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Synthesis and antimicrobial studies of thiazolotriazinones

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Dedicated to my beloved Professor B. Shivarama Holla on the occasion of his 64th birthday.

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ABSTRACT

A series of 6-substitutedphenyl thiazolo-1,2,4-triazinones (**8**) were obtained by the initial reaction of 6-substituted arylmethyl-3-mercapto-1,2,4-triazin-5-ones (**5**) with substituted phenacyl bromides (**6**) and further followed by PPA cyclization. The structures of the newly synthesized compounds were confirmed by IR, ^{1}H NMR, Mass and analytical data. Compounds **8a**, **8e**, **8f** and **8h** exhibited good antimicrobial activity.

1. Introduction

Thiazole and its derivatives have been much studied in the field of organic, medicinal chemistry and agriculture. Thiazole bearing heterocyclic system has found broad application in drug development for the treatment of inflammation [1], hypertension [2], bacterial [3] and HIV infections [4]. Some analogues are used as fungicides, as an ingredient of herbicides, as schistosomicidal and anthelmintic drugs [5].

Thiazole ring is an important pharmacophore [6] and its coupling with other rings could furnish new biologically active compounds. Some of the biologically active molecules bearing thiazole nucleus are Fanetizole, Meloxicam (anti-inflammatory agent) [7,8], Nizatidine (antiulcer agent) [9], Sulfatiazol (antimicrobial agent) [10], Bleomycine and Tiazofurin (antineoplastic agents) [11].

1,2,4-Triazin-5-ones are also very important class of heterocyclic compounds that show a wide variety of applications in both the pharmaceutical and agrochemical industries. As potential human therapies, 1,2,4-triazin-5-ones have exhibited anticancer [12], antiulcer [13] and anti-inflammatory effects [14]. Within the agrochemical field this class of compound has shown activity as herbicides [15], dessicants, plant growth regulators [16] and insecticides [17]. Meteribuzin and Metamitron are good examples for 1,2,4-triazin-5-ones herbicides [18].

Prompted by these observations it was contemplated to synthesize a novel series of halogen containing thiazolotriazinones and to screen them for their antimicrobial activities. The results of these studies are presented in this paper.

2. Chemistry

6-Substituted arylmethyl-3-mercapto-1,2,4-triazin-5-ones (**5**) were synthesized according to the reported method [19,20]. 6-(Substituted arylmethyl)-3-{[2-(substituted phenyl)-2-oxoethyl] thio}-1,2,4-triazin-5(4*H*)-one (**7**) was obtained by reaction of 6-substituted arylmethyl-3-mercapto-1,2,4-triazin-5-ones (**5**) with various substituted phenacyl bromides [21] (**6**) in presence of base. Compound **7** on cyclization with PPA yielded 3-(4-substituted arylmethyl)-6-(substituted phenyl)-4*H*-1,3-thiazolo[2,3-*c*]-1,2,4-triazin-5-one (**8**) in good yields. The reaction sequences are outlined in Scheme 1.

3. Results and discussion

The IR spectrum of 3-(4-chlorobenzyl)-6-(4-chlorophenyl)-4*H*-[1,3]thiazolo[2,3-*c*][1,2,4]triazin-4-one (**8a**) showed an absorption band at 3102 cm^{-1} indicates the Ar-H stretching. The absorption

