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Microwave Assisted Synthesis of Chalcone based 1,2,4-triazolo [1,5-a] Pyrimidines

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ABSTRACT

While fire is now rarely used in synthetic chemistry, it was not until Robert Bunsen invented the burner in 1855 that the energy from this heat source could be applied to a reaction vessel in a focused manner. The Bunsen burner was later superseded by the isomantle, the oil bath or the hot plate as a means of applying heat to a chemical reaction. In the past few years, heating and driving chemical reactions by microwave energy has been an increasingly popular theme in the scientific community [1, 2].

Keywords : Pyrimidines, MAOS, TLC, Histoprocessing, Tissue Fixation, Protein Hydrolysis, Sterilization

I. INTRODUCTION

Microwave energy, originally applied for heating foodstuffs by Percy Spencer in the 1940s, has found a variety of technical applications in the chemical and related industries since the 1950s, in particular in the food-processing, drying and polymer industries. Other applications range from analytical chemistry (microwave digestion, ashing and extraction) [3] to biochemistry (protein hydrolysis, sterilization) [3], pathology (histoprocessing, tissue fixation) [4] and medical treatments (diathermy) [5]. Somewhat surprisingly, microwave heating has only been implemented in organic synthesis since the mid-1980s. The first reports on the use of microwave heating to accelerate organic chemical transformations (MAOS) were published by the groups of Richard Gedye [6] and Raymond J. Giguere/George Majetich [7] in 1986.

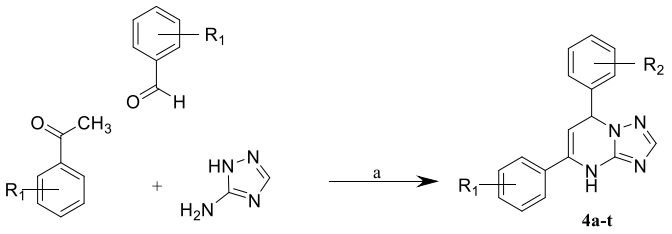
By far the most triazolo[1,5-a]pyrimidine synthesis are condensations of dinucleophilic 5-amino-1,2,4-triazoles with 1,3-bifunctional synthons as shown in the formation of triazolo[1,5-a]pyrimidine [8-11]. New synthetic conditions recently described involve melting under microwave irradiation, a reaction that is environmental friendly and gives higher yields than conventional heating in solvent [12]. Furthermore, certain lithium 1,3-diketonates have proven to be better synthons than the corresponding diketones [13].

II. EXPERIMENTAL

Materials and Methods

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine. IR spectra were recorded Shimadzu FT-IR-8400 instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. ^{1}H NMR was determined in DMSO-d_6 solution on a Bruker Ac 400 MHz spectrometer. Elemental analysis of the all the synthesized compounds was carried out on Elemental Vario EL III Carlo Erba 1108 model and the results are in agreements with the structures assigned.

Reaction scheme



Reagents and conditions: (a) gl. AcOH, MW, 120 ºC, 10-12 min

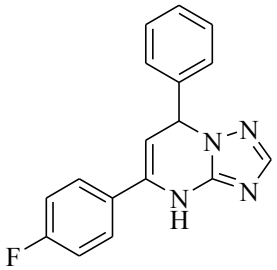
Table 1. Physical data of synthesized compounds

