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SYNTHESIS AND ANTIMICROBIAL EVALUATION OF 2-(4-FLUORO BENZYLTHIO)-N-(SUBSTITUTED PHENYL)PYRIMIDINE-4-AMINES

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Pyrimidines, Anilines, Antibacterial activity, Antifungal activity

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ABSTRACT: Reaction of 4-fluorobenzylchloride with 2-thiouracil **(1)** gave 2-(4-fluorobenzylthio)pyrimidin-4(3H)-one **(2)**, which on chlorination with $POCl_3$ furnished 4-chloro-2-(4-fluorobenzylthio)-4-chloropyrimidine **(3)**. This intermediate when treated with various substituted anilines gave desired targeted compounds **4(a-k)** in 50-90% yield. Structural assignments of the synthesized compounds were based on their IR, ^{1}H NMR, Mass and analytical data. The antimicrobial evaluation of newly synthesized compounds was carried out by cup-plate method. The investigation of antimicrobial screening reveals that the compounds **4b**, **4g**, **4c and 4f** showed good activity against bacterial strain *B. subtilis.* Compounds **4a**, **4e**, **4b**, **4c, 4f, 4g and 4h** were active against bacterial strain *P. aeruginosa***.** Compounds **4a** and **4c** were active against fungul strain *A. niger*. Compounds **4e**, **4b** and **4j** showed good activity against fungal strain *A. flavus.* All the synthesized compounds showed excellent antifungal activity against *T.viridae*. Remaining compounds exhibited moderate to poor activity against bacterial and fungal strains when compared to standard drugs Gentamycin and Fluconazole respectively. So, further we have carried out the antifungal screening of all the synthesized compounds at different concentrations against *T. viridae* to determine their IC_{50} values. Compounds **4e**, **4b, 4g, 4i, 4d, 4f and 4j** have shown better IC_{50} values.

INTRODUCTION: Pyrimidines have a long and distinguished history extending from the days of their discovery as important constituents of nucleic acids to their current use in medicinal chemistry. Pyrimidine derivatives are well known to exhibit various biological and pharmacological activities such as antitumour [1], anti-HIV [2, 3], antimicrobial[4-6], antidepressants [7], hypnotics and sedatives [8], analgesic and anti-inflammatory [9], antioxidant [10] and acid-pump antagonist [11] activities

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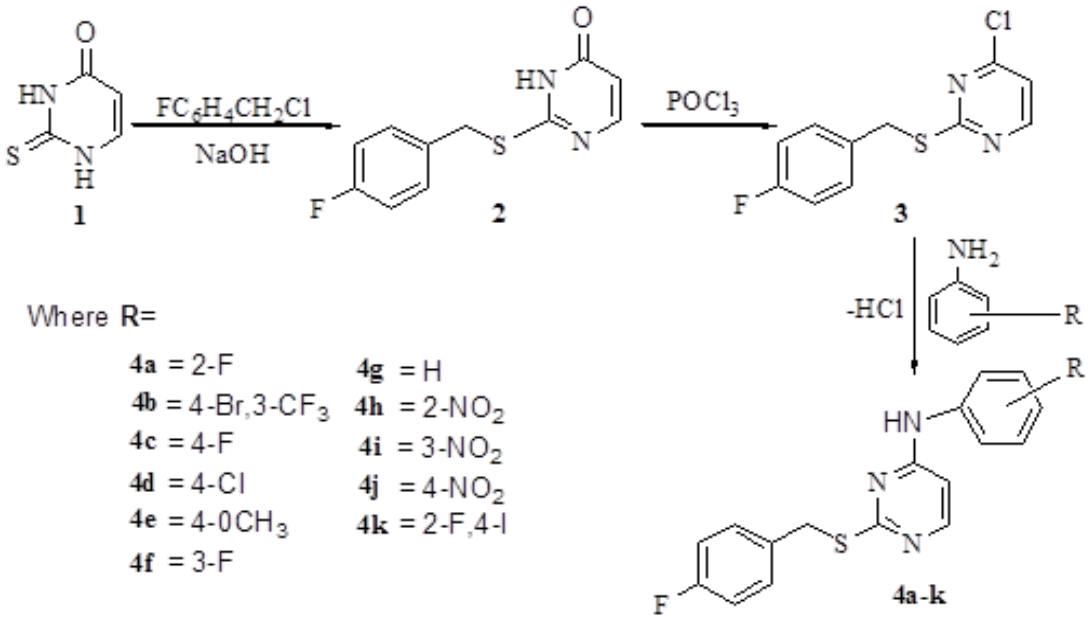
The presence of fluorine increases thermal stability, lipophilicity and bioavailability [12]. Although the utility of fluorine substituents is there, only few methods are available for carbon-fluorine bond formation [13-14], which indicates the unavailability of suitable fluorination methods.

