

Multiple-conformers EVA descriptors applied to non-peptide angiotensin II receptor antagonist

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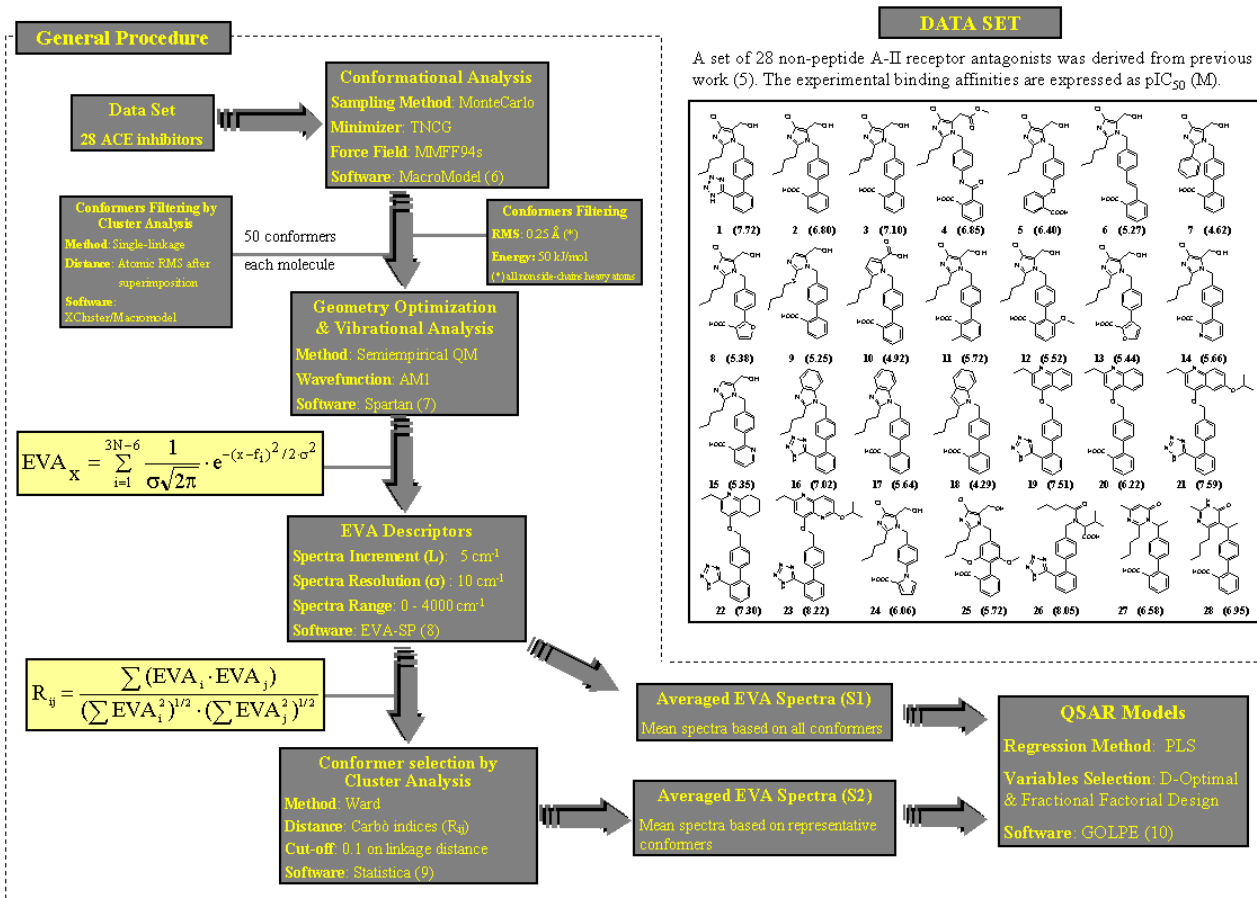
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Introduction

EVA descriptors, based upon calculated fundamental molecular vibrational frequencies, have been widely employed and reported in literature (1-4) to establish QSAR's. One of the main advantages of such descriptors is that they do not depend on molecular superposition criteria, indeed one of the most critical steps to generate any 3D grid-based descriptors. Nevertheless, EVA descriptors do depend on 3D arrangements in space of the atoms constituting a molecule, i.e. they are somehow dependent on which conformation(s) is(are) chosen to represent a molecular structure. A modification of the original EVA description is put forward in order to take into account and explore the effect of the conformational flexibility of molecules.

