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Short communication

Synthesis and antimicrobial activities of some novel 1,2,4-triazolo [3,4-*b*]-1,3,4-thiadiazoles and 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines carrying thioalkyl and sulphonyl phenoxy moieties

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Abstract

Thirty one new 6-aryl-3-{(4-substituted phenoxy) methyl}-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles (**6a–s**) and 6-aryl-3-{(4-substituted phenoxy methyl}-7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines (**7a–l**) have been synthesized from 4-thioalkyl phenols (**1a–b**) through a multi-step reaction sequence. Compounds **1a–b** reacted with ethyl chloroacetate in presence of acetone and potassium carbonate to give ethyl [4-(thioalkyl) phenoxy] acetates (**2a–b**). Further, **2a** was oxidized to [4-(methyl sulphonyl) phenoxy] acetate (**2c**) using hydrogen peroxide in acetic acid. Reactions of (**2a–c**) with hydrazine hydrate in alcoholic medium furnished 2-[4-thiosubstituted phenoxy] acetohydrazides (**3a–b**) and 2-[4-methyl sulphonyl phenoxy] acetohydrazide (**3c**) which on treatment with carbon disulphide and methanolic potassium hydroxide yielded corresponding potassium dithiocarbazates (**4a–c**). They were then converted to 4-amino-5-{(4-thioalkyl phenoxy) methyl}-4*H*-1,2,4-triazole-3-thiols (**5a–b**) and 4-amino-5-{(4-methyl sulphonyl phenoxy) methyl}-4*H*-1,2,4-triazole-3-thiol (**5c**) by refluxing them with aqueous hydrazine hydrate. The title compounds **6a–s** were prepared by condensing **5a–c** with various aromatic carboxylic acids in presence of phosphorus oxychloride. The intermediates **5a–c**, on condensation with various substituted phenacyl bromides afforded a series of title compounds (**7a–l**). The structures of new compounds **2a–7l** were established on the basis of their elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. All the title compounds were subjected to *in vitro* antibacterial testing against four pathogenic strains and antifungal screening against three fungi. Preliminary results indicate that some of them exhibited promising activities and they deserve more consideration as potential antimicrobials.

Keywords: 6-Aryl-3-[(4-thio alkyl phenoxy) methyl]-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles; 6-Aryl-3-[(4-methyl sulphonyl phenoxy) methyl]-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles; 6-Aryl-3-[(4-thioalkyl phenoxy) methyl]-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines; 6-Aryl-3-[(4-methyl sulphonyl phenoxy) methyl]-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines; Antibacterial and antifungal screening

1. Introduction

Various 1,2,4-triazole derivatives have been reported to possess diverse types of biological properties such as antibacterial [1], antifungal [2,3], anti-inflammatory [4] antihypertensive [5], antiviral [6], antileishmanial [7] and anti-migraine activities [8]. A thorough literature survey reveals that presence of 4-substituted thio phenoxy and 4-methyl sulphonyl phenoxy moieties is an important structural feature of wide variety of synthetic drugs [9–11]. It has been established that introduction of 4-methyl mercapto phenyl and 4-methyl sulphonyl phenyl groups to different heterocycles has yielded many biologically active compounds endowed with wide

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spectrum of pharmacological and antimicrobial activities [12,13]. It is well known that the N-bridged heterocycles derived from 1,2,4-triazoles find applications in the field of medicine, agriculture and industry. A large number of triazolothiadiazoles and triazolothiadiazines have been reported to possess CNS depressant, antibacterial, antifungal, antitumour, anti-inflammatory, herbicidal, pesticidal and insecticidal properties [14–17]. Therefore, it was envisaged that chemical entities with both 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles/1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines and 4-sulphur substituted phenyl moieties, containing aryl ether linkage would result in compounds of interesting biological activities. In continuation of our research program on the synthesis of novel heterocyclic compounds exhibiting biological activity, it was thought to be interesting to synthesize compounds containing the features, namely, 1,2,4-triazole moiety fused with the 1,3,4-thiadiazole/1,3,4-thiadiazine rings, in addition to have a sulphur substituted phenoxy group and to study their antimicrobial activities. The present study describes the synthesis of hither to unreported 6-aryl-3-{(4-thiosubstituted/methyl sulphonyl phenoxy)methyl}-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles (**6a–s**) and 6-aryl-3-{(4-thiosubstituted/methyl sulphonyl phenoxy) methyl}-7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines (**7a–l**) and evaluation of their antibacterial and antifungal activities.

2. Chemistry

The reaction sequences employed for synthesis of title compounds are shown in Fig. 1. The key intermediate, ethyl [4-(thioalkyl) phenoxy] acetates (**2a–b**) was prepared by treating ethyl chloroacetate with 4-(thioalkyl) phenols (**1a–b**) in boiling dry acetone in presence of potassium carbonate. The compound, ethyl [4-(methyl sulphonyl phenoxy] acetate (**2c**) was obtained by the oxidation of ethyl [4-(methyl thio) phenoxy] acetate (**2a**) with 30% hydrogen peroxide in acetic acid. These esters (**2a–c**) were conveniently converted to 2-[4-(thioalkyl/methyl sulphonyl phenoxy] acetohydrazides (**3a–c**) by refluxing it with hydrazine hydrate in methanol. The compounds **3a–c** on reaction with carbon disulphide in methanolic potassium hydroxide yielded corresponding potassium dithiocarbazates (**4a–c**) in good yield. The required 4-amino-5-{[thioalkyl/methyl sulphonyl phenoxy) methyl}-4*H*-1,2,4-triazole-3-thiols (**5a–c**) were synthesized by refluxing **4a–c** with aqueous hydrazine hydrate. Condensation of **5a–c** with various aromatic carboxylic acids in presence of boiling phosphorous oxychloride yielded 6-aryl-3-{(4-thioalkyl/methyl sulphonyl phenoxy) methyl}-1,2,4-triazolo [3,4-*b*]-1,3,4-thiadiazoles (**6a–s**) and with various phenacyl bromides in refluxing ethanol gave 6-aryl-3-{(4-thioalkyl/methyl sulphonyl phenoxy) methyl}-7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines (**7a–l**) in good yield.

