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Application of Conformational Space Search in Drug Action

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Abstract
The role of conformational space in drug action is presented. Two examples of molecules in different therapeutic groups are presented. Conformational space search will lead to isolating the exact conformation with the desired medicinal properties. Many conformations of a plant isolate may exist which are active, weakly active or inactive.

Key Words: Conformational, Space, Drug Action

Introduction

It is a common knowledge that many medicinal plant products exist in different isomers one of which is the most active (Olaniyi, 2000). It is also common knowledge that many plant extracts are active in the crude or 'natural' form but may decrease in activity or lose activity totally during processing, such as extraction with different solvents under different environmental conditions (Trease and Evans, 1981). This decrease or loss in activity is often ascribed to degradative changes. There is also the possibility that the form that is isolated is the inactive or less active isometric form.

A more complex phenomenon is the many conformational spaces that a molecule could occupy. Most molecules exist at a minimum energy level at which the molecule has the greatest stability (Holtje and Folkers, 1997). In the natural state in plants, most molecules are likely to exist in this form. At other energy levels the molecule is considered to be relatively unstable. This form may be the most biologically active but that may not always be the case.

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Since most molecules exert their biological or therapeutic activity by combination with receptors (Lawrence and Bennett, 1992), a small change in conformation could lead to decrease or loss of activity as the point of interaction with the receptor may be displaced. Changes in conformation could occur during extraction in a solvent as is seen in molecular dynamics simulations (Van Gunteren and Berendsen, 1985). The presence of large conformers that are inactive could lead to dilution of the effect of the active conformer. Since a flexible molecule with many rotational bonds could produce millions of conformations, which may be difficult to calculate or data generated may be difficult to analyse, it is often necessary to search around the molecule with the least minimum energy. Similarly, it has been useful to use a very active molecule (whose conformational properties are already known) that would act on the same receptor as the compound in question. The above phenomena are illustrated in this study with molecular modelling studies of two anti-histamines, tiotidine and ICI127032. The anti-histamines belong to the same isomeric groups to eliminate the effect of isomerism. The interaction of acetylcholine with tryptophan is also presented from the Cambridge Crystallographic Database (Cambridge Structural Database) to further illustrate the situation.

Materials and Methods

All molecular modelling studies were carried out using Silicon Graphics Impact 10000 (model CMNBO07Y125). The molecular modelling package SYBYL 6.5 (MIPS3-IRIX 6.2) with update #3 using terminal type "OGLX" displayed on "0.0" (SYBYL Tripos Associates, USA) was used for all the studies. The two antihistaminics were constructed using the SKETCH module within the molecular modelling program SYBYL and geometry optimised using the force field MAXIMIN of the same program (SYBYL, Tripos Associates, USA). The conformational space search was carried out using the SEARCH module of the same program. The acetylcholine-tryptophan complex was obtained from the Cambridge Crystallographic Database (Cambridge Structural Database).

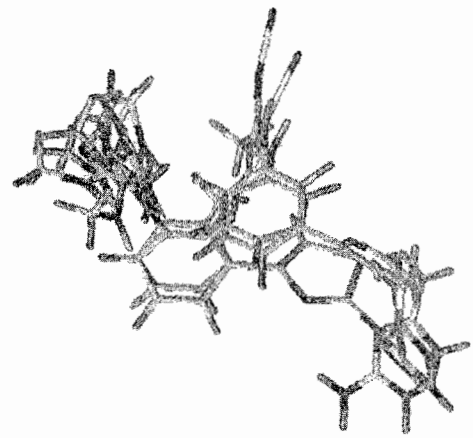

Fig. 1: Possible confirmations of ICI127032

Results and Discussion

Table 1 shows the minimum force field energy terms calculated in vacuum using a dielectric constant of 1 while Table 2 shows the force field energy terms calculated for the molecules in water using a dielectric constant of 88. Table 1 illustrates the absolute minimum energy levels in which there is no interference from the environment, while Table 2 illustrates the importance of environmental conditions on the minimum energy level attained by the molecules. From the two tables it could be observed that there was a sharp increase of the total energy from -56.4 kcals/mol in vacuum to 17.1 kcals/mol in water and -59.6 kcals/mol in vacuum to 21.4 kcals/mol for tiotidine and ICI127032 respectively. This shows the importance of the vehicle on the stability of the molecules. The larger energy content in water shows a decrease in stability. The solvent (water) affects mostly the electrostatic energy terms of the molecule.

