SYNTHESIS AND NON-AQUEOUS MEDIUM TITRATIONS OF SOME NEW 4,5-DIHYDRO-1*H*-1,2,4-TRIAZOL-5-ONE DERIVATIVES

Şule Bahçeci,[a] Haydar Yüksek,[b*] Zafer Ocak,[c] Canan Köksal,[a] Mustafa Özdemir[c]

[a]*Fatih Education Faculty, Karadeniz Technical University, 61335 Trabzon, Turkey*
[b]*Department of Chemistry, Kafkas University, 36100 Kars, Turkey*
[c]*Department of Chemistry, Karadeniz Technical University, 61080 Trabzon, Turkey*
**Corresponding author : e-mail.* hyuksek98@yahoo.com

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Abstract

3-Alkyl(Aryl)-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**2**) reacted with 3,4-dihydroxybenzaldehyde to afford the corresponding 3-alkyl(aryl)-4-(3,4-dihydroxybenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**3**). The acetylation and methylation reactions of the latter compounds were investigated, and **4** and **5** type compounds were obtained, respectively. The new compounds were characterized using IR, ^{1}H-NMR, ^{13}C-NMR and UV spectral data. In addition, solutions of the compounds **3a**-**3e** were titrated potentiometrically with tetrabutylammonium hydroxide in three different non-aqueous solvents such as acetonitrile, isopropyl alcohol and *N,N*-dimethylformamide. The half-neutralization potential values and the corresponding pK_a values of these compounds were determined in the solvents described above. Thus, the effects of solvents and molecular structure upon acidity were investigated.

Key words: 4,5-Dihydro-1*H*-1,2,4-triazol-5-one, Schiff base, methylation, acetylation, acidity, potentiometric titrations.

Introduction

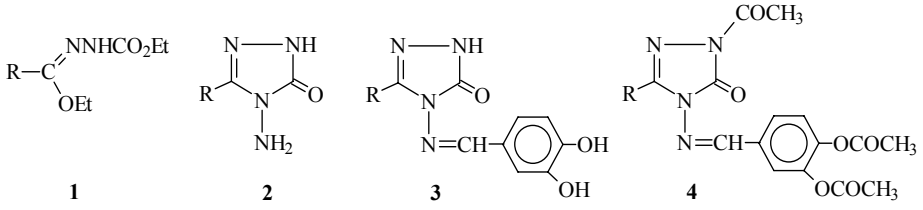
Several studies, involving the formation and investigation of biological activities of some *N*-arylidenamino-1,2,4-triazoles and *N*-arylidenamino-4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives, have been reported.[1-12] The acetylation and methylation of 1,2,4-triazole and 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives have also been reported.[13-16]

On the other hand, it is known that 1,2,4-triazole and 4,5-dihydro-1*H*-1,2,4-triazol-5-one rings have weak acidic properties, so some 1,2,4-triazole and 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives were titrated potentiometrically with tetrabutylammonium hydroxide in non-aqueous solvents, and the pK_a values of the compounds were determined.[16-26]

This paper describes the synthesis of a series of 3-alkyl(aryl)-4-(3,4-dihydroxybenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**3**) from the reactions of 3-alkyl (aryl)-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**2**) with 3,4-dihydroxybenzaldehyde. In addition, the reactions of compounds **3** with acetic anhydride and NaOH/dimethyl sulphate were investigated, and **4** and **5** type compounds were obtained, respectively, Scheme **1**. Furthermore, in order to determine the pK_a values of the compounds **3a-3e** they were titrated potentiometrically with tetrabutylammonium hydroxide in three non-aqueous solvents, including acetonitrile, isopropyl alcohol and *N,N*-dimethylformamide. For each new compounds **3a-e**, the half-neutralization potential (HNP) values and the corresponding pK_a values were determined in the three different non-aqueous solvents. The data obtained from the potentiometric titrations were interpreted, and substituent effects attached to C-3 position in 4,5-dihydro-1*H*-1,2,4-triazol-5-one ring and solvent effects were studied.[22-25] Determination of pK_a values of the active constituent of certain pharmaceutical preparations is important because the distribution, transport behavior, bonding to receptors, and contributions to the metabolic behavior of the active constituent molecules depend on the ionization constant.[27-29]

