ISSN No:-2456-2165

One-Pot Multicomponent Ultrasound Irradiated Synthesis of Heterocyclic Pyrimidines and Their Microbial Assay

Lekhni Sharma[1]
Department of Chemistry,
Faculty of Science, Mewar University,
Gangrar, Chittorgarh (Raj.) INDIA

Prakash C. Choudhary*
Department of Chemistry,
Faculty of Science, Mewar University,
Gangrar, Chittorgarh (Raj.) INDIA

Abstract:- Multicomponent reactions (MCR's) play an important role in the synthetic chemistry. It enables the synthesis of small drug like molecules with many degree of structural viability. Use of green alternatives for this type of synthesis is the demand. Therefore, we developed an ecofriendly method using USI and flyash support $Ba(OH)_2$ as catalyst. 18 molecules of 2-substituted-4,6-diheteroaryl pyrimidines were prepared by this method. The antibacterial screening against different pathogens were also studied and found compounds 3f and 3m as most effective one.

Keywords:- *Pyrimidines, MCR's , USI, Green Synthesis.*

I. INTRODUCTION

Heterocyclic chemistry contributes major part in all segments of Organic Chemistry research going on all over the world not only in medicinal, Pharmaceutical but also in agricultural and veterinary fields also. Heterocyclic moiety plays a crucial role in nature as being part of natural drugs i.e. quinine, emetine, atropine, codinne, morphine etc., natural dyes, luminophores, pesticides and herbicides also. Heterocycles having one or two heteroatom in a ring specially nitrogen has a great value in therapeutics. There are numerous agents, where pyridines and pyrimidines part have major impact on the biological activity. Pyrimidine skeleton is widely present in many natural such as Vitamin B1, nucleic acid as a part of RNA and DNA and synthetic as barbituric acid etc. The importance of pyrimidines are also judged by its tremendous applications in the form of biological efficacy for antibacterial[1], Alzheimer[2], anti-angiogenic agent[3], anti-cancer[4], anti-convulsant[5], anti-diabetic[6], anti-hepatitis[7], anti-inflammatory[8], antimalarial[9], anti-microbial[10], anti-oxidant[11], anti-parkinson[12], anti-protozoal[13], anti-tubercular[14], anti-viral[15] etc.

Environmental protection has become a global concern and the chemical industry is increasingly searching the ways of developing and applying more efficiently and environmentally benign strategies for future sustainable growth. An important part of our effort towards ecofriendly synthesis [16] is aimed at reduction of use of solvents, hazardous and excessive use of catalysts and atom efficiency of reaction. Therefore a new reaction technique with energy efficient, solvent-free or less solvent conditions on solid support procedures were adopted for the synthesis of pyrimidines with higher atom efficacy and sustainability. The use of ultrasound Irradiation technique [1] and bio potential of pyrimidine drew our attention to prepare a mind-set towards these environmentally benign multicomponent synthesis using heterocyclic chalcones with S-Benzylthiuronium chloride (SBT) in the presence of fly ash supported $Ba(OH)_2$ to afford 2-substituted-4,6-diheteroaryl pyrimidines. The biological efficacy was also studied with different biological strains.

II. EXPERIMENTAL

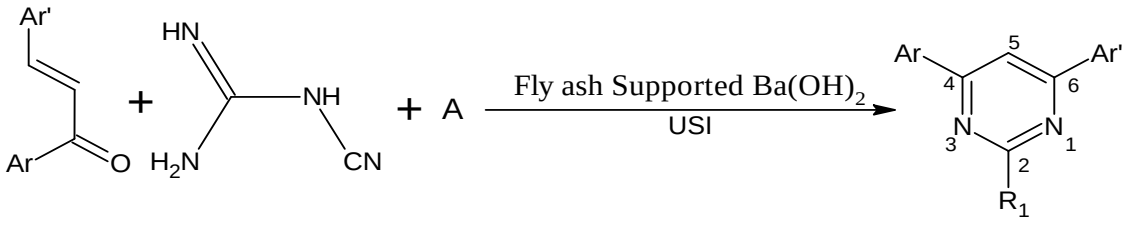
A. Synthesis of 1,3-diheteroaryl propenones (1a-f) : The following 1,3-diheteroaryl propenones used for the synthesis of 2-substituted-4,6-diheteroaryl substituted pyrimidines **3a-r** were prepared by conventional method.[17]