As incorporating fluorine into system is not easy, we have reacted different fluorine substituted reagents with 2-thiouracil derivatives so as to get pyrimidine molecule bearing fluorine on its substituent. In view of potent pharmacological activity associated with pyrimidines and enhancement of activity by introducing fluorine in the molecule, We herein report the synthesis and antimicrobial activities of 2-(4-fluorobenzylthio)-N-(substituted phenyl)pyrimidine-4-amines (**Scheme 1**).

MATERIALS AND METHODS: All the solvents and chemicals were obtained from S. D. Fine-Chem Ltd. Mumbai and were purified by standard procedures. Melting points were determined in open capillary and were uncorrected. IR spectra in KBr disc were recorded on Perkin-Elmer-Spectrum-one FT-IR spectrophotometer (ν_{max} in cm^{-1}). ^1H NMR spectra were recorded in *DMSO-d_6* with a BRUKER NMR 500 MHz Spectrophotometer using TMS as internal standard (chemical shift in δ or ppm). Mass spectra were recorded on LCMS 2010A, SHIMADZU Mass Spectrophotometer.

Purity of the compounds was checked by TLC using silica gel 'G' plates obtained from Whatman Inc, and a fluorescent indicator.

RESULT AND DISCUSSION: Reaction of 2-thiouracil (**1**) with 4-flourobenzylchloride in aq. NaOH gave compound **2** in 85% yield having m.p. 158-160˚C (**Scheme 1**). ^1H NMR spectra displayed a singlet at δ 4.39 due to two protons of CH_2 and two doublet peaks, one at δ 7.24 due to C_5H of pyrimidine and another at δ 7.39 due to C_6H of pyrimidine ring and multiplet from δ 7.25-7.90 due to four aromatic protons confirms the formation of compound **2**.



SCHEME 1

Further formation of compound **2** is confirmed by the presence of absorption bands at 1708, 1574cm^{-1} assigned to C=O, C=N with 687 cm^{-1} characterized by C-F stretching were shown in its IR spectrum. Chlorination of compound **2** with $POCl_3$ yielded 4-chloro-2-(4-fluorobenzylthio)pyrimidine **(3)** in 90% yield, m.p. 44-46˚C. Formation of this compound **3** was confirmed by the presence of absorption peaks at 1575, 736 and 707 cm^{-1} due to C=N, C-Cl and C-F in its IR spectrum.

Further confirmation of compound **3** is by the presence of singlet at δ 4.4 due to two protons of SCH_2PhF, aromatic protons signal as a multiplet at δ 7.14 -7.16, characteristic absorption of C_5H and C_6H of pyrimidine ring as a doublet at δ 7.40 and δ 8.60 respectively in its ^1H NMR spectrum. This intermediate on reaction with various aromatic amines in presence of piperidine in methanol furnished the desired targeted compounds (**4a-k)** in 50 - 80% yield. Compound **4a** was obtained in 50% yield having m.p. 104˚-106˚C. The IR (cm^{-1}) spectrum of compound **4a** showed absorptions at 3081, 1575 and 707 cm^{-1} due to the presence of aromatic NH, C=N and C-F groups.

^1H NMR displayed singlet at δ 4.34 due to two protons of SCH_2PhF, multiplet in the region δ 6.77-7.40 due to eight aromatic protons and a singlet at δ 6.42 due to NH proton and two doublet peaks at δ 6.20 and δ 8.18 due to C_5H and C_6H of pyrimidine ring.

