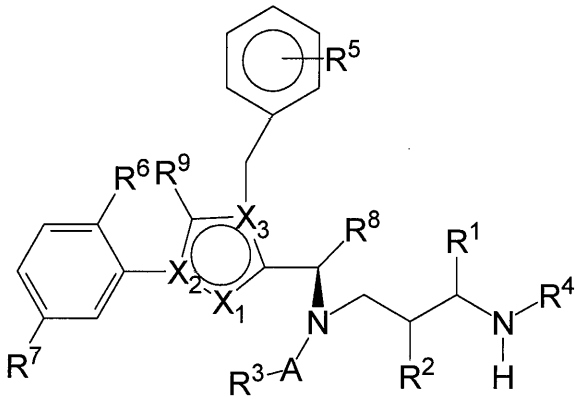
Claims

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 kinesin spindle protein inhibitor has 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, 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 Z represents -H, $-NHY^3$, $-OY^3$, $-SY^3$, halogen, $-CO-NY^1Y^2$ or $-CO-OY^3$,

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 $-CH(CH_2W)Z'$, and Y^3 represents H or $-(CH_2)_{0-3}Z'$, where Z' represents H, NH_2, SO_2H, COOH, $-NH-CO-CH_2-CH_2-CH(NH_2)COOH$ or $-(CO-NH-CHY^4)_{1-3}COOH$, where W represents H or OH,

where Y^4 independently of one another represents straight-chain or branched C_{1-6}-alkyl which is optionally substituted by $–NHCONH_2$, or represents aryl or benzyl which are optionally substituted by $–NH_2$;

R^2 represents –L-#1, H, -MOD, $-CO-CHY^4-NHY^5$ or $-(CH_2)_{0-3}Z$, 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 L-#1, H, NH_2, SO_3H, COOH, SH, or OH;

where Z represents -H, halogen, $-OY^3$, $-SY^3$, NHY^3, $-CO-NY^1Y^2$ or $-CO-OY^3$,

where Y^1 and Y^2 independently of one another represent H, NH_2 or $-(CH_2)_{0-3}Z'$, and Y^3 represents H or $-(CH_2)_{0-3}Z'$, where Z' represents H, SO_3H, NH_2 or COOH;
where Y^4 independently of one another represents straight-chain or branched C_{1-6} alkyl which is optionally substituted by $-NHCONH_2$, or represents aryl or benzyl which are optionally substituted by $-NH_2$, and Y^5 represents H or $-CO-CHY^6-NH_2$, where Y^6 represents straight-chain or branched C_{1-6}-alkyl;

R^4 represents -L-#1, H, $-CO-CHY^4-NHY^5$ or $-(CH_2)_{0-3}Z$,
where Z represents -H, halogen, $-OY^3$, $-SY^3$, NHY^3, $-CO-NY^1Y^2$ or $-CO-OY^3$,
where Y^1 and Y^2 independently of one another represent H, NH_2 or $-(CH_2)_{0-3}Z'$, and Y^3 represents H or $-(CH_2)_{0-3}Z'$, where Z' represents H, SO_3H, NH_2 or COOH;
where Y^4 independently of one another represents straight-chain or branched C_{1-6} alkyl which is optionally substituted by $-NHCONH_2$, or represents aryl or benzyl which are optionally substituted by $-NH_2$, and Y^5 represents H or $-CO-CHY^6-NH_2$, where Y^6 represents straight-chain or branched C_{1-6}-alkyl;
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 L-#1, H, NH_2, SO_3H, COOH, SH or OH;

A represents CO, SO, SO_2, or SO_2NH;

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-CO-alkyl groups, 1-3 -O-CO-NH-alkyl groups, 1-3 -NH-CO-alkyl groups, 1-3 -NH-CO-NH-alkyl groups, 1-3 $-S(O)_n$-alkyl groups, 1-3 $-SO_2$-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, $-OY^3$, $-SY^3$, $-NHY^3$, $-CO-NY^1Y^2$ or $-CO-OY^3$, where Y^1 and Y^2 independently of one another represent H, NH_2 or $-(CH_2)_{0-3}Z'$ and Y^3 represents H, $-(CH_2)_{0-3}-CH(NHCOCH_3)Z'$, $-(CH_2)_{0-3}-CH(NH_2)Z'$ or $-(CH_2)_{0-3}Z'$, where Z' represents H, SO_3H, NH_2 or COOH
(where "alkyl" preferably represents C_{1-10}-alkyl);

R^5 represents -L-#1, H, 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, $-CO-NY^1Y^2$ or $-CO-OY^3$,

where Y^1 and Y^2 independently of one another represent H, NH_2 or $-(CH_2)_{0-3}Z'$, and Y^3 represents H or $-(CH_2)_{0-3}Z'$, where Z' represents H, SO_3H, NH_2 or COOH;

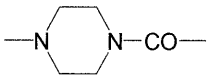
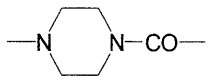
R^6 and R^7 independently of one another represent H, cyano, (optionally fluorinated) C_{1-10}-alkyl, (optionally fluorinated) C_{2-10}-alkenyl, (optionally fluorinated) C_{2-10}-alkynyl, hydroxy, NO_2, NH_2, COOH or halogen (in particular F, Cl, Br),

R^8 represents (optionally fluorinated) C_{1-10}-alkyl, (optionally fluorinated) C_{2-10}-alkenyl, (optionally fluorinated) C_{2-10}-alkynyl, (optionally fluorinated) 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, CO_2H or NH_2 or –L-#1;

where one or none 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,
L represents the linker and #1 represents the bond to the binder or derivative thereof,

where –MOD represents $-(NR^{10})_n-(G1)_o-G2-H$, where

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

G1 represents –NHCO- , -CONH- or  (where, if G1 represents –NHCO- or  , R^{10} does not represent NH_2);
n is 0 or 1;
o is 0 or 1; and

G2 represents a straight-chain 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-, -SO-, SO_2, $-NR^y-$, $-NR^yCO-$, $CONR^y-$, $-NR^yNR^y-$, $-SO_2NR^yNR^y-$, $-CONR^yNR^y-$ (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 $-NHCONH_2$, -COOH, -OH, $-NH_2$, NH-$CNNH_2$, sulphonamide, sulphone, sulphoxide or sulphonic acid), -CO-, $-CR^x=N-O-$ (where Rx represents H, C_1-C_3-alkyl or phenyl), where the hydrocarbon chain including any side

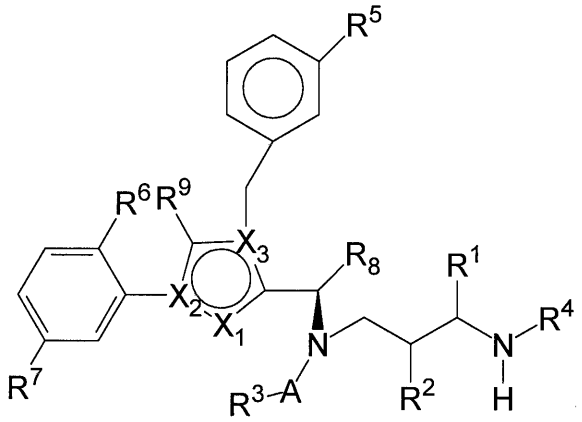
chains may be substituted by -NHCONH$_2$, -COOH, -OH, -NH$_2$, NH-CNNH$_2$, sulphonamide, sulphone, sulphoxide or sulphonic acid, where the group –MOD preferably has at least one group -COOH;

and the salts, solvates and salts of the solvates 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 represents –L-#1.

4. Conjugate according to one or more of the preceding claims 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, 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, –L-#1 or -$(CH_2)_{0-3}$Z, where Z represents -H, -NHY^3, -OY^3, -SY^3, halogen, -CO-NY^1Y^2 or -CO-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‘, and Y^3 represents H or -$(CH_2)_{0-3}$Z‘, where Z‘ represents H, NH_2, SO_3H, COOH, -NH-CO-CH_2-CH_2-$CH(NH_2)$COOH or -$(CO\text{-}NH\text{-}CHY^4)_{1-3}$COOH, where W represents H or OH, where Y^4 independently of one another represents straight-chain or branched C_{1-6}-alkyl which is

optionally substituted by $-NHCONH_2$, 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, $-CO-CHY^4-NHY^5$ or $-(CH_2)_{0-3}Z$, 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 L-#1, H, NH_2, SO_3H, COOH, SH or OH,

where Z represents -H, OY^3, $-SY^3$, halogen, NHY^3, $-CO-NY^1Y^2$ or $-CO-OY^3$,

where Y^1 and Y^2 independently of one another represent H, NH_2 or $-(CH_2)_{0-3}Z'$, and Y^3 represents H or $-(CH_2)_{0-3}Z'$, where Z' represents H, SO_3H, NH_2 or COOH;

where Y^4 independently of one another represents straight-chain or branched C_{1-6} alkyl which is optionally substituted by $-NHCONH_2$, or represents aryl or benzyl which are optionally substituted by $-NH_2$, and Y^5 represents H or $-CO-CHY^6-NH_2$, where Y^6 represents straight-chain or branched C_{1-6}-alkyl;

A represents CO, SO, SO_2, or SO_2NH;

R^3 represents –L-#1 or an optionally substituted alkyl, aryl, heteroaryl, heteroalkyl or heterocycloalkyl group,

preferably –L-#1 or a C_{1-10}-alkyl, C_{6-10}-aryl, 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 (which may each have 1-3 halogen atoms), 1-3 O-alkyl groups, 1-3 –SH groups, 1-3 -S-alkyl groups, 1-3 -O-CO-alkyl groups, 1-3 -O-CO-NH-alkyl groups, 1-3 -NH-CO-alkyl groups, 1-3 -NH-CO-NH-alkyl groups, 1-3 $-S(O)_n$-alkyl groups, 1-3 $-SO_2$-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, $-OY^3$, $-SY^3$, $-NHY^3$, $-CO-NY^1Y^2$ or $-CO-OY^3$, where Y^1 and Y^2 independently of one another represent H, NH_2 or $-(CH_2)_{0-3}Z'$ and Y^3 represents H, $-(CH_2)_{0-3}-CH(NHCOCH_3)Z'$, $-(CH_2)_{0-3}-CH(NH_2)Z'$ or $-(CH_2)_{0-3}Z'$, where Z' represents H, SO_3H, NH_2 or COOH

(where "alkyl" preferably represents C_{1-10}-alkyl);

R^5 represents –L-#1, H, F, NH_2, NO_2, halogen, SH or $-(CH_2)_{0-3}Z$, where Z represents -H, OY^3, $-SY^3$, halogen, NHY^3, $-CO-NY^1Y^2$ or $-CO-OY^3$,

where Y^1 and Y^2 independently of one another represent H, NH_2 or $-(CH_2)_{0-3}Z'$, and Y^3 represents H or $-(CH_2)_{0-3}Z'$, where Z' represents H, SO_3H, NH_2 or COOH;

where one of the substituents R^1, R^2, R^3, R^4 and R^5 represents –L-#1,

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

R^6 and R^7 independently of one another represent H, cyano, (optionally fluorinated) C_{1-10}-alkyl, (optionally fluorinated) C_{2-10}-alkenyl, (optionally fluorinated) C_{2-10}-alkynyl, hydroxy or halogen,

R^8 represents (optionally fluorinated) C_{1-10}-alkyl, (optionally fluorinated) 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 and salts of the solvates thereof.

5. Conjugate according to Claim 4,

where R^1 represents –L-#1, H, $-(CH_2)_{0-3}Z$, where Z represents –H, $-CO-NY^1Y^2$, NHY^3, OY^3, $-SY^3$ or $-CO-OY^3$,
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 $-CH(CH_2W)Z'$, and Y^3 represents H or $-(CH_2)_{0-3}Z'$, where Z' represents H, NH_2, COOH, $-NH-CO-CH_2-CH_2-CH(NH_2)COOH$ or $-(CO-NH-CHY^4)_{1-3}COOH$, where W represents H or OH, where Y^4 independently of one another represents straight-chain or branched C_{1-6}-alkyl which is optionally substituted by $–NHCONH_2$, or represents aryl or benzyl which are optionally substituted by $–NH_2$;

R^2 and R^4 independently of one another represent –L-#1, $-CO-CHY^4-NHY^5$ or H or R^2 and R^4 together (with formation of a pyrrolidine ring) represent $–CH_2-CHR^{10}-$, where R^{10} represents H, –L-#1, NH_2, COOH, SH, OH or SO_3H,
where Y^4 independently of one another represents straight-chain or branched C_{1-6} alkyl which is optionally substituted by $–NHCONH_2$, or represents aryl or benzyl which are optionally substituted by $–NH_2$, and Y^5 represents H or $–CO-CHY^6-NH_2$, where Y^6 represents straight-chain or branched C_{1-6}-alkyl;
A represents CO,
R^3 represents $–(CH_2)OH$ or –L-#1, and
R^5 represents –L-#1 or H,
where one of the substituents R^1, R^2, R^3, R^4 and R^5 represents –L-#1.

6. Conjugate according to Claim 4 or 5 where R^6 and R^7 independently of one another represent H, C_{1-3}-alkyl or halogen.

7. Conjugate according to one or more of Claims 4 to 6 where R^8 represents C_{1-4}-alkyl (preferably tert-butyl).

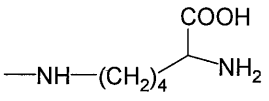
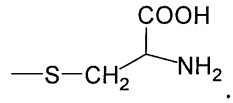
8. Conjugate according to one or more of Claims 4 to 7 where R^9 represents H.

9. Conjugate according to one or more of Claims 4 to 8 where R^6 and R^7 represent F.

10. 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.

11. Conjugate according to Claim 10 where each active compound molecule is attached to different amino acids of the binder peptide or protein or derivative thereof via the linker.

12. Conjugate according to one or more of the preceding claims where the conjugate has on average 1.2 to 20 active compound molecules per binder.

13. Conjugate according to one or more of Claims 10 to 12 where the binder peptide or protein represents an antibody or the derivative of the binder peptide or protein  or .

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

15. Conjugate according to Claim 14 where the binder binds to an extracellular target molecule.

16. Conjugate according to Claim 15 where the binder, after binding to the extracellular target molecule, is internalized and processed intracellularly (preferably lysosomally) by the cell expressing the target molecule.

17. Conjugate according to one or more of Claims 10 to 16 where the binder peptide or protein is a human, humanized or chimeric monoclonal antibody or an antigen-binding fragment thereof.

18. Conjugate according to Claim 17 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.

19. Conjugate according to Claim 18 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.

20. Conjugate according to Claim 18 where the binder peptide or protein is an anti-EGFR antibody and R3 represents –L-#1.

21. Conjugate according to one or more of the preceding claims where the linker –L- has one of the basic structures (i) to (iv) below:

1. $-(CO)_m$–SG1-L1-L2-

(ii) $-(CO)_m$ –L1-SG-L1-L2-

(iii) $-(CO)_m$ –L1-L2-

(iv) $-(CO)_m$ –L1-SG-L2

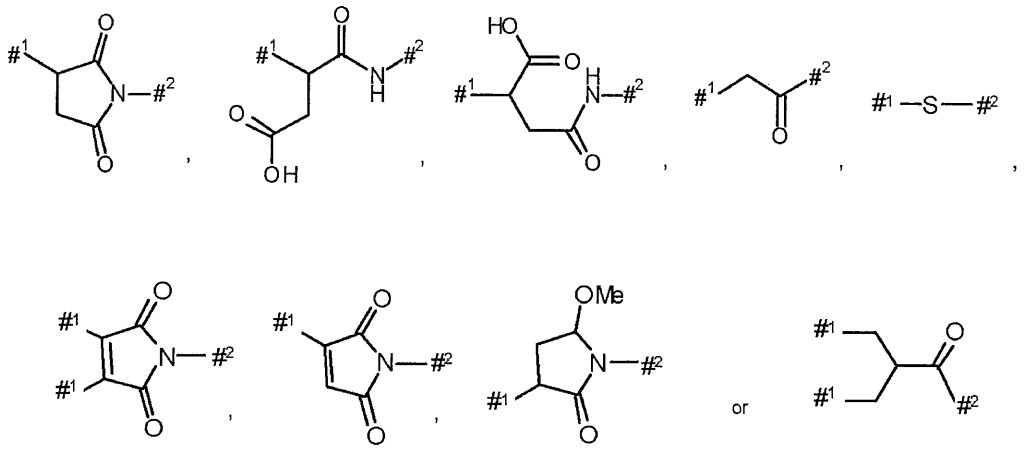
where m is 0 or 1, SG and SG1 are *in vivo* cleavable groups, L1 independently of one another represent organic groups not cleavable *in vivo*, and L2 represents a coupling group to the binder.

22. Conjugate according to Claim 21 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.

23. Conjugate according to one or more of the preceding claims
where the linker is attached to a cysteine side chain or a cysteine residue and has the formula below:

§-(CO)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
-L2- represents

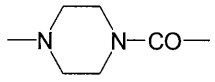


where

$\#^1$ denotes the point of attachment to the sulphur atom of the binder,

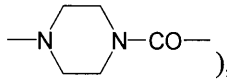
$\#^2$ denotes the point of attachment to group L^1,

L1 represents $-(NR^{10})n-(G1)o-G2-$,
where R^{10} represents H, NH_2 or C_1-C_3-alkyl;

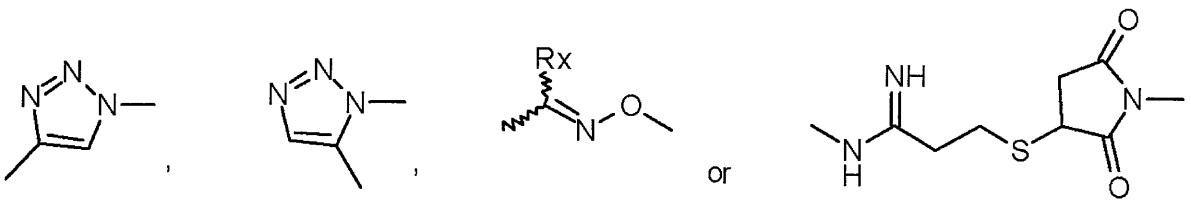
G1 represents –NHCO- or ;

n is 0 or 1;

o is 0 or 1; and

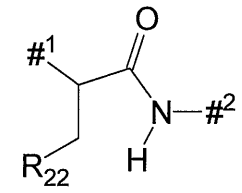
G2 represents a straight-chain or branched hydrocarbon chain having 1 to 100 carbon atoms from arylene groups and/or straight-chain and/or branched and/or cyclic alkylene groups and which may be interrupted once or more than once by one or more of the groups -O-, -S-, -SO-, SO_2, -NH-, -CO-, -NMe-, -NHNH-, $-SO_2NHNH-$, -NHCO-, -CONH-, -CONHNH- 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, -SO- or $-SO_2-$ (preferably ), where the side chains, if present, may be substituted by $-NHCONH_2$, -COOH, -OH, $-NH_2$, NH-$CNNH_2$, sulphonamide, sulphone, sulphoxide or sulphonic acid,

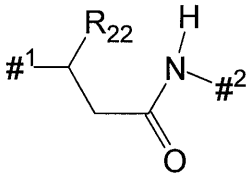
or represents one of the groups below:



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

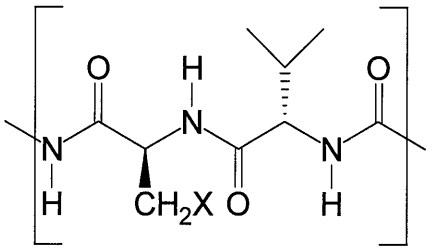
24. Conjugate according to Claim 23 where L2 is represented by one or both of the formulae below:

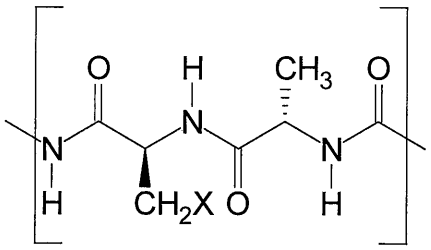




where $\#^1$ denotes the point of attachment to the sulphur atom of the binder, $\#^2$ denotes the point of attachment to group L^1, R^{22} represents COOH and more than 80% (based on the total number of bonds of the linker to the binder) of the bonds to the sulphur atom of the binder are present in one of these two structures.

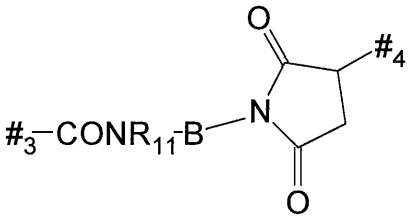
25. Conjugate according to Claim 23 or 24 where the hydrocarbon chain is interrupted by one of the groups below:





where X represents H or a C_{1-10}-alkyl group which may optionally be substituted by –NHCONH$_2$, -COOH, -OH, NH$_2$, -NH-CNNH$_2$, sulphone, sulphoxide or sulphonic acid.

26. Conjugate according to Claim 23 where the linker has the formula below:



where

#3 represents the bond to the active compound molecule,

#4 represents the bond to the binder peptide or protein,

R^{11} represents H or NH$_2$;

B represents –[(CH$_2$)$_x$-(X^4)$_y$]w-(CH$_2$)$_z$-,

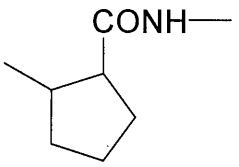
w = 0 to 20;

x = 0 to 5;

x = 0 to 5;

y = 0 or 1;

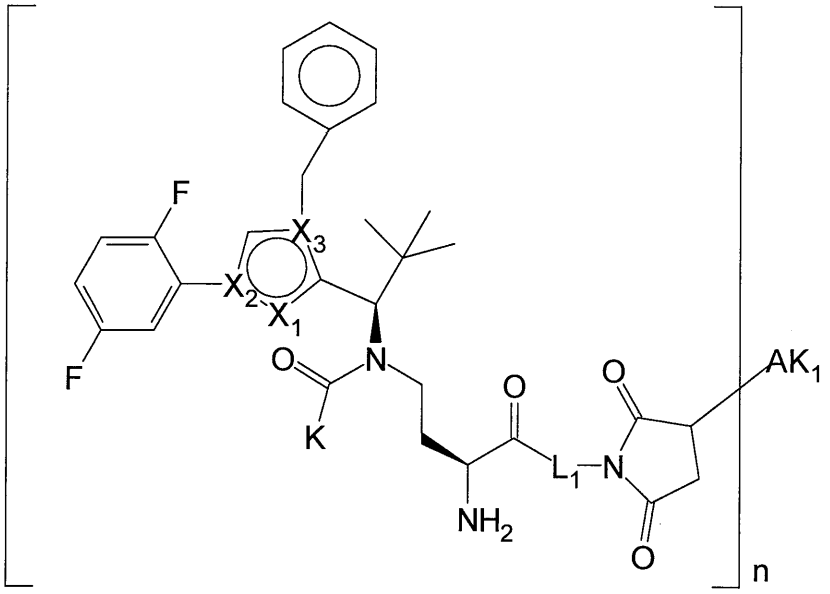
z = 0 to 5; and

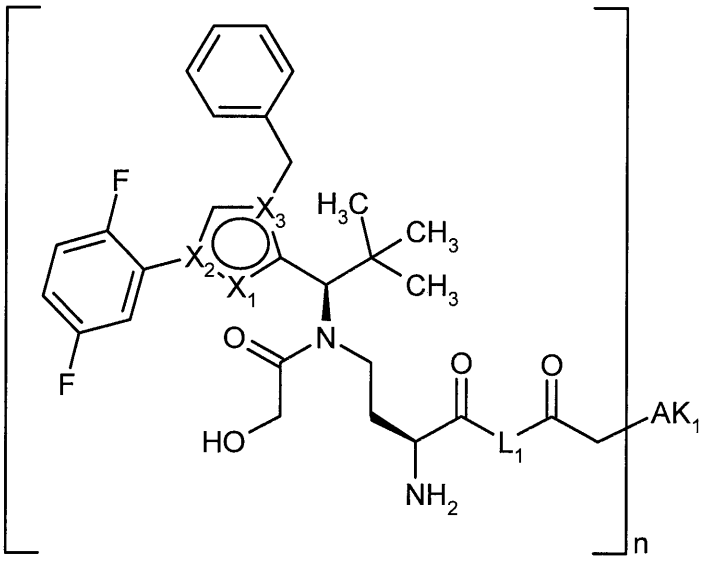
X^4 represents –O-, -CONH- or –NHCO- 

.

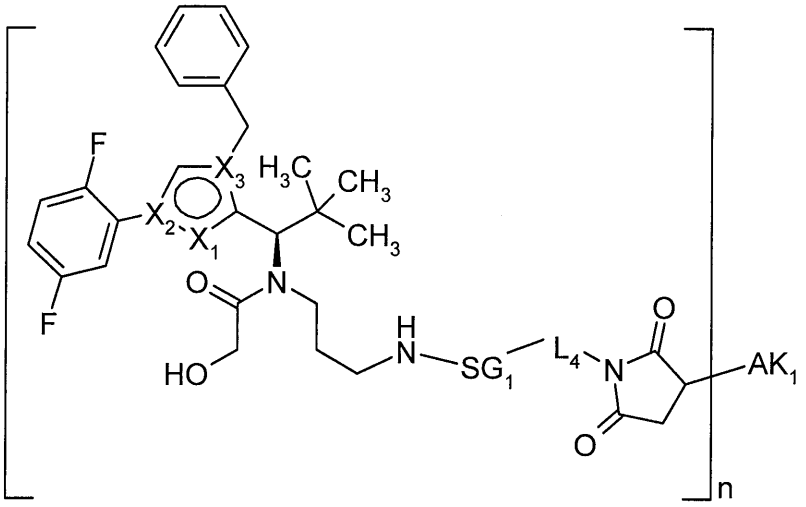
27. Conjugate according to Claim 23 where R^1 or R^4 represents –L-#1.

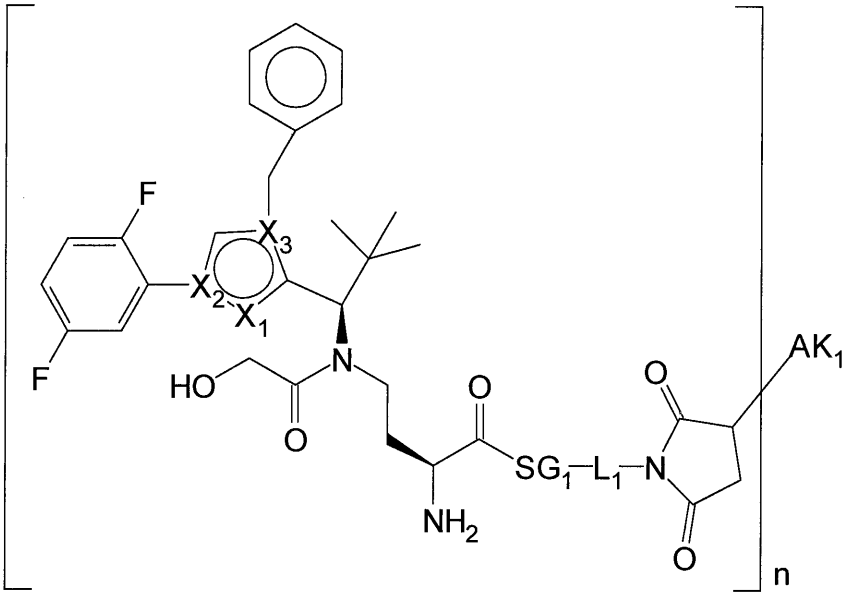
28. Conjugate according to one or more of Claims 23 to 27 where the conjugate has one of the formulae below:

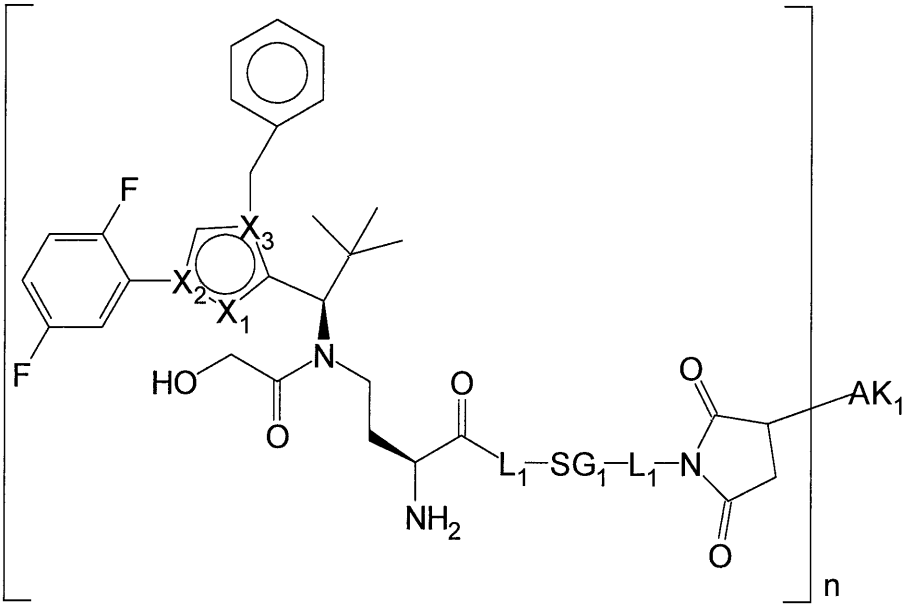

F
F
X3
X2
X1
O
N
K
O
L1
N
O
O
AK1
NH2
n

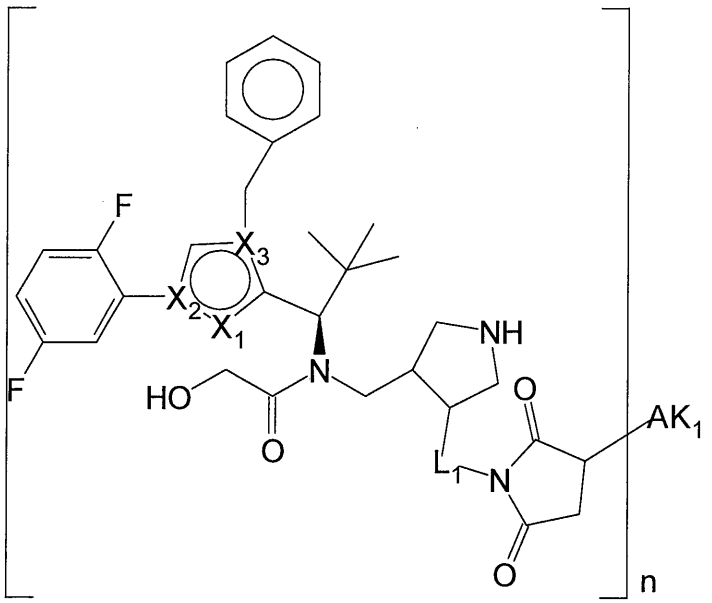

F
F
X3
X2
X1
H3C
CH3
CH3
O
N
HO
O
L1
O
AK1
NH2
n

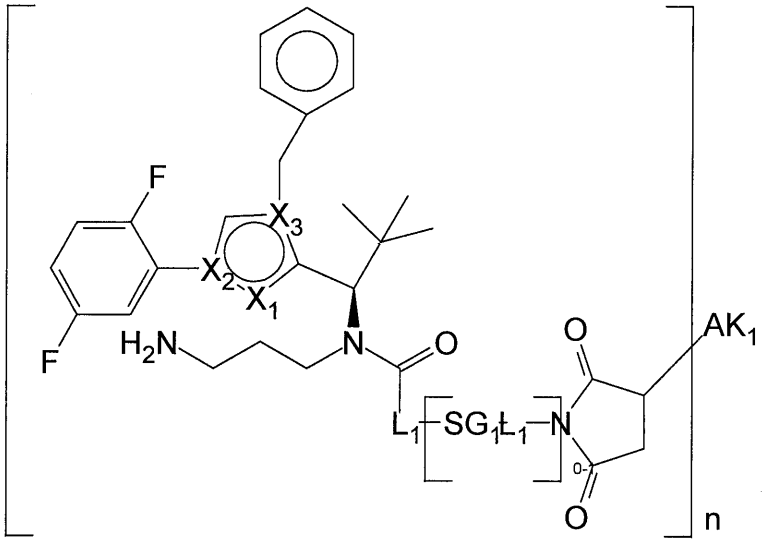
5

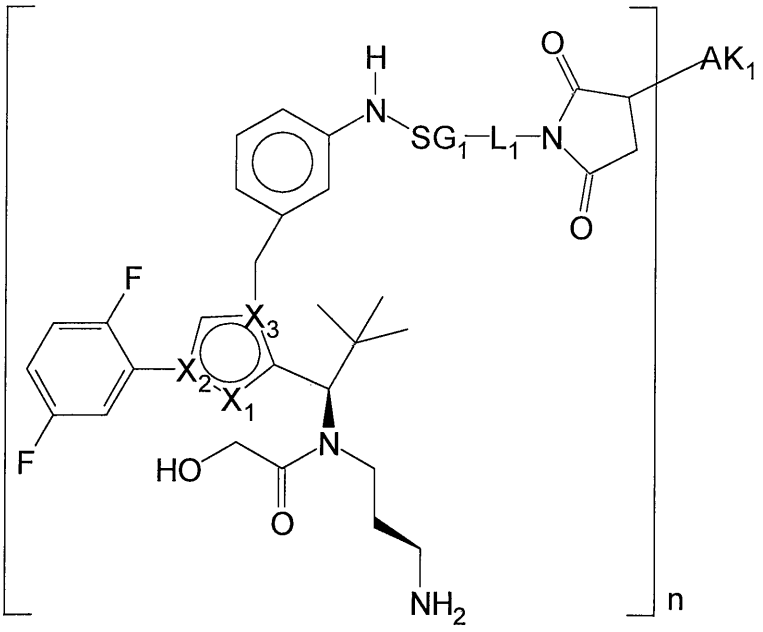






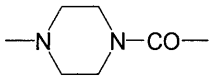






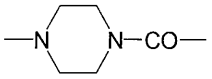
where

X_1, X_2 and X_3 have the same meaning as in Claim 1,

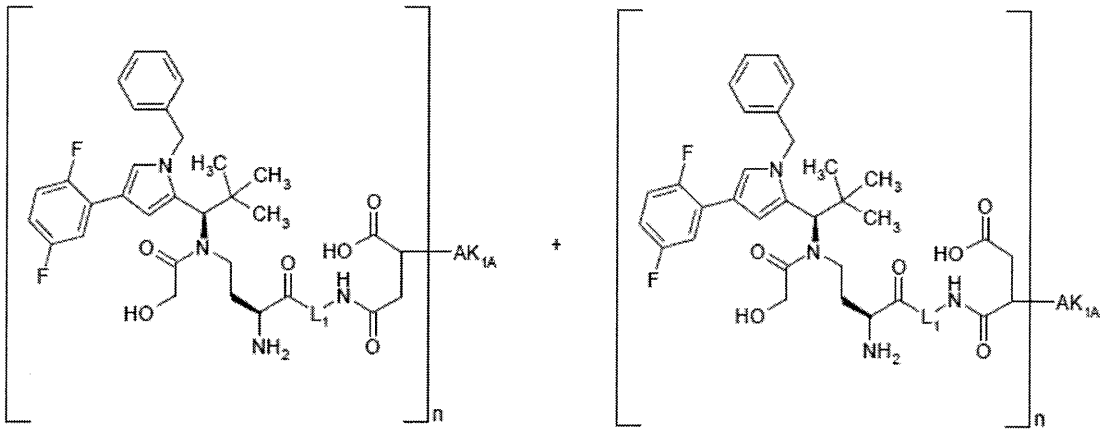
AK_1 represents a binder peptide or protein which is attached via a sulphur atom of the binder; n represents a number from 1 to 20; and L1 represents an optionally branched hydrocarbon group having 1 to 70 carbon atoms, which represents a straight-chain or branched chain having 1 to 100 carbon atoms from arylene groups and/or straight-chain 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-, -SO-, SO_2, -NH-, -CO-, -CONH-, -NHCO-, -NMe-, -NHNH-, $-SO_2NHNH-$, -CONHNH- 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, or -SO- or $-SO_2-$ (preferably ), where the side chains, if present, may be substituted by $-NHCONH_2$, -COOH, -OH, $-NH_2$, NH-$CNNH_2$, sulphonamide, sulphone, sulphoxide or sulphonic acid,

and SG1 is a 2-8 oligopeptide, preferably a dipeptide;

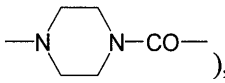
L4 is a single bond or a group $-(CO)_y-G4-$, where y represents 0 or 1, and G4 represents a straight-chain or branched hydrocarbon chain having 1 to 100 carbon atoms from arylene groups and/or straight-chain and/or branched and/or cyclic alkylene groups and which may be interrupted once or more than once by one or more of the groups -O-, -S-, -SO-, SO_2, -NH-, -CO-, -NHCO-, -CONH-, -NMe-, -NHNH-, $-SO_2NHNH-$, -CONHNH- 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, or -SO- or $-SO_2-$ (preferably ), where the side chains, if present, may be substituted by $-NHCONH_2$, -COOH, -OH, $-NH_2$, NH-$CNNH_2$, sulphonamide, sulphone, sulphoxide or sulphonic acid.

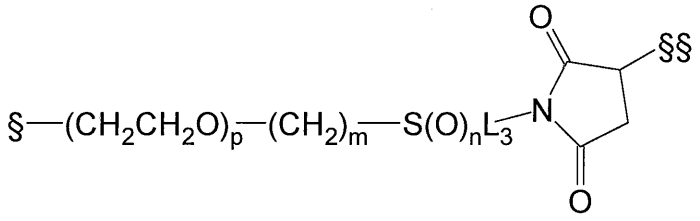
29. Conjugate of a binder or derivative thereof with one or more active compound molecules where the conjugate has one or both of the formulae below:



where

AK_{1A} represents a binder peptide or protein which is attached via a sulphur atom of the binder; n represents a number from 1 to 20; and L1 represents a straight-chain or branched hydrocarbon chain having 1 to 100 carbon atoms from arylene groups and/or straight-chain 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-, -SO-, SO_2, -NH-, -CO-, -CONH-, -NHCO-, -NMe-, -NHNH-, -SO_2NHNH-, -CONHNH- 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, -SO- or $-SO_2-$ (preferably ), where the side chains, if present, may be substituted by $-NHCONH_2$, -COOH, -OH, $-NH_2$, NH-$CNNH_2$, sulphonamide, sulphone, sulphoxide or sulphonic acid.

30. Conjugate according to one or more of the preceding claims where the linker –L- is attached to a cysteine side chain or a cysteine residue and has the formula below:



where

§ represents the bond to the active compound molecule and

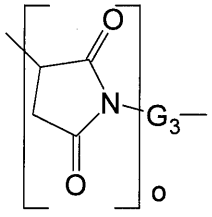
§§ represents the bond to the binder peptide or protein,

m is 0, 1, 2 or 3;

n is 0, 1 or 2;

p is 0 to 20; and

L3 represents

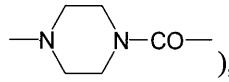


;

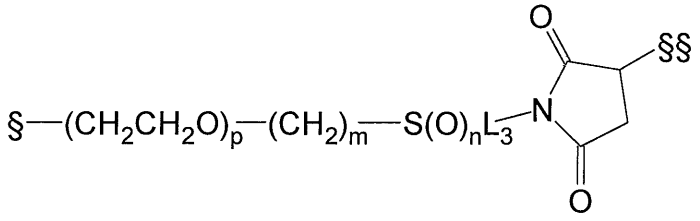
where

o is 0 or 1;

and

G3 represents a straight-chain or branched hydrocarbon chain having 1 to 100 carbon atoms from arylene groups and/or straight-chain 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-, -SO-, SO_2, -NH-, -CO-, -NHCO-, -CONH-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, -NMe-, -NHNH-, -SO_2NHNH-, -CONHNH-, -SO- or –SO_2- (preferably ), where the side chains, if present, may be substituted by –$NHCONH_2$, -COOH, -OH, sulphone, sulphoxide or sulphonic acid.

31. Conjugate according to Claim 30 where the linker –L- is attached to a cysteine side chain or a cysteine residue and has the formula below:



where

§ represents the bond to the active compound molecule and

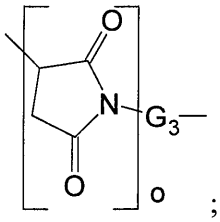
§§ represents the bond to the binder peptide or protein,

m is 1;

p is 0;

n is 0;

and L3 represents



;

where

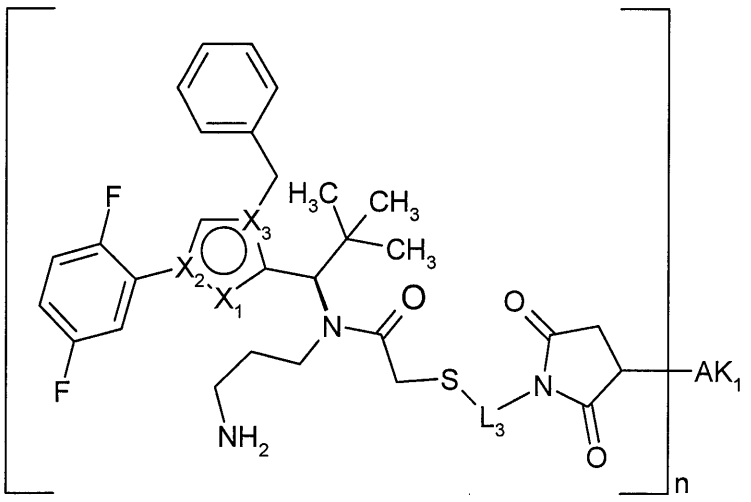
o is 0 or 1; and

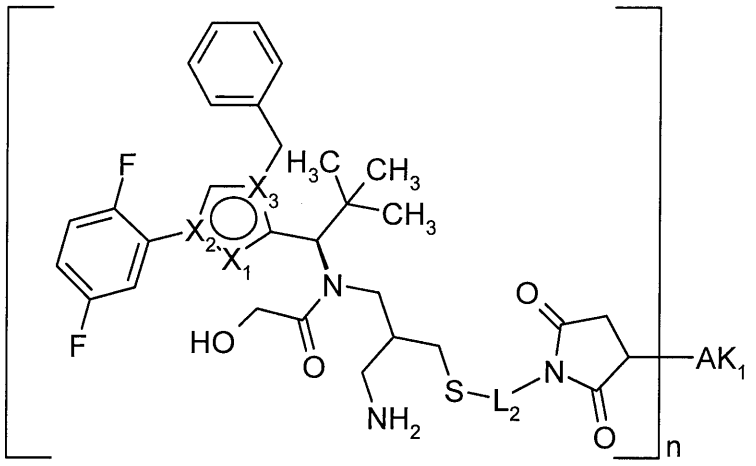
G3 represents $-(CH_2CH_2O)_s(CH_2)_t(CONH)_u(CH_2CH_2O)_v(CH_2)_w-$, where

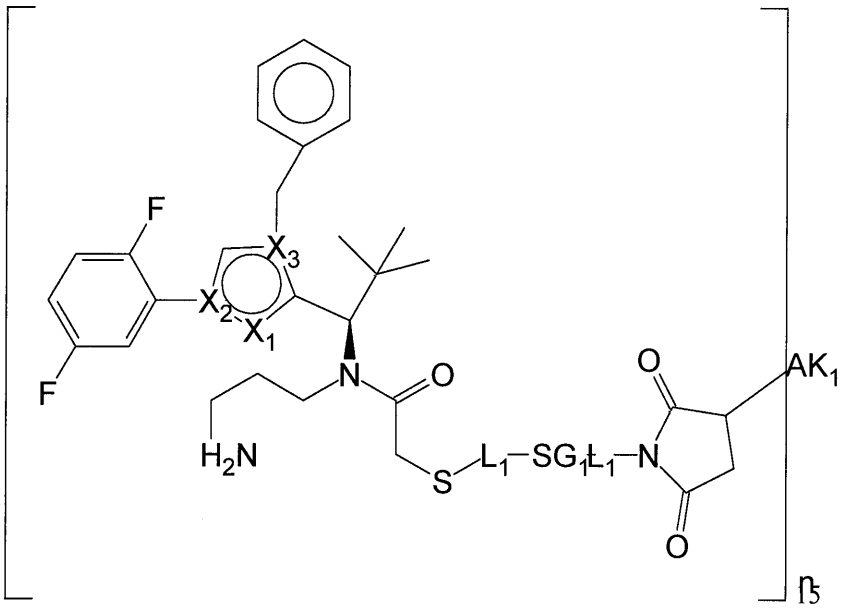
s, t, v and w each independently of one another are from 0 to 20 and u is 0 or 1.

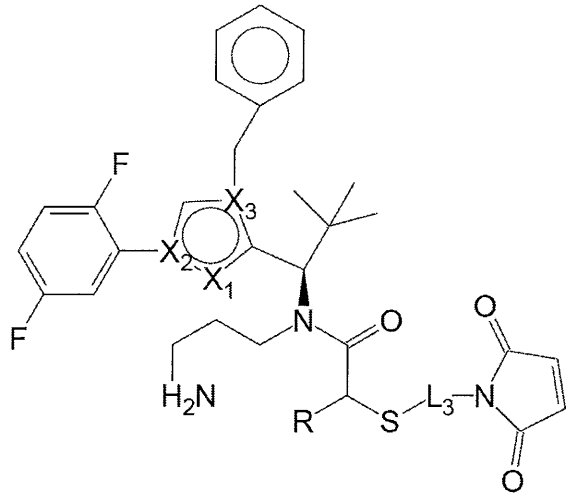
32. Conjugate according to Claim 30 or 31 where R^2 or R^3 represents –L-#1.

33. Conjugate according to Claim 1 where the conjugate has one of the formulae below:

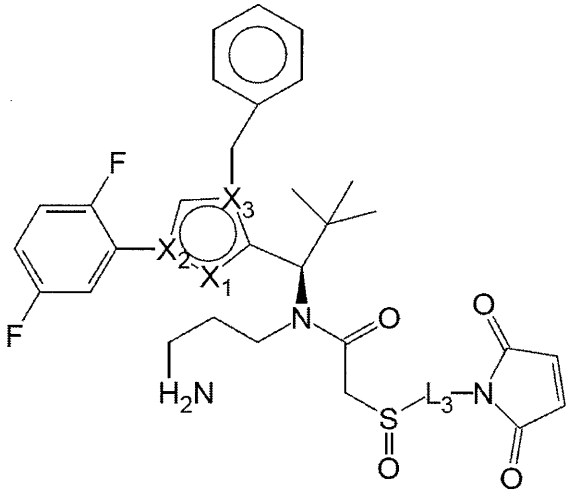




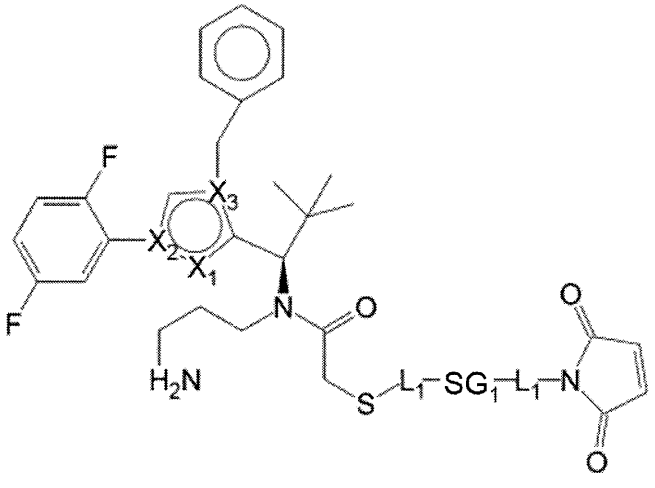




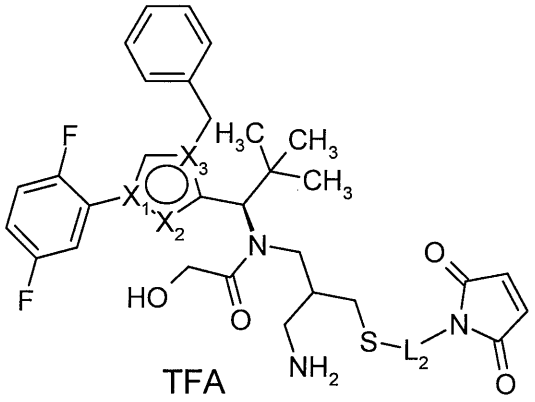
TFA



TFA

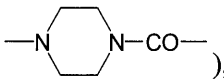


TFA



where

X_1, X_2 and X_3 have the same meaning as in Claim 1,

AK_1 represents a binder peptide or protein which is attached via a sulphur atom of the binder; n represents a number from 1 to 20; and L2 and L3 represent a straight-chain or branched hydrocarbon chain having 1 to 100 carbon atoms from arylene groups and/or straight-chain 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-, -SO-, SO_2, -NH-, -CO-, -NMe-, -NHNH-, -SO_2NHNH-, -NHCO-, -CONH-, -CONHNH- 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, -SO- or –SO_2- (preferably ), where the side chains, if present, may be substituted by –$NHCONH_2$, -COOH, -OH, -NH_2, NH-$CNNH_2$, sulphonamide, sulphone, sulphoxide or sulphonic acid.

34. Conjugate according to Claim 1 where the linker –L- is attached to a lysine side chain and has the formula below:

-§-$(SG)_x$-L4-CO-§§

where

§ represents the bond to the active compound molecule and

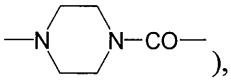
§§ represents the bond to the binder peptide or protein,

x represents 0 or 1,

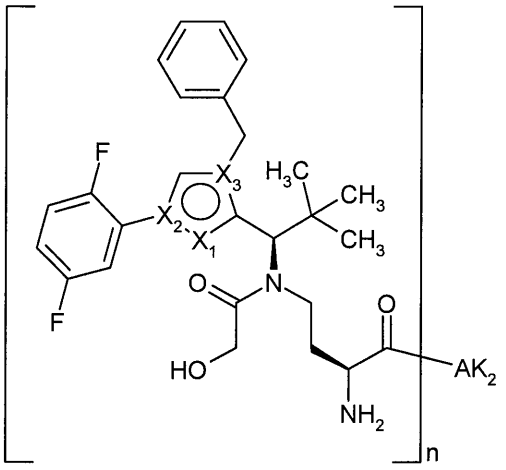
SG represents a cleavable group, preferably a 2-8 oligopeptide, particularly preferably a dipeptide,

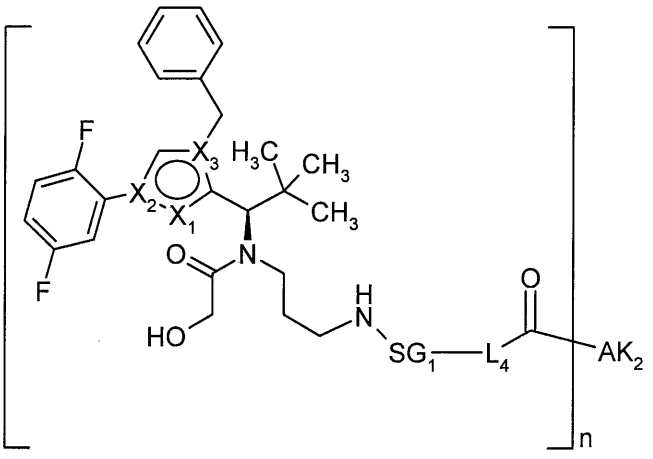
and

L4 represents a single bond or a group $-(CO)_y$-G4-, where y represents 0 or 1, and

G4 represents a straight-chain or branched hydrocarbon chain having 1 to 100 carbon atoms from arylene groups and/or straight-chain 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-, -SO-, SO_2, -NH-, -CO-, -NHCO-, -CONH-, -NMe-, -NHNH-, $-SO_2NHNH$-, -CONHNH- 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, or -SO- (preferably ), where the side chains, if present, may be substituted by $-NHCONH_2$, -COOH, -OH, $-NH_2$, NH-$CNNH_2$, sulphonamide, sulphone, sulphoxide or sulphonic acid.

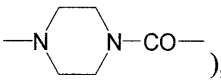
35. Conjugate of a binder peptide or protein according to Claim 1 where the conjugate has one of the formulae below:





where

X_1, X_2 and X_3 have the same meaning as in Claim 1,

AK_2 represents a binder peptide or protein which is attached via a sulphur atom of the binder; n represents a number from 1 to 20; and L4 represents an optionally straight-chain or branched hydrocarbon chain having 1 to 100 carbon atoms from arylene groups and/or straight-chain 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-, -SO-, SO_2, -NH-, -CO-, -NMe-, -NHNH-, -SO_2NHNH-, -NHCO-, -CONH-, -CONHNH- 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, -SO- or $-SO_2$- (preferably ), where the side chains, if present, may be substituted by $-NHCONH_2$, -COOH, -OH, $-NH_2$, NH-$CNNH_2$, sulphonamide, sulphone, sulphoxide or sulphonic acid, and

SG1 represents a cleavable group, preferably a 2-8 oligopeptide, particularly preferably a dipeptide.

36. Conjugate according to one or more of Claims 18 to 35 where the anti-TWEAKR antibody is an agonistic antibody.

37. Conjugate according to one or more of Claims 18 to 36 which comprises:

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 one or more of Claims 18 to 37 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 Claims 18 to 38 where the antibody is an IgG antibody.

40. Conjugate according to one or more of Claims 18 to 39 which comprises:

a. a sequence of the heavy chain, as shown in SEQ ID NO:2, and also a sequence of the light chain, as shown in SEQ ID NO:1, or

b. a sequence of the heavy chain, as shown in SEQ ID NO:12, and also a sequence of the light chain, as shown in SEQ ID NO:11, or

c. a sequence of the heavy chain, as shown in SEQ ID NO:22, and also a sequence of the light chain, as shown in SEQ ID NO:21, or

d. a sequence of the heavy chain, as shown in SEQ ID NO:32, and also a sequence of the light chain, as shown in SEQ ID NO:31, or

e. a sequence of the heavy chain, as shown in SEQ ID NO:42, and also a sequence of the light chain, as shown in SEQ ID NO:41, or

f. a sequence of the heavy chain, as shown in SEQ ID NO:52, and also a sequence of the light chain, as shown in SEQ ID NO:51, or

g. a sequence of the heavy chain, as shown in SEQ ID NO:62, and also a sequence of the light chain, as shown in SEQ ID NO:61, or

h. a sequence of the heavy chain, as shown in SEQ ID NO:72, and also a sequence of the light chain, as shown in SEQ ID NO:71, or

i. a sequence of the heavy chain, as shown in SEQ ID NO:82, and also a sequence of the light chain, as shown in SEQ ID NO:81, or

j. a sequence of the heavy chain, as shown in SEQ ID NO:92, and also a sequence of the light chain, as shown in SEQ ID NO:91, or

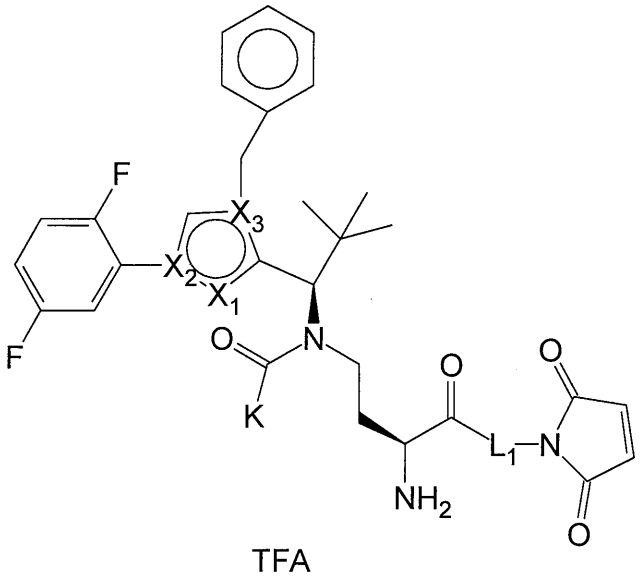
k. a sequence of the heavy chain, as shown in SEQ ID NO:102, and also a sequence of the light chain, as shown in SEQ ID NO:101, or

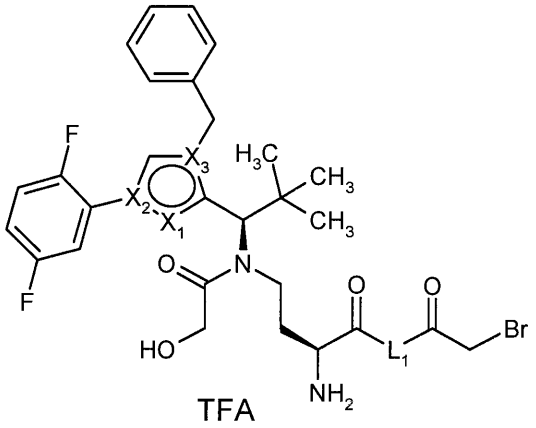
l. a sequence of the heavy chain, as shown in SEQ ID NO:112, and also a sequence of the light chain, as shown in SEQ ID NO:111.

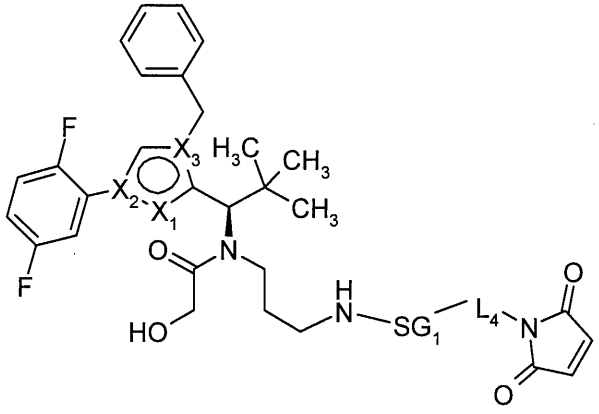
41. Spindle conjugate according to one or more of the preceding claims where the conjugate has 1 to 10, preferably 2 to 8, active compound molecules per binder peptide or protein.

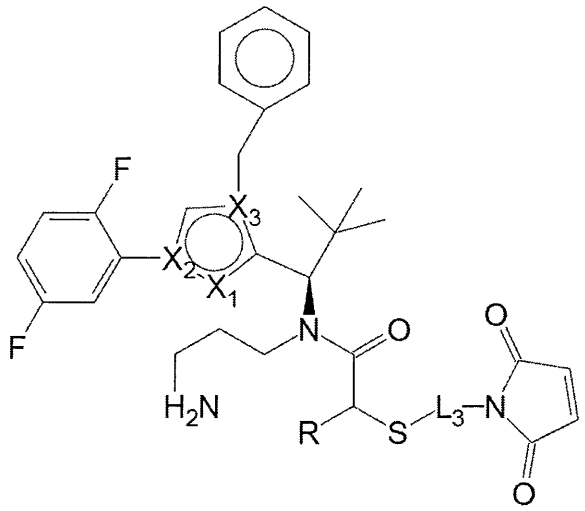
42. Process for preparing the conjugate according to Claim 1 where a compound of one of the formulae below, preferably in the form of its trifluoroacetic acid salt, is attached to a cysteine

residue of a binder peptide or protein which is optionally partially reduced beforehand, where the compound is preferably employed in a 2- to 12-fold molar excess with respect to the binder peptide or protein:

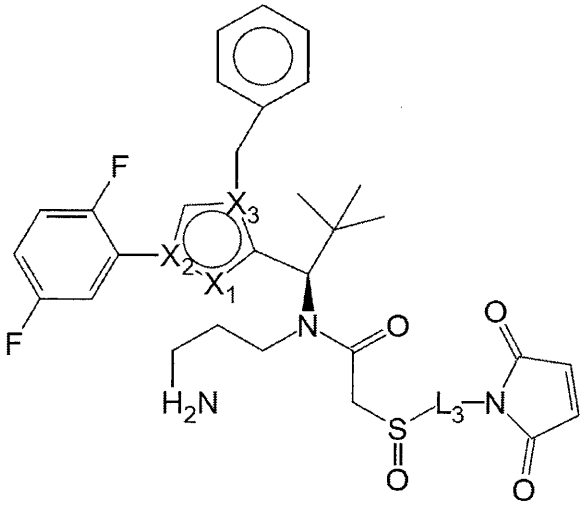








TFA



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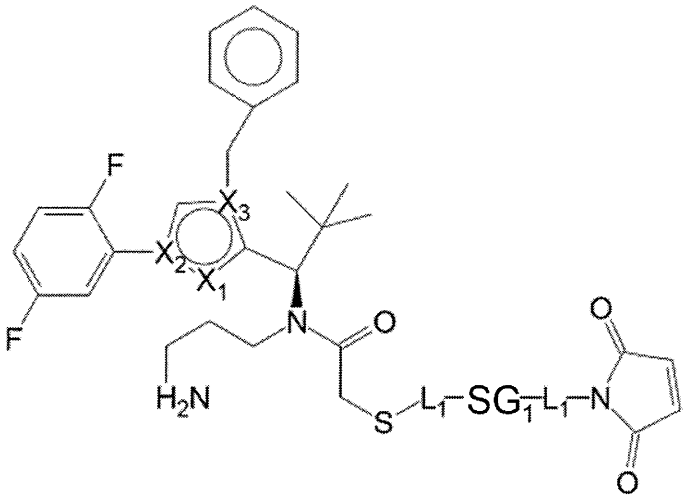
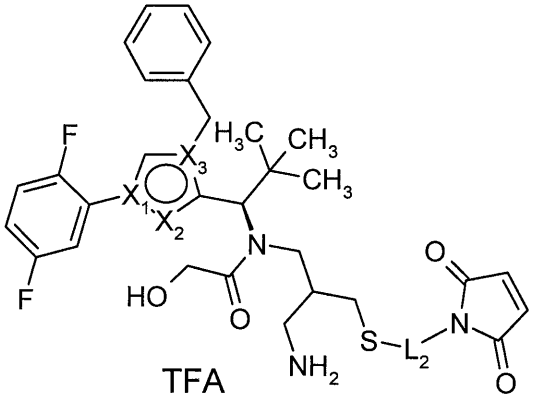
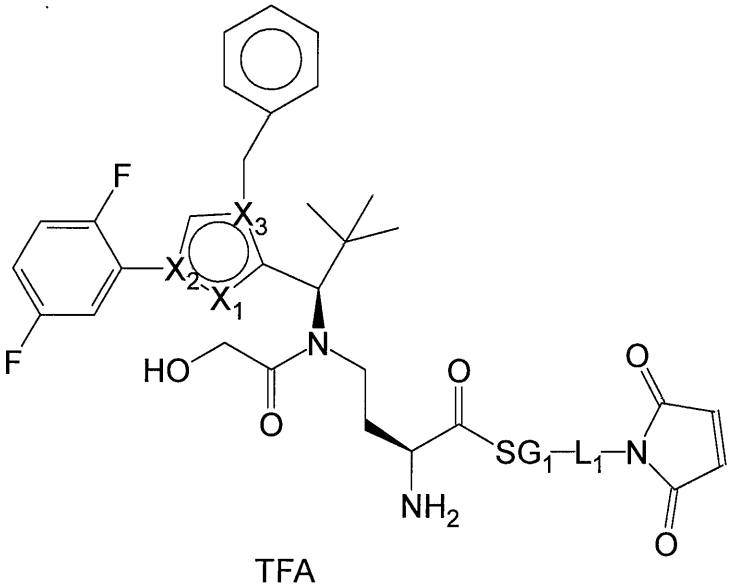

