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3 D-QSAR Analysis of Agonists of nAChRs: Epibatidine Analogues

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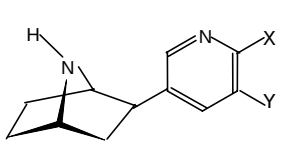
Abstract: A 3 D-QSAR about nAChRs agonists–epibatidine analogues was performed using the CoMFA and CoMSIA. The correlation coefficients were $R^2_{cv} = 0.546$, $R^2_{ncv} = 0.907$ in CoMFA and $R^2_{cv} = 0.655$, $R^2_{ncv} = 0.962$ in CoMSIA of the final model. The prediction using the final models to the test set was $r^2 = 0.675$ in CoMFA and $r^2 = 0.462$ in CoMSIA. This model will be useful in the design of novel compounds with high affinity.

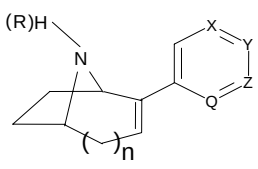
Keywords: 3 D - QSAR, CoMFA, CoMSIA, nAChRs, agonists.

Neuronal nicotinic acetylcholine receptors (nAChRs) are pentameric ligand-gated channel, which are comprised of various combinations of α and β subunits (α 2–10, β 2–4)[1-3]. A few subtype of nAChRs predominate ; notably, α4β2 subtype is widespread in the vertebrate central nervous system (CNS) and the subtype binds epibatidine with high affinity[4-5]. In recent years, there has steadily increasing interest in nAChRs as potential analgesic and therapeutics for the treatment of various neurological and mental disorders related to the decrease in cholinergic function. Thus, for the advance of nAChR-based therapeutics[6-8], many efforts have been directed toward the identification and characterization of novel, potent nAChRs ligands.This was stimulated by considerable evidence suggesting that selective neuronal nAChR agonists may provide therapeutic utility in the treatment of Alzheimer's and Parkinson's diseases, attention deficit / hyperactivity disorder, schizophrenia, and depression.

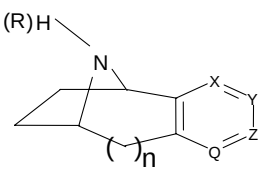
Figure 1 Structure of the nAChRs ligands (except some especial compounds)



X , Y = H , X , OH , NH_2 , Ph , N (CH_3)$_2$, and so on



n = 1 , 2
X , Y , Z , Q = N , CH , or CCl



n = 1 , 2
X , Y , Z , Q = N , CH , or CCl

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The nAChRs ligands with affinity determined in the same experimental method were collected[9-17] and used to built the training set(41 compounds) and test set(11 compounds) (**Figure 1**). All molecular modeling and comparative molecular field evaluations were performed using SYBYL version 6.8[18] running on a Silicon Graphics Indigo 2 workstation. The orders of optimization were : the conjugate gradient algorithm in the Tripos field, a systematic conformational search, and finally semiempirical quantum mechanical AM1 to calculate partial atomic charges using Mulliken method. As best of our knowledge, the current providing pharmocophoric elements[19] are as follows: a quaternary or protonatable nitrogen, an electronegative atom capable of accepting hydrogen bond, and a dummy point or an atom that define a line along which the hydrogen bond may form. Based on the traditional pharmacophore as aligned fitted elements, we have performed alignment with fit atom in SYBYL procedures.

CoMFA and CoMSIA were carried out using the QSAR options of SYBYL. Steric and eletrostatic fields of CoMFA were calculated using Lennard - Jones and Coulombic potential, respectively. The five physicochemical properties for CoMSIA(steric, eletrostatic, hydrophobic, and hydrogen bond donor and acceptor) were evaluated in the QSAR options of SYBYL. To test the statistical significance of the models, cross-validations were done by means of the "leave – one – out" (LOO) procedure using the enhanced version of "partial least square" PLS, the SAMPLS method. Based on the optimal number of components, the final model was built using the result of non - cross - validation to perdict the affinities of the compounds in the training set and test set.

The results of models generated by CoMFA and CoMSIA methods were $R^2_{cv} = 0.546$, $R^2_{ncv} = 0.907$ in CoMFA (5 components) and $R^2_{cv} = 0.655$, $R^2_{ncv} = 0.962$ in CoMSIA (6 componets). The prediction using the final models to the test set was $r^2 = 0.675$ in CoMFA and $r^2 = 0.462$ in CoMSIA.

Consulting the contribution maps in CoMFA and CoMSIA, we draw some conclusions. The position of N on the heteroaromatic moiety was crucial, so it was an indispensable pharmcophore element. On the other hand in our system the position of the N mostly was the 1 -, 5 -, 1 - and 5 -, 1 - and 6 - or 1 - and 4 - on the heteroaromatic moiety. In general, when the nitrogen containing bicycle was on the meta - substituent of the heteroaromatic moiety the affinity of ligand was higher than that on the ortho - and para - substitute, no matter there was one or two nitrogen on the heteroaromatic moiety. So we especially paid attention in this aspect in our synthetic work. According to the force field analysis, bulky, hydrophobic and rich electronic groups on the 5 - position of heteroaromatic moiety would increase the binding affinity. If ligands have hydrophilic and H bond acceptors or rich electronic groups on the 6 - position of heteroaromatic moiety, it would show high binding affinity based on the conclusion of hydrophobic and H bond field distribution. Finally, for the steric bulk of the nitrogen containing bicycle moiety had almost no effect on the binding affinity. We hypothesized that the bicycle moiety was not an important pharmacophore, but it is essential for the orientation of the nitrogen on the bicycle, when it binds with the site of receptor. In some papers[20-21], compounds comprised of N - alkyl chain， which can ensure the distance request between N - N (5.9 Å)[19] of the hypothetical pharmacophore, but their binding affinity was not so good. Possibly the orientation of N on the alkyl chain can not fit to the need of spatial

occupancy of the receptor because of the flexibility and bulk of the alkyl chain. We design the target compounds which fit the spatial demand of receptor and are easy to be synthesized, for example, the single compounds.

The prediction of ligand affinity is vital to our goal of developing computer - aided drug design. Two new 3 D-QSAR models (CoMFA and CoMSIA) of convincing predictive power were developed for the α4β2 nAChRs ligands. In this paper the relationship between the structure and binding affinity has been analyzed from three aspects. The model and the analysis results supplied the theoretical foundation for our next synthetic work.

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