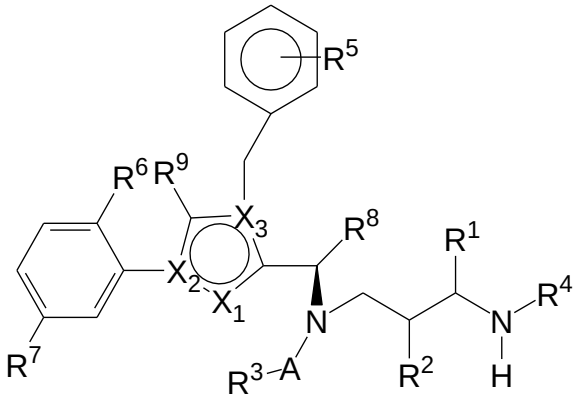
Claims

1. Conjugate of a binder or derivative thereof with one or more active compound molecules, the active compound molecule being a kinesin spindle protein inhibitor attached to the binder via a linker L, where the linker L is attached to a glutamine side chain of the binder, where 1 to 5 kinesin spindle protein inhibitors are attached to the linker L, where the kinesin spindle protein inhibitor attached to the linker L has the formula (IIa) below:



(IIa)

where

X_1 represents N, X_2 represents N and X_3 represents C; or
X_1 represents CH or CF, X_2 represents C and X_3 represents N; or
X_1 represents NH, X_2 represents C and X_3 represents C; or
X_1 represents CH or CF, X_2 represents N and X_3 represents C;
(with X_1 representing CH, X_2 representing C and X_3 representing N being preferred);

R^1 represents -H, –L-#1, –MOD or $-(CH_2)_{0-3}Z$,

where –L-#1 represents the linker and #1 represents the bond to the binder or derivative thereof.

where –MOD is represented as defined infra,
where Z represents -H, halogen, $-OY^3$, $-SY^3$, $-NHY^3$, $-C(=O)-NY^1Y^2$ or $-C(=O)-OY^3$,
where Y^1 and Y^2 independently of one another represent -H, $-NH_2$, $-(CH_2CH_2O)_{0-3}-(CH_2)_{0-3}Z$‘ (e.g. $-(CH_2)_{0-3}Z$‘) or $-CH(CH_2W)Z$‘,
where Y^3 represents -H or $-(CH_2)_{0-3}Z$‘,
where Z‘ represents -H, $-NH_2$, $-SO_3H$, -COOH,

-NH-C(=O)-CH_2-CH_2-CH(NH_2)COOH or
-(C(=O)-NH-CHY^4)$_{1-3}$COOH,

where W represents -H or -OH,

where Y^4 represents linear or branched C_{1-6}-alkyl which is optionally substituted by –NHC(=O)-NH_2, or represents aryl or benzyl which are optionally substituted by –NH_2;

R^2 represents -H, –L-#1, -MOD, -C(=O)-CHY^4-NHY^5 or -$(CH_2)_{0-3}$Z,

where –L-#1 represents the linker and #1 represents the bond to the binder or derivative thereof,

where –MOD is represented as defined infra,

where Z represents -H, halogen, -OY^3, -SY^3, NHY^3, -C(=O)-NY^1Y^2 or -C(=O)-OY^3,

where Y^1 and Y^2 independently of one another represent -H, -NH_2 or -$(CH_2)_{0-3}$Z‘, and

where Y^3 represents -H or -$(CH_2)_{0-3}$Z‘,

where Z‘ represents -H, -SO_3H, -NH_2 or -COOH;

where Y^4 represents linear or branched C_{1-6}-alkyl which is optionally substituted by –NHC(=O)-NH_2, or represents aryl or benzyl which are optionally substituted by –NH_2,

where Y^5 represents -H or -C(=O)-CHY^6-NH_2,

where Y^6 represents linear or branched C_{1-6}-alkyl;

R^4 represents -H, –L-#1, -C(=O)-CHY^4-NHY^5 or -$(CH_2)_{0-3}$Z,

where –L-#1 represents the linker and #1 represents the bond to the binder or derivative thereof,

where Z represents -H, -OY^3, -SY^3, -NHY^3, -C(=O)-NY^1Y^2 or -C(=O)-OY^3,

where Y^1 and Y^2 independently of one another represent -H, -NH_2 or -$(CH_2)_{0-3}$Z‘,

where Y^3 represents -H or -$(CH_2)_{0-3}$Z‘,

where Z‘ represents -H, -SO_3H, -NH_2 or -COOH;

where Y^4 represents linear or branched C_{1-6}-alkyl which is optionally substituted by

–NHC(=O)-NH_2, or represents aryl or benzyl which are optionally substituted by –NH_2, and

where Y^5 represents -H or -C(=O)-CHY^6-NH_2,

where Y^6 represents linear or branched C_{1-6}-alkyl,

or

R^4 represents a group of

R^{21}-$(C=O)_{(0-1)}$-$(P3)_{(0-2)}$-P2-NH-$CH(CH_2C(=O)-NH_2)$-C(=O)- or

R^{21}-$(C=O)_{(0-1)}$-$(P3)_{(0-2)}$-P2-NH-$CH(CH_2COOH)$-C(=O)- or the cathepsin cleavable group R^{21}-$(C=O)_{(0-1)}$-$(P3)_{(1-2)}$-P2-,

where R^{21} represents H, C_{1-10}-alkyl-, C_{5-10}-aryl- or C_{6-10}-aralkyl-, C_{5-10}-heteroalkyl-, C_{1-10}-alkyl-O-C_{6-10}-aryl-, C_{5-10}-heterocycloalkyl-, heteroaryl-, heteroaryl-alkyl-, C_{1-10}-alkoxy-, C_{6-10}-aryloxy- or C_{6-10}-aralkoxy-, C_{5-10}-heteroalkoxy-, C_{1-10}-alkyl-O-C_{6-10}-aryloxy-, C_{5-10}-heterocycloalkoxy group (which may be substituted one or more times with - NH_2, -NH-alkyl, -$N(alkyl)_2$, -NH-C(=O)-alkyl, N(alkyl)-C(=O)-alkyl, -SO_3H, -SO_2NH_2, -$S(O)_2$-$N(alkyl)_2$, -COOH, -C(=O)-NH_2, -C(=O)-$N(alkyl)_2$, or –OH), -H or a group –$(O)_x$-$(CH_2CH_2O)_y$-R^{22},

where x is 0 or 1 and

where v is a number from 1 to 20,

where R^{22} represents –H, –alkyl (preferably C_{1-12}-alkyl), -CH_2-COOH, -CH_2-CH_2-COOH, or -CH_2-CH_2-NH_2);

where P2 is an amino acid selected from Gly, Pro, Ala, Val, Nva, Leu, Ile, Met, Phe, Tyr, Trp, Ser, Thr, Cys, Asn, Gln, Asp, Glu, Lys, Arg, citrulline and His;

where P3 is an amino acid independently selected from Gly, Pro, Ala, Val, Nva, Leu, Ile, Met, Phe, Tyr, Trp, Ser, Thr, Cys, Asn, Gln, Asp, Glu, Lys, Arg, citrulline and His or one of the corresponding N-alkyl amino acids, preferably N-methyl amino acids; in case there is more than one amino acid

P3, P3 may have the same or different amino acids, as defined above;

or

R^2 and R^4 together (with formation of a pyrrolidine ring) represent $–CH_2-CHR^{10}-$ or $-CHR^{10}-CH_2-$,

where R^{10} represents -H, halogen (preferably –F or -Cl), $-NH_2$, $-SO_3H$, -COOH, -SH, C_{1-4}-alkyl, halo-C_{1-4}-alkyl, C_{1-4}-alkoxy, hydroxy substituted C_{1-4}-alkyl, $-C(=O)-O-(C_{1-4}$-alkyl) or -OH, and wherein the hydrogen atom of the secondary amino group in the pyrrolidine ring may be replaced by $R^{21}-C(=O)-P3_{(0-2)}-P2-NH-CH(CH_2C(=O)-NH_2)-C(=O)-SIG-$;

where P2 is an amino acid selected from Gly, Pro, Ala, Val, Nva, Leu, Ile, Met, Phe, Tyr, Trp, Ser, Thr, Cys, Asn, Gln, Asp, Glu, Lys, Arg, citrulline and His;

where P3 is an amino acid independently selected from Gly, Pro, Ala, Val, Nva, Leu, Ile, Met, Phe, Tyr, Trp, Ser, Thr, Cys, Asn, Gln, Asp, Glu, Lys, Arg, citrulline and His or one of the corresponding N-alkyl amino acids, preferably N-methyl amino acids; in case there is more than one amino acid P3, P3 may have the same or different amino acids, as defined above;

where –SIG is a self-immolative group, which, upon cleavage of the –C(=O)-SIG bond provides the free secondary amine;

A represents -C(=O)-, -S(=O)-, $-S(=O)_2-$, $-S(=O)_2-NH-$ or

–C(=N-NH_2)-;

R^3 represents –L-#1, -MOD or an optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, heteroalkyl, heterocycloalkyl group, preferably a C_{1-10}-alkyl, C_{6-10}-aryl or C_{6-10}-aralkyl, C_{5-10}-heteroalkyl, C_{1-10}-alkyl-O-C_{6-10}-aryl or C_{5-10}-heterocycloalkyl group which may be substituted by 1-3 –OH groups, 1-3 halogen atoms, 1-3 halogenated alkyl groups (each having 1-3 halogen atoms), 1-3 O-alkyl groups, 1-3 –SH groups, 1-3 -S-alkyl groups, 1-3 -O-C(=O)-alkyl groups, 1-3 -O-C(=O)-NH-alkyl groups, 1-3 -NH-C(=O)-alkyl groups, 1-3 -NH-C(=O)-NH-alkyl groups, 1-3 -S(=O)$_n$-alkyl groups, 1-3 -S(=O)$_2$-NH-alkyl groups, 1-3 -NH-alkyl groups, 1-3 -N(alkyl)$_2$ groups, 1-3 -NH((CH_2CH_2O)$_{1-20}$H) groups, 1-3 -NH_2 groups or 1-3 -(CH_2)$_{0-3}$Z groups,

where –L-#1 represents the linker and #1 represents the bond to the binder or derivative thereof,
where –MOD is represented as defined infra,
where n represents 0, 1 or 2,
where Z represents -H, halogen, -OY^3, -SY^3, -NHY^3, -C(=O)-NY^1Y^2 or -C(=O)-OY^3,
where Y^1 and Y^2 independently of one another represent -H, -NH_2 or -(CH_2)$_{0-3}$Z‘ and
where Y^3 represents -H, -(CH_2)$_{0-3}$-CH(NH-C(=O)-CH_3)Z‘, -(CH_2)$_{0-3}$-CH(NH_2)Z‘ or -(CH_2)$_{0-3}$Z‘, where
where Z‘ represents -H, -SO_3H, -NH_2 or –COOH

R^5 represents –L-#1, H, -MOD, -NH_2, -NO_2, halogen (in particular -F, -Cl, -Br), -CN, -CF_3, -OCF_3, -CH_2F, -CH_2F, -SH or -(CH_2)$_{0-3}$Z,
where Z represents -H, -OY^3, -SY^3, halogen, -NHY^3, -C(=O)-NY^1Y^2 or -C(=O)-OY^3,
where Y^1 and Y^2 independently of one another represent -H, -NH_2 or -(CH_2)$_{0-3}$Z‘,
where Y^3 represents -H or -(CH_2)$_{0-3}$Z‘,
where Z‘ represents -H, -SO_3H, -NH_2 or -COOH;

R^6 and R^7 independently of one another represent -H, cyano, C_{1-10}-alkyl, fluoro-C_{1-10}-alkyl, C_{2-10}-alkenyl, fluoro- C_{2-10}-alkenyl, C_{2-10}-alkynyl, fluoro-C_{2-10}-

alkynyl, hydroxy, -NO_2, -NH_2, -COOH or halogen (in particular -F, -Cl, -Br),

R^8 represents C_{1-10}-alkyl, fluoro-C_{1-10}-alkyl, C_{2-10}-alkenyl, fluoro-C_{2-10}-alkenyl, C_{2-10}-alkynyl, fluoro-C_{2-10}-alkynyl, C_{4-10}-cycloalkyl, fluoro-C_{4-10}-cycloalkyl, - or–$(CH_2)_{0-2}$-(HZ^2),

where HZ^2 represents a 4- to 7-membered heterocycle having up to two heteroatoms selected from the group consisting of N, O and S, where each of these groups may be substituted by –OH, -COOH or -NH_2 or –L-#1;

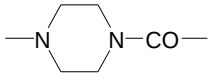
where –L-#1 represents the linker and #1 represents the bond to the binder or derivative thereof,

where one of the substituents R^1, R^2, R^3, R^4 R^5, R^8 and R^{10} represents (or in the case of R^8 contains) –L-#1,

R^9 represents -H, -F, -CH_3, -CF_3, -CH_2F or -CHF_2;

–MOD as defined supra represents –(NR^{10})n-(G1)o-G2-G3,

where R^{10} represents -H or C_1-C_3-alkyl;

where G1 represents –NH-C(=O)-, -C(=O)-NH- or ;

where n is 0 or 1;

where o is 0 or 1;

where G2 represents a linear and/or branched hydrocarbon group which has 1 to 10 carbon atoms and which may be interrupted once or more than once by one or more of the groups -O-, -S-, -S(=O)-, -$S(=O)_2$-, -NR^y-, -NR^yC(=O)-, -C(=O)-NR^y-, -$NR^y$$NR^y$-, -$S(=O)_2$-NRyNRy-, -C(=O)-$NR^y$$NR^y$-, -C(=O)-, -$CR^x$=N-O-,

and where the hydrocarbon chain including any side chains may be substituted by –NH-C(=O)-NH_2, -COOH, -OH, -NH_2, NH-CN-NH_2, sulphonamide, sulphone, sulphoxide or sulphonic acid,

where R^y represents -H, phenyl, C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl or C_2-C_{10}-alkynyl, each of which may be substituted by –NH-C(=O)-NH_2, -COOH, -OH, -NH_2, NH-CN-NH_2, sulphonamide, sulphone, sulphoxide or sulphonic acid,

where R^x represents -H, C_1-C_3-alkyl or phenyl,

where G3 represents -H or –COOH, and

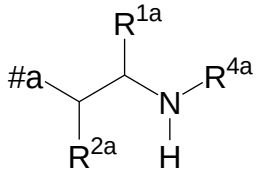
where –MOD preferably has at least one -COOH group;

and the salts, solvates, salts of the solvates,and epimers thereof.

2. Conjugate according to Claim 1 where X_1 represents CH, X_2 represents C and X_3 represents N.

3. Conjugate according to Claim 1 or 2 where the substituent R^1 or substituent R^3 represents –L-#1.

4. Conjugate of a binder or derivative thereof with the active compound molecule being a kinesin spindle protein inhibitor attached to the binder via a linker L, where the linker L is attached to a glutamine side chain of the binder, where the kinesin spindle protein inhibitor has the substructure below:



where

#a represents a bond;

R^{1a} represents –H, -MOD, or -$(CH_2)_{0-3}$Z,

where –MOD is represented as defined infra,

where Z represents -H, halogen, -OY^3, -SY^3, -NHY^3, -C(=O)-NY^1Y^2 or -C(=O)-OY^3,

where Y^1 and Y^2 independently of one another represent -H, -NH_2, -$(CH_2CH_2O)_{0-3}$-$(CH_2)_{0-3}$Z‘ (e.g. -$(CH_2)_{0-3}$Z‘) or -$CH(CH_2W)$Z‘,

where Y^3 represents H or -$(CH_2)_{0-3}$Z‘,

where Z‘ represents -H, -SO_3H, -NH_2, -COOH, -NH-C(=O)-CH_2-CH_2-$CH(NH_2)$COOH or -$(C=O\text{-}NH\text{-}CHY^4)_{1-3}$COOH,

where W represents -H or -OH,

where Y^4 represents linear or branched C_{1-6}-alkyl which is optionally substituted by –NH-C(=O)-NH_2, or represents aryl or benzyl which are optionally substituted by –NH_2;

R^{2a} represents -H, -C(=O)-CHY^4-NHY^5 or -$(CH_2)_{0-3}$Z,

where Z represents -H, -OY^3, -SY^3, -NHY^3, -C(=O)-NY^1Y^2 or -C(=O)-OY^3,

where Y^1 and Y^2 independently of one another represent -H, -NH_2 or -$(CH_2)_{0-3}$Z‘,

where Y^3 represents -H or -$(CH_2)_{0-3}$Z‘,

where Z‘ represents -H, -SO_3H, -NH_2 or -COOH;

where Y^4 represents linear or branched C_{1-6}-alkyl which is optionally substituted by –NH-C(=O)-NH_2, or represents aryl or benzyl which are optionally substituted by –NH_2,

where Y^5 represents -H or -C(=O)-CHY^6-NH_2,

where Y^6 represents linear or branched C_{1-6}-alkyl;

R^{4a} represents H, -C(=O)-CHY^4-NHY^5 or -$(CH_2)_{0-3}$Z,

where Z represents -H, -OY^3, -SY^3, -NHY^3, -C(=O)-NY^1Y^2 or -C(=O)-OY^3,

where Y^1 and Y^2 independently of one another represent -H, -NH_2 or -$(CH_2)_{0-3}$Z‘,

where Y^3 represents -H or -$(CH_2)_{0-3}$Z‘,

where Z‘ represents -H, -SO_3H, -NH_2 or -COOH;

where Y^4 represents linear or branched C_{1-6}-alkyl which is optionally substituted by $–NH-C(=O)-NH_2$, or represents aryl or benzyl which are optionally substituted by $–NH_2$,

where Y^5 represents -H or $-C(=O)-CHY^6-NH_2$,

where Y^6 represents linear or branched C_{1-6}-alkyl,

or

R^{4a} represents a group of $R^{21}-(C=O)_{(0-1)}-(P3)_{(0-2)}-P2-NH-CH(CH_2C(=O)-NH_2)-C(=O)-$ or the cathepsin cleavable group or a group $R^{21}-(C=O)_{(0-1)}-(P3)_{(0-2)}-P2-$,

where R^{21} represents C_{1-10}-alkyl-, C_{5-10}-aryl- or C_{6-10}-aralkyl-, C_{5-10}-heteroalkyl-, C_{1-10}-alkyl-O-C_{6-10}-aryl-, C_{5-10}-heterocycloalkyl-, heteroaryl-, heteroaryl-alkyl-, C_{1-10}-alkoxy-, C_{6-10}-aryloxy- or C_{6-10}-aralkoxy-, C_{5-10}-heteroalkoxy-, C_{1-10}-alkyl-O-C_{6-10}-aryloxy-, C_{5-10}-heterocycloalkoxy group, which may be substituted one or more times with - NH_2, -NH-alkyl, $-N(alkyl)_2$, -NH-C(=O)-alkyl, -N(alkyl)-C(=O)-alkyl, $-SO_3H$, $-SO_2NH_2$, $-SO_2-N(alkyl)_2$, -COOH, $-C(=O)-NH_2$, $-C(=O)-N(alkyl)_2$, or –OH; or which represents -H or a group $-(O)_x-(CH_2CH_2O)_y-R^{22}$,

where x is 0 or 1,

where v is a number from 1 to 10,

where R^{22} represents –H, –alkyl (preferably C_{1-12}-alkyl), $-CH_2-COOH$, $-CH_2-CH_2-COOH$, or $-CH_2-CH_2-NH_2$);

where P2 is an amino acid selected from Gly, Pro, Ala, Val, Nva, Leu, Ile, Met, Phe, Tyr, Trp, Ser, Thr, Cys, Asn, Gln, Asp, Glu, Lys, Arg, citrulline and His;

where P3 is an amino acid selected from Gly, Pro, Ala, Val, Nva, Leu, Ile, Met, Phe, Tyr, Trp, Ser, Thr, Cys, Asn, Gln, Asp, Glu, Lys, Arg, citrulline and His or one of the corresponding N-alkyl amino acids, preferably N-methyl amino acids;or

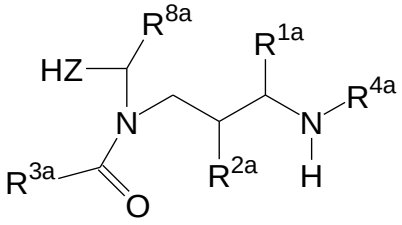
R^{2a} and R^{4a} together represent (with formation of a pyrrolidine ring) $–CH_2-CHR^{10}-$ or $-CHR^{10}-CH_2-$,

where R^{10} represents -H, halogen (preferably -F), $-NH_2$, -COOH, $-SO_3H$, -SH or -OH.

where the kinesin spindle protein inhibitor is attached to the linker by substitution of a hydrogen atom at R^{1a}, R^{2a}, R^{4a} or at the pyrrolidine ring formed by R^{2a} and R^{4a},

and the salts, solvates, salts of the solvates,and epimers thereof.

