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Synthesis and Antitumor Activities of Some New 4-(1-Naphthylidenamino)- and 4-(1-Naphthylmethylamino)-1,2,4-Triazol-5-one Derivatives

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A series of 4-(1-naphthylidenamino)-1,2,4-triazol-5-one derivatives (**3a-e**) were synthesized by condensation of corresponding 3-alkyl-4-amino-4,5-dihydro-1H-1,2,4-triazol-5-ones with 1-naphthaldehyde. Acetylation and alkylation of these compounds gave **4a-e** and **5a-e**, respectively. Sodium borohydride reduction of 1-naphthylidenamino derivatives afforded naphthylmethylamino derivatives, which were subsequently acetylated. Depending on the duration of the acetylation, mono or bis acetamide derivatives were obtained.

The in vitro antitumor activities of some selected compounds were screened and compounds **3e**, **5c**, **6e** and **9c** were found to be active.

Key Words: 1,2,4-triazol-5-one, 1-naphthaldehyde, Acetylation, Alkylation, Antitumor activity.

Introduction

The Compounds incorporating a 1,2,4-triazole ring with diverse pharmacological effects have been reported as therapeutical agents in medicinal chemistry[1−5], and several of these compounds have been shown to be antitumor agents [6−11]. Some of them also incorporate a Schiff base structure[6,7]. In one of our previous studies[7], we reported that 1,2,4-triazol-5-ones exhibit the highest antitumoral activity when this ring substituted alkyl/aryl and 2-phenyl ethyliden/ethyl amino groups at positions 3 and 4, respectively. Furthermore, Schiff base derivatives with arilidenhydrazide group (**1**) (Scheme 1) of compounds **2** were synthesized in our laboratory and found to possess antitumoral activity against only breast cancer[12]. In addition, it was reported that, compounds having triazole moieties, such as Vorozole, Letrozole and Anastrozole (Scheme 1), appear to be very effective aromatase inhibitors very useful for preventing breast cancer[13−15]. It is known that 1,2,4-triazole moieties interact strongly with heme iron, and aromatic substituents on the triazoles are very effective for interacting with the active site of aromatase[16]. Therfore, as part of our continuing studies

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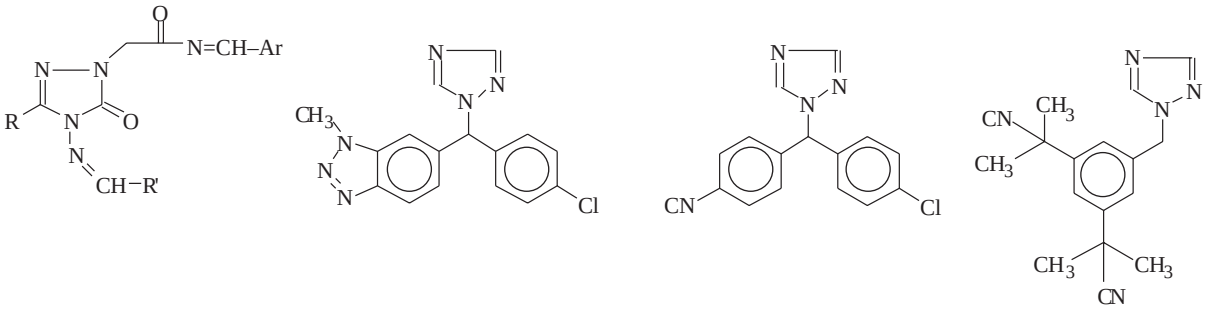
on triazoles and their pharmacological profile, we aimed to discover novel 1,2,4-triazol-5-one derivatives with probable antitumoral activity.



1 Vorozole Letrozole Anastrozole

Scheme 1.

Results and Discussion

In order to synthesize 3-alkyl-4-alkylamino-4,5-dihydro-1H-1,2,4-triazol-5-ones, 2 methods have been developed [17,18]. One of them involves the reaction of alkyl or aryl hydrazines[17]. However, there are only a few known alkyl or aryl hydrazines and they are also unstable in the reaction temperature. In the other method[18], 4-alkylamino-4,5-dihydro-1H-1,2,4-triazol-5-ones have been obtained by the reduction of 4-arylidenamino-4,5-dihydro-1H-1,2,4-triazol-5-ones, which were obtained by the treatment of compounds **2** with some halogeno benzaldehydes or *p*-tolualdehyde. We tried to improved the reported method[18] as well. Compounds **3a-e** were obtained from the reaction of compounds **2a-e** with 1-naphthaldehyde (Scheme 2). The signal observed at 10.25-10.50 ppm in the ^{1}H-NMR spectra of compounds **3a-e** was attributed to the –N=CH proton. The ^{13}C signal of the same group was observed at 153.02-155.92 ppm.

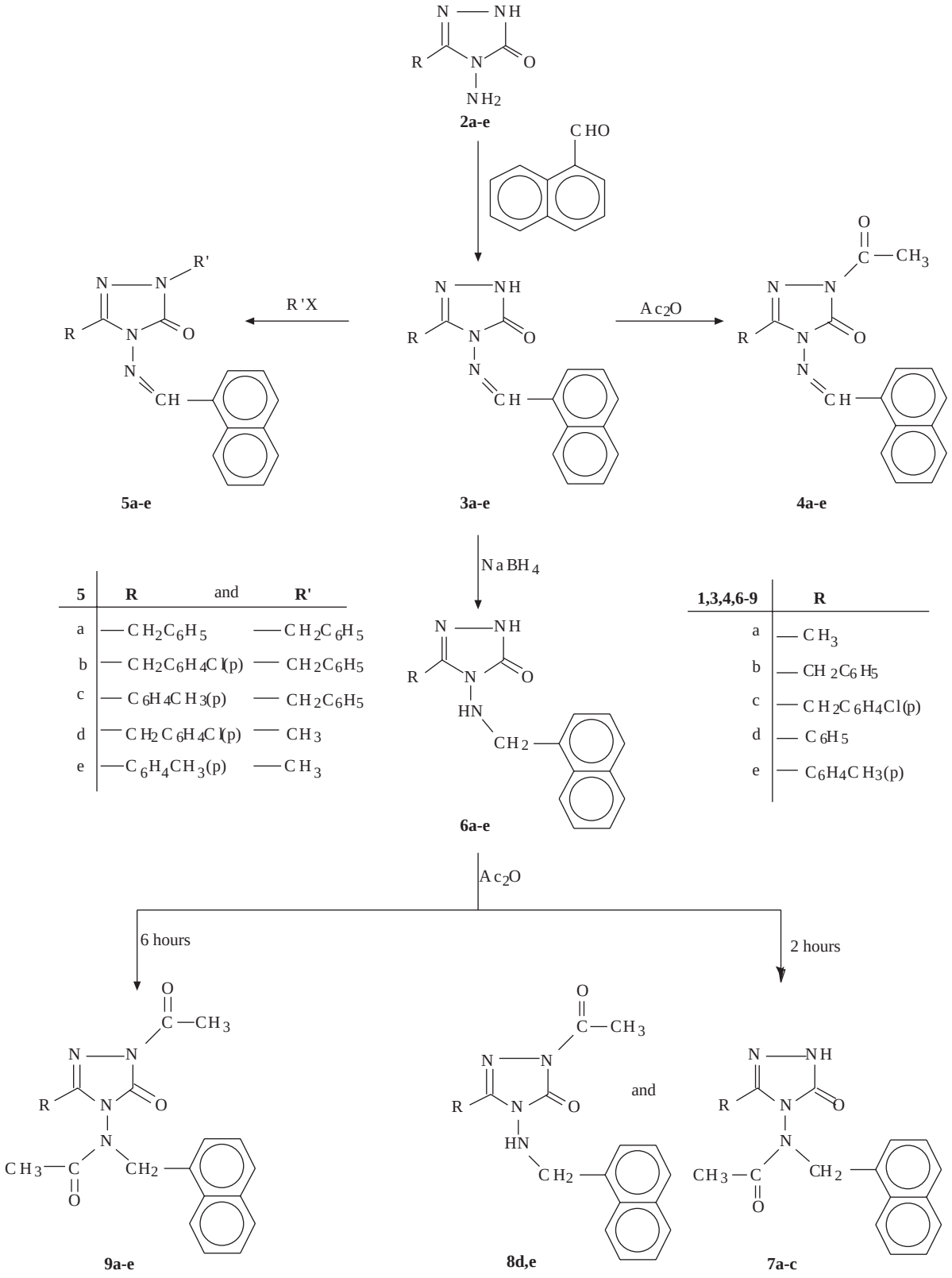
The acetylation of compounds **3a-e** was performed with acetic anhydride to obtain 1-acetyl-3-alkyl-4-(1-naphthylidenamino)-4,5-dihydro-1H-1,2,4-triazol-5-ones **(4a-e)**.

