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Synthesis and determination of pK_a values of some new di-{2-ethoxy-6-[(3-substitue-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)azomethine]phenyl} terephthalates

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Abstract

In this study, seven novel di-{2-ethoxy-6-[(3-substitue-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)azomethine]phenyl} terephthalates (**4a–g**) were synthesized from the reaction of 3-alkyl(aryl)-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**2a-g**) with di-(2-formyl-6-ethoxyphenyl) terephthalate (**3**). The compounds **4a–g** were characterized using IR, ^{1}H-NMR, ^{13}C-NMR, and UV spectral data. In addition, **4** types of compounds were titrated potentiometrically with tetrabutylammonium hydroxide in four non-aqueous solvents such as isopropyl alcohol, *tert*-butyl alcohol, acetone, *N,N*-dimethylformamide and the half-neutralization potential values and the corresponding pK_a values were determined for all cases.

Keywords: 1,2,4-triazole, Schiff base, acidity, potentiometric titrations, pK_a

1. Introduction

It is known that 4,5-dihydro-1*H*-1,2,4-triazol-5-one ring has 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 TBAH in non-aqueous solvents [1–6]. Determination of pK_a values of the active constituent of definite pharmaceutical preparations is significant because of the distribution, transport behavior, bonding to receptors, and contributions to the metabolic behavior of the active constituent molecules depend on the ionization constant [7–9].

1,2,4-Triazole derivatives are documented to have a broad spectrum of biological activities such as antitumor, antibacterial, antioxidant, and anti-inflammatory properties [2–4,10–13]. Several articles, involving the synthesis of some Schiff bases having 4,5-dihydro-1*H*-1,2,4-triazol-5-one ring have been published up to date [1–4,10–13].

In this paper, we present the synthesis of seven new di-{2-ethoxy-6-[(3-substitue-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)azomethine]phenyl} terephthalates (**4a–g**) were synthesized from the reaction of 3-alkyl(aryl)-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**2a–g**) with di-(2-formyl-6-ethoxyphenyl) terephthalate (**3**), which were synthesized by the reactions of 3-ethoxy-2-hydroxybenzaldehyde with terephthaloyl chloride by using triethylamine (Scheme 1). The starting compound 3-alkyl(aryl)-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones **(2)** was prepared with the reactions of the related ester ethoxycarbonyl-hydrazones **(1)** by using an aqueous solution of hydrazine hydrate according to the literature [14,15]. Additionally, the potentiometric titrations of the synthesized compounds **4** were also carried out 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.

2. Experimental

2.1. Chemistry

Chemical reagents used were provided by Merck AG, Aldrich, and Fluka. Melting points were determined in open glass capillaries using a Stuart SMP30 melting point apparatus and were not corrected. The infrared spectra were taken on an Alpha-P Bruker FT-IR

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Spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were determined in deuterated dimethyl sulfoxide with TMS as an internal standard using a Varian Mercury spectrophotometer at 400 MHz and 100 MHz, respectively.

2.1.1. General procedure for the synthesis of di-{2-ethoxy-6-[(3-substitue-4,5-dihydro-1H-1,2,4-triazol-5-one-4-yl)azomethine]phenyl} terephthalates (4a–g):

3-Ethoxy-2-hydroxybenzaldehyde (0.01 mol) dissolved in ethyl acetate (15 mL) was treated with terephthaloyl chloride (0.01 mol), and to this solution was added triethylamine (0.02 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 **3**, yield 81%, mp 45 °C; IR (KBr) (υ, cm^{-1}): 2845 and 2760 (CHO); 1730, 1695 (C=O); 1255 (COO). UV (ethanol) λ_{max} (ε, L mol^{-1} cm^{-1}): 3602 (8045), 254 (25940), 242 (27370) nm. The corresponding compound **2** (0.01 mol) was dissolved in acetic acid (15 mL) and treated with di-(2-formyl-6-ethoxyphenyl) terephthalate (**3**) (0.01 mol). The mixture was evaporated at 50–55 °C in vacuo after it refluxed for 1.5 h. Several recrystallizations of the residue from DMSO-H_2O (1:3) gave pure compounds **4** as colorless crystals.

