Synthesis of Unsymmetrical 3,5-disubstituted 1,2,4-triazole Derivatives with Their pKa Values

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*Acylhydrazones (**2a-b**) were synthesized by the condensation of iminoester hydrochlorides (**1a-b**) with benzhydrazide. The treatment of acylhydrazones with hydrazine hydrate afforded 4-amino-4H-1,2,4-triazoles (**3a-b**). 4-Benzylidenamino-4H-1,2,4-triazole derivatives (**4a-f**) to be synthesized by treatment of compounds (**3a-b**) with benzaldehydes. Compounds (**4a-f**) were reduced with $NaBH_4$ to afford the corresponding 4-benzylamino-4H-1,2,4-triazole derivatives (**4a-f**). All synthesized compounds were titrated potentiometrically with tetrabutylammonium hydroxide in four non-aqueous solvents such as isopropyl alcohol, tert-butyl alcohol, acetonitrile and N,N-dimethylformamide and the half-neutralization potential values and the corresponding pKa values were determined for all cases.*

Keywords: Acylhydrazones, 4-Amino-4H-1,2,4-triazoles, 4-Benzylidenamino-4H-1,2,4-triazoles, 4-Benzylamino-4H-1,2,4-triazoles, pKa, Half-neutralization potential

Heterocyclic moieties can be found in a large number of compounds which display biological activity. The biological activity of the compounds is mainly dependent on their molecular structures [1]. 1,2,4-triazoles are very interesting compounds due to their important applications in the pharmaceutical, biological and analytical field [2, 3]. In addition, it was reported that compounds having triazole rings, such as vorozole, letrozole and anastrozole appeared to be very effective aromatase inhibitors, which in turn prevented breast cancer [4,5]. Moreover, 1,2,4-triazoles are a new class of antimicrobial agents. For instance, fluconazole and itraconazole are used as antimicrobial drugs in medicine [6,7]. On the other hand, Schiff bases of 4-amino-1,2,4-triazoles have been synthesized for various reasons, one of which is their biological activities [8-12]. Some of the other reasons are the investigation of their ability to make a coordination complex with transition metal cations and the improvement of their properties for analytical applications [13-16].

Acidity measurements of organic compounds have a long history dating back to the end of the 19th century, when the first pKa was measured. Since then a vast body of data on acidities in various solvents has been collected [17-20]. The measurements have mostly been limited to polar solvents, however, with H_2O being by far the most exploited medium, followed by alcohols and dipolar aprotic solvents.

The acidity of a compound in a given medium is influenced both by the electronic effects of the substituents and the solvent effects of the medium. Moreover, it is sometimes extremely difficult to assess how much each effect contributes to the acidity. Small differences in acidity between similar molecules are also extremely difficult to interpret and one must be very careful in deciding which structural effect has the main influence on acidity [21].

A number of studies have been reported on the protonation constants of these derivatives in different media [22-25], however, very little information on the protonation constants of these derivatives in organic mixtures has been published so far [26-28].

In the present paper, the potentiometric titrations of synthesized compounds **2-5** with tetrabutylammonium hydroxide (TBAH) in four non-aqueous solvents (isopropyl alcohol, *tert*-butyl alcohol, acetonitrile and *N,N*-dimethylformamide) are examined to determine the corresponding half-neutralization potentials (HNP) and pKa values. The potentiometric titrations data are in good agreement with the effect of the substituent in these compounds.

Experimental part

Synthesis – General Procedures

Melting points were determined on a *Büchi* oil-heated melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra (δ, ppm) were recorded on a *Varian-Mercury 200* MHz spectrometer using tetramethylsilane as the internal reference. IR spectra (υ, cm^{-1}) were obtained with a *Perkin-Elmer 1600* FTIR spectrometer in KBr pellets. Elemental analyses were performed on an *ECS 4010* elemental combustion system CHNS-O. A mono- mode CEM- Discover microwave was used to carry out microwave reactions in 30 mL microwave process vials with temperature control by infrared detection temperature sensor. All reactions were monitored by TLC using precoated aluminum sheets (silica gel 60 F 2.54 0.2 mm thickness).

General method for the synthesis of compounds **2a-b**

To the solution of corresponding iminoester hydrochloride (1) in absolute ethanol (0.01 mol) was added the solution of benzhydrazide (0.01 mol) in absolute EtOH and the mixture was stirred at 0-5° for 6 h. The reaction mixture was poured into a beaker containing 40 mL of cold water and 10 g of ice. The precipitate formed was washed with 50 mL of ice-water and then dried. This crude product was recrystallized from benzene-petroleum ether (1:2) to afford compounds **2**.

Ethyl p-methoxyphenylacetate benzoylhydrazone **(2a)** Yield 75%, m.p. 110-111°, IR (KBr) cm^{-1}: 3191 (ν_{NH}), 1675 ($\nu_{C=O}$), 1611, 1626 ($\nu_{C=N}$); ^{1} H-NMR (DMSO-d_6) δ ppm 1.15

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(t, 3H, CH_3), 3.71 (s, 3H, OCH_3), 4.12 (q, 2H, OCH_2), 4.27 (s, 2H, CH_2), Ar-H: [6.89 (d, 2H), 7.17 (d, 2H), 7.48 (m, 3H), 7.92 (m, 2H)], 10.35 (NH); ^{13}C- NMR (DMSO-d_6) δ ppm 14.71 (CH_3), 30.67 (CH_2), 55.73 (OCH_3), 60.87 (OCH_2), Ar-C: [114.84 (2C), 126.92, 127.07 (2C), 130.11(2C), 130.49, 131.02, 132.57 (2C), 158.52], 155.56 (C=N), 166.60 (C=O); Anal. Calcd. for ($C_{18}H_{20}N_2O_3$): C: 69.21, H: 6.45, N: 8.97. Found: C: 68.98, H: 6.73; N: 9.03.

Ethyl p-nitrophenylacetate benzoylhydrazone **(2b)** Yield 68%, m.p. 125-126°, IR (KBr) cm^{-1}: 3112 (ν_{NH}), 1686 ($\nu_{C=O}$), 1606, 1571($\nu_{C=N}$); ^{1}H-NMR (DMSO-d_6) δ ppm 1.17 (t, 3H, CH_3), 4.02 (q, 2H, OCH_2), 4.56 (s,2 H, CH_2), Ar-H: [7.49-7.79 (m, 4H), 7.83-7.96 (m, 2H), 8.15-8.24 (m, 3H)], 9.95 (NH); ^{13}C- NMR (DMSO-d_6) δ ppm 13.71 (CH_3), 31.79 (CH_2), 61.28 (OCH_2), Ar-C: [124.49 (2C), 127.14 (2C), 129.59 (2C), 130.99, 131.17 (2C), 131.56, 142.95, 147.45], 154.51 (C=N), 165.40 (C=O); Anal. Calcd. for ($C_{17}H_{17}N_3O_4$): C: 62.38, H: 5.23, N: 12.84. Found: C: 62.85, H: 4.98; N: 12.67.