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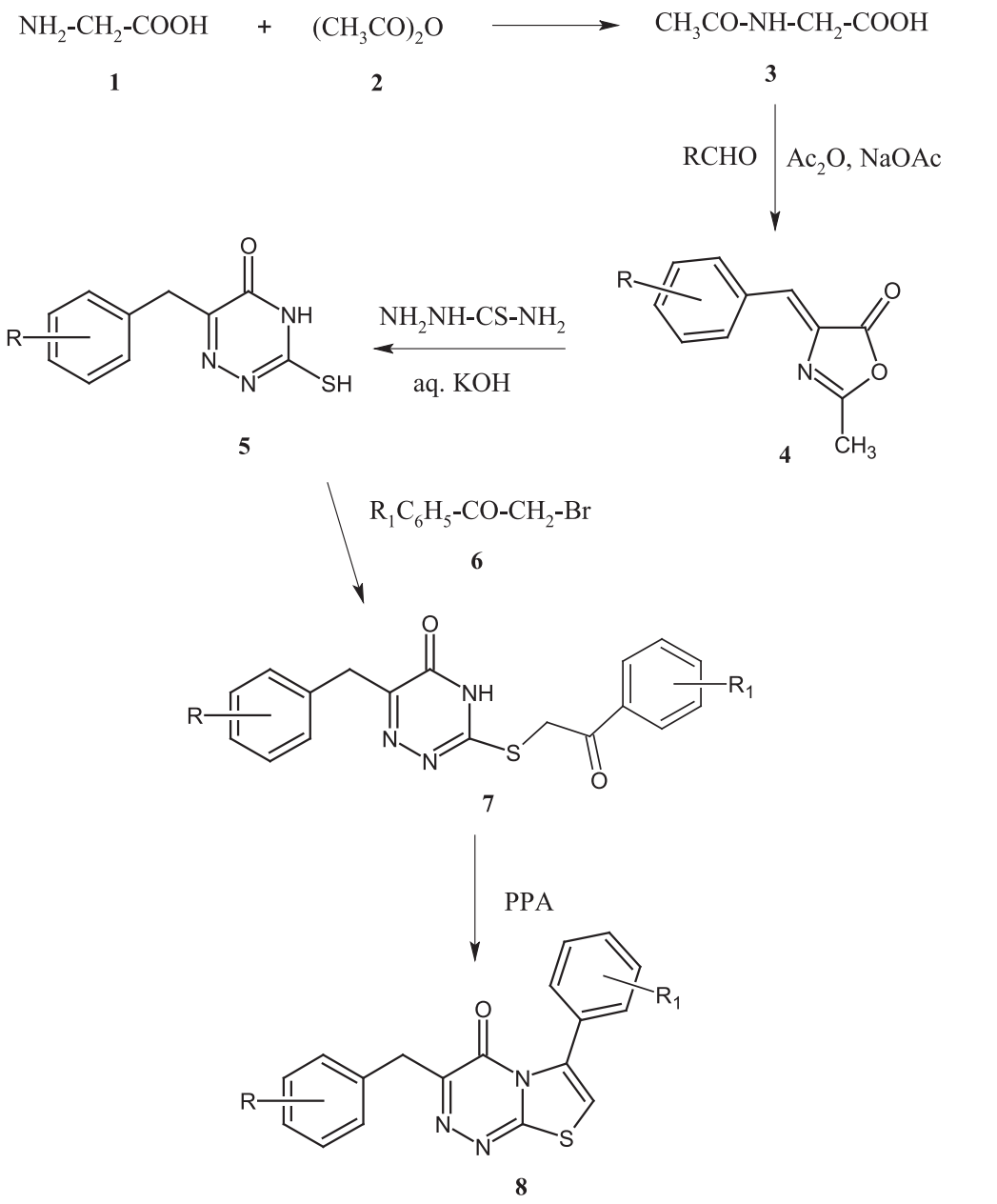

Scheme 1. Synthesis 6-(substituted phenyl)-4*H*-1,3-thiazolo[2,3-*c*]-1,2,4-triazin-5-one (**8**).

band at 1712 cm^{-1} due to the presence of −C═O-stretching of the triazinone ring system. Other prominent absorption bands are observed at 1542 cm^{-1} (C═N) and 812 cm^{-1} (C—Cl).

The 400 MHz ^1H NMR spectrum of compound **8a** showed a singlet at δ 3.95 integrating for two protons, which is attributed to the methylene protons of the benzyl group. The aromatic protons resonated as four doublets at δ 7.27 and 7.34 (J = 8.4 Hz), 7.45 and 7.58 (J = 8.8 Hz). The signal due to thiazole ring proton appeared as a singlet at δ 7.55. The 400 MHz ^{13}C NMR spectrum of compound **8a** showed the following signal 38.52, 116.28, 124.50, 127.81, 128.35, 128.77, 129.35, 132.23, 132.76, 134.71, 144.69, 150.08, 159.59, 161.79.

