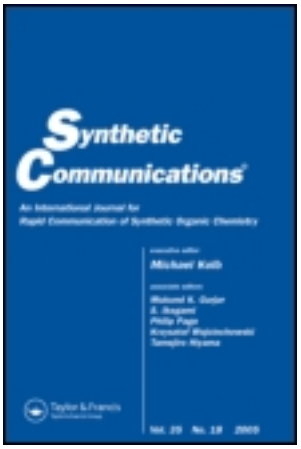

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New Synthetic Approaches to Substituted Pyridine-2-(1H)-ones Clubbed with Substituted Aryl Diazo Substituents

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NEW SYNTHETIC APPROACHES TO SUBSTITUTED PYRIDINE-2-(1*H*)-ONES CLUBBED WITH SUBSTITUTED ARYL DIAZO SUBSTITUENTS

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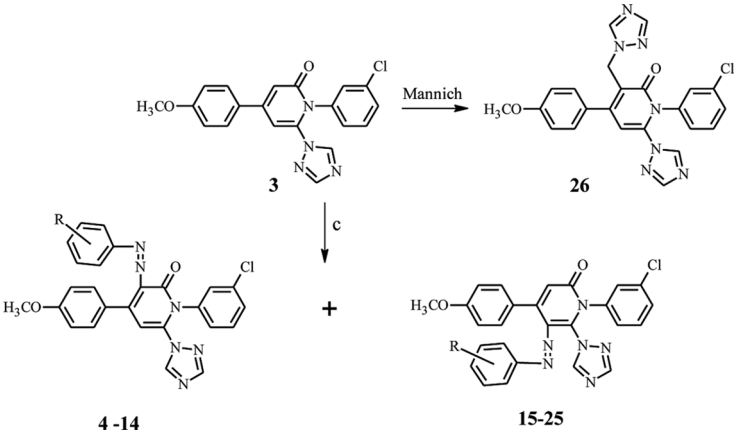
GRAPHICAL ABSTRACT



Abstract *6-Triazolylpyridone derivatives were synthesized by coupling 4-(4-methoxyphenyl)-6-(1*H*-1,2,4-triazol-1-yl)-1-(3-chlorophenyl)pyridin-2(1*H*)-one with substituted benzenediazonium chlorides in the form of two isomers, which were separated by column chromatography and characterized by ^{1}H and ^{13}C NMR. Following the green approach, solvents were avoided as much as possible. The reaction monitoring was carried out by gas chromatography as well as thin-layer chromatography. The scope and limitation of the method are discussed. The structures of all the compounds have been assigned unambiguously on the basis of elemental analysis, infrared, and NMR spectral data and have been evaluated for antimicrobial and antitubercular activities.*

Keywords Aryldiazonium chlorides; β-aryl glutaconic acid; microbial activity; 2-pyridones; 1,2,4-triazole

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INTRODUCTION

The heterocyclic skeleton containing nitrogen atoms is the basis of many essential pharmaceuticals and of many physiologically active natural products. 2-Pyridone is a nitrogen containing synthetically designed scaffold with a broad spectrum of biological activities. Its derivatives have been claimed to be nonnucleoside HIV type I specific reserve transcriptase inhibitors[1] and anti-inflammatory agents.[2] The 2-pyridone moiety frequently found in a variety of interesting compounds has received remarkable attention because of its promising features as a key scaffold and in privileged building blocks.[3] A wide range of biological activities has been observed in compounds possessing a 2-pyridone motif, including antitumor,[4] antifungal,[5] antibacterial,[6] anti-inflammatory,[7] antiviral[8] and antithrombotic properties.[9] (20S)-Camptothecin is a well-known anticancer natural product that was first isolated from *Camptotheca acuminate* in 1966.[10,11] 2-Pyridones act as potent bacterial DNA gyrase inhibitors,[12] active cytotoxic agents as determined in the in vitro L1210 screen,[13] and potent inhibitors of BaENR.[14] 3-Acetoxy-2-pyridone had reproducible activity against murine P-388 lymphocytic leukemia.[15]

Table 1. Characterization data of compounds **1–26**

				C (%) #		N (%) #		H (%)	
Comp. no.	R	M.R.	Mol. formula	Found	Calcd.	Found	Calcd.	Found	Calcd.
1	–	206–208	$C_{18}H_{14}NO_3Cl$	66.05	66.04	4.27	4.28	4.31	4.31
2	–	179–181	$C_{18}H_{13}NO_2Cl_2$	62.42	62.42	4.07	4.05	4.07	4.08
3	–	170–172	$C_{20}H_{15}N_4O_2Cl$	63.49	63.48	14.78	14.81	4.02	4.00
4	H	172–174	$C_{26}H_{19}N_6O_2Cl$	64.69	64.67	17.39	17.40	3.97	3.93
5	o-Cl	184–186	$C_{26}H_{18}N_6O_2Cl_2$	60.35	60.36	16.24	16.24	3.51	3.56
6	m-Cl	189–191	$C_{26}H_{18}N_6O_2Cl_2$	60.38	60.36	16.25	16.24	3.51	3.54
7	p-Cl	196–198	$C_{26}H_{18}N_6O_2Cl_2$	60.36	60.36	16.25	16.24	3.51	3.55
8	o-CH_3	161–163	$C_{27}H_{21}N_6O_2Cl$	65.25	65.26	16.91	16.91	4.26	4.24
9	m-CH_3	165–167	$C_{27}H_{21}N_6O_2Cl$	65.27	65.26	16.90	16.91	4.26	4.21
10	p-CH_3	157–159	$C_{27}H_{21}N_6O_2Cl$	65.27	65.26	16.91	16.91	4.26	4.20
11	o-NO_2	171–173	$C_{26}H_{18}N_7O_4Cl$	59.13	59.15	18.58	18.57	3.44	3.47
12	m-NO_2	199–201	$C_{26}H_{18}N_7O_4Cl$	59.13	59.15	18.58	18.57	3.44	3.44
13	p-NO_2	177–179	$C_{26}H_{18}N_7O_4Cl$	59.17	59.15	18.56	18.57	3.44	3.49
14	o-OCH_3	167–169	$C_{27}H_{21}N_6O_3Cl$	63.33	63.22	16.39	16.38	3.97	3.93
15	H	152–154	$C_{26}H_{19}N_6O_2Cl$	64.68	64.67	17.39	17.40	3.97	3.94
16	o-Cl	194–196	$C_{26}H_{18}N_6O_2Cl_2$	60.34	60.36	16.27	16.24	3.51	3.55
17	m-Cl	187–189	$C_{26}H_{18}N_6O_2Cl_2$	60.37	60.36	16.24	16.24	3.51	3.52
18	p-Cl	209–211	$C_{26}H_{18}N_6O_2Cl_2$	60.36	60.36	16.25	16.24	3.51	3.57
19	o-CH_3	155–157	$C_{27}H_{21}N_6O_2Cl$	65.27	65.26	16.90	16.91	4.26	4.29
20	m-CH_3	163–165	$C_{27}H_{21}N_6O_2Cl$	65.26	65.26	16.92	16.91	4.26	4.31
21	p-CH_3	157–159	$C_{27}H_{21}N_6O_2Cl$	65.24	65.26	16.94	16.91	4.26	4.25
22	o-NO_2	161–163	$C_{26}H_{18}N_7O_4Cl$	59.16	59.15	18.55	18.57	3.44	3.49
23	m-NO_2	172–174	$C_{26}H_{18}N_7O_4Cl$	59.15	59.15	18.58	18.57	3.44	3.45
24	p-NO_2	158–160	$C_{26}H_{18}N_7O_4Cl$	59.16	59.15	18.55	18.57	3.44	3.48
25	o-OCH_3	177–179	$C_{27}H_{21}N_6O_3Cl$	63.23	63.22	16.38	16.38	4.11	4.13
26	–	182–184	$C_{23}H_{18}N_7O_2Cl$	60.07	60.07	21.33	21.32	3.98	3.95

