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SYNTHESIS, BIOLOGICAL AND ACIDIC PROPERTIES OF NOVEL 2-METHOXY-6-[(3-ALKYL/ARYL-4,5-DIHYDRO-1*H*-1,2,4-TRIAZOL-5-ONE-4-YL)-AZOMETHINE]-PHENYL *p*-NITROBENZOATE DERIVATIVES

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Abstract. 3-Alkyl/Aryl-4-amino-4,5-dihydro-1H-1,2,4-triazol-5-ones (**2**) reacted with 2-(*p*-nitrobenzoxy)-3-methoxybenzaldehyde (**3**) to afford the corresponding 2-methoxy-6-[(3-alkyl/aryl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethine]-phenyl *p*-nitrobenzoates (**4**). The acetylation reactions of compounds **4** were investigated, and **5** type *N*-acetyl derivatives were obtained. The newly synthesized compounds were fully characterized. Also, *in vitro* antibacterial activities of the fourteen new compounds were screened against six bacteria according to agar well diffusion method. Finally, the newly synthesized **4** type compounds were titrated potentiometrically with tetrabutylammonium hydroxide (TBAH) in five non-aqueous solvents.

Keywords: 1,2,4-triazol-5-one, Schiff base, acetylation, antimicrobial activity, pK_a.

1. Introduction

The 1,2,4-triazoles are an important class of heterocyclic molecules that are being used in more and more ways in medicine and materials science. In particular, 1,2,4-triazole derivatives exhibit a wide range of biological actions, including anticancer, antitumor, antibacterial, antioxidant, anti-inflammatory, and antipsychotic activities.[1-9] Furthermore, among many organic scaffolds, Schiff bases with an azomethine linkage are well-documented as promising and modifiable molecules in drug discovery. Several articles, about the synthesis of some Schiff bases with 4,5-dihydro-1*H*-1,2,4-triazol-5-one ring have also been published.[4,8-13]

Among these, it is also known that 4,5-dihydro-1*H*-1,2,4-triazol-5-one ring has weak acidic properties, so that some 1,2,4-triazole and 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives were titrated potentiometrically with TBAH in non-aqueous solvents.[11-16] Determining the pK_a values of the active constituent of particular pharmaceutical preparations is crucial since the distribution, transport behavior, bonding to receptors, and contributions to the active constituent molecules' metabolic behavior depend on the ionization constant.[17-18]

In this paper, we present the synthesis of nine new 2-methoxy-6-[(3-alkyl/aryl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethine]-phenyl *p*-nitrobenzoates (**4**). They were produced *via* the reactions of 3-alkyl(aryl)-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**2**) with 2-(*p*-nitrobenzoxy)-3-methoxybenzaldehyde (**3**). The latter was synthesized by the reaction of 2-hydroxy-3-methoxybenzaldehyde with *p*-nitrobenzoyl chloride by using triethylamine. The acetylation reactions of compounds **4** with acetic anhydride were also investigated, and 2-methoxy-6-[(1-acetyl-3-alkyl/aryl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethine]-phenyl *p*-nitrobenzoates (**5**) were obtained. (Scheme **1**). The starting compounds 3-alkyl(aryl)-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**2**) were prepared from the reactions of the corresponding ester ethoxycarbonylhydrazones (**1**) with an aqueous solution of hydrazine hydrate as described in the literature.[11,19]

2. Experimental

2.1. Materials and Synthetic Methods

Chemical reagents for this study were purchased from Fluka, Aldrich, and Merck AG. The melting points were taken using an electrothermal melting-point apparatus in open capillary tubes and were not corrected. The infrared spectra were recorded on a Perkin Elmer Instruments Spectrum One FT-IR spectrophotometer. The ^{1}H and ^{13}C-NMR spectra were measured in deuterated dimethyl sulfoxide with TMS as an internal standard via a Bruker DPX-400 FT-NMR spectrophotometer at 400 MHz and 100 MHz,

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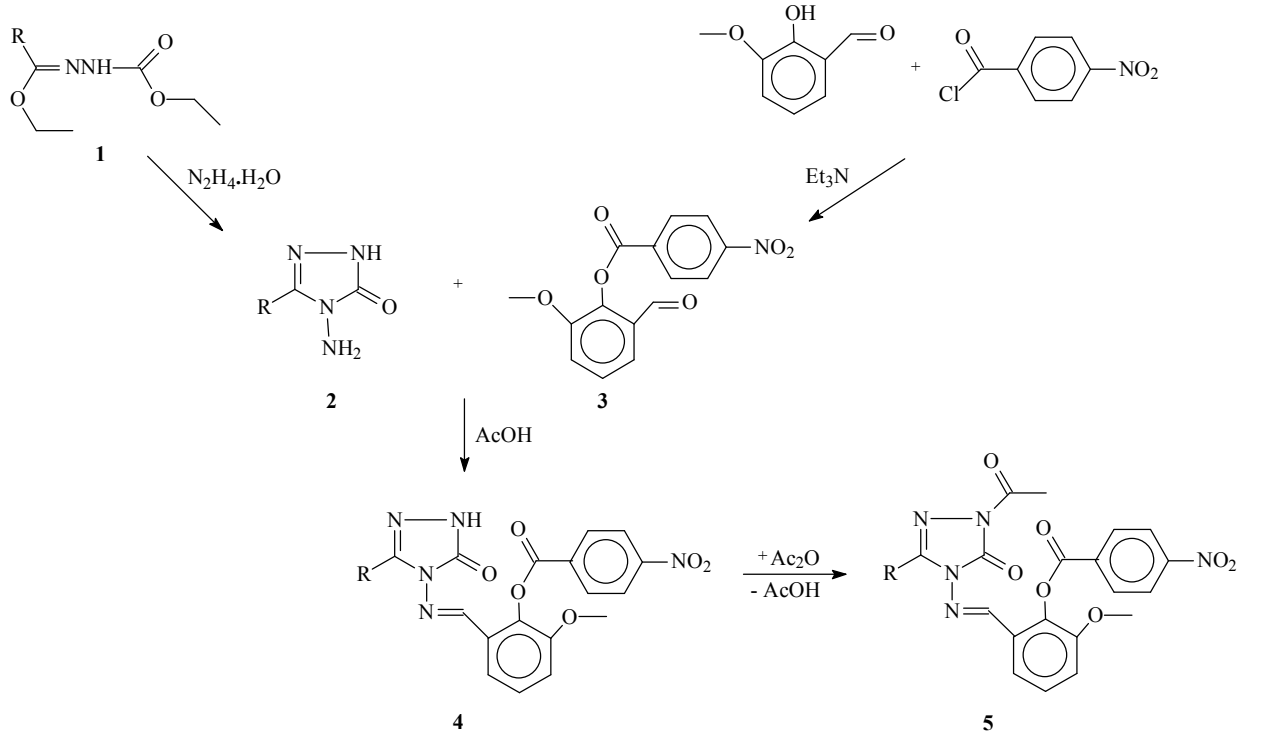
respectively. A PG Instruments Ltd T80 UV/Vis spectrometer was used to measure UV absorption spectra in 10 mm quartz cells between 200 and 400 nm. The units for extinction coefficients (ε) are $L \cdot mol^{-1} \cdot cm^{-1}$.



