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HYBRID ANTIOXIDANTS

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Abstract. The article is a review of the data on synthesis and physiological activity of hybrid antioxidants. The introduction offers an explanation to the fact why, in some cases, it is necessary to add drug molecules with fragments responsible for various properties and aimed at various targets. A large group of hybrid antioxidants comprise stable nitroxyl radicals that behave as antioxidants in free-radical reactions of oxidation. Compounds of this type were synthesized extensively to form a group of antitumor agents. As a rule, the specific (antitumor) activity retained or even increased as compared with the initial compounds (without nitroxyl radicals); the toxicity decreased 5 to 10 times, which made it possible to apply the drug in considerably higher concentrations. There are reported data on nitroxyl derivatives of anthracycline antibiotics, antimetabolites, alkyl ting agents, and the recent results on platinum complexes with nitroxyl fragments. Much attention is given to hindered phenols with "buoyancy" properties, particularly, to biochemical effects, making them promising agents to treat Alzheimer's disease.

Key words: hybrid antioxidant, radical, synthesis, antitumor effect, nitroxyl

1. Introduction

At present, scientists-pharmacologists have to answer the question whether all pharmacologically active compounds should be the medicines with a poly-target effect. The answer to this question is not unambiguous, although the scientists who put it refer to the data that most diseases are associated with changes and defects of various kinds of metabolism; therefore, medicines should not focus on one critical target but on all of them related to a disease.

An alternative to this view is a complex therapy that uses several medicines that may be applied in different concentrations (and not only in relative concentrations determined by the structure), time intervals, solvents, *etc*.

To our opinion, both of these viewpoints are valid; in each separate case a particular approach should be taken to provide the maximum effect for a patient.

In the study on the mechanism of action of bioantioxidants it was determined that there exists an integrated system of correlations between separate indices of cellular metabolism that is modified by antioxidants (AO).

Currently, a great progress was made in studying the physicochemical system of regulation that maintains the level of free-radical reactions, on the one hand, and controls metabolism of membrane lipids and rate of consumption of antioxidants in lipids, on the other hand (Fig. 1) [1, 2].

The components of this system are antioxidants, free radicals, and products of lipids peroxidation (LPO), composition and oxidizability, and the rate of antioxidants utilization.

It was shown that an increase in the antioxidant level results in (i) decreasing of the LPO rate, concentration of oxidation products, and the rate of output of lipids from membranes, (ii) enrichment of membranes with unsaturated lipids, and, correspondingly, (iii) enhancement of oxidizability of lipids. The enhancement of oxidizability, in turn, results in increasing of the rate of consumption of antioxidants and, correspondingly, in subsequent return of the antioxidative activity (AOA) and peroxidation rate to the normal level. An opposite situation is observed with decrease in the AOA concentration, increase in the LPO rate *etc*. It should be noted that variations in the lipid composition and oxidizability cause changes in the fluidity of various layers of membranes. The above parameters affect the activity and kinetic behavior of membrane-bound proteins – enzymes and receptors; therefore, the changes in the LPO rate may not only cause the changes in the membranes structure but also in their functional activity. The existence of this regulation system was determined almost for all intracellular and cell membranes of animals and microorganisms studied. For all normal membranes, similar correlations between the parameters are observed; the difference is in the time of relaxation of the system (from several minutes to days).

The action of any damaging factor on an organism causes changes in the regulation system. Long-term changes may be caused by the following factors: (i) chronic exposures, which do not cause breaks in the connections of the regulation system (in this case the
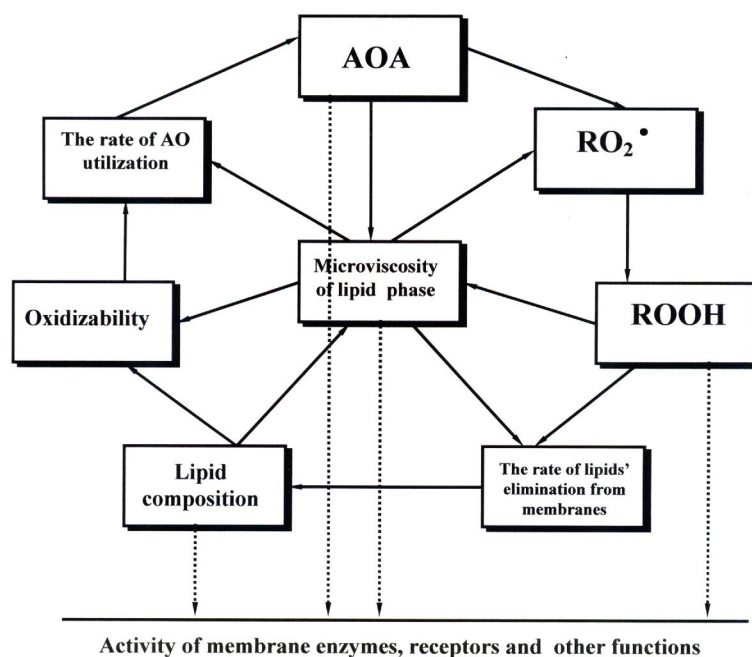
Fig. 1. The scheme of the regulation of lipid peroxidation level in biological membranes:

AOA – antioxidative activity, $RO_2^{\bullet}$ – peroxy-radical, ROOH – hydroxyperoxide

system may return to the normal state after the end of the exposure); (ii) the situation when the effect of a damaging factor is associated with transition to a new level of regulation; and (iii) possible breaks of correlations in the regulation system, which do not permit the system parameters to return to the normal level (in this case, antioxidants may be helpful as a component of combined therapy.) Similar relationships were determined in experimental and clinical studies.