Code	R_1	R_2	M.F.	M.W.	M.P. ºC	Yield %	R_{f1}	R_{f2}
4a	4-F	H	$C_{17}H_{13}FN_4$	292	175-177	70	0.45	0.67
4b	4-F	4-F	$C_{17}H_{12}F_2N_4$	310	158-160	76	0.41	0.61
4c	4-F	4-Cl	$C_{17}H_{12}ClFN_4$	326	231-233	62	0.50	0.60
4d	4-F	4-NO_2	$C_{17}H_{12}FN_5O_2$	337	165-167	78	0.54	0.69
4e	4-F	4-CH_3	$C_{18}H_{15}FN_4$	306	185-187	65	0.51	0.74
4f	4-F	4-OCH_3	$C_{18}H_{15}FN_4O$	322	217-219	72	0.57	0.78
4g	4-F	3,4-OCH_3	$C_{19}H_{17}FN_4O_2$	352	204-206	60	0.53	0.70
4h	4-F	3-NO_2	$C_{17}H_{12}FN_5O_2$	337	191-193	62	0.42	0.63
4i	4-F	3-Cl	$C_{17}H_{12}ClFN_4$	326	224-226	71	0.46	0.67
4j	4-F	2-Cl	$C_{17}H_{12}ClFN_4$	326	199-201	79	0.40	0.60
4k	4-CH_3	H	$C_{18}H_{16}N_4$	288	214-216	68	0.48	0.66
4l	4-CH_3	4-F	$C_{18}H_{15}FN_4$	306	201-203	80	0.53	0.71
4m	4-CH_3	4-Cl	$C_{18}H_{15}ClN_4$	322	179-181	73	0.43	0.69
4n	4-CH_3	4-NO_2	$C_{18}H_{15}N_5O_2$	333	197-199	70	0.49	0.73
4o	4-CH_3	4-CH_3	$C_{19}H_{18}N_4$	302	185-187	75	0.54	0.72
4p	4-CH_3	4-OCH_3	$C_{19}H_{18}N_4O$	318	224-226	60	0.60	0.64
4q	4-CH_3	3,4-OCH_3	$C_{20}H_{20}N_4O_2$	348	161-163	72	0.63	0.75
4r	4-CH_3	3-NO_2	$C_{18}H_{15}N_5O_2$	333	148-150	64	0.50	0.70
4s	4-CH_3	3-Cl	$C_{18}H_{15}ClN_4$	322	166-168	72	0.52	0.62
4t	4-CH_3	2-Cl	$C_{18}H_{15}ClN_4$	322	210-212	76	0.48	0.61

General procedure for the synthesis of 5-(4-fluorophenyl)-4,7-dihydro-7-(aryl)-[1,2,4]triazolo[1,5-a]pyrimidines (4a-t)

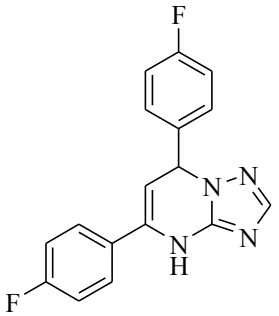
A mixture of the 5-amino-1,2,4-triazole (0.01 mol), 4-fluoro(or methyl)acetophenone (0.01 mol) and an appropriate aromatic aldehyde (0.01 mol) in glacial acetic acid (10 mL) was irradiated under microwave conditions at 120 ºC for 10-12 min. The microwave irradiation was operated in 30-second cycles. After cooling, methanol (10 mL) was added. The reaction mixture was allowed to stand overnight and then filtered to give the solid triazolopyrimidine products 4a-t, which were recrystallized from ethanol.

5-(4-fluorophenyl)-4,7-dihydro-7-phenyl-[1,2,4]triazolo[1,5-a]pyrimidine(4a)



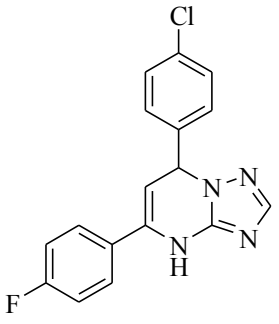
Yield: 70%; mp 201-203 ºC; MS: m/z 280; Anal. Calcd. for $C_{16}H_{16}N_4O$: C, 68.55; H, 5.75; N, 19.99. Found: C, 68.55; H, 5.75; N, 19.99%.

5,7-bis(4-fluorophenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine (4b)



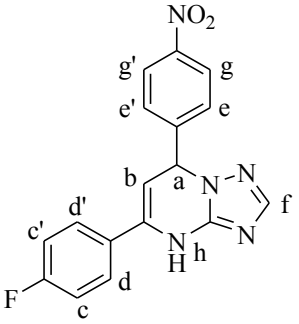
Yield: 76%; mp 158-160 ºC; MS: m/z 310; Anal. Calcd. for $C_{17}H_{12}F_2N_4$: C, 65.80; H, 3.90; N, 18.06. Found: C, 65.68; H, 3.82; N, 17.97%.

