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Synthesis and Determination of pK_a Values of Some New 3,4-Disubstituted-4,5-Dihydro-1*H*-1,2,4-triazol-5-one Derivatives in Non-aqueous Solvents

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Abstract: 3-Alkyl(Aryl)-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**2**) reacted with 2-furoyl chloride and thiophene-2-carbonyl chloride to afford the corresponding 3-alkyl(aryl)-4-(2-furoylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**3**) and 3-alkyl(aryl)-4-(2-thienylcarbonylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**4**), respectively. The new compounds synthesized were characterized by using IR, ^{1}H-NMR, ^{13}C-NMR and UV spectral data together with elemental analysis. In addition, to investigate the effects of solvents and molecular structure upon acidity, compounds **3** and **4** were titrated potentiometrically with tetrabutylammonium hydroxide in four non-aqueous solvents (isopropyl alcohol, *tert*-butyl alcohol, *N,N*-dimethylformamide and acetonitrile). The half-neutralization potential values and the corresponding pK_a values were determined for all cases.

Keywords: 4,5-Dihydro-1*H*-1,2,4-triazol-5-ones; acylation; acidity; potentiometric titration; syntheses.

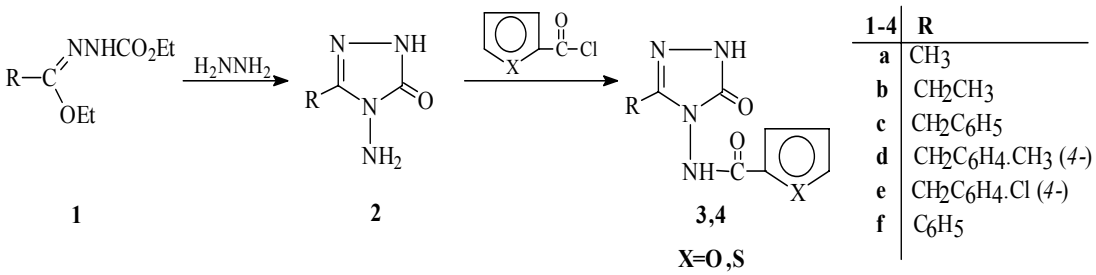
Introduction

1,2,4-Triazole and 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives are reported to show a broad spectrum of biological activities such as antifungal, antimicrobial, hypoglycemic, antihypertensive, analgesic, antiparasitic, hypocholesteremic, antiviral, anti-inflammatory, antitumor and anti-HIV properties [1-14]. These observations prompted us to synthesize some new 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives with potential biological activity. In addition, several articles, involving the acylation of 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives, have also been published up to date [11, 12,15,16].

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 [11, 17-20]. We have previously described the synthesis and potentiometric titrations of some new 4,5-dihydro-1H-1,2,4-triazol-5-one derivatives in different non-aqueous medium [21, 22], where we determined the pKa values of these compounds for each non-aqueous solvent.

The aim of this work is to synthesize a series of 3-alkyl(aryl)-4-(2-furoylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**3**) and 3-alkyl(aryl)-4-(2-thienylcarbonylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**4**) from the reactions of 3-alkyl(aryl)-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**2**) with 2-furoyl chloride and thiophene-2-carbonyl chloride, respectively (Scheme 1). Moreover, the synthesized compounds **3** and **4** were titrated potentiometrically with tetrabutylammonium hydroxide (TBAH) in four non-aqueous solvents, including isopropyl alcohol, *tert*-butyl alcohol, *N,N*-dimethylformamide and acetonitrile to determine their pK_a values. For each new compound synthesized, the half-neutralization potential (HNP) and the corresponding pK_a value were determined in the four mentioned non-aqueous solvents. The data obtained from the potentiometric titrations were interpreted, and the effect of the C-3 substituent and solvent effects were studied [17-22]. Determination of pK_a values of active constituents of certain pharmaceutical preparations is important, because their distribution, transport behavior, bonding to receptors, and contributions to metabolic behavior depend on the ionization constant [23].