F
F
X3
X2
X1
N
O
H2N
S
L1
SG1
L1
N
O
O

TFA

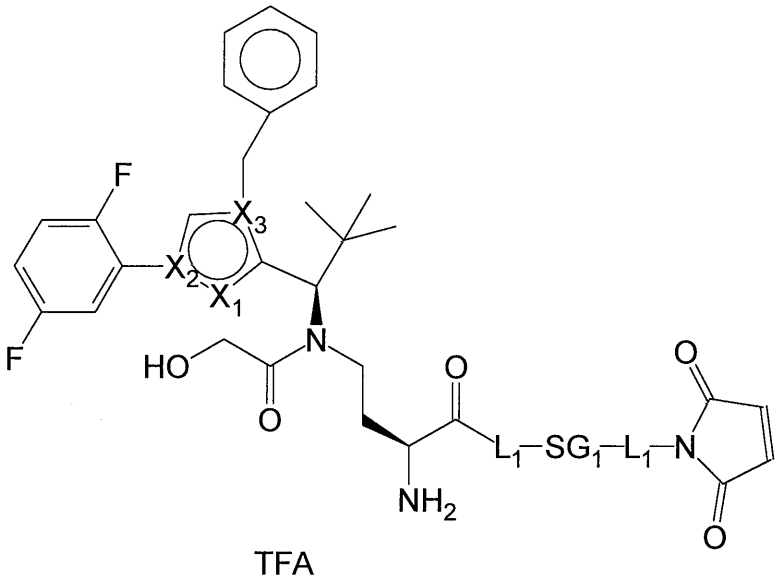

F
F
H3C
CH3
CH3
X3
X1
X2
N
HO
O
O
NH2
S
L2
N
O
O

TFA

5


F
F
X3
X2
X1
N
HO
O
O
NH2
SG1
L1
N
O
O

TFA



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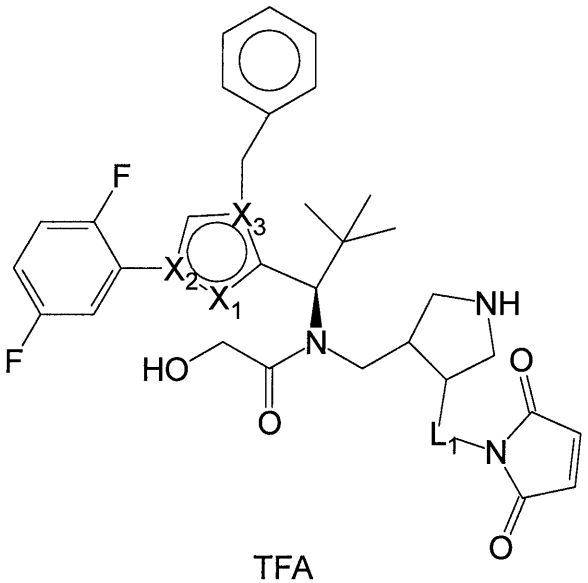

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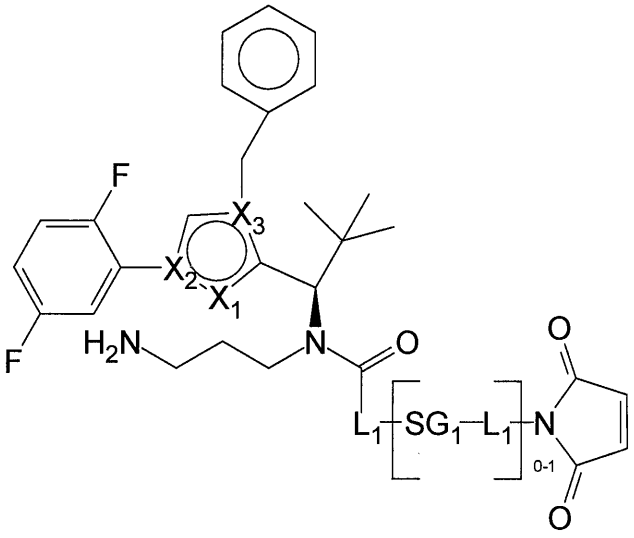

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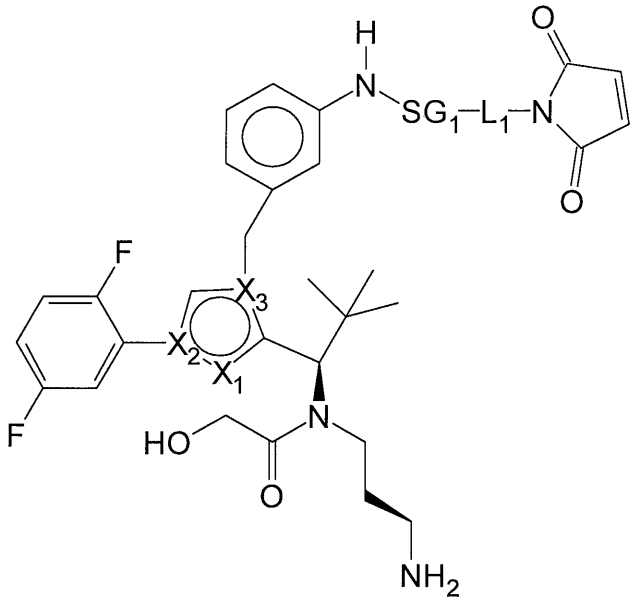


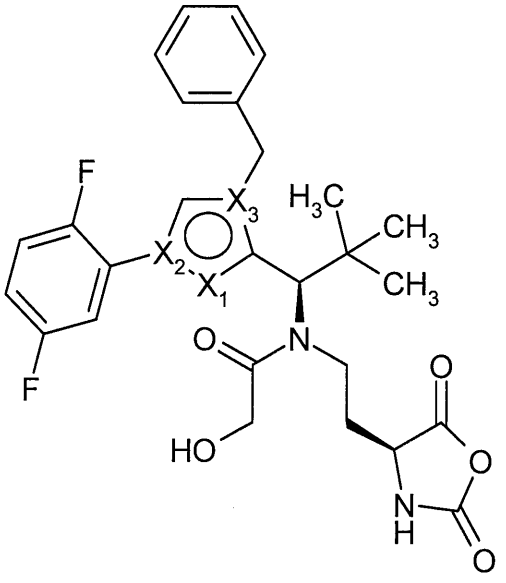
TFA

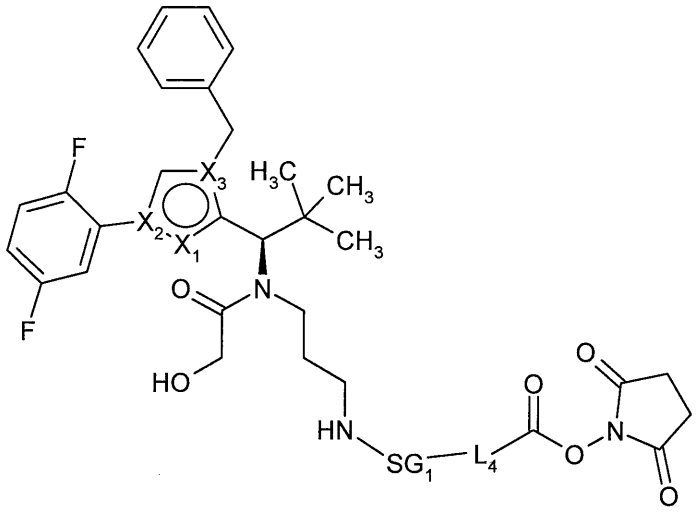
where R represents -H or –COOH,

where K represents straight-chain or branched optionally substituted by C_1-C_6-alkoxy or –OH-C_1-C_6-alkyl, and

where X_1, X_2, X_3, SG1, L1, L2, L3 and L4 have the same meaning as in Claim 28 or 32.

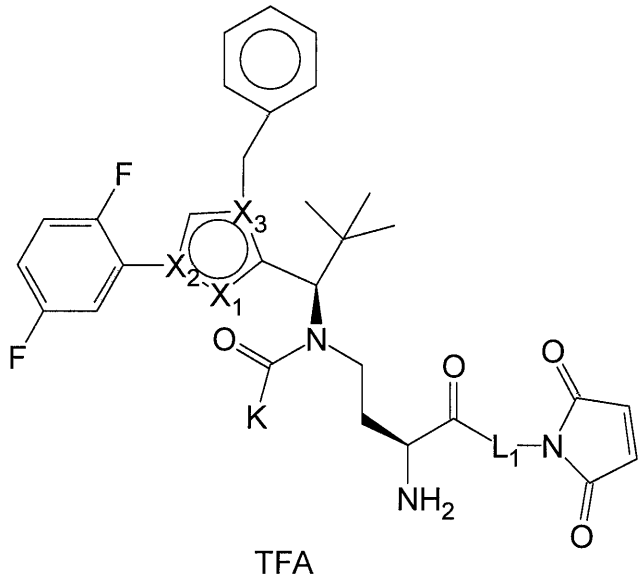
43. Process for preparing the conjugate according to Claim 42 where a compound of one of the formulae below, preferably in the form of its trifluoroacetic acid salt, is attached to a lysine residue of a binder peptide or protein, where the compound is preferably employed in a 2- to 12-fold molar excess with respect to the binder peptide or protein:





where X_1, X_2, X_3, SG1 and L4 have the same meaning as in Claim 42.

44. Compound of one of the formulae below:



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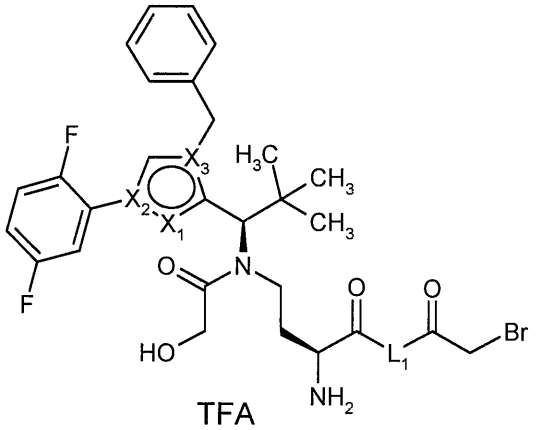

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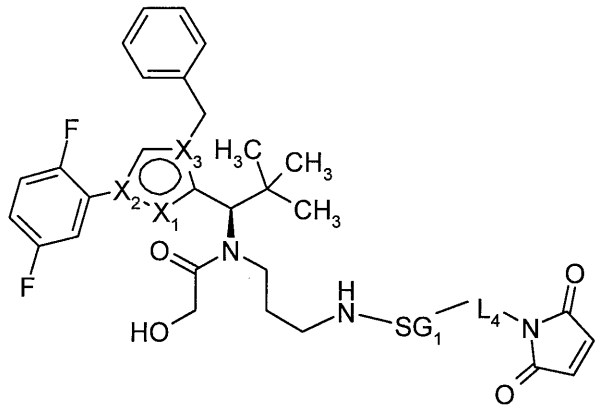

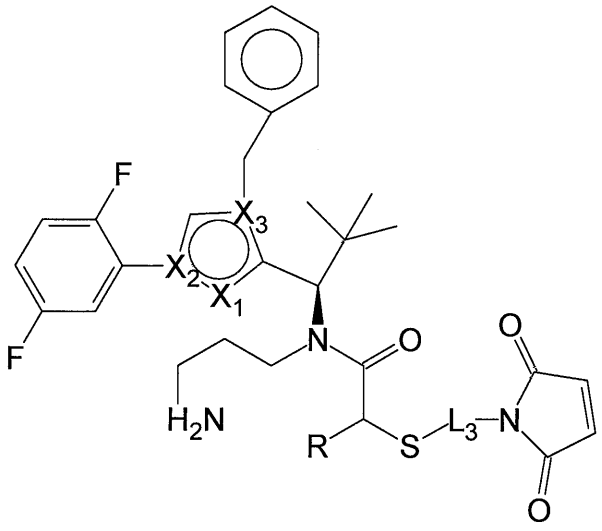

TFA

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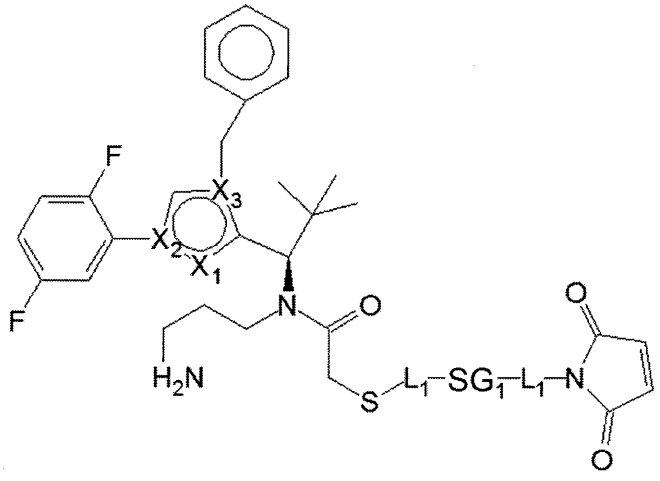
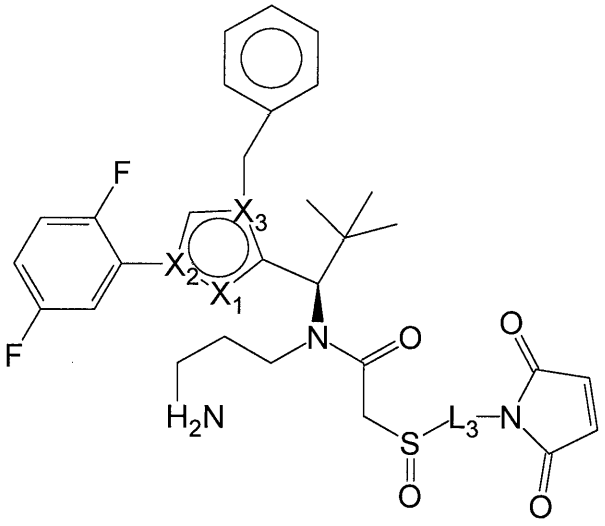
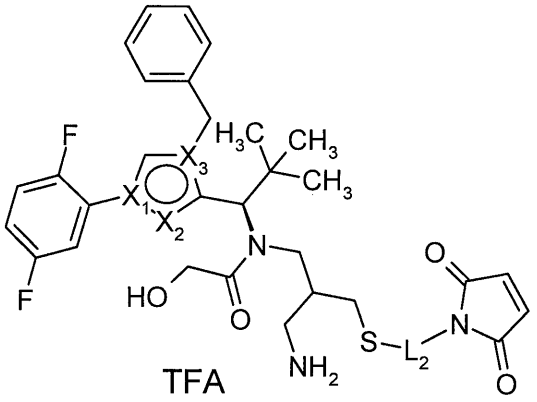


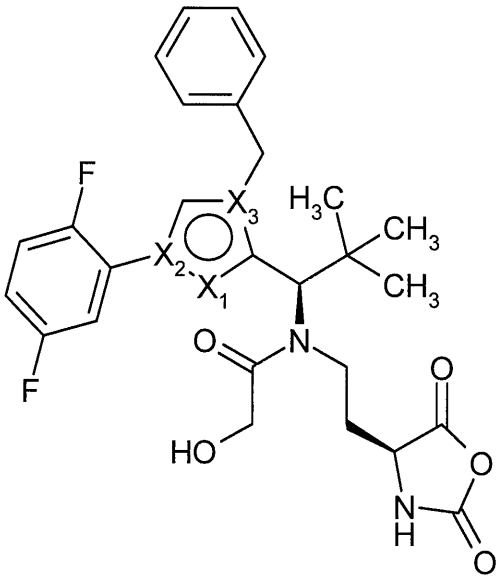
TFA


F
F
X3
X2
X1
N
O
H2N
S
L3
N
O
O
O

TFA


F
F
X3
X1
X2
H3C
CH3
CH3
N
HO
O
NH2
S
L2
N
O
O

TFA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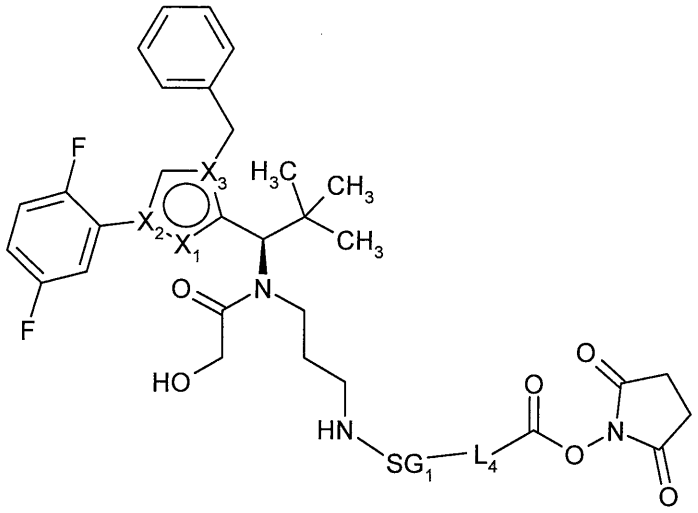
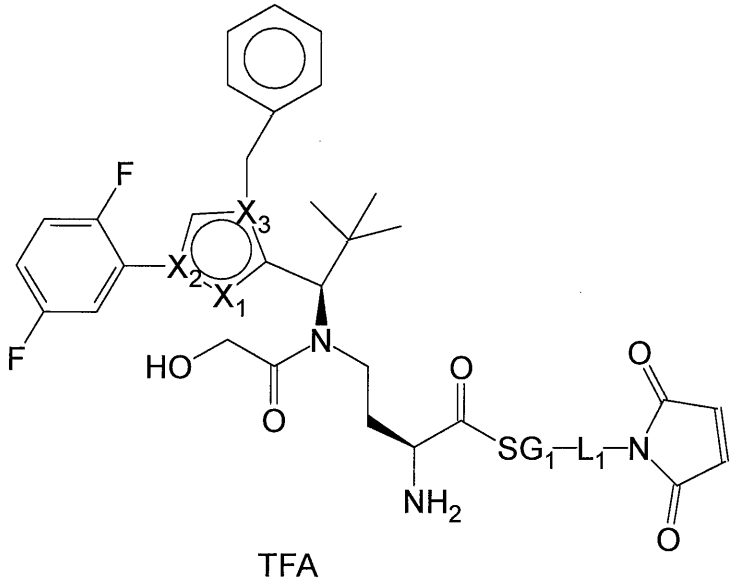
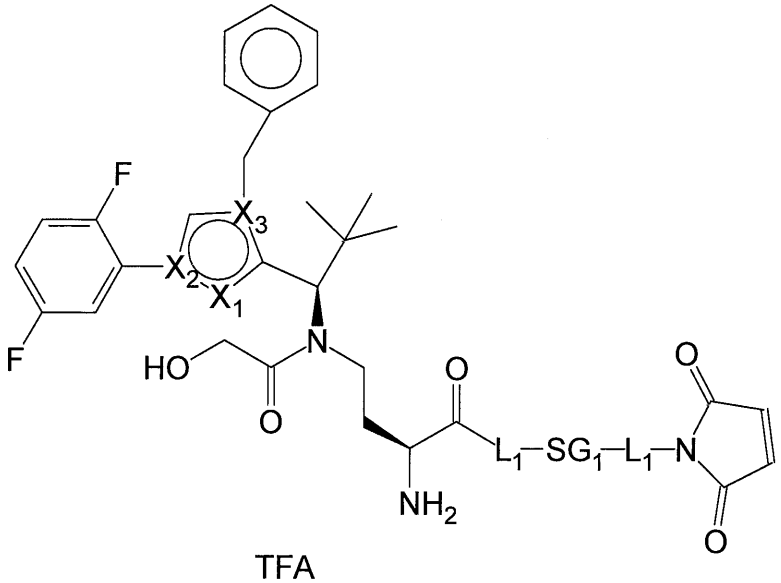
X3
X2
X1
H3C
CH3
CH3
O
N
HO
O
N
H
O
O


F
F
X3
X2
X1
H3C
CH3
CH3
O
N
HO
HN
SG1
L4
O
O
N
O
O

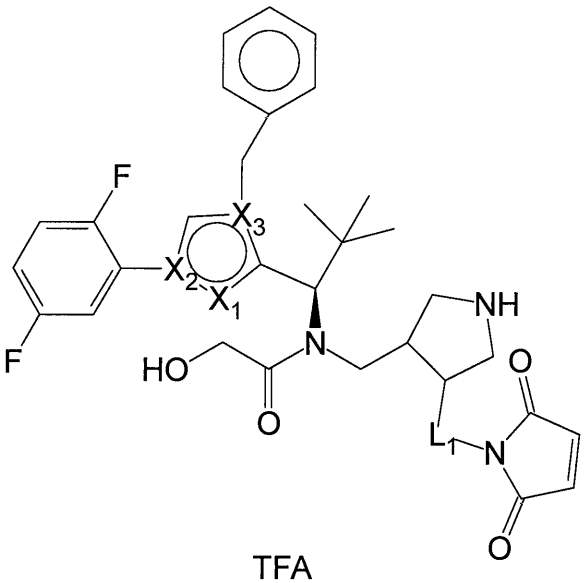

F
F
X3
X2
X1
HO
O
N
O
SG1
L1
N
O
O
NH2

TFA


F
F
X3
X2
X1
HO
O
N
O
L1
SG1
L1
N
O
O
NH2

TFA

5



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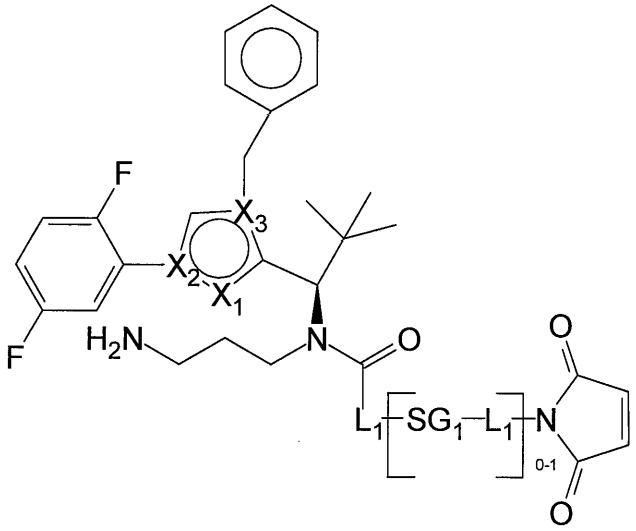

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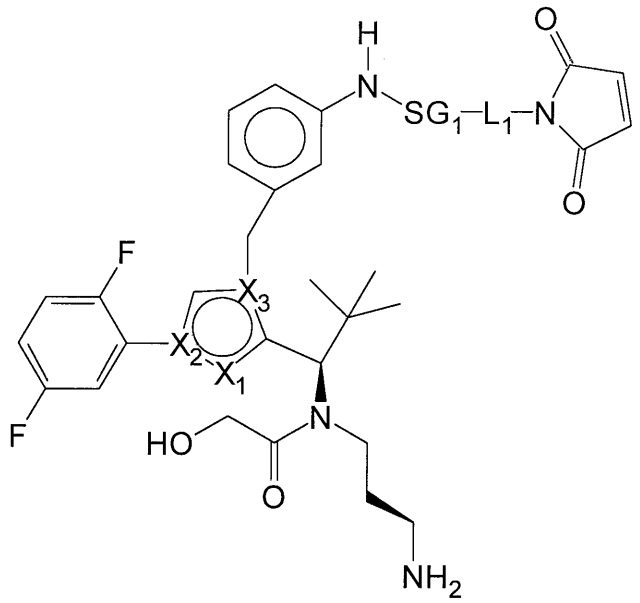


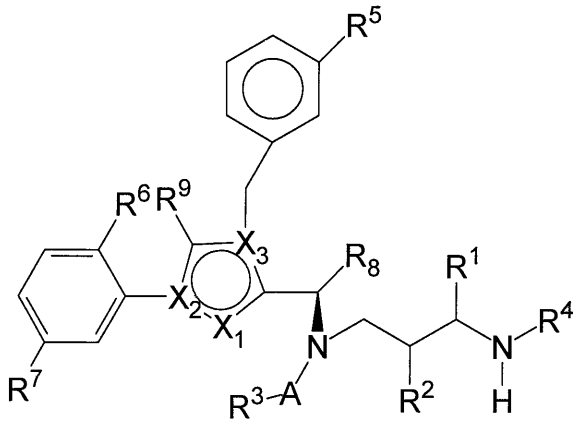
TFA

where R represents -H or –COOH,

where K represents straight-chain or branched optionally substituted by C_1-C_6-alkoxy or –OH C_1-C_6-alkyl, and

where X_1, X_2, X_3, SG1, L1, L2, L3 and L4 have the same meaning as in Claim 1.

45. Compounds of the general formula (III):



(III)

where

X_1 represents N, X_2 represents N and X_3 represents C, or X_1 represents CH, 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 –L-BINDER, H or -$(CH_2)_{0\text{-}3}$Z, where Z represents -H, -NHY^3, -OY^3, -SY^3, halogen, -CO-NY^1Y^2 or -CO-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 $-CH(CH_2W)Z'$, and Y^3 represents H or $-(CH_2)_{0-3}Z'$, where Z' represents H, NH_2, SO_3H, COOH, $-NH-CO-CH_2-CH_2-CH(NH_2)COOH$ or $-(CO-NH-CHY^4)_{1-3}COOH$; where W represents H or OH; where Y^4 independently of one another represents straight-chain or branched C_{1-6}-alkyl which is optionally substituted by $-NHCONH_2$, or represents aryl or benzyl which are optionally substituted by $-NH_2$;

R^2 and R^4 independently of one another represent –L-BINDER, H, $-CO-CHY^4-NHY^5$ or $-(CH_2)_{0-3}Z$, 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 L-#1, H, NH_2, SO_3H, COOH, SH or OH,
where Z represents -H, halogen, $-OY^3$, $-SY^3$, NHY^3, $-CO-NY^1Y^2$ or $-CO-OY^3$,
where Y^1 and Y^2 independently of one another represent H, NH_2 or $-(CH_2)_{0-3}Z'$, and Y^3 represents H or $-(CH_2)_{0-3}Z'$, where Z' represents H, SO_3H, NH_2 or COOH;
where Y^4 independently of one another represents straight-chain or branched C_{1-6} alkyl which is optionally substituted by $-NHCONH_2$, or represents aryl or benzyl which are optionally substituted by $-NH_2$, and Y^5 represents H or $-CO-CHY^6-NH_2$, where Y^6 represents straight-chain or branched C_{1-6}-alkyl;

A represents CO, SO, SO_2, or SO_2NH;

R^3 represents –L-BINDER or an optionally substituted alkyl, 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-CO-alkyl groups, 1-3 -O-CO-NH-alkyl groups, 1-3 -NH-CO-alkyl groups, 1-3 -NH-CO-NH-alkyl groups, 1-3 $-S(O)_n$-alkyl groups, 1-3 $-SO_2$-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, $-OY^3$, $-SY^3$, $-NHY^3$, $-CO-NY^1Y^2$ or $-CO-OY^3$, where Y^1 and Y^2 independently of one another represent H, NH_2 or $-(CH_2)_{0-3}Z'$ and Y^3 represents H, $-(CH_2)_{0-3}-CH(NHCOCH_3)Z'$, $-(CH_2)_{0-3}-CH(NH_2)Z'$ or $-(CH_2)_{0-3}Z'$, where Z' represents H, SO_3H, NH_2 or COOH
(where "alkyl" preferably represents C_{1-10}-alkyl);

R^5 represents –L-BINDER, H, F, NH_2, NO_2, halogen, SH or $-(CH_2)_{0-3}Z$, where Z represents -H, halogen, $-OY^3$, $-SY^3$, $-NHY^3$, $-CO-NY^1Y^2$ or $-CO-OY^3$,

where Y^1 and Y^2 independently of one another represent H, NH_2 or $-(CH_2)_{0-3}Z'$, and Y^3 represents H or $-(CH_2)_{0-3}Z'$, where Z' represents H, SO_3H, NH_2 or COOH;

where L represents a linker and BINDER represents a binder or a derivative thereof, where the binder may optionally be attached to a plurality of active compound molecules,

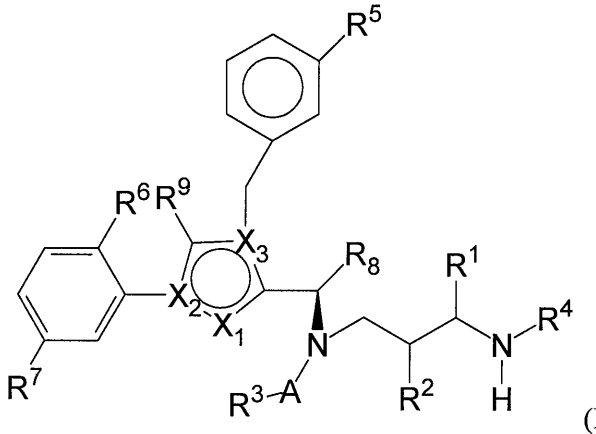
R^6 and R^7 independently of one another represent H, cyano, (optionally fluorinated) C_{1-10}-alkyl, (optionally fluorinated) C_{2-10}-alkenyl, (optionally fluorinated) C_{2-10}-alkynyl, hydroxy or halogen,

R^8 represents (optionally fluorinated) C_{1-10}-alkyl, (optionally fluorinated) 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 and salts of the solvates thereof.

46. Compounds of the general formula (IV):



(IV)

where

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

R^1 represents –L-BINDER, H or $-(CH_2)_{0-3}Z$, where Z represents -H, $-NHY^3$, $-OY^3$, $-SY^3$, halogen, $-CO-NY^1Y^2$ or $-CO-OY^3$,

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 $-CH(CH_2W)Z'$, and Y^3 represents H or $-(CH_2)_{0-3}Z'$, where Z' represents H, NH_2, SO_3H, COOH, $-NH-CO-CH_2-CH_2-CH(NH_2)COOH$ or $-(CO-NH-CHY^4)_{1-3}COOH$; where W represents H or OH;

where Y^4 independently of one another represents straight-chain or branched C_{1-6}-alkyl which is optionally substituted by $-NHCONH_2$, or represents aryl or benzyl which are optionally substituted by $-NH_2$;

R^2 and R^4 independently of one another represent –L-BINDER, H, $-CO-CHY^4-NHY^5$ or $-(CH_2)_{0-3}Z$, 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 L-#1, H, NH_2, SO_3H, COOH, SH or OH,
where Z represents -H, halogen, $-OY^3$, $-SY^3$, NHY^3, $-CO-NY^1Y^2$ or $-CO-OY^3$,
where Y^1 and Y^2 independently of one another represent H, NH_2 or $-(CH_2)_{0-3}Z'$, and Y^3 represents H or $-(CH_2)_{0-3}Z'$, where Z' represents H, SO_3H, NH_2 or COOH;
where Y^4 independently of one another represents straight-chain or branched C_{1-6} alkyl which is optionally substituted by $-NHCONH_2$, or represents aryl or benzyl which are optionally substituted by $-NH_2$, and Y^5 represents H or $-CO-CHY^6-NH_2$, where Y^6 represents straight-chain or branched C_{1-6}-alkyl;

A represents CO, SO, SO_2, or SO_2NH;

R^3 represents –L-BINDER or an optionally substituted alkyl, aryl, heteroaryl, heteroalkyl or heterocycloalkyl group,
preferably –L-#1 or a C_{1-10}-alkyl, C_{6-10}-aryl, 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-CO-alkyl groups, 1-3 –O-CO-NH-alkyl groups, 1-3 –NH-CO-alkyl groups, 1-3 –NH-CO-NH-alkyl groups, 1-3 $-S(O)_n$-alkyl groups, 1-3 $-SO_2$-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, $-OY^3$, $-SY^3$, $-NHY^3$, $-CO-NY^1Y^2$ or $-CO-OY^3$, where Y^1 and Y^2 independently of one another represent H, NH_2 or $-(CH_2)_{0-3}Z'$ and Y^3 represents H, $-(CH_2)_{0-3}-CH(NHCOCH_3)Z'$, $-(CH_2)_{0-3}-CH(NH_2)Z'$ or $-(CH_2)_{0-3}Z'$, where Z' represents H, SO_3H, NH_2 or COOH,
(where "alkyl" preferably represents C_{1-10}-alkyl);

R^5 represents –L-BINDER, H, F, NH_2, NO_2, halogen, SH or $-(CH_2)_{0-3}Z$, where Z represents -H, halogen, $-OY^3$, $-SY^3$, $-NHY^3$, $-CO-NY^1Y^2$ or $-CO-OY^3$,
where Y^1 and Y^2 independently of one another represent H, NH_2 or $-(CH_2)_{0-3}Z'$, and Y^3 represents H or $-(CH_2)_{0-3}Z'$, where Z' represents H, SO_3H, NH_2 or COOH;

where L represents a linker and BINDER represents a binder or a derivative thereof, where the binder may optionally be attached to a plurality of active compound molecules,

R^6 and R^7 independently of one another represent H, cyano, (optionally fluorinated) C_{1-10}-alkyl, (optionally fluorinated) C_{2-10}-alkenyl, (optionally fluorinated) C_{2-10}-alkynyl, hydroxy or halogen,

R^8 represents (optionally fluorinated) C_{1-10}-alkyl, (optionally fluorinated) 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 and salts of the solvates thereof.