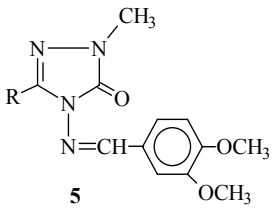
In order to identify the new compounds synthesized in this study, spectroscopic methods, including IR, ^{1}H-NMR, ^{13}C-NMR and UV, were used, and the observed values were interpreted.[30-32]

Scheme 1



1 **2** **3** **4**

1-4	R
a	CH_3
b	$CH_2C_6H_5$
c	$CH_2C_6H_4.CH_3$ (*p*-)
d	$CH_2C_6H_4.Cl$ (*p*-)
e	C_6H_5



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Experimental

Melting points were taken on an Electrothermal digital melting point apparatus and are uncorrected. IR spectra were registered on a Perkin-Elmer 1600 FTIR spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in deuterated dimethylsulphoxide on a Varian Mercury Apparatus at 200 MHz with TMS as internal standard. UV absorption spectra were measured in 10 mm quartz cells between 200 and 400 nm with a Shimadzu UV-1201 spectrophotometer. For the potentiometric titrations, a Jenway 3040 ion analyzer pH meter equipped with an Ingold pH electrode was used. Also, a magnetic stirrer, a semi micro burette and a 25 mL beaker were used in the titrations. Before potentiometric titrations, the pH meter was calibrated according to the instructions supplied by the manufactures of the pH meter. During the titrations, the titrant was added in increments of 0.05 mL after each stable reading, and mV values were recorded.

The necessary chemicals were supplied from Fluka and Merck. After purifications, isopropyl alcohol was used to prepare 0.05 *N*-tetrabutylammonium hydroxide (TBAH). For all potentiometric titrations, 0.05 N tetrabutylammonium hydroxide (TBAH) in isopropyl alcohol, which was prepared from the 0.1 N TBAH by dilution, was used.

The starting compounds **2a-e** were prepared from the reactions of the corresponding ester ethoxycarbonylhydrazones **(1a-e)** with an aqueous solution of hydrazine hydrate according to the literature.[15,33]

Preparation of 3-alkyl(aryl)-4-(3,4-dihydroxybenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (3). General Procedure. The corresponding compound 2 (0.01 mole) was dissolved in acetic acid (15 mL) and treated with 3,4-dihydroxybenzaldehyde (1.38 g, 0.01 mole). The mixture was refluxed for 1 h and then evaporated at 50-55 °C in vacuo. Several recrystallizations of the residue from a proper solvent gave pure compound **3**. The following compounds were prepared applying this procedure:

3-Methyl-4-(3,4-dihydroxybenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**3a**). White crystals (1.88 g, 80%). M.p. 275-276 °C (EtOH). IR: 3440 (OH), 3150 (NH), 1710 (C=O), 1610, 1580 (C=N) cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6): δ 2.25 (s, 3H, CH_3), 6.84 (d, J=8.2 Hz, 1H, Ar-H), 7.10 (d, J=8.2 Hz, 1H, Ar-H), 7.30 (s, 1H, Ar-

H), 9.45 (s, 2H, CH+OH), 9.73 (s, 1H, OH), 11.78 (s, 1H, NH). ^{13}C-NMR (50 MHz, DMSO-d_6): δ 11.11 (aliphatic carbon), 112.79, 115.54, 121.76, 124.66, 144.09, 149.20 (aromatic carbons), 145.72 (triazole C_3), 151.30 (N=CH), 154.81 (triazole C_5). UV (ethanol) λ_{max} (ε, L mol^{-1} cm^{-1}): 322 (20086), 237 (12086), 214 (16623) nm. *Anal.* Calculated for $C_{10}H_{10}N_4O_3$: C, 51.28; H, 4.30; N, 23.92. Found: C, 51.15; H, 4.38; N, 23.73.

