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PHYSICO-CHEMICAL CHARACTERISTICS OF NEW PYRROLIDINE-2,5-DIONE DERIVATIVES AND COMPARATIVE EVALUATION OF THEIR ANTICONVULSANT PROPERTIES

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The series of pyrrolidine-2,5-dione derivatives, including N-aryl and N-arylaminomethyl analogs, few of which have anticonvulsant properties, have been synthesized and their structure has been confirmed with instrumental analytical methods. The data of analyses are presented in this article.

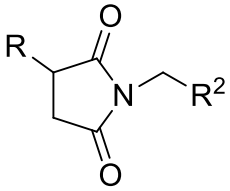
References 16.

Introduction

A large number of publications on the search for new substances possessing the anticonvulsant action confirm the fact that treatment of epilepsy is still a topical problem and clinicians today do not dispose a sufficient arsenal of highly effective drugs devoid of any substantial undesired effects. This is why a need for newer antiepileptic drugs is obvious. Several classes of structurally unrelated organic compounds are used in therapy of this neurological disorder, but they all have certain drawbacks [1]. Earlier a series of 3-(4-alkoxyphenyl)pyrrolidine-2,5-diones were synthesized in Mnjoyan Institute of Fine Organic Chemistry (Yerevan, Armenia) [2], and 4-isopropoxyphenyl analog was licensed in the former USSR as an efficacious antiepileptic drug (Pufemid) [2,3]. Moreover, it has been shown that this compound significantly enhanced the anticonvulsant action of phenytoin and valproate in the mouse seizure model, hence it may find potential application also in polytherapy of epilepsy [4].

With the purpose of searching for the influence of additional aryl residue on its anticonvulsant properties a series of N-aryl (**2-14**), N-hydroxymethyl (**15**), N-morpholinomethyl (**16**), and N-arylaminomethyl (**17-25**) derivatives were synthesized.

1 – 14



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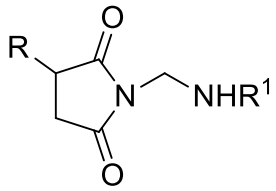

17 - 25

R = 4-$(CH_3)_2CHO$-C_6H_4; R^1 = H (**1**), C_6H_5 (**2, 17**), 4-CH_3O-C_6H_4 (**3**), 4-$CH_3C(O)$-C_6H_4 (**4, 18**), 4-$(CH_3)_2N$-C_6H_4 (**5**), 3-Br-C_6H_4 (**6, 19**), 3-HOOC-CH=CH-C_6H_4 (**7, 20**), 2-HOOC-C_6H_4 (**8, 21**), 3-HOOC-C_6H_4 (**9, 22**), 4-HOOC-C_6H_4(**10, 23**), 4-C_2H_5OOC-C_6H_4 (**11, 24**), 3-HOOC-4-HO-C_6H_3 (**12**), 2,4-NO_2-C_6H_3-NH (**13**), 4-[2-F-C_6H_4-C(O)NH]-C_6H_4 (**14, 25**); R^2 = OH (**15**), $N(CH_2CH_2)_2O$ (**16**).

Results and Discussion

All the synthesized 3-(4′-iso-propoxyphenyl)pyrrolidine-2,5-dione N-substituted derivatives were evaluated for their anticonvulsant properties *in vivo* screening tests in rodents. The screening has demonstrated the folowing: introduction of phenyl and substituted phenyl ring in position 1 of precursor **1** results in the complete disappearance of tested activity except for **4**. The replacement of hydrogen at N atom of imide ring by hydroxymethyl group (**15**) preserves bioactivity. Seven derivatives, namely from the class of Mannich bases (**16**, **17**, **19**, **21-24**) were determined as having anticonvulsant potency. Data of biotests have been represented in [5-12]. The studied compounds with respect to their anticonvulsant potency in the maximal electroshock-induced seizure threshold model in mice test can be arranged as follows: **21** >**15** >**17** > **22** >**16** > **1** >**23** > **4** >**19** >**24** [12].

Thus obtained results confirm that research in the class of pyrrolidine-2,5-diones with the aim of creating new compounds with anticonvulsant properties remains relevant.

Experimental Section

Materials and methods

All chemicals used were of analytical or reagent grade. Melting points were determined on a Boetius PHMK 76/0904 hot stage microscope (GDR) and are uncorrected. Infrared spectra were obtained in Nujol on a spectrometer. ^{1}H NMR spectra were recorded on a Varian Mercury-300

spectrometer, operating at 300 *MHz*; chemical shifts are reported in δ values (ppm) relative to tetramethylsilane as internal standard. Coupling constants (*J* values) are given in Hertz (Hz). The solvents mixture was DMSO-d_6/CCl_4, 1:3; the signals are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), p (pentet), m (multiplet), br (broad). Analytical TLC was used to check the purity of products and performed on Silasorb 600 silica gel (5 μ) (Czech Republic) glass-backed plates developed in chloroform-hexane-ethanol, 2:2:0.1 (system A), benzene-AcOH-H_2O, 7:3:1 (upper layer) (system B). Compounds were detected stained with I_2 (iodine), spraying with a 5% solution of phosphomolybdic acid in ethanol followed by heating at 80-90^{o}C during 5 *min*; if there is a free carboxyl group in a molecule, Bromocresol Purple indicator (as water solution spray) was also used.

Homogeneity of all final substances was checked by thin layer chromatography (TLC), purity by elemental analysis, and their structure was confirmed based on data of IR and ^{1}H NMR spectroscopy. Each sample tested by TLC was detected on chromatograms as a single spot. The analytical samples gave combustion values for carbon, hydrogen, nitrogen and when needed halogen within ±0.4% of the theoretical values. IR spectra contained all characteristic absorption bands attributable to succinimide [13-15] and benzene rings and other fragments. ^{1}H NMR spectra of all compounds were consistent with the assigned structures.

All compounds were synthesized from isopropoxyphenylsuccinic acid according to the scheme as shown in [12].

General procedure for the syntheses of compounds 3-14. The mixture of 3-(4-isopropoxy-phenyl)-succinic acid (0.012 *mol*) and acetic anhydride (10 *ml*) was heated for 6 *h* at 100^{o}C and excess of acetic anhydride and acetic acid formed was removed at a reduced pressure. To a residue primary amine (0.012 *mol*) and glacial acetic acid (7 *ml*) were added and the mixture was refluxed for 2-3 *h*. The product precipitated on cooling was filtered, washed by a small volume of acetic acid, water, dried and recrystallized. If no precipitate was on cooling of the reaction mixture, the latter was either concentrated till solid appeared or evaporated to dryness in a rotary evaporator under a reduced pressure. The residue was recrystallized with addition of activated charcoal (Norit).