General method for the synthesis of compounds **3a-b**

A solution of the corresponding compound **2** (0.01 mol) in ^{n}PrOH was refluxed with hydrazine hydrate (0.025 mol) for 24 h. After it was cooled to room temperature, a white solid appeared. This crude product was filtered off, washed with benzene 3 times, and recrystallized from an appropriate solvent to afford the desired compound.

4-Amino-3-(p-methoxybenzyl)-5-phenyl-4H-1,2,4-triazole (3a) Yield 88%, m.p. 160-161°, IR (KBr) cm^{-1}: 3315-3248 (ν_{NH2}), 1611, 1583 ($\nu_{C=N}$); ^{1}H-NMR (DMSO-d_6) δ ppm 3.72 (s, 3H, OCH_3), 4.10 (s, 2H, CH_2), 6.10 (s, 2H, NH_2), Ar-H: [6.88 (d, 2H), 7.25 (d, 2H), 7.48 (m, 3H), 8.02 (m, 2H)]; ^{13}C- NMR (DMSO-d_6) δ ppm 29.45 (CH_2), 55.73 (OCH_3), Ar-C: [114.52 (2C), 128.14, 128.60 (2C), 129.12 (2C), 129.36, 130.04, 130.63 (2C), 158.65], 153.23 (triazole C3), 154.45 (triazole C5); Anal. Calcd. for ($C_{16}H_{16}N_4O$): C: 68.55, H: 5.75, N: 19.99. Found: C: 68.73, H: 5.38; N: 20.17.

4-Amino-3-(p-nitrobenzyl)-5-phenyl-4H-1,2,4-triazole (3b) Yield 75%, m.p. 175-176°, IR (KBr) cm^{-1}: 3329-3252 (ν_{NH2}), 1651, 1580 ($\nu_{C=N}$); ^{1}H-NMR (DMSO-d_6) δ ppm 4.22 (s, 2H, CH_2), 6.15 (s, 2H, NH_2), Ar-H: [7.52-7.60 (m, 4H), 8.14-8.16 (m, 2H), 8.20-8.22 (m, 3H)]; ^{13}C- NMR (DMSO-d_6) δ ppm 30.19 (CH_2), Ar-C: [124.24 (2C), 127.92, 128.63 (2C), 129.16 (2C), 130.20, 130.93 (2C), 145.52, 147.03], 155.17 (triazol C3), 153.69 (triazol C5); Anal. Calcd. for ($C_{15}H_{13}N_5O_2$): C: 61.01, H: 4.44, N: 23.72. Found: C: 61.27, H: 4.38; N: 23.47.

General method for the synthesis of compounds **4a-f**

The corresponding aldehyde (0.005 mol) was added to solution of compound **2** (0.005 mol) in 0.5 mL of glacial acetic acid and were taken in a closed vessel. The mixture was iradiated in microwave at 125°C for 7 min at 300W maximum power. After cooling, the mixture was poured into a beaker containing 100 mL of ice-water. The precipitate formed was filtered. After drying in vacuo, the product was recrystallized from EtOH-water (1:1) to afford the desired compound.

3-(p-Methoxybenzyl)-5-phenyl-4-(2,6-difluorobenzylidenamino)-4H-1,2,4-triazole **(4a)** Yield 72%, m.p. 123-124°, IR (KBr) cm^{-1}: 1624, 1583 ($\nu_{C=N}$); ^{1}H-NMR (DMSO-d_6) δ ppm 3.67 (s, 3H, OCH_3), 4.22 (s, 2H, CH_2), Ar-H: [6.82-6.85 (m, 3H), 7.15-7.31 (m, 4H), 7.47-7.48 (m, 2H), 7.75-7.79 (m, 3H)], 8.69 and 8.59 (s, 1H, NH, *E* and *Z* isomers); ^{13}C- NMR (DMSO-d_6) δ ppm 30.38 (CH_2), 55.70 (OCH_3), Ar-C: [110.01, 113.26 (2C), 114.66 (2C), 127.32, 128.39, 128.80 (2C), 129.44 (2C), 130.27 (2C), 130.49, 136.12, 158.74, 164.28 (2C)], 150.22 (triazole C-3), 151.10 (triazole C-5), 159.53 and 159.15 (s, 1H, -N=CH-, *E* and *Z* isomers); Anal. Calcd. for ($C_{23}H_{18}F_2N_4O$): C: 68.31, H: 4.49, N: 13.85. Found: C: 68.00, H: 4.38; N: 14.07.

3-(p-Methoxybenzyl)-5-phenyl-4-(2,6-dichlorobenzylidenamino)-4H-1,2,4-triazole **(4b)** Yield 80%, m.p. 163-164°, IR (KBr) cm^{-1}: 1626, 1581 ($\nu_{C=N}$); ^{1}H-NMR (DMSO-d_6) δ ppm 3.70 (s, 3H, OCH_3), 4.26 (s, 2H, CH_2), Ar-H: [6.85-6.90 (m, 2H), 7.08-7.21 (m, 4H), 7.49-7.70 (m, 6H)], 8.83 and 8.78 (s, 1H, NH, *E* and *Z* isomers); ^{13}C- NMR (DMSO-d_6) δ ppm 30.22 (CH_2), 55.73 (OCH_3), Ar-C: [114.65 (2C), 127.16, 128.46, 128.75, 129.36 (2C), 129.56 (2C), 130.20 (2C), 130.29, 130.40 (2C), 130.61, 134.13, 135.09], 152.47 (triazole C-3), 153.97 (triazole C-5), 164.70 and 161.90 (s, 1H, -N=CH-, *E* and *Z* isomers); Anal. Calcd. for ($C_{23}H_{18}Cl_2N_4O$): C: 63.17, H: 4.15, N: 12.81. Found: C: 62.87, H: 4.42; N: 13.17.

