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# Scientific-Methodical Approach to Extension of the Nomenclature for New Class AMPA-Receptor Allosteric Modulators – 3,7-Diazabicyclo[3.3.1]nonane Derivatives for Rehabilitation of Patients after Cerebral Accidents

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**Abstract:**

As a result of the study carried out by project developers, computer modeling and optimization of more than 200 new structures of 3,7-diazabicyclo[3.3.1]nonane derivatives, possessing positive modulatory activity towards AMPA-receptor, were carried out, and the most promising candidate drug molecules were synthesized. We developed approaches to the synthesis of 3,7-diazabicyclo[3.3.1]nonane derivatives, which (according to docking data) bind well to modulator sites of AMPA-receptor. Based on the AMPA-receptor's spatial structure analysis, its complexes with known PAMs of the AMPA-receptor (AMPA-PAMs) and results of their molecular docking, it was shown that new compounds, based on 3,7-diazabicyclo[3.3.1]nonane derivatives, can be highly effective AMPA-receptor modulators with pronounced physiological effect. During the study of compounds that can positively modulate the function of the AMPA receptor, it was found that AMPA-PAMs possess a number of useful properties, improve memory and cognitive functions in both human and animals. AMPA-PAMs are true modulators, rather than agonists, as they do not cause synaptic currents by themselves at any concentration. The AMPA-PAMs unique property is the ability to slow down (inhibit) or block the transition of the receptor to desensitized state; this ability mediates the improvement of learning and memory.

**Keywords:** AMPA receptors, 3,7-diazabicyclo[3.3.1]nonane derivatives, brain-derived neurotrophic factor, positive allosteric modulator PAM, rehabilitation of patients after cerebral accidents.

## INTRODUCTION

Belgian pharmacologists C. Giurgea and V. Skondia were the first to formulate the concept of nootropic drugs. In 1963 they successfully synthesized Piracetam (Nootropil) – the first nootropic, which was brought to the world pharmaceutical market by the Belgian company UCB Pharma. In 1972 Corneliu Giurgea discovered that piracetam improves cognitive functions and memory. Just like psychostimulants, piracetam increases mental capacity, but does not have their adverse effects. The term *nootropic* (from the Greek *nous* – "mind", and *trepein* – "to turn") was coined by Corneliu Giurgea in 1972 to designate a class of drug products that positively affect the higher integrative functions of the brain. After that, a new class - nootropics - was introduced into the classification of neuro- and psychotropic drugs. Thus, with the discovery of piracetam, the history of the use of nootropic drugs began.

Nootropic drugs are a special group of neuropsychotropic drugs, which possess the ability to enhance memory and cognitive processes, improve learning ability, and positively affect intellectual capacity of both healthy individuals and those suffering from various disorders. Throughout the literature sources, "smart drugs" and "cognitive enhancers" are often used as synonyms for nootropics.

These medicinal products are prescribed for class V disorders – mental and behavioral disorders. Nootropics have a wide range of indications: aging cognitive problems; psychoorganic syndromes of neurodegenerative or vascular origin (including Alzheimer's disease); acute or chronic cerebral circulation disturbance (including those after stroke or encephalopathy); craniocerebral injuries, neuroinfections; acute and chronic fatigue, chronic fatigue syndrome, stress, pain syndrome; diseases caused by prolonged alcohol and drug intake, conditions due to prolonged central nervous system (CNS) depressants administration (anxiolytics, antipsychotics, etc.); asthenic, astheno-depressive and depressive syndromes, neurotic disorders, vegetovascular dystonia, dizziness; prevention of motion sickness.

In pediatric practice, nootropic medicinal products are used for treatment of cerebroastenic and encephalopathic disorders, memory defects, mental and lexical retardation, perinatal CNS damage consequences, and attention deficit hyperactivity disorder (ADHD) (Table 1).

Healthy individuals usually use nootropics in case there is a certain need to increase mental capacity, improve mental alertness, work productivity, planning and decision-making ability, and speed up memory recall (retrieval) processes [1].

In recent years, much attention is paid to the creation of new nootropic drugs, the main target of which is glutamatergic system – the main excitatory mediator system of mammalian's brain.

There are two main classes of glutamate receptors – ionotropic and metabotropic. Activation of ionotropic receptors by an agonist causes a change in their conformation and results in ion channel opening. Inotropic glutamate receptors include three types by the name of selective agonists: 2-amino-3-(3-hydroxy-5-methyl-4-isoxazolepropionic) acid (AMPA) receptor, N-methyl-d-aspartic acid (NMDA-receptors) and kainic acid (kainate receptors).

