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Potentiometric Titrations of New 1,3,5-Tri-{4-[(3-alkyl/aryl-4,5-dihydro-1H-1,2,4-triazol-5-one-4-yl)-azomethin]-phenoxycarbonyl} Benzenes

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Abstract A series of new 1,3,5-tri-{4-[(3-alkyl/aryl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethin]-phenoxycarbonyl} benzenes (**4**) were obtained from the reactions of 3-alkyl/aryl-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**2**) with 1,3,5-tri-(4-formylphenoxycarbonyl)-benzene (**1**) and characterized by IR, ^{1}H-NMR and ^{13}C-NMR spectral data. In addition, to investigate the effects of solvents and molecular structure upon acidity, the new nine compounds **4** were titrated potentiometrically with tetrabutylammonium hydroxide in four non-aqueous solvents (isopropyl alcohol, *tert*-butyl alcohol, *N*,*N*-dimethylformamide and acetone). The half-neutralization potential values and the corresponding pK_a values were determined for all cases.

Keywords: 4,5-Dihydro-1H-1,2,4-triazol-5-one, Schiff base, Syntheses, Acidity, Potentiometric titration, pKa.

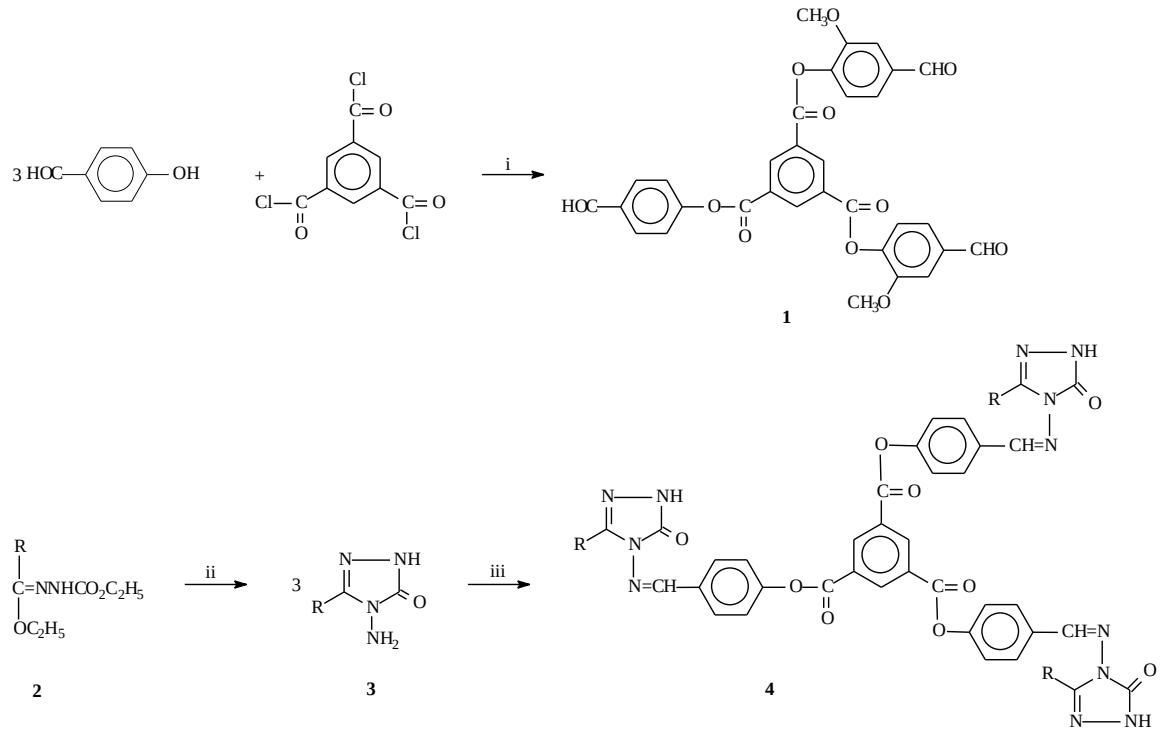
Introduction

Triazoles are heterocyclic compounds that contain three nitrogen atoms. 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 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 [1-4]. 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 [5-7].

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 antitumor, antibacterial, antioxidant and anti-inflammatory properties [1-4, 8, 9].