3-Benzyl-4-(3,4-dihydroxybenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (3b). White crystals (2.65 g, 85%). M.p. 265-267 °C (EtOH/water, 1:3). IR: 3380 (OH), 3196 (NH), 1715 (C=O), 1595, 1580 (C=N), 768, 700 (monosubstituted benzenoid ring) cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6): δ 4.02 (s, 2H, CH_2), 6.83 (d, J=8.2 Hz, 1H, Ar-H), 7.05 (d, J=8.2 Hz, 1H, Ar-H), 7.20-7.34 (m, 6H, Ar-H), 9.43 (s, 2H, CH+OH), 9.52 (s, 1H, OH), 11.93 (s, 1H, NH). ^{13}C-NMR (50 MHz, DMSO-d_6): δ 30.00 (aliphatic carbon), 112.83, 115.52, 121.77, 124.64, 126.64, 128.38 (2C), 128.75 (2C), 135.77, 146.07, 149.24 (aromatic carbons), 145.72 (triazole C_3), 151.26 (N=CH), 154.51 (triazole C_5). UV (ethanol) λ_{max} (ε, L mol^{-1} cm^{-1}): 323 (14783), 213 (16556) nm. *Anal*. Calculated for $C_{16}H_{14}N_4O_3$: C, 61.93; H, 4.55; N, 18.06. Found: C, 62.15; H, 4.67; N, 18.39.

3-*p*-Methylbenzyl-4-(3,4-dihydroxybenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (3c). White crystals (2.48 g, 77%). M.p. 266-267 °C (EtOH/water, 1:3). IR: 3455, 3350 (OH), 3100 (NH), 1700 (C=O), 1610, 1580 (C=N), 800 (1,4-disubstituted benzenoid ring) cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6): δ 2.24 (s, 3H, CH_3), 3.95 (s, 2H, CH_2), 6.82 (d, J=7.9 Hz, 1H, Ar-H), 7.02-7.27 (m, 6H, Ar-H), 9.41 (s, 2H, CH+OH), 9.72 (s, 1H, OH), 11.90 (s, 1H, NH). ^{13}C-NMR (50 MHz, DMSO-d_6): δ 20.51, 30.59 (aliphatic carbons), 112.79, 115.49, 121.74, 124.63, 128.59, 128.92 (2C), 132.64 (2C), 135.66, 146.19, 149.20 (aromatic carbons), 145.70 (triazole C_3), 151.25 (N=CH), 154.41 (triazole C_5). UV (ethanol) λ_{max} (ε, L mol^{-1} cm^{-1}): 320 (11813), 213 (15767) nm. *Anal.* Calculated for $C_{17}H_{16}N_4O_3$: C, 62.95; H, 4.97; N, 17.27. Found: C, 62.94; H, 4.75; N, 16.94.

3-*p*-Chlorobenzyl-4-(3,4-dihydroxybenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (3d). White crystals (2.35 g, 68%). M.p. 290-292 °C (EtOH). IR: 3336

(OH), 3150 (NH), 1715 (C=O), 1590, 1580 (C=N), 805 (1,4-disubstituted benzenoid ring) cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6): δ 4.02 (s, 2H, CH_2), 6.82 (d, J=7.9 Hz, 1H, Ar-H), 7.05 (d, J=7.6 Hz, 1H, Ar-H), 7.25-7.37 (m, 5H, Ar-H), 9.42 (s, 2H, CH+OH), 9.75 (s, 1H, OH), 11.95 (s, 1H, NH). ^{13}C-NMR (50 MHz, DMSO-d_6): δ 30.35 (aliphatic carbon), 112.86, 115.53, 121.75, 124.57, 128.59 (2C), 130.69 (2C), 131.31, 134.72, 145.71, 149.25 (aromatic carbons), 145.71 (triazole C_3), 151.24(N=CH), 154.57(triazole C_5). UV (ethanol) λ_{max} (ε, L mol^{-1} cm^{-1}): 323 (15663), 217 (20945) nm. *Anal.* Calculated for $C_{16}H_{13}N_4O_3Cl$: C, 55.74; H, 3.80; N, 16.25. Found: C, 55.43; H, 3.73; N, 16.60.

