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Original article

Synthesis and antimicrobial studies of novel dichlorofluorophenyl containing aminotriazolothiadiazines

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Abstract

Dichlorofluorophenyl containing aminotriazolothiadiazines (**6**) were synthesized by initial condensation of 2-chloro-*N*-(substituted phenyl) acetamides (**4**) with triazole (**3**) and further cyclization using $POCl_3$. The structures of newly synthesized compounds were confirmed by IR, NMR, mass and elemental analysis. All the compounds were screened for their antibacterial and antifungal activities. Compounds **5a**, **5e**, **5n**, **5o**, **6a**, **6n**, and **6o** showed very good antibacterial and antifungal activities at 6.25 μg/ml concentrations.

Keywords: 2,4-Dichloro-5-fluorophenyl triazole; Intramolecular cyclization; Aminotriazolothiadiazines; Antimicrobial activity

1. Introduction

1,2,4-Triazoles have been reported to possess antibacterial, antifungal [1], antitubercular [2], anticancer [3], anticonvulsant [4], anti-inflammatory and analgesic properties [5]. The arrangement of three basic nitrogen atoms in triazole is needed for the antiviral activity [6]. 1,2,4-Triazole nucleus has been incorporated into a wide variety of therapeutically interesting drug candidates including H_1/H_2 histamine receptor blockers, cholinesterase active agents, CNS stimulants, antianxiety and sedative agents [7]. Thiadiazines were reported to possess a wide spectrum of biological activities such as anti-inflammatory [8], anti-HIV [9], antiplatelet, antithrombic [10] and antifibrinolytic properties [11].

N-bridged heterocycles derived from 1,2,4-triazoles find applications in the field of medicine, agriculture and industry. Triazolothiadiazines represent an important class of *N*-bridged heterocyclic compounds with a wide range of applications. These fused heterocycles are used as sedatives and antisecretory agents [12], and also reported to exhibit antibacterial, antifungal and anticancer activities [13]. 6-Aminotriazolothiadiazines were reported to possess good tuberculostatic activity [14]. The presence of an amino group at 6th position of fused triazolothiadiazine system could considerably enhance the biological potential of these compounds.

It was reported that the introduction of a halogen atom augments the antimicrobial activity [15]. Numerous dichlorophenyl bearing organic compounds have various bioactivities, which render them as valuable active ingredients of medicines or plant protecting agents. Fluorinated compounds are of growing importance with applications in medicine. Fluorine substitution has profound effects on the properties of organic compounds. The very high electronegativity of fluorine can modify the electronic distribution in the molecule, affecting its absorption, distribution and metabolism. At present, more than 200 fluorinated pharmaceuticals are available and many other fluorinated pharmaceuticals are about to appear. Fluorine containing molecules are used in medicine as anesthetics, antibiotics, anticancer, anti-inflammatory agents and psychopharmaceuticals, and have many other applications [16,17].

In light of such stimulating properties, it was contemplated to synthesize some newer congeners of aminotriazolothiadiazines

