ISSN 1070-3632, Russian Journal of General Chemistry, 2020, Vol. 90, No. 3, pp. 385–389. © Pleiades Publishing, Ltd., 2020.
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Synthesis and Antioxidant Activity of *N*-Aminomethyl Derivatives of Ethosuximide and Pufemide Anticonvulsants

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Received July 31, 2019; revised February 6, 2020; accepted February 8, 2020

Abstract—Aminomethylation of 3-methyl-3-ethylpyrrolidin-2,5-dione (ethosuximide) and 3-(4-isopropoxyphenyl)-pyrrolidine-2,5-dione (pufemide) with a 25% aqueous formalin solution and alkyl(aryl)amines yielded corresponding *N*-aminomethyl derivatives. The antioxidant activity of the synthesized compounds and their effect on some parameters of the blood coagulation system were studied.

Keywords: *N*-aminomethylation, ethosuximide, pufemide, antioxidant activity, blood coagulation system

DOI: 10.1134/S1070363220030093

Imides are known to be physiologically active substances with a wide spectrum of activity, possessing antimicrobial, antituberculous, antiviral, antitumor, anticonvulsant and other types of activity [1]. The most famous compounds of this type Ethosuximide and Pufemide are used as effective anticonvulsant and antiepileptic drugs [2]. On the other hand, it is known that the Mannich *N*-bases show various pharmacological activities (antibacterial, anticonvulsant, antioxidant, etc.) [3, 4]. Based on the available literature data, in order to expand the spectrum of biological activity, we synthesized *N*-aminomethyl derivatives of Ethosuximide and Pufemide; their antioxidant activity and the effect on some parameters of the blood coagulation system were investigated.

Aminomethylation of 3-methyl-3-ethylpyrrolidine-2,5-dione (Ethosuximide) **1** and 3-(4-isopropoxyphenyl)-pyrrolidine-2,5-dione (Pufemide) **2** with 25% aqueous formalin and alkyl, aryl or cyclic amines in ethanol (dioxane), the corresponding *N*-aminomethyl derivatives **3–19** were obtained (Scheme 1). Compounds **3**, **4**, **7**, **8**, soluble in diethyl ether, were converted into oxalates **20–23** with an oxalic acid ethereal solution. The corresponding hydrochloride **24** was obtained by reacting compound **13** with a solution of hydrogen chloride in diethyl ether.

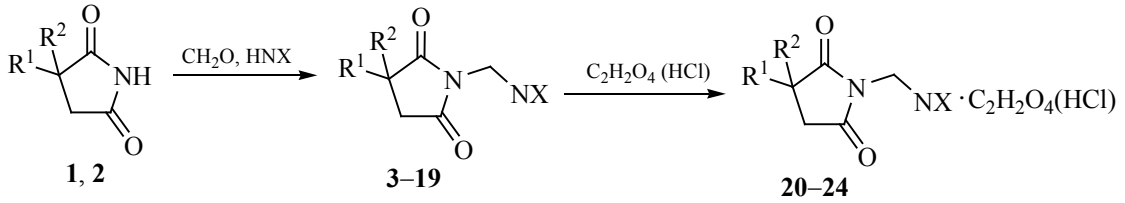
Structure of the obtained compounds was confirmed by ^{1}H, ^{13}C NMR and IR spectroscopy. In the IR spectra of compounds **3–7**, **14**, stretching vibrations of the C=O group are observed in the regions of 1777–1766, 1713–1705 cm^{-1}. The absorption at 3472–3442 cm^{-1} can be attributed to their overtone [5].

Antioxidant activity (AOA) of the synthesized compounds **6–8**, **11–15**, **17**, **21**, **24** and their effect on some parameters of the blood coagulation system were studied. According to the results obtained, the Ethosuximide derivatives **6**, **8**, **10**, **11**, **12** and **21** exhibit a weak prooxidant effect, whereas the Pufemide derivatives **15** and **24** show a weak antioxidant effect. Compounds **7**, **14** and **17** do not possess activity (Table 1).

The results of the study of the effect on some parameters of the blood coagulation system led to the conclusion that, in addition to substances **8**, **10**, **11** and **21**, which have procoagulant activity, the studied compounds do not act on the blood coagulation system.

In summary, aminomethylation of Ethosuximide and Pufemide with an aqueous solution of formalin and alkyl (aryl) amines yielded the corresponding *N*-aminomethyl derivatives, which did not exhibit noticeable antioxidant activity.

Scheme 1.



