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Multicomponent Synthesis and Antimicrobial Activity of Alkyl 4-Arylamino-1,2,6-triaryl-1,2,5,6-tetrahydropyridine-3-carboxylates

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Abstract—Reaction of arylamines with aromatic aldehydes and β-ketoesters in the presence of bismuth nitrate or crystalline iodine as a catalyst afforded to alkyl 4-arylamino-1,2,6-triaryl-1,2,5,6-tetrahydropyridine-3-carboxy-lates. Antimicrobial activity of the obtained compounds was studied.

Keywords: multicomponent synthesis, tetrahydropyridines, antimicrobial activity

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Tetrahydropyridine derivatives are widely used as antibacterial [1], antimalarial [2], antihypertensive [3], anti-inflammatory, anticonvulsant [4] and other pharmaceuticals [5]. Furthermore, some of them possess enzyme-inhibiting properties [6]. Consequently, the development of effective methods for the preparation of this class of compounds is of interest as evidenced by a number of publications [7–10]. Over the last few years a large number of tetrahydropyridine derivatives have been in preclinical and clinical trials [11].

Lately, multicomponent synthesis of tetrahydropyridine derivatives via reacting aldehydes, nucleophiles and 1,3-dicarbonyl compounds in the presence of various Lewis acids acting as catalysts has been of special interest. The advantages of this method are as follows: eco-friendly mild reaction conditions, the cheapness and availability of the reagents, and small reaction time [12–16].

In order to search for new bioactive substances among the tetrahydropyridine derivatives and to establish the structure–activity relationship we performed the synthesis of these compounds by reacting [12–17] aromatic aldehydes with arylamines and β-ketoesters. It was found that the reaction of these reagents at a molar ratio of 2 : 2 : 1 at room temperature in the presence of bismuth nitrate and crystalline iodine as catalyst in ethanol afforded to alkyl 4-arylamino-1,2,6-triaryl-1,2,5,6-tetrahydropyridine-3-carboxylates **Ia**–**Iy** (Scheme 1).

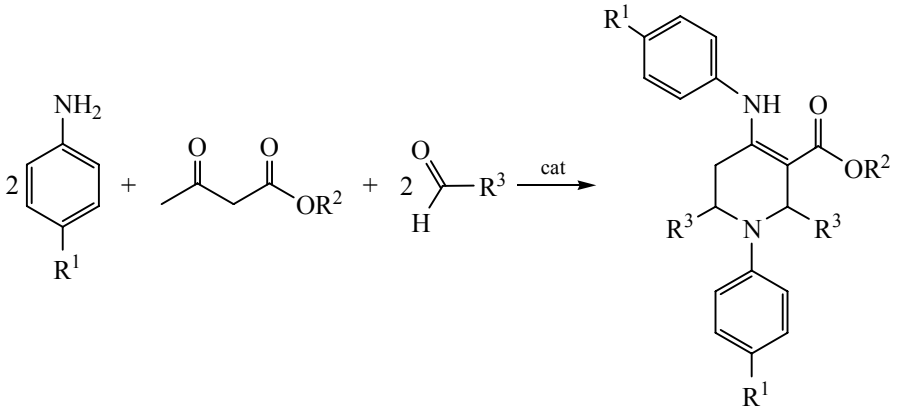
The obtained compound **Ia**–**Iy** were white or pale yellow crystalline solids soluble in DMF, DMSO and acetic acid, upon heating in chloroform, ethyl acetate, methanol, ethanol, and 2-propanol, insoluble in water.

The IR spectra of compounds **Ia**–**Iy** contained absorption bands of stretching vibrations of amino group (3220–3280 cm^{-1}) and ester carbonyl moiety in the position *3* (1644–1670 cm^{-1}). In the ^1H NMR spectra of compounds **Ia**–**Iy** there were the signals of aromatic ring (6.06–7.88 ppm), methylene group in the position *5* as AB system (2.42–2.97, 2.61–3.38 ppm, *J* 15.6 Hz), the protons H^6 (4.93–6.12 ppm) and H^2 (5.50–6.40 ppm) as well as of NH group (9.89–10.69 ppm).

Mass spectrum of **Ia** contained the molecular ion peak $[M]^+$ with *m*/*z* 460 and the fragment ion peaks with *m*/*z* 383 $[M - Ph]^+$, 368 $[M - PhNH]^+$, 180 $[PhNCH_2Ph]^+$, 77 $[Ph]^+$ that confirmed the suggested structure. Mass spectra of other compounds **Ib**–**Iy** were similar.

The assumed mechanism of this reaction is analogous to that described previously in the literature [2, 10, 12, 13, 17]. The aromatic amine reacts with β-ketoester and an aromatic aldehyde in the presence of a catalyst to form enamine **A** and imine **B**, respectively.

Scheme 1.