The synthesis of 3-alkyl-4-(1-naphthylmethylamino)-4,5-dihydro-1H-1,2,4-triazol-5-ones **(6a-e)** was carried out by the reduction of compounds **3a-e** with $NaBH_4$. Although the reduction of the 1,2,4-triazol-5-one ring is also possible[19], only the exocyclic imine bond of compounds **3a-e** was reduced in the present study. No reduction took place in compounds **3a-e** when $NaCNBH_3$was used instead of $NaBH_4$.

When compounds **3a-e** were converted to their reduced derivatives (**6a-e**) 2 different proton signals due to $–NHCH_2$ were observed. The signal originating from $–NH-CH_2$ appeared at 49.5-50.5 ppm in the ^{13}C NMR spectra.

The acetylation of compounds **6a-e** resulted in the formation of 2 different types of monoacetyl derivatives (**7a-c** and **8d,e**). In the present study, when compounds **6a-e** were treated with acetic anhydride for 2 h, the exocyclic –NH protons of compounds **6a-c** and the endocyclic –NH protons of compounds **6d** and **6e** were acetylated; thus, compounds **7a-c** and **8d**,**8e** were obtained. In the ^{1}H NMR spectra of compounds **7a-c,** the endocyclic -NH signals were recorded at 11.90-12.05 ppm. Similarly, the exocyclic –NH signals of compounds **8d** and **8e** appeared at 6.78-6.82 ppm (exchangeable with D_2O).

The geometrical optimization of compounds **6a** and **6d** was achieved by the AM1 method and the charge density of each atom was calculated (Scheme 3). According to these results, either endocyclic or

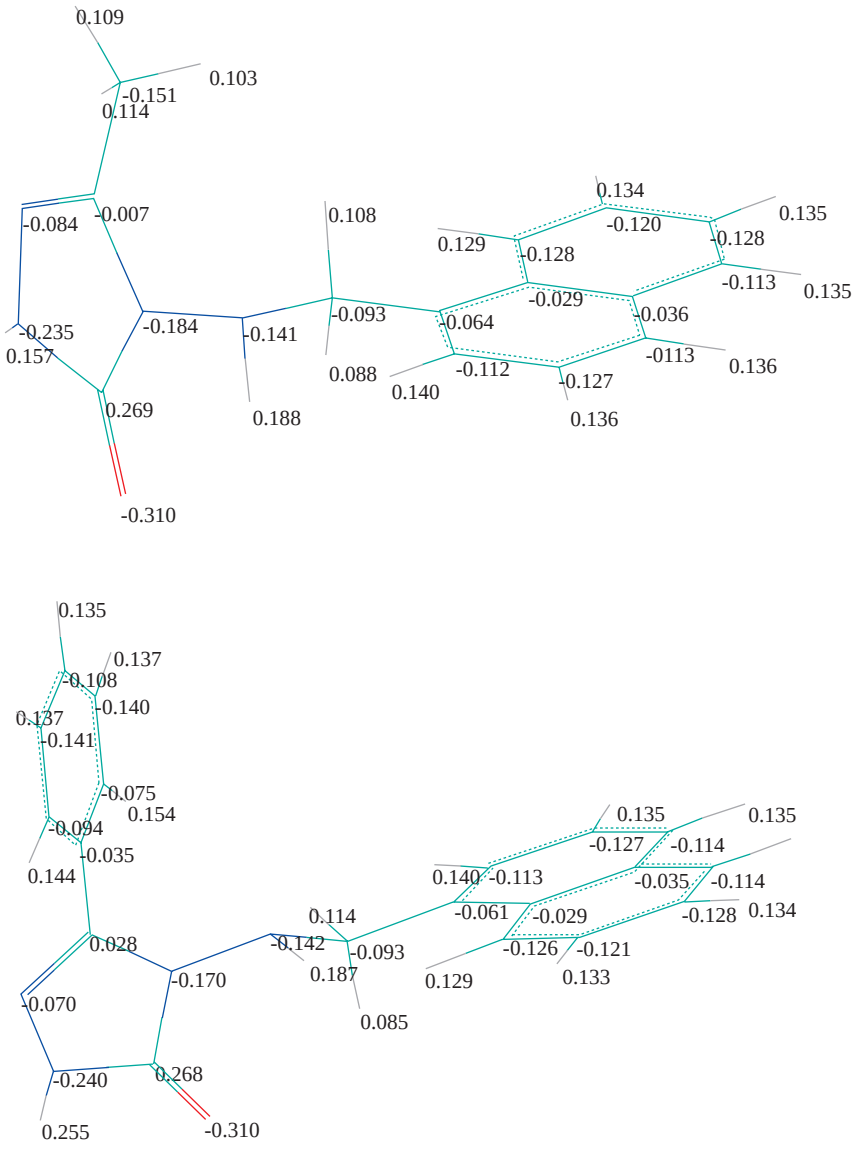


5	R	and	R'
a	$CH_2C_6H_5$		$CH_2C_6H_5$
b	$CH_2C_6H_4Cl$(p)		$CH_2C_6H_5$
c	$C_6H_4CH_3$(p)		$CH_2C_6H_5$
d	$CH_2C_6H_4Cl$(p)		CH_3
e	$C_6H_4CH_3$(p)		CH_3