3-(p-Methoxybenzyl)-5-phenyl-4-(2-chloro-6-fluorobenzylidenamino)-4H-1,2,4-triazole **(4c)** Yield 67%, m.p. 120-121°, IR (KBr) cm^{-1}: 1610, 1583 ($\nu_{C=N}$); ^{1}H-NMR (DMSO-d_6) δ ppm 3.67 (s, 3H, OCH_3), 4.24 (s, 2H, CH_2), Ar-H: [7.60-7.78 (m, 5H), 7.16 (d, 2H), 6.83 (d, 2H), 7.78-7.92 (m, 3H)], 8.73 and 8.68 (s, 1H, NH, *E* and *Z* isomers); ^{13}C-NMR (DMSO-d_6) δ ppm 30.45 (CH_2), 55.67 (OCH_3), Ar-C: [114.66 (2C), 117.65 (2C), 118.14, 126.51, 127.36, 128.25, 128.79 (2C), 129.45 (2C), 130.09, 130.42 (2C), 139.47, 139.67, 158.81, 164.68], 150.52 (triazole C-3), 151.11 (triazole C-5), 161.05 and 159.52 (s, 1H, -N=CH-, *E* and *Z* isomers); Anal. Calcd. for ($C_{23}H_{18}ClFN_4O$): C: 65.64, H: 4.31, N: 13.31. Found: C: 65.27, H: 4.53; N: 12.93.

3-(p-Nitrobenzyl)-5-phenyl-4-(2,6-difluoro benzylidenamino)-4H-1,2,4-triazole **(4d)** Yield 72%, m.p. 147-148°, IR (KBr) cm^{-1}: 1624, 1602 ($\nu_{C=N}$); ^{1}H-NMR (DMSO-d_6) δ ppm 4.46 (s, 2H, CH_2), Ar-H: [7.22-7.31 (m, 3H), 7.48-7.54 (m, 5H), 7.66-7.78 (m, 2H), 8.15-8.19 (m, 2H)]; 8.71 and 8.67 (s, 1H, NH, *E* and *Z* isomers); ^{13}C- NMR (DMSO-d_6) δ ppm 30.94 (CH_2), Ar-C: [113.22 (2C), 113.64, 124.26 (2C), 127.16, 128.81 (2C), 129.53 (2C), 130.61, 130.83 (2C), 136.27, 144.36, 147.11, 164.27 (2C)], 149.72 (triazole C-3), 150.03 (triazole C-5), 161.36 and 158.47 (s, 1H, -N=CH-, *E* and *Z* isomers); Anal. Calcd. for ($C_{22}H_{15}F_2N_5O_2$): C: 63.01, H: 3.61, N: 16.70. Found: C: 62.73, H: 3.53; N: 16.87.

3-(p-Nitrobenzyl)-5-phenyl-4-(2,6-dichloro benzylidenamino)-4H-1,2,4-triazole **(4e)** Yield 76%, m.p. 174-175°, IR (KBr) cm^{-1}: 1637, 1577 ($\nu_{C=N}$); ^{1}H-NMR (DMSO-d_6) δ ppm 4.50 (s, 2H, CH_2), Ar-H: [7.52-7.71 (m, 10H), 8.19 (bs, 2H)], 8.98 and 8.87 (s, 1H, NH, *E* and *Z* isomers); ^{13}C- NMR (DMSO-d_6) δ ppm 31.01 (CH_2), Ar-C: [124.34 (2C), 127.00, 129.40 (2C), 129.66 (2C), 130.13, 130.76 (2C), 130.89 (2C), 133.98, 134.18, 135.09 (2C), 144.74, 147.14]; 156.48 (triazole C-3), 158.75 (triazole C-5), 165.26 and 163.32 (s, 1H, -N=CH-, *E* and *Z* isomers); Anal. Calcd. for ($C_{22}H_{15}Cl_2N_5O_2$): C: 58.42, H: 3.34, N: 15.48. Found: C: 58.053, H: 3.72; N: 15.94.

3-(p-Nitrobenzyl)-5-phenyl-4-(2-chloro-6-fluorobenzylidenamino)-4H-1,2,4-triazole **(4f)** Yield 68%, m.p. 140-141°, IR (KBr) cm^{-1}: 1607, 1567 ($\nu_{C=N}$); ^{1}H-NMR (DMSO-d_6) δ ppm 4.41 (s, 2H, CH_2), Ar-H: [7.48-7.74 (m, 6H), 7.84-7.97 (m, 2H), 8.14-8.17 (m, 4H)], 8.75 and 8.72 (s, 1H, NH, *E* and *Z* isomers); ^{13}C- NMR (DMSO-d_6) δ ppm 30.92 (CH_2), Ar-C: [117.69, 119.37, 124.49 (2C), 126.45, 127.15, 128.81 (2C), 129.56 (2C), 129.96, 130.93, 139.61, 139.84, 144.65, 147.09, 164.96], 149.98 (triazole C-3), 150.45 (triazole C-5), 161.95 and 159.40 (s, 1H, -N=CH-, *E* and *Z* isomers); Anal. Calcd. for ($C_{22}H_{15}ClFN_5O_2$): C: 60.63, H: 3.47, N: 16.07. Found: C: 60.27, H: 3.63; N: 15.87.

General method for the synthesis of solutions of **5a-f**

The methanolic solutions of corresponding compounds **4a-f** (0.001 mol) were refluxed with $NaBH_4$ (0.001 mol)

for 30 min. After the solvent was evaporated at 35-40° under reduced pressure, a solid was obtained. This crude product was treated with water, filtered off, and washed with water twice. The obtained white solid was recrystallized from EtOH-water (1:1) to afford the desired compound.

3-(p-Methoxybenzyl)-5-phenyl-4-(2,6-difluorobenzylamino)-4H-1,2,4-triazole **(5a)** Yield 92%, m.p. 156-157°, IR (KBr) cm^{-1}: 3194 (ν_{NH}), 1628, 1596 ($\nu_{C=N}$); ^{1}H-NMR (DMSO-d_6) δ ppm 3.70 (s, 3H, OCH_3), 3.82 (bs, 2H, -NH-CH_2-), 3.90 (s, 2H, CH_2), 7.87 (bs, 1H, NH), Ar-H: [6.84-6.95 (m, 5H), 7.14-7.20 (m, 4H), 7.33-7.45 (m, 3H)]; ^{13}C-NMR (DMSO-d_6) δ ppm 29.19 (CH_2), 42.39 (-NH-CH_2-), 55.71 (OCH_3), Ar-C: [111.85, 112.08 (2C), 114.46 (2C), 127.81, 128.03 (2C), 128.91, 129.12 (2C), 130.20, 130.45 (2C), 131.53, 158.66, 164.45 (2C)], 152.61 (triazole C-3), 155.78 (triazole C-5); Anal. Calcd. for ($C_{23}H_{20}F_2N_4O$): C: 67.97, H: 4.96, N: 13.78. Found: C: 67.63, H: 5.05; N: 13.62.