Ligands, which can bind to the AMPA-receptor, draw attention of researchers developing new drugs for the treatment of Alzheimer's disease, Parkinson disease, schizophrenia, depression, epilepsy, amniotrophic lateral sclerosis, Huntington's chorea, Niemann-Pick disease, multiple sclerosis, mild cognitive impairment, age-related disorders of cognitive functions. Among various types of AMPA-receptors' ligands, positive allosteric modulators (PAMs) are of particular interest; they improve memory and cognitive functions in both human and animals, because it was found experimentally that intensive ion current, caused by action of such modulators on AMPA-receptor with subsequent postsynaptic membrane depolarisation, triggers the

mechanism of expression of genes responsible for the synthesis of neurotrophins – nervous tissue growth factors (*NGF - nerve growth factor, BDNF - brain-derived neurotrophic factor*). For this reason, drugs acting on the AMPA-receptor can be highly effective as nootropic and neuroprotective agents. However, despite the fact that leading pharmacological companies are constantly engaged in this area, at the moment there is a very limited number of such drugs due to side effects, high therapeutic doses and toxicity.

**The aim** of this study was to develop scientific and methodological approach to the widening of the range of innovative medical products with "pro-cognitive" effect, based on the 3,7-diazabicyclo[3.3.1]nonane (bispidine) derivatives.

**Table 1 – Main therapeutic applications of nootropics [2, 3].**

| | |
|---|---|
| Neurology | • Pharmacotherapy of cognitive disorders (decrease of concentration, attention, memory, learning ability) caused by neuroses, neurodegenerative and cerebrovascular pathology;<br>• correction of manifestations of psychoorganic syndrome owing to the neurodegenerative, vascular, toxic, infectious nature (psychoemotional imbalance, psychasthenia, ringing in ears, dizziness);<br>• correction of neurologic semiology of various genesis (cortical myoclonia, post-stroke aphasia) |
| Therapy<br>Family medicine<br>Cardiology<br>Gastroenterology<br>Pulmonology | • Pharmacotherapy of cognitive, psychoemotional, psychasthenic disorders in the course of neuro-circulatory psychosomatic dystonia (arterial hypertension, ischemic heart disease, bronchial asthma);<br>• prevention of cognitive, psychoemotional and psychasthenic disorders at chronic stress and ageing (manager's syndrome, age-related impairment of cognitive functions);<br>• pharmacotherapy of chronic fatigue syndrome |
| Psychiatry<br>Narcology | As part of complex therapy of:<br>• Alzheimer's disease and other forms of dementia;<br>• ageing and cognitive impairment due to alcoholism |
| Gynecology | Correction of cognitive, psychoemotional and psychasthenic disorders associated with premenstrual dysphoric syndrome or climacteric syndrome |
| Paediatrics | Pharmacotherapy of dyslexia |

## MATERIALS AND METHODS

Development of scientific and methodological approach to objective assessment of innovative medicinal products based on 3,7-diazabicyclo[3.3.1]nonane (bispidine) derivatives development prospects was carried out using information analysis methods. Systemic analysis of ampakines used for cognitive disorders therapy and treatment of patients after acute brain hypoxia due to ischemia was also employed in this study.

## RESULTS

The search strategy for new drugs for the therapy of cognitive impairment and rehabilitation of patients with acute brain hypoxia due to ischemia, or other brain damage, involves the search for substances that have synaptic plasticity and the ability to increase the production of neurotrophic factors. Many substances having neuroprotective activity, either act at high doses, or possess increased toxicity. Substances of a relatively new class of "ampakines" are of undoubted interest; in their physiological action they are allosteric modulators of the AMPA-receptor [4].

About 500 abstracts and full patents were selected using different variations of search queries from databases of European Patent Office (Espacenet), World Intellectual Property Organization, Federal Institute of Industrial Property of Russia (www.fips.ru), United States Patent and Trademark Office and from other available databases. These abstracts were analyzed during the study.

A total of 81 patents were selected for detailed examination.

During analysis of selected patents it was found that international and European patent applications were filed from a wide range of countries (USA, Japan, Germany, Luxembourg, Denmark, France, Poland, Norway, Canada, and Great Britain). A significant number of patenting countries should also be noted, which indicates high demand and importance of the studies in this field. It should be also noted, that applicants from all of the abovementioned countries preferred to protect their inventions both in USA (81 protection documents) and through the procedure for filing International applications (64 protection documents).

