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Pharmacophore Modeling of Angiotensin-II from Study of Its Nonpeptidic Antagonists

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Early attempts to identify plausible conformations of a linear octapeptide hormone, angiotensin-II (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe), using various theoretical and experimental methods, have led to various conformational models. So far, no consensus has been made about the solution phase structure and the receptor binding structure of angiotensin-II. The ultimate goal for the conformation study of the peptide hormone is to develop a new potent drug. Therefore, we have devised a strategy for designing the pharmacophore by studying thermodynamically possible conformations of various kinds of angiotensin-II antagonists and angiotensin-II.

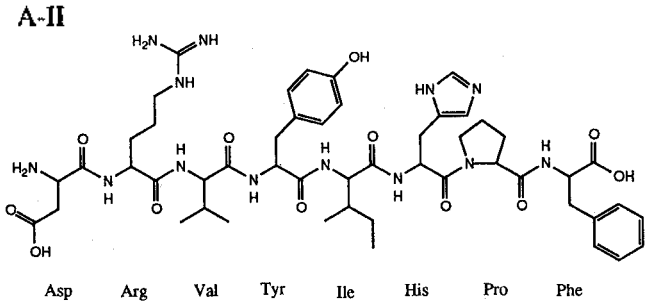
Introduction

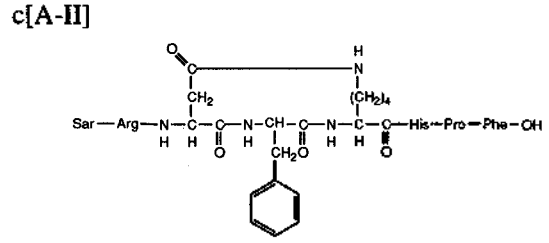
Human angiotensin-II (A-II), a linear octapeptide hormone of sequence Asp-Arg-Val-Tyr-Ile-His-Pro-Phe, is a major active component of the renin-angiotensin system (RAS)[1] which plays a central role in the regulation of blood pressure. It is generally believed that the biological activity of a hormone is closely related to its three dimensional (3D) conformation.

The conformation of A-II has been studied with a variety of methods.[2~14] On the basis of these studies, various conformational models of A-II in aqueous solution have been proposed. These are α-helix,[2] random coil,[3] β-turn,[4] γ-turn,[4] cross β-structure,[5] S-shape,[6] and more complex models.[7~9] However, no consensus has been reached yet about the 3D conformation of A-II in aqueous solution. These various models suggest that it is unlikely that only one or a few conformations are present in solution for such a relatively small linear peptide. Thus, it is believed that the conformation of A-II is in rapid thermodynamic equilibrium in aqueous solution, and there exist a large number of conformational states.[9,15]

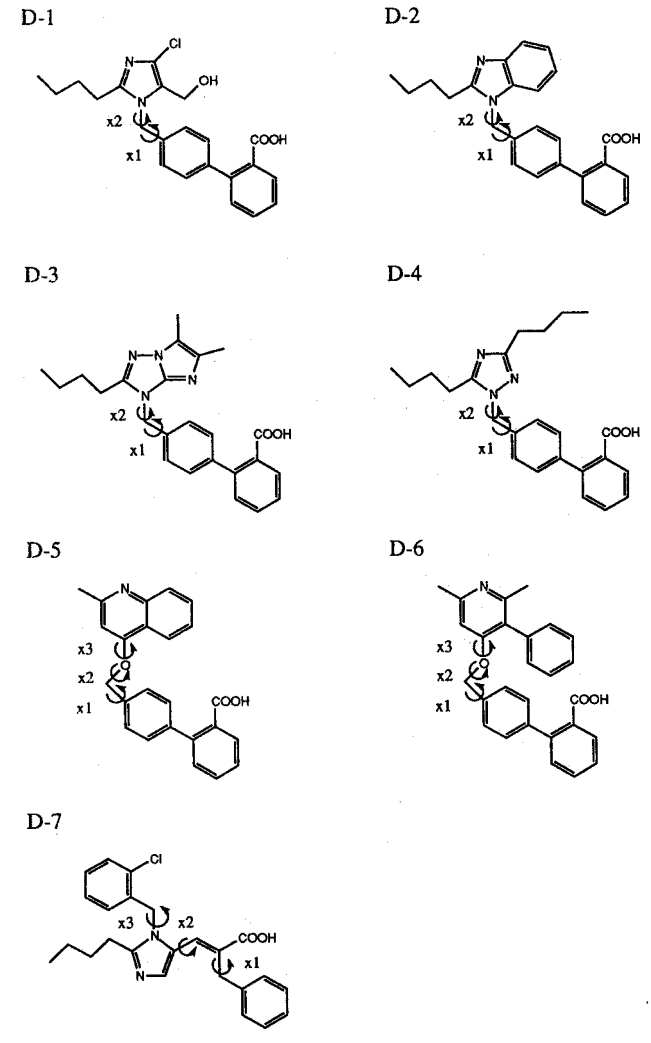
The purpose of the conformational study of A-II may be to develop a new potent drug which can be used as an inhibitor of A-II. The structure of a potential drug is related with the 3D conformation of A-II at the receptor binding site which is, unfortunately, not available. Alternatively, the conformation study on A-II analogues that are biologically active and are more rigid than A-II may give useful information for the development of the potent drug because these analogues should share some common 3D structural features with A-II.