For example, the development of radiation disease is associated with breaks of correlations between the process of peroxidation and oxidizability of lipids [3]. On the background of peroxidation enhancement, lipids should have been enriched with hardly oxidizable fractions; the result would be a reduction in oxidizability and return to the normal state. In reality, an opposite situation is observed: oxidizability increases, which prevents the system from returning to the normal state and decreases the efficiency of antioxidants as radioprotectors. In the course of carcinogenesis, principal disturbances between the lipid composition and activity of membrane-bound enzymes are observed in early periods after of a carcinogen intake [4]. In cases of epileptic attacks in experiments with KM rats, breaks of correlations between the changes in the amount of antioxidants and peroxidation rate were observed [5]. On the background of a higher antioxidative activity, an enhanced level of peroxidation products was

observed. A similar character of disturbances in correlations in the system of regulation of peroxidation was determined for the effect of a synthetic antioxidant on the rats: the system responds by an increase in the AOA and, simultaneously, by enhancement of LPO; the result is a decrease in the normalizing effect of antioxidants.

In case of atherosclerosis, the system functions in the normal mode in the first stage of the disease. The administration of antioxidants to patients in this stage normalizes not only peroxidation but also the lipid composition. In the third stage of the process, there occur breaks of the correlations in the system; therefore, it is necessary to administer, at least, two different medicines to patients: to affect LPO and normalize the lipid composition [6].

Similar effects manifest themselves in cases of tumor growth. In oncology, antioxidants are mainly effective as additional drugs in a combined therapy of patients. In these cases, at the early stages of the disease, the agents are effective only in high doses: they produce a prooxidant effect that is necessary to destroy tumor cells. Their administration in low doses may result in acceleration of the tumor growth. In the late stages of the tumor growth, there is an opposite situation. Antioxidants can reduce toxic effects when applied in low doses [7].

Here, we do not dwell on the causes of breaks in the regulation systems that are specific for each particular

disease. We only emphasize that changes in the LPO rate (increase or decrease) are not specific to any particular pathologic state because changes in the LPO rate are observed almost in all these cases. The specificity manifests itself only at the level of the regulation system as a whole.

Investigation of the regulation system as a whole rather than some particular changes in it makes it possible to determine the cases when monotherapy (with antioxidants) is sufficient and when a combined therapy (with antioxidants in combination with other biologically active substances) is necessary. To a certain extent this requirement may be satisfied by to the synthesis of "hybrid molecules".

2. Results and Discussion

2.1. Hybrid atioxidants on the basis of nitroxyl radical

One of the most promising and important branches in the chemistry of phenol bioantioxidants is the synthesis of hybrid compounds that combine the antioxidant activity with the ability to structural and specific interactions with a biosystem [8]. This type of bioantioxidants incorporates the so-called "buoy"-compounds synthesized on the base of quaternized derivatives of dialkylaminoalkylsubstituted 2,4-2,6-di-*tert*-butylphenols and dialkylaminoalkyl ethers of phenozan acid. For these compounds, a wide spectrum of biological activity was determined: antimicrobial, antiviral, analgetic *etc*. It was also determined that multistep redox and solvation conversions result in a cascade of intermediates with different kinds of the own activity – antioxidative, chelate, ability to incorporate into the charge transfer chain *etc*. In the cascade mechanism of the effect of 2,4-2,6-di-*tert*-butylphenol derivatives, the tendency to formation of heterocyclic compounds that also make a contribution to the biological activity plays a great role. Another important aspect that is in progress now is the synthesis of hybrids of functional di-*tert*-butylphenols and biocompatible macromolecules. In this direction it is possible to reach record values of antioxidative activity of hybrid compounds with wide variations of hydrophobic-hydrophilic relationships and particular structural parameters in solutions [8].

Hybrid antioxidants are extensively used in medical treatment of patients. By hybrid antioxidants we mean molecules that contain in their structure parts responsible for antioxidative properties and molecules fragments responsible for other specific functions.

In most cases the synthesis of hybrid molecules does not yield a polyfunctional structure but results in cross-linking, integration of molecules that possess the activity as antioxidants and those that affect the targets specific for a given disease.

Often constructing molecules involves a task to retain the specific activity of one of the hybrid components and, simultaneously, to reduce the side-effects, the toxicity of the compound in particular. One of the promising ways in this direction is adding nitroxyl radicals to the molecule structure.

