IN SILICO STUDIES IN DIRECTED SYNTHESIS OF PERSPECTIVE ANTICONVULSANTS

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Introduction. The treatment of epilepsy is always a challenge for researchers and clinical practitioners. Over the last decades, several new drugs for the treatment of epilepsy have been introduced. Despite this progress, about 30% of patients with epilepsy are resistant to current pharmacotherapy and many of the available antiepileptic drugs. Based on this reason, there has been a continuous attempt to find new antiepileptic drugs, which increases the demand to conduct more studies in this area.

Thus, the reviewed literature data about 2-amino-5-mercapto-1,3,4-thiadiazole derivatives as anticonvulsant agents as well as results of our previous studies allow us to anticipate their anticonvulsant properties that are tested at the moment.

Current approaches to the rational design of drugs definitely include the use *in silico* methods. Synthetic strategy of this study is the structure modification of 1,3,4-thiadiazoles ring scaffolds in the positions 2 and 5 with the aim of obtaining more potent pharmacologically active compounds. That is why we have used a series of promising anticonvulsant, namely 2,5 substituted 1,3,4-thiadiazoles, to identify the main descriptors that have an impact on the activity.

Aim. The aim of this work was to identify correlations and to make on their basis some recommendations for rational design of anticonvulsant agents among of substituted 1,3,4-thiadiazoles.

Materials and Methods. Software packages Hyper-Chem 7.5 and BuildQSAR have been used to calculate the 3D molecular descriptors and to build QSAR models.

The protective activity of 2,5 substituted 1,3,4-thiadiazoles against the pentylentetrazole-induced seizures (at the doses of 50 mg/kg; 100 mg/kg) was evaluated after administering orally 30 min. Distilled water or depakine 5 mg/kg were administered orally 30 min or 60 min before injecting pentylentetrazole, as control and positive control group, respectively. Mice were observed for 60 min after receiving water or testing chemicals. The latency of convulsive onset, severity of seizures and mortality rate was measured.

Results and discussions. The 3D molecular descriptors, namely (Total Energy, Binding Energy, Isolated Atomic Energy, Electronic Energy, Core-Core Interaction, Heat of Formation, $E_{HOMO,}$ $E_{LUMO,}$ D, logP, Refractivity , Polarizability, Aprox, Grid) were calculate. Regression analysis was carried out for identification of the important

3D molecular descriptors that most adequately reflect the features of the molecules that are responsible for anticonvulsant activity. Experimental parameters of seizures severity, duration of seizures, latent period and the percentage of animals surviving as dependent variables and calculated 3D molecular descriptors of the compounds as independent variables were used for this calculation. The two-parameter linear QSAR-models were built. A statistically significant number of QSAR-models intended for the pre-experimental prediction of the effective anticonvulsants with prescribed set of properties of 1,3,4-thiadiazole derivatives. The accuracy, reliability, and prognostic value these models were confirmed by statistical criteria. (Fig.1)

Severity of seizures = +0,00002(±0,00001) IAE +0,25730(±0,17725) D +4,78311(±0,681948)

(n=014; r=0,763; s=0,461; F=7,641; Q2=0,225; S_{PRESS}=0,627)

QSAR-model *1*

Severity of seizures = +0,30473(±0,17946) P -0,01577(±0,00860) V +7,49729(±1,671281)

(n=014; r=0,795; s=0,432; F=9,462; Q2=0,187; S_{PRESS}=0,642)

QSAR-model *2*

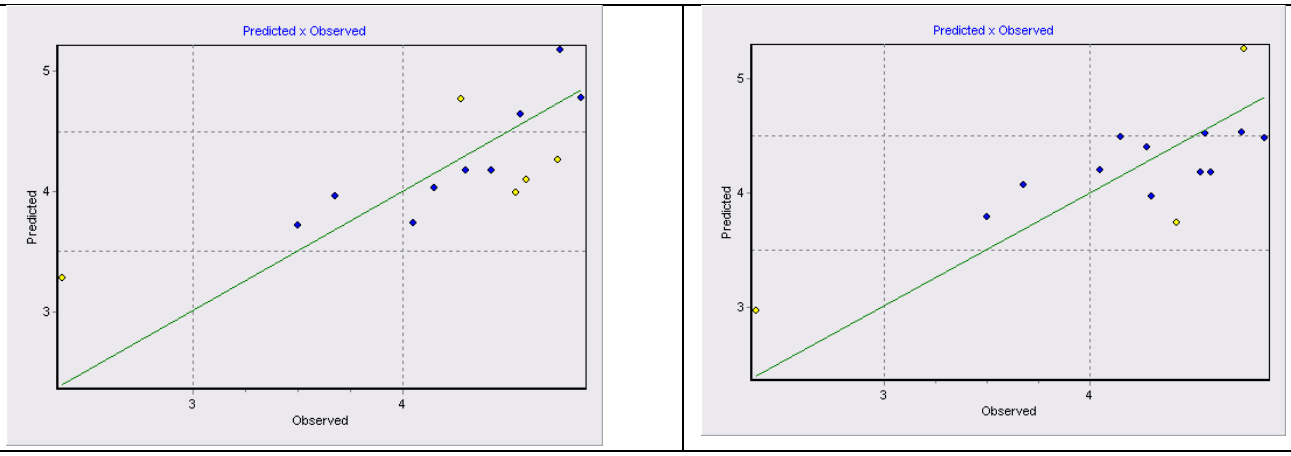

Fig.1. *A graphical comparison of predicted values and experimental activity for A)QSAR-model 1 and B) QSAR-model 2*

As a result, it was found that the anticonvulsant activity of the compounds depends on the value of isolated energy atoms, dipole moment, polarizability and volume of the molecule.

Conclusions. Based on structure activity relationship, the number of statistically probable two-parameter QSAR models was built. It has been shown, that anticonvulsant activity of the analyzed substances depends on the isolated energy atoms, dipole moment, polarizability and volume of the molecule.