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A GREEN CATALYST ALUMINA SUPPORTED SODIUM HYDROGEN SULFATE MEDIATED AN EFFICIENT ONE-POT SYNTHESIS OF SUBSTITUTED PYRIMIDINE CONTAINING IMIDAZOLES IN DRY MEDIA AND SCREENING IN VITRO MICROBIOLOGICAL EVALUATION

V. Thamodhiran*, R. Magesh Samuvel*, V. Ponvannan*, J. Thanusu & M. Gopalakrishnan****

* Department of Bio Medical Engineering and Department of Chemistry, Alpha College of Engineering, Chennai, Tamilnadu

** Department of Chemistry, Annamalai University, Annamalainagar, Tamilnadu

Abstract:

*A simple, green and effective one-pot synthesis of 4,6-diaryl-2-(2-aryl-4,5-diphenyl-1H-imidazol-1-yl)pyrimidines **13-24** from substituted 2-amino pyrimidine **1-12**, benzil, substituted aromatic aldehyde and ammonium acetate in presence of alumina supported sodium hydrogen sulfate ($NaHSO_4$ .Al_2O_3) catalyst in dry media under microwave irradiation in solvent free has been described. This effective one-pot green synthetic technology is very simple, affording high yields in shorter reaction.The structures of all the newly synthesized compounds **5-15** have been confirmed by elemental analysis, FT-IR, MS, ^1H NMR and ^{13}C NMR spectral data. All the synthesized compounds have been screened for their in vitro antimicrobial activity against selected clinically isolated bacterial and fungal strains by disc diffusion and minimum inhibitory concentration method.*

Key Words: Alumina Supported Sodium Hydrogen Sulfate Catalyst ($NaHSO_4$ .Al_2O_3), Dry Media, Pyrimidine Containing Imidazole, One-Pot Green Synthetic Methodology & Antimicrobial Activity.

Introduction:

Multicomponent reactions (MCRs) are important for the achievement of high levels of diversity, as they allow more than two building blocks to be combined in practical, time saving one-pot operations, giving rise to complex structures by simultaneous formation of two or more bonds, according to the domino principle[1]. MCRs contribute to the requirements of an environmentally friendly process by reducing the number of synthetic steps, energy consumption and waste production. Researchers have transformed this powerful technology into one of the most efficient and economic tools for combinatorial and parallel synthesis [1, 2]. Due to their inherent simple experimental procedures and their one-pot character, they are perfectly suited for automated synthesis. Thus, MCRs have attracted considerable interest owing to their exceptional synthetic efficiency [1, 3].

The imidazole ring system is one of the most important substructures found in a large number of natural products and pharmacologically active compounds [4, 5]. Triarylimidazole derivatives have many biological activities, for example, herbicidal [6], fungicidal [7], anti-inflammatory [8] and antithrombotic activities [9]. In addition, they are used in photography as photosensitive compound [10]. Tetrasubstituted imidazole is frequently found in many biological systems such as Losartan and Olmesartan[11]. Imidazoles like lepidilines A and B exhibit cytotoxicity against several human cancer cell lines [12]. Only few general methods exist for the synthesis of tetrasubstituted imidazoles catalyzed by silica gel or Zeolite HY [13], silica gel-$NaHSO_4$ [14], molecular

iodine [15], $K_5CoW_{12}O_{40}.3H_2O$ [16], heteropolyacids [17]. Many of these methods are associated with one or more disadvantages such as expensive or toxic reagents, long reaction times, tedious work-up and low yields. Thus, development of new methods using cheap and commercially available less toxic reagents to afford high yields of products in short reaction times required.

Pyrimidines being an integral part of nucleic acids and many chemotherapeutic agents display a wide range of pharmacological activities as bactericide [18], fungicide [19], phosphodiesterase inhibitor [20], viricide [21], and leishmancide [22]. Pyrimidines are the basic nucleus in nucleic acids and have been associated with a number of biological activities [23]. Substituted aminopyrimidine nuclei are common in marketed drugs such as anti-atherosclerotic aronixil, anti-histaminic thonzylamine, anti-anxielytic buspirone, anti-psoriatic enazadrem, and other medicinally relevant compounds [24]. Many pyrimidine derivatives have been found to be active against different forms of cancer [25]. Various method of synthesis and reactions of aminopyrimidines are reported [26, 27].

The challenge in chemistry to develop practical process, reaction media, conditions and utility of materials based on the idea of green chemistry is one of the most important issues in the scientific community [28]. Heterogeneous reactions facilitated by supported reagents on various mineral oxides have received special attention in recent years [29]. Heterogeneous alumina supported sodium hydrogensulfate ($NaHSO_4$ .Al_2O_3), a non-toxic and inexpensive catalyst, has been used for this one-pot conversion and this catalyst was shown to be one of the most efficient MW absorbers with a very high specificity to MW heating. Owing to our interest in coupling dry media technique with microwave irradiation(MWI), We attempted to use neutral alumina supported hydrogen sulphate($NaHSO_4$ .Al_2O_3) as heterogeneous catalyst for one-pot synthesis of 4,6-diaryl-2-(2-aryl-4,5-diphenyl-1*H*-imidazol-1-yl)pyrimidines **13-24**.

