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Studies on Synthesis and Antimicrobial Activity of Quinoline Pyrimidine Derivatives

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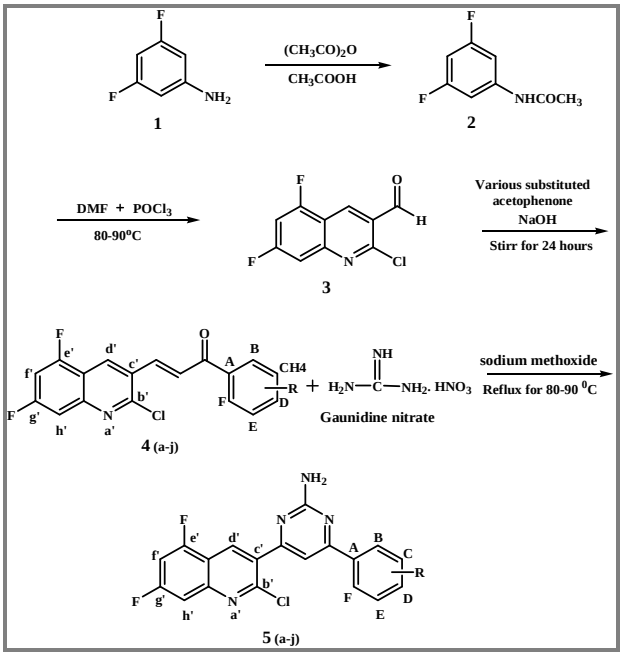
ABSTRACT

A series of various substituted pyrimidine derivatives has been synthesized by reacting chalcones with guanidine nitrate in presence of sodium methoxide in methanol. The structure of newly synthesized heterocycles was confirmed by their elemental analysis, IR spectra and ^{1}H NMR spectra. They were subjected to biological studies.

Graphical Abstract



Where, **R** = 4-Cl, 4-Br, 4-OCH_3, 4-NH_2, 3-F, 3-OCH_3, 2,4-di F, 2,4-di Cl 5-F,2,4-di F 5-Cl,2,4,5- tri Cl.

Keywords: Quinoline chalcones, pyrimidine derivatives, antibacterial and antifungal activity.

INTRODUCTION

Chalcone derivatives are important starting materials for the synthesis of different classes of heterocyclic compounds such as pyrimidines, pyrazolines and thiophenes etc. Pyrimidine itself is not found in nature but substituted pyrimidines and compounds containing the pyrimidine ring are widely distributed in nature. Since the late 1980s, a tremendous interest in the pyrimidine derivatives has been observed, as evidenced by the growing number of publications [**1-2**].

The quinoline skeleton is often used for the design of many synthetic compounds with diverse pharmaceutical properties [**3**]. The α, β-unsaturated ketonic group which is responsible for bactericidal activity of chalcones is also of great use in further chemical modification into various heterocyclic moieties. The various properties of chalcones have prompted us to synthesis pyrimidine derivatives to study their antimicrobial activity [**4-6**]. Among the important heterocyclic moieties of biological and pharmacological interest, the quinoline ring is endowed with various activities, such as antimalarial [**7**], anti inflammatory [**8**], anticancer activities [**9**] and antioxidant [**10**].

