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Full Length Article

Molecular docking and QSAR analysis of a few Gama amino butyric acid aminotransferase inhibitors

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ABSTRACT

Molecular docking and quantitative structure–activity relationship (QSAR) studies were carried out on 37 anticonvulsant compounds to develop a robust model for the prediction of anticonvulsant activities against Gama amino butyric acid aminotransferase ($GABA_{AT}$) and to determine the dominant structural amino acid residues responsible for the binding affinity of the ligand-$GABA_{AT}$ complex. AutoDock Vina of PyRx virtual screening software was used to perform the molecular docking while Genetic function algorithm (GFA) was used to select the descriptors and to generate the correlation models that relate the structural features to the biological activities. The best binding affinity was found to be −11.9 Kcal/mol (compound 5a) while best QSAR model (model 1) was obtained with R^2 of 0.970192, an R^2_{adj} value of 0.963095, Q^2LOO value of 0.947995 and R^2pred of 0.813. These confirms the stability, reliability, robustness and predictability of the model. Our research has shown that the binding affinity generated was found to be better than the one reported by another researcher. And the high correlation coefficient, (R^2) shows that the model was reliable, robust and predictable. Our QSAR model and molecular docking results corroborate with each other (most especially in the area of binding affinity and atomic electronegativity of the inhibitors) and propose the directions for the design of new inhibitors with better activity against an enzyme that is responsible for epilepsy (GABAAT).

1. Introduction

Epilepsy is a well-documented neurological issue that influences roughly 65 to 75 million individuals around the world, of which 10.5 million are children [1,2]. However, the worldwide prevalence of epilepsy varies from 2.8 to 19.5 per 1000 of the general population [3]. Epilepsy is basically a chronic brain disorder characterized by recurrent derangement of the nervous system due to the sudden excessive disorderly discharge of neurons that result in almost instantaneous disturbance of sensation and loss of consciousness [4]. Seizures which is usually caused by epilepsy can cause a variety of symptoms depending on the areas of the brain affected. Symptoms may be the complete or partial loss of consciousness, loss of speech and uncontrollable motor behavior [5].

The in silico approaches like Quantitative Gama amino butyric acid aminotransferase ($GABA_{AT}$) catalyzes the conversion of GABA to succinylic semialdehyde. Convulsion is always triggered by reduced levels of GABA, while the high level of GABA in the brain has an anticonvulsant effect [6–9]. $GABA_{AT}$ is a receptor for most anti-epileptic drugs because of its selective deactivation raises GABA concentration in the brain [10]. This understanding of GABA neurotransmitter paved the way for future research and some of the disorder's first effective treatments [11–13].

Structure-Activity Relationships (QSAR) and molecular docking are widely used in the fields of structural molecular biology and structure-based drug design. Molecular docking is a computational procedure used in the field of structure-based rational drug design to identify correct conformations of small molecule and also to estimate the strength of the protein-ligand interaction [14–16]. Quantitative Structure-Activity Relationships (QSAR) models have gained an extensive recognition in the field of sciences [17–24].

The aim of this research is to develop good and rational QSAR models that could predict the activities (pED_{50}) values of quinoxaline and thiadiazoles derivatives (inhibitors) whose biological activities (ED_{50}) against Gama amino butyric acid aminotransferase ($GABA_{AT}$) and to predict the interactions energy between $GABA_{AT}$ and the inhibitors

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2. Material and methods

2.1. Data sets used

Some quinoxaline and thiadiazoles derivatives were selected from the literature and used as anticonvulsant activity for this study [25–27]. The logarithm of measured ED_{50} against an anticonvulsant activity as pED_{50} ($pED_{50} = \log 1/ED_{50}$) was used as dependent variable, consequently correlating the data linearly to the independent variable/descriptors. The observed structures and the biological activities of these compounds are presented in Table 1.

2.2. Docking study

2.2.1. Selection and refinement of receptors

Computer-aided drug design involves the identification and selection of the appropriate drug target [28]. Gama amino butyric acid aminotransferase ($GABA_{AT}$) was the target for the quinoxaline and thiadiazoles derivatives, and the three-dimensional structure of this protein was retrieved from Protein Data Bank (www.rcsb.org/pdb) using PDB ID: 10HV. The target protein was prepared by removing water molecules, adding Polar hydrogen atoms, minimizing energy, and the structure was saved as the pdbqt format. Fig. 1 shows the prepared receptor ($GABA_{AT}$).

