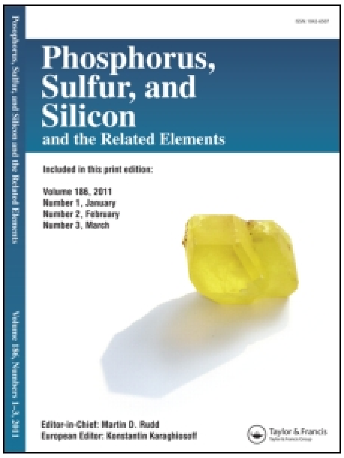

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Synthesis of Some New 2-(4-Nitrobenzothiazol-2'-ylamino)-4-(2-chloro-4-trifluoromethylanilino)-6-(substituted Thioureido)-1,3,5-triazines as Antifungal Agents

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Synthesis of Some New 2-(4-Nitrobenzothiazol-2′-ylamino)-4-(2-chloro-4-trifluoromethylanilino)-6-(substituted Thioureido)-1,3,5-triazines as Antifungal Agents

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Some new 2-(4-nitrobenzothiazol-2′-ylamino)-4-(2-chloro-4-trifluoro-methylanilino)-6-(substituted thioureido)-1,3,5-triazine **4** *have been prepared by reacting 2,4,6-trichloro-1,3,5-triazine with nucleophilic reagents, 2-amino-4-nitrobenzothiazol* ***1****, 2-chloro-4-trifluoromethylaniline* **2** *and different substituted thioureas* **3** *to give the title compound. These compounds are evaluated for their antimicrobial activity. The structure of all of these compounds has been confirmed by IR, ^{1}H NMR, ^{19}F NMR, mass spectral data and elemental analysis.*

Keywords 2-(4-Nitrobenzothiazol-2′-ylamino)-4,6-dichloro-1,3,5-triazine; 2-(4-Nitrobenzothiazol-2′-ylamino)-4-(2-chloro-4-trifluoromethyl-anilino) -6-chloro-1,3,5-triazine, 2- (4-Nitrobenzothiazol-2′-ylamino) -4-(2-chloro-4-trifluoromethylanilino)-6-(substituted thioureido)-1,3,5-triazine; antimicrobial activity

INTRODUCTION

Benzothiazoles, s-triazines, and thioureas exhibit various biological activities.[1] In continuation of our work on triazines,[2,3] we have synthesized some new fluorinated derivatives of 2,4,6-trisubstituted 1,3,5-triazine with enhanced fungicidal activity. Fungicidal activity was evaluated against *Alternaria alternata*, Aspergillus niger, and *Macrophomina*. Three chlorine atoms of 2,4,6-trichloro-1,3,5-triazine

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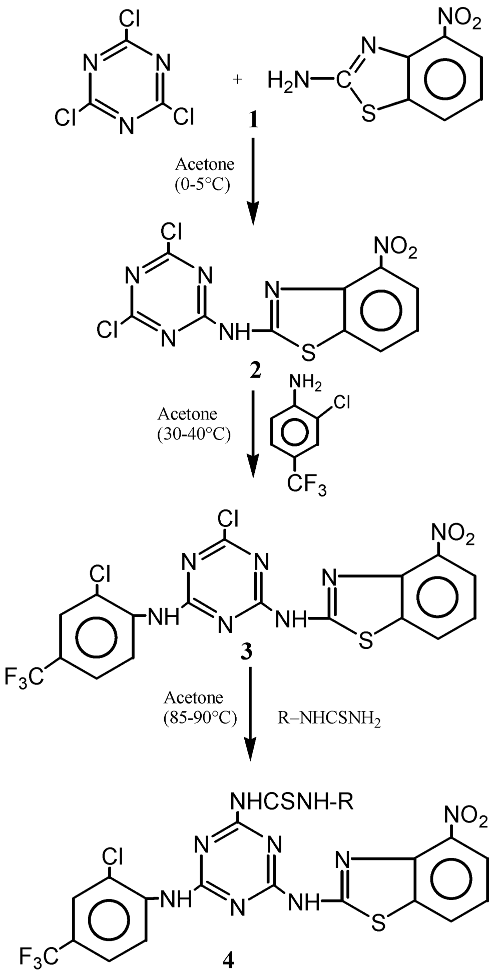
(cyanuric chloride) have been replaced subsequently by 2-amino-4-nitrobenzothiazole (which in turn is prepared by condensing nitroaniline with ammonium thiocyanate,[3] 2-chloro-4-trifluoromethyl aniline and substituted thioureas in alkaline medium selectivity to give the title compound **4** (Scheme-1).