Ia–Iy

cat = $Bi(NO_3)_3$; R^1 = H, R^2 = CH_3, R^3 = C_6H_5 (**Ia**); R^1 = H, R^2 = C_2H_5, R^3 = C_6H_5 (**Ib**); R^1 = H, R^2 = $CH_2C_6H_5$, R^3 = 4-$(CH_3)_3CC_6H_4$ (**Ic**); R^1 = CH_3, R^2 = C_2H_5, R^3 = C_6H_5 (**Id**); R^1 = CH_3, R^2 = $(CH_3)_2CH$, R^3 = 4-$C_2H_5C_6H_4$ (**Ie**); R^1 = CH_3, R^2 = $CH_2C_6H_5$, R^3 = 4-$C_2H_5C_6H_4$ (**If**); R^1 = CH_3O, R^2 = CH_3, R^3 = 4-$CH_3OC_6H_4$ (**Ig**); R^1 = CH_3O, R^2 = C_2H_5, R^3 = 4-$C_2H_5C_6H_4$ (**Ih**); R^1 = CH_3O, R^2 = $(CH_3)_2CH$, R^3 = 4-$C_2H_5C_6H_4$ (**Ii**); kt = I_2; R^1 = H, R^2 = CH_3, R^3 = 2-thienyl (**Ij**); R^1 = H, R^2 = C_2H_5, R^3 = 4-$C_2H_5C_6H_4$ (**Ik**); R^1 = H, R^2 = C_2H_5, R^3 = 2-thienyl (**Il**); R^1 = H, R^2 = $(CH_3)_2CH$, R^3 = 2-thienyl (**Im**); R^1 = H, R^2 = $(CH_3)_3C$, R^3 = 2-thienyl (**In**); R^1 = H, R^2 = $CH_2C_6H_5$, R^3 = C_6H_5 (**Io**); R^1 = CH_3, R^2 = CH_3, R^3 = C_6H_5 (**Ip**); R^1 = CH_3, R^2 = CH_3, R^3 = 4-$CH_3OC_6H_4$ (**Iq**); R^1 = CH_3, R^2 = $(CH_3)_3C$, R^3 = 4-$CH_3OC_6H_4$ (**Ir**); R^1 = CH_3, R^2 = $CH_2C_6H_5$, R^3 = 4-$CH_3OC_6H_4$ (**Is**); R^1 = CH_3O, R^2 = CH_3, R^3 = C_6H_5 (**It**); R^1 = CH_3O, R^2 = C_2H_5, R^3 = C_6H_5 (**Iu**); R^1 = CH_3O, R^2 = C_2H_5, R^3 = 4-$(CH_3)_3CC_6H_4$ (**Iv**); R^1 = CH_3O, R^2 = C_2H_5, R^3 = 2-thienyl (**Iw**); R^1 = CH_3O, R^2 = $(CH_3)_2CH$, R^3 = C_6H_5 (**Ix**); R^1 = CH_3O, R^2 = $CH_2C_6H_5$, R^3 = C_6H_5 (**Iy**).

Next, the imine reacts with the enamine followed by inter- and intramolecular Mannich reactions to form alkyl 4-arylamino-1,2,6-triaryl-1,2,5,6-tetrahydropyridine-3-carboxylates **Ia**–**Iy**.

Compounds **Ia**, **Ic–Id**, **If–Ig**, **Ij**, **Im–Ip**, and **Io–Iw** were tested for antimicrobial activity against strains of *Escherichia coli* ATCC 6538-P and *Staphylococcus aureus* ATCC 25922. Minimum inhibitory concentration (MIC) values are presented in the table. The most active of the compounds studied by us were derivatives **Ia**, **Ig**, **Im**, **Io**) (Scheme 2).

