody or fragment thereof comprising at least one amino acid of Formula (I), the method comprising contacting the antibody or fragment with a reagent of Formula (XIX), wherein Formula (I) corresponds to:

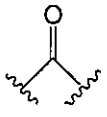


(I)

wherein:

A is phenylene;

B is a bond;

J is ;

R is alkyl;

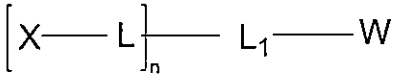
each R' is independently H, alkyl, or substituted alkyl;

R_1 is H, an amino protecting group, or at least one amino acid;

R_2 is OH, an ester protecting group, or at least one amino acid; and

R_3 and R_4 are H;

wherein Formula (XIX) corresponds to:



(XIX)

wherein:

X is a drug or a detectable label, wherein the detectable label is selected from a fluorescent, phosphorescent, chemiluminescent, chelating, intercalating, radioactive, and chromophoric moiety, and combinations thereof, or a polyalkylene glycol;

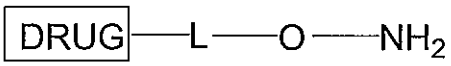
L is a linker selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, -O-, -O-(alkylene or substituted alkylene)-, -S-, -S-(alkylene or substituted alkylene)-, $-S(O)_k-$ where k is 1, 2, or 3, $-S(O)_k$(alkylene or substituted alkylene)-, -C(O)-, -C(O)-(alkylene or substituted alkylene)-, -C(S)-, -C(S)-(alkylene or substituted alkylene)-, -N(R')-, -NR'-(alkylene or substituted alkylene)-, -C(O)N(R')-, -CON(R')-(alkylene or substituted alkylene)-, -(alkylene or substituted alkylene)NR'C(O)O-(alkylene or substituted alkylene)-, -O-CON(R')-(alkylene or substituted alkylene)-, -CSN(R')-, -CSN(R')-(alkylene or substituted alkylene)-, -N(R')CO-(alkylene or substituted alkylene)-, -N(R')C(O)O-, -N(R')C(O)O-(alkylene or substituted alkylene)-, $-S(O)_kN(R')-$, -N(R')C(O)N(R')-, -N(R')C(O)N(R')-(alkylene or substituted alkylene)-, -N(R')C(S)N(R')-, $-N(R')S(O)_kN(R')-$, -N(R')-N=, -C(R')=N-, -C(R')=N-N(R')-, -C(R')=N-N=, $-C(R')_2-N=N-$, and $-C(R')_2-N(R')-N(R')-$, where each R' is independently H, alkyl, or substituted alkyl;

L_1 is optional, and when present, is $-C(R')_p-NR'-C(O)O-$(alkylene or substituted alkylene)- where p is 0, 1, or 2;

W is $-ON(R_1)_2$, where each R_1 is independently H or an amino protecting group; and

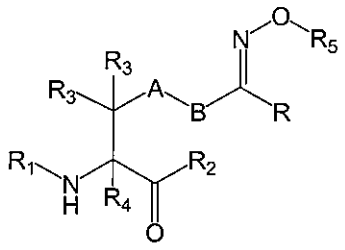
n is 1.

2. The method of claim 1, wherein the reagent corresponds to Formula (XXVII):



(XXVII).

3. The method of claim 1, wherein the derivatized antibody or fragment thereof comprises at least one oxime containing amino acid having the structure



(XI)

wherein:

A is phenylene;

B is a bond;

R is alkyl;

each R_3 and R_4 is H;

R_1 is H, an amino protecting group, or at least one amino acid;

R_2 is OH, an ester protecting group, or at least one amino acid; and

R_5 is L-X, where

X is a drug or a detectable label, wherein the detectable label is selected from a fluorescent, phosphorescent, chemiluminescent, chelating, intercalating, radioactive, and chromophoric moiety, and combinations thereof, or a polyalkylene glycol;

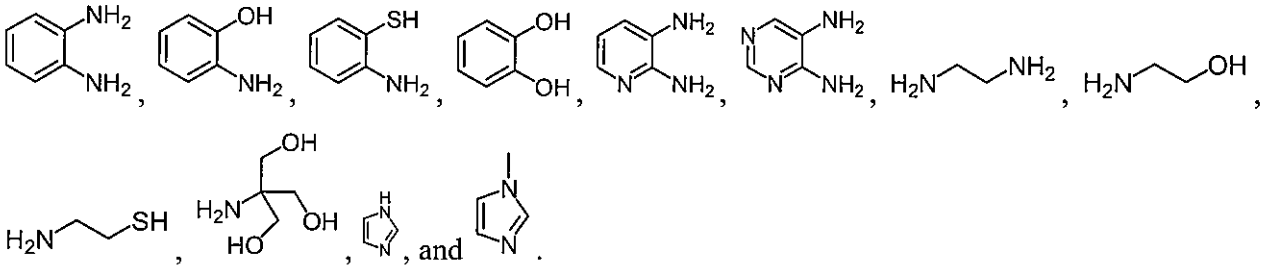
L is optional, and when present is a linker selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, -O-(alkylene or substituted alkylene)-, -S-(alkylene or substituted alkylene)-, -$S(O)_k$(alkylene or substituted alkylene)-, -C(O)-, -C(O)-(alkylene or substituted alkylene)-, -C(S)-, -C(S)-(alkylene or substituted alkylene)-, -NR'-(alkylene or substituted alkylene)-, -C(O)N(R')-, -CON(R')-(alkylene or substituted alkylene)-, -(alkylene or substituted alkylene)NR'C(O)O-(alkylene or substituted alkylene)-, -O-CON(R')-(alkylene or substituted alkylene)-, -CSN(R')-, -CSN(R')-(alkylene or substituted alkylene)-, -N(R')CO-(alkylene or substituted alkylene)-, -N(R')C(O)O-, -N(R')C(O)O-(alkylene or substituted alkylene)-, -C(R')=N-, -C(R')=N-N(R')-, -C(R')=N-

N=, -C(R')$_2$-N=N-, and -C(R')$_2$-N(R')-N(R')-, where each R' is independently H, alkyl, or substituted alkyl.

4. The method of claim 1, comprising contacting the antibody or fragment thereof with the reagent of Formula (XIX) in aqueous solution under acidic to mildly basic conditions.

5. The method of claim 4, wherein the conditions are pH 2 to 8.

6. The method of claim 1, comprising contacting the antibody or fragment thereof with the reagent of Formula (XIX) in the presence of an accelerant selected from the group consisting of:



7. The method of claim 1, wherein X is a drug selected from the group consisting of a toxic moiety, polynucleotide, steroidal agent, cytotoxic compound, and combinations thereof.

8. The method of claim 1, wherein X is a detectable label selected from the group consisting of a fluorescent, phosphorescent, chemiluminescent, chelating, intercalating, radioactive, chromophoric, and combinations thereof.

9. The method of claim 1, wherein L is a bond.

10. The method of claim 1, wherein each R_1 is H.

11. The method of claim 1, wherein L is -O-(alkylene or substituted alkylene)-, -C(O)-(alkylene or substituted alkylene)-, -NR'-(alkylene or substituted alkylene)-, -CON(R')-(alkylene or substituted alkylene)-, -N(R')CO-(alkylene or substituted alkylene)-, where each R' is independently H, alkyl, or substituted alkyl.

12. The method of claim 11, wherein L is -CON(R')-(alkylene or substituted alkylene)-, and R' is H.