opioids and non-steroidal anti-inflammatory drugs (NSAIDs). NMDA receptor antagonists block sensitization of pain responses and display good analgesic properties in animal models and clinical settings, but they are associated with unacceptable side-effects and can therefore not be used clinically. Accordingly there is a need for alternative drugs capable of providing improved pain treatments, particularly NMDA receptor related pain symptoms, while avoiding the unacceptable side-effects of current drugs.

Summary of the invention

In one aspect, there is provided a compound comprising a first peptide linked to a second peptide by a linker, wherein the first and the second peptide comprise at least four amide-bonded residues having a sequence YTXV or YSXV, wherein

a. Y is selected from among E, Q, and A, and

b. X is selected from among A, Q, D, N, *N*-Me-A, *N*-Me-Q, *N*-Me-D, and *N*-Me-N, and

wherein the linker comprises PEG and, wherein at least one oxygen atom of the PEG is substituted with a nitrogen atom to give *N*PEG,

wherein a Cell Penetrating Peptide (CPP) is linked to the nitrogen atom of the linker by an amide bond, and

wherein the CPP comprises at least 4 amino acid residues selected from arginine and/or lysine.

Also provided is ~~first embodiment of the present invention provides~~ a compound comprising a first peptide or peptide analogue linked to a second peptide or peptide analogue by a linker, wherein the first and the second peptide or peptide analogue comprise at least four amide-bonded residues having a sequence YTXV or YSXV, wherein

a. Y is selected from among E, Q, and A, or an analogue thereof, and

b. X is selected from among A, Q, D, N, *N*-Me-A, *N*-Me-Q, *N*-Me-D, and *N*-Me-N or an analogue thereof, and

wherein a third peptide having the function of a Cell Penetrating Peptide (CPP) is linked to the linker, wherein the third peptide comprises at least 4 amino acid residues selected from arginine and/or lysine. Preferably the linker comprises PEG,

wherein at least one oxygen atom of the PEG is substituted with a nitrogen atom to give *N*PEG, and preferably the third peptide is linked to the nitrogen atom of the *N*PEG linker, preferably by an amide bond,

An ~~second embodiment~~example of the ~~invention~~disclosure provides a compound comprising a first peptide or peptide analogue linked to a second peptide or peptide analogue by a linker, wherein the linker comprises PEG and wherein the first and the second peptide or peptide analogue comprise at least four amide-bonded residues having a sequence YTXV or YSXV, wherein

a. Y is selected from among E, Q, and A, or an analogue thereof, and

b. X is selected from among A, Q, D, N, *N*-Me-A, *N*-Me-Q, *N*-Me-D, and *N*-Me-N or an analogue thereof, characterised in that a third peptide is linked to a side chain

of one of the residues of the first and second peptide or peptide analogue, wherein the third peptide comprises at least 4 amino acid residues selected from arginine and/or lysine and has the function of a Cell Penetrating Peptide (CPP).

In a further ~~embodiment~~example of the above compounds of the ~~invention~~disclosure, the linker is a PEG linker comprising 1-28 ethylene glycol moieties (N=1-28), preferably 4 to 12 ethylene glycol moieties (N=4-12), more preferably 4 to 6 ethylene glycol moieties (N=4-6). In a further ~~embodiment~~example of the compound of the ~~invention~~disclosure, the linker is a PEG-diacid or an *N*PEG-diacid, and wherein each carboxyl group of the linker is linked to the terminal amino group of a terminal residue of the first or the second peptide or peptide analogue via an amide bond.

In a further ~~embodiment~~example of the above compounds of the ~~invention~~disclosure, the third peptide (CPP) comprises a retroinverso peptide. In a further ~~embodiment~~example of the above compounds of the ~~invention~~disclosure, the third peptide (CPP) is Tat peptide (YGRKKRRQRRR) or Retroinverso-D-Tat peptide (rrrqrrkkr).

