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SYNTHESIS OF 2- (6 -CHLOROBENZOTHIAZOL-2'-YL AMINO) -4- (2-CHLORO-4-TRIFLUOROMETHYL PHENYL THIOUREIDO)-6-(SUBSTITUTED THIOUREIDO)-1,3,5-TRIAZINE AS ANTIFUNGAL AGENTS

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ABSTRACT
2,4, 6-Trichloro-1,3,5-triazine has been reacted selectively with nucleophilic reagents, 2-amino -6- chlorobenzothiazole **I**, and then the product **II** so obtained is reacted with 2-chloro -4- trifluoromethyl phenyl thiourea **III** to give **IV** and then **IV** is reacted with different substituted thioureas **V** to give 2-(6-chlorobenzothiazol - 2'-yl amino) -4- (2- chloro -4- trifluoromethyl phenyl thioureido) -6-(substituted thioureido)-1, 3, 5-triazine **VI**. These compounds are evaluated for their antifungal activity and shown promising results. The structure of all these compounds have been confirmed by IR, ^{1}HNMR, mass spectral data and elemental analysis.

KEYWORDS
2-amino -6- chlorobenzothiazole, 2-chloro -4- trifluoromethyl phenyl thiourea, 2-(6-chlorobenzothiazol-2'-yl amino)-4,6-dichloro-1, 3, 5-triazine, 2-(6-chlorobenzothiazol - 2'-yl amino) -4- (2- chloro -4- trifluoromethyl phenyl thioureido) -6-(substituted thioureido)-1, 3, 5-triazine.

INTRODUCTION
Triazine nucleus has received the attention of synthetic chemists during the past few decades. Various pharmacological activities such as antibacterial, antifungal, herbicidal, metabolites and antifolate[1-4] have been reported for triazine and its derivatives. The lipophilic behaviour of triazine derivatives imparts them with antimicrobial activity. S-triazines have chlorine atoms that can react with NH_2 group which are capable of copolymerization and appear to be promising dentin bonding agents[5]. Benzothiazole and thioureas also exhibit broad spectrum of biological activities.In continuation of our work on triazines[6,7] we have synthesized some new derivatives of 2- (6-chlorobenzothiazol -2'-yl amino) -4- (2-chloro -4-trifluoro-methyl phenyl thioureido) -6-(substituted thioureido)-1, 3, 5-triazine **VI** (***Scheme-I***) with enhanced antifungal activity. 2,4,6-Trichloro-1,3,5-triazine (cyanuric chloride) is reacted selectively with nucleophilic reagents. Cyanuric chloride is a weak base, if one of the chlorine is replaced by –NHR, OR or SR, the basicity is increased because of the electron releasing effect of –NHR, OR or SR substituted at α-positions of the ring nitrogen atoms. Three chlorine atoms of 2,4,6-trichloro- 1,3,5-triazine have been replaced subsequently by 2-amino-6-chlorobenzothiazole (which in turn is prepared

by condensing chloroaniline with ammonium thiocyanate), 2-chloro-4-trifluoromethyl phenyl thiourea and substituted thioureas in alkaline medium selectively to give the title compound **VI**.2-(6-Chlorobenzothiazol-2'-yl amino) 4, 6-dichloro-1, 3, 5- triazine **II** has been prepared by treating cyanuric chloride in acetone with 2-amino-6-chlorobenzo-thiazole **I** at 0-5^{o}C and stirring for 3 hrs. The second chlorine atom of **II** has been replaced by 2-chloro-4-trifluoromethyl phenyl thiourea at 30-40^{o}C in acetone by constant stirring for 3 hrs to give 2-(6-chlorobenzothiazol-2'-yl amino)-4-(2'-chloro-4-trifluoro methyl phenyl thioureido)-6-chloro-1, 3, 5-triazine **IV**. The third chlorine atom of triazine has been replaced by different substituted thioureas at 80-90^{o}C in acetone to give the title compound **VI**.**FUNGICIDAL ACTIVITY**Compounds **VI**a-h were screened for antifungal activity against Alternaria alternata, Aspergillus niger and Macrophomina using agar diffusion technique[8]. Culture media were prepared using aseptic and sterilization techniques. Incubation period is 72 hrs at 28^{o}C. All the solutions of test compounds were prepared by dissolving 1mg of testing sample in 1ml of acetone. This gives the concentration of sample 1000 µg/ml or 1000 ppm. Different dilutions such as 500 and 1000 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 spores obtained from ten days 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:

$$\text{Inhibition} = \frac{\text{Number of Spores (ungermina ted)} * 100}{\text{Total Number of Spores}}$$

