ՀԱՅԱՍՏԱՆԻ ՀԱՆՐԱՊԵՏՈՒԹՅԱՆ ԳԻՏՈՒԹՅՈՒՆՆԵՐԻ
ԱԶԳԱՅԻՆ ԱԿԱԴԵՄԻԱ
НАЦИОНАЛЬНАЯ АКАДЕМИЯ НАУК РЕСПУБЛИКИ АРМЕНИЯ
NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF ARMENIA

Հայաստանի քիմիական հանդես
Химический журнал Армении **74, №1-2, 2021** Chemical Journal of Armenia

SYNTHESIS AND STUDY OF ANTIOXIDANT ACTIVITY OF HYDROCHLORIDES OF SUBSTITUTED PIPERAZINOPROPIOPHENONES

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We have prepared a series of new 1-(4-substituted phenyl)-3-[4-2(4)-substituted phenyl]-2-H(phenyl)-propane-1-ones dihydrochlorides and examined their antioxidant activities. Ketones reacted with paraformaldehyde and 4-[2(4)-substituted phenyl]–piperazin-1-yls in anhydrous ethanol and dioxanes to produce 1-(4-substituted phenyl)-3-[4- 2(4)-substituted phenyl]-2-H(phenyl)-propane-1-ones, which were isolated as thick oily substances and converted into the corresponding hydrochlorides. With the help of the photochemiluminescent method of analysis the antioxidant properties of the compounds obtained have been studied. It is established that some of the synthesized compounds manifest antioxidant and anti-inflammatory activities from weak to slowly expressed.

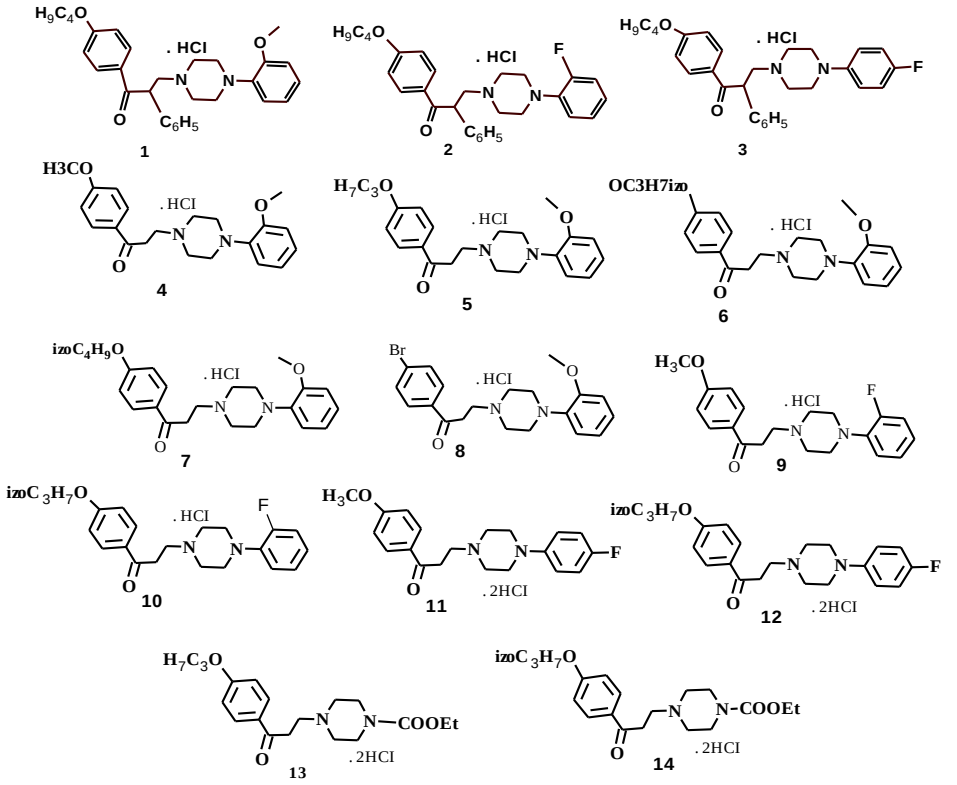
References 8.

