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Combining DFT and QSAR computation to predict the interaction of flavonoids with the GABA (A) receptor using electronic and topological descriptors

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Abstract

To establish a quantitative structure-activity relationship model of the binding affinity constants ($-\log K_i$) of 41 flavonoid derivatives towards the GABA (A) receptor, the DFT-B3LYP method with basis set 6-31G (d) was performed to gain insights into the chemical structure and property information for the studied compounds. The best topological and electronic descriptors were selected. This work was conducted with principal component analysis (PCA), multiple linear regression (MLR), multiple non-linear regression (MNLR) and artificial neural network (ANN). According to these analyses, we propose quantitative models and interpret the activity of the compounds based on multivariate statistical analysis. The statistical results of the MLR, MNLR and ANN indicate that the determination coefficients R^2 were 0.896, 0.925 and 0.916, respectively. The results show that the three modelling methods can predict the studied activity well and may be useful for predicting the biological activity of new compounds. The statistical results indicate that the models are statistically significant and stable with data variation in the external validation.

Keywords: QSAR model; DFT study; Flavonoid derivatives; GABA (A) receptor; Artificial neural network (ANN)

1. Introduction

The increase in the speed and efficiency of drug discovery has been aided by large investments from major pharmaceutical companies to reduce the cost per synthesized compound or assay. Computational models that can predict the biological activity of compounds based on their structural properties are powerful tools to design highly active molecules. In this sense, quantitative structure–activity relationship (QSAR) studies have been successfully used to model the biological activities of natural and synthetic chemicals [1].

Flavonoids are a group of naturally existing polyphenolic compounds that are ubiquitously found in fruits and vegetables [2–4]. Chemically, flavonoids are benzo-γ-pyrone derivatives. They have shown potential for application in various pharmacological targets. Flavonoids have been the aim of many intense studies

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because of their great number and interesting biological activities [5–8]. Thus, this class of molecules is considered to be an ideal subject of QSAR studies using different descriptors and modelling methods. Amić et al. derived a QSAR model to predict the free-radical-scavenging activity for 29 flavonoids using topological and electronic descriptors; the authors suggest that the free-radical scavenger potential of these polyphenolic compounds closely depends on the particular substitution pattern of free hydroxyl groups on the flavonoid skeleton [9]. Stefanic et al. performed a quantum chemical/classical QSAR study on a dataset of flavonoid derivatives and closely related compounds, which were tested as $p56^{lck}$ protein tyrosine kinase and aldose reductase inhibitors, and the obtained structure-activity relationships of both enzyme systems were compared [10]. Sivakumar et al. established QSARs for the reported anti-tuberculosis activity of chalcones compounds, flavones and flavanones using a robust statistical technique (GFA) [11]. Rasulev et al. applied various descriptors with the DRAGON software and quantum-chemical using GA-MLR analysis [12]. Here, we consider the biological activity of flavonoids towards the GABA receptor, which can be a guide for the rational design of further potent and selective inhibitors, particularly for their actions in the central nervous system (CNS). Although their actions in the central nervous system occur through a diversity of interactions with diverse receptors and signalling pathways, some of these special effects should be mediated by ionotropic GABA, particularly GABA (A) receptors. These compounds have been shown to have a potent anxiolytic effect that is not associated with side effects, such as myorelaxant, amnestic, or sedative actions [13]. Thus, they are considered to be the safest available psychoactive drugs for clinical use [14]. As a result, several attempts have been made to make synthetic flavonoid derivatives with higher affinities for the GABA (A) receptor [15–17]. In addition, although various QSAR studies have analysed the interaction of flavonoids with the GABA receptor [18–20], only a few QSAR models have been developed [21,22]. These QSAR models involved only a few flavonoid derivatives in the training step; thus, they result in an incomplete description of the chemical space. Based on 37 flavones, Marder et al. found that the best linear model is described by the following statistical quality: $R^2 = 0.817$, MSE = 0.929 and $F = 49.38$. The other QSAR model that Hadjipavlou-Litina et al. proposed using a set of 17 flavones has $R^2 = 0.819$, MSE = 0.576, $R^2_{LOO} = 0.725$ and $F = 19.65$.

In this study, we attempt to build new QSAR models for the interaction of 41 flavonoid derivatives with the GABA (A) receptor using several statistical tools: principal components analysis (PCA), multiple linear regression (MLR), nonlinear regression (RNLM) and artificial neural network (ANN) calculations. To test the performance and stability of this model, we used the validation method.

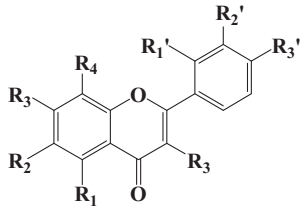

Fig. 1. Chemical structure of the studied compounds.

2. Materials and methods

2.1. Data sources

In the present study, we selected 41 flavonoid derivatives with reported activity values in the literature by [23]. The activity was expressed as K_i and is defined as the binding affinity constants of flavonoid derivatives to the GABA (A) receptor. Because the potency values cover a wide range, they are converted into logarithm units (log $1/K_i$) (K_i in nM) for modelling purposes. Fig. 1 shows the basic structure of the flavones, and Table 1 shows the substitutes of the studied compounds and corresponding experimental activities ($-\log K_i$). To properly validate our data set with a QSAR model, 41 flavonoid derivatives were divided into training and test sets. In total, 28 molecules were placed in the training set to build the QSAR models, and the remaining 13 molecules composed the test set. The division was performed using random selection.

2.2. Molecular descriptors

At present, many molecular descriptors are used in QSAR studies. After they are validated, the findings can be used to predict the activity of untested compounds.

3D structures of molecules were generated using Gaussian View 3.0. Then, the electronic descriptors were computed using the Gaussian 03W package [24]. The geometries of the 41 flavonoids were optimized using the DFT method with the B3LYP functional and 6-31G (d) base set. Then, several related structural parameters were selected from the quantum computation results: highest occupied molecular orbital energy E_{HOMO} (eV), lowest unoccupied molecular orbital energy E_{LUMO} (eV),

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