1,3,4,6-9	R
a	CH_3
b	$CH_2C_6H_5$
c	$CH_2C_6H_4Cl$(p)
d	C_6H_5
e	$C_6H_4CH_3$(p)

Scheme 2. Synthetic pathway for the preparation of compounds **3-9**.

exocyclic nitrogen atoms can behave as nucleophiles to attack the carbonyl carbon of acetic anhydride. On the other hand, according to the steric energy calculations (MOPAC, MM2) more stable products can be obtained when the acetylation occurs at the exocyclic –NH group. In the case of compounds **6d** and **6e**, phenyl and *p*-tolyl groups at position 3 the of 1,2,4-triazole ring might cause partial hindrance on the exocyclic nitrogen atom. As a result, compounds **8d** and **8e** were obtained only after acetylation for 2 h. Only upon acetylation for 6 h could the diacetylated products **(9a-e)** be obtained.



Scheme 3. Geometric optimizations and charge density of compounds **6a** and **6d**.

Antitumor screening studies

The screening experiments were performed by the Developmental Therapeutic Program of the National Cancer Institute (NCI), Bethesda, Maryland, USA. Twenty one compounds (**3b**, **3e**, **4a-e**, **5c**, **6a-e**, **7a**, **7b**, **7d**, **8e**, **9a-c**, **9e**) were selected by the NCI for screening for 3 human tumor cell lines, i.e. breast cancer (MCF7), non small cell lung cancer (NCI-H460) and CNS (SF-268). Each cell line was inoculated

and preincubated on a microtiter plate. Test agents were then added at a single concentration and culture incubated for 48 h. End-point determinations were made with alamar blue[20]. The screening results are summarized in the Table. Results for each test agents are reported as the percent of growth of the treated cells when compared to the untreated control cells. The compounds that reduce the growth any one of the cell lines to approximately 32% or less were evaluated as having antitumor activity.

Table. Antitumor activity data for the selected compounds.

Compound No.	Number Assigned by NCI	Sample Concentration x 10^{-4} (M)	Growth Percentage of Tumor Cells			Activity
			Growth Percentage of Tumor Cells			
			MCF7	NCI-H460	SF-268	
3b	723033	1.00	89	99	110	Inactive
3e	723032	1.00	5	22	78	Active
4a	722891	1.00	80	97	90	Inactive
4b	723216	1.00	121	105	118	Inactive
4c	722892	1.00	91	87	104	Inactive
4d	722898	1.00	69	100	98	Inactive
4e	723028	1.00	42	68	73	Inactive
5c	729904	1.00	2	30	62	Active
6a	721930	1.00	108	91	125	Inactive
6b	723035	1.00	97	97	88	Inactive
6c	723037	1.00	97	105	104	Inactive
6d	721931	1.00	68	57	62	Inactive
6e	723031	1.00	14	10	42	Active
7a	723025	1.00	77	81	93	Inactive
7b	723212	1.00	70	66	57	Inactive
7d	723027	1.00	83	96	100	Inactive
8e	723029	1.00	78	97	105	Inactive
9a	723026	1.00	67	65	76	Inactive
9b	723213	1.00	47	38	67	Inactive
9c	723216	1.00	39	6	18	Active
9e	723030	1.00	79	108	122	Inactive

The highest inhibition of the 3 tumor cell lines was observed for 4 compounds, 2 of which contain a p-tolyl group at the position 3 of the -1,2,4-triazol-5-one ring (**3e** and **6e**) while the other 2 contain a p-chlorobenzyl group at the same position (**5c** and **9c**).

Experimental

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian-Mercury 200 MHz spectrometer. The IR spectra were measured as potassium bromide pellets using a Perkin-Elmer 1600 series FTIR spectrophotometer. Combustion analysis was performed on a Carlo Erba 1106 elemental analyzer. All the chemicals were obtained from Fluka Chemie AG Buchs (Switzerland). Compounds **2a-e** were synthesized according to the published method[17].

General Method for Synthesis of 3-Alkyl-4-(1-naphthylidenamino)-4,5-dihydro-1H-1,2,4-triazol-5-ones (3)

The corresponding 3-alkyl-4-amino-4,5-dihydro-1H-1,2,4-triazol-5-one **2** (0.01 mol) was heated in an oil bath with 1-naphthaldehyde (1.36 mL, 0.01 mol) at 120-130 °C for 2 h. After cooling the mixture to room temperature, a solid appeared. This was recrystallized from an appropriate solvent to afford the desired compound.

(3a): Recrystallization from ethanol (yield: 81%). M.p. 193-194 °C. Analysis (% Calc/found): for $C_{14}H_{12}N_4O$ C: 66.66/65.87, H: 4.79/4.85, N: 22.21/21.98; IR (KBr) cm^{-1}: 3170 (ν_{NH}), 1697 ($\nu_{C=O}$), 1611 ($\nu_{C=N}$); ^{1}H NMR (DMSO-d_6) δ ppm 2.30 (s, 3H, CH_3), [ar H: 7.60-7.75 (m, 3H), 8.05-8.30 (m, 3H), 8.60 (d, 1H, J=7.8 Hz)], 10.25 (s, 1H, N=CH), 11.95 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ ppm 153.02, 150.80, 143.95, 132.90, 131.20, 129.95, 128.10, 128.08, 127.50, 127.45, 125.95, 124.95, 123.00, 10.50.

3b: Recrystallization from ethanol (yield: 91%). M.p. 180-181 °C. Analysis (% Calc/found): for $C_{20}H_{16}N_4O$ C: 73.16/74.01, H: 4.91/4.86, N: 17.06/16.54; IR (KBr) cm^{-1}: 3178 (ν_{NH}), 1707 ($\nu_{C=O}$), 1654 ($\nu_{C=N}$); ^{1}H NMR (DMSO-d_6) δ 4.18 (s, 2H, CH_2), [ar-H: 7.25-7.45 (m, 5H), 7.50-7.60 (m, 3H), 7.85-7.98 (m, 3H), 8.60 (d, 1H, J=7.9 Hz)], 10.50 (s, 1H, N=CH), 10.70 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ ppm 154.10, 152.05, 147.20, 135.00, 133.72, 132.00, 131.12, 129.24, 128.92, 128.74, 127.90, 127.46, 175.10, 126.27, 125.20, 123.97, 123.00, 32.00.