2.1.2. Di-{2-ethoxy-6-[(3-methyl-4,5-dihydro-1H-1,2,4-triazol-5-one-4-yl)azomethine]phenyl} terephthalates (4a):

Yield: 99%, m.p. 209 °C. IR (KBr, υ, cm^{-1}): 3181 (NH), 1737, 1709 (C=O), 1602 (C=N), 1246 (COO), 820 (1,4-disubstituted benzenoid ring). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.21 (t, 6H, 2CH$_2$<u>CH$_3$</u>; *J* = 6.8 Hz), 2.11 (s, 6H, 2CH$_3$), 4.12 (q, 4H, 2<u>CH$_2$</u>CH$_3$; *J* = 6.8 Hz), 7.36-7.45 (m, 4H, ArH), 7.58 (d, 2H, ArH; *J*=8.0 Hz), 8.38 (s, 4H, ArH), 9.91 (s, 2H, 2N=CH), 11.80 (s, 2H, 2NH). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 11.35 (2CH$_3$), 14.90 (2CH$_2$<u>C</u>H$_3$), 64.92 (2<u>C</u>H$_2$CH$_3$), [116.94 (2C), 118.92 (2C), 127.52 (2C), 127.86 (2C), 130.98 (4C), 133.39 (2C), 139.50 (2C), 151.03 (2C)] (arom-C), 144.06 (2Triazole C3), 149.06 (2N=CH), 151.63 (2Triazole C5), 163.59 (2COO). UV (ethanol) λ_{max} (ε, L mol^{-1} cm^{-1}): 294 (25450), 242 (37990), 234 (38730) nm.

2.1.3. Di-{2-ethoxy-6-[(3-ethyl-4,5-dihydro-1H-1,2,4-triazol-5-one-4-yl)azomethine]phenyl} terephthalates (4b):

Yield: 97%, m.p. 244 °C. IR (KBr, υ, cm^{-1}): 3174 (NH), 1739, 1702 (C=O), 1595 (C=N), 1276 (COO), 820 (1,4-disubstituted benzenoid ring). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.07 (t, 6H, 2CH$_2$<u>CH$_3$</u>; *J* = 7.2 Hz), 1.21 (m, 6H, 2OCH$_2$<u>CH$_3$</u>), 2.45 (t, 4H, 2<u>CH$_2$</u>CH$_3$; *J* = 7.2 Hz), 4.10 (m, 4H, 2O<u>CH$_2$</u>CH$_3$), 7.35-7.42 (m, 4H, ArH), 7.54-7.55 (m, 2H, ArH), 8.39 (s, 4H, ArH), 9.91 (s, 2H, 2N=CH), 11.81 (s, 2H, 2NH). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 9.77 (2CH$_2$<u>C</u>H$_3$), 14.37 (2OCH$_2$<u>C</u>H$_3$), 18.28 (2<u>C</u>H$_2$CH$_3$), 64.41 (2O<u>C</u>H$_2$CH$_3$), [116.39 (2C), 118.81 (2C), 127.01 (2C), 127.35 (2C), 130.46 (4C), 132.93 (2C), 138.86 (2C), 150.58 (2C)] (arom-C), 147.81 (2Triazole C3), 148.80 (2N=CH), 151.27 (2Triazole C5), 163.06 (2COO). UV (ethanol) λ_{max} (ε, L mol^{-1} cm^{-1}): 296 (25285), 234 (39840), 222 (36820) nm.

