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(54) **PSD-95 INHIBITORS AND USES THEREOF**

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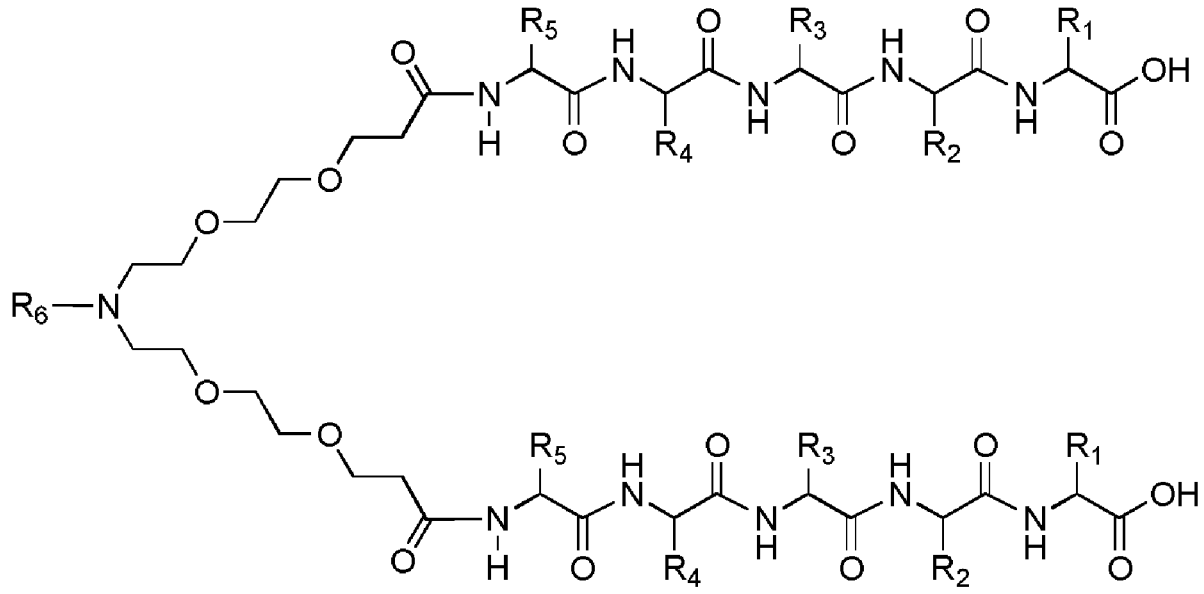
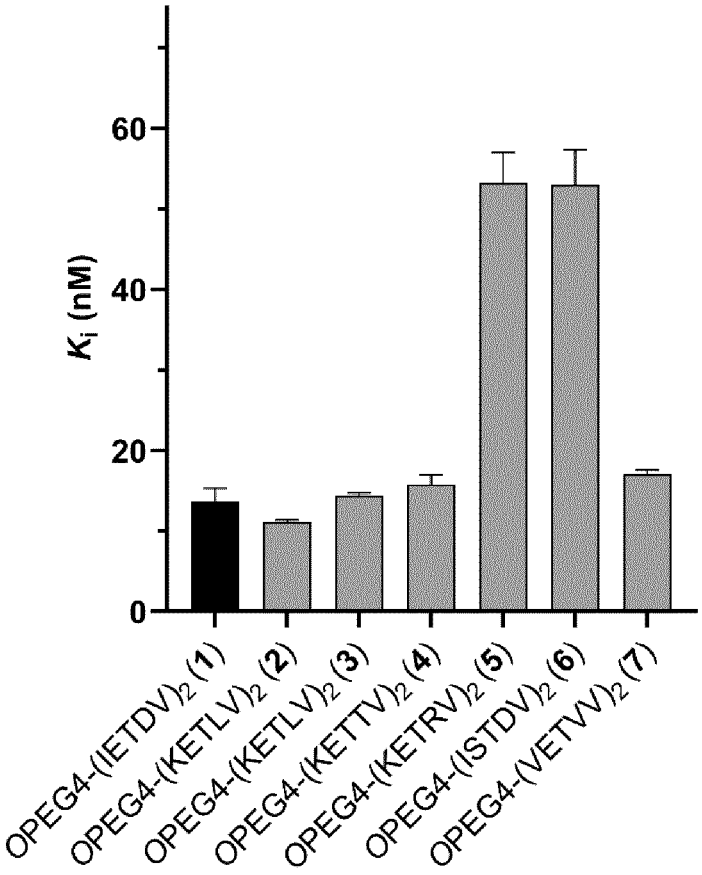
(57) **ABSTRACT**

The present invention relates to compounds capable of binding to the PDZ domains of PSD-95 and their medical use as inhibitors of protein-protein interaction mediated by PSD-95.

Specification includes a Sequence Listing.




K_i (nM)
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20
40
60
OPEG4-(IETDV)2 (1)
OPEG4-(KETLV)2 (2)
OPEG4-(KETLV)2 (3)
OPEG4-(KETTV)2 (4)
OPEG4-(KETRV)2 (5)
OPEG4-(ISTDV)2 (6)
OPEG4-(VETVV)2 (7)

Fig. 1

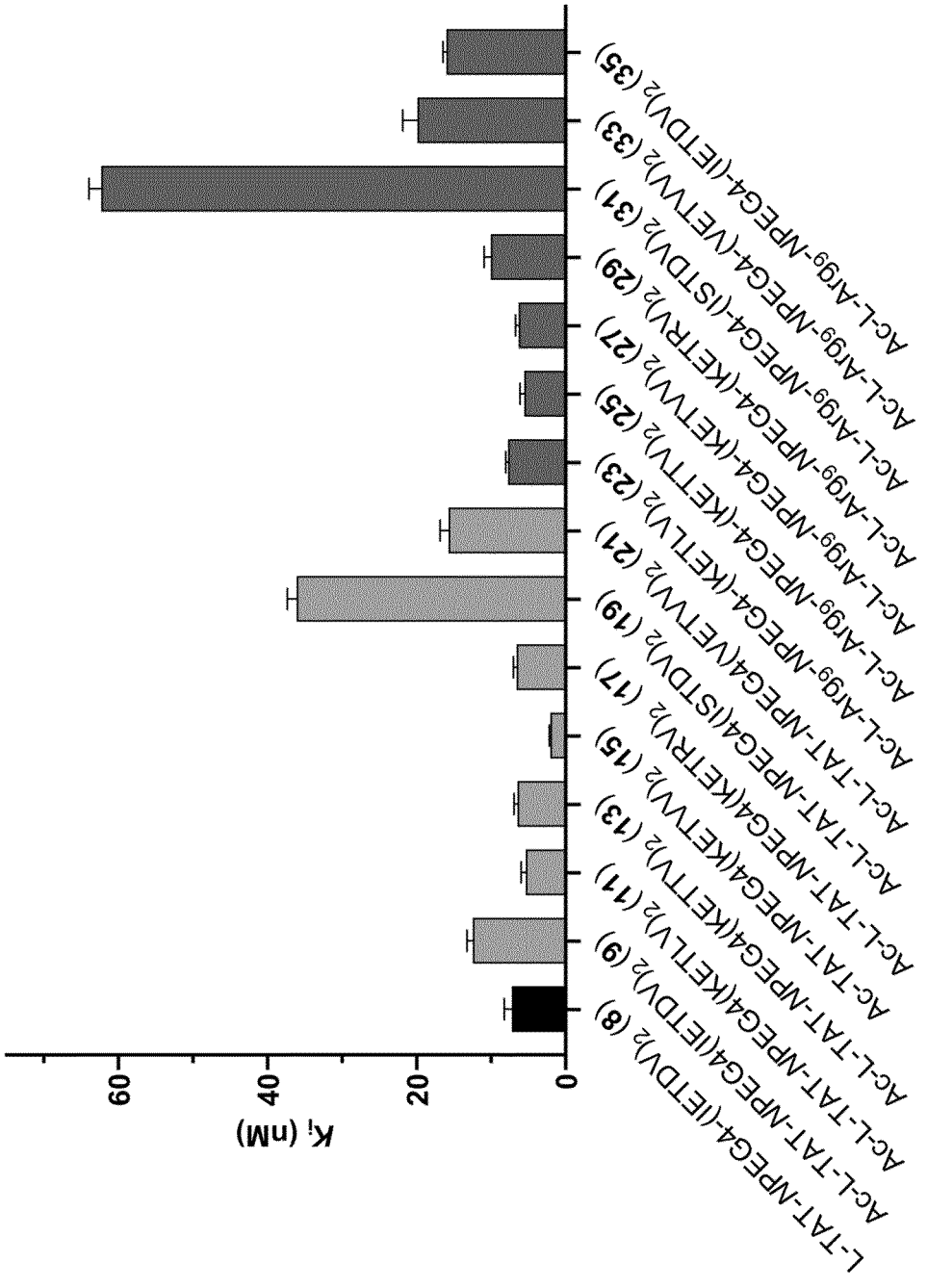

K_i (nM)
0
20
40
60
L-TAT-NPEG4-(IETDV)2 (8)
Ac-L-TAT-NPEG4(IETDV)2 (9)
Ac-L-TAT-NPEG4(KETLV)2 (11)
Ac-TAT-NPEG4(KETTV)2 (13)
Ac-L-TAT-NPEG4(KETWV)2 (15)
Ac-L-TAT-NPEG4(KETRV)2 (17)
Ac-L-TAT-NPEG4(ISTDV)2 (19)
Ac-L-TAT-NPEG4(VETWV)2 (21)
Ac-L-Arg9-NPEG4-(KETLV)2 (23)
Ac-L-Arg9-NPEG4-(KETTV)2 (25)
Ac-L-Arg9-NPEG4-(KETWV)2 (27)
Ac-L-Arg9-NPEG4-(KETRV)2 (29)
Ac-L-Arg9-NPEG4-(ISTDV)2 (31)
Ac-L-Arg9-NPEG4-(VETWV)2 (33)
Ac-L-Arg9-NPEG4-(IETDV)2 (35)

Fig. 2

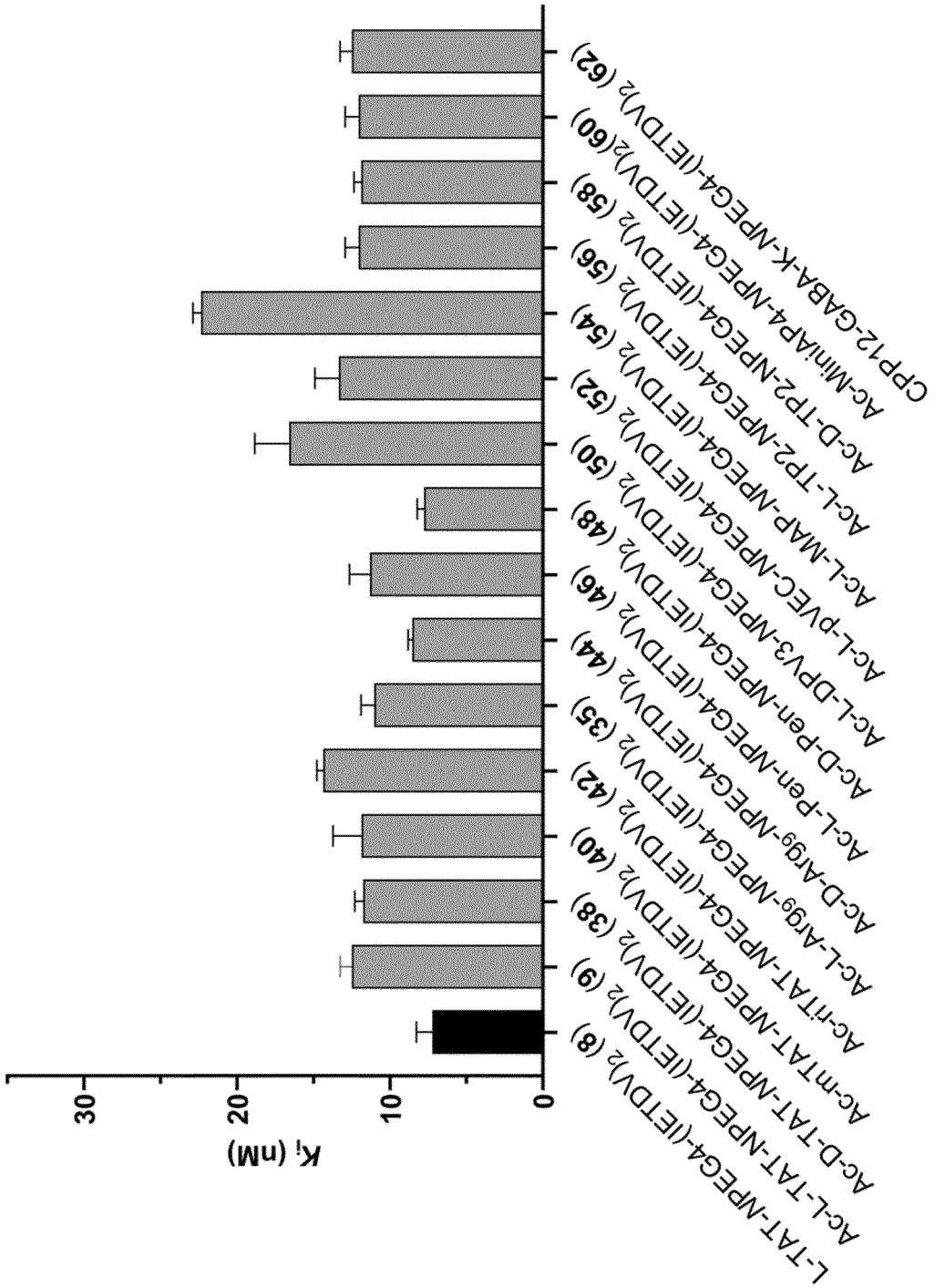

K_i (nM)
0
10
20
30
L-TAT-NPEG4-(IETDV)2 (8)
Ac-L-TAT-NPEG4-(IETDV)2 (9)
Ac-D-TAT-NPEG4-(IETDV)2 (38)
Ac-mTAT-NPEG4-(IETDV)2 (40)
Ac-rfTAT-NPEG4-(IETDV)2 (42)
Ac-L-Arg9-NPEG4-(IETDV)2 (35)
Ac-D-Arg9-NPEG4-(IETDV)2 (44)
Ac-L-Pen-NPEG4-(IETDV)2 (46)
Ac-D-Pen-NPEG4-(IETDV)2 (48)
Ac-L-DPV3-NPEG4-(IETDV)2 (50)
Ac-L-pVEC-NPEG4-(IETDV)2 (52)
Ac-L-MAP-NPEG4-(IETDV)2 (54)
Ac-D-TP2-NPEG4-(IETDV)2 (56)
Ac-Mlin1AP4-NPEG4-(IETDV)2 (58)
CPP12-GADBA-K-NPEG4-(IETDV)2 (60)
Ac-L-TP2-NPEG4-(IETDV)2 (62)

Fig. 3

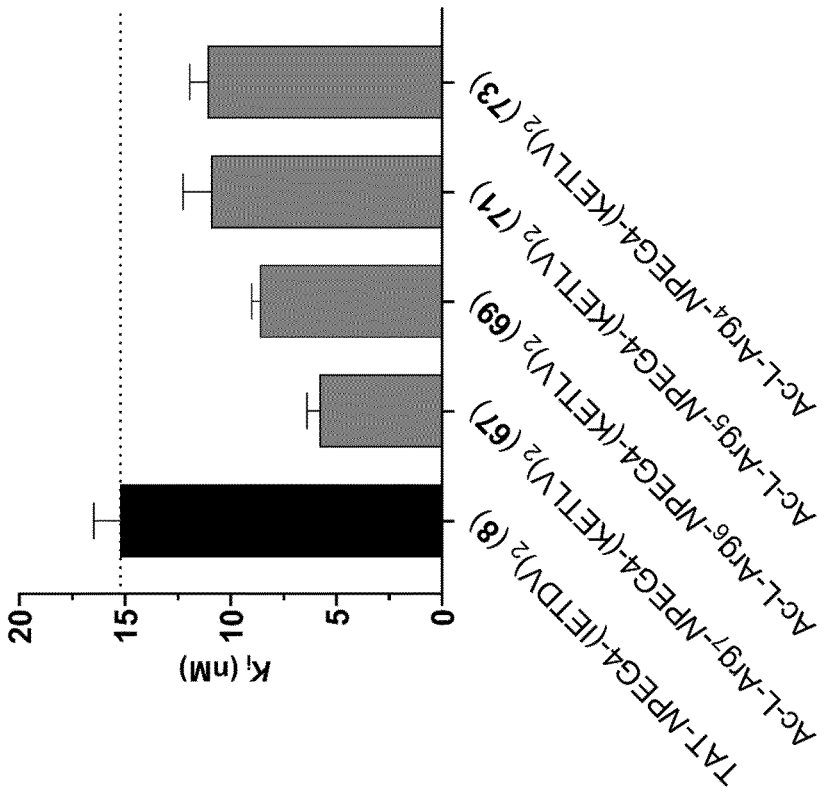

K_i (nM)
0
5
10
15
20
TAT-NPEG4-(IETDV)2 (8)
Ac-L-Arg7-NPEG4-(KETLV)2 (67)
Ac-L-Arg6-NPEG4-(KETLV)2 (69)
Ac-L-Arg5-NPEG4-(KETLV)2 (71)
Ac-L-Arg4-NPEG4-(KETLV)2 (73)

Fig. 4

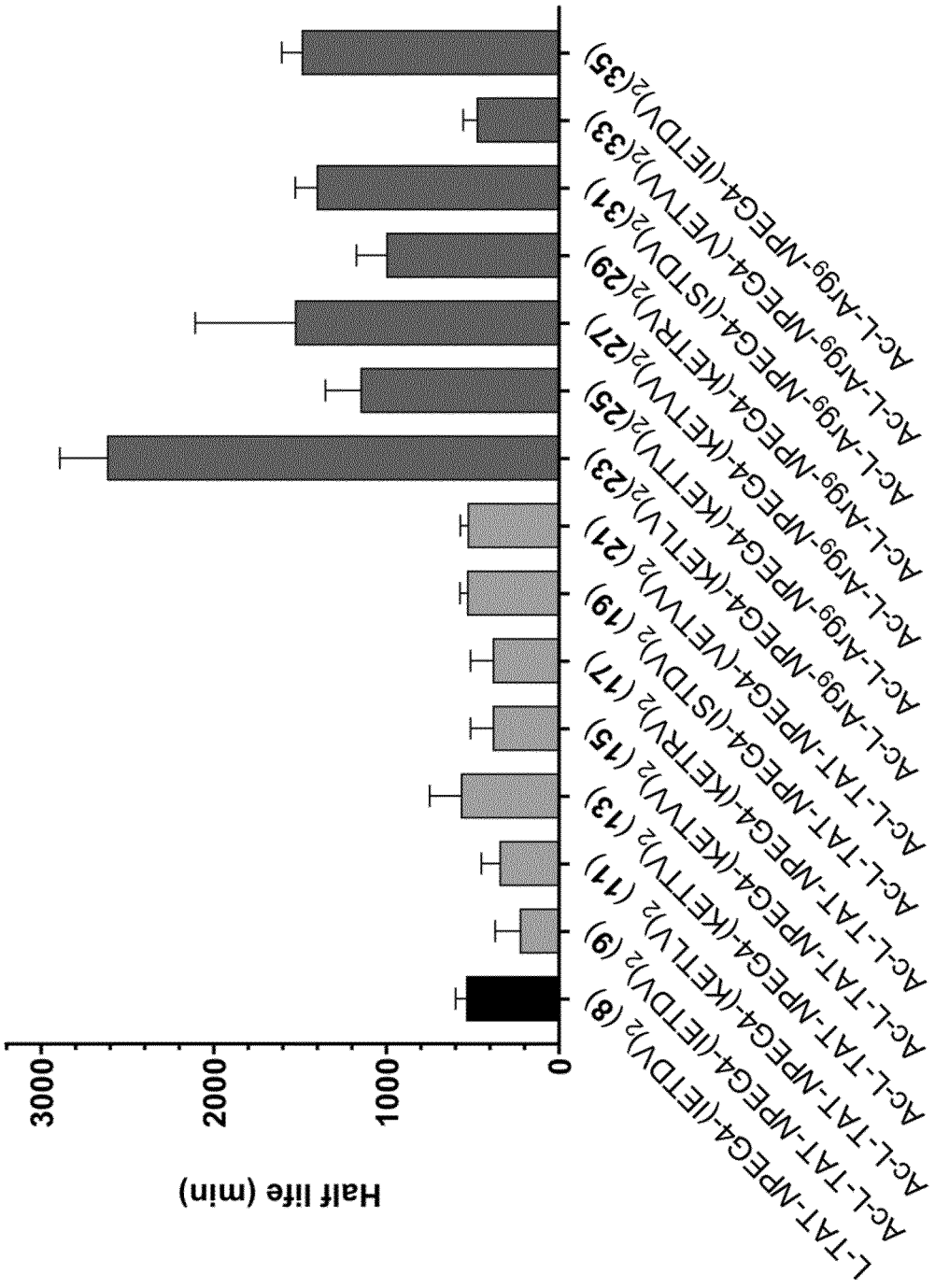

Half life (min)
0
1000
2000
3000
L-TAT-NPEG4-(IETDV)2 (8)
Ac-L-TAT-NPEG4-(IETDV)2 (9)
Ac-L-TAT-NPEG4-(KETLV)2 (11)
Ac-L-TAT-NPEG4-(KETTV)2 (13)
Ac-L-TAT-NPEG4-(KETRV)2 (15)
Ac-L-TAT-NPEG4-(ISTDV)2 (17)
Ac-L-TAT-NPEG4-(VETVV)2 (19)
Ac-L-TAT-NPEG4-(KETLV)2 (21)
Ac-L-TAT-NPEG4-(KETTV)2 (23)
Ac-L-Ar99-NPEG4-(KETVV)2 (25)
Ac-L-Ar99-NPEG4-(KETRV)2 (27)
Ac-L-Ar99-NPEG4-(ISTDV)2 (29)
Ac-L-Ar99-NPEG4-(VETVV)2 (31)
Ac-L-Ar99-NPEG4-(IETDV)2 (33)
Ac-L-Ar99-NPEG4-(IETDV)2 (35)

Fig. 5

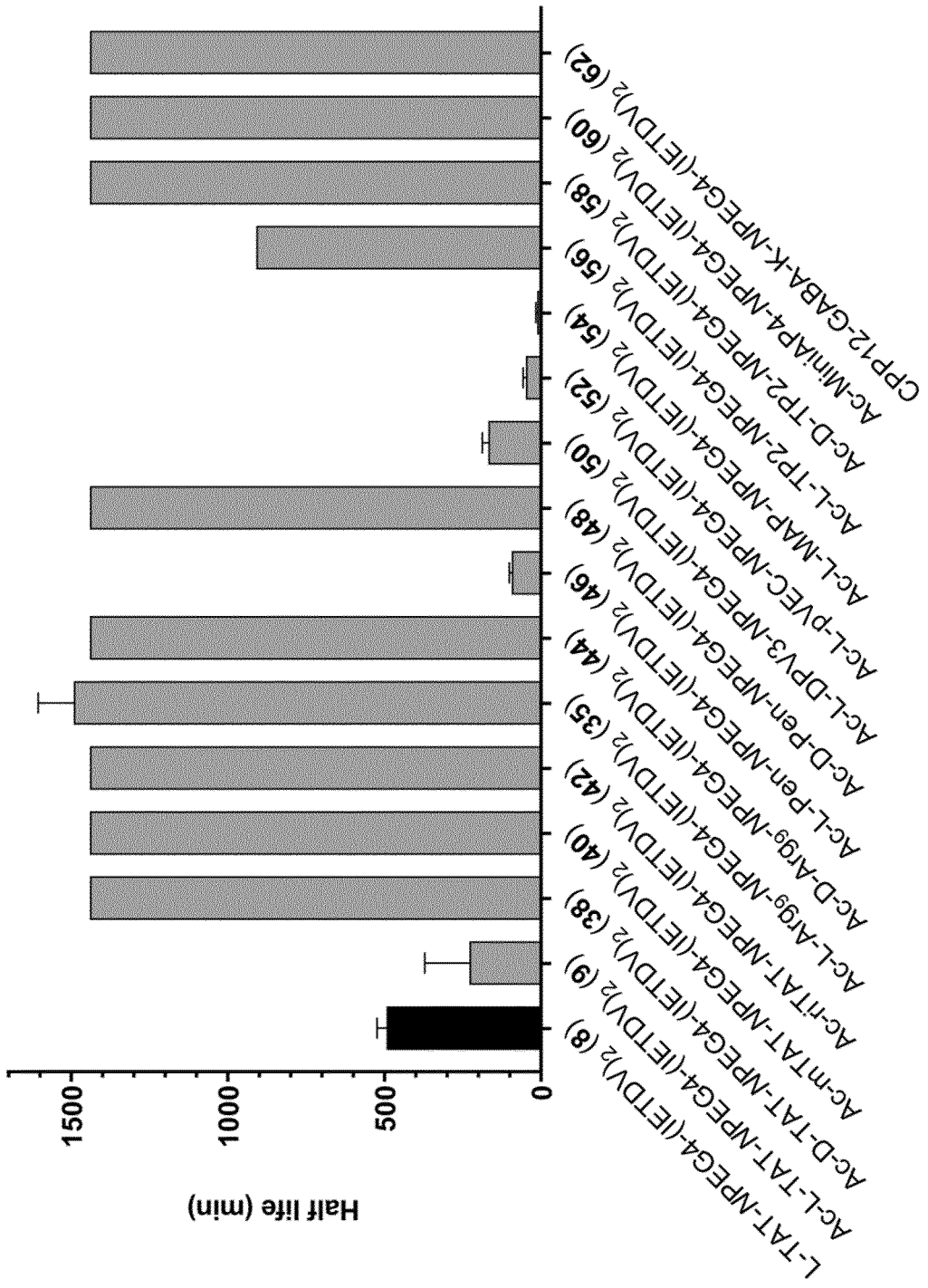

Half life (min)
0
500
1000
1500
L-TAT-NPEG4-(IETDV)2 (8)
Ac-L-TAT-NPEG4-(IETDV)2 (9)
Ac-D-TAT-NPEG4-(IETDV)2 (38)
Ac-m1TAT-NPEG4-(IETDV)2 (40)
Ac-r1TAT-NPEG4-(IETDV)2 (42)
Ac-L-Arg9-NPEG4-(IETDV)2 (35)
Ac-D-Arg9-NPEG4-(IETDV)2 (44)
Ac-L-Pen-NPEG4-(IETDV)2 (46)
Ac-D-Pen-NPEG4-(IETDV)2 (48)
Ac-L-DPV3-NPEG4-(IETDV)2 (50)
Ac-L-pVEC-NPEG4-(IETDV)2 (52)
Ac-L-MAP-NPEG4-(IETDV)2 (54)
Ac-L-TP2-NPEG4-(IETDV)2 (56)
Ac-D-TP2-NPEG4-(IETDV)2 (58)
Ac-MiniAP4-NPEG4-(IETDV)2 (60)
CPP12-GABA-K-NPEG4-(IETDV)2 (62)

Fig. 6

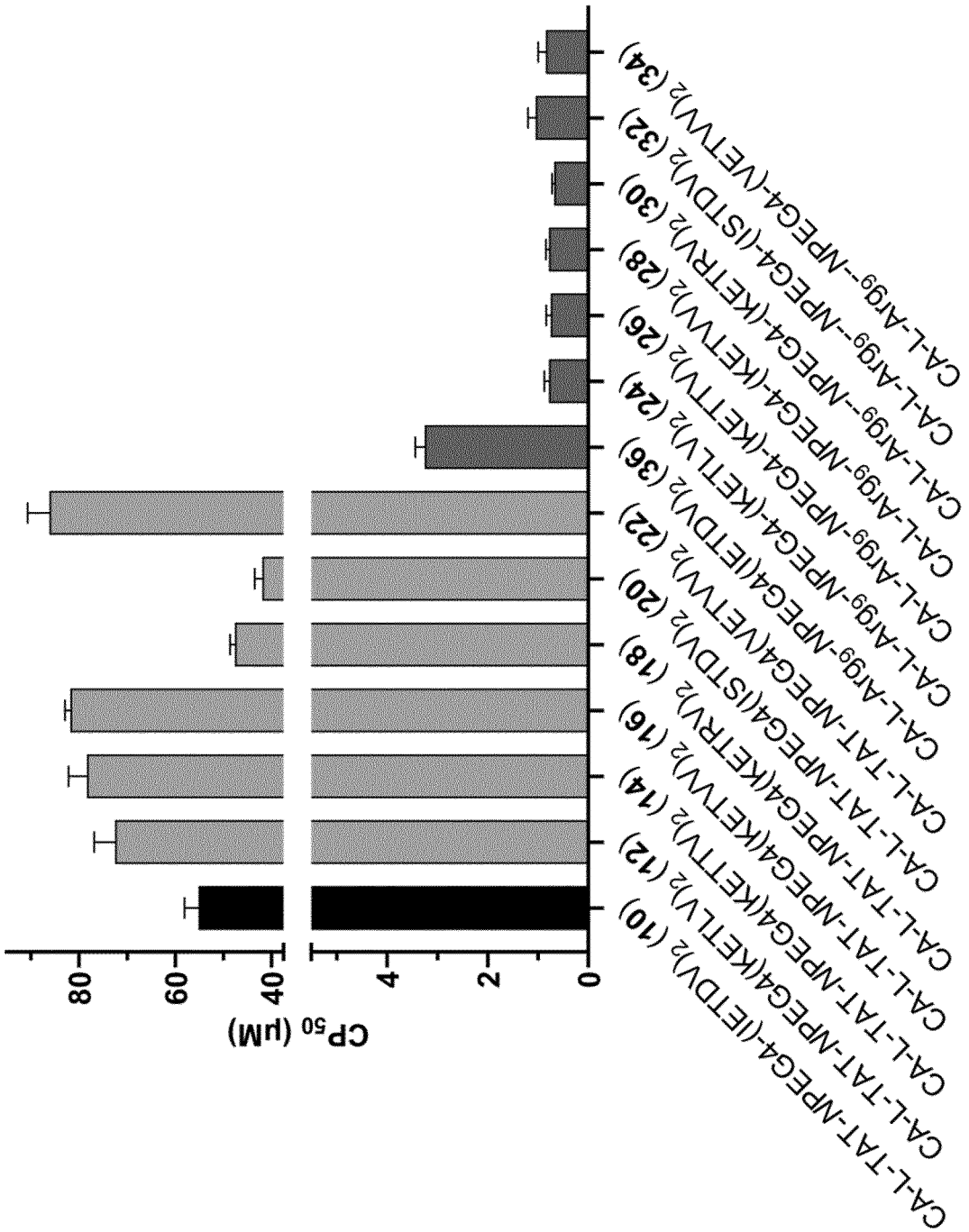

CP50 (μM)
0
2
4
40
60
80
CA-L-TAT-NPEG4-(IETDV)2 (10)
CA-L-TAT-NPEG4-(KETLV)2 (12)
CA-L-TAT-NPEG4-(KETVV)2 (14)
CA-L-TAT-NPEG4-(KETRV)2 (16)
CA-L-TAT-NPEG4-(ISTDV)2 (18)
CA-L-TAT-NPEG4-(VETVV)2 (20)
CA-L-Arg9-NPEG4-(IETDV)2 (22)
CA-L-Arg9-NPEG4-(KETLV)2 (24)
CA-L-Arg9-NPEG4-(KETVV)2 (26)
CA-L-Arg9-NPEG4-(KETRV)2 (28)
CA-L-Arg9--NPEG4-(ISTDV)2 (30)
CA-L-Arg9--NPEG4-(VETVV)2 (32)
CA-L-Arg9--NPEG4-(VETVV)2 (34)