3-Phenyl-4-(3,4-dihydroxybenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (3e). White crystals (2.14 g, 72%). M.p. 276-277 °C (EtOH/water, 1:3). IR: 3427 (OH), 3232 (NH), 1700 (C=O), 1610, 1590 (C=N), 765, 700 (monosubstituted benzenoid ring) cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6): δ 6.85 (d, J=7.9 Hz, 1H, Ar-H), 7.09(d, J=7.6 Hz, 1H, Ar-H), 7.62 (s, 1H, Ar-H), 7.25 (s, 3H, Ar-H), 7.89 (s, 2H, Ar-H), 9.33 (s, 2H, CH+OH), 9.52 (s, 1H, OH), 12.32 (s, 1H, NH). ^{13}C-NMR (50 MHz, DMSO-d_6): δ 112.84, 115.57, 122.20, 124.40, 126.73, 127.68 (2C), 128.44 (2C), 129.92, 144.35, 149.50 (aromatic carbons), 145.76 (triazole C_3), 151.39 (N=CH), 158.00 (triazole C_5). UV (ethanol) λ_{max} (ε, L mol^{-1} cm^{-1}): 326 (17811), 282 (13297), 216 (20366) nm. *Anal.* Calculated for $C_{15}H_{12}N_4O_3$: C, 60.81; H, 4.08; N, 18.91. Found: C, 61.20; H, 3.77; N, 18.60.

Preparation of 1-Acetyl-3-alkyl(aryl)-4-(3,4-diacetyloxybenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (4). General Procedure. The corresponding compound **3** (0.01 mole) was refluxed with acetic anhydride (15 mL) for 0.5 h. After addition 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 proper solvent gave pure compound **4**. The following compounds were prepared applying this procedure:

1-Acetyl-3-methyl-4-(3,4-diacetyloxybenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (4a). White crystals (2.95 g, 82%). M.p. 196-197 °C (EtOH). IR: 1780, 1760, 1705 (C=O), 1630, 1610 (C=N) cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6): δ 2.32 (s,

9H, $3CH_3$), 2.49 (s, 3H, CH_3), 7.45 (d, J=8.9 Hz, 1H, Ar-H), 7.80-7.83 (m, 2H, Ar-H), 9.61 (s, 1H, CH). ^{13}C-NMR (50 MHz, DMSO-d_6): δ 11.13, 20.28 (2C), 23.39 (aliphatic carbons), 122.25, 124.25, 126.90, 131.69, 142.46, 146.63 (aromatic carbons), 144.59 (triazole C_3), 147.73 (N=CH), 153.74 (triazole C_5), 165.96, 167.96, 168.14 (C=O). UV (ethanol) λ_{max} (ε, L mol^{-1} cm^{-1}): 293 (17500), 254 (18738), 216 (21784) nm. *Anal.* Calculated for $C_{16}H_{16}N_4O_6$: C, 53.33; H, 4.48; N, 15.55. Found: C, 53.62; H, 4.18; N, 15.60.