1, **2** **3–19** **20–24**

$R^1 = CH_3$, $R^2 = C_2H_5$, NX = dietylamino (**3**, **20**), ethylbutylamino (**4**, **21**), dicyclohexylamino (**5**), morpholin-4-yl (**6**, **22**), piperidin-1-yl (**7**, **23**), (4-methylphenyl)amino (**8**), (4-isopropoxybenzyl)amino (**9**), (4-carboxyphenyl)amino (**10**), (4-acetylphenyl)amino (**11**), 4-amino-*N*-(5-ethyl-1,3,4-thiadiazol-2-yl)benzenesulfonamide (**12**), (1-benzylphenylcyclohexyl)ethyl]amino (**13**, **24**); $R^1 = H$, $R^2 = i\text{-PrOC}_6H_4$, NX = 4-(4-fluorophenyl)piperazino (**14**), (4-carboxyphenyl)amino (**15**), (4-acetylphenyl)amino (**16**), 4-(ethoxycarboxyphenyl)amino (**17**), (3-bromophenyl)amino (**18**), (4-bromophenyl)amino (**19**).

EXPERIMENTAL

IR spectra were recorded on a Nicolet Avatar 330 FT-IR instrument from liquid paraffin. ^1H and ^{13}C NMR spectra were recorded on a Mercury-300 Varian spectrometer (300 and 75 MHz, respectively) from DMSO-d_6–CCl_4 solutions relative to internal TMS. Melting points were determined on a Boetius instrument.

The starting 3-methyl-3-ethylpyrrolidine-2,5-dione (Ethosuximide) **1** and 3-(4-isopropoxyphenyl)pyrrolidine-2,5-dione (Pufemide) **2** were synthesized according to the known procedures [6] and [7], respectively.

Table 1. Evaluation of intensity of lipid peroxidation processes (*I*)[a]

Comp. no.	*I*	Difference compared to control, %
6	12.01	20.0
7	10.44	4.0
8	12.00	20.0
10	11.50	14.5
11	12.24	22.0
12	12.11	10.6
14	10.00	0.4
15	9.33	7.0
17	10.45	4.0
21	11.21	12.0
24	9.73	3.0

[a] With respect to the content (nM.) of malonodialdehyde in 1 mg of protein. Control is 10.04.

***N*-Aminomethyl derivatives 3–19.** A mixture of 0.01 mol of 3-methyl-3-ethylpyrrolidine-2,5-dione **1** or 3-(4-isopropoxyphenyl)pyrrolidine-2,5-dione **2**, 1.3 g (0.011 mol) of 25% formalin, 0.011 mol of amine in 15 mL of ethanol (dioxane) was heated at 70–80°C for 6–7 h. After ethanol was removed, hexane was added to the oily residue. The substance was triturated, then the solvent was decanted. After some time, the substance crystallized. Recrystallized from diethyl ether–ethanol mixture (3 : 1) or acetone. Compounds **3**, **4**, and **6**, which failed to crystallize, were distilled under reduced pressure.

Oxalates 20–23 and hydrochloride 24. An diethyl ether solution of oxalic acid was slowly added dropwise to an ether solution of compounds **3**, **4**, **7**, **8**, and an diethyl ether solution of HCl to compound **13**. The precipitate was filtered off, and recrystallized from absolute acetone.

1-[(Diethylamino)methyl]-3-methyl-3-ethylpyrrolidine-2,5-dione (3). Yield 77%, bp 105–107°C (2 mmHg). IR spectrum, ν, cm^{-1}: 3471, 1776, 1706 (CONCO). ^1H NMR spectrum, δ, ppm: 0.87 t (3H, $CCH_2C\mathbf{H}_3$, J = 7.4 Hz), 1.06 t [6H, $N(CH_2C\mathbf{H}_3)_2$, J = 7.1 Hz], 1.25 s (3H, CCH_3), 1.55 d. q (1H, $CC\mathbf{H}_2CH_3$, J = 13.7, 7.4 Hz), 1.67 d. q (1H, $CC\mathbf{H}_2CH_3$, J = 13.7, 7.4 Hz), 2.38 d (1H, CH_2, J = 18.1 Hz), 2.51 q [4H, $N(CH_2)_2$, J = 7.1 Hz], 2.57 d (1H, CH_2, J = 18.1 Hz), 4.34 s (2H, NCH_2N). ^{13}C NMR spectrum, δ_C, ppm: 8.2 ($\mathbf{C}H_3CH_2C$), 12.6 [$(\mathbf{C}H_3CH_2)_2N$], 23.4 (CH_3), 30.4 ($C\mathbf{C}H_2CH_3$), 39.6 ($\mathbf{C}H_2C$), 43.3 (C*), 45.0 [$N(\mathbf{C}H_2CH_3)_2$], 55.5 (NCH_2N). Found, %: C 63.60; H 9.93; N 12.32. $C_{12}H_{22}N_2O_2$. Calculated, %: C 63.68; H 9.80; N 12.38. Oxalate **20**. Mp 169–170°C.

