Beni-Suef University Journal of Basic and Applied Sciences xxx (2017) xxx–xxx

HOSTED BY

Contents lists available at ScienceDirect

Beni-Suef University
Journal of Basic and Applied Sciences

journal homepage: www.elsevier.com/locate/bjbas

Full Length Article

Molecular docking and quantitative structure-activity relationship study of anticonvulsant activity of aminobenzothiazole derivatives

Usman Abdulfatai *, Adamu Uzairu, Sani Uba

Department of Chemistry, Faculty of Science, Ahmadu Bello University, P.M.B 1045, Zaria, Nigeria

ARTICLE INFO

Article history:
Received 30 January 2017
Received in revised form 24 October 2017
Accepted 22 November 2017
Available online xxxx

Keywords:
Epilepsy
$GABA_{AT}$
QSAR
DFT (B3LYP/6-31G*)

ABSTRACT

In silico studies which include Quantitative structure-activity relationship (QSAR) and molecular docking studies were carried out on the 37 amino-benzothiazole derivatives (anticonvulsant agents). Genetic function approximation (GFA) of Material studio software version 8 was used to perform the QSAR study while Autodock vina version 4.0 of Pyrx software was used to perform the molecular docking of all the anticonvulsant agents. The high value of the correlation coefficient (R^2) of 0.961 and the R^2pred = 0.925 indicated that the model was satisfactory. Molecular docking analyses with Gamma-aminobutyric acid aminotransferases ($GABA_{AT}$) revealed that aminobenzothiazole derivatives (anticonvulsant agents) with the best binding affinity was found to be −9.1 kcal/mol. The proposed model has good stability, robustness, and predictability on verifying with internal and external validation. The physicochemical parameters are to be considered when improving the inhibitory activities of the aminobenzothiazole derivatives against an enzyme that causes epilepsy ($GABA_{AT}$).

1. Introduction

Epilepsy is a disorder of the brain function which characterized by the periodic and unpredictable occurrence of seizures (Goodman et al., 1996; Rang et al., 1991). Seizures are transient change of conduct because of hyper-synchronous discharges from an aggregate of CNS neurons. Epilepsy is responsible for the occurrence of the seizure and these seizures can bring about an assortment of side effects relying upon the central nervous system influence. Manifestations can fluctuate from mellow to serious and can incorporate complete or fractional loss of awareness, loss of discourse, wild engine conduct, and surprising tangible encounters (Atshunler et al., 1990).

Epilepsy is a standout amongst the most well-known genuine neurological issue, in charge of generous bleakness and mortality because of the seizures and the accessible drugs. Around 50 million individuals on the planet have epilepsy and roughly 5% of the all inclusive community involvement with minimum one seizure, barring febrile seizures, eventually in their lives (Sander et al., 1996; Brodie et al., 1997; Banerjee et al., 2009) The prevalence of epilepsy is around 0.5–1% (Bell et al., 2001). Furthermore, its general yearly occurrence ranges from 50-70 cases for every 100,000 in industrialized nations and up to 190 for every 100,000 in developing nations (Sander et al., 1996; Scott et al., 2001). About 80% of people with epilepsy reside in developing countries (Meinardi et al., 2001; Mbuba et al., 2008; Radhakrishnan et al., 2009).

Studies show that Gama aminobutyric acid (GABA) is the main inhibitory neurotransmitter in mammalian central nervous system modulating central inhibitory. From the literature reviewed, it was reported that lower levels of Gama aminobutyric acid have been reported to cause convulsions (Karlsson et al., 1974). While the raise levels of GABA in the brain has an anticonvulsant effect (Krogsgaard-Larsen et al., 1981). Gamma-aminobutyric acid aminotransferases ($GABA_{AT}$) is a validated receptor for anticonvulsant drugs because of its selective deactivation increases GABA concentration in the brain (Storici et al., 1999). This understanding of Gama aminobutyric acid neurotransmitter made ready for future examination and a percentage of the turmoil's first compelling medications. Several new compounds such as zonisamide, vigabatrin and gabapentin have emerged following the widely used antiepileptic drugs (White et al., 1999; Xu et al., 2002; Dichter and Brodie, 1996; Malawska et al., 1995). Today medical researchers and scientists are actively pursuing better treatments for epilepsy and ultimately a cure. Therefore, the need to search for safer and more potent anticonvulsant remains a drug design priority and the continued search for the safer and more effective antiepileptic drugs became an important challenge for medicinal researchers.

* Corresponding author.
E-mail address: faithyikare4me@gmail.com (U. Abdulfatai).

https://doi.org/10.1016/j.bjbas.2017.11.002
2314-8535/

Please cite this article in press as: Abdulfatai, U., et al. Molecular docking and quantitative structure-activity relationship study of anticonvulsant activity of aminobenzothiazole derivatives. Beni-Suef Univ. J. Basic Appl. Sci. (2017), https://doi.org/10.1016/j.bjbas.2017.11.002

In silico study tools have become a close counterpart to experiment in the understanding of molecular aspects of biological systems (Ding et al., 2002; Lu et al., 2014; Smith et al., 2013; Vilela et al., 2014). The computational approaches like molecular docking and quantitative structure-activity relationships (QSAR) are widely employed to discover the novel hits for various therapeutic targets. In recent years, QSAR method of drug design has gained an extensive recognition in physical, organic, analytical, pharmaceutical, medicinal chemistry, biochemistry, chemical engineering, toxicology, nanotechnology and environmental sciences (Hansch and Leo, 1995; Kubinyi et al., 1997; Cramer et al., 1988; Robinson et al., 1999; Kellogg et al., 1991; Ivanciuc et al., 2000). The widespread use of QSAR method comes from the development of novel structural descriptors and statistical equations relating various physical, chemical, and biological properties to the chemical structure (Garro et al., 2011). The success of the QSAR approach can be explained by the insight offered into the structural determination of chemical properties and biological activities, and the possibility to estimate the properties of new chemical compounds without the need to carry out synthesize and testing (Tarko et al., 2001; Garro et al., 2011).