Satisfactory C, N, and H analysis were obtained for all the compounds.

Table 2. Antimicrobial and antifungal activity data of **1–26**

	Minimal bactericidal concentration μg/mL						
	Gram negative		Gram positive		Minimal fungicidal concentration μg/Ml		
Comp. no.	*E. coli*	*P. aeruginosa*	*S. aureus*	*S. pyogenes*	*C. albicans*	*A. niger*	*A. clavatus*
1	200	250	250	250	1000	1000	1000
2	200	200	100	100	500	500	500
3	100	100	200	200	500	500	500
4	62.5	100	200	250	200	500	500
5	100	100	250	250	500	250	250
6	500	500	100	100	250	500	500
7	500	500	500	500	1000	1000	1000
8	200	500	500	500	1000	1000	1000
9	250	250	150	200	500	500	500
10	200	200	200	200	250	250	250
11	100	200	100	100	500	500	500
12	200	200	250	250	500	500	500
13	62.5	100	200	250	200	500	500
14	500	500	200	100	250	500	500
15	250	500	250	250	500	250	500
16	250	100	250	250	250	500	250
17	500	500	100	100	250	500	500
18	100	500	500	500	100	500	500
19	200	500	500	500	250	1000	1000
20	250	250	250	200	500	500	500
21	200	250	200	200	250	250	500
22	200	200	100	100	250	500	250
23	250	200	250	250	500	500	500
24	250	250	500	250	500	>1000	500
25	250	200	250	250	500	500	500
26	250	100	250	250	250	500	250
Ampicillin	100	100	250	100	–	–	–
Ciprofloxacin	25	25	50	50	–	–	–
Greseofulvin	–	–	–	–	500	100	100

Girardet has synthesized and reported a new series of 1,2,4-triazoles tested against several nonnucleoside reverse transcriptase inhibitor (NNRTI)–resistant HIV-I isolutes.[16] and demonstrated its activity against malarial and bronchospasm. It has activity as coronary, vasodilator, antihypertensive, antidepressive,[17] leishmanicidic, antibiotic, adenosine antagonist, immunosuppressant, antitumor, fungicidal,

Table 3. Anti-tuberculosis activity of selected compounds

Comp. No.	MIC values (μg /mL) of M. tuberculosis H37Rv	% Inhibition
2	250	99
10	250	98
11	12.5	98
12	125	99
Rifampicin	40	98

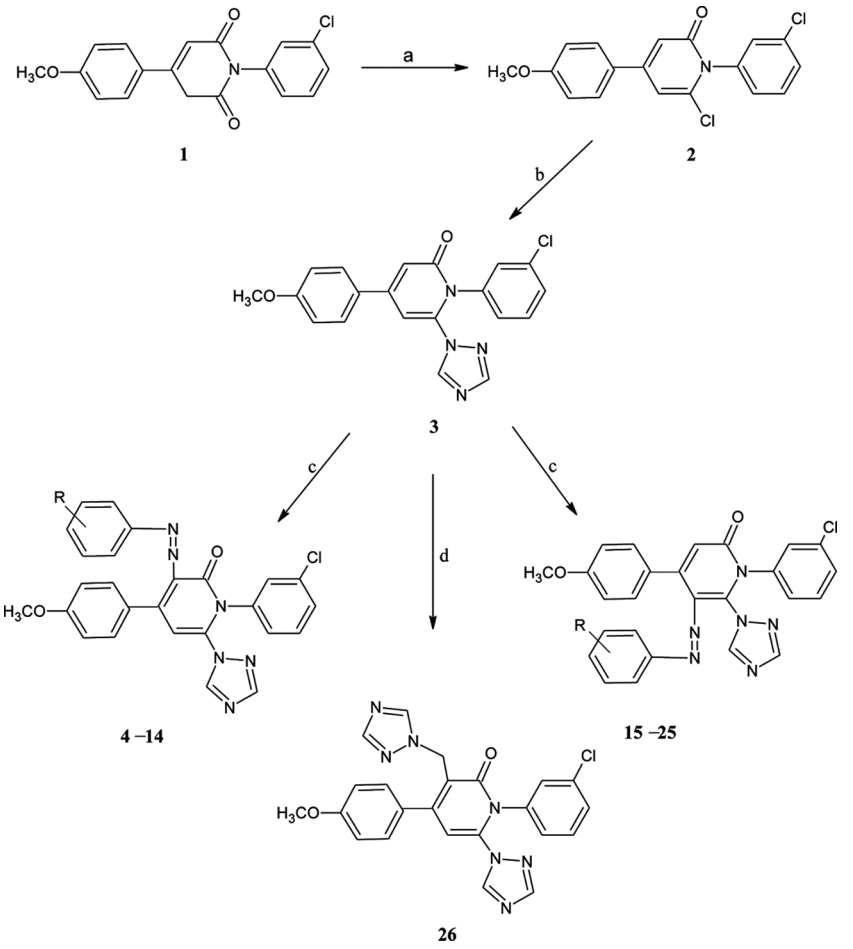
xanthine oxidase inhibitor, and anticonvulsant[18] agents. Triazoles possess significant antifungal[19] and antiviral properties.[20] They are strong cemtral nervous system depressant and mild to moderate anti-inflammatory, hypocholesterimic, hypertensive, antimicrobial, and antibactacterial agents.[20–22] Amino acid ester functional pyrazolyl compounds have also been reported as antifungal agents.[23]

