QSPR MODELS FOR CATIONIC NEUROTRANSMITTER RECEPTORS: 5-HT_{1A} RECPETOR LIGANDS

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Serotonin 1A (5-HT_{1A}) receptor is among the most studied types of G-protein coupled receptors, and the role of 5-HT_{1A} receptors in various central nervous system diseases have been well documented. The recently growing interest for 5-HT_{1A} receptor agonists has been due to their neuroprotective action in different models of CNS injury. Activation of neuronal $5HT_{1A}$ receptors appears to be involved in neuroprotective effects.
Most of the previous QSAR models of 5-HT_{1A} ligands have been developed by using small number of ligands some of them possessing similar chemical structures. The quantitative models, moreover, have not been validated by strict statistical procedures.
The aim of our study was to develop a more general model for ligands of $5HT_{1A}$ receptors using the 3DNET method. In the study a database was built, which contained structurally diverse ligands with their affinities. We selected 167 compounds with pKi values (measured in rat cortex); the affinities spanned a difference of 5 orders of magnitude (the highest and the lowest pKi values were 5.00 and 9.82, respectively). For model validation, leave-one-out, leave-n-out cross-validations, and an external validation were used. As the statistical test, a new method (shuffle) was also applied.
The 3D structures were obtained by (PM3 method, Hyperchem Release 7). The descriptors were calculated with Dragon program (Version 3.0, Milan Chemometrics, Milan). The 3DNET program (Version Beta 1.1.50) was used for selection of descriptors and for MLR, PLS and neural network computations. The predictivity of the artificial neural network was compared to other model building methods, like multiple linear regressions and partial least square projection to latent variables.
In the best model we have developed, values of Q^2 obtained by the bootstrap and external validation were higher than 0.4 and 0.3, respectively. The shuffle test did not draw any overlap, re-affirming the validity of the model.