a) R = CH_3, b) R = CH_2CH_3, c) R = $CH_2CH_2CH_3$, d) R = $CH_2C_6H_5$, e) R = $CH_2C_6H_4CH_3$ (*p*-), f) R = $CH_2C_6H_4OCH_3$ (*p*-), g) R = $CH_2C_6H_4Cl$ (*p*-), h) R = $CH_2C_6H_4Cl$ (*m*-), i) R = C_6H_5

Scheme 1. Synthetic route of compounds **2-5**

2.2. General Procedure for the Synthesis of 2-Methoxy-6-[(3-alkyl/aryl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethine]-phenyl *p*-nitrobenzoates (4)

2-Hydroxy-3-methoxybenzaldehyde (o-vanillin) (0.01 mol) dissolved in ethyl acetate (100 mL) was reacted with *p*-nitrobenzoyl chloride (0.01 mol), and to this solution was slowly mixed trimethylamine (0.01 mol) by stirring at 0-5 °C. Stirring was continued for 2 h, and after that, the mixture was refluxed for 3 hours and filtered. The filtrate was evaporated *in vacuo*, and the crude product was washed with water and recrystallized from ethyl acetate-petroleum ether (1:3) to afford novel compound **3**. Yield (97%); m.p. 150 °C; IR (ATR, cm^{-1}): 2847 and 2780 (CHO), 1742, 1702 (C=O), 1525 and 1352 (NO_2), 1267 (COO), 846 (*p*-disubstituted benzenoid ring). Then, the corresponding compound **2** (0.01 mol) was dissolved in acetic acid (20 mL) and treated by 2-(*p*-nitrobenzoxy)-3-methoxybenzaldehyde (**3**) (0.01 mol). The mixture was refluxed for 1.5 hours and then evaporated at 50-55 °C *in vacuo*. A few recrystallizations of the residue from ethanol gave pure compounds **4**.

2-Methoxy-6-[(3-methyl-4,5-dihydro-1H-1,2,4-triazol-5-one-4-yl)-azomethine]-phenyl p-nitrobenzoate **(4a).** Yield (81%); m.p. 273 °C; IR (ATR, cm^{-1}): 3174 (NH), 1752, 1694 (C=O), 1607, 1595 (C=N), 1530 and 1354 (NO_2), 1257 (COO), 849 (*p*-disubstituted benzenoid ring). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.09 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 7.39 (d, 1H, ArH, J=8.2Hz), 7.45 (t, 1H, ArH, J=8.0Hz), 7.59 (d, 1H, ArH, J=7.8Hz), 8.43 (q, 4H, ArH, J=8.8Hz), 9.88 (s, 1H, N=CH), 11,91 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ ppm: 11.93 (CH_3), 56.77 (OCH_3), [115.96, 119.05, 124.74 (2C), 127.41, 128.08, 131.95 (2C), 133.76, 138.86, 144.56, 151.58] (ArC), 149.04 (Triazole C_3), 151.36 (Triazole C_5), 151.75 (N=CH), 162.88 (COO). UV [Etanol, λ_{max}, nm (ε, $L.mol^{-1}.cm^{-1}$)]: 300 (31.180), 252 (40.550), 232 (43.100). *Anal.* Calculated for $C_{18}H_{15}N_5O_6$: C, 54.41; H, 3.81; N, 17.63. Found: C, 54.44; H, 3.85; N, 17.62.

2-Methoxy-6-[(3-ethyl-4,5-dihydro-1H-1,2,4-triazol-5-one-4-yl)-azomethine]-phenyl p-nitrobenzoate **(4b).** Yield (75%); m.p. 244 °C; IR (ATR, cm^{-1}): 3162

(NH), 1751, 1705 (C=O), 1605, 1591 (C=N), 1524 and 1353 (NO_2), 1283 (COO), 849 (*p*-disubstituted benzenoid ring). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.27 (t, 3H, CH_2CH_3, J=7.5Hz), 2.47 (q, 2H, CH_2CH_3, J=7.5Hz), 3.83 (s, 3H, OCH_3), 7.41 (d, 1H, ArH, J=8.2Hz), 7.47 (t, 1H, ArH, J=8.0Hz), 7.56 (d, 1H, ArH, J=8.0Hz), 8.43 (q, 4H, ArH, J=8.8Hz), 9.88 (s, 1H, N=CH), 11,80 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ ppm: 10.36 ($CH_2\underline{C}H_3$), 18.79 ($\underline{C}H_2CH_3$), 56.75 (OCH_3), [115.92, 119.14, 124.71 (2C), 127.42, 128.09, 131.97 (3C), 133.77, 138.82, 151.34] (ArC), 148.30 (Triazole C_3), 149.11 (Triazole C_5), 151.73 (N=CH), 162.87 (COO). UV [Etanol, λ_{max}, nm (ε, L.mol^{-1}.cm^{-1})]: 300 (6.610), 258 (15.440), 228 (17.065). *Anal.* Calculated for $C_{19}H_{17}N_5O_6$: C, 55.47; H, 4.17; N, 17.02. Found: C, 55.29; H, 4.43; N, 16.91.