1-{[Butyl(ethyl)amino]methyl}-3-methyl-3-ethylpyrrolidine-2,5-dione (4). Yield 48%, bp 115–118°C (2 mmHg). IR spectrum, ν, cm^{-1}: 3472, 1777, 1707 (CONCO). ^1H NMR spectrum, δ, ppm: 0.87 t (3H,

$CCH_2C\mathbf{H}_3$, *J* = 7.4 Hz), 0.92 t (3H, CH_3, Bu, *J* = 7.2 Hz), 1.05 t (3H, $NCH_2C\mathbf{H}_3$, *J* = 7.1 Hz), 1.25 s (3H, CCH_3), 1.23–1.36 m (2H, $C\mathbf{H}_2CH_3$, Bu), 1.39–1.50 m (2H, $C\mathbf{H}_2C_2H_5$, Bu), 1.55 d. q (1H, $CC\mathbf{H}_2CH_3$, *J* = 13.7, 7.4 Hz), 1.67 d. q (1H, $CC\mathbf{H}_2CH_3$, *J* = 13.7, 7.4 Hz), 2.38 d (1H, CH_2, *J* = 18.1 Hz), 2.43 t (2H, $NC\mathbf{H}_2C_3H_7$, *J* = 6.9 Hz), 2.50 q (2H, $NC\mathbf{H}_2CH_3$, *J* = 7.1 Hz), 2.57 d (1H, CH_2, *J* = 18.1 Hz), 4.33 s (2H, NCH_2N). ^{13}C NMR spectrum, δ_C, ppm: 8.2 ($\mathbf{C}H_3CH_2C$), 12.7 (CH_3), 13.5 (CH_3), 19.7 (CH_2), 23.4 (CH_3), 29.3 (CH_2), 30.4 (CH_2), 39.6 (CH_2), 43.2 (C), 45.4 (NCH_2), 50.6 (NCH_2), 56.0 (NCH_2) 175.6 (CO), 182.4 (CO). Found, %: C 66.15; H 10.22; N 11.16. $C_{14}H_{26}N_2O_2$. Calculated, %: C 66.10; H 10.30; N 11.01. Oxalate **21**. Mp 136–138°C.

1-[(Dicyclohexylamino)methyl]-3-methyl-3-ethylpyrrolidine-2,5-dione (5). Yield 48%, mp 69–70°C. IR spectrum, ν, cm^{-1}: 3442, 1773, 1706 (CONCO). ^1H NMR spectrum, δ, ppm: 0.85 t (3H, $C\mathbf{H}_3CH_2$, *J* = 7.4 Hz), 1.20 s (3H, CH_3), 0.94–1.43 m (10H, $11CH_2$), 1.47–1.79 m (12H, $11CH_2$), 2.30 d (1H, CH_2, *J* = 18.0 Hz), 2.50 d (1H, CH_2, *J* = 18.0 Hz), 2.66 t. t [2H, $N(CH)_2$, *J* = 11.3, 6.7 Hz], 4.36 d (1H, NCH_2N, *J* = 13.6 Hz), 4.40 d (1H, NCH_2N, *J* = 13.6 Hz). ^{13}C NMR spectrum, δ_C, ppm: 8.1 ($\mathbf{C}H_3CH_2$), 23.1 (CH_3), 25.3, 26.0, 30.3, 32.2, 39.9, 42.8, 52.7, 57.4 (NCH), 174.9 (CO), 181.6 (CO). Found, %: C 71.90; H 10.18; N 8.35. $C_{20}H_{34}N_2O_2$. Calculated, %: C 71.81; H 10.25; N 8.37.