3-(p-Methoxybenzyl)-5-phenyl-4-(2,6-dichlorobenzylamino)-4H-1,2,4-triazole **(5b)** Yield 95%, m.p. 144-145°, IR (KBr) cm^{-1}: 3176 (ν_{NH}), 1612, 1582($\nu_{C=N}$); ^{1}H-NMR (DMSO-d_6) δ ppm 3.71 (bs, 5H, OCH_3+ -NH-CH_2), 3.82 (bs, 2H, -NH-CH_2-), 4.08 (s, 2H, CH_2), 7.97 (bs, 1H, NH), Ar-H: [6.82-6.90 (m, 4H), 7.16-7.24 (m,5H), 7.27-7.50 (m, 3H)]; ^{13}C- NMR (DMSO-d_6) δ ppm 29.47 (CH_2), 41.93 (-NH-CH_2-), 55.73 (OCH_3), Ar-C: [114.46, 114.52 (2C), 124.15, 127.87, 128.14, 128.60 (2C), 129.12 (2C), 129.26, 129.36, 130.54, 130.63 (2C), 134.27, 158.65, 164.28], 154.46 (triazole C-3), 152.27 (triazole C-5); Anal. Calcd. for ($C_{23}H_{20}Cl_2N_4O$): C: 62.88, H: 4.59, N: 12.75. Found: C: 62.44, H: 4.78; N: 13.07.

3-(p-Methoxybenzyl)-5-phenyl-4-(2-chloro-6-fluorobenzylamino)-4H-1,2,4-triazole **(5c)** Yield 87%, m.p. 163-164°, IR (KBr) cm^{-1}: 3184 (ν_{NH}),1610, 1583 ($\nu_{C=N}$); ^{1}H-NMR (DMSO-d_6) δ ppm 3.66 (s, 3H, OCH_3), 3.82 (bs, 2H, -NH-CH_2), 4.02 (s, 2H, CH_2), 7.78 (t, 1H, NH), Ar-H: [6.77-6.84 (m, 3H), 7.07-7.24 (m, 5H), 7.29-7.41 (m, 4H)]; ^{13}C-NMR (DMSO-d_6) δ ppm 28.35 (CH_2), 49.32 (-NH-CH_2-), 54.88 (OCH_3), Ar-C: [113.59 (2C), 126.96, 127.40 (2C), 128.09, 128.17 (2C), 128.23 (2C), 129.24, 129.78 (2C), 131.53, 135.61 (2C), 135.83, 157.82], 152.02 (triazole C-3), 154.97 (triazole C-5), Anal. Calcd. for ($C_{23}H_{20}ClFN_4O$): C: 65.33, H: 4.77, N: 13.25. Found: C: 62.95, H: 4.44; N: 13.11.

3-(p-Nitrobenzyl)-5-phenyl-4-(2,6-difluorobenzylamino)-4H-1,2,4-triazole **(5d)** Yield 93%, m.p. 148-149°, IR (KBr) cm^{-1}: 3203 (ν_{NH}), 1627, 1596 ($\nu_{C=N}$); ^{1}H-NMR (DMSO-d_6) äδppm 3.92 (s, 2H, CH_2), 4.15 (d, 2H, -NH-CH_2-), 7.88 (t, 1H, NH), Ar-H: [6.70-6.94 (m, 3H), 7.07-7.27 (m, 3H), 7.36-7.47 (m, 4H), 8.16 (d, 2H)]; ^{13}C- NMR (DMSO-d_6) δ ppm 32.09 (CH_2), 44.48 (-NH-CH_2-), Ar-C: [113.96, 114.67 (2C), 126.38 (2C), 129.80 (2C), 129.47, 131.37 (2C), 133.01 (2C), 133.74, 134.00, 147.22, 149.25, 161.64 (2C)], 154.87 (triazole C-3), 156.45 (triazole C-5); Anal. Calcd. for ($C_{22}H_{17}F_2N_5O_2$): C: 62.70, H: 4.07, N: 16.62. Found: C: 63.00, H:4.33; N: 16.93.

3-(p-Nitrobenzyl)-5-phenyl-4-(2,6-dichlorobenzylamino)-4H-1,2,4-triazole **(5e)** Yield 95%, m.p. 180-181°, IR (KBr) cm^{-1}: 3195 (ν_{NH}), 1606, 1563 ($\nu_{C=N}$); ^{1}H-NMR (DMSO-d_6) δ ppm4.12 (s, 2H, CH_2), 4.28 (bs, 2H, -NH-CH_2-), 7.85 (bs, 1H, NH), Ar-H: [7.18-7.22 (m, 3H), 7.42-7.53 (m, 6H), 8.15-8.20 (m, 3H)]; ^{13}C- NMR (DMSO-d_6) δ ppm 29.88 (CH_2), 50.11 (-NH-CH_2-), Ar-C: [124.18 (2C), 127.62, 128.29 (2C), 129.10 (2C), 129.47, 130.25 (2C), 130.86 (2C), 131.31, 132.22, 136.41 (2C), 145.15, 147.01], 152.65 (triazole C-3), 154.03 (triazole C-5); Anal. Calcd. for ($C_{22}H_{17}Cl_2N_5O_2$): C: 58.16, H: 3.77, N: 15.42. Found: C: 57.80, H: 3.99; N: 15.27.

3-(p-Nitrobenzyl)-5-phenyl-4-(2-chloro-6-fluorobenzylamino)-4H-1,2,4-triazole **(5f)** Yield 85%, m.p. 174-175°, IR (KBr) cm^{-1}: 3252 (ν_{NH}),1605, 1583 ($\nu_{C=N}$); ^{1}H-NMR (DMSO-d_6) δ ppm4.22 (s, 2H, CH_2), 4.32 (d, 2H, -NH-CH_2-), 7.97 (bs, 1H, NH), Ar-H: [7.49-7.62 (m, 8H), 8.16-8.20 (m, 4H)]; ^{13}C- NMR (DMSO-d_6) δ ppm 30.26 (CH_2), 44.42 (-NH-CH_2-), Ar-C: [115.16, 123.87, 124.21 (2C), 127.17, 127.93, 128.62 (2C), 129.16 (2C), 130.18, 130.93 (2C), 130.99, 135.75, 145.55, 147.01, 164.32], 153.66 (triazole C-3), 155.15 (triazole C-5); Anal. Calcd. for ($C_{22}H_{17}ClFN_5O_2$): C: 60.35, H: 3.91, N: 15.99. Found: C: 59.98, H: 3.59; N: 15.40.