The structural assignments to new compounds were based on their elemental analysis and spectral (IR, ^{1}H NMR, ^{13}C NMR and mass) data. The characterization data of all the new compounds are summarized in Table 1.

The formation of 2-[4-(methyl thio) phenoxy] acetohydrazide (**3a**) from ethyl [4-(thioalkyl) phenoxy] acetate (**2a**) was confirmed by its IR, ^{1}H NMR and elemental analyses. IR spectrum showed absorption band at 3310, 3224, 3045, 1680, 1544 cm^{-1} due to $-NH_2$, $-NH$, $-SCH_3$, $>C=O$, and $>C=C<$ groups, respectively, while ^{1}H NMR showed sharp singlets at δ 2.4 and 4.46, which correspond to $-SCH_3$ and CH_2 protons. It appeared as two doublets at δ 6.94 and 7.24 indicating the presence of four aromatic protons. The potassium dithiocarbazate (**4a**) was directly used for the next step without characterization. Further, the cyclization of **4a** to 4-amino-5-{(methyl thio) methyl}-4*H*-1,2,4-triazole-3-thiol (**5a**) was confirmed by its IR spectrum which showed absorption bands at 3313, 2667 and 1617 cm^{-1} due to $-NH_2$, $-SH$, and $>C=N$, respectively. Its ^{1}H NMR spectrum showed two singlets at δ 2.4 and 5.1 due to $-SCH_3$ and $-CH_2$ protons and two doublets at δ 6.94 and 7.24 due to four aromatic protons. It appeared as a sharp singlet at δ 13 for $-SH$ group. The disappearance of characteristic peak due to $>C=O$ group of **4a** is clearly indicated the smooth cyclization.

The structural elucidation of title compound **6a** is based on its IR, ^{1}H NMR, ^{13}C NMR and mass spectral studies. IR spectrum of **6a** showed absorption bands at 3061, 2990, 1593 and 689 cm^{-1} indicating the presence of $-CH_3$, $-CH_2$, phenyl and $C=S$ groups, respectively. In its ^{1}H NMR spectrum, peaks due to $-SCH_3$ and CH_2 protons appeared at δ 2.4 and 5.6, respectively. Peaks due to two phenyl groups appeared at δ 7, 7.2, 8 as doublets and 7.6 as multiplet. Further, LC mass spectrum showed molecular ion peak at *m*/*z* 354.9 (100%) which is in agreement with the molecular formula $C_{17}H_{14}N_4OS_2$. The peaks at *m*/*z* 215, 150 and 84 were due to the fragmentation of molecular ion. ^{13}C NMR spectrum of **6h** showed signals at δ 29.36 and 14.52 due to $-S-CH_2CH_3$ group and peaks at δ 59.76, 115.69, 127.25, 128.31, 129.16, 129.44, 132.6, 132.8, 144.07, 156.0, and 167.39 are due to OCH_2, C_2H and C_6H of phenoxy moiety, C_4H of 6-phenyl moiety, C_4 of phenoxy group, C_3H and C_5H of 6-phenyl group, C_1 of 6-phenyl group, C_2H and C_6H of 6-phenyl moiety, C_3H and C_5H of phenoxy moiety, C_3 and C_5 of triazole, C_1 of phenoxy moiety, and C_7 of thiadiazole group, respectively. The peaks due to quaternary carbon atoms of the structure disappeared on DEPT experimentation. The absence of characteristic absorption peaks due to $-NH_2$ and $-SH$ groups of **5a** clearly confirmed the formation of **6a**.

The build up of N-bridged condensed heterocycle, **7a** from **5a** is evidenced by its IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. IR spectrum of **7a** indicates the presence of $-NH_2$, $-SCH_3$, $>C=O$, $>C=N$, phenyl groups due to absorption bands at 3380, 3024, 1699, 1599, and 1462 cm^{-1}, respectively. Peaks observed at δ 2.4, 4.4, 5.4, 8, 8.2 and 13.46 as singlets in its ^{1}H NMR spectrum showed the presence of $-SCH_3$, $-CH_2$ (ring), $-OCH_2$, C_2H of phenyl ring, $-CONH_2$ and OH groups, respectively. Also, three doublets at δ 7, 7.3, and 7.4 are due to aromatic protons. Further, the peak at 8.2 disappeared on D_2O exchange. ^{13}C NMR spectrum of **7e** showed signals at δ 28.66 and 13.97 due to $-SCH_2CH_3$ while peaks at δ 22.31, 58.94, 113.52, 115.27,