The largest groups of hybrid antioxidants synthesized earlier are nitroxyl derivatives of various biologically active substances (BAS). Previously, it was shown that the nitroxyl radical exhibits the properties of antioxidants both in model reactions of oxidation *in vitro* and *in vivo* studies [9, 10]. One of the first among the organic chemists who synthesized nitroxyl derivatives of BAS was Soviet scientist A.B. Shapiro [11]. Since that time nitroxylation of BAS has become of wide use in pharmacology. Most extensively antitumor compounds were nitroxylated. In the article by N.P. Konovalova [12], a list of synthesized and best studied antitumor compounds of the class of antibiotics, antimetabolics, alkylating agents and other compounds containing nitroxyl in the composition is present (*vide* Table 1) [13-18]. It is evident from Table 1 that nitroxyl derivatives are 5 to 10 times less toxic than the initial compounds. The best studied group of compounds comprises nitroxyl derivatives of anthracycline antibiotics. One of the important achievements of chemistry and biochemistry of hybrid antioxidants of this class is the development of emoxyl (ruboxyl) – a nitroxyl derivative of the anthracycline antibiotic – rubomycin [12]. This compound features the advantages of hybrid molecules: along with a high antitumor effectiveness (that is higher than that of the initial compound – rubomycin) its toxicity is lower, particularly cardiotoxicity almost vanished. The compound has acquired new properties that are lacking both in rubomycin and nitroxyl radical [12]. The compound is the most efficient practical advance in this field. It has passed the second stage of clinical tests.
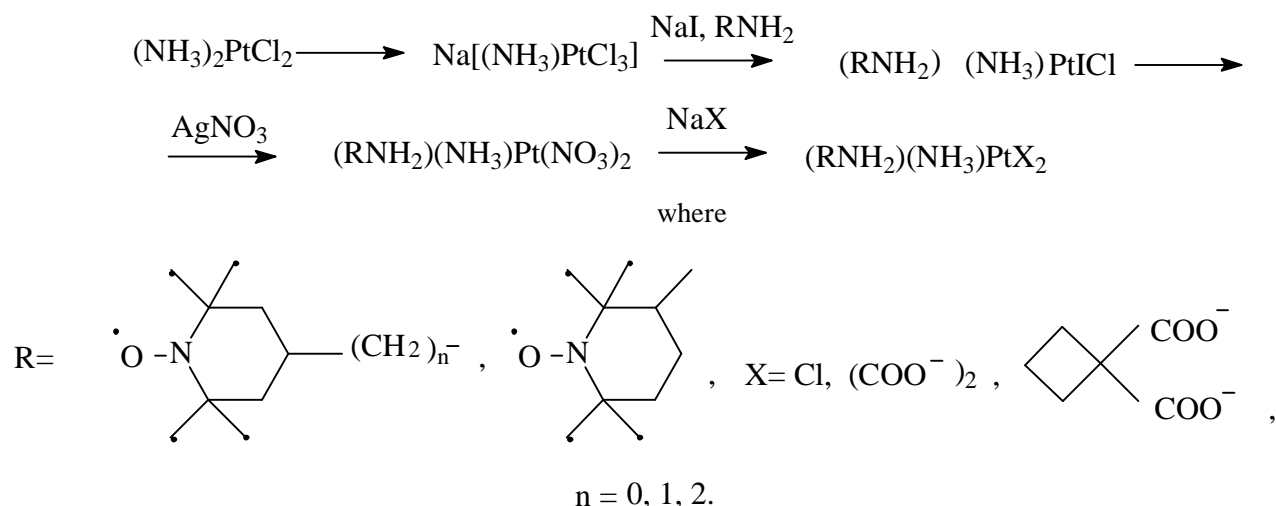
At present, derivatives of platinum compounds have found wide use in chemotherapy of malignant neoplasms. It should be noted that along with high antitumor activity these compounds are highly toxic. Supposedly, the cytotoxic effect and the main side effects (nephro- and ototoxicity and nausea) are related to enhancement of free-radical processes and formation of active oxygen species [O_2^-, $OH^.$] induced in the cell by cisplatin. To produce the antitumor effect, apart from the interaction with the DNA molecule, the enhancement of free-radical reactions is of importance. Therefore, as a rule, decrease in toxicity is associated with decrease in the specific antitumor effect. The development of hybrid molecules made up on the

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base of derivatives of platinum and nitroxyl radical is a solution to this problem: to decrease the toxicity and retain the activity of the compound.

In [19] the data on the synthesis, structure, and biological activity of mixed-ligand complexes of platinum II with aminonitroxyl radicals are present.