In connection with our earlier work on the synthesis of structurally diverse biologically active hybrid heterocyclic ring systems and as part of our ongoing research programme[30-32], we planned to design a system, which combines together two biolabile nuclei which are imidazole and aminopyrimidine, to give a compact structure like the title hybrid bioactive compounds. In the present work, a new series of bis heterocycles comprising two biolabile nuclei which are imidazole and aminopyrimidine nuclei together namely 4,6-diaryl-2-(2-aryl-4,5-diphenyl-1*H*-imidazol-1-yl)pyrimidines **13-24** was synthesized by treatment of the respective aminopyrimidine **1-12**, substituted aromatic aldehyde with benzil and ammonium acetate in the presence of $NaHSO_4.Al_2O_3$ via one-pot green synthetic operations. The synthetic route for the formation of compounds **13-24** was given in **scheme-1**.

Results and Discussion:

A number of methods have been developed for the synthesis of trisubstituted and tetrasubstituted by multicomponent synthetic technology [13-17,34-38]. Most of these synthetic methods suffer from one or more serious drawbacks, such as laborious and complex work-up and purification, significant amount of waste materials, side reactions, low yields and uses of expensive reagents. The Claisen-Schmidt condensation of equimolar quantities of various *p*-substituted acetophenones with different *p*-substituted benzaldehydes in the presence of sodium hydroxide base as a catalyst yields 1,3-diaryl-prop-2-en-1-ones**.** When 1,3-diaryl-prop-2-en-1-ones are treated with guanidine nitrate in the presence of sodium hydroxide alkali in refluxing ethanol for

10h, it gives 2-amino-4,6-diarylpyrimidines **1-12**. Novel title compounds, 4,6-diaryl-2-(2-aryl-4,5-diphenyl-1*H*-imidazol-1-yl)pyrimidines **13-24** were synthesized by the one-pot four component cyclocondesation reaction of benzil (1equiv), 2-amino-4,6-diarylpyrimidines (1equiv), substituted benzaldehydes (1equiv), and ammonium acetate (1equiv) in the presence of alumina supported hydrogen sulphate($NaHSO_4$ .Al_2O_3) in solvent-free conditions under microwave irradiation (MWI), since the applications of microwave technology to rapid synthesis of biologically significant heterocyclic molecules under solvent-free conditions are very promising, numerous and has recently been recognized as a useful tool for a drug-discovery program especially in combinatorial chemistry. The reactions were performed at 120 · C for 6 min. After completion of the reaction as indicated by the TLC, the reaction mixture was poured into ice water. The mixture was extracted with dichloromethane and washed with 10% sodium bicarbonate solution, finally washed with distilled water, concentrated in rotary evaporator and purified by flash column chromatography using ethyl acetate-Petroleum ether (bp40-60) in the ratio (2:8) as eluent.

The green synthetic pathway for the formation of compounds **13-24** was given in **Scheme-1.** The physical and analytical data was given **Table-1**. The importance of the title compounds is due to their diverse potential, broad-spectrum biological activity. The structure of the newly synthesized compounds **13-24** is confirmed by melting point, elemental analysis, MS, FT-IR, one-dimensional NMR (^1H & ^{13}C) spectroscopic data. In order to discuss the spectral characterization, 4,6-diphenyl-2-(2,4,5-triphenyl-1H-imidazol-1-yl)pyrimidine **13** was chosen as the representative compound. The compound was obtained as a white powder in a yield of 94%. IR spectrum of **13** showed characteristic absorption frequency at 1642 cm^{-1} suggested the presence of C=N stretching vibration. In addition a strong absorption was observed at 1592 cm^{-1} due to the presence of C=C stretching frequency. The mass spectrum of **13** showed molecular ion peak at m/z **527** ($M^{+\bullet}$+1), which was consistent with the proposed molecular formula of **13**. IR (KBr) (cm^{-1}): 3314, 3193, 3058, 3030, 2920, 2851, 1642, 1592, 1360, 1236, 1112, 761, 693.

The elemental analysis [C_{cal}84.38, C_{obs}84.31; H_{cal}4.98, H_{obs}4.93; N_{cal}10.64, N_{obs}10.60] were consistent with the proposed molecular formula [$C_{37}H_{26}N_4$] of **13.** In the ^1H NMR spectrum of **13**, A singlet for CH proton at position 5′ of pyrimidine moiety is merged with aromatic protons. The aromatic protons appeared in the range of 7.50-8.23 ppm. In the ^{13}C NMR Spectrum, resonance at 108.1 ppm was assigned to methane carbon at C-5′ of pyrimidine moiety. The signal at 163.8 ppm is due to C-2′ of pyrimidine moiety and the signal at 161.3 ppm is assigned to C-4′ and C-6′ carbons of pyrimidine moiety. The ^{13}C resonance at 139.1 ppm is due to the phenyl quaternary carbons C-4″ and C-6″ attached to pyrimidine ring. The signal at 131.4, 132.4, 133.4 ppm were due to the phenyl quaternary carbons C-2‴, C-4‴ and C-5‴attached to imidazole ring. The signals at 150.3, 151.2 ppm were assigned to C-4 and C-5 carbons of imidazole moiety respectively. Resonance at 155.7 ppm was due to C-2 carbon of imidazole moiety. The rest of the aromatic carbons resonante in the region 126.9 -129.8 ppm.

