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Environmentally Benign Synthesis of 2-Substituted-4,6-Diaryl Pyrimidines Using Inorganic Solid Supports and their Biological Screening

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Abstract:- A series of 2-(4-morpholinyl/1-piperidinyl/1-pyrrolidinyl)-4,6-diaryl pyrimidines (4a-r) have been synthesized by the condensation of 1,3-diarylpropenones with dicyandiamide (DDA) in presence of heterocyclic secondary amines such as morpholine, piperidine and pyrrolidine under conventional and nonconventional method, using inorganic supports {Fly ash supported $Ba(OH)_2$}. The synthesis highlights a comparative study of conventional, and ultrasonication technique. The reaction time decreases from hours to minutes along with yields enhancement under ultrasound irradiation. In addition, catalytic role of Fly ash supported $Ba(OH)_2$ was studied with different catalytic load. All the products have been characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral studies. Some representative compounds were screened for their antibacterial assay and showed excellent activity.

Keywords:- *Pyrimidine, DDA, heterocyclic secondary amines, ultrasound irradiation, antibacterial screening.*

I. INTRODUCTION

Heterocyclic compounds are of immense importance due to their wide spectrum of pharmacodynamic applications. Thiourea and thioamide having the functionals NH-(C=S)-NH and -NH-(C=S)– possess four and three reaction sites respectively and constitute versatile starting material for condensation with a variety of reagents for procuring various sized heterocycles [1-4]. In this connection pyrimidines are extremely important compounds with a wide array of synthetic & industrial applications not only they are an integral part of the genetic materials, viz. DNA and RNA as nucleotides & nucleosides but also play critical roles especially in pharmaceutical fields [5] i.e. significant *in vitro* activity against unrelated DNA or RNA viruses, including polio and herpes viruses, diuretic [6], antitumor [7], anti-HIV [8], cardiovascular [9], antibacterial [10], antimicrobial [11], antiviral [12] and antitumor agents [13], Antihypertensive [14] etc.

Dicyandiamide, (DDA) is a versatile reagent and used for the synthesis of different kind of cyclic biologically important compounds along with different heterocyclic Pharmaceutically important agents. It is used in our laboratory along with SBT as most versatile reagent for the facile one pot conversion of chalcone to pyrimidines via different methods [15] (conventional / nonconventional MWI).

Numerous synthetic modes of pyrimidines have been reported [16-20]. But these generally afford pyrimidone derivatives. Classically[15] 2,4,6-trisubstituted pyrimidines are obtained by refluxing α,β-unsaturated ketones **1** with DDA **2** and heterocyclic secondary amines in ethanol for 10-15 hrs in 40-50% yield. This 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. However, In view of the environmentally benign role of solvent less approach under ultrasound irradiation (USI), the bio potential of pyrimidines and our ongoing program towards green synthesis [21] we herein report for the first time USI facile, rapid one-pot condensation of chalcones with dicyandiamide (DDA) in presence of organic bases to afford 2-(4-morpholinyl/1-piperidinyl/1-pyrrolidinyl)-4,6-diarylpyrimidines.

II. RESULTS AND DISCUSSION

Different experimental trials were carried out to standardize the reaction under USI. The trials were also conducted to verify the catalytic load on solid support and concluded that 20% load showed excellent results. The reaction of chalcones **1** with DDA **2** initially resulted the 2-(cyanamido)-pyrimidine derivatives **3** in presence of fly ash supported $Ba(OH)_2$ under USI. Reaction of intermediate **3** with heterocyclic secondary amine- morpholine, piperidine and pyrrolidine absorbed over fly ash supported $Ba(OH)_2$ under USI resulted final products **4a-r** (Table. I) (Scheme:I). Further the formation of the precursors **3** as well as the final cyclized products **4a-r** over fly ash supported $Ba(OH)_2$ under USI prompted us to attempt one-pot synthesis of the

