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DESIGN, SYNTHESIS AND ANTIMICROBIAL EVALUATION OF NOVEL 1-(2-(4-FLUORO BENZYLTHIO)PYRIMIDIN-4-YL-AMINO)-4-(SUBSTITUTED PHENYL)AZETIDIN-2-ONES

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Keywords:

Pyrimidines, Azetidin-2-ones, Antibacterial activity, Antifungal activity

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ABSTRACT: A series of novel 1-(2-(4-fluorobenzylthio)pyrimidin-4-yl-amino)-4-(substituted phenyl)azetidin-2-one analogues **(3a-e)** were synthesized starting from 2-thiouracil. Reaction of 2-thiouracil with 4-fluorobenzylchloride gave 2-(4-fluorobenzylthio) pyrimidin-4(3H)-one which on chlorination with $POCl_3$ yielded 2-(4-fluorobenzylthio)-4-chloropyrimidine. Further reaction of compound 2-(4-fluorobenzylthio)-4-chloropyrimidine with hydrazine hydrate generated the key intermediate 1-(2-(4-fluorobenzylthio)pyrimidin-4-yl)hydrazine **(1)**. Reaction of compound **1** with appropriate substituted aromatic aldehydes furnished 2-(substituted benzylidene)-1-(2-(4-fluorobenzylthio) pyrimidin-4-yl)hydrazine **(2a-e),** which on further cyclisation with acetyl chloride in dry benzene furnished 1-(2-(4-fluorobenzylthio)pyrimidin-4-yl-amino)-4-(substituted phenyl) azetidin-2-one analogues **(3a-e).** Structural assignments of the synthesized compounds were based on their IR, ^{1}H NMR, Mass and analytical data. All the synthesized compounds **3a-e** were screened for their preliminary antimicrobial properties. Some of the compounds exhibited promising antimicrobial activities

INTRODUCTION: Among a wide variety of heterocycles that have been explored for developing medicinally important molecules, pyrimidine derivatives occupy an important place in the present day therapeutics. Pyrimidine scaffold being an integral part of DNA and RNA, occupy a unique and distinctive role in medicinal chemistry as nucleotides and nucleosides but they also impart numerous biological activities such as bactericides, fungicides, vermicides and insecticides. Introduction of fluorine atom selectively on heterocyclic moieties often exhibited enhanced bioactivity. Hence, much attention has been paid to the development of new methods for the synthesis of fluorine containing pyrimidines to improve drug physico-chemical properties [1-3].