In this paper, we present the synthesis of nine new 1,3,5-tri-{4-[(3-alkyl/aryl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethin]-phenoxycarbonyl} benzenes. 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 ethoxycarbonyl-hydrazones (**1**) with an aqueous solution of hydrazine hydrate as described in the literature [10, 11]. Compounds **4** were synthesized from the reactions of compounds **2** with 1,3,5-tri-(4-formylphenoxycarbonyl)-benzene (**3**), which were synthesized by the reactions of 4-hydroxybenzaldehyde with 1,3,5-benzenetricarbonyl chloride by using triethylamine (Scheme 1).

In addition, we also examined the potentiometric titrations of the synthesized compounds **4** with tetrabutylammonium hydroxide (TBAH) in four non-aqueous solvents such as isopropyl alcohol, *tert*-butyl alcohol, *N*,*N*-dimethylformamide (DMF) and acetone to determine the half-neutralization potential (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 [1-4, 12].



*Scheme 1: Synthesis route of compounds **1** – **4**: i) Et_3N, AcOEt, 0-5 °C; ii) N_2H_4, H_2O, reflux, 6 h; iii) AcOH, reflux, 1 h; a) R= CH_3, b) R= CH_2CH_3, c) R= $CH_2CH_2CH_3$, d) R= $CH_2C_6H_5$, e) R= $CH_2C_6H_4.CH_3$ (p-), f) R= $CH_2C_6H_4.OCH_3$ (p-), g) R= $CH_2C_6H_4.Cl$ (p-), h) R= $CH_2C_6H_4.Cl$ (m-), i) R= C_6H_5*

Materials and Methods

Chemical reagents used in this paper were bought from Merck AG, Aldrich and Fluka. Melting points were recorded in open glass capillaries using a Stuart SMP30 melting point apparatus and were not corrected. The infrared spectra were recorded on an Alpha-P Bruker FT-IR Spectrometer. ^1H and ^{13}C NMR spectra were determined in deuterated dimethyl sulfoxide with TMS as internal standard using a Bruker Avance III spectrophotometer at 400 MHz and 100 MHz, respectively. In this study, a Jenway 3040 ion analyzer 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, HNP values were determined by plotting the volume (mL) (TBAH)-mV graph.

General procedure for the synthesis of 1,3,5-tri-{4-[(3-alkyl/aryl-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl)-azomethin]-phenoxycarbonyl}-benzenes (4a-h)

4-Hydroxybenzaldehyde (0.03 mol) dissolved in ethyl acetate (15 mL) was treated with 1,3,5-benzenetricarbonyl chloride (0.01 mol), and to this solution was added triethylamine (0.03 mol) slowly with stirring at 0-5 °C. Stirring was continued for 2 h; then the mixture was refluxed for 3 h and filtered. The filtrate was evaporated in vacuo and the crude product was washed with water and recrystallized from ethanol to afford compound **1**, yield 89%, mp 218.5 °C; IR (KBr) (υ, cm^{-1}): 2827 and 2739 (CHO); 1741, 1693 (C=O); 1198 (COO). The corresponding compound **3** (0.003 mol) was dissolved in acetic acid (15 mL) and treated with 1,3,5-tri-(4-formylphenoxycarbonyl)-benzene 1 (0.001 mol). The mixture was refluxed for 1.5 h and then evaporated at 50-55 °C in vacuo. Several recrystallizations of the residue from DMSO-H_2O (1:3) gave pure compounds 1,3,5-tri-{4-[(3-alkyl/aryl-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl)-azomethin]-phenoxycarbonyl}-benzenes (**4)** as colorless crystals.

1,3,5-Tri-{4-[(3-methyl-4,5-dihydro-1H-1,2,4-triazol-5-on-4-yl)-azomethin]-phenoxycarbonyl}-benzene (4a): Yield: 99%, m.p. 280°C. IR (KBr, υ, cm^{-1}): 3175 (NH), 1740, 1694 (C=O), 1596 (C=N), 1197 (COO), 808 (1,4-disubstituted benzenoid ring). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.29 (s, 9H, $3CH_3$), 7.52 (d, 6H, ArH; *J*=8.40 Hz), 7.96 (d, 6H, ArH; *J*=8.80 Hz), 9.03 (s, 3H, ArH), 9.78 (s, 3H, 3N=CH), 11.83 (s, 3H, 3NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.06 ($3CH_3$), [122.53 (6CH), 129.04 (6CH), 129.61 (3CH), 130.36 (3C), 131.78 (3C), 151.22 (3C)] (arom-C), 144.27 (3triazole C_3), 152.48 (3N=CH), 152.50 (3triazole C_5), 162.85 (3COO).