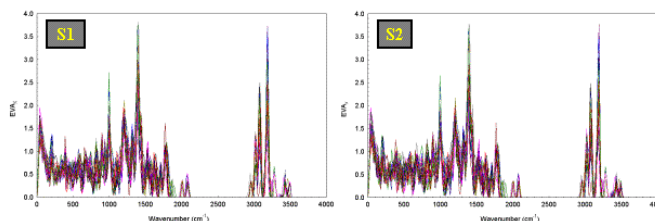
Methods



Results

Averaged EVA Spectra

The figures in this section depict the overlaid averaged EVA spectra of the 28 inhibitors in the original data set. These plots indicate that there is a great deal of vibrational information in the fingerprint region (1-1500) and considerably less information in the functional groups region (1500-4000). The two averaging methods proposed in this work to create a multi-conformational spectrum of each compound, do not seem to generate major differences between the two spectral plots.



PLS results

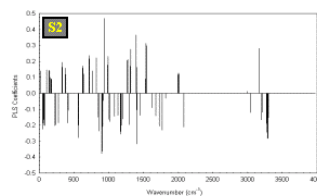
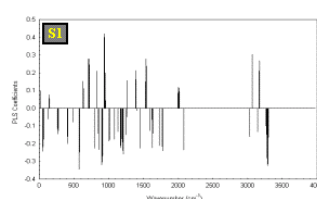
PLS modeling was carried out in conjunction with a variables selection procedure to improve the predictiveness of preliminary PLS models: using all non-zero spectra variables, the predictive power (leave-one out) of the obtained PLS models were 0.389 (4 LVs) and 0.401 (4 LVs) for S1 and S2, respectively. Models dimension reduction was achieved combining a D-Optimal variables selection (up to 50% of the original variables) with the FFD variable selection applied several

times until no further variables were deleted. The obtained models for the two sets of averaged EVA spectra are summarized in Table 1. For comparison purposes, the selected variables and their real coefficients are provided for each model, together with the predicted vs. experimental pIC₅₀ plots.

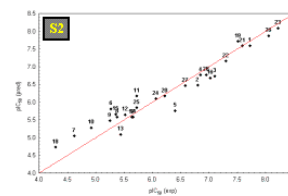
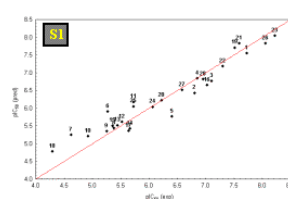
Table 1. Summary of PLS results for the two sets of EVA spectra

	S1	S2
n. var.	87	90
PLS (LVs)	4	4
R ²	0.9803	0.9869
Q ²	0.9129	0.9251
SDEP	0.3089	0.2863
SDEC	0.1468	0.1198

Selected Variables & Coefficients



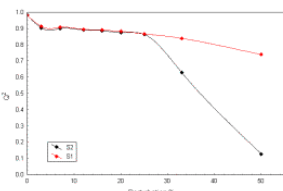
Models Predictions



Models validation

The obtained models were further validated using cross-validation procedures. The predictive power of each model was investigated at increasing perturbation levels from leave-one-out up to about 50%.

Perturbation levels higher than 6% (leave-two-out) were performed assigning the objects to N groups filled in a random way. Formation of groups and validation were repeated 200 times.



Models interpretation

The 2D plots of the magnitude of the regression coefficients can be used to indicate the relative importance of the EVA variables for modeling of pIC₅₀. The two plots show a quite complex discontinuous pattern of the coefficient values for the selected wavenumbers that reduce the interpretability of the models. However some common features can be highlighted:

- the negative region between 3280-3295 contains only the vibrational modes of furane and pyrrole rings having a hydrogen bond acceptor site.
- the negative region between 900-915 is dedicated to model the increased steric hindrance at the imidazole ring due to the presence of a benzene ring as in molecule 7.
- the positive region between 1390-1400 is peculiar for the inhibitors with higher activities such as 21, 22, 23 and 26.

Conclusions

This study has demonstrated that multi-conformational averaged EVA spectra can be used to develop highly predictive and robust QSAR models. The method to generate the averaged spectra does not seem to have significant effect on the quality of the obtained models. The extension of the use of the Carbo similarity index to EVA spectra enables the evaluation of conformational effects over the EVA description. Variable selection procedures such as those applied in this work, can provide better models with high predictivities and simplify their interpretation. However, the densely populated skeletal region of the spectrum provides most of the selected variables, making the decomposition of their meaning more difficult.

References

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