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Synthesis of novel heterocyclic compounds and their biological evaluation

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Abstract

Some new N4-[4,6-diarylsubstituted-2-pyrimidinyl]-6-methoxy-2-methyl-4-quinolinamine **3a-h** were synthesized and studied for their microbicidal efficacy. These compounds were prepared from chalcones **1a-h** on cyclized with guanidine nitrate, yielded 4-(substituted phenyl)-6-(substituted phenyl)-2-pyrimidinamine **2a-h** and then refluxing with 4-chloro-6-methoxy-2-methylquinoline yield the title compounds **3a-h**. All the compounds were characterized by elemental analysis and spectral studies. The newly synthesized compounds were evaluated for their antibacterial and antifungal activity.

Key Words: Pyrimidine-Quinoline clubbed derivatives, Quinoline derivative, Spectral studies, Antibacterial activity, Antifungal activity.

Introduction

Heterocyclic compounds are widely distributed in nature and are essential for life. They play a vital role in the metabolism of all living cells. There are vast numbers of pharmacologically active heterocyclic compounds, many of which are in regular clinical use [1]. Pyrimidine has played a vital role in the manufacture of various biologically active drugs as antimicrobial [2-3], calcium channel blockers [4], antitubercular [5], antibacterial [6], anti-inflammatory [7] and many classes of chemotherapeutic agents containing pyrimidine nucleus are in clinical use. Quinoline derivatives are also drugs of therapeutic importance showing wide spectrum of biological activities. Some 4-substituted quinoline derivatives have been found to possess enhanced antibacterial activity [8-11]. If pyrimidine and quinoline moieties clubbed into one molecule, the resultant molecule may enhance the pharmaceutical activity up to some extent. Hence, it was thought interesting to explore the study of such molecules. Thus the present paper

describes the synthesis of N4-[4-6-diaryl substituted phenyl-2-pyrimidinyl]-6-methoxy-2-methyl-4-quinolinamine derived from 2-amino-4,6-diarylsubstituted pyrimidine derivatives and 4-chloro-6-methoxy-2-methylquinoline [12-14]. The research work is scanned in scheme-1 and scheme-2.

Results and Discussion

Chemistry

Chalcones **1a-h** was prepared by the reported method and was cyclized with guanidine nitrate to give 4-6-diarylsubstituted-2-pyrimidinamine **2a-h**. The latter compounds further reacted with 4-chloro-6-methoxy-2-methylquinoline to give corresponding compound **3a-h**.

Compounds **2a-h** and **3a-h** was confirmed on the basis of elemental analysis and spectroscopic investigation. IR spectrum of **2a-h** revealed characteristic bands at 3460-3300cm^{-1} (-NH_2), 1340-1250cm^{-1} (C-N) and confirmatory by ^{1}H NMR signal at δ 5.4 (2H, s,-NH_2). Further, IR spectroscopic investigation of **3a-h** revealed bands at 3376-3330cm^{-1} (N-H) and 1608 (C=N) while additional peak appears due to substitution in the aromatic ring showing absorption band at ~2953 (-CH_3), ~2810 (-OCH_3), ~1528 (-NO_2), ~1100 (C-F), ~1050 (C-Br), ~810 (C-Cl). ^{1}H NMR signal at δ 6.8 (1H, s,-NH) and additional signal appear due to substitution in aromatic ring showing common signals at δ 2.3 (3H, s,-CH_3), δ 3.7 (3H, s,-OCH_3) and δ (6.9-8.0, m, aromatic protons).

The final structure of all compounds was confirmed by ^{13}C NMR and LC-MS data of selected samples. The LC-MS of samples 2a, 2g, 3a and 3g give the molecular ion peak (m/z) at 353, 327, 523 and 498 respectively. These values correspond to their molecular weight.