There have been various kinds of well known A-II antagonists, e.g., saralasin ([Sar[1], Ala[8]]A-II)[12] and DUP-753 (brand-name losartan).[16] In this study, the conformation of A-II and its peptide analogues are investigated by molecular dynamics (MD) method, and the conformation of rather rigid organic antagonists are studied by a conventional conformation search method. From the results, we propose that A-II and its antagonists share common 3D structural features which would be important in the binding mode of A-II to the receptor.





(a)



(b)

Figure 1. Molecular structure of the model compounds. (a), A-II and c[A-II]. (b), Nonpeptidic A-II antagonists.

Table 1. Activities of Model Compounds

	AT1 IC_{50} (nM)	
	Model Structure[a]	Optimal Structure[b]
AII	1.02	
c[A-II]	12.	
D-1	480.	18.
D-2	2300.	96.
D-3		7.8
D-4		6.5
D-5	180.	16.
D-6	6.	
D-7	2600.	90.

[a] model structure used in this study. [b] see references 17-24.

Table 2. Distance Constraints used for Initial Conformations of A-II

Constraints	Description
[a](Tyr[4])OH-N(His[6] ring)	r(N-H)=2.0-2.5 Å
[a](Tyr[4])C_δH-HC(His[6] ring)	r(H-H)=2.0-7.0 Å
[a](Phe[8])CO_2-N(His[6] ring)	R(O-N)=2.0-3.5 Å
[b](His[6])C_βH-HC(Phe[8] ring)	R(H-H)=3.5-6.5 Å
[b](His[6])C_βH-HC(Tyr[4] ring)	R(H-H)=3.5-6.5 Å
[b](Asp[1])C_αH-HC(Phe[8] ring)	R(H-H)=1.5-6.5 Å
[b](Asp[1])C_αH-HC(Tyr[4] ring)	R(H-H)=1.5-6.5 Å
[b](Arg[2])C_δH-HC(Tyr[4] ring)	R(H-H)=3.5-6.5 Å

[a] reference 6 and [b] reference 27.

Methods

Model compounds. Human angiotensin-II (A-II) and cyclic[Sar[1], Asp[3], Lys5]A-II (c[A-II])[17] are selected as peptide model compounds, while seven organic A-II antagonists[18~24] are selected as rather rigid model compounds, which are shown in Figure 1. The biological activities (IC_{50} values) of these model compounds are shown in Table 1. The organic antagonists are chosen for the reason that (1) their biological activities are in the same range, (2) their back bone structures are moderately or significantly different, and (3) their functional groups can be matched with each other.

In order to avoid the computational mis-interpretation caused by force field parameters, the tetrazol moiety that is believed to act as an acidic group in various A-II antagonists is substituted by carboxyl group (See Table 1). Compound D-7, which is quite different in backbone structure compared to other compounds, is modified with phenyl group instead of 2-(5-OMe)thienyl group of optimal compound in order to maintain the compatibility of structure-functional features among these antagonists.

