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# MOLECULAR DESIGN AND MATHEMATICAL PREDICTION IN THE CREATION OF NEUROPROTECTORS WITH AN ANTIOXIDANT MECHANISM OF ACTION

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Vascular diseases of the brain - one of the leading causes of morbidity and mortality and disability in the population of the EU countries, the USA and Japan. Every year in the world suffer a stroke of about 6 million

people. The increase in the prevalence of stroke seen in people of the working age - to 60 years. According to international EP and demiological studies, 4.7 million people die of stroke every year in the world. In most industrialized countries, stroke takes 2-3 place in the structure of total mortality of the population, second only to cardiovascular pathology. Early 30-day mortality after a stroke averages 30-40%, and about 50% of patients die within a year. Stroke is the main cause of disability in the population. Only about 20% of surviving patients can return to their previous work. According to the WHO, the average cost of direct and indirect costs per patient is about 80 thousand US dollars per year. Thus, vascular diseases of the brain are an extremely important problem of modern medicine.

Numerous experimental and clinical studies allowed us to formulate approaches to rational neuroprotection by the mid-1990s. There is a primary neuroprotection aimed at interrupting the earliest processes of the ischemic (glutamate-calcium) cascade, which unfolds within the "therapeutic windows" and underlies the rapid necrotic damage to brain tissue [10]. Primary neuroprotectors, which have been clinically proven to be effective, include potential-dependent calcium channel blockers (nimodipine, cerebrocrast, isradipine), sodium channel blockers that prevent the presynaptic release of glutamate (lobeluzole, fenitoin). Primary neuroprotectors include antagonists of the phencyclidine and glutamine NMDA receptor sites (dizolcipin, cerestate, selfbody, magnesium sulfate) [1]. Glycine is a natural activator of inhibitory neurotransmitter systems, which, along with neurotransmittive action, has a metabolitotropic, antioxidant and antiischemic effect.

Secondary neuroprotection is included in the complex of emergency treatment and ischemic stroke, its action is aimed at preventing neuron maturation (oxidative stress, expression of pro-inflammatory cytokines, development of inflammatory reactions, induction of apoptosis, discoordination of metabolic cycles, reduction of trophic dysfunction, etc.). The means of secondary neuroprotection include antioxidants (emoxipin, mexidol, thiotriazolin), nootropes (piracetam, cemax, neoglutyl, noopept, phenotropil), metabolithotropic drugs (mildronate), etc. [9].

However, the modern arsenal of neuroprotective therapy does not meet all the requirements of clinicians. Thus, primary neuroprotection drugs, especially glutamate receptor antagonists, have gross side effects, which makes it impossible for them to be used in the clinic, and the self-efficacy of other drugs has been little proven. All this leads to the creation of new highly effective and low-toxic drugs of neuroprotective action. Fundamental research in the field of neurochemistry, cytoimmunology, molecular biology, physical and theoretical chemistry, and genetics plays the main role in creating new neuroprotective agents.

Thus, the discovery of endogenous ligands of secondary transmitters, presynaptic receptors, neuromodulators, the development of methods for studying the function of ion channels and the binding of substances to receptors, the decoding of the human genome, the success of genetic engineering gives the most promising direction in the design of neuroprotective agents. Designing a new group of neuroprotective drugs goes through two main stages. The first stage involves the discovery of a new pharmacologically active class of chemical compounds. At the second stage, the structure is optimized in terms of greater activity, bioavailability, and reduction of side effects.

The most difficult and expensive task is to detect new chemical groups of biologically active compounds. Leading US pharmaceutical companies spend about $ 15 billion a year on the development and production of medicines, of which $ 7–9 billion are spent on opening new chemical groups with specific pharmacological activity [4]. The selected pharmacologically active structure is then optimized using computer programs, in particular QSAR (quantitative structure structure, activity, activity, relationship) [3].

