# CONSTRUCTION, SYNTHESIS AND PREDICTION OF THE ACTIVITY OF QUINAZOLIN-4(3H)-ONE DERIVATIVES AS NEW ANTICONVULSANTS

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**Introduction**. Epilepsy is one of the most widespread neurological diseases with dynamically increasing drug-resistant forms development. The mentioned disease is a complex systemic process associated with a tendency to seizures and a whole spectrum of various cognitive, behavioral, psychiatric disorders, and the development of accompanying comorbid conditions – neuropathic pain, depression, anxiety, psychosis, and even schizophrenia, etc. [1]. Nowadays, existent antiepileptic drugs (AEDs) are characterized by a wide range of side effects, and the CNS disorders are the lion's share of them [2]. Therefore, the search for new innovative AEDs having better efficacy and tolerability remains an important task, the solution of which largely depends on the comprehensive preclinical use of animal screening models.

**The aim of the study**. The aim of the present research was design, synthesis and prediction of the activity of innovative quinazolin-3(4*H*)-one derivatives as promising anticonvulsants.

**Materials and methods**. General organic synthesis methods were used to obtain the substances. Modern physicochemical methods – elemental analysis, UV-, IR-, $^{1}H$, $^{13}C$ NMR-spectroscopy, HPLC-MS – were used to determine the chemical structure, individuality and purity degree of the synthesized compounds. AutoDock Vina and AutoDockTools1.5.6, BIOVIADraw 2017R2, Chem3D, HyperChem 7.5, Discovery Studio Visualizer 2017/R2, and SwissADME software were used for *in silico* studies.

**Results**. The major vector of rational drug-design of new AEDs is the structural modification of known drugs in order to improve their pharmacological profile and create the optimal conformation of ligand-receptors. Methaqualone, a positive allosteric modulator of the GABA receptor with pronounced anticonvulsant, hypnotic and hypnotic activity, is of considerable interest in this direction. Anticonvulsants having a specific activity in models of chemotoxic and electroshock convulsions were obtained by modifying methaqualone structure, but none is currently used due to their addictive ability [4]. The structure of methaqualone was modified to optimize and improve the pharmacological profile. The design was based on a combination of the principles of the modern pharmacophoric model of anticonvulsant action and logo-structural analysis of the literature data, followed by the application of virtual target-oriented screening and additional determination of "drug-likeness" parameters. The substance having potential anticonvulsant activity was designed following the principles of modern pharmacophore concepts for the creation of new AEDs, according to which the structure should include a lipophilic aryl ring (A), a hydrogen bond domain – a donor/acceptor (HAD), an electron donor (D) and a distally placed aryl ring or its equivalent, as an additional

hydrophobic center, as well as the presence of a distal region with functional groups capable of forming hydrogen bonds was desirable (Fig. 1).

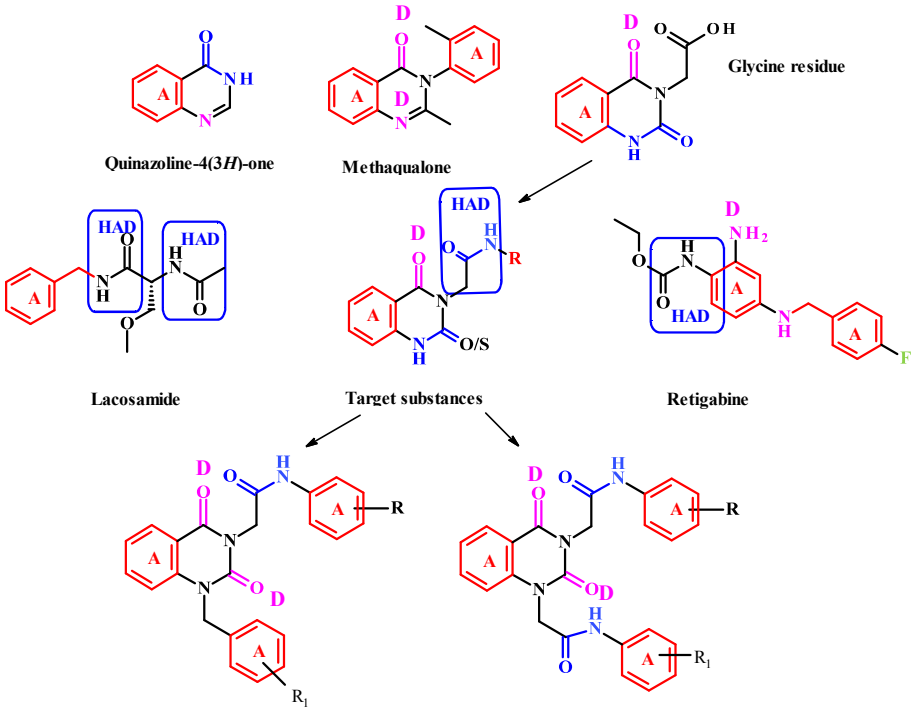



Figure 1. Pharmacophore model implementation of the anticonvulsant activity in the target compounds design