MD simulation. Several independent MD simulations are carried out for A-II and for c[A-II] at constant temperature of 300 K. The CHARMm[25] program on Silicon Graphics Workstation (R4000 and R4400) is used throughout the calculation. QUANTA[26] was used for the graphic user interface. For the starting conformation of A-II, we used the proton-

proton distance constraints from NOE constraints reported by Matsoukas *et al.*[6,27] which are shown in Table 2. Since these NOE constraints are not sufficient for the structural determination but only provide very rough structural restriction for A-II, we have recompiled these information to use in the calculation (see Table 2). The potential function for the NOE constraints are:

$$\mathbf{E}(R)=\begin{bmatrix} 0.5\times k_r(r-r_{min})^2, & r<r_{min} \\ 0.0, & r_{min}<r<r_{max} \\ 0.5\times k_r(r-r_{max})^2, & r_{max}<r<r_{lim} \\ f_{max}\left(r-\frac{r_{lim}+r_{max}}{2}\right) & r>r_{lim} \end{bmatrix}$$

where k_r is the force constant of value 25.0 kcal/molÅ^2, r is the distance between constrained atoms, or groups in this study, r_{min} and r_{max} are lower and upper bound for the restrained atoms, respectively, and r_{lim} is upper limit of the harmonic potential, and f_{max} is the force at $r=r_{lim}$ where $r_{lim}=r_{max}+0.5$ for usual case. For A-II, initial conformations are prepared by the simulated annealing procedure from 1000 K to 300 K with the constraints described above. In this study, since the conformational possibility is regarded more importantly than the exact energy calculation, neither periodic boundary condition (PBC) nor explicit water molecules are considered. Several values between 4 and 10 for the dielectric constant are used to represent aqueous and receptor environments. In MD calculations, the SHAKE[28] algorithm is applied with 1 femto second (fs) time step. The subsequent analysis is made from the MD trajectory files which have been saved at every 0.5 ps during 200 ps MD runs.

Conformational search for the organic A-II antagonists. Conventional grid search for the main backbone torsion angles was made for seven organic A-II antagonists. Each torsion angle was scanned at every 15° in the torsional space to construct the search grid. At each grid point, these torsion angles are constrained during 2000 cycles of energy minimization with the Powell method. For the model compounds D-5 and D-6, the torsion angle X2 was fixed either at 180° because other regions for this torsion angle resulted too high potential energy. In addition, torsion angle X1 in compound D-7 was fixed either at 90° or 270° for the same reason.

Results and Discussions

Conformation of A-II. During 200 ps MD simulations of A-II and c[A-II], it is observed that these peptides are highly flexible and dynamic. The dynamics average structure of A-II is shown in Figure 2. The conformation of A-II changes very much from the starting conformation obtained by using NOE constraints. The overall structure is compact and its molecular size is about 15 Å which is in good agreement with the dialysis experiments.[29] Several MD simulations with different initial conformations result in different averaged conformations, indicating that the conformation of A-II is highly dynamic[15] and that there is no preferred conformation in receptor-free state. The study on several peptide agonists and antagonists including cyclic peptides by Marshell *et al.*[17] suggests that peptide agonists or antagonists of A-II bind to the receptor in different backbone conformation, especially in the region of the central Tyr[4] residue. c[A-II] is one of these A-II analogues. The averaged conformation obtained from 200 ps MD simulations of c[A-II] is shown in Figure 2(b). Although the conformational degree of freedom of c[A-II] is more restricted than that of a linear peptide due to the cyclic restraint, our MD simulation shows that c[A-II] still have numerous conformations that are thermodynamically accessible at room temperature.

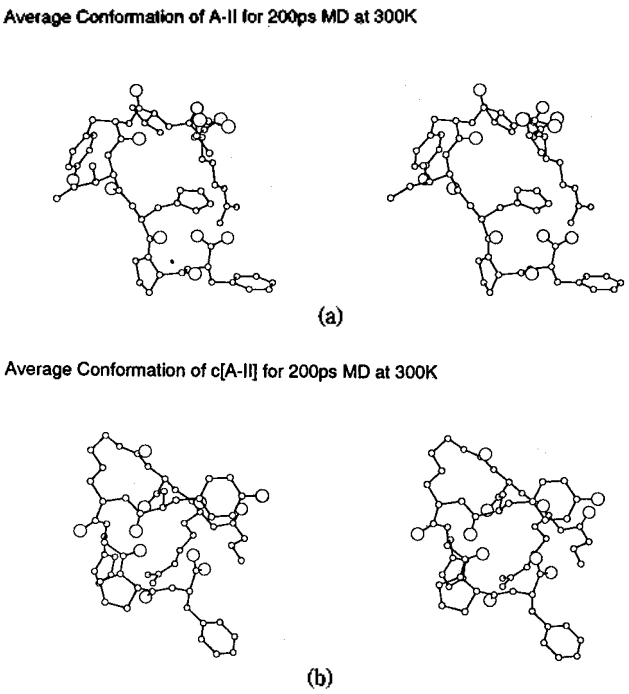


Figure 2. Stereoview of an example of 200 ps MD averaged structure of A-II (a) and c[A-II] (b).