The Reuse Ability of $NaHSO_4$ .Al_2O_3 Catalyst:

The reuse ability of $NaHSO_4$ .Al_2O_3 catalyst was studied for this conversion, after filtration washed with diethyl ether and then dried at 120· C for 1h and successfully reused several times for the next round of reaction as shown in **Table-2**. As depicted in **Table -2**, it is evident that the system still retains high conversion after repeating the reuse procedure up to 3 times

Experimental Chemistry:

We used TLC to assess the reactions and the purity of the products. All the reported melting points were taken in open capillaries and were uncorrected. A conventional (*unmodified*) domestic microwave oven equipped with a turntable (LG, MG-395 WA, 230V~50Hz, 760 W) was used for the irradiation. IR spectra were recorded in KBr (pellet forms) on a Thermo Nicolet-Avatar–330 FT-IR spectrophotometer and noteworthy absorption values (cm^{-1}) alone were listed. One dimensional ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz respectively on Bruker AMX 400 NMR spectrometer using DMSO-*d* as solvent and tetramethylsilane (TMS) as internal standard. The electron spray ionization (ESI) positive (+ve) mass (MS) spectra were recorded on a Bruker Daltonics Esquire 3000 mass spectrometry. Satisfactory microanalysis was obtained on Carlo Erba 1106 CHN analyzer. By adopting the literature precedent 1,3-diaryl-prop-2-en-1-ones [26] and 2-amino-4,6-diarylpyrimidines[27] **1-12** were synthesized. *In vitro* antibacterial and antifungal activity were carried out by following the literature procedure [33].

$NaHSO_4.Al_2O_3$ Catalyst was Prepared as Follows:

$NaHSO_4.H_2O$ (4.14g, 0.03 mol) in 20 mL of water was stirred with neutral alumina (10g) for 15min and then gently heated on a hot plate with intermittent swirling, until a free-flowing white solid was obtained. It was further dried in an oven maintained at 120· C for at least 48h prior to use

General method for the synthesis of 4,6-diphenyl-2-(2,4,5-triphenyl-1H-imidazol-1-yl)pyrimidine 13:

In a 25 ml pyrex glass beaker, ammonium acetate (1equiv),4,6-diphenylpyrimidin-2-amine(1equiv), benzaldehyde(1equiv), benzil(1equiv) were mixed thoroughly with $NaHSO_4.Al_2O_3$(100mg) catalyst for 15s with the help of aglass rod. The mixture was placed in an alumina bath inside a microwave oven (LG, MG-395 WA, 230V~50Hz, 760 W) and irradiated for 5min at 320 W (monitored by TLC). The reaction mixture was cooled and extracted with ethyl acetate (2×15 ml). The catalyst was removed by filtration and reused. The filtrate was concentrated in vacuum to obtain the respective products **13 – 24**.

The reaction mixture was cooled to room temperature and poured into ice-water (75 ml) to get the precipitated solid. It was collected by filtration, washed with 10% sodium bicarbonate, brine solution, finally with water and dried over anhydrous sodium sulfate. After evaporation of the solvent under reduced pressure, a gummy mass was obtained, which was solidified on treatment of petroleum ether (bp40-60). Final purification of 4,6-diphenyl-2-(2,4,5-triphenyl-1*H*-imidazol-1-yl)pyrimidine **13** was done by column chromatography using silica gel (100-200 mesh), with ethyl acetate-Petroleum ether (bp40-60)in the ratio (2:8) as eluent. The compounds **14-24** were synthesized correspondingly.

4,6-diphenyl-2-(2,4,5-triphenyl-1H-imidazol-1-yl)pyrimidine13:

The compound was obtained as a white powder with a yield of 96%; IR (KBr) (cm^{-1}): 3314, 3193, 3058, 3030, 2920, 2851, 1642, 1592, 1360, 1236, 1112, 761, 693; ^{1}H NMR (δ ppm): A singlet for CH proton at position 5′of pyrimidine moiety is merged with aromatic protons(s, 1H, H-5′), 7.50-8.23 (m, 23H, H_{arom}). ^{13}C NMR (δ ppm): 163.8 C-2', 161.3 C-4′, 108.1 C-5′, 161.3 C-6′, 139.1 C-4″ & C-6″, 155.7 C-2, 150.3 C-4, 151.2 C-5, 131.4 C-2‴, 132.4 C-4‴, 133.4 C-5‴, 126.9-129.8 – C_{arom}.

4-(4-fluorophenyl)-2-(2,4,5-triphenyl-1H-imidazol-1-yl)-6-p-tolylpyrimidine14:

The compound was obtained as a white powder with a yield of 94%; IR (KBr)

(cm^{-1}): 3317, 3293, 3058, 3036, 2928, 2851, 1645, 1582, 1366, 1236, 1112, 762, 696; ^1H NMR (δ ppm): A singlet for CH proton at position 5′of pyrimidine moiety is merged with aromatic protons(s, 1H, H-5′), 2.49 (s, 3H, CH_3), 7.31-8.44 (m, 23H, H_{arom}). ^{13}C NMR (δ ppm): 24.5 CH_3 on aryl ring, 163.6 C-2', 164.9 C-4′, 108.4 C-5′, 163.5 C-6′, 138.7 C-4″, 139.1 C-6″, 156.6 C-2, 151.9 C-4, 152.9 C-5, 134.4 C-2‴, 132.4 C-4‴, 132.4 C-5‴, 127.5-133.1 – C_{arom}.