MATERIALS AND METHODS

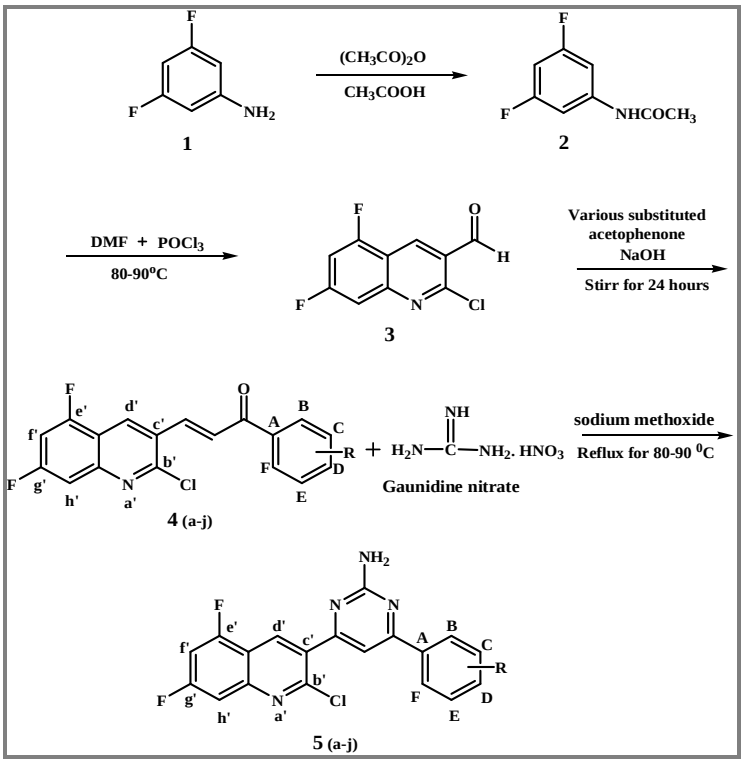
All the melting points were measured in open capillary tube in scientific melting point apparatus and were uncorrected. The completion of the reaction was checked by thin-layer chromatography (TLC) on silica gel plates (Merck, 60, F254) and observed in UV light. IR spectra of synthesized compound were scanned on Shimashu–FTIR. PMR spectra of the synthesized compounds were measured in DMSO on a BRUKER AVANCE II 400 spectrometer and tetramethylsilane (TMS) as an internal standard. Chemical shift are expressed in δ (ppm) downfield from the internal standard and signals are quoted as *s* (singlet), *d* (doublet), *t* (triplet) and *m* (multiplate). All reagents used in the present work were of analytical grade.

RESULTS AND DISCUSSION

If pyrimidine and quinoline moieties clubbed into one molecule, the resultant molecule may enhance the pharmaceutical activity up to some extent. Hence, the biological significance of the pyrimidine derivatives has led us to the synthesis substituted pyrimidine derivatives. 2-Chloro-5,7-difluoro quinoline -3-carbaldehyde [**3**] was synthesized by Vilsemeir-Haack reaction. From 3,5-Difluoro acetanilide [**2**] was reacted with substituted acetophenone **(a-j)** in methanolic NaOH to obtain (E)-3-(2-Chloro-5,7-diflouroquinoline-3-yl)-1-(4- substituted phenyl) prop-2-en-1-one **[4(a-j)]**, which were condensed with guanidine nitrate in presence of sodium methoxide to obtain amino pyrimidine derivatives **[5(a-j)]**. The structures of synthesized quinolinyl pyrimidine derivatives have been elucidated by spectroscopic data and elemental analysis. IR spectra of the synthesized compounds reveal that all the chalcone derivatives exhibited a stronge absorption near at 1644-1618 cm^{-1} and at 1685-1660 cm^{-1} indicates the presence of -CH=CH- [**11**] and C=O [**11**] group. N-H stretching vibrations of Primary and secondary amines [**12**] showed in the range of 3500, 3400 and 3350-3310 cm^{-1} region. C-F [**11**] absorption is observed in the broad regionbetween1000-1400 cm^{-1}. C-Cl [**11**] absorption is observed in the broad region between 750-700 cm^{-1}. C-Br [**11**] absorption is observed in the broad region between 600-500 cm^{-1}. Formation of pyrimidine derivatives was confirmed by the presence of singlet signal of primary amine at 5.25-5.31δ ppm in ^{1}H NMR spectrum [**12**]. The synthetic route of the compounds is outlined in scheme 1.