Biological Activity

Antibacterial activity

Antibacterial activities of all the compounds were studied against Gram-positive bacteria [*Staphylococcus aureus (MTCC96), Streptococcus pyogenes (MTCC442)*] and Gram-negative bacteria [*Escherichia coli (MTCC443), Pseudomonas aeruginosa (MTCC424)*] at a concentration of 100µg/ml by agar cup plate method. The test compounds were dissolved in DMF at a concentration of 100 μg/mL using Chloramphenicol, Ciprofloxacin as a standard for comparison control experiment was carried out. The area of inhibition of zone measured in mm. An examination of the data reveals that all compounds showed antibacterial activity. Results are presented in Table-1.

Antifungal activity

The synthesized compounds were also screened for their antifungal activity against *Candida albicans (MTCC227), Aspergillus niger (MTCC282) using* the agar cup plate diffusion method by dissolving in DMF at a concentration of 100 μg/mL. The zone of inhibition was at after 7 days and 20 °C and it was compared with Greseofulvin and Nystatin as standard drugs as shown in Table-1.

Table-1: Biological activity N4-[4,6-diaryl substituted phenyl-2-pyrimidinyl]-6-methoxy-2-methyl-4-quinolinamine 3a-h

Zone of Inhibition* (mm) (Activity Index) std.						
Compd.	Antibacterial activity				Antifungal activity	
	Gram-positive		Gram-negative			
	S. aureus	*S. pyogenes*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*
3a	18(0.90) (0.81)	19(0.95) (0.90)	21(0.91) (0.75)	18(0.94) (0.69)	21(0.95) (0.77)	24(0.96) (0.82)
3b	19(0.95) (0.86)	18(0.90) (0.85)	20(0.86) (0.71)	17(0.89) (0.65)	20(0.90) (0.74)	23(0.92) (0.79)
3c	16(0.80) (0.72)	14(0.70) (0.66)	15(0.65) (0.53)	16(0.84) (0.61)	18(0.81) (0.66)	20(0.80) (0.68)
3d	19(0.95) (0.86)	18(0.90) (0.85)	20(0.86) (0.71)	18(0.94) (0.69)	21(0.95) (0.77)	23(0.92) (0.79)
3e	15(0.75) (0.68)	14(0.70) (0.66)	18(0.78) (0.64)	15(0.78) (0.57)	19(0.86) (0.70)	21(0.84) (0.72)
3f	19(0.95) (0.86)	19(0.95) (0.90)	21(0.91) (0.75)	18(0.94) (0.69)	21(0.95) (0.77)	23(0.92) (0.79)
3g	16(0.80) (0.72)	15(0.75) (0.71)	16(0.69) (0.57)	15(0.78) (0.57)	19(0.86) (0.70)	20(0.80) (0.68)
3h	14(0.70) (0.63)	15(0.75) (0.71)	17(0.73) (0.60)	15(0.78) (0.57)	20(0.90) (0.74)	22(0.88) (0.75)
Std.1	20	20	23	19	22	25
Std.2	22	21	28	26	27	29

*= average zone of inhibition in mm,
(Activity index) = Inhibition zone of the sample / Inhibition zone of the standard,
For antibacterial activity: Std. 1 = Chloramphenicol and Std. 2 = Ciprofloxacin
For antifungal activity: Std. 1 = Greseofulvin and Std. 2 = Nystatin.

Materials and Methods

All reagents were obtained from commercial sources. Solvents were dried and purified with known conventional methods.

Analytical methods:
All melting points were taken in open capillary tubes and were uncorrected. Thin layer chromatography was performed on precoated TLC plates with silica gel (Merck GF_{254}) and detection was done by UV lamp (254 nm). The IR spectra were obtained on a Perkin-Elmer BX series FTIR-5000 spectrophotometer using KBr pellets. The ^{1}H NMR and ^{13}C NMR spectra in DMSO-d_6 and $CDCl_3$ were recorded on Varian Gemini 400 MHz spectrometer and chemical shift were reported as parts per million (δ ppm) down field using TMS as internal standard. LC-MS of selected sample has been carried out on LC-MSD Trap-SL 01046 instrument.