3-Methyl-3-ethyl-1-(morpholin-4-ylmethyl)-pyrrolidine-2,5-dione (6). Yield 94%, bp 130–132°C (2 mmHg). IR spectrum, ν, cm^{-1}: 3470, 1775, 1706 (CONCO). ^1H NMR spectrum, δ, ppm: 0.90 t (3H, $C\mathbf{H}_3CH_2$, *J* = 7.4 Hz), 1.28 s (3H, CCH_3), 1.58 d. q (1H, $C\mathbf{H}_2CH_3$, *J* = 13.7, 7.4 Hz), 1.69 d. q (1H, $C\mathbf{H}_2CH_3$, *J* = 13.7, 7.4 Hz), 2.44 d (1H, CH_2, *J* = 18.1 Hz), 2.45–2.49 m [4H, $N(CH_2)_2$], 2.61 d (1H, CH_2, *J* = 18.1 Hz), 3.52–3.56 m [4H, $O(CH_2)_2$], 4.27 d (1H, NCH_2, *J* = 13.1 Hz), 4.29 d (1H, NCH_2, *J* = 13.1 Hz). ^{13}C NMR spectrum, δ_C, ppm: 8.4 ($\mathbf{C}H_3CH_2$), 23.5 ($\mathbf{C}H_3C$), 30.4 ($\mathbf{C}H_2CH_3$), 39.5 (CH_2), 43.5 (C), 50.4 [$N(CH_2)_2$], 59.1 (NCH_2), 65.9 [$O(CH_2)_2$], 175.6 (CO), 182.3 (CO). Found, %: C 59.82; H 8.50; N 11.57. $C_{12}H_{20}N_2O_3$. Calculated, %: C 59.98; H 8.39; N 11.66. Oxalate **22**. Mp 124–126°C.

3-Methyl-3-ethyl-1-(piperidin-1-ylmethyl)-pyrrolidine-2,5-dione (7). Yield 94%, mp 65–67°C. IR spectrum, ν, cm^{-1}: 3450, 1772, 1705 (CONCO). ^1H NMR spectrum, δ, ppm: 0.89 t (3H, $C\mathbf{H}_3CH_2$, *J* = 7.4 Hz), 1.26 s (3H, CH_3), 1.30–1.38 m (2H, γ-CH_{2Pip}), 1.46–1.54 m (4H, β,β'-CH_{2Pip}), 1.56 d. q (1H, $C\mathbf{H}_2CH_3$, *J* = 13.7, 7.4 Hz), 1.68 d. q (1H, $C\mathbf{H}_2CH_3$, *J* = 13.7, 7.4 Hz), 2.40 d (1H, CH_2, *J* = 18.1 Hz), 2.42–2.46 m (4H, α,α'-CH_{2Pip}), 2.58 d (1H, CH_2, *J* = 18.1 Hz), 4.25 d (1H, *J* = 13.0 Hz), 4.27 d (1H, NCH_2, *J* = 13.0 Hz). Found, %: C 65.60; H 9.25; N 11.70. $C_{13}H_{22}N_2O_2$. Calculated, %: C 65.51; H 9.30; N 11.75. Oxalate **23**. Mp 123–124°C.

3-Methyl-3-ethyl-1-{[(4-methylphenyl)amino]methyl}pyrrolidine-2,5-dione (8). Yield 72%, mp 65°C. IR spectrum, ν, cm^{-1}: 3357 (NH), 1772, 1694 (CONCO). ^1H NMR spectrum, δ, ppm: 0.71 t (3H, $C\mathbf{H}_3CH_2$, *J* = 7.5 Hz), 1.18 s (3H, CCH_3), 1.47 d. q (1H, $C\mathbf{H}_2CH_3$, *J* = 13.9, 7.5 Hz), 1.59 d. q (1H, CH_2CH_3, *J* = 13.9, 7.5 Hz), 2.19 s (3H, $C\mathbf{H}_3$-Ar), 2.34 d (1H, CH_2, *J* = 18.1 Hz), 2.50 d (1H, CH_2, *J* = 18.1 Hz), 4.80 d (2H, NCH_2, *J* = 7.7 Hz), 5.67 t (1H, NH, *J* = 7.7 Hz), 6.60–6.65 m (2H, C_6H_4), 6.83–6.88 m (2H, C_6H_4). ^{13}C NMR spectrum, δ_C, ppm: 7.9 ($\mathbf{C}H_3CH_2$), 19.9 ($\mathbf{C}H_3$-Ar), 23.1 ($C\mathbf{C}H_3$), 30.4 ($\mathbf{C}H_2CH_3$), 39.6 (CH_2), 43.2 ($\mathbf{C}CH_3$), 48.0 (NCH_2), 113.0 (2CH), 125.8, 128.8 (2CH), 142.7, 174.9 (CON), 181.6 (CON). Found, %: C 69.28; H 7.65; N 10.69. $C_{15}H_{20}N_2O_2$. Calculated, %: C 69.20; H 7.74; N 10.76.