Table 1: Force field energy terms computed in vacuum

Energy term	Energy value (kcals/mol)	
	ICI127032	**Tiotidine**
Bond stretching energy	0.475	0.689
Angle bending energy	10.498	11.810
Torsional energy	7.478	2.732
Out of plane bending energy	0.011	0.006
1-4 Van der Waal's energy	2.853	1.985
Van der Waal's energy	1.562	1.279
1-4 Electrostatic energy	-103.541	-90.153
Electrostatic energy	21.085	15.273
Total energy	-59.580	-56.379

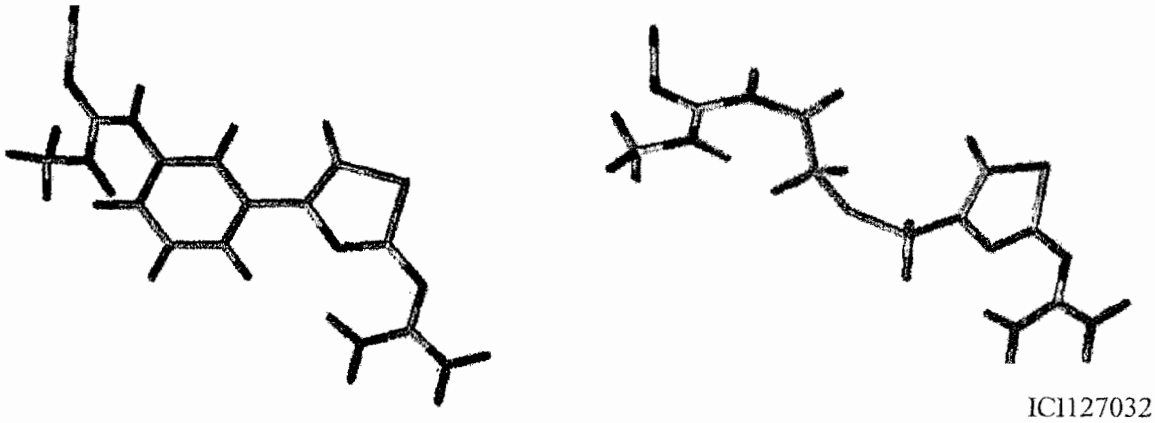

Fig. 2: Orientation showing similarities in the chemical structure of tiotidine and ICI127032

Table 2: Force field energy terms computed in water

Energy term	Energy value (kcals/mol)	
	ICI127032	**Tiotidine**
Bond stretching energy	0.745	0.929
Angle bending energy	10.986	12.026
Torsional energy	7.220	2.578
Out of plane bending energy	0.013.	0.005
1-4 Van der Waal's energy	2.540	1.638
Van der Waal's energy	0.833	0.703
1-4 Electrostatic energy	-1.169	-1.018
Electrostatic energy	0.244	0.18
Total energy	21.412	17.142

Table 3: Energy values for the 10 least conformations of ICI127032 and tiotidine

ICI127032		Tiotidine	
Conformation	**Energy values (kcals/mol)**	**Conformation**	**Energy values (kcals/mol)**
CNF-19	17.716	CNF-31	17.069
CNF-32	17.717	CNF-32	17.069
CNF-37	17.717	CNF-28	17.070
CNF-55	17.717	CNF-30	17.072
CNF-18	17.718	CNF-29	17.074
CNF-59	17.718	CNF-23	17.657
CNF-61	17.721	CNF-22	17.665
CNF-13	17.722	CNF-24	17.665
CNF-46	17.722	CNF-18	18.763
CNF-34	17.723	CNF-19	18.779