5. Conjugate according to Claim 4 where the kinesin spindle protein inhibitor is represented by general formula (Ia):



(Ia)

where

R^{1a} represents -H, -MOD or $-(CH_2)_{0-3}Z$,

where Z represents -H, halogen, $-OY^3$, $-SY^3$, $-NHY^3$, $-C(=O)-NY^1Y^2$ or $-C(=O)-OY^3$,

where Y^1 and Y^2 independently of one another represent -H, $-NH_2$, $-(CH_2CH_2O)_{0-3}-(CH_2)_{0-3}Z$‘ (e.g. $-(CH_2)_{0-3}Z$‘) or $-CH(CH_2W)Z$‘,

where Y^3 represents -H or $-(CH_2)_{0-3}Z$‘,

where Z‘ represents -H, $-SO_3H$, $-NH_2$, -COOH, $-NH-C(=O)-CH_2-CH_2-CH(NH_2)COOH$ or $-(C(=O)-NH-CHY^4)_{1-3}COOH$,

where W represents -H or -OH,

where Y^4 represents linear or branched C_{1-6}-alkyl which is optionally substituted by $–NH-C(=O)-NH_2$, or represents aryl or benzyl which are optionally substituted by $–NH_2$;

R^{2a} represents -H, –MOD, $-C(=O)-CHY^4-NHY^5$ or $-(CH_2)_{0-3}Z$,

where Z represents -H, $-OY^3$, $-SY^3$, $-NHY^3$, $-C(=O)-NY^1Y^2$ or $-C(=O)-OY^3$,

where Y^1 and Y^2 independently of one another represent -H, $-NH_2$ or $-(CH_2)_{0-3}Z$‘,

where Y^3 represents -H or $-(CH_2)_{0-3}Z$‘,

where Z‘ represents -H, $-SO_3H$, $-NH_2$ or -COOH;

where Y^4 represents linear or branched C_{1-6}-alkyl which is optionally substituted by –NH-C(=O)-NH_2, or represents aryl or benzyl which are optionally substituted by –NH_2,

where Y^5 represents -H or -C(=O)-CHY^6-NH_2,

where Y^6 represents linear or branched C_{1-6}-alkyl;

R^{4a} represents -H, -C(=O)-CHY^4-NHY^5 or -$(CH_2)_{0-3}$Z,

where Z represents -H, -OY^3, -SY^3, -NHY^3, -C(=O)-NY^1Y^2 or -C(=O)-OY^3,

where Y^1 and Y^2 independently of one another represent -H, -NH_2 or -$(CH_2)_{0-3}$Z‘,

where Y^3 represents -H or -$(CH_2)_{0-3}$Z‘,

where Z‘ represents -H, -SO_3H, -NH_2 or -COOH;

where Y^4 represents linear or branched C_{1-6}-alkyl which is optionally substituted by –NH-C(=O)-NH_2, or represents aryl or benzyl which are optionally substituted by –NH_2,

wheer Y^5 represents H or -C(=O)-CHY^6-NH_2,

where Y^6 represents linear or branched C_{1-6}-alkyl,

or

R^{4a} represents a group of R^{21}-$(C=O)_{(0-1)}$-$(P3)_{(0-2)}$-P2-NH-$CH(CH_2$-(C=O)-$NH_2)$-C(=O)- or R^{21}-$(C=O)_{(0-1)}$-$(P3)_{(0-2)}$-P2-NH-$CH(CH_2COOH)$-C(=O)- or the cathepsin cleavable group or formula R^{21}-$(C=O)_{(0-1)}$-$(P3)_{(1-2)}$-P2-,

where R^{21} represents -H, C_{1-10}-alkyl-, C_{5-10}-aryl- or C_{6-10}-aralkyl-, C_{5-10}-heteroalkyl-, C_{1-10}-alkyl-O-C_{6-10}-aryl-, C_{5-10}-heterocycloalkyl-, heteroaryl-, heteroaryl-alkyl-, C_{1-10}-alkoxy-, C_{6-10}-aryloxy- or C_{6-10}-aralkoxy-, C_{5-10}-heteroalkoxy-, C_{1-10}-alkyl-O-C_{6-10}-aryloxy-, C_{5-10}-heterocycloalkoxy group, which may be substituted one or more times with -NH_2, -NH-alkyl, -$N(alkyl)_2$, -NH-C(=O)-alkyl, -N(alkyl)-C(=O)-alkyl, -SO_3H, -SO_2NH_2, -$S(=O)_2$-$N(alkyl)_2$, -COOH, -C(=O)-NH_2, -C(=O)-$N(alkyl)_2$, or –OH; orrepresents -H or a group -O_x-$(CH_2CH_2O)_y$-R^{22},

where x is 0 or 1

where v s a number from 1 to 20,

where R^{22} represents –H, –alkyl (preferably C_{1-12}-alkyl), $-CH_2$-COOH, $-CH_2-CH_2$-COOH, or $-CH_2-CH_2-NH_2$);

where P2 is an amino acid selected from Gly, Pro, Ala, Val, Nva, Leu, Ile, Met, Phe, Tyr, Trp, Ser, Thr, Cys, Asn, Gln, Asp, Glu, Lys, Arg, citrulline and His;

where P3 is an amino acid selected from Gly, Pro, Ala, Val, Nva, Leu, Ile, Met, Phe, Tyr, Trp, Ser, Thr, Cys, Asn, Gln, Asp, Glu, Lys, Arg, citrulline and His or one of the corresponding N-alkyl amino acids, preferably N-methyl amino acids;

or

R^{2a} and R^{4a} together represent (with formation of a pyrrolidine ring) $–CH_2-CHR^{10}$- or $-CHR^{10}-CH_2$-,

where R^{10} represents H, halogen (preferably F), $-NH_2$, -COOH, $-SO_3H$, -SH or -OH, and wherein the hydrogen atom of the secondary amino group in the pyrrolidine ring may be replaced by R^{21}-C(=O)-$P3_{(0-2)}$-P2-NH-CH(CH_2C(=O)NH_2)-C(=O)-SIG-;

where P2 is an amino acid selected from Gly, Pro, Ala, Val, Nva, Leu, Ile, Met, Phe, Tyr, Trp, Ser, Thr, Cys, Asn, Gln, Asp, Glu, Lys, Arg, citrulline and His;

where P3 is an amino acid selected from Gly, Pro, Ala, Val, Nva, Leu, Ile, Met, Phe, Tyr, Trp, Ser, Thr, Cys, Asn, Gln, Asp, Glu, Lys, Arg, citrulline and His or one of the corresponding N-alkyl amino acids, preferably N-methyl amino acids;

where –SIG is a self-immolative group, which, upon cleavage of the C(=O)-SIG bond provides the free secondary amine;

R^{3a} represents –MOD or an optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, heteroalkyl or heterocycloalkyl group, preferably a C_{1-10}-alkyl, C_{6-10}-aryl or C_{6-10}-aralkyl, C_{5-10}-heteroalkyl, C_{1-10}-alkyl-O-C_{6-10}-aryl or C_{5-10}-heterocycloalkyl group which may be substituted by 1-3 –OH groups, 1-3 halogen atoms, 1-3 halogenated alkyl groups (each having 1-3 halogen atoms), 1-3 O-alkyl groups, 1-3 –SH groups, 1-3 -S-alkyl groups, 1-3 -O-C(=O)-alkyl groups, 1-3 -O-C(=O)-NH-alkyl groups, 1-3 -NH-C(=O)-alkyl groups, 1-3 -NH-C(=O)-NH-alkyl groups, 1-3 -$S(=O)_n$-alkyl groups, 1-3 -$S(=O)_2$-NH-alkyl groups, 1-3 -NH-alkyl groups, 1-3 -$N(alkyl)_2$ groups, 1-3 -NH_2 groups or 1-3 -$(CH_2)_{0-3}Z$ groups,

where Z represents -H, halogen, -OY^3, -SY^3, -NHY^3, -C(=O)-NY^1Y^2 or -C(=O)-OY^3,

where –MOD is represented as defined infra,

where n is 0, 1 or 2,

where Y^1 and Y^2 independently of one another represent -H, -NH_2 or -$(CH_2)_{0-3}Z$‘,

where Y^3 represents -H, -$(CH_2)_{0-3}$-CH(NH-C(=O)-CH_3)Z‘, -$(CH_2)_{0-3}$-$CH(NH_2)$Z‘ or -$(CH_2)_{0-3}$Z‘,

where Z‘ represents -H, -SO_3H, -NH_2 or -COOH

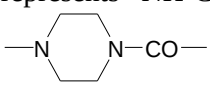
R^{8a} represents C_{1-10}-alkyl;

HZ represents a mono- or bicyclic heterocycle which may be substituted by one or more substituents selected from the group consisting of halogen, C_{1-10}-alkyl groups, C_{6-10}-aryl groups and C_{6-10}-aralkyl groups which may optionally be substituted by halogen;

–MOD as defined supra represents –(NR^{10})n-(G1)o-G2-G3,

where R^{10} represents -H; halogen or C_1-C_3-alkyl;

where G1 represents –NH-C(=O)- , -C(=O)-NH- or



where n is 0 or 1;

where o is 0 or 1;

where G2 represents a linear and/or branched hydrocarbon group which has 1 to 10 carbon atoms and which may be interrupted once or more than once by one or more of the groups
-O-, -S-, -S(=O)-, -$S(=O)_2$-, -NR^y-, -$NR^yC(=O)$-,
-$C(=O)$-NR^y-, -NR^yNR^y-, -$S(=O)_2$-NRyNRy-,
-$C(=O)$-NR^yNR^y-, -C(=O)-, -CR^x=N-O-,
and where the hydrocarbon group including any side chains may be substituted by –$NHC(=O)$-NH_2, -COOH, -OH, -NH_2, -NH-CN-NH_2, sulphonamide, sulphone, sulphoxide or sulphonic acid,

where R^y represents H, phenyl, C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl or C_2-C_{10}-alkynyl, each of which may be substituted by -NH-C(=O)-NH_2, -COOH, -OH, -NH_2, -NH-$CNNH_2$, sulphonamide, sulphone, sulphoxide or sulphonic acid,

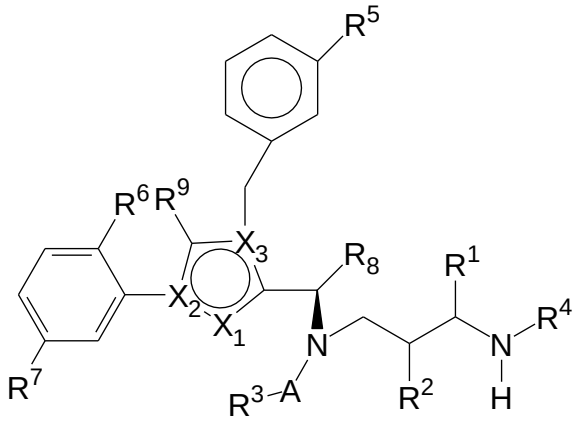
where R^x represents -H, C_1-C_3-alkyl or phenyl),

where G3 represents –H or –COOH,

where –MOD preferably has at least one group -COOH;

and the salts, solvates, salts of the solvates,and epimers thereof.

6. Conjugate according to one or more of the preceding claims, where the linker L is attached to a glutamine side chain of the binder, where 1 to 5 kinesin spindle protein inhibitors are attached to the linker L, where the active compound molecule linker is represented by general formula (II):



(II)

where

X_1 represents N, X_2 represents N and X_3 represents C; or

X_1 represents CH or CF, X_2 represents C and X_3 represents N; or

X_1 represents NH, X_2 represents C and X_3 represents C; or

X_1 represents CH, X_2 represents N and X_3 represents C

R^1 represents -H, -MOD, –L-#1 or $-(CH_2)_{0-3}Z$,

where –L-#1 represents the linker and #1 represents the bond to the binder or derivative thereof.

where –MOD is represented as defined infra,

where Z represents -H, halogen, $-OY^3$, $-SY^3$, $-NHY^3$, $-C(=O)-NY^1Y^2$ or $-C(=O)-OY^3$,

where Y^1 and Y^2 independently of one another represent -H, $-NH_2$, $-(CH_2CH_2O)_{0-3}-(CH_2)_{0-3}Z‘$ (e.g. $-(CH_2)_{0-3}Z‘$) or $-CH(CH_2W)Z‘$,

where Y^3 represents -H or $-(CH_2)_{0-3}Z‘$,

where Z‘ represents -H, $-NH_2$, $-SO_3H$, -COOH, $-NH-C(=O)-CH_2-CH_2-CH(NH_2)COOH$ or $-(C(=O)-NH-CHY^4)_{1-3}COOH$,

where W represents -H or -OH,

where Y^4 represents linear or branched C_{1-6}-alkyl which is optionally substituted by $–NH-C(=O)-NH_2$, or represents aryl or benzyl which are optionally substituted by $–NH_2$;

R^2 represents –L-#1, H, -MOD, $-C(=O)-CHY^4-NHY^5$ or $-(CH_2)_{0-3}Z$,

where –L-#1 represents the linker and #1 represents the bond to the binder or derivative thereof,

where –MOD is represented as defined infra,

where Z represents -H, halogen, $-OY^3$, $-SY^3$, NHY^3, $-C(=O)-NY^1Y^2$ or $-C(=O)-OY^3$,

where Y^1 and Y^2 independently of one another represent -H, $-NH_2$ or $-(CH_2)_{0-3}Z‘$, and

where Y^3 represents -H or $-(CH_2)_{0-3}Z‘$,

where Z‘ represents -H, $-SO_3H$, $-NH_2$ or -COOH;

where Y^4 represents linear or branched C_{1-6}-alkyl which is optionally substituted by –NH-C(=O)-NH_2, or represents aryl or benzyl which are optionally substituted by –NH_2,

where Y^5 represents -H or -C(=O)-CHY^6-NH_2,

where Y^6 represents linear or branched C_{1-6}-alkyl;

R^4 represents –L-#1, -H, -C(=O)-CHY^4-NHY^5 or -$(CH_2)_{0-3}$Z,

where –L-#1 represents the linker and #1 represents the bond to the binder or derivative thereof,

where Z represents -H, -OY^3, -SY^3, -NHY^3, -C(=O)-NY^1Y^2 or -C(=O)-OY^3,

where Y^1 and Y^2 independently of one another represent -H, -NH_2 or -$(CH_2)_{0-3}$Z‘,

where Y^3 represents -H or -$(CH_2)_{0-3}$Z‘,

where Z‘ represents -H, -SO_3H, -NH_2 or -COOH;

where Y^4 represents linear or branched C_{1-6}-alkyl which is optionally substituted by –NH-C(=O)-NH_2, or represents aryl or benzyl which are optionally substituted by –NH_2, and

where Y^5 represents -H or -C(=O)-CHY^6-NH_2,

where Y^6 represents linear or branched C_{1-6}-alkyl,

or

R^4 represents a group of R^{21}-$(C=O)_{(0-1)}$-$(P3)_{(0-2)}$-P2-NH-CH(CH_2C(=O)-NH_2)-C(=O)- or R^{21}-$(C=O)_{(0-1)}$-$(P3)_{(0-2)}$-P2-NH-CH(CH_2COOH)-C(=O)- or the cathepsin cleavable group R^{21}-$(C=O)_{(0-1)}$-$(P3)_{(1-2)}$-P2-,

where R^{21} represents -H, C_{1-10}-alkyl-, C_{5-10}-aryl- or C_{6-10}-aralkyl-, C_{5-10}-heteroalkyl-, C_{1-10}-alkyl-O-C_{6-10}-aryl-, C_{5-10}-heterocycloalkyl-, heteroaryl-, heteroaryl-alkyl-, C_{1-10}-alkoxy-, C_{6-10}-aryloxy- or C_{6-10}-aralkoxy-, C_{5-10}-heteroalkoxy-, C_{1-10}-alkyl-O-C_{6-10}-aryloxy-, C_{5-10}-heterocycloalkoxy group, which may be substituted one or more times with - NH_2,

-NH-alkyl, -N(alkyl)$_2$, -NH-C(=O)-alkyl, N(alkyl)-C(=O)-alkyl, -SO_3H, -S(=O)$_2$NH$_2$, -S(=O)$_2$-N(alkyl)$_2$, -COOH, -C(=O)-NH$_2$, -C(=O)-N(alkyl)$_2$, or –OH, or represent -H or a group –$(O)_x$-$(CH_2CH_2O)_y$-R^{22},

where x is 0 or 1 and

where v is a number from 1 to 20,

where R^{22} represents –H, –alkyl (preferably C_{1-12}-alkyl), -CH_2-COOH, -CH_2-CH_2-COOH, or -CH_2-CH_2-NH_2);

where P2 is an amino acid selected from Gly, Pro, Ala, Val, Nva, Leu, Ile, Met, Phe, Tyr, Trp, Ser, Thr, Cys, Asn, Gln, Asp, Glu, Lys, Arg, citrulline and His;

where P3 is an amino acid independently selected from Gly, Pro, Ala, Val, Nva, Leu, Ile, Met, Phe, Tyr, Trp, Ser, Thr, Cys, Asn, Gln, Asp, Glu, Lys, Arg, citrulline and His or one of the corresponding N-alkyl amino acids, preferably N-methyl amino acids; in case there is more than one amino acid P3, P3 may have the same or different amino acids, as defined above;

or

R^2 and R^4 together (with formation of a pyrrolidine ring) represent –CH_2-CHR^{10}- or -CHR^{10}-CH_2-,

where R^{10} represents -H, halogen (preferably -F), -NH_2, -SO_3H, -COOH, -SH or -OH, and wherein the hydrogen atom of the secondary amino group in the pyrrolidine ring may be replaced by R^{21}-C(=O)-$P3_{(0-2)}$-P2-NH-CH(CH_2C(=O)-NH_2)-C(=O)-SIG-;

where P2 is an amino acid selected from Gly, Pro, Ala, Val, Nva, Leu, Ile, Met, Phe, Tyr, Trp, Ser, Thr, Cys, Asn, Gln, Asp, Glu, Lys, Arg, citrulline and His;

where P3 is an amino acid independently selected from Gly, Pro, Ala, Val, Nva, Leu, Ile, Met, Phe, Tyr, Trp, Ser, Thr, Cys, Asn, Gln, Asp, Glu, Lys, Arg, citrulline and His or one of the corresponding N-alkyl amino acids, preferably N-methyl amino acids;

where –SIG is a self-immolative group, which, upon cleavage of the –C(=O)-SIG bond provides the free secondary amine;