Experimental

Preparation of 2-amino-4,6-diaryl substituted pyrimidine (2a-h):

A mixture of substituted chalcones (0.01 mol) **1a-h** and guanidine nitrate (0.01 mol) was dissolved in ethanol (30 ml). Aqueous sodium hydroxide (40%, 1ml) was added and the reaction mixture was refluxed. Further installments of sodium hydroxide (4x1 ml) were added during two hours to the refluxing solution. Refluxing was continued (10-12 hr) and the completion of the reaction was monitored by TLC. The resultant mixture was cooled at room temperature, diluted with water (3 x 100 ml) and neutralized with cold dilute HCl (10%). The product thus separated was filtered out, washed with water dried & crystallized from ethanol.

Following the same procedure all the compounds of this series were prepared.

4-(2,4-dichloro-5-fluorophenyl)-6-(4'-fluorophenyl)-2-pyrimidinamine **(2a)**
Yield 70%; mp: 153 ^{o}C; FT-IR [ν, cm^{-1}, KBr]: 3420 (-NH_2), 1257 (C-N), 1109 (C-F), 820 (C-Cl). ^{1}H NMR [400MHz, δ, ppm, $CDCl_3$]: 5.39 (2H,s,NH_2), 6.95-7.86 (7H,m,Ar-H). LC-MS: m/z 353 (M^+). Anal. Calcd for $C_{16}H_9N_3Cl_2F_2$ (352.16); C, 54.57; H, 2.58; N, 11.93 found: C, 54.50; H, 2.51; N, 11.87.

4-(4-methoxyphenyl)-6-(4'-fluorophenyl)-2-pyrimidinamine **(2b)**
Yield 68%; mp: 149 ^{o}C; FT-IR [ν, cm^{-1}, KBr]: 3433 (-NH_2), 1291 (C-N), 2826 (OCH_3), 1182 (C-F). ^{1}H NMR [400MHz, δ, ppm, $CDCl_3$]: 5.43 (2H, s, NH_2), 3.75 (3H, s,-OCH_3), 6.80-7.98 (9H, m, Ar-H). Anal. Calcd for $C_{17}H_{14}FN_3O$ (295.31); C, 69.10; H, 4.78; N, 14.23 found: C, 69.07; H, 4.69; N, 14.16.

4-(4-methylphenyl)-6-(4'-fluorophenyl)-2-pyrimidinamine **(2c)**
Yield 65%; mp: 139 ^{o}C; FT-IR [ν, cm^{-1}, KBr]: 3449 (-NH_2), 1340 (C-N), 2919 (CH_3), 1161 (C-F). ^{1}H NMR [400MHz, δ, ppm, $CDCl_3$]: 5.35 (2H,s,NH_2), 2.39 (3H,s,-CH_3), 6.94-7.81 (9H,m,Ar-H). Anal. Calcd for $C_{17}H_{14}N_3F$ (279.31); C, 73.10; H, 5.05; N, 15.04 found C, 73.02; H, 4.95; N, 14.98.

4-(4-chlorophenyl)-6-(3'-bromophenyl)-2-pyrimidinamine **(2d)**
Yield 69%; mp: 168 ^{o}C; FT-IR [ν, cm^{-1}, KBr]: 3460 (-NH_2), 1311 (C-N), 1019 (C-Br), 803 (C-Cl). ^{1}H NMR [400MHz, δ, ppm, $CDCl_3$]: 5.47 (2H,s,NH_2), 7.01-8.11 (9H,m,Ar-H). Anal. Calcd for $C_{16}H_{11}N_3ClBr$ (360.63); C, 53.29; H, 3.07; N, 11.65 found C, 53.20; H, 3.01; N, 11.60.