3c: Recrystallization from ethanol (yield: 88%). M.p. 206-207 °C. Analysis (% Calc/found): for $C_{20}H_{15}ClN_4O$ C: 66.21/66.69, H: 4.17/4.64, N: 15.44/15.32; IR (KBr) cm^{-1}: 3184 (ν_{NH}), 1703 ($\nu_{C=O}$), 1588 ($\nu_{C=N}$); ^{1}H NMR (DMSO-d_6) δ ppm 4.15 (s, 2H, CH_2), [ar-H: 7.38-7.45 (m, 4H), 7.60-7.75 (m, 3H), 7.95-8.18 (m, 3H), 8.45-8.55 (m, 1H)], 10.32 (s, 1H, N=CH), 12.15 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ ppm 153.47, 150.87, 145.26, 134.25, 132.94, 131.51, 130.93, 130.06, 129.75, 128.41, 128.12, 128.10, 127.94, 127.20, 125.96, 125.05, 123.26, 30.20.

3d: Recrystallization from ethyl acetate (yield: 76%). M.p. 214-215 °C. Analysis (% Calc/found): for $C_{19}H_{14}N_4O$ C: 72.60/72.24, H: 4.49/4.78, N: 17.82/16.94; IR (KBr) cm^{-1}: 3159 (ν_{NH}), 1718 ($\nu_{C=O}$), 1654 ($\nu_{C=N}$); ^{1}H NMR (DMSO-d_6) δ ppm [ar-H: 7.55-7.75 (m, 6H), 7.95-8.18 (m, 5H), 8.60-8.70 (m,1H)], 10.20 (s, 1H, N=CH), 12.60 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ ppm 155.80, 151.02, 144.30, 132.5, 131.60, 130.0, 129.62, 128.40, 128.18, 127.90, 127.75, 127.62, 127.12, 126.22, 125.90, 125.05, 123.23.

3e: Recrystallization from ethanol (yield: 78%). M.p. 204-205 °C. Analysis (% Calc/found): for $C_{20}H_{16}N_4O$ C: 73.16/73.68, H: 4.91/4.60, N: 17.06/16.67; IR (KBr) cm^{-1}: 3167 (ν_{NH}), 1720 ($\nu_{C=O}$), 1654 ($\nu_{C=N}$); ^{1}H NMR (DMSO-d_6) δ ppm 2.38 (s, CH_3), [ar-H: 7.35 (d, 2H, J=7.9Hz), 7.60-7.72 (m, 3H), 7.85 (d, 2H, J=8.0 Hz), 8.05-8.18 (m, 3H), 8.60-8.70 (m, 1H)], 10.30 (s, 1H, N=CH), 12.45 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ ppm 155.92, 150.92, 144.32, 139.42, 132,94, 131.60, 129.99, 128.56, 128.43, 128.19, 127.70, 127.46, 127.16, 125.98, 125.09, 123.40, 123.15.

General Method for Synthesis of 1-Acetyl-3-alkyl-4-(1-naphthylidenamino)-4,5-dihydro-1H-1,2,4-triazol-5-ones (4)

The corresponding compound **3** (0.01 mol) was refluxed with 10 mL of acetic anhydride for 2 h. Then the mixture was cooled to room temperature and after 40 mL ethanol was added it was refluxed for an additional 30 min. On cooling the mixture in a deep-freeze, a solid appeared. This crude product was recrystallized from an appropriate solvent to give the desired compound.

4a: Recrystallization from ethyl acetate-petroleum ether (1:2) (yield: 89%). M.p. 198-199 °C. Analysis (% Calc/found): for $C_{16}H_{14}N_4O_2$ C: 65.30/64.56, H: 4.80/4.75, N: 19.04/19.93; IR (KBr) cm^{-1}: 1731 ($\nu_{2C=O}$), 1617 ($\nu_{C=N}$); ^{1}H NMR ($CDCl_3$) δ ppm 2.44 (s, 3H, CH_3), 2.63 (s, 3H, -CO$\underline{CH_3}$), [ar-H: 8.50 (bs, 2H), 8.10-7.90 (m, 3H), 7.65-7.50 (m, 2H)]; 10.40 (s, 1H, N=CH); ^{13}C NMR ($CDCl_3$) δ ppm 166.32, 154.91, 148.61, 147.57, 133.56, 132.53, 131.16, 128.97, 128.56, 127.84, 127.80, 126.43, 125.24, 123.43, 23.63, 11.17.

4b: Recrystallization from benzene-petroleum ether (1:2) (yield: 89%). M.p. 198-199 °C. Analysis (% Calc/found): for $C_{22}H_{18}N_4O_2$ C: 71.34/72.02, H: 4.90/4.56, N: 15.13/14.46; IR (KBr) cm^{-1}: 1738 ($\nu_{2C=O}$), 1613 ($\nu_{C=N}$); ^{1}H NMR (DMSO-d_6) δ ppm 2.54 (s, 3H, -CO$\underline{CH_3}$), 4.18 (s, 2H, CH_2), [ar-H: 8.58-8.40 (m, 1H), 8.15-7.90 (m, 3H), 7.72-7.50 (m, 3H), 7.50-7.37 (m, 5H)]; 10.14 (s, 1H, N=CH); ^{13}C NMR (DMSO-d_6) δ ppm 165.98, 155.97, 147.94, 134.43, 133.26, 132.38, 130.06, 129.13, 128.79, 128.67, 128.41, 128.15, 127.91, 127.73, 126.83, 126.37, 125.33, 123.60, 31.03, 23.44.

4c: Recrystallization from benzene-petroleum ether (1:2) (yield: 90%). M.p. 200-201 °C. Analysis (% Calc/found): for $C_{22}H_{17}ClN_4O_2$ C: 65.27/65.94, H: 4.23/4.16, N: 13.84/13.46; IR (KBr) cm^{-1}: 1726 ($\nu_{2C=O}$), 1609 ($\nu_{C=N}$); ^{1}H NMR (DMSO-d_6) δ ppm 2.54 (s, 3H, -CO$\underline{CH_3}$), 4.21 (s, 2H, CH_2), [ar-H: 8.50-8.40 (m, 1H), 8.15 (bs, 1H), 8.10-8.00 (m, 2H), 7.70-7.60 (m, 3H), 7.48-7.40 (m, 4H)], 10.16 (s, 1H, N=CH); ^{13}C NMR (DMSO-d_6) δ ppm 165.98, 156.31, 148.00, 147.70, 133.52, 133.30, 132.50, 131.30, 130.64, 130.05, 129.30, 128.87, 128.37, 127.92, 127.80, 126.47, 125.43, 123.61, 31.41, 23.48.