Examples of hybrid compounds are antitumor ones made up on the base of mixed-ligand complexes of platinum II and IV that contain antioxidant fragments of the array of amino nitroxyl radicals [19, 20]. The feasibility of preparing these mixed complexes stems from the fact that cisplatin ($[NH_3]_2PtCl_2$) transforms readily into the $Na[(NH_3)PtCl_3]$ complex, which interacts with initial amines on the background of sodium iodide and transforms into the $(RNH_2)(NH_3)PtICl$ complex. The latter complex, when treated with silver nitrate exchanges readily halogen anions for the mobile NO_3^- anion, which permits exchanging them for other anions (Cl^- and anions of dicarboxylic acids).

$$(NH_3)_2PtCl_2 \longrightarrow Na[(NH_3)PtCl_3] \xrightarrow{NaI,\ RNH_2} (RNH_2)\ (NH_3)\,PtICl \longrightarrow$$

$$\xrightarrow{AgNO_3} (RNH_2)(NH_3)Pt(NO_3)_2 \xrightarrow{NaX} (RNH_2)(NH_3)PtX_2$$

where

n = 0, 1, 2.

To obtain mixed-ligand platinum IV complexes, a special method of mild catalytic oxidation of $(RNH_2)(NH_3)PtCl$ by hydrogen peroxide in the presence of tungstate was developed:

$$(RNH_2)(NH_3)PtCl_2 \xrightarrow{H_2O_2/WO_4^-} (R'NH_2)(NH_3)Pt(OH)_2Cl_2$$
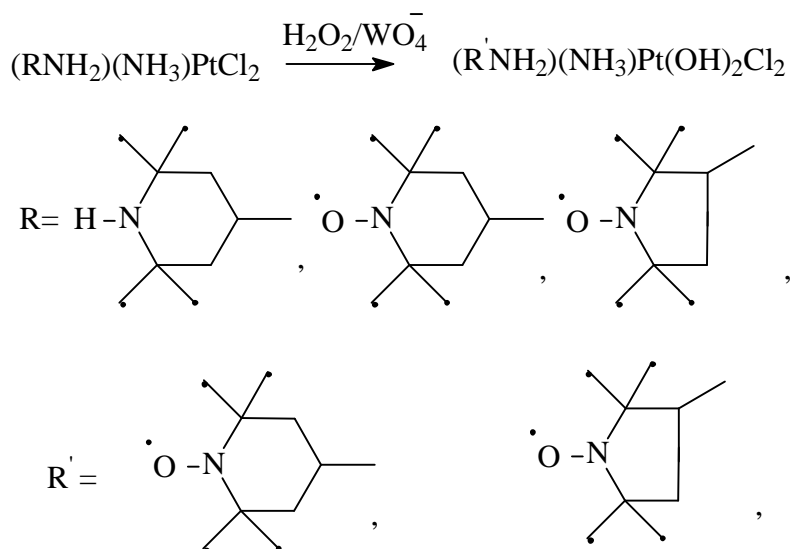
The above methods of synthesis of mixed-ligand complexes of platinum II and IV are simple in implementation and make it possible to obtain target products with the yield of 65–75 %.

The substitution of the ligand ammonia in cisplatin for the fragment of amino nitroxyl radical makes it possible to reduce the toxicity of cisplatin, enhance significantly its antitumor activity, and eliminate the side effects associated with the application of cisplatin.

The complexes obtained were characterized by various models; it was shown that the rate of binding with DNA for the new complexes is comparable with that of cisplatin. At the same time, the effect on the antioxidative properties is opposite: while the initial cisplatin accelerated oxidation in model radical reactions, the platinum–nitroxyl complexes, *vice versa*, inhibited oxidation. From this point of view, it is easy to explain the reduction of toxicity of the synthesized complexes. The results obtained show that free-radical reactions do not contribute much to the antitumor activity of mixed-ligand complexes.

In the recent time great interest was attracted to platinum IV compounds. The specialists in organic chemistry of the Institute of Theoretical Problems of Chemical Physics synthesized complexes of platinum IV with amino nitroxyl radicals [20]. On the experimental model of leukemia P-388 tumor, the complexes produced a high effect on leucosis mice up to complete recovery; the toxicity was decreased 2 to 4 times. The most impressive results were obtained for low doses of cisplatin and platinum IV complexes with amino nitroxyl radicals in case of their combined use in the therapy of leukemia P-388. The survival rate of the leucemic mice was 100 %.

As mentioned above, nitroxylation of antitumor compounds was successful. However, there are other examples of using hybrid compounds with nitroxyl radicals in the molecule.

At the Institute of Problems of Chemical Physics, new biologically active compounds were synthesized – nitroxyl derivatives of azidothymidine of the common formula:
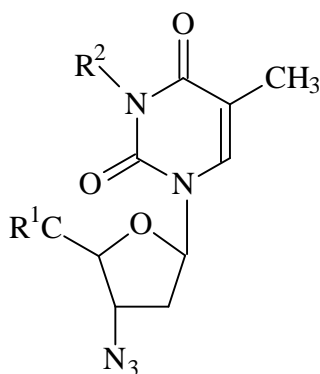
where R^1 is the radical containing a nitroxyl group $> N - O$, and $R^2 = R^1$ or H.