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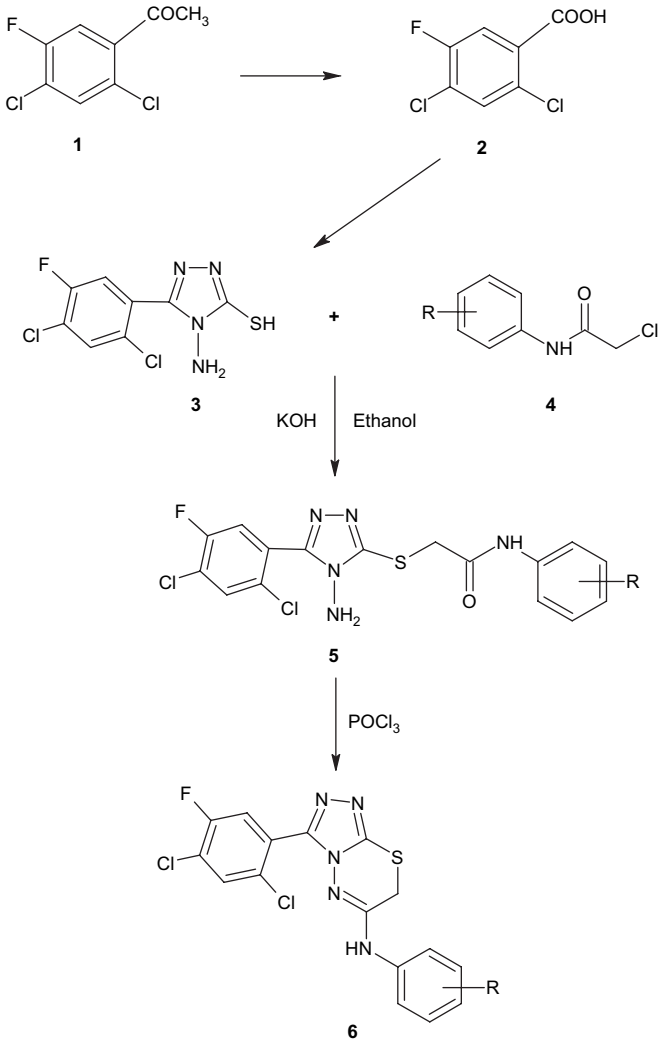
containing dichlorofluorophenyl moiety with a view to explore their potency as better chemotherapeutic agents. Antibacterial and antifungal activity results of newly synthesized aminotriazolothiadiazines were discussed in this paper.

2. Chemistry

4-Amino-3-(2,4-dichloro-5-fluorophenyl)-5-mercapto-1,2,4-triazole (**3**) was synthesized from 2,4-dichloro-5-fluoroacetophenone (**1**) as per the reported method [18]. Triazole (**3**) was treated with 2-chloro-*N*-(substituted phenyl) acetamides [19] (**4**) in the presence of potassium hydroxide in ethanol afforded *N*-(substituted phenyl)-2-{[4-amino-5-(2,4-dichloro-5-fluorophenyl)-4*H*-1,2,4-triazol-3-yl]thio}acetamides (**5**). Compound **5** on heating with phosphorus oxychloride underwent intramolecular ring closure with the formation of 6-arylamino-3-(2,4-dichloro-5-fluorophenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**6**) in good yields. The reaction sequence is outlined in Scheme 1.



R = 4-CH_3, 4-Cl, 4-OCH_3, 4-OC_2H_5, 4-F, 2,3-Cl_2, 2,4-Cl_2, 2,6-Cl_2, 2,3-$(CH_3)_2$, 2,4-$(CH_3)_2$, 2,6-$(CH_3)_2$, 3,Cl-4F, 2,4,6-$(CH_3)_3$, 2,4,5-Cl_3, 2-CF_3

Scheme 1. Synthesis of aminotriazolothiadiazines (**6**).

3. Results and discussion

Formation of compounds **5** and aminotriazolothiadiazines (**6**) was confirmed on the basis of IR, NMR, mass spectral data and elemental analysis.

The IR spectrum of compound **5a** showed a sharp absorption band at 3338 cm^{-1} indicating the presence of secondary amino group. Asymmetric and symmetric stretching frequencies of primary amino group appeared at 3269 and 3180 cm^{-1}, respectively. The amide carbonyl stretching frequency was observed at 1662 cm^{-1}. The other prominent absorption bands observed in the IR spectrum are at 3028 (Ar-H), 2920 (C–H), 1600 (C=N), 1097 (C–F), 821 and 729 (C–Cl) cm^{-1}.

