3D-QSAR based on Quantum-Chemical Molecular Fields: Towards an Improved Description of Halogen Interactions

Stefan Güssregen[1)], Hans Matter[1)], Gerhard Hessler[1)], Marco Müller[1)], Friedemann Schmidt[1)], Timothy Clark[2)]

1) *Sanofi-Aventis Deutschland GmbH, Industriepark Höchst, 65926 Frankfurt am Main, Germany*
2) *Computer-Chemie-Centrum, Universität Erlangen Nürnberg, Nägelsbachstr. 25, 91052 Erlangen, Germany*

Current force field-based methods have limitations in the description of molecules. This is especially true for halogens and hypervalent elements such as sulphur. Here, the anisotropy of the electron density distribution ('σ-hole') is ignored. As a consequence, some important non-covalent interactions such as halogen-bonds or halogen-pi interactions, which are of high relevance in lead optimization [1,2], can not be accounted for.

Using tailored scoring functions or 3D-QSAR techniques employing molecular fields it is possible to compensate in part for such limitations. It is interesting to note that QM-based methods, which do not suffer from those limitations, have not been used widely in the context of 3D-QSAR in the past. Recently, the concept of calculating QM properties such as ionization potential, electron affinity or polarizability in a local context was introduced [3].

We have demonstrated the usefulness such local properties in molecular-field-based 3D-QSAR with a public data set of $GABA_A$/Benzodiazapine receptor ligands and an internal data set for factorXa (fXa) inhibitors.

A ligand-based alignment of a set of 1,4-diazepine inhibitors [5] formed the starting point for 3D-QSAR models predicting the affinity against two receptor subtypes, $GABA_A$ and Benzodiazapine receptor. Here, models of higher predictive power were obtained for the QM-based properties based molecular fields than for those derived with the standard CoMFA method.

Furthermore, a structure-based alignment was created for a set of fXa inhibitors by docking into a representative crystal structure. This alignment was previously used to deduce 3D-QSAR models based on CoMFA and CoMSIA methods [4]. While predictive models have been obtained, important SAR-features have not been picked up, such as the interaction of chlorine and bromine atoms with a tyrosine side-chain that ultimately led to the development of orally active fXa drugs. Using QM-based molecular fields models of equal predictive power were obtained that were able to provide additional insights into the SAR.

[1] Matter, H.; Nazaré; M.; Güssregen, S. Halogen-π Interactions as Important Contribution to Binding Affinity in Medicinal Chemistry, in The Importance of Pi-Interactions in Crystal Engineering: Frontiers in Crystal Engineering 3, Tiekink, E.; Zukerman-Schpector, J. (Eds.), Wiley, in press.
[2] Matter, H.; Nazaré, M.; Güssregen, S.; Will, D.W.; Schreuder, H.; Bauer, A.; Urmann, M.; Ritter, K.; Wagner, M. and Wehner, V.; Angew. Chem. Int. Ed. 2009, 48, 2911.
[3] Ehresmann, B.; de Groot, M.J.; Alex, A.; Clark, T.; J. Mol. Model., 2003, 9, 342.
[4] Matter, H.; Will, D.W., Nazaré, N.; Schreuder, H; Laux, V.; Wehner, V.; J. Med. Chem. 2005, 48, 3290.
[5] Wong, G.; Koehler, K.F.; Skolnick, P.; Gu, Z.Q.; Ananthan, S.; Schonholzer, P.; Hunkeler, W.; Zhang, W.; Cook, J.M.; J. Med. Chem., 1993, 26, 1820.