4-(4-methylphenyl)-6-(3'-bromophenyl)-2-pyrimidinamine **(2e)**
Yield 61%; mp: 159 ^{o}C; FT-IR [ν, cm^{-1}, KBr]: 3452 (-NH_2), 1296 (C-N), 2913 (CH_3), 1074 (C-Br). ^{1}H NMR [400MHz, δ, ppm, $CDCl_3$]: 5.39 (2H,s,NH_2), 2.48 (3H,s,-CH_3), 6.94-7.91 (9H,m,Ar-H). Anal. Calcd for $C_{17}H_{14}N_3Br$ (340.21); C, 60.02; H, 4.15; N, 12.35 found C, 59.97; H, 4.09; N, 12.26.

4-(4-methoxyphenyl)-6-(3'-bromophenyl)-2-pyrimidinamine **(2f)**
Yield 66%; mp: 171 ^{o}C; FT-IR [ν, cm^{-1}, KBr]: 3432 (-NH_2), 1287 (C-N), 2816 (OCH_3), 1069 (C-Br). ^{1}H NMR [400MHz, δ, ppm, $CDCl_3$]: 5.37 (2H, s, NH_2), 3.77 (3H,s,-OCH_3), 6.97-8.19 (9H,m,Ar-H). Anal. Calcd for $C_{17}H_{14}ON_3Br$ (356.21); C, 57.32; H, 3.96; N, 11.80 found C, 57.27; H, 3.89; N, 11.75.

4-(4-chlorophenyl)-6-(3'-nitrophenyl)-2-pyrimidinamine **(2g)**
Yield 60%; mp: 191 ^{o}C; FT-IR [ν, cm^{-1}, KBr]: 3428 (-NH_2), 1517 (NO_2), 1277 (C-N), 783 (C-Cl). ^{1}H NMR [400MHz, δ, ppm, $CDCl_3$]: 5.48 (2H, s, NH_2), 7.18-8.39 (9H, m, Ar-H). ^{13}C NMR [400MHz, δ, ppm, $CDCl_3$]: 155.8 (C-NH_2), 133.4 (C-Cl), 148.2 (C-NO_2), 155.8- 163.0(C=N), 155.8-168.5 (C-N), 118.6 to 137.6 (aromatic carbons). LC-MS: m/z 327 (M^+). Anal. Calcd for $C_{16}H_{11}O_2N_4Cl$ (326.7); C, 58.82; H, 3.39; N, 17.15 found C, 58.78; H, 3.30; N, 17.10.

4-(4-methoxyphenyl)-6-(3'-nitrophenyl)-2-pyrimidinamine **(2h)**
Yield 64%; mp: 161 ^{o}C; FT-IR [ν, cm^{-1}, KBr]: 3458 (-NH_2), 2826 (OCH_3), 1545 (NO_2), 1250 (C-N). ^{1}H NMR [400MHz, δ, ppm, $CDCl_3$]: 5.44 (2H,s,NH_2), 3.69 (3H,s,-OCH_3), 7.09-8.33 (9H,m,Ar-H). Anal. Calcd for $C_{17}H_{14}O_3N_4$ (322.31); C, 63.35; H, 4.38; N, 17.38 found C, 63.26; H, 4.25; N, 17.29.

Preparation of 4-chloro-6-methoxy-2-methylquinoline (Scheme-1):