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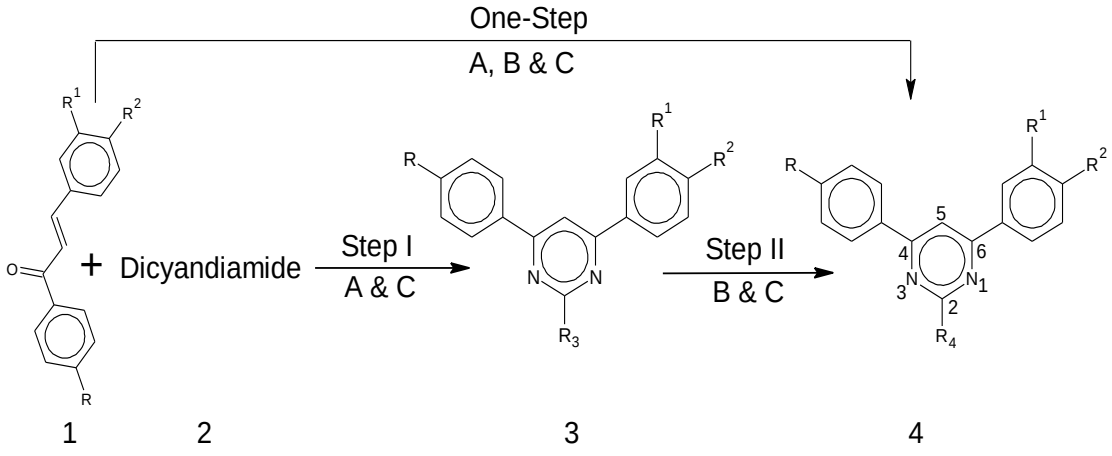
required pyrimidine derivatives (Table II) starting from the reactants chalcones **1**, DDA **2** and heterocyclic secondary amines. The one-pot synthesis under USI is more convenient, shorter reaction time and higher yield. These methods proved to be attractive alternatives to existing methodologies under conventional homogeneous base catalysis with the frequent troublesome manipulation and work-up. From the comparative results (Tables I-II), it can be concluded that fly ash supported $Ba(OH)_2$ under USI is most effective support and further best results in term of yields were obtained as the experimental work up was the simplest. Hence, other compounds **3d-l** (Table I), **4d-r** (Table II) in two step and compounds **4d-r** (Table III) in one step method were prepared by this method. Ultrasound irradiation method requires only 200-500 mg of inorganic basic support. The structures of the compounds were established on the basis of spectroscopic data and elemental analysis. In general IR spectrum (cm^{-1}) of **3** showed disappearance of absorption bands in the region 1660-1630 cm^{-1} (enone carbonyl) of their precursors and appearance of bands at 3422-3164 (-NH), 3087-3012 (Ar-H), 2260-2166 (-C≡N), 1639-1494 (C=N & C=C) cm^{-1} in the case **3a-f.** Disappearance of absorption bands of –NH & -CN and appearance of aliphatic C-H stretching frequency in the regions 2976-2851 cm^{-1} due to $(CH_2)_n$ confirms the incorporation of organic base nucleophile in the compounds. ^1H NMR spectra (δ) of compounds 4a-f showed triplets centered around 3.30-3.55 and 3.60-3.98 δ due to methylene protons of $–CH_2$-N-CH_2- and $–CH_2$-O-CH_2- of morpholine. It also revealed multiplets in the region 6.8-8.5 δ due to aromatic protons and H_5- of pyrimidine ring. ^{13}C NMR spectroscopic data were also comparable with their relevant substituent group patterns.



Reagents A. Fly ash supported fused $Ba(OH)_2$ B. sec. amine C. Conv./ USI

Scheme:1

No.	R	R_1	R_2	R_3	No.	R	R_1	R_2	R_3
3a	OH	NO_2	H	NH-CN	4g	OH	NO_2	H	Piperidinyl
3b	CH_3	NO_2	H	NH-CN	4h	CH_3	NO_2	H	Piperidinyl
3c	Cl	NO_2	H	NH-CN	4i	Cl	NO_2	H	Piperidinyl
3d	Br	NO_2	H	NH-CN	4j	Br	NO_2	H	Piperidinyl
3e	NH_2	NO_2	H	NH-CN	4k	NH_2	NO_2	H	Piperidinyl
3f	Cl	H	$N(CH_3)_2$	NH-CN	4l	Cl	H	$N(CH_3)_2$	Piperidinyl
4a	OH	NO_2	H	Morpholinyl	4m	OH	NO_2	H	Pyrrolidinyl
4b	CH_3	NO_2	H	Morpholinyl	4n	CH_3	NO_2	H	Pyrrolidinyl
4c	Cl	NO_2	H	Morpholinyl	4o	Cl	NO_2	H	Pyrrolidinyl
4d	Br	NO_2	H	Morpholinyl	4p	Br	NO_2	H	Pyrrolidinyl
4e	NH_2	NO_2	H	Morpholinyl	4q	NH_2	NO_2	H	Pyrrolidinyl
4f	Cl	H	$N(CH_3)_2$	Morpholinyl	4r	Cl	H	$N(CH_3)_2$	Pyrrolidinyl

Scheme: I

No.	Reaction time (Min)	Yield %
3a	51	88
3b	56	91
3c	45	92
3d	37	89
3e	28	94
3f	98	88
3g	48	87
3h	62	86
3i	43	89
3j	35	90
3k	31	93
3l	43	89
4a	45	87
4b	35	84
4c	34	81
4d	60	81
4e	40	86
4f	95	84
4g	50	86
4h	30	83
4i	45	87
4j	60	88
4k	30	89
4l	30	85
4m	40	87
4n	65	84
4o	35	86
4p	50	88
4q	30	88
4r	34	86

Table 1:- Experimental data of compounds prepared by two step synthesis

No.	Reaction time (Min)	Yield %
4a	60	88
4b	45	86
4c	34	88
4d	122	89
4e	95	90
4f	115	87
4g	45	84
4h	54	85
4i	59	87
4j	54	90
4k	25	91
4l	35	86
4m	50	89
4n	65	85
4o	38	83
4p	45	89
4q	22	85
4r	28	85