1a. (2*E*)-1,3-di(2-pyridyl) propenone
1b. (2*E*)-1,3-di(3-pyridyl) propenone
1c. (2*E*)-1,3-di(4-pyridyl) propenone
1d. (2*E*)-1-(2-pyridyl)-3-(2-thienyl) propenone
1e. (2*E*) -1-(2-thienyl)-3-(2-pyridyl) propenone
1f (2*E*)-1,3-di(2-thienyl) propenone

B. General procedure for synthesis of 2-substituted-4,6-diheteroaryl substituted pyrimidines (3a-r):

Propenones **1** (0.02 mol), SBT **2** (0.025 mol), organic base (0.03 mol) and Flyash supported $Ba(OH)_2$ (200-500 mg) in ethanol/ methanol (10 mL) was added in a 50 mL conical pyrex flask. The reaction mixture was irradiated in the water bath of the ultrasonic cleaner at 30-35°C for a period as indicated in Table I (monitored by TLC). After the completion of the reaction, it was filtered and in filtrate, water was added and stirred for a while, then it was filtered, washed with water (3X50 mL) and dried. Further purification was accomplished by crystallization from ethanol or ethanol: benzene mixture (1:1; v/v) to yield compound **3.** Authenticity of the products **3** obtained was established by spectral data.

ISSN No:-2456-2165



1 2 3

A. Morpholine / Piperidine / Pyrrolidine

Scheme: 1

Comp. No.	Ar	Ar′	R_1	USI	
				Time (min.)	Yield (%)
3a	2-pyridyl	2-pyridyl	morpholinyl	45	78
3b	3-pyridyl	3-pyridyl	morpholinyl	35	80
3c	4-pyridyl	4-pyridyl	morpholinyl	34	79
3d	2-pyridyl	2-thienyl	morpholinyl	60	75
3e	2-thienyl	2-pyridyl	morpholinyl	40	80
3f	2-thienyl	2-thienyl	morpholinyl	95	82
3g	2-pyridyl	2-pyridyl	piperidinyl	50	85
3h	3-pyridyl	3-pyridyl	piperidinyl	30	81
3i	4-pyridyl	4-pyridyl	piperidinyl	45	84
3j	2-pyridyl	2-thienyl	piperidinyl	60	82
3k	2-thienyl	2-pyridyl	piperidinyl	30	78
3l	2-thienyl	2-thienyl	piperidinyl	30	75
3m	2-pyridyl	2-pyridyl	pyrrolidinyl	40	78
3n	3-pyridyl	3-pyridyl	pyrrolidinyl	65	74
3o	4-pyridyl	4-pyridyl	pyrrolidinyl	35	76
3p	2-pyridyl	2-thienyl	pyrrolidinyl	50	78
3q	2-thienyl	2-pyridyl	pyrrolidinyl	30	80
3r	2-thienyl	2-thienyl	pyrrolidinyl	34	76

Table 1: Substituents and Experimental data of compounds (3a-r)

C. Spectral studies:

The IR spectra of the final products **3a-r** did not show the characteristic absorption for C=O of propenones in the regions 1650-1690 cm^{-1}. On the other hand absorption in the range 1620-1500 cm^{-1} (C=N and C=C), 3100-3000cm^{-1} (aromatic C-H), 2980-2850 cm^{-1} (aliphatic C-H), and 900-700 cm^{-1} (substituted heteroaryl) were observed in the synthesised compound. (Table- II) In the ^{1} H NMR spectrum, the characterstic C_5-H of the pyrimidine ring was overlapped as multiplets with aromatic protons in the range of (δ) 6.80 to 8.15. The chemical shift of morpholinyl, piperdinyl and pyrrolidinyl moieties were observed as multiplets at δ 1.94-3.68 (Table- III) confirming the proposed structure. ^{13}C NMR spectra of **3a** showed signals for C-2, C-4/C6 and C-5 of pyrimidine ring at 167.49, 161.93 and 123.95 respectively. Similarly, the signals of morpholinyl/piperidinyl/pyrrolidinyl moiety of the compounds are also in the expected regions. (Table: IV).