Final confirmation of compound **4a** is by the appearance of molecular ion peak at m/z = 330 (M^{+1}, 100%) in its mass spectrum. Physical data of all the synthesized compounds are tabulated in **Table 1.**

TABLE 1: PHYSICAL DATA OF SYNTHESIZED COMPOUNDS (2, 3 & 4a-k)

Comp. No.	R	Molecular formula	M. P (ºC)	Yield (%)	Elemental Analysis Calc, (Found) (%)		
					C	H	N
2	--	$C_{11}H_9FN_2OS$	158-160 ºC	85	51.76 (51.70)	3.55 (3.50)	10.97 (10.91)
3	--	$C_{11}H_8N_2ClFS$	44-46 ºC	90	53.33 (53.28)	3.25 (3.20)	11.31 (11.28)
4a	2-F	$C_{17}H_{13}N_3F_2S$	103-106 ºC	50	61.99 (61.95)	3.97 (3.93)	12.75 (12.71)
4b	4-Br,3-CF_3	$C_{18}H_{12}N_3BrF_4S$	195-198 ºC	62	47.18 (47.14)	2.63 (2.59)	9.17 (9.13)
4c	4-F	$C_{17}H_{13}N_3F_2S$	102-104 ºC	65	61.99 (61.95)	3.97 (3.93)	12.75 (12.71)
4d	4-Cl	$C_{17}H_{13}N_3ClFS$	99-100 ºC	80	59.10 (59.06)	3.78 (3.73)	12.15 (12.11)
4e	4-OCH_3	$C_{18}H_{16}N_3OFS$	118-120 ºC	70	63.32 (63.25)	4.72 (4.67)	12.31 (12.28)
4f	3-F	$C_{17}H_{13}N_3F_2S$	135-138 ºC	62	61.99 (61.95)	3.98 (3.94)	12.76 (12.70)
4g	H	$C_{17}H_{14}N_3FS$	114-116 ºC	72	65.57 (65.53)	4.53 (4.49)	13.49 (13.45)
4h	2-NO_2	$C_{17}H_{13}N_4O_2FS$	95-98 ºC	66	57.29 (57.25)	3.68 (3.64)	15.72 (15.68)
4i	3-NO_2	$C_{17}H_{13}N_4O_2FS$	118-120 ºC	62	57.29 (57.25)	3.68 (3.64)	15.72 (15.68)
4j	4-NO_2	$C_{17}H_{13}N_4O_2FS$	91-92 ºC	60	57.29 (57.25)	3.68 (3.64)	15.72 (15.68)
4k	2-F,4-I	$C_{17}H_{12}N_3IF_2S$	102-104 ºC	67	44.85 (44.80)	2.65 (2.61)	9.23 (9.19)

EXPERIMENTAL:

Synthesis of 2-(4-fluorobenzylthio)pyrimidine-4(3H)-one (2): 2-Thiouracil (**1**) (0.075 mole) and NaOH (0.1 mole) were dissolved in hot water (450 ml) and then mixed with 4-fluorobenzylchloride (0.1 mole). The temperature was increased until all the 4-fluorobenzylchloride went into the solution for about one hour. On cooling the separated solid product was collected by filtration, washed with water, dried and crystallized from ethanol to afford compound **2**.

Yield: 85%. M.P: 158-160 ^oC. IR(cm^{-1}): 1708 (C=O), 1574 (C=N), 687 (C-F). ^1H NMR (DMSO-d_6): δ 4.39 (s, 2H, SCH_2 PhF), 7.24 (d, 1H, C_5H of pyrimidine), 7.25-7.90 (m, 4H, ArH), 7.39 (d, 1H, C_6H of pyrimidine). Anal. Calcd. for $C_{11}H_9FN_2OS$: C, 51.76; H, 3.55; N, 10.97. Found: C, 51.72; H, 3.51; N, 10.92%.

Synthesis of 2-(4-fluorobenzylthio)-4-chloro pyrimidine (3): A mixture of 2-(4-fluorobenzylthio)pyrimidine-4(3H)-one (**2**) (0.01 mole) and $POCl_3$ (0.1 mole) was refluxed for 3 hours. Excess of $POCl_3$ was removed under reduced pressure and the reaction mixture was treated with ice/water. The separated solid was extracted with ether (3 x 100 ml) and the ether extract was washed with 5% aq.$NaHCO_3$ solution (1 x 25 ml), water (1 x 25 ml) and then dried over anhydrous sodium sulphate and after solvent evaporation yielded the crude compound **3** was recrystallized from EtOH.

