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Facile and efficient one-pot multicomponent synthesis of a new class of substituted pyrimidine containing imidazoles catalyzed by ceric ammonium nitrate: Screening *in vitro* microbiological evaluation with various microorganisms

P V Rajeev[a,]*, A K Ameerunisha Begam[a], R Keerthana[a] & J Thanusu[b]

[a]Department of Chemistry, Hindustan Institute of Technology and Science, Chennai-600 016. Tamil Nadu, India
[b]Department of Chemistry, Alpha College of Engineering, Chennai-600 124. Tamil Nadu, India

*E-mail: pvrajeev25@gmail.com

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An effective and simple method for the one-pot synthesis of 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 methanol by using ceric ammonium nitrate (CAN) as catalyst has been described. This CAN catalyzed reactions are carried out at a temperature of 70-75°C and give very high yields in a lesser reaction time. All the synthesized compounds have been characterized by elemental analysis, FT-IR, ^{1}H NMR ^{13}C NMR and MS spectral data. All the newly synthesized compounds are tested for their *in vitro* antimicrobial activity against selected clinically isolated bacterial and fungal strains by disc diffusion and minimum inhibitory concentration method.

Keywords: Ceric ammonium nitrate, Imidazole, One-pot synthesis, Antimicrobial

Multicomponent reactions (MCRs) are important class of organic reactions and attracting the researchers do to its exceptional synthetic efficiency. MCRs allows more than two reactants to be combined in practical, time saving one-pot operations, giving rise to complex structures by simultaneous formation of two or more bonds with high levels of diversity[1]. The reactions are environmental friendly process by reducing the number of synthetic steps, waste productions and energy consumption. Researchers have transformed this powerful technology into one of the most efficient and economic tools for synthetic organic chemistry[1,2]. Due to their inherent simple experimental procedures and their one-pot synthetic procedure, they are perfectly suited for automated synthesis[1,3].

The imidazole moiety is found in a large number of natural products and pharmacologically active compounds[4,5]. The derivatives of triarylimidazole found many biological activities like herbicidal[6], fungicidal[7], anti-inflammatory[8] and antithrombotic activities[9]. In addition to the biomedical activities they are also used as photosensitive compounds in photography[10]. Tetrasubstituted imidazolemoiety exists 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]. Very few general methods are reported 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]. But most of these synthetic methods are associated with disadvantages such as low yields, expensive and toxic reagents, prolonged reaction time, and tedious work-up procedures. Hence the development of new synthetic methods with readily available and less toxic reagents with a high yield of production in a short reaction time is required.

Pyrimidine ring system is found as an integral part of nucleic acids and many chemotherapeutic agents and showed a wide range of pharmacological activities such as bactericide[18], fungicide[19], phosphodiesterase inhibitor[20], viricide[21], and leishmancide[22,23]. Substituted amino pyrimidine nuclei are commonly using in drugs such as anti-atherosclerotic aronixil, anti-histaminic thonzylamine, anti-anxiolytic buspirone, and anti-psoriatic enazadrem[24] and used as an anti-cancer drug[25]. Various methods of synthesis and reactions of amino pyrimidines are reported[26, 27].

Ceric (IV) ammonium nitrate (CAN) has emerged as a precious reagent for carbon-carbon and carbon-heteroatom bond formation[28]. In addition, many