It is well known that the development of most diseases such as stress, neuroses, cardiovascular diseases, malignant neoplasms, inflammation of various etiologies are accompanied by the activation of the process of free radical lipid peroxidation. Diseases of the cardiovascular system are referred to as "diseases of free radicals", since in these diseases the development of oxidative stress is noted and oxidative reactions become the main pathogenetic factor in the development of the disease. So, as a result of the induction of lipid peroxidation in the endothelium and membranes of the smooth muscle elements of the vessels, the permeability to calcium increases and hypoxic damage to the myocardium occurs, which leads to its ischemia. Protection of human tissues and organs from free radicals is provided by the endogenous antioxidant system of the body. However, endogenous

antioxidants by no means in all cases can protect a person from the development of oxidative stress. For this reason, the interest of researchers in the search for drugs with antioxidant properties for the prevention and treatment of diseases accompanied by an increase in free-radical oxidation reactions continues.

The aim of this study is to search for pharmacologically active compounds in the series of new β-amino ketones, and in particular, to study the antioxidant activity of hydrochlorides of substituted piperazinopropiophenones – Mannich bases **1-14.**

Scheme



Experimental pharmacological part

Antioxidant and antiradical activity (AOA and ARA) of substituted piperazinopropiophenone hydrochlorides was studied *in vitro* model systems. On the model of ascorbate-dependent Fe(II)-stimulated peroxidation, the AOA of the studied compounds was expressed as a percentage of the extent to which they contributed to a decrease in the formation of one of the end products of peroxidation, malondialdehyde (MDA), compared with control samples that did not contain these compounds. [5]. This method uses the ability to oxidize with atmospheric oxygen in dilute aqueous solutions of oleic acid residues in Tween-80 in the

presence of ferrous iron and ascorbic acid as peroxidation cofactors. To test the AOA/ARA of the studied compounds according to 2 other methods, it was necessary that the substances dissolve well in methanol, which somewhat limited the number of compounds tested. One of these methods is based on the principle of decolorization of alcohol solutions of a stable 2,2-diphenyl-1-picrylhydrazyl (DPPH*) radical under the action of compounds capable of neutralizing the DPPH* radical. ARA of substances is assessed by the decrease in the optical density of the DPPH* solution (λ_{max} = 516 *nm*) when compounds are introduced into the reaction medium in increasing concentrations and is calculated as 1/C50, where C50 is the amount of substance in moles required to reduce the initial concentration of DPPH* by 50% [6]. For comparison, the ARA of butylhydroxytoluene (W218405, ALDRICH), a synthetic analogue of vitamin E, was measured. The photochemiluminescent method was also used to assess the antioxidant capacity of hydrochlorides of substituted piperazinopropiophenones [7]. This method combines very fast photochemical activation of radical formation with highly sensitive luminometric detection: Free radicals are recorded by their reaction with a chemiluminescent substance (luminol) by measuring the emitted light. In the presence of compounds acting as "radical traps", the intensity of photochemiluminescence is suppressed. Software data processing is performed automatically immediately after the samples are entered into the device and the "Measurement" mode is switched on. Determination of the AOA of each sample was carried out at least three times in order to ensure the constancy of the effect obtained. Statistical processing of the obtained results was carried out based on the calculation of the arithmetic mean and standard error.

Results and its discussion

According to the obtained data, all tested β-amino ketone **1-14** hydrochlorides exhibited weak or moderate AOA: relative to the control in their presence, the formation of MDA was suppressed in the range from 6% to 22%. The experimental results showed that the majority of β-amino ketone dihydrochlorides tested by the DPPH* method did not have sufficient activity to reduce the initial concentration of DPPH* in solution to 50%: they reduced the concentration of DPPH* only to 70-80% of the initial, which did not allow calculating the 1/C50 coefficient. However, 3 compounds were identified, in the presence of which the DPPH* solution was intensely discolored, although this required a long time. Based on this, i.e. taking into account the slow kinetics of antioxidant activity, these compounds can be classified as slow antioxidants, according to the proposed classification [8]. The coefficient characterizing the APA of these compounds was 0.99-1.12,

while the APA of butylhydroxytoluene was 2.0. These are the following connections: **8**. APA = 0.99; **5.** APA = 1.19; **7. ;—**ARA = 1.12.