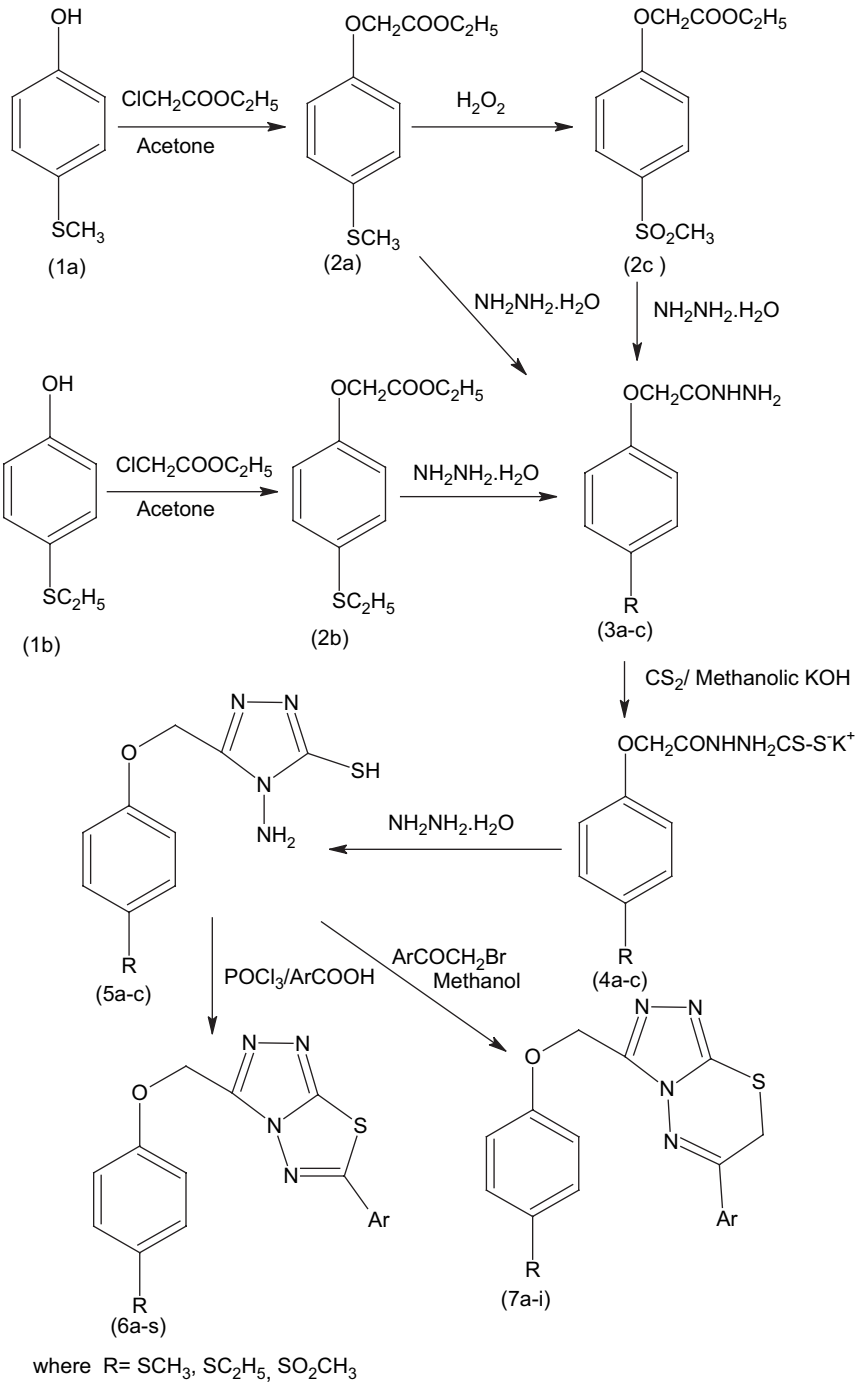

Fig. 1.

118.66, 122.67, 127.51, 128.33, 131.82, 132.11, 153.28, 154.88, 156.56, 164.73 and 171.43 are due to C_7H of thiadiazine, OCH_2, C_8 of thiadiazine, C_2H and C_6H of phenoxy group, C_3H of 6-phenyl moiety, C_5 of 6-phenyl moiety, C_4 of phenoxy moiety, C_4H of 6-phenyl moiety, C_6H of 6-phenyl moiety, C_3H and C_5H of phenoxy moiety, C_3 and C_5 of triazole, C_2 of 6-phenyl moiety, C_1 of phenoxy moiety, C_1 of 6-phenyl moiety, and carbon of amide in 6-phenyl group, respectively. The peaks due to quaternary carbon atoms disappeared on DEPT experimentation. Further, LCMS of **7a** showed the base peak at *m/z* 427.9 which is in agreement with their molecular formula, $C_{19}H_{17}N_5O_3S_2$.

3. Biological activities

3.1. Antibacterial studies

The newly synthesized compounds were screened for their antibacterial activity against *Escherichia coli* (ATTC-25922), *Staphylococcus aureus* (ATTC-25923), *Pseudomonas*

Table 1
Characterization data of compounds **6a–s** and **7a–l**

Compound	Ar	R	Mol. formula	Mol. mass	MP (°C)	Yield (%)
6a	C_6H_5	SCH_3	$C_{17}H_{14}N_4OS_2$	354	140	65
6b	2-ClC_6H_4	SCH_3	$C_{17}H_{13}ClN_4OS_2$	389	110	63
6c	4-$CH_3C_6H_4$	SCH_3	$C_{18}H_{16}N_4OS_2$	368	142	60
6d	4-$OCH_3C_6H_4$	SCH_3	$C_{18}H_{16}N_4O_2S_2$	384	110	64
6e	4-$NH_2C_6H_4$	SCH_3	$C_{17}H_{15}N_5OS_2$	369	120	66
6f	2,3-$(Cl)_2C_6H_4$	SCH_3	$C_{17}H_{12}Cl_2N_4OS_2$	371.5	106	63
6g	$C_6H_5CH_2$	SCH_3	$C_{18}H_{16}N_4O_2S_2$	368	112	68
6h	C_6H_5	SC_2H_5	$C_{18}H_{16}N_4OS_2$	368	129	66
6i	2-ClC_6H_4	SC_2H_5	$C_{18}H_{15}ClN_4OS_2$	402	102	67
6j	4-$CH_3C_6H_4$	SC_2H_5	$C_{19}H_{18}N_4OS_2$	382	105	63
6k	4-CH_3O–C_6H_4	SC_2H_5	$C_{19}H_{18}N_4O_2S_2$	398	98	64
6l	2-$NH_2C_6H_4$	SC_2H_5	$C_{18}H_{17}N_5OS_2$	383	120	66
6m	2,3-$(Cl)_2C_6H_4$	SC_2H_5	$C_{18}H_{14}Cl_2N_4OS_2$	437	118	63
6n	2-OHC_6H_4	SC_2H_5	$C_{18}H_{16}N_4O_2S_2$	384	185	67
6o	C_6H_5	SO_2CH_3	$C_{17}H_{14}N_4O_3S_2$	386	220	65
6p	2-ClC_6H_4	SO_2CH_3	$C_{17}H_{13}ClN_4O_3S_2$	420	200	65
6q	3-ClC_6H_4	SO_2CH_3	$C_{17}H_{13}ClN_4O_3S_2$	420	196	65
6r	$CH_2C_6H_5$	SO_2CH_3	$C_{18}H_{16}N_4O_3S_2$	400	170	65
6s	2,3-Dichloro-C_6H_4	SO_2CH_3	$C_{17}H_{12}Cl_2N_4O_3S_2$	400	110	65
7a	2-OH-benzamide	SCH_3	$C_{19}H_{17}N_5O_3S_2$	427	180	68
7b	Biphenyl	SCH_3	$C_{24}H_{20}N_4OS_2$	444	100	69
7c	2,4-Dichloro-C_6H_3	SCH_3	$C_{18}H_{14}Cl_2N_4OS_2$	437	110	69
7d	4-ClC_6H_4	SCH_3	$C_{18}H_{15}Cl_2N_4OS_2$	402	190	69
7e	2-OH-benzamide	SC_2H_5	$C_{20}H_{19}N_5O_3S_2$	441	175	68
7f	Biphenyl	SC_2H_5	$C_{25}H_{22}N_4OS_2$	458	136	69
7g	2,4-Dichloro-C_6H_3	SC_2H_5	$C_{19}H_{16}Cl_2N_4OS_2$	451	104	69
7h	4-ClC_6H_4	SC_2H_5	$C_{19}H_{17}ClN_4OS_2$	416	116	69
7i	2-OH-benzamide	SO_2CH_3	$C_{19}H_{17}N_5O_5S_2$	459	218	68
7j	Biphenyl	SO_2CH_3	$C_{24}H_{20}N_4O_3S_2$	476	120	69
7k	2,4-Dichloro-C_6H_3	SO_2CH_3	$C_{18}H_{14}Cl_2N_4O_3S_2$	469	110	69
7l	4-ClC_6H_4	SO_2CH_3	$C_{18}H_{15}ClN_4O_3S_2$	434	180	69