ISSN No:-2456-2165

Compd. No.	=C-H (sp^2)	-C-H (sp^3)	C=C/C=N	Substituted heteroaryl
3a	3079	2937,2838	1614,1511,1459	855,820,730
3b	3082	2925,2826	1628,1522,1478	865,828,742
3c	3055	2990	1590,1578,1508	856,839,773,698
3d	3065	2985	1589,1572,1515	849,831,768,688
3e	3043	2983,2950,2967	1605,1541,1511,1406	859,815,755
3f	3041	2982,2975	1602,1575	873,820,765,690
3g	3045	2919,2850	1621,1585,1576	871,770,688
3h	3081,3044	2929	1609,1578,1562,1515	860,788,768,740
3i	3080	2925	1605,1572,1525	875,798,754,712
3j	3075	2912	1598,1658,1524	895,845,802,790
3k	3083,3067	2982,2978	1629,1585,1556,1476	838,798
3l	3078,3065	2970	1601,1578,1495	871,832,796,750
3m	3064	2980,2953	1625,1598,1542,1493	875,812,789
3n	3086,3043	2977,2924	1599,1577,1506,1477	868,800,767,738
3o	3041	2967,2934	1608,1591,1583,1501	899,864,802,756,
3p	3053,3031	2904,2851	1621,1614,1596,1556	823,778,700,655
3q	3061	2921	1599,1575	856,804,782,710,685
3r	3056	2935,2911	1625,1595,1558,1511	806,782,738

Table II: IR (KBr, ῡ/ cm^{-1}) spectral data of compounds (3a-r)

Compd. No.	CH_2-O-CH_2 (m,4H)	CH_2-N-CH_2 (m,4H)	-$(CH_2)_3$ (m,6H)	-$(CH_2)_2$ (m,4H)	Ar-H & Pyrimidine-H_5 (m, 9H)
3a	3.55	3.13	-	-	7.40-8.95
3b	3.58	3.18	-	-	7.43-9.00
3c	3.62	3.17	-	-	7.90-8.60
3d	3.68	3.29	-	-	7.84-8.59
3e	3.65	3.22	-	-	7.80-8.60
3f	3.66	3.25	-	-	7.30-7.90
3g	-	3.56	2.03	-	7.33-8.90
3h	-	3.53	1.99	-	7.30-9.00
3i	-	3.56	1.94	-	7.34-8.96
3j	-	3.64	1.93		7.31-8.64
3k	-	3.62	1.96	-	7.32-8.60
3l	-	3.66	1.94	-	7.34-8.68
3m	-	3.61	-	2.00	7.37-8.90
3n	-	3.65	-	1.99	7.35-9.00
3o	-	3.66	-	1.98	7.30-8.96
3p	-	3.62	-	1.96	7.33-8.62
3q	-	3.61	-	1.95	7.34-8.65
3r	-	3.60	-	1.94	7.32-8.72

Table III: ^1H NMR ($CDCl_3$, δ, ppm) spectral data of compounds (3a-r)

No.	C-2	C-5	C-4 , C-6	CH_2-O-CH_2	CH_2-N-CH_2	$(CH_2)_3$	$(CH_2)_2$	Ar-C
3a	167.49	123.95	161.93	67.89	43.70	-	-	147.39,123.19,135.36,122.01,149.82
3b	167.44	122.56	162.82	67.91	44.45	-	-	152.28,150.21,122.77,138.09,124.67
3c	166.99	122.37	164.76	67.01	44.48	-	-	139.10,121.69,148.65
3d	166.46	128.81	161.80,164.02	67.92	44.31	-	-	139.06,128.20,127.13,128.29,150.11, 121.82,135.36,123.19,147.39
3e	165.83	123.67	164.99	67.55	44.92	-	-	137.92,128.20,127.13,129.05
3f	165.46	127.18	162.30,163.82	67.89	44.31	-	-	139.06,128.20,127.13,128.29,150.11, 121.82,135.36,123.19,147.39
3g	164.49	125.36	162.43	-	43.51	26.11,25.05	-	149.09,122.01,135.36,123.19,147.39
3h	165.99	124.84	162.82	-	44.29	26.07,25.01	-	123.94,152.28,150.21,122.77,138.09
3i	165.49	124.64	162.76	-	44.34	26.11,25.05	-	138.37,121.71,148.61
3j	165.96	123.08	164.30,156.02	-	44.15	26.07,25.18	-	137.47,127.20,125.18,149.08 146.99,134.96,121.82
3k	165.08	123.19	163.96,155.12	-	44.12	26.17,25.08	-	138.47,128.29,127.13,149.38 147.39,135.36,125.36
3l	165.49	123.94	165.83	-	44.73	26.27,25.15	-	137.33,127.80,126.53,130.25
3m	164.72	123.00	162.37	-	46.55	-	26.05	149.45,122.01,135.36,123.19,147.39
3n	164.77	122.30	162.70	-	46.81	-	26.02	124.30,152.28,150.21,122.77,138.09
3o	165.78	124.10	162.65	-	46.65	-	26.10	138.73,121.69,148.65
3p	165.90	125.44	162.25,155.00	-	46.63	-	26.02	149.74,147.39,123.19,135.36,121.82, 139.18,128.29,127.13
3q	162.09	125.36	162.52,157.25	-	46.43	-	26.06	149.74,147.93,123.19,135.63,121.28, 139.65,128.92,127.27
3r	162.69	124.30	164.42	-	46.71	-	26.04	138.04,129.05,127.13,128.20