1-{[(4-Isopropoxybenzyl)amino]methyl}-3-methyl-3-ethylpyrrolidine-2,5-dione (9). Yield 53%, mp 124–125°C. IR spectrum, ν, cm^{-1}: 3455 (NH), 1771, 1703 (CONCO). ^1H NMR spectrum, δ, ppm: 0.86 t (3H, $C\mathbf{H}_3CH_2$, *J* = 7.4 Hz), 1.22 s (3H, CCH_3), 1.30 d (6H, $2CH_3$, *J* = 6.0 Hz), 1.54 d. q (1H, CH_2CH_3, *J* = 13.7, 7.4 Hz), 1.65 d. q (1H, CH_2CH_3, *J* = 13.7, 7.4 Hz), 2.36 d (1H, CH_2, *J* = 18.0 Hz), 2.55 d (1H, CH_2, *J* = 18.0 Hz), 3.39 br. s (1H, NH), 3.60 br. s (2H, NCH_2), 4.47 br. s (2H, NCH_2N), 4.50 septet (1H, OCH, *J* = 6.0 Hz), 6.69–6.74 m (2H, C_6H_4), 7.14–7.19 m (2H, C_6H_4). ^{13}C NMR spectrum, δ_C, ppm: 8.2 ($\mathbf{C}H_3CH_2$), 21.6 $(CH_3)_2$, 23.3 ($C\mathbf{C}H_3$), 30.4 ($\mathbf{C}H_2CH_3$), 39.7 (CH_2), 43.2 ($C\mathbf{C}H_3$), 55.1 (NCH_2), 54.4 (NCH_2), 68.6 (OCH), 114.7 (2CH), 129.3 (2CH), 130.5, 156.1, 175.7 (CO), 182.5 (CO). Found, %: C 67.79; H 8.28; N 8.85. $C_{18}H_{26}N_2O_3$. Calculated, %: C 67.90; H 8.23; N 8.80.

4-{[(3-Methyl-3-ethyl-2,5-dioxopyrrolidin-1-yl)-methyl]amino}benzoic acid (10). Yield 70%, mp 186–188°C. IR spectrum, ν, cm^{-1}: 3358 (NH), 1775, 1698 (CONCO). ^1H NMR spectrum, δ, ppm: 0.75 t (3H, $C\mathbf{H}_3CH_2$, *J* = 7.4 Hz), 1.21 s (3H, CH_3), 1.43–1.69 m (2H, $C\mathbf{H}_2CH_3$), 2.40 d (1H, CH_2, *J* = 18.2 Hz), 2.55 d (1H, CH_2, *J* = 18.2 Hz), 4.84 d (2H, NCH_2, *J* = 7.1 Hz), 6.74–6.79 m (2H, C_6H_4), 6.89 br. t (1H, NH, *J* = 7.1 Hz), 7.67–7.72 m (2H, C_6H_4), 11.68 br. s (1H, COOH). ^{13}C

NMR spectrum, δ_C, ppm: 8.0 (CH_3), 23.0 (CH_3), 30.5 (**C**H_2CH_3), 39.6 (CH_2), 43.3 (**C**CH_3), 46.7 (NCH_2), 111.4 (2CH), 119.3, 130.7 (2CH), 149.4, 167.0 (COOH), 174.9 (CON), 181.5 (CON). Found, %: C 62.12; H 6.32; N 9.59. $C_{15}H_{18}N_2O_4$. Calculated, %: C 62.06; H 6.25; N 9.65.

1-{[(4-Acetylphenyl)amino]methyl}-3-methyl-3-ethylpyrrolidine-2,5-dione (11). Yield 78%, mp 110–112°C. IR spectrum, ν, cm^{-1}: 3360 (NH), 1770, 1698 (CONCO), 1662 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.75 t (3H, C**H**$_3$CH$_2$, J = 7.5 Hz), 1.22 s (3H, CH_3), 1.52 d. q (1H, C**H**$_2$CH$_3$, J = 13.8, 7.5 Hz), 1.63 d. q (1H, C**H**$_2$CH$_3$, J = 13.8, 7.5 Hz), 2.40 s (3H, $COCH_3$), 2.40 d (1H, CH_2, J = 18.2 Hz), 2.56 d (1H, CH_2, J = 18.2 Hz), 4.84 d (2H, NCH_2, J = 6.8 Hz), 6.77–6.82 m (2H, C_6H_4), 7.09 br. t (1H, NH, J = 6.8 Hz), 7.65–7.70 m (2H, C_6H_4). ^{13}C NMR spectrum, δ_C, ppm: 8.0 (CH_3), 23.0 (CH_3), 25.3 (CH_3), 30.5 (**C**H_2CH_3), 39.6 (CH_2), 43.3 (**C**CH_3), 46.5 (NCH_2), 111.4 (2CH), 126.6, 129.7 (2CH), 149.9, 174.8 (CON), 181.5 (CON), 193.7 (**C**OCH_3). Found, %: C 66.61; H 6.91; N 9.80. $C_{16}H_{20}N_2O_3$. Calculated, %: C 66.65; H 6.99; N 9.72.