Further evidence for the formation of compound **8a** was obtained by recording its mass spectra. The mass spectrum of compound **8a** showed a molecular ion peak at m/z 388 (M^++1), which is in consistent with its molecular formula $C_{18}H_{11}Cl_2N_3OS$. The characterization data of thiazolotriazinones (**8a**–**j**) are given in Table 1.

4. Pharmacological studies

4.1. Antibacterial studies

The newly synthesized compounds were screened for their antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Streptococcus pyogenes* and *Klebsiella pneumoniae* (recultured) bacterial strains by disc diffusion method [22,23]. The investigation of antibacterial screening data revealed that all the tested compounds showed moderate to good bacterial

Table 1
Characterization data of thiazolotriazinoes (**8a**–**j**).

Compd. No.	*R*	R_1	Mol. formula	m.p. °C	Yield %	Analysis (%) found (calculated)		
						C	H	N
8a	4-Cl	4-Cl	$C_{18}H_{11}Cl_2N_3OS$	198–200	73	55.65 (55.81)	2.71 (2.84)	10.63 (10.85)
8b	4-Cl	4-Br	$C_{18}H_{11}BrClN_3OS$	245–48	82	49.85 (50.00)	2.37 (2.55)	9.57 (9.72)
8c	4-Cl	4-OCH_3	$C_{19}H_{14}ClN_3O_2S$	180–83	69	59.27 (59.53)	3.48 (3.66)	10.59 (10.97)
8d	4-Cl	4-NO_2	$C_{18}H_{11}ClN_4O_3S$	160–62	62	53.85 (54.27)	2.52 (2.76)	14.07 (13.81)
8e	4-Cl	2,4-Cl_2-5-F	$C_{18}H_9Cl_3FN_3OS$	220–22	74	48.94 (49.20)	1.91 (2.05)	9.32 (9.57)
8f	2,4-Cl_2	4-Cl	$C_{18}H_{10}Cl_3N_3OS$	210–12	70	50.95 (51.31)	2.26 (2.38)	9.98 (9.75)
8g	2,4-Cl_2	4-Br	$C_{18}H_{10}BrCl_2N_3OS$	194–96	75	46.03 (46.35)	2.08 (2.15)	8.93 (9.01)
8h	2,4-Cl_2	4-OCH_3	$C_{19}H_{13}Cl_2N_3O_2S$	135–38	65	54.35 (54.67)	3.05 (3.11)	9.95 (10.07)
8i	2,4-Cl_2	4-NO_2	$C_{18}H_{10}Cl_2N_4O_3S$	176–78	60	49.81 (50.00)	2.24 (2.31)	12.82 (12.96)
8j	2,4-Cl_2	2,4-Cl_2-5-F	$C_{18}H_8Cl_4FN_3OS$	168–70	73	45.28 (45.66)	1.58 (1.69)	7.42 (7.61)

inhibition. The compounds **8a**, **8e**, **8f**, **8g**, and **8j** showed very good activity against all the bacterial strains.

4.2. Antifungal studies

Newly prepared compounds were screened for their antifungal activity against *Aspergillus flavus*, *Aspergillus fumigatus*, *Candida albicans*, *Penicillium marneffei* and *Trichophyton mentagrophytes* (recultured) in DMSO by serial plate dilution method [24,25]. The antifungal screening data showed moderate to good activity. Compounds **8a**, **8e**, **8f** and **8j** emerged as very active against all the fungal strains.

5. Conclusion

The investigation of antibacterial screening data reveals that among the 10 compounds screened, four compounds showed good bacterial and fungal inhibition almost equivalent to that of standard.

6. Experimental

Melting points were determined by open capillary method and are uncorrected. The IR spectra (in KBr pellets) were recorded on a Shimadzu FT-IR 157 spectrophotometer. ^{1}H NMR spectra were recorded either on a Bruker or 300 MHz or 400 MHz NMR spectrometer using TMS as an internal standard. The mass spectra were recorded on a MASPEC low resolution mass spectrometer operating at 70 eV. The purity of the compounds was checked by thin layer chromatography (TLC) on silica gel plate using petroleum ether and ethyl acetate.