Table 2:- Experimental data of compounds (4a-r) One-pot synthesis

III. EXPERIMENTAL

➢ *General information*

Reagents and solvents were from commercial suppliers (Sigma-Aldrich, CDH, Thomas-Baker etc.) and used as provided, unless indicated otherwise. Solvents were analytical grade and were stored over molecular sieves (4A°). Reactions were carried out in oven-dried glassware. Melting points were determined in open glass capillaries and are uncorrected. IR spectra were recorded on Perkin-Elmer spectrum GX spectrophotometer on KBr plate. ^{1}H NMR and ^{13}C NMR spectra were recorded by using Bruker F 113V (200 MHz) FT NMR spectrometer at 200 and 75 MHz, respectively with $CDCl_3$/DMSO-d_6 as solvent & TMS as internal reference. Chemical shifts are expressed in δ ppm. Mass spectral analysis was carried out on Shimadzu GCMS-QP2010 spectrometer. Experiments were performed using Systronic 320 ultrasound cleaner, with output power watts 200 and output frequency 33 KHz. The purity of the compounds were checked on MERCK 25 DC-Alufolien Silica Gel 60 F_{254} TLC Plates.

➢ *Preparation of catalysts*

For the preparation of catalyst 5 gram of fly ash was properly washed with DM water and added different proportions of fused $Ba(OH)_2$ (5% ,10%, 20%, 30% and 50%) in 20 ml of DM water. The mixture was stirred at 50°C for 12 hour then the mixture was heated in hot air oven till dryness at 105°C. After it, temperature of oven was raised to 200°C and maintained for 2 hours. This mixture after getting cold in desiccator was mixed properly and stored in air tight container.

➢ *General procedure for the synthesis of (4a-r)*

Two step process:

Step I: Synthesis of 4,6-diaryl-2-(cyanamido)-pyrimidines (3a-l)

A mixture of chalcone **1** (2.5 mmol), dicyandiamide **2** (1.25 mmol) was added fly ash supported $Ba(OH)_2$ (200-500 mg) and ethanol/ methanol (10 mL) in a 100 mL conical flask. The reaction mixture was (heated at 80°C for 12 to 24 Hrs for trial 2-3 reactions) irradiated by an ultrasonic generator in a water bath at 30-35°C for a period (monitored by TLC) as indicated in Table I. The solid product formed was filtered under reduced pressure, washed with water and dried. The dried crude product was recrystallized from ethanol or ethanol: benzene mixture (1:1; v/v).

Step II: Synthesis of 4,6-diaryl-2-(4-morpholinyl / 1-piperidinyl / 1-pyrrolidinyl)- pyrimidines (4a-r).

To the solution of compound **3** (1 mmol) and morpholine/ piperidine / morpholine, piperidine and pyrrolidine (7.5 mmol) in ethanol/ methanol (20 mL). It was then subjected (to heating at 80°C for 12 to 24 Hrs for trial 2-3 reactions) or to ultrasonic generator in a water bath at 30-35°C for a period (monitored by TLC) as indicated in table II. The rest procedure is same as described in step I.

➢ *One-pot synthesis:*

To a mixture of chalcone **1** (2.5 mmol), dicyandiamide **2** (1.25 mmol) and morpholine/ piperidine / morpholine, piperidine and pyrrolidine (7.5 mmol) and catalyst fly ash supported $Ba(OH)_2$ (200-500 mg) in ethanol/ methanol (10 mL) was added in a 100 mL conical flask. The reaction mixture was (heated at 80°C for 12 to 24 Hrs for trial 2-3 reactions). or irradiated by an ultrasonic generator in a water bath at 30-35°C for a period (monitored by TLC) as indicated in Table III. After the completion of the reaction water (50 mL) was added to the product and stirred for a while, then it was filtered under reduced pressure and dried. Further purification was accomplished by crystallization from ethanol or ethanol: benzene mixture (1:1; v/v) to yield compound **4.** Authenticity of the products (3a-l) & (4a-r) obtained by methods A, B was established by m.m.ps and co-TLC and finally characterized by elemental analysis and spectral IR, ^{1}H NMR, ^{13}C NMR and MS data.

IV. SPECTRAL DATA

➢ *Intermediate compounds*

2-Cyanamido-4-(4-hydroxyphenyl)-6-(3-nitrophenyl)pyrimidine (3a), m.p. 165 °C ; IR (KBr/cm^{-1}); 3388 (-NH), 3012 (=C-H (sp^2)), 2166 (-C≡N), 1514, 1324 (-NO_2), 1633, 1613,1583 (C=C/C=N), 873, 765, 706, 666 (substituted phenyl); Anal. calcd. for $C_{17}H_{11}N_5O_3$ (333.301): C 61.26 H 3.35 N 21.10 Found: C 61.20 H 3.30 N 21.07.

2-Cyanamido-4-(4-methylphenyl)-6-(3-nitrophenyl)pyrimidine (3b), m.p. 137°C IR (KBr/cm^{-1}); 3382 (-NH), 3087 (=C-H (sp^2)),2854 (-sp^3), 2178 (-C≡N), 1521,1355 (-NO_2), 1639, 1610,1588 (C=C/C=N), 859, 826,802, 742 (substituted phenyl); Anal. calcd. for $C_{18}H_{13}N_5O_3$ (331.328): C 65.25 H 3.95 N 21.14 Found: C 65.21 H 3.90 N 21.07.