When creating a drug using a screening strategy, compounds are taken from the entire arsenal of organic chemistry, including tens and hundreds of thousands of chemical groups. While the system of cellular neuroprotection and neurodestructive includes only a few dozen chemical compounds - amino acids, peptides, nucleic acids, nitro derivatives, lipids. Based on this, at the beginning of the XXI century, the concept of creating neuroprotectors based on chemical structures that mimic the

endogenous ligands of neuronal receptors, as well as their analogues and antagonists, was proposed. The construction of such structures is carried out using heuristic or computer simulation methods that allow the creation of substances of a non-peptide nature with the preservation of the main pharmacological activity.

Of particular interest in this regard is information encoded in the structure of the endogenous ligand on lipophilicity, the ability to overcome histohematological barriers, deposition in organs and tissues, the ability to bind to blood proteins, the ability to resist the action of degrading enzymes, and bioavailability. When constructing neuroprotectors, one should take into account data on protein conformational changes (receptors, ion channels), changes in the physicochemical properties of protein structures during oxidative modification under oxidative and nitrosing stress under neurodestructive pathology, resulting in distorted sensitivity, specificity and adaptability of receptors, selectivity, excitability of ion channels, activity of regulating proteins of the redoxi system of the neuron. A sufficiently large number of the studied structures of both synthetic compounds with neuroprotective action and endogenous neuroprotectors is also necessary.

Imitation of the structural and chemical features of endogenous ligand molecules of target receptors, endogenous neuroprotectors and the most studied drugs with the desired activity allows the pharmacologist to create a combinatorial library to highlight the structure that carries information about the recognition of receptors, receptor proteins, or determine the fragment of the molecule that would provide neuroprotective effect of the created compound. [7]

In the construction of molecules with given neuroprotective properties, it is necessary to use the structures of endogenous ligands, as well as agonists and antagonists of various sites (phencyclidine, glutamine and glycine) of the NMDA subtype of glutamine receptors. A computer prediction using the PASS C & T program (Prediction of Activity for Substances: Complex and Training) indicates that these structures will show primary neuroprotective activity. In this regard, compounds that mimic the structures of the ligands of the glycine site of the NMDA receptors will be the most promising. For such structures, it was shown that the

desired activity is most pronounced when the molecule has a relatively small hydrophobic group to bind the benzene cycle in the recognition site of the receptor, a donor group that forms an ionic bond with the carboxyl group. These provisions must be taken into account in computer modeling of substances with predicted neuroprotective activity.

Another direction in the creation of neuroprotective agents is the search for compounds that block calcium channels, especially the L-subtype, which reduce the development of the glutamate-calcium cascade in the ischemic brain. 1,4 - dihydropyridine, as well as its derivatives, having in its structure o - nitrophenyl, m -; o - difluoromethoxyphenyl. In order to increase the binding energy of a future drug with various structures of the cell membrane in its molecule, short isocyclic C – C bonds in bulk C (CH3) - and C (O) OCH3 substituents, nitro group are obligatory.

As a basis for constructing calcium channel blockers with neuroprotective effects, can serve as a molecule of 8-hydroxy-2- (di-n-propyl-amino) -tetralin, which is able to block Ca ++ - currents caused by activation of NMDA receptors .

Among the means of secondary neuroprotection, an important place is occupied by antioxidants, energy-tropic drugs, nootropics and inhibitors of apoptosis. Approaches to the creation of highly effective antioxidants are described in detail in a number of papers. It is worth noting that only compounds that easily perceive reactive oxygen species and free oxygen itself can be used as secondary neuroprotectors, as well as easily penetrate the blood-brain barrier.

Analyzing numerous studies in this area, including our own, we identified several basic structures for the design of antioxidants-neuroprotectors. First of all, it is quite well-known derivatives of oxypyridine. Secondly, it is phenyl-N-tert-butyl-nitrone and its derivatives - 2-sulfo-phenyl-N-tert-butyl-nitrone. This structure has rather pronounced neuroprotective properties directly related to its ability to accept the hydroxyl radical. Thirdly, 1,2,4-triazole is a rather interesting object for the design of antioxidants with neuroprotective action. Our research has shown that antioxidant activity, combined with neuroprotective and anti-ischemic, is predicted

when thioalkylcarboxylic, benzylidene and N-alkylhydrazine substituents are introduced into the 1,2,4-triazole structure.