2-Methoxy-6-[(3-n-propyl-4,5-dihydro-1H-1,2,4-triazol-5-one-4-yl)-azomethine]-phenyl p-nitrobenzoate **(4c).** Yield (75%); m.p. 223 °C; IR (ATR, cm^{-1}): 3169 (NH), 1750, 1704 (C=O), 1584 (C=N), 1530 and 1349 (NO_2), 1263 (COO), 801 (*p*-disubstituted benzenoid ring). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.84 (t, 3H, $CH_2CH_2\underline{CH_3}$, J=7.2Hz), 1.56 (sext, 2H, $CH_2\underline{CH_2}CH_3$, J=7.2Hz), 2.42 (t, 2H, $\underline{CH_2}CH_2CH_3$, J=7.2Hz),3.83 (s, 3H, OCH_3), 7.40 (d, 1H, ArH, J=8.0Hz), 7.47 (t, 1H, ArH, J=8.0Hz), 7.56 (d, 1H, ArH, J=8.0Hz), 8.43 (q, 4H, ArH, J=8.8Hz), 9.87 (s, 1H, N=CH), 11,80 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ ppm: 11.80 ($CH_2CH_2\underline{C}H_3$), 19.11 ($CH_2\underline{C}H_2CH_3$), 26.94 ($\underline{C}H_2CH_2CH_3$), 56.74 (OCH_3), [115.90, 119.15, 124.71 (2C), 127.41, 128.08, 131.96 (2C), 133.80, 138.81, 149.20, 151.68] (ArC), 147.14 (Triazole C_3), 151.32 (Triazole C_5), 151.75 (N=CH), 162.86 (COO). *Anal.* Calculated for $C_{20}H_{19}N_5O_6$: C, 56.47; H, 4.50; N, 16.46. Found: C, 56.65; H, 4.64; N, 15.80.

2-Methoxy-6-[(3-benzyl-4,5-dihydro-1H-1,2,4-triazol-5-one-4-yl)-azomethine]-phenyl p-nitrobenzoate **(4d).** Yield (80%); m.p. 234 °C; IR (ATR, cm^{-1}): 3159 (NH), 1753, 1705 (C=O), 1606, 1591 (C=N), 1528 and 1351 (NO_2), 1284 (COO), 849 (*p*-disubstituted benzenoid ring), 700 and 704 (monosubstituted benzenoid ring). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 3.84 (s, 3H, OCH_3), 3.90 (s, 2H, CH_2Ph), 7.22-7.29 (m, 5H, ArH), 7.39 (d, 1H, ArH, J=8.4Hz), 7.46 (t, 1H, ArH, J=8.0Hz), 7.54 (d, 1H, ArH, J=7.6Hz), 8.40-8.43 (m, 4H, ArH), 9.86 (s, 1H, N=CH), 11,92 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ ppm: 31.25 (CH_2Ph), 56.74 (OCH_3), [115.95, 118.57, 124.71 (2C), 127.19, 127.39, 128.09, 128.87 (2C), 129.20 (2C), 131.93 (2C), 133.65, 136.02, 139.04, 146.55, 151.58] (ArC), 148.62 (Triazole C_3), 151.31 (Triazole C_5), 151.70 (N=CH), 162.89 (COO). UV [Etanol, λ_{max}, nm (ε, L.mol^{-1}.cm^{-1})]: 302 (15.680), 258 (25.520), 232 (27.490). *Anal.* Calculated for $C_{24}H_{19}N_5O_6$: C, 60.89; H, 4.05; N, 14.79. Found: C, 60.35; H, 4.41; N, 14.66.

2-Methoxy-6-[(3-p-methylbenzyl-4,5-dihydro-1H-1,2,4-triazol-5-one-4-yl)-azomethine]-phenyl p-nitrobenzoate **(4e).** Yield (97%); m.p. 236 °C; IR (ATR, cm^{-1}): 3163 (NH), 1756, 1704 (C=O), 1607, 1590 (C=N), 1531 and 1353 (NO_2), 1283 (COO), 824 (*p*-disubstituted benzenoid ring). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.25 (s, 3H, $PhCH_3$), 3.82 (s, 3H, OCH_3), 3.84 (s, 2H, CH_2Ph), 7.09 (q, 4H, ArH, J=8.4Hz), 7.39 (d, 1H, ArH, J=8.4Hz), 7.46 (t, 1H, ArH, J=8.0Hz), 7.56 (d, 1H, ArH, J=8.0Hz), 8.37-8.40 (m, 4H, ArH), 9.86 (s, 1H, N=CH), 11,90 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ ppm: 21.07 ($PhCH_3$), 30.83 (CH_2Ph), 56.76 (OCH_3), [115.98, 118.66, 124.71 (2C), 127.38, 128.11, 129.05 (2C), 129.43 (2C), 131.93 (2C), 132.92, 133.65, 136.23, 139.01, 146.69, 151.56] (ArC), 148.69 (Triazole C_3), 151.31 (Triazole C_5), 151.71 (N=CH), 162.88 (COO). UV [Etanol, λ_{max}, nm (ε, L.mol^{-1}.cm^{-1})]: 298 (10.790), 260 (19.210), 224 (23.260). *Anal.* Calculated for $C_{25}H_{21}N_5O_6$: C, 61.60; H, 4.34; N, 14.37. Found: C, 61.62; H, 4.36; N, 14.35.