Among the eight amino acid residues in A-II and c[A-II], three carboxyl terminal residues, which are considered to be important for the activity,[1] show more dynamic behavior than other residues. The average molecular dimension of c[A-II] is almost the same as that of A-II. It seems that the aliphatic group of the Lys[5] in c[A-II] plays the same role with the aliphatic side chain of Ile[5] in A-II. Figure 3 shows the distance profile and the corresponding number of populations of the major side chains of A-II and c[A-II] for 200 ps MD simulation. It is clear that there are significant conformational fluctuations of A-II and c[A-II] due to the flexibility.

Conformation of Nonpeptidic A-II antagonists. The energy contour maps obtained from the grid conformational search for the seven organic model compounds (Figure 1) are shown in Figure 4. The energy contour maps indicate that four conformations for each compound are possible, which correspond to local energy minima. The conformations at these local energy minima are compared. The results are summarized in Table 3, where the distance between center of mass of each functional groups are shown. Among these local energy minima conformations, the best fit conformation for each compound is chosen for the structural match, which is shown in Figure 5. Since compounds D-1, D-2, D-3, and D-4 share common backbone structure, it is not difficult to

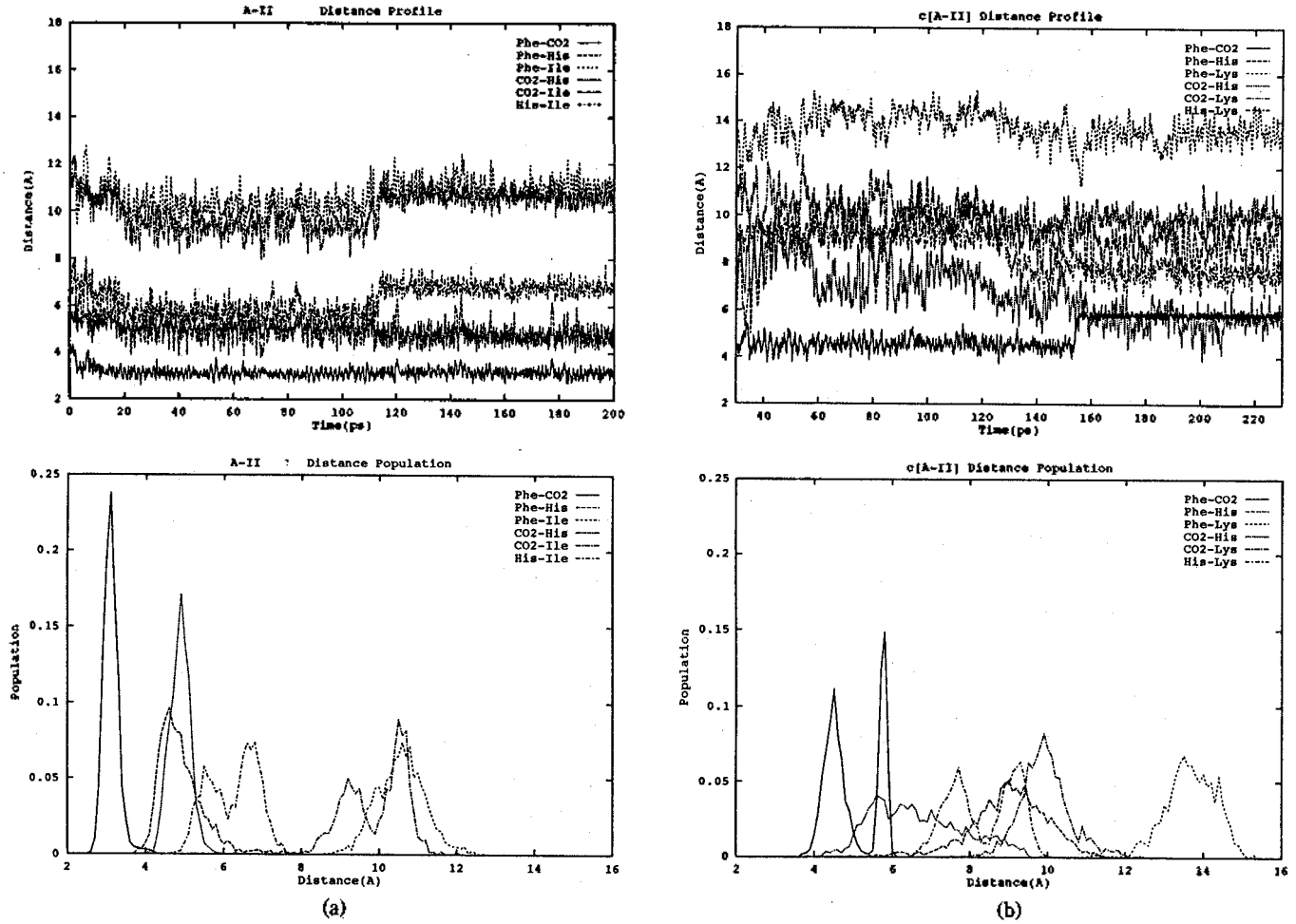


Figure 3. Distance profile of A-II and the population from 200 ps MD simulation among the important functional groups of A-II (a) and of c[A-II] (b). Distances are calculated from the average coordinates of the non-hydrogen atoms of each side chain. For example, Phe-CO2 means the distance between the center of side chain of Phe[8] and the center of C-terminal CO2 group.

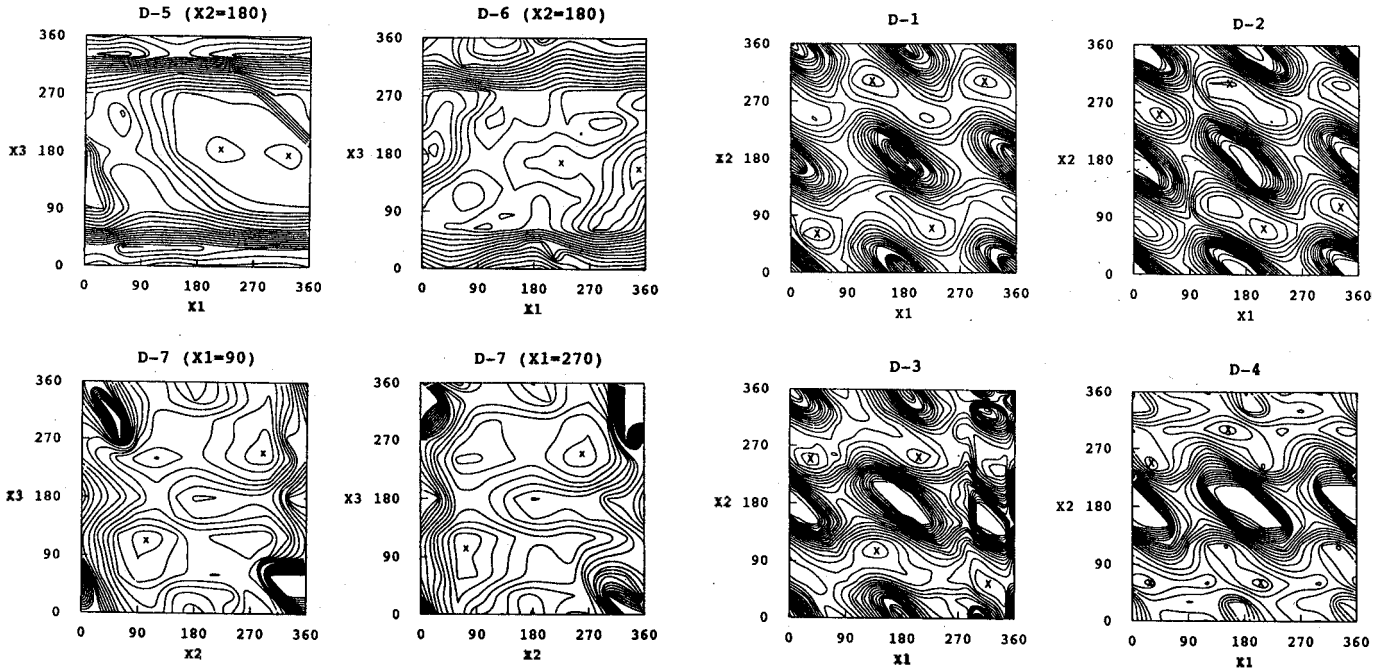


Figure 4. Potential energy contour maps of model compounds. Back bone torsion angles are defined in Figure 1b.