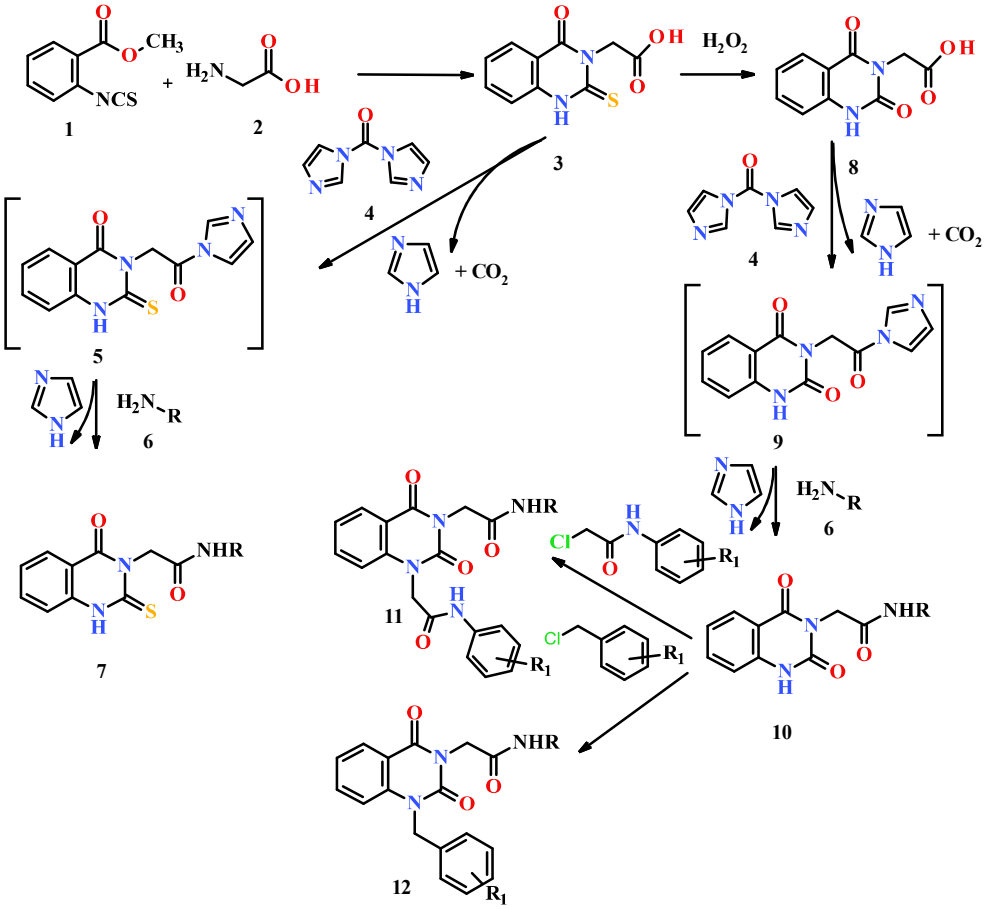
The first step was methylphenyl radical replacement in the 3rd position with an acetic acid residue, which will allow connecting the quinazoline scaffold with the neurotropic mediator glycine. Most of the newest AEDs contain an amide fragment in their structure – lacosamide, retigabine, rufinamide, felbamate, levetiracetam, brivaracetam, etc. Transformation of a hydrophilic carboxyl group into an amide one by interaction with alkyl and arylamines will lead to the additional domain of hydrogen bonds that can stabilize the ligand-receptor conformation. In the case of aryl-substituted derivatives, the distal distance between the aromatic fragments of the molecule increases compared to methaqualone. Replacement of the lipophilic methyl group in the 2nd position of the quinazoline ring with a carbonyl group leads to the appearance of a cyclic amide one as another domain of hydrogen bonds in the active site, and the further introduction of a thio-group acts as an electron-donating fragment for the formation of possible covalent bonds in the receptor site. Besides, there is information about the influence of the sulfur atom on increasing anticonvulsant activity, both on the example of thiopyrimidines and, actually, thioquinazolines.