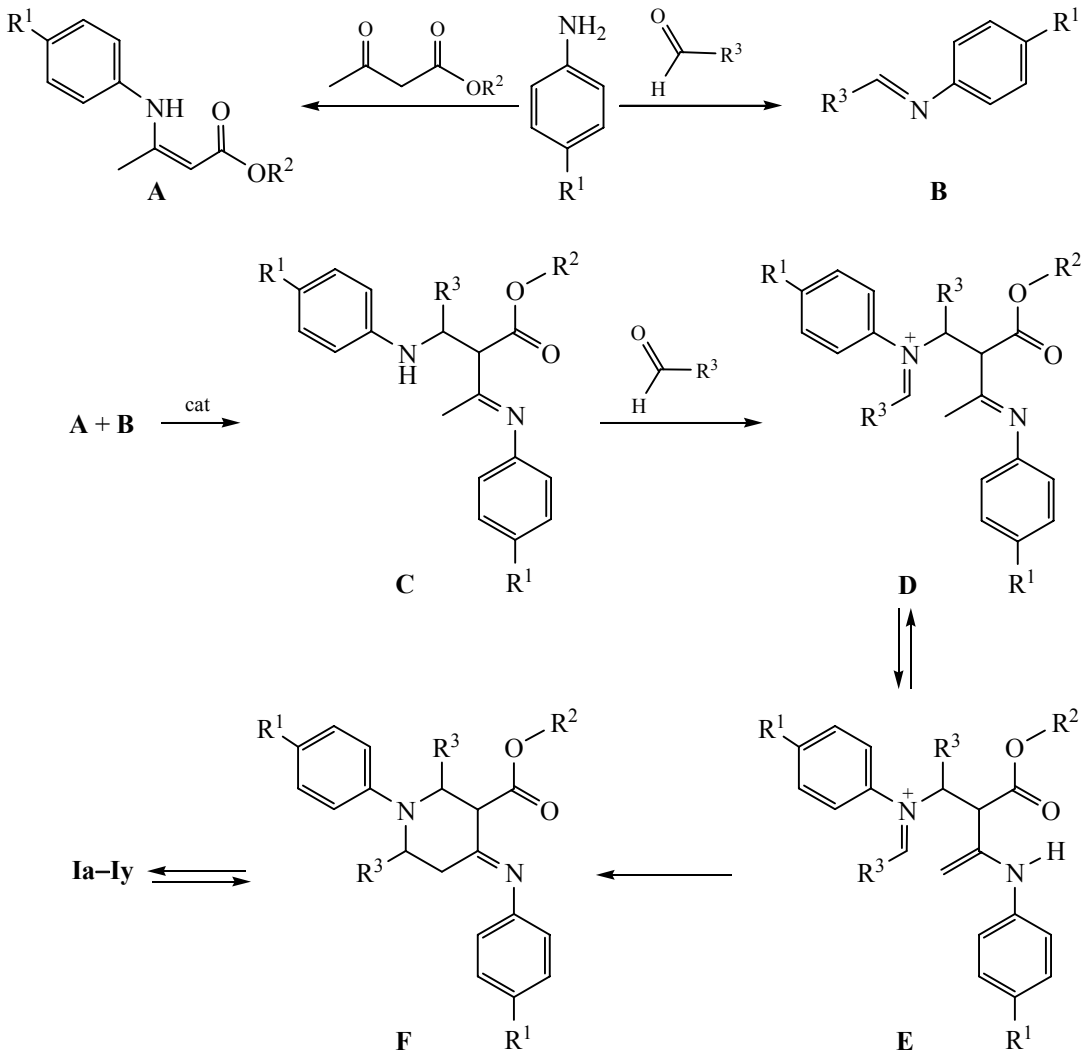
EXPERIMENTAL

IR spectra were recorded on a Specord M-80 spectrometer from KBr pellets. ^{1}H NMR spectra were registered on a Bruker DRX 500 (500 MHz), Bruker AVANCE III HD 400 (400 MHz) and Bruker AM-300 (300 MHz) spectrometers in DMSO-d_6 or $CDCl_3$, internal reference TMS. ^{13}C NMR spectra were obtained on a Bruker AVANCE III HD 400 spectrometer operating at 100 MHz in $CDCl_3$. Mass spectra were taken on a Finnigan MAT INCOS-50 spectrometer (70 eV). Elemental analysis was performed on a Perkin Elmer 2400 instrument. Melting points were determined on a Melting Point M-565 instrument.

Antimicrobial activity of alkyl 4-arylamino-1,2,6-triaryl-1,2,5,6-tetrahydropyridine-3-carboxylates

Compound	MIC, μg mL^{-1}	
	Escherichia coli ATCC 6538-P	*Staphylococcus aureus* ATCC 25922
Ia	250	250
Ic	>1000	1000
Id	1000	1000
If	1000	1000
Ig	250	250
Ij	1000	1000
Im	250	250
In	500	500
Io	250	250
Ip	>1000	1000
Iv	1000	500
Iw	>1000	1000
Furacilin	125	250
Dioxidine	62.5–1000	3.9–62.5

Scheme 2.



Methyl 1,2,6-triphenyl-4-phenylamino-1,2,5,6-tetrahydropyridine-3-carboxylate (Ia). A mixture of 0.02 mol of the aromatic amine, 0.01 mol of β-ketoester, and 0.01 mol of catalyst [$Bi(NO_3)_3$ or I_2] dissolved in 25 mL of ethanol was stirred at room temperature for 25 min. Then 0.02 mol of aromatic aldehyde was added. The mixture was kept at room temperature for 1–3 days. The resulting precipitate was filtered off and recrystallized from a mixture of ethanol–ethyl acetate (2 : 1). Yield 3.69 g (81%), mp 168–170°C. IR spectrum, ν, cm^{-1}: 3260 (NH), 1670 (C=O). ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.78 d.d (1H, $C^5\underline{H}_AH_B$, *J* 15.6, 2.3), 2.93 d.d (1H, $C^5H_A\underline{H}_B$, *J* 15.6, 5.8), 3.88 s (3H, OCH_3), 5.37–5.39 m (1H, C^6H), 6.33 s (1H, C^2H), 6.36–7.35 m (20H, $4C_6H_5$), 10.15 s (1H, NH). Found, %: C 80.70; H 6.15; N 6.19. $C_{31}H_{28}N_2O_2$. Calculated, %: C 80.84; H 6.13; N 6.08.

Compounds **Ib**–**Iy** were prepared similarly.

Ethyl 1,2,6-triphenyl-4-phenylamino-1,2,5,6-tetrahydropyridine-3-carboxylate (Ib). Yield 3.94 g (82%), mp 173–175°C. IR spectrum, ν, cm^{-1}: 3256 (NH), 1660 (C=O). ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.44 t (3H, $OCH_2\underline{CH}_3$, *J* 7.0), 2.80 d.d (1H, $C^5\underline{H}_AH_B$, *J* 15.6, 2.4), 2.92 d.d (1H, $C^5H_A\underline{H}_B$, *J* 15.6, 5.9), 4.31 m (1H, $OC\underline{H}_AH_BCH_3$), 4.42 m (1H, $OCH_A\underline{H}_BCH_3$), 5.31–5.32 m (1H, C^6H), 6.33 s (1H, C^2H), 6.34–7.57 m (20H, $4C_6H_5$), 10.26 s (1H, NH). Found, %: C 81.09; H 6.35; N 5.79. $C_{32}H_{30}N_2O_2$. Calculated, %: C 80.98; H 6.37; N 5.90.

Benzyl 2,6-di(4-*tert*-butylphenyl)-1-phenyl-4-phenylamino-1,2,5,6-tetrahydropyridine-3-carboxylate (Ic). Yield 4.54 g (70%), mp 171–172°C. IR spectrum, ν, cm^{-1}: 3220 (NH), 1648 (C=O). ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.25 s [3H, ($\underline{CH_3}$)$_3$CC$_6$H$_4$], 1.29 s [3H, ($\underline{CH_3}$)$_3$CC$_6$H$_4$], 2.69 d.d (1H, C$^5\underline{H_A}H_B$, *J* 15.6, 2.6), 2.71 d.d (1H, C$^5H_A\underline{H_B}$, *J* 15.6, 6.0), 5.20 d (1H, OC$\underline{H_A}H_BC_6H_5$, *J* 3.0), 5.42 d (1H, OCH$_A\underline{H_B}$C$_6$H$_5$, *J* 3.0), 6.00–6.12 m (1H, C^{6}H), 6.40 s (1H, C^{2}H), 6.55–7.40 m (23H, 2C$_6$H$_4$, 3C$_6$H$_5$), 10.14 s (1H, NH). Found, %: C 83.47; H 4.51; N 4.16. $C_{45}H_{48}N_2O_2$. Calculated, %: C 83.30; H 4.46; N 4.32.