4a, R = 4-FC_6H_4; e, R = 2-$CH_3C_6H_4$
b, R = 2-F C_6H_4 ; f, R = C_6H_{0035}
c, R = 2-$CF_3C_6H_4$; g, R = NH_2
d, R = 2-$NO_2C_6H_4$; h, R = CH_2=CH-CH_2

SCHEME 1

RESULTS AND DISCUSSION

2-(4-Nitrobenzothiazol-2′-ylamino)-4,6-dichloro-1,35-triazine **2** has been prepared by treating cyanuric chloride in acetone with 2-amino-4-nitrobenzothiazol **1** at 0–5°C and stirring for 3 h. The second chlorine atom of **2** has been replaced by 2-chloro-4-trifluoromethylaniline at 30–40°C in acetone by constant stirring for 3 h to give 2-(4-nitrobenzothiazol-2′-ylamino)-4-(2-chloro-4-trifluoromethylanilino)-6-chloro-1,3,5-trizine **3**. The third chlorine atom of **3** has been replaced by different substituted thioureas at 80–90°C in acetone to give 2-(4-nitrobenzothiazol-2′-ylamino)-4-(2-chloro-4-trifluoromethylanilino)-6-(substituted thioureido)-1,3,5-triazine **4**.

Compound **2** showed the presence of >NH group in both of its IR spectrum (3160 cm^{-1}) and ^{1}H NMR spectrum which showed a signal at δ 9.2 ppm.

The IR spectrum of compound **3** showed peak at 3150 cm^{-1} (broad band for >NH) and its ^{1}H NMR shows peak at δ 9.7 (a singlet for two >NH protons). Further, in ^{19}F NMR it shows peak at δ −5 to −10 ppm for $\geq$C—CF_3 group. Mass spectrum shows M^+ at m/z 501.9. Compound **4a** showed peaks at 3140 (>NH, broad) 3080 (>NHCSNH<) and 1115 (CS) cm^{-1} in IR spectrum. ^{1}H NMR show peaks at δ 9.8 (brs, two > NH), δ 4.9 (>NHCSNH<) and δ.5–7.8 ppm for aromatic protons. In ^{19}F NMR peaks at δ −5 to 10 for ($\geq$C–CF_3) and −30 to −40 ppm for ($\geq$C–F) group was observed. Finally, mass spectrum of **4a** shows M^+ at m/z 635.5.

FUNGICIDAL ACTIVITY

Compounds **4a–g** were screened for antifungal activity against *Alternaria alternata*, *Aspergillus niger* and *Macrophomina* using agar diffusion techniques[4]. Culture media were prepared using aseptic and sterilization techniques. Incubation period is 72 h at 28°C. All the solutions of the test compounds were prepared by dissolving 1 mg of testing sample in 1 ml of acetone. This gives the conc. of sample 1000 μg/mL or 1000 ppm. Different solutions such a 500 and 100 ppm were prepared from the sample solution. Pure cultures of *Alternaria alternata*. *Aspergillus niger,* and *Macrophomina* were raised in conical flask (100 mL) containing potato dextrose agar (PDA) medium. The sporequery obtained from 10-day old cultures were used for testing the efficacy of test compounds against inhibition of spore germination. Sterilized acetone was used as control. Percent spore inhibition is calculated by formula as –

$$\%\ \text{inhibition} = \frac{\text{Number of spores ungerminated}}{\text{Total number of spores}} \times 100 \qquad (1)$$