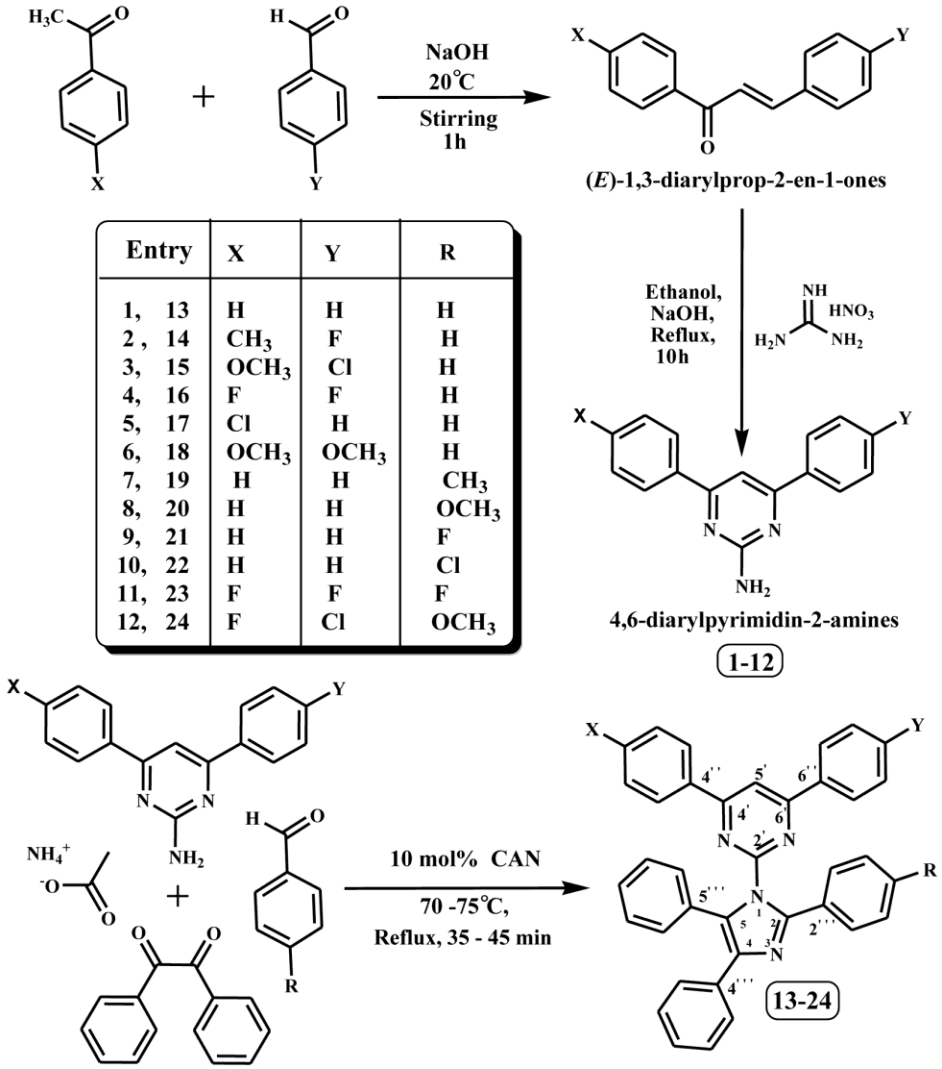
advantages such as excellent solubility in water, cost-effectiveness, eco-friendly nature, easy handling, high reactivity, and easy work-up procedures make CAN a potent catalyst in organic synthesis. Besides, CAN can catalyze various organic transformations based on its electron transfer capacity and Lewis acidic property[29].

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 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 CAN in refluxing methanol for 35-45 min. via one-pot synthetic operations. The synthetic procedure for the compounds **13-24** was given in Scheme 1.

Experimental Details

Chemistry

The progress of the reaction and the purity of the synthesised compounds were assessed with TLC. All the reported melting points were taken in open capillaries and were uncorrected. IR spectra were recorded in KBr (pellet forms) on a Thermo Nicolet-Avatar–330 FT-IR spectrophotometer. One dimensional ^{1}H and ^{13}C NMR spectra were recorded



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

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

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 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].

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

A mixture of 4,6-diphenylpyrimidin-2-amine **1**, ammonium acetate, benzaldehyde, benzil and CAN was dissolved in methanol and refluxed at a temperature of 65-70°C. The progress of the reaction was monitored by TLC. After the completion, the reaction product was cooled to room temperature and poured into ice water (75 mL) to get the precipitated solid. The obtained solid was filtered and washed with 10% sodium bicarbonate solution followed by brine solution and fresh water and dried over anhydrous sodium sulphate. After the evaporation of the solvent under reduced pressure, a gummy mass was obtained, which solidified by the treatment of petroleum ether (b.p. 40-60°C). The final purification of 4,6-diphenyl-2-(2,4,5-triphenyl-1*H*-imidazol-1-yl)-pyrimidine **13** was carried out by column chromatography using silica gel (100-200 mesh), with ethyl acetate-petroleum ether as eluent with a ratio of 2:8.