Minimum inhibitory concentration of all the synthesized pyrimidine derivatives has been screened against Gram-positive, Gram-negative bacterial and fungal species. From the antibacterial results of **[5(a-j)]**, compounds 5c and 5g displayed excellent activity of 62.5 μg mL^{-1} against *E. coli*. Compound 5h displayed better activity of 125 μg mL^{-1} against *E. coli*. Compound 5a, 5c, and 5g possessed good activity of 100-125 μg mL^{-1} against *P. aeruginosa*. Compound 5a and 5 g showed very good activity of 125 μg mL^{-1} against *S. aureus*. Rest of compound showed good to moderate activity. The

antifungal results of compound 5i possessed good activity of 250 µg mL^{-1} against *C. albicans*, while 5g and 5h showed very good activity of 250 µg mL^{-1} against *S.cervecea*. The rest of compounds showed moderate and good activity against remaining fungal species.



Where, **R** = 4-Cl, 4-Br, 4-OCH_3, 4-NH_2, 3-F, 3-OCH_3,
2,4-di F, 2,4-di Cl 5-F,2,4-di F 5-Cl,2,4,5- tri Cl.

Scheme 1. Pyrimidine derivatives 5(a-j)

Synthesis of 2-chloro-5, 7-difluoro quinoline-3-carbaldehyde [3]: Phosphoryl chloride (53.58 g, 0.35 mol) was added drop wise to a solution of 3,5-difluoro acetanilide (8.56 g, 0.05 mol) in dry DMF (10.9 g, 0.15 mol) at 0-5°C temperature, with stirring and mixture was refluxed at 85-90°C for time ranging between 4-16 h [**13-15**]. The mixture was poured on to crushed ice, stirred for 1h and kept overnight. The resulting solid was filtered, washed well with water and dried. The compound was recrystallised from ethyl acetate, yield: 72 %, m.p.170-180°C.

Synthesis of (E)-3-(2-chloro-5,7-difluoro quinoline-3-yl)-1-(substituted phenyl)prop-2-en-1-one [4(a-j)] Equimolar quantities of 2-chloro-5,7-difluoroquinoline-3-carbaldehyde (0.01 mol) and substituted acetophenone (0.01 mol) in methanol was stirred at 0-5°C and then NaOH (25%, 4 mL) was added within 2.0 h **[16, 17]**. The stirring was continuous for 24 h at room temperature. The reaction mixture was poured into crushed ice and acidified if necessary with dilute hydrochloric acid (10% HCl). The solid mass separated out was filtered, washed with water and recrystallised from ethanol. The residue was purified by column chromatography using ethanol.

(E)-3-(2-Chloro-5,7-difluoroquinoline-3-yl)-1-(4-chlorophenyl)prop-2-en-1-one[4a]: m.p.: 153°C, **Yield:** 70%, **IR (KBr in cm^{-1}):** 3085 (Ar-H C-H str.), 1681(C=O str., chalcone gr.), 1639 (CH=CH str.), 1581(C=N str.)., 1445 (Ar C=C str.), 1213 (C-N str.), 1125 (Ar C-F str.), 736 (C-Cl str.). **^{1}H NMR (400MHz, DMSO-d6, δ ppm):** 7.73(1H, d, $H_α$), 8.03 (1H, d, $H_β$), 6.59 (1H, s, Ar-$H_{f'}$), 7.09 (1H, s, Ar-$H_{h'}$), 7.61 (2H, d, Ar-$H_{C,E}$), 7.92 (2H, d, Ar-H $_{B,F}$), 8.58 (1H, s, Ar-$H_{d'}$).**Anal. Calcd for:** $C_{18}H_9Cl_2F_2NO$: (364.17) : C, 59.37; H, 2.49; N, 3.85. Found: C, 59.32; H, 2.44; N, 3.80.