It is noteworthy, that as a result of patent search no analogs to the proposed product were found. The proposed works and innovative researches in our project differ from existing projects in a way that offered drug product for restoration of motor and cognitive functions after brain damage is based on 3,7-diazabicyclo[3.3.1]nonane derivatives [5].

The obtained data demonstrate high significance of the selected study field and high competitiveness of the proposed drug [6].

During the patent search, we confirmed that there are no current Russian and foreign objects of intellectual property, which can be equivalent to the technological solutions described in this article. No patent applications, which describe promising use of 3,7-diazabicyclo[3.3.1]nonane derivatives as pharmacologically active pharmaceutical substances or drug product components, have been found. There were also no patent applications that reflect the possibility of application of 3,7-diazabicyclo[3.3.1]nonane derivatives for the recovery of motor and cognitive functions after brain damage.

An important issue in the study of new pharmacologically active compounds is the determination of their potential toxicological activity. Thus, a number of ampakines from an innovative class of 3,7-diazabicyclo[3.3.1]nonane (bispidine) derivatives are promising as "candidates" for development of an innovative drug product with a "procognitive effect", which can also be used for rehabilitation of cognitive and motor functions after brain damage caused by acute injury and acute ischemia.

Glutamatergic receptors are expressed on neuronal synapses and activated by glutamic acid – the most common neurotransmitter, transmitting signals that excite nerve cells. AMPA-PAMs either reduce the rate at which AMPA-receptors lose sensitivity to prolonged exposure to glutamate, or slow down the deactivation process of the AMPA-receptor after the end of exposure to glutamate [7].

Thus, priority of the given topic belongs entirely to the participants of this project.

## DISCUSSION

As a result of the study carried out by project members, the computer modeling and optimization of more than 200 new structures of 3,7-diazabicyclo[3.3.1]nonane derivatives, potentially having positive modulatory activity towards AMPA receptors, was completed, and the most promising of them were selected (based on the results of modeling) and synthesized.

Approaches to the synthesis of the 3,7-diazabicyclo[3.3.1]nonane derivatives, binding well (according to docking data) to modulator sites of the AMPA-receptor, are developed. Based on the AMPA-receptor's spatial structure analysis, its complexes with known AMPA-PAMs and results of their molecular docking, it was shown that new compounds based on 3,7-diazabicyclo[3.3.1]nonane derivatives can be highly effective AMPA-receptor modulators with pronounced physiological effect.

Physiological researches of synthesized 3,7-diazabicyclo[3.3.1]nonane (bispidine) derivatives showed a high positive modulatory activity towards AMPA-receptor in *in vitro* tests, performed by electrophysiological method; *in vivo* tests showed pronounced neuroprotective properties, significant improvement of memory and cognitive functions in animals [8].

Indications for the use of obtained compounds (AMPA-PAMs) are expected to include acceleration and improvement of reconvalescence quality after cerebral accidents, since the acute phase and reconvalescence phase are facilitated by different pathogenic mechanisms.

In accordance with recommendations for preclinical research and study of drugs with nootropic type of action, the study of specific activity should be performed in comparison with the reference preparation [1]. Piracetam is the first "reference" representative of the nootropic class. Piracetam similarly to ampakines is capable to modulate efficiency of glutamatergic transmission in the central nervous system, mediated by ionotropic AMPA-receptors [2, 9, 10].

Therefore, the study of specific activity of innovative drug product Z-109 (3,7-diazabicyclo[3.3.1]nonane derivative) undoubtedly should be carried out in comparison with Pyracetam, which has similar mechanism of action on the glutamatergic mediator system.

## CONCLUSIONS

As a result of conducted informational and analytical studies it was established that priority of the given topic at present belongs entirely to the participants of this project.

Assignment of combinations of AMPA-PAMs with neuroleptics and narcotic analgesics is expected to be very effective for mitigating side effects of the latter (for example, respiratory depression without suppressing the analgesic effect of drugs). The use of ampakines for emergency care of patients with overdose of drugs, barbiturates or alcohol is also promising [11, 12].

Thus, AMPA-PAMs currently attract the interest of many scientists, the range of research areas is very diverse. The mechanism of pharmacological effects of AMPA-PAMs is associated with their ability to influence neuroplasticity and to express neurotrophic factors through the AMPA-receptors of glutamatergic mediator system.

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