5-(4-fluorophenyl)-4,7-dihydro-7-(4-chlorophenyl)-[1,2,4]triazolo[1,5-a]pyrimidine (4c)



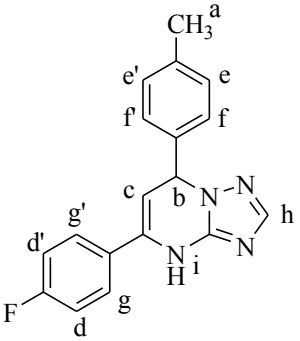
Yield: 62%; mp 231-233 ºC; MS: m/z 326; Anal. Calcd. for $C_{17}H_{12}ClFN_4$: C, 62.49; H, 3.70; N, 17.15. Found: C, 62.37; H, 3.64; N, 17.05%.

5-(4-fluorophenyl)-4,7-dihydro-7-(4-nitrophenyl)-[1,2,4]triazolo[1,5-a]pyrimidine (4d)



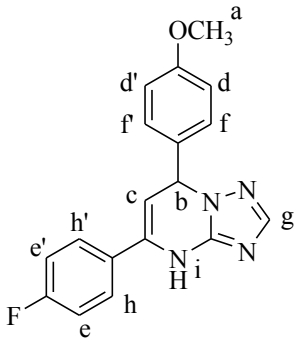
Yield: 78%; mp 165-167 ºC; IR (cm^{-1}): 3281 (N-H stretching of secondary amine), 3109 (C-H stretching of aromatic ring), 1626 (C=N stretching of triazole ring), 1552 and 1498 (C=C stretching of aromatic ring), 1377 (NO_2 stretching), 1294 (C-N stretching), 1269 (C-H in plane deformation of aromatic ring), 1197 (C-F stretching), 804 (C-H out of plane deformation of 1,4-disubstitution); ^{1}H NMR (DMSO-d_6) δ ppm: 5.08-5.09 (d, 1H, H_a, J = 2.3 Hz), 6.37-6.38 (d, 1H, H_b, J = 3.6 Hz), 7.13-7.18 (t, 2H, $H_{cc'}$, J = 8.6 Hz), 7.53-7.55 (d, 2H, $H_{dd'}$, J = 8.6 Hz), 7.60-7.65 (m, 3H, $H_{ee'-f}$), 8.21-8.23 (d, 2H, $H_{gg'}$, J = 8.6 Hz), 10.15 (s, 1H, H_h); MS: m/z 337; Anal. Calcd. for $C_{17}H_{12}FN_5O_2$: C, 60.53; H, 3.59; N, 20.76. Found: C, 60.40; H, 3.53; N, 20.68%.

5-(4-fluorophenyl)-4,7-dihydro-7-p-tolyl-[1,2,4]triazolo[1,5-a]pyrimidine (4e)



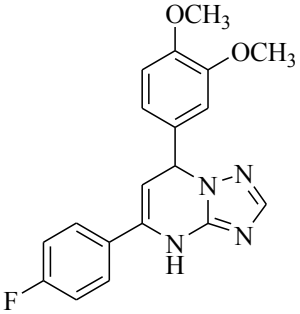
Yield: 65%; mp 185-187 ºC; IR (cm^{-1}): 3282 (N-H stretching of secondary amine), 3107 (C-H stretching of aromatic ring), 2956 (C-H symmetrical stretching of CH_3 group), 2839 (C-H asymmetrical stretching of CH_3 group), 1626 (C=N stretching of triazole ring), 1552 and 1498 (C=C stretching of aromatic ring), 1292 (C-N stretching), 1269 (C-H in plane deformation of aromatic ring), 1197 (C-F stretching), 804 (C-H out of plane deformation of 1,4-disubstitution); ^{1}H NMR (DMSO-d_6) δ ppm: 2.35 (s, 3H, H_a), 5.03-5.04 (d, 1H, H_b, J = 3.6 Hz), 6.10-6.11 (d, 1H, H_c, J = 3.6 Hz), 7.13-7.21 (m, 6H, $H_{d-f'}$), 7.47-7.49 (d, 2H, $H_{gg'}$, J = 8.2 Hz), 7.54 (s, 1H, H_h), 9.90 (s, 1H, H_i); MS: m/z 306; Anal. Calcd. for $C_{18}H_{15}FN_4$: C, 70.57; H, 4.94; N, 18.29. Found: C, 70.41; H, 4.90; N, 18.21%.

