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Synthesis and Potentiometric Titrations of 3-Alkyl(Aryl)-4-[3-etoxy-4-(4-methoxybenzensulfonyloxy)-benzylidenamino]-4,5-dihydro-1H-1,2,4-triazol-5-ones

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Abstract: Determination of pK_a values of the active constituent of certain pharmaceutical preparations is important because the distribution, transport behaviour, bonding to receptors, and contributions to the metabolic behaviour of the active constituent molecules depend on the ionization constant. It is known that 1,2,4-triazole and 4,5-dihydro-1H-1,2,4-triazol-5-one rings have weak acidic properties, so that some 1,2,4-triazole and 4,5-dihydro-1H-1,2,4-triazol-5-one derivatives were titrated potentiometrically with tetrabutyl ammonium hydroxide (TBAH) in non-aqueous solvents, and the pK_a values of the compounds were determined. In this study, the first part of the study nine novel 3-alkyl(aryl)-4-[3-etoxy-4-(4-methoxybenzensulfonyloxy)-benzylidenamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones were synthesized from the reactions of the corresponding 3-alkyl(aryl)-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones with 2-ethoxy-4-formylphenyl 4-methoxybenzenesulfonate, which was obtained from the reaction of 3-ethoxy-4-hydroxybenzaldehyde with 4-methoxybenzensulfonyl chloride by using triethylamine. The new compounds synthesized were also characterized by using IR and ^{1}H-NMR, ^{13}C-NMR spectral data. The second part of the study, nine novel 3-alkyl(aryl)-4-[3-etoxy-4-(4-methoxybenzensulfonyloxy)-benzylidenamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones were titrated potentiometrically with TBAH (tetrabutylammonium hydroxide) in four different non-aqueous solvents (isopropyl alcohol, tert-butyl alcohol, acetone and *N*,*N*-dimethylformamide) and graphs were drawn for all cases. The half notralization potentials and pK_a values were determined by half neutralization method. The effects of solvents and molecular structure upon acidity were also discussed.

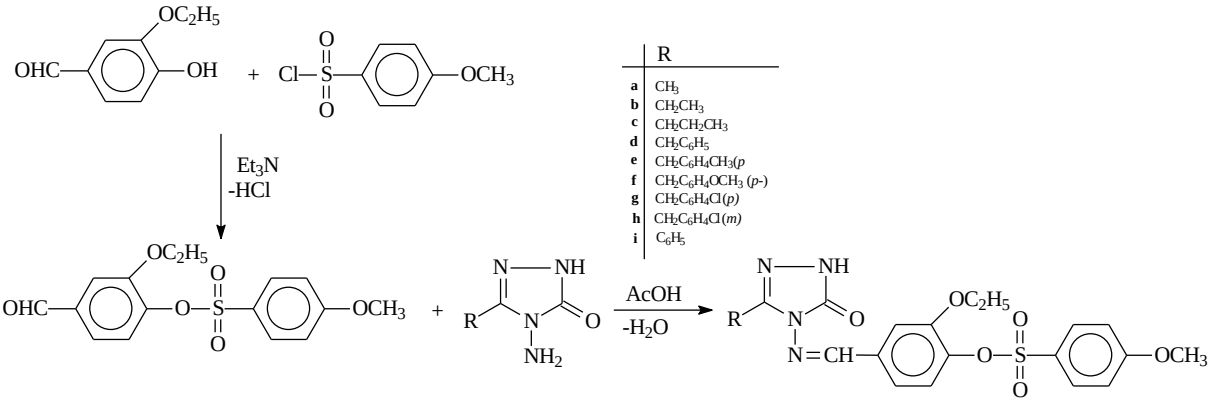
Keywords: Synthesis, 4,5-dihydro-1H-1,2,4-triazol-5-one, TBAH, pK_a, Half-neutralization method

Introduction

1,2,4-Triazole and 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives are reported to possess a broad spectrum of biological activities such as antifungal, antimicrobial, hypoglycemic, antihypertensive, analgesic, antiparasitic, hypocholesteremic, antiviral, anti-inflammatory, antitumor and anti-HIV properties (Bhat, Bhat & Shenoy, 2001; Modzelewska-Banachiewicz et al., 2000; Varvaresou, 2000; Witkowski, 1973; Burzozowski, 1998; Katica et al., 2001; Wang, You & Xu, 1996; Ikizler, 1998; Demirbaş, 2001; Ulusoy, Gursoy & Otuk, 2001; Yüksek et al., 1997; Ikizler et al., 1997). In addition, several articles reporting the synthesis of some *N*-arylidenamino-4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives have been published (Ikizler et al., 1997; Ikizler et al., 1998; Ikizler & Yüksek, 1994; Bahçeci et al., 2002a; Bahçeci et al., 2002b). The acetylation and

methylation of 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives have also been reported (Yüksek et al., 1997; Bahçeci et al., 2002a; Bahçeci et al., 2002b; Ikizler & Yüksek, 1993). 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 corresponding pK_a values of the compounds were determined (Bahçeci et al., 2002a; Bahçeci et al., 2002b; Yüksek et al., 2003; Yüksek et al., 2004; Ikizler et al., 1988; Ikizler & Erdoğan, 1988; Ikizler et al., 1988).

