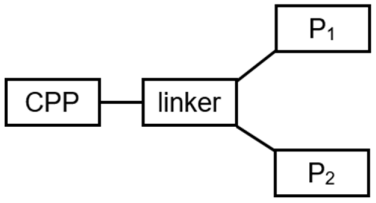
Claims

1. A PSD-95 inhibitor comprising:
    a. a first peptide (P_1) comprising or consisting of the amino acid sequence X_2TX_3V (SEQ ID NO: 53), wherein
    X_2 is selected from the group consisting of E and S;
    X_3 is selected from the group consisting of L, T, V, R and D;
    b. a second peptide (P_2) comprising or consisting of the amino acid sequence X_5TX_6V (SEQ ID NO: 55), wherein
    X_5 is selected from the group consisting of E and S;
    X_6 is selected from the group consisting of L, T, V, R and D; and
    c. a Cell Penetrating Peptide (CPP) selected from the group consisting of:
        i. a poly-L-arginine peptide (poly-Arg) consisting of 3 to 9 L-arginine residues;
        ii. yGrkkrrqrrr (SEQ ID NO: 9, D-TAT);
        iii. RQIKIWFQNRRMKWKK (SEQ ID NO: 14, L-Pen);
        iv. rqikiwfqnrrmkwkk (SEQ ID NO: 15, D-Pen);
        v. RKKRRRESRKKRRRES (SEQ ID NO: 17, L-DPV3);
        vi. LLIILRRRIRKQAHAHSK (SEQ ID NO: 18, L-pVEC);
        vii. KLALKLALKALKAALKLA (SEQ ID NO: 16, L-MAP);
        viii. PLIYLRLLRGQF (SEQ ID NO: 19, L-TP2);
        ix. |(Dap)KAPETALD| (SEQ ID NO: 21, MiniAp4); and
        x. |Ff(Nal2)RrRrQ|GABA-K (SEQ ID NO: 22, CPP12),

    wherein the CPP is linked to a linker via its C-terminal, and P_1 and P_2 are conjugated to the linker via their N-termini, and the PSD-95 inhibitor has the general structure of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof.

2. The PSD-95 inhibitor according to claim 1, wherein P_1 comprises or consists of the sequence $X_1X_2TX_3V$ (SEQ ID NO: 54), wherein

X_1 is selected from the group consisting of K, V and I;

X_2 is selected from the group consisting of E and S; and

X_3 is selected from the group consisting of L, T, V, R and D;

and wherein P_2 comprises or consists of the sequence $X_4X_5TX_6V$ (SEQ ID NO: 56), wherein

X_4 is selected from the group consisting of K, V and I;

X_5 is selected from the group consisting of E and S; and

X_6 is selected from the group consisting of L, T, V, R and D.

3. The PSD-95 inhibitor according to any one of the preceding claims, wherein P_1 and/or P_2 consist of 4 to 10 amino acid residues, such as 5 amino acid residues.

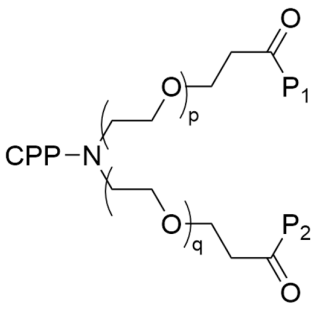
4. The PSD-95 inhibitor according to any one of the preceding claims, wherein X_3 and X_6 are selected from the group consisting of L, T, V, and R.

5. The PSD-95 inhibitor according to any one of the preceding claims, wherein the linker comprises one or more PEG units.

6. The PSD-95 inhibitor according to any one of the preceding claims, wherein the linker comprises one or more PEG units wherein at least one oxygen atom of one of the PEG units is replaced with a nitrogen atom to give NPEG.

7. The PSD-95 inhibitor according to any one of the preceding claims, wherein the linker comprises one or more PEG units wherein at least one oxygen atom of one of the PEG units is replaced with a nitrogen atom to give NPEG, and wherein the CPP is linked to the nitrogen atom of the linker by an amide bond.