HNP and pK_a Value Determination

In this study, Orion Model 720A pH ion meter, fitted with a combined *p*H electrode (Ingold) was used for potentiometric titrations. An Ingold *p*H electrode was preferred because of the advantage. For each compound that would be titrated, the 0.001 M solution was separately prepared in each non-aqueous solvent. The 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, that were obtained in pH-meter, were recorded. Finally, the HNP values were determined by drawing the mL (TBAH)-mV graphic (fig. 2). The HNP values and the corresponding pK_a values of all compounds, obtained from the potentiometric titrations with 0.05 M TBAH in isopropyl alcohol, *tert*-butyl alcohol, acetonitrile and *N,N*-dimethylformamide.

The pH of the weak acids are given by the following equation:

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

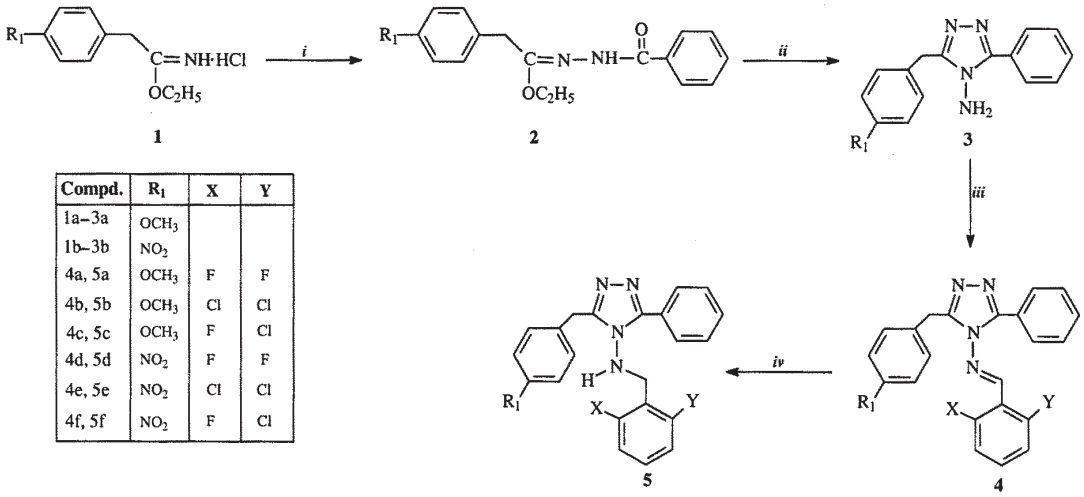
*p*H = pK_a occurs when [A^-] is equal to [HA] at the half-neutralization point. Therefore, the pH values can be regarded as pK_a at the half-neutralization points.

Results and discussions

Compounds **2a-b** were obtained from the reaction of **1a-b** with benzhydrazide, and compounds **3a-b** were obtained by treatment of **2a-b** with $NH_2NH_2.H_2O$. The reaction was carried out in refluxing isopropyl alcohol at for 24 h and the desired 4-amino-1,2,4-triazoles (**3a-b**) were obtained. The latter were converted to their Schiff bases (**4a-f**) by refluxing with various aromatic aldehydes (2,6-difluorobenzaldehyde, 2,6-dichloro benzaldehyde, 2-fluoro-6-chloro benzaldehyde) in AcOH. Compounds **4a-f** were converted to their reduced derivatives **(5a-f)** by treatment with $NaBH_4$ in MeOH. Since $NaBH_4$ is selective reducing agent, reduction took place only at the azomethyne bond and the 1,2,4-triazole ring remained unchanged (scheme1) [29].

It was reported that Schiff bases can be obtained as their *E* and *Z* isomers [8, 30-32]. According to literatüre data, the signals of the azomethine protons and C-atoms of the *E* isomers of triazole derivatives of type H appear at higher field with respect to the corresponding signals of the *Z* isomers [8, 33-34]. On the basis of these findings, we assigned the *E* configuration to the major isomers in the mixtures. The percentage of each isomers was calculated using the integral values of each singlet pair. The chemical shift values of *E* and *Z* isomers belong to protons and carbons of –N=CH- in the ^{1}H NMR and ^{13}C NMR spectra of compounds **4a-f** are given in table 1.

The IR spectrum of compound **2** showed absorption bands around at 3180 cm^{-1} and 1675cm^{-1} due to NH and C=O, respectively, and its ^{1}H-NMR spectrum in (D_6) DMSO revealed four signals at 1.17, 4.12, 4.56 and 10.35 assigned to CH_3, CH_2, OCH_2 and NH protons, compound **2**



Compd.	R_1	X	Y
1a–3a	OCH_3		
1b–3b	NO_2		
4a, 5a	OCH_3	F	F
4b, 5b	OCH_3	Cl	Cl
4c, 5c	OCH_3	F	Cl
4d, 5d	NO_2	F	F
4e, 5e	NO_2	Cl	Cl
4f, 5f	NO_2	F	Cl

Scheme 1. Reagents and conditions: *i.* benzhydrazide, EtOH, 0-5°C, 6 h, *ii.* $NH_2NH_2.H_2O$, PrOH, reflux, 24 h, *iii.* Corresponding aldehyde, AcOH, reflux, 6 h *iv*. MeOH, reflux, 1 h, $NaBH_4$

Compounds	Isomers	- δ(ppm) - NMR	-N=CH-	Percentage of (%)
4a	*E*	H	8.69	78.35
		C	159.53	
	Z	H	8.59	21.65
		C	159.15	
4b	*E*	H	8.83	71.43
		C	164.70	
	Z	H	8.78	28.67
		C	161.90	
4c	*E*	H	8.73	82.83
		C	161.05	
	Z	H	8.68	17.27
		C	159.52	
4d	*E*	H	8.71	70.90
		C	161.36	
	Z	H	8.67	29.10
		C	158.47	
4e	*E*	H	8.98	73.26
		C	165.26	
	Z	H	8.87	26.84
		C	163.32	
4f	*E*	H	8.75	67.52
		C	161.95	
	Z	H	8.72	32.58
		C	159.40	