Scheme 1



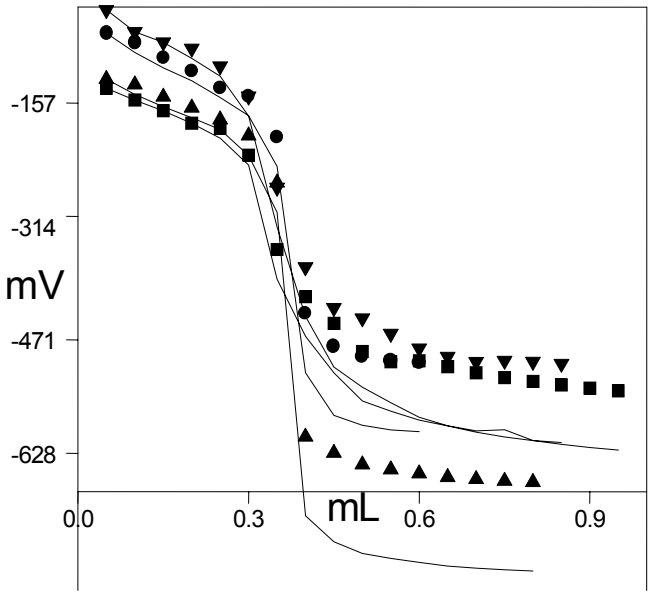
Results and Discussion

In this study, the structures of the newly synthesized 3-alkyl(aryl)-4-(2-furoylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**3**) and 3-alkyl(aryl)-4-(2-thienyl-carbonylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**4**) were identified using elemental analysis and IR, ^{1}H-NMR, ^{13}C-NMR and UV spectral data, and these obtained spectral values were seen to be compatible with literature reports [24, 25]. In addition, these newly synthesized compounds **3** and **4** were titrated potentiometrically with tetrabutyl-ammonium hydroxide (TBAH) in non-aqueous solvents such as isopropyl alcohol (ε=19.4), *tert*-butyl alcohol (ε=12), *N,N*-dimethylformamide (ε=37) and acetonitrile (ε=36).

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 pK_a values were calculated.

As an example, the potentiometric titration curves for 0.001 M 3-Benzyl-4-(2-furoylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**3c**) solutions titrated with 0.05 M TBAH in isopropyl alcohol, *tert*-butyl alcohol, *N*,*N*-dimethylformamide and acetonitrile are given in Figure **1**. As it is clearly seen in Figure **1**, a typical S-shaped titration curve was obtained.

Figure 1. Potentiometric titration curves of 10^{-3} M 3-Benzyl-4-(2-furoylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**3c**) solutions titrated with 0.05 M TBAH in isopropyl alcohol (●), *tert*-butyl alcohol (▲), *N*,*N*-dimethylformamide (■) and acetonitrile (▼) at 25 °C.



The half-neutralization potentials (HNP) and the corresponding pK_a values for compounds **3** and **4**, obtained from the potentiometric titrations with 0.05 M TBAH in isopropyl alcohol, *tert*-butyl alcohol, *N*,*N*-dimethylformamide and acetonitrile, are given in Table **1**.

Table 1. The half-neutralization potentials (HNP) and the corresponding pK_a values of compounds **3** and **4** in isopropyl alcohol, *tert*-butyl alcohol, *N*,*N*-dimethylformamide and acetonitrile.

Compd. no	Isopropyl alcohol		*Tert*-butyl alcohol		*N*,*N*-Dimethyl formamide		Acetonitrile	
	HNP (mV)	pK_a	HNP (mV)	pK_a	HNP (mV)	pK_a	HNP (mV)	pK_a
3a	-292	11.63	-206	9.84	-447	14.56	-430	14.57
3b	-298	11.69	-260	11.01	-459	15.69	-388	13.69
3c	-111	8.79	-162	9.49	-172	10.38	-96	8.48
3e	-290	11.52	-248	10.76	-443	15.30	-409	14.10
3f	-312	11.97	-186	9.52	-491	15.26	-329	12.48
4a	-275	11.07	-273	11.10	-450	14.37	-374	13.38
4b	-297	11.87	-254	10.86	-324	12.39	-333	12.54
4c	-291	11.42	-175	11.63	-347	12.42	-352	12.91
4d	-214	10.66	-285	11.84	-320	12.82	-227	11.52
4e	-286	11.48	-277	11.26	-436	14.23	-284	11.60
4f	-293	11.47	-291	11.40	-388	13.17	-333	12.51