Ethyl 1-(4-methylphenyl)-4-(4-methylphenylamino)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (Id). Yield 3.92 g (78%), mp 173–175°C. IR spectrum, ν, cm^{-1}: 3240 (NH), 1652 (C=O). ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.42 t (3H, OCH$_2\underline{CH_3}$, *J* 7.0), 2.12 s (3H, 4-$\underline{CH_3}$C$_6$H$_4$), 2.21 s (3H, 4-$\underline{CH_3}$C$_6$H$_4$), 2.72 d.d (1H, C$^5\underline{H_A}H_B$, *J* 15.6, 2.3), 2.76 d.d (1H, C$^5H_A\underline{H_B}$, *J* 15.6, 5.7), 4.25 m (1H, OC$\underline{H_A}H_BCH_3$), 4.31 m (1H, OCH$_A\underline{H_B}$CH$_3$), 5.03 m (1H, C^{6}H), 6.03 s (1H, C^{2}H), 6.33–7.43 m (18H, 2C$_6$H$_4$, 2C$_6$H$_5$), 10.07 s (1H, NH). Found, %: C 81.40; H 6.79; N 5.44. $C_{34}H_{34}N_2O_2$. Calculated, %: C 81.24; H 6.82; N 5.57.

Isopropyl 1-(4-methylphenyl)-4-(4-methylphenylamino)-2,6-di(4-ethylphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (Ie). Yield 4.29 g (75%), mp 168–169°C. IR spectrum, ν, cm^{-1}: 3240 (NH), 1656 (C=O). ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.13 d [3H, OCH($\underline{CH_3}$)$_2$, *J* 6.0], 1.15 t (3H, $\underline{CH_3}$CH$_2$C$_6$H$_4$, *J* 7.5), 1.25 t (3H, $\underline{CH_3}$CH$_2$C$_6$H$_4$, *J* 7.5), 1.30 d [3H, OCH($\underline{CH_3}$)$_2$, *J* 6.0], 2.05 s (3H, 4-$\underline{CH_3}$C$_6$H$_4$), 2.19 s (3H, 4-$\underline{CH_3}$C$_6$H$_4$), 2.42 d.d (1H, C$^5\underline{H_A}H_B$, *J* 15.6, 2.9), 2.45 q (2H, CH$_3\underline{CH_2}$C$_6$H$_4$, *J* 7.5), 2.53 q (2H, CH$_3\underline{CH_2}$C$_6$H$_4$, *J* 7.5), 2.61 d.d (1H, C$^5H_A\underline{H_B}$, *J* 15.6, 5.8), 4.98 m [1H, O$\underline{CH}$(CH$_3$)$_2$], 5.11 m (1H, C^{6}H), 5.80 s (1H, C^{2}H), 6.08–7.30 m (16H, 4C$_6$H$_4$), 10.09 s (1H, NH). Found, %: C 81.61; H 7.78; N 5.01. $C_{39}H_{44}N_2O_2$. Calculated, %: C 81.78; H 7.74; N 4.89.

Benzyl 1-(4-methylphenyl)-4-(4-methylphenylamino)-2,6-di(4-ethylphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (If). Yield 4.18 g (69%), mp 165–166°C. IR spectrum, ν, cm^{-1}: 3220 (NH), 1648 (C=O). ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.08 t (3H, 4-$\underline{CH_3}$CH$_2$C$_6$H$_4$, *J* 7.0), 1.21 t (3H, 4-$\underline{CH_3}$CH$_2$C$_6$H$_4$, *J* 7.0), 2.11 s (3H, 4-$\underline{CH_3}$C$_6$H$_4$), 2.25 s (3H, 4-$\underline{CH_3}$C$_6$H$_4$), 2.63 q (2H, 4-CH$_3\underline{CH_2}$C$_6$H$_4$, *J* 7.0), 2.64 d.d (1H, C$^5\underline{H_A}H_B$, *J* 15.6, 2.3), 2.69 q (2H, 4-CH$_3\underline{CH_2}$C$_6$H$_4$, *J* 7.0), 2.82 d.d (1H, C$^5H_A\underline{H_B}$, *J* 15.6, 5.8), 4.58 d (1H, OC$\underline{H_A}H_BC_6H_5$, *J* 3.0), 4.61 d (1H, OCH$_A\underline{H_B}$C$_6$H$_5$, *J* 3.0), 5.13–5.25 m (1H, C^{6}H), 5.90 s (1H, C^{2}H), 6.65–7.88 m (21H, 4C$_6$H$_4$, C$_6$H$_5$), 10.43 s (1H, NH). Found, %: C 83.28; H 6.95; N 4.49. $C_{42}H_{42}N_2O_2$. Calculated, %: C 83.13; H 6.98; N 4.62.

Methyl 1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-2,6-di(4-methoxyphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (Ig). Yield 4.76 g (82%), mp 179–180°C. IR spectrum, ν, cm^{-1}: 3220 (NH), 1664 (C=O). ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.46 d.d (1H, C$^5\underline{H_A}H_B$, *J* 15.6, 2.4), 2.66 d.d (1H, C$^5H_A\underline{H_B}$, *J* 15.6, 5.6), 3.59 s (3H, 4-$\underline{CH_3}$OC$_6$H$_4$), 3.66 s (3H, 4-$\underline{CH_3}$OC$_6$H$_4$), 3.69 s (3H, 4-$\underline{CH_3}$OC$_6$H$_4$), 3.72 s (3H, 4-$\underline{CH_3}$OC$_6$H$_4$), 3.78 s (3H, OCH$_3$), 5.01 m (1H, C^{6}H), 6.02 s (1H, C^{2}H), 6.21–7.35 m (16H, 4C$_6$H$_4$), 9.92 s (1H, NH). Found, %: C 72.25; H 6.29; N 4.69. $C_{35}H_{36}N_2O_6$. Calculated, %: C 72.40; H 6.25; N 4.82.