By the photochemiluminescent method, it was revealed that the activity of the dihydrochlorides of substituted piperazinopropiophenones, as well as the control preparation of butylhydroxytoluene, was within the measurable range only in the presence of 10 nanomoles in the reaction medium. The measurements showed that the studied compounds had a weakly expressed activity: 10 nanomoles of most of the substituted piperazinopropiophenone dihydrochlorides tested had the same effect as an average of 0.69 nanomoles of trolox. For comparison: AOA of 10 nanomoles of butylhydroxytoluene was equivalent to the activity of 1.64 ± 0.05 nanomoles of trolox. However, among the studied drugs, compounds were identified the activity of which in suppressing photo-induced chemiluminescence was rather high. These are **7** connections: AOA = 1.35 ± 0.06 c.u. and **2**. AOA = 2.04 ± 0.08 c.u.

Thus, analyzing the results obtained, a definite relationship was revealed between the chemical structure of compounds and their biological activity. Thus, on the basis of experimental data obtained by 3 different methods, it can be concluded that some of the tested compounds have antioxidant properties from weak to moderate severity; among the studied compounds, compounds (**7, 2**) the activity of which in suppressing photo-induced chemiluminescence was quite high. The activity of the compounds under study depends on their structure. Thus, in the amine part of the molecule of compounds (**1-14**), the replacement of 4-(4-substituted phenyl)piperazine by 4-(2-substituted phenyl)piperazine **(2, 5, 7, 8**) leads to the appearance of pronounced antioxidant properties.

Experimental chemistry

IR spectra were recorded on a NICOLET AVATAR 330 FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Mercury VX-300 spectrometer with a resonance frequency of 300.08 *MHz*, in a DMSO + CF_3COOD solution; internal standard – TMS. The melting point of the obtained substances was determined on a Boetius device. The individuality of the obtained compounds was confirmed by TLC on Silufol-254 plates in the system butanol – ethanol – acetic acid – water (8: 2: 1: 3), the developer was iodine vapor, as well as by elemental analysis data.

1-(4-Substituted phenyl)ethan-1-ones (I) and 1-(4-butoxyphenyl)-2-phenylethan-1-one (II) were obtained by the method [1-4].

Hydrochlorides of 1-(4-substituted phenyl)-3-{4-[2(4)-substituted phenyl]piperazin-1-yl}propan-1-ones (1-14). (**General production method**). A mixture of 0.1 *mol* of 1-(4-substituted phenyl)ethanone, 3.3 *g* (0.11 *mol*) of paraformaldehyde, 0.11 *mol* of amine hydrochloride and 5-6

drops of hydrochloric acid (to pH 1) in dry dioxane was heated on water bath for 8-10 *hours* at a temperature of 85-90°C. After distilling off dioxane, the residue was dissolved in water and extracted with ether (3×100 *ml*) to remove the unreacted ketone. To the aqueous layer was added 40% sodium hydroxide solution to pH 8-9 and extracted with ether (3×100 *ml*). The ether extracts were dried over dry Na_2SO_4 and ether was distilled off. To the residue was slowly added dropwise a saturated solution of hydrogen chloride (to pH 1 using universal indicator paper). The precipitate **1-14** was filtered off, recrystallized from abs. acetone.