A represents -C(=O)-, -S(=O)-, -$S(=O)_2$-, -$S(=O)_2$-NH- or –C(=N-NH_2)-;

R^3 represents –L-#1, -MOD or an optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, heteroalkyl, heterocycloalkyl group, preferably –L-#1 or a C_{1-10}-alkyl, C_{6-10}-aryl or C_{6-10}-aralkyl, C_{5-10}-heteroalkyl, C_{1-10}-alkyl-O-C_{6-10}-aryl or C_{5-10}-heterocycloalkyl group which may be substituted by 1-3 –OH groups, 1-3 halogen atoms, 1-3 halogenated alkyl groups (each having 1-3 halogen atoms), 1-3 -O-alkyl groups, 1-3 –SH groups, 1-3 -S-alkyl groups, 1-3 -O-C(=O)-alkyl groups, 1-3 -O-C(=O)-NH-alkyl groups, 1-3 -NH-C(=O)-alkyl groups, 1-3 -NH-C(=O)-NH-alkyl groups, 1-3 -$S(=O)_n$-alkyl groups, 1-3 -$S(=O)_2$-NH-alkyl groups, 1-3 -NH-alkyl groups, 1-3 -$N(alkyl)_2$ groups, 1-3 -NH_2 groups or 1-3 -$(CH_2)_{0-3}$Z groups,

where –L-#1 represents the linker and #1 represents the bond to the binder or derivative thereof,

where –MOD is represented as defined infra,

where n represents 0, 1 or 2,

where Z represents -H, halogen, -OY^3, -SY^3, -NHY^3, -C(=O)-NY^1Y^2 or -C(=O)-OY^3,

where Y^1 and Y^2 independently of one another represent -H, -NH_2 or -$(CH_2)_{0-3}$Z‘ and

where Y^3 represents -H, -$(CH_2)_{0-3}$-CH(NHC(=O)-CH_3)Z‘, -$(CH_2)_{0-3}$-CH(NH_2)Z‘ or -$(CH_2)_{0-3}$Z‘, where

where Z‘ represents -H, -SO_3H, -NH_2 or –COOH;

R^5 represents -H, -NH_2, -NO_2, halogen (in particular -F, -Cl, -Br), -SH or -$(CH_2)_{0-3}$Z,

where Z represents -H, -OY^3, -SY^3, halogen, -NHY^3, -C(O)-NY^1Y^2 or -C(O)-OY^3,

where Y^1 and Y^2 independently of one another represent -H, -NH_2 or -$(CH_2)_{0-3}Z$‘,

where Y^3 represents -H or -$(CH_2)_{0-3}Z$‘,

where Z‘ represents -H, -SO_3H, -NH_2 or -COOH;

R^6 and R^7 independently of one another represent -H, cyano, C_{1-10}-alkyl, fluoro-C_{1-10}-alkyl, C_{2-10}-alkenyl, fluoro-C_{2-10}-alkenyl, C_{2-10}-alkynyl, fluoro-C_{2-10}-alkynyl, hydroxy or halogen (in particular -F, -Cl, -Br),

R^8 represents C_{1-10}-alkyl, fluoro-C_{1-10}-alkyl, C_{4-10}-cycloalkyl, fluoro-C_{4-10}-cycloalkyl, or optionally substituted oxetane; and

R^9 represents -H, -F, -CH_3, -CF_3, -CH_2F or -CHF_2;

and the salts, solvates, salts of the solvates,and epimers thereof.

7. Conjugate according to Claim 6,

R^1 represents -H, –L-#1 or -$(CH_2)_{0-3}Z$,

where –L-#1 represents the linker and #1 represents the bond to the binder or derivative thereof.

where Z represents -H, -OY^3, -SY^3, -NHY^3, -C(=O)-NY^1Y^2 or -C(=O)-OY^3,

where Y^1 and Y^2 independently of one another represent -H, -NH_2, -$(CH_2CH_2O)_{0-3}$-$(CH_2)_{0-3}Z$‘ or -$CH(CH_2W)Z$‘,

where Y^3 represents -H or -$(CH_2)_{0-3}Z$‘,

where Z‘ represents -H, -NH_2, -COOH, -NH-C(=O)-CH_2-CH_2-$CH(NH_2)$COOH or -$(C(=O)$-NH-$CHY^4)_{1-3}$COOH,

where W represents -H or -OH,

where Y^4 represents linear or branched C_{1-6}-alkyl which is optionally substituted by –NH-C(=O)-NH_2, or represents aryl or benzyl which are optionally substituted by –NH_2;

R^2 and R^4 independently of one another represent –L-#1, -H or -C(=O)-CHY^4-NHY^5,

where –L-#1 represents the linker and #1 represents the bond to the binder or derivative thereof,

where Y^4 represents linear or branched C_{1-6}-alkyl which is optionally substituted by –NH-C(=O)-NH_2, or represents aryl or benzyl which are optionally substituted by –NH_2,

where Y^5 represents -H or -C(=O)-CHY^6-NH_2,

where Y^6 represents linear or branched C_{1-6}-alkyl;

or

R^2 and R^4 together (with formation of a pyrrolidine ring) represent –CH_2-CHR^{10}-,

where R^{10} represents –L-#1, -H, -NH_2, -SO_3H, -COOH, -SH or -OH,

where L-#1 represents the linker and #1 represents the bond to the binder or derivative thereof,

A represents -C(=O);

R^3 represents –(CH_2)OH or –L-#1,

where –L-#1 represents the linker and #1 represents the bond to the binder or derivative thereof,

R^5 represents –L-#1 or -H,

where –L-#1 represents the linker and #1 represents the bond to the binder or derivative thereof,

where one of the substituents R^1, R^2, R^3, R^4 and R^5 represents –L-#1,
and the salts, solvates, salts of the solvates,and epimers thereof.

8. Conjugate according to Claim 6 where R^6 and R^7 independently of one another represent H, C_{1-3}-alkyl or halogen.

9. Conjugate according to Claim 6 where R^8 represents C_{1-4}-alkyl (preferably tert-butyl).

10. Conjugate according to Claim 6 where R^9 represents H.

11. Conjugate according to Claim 6 where R^6 and R^7 represent F.

12. Conjugate according to one or more of the preceding claims where the binder or derivative thereof is a binder peptide or protein or a derivative of a binder peptide or protein.

13. Conjugate according to one or more of the preceeding claims where the conjugate has 2 conjugation sites per binder.

14. Conjugate according to one or more of the preceeding claims where the conjugate has 4 conjugation sites per binder.

15. Conjugate according to one or more of Claims 12 to 14 where the binder peptide or protein represents an antibody or the derivative of the binder peptide or protein comprising an acceptor glutamine side chain which can be recognized by transglutaminase.

16. Conjugate according to one or more of the preceding claims where the binder binds to a cancer target molecule.

17. Conjugate according to Claim 16 where the binder binds to an extracellular target molecule.

18. Conjugate according to Claim 17 where the binder, after binding to the extracellular target molecule, is internalized and processed intracellularly (preferably lysosomally) by the cell expressing the target molecule.

19. Conjugate according to one or more of Claims 12 to 18 where the binder peptide or protein is a human, humanized or chimeric monoclonal antibody or an antigen-binding fragment thereof.

20. Conjugate according to one or more of the preceding claims where the binder peptide or protein is an antibody bearing acceptor glutamine residue(s) in its heavy chain, optionally within the CH2 domain.

21. Conjugate according to Claim 20 where the binder peptide or protein is an antibody bearing acceptor glutamine residue is in its heavy chain at position 295 (KABAT numbering system).

22. Conjugate according to Claim 20 where the binder peptide or protein is an antibody comprising a N297X substitution wherein X is any amino acid but asparagine; even more preferred are N297D, N297Q, N297S or N297A, highly preferred are N297A and N297Q.

23. Conjugate according to Claim 20 where the binder peptide or protein is an antibody comprising N297Q substitution and a Q295X substitution wherein X is any amino acid but glutamine, preferred is Q295N.

24. Conjugate according to one or more of the preceding claims where the binder peptide or protein is an antibody comprising an asparagine at residue 297 that substantially lacks N-linked glycosylation.

25. Conjugate according to Claim 24 where the binder peptide or protein is an antibody produced in a host cell that produces antibodies lacking N-linked glycosylation at amino acid residue N297.

26. Conjugate according to one or more of the preceding claims where the binder peptide or protein is an anti-HER2 antibody, an anti-EGFR antibody, an anti-TWEAKR antibody or an antigen-binding fragment thereof.

27. Conjugate according to Claim 26 where the anti-TWEAKR antibody binds specifically to amino acid D in position 47 (D47) of TWEAKR (SEQ ID NO:169), prefably the anti-TWEAKR antibody TPP2090 and aglycosylated variants thereof.

28. Conjugate according to Claims 26 and 27 where the anti-TWEAKR antibody binds specifically to amino acid D in position 47 (D47) of TWEAKR (SEQ ID NO:169), preferably the anti-TWEAKR antibody TPP-2090-HC-N297A or TPP-2090-HC-N297Q.

29.-Conjugate according to one or more of the preceding claims, where the linker L is attached to a glutamine side chain of the binder, where 1 to 5 kinesin spindle protein inhibitors are attached to the linker L, where the linker L has one of the basic structures (i) to (iv) below:

(i) $-(C=O)_m–SG1-L1-L2-$

(ii) $-(C=O)_m–L1-SG-L1-L2-$

(iii) $-(C=O)_m–L1-L2-$

(iv) $–(C=O)_m–L1-SG-L2$

where m is 0 or 1, SG and SG1 are *in vivo* cleavable groups, L1 independently of one another represent organic groups not cleavable *in vivo*, and L2 represents a coupling group to the binder.

30. Conjugate according to Claim 29, where the linker L is attached to a glutamine side chain of the binder, where 1 to 5 kinesin spindle protein inhibitors are attached to the linker L, where the *in vivo* cleavable group SG is a 2-8 oligopeptide group, preferably a dipeptide group or a disulphide, a hydrazone, an acetal or an aminal and SG1 is a 2-8 oligopeptide group, preferably a dipeptide group.

31. Conjugate according to Claim 29

where the linker is attached to a glutamine side chain and has the formula below:

§-(C=O)m-L1-L2-§§

where

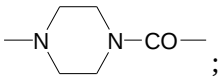
m is 0 or 1;

§ represents the bond to the active compound molecule and

§§ represents the bond to the binder peptide or protein, and

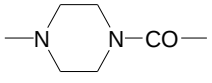
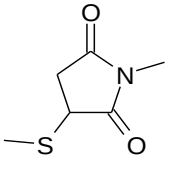
L1 represents $–(NR^{10})n-(G1)o-G3-$,

where R^{10} represents -H, $-NH_2$ or C_1-C_3-alkyl;

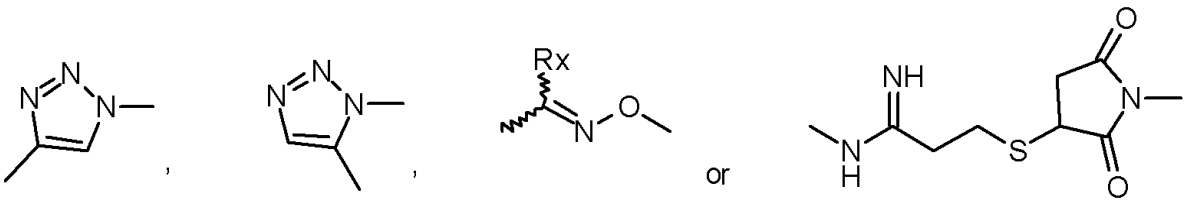
G1 represents –NH-C(=O)- or ;

n is 0 or 1;

o is 0 or 1; and

G3 represents a bond or an optionally substituted linearlinear or branched hydrocarbon chain having 1 to 100 carbon atoms from arylene groups and/or linearlinear and/or branched and/or cyclic alkylene groups and which may be interrupted once or more than once by one or more of the groups -O-, -S-, -S(=O)-, $-S(=O)_2-$, -NH-, -C(=O)-, -NMe-, -NHNH-, $-S(=O)_2-NHNH-$, -NH-C(=O)-, -C(=O)-NH-, -C(=O)-NHNH- and a 5- to 10-membered aromatic or non-aromatic heterocycle having up to 4 heteroatoms selected from the group consisting of -N-, -O- and -S-, -S(=O)- or $–S(=O)_2-$ (preferably  or ), where the side chains, if present, may be substituted by $–NH-C(=O)-NH_2$, -COOH, -OH, $-NH_2$, $-NH-CN-NH_2$, sulphonamide, sulphone, sulphoxide or sulphonic acid,

or represents one of the groups below:



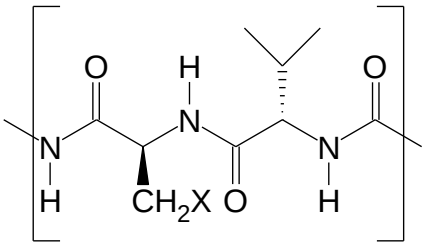
where Rx represents -H, C_1-C_3-alkyl or phenyl;

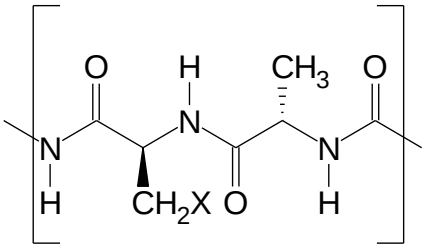
L2 represents $\#^1$–$(NH)_p$-$(C=O)_q$-G4-NH-$\#^2$ or $\#^1$–$(NH)_p$-$(C=O)_q$-G4-O-NH-$\#^2$
where
p is 0 or 1;
q is 0 or 1; and
G4 represents an optionnally substituted alkyl or heteroalkyl chain optionally wherein any carbon of the chain is substituted with an alkoxy, hydroxyl, alkylcarbonyloxy, -S-alkyl, -thiol, -C(=O)-S-alkyl, -C(=O)-NH-alkyl, -NH-C(=O)-alkyl, amine, $-C(=O)-NH_2$
where

$\#^1$ denotes the point of attachment to group L^1,

$\#^2$ denotes the point of attachment to the glutamine residue of the binder.

32. Conjugate according to Claim 31 where the hydrocarbon chain is interrupted by one of the groups below:

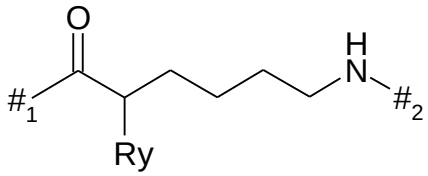


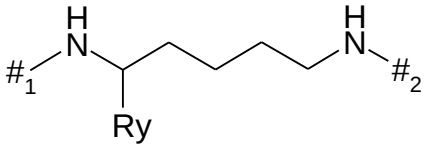


where X represents H or a C_{1-10}-alkyl group which may optionally be substituted by

–NH-C(=O)-NH_2, -COOH, -OH, -NH_2, -NH-CN-NH_2, sulphone, sulphoxide or sulphonic acid.

33. Conjugate according to one or more of Claims 29 to 32 where L2 is one of the groups below:
L2 is





with Ry is -H, -C(=O)-NH-alkyl, -NH-C(=O)-alkyl, -C(=O)-NH_2, -NH_2,
where

#[1] denotes the point of attachment to group L^1,

#[2] denotes the point of attachment to the glutamine residue of the binder.

34. Conjugate according to Claim 33 where Ry is -H or -NH-C(=O)-CH_3

35. Conjugate according to Claim 33 or 34 where R^1 or R^4 represents –L-#1.

36. Conjugate according to claims 26 to 35 where the anti-TWEAKR antibody is an agonistic antibody.

37. Conjugate according to one or more of the preceding claims where the binder peptide or protein is an antibody comprising:

a variable heavy chain comprising:

a. a CDR1 of the heavy chain encoded by an amino acid sequence comprising the formula PYPMX (SEQ ID NO: 171), where X is I or M;

b. a CDR2 of the heavy chain encoded by an amino acid sequence comprising the formula YISPSGGXTHYADSVKG (SEQ ID NO: 172), where X is S or K; and

c. a CDR3 of the heavy chain encoded by an amino acid sequence comprising the formula GGDTYFDYFDY (SEQ ID NO: 173);

and a variable light chain comprising:

d. a CDR1 of the light chain encoded by an amino acid sequence comprising the formula RASQSISXYLN (SEQ ID NO: 174), where X is G or S;

e. a CDR2 of the light chain encoded by an amino acid sequence comprising the formula XASSLQS (SEQ ID NO: 175), where X is Q, A or N; and

f. a CDR3 of the light chain encoded by an amino acid sequence comprising the formula QQSYXXPXIT (SEQ ID NO: 176), where X at position 5 is T or S, X at position 6 is T or S and X at position 8 is G or F.

