

PATENTNI ZAHTEJEVI

1. Konjugat hormona rasta s formulom (I):



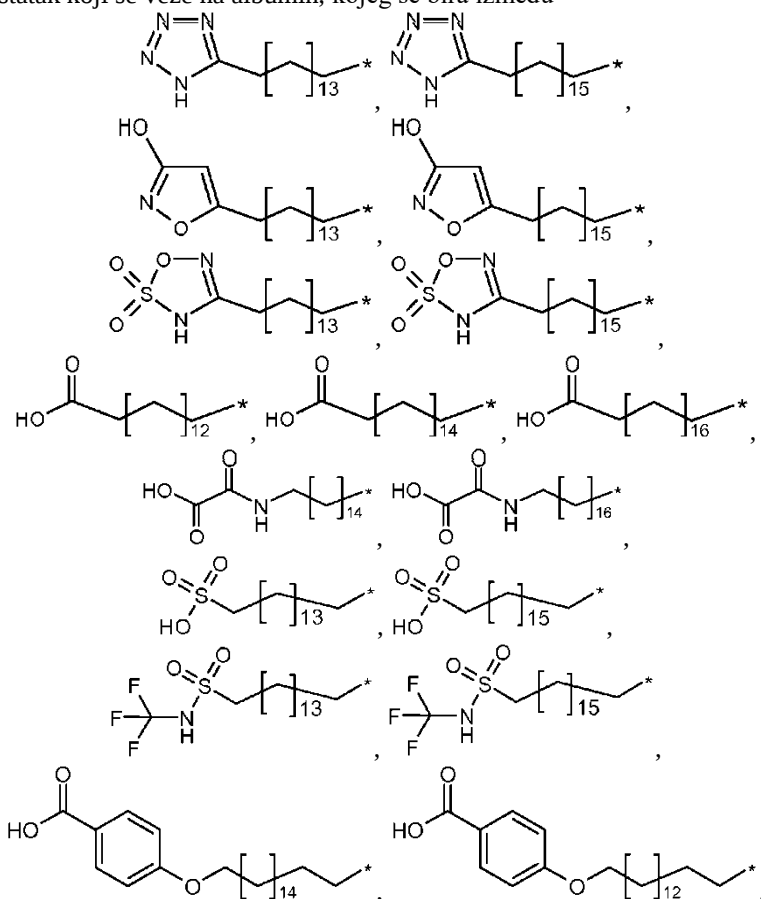
naznačen time što

GH predstavlja hormon rasta kao spoj koji ima jednu mutaciju u Cys koju se bira iz skupine mutacija koje odgovaraju: T3C, P5C, S7C, D11C, H18C, Q29C, E30C, E33C, A34C, Y35C, K38C, E39C, Y42C, S43C, D47C, P48C, S55C, S57C, P59C, S62, E65C, Q69C, E88C, Q91C, S95C, A98C, N99C, S100C, L101C, V102C, Y103C, D107C, S108C, D112C, Q122C, G126C, E129C, D130C, G131C, P133C, T135C, G136C, T142C, D147C, N149C, D154C, A155C, L156C, R178C, E186C, G187C i G190C u hGH (SEQ ID NO: 1);

B predstavlja hidrofilnu razmaknicu;

W je kemijska skupina koja spaja A s B, i

A predstavlja ostatak koji se veže na albumin, kojeg se bira između



gdje * označuje vezanje na B preko W

gdje je ostatak koji se veže na albumin (A) preko hidrofilne razmaknice (B) spojen na GH preko sumpornog ostatka u jednoj mutaciji u Cys, ili njegova farmaceutski prihvatljiva sol.

2. Konjugat u skladu s patentnim zahtjevom 1, **naznačen time** što se jednu mutaciju u Cys bira između bilo koje od: T3C, P5C, S7C, D11C, H18C, Q29C, E30C, E33C, A34C, Y35C, E88C, Q91C, S95C, A98C, N99C, S100C, L101C, V102C, Y103C, D107C, S108C, D112C, Q122C i G126C u hGH (SEQ ID NO: 1).
3. Konjugat u skladu s patentnim zahtjevom 1, **naznačen time** što se jednu mutaciju u Cys bira između bilo koje od: E88C, Q91C, S95C, A98C, N99C, S100C, L101C, V102C, Y103C, D107C, S108C, D112C, Q122C i G126C u hGH (SEQ ID NO: 1).
4. Konjugat u skladu s patentnim zahtjevom 1, **naznačen time** što je jedna mutacija u Cys L101C.
5. Konjugat u skladu s bilo kojim od prethodnih patentnih zahtjeva 1-4, **naznačen time** što GH ima dodatni disulfidni most.
6. Konjugat u skladu s patentnim zahtjevom 5, **naznačen time** što GH ima dodatni disulfidni most između najmanje jednog od aminokiselinskih parova na položajima koji odgovaraju R16C/L117C, A17C/E174C, H21C/M170C, D26C/V102C, D26C/Y103C, N47C/T50C, Q49C/G161C, F54C/Y143C, F54C/S144C, F54C/F146C, S55C/Y143C, S57C/Y143C, I58C/Q141C, I58C/Y143C, I58C/S144C, P59C/Q137C, P61C/E66C, P61C/T67C, S71C/S132C, L73C/S132C, L73C/F139C, R77C/I138C, R77C/F139C, L81C/Q141C, L81C/Y143C, Q84C/Y143C, Q84C/S144C, S85C/Y143C, S85C/S144C, P89C/F146C, F92C/F146C, F92C/T148C, R94C/D107C, V102C/A105C, L156C/F146C, L156C/T148C i/ili V185C/S188C u hGH (SEQ ID NO: 1).