Table 3. Distance Between Main Functional Groups at Local Energy Minimum Conformations

Conformer	Energy (kcal/mol)	Distance (Å)[a]				
		Ph-CO_2	Ph-Hetero	Ph-Bu	CO_2-Hetero	CO_2-Bu
D-1: a	−33.91	3.26	8.32	13.05	6.45	11.95
b	−33.47	3.27	8.38	12.99	8.02	11.29
c	−33.43	3.27	8.38	13.08	7.21	12.80
d	−32.51	3.28	9.37	12.89	8.64	12.32
D-2: a	−47.54	3.26	8.50	12.83	8.56	11.87
b	−46.20	3.27	8.48	11.26	8.79	11.48
c	−45.21	3.26	8.59	9.09	7.92	10.20
d	−44.94	3.27	8.44	6.25	7.40	4.38
D-3: a	−43.72	3.27	8.51	11.11	7.76	11.86
b	−43.43	3.27	8.41	6.95	6.64	3.70
c	−43.34	3.26	8.43	10.81	6.74	8.63
d	−42.08	3.28	8.26	13.87	5.99	11.80
D-4: a	−37.61	3.27	8.50	13.13	6.93	12.40
b	−37.43	3.27	8.51	13.13	7.64	11.01
c	−36.96	3.27	8.51	10.65	7.76	8.17
d	−36.41	3.27	8.50	10.64	8.52	11.54
D-5: a	−1.46	3.28	10.65	12.38	10.18	11.25
b	−1.44	3.28	10.65	12.38	10.17	11.23
D-6: a	19.89	3.27	10.58	12.39	10.08	11.33
b	21.20	3.28	10.61	12.37	9.81	11.37
D-7: a	−44.00	8.78	4.73	10.59	5.37	10.71
b	−42.80	8.81	4.70	7.70	5.37	9.84
c	−40.59	6.37	4.67	10.92	5.40	10.52
d	−38.73	6.34	4.58	9.51	5.40	11.12

[a]Ph: center of phenyl ring attached to carboxilic acid group. CO_2: center of carboxylic acid group. Hetero: center of five membered ring containing nitrogen atom(s). Bu: position of outer carbon atom of alkyl side chain.

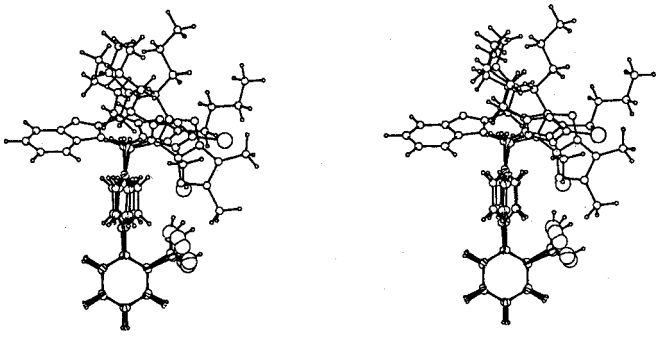


Figure 5. Overlay of model compounds D-1, D-2, D-3, and D-4. Conformations for each compounds are selected from the contour maps in Figure 4. (see also Table 3)

match the structural similarity among these compounds, *i.e.*, aliphatic, acidic, hetero-cyclic, etc. As shown in Figure 5, however, even for these four similar compounds in functional groups and in backbone structure, the match in 3D structure is not satisfied.

It is reasonable to think that the conformations of a flexible molecule like A-II and its analogues are in thermodynamic equilibrium when it is not in the receptor binding site. When the flexible molecule approaches to the receptor binding site, it is likely that among the thermodynamically accessible conformations, well fitting conformation to the binding pocket can dock into the receptor, If this is the case, all thermodynamically accessible conformations at 300 K could be a candidate conformation for binding. Figure 6 shows all conformations within 3 kcal/mol relative to the global energy minimum conformation for each model compound. From the figure, it is found that global energy minimum conformation of compound D-1 is superimposable to all other compounds, which is shown in Figure 7. Table 4 lists the distance information for this match. For molecules, D-1 to D-6, the match is almost perfect both in 3D structure and in the distance between functional groups. The compound D-7 does not show high structural similarity with the other compounds. This implies either that D-7 binds in a different receptor site or that further optimization is necessary to bind into the same receptor binding site.