38. Conjugate according to claim 12 where the binder peptide or protein is an antibody which comprises:

a. a variable sequence of the heavy chain, as shown in SEQ ID NO:10, and also a variable sequence of the light chain, as shown in SEQ ID NO:9, or

b. a variable sequence of the heavy chain, as shown in SEQ ID NO:20, and also a variable sequence of the light chain, as shown in SEQ ID NO:19, or

c. a variable sequence of the heavy chain, as shown in SEQ ID NO:30, and also a variable sequence of the light chain, as shown in SEQ ID NO:29, or

d. a variable sequence of the heavy chain, as shown in SEQ ID NO:40, and also a variable sequence of the light chain, as shown in SEQ ID NO:39, or

e. a variable sequence of the heavy chain, as shown in SEQ ID NO:50, and also a variable sequence of the light chain, as shown in SEQ ID NO:49, or

f. a variable sequence of the heavy chain, as shown in SEQ ID NO:60, and also a variable sequence of the light chain, as shown in SEQ ID NO:59, or

g. a variable sequence of the heavy chain, as shown in SEQ ID NO:70, and also a variable sequence of the light chain, as shown in SEQ ID NO:69, or

h. a variable sequence of the heavy chain, as shown in SEQ ID NO:80, and also a variable sequence of the light chain, as shown in SEQ ID NO:79, or

i. a variable sequence of the heavy chain, as shown in SEQ ID NO:90, and also a variable sequence of the light chain, as shown in SEQ ID NO:89, or

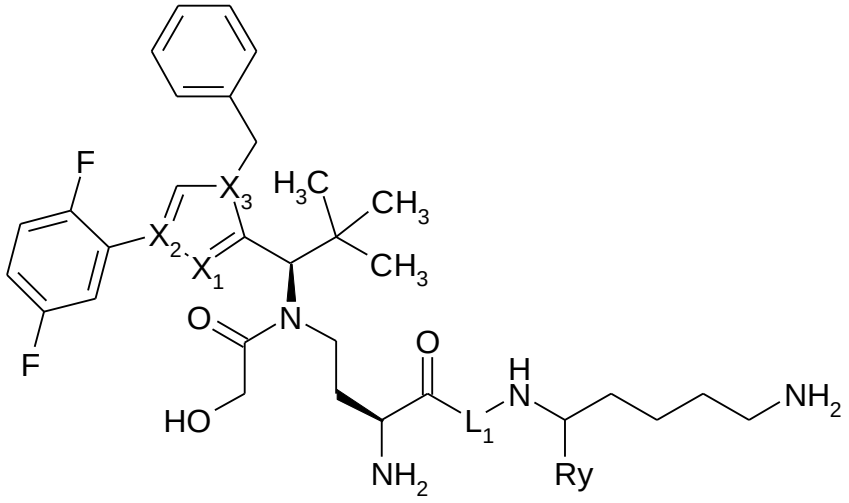
j. a variable sequence of the heavy chain, as shown in SEQ ID NO:100, and also a variable sequence of the light chain, as shown in SEQ ID NO:99, or

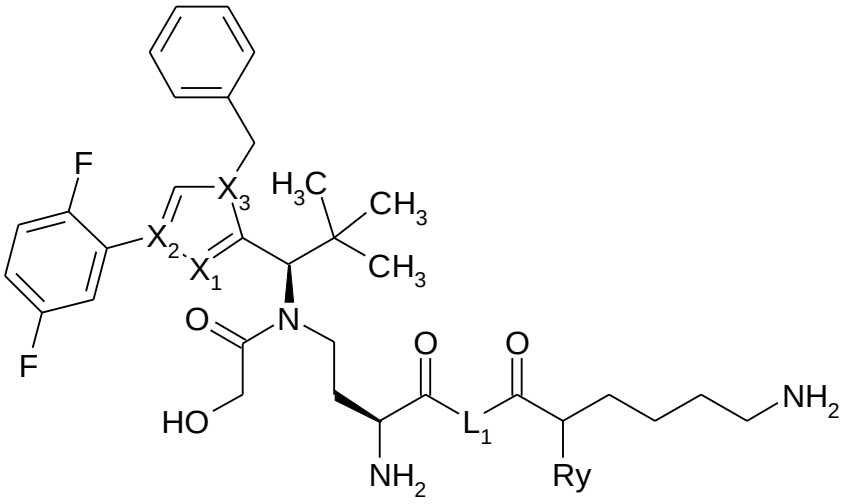
k. a variable sequence of the heavy chain, as shown in SEQ ID NO:110, and also a variable sequence of the light chain, as shown in SEQ ID NO:109, or

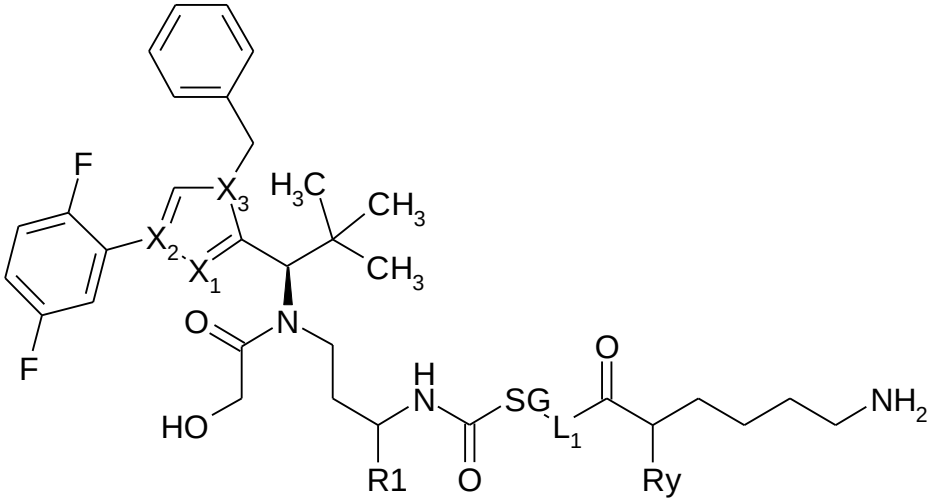
l. a variable sequence of the heavy chain, as shown in SEQ ID NO:120, and also a variable sequence of the light chain, as shown in SEQ ID NO:119.

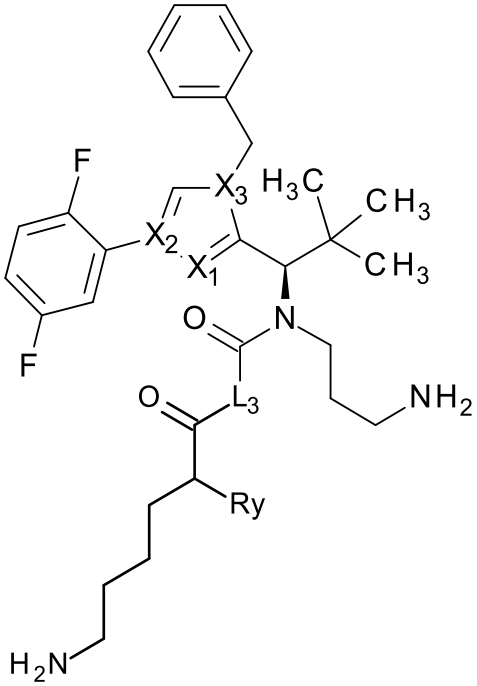
39. Conjugate according to one or more of the preceding claims where the antibody is an IgG antibody.

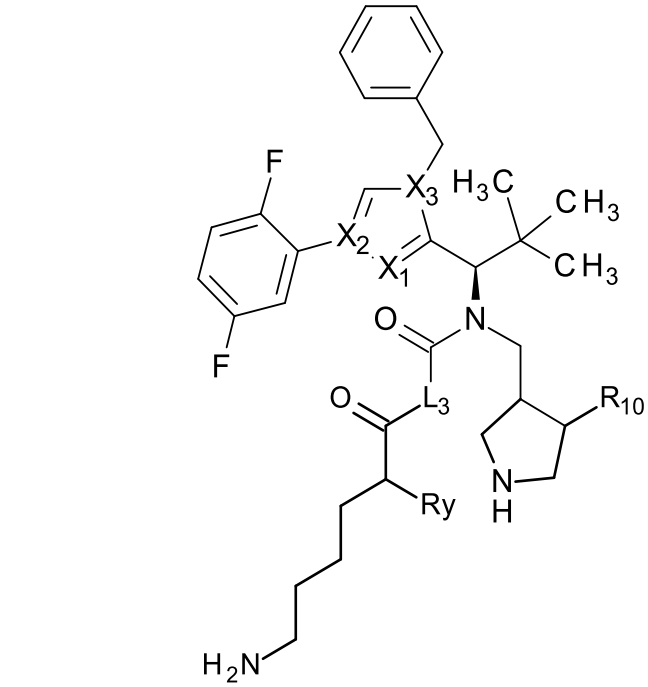
40. Process for preparing the conjugate according to one or more of the preceding claims where a compound of one of the formulae below, preferably in the form of its trifluoroacetic acid salt, is conjugated to a residue of a binder peptide or protein using transglutaminase, where the compound is preferably employed in a 2- to 100-fold molar excess with respect to the binder peptide or protein:

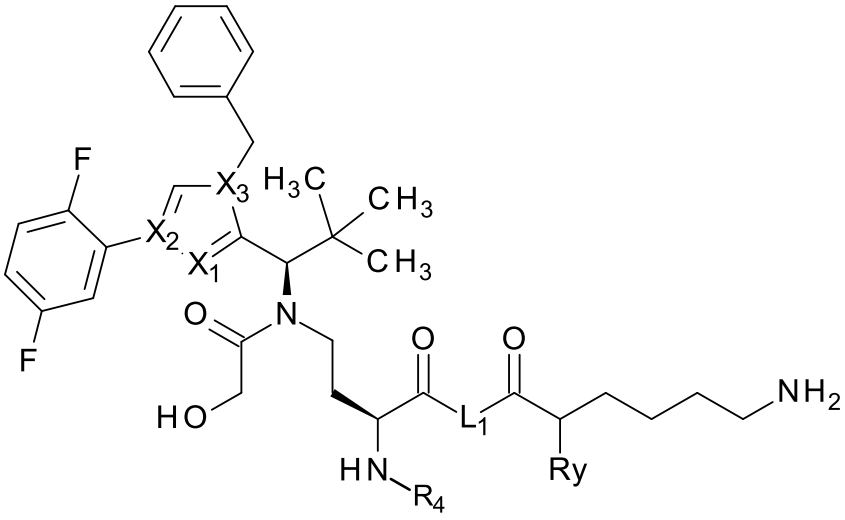



F
X3
H3C
CH3
X2
X1
CH3
O
N
O
O
F
HO
L1
NH2
NH2
Ry


F
X3
H3C
CH3
X2
X1
CH3
O
N
O
F
H
HO
N
SG
L1
NH2
R1
O
Ry

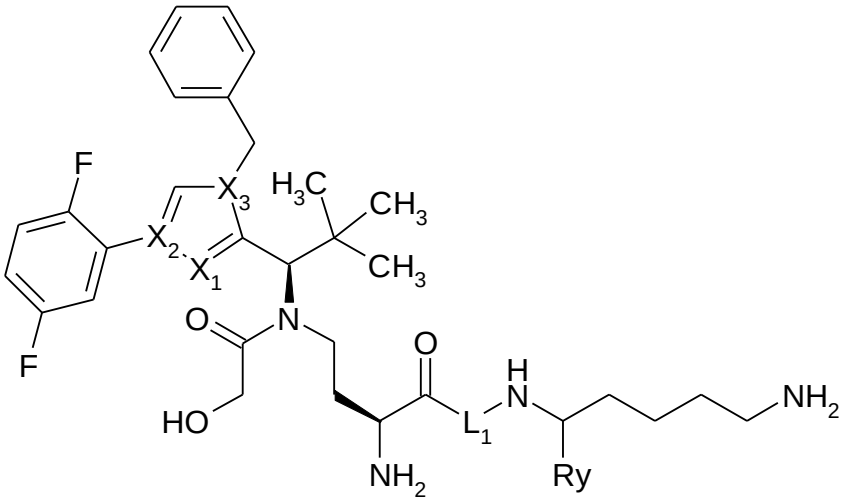

F
X3
H3C
CH3
X2
X1
CH3
O
N
F
O
L3
NH2
Ry
H2N

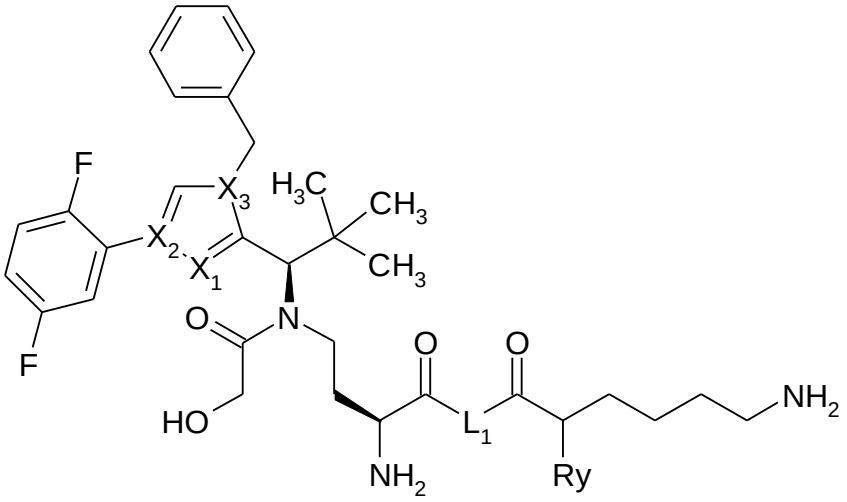


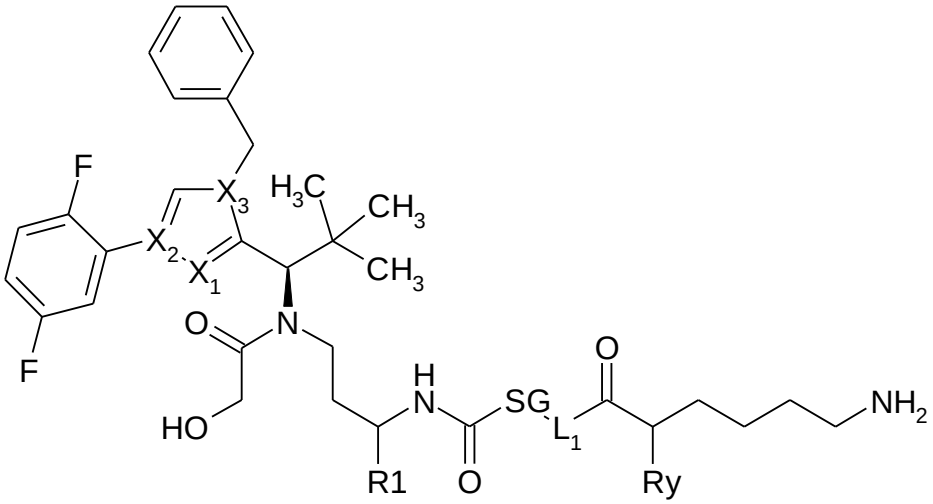


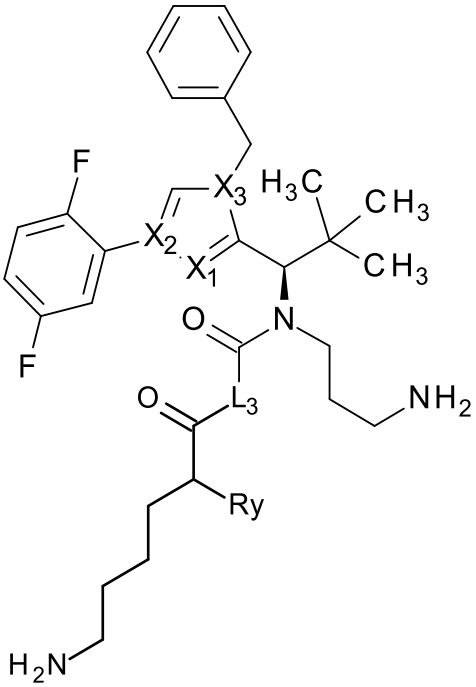
where X_1, X_2, X_3, SG, L1, L3, R1, R4, R10 and Ry have the same meaning as in Claims 1 to 39.

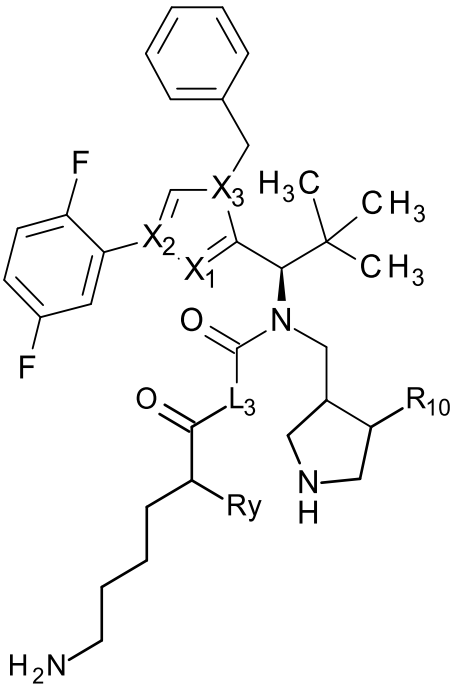
41. Compound of one of the formulae below:

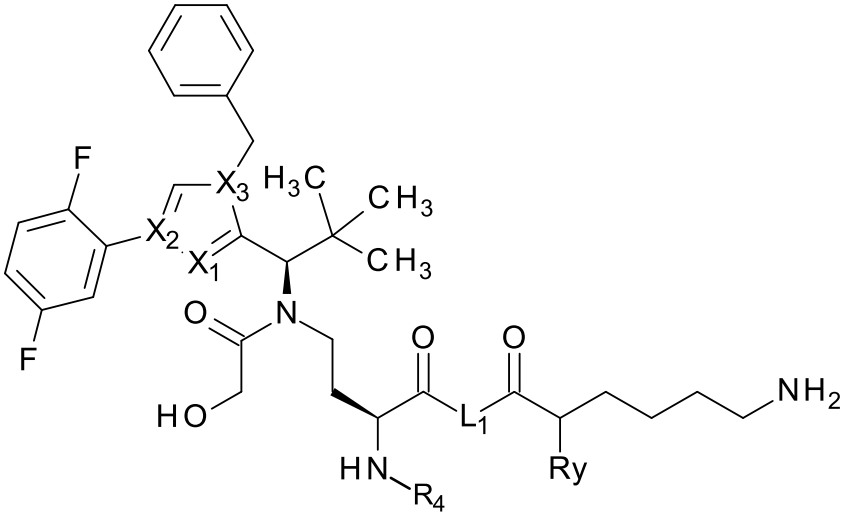

F
F
X3
X2
X1
H3C
CH3
CH3
O
N
HO
NH2
O
H
N
L1
Ry
NH2


F
F
X3
X2
X1
H3C
CH3
CH3
O
N
HO
NH2
O
O
L1
Ry
NH2


F
F
X3
X2
X1
H3C
CH3
CH3
O
N
HO
H
N
R1
O
SG
L1
O
Ry
NH2

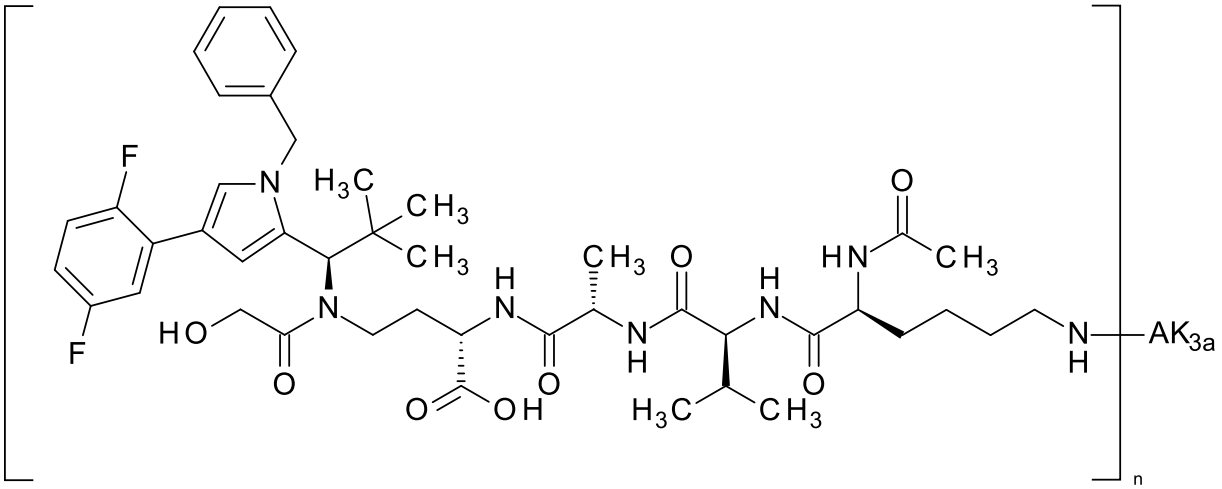


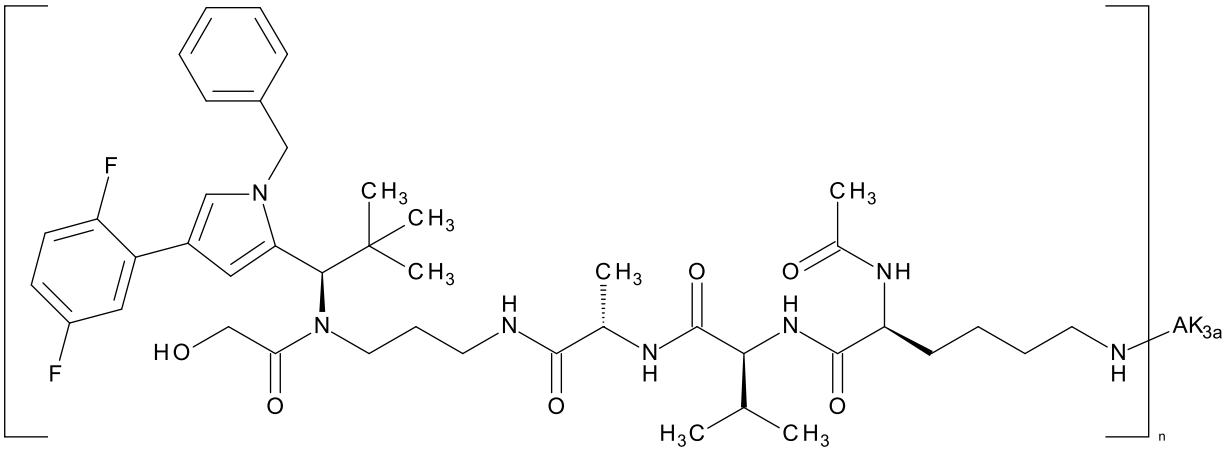


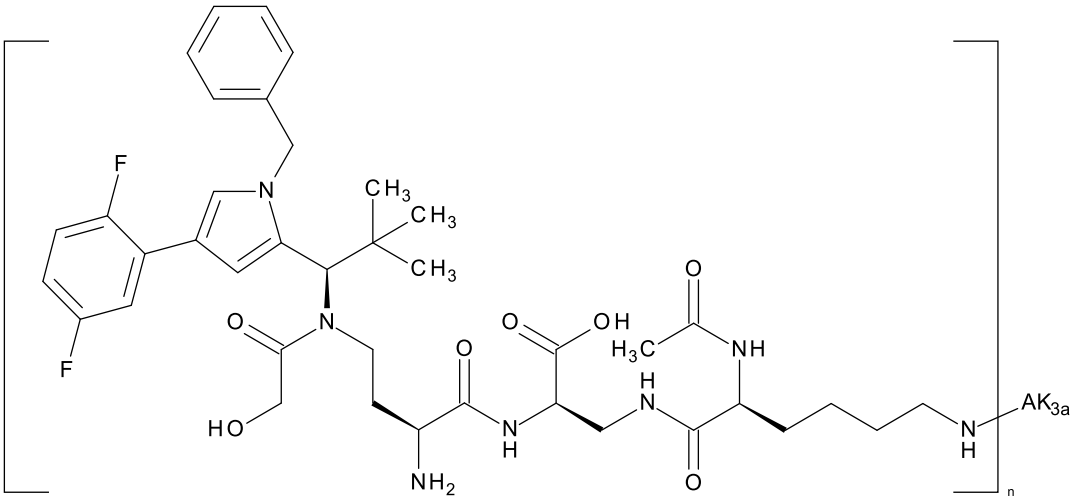


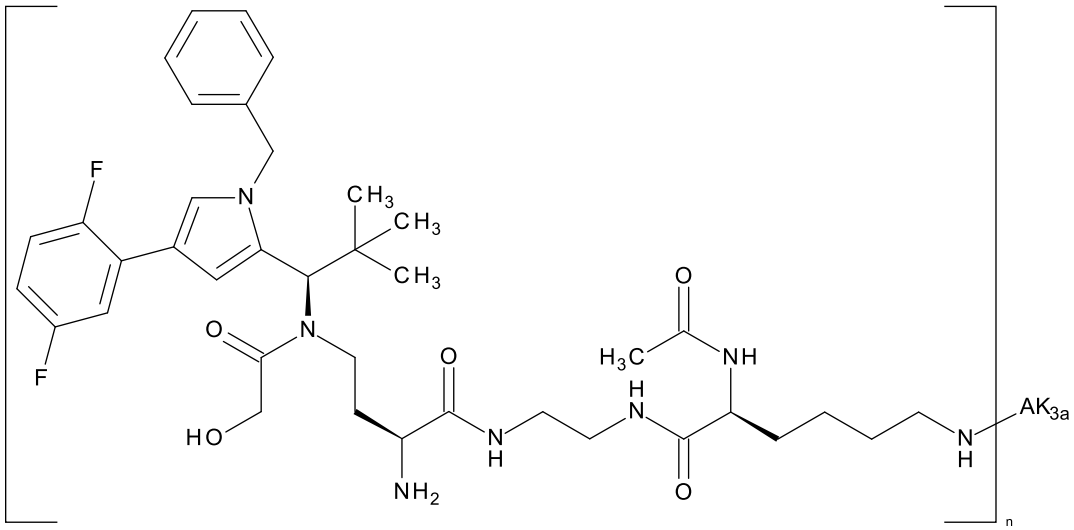
where X_1, X_2, X_3, SG, L1, L3, R1, R4, R10 and Ry have the same meaning as in Claims 1 to 39.

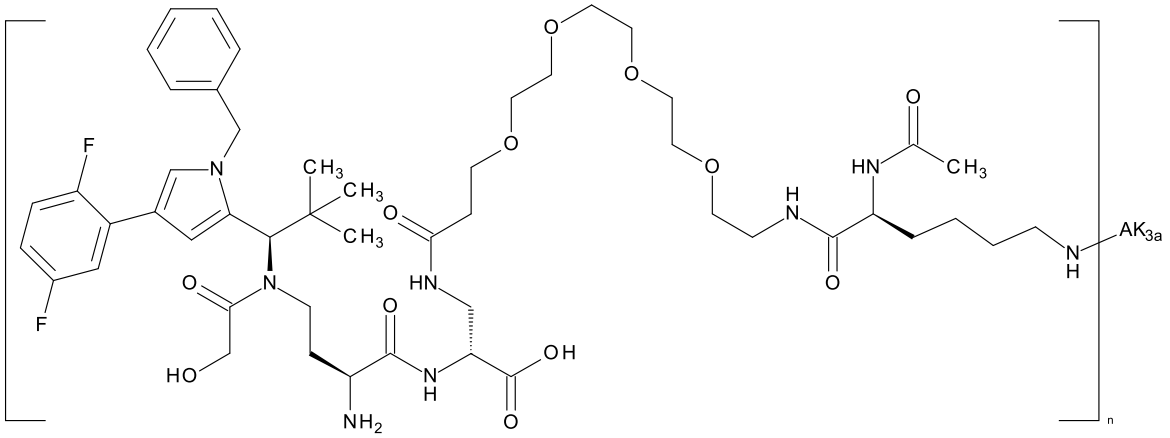
42. Conjugate according to one of the following formulae, where Ak3a, Ak3b, AD3d, Ak3e, represent a binder, preferably an antibody, and n represents 2 to 10, preferably 2 to 4, and also preferably 2 or 4:

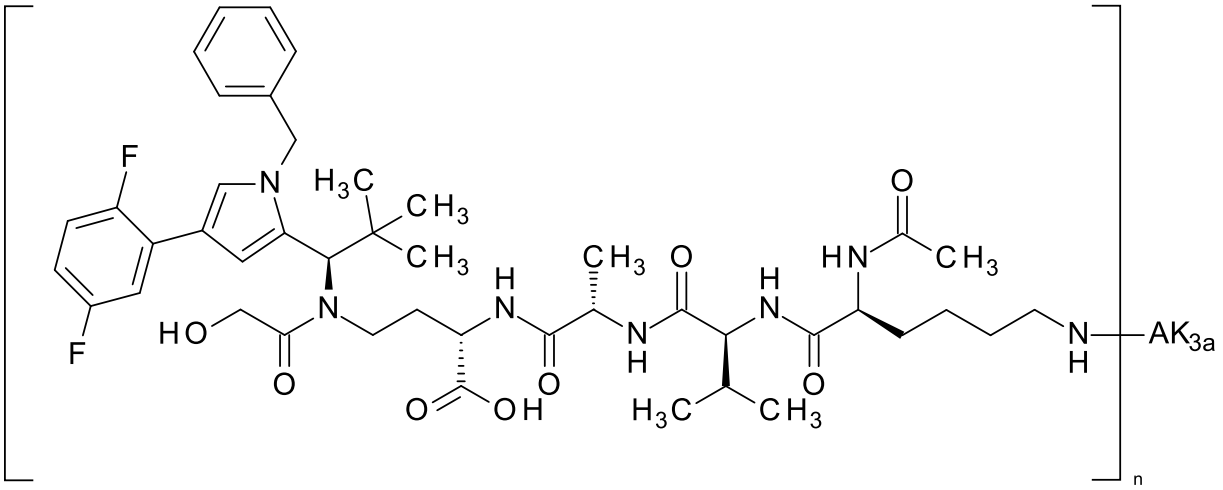




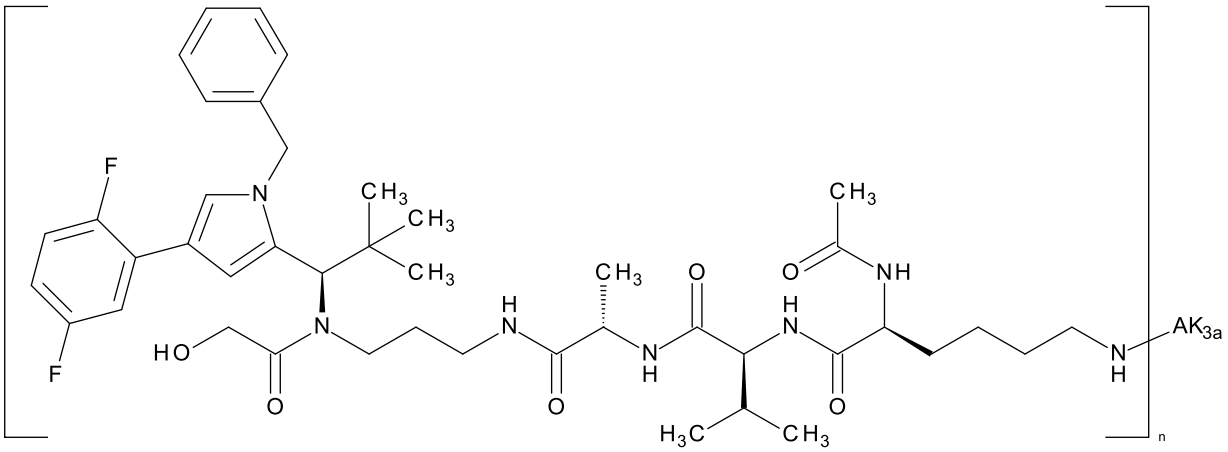


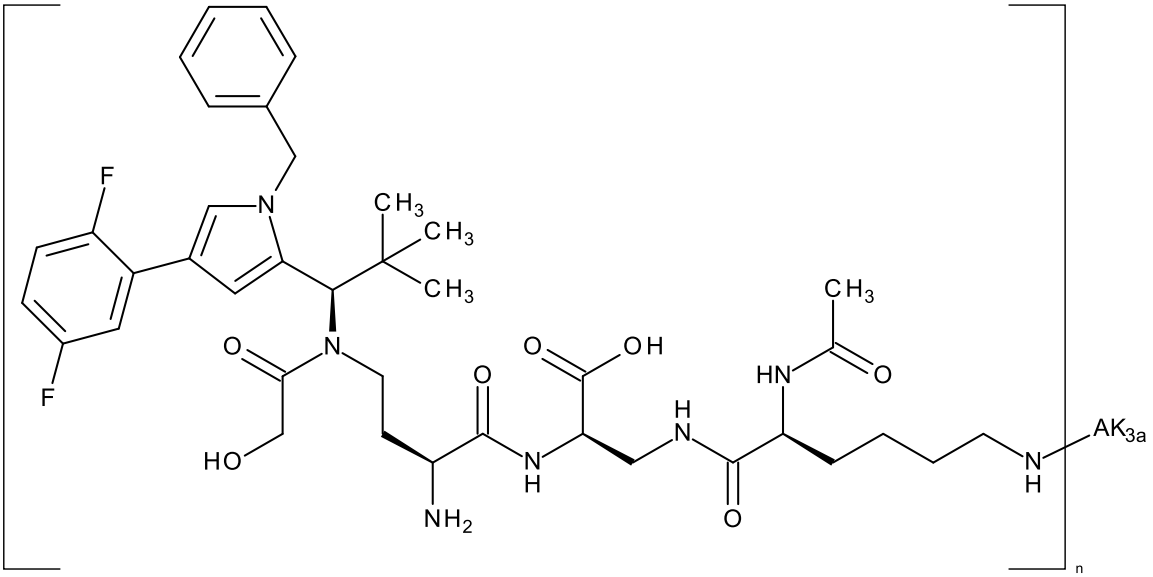


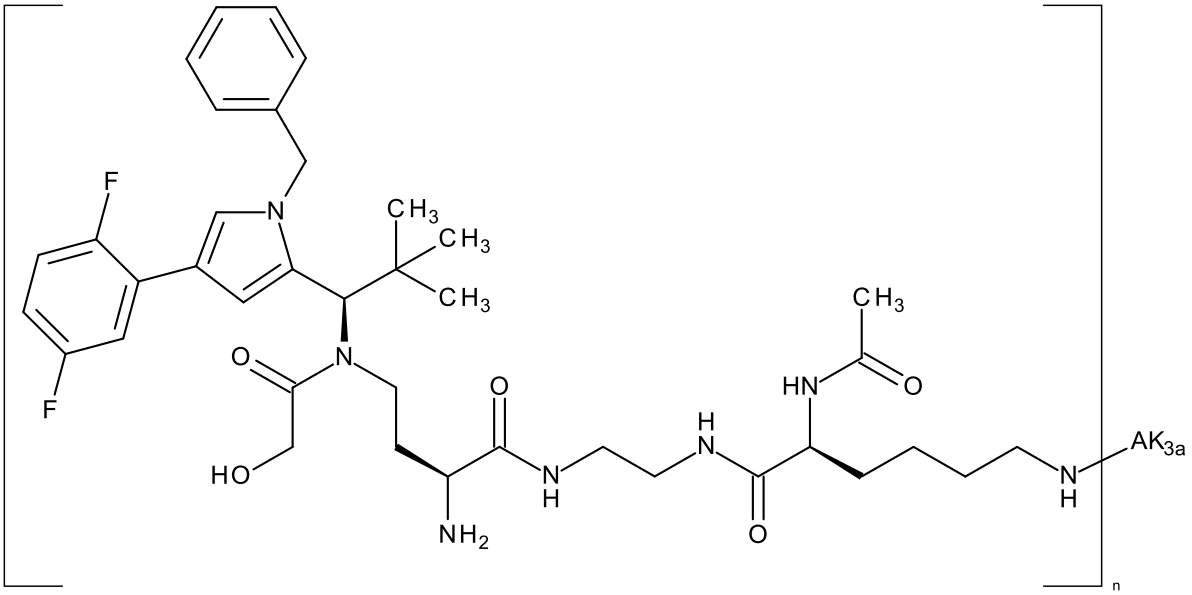


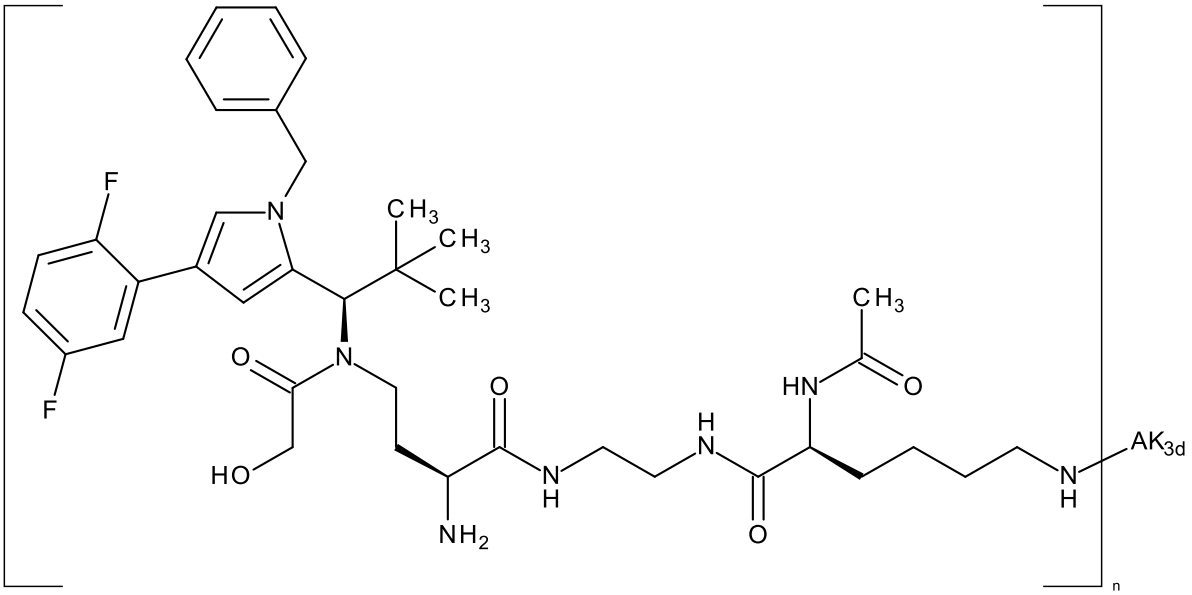


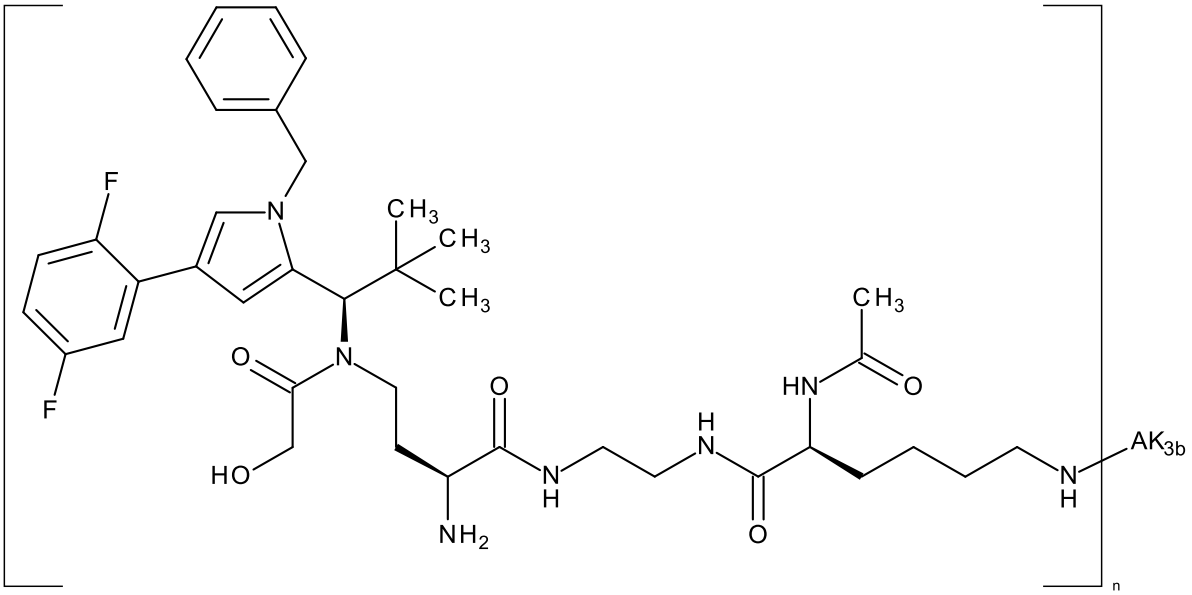
5

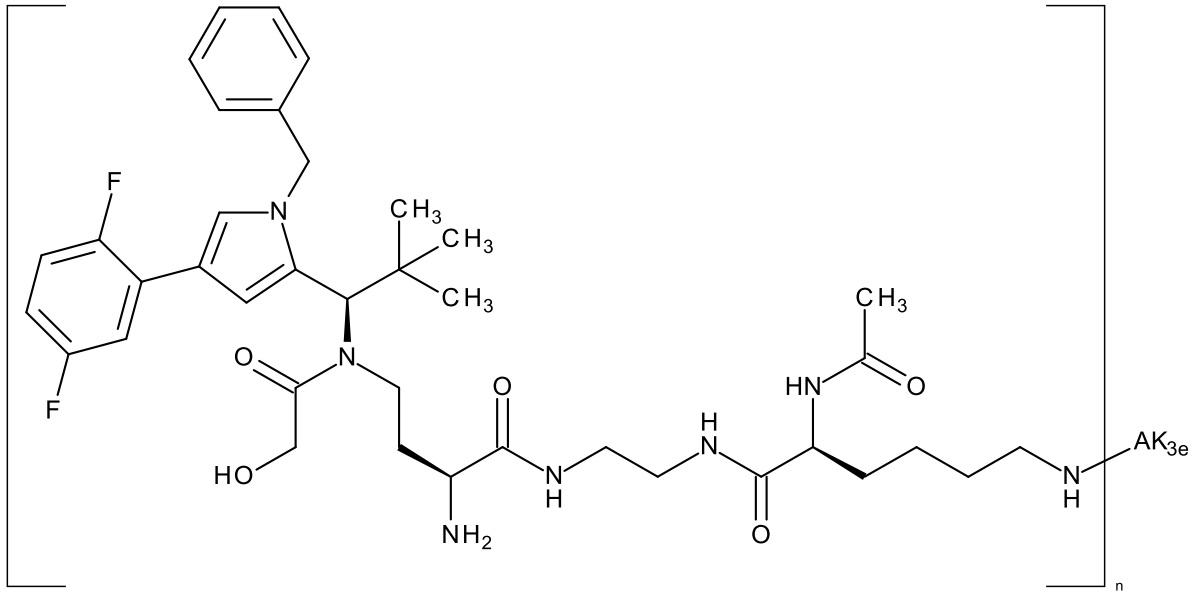


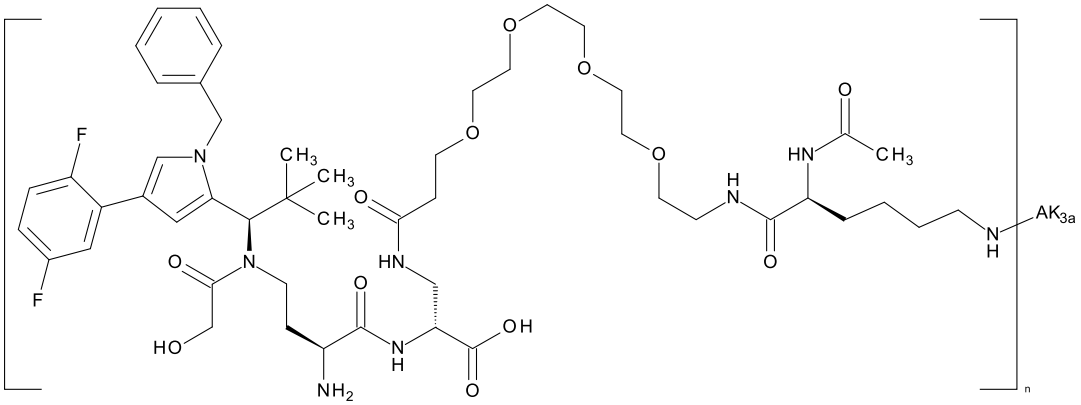

F
N
CH3
CH3
CH3
F
O
N
O
O
OH
HN
CH3
O
HO
NH2
N
H
H
N
O
N
H
AK3a
n

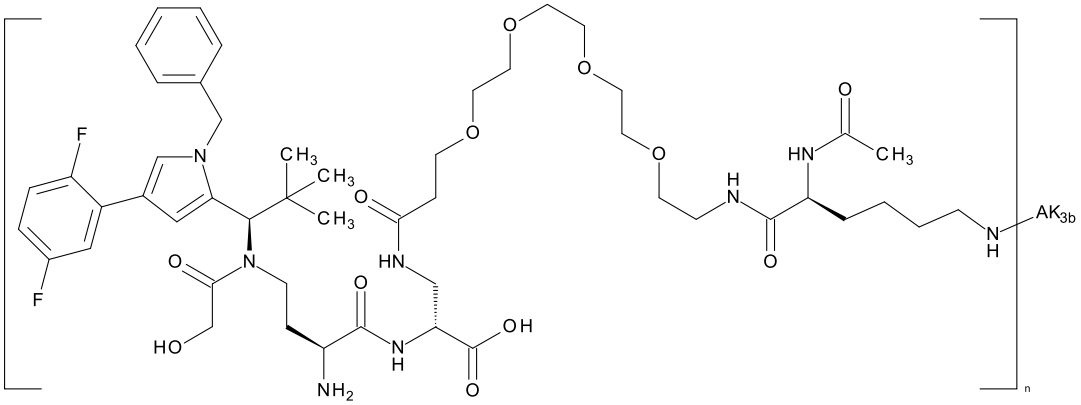

F
N
CH3
CH3
CH3
F
O
N
O
HN
CH3
O
HO
NH2
N
H
H
N
O
N
H
AK3a
n

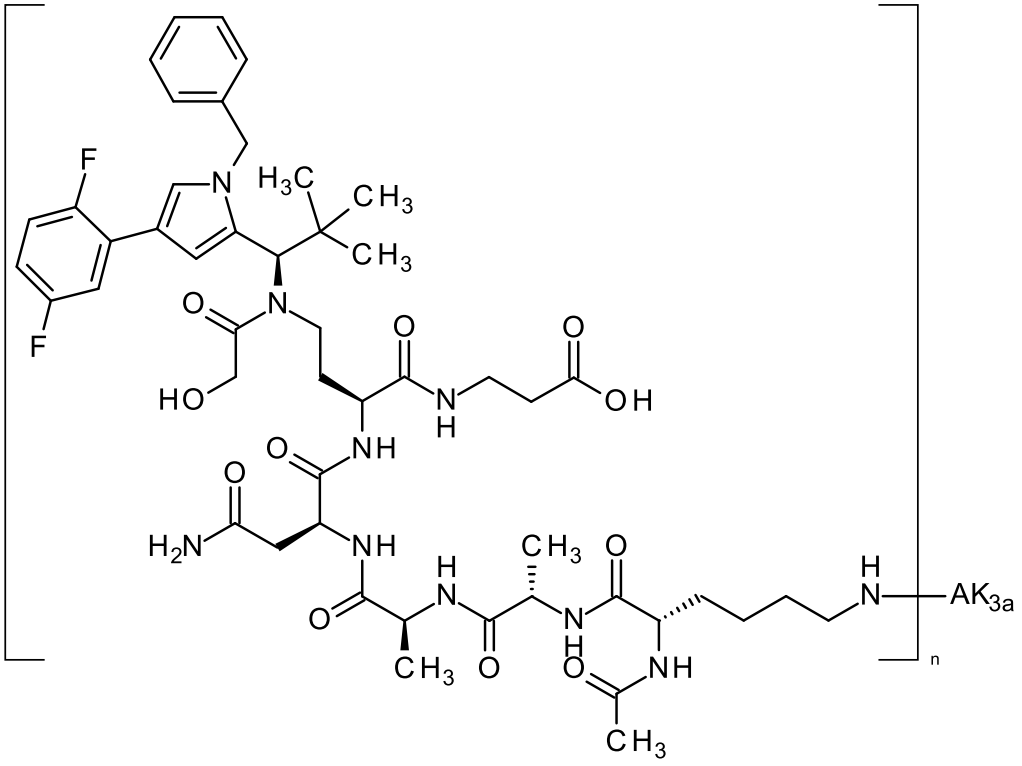

F
N
CH3
CH3
CH3
O
N
O
HN
CH3
O
F
HO
H
N
AK3d
NH2
N
H
O
N
H
n

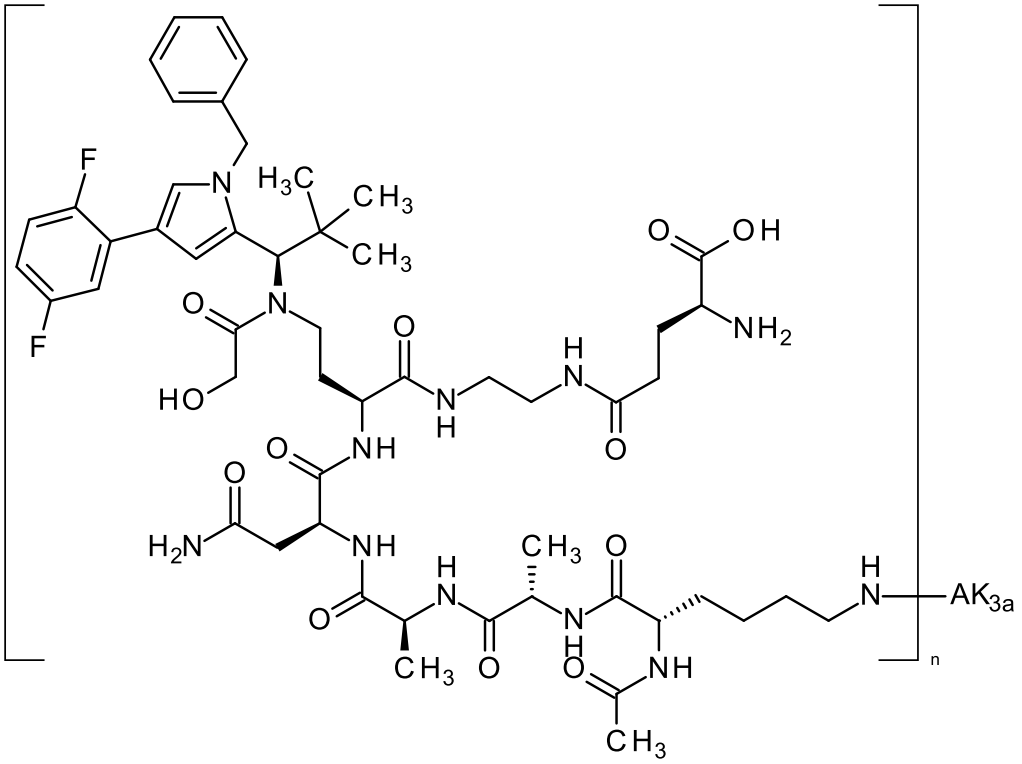

F
N
CH3
CH3
CH3
O
N
O
HN
CH3
O
F
HO
H
N
AK3b
NH2
N
H
O
N
H
n

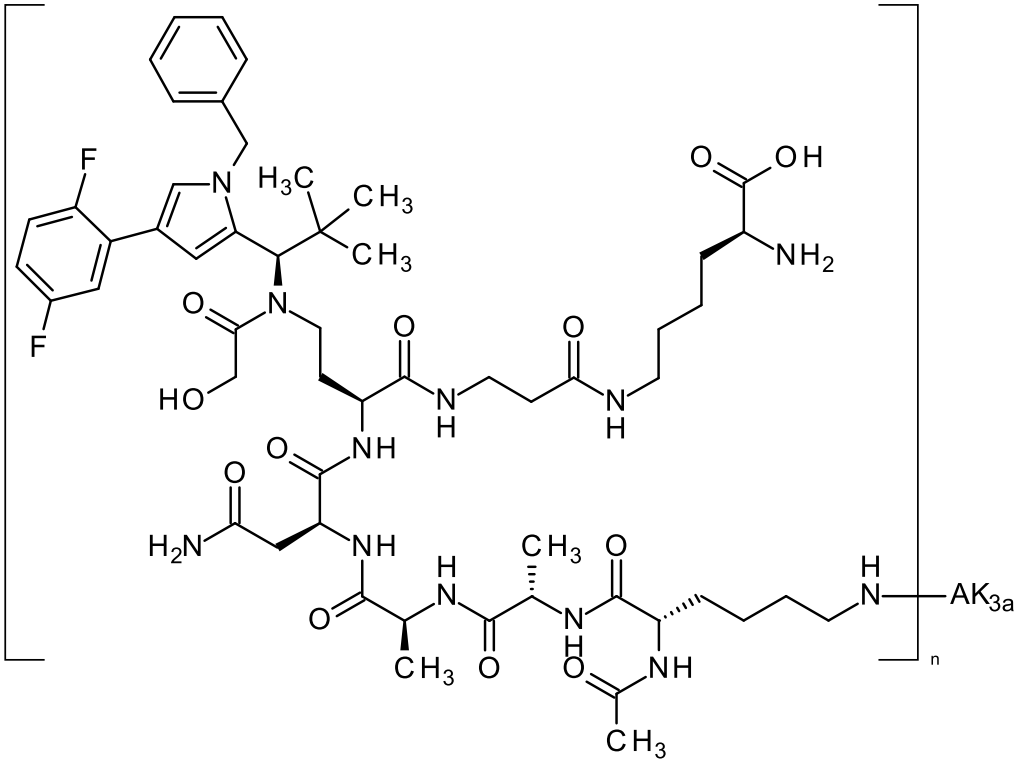


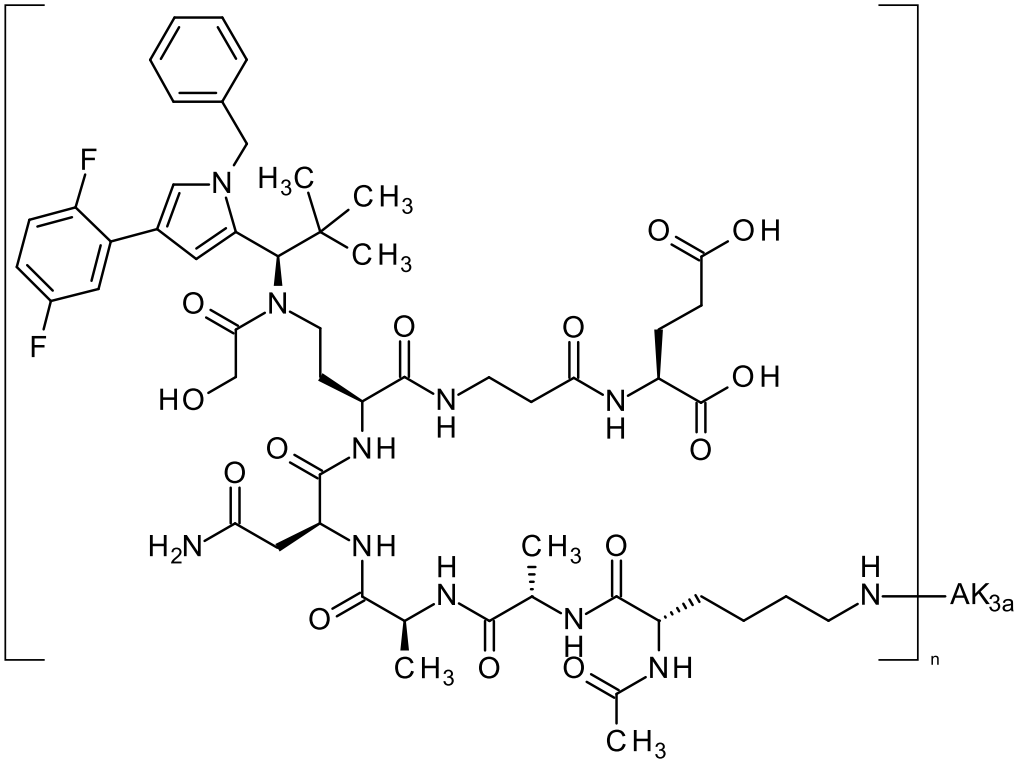


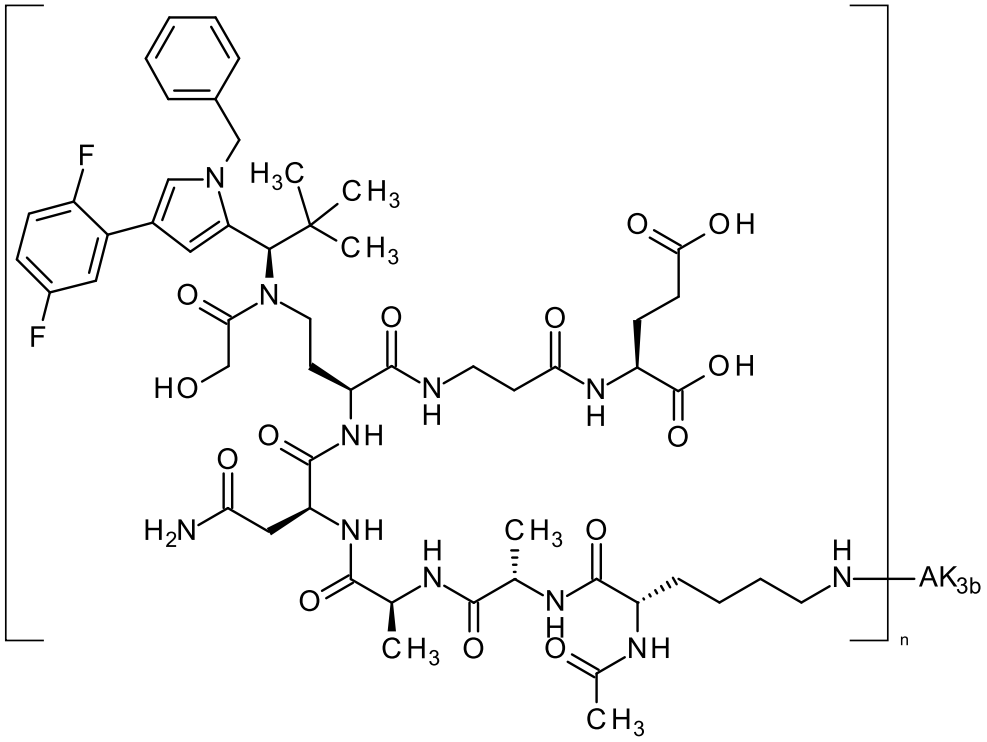


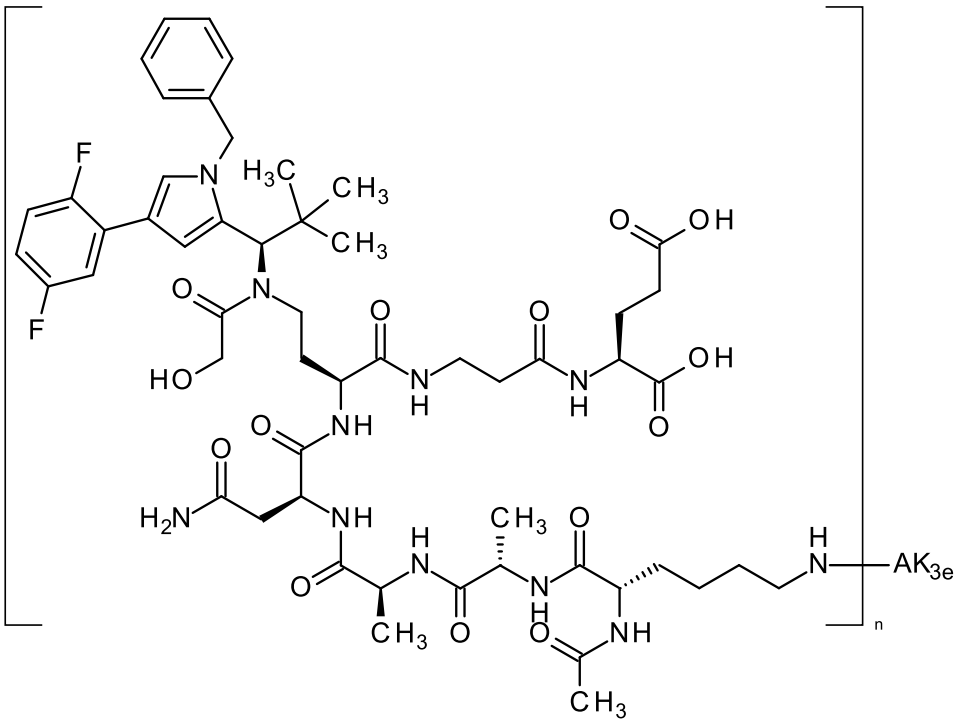


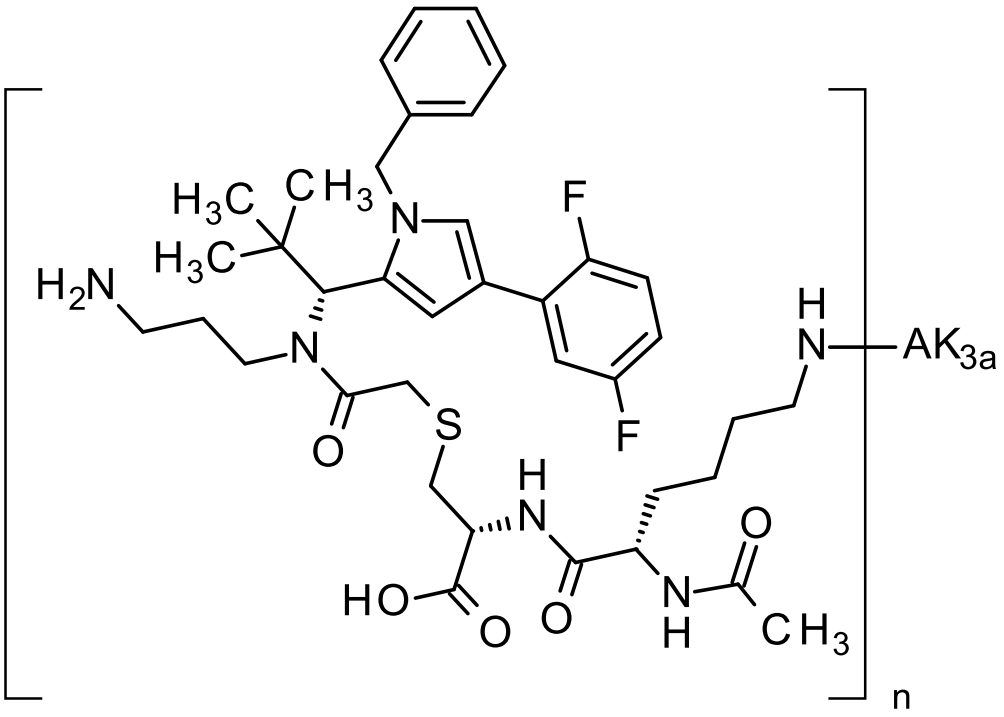


