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Syntheses of 2-(6'-Fluorobenzothiazol-2'-ylamino) -4, 6-(disubstituted thiouriedo)-1,3-pyrimidine Derivatives as Antimicrobial Agents

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Abstract: A new series of 1,3-pyrimidine derivatives (**3a-f**) have been synthesized by reacting 2,4,6-Trichloropyrimidine with nucleophilic reagents 2-amino-6-fluorobenzothiazole (**1**) in the presence of acetone. The (4,6- dichloro-pyrimidin-2-yl)-amine (**2**) so produced was then reacted to two moles of phenylthiourea derivatives to yield title compounds (**3a-f**). The structural assessment of the compounds (**3a-f**) was made on the basis of spectral data. The synthesized compounds were screened for their *in vitro* growth inhibiting activity against different strains of bacteria *viz*., *B. subtilis, E. coli, P. aeruginosa* and *S. aureus* using agar diffusion technique. Compounds **3c** and **3f** exhibited highest antibacterial activity.

Keywords: Fluorobenzothiazole, Pyrimidine derivatives, Phenyl thiourea derivatives, Antimicrobial activity.

Introduction

Pyrimidine is the most important member of all the diazines as this ring system occurs widely in living organisms. Purines, uric acid, alloxan, barbituric acid and a number of antimalarial and antibacterial drugs also contain the pyrimidine ring[1,2]. Thiazole ring system is quite common in natural products, since it can be produced by cyclization of cysteine residues in peptides[3,4]. The most important of these is Vitamin B_1 (thiamine), which contains both a pyrimidine and a thiazole ring system. The bleomycin antibiotics, which have anti-tumour properties, are complex aminoglycosidic structures containing thiazole units. Several semi-synthetic beta lactams contain 2-aminothiazole units in the side chain[5,6].

Since benzothiazoles, pyrimidines and thioureas all possess diverse biological activities[7-11]; the aim of this study was to synthesize some new derivatives incorporating these nuclei and evaluate the prepared compounds for antibacterial activity.

Experimental

To 2,4,6 trichloropyrimidine (18.3 g,0.1 mole) dissolved in acetone (100 mL) cooled at 0 °C, 2-amino-6 fluorobenzothiazole (16.8 g,0.1 mole) dissolved in acetone (100 mL) was added with stirring at 0–5 °C followed by drop wise addition of sodium hydroxide (4.0 g,0.1 mole) in water (50 mL). Contents were stirred for 3 h and poured into ice water, acidified with dilute hydrochloric acid, filtered, washed, dried and recrystallized from ethanol, melting range was 265-270 °C, yield was 53.94%, IR (KBr, cm^{-1}): (3388>NH) and MS (*m/z*): 315 (M^+).

*General procedure for synthesis of 2-(6'-fluorobenzothiazol-2'-ylamino)-4,6-(disubstituted thiouriedo)-1,3-pyrimidines (**3a-f**)*

Compound **2** (31.5 g, 0.1 mole) (Scheme 1) dissolved in acetone (100 mL) was added to substituted thiourea (0.2 mole) in acetone (100 mL), slowly with constant stirring followed by addition of sodium hydroxide (4 g, 0.1 mole) in water (50 mL) and contents were refluxed for 2 h at 85-95 °C. The mixture was poured into ice water, acidified with dilute HCl, filtered, washed and recrystallized from ethanol and melting range was determined. 195-200 °C, yield 39.83%, IR (KBr, cm^{-1}): (3446>NH); 1120 (thioureido CS); and MS (*m/z*): 547 (M^{+1}).

*Spectral data of compound **3a***

IR: (KBr cm^{-1}): 3230 (secondary amine N-H str), 1569 (secondary amine N-H ben), 3085 (Aromatic C-H str), 1622 (Aromatic C=C str) 1282 (Aromatic amine C-N str), 1120 (Aromatic C-F str); MS (FAB) *m/z:* 391(M-3). Yield 73.63%, Melting range: 265-270 °C. Compounds **3b-f** were prepared by the aforesaid procedure[12]. The quantity of phenylthiourea derivatives was changed as per Table 1.

Table 1. Quantities of different thiourea

Compd..	Name of substituent at R	Quantity
3b	Phenylthiourea	30.4 g, 0.2 mole
3c	4-fluorophenyl thiourea	34.0 g, 0.2 mole
3d	4-chlorophenyl thiourea	37.2 g, 0.2 mole
3e	4-bromophenyl thiourea	46.2 g, 0.2 mole
3f	4-nitrophenyl thiourea	39.4g, 0.2 mole