47. Compound according to Claim 46 where Z represents Cl or Br.

48. Compound according to Claim 46 where R^1 represents $-(CH_2)_{0-3}Z$, where Z represents -CO-NY^1Y^2, where Y^2 represents $-(CH_2CH_2O)_{0-3}-(CH_2)_{0-3}Z'$ and Y^1 represents H, NH_2 or $-(CH_2CH_2O)_{0-3}-(CH_2)_{0-3}Z'$.

49. Compound according to one or more of Claims 46-48 where Y^1 represents H, Y^2 represents $-(CH_2CH_2O)_3-CH_2CH_2Z'$ and Z' represents –COOH.

50. Compound according to one or more of Claims 46-48, where Y^1 represents H, Y^2 represents $-CH_2CH_2Z'$ and Z' represents $-(CONHCHY^4)_2COOH$.

51. Compound according to Claim 46 where Y^4 represents straight-chain or branched C_{1-6}-alkyl which is optionally substituted by $-NHCONH_2$.

52. Compound according to Claim 46 where at least one Y^4 representative is selected from the group consisting of *i*-propyl and $-CH_3$.

53. Compound according to one or more of Claims 46 and 48 where Y^1 represents H, Y^2 represents $-CH_2CH_2Z'$, Z' represents -CONHCHY^{4}COOH and Y^4 represents aryl or benzyl which are optionally substituted by $-NH_2$.

54. Compound according to Claim 53 where Y^4 represents aminobenzyl.

55. Compound according to Claim 46 where R^2 represents $-(CH_2)_{0-3}Z$ and Z represents $-SY^3$.

56. Compound according to Claim 46 where R^4 represents $-CO-CHY^4-NHY^5$ and Y^5 represents H.

57. Compound according to Claim 46 where R^4 represents $-CO-CHY^4-NHY^5$ and Y^5 represents $-CO-CHY^6-NH_2$.

58. Compound according to one or more of Claims 56 and 57 where Y^4 represents straight-chain or branched C_{1-6}-alkyl which is optionally substituted by $-NHCONH_2$.

59. Compound according to one or more of Claims 46 to 58 where the compound has one of the formulae below:

N-(3-aminopropyl)-N-{(1R)-1-[4-benzyl-1-(2,5-difluorophenyl)-1H-pyrazol-3-yl]-2,2-dimethylpropyl}-2-hydroxyacetamide;

N-(3-aminopropyl)-N-{(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}-2-hydroxyacetamide;

(2S)-2-amino-4-[{(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}(glycoloyl)amino]-N-methylbutanamide (1:1);

N-(3-aminopropyl)-N-{(1S)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2yl]-2,2-dimethylpropyl}acetamide;

N-(3-aminopropyl)-N-{(1S)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}-2-hydroxyacetamide;

S-[1-(2-{[2-({(2S)-2-amino-4-[{(1R)-1-[4-benzyl-1-(2,5-difluorophenyl)-1H-pyrazol-3-yl]-2,2-dimethylpropyl}(glycoloyl)amino]butanoyl}amino)ethyl]amino}-2-oxoethyl)-2,5-dioxopyrrolidin-3-yl]-L-cysteine;

N-{(2S)-2-amino-4-[{(1R)-1-[4-benzyl-1-(2,5-difluorophenyl)-1H-pyrazol-3-yl]-2,2-dimethylpropyl}(glycoloyl)amino]butanoyl}-beta-alanyl-L-alanyl-N-[4-(3-{[(2R)-2-amino-2-carboxyethyl]sulphanyl}-2,5-dioxopyrrolidin-1-yl)phenyl]-N^5-carbamoyl-L-ornithinamide;

S-(1-{2-[(N-{(2S)-2-amino-4-[{(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}(glycoloyl)amino]butanoyl}-beta-alanyl)amino]ethyl}-2,5-dioxopyrrolidin-3-yl)-L-cysteine;

S-[1-(2-{[2-({(2S)-2-amino-4-[{(1R)-1-[4-benzyl-1-(2,5-difluorophenyl)-1H-pyrazol-3-yl]-2,2-dimethylpropyl}(glycoloyl)amino]butanoyl}amino)ethyl]amino}-2-oxoethyl)-2,5-dioxopyrrolidin-3-yl]-

L-cysteine; N-{(2S)-2-amino-4-[{(1R)-1-[4-benzyl-1-(2,5-difluorophenyl)-1H-pyrazol-3-yl]-2,2-dimethylpropyl}(glycoloyl)amino]butanoyl}-beta-alanyl-L-alanyl-N-[4-(3-{[(2R)-2-amino-2-carboxyethyl]sulphanyl}-2,5-dioxopyrrolidin-1-yl)phenyl]-N^5-carbamoyl-L-ornithinamide;

S-(1-{2-[(N-{(2S)-2-amino-4-[{(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}(glycoloyl)amino]butanoyl}-beta-alanyl)amino]ethyl}-2,5-dioxopyrrolidin-3-yl)-L-cysteine;

N-[6-(3-{[(2R)-2-amino-2-carboxyethyl]sulphanyl}-2,5-dioxopyrrolidin-1-yl)hexanoyl]-L-valyl-N^5-carbamoyl-L-ornithyl-N^6-{(2S)-2-amino-4-[{(1R)-1-[4-benzyl-1-(2,5-difluorophenyl)-1H-pyrazol-3-yl]-2,2-dimethylpropyl}(glycoloyl)amino]butanoyl}-L-lysine;

S-[1-(2-{[2-({(2S)-2-amino-4-[{(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}(glycoloyl)amino]butanoyl}amino)ethyl]amino}-2-oxoethyl)-2,5-dioxopyrrolidin-3-yl]-L-cysteine;

S-(2-{[2-({(2S)-2-amino-4-[{(1R)-1-[4-benzyl-1-(2,5-difluorophenyl)-1H-pyrazol-3-yl]-2,2-dimethylpropyl}(glycoloyl)amino]butanoyl}amino)ethyl]amino}-2-oxoethyl)-L-cysteine;

S-{1-[6-(2-{(2S)-2-amino-4-[{(1R)-1-[4-benzyl-1-(2,5-difluorophenyl)-1H-pyrazol-3-yl]-2,2-dimethylpropyl}(glycoloyl)amino]butanoyl}hydrazino)-6-oxohexyl]-2,5-dioxopyrrolidin-3-yl}-L-cysteine;

N-[19-(3(R/S)-{[(2R)-2-amino-2-carboxyethyl]sulphanyl}-2,5-dioxopyrrolidin-1-yl)-17-oxo-4,7,10,13-tetraoxa-16-azanonadecan-1-oyl]-R/S-{2-[(3-aminopropyl){(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}amino]-2-oxoethyl}homocysteine;

S-{(3R/S)-1-[2-({(2S)-2-amino-4-[{(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}(glycoloyl)amino]butanoyl}amino)ethyl]-2,5-dioxopyrrolidin-3-yl}-L-cysteine;

S-[(3R/S)-1-(2-{[6-({2-[(3-aminopropyl){(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}amino]-2-oxoethyl}sulphanyl)hexanoyl]amino}ethyl)-2,5-dioxopyrrolidin-3-yl]-L-cysteine;

S-{1-[2-({[(1R,3S)-3-({(2S)-2-amino-4-[{(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}(glycoloyl)amino]butanoyl}amino)cyclopentyl]carbonyl}amino)ethyl]-2,5-dioxopyrrolidin-3-yl}-L-cysteine;

S-(2-{[2-({(2S)-2-amino-4-[{(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}(glycoloyl)amino]butanoyl}amino)ethyl]amino}-2-oxoethyl)-L-cysteine;

N^6-(N-{(2S)-2-amino-4-[{(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}(glycoloyl)amino]butanoyl}-beta-alanyl)-N^2-{N-[6-(3-{[(2R)-2-amino-2-carboxyethyl]sulphanyl}-2,5-dioxopyrrolidin-1-yl)hexanoyl]-L-valyl-L-alanyl}-L-lysine;

N-[2-({(2S)-2-amino-4-[{(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}(glycoloyl)amino]butanoyl}amino)ethyl]-L-glutamine;

N^6-(N-{(2S)-2-amino-4-[{(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}(glycoloyl)amino]butanoyl}-beta-alanyl)-L-lysine;

N-(3-aminopropyl)-N-{(1R)-1-[4-benzyl-1-(2,5-difluorophenyl)-1H-pyrazol-3-yl]-2,2-dimethylpropyl}acetamide;

N-(3-aminopropyl)-N-{(1R)-1-[4-benzyl-1-(2,5-difluorophenyl)-1H-pyrazol-3-yl]-2,2-dimethylpropyl}-2-methoxyacetamide;

N-(3-aminopropyl)-N-{(1R)-1-[4-benzyl-1-(2,5-difluorophenyl)-1H-pyrazol-3-yl]-2,2-dimethylpropyl}-2,4-difluorobenzamide;

N-(3-aminopropyl)-N-{(1R)-1-[4-benzyl-1-(2,5-difluorophenyl)-1H-pyrazol-3-yl]-2,2-dimethylpropyl}-4-methylbenzamide;

N-(3-aminopropyl)-N-{(1R)-1-[4-benzyl-1-(2,5-difluorophenyl)-1H-pyrazol-3-yl]-2,2-dimethylpropyl}-2-ethoxyacetamide;

N-(3-aminopropyl)-N-{(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}-3,3,3-trifluoropropanamide;

N-(3-aminopropyl)-N-{(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}-4-fluorobenzamide;

N-(3-aminopropyl)-N-{(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}acetamide;

N-(3-aminopropyl)-N-{(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}-4-(trifluoromethyl)benzamide;

N-(3-aminopropyl)-N-{(1R)-1-[4-benzyl-1-(2,5-difluorophenyl)-1H-pyrazol-3-yl]-2,2-dimethylpropyl}-2-ethoxyacetamide;

N-(3-aminopropyl)-N-{(1R)-1-[4-benzyl-1-(2,5-difluorophenyl)-1H-pyrazol-3-yl]-2,2-dimethylpropyl}-2-ethoxyacetamide;

(2S)-2-amino-4-[{(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}(glycoloyl)amino]butanoic acid;

(2S)-2-amino-N-(2-aminoethyl)-4-[{(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}(glycoloyl)amino]butanamide;

4-[(2-{[2-({(2S)-2-amino-4-[{(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}(glycoloyl)amino]butanoyl}amino)ethyl]amino}-2-oxoethyl)amino]-3-{[(2R)-2-amino-2-carboxyethyl]sulphanyl}-4-oxobutanoic acid;

4-[(2-{[2-({(2S)-2-amino-4-[{(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}(glycoloyl)amino]butanoyl}amino)ethyl]amino}-2-oxoethyl)amino]-2-{[(2R)-2-amino-2-carboxyethyl]sulphanyl}-4-oxobutanoic acid;

N-{(2S)-2-amino-4-[{(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}(glycoloyl)amino]butanoyl}-beta-alanine;

N-{(2S)-2-amino-4-[{(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}(glycoloyl)amino]butanoyl}-L-serine;

N-{(2S)-2-amino-4-[{(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}(glycoloyl)amino]butanoyl}-L-alanine;

N-{(2S)-2-amino-4-[{(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}(glycoloyl)amino]butanoyl}glycine;

N-(3-aminopropyl)-N-{(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}-4-methylbenzamide;

N-(3-aminopropyl)-N-{(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}-4-(methylsulphanyl)benzamide;

(2S)-N-(3-aminopropyl)-N-{(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}-2-hydroxypropanamide;

N-(3-aminopropyl)-N-{(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}-2-(methylsulphanyl)acetamide;

(2S)-N-(3-aminopropyl)-N-{(1R)-1-[4-benzyl-1-(2,5-difluorophenyl)-1H-pyrazol-3-yl]-2,2-dimethylpropyl}-2-hydroxypropanamide;

methyl 4-[(3-aminopropyl){(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}amino]-4-oxobutanoate;

4-[(3-aminopropyl){(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}amino]-4-oxobutanoic acid;

(2R)-22-[(3R/S)-3-{[(2R)-2-amino-2-carboxyethyl]sulphanyl}-2,5-dioxopyrrolidin-1-yl]-2-[({2-[(3-aminopropyl){(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}amino]-2-oxoethyl}sulphanyl)methyl]-4,20-dioxo-7,10,13,16-tetraoxa-3,19-diazadocosan-1-oic acid;

4-amino-N-(3-aminopropyl)-N-{(1R)-1-[4-benzyl-1-(2,5-difluorophenyl)-1H-pyrazol-3-yl]-2,2-dimethylpropyl}benzamide;

N-acetyl-S-{2-[(3-aminopropyl){(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}amino]-2-oxoethyl}-L-cysteine;

N-acetyl-S-[2-([3-(L-alanylamino)propyl]{(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}amino)-2-oxoethyl]-L-cysteine;

(2S)-N-(3-aminopropyl)-N-{(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}tetrahydrofuran-2-carboxamide;

3-({2-[(3-aminopropyl){(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}amino]-2-oxoethyl}sulphanyl)propanoic acid;

S-{2-[(3-aminopropyl){(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}amino]-2-oxoethyl}homocysteine;

4-amino-N-(3-aminopropyl)-N-{(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}benzamide;

4-[(2-{[(2R)-2-({(2S)-2-amino-4-[{(1R)-1-[1-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl}(glycoloyl)amino]butanoyl}amino)-2-carboxyethyl]amino}-2-oxoethyl)amino]-3-{[(2R)-2-amino-2-carboxyethyl]sulphanyl}-4-oxobutanoic acid;

4-[(2-{[(2R)-2-({(2S)-2-amino-4~[{(lR)-l-[l-benzyl-4-(2,5-difluorophenyl)-1H-pyrrol-2-yl]-2,2-dimethylpropyl} (glycoloyl)amino]butanoyl}ammo)-2-carboxyethyl]amino}-2-oxoethyl)amino]-2-{[(2R)-2-amino-2-carboxyethyl]sulphonyl}-4-oxobutanoicacid.

60. Pharmaceutical composition comprising a conjugate according to one or more of Claims 1 to 41 or a compound according to Claims 46-59 in combination with an inert non-toxic pharmaceutically suitable auxiliary.

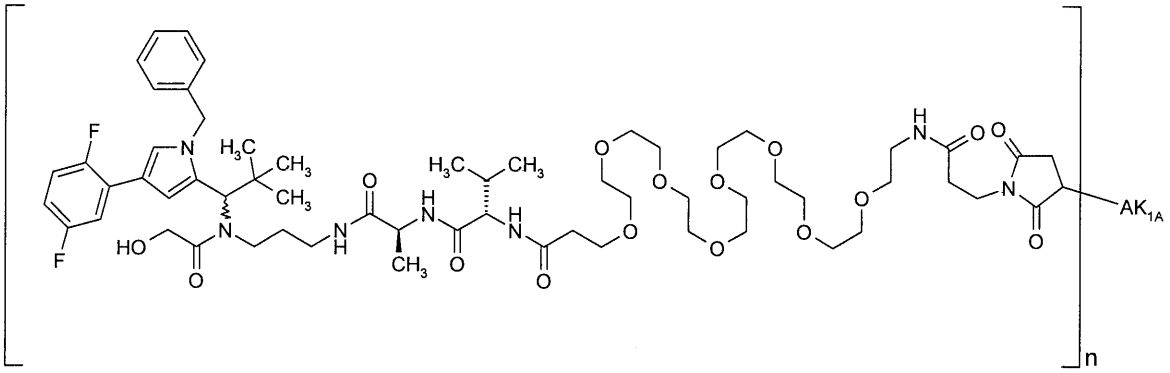
61. Conjugate according to one or more of Claims 1 to 41 or compound according to Claims 46-59 for use in a method for the treatment and/or prophylaxis of diseases.

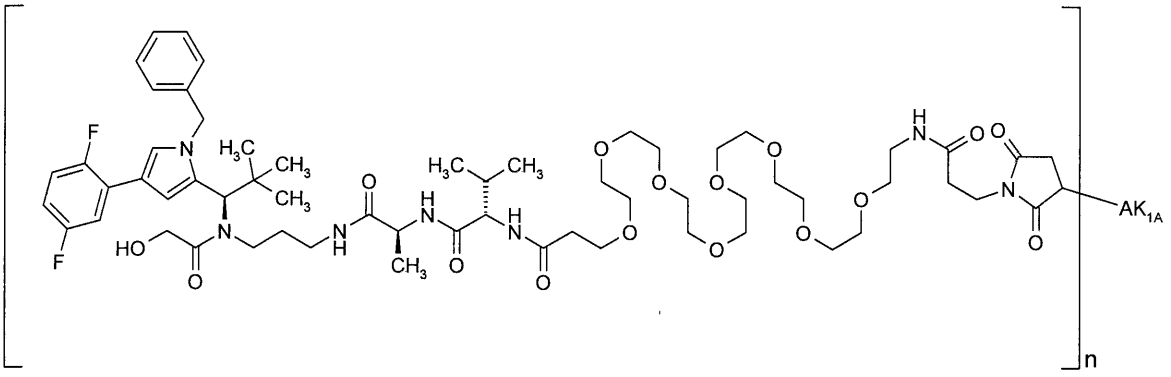
62. Conjugate according to one or more of Claims 1 to 41 or compound according to Claims 46-59 for use in a method for the treatment of hyperproliferative and/or angiogenic disorders.

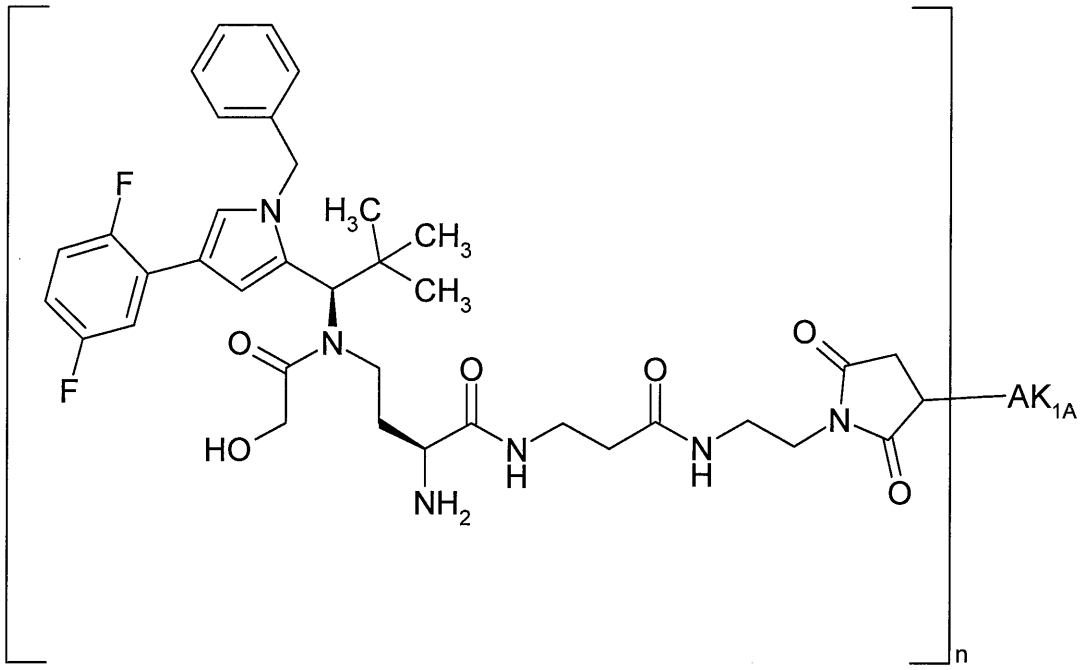
63. Conjugate according to one or more of Claims 1 to 41 or compound according to Claims 46-59 where R^{3a} or R^3 represents –L-BINDER or a substituted alkyl, aryl or heteroaryl group, preferably –L-#1 or a C_{1-10}-alkyl, C_{6-10}-aryl or C_{6-10}-aralkyl group or C_{5-10}-heteroalkyl, which may be substituted by –OH, O-alkyl, SH, S-alkyl, O-CO-alkyl, O-CO-NH-alkyl, NH-CO-alkyl, NH-CO-NH-alkyl, $S(O)_n$-alkyl, SO_2-NH-alkyl, NH-alkyl, $N(alkyl)_2$, NH_2 or $-(CH_2)_{0-3}Z$, where Z represents -H, halogen, $-OY^3$, $-SY^3$, $-NHY^3$, $-CO-NY^1Y^2$ or $-CO-OY^3$, where Y^1 and Y^2 independently of one another represent H, NH_2 or $-(CH_2)_{0-3}Z'$ and Y^3 represents H or $-(CH_2)_{0-3}Z'$, where Z' represents H, SO_3H, NH_2 or COOH,
(where "alkyl" preferably represents C_{1-10}-alkyl).

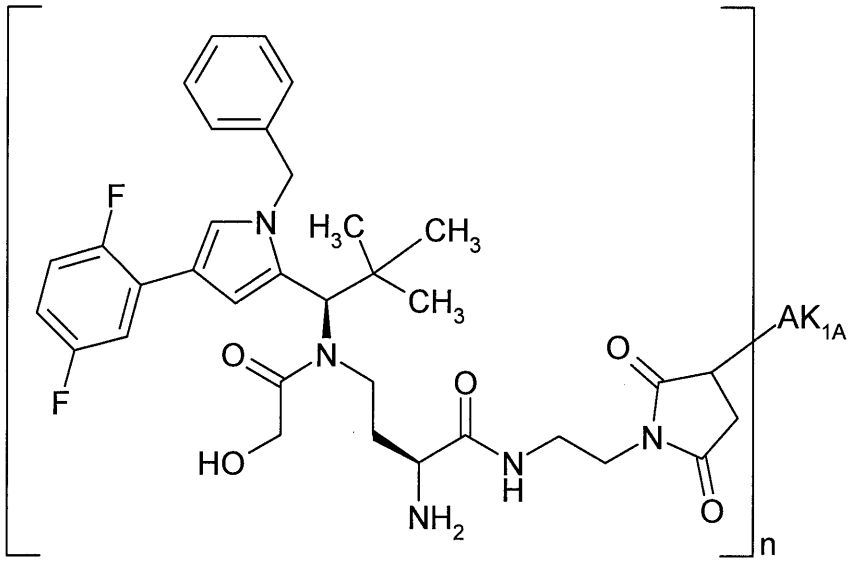
64. The use of at least one conjugate according to one or more of Claims 1 to 41 or compound according to Claims 46-59 in the manufacture of a medicament for the treatment and/or prophylaxis of hyperproliferative and/or angiogenic disorders.

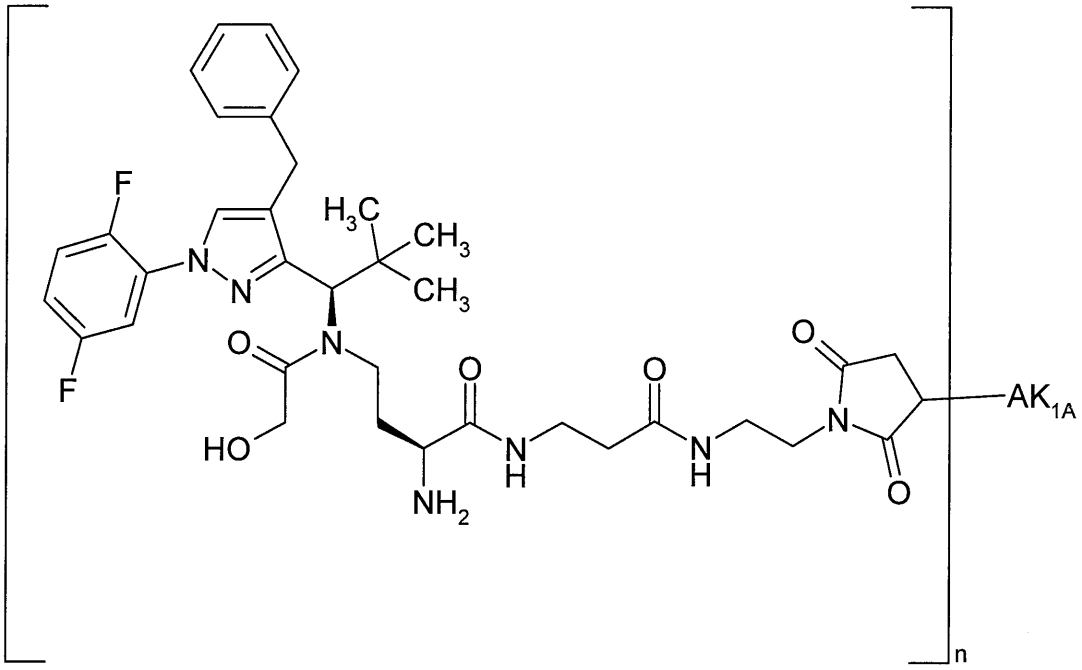
65. Antibody conjugate according to one of the formulae below, where n is a number from 1 to 20 and AK_{1A} and AK_{2A} represent an antibody:

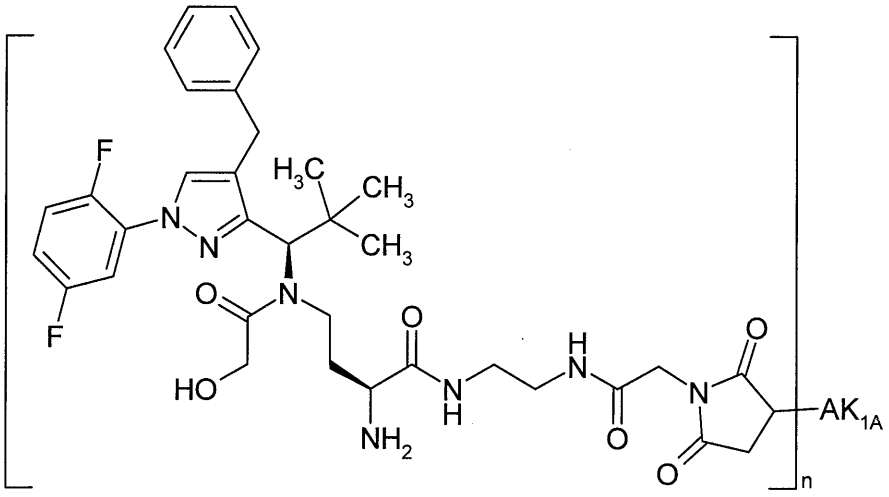


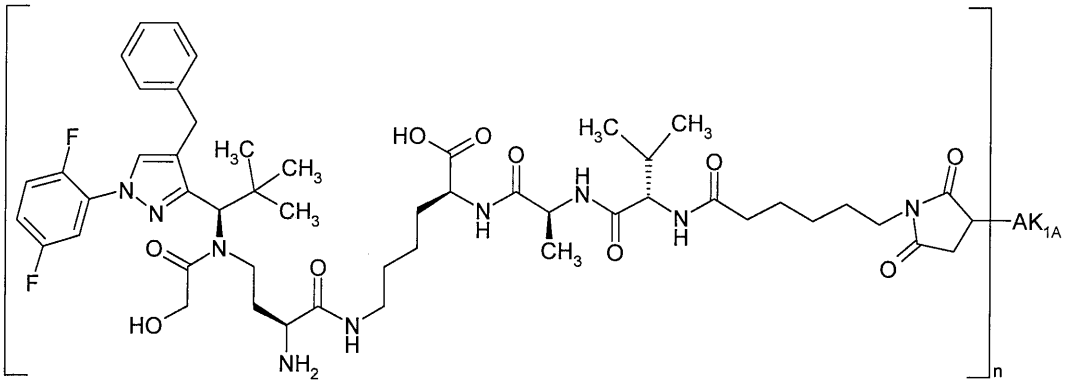


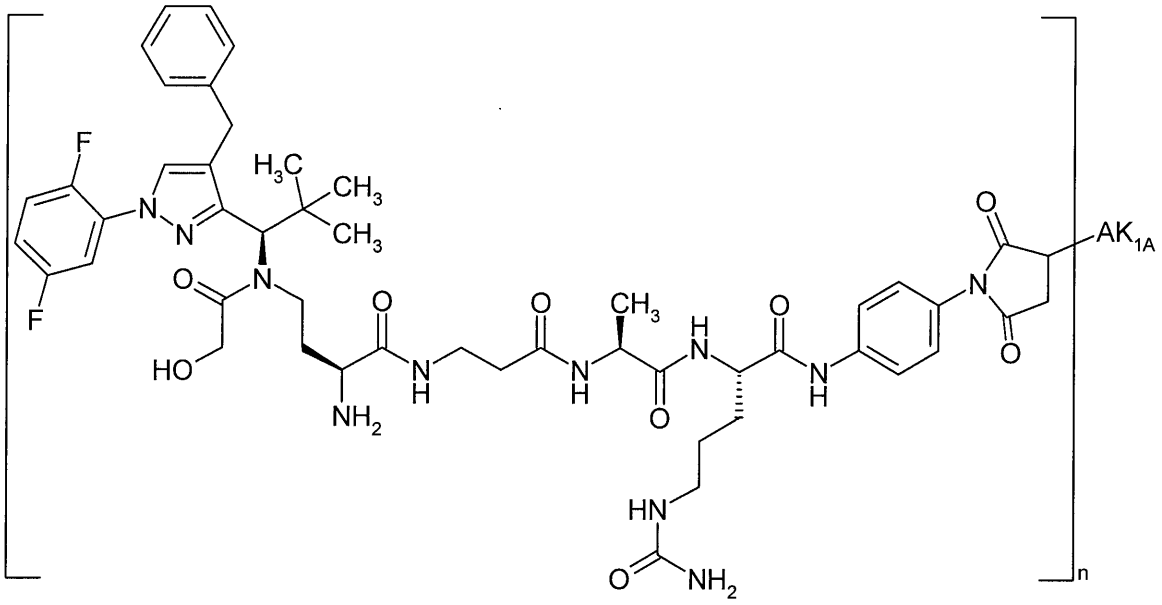


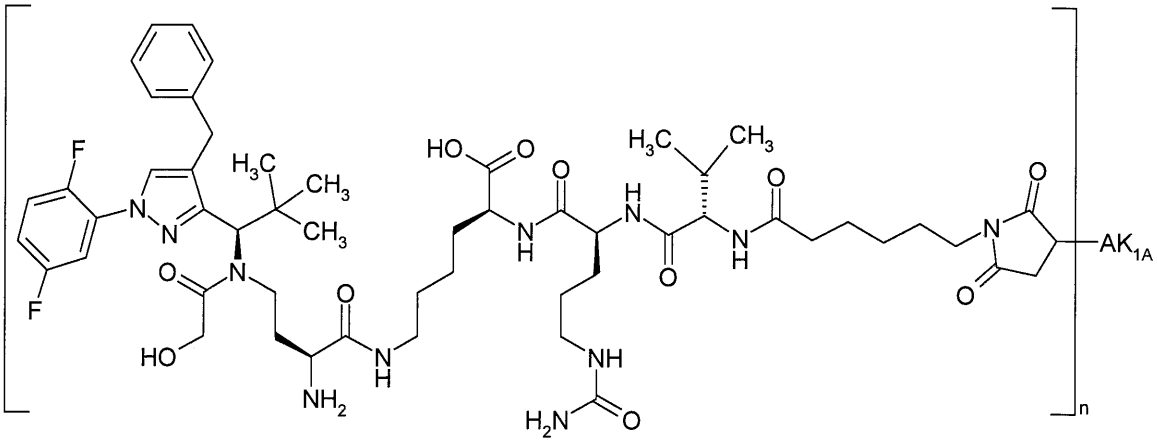


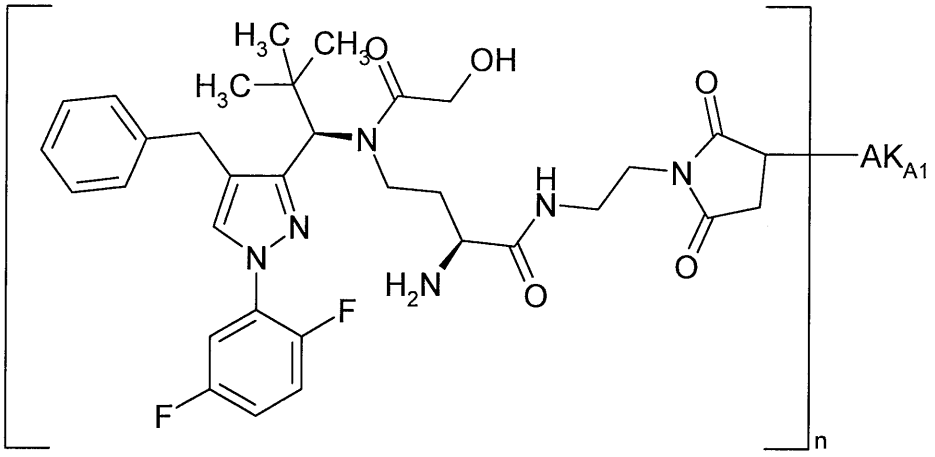












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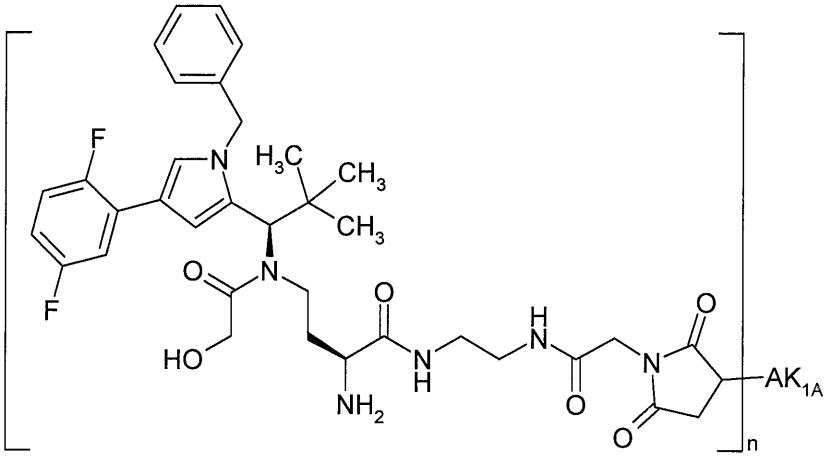