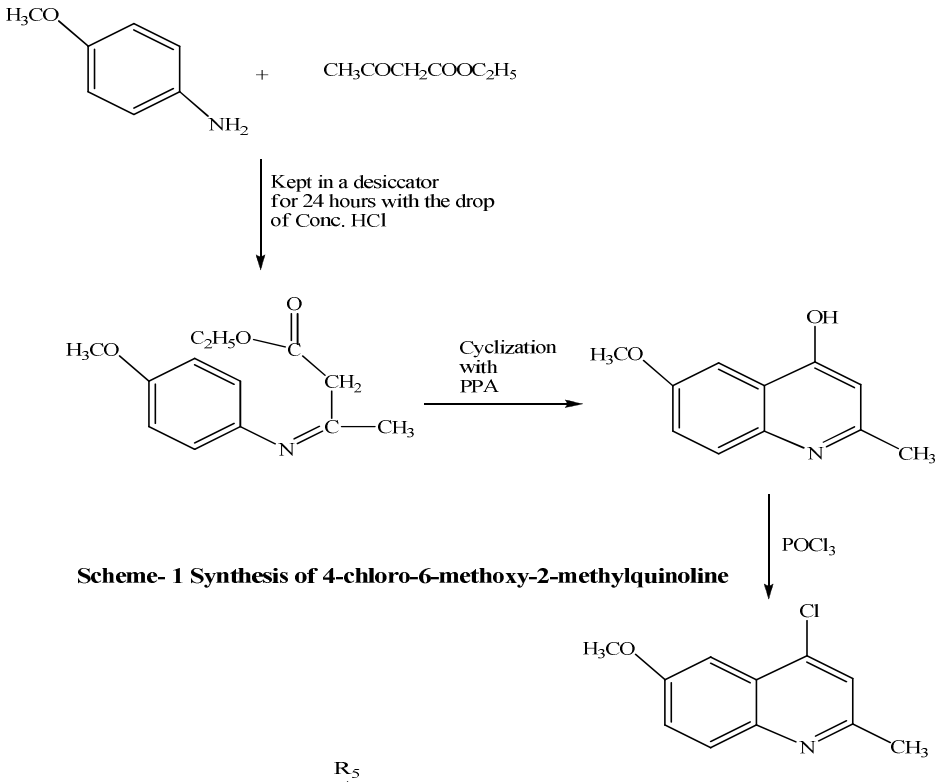
Ethyl-β-4-chloroanilinocrotonate
A mixture of p-methoxyaniline (0.05 mol) and acetoacetic ester (0.05 mol) with a trace of concentrated hydrochloric acid was kept in a desiccator for 24 hours. The residue was cyclized by PPA.

Preparation of polyphosphoric acid (PPA)
Polyphosphoric acid was prepared by dissolving phosphorus pentoxide (40.0 gm) into orthophosphoric acid (24 ml; d= 1.75). The mixture was heated at 95-100 ^{o}C for half an hour; the scum was removed and clear solution thus obtained was used for cyclisation purpose.

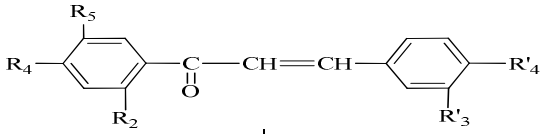
6-methoxy-2-methyl-4-quinolinol
The crude crotonate was mixed with freshly prepared PPA at room temperature, stirred well for some time and then the temperature was raised to 100^{o}C effervescences and was kept in desiccators for 24 hours. Next day, the temperature was slowly raised and lowered by 10^{o}C until it reached 140^{o}C over 1 hr. This treatment helps in getting clean product in high yield. The reaction mass was cooled and decomposed with crushed ice and neutralized with ammonium hydroxide on the acidic side. The product was filtered washed with water dried and crystallized from alcohol, yield 75%, m.p. 315^{o}C.

4-chloro-6-methoxy-2-methylquinoline
6-methoxy-2-methyl-4-quinolinol (3.0 g) was refluxed with phosphorus oxychloride (25.0 ml) for half an hour. After cooling to room temperature, it was poured in ice and neutralized with ammonium hydroxide on the acidic side, when a voluminous mass of chloro compound separated. The product was washed with water and crystallized from ethanol.