6-Substituted arylmethyl-3-mercapto-triazin-5-(4*H*)-ones (**5**) were synthesized according to reported method [19,20]. Substituted phenacyl bromides were prepared according to reported method [21].

6.1. Preparation of 6-(substituted arylmethyl)-3-{[2-(substitutedphenyl)-2-oxoethyl]thio}-1,2,4-triazin-5(4H)-one (7)

A mixture of appropriate 6-substituted arylmethyl-3-mercapto-triazin-5-(4*H*)-ones (**5**, 0.01 mol), substituted phenacyl bromide (0.01 mol) and KOH (0.002 mol) in ethanol was refluxed for 5 h. The reaction mixture was cooled and poured onto crushed ice with vigorous stirring. The solid obtained was filtered, washed with water and dried was taken for next step without purification.

6.2. Preparation of 3-(4-substituted arylmethyl)-6-(substituted phenyl)-4H-1,3-thiazolo[2,3-c]-1,2,4-triazin-5-one (8)

6-(Substitutedarylmethyl)-3-{[2-(substitutedphenyl)-2-oxoethyl]thio}-1,2,4-triazin-5(4*H*)-one (**7**, 0.01 mol) was added to PPA (0.04 mol) at hot condition and heated to 120 °C for 6 h. The reaction mixture was cooled and poured onto crushed ice and neutralized by adding $NaHCO_3$ solution. The resulting solid was filtered, dried and recrystallized from a mixture of ethanol and dimethylformamide.

6.2.1. 6-(4-Bromophenyl)-3-(4-chlorobenzyl)-4H-[1,3]thiazolo[2,3-][1,2,4]triazin-4-one (8b)

IR (KBr) ν/cm^{-1}: 3085 (Ar-H), 1718 (C=O), 1532 (C=N), 827 (C–Cl); ^{1}H NMR ($CDCl_3$) δ: 3.94 (s, 2H, CH_2), 7.34 (d, 2H, Ar-H, J = 8.2 Hz), 7.46 (d, 2H, Ar-H, J = 8.2 Hz), 7.55 (d, 2H, Ar-H, J = 8.8 Hz), 7.58 (s,1H, Ar-H), 7.61 (d, 2H, Ar-H, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ: 38.54, 116.31, 123.67, 124.10, 127.81, 129.35, 130.01, 130.30, 132.23, 132.76, 144.69, 150.08, 159.59, 161.79. MS (*m*/*z*, %): 434 (M^++1, 34).

6.2.2. 3-(4-Chlorobenzyl)-6-(4-methoxyphenyl)-4H-[1,3]thiazolo[2,3-][1,2,4] triazin-4-one (8c)

IR (KBr) ν/cm^{-1}: 3100 (Ar-H), 1736 (C=O), 1545 (C=N), 832 (C–Cl); ^{1}H NMR ($CDCl_3$) δ: 3.95 (s, 2H, CH_2), 4.02(s, 3H, OCH_3), 7.29 (d, 2H, Ar-H, J = 8.4 Hz), 7.35 (d, 2H, Ar-H, J = 8.4 Hz), 7.77 (s,1H, Ar-H), 7.85 (d, 2H, Ar-H, J = 8.8 Hz), 8.22 (d, 2H, Ar-H, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ: 38.54, 55.14, 112.88, 116.28, 118.65, 127.81, 129.35, 129.64, 132.23, 132.76, 144.69, 150.08, 159.59, 160.58, 161.79. MS (*m*/*z*, %): 384 (M^+ + 1, 15).

6.2.3. 3-(4-Chlorobenzyl)-6-(4-nitrophenyl)-4H-[1,3]thiazolo[2,3-c][1,2,4]triazin-4-one (8d)

IR (KBr) ν/cm^{-1}: 3091 (Ar-H), 1715 (C=O), 1528 (C=N), 817 (C–Cl); ^{1}H NMR($CDCl_3$) δ: 4.00 (s, 2H, CH_2), 7.29 (d, 2H, Ar-H, J = 8.4 Hz), 7.35 (d, 2H, Ar-H, J = 8.4 Hz), 7.77 (s,1H, Ar-H), 7.85 (d, 2H, Ar-H, J = 8.8 Hz), 8.22 (d, 2H, Ar-H, J = 8.8 Hz); MS (*m*/*z*, %): 399 (M^+ + 1, 45).

