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Synthesis and Structural Investigation of New Analogues of Luteinizing Hormone – Releasing Hormone (LHRH)

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Luteinizing Hormone–Releasing Hormone plays a central role in the biology of reproduction and synthetic LHRH analogues have been proven valuable in the treatment of a wide variety of endocrinological and nonendocrinological disorders. Released in a pulsatile manner into the portal circulation, LHRH interacts with high-affinity receptors on the gonadotropes in the anterior pituitary, leading to the biosynthesis and release of the gonadotropins LH and FSH. Agonistic synthetic analogues of LHRH, represented by Leuprolide ([DLeu^6, desGly^{10}]-LHRH-ethylamide), have been widely used in oncology and gynecology for nearly two decades. In this study, we report an improved synthesis of new analogues of the LHRH by the solid phase methology on a [3-((Ethyl-Fmoc-amino)-methyl)-1-indol-1-yl]-acetyl AM resin via Fmoc/tBu methology and the conformational analysis in solution of the LHRH analogue namely [Aib^6, desGly^{10}]-LHRH-ethylamide using NMR spectroscopy. Key considerations in the synthesis of the LHRH analogues were on the basis that the central characteristic of the bioactive conformation of LHRH is the β-turn involving the Tyr-Gly-Leu-Arg in positions 5–8.

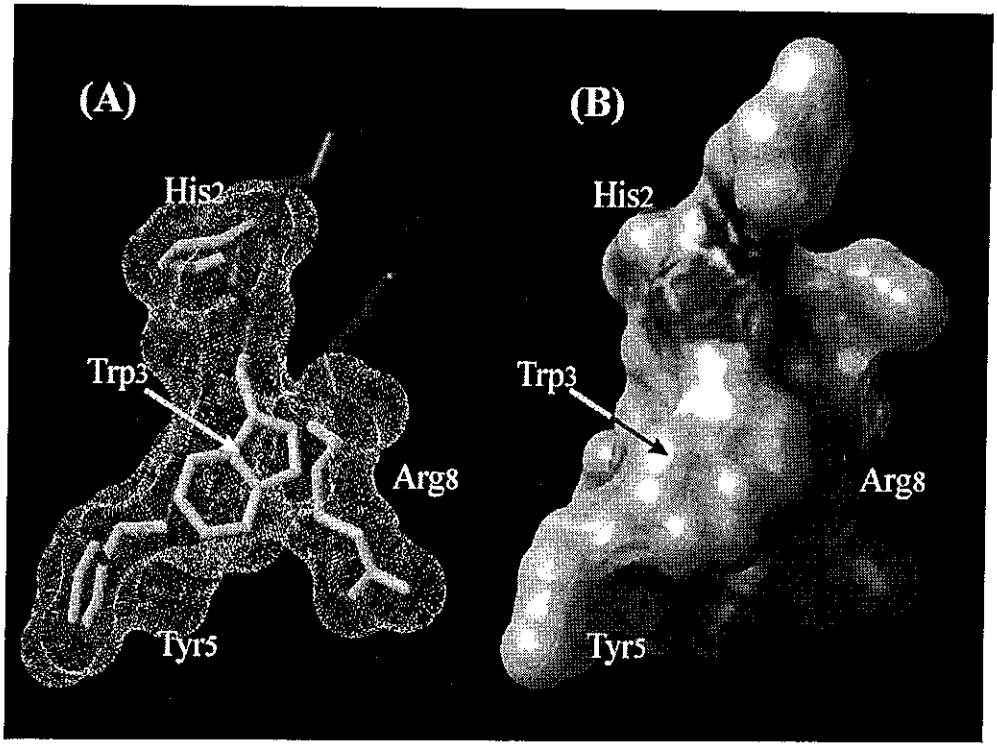

Figure. (A) Mean, energy minimized, NMR structure and Van der Waals surfaces for His^2, Trp^3, Tyr^5 and Arg^8 residues, (B) Distribution of the electrostatic potentials on the surface of the mean structure of [Aib^6, desGly^{10}]-LHRH-ethylamide. Figures are generated with MOLMOL