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Abstract

3D and 4D-QSAR of Dopamine Transporter Inhibitors (DAT) Using the LQTA-QSAR Approach †

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At present, drug abuse has developed into a social problem and begun to demand specific measures from different social sectors and government agencies all over the world. Despite significant efforts, the development of pharmacotherapeutic treatments of psychostimulant abuse has remained a challenge so far. Using 49 2-[(diphenylmethyl)sulfanyl]ethanamines described as dopamine transporter (DAT) inhibitors, 3D and 4D-QSAR studies were performed using the LQTA-QSAR approach. This method, initially created for the construction of models based on conformational sampling profiles obtained by molecular dynamics, has been adapted to allow studies based on only a single optimized geometry. In both studies, Coulomb and Lennard-Jones descriptors were used, which were generated with the NH_3^+ probe atom. The variable selection was carried out using the ordered predictors selection (OPS) method in the free QSAR modeling program. Both regression models were constructed using PLS. The models were formed by two latent variables, which in turn were constructed based on five Coulomb and six Lennard-Jones descriptors in both cases. These results appear to be related to the presence of hydrophobic and polar amino acid residues at the binding site. The overall test indicated that the 3D model (Average r^2_m overall = 0.849, Delta r^2_m overall = 0.082) is slightly superior to the 4D model (Average r^2_m overall = 0.762, Delta r^2_m overall = 0.129). To test the models for purposes of prediction, a virtual screening based on 2D similarity (Dice 60%) was performed in the ZINC15 Database, and 12 compounds were selected. The Euclidean applicability domain test showed that all compounds presented a normalized mean distance inferior to 1. On the other hand, the PRI test indicated that predictions by both models can be considered moderate, an adequate result considering that all compounds selected in the VS are structurally related to the data set but do not present a test for the inhibition of the DAT described in literature.