European Journal of Medicinal Chemistry 44 (2009) 1926–1932

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

GRIND-based 3D-QSAR and CoMFA to investigate topics dominated by hydrophobic interactions: The case of hERG K^+ channel blockers

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ARTICLE INFO

Article history:
Received 24 February 2008
Received in revised form
18 September 2008
Accepted 17 November 2008
Available online 28 November 2008

Keywords:
3D-QSAR
ALMOND
hERG
GRIND
Molecular modelling

ABSTRACT

The study compares GRIND-based 3D-QSAR and CoMFA [A. Cavalli, E. Poluzzi, F. De Ponti, M. Recanatini, J. Med. Chem, 45(2002), 3844–53] to investigate a biological topic dominated by hydrophobic interactions, e.g. hERG K^+ channel blocking activity.
As expected, models are found by both methods and there is a fine agreement between statistical and graphical results as well. However, a closer inspection revealed that failures in the prediction of hERG blocking activity for lipophilic compounds were registered for both methods. The study explores the reasons for these failures which are strongly dependent on the chosen method, and gives some suggestions to handle with these topics.

1. Introduction

The human ether-à-go-go related gene (hERG) potassium channel is a key cardiac ion channel that regulates the duration of the plateau phase of the cardiac action potential. Delayed activation of hERG due to chemical blockade, or certain types of inherited dysfunction, results in increased duration of ventricular repolarization, appearing as a prolongation of the time interval between the Q and T waves (LQT) in the electrocardiogram. LQT is considered a major risk factor for torsades de pointes, a life-threatening arrhythmia [2]. Diverse types of organic compounds are believed to disrupt hERG current upon binding within the lumen of the homotetrameric pore domain. The understanding of the chemical requirements for hERG blockade is thus a topic of huge interest in drug design and requires the support of powerful molecular modelling strategies.

3D-QSAR methods are standard tools in medicinal chemistry projects and a lot of software is today available to calculate molecular descriptors and perform chemometric analysis. CoMFA (comparative molecular field analysis) methodology implemented in SYBYL package [3] and GRIND (Grid-INdependent Descriptors)-based 3D-QSAR implemented in ALMOND software [4–6] are the two of the most common and powerful tools in the field, already used to address a number of biological topics [6–10].

Recently, to deeply explore ALMOND methodology, we investigated the influence of ligand flexibility in the generation of the model [11] and the skills of GRIND-based 3D-QSAR approach to reliably predict two different biological activities for the same series of compounds [12]. An additional issue about GRIND-based 3D-QSAR concerns the degree of superposition with CoMFA methodology. To the best of our knowledge, this topic was only addressed by a paper by Menezes et al. [13] which compares the two computational tools to describe the binding mode of a set of estrogen receptor ligands. In this study, the inhibitory activities (expressed as $\log 1/IC_{50}$ and measured in MCF7 cells) calculated with the two methodologies were not in excellent agreement since CoMFA systematically overestimated experimental values, whereas the reverse was true for ALMOND predictions. Graphical results comparison was not specifically addressed by the authors, but visual inspection of reported figures showed similar profiles being key interactions in larger part of polar nature (contribution of steric field and electrostatic field: 40% and 60%, respectively).

These results suggested us to explore in more detail the degree of superposition of ALMOND and CoMFA methodologies applied to a topic for which hydrophobic interactions are largely dominant. This is a highly relevant aspect in the effort of comparing the two computational tools since they differ in at least two characteristics

Abbreviations: CoMFA, comparative molecular field analysis; GRIND, grid independent descriptors; hERG, human ether-à-go-go related gene; LV, latent variable; MIF, molecular interaction fields; PLS, partial least squares; SDEP, standard deviation of errors of prediction; VIP, variable importance in the projection.

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doi:10.1016/j.ejmech.2008.11.009

related to the treatment of hydrophobic interactions: (a) the entropy component is taken into consideration by the DRY probe in ALMOND but not by the steric field in CoMFA (in fact to overcome this limit it has been proposed to add a third field, i.e. the molecular lipophilicity potential, MLP [7]) and (b) the alignment of the molecules in CoMFA procedure is very often performed on the most active compound using at least one hydrophobic moiety (generally an aromatic ring). Given these differences, we were interested in understanding which approach works better when the investigated interaction is dominated by hydrophobic interactions.

In the present paper a series of hERG potassium channel blockers were thus submitted to ALMOND software and the resulting model was compared with the corresponding model (= obtained using the same series of compounds) found by a CoMFA procedure and reported in the literature some years ago [1]. Comparison was possible because the study by Cavalli et al. [1] avoids any misunderstanding about both the quality of the biological data (drugs span a potency interval as hERG K^+ channel blockers of more than 5 log units with IC_{50} values expressed exclusively in mammalian cells) and the adopted methodology. In addition, the paper furnishes a clear and complete depiction of the results enriched with a wise discussion.

Results indicate that ALMOND and CoMFA give good and comparable predictions of the hERG potassium channel blocking activity. Both methods show limits in predicting hERG blocking activity of very lipophilic molecules and CoMFA is slightly more accurate when flexible compounds are considered. Finally, a deeper and expert insight into the hydrophobic content of the ALMOND results gave more details about the structural features that are responsible for hydrophobic interactions, but how to link this finding to interpretable features remains doubtful.

Table 1
Experimental and calculated pIC_{50} (ALMOND and CoMFA [1] data), differences between experimental and calculated values and log $D^{7.0}$ produced by ADME Boxes software.