4-(4-chlorophenyl)-6-(4-methoxyphenyl)-2-(2,4,5-triphenyl-1H-imidazol-1-yl)pyrimidine15:

The compound was obtained as a white powder with a yield of 92%; IR (KBr) (cm^{-1}): 3320, 3273, 3158, 3036, 2928, 2851, 1642, 1582, 1366, 1246, 1112, 760, 694; ^1H NMR (δ ppm): A singlet for CH proton at position 5′of pyrimidine moiety is merged with aromatic protons(s, 1H, H-5′), 3.84 (s, 3H, OCH_3), 7.34-8.54 (m, 23H, H_{arom}). ^{13}C NMR (δ ppm): 54.5 OCH_3 on aryl ring, 163.9 C-2', 165.9 C-4′, 109.4 C-5′, 162.5 C-6′, 139.7 C-4″, 139.1 C-6″, 155.9 C-2, 152.1 C-4, 153.2 C-5,134.7 C-2‴, 132.7 C-4‴, 132.9 C-5‴, 128.5-133.9 – C_{arom}.

4,6-bis(4-fluorophenyl)-2-(2,4,5-triphenyl-1H-imidazol-1-yl)pyrimidine16:

The compound was obtained as a white powder with a yield of 95%; IR (KBr) (cm^{-1}): 3310, 3255, 3158, 3018, 2968, 2893, 1647, 1576, 1366, 1256, 1120, 769, 697; ^1H NMR (δ ppm): A singlet for CH proton at position 5′of pyrimidine moiety is merged with aromatic protons(s, 1H, H-5′), 7.56-8.69 (m, 23H, H_{arom}). ^{13}C NMR (δ ppm): 164.3 C-2', 166.4 C-4′, 109.9 C-5′, 163.4 C-6′, 138.7 C-4″, 139.1 C-6″, 156.2 C-2, 153.1 C-4, 153.5 C-5, 133.7 C-2‴, 131.9 C-4‴, 132.9 C-5‴, 128.7-134.5 – C_{arom}.

4-(4-chlorophenyl)-6-phenyl-2-(2,4,5-triphenyl-1H-imidazol-1-yl)pyrimidine17:

IR (KBr) (cm^{-1}): 3309, 3300, 3138, 3018, 2959, 2868, 1640, 1560, 1372, 1267, 1118, 760, 691; ^1H NMR (δ ppm): A singlet for CH proton at position 5′of pyrimidine moiety is merged with aromatic protons(s, 1H, H-5′), 7.62-8.88 (m, 24H, H_{arom}). ^{13}C NMR (δ ppm): 164.3 C-2', 166.1 C-4′, 109.5 C-5′, 163.2 C-6′, 137.7 C-4″, 139.5 C-6″, 155.6 C-2, 152.2 C-4, 153.7 C-5, 131.4 C-2‴, 131.7 C-4‴, 132.6 C-5‴, 127.9-134.8 – C_{arom}.

4,6-bis(4-methoxyphenyl)-2-(2,4,5-triphenyl-1H-imidazol-1-yl)pyrimidine18:

The compound was obtained as a white powder with a yield of 95%; IR (KBr) (cm^{-1}): 3343, 3321, 3178, 3049, 2950, 2898, 1649, 1567, 1383, 1255, 1143, 768, 693; ^1H NMR (δ ppm): A singlet for CH proton at position 5′of pyrimidine moiety is merged with aromatic protons(s, 1H, H-5′), 3.82 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 7.58-8.79 (m, 23H, H_{arom}). ^{13}C NMR (δ ppm): 54.5 OCH_3 , 54.7 OCH_3 on aryl ring, 163.2 C-2', 164.9 C-4′, 108.7 C-5′, 164.2 C-6′, 138.9 C-4″, 139.6 C-6″, 155.4 C-2, 154.1 C-4, 153.9 C-5, 131.7 C-2‴, 131.8 C-4‴, 133.2 C-5‴, 127.5-133.5 – C_{arom}.

4,6-diphenyl-2-(4,5-diphenyl-2-p-tolyl-1H-imidazol-1-yl)pyrimidine19:

The compound was obtained as a white powder with a yield of 94%; IR (KBr) (cm^{-1}): 3333, 3310, 3180, 3149, 2969, 2859, 1644, 1550, 1378, 1265, 1243, 769, 699; ^1H NMR (δ ppm): A singlet for CH proton at position 5′of pyrimidine moiety is merged with aromatic protons(s, 1H, H-5′), 2.38 (s, 3H, CH_3), 7.39-8.74 (m, 24H, H_{arom}). ^{13}C NMR (δ ppm): 24.6 CH_3 on aryl ring, 163.1 C-2', 163.7 C-4′, 107.7 C-5′, 163.3 C-6′, 137.8 C-4″, 138.9 C-6″, 154.3 C-2, 152.4 C-4, 153.6 C-5, 132.4 C-2‴, 131.9 C-4‴, 132.9 C-5‴, 127.9-135.4 – C_{arom}.