This paper describes the synthesis of a series of novel 3-alkyl(aryl)-4-[3-etoxy-4-(4-methoxybenzensulfonyloxy)-benzylidenamino]-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 2-ethoxy-4-formylphenyl 4-methoxybenzenesulfonate **(1)** (Scheme **1**). The starting compounds **2a-i** were prepared from the reactions of the corresponding ester ethoxycarbonylhydrazones with an aqueous solution of hydrazine hydrate as described in the literatüre (Ikizler & Yüksek, 1994; Ikizler & Un, 1979). Furthermore, we also examined the potentiometric titrations of the synthesized compounds **3a-i** with tetrabutylammonium hydroxide (TBAH) in four non-aqueous solvents (isopropyl alcohol, *tert*-butyl alcohol, acetone and *N*,*N*-dimethylformamide} to determine the corresponding half-neutralization potentials (HNP) and the corresponding pK_a values. The data obtained from the potentiometric titrations were interpreted and the effects of molecular structure and solvents were studied (Bahçeci et al., 2002a; Bahçeci et al., 2002b; Yüksek et al., 2003; Yüksek et al., 2004; Ikizler et al., 1988; Ikizler & Erdoğan, 1988; Ikizler et al., 1988; Gündüz, 1998).



Scheme 1: Synthesis of compounds of type 3

Method

Chemicals and Apparatus

In this study, a Jenway 3040 ion analyser pH meter equipped with an Ingold pH electrode was used for potentiometric titrations. For each compound titrated, a 0.001 M solution was separately prepared in each non-aqueous solvent. A 0.05 M solution of TBAH in isopropyl alcohol, which is widely used in the titration of acids, was used as titrant. The mV values obtained on the pH meter were recorded. Finally, the half-neutralization potential (HNP) values were determined by plotting the volume (mL) (TBAH)-mV graph.

Procedure for the synthesis of 2-ethoxy-4-formylphenyl 4-methoxybenzenesulfonate (1)

4-methoxybenzensulfonyl chloride (10 mmol) was reacted with 3-ethoxy-4-hydroxybenzaldehyde (10 mmol) in ethyl acetate (100 mL). Then, triethylamine (20 mmol) was slowly added in the solution at stirring at 0-5 °C with magnetic stirring. After stirring for 2 hours at room temperature, it was refluxed for 3 hours and filtered. The crude product was crystallized several times in ethanol to afford compound **1**. Yield 93.75%. Mp: 61°C. ^{1}H NMR (400MHz, DMSO-d_6, δ): 1.17 (t, 3H, $OCH_2C\underline{H}_3$; *J*=6.80 Hz), 3.87 (s, 3H, OCH_3), 3.91 (q, 3H, $OC\underline{H}_2CH_3$; *J*=6.80 Hz), 7.15-7.18 (m, 2H, ArH), 7.41 (d, 1H, ArH; *J*=8.40 Hz), 7.51 (d, 1H, ArH; *J*=1.60 Hz), 7.55 (dd, 1H, ArH; *J*=8.00 Hz, 1.60 Hz), 7.75-7.78 (m, 2H, ArH), 9.95 (s, 1H, CHO), ^{13}C NMR (100MHz, DMSO-d_6, δ): 14.02 ($OCH_2\underline{C}H_3$), 55.96 (OCH_3), 64.22 ($O\underline{C}H_2CH_3$), 113.39; 114.69 (2C); 122.75; 124.48; 126.20; 130.28; 130.58, 135.79; 141.95; 151.24; 164.13 (Ar-C), 191.94 (2CHO).

General procedure for the synthesis of compounds 3a-I

2-ethoxy-4-formylphenyl 4-methoxybenzenesulfonate (**1)** (10 mmol) was dissolved in acetic acid (15 mL) and reacted with the corresponding compound **2** (10 mmol) to synthesize3-alkyl(aryl)-4-[3-etoxy-4-(4-methoxybenzensulfonyloxy)-benzylidenamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones and was refluxed for 1.5 hour. Then, the solution evaporated at 50-55 °C *in vacuo*. The residue was crystallized several times in ethanol and pure **3a-i** compounds were obtained as colorless crystals.