Table IV: ^{13}C NMR ($CDCl_3$, δ ppm) spectral data of compounds (3a-r)

D. Anti-bacterial activity :

All the Synthesized pyrimidine compounds were screened for antibacterial activity by the method mentioned as under, against *S. aureus, B. subtilis* and *E. coli* and the results are tabulated in table :V. In vitro antibacterial activity of synthesized pyrimidine derivatives (in DMSO solution at the concentration of 500 ppm/mL) was studied by reported method [18] which is the agar well diffusion method [19]. Antibacterial assay of the test compounds were determined in terms of zone of inhibition around each well. Diameter of inhibition zone produced by the test compound was compared with that of standard Streptomycin. For each bacterial strain, controls were maintained using pure solvent instead of the sample solution. Experiments were performed in triplicate for constant results.

D. Compd. No.	*S. aureus*	*B. subtilis*	*E. coli*
3a	10	22	09
3b	11	21	10
3c	10	18	07
3d	15	19	11
3e	09	17	07
3f	16	28	18
3g	12	13	16
3h	09	19	10
3i	08	18	10
3j	09	17	09
3k	11	25	16
3l	5	12	8
3m	15	25	17
3n	07	16	11
3o	10	16	10
3p	09	15	07
3q	15	10	14
3r	8	23	19
Streptomycin (STD)	21	30	20
Control (DMSO)	00	00	00

Table: V Anti-bacterial activity (zone of inhibition in mm)

III. RESULTS AND DISCUSSION

The chemistry of pyrimidines and its derivatives have been studied for over a century due to their diverse biological activities and due to their synthetic and industrial applications. Numerous synthetic modes of pyrimidines have been reported, but these generally afford pyrimidone derivatives. Classically 2,4,6-trisubstituted pyrimidines are obtained by refluxing α,β-unsaturated ketones with SBT and heterocyclic secondary amines in ethanol for 10-15 hrs in 40-50% yield [20-21]. Now a days microwave irradiation technique is also getting popularity for this type of reaction but due to less possibilities of reproducibility and scale up to large production, it is not widely accepted [22-23]. The classical procedure is tedious, time consuming, gives low yield and requires an appreciable amount of solvent as well as secondary amines, which is used as a base. Subsequently, synthetic procedure utilizing ultrasonic irradiation (USI), the above three component one-pot (MCR's) synthesis was carried out successfully under less solvent condition. However, in view of the synthetic efficiency of one-pot multicomponent process gaining a considerable academic, econimic and ecological interest, promising manifold opportunities for generating novel structures of pharmaceuticals, biopotential of 2,4,6-tri substituted pyrimidines as anticancer agents and an our ongoing programe towards green synthesis, we here in report the combination of one-pot three component reaction with USI using 1,3-diheteroaryl propenones, SBT and heterocyclic organic secondary bases resulting 2-(4-morpholinyl / 1-piperidinyl / 1-pyrrolidinyl)-4,6-diheteroarylpyrimidines 3a-r. (Scheme:I). The reaction has been carried out using Flyash supported Ba $(OH)_2$ as a catalyst. Different experimental trials were carried out to standardize the reaction under USI and solid support and concluded that 25 % of $Ba(OH)_2$ (200-500 mg) load showed best results (Table-I). The synthesis under USI is more convenient, shorter reaction time and higher yield. This method proved to be better and attractive alternative to existing methodologies under conventional homogeneous base catalysis with the frequent troublesome manipulation and work-up. The structural assignments of 3a-r were based on characteristic IR, ^{1}H NMR, ^{13}C NMR (Tables- II-IV).