4-{[(3-Methyl-3-ethyl-2,5-dioxopyrrolidin-1-yl)-methyl]amino}-*N*-(5-ethyl-1,3,4-thiadiazol-2-yl) benzenesulfonamide (12). Yield 27.45%, mp 257–260°C. IR spectrum, ν, cm^{-1}: 3379 (NH), 1770, 1689 (CONCO). ^{1}H NMR spectrum, δ, ppm: 0.72 t (3H, CCH_2C**H**$_3$, J = 7.4 Hz), 1.19 s (3H, CCH_3), 1.25 t (3H, C**H**$_3CH_2$, J = 7.5 Hz), 1.49 d. q (1H, CC**H**$_2CH_3$, J = 13.7, 7.4 Hz), 1.60 d. q (1H, CC**H**$_2CH_3$, J = 13.7, 7.4 Hz), 2.41 d (1H, CH_2, J = 18.1 Hz), 2.55 d (1H, CH_2, J = 18.1 Hz), 2.74 q (2H, C**H**$_2CH_3$, J = 7.5 Hz), 4.80 d (2H, NCH_2, J = 7.3 Hz), 6.67 br. t (1H, NH, J = 7.3 Hz), 6.70–6.75 m (2H, C_6H_4), 7.48–7.53 m (2H, C_6H_4). ^{13}C NMR spectrum, δ_C, ppm: 8.0 (**C**H_3CH_2C), 13.6 (**C**H_3CH_2), 23.0 (**C**H_3C), 23.4 (**C**H_2CH_3), 30.4 (CCH_2), 39.6 (CH_2), 43.3 (C), 47.0 (NCH_2), 111.1 (2CH), 127.4 (2CH), 133.4, 147.3, 159.1, 169.1, 175.1 (CO), 181.7 (CO). Found, %: C 49.50; H 5.35; N 16.11. $C_{18}H_{23}N_5O_4S_2$. Calculated, %: C 49.41; H 5.30; N 16.01.

1-({[2-(1-Benzylcyclohexyl)ethyl]amino}methyl)-3-methyl-3-ethylpyrrolidine-2,5-dione (13). Yield 30%, viscous oil. Hydrochloride **24**. Mp 154–155°C. IR spectrum, ν, cm^{-1}: 3361 (NH), 1773, 1702 (CONCO). ^{1}H NMR spectrum, δ, ppm: 0.92 t (3H, C**H**$_3CH_2$, J = 7.4 Hz), 1.19–1.37 m (5H, C_6H_{10}), 1.33 s (3H, CH_3), 1.45–1.58 m (5H, C_6H_{10}), 1.60–1.81 m (4H, C**H**$_2CH_3$ + C**H**$_2CH_2N$), 2.54 s (2H, C**H**$_2$Ph), 2.55 d (1H, CH_2, J = 18.1 Hz), 2.67 d (1H, CH_2, J = 18.1 Hz), 2.99 br. s (2H, NC**H**$_2CH_2$), 4.56 br. s (2H, NCH_2N), 7.11–7.25 m (5H, C_6H_5), 10.24 br. s (2H, NH + HCl). ^{13}C NMR spectrum, δ_C, ppm: 8.1 (CH_3), 20.9, 22.4, 25.4, 30.2, 30.4, 34.3, 35.4, 39.9, 42.6, 43.4, 44.1, 48.0, 125.3 (CH), 127.3 (2CH), 130.2 (2CH), 137.2, 174.0, 180.8. Found, %: C 67.75; H 8.71; N 6.81. $C_{23}H_{34}N_2O_2$·HCl. Calculated, %: C 67.88; H 8.67; N 6.88.

3-(4-Isopropoxyphenyl)-1-{[4-(4-fluorophenyl)-piperazin-1-yl]methyl}pyrrolidine-2,5-dione (14). Yield 36%, mp 157–158°C. IR spectrum, ν, cm^{-1}: 3333, 3177, 1792, 1766, 1713 (CONCO). ^{1}H NMR spectrum, δ, ppm: 1.30 d (6H, $2CH_3$, *i*-Pr, J = 6.0 Hz), 2.63–2.75 m [4H, $N(CH_2)_2$], 2.72 d. d (1H, $COCH_2$, J = 18.1, 5.1 Hz), 3.03–3.08 m [4H, $N(CH_2)_2$], 3.20 d. d (1H, $COCH_2$, J = 18.1, 9.6 Hz), 4.05 d. d (1H, CH, J = 9.6, 5.1 Hz), 4.42 s (2H, NCH_2N), 4.53 septet (1H, OCH, J = 6.0 Hz), 6.77–6.82 m (2H, C_6H_4O), 7.10–7.15 m (2H, C_6H_4O), 6.80–6.93 m (4H, C_6H_4F). ^{13}C NMR spectrum, δ_C, ppm: 21.5 ($2CH_3$), 36.5 (CH_2), 44.5 (CH), 49.2 and 49.8 ($4CH_2$, piperazine), 59.2 (NCH_2N), 68.7 (OCH), 114.7 d (2CH, J_{CF} = 21.9 Hz), 115.4 (2CH), 117.0 d (2CH, J_{CF} = 7.5 Hz), 128.2 (2CH), 129.1, 147.4 d (J_{CF} = 2.2 Hz), 156.0 d (J_{CF} = 238.0 Hz), 156.6, 176.1 (CO), 178.1 (CO). Found, %: C 67.68; H 6.71; N 9.81. $C_{24}H_{28}FN_3O_3$. Calculated, %: C 67.75; H 6.63; N 9.88.