2-(2-(4-methoxyphenyl)-4,5-diphenyl-1H-imidazol-1-yl)-4,6-diphenylpyrimidine20:

The compound was obtained as a white powder with a yield of 94%; IR (KBr) (cm^{-1}): 3370, 3344, 3134, 3167, 2972, 2864, 1648, 1544, 1368, 1250, 1233, 776, 677; ^1H

NMR (δ ppm): A singlet for CH proton at position 5′of pyrimidine moiety is merged with aromatic protons(s, 1H, H-5′), 3.86 (s, 3H, OCH_3), 7.46-8.64 (m, 23H, H_{arom}). ^{13}C NMR (δ ppm): 54.3 OCH_3 on aryl ring, 163.3 C-2', 163.5 C-4′, 108.3 C-5′, 162.9 C-6′, 137.9 C-4″, 138.8 C-6″, 154.5 C-2, 153.3 C-4, 154.2 C-5, 133.2 C-2‴, 132.8 C-4‴, 133.9 C-5‴, 127.5-133.2 – C_{arom}.

2-(2-(4-fluorophenyl)-4,5-diphenyl-1H-imidazol-1-yl)-4,6-diphenylpyrimidine21:

The compound was obtained as a white powder with a yield of 94%; IR (KBr) (cm^{-1}): 3317, 3258, 3154, 3016, 2969, 2899, 1641, 1575, 1365, 1252, 1125, 764, 692; ^1H NMR (δ ppm): A singlet for CH proton at position 5′of pyrimidine moiety is merged with aromatic protons(s, 1H, H-5′), 7.46-8.59 (m, 23H, H_{arom}). ^{13}C NMR (δ ppm): 164.9 C-2', 164.1 C-4′, 109.7 C-5′, 162.8 C-6′, 138.9 C-4″, 137.9 C-6″, 156.2 C-2, 153.2 C-4, 153.9 C-5, 133.9 C-2‴, 133.1 C-4‴,132.8 C-5‴, 126.7-135.9 – C_{arom}.

2-(2-(4-chlorophenyl)-4,5-diphenyl-1H-imidazol-1-yl)-4,6-diphenylpyrimidine22:

The compound was obtained as a white powder with a yield of 95%; IR (KBr) (cm^{-1}): 3340, 3232, 3155, 3032, 2950, 2839, 1642, 1544, 1375, 1233, 1156, 786, 697; ^1H NMR (δ ppm): A singlet for CH proton at position 5′of pyrimidine moiety is merged with aromatic protons(s, 1H, H-5′), 7.49-8.67 (m, 23H, H_{arom}). ^{13}C NMR (δ ppm): 163.8 C-2', 163.3 C-4′, 108.6 C-5′, 162.5 C-6′, 138.7 C-4″, 139.2 C-6″, 156.3 C-2, 153.4 C-4, 153.8 C-5, 133.5 C-2‴, 132.8 C-4‴,132.8 C-5‴, 127.1-136.2 – C_{arom}.

4,6-bis(4-fluorophenyl)-2-(2-(4-fluorophenyl)-4,5-diphenyl-1H-imidazol-1-yl)pyrimidine23:

The compound was obtained as a white powder with a yield of 95%; IR (KBr) (cm^{-1}): 3359, 3330, 3158, 3028, 2949, 2868, 1637, 1543, 1352, 1255, 1123, 768, 689; ^1H NMR (δ ppm): A singlet for CH proton at position 5′of pyrimidine moiety is merged with aromatic protons(s, 1H, H-5′), 7.45-8.69 (m, 23H, H_{arom}). ^{13}C NMR (δ ppm): 165.1 C-2', 164.4 C-4′, 110.1 C-5′, 163.7 C-6′, 137.9 C-4″, 138.3 C-6″, 156.9 C-2, 152.9 C-4, 153.4 C-5, 132.5 C-2‴, 132.8 C-4‴,132.7 C-5‴, 128.4-135.9 – C_{arom}.

4-(4-chlorophenyl)-6-(4-fluorophenyl)-2-(2-(4-methoxyphenyl)-4,5-diphenyl-1H-imidazol-1-yl) Pyrimidine24:

The compound was obtained as a white powder with a yield of 96%; IR (KBr) (cm^{-1}): 3340, 3333, 3155, 3128, 2940, 2844, 1640, 1551, 1358, 1245, 1113, 771, 669; ^1H NMR (δ ppm): A singlet for CH proton at position 5′of pyrimidine moiety is merged with aromatic protons(s, 1H, H-5′), 3.87 (s, 3H, OCH_3), 7.57-8.78 (m, 23H, H_{arom}). ^{13}C NMR (δ ppm): 54.6 OCH_3 on aryl ring, 164.3 C-2', 165.2 C-4′, 109.8 C-5′, 163.7 C-6′, 138.9 C-4″, 139.3 C-6″, 155.5 C-2, 152.8 C-4, 153.9 C-5, 132.7 C-2‴, 132.5 C-4‴, 132.9 C-5‴, 127.9-135.4 – C_{arom}.