Fig. 7

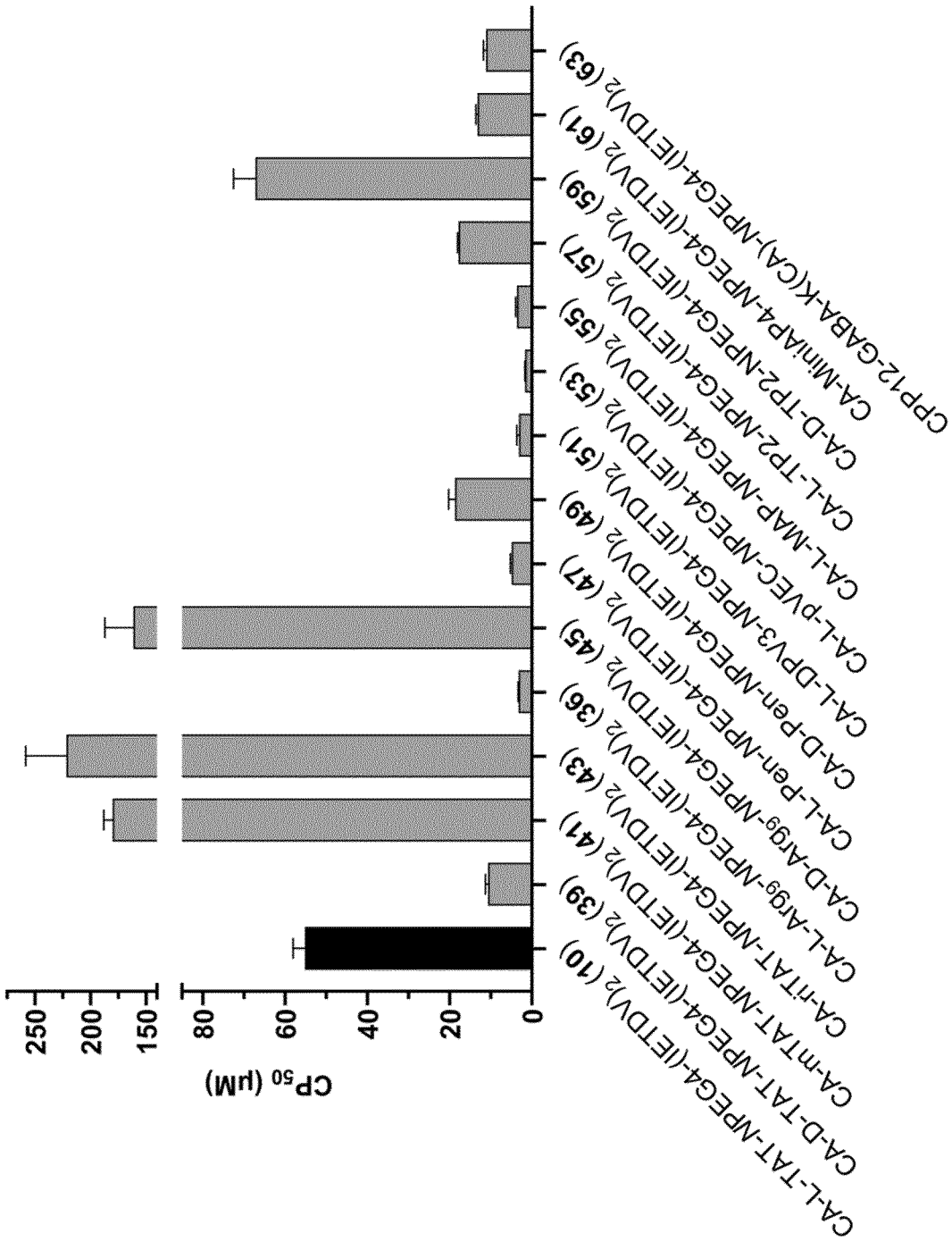

CP50 (μM)
0
20
40
60
80
150
200
250
CA-L-TAT-NPEG4-(IETDV)2 (10)
CA-D-TAT-NPEG4-(IETDV)2 (39)
CA-mTAT-NPEG4-(IETDV)2 (41)
CA-rTAT-NPEG4-(IETDV)2 (43)
CA-L-Arg9-NPEG4-(IETDV)2 (36)
CA-D-Arg9-NPEG4-(IETDV)2 (45)
CA-L-Pen-NPEG4-(IETDV)2 (47)
CA-D-Pen-NPEG4-(IETDV)2 (49)
CA-L-DPV3-NPEG4-(IETDV)2 (51)
CA-L-pVEC-NPEG4-(IETDV)2 (53)
CA-L-MAP-NPEG4-(IETDV)2 (55)
CA-D-TP2-NPEG4-(IETDV)2 (57)
CA-L-TP2-NPEG4-(IETDV)2 (59)
CA-MiniAP4-NPEG4-(IETDV)2 (61)
CPP12-GABA-K(CA)-NPEG4-(IETDV)2 (63)

Fig. 8

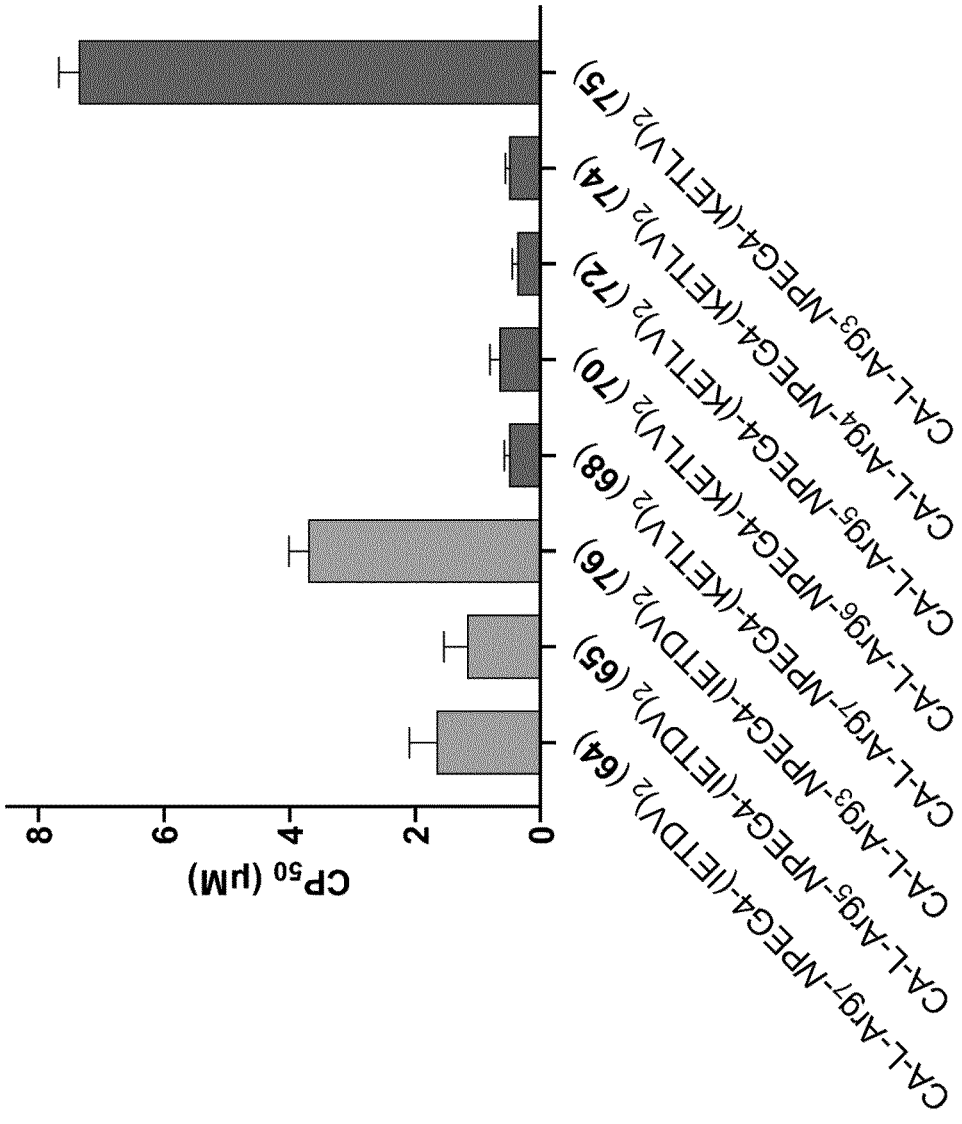

CP50 (μM)
0
2
4
6
8
CA-L-Arg7-NPEG4-(IETDV)2 (64)
CA-L-Arg5-NPEG4-(IETDV)2 (65)
CA-L-Arg3-NPEG4-(IETDV)2 (76)
CA-L-Arg7-NPEG4-(KETLV)2 (68)
CA-L-Arg6-NPEG4-(KETLV)2 (70)
CA-L-Arg5-NPEG4-(KETLV)2 (72)
CA-L-Arg4-NPEG4-(KETLV)2 (74)
CA-L-Arg3-NPEG4-(KETLV)2 (75)

Fig. 9

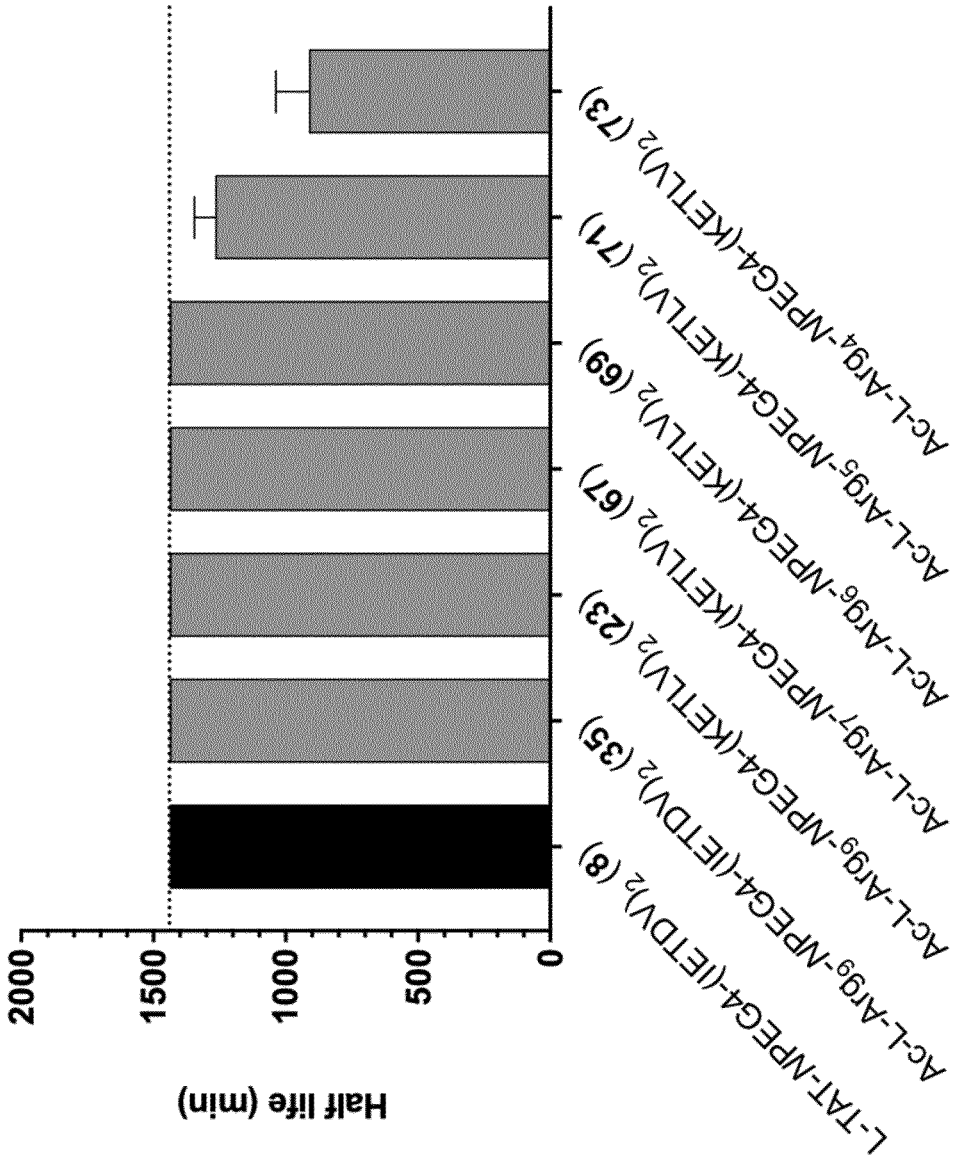

Half life (min)
2000
1500
1000
500
0
L-TAT-NPEG4-(IETDV)2 (8)
Ac-L-Ar9-NPEG4-(IETDV)2 (35)
Ac-L-Ar9-NPEG4-(KETLV)2 (23)
Ac-L-Ar97-NPEG4-(KETLV)2 (67)
Ac-L-Ar96-NPEG4-(KETLV)2 (69)
Ac-L-Ar95-NPEG4-(KETLV)2 (71)
Ac-L-Ar94-NPEG4-(KETLV)2 (73)

Fig. 10

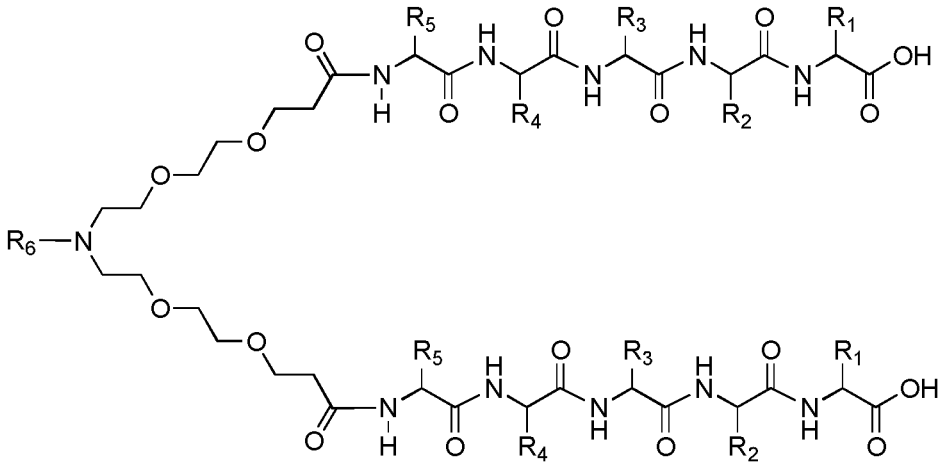


Fig. 11

PSD-95 INHIBITORS AND USES THEREOF

FIELD OF INVENTION

[0001] The present invention relates to compounds capable of binding to the PDZ domains of PSD-95 and their medical use as inhibitors of protein-protein interaction mediated by PSD-95.

BACKGROUND

[0002] PSD-95 is a scaffolding protein in neuronal synapses that interacts with N-methyl-D-aspartate (NMDA) receptors (Kornau et al. 1995) and neuronal nitric oxide synthase (nNOS) through its PSD-95/Discs-large/ZO-1 (PDZ) domains. During cerebral ischemia, excessive glutamate release leads to hyperactivation of the NMDA receptors and harmful elevation of intracellular levels of Ca^{2+} and NO, which ultimately induces excitotoxicity, leading to neuronal death and brain damage (Aarts et al., 2002; Dawson et al., 1991; Huang et al., 1994; Sattler et al., 1999). PSD-95 is being explored as a drug target in acute ischemic stroke (AIS) and related ischemic conditions in the brain.

[0003] The 20-mer peptide nerinetide (also known as Tat-NR2B9c or NA-1) was recently examined in a Phase 3 clinical trial ESCAPE-NA1 (Hill et al., 2020), which evaluated whether treatment with nerinetide, in addition to standard of care such as alteplase (tissue plasminogen activator, tPA), would improve clinical outcomes for patients with ischemic stroke and who were undergoing endovascular thrombectomy (Hill et al., 2020).

[0004] A total of 1105 patients were included in the study, where 659 patients received tPA treatment, and 446 patients did not. It was found that, while nerinetide was not effective in patients receiving alteplase, in the group not receiving alteplase, nerinetide resulted in improved functional outcomes, reduced mortality, and reduced infarction volumes (Hill et al., 2020). It was recently demonstrated that the lack of effect in the tPA-treated group could be explained by a drug-drug interaction between nerinetide and tPA. Specifically, tPA generates plasmin, a serine protease which cleaves nerinetide (Mayor-Nunez et al. 2021). Thus, it is highly advantageous that a drug is compatible with administration of thrombolytic agents, which is standard of care for AIS.

[0005] Nerinetide suffers from a relatively low affinity to the target PSD-95, which has prompted the design of dimeric compounds such as Tat-N-dimer and O-dimer, also known as UCCB01-144 (AB144) and UCCB01-125, respectively (Bach et al., 2009, 2012; WO 2010/004003, WO 2012/156308; Kucharz et al., 2017). In an in vitro fluorescence polarization (FP) assay the K_i values of nerinetide towards PDZ1 and PDZ2 of PSD-95 were 5-10 μM (Bach et al., 2012). In contrast, AB144 and UCCB01-125, due to their dimeric structures and bivalent properties, bind PDZ1 and PDZ2 of PSD-95 simultaneously, leading to a 500-1000-fold higher affinity towards PDZ1-2 (K_i values of 4.6 and 9.5 nM, respectively) relative to that of monomeric nerinetide (Bach et al., 2012). In mice that underwent permanent middle cerebral artery occlusion (pMCAO), a single intravenous (i.v.) bolus injection of AB144 (3 nmol/g) given 30 min post-ischemia reduced the infarct volumes by 40% and 37% at 6 h and 48 h of the post-ischemic survival period, respectively, compared to the effect of saline (Bach et al., 2012). Furthermore, functional outcomes such as grip strength and rotarod performance were improved and thus correlated with reductions in infarct size. Under the same experimental conditions and dose (3 nmol/g), nerinetide did not show significant neuroprotective properties (Bach et al., 2012). Likewise, UCCB01-125 without the Tat moiety did not reach the brain and showed no neuroprotective properties (Bach et al., 2012).

[0006] PSD-95 is therefore considered a particular promising drug target for the treatment of acute conditions such as subarachnoid hemorrhage (SAH) and AIS. Importantly, PSD-95 is located intracellularly, thus any drug targeting PSD-95 needs to efficiently cross the cell membrane and bind to PSD-95.

SUMMARY

[0007] The present inventors have developed a series of novel compounds with high affinity for PSD-95. As compared to known PSD-95 inhibitors like nerinetide, the compounds of the present invention have improved cellular uptake and much higher plasmin stability. Thus, the compounds of the present invention are useful in the treatment of excitotoxic-related diseases such as AIS and SAH, and are compatible with standard of care, such as thrombolytic agents.

[0008] In one aspect, the present invention relates to a compound comprising:

[0009] a. a first peptide (P_1) comprising or consisting of the amino acid sequence

[0010] X_2TX_3V (SEQ ID NO: 53), wherein

[0011] X_2 is selected from the group consisting of E and S;

[0012] X_3 is selected from the group consisting of L, T, V, R and D;

[0013] b. a second peptide (P_2) comprising or consisting of the amino acid sequence X_5TX_6V (SEQ ID NO: 55), wherein

[0014] X_5 is selected from the group consisting of E and S;

[0015] X_6 is selected from the group consisting of L, T, V, R and D; and

[0016] c. a Cell Penetrating Peptide (CPP) selected from the group consisting of:

[0017] i. a poly-L-arginine peptide (poly-Arg) consisting of 3 to 20 L-arginine residues;

ii. (SEQ ID NO: 9, D-TAT) yGrkkrrqrrr

iii. (SEQ ID NO: 14, L-Pen) RQIKIWFQNRRMKWKK;

iv. (SEQ ID NO: 15, D-Pen) rqikiwfqnrrmkwkk;

v. (SEQ ID NO: 17, L-DPV3) RKKRRRESRKKRRRES;

vi. (SEQ ID NO: 18, L-pVEC) LLIILRRRIRKQAHAHSK;

-continued

vii.
(SEQ ID NO: 16, L-MAP)
KLALKLALKALKAALKLA;

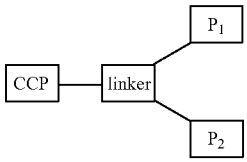
viii.
(SEQ ID NO: 19, L-TP2)
PLIYLRLLRGQF;

ix.
(SEQ ID NO: 21, MiniAp4)
|(Dap)KAPETALD|;
and

x.
(SEQ ID NO: 22, CPP12)
|Ff(Nal2)RrRrQ|GABA-K,

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 compound has the general structure of Formula (I):

Formula (I)



or a pharmaceutically acceptable salt thereof.

[0018] In another aspect, the present invention relates to a compound as defined herein for use as a medicament.

[0019] In another aspect, the present invention relates to a compound as defined herein for use in treating, preventing, reducing and/or delaying development of an excitotoxic-related disease such as stroke, for example selected from acute ischemic stroke and subarachnoid hemorrhage.

[0020] In a further aspect, the present invention relates to a compound as defined herein for use in the treatment or prophylaxis of pain.

[0021] Furthermore, the present invention relates to a method for manufacturing a compound as defined herein.

DESCRIPTION OF DRAWINGS

[0022] FIG. **1**. Affinity of O-PEG_4 dimers (compounds 1 to 7) towards PSD-95 PDZ1-2 as determined by FP. Data presented as mean+SEM, n=3.

[0023] FIG. **2**. Affinity of dimeric ligands fused to Ac-TAT and Ac-polyArg towards PSD-95 PDZ1-2 as determined by FP. Data presented as mean+SEM, n=3.

[0024] FIG. **3**. Affinity of N-PEG_4(IETDV)$_2$ fused to various CPP-tags (SEQ IDs 8 to 22) towards PSD-95 PDZ1-2 as determined by FP. Data presented as mean+SEM, n=3.

[0025] FIG. **4**. Affinity of NPEG$_4$-(KETLV)$_2$ dimeric ligands fused to polyArg CPP-tags towards PSD-95 PDZ1-2 as determined by FP. Data presented as mean+SEM, n=3.

[0026] FIG. **5**. Half-life of dimeric ligands fused to Ac-TAT and Ac-polyArg as determined in in vitro plasmin stability assay. Data presented as mean+SEM, n=3.

[0027] FIG. **6**. Half-life of N-PEG_4(IETDV)$_2$ fused to various CPP-tags (SEQ IDs 8 to 22) as determined in in vitro plasmin stability assay. Data presented as mean+SEM, n=3.

[0028] FIG. **7**. Cellular uptake of dimeric ligands fused to Ac-TAT and Ac-polyArg as determined by CAPA. Data presented as mean+SEM, n=3.

[0029] FIG. **8**. Cellular uptake of N-PEG_4(IETDV)$_2$ fused to various CPP-tags (SEQ IDs 8 to 22) as determined by CAPA. Data presented as mean+SEM, n=3.

[0030] FIG. **9**. Cellular uptake of N-PEG_4(IETDV)$_2$ and N-PEG_4(KETLV)$_2$ fused to various polyArg CPP-tags as determined by CAPA. Data presented as mean+SEM, n=3.

[0031] FIG. **10**. Half-life of N-PEG_4(IETDV)$_2$ and N-PEG_4(KETLV)$_2$ fused to polyArg CPP-tags as determined in human plasma stability assay. Data presented as mean±SEM, n=3.

[0032] FIG. **11**. Generic structure of compounds binding to PDZ1-2 of PSD-95. R_1 through R_5 are amino acid side-chains as described herein and R_6 represents a CPP-tag as described herein.

DETAILED DESCRIPTION

Definitions

[0033] Amide bond: The term 'amide bond' as used herein is a chemical bond formed by a reaction between a carboxylic acid and an amine (and concomitant elimination of water).

[0034] Where the reaction is between two amino acid residues, the bond formed as a result of the reaction is known as a peptide linkage (peptide bond).

[0035] Comprising: The term 'comprising' as used herein should be understood in an inclusive manner. Hence, by way of example, a composition comprising compound X, may comprise compound X and optionally additional compounds.

[0036] Dimer: The term dimer as used herein refers to two identical or non-identical chemical moieties associated by chemical or physical interaction. By way of example, the dimer can be a homodimer such as two identical chemical moieties linked by a linker. The dimer may also be a heterodimer such as two different chemical moieties linked by a linker. An example of a dimer is a PSD-95 inhibitor of the present invention which is a compound comprising two peptides that are covalently linked by means of a linker, wherein the peptides are capable of binding to, or interacting with, PDZ1 and PDZ2 domains of PSD-95 simultaneously.

[0037] Dipeptide: The term 'dipeptide' as used herein refers to two natural or non-natural amino acids linked by a peptide bond.

[0038] Fatty acid: The term fatty acid (abbreviated FA) as used herein typically refers to a carboxylic acid with a long aliphatic carbon chain, which can be either saturated or unsaturated. The fatty acid can be selected from Short-chain fatty acids (SCFA), Medium-chain fatty acids (MCFA), Long-chain fatty acids (LCFA) and Very long chain fatty acids (VLCFA). Short-chain fatty acids (SCFA) are fatty acids with aliphatic tails of fewer than six carbons (i.e. butyric acid). Medium-chain fatty acids (MCFA) are fatty acids with aliphatic tails of 6-12 carbons, which can form medium-chain triglycerides. Long-chain fatty acids (LCFA) are fatty acids with aliphatic tails 13 to 21 carbons. Very long chain fatty acids (VLCFA) are fatty acids with aliphatic tails longer than 22 carbons. The fatty acid of the present invention can be any suitable fatty acid or fatty acid derivative known by those of skill in the art.

[0039] Non-proteinogenic amino acids: Non-proteinogenic amino acids also referred to as non-coded, non-standard or non-natural amino acids are amino acids which are not encoded by the genetic code. A non-exhaustive list

of non-proteinogenic amino acids include γ-aminobutyric acid, L-3-(2-naphthyl)alanine, L-2,3-diaminopropionic acid, α-amino-n-butyric acid, norvaline, norleucine, isoleucine, alloisoleucine, tert-leucine, α-amino-n-heptanoic acid, pipecolic acid, α,β-diaminopropionic acid, α,γ-diaminobutyric acid, ornithine, allothreonine, homocysteine, homoserine, β-alanine, β-amino-n-butyric acid, β-aminoisobutyric acid, α-aminoisobutyric acid, isovaline, sarcosine, N-ethyl glycine, N-propyl glycine, N-isopropyl glycine, N-methyl alanine, N-ethyl alanine, N-methyl β-alanine, N-ethyl β-alanine, isoserine and α-hydroxy-γ-aminobutyric acid.

[0040] Proteinogenic amino acids: Proteinogenic amino acids, also referred to as natural amino acids, include alanine, cysteine, selenocysteine, aspartic acid, glutamic acid, phenylalanine, glycine, histidine, isoleucine, lysine, leucine, methionine, asparagine, proline, pyrrolysine, glutamine, arginine, serine, threonine, valine, tryptophan and tyrosine. Capital letter abbreviations indicate L-amino acids, whereas lower case letter abbreviations indicate D-amino acids.

[0041] PDZ: The term 'PDZ' as used herein refers to Postsynaptic density protein-95 (PSD-95), *Drosophila* homologue discs large tumor suppressor (DlgA), Zonula occludens-1 protein (zo-1).

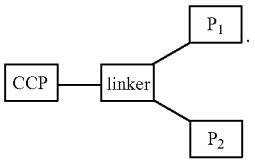
[0042] PSD-95: The term 'PSD-95' as used herein refers to postsynaptic density protein-95.

[0043] PSD-95 inhibitor: The term 'PSD-95 inhibitor' as used herein refers to a compound that binds to PDZ1, PDZ2, or both PDZ1 and PDZ2 of PSD-95 and inhibits the protein-protein interactions facilitated by these PDZ domains in a cell. An example of an interaction that is inhibited by a PSD-95 inhibitor is the ternary complex formation between nNOS, PSD-95 and the NMDA receptor.