A number of synthetic methods for the preparation of 2-pyridones have been reported, and some of them have been used to obtain milrinone analogs with improved activity.[24] 2-Pyridones were synthesized from cyanoacetamides and enecarbonyl compounds via chemo- and regioselective[25] tandem Blaise reaction of nitriles with propiolates,[26] from fluoroquinolones,[27] and from annulation of ketones and esters.[28] The most straightforward and versatile approach to *N*-aryl pyridine-2-ones is the coupling reaction of pyridin-2-(1*H*)-one with highly electron-deficient aryl halides through nucleophilic substitution.[29] Recently, *N*-arylation of pyridine-2(1*H*)-ones with pentavalent organobismuth reagents to give pyridine-2-ones under copper-free conditions was also reported.[30] A recent approach to the synthesis of *N*-aryl substituted pyridones from β-aryl glutaconic acid using aromatic amine prompted us to present our results in this field.

Keeping applications of 2-pyridones and 1,2,4-triazole in mind and in continuation of our earlier work we have decided to synthesize 6-triazolyl-2(1*H*)-pyridinones from β-aryl glutaconic acid.[31] Substituted 2-pyridones have been prepared by nucleophilic substitution reactions using heterocyclic groups suca as triazolyl under basic conditions. These substituted pyridinones have two nucleophilic positions, 3 and 5.[32] To check the nucleophilicity of these positions they were subjected to electrophilic substitutions and then characterized by spectral data.[33,34] The purpose of the present work was to observe the variation in antimicrobial properties after structural changes.

RESULTS AND DISCUSSION

In continuation of our research on the synthesis of heterocyclic molecules using diazotization, coupling, and Mannich reaction.[31] herein we report the studies of a facile synthesis of the substituted 6-(1*H*-1,2,4-triazol-1-yl)-2(1*H*)-pyridinones via azo coupling using column chromatography. The replacement of the carbonyl by chloro group was confirmed by ^{13}C NMR.; lower-field resonance at δ 141.32 ppm was attributed to the chloro group at C-6 in compound **2** in place of the carbonyl at 169.82 ppm in compound **1**. Azo coupling of diazonium salts with compound **2** was confirmed by infrared(IR) spectra, and a sharp band was observed near 1575 cm^{-1} due to the –N=N– group. Most excitingly, two azo-coupled products were obtained, which were separated by column chromatography over activated silica gel using ethyl acetate–chloroform (70:30) as mobile phase. Two compounds were characterized as 6-substituted-amino-4-(4-methoxyphenyl)-1-(3-chlorophenyl)-3-(arylazo) pyridin-2(1*H*)-ones **4–14** and their 5-(arylazo) isomers **15–25** (Scheme 1), on the basis of spectral data.[35] In the ^{1}H NMR spectrum of 4-(4-methoxyphenyl)-1-(3-chlorophenyl)-3-(4-chlorophenylazo)-6-triazolyl-2(1*H*)-pyridinone **7**, a proton singlet was observed at 5.9 ppm due to a proton at the C-5 position, whereas for 4-(4-methoxyphenyl)-1-(4-chlorophenylazo)-5-(4-chlorophenylazo)-6-triazolyl-2(1*H*)-pyridinone **18**, a proton singlet was observed at 6.6 ppm due to a proton at the C-3 position.



Scheme 1. R=H, o-OCH_3, o, m, p - Cl, CH_3, NO_2 Reagents and conditions: (a) $POCl_3$, reflux (b) 1, 2, 4-triazole, DMF, $NaNo_2$, reflux (c) coupling with substituted aryldiazonium chlorides (d) mannich reaction.

After having checked the nucleophilicity at positions 3 and 5, the Mannich reaction was also carried out on compounds **3** using a secondary amine as 1,2,4-triazole. The compound that resulted, **26**, proves that position 3 is more nucleophilic than 5.[24]

Limitation

In our present study we synthesized 6-triazolyl-2(1*H*)-pyridinone from β-aryl glutaconic acid, which was synthesized from citric acid, but poor yield of β-aryl glutaconic acid is a major limitation of the method.

Microbial and Antitubercular Studies

The experimental testing of antibacterial studies[30,36,37] did not show comparable results with standard drug cefoperazone against the two Gram-positive (*S. aureus*

and *B. subtilius*) and two Gram-negative (*E. coli* and *P. vulgarius*) bacteria, and an antifungal study was done for three fungal species, *C. albicans, A. niger,* and *A. clavatus* and compared with the standard drug greseofulvin. All synthesized compounds showed moderate to good activity except **6, 13, 19**, and **24**, which showed poor activity. The compounds **2, 4, 5, 6, 7, 10, 11, 13, 18, 21, 22**, and **26** showed good activity The active ones, **2, 10, 11**, and **12**, were further tested in a secondary screening against *Mycobacterium tuberculosis* $H_{37}Rv$ in Lowenstein–Jensen (LJ) medium (conventional method) and displayed good antitubercular activity when compared with the standard drug rifampicin at 40 μg/ml.

CONCLUSION

In summary, we have demonstrated an efficient method for the synthesis of substituted 6-(4*H*-1,2,4-triazol-4-yl)-2(1*H*)-pyridinones via azo coupling in the form of two isomers, which were separated by column chromatography. The reactions were clean, and the products were obtained in good yields without the formation of any side products. The synthesized compounds showed moderate to good antimicrobial and antitubercular activity.