7. Konjugat u skladu s bilo kojim od prethodnih patentnih zahtjeva 5 i 6, **naznačen time** što je najmanje jedan od cisteina u dodatnoj disulfidnoj vezi prisutan u segmentu petlju, primjerice iz aminokiselinskih ostataka 128-154 (L3).
8. Konjugat u skladu s patentnim zahtjevom 7, **naznačen time** što dodatna disulfidna veza spaja L3 s uzvojnicom 2.
9. Konjugat u skladu s bilo kojim od prethodnih patentnih zahtjeva 1-8, **naznačen time** što je GH najmanje 95% istovjetan s hGH (SEQ ID 1).
10. Konjugat u skladu s bilo kojim od patentnih zahtjeva 2-9, **naznačen time** što W ima formulu



gdje

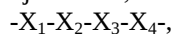
Y je $-(CH_2)_{17}-C_{3-10}$ -cikloalkil- W_8 - ili valentna veza,

17 je 0-6,

W_7 se bira između $-C(O)NH-$, $-NHC(O)-$, $-C(O)NHCH_2-$, $-CH_2NHC(O)-$, $-C(O)NHS(O)_2-$, $-S(O)_2NHC(O)-$, $-OC(O)NH-$, $-NHC(O)O-$, $-C(O)CH_2-$, $-CH_2C(O)-$, $-C(O)CH=CH-$, $-CH=CHC(O)-$, $-(CH_2)_{s3}-$, $-C(O)-$, $-C(O)O-$, $-OC(O)-$ ili valentne veze; gdje je $s3$ 0 ili 1,

W_8 se bira između $-C(O)NH-$, $-NHC(O)-$, $-C(O)NHCH_2-$, $-CH_2NHC(O)-$, $-C(O)NHS(O)_2-$, $-S(O)_2NHC(O)-$, $-OC(O)NH-$, $-NHC(O)O-$, $-C(O)CH_2-$, $-CH_2C(O)-$, $-C(O)CH=CH-$, $-CH=CHC(O)-$, $-(CH_2)_{s4}-$, $-C(O)-$, $-C(O)O-$, $-OC(O)-$ ili valentne veze; gdje je $s4$ 0 ili 1.

11. Konjugat u skladu s bilo kojim od patentnih zahtjeva 2-10, **naznačen time** što B ima formulu



gdje

X_1 je $-W_1-[(CHR^1)_{l1}-W_2]_{m1}-\{[(CH_2)_{n1}E1]_{m2}-[(CHR^2)_{l2}-W_3]_{m3}\}_{n2}-$,

X_2 je $-(CHR^3)_{l3}-W_4]_{m4}-\{[(CH_2)_{n3}E2]_{m5}-[(CHR^4)_{l4}-W_5]_{m6}\}_{n4}-$,

X_3 je $-(CHR^5)_{l5}-W_6]_{m7}-$,

X_4 je $F-D1-(CH_2)_{l6}-D2-$,

11, 12, 13, 14, 15 i 16 se neovisno bira između 0-16, primjerice od 0-6, $m1$, $m3$, $m4$, $m6$ i $m7$ se neovisno bira između 0-10, primjerice od 0-6, $m2$ i $m5$ se neovisno bira između 0-25, primjerice od 0-10, $n1$, $n2$, $n3$ i $n4$ se neovisno bira između 0-16, primjerice od 0-10, F je aril, hetaril, pirolidin-2,5-dion ili valentna veza, gdje arilna i hetarilna skupina mogu biti supstituirane s halogenom, $-CN$, $-OH$, $-C(O)OH$, $-C(O)NH_2$, $-S(O)_2OH$ ili C_{1-6} -alkilom,

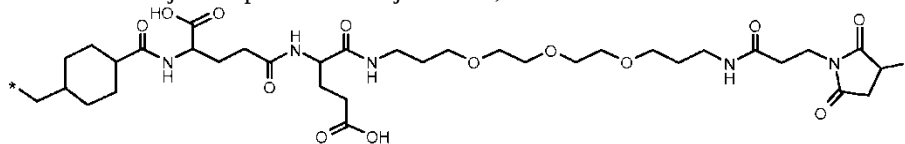
R^1 , R^2 , R^3 , R^4 i R^5 se neovisno bira između vodika, $-C(O)OH$, $-C(O)NH_2$, $-S(O)_2OH$, $-S(O)_2OH$, $-NHC(=NH)-NH_2$, C_{1-6} -alkila, arila ili hetarila; gdje alkilna, arilna i hetarilna skupina mogu biti supstituirane s halogenom, $-C(O)OH$, $-C(O)NH_2$, $-S(O)_2OH$, $-S(O)_2OH$, $-CN$ ili $-OH$,

$D1$, $D2$, $E1$ i $E2$ se neovisno bira između $-O-$, $-N(R^6)-$, $-N(C(O)R^7)-$ ili valentne veze; gdje R^6 i R^7 neovisno predstavljaju vodik ili C_{1-6} -alkil, W_1 do W_5 se neovisno bira između $-C(O)NH-$, $-NHC(O)-$, $-C(O)NHCH_2-$, $-CH_2NHC(O)-$, $-C(O)NHS(O)_2-$, $-S(O)_2NHC(O)-$, $-OC(O)NH-$, $-NHC(O)O-$, $-C(O)CH_2-$, $-CH_2C(O)-$, $-C(O)CH=CH-$, $-CH=CHC(O)-$, $-(CH_2)_{s2}-$, $-C(O)-$, $-C(O)O-$, $-OC(O)-$ ili valentne veze; gdje je $s2$ 0 ili 1,