*Compound **3b***

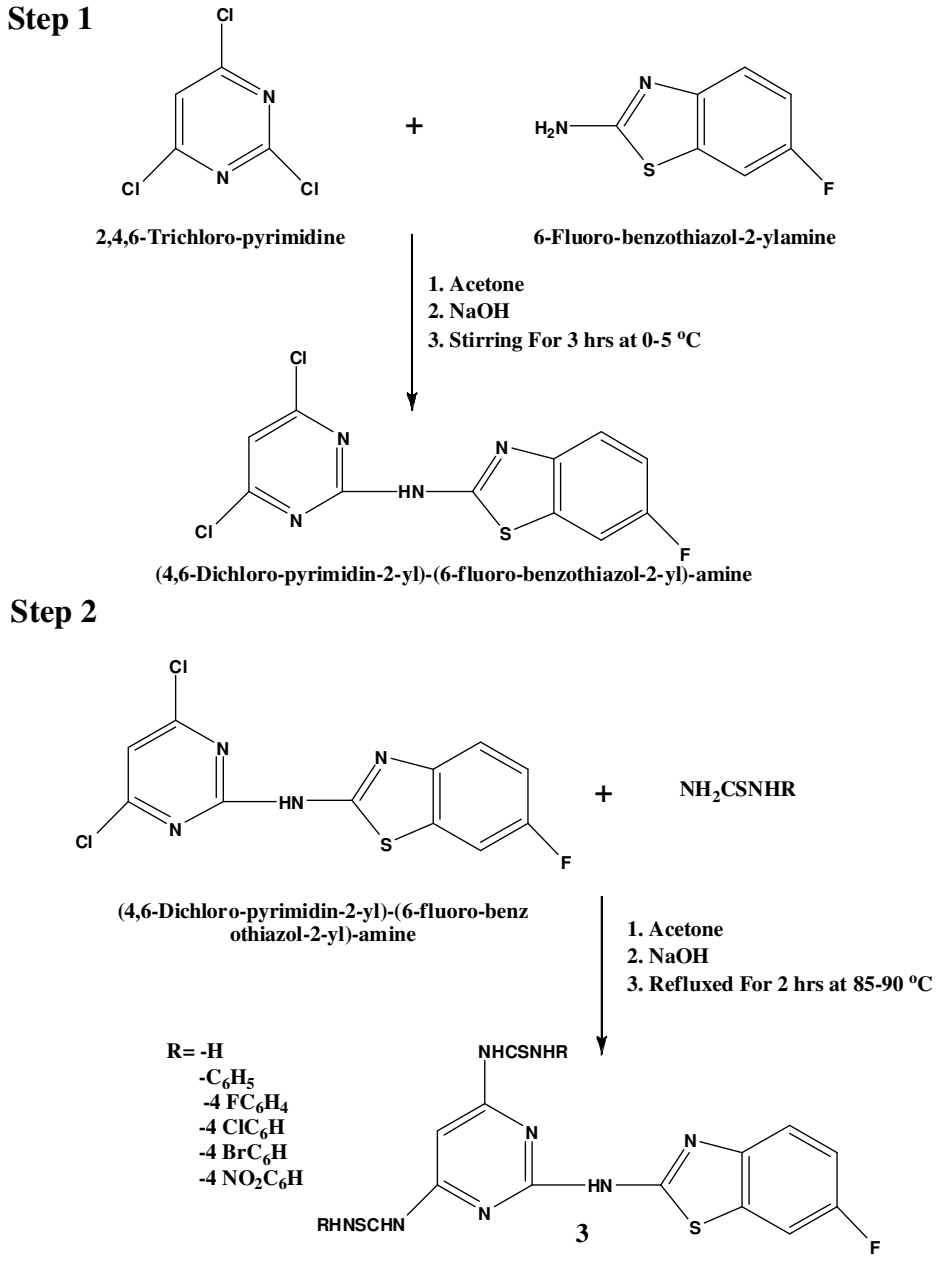
IR: (KBr cm^{-1}): 3446 (secondary amine N-H str), 1569 (secondary amine N-H ben), 3072 (Aromatic C-H str), 1627 (Aromatic C=C str), 1253 (Aromatic amine C-N str), 1012 (Aromatic C-F str) MS (FAB) *m/z*: 547(M+1).

*Compound **3c***

IR: (KBr cm^{-1}): 3446 (secondary amine N-H str), 1568 (secondary amine N-H ben), 3087 (Aromatic C-H str), 1620 (Aromatic C=C str), 1255 (Aromatic amine C-N str), 1014 (Aromatic C-F str); MS (FAB) *m/z*: 582 (M+).

*Compound **3d***

IR: (KBr cm^{-1}): 3434 (secondary amine N-H str), 1569 (secondary amine N-H ben), 3085 (Aromatic C-H str), 1623 (Aromatic C=C str), 1255 and 1120 (Aromatic amine C-N str), 1014 (Aromatic C-F str), 804 (Aromatic C-Cl str); MS (FAB) *m/z*: 615 (M+11).



Scheme 1. Synthetic procedure for preparation of 2-(6'-fluorobenzothiazol-2'-ylamino)-4,6-(disubstituted thiouriedo)-1,3-pyrimidine derivatives

*Compound **3e***

IR: (KBr cm^{-1}): 3446 (secondary amine N-H str), 1568 (secondary amine N-H ben), 3087 (Aromatic C-H str), 1620 (Aromatic C=C str), 1255 (Aromatic amine C-N str), 1014 (Aromatic C-F str); MS (FAB) *m/z*: 703 (M-1).