EXPERIMENTAL

Melting points were determined by means of the open capillary method and are uncorrected. IR spectra (KBr pellets) were recorded on a Thermo Scientific spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker Avance II 400-MHz instrument using tetramethylsilane (TMS) as internal standard. Elemental analyses were performed by means of a Heraeus CHN rapid analyzer; their results agreed satisfactorily with the calculated values. All reactions were monitored by thin-layer chromatography (TLC) on aluminum sheets (silica gel 60-F_{254}, E. Merck). Compounds were visualized by ultraviolet (UV) light or by dipping the solution containg 5% $KMnO_4$ solution. Column chromatography was carried out using silica gel (100–200 mesh).

4-(4-Methoxyphenyl)-1-(3-chlorophenyl)pyridine-2,6-(1*H*,5*H*)-dione 1

A mixture of 3-(4-methoxyphenyl)-2,3-ene-pentanedioic acid (2.4 g, 0.1 mol) and *m*-chloroaniline (11.2 g, 0.1 mol) was slowly heated in an oil bath at 220 °C for 1 hr. It was cooled to room temperature and crystallized from absolute alcohol to obtain a pale yellow crystalline product **2**, yield 23.0 g (78.5%); IR (KBr, cm^{-1}): 3020 (C-H, C-H), 1620 (C=C), 1240 (C-O-C), 1675 & 1600 (C=O), 1510 (-N-Ph); ^{1}H NMR (400 MHz, $CDCl_3$): 2.57 (s, 2H, -CH_2), 3.88 (s, 3H, -OCH_3), 6.64 (s, 1H, C_3-H pyridone), 6.74–7.92 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 36.4, 63.8, 115.1, 121.3, 124.2, 127.0, 127.5, 128.1, 129.1, 129.6, 134.8, 135.5, 151.7, 161.6, 165.6, 169.8; MS: $m/z = 327.77$ (M^+).

6-Chloro-4-(4-methoxyphenyl)-1-(3-chlorophenyl)-pyridin-2(1*H*)-one 2

A mixture of **1** (3.28 g, 0.01 mol) and phosphorous oxychloride (9 ml) was refluxed for 1 h and poured onto crushed ice, when **2** was obtained as solid. It was

crystallized from ethanol, yield 2.5 g (79.26%); IR (KBr): 3000 (C-H), 3030 (C-H), 1620 (C=C), 1260 (C-O-C), 1700 (C=O), 1520 (-N-Ph), 1040 (Ar-Cl); ^{1}H NMR (400 MHz, $CDCl_3$): 3.64 (s, 3H, -OCH_3), 5.97 (s, 1H, C_5-H pyridone), 6.64 (s, 1H, C_3-H pyridone), 6.69–7.52 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 63.7, 106.0, 114.2, 115.0, 120.6, 128.1, 128.5, 129.2, 129.5, 131.8, 137.4, 138.1, 141.3, 151.3, 160.6, 163.6; MS: $m/z = 346.21$ (M^+), 348.21 ($M^+ + 2$), 350.21 ($M^+ + 4$).

4-(4-Methoxyphenyl)-6-(1*H*-1,2,4-triazol-1-yl)-1-(3-chlorophenyl) pyridin-2(1*H*)-one 3

A mixture of **2** (3.47 g, 0.01 mol) and 1,2,4-triazole(0.69 g, 0.01 mol) was refluxed for 12 h in dimethylformamide (DMF) and thereafter the reaction mass was poured in acidic crushed ice and then resultant solid was filtered, washed with water and crystallized from acetone to get **3**. Yield 2.7 g (69.40%); IR (KBr): (1665 > C=O); ^{1}H NMR (400 MHz, $CDCl_3$): 3.67 (s, 3H, -OCH_3), 5.90 (s, 1H, C_5-H pyridone), 6.68 (s, 1H, C_3-H pyridone), 6.69–7.52 (m, 8H, Ar-H), 8.39 (s, 2H, C_3-H & C_5-H triaz.); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.9, 84.6, 114.3, 118.9, 119.7, 121.1, 122.0, 124.5, 129.8, 129.8, 130.4, 134.2, 134.5, 138.8, 139.0, 146.0, 151.0,160.7, 160.7; MS: $m/z = 378.82$ (M^+), ($M^+ + 2$).

4-(4-Methoxyphenyl)-1-(3-chlorophenyl)-3/5-(substitutedphenylazo)-6-(1*H*-1,2,4-triazol-1-yl)-pyridin-2(1*H*)-one 4–14 and 15–25

A precooled (0–5 °C) solution of benzenediazonium chloride [prepared by diazotizing substituted aniline (0.01 mol) in 6 ml of 1:1 HCl with $NaNO_2$ (0.69 g, 0.01 mol) in 10 ml water] was added to a precooled (0–5 °C) solution of **3** (0.01 mol) in 100 ml acetone. The reaction mixture was poured in 200 ml water and then basified with diluted NaOH. The colored product was filtered, washed with water, and dried. Two azo-coupled products were obtained, which were separated by column chromatography over activated silica gel using ethyl acetate–chloroform (70:30) as mobile phase.

4-(4-Methoxyphenyl)-1-(3-chlorophenyl)-3-(phenylazo)-6-(1*H*-1,2,4-triazol-1-yl)-pyridin-2(1*H*)-one 4 ($C_{26}H_{19}N_6O_2Cl$). IR (KBr): 1260 (C-O-C), 1650 (>C=O), 1570 (-N=N-), 1435 (C-N), 3010 & 2920 (C-H str); ^{1}H NMR (400 MHz, $CDCl_3$): 3.9–4.0 (q, 3H, OCH_3), 5.9 (s, 1H, C_5-H), 7.0–7.7 (m, 13H, Ar-H), 8.1–8.2 (s, 2H, tr-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.9, 84.6, 114.3, 114.5, 119.7, 121.1, 122.1, 124.0, 124.5, 128.7, 128.8, 128.8, 128.8, 128.8, 128.8, 128.9, 128.9, 130.4, 134.2, 134.5, 139.0, 146.0, 146.5, 151.1, 158.4 160.7; MS: $m/z = 428.13$ (M^+), 430.13 ($M^+ + 2$).