6.2.4. 3-(4-Chlorobenzyl)-6-(2,4-dichloro-5-fluorophenyl)-4H-[1,3]thiazolo[2,3-c][1,2,4]triazin-4-one (8e)

IR (KBr) ν/cm^{-1}: 3085 (Ar-H), 1731 (C=O), 1526 (C=N), 1098 (C–F), 825 (C–Cl); ^{1}H NMR ($CDCl_3$) δ: 3.87 (s, 2H, CH_2), 7.19 (d, 2H, Ar-H, J = 8 Hz), 7.25 (d, 2H, Ar-H, J = 8 Hz), 7.61 (s,1H, Ar-H), 7.66 (d, 1H, Ar-H, J = 9.2 Hz), 7.98 (d, 1H, Ar-H, J = 6.8 Hz); MS (*m*/*z*, %): 440 (M^+, 85).

6.2.5. 6-(4-Chlorophenyl)-3-(2,4-dichlorobenzyl)-4H-[1,3]thiazolo[2,3-c][1,2,4] triazin-4-one (8f)

IR (KBr) ν/cm^{-1}: 3091 (Ar-H), 1725 (C=O), 1530 (C=N), 832 (C–Cl); ^{1}H NMR ($CDCl_3$) δ: 4.1 (s, 2H, CH_2), 7.35–7.38 (m, 3H, Ar-H), 7.42–7.44 (m, 1H, Ar-H), 7.57 (s,1H, Ar-H), 7.63–7.65 (m, 3H, Ar-H); ^{13}C NMR ($CDCl_3$) δ: 36.88, 116.32, 116.28, 124.50, 127.57,128.35, 128.44, 128.77, 132.17, 133.01, 134.71, 136.00, 144.69, 150.08, 160.58, 161.79. MS (*m*/*z*, %): 424 (M^+ + 159).

*6.2.6. 6-(4-Bromophenyl)-3-(2,4-dichlorobenzyl)-4H-[1,3]thiazolo [2,3-c][1,2,4] triazin-4-one (**8g**)*

IR (KBr) ν/cm^{-1}: 3095 (Ar-H), 1712 (C=O), 1533 (C=N), 828 (C–Cl); ^{1}H NMR ($CDCl_3$) δ: 4.09 (s, 2H, CH_2), 7.27–7.40 (m, 3H, Ar-H), 7.48–7.50 (d, 2H, Ar-H, J = 8.4 Hz), 7.58–7.69 (m, 2H, Ar-H). ^{13}C NMR ($CDCl_3$) δ: 36.68, 116.28, 124.10, 127.57, 128.44, 130.01, 130.31, 132.17, 133.01, 134.05, 136.00, 144.69, 150.08, 160.58, 161.79.

*6.2.7. 3-(2,4-Dichlorobenzyl)-6-(4-methoxyphenyl)-4H-[1,3] thiazolo[2,3-c][1,2,4] triazin-4-one (**8h**)*

IR (KBr) ν/cm^{-1}: 3105 (Ar-H), 1729 (C=O), 1545 (C=N), 837 (C–Cl); ^{1}H NMR ($CDCl_3$) δ: 3.98 (s, 2H, CH_2), 4.15 (s, 3H, CH_3), 7.23 (d, 2H, Ar-H, J = 8.2 Hz), 7.38–7.42 (m, 3H, Ar-H), 7.61–7.63 (m, 3H, Ar-H); MS (m/z, %): 418 (M^+, 11).

*6.2.8. 3-(2,4-Dichlorobenzyl)-6-(4-nitrophenyl)-4H-[1,3]thiazolo [2,3-c][1,2,4] triazin-4-one (**8i**)*

IR (KBr) ν/cm^{-1}: 3087 (Ar-H), 1710 (C=O), 1525 (C=N), 812 (C–Cl); ^{1}H NMR ($CDCl_3$) δ: 4.11 (s, 2H, CH_2), 7.35–7.41 (m, 2H, Ar-H), 7.65–7.66 (m, 1H, Ar-H), 7.73 (d, 2H, Ar-H, J = 8.4 Hz), 7.86 (s,1H, Ar-H), 8.13 (d, 2H, Ar-H, J = 8.4 Hz).