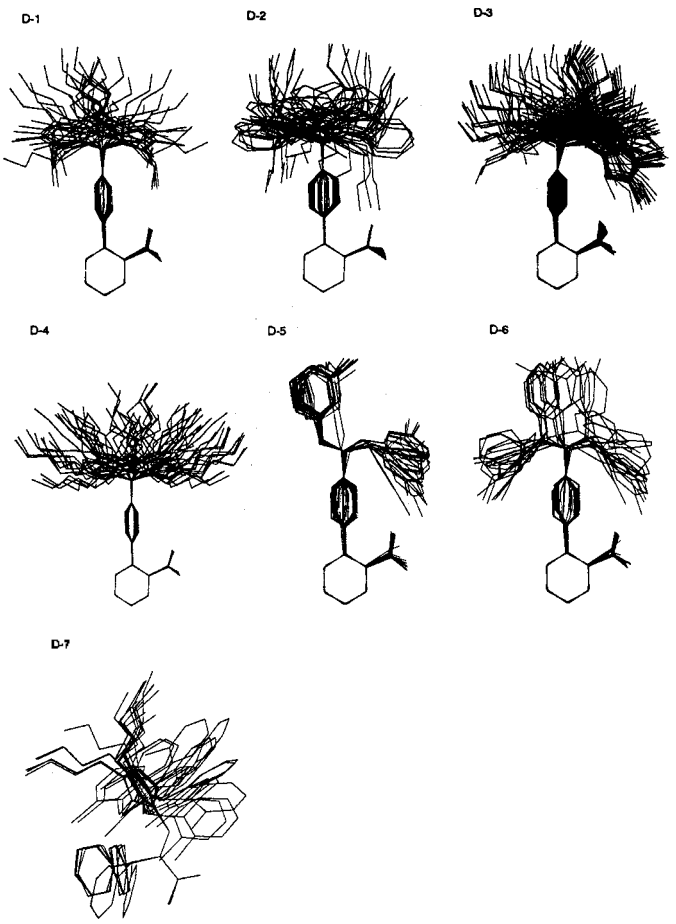


Figure 6. Overlay plot of all thermodynamically possible conformation of nonpeptidic model compounds (see text).

The pharmacophore model. Both A-II and its antagonists contain a number of freely rotatable bonds. In our previous study,[15] we proposed that the significant population of A-II in aqueous solution is well superimposable to the global energy minimum conformation of D-1. Figure 7 further suggests that the global energy minimum conformation of

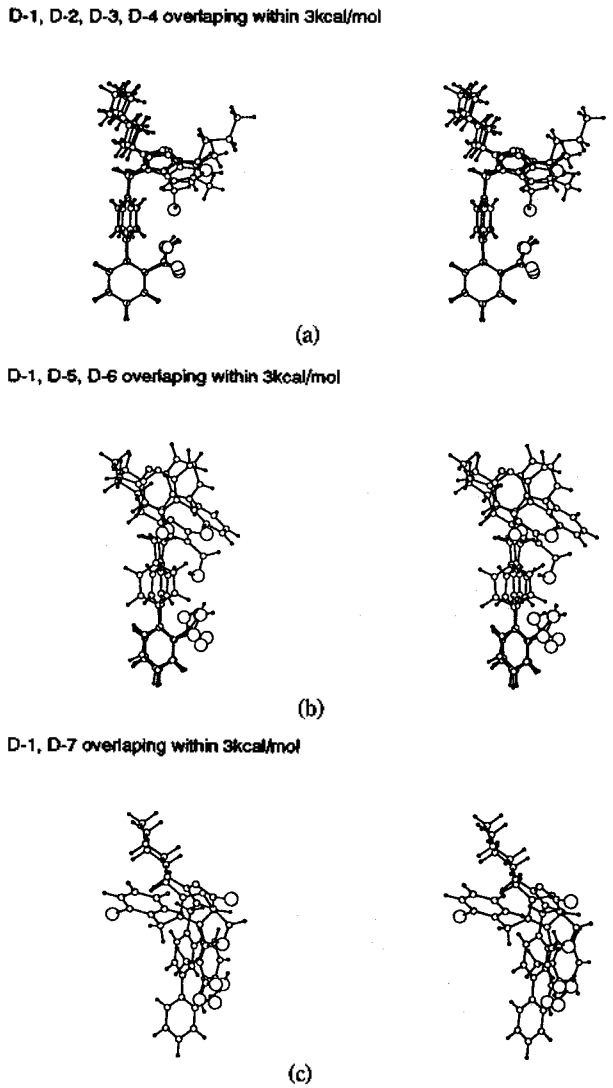


Figure 7. Stereoplot of the best fit conformations among the conformations in Figure 6 of the model compounds. a, D-1, D-2, D-3, and D-4; (b), D-1, D-5, and D-6; (c) D-1 and D-7.