4-(4-Methoxyphenyl)-1-(3-chlorophenyl)-3-(2-chlorophenylazo)-6-(1*H*-1,2,4-triazol-1-yl)-pyridin-2(1*H*)-one 5 ($C_{26}H_{18}N_6O_2Cl_2$). IR (KBr): 1250 (C-O-C), 1660 (>C=O), 1575 (-N=N-), 1425 (C-N), 3020 & 2910 (C-H str); ^{1}H NMR (400 MHz, $CDCl_3$): 3.9–nbsp;4.0 (q, 3H, OCH_3), 6.0 (s, 1H, C_5-H), 7.0–7.7 (m, 12H, Ar-H), 8.1–8.2 (s, 2H, tr-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.9, 84.6, 114.3, 114.3, 119.7, 121.1, 122.0, 124.1, 124.5, 126.9, 128.9, 129.0, 129.8, 129.8,

130.2, 130.2, 130.4, 134.2, 134.3, 134.5, 139, 146.2, 146.5, 151.0, 158.4, 160.7; MS: $m/z = 516.09$ (M^+), 518.09 ($M^+ + 2$), 520.09 ($M^+ + 4$).

4-(4-Methoxyphenyl)-1-(3-chlorophenyl)-3-(3-chlorophenylazo)-6-(1*H*-1,2,4-triazol-1-yl)-pyridin-2(1*H*)-one 6 ($C_{26}H_{18}N_6O_2Cl_2$). IR (KBr): 1250 (C-O-C), 1670 (>C=O), 1575 (-N=N-), 1420 (C-N), 3020 & 2915 (C-H str); ^{1}H NMR (400 MHz, $CDCl_3$): 3.9–4.0 (q, 3H, OCH_3), 6.0 (s, 1H, C_5-H), 7.0–7.6 (m, 12H, Ar-H), 8.1–8.2 (s, 2H, tr-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.9, 84.6, 114.3, 114.4, 119.7, 121.1, 122.0, 123.9, 124.5, 126.9, 128.9, 129.1, 129.8, 129.8, 130.1, 130.2, 130.4, 134.2, 134.3, 134.5, 139.2, 146.1, 146.5, 151.0, 158.4, 160.7; MS: $m/z = 516.09$ (M^+), 518.09 ($M^+ + 2$), 520.09 ($M^+ + 4$).

4-(4-Methoxyphenyl)-1-(3-chlorophenyl)-3-(4-chlorophenylazo)-6-(1*H*-1,2,4-triazol-1-yl)-pyridin-2(1*H*)-one 7 ($C_{26}H_{18}N_6O_2Cl_2$). IR (KBr): 3068 (Ar C-H), 2976, 2929 (C-H), 1659 (C=N), 1604 (C=C), 1249 (C-O-C), 1714 (C=O), 1560 (-N=N-), 1511 (N -Ph); ^{1}H NMR (400 MHz, $CDCl_3$): 4.1 (s, 3H, -OCH_3), 5.92 (s, 1H, C_5-H pyridone), 6.66–7.52 (m, 12H, Ar-H), 8.39 (s, 2H, C_3-H & C_5-H triaz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 63.9, 88.7, 105.9, 114.2, 115.0, 199.3, 120.6, 122.9, 123.8, 128.1, 128.3, 128.5, 129.2, 129.5, 131.8, 134.5, 137.4, 138.1, 141.3, 145.9, 151.3, 154.9, 160.6, 163.6; MS: $m/z = 516.09$ (M^+), 518.09 ($M^+ + 2$), 520.09 ($M^+ + 4$).

4-(4-Methoxyphenyl)-1-(3-chlorophenyl)-3-(2-methylphenylazo)-6-(1*H*-1,2,4-triazol-1-yl)-pyridin-2(1*H*)-one 8 ($C_{27}H_{21}N_6O_2Cl$). IR (KBr): 1255 (C-O-C), 1655 (>C=O), 1570 (-N=N-), 1435 (C-N), 3030 & 2910 (C-H str); ^{1}H NMR (400 MHz, $CDCl_3$): 2.3 (s, 3H, CH_3), 3.9–4.1 (q, 3H, OCH_3), 5.9 (s, 1H, C_5-H), 7.0–7.7 (m, 12H, Ar-H), 8.1–8.2 (s, 2H, tr-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.2, 55.9, 84.6, 114.3, 114.3, 119.7, 121.1, 122.0, 124.0, 124.5, 125.8, 128.1, 128.7, 128.7, 129.1, 129.8, 129.8, 130.4, 134.2, 134.5, 137.1, 139.0, 146.2, 146.5, 151.0, 158.4, 160.7; MS: $m/z = 496.14$ (M^+), 498.14 ($M^+ + 2$).

4-(4-Methoxyphenyl)-1-(3-chlorophenyl)-3-(3-methylphenylazo)-6-(1*H*-1,2,4-triazol-1-yl)-pyridin-2(1*H*)-one 9 ($C_{27}H_{21}N_6O_2Cl$). IR (KBr): 1240 (C-O-C), 1660 (>C=O), 1565(-N=N-), 1420 (C-N), 3025 & 2915 (C-H str); ^{1}H NMR (400 MHz, $CDCl_3$): 2.3 (s, 3H, CH_3), 3.9–4.0 (q, 3H, OCH_3), 6.0 (s, 1H, C_5-H), 7.0–7.6 (m, 12H, Ar-H), 8.2–8.3 (s, 2H, tr-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.3, 55.9, 84.6, 114.3, 114.3, 119.7, 121.1, 122.0, 124.0, 124.5, 125.8, 128.6, 128.8, 129.1, 129.8, 129.8, 130.4, 130.4, 134.2, 134.5, 138.4, 139.0, 146.1, 146.5, 151.0, 158.4, 160.7; MS: $m/z = 496.14$ (M^+), 498.14 ($M^+ + 2$).

4-(4-Methoxyphenyl)-1-(3-chlorophenyl)-3-(4-methylphenylazo)-6-(1*H*-1,2,4-triazol-1-yl)-pyridin-2(1*H*)-one 10 ($C_{27}H_{21}N_6O_2Cl$). IR (KBr): 1250 (C-O-C), 1650 (>C=O), 1560 (-N=N-), 1425 (C-N), 3010 & 2910 (C-H str); ^{1}H NMR (400 MHz, $CDCl_3$): 2.3 (s, 3H, CH_3), 3.9–4.0 (q, 3H, OCH_3), 6.0 (s, 1H, C_5-H), 7.0–7.7 (m, 12H, Ar-H), 8.1–8.2 (s, 2H, tr-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.3, 55.9, 84.6, 114.3, 114.3, 119.7, 121.1, 122.0, 124.0, 124.5, 125.7, 128.7, 128.7, 129.1, 129.1, 129.8, 129.8, 130.4, 134.2, 134.5, 138.4, 139.0, 146.0, 146.5, 151.1, 158.4, 160.7; MS: $m/z = 496.14$ (M^+), 498.14 ($M^+ + 2$).