Yield: 90%. M.P: 44-46 ^oC. IR(cm^{-1}): 1575 (C=N), 707 (C-F), 736 (C-Cl). ^1H NMR (DMSO-d_6): δ 4.4 (s, 2H, CH_2),7.14-7.16 (m, 4H, ArH), 7.40 (d, 1H, C_5H of pyrimidine), 8.6 (d, 1H, C_6H of pyrimidine). Anal. Calcd. for $C_{11}H_8N_2ClFS$: C, 53.33; H, 3.25; N,11.31. Found: C, 53.28; H, 3.21; N, 11.27%.

Synthesis of 2-(4-fluorobenzylthio)-N-(substituted phenyl)pyrimidine-4-amines (4a-k): To a solution of 2-(4-fluorobenzylthio)-4-chloropyrimidine (**3**) (0.001 mole) in methanol (20 ml) and catalytic amount of piperidine, appropriate aromatic primary amine (0.001 mole) was added and refluxed for 12-15 hours on water bath. Concentrated the reaction mixture under reduced pressure and the residue triturated with little crushed ice and neutralized the aqueous layer with 0.1N HCl. Solid separated was filtered, washed with cold water and recrystallized from ethanol to yield the target compounds (**4a-k**).

Spectral data of compounds (4a-k):

2-(4-Fluorobenzylthio)-N-(2-fluorophenyl) pyrimidine-4-amine (4a): Yield: 50%. M.P: 103-106ºC. IR (cm^{-1}): 3081 (NH), 1575 (C=N), 707 (C-F). ^{1}H NMR (DMSO-d_6): δ 4.34 (s, 2H, SCH_2PhF), 6.77-7.40 (m, 8H, ArH), 6.42 (s, 1H, NH), 6.20 (d, 1H, C_5H of pyrimidine), 8.18 (d, 1H, C_6H of pyrimidine). Mass: m/z = 330 (M^{+1}, 100%). Anal. Calcd. for $C_{17}H_{13}N_3F_2S$: C, 61.99; H, 3.97; N, 12.75. Found: C, 61.95; H, 3.93; N, 12.71%.

2-(4-Fluorobenzylthio)-N-(4-bromo-3-trifluoro methylphenyl)pyrimidin-4-amine (4b): Yield: 62%. M.P: 195-198ºC. IR (cm^{-1}): 3078 (NH), 1624 (C=N), 697 (C-F). ^{1}H NMR (DMSO-d_6): δ 4.418 (s, 2H, SCH_2PhF), 7.23-7.83 (m,7H, ArH), 8.23 (d, 1H, C_6H of pyrimidine), 8.377 (s, 1H ,NH), 6.70 (d, 1H, C_5H of pyrimidine). Mass: m/z= 455 (M^{+2}, 100%). Anal. Calcd. for $C_{18}H_{12}N_3BrF_4S$: C, 47.18; H, 2.63; N, 9.17. Found: C, 47.14; H, 2.59; N, 9.13%.

2-(4-Fluorobenzylthio)-N-(4-fluorophenyl) pyrimidine-4-amine (4c): Yield: 65%. M.P: 102-104ºC. IR (cm^{-1}): 3076 (NH),1601 (C=N), 697 (C-F). ^{1}H NMR (DMSO-d_6): δ 4.30 (s, 2H, SCH_2PhF), 6.51(d, 1H, C_5H of pyrimidine), 7.20-7.40(m, 9H, 8ArH & NH), 7.96 (d, 1H, C_6H of pyrimidine). Mass: m/z = 330 (M^{+1}, 100%). Anal. Calcd. for $C_{17}H_{13}N_3F_2S$: C, 61.99; H, 3.97; N, 12.75. Found: C, 61.95; H, 3.93; N, 12.71%.

2-(4-Fluorobenzylthio)-N-(4-chlorophenyl) pyrimidine-4-amine (4d): Yield: 80%. M.P: 99-100ºC. IR(cm^{-1}): 3076 (NH), 1601(C=N), 697 (C-F), 733 (C-Cl). ^{1}H NMR (DMSO-d_6): δ 4.32 (s, 2H, SCH_2PhF), 6.94-7.40 (m,8H, ArH), 7.26 (s, 1H, NH), 6.17 (d, 1H, C_5H of pyrimidine), 7.90 (d, 1H, C_6H of pyrimidine). Mass: m/z = 347 (M^{+2}, 100%). Anal. Calcd. for $C_{17}H_{13}N_3ClFS$: C, 59.10; H, 3.78; N, 12.15. Found: C, 59.06; H, 3.73; N, 12.11%.