The ^{1}H NMR spectrum of compound **5a** showed a singlet at δ 2.17 due to the presence of CH_3 protons. The SCH_2 protons resonated as a singlet at δ 3.97. A broad singlet at δ 4.78 integrating for two protons was attributable to NH_2 protons. The four protons of *p*-toludino moiety resonated as two doublets at δ 7.09 and 7.43 ($J = 8.2$ Hz), respectively. A doublet at δ 7.36 ($J_{\mathrm{H-F\ ortho}} = 8.4$ Hz) integrating for one proton was attributable to the C_6 proton of 2,4-dichloro-5-fluorophenyl moiety. The C_3 proton of 2,4-dichloro-5-fluorophenyl moiety resonated as a doublet at δ 7.61 ($J_{\mathrm{H-F\ meta}} = 6.5$ Hz). The signal of the NH proton appeared as a singlet at δ 9.69.

In the IR spectrum of compound **6a**, a sharp absorption band at 3292 cm^{-1} indicates the presence of secondary amino group in the compound. The disappearance of the characteristic primary amino and amide carbonyl stretching frequencies of the starting materials indicates that the open chain compound underwent intramolecular cyclization. The other prominent absorption bands observed in the IR spectrum of **6a** are at 3070 (Ar-H), 2989 (C–H), 1591 (C=N), 1099 (C–F), 812 and 729 (C–Cl) cm^{-1}.

The ^{1}H NMR spectrum of compound **6a** showed a singlet at δ 2.22 due to the presence of CH_3 protons. The methylene protons of the thiadiazine ring resonated as a singlet at δ 3.98. The protons of *p*-toludino moiety resonated as two doublets at δ 7.03 and 7.4 ($J = 8.4$ Hz) each integrating for two protons. A doublet at δ 7.85 ($J_{\mathrm{H-F\ ortho}} = 9.6$ Hz) integrating for one proton was attributable to the C_6 proton of 2,4-dichloro-5-fluorophenyl moiety. The C_3 proton of 2,4-dichloro-5-fluorophenyl moiety resonated as a doublet at δ 8.08 ($J_{\mathrm{H-F\ meta}} = 6.8$ Hz). The signal of the NH proton appeared as a singlet at δ 9.65.

Further evidence for the formation of arylaminotriazolothiadiazine (**6a**) was obtained by recording its mass spectrum. The mass spectrum of the compound **6a** showed molecular ion peak and protonated molecular ion peak at *m/z* 407 and 408, respectively, in conformity with the molecular formula $C_{17}H_{12}Cl_2FN_5S$. The other prominent fragmentation peak was observed at *m/z* 191 (10%) due to the formation of 2,4-dichloro-5-fluorobenzonitrile molecular cation. The characterization data of aminotriazolothiadiazines (**6a–o**) are given in Table 1.

Table 1
Characterization table of aminotriazolothiadiazines (**6a–o**)

Compound	R	Molecular formula	Mp (°C)	Yield (%)	Analysis (%) found (calculated)		
					C	H	N
6a	4-CH_3	$C_{17}H_{12}Cl_2FN_5S$	261–263	76	49.75 (50.00)	2.77 (2.94)	17.07 (17.16)
6b	4-Cl	$C_{16}H_9Cl_3FN_5S$	268–270	65	44.58 (44.81)	2.00 (2.10)	16.10 (16.34)
6c	4-OCH_3	$C_{17}H_{12}Cl_2FN_5OS$	265–267	72	47.88 (48.11)	2.71 (2.83)	16.37 (16.51)
6d	4-OC_2H_5	$C_{18}H_{14}Cl_2FN_5OS$	303–305	63	49.18 (49.32)	3.16 (3.20)	15.75 (15.98)
6e	4-F	$C_{16}H_9Cl_2F_2N_5S$	306–308	70	46.38 (46.60)	2.11 (2.18)	16.67 (16.99)
6f	2,3-Cl_2	$C_{16}H_8Cl_4FN_5S$	298–300	68	41.24 (41.47)	1.65 (1.73)	14.92 (15.12)
6g	2,4-Cl_2	$C_{16}H_8Cl_4FN_5S$	227–229	80	41.12 (41.47)	1.66 (1.73)	15.01 (15.12)
6h	2,6-Cl_2	$C_{16}H_8Cl_4FN_5S$	267–269	76	41.22 (41.47)	1.68 (1.73)	14.91 (15.12)
6i	2,3-$(CH_3)_2$	$C_{18}H_{14}Cl_2FN_5S$	253–255	63	51.03 (51.18)	3.24 (3.32)	16.41 (16.59)
6j	2,4-$(CH_3)_2$	$C_{18}H_{14}Cl_2FN_5S$	251–253	84	51.06 (51.18)	3.27 (3.32)	16.38 (16.59)
6k	2,6-$(CH_3)_2$	$C_{18}H_{14}Cl_2FN_5S$	267–269	74	50.88 (51.18)	3.25 (3.32)	16.35 (16.59)
6l	3-Cl-4-F	$C_{16}H_8Cl_3F_2N_5S$	312–314	62	42.81 (43.00)	1.71 (1.79)	15.46 (15.68)
6m	2,4,6-$(CH_3)_3$	$C_{19}H_{16}Cl_2FN_5S$	295–298	68	52.10 (52.29)	3.60 (3.67)	15.88 (16.05)
6n	2,4,5-Cl_3	$C_{16}H_7Cl_5FN_5S$	160–162	60	38.36 (38.59)	1.28 (1.40)	13.89 (14.07)
6o	2-CF_3	$C_{17}H_9Cl_2F_4N_5S$	244–246	73	44.01 (44.16)	1.82 (1.95)	14.92 (15.15)