2.1.4. Di-{2-ethoxy-6-[3-n-propyl-4,5-dihydro-1H-1,2,4-triazol-5-one-4-yl)azomethine]phenyl} terephthalates (4c):

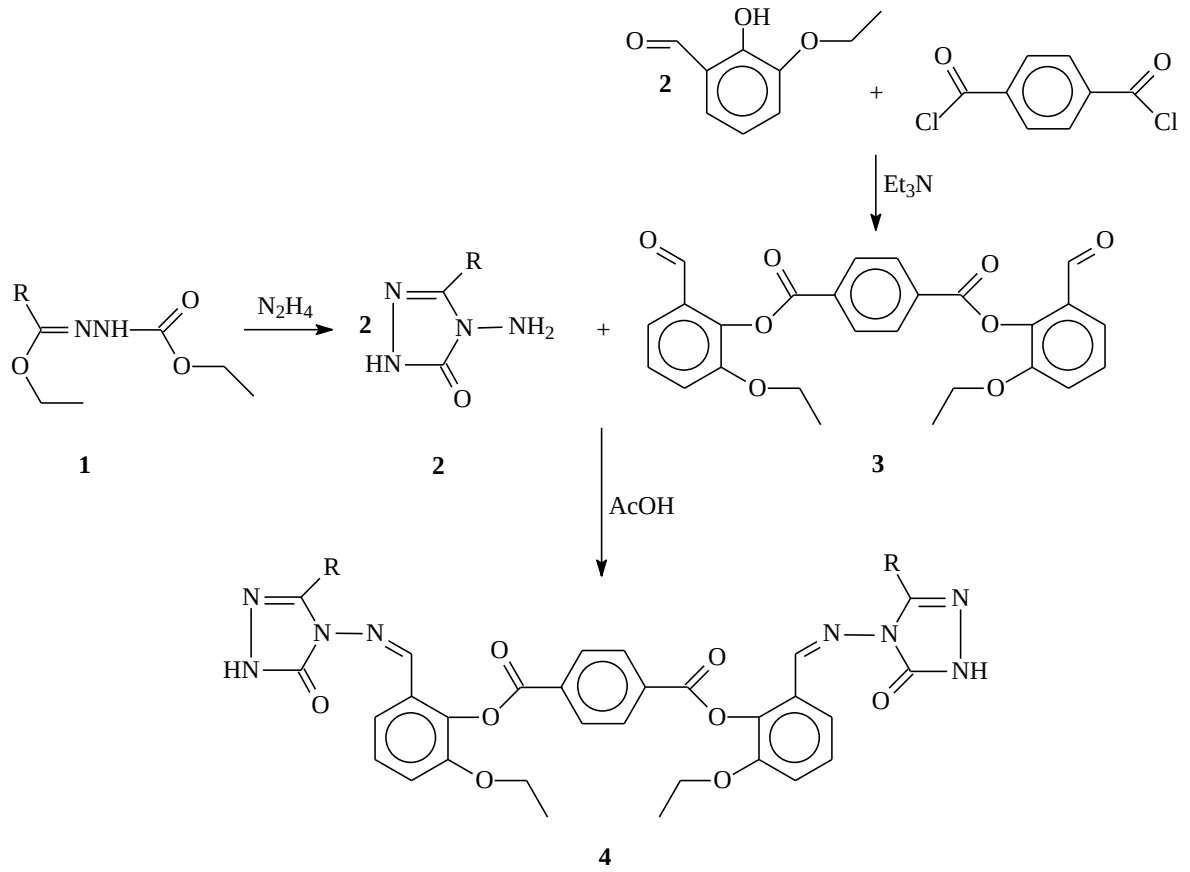
Yield: 95%, m.p. 249 °C. IR (KBr, υ, cm^{-1}): 3172 (NH), 1735, 1703 (C=O), 1595 (C=N), 1270 (COO), 820 (1,4-disubstituted benzenoid ring). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 0.83 (m, 6H, 2CH$_2$CH$_2$<u>CH$_3$</u>), 1.20 (m, 6H, 2OCH$_2$<u>CH$_3$</u>), 1.56 (m, 4H, 2CH$_2$<u>CH$_2$</u>CH$_3$), 2.42 (m, 4H, 2<u>CH$_2$</u>CH$_2$CH$_3$), 4.09 (m, 4H, 2O<u>CH$_2$</u>CH$_3$), 7.34-7.40 (m, 4H, ArH), 7.53 (m, 2H, ArH), 8.39 (s, 4H, ArH), 9.92 (s, 2H, 2N=CH), 11.83 (s, 2H, 2NH). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 13.27 (2CH$_2$CH$_2$<u>C</u>H$_3$), 14.34 (2OCH$_2$<u>C</u>H$_3$), 18.57 (2CH$_2$<u>C</u>H$_2$CH$_3$), 26.45 (2<u>C</u>H$_2$CH$_2$CH$_3$), 64.39 (2O<u>C</u>H$_2$CH$_3$), [116.30 (2C), 118.76 (2C), 127.04 (2C), 127.29 (2C), 130.45 (4C), 132.97 (2C), 138.89 (2C), 150.58 (2C)] (arom-C), 146.67 (2Triazole C3), 148.85 (2N=CH), 151.23 (2Triazole C5), 163.06 (2COO). UV (ethanol) λ_{max} (ε, L mol^{-1} cm^{-1}): 294 (20640), 230 (38820), 218 (34985) nm.

