Medicinal Chemistry

Title: Quantitative Structure Activity Relationship Studies of Sulfamide Derivatives as Carbonic Anhydrase Inhibitor: As Antiglaucoma Agents

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Abstract: Selective inhibition of Ciliary process enzyme i.e. Carbonic Anhydrase-II is an excellent approach in reducing elevated intraocular pressure, thus treating glaucoma. Due to characteristic physicochemical properties of sulphonamide (Inhibition of Carbonic Anhydrase), they are clinically effective against glaucoma. But the non-specificity of sulphonamide derivatives to isozyme, leads to a range of side effects. Presently, the absence of comparative studies related to the binding of the sulphonamides as inhibitors to CA isozymes limits their use. In this paper we have represented “Three Dimensional Quantitative Structure Activity Relationship” study to characterize structural features of Sulfamide derivative [RRNSO2NH2] as inhibitors, that are required for selective binding of carbonic anhydrase isozymes (CAI and CAII). In the analysis, stepwise multiple linear regression was performed using physiochemical parameters as independent variable and CA-I and CA-II inhibitory activity as dependent variable, respectively. The best multiparametric QSAR model obtained for CA-I inhibitory activity shows good statistical significance (r= 0.9714) and predictability (Q2=0.8921), involving the Electronic descriptors viz. Highest Occupied Molecular Orbital, Lowest Unoccupied Molecular Orbital and Steric descriptors viz. Principal moment of Inertia at X axis. Similarly, CA-II inhibitory activity also shows good statistical significance (r=0.9644) and predictability (Q2=0.8699) involving aforementioned descriptors. The predictive power of the model was successfully tested externally using a set of six compounds as test set for CA-I inhibitory activity and a set of seven compounds in case of CA-II inhibitory activity with good predictive squared correlation coefficient, r2 pred=0.6016 and 0.7662, respectively. Overview of analysis favours substituents with high electronegativity and less bulk at R and R positions of the parent nucleus, provides a basis to design new Sulfamide derivatives possessing potent and selective carbonic anhydrase-II inhibitory activity.