Evaluation of the fungicidal activity shows at 30-35 % activity is observed at 100 ppm, 36-50 % at 500 ppm and 55-72 % activity observed at 1000 ppm. Further, compounds **VI**a and **VI**b show maximum inhibition at all concentrations which may be attributed to, maximum fluoro substitution in these compounds. The fungicidal screening results are recorded in Table-II.

EXPERIMENTAL: Purity of all the compounds was checked on silica gel G plates using iodine vapour as the detecting agent. Melting points were determined in open capillary tubes using Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 577 spectrometer in KBr pellets. ^{1}HNMR spectra were recorded on JEOL (model AL-300) spectrophotometer using TMS as an internal standard (chemical shifts are recorded in δ ppm). The mass spectra were recorded on Kratos MS-30 and MS-50 spectrometer operating at an ionization potential of 70 eV. Physical and analytical data of the compounds are recorded in

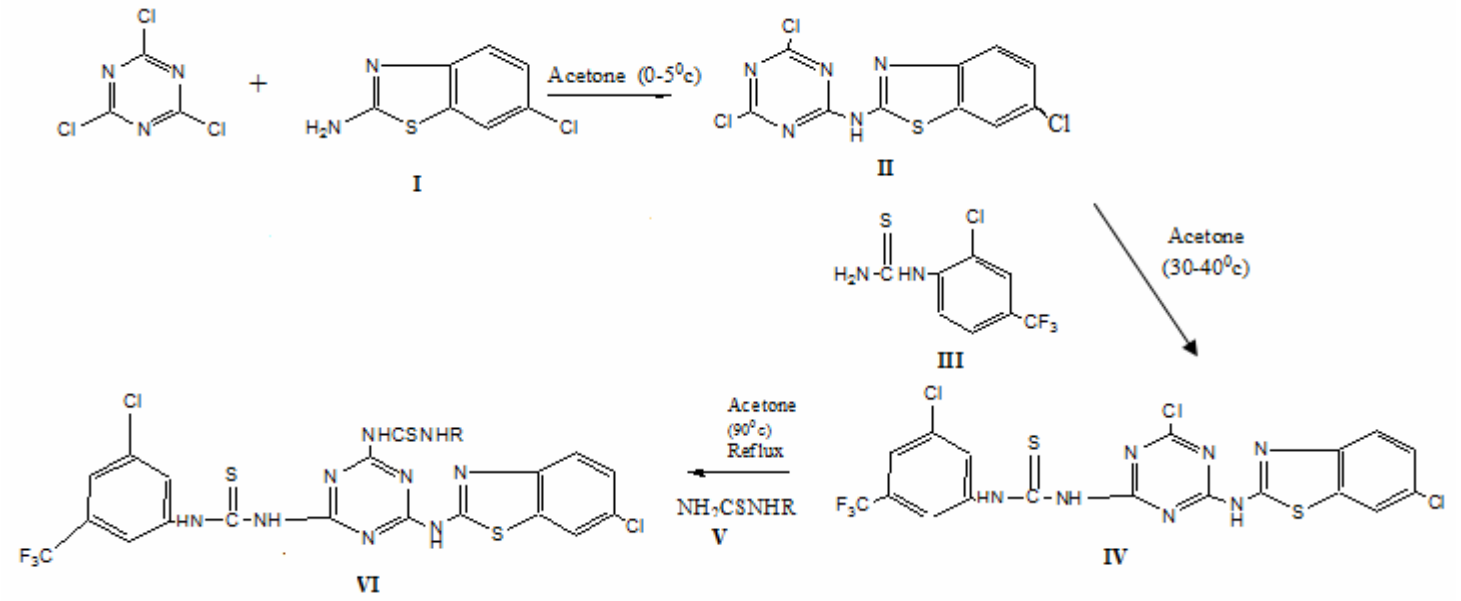
Table-I. 2-(6-Chlorobenzothiazol-2'-yl amino)-4, 6-dichloro 1, 3, 5-triazine II:
To 2, 4, 6-trichloro-1, 3, 5-triazine (18.4 g, 0.1mole) dissolved in acetone (100ml) cooled at 0^{o}C, 2-amino-6-chloro-benzothiazole (17.05g, 0.1mole) dissolved in acetone (100ml) was added with stirring at 0-5^{o}C followed by dropwise addition of sodium hydroxide (4.0g, 0.1mole) in water (50ml). Contents were stirred for 3 hrs and poured into ice water acidified with dilute HCl, filtered, washed, dried and recrystallized from ethanol, m.p. 210^{o}C, yield (78 %).**2,6-**