3-Methyl-4-[3-etoxy-4-(4-methoxybenzensulfonyloxy)-benzylidenamino]-4,5-dihydro-1H-1,2,4-triazol-5-ones (3a)

Yield 95.03%. M.p. 186°C. IR (KBr, υ, cm^{-1}): 3189 (NH), 1708 (C=O), 1579 (C=N), 1353 and 1196 (SO_2) 741 and 700 (1,4-disubstituted benzenoid ring). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.16 (t, 3H, $OCH_2C\underline{H}_3$, *J*=7.20 Hz), 2.27 (s, 3H, CH_3), 3.84-3.90 (m, 5H, $OC\underline{H}_2CH_3$ + OCH_3), 7.15-7.17 (m, 2H, ArH), 7.27 (d, 1H, ArH, *J*=8.00 Hz), 7.43-7.47 (m, 2H, ArH), 7.74-7.77 (m, 2H, ArH), 9.67 (s, 1H, N=CH), 11.82 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.00 (CH_3), 14.08 ($OCH_2\underline{C}H_3$), 55.94 (OCH_3), 64.07 ($O\underline{C}H_2CH_3$), 112.74, 114.63 (2C), 119.99, 124.22, 126.32, 130.58 (2C), 133.59, 139.64, 150.96, 164.05 (Ar-C), 144.29 (triazole C_3), 151.15 (triazole C_5), 152.48 (N=CH).

3-Ethyl-4-[3-etoxy-4-(4-methoxybenzensulfonyloxy)-benzylidenamino]-4,5-dihydro-1H-1,2,4-triazol-5-ones (3b)

Yield 88.70%. M.p. 172°C. IR (KBr, υ, cm^{-1}): 3191 (NH), 1698 (C=O), 1593 (C=N), 1364 and 1199 (SO_2) 751 and 707 (1,4-disubstituted benzenoid ring). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.15 (t, 3H, $OCH_2C\underline{H}_3$, *J*=7.20 Hz), 1.20 (t, 3H, $CH_2C\underline{H}_3$, *J*=7.60 Hz), 2.68 (q, 2H, $C\underline{H}_2CH_3$, *J*=7.60 Hz), 3.84-3.89 (m, 5H, $OC\underline{H}_2CH_3$ + OCH_3), 7.14-7.18 (m, 2H, ArH), 7.14 (d, 1H, ArH, *J*=8.40 Hz), 7.44 (d, 2H, ArH, *J*=8.40 Hz), 7.73-7.76 (m, 2H, ArH), 9.67 (s, 1H, N=CH), 11.85 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 9.96 ($CH_2\underline{C}H_3$), 14.09 ($OCH_2\underline{C}H_3$), 18.43 ($\underline{C}H_2CH_3$), 55.96 (OCH_3), 64.04 ($O\underline{C}H_2CH_3$), 112.80, 114.65 (2C), 119.86, 124.28, 126.31, 130.59 (2C), 133.63, 139.60, 150.96, 164.04 (Ar-C), 148.05 (triazole C_3), 151.28 (triazole C_5), 152.49 (N=CH).

3-n-Propyl-4-[3-etoxy-4-(4-methoxybenzensulfonyloxy)-benzylidenamino]-4,5-dihydro-1H-1,2,4-triazol-5-ones (3c)

Yield 83.33%. M.p. 163°C. IR (KBr, υ, cm^{-1}): 3172 (NH), 1697 (C=O), 1594 (C=N), 1368 and 1196 (SO_2) 748 and 690 (1,4-disubstituted benzenoid ring). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.97 (t, 3H, $CH_2CH_2C\underline{H}_3$, *J*=7.20 Hz), 1.17 (t, 3H, $OCH_2C\underline{H}_3$, *J*=7.20 Hz), 1.69 (sext, 2H, $CH_2\underline{C}H_2CH_3$, *J*=7.60 Hz), 2.60 (t, 2H, $\underline{C}H_2CH_2CH_3$, *J*=7.20 Hz), 3.84-3.89 (m, 5H, $OC\underline{H}_2CH_3$ + OCH_3), 7.15-7.17 (m, 2H, ArH), 7.28 (d, 1H, ArH, *J*=8.00 Hz), 7.43-7.46 (m, 2H, ArH), 7.73-7.77 (m, 2H, ArH), 9.67 (s, 1H, N=CH), 11.86 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.45 ($CH_2CH_2\underline{C}H_3$), 14.07 ($OCH_2\underline{C}H_3$), 18.92 ($CH_2\underline{C}H_2CH_3$), 26.64 ($\underline{C}H_2CH_2CH_3$), 55.95 (OCH_3), 64.02 ($O\underline{C}H_2CH_3$), 112.85, 114.64 (2C), 119.79, 124.30, 126.32, 130.59 (2C), 133.63, 139.60, 150.94, 164.04 (Ar-C), 146.92 (triazole C_3), 151.21 (triazole C_5), 152.44 (N=CH).