2-Methoxy-6-[(3-p-methoxybenzyl-4,5-dihydro-1H-1,2,4-triazol-5-one-4-yl)-azomethine]-phenyl p-nitrobenzoate **(4f).** Yield (74%); m.p. 241 °C; IR (ATR, cm^{-1}): 3188 (NH), 1748, 1693 (C=O), 1607, 1584 (C=N), 1517 and 1354 (NO_2), 1250 (COO), 807 (*p*-disubstituted benzenoid ring). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 3.71 (s, 3H, *p*-OCH_3), 3.82 (s, 5H, OCH_3 + CH_2Ph), 6.84 (d, 2H, ArH, J=8.4Hz), 7.15 (d, 2H, ArH, J=8.4Hz), 7.39 (d, 1H, ArH, J=8.4Hz), 7.47 (t, 1H, ArH, J=8.0Hz), 7.57 (d, 1H, ArH, J=8.0Hz), 8.37-8.44 (m, 4H, ArH), 9.86 (s, 1H, N=CH), 11,89 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ ppm: 30.39 (CH_2Ph), 55.45 (*p*-OCH_3), 56.75 (OCH_3), [114.26 (2C), 115.96, 118.55, 124.71 (2C), 127.41, 127.78, 128.12, 130.25 (2C), 131.93 (2C), 133.65, 139.02, 148.66, 151.71, 158.51] (ArC), 148.69 (Triazole C_3), 151.31 (Triazole C_5), 151.71 (N=CH), 162.88 (COO).

2-Methoxy-6-[(3-p-chlorobenzyl-4,5-dihydro-1H-1,2,4-triazol-5-one-4-yl)-azomethine]-phenyl p-nitrobenzoate **(4g).** Yield (99%); m.p. 246 °C; IR (ATR, cm^{-1}): 3159 (NH), 1756, 1703 (C=O), 1605, 1589 (C=N), 1522 and 1350 (NO_2), 1287 (COO), 827 (*p*-disubstituted benzenoid ring). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 3.82 (s, 3H, OCH_3), 3.91 (s, 2H, CH_2Ph), 7.26 (d, 2H, ArH, J=8.4Hz), 7.35 (d, 2H, ArH, J=8.4Hz), 7.39 (d, 1H, ArH, J=8.2Hz), 7.46 (t, 1H, ArH, J=8.0Hz), 7.54 (d, 1H, ArH, J=8.0Hz), 8.37-8.43 (m, 4H, ArH), 9.87 (s, 1H, N=CH), 11,94 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ ppm: 30.56 (CH_2Ph), 56.76 (OCH_3), [116.01, 118.64, 124.72 (2C), 127.34, 128.12, 128.80 (2C), 131.13 (2C), 131.88, 131.94 (2C), 133.64, 135.00, 139.03, 146.21, 151.55] (ArC), 148.78 (Triazole C_3), 151.32 (Triazole C_5), 151.71 (N=CH), 162.88 (COO). UV [Etanol, λ_{max}, nm (ε, L.mol^{-1}.cm^{-1})]: 300 (20.840), 258 (34.720), 230 (40.830). *Anal.* Calculated for

$C_{24}H_{18}N_5O_6Cl$: C, 56.76; H, 3.57; N, 13.79. Found: C, 56.61; H, 3.98; N, 13.61.

2-Methoxy-6-[(3-m-chlorobenzyl-4,5-dihydro-1H-1,2,4-triazol-5-one-4-yl)-azomethine]-phenyl p-nitrobenzoate **(4h).** Yield (85%); m.p. 228 °C; IR (ATR, cm^{-1}): 3185 (NH), 1747, 1693 (C=O), 1579 (C=N), 1523 and 1352 (NO_2), 1252 (COO), 870 and 778 (*m*-disubstituted benzenoid ring), 820 (*p*-disubstituted benzenoid ring). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 3.82 (s, 3H, OCH_3), 3.93 (s, 2H, CH_2Ph), 7.19 (d, 1H, ArH, J=7.6Hz), 7.28-7.34 (m, 3H, ArH), 7.39 (d, 1H, ArH, J=7.6Hz), 7.46 (t, 1H, ArH, J=8.0Hz), 7.55 (d, 1H, ArH, J=8.0Hz), 8.37-8.44 (m, 4H, ArH), 9.87 (s, 1H, N=CH), 11,96 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ ppm: 30.85 (CH_2Ph), 56.74 (OCH_3), [115.98, 118.66, 124.68 (2C), 127.22, 127.35, 128.00, 128.06, 128.55, 130.67, 131.93 (2C), 133.38, 133.65, 138.37, 139.04, 148.72, 151.71] (ArC), 148.78 (Triazole C_3), 151.32 (Triazole C_5), 151.71 (N=CH), 162.88 (COO).

2-Methoxy-6-[(3-phenyl-4,5-dihydro-1H-1,2,4-triazol-5-one-4-yl)-azomethine]-phenyl p-nitrobenzoate **(4i).** Yield (84%); m.p. 262 °C; IR (ATR, cm^{-1}): 3197 (NH), 1749, 1714 (C=O), 1606, 1576 (C=N), 1531 and 1350 (NO_2), 1267 (COO), 820 (*p*-disubstituted benzenoid ring), 769 and 695 (monosubstituted benzenoid ring). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 3.82 (s, 3H, OCH_3), 7.41 (d, 1H, ArH, J=8.4Hz), 7.45-7.50 (m, 4H, ArH), 7.53 (d, 1H, ArH, J=7.8Hz), 7.64-7.69 (m, 2H, ArH), 8.29 (d, 2H, ArH, J=8.0Hz), 8.37 (d, 2H, ArH, J=8.0Hz), 9.80 (s, 1H, N=CH), 12,12 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ ppm: 56.77 (OCH_3), [116.17, 119.10, 124.52 (2C), 126.85, 127.25, 128.15, 128.35 (2C), 128.91 (2C), 130.56, 131.82 (2C), 133.78, 139.09, 145.04, 151.81] (ArC), 151.13 (Triazole C_3), 151.69 (Triazole C_5), 152.00 (N=CH), 162.88 (COO). UV [Etanol, λ_{max}, nm (ε, $L.mol^{-1}.cm^{-1}$)]: 306 (12.300), 260 (34.880), 232 (28.770). *Anal.* Calculated for $C_{23}H_{17}N_5O_6$: C, 60.13; H, 3.73; N, 15.24. Found: C, 60.14; H, 3.74; N, 15.23.