1-Acetyl-3-benzyl-4-(3,4-diacetyloxybenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (4b). White crystals (3.72 g, 85%). M.p. 129-130 °C (EtOH). IR: 1780, 1760, 1700 (C=O), 1610, 1590 (C=N), 770, 715 (monosubstituted benzenoid ring) cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6): δ 2.23 (s, 6H, $2CH_3$), 2.40 (s, 3H, CH_3), 4.06 (s, 2H, CH_2), 7.12-7.40 (m, 6H, Ar-H), 7.64-7.78 (m, 2H, Ar-H), 9.55 (s, 1H, CH). ^{13}C-NMR (50 MHz, DMSO-d_6): δ 20.26 (2C), 23.48, 30.92 (aliphatic carbons), 122.34, 124.35, 126.81, 126.88, 128.42 (2C), 128.93 (2C), 131.68, 134.56, 142.39, 147.89 (aromatic carbons), 144.53 (triazole C_3), 148.21 (N=CH), 153.26 (triazole C_5), 165.90, 167.98, 168.10 (C=O). UV (ethanol) λ_{max} (ε, L mol^{-1} cm^{-1}): 295 (17296), 254 (18252), 217 (23879) nm. *Anal.* Calculated for $C_{22}H_{20}N_4O_6$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.84; H, 4.76; N, 12.62.

1-Acetyl-3-(*p*-methylbenzyl)-4-(3,4-diacetyloxybenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (4c). White crystals (4.02 g, 89%). M.p. 159-160 °C (EtOH). IR: 1775, 1765, 1735 (C=O), 1605, 1585 (C=N), 810 (1,4-disubstituted benzenoid ring) cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6): δ 2.09 (s, 3H, CH_3), 2.18 (s, 6H, $2CH_3$), 2.36 (s, 3H, CH_3), 3.90 (s, 2H, CH_2), 6.97 (d, J=7.6 Hz, 2H, Ar-H), 7.09 (d, J=7.6 Hz, 2H, Ar-H), 7.26 (d, J=7.9 Hz, 1H, Ar-H), 7.54 (s, 1H, Ar-H), 7.56 (d, J=8.9 Hz, 1H, Ar-H), 9.36 (s, 1H, CH). ^{13}C-NMR (50 MHz, DMSO-d_6): δ 20.75 (2C), 21.04, 23.92, 31.15 (aliphatic carbons), 122.77, 124.90, 127.38, 129.36 (2C), 129.60 (2C), 131.83, 132.18, 136.77, 142.95, 148.40 (aromatic carbons), 145.10 (triazole C_3), 149.02 (N=CH), 153.76 (triazole C_5), 166.80, 168.80, 168.90 (C=O). UV (ethanol) λ_{max} (ε, L mol^{-1} cm^{-1}): 295 (10145), 254 (10973), 217 (18082) nm. *Anal.* Calculated for $C_{23}H_{22}N_4O_6$: C, 61.32; H, 4.92; N, 12.44. Found: C, 61.24; H, 5.19; N, 12.39.

1-Acetyl-3-*p*-chlorobenzyl-4-(3,4-diacetyloxybenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (4d). White crystals (3.55 g, 76%). M.p. 167-169 °C (EtOH). IR: 1780, 1760, 1700 (C=O), 1610, 1590 (C=N), 810 (1,4-disubstituted benzenoid ring) cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6): δ 2.32 (s, 6H, $2CH_3$), 2.50 (s, 3H, CH_3), 4.17 (s, 2H, CH_2), 7.40-7.45 (m, 5H, Ar-H), 7.74-7.79 (m, 2H, Ar-H), 9.58 (s, 1H, CH). ^{13}C-NMR (50 MHz, DMSO-d_6): δ 20.29 (2C), 23.48, 30.92 (aliphatic carbons), 122.36, 124.38, 126.82, 128.34 (3C), 130.90 (3C), 131.85, 133.95, 142.35 (aromatic carbons), 144.55 (triazole C_3), 148.20 (N=CH), 153.24 (triazole C_5), 165.90, 167.98, 168.10 (C=O). UV (ethanol) λ_{max} (ε, L mol^{-1} cm^{-1}): 295 (17692), 257 (18372), 219 (27571) nm. *Anal.* Calculated for $C_{22}H_{19}N_4O_6Cl$: C, 56.12; H, 4.07; N, 11.90. Found: C, 56.47; H, 4.07; N, 11.91.