Note: Microanalysis data is summarized in Table 4 and included in supplementary material.

aeruginosa (ATCC-27853) and *Klebsiella pneumoniae* (recultured) bacterial stains by serial plate dilution method [18,19]. Serial dilutions of the drug in Muller–Hinton broth were taken in tubes and their pH was adjusted to 5.0 using phosphate buffer. A standardized suspension of the test bacterium was inoculated and incubated for 16–18 h at 37 °C. The minimum inhibitory concentration (MIC) was noted by seeing the lowest concentration of the drug at which there was no visible growth.

A number of antimicrobial discs are placed on the agar for the sole purpose of producing zones of inhibition in the bacterial lawn. Twenty milliliters of agar media was poured into each Petri dish. Excess of suspension was decanted and plates were dried by placing in an incubator at 37 °C for an hour. Using a punch, wells were made on these seeded agar plates and minimum inhibitory concentrations of the test compounds in dimethylsulfoxide (DMSO) were added into each labeled well. A control was also prepared for the plates in the same way using solvent DMSO. The Petri dishes were prepared in triplicate and maintained at 37 °C for 3–4 days. Antibacterial activity was determined by measuring the diameter of inhibition zone. Activity of each compound was compared with ciprofloxacin as standard [22,23]. Zone of inhibition was determined for **6a–7l** and the results are summarized in Table 2.

3.2. Antifungal studies

Newly prepared compounds were screened for their antifungal activity against *Aspergilus flavus* (NCIM No.524), *Aspergilus fumigatus* (NCIM No. 902), *Penicillium marneffei* (recultured) and *Trichophyton mentagrophytes* (recultured) in DMSO by serial plate dilution method [20,21]. Sabourands agar media was prepared by dissolving peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled water (100 ml) and adjusting the pH to 5.7. Normal saline was used to make a suspension of spore of fungal strains 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 into each Petri dish. Excess of suspension was decanted and plates were dried by placing in incubator at 37 °C for 1 h. Using a punch, wells were made on these seeded agar plates minimum inhibitory concentrations of the test compounds in DMSO were added into each labeled well. A control was also prepared for the plates in the same way using solvent DMSO. The Petri dishes were prepared in triplicate and maintained at 37 °C for 3–4 days. Antifungal activity was determined by measuring the diameter of inhibition zone. Activity of each compound was compared with cyclopiroxolamine as standard. Zones of inhibition were determined for **6a–7l** and the results are summarized in Table 3.

Table 2
Antibacterial activity of title compounds

Compound	MIC in μg/ml and zone of inhibition in mm			
	E. coli	*K. pneumoniae*	*P. aeruginosa*	*S. aureus*
6a	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
6b	25 (<10)	25 (<10)	25 (<10)	25 (<10)
6c	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
6d	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
6e	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
6f	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
6g	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
6h	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
6i	25 (<10)	25 (<10)	25 (<10)	25 (<10)
6j	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
6k	25 (<10)	25 (<10)	25 (<10)	25 (<10)
6l	25 (<10)	25 (<10)	25 (<10)	25 (<10)
6m	25 (<10)	25 (<10)	25 (<10)	25 (<10)
6n	25 (<10)	25 (<10)	25 (<10)	25 (<10)
6o	12.5 (11–15)	12.5 (11–15)	12.5 (11–15)	12.5 (11–15)
6p	12.5 (11–15)	12.5 (11–15)	12.5 (11–15)	12.5 (11–15)
6q	12.5 (11–15)	12.5 (11–15)	12.5 (11–15)	12.5 (11–15)
6r	12.5 (11–15)	12.5 (11–15)	12.5 (11–15)	12.5 (11–15)
6s	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
7a	25 (<10)	25 (<10)	25 (<10)	25 (<10)
7b	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
7c	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
7d	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
7e	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
7f	25 (<10)	25 (<10)	25 (<10)	25 (<10)
7g	25 (<10)	25 (<10)	25 (<10)	25 (<10)
7h	25 (<10)	25 (<10)	25 (<10)	25 (<10)
7i	12.5 (11–15)	12.5 (11–15)	12.5 (11–15)	12.5 (11–15)
7j	12.5 (11–15)	12.5 (11–15)	12.5 (11–15)	12.5 (11–15)
7k	12.5 (11–15)	12.5 (11–15)	12.5 (11–15)	12.5 (11–15)
7l	25 (<10)	25 (<10)	25 (<10)	25 (<10)
Standard (ciprofloxacin)	6.25 (30–40)	6.25 (23–27)	6.25 (25–33)	1.56 (22–30)

Note: The MIC values were evaluated at concentration range, 1.56–25 μg/ml. The figures in the table show the MIC values in μg/ml and the corresponding zone of inhibition in mm.