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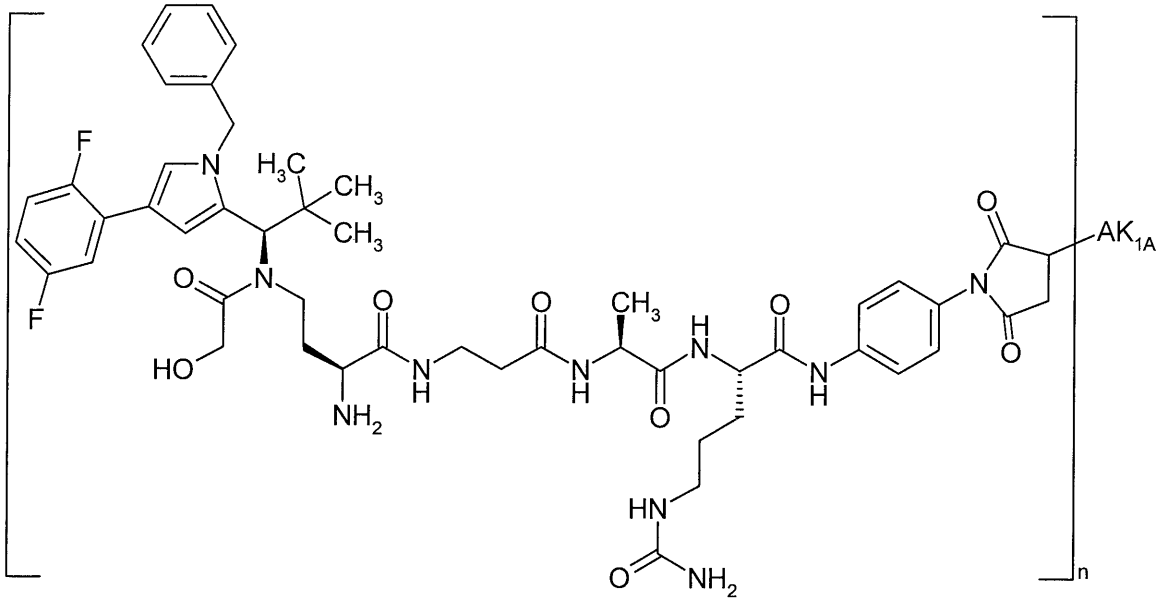

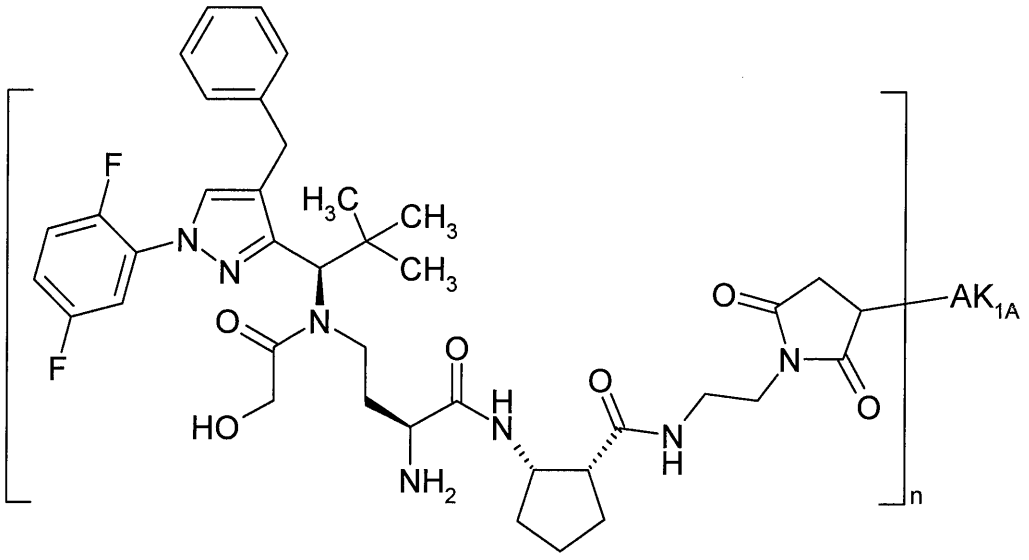

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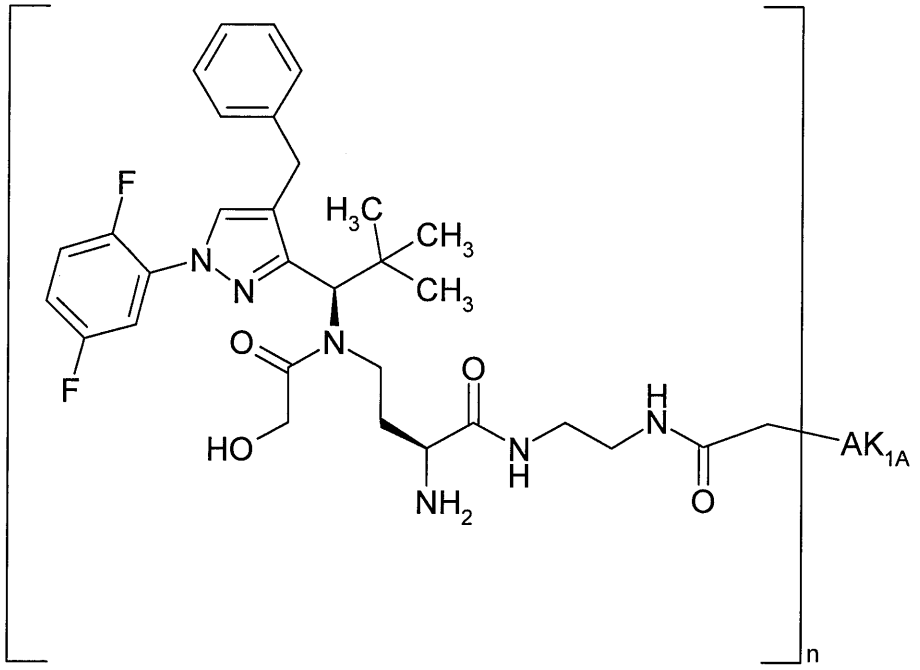
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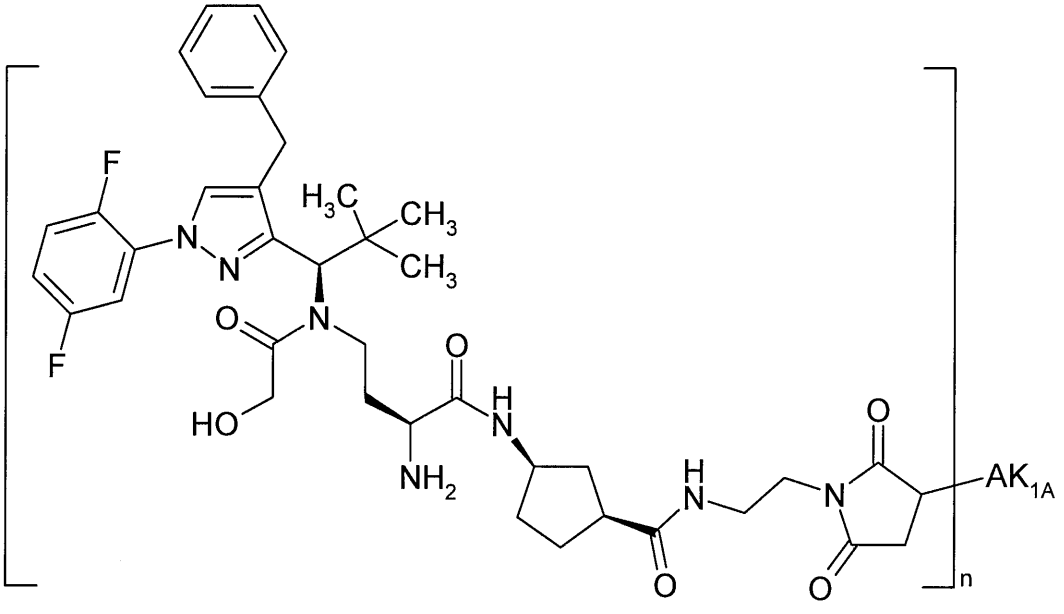
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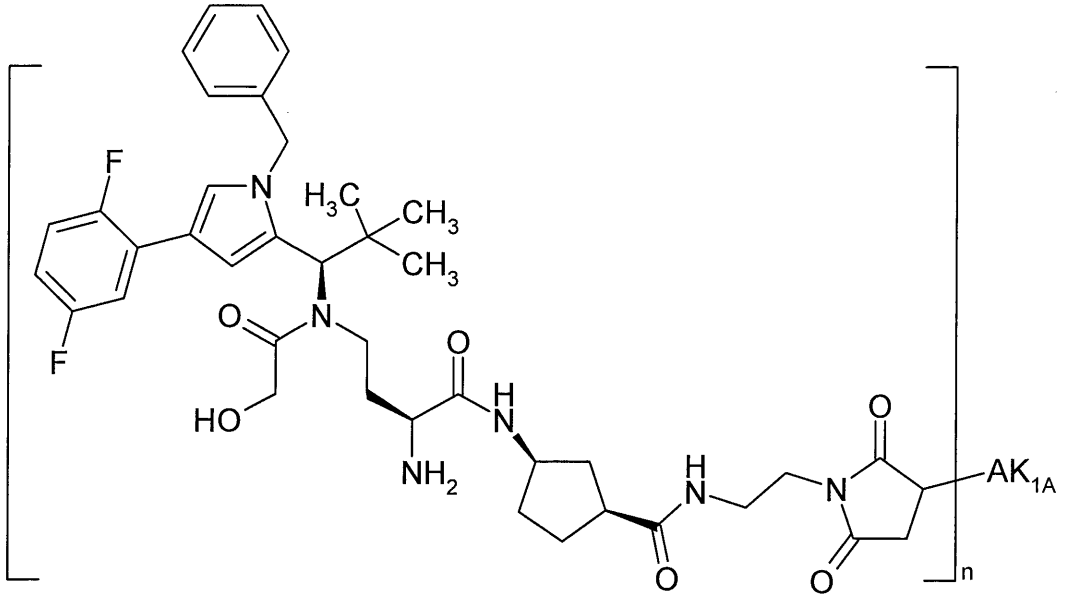

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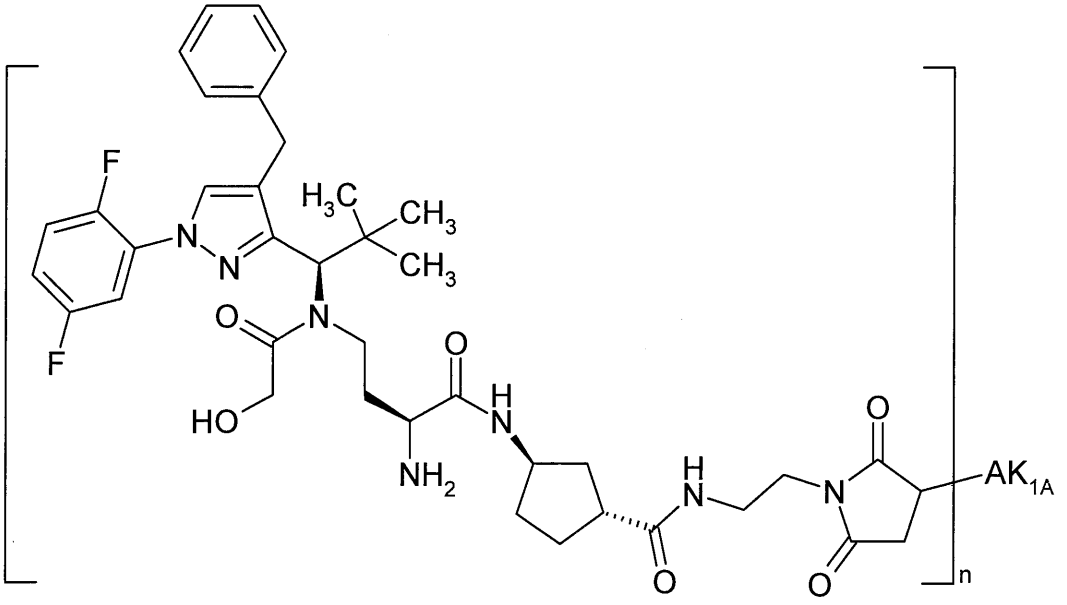

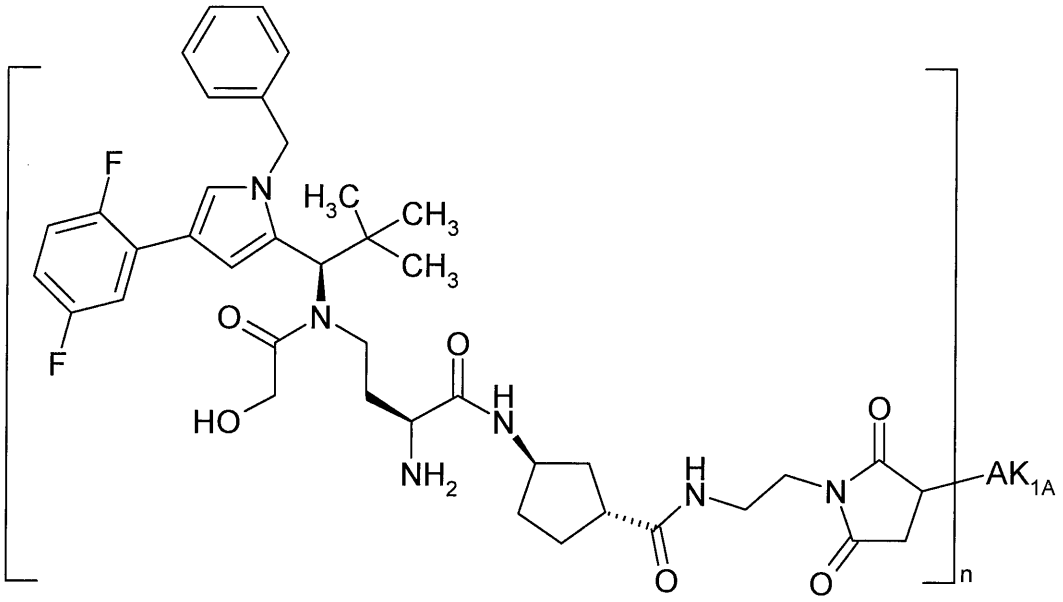

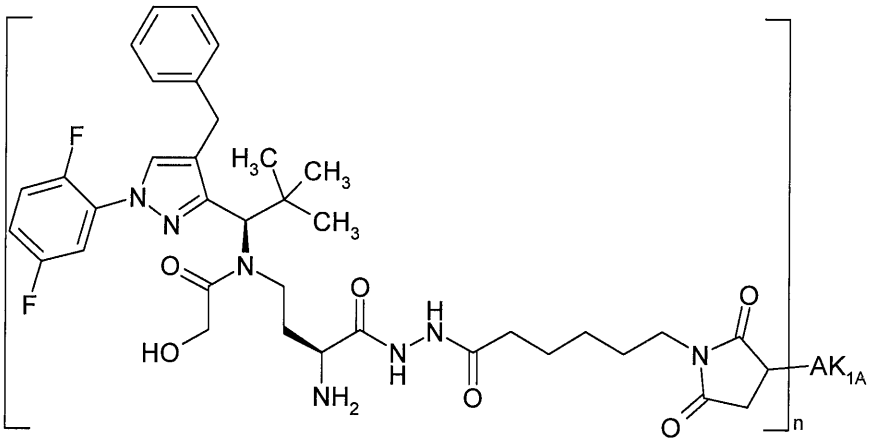

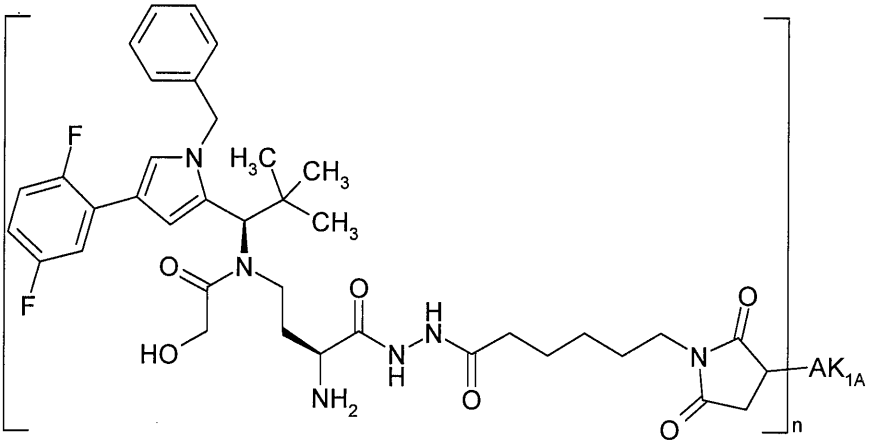

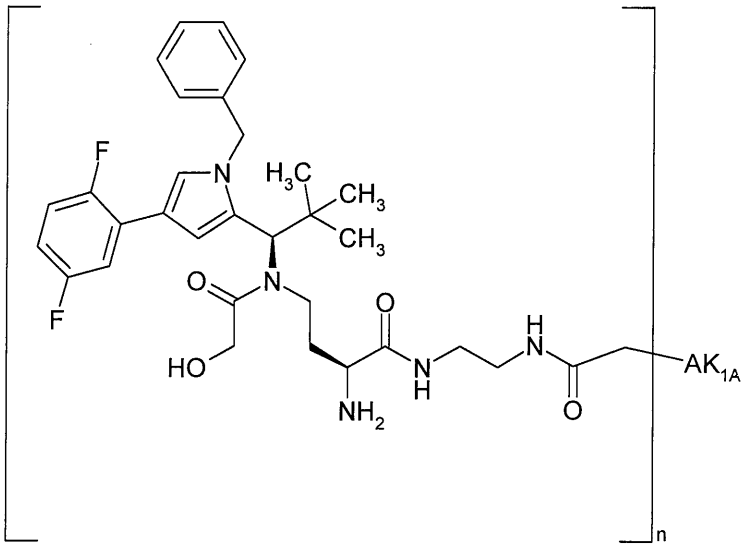

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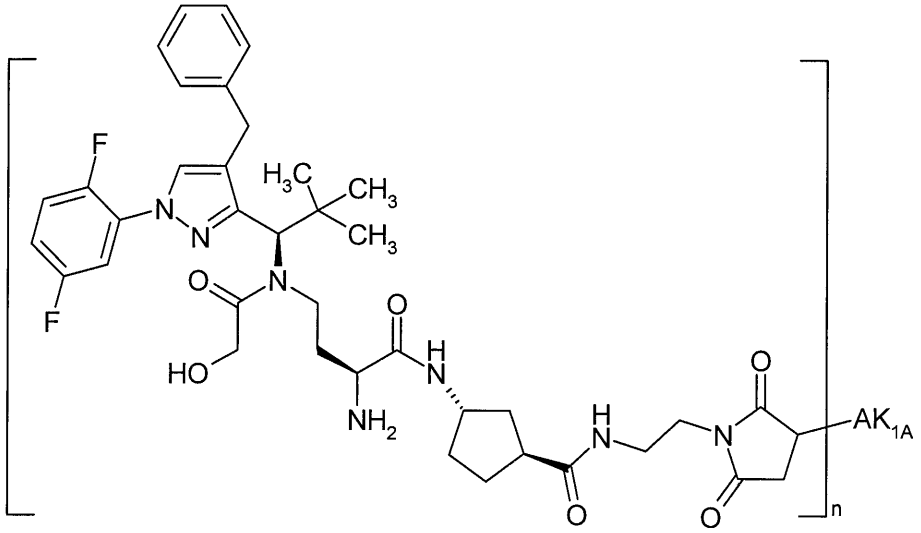

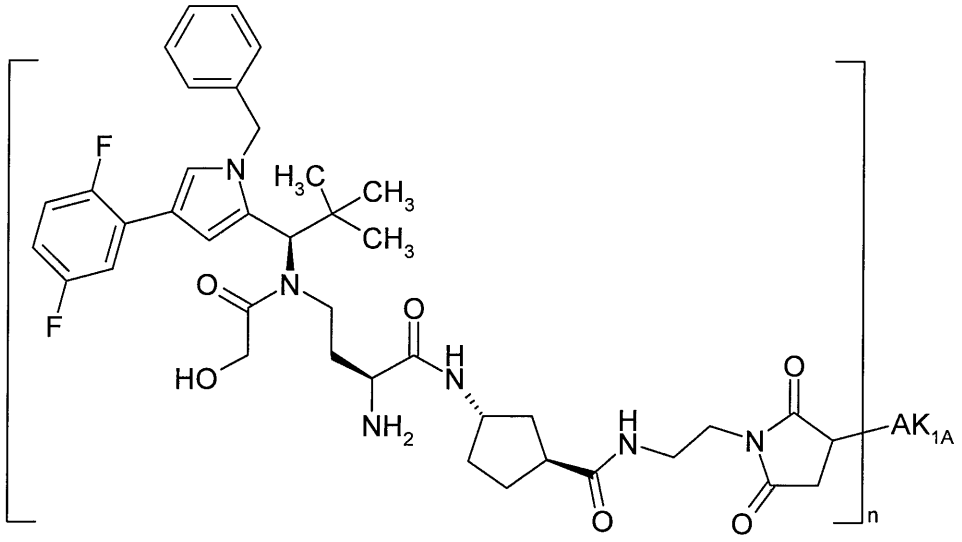

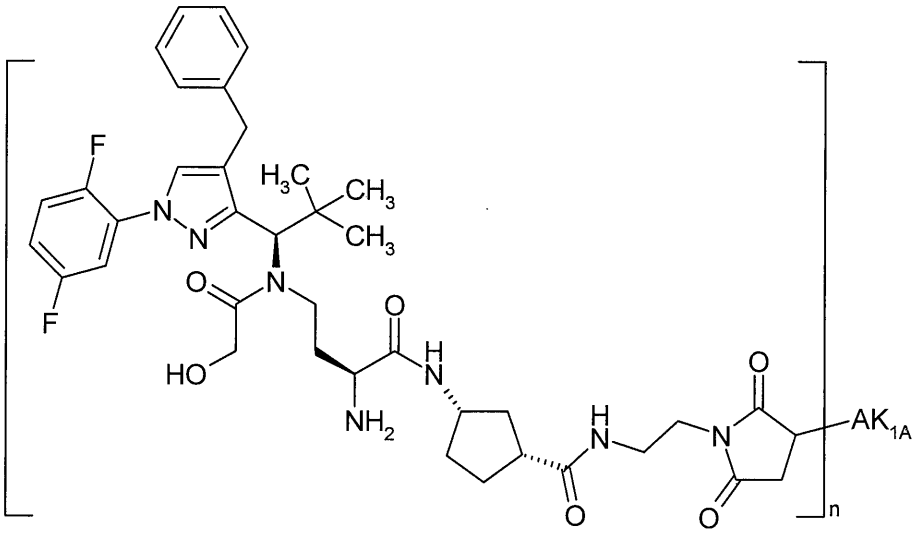

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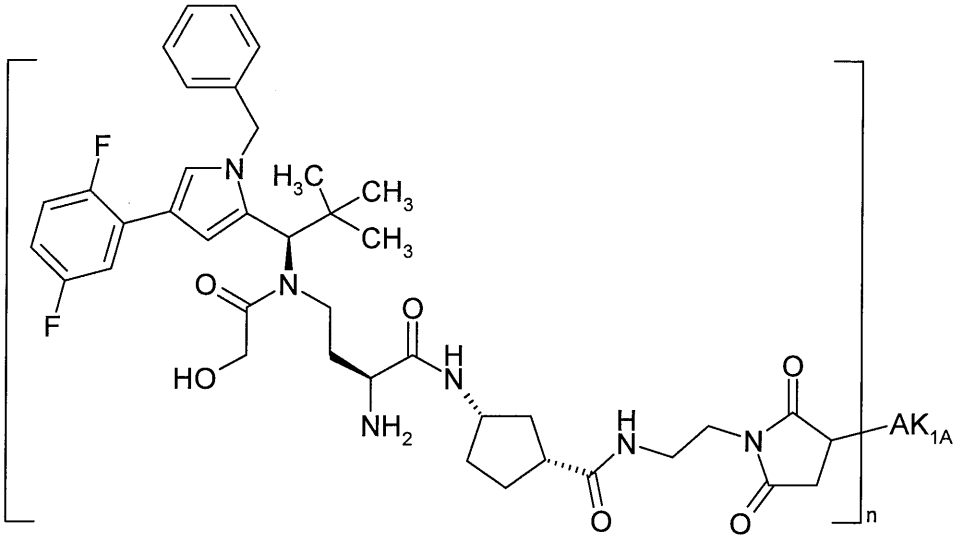