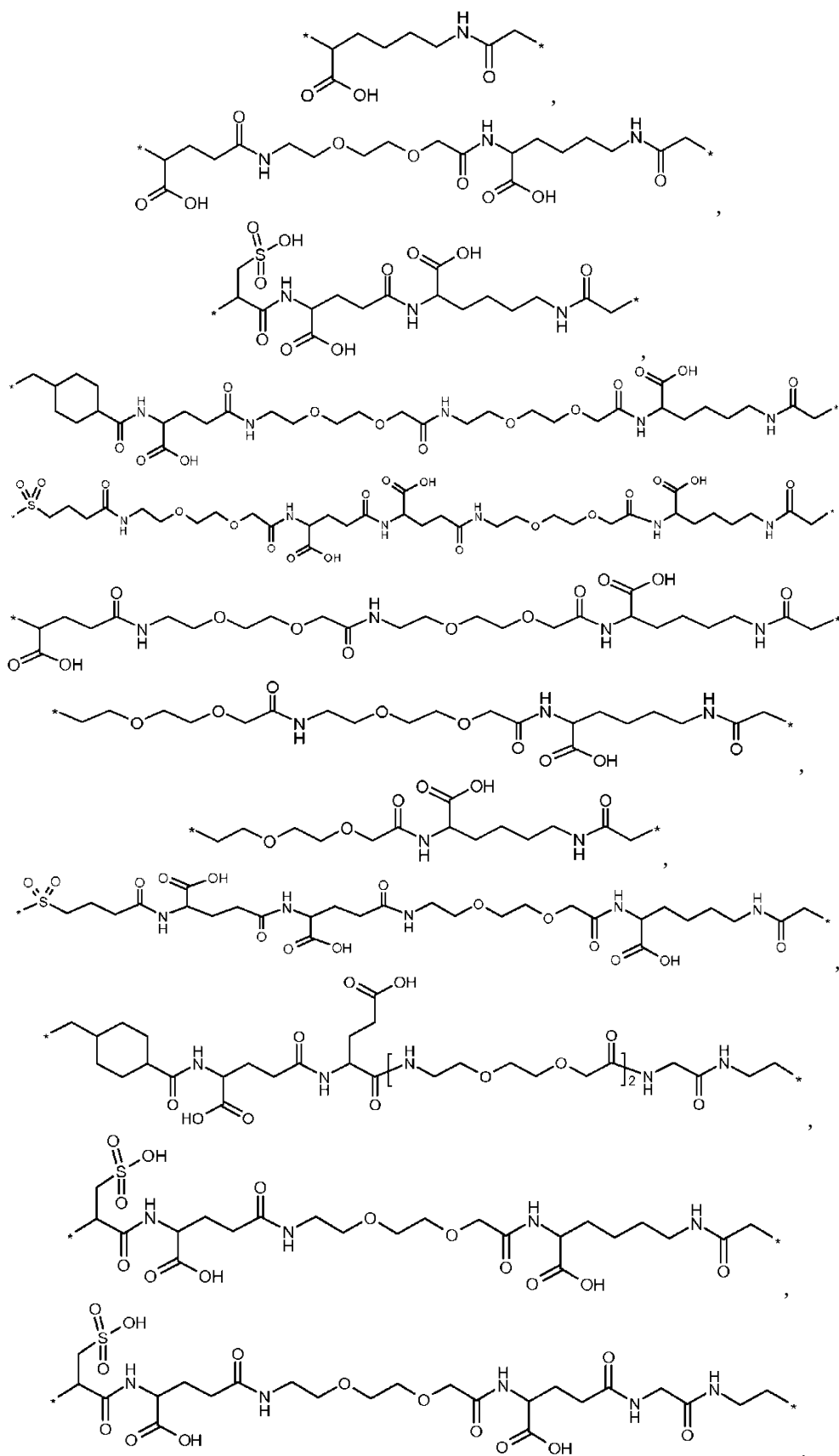
W_6 se bira između $-C(O)NH-$, $-NHC(O)-$, $-C(O)NHCH_2-$, $-CH_2NHC(O)-$, $-C(O)NHS(O)_2-$, $-S(O)_2NHC(O)-$, $-OC(O)NH-$, $-NHC(O)O-$, $-C(O)CH_2-$, $-CH_2C(O)-$, $-C(O)CH=CH-$, $-CH=CHC(O)-$, $-(CH_2)_{s1}-$, $-C(O)-$, $-C(O)O-$, $-OC(O)-$, $-NHC(O)C_{1-6}$ -alkil, $-C(O)NHC_{1-6}$ -alkila ili valentne veze; gdje je $s1$ 0 ili 1, a C_{1-6} -alkilna skupina može biti supstituirana s okso, pirolidin-2,5-dionom, $-NHC(O)CH^*CH_2COOH$ ili $-NHC(O)CH_2CH^*COOH$;

gdje (*) ukazuje na mjesto vezanja od atoma ugljika u CH na X_4 .

12. Konjugat u skladu s patentnim zahtjevom 11, **naznačen time** što se $D1$ i $D2$ neovisno bira između $-O-$ ili $-N(R^6)-$ ili valentne veze.
13. Konjugat u skladu s patentnim zahtjevom 11 ili 12, **naznačen time** što se $E1$ i $E2$ neovisno bira između $-O-$ ili $-N(R^6)-$ ili valentne veze.
14. Konjugat u skladu s bilo kojim od patentnih zahtjeva 10-13, **naznačen time** što se W_1 do W_8 neovisno bira iz skupine koju čine $-C(O)NH-$, $-NHC(O)-$, $-CH_2NHC(O)-$, $-C(O)NHS(O)_2-$, $-S(O)_2NHC(O)-$, $-NHC(O)C_{1-6}$ -alkil ili $-C(O)NHC_{1-6}$ -alkil ili valentna veza; gdje alkilna skupina može biti supstituirana s okso, pirolidin-2,5-dionom, $-NHC(O)CH^*CH_2COOH$ ili $-NHC(O)CH_2CH^*COOH$; gdje (*) ukazuje na mjesto vezanja od atoma ugljika u CH na X_4 .
15. Konjugat u skladu s bilo kojim od patentnih zahtjeva 11-14, **naznačen time** što se R^1 , R^2 , R^3 , R^4 i R^5 neovisno bira između vodika, $-C(O)OH$, $-C(O)NH_2$, $-S(O)_2OH$ ili C_{1-6} -alkila; gdje alkilna skupina može biti supstituirana s $-C(O)OH$, $-C(O)NH_2$ ili $-S(O)_2OH$.
16. Konjugat u skladu s bilo kojim od patentnih zahtjeva 11-15, **naznačen time** što je X_4 valentna veza, a W_6 se bira između bilo pirolidin-2,5-diona, $-NHC(O)CH^*CH_2COOH$ ili $-NHC(O)CH_2CH^*COOH$, gdje (*) ukazuje na mjesto vezanja od atoma ugljika u CH na GH.
17. Konjugat u skladu s bilo kojim od patentnih zahtjeva 2-16, **naznačen time** što se B bira između