4. Results and discussion

The investigation of antibacterial and antifungal screening data revealed that all the tested compounds **6a–s** and **7a–l** showed moderate to good inhibition at 1.56–25 μg/ml in DMSO. The compounds **6a**, **6c**, **6d**, **6e**, **6f**, **6g**, **6h**, **6j**, **6s**, and **7b–e** showed comparatively good activity against all the bacterial strains. The good activity is attributed to the presence of pharmacologically active $-CH_3$, OCH_3, NH_2, and 2,3-dichloro groups attached to phenyl group at position 6 of the thiadiazole ring. Introduction of aryl moiety carrying phenyl, 2,3-dichloro, 4-chloro, and 2-hydoxy-4-amide groups at position 6 of thiadiazine caused enhanced activity. The presence of $S-CH_3$ and $S-C_2H_5$ groups at position 4 of phenoxy group caused good antibacterial activity while methyl sulphonyl group caused decrease in activity against most of the strains. The compounds **6o**, **6p**, **6q**, **6r**, and **7i–k**, exhibited moderate activity compared to that of standard against all the bacterial strains. This may be due to presence of methyl sulphonyl group in position 4 of phenoxy moiety.

The compounds **6a**, **6c**, **6d**, **6e**, **6f**, **6g**, **6h**, **6j**, **6s**, and **7b–e** showed comparatively good activity against all the fungal strains. The structure of these compounds contains biologically active $-CH_3$, OCH_3, NH_2, 2,3-dichloro groups attached to phenyl group in position 6 of the thiadiazole ring and aryl moiety carrying phenyl, 2,4-dichloro, 4-chloro, and 2-hydoxy-4-amide groups, in position 6 of thiadiazine. The compounds **6o**, **6p**, **6q**, **6r**, and **7i–k** exhibited moderate activity compared to that of standard against *T. mentagrophytes*, *A. flavus*, and *A. fumigatus*. Results of antifungal screening showed that the presence of $S-CH_3$ and $S-C_2H_5$ groups at position 4 of phenoxy group caused increased activity. It has been observed that the thiadiazole derivatives are found to be more active than thiadiazines.

5. Conclusion

The research study reports the successful synthesis and antimicrobial activity of new 1,2,4-triazolothiadiazoles and 1,2,4-trazolothiadiazines carrying 4-methyl/ethyl thio and methyl sulphonyl phenoxy moieties at position 3. The antimicrobial activity study revealed that all the compounds tested showed moderate to good antibacterial and antifungal activities against pathogenic strains. Structure–biological activity

Table 3
Antifungal activity of title compounds

Compound	MIC in μg/ml and zone of inhibition in mm			
	P. marneffei	*T. mentagrophytes*	*A. flavus*	*A. fumigatus*
6a	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
6b	25 (<10)	25 (<10)	25 (<10)	25 (<10)
6c	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
6d	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
6e	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
6f	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
6g	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
6h	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
6i	25 (<10)	25 (<10)	25 (<10)	25 (<10)
6j	6.25 (16–20)	25 (<5)	25 (<5)	25 (<5)
6k	25 (<10)	25 (<10)	25 (<10)	25 (<10)
6l	25 (<10)	25 (<10)	25 (<10)	25 (<10)
6m	25 (<10)	25 (<10)	25 (<10)	25 (<10)
6n	25 (<10)	25 (<10)	25 (<10)	25 (<10)
6o	25 (<10)	12.5 (11–15)	12.5 (11–15)	12.5 (11–15)
6p	25 (<10)	12.5 (11–15)	12.5 (11–15)	12.5 (11–15)
6q	25 (<10)	12.5 (11–15)	12.5 (11–15)	12.5 (11–15)
6r	25 (<10)	12.5 (11–15)	12.5 (11–15)	12.5 (11–15)
6s	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
7a	25 (<10)	25 (<10)	25 (<10)	25 (<10)
7b	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
7c	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
7d	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
7e	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
7f	25 (<10)	25 (<10)	25 (<10)	25 (<10)
7g	25 (<10)	25 (<10)	25 (<10)	25 (<10)
7h	25 (<10)	25 (<10)	25 (<10)	25 (<10)
7i	25 (<10)	12.5 (11–15)	12.5 (11–15)	12.5 (11–15)
7j	25 (<10)	12.5 (11–15)	12.5 (11–15)	12.5 (11–15)
7k	25 (<10)	12.5 (11–15)	12.5 (11–15)	12.5 (11–15)
7l	25 (<10)	25 (<10)	25 (<10)	25 (<10)
Standard (cyclo-piroxolamine)	6.25 (20–27)	3.125 (27–33)	3.125 (25–30)	6.25 (25–30)

Note: The MIC values were evaluated at concentration range, 1.56–25 μg/ml. The figures in the table show the MIC values in μg/ml and the corresponding zone of inhibition in mm.

relationship of title compounds showed that the presence 4-thioalkyl phenoxy groups at position 3 and biologically active groups like $-CH_3$, OCH_3, NH_2, and 2,3-dichloro groups at aryl moiety attached to position 6 of title compounds are responsible for increased antimicrobial activity in newly synthesized title compounds.