These compounds exhibit the antiviral activity against RNA-containing viruses (virus of human immunodeficiency and virus of vesicular stomatitis) and DNA-containing virus –cytomegalovirus) [21].

It should be noted that hybrid molecules containing antioxidant fragments in the structure inhibit the reproduction of cytomegalovirus whereas other azidothymidine derivatives do not possess this property. With regard to the fact that death of HID patients is caused mainly by diseases induced by cytomegalovirus, it is necessary to emphasize this property of hybrid molecules made up on the base of antioxidant and azidothymidine. Hybrid molecules – ichphans (see below) – also exhibit this property.

2.2. Hybrid molecules on the basis of hindered phenols

Synthesis. As it was mentioned above, new hybrid phenolic antioxidants of the buoyancy-type were developed [8]. These bioantioxidants contain a 2,6-di-*tert*-butyl-4-hydroxyphenyl fragment and a charged "anchor" group with a lipophilic [~$N^+(CH_3)$ R.X^-] substituent ("buoy"). To maintain the antioxidant activity, this "anchor" group should be distanced from the phenyl ring by a bridge fragment, *e.g.* alkylcarbalkoxyl [~$(CH_2)nCOOAlk$].

The synthesis of such kind of hybrid bioantioxidants (III) is depicted in Fig. 2. The initial substances used were commercial 2,6-di-*tert*-butylphenol, methyl ester of (beta-(4-hydroxy-2,6-di-*tert*-butylphenyl)-propionic acid (methylox) and colamine. In the first stage, in the course of the phenolate-ion addition *via* the multiple bond of activated olefin (methylacrylate) or substitution of halogen in methyl-alpha-bromopropionate or methyl ester of alpha-bromophenylacetic acid, methyl esters (I) are formed. The reetherification of the esters performed under conditions of the alkaline catalysis by colamine yields the corresponding esters (II). Finally, the quaternization of the nitrogen atom in the esters (II) by alkylhalides yields the target hybrid bioantioxidants (III).

The presence of the positively charged nitrogen atom in the hybrid molecule makes it possible to localize the antioxidant on the surface of cell membranes and fix it at a certain site by the lipophilic long-chain alkyl fragment (R_l). This structure provides for a targeted localization of the antioxidant and facilitates the suppression of pathological cellular processes responsible for intensification of lipid peroxidation (LPO) and disturbances in the functions of cell membranes.

The hybrid molecule of this structure is an analog of acetylcholine [$CH_3COOCH_2CH_2N^+(CH_3)_3OH^-$], in which the ester bond is formed, instead of acetic acid, by carboxylic acids that contain a 2,6-di-*tert*-butyl-4-hydroxyphenyl fragment. We called these synthetic hybrid bioantioxidants ichphans.
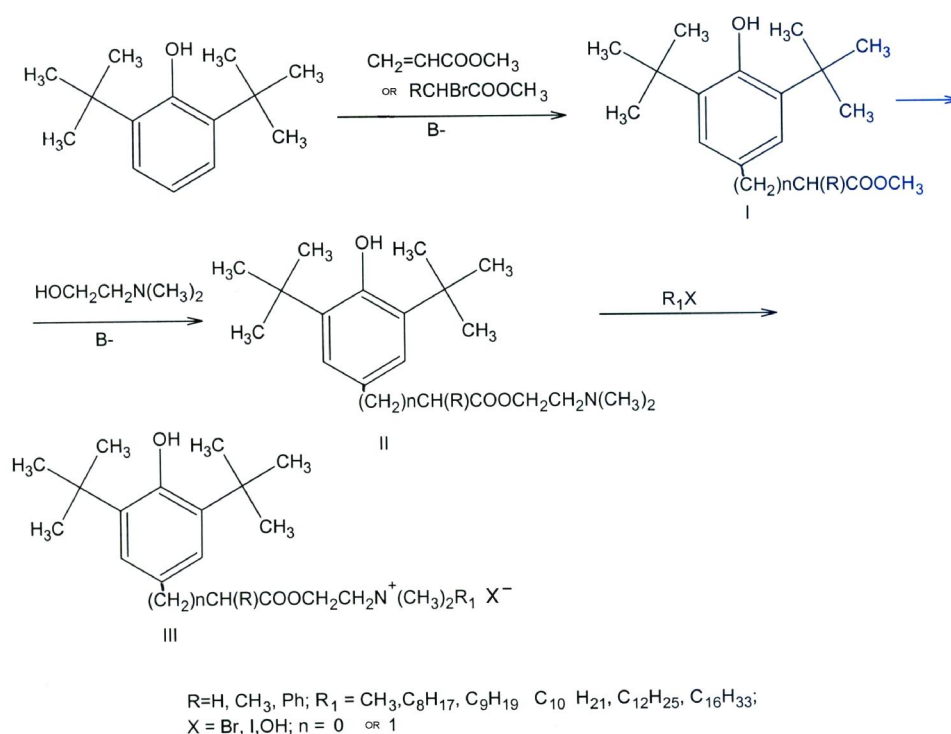
Fig. 2. The scheme of ichphans synthesis

Hybrid antioxidants of new generation as a remedy for correcting structural and functional disorders in cell membranes associated with Alzheimer's disease. It is safe to suggest that the above structure of the hybrid molecule will yield a bioantioxidant with the anticholinesterase effect. In fact, anticholinesterase agents are the most effective therapeutic remedies for Alzheimer's disease (AD); they maintain the acetylcholine level responsible for memory and recognition functions in the disease-damaged segments of brain. On the other hand, the oxidative stress and enhancement of lipid peroxidation (LPO) in cell membranes of brain and in cells of peripheral systems and organs play a significant role in the development of AD [22-29].