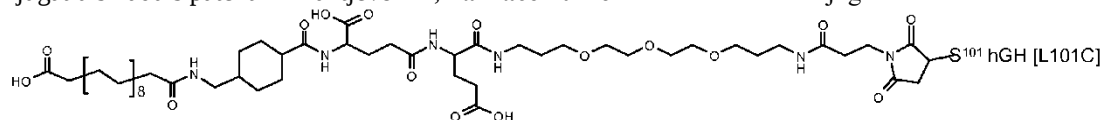


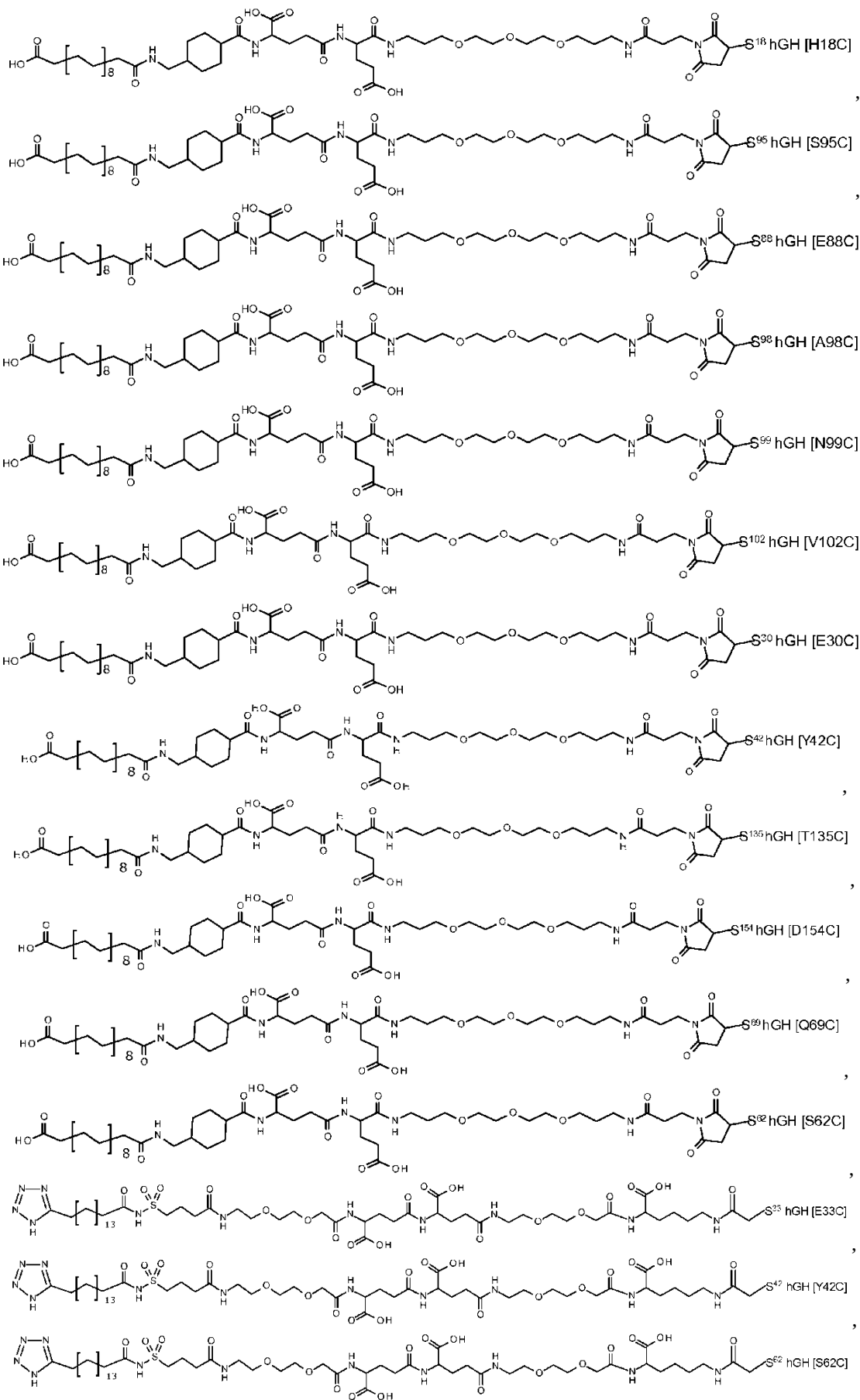
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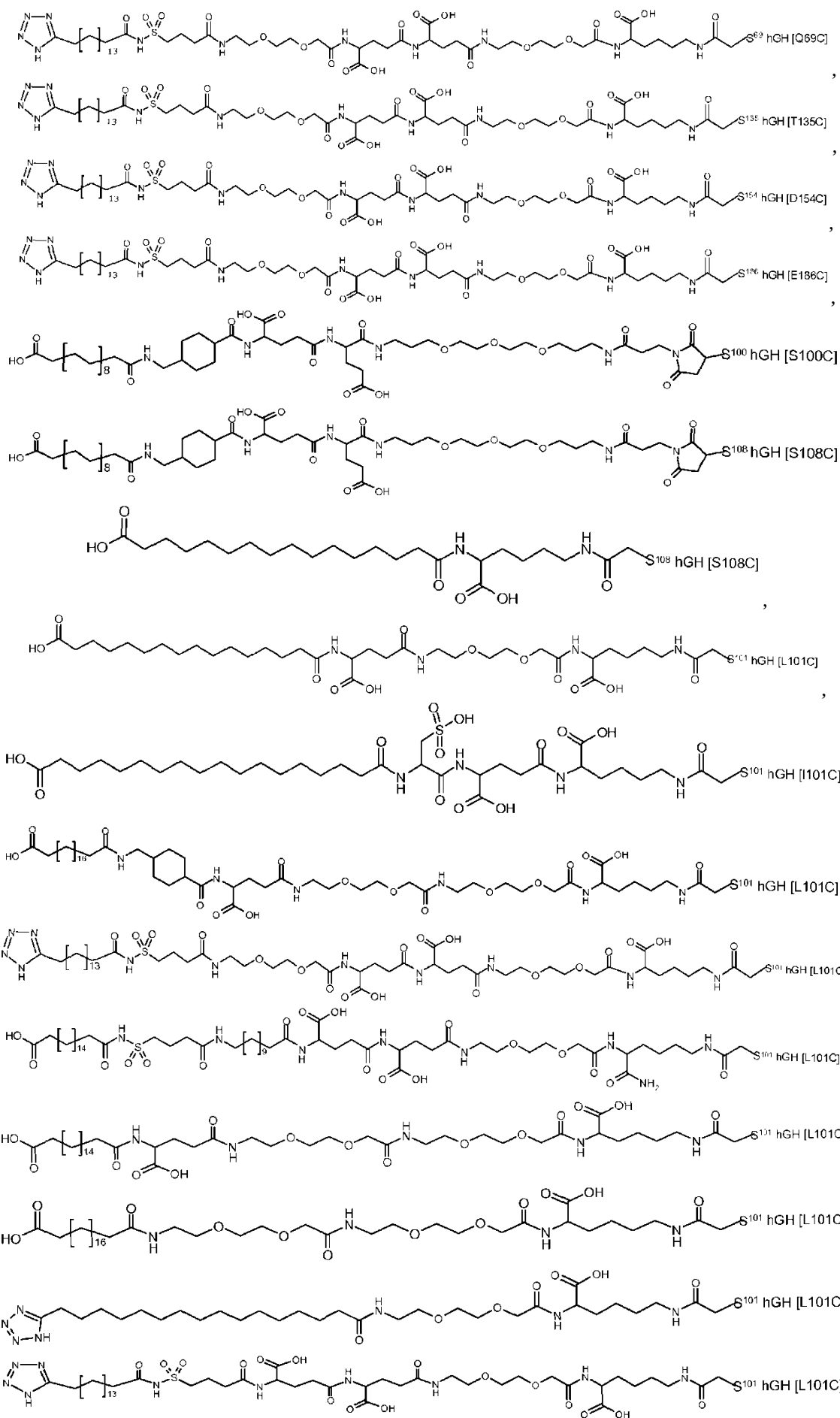