Table 1
^{1}H- AND ^{13}C-NMR CHEMICAL SHIFTS AND PERCENTAGE OF *E* AND *Z* ISOMERS

respectively. Compound **3** showed two peaks in the region of 3315-3248 cm^{-1} for **3a** due to asymmetric and symmetric vibration of the primary amino group. In the IR spectra of compounds **4** the characteristic C=N absorption bands appeared at 1637-1607, 1602-1567 cm^{-1}. The ^{1}H-NMR signals for the -N=CH group were observed at δ 8.80-8.70 ppm. The ^{13}C-NMR signals for the –N=CH- group were recorded at δ 160 ppm. Reduced compounds **5** showed IR absorption bands around 3190 cm^{-1} (νNH). The ^{1}H-NMR signals for the -NH-CH_2- group of these compounds were observed as a doublet or strong singlet at around δ 3.82 ppm and the proton signals of –NH-CH_2- groups were recorded as a triplet or strong singlet about δ ~ 7.80 ppm. The NH-CH_2- carbon signals of compounds **5** were recorded at δ 49 ppm in the ^{13}C-NMR.

The mV values were plotted versus TBAH volumes (mL) added, and thus potentiometric titration curve was formed for all the cases. From these curves, the HNP values were measured, and the corresponding p*K*a values were calculated. As an example, the potentiometric titration curves for 0.001 M compound 1 solutions titrated with 0.05 M TBAH in isopropyl alcohol, *tert*-butyl alcohol, *N,N*-dimethylformamide and acetonitrile are given in figure 1-5. As it is clearly seen in figure 1 and 2, typical S-shaped titration curves were obtained. When the dielectric permittivity of solvents is taken into consideration, the acidic arrangement can be expected as follows: *N,N*-dimethylformamide (ε = 36.7)> acetonitrile (ε = 36) > isopropyl alcohol (ε = 19.4) > *tert*-butyl alcohol (ε = 12). The half-neutralization potentials (HNP) and the corresponding *pK*a values of all compounds in isopropyl alcohol, *N,N*-dimethylformamide, *tert*-butyl alcohol and acetonitrile are given in table 2.

As seen in table 2, the acidic arrangement for compounds **2a-b**: isopropyl alcohol > *tert*-butyl alcohol > *N,N*-dimethylformamide > acetonitrile, compound **2b** shows high (14.95±0.06) acidic properties in isopropyl alcohol, compound **2a** shows low (16.37±0.04) acidic properties in acetonitrile. The acidic arrangement for compounds **3a-b**: isopropyl alcohol > *tert*-butyl alcohol > *N,N*-dimethylformamide > acetonitrile, compound **3b** shows high (14.44±0.07) acidic properties in isopropyl alcohol, compound **2a** shows low (16.27±0.06) acidic properties in acetonitrile. The acidic arrangement for compounds **4a-f**: **4a**, **4b**, **4d** and **4e**; isopropyl alcohol > *tert*-butyl alcohol > acetonitrile > *N,N*-dimethylformamide, **4c** and **4f**; isopropyl alcohol > *tert*-butyl alcohol > *N,N*-dimethylformamide > acetonitrile, compound **4d** shows high (15.43±0.09) acidic properties in isopropyl alcohol, compound **4c** shows low (17.02±0.04) acidic properties in acetonitrile. The acidic arrangement for compounds

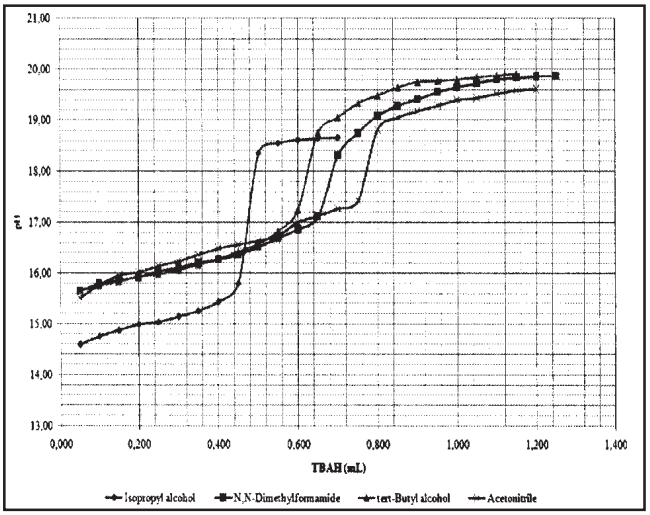


Fig. 1. pH – mL Potentiometric titration curves of 0.001 M solutions of compound **2a** titrated with 0.05 M TBAH in acetonitrile at 25°C.

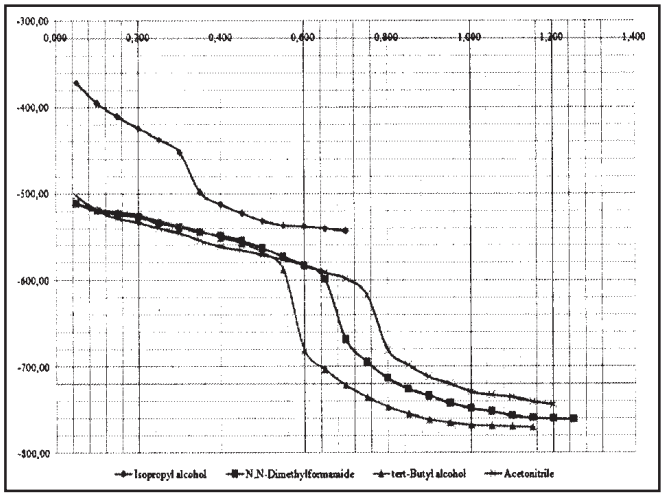


Fig. 2. mV – mL Potentiometric titration curves of 0.001 M solutions of compound **2a** titrated with 0.05 M TBAH in acetonitrile at 25°C

Table 2

THE HALF-NEUTRALIZATION POTENTIALS (HNP) AND THE CORRESPONDING *pK*a VALUES OF ALL COMPOUNDS IN ISOPROPYL ALCOHOL, *N,N*-DIMETHYLFORMAMIDE, *TERT*-BUTYL ALCOHOL AND ACETONITRILE