3-Benzyl-4-[3-etoxy-4-(4-methoxybenzensulfonyloxy)-benzylidenamino]-4,5-dihydro-1H-1,2,4-triazol-5-ones (3d)

Yield 95.58%. M.p. 136°C. IR (KBr, υ, cm^{-1}): 3197 (NH), 1725, 1705 (C=O), 1580 (C=N), 1356 and 1199 (SO_2) 753 and 701 (1,4-disubstituted benzenoid ring). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.17 (t, 3H, $OCH_2C\underline{H}_3$, *J*=6.80 Hz), 3.84 (q, 2H, $OC\underline{H}_2CH_3$, *J*=6.80 Hz), 3.87 (s, 3H, OCH_3), 4.05 (s, 2H, CH_2Ph), 7.16 (d, 2H, ArH, *J*=8.80 Hz), 7.22-7.31 (m, 6H, ArH), 7.35-7.37 (m, 2H, ArH), 7.73-7.76 (m, 2H, ArH), 9.63 (s, 1H, N=CH), 11.12 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.07 ($OCH_2\underline{C}H_3$), 31.15 (CH_2Ph), 55.06 (OCH_3), 66.00 ($O\underline{C}H_2CH_3$), 111.93, 114.63 (2C), 120.53, 124.22, 126.28, 126.67, 128.41 (2C), 128.65 (2C), 130.60 (2C), 133.56, 135.82, 139.62, 150.90, 164.05 (Ar-C), 146.15 (triazole C_3), 151.14 (triazole C_5), 151.93 (N=CH).

3-p-methylbenzyl-4-[3-etoxy-4-(4-methoxybenzensulfonyloxy)-benzylidenamino]-4,5-dihydro-1H-1,2,4-triazol-5-ones (3e)

Yield 92.19%. M.p. 167°C. IR (KBr, υ, cm^{-1}): 3168 (NH), 1701 (C=O), 1575 (C=N), 1363 and 1197 (SO_2) 746 and 703 (1,4-disubstituted benzenoid ring). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.17 (t, 3H, $OCH_2C\underline{H}_3$, *J*=7.20 Hz), 2.24 (s, 3H, $PhCH_3$), 3.84 (q, 2H, $OC\underline{H}_2CH_3$, *J*=6.40 Hz), 3.87 (s, 3H, OCH_3), 3.99 (s, 2H, CH_2Ph), 7.09 (d, 2H, ArH, *J*=8.00 Hz), 7.14-7.19 (m, 4H, ArH), 7.26 (d, 1H, ArH, *J*=8.80 Hz), 7.37 (d, 2H, ArH, *J*=8.40 Hz),

7.73-7.76 (m, 2H, ArH), 9.62 (s, 1H, N=CH), 11.98 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.08 ($OCH_2\underline{C}H_3$), 20.55 ($PhCH_3$), 30.76 (CH_2Ph), 55.96 (OCH_3), 63.99 ($O\underline{C}H_2CH_3$), 111.89, 114.63 (2C), 120.55, 124.23, 126.29, 128.52 (2C), 128.97 (2C), 130.60 (2C), 132.71, 133.58, 135.73, 139.62, 151.14, 164.05 (Ar-C), 146.29 (triazole C_3), 150.90 (triazole C_5), 151.86 (N=CH).

3-p-Methoxybenzyl-4-[3-etoxy-4-(4-methoxybenzensulfonyloxy)-benzylidenamino]-4,5-dihydro-1H-1,2,4-triazol-5-ones (3f)

Yield 90.24%. M.p. 151°C. IR (KBr, υ, cm^{-1}): 3181 (NH), 1699 (C=O), 1577 (C=N), 1346 and 1198 (SO_2) 744 and 702 (1,4-disubstituted benzenoid ring). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.10 (t, 3H, $OCH_2C\underline{H}_3$, *J*=6.80 Hz), 3.70 (s, 3H, *p*-OCH_3), 3.85 (q, 2H, $OC\underline{H}_2CH_3$, *J*=6.80 Hz), 3.88 (s, 3H, OCH_3), 3.97 (s, 2H, CH_2Ph), 6.85 (d, 2H, ArH, *J*=8.40 Hz), 7.17-7.19 (m, 2H, ArH), 7.21-7.28 (m, 3H, ArH), 7.37-7.40 (m, 2H, ArH), 7.74-7.76 (m, 2H, ArH), 9.63 (s, 1H, N=CH), 11.96 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.08 ($OCH_2\underline{C}H_3$), 30.29 (CH_2Ph), 55.00 (*p*-OCH_3), 55.95 (OCH_3), 64.01 ($O\underline{C}H_2CH_3$), 112.03, 113.86 (2C), 114.63 (2C), 120.67, 124.24, 126.30, 127.58, 129.72 (2C), 130.59 (2C), 133.59, 139.62, 151.15, 158.07, 164.05 (Ar-C), 146.45 (triazole C_3), 150.91 (triazole C_5), 151.96 (N=CH).