Ethyl 1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-2,6-di(4-ethylphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (Ih). Yield 5.01 g (85%), mp 172–173°C. IR spectrum, ν, cm^{-1}: 3220 (NH), 1648 (C=O). ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.09 t (3H, $\underline{CH_3}$CH$_2$C$_6$H$_4$, *J* 7.5), 1.21 t (3H, $\underline{CH_3}$CH$_2$C$_6$H$_4$, *J* 7.5), 1.39 t (3H, OCH$_2\underline{CH_3}$, *J* 7.0), 2.49 d.d (1H, C$^5\underline{H_A}H_B$, *J* 15.6, 2.5), 2.55 q (2H, CH$_3\underline{CH_2}$C$_6$H$_4$, *J* 7.5), 2.63 q (2H, CH$_3\underline{CH_2}$C$_6$H$_4$, *J* 7.5), 2.75 d.d (1H, C$^5H_A\underline{H_B}$, *J* 15.6, 5.8), 3.65 s (3H, 4-$\underline{CH_3}$OC$_6$H$_4$), 3.73 s (3H, 4-$\underline{CH_3}$OC$_6$H$_4$), 4.27 m (1H, OC$\underline{H_A}H_BCH_3$), 4.33 m (1H, OCH$_A\underline{H_B}$CH$_3$), 5.08 m (1H, C^{6}H), 6.08 s (1H, C^{2}H), 6.16–7.76 m (16H, 4C$_6$H$_4$), 9.95 s (1H, NH). Found, %: C 77.09; H 7.21; N 4.87. $C_{38}H_{42}N_2O_4$. Calculated, %: C 77.26; H 7.17; N 4.74.

Isopropyl 1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-2,6-di(4-ethylphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (Ii). Yield 4.41 g (73%), mp 162–163°C. IR spectrum, ν, cm^{-1}: 3220 (NH), 1648 (C=O). ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.09 t (3H, $\underline{CH_3}$CH$_2$C$_6$H$_4$, *J* 7.5), 1.19 t (3H, $\underline{CH_3}$CH$_2$C$_6$H$_4$, *J* 7.5), 1.33 d [3H, OCH($\underline{CH_3}$)$_2$, *J* 6.0], 1.38 d [3H, OCH($\underline{CH_3}$)$_2$, *J* 6.0], 2.49 d.d (1H, C$^5\underline{H_A}H_B$, *J* 15.6, 2.9), 2.54 q (2H, CH$_3\underline{CH_2}$C$_6$H$_4$, *J* 7.5), 2.57 q (2H, CH$_3\underline{CH_2}$C$_6$H$_4$, *J* 7.5), 2.69 d.d (1H, C$^5H_A\underline{H_B}$, *J* 15.6, 5.8), 3.52 s (3H, 4-$\underline{CH_3}$OC$_6$H$_4$), 3.64 s (3H, 4-$\underline{CH_3}$OC$_6$H$_4$), 4.51 m [1H, O$\underline{CH}$(CH$_3$)$_2$], 5.10 m (1H, C^{6}H), 5.50 s (1H, C^{2}H), 6.06–7.20 m (16H,

4C_6H_4), 9.99 s (1H, NH). Found, %: C 77.29; H 7.36; N 4.81. $C_{39}H_{44}N_2O_4$. Calculated, %: C 77.45; H 7.33; N 4.63.

Methyl 2,6-di(2-thienyl)-1-phenyl-4-phenylamino-1,2,5,6-tetrahydropyridine-3-carboxylate (Ij). Yield 3.82 g (81%), mp 171–172°C. IR spectrum, ν, cm^{-1}: 3280 (NH), 1660 (C=O). ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.77 d.d (1H, $C^5\underline{H}_AH_B$, *J* 15.2, 12.0), 2.85 d.d (1H, $C^5H_A\underline{H}_B$, *J* 15.2, 4.0), 3.71 s (3H, OCH_3), 5.07–5.15 m (1H, C^6H), 6.01 s (1H, C^2H), 6.70–7.48 m (16H, 2C_6H_5, 2-thienyl), 10.44 s (1H, NH). Found, %: C 68.51; H 5.15; N 5.86. $C_{27}H_{24}N_2O_2S_2$. Calculated, %: C 68.62; H 5.12; N 5.93.

Ethyl 1-phenyl-4-phenylamino-2,6-di(4-ethylphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (Ik). Yield 4.14 g (78%), mp 176–178°C. IR spectrum, ν, cm^{-1}: 3232 (NH), 1660 (C=O). ^1H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.10 t (3H, $\underline{CH}_3CH_2C_6H_4$, *J* 7.5), 1.24 t (3H, $\underline{CH}_3CH_2C_6H_4$, *J* 7.5), 1.41 t (3H, $OCH_2\underline{CH}_3$, *J* 7.0), 2.46 d.d (1H, $C^5\underline{H}_AH_B$, *J* 15.6, 2.5), 2.53 q (2H, $CH_3\underline{CH}_2C_6H_4$, *J* 7.5), 2.60 q (2H, $CH_3\underline{CH}_2C_6H_4$, *J* 7.5), 2.76 d.d (1H, $C^5H_A\underline{H}_B$, *J* 15.6, 5.8), 4.22 m (1H, $OC\underline{H}_AH_BCH_3$), 4.36 m (1H, $OCH_A\underline{H}_BCH_3$), 5.19 m (1H, C^6H), 6.21 s (1H, C^2H), 6.29–7.41 m (18H, 2C_6H_5, 2C_6H_4), 10.11 s (1H, NH). Found, %: C 81.56; H 7.25; N 5.39. $C_{36}H_{38}N_2O_2$. Calculated, %: C 81.48; H 7.22; N 5.28.