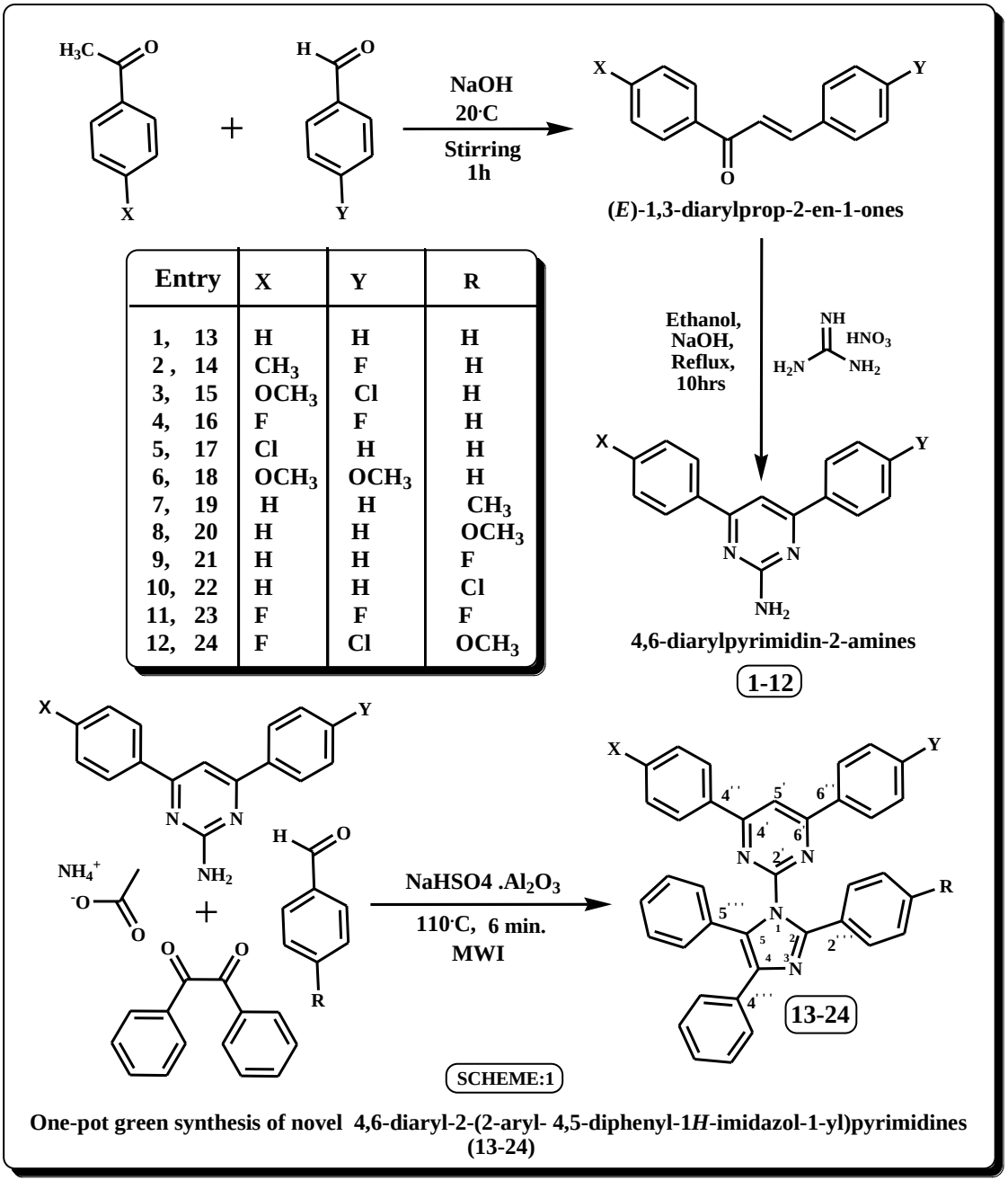
Table 1: Physical and analytical data of 4,6-diaryl-2-(2-aryl-4,5-diphenyl-1*H*-imidazol-1-yl)pyrimidines 13-24

Entry	Reaction conditions		m.p (°C)	Elemental analysis (%)			m/z $(M+1)^{+\cdot}$ Molecular formula	
	Temp. (°C)	Time (min)		C Found (Calculated)	H Found (Calculated)	N Found (Calculated)		
13	70	40	178	84.31 (84.38)	4.93 (4.98)	10.60 (10.64)	527	$C_{37}H_{26}N_4$
14	70	40	161	81.64 (81.70)	4.82 (4.87)	10.00 (10.03)	559	$C_{38}H_{27}FN_4$
15	75	35	178	77.17 (77.21)	4.55 (4.60)	09.43 (09.48)	592	$C_{38}H_{27}ClN_4O$
16	75	35	181	78.96 (78.99)	4.26 (4.30)	09.93 (09.96)	563	$C_{37}H_{24}F_2N_4$
17	70	45	173	79.15 (79.20)	4.45 (4.49)	09.92 (09.96)	562	$C_{37}H_{25}ClN_4$
18	70	40	193	79.80 (79.84)	5.10 (5.15)	09.51 (09.55)	587	$C_{39}H_{30}N_4O_2$
19	70	45	160	84.37 (84.42)	5.17 (5.22)	10.33 (10.36)	542	$C_{38}H_{28}N_4$

20	75	40	180	81.95 (81.99)	5.01 (5.07)	10.01 (10.06)	557	$C_{38}H_{28}N_4O$
21	75	35	197	81.55 (81.60)	4.58 (4.63)	10.25 (10.29)	546	$C_{37}H_{25}N_4F$
22	75	35	183	79.16 (79.20)	4.44 (4.49)	09.94 (09.99)	562	$C_{37}H_{25}ClN_4$
23	70	45	168	76.50 (76.54)	3.96 (3.99)	09.60 (09.65)	581	$C_{37}H_{23}N_4F_3$
24	70	45	168	74.88 (74.93)	4.25 (4.30)	09.16 (09.20)	610	$C_{38}H_{26}ClFN_4O$

Table 2: The reuse ability of $NaHSO_4.Al_2O_3$ catalyst

Run	Time(min)	Yield (%)	Run	Time(min)	Yield (%)
1	4	96	4	4	75
2	4	95	5	4	50
3	4	95	6	4	30