Table 4. Distance Between Main Functional Groups for Conformation which is within 3 kcal/mol in conformation search

Conformer	Energy (kcal/mol)	Distance (Å)[a]				
		Ph-CO_2	Ph-Hetero	Ph-Bu	CO_2-Hetero	CO_2-Bu
D-1:	−33.91	3.26	8.32	13.05	6.45	11.95
D-2:	−46.07	3.27	8.51	12.95	6.80	12.00
D-3:	−43.32	3.27	8.54	13.23	6.87	12.34
D-4:	−37.61	3.27	8.50	13.12	6.92	12.38
D-5:	−1.44	3.28	10.62	11.85	9.77	11.34
D-6:	20.29	3.27	10.60	12.30	9.33	11.28
D-7:	−42.88	4.01	6.50	10.75	5.37	11.10

[a] Ph: center of phenyl ring attached to carboxilic acid group. CO_2: center of carboxylic acid group. Hetero: center of five membered ring containing nitrogen atom(s). Bu: position of outer carbon atom of alkyl side chain.

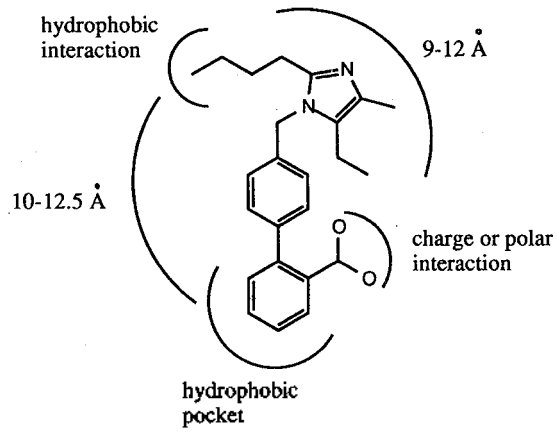


Figure 8. Proposed receptor binding mode for the model compound D-1.

compound D-1 is the most plausible structure in the receptor binding mode. Figure 8 shows the schematic drawing of the pharmacophore model for the D-1 compounds.

The x-ray crystal structure of the complex between A-II and its antibody has been reported.[30] It is striking that the conformation of A-II in this complex is dissimilar to all previously reported solution conformations of A-II. The overall molecular compactness is about same but the detailed orientations of side chains are much different. However, it is not likely that this A-II conformation is the same as the active conformation for the receptor binding.[17]

Conclusion

Conformations of A-II and its organic antagonists are investigated to figure out the pharmacophore structure that is important in 3D structure based new drug development. Since A-II is small linear peptide and very flexible, rather rigid nonpeptidic antagonists are used for the study. From this study, we have found a common conformation for these molecules. This strategy would be useful for drug design when the receptor structure is not available.

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$\pi/2$ Pulse Shaping *via* Inverse Scattering of Central Potentials

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It is shown that the inversion of the undamped Bloch equation for an amplitude-modulated broadband $\pi/2$ pulse can be precisely treated as an inverse scattering problem for a Schrödinger equation on the positive semiaxis. The pulse envelope is closely related to the central potential and asymptotically the wave function takes the form of a regular solution of the radial Schrödinger equation for *s*-wave scattering. An integral equation, which allows the calculation of the pulse amplitude (the potential) from the phase shift of the asymptotic solution, is derived. An exact analytical inversion of the integral equation shows that the detuning-independent $\pi/2$ pulse amplitude is given by a delta function. The equation also provides a means to calculate numerically approximate $\pi/2$ pulses for broadband excitation.

Introduction

The transient response of a system of atoms or spins to a coherent pulsed excitation may be predicted by the solution of a Maxwell-Bloch equation. When the sample of such a system is "thin", the reaction of the induced field back upon the exciting field may be ignored, and then it suffices to solve the Bloch equation alone. The equation has been