3D-QSAR STUDIES ON SUBSTITUTED DIHYDROPYRIDINES FOR THEIR $\alpha_{1A}$-ADRENERGIC RECEPTOR BINDING AFFINITY$^1$

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Abstract. $\alpha$-Adrenergic receptors (ARs) are of current medicinal interest. In order to identify the essential structural and physicochemical requirements in terms of common biophoric sites and secondary sites for binding with $\alpha_{1A}$-adrenergic receptors, a series of 25 compounds of substituted dihydropyridines was divided into training set of 19 compounds and test set of 6 compounds both for R and S enantiomers for deriving 3D-QSAR models. Among several models the best model (model no. 1) for R isomers with correlation coefficient $r = 0.9$, chance = 0.05 and match $= 0.47$ has four biophoric sites and three secondary sites while the best model for S isomers (model no. 2) with correlation coefficient $r = 0.86$, chance = 0.01 and match $= 0.45$ has three biophoric sites and two secondary sites. Both these models predicted binding affinity of internal and external test set compounds including the enantiomers of compound no. 25.

The $\alpha$-adrenergic receptors belong to the seven transmembrane (7TM) G-protein coupled receptors (GPCR) and are activated by the neurotransmitter norepinephrine and the neurohormone epinephrine$^1$. The $\alpha$-adrenergic receptors (ARs) have been implicated in various diseases like hypertension$^2$, high intraocular pressure$^3$, benign prostatic hyperplasia (BPH)$^4$, impotence$^5$, cardiac arrhythmias$^6$, ischemic myocardium$^7$ etc. The common side effects associated with $\alpha$-AR antagonists are dizziness, decreased blood pressure, nasal congestion and impotence presumably as a result of their lack of selectivity for any particular $\alpha$-adrenergic receptors. The $\alpha$-ARs have been classified into $\alpha_1$- and $\alpha_2$-ARs. $\alpha_1$-ARs are found in human brain and can decrease the propensity for abnormal heart rhythm while $\alpha_2$-ARs are involved in hypertension.

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sedation, anxiety and analgesia. The α₁-ARs and α₂-ARs have been further subclassified as α₁a, α₁b, α₁d, α₂a, α₂b, α₂c and α₂d. The α-AR antagonists belong to a variety of chemical classes such as 2,4-diaminoquinazolines, arylpiperazines, imidazolines, dihydropyridines, phenylethylamines, pyrazinones, pyrrolidines, imidazolidinone, cyclic imides, phenylacetamides, saccharins etc. Some of the α₁-AR selective chemical entities are prazosin, SNAP 5089, cyclazosin, sertindole, SNAP 8179 and phenetolamine. Sertindole, SNAP 5089 and phenetolamine are α₁a-ARs selective, cyclazosin is α₁b AR selective and SNAP 8179 is α₁d AR selective while prazosin is α₁ subtype unselective. Idaxosan is unselective α₂ – AR antagonist while clonidine and naphazoline are unselective α-AR antagonists. In view of the importance of α₁a selective AR antagonists in the treatment of BPH, attempts are being made to design and synthesise α₁a antagonists as potential therapeutic agents. In view of high selectivity shown by S- (+)-niguldipine towards α₁a-ARs relative to α₁b-ARs, a series of dihydropyridines has been synthesised as potent α₁-AR antagonists. In order to identify essential structural (pharmacophore) and physicochemical requirements for α₁a AR antagonistic activity in these compounds, the 3D QSAR models were derived using APEX-3D system. The APEX-3D approach recognizes the pharmacophore in the biologically active molecules and compares different physicochemical and structural properties and their distances with respect to active and inactive analogue, which are be used to predict the activity of new compounds. It finds the common features of the low energy conformations of each compound, in terms of ring center, hydrophobic center, atomic charges, pi-population and hydrogen bond donor and acceptor indexes. During the compilation of this work, SOMFA studies were reported on dihydropyridines, which also included most of these molecules but the reported model, developed on training set, had a very poor test set prediction (r=0.288) and also did not explain enantioselectivity, hence we also used our APEX-3D derived model to explain enantioselectivity as well as the prediction of this test set. These results are reported in this paper.

Material and Methods
A series of 25 compounds of dihydropyridines (SNAP 5089 analogues) (Table 1) was collected from literature for 3D-QSAR studies. The total set of 25 racemic molecules reported in the literature was divided into two training sets of 19 molecules corresponding to R and S enantiomers and corresponding two test sets of six compounds each. An external test set of 13 compounds has also been included for comparison of models derived from these studies and the recently published SOMFA studies. All molecular modelling and 3D-QSAR studies were