4. Pharmacological studies

4.1. Antibacterial studies

The newly prepared compounds were screened for their antibacterial activity against *Escherichia coli* (ATCC-25922), *Staphylococcus aureus* (ATCC-25923), *Pseudomonas aeruginosa* (ATCC-27853), *Streptococcus pyogenes* and *Klebsiella pneumoniae* (recultured) bacterial strains by disc diffusion method [20,21]. A standard inoculum ($1-2 \times 10^7$ c.f.u/ml 0.5 McFarland standards) was introduced onto 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 an hour. The sterile discs 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. Ciprofloxacin was used as a standard drug. 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 twofold diluted amount of test compound and controls was 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 concentration (MIC). The bacterial zone of inhibition and minimum inhibitory concentration values are given in Table 2.

The investigation of antibacterial screening data revealed that all the tested compounds showed moderate to good bacterial inhibition. The compounds **5a**, **5c**, **5e**, **5l**, **5n**, **5o**, **6a**, **6b**, **6n** and **6o** showed good inhibition towards all tested species at 6.25 μg/ml concentrations.

4.2. Antifungal studies

The newly prepared compounds were screened for their antifungal activity against *Candida albicans*, *Aspergillus flavus* (NICM no. 524), *Aspergillus fumigatus* (NICM no. 902), *Penicillium marneffei* and *Trichophyton mentagrophytes* (recultured) in DMSO by agar dilution method [22,23]. Sabouraud's agar media were prepared by dissolving peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled water (100 ml) and adjusted the pH to 5.7. 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 ml saline to get a suspension of corresponding species. Twenty milliliters of agar media was poured in to each Petri dish. Excess of suspension was decanted and the plates were dried by placing in an incubator at 37 °C for 1 h. Using an agar punch, wells were made and each well were labeled. A control was also prepared in triplicate and maintained at 37 °C for 3–4 days. The fungal activity of each compound was compared with amphotericin B as standard drug. The inhibition zones were measured and compared with the controls. The nutrient broth, which contained logarithmic serially twofold diluted amount of test compound and controls inoculated with approximately $1.6 \times 10^4 - 6 \times 10^4$ c.f.u/ml was used. 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 concentration (MIC). The fungal zone of inhibition and minimum inhibitory concentration values are given in Table 3.

The antifungal screening data showed only moderate activity. Among the screened compounds, compounds **5a**, **5e**, **5n**, **5o**, **6a**, **6n** and **6o** emerged as active against all fungal strains at 6.25 μg/ml concentrations.