3-p-Chlorobenzyl-4-[3-etoxy-4-(4-methoxybenzensulfonyloxy)-benzylidenamino]-4,5-dihydro-1H-1,2,4-triazol-5-ones (3g)

Yield 95.58%. M.p. 181°C. IR (KBr, υ, cm^{-1}): 3177 (NH), 1703 (C=O), 1576 (C=N), 1364 and 1198 (SO_2), 751 and 707 (1,4-disubstituted benzenoid ring). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.17 (t, 3H, $OCH_2C\underline{H}_3$, *J*=7.20 Hz), 3.83 (q, 2H, $OC\underline{H}_2CH_3$, *J*=7.20 Hz), 3.87 (s, 3H, OCH_3), 4.06 (s, 2H, CH_2Ph), 7.15-7.17 (m, 2H, ArH), 7.26 (d, 1H, ArH, *J*=8.00 Hz), 7.32-7.37 (m, 6H, ArH), 7.73-7.76 (m, 2H, ArH), 9.63 (s, 1H, N=CH), 12.01 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.09 ($OCH_2\underline{C}H_3$), 30.47 (CH_2Ph), 55.96 (OCH_3), 64.00 ($O\underline{C}H_2CH_3$), 111.99, 114.63 (2C), 120.52, 124.24, 126.89, 128.35 (2C), 130.57 (2C), 130.60 (2C), 131.37, 133.51, 134.83, 139.65, 151.12, 164.05 (Ar-C), 145.80 (triazole C_3), 150.91 (triazole C_5), 152.08 (N=CH).

3-m-Chlorobenzyl-4-[3-etoxy-4-(4-methoxybenzensulfonyloxy)-benzylidenamino]-4,5-dihydro-1H-1,2,4-triazol-5-ones (3h)

Yield 92.85%. M.p. 175°C. IR (KBr, υ, cm^{-1}): 3166 (NH), 1688 (C=O), 1575 (C=N), 1345 and 1166 (SO_2) 743 and 704 (1,4-disubstituted benzenoid ring). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.17 (t, 3H, $OCH_2C\underline{H}_3$, *J*=7.20 Hz), 3.86 (q, 2H, $OC\underline{H}_2CH_3$, *J*=6.80 Hz), 3.88 (s, 3H, OCH_3), 4.09 (s, 2H, CH_2Ph), 7.15 (d, 2H, ArH, *J*=8.80 Hz), 7.24-7.42 (m, 7H, ArH), 7.74 (d, 2H, ArH, *J*=8.80 Hz), 9.63 (s, 1H, N=CH), 12.03 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.08 ($OCH_2\underline{C}H_3$), 30.70 (CH_2Ph), 55.96 (OCH_3), 64.02 ($O\underline{C}H_2CH_3$), 111.81, 114.62 (2C), 120.69, 124.20, 126.25, 126.73, 127.40, 128.74, 130.25, 130.61 (2C), 132.94, 133.50, 138.26, 139.66, 151.10, 164.05 (Ar-C), 145.64 (triazole C_3), 150.94 (triazole C_5), 152.04 (N=CH).

3-Phenyl-4-[3-etoxy-4-(4-methoxybenzensulfonyloxy)-benzylidenamino]-4,5-dihydro-1H-1,2,4-triazol-5-ones (3i)

Yield 94.73%. M.p. 217°C. IR (KBr, υ, cm^{-1}): 3154 (NH), 1691 (C=O), 1575 (C=N), 1364 and 1196 (SO_2) 747 and 699 (1,4-disubstituted benzenoid ring). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.14 (t, 3H, $OCH_2C\underline{H}_3$, *J*=6.80 Hz), 3.85 (q, 2H, $OC\underline{H}_2CH_3$, *J*=6.80 Hz), 3.86 (s, 3H, OCH_3), 7.16 (d, 2H, ArH, *J*=8.80 Hz), 7.29 (d, 1H, ArH, *J*=8.40 Hz), 7.41-7.43 (m, 1H, ArH), 7.46 (d, 1H, ArH, *J*=2.00 Hz), 7.52-7.54 (m, 3H, ArH), 7.75-7.77 (m, 2H, ArH), 7.89-7.91 (m, 2H, ArH), 9.64 (s, 1H, N=CH), 12.40 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.06 ($OCH_2\underline{C}H_3$), 55.95 (OCH_3), 63.97 ($O\underline{C}H_2CH_3$), 112.71, 114.66 (2C), 120.25, 124.39, 126.32, 126.53, 127.99 (2C), 128.47 (2C), 130.14, 130.58 (2C), 133.45, 139.77, 151.25, 164.05, (Ar-C), 144.58 (triazole C_3), 150.94 (triazole C_5), 154.77 (N=CH).