5-(4-fluorophenyl)-4,7-dihydro-7-(4-methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidine (4f)



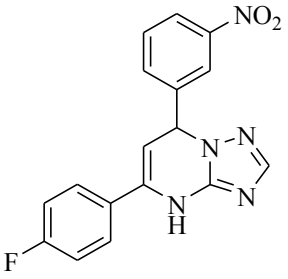
Yield: 72%; mp 217-219 ºC; IR (cm^{-1}): 3281 (N-H stretching of secondary amine), 3111 (C-H stretching of aromatic ring), 1624 (C=N stretching of triazole ring), 1552 and 1498 (C=C stretching of aromatic ring), 1427 (C-H asymmetrical deformation of CH_3 group), 1294 (C-N stretching), 1269 (C-H in plane deformation of aromatic ring), 1197 (C-F stretching), 1058 (C-O-C symmetrical stretching of ether linkage), 804 (C-H out of plane deformation of 1,4-disubstitution); ^{1}H NMR (DMSO-d_6) δ ppm: 3.76 (s, 3H, H_a), 5.02 (d, 1H, H_b, J = 2.4 Hz), 6.10 (d, 1H, H_c, J = 3.4 Hz), 6.86-6.88 (d, 2H, $H_{dd'}$, J = 8.5 Hz), 7.10-7.14 (t, 2H, $H_{ee'}$, J = 8.6 Hz), 7.25-7.27 (d, 2H, $H_{ff'}$, J = 8.5 Hz), 7.50 (s, 1H, H_g), 7.61-7.64 (t, 2H, $H_{hh'}$), 10.04 (s, 1H, H_i); MS: m/z 322; Anal. Calcd. for $C_{18}H_{15}FN_4O$: C, 67.07; H, 4.69; N, 17.38. Found: C, 66.90; H, 4.63; N, 17.30%.

5-(4-fluorophenyl)-4,7-dihydro-7-(3,4-dimethoxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidine (4g)



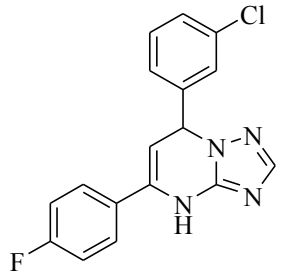
Yield: 60%; mp 204-206 ºC; MS: m/z 352; Anal. Calcd. for $C_{19}H_{17}FN_4O_2$: C, 64.76; H, 4.86; N, 15.90. Found: C, 64.61; H, 4.81; N, 15.79%.

5-(4-fluorophenyl)-4,7-dihydro-7-(3-nitrophenyl)-[1,2,4]triazolo[1,5-a]pyrimidine (4h)



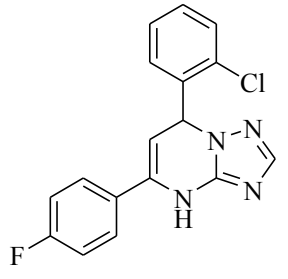
Yield: 62%; mp 191-193 ºC; MS: m/z 337; Anal. Calcd. for $C_{17}H_{12}FN_5O_2$: C, 60.53; H, 3.59; N, 20.76. Found: C, 60.38; H, 3.51; N, 20.65%.

5-(4-fluorophenyl)-4,7-dihydro-7-(3-chlorophenyl)-[1,2,4]triazolo[1,5-a]pyrimidine (4i)



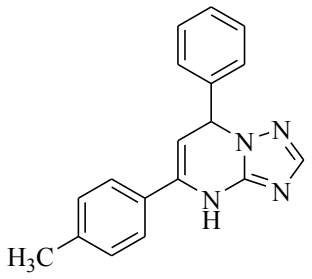
Yield: 71%; mp 224-226 ºC; MS: m/z 326; Anal. Calcd. for $C_{17}H_{12}ClFN_4$: C, 62.49; H, 3.70; N, 17.15. Found: C, 62.34; H, 3.65; N, 17.08%.

5-(4-fluorophenyl)-4,7-dihydro-7-(2-chlorophenyl)-[1,2,4]triazolo[1,5-a]pyrimidine (4j)



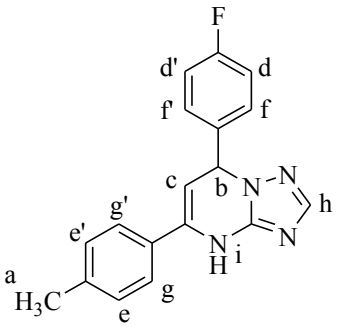
Yield: 79%; mp 199-201 ºC; MS: m/z 326; Anal. Calcd. for $C_{17}H_{12}ClFN_4$: C, 62.49; H, 3.70; N, 17.15. Found: C, 62.36; H, 3.66; N, 17.10%.