*6.2.9. 3-(2,4-Dichlorobenzyl)-6-(2,4-dichloro-5-fluorophenyl)-4H-[1,3]thiazolo [2,3-c][1,2,4]triazin-4-one (**8j**)*

IR (KBr) ν/cm^{-1}: 3099 (Ar-H), 1735 (C=O), 1543 (C=N), 1105 (C–F), 838 (C–Cl); ^{1}H NMR ($CDCl_3$) δ: 4.02 (s, 2H, CH_2), 7.24–7.29 (m, 2H, Ar-H), 7.42–7.43 (m, 1H, Ar-H), 7.53 (d, 1H, Ar-H, J = 9.6 Hz), 7.61 (s,1H, Ar-H), 7.84 (d, 2H, Ar-H, J = 6.8 Hz); MS (m/z, %): 476 (M^+ + 1, 79).

7. Pharmacological assay

7.1. Antibacterial assay

A standard inoculum (1–2 10^7 c.f.u/cm^3 0.5 *McFarland* standards) was introduced on to the surface of sterile agar plates, and a sterile glass spreader was used for even distribution of the inoculum. The discs measuring 6.25 mm in diameter were prepared from Whatman no.1 filter paper and sterilized by dry heat at 140 °C for 1 h. The sterile disc previously soaked in a known concentration of the test compounds were placed in nutrient agar medium. Solvent and growth controls were kept. The plates were inverted and incubated for 24 h at 37 °C. The inhibition zones were measured and compared with the controls. Minimum inhibitory concentration (*MIC*) was determined by broth dilution technique. The nutrient broth, which contained logarithmic serially two fold diluted amount of test compound and controls were inoculated with approximately 5 10^5 c.f.u of actively dividing bacteria cells. The cultures were incubated for 24 h at 37 °C and the growth was monitored visually and spectrophotometrically. The lowest concentration (highest dilution) required to arrest the growth of bacteria was regarded as minimum inhibitory concentrations (*MIC*). Ciprofloxacin was used as a standard drug. The diameter of the zone of inhibition and minimum inhibitory concentration values are given in Table 2.

Table 2
Antibacterial activity of thiazolotriazinoes (**8a**–**j**).

Compd. no.	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Klebsiella pneumoniae*	*Streptococcus pyogenes*
8a	23 (6.25)	26 (6.25)	33 (6.25)	20 (6.25)	23 (6.25)
8b	23 (6.25)	9 (25)	14 (12.5)	19 (6.25)	21 (6.25)
8c	12 (12.5)	–	14 (12.5)	19 (6.25)	10 (25)
8d	9 (25)	25 (6.25)	8 (25)	–	9 (25)
8e	21 (6.25)	27 (6.25)	29 (6.25)	18 (6.25)	24 (6.25)
8f	21 (6.25)	29 (6.25)	32 (6.25)	19 (6.25)	23 (6.25)
8g	21 (6.25)	26 (6.25)	29 (6.25)	18 (6.25)	20 (6.25)
8h	12 (12.5)	22 (6.25)	–	–	8 (25)
8i	20 (6.25)	15 (12.5)	27 (6.25)	–	17 (6.25)
8j	21 (6.25)	29 (6.25)	31 (6.25)	19 (6.25)	24 (6.25)
Standard[a]	23 (6.25)	30 (6.25)	33 (6.25)	22 (6.25)	25 (6.25)

– Indicates bacteria is resistant to the compounds at >100 μg/ml, MIC values are given in brackets. MIC (μg/ml) = minimum inhibitory concentration, ie. lowest concentration to completely inhibit bacterial growth. Zone of Inhibition in mm.
[a] Ciprofloxacin was used as standard.

Table 3
Antifungal activity of thiazolotriazinoes (**8a**–**j**).