4d: Recrystallization from benzene-petroleum ether (1:2) (yield: 92%). M.p. 156-157 °C. Analysis (% Calc/found): for $C_{21}H_{16}O_2N_4$ C: 70.78/71.20, H: 4.53/4.97, N: 15.72/16.20; IR (KBr) cm^{-1}: 1730 and 1725 ($\nu_{2C=O}$), 1603 ($\nu_{C=N}$); ^{1}H NMR (DMSO-d_6) δ ppm 2.63 (s, -CO$\underline{CH_3}$), [ar-H: 7.65-7.50 (m, 6H), 8.15-7.95 (m, 5H), 8.62-8.50 (m,1H)], 10.19 (s, N=CH) ; ^{13}C NMR (DMSO-d_6) δ ppm 166.10, 158.78, 148.11, 146.05, 133.27, 132.58, 132.20, 130.7, 128.86, 128.58, 128.52, 127.89, 127.73, 126.45, 125.45, 125.14, 123.46, 23.47.

4e: Recrystallization from benzene-petroleum ether (1:2) (yield: 85%). M.p. 170-171 °C. Analysis (% Calc/found): for $C_{22}H_{18}N_4O_2$ C: 71.24/71.26, H: 4.89/4.77, N: 15.11/15.29; IR (KBr) cm^{-1}: 1724 and 1722 ($\nu_{2C=O}$), 1586 ($\nu_{C=N}$); ^{1}H NMR (DMSO-d_6) δ ppm 2.38 (s, 3H, ar-$\underline{CH_3}$), 2.58 (s, 3H, -CO$\underline{CH_3}$), [ar-H: 8.60-8.50 (m, 1H), 8.20-7.95 (m, 3H), 7.90-7.80 (m, 2H), 7.70-7.60 (m, 3H), 7.40-7.30 (m, 2H)], 10.09 (s, 1H, N=CH); ^{13}C NMR ($CDCl_3$) δ ppm 165.69, 158.25, 147.77, 145.66, 140.88, 132.93, 132.20, 129.96, 128.72, 128.52, 128.27, 128.09, 127.56, 127.38, 126.11, 125.10, 123.05, 121.91, 23.12, 20.58.

General Method for Synthesis of 1,3-Alkyl-4-(1-naphthylidenamino)-4,5-dihydro-1H-1,2,4-triazol-5-ones (5)

To a solution of corresponding compound **3** (0.01 mol) an equivalent amount of sodium ethoxide was added, followed by refluxing for 2 h. After adding an equivalent amount of corresponding alkyl halide (benzyl chloride or methyl iodide) the mixture was refluxed for an additional 4 h. Then it was cooled to room temperature and a solid obtained. This crude product was recrystallized from an appropriate solvent.

5a: Recrys-tallization from ethanol-water (1:3) (yield: 70%). M.p. 133-134 °C. Analysis (% Calc/found): for $C_{27}H_{22}N_4O$ C: 77.49/77.92, H: 5.30/5.41, N: 13.39/13.01; IR (KBr) cm^{-1}: 1695 ($\nu_{C=O}$), 1602 ($\nu_{C=N}$); ^{1}H NMR (DMSO-d_6) δ 4.14 (s, 2H, -CH_2), 5.02 (s, 2H, -CH_2), [ar-H: 7.25-7.51(m, 10H), 7.75-7.91 (m, 5H), 8.50 (bs, 2H)], 10.53 (bs, 1H, -N=CH); ^{13}C NMR (DMSO-d_6) δ ppm 153.75, 150.52, 145.80, 136.07, 135.38, 131.91, 129.40, 128.80, 128.65, 128.27, 127.98, 127.81, 127.39, 127.05, 126.28, 125.26,

124.04, 49.19, 31.92.

5b: Recrystallization from ethanol (yield: 80%). M.p. 146-147 °C. Analysis (% Calc/found): for $C_{27}H_{21}ClN_4O$ C: 71.59/71.88, H: 4.67/4.41, N: 12.36/13.01; IR (KBr) cm^{-1}: 1707 ($\nu_{C=O}$), 1574 ($\nu_{C=N}$); ^{1}H NMR (DMSO-d_6) δ ppm 4.09 (s, 2H, -CH_2), 5.01 (s, 2H, -CH_2), [ar-H: 7.27-7.55(m, 10H), 7.90-7.93 (m, 4H), 8.48 (bs, 2H], 10.53 (bs, 1H, -N=CH); ^{13}C NMR (DMSO-d_6) δ ppm 153.91, 150.01, 145.21, 135.97, 133,76, 132.95, 132.03, 131.21, 130.16, 129.14, 128.77, 128.02, 123.73, 127.40, 126.32, 125.24, 123.28, 49.20, 31.28.

5c: Recrystallization from ethanol (yield: 80%). M.p. 144-145 °C. Analysis (% Calc/found): for $C_{27}H_{22}N_4O$ C: 77.49/77.64, H: 5.30/5.86, N: 13.39/13.25; IR (KBr) cm^{-1}: 1696 ($\nu_{C=O}$), 1582 ($\nu_{C=N}$); ^{1}H NMR (DMSO-d_6) δ ppm 2.42 (s, 3H, -CH_3), 5.11 (s, 2H, -CH_2), 5.01 (s, 2H, -CH_2), [ar-H: 7.25-7.58 (m, 10H), 7.86-8.05 (m, 4H), 8.61 (bs, 2H], 10.59 (bs, 1H, -N=CH); ^{13}C NMR (DMSO-d_6) δ ppm 155.14, 150.50, 144.80, 140.49, 136.03, 133.79, 132.04, 131.28, 129.20, 129.09, 128.80, 128.75, 128.57, 128.32, 127.99, 127.92, 127.44, 126.31, 125.33, 124.08, 49.20, 21.52.

5d: Recrystallization from ethanol (yield: 80%). M.p. 153-154 °C. Analysis (% Calc/found): for $C_{21}H_{17}ClN_4O$ C: 66.93/66.92, H: 4.55/4.47, N: 14.87/14.43; IR (KBr) cm^{-1}: 1703 ($\nu_{C=O}$), 1574 ($\nu_{C=N}$); ^{1}H NMR (DMSO-d_6) δ ppm 3.48 (s, 3H, -CH_3), 4.06 (s, 2H, -CH_2), [ar-H: 7.23-7.28(m, 4H), 7.46-7.54 (m, 3H), 7.83-7.93 (m, 3H), 8.44-8.47 (m, 1H], 10.51 (bs, 1H, -N=CH); ^{13}C NMR (DMSO-d_6) δ ppm 155.14, 150.35, 144.98, 133.72, 133.67, 132.94, 131.10, 130.21, 129.10, 128.76, 128.50, 127.80, 127.60, 126.27, 125.20, 123.81, 32.22, 22.08.