Ethyl 2,6-di(2-thienyl)-1-phenyl-4-phenylamino-1,2,5,6-tetrahydropyridine-3-carboxylate (Il). Yield 4.09 g (84%), mp 205–206°C. IR spectrum, ν, cm^{-1}: 3240 (NH), 1656 (C=O). ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.37 t (3H, $OCH_2\underline{CH}_3$, *J* 7.0), 2.97 d.d (1H, $C^5\underline{H}_AH_B$, *J* 15.6, 12.2), 3.04 d.d (1H, $C^5H_A\underline{H}_B$, *J* 15.6, 4.2), 4.22 m (1H, $OC\underline{H}_AH_BCH_3$), 4.39 m (1H, $OCH_A\underline{H}_BCH_3$), 4.93–5.01 m (1H, C^6H), 6.26 s (1H, C^2H), 6.81–7.41 m (16H, 2C_6H_5, 2-thienyl), 10.69 s (1H, NH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ_C, ppm: 14.05, 36.52, 55.71, 59.11, 59.31, 98.50, 116.11, 118.87, 123.48, 123.52, 123.59, 124.10, 124.57, 125.99, 126.53, 128.53, 128.86, 138.00, 147.97, 149.64, 142.31, 156.55, 167.37. Found, %: C 69.22; H 5.35; N 5.78. $C_{28}H_{26}N_2O_2S_2$. Calculated, %: C 69.11; H 5.39; N 5.93.

Isopropyl 2,6-di(2-thienyl)-1-phenyl-4-phenylamino-1,2,5,6-tetrahydropyridine-3-carboxylate (Im). Yield 3.95 g (79%), mp 209–210°C. IR spectrum, ν, cm^{-1}: 3240 (NH), 1648 (C=O). ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.30 d [3H, OCH($\underline{CH}_3$)$_2$, *J* 6.0], 1.36 d [3H, OCH($\underline{CH}_3$)$_2$, *J* 6.0], 2.77 d.d (1H, $C^5\underline{H}_AH_B$, *J* 15.6, 12.0), 2.85 d.d (1H, $C^5H_A\underline{H}_B$, *J* 15.6, 4.4), 4.93 m [1H, O$\underline{CH}$(CH_3)$_2$], 5.13–5.20 m (1H, C^6H), 6.21 s (1H, C^2H), 6.71–7.41 m (16H, 2C_6H_5, 2-thienyl), 10.67 s (1H, NH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ_C, ppm: 21.60, 36.47, 55.82, 58.93, 66.73, 98.90, 116.08, 118.79, 123.36, 123.45, 123.54, 124.07, 124.44, 125.94, 126.43, 128.17, 128.80, 138.05, 148.00, 149.65, 152.27, 156.27, 166.96. Found, %: C 69.70; H 5.66; N 5.43. $C_{29}H_{28}N_2O_2S_2$. Calculated, %: C 69.57; H 5.64; N 5.59.

***tert*-Butyl 2,6-di(2-thienyl)-1-phenyl-4-phenylamino-1,2,5,6-tetrahydropyridine-3-carboxylate (In).** Yield 4.01 g (78%), mp 180–181°C. IR spectrum, ν, cm^{-1}: 3250 (NH), 1648 (C=O). ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.58 s [9H, OC(CH_3)$_3$], 2.92 d.d (1H, $C^5\underline{H}_AH_B$, *J* 15.2, 12.0), 3.01 d.d (1H, $C^5H_A\underline{H}_B$, *J* 15.2, 4.0), 4.93–4.97 m (1H, C^6H), 6.19 s (1H, C^2H), 6.81–7.41 m (16H, 2C_6H_5, thienyl), 10.60 s (1H, NH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ_C, ppm: 27.73, 28.00, 36.48, 55.77, 59.31, 79.84, 100.15, 115.95, 123.31, 123.38, 123.43, 123.50, 124.05, 124.25, 125.94, 126.34, 128.16, 128.76, 138.22, 148.11, 149.69, 152.25, 155.53, 167.13. Found, %: C 70.18; H 5.84; N 5.57. $C_{30}H_{30}N_2O_2S_2$. Calculated, %: C 70.01; H 5.87; N 5.44.

Benzyl 1,2,6-triphenyl-4-phenylamino-1,2,5,6-tetrahydropyridine-3-carboxylate (Io). Yield 3.86 g (72%), mp 218–220°C. IR spectrum, ν, cm^{-1}: 3240 (NH), 1648 (C=O). ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.70 d.d (1H, $C^5\underline{H}_AH_B$, *J* 15.6, 2.7), 2.82 d.d (1H, $C^5H_A\underline{H}_B$, *J* 15.6, 6.0), 4.01 d (1H, $OC\underline{H}_AH_BC_6H_5$, *J* 3.0), 4.08 d (1H, $OCH_A\underline{H}_BC_6H_5$, *J* 3.0), 5.40 m (1H, C^6H), 6.34 s (1H, C^2H), 6.37–7.61 m (25H, 5C_6H_5), 10.12 s (1H, NH). Found, %: C 82.69; H 6.04; N 5.35. $C_{37}H_{32}N_2O_2$. Calculated, %: C 82.81; H 6.01; N 5.22.

Methyl 1-(4-methylphenyl)-4-(4-methylphenylamino)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (Ip). Yield 4.05 g (83%), mp 181–182°C. IR spectrum, ν, cm^{-1}: 3256 (NH), 1656 (C=O). ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.08 s (3H, 4-$\underline{CH}_3C_6H_4$), 2.22 s (3H, 4-$\underline{CH}_3C_6H_4$), 2.74 d.d (1H, $C^5\underline{H}_AH_B$, *J* 15.6, 2.3), 3.03 d.d (1H, $C^5H_A\underline{H}_B$, *J* 15.6, 5.7), 3.84 s (3H, OCH_3), 5.14 m (1H, C^6H), 6.07 s (1H, C^2H), 6.15–7.14 m (18H, 2C_6H_4, 2C_6H_5), 10.01 s (1H, NH). Found, %: C 81.29; H 6.57; N 5.88. $C_{33}H_{32}N_2O_2$. Calculated, %: C 81.12; H 6.60; N 5.73.