*Compound **3f***

IR: (KBr cm^{-1}): 3253 (secondary amine N-H str), 1569 (secondary amine N-H ben), 3070 (Aromatic C-H str), 1623 (Aromatic C=C str), 1255 and 1120 (Aromatic amine C-N str), 1014 (Aromatic C-F str), 1521 and 1353 (symmetrical and asymmetrical aromatic NO str); MS (FAB) *m/z*: 637 (M+1).

Purity of all the compounds was checked on silica gel G plates using iodine vapour and UV lamp (at short and long wavelength) as the detecting agent. Thin layer chromatography was used for monitoring the progress of reaction and product formation. Melting points of the synthesized compounds were taken by open capillary method and are uncorrected. The infra-red spectra of the synthesized compounds were recorded on a SHIMADZU FTIR 8400 spectrophotometer using potassium bromide pellets. The FAB mass spectra were recorded on a JEOL SX 102/DA-6000 mass spectrometer/ data system using Argon/Xenon (6 kV, 10 m A) as the FAB gas. The accelerating voltage was 10 kV and the spectra were recorded at room temperature. The physical and analytical data of synthesized compounds is summarized in Table 2.

Table 2. Physical and analytical data of the synthesized compounds (**3a -f**)

Compd.	R	Mol. formula	Mol Wt	Calculated				Melting Range, °C	Yield, %
				C	H	N	S		
3a	H	$C_{13}H_{11}FN_8S_3$	394	39.6	2.8	28.4	24.4	260-265	74
3b	C_6H_5	$C_{25}H_{19}FN_8S_3$	546	54.9	3.5	20.5	17.6	195-200	40
3c	$4FC_6H_4$	$C_{25}H_{17}F_3N_8S_3$	582	51.5	2.9	19.2	16.5	260-265	38
3d	$4ClC_6H_4$	$C_{25}H_{17}Cl_2FN_8S_3$	626	48.8	2.8	18.2	15.6	245-250	16
3e	$4BrC_6H_4$	$C_{25}H_{17}Br_2FN_8S_3$	704	42.6	2.4	15.9	13.7	240-245	17
3f	$4NO_2C_6H_4$	$C_{25}H_{17}FN_{10}O_4S_3$	636	47.2	2.7	22.0	15.1	235-240	60

Antibacterial activity

Compounds **3a-f** were screened for antibacterial activity against strains of *Bacillus subtilis* (MTCC 441), *Pseudomonas aeruginosa* (MTCC 424), *Escherichia coli* (MTCC 1573) and *Staphylococcus aureus* (MTCC 1430) using cylinder-plate method[13]. Culture media were prepared using aseptic and sterilization techniques[14]. Incubation period was 24 h at 37 °C in order to activate the bacterial strain. All the solutions of test compounds were prepared by dissolving 1 mg of testing sample in 1 mL of DMF (*N, N*-Dimethylformamide). This gives the conc. of sample 1000 µg/mL or 1000 ppm. Different dilutions such as 200 µg/mL and 100 µg/mL were prepared from the sample solution. A solution of DMF (10%) was used as control. Pure cultures of *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Staphylococcus aureus* were procured from Institute of Microbial Technology (IMTECH), Chandigarh, India and raised in conical flask (100 mL) containing potato dextrose agar (PDA). The evaluation of the antibacterial activity was done by measuring the zone of inhibition in different petri plates and taking average for each strain.

Results and Discussion

The compounds (**3a-f**) were synthesized by reacting 2,4,6-trichloropyrimidine with 2-amino-6-fluorobenzothiazole yielding (4,6-dichloropyrimidin-2-yl-6-fluorobenzothiazol-2-yl)-amine followed by reaction with two moles of phenylthiourea. The physical and analytical data of the compounds are presented in Table 2.

The yields of compounds fall in the range of 16% to 74%. The spectral data (IR and MS) are in good agreement with their structures. Scanning results of antimicrobial activity (Table 3) reveal that the known standard antibiotic produced a zone of inhibition of the order

of 20-23 mm. Compounds **3c** and **3f** displayed good activity against *E. coli*, *P. aeruginosa*, *B. subtilis* and *S. aureus*. This could be due to the presence of fluoro and nitro groups. Other compounds (**3a, 3b, 3d** and **3f**) exhibited less pronounced activity against the tested strains.

Table 3. Antibacterial screening data of compounds **3a-f**

Compound	Average diameter of zone of inhibition, in mm			
	E. coli	*P. aeruginosa*	*B. subtilis*	*S. aureus*
3a	15	15	14	16
3b	18	16	13	16
3c	19	20	18	19
3d	14	15	12	16
3e	16	16	14	15
3f	19	19	15	15
Standard (Ciprofloxacin)	23	21	20	21
Control (DMF)	00	00	00	00

Conclusion

A series of 1,3 pyrimidine derivatives have been synthesized and characterized on the basis of IR and MS spectral data. The compounds exhibited antibacterial activity with two compounds showing good activity against selected strains.

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