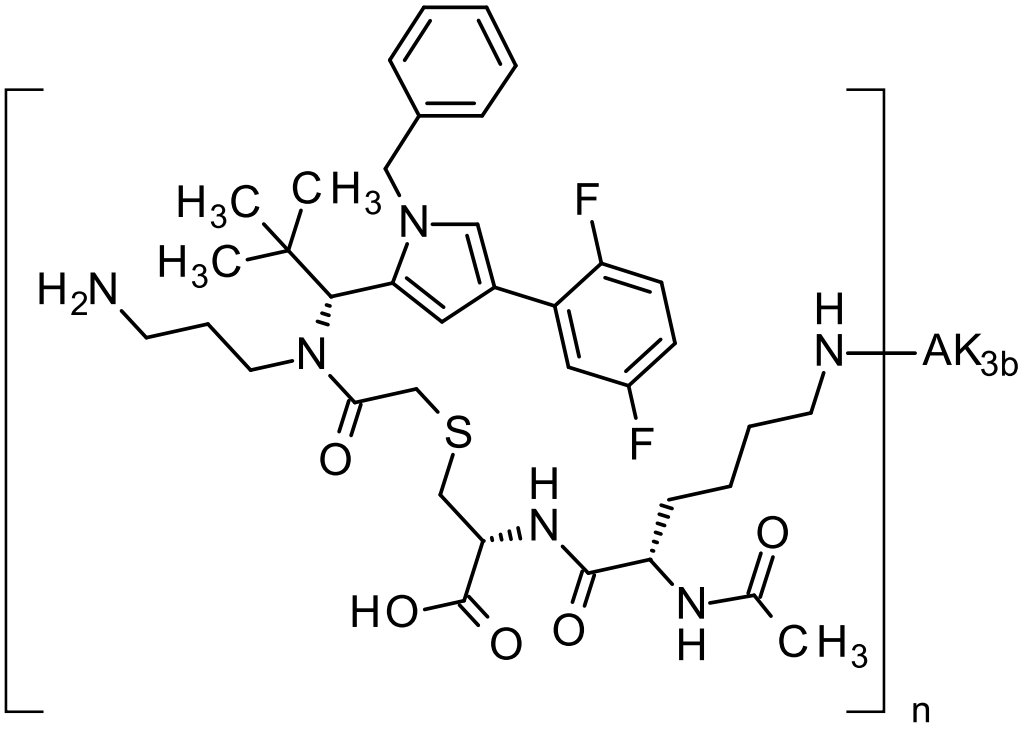


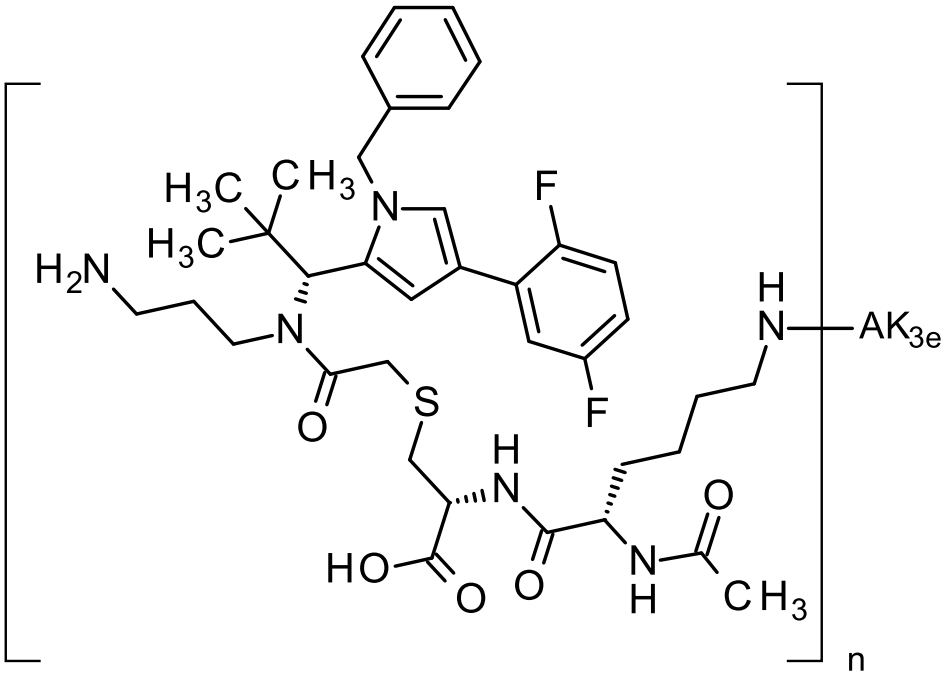



F
F
N
H3C
CH3
CH3
O
OH
O
N
O
O
HO
N
H
N
H
OH
O
O
NH
O
H2N
NH
H
N
CH3
O
O
CH3
O
H
N
N
H
O
NH
CH3
H
N
AK3b
n

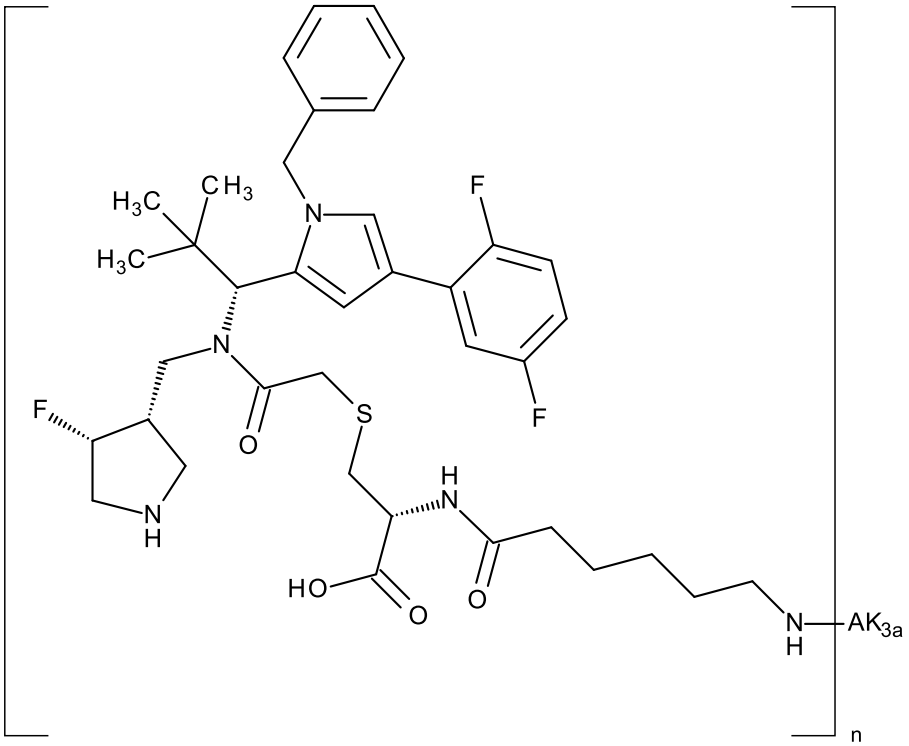

F
F
N
H3C
CH3
CH3
O
OH
O
N
O
O
HO
N
H
N
H
OH
O
O
NH
O
H2N
NH
H
N
CH3
O
O
CH3
O
H
N
N
H
O
NH
CH3
H
N
AK3e
n

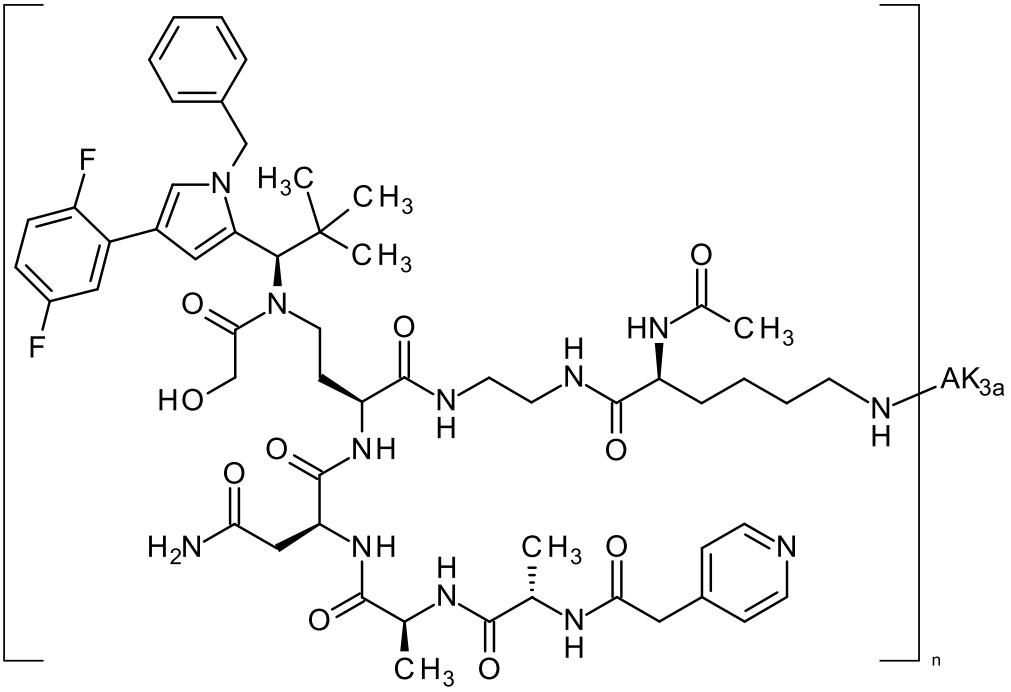

H3C
CH3
H3C
N
F
H2N
N
O
S
F
H
N
HO
O
O
N
H
CH3
H
N
AK3a
n

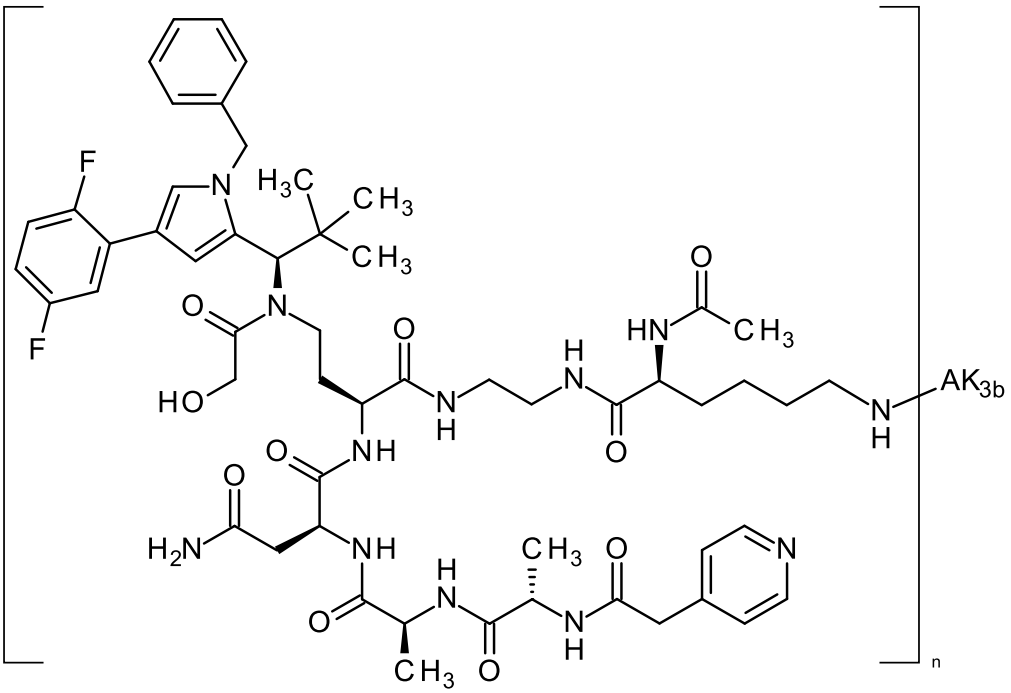

H3C
CH3
H3C
N
F
H2N
N
O
S
F
H
N
HO
O
O
N
H
CH3
H
N
AK3b
n


H3C
CH3
H3C
N
F
H2N
N
H
N
AK3e
O
S
F
H
N
HO
O
O
N
H
O
CH3
n

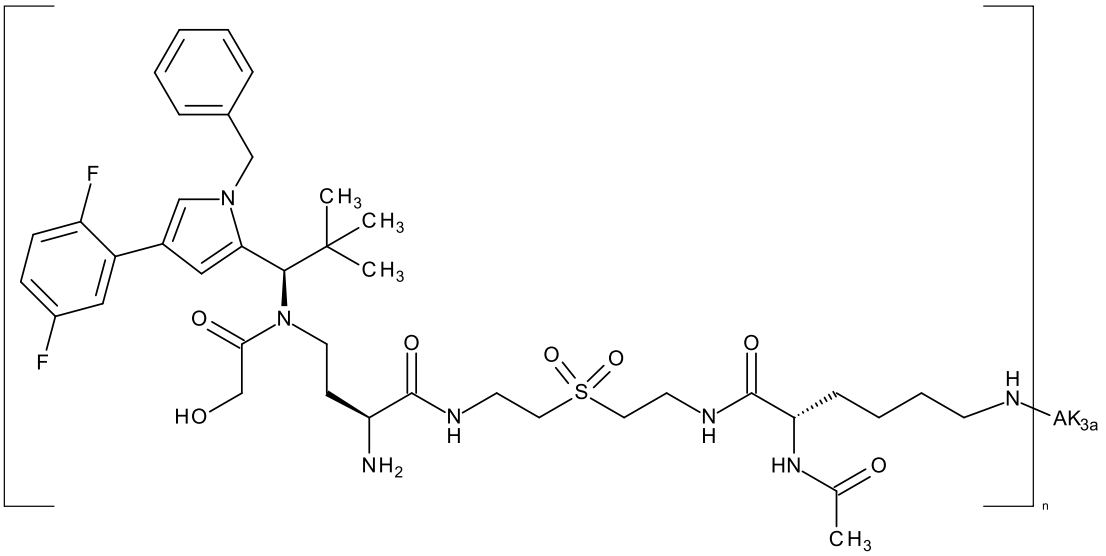
5

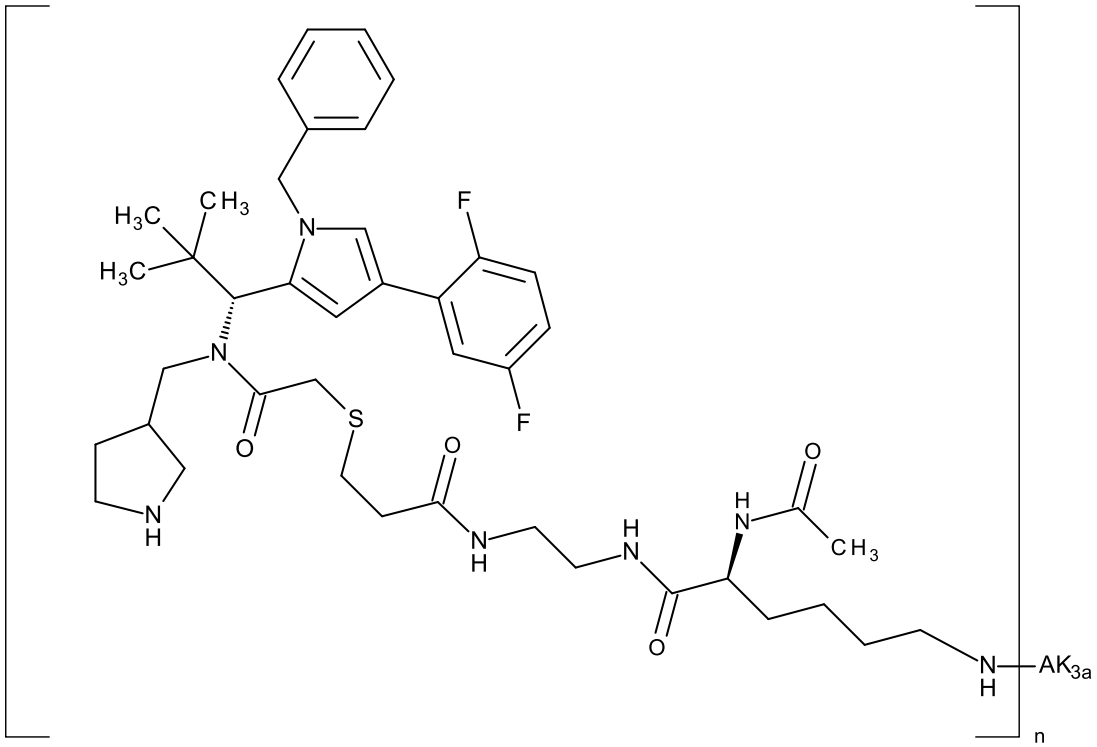

H3C
CH3
H3C
N
F
N
F
F
S
O
N
H
H
N
HO
O
O
N
H
AK3a
n



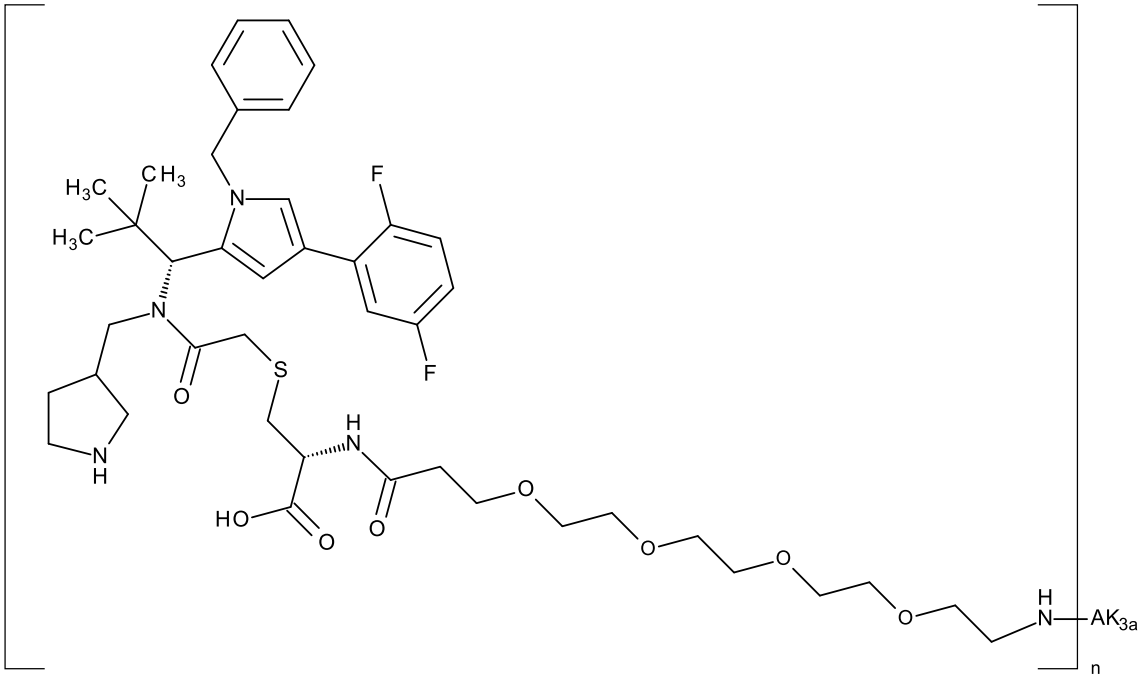


5

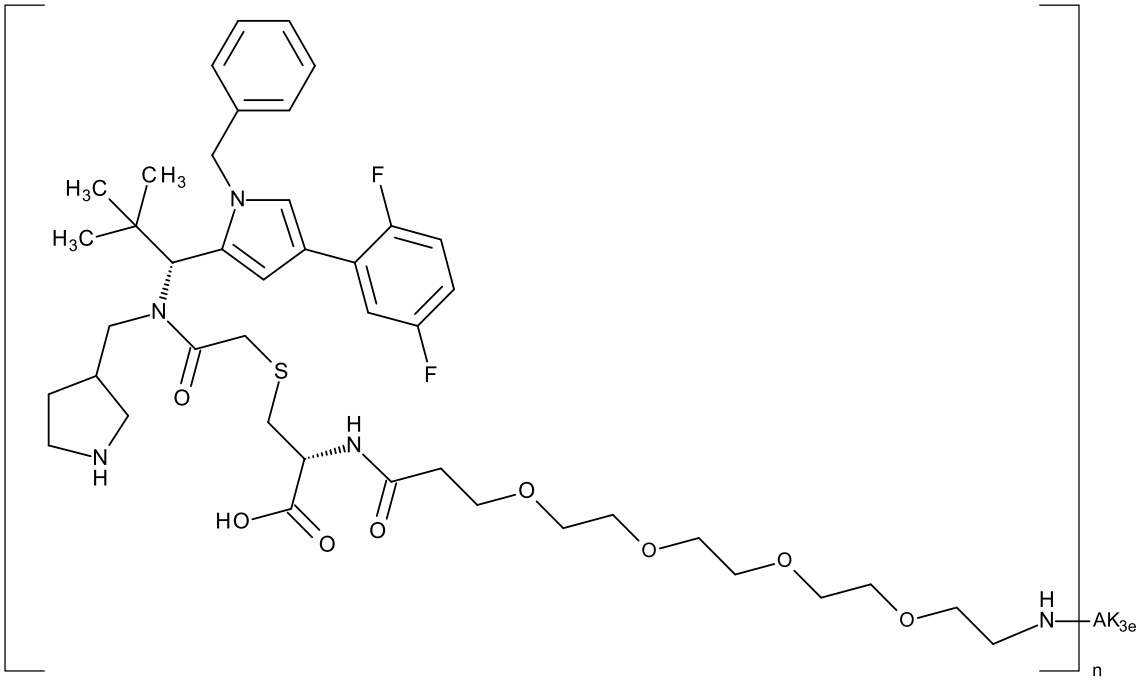


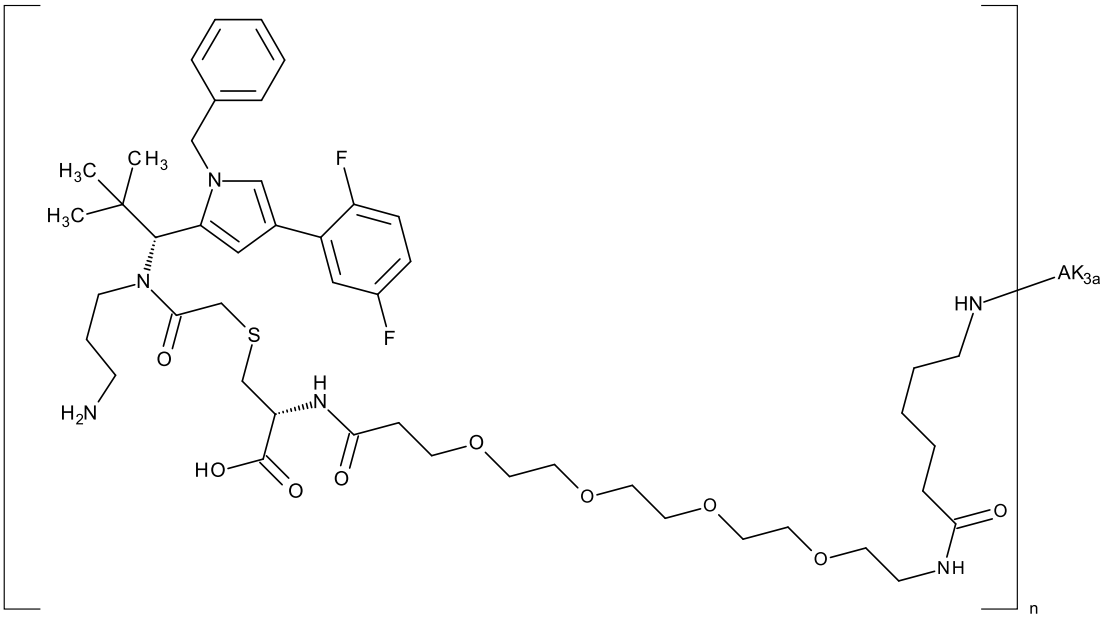


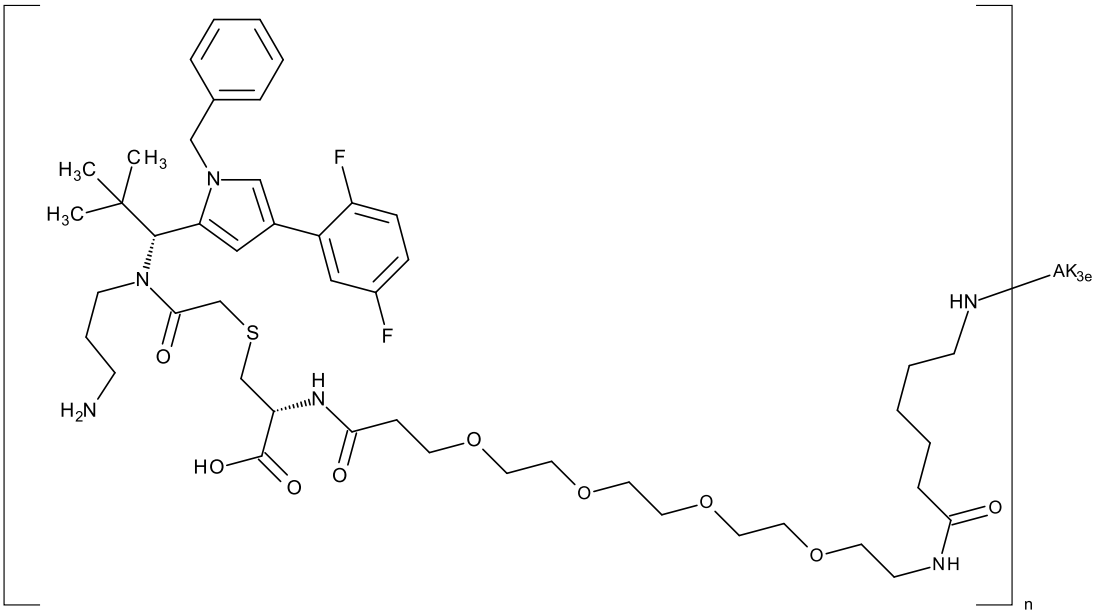
5