Entry	X	Y	R
1, 13	H	H	H
2, 14	CH_3	F	H
3, 15	OCH_3	Cl	H
4, 16	F	F	H
5, 17	Cl	H	H
6, 18	OCH_3	OCH_3	H
7, 19	H	H	CH_3
8, 20	H	H	OCH_3
9, 21	H	H	F
10, 22	H	H	Cl
11, 23	F	F	F
12, 24	F	Cl	OCH_3

One-pot green synthesis of novel 4,6-diaryl-2-(2-aryl- 4,5-diphenyl-1*H*-imidazol-1-yl)pyrimidines (13-24)

Microbiology Materials:

All the clinically isolated bacterial strains namely *Staphylococcus aureus, β-Heamolytic streptococcus, Vibreo cholerae, Salmonella typhii, Shigella felxneri, Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa* and fungal strains namely *Aspergillus flavus, Mucor, Rhizopus* and *Microsporum gypsuem* were obtained from the Faculty of Medicine, Annamalai University, Annamalainagar-608 002, Tamil Nadu, India.

In Vitro Antibacterial and Antifungal Activity:

Minimum inhibitory concentration (MIC) in µg/mL values was carried out by two-fold serial dilution method [33]. The respective test compounds **13-24** were dissolved in dimethyl sulphoxide (DMSO) to obtain 1 mg mL^{-1} stock solution. Seeded broth (broth containing microbial spores) was prepared in NB from 24 h old bacterial cultures on nutrient agar (Hi-media, Mumbai) at 37 ± 1 °C while fungal spores from 1 to 7 days old Sabourauds agar (Hi-media, Mumbai) slant cultures were suspended in SDB. The colony forming units (cfu) of the seeded broth were determined by plating technique and adjusted in the range of 10^4-10^5 cfu/mL. The final inoculums size was 10^5cfu/mL for antibacterial assay and 1.1-1.5 X 10^2 cfu/mL for antifungal assay. Testing was performed at pH 7.4±0.2 for bacteria (NB) and at a pH 5.6 for fungi (SDB). Exactly 0.4 mL of the solution of test compound was added to 1.6 mL of seeded broth to form the first dilution. One millilitre of this was diluted with a further 1 mL of seeded broth to give the second dilution and so on till six such dilutions were obtained. A set of assay tubes containing only seeded broth was kept as control. The tubes were incubated in BOD incubators at 37±1^{0}C for bacteria and 28±1^{0}C for fungi. The minimum inhibitory concentrations (MICs) were recorded by visual observations after 24 h (for bacteria) and 72-96 h (for fungi) of incubation. Ciprofloxacin was used as standard for bacteria studies and Fluconazole was used as standards for fungal studies.

Antibacterial Activity:

Novel 4,6-diaryl-2-(2-aryl-4,5-diphenyl-1*H*-imidazol-1-yl)pyrimidines **13-24** were tested for their antibacterial activity *in vitro* against *S.aureus, β-H.streptococcus, V.cholerae, S.typhii, S.felxneri, E.coli, K.pneumonia* and *P.aeruginosa*. Ciprofloxacin was used as a standard drug. Minimum inhibitory concentration (MIC) in µg/mL values is reproduced in **Table-3**. Compound **13** which has no substitution at the *para* position of phenyl rings only exerted moderate activities against all the used bacterial strains. Compounds **16, 17** and **22**which contain electron withdrawing chloro and fluoro functional group respectively at the *para* position of phenyl ring attached to pyrimidine and imidazole ring did not promote much activity against *β-H.streptococcus, S.felxneri* and *E.coli.* Structure-activity relationship results for the synthesized compounds have shown that 4,6-diaryl-2-(2-aryl-4,5-diphenyl-1*H*-imidazol-1-yl)pyrimidines with electron donating methoxy and methyl functional groups at the *para* position of the phenyl ring attached to the pyrimidine ring and imidazole ring **14, 15** and **24** exerted strong antibacterial activity against all the tested bacterial strains. Also compound **14**, which contains both electron withdrawing fluoro and electron donating methyl groups shows potent activity against all the tested bacterial strains whereas compounds **15, 20** and **24** which contain electron donating methoxy functional group at the *para* position of phenyl ring attached to pyrimidine ring shows promising activity against *S.aureus*, *S.typhii* and *E.coli*.

Antifungal Activity:

The *in vitro* antifungal activity of 4,6-diaryl-2-(2-aryl-4,5-diphenyl-1*H*-imidazol-1-yl)pyrimidines **13-24** was studied against the fungal strains *viz., A.flavus, Mucor, Rhizopus* and *M.gypsuem.* Fluconazole was used as a standard drug. Minimum inhibitory concentration (MIC) in µg/mL values is reproduced in **Table-4**. Compound **13** did not exhibit antifungal activity against *A.flavus* and *M.gypsuem*. Further introduction of electron withdrawing chloro functional group at the *para* position of phenyl ring attached to pyrimidine ring and imidazole ring in compounds **15, 17, 22** and **24** also did not promote much activity against *A.flavus* and *M.gypsuem* while against *Mucor* and *Rhizopus*, it has registered maximum activity at 25 µg/mL. Compounds **16, 21, 23** and **24** show excellent activitites against all the tested clinically isolated fungal strains, while against *Mucor*, compounds **14** and **19** which contain electron donating methyl group at the *para* position of phenyl ring attached to pyrimidine ring showed promisable activities. Compounds **18** and **20** which contain electron donating methoxy functional group at the *para* position of phenyl ring attached to pyrimidine ring andmidazole ring did not promote much activity against *Mucor* and *Rhizopus.* Also compounds **23** and **24** which contain both electron withdrawing chloro and electron donating methyl groups shows potent activity against *A. flavus* and *Rhizopus*.