Compounds

[0044] In one aspect, the present invention concerns a compound comprising a first peptide (P_1) linked to a Cell Penetrating Peptide (CPP). In one embodiment, P_1 is linked to the CPP via a linker. In one embodiment, the compound further comprises a second peptide (P_2). In one embodiment, the CPP is linked to P_1 and P_2 via the linker. Thus, in one embodiment, the CPP, is linked to the linker via its C-terminal, and P_1 and P_2 are conjugated to a linker via their N-termini, and the compound has the following general structure of Formula (I):

Formula (I)



[0045] Thus, in one embodiment, the compound of the present invention comprises a first peptide (P_1) and a second peptide (P_2), wherein both P_1 and P_2 are able to simultaneously bind to the PDZ1 and PDZ2 domains of PSD-95, i.e. the compound is a dimeric PSD-95 inhibitor.

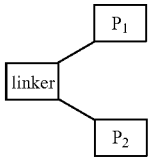
[0046] In one aspect, the present invention concerns a compound comprising a peptide (P_1) comprising or consisting of the amino acid sequence X_2TX_3V (SEQ ID NO: 53), wherein

[0047] a. X_2 is selected from the group consisting of E and S; and

[0048] b. X_3 is selected from the group consisting of L, T, V, R and D, and wherein P_1 is linked to a Cell Penetrating Peptide (CPP).

[0049] In a further aspect, the present invention relates to a compound comprising a first peptide (P_1) linked to a second peptide (P_2) via a linker, such as the compound having the general structure of Formula (XXIV):

Formula (XXIV)



wherein the linker, P_1 and P_2 are as defined herein. Preferably, P_1 and P_2 comprise or consist of KETLV (SEQ ID NO: 2), KETTV (SEQ ID NO: 3), KETVV (SEQ ID NO: 4), KETRV (SEQ ID NO: 5), ISTDV (SEQ ID NO: 6) or VETVV (SEQ ID NO: 7). Optionally, the linker is further conjugated to a Cell Penetrating Peptide (CPP) or an albumin binding moiety, thereby increasing passage of the peptide across a membrane or the blood brain barrier. The albumin binding moiety can be any suitable chemical group binding albumin.

[0050] Preferably, the albumin binding moiety is a fatty acid. In one embodiment, the linker is further conjugated to a CPP, i.e. the compound has the general structure of Formula (I).

[0051] In one aspect, the present invention relates to a compound comprising:

[0052] a. a first peptide (P_1) comprising or consisting of the amino acid sequence

[0053] X_2TX_3V (SEQ ID NO: 53), wherein

[0054] X_2 is selected from the group consisting of E and S;

[0055] X_3 is selected from the group consisting of L, T, V, R and D;

[0056] b. a second peptide (P_2) comprising or consisting of the amino acid sequence X_5TX_6V (SEQ ID NO: 55), wherein

[0057] X_5 is selected from the group consisting of E and S;

[0058] X_6 is selected from the group consisting of L, T, V, R and D; and

[0059] c. a Cell Penetrating Peptide (CPP) selected from the group consisting of:

[0060] i. a poly-L-arginine peptide (poly-Arg) consisting of 3 to 20 L-arginine residues;

ii.

yGrkkrrqrrr (SEQ ID NO: 9, D-TAT)

iii.

RQIKIWFQNRRMKWKK; (SEQ ID NO: 14, L-Pen)

-continued

iv.
(SEQ ID NO: 15, D-Pen)
rqikiwfqnrrmkwkk;

v.
(SEQ ID NO: 17, L-DPV3)
RKKRRRESRKKRRRES;

vi.
(SEQ ID NO: 18, L-pVEC)
LLIILRRRIRKQAHAHSK;

vii.
(SEQ ID NO: 16, L-MAP)
KLALKLALKALKAALKLA;

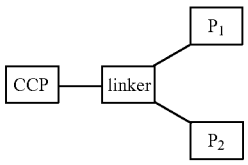
viii.
(SEQ ID NO: 19, L-TP2)
PLIYLRLLRGQF;

ix.
(SEQ ID NO: 21, MiniAp4)
|(Dap)KAPETALD|;
and

x.
(SEQ ID NO: 22, CPP12)
|Ff(Nal2)RrRrQ|GABA-K,

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 compound has the general structure of Formula (I):

Formula (I)



or a pharmaceutically acceptable salt thereof.

Binding Peptides P_1 and P_2

[0061] The peptides P_1 and P_2 have high affinity for PDZ1 and PDZ2 domains of PSD-95. In one embodiment, the compound is a PSD-95 inhibitor, i.e. the compound is capable of binding to one or more of the PDZ domains of PSD-95.

[0062] In one embodiment, the compound comprises a first peptide (P_1) comprising or consisting of the amino acid sequence X_2TX_3V (SEQ ID NO: 53), wherein

[0063] a. X_2 is selected from the group consisting of E and S; and b. X_3 is selected from the group consisting of L, T, V, R and D.

[0064] In one embodiment, P_1 comprises or consists of the sequence $X_1X_2TX_3V$ (SEQ ID NO: 54), wherein

[0065] a. X_1 is selected from the group consisting of K, V and I;

[0066] b. X_2 is selected from the group consisting of E and S; and

[0067] c. X_3 is selected from the group consisting of L, T, V, R and D.

[0068] In one embodiment, P_1 comprises or consists of IETDV (SEQ ID NO: 1). In one embodiment, P_1 comprises or consists of KETLV (SEQ ID NO: 2). In one embodiment, P_1 comprises or consists of KETTV (SEQ ID NO: 3). In one embodiment, P_1 comprises or consists of KETVV (SEQ ID NO: 4). In one embodiment, P_1 comprises or consists of KETRV (SEQ ID NO: 5). In one embodiment, P_1 comprises or consists of ISTDV (SEQ ID NO: 6). In one embodiment, P_1 comprises or consists of VETVV (SEQ ID NO: 7).

[0069] In one embodiment, P_1 consists of 4 to 10 amino acid residues, such as 5 amino acid residues, such as 6 amino acid residues. The amino acid residues in excess of the amino acid residues given in SEQ ID NO: 53 or SEQ ID NO: 54 may be proteinogenic or non-proteinogenic amino acids.

[0070] In one embodiment, the compound further comprises a second peptide (P_2) comprising or consisting of the amino acid sequence X_5TX_6V (SEQ ID NO: 55), wherein

[0071] a. X_5 is selected from the group consisting of E and S; and

[0072] b. X_6 is selected from the group consisting of L, T, V, R and D.

[0073] In one embodiment, P_2 comprises or consists of the sequence $X_4X_5TX_6V$ (SEQ ID NO: 56), wherein

[0074] a. X_4 is selected from the group consisting of K, V and I;

[0075] b. X_5 is selected from the group consisting of E and S; and

[0076] c. X_6 is selected from the group consisting of L, T, V, R and D.

[0077] In one embodiment, P_2 comprises or consists of IETDV (SEQ ID NO: 1). In one embodiment, P_2 comprises or consists of KETLV (SEQ ID NO: 2). In one embodiment, P_2 comprises or consists of KETTV (SEQ ID NO: 3). In one embodiment, P_2 comprises or consists of KETVV (SEQ ID NO: 4). In one embodiment, P_2 comprises or consists of KETRV (SEQ ID NO: 5). In one embodiment, P_2 comprises or consists of ISTDV (SEQ ID NO: 6). In one embodiment, P_2 comprises or consists of VETVV (SEQ ID NO: 7).

[0078] In one embodiment, P_2 consists of 4 to 10 amino acid residues, such as 5 amino acid residues, such as 6 amino acid residues. The amino acid residues in excess of the amino acid residues given in SEQ ID NO: 55 or SEQ ID NO: 56 may be proteinogenic or non-proteinogenic amino acids.

[0079] In one embodiment, P_1 and P_2 are identical.

[0080] In one embodiment, when X_2 is E, then X_3 is not D. In one embodiment, when X_5 is E, then X_6 is not D. In one embodiment, P_1 and/or P_2 are not IETDV (SEQ ID NO: 1).

[0081] In a preferred embodiment, the peptides P_1 and P_2 are conjugated via their N-termini to a linker or a CPP. In one embodiment, the amino acid sequence X_2TX_3V (SEQ ID NO: 53) is the C-terminal of P_1. In one embodiment, the amino acid sequence X_5TX_6V (SEQ ID NO: 55) is the C-terminal of P_2.

Cell Penetrating Peptide (CPP)

[0082] The compounds of the present invention comprises a peptide P_1 linked to a Cell Penetrating Peptide (CPP). A CPP is characterised by the ability to cross the blood brain barrier (BBB) and/or the plasma membrane of mammalian cells, and thereby may give rise to the intracellular delivery of cargo molecules, such as peptides, proteins, oligonucleotides to which it is linked.

[0083] In one embodiment, the CPP is a poly-L-arginine peptide (poly-Arg). In one embodiment, the poly-Arg consists of 3 to 20 L-arginine residues. In one embodiment, the poly-Arg consists of 5 to 10 L-arginine residues, such as 7 to 10 L-arginine residues, such as 8 or 9 L-arginine residues. In one embodiment, the poly-Arg consists of 3 to 10 L-arginine residues. In one embodiment, the CPP comprises or consists of the amino acid sequence RRRRRRRRR

(L-Arge, SEQ ID NO: 12). In one embodiment, the CPP comprises or consists of the amino acid sequence RRRRRRRR (L-Arg_8, SEQ ID NO: 57). In one embodiment, the CPP comprises or consists of the amino acid sequence RRRRRRR (L-Arg_7, SEQ ID NO: 58). In one embodiment, the CPP comprises or consists of the amino acid sequence RRRRRR (L-Arg_8, SEQ ID NO: 59). In one embodiment, the CPP comprises or consists of the amino acid sequence RRRRR (L-Arg_8, SEQ ID NO: 60). In one embodiment, the CPP comprises or consists of the amino acid sequence RRRR (L-Arg_4, SEQ ID NO: 61). In one embodiment, the CPP comprises or consists of the amino acid sequence RRR (L-Arg_3).

[0084] In one embodiment, the CPP is selected from the CPPs given in table 1.

TABLE 1

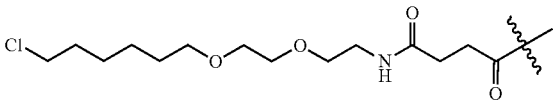
Cell Penetrating Peptides.

Name	Sequence	SEQ ID NO:
L-TAT	YGRKKRRQRRR	8
D-TAT	yGrkkrrqrrr	9
mTAT	rRrGrKkRr	10
riTAT	rrrqrrkkr	11
L-Arg_9	RRRRRRRRR	12
L-Arg_8	RRRRRRRR	57
L-Arg_7	RRRRRRR	58
L-Arg_6	RRRRRR	59
L-Arg_5	RRRRR	60
L-Arg_4	RRRR	61
L-Arg_3	RRR	
D-Arg_9	rrrrrrrrr	13
L-Pen	RQIKIWFQNRRMKWKK	14
D-Pen	rqikiwfqnrrmkwkk	15
L-MAP	KLALKLALKALKAALKLA	16
L-DPV3	RKKRRRESRKKRRRES	17
L-pVEC	LLIILRRRIRKQAHAHSK	18
L-TP2	PLIYLRLLRGQF	19
D-TP2	pliylrilrGqf	20
MiniAp4	|(Dap)KAPETALD|	21
CPP12	|Ff(Nal2)RrRrQ|GABA-K	22

[0085] In one embodiment, the CPP comprises a peptide selected from the group consisting of poly-L-arginine peptide (poly-Arg), such as L-Arg_8; D-TAT; L-Pen; D-Pen; L-DPV3; L-pVEC; L-MAP; L-TP2; MiniAp4 and CPP12. In one embodiment, the CPP is selected from the group consisting of poly-L-arginine peptide (poly-Arg), such as L-Arg_8; D-TAT; L-Pen; D-Pen; L-DPV3; L-pVEC; L-MAP; L-TP2; MiniAp4 and CPP12. In one embodiment, the CPP is D-TAT. In one embodiment, the CPP is L-Pen. In one embodiment, the CPP is D-Pen. In one embodiment, the CPP is L-DPV3. In one embodiment, the CPP is L-pVEC. In one embodiment, the CPP is L-MAP. In one embodiment, the CPP is L-TP2. In one embodiment, the CPP is MiniAp4. In one embodiment, the CPP is CPP12.

[0086] In one embodiment, the CPP comprises no more than 20 amino acid residues, such as no more than 19, such as no more than 18, such as no more than 17, such as no more than 16, such as no more than 15, such as no more than 14, such as no more than 13, such as no more than 12, such as no more than 11, such as no more than 10, such as no more than 9, such as no more than 8, such as no more than 7 amino acid residues.

[0087] In some embodiments, the CPP is conjugated to a non-peptide moiety. For example, the CPP may be methylated or acetylated. In some embodiments, when a peptide is defined herein to consist of a specific sequence of amino acid residues, said peptide is not conjugated to any other amino acid residue but said peptide may be conjugated to a non-peptide moiety, as long as the conjugation to a non-peptide moiety does not render another amino acid sequence. In some embodiments, the N-terminal of the CPP is conjugated to a non-peptide moiety. In some embodiments, the C-terminal of the CPP is conjugated to a non-peptide moiety. In some embodiments, the N-terminal of the CPP is acetylated i.e. bound to the chemical structure $CH_3C(O)$—. For example, the CPP may be a poly-Arg peptide consisting of nine L-arginine residues that is acetylated in the N-terminal. In some embodiments, the N-terminal of the CPP is conjugated to a chloroalkane tag (CA), which has the structure of:

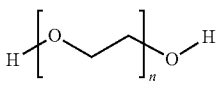


[0088] In one embodiment, the N-terminal of the CPP is methylated. In another embodiment, the N-terminal of the CPP is formylated.

Linker

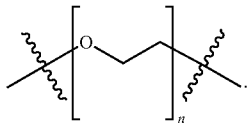
[0089] The term 'linker' as used herein refers to one or more atoms forming a connection from one chemical entity to another. By way of example, the 'linker' referred to herein may join the two PDZ-domain binding peptides P_1 and P_2 by forming a link to each of their N-termini. Various linkers are known in the art. The linker may for example be a chemical linker or a peptide linker, or a combination thereof. In one embodiment, the linker comprises an active functional group, such as an electrophilic or nucleophilic functional group, which can be used to attach the linker to each peptide.

[0090] In one embodiment, the linker comprises one or more polyethylene glycol (PEG) units. PEG is a polymer of ethylene glycol having the chemical formula $C_{2n}H_{4n+2}O_{n+1}$, and the repeating structure:



where n is an integer.

[0091] A PEG unit thus has the following structure:



[0092] For example, a polymer consisting of 4 PEG moieties, or PEG4, corresponds to a polymer of 4 ethylene glycol moieties (n=4).

[0093] The terms "PEG unit" and "PEG moiety" are used interchangeably herein.

[0094] In one embodiment, at least one oxygen atom of one of the PEG units is replaced with a nitrogen atom to give NPEG. The term 'ethylene glycol moiety' as used herein refers to the structural unit that constitutes a PEG or NPEG linker.

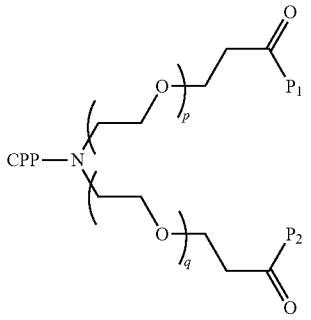
[0095] In one embodiment, the N-termini of the two PDZ-domain binding peptides P_1 and P_2 are linked to each other via a linker comprising one or more PEG units, wherein at least one oxygen atom of the PEG units is optionally replaced with a nitrogen atom. In one embodiment, P_1 and/or P_2 are individually bound to the PEG/NPEG units via a spacer group, such as via a short alkane chain.

[0096] In one embodiment, 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.

[0097] In one embodiment, the linker comprises a NPEG unit and the CPP is linked to the linker via a chemical bond either directly or indirectly to the nitrogen atom in the backbone of the NPEG linker. Linkage of the CPP to the nitrogen of the NPEG linker may be mediated via an amide bond, a 1,3-dipolar cycloaddition such as copper catalyzed azide-alkyne cycloaddition, a maleimide coupling, a disulfide bond, or amino-reactive electrophilic groups, selected from among N-hydroxysuccinimide (NHS) ester, p-nitrophenyl ester, succinimidyl carbonate, p-nitrophenyl carbonate, succinimidyl urethane, isocyanate, isothiocyanate, acyl azide, sulfonyl chloride, aldehyde, carbonate, imidioester or anhydride; and thio-reactive groups selected from among haloacetyl, alkyl halide derivatives, aziridine, acryloyl derivatives arylating agents. In one embodiment, 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. Alternatively, linkage of the CPP to the nitrogen of the linker comprising a NPEG unit may be mediated via a spacer group, where a suitable spacer group can for example be any amino acid(s); short alkane chains or short PEG/NPEG chains.

[0098] In one embodiment, the linker comprises a NPEG unit and the CPP is linked to the nitrogen atom of the linker by an amide bond. For example, in one embodiment, the compound has the general structure of Formula (III):

Formula (III)



[0099] wherein

[0100] CPP, P_1 and P_2 are as defined herein;

[0101] p is an integer 0 to 10; and

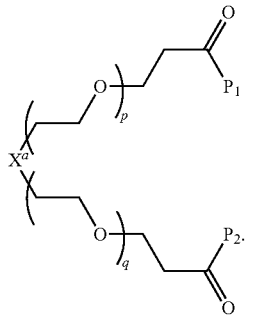
[0102] q is an integer 0 to 10.

[0103] In one embodiment, p=q. In one embodiment, p>q. In one embodiment, p<q. In one embodiment, the sum of p and q is an integer between 1 and 20. In one embodiment, p is an integer selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10. In one embodiment, p is an integer of 0 to 4. In one embodiment, q is an integer selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10. In one embodiment, q is an integer of 0 to 4. In one embodiment, the total number of ethylene glycol moieties p+q is between 2 and 12, such as 2, such as 4, such as 6, such as 8, such as 10, such as 12. In one embodiment, the total number of ethylene glycol moieties p+q is 4. In one embodiment, p is 2 and q is 2.

Overall dimeric structure

[0104] In one embodiment, the compound has the general structure of Formula (XXV):

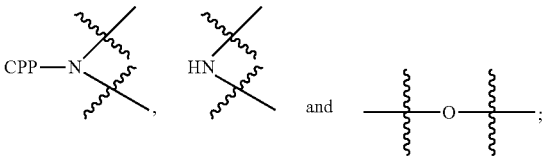
Formula (XXV)



wherein

[0105] P_1 and P_2 are as defined herein;

[0106] X^a is selected from the group consisting of



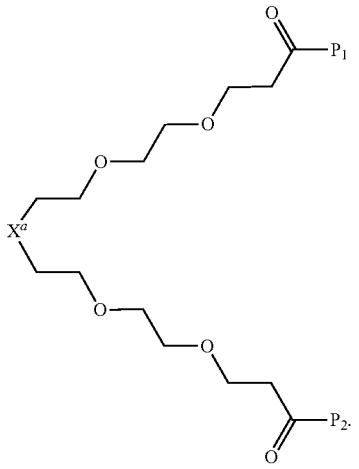
[0107] CPP is as defined herein;

[0108] p is an integer 0 to 10; and

[0109] q is an integer 0 to 10.

[0110] In one embodiment, p and q are 2, and the compound has the general structure of Formula (XXVI):

Formula (XXVI)



[0111] In one embodiment, the compound is of Formula (XXVI) wherein X^a is —O— and P_1 and P_2 are KETLV (SEQ ID NO: 2), thus forming compound 2, i.e. $OPEG_4$-$(KETLV)_2$.

[0112] In one embodiment, the compound is of Formula (XXVI) wherein X^a is —O— and P_1 and P_2 are KETTV (SEQ ID NO: 3), thus forming compound 3, i.e. $OPEG_4$-$(KETTV)_2$.

[0113] In one embodiment, the compound is of Formula (XXVI) wherein X^a is —O— and P_1 and P_2 are KETVV (SEQ ID NO: 4), thus forming compound 4, i.e. $OPEG_4$-$(KETVV)_2$.

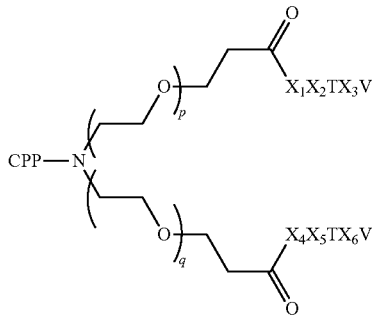
[0114] In one embodiment, the compound is of Formula (XXVI) wherein X^a is —O— and P_1 and P_2 are KETRV (SEQ ID NO: 5), thus forming compound 5, i.e. $OPEG_4$-$(KETRV)_2$.

[0115] In one embodiment, the compound is of Formula (XXVI) wherein X^a is —O— and P_1 and P_2 are ISTDV (SEQ ID NO: 6), thus forming compound 6, i.e. $OPEG_4$-$(ISTDV)_2$.

[0116] In one embodiment, the compound is of Formula (XXVI) wherein X^a is —O— and P_1 and P_2 are VETVV (SEQ ID NO: 7), thus forming compound 7, i.e. $OPEG_4$-$(VETVV)_2$.

[0117] In one embodiment, the compound has the general structure of Formula (V):

Formula (V)



wherein

[0118] CPP is as defined herein;

[0119] X_1 is selected from the group consisting of K, V and I;

[0120] X_2 is selected from the group consisting of E and S; and

[0121] X_3 is selected from the group consisting of L, T, V, R and D.

[0122] X_4 is selected from the group consisting of K, V and I;

[0123] X_5 is selected from the group consisting of E and S;

[0124] X_6 is selected from the group consisting of L, T, V, R and D.

[0125] p is an integer 0 to 10; and

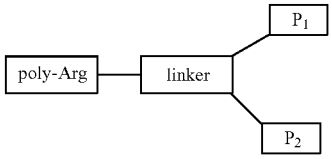
[0126] q is an integer 0 to 10.

[0127] The compound of Formula (V) wherein p and q are 2 is further depicted in FIG. **11**. R_1 through R_5 are amino acid side-chains of the peptides $X_1X_2TX_3V$ (SEQ ID NO: 54) and $X_4X_5TX_6V$ (SEQ ID NO: 56), and R_s represents a CPP-tag as described herein.

Poly-Arg as CPP

[0128] In one embodiment, the CPP is a poly-L-arginine peptide (poly-Arg). Thus, in one embodiment, the compound has the following general structure of Formula (II):

Formula (II)



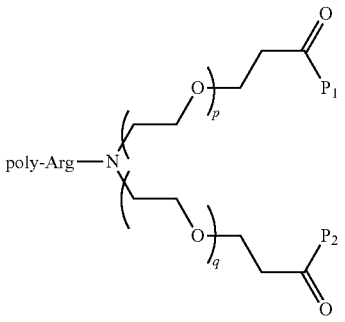
wherein poly-Arg, linker, P_1 and P_2 are as defined herein.

[0129] In one embodiment, the CPP is a poly-L-arginine peptide (poly-Arg) consisting of 3 to 20 L-arginine residues. In one embodiment, the CPP is a poly-L-arginine peptide (poly-Arg) consisting of 3 to 15 L-arginine residues. In one embodiment, the CPP is a poly-L-arginine peptide (poly-Arg) consisting of 3 to 12 L-arginine residues. In one embodiment, the CPP is a poly-L-arginine peptide (poly-Arg) consisting of 3 to 10 L-arginine residues. In one embodiment, the N-terminal of the poly-Arg is optionally modified, such as optionally acetylated.

[0130] Compounds of the present invention with poly-Arg CPP-tags, such as L-Arg9 (SEQ ID NO: 12), have low CP_{50} values (Example 4, FIG. **7-9**), i.e. the cellular uptake is highly efficient, suggesting superior BBB penetration and intracellular delivery. Surprisingly, compounds containing the CPP L-Arg_9(SEQ ID NO: 12) exhibited in vitro plasmin half-life times comparable to compounds containing D-amino acids or macrocyclic CPPs (FIG. **5-6**). Interestingly, the half-life of L-Arg_9 containing compounds was significantly better than those of L-TAT (SEQ ID NO 8) (FIG. **5**).

[0131] In one embodiment, the CPP is poly-Arg and the linker is a PEG linker comprising a NPEG unit, and the CPP is linked to the nitrogen atom of the linker by an amide bond. Thus, in one embodiment, the compound has the general structure of Formula (IV):

Formula (IV)



wherein

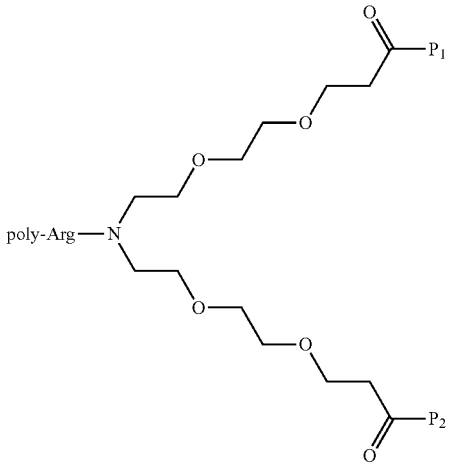
[0132] poly-Arg, P_1 and P_2 are as defined herein;

[0133] p is an integer 0 to 10; and

[0134] q is an integer 0 to 10.

[0135] In one embodiment, p is 2 and q is 2. Thus, in one embodiment, the compound has the general structure of Formula (VII):

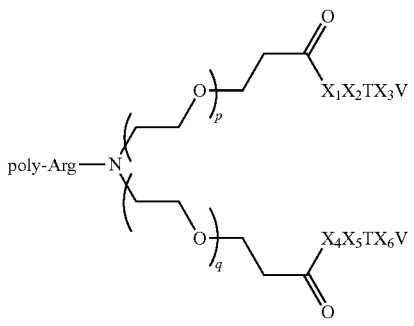
Formula (VII)



wherein poly-Arg, P_1 and P_2 are as defined herein.

[0136] In one embodiment, the compound has the general structure of Formula (VI):

Formula (VI)



[0137] wherein

[0138] X_1 is selected from the group consisting of K, V and I;

[0139] X_2 is selected from the group consisting of E and S; and

[0140] X_3 is selected from the group consisting of L, T, V, R and D.

[0141] X_4 is selected from the group consisting of K, V and I;

[0142] X_5 is selected from the group consisting of E and S;

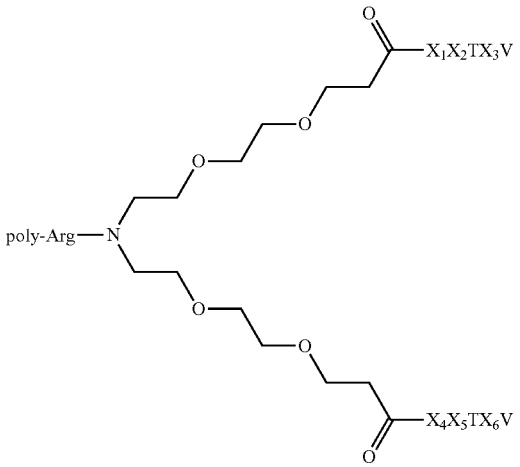
[0143] X_6 is selected from the group consisting of L, T, V, R and D.

[0144] p is an integer 0 to 10; and

[0145] q is an integer 0 to 10.

[0146] In one embodiment, p is 2 and q is 2. Thus, in one embodiment, the compound has the general structure of Formula (VIII):

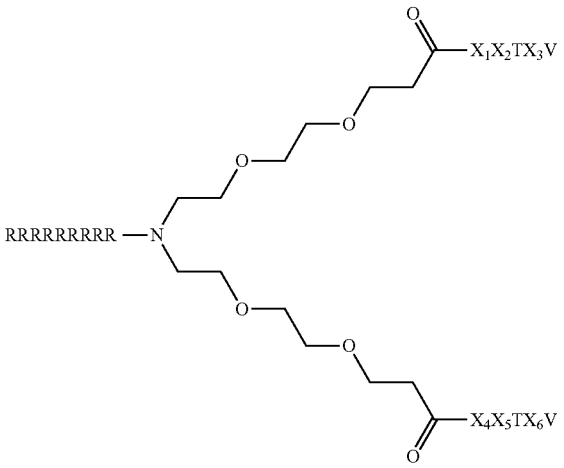
Formula (VIII)



wherein poly-Arg, X_1, X_2, X_3, X_4, X_5, and X_6 are as defined herein.

[0147] In one embodiment, the CPP is L-Arg_8, p is 2 and q is 2. Thus, in one embodiment, the compound has the general structure of Formula (IX):

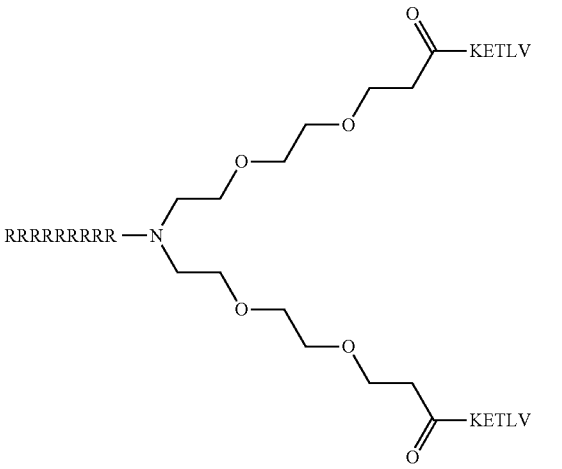
Formula (IX)



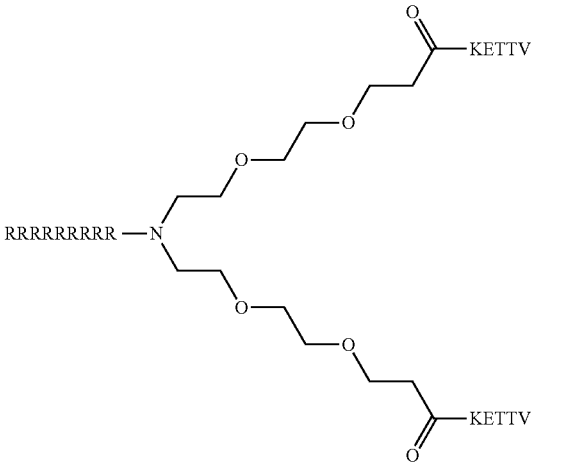
wherein X_1, X_2, X_3, X_4, X_5, and X_6 are as defined herein.

