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ORIGINAL ARTICLE

Quantitative structure-activity relationship and molecular docking studies of a series of quinazolinonyl analogues as inhibitors of gamma amino butyric acid aminotransferase

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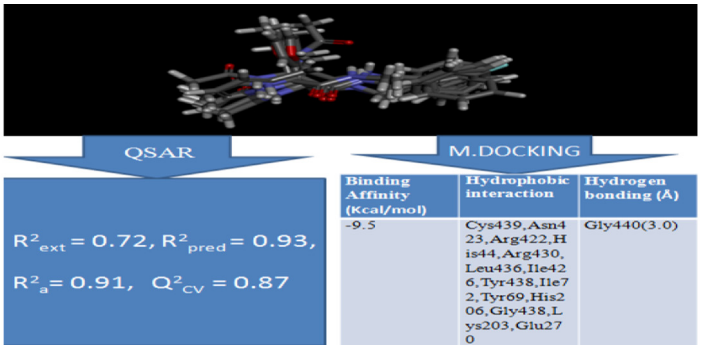
GRAPHICAL ABSTRACT



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ABSTRACT

Quantitative structure-activity relationship and molecular docking studies were carried out on a series of quinazolinonyl analogues as anticonvulsant inhibitors. Density Functional Theory (DFT) quantum chemical calculation method was used to find the optimized geometry of the anticonvulsants inhibitors. Four types of molecular descriptors were used to derive a quantitative relation between anticonvulsant activity and structural properties. The relevant molecular

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descriptors were selected by Genetic Function Algorithm (GFA). The best model was validated and found to be statistically significant with squared correlation coefficient (R^2) of 0.934, adjusted squared correlation coefficient (R^2_{adj}) value of 0.912, Leave one out (LOO) cross validation coefficient (Q^2) value of 0.8695 and the external validation (R^2_{pred}) of 0.72. Docking analysis revealed that the best compound with the docking scores of −9.5 kcal/mol formed hydrophobic interaction and H-bonding with amino acid residues of gamma aminobutyric acid aminotransferase ($GABA_{AT}$). This research has shown that the binding affinity generated was found to be better than the commercially sold anti-epilepsy drug, vigabatrin. Also, it was found to be better than the one reported by other researcher. Our QSAR model and molecular docking results corroborate with each other and propose the directions for the design of new inhibitors with better activity against $GABA_{AT}$. The present study will help in rational drug design and synthesis of new selective $GABA_{AT}$ inhibitors with predetermined affinity and activity and provides valuable information for the understanding of interactions between $GABA_{AT}$ and the anticonvulsants inhibitors.

Introduction

Epilepsy is a perpetual and regularly dynamic issue described by the occasional and erratic event of epileptic seizures, which are brought on by an anomalous release of cerebral neurons [1]. It is a standout among the most widely recognized neurological issue that influences around 70 million individuals around the world [2]. Epilepsy causes seizure to occur and these seizures can cause a variety of symptoms depending on the areas of the brain affected. Symptoms can vary from mild to severe and can include complete or partial loss of consciousness, loss of speech, uncontrollable motor behavior, and unusual sensory experiences [3]. Gamma aminobutyric acid aminotransferase ($GABA_{AT}$) is a validated target for anti-epileptic drugs because its selective inhibition raises GABA concentration in brain which has an antiepileptic effect [4]. There is a proceeding with an interest for new anticonvulsant agents, as it has not been conceivable to control each sort of seizure with the right now accessible antiepileptic drugs. Additionally, the present treatment of epilepsy, with advanced antiepileptic medications, is connected with measurement related symptoms, unending lethality, and teratogenic impacts [5–6]. Therefore, developing a new antiepileptic drug with approved therapeutic properties is an important challenge for medicinal chemists.

Quantitative Structure-Activity Relationships (QSAR) are mathematical frameworks which interface molecular structures of compounds with their natural activities in a quantitative way [7]. The main success of the QSAR method is the possibility to estimate the properties of new chemical compounds without the need to synthesize and test them. This analysis represents an attempt to relate structural descriptors of compounds to their physicochemical properties and biological activities. This is broadly utilized for the prediction of physicochemical properties in the chemical, pharmaceutical, and environmental spheres [8]. Moreover, the QSAR strategies can save resources and accelerate the process of developing new molecules for use as drugs, materials, and additives or for whatever purposes [9]. Molecular docking is a computational method used to determine the binding compatibility of the active site residues to specific groups and to reveal the strength of interaction [10,11]. Molecular docking is a very popular and useful tool used in the drug discovery arena to investigate the binding of small molecules (ligands) to macromolecule (receptor) [12–14]. The objective of this research was to develop various QSAR models using Genetic Function Algorithm (GFA) method and to predict the $GABA_{AT}$ inhibitory activity of the compounds. We also docked the compounds against $GABA_{AT}$ protein (10HV) with bound ligand (quinazolinonyl analogues).

Material and methods

Data sets used

24 Molecules of quinazolinonyl derivatives used as anticonvulsant activity were selected from the literature and used for the present study [15]. The anticonvulsant activities of the molecules measured as ED50 (μM) were expressed as logarithmic scale as pED_{50} ($pED_{50} = \log 1/ED_{50}$) was used as dependent variable, consequently correlating the data linearly with the independent variable/ descriptors. The observed structures and the biological activities of these compounds are presented in Table 1.

Molecular modeling

All molecular modeling studies were done utilizing Spartan'14 version 1.1.2 [16] and PaDEL Descriptor version 2.18 [17] running on Toshiba Satellite, Dual-core processor window 8.0 operating system. The molecular structures of the compounds were drawn in the graphic user interface of the software. 2D application tool was used to build the structures and exported in 3D format. All 3D structures were geometrically optimized by minimizing energy. Calculation of the structural electronic and other descriptors of all the 24 quinazolinonyl derivatives was conducted by means of density functional theory (DFT) using the B3LYP method and 6-31G* basis set. The lowest energy structure was used for each molecule to calculate their physicochemical properties. The optimized structures that were from the Spartan'14 version 1.1.2 quantum chemistry package [16] were saved in sdf format, and transferred to PaDEL-Descriptor version 2.18 tool kits [17] where the calculation of 1D, 2D and 3D descriptors took place.