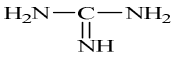
Yield 77%, m.p. 82-85^{o}C. FT-IR [ν, cm^{-1}, KBr]: 3052(C-H aromatic), 2974 (CH_3), 2814(OCH_3), 821 (C-Cl). ^{1}H NMR [400MHz, δ, ppm, $CDCl_3$]: 2.61 (3H,s,-CH_3), 3.84 (3H,s,-OCH_3), 7.13-7.82 (4H,m,Ar-H). Anal. Calcd for $C_{11}H_{10}ClNO$ (207.65); C, 63.62; H, 4.85; N, 6.75 found: C, 63.57; H, 4.77; N, 6.70.



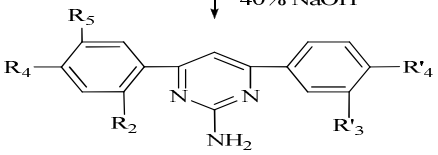
Scheme- 1 Synthesis of 4-chloro-6-methoxy-2-methylquinoline



1a-h

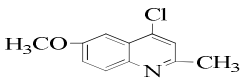


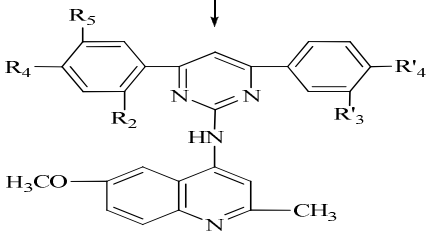
(1) Conventional heating
(2) Heterocyclization
C_2H_5OH
40% NaOH



2a-h

THF
Anhy. K_2CO_3





3a-h

Scheme- 2 Synthesis route of compounds 3a-h.

Where

(a) R_2=R_4=Cl; R'$_4$=R_5=F; R'$_3$=H

(b) R_2=R_5=R'$_3$=H; R_4=OCH_3; R'$_4$=F

(c) R_2=R_5=R'$_3$=H; R_4=CH_3; R'$_4$=F

(d) R_2=R5=R'$_4$=H; R_4=Cl; R'$_3$=Br

(e) R_2=R_5=R'$_4$=H; R_4=CH_3; R'$_3$=Br

(f) R_2=R_5=R'$_4$=H; R_4=OCH_3; R'$_3$=Br

(g) R_2=R_5=R'$_4$=H; R_4=Cl; R'$_3$=NO_2

(h) R_2=R_5=R'$_4$=H; R_4=OCH_3; R'$_3$=NO_2

General procedure for the preparation of N4-[4,6-diaryl substituted phenyl-2-pyrimidinyl]-6-methoxy-2-methyl-4-quinolinamine (3a-h):

To a mixture of 2-amino-4,6-diaryl substituted pyrimidine (0.01mol) **2a-h** and 4-chloro-6-methoxy-2-methylquinoline (0.01mol) in THF, anhydrous K_2CO_3 (0.11 mol) was added. The reaction mixture was refluxed. TLC [Toluene-ethyl acetate-acetone; 5:3:2] showed that reaction was complete after 8 hrs. The reaction mixture was poured in ice water and the precipitate was filtered, washed with water, dried and crystallized from ethanol.

N4-[4-(2,4-dichloro-5-fluorophenyl)-6-(4'-fluorophenyl)-2-pyrimidinyl]-6-methoxy-2-methyl-4-quinolinamine **(3a)**

Yield 88%; mp: 210 ^{o}C; FT-IR [ν, cm^{-1}, KBr]: 3368 (N-H), 2975 (CH_3), 2835 (OCH_3), 1356 (C-N), 1114 (C-F), 820 (C-Cl). ^{1}H NMR [400MHz, δ, ppm, DMSO-d_6]: 6.83 (1H,s,-NH), 2.31 (3H,s,-CH_3), 3.88 (3H,s,-OCH_3), 6.98-7.71 (11H,m,Ar-H). ^{13}C NMR [400MHz, δ, ppm, DMSO-d_6]: 144.3-159.2 (C-NH-C), 120.1-131.6 (C-Cl), 158.9-162.6 (C-F), 23.43 (C-CH_3), 56.6 (C-OCH3) in pyrimidine ring 159.2- 162.2(C=N), 159.2-163.0 (C-N), in Quinoline ring 154.7(C=N), 145.9 (C-N) and 107.5 to 145.9 (aromatic carbons). LC-MS: m/z 523 (M^+).Anal. Calcd for $C_{27}H_{18}C_{l2}F_2N_4O$ (523.36); C, 61.96; H, 3.47; N, 10.71; found: C, 61.92; H, 3.43; N, 10.69.