4-({[3-(4-Isopropoxyphenyl)-2,5-dioxopyrrolidin-1-yl]methyl}amino)benzoic acid (15). Yield 65%, mp 204–205°C. IR spectrum, ν, cm^{-1}: 3345 (NH), 1768, 1686 (CONCO). ^{1}H NMR spectrum, δ, ppm: 1.29 d (6H, $2CH_3$, *i*-Pr, J = 6.0 Hz), 2.62 d. d (1H, C**H**$_2$CH, J = 18.1, 4.9 Hz), 3.16 d. d (1H, C**H**$_2$CH, J = 18.1, 9.5 Hz), 4.01 d. d (1H, CH_2C**H**, J = 9.5, 4.9 Hz), 4.51 septet (1H, OCH, J = 6.0 Hz), 4.91 d (2H, NCH_2, J = 7.2 Hz), 6.71–6.76 m (2H, C_6H_4), 6.78–6.83 m (2H, C_6H_4), 6.96 br. t (1H, NH, J = 7.2 Hz), 6.98–7.03 m (2H, C_6H_4), 7.68–7.73 m (2H, C_6H_4), 11.70 br. s (1H, COOH). ^{13}C NMR spectrum, δ_C, ppm: 21.6 ($2CH_3$), 36.8 (CH_2), 44.5 (CH), 47.1 (NCH_2), 68.8 (OCH), 111.5 (2CH), 115.4 (2CH), 119.4, 128.3 (2CH), 129.0, 130.8 (2CH), 149.6, 156.6, 167.1 167.0 (CON), 175.4 (CON), 177.3 (COOH). Found, %: C 65.88; H 5.85; N 7.28. $C_{21}H_{22}N_2O_5$. Calculated, %: C 65.96; H 5.80; N 7.33.

1-{[(4-Acetylphenyl)amino]methyl}-3-(4-isopropoxyphenyl)pyrrolidine-2,5-dione (16). Yield 85%, mp 160–161°C. IR spectrum, ν, cm^{-1}: 3342 (NH), 1766, 1693 (CONCO), 1663 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.29 d (6H, $2CH_3$, *i*-Pr, J = 6.0 Hz), 2.41 s (3H, $COCH_3$), 2.63 d. d (1H, C**H**$_2$CH, J = 18.1, 4.9 Hz), 3.17 d. d (1H, C**H**$_2$CH, J = 18.1, 9.5 Hz), 4.01 d. d (1H,

$CH_2C\mathbf{H}$, J = 9.5, 4.9 Hz), 4.51 septet (1H, OCH, J = 6.0 Hz), 4.91 d (2H, NCH_2, J = 7.0 Hz), 6.71–6.76 m (2H, C_6H_4), 6.81–6.86 m (2H, C_6H_4), 7.00–7.05 m (2H, C_6H_4), 7.16 br. t (1H, NH, J = 7.0 Hz), 7.67–7.72 m (2H, C_6H_4). ^{13}C NMR spectrum, δ_C, ppm: 21.5 ($2CH_3$), 25.3 (CH_3), 36.7 (CH_2), 44.4 (CH), 46.8 (NCH_2), 68.7 (OCH), 111.5 (2CH), 115.3 (2CH), 126.6, 128.2 (2CH), 128.9, 129.7 (2CH), 150.0, 156.5, 175.3 (CON), 177.2 (CON), 193.8 ($\mathbf{C}OCH_3$). Found, %: C 69.52; H 6.30; N 7.40. $C_{22}H_{24}N_2O_4$. Calculated, %: C 69.46; H 6.36; N 7.36.