Compound	Isopropyl alcohol		*N,N*-Dimethylformamide		*tert*-Butyl alcohol		Acetonitrile	
	*pK*a	HNP (mV)	*pK*a	HNP (mV)	*pK*a	HNP (mV)	*pK*a	HNP (mV)
2a	15.03±0.04	-415.8±2.6	16.12±0.05	-536.6±5.1	16.09±0.08	-527.6±4.7	16.37±0.04	-550.4±2.6
2b	14.95±0.06	-403.5±3.3	15.99±0.04	-523.8±6.4	15.97±0.07	-514.3±5.8	16.29±0.05	-541.1±4.7
3a	14.53±0.07	-358.2±2.5	16.13±0.04	-535.2±3.1	15.58±0.09	-488.7±6.3	16.27±0.06	-541.5±4.2
3b	14.44±0.07	-348.7±3.6	16.01±0.05	-524.6±5.3	15.47±0.08	-476.4±5.7	16.15±0.06	-530.9±6.1
4a	15.54±0.05	-486.4±5.3	16.81±0.06	-580.3±6.5	16.53±0.03	-551.7±3.9	16.76±0.07	-575.2±5.7
4b	15.61±0.07	-490.7±6.7	16.87±0.05	-583.8±8.3	16.65±0.04	-567.3±4.7	16.82±0.06	-578.5±6.6
4c	16.01±0.08	-527.6±7.2	16.93±0.05	-592.1±6.3	16.64±0.07	-570.7±4.6	17.02±0.04	-607.9±5.4
4d	15.43±0.09	-475.2±6.8	16.70±0.05	-571.5±7.4	16.41±0.07	-540.6±5.9	16.65±0.08	-564.3±5.6
4e	15.52±0.06	-481.7±7.4	16.76±0.05	-572.6±7.8	16.53±0.09	-558.2±5.6	16.71±0.04	-569.4±4.7
4f	15.90±0.05	-515.8±6.5	16.81±0.07	-580.4±8.1	16.52±0.08	-559.6±6.6	16.91±0.05	-596.3±7.3
5a	15.58±0.07	-489.6±4.2	16.85±0.05	-584.6±5.6	16.57±0.08	-556.4±6.8	16.79±0.07	-579.1±6.3
5b	15.65±0.06	-495.2±5.4	16.91±0.09	-588.5±6.5	16.69±0.05	-571.4±5.9	16.86±0.04	-582.9±7.3
5c	16.06±0.07	-532.5±6.1	16.98±0.04	-597.6±5.8	16.68±0.09	-575.1±6.7	17.06±0.05	-611.5±7.3
5d	15.51±0.06	-481.2±5.9	16.78±0.04	-578.2±3.8	16.51±0.06	-548.9±5.5	16.72±0.05	-571.4±7.1
5e	15.56±0.04	-486.3±7.2	16.81±0.07	-580.2±4.9	16.61±0.06	-563.5±5.4	16.79±0.07	-576.8±6.2
5f	15.97±0.06	-523.4±7.5	16.87±0.05	-588.3±4.8	16.59±0.05	-566.6±7.3	16.95±0.08	-601.8±6.7

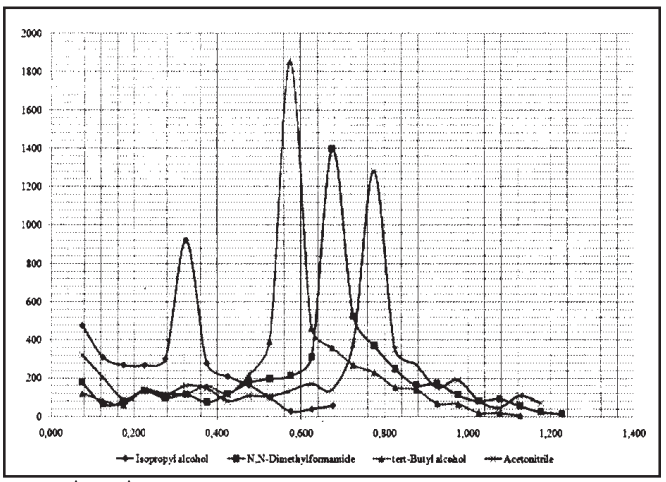


Fig. 3.ΔE - ΔV Potentiometric titration curves of 0.001 M solutions of compound **2a** titrated with 0.05 M TBAH in acetonitrile at 25°C

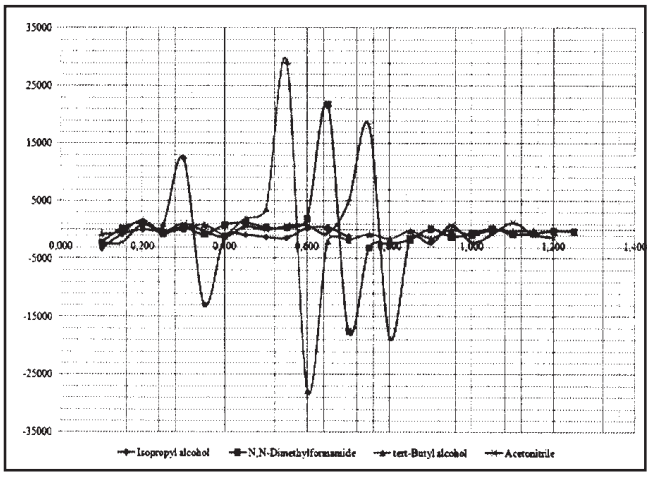


Fig. 4. ΔE^2 - ΔV^2 Potentiometric titration curves of 0.001 M solutions of compound **2a** titrated with 0.05 M TBAH in acetonitrile at 25°C.

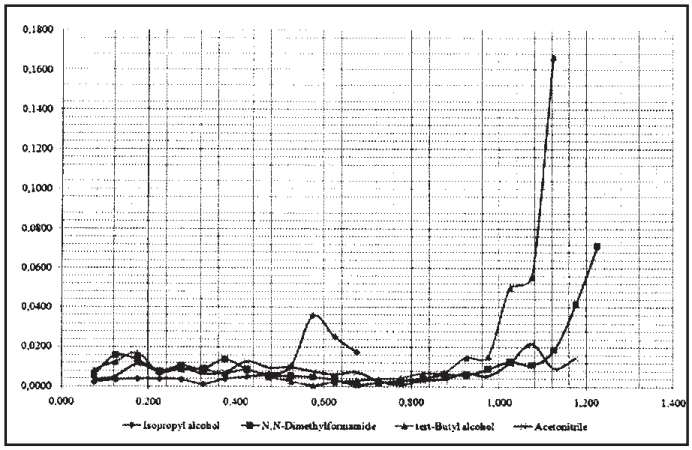


Fig. 5. ΔV - ΔE Potentiometric titration curves of 0.001 M solutions of compound **1** titrated with 0.05 M TBAH in acetonitrile at 25°C.