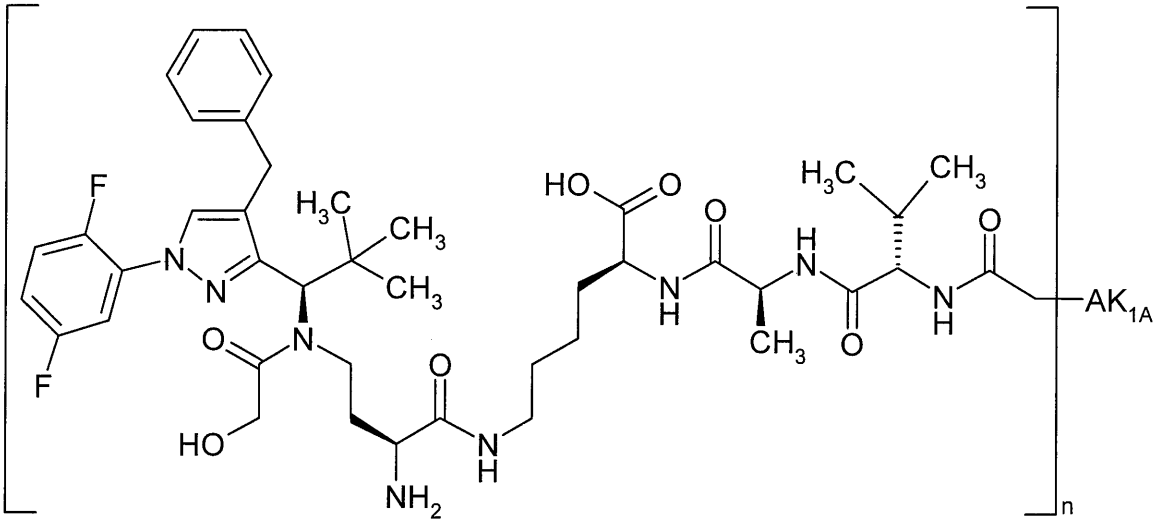

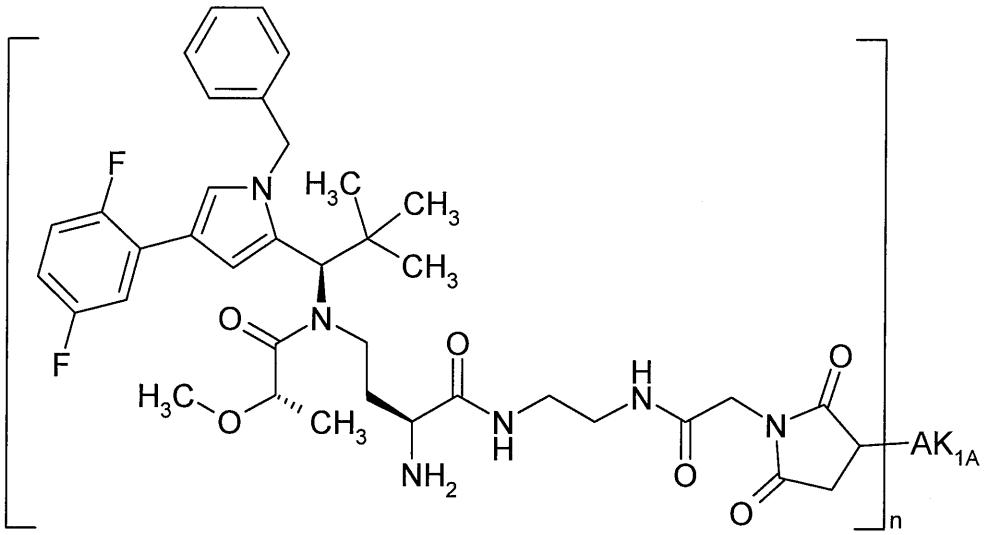

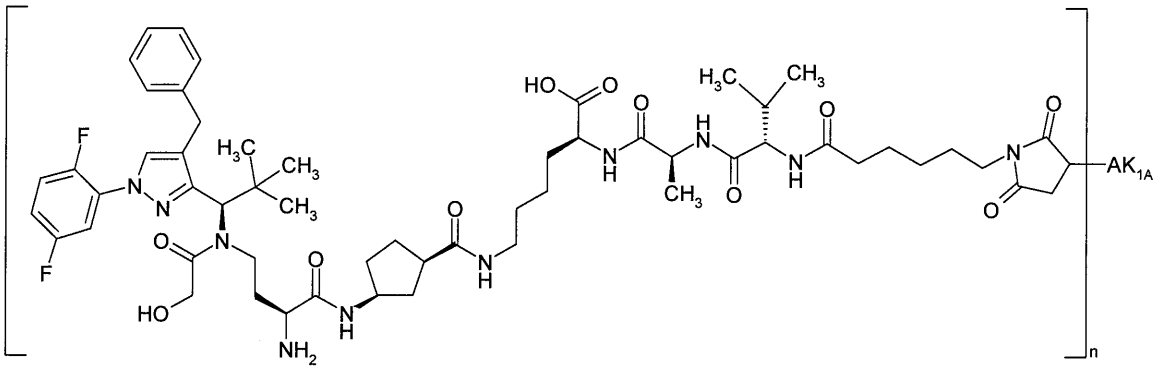

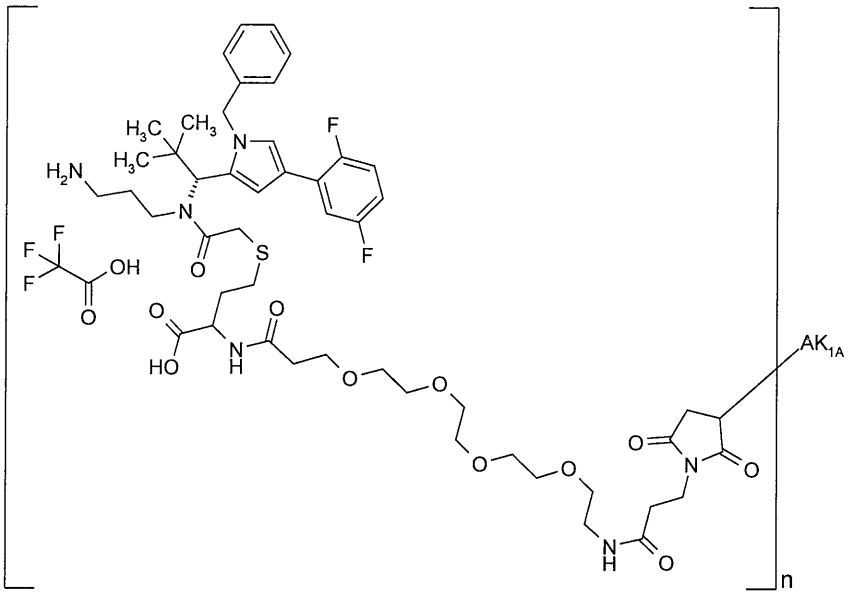

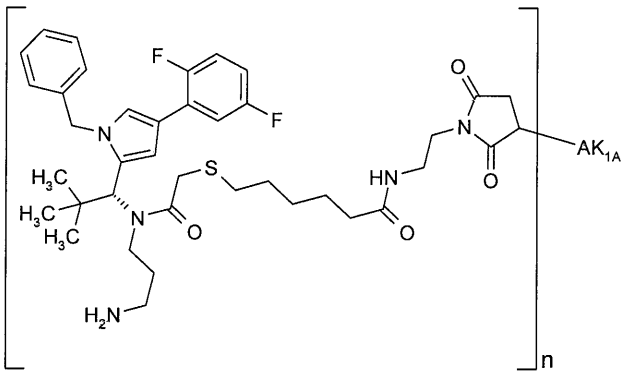

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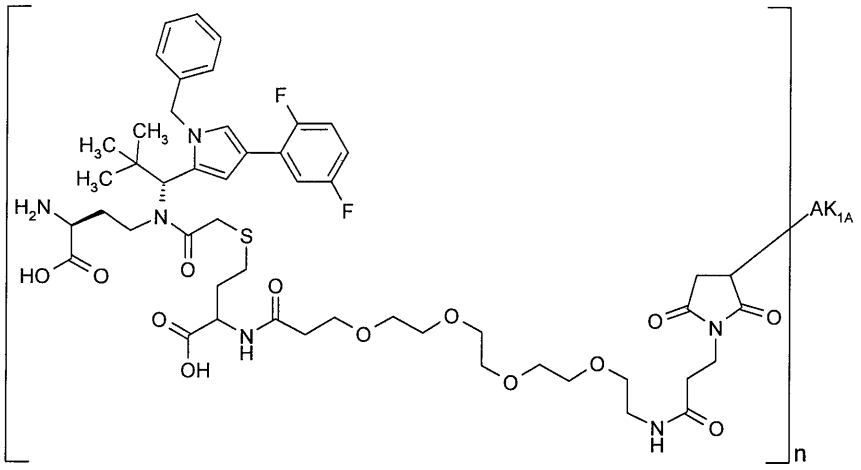

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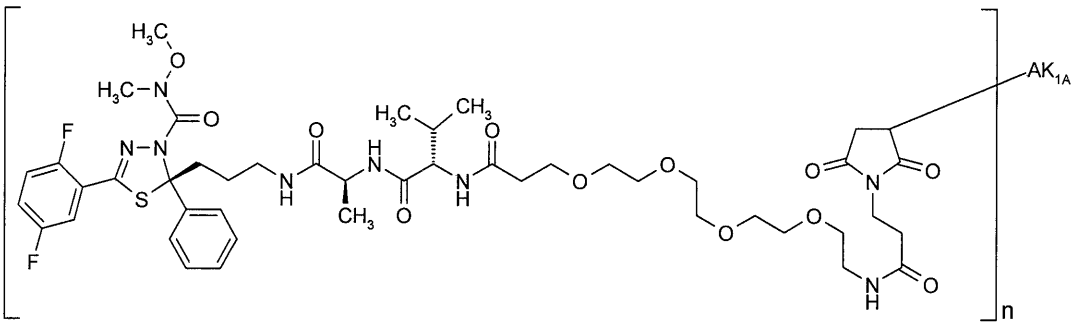

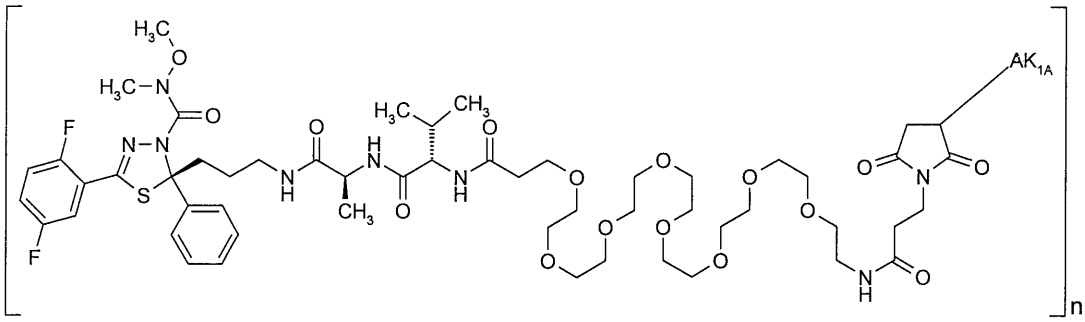

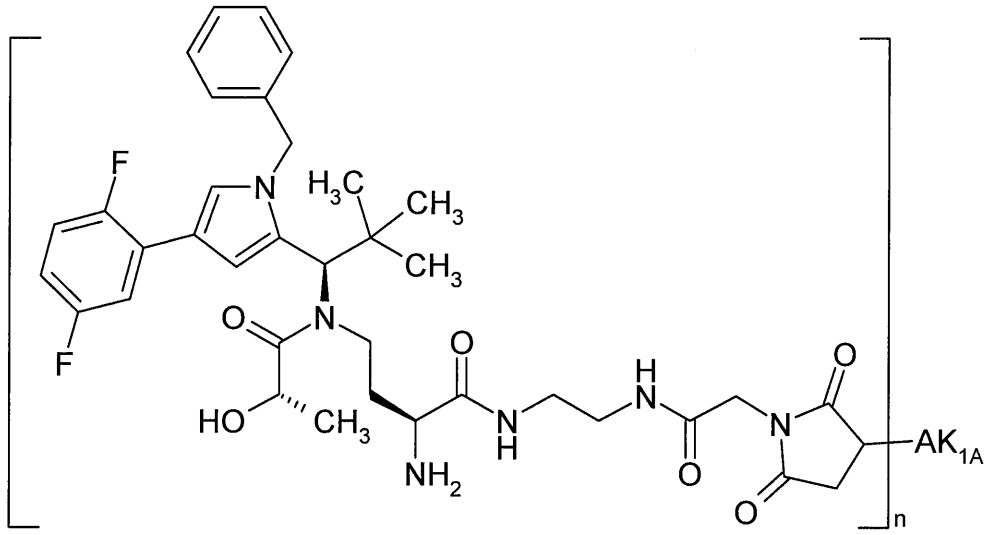

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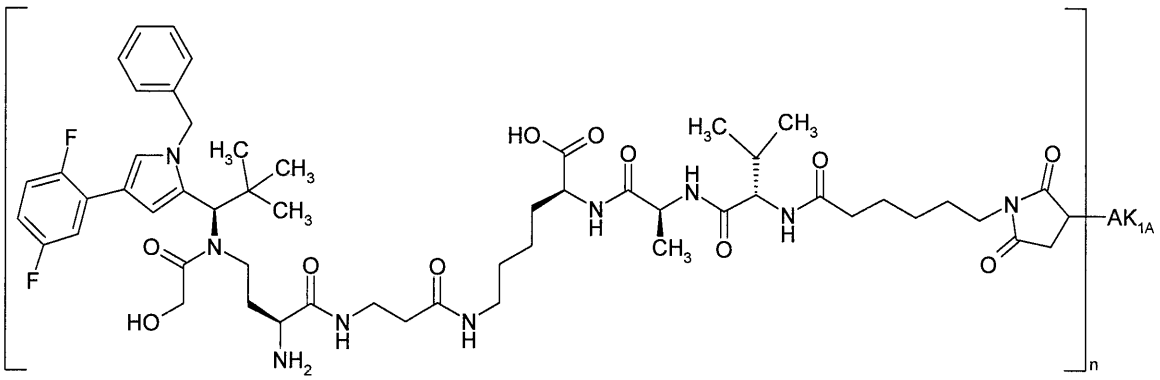

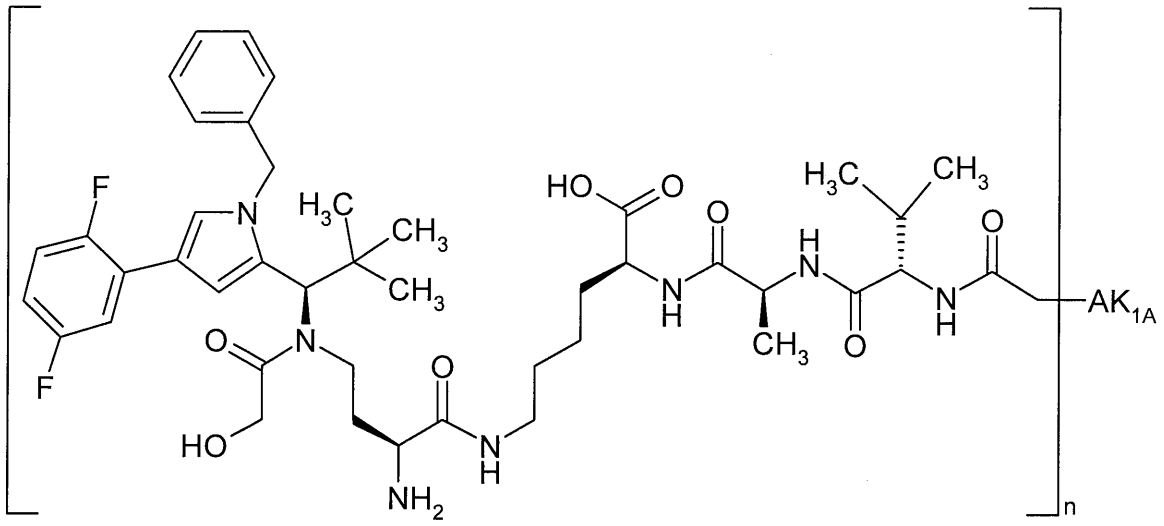

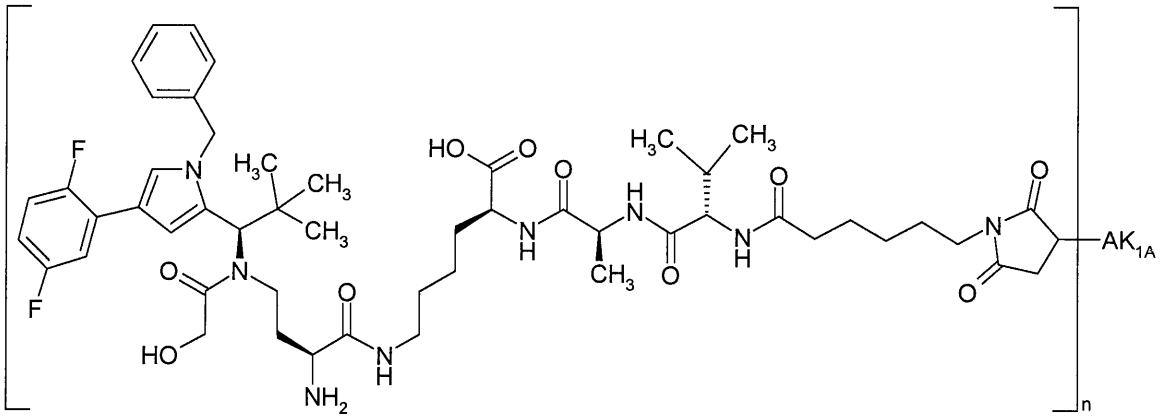

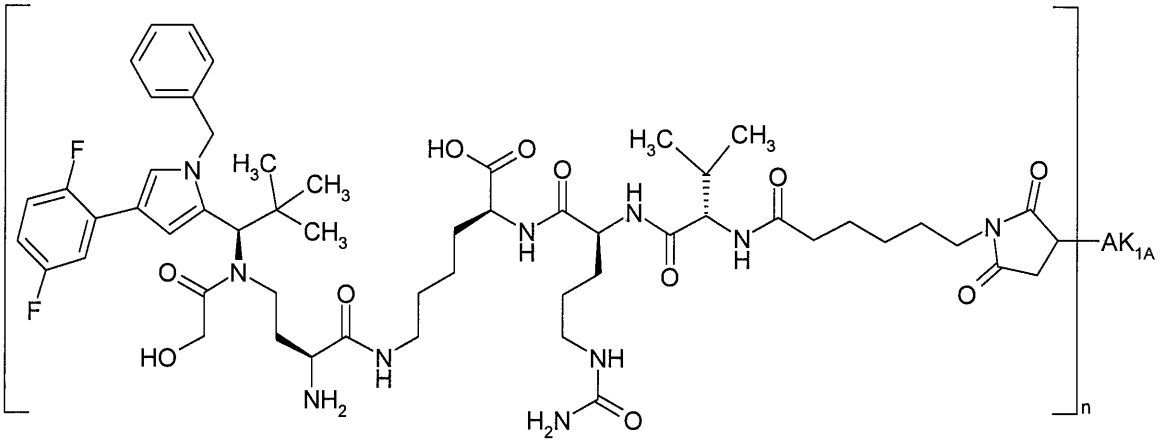

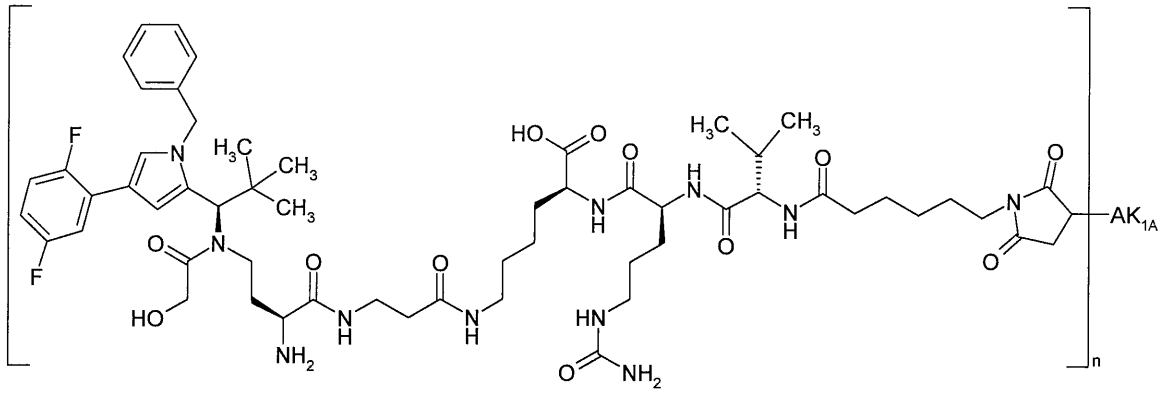

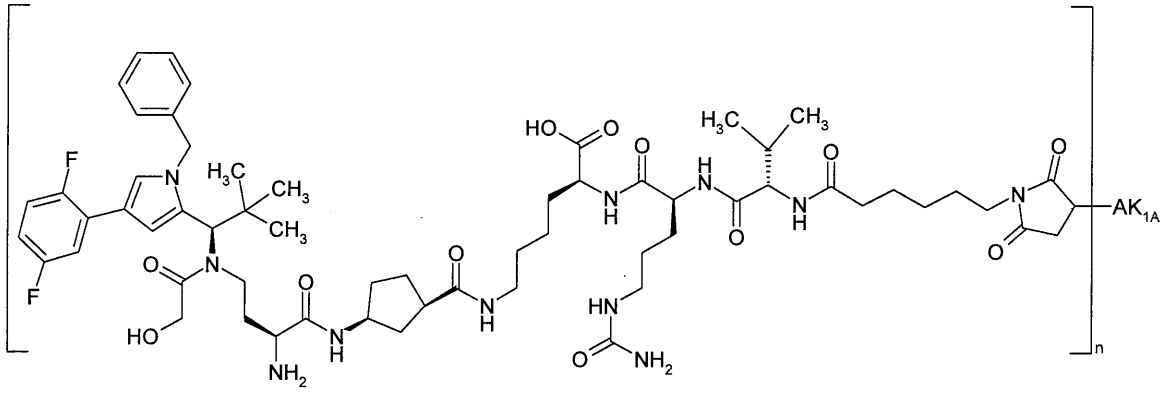

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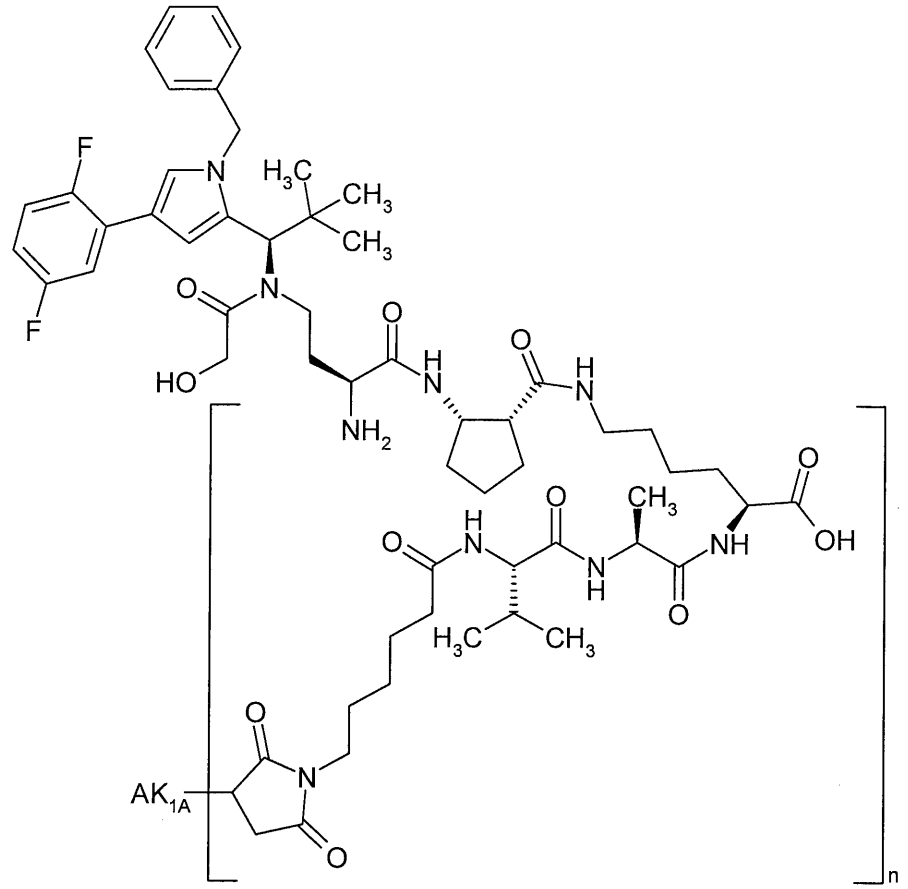

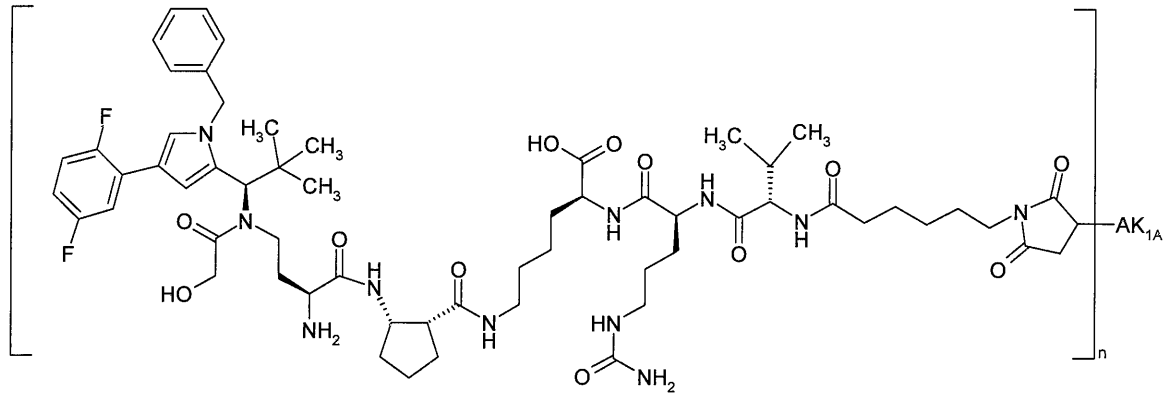

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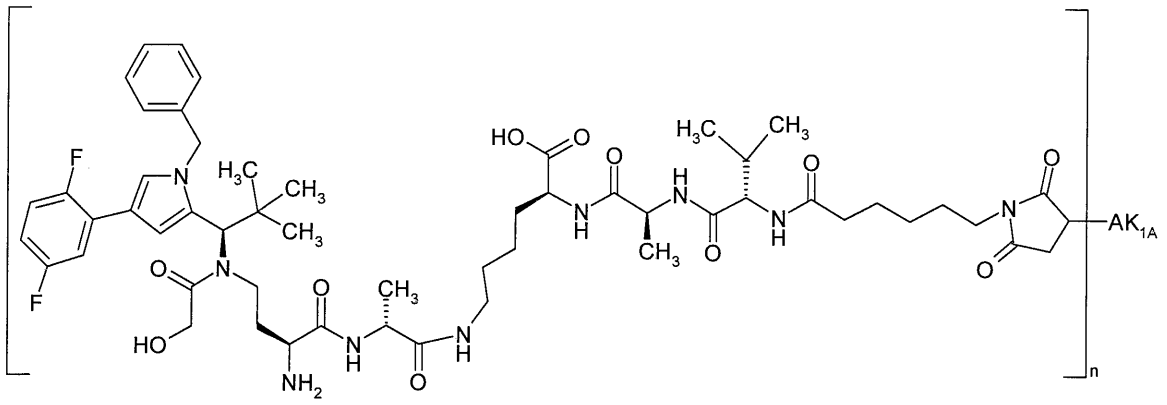