2-Cyanamido-4-(4-chlorophenyl)-6-(3-nitrophenyl)pyrimidine (3c), m.p. 159°C IR (KBr/cm^{-1}); 3222 (-NH), 3047 (=C-H (sp^2)), 2214 (-C≡N), 1505, 1362 (-NO_2), 1622, 1598,1576 (C=C/C=N), 828, 763, 707, (substituted phenyl); Anal. calcd. for $C_{17}H_{10}ClN_5O_2$ (351.747) : C 58.05 H 2.87 N 19.91 Found: C 57.90 H 2.80 N 19.87.

2-Cyanamido-4-(4-bromophenyl)-6-(3-nitrophenyl)pyrimidine (3d), m.p. 171°C IR (KBr/cm^{-1}); 3422 (-NH), 3030 (=C-H (sp^2)), 2260 (-C≡N), 1507, 1337 (-NO_2), 1598, 1446 (C=C/C=N), 828, 763, 726, 689 (substituted phenyl); Anal. calcd. for $C_{17}H_{10}BrN_5O_2$ (396.198) : C 51.54 H 2.54 N 17.68 Found: C 51.49 H 2.50 N 17.60.

2-Cyanamido-4-(4-aminophenyl)-6-(3-nitrophenyl)pyrimidine (3e), m.p. 227°C IR (KBr/cm^{-1}); 3457, 3342 (-NH/NH_2), 3073 (=C-H (sp^2)), 2234 (-C≡N),1511,1362 (-NO_2), 1610, 1555 (C=C/C=N), 845, 771, 732, 684 (substituted phenyl); Anal. calcd. for $C_{17}H_{12}N_6O_2$ (332.316): C 61.44 H 3.64 N 25.29 Found: C 61.36 H 3.53 N 25.20.

2-Cyanamido-4-(4-chlorophenyl)-6-(4-dimethylaminophenyl)pyrimidine (3f), m.p. 141°C IR (KBr/cm^{-1}); 3164 (-NH), 3043 (=C-H (sp^2)), 2957 (sp^3), 2219 (-C≡N), 1635, 1596,1514 (C=C/C=N), 859, 812,760, 711 (substituted phenyl); Anal. calcd. for $C_{19}H_{16}ClN_5$ (349.816): C 65.24 H 4.61 N 20.02 Found: C 65.19 H 4.50 N 19.87.

➢ *Final compounds*

2-(4-Morpholinyl)-4-(4-hydroxyphenyl) -6-(3-nitrophenyl) pyrimidine (4a) m.p. 232°C; IR (KBr/cm^{-1}); 3452(OH), 3089(=C-H (sp^2)), 2953, 2887(-C-H (sp^3)), 1517, 1356(-NO_2), 1617, 1568, 1555(C=C/C=N), 912, 850, 761 (Substituted Phenyl) ; ^{1}H NMR (δ, ppm, $CDCl_3$); 3.75 CH_2-O-CH_2 (t,4H), 3.40 CH_2-N-CH_2 (t,4H), 10.13 OH (s, 1H, OH), 6.98-8.2 Ar-H & Pyrimidine-H_5 (m, 9H); ^{13}C NMR (δ, ppm, $CDCl_3$);168.91,124.7,,164.07, 161.7, 65.50, 44.50, 130.15, 126.43, 128.54, 130.47, 136,31, 132.5, 125.2, 147.3, 135.4; Anal. calcd. for $C_{20}H_{18}N_4O_4$ (378.381) C 63.48 H 4.79 N 14.81Found: C 63.41 H 4.70 N 14.73.

2-(4-Morpholinyl)-4-(4-methyl phenyl)-6-(3-nitrophenyl) pyrimidine (4b), m.p. 187°C IR (KBr/cm^{-1}); 3061(=C-H (sp^2)), 2961, 2851(-C-H (sp^3)), 1511, 1361(-NO_2), 1631, 1573, 1511(C=C/C=N), 873, 723(Substituted Phenyl); ^{1}H NMR (δ, ppm, $CDCl_3$); 3.60 CH_2-O-CH_2 (t,4H), 3.30 CH_2-N-CH_2 (t,4H), 1.91 CH_3(s,3H), 7.1-8.2 Ar-H & Pyrimidine-H_5 (m, 9H); ^{13}C NMR (δ, ppm, $CDCl_3$);168.53,124.1,164.1, 161.6,66.8,44.40,21.16,129.4, 126.2, 128.2, 137.2, 133.1, 127.4, 144.7, 123.1, 129.2, 134.4; Anal. calcd. for $C_{21}H_{20}N_4O_3$ (376.409) C 67.01 H 5.36 N 14.88; Found: C 66.81 H 5.30 N 14.82.