1-Acetyl-3-phenyl-4-(3,4-diacetyloxybenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (4e). White crystals (3.78 g, 90%). M.p. 133-134 °C (EtOH). IR: 1780, 1765, 1735 (C=O), 1615, 1598 (C=N), 750, 700 (monosubstituted benzenoid ring) cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6): δ 2.17 (s, 6H, $2CH_3$), 2.42 (s, 3H, CH_3), 7.28 (d, J=7.9 Hz, 1H, Ar-H), 7.35-7.82 (m, 7H, Ar-H), 9.31 (s, 1H, CH). ^{13}C-NMR (50 MHz, DMSO-d_6): δ 20.78 (2C), 23.99 (aliphatic carbons), 123.29, 125.10, 125.49, 127.28, 129.19 (3C), 131.93 (2C), 132.29, 143.00, 146.58 (aromatic carbons), 145.34 (triazole C_3), 148.55 (N=CH), 157.60 (triazole C_5), 167.13, 168.82, 168.95 (C=O). UV (ethanol) λ_{max} (ε, L mol^{-1} cm^{-1}): 263 (12768), 217 (12081) nm. *Anal.* Calculated for $C_{21}H_{18}N_4O_6$: C, 59.71; H, 4.30; N, 13.26. Found: C, 59.49; H, 4.24; N, 13.45.

Preparation of 1-Methyl-3-alkyl(aryl)-4-(3,4-dimethoxybenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (5). General Procedure. The corresponding compound **3** (0.01 mole) was dissolved in 2N NaOH (10 mL) and treated dimethyl sulphate (3.2 mL). After stirring of the mixture at room temperature for 1 h, the solid formed was filtered, washed with cold water (15 mL) and dried in vacuo. Several recrystallizations of crude product from a proper solvent gave pure compound **5**. The following compounds were prepared applying this procedure:

1,3-Dimethyl-4-(3,4-dimethoxybenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (5a). White crystals (1.88 g, 68%). M.p. 137-139 °C (EtOH). IR: 1710 (C=O),

1600,1580 (C=N) cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6): δ 2.19 (s, 3H, CH_3), 3.22 (s, 3H, CH_3), 3.80 (s, 6H, $2CH_3$), 6.96 (d, J=8.1 Hz, 1H, Ar-H), 7.25-7.35 (m, 2H, Ar-H), 9.45 (s, 1H, CH). ^{13}C-NMR (50 MHz, DMSO-d_6): δ 10.83, 31.70, 55.35, 55.52 (aliphatic carbons), 108.73, 111.37, 122.76, 125.75, 148.95, 149.31 (aromatic carbons), 142.66 (triazole C_3), 151.72 (N=CH), 154.31 (triazole C_5). UV (ethanol) λ_{max} (ε, L mol^{-1} cm^{-1}): 315 (21065), 235 (15144), 215 (17657) nm. *Anal.* Calculated for $C_{13}H_{16}N_4O_3$: C, 56.51; H, 5.84; N, 20.28. Found: C, 56.22; H, 5.57; N, 20.04.

1-Methyl-3-benzyl-4-(3,4-dimethoxybenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (5b). White crystals (2.30 g, 65%). M.p. 150-152 °C (EtOH). IR: 1715 (C=O), 1610, 1580 (C=N), 760, 720 (monosubstituted benzenoid ring) cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6): δ 3.22 (s, 3H, CH_3), 3.82 (s, 6H, $2CH_3$), 4.07 (s, 2H, CH_2), 7.05 (d, J=7.9 Hz, 1H, Ar-H), 7.22-7.45 (m, 7H, Ar-H), 9.54 (s, 1H, CH). ^{13}C-NMR (50 MHz, DMSO-d_6): δ 30.97, 31.83, 55.31, 55.51 (aliphatic carbons), 108.18, 111.29, 123.03, 125.78, 126.66, 128.37 (2C), 128.72 (2C), 135.64, 148.93, 149.45 (aromatic carbons), 144.56 (triazole C_3), 151.70 (N=CH), 153.46 (triazole C_5). UV (ethanol) λ_{max} (ε, L mol^{-1} cm^{-1}): 318 (34597), 216 (25068) nm. *Anal.* Calculated for $C_{19}H_{20}N_4O_3$: C, 64.76; H, 5.72; N, 15.90. Found: C, 64.89; H, 5.85; N, 15.81.

