# Synthesis of 1-acetamide derivatives of N-[(2,4-dichlorophenyl)methyl]-2-(2,4-dioxo-1*H*-quinazolin-3-yl)acetamide as new anticonvulsant agents

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**Introduction.** The search for new antiepileptic drugs in accordance with the International League Against Epilepsy recommendations consists of the integrated use of screening models of seizures with different pathogenesis [1]. Previously, we proposed an algorithm for the search for AEDs, consisting of the stepwise use of molecular docking in anticonvulsant biotargets and subsequent pharmacological screening in animals. The use of the given algorithm resulted in detection of an effective anticonvulsant N-[(2,4-dichlorophenyl) methyl]-2-(2,4-dioxo-1*H*-quinazolin-3-yl)acetamide having a wide spectrum of activity in different models of seizures and together with low toxicity [2]. The aim of the present study was the synthesis of its alkylated structural analogues, as well as prediction of their effect on GABAergic biotargets to optimize *in vivo* research on a pentylenetetrazole-induced (PTZ) model of seizures.
**Materials and methods.** The following software was used for molecular docking and visualization of results: AutoDock Vina [3], BIOVIADraw 2017R2, Chem3D, Discovery Studio Visualizer 2017/R2. Biotargets were downloaded from the Protein Data Bank [4]: $GABA_A$ (PDB ID – 4COF, 6HUP), $GABA_{AT}$ (PDB ID – 10HW). The structure of the synthesized compounds was proved by elemental analysis method, as well as $^1H$ and $^{13}C$ NMR spectroscopy, and GC/MS method.
**Results and discussion.** The synthesis of the target compounds was carried out by alkylation with chloroacetamides of the starting N-[(2,4-dichlorophenyl)methyl]-2-(2,4-dioxo-1*H*-quinazolin-3-yl)acetamide in DMF medium in the presence of potassium carbonate with constant stirring during 8 hours at 80 °C. Results of molecular docking of the studied compounds into the active sites of the positive allosteric modulator benzamidine and diazepam in $GABA_A$ receptor, as well as into the site of GABA-aminotransferase enzyme inhibitor – vigabatrin, turned out to be ambiguous. According to the binding energy indexes, the studied ligands were significantly inferior to the reference ligands – benzamide (-8.5 kcal/mol) and vigabatrin (-8.4 kcal/mol), but they showed their scoring functions at the level of diazepam (-9.9 kcal / mol) – a positive allosteric $GABA_A$ receptor modulator.
**Conclusions.** The synthesized 1-acetamide derivatives of N-[(2,4-dichlorophenyl)methyl]-2-(2,4-dioxo-1*H*-quinazolin-3-yl)acetamide in the docking studies into GABAergic biotargets demonstrated probability of realization of the anticonvulsant effect by allosteric modulation of the $GABA_A$ receptor through benzodiazepine active site. Therefore, accordingly, the further *in vivo* study using PTZ-induced seizures is advisable.

**References**

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