2-(4-Morpholinyl)-4-(4-chlorophenyl)-6-(3-nitrophenyl) pyrimidine(4c) m.p.204°C; IR (KBr/cm^{-1}); 3084, 3058, 3026(=C-H (sp^2)), 2905,2857(-C-H (sp^3)), 1524, 1345(-NO_2), 1628,1597, 1581 (C=C/ C=N), 887, 808,757, 711(Substituted Phenyl); ^{1}H NMR (δ, ppm, $CDCl_3$); 3.80 CH_2-O-CH_2 (t,4H), 3.47 CH_2-N-CH_2 (t,4H), 7.25-8.5 Ar-H & Pyrimidine-H_5 (m, 9H); ^{13}C NMR (δ, ppm, $CDCl_3$);168.56,124.40,164.63, 160.50,67.89,44.48,144.77, 134.40, 133.65, 130.3, 129.27, 127.85; Anal. calcd. for $C_{20}H_{17}ClN_4O_3$ (396.827) C 60.53 H 4.32 N 14.12Found: C 60.50 H 4.29 N 14.08.

2-(4-Morpholinyl)-4-(4-bromophenyl)-6-(3-nitrophenyl) pyrimidine(4d) m.p.205°C ; IR (KBr/cm^{-1}); 3086, 3058, 3027(=C-H (sp^2)), 2920, 2853(-C-H (sp^3)), 1524, 1348(-NO_2), 1642, 1585, 1493 (C=C/ C=N), 887, 880, 795, 756, 723, 711 (Substituted Phenyl); ^{1}H NMR (δ, ppm, $CDCl_3$); 3.98 CH_2-O-CH_2 (t,4H), 3.55 CH_2-N-CH_2 (t,4H), 7.2-8.4 Ar-H & Pyrimidine-H_5 (m, 9H); ^{13}C NMR (δ, ppm, $CDCl_3$);168.56, 123.16,164.57, 160.50, 67.89, 44.48, 145.01, 134.40, 135.50, 133.98, 129.91, 129.23, 127.44, 125.91, 122.09; Anal. calcd. for $C_{20}H_{17}BrN_4O_3$ (441.278) C 54.44 H 3.88 N 12.70 Found: C 54.34 H 3.80 N 12.58.

ISSN No:-2456-2165

2-(4-Morpholinyl)-4-(4-aminophenyl)-6-(3-nitrophenyl) pyrimidine(4e) m.p. >240°C; IR (KBr/cm^{-1}); 3339, 3399(-NH_2), 3069(=C-H (sp^2)), 2926(-C-H (sp^3)), 1527, 1349(-NO_2), 1599,1573, 1539(C=C/C=N), 919,777,734, 683 (Substituted Phenyl); ^{1}H NMR (δ, ppm, $CDCl_3$); 3.70 CH_2-O-CH_2 (t,4H), 3.42 CH_2-N-CH_2 (t,4H), 6.30 NH_2 (br, 2H), 6.8-8.1 Ar-H & Pyrimidine-H_5 (m, 9H); ^{13}C NMR (δ, ppm, $CDCl_3$);168.93,125.8,162.91, 161.77, 65.49, 44.92,128.7, 131.3, 112.7, 148.7, 132.7, 129.5, 144.8, 123.9, 129.7, 135.5; Anal. calcd. for $C_{20}H_{19}N_5O_3$ (377.397) C 63.65 H 5.07 N 18.56 Found: C 63.58 H 4.98 N 18.41.

2-(4-Morpholinyl)-4-(4-chlorophenyl)-6-(4-dimethylaminophenyl)pyrimidine (4f) m.p.191°C ;IR (KBr/cm^{-1}); 3052, 3026(=C-H (sp^2)), 2964, 2909(-C-H (sp^3)), 1599, 1493, 1451(C=C/C=N), 863, 765, 757, 694(Substituted Phenyl); ^{1}H NMR (δ, ppm, $CDCl_3$); 3.85 CH_2-O-CH_2 (t,4H), 3.42 CH_2-N-CH_2 (t,4H), 3.05 $N(CH_3)_2$(s,6H), 7.1-8.2 Ar-H & Pyrimidine-H_5 (m, 9H); ^{13}C NMR (δ, ppm, $CDCl_3$); 168.75, 124.85, 164.84, 161.73,67.89,44.48, 39.70,133.80, 131.90, 127.85, 129.80, 109.99, 126.60; Anal. calcd. for $C_{22}H_{23}ClN_4O$ (394.897) C 66.91 H 5.87 N 14.19 Found: C 66.87 H 5.67 N 14.11.

2-(1-Piperidinyl)-4-(4-hydroxyphenyl) -6-(3-nitrophenyl) pyrimidine (4g) m.p 185°C; IR (KBr/cm^{-1}); 3444 (OH), 3080(=C-H (sp^2)), 2965, 2889(-C-H (sp^3)), 1521, 1359 (-NO_2), 1611, 1576, 1542(C=C/C=N), 907, 843, 793 (Substituted Phenyl); ^{1}H NMR (δ, ppm, $CDCl_3$); 3.23 CH_2-N-CH_2 (t,4H), 2.00-$(CH_2)_3$ (m,6H), 10.17 OH (s, 1H, OH),7.2-8.3 Ar-H & Pyrimidine-H_5 (m, 9H); ^{13}C NMR (δ, ppm, $CDCl_3$);167.03,125.1,163.79, 162.2, 44.55, 26.1, 25.3,129.77, 127.5, 129.4, 131.3, 139.2, 134.6, 126.4, 148.2, 136.2; Anal. calcd. for $C_{21}H_{20}N_4O_3$ (376.409) C 67.01 H 5.36 N 14.88 Found: C 66.86 H 5.27 N 14.79.