3-(4-Isopropoxyphenyl)pyrrolidine-2,5-dione monohydrate (1) was prepared as described in [2].

3-(4-Isopropoxyphenyl)-1-phenylpyrrolidine-2,5-dione (2) was synthesized from 3-(4-isopropoxyphenylsuccinic acid and 1,3-diphenylurea according to [16]. Cream-coloured scaly crystals. Yield: 83%, mp. 129-130 ^{o}C (ethanol). R_f 0.90 (A). IR, ν, cm^{-1}: 1784, 1707 (C=O), 1609, 1596, 1512, 1463 (C=C), 1377, 1365 (i-Pr). ^{1}H NMR: 1.33 [d, ^{3}J=6.0 Hz, 6H, (C**H**$_3$)$_2$CH], 2.84 [dd, ^{2}J=18.0 Hz, ^{3}J=5.2 Hz, 1H, C(O)-C**H**$_a$-CH], 3.31 [dd,

^{2}J=18.0 Hz, ^{3}J=9.6 Hz, 1H, C(O)-C**H**$_b$-CH], 4.18 (dd, ^{3}J=9.6 Hz, ^{3}J=5.2 Hz, 1H, Ph-C**H**), 4.56 (sp, ^{3}J=6.0 Hz, 1H, O-CH) 6.84, 7.23, 7.30-7.50 (m, m, m, 2H, 2H, 5H resp., arom.). Found, %: C 73.54; H 6.33; N 4.79. $C_{19}H_{19}NO_3$. Calculated, %: C 73.77; H 6.19; N 4.53.

3-(4-Isopropoxyphenyl)-1-(4-methoxyphenyl)pyrrolidine-2,5-dione (**3**) was synthesized from anhydride and *p*-anisidine. White scaly crystals. Yield: 75%, mp 171ºC (gl. AcOH). R_f 0.84 (A). IR, ν, cm^{-1}: 1775, 1702 (C=O), 1608, 1513, 1463 (C=C). ^{1}H NMR: 1.32 [d, J=6.0, 6H, (C**H**$_3$)$_2$CH], 2.81 (dd, ^{1}J=18.0 Hz, ^{2}J=5.2 Hz, 1H, C**H**$_a$-CH), 3.28 (dd, ^{1}J=18.0 Hz, ^{2}J=9.6 Hz, C**H**$_b$-CH), 3.83 (s, 3H, OCH_3), 4.14 (dd, ^{1}J=9.6 Hz, ^{2}J=5.2 Hz, 1H, CH_2-C**H**), 4.55 (sp, J=6.0 Hz, 1H, O-CH), 6.83, 6.96 (m, m, 2H, 2H, O-C_6H_4), 7.20, 7.21 (m, m, 2H, 2H, N-C_6H_4-O). Found, %: C 71.05; H 6.02; N 4.44. $C_{20}H_{21}NO_4$. Calculated, %: C 70.78; H 6.24; N 4.13.

1-(4-Acetylphenyl)-3-(4-isopropoxyphenyl)pyrrolidine-2,5-dione (**4**) was synthesized from anhydride and 4′-aminoacetophenone. White bright scaly crystals. Yield: 60%, mp 199-201ºC (gl. AcOH). R_f 0.66 (A). IR, ν, cm^{-1}: 1777, 1707 (C=O imide), 1691 (C=O ketone), 1612, 1600, 1579, 1514, 1474 (C=C), 1377, 1352 (i-Pr). ^{1}H NMR: 1.32 [d, ^{3}J=6.0 Hz, 6H, (C**H**$_3$)$_2$CH], 2.61 [s, 3H, CH_3-C(O)], 2.87 [dd, ^{2}J=18.0 Hz, ^{3}J=5.4 Hz, 1H, C(O)-C**H**$_a$-CH], 3.33 [dd, ^{2}J=18.0 Hz, ^{3}J=9.6 Hz, 1H, C(O)-C**H**$_b$-CH], 4.21 (dd, ^{3}J=9.6 Hz, ^{3}J=5.4 Hz, 1H, C**H**-CH_2), 4.56 (sp, ^{3}J=6.0 Hz, 1H, O-CH), 6.84, 7.24 (m, m, 2H, 2H, O-C_6H_4), 7.49, 8.04 (m, m, 2H, 2H, N-C_6H_4). Found, %: 71.61; H 6.40; N 4.12. $C_{21}H_{21}NO_4$. Calculated, %: C 71.78; H 6.03; N 3.99.

1-(4-Dimethylaminophenyl)-3-(4-isopropoxyphenyl)pyrrolidine-2,5-dione (**5**) was synthesized from anhydride and N,N-dimethyl-1,4-phenylenediamine. Cream-coloured bright scaly crystals. Yield: 58%, mp 179-180ºC (i-PrOH – dioxane, 3:1). R_f 0.83 (A). IR, ν, cm^{-1}: 1786, 1704 (C=O), 1609, 1580, 1521, 1511, 1465 (C=C), 1377, 1348 (i-Pr). ^{1}H NMR: 1.32 [d, ^{3}J=6.0 Hz, 6H, (C**H**$_3$)$_2$CH], 2.78 (dd, ^{2}J=17.9 Hz, ^{3}J=5.1 Hz, 1H, C**H**$_a$-CH), 3.00 [s, 6H, N(CH_3)$_2$], 3.26 [dd, ^{2}J=17.9 Hz, ^{3}J=9.6, 1H, C**H**$_b$-CH), 4.12 [dd, ^{3}J=9.6 Hz, ^{3}J=5.1 Hz, 1H, CH_2-C**H**], 4.56 (sp, ^{3}J=6.0 Hz, 1H, O-CH**),** 6.73, 6.83 (m, m, 2H, 2H, O-C_6H_4), 7.07, 7.21 (m, m, 2H, 2H, N-C_6H_4). Found, %: 71.44; H 6.54; N 7.71. $C_{21}H_{24}N_2O_3$. Calculated, %: 71.57; H 6.86; N 7.95.