The results of physical and analytical evaluations are given in Table 1. The structures of all the synthesized compounds **13-24** were interpreted with the help of melting point, elemental analysis, FT-IR, MS, one-dimensional ^{1}H NMR, and ^{13}C NMR. To discuss the spectral characterization, 4,6-diphenyl-2-(2,4,5-triphenyl-1H-imidazol-1-yl)pyrimidine **13** was taken as the representative compound. The compound obtained as a white powder with a yield of 94%. IR spectrum of **13** showed characteristic absorption frequency at 1642 cm^{-1} indicates the presence of C=N stretching vibration. In addition, a strong absorption observed at 1592 cm^{-1} shows the presence of C=C stretching frequency. The mass spectrum showed a molecular ion peak at m/z **527** ($M^{+\cdot}$+1), which 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 ^{1}H NMR spectrum of **13**, a singlet for CH proton at position 5' of pyrimidine moiety merged with aromatic protons. The aromatic protons have appeared in the range of 7.50-8.23 ppm. In the ^{13}C NMR Spectrum, resonance at 108.1 ppm assigned to methane carbon at C-5' of pyrimidine moiety. A peak at 163.8 ppm is due to C-2' of pyrimidine moiety, and 161.3 ppm is due 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

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	$C_{38}H_{26}ClFN_4O$

the imidazole ring. The peak at 150.3, 151.2 ppm was assigned to C-4 and C-5 carbons of imidazole moiety. Resonance at 155.7 ppm was due to C-2 carbon of imidazole moiety. The rest of the aromatic carbons resonate in the region 126.9 - 129.8ppm. The compounds **14-24** were synthesized correspondingly.

4-(4-fluorophenyl)-2-(2,4,5-triphenyl-1H-imidazol-1-yl)-6-p-tolylpyrimidine 14: The compound was obtained as a white powder with yield of 94%; IR (KBr) (cm^{-1}): 3317, 3293, 3058, 3036, 2928, 2851, 1645, 1582, 1366, 1236, 1112, 762, 696;^{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'), 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)pyrimidine 15: The compound was obtained as a white powder and the yield was 92%; IR (KBr) (cm^{-1}): 3320, 3273, 3158, 3036, 2928, 2851, 1642, 1582, 1366, 1246, 1112, 760, 694;^{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'), 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)pyrimidine 16: The compound was obtained as a white powder in a yield of 93%; IR (KBr) (cm^{-1}): 3310, 3255, 3158, 3018, 2968, 2893, 1647, 1576, 1366, 1256, 1120, 769, 697; ^{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'), 7.56-8.69 (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)pyrimidine 17: The compound was obtained as a white powder in a yield of 92%; IR (KBr) (cm^{-1}): 3309, 3300, 3138, 3018, 2959, 2868, 1640, 1560, 1372, 1267, 1118, 760, 691;^{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'), 7.62-8.88 (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)pyrimidine 18: The compound was obtained as a white powder in a yield of 95%; IR (KBr) (cm^{-1}): 3343, 3321, 3178, 3049, 2950, 2898, 1649, 1567, 1383, 1255, 1143, 768, 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'), 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)pyrimidine 19: The compound was obtained as a white powder in a yield of 94%; IR (KBr) (cm^{-1}): 3333, 3310, 3180, 3149, 2969, 2859, 1644, 1550, 1378, 1265, 1243, 769, 699; ^{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'), 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-diphenylpyrimidine 20: The compound was obtained as a white powder in a yield of 92%; IR (KBr) (cm^{-1}): 3370, 3344, 3134, 3167, 2972, 2864, 1648, 1544, 1368, 1250, 1233, 776, 677; ^{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'), 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-diphenylpyrimidine 21: The compound was obtained as a white powder in a yield of 94%; IR (KBr) (cm^{-1}): 3317, 3258, 3154, 3016, 2969, 2899, 1641, 1575, 1365, 1252, 1125, 764, 692; ^{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'), 7.46-8.59 (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-diphenylpyrimidine 22: The compound was obtained as a white powder in a yield of 93%; 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)pyrimidine 23: The compound was obtained as a white powder in 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)pyrimidine 24: The compound was obtained as a white powder in a yield of 92%; 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}.

