[P31] Identifying specific binding modes for the ligands of a multi-site GPCR by a 3D-QSAR pharmacophore approach

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The study of the interaction between a ligand and its receptor requires to know the structure of the receptor and/or that of its ligands. When the receptor structure is unknown, as it is the case for most of GPCRs, ligand-based approaches are essential. The HypoGen module, formerly implemented in the Catalyst environment (Accelrys Inc, which became Discovery Studio Biovia), was one of the first algorithms associating the identification of common spatial features in a three-dimensional space (pharmacophore approach) with the statistical analysis of quantitative relationships between molecular properties and ligand activity (3D-QSAR) [1, 2].

Obtaining reliable HypoGen models can only be achieved if all the tested ligands bind in the same way to the same active site. However, different modes of binding may exist on the same receptor [3]. Paradoxically, this limit can be used to identify subgroups of ligands, as we have shown in the case of ligands of the human olfactory receptor OR1G1 [4], of which one main characteristic is to be a multi-site receptor [5, 6].

Our procedure [4] involves two main steps. Firstly, the crucial step is to identify a "core subset" of 5 to 10 ligands to obtain models of satisfactory quality. Secondly, it is to add ligands to the core subset that allows improving the quality of the generated pharmacophore model. Starting from a dataset of 98 ligands, we thus obtained a subset of 36 ligands which generated a reliable pharmacophore model constituted by one hydrogen bond acceptor (HBA) and two hydrophobic features (HY). This pharmacophore model corresponds to one binding mode whose significance of the spatial characteristics has been confirmed by molecular modeling [7, 8].

We got this result with Catalyst 4.9. However, the results may differ depending on the version of the software and the operating system used [9]. This is why we wanted to test the capacity of the new environment Discovery Studio 2017 (Biovia) to reproduce the procedure that we had developed. We did not get the same subset of ligands nor a pharmacophore model identical to that provided in our prior modelling experiments. Interestingly, we obtained two subsets of 20 and 21 ligands respectively, and 5 ligands are common to the two groups. Combining both new subsets corresponds in large part to the previous subset of 36 ligands. The two new subsets generated two slightly different models sharing the same features than the previous model; besides, the spatial characteristics of the models obtained by DS 2017 are comparable to the models provided by Catalyst 4.9.

These results suggest an accurate discriminatory power of Discovery Studio regarding ligands with close but different binding modes. Our approach can then be transposed to the ligands of other receptors, as we have initiated in the case of agonists and antagonists of the CB1 cannabinoids receptor [10].

Bibliography:

[1]. D. Barnum; J. Greene et al. J. Chem. Inf. Comput. Sci. 36 (1996) 563-571.
[2]. Q.Z. Gao; L.L. Yang et al. Curr. Comput.-Aided Drug Des. 6 (2010) 37-49.
[3]. S. Malhotra; J. Karanicolas J. Med. Chem. 60 (2017) 128-145.
[4]. G. Sanz; T. Thomas-Danguin et al. Chem. Senses 33 (2008) 639-653.
[5]. A. Belhassan; H. Zaki et al. Egypt. J. Ear Nose Throat Allied Sci. 18 (2017) 257-265.
[6]. L. Charlier; J. Topin et al. Cell. Mol. Life Sci. 69 (2012) 4205-4213.
[7]. G. Launay; S. Teletchea et al. Protein Eng. Des. Sel. 25 (2012) 377-386.
[8]. J. Topin; C.A. de March et al. Chem.-Eur. J. 20 (2014) 10227-10230.
[9]. R. Kristam; V.J. Gillet et al. J. Chem Inf. Model. 45 (2005) 461-476.
[10]. A. Tromelin; E. Guichard 45th RICT (2009) Orléans, France July 1th-3th.