[0148] In one embodiment, compound is selected from the group consisting of formulas (X) to (XVI):

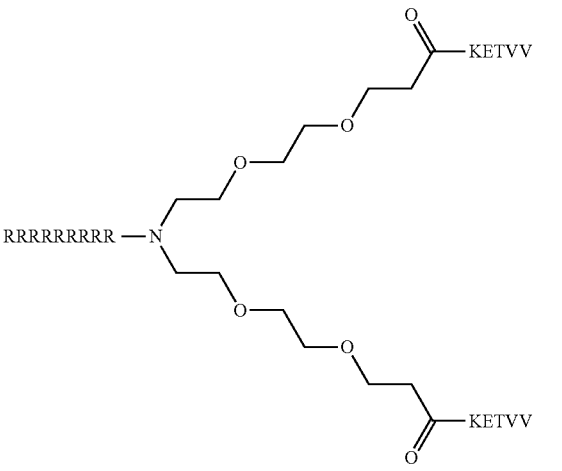
Formula (X)



Formula (XI)



Formula (XII)



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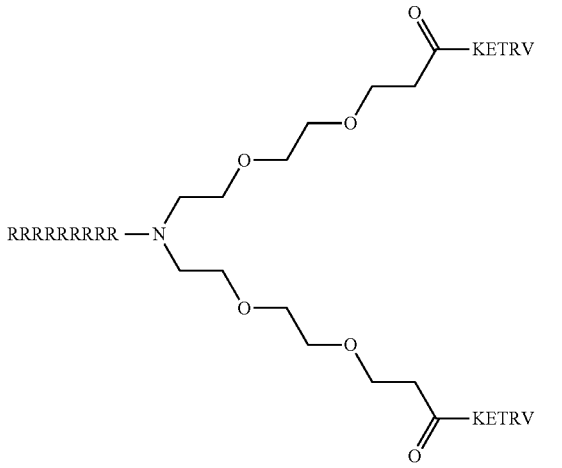
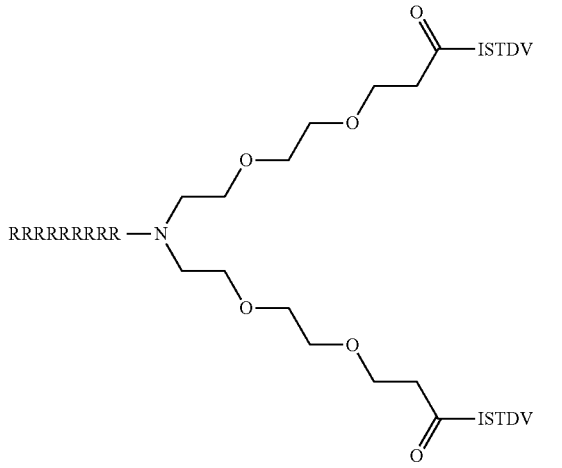
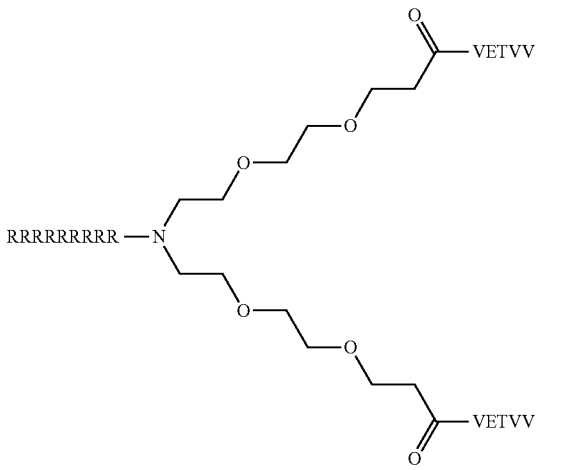
Formula (XIII)



Formula (XIV)



Formula (XV)



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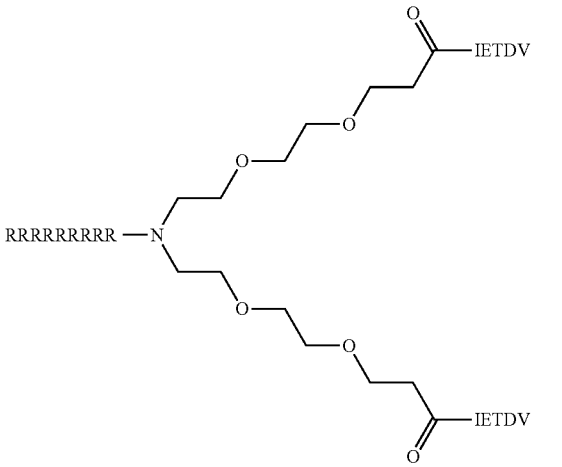
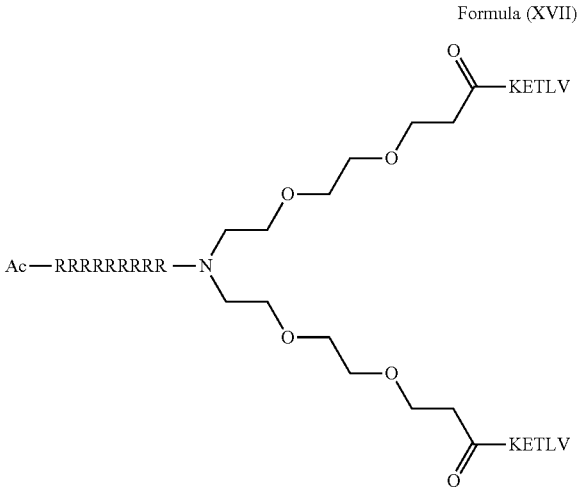
Formula (XVI)

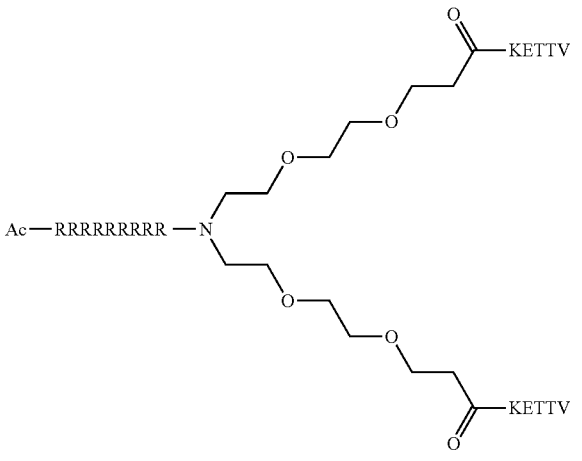


[0149] In one embodiment, any of the peptides P, P_2 and/or the CPP are further modified. For example, in one embodiment, the N-terminal of the CPP is optionally acetylated. Thus, in one embodiment, the compound is selected from the group consisting of formulas (XVII) to (XXIII):

Formula (XVII)



Formula (XVII)



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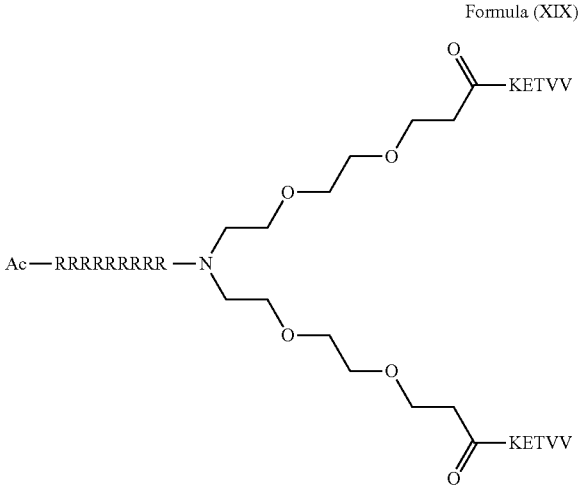
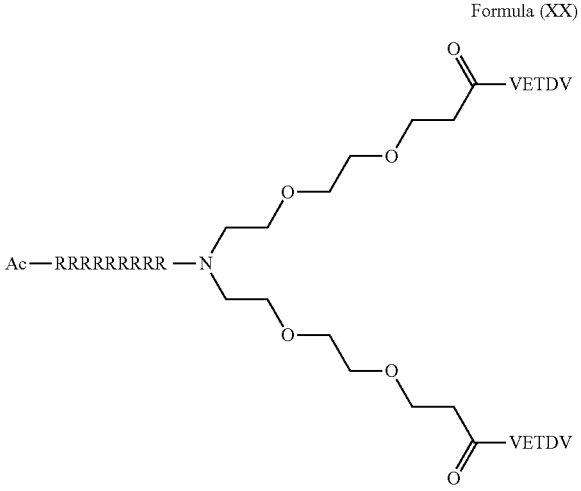
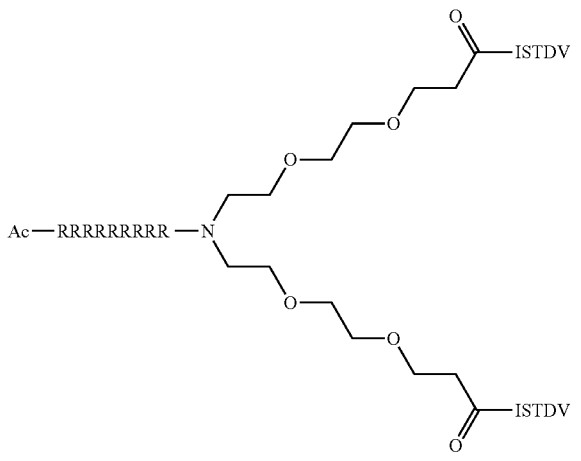
Formula (XIX)



Formula (XX)



Formula (XXI)



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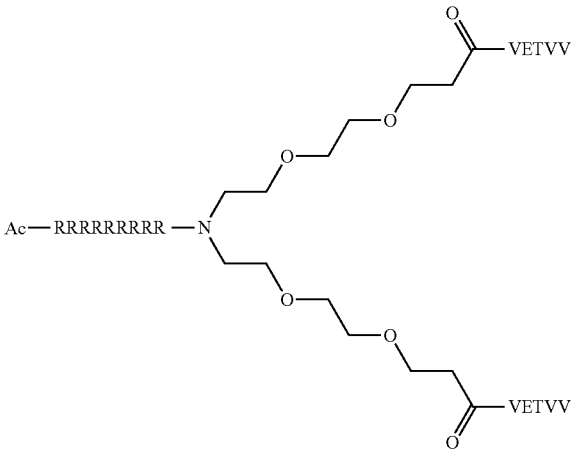
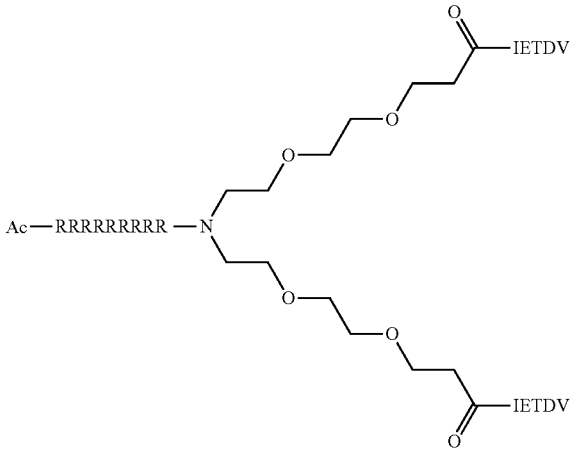
Formula (XXII)



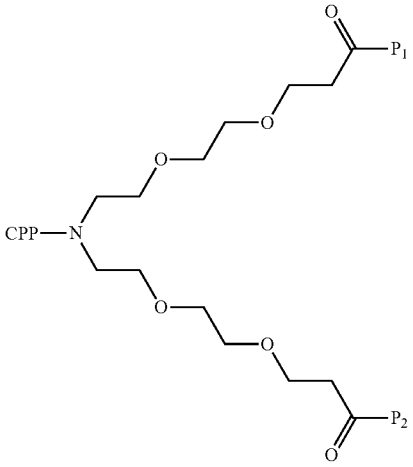
Formula (XXIII)



Specific Compounds

[0150] In one embodiment, the compound has the general structure of CPP-NPEG$_4$-(P_1)(P_2), i.e. the compound is of formula (XXVIII):

Formula (XXVIII)



and CPP, P_1 and P_2 are as defined in table 2. In one embodiment, the compound is selected from the group consisting of compounds 9 to 63.

TABLE 2

Exemplified compounds of the invention.

Compound	Formula	P_1, P_2	CPP	
8 (AB144)		*IETDV* (SEQ ID NO: 1)	L-TAT	*YGRKKRRQRRR-* (SEQ ID NO: 8)
9		IETDV (SEQ ID NO: 1)	L-TAT	Ac-YGRKKRRQRRR- (SEQ ID NO: 23)
10		IETDV (SEQ ID NO: 1)	L-TAT	CA-YGRKKRRQRRR- (SEQ ID NO: 24)
11		KETLV (SEQ ID NO: 2)	L-TAT	Ac-YGRKKRRQRRR- (SEQ ID NO: 23)
12		KETLV (SEQ ID NO: 2)	L-TAT	CA-YGRKKRRQRRR- (SEQ ID NO: 24)
13		KETTV (SEQ ID NO: 3)	L-TAT	Ac-YGRKKRRQRRR- (SEQ ID NO: 23)
14		KETTV (SEQ ID NO: 3)	L-TAT	CA-YGRKKRRQRRR- (SEQ ID NO: 24)

TABLE 2-continued

Exemplified compounds of the invention.

Compound	Formula	P_1, P_2	CPP	
15		KETVV (SEQ ID NO: 4)	L-TAT	Ac-YGRKKRRQRRR- (SEQ ID NO: 23)
16		KETVV (SEQ ID NO: 4)	L-TAT	CA-YGRKKRRQRRR- (SEQ ID NO: 24)
17		KETRV (SEQ ID NO: 5)	L-TAT	Ac-YGRKKRRQRRR- (SEQ ID NO: 23)
18		KETRV (SEQ ID NO: 5)	L-TAT	CA-YGRKKRRQRRR- (SEQ ID NO: 24)
19		ISTDV (SEQ ID NO: 6)	L-TAT	Ac-YGRKKRRQRRR- (SEQ ID NO: 23)
20		ISTDV (SEQ ID NO: 6)	L-TAT	CA-YGRKKRRQRRR- (SEQ ID NO: 24)
21		VETVV (SEQ ID NO: 7)	L-TAT	Ac-YGRKKRRQRRR- (SEQ ID NO: 23)
22		VETVV (SEQ ID NO: 7)	L-TAT	CA-YGRKKRRQRRR- (SEQ ID NO: 24)
23	(XVII)	KETLV (SEQ ID NO: 2)	L-Arg_9	Ac-RRRRRRRRR- (SEQ ID NO: 25)
24		KETLV (SEQ ID NO: 2)	L-Arg_9	CA-RRRRRRRRR- (SEQ ID NO: 26)
25	(XVIII)	KETTV (SEQ ID NO: 3)	L-Arg_9	Ac-RRRRRRRRR- (SEQ ID NO: 25)
26		KETTV (SEQ ID NO: 3)	L-Arg_9	CA-RRRRRRRRR- (SEQ ID NO: 26)
27	(XIX)	KETVV (SEQ ID NO: 4)	L-Arg_9	Ac-RRRRRRRRR- (SEQ ID NO: 25)
28		KETVV (SEQ ID NO: 4)	L-Arg_9	CA-RRRRRRRRR- (SEQ ID NO: 26)
29	(XX)	KETRV (SEQ ID NO: 5)	L-Arg_9	Ac-RRRRRRRRR- (SEQ ID NO: 25)
30		KETRV (SEQ ID NO: 5)	L-Arg_9	CA-RRRRRRRRR- (SEQ ID NO: 26)
31	(XXI)	ISTDV (SEQ ID NO: 6)	L-Arg_9	Ac-RRRRRRRRR- (SEQ ID NO: 25)
32		ISTDV (SEQ ID NO: 6)	L-Arg_9	CA-RRRRRRRRR- (SEQ ID NO: 26)
33	(XXII)	VETVV (SEQ ID NO: 7)	L-Arg_9	Ac-RRRRRRRRR- (SEQ ID NO: 23)
34		VETVV (SEQ ID NO: 7)	L-Arg_9	CA-RRRRRRRRR- (SEQ ID NO: 26)
35	(XXIII)	IETDV (SEQ ID NO: 1)	L-Arg_9	Ac-RRRRRRRRR- (SEQ ID NO: 25)
36		IETDV (SEQ ID NO: 1)	L-Arg_9	CA-RRRRRRRRR- (SEQ ID NO: 26)
38		IETDV (SEQ ID NO: 1)	D-TAT	Ac-ygrkkrrqrrr- (SEQ ID NO: 27)
39		IETDV (SEQ ID NO: 1)	D-TAT	CA-ygrkkrrqrrr- (SEQ ID NO: 28)
40		IETDV (SEQ ID NO: 1)	mTAT	Ac-rRrGrKkRr- (SEQ ID BO: 29)

TABLE 2-continued

Exemplified compounds of the invention.

Compound	Formula	P_1, P_2	CPP	
41		IETDV (SEQ ID NO: 1)	mTAT	CA-rRrGrKkRr- (SEQ ID NO: 30)
42		IETDV (SEQ ID NO: 1)	riTAT	Ac-rrrqrrkkr- (SEQ ID NO: 31)
43		IETDV (SEQ ID NO: 1)	riTAT	CA-rrrqrrkkr- (SEQ ID NO: 32)
44		IETDV (SEQ ID NO: 1)	D-Arg_9	Ac-rrrrrrrrr- (SEQ ID NO: 33)
45		IETDV (SEQ ID NO: 1)	D-Arg_9	CA-rrrrrrrrr- (SEQ ID NO: 34)
46		IETDV (SEQ ID NO: 1)	L-Pen	Ac-RQIKIWFQNRRMKWKK- (SEQ ID NO: 35)
47		IETDV (SEQ ID NO: 1)	L-Pen	CA-RQIKIWFQNRRMKWKK- (SEQ ID NO: 36)
48		IETDV (SEQ ID NO: 1)	D-Pen	Ac-rqikiwfqnrrmkwkk- (SEQ ID NO: 37)
49		IETDV (SEQ ID NO: 1)	D-Pen	CA-rqikiwfqnrrmkwkk- (SEQ ID NO: 38)
50		IETDV (SEQ ID NO: 1)	L-DPV3	Ac-RKKRRRESRKKRRRES- (SEQ ID NO: 39)
51		IETDV (SEQ ID NO: 1)	L-DPV3	CA-RKKRRRESRKKRRRES- (SEQ ID NO: 40)
52		IETDV (SEQ ID NO: 1)	L-pVEC	Ac-LLIILRRRIRKQAHAHSK- (SEQ ID NO: 41)
53		IETDV (SEQ ID NO: 1)	L-pVEC	CA-LLIILRRRIRKQAHAHSK- (SEQ ID NO: 42)
54		IETDV (SEQ ID NO: 1)	L-MAP	Ac-KLALKLALKALKAALKLA- (SEQ ID NO: 43)
55		IETDV (SEQ ID NO: 1)	L-MAP	CA-KLALKLALKALKAALKLA- (SEQ ID NO: 44)
56		IETDV (SEQ ID NO: 1)	L-TP2	Ac-PLIYLRLLRGQF- (SEQ ID NO: 45)
57		IETDV (SEQ ID NO: 1)	L-TP2	CA-PLIYLRLLRGQF- (SEQ ID NO: 46)
58		IETDV (SEQ ID NO: 1)	D-TP2	Ac-pliylrllrGqf- (SEQ ID NO: 47)
59		IETDV (SEQ ID NO: 1)	D-TP2	CA-pliylrllrGqf- (SEQ ID NO: 48)
60		IETDV (SEQ ID NO: 1)	MiniAp4	Ac-|(Dap)KAPETALD|- (SEQ ID NO: 49)
61		IETDV (SEQ ID NO: 1)	MiniAp4	CA-|(Dap)KAPETALD|- (SEQ ID NO: 50)

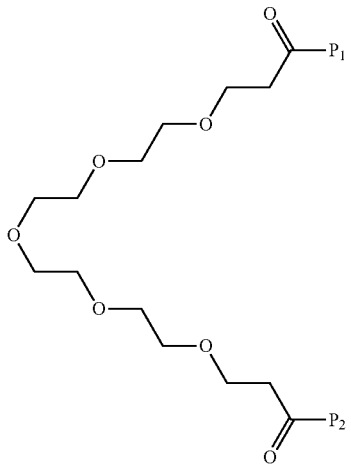
TABLE 2-continued

Exemplified compounds of the invention.

Compound	Formula	P_1, P_2	CPP	
62		IETDV (SEQ ID NO: 1)	CPP12	|Ff(Nal2)RrRrQ|GABA-K- (SEQ ID NO: 51)
63		IETDV (SEQ ID NO: 1)	CPP12	|Ff(Nal2)RrRrQ|GABA-K(CA)- (SEQ ID NO: 52)
64		IETDV (SEQ ID NO: 1)	L-Arg_7	CA-RRRRRRR- (SEQ ID NO: 68)
65		IETDV (SEQ ID NO: 1)	L-Arg_5	CA-RRRRR- (SEQ ID NO: 70)
66		IETDV (SEQ ID NO: 1)	L-Arg_3	CA-RRR-
67		KETLV (SEQ ID NO: 2)	L-Arg_7	Ac-RRRRRRR- (SEQ ID NO: 63)
68		KETLV (SEQ ID NO: 2)	L-Arg_7	CA-RRRRRRR- (SEQ ID NO: 68)
69		KETLV (SEQ ID NO: 2)	L-Arg_6	Ac-RRRRRR- (SEQ ID NO: 64)
70		KETLV (SEQ ID NO: 2)	L-Arg_6	CA-RRRRRR- (SEQ ID NO: 69)
71		KETLV (SEQ ID NO: 2)	L-Arg_5	Ac-RRRRR- (SEQ ID NO: 65)
72		KETLV (SEQ ID NO: 2)	L-Arg_5	CA-RRRRR- (SEQ ID NO: 70)
73		KETLV (SEQ ID NO: 2)	L-Arg_4	Ac-RRRR- (SEQ ID NO: 66)
74		KETLV (SEQ ID NO: 2)	L-Arg_4	CA-RRRR- (SEQ ID NO: 71)
75		KETLV (SEQ ID NO: 2)	L-Arg_3	CA-RRR-

[0151] In one embodiment, the compound is of formula (XXVII):

Formula (XXVII)



and P_1 and P_2 are as defined in table 3. In one embodiment, the compound is selected from the group consisting of compounds 2 to 7.

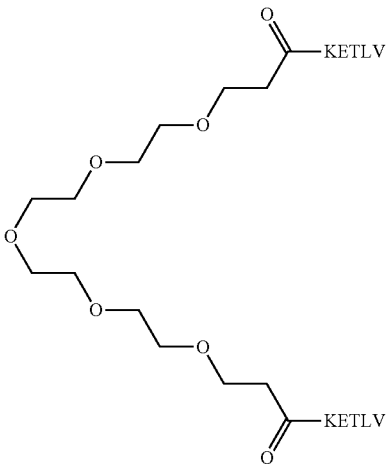
TABLE 3

Exemplified compounds of the invention.

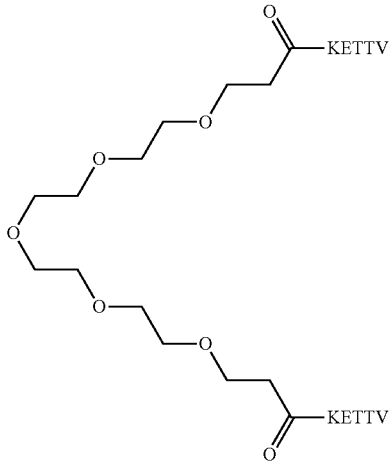
Compound	Formula	P_1, P_2	Name
1 (UCCB01-125)		*IETDV* (SEQ ID NO: 1)	*OPEG4*-(*IETDV*)$_2$
2	(XXIX)	KETLV (SEQ ID NO: 2)	OPEG$_4$-(KETLV)$_2$
3	(XXX)	KETTV (SEQ ID NO: 3)	OPEG$_4$-(KETTV)$_2$
4	(XXXI)	KETVV (SEQ ID NO: 4)	OPEG$_4$-(KETVV)$_2$
5	(XXXII)	KETRV (SEQ ID NO: 5)	OPEG$_4$-(KETRV)$_2$
6	(XXXIII)	ISTDV (SEQ ID NO: 6)	OPEG$_4$-(ISTDV)$_2$
7	(XXXIV)	VETVV (SEQ ID NO: 7)	OPEG$_4$-(VETVV)$_2$

[0152] In one embodiment, the compound is selected from the group consisting of formulas (XXIX) to (XXXIV):

Formula (XXIX)



Formula (XXX)



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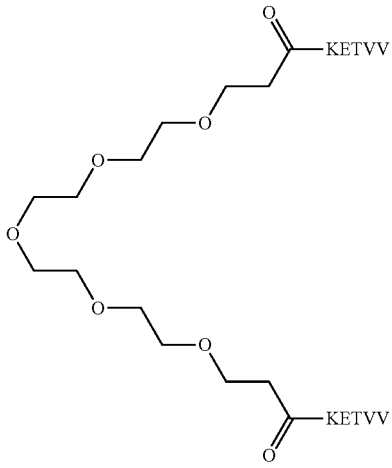
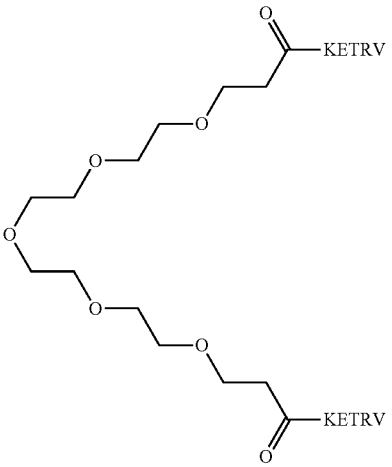
Formula (XXXI)



Formula (XXXII)



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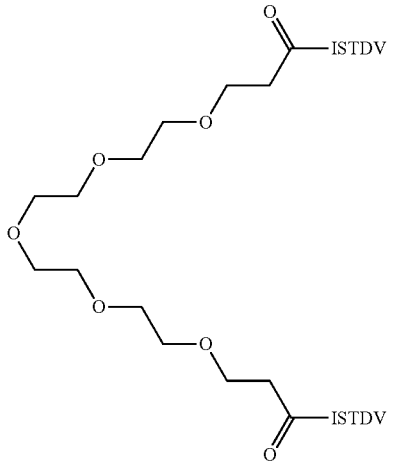
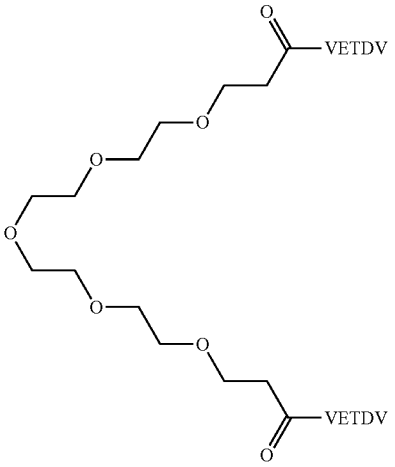
Formula (XXXIII)



Formula (XXXIV)



[0153] In one embodiment, 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 D-Pen (rqikiwfqnrrmkwkk, SEQ ID NO: 15); L-pVEC (LLIILRR-RIRKQAHAHSK, SEQ ID NO: 18); L-TP2 (PLIYLRLLRGQF, SEQ ID NO: 19); MiniAp4 (I(Dap) KAPETALDI, SEQ ID NO: 21); and CPP12 (IFf(Nal2) RrRrQIGABA-K, SEQ ID NO: 22).

Salts and Prodrugs

[0154] The compound as defined herein can be in the form of a pharmaceutically acceptable salt or prodrug of said compound. In one embodiment of the present invention the compound as defined herein can be formulated as a pharmaceutically acceptable addition salt or hydrate of said compound, such as but not limited to K^+, Na^+, as well as non-salt e.g. H^+.

Pharmaceutical Composition

[0155] In one aspect, the present invention concerns a pharmaceutical composition comprising the compound as defined herein. Formulation of a compound of the present invention into pharmaceutical compositions is well known in the art, and is further described in Gennaro (ed.), 2000, Remington: The Science and Practice of Pharmacy, 20th ed., Lippincott, Williams & Wilkins (2000); and Ansel et al., 1999, Pharmaceutical Dosage Forms and Drug Delivery Systems, 7th ed., Lippincott Williams & Wilkins Publishers.