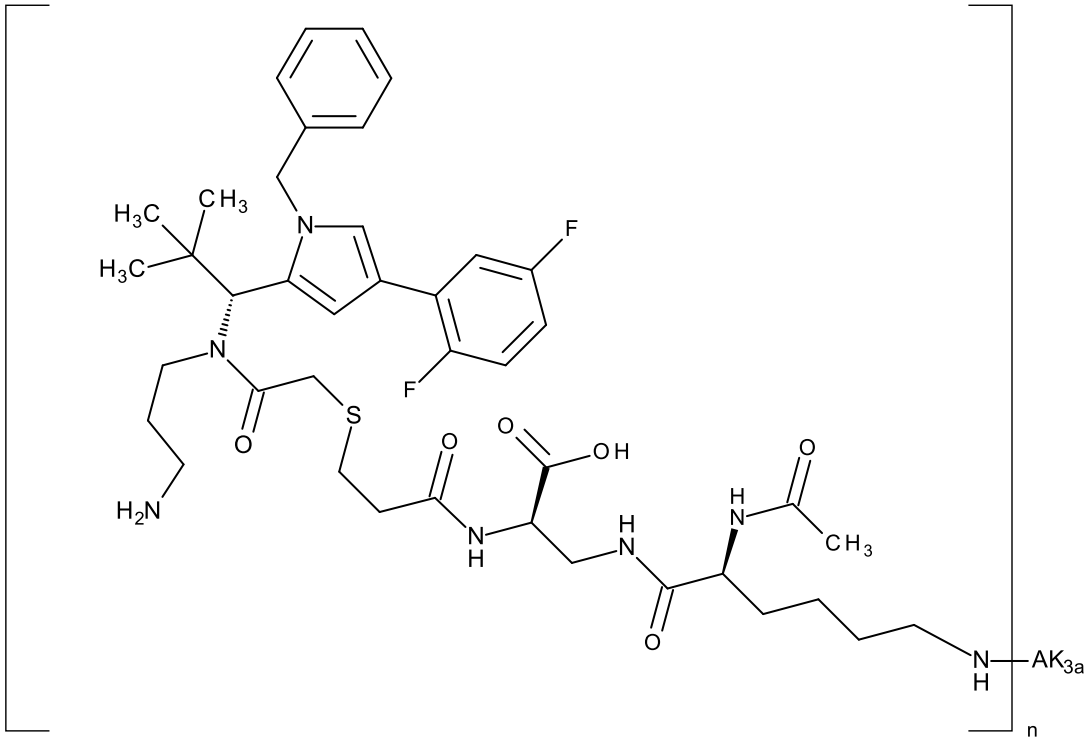

H3C
CH3
H3C
N
F
F
N
O
S
H
N
HO
O
O
O
O
O
O
H
N
AK3a
n

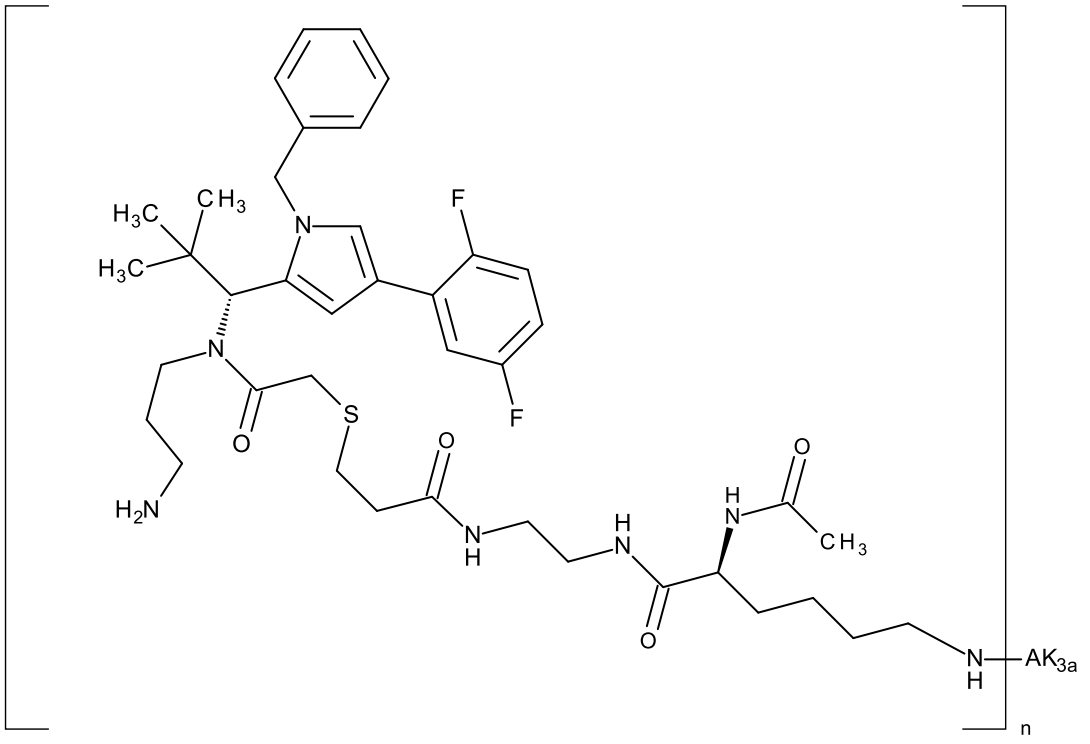
5


H3C
CH3
H3C
N
F
F
N
O
S
H
N
HO
O
O
O
O
O
O
H
N
AK3e
n

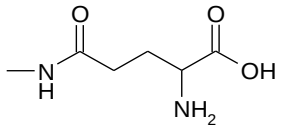








43. Conjugate according to one or more of Claims 1 to 39 and 42 where the binder is a residue according to the following formula



44. Pharmaceutical composition comprising a conjugate according to Claims 1 to 39, 42 and 43 or a compound according to Claim 41 in combination with an inert non-toxic pharmaceutically suitable auxiliary.

45. Conjugate according to one or more of Claims 1 to 39, 42 and 43 or compound according to Claim 41 for use in a method for the treatment and/or prophylaxis of diseases.

46. Conjugate according to one or more of Claims 1 to 39, 42 and 43 or composition according to Claim 44 for use in a method for the treatment of hyperproliferative and/or angiogenic disorders.