(E)-3-(2-Chloro-5,7-difluoroquinoline-3-yl)-1-(2,4-difluorophenyl)prop-2-en-1-one[4g]: m.p.: 112°C, **Yield:** 79%, **IR (KBr in cm^{-1}):** 3070 (Ar C-H str.), 1676(C=O str., chalcone gr.), 1641 (CH=CH str.), 1596 (C=N str.)., 1488 (Ar C=C str.), 1122 (C-F str.), 761(C-Cl str.) **^{1}H NMR (400MHz, DMSO-d6, δ ppm) :**7.67 (1H, d, $H_α$), 8.01 (1H, d, $H_β$), 6.61 (1H, s, Ar-$H_{f'}$), 6.73 (1H, s, Ar-H_C), 7.28 (1H, d, Ar-H_E), 7.35 (1H, s, Ar-$H_{h'}$), 7.92 (1H, d, Ar-H_F), 8.53 (1H, s, Ar-$H_{d'}$). **Anal. Calcd for:** $C_{18}H_8ClF_4NO$: (365.71) : C,59.12; H, 2.20; N, 3.83. Found: C, 59.17; H, 2.12; N, 3.77.

Synthesis of of 4-(2-chloro-5,7-diflouro quinolin-3-yl)-6-(substituted phenyl) pyrimidine-2-amine [5(a-j)]: E)-3-(2-Chloro-5,7-difluoro quinoline-3-yl)-1-(substituted phenyl)prop-2-en-1-one (0.01 mol) and guanidine nitrate (0.015 mol) were added to sodium methoxide (0.01 mol) dissolved in methanol [**18, 19**]. The reaction was refluxed on water bath at 80-90°C for 10-12 h. The process of the reaction was monitored by TLC (toluene**:** ethyl acetate, 8:2). After completion of reaction, mixture was cooled and poured into crushed ice with constant stirring for an hour. Then the precipitate was filtered and washed with water. The crude product was dried and crystallized from ethanol (99.9 %).

4-(2-Chloro-5,7-diflouroquinolin-3-yl)-6-(4-chlorophenyl)pyrimidine-2-amine[5a]:m.p.: 252°C, **Yield:** 70%, **IR (KBr cm^{-1}):** 3414, 3362 (N-H str., primary amine), 3009 (Ar. C-H str.), 1610 (N-H ben., primary amine), 1585(C=N str.), 1473 (Ar C=C str.), 1267 (C-N str.), 1126 (C-F str.), 788 (C-Cl str.). **^{1}H NMR (400MHz, DMSO-d6, δ ppm):**5.25 (s, 2H, pyrimidine –NH_2), 8.20 (s,1H, pyrimidine ring), 7.07 (s, 1H, Ar-$H_{f'}$), 7.50-7.70(m, 3H,Ar-H $_{h'/C,E}$), 8.10 (d, 2H, Ar-$H_{B,F}$), 8.70 (s, 1H, Ar-$H_{d'}$). **Anal. Calcd for:** $C_{19}H_{10}Cl_2F_2N_4$: (403.21): C, 56.60; H, 2.50; N,13.90. Found: C, 56.54; H, 2.53; N,13.87.

4-(4-Bromophenyl)-6-(2-chloro-5,7-diflouroquinolin-3-yl)pyrimidine-2-amine[5b]: m.p.: 274°C, **Yield:** 79%, **IR (KBr cm^{-1}):** 3382, 3232 (N-H str., primary amine), 3028, 2983 (Ar. C-H str.), 1616 (N-H ben., primary amine), 1583 (C=N str.), 1458 (Ar C=C str.), 1261 (C-N str.), 1128(C-F str.), 729 (C-Cl str.) **^{1}H NMR (400MHz, DMSO-d6, δ ppm) :**5.30 (s, 2H, pyrimidine –NH_2),7.91 (s,1H, pyrimidine ring), 7.05 (s, 1H, Ar-$H_{f'}$), 7.40-7.60 (m, 3H, Ar-H $_{h'/C,E}$), 8.00 (d, 2H, Ar-$H_{B,F}$), 8.62 (s, 1H, Ar-$H_{d'}$). **Anal. Calcd for:** $C_{19}H_{10}BrClF_2N_4$: (447.9 7): C, 50.90; H, 2.21; N, 12.22. Found: C, 50.98; H, 2.25; N, 12.25.