As it is well known, the acidity of a compound depends on some factors. The two most important factors are the solvent effect and molecular structure [18-22, 26-28]. Table **1** shows that the HNP values and the corresponding pK_a values obtained from potentiometric titrations depend on the non-aqueous solvents used. The results obtained illustrate that *tert*-butyl alcohol is the best solvent. As can be observed in Figure **1**, for example, the potential jump of compound **3c** in the end-point is very large for *tert*-butyl alcohol ranging from –266 mV to –599 mV. In addition, Table **1** shows that the molecular structure of titrated compounds affects the HNP and corresponding pK_a values depending on the substituents at C-3 in the same solvent.

Experimental

General

Melting points were taken on a Electrothermal digital melting point apparatus and are uncorrected. IR spectra were registered using KBr disks on a Perkin-Elmer 1600 FTIR spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in DMSO-d_6 with TMS as internal standard on a Varian Mercury spectrometer at 200 MHz and 50 MHz, respectively. UV absorption spectra were measured for ethanol solutions in 10 mm quartz cells between 200 and 400 nm using a Shimadzu UV-1201 spectrophotometer. For potentiometric titrations, a Jenway 3040 ion analyser pH meter (calibrated according to the instructions of the manufacturer) equipped with an Ingold pH electrode were used. During the titrations, the titrant was added in increments of 0.05 mL after each stable reading, and the corresponding mV values were recorded. Chemicals were supplied from Fluka and Merck. After purification, isopropyl alcohol was used to prepare 0.05 M tetrabutylammonium hydroxide (TBAH). For all potentiometric titrations, 0.05 M TBAH in isopropyl alcohol was used. The starting compounds **2a-e** were prepared from the reactions of the corresponding ester ethoxycarbonylhydrazones (**1a-e**) with hydrazine hydrate according to literature [16,29].

General Method for the Preparation of 3-alkyl(aryl)-4-[2-furoylamino]-4,5-dihydro-1H-1,2,4-triazol-5-ones (**3**) or *3-alkyl(aryl)-4-[2-thienylcarbonyamino]-4,5-dihydro-1H-1,2,4-triazol-5-ones* (**4**):

3-Alkyl(aryl)-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**2**) (0.01 mol) was refluxed with a solution of the appropriate heteroaroyl chloride (2-furoyl chloride or 2-thiophenecarbonyl chloride) (0.01 mol) in n-butyl acetate (40 mL) for 6 hours and then allowed to cool. The product was recrystallized from an appropriate solvent to give **3** or **4**. The following compounds were prepared applying this procedure:

3-Methyl-4-(2-furoylamino)-4,5-dihydro-1H-1,2,4-triazol-5-one (**3a**). Yield 90%; m.p. 83 °C (H_2O); Calculated for $C_8H_8N_4O_3$ (208.18): 46.16% C, 3.87% H, 26.91% N; found: 46.70% C, 4.18% H, 26.79% N. ^{1}H-NMR: δ 2.06 (s, 3H, CH_3), 6.76 (s, 1H, Ar-H), 7.40 (s, 1H, Ar-H), 8.02 (s, 1H, Ar-H), 11.38 (s, 1H, NH); 11.73 (s, 1H, NH); ^{13}C-NMR: δ 10.72 (aliphatic carbon), 112.65, 116.87, 145.05, 147.07 (aromatic carbons), 145.36 (triazole C_3), 152.89 (triazole C_5), 157.24 (C=O); IR: 3500, 3170 (NH), 1715, 1680 (C=O), 1596 (C=N) cm^{-1}; UV λ_{max} nm, (ε, L·mol^{-1}·cm^{-1}): 253 (26350), 212 (16510) nm.

