

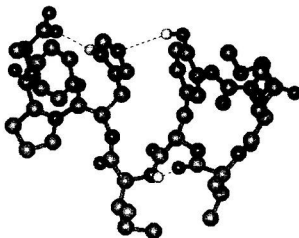
# Study of the Molecular Basis of Hypertension Using NMR spectroscopy and Computational Analysis Studies

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Hypertension is a growing disease in the civilised societies due to the gained life style and diet of their majority of population. Angiotensin II (AII) is an octapeptide hormone (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe) well known to be implicated in the cause of hypertension disease. We have constructed a model of AII based on NMR and fluorescence spectroscopy and computational analysis studies. The major stereoelectronic features revealed in this model are (Scheme 1): (a) a *trans* configuration of His<sup>6</sup>-Pro<sup>7</sup> aminoacids peptide bond which contributes to a  $\gamma$ -turn conformation around the proline aminoacid; (b) a Tyr<sup>4</sup>-Ile<sup>6</sup>-His<sup>8</sup> bend (c) the side groups of the key aminoacids Tyr<sup>4</sup>-His<sup>6</sup>-Phe<sup>8</sup> form a cluster of aromatic rings governed by a charge relay transfer which lead to the formation of a tyrosinate anion; (d) Arg<sup>2</sup> side chain is protruding towards the relay system possibly stabilizing the tyrosinate anion. Similar stereoelectronic features were also observed for the superagonist [Sar<sup>1</sup>]AII. Conformational analysis studies on Sarmesin and Sarilesin revealed that: (a) Sarmesin because it lacks of Tyr<sup>4</sup> phenolic hydroxyl group can not form a charge relay system while it keeps all other important stereoelectronic features present in AII. (b) Sarilesin does form neither a cluster nor consequently a charge relay system. To confirm that all the above mentioned stereoelectronic features presented in AII are critical for exerting its biological activity the c-[Sar<sup>1</sup>,Lys<sup>3</sup>,Glu<sup>5</sup>]AII was synthesized. Conformational analysis of this molecule showed that it keeps almost intact all conformational properties of AII as it is designed. Indeed, the agonistic activity of the cyclic analog resembles that of AII. Presently, we performed superimposition studies with Losartan and Sarmesin. The conformational analysis of Losartan based on NMR and theoretical calculations shows that this molecule can adopt two low energy enantiomeric conformers in which imidazole and tetrazole have an *anti*-relationship with respect to spacer phenyl ring. Interestingly, the one enantiomer has a better fit to Losartan. The overlay of the two molecules was very succesfull. All these studies point out that agonist activity of AII is mainly attributed to the capability of the side groups of the three important aminoacids Tyr<sup>4</sup>-His<sup>6</sup>-Phe<sup>8</sup> to form a cluster and a charge transfer system. Lack of these properties in structurally similar peptides or peptidomimetic molecules lead either to partial agonist or antagonist activities.



Scheme 1. A possible model of [Sar<sup>1</sup>]AII bioactive conformation as resulted using a combination of NMR and fluorescence spectroscopies and computational chemistry.