N4-[4-(4'-fluorophenyl)-6-(4-methoxyphenyl)-2-pyrimidinyl]-6-methoxy-2-methyl-4-quinolin amine **(3b)**

Yield 84%; mp: 205 ^{o}C; FT-IR [ν, cm^{-1}, KBr]: 3347 (N-H), 2950 (CH_3), 2840 (OCH_3), 1349 (C-N), 1157 (C-F). ^{1}H NMR [400MHz, δ, ppm, DMSO-d_6]: 6.85 (1H,s,-NH), 2.34 (3H,s,-CH_3), 3.69 (3H,s,-OCH_3), 3.87 (3H,s,-OCH_3), 7.06-7.90(13H,m,Ar-H). Anal. Calcd for $C_{28}H_{23}FN_4O_2$ (466.51); C, 72.09; H, 4.97; N, 12.01found: C, 72.02; H, 4.90; N, 12.00.

N4-[4-(4'-fluorophenyl)-6-(4-methylphenyl)-2-pyrimidinyl]-6-methoxy-2-methyl-4-quinolinamine **(3C)**

Yield 82%; mp: 201 ^{0}C; FT-IR [ν, cm^{-1}, KBr]: 3330 (N-H), 2931 (CH_3), 2833 (OCH_3), 1350 (C-N), 1159 (C-F). ^{1}H NMR [400MHz, δ, ppm, DMSO-d_6]: 6.84 (1H,s,-NH), 2.33 (3H,s,-CH_3), 2.37 (3H,s,-CH_3), 3.90(3H,s,-OCH_3), 7.14-7.75 (13H,m,Ar-H). Anal. Calcd for $C_{28}H_{23}FN_4O$ (450.51); C, 74.65; H, 5.15; N, 12.44found: C, 74.60; H, 5.11; N, 12.39.

N4-[4-(3'-bromophenyl)-6-(4-chlorophenyl)-2-pyrimidinyl]-6-methoxy-2-methyl-4-quinolin amine **(3d)**

Yield 86%; mp: 196 ^{o}C; FT-IR [ν, cm^{-1}, KBr]: 3365 (N-H), 2934 (CH_3), 2830 (OCH_3), 1336 (C-N), 1020 (C-Br), 814 (C-Cl). ^{1}H NMR [400MHz, δ, ppm, DMSO-d_6]: 6.85 (1H,s,-NH), 2.30 (3H,s,-CH_3), 3.87 (3H,s,-OCH_3), 7.10-8.13 (13H,m,Ar-H). Anal. Calcd for $C_{27}H_{20}BrClN_4O$ (531.83); C, 60.98; H, 3.79; N, 10.50 found: C, 60.91; H, 3.72; N, 10.46.

N4-[4-(3'-bromophenyl)-6-(4-methylphenyl)-2-pyrimidinyl]-6-methoxy-2-methyl-4-quinolin amine **(3e)**

Yield 83%; mp: 204 ^{o}C; FT-IR [ν, cm^{-1}, KBr]: 3392 (N-H), 2933 (CH_3), 2840 (OCH_3), 1329 (C-N), 1071 (C-Br). ^{1}H NMR [400MHz, δ, ppm, DMSO-d_6]: 6.81 (1H,s,-NH), 2.31 (3H,s,-CH_3), 2.35 (3H,s,-CH_3), 3.88 (3H,s,-OCH_3), 7.12-8.12 (13H,m,Ar-H). Anal. Calcd for $C_{28}H_{23}BrN_4O$ (511.41); C, 65.76; H, 4.53; N, 10.96 found: C, 65.71; H, 4.49; N, 10.93.

