

## An investigation into the effects of conformational flexibility on EVA descriptors.

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EVA descriptors are derived from fundamental IR and Raman range molecular vibrational frequencies. They have been widely employed and reported in literature to establish QSARs<sup>1,2,3</sup> and have been shown to perform well with a wide range of datasets<sup>4</sup>.

Although EVA descriptors are sensitive to 3-D spatial arrangements of the atoms constituting a molecule, they are invariant to rotation and translation of structures. This represents the main advantage of EVA over 3-D descriptors generated by means of field-based techniques. In fact, the major difficulties related to the latter descriptors are due to the need of aligning all structures of interest, where the term 'alignment' implies both conformation selection and superimposition of the chosen conformers as a preliminary step towards the development of predictive regression models. Nevertheless, EVA descriptors do depend on 3-D structures and it has been demonstrated in literature that better models can be generated 'matching' conformations across a dataset rather than using randomly selected 3-D structures<sup>3</sup>.

The main purposes of this study are two-fold.

Initially the conformational sensitivity of EVA is studied analyzing its dependence on increasing flexibility of structures.

Secondly a modification of the original EVA description able to take into account the contributions from different conformers is put forward. The dependence of developed QSAR models on the criteria applied to selecting the 3D conformations of the molecules of the dataset is investigated together with the possibility to improve the quality of QSAR models employing the previously defined modification of the original EVA descriptor.

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<sup>1</sup> Ferguson, A.M., Heritage, T., Pack, S.E., Philips, L., Rogan, J. and Snaith, P.J., *J. Comput.-Aided Mol. Design*, 11 (1997) 143.

<sup>2</sup> Turner, D.B., Willett, P., Ferguson, A.M. and Heritage, T., *J. Comput.-Aided Mol. Design*, 11 (1997) 409.

<sup>3</sup> Turner, D.B., Willett, P., Ferguson, A.M. and Heritage, T., *J. Comput.-Aided Mol. Design*, 13 (1999) 271.

<sup>4</sup> Turner, D.B., Willett, P., *Eur. J. Med. Chem.* 35 (2000) 367.