2.3. General Procedure for the Synthesis of 2-Methoxy-6-[(1-acetyl-3-alkyl/aryl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethine]-phenyl *p*-nitrobenzoates (5)

The corresponding compound **4** (0.01 mol) was refluxed with acetic anhydride (15 mL) for 0.5 h. After addition of absolute ethanol (50 mL), the mixture was refluxed for 1 h. Evaporation of the resulting solution at 40-45 °C *in vacuo* and several recrystallizations of the residue from an appropriate solvent gave pure compounds **5**.

2-Methoxy-6-[(1-acetyl-3-methyl-4,5-dihydro-1H-1,2,4-triazol-5-one-4-yl)-azomethine]-phenyl p-nitrobenzoate **(5a).** Yield (85%); m.p. 223 °C; IR (ATR, cm^{-1}): 1757, 1733, 1713 (C=O), 1611, 1573 (C=N), 1526 and 1353 (NO_2), 1246 (COO), 811 (*p*-disubstituted benzenoid ring). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.18 (s, 3H, CH_3), 2.39 (s, 3H, $COCH_3$), 3.83 (s, 3H, OCH_3), 7.42 (d, 1H, ArH, J=8.4Hz), 7.48 (t, 1H, ArH, J=8.0Hz), 7.62 (d, 1H, ArH, J=8.0Hz), 8.40-8.46 (m, 4H, ArH), 9.72 (s, 1H, N=CH). ^{13}C NMR (DMSO-d_6) δ ppm: 10.95 (CH_3), 23.27 ($CO\underline{C}H_3$), 56.24 (OCH_3), [115.88, 118.53, 124.23 (2C), 126.38, 127.60, 131.39 (2C), 133.05, 138.56, 146.28, 150.84] (ArC), 147.61 (Triazole C_3), 150.26 (Triazole C_5), 151.14 (N=CH), 162.27 (COO), 166.00 ($\underline{C}OCH_3$). UV [Etanol, λ_{max}, nm (ε, $L.mol^{-1}.cm^{-1}$)]: 296 (10.170), 258 (17.160), 228 (19.370). *Anal.* Calculated for $C_{20}H_{17}N_5O_7$: C, 54.67; H, 3.90; N, 15.94. Found: C, 54.22; H, 4.00; N, 15.97.

2-Methoxy-6-[(1-acetyl-3-ethyl-4,5-dihydro-1H-1,2,4-triazol-5-one-4-yl)-azomethine]-phenyl p-nitrobenzoate **(5b).** Yield (85%); m.p. 190 °C; IR (ATR, cm^{-1}): 1732 (C=O), 1606, 1573 (C=N), 1526 and 1349 (NO_2), 1244 (COO), 845 (*p*-disubstituted benzenoid ring). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.12 (t, 3H, CH_2CH_3, J=7.6Hz), 2.54 (q, 2H, CH_2CH_3, J=7.6Hz), 2.40 (s, 3H, $COCH_3$), 3.83 (s, 3H, OCH_3), 7.42 (d, 1H, ArH, J=8.4Hz), 7.48 (t, 1H, ArH, J=8.0Hz), 7.60 (d, 1H, ArH, J=8.0Hz), 8.40-8.46 (m, 4H, ArH), 9.72 (s, 1H, N=CH). ^{13}C NMR (DMSO-d_6) δ ppm: 9.24 ($CH_2\underline{C}H_3$), 18.36 ($\underline{C}H_2CH_3$), 23.29 ($CO\underline{C}H_3$), 56.45 (OCH_3), [115.88, 118.65, 124.21 (2C), 126.40, 127.62, 131.42 (2C), 133.10, 138.54, 149.77, 150.85] (ArC), 147.86 (Triazole C_3), 150.36 (Triazole C_5), 151.17 (N=CH), 162.28 (COO), 165.95 ($\underline{C}OCH_3$). UV [Etanol, λ_{max}, nm (ε, $L.mol^{-1}.cm^{-1}$)]: 302 (12.520), 258 (25.440), 226 (48.110). *Anal.* Calculated for $C_{21}H_{19}N_5O_7$: C, 55.63; H, 4.22; N, 15.45. Found: C, 55.50; H, 4.36; N, 15.53.

2-Methoxy-6-[(1-acetyl-3-benzyl-4,5-dihydro-1H-1,2,4-triazol-5-one-4-yl)-azomethine]-phenyl p-nitrobenzoate **(5d).** Yield (77%); m.p. 173 °C; IR (ATR, cm^{-1}): 1755, 1738, 1717 (C=O), 1606, 1573 (C=N), 1530 and 1350 (NO_2), 1249 (COO), 842 (*p*-disubstituted benzenoid ring), 784 and 707 (monosubstituted benzenoid ring). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.40 (s, 3H, $COCH_3$), 3.82 (s, 3H, OCH_3), 4.00 (s, 2H, CH_2Ph), 7.29-7.33 (m, 5H, ArH), 7.41 (d, 1H, ArH, J=8.0Hz), 7.48 (t, 1H, ArH, J=8.0Hz), 7.60 (d, 1H, ArH, J=8.0Hz), 8.40-8.46 (m, 4H, ArH), 9.72 (s, 1H, N=CH). ^{13}C NMR (DMSO-d_6) δ ppm: 23.35 ($CO\underline{C}H_3$), 30.66 (CH_2Ph), 56.24 (OCH_3), [115.90, 118.18, 124.21 (2C), 126.38, 126.86, 127.61, 128.37 (2C), 128.81 (2C), 131.37 (2C), 132.97, 134.37, 138.41, 147.91, 150.81] (ArC), 147.80 (Triazole C_3), 149.89 (Triazole C_5), 151.11 (N=CH), 162.28 (COO), 165.94 ($\underline{C}OCH_3$). UV [Etanol, λ_{max}, nm (ε, $L.mol^{-1}.cm^{-1}$)]: 298 (11.660), 258 (20.400), 230 (21.860).