Membrane Permeability

[0156] Since PSD-95 is located intracellularly, it is essential for any drug targeting PSD-95 to efficiently cross the cell membrane. To assess the cellular permeability and delivery to the cytosol of the compounds as defined herein, the cellular chloroalkane penetration assay (CAPA) may be used (Peraro et al. 2018). This assay takes advantage of a modified haloalkane dehalogenase designed to covalently bind chloroalkane (CA) molecules. A HeLa cell line expressing a fusion protein comprising a HaloTag, a green fluorescent protein (GFP) and a mitochondria-targeting peptide is used to report cytosolic delivery. The general format of the CAPA is a pulse-chase assay (Deprey & Kritzer, 2020). Cells expressing the HaloTag enzyme are incubated with CA-tagged peptides. When these CA-peptides penetrate the cell membrane and reach the cytosol, they will bind to and react with the HaloTag (pulse step). Following a washing step, the cells are incubated with a CA-tagged dye that quantitatively penetrates the cell membrane and reacts with remaining unreacted HaloTag sites (chase step). Flow cytometry is used to measure the fluorescence intensity of the cells and the measured fluorescence is inversely proportional to the amount of CA-peptides that reach the penetrated the cells and can thus be used to assess cytosolic delivery. The obtained data is commonly expressed as CP_{50} values, the concentration at which 50% cell penetration is observed. The CP_{50} value of a compound may be measured as described in example 4. Example 4 shows that the cellular uptake of described compounds greatly depend on the employed CPP, measuring CP_{50} values ranging from 86.1 μM (compound 22) to 0.68 μM (compound 30) (FIG. **7**). Further, the cellular uptake efficiency for $NPEG_4(IETDV)_2$ conjugated to a range of CPP-tags (SEQ ID NO 8 to 22) resulted in an unpredictable range of CP_{50} values (FIG. **8**).

[0157] In one embodiment, the compound has a CP_{50} value of no more than 250 μM, such as no more than 200 μM, such as no more than 150 μM, such as no more than 100 μM, such as no more than 80 μM, such as no more than 70 μM, such as no more than 60 μM, such as no more than 50 μM, such as no more than 40 μM, such as no more than 30 μM, such as no more than 20 μM, such as no more than 15 μM, such as no more than 10 μM, such as no more than 5 μM. Preferably, the compound has a CP_{50} value of no more than 60 μM.

Plasmin Stability

[0158] Ischemic stroke (also referred to as 'brain ischemia' or 'cerebral ischemia') is usually caused by a blockage in an artery that supplies blood to the brain. The blockage reduces the blood flow and oxygen to the brain, leading to damage or death of brain cells. The blockage of the blood vessels can be removed using a range of mechanical devices, or using "clot busting agents" which are delivered intravenously or intra-arterially. Among such clot busting agents is Tissue plasminogen factor (tPA), which generates plasmin from plasminogen. Examples of recombinant tPA's are

alteplase, reteplase and tenecteplase, and other thrombolytic drugs that break down clots include streptokinase, urokinase and desmotaplase.

[0159] In one embodiment, the compounds of the present invention are administered to subjects receiving tPA or a recombinant tPA, which is the standard-of-care for AIS. Thus, it is essential that the compound is compatible with the administration of tPA, including the generation of plasmin, which is a serine protease.

[0160] The in vitro plasmin stability of compounds of the present invention were determined in example 3. In one embodiment, the compound has a half-life in the plasmin stability assay described in example 3 of at least 10 min in the presence pf plasmin, such as at least 30 min, such as at least 1 h, such as at least 2 h, such as at least 3 h, such as at least 4 h, such as at least 5 h, such as at least 6 h, such as at least 7 h, such as at least 8 h, such as at least 9 h, such as at least 10 h, such as at least 15 h, such as at least 20 h, such as at least 30 h.

Affinity to PDZ1-2 of PSD-95

[0161] Preferably, the compounds of the present invention have an affinity for the PDZ1-2 of PSD-95 in the nanomolar range, making them highly potent inhibitors. The affinity of the for the PDZ1-2 of PSD-95 is a critical factor in reducing the threshold concentration of drug needed to attain a therapeutic effect, which is particularly important when the drug must cross the blood brain barrier (BBB) to reach its target, since the BBB will tend to limit the accumulation of drug concentration at the target.

[0162] In some embodiments, the compound of the present invention is a dimeric PSD-95 inhibitor binding to PDZ1 and PDZ2 simultaneously, which may account for their high affinity for these domains.

[0163] As described in Example 2, the obtained affinities towards PDZ1-2 of PSD-95 for compounds of the present invention are in the low nanomolar range and similar to L-TAT-NPEG$_4$(IETDV)$_2$.

[0164] In one embodiment, the K_i value for PDZ1-2 of PSD-95 of the compound is no more than 25 100 nM, such as no more than 80 nM, such as no more than 70 nM, such as no more than 60 nM, such as no more than 50 nM, such as no more than 40 nM, such as no more than 30 nM, such as no more than 20 nM, such as no more than 10 nM.

Medical Use

[0165] In one aspect the compound of the present invention as defined herein, is for use as a medicament.

[0166] The PDZ1 and PDZ2 domains of PSD-95 interact with several proteins including the simultaneous binding of the NMDA-type of ionotropic glutamate receptors and the nitric oxide (NO) producing enzyme nNOS. NMDA receptors are the principal mediators of excitotoxicity, i.e. glutamate-mediated neurotoxicity, which is implicated in neurodegenerative diseases and acute brain injuries. PSD-95 simultaneously binds the NMDA receptor, primarily GluN2A and GluN2B subunits, and nNOS via PDZ1 and PDZ2, respectively. Activation of the NMDA receptor causes influx of calcium ions, which activates nNOS thereby leading to NO generation. Thus, PSD-95 mediates a specific association between NMDA receptor activation and NO production, which can be detrimental for the cells if sustained for a longer period, and is a key facilitator of glutamate-mediated neurotoxicity. Inhibition of the ternary complex of nNOS/PSD-95/NMDA receptor interaction by targeting PSD-95 is known to prevent ischemic brain damage in mice, by impairing the functional link between calcium ion entry and NO production, while the physiological function, such as ion-flux and pro-survival signaling pathways of the NMDA receptor remains intact. Specific inhibition of excitotoxicity can be obtained by perturbing the intracellular nNOS/PSD-95/NMDA receptor complex using PSD-95 inhibitors.

[0167] The compounds of the present invention are PSD-95 inhibitors and are thus able to inhibit excitotoxicity. Hence, the compounds of the present invention are useful in treating a variety of diseases, particularly neurological diseases, and especially diseases mediated in part by excitotoxity. Such diseases and conditions include stroke, epilepsy, hypoxia, traumatic injury to the CNS not associated with stroke such as traumatic brain injury and spinal cord injury, other cerebral ischemia, Alzheimer's disease and Parkinson's disease.

[0168] In one aspect, the present invention relates to a compound as defined herein for use in preventing, treating, reducing and/or delaying development of an excitotoxic-related disease. In one embodiment, the excitotoxic-related disease is stroke. In one embodiment, the excitotoxic-related disease is ischemic stroke. In one embodiment, the excitotoxic-related disease is cerebral ischemia. In one embodiment, the excitotoxic-related disease is acute ischemic stroke. In one embodiment, the excitotoxic-related disease is subarachnoid hemorrhage.

[0169] In one aspect, the present invention relates to use of a compound as defined herein for the manufacture of a medicament for preventing, treating, reducing and/or delaying development of an excitotoxic-related disease.

[0170] In one aspect, the present invention relates to a method for preventing, treating, reducing and/or delaying development of an excitotoxic-related, said method comprising administering a therapeutically effective amount of compound as defined herein.

[0171] In one aspect, the present invention relates to a compound for use in reducing and/or protecting against a damaging effect of excitotoxicity. In one embodiment, the compound is for use in reducing the damaging effect of stroke. In one embodiment, the compound is for use in treating a damaging effect of acute ischemic stroke. In one embodiment, the compound is for use in treating a damaging effect of subarachnoid hemorrhage.

[0172] In one aspect, the present invention relates to a method for protecting against and/or reducing the damaging effect of excitotoxicity to the brain or spinal cord in a subject, said method comprising the step of administering an effective amount of the compound as defined herein to the subject to protect against and/or reduce the damaging effect.

[0173] In one aspect, the present invention relates to a method of treating, reducing, or delaying development of a condition mediated by excitotoxicity comprising administering to a human subject having or at risk of the condition a compound as defined herein.

[0174] In one aspect, the present invention relates to a method of treating or inhibiting or delaying at least one sign or symptom of a condition mediated by excitotoxicity in a subject, comprising administering to the subject having the conditions, or a risk factor associated with the condition a compound as defined herein. In one embodiment, said

condition is stroke or traumatic injury to the CNS. In one embodiment, the excitotoxic-related disease is ischemic or traumatic injury to/in/of the CNS.

[0175] In one aspect, the present invention relates to a method of reducing the damaging effect of stroke in a subject having stroke, comprising administering to the subject an effective amount of the compound as defined herein to reduce the damaging effect of the stroke.

[0176] As used herein, "stroke" is a general term that refers to conditions caused by the occlusion or hemorrhage of one or more blood vessels supplying the brain, leading to cell death. "Ischemic stroke", as used herein, refers to stroke caused by an occlusion of one or more blood vessels supplying the brain. Types of ischemic stroke include, e.g., embolic stroke, cardioembolic stroke, thrombotic stroke, large vessel thrombosis, lacunar infarction, artery-artery stroke and cryptogenic stroke. "Cerebral ischemia" is a condition in which a blockage in an artery restricts the delivery of oxygen-rich blood to the brain, resulting in damage to brain tissue. Cerebral ischemia is sometimes called brain ischemia or cerebrovascular ischemia.

[0177] "Hemorrhagic stroke", as used herein, refers to stroke caused by hemorrhage of one or more blood vessels supplying the brain. Types of hemorrhagic stroke include, e.g., subdural stroke, intraparenchymal stroke, epidural stroke and subarachnoid stroke.

[0178] In one embodiment, the disease treatable by the compound of the present invention is ischemic or traumatic injury of the CNS. In one aspect, the present invention relates to a method of reducing the damaging effect of traumatic injury or ischemia to the brain or spinal cord in a subject, said method comprising treating said subject with a compound as defined herein to effect said reduction.

[0179] In one aspect, the present invention relates to a method of inhibiting cerebral ischemia due to endovascular surgery, comprising administering to a subject undergoing endovascular surgery a compound as defined herein in a regime effective to inhibit cerebral ischemia.

[0180] In one aspect, the present invention relates to a method of inhibiting ischemic damage from endovascular surgery to treat an aneurysm, diagnostic angiography or carotid stenting comprising administering an effective regime of a compound as defined herein to a subject undergoing endovascular surgery to treat an aneurysm or diagnostic angiography.

[0181] In one aspect, the present invention relates to a compound as defined herein for use in inhibiting ischemic damage from neurosurgery. In one embodiment, said neurosurgery is diagnostic angiography of the brain or endovascular surgery to treat an aneurysm.

[0182] In some embodiments, the compound is administered in combination with reperfusion therapy. In one embodiment, the compound and the reperfusion are administered simultaneously, sequentially or separately to the subject.

[0183] The term 'reperfusion therapy' as used herein refers to a medical treatment to restore blood flow, either through or around, blocked arteries. Reperfusion therapy includes medical agents and mechanical reperfusion. Said medical agents may be thrombolytics or fibrinolytics used in a process called thrombolysis. In some embodiments, reperfusion therapy is performed by administering a thrombolytic agent, such as a plasminogen activator, for example tPA.

[0184] In one embodiment, the compound is compound 8 (AB144), and said compound is administered in combination with a plasminogen activator, for example tPA.

[0185] In some embodiments, the reperfusion therapy is mechanical reperfusion including surgery. Surgeries performed may be minimally-invasive endovascular procedures.

[0186] Among mechanical reperfusion devices, there are intra-arterial catheters, balloons, stents, and various clot retrieval devices.

[0187] In one embodiment, the compound is administered in combination with a thrombolytic agent, and the compound and the thrombolytic agent are administered simultaneously, sequentially or separately to the subject.

[0188] In one aspect, the present invention relates to a method of treating a damaging effect of ischemia on the central nervous system, comprising

[0189] a) administering a compound as defined herein to a subject having or at risk of ischemia, and

[0190] b) performing reperfusion therapy on the subject,

[0191] wherein the compound and reperfusion therapy treat a damaging effect of the ischemia on the central nervous system of the subject.

[0192] In one aspect, the present invention relates to a compound as defined herein for use in treating a damaging effect of ischemia on the central nervous system in a subject having or at risk of ischemia, wherein reperfusion therapy is performed on the subject, and the compound and reperfusion therapy treat a damaging effect of the ischemia on the central nervous system of the subject.

[0193] In one embodiment, the method further comprising administering a thrombolytic agent simultaneously, sequentially or separately to the subject.

[0194] In one aspect, the present invention relates to a kit of parts comprising at least two separate unit dosage forms (A) and (B), wherein

[0195] (A) comprises a compound as defined herein; and

[0196] (B) comprises a thrombolytic agent.

[0197] In one aspect, the kit of parts as defined herein is for use in the treatment of a damaging effect of ischemia on the central nervous system, wherein (A) and (B) are administered simultaneously, sequentially or separately to the subject.

[0198] In one aspect, the present invention relates to a compound as defined herein for use in treating a damaging effect of subarachnoid hemorrhage. The term "subarachnoid hemorrhage" as used herein refers to a hemorrhage state in a subarachnoid cavity.

[0199] In one aspect, the present invention relates to a method of treating a subarachnoid hemorrhage in a subject, comprising administering a compound as defined herein to a subject having a subarachnoid hemorrhage, wherein development of neurocognitive deficits in the subject is inhibited.

[0200] In one aspect, the present invention relates to a method of inhibiting development of a neurologic or neurocognitive deficit of subarachnoid hemorrhage in a subject, comprising administering a compound as defined herein to a subject having a subarachnoid hemorrhage, wherein development of a neurologic or neurocognitive deficit in the subject is inhibited.

[0201] Other neurological diseases treatable by the compounds of the present invention not known to be associated

with excitotoxicity include anxiety and pain. Dimeric ligands targeting PSD-95 are under pre-clinical/clinical evaluation as a treatment for chronic pain and ischemic stroke (Andreasen et al., Neuropharmacol, 2013, 67, 193-200; Bach et al, PNAS USA, 2012, 109, 3317-3322). In one embodiment the compound as defined herein is for use in the treatment or prophylaxis of pain.

[0202] In one embodiment, the subject as referred to herein is a mammal, such as a human.

Synthesis

[0203] The compounds of the present invention as defined herein may be manufactured by a method comprising the general steps of:

[0204] a) Synthesizing a peptide P_1/P_2 as defined herein;

[0205] b) Dimerizing the peptide of a) with an $OPEG_n$ or $NPEG_n$ linker, wherein 'n' is the number of PEG moieties;

[0206] c) Attaching a CPP tag at the N of the NPEG linker, for example by using an automated peptide synthesizer.

[0207] In one embodiment, the compounds are manufactured by a method comprising the general steps of:

[0208] a) providing a Ns-NPEG diacid linker;

[0209] b) preparing a peptide P_1/P_2 using Fmoc-based solid-phase peptide synthesis;

[0210] c) dimerizing Fmoc-deprotected peptide P_1/P_2 with Ns-NPEG diacid linker forming a linker-dimer conjugate; and

[0211] d) attaching a CPP to the N of the NPEG linker of the linker-dimer conjugate, for example by using an automated peptide synthesizer.

[0212] In one embodiment, the compounds of the present invention are synthesized as described below.

Ns-NPEG Diacid Linker:

[0213] The 'Ns-NPEG diacid linker' is the structure where an NPEG linker is protected on the nitrogen with an ortho-nitrobenzenesulfonyl (Ns) protection group on the linker nitrogen, and where the termini of the NPEG linker comprise carboxylic acids. This chemical reagent or building block is used to dimerize the two peptide moieties, P_1 and P_2.

[0214] The ortho-nitrobenzenesulfonyl (Ns)-protected NPEG linker is produced either on solid-phase or in solution.

[0215] The solid-phase procedure typically starts by loading a solid support useful for solid-phase peptide synthesis, such as 2-chlorotrityl chloride resin, with Fmoc-NH-PEG-CH_2CH_2O0H, using appropriate organic solvent for the specific resin (e.g. DCM, DMF, ACN, THF) and a base (e.g. DIPEA, DBU, collidine, NMM)

[0216] The Fmoc group can be removed by base (e.g. piperidine, dimethylamine, morpholine, piperazine, dicyclohexylamine, DMAP) in appropriate solvent (e.g. DMF, DCM, ACN, THF).

[0217] Ortho-nitrobenzenesulfonyl chloride can be coupled to the free amine using base (e.g. DIPEA, DBU, collidine, NMM) and appropriate solvent (e.g. THF, DCM) to get Ns-NH-PEG-CH_2CH_2O00-Resin.

[0218] The second part of the linker product can be connected to the resin-bound linker-part by the use of Mitsunobu-chemistry. Resin is treated with triphenylphosphine, HO-PEG-$CH_2CH_2COOtBu$, solvent, and ester- or amide reagents of azodicarboxylic acid (e.g. diisopropyl azodicarboxylate, DIAD; diethyl azodicarboxylate, DEAD; 1,1'-(Azodicarbonyl)-dipiperidine, ADDP).

[0219] The final Ns-NPEG diacid linker is obtained by treating the resin with acid, such as trifluoroacetic acid (TFA).

[0220] The solution-phase procedure can be performed by protection of the amine group of NH_2—PEG-$CH_2CH_2COOtBu$ with Ns, followed by Mitsunobu chemistry in solution using triphenylphosphine and DIAD, DEAD, or ADDP, or similar reagents, HO-PEG-$CH_2CH_2COOtBu$, and appropriate solvent (THF, DCM). Final Ns-protected NPEG-linker is then obtained by treatment with acids, such as TFA.

[0221] Peptide synthesis: The peptide sequence is synthesized by Fmoc-based solid-phase peptide synthesis using a solid support, such as 2-chlorotrityl chloride resin or Wang resin, Fmoc-protected amino acids, base, coupling reagents (e.g. HBTU [N,N,N',N' Tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate], 0-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate [HATU], PyBOB, DIC/HOBt) and solvents. Alternatively, to coupling reagents, activated ester of Fmoc-protected amino acids (e.g. pentafluorophenyl, succinimide) can be used.

[0222] Dimerization: The Fmoc-deprotected resin-bound peptide is dimerized with the Ns-NPEG diacid linker by an on-resin dimerization process by repetitive treatments of the resin with the Ns-NPEG diacid linker in sub-stoichiometric amounts (e.g. ⅙), base, coupling reagent, and appropriate solvents (e.g. DMF, DCM, THF). Alternatively to coupling reagents, activated ester of the Ns-NPEG linker can be used.

[0223] The dimerization process can also be formed in solution using either the activated ester (e.g. pentafluorophenyl, succinimide) of the Ns-NPEG linker together with 1-Hydroxy-7-azabenzotriazole (HOAt) or Hydroxybenzotriazole (HOBt) and appropriate side chain-protected peptide (e.g. tert-butyl) in solvent (e.g. ACN, DMF, DCM, THF). Also, dimerization in solution can be performed using the Ns-NPEG diacid linker, coupling reagents (e.g. HBTU, HATU etc), base and solvents.

[0224] The Ns-group is removed by mercaptoethanol and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or by sodium thiophenolate.

[0225] Attachment of a CPP to the NH moiety of the NPEG linker of the linker-dimer conjugate: First, an amino acid is coupled to the NH moiety of the NPEG linker, and subsequently the CPP is synthesized following standard (manual/automated) Fmoc SPPS on resin.

[0226] Ester protection groups can be removed by stirring the cleaved products in aqueous base (e.g. NaOH, LiOH) and acetonitrile followed by acidification with TFA or HCl.

[0227] The final compound of the present invention is obtained by lyophilization and purification by HPLC or similar chromatographic methods.

[0228] In a further embodiment, the synthesis of the compounds of the present invention is performed as outlined in example 1.

Items

[0229] 1. A compound comprising a first peptide (P_1) comprising or consisting of the amino acid sequence X_2TX_3V (SEQ ID NO: 53), wherein

[0230] a. X_2 is selected from the group consisting of E and S; and

[0231] b. X_3 is selected from the group consisting of L, T, V, R and D, wherein P_1 is linked to a Cell Penetrating Peptide (CPP).

[0232] 2. A compound comprising a first peptide (P_1) linked to a second peptide (P_2) by a linker, wherein P_1 and P_2 comprise or consist of an amino acid sequence selected from the group consisting of KETLV (SEQ ID NO: 2), KETTV (SEQ ID NO: 3), KETVV (SEQ ID NO: 4), KETRV (SEQ ID NO: 5), ISTDV (SEQ ID NO: 6) and VETVV (SEQ ID NO: 7).

[0233] 3. The compound according to item 2, wherein P_1 and P_2 are linked to a Cell Penetrating Peptide (CPP) or an albumin binding moiety via the linker, thereby increasing passage of the peptide across a membrane or the blood brain barrier.

[0234] 4. The compound according to any one of the preceding items, wherein the compound has a CP_{50} value of no more than 250 μM, such as no more than 200 μM, such as no more than 150 μM, such as no more than 100 μM, such as no more than 80 μM, such as no more than 70 μM, such as no more than 60 μM, such as no more than 50 μM, such as no more than 40 μM, such as no more than 30 μM, such as no more than 20 μM, such as no more than 15 μM, such as no more than 10 μM, such as no more than 5 μM.

[0235] 5. The compound according to any one of the preceding items, wherein the compound has a half life in a plasmin stability assay of at least 10 min, such as at least 30 min, such as at least 1 h, such as at least 2 h, such as at least 3 h, such as at least 4 h, such as at least 5 h, such as at least 6 h, such as at least 7 h, such as at least 8 h, such as at least 9 h, such as at least 10 h, such as at least 15 h, such as at least 20 h, such as at least 30 h.

[0236] 6. The compound according to any one of the preceding items, wherein the K value for PDZ1-2 of PSD-95 of the compound is no more than 100 nM, such as no more than 80 nM, such as no more than 70 nM, such as no more than 60 nM, such as no more than 50 nM, such as no more than 40 nM, such as no more than 30 nM, such as no more than 20 nM, such as no more than 10 nM.

[0237] 7. The compound according to any one of the preceding items, wherein CPP is a poly-L-arginine peptide (poly-Arg).

[0238] 8. The compound according to item 7, wherein the poly-Arg consists of 5 to 10 L-arginine residues, such as 7 to 10 L-arginine residues, such as 8 or 9 L-arginine residues.

[0239] 9. The compound according to item 7, wherein the poly-Arg comprises or consists of the amino acid sequence RRRRRRRRR (SEQ ID NO: 12).

[0240] 10. The compound according to any one items 1 to 6, wherein the CPP is L-TAT (YGRKKRRQRRR, SEQ ID NO: 8).

[0241] 11. The compound according to any one items 1 to 6, wherein the CPP is D-TAT (yGrkkrrqrrr, SEQ ID NO: 9).

[0242] 12. The compound according to any one items 1 to 6, wherein the CPP is mTAT (rRrGrKkRr, SEQ ID NO: 10).

[0243] 13. The compound according to any one items 1 to 6, wherein the CPP is riTAT (rrrqrrkkr, SEQ ID NO: 11).

[0244] 14. The compound according to any one items 1 to 6, wherein the CPP is D-Arge (rrrrrrrrr, SEQ ID NO:13).

[0245] 15. The compound according to any one items 1 to 6, wherein the CPP is L-Pen (RQIKIWFQNRRMKWKK, SEQ ID NO: 14).

[0246] 16. The compound according to any one items 1 to 6, wherein the CPP is D-Pen (rqikiwfqnrrmkwkk, SEQ ID NO: 15).

[0247] 17. The compound according to any one items 1 to 6, wherein the CPP is L-DPV3 (RKKRR-RESRKKRRRES, SEQ ID NO: 17).

[0248] 18. The compound according to any one items 1 to 6, wherein the CPP is L-pVEC (LLIILRRRIRKQA-HAHSK, SEQ ID NO: 18).

[0249] 19. The compound according to any one items 1 to 6, wherein the CPP is L-MAP (KLALKLALKAL-KAALKLA, SEQ ID NO: 16).

[0250] 20. The compound according to any one items 1 to 6, wherein the CPP is L-TP2 (PLIYLRLLRGQF, SEQ ID NO: 19).

[0251] 21. The compound according to any one items 1 to 6, wherein the CPP is D-TP2 (pliylrllrGqf, SEQ ID NO: 20).

[0252] 22. The compound according to any one items 1 to 6, wherein the CPP is MiniAp4 (I(Dap)KAPET-ALDI, SEQ ID NO: 21).

[0253] 23. The compound according to any one items 1 to 6, wherein the CPP is CPP12 (IFf(Nal2)RrRrQI-GABA-K, SEQ ID NO: 22).

[0254] 24. The compound according to any one of the preceding items, wherein the amino acid sequence X_2TX_3V (SEQ ID NO: 53) is the C-terminal of P_1.

[0255] 25. The compound according to any one of the preceding items, wherein P, consists of 4 to 10 amino acid residues, such as 5 amino acid residues, such as 6 amino acid residues.

[0256] 26. The compound according to any one of the preceding items, wherein P, comprises or consists of the sequence $X_1X_2TX_3V$ (SEQ ID NO: 54), wherein

[0257] a. X_1 is selected from the group consisting of K, V and I;

[0258] b. X_2 is selected from the group consisting of E and S; and

[0259] c. X_3 is selected from the group consisting of L, T, V, R and D.

[0260] 27. The compound according to any one of the preceding items, wherein P, comprises or consists of KETLV (SEQ ID NO: 2), KETTV (SEQ ID NO: 3), KETVV (SEQ ID NO: 4), KETRV (SEQ ID NO: 5), ISTDV (SEQ ID NO: 6), VETVV (SEQ ID NO: 7) and IETDV (SEQ ID NO: 1),

[0261] 28. The compound according to any one of the preceding items, wherein the compound comprises a second peptide (P_2) comprising or consisting of the amino acid sequence X_5TX_6V (SEQ ID NO: 55), wherein

[0262] a. X_5 is selected from the group consisting of E and S; and

[0263] b. X_6 is selected from the group consisting of L, T, V, R and D.

[0264] 29. The compound according to any one of the preceding items, wherein the amino acid sequence X_5TX_6V (SEQ ID NO: 55) is the C-terminal of P_2.

[0265] 30. The compound according to any one of the preceding items, wherein P_2 consists of 4 to 10 amino acid residues, such as 5 amino acid residues, such as 6 amino acid residues.

[0266] 31. The compound according to any one of the preceding items, wherein P_2 comprises or consists of the sequence $X_4X_5TX_6V$ (SEQ ID NO: 56), wherein

[0267] a. X_4 is selected from the group consisting of K, V and I;

[0268] b. X_5 is selected from the group consisting of E and S; and

[0269] c. X_6 is selected from the group consisting of L, T, V, R and D.

[0270] 32. The compound according to any one of the preceding items, wherein P_2 comprises or consists of an amino acid sequence selected from the group consisting of KETLV (SEQ ID NO: 2), KETTV (SEQ ID NO: 3), KETVV (SEQ ID NO: 4), KETRV (SEQ ID NO: 5), ISTDV (SEQ ID NO: 6), VETVV (SEQ ID NO: 7) and IETDV (SEQ ID NO: 1).

[0271] 33. The compound according to any one of the preceding items, wherein P_1 and P_2 are identical.

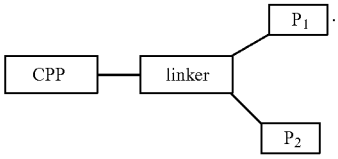
[0272] 34. The compound according to any one of the preceding items, wherein P_1 and P_2 are conjugated to a linker via their N-termini.

[0273] 35. The compound according to any one of the preceding items, wherein the CPP, such as poly-Arg, is linked to P_1 via a linker.

[0274] 36. The compound according to any one of the preceding items, wherein the CPP, such as poly-Arg, is linked to P_1 and P_2 via a linker.

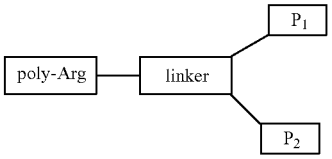
[0275] 37. The compound according to any one of the preceding items, wherein the CPP, such as poly-Arg, is linked to the linker via its C-terminal, and P_1 and P_2 are conjugated to a linker via their N-termini, and the compound has the following general structure of Formula (1):

Formula (I)



[0276] 38. The compound according to any one of the preceding items, wherein the CPP is poly-Arg and the compound has the following general structure of Formula (II):

Formula (II)



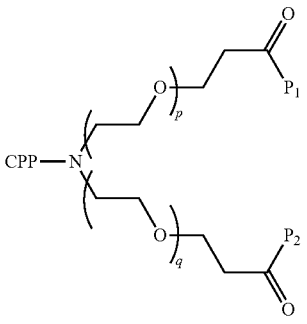
[0277] 39. The compound according to any one of the preceding items, wherein the linker comprises one or more PEG units.

[0278] 40. The compound according to item 39, wherein at least one oxygen atom of one of the PEG units is substituted with a nitrogen atom to give NPEG.

[0279] 41. The compound according to any one of the preceding items, wherein the linker comprises a NPEG unit and the CPP, such as poly-Arg, is linked to the nitrogen atom of the linker by an amide bond.

[0280] 42. The compound according to any one of the preceding items, wherein the compound has the general structure of Formula (III):

Formula (III)



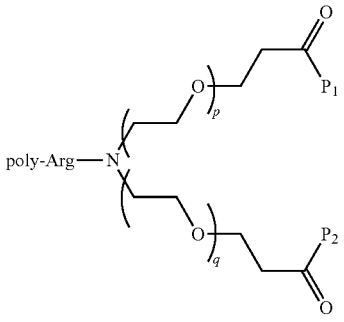
[0281] wherein

[0282] p is an integer 0 to 10; and

[0283] q is an integer 0 to 10.

[0284] 43. The compound according to any one of the preceding items, wherein the compound has the general structure of Formula (IV):

Formula (IV)



[0285] wherein

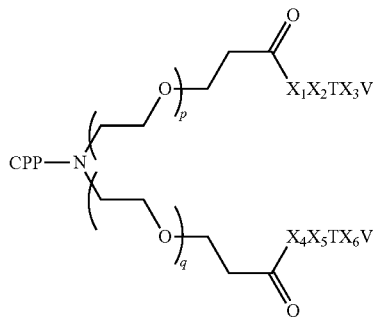
[0286] p is an integer 0 to 10; and

[0287] q is an integer 0 to 10.