8. The PSD-95 inhibitor according to any one of the preceding claims, wherein the linker comprises one or more PEG units wherein at least one oxygen atom of one of the PEG units is replaced with a nitrogen atom to give NPEG, and wherein the CPP is linked to the nitrogen atom of the linker by an amide bond, and the PSD-95 inhibitor has the general structure of Formula (III):



Formula (III)

wherein

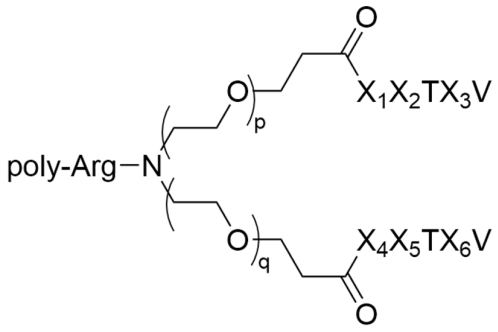
p is an integer 0 to 10; and

q is an integer 0 to 10.

9. The PSD-95 inhibitor according to any one of the preceding claims, wherein P_1 is identical to P_2.

10. The PSD-95 inhibitor according to any one of the preceding claims, wherein P_1 and P_2 consist of the amino acid sequence:
    a. KETLV (SEQ ID NO: 2);
    b. KETTV (SEQ ID NO: 3);
    c. KETVV (SEQ ID NO: 4);
    d. KETRV (SEQ ID NO: 5);
    e. ISTDV (SEQ ID NO: 6); or
    f. VETVV (SEQ ID NO: 7).

11. The PSD-95 inhibitor according to any one of the preceding claims, wherein the PSD-95 inhibitor has the general structure of Formula (VI):



Formula (VI)

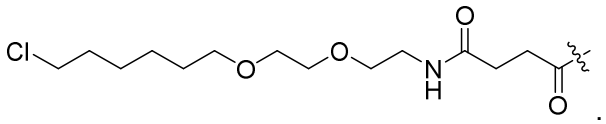
wherein

X_1 is selected from the group consisting of K, V and I;
X_2 is selected from the group consisting of E and S; and
X_3 is selected from the group consisting of L, T, V, R and D.
X_4 is selected from the group consisting of K, V and I;
X_5 is selected from the group consisting of E and S;
X_6 is selected from the group consisting of L, T, V, R and D.
p is an integer 0 to 10;
q is an integer 0 to 10; and
poly-Arg is a poly-L-arginine peptide consisting of 3 to 9 L-arginine residues.

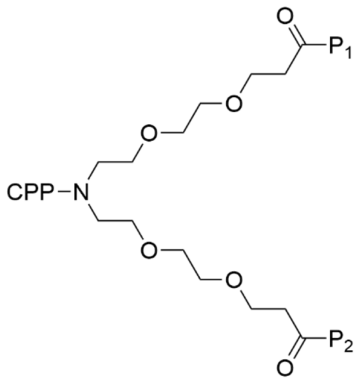
12. The PSD-95 inhibitor according to any one of the preceding claims, wherein the CPP is RRRRRRRRR (SEQ ID NO: 12), RRRRRRRR (SEQ ID NO: 57), RRRRRRR (SEQ ID NO: 58), RRRRRR (SEQ ID NO: 59), RRRRR (SEQ ID NO: 60), RRRR (SEQ ID NO: 61), or RRR.

13. The PSD-95 inhibitor according to any one of claims 8 or 11, wherein p is 2 and q is 2.

14. The PSD-95 inhibitor according to any one of the preceding claims, wherein the N-terminal of the CPP is acetylated or wherein the N-terminal of the CPP is conjugated to a chloroalkane tag (CA), which has the structure of:



15. The PSD-95 inhibitor according to claim 1, wherein the PSD-95 inhibitor has the general structure of Formula (XXVIII):



Formula (XXVIII)

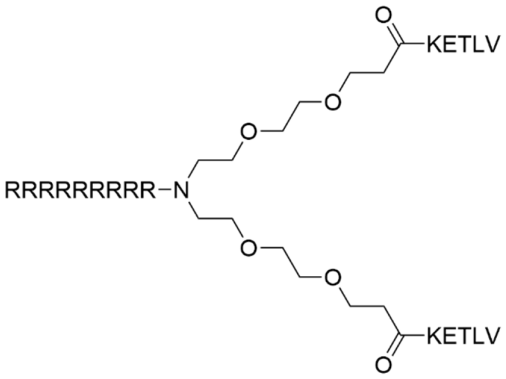
wherein P_1, P_2 and CPP are:

	P_1	**P_2**	**CPP**	
i.	KETLV (SEQ ID NO: 2)	KETLV (SEQ ID NO: 2)	L-Arg_9	RRRRRRRRR (SEQ ID NO: 12)
ii.	KETLV (SEQ ID NO: 2)	KETLV (SEQ ID NO: 2)	L-Arg_7	RRRRRRR (SEQ ID NO: 58)
iii.	KETLV (SEQ ID NO: 2)	KETLV (SEQ ID NO: 2)	L-Arg_6	RRRRRR (SEQ ID NO: 59)
iv.	KETLV (SEQ ID NO: 2)	KETLV (SEQ ID NO: 2)	L-Arg_5	RRRRR (SEQ ID NO: 60)
v.	KETLV (SEQ ID NO: 2)	KETLV (SEQ ID NO: 2)	L-Arg_4	RRRR (SEQ ID NO: 61)
vi.	KETLV (SEQ ID NO: 2)	KETLV (SEQ ID NO: 2)	L-Arg_3	RRR
vii.	KETTV (SEQ ID NO: 3)	KETTV (SEQ ID NO: 3)	L-Arg_9	RRRRRRRRR (SEQ ID NO: 12)
viii.	KETVV (SEQ ID NO: 4)	KETVV (SEQ ID NO: 4)	L-Arg_9	RRRRRRRRR (SEQ ID NO: 12)
ix.	KETRV (SEQ ID NO: 5)	KETRV (SEQ ID NO: 5)	L-Arg_9	RRRRRRRRR (SEQ ID NO: 12)
x.	ISTDV (SEQ ID NO: 6)	ISTDV (SEQ ID NO: 6)	L-Arg_9	RRRRRRRRR (SEQ ID NO: 12)
xi.	VETVV (SEQ ID NO: 7)	VETVV (SEQ ID NO: 7)	L-Arg_9	RRRRRRRRR (SEQ ID NO: 12)
xii.	IETDV	IETDV	L-Arg_9	RRRRRRRRR

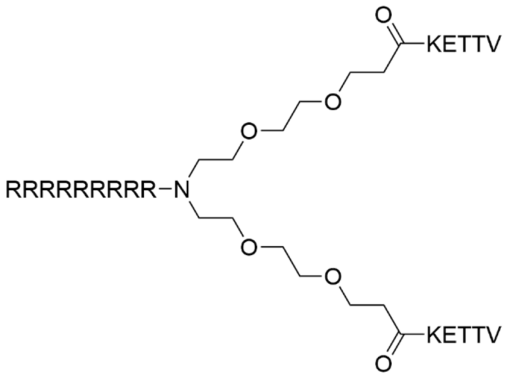
	(SEQ ID NO: 1)	(SEQ ID NO: 1)		(SEQ ID NO: 12)
xiii.	IETDV (SEQ ID NO: 1)	IETDV (SEQ ID NO: 1)	L-Arg_7	RRRRRRR (SEQ ID NO: 58)
xiv.	IETDV (SEQ ID NO: 1)	IETDV (SEQ ID NO: 1)	L-Arg_5	RRRRR (SEQ ID NO: 60)
xv.	IETDV (SEQ ID NO: 1)	IETDV (SEQ ID NO: 1)	L-Arg_3	RRR

and wherein the N-terminal of the CPP is optionally acetylated.

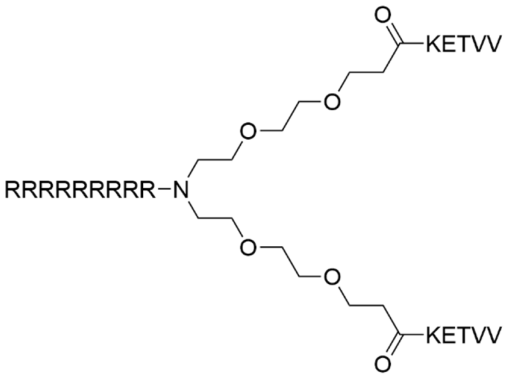
16. The PSD-95 inhibitor according to claim 1, wherein the PSD-95 inhibitor is selected from the group consisting of formulas (X) to (XXIII):



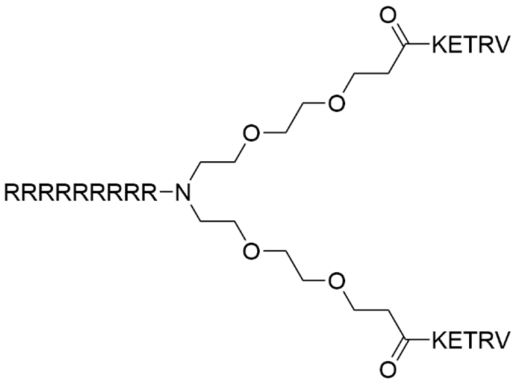
Formula (X)