4-(4-Methoxyphenyl)-1-(3-chlorophenyl)-3-(2-nitrophenylazo)-6-(1*H*-1,2,4-triazol-1-yl)-pyridin-2(1*H*)-one 11 ($C_{26}H_{18}N_7O_4Cl$). IR (KBr): 1245 (C-O-C), 1660 (>C=O), 1570 (-N=N-), 1435 (C-N), 3020 & 2910 (C-H str), ^{1}H NMR (400 MHz, $CDCl_3$): 3.9–4.0 (q, 3H, OCH_3), 6.0 (s, 1H, C_5-H), 7.0–7.7 (m, 12H, Ar-H), 8.1–8.2 (s, 2H, tr-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.9, 84.6, 114.3, 114.3, 119.7, 121.2, 121.1, 122.0, 124.0, 124.0, 124.5, 129.7, 129.7, 129.8, 129.8, 130.4, 134.2, 134.5, 134.9, 139.0, 141.2, 146.5, 148.0, 151.1, 158.4, 160.7; MS: $m/z = 527.11$ (M^+), 529.11 ($M^+ + 2$).

4-(4-Methoxyphenyl)-1-(3-chlorophenyl)-3-(3-nitrophenylazo)-6-(1*H*-1,2,4-triazol-1-yl)-pyridin-2(1*H*)-one 12 ($C_{26}H_{18}N_7O_4Cl$). IR (KBr): 1260 (C-O-C), 1655 (>C=O), 1570 (-N=N-), 1430 (C-N), 3020 & 2920 (C-H str); ^{1}H NMR (400 MHz, $CDCl_3$): 3.8–3.9 (q, 3H, OCH_3), 5.9 (s, 1H, C_5-H), 7.0–7.7 (m, 12H, Ar-H), 8.1–8.2 (s, 2H, tr-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.9, 84.6, 114.3, 114.3, 119.7, 121.1, 121.1, 122.0, 124.0, 124.0, 124.5, 129.6, 129.7, 129.8, 129.8, 130.4, 134.2, 134.5, 134.9, 139.0, 146.1, 146.5, 148.0, 151.1, 158.5, 160.7; MS: $m/z = 527.11$ (M^+), 529.11 ($M^+ + 2$).

4-(4-Methoxyphenyl)-1-(3-chlorophenyl)-3-(4-nitrophenylazo)-6-6-(1*H*-1,2,4-triazol-1-yl)-pyridin-2(1*H*)-one 13 ($C_{26}H_{18}N_7O_4Cl$). IR (KBr): 1250 (C-O-C), 1650 (>C=O), 1575 (-N=N-), 1435 (C-N), 3010 & 2925 C-H str), ^{1}H NMR (400 MHz, $CDCl_3$): 3.9–4.1 (q, 3H, OCH_3), 5.9 (s, 1H, C_5-H), 6.9–7.6 (m, 12H, Ar-H), 8.1–8.2 (s, 2H, tr-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.9, 84.6, 114.3, 114.3, 119.7, 121.1, 121.1, 121.1, 122.0, 124.0, 124.5, 129.7, 129.7, 129.8, 129.8, 130.4, 134.2, 134.5, 134.8, 139.0, 146.1, 146.5, 148.0, 151.0, 158.4, 160.7; MS: $m/z = 527.11$ (M^+), 529.11 ($M^+ + 2$).

4-(4-Methoxyphenyl)-1-(3-chlorophenyl)-3-(2-methoxyphenylazo)-6-(1*H*-1,2,4-triazol-1-yl)-pyridin-2(1*H*)-one 14 ($C_{27}H_{21}N_6O_3Cl$). IR (KBr): 1255 & 1240 (C-O-C), 1670 (>C=O), 1565 (-N=N-), 1425 (C-N), 3020 & 2915 (C-H str); ^{1}H NMR (400 MHz, $CDCl_3$): 3.8–4.0 (q, 6H, OCH_3), 6.0 (s, 1H, C_5-H), 7.0–7.7 (m, 12H, Ar-H), 8.1–8.2 (s, 2H, tr-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.9, 55.9, 84.6, 99.6, 114.3, 114.3, 114.3, 119.7, 121.1, 121.1, 122.0, 124.0, 124.5, 129.8, 129.8, 129.8, 129.9, 130.4, 134.2, 134.5, 139.0, 146.0, 146.5, 151.0, 158.4, 159.1, 160.7; MS: $m/z = 512.14$ (M^+), 514.14 ($M^+ + 2$).

4-(4-Methoxyphenyl)-1-(3-chlorophenyl)-5-(phenylazo)-6-(1*H*-1,2,4-triazol-1-yl)-pyridin-2(1*H*)-one 15 ($C_{26}H_{19}N_6O_2Cl$). IR (KBr): 1250 (C-O-C), 1660 (>C=O), 1565 (-N=N-), 1430 (C-N), 3020 & 2910 (C-H str); ^{1}H NMR (400 MHz, $CDCl_3$): 4.0–4.1 (q, 3H, OCH_3), 6.6 (s, 1H, C_3-H), 7.0–7.7 (m, 13H, Ar-H), 8.1–8.2 (s, 2H, tr-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 50.1, 55.9, 85.0, 111.6, 112.5, 113.9, 114.3, 114.3, 117.3, 121.1, 128.5, 128.7, 128.8, 128.8, 128.8, 128.8, 128.9, 129.8, 129.8, 131.0, 135.1, 139.1, 145.8, 146.0, 151.0, 160.7; MS: $m/z = 482.13$ (M^+), ($M^+ + 2$).