1,3,5-Tri-{4-[(3-ethyl-4,5-dihydro-1H-1,2,4-triazol-5-on-4-yl)-azomethin]-phenoxycarbonyl}-benzene (4b): Yield 95%, m.p. 267°C. IR (KBr, υ, cm^{-1}): 3179 (NH), 1741, 1702 (C=O), 1596 (C=N), 1191 (COO), 809 (1,4-disubstituted benzenoid ring). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.23 (t, 9H, $3CH_2CH_3$; *J*=7.60 Hz), 2.70 (q, 6H, $3CH_2CH_3$; *J*=7.60 Hz), 7.54 (d, 6H, ArH; *J*=8.40 Hz), 7.96 (d, 6H, ArH; *J*=8.80 Hz), 9.04 (s, 3H, ArH), 9.77 (s, 3H, 3N=CH), 11.86 (s, 3H, 3NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.04 ($3CH_2\underline{C}H_3$), 18.50 ($3\underline{C}H_2CH_3$), [122.55 (6CH), 129.01 (6CH), 129.58 (3CH), 130.36 (3C), 131.76 (3C), 151.36 (3C)] (arom-C), 148.05 (3triazole C_3), 152.49 (3N=CH), 152.56 (3triazole C_5), 162.86 (3COO).

1,3,5-Tri-{4-[(3-n-propyl-4,5-dihydro-1H-1,2,4-triazol-5-on-4-yl)-azomethin]-phenoxycarbonyl}-benzene (4c): Yield 98%, m.p. 284°C. IR (KBr, υ, cm^{-1}): 3180 (NH), 1741, 1703 (C=O), 1597 (C=N), 1193 (COO), 809 (1,4-disubstituted benzenoid ring). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.97 (t, 9H, $3CH_2CH_2CH_3$; *J*=7.60 Hz), 1.70 (sext, 6H, $3CH_2\underline{CH_2}CH_3$; *J*=7.60 Hz), 2.66 (t, 6H, $3\underline{CH_2}CH_2CH_3$; *J*=7.60 Hz), 7.55 (d, 6H, ArH; *J*=8.40 Hz), 7.97 (d, 6H, ArH; *J*=8.80 Hz), 9.05 (s, 3H, ArH), 9.79 (s, 3H, 3N=CH), 11.87 (s, 3H, 3NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.47 ($3CH_2CH_2\underline{C}H_3$), 18.91 ($3CH_2\underline{C}H_2CH_3$), 26.69 ($3\underline{C}H_2CH_2CH_3$), [122.60 (6CH), 129.02 (6CH), 129.58 (3CH), 130.39 (3C), 131.83 (3C), 151.30 (3C)] (arom-C), 146.92 (3triazole C_3), 152.51 (3N=CH), 152.61 (3triazole C_5), 162.69 (3COO).

1,3,5-Tri-{4-[(3-benzyl-4,5-dihydro-1H-1,2,4-triazol-5-on-4-yl)-azomethin]-phenoxycarbonyl}-benzene (4d): Yield 95%, m.p. 311°C. IR (KBr, υ, cm^{-1}): 3188 (NH), 1741, 1703 (C=O), 1598 (C=N), 1219 (COO), 815 (1,4-disubstituted benzenoid ring). ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.08 (s, 6H, $3CH_2$), 7.21-7.25 (m, 3H, ArH), 7.30-7.36 (m, 12H, ArH), 7.54 (d, 6H, ArH; *J*=8.80 Hz), 7.94 (d, 6H, ArH; *J*=8.80 Hz), 9.07 (s, 3H, ArH), 9.75 (s, 3H, 3N=CH), 12.00 (s, 3H, 3NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 31.07 ($3CH_2Ph$), [122.60 (6CH), 129.09 (6CH), 129.46 (3CH), 130.21 (3C), 131.78 (3C), 151.22 (3C)] (arom-C), [126.71 (3CH), 128.44 (6CH), 128.79 (6CH), 135.80 (3C)] (Ar-C linked C3), 146.24 (3triazole C_3), 151.22 (3N=CH), 152.54 (3triazole C_5), 162.72 (3COO).