TABLE I Physical and Analytical Data of the Compounds 4a–h

Compound	Yield (%)	M.P. (°C)	Mol. formula (mol. wt.)	Analysis % found (calcd.)			
				C	H	N	S
4a	75	205	$C_{24}H_{14}N_9O_2S_2ClF_4$ (635.5)	45.29 (45.31)	2.18 (2.20)	19.80 (19.82)	10.00 (10.07)
4b	70	174	$C_{24}H_{14}N_9O_2S_2ClF_4$ (635.5)	45.28 (45.31)	2.19 (2.20)	19.80 (19.82)	10.00 (10.07)
4c	60	200	$C_{25}H_{14}N_9O_2S_2ClF_6$ (685.5)	43.74 (43.76)	2.00 (2.04)	18.36 (18.38)	9.30 (9.33)
4d	65	160	$C_{24}H_{14}N_{10}O_4S_2ClF_3$ (662.5)	43.45 (47.47)	2.09 (2.11)	21.11 (21.13)	9.63 (9.66)
4e	70	185	$C_{25}H_{17}N_9O_2S_2ClF_3$ (631.5)	47.48 (47.50)	2.66 (2.69)	19.93 (19.95)	10.11 (10.13)
4f	50	180	$C_{24}H_{15}N_9O_2S_2ClF_3$ (617.5)	46.61 (46.63)	2.40 (2.42)	20.38 (20.40)	10.34 (10.36)
4g	70	165	$C_{18}H_{12}N_{10}O_2S_2ClF_3$ (556.5)	38.79 (38.81)	2.13 (2.15)	25.13 (25.15)	11.48 (11.50)
4h	60	190	$C_{21}H_{15}N_9O_2S_2ClF_3$ (581.5)	43.30 (43.33)	2.55 (2.57)	21.64 (21.66)	10.99 (11.00)

Evaluation of the fungicidal activity shows that compounds **4a**, **4b**, **4c,** and **4e** showed maximum inhibition which may be attributed to maximum fluoro substitution in compound **4a**, **4b**, and **4c**, while in compound **4e** presence of —CH_3 group along with fluoro group also activates the compound. The fungicidal screening results are recorded in Table II.

EXPERIMENTAL

Purity of all the compounds was checked on silica gel G plates using iodine vapor as the detecting agent. Melting points were determined

TABLE II Fungicidal Screening Data of Compounds 4a–h

	Average % inhibition of spore germination after 72 h								
	Alternaria alternata			*Aspergillus niger*			*Macrofomina*		
Compound	100	500	1000	100	500	1000	100	500	1000
4a	32	44	68	30	41	69	30	42	70
4b	31	42	66	31	41	68	31	41	69
4c	38	49	72	39	50	73	30	50	72
4d	28	37	55	27	35	53	27	36	56
4e	30	35	62	29	40	61	26	38	63
4f	30	36	59	30	35	58	29	35	58
4g	29	38	56	27	38	57	28	38	56
4h	30	40	60	29	38	58	30	39	59

in open capillary tubes using Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 577 spectrophotometer in KBr pellets. ^{1}H NMR spectra (chemical shifts in δ ppm) were recorded at 89.99 MHz using GEOL (model Al-300) apparatus with TMS as the internal standard. In ^{19}F NMR spectra TFA was taken as an external standard. The mass spectra were recorded on Kratos MS-30 and MS-50 spectrometer operating at an ionization potential of 70 eV.

