PHARMACOLOGICAL EFFECTS' SPECTRUM OF A PROMISING ANTICONVULSANT – 1-(4-METHOXYPHENYL)-5-{2-[4-(4-METHOXYPHENYL)PIPERAZINE-1-YL]-2-OXOETHYL}-1,5-DIHYDRO-4H-PYRAZOLO[3,4-D]PYRIDINE-4-ON

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Introduction. 1-(4-Methoxyphenyl)-5-{2-[4-(4-methoxyphenyl)piperazine-1-yl]-2-oxoethyl}-1,5-dihydro-4H-pyrazolo[3,4-D]pyridine-4-on (laboratory code - compound 78553) was synthesized by assoc. prof. G.I. Severina under the direction of prof. V.A. Georgiyants in National Pharmacy University. During preclinical studies this compound revealed strong anticonvulsant properties among 35 pyrazolo[3,4-D]pyridine-4-one derivatives, and high efficiency in several experimental models of seizures with different mechanisms of paroxysmal. These results gave a reason to consider this compound as leader. Given the fact that epilepsy is characterized not only by the complexity of treatment and a high frequency of drug-resistant cases, but the probability of personality changes and mental disorders in the form of anxiety, depression, anxiety, memory loss, etc., it is useful to evaluate the ability of leader compound to influence these disorders. In addition, according to the PASS prediction compound 78553 has a high probability to demonstrate an anti-inflammatory and analgesic effects. The presence of these additional properties is important in the prospects of introducing compound 78553 in clinical practice as antiepileptic drug.

Aim. Find out the existence of 1-(4-methoxyphenyl)-5-{2-[4-(4-methoxyphenyl)piperazine-1-yl]-2-oxoethyl}-1,5-dihydro-4H-pyrazolo[3,4-D]pyridine-4-on's influence on behavioral reactions, anxiety, depression, animal's memory, muscle tone and coordination, and the presence of anti-inflammatory and analgesic effects in the experiment.

Materials and methods. Studies were conducted in albino mature male mice. The compound 78553 was administered intragastric at the most effective anticonvulsant dose of 200 mg/kg 30 minutes before the experiments. To determine the effect on behavior and emotional state were elected the following tests: open-field test, elevated plus-maze test, immobilization test. Antiamnesic properties of the compound were studied in passive avoidance test in anterograde amnesia model induced by intraperitoneal injection of 1.5 mg/kg scopolamine hydrochloride. The effect on muscle tone and coordination was evaluated in a rota rod test (10 rotates/min). Anti-inflammatory properties – in the carrageenin-induced paw edema

model and analgesic – in a models of somatic (tail-flick test) and visceral (acetic acid-induced writhing) pain. All experiments were conducted in accordance with current guidelines. The results were processed statistically using STATISTICA® 13.0.

Results and discussion. Administration of compound 78553 caused decrease in motor activity by 60%, research activity - by 65% that generally reduced the total amount of all types of activity by 62% in open-field test. Reduction of locomotion indicates the prevalence of inhibitory over excitatory processes in the central nervous system. There was also a trend towards the emotion reduction that in total indicates the sedative properties of the test compound. In immobilization test compound 78553 didn't affect significantly the depressive behavior, there was only a tendency to increase the latent period of the first hovering at 40%. The results of elevated plus-maze test demonstrate a significant decrease in the number of visits dark parts of maze by 30% and vegetative response's markers of emotional reactions in 5.5 times, that indicating a decrease in anxiety animals. Compound 7553 reduced the effect of scopolamine in passive avoidance test, significantly increased the latent period of entry to the dark chamber to the level of intact mice and increased the number of trained mice. Antiamnesic activity was 110%. Therefore, the passive avoidance test showed powerful positive effect of test compound on memory. There was not significant difference between groups' results of test compound and control in rota rod test, therefore compound 78553 has not myorelaxation and does not affect coordination of movement. Model of carrageenin-induced paw edema demonstrated that the average increase of paw mass in test compound's group was 1.5-fold lower than in control. Anti-inflammatory activity was 41%, which is rather significant, as far as the significant level is considered to be at least 20%. Increase of latent period of tail flicking out after 30 minutes in model of somatic pain indicated significant analgesic effect of compound 78553, that persisted for 2.5 hours of observation. The model of visceral pain also confirmed the presence of analgesic effect: observed a significant reduction of acetic writhing almost in 2-fold.

Conclusions. Promising anticonvulsant 1-(4-methoxyphenyl)-5-{2-[4-(4-methoxyphenyl)piperazine-1-yl]-2-oxoethyl}-1,5-dihydro-4H-pyrazolo[3,4-D]pyridine-4-on has tolerable profile of pharmacological properties, that characterized by sedative effect, weak anxiolytic effect without muscle relaxation, favorable effect on memory, as well as anti-inflammatory and analgesic effects.