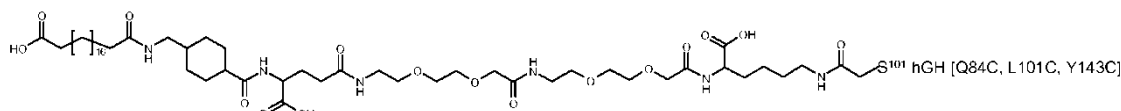
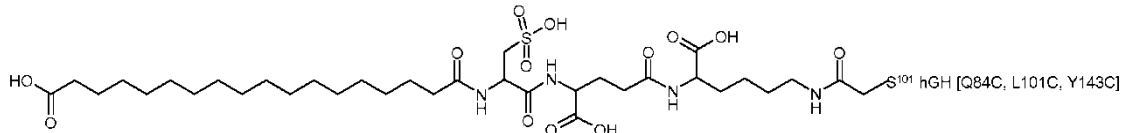
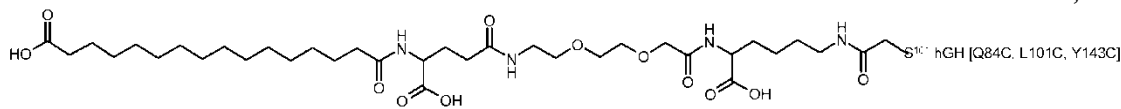
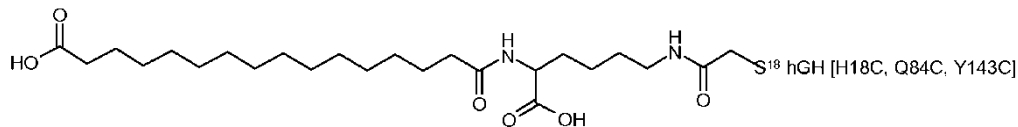
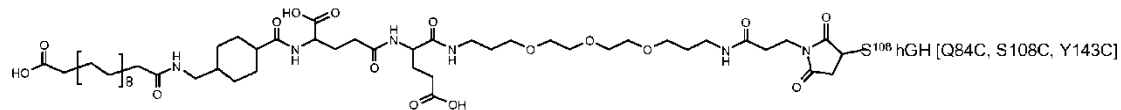
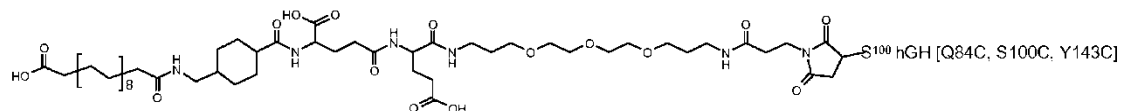
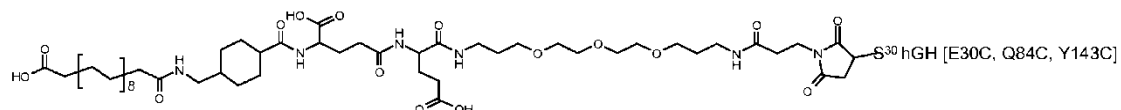
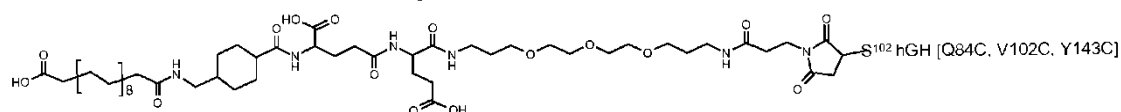
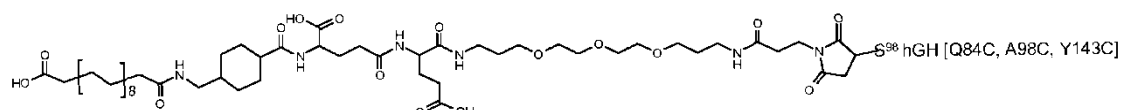
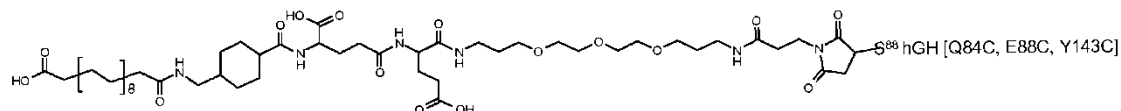