6. Experimental protocols

Melting points were determined in open capillaries and uncorrected [melting point apparatus: SERWELL Instruments Inc., India]. Purity of the compounds was checked by thin layer chromatography (TLC) on a silica coated aluminum sheet (silica gel 60 F_{254}) using chloroform and methanol (9:1, v/v). IR spectra were recorded on NICOLET AVATAR 330-FTIR spectrometer. ^1H and ^{13}C NMR spectra recorded on a Varian 300 MHz NMR spectrometer using TMS as an internal standard. Chemical shifts are reported in ppm (δ) and signals are described as singlet (s), doublet (d), triplet (t), quartet (q), broad (br), and multiplet (m). The FAB mass spectra were recorded on a JEOL SX 102/DA-6000 spectrophotometer/Data system using Argon/Xenon (6 KV, 10 mA) FAB gas, at 70 eV. Elemental analysis was carried out using Flash EA 1112 Series, CHNSO Analyzer (Thermo). Solvents and reagents were purchased from the commercial venders in the appropriate grade and were used without purification.

*6.1. General procedure for the preparation of ethyl [4-(thioalkyl) phenoxy] acetates (**2a–b**)*

4-Thioalkyl phenols, **1a–b** (1 mmol) were dissolved in 5 ml of super dry acetone and mixed with 1.2 mmol of anhydrous potassium carbonate. This was treated with 1.2 mmol of ethyl chloroacetate slowly with shaking for 10 min and the mixture was heated under reflux for 3 h. When the reaction was complete (monitored by TLC), the reaction mixture was filtered and the filtrate was distilled under reduced pressure. The fraction collected at 140–144 °C, **2a–c** was directly used for the next step without further purification.

*6.2. Procedure for the preparation of ethyl [4-methyl sulphonyl phenoxy] acetate (**2c**)*

The compound **2a** (1 mmol), dissolved in 10 ml of glacial acetic acid was added slowly with 2 mmol of 30% hydrogen peroxide over a period of 1 h, below 70 °C. It was further kept at 70–75 °C with stirring for 3 h, cooled to ambient temperature and finally quenched in 20 ml ice cold water. The compound **2c** was extracted with ethyl acetate and after giving water wash, the solvent was removed by distillation; the liquid left over was further purified by distillation under reduced pressure. The fraction collected at 160–164 °C at 10 mm pressure was used directly for the next step.

*6.3. General procedure for the preparation of 2-[4-(thioalkyl) phenoxy] acetohydrazides (**3a–b**) and 2-[4-methyl sulphonyl phenoxy] acetohydrazide (**3c**)*

A mixture of [4-(thioalkyl)/methyl sulphonyl phenoxy] acetate (1 mmol), and hydrazine hydrate (2 mmol) in 10 ml of methanol was heated under reflux for 5–6 h. The reaction mixture was left overnight at room temperature and the solid separated was collected by filtration. It was washed with methanol, dried and recrystallized from methanol.

*6.3.1. 2-[4-(Methyl thio) phenoxy] acetohydrazide (**3a**)*

Compound **3a** was obtained as white solid in 90% yield, mp 128–129 °C, IR: 3310 cm^{-1} (NH_2), 3224 cm^{-1} (NH), 3045 cm^{-1} (SCH_3), 1680 cm^{-1} (>C=O), 1544 cm^{-1} (C=C), 814 cm^{-1} (SCH_3); ^1H NMR (DMSO-d_6): δ 2.4 (s, 3H, SCH_3), δ 4.46 (s, 2H, CH_2), δ 6.94 (d, 2H, C_3, C_5-H of 4-methyl thio phenoxy moiety $J = 8.5$ Hz), δ 7.24 (d, 2H, C_2, C_6-H of 4-ethylthio phenoxy moiety $J = 8.5$ Hz); Anal. Calculated for $C_9H_{12}N_2O_2S$: C, 50.92; H, 5.7; N, 13.2; found: C, 50.8; H, 5.9; N, 13.1.

*6.3.2. 2-[4-(Ethyl thio) phenoxy] acetohydrazide (**3b**)*

Compound **3b** was obtained as white solid in 92% yield, mp 126 °C (methanol), IR: 3310 cm^{-1} (NH_2), 3224 cm^{-1} (NH), 3041 cm^{-1} (SCH_3), 1680 cm^{-1} (C=O), 1547 cm^{-1} (C = C), 813 cm^{-1} (SCH_3); Anal. Calculated for $C_{10}H_{14}N_2O_2S$: C, 53.08; H, 6.24; N, 12.38; found: C, 53.12; H, 6.3; N, 12.45.

*6.3.3. 2-[4-Methyl sulphonyl phenoxy] acetohydrazide (**3c**)*

Compound **3c** was obtained as white solid in 85% yield, mp 190 °C, IR: 3315 cm^{-1} (NH_2), 3276 cm^{-1} (NH), 3101 cm^{-1} (SCH_3), 1689 cm^{-1} (C=O), 1615 cm^{-1} (C=C), 1496 cm^{-1} (C=C); Anal. Calculated for $C_9H_{12}N_2O_4S$: C, 44.25; H, 4.95; N, 11.47; found: C, 44.28; H, 4.99; N, 11.45.

*6.4. General procedure for the preparation of 4-amino-5-{(methyl thio) methyl}-4H-1,2,4-triazole-3-thiols (**5a–c**)*

[4-(Thioalkyl/methyl sulphonyl) phenoxy] acetohydrazides (**3a–c**) (1 mmol) was treated with a solution of potassium hydroxide (1.5 mmol) dissolved in methanol (10 ml) at 0–5 °C under stirring. Then 1.5 mmol of carbon disulfide was added slowly and the reaction mixture was stirred overnight at room temperature. The solid product of potassium dithiocarbazates (**4a–c**), separated were filtered, washed with chilled methanol and finally dried. It was directly used for next step without purification.

The above potassium dithiocarbazates (**4a–c**) were mixed with a mixture of water (8 ml) and hydrazine hydrate (2 mmol) and was refluxed for 4–5 h. During progress of the reaction, the reaction mixture turned to green with evolution of hydrogen sulphide and finally it became homogeneous. It was then diluted with little cold water and treated with concentrated hydrochloric acid. The white precipitate was filtered, washed with cold water and recrystallized from aqueous methanol.