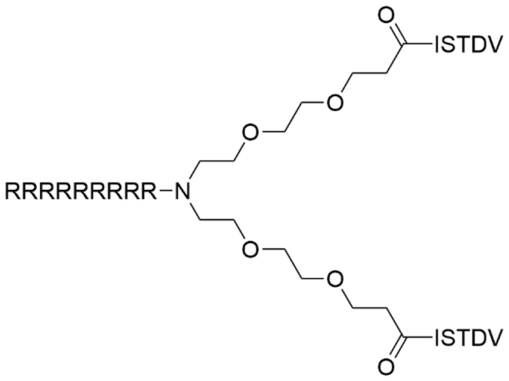
Formula (XI)



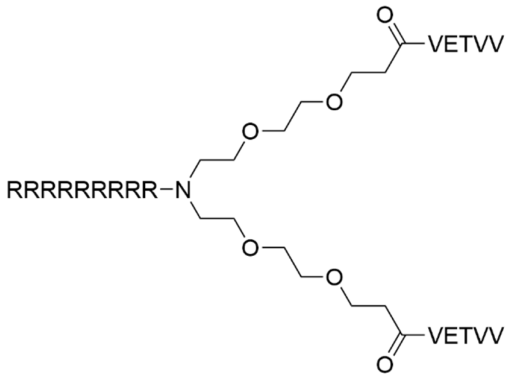
Formula (XII)



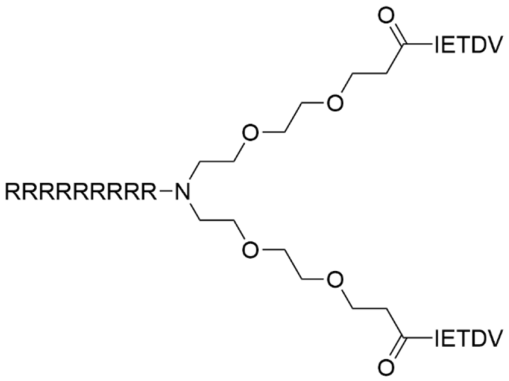
Formula (XIII)



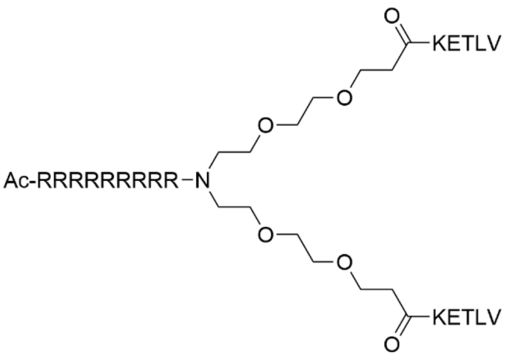
Formula (XIV)



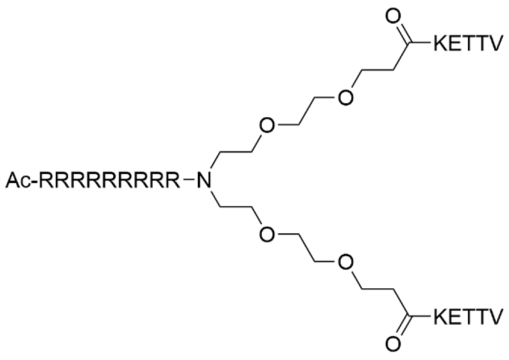
Formula (XV)



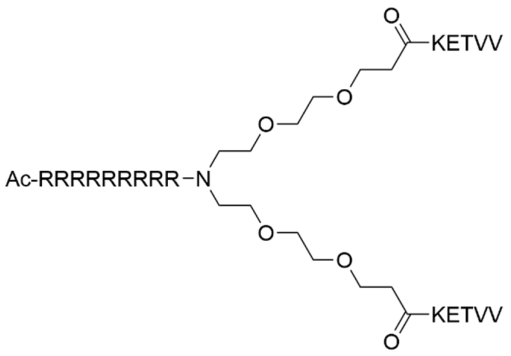
Formula (XVI)



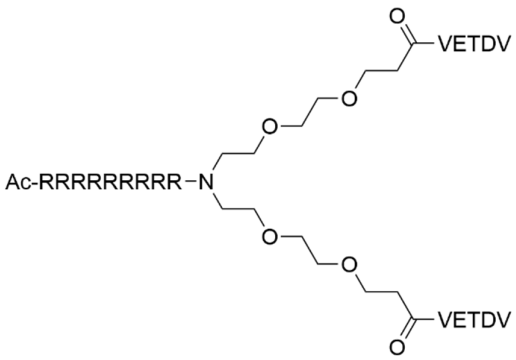
Formula (XVII)