Quite a clear result of work in this direction can serve as a drug thiotriazolin. Thiotriazolin, reducing the hyperproduction of reactive oxygen species under various pathological conditions, is able to inhibit the oxidative modification of receptors, ion channels and enzymes. Thiotriazolin, while maintaining the thiosulfide equilibrium in the cell under oxidative stress, has a protective effect on the transmitters of the redoxi mechanisms of cell regulation. At present, a combined preparation of thiotriazolin with piracetam - "Thiocetam", with pronounced nootropic, cerebroprotective and antioxidant properties, has been created.

Cysteine and melatonin can be used as basic structures for the design of antioxidants-neuroprotectors. An interesting direction in the development of neuroprotectors is the search for compounds of inducible NO synthase inhibitors. Here, L-arginine and its nitro and methyl derivatives, as well as 7-nitroindole, can serve as the basic structure. However, the question of the use of regulators of nitric oxide (both pre-nators and synthesis inhibitors) is open. One of the promising areas of creating the means of neuroprotective therapy is to use as the basis for the design of natural metabolites that activate their own bioenergetic processes and guide them along the natural physiological channel. It is γ-butyrobetaine, its structural analogue is mildronate, which have neuroprotective, energotropic, adaptogenic, act-protective and antiischemic action.

Recent studies have proven the involvement of genetically determined cell death programs in the formation of cerebral infarction and the approval of sound development of antioxidant protection agents. Due to the fact that inhibitors of apoptosis enhance the action of primary neuroprotectors. The mechanism of action can perform cyclohexamide.

A number of studies have shown that the proinflammatory cytokine IL-1β is the main trigger of a local inflammatory reaction in the ischemic focus. In addition, IL-1β mediates excitotoxicity via glutamate NMDA receptors, promotes the synthesis of NO synthase, and activates surface adhesive molecules and free radical oxidation.

All this determines the creation of neuroprotectors based on compounds that mimic the structure of the endogenous ligand IL-1β receptors and its antagonists. Here, a protoporphyrin molecule can be proposed as an initial structure for construction.

The basis for the creation of neuroprotective agents are also pyrolidine-containing amino acids, like pyroglutamine and proline. Thus, the resulting N-acylproline-containing dipeptides and pyroglutamyl-containing dipeptides have a rather high neuroprotective and cerebroprotective activity, several times higher than the activity of pyracetam. The Russian drug "Noopept" was created on the basis of the proline glycine dipeptide.

Based on the foregoing, in the creation of drugs neuroprotective action can distinguish the following steps:

1. Creating a database of chemical compounds with neuroprotective, antioxidant, antiischemic, nootropic, energy-growing, antiapoptotic activity, properties of agonists and antagonists of glutamine receptors, IL-1β receptors, GABA receptors, inhibitors of Ca ++ channels, "Traps" of active forms of oxygen using computer programs (ISIS Base, Chem Office, ACD Labs).

2. To carry out the synthesis of chemical series on the basis of the basic structures of the main groups of primary and secondary neuroprotection identified above, optimizing in advance using a computer program (QSAR).

3. Conduct a virtual screening using the PASS C & T program, and test selected compounds in vitro for properties such as reducing stable free radical oxidation products, inhibiting stable radicals and active forms of oxygen in model systems, and surviving neurons in tissue culture.

4. Selected as a result of virtual screening and in vitro studies of the substance to study on cerebral ischemia models in both acute and in the recovery period for indicators such as survival, neurological and cognitive deficit, oxidative stress, energy deficit, the preservation of neurons in the most damaged areas of the brain, apoptosis, local inflammation, cytokine imbalance. [6,8].