5. Conclusion

We have synthesized a series of dichlorofluorophenyl bearing uncyclized intermediates (**5a–o**) and aminotriazolothiadiazines

Table 2
Antibacterial activity data of **5 a–o** and **6 a–o**

Compound	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Klebsiella pneumoniae*	*Streptococcus pyogenes*
5a	25 (6.25)	29 (6.25)	31 (6.25)	20 (6.25)	22 (6.25)
5b	17 (12.5)	14 (12.5)	18 (12.5)	12 (12.5)	10 (25)
5c	24 (6.25)	30 (6.25)	32 (6.25)	21 (6.25)	23 (6.25)
5d	–	–	–	–	–
5e	23 (6.25)	28 (6.25)	30 (6.25)	21 (6.25)	22 (6.25)
5f	–	–	–	–	–
5g	–	–	–	–	–
5h	18 (6.25)	20 (12.5)	23 (12.5)	21 (6.25)	19 (6.25)
5i	20 (6.25)	18 (12.5)	20 (12.5)	17 (12.5)	24 (6.25)
5j	17 (6.25)	28 (6.25)	30 (6.25)	10 (25)	18 (6.25)
5k	–	–	–	–	–
5l	24 (6.25)	29 (6.25)	31 (6.25)	20 (6.25)	23 (6.25)
5m	–	–	–	–	–
5n	22 (6.25)	27 (6.25)	30 (6.25)	21 (6.25)	25 (6.25)
5o	25 (6.25)	30 (6.25)	29 (6.25)	20 (6.25)	22 (6.25)
6a	21 (6.25)	27 (6.25)	29 (6.25)	21 (6.25)	23 (6.25)
6b	24 (6.25)	28 (6.25)	32 (6.25)	20 (6.25)	25 (6.25)
6c	22 (6.25)	–	15 (25)	12 (12.5)	16 (12.5)
6d	20 (6.25)	–	15 (25)	12 (12.5)	–
6e	15 (12.5)	22 (6.25)	24 (12.5)	16 (12.5)	22 (6.25)
6f	–	20 (12.5)	17 (12.5)	14 (12.5)	–
6g	–	22 (12.5)	–	17 (12.5)	–
6h	–	10 (25)	–	–	15 (12.5)
6i	25 (6.25)	13 (12.5)	12 (25)	19 (6.25)	10 (25)
6j	–	23 (12.5)	18 (12.5)	14 (12.5)	11 (12.5)
6k	23 (6.25)	18 (12.5)	15 (6.25)	12 (12.5)	21 (6.25)
6l	–	22 (6.25)	20 (12.5)	11 (12.5)	18 (6.25)
6m	23 (6.25)	15 (12.5)	16 (25)	8 (25)	15 (12.5)
6n	24 (6.25)	28 (6.25)	32 (6.25)	20 (6.25)	23 (6.25)
6o	22 (6.25)	29 (6.25)	30 (6.25)	21 (6.25)	23 (6.25)
Ciprofloxacin	25 (6.25)	30 (6.25)	33 (6.25)	22 (6.25)	25 (6.25)

The representation '–' indicates that bacteria are resistant to the compounds >100 μg/ml. Diameter zone of inhibition is in millimeter. MIC values are given in brackets. MIC (μg/ml) = minimum inhibitory concentration, i.e., lowest concentration to completely inhibit bacterial growth.

(**6a–o**). Among the newly synthesized uncyclized intermediates, compounds containing 4-methyl, 4-fluoro, trichloro, 2-trifluoromethyl showed good antibacterial and antifungal activities. In case of aminotriazolothiadiazines, compounds with 4-methyl, trichloro and 2-trifluoromethyl showed good antibacterial and antifungal activities.

6. Experimental protocols

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 300 MHz or 400 MHz NMR spectrometer using TMS as an internal standard. The mass spectra were recorded on a MASPEC/FAB 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 (2:1).

*6.1. Procedure for the preparation of 4-amino-3-(2,4-dichloro-5-fluorophenyl)-5-mercapto-1,2,4-triazole (**2**)*

4-Amino-3-(2,4-dichloro-5-fluorophenyl)-5-mercapto-1,2,4-triazole (**2**) was synthesized according to the literature [18].