Microbiology materials

All the clinically isolated bacterial strains namely *Staphylococcus aureus, b-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* are 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 were done by a two-fold serial dilution method[33]. The respective test compounds **13-24** were dissolved in dimethyl sulphoxide (DMSO) to obtain a 1 mg mL^{-1} stock solution. Seeded broth (broth containing microbial spores) prepared in NB from 24 h old bacterial cultures on nutrient agar (Hi-media, Mumbai) medium at 37 ±1°C. The fungal spores prepared from 1 to 7 days old Sabourauds agar (Hi-media, Mumbai) slant cultures suspended in SDB. The colony-forming units (cfu) of the seeded broth were determined by plating technique and adjusted in the range of 10^4-10^5cfu/mL. The final inoculums size was 105 cfu/mL for antibacterial assay and 1.1-1.5 X 10^2cfu/mL for the antifungal assay. Testing performed at pH 7.4±0.2 for bacteria (NB) and pH 5.6 for fungi (SDB). Exactly 0.4 mL of the test compound solution were prepared and added to 1.6 mL of seeded broth to form the first dilution. The second dilution prepared by taking one millilitre of the first solution with 1mL of seeded broth, and so on the sixth dilution obtained. A set of assay tubes containing only seeded broth kept as control. The tubes were incubated in BOD incubators at 37±10°C for bacteria and 28±10°C for fungi. The MICs recorded by visual observations after 24 h (for bacteria) and 72-96 h (for fungi) of incubation. Ciprofloxacin and Fluconazole used as the standard for bacteria studies and fungal studies.