5e: Recrystallization from ethanol (yield: 80%). M.p. 150-151 °C. Analysis (% Calc/found): for $C_{21}H_{18}N_4O$ C: 73.66/73.95, H: 5.30/5.41, N: 16.36/16.23; IR (KBr) cm^{-1}: 1698 ($\nu_{C=O}$), 1602 ($\nu_{C=N}$); ^{1}H NMR (DMSO-d_6) δ ppm 3.35 (s, 3H, -CH_3), 2.40 (s, 3H, -CH_3), [ar-H: 7.20-7.50 (m, 7H), 8.05-8.20 (m, 4H)], 10.55 (bs, 1H, -N=CH); ^{13}C NMR (DMSO-d_6) δ ppm 155.14, 150.35, 144.98, 140.30, 135.03, 133.80, 132.04, 131.28, 129.20, 129.10, 128.90, 128.15, 128.08, 127.90, 127.80, 127.40, 127.30, 125.35, 124.15, 21.00, 21.90.

General Method for Synthesis of 3-Alkyl-4-(1-naphthylmethylamino)-4,5-dihydro-1H-1,2,4-triazol-5-ones (6)

A solution of corresponding compound **3** (0.01 mol) in 40 mL of diglime was treated with a solution of $NaBH_4$ (0.03 mol) in 30 mL of diglime. The mixture was refluxed for 8 h, and then poured into 500 mL of water. On cooling in a deep-freeze a solid appeared. This was recrystallized from an appropriate solvent to afford the desired compound.

6a: Recrystallization from ethyl acetate (yield: 89%). M.p. 239-240 °C. Analysis (% Calc/found): for $C_{14}H_{14}N_4O$ C: 66.13/65.92, H: 5.55/5.81, N: 22.03/22.01; IR (KBr) cm^{-1}: 3222, 3155 (ν_{2NH}), 1715 ($\nu_{C=O}$), 1590 ($\nu_{C=N}$); ^{1}H NMR (DMSO-d_6) δ ppm 1.42 (s, 3H, CH_3), 4.63 (bs, 2H, NH$\underline{CH_2}$), 6.04 (bs, 1H, N-NH), [ar-H: 7.32-7.41(m, 2H), 7.49-7.56 (m, 2H), 7.89-7.80 (m, 2H), 8.35 (d, 1H, J= 8.7 Hz)], 11.30 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ ppm 152.77, 144.12, 132.03, 131.03, 130.56, 127.11, 126.95, 126.86, 124.69, 124.31, 123.71, 122.82, 49.55, 8.93.

6b: Recrystallization from ethyl acetate (yield: 65%). M.p. 225-226 °C. Analysis (% Calc/found): for $C_{20}H_{18}N_4O$ C: 72.71/72.86, H: 5.49/5.78, N: 16.96/16.54; IR (KBr) cm^{-1}: 3254, 3154 (ν_{2NH}), 1707 ($\nu_{C=O}$), 1578 ($\nu_{C=N}$); ^{1}H NMR (DMSO-d_6) δ ppm 3.12 (s, 2H, CH_2), 4.51 (bs, 1H, NH$\underline{CH_2}$), 6.45 (bs, 1H, N-NH),

[ar-H: 6.85 (bs, 2H), 7.15-7.29(m, 3H), 7.40-7.60 (m, 4H), 7.89-8.22 (m, 2H), 8.25 (d, 1H, J=8.8Hz)], 11.55 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ ppm 154.02, 147.50, 135.70, 133.60, 132.76, 131.95, 128.58, 128.31, 126.60, 126.58, 126.33, 125.99, 125.46, 50.08, 30.02.

6c: Recrystallization from ethyl acetate (yield: 52%). M.p. 220-221 °C. Analysis (% Calc/found): for $C_{20}H_{17}ClN_4O$ C: 65.85/65.99, H: 4.70/4.78, N: 15.36/15.13; IR (KBr) cm^{-1}: 3156, 3123 (ν_{2NH}), 1706 ($\nu_{C=O}$), 1578 ($\nu_{C=N}$); ^{1}H NMR (DMSO-d_6) δ ppm 3.11 (s, 2H, CH_2), 4.53 (bs, 2H, NH$\underline{CH_2}$), 6.47 (bs, 1H, N-NH), [ar-H: 6.82 (d, 2H, J=6,4 Hz), 7.22 (t, 3H, J=4,6 Hz), 7.39-7.65 (m, 3H), 7.88-7.98 (m, 2H), 8.23 (d, 1H, J=8.2Hz)], 11.58 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ ppm 154.03, 147.27, 134.68, 133.51, 132.75, 131.75, 131.25, 130.37, 128.58, 128.34, 128.20, 126.34, 126.00, 125.45, 50.08, 9.51.

6d: Recrystallization from benzene (yield: 50%). M.p. 206-207 °C. Analysis (% Calc/found): for $C_{19}H_{16}N_4O$ C: 72.14/72.87, H: 5.10/4.92, N: 17.71/17.92; IR (KBr) cm^{-1}: 3230, 3149 (ν_{2NH}), 1725 ($\nu_{C=O}$), 1508 ($\nu_{C=N}$); ^{1}H NMR (DMSO-d_6) δ ppm 4.59 (bs, 2H, NH$\underline{CH_2}$), 5.41 (bs, 1H, N-NH), [ar-H: 7.15-7.42 (m, 7H), 7.68-7.73 (m, 4H,), 8.05-8.08 (m, 1H)], 11.65 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ ppm 154.80, 147.50, 133.30, 134.90, 131.30, 129.45, 128.82, 128.24, 127.74, 127.31, 126.10, 125.57, 125.00, 123.98, 52.16.

6e: Recrystallization from benzene (yield: 51%). M.p. 231-232 °C. Analysis (% Calc/found): for $C_{20}H_{18}N_4O$ C: 72.71/72.52, H: 5.49/5.85, N: 16.96/17.26; IR (KBr) cm^{-1}: 3225, 3158 (ν_{2NH}), 1706 ($\nu_{C=O}$), 1617 ($\nu_{C=N}$); ^{1}H NMR (DMSO-d_6) δ ppm 2.25 (s, 3H, CH_3), 4.69 (d, 2H, NH$\underline{CH_2}$, J=4.2 Hz), 6.55 (t, 1H, N-NH, J=4.6 Hz), [ar-H: 6.96 (d, 2H, J=9.8Hz), 7.27-7.31 (m, 1H), 7.32-7.50 (m, 5H), 7.75-7.85 (m, 2H), 8.07 (d, 1H, J=7.4Hz)], 11.95 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ ppm 154.45, 147.73, 139.36, 133.36, 132.32, 131.79, 128.43, 128.30, 127.87, 127.15, 126.11, 125.62, 125.20, 124.34, 123.75, 50.50, 21.00.

General Method for Synthesis of *N*-(3-Alkyl-4,5-dihydro-1H-1,2,4-triazol-5-on-4-yl)-*N*-(1-naphthylmethyl) acetamides (7), 1-Acetyl-3-aryl-4-(1-naphthylmethylamino)-4,5-dihydro-1H-1,2,4-triazol-5-ones (8) and *N*-(1-Acetyl-3-alkyl-4,5-dihydro-1H-1,2,4-triazol-5-on-4-yl)-*N*-1-naphthylmethyl-acetamides (9)

The corresponding compound **6** (0.01 mol) was refluxed with 10 mL of acetic anhydride for 2 h (for compounds **7** and **8**) (or 6 h for compounds **9**). The mixture was cooled to room temperature, 40 mL of ethanol added and then refluxed for an additional 30 min. After evaporating the mixture at 35-40 °C under reduced pressure, a solid appeared. This was recrystallized from an appropriate solvent to afford the desired compound.