*6.2. Procedure for the preparation of 2-chloro-N-(substituted phenyl) acetamides (**4**)*

2-Chloro-*N*-(substituted phenyl) acetamides (**4**) were prepared according to the literature method [19].

*6.3. Procedure for the preparation of 2-{[4-amino-5-(2,4-dichloro-5-fluorophenyl)-4H-1,2,4-triazol-3-yl] thio}-N-phenyl acetamide (**5**)*

A solution of 2-chloro-*N*-(substituted phenyl) acetamides (**4**) (0.01 mol) in ethanol (20 ml) was added to a solution of triazole (**2**) (0.01 mol) in ethanol containing KOH (0.01 mol). The reaction mixture was refluxed for 1 h, cooled and then diluted with 50 ml of water. The precipitated solid was filtered, washed with water, dried and recrystallised from ethanol.

*6.4. General procedure for the preparation of 6-arylamino-3-(2,4-dichloro-5-fluorophenyl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**6**)*

A mixture of 2-{[4-amino-5-(2,4-dichloro-5-fluorophenyl)-4*H*-1,2,4-triazol-3-yl]thio}-*N*-phenyl acetamide (**5**) (0.01 mol) and 25 ml of phosphorous oxychloride was added and refluxed

Table 3
Antifungal activity data of **5 a–o** and **6 a–o**

Compound	*Candida albicans*	*Aspergillus flavus*	*Aspergillus fumigatus*	*Trichophyton mentagrophytes*	*Penicillium marneffei*
5a	18 (6.25)	22 (6.25)	20 (6.25)	18 (6.25)	23 (6.25)
5b	12 (12.5)	10 (25)	15 (12.5)	8 (25)	17 (12.5)
5c	–	–	–	–	–
5d	–	–	–	–	–
5e	19 (6.25)	21 (6.25)	19 (6.25)	17 (6.25)	24 (6.25)
5f	–	–	–	–	–
5g	–	–	–	–	–
5h	12 (12.5)	17 (6.25)	15 (12.5)	10 (25)	13 (12.5)
5i	18 (6.25)	15 (12.5)	20 (6.25)	16 (6.25)	15 (12.5)
5j	14 (12.5)	10 (25)	8 (25)	12 (6.25)	9 (25)
5k	–	–	–	–	–
5l	15 (12.5)	8 (25)	16 (12.5)	11 (12.5)	20 (6.25)
5m	11 (12.5)	23 (6.25)	15 (12.5)	17 (6.25)	13 (12.5)
5n	20 (6.25)	25 (6.25)	21 (6.25)	19 (6.25)	23 (6.25)
5o	19 (6.25)	21 (6.25)	19 (6.25)	18 (6.25)	22 (6.25)
6a	18 (6.25)	19 (6.25)	20 (6.25)	17 (6.25)	23 (6.25)
6b	16 (6.25)	20 (6.25)	18 (6.25)	11 (12.5)	15 (12.5)
6c	19 (6.25)	18 (6.25)	12 (12.5)	13 (12.5)	–
6d	12 (12.5)	10 (25)	15 (12.5)	–	17 (12.5)
6e	14 (12.5)	–	6 (25)	18 (6.25)	19 (6.25)
6f	–	–	11 (12.5)	8 (25)	12 (12.5)
6g	15 (12.5)	8 (25)	19 (6.25)	11 (12.5)	12 (12.5)
6h	18 (6.25)	–	10 (25)	12 (12.5)	10 (25)
6i	10 (25)	–	16 (12.5)	–	18 (6.25)
6j	8 (25)	15 (12.5)	9 (25)	12 (12.5)	–
6k	15 (12.5)	24 (6.25)	10 (25)	19 (6.25)	12 (12.5)
6l	–	–	–	10 (25)	16 (12.5)
6m	13 (12.5)	–	–	14 (12.5)	11 (12.5)
6n	20 (6.25)	23 (6.25)	19 (6.25)	18 (6.25)	24 (6.25)
6o	18 (6.25)	21 (6.25)	21 (6.25)	17 (6.25)	21 (6.25)
Amphotericin B	20 (6.25)	25 (6.25)	22 (6.25)	19 (6.25)	23 (6.25)

