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[54] **CYCLIC PEPTIDE SURFACE FEATURE MIMICS OF ENDOTHELIN**

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[52] **U.S. Cl.** **514/9**; 514/17; 530/317; 530/330; 930/270

[58] **Field of Search** 514/9, 17; 530/317, 530/330; 930/270

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[57] **ABSTRACT**

Cyclic peptides and pharmaceutically acceptable salts and esters thereof are provided. The cyclic peptides and pharmaceutically acceptable salts and esters thereof mimic surface features of the C-terminus of endothelin and thereby can be used modulate or alter the activity of the endothelin family of peptides. More particularly, cyclic pentapeptides, cyclic hexapeptides, cyclic heptapeptides and pharmaceutically acceptable derivatives of the peptides that specifically inhibit the activity of endothelin are provided. Among the cyclic peptides are those that have the formula: cyclo(X^1-X^2-X^3-X^4-D-Trp): X^1 is D-Tyr or D-Asp; X^2 is Phe, Ala, Ac_3c or Pro; X^3 is D-His, D-Ala, D-Val, Gly or β-Ala; and X^4 is His, Ala, β-Ala, Aib, Gly, D-His-gly or Leu; cyclo (X^1-L-Phe-X^3-X^4-X^5) in which X^1 is D-Tyr, D-Asp or D-Glu, X^3 is selected from among D-His, β-Ala-D-His or gly-D-His; X^4 is Ser, Gly or β-Ala, and X^5 is D-Trp or N-Me-D-Trp; cyclo(X^1-X^2-X^3-X^4-L-Trp) in which X^1 is D-Ala, Aib, Gly, D-Val, D-Leu, D-Ile, D-Nva, D-Nle, or D-Alle; X^2 is D-Val, D-Leu, D-Ile, D-Ala, D-Gln, Gly, Aib, D-Nva, D-Nle, or D-Alle; X^3 is Pro, Gly, Aib, Val, Leu, L-Nva, L-Nle, L-Alle or L-Hyp and X^4 is D-Asp, D-Glu, D-Ser, D-Thr, D-Tyr, D-Cys(O_3H) or D-Pen(O_3H); and cyclo(X^1-X^2-X^3-X^4-L-Trp) in which X^1 is D-Leu, D-Val, D-Ile, D-Ala, Gly, Aib, D-Nva, D-Nle or D-Alle; X^2 is Val, Ile, Leu, Ala, Gln, Gly, Aib, L-Nva, L-Nle or L-Alle; X^3 is D-Pro, D-Hyp, D-Ala, D-Val, D-Ile, Gly, Aib, D-Nva, D-Nle or D-Alle; and X^4 is Asp, Glu, Tyr, Ser, Thr, L-Cys(O_3H) or L-Pen(O_3H). Pharmaceutical compositions containing the peptides and methods of modulating the activity of endothelin peptides are also provided.

41 Claims, 6 Drawing Sheets