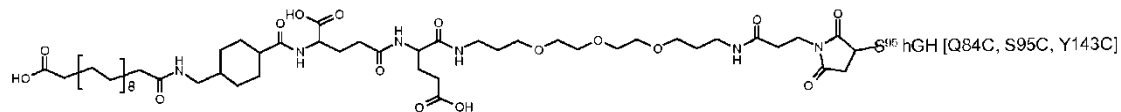
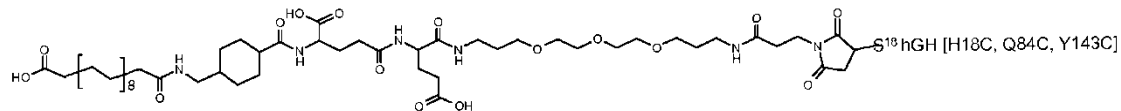
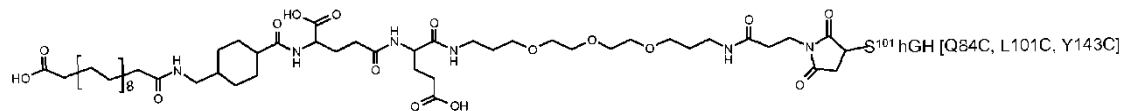
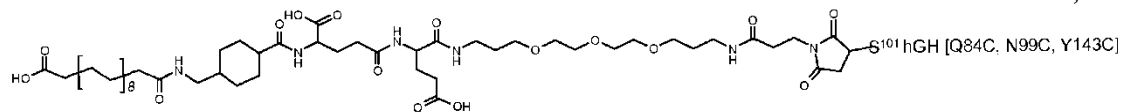
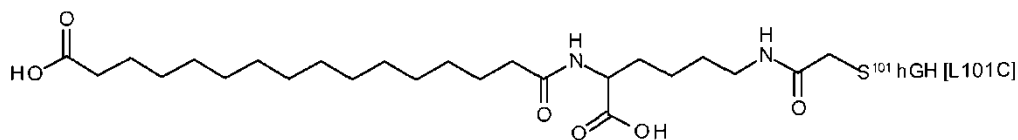
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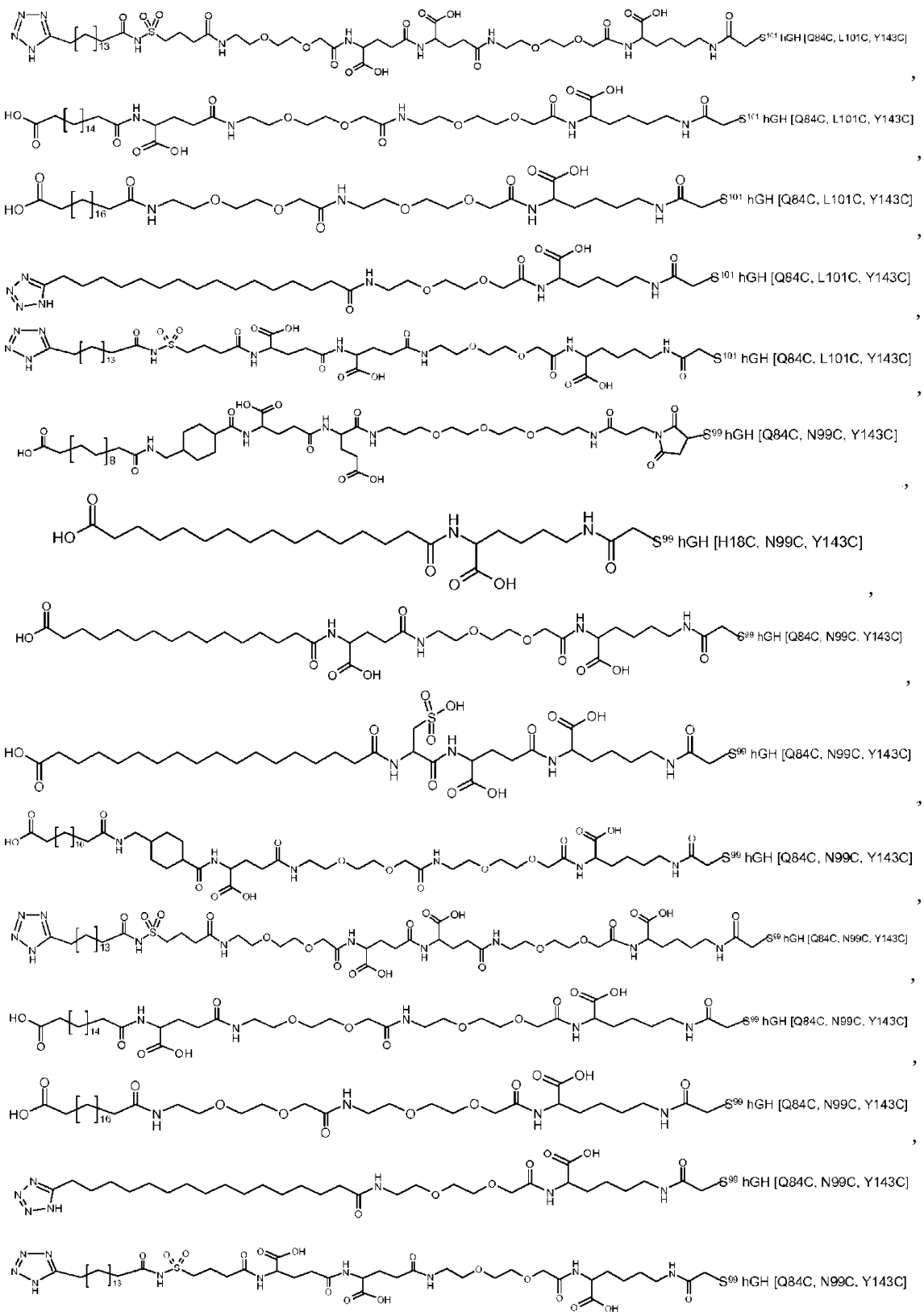
18. Konjugat u skladu s patentnim zahtjevom 1, **naznačen time** što se navedeni konjugat bira između