2-(4-Nitrobenzothiazol-2′-ylamino)-4,6-dichloro-1,3,5-traizine (2)

A solution of 2-amino-4-nitrobenzothiazole (1.63 g, 0.1 mmol) in acetone was added with constant stirring to a cooled solution (0–5°C) of 2,4,6-trichloro-1,3,5-triazine (1.84 g, 0.1 mmol) in acetone. The solution was kept alkaline during the reaction with sodium hydroxide (0.4 g, 0.1 mmol). The reaction mixture was stirred for 2 h at 0–5°C. It was then poured into the crushed ice, acidified with diluted HCl and resulting solid was dried and crystallized from ethanol. m.p. 163°C, yield (71%); IR (KBr) $\nu_{\max}$: 3160 (>NH); 1340 $(\mathrm{N{=}O})_{2\mathrm{asym}}$, 1520 $(\mathrm{N{=}O})_{2\mathrm{sym}}$ and 740 ($\geq$C—Cl); ^{1}H NMR ($CDCl_3$) : δ 9.2 (s, 1H, >NH), 6.6–7.5 (m, 3H, aromatic). (Found C, 34.97, H, 1.16, N, 24.47, S, 9.34, S, 9.34, $C_{10}H_4N_6SCl_2O_2$ requires C, 34.99, H, 1.17, N, 24.49, S, 9.36%).

2-(4-Nitrobenzothiazol-2′-ylamino)-4-(2-chloro-4-trifluoromethylanilino)-6-chloro- 1,3,5-triazine (3)

2-(4-Nitrobenzothiazol-2′-ylamino)-2,4-dichloro-1,3,5-traizine (3.53 g, 0.1m mole) dissolved in acetone (100 ml) was added 2-chloro-4-trifluoromethylaniline (1.80, 0.1 mmol) in acetone (100 ml) slowly with constant stirring, followed by the addition of sodium hydroxide (0.4 g, 0.1mmol) in water (50 ml) stirred for 3 h at 30–40°C poured into ice water, acidified with diluted HCl, filtered, washed with water, dried, and crystallized from ethanol. m.p., 180°C, yield (65%); IR (KBr) $\nu_{\max}$: 3150 (br) (>NH), 1340, 1520 (—NO_2), 745 ($\geq$C—Cl). ^{1}H NMR ($CDCl_3$) : δ 9.7 (s, 2H, 2x > NH), 6.6–7.8 (m, 6H, aromatic), ^{19}F NMR : δ (−5) to (−10) ($\geq$C—CF_3), MS : 501.9 (m/z). (Found C, 40.62, H, 1.57, N, 19.50, S, 6.35, $C_{17}H_8N_7O_2Cl_2SF_3$ requires C, 40.64, H, 1.59, N, 19.52, S, 6.37%).

2-(4-Nitrobenzothiazol-2′-ylamino)-4-(2-chloro-4-trifluoromethylanilino)-6-(substituted Thioureido)-1,3,5-triazine (4)

Compound **3** (1 mmol) dissolved in acetone was added to allyl thiourea/thiosemicarbazide/substituted thiourea/arylthiourea (1 mmole) in acetone (100 ml) slowly with constant stirring, followed by the addition of sodium (1 mmol) in water (50 ml) and stirred for 3 h at 30–40°C poured into ice water, acidified with diluted HCl, filtered, washed, dried, and crystallized from ethanol, **4a**, m.p. 205°C, yield (75%); IR (KBr) $\nu_{\max}$: 3140 (>NHbr) 3080 (>NHCSNH<), 1340, 1520 (—NO_2), 1115 (thioureido CS), 740 ($\geq$C—Cl). ^{1}H NMR ($CDCl_3$)δ : 4.9 (s, 2H, NHCSNH), 9.8 (br, 2H, 2x > NH), 6.5–7.8 (m, 9H, aromatic), ^{19}F NMR : δ (−5) to (−12) ($\geq CF_3$), 30–40 ($\geq$C—F), MS : 635.5 (m/z). (Found C, 45.29, H, 2.18 N, 19.80, S, 10.00. $C_{24}H_{14}N_9O_2S_2ClF_4$ require C, 45.31, 2.20, N, 19.82, S, 10.07%).

Compounds **4b–h** were prepared similarly. Their physical and analytical data are recorded in Table I.

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