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Design and Synthesis of Novel Antihypertensive Drugs

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Abstract—AT1 antagonists constitute a new generation of drugs for the treatment of hypertension and are designed and synthesized to mimic the C-terminal segment of Angiotensin II (Ang II) and to block its binding action on AT1 receptor. For this reason, the conformational analysis of Ang II and its derivatives as well as the AT1 antagonists belonging to SARTANs class of molecules were studied. Such studies offer the possibility to reveal the stereoelectronic factors responsible for bioactivity of AT1 antagonists and to design and synthesize new analogues with better pharmacological and financial profiles. An example of a novel synthetic non-peptide molecule is given which mimics the His^6-Pro^7-Phe^8 part of Ang II and is based on the (*S*)-pyroglutamic acid.

Hypertension is a growing undesired symptom which damages health and threatens mostly the developed societies. It is estimated that 20% of the Greek population suffers from hypertension.[1–3] Research efforts for the controlling of hypertension are focused in blocking Ang II release and more recently in competing Ang II binding on AT_1 receptors. This latest approach generated the synthesis of losartan and promoted it in the pharmaceutical market (COZAAR). Other derivative drugs which fall into SARTAN's class followed.[2,3] To comprehend the stereoelectronic requirements which may lead to the better understanding of the molecular basis of hypertension, the stereochemical features of angiotensin II, its peptide antagonists sarmesin and sarilesin, synthetic peptide analogues, AT_1 non-peptide antagonists commercially available as well as synthetic ones were explored. AT_1 antagonists are designed to mimic the C-terminal part of Ang II.[4]

In this aspect, it is proposed that the butyl chain of losartan may mimic the isopropyl chain of Ile, the tetrazole ring mimics the C-terminal carboxylate group and the imidazole ring the corresponding imidazole ring of His^6. This mimicry can be revised if future literature shows unequivocally that AT1 antagonists possessing tetrazole may anchor in a different aminoacid of AT1 receptor than C-carboxylate terminal of Ang II.[3] At the moment such definite evidence is lacking and drug design can be based on the optimization of superimposition studies of losartan with C-terminal part of sarmesin.[5] Based on these superimposition studies and the model proposed of sarmesin we synthesized (5*S*)-1-benzylo-5-(1H imidazol-1ylo-methylo-)-2-pyrrolidinone (MM1) and we analyzed its stereoelectronic properties in comparison with losartan (Fig. 1).

Imidazole of MM1 mimics imidazole of losartan, pyrrilidinone, mimicks phenyl ring A and phenyl ring of MM1 mimicks phenyl ring B of losartan. Losartan has more complicated structure with additional features (i.e., butyl chain, hydroxymethyl group and tetrazole). MM1 is a simple molecule which has characteristics of the C-terminal of sarmesin and it is designed to mimic conformational characteristics of His^6-Pro^7-Phe^8. MM1 is mounted into pyrrolidine scaffold. The pyrrolidinone scaffold has already been used for the development of CCK peptide mimetics.[6] MM1 is the first lead compound and many others have been designed and are in the process of being synthesized. It has significant antihypertensive activity (71% compared to losartan) as it is shown in Figure 2.

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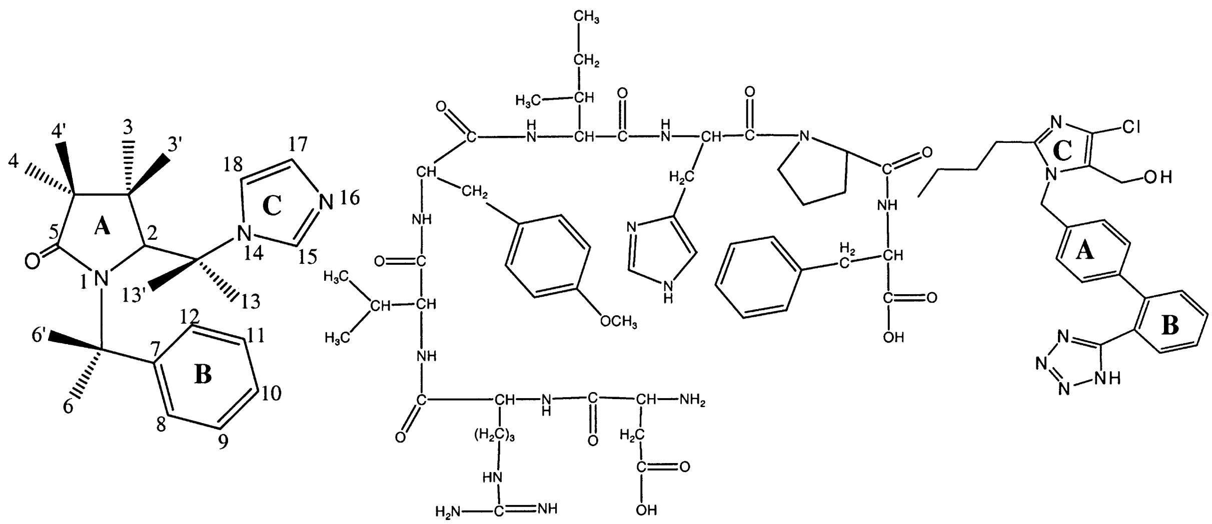

Figure 1. Molecular structures of MM1 (left), sarmesin (middle), and losartan (right). The letters in the aromatic rings show their equivalency in the design.