4,7-dihydro-7-phenyl-5-p-tolyl-[1,2,4]triazolo[1,5-a]pyrimidine(4k)



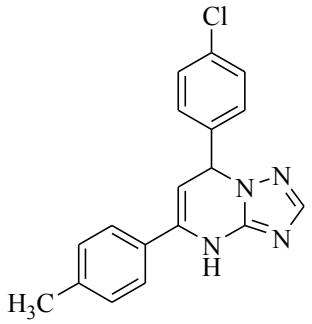
Yield: 68%; mp 214-216 ºC; MS: m/z 288; Anal. Calcd. for $C_{18}H_{16}N_4$: C, 74.98; H, 5.59; N, 19.43. Found: C, 74.83; H, 5.52; N, 19.31%.

4,7-dihydro-7-(4-fluorophenyl)-5-p-tolyl-[1,2,4]triazolo[1,5-a]pyrimidine (4l)



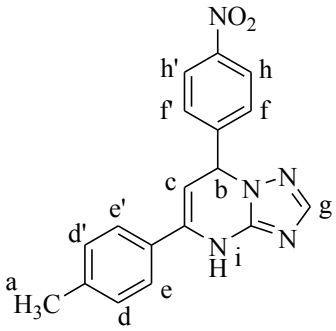
Yield: 80%; mp 201-203 ºC; IR (cm^{-1}): 3194 (N-H stretching of secondary amine), 3090 (C-H stretching of aromatic ring), 2972 (C-H symmetrical stretching of CH_3 group), 2860 (C-H asymmetrical stretching of CH_3 group), 1658 (N-H deformation of pyrimidine ring), 1597 (C=N stretching of triazole ring), 1550 and 1475 (C=C stretching of aromatic ring), 1330 (C-N stretching), 1070 (C-F stretching), 941 (C-H in plane deformation of aromatic ring), 825 (C-H out of plane deformation of 1,4-disubstitution); ^{1}H NMR (DMSO-d_6) δ ppm: 2.35 (s, 3H, H_a), 5.04-5.05 (d, 1H, H_b, J = 3.6 Hz), 6.18 (d, 1H, H_c, J = 3.6 Hz), 7.07-7.11 (t, 2H, $H_{dd'}$, J = 8.7 Hz), 7.19-7.21 (d, 2H, $H_{ee'}$, J = 8.0 Hz), 7.32-7.36 (t, 2H, $H_{ff'}$), 7.48-7.50 (d, 2H, $H_{gg'}$, J = 8.2 Hz), 7.55 (s, 1H, H_h), 9.96 (s, 1H, H_i); MS: m/z 306; Anal. Calcd. for $C_{18}H_{15}FN_4$: C, 70.57; H, 4.94; N, 18.29. Found: C, 70.64; H, 4.90; N, 18.20%.

4,7-dihydro-7-(4-chlorophenyl)-5-p-tolyl-[1,2,4]triazolo[1,5-a]pyrimidine (4m)



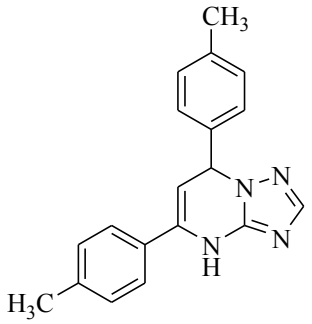
Yield: 73%; mp 179-181 ºC; MS: m/z 322; Anal. Calcd. for $C_{18}H_{15}ClN_4$: C, 66.98; H, 4.68; N, 17.36. Found: C, 66.87; H, 4.65; N, 17.29%.