Conclusion:

To conclude, we have proposed an efficient green method for the synthesis of novel 4,6-diaryl-2-(2-aryl-4,5-diphenyl-1*H*-imidazol-1-yl)pyrimidines **13-24** from substituted 2-amino pyrimidine **1-12**, benzil, substituted aromatic aldehyde and ammonium acetate in the presence of alumina supported sodium hydrogen sulfate catalyst in dry media under microwave irradiation(MWI) and their structures were characterized by their spectral and analytical data. The advantages of the present reaction procedure include short reaction times for product formation, easy workup, clean reaction profiles, reusable catalyst and high yields.

The microbiological screening studies carried out to evaluate the antibacterial and antifungal potencies of the newly synthesized 4,6-diaryl-2-(2-aryl-4,5-diphenyl-1*H*-imidazol-1-yl)pyrimidines **13-24** are clearly known from **Table-2** and **Table-3**. A close inspection of the *in vitro* antibacterial and antifungal activity profile in differently electron donating (CH_3 and OCH_3) and electron withdrawing (-Cl and -F) functional group substituted phenyl rings of novel 4,6-diaryl-2-(2-aryl-4,5-diphenyl-1*H*-imidazol-1-yl)pyrimidines **13-24** exerted strong anti-bacterial activity against all the tested bacterial strains. Compounds **14**, **15, 24** and **23** which contain both electron withdrawing chloro and electron donating methyl groups shows potent activity against all the tested bacterial strains whereas compounds **18,** and **20** which contain electron donating methoxy functional group at the *para* position of phenyl ring attached to pyrimidine ring and imidazole ring shows promising activity against *S.aureus*, *S.typhii* and *E.coli*. Results of the anti-fungal activity study shows that the nature of substituents on the phenyl ring viz., methyl, fluoro and chloro functions at the *para* positions of the aryl moieties are determinant for the nature and extent of the anti-fungal activity of all the synthesized compounds **13-24** over fungal strains namely *A.flavus, Mucor, Rhizopus* and M.gypsuem. Compound **24**, which contains both electron withdrawing chloro, fluoro and electron donating methoxy groups shows potent activity against *A. flavus* and *Rhizopus*. The method of action of these compounds is unknown. These observations may promote a further development of our research in this field. Further development of this group of 4,6-diaryl-2-(2-aryl-4,5-diphenyl-1*H*-imidazol-1-yl)pyrimidines may

lead to compounds with better pharmacological profile than standard antibacterial and antifungal drugs.

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Table 3: *In vitro* antibacterial activity (MIC) values for compounds 13-24

[a] - No inhibition even at higher concentration i.e., at 200 µg/mL

Compounds	Minimum Inhibitory Concentration (MIC) in µg/mL							
	S.aureus	*β-H streptococcus*	*V.cholerae*	*S.typhii*	*S.felxneri*	*E.coli*	*K.pneumonia*	*P.aeruginosa*
13	200.00	100.00	50.00	200.00	200.00	100.00	100.00	50.00
14	12.50	06.25	50.00	06.25	06.25	12.50	06.25	12.50
15	06.25	06.25	50.00	06.25	50.00	06.25	50.00	06.25
16	06.25	*a*	100.00	50.00	*a*	*a*	06.25	50.00
17	50.00	*a*	06.25	100.00	*a*	*a*	06.25	50.00
18	12.50	12.50	50.00	06.25	12.50	12.50	06.25	12.50
19	06.25	12.50	100.00	50.00	06.25	12.50	100.00	50.00
20	12.50	06.25	50.00	06.25	06.25	12.50	06.25	12.50
21	06.25	06.25	50.00	06.25	50.00	06.25	50.00	06.25
22	50.00	*a*	50.00	50.00	*a*	*a*	06.25	12.50
23	12.50	12.50	50.00	06.25	12.50	12.50	06.25	12.50
24	12.50	06.25	50.00	06.25	06.25	12.50	06.25	12.50
Ciprofloxacin	25.00	50.00	50.00	50.00	25.00	25.00	50.00	50.00

Table 4: *In vitro* antifungal activity (MIC) values for compounds 13-24

[a] - No inhibition even at higher concentration i.e., at 200 µg/mL

Compounds	Minimum Inhibitory Concentration (MIC) in µg/mL			
	A.flavus	*Mucor*	*Rhizopus*	*M. gypsuem*
13	200.00	100.00	200.00	200.00
14	12.50	06.25	50.00	06.25
15	*a*	06.25	12.50	*a*
16	50.00	06.25	50.00	12.50
17	*a*	06.25	06.25	*a*
18	50.00	*a*	*a*	50.00
19	06.50	06.25	50.00	06.25
20	100.00	*a*	*a*	50.00
21	50.00	12.50	12.50	06.25
22	*a*	06.25	06.25	*a*
23	100.00	50.00	50.00	100.00
24	50.00	12.50	06.25	06.25
Fluconazole	50.00	25.00	25.00	25.00