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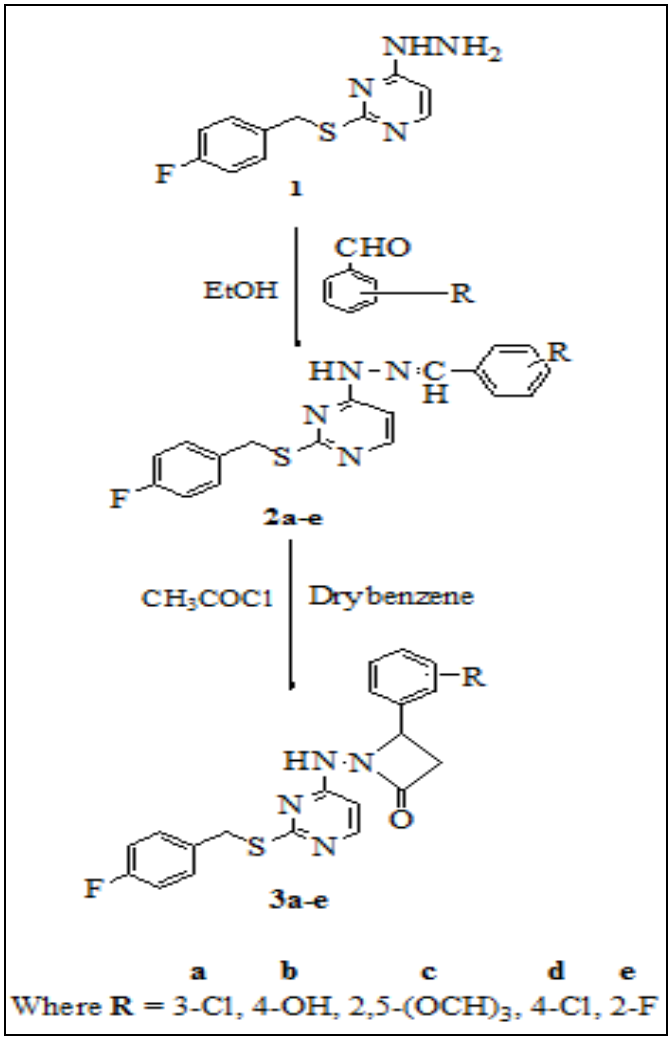
Pyrimidine analogs have been reported to possess a variety of pharmacological activities, notable among are the antibacterial [4], antihypertensive [5], antihistaminic [6], antifungal [7], anti-inflammatory [8], antiviral [9, 10], antimicrobial [11, 12] and anticancer drugs [13]. The 2-azetidinone nucleus is the central building block of β-lactam antibiotics, so functionalization of the 2-azetidinone framework is pivotal for the development of new β-lactam antibiotics. Almost seventy years after the first report on the antibacterial properties of penicillin, β-lactam antibiotics still remain the most widely prescribed drugs for the treatment of infectious diseases.

Some of the biological activities of β-lactam antibiotics includes antimicrobial, antitubercular, antiinflammatory, anticonvulsant, local anesthetics, hypoglycemic agents [14] and inhibition of cholesterol absorption [15, 16]. Thus, in the light of numerous biological activities exhibited by the pyrimidines and 2- azetidinones and in continuation of our drug discovery program [17] we report herein

the synthesis and antimicrobial evaluation of novel 1-(2-(4-fluorobenzylthio)pyrimidin-4-yl-amino)-4-(substituted phenyl)azetidin-2-one analogues **(3a-e) (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.



SCHEME: 1

RESULTS AND DISCUSSION:

We have reported earlier the synthesis of 2-(4-fluorobenzylthio)-4-chloropyrimidine [17] starting from 2-thiouracil. Reaction of 2-(4-fluorobenzylthio)-4-chloropyrimidine with hydrazine hydrate in refluxing methanol generated the key intermediate 1-(2-(4-fluorobenzylthio) pyrimidin-4-yl)hydrazine **(1) (Scheme-1)** in 50% yield, m.p 130-133˚C. Formation of compound **1** was confirmed by the presence of absorption bands at 3336, 3283, 1623 and 668 cm^{-1} due to NH_2, NH, C=N and C-F stretching in its IR spectrum.

Further Formation of this compound **1** was confirmed by the presence of singlet at δ 3.94 due to two protons of SCH_2PhF, aromatic protons signal as a multiplet at δ 7.17 -7.37, singlet at δ 6.89 due to NH, singlet at δ 2.58 due to NH_2, characteristic absorption of C_5H and C_6H of pyrimidine ring as a doublet at δ 7.38 and δ 8.42 respectively in its ^1H NMR spectrum. Final confirmation of compound **1** is by the appearance of molecular ion peak at m/z = 250 (M^{-1}, 100%) in its mass spectrum. Reaction of compound **1** with various substituted aromatic aldehydes in refluxing methanol in presence of a catalytic amount of conc. HCl afforded corresponding Schiff bases (**2a-e)** in 50-90% yield.