Chlorobenzothiazol-2'-yl amino-4-(2-chloro-4-trifluoromethyl phenyl thioureido)-6-chloro-1, 3, 5-triazine IV. Compound II (33.2g, 0.1mole) dissolved in acetone (100ml) was added to 2-Chloro-4-trifluoromethyl Phenylthiourea (25.4g, 0.1mole) in acetone (100ml) slowly with

constant stirring followed by addition of sodium hydroxide (4.0g, 0.1mole) in water (50ml) and stirred for 3 hrs at 30-40^{o}C poured in ice water, acidified with dilute HCl, filtered washed, dried and recrystallized from ethanol, m.p. 175^{o}C, yield 75%.

2-(6-Chlorobenzothiazol-2'-yl amino)-4-(2-chloro-4-trifluoromethyl phenyl thioureido)-6-(p-fluorophenyl thioureido)-1, 3, 5-triazine VIa.

To compound **IV** (5.18 g, 0.01mole) in acetone (50ml) was added p-fluorophenyl thiourea (1.6 g, 0.01 mole) and sodium hydroxide (0.01mole) in water (10ml) refluxed at 85-90^{o}C for 2 hrs.
The contents were poured into ice water, filtered, dried and recrystallized from ethanol, m.p. 178^{o}C, yield 74 %.



R = 4-FC$_6$H$_4$, 2-FC$_6$H$_4$, 2-NO$_2$-C$_6$H$_4$, 2-OCH$_3$C$_6$H$_4$,
4-Cl C$_6$H$_4$, CH$_2$=CH-CH$_2$, C$_6$H$_5$, NH$_2$

Scheme-I

RESULTS AND DISCUSSION

IR spectra of 2-(6-Chlorobenzothiazol-2'-yl amino)-4, 6-dichloro 1, 3, 5-triazine II shows significant characteristic absorption band in the region of ν_{max} 3200 (>NH) cm^{-1}, ^{1}HNMR ($CDCl_3$): δ 9.0 (s, 1H, >NH), 6.5-6.8 (m, 3H, aromatic) ppm. In mass spectrometry of IIa (m/z): 332.5 (M+) was observed. (Found C, 36.00; H, 1.18; N, 21.00; S, 9.60; $C_{10}H_4N_5SCl_3$ requires C, 36.09; H, 1.20; N, 21.05; S, 9.62 %);

IR spectra of 2,6-Chlorobenzothiazol-2'-yl amino-4-(2-chloro-4-trifluoromethyl phenyl thioureido)-6-chloro-1, 3, 5-triazine IV shows significant characteristic absorption band in the region of ν_{max}: 3160 (>NH) 1120 (thioureido CS), 740 (C–Cl) cm^{-1}. ^{1}HNMR: δ 4.80 (s, 2H, >NH CS NH), 9.5 (s, 1H, >NH), 6.5-7.2 (m, 8H, aromatic) ppm. MS (m/z): 518.5 (M+) IVa (Found C, 39.20; H, 1.60; N, 17.77; S, 11.60 $C_{18}H_9N_7S_2Cl_3F_3$ requires C, 39.23; H, 1.63; N, 17.80; S, 11.62 %);

IR spectra of 2-(6-Chlorobenzothiazol-2'-yl amino)-4-(2-chloro-4-trifluoromethyl phenyl thioureido)-6-(p-fluorophenyl thioureido)-1, 3, 5-triazine VIa shows significant characteristic absorption band in the region of ν_{max}: 3130 (>NH), 1115 (thioureido CS) cm^{-1}, ^{1}HNMR: δ 4.90 (s, 4H, 2 x NHCSNH), 10.20 (br, 1H, >NH), 6.85-7.45 (m, 12H, Ar-H) ppm. MS (m/z): 684 (M+). (Found: C, 43.82; H, 2.17; N, 10.29; S, 18.40. $C_{25}H_{15}N_9S_3F_4Cl_2$ requires C, 43.85; H, 2.19; N, 10.31; S, 18.42).