2-(1-Piperidinyl)-4-(4-methylphenyl)-6-(3-nitrophenyl) pyrimidine (4h) m.p.176°C; IR (KBr/cm^{-1}); 3065(=C-H (sp^2)), 2919,2873(-C-H (sp^3)), 1528, 1349(-NO_2), 1632,1609(C=C/C=N), 862, 808, 776,734, 685(Substituted Phenyl); ^{1}H NMR (δ, ppm, $CDCl_3$); 3.30 CH_2-N-CH_2 (t,4H), 1.90-$(CH_2)_3$ (m,6H), 1.87 CH_3(s,3H), 7.2-8.3 Ar-H & Pyrimidine-H_5 (m, 9H); ^{13}C NMR (δ, ppm, $CDCl_3$); 168.56,123.16, 164.03, 162.00,44.29,26.17, 25.08, 21.61, 146.7, 136.30, 134.40, 132.81, 129.87, 128.22, 126.92, 126.22, 127.44; Anal. calcd. for $C_{22}H_{22}N_4O_2$ (374.436) C 70.54 H 5.92 N 14.96 Found: C 70.38 H 5.80 N 14.90.

2-(1-Piperidinyl)-4-(4-chlorophenyl)-6-(3-nitrophenyl) pyrimidine (4i) m.p.180°C; IR (KBr/cm^{-1}); 3059(=C-H (sp^2)), 2976(-C-H (sp^3)), 1520, 1365(-NO_2), 1617, 1581, 1507(C=C/C=N), 819, 735, 689(Substituted Phenyl); ^{1}H NMR (δ, ppm, $CDCl_3$); 3.15 CH_2-N-CH_2 (t,4H), 2.14-$(CH_2)_3$ (m,6H), 7.29-8.6 Ar-H & Pyrimidine-H_5 (m, 9H); ^{13}C NMR (δ, ppm, $CDCl_3$);167.95, 126.7,164.69, 162.4,44.2,26.1, 25.08, 127.6, 127.8, 135.25, 134.7, 126.4, 144.8, 125.18, 130.21, 134.94; Anal. calcd. for $C_{21}H_{19}ClN_4O_2$ (394.854) C 63.88 H 4.85 N 14.19 Found: C 63.81 H 4.80 N 14.13.

2-(1-Piperidinyl)-4-(4-bromophenyl)-6-(3-nitrophenyl) pyrimidine (4j) m.p.189°C; IR (KBr/cm^{-1}); 3056(=C-H (sp^2)), 2960(-C-H (sp^3)), 1499, 1352(-NO_2), 1607, 1567, 1509(C=C/C=N), 869, 768 (Substituted Phenyl); ^{1}H NMR (δ, ppm, $CDCl_3$); 3.35 CH_2-N-CH_2 (t,4H), 2.13-$(CH_2)_3$ (m,6H), 7.15-8.35 Ar-H & Pyrimidine-H_5 (m, 9H); ^{13}C NMR (δ, ppm, $CDCl_3$);168.56,126.9,164.57, 162.47,44.29,26.17, 25.18,135.50, 129.23, 122.09, 132.7, 127.4, 144.56, 123.16. 124.24. 135.49; Anal. calcd. for $C_{21}H_{19}BrN_4O_2$ (439.305) C 57.41 H 4.36 N 12.75 Found: C 57.33 H 4.30 N 12.70.

2-(1-Piperidinyl)-4-(4-aminophenyl)-6-(3-nitrophenyl)pyrimidine(4k) m.p.>240°C; IR (KBr/cm^{-1}); 3340, 3215(-NH_2), 3052, 3027(=C-H (sp^2)), 2910(-C-H (sp^3)), 1524, 1345(-NO_2), 1595,1493(C=C/C=N), 830,765,757, 694, 659(Substituted Phenyl); ^{1}H NMR (δ, ppm, $CDCl_3$); 3.08 CH_2-N-CH_2 (t,4H), 1.78-$(CH_2)_3$ (m,6H), 5.8 NH_2 (br, 2H), 6.5-8.2 Ar-H & Pyrimidine-H_5 (m, 9H); ^{13}C NMR (δ, ppm, $CDCl_3$);168.56,125.40,164.20, 162.56,45.17,26.29, 25.71,148.74, 144.30, 134.40, 131.37, 129.27, 127.41, 123.40, 122.90, 112.71; Anal. calcd. for $C_{21}H_{21}N_5O_2$ (375.424) C 67.18 H 5.64 N 18.65 Found: C 67.00 H 5.60 N 18.55.