*6.4.1. 4-Amino-5-{(methyl thio) methyl}-4H-1,2,4-triazole-3-thiol (**5a**)*

Compound **5a** was obtained as white solid in 85% yield, mp 200–201 °C (methanol), IR: 3313 cm^{-1} (NH_2), 2667 cm^{-1} (SH), 1617 cm^{-1} (C=N), 964 cm^{-1} (N–C=S); ^1H NMR (DMSO-d_6): δ 2.4 (s, 3H, SCH_3), δ 5.1 (s, 2H, CH_2), δ 5.63 (s 2H, NH_2), δ 6.94 (d, 2H, C_3, C_5-H of phenoxy moiety), δ 7.24 (d, 2H, C_2, C_6-H of phenoxy moiety), δ 13 (s, 1H, SH); Anal. Calculated for $C_{10}H_{12}N_4OS_2$: C, 44.76; H, 4.51; N, 20.88; found: C, 44.8; H, 4.55; N, 20.9.

*6.4.2. 4-Amino-5-{(ethyl thio) methyl}-4H-1,2,4-triazole-3-thiol (**5b**)*

Compound **5b** was obtained as white solid in 80% yield, mp 198–200 °C (methanol), IR: 3312 cm^{-1} (NH_2), 2667 cm^{-1} (SH), 1617 cm^{-1} (C=N), 962 cm^{-1} (N–C=S); Anal. Calculated for $C_{11}H_{14}N_4OS_2$: C, 46.79; H, 5.0; N, 19.84; found: C, 46.82; H, 5.1; N, 19.9.

*6.4.3. 4-Amino-5-{(methyl sulphonyl) methyl}-4H-1,2,4-triazole-3-thiol (**5c**)*

Compound **5c** was obtained as white solid in 72% yield, mp 218–219 °C (methanol), IR: 3310 cm^{-1} (NH_2), 2667 cm^{-1} (SH), 1617 cm^{-1} (C=N), 962 cm^{-1} (N–C=S); Anal. Calculated for $C_{10}H_{12}N_4O_3S_2$: C, 39.99; H, 4.03; N, 18.65; found: C, 39.96; H, 4.05; N, 18.71.

*6.5. General procedure for the preparation of 3-{[4-thioalkyl/methyl sulphonyl phenoxy] methyl}-6-aryl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles (**6a–s**)*

A mixture 4-amino-5-{thio alkyl/methyl sulphonyl phenoxy) methyl}-4*H*-1,2,4-triazole-3-thiols (**5a–c**) (1 mmol) and (un)substituted benzoic acid (1.1 mmol) in $POCl_3$ (5 ml) was refluxed for 6–7 h. The reaction mixture was slowly quenched into crushed ice with stirring and neutralized it with solid sodium bicarbonate. The solid which separated after standing overnight was filtered, washed with cold water, dried, and recrystallized from appropriate solvent to afford the title compounds. Characterization data of compounds **6a–s** are summarized in Table 1.

*6.5.1. 3-{[4-Methyl thio phenoxy] methyl}-6-phenyl-1,2, 4-triazolo[3,4-b]-1,3,4-thiadiazole (**6a**)*

IR: 3061 cm^{-1}, 2990 cm^{-1} (CH_3), 1593 cm^{-1}, 1492 cm^{-1}, 1466 cm^{-1} (aromatic skeleton), 1276 cm^{-1} (N–N=C), 689 cm^{-1} (C–S–C); ^{1}H NMR (DMSO-d_6): δ 2.4 (s, 3H, SCH_3), δ 5.6 (s, 2H, CH_2), δ 7 (d, 2H, C_3, C_5-H of 4-methyl thio phenoxy moiety $J = 8.72$ Hz), δ 7.2 (d, 2H, C_2, C_6-H of 4-methyl thio phenoxy moiety $J = 8.82$ Hz), δ 7.6 (m, 3H, C_3, C_4, C_5-H of 6-phenyl moiety), δ 8 (d, 2H, C_2, C_6-H of 6-phenyl moiety $J = 6.93$ Hz); LCMS: *m/z* 354.9 (M^+, 100%), 215 (30%), 150 (10%), 84 (10%).

*6.5.2. 3-{[4-Methyl thio phenoxy] methyl}-6-(4-methyl phenyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (**6c**)*

IR: 3061, 2990 cm^{-1} (S–CH_3), 1593 cm^{-1}, 1492 cm^{-1}, 1466 cm^{-1} (aromatic skeleton), 1276 cm^{-1} (N–N=C), 689 cm^{-1} (C–S–C); ^{1}H NMR ($CDCl_3$): δ 2.4 (s, CH_3), δ 2.55 (s, 3H, SCH_3), δ 5.59 (s, 2H, CH_2), δ 7 (d, 2H, C_3, C_5-H of phenoxy moiety $J = 8.72$ Hz), δ 7.29 (d, 2H, C_2, C_6-H of phenoxy moiety $J = 8.8$ Hz), δ 7.35 (d, 2H, C_3, C_5-H of 6-phenyl moiety $J = 8.6$ Hz), δ 7.67 (d, 2H, C_2, C_6-H of 6-phenyl moiety $J = 8.5$ Hz); MS FAB$^+$ (*m/z*, %): ($M^+ + 1$) 369 (86%), M^+ 368 (45%), 229 (70%), 165 (10%), 107 (25%), 89 (15%).