Compounds VIb-h were prepared similarly. Their physical and analytical data are recorded in Table-I.

Table – I

Compound	R	Mol. Formula	M.P.°C	Yield (%)	Found/(Calculated) %			
					C	H	N	S
VIa	4-FC_6H_4	$C_{25}H_{15}N_9S_3F_4Cl_2$	178	74	73.82 (73.85)	2.17 (2.19)	10.29 (10.31)	18.40 (18.42)
VIb	2-FC_6H_4	$C_{25}H_{15}N_9S_3F_4Cl_2$	182	72	43.80 (43.85)	2.16 (2.19)	10.28 (10.31)	18.39 (18.42)
VIc	2-$NO_2C_6H_4$	$C_{25}H_{15}N_{10}Cl_2S_3O_2F_3$	160	68	42.15 (42.19)	2.07 (2.10)	10.36 (10.38)	19.65 (19.69)
VId	2-$OCH_3C_6H_4$	$C_{26}H_{18}N_9Cl_2S_3OF_3$	194	71	43.82 (43.85)	2.61 (2.63)	18.08 (18.10)	13.77 (13.79)
Vie	4-ClC_6H_4	$C_{25}H_{15}N_9Cl_3S_3F_3$	192	70	42.80 (42.80)	2.12 (2.14)	9.52 (9.54)	17.96 (17.98)
VIf	CH_2=CH-CH_2	$C_{22}H_{16}N_9Cl_2S_3F_3$	173	65	41.88 (41.90)	2.50 (2.53)	9.85 (9.88)	19.96 (20.00)
VIg	C_6H_5	$C_{25}H_{16}N_9Cl_2S_3F_3$	170	69	45.00 (45.04)	2.37 (2.40)	10.09 (10.11)	18.89 (18.91)
VIh	NH_2	$C_{19}H_{13}N_{10}Cl_2S_3F_3$	165	73	37.65 (37.68)	2.10 (2.14)	10.60 (10.62)	23.10 (23.14)

Table-II

Fungicidal screening data of 2-(6-chlorobenzothiazol-2'-yl amino)-4-(2-chloro-4-trifluoromethyl phenyl thioureido)-6-(substituted thioureido)-1, 3, 5-triazine

Compound	Average % inhibition of spore germination after 72 hrs								
	Alternaria Alternata Concentration (ppm)			Aspergillus Niger Concentration (ppm)			Macrophomina Concentration (ppm)		
	100	500	1000	100	500	1000	100	500	1000
VIa	35	50	72	30	50	71	32	50	72
VIb	34	49	70	33	47	72	32	48	72
VIc	31	42	65	28	40	61	30	38	64
VId	32	36	60	32	45	70	31	35	68
Vie	30	35	62	33	44	69	32	37	61
VIf	30	38	68	31	44	67	30	35	69
VIg	31	37	55	30	42	64	31	34	66
VIh	32	35	68	30	43	67	31	35	67

REFERENCES:

[1] Schulze W., Neubert E., Wittchem S. K. and Geiber R. M.; Ger. (East) D D 20464.3 V (1987) Chem. Abstr. 108 (1987), 248500.

[2] Garner G., Sohborn, J. R. and Goss J. R.; Weeds Sci, (1987) 35, 763; Chem. Abstr. 108 (1987), 89348.

[3] Sanderson J. T. and Let Char R. J.; Environmental Health Perspectives, 109, (2001), 10.

[4] Shabadi C. V., Shelar M. A. and Shelar A. R.; Indian Drugs, 35, (1998), 480.

[5] Desai P. S. and Desai K. R.; J. Indian Chem. Soc., 71, (1994), 155.

[6] Sareen V., Khatri V., Garg U., Jain P. and Sharma K.; Phosphorus, Sulphur and Silicon, 182, (2007), 2943.

[7] Sareen V., Khatri V., Jain P. and Sharma K.; Phosphourus, Sulphur and Silicon, 185, (2010), 140.

[8] Sareen V., Khatri V., Jain P. and Sharma K.; Indian J. Heterocyclic Chem., 20, (2010), 91.

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