3-Ethyl-4-(2-furoylamino)-4,5-dihydro-1H-1,2,4-triazol-5-one (**3b**). Yield 87%; m.p. 111-112 °C (EtOH-toluene, 1:3); Calculated for $C_9H_{10}N_4O_3$ (222.20): 48.65% C, 4.54% H, 25.21% N; found: 48.35% C, 4.74% H, 24.93% N. ^{1}H-NMR: δ 1.11 (t, 3H, CH_3), 2.33 (q, 2H, CH_2), 6.70 (s, 1H, Ar-H), 7.33 (s, 1H, Ar-H), 7.95 (s, 1H, Ar-H), 11.33 (s, 1H, NH); 11.70 (s, 1H, NH); ^{13}C-NMR: δ 9.88, 18.17

(aliphatic carbons), 112.57, 116.74, 145.00, 149.10 (aromatic carbons), 147.00 (triazole C_3), 152.96 (triazole C_5), 157.14 (C=O); IR: 3450, 3260 (NH), 1715, 1695 (C=O), 1595 (C=N) cm^{-1}; UV λ_{max} nm, (ε, $L \cdot mol^{-1} \cdot cm^{-1}$): 211 (11390) nm.

3-Benzyl-4-(2-furoylamino)-4,5-dihydro-1H-1,2,4-triazol-5-one (**3c**). Yield 82%; m.p. 160-162 °C (EtOH); Calculated for $C_{14}H_{12}N_4O_3$ (284.27): 59.15% C, 4.25% H, 19.71% N; found: 59.48% C, 4.18% H, 18.79% N. ^{1}H-NMR: δ 3.72 (s, 2H, CH_2), 6.74 (s, 1H, Ar-H), 7.20-7.36 (m, 7H, Ar-H), 11.71 (s, 1H, NH); 11.90 (s, 1H, NH); ^{13}C NMR: δ 30.40 (aliphatic carbon), 112.80, 117.10, 126.89, 128.47 (3C), 128.63 (3C), 134.60 (aromatic carbons), 146.20 (triazole C_3), 152.00 (triazole C_5), 163.30 (C=O); IR: 3450, 3230 (NH), 1746, 1715 (C=O), 1590 (C=N), 770, 705 (monosubstituted benzenoid ring) cm^{-1}; UV λ_{max} nm, (ε, $L \cdot mol^{-1} \cdot cm^{-1}$): 246 (28720), 221 (23950) nm.

3-(4-Chlorobenzyl)-4-(2-furoylamino)-4,5-dihydro-1H-1,2,4-triazol-5-one (**3e**). Yield 90%; m.p. 177-178 °C (EtOH-H_2O, 1:3); Calculated for $C_{14}H_{11}N_4O_3Cl$ (318.72): 52.76% C, 3.48% H, 17.58% N; found: 52.45% C, 3.87% H, 17.56% N. ^{1}H-NMR: δ 3.82 (s, 2H, CH_2), 6.75 (s, 1H, Ar-H), 7.25-7.38 (m, 5H, Ar-H), 8.02 (s, 1H, Ar-H), 11.36 (s, 1H, NH); 11.92 (s, 1H, NH); ^{13}C-NMR: δ 30.30 (aliphatic carbon), 112.40, 117.10, 128.58 (3C), 130.96 (2C), 131.90, 134.10, 147.03 (aromatic carbons), 145.00 (triazole C_3), 153.00 (triazole C_5), 157.30 (C=O); IR: 3400, 3210 (NH), 1725, 1688 (C=O), 1595 (C=N), 810 (1,4-disubstituted benzenoid ring) cm^{-1}; UV λ_{max} nm, (ε, $L \cdot mol^{-1} \cdot cm^{-1}$): 256 (14340), 221 (16830) nm.