Results and Discussion

In this study, the structures of nine new 3-alkyl(aryl)-4-[3-etoxy-4-(4-methoxybenzensulfonyloxy)-benzylidenamino]-4,5-dihydro-1H-1,2,4-triazol-5-ones (**3**) were characterized with IR, ^{1}H NMR and ^{13}C NMR spectral data. In order to determine the pK_a values of the compounds **3a–i**, they were titrated potentiometrically with TBAH in four non-aqueous solvents: isopropyl alcohol, tert-butyl alcohol, acetone and DMF. The mV values read in each titration were plotted against 0.05 M TBAH volumes (mL) added, and potentiometric

titration curves were obtained for all the cases. From the titration curves, the HNP values were measured, and the corresponding pK_a values were calculated.

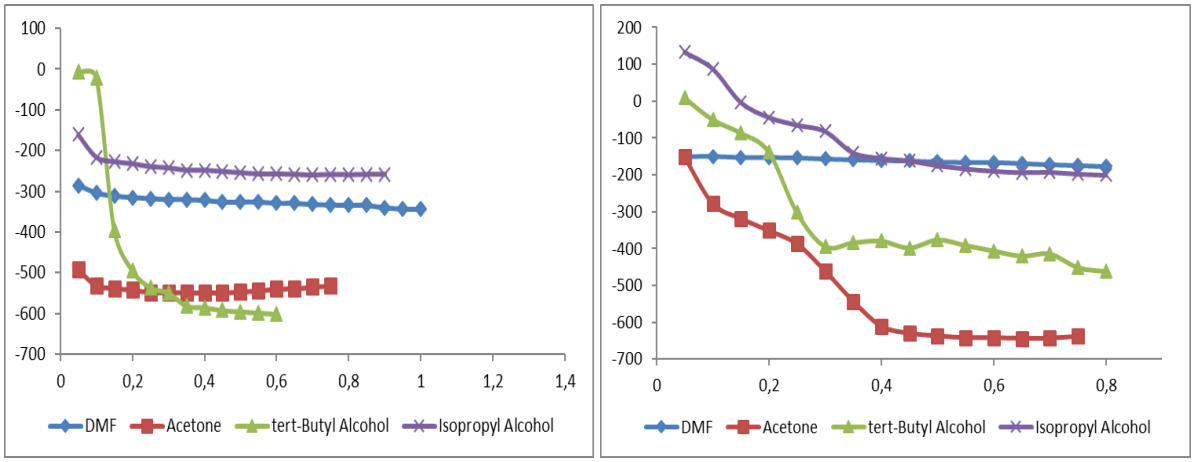


Figure 1. Potentiometric titration curves of 0.001 M solutions of compounds 3a and 3b titrated with 0.05 M TBAH in isopropyl alcohol, tert-butyl alcohol, DMF and acetone at 25 °C