IV. CONCLUSION

In this one-pot three component synthesis of 4,6-diheteroaryl-2-(4-morpholinyl / 1-piperidinyl / 1-pyrrolidinyl)- pyrimidines using 1,3-diheteroaryl propenones, SBT, organic bases on a solid support of flyash supported $Ba(OH)_2$ under USI. In short, we have developed the facile, rapid and economic methodology for various useful pyrimidines by modernization and simplification of classical procedure. The results demonstrate the versatility of the process as considerable reaction rate enhancement has been observed by bringing down the reaction time from hours to minutes with improved yield (up to 90%) as compared to conventional heating. Use of catalyst as solid support has excluded the need of excess organic solvents and organic bases, keeping the environment ecofriendly. All the tested compounds showed moderate to good antibacterial activity against the tested bacterial strains. Compound 3f and 3m showed excellent activity against all the tested bacterial strains. The zone of inhibition of compound 3f against *E. coli and B. subtilis* and compound 3r against *E. coli* was comparable with that of the standard drug whereas other compounds 3g, 3k & 3m against *E. coli*, 3k, 3m, and 3r against *B. subtilis* and 3d, 3m & 3q against *S. aureus* have also shown moderate to good activity. From the structural activity relationship (SAR) study it may be revealed that 3f and 4 3m were found most active against all bacterial strains whereas 3r showed good to excellent activity against *B. subtilis* and *E. coli.* In compound 3g, 3k & 3l showed moderate to good activity against *B. subtilis* and *E. coli. w*hereas compound 3g was moderately active against *E. coli.* only. Compound 3l in this group showed weak activity. From this study compound 3f against *B. subtilis* and *E. coli* and compound 3r against *E. coli* have emerged interesting lead molecules for further synthetic and biological evaluation.

REFERENCES

[1]. Sharma, L., Choudhary, P.C.; Environmentally Benign Synthesis of 2-Substituted-4,6-Diaryl Pyrimidines Using Inorganic Solid Supports and their Biological Screening; *Int. j. innov. res. sci. eng. technol.*; **2021**, 6(8), 1152-1158.

[2]. Shivani Singh , Meenakshi Dhanawat, Sumeet Gupta , Deepak Kumar , Saloni Kakkar , Anroop Nair, Inderjeet Verma, Prerna Sharma; Naturally Inspired Pyrimidines Analogues for Alzheimer's Disease; *Curr Neuropharmacol* . **2021**; 19(2): 136-151.

[3]. Perspicace E, Jouan-Hureaux V, Ragno R, Ballante F, Sartini S, Motta CL, *et al.* Design, synthesis and biological evaluation of new classes of thieno [3,2-*d*] pyrimidinone and thieno[1,2,3]triazine as an inhibitor of vascular endothelial growth factor receptor-2 (VEGFR-2). *Eur J Med Chem* **2013;**63:765-81.

[4]. Ma L, Wang B, Pang L, Zhang M, Wang S, Zheng Y, *et al.* Design and synthesis of novel 1,2,3-triazole–pyrimidine–urea hybrids as potential anticancer agents. *Bioorg Med Chem Lett* **2015**;25:1124–8.

[5]. Wang S, Deng X, Zheng Y, Yuan Y, Quan Z, Guan L. Synthesis and evaluation of anticonvulsant and antidepressant activities of 5-alkoxy tetrazolo[1,5-*c*]thieno[2,3-*e*]pyrimidine derivatives. *Eur J Med Chem* **2012**;56:139-44.

[6]. Yang Z, Fang Y, Pham TN, Lee J, Park H. Synthesis and biological evaluation of 5-nitropyrimidine analogs with azabicyclic substituents as GPR119 agonists. *Bioorg Med Chem Lett.;* **2013**;23:1519–21.

[7]. Hwang JY, Windisch MP, Jo S, Kim K, Kong S, Kim HC, *et al.* Discovery and characterization of a novel 7-aminopyrazolo[1,5-*a*]pyrimidine analog as a potent hepatitis C virus inhibitor. *Bioorg Med Chem Lett* ; **2012**;22:7297–301.