5a-f : **5a**, **5b**, **5d** and **5e**; isopropyl alcohol > *tert*-butyl alcohol > acetonitrile > *N,N*-dimethyl formamide, **5c** and **5f**; isopropyl alcohol > *tert*-butyl alcohol > *N,N*-dimethyl formamide > acetonitrile, compound **5d** shows high (15.51±0.06) acidic properties in isopropyl alcohol, compound **5c** shows low (17.06±0.05) acidic properties in acetonitrile. This situation may be attributed to the hydrogen bonding between the negative ions formed and the solvent molecules in the amphiprotic neutral solvents. Autoprotolysis is an acidbase reaction between identical solvent molecules in which some act as an acid and others as a base.

Conclusions

The extent of an autoprotolysis reaction depends both on the intrinsic acidity and the instrinsic basicity of the solvent. The importance of the autoprotolysis constant in titrations lies in its effect on the completeness of a titration reaction. The acidity of a compound depends on mainly two factors, *i.e.* solvent effect and molecular structure. Half-neutralization potential (HNP) values and corresponding pKa values obtained from the potentiometric titrations rely on the nonaqueous solvents used and the substituents in triazole ring.

The degree to which a pure solvent ionizes was represented by its autoprotolys in constant, K_{HS}.

$$2HS \rightleftharpoons H_2S^+ + S^-$$

For the above reaction the constant is defined by $K_{HS} = [H_2S^+][S^-]$. Autoprotolysis is an acid-base reaction between identical solvent molecules in which some act as an acid and others as a base.

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References

1. OMAR, A. M. M. E., ABOULWAFE, O. M., J. Heterocyclic. Chem., 23, 1986, p. 1339.
2. GALIC, N., PERIC, B., CIMERMAN, Z. J., Mol. Stuc., 559, 2001, p. 187.
3 .WYRZYKIEWICZ, E., PRUKAH, D., J. Het. Chem., 35, 1998, p. 381.
4.SUN, S., LOU, H., GAO, Y., FAN, P., MA, B., GE, W., WANG, X. J., Pharm. Biomed. Anal., 34, 2004, p. 1117.
5.CLEMONS, M., COLEMAN, R. E., VERMA, S., Cancer Treat. Rev., 30, 2004, p. 325.
6.JOHNSTON, G. A. R., Curr. Top. Med. Chem., 11, 2002, p. 903.
7.ISLOOR, A. M., KALLURAYA, B., RAO, M., RAHIMAN, A. M., J. Saudi Chem. Soc., 4, 2000, p. 265.
8. BEKIRCAN, O., OZEN, T., GUMRUKCUOGLU, N., BEKTAS, H., Z. Naturforsh, 63B, 2008, p. 548.
9.BEKIRCAN, O., KAHVECI, B., KUCUK, M., Turk. J. Chem., , 30, 2006, p. 29.
10.DEMIRBAS, N., ALPAY KARAOGLU, S., DEMIRBAS, A., SANCAK, K., Eur. J. Med.Chem., 39, 2004, p. 793.
11. KHALIL, S. A. Eur. J. Med. Chem., 45, 2010, p. 5265.
12BAIRAK, H., DEMIRBAS, A., DEMIRBAS, N., ALPAI KARAOGLU, S., Eur. J. Med. Chem., 44, 2009, p. 4362.
13.ÝSLAMOGLU, F., KAHVECI, B., BEKIRCAN, O., Asian J. Chem., 21, 2009, p. 5523.
14. BULUT, V. N., OZDES, D., BEKIRCAN, O., GUNDOGDU, A., DURAN, C., SOYLAK, M., Anal. Chim. Acta, 632, 2009, p. 35.
15.REDDI, H., LIRGAPPA, Y., Ind. J. Het. Chem., 33, 1994, p. 919.
16AL-SHAALAN, N. H., Molecules, 16, 2011, p. 8629.
17.KORTÜM, G., VOGEL, W., ANDRUSSOW, K., Dissociation Constants Of Organic Acids In Aqueous Solution, Plenum Press, New York, 1961.
18.PALM, V. A. (Ed.), Tables Of Rate And Equilibrium Constants Of Heterolytic Organic Reactions, Viniti, Moscow, 1976.
19.MILCENT, R., REDEUILH, C., J. Heterocycl. Chem., 16, 1979,p. 403.
20. MILCENT, R., VICART, P., J. Med. Chem., 18, 1983,p. 215.
21.IZUTSU, K., Acid-Base Dissociation Constants In Dipolar Aprotic Solvents, Iupac Chemical Data Series No. 35, Blackwells Scientific, Oxford, 1990.
22. BORDWELL, F. G., Acc. Chem. Res., 21, 1988, p. 456.
23. ÖZIL, M., ISLAMOGLU, F., MENTEŞE, E., KAHVECÝ, B., Helv. Chim. Acta, 2010, 93, p. 1967.
24. HERBERT, S. H., BIRDSALL, C. M., J. Am. Chem. Soc., 65, 1943, p. 54.
25. NOWAK, B., PAWLAK, Z., J. Chem. Soc., Faraday Trans. I, 78, 1982, p. 2693.
26. WADA, G., TAMURA, E., OKINA, M., NAKAMURA, M. Bull. Chem. Soc. Jpn., 55, 1982, p. 3064.
27. KÖSEOGLU, F., KILIÇ, E., DOGAN, A., Anal. Biochem., 277, 2000, p. 243.
28. HUGHES, D. L., BERGAN, J. J., GRABOWSKI, E. J. J., J. Org. Chem., 51, 1986, p. 2579.
29. BENESCH, E. R., BENESCH, R., J. Am. Chem. Soc., 77, 1955, p. 5877.
30. EDSALL J. T., BLANCHARD, M. H., J. Am. Chem. Soc., 55, 1933, p. 2337.
31. KATRITZKY, A. R., LAURENZO, K. S., J. Org. Chem., 53, 1988, p. 3978.
32. BROKAITE, K., MICKEVICIUS, V., MIKULSKIENE, G., Arkivoc, 2, 2006, p. 61.
33. MAMOLO, M. G., FALAGIANI, V., ZAMPIERI, D., VIO, L., BANFI, E., Il. Farmaco, 56, 2001, p. 587.
34. TODESCHINI, A. R., DE MIRANDA, A. L. P., DA SILVA, K. C. M., PARRINI, S. C., BARREÝRO, E. J., Eur. J. Med. Chem., 33, 1998, p. 189

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