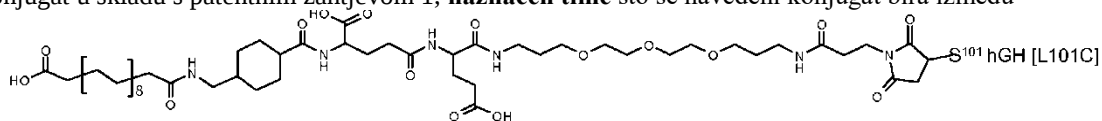


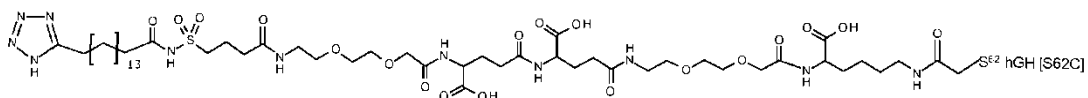
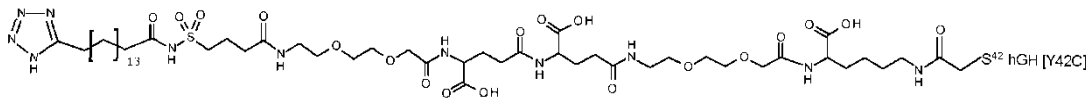
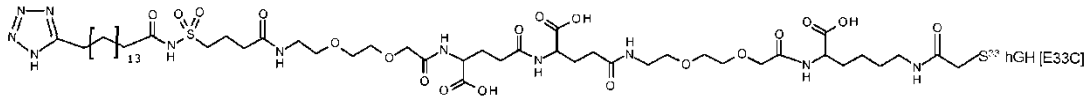
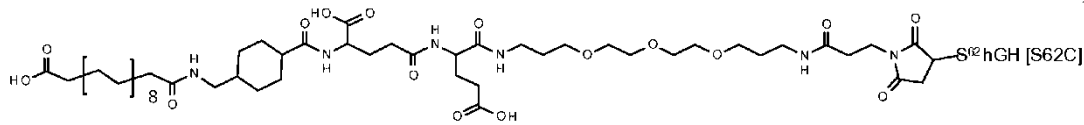
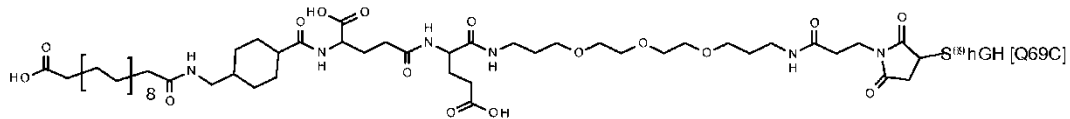
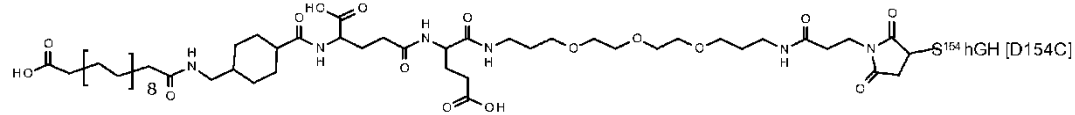
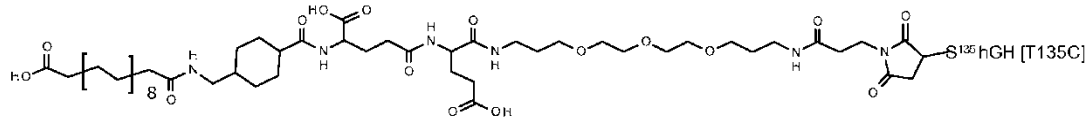
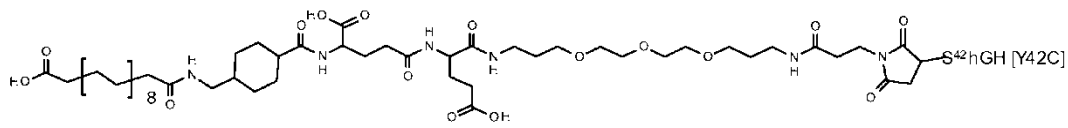
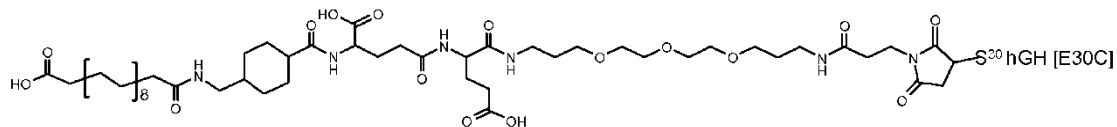
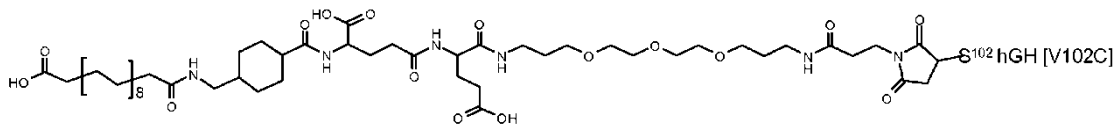
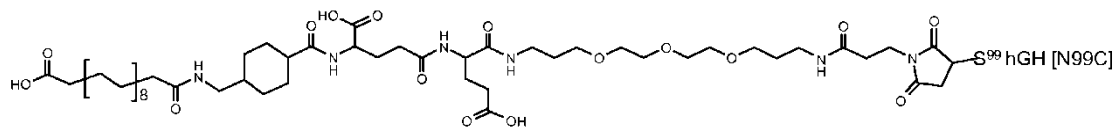
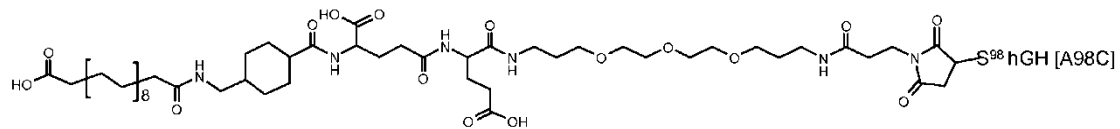
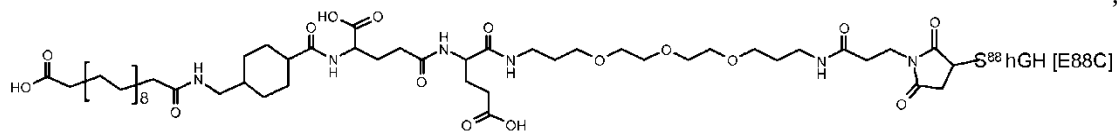
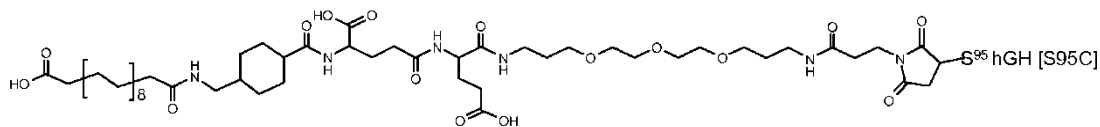
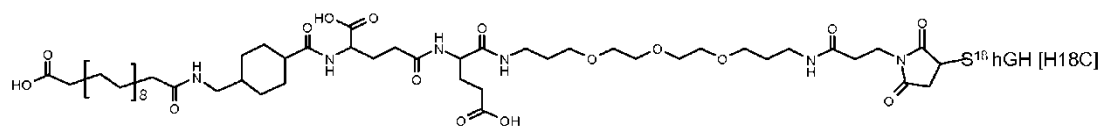