[8]. McIver EG, Bryans J, Birchall K, Chugh J, Drake J, Lewis SJ, *et al.* Synthesis and structure–activity relationships of a novel series of pyrimidines as potent inhibitors of TBK1/IKKε kinases. *Bioorg Med Chem Lett* ; **2012**;22:7169–73.
[9]. Singh K, Kaur H, Chibale K, Balzarini J. Synthesis of 4-amino quinoline-pyrimidine hybrids as potent antimalarials and their mode of action studies. *Eur J Med Chem* **2013**;66:314-23.
[10]. Ramiz MMM, El-Sayed WA, El-Tantawy AI, Abdel-Rahman AAH. Antimicrobial activity of new 4,6-disubstituted pyrimidine, pyrazoline, and pyran derivatives. *Arch Pharm Res* **2010**;33:647-54.
[11]. Yousefia A, Yousefia R, Panahi F, Sarikhani S, Zolghadr AR, Bahaoddini A, *et al.* Novel curcumin-based pyrano[2,3-*d*] pyrimidine anti-oxidant inhibitors for-amylase and-glucosidase: implications for their pleiotropic effects against diabetes complications. *Int J Biol Macromol* **2015**;78:46–55.
[12]. Shook BC, Chakravarty D, Barbay JK, Wang A, Leonard K, Alford V, *et al.* Substituted thieno[2,3-*d*]pyrimidines as adenosine A_{2A} receptor antagonists. *Bioorg Med Chem Lett* **2013**;23: 2688–91.
[13]. Suryawanshi SN, Kumar S, Shivahare R, Pandey S, Tiwari A, Gupta S. Design, synthesis and biological evaluation of aryl pyrimidine derivatives as potential leishmanicidal agents. *Bioorg Med Chem Lett* **2013**;23:5235–8.
[14]. Chikhale R, Menghani S, Babu R, Bansode R, Bhargavi G, Karodia N, et al. Development of selective DprE1 inhibitors: design, synthesis, crystal structure and antitubercular activity of benzothiazolylpyrimidine-5-carboxamides. *Eur J Med Chem* **2015**;96:30-46.
[15]. Guo D, Zhang X, Wang R, Zhou Y, Li Z, Xu J, *et al.* Structural modifications of 5,6-dihydroxypyrimidines with anti-HIV activity. *Bioorg Med Chem Lett* **2012**;22:7114–8.
[16]. Choudhary P.C., Sharma H., Verma B.L.; Synthesis of 2-amino-4,6-diarylpyrimidines using inorganic solid support under microwave and ultrasound irradiation and their antibacterial activity; *Indian J. Heterocyclic Chem.;* **2011**, 20; 209-212.
[17]. Ahmad M.R., Sastry V.G., Bano N., Anwar S.; Synthesis of novel chalcone derivatives by conventional and microwave irradiation methods and their pharmacological activities; *Arab. J. Chem.;* **2016**, 9 (1), S931-S935.
[18]. Santra S, Jat B, Santra PK. Synthesis and antibacterial activities of chalcones and indole derived from acetyl pyridines. *Asian J Chem;* **2018**; 30: 883-8.
[19]. Perez C, Paul M, Bazerque P. An antibiotic assay by the agar-well diffusion method. *Acta Biol Med Exp*; **1990**;15:113-5.
[20]. K. L. Ameta, Biresh Kumar, and Nitu S. Rathore; ZnO Catalyzed Efficient Synthesis of Some New 2-Substituted-4,6-diarylpyrimidines ; *ISRN Org. Chem.;***2012**; 6; Article ID 242569, 6 pages.
[21]. (a) Sharma, P. & Hussain, Kaneez & Sukhwal, S. & Kothari, Sovith & Singhal, M. & Verma, B.L.; A Convenient One-Pot Synthesis of 2-Substituted-4,6-diarylpyrimidines. *Cheminform.;* **2010** ; 31. 10.1002/chin.200009156. (b). Ameta, K.L. , Kumar, B. , Rathore N.S. and B. L. Verma; Facile synthesis of some novel 2-substituted-4,6- diarylpyrimidines using 4'-hydroxy-3',5'-dinitrochalcones and S-benzylthiouronium chloride; *Org. Commun.* ; **2012**; 5(1); 1-11
[22]. Priecel, P. and Lopez-Sanchez, J.A.; Advantages and Limitations of Microwave Reactors: From Chemical Synthesis to the Catalytic Valorization of Biobased Chemicals; *ACS Sustainable Chem. Eng.* ; **2019**, 7, 3−21.
[23]. Kidwai, M., Rastogi, S., Saxena, S.; Base Catalysed Pyrimidine Synthesis Using Microwave; *Bull. Korean Chem. Soc.*; **2003**, 24(11); 1575-1578.