Because of the above properties, the antioxidants (AO) may interact with the biological system, in particular with cell membranes; therefore, they may be effective as remedies for curing the Alzheimer's disease.
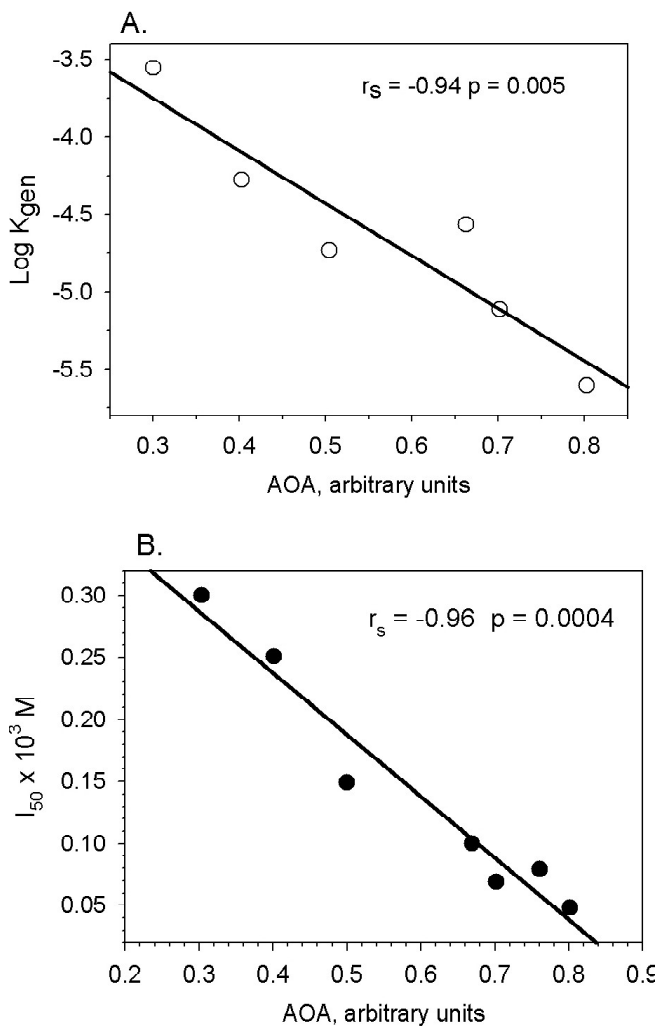
The antioxidant (AO) activity of ichphans. In the studies performed with various oxidation models, the antioxidative properties of ichphans were determined and evaluated quantitatively [8, 30]. The antioxidant activity of the compounds differs depending on the structure of the radicals R and R_1. One of the criteria for assessment of antioxidative properties of ichphans is their ability to inhibit the accumulation of LPO products in the mice brain homogenate under conditions of oxidation by air oxygen [8].

The anticholinesterase activity of ichphans was assessed with regard to soluble and membrane-bound acetylcholinesterase (AChE) of human blood erythrocytes; it was determined from the inhibition constants and influence on the enzyme efficacy. All ichphans behaved as reversible inhibitors of AChE [31-34].
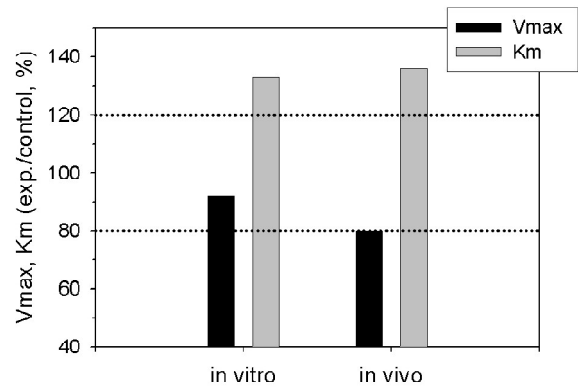
It was found that the new hybrid AO of the ichphans group exhibit the enhanced antioxidantive (in the model of oxidation of homogenate lipids) and anticholinesterase activities as compared with the corresponding values of the parent substances – phenozan and acetylcholine. The addition of the molecule with alkyl substituents on the nitrogen atom with different length of aliphatic chain considerably enhances the antioxidative activity (AOA) and inhibiting effect. With an increase in the length of the carbon chain in the alkyl substituent, the ability of the compounds to inhibit AChE increases. The type of inhibition depends on the alkyl substituent. Although, for the substances studied, the inhibiting effect for the membrane-bound enzyme is by an order of magnitude lower than that for soluble AChE, in both cases, similar relations exist between the structure and inhibiting activity of the compounds [31-34].

