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 benzenetetracarboxylic 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® and voltaren® (100%), the determined antiinflammatory potency of the candidates (carrageenan® 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®. Additionally, an acceptable acute toxicity was observed (LD$_{50}$: 2833 mg/kg, comparable to 2700 and 2850 for indomethacin® and voltaren® respectively).

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