Quantum-Mechanics Based Molecular Field Analysis (QMFA)

Ahmed El Kerdawy, [a] Stefan Güssregen, [b] Matthias Hennemann [a,c] and Timothy Clark [a,c,d]

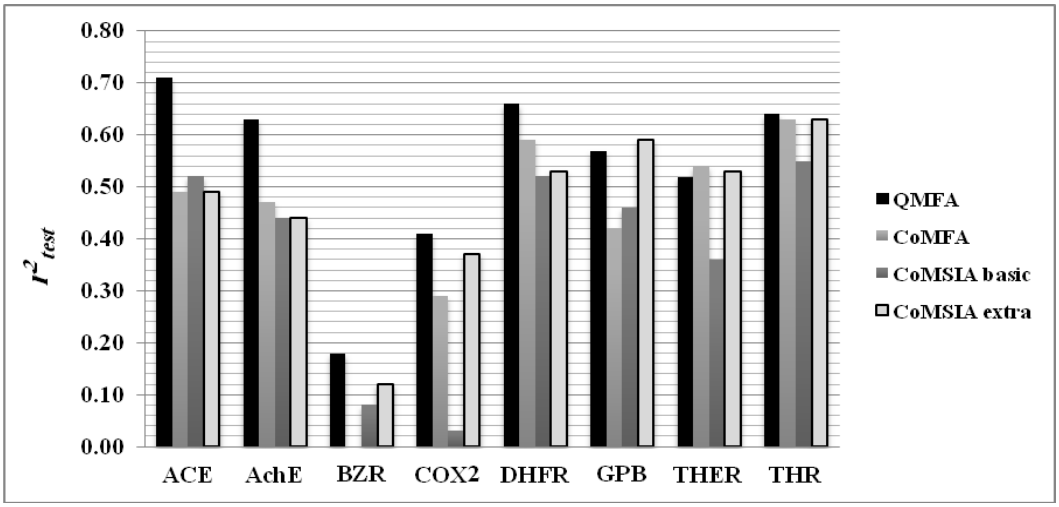
[a] *Computer-Chemie-Centrum, Friedrich-Alexander-Universität Erlangen-Nürnberg, Nägelsbachstraβe 25, 91052 Erlangen, Germany.*

[b] *Sanofi-Aventis Deutschland GmbH,R&D, LGCR, Structure, Design and Informatics, Building G 878, 65926, Frankfurt am Main, Germany.*

[c] *Interdisciplinary Center for Molecular Materials, Friedrich-Alexander-Universität Erlangen-Nürnberg, Nägelsbachstraβe 49, 91052 Erlangen, Germany.*

[d] *Centre for Molecular Design, University of Portsmouth, King Henry Building, Portsmouth PO1 2DY, United Kingdom.*

Despite the steady development in the techniques used for elucidating biomolecular structures, many therapeutic targets are still challenges to structural biology. [1] In such cases, ligand-based drug design (LBDD) plays a crucial role with its different approaches. Currently 3D-QSAR with its CoMFA and CoMSIA techniques is the most widely used LBDD approach for designing ligands with improved activity. [2] In these techniques, statistical analysis of the molecular interaction fields (MIFs) is carried out. The success of 3D-QSAR studies depends strongly on the quality, completeness and balance of the MIFs used. [3] Conventional MIFs have the drawbacks of being not very accurate where they are force field based and using heuristic description of intermolecular interactions. Additionally, they are unable to describe some intermolecular forces involving halogen atoms and hypervalent atoms such as sulfur. [4] In this work, we present a set of four quantum-mechanics based MIFs as descriptors for 3D-QSAR in a trial to overcome the conventional MIFs drawbacks. The new MIFs have been tested on several datasets and they showed comparable performance to the currently available 3D-QSAR techniques or surpass them for some datasets.



[1] Marshall, G. R.; Taylor, C. M., Introduction to computer-assisted drug design – Overview and perspective for the future. In *Comprehensive Medicinal Chemistry II*, Taylor, J. B.; Triggle, D. J., Eds. Elsevier: 2007; Vol. 4 : Computer-Assisted Drug Design, pp 13-41.
[2] Verma, J. *et al., Curr. Top. Med. Chem.* **2010,** 10, 95-115.
[3] Klamt, A. *et al., J. Chem. Info. Model.* **2012,** 52, 2157-2164.
[4] Güssregen, S. *et al., J. Chem. Info. Model.* **2012,** 52, 2441-2453.