[0288] 44. The compound according to any one of the preceding items, wherein the compound has the general structure of Formula (V):

[0289] wherein

Formula (V)



[0290] X_1 is selected from the group consisting of K, V and I;

[0291] X_2 is selected from the group consisting of E and S; and

[0292] X_3 is selected from the group consisting of L, T, V, R and D.

[0293] X_4 is selected from the group consisting of K, V and I;

[0294] X_5 is selected from the group consisting of E and S;

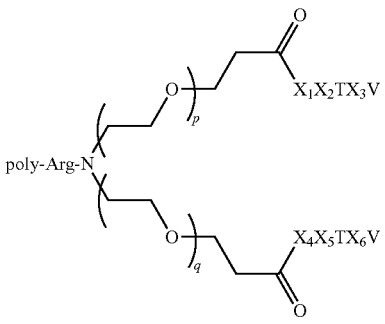
[0295] X_6 is selected from the group consisting of L, T, V, R and D.

[0296] p is an integer 0 to 10; and

[0297] q is an integer 0 to 10.

[0298] 45. The compound according to any one of the preceding items, wherein the compound has the general structure of Formula (VI):

Formula (VI)



[0299] wherein

[0300] X_1 is selected from the group consisting of K, V and I;

[0301] X_2 is selected from the group consisting of E and S; and

[0302] X_3 is selected from the group consisting of L, T, V, R and D.

[0303] X_4 is selected from the group consisting of K, V and I;

[0304] X_5 is selected from the group consisting of E and S;

[0305] X_6 is selected from the group consisting of L, T, V, R and D.

[0306] p is an integer 0 to 10; and

[0307] q is an integer 0 to 10.

[0308] 46. The compound according to any one of the preceding items, wherein p=q.

[0309] 47. The compound according to any one of the preceding items, wherein p>q.

[0310] 48. The compound according to any one of the preceding items, wherein p<q.

[0311] 49. The compound according to any one of the preceding items, wherein the sum of p and q is an integer between 1 and 20.

[0312] 50. The compound according to any one of the preceding items, wherein the number of ethylene glycol moieties, p is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 ethylene glycol moieties.

[0313] 51. The compound according to any one of the preceding items, wherein the number of ethylene glycol moieties, p, is 0 to 4.

[0314] 52. The compound according to any one of the preceding items, wherein the number of ethylene glycol moieties, q is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 ethylene glycol moieties.

[0315] 53. The compound according to any one of the preceding items, wherein the number of ethylene glycol moieties, q, is 0 to 4.

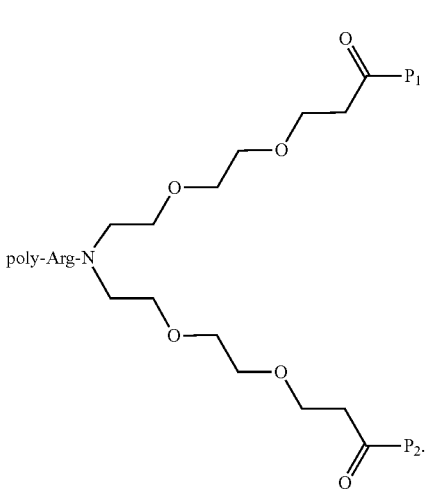
[0316] 54. The compound according to any one of the preceding items, wherein the total number of ethylene glycol moieties p+q is between 2 and 12, such as 2, such as 4, such as 6, such as 8, such as 10, such as 12.

[0317] 55. The compound according to any one of the preceding items, wherein the total number of ethylene glycol moieties p+q is 4.

[0318] 56. The compound according to any one of the preceding items, wherein p is 2 and q is 2.

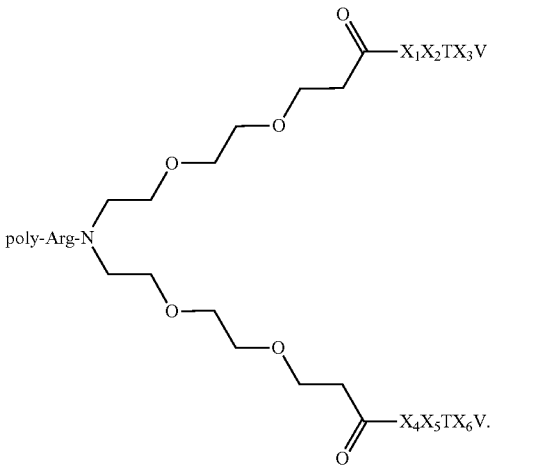
[0319] 57. The compound according to any one of the preceding items, wherein the compound has the general structure of Formula (VII):

Formula (VII)



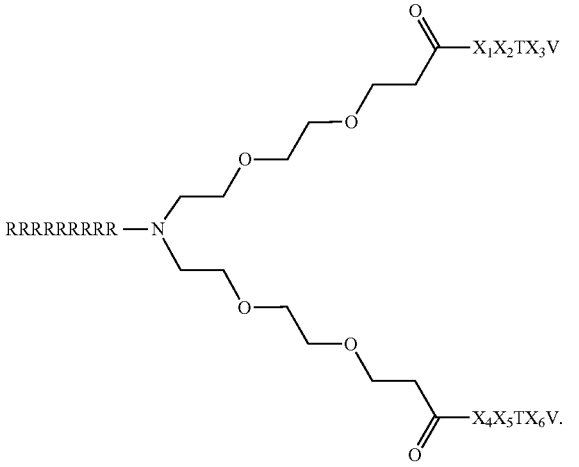
[0320] 58. The compound according to any one of the preceding items, wherein the compound has the general structure of Formula (VIII):

Formula (VIII)



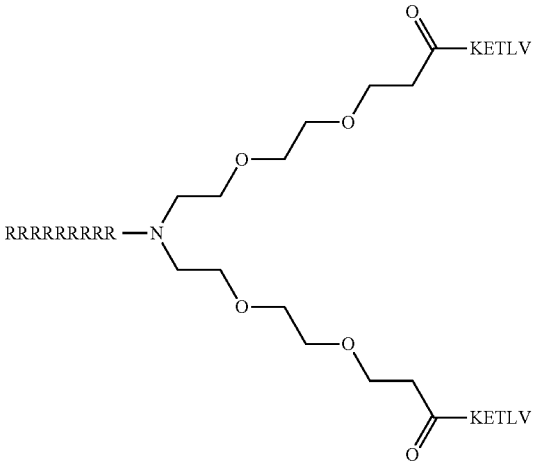
[0321] 59. The compound according to any one of the preceding items, wherein the compound has the general structure of Formula (IX):

Formula (IX)

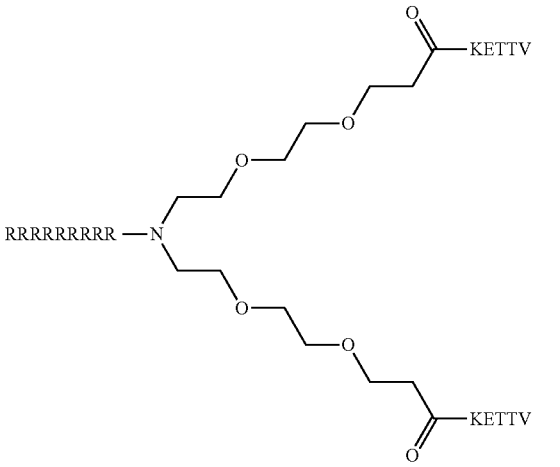


[0322] 60. The compound according to any one of the preceding items, wherein the compound is selected from the group consisting of formulas (X) to (XVI):

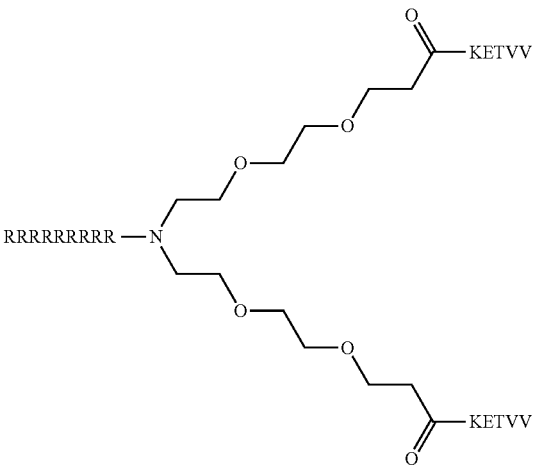
Formula (X)



Formula (XI)



Formula (XII)



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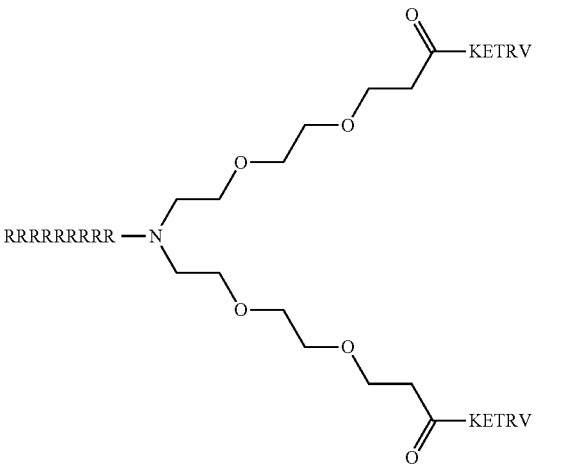
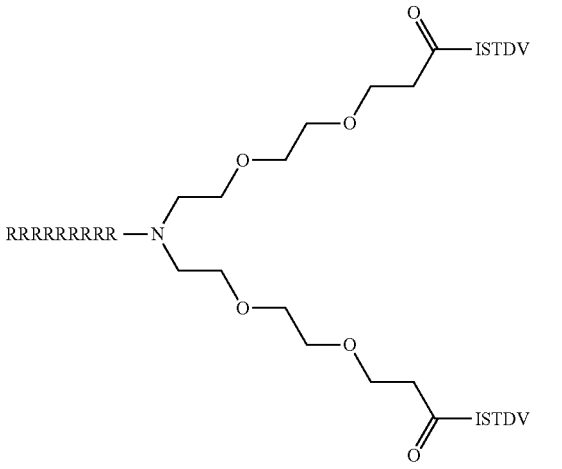
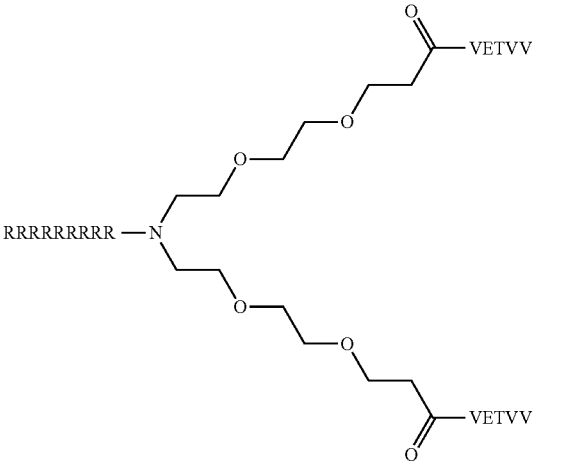
Formula (XIII)



Formula (XIV)

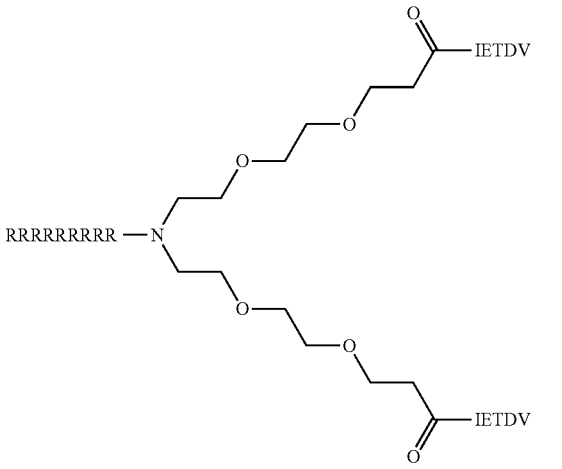


Formula (XV)



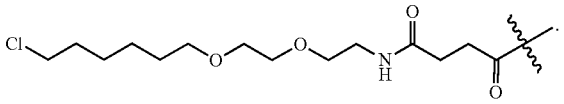
-continued

Formula (XVI)



[0323] 61. The compound according to any one of the preceding items, wherein the N-terminal of the CPP is acetylated.

[0324] 62. The compound according to any one of items 1 to 60, wherein the N-terminal of the CPP is conjugated to a chloroalkane tag (CA), which has the structure of:



[0325] 63. The compound according to any one of items 1 to 60, wherein the N-terminal of the CPP is methylated.

[0326] 64. The compound according to any one of items 1 to 60, wherein the N-terminal of the CPP is formylated.

[0327] 65. The compound according to any one of the preceding items, in the form of a pharmaceutically acceptable salt or prodrug of said compound.

[0328] 66. A compound comprising

[0329] a. a first peptide (P_1) comprising or consisting of the amino acid sequence

[0330] X_2TX_3V (SEQ ID NO: 53), wherein

[0331] X_2 is selected from the group consisting of E and S;

[0332] X_3 is selected from the group consisting of L, T, V, R and D;

[0333] b. a second peptide (P_2) comprising or consisting of the amino acid sequence X_5TX_6V (SEQ ID NO: 55), wherein

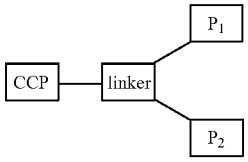
[0334] X_5 is selected from the group consisting of E and S;

[0335] X_6 is selected from the group consisting of L, T, V, R and D; and

[0336] c. a Cell Penetrating Peptide (CPP),

[0337] 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 compound has the general structure of Formula (I):

Formula (I)



and wherein the compound has a CP_{50} value of no more than 20 μM.

[0338] 67. The compound according to item 66, wherein P, comprises or consists of the sequence $X_1X_2TX_3V$ (SEQ ID NO: 54), wherein

[0339] X_1 is selected from the group consisting of K, V and I;

[0340] X_2 is selected from the group consisting of E and S; and

[0341] 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

[0342] X_4 is selected from the group consisting of K, V and I;

[0343] X_5 is selected from the group consisting of E and S; and

[0344] X_6 is selected from the group consisting of L, T, V, R and D.

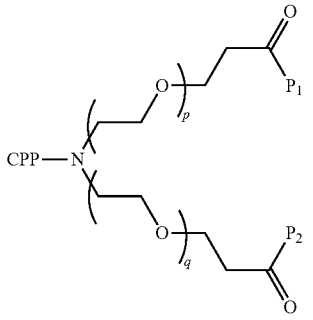
[0345] 68. The compound according to any one of item 66 or 67, wherein P_1 and/or P_2 consist of 4 to 10 amino acid residues, such as 5 amino acid residues.

[0346] 69. The compound according to any one of items 66 to 68, wherein X_3 and X_6 are selected from the group consisting of L, T, V, and R.

[0347] 70. The compound according to any one of items 66 to 68, wherein P_1 and P_2 consist of an amino acid sequence selected from the group consisting of KETLV (SEQ ID NO: 2), KETTV (SEQ ID NO: 3), KETVV (SEQ ID NO: 4), KETRV (SEQ ID NO: 5), ISTDV (SEQ ID NO: 6), and VETVV (SEQ ID NO: 7).

[0348] 71. The compound according to any one of items 66 to 70, 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 compound has the general structure of Formula (III):

Formula (III)



[0349] wherein

[0350] p is an integer 0 to 10; and

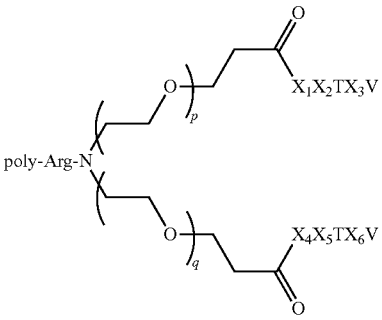
[0351] q is an integer 0 to 10.

[0352] 72. The compound according to any one of items 66 to 71, wherein the CPP is selected from the group consisting of poly-L-arginine peptide (poly-Arg); D-TAT (yGrkkrrqrrr, SEQ ID NO: 9), L-Pen (RQIKIWFQNRRMKWKK, SEQ ID NO: 14); D-Pen (rqikiwfqnrrmkwkk, SEQ ID NO: 15); L-DPV3 (RKKRRRESRKKRRRES, SEQ ID NO: 17); L-pVEC (LLIILRRRIRKQAHAHSK, SEQ ID NO: 18); L-MAP (KLALKLALKALKAALKLA, SEQ ID NO: 16); L-TP2 (PLIYLRLLRGQF, SEQ ID NO: 19); Min-iAp4 (I(Dap)KAPETALDI, SEQ ID NO: 21); and CPP12 (IFf(Nal2)RrRrQIGABA-K, SEQ ID NO: 22).

[0353] 73. The compound according to any one of items 66 to 72, wherein the CPP comprises or consists of a poly-L-arginine peptide (poly-Arg), for example a poly-Arg consisting of 5 to 10 L-arginine residues, such as 8 or 9 L-arginine residues, for example wherein the poly-Arg comprises or consists of the amino acid sequence RRRRRRRRR (SEQ ID NO: 12).

[0354] 74. The compound according to any one of items 66 to 73, wherein the compound has the general structure of Formula (VI):

Formula (VI)



[0355] wherein

[0356] X_1 is selected from the group consisting of K, V and I;

[0357] X_2 is selected from the group consisting of E and S; and

[0358] X_3 is selected from the group consisting of L, T, V, R and D.

[0359] X_4 is selected from the group consisting of K, V and I;

[0360] X_5 is selected from the group consisting of E and S;

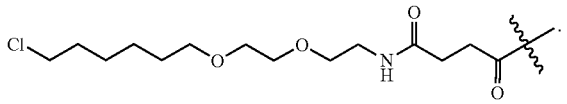
[0361] X_6 is selected from the group consisting of L, T, V, R and D.

[0362] p is an integer 0 to 10; and

[0363] q is an integer 0 to 10.

[0364] 75. The compound according to any one of items 66 to 74, wherein p is 2 and q is 2.

[0365] 76. The compound according to any one of items 66 to 75, 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:



[0366] 77. The compound according to any one of the preceding items, wherein the compound is a PSD-95 inhibitor.

[0367] 78. A pharmaceutical composition comprising the compound according to any one of the preceding items.

[0368] 79. A compound according to any one of the preceding items for use as a medicament.

[0369] 80. A compound according to any one items 1 to 77 for use in treating, preventing, reducing and/or delaying development of an excitotoxic-related disease.

[0370] 81. The compound for use according to item 80, wherein the excitotoxic-related disease is stroke.

[0371] 82. The compound for use according to item 80, wherein the excitotoxic-related disease is ischemic stroke.

[0372] 83. The compound for use according to item 80, wherein the excitotoxic-related disease is cerebral ischemia.

[0373] 84. The compound for use according to item 80, wherein the excitotoxic-related disease is acute ischemic stroke.

[0374] 85. The compound for use according to item 80, wherein the excitotoxic-related disease is subarachnoid hemorrhage.

[0375] 86. A compound according to any one of items 1 to 77 for use in the treatment or prophylaxis of pain.

[0376] 87. A kit of parts comprising at least two separate unit dosage forms (A) and (B), wherein

[0377] (A) comprises a compound according to any one of items 1 to 77; and

[0378] (B) comprises a thrombolytic agent.

[0379] 88. The kit of parts according to item 87 for use in in treating, preventing, reducing and/or delaying development of an excitotoxic-related disease and/or pain, wherein (A) and (B) are administered simultaneously, sequentially or separately to the subject.

EXAMPLES

Example 1: Synthesis

[0380] The resin bound compounds 2 to 7 ($OPEG_4$-KETLV, $OPEG_4$-KETTV, $OPEG_4$-KETVV, $OPEG_4$-KETRV, $OPEG_4$-ISTDV and $OPEG_4$-VETVV) were synthesized as previously described: Bach et al., Angew. Chem. Int. Ed., 2009, 48, 9685.

[0381] The resin bound $NPEG_4$-IETDV, $NPEG_4$-KETLV, $NPEG_4$-KETTV, $NPEG_4$-KETVV, $NPEG_4$-KETRV, $NPEG_4$-ISTDV and $NPEG_4$-VETVV were synthesized as previously described by Bach et al, Proc. Natl. Acad. Sci. USA, 2012, 109, 3317. The first C-terminus amino acid (Fmoc-Ala-OH, Fmoc-L-Arg(Pbf)-OH, Fmoc-D-Arg(Pbf)-OH, Fmoc-Asp(OAII)-OH, Fmoc-L-Lys(Boc)-OH, Fmoc-D-Lys(Boc)-OH, Fmoc-L-Lys(Ns)-OH, Fmoc-L-Phe-OH, Fmoc-D-Phe-OH, Fmoc-L-Ser(tBu)-OH) of the linear CPPs (L-TAT, DTAT, mTAT, riTAT, polyR, D-polyR, L-Pen, D-Pen, L-pVEC, L-MAP, L-DPV3, L-TP2, D-TP2, MiniAp4, CPP12) was coupled manually to the nitrogen of the NPEG4 linker three times using O-(1H-6-chlorobenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HCTU) as coupling reagent. Subsequent, synthesis of the CPPs was achieved using an automated peptide synthesizer (Prelude X, Gyros Protein Technologies, US). For the synthesis using Prelude X all reagents were prepared as solutions in DMF: Fmoc-protected amino acids (0.2 M), HCTU (0.4 M), and DIPEA (1.0 M). Sequence elongation was achieved using the following protocol: deprotection (2×2 min, rt, 350 rpm shaking) and coupling (3×10 min, 50° C., 350 rpm shaking). Amino acids were triple coupled using a mixture of Fmoc-amino acid/HCTU/DIPEA (1:1:2.5) in 5-fold excess over the resin loading. The cyclic CPP (MiniAp4 and CPP12) containing peptides were treated with 20 eq. $PhSiH_3$ and 0.2 eq. $Pd(PPh_3)_4$ in dichloromethane (DCM) under nitrogen for 2×15 min to remove allyl and alloc protecting groups. The resin was washed with DCM followed by dimethylformamide (DMF). The cyclization reaction between the side chains of Asp/Dap and or C-terminus of Glu and N-terminus of Phe was performed by treatment of the peptide with 2 eq. (benzotriazol-1-yloxy) tripyrrolidinophosphonium hexafluorophosphate (PyBOP) and 2 eq. DIPEA in DMF for 16 h at room temperature followed by DMF wash. After successful synthesis of CPP tagged dimeric peptides, the resin was split into two. The N-terminus of one part of resin-bound peptides was capped using a mixture of DMF:acetic anhydride:DIPEA (8:1.5:0.5) twice for 10 min. The N-terminus of other part of the resin-bound peptides was functionalized with chloroalkane tag (CA). The CA tag was coupled to the nitrogen group of the N-terminus of the CPP tagged peptides using a mixture of CA:PyBOP:DIPEA in DMF (3:3:10) for 16 h. In case of CPP12 containing peptide, prior to CA tag coupling the ortho-nitrobenzenesulfonyl (Ns) group was removed by adding 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.5 mmol) in DMF (2 mL) and mercaptoethanol (0.5 mmol) in DMF (2 mL) and shaking for 30 min. After a flow-wash in DMF, the mercaptoethanol/DBU treatment was repeated four times. After a final flow-wash in DMF, the CA tag was coupled to the side chain nitrogen of Lys residue.

[0382] The peptide compounds 2 to 75 were cleaved from dried resin with TFA/triisopropylsilane/2,2'-(ethylenedioxy) diethanethiol(DODT)/H_2O (90/2.&2.5) for 2 h followed by filtration, evaporation, precipitation with ice-cold ether, lyo-

philization, and purification by preparative RP-HPLC. The final peptide ligands were characterised by LC-MS for molecular weight determination and UPLC (214 nm) for purity (>95%).

[0383] The synthesis, as described above, can also be conducted at 40 mmol or up to 100 mmol scale resulting multi-gram preparation of the peptide compounds reported herein.

[0384] The peptide compounds described herein exhibited excelled solubility properties reaching 25 mg/mL concentrations and higher.

[0385] This example demonstrates that the ligands can be synthesized, purified and obtained in pure form.

Example 2: Determination of Affinity to PDZ1-2 of PSD-95

[0386] The binding affinity of the compounds 1 to 75 to PDZ1-2 of PSD-95 was measured using an in vitro fluorescent polarization (FP) assay as described by Bach et al., Proc. Natl. Acad. Sci. USA, 2012, 109, 3317. First, a saturation binding curve was obtained to determine K_D values for the interaction between a fluorescent dimeric probe and PDZ1-2 of PSD-95. Increasing concentrations of PDZ1-2 (0.015-30 nM) were added to a constant concentration of the probe (0.5 nM). The fluorescence polarization (FP) of the sample was measured at excitation/emission wavelength of 635/670 nm and the generated FP values were fitted to a one site binding model using the software GraphPad Prism. Then, the affinity of non-labeled peptides to PSD-95 PDZ12 was evaluated by a heterologous competition binding assay in which tested peptides were added in increasing concentrations (0.4-960 nM, final concentration) to a fixed amount of PSD-95 PDZ12 (4 nM) and probe (0.5 nM) using the same conditions as for the saturation binding experiment. The FP values were fitted to a one site competition (variable slope) model in GraphPad prism. The resulting IC_{50} values were converted to K_i values as described previously by Nikolovska-Coleska et al., Anal. Biochem., 2004, 332, 261).

[0387] This example describes how to determine the affinity of ligands binding to PDZ1-2 of PSD-95. The results are presented in tables 4 to 7, and FIGS. **1** to **4**. In conclusion, the tested compounds exhibited affinities (K_i values) in the low nanomolar range which are comparable to compound 1.

TABLE 4

Binding affinities (K_i), presented as mean ± SEM (FIG. 1).

Compound	Ligand	CPP	CPP sequence	K_i [nM]
1	$OPEG_4$-$(IETDV)_2$	—	—	13.7 ± 1.6
2	$OPEG_4$-$(KETLV)_2$	—	—	11.1 ± 0.3
3	$OPEG_4$-$(KETTV)_2$	—	—	14.4 ± 0.4
4	$OPEG_4$-$(KETVV)_2$	—	—	15.8 ± 1.2
5	$OPEG_4$-$(KETRV)_2$	—	—	53.2 ± 3.8
6	$OPEG_4$-$(ISTDV)_2$	—	—	53.1 ± 4.4
7	$OPEG_4$-$(VETVV)_2$	—	—	17.0 ± 0.6

Data represented as n ≥ 3.

TABLE 5

Binding affinities (K_i), presented as mean ± SEM, for dimeric ligands fused to L-TAT and L-Arg_9 (FIG. 2).

Compound	Ligand	CPP	CPP sequence	K_i [nM]
8	$NPEG_4$-$(IETDV)_2$	L-TAT	YGRKKRRQRRR-	7.2 ± 1.5
9	$NPEG_4$-$(IETDV)_2$	L-TAT	Ac-YGRKKRRQRRR-	12.5 ± 1.1
11	$NPEG_4$-$(KETLV)_2$	L-TAT	Ac-YGRKKRRQRRR-	5.4 ± 0.9
13	$NPEG_4$-$(KETTV)_2$	L-TAT	Ac-YGRKKRRQRRR-	6.5 ± 0.7

TABLE 5-continued

Binding affinities (K_i), presented as mean ± SEM, for dimeric ligands fused to L-TAT and L-Arg_9 (FIG. 2).

Compound	Ligand	CPP	CPP sequence	K_i [nM]
15	$NPEG_4$-$(KETVV)_2$	L-TAT	Ac-YGRKKRRQRRR-	2.1 ± 0.2
17	$NPEG_4$-$(KETRV)_2$	L-TAT	Ac-YGRKKRRQRRR-	6.6 ± 0.6
19	$NPEG_4$-$(ISTDV)_2$	L-TAT	Ac-YGRKKRRQRRR-	36.1 ± 1.8
21	$NPEG_4$-$(VETVV)_2$	L-TAT	Ac-YGRKKRRQRRR-	15.8 ± 1.6
35	$NPEG_4$-$(IETDV)_2$	L-Arg_9	Ac-RRRRRRRRR-	16.0 ± 0.6
23	$NPEG_4$-$(KETLV)_2$	L-Arg_9	Ac-RRRRRRRRR-	7.8 ± 0.4
25	$NPEG_4$-$(KETTV)_2$	L-Arg_9	Ac-RRRRRRRRR-	5.6 ± 0.8
27	$NPEG_4$-$(KETVV)_2$	L-Arg_9	Ac-RRRRRRRRR-	6.3 ± 0.7
29	$NPEG_4$-$(KETRV)_2$	L-Arg_9	Ac-RRRRRRRRR-	10.1 ± 1.3
31	$NPEG_4$-$(ISTDV)_2$	L-Arg_9	Ac-RRRRRRRRR-	62.3 ± 2.4
33	$NPEG_4$-$(VETVV)_2$	L-Arg_9	Ac-RRRRRRRRR-	19.9 ± 2.8

Data represented as n ≥ 3; Ac = N-terminal acetylation.

TABLE 6

Binding affinities (K_i), presented as mean ± SEM, for $NPEG_4$-$(IETDV)_2$ dimeric ligands fused to various CPP-tags (FIG. 3).