2-(4-Fluorobenzylthio)-N-(4-methoxyphenyl) pyrimidin-4-amine (4e): Yield: 70%. M.P: 118-120ºC. IR(cm^{-1}): 3076 (NH), 1601 (C=N), 697 (C-F). ^{1}H NMR (DMSO-d_6): δ 3.61 (s, 3H, OCH_3), 4.34 (s, 2H, SCH_2PhF), 6.96-7.41(m, 8H, ArH), 6.19 (d, 1H, C_5H of pyrimidine), 7.28 (s, 1H, NH), 7.98 (d, 1H, C_6H of pyrimidine). Mass: m/z = 342 (100%). Anal. Calcd. for $C_{18}H_{16}N_3OFS$: C, 63.32; H, 4.72; N, 12.31. Found: C, 63.25; H, 4.67; N, 12.28%.

2-(4-Fluorobenzylthio)-N-(3-fluorophenyl) pyrimidine-4-amine (4f): Yield: 62%. M.P: 135-138ºC. IR(cm^{-1}): 3286 (NH), 1628 (C=N), 696 (C-F). ^{1}H NMR (DMSO-d_6): δ 4.34 (s, 2H, SCH_2PhF), 6.19 (d, 1H, C_5H of pyrimidine), 6.96-7.41 (m, 8H, ArH), 7.28 (s, 1H, NH), 7.98 (d, 1H, C_6H of pyrimidine). Mass: m/z = 328(M^{+1}, 100%). Anal. Calcd. for $C_{17}H_{13}N_3F_2S$: C, 61.99; H, 3.98; N, 12.76. Found: C, 61.95; H, 3.94; N, 12.70%.

2-(4-Fluorobenzylthio)-N-(phenyl)pyrimidine-4-amine (4g): Yield: 72%. M.P: 114-116ºC. ^{1}H NMR (DMSO-d_6): δ 4.31 (s, 2H, SCH_2PhF), 6.17 (d, 1H, C_5H of pyrimidine), 6.94-7.39 (m, 9H, ArH), 7.26 (s, 1H, NH), 7.96 (d, 1H, C_6H of pyrimidine). Mass: m/z = 312 (100%). Anal. Calcd. for $C_{17}H_{14}N_3FS$: C, 65.57; H, 4.53; N, 13.49. Found: C, 67.53; H, 4.49; N, 13.45%.

2-(4-Fluorobenzylthio)-N-(2-nitrophenyl) pyrimidine-4-amine (4h): Yield: 66%. M.P: 95-98ºC. ^{1}H NMR (DMSO-d_6): δ 4.36 (s, 2H, SCH_2PhF), 6.17 (d, 1H, C_5H of pyrimidine), 7.22-7.43 (m, 9H, 8ArH & NH), 7.97 (d, 1H, C_6H of pyrimidine). Mass: m/z = 356 (100%). Anal. Calcd. for $C_{17}H_{13}N_4O_2FS$: C, 57.29; H, 3.68; N, 15.72. Found: C, 57.25; H, 3.64; N, 15.68%.

2-(4-Fluorobenzylthio)-N-(3-nitrophenyl) pyrimidine-4-amine (4i): Yield: 62%. M.P: 118-120ºC. ^{1}H NMR (DMSO-d_6): δ 4.33 (s, 2H, SCH_2PhF), 6.19 (d, 1H, C_5H of pyrimidine), 7.23-7.45 (m, 9H, 8ArH & NH), 11.33 (s, 1H, NH), 7.99 (d, 1H, C_6H of pyrimidine). Mass: m/z = 356 (100%). Anal. Calcd. for $C_{17}H_{13}N_4O_2FS$: C, 57.29; H, 3.68; N, 15.72. Found: C, 57.25; H, 3.64; N, 15.68%.