2-(1-Piperidinyl)-4-(4-chlorophenyl)-6-(4-dimethylaminophenyl) pyrimidine (4l) m.p.163°C ; IR (KBr/cm^{-1}); 3098, 3086(=C-H (sp^2)), 2922(-C-H (sp^3)), 1602,1575, 1529, 1457(C=C/C=N), 858, 849, 762, 734,726(Substituted Phenyl); ^{1}H NMR (δ, ppm, $CDCl_3$); 3.30 CH_2-N-CH_2 (t,4H), 2.18-$(CH_2)_3$ (m,6H), 2.65 $N(CH_3)_2$ (s,6H) 7.2-8.3 Ar-H & Pyrimidine-H_5 (m, 9H); ^{13}C NMR (δ, ppm, $CDCl_3$);168.85,126.80,163.48, 162.23,44.29,25.08, 26.17,39.70, 151.78, 129.0, 127.60, 127.95, 123.07, 131.91, 109.8; Anal. calcd. for $C_{23}H_{25}ClN_4$ (392.924) C 70.31 H 6.41 N 14.26 Found: C 70.25 H 6.35 N 14.14.

2-(1-Pyrrolidinyl)-4-(4-hydroxyphenyl)-6-(3-nitrophenyl) pyrimidine(4m) m.p.198°C ; IR (KBr/cm^{-1}); 3463(OH), 3079(=C-H (sp^2)), 2971, 2881(-C-H (sp^3)), 1531, 1363(-NO_2), 1621, 1580, 1547 (C=C/C=N), 899, 832, 698(Substituted Phenyl); ^{1}H NMR (δ, ppm, $CDCl_3$); 3.45 CH_2-N-CH_2 (t,4H), 2.03-$(CH_2)_2$ (t,4H), 10.07 OH (s, 1H, OH), 7.0-8.2 Ar-H & Pyrimidine-H_5 (m, 9H); ^{13}C NMR (δ, ppm, $CDCl_3$);167.04, 125.9, 163.39, 160.3, 47.7, 25.45, 130.27, 126.86, 128.14, 131.17, 137,12, 132.75, 124.99, 146.41, 135.62; Anal. calcd. for $C_{20}H_{18}N_4O_3$ (362.382) C 66.29 H 5.01 N 14.46 Found: C 66.20 H 4.87 N 14.35.

2-(1-Pyrrolidinyl)-4-(4-methylphenyl)-6-(3-nitrophenyl) pyrimidine(4n) m.p.184°C; IR (KBr/cm^{-1}); 3068(=C-H (sp^2)), 2917, 2849(-C-H (sp^3)), 1527, 1349(-NO_2), 1612, 1608, 1446(C=C/C=N), 861, 808, 777, 734(Substituted Phenyl); ^{1}H NMR (δ, ppm, $CDCl_3$); 3.55 CH_2-N-CH_2 (t,4H), 1.95-$(CH_2)_2$ (t,4H), 2.2 CH_3 (s,3H), 7.2-8.4 Ar-H & Pyrimidine-H_5 (m, 9H); ^{13}C NMR (δ, ppm, $CDCl_3$);169.43,127.44,163.90, 160.29,47.81,26.02,21.61,129.27, 126.22, 128.22, 137.20, 144.80, 123.16, 142.31,134.40, 133.98; Anal. calcd. for $C_{21}H_{20}N_4O_2$ (360.409) C 69.98 H 5.59 N 15.55 Found: C 69.91 H 5.52 N 15.49.

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2-(1-Pyrrolidinyl)-4-(4-chlorophenyl)-6-(3-nitrophenyl) pyrimidine (4o) m.p.178°C ; IR (KBr/cm^{-1}); 3151, 3087(=C-H (sp^2)), 2961, 2871(-C-H (sp^3)), 1526, 1348(-NO_2), 1609,1587(C=C/C=N), 825, 803, 741, 684 (Substituted Phenyl); ^{1}H NMR (δ, ppm, $CDCl_3$); 3.45 CH_2-N-CH_2 (t,4H), 1.99-$(CH_2)_2$ (t,4H), 7.4-8.3 Ar-H & Pyrimidine-H_5 (m, 9H); ^{13}C NMR (δ, ppm, $CDCl_3$);167.43, 126.40, 163.51, 160.49, 47.81, 25.72, 126.98, 127.60, 133.1, 127.60, 144.8, 123.16, 129.27, 134.40; Anal. calcd. for $C_{20}H_{17}ClN_4O_2$ (380.828) C 63.08 H 4.50 N 14.71 Found: C 63.01 H 4.41 N 14.65.

2-(1-Pyrrolidinyl)-4-(4-bromophenyl)-6-(3-nitrophenyl) pyrimidine(4p) m.p.193°C ; IR (KBr/cm^{-1}); 3068(=C-H (sp^2)), 2978, 2855(-C-H (sp^3)), 1513, 1361(-NO_2), 1632, 1578, 1557(C=C/C=N), 875, 718, 693(Substituted Phenyl); ^{1}H NMR (δ, ppm, $CDCl_3$); 3.47 CH_2-N-CH_2 (t,4H), 2.06-$(CH_2)_2$ (t,4H), 7.1-8.3 Ar-H & Pyrimidine-H_5 (m, 9H); ^{13}C NMR (δ, ppm, $CDCl_3$);168.74,126.1,164.43, 160.2,47.5,25.85,129.7, 135.3, 127.7, 122.9, 133.1, 127.4, 144.7, 123.1, 129.2, 134.5; Anal. calcd. for $C_{20}H_{17}BrN_4O_2$ (425.279) C 56.48 H 4.03 N 13.17 Found: C 56.41 H 3.78 N 13.07.