1,3,5-Tri-{4-[(3-p-methylbenzyl-4,5-dihydro-1H-1,2,4-triazol-5-on-4-yl)-azomethin]-phenoxycarbonyl}-benzene (4e): Yield 88%, m.p. 306°C. IR (KBr, υ, cm^{-1}): 3196 (NH), 1749, 1715 (C=O), 1592 (C=N), 1206 (COO), 833, 808 (1,4-disubstituted benzenoid ring). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.25 (s, 9H, $3PhCH_3$), 4.02 (s, 6H, $3CH_2$), 7.12 (d, 6H, ArH; *J*=8.00 Hz), 7.23 (d, 6H, ArH; *J*=8.00 Hz), 7.54 (d, 6H, ArH; *J*=8.40 Hz), 7.94 (d, 6H, ArH; *J*=8.40 Hz), 9.06 (s, 3H, ArH), 9.75 (s, 3H, 3N=CH), 12.00 (s, 3H, 3NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.56 ($3PhCH_3$), 30.67 ($3CH_2Ph$), [122.55 (6CH), 129.05 (6CH), 129.63 (3CH), 130.39 (3C), 131.77 (3C), 151.27 (3C)] (arom-C), [128.65 (6CH), 128.99 (6CH), 132.65 (3CH), 135.78 (3C)] (Ar-C linked C3), 146.38 (3triazole C_3), 152.32 (3N=CH), 152.50 (3triazole C_5), 162.67 (3COO).

1,3,5-Tri-{4-[(3-p-methoxybenzyl-4,5-dihydro-1H-1,2,4-triazol-5-on-4-yl)-azomethin]-phenoxycarbonyl}-benzene (4f): Yield 84%, m.p. 296°C. IR (KBr, υ, cm^{-1}): 3195 (NH), 1748, 1715 (C=O), 1592 (C=N), 1207 (COO), 834, 814 (1,4-disubstituted benzenoid ring). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.70 (s, 9H, $3OCH_3$), 4.00 (s, 6H, $3CH_2$), 6.88 (d, 6H, ArH; *J*=8.00 Hz), 7.26 (d, 6H, ArH; *J*=8.00 Hz), 7.53 (d, 6H, ArH; *J*=8.40 Hz), 7.96 (d, 6H, ArH; *J*=8.00 Hz), 9.07 (s, 3H, ArH), 9.75 (s, 3H, 3N=CH), 11.97 (s, 3H, 3NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 30.21 ($3CH_2Ph$), 55.01 ($3OCH_3$), [122.60 (6CH), 129.09 (6CH), 129.85 (3CH), 130.77 (3C), 131.83 (3C), 151.23

(3C)] (arom-C), [113.89 (6CH), 127.56 (3C), 130.42 (6CH), 158.11 (3C)] (Ar-C linked C3), 146.55 (3triazole C_3), 152.39 (3N=CH), 152.53 (3triazole C_5), 162.71 (3COO).

1,3,5-Tri-{4-[(3-p-chlorobenzyl-4,5-dihydro-1H-1,2,4-triazol-5-on-4-yl)-azomethin]-phenoxycarbonyl}-benzene (4g): Yield 95%, m.p. 297°C. IR (KBr, υ, cm^{-1}): 3194 (NH), 1743, 1706 (C=O), 1593 (C=N), 1193 (COO), 812 (1,4-disubstituted benzenoid ring). ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.09 (s, 6H, $3CH_2$), 7.38 (m, 12H, ArH), 7.55 (d, 6H, ArH; *J*=8.40 Hz), 7.94 (d, 6H, ArH; *J*=8.40 Hz), 9.07 (s, 3H, ArH), 9.75 (s, 3H, 3N=CH), 12.03 (s, 3H, 3NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 30.39 ($3CH_2$Ph), [122.59 (6CH), 129.11 (6CH), 129.66 (3CH), 130.73 (3C), 131.72 (3C), 151.19 (3C)] (arom-C), [128.26 (6CH), 130.61 (6CH), 131.44 (3C), 134.76 (3C)] (Ar-C linked C3), 145.91 (3triazole C_3), 152.49 (3N=CH), 152.60 (3triazole C_5), 162.70 (3COO).