2-Methoxy-6-[(1-acetyl-3-p-methylbenzyl-4,5-dihydro-1H-1,2,4-triazol-5-one-4-yl)-azomethine]-phenyl p-nitrobenzoate **(5e).** Yield (84%); m.p. 204 °C; IR (ATR, cm^{-1}): 1750, 1717 (C=O), 1609, 1573 (C=N), 1527 and 1351 (NO_2), 1252 (COO), 845, 802 (*p*-disubstituted benzenoid ring). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.25 (s, 3H, $PhCH_3$), 2.39 (s, 3H, $COCH_3$), 3.82 (s, 3H, OCH_3), 3.93 (s, 2H, CH_2Ph), 7.10 (d, 2H, ArH, J=8.0Hz), 7.16 (d, 2H, ArH, J=8.0Hz), 7.41 (d, 1H, ArH, J=8.4Hz), 7.46 (t, 1H, ArH, J=8.0Hz), 7.57 (d, 1H, ArH, J=7.6Hz), 8.37-8.43 (m, 4H, ArH), 9.70 (s, 1H, N=CH). ^{13}C NMR (DMSO-d_6) δ ppm: 20.60 ($PhCH_3$), 23.44 ($CO\underline{C}H_3$), 30.34 (CH_2Ph), 56.33 (OCH_3), [115.99, 118.37, 124.29 (2C), 126.46, 127.71, 128.76 (2C), 129.01 (2C), 131.32, 131.45 (2C), 133.05, 136.05, 138.76, 148.13, 150.89] (ArC), 147.87 (Triazole C_3), 150.05 (Triazole C_5), 151.20 (N=CH), 162.36 (COO), 166.03 ($\underline{C}OCH_3$). UV [Etanol, λ_{max}, nm (ε, $L.mol^{-1}.cm^{-1}$)]: 294 (21.950), 256 (38.810), 226 (55.670). *Anal.* Calculated for $C_{27}H_{23}N_5O_7$: C, 61.24; H, 4.38; N, 13.23. Found: C, 61.13; H, 4.66; N, 13.22.

2-Methoxy-6-[(1-acetyl-3-p-chlorobenzyl-4,5-dihydro-1H-1,2,4-triazol-5-one-4-yl)-azomethine]-phenyl p-nitrobenzoate **(5g).** Yield (79%); m.p. 184 °C; IR (ATR, cm^{-1}): 1750, 1716 (C=O), 1611, 1574 (C=N), 1530 and 1347 (NO_2), 1252 (COO), 846 (*p*-disubstituted benzenoid ring). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.39 (s, 3H, $COCH_3$), 3.82 (s, 3H, OCH_3), 4.01 (s, 2H, CH_2Ph), 7.33-7.39 (m, 4H, ArH), 7.42 (d, 1H, ArH, J=8.4Hz), 7.47 (t, 1H, ArH, J=8.0Hz), 7.55 (d, 1H, ArH, J=8.0Hz), 8.38-8.43 (m, 4H, ArH), 9.72 (s, 1H, N=CH). ^{13}C NMR (DMSO-d_6) δ ppm: 23.33 ($CO\underline{C}H_3$), 29.98 (CH_2Ph), 56.24 (OCH_3), [115.93, 118.20, 124.21 (2C), 126.34, 127.62, 128.28 (2C), 130.73 (2C), 131.37 (2C), 131.58, 132.94, 133.38, 138.71, 147.78, 150.81] (ArC), 147.61 (Triazole C_3), 149.93 (Triazole C_5), 151.10 (N=CH), 162.27 (COO), 165.92 ($\underline{C}OCH_3$). UV [Etanol, λ_{max}, nm (ε, $L.mol^{-1}.cm^{-1}$)]: 300 (20.080), 258 (37.580), 224 (87.760).

2-Methoxy-6-[(1-acetyl-3-phenyl-4,5-dihydro-1H-1,2,4-triazol-5-one-4-yl)-azomethine]-phenyl p-nitrobenzoate **(5i).** Yield (87%); m.p. 173 °C; IR (ATR, cm^{-1}): 1747, 1727 (C=O), 1604, 1577 (C=N), 1523 and 1346 (NO_2), 1255 (COO), 809 (*p*-disubstituted benzenoid ring), 751 and 691 (monosubstituted benzenoid ring). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.49 (s, 3H, $COCH_3$), 3.82 (s, 3H, OCH_3), 7.44 (d, 1H, ArH, J=8.4Hz), 7.46 (t, 1H, ArH, J=8.0Hz), 7.50-7.60 (m, 4H, ArH), 7.80-7.83 (m, 2H, ArH), 8.29 (d, 2H, ArH, J=8.4Hz), 8.36 (d, 2H, ArH, J=8.4Hz), 9.64 (s, 1H, N=CH). ^{13}C NMR (DMSO-d_6) δ ppm: 23.40 ($CO\underline{C}H_3$), 56.27 (OCH_3), [116.15, 118.80, 124.03 (2C), 124.95, 126.19, 127.71, 128.46 (2C), 128.52 (2C), 131.19, 131.27 (2C), 133.08, 138.70, 147.89, 151.23] (ArC), 145.81 (Triazole C_3), 150.63 (Triazole C_5), 153.20 (N=CH), 162.28 (COO), 166.24 ($\underline{C}OCH_3$). UV [Etanol, λ_{max}, nm (ε, $L.mol^{-1}.cm^{-1}$)]: 304 (13.420), 260 (36.480), 226 (45.400).