2.1.5. Di-{2-ethoxy-6-[(3-benzyl-4,5-dihydro-1H-1,2,4-triazol-5-one-4-yl)azomethine]phenyl} terephthalates (4d):

Yield: 99%, m.p. 268 °C. IR (KBr, υ, cm^{-1}): 3179 (NH), 1738, 1713 (C=O), 1604 (C=N), 1273 (COO), 815 (1,4-disubstituted benzenoid ring), 778 and 715 (monosubstituted benzenoid ring). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.20 (t, 6H, 2CH$_2$<u>CH$_3$</u>; *J* = 6.8 Hz), 3.95 (s, 4H, 2CH$_2$Ph), 4.10 (q, 4H, 2<u>CH$_2$</u>CH$_3$; *J* = 6.8 Hz), 7.21-7.43 (m, 14H, ArH), 7.55 (d, 2H, ArH; *J*=7.6 Hz), 8.35 (s, 4H, ArH), 9.92 (s, 2H, 2N=CH), 11.96 (s, 2H, 2NH). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 14.37 (2CH$_2$<u>C</u>H$_3$), 30.83 (2CH$_2$Ph), 64.41 (2<u>C</u>H$_2$CH$_3$), [116.41 (2C), 117.76 (2C), 126.67 (2C), 127.04 (2C), 127.35 (2C), 128.38 (4C), 128.71 (4C), 130.43 (4C), 132.83 (2C), 135.57 (2C), 139.27 (2C), 150.48 (2C)] (arom-C), 146.07 (2Triazole C3), 148.08 (2N=CH), 151.14 (2Triazole C5), 163.10 (2COO). UV (ethanol) λ_{max} (ε, L mol^{-1} cm^{-1}): 280 (17880), 230 (45040), 218 (40390) nm. *Anal.* Calculated for $C_{44}H_{38}N_8O_8$: C, 65.50; H, 4.75; N, 13.99. Found: C, 64.77; H, 4.44; N, 13.32.

2.1.6. Di-{2-ethoxy-6-[(3-p-methylbenzyl-4,5-dihydro-1H-1,2,4-triazol-5-one-4-yl)azomethine]-phenyl} terephthalates (4e):

Yield: 98%, m.p. 244 °C. IR (KBr, υ, cm^{-1}): 3191 (NH), 1740, 1708 (C=O), 1595 (C=N), 1273 (COO), 820 (1,4-disubstituted benzenoid ring). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.20 (m, 6H, 2CH$_2$<u>CH$_3$</u>), 2.23 (s, 6H,



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 = $CH_2C_6H_4Cl$ (*p*-), g) R = C_6H_5

Scheme 1. Synthetic route of di-{2-ethoxy-6-[(3-substitue-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)azomethine]phenyl} terephthalates

