QSPR MODELS FOR CATIONIC NEUROTRANSMITTER RECEPTORS: α_1-ADRENOCEPTOR LIGANDS

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The α_1-adrenoceptors are involved in the pathomechanisms of various diseases. In particular, α_1-adrenoceptor antagonists have attracted much attention over the past decade, due to their potential utility for the treatment of benign prostatic hiperplasia. In parallel, structure - affinity relationship studies on various classes of ligands of α_1-adrenoceptors have been carried out to develop three dimensional models for qualitative or even quantitative prediction of the binding affinity. However, most of the models reported so far have been elaborated using ligands with a common structural skeleton. Consequently, their predictivity with acceptable accuracy has generally been limited to structurally relating compounds. In an effort to develop a model with wider scope, which can even be useful for screening of libraries with high diversity, we now describe our QSPR approach using DRAGON (Version 3.0, Milan Chemometrics, Milan) and, for the descriptor selection, 3DNET (Version 1.1.50 beta, Compelit, Budapest) programs.

In the database we included 230 compounds with published α_1-adrenoceptor affinities (measured uniformly in rat brain using radioligand [^{3}H]-prazosin). For the model building, two third of the data was used, whereas one third of the full data set was used for external validation.

UFS (Unseen Forward Selection) method was applied for descriptor selection.

Several MLR (multilinear regression), PLS (partial least square) and ANN (artificial neural network) models were developed using scout scan, sequential trial & error and genetic algorithms. In generation of the model, model banks were built, and the best models were selected from the banks using bootstrap test.

All models we developed were carefully validated using bootstrap test, shuffle test and external validation. The best model we have reached is characterized by a value of 0.4 for Q^2 in external validation. Taking into consideration the high number and diversity of compounds included, the model seems to be acceptable for first prioritizations in virtual screening.