3-Phenyl-4-(2-furoylamino)-4,5-dihydro-1H-1,2,4-triazol-5-one (**3f**). Yield 79%; m.p. 278-239 °C (H_2O); Calculated for $C_{13}H_{16}N_4O_3$ (270.25): 57.78% C, 3.73% H, 20.73% N; found: 58.02% C, 3.50% H, 20.43% N. ^{1}H-NMR: δ 6.75 (s, 1H, Ar-H), 7.47-7.52 (m, 4H, Ar-H), 7.85-7.86 (m, 2H, Ar-H), 8.03 (s, 1H, Ar-H), 11.82 (s, 1H, NH); 12.49 (s, 1H, NH); ^{13}C-NMR: δ 112.80, 117.20, 126.25, 127.14 (2C), 129.30 (2C), 130.91, 146.53, 147.17 (aromatic carbons), 145.21 (triazole C_3), 153.62 (triazole C_5), 157.45 (C=O); IR: 3450, 3150 (NH), 1713, 1670 (C=O), 1590 (C=N), 760, 695 (monosubstituted benzenoid ring) cm^{-1}; UV λ_{max} nm, (ε, $L \cdot mol^{-1} \cdot cm^{-1}$): 246 (29600), 216 (22900) nm.

3-Methyl-4-(2-thienylcarbonylamino)-4,5-dihydro-1H-1,2,4-triazol-5-one (**4a**). Yield 83%; m.p. 255-256 °C (EtOH); Calculated for $C_8H_8N_4O_2S$ (224.24): 42.85% C, 3.60% H, 24.99% N; found: 43.26% C, 3.45% H, 24.98% N. ^{1}H-NMR: δ 1.99 (s, 3H, CH_3), 7.06-7.29 (m, 1H, Ar-H), 7.45-8.22 (m, 2H, Ar-H), 11.46 (s, 1H, NH); 11.70 (s, 1H, NH); ^{13}C-NMR: δ 11.87 (aliphatic carbon), 129.30, 131.56, 134.00, 135.84 (aromatic carbons), 146.21 (triazole C_3), 153.82 (triazole C_5), 161.84 (C=O); IR: 3300, 3150 (NH), 1720, 1660 (C=O), 1610 (C=N) cm^{-1}; UV λ_{max} nm, (ε, $L \cdot mol^{-1} \cdot cm^{-1}$): 248 (29140), 212 (19790) nm.

3-Ethyl-4-(2-thienylcarbonylamino)-4,5-dihydro-1H-1,2,4-triazol-5-one (**4b**). Yield 82%; m.p. 202-203 °C (EtOH-H_2O, 1:3); Calculated for $C_9H_{10}N_4O_2S$ (238.26): 45.37% C, 4.23% H, 23.51% N;

found: 45.03% C, 4.18% H, 23.57% N. ^{1}H-NMR: δ 1.14 (t, 3H, CH_3), 2.41 (q, 2H, CH_2), 7.27-7.29 (m, 1H, Ar-H), 7.97-7.99 (m, 2H, Ar-H), 11.47 (s, 1H, NH); 11.79 (s, 1H, NH); ^{13}C-NMR: δ 10.11, 18.34 (aliphatic carbons), 128.79, 130.76, 133.47, 135.40 (aromatic carbons), 149.26 (triazole C_3), 153.19 (triazole C_5), 161.05 (C=O); IR: 3500, 3175 (NH), 1720, 1675 (C=O), 1600 (C=N) cm^{-1}; UV λ_{max} nm, (ε, $L \cdot mol^{-1} \cdot cm^{-1}$): 250 (22220), 207 (16500) nm.

3-Benzyl-4-(2-thienylcarbonylamino)-4,5-dihydro-1H-1,2,4-triazol-5-one (**4c**). Yield 86%; m.p. 220-222 °C (EtOH-H_2O, 1:3); Calculated for $C_{14}H_{12}N_4O_2S$ (300.33): 55.99% C, 4.03% H, 18.65% N; found: 55.73% C, 3.73% H, 18.38% N. ^{1}H-NMR: δ 3.82 (s, 2H, CH_2), 7.26 (s, 6H, Ar-H), 7.95 (s, 2H, Ar-H), 11.46 (s, 1H, NH); 11.94 (s, 1H, NH); ^{13}C-NMR: δ 31.10 (aliphatic carbon), 127.18, 128.76 (3C), 129.08 (2C), 131.10, 133.90, 135.40, 135.90 (aromatic carbons), 147.90 (triazole C_3), 153.40 (triazole C_5), 161.20 (C=O); IR: 3250, 3100 (NH), 1725, 1660 (C=O), 1600 (C=N), 770, 705 (monosubstituted benzenoid ring) cm^{-1}; UV λ_{max} nm, (ε, $L \cdot mol^{-1} \cdot cm^{-1}$): 251 (22220), 210 (30440) nm.