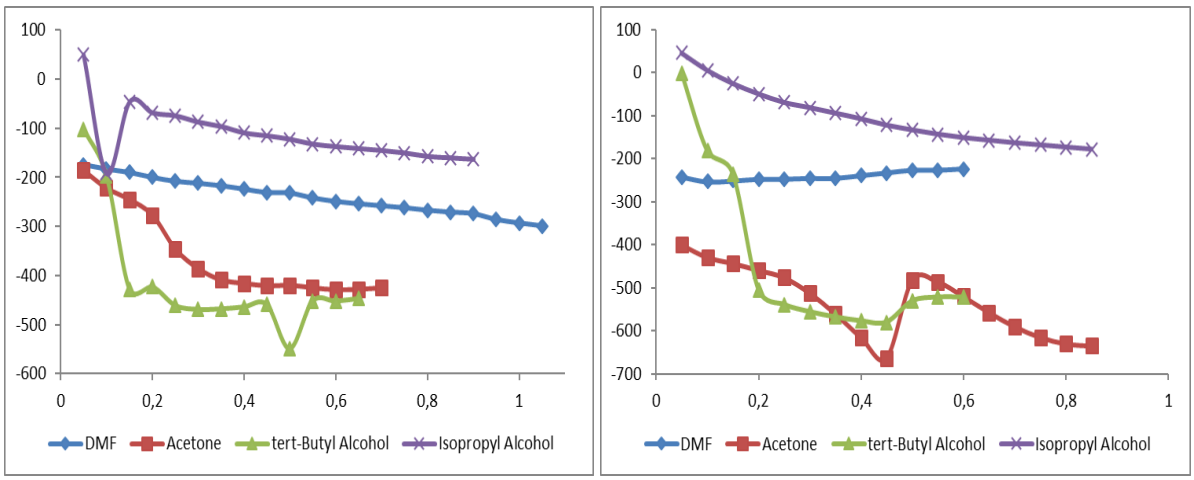


Figure 2. Potentiometric titration curves of 0.001 M solutions of compounds 3c and 3d titrated with 0.05 M TBAH in isopropyl alcohol, tert-butyl alcohol, DMF and acetone at 25 °C

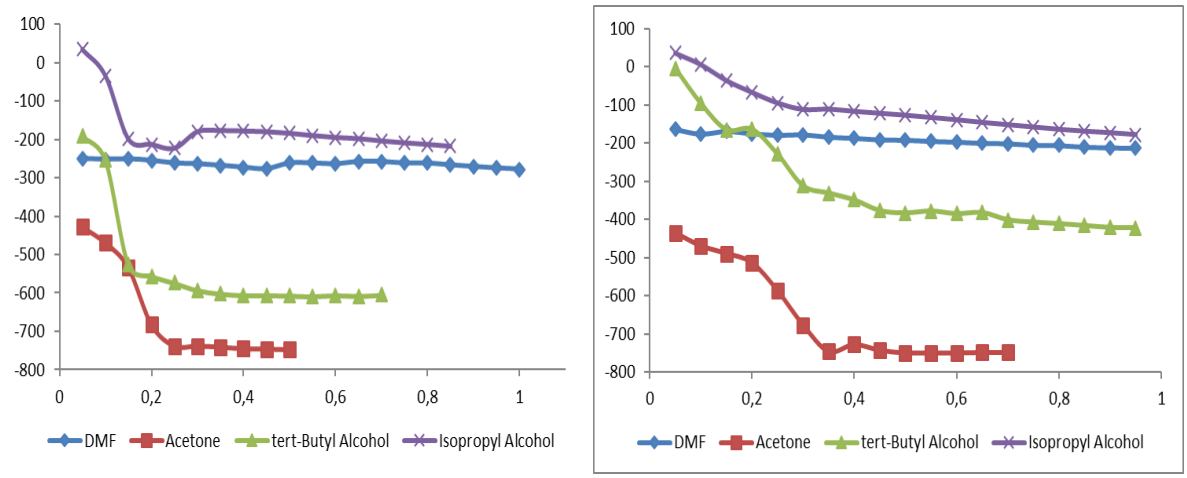


Figure 3. Potentiometric titration curves of 0.001 M solutions of compounds 3e and 3f titrated with 0.05 M TBAH in isopropyl alcohol, tert-butyl alcohol, DMF and acetone at 25 °C

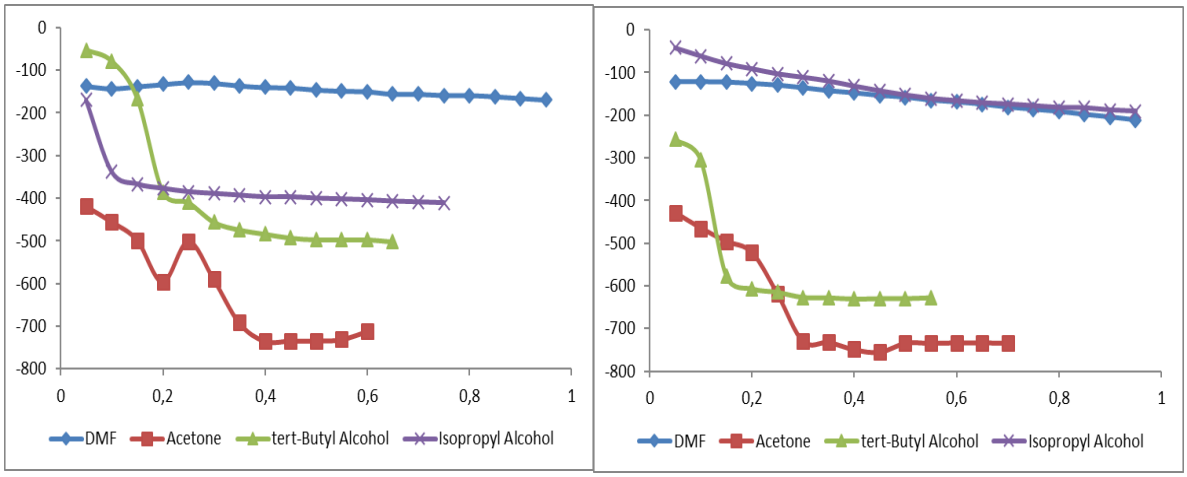


Figure 4. Potentiometric titration curves of 0.001 M solutions of compound 3g and 3h titrated with 0.05 M TBAH in isopropyl alcohol, tert-butyl alcohol, DMF and acetone at 25 °C