Molecular docking studies indicate how two or more molecular structures interact with each other for example, drug and enzyme or receptor of protein, fit together. Molecular docking software's are mainly used in drug research. The most important application of docking software is virtual screening. Virtual screening selects the most interesting and promising molecules from an existing database for advanced research. This place demands on the use of the computational method, which must be fast and reliable (Yang et al., 2011; Ai et al., 2011). This research work was focused on the search for potent aminobenzothiazole derivatives (Amnerkar and Bhusari, 2010) via QSAR and molecular docking studies.

2. Material and methodology

2.1. Data collection

37 reliable anticonvulsant agents (aminobenzothiazole derivatives) were screen from the literature and used for the present research (Amnerkar and Bhusari, 2010). The anticonvulsant activities of the molecules measured as ED50 (μM) were expressed in logarithmic scale as pED_{50} ($pED_{50} = \log 1/ED_{50}$) and then used as dependent variable. Consequently, the data was correlated linearly to the independent variable/descriptors. The observed structures, the biological activities of the training (a) and test (b) sets of these compounds were presented in Table 1.

2.2. Descriptor calculation and computational methods

The molecular structures of the compounds in the selected series were drawn in the graphic user interface of the Spartan'14 version 1.1.2 (Nikhil and Kishore, 2010) software. 2D application tool was used to build the structures and exported in 3D format. All 3D structures were geometrically optimized by using the Spartan'14 version 1.1.2 (Nikhil and Kishore, 2010) Software. The structural electronic and other descriptors of all the 37 aminobenzothiazole derivatives (Amnerkar and Bhusari, 2010)was calculated by means of Density functional theory (DFT) using the B3LYP methods and 6-31G* basis set of the Spartan'14 version 1.1.2 (Nikhil and Kishore, 2010) Software. The optimized structures from the Spartan'14 version 1.1.2 (Nikhil and Kishore, 2010) Quantum chemistry package was saved in sdf format, and transferred to PaDEL-Descriptor version 2.18 tool kit (Anonymous, 2013). Where the calculation of 1D, 2D and 3D descriptors took place.

The developed descriptors (1D-3D) of the 37 data sets from the PaDEL version 2.18 toolkit (Anonymous, 2013) were splinted into 27 training and 10 test sets. The training set was used to develop the models, while the test set was used for the external assurance of the developed models. The correlation between activity values of the molecules against neurotransmitter and the calculated descriptors were obtained through correlation analysis using the Material studio software version 8. Pearson's correlation matrix was used as a qualitative model, in order to select the suitable descriptors for regression analysis. The generated descriptors from the PaDEL version 2.18 tool kit (Anonymous, 2013) were subjected to regression analysis with the experimentally determined activities as the dependent variable and the selected descriptors as the independent variables using Genetic Function Approximation (GFA) method in material studio software version.

The number of top equations returned was 5. Mutation probability was 0.1, and the smoothing parameter was 0.5. The models were scored based on Friedman's Lack of Fit. In GFA algorithm, an individual or model was represented as the one-dimensional string of bits. It was a distinctive characteristic of GFA that it could create a population of models rather than a single model. GFA algorithm, selecting the basic functions genetically, developed better models than those made using stepwise regression methods. And then, the models were estimated using the LOF, which was measured using a slight variation of the original Friedman formula, so that the best fitness score can be received.

2.3. Model validation

The internal and external validation parameters were used to evaluate the fitting ability, stability, reliability and predictive ability of the developed models. The validation parameters were compared with the minimum recommended value for a generally acceptable QSAR model (Yap, 2011) shown in Table 2.

The square of the correlation coefficient (R^2) describes the fraction of the total variation attributed to the model. The closer value of R^2 is to 1.0, the better the regression equation explains the Y variable. R^2 is the most commonly used internal validation indicator.

2.4. Applicability domain

Applicability Domain (AD) is the chemical descriptor space spanned by a particular training set of chemicals. The applicability domain of the developed models was assessed in order to specify the scope of their proposed models by defining the model limitations with respect to its structural domain and response space.

2.5. Docking study

Ligand—receptor interaction is an important initial step in protein function. The structure of ligand receptor complex profoundly affects the specificity and efficiency of protein action. The molecular docking studies of active anticonvulsant compounds were performed by AutoDock Vina by PyRx virtual screening software using the reference of the template substrate. Running on Toshiba Satellite, Dual-core processor window 8 operating system. The score function, dock function (S, kcal/mol) developed by Autodock program was used for evaluation of the binding affinity of the aminobenzothiazole derivatives (ligands) with the Gama amino butyric acid aminotransferase ($GABA_{AT}$) receptor.

2.5.1. Preparation of ligands for docking

The preparation of aminobenzothiazole derivatives was performed as follows: (i) conversions of 2D to 3D, (ii) correcting structures, (iii) generating variations of these structures, (iv) validation

Please cite this article in press as: Abdulfatai, U., et al. Molecular docking and quantitative structure-activity relationship study of anticonvulsant activity of aminobenzothiazole derivatives. Beni-Suef Univ. J. Basic Appl. Sci. (2017), https://doi.org/10.1016/j.bjbas.2017.11.002