7a: Recrystallization from benzene-petroleum ether (1:2) (yield: 49%). M.p. 195-196 °C. Analysis (% Calc/found): for $C_{16}H_{16}N_4O_2$ C: 64.85/65.49, H: 5.44/5.68, N: 18.90/18.57; IR (KBr) cm^{-1}: 3295 (ν_{NH}), 1713 and 1710 ($\nu_{2C=O}$), 1506 ($\nu_{C=N}$); ^{1}H NMR (DMSO-d_6) δ ppm 1.00 (s, 3H, CH_3), 1.91 (s, 3H, -$COCH_3$), 4.57 (d, 1H, NCH_2, J=14.2 Hz), 6.03 (d, 1H, NCH_2 J=14.2Hz), [ar-H: 7.38-7.05 (m, 1H), 7.70-7.38 (m, 3H), 7.90-8.10 (m, 2H), 8.15 (d, 1H, J=7.2 Hz)], 11.90 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ ppm 171.55, 150.91, 143.32, 132.80, 132.40, 131.05, 129.86, 128.80, 128.32, 126.51, 125.79, 124.94, 122.83, 46.96, 19.95, 9.05.

7b: Recrystallization from benzene-petroleum ether (1:2) (yield: 49%). M.p. 228-229 °C. Analysis (% Calc/found): for $C_{22}H_{20}N_4O_2$ C: 70.95/71.13, H: 5.41/5.53, N: 15.04/15.46; IR (KBr) cm^{-1}: 3291 (ν_{NH}), 1740 and 1675 ($\nu_{2C=O}$), 1589 ($\nu_{C=N}$); ^{1}H NMR (DMSO-d_6) δ ppm 1.33 (s, 3H, -$COCH_3$), 2.35 (d, 1H, CH_2, J=15.80 Hz), 2.80 (d, 1H, CH_2, J=15.80 Hz), 4.57 (d, 1H, N$\underline{CH_2}$, J=14.2 Hz), 5.92 (d, 1H, N$\underline{CH_2}$, J=14.2Hz), [ar-H: 6.65-6.60 (m, 2H), 7.25-7.10 (m, 3H,), 7.34-7.28 (m, 1H),7.50 (t, 1H, J= 7.6 Hz), 7.78-

7.68 (m, 2H), 8.15-7.95 (m, 2H), 8.20 (d, 1H, J= 7.6 Hz)], 12.03 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ ppm 172.08, 151.25, 145.68, 133.39, 133.33, 131.20, 130.34, 129.39, 129.24, 128.78, 128.49, 128.31, 127.00, 126.92, 126.29, 125.41, 123.40, 47.56, 29.82, 19.36.

7c: Recrystallization from benzene-petroleum ether (1:2) (yield: 51%). M.p. 202-203 °C. Analysis (% Calc/found): for $C_{22}H_{19}ClN_4O_2$ C: 64.95/65.47, H: 4.71/5.13, N: 13.77/13.46; IR (KBr) cm^{-1}: 3166 (ν_{NH}), 1745 and 1701 ($\nu_{2C=O}$), 1591 ($\nu_{C=N}$); ^{1}H NMR (DMSO-d_6) δ ppm 1.54 (s, 3H, -COCH$_3$), 2.10 (bs, 1H, CH$_2$), 2.58 (bs, 1H, CH$_2$), 4.55 (d, NCH$_2$, 1H, J=14.6 Hz), 5.92 (d, 1H, NCH$_2$ J=14.6 Hz), [ar-H: 6.50-6.65 (m, 2H), 7.40-7.20 (m, 3H), 7.75-7.40 (m, 3H), 8.10-7.92 (m, 2H), 8.18 (bs, 1H)], 12.05 (s, NH); ^{13}C NMR (DMSO-d_6) δ ppm 172.03, 151.21, 145.31, 133.30, 132.29, 131.35, 131.65, 130.40, 130.26, 129.37, 129.22, 128.79, 128.17, 126.98, 126.29, 125.42, 123.427, 47.72, 29.01, 19.92.

8d: Benzene-petroleum ether (1:2) (yield: 53%). M.p. 160-161 °C. Analysis (% Calc/found): for $C_{21}H_{18}N_4O_2$ C: 70.38/71.17, H: 5.06/5.48, N: 15.63/15.42; IR (KBr) cm^{-1}: 3258 (ν_{NH}), 1718 ($\nu_{2C=O}$), 1522 ($\nu_{C=N}$); ^{1}H NMR (DMSO-d_6) δ ppm 2.58 (s, 3H, -COCH$_3$), 4.62 (s, 2H, NCH$_2$), 6.82 (bs, 1H, N-NH) [ar-H: 7.10-7.25 (m, 2H), 7.55-7.30 (m, 5H), 7.61 (d, 2H, J=7.6 Hz), 7.84 (t, 2H, J=8.6 Hz), 8.02 (d, 1H, J= 7.6 Hz)]; ^{13}C NMR (DMSO-d_6) δ ppm 165.91, 150.90, 147.11, 132.75, 131.34, 131.11, 130.09, 128.02, 127.75, 127.39, 127.38, 125.48, 125.17, 124.64, 124.32, 123.58, 49.60, 20.50.

8e: Recrystallization from benzene-petroleum ether (1:2) (yield: 51%). M.p. 150-151 °C. Analysis (% Calc/found): for $C_{22}H_{20}N_4O_2$ C: 70.95/70.67, H: 5.41/5.09, N: 15.04/15.56; IR (KBr) cm^{-1}: 3252 (ν_{NH}), 1715 ($\nu_{2C=O}$), 1524 ($\nu_{C=N}$); ^{1}H NMR (DMSO-d_6) δ ppm 2.25 (s, 3H, CH$_3$), 2.58 (s, 3H, -COCH$_3$), 4.58 (s, 2H, NCH$_2$), 6.78 (bs, 1H, N-NH) [ar-H: 7.00 (d, 2H, J=8.2), 7.55-7.25 (m, 6H), 7.80 (t, 2H, J=7.4 Hz), 8.02 (d, 1H, J=7.4 Hz),]; ^{13}C NMR (DMSO-d_6) δ ppm 165.88, 150.91, 147.13, 132.78, 131.34, 131.10, 127.97, 127.86, 127.75, 127.43, 127.25, 125.48, 125.07, 124.62, 123.64, 121.43, 49.65, 23.17, 2 0.50.