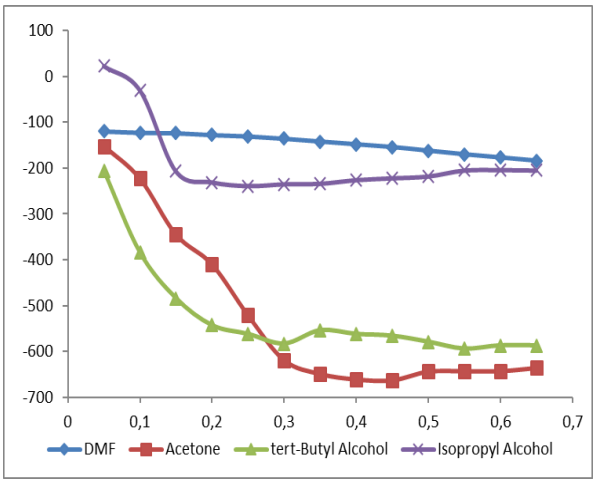


Figure 5. Potentiometric titration curves of 0.001 M solutions of compound 3i titrated with 0.05 M TBAH in isopropyl alcohol, tert-butyl alcohol, DMF and acetone at 25 °C

Table 1. The HNP and the corresponding pK_a values of compounds 3a-i in isopropyl alcohol, *tert*-butyl alcohol, DMF and acetone.

	DMF		**Acetone**		**tert-butyl alcohol**		**isopropyl alcohol**	
	pK_a	HNP	pK_a	HNP	pK_a	HNP	pK_a	HNP
3a	-	-	-	-	8,07	-14	-	-
3b	-	-	13,66	-335	8,95	-68	5,92	111
3c	-	-	11,97	-234	10,21	-150	-	-
3d	-	-	15,83	-459	10,77	-181	-	-
3e	-	-	16,03	-469	11,59	-222	7,23	34
3f	-	-	16,36	-490	10,41	-165	-	-
3g	-	-	16,50	-498	8,95	-66	-	-
3h	-	-	16,43	-496	12,65	-280	-	-
3i	-	-	12,8	-284	-	-	7,90	-4

The data obtained from the potentiometric titrations were interpreted, and the effect of the C-3 substituent in the 4,5-dihydro-1H-1,2,4-triazol-5-one ring as well as solvent effects was studied. As an example for the potentiometric titration curves for 0.001M solutions of compounds **3a-i** titrated with 0.05 M TBAH in isopropyl alcohol, tert-butyl alcohol, DMF and acetone are shown in Fig. **1-5**.

When the dielectric permittivity of solvents is taken into consideration, the acidity order can be given as follows: DMF (e= 36.7)> acetone (e =36) >isopropyl alcohol (e= 19.4)> tert-butyl alcohol (e =12).

3a **:** tert-butyl alcohol
3b **:** isopropyl alcohol > tert-butyl alcohol > acetone
3c **:** tert-butyl alcohol > acetone
3d **:** tert-butyl alcohol > acetone
3e **:** isopropyl alcohol > tert-butyl alcohol > acetone
3f **:** tert-butyl alcohol > acetone
3g **:** tert-butyl alcohol > acetone
3h **:** tert-butyl alcohol > acetone
3i **:** tert-butyl alcohol > acetone

When examined according to functional groups: The effect of the R functional groups on the distance from the acidic proton is very small. When the acidity of the compounds according to each solvent is examined;

***N,N*-dimethylformamid** **:** -
Acetone **:** 3c > 3i > 3b > 3d > 3e > 3f > 3h > 3i
tert-Butyl alcohol **:** 3a > 3b = 3i > 3c > 3f > 3d > 3e > 3h
isopropyl alcohol **:** 3b > 3e > 3i

Conclusion

The synthesis, acidic properties and *in vitro* antioxidant evaluation of new 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives are described. Design and synthesis of novel small molecules can play specifically a protective role in biological systems and in modern medicinal chemistry. Determination of pK_a values of the active constituent of certain pharmaceutical preparations are also important because of the distribution, transport behavior, bonding to receptors

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