The representation '–' indicates that fungi are resistant to the compounds >100 μg/ml. Diameter zone of inhibition is in millimeter. MIC values are given in brackets. MIC (μg/ml) = minimum inhibitory concentration, i.e., lowest concentration to completely inhibit fungal growth.

for 2–3 h. Excess of $POCl_3$ was removed by reduced pressure and poured onto crushed ice and neutralized. The solid obtained was filtered, washed, dried and recrystallised from suitable solvents.

6.4.1. Compound **6b**

IR (KBr) γ (cm^{-1}): 3310 (NH), 3075 (Ar-H), 2976 (C–H), 1593 (C=N), 1089 (C–F), 821 and 735 (C–Cl); ^1H NMR ($CDCl_3$) δ: 4.01 (s, 2H, SCH_2), 7.28 (d, 2H, *p*-chloroanilino protons, $J = 8.8$ Hz), 7.54 (d, 2H, *p*-chloroanilino protons, $J = 8.8$ Hz), 7.84 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ ortho} = 9.2$ Hz), 8.09 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ meta} = 6.8$ Hz), 9.89 (s, 1H, NH proton).

6.4.2. Compound **6c**

IR (KBr) γ (cm^{-1}): 3294 (NH), 3094 (Ar-H), 1593 (C=N), 1097 (C–F), 816 and 735 (C–Cl); ^1H NMR ($CDCl_3$) δ: 3.70 (s, 3H, OCH_3), 3.97 (s, 2H, SCH_2), 6.80 (d, 2H, *p*-anisidino protons, $J = 8.8$ Hz), 7.43 (d, 2H, *p*-anisidino protons, $J = 8.8$ Hz), 7.84 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ ortho} = 9.2$ Hz), 8.08 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ meta} = 6.8$ Hz), 9.60 (s, 1H, NH protons); FABMS (*m/z*, % abundance): 423 (M^+, 50), 408 (20), 191 (8).

6.4.3. Compound **6d**

IR (KBr) γ (cm^{-1}): 3295 (NH), 3081 (Ar-H), 2928 (C–H), 1599 (C=N), 1095 (C–F) and 829 (C–Cl); ^1H NMR ($CDCl_3$) δ: 3.99 (s, 2H, SCH_2), 7.07 (m, 2H, *p*-fluoroanilino protons), 7.53 (dd, 2H, *p*-fluoroanilino protons), 7.84 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ ortho} = 9.6$ Hz), 8.08 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ meta} = 6.8$ Hz), 9.79 (s, 1H, NH proton); FABMS (*m/z*, % abundance): 411 (M^+, 10), 412 (M^++1, 100).

6.4.4. Compound **6e**

IR (KBr) γ (cm^{-1}): 3295 (NH), 3081 (Ar-H), 2928 (C–H), 1599 (C=N), 1095 (C–F) and 829 (C–Cl); ^1H NMR ($CDCl_3$) δ: 3.99 (s, 2H, SCH_2), 7.07 (m, 2H, *p*-fluoroanilino protons), 7.53 (dd, 2H, *p*-fluoroanilino protons), 7.84 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ ortho} = 9.6$ Hz), 8.08 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ meta} = 6.8$ Hz), 9.79 (s, 1H, NH proton); FABMS (*m/z*, % abundance): 411 (M^+, 10), 412 (M^++1, 100).

6.4.5. Compound **6f**

IR (KBr) γ (cm^{-1}): 3315 (NH), 3099 (Ar-H), 2937 (C–H), 1595 (C=N), 1085 (C–F), 821 and 796 (C–Cl); ^1H NMR ($CDCl_3$) δ: 4.11 (s, 2H, SCH_2), 7.22 (t, 1H, dichloroanilino

proton), 7.43 (d, 1H, dichloroanilino proton, $J = 7$ Hz), 7.67 (d, 1H, dichloroamidinophenyl proton, $J = 7.7$ Hz), 7.74 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ ortho} = 9.6$ Hz), 7.99 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ meta} = 6.8$ Hz), 9.44 (s, 1H, NH proton).