In the course of our study, quantum-mechanical calculations of the HOMOEnergy descriptors (highest occupied molecular orbital) and LUMOEnergy

(lowest vacant molecular orbital) were performed using the WinMopac software package (v. 7.2). Next, we calculated the indicators of the reactive index (ω). [13]

An antioxidant activity (AOA) was evaluated [11]. The method is based on photoinduction of sodium nitroprusside, accompanied by the accumulation of the NO-radical [12]. The AOA values are calculated.

Quantum-mechanical calculations showed that the reactive index of the compounds under study is in the range from –1.9605 eV to –2.9398 eV [2]. HOMO and LUMO data of the compounds are also at a high level. The compounds tested showed high AOA performance and in most cases exceeded the standard. The AOA values of the studied compounds are within 49.43–82.16% (concentration of 10-3 mol / l). At a concentration of 10–5 mol / l, the AOA indices of almost all compounds decreased, but exceeded the standard. When the concentration decreased to 10–7 mol / l, the antioxidant properties decreased, but all the compounds showed an activity that exceeded the standard indicator.

Thus, in the study of compounds, it was found that all of them possess antioxidant properties in vitro on the photoinduction model of sodium nitroprusside due to the properties of NO scavengers. When comparing the values of the calculated descriptors with the obtained in vitro data, it was possible to establish the linear dependence of the AOA on the HOMO and LUMO values [5]. During the analysis of the research results, we found that the AOA of the studied compounds is directly dependent on reactive index (Fig. 1). In this regard, it was decided to determine the probable activity of compounds based on linear interpolation.

Fig. 1. The dependence of the AOA from the reactive index

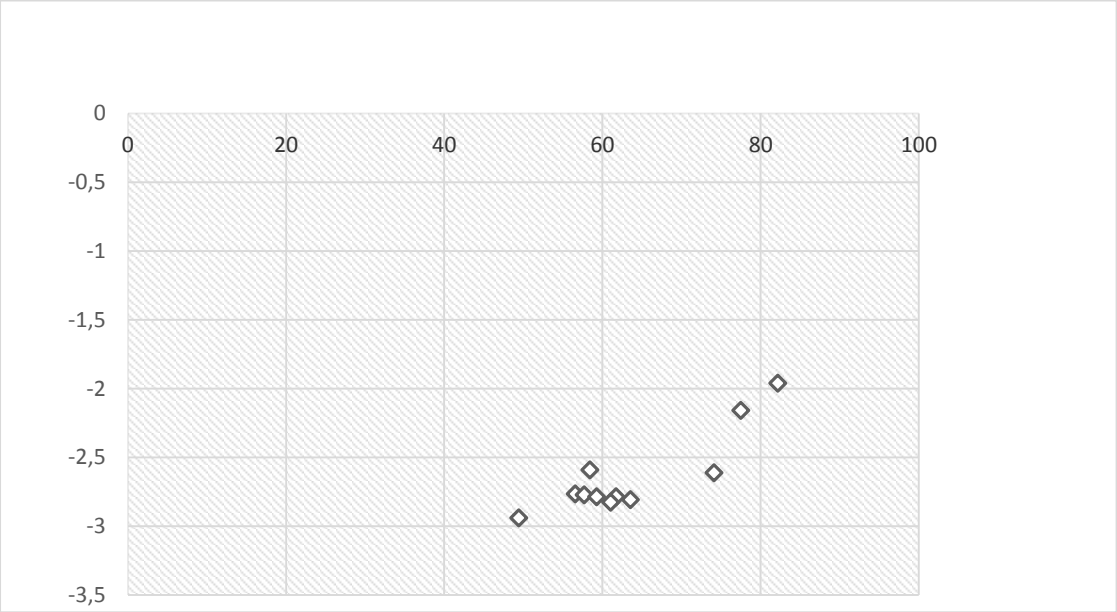


Table 1. Antioxidant activity of test compounds (n = 5) by inhibition of $NO^-$ radical (M±m).