Ethyl 4-({[3-(4-isopropoxyphenyl)-2,5-dioxopyrrolidin-1-yl]methyl}amino)benzoate (17). Yield 89%, mp 144–146°C. IR spectrum, ν, cm^{-1}: 3336 (NH), 1773, 1688 (CONCO). ^1H NMR spectrum, δ, ppm: 1.29 d (6H, $2CH_3$, *i*-Pr, J = 6.0 Hz), 1.34 t (3H, CH_3, J = 7.1 Hz), 2.62 d. d (1H, $C\mathbf{H}_2CH$, J = 18.2, 4.9 Hz), 3.16 d. d (1H, $C\mathbf{H}_2CH$, J = 18.2, 9.5 Hz), 4.00 d. d (1H, $CH_2C\mathbf{H}$, J = 9.5, 4.9 Hz), 4.23 q (2H, OCH_2, J = 7.1 Hz), 4.50 septet (1H, OCH, J = 6.0 Hz), 4.91 d (2H, NCH_2, J = 7.2 Hz), 6.70–6.75 m (2H, C_6H_4), 6.79–6.84 m (2H, C_6H_4), 6.98–7.03 m (2H, C_6H_4), 7.04 br. t (1H, NH, J = 7.2 Hz), 7.70–7.75 m (2H, C_6H_4). ^{13}C NMR spectrum, δ_C, ppm: 14.0 ($\mathbf{C}H_3CH_2$), 21.5 ($2CH_3$), 36.8 (CH_2), 44.4 (CH), 46.9 (NCH_2), 58.9 (OCH_2), 68.7 (OCH), 111.5 (2CH), 115.3 (2CH), 118.4, 128.2 (2CH), 129.0, 130.5 (2CH), 149.8, 156.5, 165.1, 175.3, 177.2. Found, %: C 67.41; H 6.45; N 6.87. $C_{23}H_{26}N_2O_5$. Calculated, %: C 67.30; H 6.38; N 6.82.

1-{[(3-Bromophenyl)amino]methyl}-3-(4-isopropoxyphenyl)pyrrolidine-2,5-dione (18). Yield 52%, mp 107–109°C. IR spectrum, ν, cm^{-1}: 3415, 3377 (NH), 1769, 1699 (CONCO). ^1H NMR spectrum, δ, ppm: 1.30 d (6H, $2CH_3$, *i*-Pr, J = 6.0 Hz), 2.60 d. d (1H, $C\mathbf{H}_2CH$, J = 18.1, 4.9 Hz), 3.16 d. d (1H, $C\mathbf{H}_2CH$, J = 18.1, 9.5 Hz), 4.00 d. d (1H, $CH_2C\mathbf{H}$, J = 9.5, 4.9 Hz), 4.51 septet (1H, OCH, J = 6.0 Hz), 4.85 d (2H, NCH_2, J = 7.3 Hz), 6.60 br. t (1H, NH, J = 7.3 Hz), 6.70–6.78 m (4H, C_6H_4), 6.94–7.03 m (4H, C_6H_4). ^{13}C NMR spectrum, δ_C, ppm: 21.5 ($2CH_3$), 36.8, 44.4, 47.3, 68.7, 111.1, 115.3, 115.4, 119.5, 122.2, 128.2, 129.1, 129.8, 147.3, 156.5, 175.4, 177.3. Found, %: C 57.47; H 5.16; N 6.65. $C_{20}H_{21}BrN_2O_3$. Calculated, %: C 57.56; H 5.07; N 6.71.

1-{[(4-Bromophenylamino)amino]methyl}-3-(4-isopropoxyphenyl)pyrrolidine-2,5-dione (19). Yield 80%, mp 136–138°C. IR spectrum, ν, cm^{-1}: 3328 (NH), 1772, 1693 (CONCO). ^1H NMR spectrum, δ, ppm: 1.30 d (6H, $2CH_3$, *i*-Pr, J = 6.0 Hz), 2.58 d. d (1H, $C\mathbf{H}_2CH$, J = 18.2, 4.8 Hz), 3.15 d. d (1H, $C\mathbf{H}_2CH$, J = 18.2, 9.5 Hz), 3.98 d. d (1H, $CH_2C\mathbf{H}$, J = 9.5, 4.8 Hz), 4.51 septet (1H, OCH, J = 6.0 Hz), 4.85 d (2H, NCH_2, J = 7.4 Hz), 6.44 br. t (1H, NH, J = 7.4 Hz), 6.70–6.76 m (4H, C_6H_4), 6.93–6.98 m (2H, C_6H_4), 7.13–7.18 m (2H, C_6H_4). Found, %: C 57.68; H 5.10; N 6.64. $C_{20}H_{21}BrN_2O_3$. Calculated, %: C 57.56; H 5.07; N 6.71.

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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