1,3,5-Tri-{4-[(3-m-chlorobenzyl-4,5-dihydro-1H-1,2,4-triazol-5-on-4-yl)-azomethin]-phenoxycarbonyl}-benzene (4h): Yield 85%, m.p. 296°C. IR (KBr, υ, cm^{-1}): 3192 (NH), 1744, 1705 (C=O), 1595 (C=N), 1191 (COO), 841 (1,4-disubstituted benzenoid ring), 812 and 702 (1,3-disubstituted benzenoid ring). ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.11 (s, 6H, $3CH_2$), 7.32-7.51 (m, 12H, ArH), 7.53 (d, 6H, ArH; *J*=8.40 Hz), 7.93 (d, 6H, ArH; *J*=8.40 Hz), 9.05 (s, 3H, ArH), 9.75 (s, 3H, 3N=CH), 12.05 (s, 3H, 3NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 30.69 ($3CH_2$Ph), [122.49 (6CH), 129.05 (6CH), 129.64 (3CH), 130.26 (3C), 131.70 (3C), 151.18 (3C)] (arom-C), [126.65 (3CH), 127.57 (3CH), 128.96 (3CH), 130.21 (3CH), 132.97 (3C), 138.12 (3C)] (Ar-C linked C3), 145.69 (3triazole C_3), 152.51 (3N=CH), 152.57 (3triazole C_5), 162.62 (3COO).

1,3,5-Tri-{4-[(3-phenyl-4,5-dihydro-1H-1,2,4-triazol-5-on-4-yl)-azomethin]-phenoxycarbonyl}-benzene (4i): Yield 93%, m.p. 311°C. IR (KBr, υ, cm^{-1}): 3174 (NH), 1739, 1695 (C=O), 1595 (C=N), 1195 (COO), 835 (1,4-disubstituted benzenoid ring), 762 and 692 (monosubstituted benzenoid ring). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.52-7.57 (m, 15H, ArH), 7.91-7.96 (m, 12H, ArH), 9.04 (s, 3H, ArH), 9.72 (s, 3H, 3N=CH), 12.40 (s, 3H, 3NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ [122.69 (6CH), 129.28 (6CH), 129.92 (3CH), 130.35 (3C), 131.58 (3C), 151.33 (3C)] (arom-C), [126.62 (3CH), 128.24 (6CH), 128.52 (6CH), 130.09 (3C)] (Ar-C linked C3), 144.58 (3triazole C_3), 152.69 (3triazole C_5), 155.43 (3N=CH), 162.64 (3COO).

Results and Discussion

In this study, the structures of nine new 1,3,5-tri-{4-[(3-alkyl/aryl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethin]-phenoxycarbonyl} benzenes (**4a-i**) were characterized with IR, ^{1}H NMR and ^{13}C NMR spectral data. Then, synthesized **4** type compounds were titrated potentiometrically with TBAH in four non-aqueous solvents, the mV values from each titration were plotted against TBAH volumes used (mL), and the potentiometric titration curves were formed for all the cases. From the titration curves, the HNP values were measured, and the corresponding pK_a values were calculated. As an example, the potentiometric titration curves for 0.001 M solutions of 1,3,5-tri-{4-[(3-methyl-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl)-azomethin]-phenoxy-carbonyl}-benzene (**4a**) titrated with 0.05 N TBAH in isopropyl alcohol, *tert*-butyl alcohol, DMF and acetone are presented in Figure 1.

The half-neutralization potential values and the corresponding pK_a values of the compounds **4**, obtained from the potentiometric titrations with 0.05 M TBAH in isopropyl alcohol, *tert*-butyl alcohol, DMF and acetone are presented in Table 1.

The pH 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. Therefore, the pH values at the half-neutralization points were taken as pK_a. Taking into consideration the dielectric permittivity of the solvents, the acidity ranking might be expected to be as follows: *N*,*N*-dimethylformamide (ε=37) > acetone (20,6) > isopropyl alcohol (ε=19.4) > *tert*-butyl alcohol (ε=12.0). As seen in Table 1, in isopropyl alcohol only for compounds **4d** and **4i**, in *tert*-butyl alcohol only for compounds **4a** and **4d**, in acetone only for compound **4i** the HNP values and the corresponding pK_a values were obtained. For compound **4d** and **4i** in DMF the HNP values and the corresponding

pK_a values have not been obtained. In addition, the pK_a values bigger than 20.00 have not been determined due to the fact that this value is outside the range of the pH meter.