1-(3-Bromophenyl)-3-(4-isopropoxyphenyl)pyrrolidine-2,5-dione (**6**) was synthesized from anhydride and 3-bromoaniline. Light-yellow powdery crystals. Yield: 55%, mp 124.5-125.5ºC (ethanol). R_f 0.90 (A). IR, ν, cm^{-1}: 1779, 1708 (C=O), 1610, 1573, 1512, 1463 (C=C), 1376, 1366 sh. (i-Pr). ^{1}H NMR: 1.32 [d, ^{3}J=6.0 Hz, 6H, (C**H**$_3$)$_2$CH], 2.84 (dd, ^{2}J=18.0 Hz, ^{3}J=5.4 Hz, 1H, C**H**$_a$-CH), 3.30 (dd, ^{2}J=18.0 Hz, ^{3}J=9.6 Hz, 1H, C**H**$_b$-CH), 45.18 (dd, ^{3}J=9.6 Hz, ^{3}J=5.4 Hz, 1H, CH_2-C**H**), 4.55 (sp, ^{3}J=6.0, 1H, O-CH), 6.83, 7.23 (m, m, 2H, 2H, O-C_6H_4), 7.32-7.43, 7.51-7.56 (m, m, 2H, 2H, N-C_6H_4).

Found, %: C 58.49; H 5.00; N 3.70; Br 20.35. $C_{19}H_{18}BrNO_3$. Calculated, %: C 58.77; H 4.67; N 3.61; Br 20.58.

(E)-3-{3-[3-(4-Isopropoxyphenyl)-2,5-dioxotetrahydro-1*H*-1-pyrolyl]phenyl}propenoic acid (**7**) was synthesized from anhydride and 3-amino cinnamic acid. White crystals. Yield: 73%, mp 211-212°C (i-PrOH). R_f 0.74 (B). IR, ν, cm^{-1}: 1777, 1703, 1683 (C=O imide, carboxyl), 1632, 1584, 1512, 1464 (C=C), 1379, 1369 sh. (i-Pr). ^{1}H NMR: 1.32 [d, J=6.0 Hz, 6H, (C**H**$_3$)$_2$CH], 2.85 (dd, ^{1}J=18.0 Hz, ^{2}J=5.3 Hz, 1H, C**H**$_a$-CH), 3.32 (dd, ^{1}J=18.0 Hz, ^{2}J=9.6 Hz, 1H, C**H**$_b$-CH), 4.19 (dd, ^{1}J=9.6 Hz, ^{2}J=5.3 Hz, 1H, CH$_2$-C**H**), 4.56 (sp, J=6.0 Hz, 1H, O-CH), 6.44 (d, J=16.0 Hz, 1H, =CH), 6.84, 7.25 (m, m, 2H, 2H, O-C$_6$H$_4$), 7.34 (dt, ^{1}J=8.0 Hz, ^{2}J= 1.6 Hz, 1H, N-C$_6$H$_4$), 7.50 (t, J=7.8 Hz, 1H, N-C$_6$H$_4$), 7.56-7.62 (m, 2H, N-C$_6$H$_4$), 7.59 (d, J=16.0, 1H, =CH). Found, %: C 70.01; H 5.72; N 3.81. $C_{22}H_{21}NO_5$. Calculated, %: C 69.64; H 5.58; N 3.69.

2-[3-(4-Isopropoxyphenyl)-2,5-dioxotetrahydro-1*H*-1-pyrrolyl]benzoic acid (**8**) was synthesized from anhydride and anthranilic acid. After reaction was complete, the reaction mixture was cooled, diluted with water. The precipitated crude product was filtered, washed by water, dried. It was resolved in boiling ethanol with addition of Norit and filtered. After concentration of filtrate ether was added and R_f 0.71 (B). IR, ν, cm^{-1}: 3194 (OH), 1766, 1740, 1691 (C=O imide, carboxyl), 1609, 1604, 1583, 1513, 1465, 1457 (C=C), 1376, 1366 (i-Pr). ^{1}H NMR: 1.32 [d, ^{3}J=6.0 Hz, 6H, (C**H**$_3$)$_2$CH], 2.77 (dd, ^{2}J=18.0 Hz, ^{3}J=6.0 Hz, 1H, C**H**$_a$-CH), 3.30 (dd, ^{2}J=18.0 Hz, ^{3}J=9.7 Hz, 1H, C**H**$_b$-CH), 4.19 (dd, ^{3}J=9.7 Hz, ^{3}J=6.0 Hz, 1H, CH$_2$-C**H**), 4.57 (sp, ^{3}J=6.0 Hz, 1H, O-CH), 6.84, 7.25-7.33, 7.55, 7.67 (m, m, m, m, 2H, 3H, 1H, 1H, resp., arom.), 8.09 (d, ^{3}J=7.7 Hz, 1H, arom.), 12.89 (br, 1H, COOH). Found, %: C 67.79; H 5.55; N 3.73. $C_{20}H_{19}NO_5$. Calculated, %: C 67.98; H 5.42; N 3.96.

3-[3-(4-Isopropoxyphenyl)-2,5-dioxotetrahydro-1*H*-1-pyrrolyl]benzoic acid (**9**) was synthesized from anhydride and m-aminobenzoic acid. Cream-coloured crystals. Yield: 59%, mp 228-229°C (ethanol). *Rf* 0.61 (B). IR, ν, cm^{-1}: 1783, 1707, 1685 (C=O imide, carboxyl), 1610, 1590, 1511, 1458 (C=C), 1377, 1365 sh. (i-Pr). ^{1}H NMR: 1.31 [d, ^{3}J=6.0 Hz, 6H, (C**H**$_3$)$_2$CH], 2.87 (dd, ^{2}J=17.9 Hz, ^{3}J= 5.5 Hz, 1H, C**H**$_a$-CH), 3.31 (dd, ^{2}J=17.9 Hz, ^{3}J=9.5 Hz, 1H, C**H**$_b$-CH), 4.22 (dd, ^{3}J=9.5 Hz, ^{3}J=5.5 Hz, 1H, CH$_2$-C**H**), 4.57 (sp, ^{3}J=6.0 Hz, 1H, O-CH), 6.85, 7.27 (m, m, 2H, 2H, O-C$_6$H$_4$), 7.52-7.61, 7.94-8.01 (m, m, 2H, 2H, N-C$_6$H$_4$), 12.89 (br, 1H, COOH). Found, %: C 67.67; H 5.28; N 4.01. $C_{20}H_{19}NO_5$. Calculated, %: C 67.98; H 5.42; N 3.96.