2-(4-Fluorobenzylthio)-N-(4-nitrophenyl) pyrimidine-4-amine (4j): Yield: 60%. M.P: 91-92ºC. ^{1}H NMR (DMSO-d_6): δ 4.38 (s, 2H, SCH_2PhF), 6.93 (d, 1H, C_5H of pyrimidine), 7.26-7.85 (m, 9H, 8ArH & NH), 8.15 (d, 1H, C_6H of pyrimidine). Mass: m/z = 356 (100%). Anal. Calcd. for $C_{17}H_{13}N_4O_2FS$: C, 57.29; H, 3.68; N, 15.72. Found: C, 57.25; H, 3.64; N, 15.68%.

2-(4-Fluorobenzylthio)-N-(2-fluoro-4-iodo phenyl)pyrimidine-4-amine (4k): Yield: 67%. M.P: 102-104ºC. IR (cm^{-1}): 3073 (NH), 1578 (C=N), 695 (C-F). ^{1}H NMR (DMSO-d_6): δ 4.34 (s, 2H, SCH_2PhF), 6.19 (d, 1H, C_5H of pyrimidine), 6.96-7.41 (m, 8H, 7ArH & NH), 7.98 (d, 1H, C_6H of pyrimidine). Mass: m/z = 456 (M^{+1}, 100%). Anal. Calcd. for $C_{17}H_{12}N_3IF_2S$: C, 44.85; H, 2.65; N, 9.23. Found: C, 44.80; H, 2.61; N, 9.19%.

Antimicrobial Activity: The antimicrobial activities were performed by cup plate method [15]. The sample was dissolved in DMF at the concentration of 1000 µg/ml. Antibacterial activity was carried out against two gram +ve *S. aureus, B. subtilis* and two gram -ve *P. aeruginosa* and *E. coli* bacterial strains.

Antifungal activity was carried out against *A. niger* and *A. flavus* and *T. viridae* under aseptic conditions. Gentamycin and Fluconazole were used as standard drug for antibacterial and antifungal activities respectively.

The zone of inhibition was compared with standard drug after 24 hours of incubation at 25°C for antibacterial activity and 48 hours at 30°C for antifungal activity. The investigation of anti-microbial screening reveals that the compounds **4b**, **4g**, **4c and 4f** showed good activity against bacterial strain *B. subtilis.* Compounds **4a**, **4e**, **4b**, **4c, 4f, 4g and 4h** were active against bacterial strain *P. aeruginosa***.** Compounds **4a** and **4c** were active against fungul strain *A. niger*.

Compounds **4e**, **4b** and **4j** showed good activity against fungal strain *A. flavus.* All the synthesized compounds showed excellent antifungal activity against *T. viridae*. Remaining compounds exhibited moderate to poor activity against bacterial and fungal strains when compared to standard drug. Results are tabulated in **Table 2.**

Further the antifungal screening of all the synthesized compounds at different concentrations 1000, 750, 500, and 250 µg/ml to determine the IC_{50} (50% inhibition concentration) values against *T. viridae*.

Compounds **4e**, **4b, 4g, 4i, 4d, 4f and 4j** have exhibited better IC_{50} values. IC_{50} is defined as the drug concentration that produces 50% of the maximal effect. The values are tabulated in **Table 3** and percentages of inhibition are shown graphically in **Figure 1.**

TABLE 2: ANTIMICROBIAL ACTIVITY OF SYNTHESIZED COMPOUNDS (4a-k)

Compound No.	Dose µg/ml	Zone of inhibition in mm						
		E. coli	*B. substilis*	*S. aureus*	*P. aeruginosa*	*A.niger*	*A. flavus*	*T. viridae*
4a	1000	--	15	09	15	20	15	18
4b	1000	14	26	14	14	08	16	22
4c	1000	--	24	08	14	18	15	20
4d	1000	26	18	11	10	--	15	21
4e	1000	22	17	14	15	10	18	23
4f	1000	25	22	14	14	08	--	24
4g	1000	20	25	14	14	10	13	25
4h	1000	24	20	13	13	05	12	24
4i	1000	20	18	14	12	14	15	21
4j	1000	18	17	10	11	08	16	21
4k	1000	20	22	12	10	12	13	15
Gentamycin	1000	33	30	18	16	--	--	--
Fluconazole	1000	--	--	--	--	20	20	23

TABLE 3: IC_{50} VALUES OF SYNTHESIZED COMPOUNDS (4a-k)