4,7-dihydro-7-(4-nitrophenyl)-5-p-tolyl-[1,2,4]triazolo[1,5-a]pyrimidine (4n)



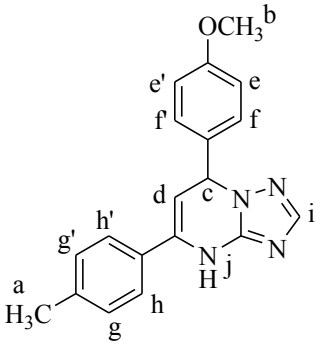
Yield: 70%; mp 197-199 ºC; IR (cm^{-1}): 3192 (N-H stretching of secondary amine), 3093 (C-H stretching of aromatic ring), 2976 (C-H symmetrical stretching of CH_3 group), 2862 (C-H asymmetrical stretching of CH_3 group), 1658 (N-H deformation of pyrimidine ring), 1593 (C=N stretching of triazole ring), 1548 (NO_2 stretching), 1523 and 1473 (C=C stretching of aromatic ring), 1352 (C-N stretching), 943 (C-H in plane deformation of aromatic ring), 823 (C-H out of plane deformation of 1,4-disubstitution); ^{1}H NMR (DMSO-d_6) δ ppm: 2.37 (s, 3H, H_a), 5.02-5.03 (d, 1H, H_b, J = 3.0 Hz), 6.33-6.34 (d, 1H, H_c, J = 3.2 Hz), 7.20-7.22 (d, 2H, $H_{dd'}$, J = 7.8 Hz), 7.47-7.49 (d, 2H, $H_{ee'}$, J = 7.6 Hz), 7.52-7.55 (d, 2H, $H_{ff'}$, J = 8.1 Hz), 7.58 (s, 1H, H_g), 8.20-8.22 (d, 2H, $H_{hh'}$, J = 8.0 Hz), 9.96 (s, 1H, H_i); MS: m/z 333; Anal. Calcd. for $C_{18}H_{15}N_5O_2$: C, 64.86; H, 4.54; N, 21.01. Found: C, 64.69; H, 4.49; N, 20.91%.

4,7-dihydro-5,7-di-p-tolyl-[1,2,4]triazolo[1,5-a]pyrimidine (4o)



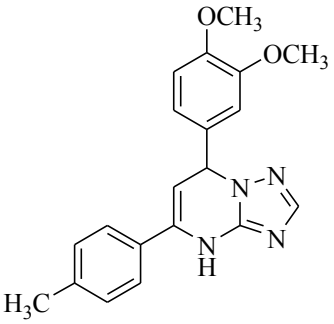
Yield: 75%; mp 185-187 ºC; MS: m/z 302; Anal. Calcd. for $C_{19}H_{18}N_4$: C, 75.47; H, 6.00; N, 18.53. Found: C, 75.31; H, 5.95; N, 18.43%.

4,7-dihydro-7-(4-methoxyphenyl)-5-p-tolyl-[1,2,4]triazolo[1,5-a]pyrimidine (4p)



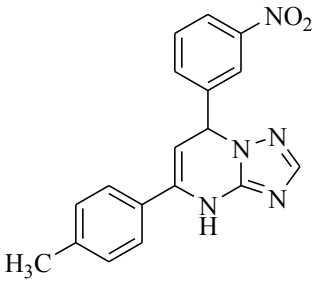
Yield: 60%; mp 224-226 ºC; IR (cm^{-1}): 3196 (N-H stretching of secondary amine), 3086 (C-H stretching of aromatic ring), 3020 (C-H symmetrical stretching of CH_3 group), 2858 (C-H asymmetrical stretching of CH_3 group), 1662 (N-H deformation of pyrimidine ring), 1595 (C=N stretching of triazole ring), 1550 and 1467 (C=C stretching of aromatic ring), 1429 (C-H asymmetrical deformation of CH_3 group), 1330 (C-N stretching), 1176 (C-O-C asymmetrical stretching of ether linkage), 941 (C-H in plane deformation of aromatic ring), 829 (C-H out of plane deformation of 1,4-disubstitution); ^{1}H NMR (DMSO-d_6) δ ppm: 2.36 (s, 3H, H_a), 3.76 (s, 3H, H_b), 5.04-5.05 (d, 1H, H_c, J = 3.4 Hz), 6.10-6.11 (d, 1H, H_d, J = 3.5 Hz), 6.86-6.88 (d, 2H, $H_{ee'}$, J = 8.6 Hz), 7.19-7.21 (d, 2H, $H_{ff'}$, J = 8.1 Hz), 7.24-7.26 (d, 2H, $H_{gg'}$, J = 8.6 Hz), 7.48-7.50 (d, 2H, $H_{hh'}$, J = 8.1 Hz), 7.56 (s, 1H, H_i), 9.92 (s, 1H, H_j); MS: m/z 318; Anal. Calcd. for $C_{19}H_{18}N_4O$: C, 71.68; H, 5.70; N, 17.60. Found: C, 71.68; H, 5.70; N, 17.60%.