4-[3-(4-Isopropoxyphenyl)-2,5-dioxotetrahydro-1*H*-1-pyrrolylamino]benzoic acid (**10**) was synthesized from anhydride and p-aminobenzoic acid. Yield: 64%, mp 242-244°C (ethanol). R_f 0.71 (B). IR, ν, cm^{-1}: 1783, 1702, 1692 (C=O imide, carboxyl), 1586, 1512, 1464 (C=C). ^{1}H NMR: 1.31

[d, ^{3}J=6.0 Hz, 6H, (C**H**$_3$)$_2$CH], 2.88 (dd, ^{2}J=18.0 Hz, ^{3}J=5.4 Hz, 1H, C**H**$_a$-CH), 3.32 (dd, ^{2}J=18.0 Hz, ^{3}J=9.5 Hz, 1H, C**H**$_b$-CH), 4.22 (dd, ^{3}J=9.5 Hz, ^{3}J=5.4 Hz, 1H, CH$_2$-C**H**), 4.57 (sp, ^{3}J=6.0 Hz, 1H, O-CH), 6.85, 7.26, 7.45, 8.06 (m, m, m, m, 2H, 2H, 2H, 2H 2C$_6$H$_4$), 12.80 (br, 1H, COOH). Found, %: C 68.09; H 5.64; N 3.69. $C_{20}H_{19}NO_5$. Calculated, %: C 67.98; H 5.42; N 3.96.

Ethyl 4-[3-(4-Isopropoxyphenyl)-2,5-dioxotetrahydro-1*H*-1-pyrrolyl]benzoate (**11**) was synthesized from anhydride and ethyl p-aminobenzoate. White crystals. Yield: 85%, mp 173-175^{o}C (ethanol). R_f 0.85 (B). IR, ν, cm^{-1}: 3466 (NH), 1779, 1705, 1685 sh. (C=O imide, ester), 1600, 1583, 1510, 1465 (C=C), 1396, 1379 (i-Pr). ^{1}H NMR: 1.32 [d, ^{3}J=6.0 Hz, 6H, (C**H**$_3$)$_2$CH], 1.40 (t, ^{3}J=7.1 Hz, 3H, C**H**$_3$-CH$_2$), 2.87 (dd, ^{2}J=18.0 Hz, ^{3}J=5.4 Hz, 1H, C**H**$_a$-CH), 3.32 (dd, ^{2}J=18.0 Hz, ^{3}J=9.6 Hz, 1H, C**H**$_b$-CH), 4.20 (dd, ^{3}J=9.6 Hz, ^{3}J=5.4 Hz, 1H, CH$_2$-C**H**), 4.36 (q, ^{3}J=7.1 Hz, 2H, O-CH$_2$), 4.56 (sp, ^{3}J=6.0 Hz, 1H, O-CH), 6.8ν4, 7.24 (m, m, 2H, 2H, O-C$_6$H$_4$), 7.47, 8.08 (m, m, 2H, 2H, N-C$_6$H$_4$). Found, %: C 68.97; H 6.34; N 3.71. $C_{22}H_{23}NO_5$. Calculated, %: C 69.28; H 6.08; N 3.67.

1-(3-Carboxy-4-hydroxyphenyl)-3-(4-isopropoxyphenyl)pyrrolidine-2,5-dione (**12**) was synthesized from anhydride and 5-aminosalicylic acid. Cream-coloured crystals. Yield: 86%, mp 206^{o}C (i-PrOH – H$_2$O, 1:1). R_f 0.58 (B). IR, ν, cm^{-1}: 1786, 1703, 1669 (C=O imide, carboxyl), 1610, 1587, 1513, 1462 (C=C), 1378, 1366 sh. (i-Pr). ^{1}H NMR: 1.32 [d, J=6.0, 6H, (C**H**$_3$)$_2$CH], 2.82 (dd, ^{1}J=18.0 Hz, ^{2}J=5.3 Hz, 1H, C**H**$_a$-CH), 3.27 (dd, ^{1}J=18.0 Hz, ^{2}J=9.6 Hz, 1H, C**H**$_b$-CH), 4.15 (dd, ^{1}J=9.6 Hz, ^{2}J=5.3 Hz, 1H, CH$_2$-C**H**), 4.55 (sp, J=6.0 Hz, 1H, O-CH), 6.83, 7.23 (m, m, 2H, 2H, O-C$_6$H$_4$), 6.98 (d, J=8.8 Hz, 1H, ^{5}CH C$_6$H$_3$), 7.38 (dd, ^{1}J=8.8 Hz, ^{2}J=2.6 Hz, 1H, ^{6}CH, C$_6$H$_3$), 7.77 (d, J=2.6 Hz, 1H, ^{2}CH C$_6$H$_3$), 11.42 (br, 1H, OH), 13.57 (br, 1H, COOH). Found, %: C 64.92; H 5.27; N 3.65. $C_{20}H_{19}NO_6$. Calculated, %: C 65.03; H 5.18; N 3.79.

1-(2,4-Dinitroanilino)-3-(4-isopropoxyphenyl)pyrrolidine-2,5-dione (**13**) was synthesized from anhydride and 2,4-dinitrophenylhydrazine. Light-yellow powdery crystals. Yield: 77%, mp 218-220.5^{o}C (dioxane –water). R_f 0.75 (B). IR, ν, cm^{-1}: 3341 (NH), 1786, 1732, 1721, (C=O imide), 1548 (*as.* NO$_2$), 1343(*s.*NO$_2$), 1623, 1613, 1602, 1514, 1507, 1464 (C=C), 1378, 1366 sh. (i-Pr), 1343, 1179 (C-N arom.). ^{1}H NMR: 1.33 [d, J=6.0 Hz, 6H, (C**H**$_3$)$_2$CH], 2.78 (dd, ^{1}J=18.0 Hz, ^{2}J=5.4 Hz, C**H**$_a$-CH), 3.37 (dd, ^{1}J=18.0 Hz, ^{2}J=9.4 Hz, 1H, C**H**$_b$-CH), 4.25 (dd, ^{1}J=9.4 Hz, ^{2}J=5.4 Hz, 1H, CH$_2$-C**H**), 4.57 (sp, J=6.0 Hz, 1H, O-CH), 6.84, 7.27 (m, m, 2H, 2H, O-C$_6$H$_4$), 7.34 (d, J=9.4 Hz, 1H, ^{6}CH C$_6$H$_3$), 8.28 (dd, ^{1}J=9.4 Hz, ^{2}J=2.6Hz, 1H, ^{5}CH C$_6$H$_3$), 9.00 (d, J=2.6 Hz, 1H, ^{3}CH C$_6$H$_3$), 10.30 (br, 1H, NH). Found, %: C 54.85; H 4.19; N 13.29. $C_{19}H_{18}N_4O_7$. Calculated, %: C 55.07; H 4.38; N 13.52.