Compound	Ligand	CPP	CPP sequence	K_i [nM]
8	$NPEG_4$-$(IETDV)_2$	L-TAT	YGRKKRRQRRR-	7.2 ± 1.5
9	$NPEG_4$-$(IETDV)_2$	L-TAT	Ac-YGRKKRRQRRR-	12.5 ± 1.1
38	$NPEG_4$-$(IETDV)_2$	D-TAT	Ac-yGrkkrrqrrr-	11.8 ± 0.8
40	$NPEG_4$-$(IETDV)_2$	mTAT	Ac-rRrGrKkRr-	11.9 ± 2.7
42	$NPEG_4$-$(IETDV)_2$	riTAT	Ac-rrrqrrkkr-	14.4 ± 0.6
35	$NPEG_4$-$(IETDV)_2$	L-Arg_9	Ac-RRRRRRRRR-	11.0 ± 1.3
44	$NPEG_4$-$(IETDV)_2$	D-Arg_9	Ac-rrrrrrrrr-	8.6 ± 0.4
46	$NPEG_4$-$(IETDV)_2$	L-Pen	Ac-RQIKIWFQNRRMKWKK-	11.3 ± 1.9
48	$NPEG_4$-$(IETDV)_2$	D-Pen	Ac-rqikiwfqnrrmkwkk-	7.8 ± 0.7
50	$NPEG_4$-$(IETDV)_2$	L-DPV3	Ac-RKKRRRESRKKRRRES-	16.6 ± 3.2

TABLE 6-continued

Binding affinities (K_i), presented as mean ± SEM, for $NPEG_4$-$(IETDV)_2$ dimeric ligands fused to various CPP-tags (FIG. 3).

Compound	Ligand	CPP	CPP sequence	K_i [nM]
52	$NPEG_4$-$(IETDV)_2$	L-pVEC	Ac-LLIILRRRIRKQAHAHSK-	13.3 ± 2.2
54	$NPEG_4$-$(IETDV)_2$	L-MAP	Ac-KLALKLALKALKAALKLA-	22.4 ± 0.8
56	$NPEG_4$-$(IETDV)_2$	L-TP2	Ac-PLIYLRLLRGQF-	12.1 ± 1.3
58	$NPEG_4$-$(IETDV)_2$	D-TP2	Ac-pliylrllrGqf-	11.9 ± 0.7
60	$NPEG_4$-$(IETDV)_2$	MiniAp4	Ac-|(Dap)KAPETALD|-	12.1 ± 1.3
62	$NPEG_4$-$(IETDV)_2$	CPP12	|Ff(Nal2)RrRrQ|GABA-K-	12.5 ± 1.1

Data represented as n ≥ 3; Ac = N-terminal acetylation.

TABLE 7

Binding affinities (K_i), presented as mean ± SEM, for $NPEG_4$-$(KETLV)_2$ dimeric ligands fused to polyArg CPP-tags (FIG. 4).

Compound	Ligand	CPP	CPP sequence	K_i [nM]
67	$NPEG_4$-$(KETLV)_2$	L-Arg_7	Ac-RRRRRRR-	5.8 ± 0.6
69	$NPEG_4$-$(KETLV)_2$	L-Arg_6	Ac-RRRRRR-	8.6 ± 0.3
71	$NPEG_4$-$(KETLV)_2$	L-Arg_5	Ac-RRRRR-	10.9 ± 1.3
72	$NPEG_4$-$(KETLV)_2$	L-Arg_4	Ac-RRRR-	11.1 ± 0.9

Data represented as n ≥ 3; Ac = N-terminal acetylation.

Example 3: In Vitro Plasmin Stability of Ligands

[0388] The in vitro plasmin stability of the compounds 8 to 62 was determined by incubating 100 μM of ligand in phosphate buffered saline (PBS) supplemented with plasmin (5 μg/mL) at 37° C. for 0-1440 minutes. At selected time points during the incubation, the ligands were extracted from 80 μL of assay matrix by treatment with 80 μL of 50% acetonitrile (ACN). The samples were filtered and analysed by UPLC to determine the amount of ligand remaining. LC-MS analysis was performed to confirm ligand integrity and identify cleavage sites.

[0389] This example describes how to determine the in vitro plasmin stability of ligands binding to PDZ1-2 of PSD-95. The results are presented in tables 8 and 9, and FIGS. **5** and **6**. In conclusion, the tested compounds containing the CPP L-Arg_9(SEQ ID NO 12) exhibit in vitro plasmin half-life times comparable to compounds containing D-amino acids or macrocyclic CPPs (FIG. **6**). Unexpectedly, the half-life of L-Arg_9 containing compounds was significantly better than those of L-TAT (SEQ ID NO 8) (FIGS. **5**, and **6**).

TABLE 8

In vitro plasmin stability, half-life times presented as mean ± SEM, for $NPEG_4$ dimeric ligands fused to L-TAT and L-Arg_9 (FIG. 5).

Compound	Ligand	CPP	CPP sequence	$T_{1/2}$ [min]
8	$NPEG_4$-$(IETDV)_2$	L-TAT	YGRKKRRQRRR-	543 ± 60
9	$NPEG_4$-$(IETDV)_2$	L-TAT	Ac-YGRKKRRQRRR-	229 ± 129

TABLE 8-continued

In vitro plasmin stability, half-life times presented as mean ± SEM, for $NPEG_4$ dimeric ligands fused to L-TAT and L-Arg_9 (FIG. 5).

Compound	Ligand	CPP	CPP sequence	$T_{1/2}$ [min]
11	$NPEG_4$-$(KETLV)_2$	L-TAT	Ac-YGRKKRRQRRR-	346 ± 105
13	$NPEG_4$-$(KETTV)_2$	L-TAT	Ac-YGRKKRRQRRR-	570 ± 180
15	$NPEG_4$-$(KETVV)_2$	L-TAT	Ac-YGRKKRRQRRR-	385 ± 130
17	$NPEG_4$-$(KETRV)_2$	L-TAT	Ac-YGRKKRRQRRR-	385 ± 130
19	$NPEG_4$-$(ISTDV)_2$	L-TAT	Ac-YGRKKRRQRRR-	534 ± 40
21	$NPEG_4$-$(VETVV)_2$	L-TAT	Ac-YGRKKRRQRRR-	532 ± 41
35	$NPEG_4$-$(IETDV)_2$	L-Arg_9	Ac-RRRRRRRRR-	1492 ± 114
23	$NPEG_4$-$(KETLV)_2$	L-Arg_9	Ac-RRRRRRRRR-	2618 ± 276
25	$NPEG_4$-$(KETTV)_2$	L-Arg_9	Ac-RRRRRRRRR-	1152 ± 203
27	$NPEG_4$-$(KETVV)_2$	L-Arg_9	Ac-RRRRRRRRR-	1530 ± 578
29	$NPEG_4$-$(KETRV)_2$	L-Arg_9	Ac-RRRRRRRRR-	1003 ± 171
31	$NPEG_4$-$(ISTDV)_2$	L-Arg_9	Ac-RRRRRRRRR-	1405 ± 124
33	$NPEG_4$-$(VETVV)_2$	L-Arg_9	Ac-RRRRRRRRR-	479 ± 77

Data represented as n ≥ 3; Ac = N-terminal acetylation.

TABLE 9

In vitro plasmin stability, half-life times presented as mean ± SEM, for $NPEG_4$-$(IETDV)_2$ dimeric ligands fused to various CPP-tags (FIG. 6).

Compound	Ligand	CPP	CPP sequence	$T_{1/2}$ [min]
8	$NPEG_4$-$(IETDV)_2$	L-TAT	YGRKKRRQRRR-	543 ± 60
9	$NPEG_4$-$(IETDV)_2$	L-TAT	Ac-YGRKKRRQRRR-	229 ± 129
38	$NPEG_4$-$(IETDV)_2$	D-TAT	Ac-ygrkkrrqrrr-	1440 ± 0
40	$NPEG_4$-$(IETDV)_2$	mTAT	Ac-rRrGrKkRr-	1440 ± 0
42	$NPEG_4$-$(IETDV)_2$	riTAT	Ac-rrrqrrkkr-	1440 ± 0
35	$NPEG_4$-$(IETDV)_2$	L-Arg_9	Ac-RRRRRRRRR-	1492 ± 114
44	$NPEG_4$-$(IETDV)_2$	D-Arg_9	Ac-rrrrrrrrr-	1440 ± 0

TABLE 9-continued

In vitro plasmin stability, half-life times presented as mean ± SEM, for $NPEG_4$-$(IETDV)_2$ dimeric ligands fused to various CPP-tags (FIG. 6).

Compound	Ligand	CPP	CPP sequence	$T_{1/2}$ [min]
46	$NPEG_4$-$(IETDV)_2$	L-Pen	Ac-RQIKIWFQNRRMKWKK-	94 ± 8
48	$NPEG_4$-$(IETDV)_2$	D-Pen	Ac-rqikiwfqnrrmkwkk-	1440 ± 0
50	$NPEG_4$-$(IETDV)_2$	L-DPV3	Ac-RKKRRRESRKKRRRES-	169 ± 20
52	$NPEG_4$-$(IETDV)_2$	L-pVEC	Ac-LLIILRRRIRKQAHAHSK-	49 ± 9
54	$NPEG_4$-$(IETDV)_2$	L-MAP	Ac-KLALKLALKALKAALKLA-	13 ± 4
56	$NPEG_4$-$(IETDV)_2$	L-TP2	Ac-PLIYLRLLRGQF-	910 ± 0
58	$NPEG_4$-$(IETDV)_2$	D-TP2	Ac-pliylrllrGqf-	1440 ± 0
60	$NPEG_4$-$(IETDV)_2$	MiniAp4	Ac-|(Dap)KAPETALD|-	1440 ± 0
62	$NPEG_4$-$(IETDV)_2$	CPP12	|Ff(Nal2)RrRrQ|GABA-K-	1440 ± 0

Data represented as n ≥ 3; Ac = N-terminal acetylation.

Example 4: Determination of Membrane Permeability and Cellular Uptake of Ligands

[0390] The membrane permeability of compounds 10 to 75 was determined in HeLa cells stably expressing HaloGFP exclusively located in the cytosol. Cells were seeded at a density of 40.000 cells/well one day prior to the experiment. After the growth media was aspirated and replaced by 100 µL of Opti-MEM, 25 µL of a prepared serial dilution of the ligand in Opti-MEM was added to the cells (constant DMSO concentration), and the plate was incubated for 4 h at 37° C. and 5% CO_2. The contents of the wells were aspirated, and cells were washed with fresh Opti-MEM for 15 min. After aspiration of the wash, the cells were incubated with TAMRA-CA (5 µM) for 15 min. After aspiration of the chase solution, cells were washed with Opti-MEM for 30 min. Following removal of the wash, cells were trypsinized, resuspended in PBS (2% FBS), and analyzed using a bench-top flow cytometer. Using no ligand and no TAMRA-CA control well, the obtained fluorescence intensity data was normalized and plotted as dose-response curves. Reported CP_{50} values represent half-maximum red fluorescence which behaves inverse to cell penetration of the ligand.

[0391] This example describes how to determine the membrane permeability and cellular uptake of CA-tagged compounds binding to PDZ1-2 of PSD-95. The results are presented in tables 10 to 12, and FIGS. **7** to **9**. In conclusion, the tested compounds show significantly different cellular uptake efficiencies, which greatly depend on the employed CPP. Surprisingly, the CPP-tag L-Arg_9(SEQ ID NO 12) and L-pVEC (SEQ ID NO: 18) result in the lowest CP_{50} values (FIG. **8**). Dependent on the dimeric ligand, L-Arg_9 further promotes highly efficient cellular uptake with CP_{50} values below 1 µM (FIG. **7**) suggesting superior BBB penetration and intracellular delivery. In addition, the L-Arge CPP-tag can be truncated to 7, 6, 5, or 4 Arginines (see table 12) without losing its cell-permeable properties (FIG. **9**).

TABLE 10

Membrane permeability and cellular uptake, CP_{50} presented as mean ± SEM, for $NPEG_4$ dimeric ligands fused to L-TAT and L-Arg_9 (FIG. 7).

Compound	Ligand	CPP	CPP sequence	CP_{50} [µM]
10	$NPEG_4$-$(IETDV)_2$	L-TAT	CA-YGRKKRRQRRR-	55.1 ± 3.0
12	$NPEG_4$-$(KETLV)_2$	L-TAT	CA-YGRKKRRQRRR-	72.5 ± 4.4
14	$NPEG_4$-$(KETTV)_2$	L-TAT	CA-YGRKKRRQRRR-	78.4 ± 3.9
16	$NPEG_4$-$(KETVV)_2$	L-TAT	CA-YGRKKRRQRRR-	81.8 ± 1.2

TABLE 10-continued

Membrane permeability and cellular uptake, CP_{50} presented as mean ± SEM, for $NPEG_4$ dimeric ligands fused to L-TAT and L-Arg_9 (FIG. 7).

Compound	Ligand	CPP	CPP sequence	CP_{50} [μM]
18	$NPEG_4$-$(KETRV)_2$	L-TAT	CA-YGRKKRRQRRR-	47.7 ± 1.0
20	$NPEG_4$-$(ISTDV)_2$	L-TAT	CA-YGRKKRRQRRR-	41.9 ± 1.6
22	$NPEG_4$-$(VETVV)_2$	L-TAT	CA-YGRKKRRQRRR-	86.1 ± 4.5
36	$NPEG_4$-$(IETDV)_2$	L-Arg_9	CA-RRRRRRRRR-	3.25 ± 0.19
24	$NPEG_4$-$(KETLV)_2$	L-Arg_9	CA-RRRRRRRRR-	0.78 ± 0.05
26	$NPEG_4$-$(KETTV)_2$	L-Arg_9	CA-RRRRRRRRR-	0.74 ± 0.09
28	$NPEG_4$-$(KETVV)_2$	L-Arg_9	CA-RRRRRRRRR-	0.79 ± 0.06
30	$NPEG_4$-$(KETRV)_2$	L-Arg_9	CA-RRRRRRRRR-	0.68 ± 0.05
32	$NPEG_4$-$(ISTDV)_2$	L-Arg_9	CA-RRRRRRRRR-	1.05 ± 0.15
34	$NPEG_4$-$(VETVV)_2$	L-Arg_9	CA-RRRRRRRRR-	0.84 ± 0.15

Data represented as n ≥ 3; Ac = N-terminal acetylation.

TABLE 11

Membrane permeability and cellular uptake, CP_{50} presented as mean ± SEM, for $NPEG_4$-$(IETDV)_2$ dimeric ligands fused to various CPP-tags (FIG. 8).

Compound	Ligand	CPP	CPP sequence	CP_{50} [μM]
10	$NPEG_4$-$(IETDV)_2$	L-TAT	CA-YGRKKRRQRRR-	55.1 ± 3.0
39	$NPEG_4$-$(IETDV)_2$	D-TAT	CA-yGrkkrrqrrr-	10.7 ± 0.7
41	$NPEG_4$-$(IETDV)_2$	mTAT	CA-rRrGrKkRr-	180 ± 8.2
43	$NPEG_4$-$(IETDV)_2$	riTAT	CA-rrrqrrkkr-	221 ± 36
36	$NPEG_4$-$(IETDV)_2$	L-Arg_9	CA-RRRRRRRRR-	3.3 ± 0.2
45	$NPEG_4$-$(IETDV)_2$	D-Arg_9	CA-rrrrrrrrr-	161 ± 25
47	$NPEG_4$-$(IETDV)_2$	L-Pen	CA-RQIKIWFQNRRMKWKK-	5.0 ± 0.4
49	$NPEG_4$-$(IETDV)_2$	D-Pen	CA-rqikiwfqnrrmkwkk-	18.8 ± 1.5
51	$NPEG_4$-$(IETDV)_2$	L-DPV3	CA-RKKRRRESRKKRRRES-	3.2 ± 0.5
53	$NPEG_4$-$(IETDV)_2$	L-pVEC	CA-LLIILRRRIRKQAHAHSK-	1.7 ± 0.1

TABLE 11-continued

Membrane permeability and cellular uptake, CP_{50} presented as mean ± SEM, for $NPEG_4$-$(IETDV)_2$ dimeric ligands fused to various CPP-tags (FIG. 8).

Compound	Ligand	CPP	CPP sequence	CP_{50} [μM]
55	$NPEG_4$-$(IETDV)_2$	L-MAP	CA-KLALKLALKALKAALKLA-	3.7 ± 0.3
57	$NPEG_4$-$(IETDV)_2$	L-TP2	CA-PLIYLRLLRGQF-	17.9 ± 0.3
59	$NPEG_4$-$(IETDV)_2$	D-TP2	CA-pliylrllrGqf-	67.2 ± 5.3
61	$NPEG_4$-$(IETDV)_2$	MiniAp4	CA-|(Dap)KAPETALD|-	13.2 ± 0.4
63	$NPEG_4$-$(IETDV)_2$	CPP12	|Ff(Nal2)RrRrQ|GABA-K(CA)-	11.2 ± 0.7

Data represented as n ≥ 3; Ac = N-terminal acetylation.

TABLE 12

Membrane permeability and cellular uptake, CP_{50} presented as mean ± SEM, for $NPEG_4$-$(IETDV)_2$ and $MPEG_4$-$(KETLV)_2$ dimeric ligands fused to polyArg CPP-tags (FIG. 9).

Compound	Ligand	CPP	CPP sequence	CP_{50} [μM]
64	$NPEG_4$-$(IETDV)_2$	L-Arg_7	CA-RRRRRRR-	1.66 ± 0.43
65	$NPEG_4$-$(IETDV)_2$	L-Arg_5	CA-RRRRR-	1.17 ± 0.37
66	$NPEG_4$-$(IETDV)_2$	L-Arg_3	CA-RRR-	3.71 ± 0.30
68	$NPEG_4$-$(KETLV)_2$	L-Arg_7	CA-RRRRRRR-	0.58 ± 0.09
70	$NPEG_4$-$(KETLV)_2$	L-Arg_6	CA-RRRRRR-	0.51 ± 0.08
72	$NPEG_4$-$(KETLV)_2$	L-Arg_5	CA-RRRRR-	0.66 ± 0.14
74	$NPEG_4$-$(KETLV)_2$	L-Arg_4	CA-RRRR-	0.37 ± 0.08
75	$NPEG_4$-$(KETLV)_2$	L-Arg_3	CA-RRR-	7.36 ± 0.31

Data represented as n ≥ 3; Ac = N-terminal acetylation.

Example 5: Determination of In Vitro Plasma Stability

[0392] The in vitro plasma stability of the compounds 8, 23, 35, 67, 69, 71 and 73 was determined by incubating 100 μM of ligand in undiluted pooled human plasma at 37° C. for 1440 minutes. At selected time points during the incubation, the ligands were extracted from the assay matrix by adding assay matrix to 6M Urea followed by precipitation using 20% TCA in acetone. After overnight incubation, the samples were filtered and analysed by UPLC to determine the amount of ligand remaining. LC-MS analysis was performed to confirm ligand integrity and identify cleavage sites.

[0393] This example describes how to determine the in vitro plasma stability of ligands binding to PDZ1-2 of PSD-95. The results are presented in table 13, and FIG. **10**. In conclusion, the L-Arg_9 CPP-tag can be truncated to 7, 6, 5, or 4 Arginines (see table 13) without being significantly less stable to human plasma.

TABLE 13

In vitro plasma stability, half-life times presented as mean ± SEM, for $NPEG_4$-$(KETLV)_2$ dimeric ligands fused to polyArg CPP-tags (FIG. 10).

Compound	Ligand	CPP	CPP sequence	$T_{1/2}$ [min]
8	$NPEG_4$-$(IETDV)_2$	L-TAT	YGRKKRRQRRR-	1440 ± 0
35	$NPEG_4$-$(IETDV)_2$	$L\text{-}Arg_9$	Ac-RRRRRRRRR-	1440 ± 0
23	$NPEG_4$-$(KETLV)_2$	$L\text{-}Arg_9$	Ac-RRRRRRRRR-	1440 ± 0
67	$NPEG_4$-$(KETLV)_2$	$L\text{-}Arg_7$	Ac-RRRRRRR-	1440 ± 0
69	$NPEG_4$-$(KETLV)_2$	$L\text{-}Arg_6$	Ac-RRRRRR-	1440 ± 0
71	$NPEG_4$-$(KETLV)_2$	$L\text{-}Arg_5$	Ac-RRRRR-	1266 ± 138
73	$NPEG_4$-$(KETLV)_2$	$L\text{-}Arg_4$	Ac-RRRR-	912 ± 216

Data represented as n ≥ 3; Ac = N-terminal acetylation.

Example 6: Determination of In Vivo Brain Levels Post i.v. Injection

[0394] Female Balb/c mice (4 groups of 3 animals) are dosed with 18 nmol/g bodyweight with compounds of interested using isotonic saline as vehicle. Group 1 is used to obtain blood concentration profiles post i.v. injection at selected time points (max. 4h post injection). Groups 2 to 4 are used to determine blood and brain concentrations at three different timepoints. Animals are therefore terminated at selected timepoints post i.v. injection, relevant tissue is collected and analysed using appropriate methods (LC-MS/MS).

[0395] The example describes how to determine in vivo brain levels of ligands binding to PDZ1-2 of PSD-95. Furthermore, blood to brain ratios and relative tissue targeting efficiencies are determined, informing about a compounds ability to cross the blood-brain barrier and reach the target in the brain.

Example 7: Determination of In Vivo Neuroprotective Effect Against Stroke Induced Damage Using a pMCAO Mouse Model

[0396] For experimental and surgical details see Bach et al, Proc. Natl. Acad. Sci. USA, 2012, 109, 3317. In brief, the extent of ischemic infarct is being measured in a randomized, double-blinded, placebo-controlled study using a permanent middle cerebral artery occlusion (pMCAO) model in C57BL/6J mice. Following anaesthesia and artery occlusion, animals are dosed 30 min post-surgery. Animals surviving 6h post-surgery were terminated, and the brain carefully removed. Following fixation and slicing of the brains, infarct volumetric analysis was performed, and the total infarct volume calculated. The example describes how to determine the in vivo neuroprotective effect of ligans binding PDZ1-2 of PSD-95. Read out parameter is the infarct volume in the compound treated group versus placebo controlled group.

Sequences

SEQ ID NO	Sequence	Comment
1	IETDV	
2	KETLV	
3	KETTV	
4	KETVV	
5	KETRV	
6	ISTDV	
7	VETVV	
8	YGRKKRRQRRR	L-TAT
9	yGrkkrrqrrr	D-TAT
10	rRrGrKkRr	mTAT

-continued

Sequences

SEQ ID NO	Sequence	Comment
11	rrrqrrkkr	riTAT
12	RRRRRRRRR	L-Arg_9
13	rrrrrrrrr	D-Arg_9
14	RQIKIWFQNRRMKWKK	L-Pen
15	rqikiwfqnrrmkwkk	D-Pen
16	KLALKLALKALKAALKLA	L-MAP
17	RKKRRRESRKKRRRES	L-DPV3
18	LLIILRRRIRKQAHAHSK	L-pVEC
19	PLIYLRLLRGQF	L-TP2
20	pliylrllrGqf	D-TP2
21	|(Dap)KAPETALD|	MiniAp4 Side chain-to-side chain macrolactamization through D and Dap Dap is L-2,3-diaminopropionic acid
22	|Ff(Nal2)RrRrQ|GABA-K	CPP12 Head-to-tail macrolactamization through Q and F Nal2 is L-2-naphthylalanine
23	Ac-YGRKKRRQRRR-	L-TAT N-terminal acetylated
24	CA-YGRKKRRQRRR-	L-TAT N-terminal conjugated to chloroalkane (CA)
25	Ac-RRRRRRRRR-	L-Arg_9 N-terminal acetylated
26	CA-RRRRRRRRR-	L-Arg_9 N-terminal conjugated to chloroalkane (CA)
27	Ac-ygrkkrrqrrr-	D-TAT N-terminal acetylated
28	CA-ygrkkrrqrrr-	D-TAT N-terminal conjugated to chloroalkane (CA)
29	Ac-rRrGrKkRr-	mTAT N-terminal acetylated
30	CA-rRrGrKkRr-	mTAT N-terminal conjugated to chloroalkane (CA)
31	Ac-rrrqrrkkr-	riTAT N-terminal acetylated
32	CA-rrrqrrkkr-	riTAT N-terminal conjugated to chloroalkane (CA)
33	Ac-rrrrrrrrr-	D-Arg_9 N-terminal acetylated
34	CA-rrrrrrrrr-	D-Arg_9 N-terminal conjugated to chloroalkane (CA)

-continued

Sequences

SEQ ID NO	Sequence	Comment
35	Ac-RQIKIWFQNRRMKWKK-	L-Pen N-terminal acetylated
36	CA-RQIKIWFQNRRMKWKK-	L-Pen N-terminal conjugated to chloroalkane (CA)
37	Ac-rqikiwfqnrrmkwkk-	D-Pen N-terminal acetylated
38	CA-rqikiwfqnrrmkwkk-	D-Pen N-terminal conjugated to chloroalkane (CA)
39	Ac-RKKRRRESRKKRRRES-	L-DPV3 N-terminal acetylated
40	CA-RKKRRRESRKKRRRES-	L-DPV3 N-terminal conjugated to chloroalkane (CA)
41	Ac-LLIILRRRIRKQAHAHSK-	L-pVEC N-terminal acetylated
42	CA-LLIILRRRIRKQAHAHSK-	L-pVEC N-terminal conjugated to chloroalkane (CA)
43	Ac-KLALKLALKALKAALKLA-	L-MAP N-terminal acetylated
44	CA-KLALKLALKALKAALKLA-	L-MAP N-terminal conjugated to chloroalkane (CA)
45	Ac-PLIYLRLLRGQF-	L-TP2 N-terminal acetylated
46	CA-PLIYLRLLRGQF-	L-TP2 N-terminal conjugated to chloroalkane (CA)
47	Ac-pliylrllrGqf- N-terminal acetylated	D-TP2 N-terminal acetylated
48	CA-pliylrllrGqf-	D-TP2 N-terminal conjugated to chloroalkane (CA)
49	Ac-|(Dap)KAPETALD|- N-terminal acetylated	MiniAp4 N-terminal acetylated
50	CA-|(Dap)KAPETALD|-	MiniAp4 N-terminal conjugated to chloroalkane
51	|Ff(Nal2)RrRrQ|GABA-K-	CPP12 No modification of the side chain of K
52	|Ff(Nal2)RrRrQ|GABA-K(CA)-	CPP12 Chloroalkane (CA) is conjugated to the amine in the side chain of K
53	X_2TX_3V	X_2 is E or S X_3 is L, T, V, R or D
54	$X_1X_2TX_3V$	X_1 is K, V or I X_2 is E or S X_3 is L, T, V, R or D
55	X_5TX_6V	X_5 is E or S X_6 is L, T, V, R or D

-continued

Sequences

SEQ ID NO	Sequence	Comment
56	$X_4X_5TX_6V$	X_4 is K, V or I X_5 is E or S X_6 is L, T, V, R or D
57	RRRRRRRR	L-Arg_8
58	RRRRRRR	L-Arg_7
59	RRRRRR	L-Arg_6
60	RRRRR	L-Arg_5
61	RRRR	L-Arg_4
62	Ac-RRRRRRRR-	L-Arg_8 N-terminal acetylated
63	Ac-RRRRRRR-	L-Arg_7 N-terminal acetylated
64	Ac-RRRRRR-	L-Arg_6 N-terminal acetylated
65	Ac-RRRRR-	L-Arg_5 N-terminal acetylated
66	Ac-RRRR-	L-Arg_4 N-terminal acetylated
67	CA-RRRRRRRR-	L-Arg_8 N-terminal conjugated to chloroalkane (CA)
68	CA-RRRRRRR-	L-Arg_7 N-terminal conjugated to chloroalkane (CA)
69	CA-RRRRRR-	L-Arg_6 N-terminal conjugated to chloroalkane (CA)
70	CA-RRRRR-	L-Arg_5 N-terminal conjugated to chloroalkane (CA)
71	CA-RRRR-	L-Arg_4 N-terminal conjugated to chloroalkane (CA)

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through D and Dap

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<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(9)
<223> OTHER INFORMATION: D-Arg9
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(9)
<223> OTHER INFORMATION: D amino acids
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: N-terminal acetylated

<400> SEQUENCE: 33

Arg Arg Arg Arg Arg Arg Arg Arg Arg
1 5

<210> SEQ ID NO 34
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:

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<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(9)
<223> OTHER INFORMATION: D-Arg9
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(9)
<223> OTHER INFORMATION: D amino acids
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: N-terminal conjugated to chloroalkane (CA)

<400> SEQUENCE: 34

Arg Arg Arg Arg Arg Arg Arg Arg Arg
1 5

<210> SEQ ID NO 35
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(16)
<223> OTHER INFORMATION: L-Pen
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: N-terminal acetylated

<400> SEQUENCE: 35

Arg Gln Ile Lys Ile Trp Phe Gln Asn Arg Arg Met Lys Trp Lys Lys
1 5 10 15

<210> SEQ ID NO 36
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(16)
<223> OTHER INFORMATION: L-Pen
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: N-terminal conjugated to chloroalkane (CA)

<400> SEQUENCE: 36

Arg Gln Ile Lys Ile Trp Phe Gln Asn Arg Arg Met Lys Trp Lys Lys
1 5 10 15

<210> SEQ ID NO 37
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(16)
<223> OTHER INFORMATION: D-Pen
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(16)
<223> OTHER INFORMATION: D amino acids
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE

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<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: N-terminal acetylated

<400> SEQUENCE: 37

Arg Gln Ile Lys Ile Trp Phe Gln Asn Arg Arg Met Lys Trp Lys Lys
1 5 10 15

<210> SEQ ID NO 38
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(16)
<223> OTHER INFORMATION: D-Pen
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(16)
<223> OTHER INFORMATION: D amino acids
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: N-terminal conjugated to chloroalkane (CA)

<400> SEQUENCE: 38

Arg Gln Ile Lys Ile Trp Phe Gln Asn Arg Arg Met Lys Trp Lys Lys
1 5 10 15

<210> SEQ ID NO 39
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(16)
<223> OTHER INFORMATION: L-DPV3
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: N-terminal acetylated

<400> SEQUENCE: 39

Arg Lys Lys Arg Arg Arg Glu Ser Arg Lys Lys Arg Arg Arg Glu Ser
1 5 10 15

<210> SEQ ID NO 40
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(16)
<223> OTHER INFORMATION: L-DPV3
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: N-terminal conjugated to chloroalkane (CA)

<400> SEQUENCE: 40

Arg Lys Lys Arg Arg Arg Glu Ser Arg Lys Lys Arg Arg Arg Glu Ser
1 5 10 15

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<210> SEQ ID NO 41
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: L-pVEC
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: N-terminal acetylated