2.4. Antibacterial Activity

The bacterial strains, which are common infectious agents, were acquired from France. It has been reported that Microbiological Environmental Protection Laboratories generated these bacteria. For antibacterial investigation, three gram-positive bacteria strains (*Bacillus substilis, Staphylococcus aureus, and Escherichia coli*) and three gram-negative bacteria strains (*Yersinia enterocolitica, Pasteurella multocida, and Klebsiella pneumonia-ATCC4352*) were chosen. The agar well diffusion method was deemed the most suitable for antibacterial effect studies.[11, 20] Standard antibiotics, including streptomycin (3385), ampicillin (3261), and neomycin (3360), were employed to compare the effect levels of the synthesized compounds.

2.5. Potentiometric Titrations

For potentiometric titrations, a Jenco model pH meter type was employed. An Ingold pH electrode was chosen due to its advantages. The 0.001M solution was made individually in each non-aqueous solvent for each compound that would be titrated. As a titrant, we utilized 0.05M TBAH solutions in isopropyl alcohol, commonly used for acid titration. The mV values that were obtained from the pH meter were recorded. Finally, the mL (TBAH)-mV graphic was created to calculate the HNP values.

3. Results and Discussion

3.1. Chemistry

In this study, nine new 2-methoxy-6-[(3-alkyl/aryl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethine]-phenyl *p*-nitrobenzoates (**4**) were synthesized via the reactions of 3-alkyl(aryl)-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**2**) with 2-(*p*-nitrobenzoxy)-3-methoxybenzaldehyde (**3**), which was synthesized by the reactions of 2-hydroxy-4-methoxybenzaldehyde with *p*-nitrobenzoyl chloride by using triethylamine. On the other hand, the reactions of compounds **4** with acetic anhydride gave 2-methoxy-6-[(1-acetyl-3-alkyl/aryl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethine]-phenyl *p*-nitrobenzoates (**5**). The structures of the novel compounds were determined utilizing elemental analysis, IR, ^{1}H-NMR, ^{13}C-NMR, and UV spectroscopy.

3.2. Antimicrobial Activity

The microbiological results are summarized in Table 1. An average analysis of the synthesized com-

pounds reveals a medium to weak effect on the tested bacterial strains. Compared with standard antibiotics, effect values close to Neomycin and Streptomycin were obtained.

Evaluation of the results is based on the diameter of the inhibition: 5.5 mm negative effect (-); 5.5–10 mm low effect (+); 11–16 mm moderate effect (++); 17 mm great impact (+++).[21]

Table 1. Antimicrobial activity of the compounds **4** and **5**

Compounds	Microorganisms and inhibition zone (mm)					
	Bs	Ye	Sa	Ec	Pm	Kp
4a	14 (++)	7 (+)	-	8 (+)	14 (++)	13 (++)
4b	15 (++)	7 (+)	-	9 (+)	13 (++)	11 (++)
4c	10 (+)	7 (+)	-	9 (+)	11 (++)	10 (+)
4d	7 (+)	7 (+)	-	10 (+)	10 (+)	-
4e	12 (++)	-	--	8 (+)	13 (++)	10 (+)
4f	16 (++)	-	7 (+)	7 (+)	9 (+)	-
4g	15 (++)	-	7 (+)	7 (+)	11 (++)	-
4h	12 (++)	-	9 (+)	-	10 (+)	-
4i	12 (++)	-	9 (+)	-	8 (+)	-
5a	9 (+)	10 (+)	11 (++)	11 (++)	8 (+)	-
5b	9 (+)	10 (+)	11 (++)	12 (++)	13 (++)	10 (+)
5d	10 (+)	9 (+)	10 (+)	14 (++)	9 (+)	-
5e	9 (+)	11 (++)	-	12 (++)	12 (++)	-
5g	12 (++)	8 (+)	7 (+)	12 (++)	-	-
5i	10 (+)	-	10 (+)	12 (++)	7 (+)	-
Amp.	33	36	36	35	37	34
Neo.	17	17	17	16	13	16
Str.	12	12	12	11	21	10

Bs: *Bacillus subtilis*, Ye: *Yersinia enterocolitica,* Sa: *Staphylococcus aureus,* Ec: *Escherichia coli*, Pm: *Pasteurella multocida,* Kp: *Klebsiella pneumoniae*; Amp.: Ampicillin (3261), Neo.: Neomycin (3360), Str.: Streptomycin (3385).

3.3. Potentiometric Titrations

Compounds **4** (**a**, **b**, **d**, **e**, **g**, and **i**) were potentiometrically titrated with TBAH in four non-aqueous solvents. The potentiometric titration curves were formed for each example by plotting the mV values from each titration against the TBAH volumes used (mL). The HNP values were measured from the titration curves, and the corresponding pK_a values were calculated.

The potentiometric titration curves of 0.001M 2-methoxy-6-[(3-*p*-methylbenzyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethine]-phenyl *p*-nitrobenzoate (**4e**) solutions titrated with 0.05N TBAH in isopropyl alcohol, *N,N*-dimethylformamide, DMSO, and acetone are shown in Figure **1** as an example.

As a result of potentiometric titrations with 0.05M TBAH in isopropyl alcohol, tert-butyl alcohol, DMF, DMSO, and acetone, the half-neutralization potential values and corresponding pK_a values for compounds **4** (**a, b, d, e, g,** and **i**) are shown in Table **2**.

The pH value of weak acids can be calculated using the following equation:

$$pH = pK_a + \log[A^-] / [HA]$$

where pH = pK_a when [A^-] is equal to [HA] at the half-neutralization points.

As can be observed from Table **2**, the HNP values and corresponding pK_a values have not been determined for compound **4g** in acetone, for compounds **4b**, **4e**, **4g**, and **4i** in tert-butyl alcohol, and for compounds **4a** and **4i** in isopropyl alcohol. As is well-known, the compound acidity depends on some variables. The two most crucial ones are solvent effect and molecular structure.[11-16] Table **1** and Figure **1** show that the HNP and pKa values found by potentiometric titrations depend on the used non-aqueous solvents and the substituents at C-3 in the 4,5-dihydro-1*H*-1,2,4-triazol-5-one ring.