N-{4-[3-(4-Isopropoxyphenyl)-2,5-dioxotetrahydro-1*H*-1-pyrrolyl]phenyl}-2-fluorobenz-amide (**14**) was synthesized from anhydride

and 4-amino-N-(2-fluorophenyl)benzamide. Light-cream-coloured crystals. Yield: 75%, mp 187-189°C (methyl cellosolve). R_f 0.65 (B). IR, ν, cm^{-1}: 3310 (NH), 1771, 1701, 1695 sh. (C=O imide), 1667 (amide I), 1613, 1603, 1519, 1462 (C=C), 1528 (amide II), 1378, 1366 (i-Pr). ^{1}H NMR: 1.33 [d, ^{3}J=6.0 Hz, 6H, (C**H**$_3$)$_2$CH], 2.84 (dd, ^{2}J=17.9 Hz, ^{3}J=5.2 Hz, 1H, C**H**$_a$-CH), 3.31 (dd, ^{2}J=17.9 Hz, ^{3}J=9.6 Hz, 1H, C**H**$_b$-CH), 4.17 (dd, ^{3}J=9.6 Hz, ^{3}J=5.2 Hz, 1H, CH$_2$-C**H**), 4.56 (sp, ^{3}J=6.0 Hz, 1H, O-CH), 6.84 (m, 2H, arom.), 7.18-7.31 (m, 6H, arom.), 7.51 (m, 1H, arom.), 7.70 (td, ^{3}J=7.4 Hz, ^{4}J=1.9 Hz, 1H, arom.), 7.87 (m, 2H, arom.), 10.21 (s, 1H, NH). Found, %: C 69.76; H 5.21; N 6.22; F 3.95. $C_{26}H_{23}FN_2O_4$. Calculation, %: C 69.94; H 5.19; N 6.27; F 4.26.

1-Hydroxymethyl-3-(4-isopropoxyphenyl)pyrrolidine-2,5-dione (**15**). To a solution of **1** (0.1 *mol*) in 100 *ml* ethanol 37% formalin (0.33 *mol*) was added. The mixture was refluxed for 50 *min* and allowed to stand at room temperature overnight. The precipitated solid was filtered off, washed with water, dried and recrystallized from benzene–ethanol, 1:2 v/v. On concentrating the mother liquid, additional portion of product was isolated. White crystals. Yield: 95%, mp 84-85°C. R_f 0.50 (B). IR, ν, cm^{-1}: 3514, 3269 (OH), 1773, 1693 (C=O imide), 1610, 1510, 1472, 1464 (C=C). ^{1}H NMR: 1.31 [d, ^{3}J=6.0 Hz, 6H, (C**H**$_3$)$_2$CH], 2.64 (dd, ^{2}J=18.1 Hz, ^{3}J=5.0 Hz, 1H, C**H**$_a$-CH), 3.16 (dd, ^{2}J=18.1 Hz, ^{3}J=9.6 Hz, 1H, C**H**$_b$-CH), 4.00 (dd, ^{3}J=9.6 Hz, ^{3}J=5.0 Hz, 1H, CH$_2$-C**H**), 4.0 (br., 1H, OH), 4.54 (sp, ^{3}J=6.0 Hz, 1H, O-CH), 4.82, 4.83 (d, d, ^{2}J=10.3 Hz, ^{2}J=10.3 Hz , 2H, N-CH$_2$), 6.80, 7.12 (m, m, 2H, 2H, C$_6$H$_4$). Found, %: C 64.09; H 6.64; N 5.17. $C_{14}H_{17}NO_4$. Calculated, %: C 63.86; H 6.51; N 5.32.

General procedures for the syntheses of compounds 16-25. A mixture of equimolar amounts of **15** and appropriate amine (usually 0.015 *mol* of each) in ethanol (25-30 *ml*) was refluxed for 50-60 *min*. On cooling, precipitated product was isolated and recrystallized.

3-(4-Isopropoxyphenyl)-1-morpholinomethylpyrrolidine-2,5-dione (16) was synthesized from **15** and morpholine. White powdery crystals. Yield: 87%, mp 93-94°C (ethanol). R_f 0.59 (B). IR, ν, cm^{-1}: 1771, 1700 (C=O imide), 1611, 1580, 1513, 1462, 1455 (C=C). ^{1}H NMR: 1.31 [d, ^{3}J=6.0 Hz, 6H, (C**H**$_3$)$_2$CH], 2.51 (m, 4H, CH$_2$-N-CH$_2$), 2.69 (dd, ^{2}J=18.1 Hz, ^{3}J=5.1 Hz, 1H, C**H**$_a$-CH), 3.18 (dd, ^{2}J=18.1 Hz, ^{3}J=9.6 Hz, 1H, C**H**$_b$-CH), 3.55 (t, ^{3}J=4.6 Hz, 4H, CH$_2$-O-CH$_2$), 4.04 (dd, ^{3}J=9.6 Hz, ^{3}J=5.1 Hz, 1H, CH$_2$-C**H**), 4.33 (s, 2H, N-CH$_2$-N), 4.54 (sp, ^{3}J=6.0 Hz, 1H, O-CH), 4.82, 4.83 (d, ^{2}J=10.3 Hz, 1H, d, ^{2}J=10.3 Hz, 1H, N-CH$_2$), 6.81, 7.12 (m, m, 2H, 2H, C$_6$H$_4$). Found, %: C 64.96; H 7.01; N 8.49. $C_{18}H_{24}N_2O_4$. Calculated, %: C 65.04; H 7.28; N 8.43.

1-Anilinomethyl-3-(4-isopropoxyphenyl)pyrrolidine-2,5-dione ***(17)*** was synthesized from **15** and aniline. White crystals. Yield: 95%, mp. 129-130°C (ethanol). R_f 0.80 (B). IR, ν, cm^{-1}: 3369 (NH), 1764, 1683, (C=O

imide), 1605, 1520, 1509, 1500, 1458 (C=C), 1375, 1364 (i-Pr). ^{1}H NMR: 1.29 [d, ^{3}J=6.0 Hz, 6H, (C**H**$_3$)$_2$CH], 2.56 (dd, ^{2}J=18.1 Hz, ^{3}J=4.8 Hz, 1H, C**H**$_a$-CH), 3.13 (dd, ^{2}J=18.1 Hz, ^{3}J=9.5 Hz, 1H, C**H**$_b$-CH), 3.80 (br, 1H, NH), 3.96 (dd, ^{3}J=9.5 Hz, ^{3}J=4.8 Hz, 1H, CH$_2$-C**H**), 4.50 (sp, J=6.0 Hz, 1H, O-CH), 6.60-6.78 (m, 5H, N-C$_6$H$_5$), 6.94, 7.07 (m, m, 2H, 2H, O-C$_6$H$_4$). Found, %: C 71.11; H 6.39; N 7.99. $C_{20}H_{22}N_2O_3$. Calculated, %: C 70.98; H 6.55; N 8.28.