| Compound | $10^{-3}$ mol/l | | $10^{-5}$ mol/l | | $10^{-7}$ mol/l | |
|---|---|---|---|---|---|---|
| | E, M±m | % | E, M±m | % | E, M±m | % |
| 1 | 1,514 ± 0,066[2] | 56,57 | 1,115 ± 0,040[2] | 15,30 | 1,532 ± 0,057[2] | 58,43 |
| 2 | 1,564 ± 0,054[2] | 61,73 | 1,233 ± 0,084[1] | 27,50 | 1,585 ± 0,081[2] | 63,91 |
| 3 | 1,525 ± 0,055[2] | 57,70 | 1,323 ± 0,059[2] | 36,81 | 1,357 ± 0,079[2] | 40,33 |
| 4 | 1,54 ± 0,074[2] | 59,25 | 1,133 ± 0,089 | 17,16 | 1,464 ± 0,08[2] | 51,39 |
| Control | | | 0,967 ± 0,054 | | | |
| 5 | 1,603 ± 0,089[1] | 82,16 | 1,408 ± 0,079[1] | 60,00 | 1,385 ± 0,051[1] | 57,38 |
| 6 | 1,562 ± 0,082[1] | 77,50 | 1,506 ± 0,091[1] | 71,13 | 1,356 ± 0,107[1] | 54,09 |
| 7 | 1,439 ± 0,077[1] | 63,52 | 1,376 ± 0,076[1] | 56,36 | 1,371 ± 0,074[1] | 55,79 |
| 8 | 1,532 ± 0,065[1] | 74,09 | 1,383 ± 0,067[1] | 57,16 | 1,396 ± 0,083[1] | 58,63 |
| Control | | | 0,880 ± 0,024 | | | |
| 9 | 1,532 ± 0,055[2] | 58,43 | 1,072 ± 0,084 | 10,86 | 1,565 ± 0,088[2] | 61,84 |
| 10 | 1,445 ± 0,123[2] | 49,43 | 0,987 ± 0,094 | 2,07 | 1,544 ± 0,093[2] | 59,67 |
| Control | | | 0,967 ± 0,054 | | | |
| 11 | 1,417 ± 0,056[1] | 61,02 | 1,515 ± 0,074[1] | 72,16 | 1,369 ± 0,045[1] | 55,57 |
| Control | | | 0,880 ± 0,024 | | | |
| NAC | 0,901 ± 0,092 | 2,46 | 1,042 ± 0,087 | 18,47 | 0,981 ± 0,074 | 11,53 |
| Control | | | 0,880 ± 0,024 | | | |

Remark: [1] – $p<0.05$ relative to control; [2] – $p<0.01$ relative to control.

**Table 2. Quantum mechanical calculations of xanthinyl-7-acetic acids derivatives**

| **Compound** | E (LUMO), eV | E (HOMO), eV | ω, eV |
|---|---|---|---|
| 1 | -0,662058 | -8,85597 | -2,7640 |
| 2 | -0,621876 | -9,09988 | -2,7869 |
| 3 | -0,664048 | 8,88114 | -2,7719 |
| 4 | -0,617553 | -9,10999 | -2,7855 |
| 5 | 0,175988 | 8,35553 | -1,9605 |
| 6 | -0,166582 | -8,11534 | -2,1572 |
| 7 | -0,825065 | -8,38973 | -2,8062 |
| 8 | -0,683878 | -8,14727 | -2,6123 |
| 9 | -0,551883 | -8,55349 | -2,5903 |
| 10 | -0,848165 | -8,85555 | -2,9398 |
| 11 | -0,738576 | -8,81243 | -2,8246 |

The results can be used to further search for NO scavengers in the azaheterocycle series and use their reactivity index as a marker of antioxidant properties. Experimentally obtained AOA compounds data and descriptor calculations data (HOMO and LUMO) allow us to establish a direct AOA dependence on reactive index. As a result, it is possible to perform the prediction of the AOA on the basis of the linear interpolation method.