1-Methyl-3-*p*-methylbenzyl-4-(3,4-dimethoxybenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (5c). White crystals (2.52 g, 69%). M.p. 197-198 °C (EtOH). IR: 1715 (C=O), 1610, 1595 (C=N), 810 (1,4-disubstituted benzenoid ring) cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6): δ 2.20 (s, 3H, CH_3), 3.20 (s, 3H, CH_3), 3.80 (s, 6H, $2CH_3$), 3.96 (s, 2H, CH_2), 6.84 (d, J=7.8 Hz, 1H, Ar-H), 7.05-7.35 (m, 6H, Ar-H), 9.40 (s, 1H, CH). ^{13}C-NMR (50 MHz, DMSO-d_6): δ 20.82, 30.84, 31.20, 55.30, 55.62 (aliphatic carbons), 108.22, 111.30, 123.12, 125.92, 126.82, 127.22, 128.42 (2C), 128.92 (2C), 135.57, 148.33 (aromatic carbons), 145.32 (triazole C_3), 152.10 (N=CH), 153.52 (triazole C_5). UV (ethanol) λ_{max} (ε, L mol^{-1} cm^{-1}): 318 (11210), 224 (23150) nm. *Anal.* Calculated for $C_{20}H_{22}N_4O_3$: C, 65.56; H, 6.05; N, 15.29. Found: C, 65.77; H, 6.18; N, 15.20.

Results and Discussion

There have been several studies about the potentiometric titrations of some 4,5-dihydro-1*H*-1,2,4-triazol-5-on derivatives with tetrabutylammonium hydroxide (TBAH) in the non-aqueous solvents such as isopropyl alcohol, methyl alcohol, tert-butyl alcohol and acetone, and the pK_a values were found between 9.79-16.05[23-25].

In this study, five new 3-alkyl(aryl)-4-(3,4-dihydroxybenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**3**), five new 1-acetyl-3-alkyl(aryl)-4-(3,4-diacetyloxybenzyliden-amino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**4**) and three new 1-methyl-3-alkyl(aryl)-4-(3,4-dimethoxybenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**5**) were synthesized, and **3** type compounds were titrated potentiometrically with tetrabutylammonium hydroxide (TBAH) in non-aqueous solvents such as isopropyl alcohol (ε=19.4), *N,N*-dimethylformamide (ε=37) and acetonitrile (ε=36).

The mV values, which were read from pH meter, were plotted versus TBAH volumes (mL) added, and thus potentiometric titration curves were formed for all the cases. From these curves, the HNP values were measured, and the corresponding pK_a values were calculated.

As an example, the potentiometric titration curves of 0.001 M 3-benzyl-4-(3,4-dihydroxybenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**3b**) solutions titrated with 0.05 N TBAH in isopropyl alcohol, *N,N*-dimethylformamide and acetonitrile are presented in Figure **1**.

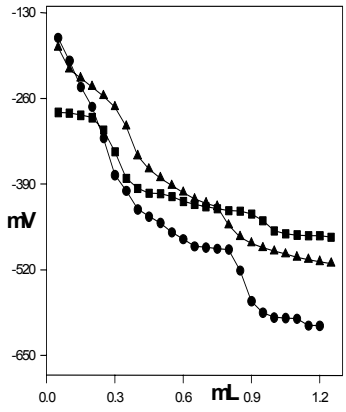

Figure 1: Potentiometric titration curves of 10^{-3} M compound **3b** solutions titrated with 0.05 N TBAH in isopropyl alcohol (►), *N,N*-dimethylformamide (■) and acetonitrile (●) at 25 °C.