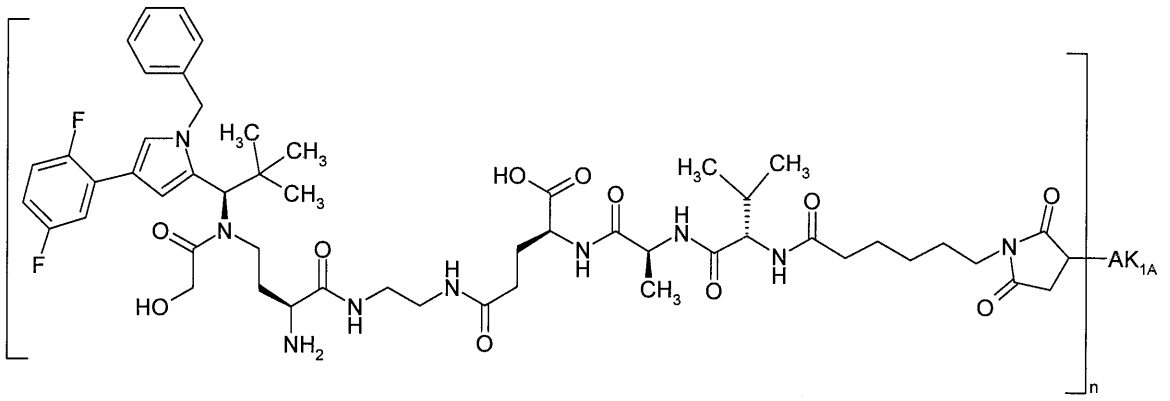

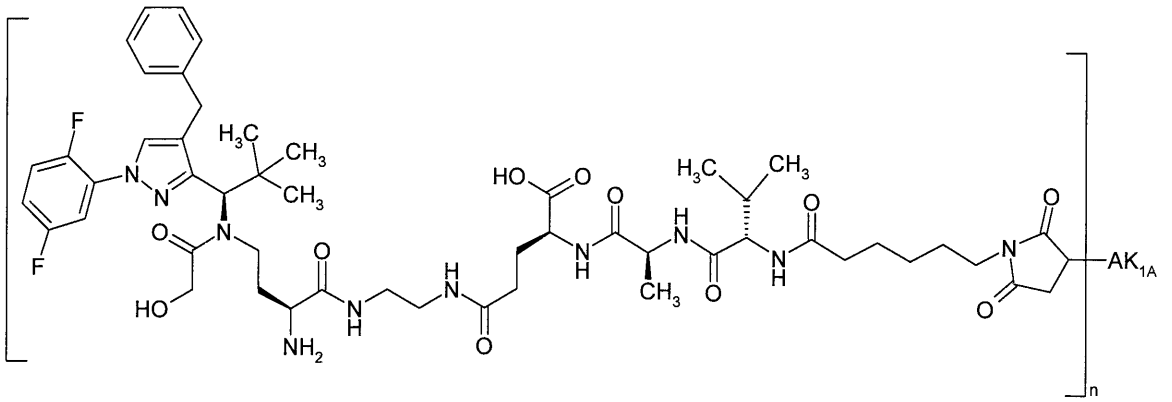

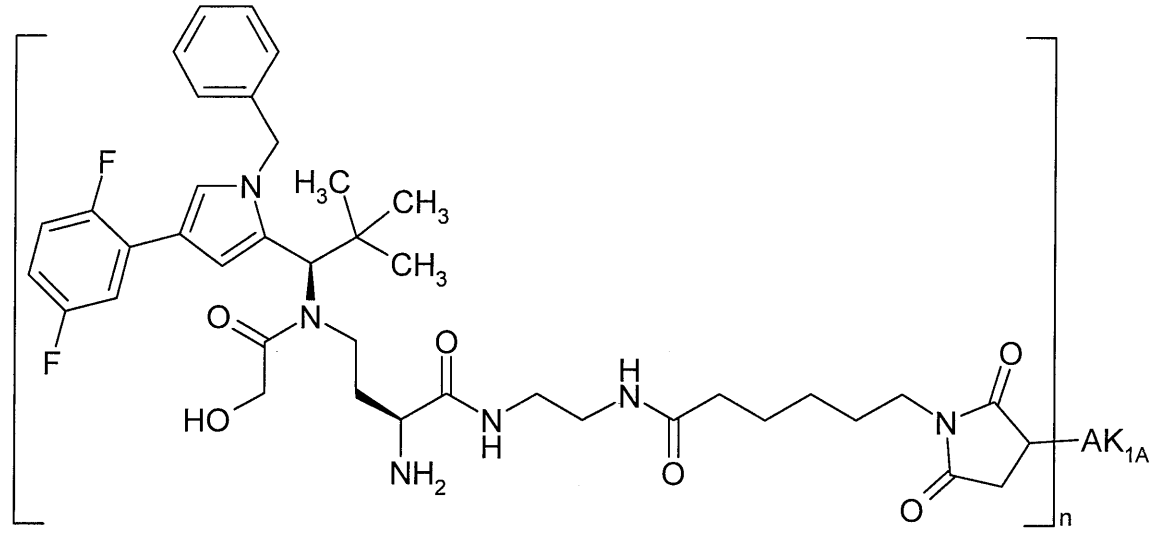

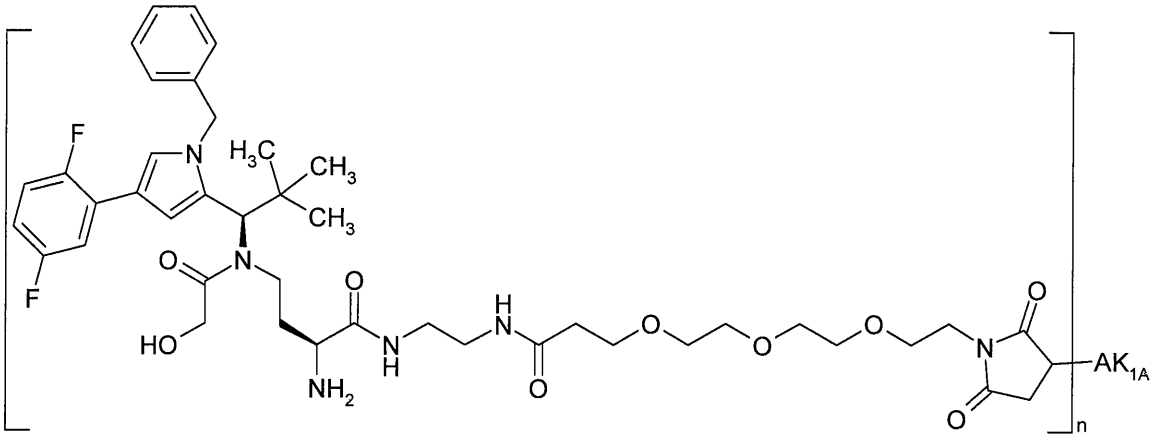

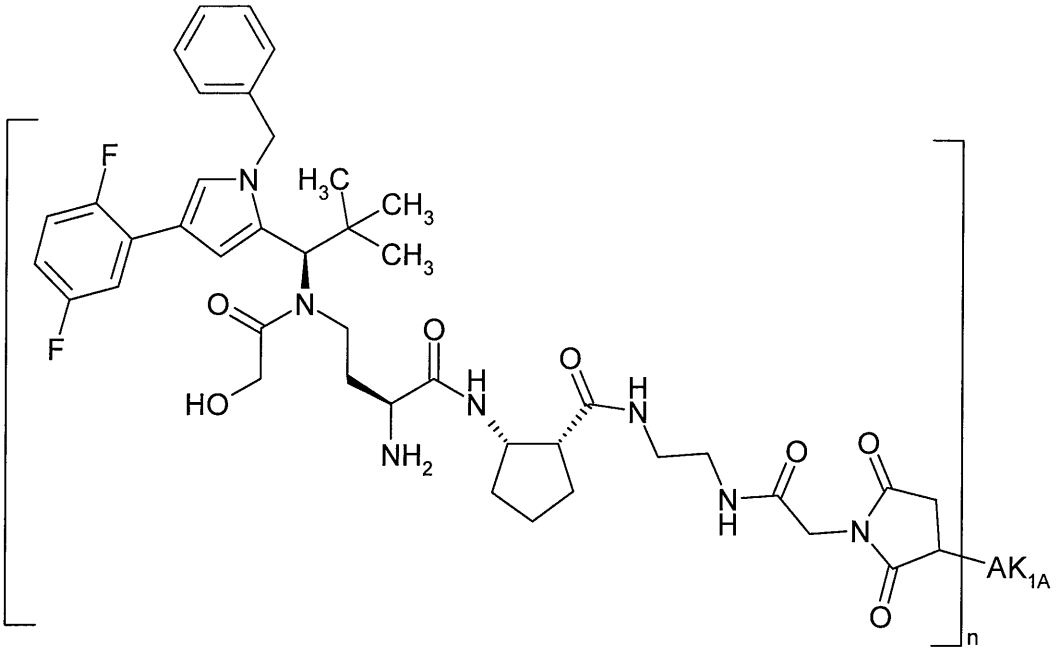

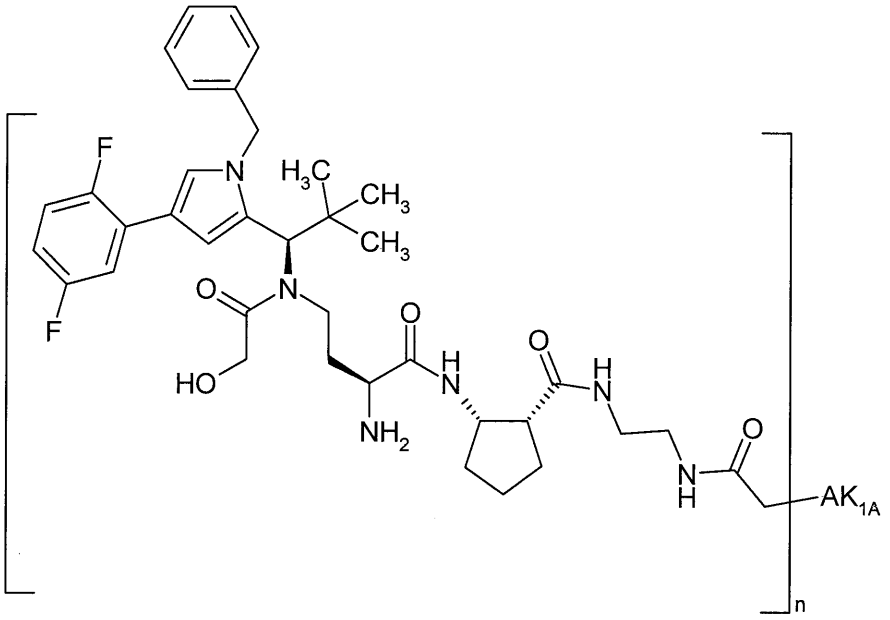

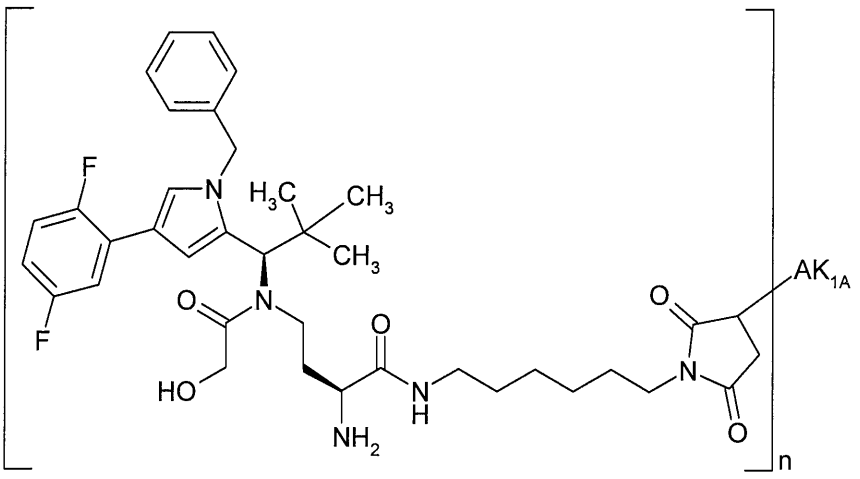

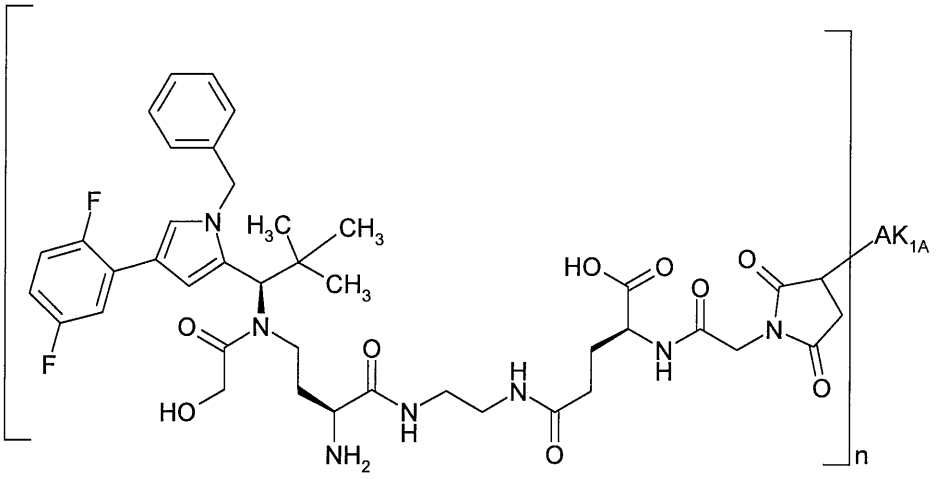
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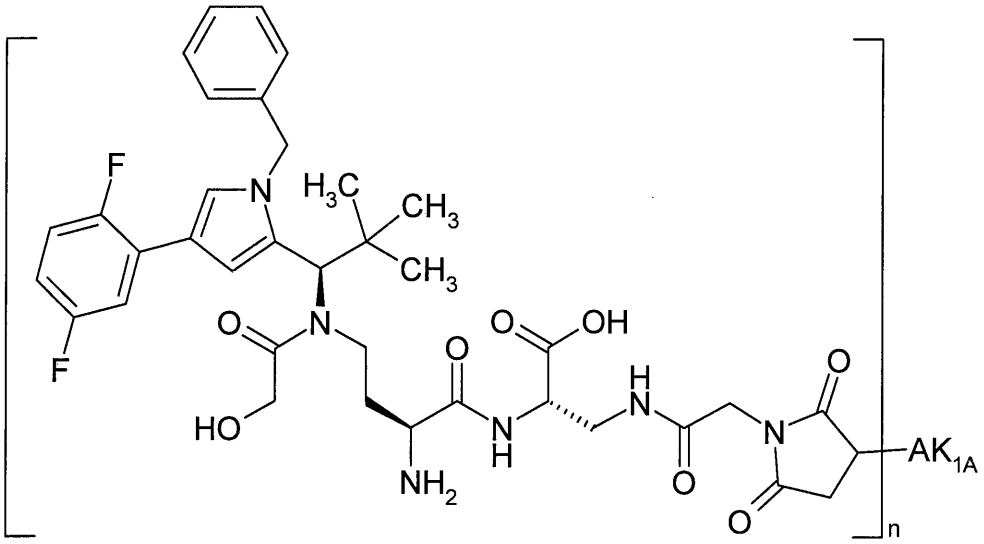
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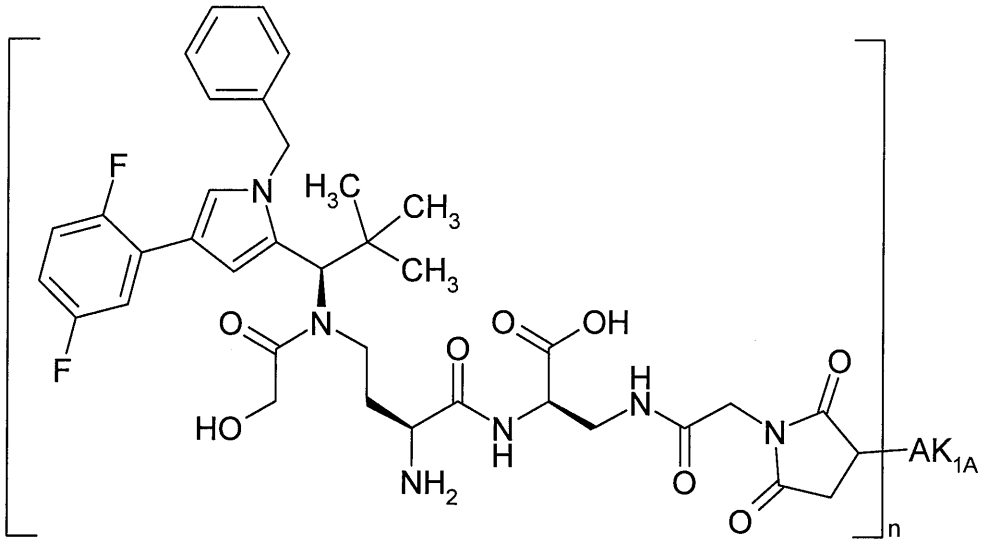

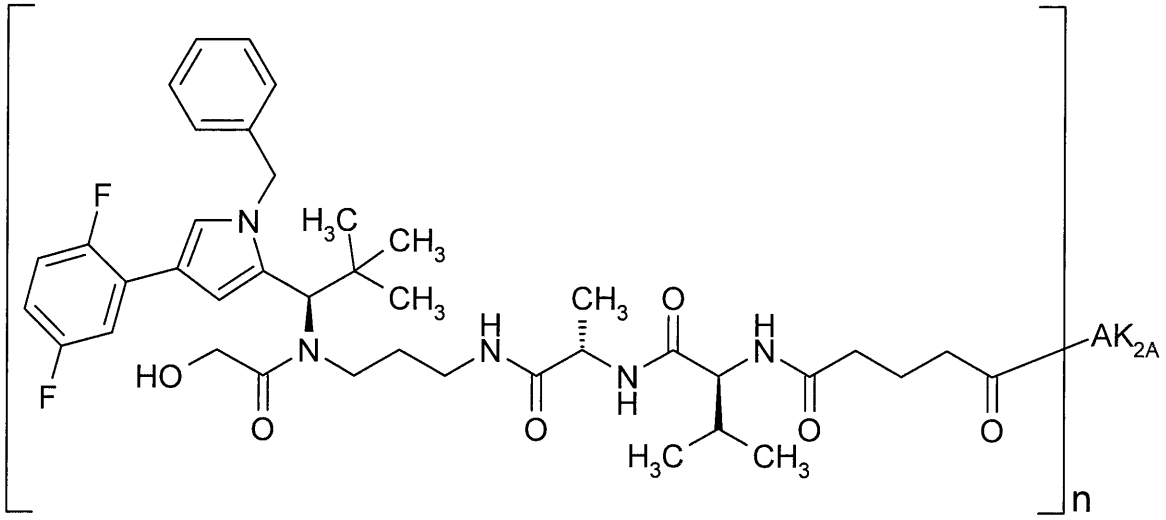

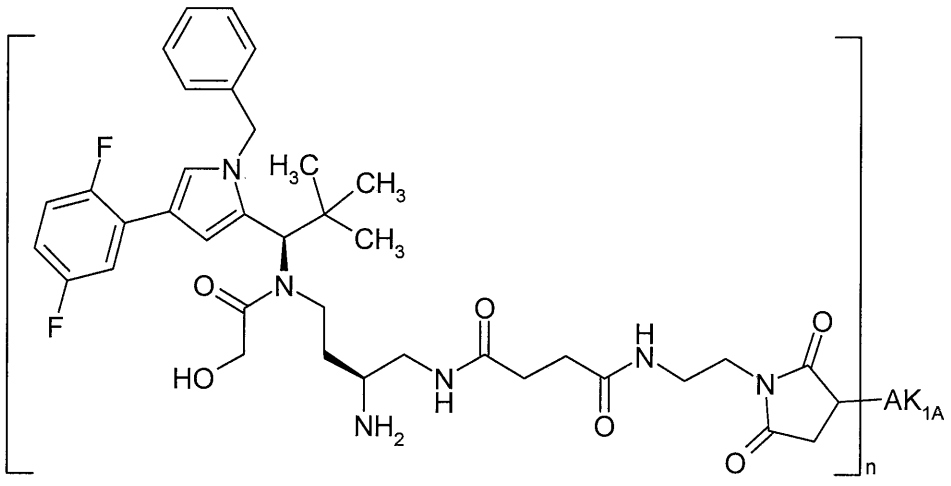

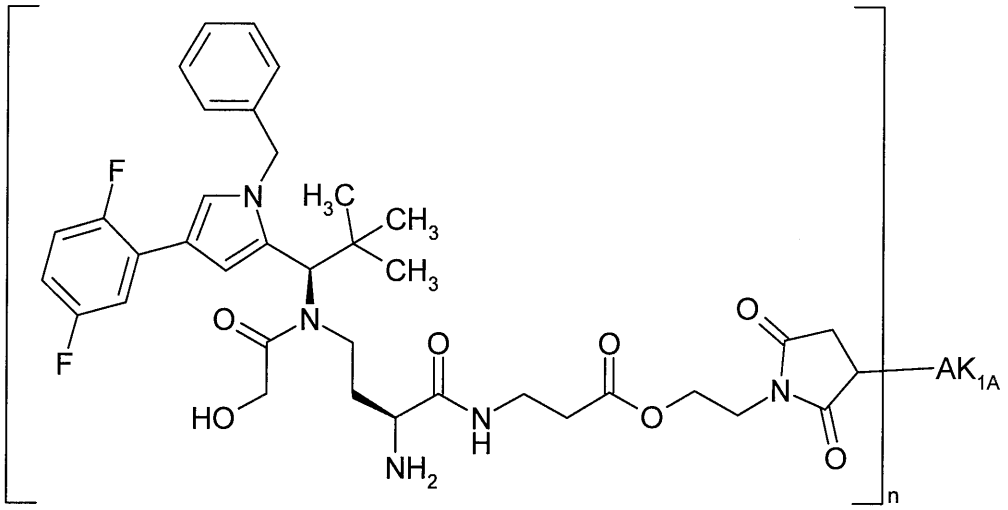

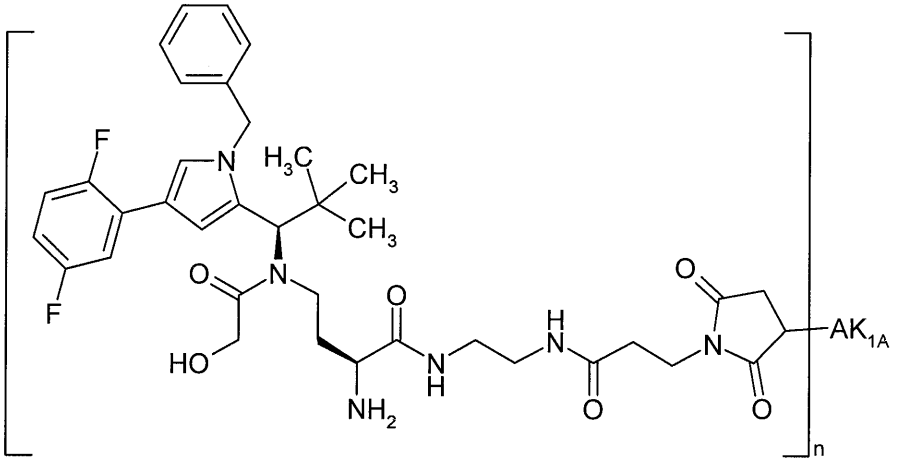

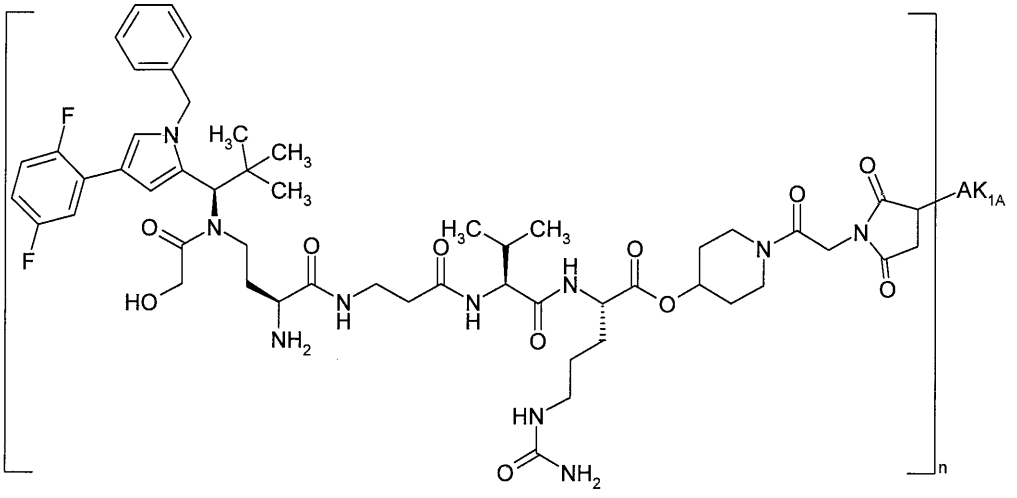

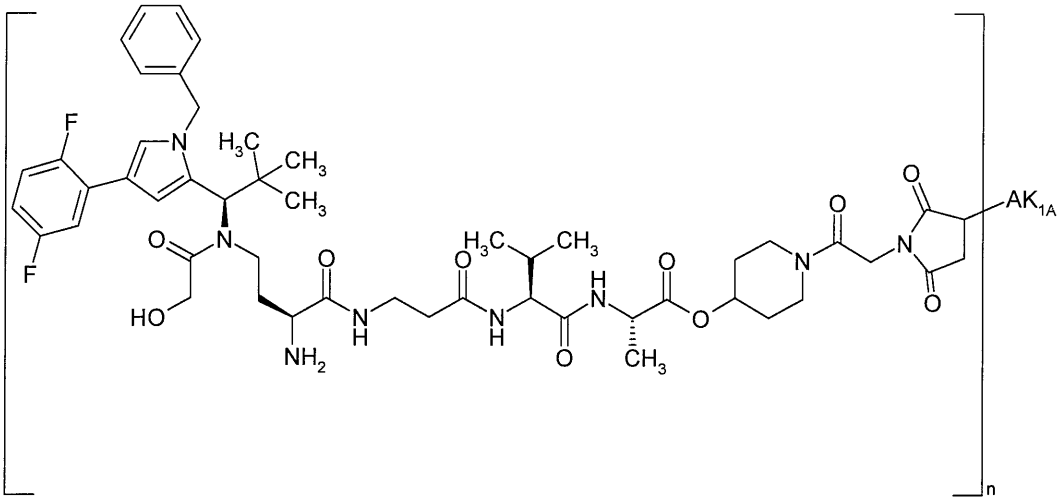

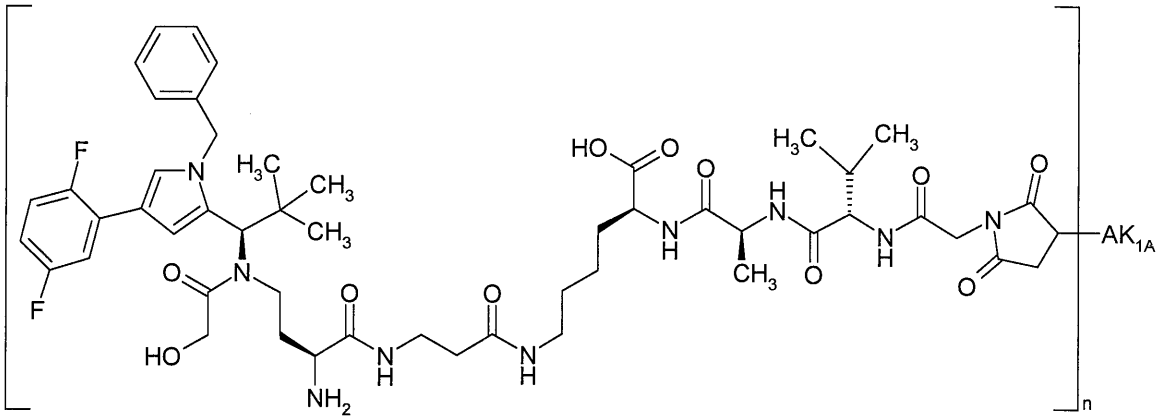

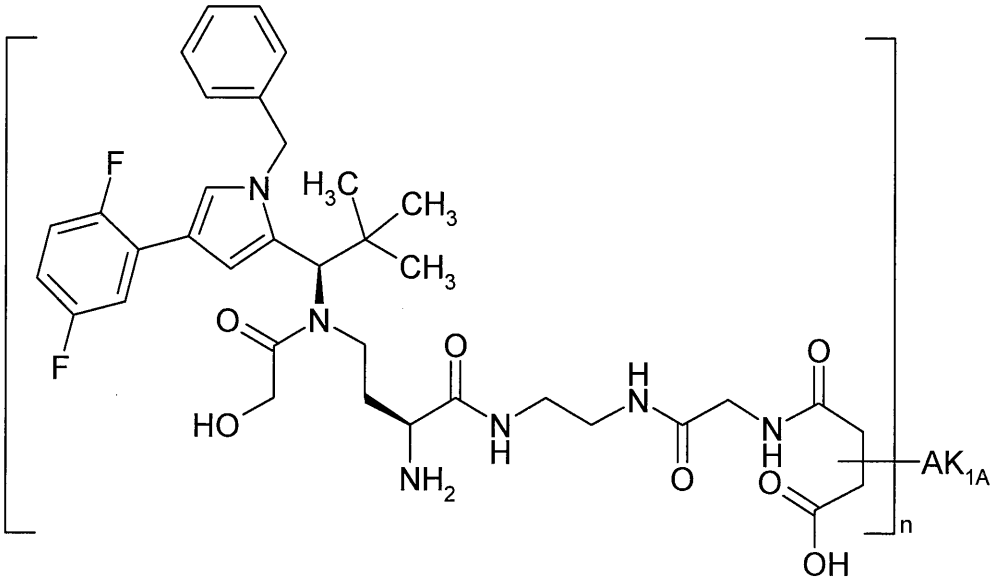

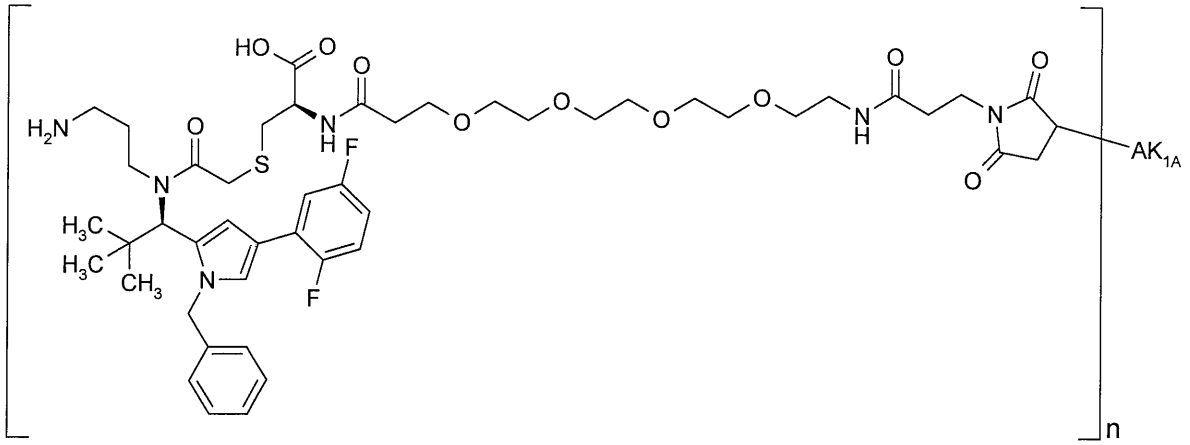

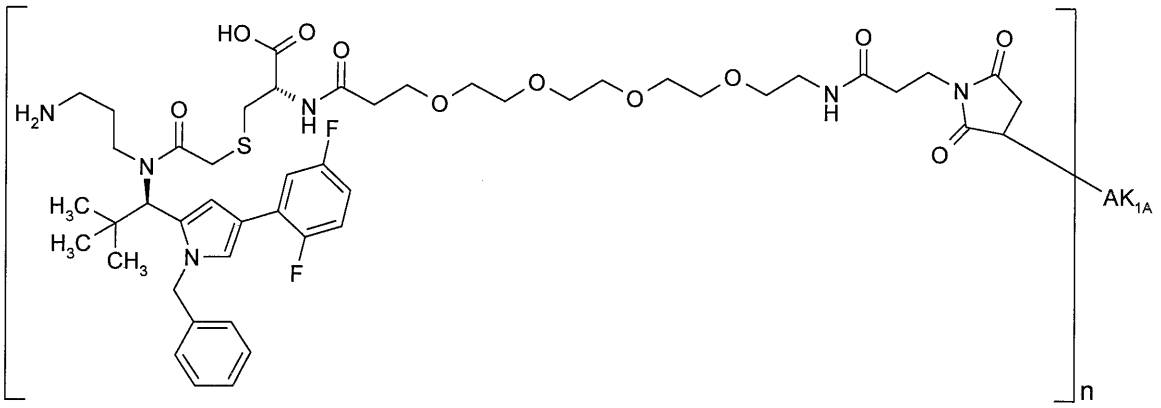

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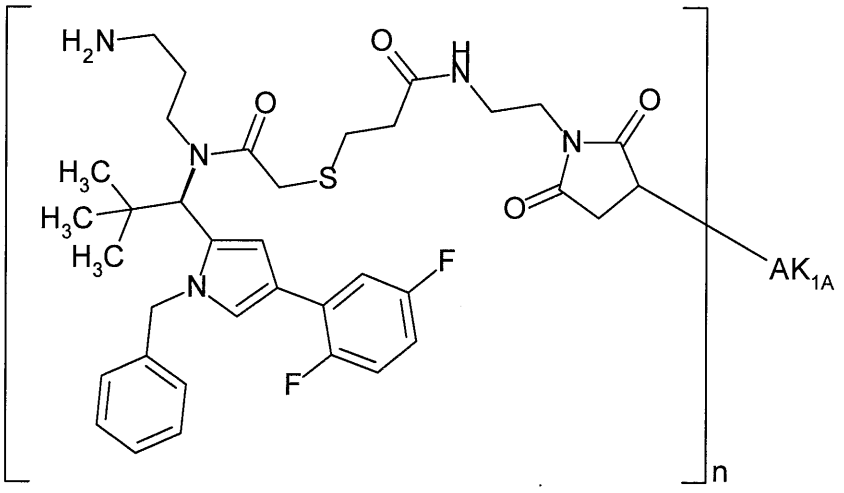

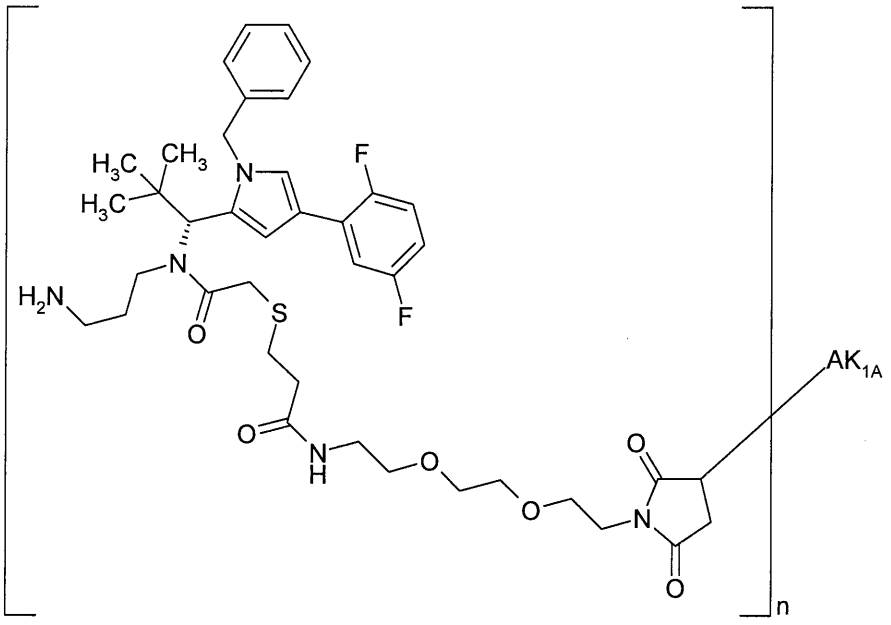

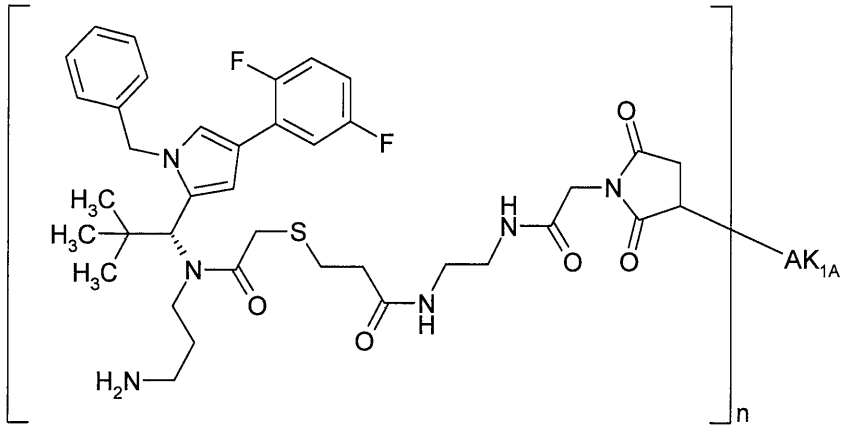

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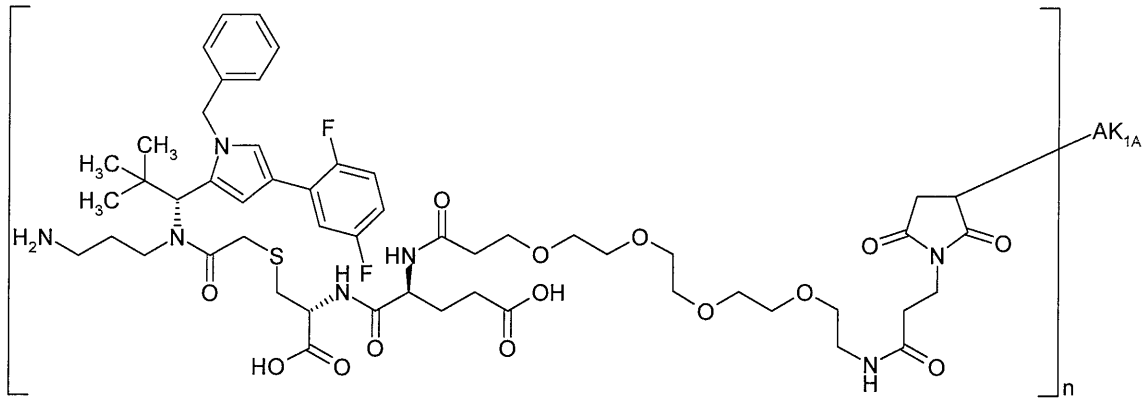

