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Prediction of potent therapeutic anticonvulsant ligands to *N*-methyl-D-aspartate receptors among substituted 4,6-dichloroindole-2-carboxylic acids: Molecular modeling approach

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Abstract

We performed two- and three-dimensional quantitative structure–activity relation (QSAR) pharmacophore studies with a series of substituted 4,6-dichloroindole-2-carboxylic acid analogs in order to elucidate the structural properties required for high affinity for the glycine binding site of the *N*-methyl-D-aspartate receptor. The partial least-squares method coupled with various feature selection methods (stepwise, genetic algorithm and simulated annealing) were used to derive QSAR models, which were validated for statistical significance and predictive ability by internal and external validation. The best two-dimensional QSAR model was selected, which had a correlation coefficient, $r^2 = 0.8577$, a cross-validated squared correlation coefficient, $q^2 = 0.7118$ and an external predictive ability $pred\_r^2 = 0.7642$. Molecular field analysis was used to construct the best three-dimensional QSAR model by the genetic algorithm–partial least-squares method, which showed good correlational and predictive capability: $q^2 = 0.7538$, $q^2\_se = 0.4833$ and $pred\_r^2 = 0.7019$. In a series of 4,6-dichloroindole-2-carboxylic acid derivatives, the pharmacophore model based on the chemical feature with the lowest root mean square deviation (2.187 nm) consisted of one aromatic feature, one hydrogen bond donor, one hydrogen bond acceptor, one aliphatic and one positive coefficient feature. A representative set of 4,6-dichloroindole-2-carboxylic acid compounds with effective biological activity and a good glycine binding site on the *N*-methyl-D-aspartate receptor were identified, which may be potential leads for drugs with anticonvulsant activity.

Keywords: 4,6-Dichloroindole-2-carboxylic acids; QSAR; Pharmacophore; NMDA receptor; Anticonvulsant activity

1. Introduction

N-Methyl-D-aspartate (NMDA) receptors are involved in neuronal development, synaptic plasticity, learning and memory in the mammalian central nervous system [1]. Glycine is an essential co-agonist for NMDA ion channel activation, and various classes of glycine-binding site antagonists with anticonvulsant and neuroprotective properties have been developed [2–4]. NMDA receptors are important ionotrophic receptors gated by the neurotransmitter glutamate. The activity-dependent Ca^{2+} flux through NMDA is thought

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to trigger downstream intracellular signalling events that initiate two major forms of synaptic plasticity: long-term potentiation and long-term depression. These changes in synaptic transmission contribute to behavioral learning, information storage, chronic pain, neuronal development and disease-related pathological changes in the brain [5–10]. The receptors are therefore implicated in a number of pathophysiological conditions, including neuropathic pain, epilepsy, stroke, neurodegenerative diseases (e.g. Parkinson, Huntington and Alzheimer diseases) and psychiatric disorders such as schizophrenia and major depression [11–14]. Clinical trials have demonstrated that enhancement of NMDA receptor function by potentiating the glycine site of the receptor is effective in the treatment of schizophrenia [15]. NMDA receptors have therefore been studied intensively in the past few decades as potential drug targets for a number of neurological and psychiatric indications [16,17]. The most recent NMDA receptor ligand to be approved for human use is the low-affinity channel blocker memantine, for Alzheimer disease [18,19].

Molecular modeling is used to narrow down a library containing an extraordinarily large number of random molecules to a shorter list of potentially effective inhibitors. The quantitative structure–activity relation (QSAR) approach is widely used for predicting biological activity, particularly in drug design. This approach is based on the assumption that variations in the properties of compounds can be correlated with changes in their molecular features [20]. New molecules have been obtained from the Specs database with the use of two-dimensional (2D) and three-dimensional (3D) QSAR models. The pharmacophore model is widely used to quantify common chemical characteristics among many diverse structures and could also be used to screen chemical databases and find new chemical entities.

The aim of this study was to elucidate the structural features of 4,6-dichloroindole-2-carboxylic acid (DICA) derivatives that are required for binding to the NMDA receptor and to obtain predictive 2D and 3D QSAR models. It is expected that application of these QSARs and the pharmacophore approach to 4,6-dichloroindole-2-carboxylic acids derivatives will allow rational design of promising anticonvulsant agents with good therapeutic safety and efficacy.

2. Materials and methods

2.1. Biological activity dataset

A set of 22 hydantoin-substituted 4,6-dichloroindole-2-carboxylic acids derivatives reported by Jansen et al. [21] was selected and analysed by QSAR for NMDA receptor activity. All QSAR studies were performed with V-Life MDS software version 3.5 (VLife Sciences, Pune, India) [22]. For the QSAR study, the reported median inhibitory concentration (IC_{50}) was converted to the negative logarithm (pIC_{50}) in molar units and subsequently used as the dependent variable for 2D and 3D QSAR analysis. Table 1 shows the structures of the 22 compounds and their biological activities.

2.2. Conformation generation of molecules

The molecular structures were built with the 2D draw application of the Molecular Design Suite of the VLife MDS software package from standard bond lengths and bond angles. Energy minimization and geometric optimization were ensured with the Merck molecular force field method [23] at a root mean square gradient set to 0.01 kcal/mol Å and the iteration limit to 10,000. The Monte Carlo search method is a random method for finding conformations of molecules with the Metropolis condition to accept or discard generated conformers. We generated conformers for all 22 optimized compounds and selected the low-energy conformer for each compound for further study.

2.3. Training and test set selection

In order to obtain a validated QSAR model for making meaningful predictions, the dataset was divided into training and test sets. For the prediction statistics to be reliable, the test set must include at least five compounds [24]. In the sphere exclusion algorithm, pIC_{50} activity was used as the dependent variable and various calculated 2D descriptors and electrostatic, steric and hydrophobic field 3D molecular descriptors as independent descriptors. This approach resulted in selection of compounds 4, 6, 10, 14 and 19 as the test set for validating the quality of the models and the remaining 17 compounds as the training set for generating QSAR models.

2.4. 2D QSAR studies

2.4.1. Calculation of 2D descriptors

Energy-minimized geometry was used to calculate 2D descriptors by encoding different aspects of their molecular structure with electronic, thermodynamic, spatial and topological E-state contribution descriptors. We also calculated various alignment-independent descriptors [25], using the attributes 2 (double-bonded atom), 3 (triple-bonded atom), C, N, O, S, H, F, Cl, Br and I and a distance range of 0–7. The QSAR models