Compound **2a** was obtained in 87% yield, having m.p 166-169˚C. Formation of compound **2a** was confirmed by the presence of absorption bands at 3178, 1581, 701 and 643 cm^{-1} due to NH, C=N, C-Cl and C-F stretching in its IR spectrum. Further confirmation of compound **2a** is by the presence of singlet at δ 4.38 due to two protons of SCH_2PhF, singlet at δ 8.68 due to N=CH and at δ 7.77 due to NH, aromatic protons signal as a multiplet at δ 7.01 -7.71, characteristic absorption of C_5H and C_6H of pyrimidine ring as a doublet at δ 7.00 and δ 8.29 respectively in its ^1H NMR spectrum.

Final confirmation of compound **2a** is by the appearance of molecular ion peak at m/z = 372 (M^{+2}, 100%) in its mass spectrum. Cyclization of compounds **2a-e** with acetyl chloride in refluxing dry benzene gave **3a-e** in 50-80% yield. Compound 3**a** was obtained in 60% yield, having m.p 182-185˚C. Formation of compound **3a** was confirmed by the presence of absorption bands at 3381, 1764,

1635, 763 and 669 cm^{-1} due to NH, C=O, C=N, C-Cl and C-F stretching in its IR spectrum. Further confirmation of compound **3a** is by the presence of triplet at δ 5.25 and doublet at δ 3.40 due to one proton of CH and two protons of CH_2 of azetidinone, singlet at δ 4.36 due to two protons of SCH_2PhF, singlet at δ 8.52 due to NH, aromatic protons signal as a multiplet at δ 6.96-7.98, characteristic absorption of C_5H and C_6H of pyrimidine ring as a doublet at δ 7.62 and 8.26 respectively in its ^1H NMR spectrum. Final confirmation of compound **3a** is by the appearance of molecular ion peak at m/z = 414 (M^{+2}, 100%) in its mass spectrum. Physical data of all the synthesized compounds are tabulated in **Table 1.**

TABLE 1: PHYSICAL DATA OF SYNTHESIZED COMPOUNDS (2a-e) & (3a-e)

Comp. No.	R	Molecular formula	M. P (°C)	Yield (%)	Elemental Analysis Calc, (Found) (%)		
					C	H	N
1	--	$C_{11}H_{11}N_4FS$	130-133	60	52.78 (52.72)	4.43 (4.38)	22.38 (22.32)
2a	3-Cl	$C_{18}H_{14}N_4ClFS$	166-169	87	57.93 (57.89)	3.72 (3.67)	14.98 (14.94)
2b	4-OH	$C_{18}H_{15}N_4OFS$	174-178	52	61.00 (60.95)	4.27 (4.22)	15.81 (15.76)
2c	2,5-$(OCH)_3$	$C_{20}H_{19}N_4O_2FS$	80-82	65	60.21 (60.17)	4.81 (4.77)	14.06 (14.00)
2d	4-Cl	$C_{18}H_{14}N_4ClFS$	208-210	85	57.98 (57.93)	3.78 (3.72)	15.03 (14.98)
2e	2-F	$C_{18}H_{14}N_4FS$	188-190	52	63.89 (63.82)	4.47 (4.42)	16.56 (16.50)
3a	3-Cl	$C_{20}H_{16}N_4OClFS$	186-189	80	57.90 (57.85)	3.89 (3.84)	13.50 (13.45)
3b	4-OH	$C_{20}H_{17}N_4O_2FS$	182-185	58	60.59 (60.54)	4.32 (4.28)	14.13 (14.08)
3c	2,5-$(OCH)_3$	$C_{22}H_{21}N_4O_3FS$	132-135	60	59.99 (59.95)	4.81 (4.77)	12.72 (12.68)
3d	4-Cl	$C_{20}H_{16}N_4OClFS$	240-242	75	57.90 (57.85)	3.89 (3.84)	13.50 (13.45)
3e	2-F	$C_{20}H_{16}N_4OF_2S$	162-164	54	60.29 (60.25)	4.05 (4.01)	14.06 (14.01)

EXPERIMENTAL:

Synthesis of 1-(2-(4-fluorobenzylthio)pyrimidin-4-yl)hydrazine (1):