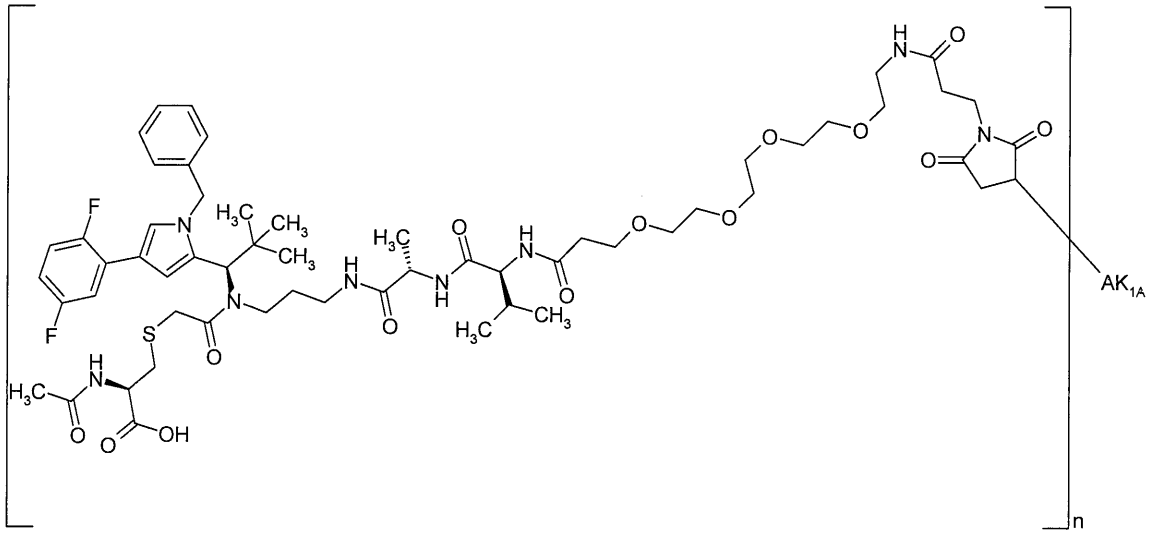

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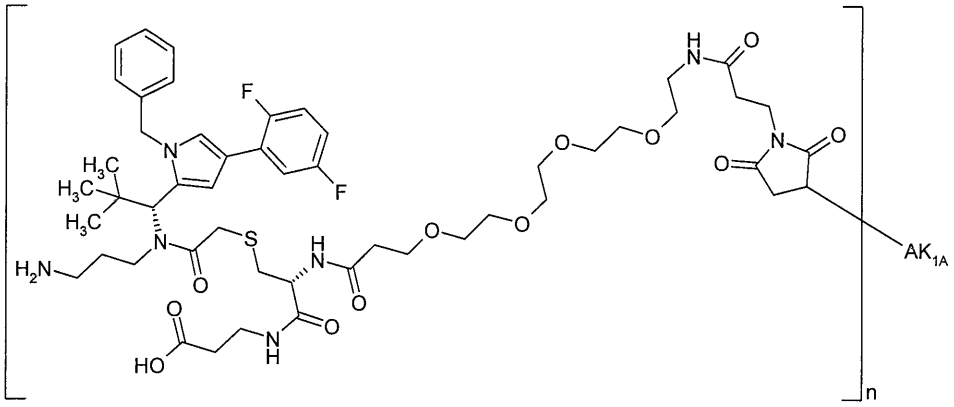

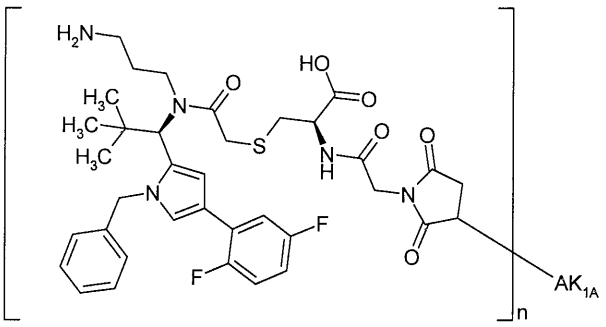

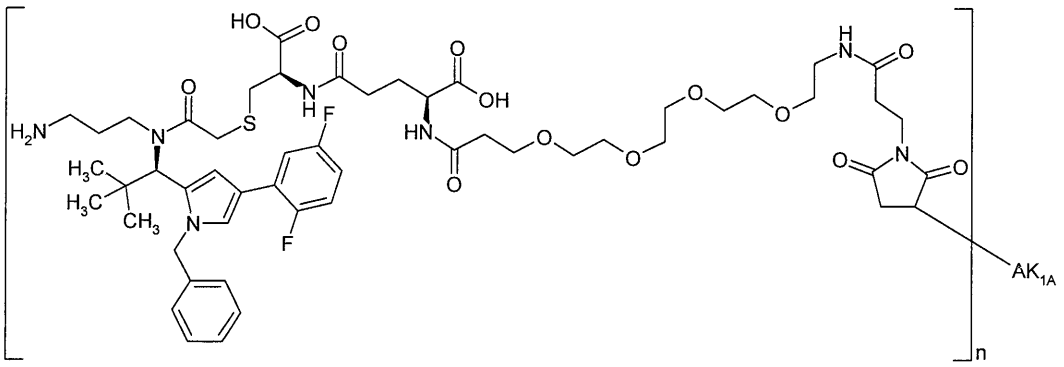

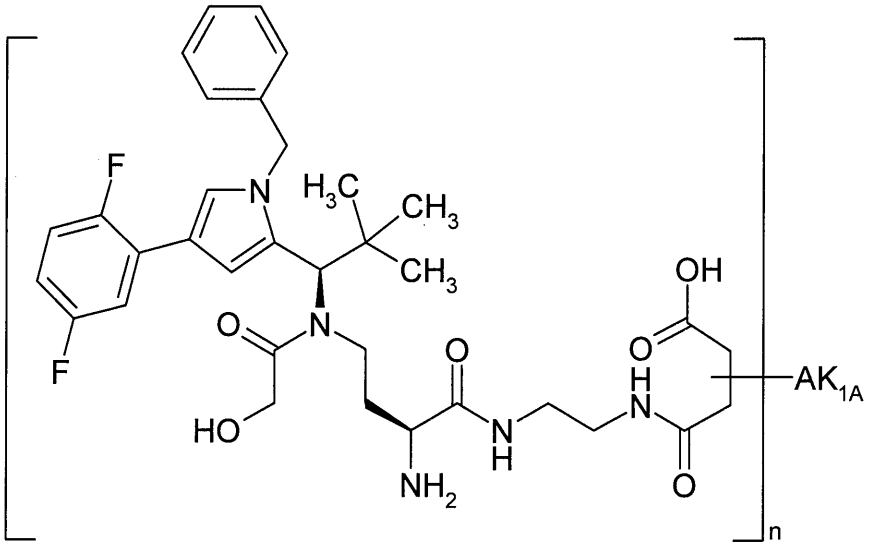

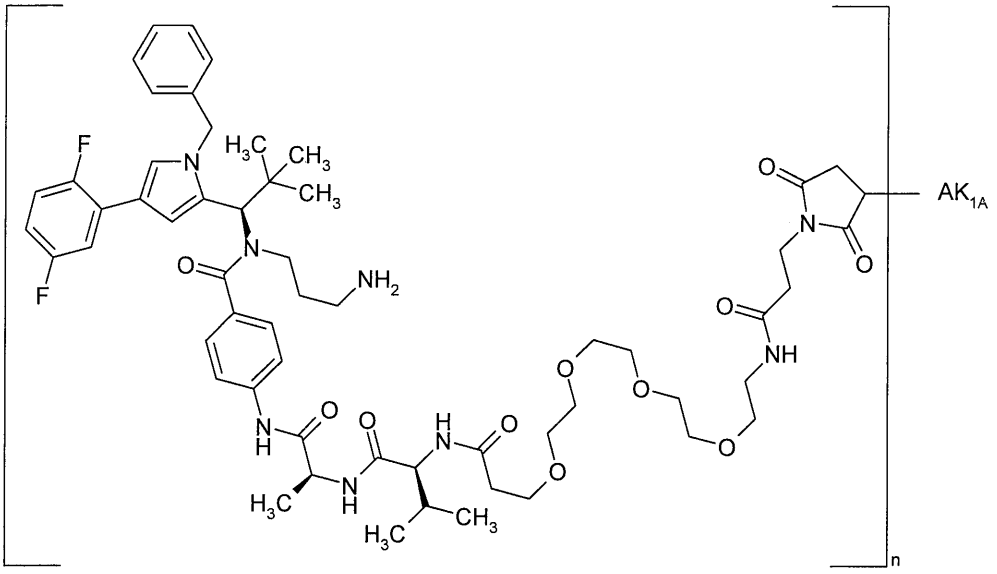
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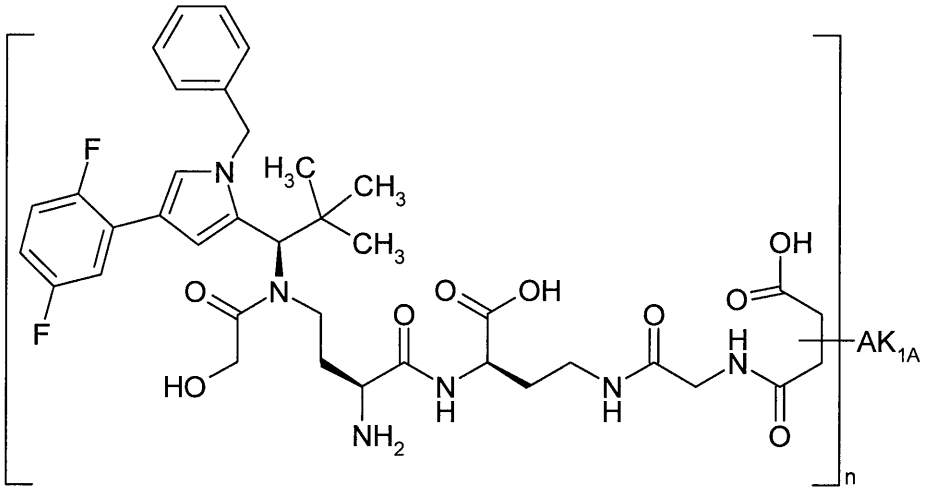
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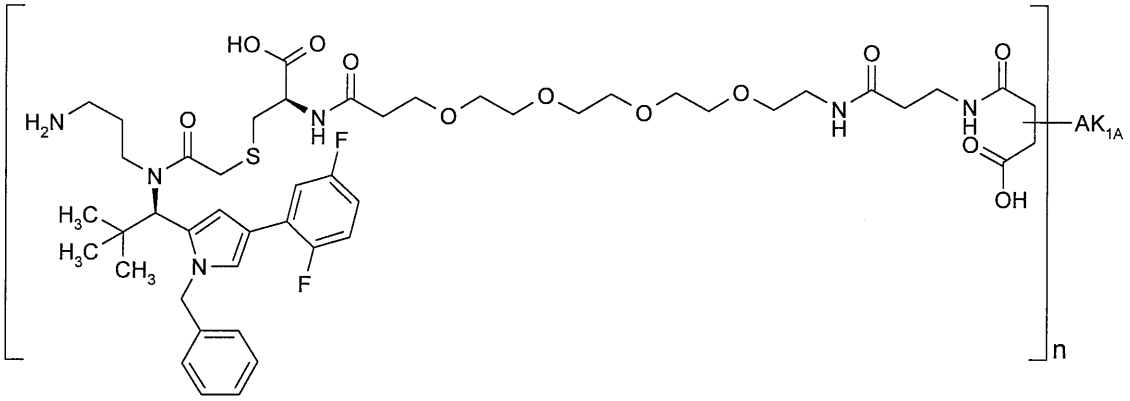

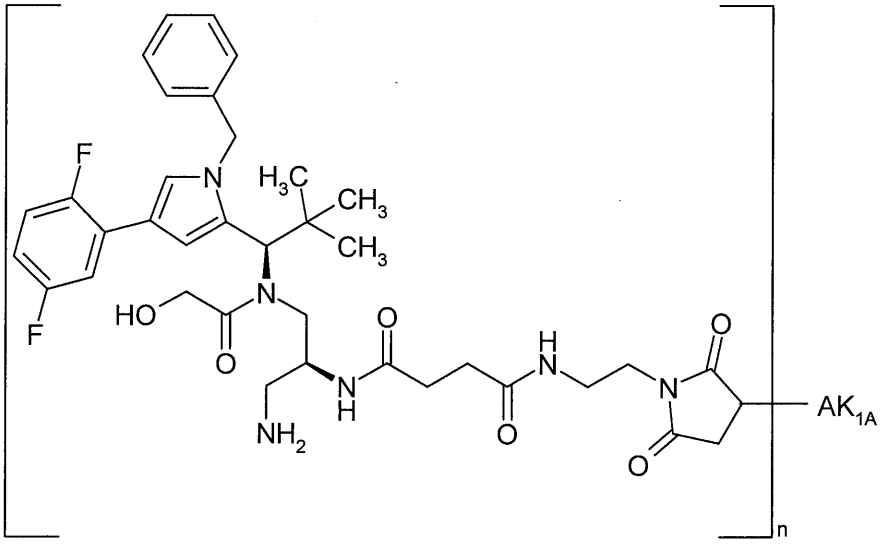

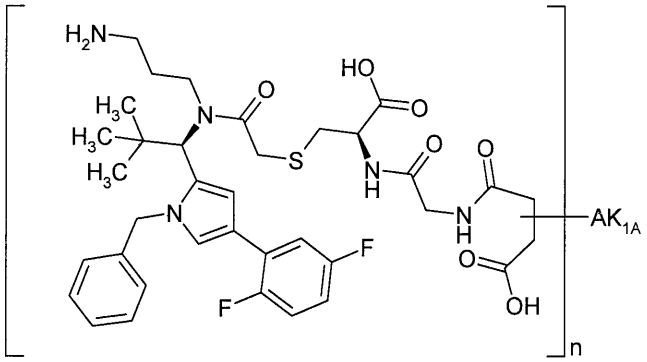

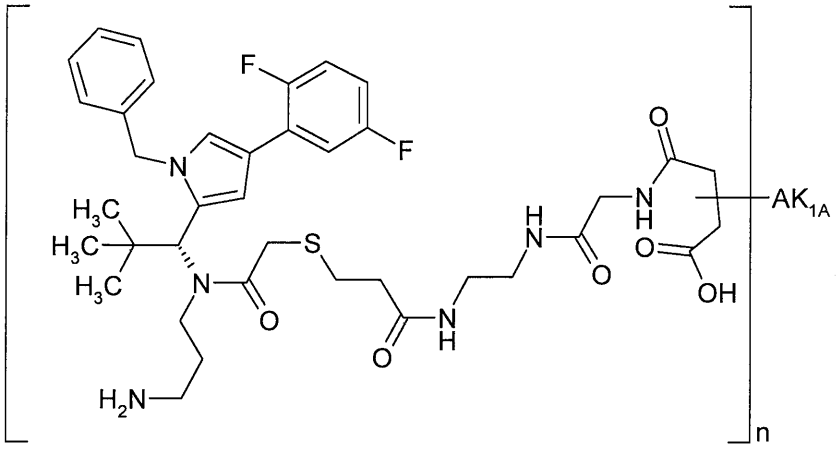

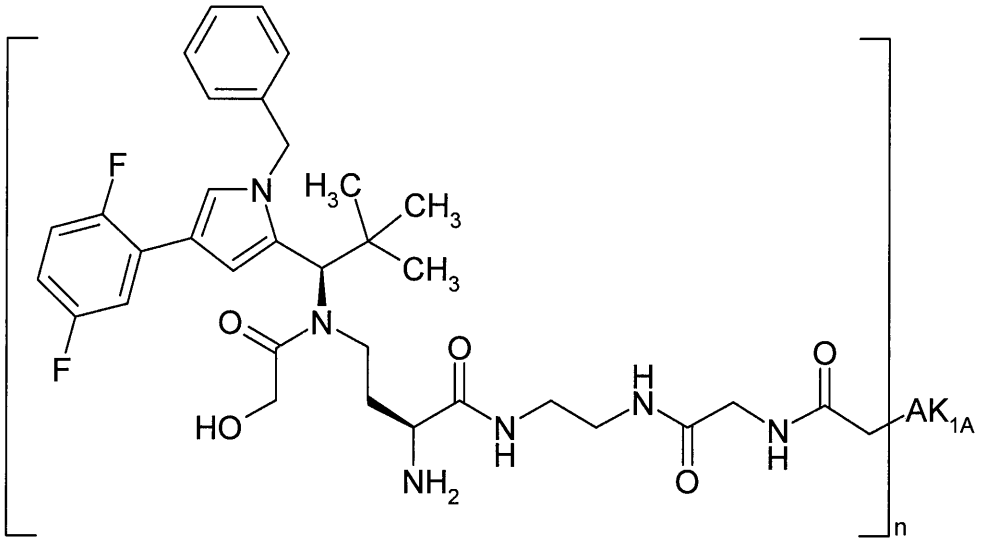

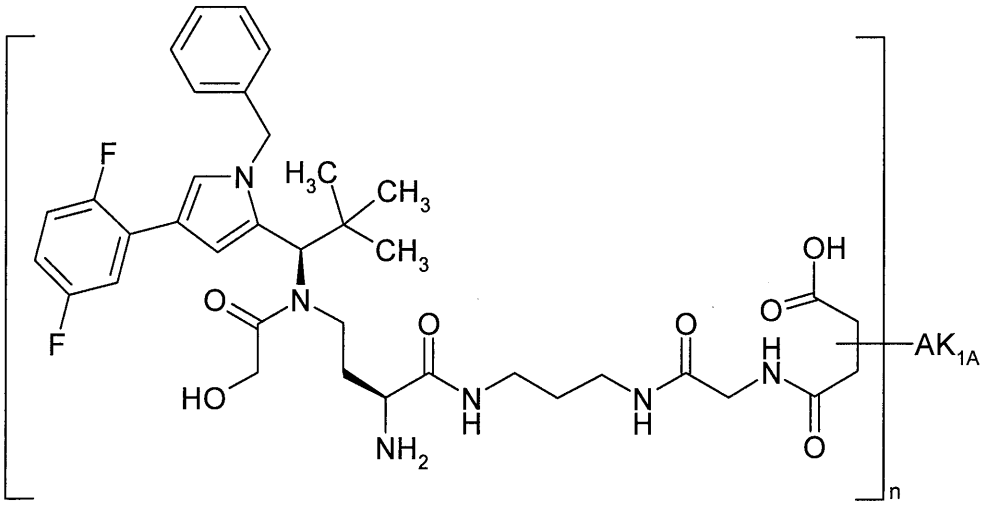

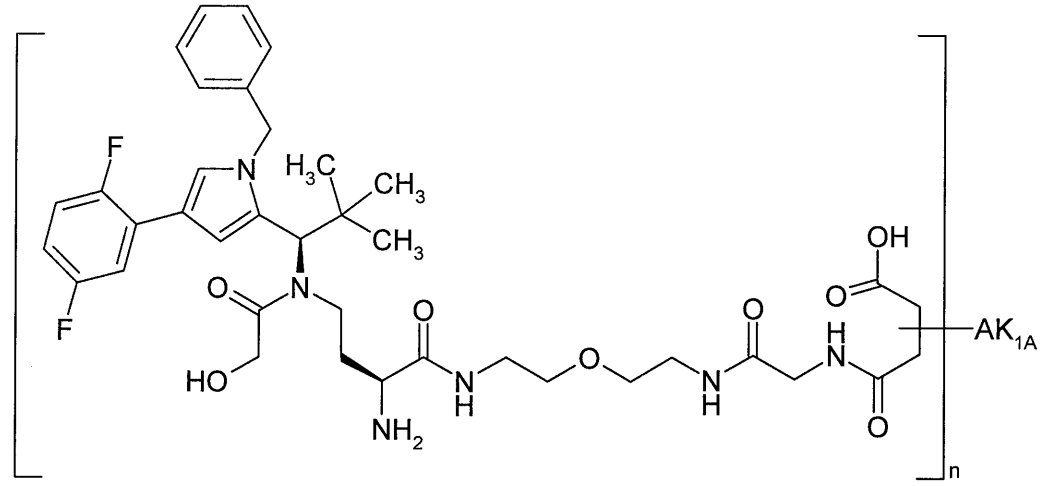

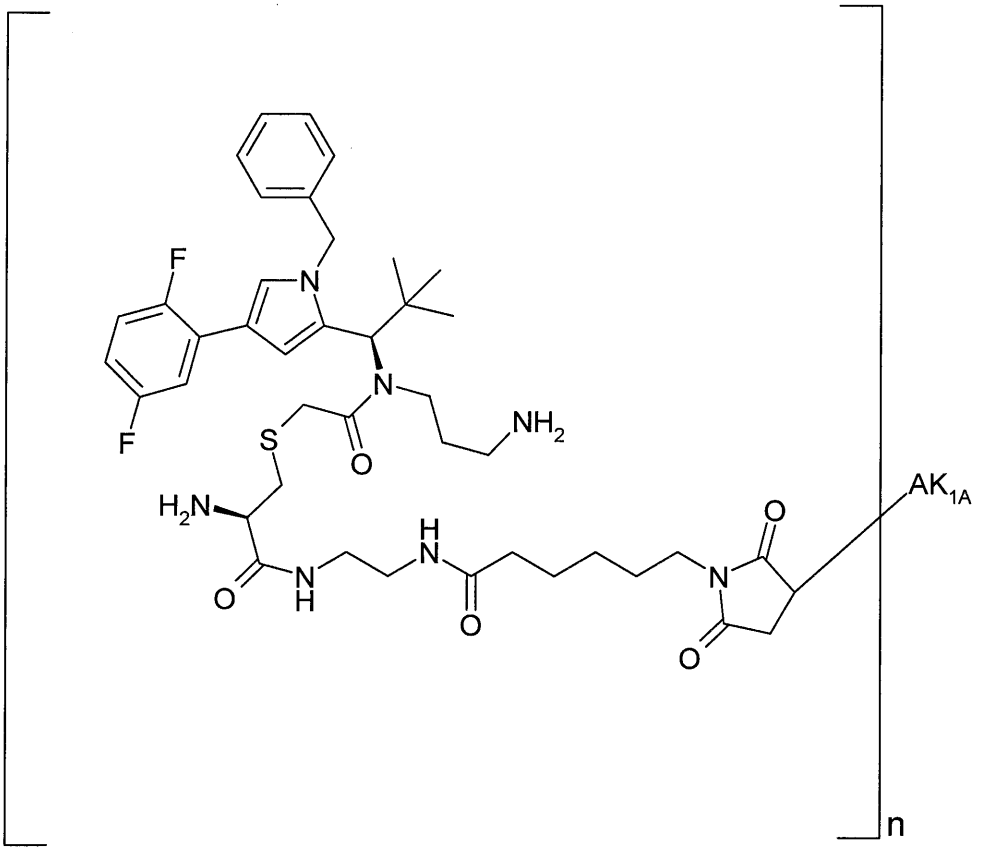

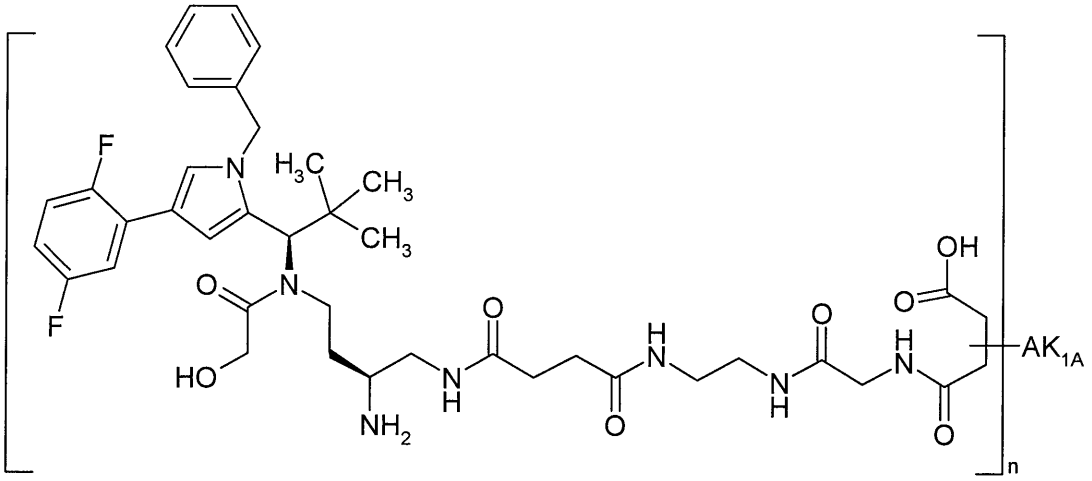
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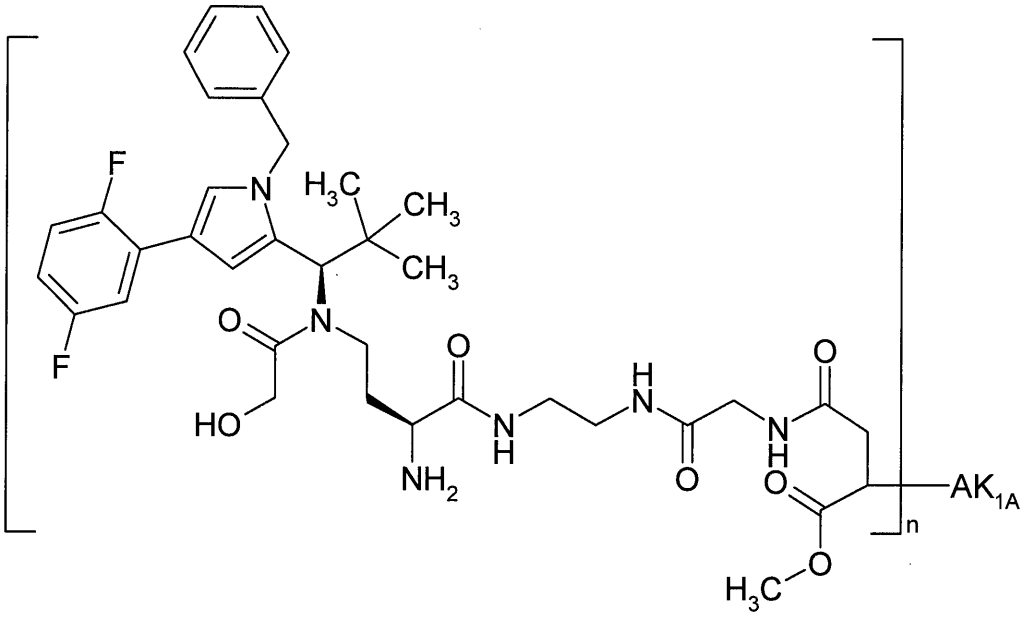
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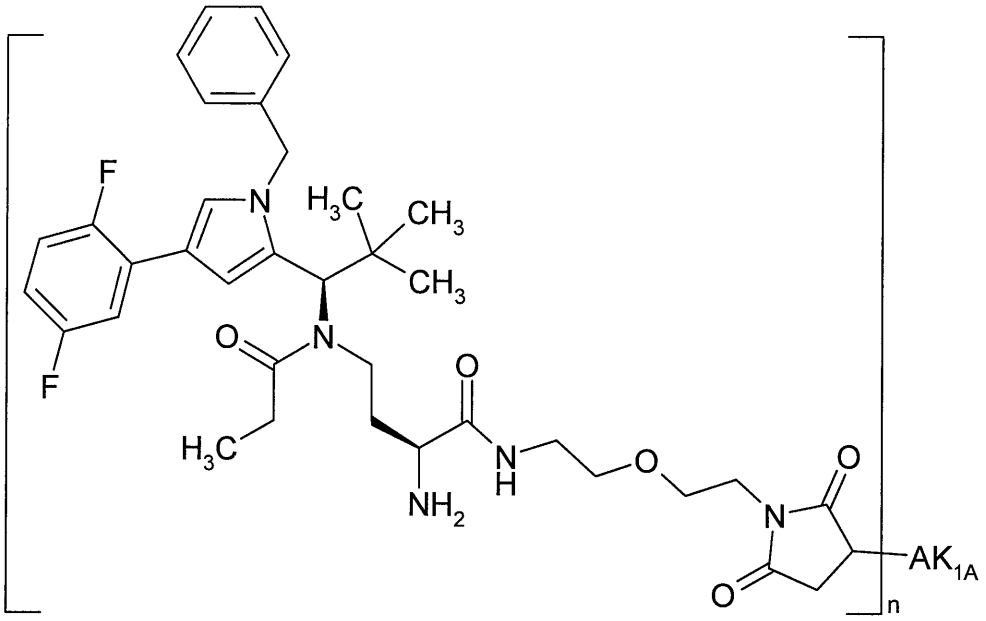

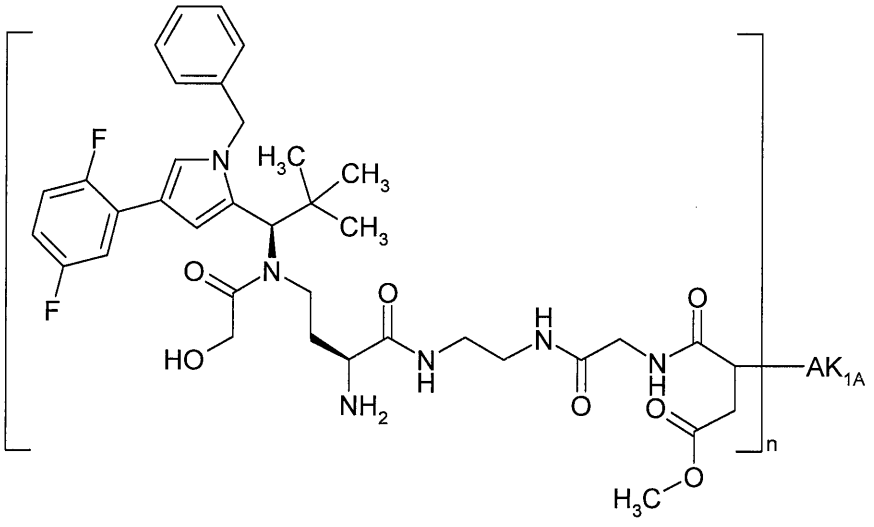

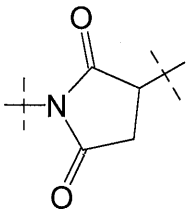

where the ADC, if attached via a group

to the antibody, may also be present instead of this group at least partially in the form of the hydrolysed open-chain succinamides.

66. Conjugate according to Claim 65 where the antibody is a human, humanized or chimeric monoclonal antibody or an antigen-binding fragment thereof.

67. Conjugate according to Claim 66 where the antibody is an anti-HER2 antibody, and anti-EGFR antibody, an anti-TWEAKR antibody or an antigen-binding fragment thereof.

68. Conjugate according to Claim 67 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.