

# Synthesis of Some New ( $N^{\alpha}$ -Dipicolinoyl)-*bis*-L-leucyl-DL-norvalyl Linear tetra and Cyclic octa Bridged Peptides as New Antiinflammatory Agents

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In continuation to our search for new amino acid and peptide based anti-inflammatory agents, the suggestion, synthesis, structure elucidation of some  $N^{\alpha}$ -*bis*-dipicolinoyl amino acids, linear tetra and cyclic octa bridged peptides **1-9**, of which four are new compounds **6-9**, were herein realized. Accordingly,  $N^{\alpha}$ -*bis*-dipicolinoyl-L-leucine methyl ester **1**, the corresponding acid **2**, its *bis*-DL-norvalyl methyl ester homologue **3**, the acid **4** and hydrazide **5** analogues were conventionally prepared.

The tetrachlorophthalic acid hydrazine conjugate **6**, anisaldehyde hydrazone **7**, the benzenetetra-carboxylic acid and naphthalenetetracarboxylic acid *bis*-L-leucyl-DL-norvalyl cyclic octa bridged peptides **8** and **9** respectively, were newly synthesized *via* condensation of the hydrazide **5** with the corresponding aldehyde or anhydride.

The chromatographic, IR, NMR and mass spectral analysis confirmed the identities of the synthesized compounds.

Comparable to the two reference antiinflammatory drugs indomethacin<sup>®</sup> and voltaren<sup>®</sup> (100%), the determined antiinflammatory potency of the candidates (carrageenan<sup>®</sup> induced paw edema in rats) revealed a general significant activity (66 – 94%), except for the practically inactive **6** (~1.5 % activity).

In particular, the potency of the ( $N^{\alpha}$ -dipicolinoyl)-*bis*-L-leucyl-DL-norvalyl anisaldehyde hydrazone **7** was of 94 and 87%, comparable to the reference drugs. However, **7** also showed 58% protection against ulcer formation, comparable to null for indomethacin<sup>®</sup>. Additionally, an acceptable acute toxicity was observed (LD<sub>50</sub>: 2833 mg/kg, comparable to 2700 and 2850 for indomethacin<sup>®</sup> and voltaren<sup>®</sup> respectively).

**Key words:** Dipicolinic Acid, Amino Acids, Peptides, Antiinflammatory Agents