To a solution of 2-(4-fluorobenzylthio)-4-chloropyrimidine (0.002 mole) in methanol (20 mL) hydrazine hydrate (0.005 mole) was added. The reaction mixture was refluxed for 4 h on a hot water bath. Concentrated the reaction solution under reduced pressure and the separated solid was filtered, dried and recrystallised from MeOH. Yield 50%; mp 130-133 °C; Ir (KBr, cm^{-1}): NH_2 3336, NH 3243, CN 1623, CF 668; ^1H nmr (500 MHz, DMSO-d_6, δ): 6.89 (s, 1H, NH), 2.58 (s, 1H, NH_2), 3.94 (s, 2H, SCH_2PhF), 7.17-7.37 (m, 4H, ArH), 7.38 (d, 1H, pyrimidine C-5), 8.42 (d, 1H, pyrimidine C-6); Mass (m/z): 250 (M^{-1}, 100%). *Anal.* Calcd. for $C_{11}H_{11}N_4FS$: C, 52.78; H, 4.43; N, 22.38. Found: C, 52.72; H, 3.98; N, 22.32%.

Synthesis of 2-(substituted benzylidene)-1-(2-(4-fluorobenzylthio)pyrimidin-4-yl)hydrazine(2ae):

To a solution of 1-(2-(4-fluorobenzylthio) pyrimidin-4-yl)hydrazine **(1)** (0.001 mole) in methanol (20 mL) and catalytic amount of conc. HCl (2-3 drops)**,** appropriate aromatic aldehyde (0.001 mole) was added. The reaction mixture was refluxed for 6 h on a hot water bath. Concentrated the reaction solution under reduced pressure, solid separated was filtered and recrystallised from EtOH yielded the desired compounds **(2a-e)**.

Synthesis of 1-(2-(4-fluorobenzylthio) pyrimidin-4-yl-amino)-4-(substituted phenyl) azetidin-2-ones (3a-e)

The appropriate schiff base 2**a-e** (0.01 mole) and acetyl chloride (0.01 mole) in dry benzene (10 mL) was stirred well to dissolve all the solids and the

reaction mixture was refluxed for 6 h. After the completion of reaction, concentrated the reaction product under reduced pressure was cooled and separated solid was filtered, dried and recrystallized from ethanol.

SPECTRAL DATA OF COMPOUNDS (2a-e)

2 - (3-chlorobenzylidene) – 1 - (2 - (4 - fluorobenzylthio)pyrimidin-4-yl)hydrazine (2a):
Ir (KBr, cm^{-1}): NH 3178, CN 1581, CCl 701, CF 643; ^{1}H nmr (DMSO-d_6, δ): 8.68 (s, 1H, N=CH), 7.77 (s, 1H, NH), 4.38 (s, 2H, SCH_2PhF), 7.01-7.71 (m, 8H, ArH), 7.0 (d, 1H, pyrimidine C-5), 8.29 (d, 1H, pyrimidine C-6); Mass (m/z): 372 (M^{+2}, 100%).

2 - (4 - hydroxybenzylidene) - 1 - (2 - (4 - fluorobenzylthio)pyrimidin- 4-yl)hydrazine (2b):
Ir (KBr, cm^{-1}): OH 3468, NH 3183, CN 1605, CF 657; ^{1}H nmr (DMSO-d_6, δ): 11.31 (s, 1H, OH), 8.01 (s, 1H, N=CH), 4.34 (s, 2H, SCH_2PhF), 7.10-7.54 (m, 9H, 8ArH & NH), 6.81 (d, 1H, pyrimidine C-5), 8.18 (d, 1H, pyrimidine C-6); Mass (m/z): 354 (M^{+1}, 100%).