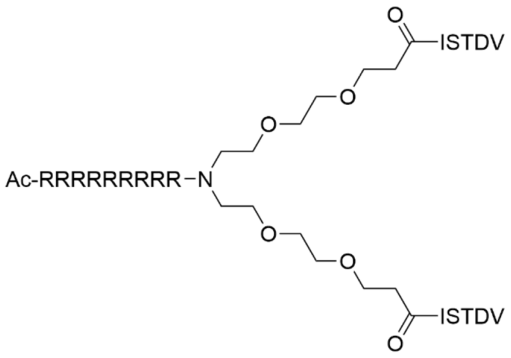
Formula (XVIII)



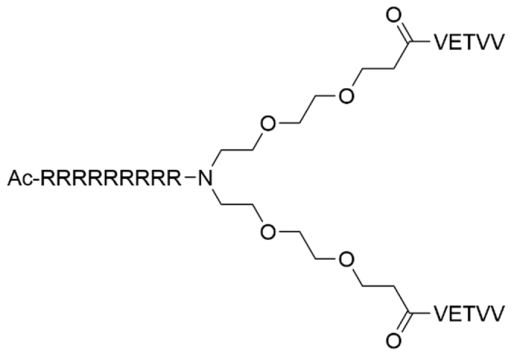
Formula (XIX)



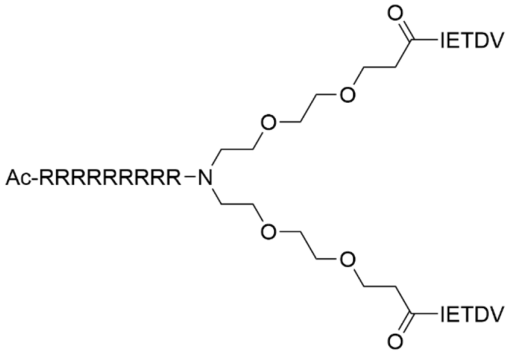
Formula (XX)



Formula (XXI)



Formula (XXII)

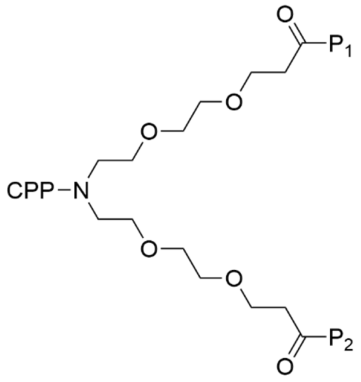


Formula (XXIII)

17. The PSD-95 inhibitor according to any one of claims 1 to 3, 5 to 9, 13 or 14, wherein P_1 and P_2 consist of the amino acid sequence IETDV (SEQ ID NO: 1)

and the CPP is selected from the group consisting of rqikiwfqnrrmkwkk (SEQ ID NO: 15, D-Pen); LLIILRRRIRKQAHAHSK (SEQ ID NO: 18, L-pVEC); PLIYLRLLRGQF (SEQ ID NO: 19, L-TP2); |(Dap)KAPETALD| (SEQ ID NO: 21, MiniAp4); and |Ff(Nal2)RrRrQ|GABA-K (SEQ ID NO: 22, CPP12).

18. The PSD-95 inhibitor according to claim 1, wherein the PSD-95 inhibitor has the general structure of Formula (XXVIII):



Formula (XXVIII)

wherein P_1 and P_2 consist of the amino acid sequence IETDV (SEQ ID NO: 1) and the CPP is selected from the group consisting of rqikiwfqnrrmkwkk (SEQ ID NO: 15, D-Pen); LLIILRRRIRKQAHAHSK (SEQ ID NO: 18, L-pVEC); PLIYLRLLRGQF (SEQ ID NO: 19, L-TP2); |(Dap)KAPETALD| (SEQ ID NO: 21, MiniAp4); and |Ff(Nal2)RrRrQ|GABA-K (SEQ ID NO: 22, CPP12).

19. A PSD-95 inhibitor according to any one of the preceding claims for use as a medicament.

20. Use of a PSD-95 inhibitor according to any one claims 1 to 39 for the manufacture of a medicament for the treatment, prevention, reduction and/or delay of development of an excitotoxic-related disease such as stroke, for example selected from acute ischemic stroke and subarachnoid hemorrhage.