Therefore, a new avenue of candidate antihypertensive drug is opened which uses a pyrrolidinone scaffold instead of a biphenyl ring. These molecules are advantageous over the known SARTANs in two aspects: (a) they are easily synthesized and (b) their structures are based on conformational analysis of sarmesin and other SARTANS. Such novel class of molecules further confirm our aromatic side-chain ring cluster model of Ang II and sarmesin.[7,8] The simplicity of the synthesis of MM1, a representative molecule of this class is shown in Figure 3.

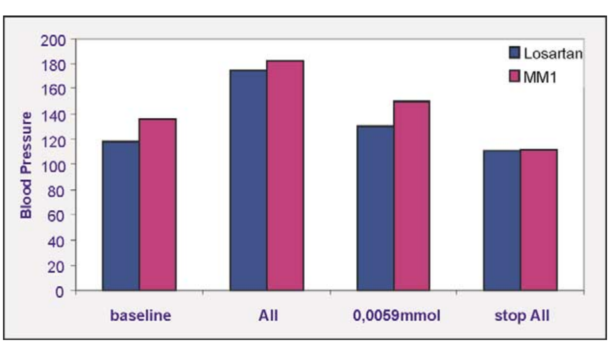

Figure 2. Adult nomotensive male New Zealand White Rabbits weighing between 2.5 and 3.3 kg were used in this study. The animals were anaesthetized by pentobarbitone (30 mg/kg) via an ear vein, intubated and mechanically ventilated with 100% oxygen using a respirator for small animals. The tidal volume was 15 mL and the rate was adjusted to keep blood gases within normal range. Two polyethylene catheters were inserted, one in the carotid artery for continuous blood pressure monitoring via a transducer attached to a multichannel recorder and the other one in the jugular vein for angiotensin II administration. Angiotensin II dependent hypertension was induced by infusing angiotensin II via a syringe pump at a constant rate (0.08 μg/min). After the establishment of hypertension boluses of the antagonist were given via the jugular vein and the changes of blood pressure were recorded. Angiotensin II and 0.0059 mol of the antagonist were diluted in 5% dextrose.

The structure of MM1 was proved unequivocally using 1D and 2D NMR COSY and NOESY spectroscopy. Spectroscopic data for MM1 are provided in Table 1. The most important NOEs for the MM1 showed that there is a spatial proximity between the two aromatic rings. Protons of the phenyl ring are in a close distance with proton 17,18. NOEs predict a close conformation of the molecule. The use of conformational search procedures provided four low energy conformers (Fig. 4). These four conformers have a diastereomeric relationship (two enantiomeric pairs). The low energy conformer best superimposed in the sarmesin supported also all observed NOEs. The superimposition matched the following equivalent groups: (a) imidazole group of MM1 with imidazole group of His^6; (b) phenyl group of MM1 with phenyl group of Phe^8; (c) lactame amide group of pyrrolidinone with amide bond of Phe^8-Pro^7. The superimposition was excellent (RMS = 0.71 Å) (Fig. 5, left). A superimposition of MM1 with losartan was also achieved using the following equivalent groups (Fig. 5, right): (a) Phenyl rings B of MM1 and losartan, (b) carbonyl group of MM1 with tetrazole ring of losartan, and (c) imidazole ring of MM1 with the corresponding imidazole ring of losartan (RMS = 1.16 Å).

Conclusions

The biological results for MM1 show that understanding of the stereoelectronic features responsible for activity in sarmesin and AT_1 antagonists may lead to new classes of molecules with certain advantages over the drugs already existing in the market. Their activity will shed light to the validity of the proposed models. From the reported models of Ang II there is no criterion for favoring a certain conformation. To our opinion a model is valuable if it aids to comprehend the pharmacophore segments responsible for activity and helps in the design of new bioactive drugs. The model of Ang II