1-(4-Butoxyphenyl)-3-[4-(2-methoxyphenyl)piperazin-1-yl]-2-phenylpropan-1-one hydrochloride (1). Yield 48%, mp 169-170°C, Rf 0.63. IR spectrum, υ, cm^{-1}: 1680 (C = O). ^{1}H NMR spectrum, δ, ppm 0.97 (t, 3H, J 7.3 CH_3); 1.48 (tp, 2H, J1 7.6, J2 7.4, CH_2); 1.75 (tt, 2H, J1 7.6, J2 6.4, CH_2); 2.81-3.54 (br, 9H, 4CH_2 CH); 3.81 (s, 3H, CH_3); 4.01 (t, 2H, J 6.4, CH_2), 4.01 (br, 1H, CH), 5.94 (br, 1H, CH); 6.79-6.96 (m, 6H, 6CH); 7.17-7.44 (m, 5H, 5CHPh); 8.02 (br.d, 2H, J 8.7, 2CH, 1.80 (br, 1H, HCl). C_{30} H_{37}CI N_2O_3.

1-(4-Butoxyphenyl)-3-[4-(2-fluorophenyl)piperazin-1-yl]-2-phenyl-propan-1-one hydrochloride (2). Yield 50%, mp 164-167°C, Rf 0.85. IR spectrum, υ, cm^{-1}: 1675 (C = O). ^{1}H NMR spectrum, δ, ppm 0.98 (t, 3H, J 7.4, CH_3); 1.48 (m, 2H, CH_2); 1.75 (m, 2H, CH_2); 2.66 (br, 5H); 2.99 (4H); 3.40 (br, 1H); 4.00 (t, 2H, J 6.4, CH_2), 4, 91 (br, 1H, CH), 6, 81 -,. 01 (m, 6H, 6CH, Ar); 7.15 (m, 1H, CH); 7.25 (m, 2H, 2CH); 7.32 (m, 2H, 2CH); 7.25 (m, 2H, 2CH); 7.96 (d, 2H, J 8.8, 2CH), 1.82 (br, 1H, HCl). C_{29} H_{34} CI FN_2O_2.

1-(4-Butoxyphenyl)-3-[4-(4-fluorophenyl)piperazin-1-yl]-2-phenylpropan-1-one hydrochloride (3). Yield 51%, mp 177-178°C, Rf 0.65 IR spectrum, υ, cm^{-1} ;1675 (C = O). ^{1}H NMR spectrum, δ, ppm 0.97 (t, 3H, J 7.3, CH_3); 1.47 (mt, 2H, J_1 7.5, J_2 7.3, CH_2); 1.74 (mt, 2H, J_1 7.5, J_2 6.4, CH_2); 2.70-3.65 (br, 9 H, 4CH_2 CH), 4.00 (t, 2H, J 6.4, CH_2); 4.00 (br, 1H, CH), 5.90 (br, 1H, CH); 6.87-6.97 (m, 6H, C_6H_4, 2CH); 7.20 (br.t, 1H, J 7.5, CH); 7.29 (br.t, 2H, J 7.5, 2CH); 7.40 (br.d, 2H, J 7.7, 2CH); 8.02 (d, 2H, J 8.7, 2CH), 1.81 (br, 1H, HCl). $C_{29}H_{34}$ CI F N_2 O_2. C_{29} H_{34} CI F N_2 O_2.

1-(4-Methoxyphenyl)-3-[4-(2-methoxyphenyl)piperazin-1-yl]propan-1-one hydro chloride (4). Yield 55%, mp 181-183°C, Rf 0.56. IR spectrum, n, cm^{-1}: 1675 (C = O). ^{1}H NMR spectrum, δ, ppm 3.34 (br, 2H, CH_2), 3.43-3.54 (m, 6H, 3CH_2), 3.67 (d br., 2H, J 11.5, CH_2); 3.78 (t, 2H, J 7.5, CH_2); 3.87 (s, 6H, 2CH_3); 4.99 (br, 1H, HCl). 6.86-7.00 (m, 4H, 4CH); 7.00 (d, 2H, J 8.8, 2CH); 7.99 (d, 2H, J 8.8, 2CH); 11.80 (br, 1H, HCl). $C_{21}H_{27}CIN_2$ O_3.