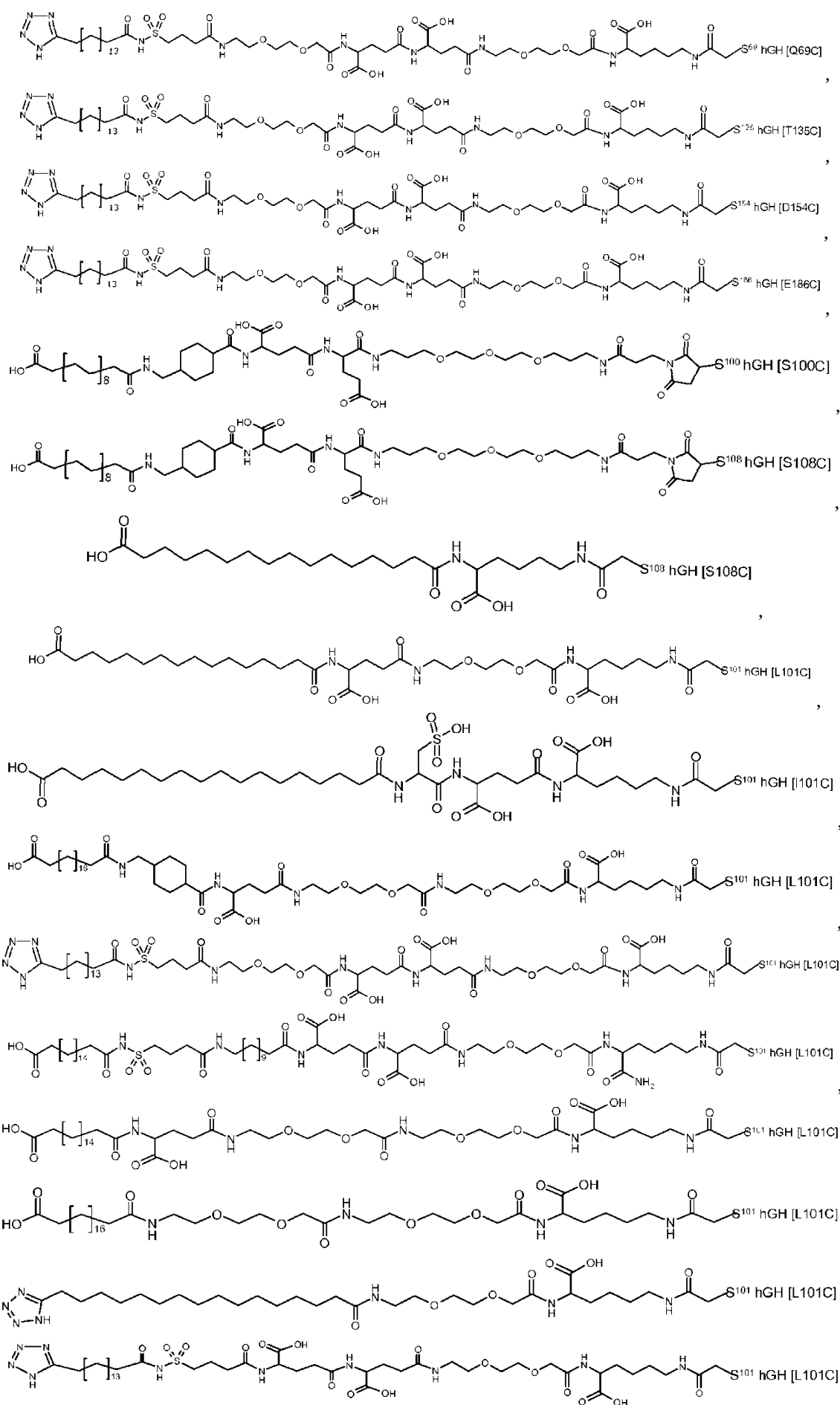




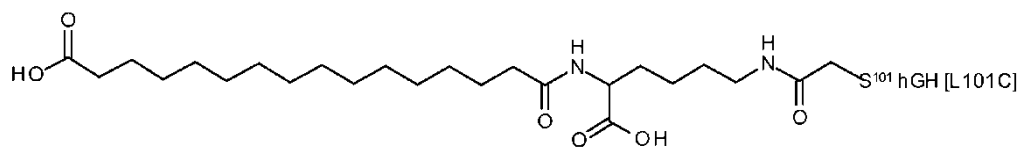
19. Konjugat u skladu s patentnim zahtjevom 1, **naznačen time** što se navedeni konjugat bira između



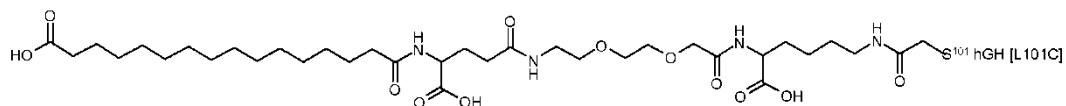
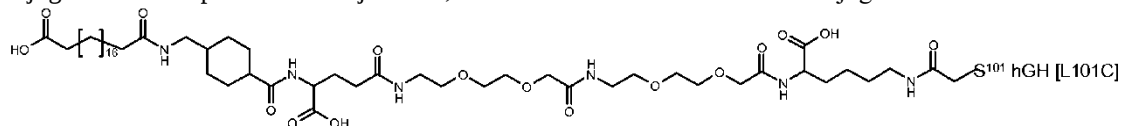




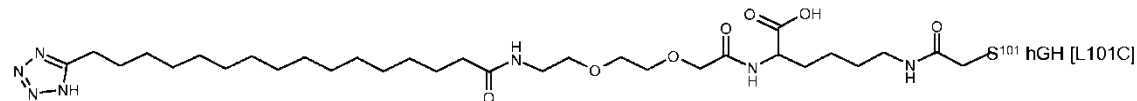
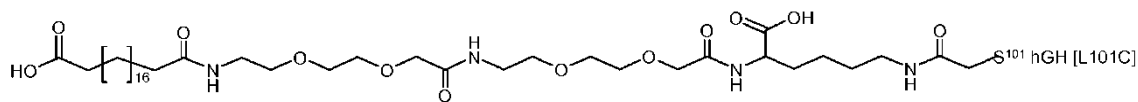
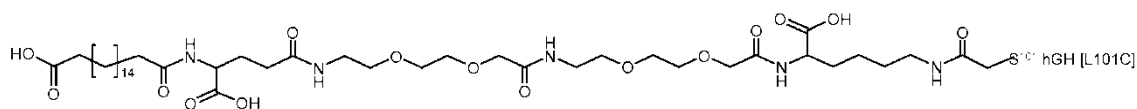
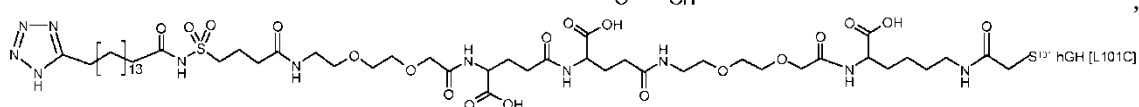
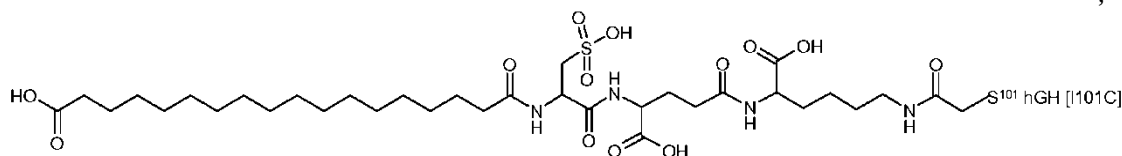
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20. Konjugat u skladu s patentnim zahtjevom 1, **naznačen time** što se navedeni konjugat bira između



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