A strictly direct correlation between anticholinesterase and antioxidative properties of the ichphans-class compounds was determined; the character of the correlation is also common for membrane-bound and soluble AChE (Fig. 3).
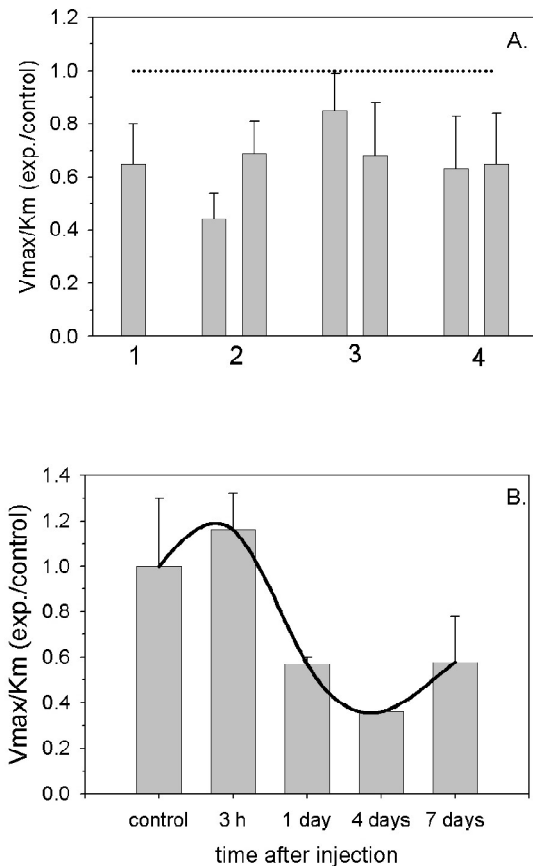
In vivo studies. Based on the results of the *in vitro* studies performed by the criteria of anticholinesterase and antioxidative properties, we chose the optimum compound for subsequent *in vivo* studies. This is a hybrid with the radical $R_1 = C_{10}H_{21}$ hereinafter referred to as ichphan. The further lengthening of the "tail" was associated with an undesirable perturbing effect on membranes; the effect manifested itself by enhancement of the sensitivity of erythrocytes to hemolysis [32]. According to the data published [35], $R_1 = C_{10}H_{21}$ imparts enough hydrophobicity to the compound to pass through the blood-brain barrier (HEB).

Fig. 4. The influence of ichphan on cholinesterase activity of rat brain homogenate *in vitro* and *in vivo*. *In vitro*: after 12 h preincubation with $7.5 \cdot 10^{-4}$ M of the antioxidant (AO). Concentration of homogenate and AO in reaction medium was 0.45 mg/ml and $5.0 \cdot 10^{-6}$ M correspondingly. *In vivo*: 2 h after injection of ichphan ($2.6 \cdot 10^{-6}$ mol/kg)

Fig. 3. The correlation between antioxidative activity of the drugs and their ability to inhibit soluble (A) and membrane-bound (B) AChE of erythrocytes *in vitro*. Points correspond to ichphans with various R and R_1 (see Fig. 2). K_{gen} – inhibitory constant considering both competitive and noncompetitive components of inhibition. I_{50} – the concentration of half-lowering the reaction rate. r_s – Spearman's correlation coefficient

Fig. 5. The influence of ichphan on cholinesterase activity: A – *Vmax/Km* for rat brain homogenate 2 h after intraperitoneal (i/p) injection of ichphan (15 mg/kg) (1), mice brain homogenate (2) 2 h (left bar) and 24 h (right bar), mice brain cytosolic and membrane fractions (3, 4) 45 min (left bar) and 2.5 h (right bar) after i/p injection of the drug (6 mg/kg). B – *Vmax/Km* of erythrocytic cetylcholinesterase after i/p injection of icphan at the dose of 6 mg/kg

The next stage of the studies was to investigate the effect of ichphan injected intraperitoneally to animals. In the study on hydrolysis of acetylthiocholine by a rat brain homogenate (Fig. 4) performed 2 h after the intraperitoneal injection of the compound ($2.6 \cdot 10^{-5}$ mol/kg), we determined a decrease in the reaction rate as compared with the control; the maximum reaction rate *Vmax* decreases, the apparent Michaelis constant *Km* increases. Figure 4 also shows the results of the effect of ichphan on the cholinesterase activity of the homogenate *in vitro*. The effect of ichphan on the kinetic parameters of AChE points to an analogy between the results of the *in vivo* and *in vitro* studies; this is evidence for the fact that this hybrid AO enters brain and inhibits the enzyme.