(9a): Recrystallization from benzene-petroleum ether (1:2) to afford the desired compound (yield: 49%). M.p. 180-181 °C. Analysis (% Calc/found): for $C_{18}H_{18}N_4O_3$ C: 63.89/64.56, H: 5.36/5.07, N: 16.56/16.23; IR (KBr) cm^{-1}: 1747 ($\nu_{2C=O}$), 1690 ($\nu_{C=O}$), 1607 ($\nu_{C=N}$); ^{1}H NMR (DMSO-d_6) δ ppm 1.15 (s, 3H, CH$_3$), 2.00 (s, 3H, -COCH$_3$), 2.56 (s, 3H, -COCH$_3$), 4.60 (d, 1H, NCH$_2$, J=14.6 Hz), 5.94 (d, 1H, NCH$_2$ J=14.6 Hz), [ar-H: 7.52-7.38 (m, 2H), 7.68-7.52 (m, 2H), 8.10-7.93 (m, 2H), 8.20-8.10 (m, 1H)]; ^{13}C NMR (DMSO-d_6) δ ppm 171.35, 165.88, 155.66, 147.98, 132.81, 130.90, 129.66, 128.99, 128.35, 128.88, 126.54, 125.81, 124.96, 122.77, 46.91, 22.82, 19.96, 9.08.

9b: Recrystallization from benzene-petroleum ether (1:2) (yield: 46%). M.p. 159-160 °C. Analysis (% Calc/found): for $C_{24}H_{22}N_4O_3$ C: 69.56/68.83, H: 5.35/5.47, N: 13.52/12.82; IR (KBr) cm^{-1}: 1761, 1732 and 1690 ($\nu_{3C=O}$), 1604 ($\nu_{C=N}$); ^{1}H NMR (DMSO-d_6) δ ppm 1.40 (s, 3H, -COCH$_3$), 2.46 (s, 5H, -COCH$_3$+ CH$_2$), 2.92 (d, 1H, CH$_2$, J=15.4Hz), 4.60 (d, 1H, NCH$_2$, J=14.4 Hz), 5.91 (d, 1H, NCH$_2$, J=14.4 Hz), [ar-H: 6.50- 6.72 (m, 2H), 7.38-7.13 (m, 3H), 7.58-7.38 (m, 2H), 7.75-7.60 (m, 2H), 8.07 (d, 2H, J=6.4 Hz), 8.20 (d, 1H, J=8.0 Hz)]; ^{13}C NMR (DMSO-d_6) δ ppm 171.60, 165.48, 155.66, 147.25, 133.00, 131.88, 130.94, 129.87, 129.16, 128.75, 128.49, 128.36, 128.08, 126.99, 126.62, 126.02, 125.12, 123.03, 47.41, 29.03, 22.93, 19.95.

9c: Recrystallization from benzene-petroleum ether (1:2) to afford the desired compound (yield: 49%). M.p. 158-159 °C. Analysis (% Calc/found): for $C_{24}H_{21}ClN_4O_3$ C: 64.22/65.07, H: 4.72/4.05, N: 12.48/13.09; IR (KBr) cm^{-1}: 1788, 1700 and 1696 ($\nu_{3C=O}$), 1565 ($\nu_{C=N}$); ^{1}H NMR (DMSO-d_6) δ ppm 1.63 (s, 3H, -COCH$_3$), 2.50 (bs, 5H, -COCH$_3$+ CH$_2$), 2.60 (d, 1H, CH$_2$, J=15.4Hz), 4.65 (d, 1H, NCH$_2$,

J=14.4 Hz), 5.93 (d, 1H, NCH$_2$ J=14.4 Hz), [ar-H: 6.50-6.90 (m, 2H), 7.48-7.10 (m, 2H), 7.62-7.48 (m, 2H), 7.90-7.62 (m, 2H), 8.18-7.90 (m, 2H), 8.30-8.18 (m, 1H)]; ^{13}C NMR (DMSO-d$_6$) δ ppm 171.91, 165.71, 148.30, 147.32, 133.30, 132.01, 131.14, 131.12, 130.57, 130.11, 129.46, 129.32, 128.80, 128.25, 126.98, 126.30, 125.42, 123.23, 47.71, 28.96, 23.20. 19.69.

9d: Recrystallization from benzene-petroleum ether (1:2) (yield: 45%). M.p. 160-161 °C. Analysis (% Calc/found): for $C_{23}H_{20}N_4O_3$ C: 68.99/69.34, H: 5.03/5.66, N: 13.99/13.36; IR (KBr) cm^{-1}: 1760, 1744 and 1704 ($\nu_{3C=O}$), 1565 ($\nu_{C=N}$);); ^{1}H NMR (DMSO-d$_6$) δ ppm 2.24 (s, 3H, -COCH$_3$), 2.60 (s, 3H, -COCH$_3$), 4.65 (d, 1H, NCH$_2$, J=14.2 Hz), 5.90 (d, 1H, NCH$_2$, J=14.2 Hz), [ar-H: 6.88-6.69 (m, 4H), 6.95-7.10 (m, 1H), 7.25-7.20 (m, 2H), 7.45-7.40 (m, 2H), 7.60-7.70 (m, 2H), 7.84 (d, 1H, J= 7.4 Hz)]; ^{13}C NMR (DMSO-d$_6$) δ ppm 172.46, 166.08, 148.93, 145.75, 132.93, 131.26, 130.34, 129.43, 129.28, 128.84, 128.31, 127.62, 126.32, 125.97, 125.57, 124.70, 123.10, 122.46, 47.94, 23.34, 20.71.

9e: Recrystallization from benzene-petroleum ether (1:2) to afford the desired compound (yield: 45%). M.p. 172-173 °C. Analysis (% Calc/found): for $C_{24}H_{22}N_4O_3$C: 69.55/69.29, H: 5.35/5.49, N: 13.52/12.74; IR (KBr) cm^{-1}: 1748 ($\nu_{3C=O}$), 1595 ($\nu_{C=N}$); ^{1}H NMR (DMSO-d$_6$) δ ppm 2.07 (s, 3H, -CH$_3$), 2.23 (s, 3H, -COCH$_3$), 2.55 (s, 3H, -COCH$_3$), 4.40 (d, 1H, NCH$_2$, J=14.2 Hz), 5.90 (d, 1H, NCH$_2$, J=14.2 Hz), [ar-H: 6.70-6.55 (m, 2H), 6.90-7.10 (m, 2H), 7.35-7.20 (m, 2H), 7.55-7.40 (m, 2H), 7.60-7.70 (m, 2H), 7.70-7.90 (m, 1H)]; ^{13}C NMR (DMSO-d$_6$) δ ppm 172.04, 165.60, 148.55, 145.59, 139.96, 132.66, 130.82, 129.07, 128.86, 128.43, 127.96, 127.84, 125.93, 125.48, 124.98, 124.26, 122.81, 119.23, 47.56, 22.97, 20.41, 20.35.

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