3-[4-(2-Methoxyphenyl)piperazin-1-yl]-1-(4-propoxyphenyl)propan-1-one hydro chloride (5). Yield 56%, mp 183-185°C, Rf 0.56. IR spectrum, υ, cm^{-1}: 1680 (C = O). ^{1}H NMR spectrum, d, ppm 1.05 (t, 3H, J 7.4, CH_3); 1.81 (br.ss, 2H, J 7.0, CH_2); 3.25 (br, 4H, N $(CH_2)_2$); 3.49 (br, 4H, N

$(CH_2)_2$); 3.61 (br, 2H, CH_2); 3.68 (br.t, 2H, J 7.5, CH_2); 3.84 (s, 3H, CH_3); 4.03 (t, 2H, J 6.5); 6.86-7.00 (m, 4H, C_6 H_4); 7.00 (d, 2H, J 8.8, 2CH); 7.99 (d, 2H, J 8.8, 2CH); 1, .80 (br, 1H, HCl). $C_{23}H_{31}ClN_2O_3$.

1-(4-Isopropoxyphenyl)-3-[4-(2-methoxyphenyl)piperazin-1-yl]propan-1-one hydro chloride (6). Yield 52%, mp 186-188°C, Rf 0.54. IR spectrum, υ, cm^{-1}: 1670 (C = O). ^{1}H NMR spectrum, δ, ppm 1.34 (d, 6H, J 6.0, $2CH_3$); 3.25 (br, 4H, $2CH_2$); 3.49 (br, 4H, $2CH_2$); 3.61 (br, 2H, $2CH_2$), 3.67 (br.t, 2H, J 7.5, CH_2); 3.84 (s, 3H, CH_3); 4.75 (sp, 1H, J 6.0, CH); 6.86-7.00 (m, 4H, 4CH); 7.00 d, 2H, J 8.8, CH); 8.00 (d, 2H, J 8.8, 2CH); 12.58 (br, H, HCl). $C_{23}H_{31}ClN_2O_3$.

1-(4-Isobutoxyphenyl)-3-[4-(2-methoxyphenyl)piperazin-1-yl]propan-1-one hydro chloride (7). Yield 49%, mp 192-193°C, Rf 0.54. IR spectrum, υ, cm^{-1}: 1680 (C=O). ^{1}H NMR spectrum, δ, ppm 1.05 (d, 6H, J 6.0, $2CH_3$); 3.25 (br, 2H, CH_2); 3.34 (m, 2H, CH_2); 3.43-3.54 (m, 6H, $3CH_2$); 3.67 (d br, 2H, J 11.5, CH_2); 3.78 (t, 2H, J 7.4, CH_2); 3.87 (s, 3H, CH_3); 4.75 (cn, H, CH); 6.86-6.94 (m, 2H, 2CH); 7.03 (ddd, 1H, J1 8.5, J2 7.1, J3 1.6, CH); 7.10 (dd, 1H, J1 7.9, J2 1.6, CH); 7.67 (d, 2H, J 8.5, 2CH); 7.98 (d, 2H, J 8.5, 2CH); 9.72 (br, 1H, HCl); 11.96 (br, 1H, HCl). $C_{24}H_{34}Cl_2N_2O_3$.

1-(4-Bromophenyl)-3-[4-(2-methoxyphenyl)piperazin-1-yl]propan-1-one hydrochloride (8). Yield 40%, mp 193-195°C, Rf 0.54. IR spectrum, υ, cm^{-1}: 1680 (C = O). ^{1}H NMR spectrum, δ, ppm 3.34 (m, 2H, CH_2); 3.43-3.54 (m, 6H, $3CH_2$); 3.67 (br.d, 2H, J1 1.5, CH_2); 3.78 (t, 2H, J 7.4, CH_2); 3.87 (s, 3H, CH_3); 6.86-6.94 (m, 2H, 2CH), 7.03 (ddd, 1H, J1 8.5, J2 7.1, J3 1.6, CH); 7.10 (dd, 1H, J1 7.9, J2 1.6, CH); 7.67 (d, 2H, J 8.5, 2CH); 7.98 (d, 2H, J 8.5, 2CH); 12.44 (br, 1H, HCl). C_{20} H_{24} CI BrN_2 O_2.