In a further ~~embodiment~~example of the above compounds of the ~~invention~~disclosure, the peptide or peptide analogue is from 5 to 10 amide-bonded residues in length. In a further ~~embodiment~~example of the above compounds of the ~~invention~~disclosure, the peptide is comprised of at least 4 L-amino acid residues. In a further ~~embodiment~~example of the above compounds of the ~~invention~~disclosure, X is selected from among A, Q, and D. In a further ~~embodiment~~example of the above compounds of the ~~invention~~disclosure, the peptide or peptide analogue is *N*-alkylated.

The present ~~invention~~disclosure further provides a linker compound comprising a PEG-diacid, wherein one oxygen atom of the PEG is substituted with a nitrogen atom to give *N*PEG-diacid. In a further ~~embodiment~~example of the linker compound of the ~~invention~~disclosure, the nitrogen atom is linked to a protecting group.

In another aspect, there is provided a compound as defined above for use as a medicament.

Also disclosed is~~The present invention further provides~~ a pharmaceutical composition comprising a compound according to any one the above ~~embodiments~~examples of the ~~invention~~disclosure for use as a

medicament. In a further ~~embodiment~~example, the pharmaceutical composition comprising a compound according to any one of the above ~~embodiments~~examples of the ~~invention~~disclosure is for use in the prophylaxis and/or treatment of an excitotoxic-related disease in a subject.

In yet another aspect, there is provided the use of a compound as defined above for the preparation of a medicament for the prophylaxis and/or treatment of an excitotoxic-related disease in a subject.

The present ~~invention~~disclosure further provides a pharmaceutical composition comprising a compound according to any one of the above ~~embodiments~~examples of the ~~invention~~disclosure for use in the prophylaxis and/or treatment of pain in a subject.

In yet another aspect, the present invention provides the use of a compound as defined above for the preparation of a medicament for the prophylaxis and/or treatment of pain in a subject.

In another aspect, the present invention further provides a kit comprising the compound disclosed herein, further comprising means for delivering said composition to a subject.

The present ~~invention~~disclosure further includes a method of providing prophylaxis and/or treatment of an excitotoxic-related disease or pain in a subject, comprising administering the above pharmaceutical composition to the subject, wherein said disease may be ischemic or traumatic injury of the CNS.

In yet another aspect, there is provided the use of a compound comprising a first peptide linked to a second peptide by a linker, wherein the first and the second peptide comprise at least four amide-bonded residues having a sequence YTXV or YSXV, wherein

a. Y is selected from among E, Q, and A, and

b. X is selected from among A, Q, D, N, N-Me-A, N-Me-Q, N-Me-D, and N-Me-N;

for the preparation of a medicament for the prophylaxis and/or treatment of pain.

In a further ~~embodiment~~example, the ~~invention~~disclosure provides a pharmaceutical composition for the prophylaxis and/or treatment of pain in a subject, said composition comprising an active compound, said active compound comprises a first peptide or peptide analogue linked to a second peptide or peptide analogue by a linker, wherein the first and the second peptide or peptide analogue comprise at least four amide-bonded residues having a sequence YTXV or YSXV, wherein (a) Y is selected from among E, Q, and A, or an analogue thereof, and (b) X is selected from among A, Q, D, N, *N*-Me-A, *N*-Me-Q, *N*-Me-D, and *N*-Me-N or an analogue thereof. In a further ~~embodiment~~example, the linker in said active compound is a PEG linker or an *N*PEG linker and comprises 4 to 28 ethylene glycol moieties (N=4-28). In a further ~~embodiment~~example, the carboxyl group of the linker in said active compound is linked to a terminal residue of the first or the second peptide or peptide analogue. In a further ~~embodiment~~example, said active compound is selected from among PEG4(IETAV)$_2$, *N*PEG4(IETAV)$_2$, PEG6(IESDV)$_2$, and PEG4(IESDV)$_2$.

Said active compound may further have a third peptide comprising at least 4 amino acid residues selected from arginine and/or lysine and having the function of a CPP,