Bibliography

1. Belenichev I.F., Cherniy V.I., Nagorn E.A., Pavlov S.V., Bukhtiyarova N.V. Neuroprotection and neuroplasticity.-Kiev: Logos, 2014.-512c.

2. X-ray Study of Energy Derivatives NO-Scavenger Properties from Energy Descriptors / Sergii V. Lev Igor F. Belenichev, Victor P. Ryzhenko1, Olexii A. Ryzhov R. 37-42.

3. Analysis of Influence of Quantum Chemical Descriptors on NO-Scavenger Properties among Xanthine Derivatives / Olexii A. Ryzhov, Victor P. Ryzhenko, Sergii V. Levich, Igor F. Belenichev // Biological Markers and Guided Therapy.-2017.-Vol . 4, № 1.- P . 39 – 48.

4. Rizhenko VP Targeted search for substances in a series of 3-aryl (aralkyl) xanthine having antiradical activity relative to shenii superoxide radical / V.P. Rizhenko, A.A. Rizhov, S.V. Levich, I. F. Belenichev, E. V. Alexandrova // Medical informatics and engineering. - 2016. - № 1. - p . 109 .

5. Ryzhenko V., Belenichev I., Ryzhov O., & Levich, S. (2018). EXPER I MENTAL AND THEORETICAL APPROACHES FOR THE CREATION OF COMPUTER PROGRAMS OF THE SCAVENGERS VIRTUAL SCREENING OF THE AGAIN OF AZAGETEROCYCLES. *Medical Informatics and Engineering.*

6. Nootropics comlex in therapy of chronic cerebral ischemia / I . S. Chekman, I.F . Belenichev, A.V. Demchenko // Science and Innovation. 2014.-№ 10 (4) .- R. 56-68.

7. Formation of combinatorial library hinazolin-4-il-gidra-zoniv s antio to a sedentary activist / I.F. Belenichev, N.O. Nest e Rova, S.I. Kovalenko, O.V. Karpenko // Honey. xand miya. - 2004. - Vol. 6, No. 3. - p. 14-21.

8. Osnovni Roads Ahead approved on rennya active form in CHIN normi that when ishemichnih patologiyah / I.F.Belenichev, YU.I. Gubsky, S.I. Kovalenko, Є.L. Levitz s cue // Sovrem. problems toksikol. - 2004. - №2. - p. 8-16.

9. Research of antioxidant properties of theophyllinyl-7 acetic- acid deriv a tives, / Igor Belenichev, Katherine Aleksandrova, Alexander Shkoda, Sergey Levich, Darja Yurchenko, Nina Buchtiyarova // Oxid Antioxid Med Sci .- 2014 .- Vol. 3, №3 .-P. 187-194

10. New xanthine derivative B-YR-2 as antioxidant modulator of post-stroke cortex neurons in rats / Igor Belenichev, Katherine Aleksandrova, Alexander Shkoda, Sergey Levich, Darja Yurchenko, Nina Buchtiyarova // Elixir Pharmacy. - 2014.-№76.-P.28286-28292

11. Anesthetic antioxidant drug of stasis: N-acetylcysteine / M. Deniz, H. Borman, T. Seyhan, M. Haberal // Burns. - 2013.

- Vol. 39, No. 2. - p. 320–325.

12. Vanin / AF Vanin / AF-Nitrothiols /

Biochemistry (Mosc). - 1998. - Vol. 63, No. 7. - p. 782–793.

13. Estimation of the relationship between the structure of the trihaloacetylazulene and the semiempirical molecular-orbital method (PM5)

their cytotoxicity / M. Ishihara, H. Wakabayashi, N. Motohashi, H. Sakagami // Anticancer Res. - 2010. - Vol. 30, No. 3. - P. 837–842.