2PhCH_3), 3.89 (s, 4H, 2CH_2Ph), 4.10 (m, 4H, 2CH_2CH_3), 7.10-7.14 (m, 8H, ArH), 7.36-7.42 (m, 4H, ArH), 7.56 (d, 2H, ArH; *J*=7.6 Hz), 8.34 (s, 4H, ArH), 9.91 (s, 2H, 2N=CH), 11.94 (s, 2H, 2NH). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 14.36 (2CH_2CH_3), 20.55 (2PhCH_3), 30.43 (2CH_2Ph), 64.41 (2CH_2CH_3), [116.40 (2C), 117.76 (2C), 127.05 (2C), 127.35 (2C), 128.56 (4C), 128.95 (4C), 130.42 (4C), 132.45 (2C), 132.83 (2C), 135.74 (2C), 139.27 (2C), 150.48 (2C)] (arom-C), 146.21 (2Triazole C3), 148.00 (2N=CH), 150.48 (2Triazole C5), 163.11 (2COO). UV (ethanol) λ_{max} (ε, L mol^{-1} cm^{-1}): 294 (12600), 254 (19510), 224 (35400) nm.

2.1.7. Di-{2-ethoxy-6-[(3-p-chlorobenzyl-4,5-dihydro-1H-1,2,4-triazol-5-one-4-yl)azomethine]-phenyl} terephthalates (4f):

Yield: 97%, m.p. 208 °C. IR (KBr, *υ*, cm^{-1}): 3194 (NH), 1750, 1704 (C=O), 1597 (C=N), 1274 (COO), 822 (1,4-disubstituted benzenoid ring). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.20 (m, 6H, 2CH_2CH_3), 3.95 (s, 4H, 2CH_2Ph), 4.10 (m, 4H, 2CH_2CH_3), 7.29-7.35 (m, 12H, ArH), 7.53 (m, 2H, ArH), 8.34 (s, 4H, ArH), 9.91 (s, 2H, 2N=CH), 11.96 (s, 2H, 2NH). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 14.35 (2CH_2CH_3), 30.17 (2CH_2Ph), 64.41 (2CH_2CH_3), [116.40 (2C), 117.78 (2C), 127.00 (2C), 127.33 (2C), 128.30 (4C), 130.41 (4C), 130.61 (4C), 131.44 (2C), 132.84 (2C), 134.48 (2C), 139.28 (2C), 150.48 (2C)] (arom-C), 145.72 (2Triazole C3), 148.15 (2N=CH), 151.14 (2Triazole C5), 163.10 (2COO). UV (ethanol) λ_{max} (ε, L mol^{-1} cm^{-1}): 294 (19730), 230 (41080), 224 (40500) nm.

2.1.8. Di-{2-ethoxy-6-[(3-phenyl-4,5-dihydro-1H-1,2,4-triazol-5-one-4-yl)azomethine]phenyl} terephthalates (4g):

Yield: 95%, m.p. 236 °C. IR (KBr, *υ*, cm^{-1}): 3176 (NH), 1739, 1697 (C=O), 1605 (C=N), 1254 (COO), 820 (1,4-disubstituted benzenoid ring), 772 and 691 (monosubstituted benzenoid ring). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.22 (m, 6H, 2CH_2CH_3), 4.12-4.13 (m, 4H, 2CH_2CH_3), 7.40-7.43 (m, 10H, ArH), 7.49 (m, 6H, ArH), 8.22 (s, 4H, ArH), 9.85 (s, 2H, 2N=CH), 12.34 (s, 2H, 2NH). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 14.40 (2CH_2CH_3), 64.46 (2CH_2CH_3), [116.68 (2C), 118.37 (2C), 126.40 (2C), 126.90 (2C), 127.44 (2C), 127.89 (4C), 128.42 (4C), 130.06 (2C), 130.23 (4C), 132.71 (2C), 139.29 (2C), 151.25 (2C)] (arom-C), 144.60 (2Triazole C3), 150.60 (2N=CH), 151.45 (2Triazole C5), 163.11 (2COO). UV (ethanol) λ_{max} (ε, L mol^{-1} cm^{-1}): 238 (43820), 226 (41780), 220 (40570) nm. *Anal.* Calculated for $C_{42}H_{34}N_8O_8$: C, 64.78; H, 4.40; N, 14.39. Found: C, 64.37; H, 4.55; N, 14.03.

