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Epilepsy belongs to the most common neurological diseases affecting over 50 million of people worldwide significantly reducing life's quality of patients and the possibility of their daily functioning as well. In the last decade, despite the introduction many new antiepileptic drugs into the treatment as well as complex therapeutic regimens and advanced clinical trials of "candidates" for modern preparations, still one has not found any substances that would be highly effective in monotherapy of many types of seizures. Currently healthcare offers a large number of antiepileptic drugs, both conventional (classical) used for many years, as well as so-called new generation drugs (second and third), implemented for the treatment from the 90s. Analysis of their effectiveness, however, shows that 30% of patients do not respond satisfactorily to the treatment, and this form of this disease is known as refractory epilepsy. In addition, many of the currently used antiepileptic drugs is known to cause numerous side effects which substantially limit patients' compliance with pharmacotherapy planned. Therefore, there is a continuous need for new, more effective and well tolerated therapeutic substances. In a view of the fact that antiepileptic drugs are the most commonly used formulations in the treatment of neuropathic pain, there is a high probability that the compounds exhibiting anticonvulsant activity will also be effective in inhibiting pain stimuli caused by damage or dysfunction of the central or peripheral nervous system. Current data indicate that in only 50% of patients one observes a reduction of neuropathic pain by 30–50%, in the remaining patients no improvement by administration of any of the drugs used is observed.

Taking into account the above-mentioned facts, the main objective of the project is to obtain highly active compounds in three animal models of epileptic seizures, i.e. maximal electroshock (MES) test, test of seizures induced by the subcutaneous administration of pentylenetetrazole (scPTZ) and six-hertz seizure test (6-Hz), which are considered to be the most important preclinical tests to identify candidates for new effective antiepileptic drugs. Application of the substances characterized by the above-mentioned pharmacological properties, may result in their potential efficiency in different types of epilepsy in human, among others in grand mal tonic-clonic seizures, absence seizures, and most importantly, refractory epilepsy. When pursuing the objective of this study, one planned to perform the synthesis of 100 original organic compounds. Their structures were designed as hybrids which in one molecule combine fragments of three clinically effective antiepileptic drugs i.e. ethosuximide, levetiracetam and lacosamide. It is worth to note that each of the above-mentioned therapeutic substances have different therapeutic indications and different molecular mechanism of action. It was therefore assumed that this procedure will allow to obtain compounds that combine pharmacological properties of individual drugs forming hybrid structure. It is worth to emphasize, that this hypothesis has partially been confirmed in our previous studies. The obtained chemical structures will be further subjected for in vivo pharmacological studies by using mice as experimental animals. The study will involve animal models of epileptic seizures: maximum electroshock test (MES - model of human tonic-clonic seizures), subcutaneous pentylenetetrazole seizure test (scPTZ - model of human absence seizures) and six-hertz seizure test (6-Hz), which are a model of drug-resistant seizures. Because antiepileptic drugs belong to most commonly used therapeutic substances in the treatment of neuropathic pain, hence while searching for new anticonvulsant substances, one should also include this direction of biological action. Thus, for the compounds characterized by the highest activity in convulsive tests, one planned studies involving animal models of pain of different origin, i.e. formalin test, capsaicin-induced pain and neuropathy model induced by streptozotocin, oxaliplatin and chronic sciatic nerve damage. When identifying new biologically active substances, it is important to identify the potential molecular mechanism determining pharmacological effect. For this reason, the project involves in vitro tests towards the affinity for ion channels and receptors involved in the regulation of nerve cells' excitability. Supplementation of the proposed study will be to pre-determine pharmacokinetics and toxicity of new substances, including among others, penetration through biological membranes, binding to plasma proteins, metabolic stability, effects on liver enzymes, cytotoxicity and hepatotoxicity. According to the latest guidelines in the search for new biologically active substances, these studies should be conducted in parallel with tests that identify particular pharmacological activity.

In more distant perspective, the results of this project can be used for many studies aimed at highly effective and well-tolerated antiepileptic drugs whose introduction into the treatment may constitute an important progress in the pharmacotherapy of epilepsy (neuropathic pain), resulting in the reduction of treatment costs for both, the budget and the patients as well.