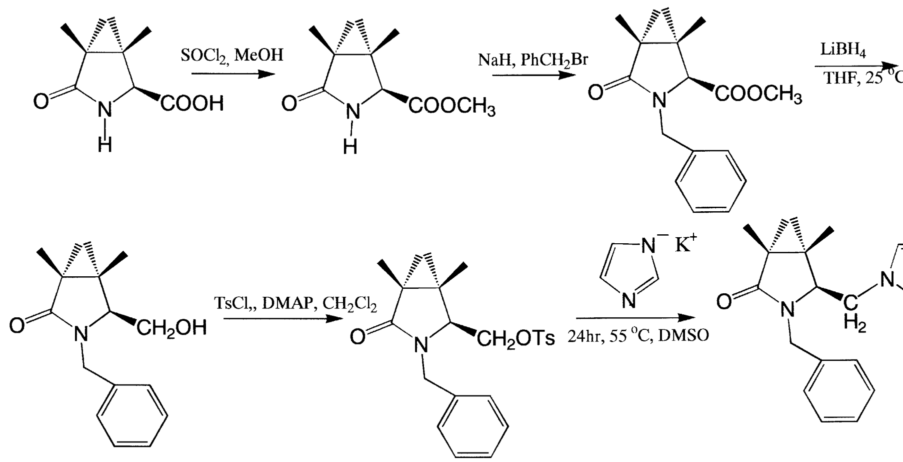

Figure 3. Chemical synthesis of MM1.

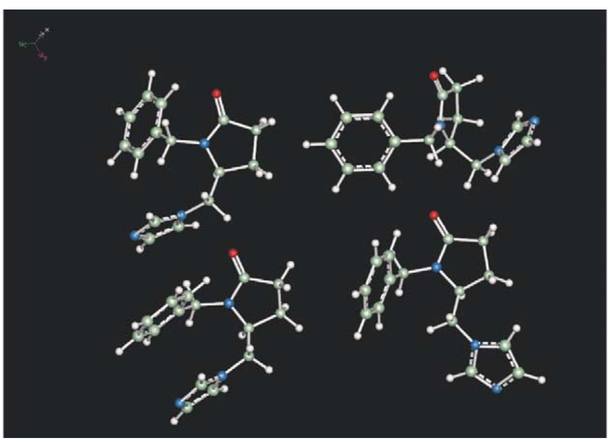

Figure 4. Low energy conformers of MM1 derived using conformational search procedures: Monte Carlo and Molecular Dynamics. These conformers were in agreement with NOEs observed using 2D NOESY experiments. The software used to generate the conformers was Quanta Charmm of MSI.

Table 1. Assignment of proton and carbon-13 NMR peaks

Carbon number	δ_H (m)	δ_c (ppm)
3	1.79, 2.13 (m)	21.94
4	2.34 (m)	28.70
2	3.79 (m)	56.42
6	3.94 (d), 5.08 (d)	44.49
13	4.04 (d)	48.27
17	6.81 (s)	129.76
18	7.12 (s)	118.79
8, 12	7.25–7.35 (m)	128.50
9, 11	7.25–7.35 (m)	127.59
10	7.40 (m)	127.59
15	7.41 (s)	137.04
7	—	135.52
5	—	174.57

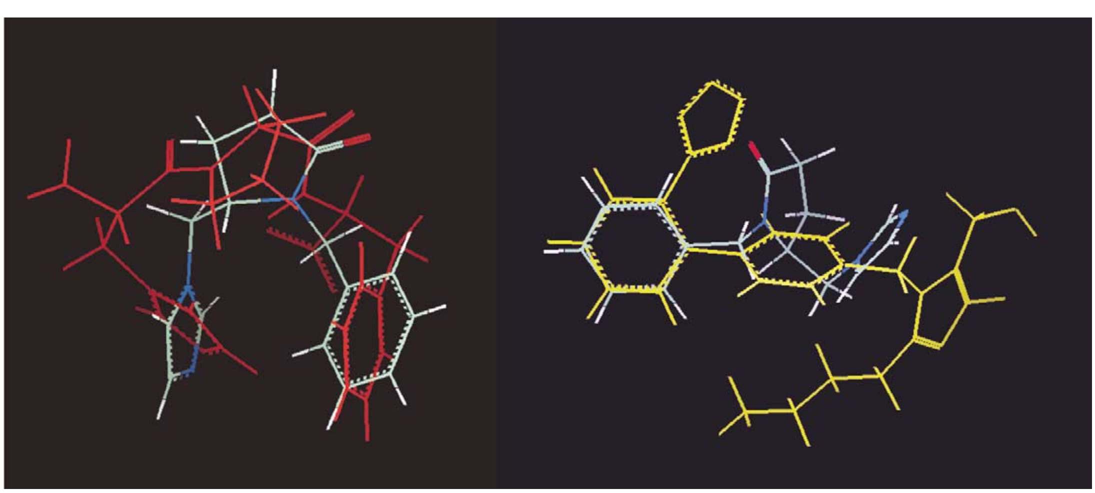

Figure 5. (left) Superimposition of MM1 with C-terminal segment of sarmesin (red); (right) superimposition of MM1 with losartan (yellow).

proposed by J. Matsoukas and his collaborators[7] appears to satisfy these criteria and it may serve to design new antihypertensive molecules.

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