The half neutralization potential (HNP) values and the corresponding pK_a values of compounds **3a-e**, which were obtained from the potentiometric titrations with 0.05 N TBAH in non aqueous solvents such as isopropyl alcohol, *N,N*-dimethylformamide and acetonitrile, are presented in Tables **1-3**.

Table 1: The half neutralization potential (HNP) values and the corresponding pK_a values of compounds **3a-e** in isopropyl alcohol at 25 °C.

Compd. no	HNP_1 (mV)	pKa_1	HNP_2 (mV)	pKa_2
3a	-231	11.41	-327	13.65
3b	-242	11.13	-419	14.25
3c	-194	10.35	-314	13.42
3d	-203	9.75	-394	13.40
3e	-224	11.22	-341	13.51

Table 2: The half neutralization potential (HNP) values and the corresponding pK_a values of compounds **3a-e** in *N,N*-dimethylformamide at 25 °C.

Compd. no	HNP_1 (mV)	pKa_1	HNP_2 (mV)	pKa_2
3a	-357	12.09	-424	13.81
3b	-287	12.03	-429	14.43
3c	-255	10.61	-371	13.75
3d	-310	12.53	-511	-
3e	-326	12.85	-506	-

Table 3: The half neutralization potential (HNP) values and the corresponding pK_a values of compounds **3a-e** in acetonitrile at 25 °C.

Compd. no	HNP_1 (mV)	pKa_1	HNP_2 (mV)	pKa_2
3a	-281	11.74	-424	13.79
3b	-243	11.15	-488	15.29
3c	-293	12.05	-593	-
3d	-182	10.27	-353	13.07
3e	-192	10.52	-271	12.08

As seen in Scheme **1**, there is one weak acidic N-H group in 4,5-dihydro-1*H*-1,2,4-triazol-5-one ring and two phenolic groups in compounds **3a-e**. Thus, these compounds give two end points as well as two half neutralization potential values. The potentiometric titration curves of these phenolic compounds **3a-e** titrated with TBAH in isopropyl alcohol, *N,N*-dimethylformamide and acetonitrile resemble the titration curves of diprotic acids. For compound **3d** and **3e,** the second pK_a values have not been obtained in *N,N*-dimethylformamide. For compound **3c,** the second pK_a value has not been obtained in acetonitrile, either.

As known, the acidity of a compound changes in relation to some factors. The two most important factors are solvent effects and molecular structure.[23-26,34-38] Tables **1-3** show that the HNP values and the corresponding pK_a values obtained from the potentiometric titrations change in connection with the non-aqueous solvents in which the titration took place. In addition, it is seen from the Tables **1-3** that the molecular structure of titrated compounds affect the HNP values as well as the corresponding pK_a values: that is, the HNP values and corresponding pK_a values are connected to the substituents linked to C-3 in 4,5-dihydro-1*H*-1,2,4-triazol-5-one ring for the same solvent.

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Povzetek

Iz 3-alkil(aril)-4-amino-4,5-dihidro-1*H*-1,2,4-triazol-5-onov (**2**) smo z 3,4-dihidroksibenzaldehidom pripravili 3-alkil(aril)-4-(3,4-dihidroksibenzilidenamino)-4,5-dihidro-1*H*-1,2,4-triazol-5-one. Raziskali smo acetiliranje in metiliranje teh produktov. Nove spojine smo karakterizirali z IR, NMR in UV spektroskopskimi tehnikami. Na osnovi rezultatov potenciometričnih titracij spojin **3a-3e** s tetrabutilamonijevim hidroksidom v treh brezvodnih topilih smo določili pK_a vrednosti.