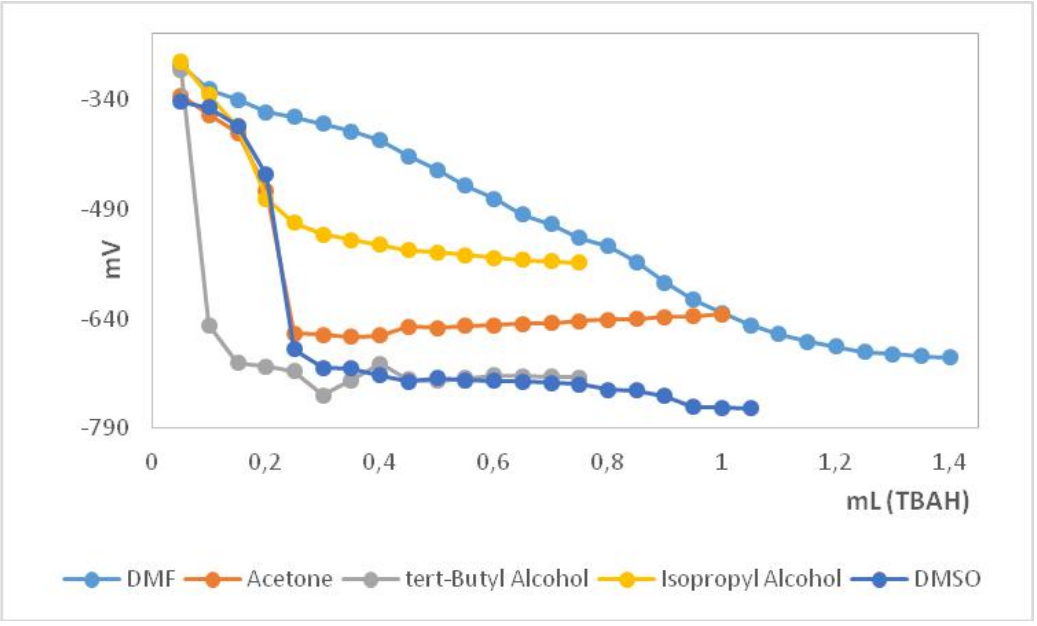


Fig. 1. Potentiometric titration curves of 10^{-3} M 2-methoxy-6-[(3-*p*-methylbenzyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethine]-phenyl *p*-nitrobenzoate (**4e**) solutions titrated with 0.05 N TBAH in four non-aqueous solvents at 25 °C

Table 2. The HNP and the corresponding pK_a values of compounds **4a-i** in isopropyl alcohol, *tert*-butyl alcohol, DMF, DMSO and acetone

Comp	DMF		Acetone		*tert*-Butyl alcohol		Isopropyl alcohol		DMSO	
	pK_a	HNP (mV)	pK_a	HNP (mV)	pK_a	HNP (mV)	pK_a	HNP (mV)	pK_a	HNP (mV)
4a	13.23	-324	15.72	-467	13.95	-410	-	-	13.98	-369
4b	13.83	-364	15.05	-433	-	-	13.05	-368	13.16	-329
4d	13.62	-351	15.85	-463	14.54	-168	13.39	-317	13.03	-320
4e	14.66	-406	13.74	-361	-	-	12.68	-310	13.63	-350
4g	13.81	-361	-	-	-	-	11.79	-256	13.18	-329
4i	14.27	-380	14.77	-379	-	-	-	-	12.57	-304

4. Conclusions

The organic materials **4a-i** and **5a-i** (the *N*-acetyl derivatives) were obtained by reacting 3-alkyl/aryl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl and *p*-nitrobenzoyl units which are linked to azomethine core *via* an imine π-bridge. The compounds **4a-i** and **5a-i** (the *N*-acetyl derivatives) were obtained in high yields through a one-step condensation procedure and characterized using several spectroscopic techniques. *In vitro* antimicrobial capacity and potentiometric titration with TBAH were evaluated in four non-aqueous solvents for the organic materials **4a-i** and **5a-i**. The results about the compounds' reported biological activities show that these compounds may help with the development of a new triazole-based potential drug candidate.

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СИНТЕЗ, БІОЛОГІЧНІ ТА КИСЛОТНІ ВЛАСТИВОСТІ НОВИХ НОВИХ ПОХІДНИХ 2-МЕТОКСИ-6-[(3-АЛКІЛ/АРИЛ-4,5-ДИГІДРО-1*H*-1,2,4-ТРИАЗОЛ-5-ОН-4-ІЛ)АЗОМЕТИН]ФЕНІЛ-*n*-НІТРОБЕНЗОАТУ

Анотація. *3-Алкіл/арил-4-аміно-4,5-дигідро-1H-1,2,4-триазол-5-они (**2**) реагують з 2-(n-нітробензокси)-3-метоксибензальдегідом (**3**) з утворенням відповідних 2-метокси-6-[(3-алкіл/арил-4,5-дигідро-1H-1,2,4-триазол-5-он-4-іл)азометин]феніл-n-нітробензоатів (**4**). Досліджено реакції ацетилювання сполук **4** й отримано N-ацетильні похідні типу **5**. Нові синтезовані сполуки було повністю охарактеризовано. Крім того, антибактеріальну активність чотирнадцяти нових сполук in vitro було перевірено проти шести бактерій за допомогою методу дифузії в агаровому середовищі. Також нові синтезовані сполуки типу **4** потенціометрично титрували тетрабутиламоній-гідроксидом (ТВАН) у п'яти неводних розчинниках.*

Ключові слова: *1,2,4-триазол-5-он, основа Шиффа, ацетилювання, антимікробна активність, pK_a.*