4-(4-Methoxyphenyl)-1-(3-chlorophenyl)-5-(2-chlorophenylazo)-6-(1*H*-1,2,4-triazol-1-yl)-pyridin-2(1*H*)-one 16 ($C_{26}H_{18}N_6O_2Cl_2$). IR (KBr): 1255(C-O-C), 1650 (>C=O), 1570(-N=N-), 1420(C-N), 3025 & 2920(C-H str); ^{1}H NMR (400 MHz, $CDCl_3$): 3.9–4.0 (q, 3H, OCH_3), 6.7 (s, 1H, C_3-H), 7.0–7.6 (m, 12H,

Ar-H), 8.1–8.2 (s, 2H, tr-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 50.1, 55.9, 85.0, 111.6, 112.4, 113.9, 114.3, 114.5, 117.3, 121.2, 126.9, 128.5, 128.9, 129.0, 129.8, 129.8, 130.2, 130.2, 131.0, 134.3, 135.1, 139.0, 145.8, 146.1, 151.0, 160.7; MS: $m/z = 516.09$ (M^+), 518.09 ($M^+ + 2$), 520.09 ($M^+ + 4$).

4-(4-Methoxyphenyl)-1-(3-chlorophenyl)-5-(3-chlorophenylazo)-6-(1*H*-1,2,4-triazol-1-yl)-pyridin-2(1*H*)-one 17 ($C_{26}H_{18}N_6O_2Cl_2$). IR (KBr): 1240 (C-O-C), 1655 (>C=O), 1560 (-N=N-), 1425 (C-N), 3025 & 2910 (C-H str); ^{1}H NMR (400 MHz, $CDCl_3$): 3.9–4.0 (q, 3H, OCH_3), 6.6 (s, 1H, C_3-H), 7.0–7.7 (m, 12H, Ar-H), 8.1–8.2 (s, 2H, tr-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 50.1, 55.9, 85.0, 111.6, 112.4, 113.9, 114.3, 114.3, 117.3, 121.1, 126.9, 128.6, 128.9, 129.1, 129.8, 130.1, 130.2, 130.8, 134.3, 135.2, 139.1, 145.8, 146.2, 151.0, 160.7; MS: $m/z = 516.09$ (M^+), 518.09 ($M^+ + 2$), 520.09 ($M^+ + 4$).

4-(4-Methoxyphenyl)-1-(3-chlorophenyl)-5-(4-chlorophenylazo)-6-(1*H*-1,2,4-triazol-1-yl)-pyridin-2(1*H*)-one 18 ($C_{26}H_{18}N_6O_2Cl_2$). IR (KBr): 3077 (Ar C-H), 2979, 2925 (C-H), 1651 (C=N), 1606 (C=C), 1248 (C-O-C), 1712 (C=O), 1572 (-N=N-), 1511 (N-Ph); ^{1}H NMR (400 MHz, $CDCl_3$): 4.12 (s, 3H, OCH_3), 6.67 (s, 1H, C_3-H), 6.67–7.52 (m, 12H, Ar-H), 8.36 (s, 2H, C_3-H & C_5-H triaz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 63.8, 89.7, 107.2, 114.2, 115.0, 115.4, 119.2, 120.6, 127.1, 127.8, 128.2, 129.1, 129.5, 131.9, 135.1, 137.4, 138.2, 141.3, 146.0, 151.3, 155.2, 160.9, 164.6; MS: $m/z = 516.09$ (M^+), 518.09 ($M^+ + 2$), 520.09 ($M^+ + 4$).

4-(4-Methoxyphenyl)-1-(3-chlorophenyl)-5-(2-methylphenylazo)-6-(1*H*-1,2,4-triazol-1-yl)-pyridin-2(1*H*)-one 19 ($C_{27}H_{21}N_6O_2Cl$). IR (KBr): 1245 (C-O-C), 1650 (>C=O), 1575 (-N=N-), 1445 (C-N), 3020 & 2920 (C-H str); ^{1}H NMR (400 MHz, $CDCl_3$): 2.3 (s, 3H, CH_3), 3.9–4.0 (q, 3H, OCH_3), 6.6 (s, 1H, C_3-H), 7.0–7.7 (m, 12H, Ar-H), 8.1–8.2 (s, 2H, tr-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.2, 50.1, 56.0, 85.0, 111.6, 112.4, 113.9, 114.3, 114.4, 117.3, 121.1, 125.8, 128.1, 128.5, 128.7, 128.7, 129.1, 129.8, 129.8, 131.3, 135.1, 137.1, 139.1, 145.8, 146.1, 151.2, 160.7; MS: $m/z = 496.14$ (M^+), 498.14 ($M^+ + 2$).

4-(4-Methoxyphenyl)-1-(3-chlorophenyl)-5-(3-methylphenylazo)-6-(1*H*-1,2,4-triazol-1-yl)-pyridin-2(1*H*)-one 20 ($C_{27}H_{21}N_6O_2Cl$). IR (KBr): 1265 (C-O-C), 1665 (>C=O), 1570(-N=N-), 1430 (C-N), 3020 & 2910 (C-H str); ^{1}H NMR (400 MHz, $CDCl_3$): 2.4 (s, 3H, CH_3), 4.0–4.1 (q, 3H, OCH_3), 6.6 (s, 1H, C_3-H), 7.0–7.7 (m, 12H, Ar-H), 8.1–8.2 (s, 2H, tr-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.3, 50.1, 55.9, 85.0, 111.6, 112.4, 113.9, 114.3, 114.5, 117.3, 121.1, 125.8, 128.5, 128.6, 128.7, 129.1, 129.8, 129.8, 130.4, 131.0, 135.1, 138.4, 139.0, 145.8, 146.1, 151.2, 160.7; MS: $m/z = 496.14$ (M^+), 498.14 ($M^+ + 2$).

4-(4-Methoxyphenyl)-1-(3-chlorophenyl)-5-(4-methylphenylazo)-6-(1*H*-1,2,4-triazol-1-yl)-pyridin-2(1*H*)-one 21 ($C_{27}H_{21}N_6O_2Cl$). IR (KBr): 1255 (C-O-C), 1660 (>C=O), 1565 (-N=N-), 1435 (C-N), 3020 & 2920 (C-H str), ^{1}H NMR (400 MHz, $CDCl_3$): 2.3 (s, 3H, CH_3), 3.9–4.1 (q, 3H, OCH_3), 6.7 (s, 1H, C_3-H), 7.0–7.7 (m, 12H, Ar-H), 8.1–8.2 (s, 2H, tr-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.3, 50.1, 55.9, 85.0, 111.6, 112.4, 113.9, 114.3, 114.3, 117.3, 121.1, 125.7, 128.5, 128.7, 128.7, 129.1, 129.1, 129.8, 129.8, 131.2, 135.1, 138.4, 139.0, 145.8, 146.0, 151.1, 160.7; MS: $m/z = 496.14$ (M^+), 498.14 ($M^+ + 2$).