<400> SEQUENCE: 41

Leu Leu Ile Ile Leu Arg Arg Arg Ile Arg Lys Gln Ala His Ala His
1 5 10 15

Ser Lys

<210> SEQ ID NO 42
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: L-pVEC
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: N-terminal conjugated to chloroalkane (CA)

<400> SEQUENCE: 42

Leu Leu Ile Ile Leu Arg Arg Arg Ile Arg Lys Gln Ala His Ala His
1 5 10 15

Ser Lys

<210> SEQ ID NO 43
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: L-MAP
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: N-terminal acetylated

<400> SEQUENCE: 43

Lys Leu Ala Leu Lys Leu Ala Leu Lys Ala Leu Lys Ala Ala Leu Lys
1 5 10 15

Leu Ala

<210> SEQ ID NO 44
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:

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<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: L-MAP
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: N-terminal conjugated to chloroalkane (CA)

<400> SEQUENCE: 44

Lys Leu Ala Leu Lys Leu Ala Leu Lys Ala Leu Lys Ala Ala Leu Lys
1 5 10 15

Leu Ala

<210> SEQ ID NO 45
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(12)
<223> OTHER INFORMATION: L-TP2
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(11)
<223> OTHER INFORMATION: N-terminal acetylated

<400> SEQUENCE: 45

Pro Leu Ile Tyr Leu Arg Leu Leu Arg Gly Gln Phe
1 5 10

<210> SEQ ID NO 46
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(12)
<223> OTHER INFORMATION: L-TP2
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: N-terminal conjugated to chloroalkane (CA)

<400> SEQUENCE: 46

Pro Leu Ile Tyr Leu Arg Leu Leu Arg Gly Gln Phe
1 5 10

<210> SEQ ID NO 47
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(12)
<223> OTHER INFORMATION: D-TP2
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(12)
<223> OTHER INFORMATION: D amino acids
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: N-terminal acetylated

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<400> SEQUENCE: 47

Pro Leu Ile Tyr Leu Arg Leu Leu Arg Gly Gln Phe
1 5 10

<210> SEQ ID NO 48
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(12)
<223> OTHER INFORMATION: D-TP2
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(12)
<223> OTHER INFORMATION: D amino acids
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: N-terminal conjugated to chloroalkane (CA)

<400> SEQUENCE: 48

Pro Leu Ile Tyr Leu Arg Leu Leu Arg Gly Gln Phe
1 5 10

<210> SEQ ID NO 49
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(9)
<223> OTHER INFORMATION: MiniAp4
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: X is Dap
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: N-terminal acetylated

<400> SEQUENCE: 49

Xaa Lys Ala Pro Glu Thr Ala Leu Asp
1 5

<210> SEQ ID NO 50
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(9)
<223> OTHER INFORMATION: MiniAp4
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: X is Dap
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: N-terminal conjugated to chloroalkane (CA)

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<400> SEQUENCE: 50

Xaa Lys Ala Pro Glu Thr Ala Leu Asp
1 5

<210> SEQ ID NO 51
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(13)
<223> OTHER INFORMATION: CPP12
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: D amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: X is Nal2
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: D amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: D amino acid

<400> SEQUENCE: 51

Phe Phe Xaa Arg Arg Arg Arg Gln Gly Ala Asx Ala Lys
1 5 10

<210> SEQ ID NO 52
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(13)
<223> OTHER INFORMATION: CPP12
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: D amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: X is Nal2
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: D amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: D amino acid

<400> SEQUENCE: 52

Phe Phe Xaa Arg Arg Arg Arg Gln Gly Ala Asx Ala Lys
1 5 10

<210> SEQ ID NO 53
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(4)
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: X is E or S
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: X is L, T, V, R or D

<400> SEQUENCE: 53

Xaa Thr Xaa Val
1

<210> SEQ ID NO 54
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(5)
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: X is K, V or I
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: X is E or S
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: X is L, T, V, R or D

<400> SEQUENCE: 54

Xaa Xaa Thr Xaa Val
1   5

<210> SEQ ID NO 55
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(4)
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: X is E or S
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: X is L, T, V, R or D

<400> SEQUENCE: 55

Xaa Thr Xaa Val
1

<210> SEQ ID NO 56
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(5)
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: X is K, V or I
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: X is E or S
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: X is L, T, V, R or D

<400> SEQUENCE: 56

Xaa Xaa Thr Xaa Val
1 5

<210> SEQ ID NO 57
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(8)
<223> OTHER INFORMATION: L-Arg8

<400> SEQUENCE: 57

Arg Arg Arg Arg Arg Arg Arg Arg
1 5

<210> SEQ ID NO 58
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(7)
<223> OTHER INFORMATION: L-Arg7

<400> SEQUENCE: 58

Arg Arg Arg Arg Arg Arg Arg
1 5

<210> SEQ ID NO 59
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(6)
<223> OTHER INFORMATION: L-Arg6

<400> SEQUENCE: 59

Arg Arg Arg Arg Arg Arg
1 5

<210> SEQ ID NO 60

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<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(5)
<223> OTHER INFORMATION: L-Arg5

<400> SEQUENCE: 60

Arg Arg Arg Arg Arg
1 5

<210> SEQ ID NO 61
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(4)
<223> OTHER INFORMATION: L-Arg4

<400> SEQUENCE: 61

Arg Arg Arg Arg
1

<210> SEQ ID NO 62
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(8)
<223> OTHER INFORMATION: L-Arg8
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: N-terminal acetylated

<400> SEQUENCE: 62

Arg Arg Arg Arg Arg Arg Arg Arg
1 5

<210> SEQ ID NO 63
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(7)
<223> OTHER INFORMATION: L-Arg7
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: N-terminal acetylated

<400> SEQUENCE: 63

Arg Arg Arg Arg Arg Arg Arg
1 5

<210> SEQ ID NO 64

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<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(6)
<223> OTHER INFORMATION: L-Arg6
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: N-terminal acetylated

<400> SEQUENCE: 64

Arg Arg Arg Arg Arg Arg
1 5

<210> SEQ ID NO 65
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(5)
<223> OTHER INFORMATION: L-Arg5
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: N-terminal acetylated

<400> SEQUENCE: 65

Arg Arg Arg Arg Arg
1 5

<210> SEQ ID NO 66
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(4)
<223> OTHER INFORMATION: L-Arg4
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: N-terminal acetylated

<400> SEQUENCE: 66

Arg Arg Arg Arg
1

<210> SEQ ID NO 67
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(8)
<223> OTHER INFORMATION: L-Arg8
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: N-terminal conjugated to chloroalkane (CA)

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<400> SEQUENCE: 67

Arg Arg Arg Arg Arg Arg Arg Arg
1 5

<210> SEQ ID NO 68
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(7)
<223> OTHER INFORMATION: L-Arg7
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: N-terminal conjugated to chloroalkane (CA)

<400> SEQUENCE: 68

Arg Arg Arg Arg Arg Arg Arg
1 5

<210> SEQ ID NO 69
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(6)
<223> OTHER INFORMATION: L-Arg6
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: N-terminal conjugated to chloroalkane (CA)

<400> SEQUENCE: 69

Arg Arg Arg Arg Arg Arg
1 5

<210> SEQ ID NO 70
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(5)
<223> OTHER INFORMATION: L-Arg5
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: N-terminal conjugated to chloroalkane (CA)

<400> SEQUENCE: 70

Arg Arg Arg Arg Arg
1 5

<210> SEQ ID NO 71
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide

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<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(4)
<223> OTHER INFORMATION: L-Arg4
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: N-terminal conjugated to chloroalkane (CA)

<400> SEQUENCE: 71

Arg Arg Arg Arg
1

1. A compound 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 20 L-arginine residues;

ii. (SEQ ID NO: 9, D-TAT)
yGrkkrrqrrr;

iii. (SEQ ID NO: 14, L-Pen)
RQIKIWFQNRRMKWKK;

iv. (SEQ ID NO: 15, D-Pen)
rqikiwfqnrrmkwkk;

v. (SEQ ID NO: 17, L-DPV3)
RKKRRRESRKKRRRES;

vi. (SEQ ID NO: 18, L-pVEC)
LLIILRRRIRKQAHAHSK;

vii. (SEQ ID NO: 16, L-MAP)
KLALKLALKALKAALKLA;

viii. (SEQ ID NO: 19, L-TP2)
PLIYLRLLRGQF;

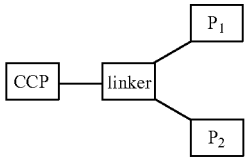
ix. (SEQ ID NO: 21, MiniAp4)
|(Dap)KAPETALD|;
and

-continued

x. (SEQ ID NO: 22, CPP12)
|Pf(Nal2)RrRrQ|GABA-K,

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 compound has the general structure of Formula (I):

Formula (I)



or a pharmaceutically acceptable salt thereof.

2. The compound according to claim **1**, wherein P, 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 compound 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 compound 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.

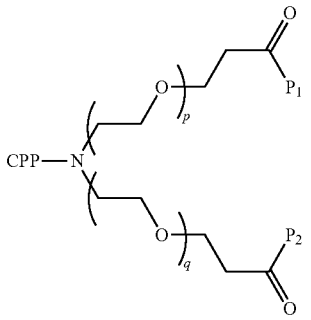
5. The compound according to any one of the preceding claims, wherein the linker comprises one or more PEG units.

6. The compound 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 compound 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 compound 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 compound 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 compound according to any one of the preceding claims, wherein P_1 is identical to P_2.

10. The compound according to any one of the preceding claims, wherein P_1 and P_2 consist of the amino acid sequence KETLV (SEQ ID NO: 2).

11. The compound according to any one of claims **1** to **9**, wherein P_1 and P_2 consist of the amino acid sequence KETTV (SEQ ID NO: 3).

12. The compound according to any one of claims **1** to **9**, wherein P_1 and P_2 consist of the amino acid sequence KETVV (SEQ ID NO: 4).

13. The compound according to any one of claims **1** to **9**, wherein P_1 and P_2 consist of the amino acid sequence KETRV (SEQ ID NO: 5).

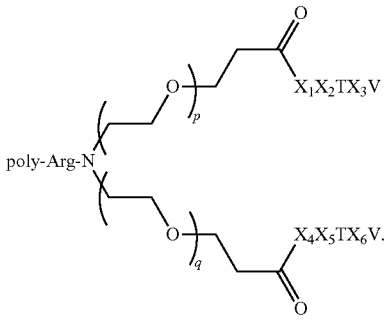
14. The compound according to any one of claims **1** to **3** or **5** to **9**, wherein P_1 and P_2 consist of the amino acid sequence ISTDV (SEQ ID NO: 6).

15. The compound according to any one of claims **1** to **9**, wherein P_1 and P_2 consist of the amino acid sequence VETVV (SEQ ID NO: 7).

16. The compound according to any one of the preceding claims, wherein the CPP is a poly-L-arginine peptide (poly-Arg) consisting of 3 to 20 L-arginine residues, such as 3 to 15, such as 3 to 12, such as 3 to 10 L-arginine residues.

17. The compound according to any one of the preceding claims, wherein the compound 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 20 L-arginine residues.

18. The compound according to any one of the preceding claims, wherein the poly-Arg consists of 3 to 20 L-arginine residues, such as 3 to 15, such as 3 to 12, such as 3 to 10 L-arginine residues.

19. The compound according to any one of the preceding claims, wherein the CPP is RRRRRRRRR (SEQ ID NO: 12).

20. The compound according to any one of claims **1** to **18**, wherein the CPP is RRRRRRRR (SEQ ID NO: 57).

21. The compound according to any one of claims **1** to **18**, wherein the CPP is RRRRRRR (SEQ ID NO: 58).

22. The compound according to any one of claims **1** to **18**, wherein the CPP is RRRRRR (SEQ ID NO: 59).

23. The compound according to any one of claims **1** to **18**, wherein the CPP is RRRRR (SEQ ID NO: 60),

24. The compound according to any one of claims **1** to **18**, wherein the CPP is RRRR (SEQ ID NO: 61).

25. The compound according to any one of claims **1** to **18**, wherein the CPP is RRR.

26. The compound according to any one of claims **1** to **15**, wherein the CPP is yGrkkrrqrrr (SEQ ID NO: 9, D-TAT).

27. The compound according to any one of claims **1** to **15**, wherein the CPP is RQIKIWFQNRRMKWKK (SEQ ID NO: 14, L-Pen).

28. The compound according to any one of claims **1** to **15**, wherein the CPP is rqikiwfqnrrmkwkk (SEQ ID NO: 15, D-Pen).

29. The compound according to any one of claims **1** to **15**, wherein the CPP is RKKRRRESRKKRRRES (SEQ ID NO: 17, L-DPV3).

30. The compound according to any one of claims **1** to **15**, wherein the CPP is LLIILRRRIRKQAHAHSK (SEQ ID NO: 18, L-pVEC).

31. The compound according to any one of claims **1** to **15**, wherein the CPP is KLALKLALKALKAALKLA (SEQ ID NO: 16, L-MAP).

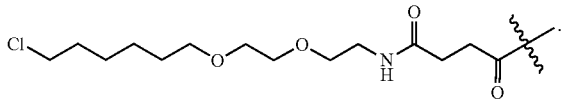
32. The compound according to any one of claims **1** to **15**, wherein the CPP is PLIYLRLLRGQF (SEQ ID NO: 19, L-TP2).

33. The compound according to any one of claims **1** to **15**, wherein the CPP is l(Dap)KAPETALDI (SEQ ID NO: 21, MiniAp4).

34. The compound according to any one of claims **1** to **15**, wherein the CPP is IFf(Nal2)RrRrQIGABA-K (SEQ ID NO: 22, CPP12).

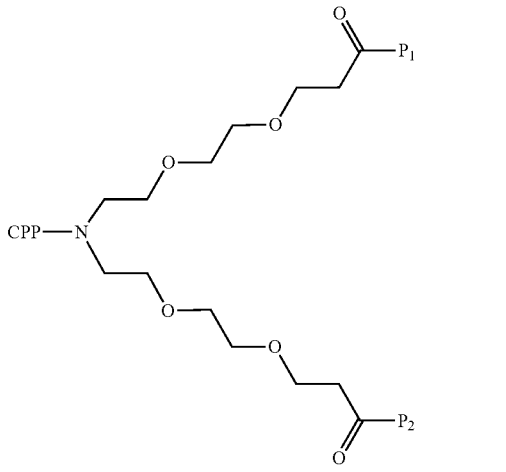
35. The compound according to any one of claims **8** or **17**, wherein p is 2 and q is 2.

36. The compound 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:



37. The compound according to claim **1**, wherein the compound has the general structure of Formula (XXVIII):

Formula (XXVIII)



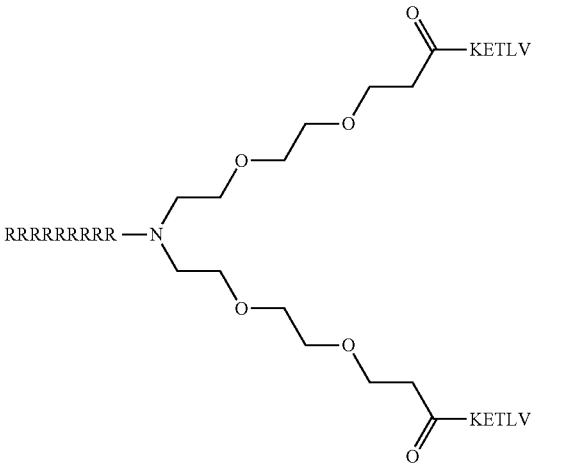
wherein P_1, P_2 and CPP are:

	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 (SEQ ID NO: 1)	IETDV (SEQ ID NO: 1)	L-Arg_9	RRRRRRRRR (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

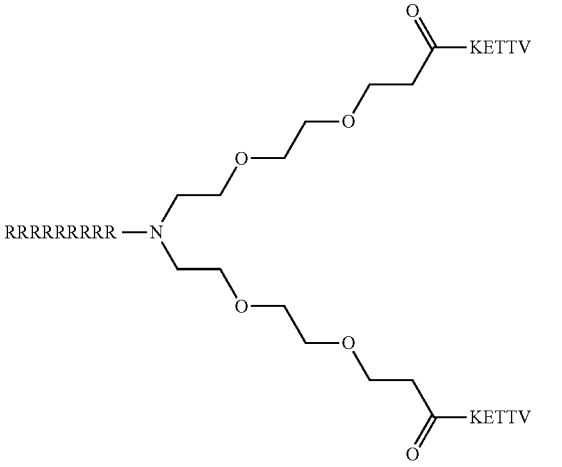
and wherein the N-terminal of the CPP is optionally acetylated.

38. The compound according to claim **1**, wherein the compound is selected from the group consisting of formulas (X) to ~(XXIII):

Formula (X)



Formula (XI)



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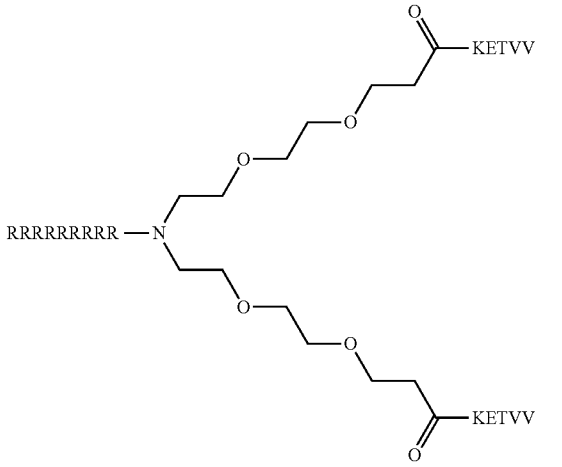
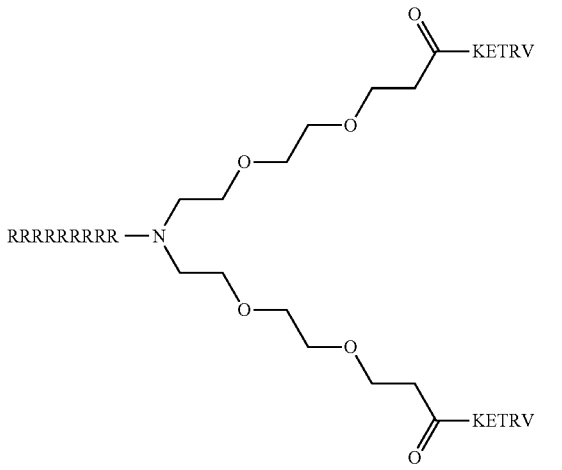
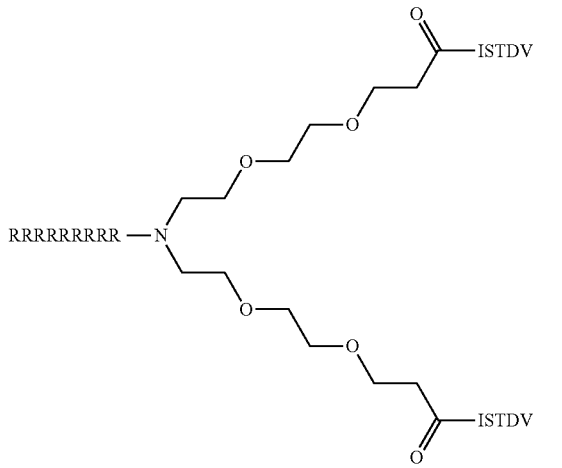
Formula (XII)



Formula (XIII)



Formula (XIV)



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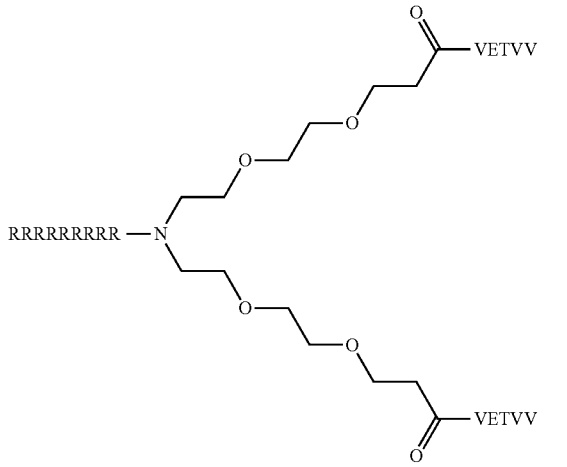
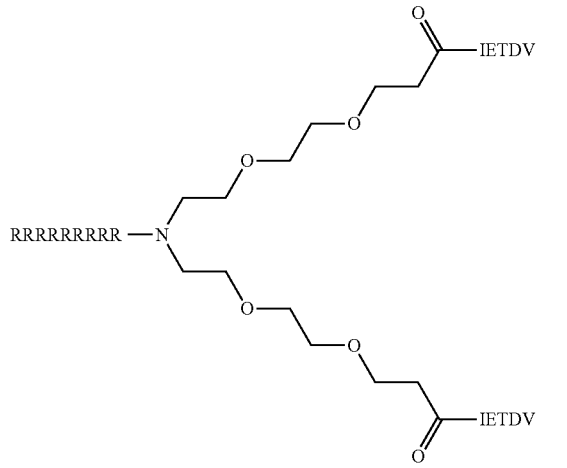
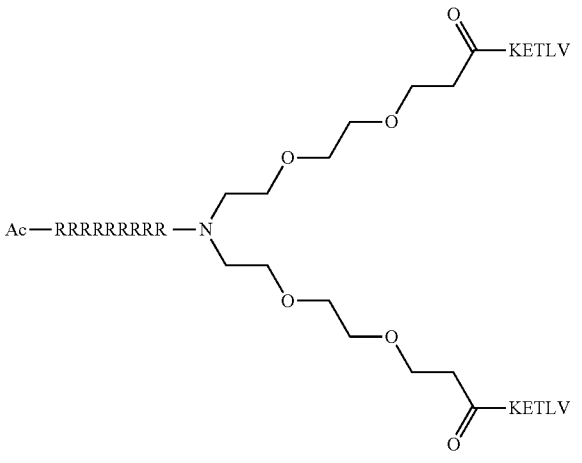
Formula (XV)



Formula (XVI)



Formula (XVII)



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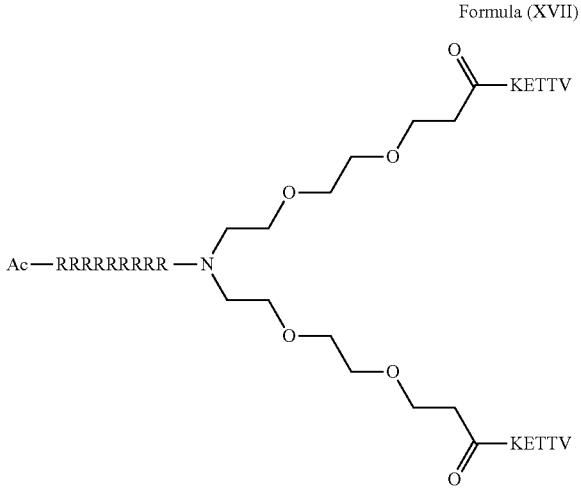
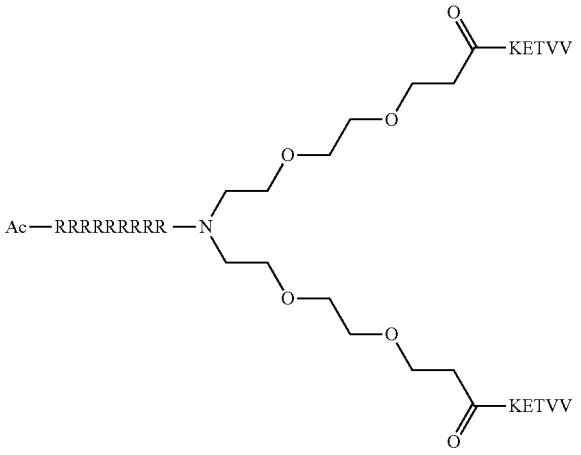
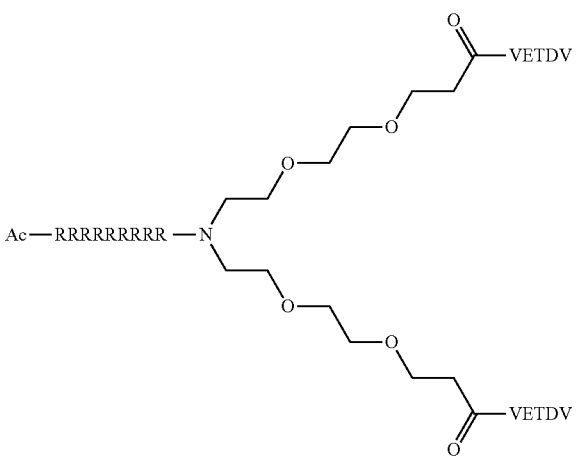
Formula (XVII)



Formula (XIX)



Formula (XX)



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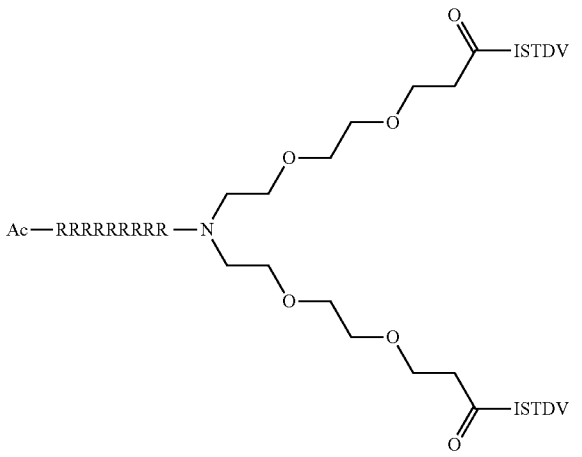
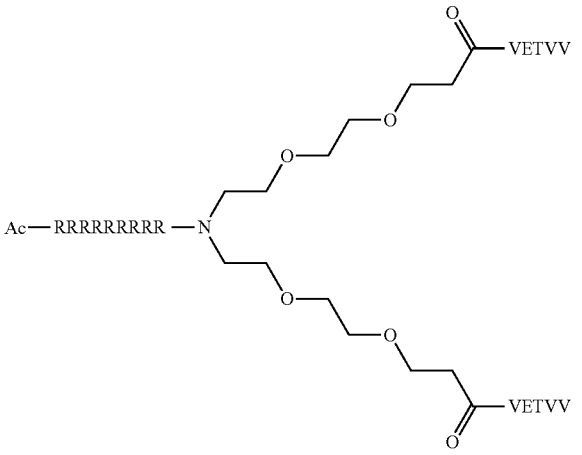
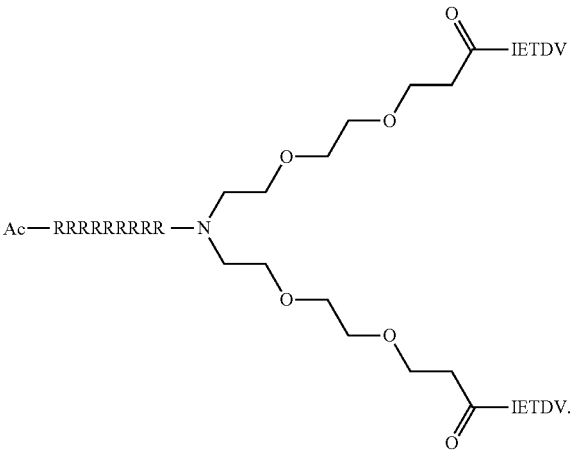
Formula (XXI)



Formula (XXII)



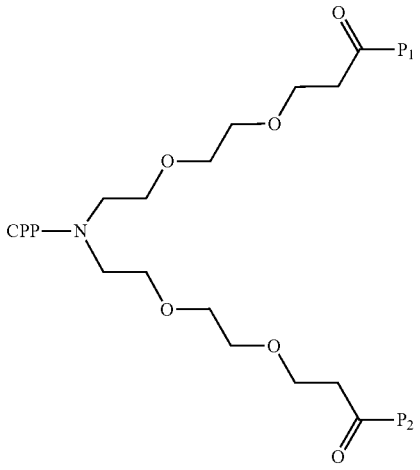
Formula (XXIII)



39. The compound according to any one of claims **1** to **3**, **5** to **9**, **35** or **36**, 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)KAPETALDI (SEQ ID NO: 21, MiniAp4); and IFf (Nal2)RrRrQIGABA-K (SEQ ID NO: 22, CPP12).

40. The compound according to claim **1**, wherein the compound 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)KAPETALDI (SEQ ID NO: 21, MiniAp4); and IFf(Nal2)RrRrQIGABA-K (SEQ ID NO: 22, CPP12).

41. The compound according to any one of the preceding claims, wherein the compound is a PSD-95 inhibitor.

42. A compound according to any one of the preceding claims for use as a medicament.

43. A compound according to any one claims **1** to **41** for use in treating, preventing, reducing and/or delaying development of an excitotoxic-related disease such as stroke, for example selected from acute ischemic stroke and subarachnoid hemorrhage.

44. A method for manufacturing the compound according to any one of claims **1** to **41** comprising the general steps of:

a. Synthesizing a peptide P_1/P_2;

b. Dimerizing the peptide of a) with an $OPEG_n$ or $NPEG_n$ linker, wherein 'n' is the number of PEG moieties;

c. Attaching a CPP tag at the N of the NPEG linker, for example by using an automated peptide synthesizer.

45. A method for manufacturing the compound according to any one of claims **1** to **41** comprising the general steps of:

a. providing a Ns-NPEG diacid linker;

b. preparing a peptide P_1/P_2 using Fmoc-based solid-phase peptide synthesis;

c. dimerizing Fmoc-deprotected peptide P_1/P_2 with the Ns-NPEG diacid linker forming a linker-dimer conjugate; and

d. attaching a CPP to the N of the NPEG linker of the linker-dimer conjugate, for example by using an automated peptide synthesizer.

* * * * *