2 - (2, 5 - dimethoxybenzylidene) – 1 - (2 - (4 - fluorobenzylthio)pyrimidin-4-yl)hydrazine (2c):
Ir (KBr, cm^{-1}): NH 3167, CN 1561, CF 712; ^{1}H NMR (DMSO-d_6, δ): 8.4 (s, 1H, N=CH), 8.21 (s, 1H, NH), 4.37 (s, 2H, SCH_2PhF), 6.93-7.50 (m, 7H, ArH), 6.88 (d, 1H, pyrimidine C-5), 8.25 (d, 1H, pyrimidine C-6), 3.85 (s, 6H, $(OCH_3)_2$); Mass (m/z): 398 (M^{+1}, 100%).

2 - (4 - chlorobenzylidene) - 1 - (2 - (4-fluorobenzylthio)pyrimidin-4-yl)hydrazine (2d):
Ir (KBr, cm^{-1}): NH 3331, CN 1594, CCl 744, CF 668; ^{1}H nmr (DMSO-d_6, δ): 8.26 (s, 1H, N=CH), 4.43 (s, 2H, SCH_2PhF), 7.11-7.55 (m, 8H, ArH), 7.05 (s, 1H, NH), 7.10 (d,1H, pyrimidine C-5), 7.80 (d, 1H, pyrimidine C-6); Mass (m/z): 372 (M^{+2}, 100%).

2 - (2 - fluorobenzylidene) – 1 - (2 - (4 - fluorobenzylthio)pyrimidin-4-yl)hydrazine (2e):
Ir (KBr, cm^{-1}): NH 3189, CN 1572, CF 684; ^{1}H nmr (DMSO-d_6, δ): 8.65 (s, 1H, N=CH), 8.09 (s, 1H, NH), 4.37 (s, 2H, SCH_2PhF), 7.10-7.72 (m, 9H, ArH), 7.13 (d, 1H, pyrimidine C-5), 8.28 (d, 1H, pyrimidine C-6); Mass (m/z): 356 (M^{-1}, 100%);

Spectral Data of Compounds (3a-e):

1-(2-(4-fluorobenzylthio)pyrimidin-4-ylamino)-4-(3-chlorophenyl)azetidin-2-one (3a):
Ir (KBr, cm^{-1}): NH 3381, C=O 1764, CN 1635, C-Cl 763, CF 669; ^{1}H nmr (DMSO-d_6, δ): 8.52 (s, 1H, NH), 4.36 (s, 2H, SCH_2PhF), 6.96-7.98 (m, 8H, ArH), 7.62 (d, 1H, pyrimidine C-5), 8.26 (d, 1H, pyrimidine C-6), 5.25 (t, 1H, azetidinone CH), 3.40 (d, 1H, azetidinone CH_2); Mass (m/z): 414 (M^{+2}, 100%).

1- (2-(4-fluorobenzylthio)pyrimidin-4-ylamino)-4-(4-hydroxyphenyl)azetidin-2-one (3b):
Ir (KBr, cm^{-1}): OH 3396, NH 3188, C=O 1745, CN 1635, CF 669; ^{1}H nmr (DMSO-d_6, δ): 8.56 (s, 1H, OH), 8.07 (s, 1H, NH), 4.36 (s, 2H, SCH_2PhF), 6.96-7.79 (m, 8H, ArH), 7.21 (d, 1H, pyrimidine C-5), 8.26 (d, 1H, pyrimidine C-6), 5.55 (t, 1H, azetidinone CH), 3.53 (d, 1H, azetidinone CH_2); Mass (m/z): 396 (M^{+1}, 100%).