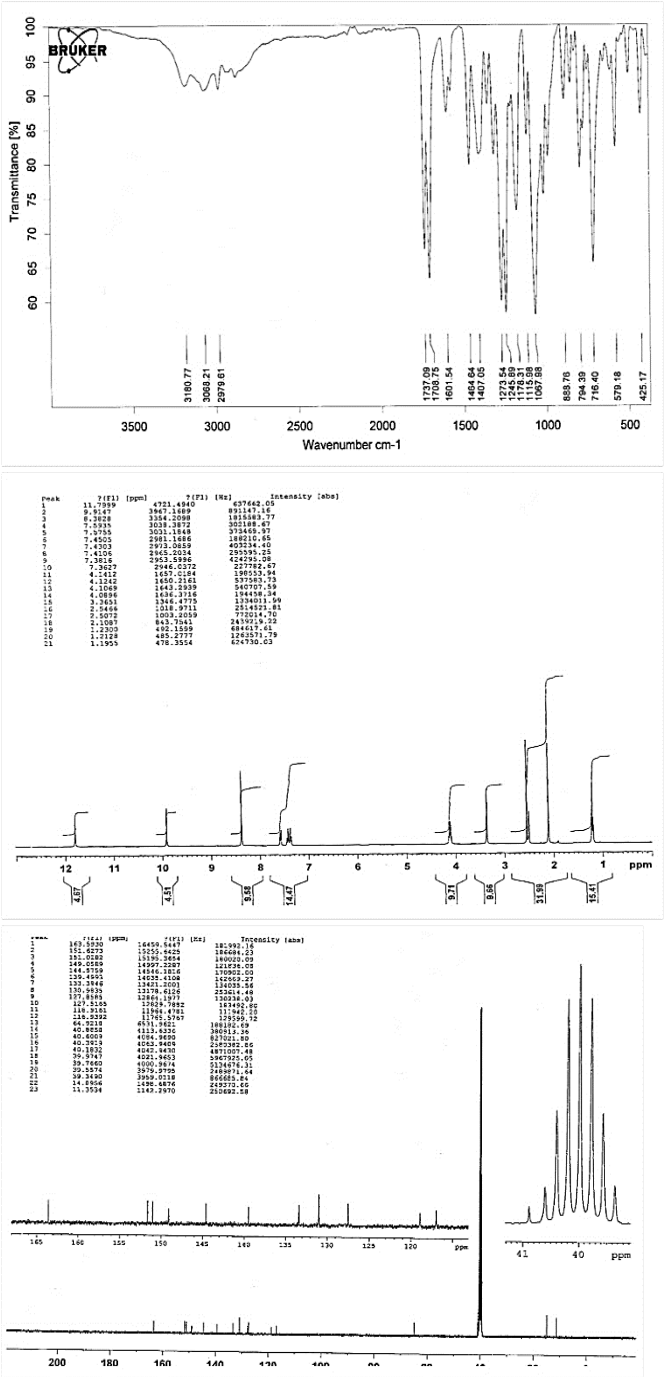


Figure 1. IR, ^{1}H-NMR, and ^{13}C-NMR spectra of compound **4a**

2.2. Determination of Acidity Constants

A Jenway 3040-model ion analyzer was employed for potentiometric titrations. An Ingold pH electrode was used because of the advantage. The 0.001 M solution was separately prepared in each non-aqueous solvent for each compound titrated. The 0.05 M solution of TBAH in isopropyl alcohol, which is widely used in the titration of acids, was employed as the titrant. The mV values obtained in pH meter were recorded. Then, the HNP values were calculated by drawing the mL (TBAH)-mV graphic. The acidity constants and HNP values of compounds were calculated using the half-neutralization method [16–20].

3. Results and discussion

In this study, seven new di-{2-ethoxy-6-[(3-substitue-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)azomethine]phenyl} terephthalates (**4a–g**) were synthesized and characterized with IR, ^{1}H-NMR, ^{13}C-NMR and UV spectral data.