4,7-dihydro-7-(3,4-dimethoxyphenyl)-5-p-tolyl-[1,2,4]triazolo[1,5-a]pyrimidine (4q)



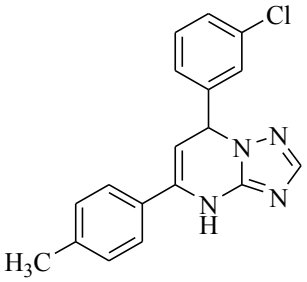
Yield: 72%; mp 161-163 ºC; MS: m/z 348; Anal. Calcd. for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.81; H, 5.76; N, 16.00%.

4,7-dihydro-7-(3-nitrophenyl)-5-p-tolyl-[1,2,4]triazolo[1,5-a]pyrimidine (4r)



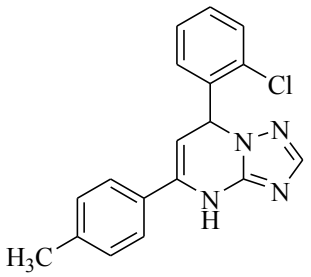
Yield: 64%; mp 148-150 ºC; MS: m/z 333; Anal. Calcd. for $C_{18}H_{15}N_5O_2$: C, 64.86; H, 4.54; N, 21.01. Found: C, 64.71; H, 4.49; N, 20.91%.

4,7-dihydro-7-(3-chlorophenyl)-5-p-tolyl-[1,2,4]triazolo[1,5-a]pyrimidine (4s)



Yield: 72%; mp 166-168 ºC; MS: m/z 322; Anal. Calcd. for $C_{18}H_{15}ClN_4$: C, 66.98; H, 4.68; N, 17.36. Found: C, 66.84; H, 4.63; N, 17.25%.

4,7-dihydro-7-(2-chlorophenyl)-5-p-tolyl-[1,2,4]triazolo[1,5-a]pyrimidine (4t)



Yield: 76%; mp 210-212 ºC; MS: m/z 322; Anal. Calcd. for $C_{18}H_{15}ClN_4$: C, 66.98; H, 4.68; N, 17.36. Found: C, 66.86; H, 4.67; N, 17.27%.

III. RESULTS AND DISCUSSION

The biological importance of 1,2,4-triazolo[1,5-a]pyrimidines is well documented. Over the years, various substituted derivatives of these heterocycles have shown utility against a range of biological targets. For example, they have demonstrated activity against malaria and bronchospasm and shown activity as coronary vasodilators, antihypertensive agents, leishmanicides, antibiotics, adenosine A_{2a} antagonists, immunosuppressants, antitumor agents, fungicides, xanthine oxidase inhibitors and phosphodiesterase inhibitors.

Recognizing these facts, we have synthesized four new series of 1,2,4- triazolo[1,5-a]pyrimidines (4a-t). It was achieved by one-pot, microwave -assisted condensation reaction of aromatic aldehyde, corresponding acetophenone and 5-amino-1,2,4-triazole using glacial acetic acid as a solvent. The structures of all the newly synthesized compounds were elucidated by FT-IR, mass spectra, ^{1}H NMR and elemental analysis.

IV. CONCLUSION

The present paper describes applications of microwaves in heterocyclic ring formation. Recently, 1,2,4-triazolo[1,5-a]pyrimidines have aroused increasing from the standpoint of biological activity, due to their diverse pharmacological activities. It includes synthesis of forty novel 1,2,4-triazolo[1,5-a]pyrimidines and brief review of the reported synthetic strategies. Forty 1,2,4-triazolo[1,5-a]pyrimidines were synthesized by one-pot, microwave-assisted condensation reaction of aromatic aldehyde, corresponding acetophenone and 5-amino-1,2,4-triazole using glacial acetic acid as a solvent. Thus,

a new green chemistry approach was developed leading to the improvement in the reaction time, yield and simplicity of work up procedure.

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