Compd. no.	*Aspergillus fumigatus*	*Aspergillus flavus*	*Trichophyton mentagrophytes*	*Penicillium marneffei*	*Candida albicans*
8a	22 (6.25)	22 (6.25)	25 (6.25)	22 (6.25)	20 (6.25)
8b	8 (25)	–	12 (12.5)	–	17 (6.25)
8c	–	19 (6.25)	14 (12.5)	9 (25)	11 (12.5)
8d	15 (6.25)	–	7 (25)	21 (6.25)	18 (6.25)
8e	25 (6.25)	18 (6.25)	21 (6.25)	25 (6.25)	17 (6.25)
8f	24 (6.25)	21 (6.25)	21 (6.25)	23 (6.25)	18 (6.25)
8g	12 (12.5)	16 (6.25)	11 (12.5)	–	7 (25)
8h	20 (6.25)	–	17 (6.25)	9 (25)	17 (6.25)
8i	–	14 (12.5)	–	10 (12.5)	–
8j	24 (6.25)	21 (6.25)	22 (6.25)	25 (6.25)	20 (6.25)
Standard	25 (6.25)	21 (6.25)	23 (6.25)	25 (6.25)	19 (6.25)

– Indicates fungus is resistant to the compounds at >100 μg/ml, MIC values are given in brackets. MIC (μg/ml) = minimum inhibitory concentration, ie. lowest concentration to completely inhibit fungal growth. Zone of Inhibition in mm. Amphotericin B.

7.2. Antifungal assay

Sabourauds agar media was prepared by dissolving 1 g peptone, 4 g D-glucose, and 2 g agar in 100 cm^3 distilled water, and adjusting *pH* to 5.7 using buffer. Normal saline was used to make a suspension of spore of fungal strain for lawning. A loopful of particular fungal strain was transferred to 3 cm^3 saline to get a suspension of corresponding species. 20 cm^3 of agar media was poured in to each Petri dish. Excess of suspension was decanted and the plates were dried by placing in a incubator at 37 °C for 1 h. Using an agar punch, wells were made and each well was labeled. A control was also prepared in triplicate and maintained at 37 °C for 3–4 d. The inhibition zones in diameter were measured and compared with the controls. The Nutrient Broth, which contained logarithmic serially two fold diluted amount of test compound and controls was inoculated with approximately 1.6 × 10^4–6 10^4 c.f.u cm^{-3}. The cultures were incubated for 48 h at 35 °C and the growth was monitored. The lowest concentration (highest dilution) required to arrest the growth of fungus was regarded as minimum inhibitory concentrations (*MIC*). Amphotericin B was used as the standard drug. The diameter of zone of inhibition and minimum inhibitory concentration values are given in Table 3.

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References

[1] F. Haviv, J.D. Ratajczyk, R.W. DeNet, F.A. Kerdesky, R.L. Walters, S.P. Schmidt, J.H. Holms, P.R. Young, G.W. Carter, J. Med. Chem. 31 (1988) 1719.
[2] W.C. Patt, H.W. Hamilton, M.D. Taylor, M.J. Ryan, D.G. . Taylor Jr., C.J.C. Connolly, A.M. Doherty, S.R. Klutchko, I. Sircar, B.A. Steinbaugh,