4-(4-Methoxyphenyl)-1-(3-chlorophenyl)-5-(2-nitrophenylazo)-6-(1*H*-1,2,4-triazol-1-yl)-pyridin-2(1*H*)-one 22 ($C_{26}H_{18}N_7O_4Cl$). IR (KBr): 1240 (C-O-C), 1665 (>C=O), 1575 (-N=N-), 1430 (C-N), 3015 & 2915 (C-H str); ^{1}H NMR (400 MHz, $CDCl_3$): 3.8–3.9 (q, 3H, OCH_3), 6.7 (s, 1H, C_3-H), 7.0–7.7 (m, 12H, Ar-H), 8.1–8.2 (s, 2H, tr-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 50.1, 55.9, 85.0, 111.6, 112.4, 113.9, 114.3, 114.4, 117.3, 121.1, 121.1, 124.0, 128.5, 129.7, 129.7, 129.8, 129.8, 131.1, 134.9, 135.1, 139.0, 145.8, 146.2, 148.0, 151.0, 160.7; MS: $m/z = 527.11$ (M^+), 529.11 ($M^+ + 2$).

4-(4-Methoxyphenyl)-1-(3-chlorophenyl)-5-(3-nitrophenylazo)-6-(1*H*-1,2,4-triazol-1-yl)-pyridin-2(1*H*)-one 23 ($C_{26}H_{18}N_7O_4Cl$). IR (KBr): 1250 (C-O-C), 1650 (>C=O), 1560 (-N=N-), 1425 (C-N), 3010 & 2910 (C-H str); ^{1}H NMR (400 MHz, $CDCl_3$): 3.9–4.0 (q, 3H, OCH_3), 6.6 (s, 1H, C_3-H), 7.0–7.7 (m, 12H, Ar-H), 8.1–8.2 (s, 2H, tr-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 50.1, 55.9, 85.0, 111.6, 112.4, 113.9, 114.3, 114.3, 117.3, 121.1, 121.1, 124.0, 128.5, 129.6, 129.7, 129.8, 129.8, 131.0, 134.9, 135.1, 139.1, 145.8, 146.1, 148.0, 151.2, 160.7; MS: $m/z = 527.11$ (M^+), 529.11 ($M^+ + 2$).

4-(4-Methoxyphenyl)-1-(3-chlorophenyl)-5-(4-nitrophenylazo)-6-(1*H*-1,2,4-triazol-1-yl)-pyridin-2(1*H*)-one 24 ($C_{26}H_{18}N_7O_4Cl$). IR (KBr): 1255 (C-O-C), 1655 (>C=O), 1570 (-N=N-), 1430 (C-N), 3020 & 2920 (C-H str); ^{1}H NMR (400 MHz, $CDCl_3$): 3.9–4.1 (q, 3H, OCH_3), 6.6 (s, 1H, C_3-H), 6.9–7.6 (m, 12H, Ar-H), 8.1–8.2 (s, 2H, tr-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 50.1, 55.9, 85.0, 111.6, 112.4, 113.9, 114.3, 114.3, 117.3, 121.1, 121.1, 121.2, 128.5, 129.7, 129.7, 129.8, 129.8, 131.1, 134.8, 135.1, 139.0, 145.8, 146.0, 148.0, 151.1, 160.7; MS: $m/z = 527.11$ (M^+), 529.11 ($M^+ + 2$).

4-(4-Methoxyphenyl)-1-(3-chlorophenyl)-5-(2-methoxyphenylazo)-6-(1*H*-1,2,4-triazol-1-yl)-pyridin-2(1*H*)-one 25 ($C_{27}H_{21}N_6O_3Cl$). IR (KBr): 1260 & 1250 (C-O-C), 1660 (>C=O), 1570 (-N=N-), 1420 (C-N), 3015 & 2910 (C-H str); ^{1}H NMR (400 MHz, $CDCl_3$): 3.9–4.0 (q, 6H, OCH_3), 5.9 (s, 1H, C_5-H), 7.0–7.7 (m, 12H, Ar-H), 8.1–8.2 (s, 2H, tr-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.9, 55.9, 85.0, 99.6, 114.3, 114.3, 114.4, 118.9, 119.7, 121.1, 121.1, 121.9, 124.5, 129.8, 129.8, 129.8, 129.9, 130.4, 134.2, 134.5, 139.1, 146.0, 146.5, 151.2, 159.1, 160.7, 160.7; MS: $m/z = 512.14$ (M^+), 514.14 ($M^+ + 2$).

4-(4-Methoxyphenyl)-1-(3-chlorophenyl)-6-(1*H*-1,2,4-triazol-1-yl)-3-[(1*H*-1,2,4-triazol-1-yl)methyl]-pyridin-2(1*H*)-one 26

A mixture of paraformaledhyde (0.3 g, 0.01 mol) and 1,2,4-triazole (0.69 g, 0.01 mol) was refluxed for 45 min in chlorobenzene (50 ml). Compound **3** (0.01 mol) was then added to the reaction mixture and refluxed for 18 h, and then the reaction mass was subjected to steam distillation to remove chlorobenzene. The solid product was filtered, washed, and crystallized from acetone.

IR (KBr): 1260 (C-O-C), 1650 (>C=O), 1570 (-N=N-), 1435 (C-N), 3010 & 2920 (C-H str); ^{1}H NMR (400 MHz, $CDCl_3$): 3.9–4.0 (q, 3H, OCH_3), 4.4(s, 2H, CH_2-tr) 5.9 (s, 1H, C_5-H), 7.0–7.7 (m, 8H, Ar-H), 8.0 (s, 2H, tr-H), 8.3 (s, 2H, tr-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 49.8, 55.7, 70.4, 76.9, 84.1, 114.2, 119.7,

122.1, 123.8, 124.5, 124.9, 127.5, 130.6, 134.1, 134.5, 139.2, 146.5, 146.8, 151.3, 158.3, 159.9; MS: $m/z = 459.12$ (M^+), 461.12 ($M^+ + 2$).

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