2-(1-Pyrrolidinyl)-4-(4-aminophenyl)-6-(3-nitrophenyl) pyrimidine(4q) m.p.>240°C; IR (KBr/cm^{-1}); 3424, 3333(-NH_2), 3040, 3025(=C-H (sp^2)), 2865(-C-H (sp^3)), 1528, 1345(-NO_2), 1633,1607,1580, 1555(C=C/C=N), 875, 829,807,748, 729, 656(Substituted Phenyl); ^{1}H NMR (δ, ppm, $CDCl_3$); 3.36 CH_2-N-CH_2 (t,4H), 2.03-$(CH_2)_2$ (t,4H), 5.9 NH_2 (br, 2H), 6.6-8.3 Ar-H & Pyrimidine-H_5 (m, 9H); ^{13}C NMR (δ, ppm, $CDCl_3$);168.56,124.40,164.63, 160.50,47.80,26.02,129.27, 131.37, 112.71, 148.74, 132.70, 127.4, 144.7, 125.60, 134.40; Anal. calcd. for $C_{20}H_{19}N_5O_2$ (361.397) C 66.47 H 5.30 N 19.38 Found: C 66.31 H 5.11 N 19.29.

2-(1-Pyrrolidinyl)-4-(4-chlorophenyl)-6-(4-dimethyl aminophenyl) pyrimidine(4r) m.p.175°C; IR (KBr/cm^{-1}); 3059(=C-H (sp^2)), 2920,2853(-C-H (sp^3)), 1642, 1585, 1526 (C=C/C=N), 887, 756,711, 689(Substituted Phenyl); ^{1}H NMR (δ, ppm, $CDCl_3$); 3.46 CH_2-N-CH_2 (t,4H), 2.04-$(CH_2)_2$ (t,4H), 1.86 $N(CH_3)_2$ (br, 2H), 7.15-8.35 Ar-H & Pyrimidine-H_5 (m, 9H); ^{13}C NMR (δ, ppm, $CDCl_3$);168.79,127.1,164.73, 160.55, 47.45,25.68, 39.89,129.8, 127.6, 127.8, 133.8, 123.8, 131.9; Anal. calcd. for $C_{22}H_{23}ClN_4$ (378.897) C 69.74 H 6.12 N 14.78 Found: C 69.70 H 6.01 N 14.73.

V. ANTIBACTERIAL EVALUATION

All the representative compounds were screened in vitro for their antibacterial activity against gram-positive *Staphylococcus aureus, Bacillus subtilis and gram-negative Escherichia coli* by using cup-plate agar diffusion method[22-23] by measuring the zone of inhibition in mm (Table III). The test compounds were used at the concentration of 100 µ/mL in DMSO and streptomycin was used as standard drug with DMSO as control.

S.No.	Compd. No.	*S. aureus*	*B. substilis*	*E. coli*
1.	4a	12	25	11
2.	4d	8	17	7
3.	4e	13	26	14
4.	4f	9	14	19
5.	4g	14	22	13
6.	4j	7	14	5
7.	4k	12	24	15
8.	4l	10	12	17
9.	4m	9	20	10
10.	4p	7	12	6
11.	4q	12	24	11
12.	4r	9	12	16
13.	Streptomycin (STD)	21	30	20
14.	Control (DMSO)	00	00	00

Table 3:- Anti-bacterial activity of 2-(4-morpholinyl/1-piperidinyl / 1- pyrrolidinyl)-4,6-diaryl pyrimidines (zone of inhibition in mm)

VI. CONCLUSION

In this report, 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 seconds with improved yield as compared to conventional heating[15]. Compared with two step method, the one step method is more convenient as it minimized the yield loss and energy loss. All the tested compounds 4a, 4d, 4e, 4f, 4g, 4j, 4k, 4l, 4m, 4p, 4q, 4r showed moderate to good antibacterial activity against the tested bacterial strains. Compound 4f (R=Cl; R_2=$N(CH_3)_2$; R_4=4-morpholinyl) showed excellent activity against *E. coli* comparable with that of the standard whereas compound 4k, 4l, 4r against *E. coli* and 4a, 4e, 4k, and 4q against *B. substilis* have shown moderate to good activity. From the structural activity relationship (SAR) study it may be revealed that 4,6-diaryl pyrimidines having 2- morpholinyl / piperidinyl / pyrrolidinyl moieties in 4f, 4l and 4r along with chloro and dimethylamino substituents in phenyl rings have shown promising results against *E. coli* whereas 2-substituted morpholinyl (4a and 4e), piperidinyl (4k) and pyrrolidinyl (4q) having substituents nitro with hydroxyl and amino in the phenyl rings may impart an important role against *B. substilis.*

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