Table 1. The HNP and the corresponding p*K*a values of compounds 4 in isopropyl alcohol, tert-butyl alcohol, DMF, and acetone at 25 °C

Compound.	DMF		Acetone		tert-Butyl alcohol		Isopropyl alcohol	
no	HNP (mV)	p*K*a	HNP (mV)	p*K*a	HNP (mV)	p*K*a	HNP (mV)	p*K*a
4a	-332	15,37	-573	-	-202	12,15	-	-
4b	-320	13,46	-175	10,92	-241	11,48	-	-
4c	-291	13,74	-259	11,8	-189	9,8	-	-
4d	-345	15,16	-296	13,37	+171	5,88	-318	13,57
4e	-345	15.08	57	5,49	-	-	-406	16,52
4f	-334	14,89	-245	12,16	-	-	-346	15,09
4g	-368	15,50	-209	11,52	-	-	-11	7,42

As an example, the IR, ^{1}H-NMR, and ^{13}C-NMR spectra of Compound **4a** are presented in Fig. **1**.

Then, synthesized **4** type compounds were titrated potentiometrically with TBAH in four non-aqueous solvents (isopropyl alcohol, *tert*-butyl alcohol, *N*,*N*-dimethylformamide (DMF), acetone), and the mV values from each titration were plotted against TBAH volumes used (mL), and the potentiometric titration curves were formed for all the cases. The HNP values were measured from the titration curves and the corresponding p*K*a values were calculated.

The half-neutralization potential values and the corresponding p*K*a values of the compounds **4**, determined from the potentiometric titrations with 0.05 M TBAH in isopropyl alcohol, *tert*-butyl alcohol, DMF, and acetone are given in Table 1. The pH of weak acids can be calculated using the following equation: pH = p*K*a + log[A$^-$] / [HA] where pH = p*K*a when [A$^-$] is equal to [HA] at the half-neutralization points. Therefore, the pH values at the half-neutralization points were taken as p*K*a. According to 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).

In amphiprotic solvents, the data obtained for compound 4d do not conform to the theoretical ordering. HNP values and corresponding p*K*a values could not be obtained for compounds **4a**, **4b**, and **4c** in isopropyl alcohol and for compounds **4e**, **4f**, and **4g** in *tert*-butyl alcohol. So, the acidity strength of the compounds between solvents could not be compared.