With real concentrations of acetylcholine, the AChE activity is determined by the *Vmax/Km* ratio ("efficacy"). It is evident from Fig. 5 that the cholinesterase activity of the homogenate, cytosol (soluble cholinesterases), and membrane-bound AChE of a crude fraction of mice brain synaptosomes after the injection of ichphan decrease drastically; the decrease being the lasting one. Figure 5 shows also the effect of injection of ichphan on AChE of blood erythrocytes. It is evident that the inhibiting effect of the compound persists within 7 days after a single injection.

Thus, in view of the effect of ichphan on the AChE activity with regard to its pronounced antioxidant activity and ability to pass through the HEB, the compound may be of great interest as a potential remedy for curing AD.

Effect on the membrane structure. It should be noted that an important factor of AD – oxidative stress – may be not only a source of free radicals that damage cell structures and macromolecules but also a symptom of disturbances in the functions of the system of homeostasis of lipid peroxidation (LPO) (Fig. 1) in biological membranes.

An analysis of the published data [36-49] on changes in the lipid metabolism, composition and structure of the membrane lipid phase, which plays a great role in transmission, processing and storage of information in cell makes it possible to conclude that along with intensification of LPO processes associated with the development of AD enrichment of lipids of cell membranes

by unsaturated compounds and an increase in the fluidity (decrease in the viscosity) of the lipid phase are frequently observed. Thus, an intensification of LPO is accompanied with an increase in the fluidity of the lipid bilayer, which facilitates the oxidation and correspondingly the development of the pathological process. This property of membranes in case of AD makes it impossible to resist the oxidative stress with the aid of the "conventional" phenol-type antioxidants, which, according to the scheme (Fig. 1) will cause further enhancement of the fluidity and aggravate the disease course.

We suggested that addition of the antioxidant molecule with a saturated fatty-acid "tail", which will be incorporated to the membrane, will make the corresponding sites of the membrane more rigid and increase the therapeutic effect of ichphan. Indeed, it is evident from Table 2 that as a result of injection of ichphan to mice, the microviscosity of subsurface membrane regions studied by the ESR technique with the use of spin probes either does not vary or increases, which is a desirable effect. It is particularly important for membranes isolated from a crude synaptosomal fraction because the main symptoms of AD are associated with damages in neuronal receptors.

According to many researchers, one of the AD risk factors is an increased level of cholesterol [50-52]. It should be noted that the content of cholesterol in a rat brain tissue reduced by 40 % within 2 h after injection of 15 mg/kg ichphan. The cholesterol content in a cytoplasm fraction isolated from mice brain 2.5 h after injection of 6 mg/kg ichphan reduced almost by half.

Thus, along with the ability to inhibit the cholinesterase activity, ichphan suppresses the oxidative stress (LPO) and can, unlike the "conventional" phenol-type antioxidant, rigidify the structure of the lipid bilayer of membranes or, at least, prevent from increasing the fluidity. The combination of these properties may be useful for the membrane therapy of the Alzheimer's disease by correcting the pathological disturbance in the system of regulation of homeostasis of lipid peroxidation that participates in the cellular metabolism controlling. A definite contribution to the therapeutic effect of ichphan may be made by a decrease in the level of cholesterol.

Table 2

Microviscosity of membrane lipid phase after intraperitoneal injection of the ichphan

	The changes of microviscosity (% of control)					
	Blood erythrocytes		Brain cell membranes		Brain microsomes	
Groups	Probe 1	Probe 2	Probe 1	Probe 2	Probe 1	Probe 2
45 min	+ 15	-	-	+10	-9	-
150 min	+3	+ 11	-	+5	+32	+8

Note: Probe 1 – 2,2,6, 6-tetramethyl-4-capryloil-hydroxypiperidine-1-oxyl; probe 2 – 5,6-benzo-2,2,6,6-tetramethyl-1,2,3,4-tetrahydro-gamma-carboline-3-oxyl

3. Conclusion

The results obtained show that hybrid antioxidants of the new generation may be regarded as potential remedy for dementias associated with the Alzheimer's disease.

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ГІБРИДНІ АНТИОКСИДАНТИ

Анотація*. Наведені дані із синтезу і фізіологічної активності гібридних антиоксидантів. Вказано, що велика група гібридних антиоксидантів містить стабільні нітроксильні радикали, які можуть слугувати антиоксидантами у вільнорадикальних реакціях окиснення. Сполуки такого типу інтенсивно синтезуються для створення протиракових агентів. Протиракова активність зберігається чи навіть підвищується у порівнянні з вихідними компонентами (без нітроксильних радикалів); токсичність зменшується у 5–10 разів, що дає можливість застосовувати транквілізатори у значно вищих концентраціях. Приведено дані стосовно нітроксильних похідних антрациклінових антибіотиків, антиметаболітів, і платинових комплексів з нітроксильними фрагментами. Значну увагу приділено блокованим фенолам з «плавучими» властивостями, а саме з біохімічним ефектом стосовно хвороби Альцгеймера.*

Ключові слова*: гібридні антиоксиданти, радикал, синтез, антираковий ефект, нітроксил.*