N4-[4-(3'-bromophenyl)-6-(4-methoxyphenyl)-2-pyrimidinyl]-6-methoxy-2-methyl-4-quinolin amine **(3f)**
Yield 89%; mp: 199 ^{o}C; FT-IR [ν, cm^{-1}, KBr]: 3356 (N-H), 2972 (CH_3), 2813 (OCH_3), 1309 (C-N), 1063 (C-Br). ^{1}H NMR [400MHz, δ, ppm, DMSO-d_6]: 6.81 (1H,s,-NH), 2.34 (3H,s,-CH_3), 3.70 (3H,s,-OCH_3), 3.87 (3H,s,-OCH_3), 7.06-8.12 (13H,m,Ar-H). Anal. Calcd for $C_{28}H_{23}BrN_4O_2$ (527.41); C, 63.76; H, 4.40; N, 10.62 found: C, 63.72; H, 4.39; N, 10.58.

N4-[4-(4-chlorophenyl)-6-(3'-nitrophenyl)-2-pyrimidinyl]-6-methoxy-2-methyl-4-quinolinamine **(3g)**
Yield 82%; mp: 203 ^{o}C; FT-IR [ν, cm^{-1}, KBr]: 3342 (N-H), 2965 (CH_3), 2841 (OCH_3),1514 (NO_2), 1397 (C-N), 820 (C-Cl). ^{1}H NMR [400MHz, δ, ppm, DMSO-d_6]: 6.83 (1H,s,-NH), 2.33 (3H,s,-CH_3), 3.88 (3H,s,-OCH_3), 7.10-8.20 (13H,m,Ar-H). LC-MS: m/z 498 (M^+). Anal. Calcd for $C_{27}H_{20}ClN_5O_3$ (497.93); C, 65.13; H, 4.05; N, 14.06 found: C, 65.10; H, 4.01; N, 14.02.

N4-[4-(4-methoxyphenyl)-6-(3'-nitrophenyl)-2-pyrimidinyl]-6-methoxy-2-methyl-4-quinolin amine **(3h)**
Yield 87%; mp: 196 ^{o}C; FT-IR [ν, cm^{-1}, KBr]: 3350 (N-H), 2946 (CH_3), 2845 (OCH_3), 1525 (NO_2), 1389 (C-N), 796 (C-Cl). ^{1}H NMR [400MHz, δ, ppm, DMSO-d_6]: 6.84 (1H,s,-NH), 2.32 (3H,s,-CH_3), 3.70 (3H,s,-OCH_3), 3.89 (3H,s,-OCH_3), 7.06-8.20 (13H,m,Ar-H). Anal. Calcd for $C_{28}H_{23}N_5O_4$ (493.51); C, 68.14; H, 4.70; N, 14.19 found: C, 68.08; H, 4.65; N, 14.11.

Conclusion

The clubbing of 2-amino-4,6-diaryl substituted pyrimidine derivatives and 4-chloro-6-methoxy-2-methylquinoline has been done successfully into one molecule. The antimicrobial activity of N4-[4,6-diaryl substituted phenyl-2-pyrimidinyl]-6-methoxy-2-methyl-4- quinolinamine **3a-h** was carried out against some strain bacteria. The results show that the synthesized compounds were toxic against the bacteria. The comparison of the antibacterial and antifungal activity of these compounds with standard drugs shows that the presence of methoxy and halogen (-Cl,-Br,-F) groups in the phenyl ring increases the antimicrobial activity. Their potency has been found to be lower than that of standard drugs, but their acute toxicity is significantly lower.

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