3-(4-Methylbenzyl)-4-(2-thienylcarbonylamino)-4,5-dihydro-1H-1,2,4-triazol-5-one (**4d**). Yield 77%; m.p. 167-168 °C (EtOH-H_2O, 1:3); Calculated for $C_{15}H_{14}N_4O_2S$ (314.36): 57.31% C, 4.48% H, 17.82% N; found: 57.10% C, 4.27% H, 17.93% N. ^{1}H-NMR: δ 2.27 (s, 3H, CH_3), 3.95 (s, 2H, CH_2), 7.11-7.27 (m, 5H, Ar-H), 7.95-8.00 (m, 2H, Ar-H), 11.43 (s, 1H, NH); 11.89 (s, 1H, NH); IR: 3250, 3120 (NH), 1760, 1670 (C=O), 1615 (C=N), 790 (1,4-disubstituted benzenoid ring) cm^{-1}; UV λ_{max} nm, (ε, $L \cdot mol^{-1} \cdot cm^{-1}$): 269 (23580), 211 (24660) nm.

3-(4-Chlorobenzyl)-4-(2-thienylcarbonylamino)-4,5-dihydro-1H-1,2,4-triazol-5-one (**4e**). Yield 90%; m.p. 190-191 °C (EtOH-H_2O, 1:3); Calculated for $C_{14}H_{11}N_4O_2SCl$ (334.78): 50.23% C, 3.31% H, 16.74% N; found: 50.55% C, 2.99% H, 16.50% N. ^{1}H-NMR: δ 3.82 (s, 2H, CH_2), 7.24-7.37 (m, 5H, Ar-H), 7.93-7.97 (m, 2H, Ar-H), 11.41 (s, 1H, NH); 11.93 (s, 1H, NH); ^{13}C-NMR: δ 29.00 (aliphatic carbon), 127.25 (3C), 129.39, 129.57 (2C), 130.90, 131.99, 132.63, 134.30 (aromatic carbons), 145.90 (triazole C_3), 152.90 (triazole C_5), 159.80 (C=O); IR: 3220, 3100 (NH), 1730, 1665 (C=O), 1595 (C=N), 805 (1,4-disubstituted benzenoid ring) cm^{-1}; UV λ_{max} nm, (ε, $L \cdot mol^{-1} \cdot cm^{-1}$): 251 (15100), 222 (24400) nm.

3-Phenyl-4-(2-thienylcarbonylamino)-4,5-dihydro-1H-1,2,4-triazol-5-one (**4f**). Yield 85%; m.p. 160-161 °C (EtOH-H_2O, 1:3); Calculated for $C_{13}H_{10}N_4O_2S$ (286.31): 55.54% C, 3.52% H, 19.57% N; found: 55.16% C, 3.52% H, 19.43% N. ^{1}H-NMR: δ 7.29-8.05 (m, 8H, Ar-H), 11.85 (s, 1H, NH); 12.46 (s, 1H, NH); ^{13}C-NMR: δ 126.10, 126.98 (2C), 127.10, 129.25 (2C), 130.90 (2C), 133.80, 135.50 (aromatic carbons), 146.20 (triazole C_3), 153.70 (triazole C_5), 161.10 (C=O); IR: 3250 (NH), 1730, 1675 (C=O), 1610 (C=N), 770, 700 (monosubstituted benzenoid ring) cm^{-1}; UV λ_{max} nm, (ε, $L \cdot mol^{-1} \cdot cm^{-1}$): 253 (25710), 210 (16990) nm.

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