Results and Discussion

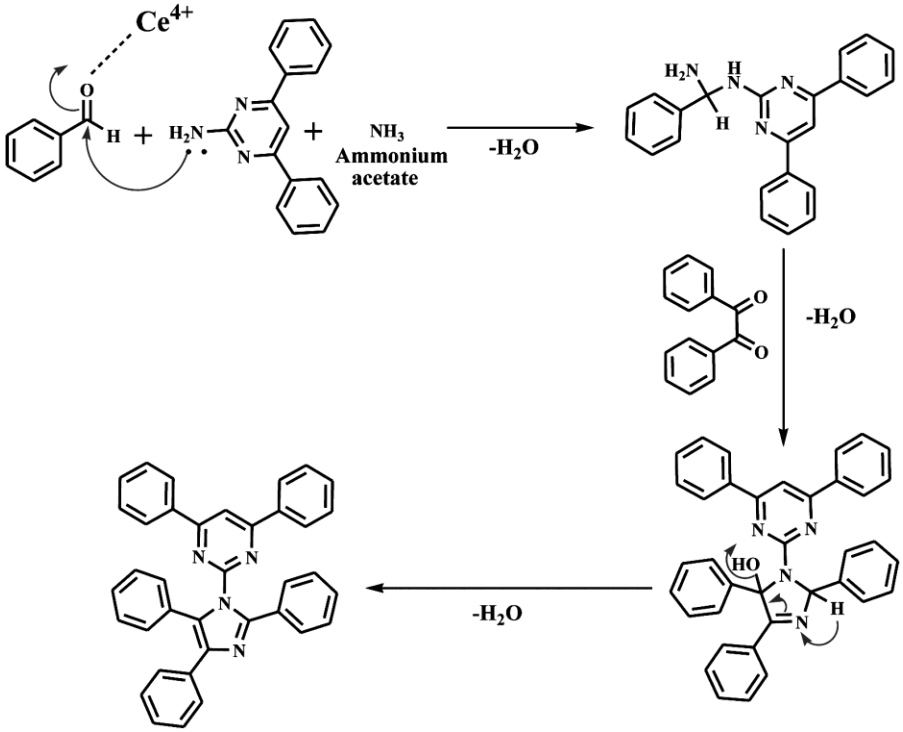
Chemistry

Several synthetic procedures are available for the synthesis of trisubstituted and tetrasubstituted pyrimidines by multicomponent reactions[13-17, 34-38]. Most of these synthetic procedures suffer from one or more serious drawbacks, such as laborious and complex work-up and purification process, a significant amount of waste materials, side reactions and by-products, low yields and uses of expensive reagents. Additionally, most reactions require elevated temperatures (180-200°C). While using CAN as a catalyst in refluxing methanol at 70-75°C, the yield of the product has been improved significantly (i.e., more than 90%). The reactions are not taking place in the absence of the catalyst. The choice of reaction solvent was crucial. If ethanol is using as a

solvent instead of methanol, the yield of the reaction reduces. The Claisen-Schmidt condensation of various *p*-substituted acetophenones with different *p*- substituted benzaldehydes in the presence of sodium hydroxide catalyst yields 1,3-diaryl-prop-2-en-1-ones. When 1,3-diaryl-prop-2-en-1-ones treated with guanidine nitrate in the presence of sodium hydroxide alkali in refluxing ethanol for 10 h, 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 (1 eqv.), respective 2-amino-4, 6-diarylpyrimidines (1 eqv.), substituted benzaldehydes (1 eqv.), and ammonium acetate (1 eqv.) in refluxing methanol catalyzed by CAN. The schematic representation of compounds **13-24** is given in Scheme 1**.** The physical and analytical data of compounds **13-24** are given in 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** are confirmed by melting point, elemental analysis, MS, FT-IR, one-dimensional NMR (1H & 13C) spectroscopic data. A possible reaction mechanism for the formation of 4,6-diaryl-2-(2-aryl-4,5-diphenyl-1*H*-imidazol-1-yl)pyrimidines **13-24** is given in Scheme 2.

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, b-H. streptococcus, V. cholerae, S. typhii, S. felxneri, E. coli, K. pneumonia* and *P. aeruginosa*. Ciprofloxacin is using as a standard drug. MIC in values are listed in Table 2. Compound **13** which, has no substitution at the *para* position of phenyl ring had exerted moderate activities against all the used bacterial strains. Compounds **16, 17** and **22** having electron-withdrawing groups like chloro and fluoro atoms at the *para* position of the phenyl ring that attached to pyrimidine and imidazole moiety were not shown much activity against *b-H. streptococcus, S. felxneri* and *E. coli.* The structure-activity relationship studies of the synthesized compounds (**14, 15** and **24**) with electron-donating methoxy and methyl functional group at the *para* position of the phenyl ring show good antibacterial activity against all the tested bacterial strains. Also, compound **14** containing both electron-withdrawing fluoro and electron-donating methyl groups, shows potent activity against all the tested bacterial strains. The compounds **15, 20** and **24** having electron-donating methoxy functional group at the *para* position of phenyl ring attached to pyrimidine ring show promising activity against *S. aureus, S. typhii* and *E. coli*.



Scheme 2 — Plausible reaction mechanism for the synthesis of 4,6-diaryl-2-(2-aryl-4,5-diphenyl-1*H*-imidazol-1-yl)pyrimidines (13-24)

Table 2 — *In vitro* antibacterial activities of compounds 13-14 by two fold serial dilution method