	Compound	Exp	Calc (ALMOND)	Exp–calc (ALMOND)	Exp–calc (CoMFA)	Log $D^{7.0}$
	Training set					
1	Astemizole	9.04	8.72	0.32	0.51	4.14
2	Cisapride	8.19	8.69	−0.50	0.23	2.05
3	E4031	8.11	7.94	0.17	0.26	0.34
4	Dofetilide	7.91	7.36	0.55	0.24	0.68
5	Sertindole	7.85	7.92	−0.07	−0.19	2.65
6	Pimozide	7.74	8.49	−0.75	−0.06	5.11
7	Haloperidol	7.55	7.22	0.33	−0.03	1.82
8	Droperidol	7.49	6.99	0.50	−0.33	2.25
9	Thioridazine	7.45	6.71	0.74	0.22	3.83
10	Terfenadine	6.89	7.15	−0.26	−0.33	4.11
11	Verapamil	6.84	7.09	−0.25	−0.21	2.79
12	Domperidone	6.79	6.99	−0.20	−0.09	3.15
13	Loratadine	6.76	6.26	0.50	0.93	4.94
14	Halofantrine	6.70	6.80	−0.10	−0.11	5.68
15	Mizolastine	6.45	6.20	0.25	−0.2	1.96
16	Bepridil	6.26	6.05	0.21	−0.04	4.49
17	Azimilide	6.25	6.64	−0.39	0.1	2.05
18	Mibefradil	5.84	5.31	0.53	0.09	1.96
19	Chlorpromazine	5.83	5.73	0.10	0.15	2.99
20	Imipramine	5.47	6.02	−0.55	−0.51	2.25
21	Granisetron	5.42	5.32	0.10	−0.22	−1.72
22	Dolasetron	5.22	5.34	−0.12	0.23	2.6
23	Perhexiline	5.11	5.48	−0.37	−0.08	2.81
24	Amitriptyline	5.00	5.18	−0.18	−0.66	3.33
25	Diltiazem	4.76	4.41	0.35	−0.26	1.62
26	Sparfloxacin	4.58	4.28	0.30	0.19	−3.4
27	Glibenclamide	4.13	4.50	−0.37	0.06	2.23
28	Grepafloxacin	4.11	4.19	−0.08	−0.24	−1.47
29	Sildenafil	4.00	4.28	−0.28	0.5	2.29
30	Moxifloxacina	3.93	4.18	−0.25	0.11	−2.9
31	Gatifloxacine	3.89	4.10	−0.21	−0.27	−2.96
	Test set					
32	Norastemizole	7.55	6.19	1.36	0.83	0.16
33	Ziprasidone	6.82	7.69	−0.87	−0.1	3.93
34	Risperidone	6.79	6.60	0.19	−0.2	0.71
35	Clozapine	6.72	6.24	0.48	0.54	4.41
36	Cocaine	5.24	4.53	0.71	−0.17	0.41
37	Fexofenadine	4.67	5.90	−1.23	−0.66	1.85

Table 2
Summary of the statistical parameters for the ALMOND model.

	ALMOND	CoMFA [1]
LV	3	3
q^2_{LOO}	0.69	0.77
r^2	0.93	0.95
a[a]	1.00 (±0.05)	N/A
b[a]	0.00 (±0.31)	N/A

N/A, not available.
[a] Coefficients of the relationship between experimental and calculated values calculated from the equation: $pIC_{50}^{exp} = a\ pIC_{50}^{calc} + b$; 95% confidence limits are given in bracket.

2. Methodology

2.1. Data set preparation

The list of compounds to be included in the data set was taken from the paper of Cavalli et al. [1] (chemical structures are available in Supporting information). The original separation into training (31 compounds) and test (6 compounds) sets was also maintained.

The ADME Boxes software (version 2.5, Pharma Algorithm, http://pharma-algorithms.com/) was used to estimate pK_as (Supporting information) and log $D^{7.0}$ (Table 1) and obtain SMILES codes [14], except for **3** whose SMILES was manually built. All compounds bear a positive charge except for **13** and **27** which are in the neutral form and **26**, **28**, **30**, **31** and **37** which are in the zwitterionic form.

The 37 SMILES strings were submitted to Omega (version 2.1.0, OpenEye Scientific software, http://www.eyesopen.com/) as described in detail elsewhere [11]. The lowest energy conformers were selected and checked with MOE (version 2006.08, Chemical Computing Group, Inc., http://www.chemcomp.com/).

2.2. ALMOND

Briefly, the ALMOND methodology involves three steps [4–6]: computing a set of molecular interaction fields (MIFs) for

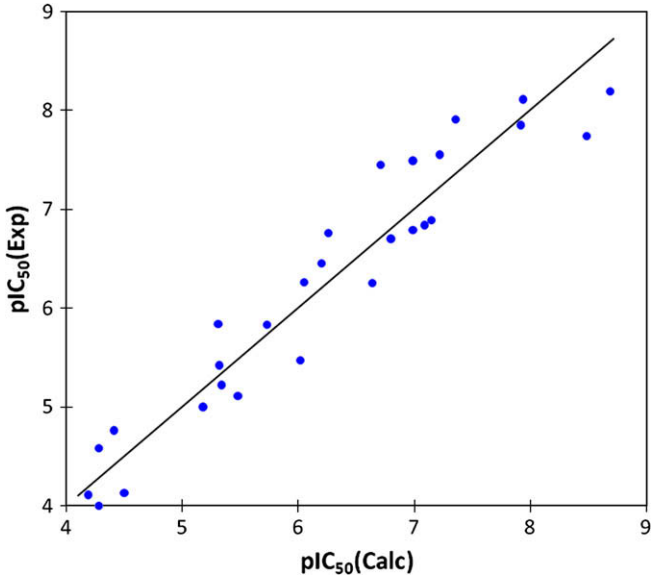

Fig. 1. The linear relationship between the experimental pIC_{50} taken from the paper of Cavalli et al. [1] and the corresponding data calculated by ALMOND.