4-(2-Chloro-5,7-diflouroquinolin-3-yl)-6-(4-methoxyphenyl)pyrimidine-2-amine[5c]: m.p.: 83°C, **Yield:** 64%, **IR (KBr cm^{-1}):** 3436, 3371(N-H str., primary amine),3013 (Ar.C-H str.), 2971,2888 (C-Hstr., Methoxy gr.), 1615(N-H ben., primary amine),1565(C=N str.), 1459 (Ar C=C str.), 1267 (C-N str.), 1210,1097(C-O-C str.) 1120 (C-F str.),762(C-Cl str.). **^{1}H NMR (400MHz, DMSO-d6,δ ppm) :**5.34 (s, 2H, pyrimidine –NH_2), 7.92 (s,1H, pyrimidine ring), 3.80(s,3H,-OCH_3), 7.00(s, 1H, Ar-$H_{f'}$), 7.40-7.60 (m, 3H,Ar-H $_{h'/C,E}$),8.20 (d, 2H, Ar-$H_{B,F}$), 8.60 (s, 1H, Ar-$H_{d'}$). **Anal. Calcd for:** $C_{20}H_{13}ClF_2N_4O$: (398.07): C, 60.19; H, 3.33; N, 13.99. Found: C, 60.24; H, 3.29; N, 14.05.

4-(4-Aminophenyl)-6-(2-chloro-5,7-diflouroquinolin-3-yl)pyrimidine-2-amine[5d]: m.p.: 179°C, **Yield:** 84%, **IR (KBr cm^{-1}):** 3473, 3267(N-H str., primary amine), 3027, 2961 (Ar. C-H str.), 1632 (N-H ben., primary amine), 1569 (C=N str.), 1454 (Ar C=C str.), 1266 (C-N str.), 1134 (C-F str.), 738 (C-Cl str.). **^{1}H NMR (400MHz, DMSO-d6, δ ppm) :**5.30 (s, 2H, pyrimidine –NH_2), 7.90 (s,1H, pyrimidine ring), 5.62(s,2H,-NH_2), 7.10 (s, 1H, Ar-$H_{f'}$), 7.50-7.70 (m, 3H, Ar-H $_{h'/C,E}$), 8.10 (d, 2H, Ar-$H_{B,F}$), 8.50 (s, 1H, Ar-$H_{d'}$).**Anal. Calcd for:** $C_{19}H_{12}ClF_2N_5$: (383.07): C, 59.36; H, 3.09; N, 18.27. Found: C, 59.40; H, 3.15; N, 18.25.

4-(2-Chloro-5,7-diflouroquinolin-3-yl)-6-(3-flourophenyl)pyrimidine-2-amine[5e]: m.p.: 116°C, **Yield:** 72%, **IR (KBr cm^{-1}):** 3426, 3365(N-H str., primary amine), 3044(Ar. C-H str.), 1633 (N-H ben., primary amine), 1570 (C=N str.), 1457 (Ar C=C str.), 1262(C-N str.), 1129 (C-F str.), 761 (C-Cl str.).**^{1}H NMR (400MHz, DMSO-d6, δ ppm) :**5.32 (s, 2H, pyrimidine –NH_2), 7.94 (s,1H, pyrimidine ring),6.88(s, 1H,Ar-$H_{f'}$), 7.10 (d, 1H, Ar-H_D), 7.30-7.70 (m, 3H, Ar-H $_{h'/F,E}$), 8.08 (s, 1H, Ar-H_B),

8.18 (s, 1H, Ar-$H_{d'}$). **Anal. Calcd for:** $C_{19}H_{10}ClF_3N_4$: (386.05): C, 58.95; H, 2.57; N, 14.44. Found: C, 59.00; H, 2.61; N, 14.49.