Methyl 1-(4-methylphenyl)-4-(4-methylphenylamino)-2,6-di(4-methoxyphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (Iq). Yield 4.49 g (82%), mp 172–173°C. IR spectrum, ν, cm^{-1}: 3220 (NH), 1660 (C=O). ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.01 s (3H, 4-$\underline{CH_3}C_6H_4$), 2.23 s (3H, 4-$\underline{CH_3}C_6H_4$), 2.72 d.d (1H, $C^5\underline{H_A}H_B$, *J* 15.6, 2.4), 2.90 d.d (1H, $C^5H_A\underline{H_B}$, *J* 15.6, 5.9), 3.68 s (3H, 4-$\underline{CH_3}OC_6H_4$), 3.70 s (3H, 4-$\underline{CH_3}OC_6H_4$), 3.82 s (3H, OCH_3), 5.10 m (1H, C^6H), 6.01 s (1H, C^2H), 6.14–7.01 m (16H, $4C_6H_4$), 10.02 s (1H, NH). Found, %: C 76.75; H 6.58; N 5.36. $C_{35}H_{36}N_2O_4$. Calculated, %: C 76.62; H 6.61; N 5.11.

***tert*-Butyl 1-(4-methylphenyl)-4-(4-methylphenylamino)-2,6-di(4-methoxyphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (Ir).** Yield 4.37 g (74%), mp 171–172°C. IR spectrum, ν, cm^{-1}: 3260 (NH), 1645 (C=O). ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.38 s [9H, $OC(CH_3)_3$], 2.02 s (3H, 4-$\underline{CH_3}C_6H_4$), 2.12 s (3H, 4-$\underline{CH_3}C_6H_4$), 2.72 d.d (1H, $C^5\underline{H_A}H_B$, *J* 15.6, 2.4), 2.81 d.d (1H, $C^5H_A\underline{H_B}$, *J* 15.6, 5.9), 3.71 s (3H, 4-$\underline{CH_3}OC_6H_4$), 3.80 s (3H, 4-$\underline{CH_3}OC_6H_4$), 5.11 m (1H, C^6H), 6.06 s (1H, C^2H), 6.19–7.81 m (16H, $4C_6H_4$), 10.05 s (1H, NH). Found, %: C 77.41; H 7.14; N 4.61. $C_{38}H_{42}N_2O_4$. Calculated, %: C 77.26; H 7.17; N 4.74.

Benzyl 1-(4-methylphenyl)-4-(4-methylphenylamino)-2,6-di(4-methoxyphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (Is). Yield 4.33 g (71%), mp 175–176°C. IR spectrum, ν, cm^{-1}: 3280 (NH), 1652 (C=O). ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.06 s (3H, 4-$\underline{CH_3}C_6H_4$), 2.22 s (3H, 4-$\underline{CH_3}C_6H_4$), 2.72 d.d (1H, $C^5\underline{H_A}H_B$, *J* 15.6, 2.4), 3.38 d.d (1H, $C^5H_A\underline{H_B}$, *J* 15.6, 5.6), 3.65 s (3H, 4-$\underline{CH_3}OC_6H_4$), 3.68 s (3H, 4-$\underline{CH_3}OC_6H_4$), 5.06 d (1H, $OC\underline{H_A}H_BC_6H_5$, *J* 3.0), 5.26 d (1H, $OCH_A\underline{H_B}C_6H_5$, *J* 3.0), 5.31 m (1H, C^6H), 6.16 s (1H, C^2H), 6.24–7.32 m (21H, $4C_6H_4$, C_6H_5), 10.10 s (1H, NH). Found, %: C 78.49; H 6.23; N 4.73. $C_{40}H_{38}N_2O_4$. Calculated, %: C 78.66; H 6.27; N 4.59.

Methyl 1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (It). Yield 4.42 g (85%), mp 172–173°C. IR spectrum, ν, cm^{-1}: 3256 (NH), 1648 (C=O). ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.46 d.d (1H, $C^5\underline{H_A}H_B$, *J* 15.6, 2.5), 2.65 d.d (1H, $C^5H_A\underline{H_B}$, *J* 15.6, 5.6), 3.64 s (3H, 4-$\underline{CH_3}OC_6H_4$), 3.72 s (3H, 4-$\underline{CH_3}OC_6H_4$), 3.78 s (3H, OCH_3), 5.19 m (1H, C^6H), 5.60 s (1H, C^2H), 6.23–7.46 m (18H, $2C_6H_4$, $2C_6H_5$), 9.89 s (1H, NH). Found, %: C 76.29; H 6.18; N 5.24. $C_{33}H_{32}N_2O_4$. Calculated, %: C 76.13; H 6.20; N 5.38.

Ethyl 1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (Iu). Yield 4.43 g (83%), mp 188–190°C. IR spectrum, ν, cm^{-1}: 3240 (NH), 1648 (C=O). ^1H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.37 t (3H, $OCH_2\underline{CH_3}$, *J* 7.0), 2.46 d.d (1H, $C^5\underline{H_A}H_B$, *J* 15.6, 2.3), 2.76 d.d (1H, $C^5H_A\underline{H_B}$, *J* 15.6, 5.9), 3.51 s (3H, 4-$\underline{CH_3}OC_6H_4$), 3.64 s (3H, 4-$\underline{CH_3}OC_6H_4$), 4.27 m (1H, $OC\underline{H_A}H_BCH_3$), 4.42 m (1H, $OCH_A\underline{H_B}CH_3$), 5.16 m (1H, C^6H), 6.14 s (1H, C^2H), 6.21–7.18 m (18H, $2C_6H_4$, $2C_6H_5$), 9.97 s (1H, NH). Found, %: C 76.25; H 6.38; N 5.38. $C_{34}H_{34}N_2O_4$. Calculated, %: C 76.38; H 6.41; N 5.24.