Microorganisms	Minimum Inhibitory Concentration (MIC) (μg/mL)												
	13	14	15	16	17	18	19	20	21	22	23	24	Ciproflox-acin
S. aureus	50.00	12.50	12.50	100	50.00	12.50	50.00	12.50	100	50.00	12.50	12.50	25
β–H. streptococcus	50.00	12.50	12.50	100	100	100	12.50	50.00	12.50	100	12.50	12.50	50
V. cholerae	50.00	12.50	12.50	50.00	50.00	50.00	12.00	100	100	12.50	12.50	12.50	25
S. typhii	50.00	12.50	12.50	12.50	50.00	12.50	50.00	12.50	50.00	50.00	50.00	12.50	50
S. felxneri	50.00	12.50	12.50	100	100	100	12.00	50.00	12.50	100	12.50	12.50	25
E. coli	50.00	12.50	12.50	100	100	12.50	100	12.50	12.50	100	12.50	12.50	50
K. pneumonia	50.00	12.50	12.50	100	100	50.00	12.50	50.00	50.00	50.00	50.00	12.50	25
Pseudomonas aeruginosa	50.00	12.50	12.50	50.00	50.00	100	50.00	100	50.00	12.50	12.50	12.50	50

Table 3 — *In vitro* antifungal activities of compounds 13-14 by two fold serial dilution method

Microorganisms	Minimum Inhibitory Concentration (MI) (μg/mL)												
	13	14	15	16	17	18	19	20	21	22	23	24	Fluconazole
Aspergillus flavus	100	06.25	100	06.25	100	50.00	16.25	100	06.25	100	06.25	12.50	25
Mucor	50.00	06.25	06.25	06.25	06.25	100	12.50	100	06.25	06.25	06.25	06.25	50
Rhizopus	12.50	50.00	06.25	06.25	06.25	06.25	06.25	06.25	06.25	06.25	06.25	06.25	25
Microsporumgypsuem	100	50.00	100	06.25	100	100	50.00	50.00	06.25	100	06.25	50.00	50

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**) were studied against the fungal strains *viz.*, *A.flavus, Mucor, Rhizopus* and *M.gypsuem.* Fluconazole is the standard drug. MIC values are listed in Table 3. Compound **13** is not exhibiting antifungal activity against *A. flavus* and *M.gypsuem*. The synthesized compounds have electron-withdrawing chloro atom in *para* position of the phenyl ring that attached to the pyrimidine and imidazole ring (**15, 17, 22** and **24**) havenot shown promised activity against *A. flavus* and *M. gypsuem.* But these compounds have maximum results against *Mucor* and *Rhizopus* at 25μg/mL. Compounds **16, 21, 23** and **24** show excellent activities against all the tested clinically isolated fungal strains, while against *Mucor*, compound **14** and **19** contain electron-donating methyl group at the *para* position of phenyl ring attached to pyrimidine ring show promise activities. The compounds which having electron-donating methoxy functional group at the *para* position of phenyl ring attached to pyrimidine ring and imidazole ring (18 and 20) did not promote much activity against *Mucor* and *Rhizopus.* Also, compound **23** and **24** which contain both electron-withdrawing chloro and electron-donating methyl groups shows potent activity against *A. flavus* and *Rhizopus*.

Conclusion

The anti-bacterial and anti-fungal studies were carried out for the newly synthesized compounds 4,6-diaryl-2-(2-aryl-4,5-diphenyl-1*H*-imidazol-1-yl)pyrimidines (**13-24**). A close inspection of the *in vitro* anti-bacterial and anti-fungal activity profile in different electron-donating (CH_3 and OCH_3) and electron-withdrawing (-Cl and -F) functional groups substituted at the 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 containing both electron-withdrawing chloro and electron-donating methyl groups (**14**, **15**, **23** and **24**) shows potent activity against all the tested bacterial strains. The compounds having electron-donating methoxy group at the *para* position of phenyl ring which attached to pyrimidine and imidazole ring (**18** and **20**) showed promising activity against *S.aureus, S.typhii* and *E.coli*. The results of the anti-fungal 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 anti-fungal activity of all the synthesized compounds **13-24.** Compound **24**, contain both electron-withdrawing chloro and fluoro and the electron-donating methoxy group shows potent activity against *A. flavus* and *Rhizopus*. The

method of action of these compounds is unknown. These observations may promote further development of our research in this field. Further studies towards the extended derivatives of 4,6-diaryl-2-(2-aryl-4,5-diphenyl-1*H*-imidazol-1-yl)pyrimidines may lead to a better pharmacological profile when compared to the existing standard anti-bacterial and anti-fungal drugs.

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