3-[4-(2-Fluorophenyl)piperazin-1-yl]-1-(4-methoxyphenyl)propan-1-one hydrochloride (9). Yield 58%, mp 202-205°C, Rf 0.55. IR spectrum, υ, cm^{-1}: 1660 (C = O). ^{1}H NMR spectrum, d, ppm 3.25 (br, 4H, $2CH_2$), 3.49 (br, 4H, $2CH_2$), 3.62 (br, 2H, CH_2), 3.69 (br.t, 2H, J 7.5, CH_2) ; 3.84 (s, 3H, CH_3); 6.98-7.03 (m, 4H, 4CH); 7.03 (d, 2H, J 8.8, 2CH); 8.00 (d, 2H, J 8.8, 2CH); 11, 80 (br, 1H, HCl). C_{20} H_{24} CI FN_2 O_2.

3-[4-(2-Fluorophenyl)piperazin-1-yl]-1-(4-isopropoxyphenyl)propan-1-one hydrochloride (10). Yield 48%, mp 190-191°C, Rf 0.55. IR spectrum, υ, cm^{-1}: 1680 (C = O). ^{1}H NMR spectrum, δ, ppm 1.34 (d, 6H, J 6.0, 2CH); 3.20-3.70 (m, 12H, $6CH_2$); 4.75 (sp, 1H, J 6.0, CH); 6.98 (d, 2H, J 8.9, 2CH); 6.95-7.15 (m, 4H, C_6 H_4); 7.98 (d, 2H, J 8.9, 2CH); 11.78 (br, 1H, HCl). C_{22} H_{28} CI FN_2 O_2.

3-[4-(4-Fluorophenyl)piperazin-1-yl]-1-(4-methoxyphenyl)propan-1-one dihydro chloride (11). Yield 56%, mp 198-199°C, Rf 0.54. IR spectrum, υ, cm^{-1}: 1670 (C = O). ^{1}H NMR spectrum, d, ppm 3.10-3.78 (br, 12H, 6 CH_2); 3.84 (s, 3H, CH_3); 6.86-7.29 (m, 8H, 8CH); 8.00 (d, 2H, J 8.9, 2CH); 9.72 (br, 1H, HCl); 11.96 (br, 1H, HCl). C_{20} H_{25} CI_2 FN_2 O_2.

3-[4-(4-Fluorophenyl)piperazin-1-yl]-1-(4-isopropoxyphenyl)propan-1-one dihydrochloride (12). The yield is 52%. mp 187-189°C. Rf 0.54. IR spectrum, υ, cm^{-1}: 1670 (C = O). ^{1}H NMR spectrum; d, ppm 1.34 (d, 6H, J 6.0, $2CH_3$), 3.10-3.78 (m, 12H, $6CH_2$), 6.86-7.29 (m, 8H, 8CH); 9.72 (br, 1H, HCl); 11.96 (br, 1H, HCl). $C_{22}H_{29}ClFN_2O_2$.

4-[3-oxo-3-(4-propoxyphenyl)propyl]piperazine-1-carboxylic acid ethyl ester dihydrochloride (13). Yield 42%, mp 185-187°C, Rf 0.54. IR spectrum, υ, cm^{-1}: 1660 (C = O), 1700 (COO). ^{1}H NMR spectrum, d, ppm 1.05 (t, 3H, J 7.4, CH_3); 1.26 (t, 3H, J 7.1, CH_3); 1.81 (br.ss, 2H, J 7.0, CH_2); 3.41 (br.t, 2H, J 7.2, CH_2); 3.50 (br, 4H, $2CH_2$); 3.63 (br.t, 2H, J 7.2, CH_2); 4.03 (t, 2H, J 6.5, CH_2); 4.10 (q, 2H, J 7.1, CH_2); 6.99 (d, 2H, J 8.8, 2CH); 7.97 (d, 2H, J 8.8, 2CH); 11.87 (br, 1H, HCl). $C_{19}H_{29}ClN_2O_4$.