1-(4-Acetylanilinomethyl)-(4-isopropoxyphenyl)pyrrolidine-2,5-dione ***(*****18*****)*** was synthesized from **15** and 4′-aminoacetophenone. White crystals. Yield: 54%, mp 161-162ºC (ethanol). R_f 0.57 (B). IR, ν, cm^{-1}: 3341 (NH), 1764, 1691, 1661 (C=O imide, ketone), 1601, 1540, 1509, 1462, 1453 (C=C), 1376, 1364 (i-Pr). ^{1}H NMR: 1.29 [d, ^{3}J=6.0 Hz, 6H, (C**H**$_3$)$_2$CH], 2.41 (s, 3H, CH$_3$-C=O), 2.63 (dd, ^{2}J=18.2Hz, ^{3}J=5.0 Hz, 1H, C**H**$_a$-CH), 3.17 (dd, ^{2}J=18.2 Hz, ^{3}J=9.5 Hz, 1H, C**H**$_b$-CH), 4.01 (dd, ^{3}J=9.5 Hz, ^{3}J=5.0 Hz, 1H, CH$_2$-C**H**), 4.51 (sp, ^{3}J=6.0 Hz, 1H, O-CH), 4.91 (br, 2H, N-CH$_2$-N), 6.73, 6.83, 7.02, 7.70 (m, m, m, m, 2H, 2H, 2H, 2H, arom.), 7.15 (br, 1H, NH). Found, %: C 69.49; H 6.15; N 7.50. $C_{22}H_{24}N_2O_4$. Calculated, %: 69.45; H 6.36; N 7.36.

1-(3-Bromoanilinomethyl)-(4-isopropoxyphenyl)pyrrolidine-2,5-dione ***(*****19*****)*** was synthesized from **15** and 3-bromoaniline. Light-yellow needles. Yield: 91%, mp 106ºC (ethanol). R_f 0.79 (B). IR, ν, cm^{-1}: 3374 (NH), 1770, 1700, 1686, (C=O imide), 1600, 1576, 1513, 1460, 1458 (C=C), 1377, 1367 sh. (i-Pr). ^{1}H NMR: 1.30 [d, J=6.0 Hz, 6H, (C**H**$_3$)$_2$CH], 2.60 (dd, ^{2}J=18.2 Hz, ^{3}J=4.9 Hz, 1H, C**H**$_a$-CH), 3.16 (dd, ^{2}J= 18.2 Hz, ^{3}J=9.6 Hz, 1H, C**H**$_b$-CH), 3.99 (dd, ^{3}J=9.6 Hz, ^{3}J=4.9 Hz, 1H, CH$_2$-C**H**), 4.51 (sp, ^{3}J=6.0 Hz, 1H, O-CH), 4.86 (d, ^{3}J=7.2 Hz, 2H, N-CH$_2$-N), 6.56 (t, ^{3}J=7.2 Hz, 1H, NH), 6.71-6.78, 6.94-7.02 (m, m, 4H, 4H, arom.). Found, %: C 57.29; H 5.28; N 6.66; Br 18.98. $C_{20}H_{21}BrN_2O_3$. Calculated, %: C 57.56; H 5.07; N 6.71; Br 19.15.

(E)-3-{3-[3-(4-Isopropoxyphenyl)-2,5-dioxotetrahydro-1*H*-1-pyrolylmethylamino]phenyl}-propenoic acid (**20**) was synthesized from **15** and 3-amino cinnamic acid. White crystals. Yield: 90%, mp 195-197ºC (decomp.) (ethanol). R_f 0.75 (B). IR, ν, cm^{-1}: 3353 (NH), 1766, 1754, 1700, 1684 (C=O imide, acid), 1609, 1602, 1586, 1510, 1463, 1456 (C=C), 1376, 1369 sh. (i-Pr). ^{1}H NMR: 1.28 [d, ^{3}J=6.0 Hz, 6H, (C**H**$_3$)$_2$CH], 2.59 (dd, ^{2}J=18.2 Hz, ^{3}J=4.8 Hz, 1H, C**H**$_a$-CH), 3.16 (dd, 2J=18.2 Hz, 3J=9.5 Hz, 1H, C**H**$_b$-CH), 3.99 (dd, ^{3}J=9.5 Hz, ^{3}J=4.8 Hz, 1H, CH$_2$-C**H**), 4.49 (sp, ^{3}J=6.0 Hz, 1H, O-CH), 4.92 (s, 2H, N-CH$_2$-N), 6.28 (d, ^{3}J=15.9 Hz, C**H**-COOH), 6.38 (br., 1H, NH), 6.70, 6.81-6.84 (m, m, 2H, 2H, O-C$_6$H$_4$), 6.97, 7.08, 7.10 (m, t, ^{4}J=1.9 Hz, t, ^{3}J=7.9 Hz, resp., 2H, 1H, 1H, resp., N-C$_6$H$_4$), 7.41 (d, ^{3}J=15.9 Hz, 1H, C$_6$H$_4$-C**H**=), 11.89 (br, 1H, COOH). Found, %: C 67.27; H 6.00; N 6.59. $C_{23}H_{24}N_2O_5$. Calculated, %: C 67.63; H 5.92; N 6.86.

2-[3-(4-Isopropoxyphenyl)-2,5-dioxotetrahydro-1*H*-1-pyrrolylmethylamino]benzoic acid *(21)* was synthesized from **15** and anthranilic acid. Cream-coloured powdery crystals. Yield: 60%, mp 137.5-139°C (ethanol). R_f 0.72 (B). IR, ν, *cm*$^{-1}$: 3371 (NH), 1771, 1719 sh., 1702, 1643 (C=O imide, carboxyl), 1610, 1588, 1520, 1512, 1463, 1456 sh. (C=C), 1378, 1367 (i-Pr).^{1}H NMR: 1.31 [d, ^{3}J=6.0 Hz, 6H, (C**H**$_3$)$_2$CH], 2.63 (dd, ^{2}J=18.1 Hz, ^{3}J=4.8 Hz, 1H, C**H**$_a$-CH), 3.16 (dd, ^{2}J=18.1 Hz, ^{3}J=9.5 Hz, 1H, C**H**$_b$-CH), 4.01 (dd, ^{3}J=9.5 Hz, ^{3}J=4.8 Hz, 1H, CH$_2$-C**H**), 4.52 (sp, ^{3}J=6.0 Hz, 1H, O-CH), 5.04 (d, ^{3}J=7.2 Hz, 2H, N-CH$_2$-N), 6.64-6.75, 7.00, 7.10, 7.34 (m, m, m, m, 3H, 2H, 1H, 1H, resp., arom.), 7.88 (dd, ^{3}J=7.9 Hz, ^{4}J=1.8 Hz, 1H, C**H**=C-COOH), 8.68 (t, ^{3}J=7.2 Hz, 1H, NH), 12.37 (br., 1H, COOH). Found, %: C 65.70; H 5.85; N 7.19. $C_{21}H_{22}N_2O_5$. Calculated, %: C 65.95; H 5.80; N 7.33.

