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(54) Title: HIGH-AFFINITY, DIMERIC INHIBITORS OF PSD-95 AS EFFICIENT NEUROPROTECTANTS AGAINST ISCHEMIC BRAIN DAMAGE AND FOR TREATMENT OF PAIN

(57) Abstract: The invention provides novel potent inhibitors of the ternary protein complex of nNOS, PSD-95, and the NMDA receptor and pharmaceutical compositions comprising the inhibitors for prophylaxis and/or treatment of excitotoxic-related disease and chronic pain conditions in a subject. The inhibitors are dimeric PSD-95 inhibitors 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 Cell Penetrating Peptide (CPP) is linked to the linker or to an amino acid side chain of the first and second peptide or peptide analogue. The linker can be a PEG or NPEG linker.