Ethyl 2,6-di(4-*tert*-butylphenyl)-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (Iv). Yield 4.53 g (70%), mp 214–216°C. IR spectrum, ν, cm^{-1}: 3248 (NH), 1648 (C=O). ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.23 s [3H, $(\underline{CH_3})_3CC_6H_4$], 1.26 s [3H, $(\underline{CH_3})_3CC_6H_4$], 1.71 t (3H, $OCH_2\underline{CH_3}$, *J* 7.0), 2.68 d.d (1H, $C^5\underline{H_A}H_B$, *J* 15.6, 2.2), 2.70 d.d (1H, $C^5H_A\underline{H_B}$, *J* 15.6, 5.7), 3.79 s (3H, 4-$\underline{CH_3}OC_6H_4$), 3.82 s (3H, 4-$\underline{CH_3}OC_6H_4$), 4.25 m (1H, $OC\underline{H_A}H_BCH_3$), 4.34 m (1H, $OCH_A\underline{H_B}CH_3$), 5.25 m (1H, C^6H), 6.09 s (1H, C^2H), 6.26–7.72 m (16H, $4C_6H_4$), 9.96 s (1H, NH). Found, %: C 77.73; H 7.81; N 4.46. $C_{42}H_{50}N_2O_4$. Calculated, %: C 77.99; H 7.79; N 4.33.

Ethyl 2,6-di(2-thienyl)-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (Iw). Yield 3.76 g (68%), mp 209–210° C. IR spectrum, ν, cm^{-1}: 3240 (NH), 1656 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.43 t (3H, $OCH_2\underline{CH_3}$, *J* 7.0), 2.81 d.d (1H, $C^5\underline{H_A}H_B$, *J* 15.6, 4.0), 3.01 d.d (1H, $C^5H_A\underline{H_B}$, *J* 15.6, 5.2), 3.72 s (3H, 4-$\underline{CH_3}OC_6H_4$), 3.80 s (3H, 4-$\underline{CH_3}OC_6H_4$), 4.29 m (1H, $OC\underline{H_A}H_BCH_3$), 4.42 m (1H, $OCH_A\underline{H_B}CH_3$), 5.26–5.31 m (1H, C^6H), 6.29 s (1H, C^2H), 6.58–7.30 m (18H, $2C_6H_4$, thienyl), 10.36 s (1H, NH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ_C, ppm: 14.15, 33.61, 53.12, 53.34, 54.91, 55.04, 59.03, 96.06, 113.73, 113.86, 115.56, 122.93, 123.66, 123.87, 125.78, 125.94, 127.15, 140.24, 147.15, 149.23, 151.68, 156.04, 157.37, 167.43. Found, %: C 65.76; H 5.57; N 5.25. $C_{30}H_{30}N_2O_4S_2$. Calculated, %: C 65.91; H 5.53; N 5.12.

Isopropyl 1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-

carboxylate (Ix). Yield 4.21 g (77%), mp 170–171°C. IR spectrum, ν, cm^{-1}: 3240 (NH), 1648 (C=O). ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.34 d [3H, OCH($\underline{CH_3}$)$_2$, *J* 6.0], 1.38 d [3H, OCH($\underline{CH_3}$)$_2$, *J* 6.0], 2.58 d.d (1H, $C^5\underline{H_A}H_B$, *J* 15.6, 2.5), 2.70 d.d (1H, $C^5H_A\underline{H_B}$, *J* 15.6, 6.0), 3.51 s (3H, 4-$\underline{CH_3}OC_6H_4$), 3.64 s (3H, 4-$\underline{CH_3}OC_6H_4$), 5.03 m [1H, O$\underline{CH}$(CH_3)$_2$], 5.14 m (1H, C^6H), 6.09 s (1H, C^2H), 6.23–7.43 m (18H, $2C_6H_5$, $2C_6H_4$), 10.04 s (1H, NH). Found, %: C 76.48; H 6.66; N 5.29. $C_{35}H_{36}N_2O_4$. Calculated, %: C 76.62; H 6.61; N 5.11.

Benzyl 1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (Iy). Yield 3.87 g (65%), mp 164–165°C. IR spectrum, ν, cm^{-1}: 3280 (NH), 1652 (C=O). ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.71 d.d (1H, $C^5\underline{H_A}H_B$, *J* 15.6, 2.5), 2.98 d.d (1H, $C^5H_A\underline{H_B}$, *J* 15.6, 5.8), 3.65 s (3H, 4-$\underline{CH_3}OC_6H_4$), 3.74 s (3H, 4-$\underline{CH_3}OC_6H_4$), 5.01 d (1H, OC$\underline{H_A}H_BC_6H_5$, *J* 3.0), 5.08 d (1H, OC$H_A\underline{H_B}C_6H_5$, *J* 3.0), 5.32 m (1H, C^6H), 6.16 s (1H, C^2H), 6.25–7.50 m (23H, $2C_6H_4$, $3C_6H_5$), 9.98 s (1H, NH). Found, %: C 76.26; H 6.23; N 4.73. $C_{39}H_{36}N_2O_4$. Calculated, %: C 76.50; H 6.08; N 4.69.

Antimicrobial activity of compounds Ia, Ic–Id, If–Ig, Ij, Im–Ip, and Io–Iw towards the strains *Escherichia Coli* ATCC 6538-P and *Staphylococcus aureus* ATCC 25922 was determined by serial dilutions of the test substances in broth solution at the bacterial load of 250 000 microbial units per 1 mL of the solution. Dioxidine and furacilin were used as references.

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