3-[3-(4-Isopropoxyphenyl)-2,5-dioxotetrahydro-1*H*-1-pyrrolylmethylamino]benzoic acid *(22)* was synthesized from **15** and m-aminobenzoic acid. Light-cream-coloured crystals. Yield: 90%, mp 156-157°C (ethanol). R_f 0.64 (B). IR, ν, *cm*$^{-1}$: 3360 (NH), 1770, 1693, 1683 (C=O imide, carboxyl), 1609, 1591, 1513, 1510, 1466, 1455 sh. (C=C), 1379, 1366 (i-Pr). ^{1}H NMR: 1.29 [d, ^{3}J=6.0 Hz, 6H, (C**H**$_3$)$_2$CH], 2.58 (dd, ^{2}J=18.1 Hz, ^{3}J=4.9 Hz, 1H, C**H**$_a$-CH), 3.15 (dd, ^{2}J=18.1 Hz, ^{3}J=9.5 Hz, 1H, C**H**$_b$-CH), 3.98 (dd, ^{3}J=9.5 Hz, ^{3}J=4.9 Hz, 1H, CH$_2$-C**H**), 4.50 (sp, ^{3}J=6.0 Hz, 1H, O-CH), 4.92 (br, 2H, N-CH$_2$-N), 6.43 (br., 1H, NH), 6.71, 6.97 (m, m, 2H, 2H, O-C$_6$H$_4$), 7.00, 7.27, 7.42 (m, m, m, 1H, 1H, 1H, N-C$_6$H$_4$), 7.16 (t, ^{3}J=7.8 Hz, 1H, N-C$_6$H$_4$), 12.22 (br, 1H, COOH). Found, %: C 65.62; H 5.61; N 7.35. $C_{21}H_{22}N_2O_5$. Calculated, %: C 65.95; H 5.80; N 7.33.

4-[3-(4-Isopropoxyphenyl)-2,5-dioxotetrahydro-1*H*-1-pyrrolylmethylamino]benzoic acid *(23)* was synthesized from **15** and p-aminobenzoic acid. White crystals. Yield: 78%, mp 196-198°C (ethanol). R_f 0.67 (B). IR ν, *cm*$^{-1}$: 3343 (NH), 1769, 1689 sh., 1683, 1671 sh. (C=O imide, carboxyl), 1605, 1535, 1508, 1462 (C=C), 1378, 1367 (i-Pr). ^{1}H NMR: 1.29 [d, ^{3}J=6.0 Hz, 6H, (C**H**$_3$)$_2$CH], 2.62 (dd, ^{2}J=18.2 Hz, ^{3}J=4.9 Hz, 1H, C**H**$_a$-CH), 3.16 (dd, ^{2}J=18.2 Hz, ^{3}J=9.6 Hz, 1H, C**H**$_b$-CH), 4.01 (dd, ^{3}J=9.6 Hz, ^{3}J=4.9 Hz, 1H, CH$_2$-C**H**), 4.51 (sp, ^{3}J=6.0 Hz, 1H, O-CH), 4.91 (d, ^{3}J=6.8, 2H, N-CH$_2$-N), 6.73, 7.01 (m, m, 2H, 2H, O-C$_6$H$_4$), 6.96 (t, ^{3}J=6.8 Hz, 1H, NH), 6.81, 7.71 (m, m, 2H, 2H, N-C$_6$H$_4$). Found, %: C 66.09; H 5.97; N 7.41. $C_{21}H_{22}N_2O_5$. Calculated, %: C 65.95; H 5.80; N 7.33.

Ethyl 4-[3-(4-Isopropoxyphenyl)-2,5-dioxotetrahydro-1*H*-1-pyrrolylmethylamino]benzoate *(24)* was synthesized from **15** and ethyl 4-aminobenzoate. White needles. Yield: 64%, mp 139-141°C (ethanol). R_f 0.81 (B). IR, ν, *cm*$^{-1}$: 3335 (NH), 1771, 1757, 1703, 1686 (C=O imide ester), 1602, 1528, 1508, 1459 (C=C), 1378, 1367 (i-Pr). ^{1}H NMR: 1.29 [d, ^{3}J=6.0 Hz, 6H, (C**H**$_3$)$_2$CH], 1.35 (t, ^{3}J=7.1 Hz, 3H, C**H**$_3$-CH$_2$), 2.62 (dd, ^{2}J=18.2 Hz, ^{3}J=4.9 Hz, 1H, C**H**$_a$-CH), 3.16 (dd, ^{2}J=18.2 Hz, ^{3}J=9.6 Hz, 1H, C**H**$_b$-CH),

4.00 (dd, ^{3}J=9.6 Hz, ^{3}J=4.9 Hz, 1H, CH_2-C**H**), 4.23 (q, ^{3}J=7.1 Hz, 2H, O-CH_2), 4.50 (sp, ^{3}J=6.0 Hz, 1H, O-CH), 4.91 (br., 2H, N-CH_2-N), 6.73, 6.82, 7.01, 7.73 (m, m, m, m, 2H, 2H, 2H, 2H, arom.), 7.04 (br, 1H, NH). Found, %: C 68.97; H 6.34; N 3.71. $C_{23}H_{26}N_2O_5$. Calculated, %: C 69.28; H 6.08; N 3.67.

