COMSIA STUDY OF OXAMIDE- AND GLYCINEAMIDE-TYPE NR2B SELECTIVE NMDA RECEPTOR ANTAGONISTS

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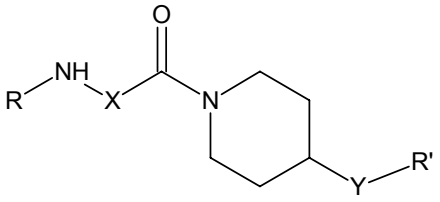
N-methyl-D-aspartate (NMDA) receptor has attracted recently significant interest as a target for the development of central nervous system (CNS) therapeutics. NMDA receptor antagonists have therapeutic potential as neuroprotectants, anticonvulsants and analgesics. The efficacy of NR2B selective NMDA antagonists has been proven in animal models as well as clinical trials. The CNS side-effect profile of NR2B selective compounds appears to be improved compared with non-subtype-selective NMDA antagonists.
A novel series of oxamides and glycineamides of the general formula **1** (X = C=O, CH_2; Y = CH_2, O, CH_2O; R, R' = substituted aryl) was synthesized and tested in a binding assay using [H3]-Ro 25-6981 as radioligand.



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3D-QSAR Comparative Molecular Similarity Indices Analysis (CoMSIA) was performed during the lead optimization process. In a total 27 oxamide and glycineamide derivatives were used for this CoMSIA study. 20 molecules were used as training set for the 3D-QSAR analysis, 7 randomly selected molecules were kept as test set for external validation of the CoMSIA model.
Regression analysis was performed by partial least square (PLS) method. The optimal number of components was chosen by leave one out (LOO) crossvalidation method on the basis of the highest q^2 value. Statistically significant CoMSIA model has been derived with a q^2 =0.544 and r^2 =0.938. The robustness of this final model was validated with the external test set The predicted pIC_{50} values differ less than 0.7 from the measured ones. This model was then used to predict the activities of further designed compounds.