4-[3-(4-isopropoxyphenyl)-3-oxopropyl]piperazine-1-carboxylic acid ethyl ester dihydrochloride (14). Yield 45%, mp 182-184°C, Rf 0.55. IR spectrum, υ, cm^{-1}: 1660 (C=O), 1700 (COO). ^{1}H NMR spectrum, d, ppm 1.15 (t, 3H, J 7.4, CH_3); 1.34 (d, 6H, J 6.0, $2CH_3$); 3.41 (br.t, 2H, J 7.0, CH_2); 3.50 (br.t, 4H, CH_2); 3.63 (br.t, 2H, J 7.2, CH_2); 4.03 (t, 2H, J 6.5, CH_2); 4.10 (q, 2H, J 7.1, CH_2); 6.99 (d, 2H, J 8.8, 2CH); 7.97 (d, 2H, J 8.8, 2CH); 11.87 (br, 1H, HCl); 12.68 (br, 1H, HCl). $C_{19}H_{30}Cl_2N_2O_2$.

ՄԱՆՆԻԽԻ ՀԻՄՔԵՐԻ ՏԵՂԱԿԱԼՎԱԾ ՊԻՊԵՐԱԶԻՆԱՊՐՈՊԻՈՖԵՆՈՆՆԵՐԻ ՀԻԴՐՈՔԼՈՐԻԴՆԵՐԻ ՍԻՆԹԵԶԸ ԵՎ ՀԱԿԱՕՔՍԻԴԱՆՏԱՅԻՆ ԱԿՏԻՎՈՒԹՅԱՆ ՈՒՍՈՒՄՆԱՍԻՐՈՒԹՅՈՒՆՆԵՐԸ

Ա. Ղ. ԻՍԱԽԱՆՅԱՆ, Լ. Ա. ՎԱՐԴԵՎԱՆՅԱՆ, Ն. Ջ. ՂԱԿՈԲՅԱՆ, Ջ. Ա. ՂՈՎԱՍՅԱՆ, Ռ. Պ. ՄԽԻԹԱՐՅԱՆ և Ղ. Ա. ՓԱՆՈՍՅԱՆ

Տեղակալված ացետոֆենոնների և էթանոնների, պարաֆորմալդեհիդի և տեղակալված ֆենիլպիպերազինների փոխազդեցությամբ, ամինամեթիլացման ռեակցիայով, խլֆթեզվել են 1-(4-տեղակալված ֆենիլ)-3-[4-[2(4)-տեղակալված ֆենիլ]-պիպերազին-1-իլ]-2-H-(ֆենիլ)պրոպան-1-ոնները և դրանց հիդրոքլորիդները: Ուսումնասիրվել է վերջիններիս հակաօքսիդանտային ակտիվությունը: Հայտնաբերվել է, որ որոշ միացություններ օժտված են միջին ուժգնության հակաօքսիդանտային ակտիվությամբ: Հաստատվել է, որ ակտիվության ի հայտ գալը պայմանավորված է հետազոտվող միացության կառուցվածքի փոփոխությունից:

СИНТЕЗ И ИЗУЧЕНИЕ АНТИОКСИДАНТНОЙ АКТИВНОСТИ ГИДРОХЛОРИДОВ ЗАМЕЩЕННЫХ ПИПЕРАЗИНОПРОПИОФЕНОНОВ

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Представлен синтез серии новых 1- (4-замещенных фенил)-3-[4-2(4)-замещенных фенил] -2-Н(фенил)пропан-1-онов и их гидрохлоридов. Исследована их антиоксидантная активность. Пиперазинопропиофеноны получены реакцией замещенных кетонов с параформальдегидом и 4-[2(4)-замещенных фенил]пиперазинами в безводном этаноле. Полученные 1-(4-замещенные фенил)-3-{4-[2(4)-замещенные фенил]пиперазин-1-ил}пропан-1-оны выделены в виде жирных маслянистых веществ и превращены в соответствующие гидрохлориды, которые являются белыми кристаллическими веществами. С помощью фотохемилюминесцентного метода анализа изучены антиоксидантные свойства полученных соединений. Установлено, что некоторые из синтезированных соединений проявляют антиоксидантную активность со слабой и умеренно выраженной активностью. Выявлено, что проявление активности зависит от изменения структуры исследуемого соединения.

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