1-(2-(4-fluorobenzylthio)pyrimidin -4-ylamino)-4-(2, 5-dimethoxyphenyl)azetidin-2-one (3c):
Ir (KBr, cm^{-1}): NH 3188, C=O 1749, CN 1575, CF 665; ^{1}H nmr (DMSO-d_6, δ): 8.45 (s, 1H, NH), 4.35 (s, 2H, SCH_2PhF), 6.84-7.47 (m, 9H, 8ArH & pyrimidine C-5H), 8.22 (d, 1H, pyrimidine C-6), 5.40 (t, 1H, azetidinone CH), 2.50 (d, 1H, azetidinone CH_2), 3.83 (s, 6H, $(OCH_3)_2$); Mass (m/z): 440 (M^{+1}, 100%);

1-(2-(4-fluorobenzylthio)pyrimidin -4-ylamino)-4-(4-chlorophenyl)azetidin-2-one (3d):
Ir (KBr, cm^{-1}): NH 3342, C=O 1749, CN 1602, CF 671; ^{1}H nmr (DMSO-d_6, δ): 11.52 (s, 1H, NH), 4.35 (s, 2H, SCH_2PhF), 7.05-7.72 (m, 8H, ArH), 7.03 (d, 1H, pyrimidine C-5), 8.20 (d, 1H, pyrimidine C-6), 5.56 (t, 1H, azetidinone CH), 3.53 (d, 1H, azetidinone CH_2); Mass (m/z): 414 (M^{+2}, 100%).

1- (2-(4-fluorobenzylthio)pyrimidin-4-ylamino)-4-(2-fluorophenyl) azetidin-2-one (3e):
Ir (KBr, cm^{-1}): NH 3188, C=O 1693, CN 1612, CF 648; ^{1}H nmr (DMSO-d_6, δ): 12.34 (s, 1H, NH), 3.62 (s, 2H, SCH_2PhF), 6.87-8.16 (m, 8H, ArH), 6.86 (d, 1H, pyrimidine C-5), 8.21 (d, 1H, pyrimidine C-6), 4.48 (t, 1H, azetidinone CH), 2.55 (d, 1H, azetidinone CH_2); Mass (m/z): 414 (M^{+2}, 100%).

Antimicrobial activity:

The antimicrobial activities were performed by cup plate method [18]. The sample was dissolved in DMF at the concentration of 1000 µg/ml. Antibacterial activity was carried out against two gram +ve bacteria *S. aureus, B. subtilis* and two gram –ve bacteria *P. aeruginosa* and *E. coli.* Antifungal activity was carried out against organisms *A. niger* and *A. flavus* 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 antimicrobial screening of the synthesized compounds **(3a-e)** reveals that **3b**, **3d**, and **3e** showed good activity against bacterial strain *E. coli.* Compounds **3b, 3c** and **3d** were active against bacterial strains *P. aeruginosa* and *S. aureus***.** Compounds **3a, 3b** and **3e** were active against fungal strain *A. niger*. Compound **3c** showed good activity against fungal strain *A. flavus.* Remaining compounds exhibited moderate to poor activity against bacterial and fungal strains when compared to standard drugs. Results are tabulated in **Table 2**.

TABLE 2: ANTIMICROBIAL ACTIVITY OF SYNTHESIZED COMPOUNDS (3a-e)

Comp No.	Dose µg/ml	Zone of inhibition in mm					
		E.coli	*B.substilis*	*S.aureus*	*P.aeruginosa*	*A.niger*	*A.flavus*
3a	1000	10	10	12	10	16	11
3b	1000	13	08	13	15	16	10
3c	1000	08	10	10	16	10	16
3d	1000	12	10	10	15	08	10
3e	1000	12	10	08	08	16	12
Gentamycin	1000	16	17	16	18	--	--
Fluconazole	1000	--	--	--	--	16	16

CONCLUSION: The present work reports the synthesis of novel 1 - (2-(4-fluorobenzylthio) pyrimidin-4-yl-amino) - 4 - (substituted phenyl) azetidin – 2 - one analogues **(3a-e)** and evaluated them for antimicrobial activities. Most of the compounds exhibited excellent activity against all bacterial and fungal strains which is equal to that of standard drug. Hence, fluorine substitution will increase the biological activity of the synthesized compounds.

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