Table 3 shows the first ten most favourable energies of the search conducted on ICI127032 and tiotidine while Table 4 shows the first ten conformations in serial order. From the two tables it is clear that none of the least ten conformations could be selected from the first ten conformations and therefore, selecting the first molecule or any molecule without proper conformational search would be erroneous. ICI127032 was used as the template in conducting the search because it has a lower number of rotatable bond of 3. The tables were obtained from conducting a search on these number of rotatable bonds using 30° as the level of increment and limiting the total value of angle of rotation to 120°. With that number of rotable bonds 63 possible conformations were obtained and are shown in Fig. I superimposed on each other. For a flexible molecule like tiotidine (see Fig.2) with many rotatable bonds it would be impossible to conduct a proper search on the molecule without restriction and comparing it with a rigid and bioactive template such as ICI127032. Attempts at doing this resulted in 500,000 conformations and the job had to be automatically "killed" by the computing machine due to excessive data overflow. When the search was conducted with the same number of rotatable bonds as ICI127032 196 different conformations were obtained. Since ICII27032 is as equally potent as tiotidine, it would be reasonable to state that the most bioactive conformation

would lie within the 45 for ICI127032 and 196 for tiotidine, Each of this conformation is at best still a family of conformations because of the large interval in the increment angle of 30°, Using smaller angles such as 5° will be better to be able to define the exact bioactive conformation or even family of conformation. All the molecules within this family are usually very close in terms of energy content and molecular orientation (Holtje and Folkers, 1997).

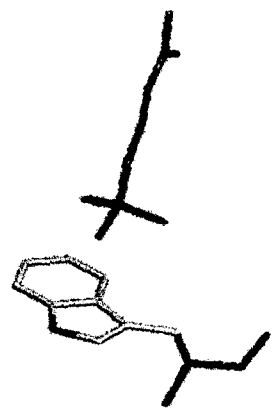

Fig. 3: Acetylcholine-tryptophan interaction
as obtained from Cambridge Crystallographic database

The importance of conformational space search is further illustrated by the interaction of acetylcholine with tryptophan -the amino acid at the receptor site of interaction (Fig.3). The interaction takes place at the anionic site with an NJ nitrogen that is protonated at the physiological state. The interaction is held in place by dispersion forces between the aromatic portion of the hydrogen atoms on the protonated nitrogen (Martin et al, 1983). A slight change in conformation of the acetylcholine will result in change in the forces of attraction. Hydrogen bonding, for instance, will only take place at a particular distance between two molecules (Adikwu and Holtje, 2001).

Table 4: Energy values of the first ten conformations of ICI127032 and tiotidine

Conformation S/N	Energy values (kcals/mol ICI127032	Tiotidine)
CNF-1	24.979	24.062
CNF- 2	24.192	24.061
CNF-3	26.581	24.058
CNF-4	25.221	24.358
CNF-5	22.749	24.363
CNF-6	22.747	24.351
CNF-7	23.616	24.358
CNF-8	23.614	24.363
CNF-9	23.600	24.060
CNF-10	22.748	24.062

Conclusion

It has been shown in this study that a large number of conformations of drugs do exist and not all are bioactive. It would, therefore, be wrong for the medicinal plant researcher to pick any conformation and take that as the active compound. It may not be exactly correct to conclude that many plants that show activity when whole may become inactive after all the extraction and purification processes. This may be as a result of the large number of conformations that may result from extraction and purification processes. Thus, medicinal plant researchers have much to gain when computer models are applied to their molecules as many molecules that are often termed inactive may actually be active if the exact conformation that is active could be defined and isolated.

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