6.4.6. Compound ***6h***

IR (KBr) γ (cm^{-1}): 3299 (NH), 3097 (Ar-H), 1594 (C=N), 1083 (C–F) and 827 (C–Cl); ^{1}H NMR ($CDCl_3$) δ: 4.07 (s, 2H, SCH_2), 7.33 (t, 1H, dichloroanilino proton), 7.51 (d, 2H, dichloroanilino protons, $J = 8$ Hz), 7.60 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ ortho} = 9.7$ Hz), 7.92 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ meta} = 6.7$ Hz), 9.70 (s, 1H, NH proton).

6.4.7. Compound ***6i***

^{1}H NMR ($CDCl_3$) δ: 2.05 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 4.06 (s, 2H, SCH_2), 7.00 (m, 1H, dimethylanilino proton), 7.17 (m, 2H, dimethylanilino protons), 7.71 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ ortho} = 9.7$ Hz), 7.97 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ meta} = 6.8$ Hz), 9.11 (s, 1H, NH proton).

6.4.8. Compound ***6j***

^{1}H NMR ($CDCl_3$) δ: 2.19 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 4.01 (s, 2H, SCH_2), 6.88 (d, 1H, dimethylanilino proton, $J = 7.5$ Hz), 7.01 (s, 1H, dimethylanilino proton, $J = 8$ Hz), 7.31 (d, 1H, dimethylanilino proton, $J = 8$ Hz), 7.76 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ ortho} = 9.7$ Hz), 8.01 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ meta} = 6.7$ Hz), 8.91 (s, 1H, NH proton).

6.4.9. Compound ***6k***

^{1}H NMR ($CDCl_3$) δ: 2.16 (s, 6H, CH_3), 4.05 (s, 2H, SCH_2), 7.02 (s, 3H, dimethylanilino protons), 7.61 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ ortho} = 9.3$ Hz), 7.90 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ meta} = 6.8$ Hz), 8.96 (s, 1H, NH proton).

6.4.10. Compound ***6l***

IR (KBr) γ (cm^{-1}): 3323 (NH), 3099 (Ar-H), 1605 (C=N), 1093 (C–F) and 818 (C–Cl); ^{1}H NMR ($CDCl_3$) δ: 4.03 (s, 2H, SCH_2), 7.24 (m, 1H, chlorofluoroanilino proton), 7.35 (t, 1H, chlorofluoroanilino proton), 7.85 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ ortho} = 9.3$ Hz), 7.97 (m, 1H, chlorofluoroamidinophenyl proton), 8.11 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ meta} = 6.6$ Hz), 10 (s, 1H, NH proton).

6.4.11. Compound ***6m***

IR (KBr) γ (cm^{-1}): 3309 (NH), 3089 (Ar-H), 1595 (C=N), 1091 (C–F), 817 and 738 (C–Cl); ^{1}H NMR ($CDCl_3$) δ: 2.07 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 3.97 (s, 2H, SCH_2), 6.81 (s, 2H, trimethylanilino protons), 7.62 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ ortho} = 9.5$ Hz), 7.90 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ meta} = 6.3$ Hz), 8.86 (s, 1H, NH proton).

6.4.12. Compound ***6o***

IR (KBr) γ (cm^{-1}): 3312 (NH), 3099 (Ar-H), 1599 (C=N), 1085 (C–F) and 823 (C–Cl); ^{1}H NMR ($CDCl_3$) δ: 4.07 (s, 2H, SCH_2), 7.55 (m, 5H, *o*-trifluoromethylanilino and dichlorofluorophenyl protons), 7.96 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ meta} = 6.8$ Hz), 9.36 (s, 1H, NH proton).

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