Another direction of modification was the introduction of substituted benzyl and arylacetamide fragments into the structure of quinazoline-2,4-diones in the first position

of the cycle. The purpose of such substitution was introduction of an additional hydrophobic domain, as well as creation of an additional distal region with functionality for possible hydrogen bonds, as well as the further determination of the role of the cyclic NHCO fragment in anticonvulsant action implementation.

In order to predict activity using PTZ-induced seizure model, we ranked the virtual database of compounds according to the affinity index for GABAergic biotargets relative to native ligands after docking into the active sites of the positive allosteric modulator benzamidine and diazepam of the $GABA_A$ receptor and the site of the GABA aminotransferase inhibitor vigabatrin. Results have shown that 55 candidate structures were formed for synthesis, for which drug similarity parameters were evaluated using the SwissADME online resource.

To synthesize the main intermediate – (4-oxo-2-thioxo-1,4-dihydroquinazolin-3(2*H*)-yl) acetic acid (3) – a reaction of the interaction of esters of substituted 2-isothiocyanobenzoic acid with primary amines, in particular glycine, was carried out. The reaction was carried out by boiling for 30 minutes in propanol-2 medium in triethylamine in the presence (Fig. 2).



6, 7,10, 11, 12 R= $CH_3$; $C_2H_5$ ; $C_3H_7$; $C_4H_9$; $CH_2$-CH-$(CH_3)_2$; $CH_2$-CH=$CH_2$; цикло-$C_6H_{11}$; $CH_2$-$C_6H_5$; $CH_2$-$C_6H_4$(Cl)-4; $CH_2$-$C_6H_3(Cl)_2$-2,4; $CH_2$-$C_6H_4(OCH_3)$-2; $CH_2$-$C_6H_4(OCH_3)$-4; $(CH_2)_2$-$C_6H_5$; $(CH_2)_2$-$C_6H_4$(Cl)-4; $(CH_2)_3$-$C_6H_5$; $C_6H_5$ ; $C_6H_4(OCH_3)$-2; т$C_6H_4(OCH_3)$-4.

R= 3-Cl; 4-Cl; 2,4-diMe; 2,5-diMe; 2-F; 2,4-diF; 2-CN; 4-$NO_2$; 4-OMe; 3-F, 4-OMe; 2-Cl, 4-F

The target carboxamides 7 synthesis was carried out using "one-pot" method by reaction of (4-oxo-2-thioxo-1,4-dihydroquinazolin-3(2*H*)-yl) acetic acid (3) with N,N'-carbonyldiimidazole (4) upon boiling in dioxane and subsequent interaction of intermediate acylimidazole 5 with the corresponding amines 6. The similar approach was used as well for the synthesis of 2-(2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl)-N-R-acetamides (10) after preliminary oxidation of the thio-group of intermediate 3 with hydrogen peroxide to the oxo-group with formation of derivative 8. The following alkylation of N-alkyl/aryl-2-(2,4-dioxo-1*H*-quinazolin-3-yl) acetamides (10) was carried out by reaction with the corresponding chloroacetamides and 1-chloromethylbenzenes in the dimethylformamide medium in the presence of potassium carbonate excess at a temperature of 70-80 ˚C, i.e., under common alkylation conditions.

The synthesized compounds 7, 8, 10, 11, 12 are white crystalline substances, easily soluble in 2-propanol, dioxane, dimethylformamide, and not soluble in water. The structure and purity of the compounds obtained were confirmed by elemental analysis, $^{1}$H NMR, $^{13}$C NMR spectroscopy and LC/MS. The reaction was monitored by thin layer chromatography.

**Conclusions**. Based on the logical-structural analysis of literature data and in accordance with the principles of the pharmacophoric concept of creating new AEDs, a database of potential anticonvulsants among quinazolin-4(3*H*)-one derivatives were constructed. The feasibility of the synthesis and the expediency of the further *in vivo* experiments on the PTZ-induced seizure model were proven by docking studies and ranking of compounds according to the affinity index to GABAergic biotargets. The techniques were developed, synthesis was carried out and the structure of previously undescribed quinazolin-4(3*H*)-one derivatives as potential anticonvulsant agents was proved. All synthesized compounds were tested for anticonvulsant activity in various seizure models.

## References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