2.2.2. Ligand input file preparation and optimization

37 quinoxaline and thiadiazoles derivatives input structures were drawn using the graphic user interface of Spartan'14 version 1.1.2 software [29]. The drawn structures were cleaned in 3D format and optimized using Spartan'14 version 1.1.2 [29]. The resulting structures were then saved in pdb format for molecular docking studies.

2.2.3. Docking

The docking of the quinoxaline and thiadiazoles derivatives into the active site of $GABA_{AT}$ protein was carried out using AutoDock Vina of PyRx virtual screening software [30]. Autodock vina has been reported to be an effective tool capable of quickly and accurately predicting bound conformations and binding energies of ligands with macromolecular targets [31]. In the graphic user interface of PyRx virtual screening software, the grid box with a dimension of $60 \times 60 \times 60$ points and 0.375 Å grid spacing was used to cover the entire protein binding site and accommodate ligand to move freely. After docking searches were completed, the best conformation was chosen from the most populated cluster with the minimum binding energy (highest binding score). The interaction of docked protein-ligand complex conformations, including hydrogen bond and hydrophobic interactions were analyzed using Discovery Studio Visualizer 4.1, Ligplot and PyMol visualization software [32].

2.2.4. Geometry optimization and calculation of physiochemical properties

The Spartan'14 version 1.1.2 software [29] running on Toshiba Satellite, Dual-core processor window eight (8) operating system was used to draw the molecular structures of the quinoxaline and thiadiazoles derivatives. All the structures of these compounds were geometrically optimized by minimizing energy (see Fig. 2). The physicochemical properties of all the 37 compounds were calculated by means of Density functional theory (DFT) using the B3LYP methods and 6-31G* basis set. The lowest energy structure was used for each molecule to calculate their physicochemical properties. The optimized structures from the Spartan'14 version 1.1.2 [29] Quantum chemistry package were saved in SDF format and transferred to PaDEL-Descriptor version 2.18 toolkit [33] where the calculation of all the dimensional descriptors took place.

The 37 data sets descriptors generated from the PaDEL version 2.18 toolkit [33] were divided into training and test sets (see Fig. 2). The training sets were used to develop the model, while the test sets were used to test for the quality assurance of the model. The Material studio software version 8 was used to perform the correlation analysis between activity values of the molecules against GABAAT and the calculated descriptors. The Genetic Function Approximation (GFA) method in material studio software versions 8 was used to perform the regression analysis of the generated descriptors.

2.2.4. Quality assurance of the developed model

The reliability and predictive ability of the generated models were assessed by internal and external validation parameters. These validation parameters were compared with the minimum recommended value for the QSAR model standard [34] showed in Table 2.

2.2.5. Determination of descriptors variance inflation factor (VIF)

The best regression model was generated by considering all the possible combination of descriptors. Variance inflation factor (VIF) [35] was used to identifying the multi-collinearity among variables. The VIF for the regression coefficient is expressed as:

$$\mathrm{VIF} = \frac{1}{1 - R_i}$$

R_i represents the coefficient produced by regressing the descriptor xi against the other descriptors, X_i ($j \neq i$) If VIF was greater than 10, it was not considered as a model

2.2.6. Calculation of physiochemical descriptors

Physicochemical descriptors are an expression of quantitative structure of a molecule, which are lipophilic, electronic and steric in nature. Physicochemical descriptors used in this study are presented in Table 3.

3. Results and discussion

All the four developed QSAR models (1, 2, 3, and 4) were reported out of which model 1 was chosen as the best model for predicting the pED_{50} of anticonvulsant molecules due to its statistical significance. As shown in Table 2, the internal and external validation parameters of the model 1 conformed to the minimum standard for a stable, reliable, predictable and robust QSAR model. Furthermore, model 1 was chosen as the best model because the highest squared correlation coefficient (R^2) of 0.970, adjusted squared correlation coefficient (R^2_{adj}) value of 0.963, Leave one out (LOO) cross-validation coefficient (Q^2) value of 0.948 and the external validation (R^2_{ext}) of 0.813 were confirmed with the minimum recommended value (Table 2) for a generally acceptable QSAR model [34].

Model 1

$$\begin{aligned} pED_{50} &= 0.263140426 * \mathrm{minHBint4} + 0.457064694 * \mathrm{ETA\_Alpha} \\ &\quad - 0.000783610 * \mathrm{DPSA\text{-}1} - 0.122305663 * \mathrm{GRAV\text{-}5} \\ &\quad - 0.031052119 * \mathrm{WT.eneg} + 5.798523557.\ \mathrm{N} \\ &= 27, R^2_{pred} = 0.813043, R^2 = 0.970192, R^2_a = 0.963095, Q^2_{cv} \\ &= 0.947995. \end{aligned}$$