Compound No.	Zone of Inhibition in mm against fungal strain *Trichoderma viridae*				
	Dose 1000 µg/ml	Dose 750 µg/ml	Dose 500 µg/ml	Dose 250 µg/ml	IC_{50} µg/ml
4a	17.7	20	20.3	17.3	149.8
4b	22	20	19.3	12.3	224.4
4c	20.3	20	16.7	17	147.9
4d	21	17.3	19	14.7	178.9
4e	23.7	19.3	18	12	247.1
4f	24.3	19.3	18.3	17.3	178.9
4g	25.7	20.3	19.7	16.3	197.5
4h	24	20.7	20	18	166.5
4i	21	21	20	14	189.2
4j	21	22.7	20.3	16	178.9
4k	20.3	20	16.3	17	147.5
Fluconazole	23.3	20.7	18.7	17	172

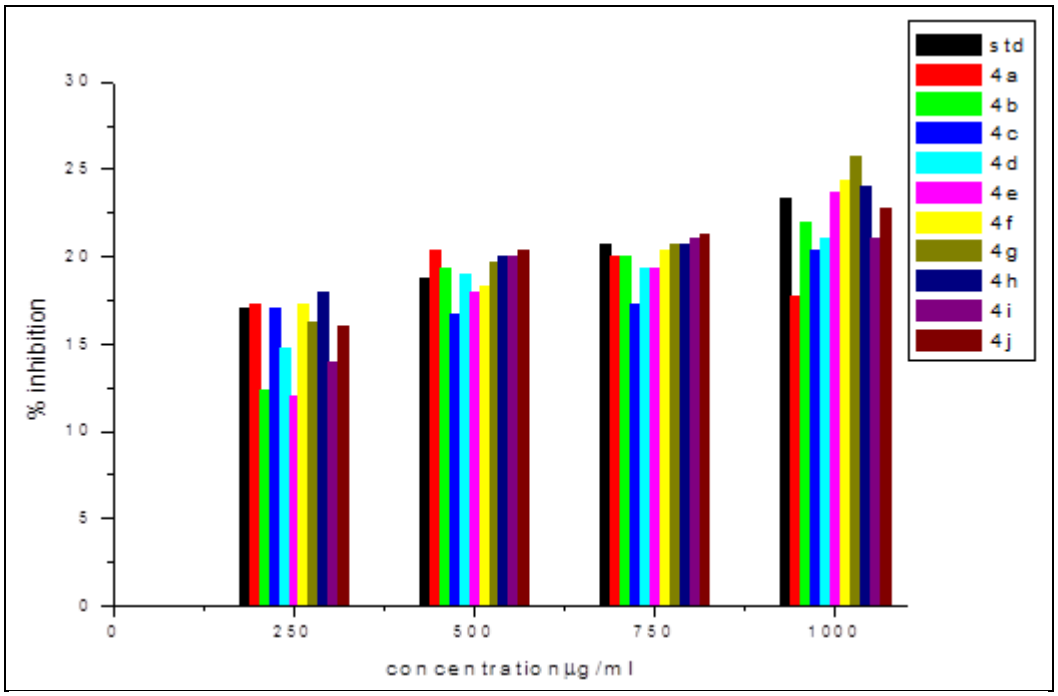


FIGURE 1: GRAPH SHOWING % INHIBITION AT DIFFERENT CONCENTRATIONS

CONCLUSION: The present work reports the synthesis and antimicrobial activities of 2-(4-Fluorobenzylthio)-N-(substituted phenyl) pyrimidine-4-amines. Among the synthesized compounds **4b**, **4g**, **4c and 4f** showed good activity against bacterial strain *B. subtilis.* Compounds **4a**, **4e**, **4b**, **4c, 4f, 4g and 4h** were active against bacterial strain *P. aeruginosa***.** Compounds **4a** and **4c** were active against fungul strain *A. niger*. Compounds **4e**, **4b** and **4j** showed good activity against fungal strain *A. flavus.* All the synthesized compounds showed excellent antifungal activity against *T. viridae*. Remaining compounds exhibited moderate to poor activity against bacterial and fungal strains when compared to standard drug. So, further we have carried out the antifungal screening of all the synthesized compounds at different concentrations against *T. viridae* to determine their IC_{50} values. Compounds **4e**, **4b, 4g, 4i, 4d, 4f and 4j** have shown better IC_{50} value. Further preclinical studies of the most potent compound are warranted.

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