As it is well known, the acidity of a compound depends on several factors. The two most important ones are the solvent effect and molecular structure [1-4, 12]. Table 1 and Figure 1 show that the HNP values and corresponding pK_a values obtained from the potentiometric titrations depend on the non-aqueous solvents used and the substituent's at C-3 in 4,5-dihydro-1*H*-1,2,4-triazol-5-one ring.

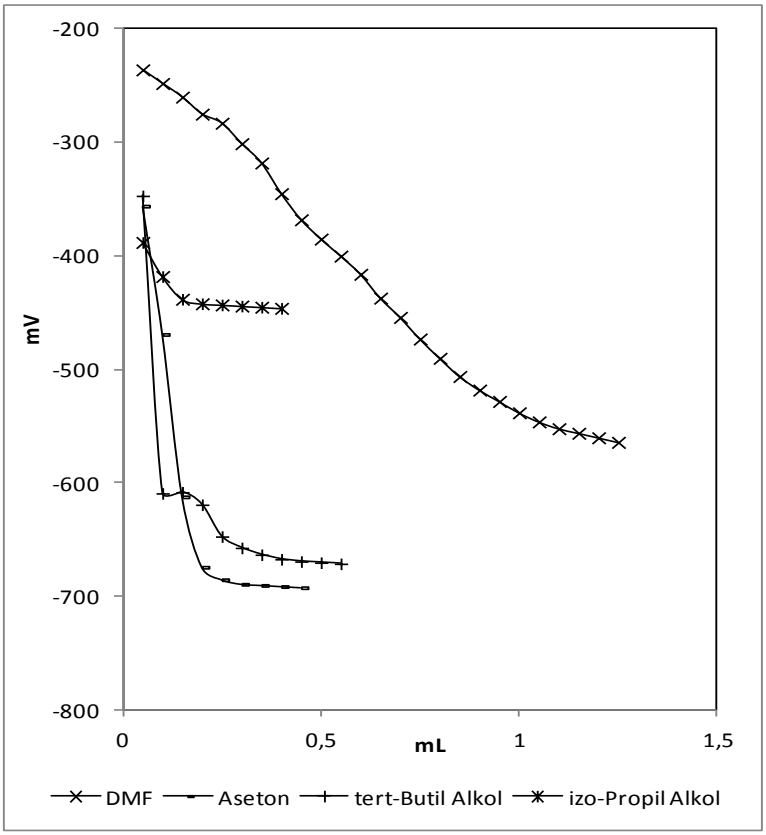


*Figure 1: Potentiometric titration curves of 0.001 M solutions of compound **4a** titrated with 0.05 M TBAH in four non-aqueous solvents at 25 °C*

Table 1: The HNP and the corresponding pK_a values of compounds 4 in isopropyl alcohol, *tert*-butyl alcohol, DMF and acetone

Comp.	Isopropyl alcohol		*tert*-Butyl alcohol		DMF		Acetone	
	HNP (mV)	pK_a	HNP (mV)	pK_a	HNP (mV)	pK_a	HNP (mV)	pK_a
4a	-	-	18,30	-608	12,54	-275	-	-
4b	-	-	-	-	11,89	-252	-	-
4c	-	-	-	-	10,05	-137	-	-
4d	9,44	-103	8,30	-36	-	-	-	-
4e	-	-	-	-	10,36	-156	-	-
4f	-	-	-	-	11,16	-200	-	-
4g	-	-	-	-	13,29	-322	-	-
4h	-	-	-	-	12,90	-305	-	-
4i	8,31	-35	-	-	-	-	15,42	-439

Conclusion

In this study, 1,3,5-tri-{4-[(3-alkyl/aryl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethin]-phenoxycarbonyl} benzenes (**4a-i**) were titrated potentiometrically with tetrabutylammonium hydroxide in four non-aqueous solvents such as isopropyl alcohol, tert-butyl alcohol, N,N-dimethylformamide and acetone, the half- neutralization potential values and the corresponding pK_a values were determined for all cases.

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