MOLDEX: A Computer System for Drug Design. 4) A Combined Electro-Geometric Method for the Identification of Pharmacophoric Structural Patterns in Drugs

Hiromi Nakatake nakatake@translell.eco.tut.ac.jp
Carlos Adriel Del Carpio carlos@translell.eco.tut.ac.jp
Laboratory for Informatics & AI in Moleclular and Biological Sciences
Department of Ecological Engineering. Toyohashi University of Technology
Tempaku, Toyohashi 441-8580, Japan

1 Introduction

In the present study we propose a methodology to extract information on common bioactive as well as pharmacophoric structural patterns from series of organic molecules recognized as candidate ligand molecules, or with known bioactive profiles. The methodology is based on a combined 3D structural similarity calculation algorithm and the analysis of the electrostatic potential generated by the common patterns within the structural environment of each organic compound. The results of the analysis lead to classification of ligands into categories reflecting the capacity of interaction of each molecule and eventually features of the ligands related to their agonist or antagonist character. Moreover, the analysis leads to a simpler docking process whenever the receptor is known or to its portrayal when that is not the case.

2 Methodology

Recently we have been developing a system for the automatization of processes of drug design. Our system, MOLDEX (MOLecular DEsign X) [3], has as main characteristic modules for mapping receptor regions on proteins, docking ligand molecules into a receptor region, a module for conformation analysis in solution, and the modules for two and three dimensional QSAR. Here we describe a new methodology to extract common 3D structural patterns in series of analogous organic compounds, and the analysis of their electrostatic characteristics within the environment of each particular molecule in order to assess strength and mode of interaction with the receptor.

The major problem in geometrical comparisons of 3D structures of chemical compounds is finding a transformation matrix to superimpose in the most optimal way two three dimensional bodies. Translational components can however be removed from the transformation matrix by referring the molecules to be compared to their mass centers. The rotation component of the matrix can be found by approaches in the literature such as the W. Kabsch method [1] or the A.L. Mackay method [4]. These approaches are however limited to the simplest two molecular case. In the present study we have embedded these algorithms into the genetic algorithm (GA) paradigm to obtain common 3D structural patterns for more than two molecules. The need for a heuristic method to select the referential points of superimposition which yield the optimal RMS value among the structures makes of the GA the most appropriate approach to solve the problem. Pharmacophoric and/or bio-active patterns among the structures compared are obtained as those where the superimposition of the molecules gives the least RMS value.

To further analyze the electrostatic characteristics of the fragments obtained by the procedure above, we have implemented a new methodology based on the mapping of the electrostatic characteristics of the molecules constituting the set. Atomic charges for the atoms constituting the molecules are computed using the MOPAC system. Electrostatic potentials are calculated at every point of an imaginary grid on the molecular surface where an imaginary probe charge of +1u.e. is placed. The resulting three dimensional distribution of the electrostatic potential so calculated is mapped into a two dimensional plot by means of the SOM algorithm [2]. Analysis performed on the 2D map of electrostatic characteristics of the molecule allows the evaluation of the electrostatic activities of the common 3D fragments within different chemical environments. Thus reactivities and/or interaction capabilities for each compound can be readily derived from this analysis.

3 Results and Discussion

We have applied the algorithm discussed in the previous section to a set of three structures known to react with the benzodiazepine receptor. Fig. 1. shows the molecular formuli of the compounds and illustrates the results of the algorithm, which shows as common fragment the one with the numbered region on the molecules.

Analysis of the electrostatic characteristics (not shown here) of the common fragment within the chemical environment of the three molecules shows a stronger interaction capability for molecule 1, while molecule 3 would be the one with the weaker reactive abilities.

These results are of the major relevance in processes where several candidate ligand molecules are generated as probable agonists or antagonists to a determined receptor molecule. Furthermore, the present methodology can very well be applied to mimetics of organic or bio-molecules.

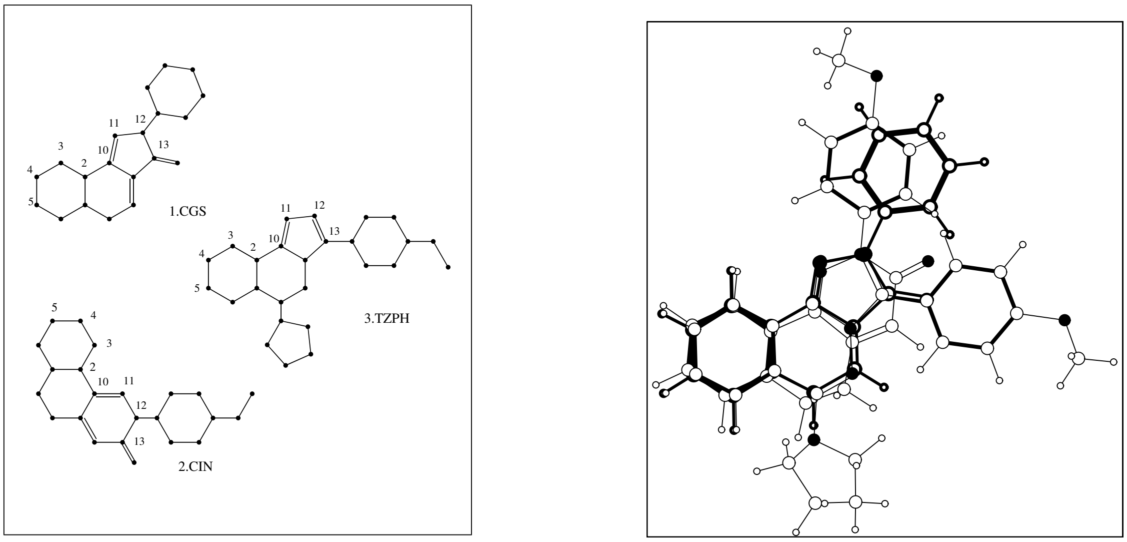

Figure 1: Identification of the pharmacophore pattern in benzodiazepine-recepter ligands by molecular structure superposition. (Ligands: CGS^1 , CIN^2 , $TZPH^3$).

References

[1] Kabsch, W., A Discussion of the Solution for the Best Rotation to Relate Two Sets of Vectors, *Acta Cryst.*, A34:828–829, 1978.

[2] Kohonen, T., The self-organizing map, *Proceedings of the IEEE*, 78:1464–1480, 1990.

[3] Nishimura, K. and Del Carpio, C.A., MOLDEX: A Computer System for Drug Design. 3) Constructing Hypothetical Ligand Molecules, *Genome Informatics 1997*, Universal Academy Press, 314–315, 1997.

[4] Mackay, A.L., Quaternion Transformation of Molecular Orientation, *Acta Cryst.*, A40:165–166, 1984.