B.L. Batley, C.A. Painchaud, S.T. Rapundalo, B.M. Michniewicz, S.C.J. Olson, J. Med. Chem. 35 (1992) 2562.
[3] K. Tsuji, H. Ishikawa, Bioorg. Med. Chem. Lett. 4 (1994) 1601.
[4] F.W. Bell, A.S. Cantrell, M. Hoegberg, S.R. Jaskunas, N.G. Johansson, C.L. Jordan, M.D. Kinnick, P. Lind, J.M. . Morin Jr., R. Noreen, B. Oberg, J.A. Palkowitz, C.A. Parrish, P. Pranc, C. Sahlberg, R.J. Ternansky, R.T. Vasileff, L. Vrang, S.J. West, H. Zhang, X.X. Zhou, J. Med. Chem. 38 (1995) 4929.
[5] J.V. Metzgar, in: A.R. Katritzky, C.W. Rees (Eds.), Comphrenesive Heterocyclic Chemistry I, vol. 6, Pergamon Press, New York, 1984, p. 328.
[6] J.J. Harnet, V. Roubert, C. Dolo, C. Charnet, B. Spinnewyn, S. Cornet, A. Rolland, J.G. Marin, D. Bigg, P.E. Chabrier, Bioorg. Med. Chem. Lett. 14 (2004) 157–160;
J. Wityak, J. Das, R.V. Moquin, Z. Shen, J. Lin, P. Chen, A.M. Doweyko, S. Pitt, S. Pang, D.R. Shen, Q. Fang, H.F. De Fex, G.L. Schieven, S.B. Kanner, J.C. Barrish, Bioorg. Med. Chem. Lett. 13 (2003) 4007–4010.
[7] D. Lednicer, L.A. Mitscher, G.I. George, Organic Chemistry of Drug Synthesis, vol. 4, Wiley, New York, 1990, pp. 95–7.
[8] M.Z. Rehman, C.J. Anwar, S. Ahmad, Bull. Korean Chem. Soc. 26 (2005) 1771–1775.
[9] M.P. Knadler, R.F. Bergstrom, J.T. Callaghan, A. Rubin, Drug Metab. Dispos. 14 (1986) 175–182.
[10] A. Kleemann, J. Engel, Pharmaceutical Substances; Syntheses, Patents and Applications, fourth ed. ThiemeStuttgart, New York, 2001.
[11] G.W.A. Milne, Ashgate (Eds.), Handbook of Antineoplastic Agents, Gower, London, UK, 2000.
[12] V. Vuddhakul, N.W. Jacobsen, S.E. Rose, B. Ioanoni, W.K. Seow, Y.H. Thong, Cancer Lett. 42 (1988) 29.
[13] K. Hirai, H. Sugimoto, T. Mizushima, Jpn. Kokai Tokkyo Koho, JP 61134389 A2 (1986).
[14] D. Bierowska-Charytonowicz, M. Konieczny, Rocz Chem. 47 (1973) 2199.
[15] (a) W. Oettmeier, U. Hilp, W. Draber, C. Fedtke, R.R. Schmidt, Pestic. Sci. 33 (1991) 399;
(b) Y. Sanemitsu, M. Shiroshita, S. Hashimaoto, H. Kato, H. Matsumoto, Eur. Pat. Appl., EP 44696 A2 (1982).
[16] E. Kranz, H.J. Santel, K. Luerssen, R.R. Schmidt, B. Krauskopf, Ger. Offen., DE 3917043 A1 (1990).
[17] B. Boehner, H. Tobler, Eur. Pat. Appl., EP 150677 (1985).
[18] D. Draber, C. Fedtke, H. Geissbuhler (Eds.), Advances in Pesticide Science, Part 3, Pergamon Press, oxford, 1978, p. 475.
[19] (a) J. Slouka, K. Nalepa, J. Pract. Chem. 18 (1962) 188 Palacky Univ. Olmuetz (Czeck);
(b) B.S. Holla, K.V. Malini, B.K. Sarojini, Boja Poojary, Synth. Commun. 35 (2005) 333.
[20] M.S. Karthikeyan, M. Mahalinga, Prakash Karegoudar, Boja poojary, B.S. Holla, Phosphorus, Sulfur Silicon Relat. Elem. 184 (2009) 3231–3240.
[21] Vogel's Text Book of Practical Organic Chemistry, fifth ed. Longman, England, 1996, p1125.
[22] R. Cruickshank, J.P. Duguid, B.P. Marion, R.H.A. Swain, Medicinal Microbiology, twelveth ed., vol. 2, Churchil Livingstone, London, 1975, 196–202.
[23] A.H. Collins, Microbiological Methods, second ed.. Butterworth, London, 1976.
[24] Z.K. Khan, In vitro and vivo screening techniques for bioactivity screening and evaluation, in: Proceeding Int. workshop UNIDO-CDRI (1997) pp. 210–211.
[25] R.S. Varma, Antifungal Agents: Past, Present & Future Prospects. National Academy of Chemistry & Biology, India, Lucknow, 1998.