N-{4-[3-(4-Isopropoxyphenyl)-2,5-dioxotetrahydro-1*H*-1-pyrrolyl-methylamino]phenyl}-2-fluorobenzamide ***(*****25*****)*** was synthesized from **15** and 4-amino-N-(2-fluorophenyl)benzamide. White crystals. Yield: 88%, mp 136-138ºC (ethanol). R_f 0.64 (B). IR, ν, cm^{-1}: 3401, 3271 (NH amine, amide), 1768, 1700, 1686, 1640 (C=O imide, amide I), 1618, 1609, 1510, 1462, 1452 (C=C), 1529 (amide II),1376, 1365 sh. (i-Pr) . ^{1}H NMR: 1.28 [d, ^{3}J=6.0 Hz, 6H, (CH_3)$_2$CH], 2.56 (dd, ^{2}J=18.2 Hz, ^{3}J=4.7 Hz, 1H, C**H**$_a$-CH), 3.15 (dd, ^{2}J=18.2 Hz, ^{3}J=9.6 Hz, 1H, C**H**$_b$-CH), 3.97 (dd, ^{3}J=9.6 Hz, ^{3}J=4.7 Hz, 1H, CH_2-C**H**), 4.51 (sp, ^{3}J=6.0 Hz, 1H, O-CH), 4.90 (s, 2H, N-CH_2-N), 5.98 (br, 1H, N**H**-CH_2), 6.71-6.79, 6.93, 7.18, 7.25 (m, m, m, m, 4H, 2H, 1H, 1H, resp., O-C_6H_4, N-C_6H_4-N), 7.43-7.51, 7.71 (m, td, resp., ^{3}J=7.5 Hz, ^{4}J=1.9 Hz, 3H, 1H, resp., F-C_6H_4), 9.60 (d, ^{5}J=3.3 Hz, 1H, NH-C=O). Found, %: C 68.43; H 5.47; N 9.00; F 4.12. $C_{27}H_{26}FN_3O_4$. Calculated, %: C 68.20; H 5.51; N 8.84; F 4.00.

ФИЗИКО-ХИМИЧЕСКИЕ ХАРАКТЕРИСТИКИ НОВЫХ ПРОИЗВОДНЫХ ПИРРОЛИДИН-2,5-ДИОНОВ И СРАВНИТЕЛЬНАЯ ОЦЕНКА ИХ ПРОТИВОСУДОРОЖНЫХ СВОЙСТВ

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Синтезирован ряд новых производных пирролидин-2,5-диона, включая N-арил- и N–ариламинометилзамещённые аналоги. В настоящей работе представлены результаты инструментальных методов анализа синтезированных соединений и проведена сравнительная оценка соединений с выявленной противосудорожной активностью.

ՊԻՐՈԼԻԴԻՆ-2,5-ԴԻՈՆՆԵՐԻ ՆՈՐ ԱԾԱՆՑՅԱԼՆԵՐԻ ՖԻԶԻԿԱ-ՔԻՄԻԱԿԱՆ ԲՆՈՒԹԱԳԻՐԸ ԵՎ ՆՐԱՆՑ ՀԱԿԱՑՆՑՈՒՄԱՅԻՆ ՀԱՏԿՈՒԹՅՈՒՆՆԵՐԻ ՀԱՄԵՄԱՏԱԿԱՆ ԲՆՈՒԹԱԳՐՈՒՄԸ

Ս. Լ. ՔՈՉԱՐՈՎ, Ղ. Ա. ՓԱՆՈՍՅԱՆ, Ս. Ե. ՉՈՒՉՎԱՐ և Յա. ԼՈՒՇՉԿԻ

Սինթեզվել է պիրոլիդին-2,5-դիոնների նոր միացությունների շարք, այդ թվում N-արիլ- և N-արիլամինոմեթիլտեղակալված ածանցյալներ: Ներկայացված են սինթեզված միացությունների անալիզի գործիքային մեթոդների արդյունքները և իրականացված հակացնցումային հատկություններ ցուցաբերած միացությունների համեմատական գնահատումը:

REFERENCES

[1] *Lason W., Dudra-Jastrzebska M., Rejdak K., Czuczwar S.J.* // Pharmacol. Rep. 2011, v. 63, p. 271.

[2] *Avetisyan S.A., Mndzhoyan O.L.* // Arm. Khim. Zh., 1970, v. 23, p. 354; Chem. Abstr., 1970, v. 73, 66218r.

[3] *Mndzhoyan O.L., Avetisyan S.A., Akopyan N.E., Gerasimyan D.A., Dzhagatspanyan I.A., Pashinyan S.A.* // Pharm. Chem. J., 1983, v. 17, №6, p. 452.

[4] *Luszczki J.J., Kocharov S.L., Czuczwar S.J.* // Pharmacol. Rep., 2010, v. 62, p. 194.

[5] *Luszczki J.J., Kocharov S.L., Czuczwar S.J.* // Neurosci. Res., 2009, v. 64, p. 267.

[6] *Luszczki J.J., Cioczek J.D., Kocharov S.L., Andres-Mach M., Kominek M., Zolkowska D.* // Eur. J. Pharmacol., 2010, v. 648, p. 74.

[7] *Luszczki J.J., Kominek M., Florek-Luszczki M., Tchaytchian D.A., Kocharov S.L., Zolkowska D.* // Epilepsy Res., 2012, v. 100, p. 27.

[8] *Luszczki J.J., Kominek M., Marzeda E., Durmowicz D., Florek-Luszczki M., Kocharov S.L.* // Curr. Issues Pharm. Med. Sci., 2013, v. 26, №1, p. 76.

[9] *Zolkowska D., Kominek M., Florek-Luszczki M., Kocharov S.L., Luszczki J.J.* // Pharmacol. Rep., 2013, v. 65, p. 389.

[10] *Luszczki J.J., Marzeda E., Kondrat-Wrobel M.W., Wrobel J., Kocharov S.L., Florek-Luszczki M.* // J. Pre-Clinical and Clinical Res., 2014, v. 8, №1, p. 34.

[11] *Kocharov S.L., Panosyan H.A., Marzeda P., Wroblewska- Luczka P., Kochman E., Wlaz A., Luszczki J.J.* // Health Problems of Civilization, 2017, v. 11, №3, p. 195.

[12] *Kocharov S.L., Panosyan H., Chmielewski J., Gworek B.. Luszczki J.J.* // Acta Poloniae Pharmaceutica, 2019, v.76, №2, p. 265.

[13] *Matsuo T.* // Bull. Chem. Soc. Japan, 1964, v. 37, p. 1844.

[14] *Buczkowski Z., Lange J., Urbanski T.* // Roczniki Chem., Ann. Soc. Chim. Polonorum, 1965, v. 39, 231.

[15] *Kutlu H.* // J. Fac. Pharm. Istanbul, 1977, v. 13, p. 125.

[16] *Rahman A., Farooq M.O.* // Chem. Ber., 1953, v. 86, №8, p. 945.