4-(2-Chloro-5,7-diflouroquinolin-3-yl)-6-(3-methoxyphenyl)pyrimidine-2-amine [5f]: m.p.208°C, **Yield:** 81%, **IR (KBr cm^{-1}):** 3430, 3381(N-H str., primary amine), 3017 (Ar. C-H str.), 2967, 2876(C-H str. Methoxy gr.), 1622 (N-H ben., primary amine), 1559(C=N str.), 1448 (Ar C=C str.), 1260 (C-N str.),1214,1092 (C-O-C str.), 1122 (C-F str.), 757 (C-Cl str.). **^{1}H NMR (400MHz, DMSO-d6, δ ppm) :**5.34 (s, 2H, pyrimidine –NH_2), 7.93(s, 1H, pyrimidine ring), 3.7-3.8(s, 3H, -OCH_3), 6.86(s, 1H,Ar-$H_{f'}$), 7.08 (d, 1H, Ar-H_D), 7.30-7.75 (m, 3H, Ar-H $_{h'/F,E}$), 8.10 (s, 1H, Ar-H_B), 8.12 (s, 1H,Ar-$H_{d'}$). **Anal. Calcd for:** $C_{20}H_{13}ClF_2N_4O$: (398.79): C, 60.27; H, 3.24; N, 13.97. Found: C, 60.24; H, 3.29; N, 14.05.

4-(2-Chloro-5,7-diflouroquinolin-3-yl)-6-(2,4-diflourophenyl)pyrimidine-2-amine [5g]: m.p. 208°C, **Yield:** 81%, **IR (KBr cm^{-1}):** 3468, 3346 (N-H str., primary amine), 3033,2954 (Ar. C-H str.), 1637(N-H ben., primary amine), 1560 (C=N str.), 1451 (Ar C=C str.), 1264 (C-N str.), 1132 (C-F str.), 737 (C-Cl str.). **^{1}H NMR (400MHz, DMSO-d6, δ ppm):** 5.32 (s, 2H, pyrimidine –NH_2), 7.92 (s,1H, pyrimidine ring), 6.88(s, 2H,Ar-$H_{C,f'}$), 7.30-7.70 (m, 3H, Ar-H $_{h'/F,E}$), 8.22 (s, 1H, Ar-$H_{d'}$). **Anal. Calcd for:** $C_{19}H_9ClF_4N_4$: (404.75): C, 56.35; H, 2.20; N, 13.87. Found: C, 56.38; H, 2.24; N, 13.84.

4-(2-Chloro-5,7-diflouroquinolin-3-yl)-6-(2,4-dichloro-5-flourophenyl)pyrimidine-2-amine[5h]: m.p.: 165°C, **Yield:** 84%, **IR (KBr cm^{-1}):** 3420, 3368 (N-H str., primary amine), 3047 (Ar. C-H str.), 1632 (N-H ben., primary amine), 1574(C=N str.), 1456 (Ar C=C str.), 1263 (C-N str.), 1131 (C-F str.), 765 (C-Cl str.). **^{1}H NMR (400MHz, DMSO-d6, δ ppm) :**5.30 (s, 2H, pyrimidine –NH_2), 7.96 (s,1H, pyrimidine ring), 6.85(s, 2H,Ar-$H_{C,f'}$), 7.30-7.60 (m, 2H, Ar-H $_{h'/E}$), 8.32 (s, 1H,Ar-$H_{d'}$). **Anal. Calcd for:** $C_{19}H_7Cl_3F_3N_4$: (455.65): C, 50.12; H, 1.72; N, 12.24. Found: C, 50.05; H, 1.77; N,12.30.