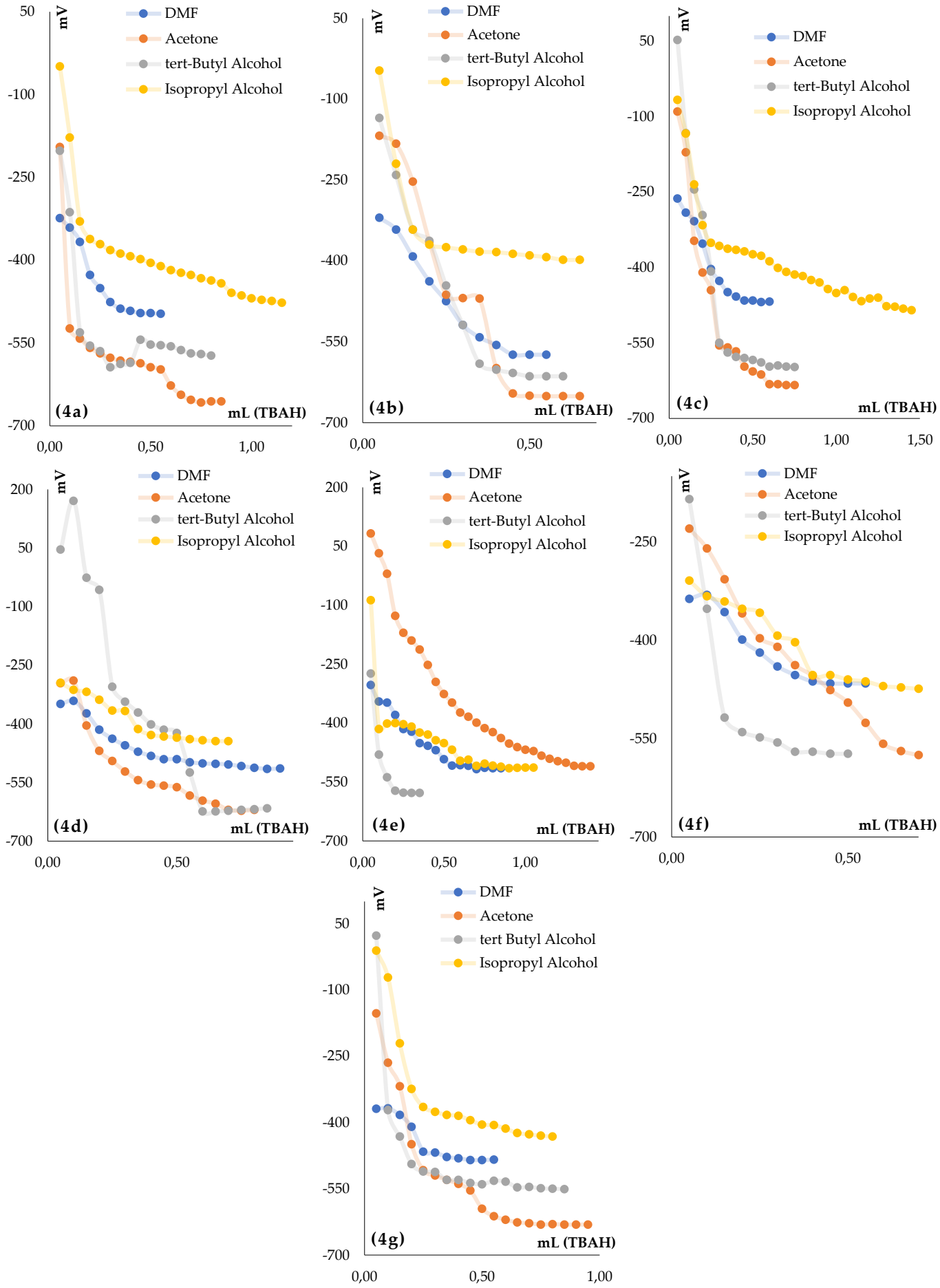


Figure 2. Potentiometric titration curves of 0.001 M solutions of compounds **4a-4g** titrated with 0.05 M TBAH in isopropyl alcohol, *tert*-butyl alcohol, acetone, and *N*,*N*-dimethylformamide at 25 °C.

Dipolar aprotic solvents give SH_2^+ ions but not S^- ions.

$$HA + S \leftrightarrow \cdots HA \leftrightarrow SH^+A^- \leftrightarrow SH^+ + A^- \quad (1)$$

(a) *(b)* *(c)*

(HA: Acid (Molecular) and S: Solvent) When the equilibrium (1) is examined, the equilibrium of (a) and (b) occur more in protophilic (DMF) solvents than in protophobic (Acetone) solvents. The equilibrium of (c) is very low in protophilic solvents, but in trace amounts in protophobic solvents. The SH^+ in the protophobic solvent is a much stronger acid. This explains why compounds **4b–4g** are more acidic in acetone. Compound **4a** conforms to the theoretical sequence.

Considering the autoprotolysis constant, it was seen that the Hnp values of the compounds and the potential measured ranges of the solvents in tert-butyl alcohol (1200), isopropyl alcohol (1000), DMF (1300), and acetone (1550) medium are weakly acidic compounds **4d** and **4e** were leveled in DMF medium. It has been differentiated in other solvents.

The half-neutralization potential (HNP) values and the corresponding pK_a values of compounds **4a-4g**, founded from the potentiometric titrations with 0.05 M TBAH in isopropyl alcohol, *tert*-butyl alcohol, acetone, and DMF, are given in Table 1.

The potentiometric titration curves for 0.001 M solutions of compouds **4a–4g** titrated with 0.05 M TBAH in isopropyl alcohol, tert-butyl alcohol, *N*,*N*-dimethylformamide, and acetone are given in Fig. 2.

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