MOLDEX : A Computer System for Drug Design. 3) Constructing Hypothetical Ligand Molecules

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1 Introduction

The present work is one of a series describing the research and development of a new computer system for drug design: MOLDEX (MOLecular DEsign X). The main characteristics of the system are the modules for receptor site mapping [1,2,3], the module for molecular three dimensional superposition [4], the module for conformation analysis in solution [5], and the molecular dynamics module [6]. Here we propose a new computer methodology for three dimensional QSAR to assist the construction of more suitable and effective ligand molecules. The proposed computer module is based on the mapping of the three dimensional characteristics of candidate ligands in two dimensions by a self organizing map (SOM) [7] algorithm. This two dimensional map allows a rapid comparison of the structural, reactivity, energetic as well as electrostatic characteristics of ligands, allowing a more robust process of construction of effective drugs automatically.

2 Methodology

In drug design processes comparison of structural and physicochemical characteristics of several candidate ligand molecules is often required to elucidate the hypothetically most effective drug. Common methodologies to perform this task range from QSAR (Quantitative Structure-Activity Relationships) where two dimensional structural characteristics are related to physicochemical parameters expressing chemical reactivity or biological activity, to more sophisticated three dimensional analysis such as CoMFA(Comparative Field Analysis) where molecules are analyzed placing them in an imaginary three dimensional grid (the field) and modelling scores representing physicochemical characteristics using PLS or MLR methods. Here we propose a novel methodology to express three dimensional characteristics of ligands in a two dimensional map easy to analyze visually and automatically. This consists in a self organizing map of the three dimensional characteristics into a two dimensional map. Models of reactivity in function of the so expressed structural and physicochemical characteristics of molecules are then derived for all the ligand candidates. The first step in the process is the computation of the three dimensional structure for the compounds, the prediction of their most relevant conformers (in gas or solution), and the computation of charges and other three dimensional parameters. In our work charges are computed using one of the semiempirical methods included in the MOPAC system. Atoms are expressed as icosahedral bodies, and electrostatic potentials are calculated at the points accessible to the solvent, using a probe charge of 1 esu. Each point can be regarded as a four (or more) dimensional pattern. Patterns are then classified and mapped in two dimensions using Kohonen Self

Organizing Map network [7]. Comparison of the electrostatic energy from the receptor cavity (in the case where it is known) as well as that from the ligand molecule can be performed easily. Furthermore, self organized maps for other candidates can be compared with that of the lead structure, and in this way evaluate their reactivity; but the most important is that several molecules can be compared straightforwardly for reactivity, and fitness.

Table1: SOM FOR THE COMPLEX DHFR-MTX

neuron	1	2	3	4	5	6	7	8	9	10
1	*0.3485	0.4183	-1.3202	-1.3202	0.3513	0.5379	-0.3089	0.3732	-0.7713	-0.0520
	**0.2258	1.0337	0.9200	0.9523	0.9200	0.8950	1.9181	0.7573	-0.9527	-1.3685
2	0.5591	-0.6305	-1.5761	-1.5761	1.3239	0.4802	-1.2027	-1.7360	-0.5196	0.5192
	-0.8551	0.1534	0.8908	0.9200	0.8950	1.8204	1.8204	1.2280	-0.3096	0.0495
3	-1.1280	-2.6249	-1.3539	-0.7612	-0.7212	-0.9826	-0.7716	-0.7716	2.5855	-1.1436
	-0.0704	0.1816	-0.0294	0.6356	1.0674	1.2572	1.2280	-0.5891	0.6572	0.6572
4	-0.9420	-0.8863	-0.1097	0.3846	2.2278	-0.2853	-0.7716	-0.7716	0.6280	-0.0704
	2.1927	-0.7716	1.0417	0.4635	0.8884	1.2781	1.1282	-0.3096	-0.1094	0.6572
5	-0.0732	-0.0381	0.1103	0.0596	-0.3277	0.0888	0.4635	1.0417	0.4069	0.2258
	-0.9079	-0.7716	-0.7716	-0.7716	0.5296	-0.8165	0.2428	0.8943	0.5536	-0.7609
6	-0.4772	0.4270	0.2369	0.8943	0.0071	0.7350	0.8950	-0.0294	0.2209	0.2258
	-1.9035	-1.0536	-1.2646	-1.0887	-1.3202	-0.5391	-0.4772	0.1166	1.4046	-1.4294
7	-1.3689	0.6443	-0.8154	0.6572	-0.3096	1.3128	1.8930	0.8275	0.9906	0.8908
	0.2244	0.4802	0.3513	-1.5761	-2.2157	1.0059	-0.0381	0.1249	-0.5290	0.5518
8	0.5518	1.0319	-0.0113	-1.3685	0.0495	-0.0541	0.3290	1.7912	0.3165	1.2388
	0.2244	0.4802	0.3513	-1.5761	-2.2157	1.0059	-0.0381	0.1249	-0.5290	0.5518
9	-0.5290	0.5518	-0.0113	-2.6141	-1.3685	0.6572	0.8049	0.9999	0.3168	0.3839
	-0.5196	0.5810	0.5160	-2.6409	-0.8863	-0.8863	-0.2571	-1.3689	-1.0570	-0.5290
10	-0.2025	-0.0138	0.5518	0.5518	0.6572	0.6572	0.3850	1.2280	0.8950	0.9906
	0.1997	-0.7713	-1.1280	-0.9420	-1.1280	0.6016	-0.7713	-1.1436	0.1938	-0.8662

* → electrostatic potential of the cavity
** → electrostatic potential of the ligand

3 Result and Discussion

We have tested out program for the MTX (methotrexate) in DHFR (Dehydrofollate Reductase) molecule (Table.1).

After receptor site identification and ligand conformer prediction, charges for the atoms in MTX(Fig.1) were computed using MOPAC, for all the conformers predicted by GAFLEX [3]. Computation of the 2D self organized maps for MTX was carried out as described above. These are shown in Table. 1. An inspection of the complementarity of electrostatic potentials suggest a high inverse correlation in several regions of the map,supporting the effectiveness of our methodology.

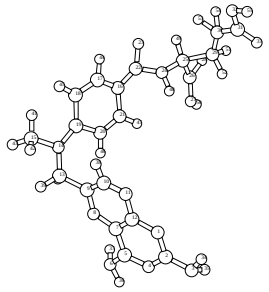

Fig1. 3D-Structure of Methotrexate (MTX)

References

[1] Del Carpio .C.A. ,Takahasi Y. ,Sasaki S.; J. Mol. Graphics. 11:23–29,(1993)

[2] Del Carpio .C.A. ,Takahasi Y. ,Sakaki S.; J. Chem. Inf. Comput. Sci. 33:769–775,(1993)

[3] Del Carpio .C.A. ,Takahasi Y. ,Sakaki S.; COmputer Aided Innovation of New Materials II. Elsevier Science Publishers B.V. 1:1151–1154,(1993)

[4] Deretey V. ,Del Carpio .C.A. ,Baranyi L. ,Okada H. ,Sasaki S.; 18th Symposium on Chemical Information and Computer Science :137–140,(1995)

[5] Del Carpio .C.A. ,Del Carpio .A.E. ,Del Carpio .F.; 20th Symposium on solvent chemistry Kyoto:(1997)

[6] Kawamura Y. ,Del Carpio .C.A.; Proceedings Genome Informatics Workshop:(1997)

[7] Kohonen T.;Proceeding of the IEEE:78–79(1990)