4-(2-Chloro-5,7-diflouroquinolin-3-yl)-6-(2,4-dichloro-5-flourophenyl)pyrimidine-2-amine[5i]: m.p.: 130°C, **Yield:** 64%, **IR (KBr cm^{-1}):** 3457, 3263 (N-H str., primary amine), 3033, 2954 (Ar. C-H str.), 1639 (N-H ben., primary amine), 1558(C=N str.), 1447(Ar C=C str.), 1255 (C-N str.), 1130 (C-F str.), 766 (C-Cl str.). **^{1}H NMR (400MHz, DMSO-d6, δ ppm):**5.20 (s, 2H, pyrimidine –NH_2), 7.90 (s,1H, pyrimidine ring), 6.82(s, 2H,Ar-$H_{C,f'}$), 7.30-7.50 (m, 2H, Ar-$H_{h'/E}$),8.20 (s, 1H, Ar-$H_{d'}$).**Anal. Calcd for:** $C_{19}H_8Cl_2F_4N_4$: (439.19): C, 51.90; H, 1.78; N, 12.70. Found: C, 51.96;H, 1.84; N, 12.76.

4-(2-Chloro-5,7-diflouroquinolin-3-yl)-6-(2,4,5-trichlorophenyl)pyrimidine-2-amine [5j]: m.p.: 285°C, **Yield:** 76%, **IR (KBr cm^{-1}):** 3431, 3348(N-H str., primary amine), 3021 (Ar. C-H str.), 1611 (N-H ben., primary amine), 1570(C=N str.), 1440 (Ar C=C str.), 1263 (C-N str.), 1143 (C-F str.), 767 (C-Cl str.).**^{1}H NMR (400MHz, DMSO-d6, δ ppm) :**5.32(s, 2H, pyrimidine –NH_2), 7.94 (s,1H, pyrimidine ring), 6.90(s, 2H,Ar-$H_{C,f'}$), 7.40-7.55 (m, 2H, Ar-H $_{h'/E}$), 8.40 (s, 1H, Ar-$H_{d'}$).**Anal. Calcd for:** $C_{19}H_8Cl_4F_2N_4$: (472.10): C, 48.30; H, 1.67; N, 11.78. Found: C, 48.34; H, 1.71; N, 11.83.

APPLICATION

The *in vitro* antimicrobial activity of synthesis compound [(**5a-j)**] was determined by using 'Broth Dilution Method [**20, 21**]. They were evaluated against four bacterial strains viz. *E. coli, P. aeruginosa, S. aureus, S. pyogenes* and two fungus strain viz. *C. albicans, S. cerevisiae*. Each of the test compound and standards were dissolved in DMSO obtaining 2000 µg mL^{-1} concentration, as a stock solution. The study was simultaneously performed for reference standards Ciprofloxacin, Gentamicin and Flucanazole.

Table 1. Antimicrobial activity

Compounds	MBC in µg mL^{-1}				MFC in µg mL^{-1}	
	Gram negative organisms		Gram positive organisms			
	E. coli	*P. aeruginosa*	*S. aureus*	*B. subtilis*	*C. albicans*	*S. cerevisiae*
5a	250	125	125	250	500	500
5b	250	250	250	250	1000	1000
5c	62.5	125	250	250	500	1000
5d	250	250	250	250	500	500
5e	500	500	250	500	500	1000
5f	250	250	500	500	1000	1000
5g	62.5	100	125	250	500	250
5h	125	250	500	500	500	250
5i	250	500	500	250	250	1000
5j	500	500	250	500	500	500
Ciprofloxacin	50	50	50	50	---	---
Gentamicin	50	50	50	50	---	---
Flucanazole	---	---	---	---	100	100

MBC- Minimal Bactericidal Concentration, MFC- Minimal Fungicidal Concentration

CONCLUSION

In conclusion, we have synthesized a series of 4-(2-chloro-5,7-diflouro quinolin-3-yl)-6-(substituted phenyl) pyrimidine-2-amine **[5(a-j)]** was characterized by spectral and elemental analysis. All the compounds exhibited promising activities against gram positive, gram negative bacterial and fungal strains. Newly synthesized substituted quinolinyl pyrimidine derivatives showed moderate to high antimicrobial activity against*E.coli, P. aeruginosa*, *S. aureus*, *S. pyogenes*, *C. albicans* and *S. cerevisiae*. Quinolinyl pyrimidine derivatives showed higher activity against gram negative organisms than gram positive organisms.

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