*6.5.3. 3-{[4-(Ethylthio) phenoxy] methyl}-6-phenyl-1,2,4-triazolo [3,4-b]-1,3,4-thiadiazole (**6h**)*

IR: 3060, 2968 cm^{-1} (S–CH_2CH_3), 1699 cm^{-1} (C=N), 1591, 1520, 1491 cm^{-1} (aromatic skeleton), 1278 cm^{-1} (N–N=C), 689 cm^{-1} (C–S–C); ^{1}H NMR (DMSO-d_6) δ 1.27 (t, 3H, CH_3), δ 2.8 (q, 2H, SCH_2), δ 5.5 (s, 2H, CH_2), δ 7 (d, 2H, C_3, C_5-H of 4-ethylthio phenoxy moiety $J = 8.1$), δ 7.3 (d, 2H, C_2, C_6-H of 4-ethylthio phenoxy moiety $J = 8.6$), δ 7.6 (m, 3H, C_3, C_4, C_5-H of 6-phenyl moiety $J = 8.0$), δ 8 (d, 2H, C_2, C_6-H of 6-phenyl moiety $J = 7.8$); ^{13}C NMR δ: 14.52 (SCH_3), 29.36 (SCH_2), 59.76 (OCH_2), 115.69 (C_2H and C_6H), 127.25 (C_4), 128.31 (C_4), 129.16 (C_3H and C_5H), 129.44 (C_1), 132.6 (C_2H and C_6H), 132.8 (C_3H and C_5H), 144.07 (C_3 and C_5 of triazole), 156.0 (C_1), 167.39 (C_7 of thiadiazole); DEPT: CH and CH_3 δ: 14.54, 115.71, 127.27, 129.46, 132.62, 132.88, CH_2 δ: 29.39, 59.78; MS FAB$^+$ (*m/z*, %): ($M^+ + 1$) 369 (100%), M^+ 368 (45%),165 (10%), 215 (60%), 107 (10%), 105 (8%).

*6.5.4. 3-{[4-(Ethylthio) phenoxy] methyl}-6-(4-methylphenyl)-1,2,4-triazolo[3,4-b]-1,3, 4-thiadiazole (**6j**)*

IR: 3060, 2968 cm^{-1} (S–CH_2CH_3), 1699 cm^{-1} (C=N), 1591, 1520, 1491 cm^{-1} (aromatic skeleton), 1278 cm^{-1} (N–N=C), 689 cm^{-1} (C–S–C); ^{1}H NMR (DMSO-d_6): δ 1.25 (t, 3H, CH_3), δ 2.4 (s 3H, CH_3), δ 2.8 (q, 2H, SCH_2), δ 5.52 (s, 2H, CH_2), δ 7.01 (d, 2H, C_3, C_5-H of 4-ethylthio phenoxy moiety $J = 8.1$), δ 7.26 (m, 4H, C_2, C_6-H of 4-ethylthio phenoxy moiety and C_3, C_5-H of 6-phenyl moiety), δ 7.75 (d, 2H, C_2, C_6-H of 6-phenyl moiety $J = 7.8$); MS FAB$^+$ (*m/z*, %): ($M^+ + 1$) 383 (100%), M^+ 382 (40%), 229 (70%), 154 (8%), 153 (8%), 135 (10%), 119 (5%).

*6.5.5. 3-{[4-(Methyl sulphonyl) phenoxy] methyl}-6-phenyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (**6o**)*

IR: 3024, 2927 cm^{-1} (S–CH_3), 1699 cm^{-1} (C=N), 1595, 1550, 1471 cm^{-1} (aromatic skeleton), 1249 cm^{-1} (N–N=C), 692 cm^{-1} (C–S–C); LCMS: *m/z* 386.9 (M^+, 100%).

Characterization data of **6a–s** are summarized in Table 1.

*6.6. General procedure for the preparation of 6-aryl-3-{(4-thioalkyl/methyl sulphonyl phenoxy) methyl}-7H-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazines (**7a–l**)*

A mixture 4-amino-5-{[thioalkyl/methyl sulphonyl phenoxy) methyl}-4*H*-1,2,4-triazole-3-thiols **5a–c** (1 mmol) and substituted phenacyl bromides (1.2 mmol) in 10 ml of absolute ethanol was refluxed for 6–7 h. The reaction mixture was slowly quenched onto crushed ice with stirring and it was neutralized with solid sodium bicarbonate. The solid which separated after standing overnight was filtered, washed with cold water, dried and recrystallized from absolute ethanol to afford the title compounds **7a–l**.

*6.6.1. 2-Hydorxy-5-(3-{[4-(methyl thio) phenoxy] methyl}-7H-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine-6-yl) benzamide (**7a**)*

IR: 3380 cm^{-1} (NH_2), 3024, 2927 cm^{-1} (S–CH_3), 1699 cm^{-1} (C=O), 1599 cm^{-1} (C=N), 1462 cm^{-1} (aromatic skeleton), 1237 cm^{-1} (N–N=C), 694 cm^{-1} (C–S–C); ^{1}H NMR (DMSO-d_6): δ 2.4 (s, 3H, SCH_3), δ 4.4 (s, 2H, CH_2), δ 5.5 (s, 2H, CH_2), δ 7 (d, 2H, C_3, C_5-H of phenoxy moiety $J = 8.8$), δ 7.3 (d, 2H, C_2, C_6-H of phenoxy moiety $J = 8.6$), δ 7.4 (d, 2H, C_5, C_6-H of 6-phenyl moiety), δ 8.0 (s, C_2-H of 6-phenyl moiety), δ 8.2 (s, 2H, $CONH_2$ of 6-phenyl moiety), 13.46 (s, 1 H, OH of 6-phenyl moiety), D_2O exchange study showed absence of peak at δ 8.2 and 8.4; LCMS: *m/z* 427.9 (M^+, 100%).

*6.6.2. 2-Hydroxy-5-(3-{[4-(ethylthio) phenoxy] methyl}-7H-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazin-6-yl) benzamide (**7e**)*

IR: 3375 cm^{-1} (NH_2), 3024, 2927 cm^{-1} (S–CH_2CH_3), 1689 cm^{-1} (C=O), 1592 cm^{-1} (C=N), 1500, 1462 cm^{-1} (aromatic skeleton), 1230 cm^{-1} (N–N=C), 688 cm^{-1} (C–S–C); ^{1}H NMR (DMSO-d_6): δ 1.2 (t, 3H, CH_3), δ 2.8 (q, 2H, SCH_2), δ 4.176 (s, 2H, CH_2), δ 5.37 (s, 2H, CH_2), δ 6.9 (d, 2H, C_3, C_5-H of phenoxy moiety $J = 8.6$), δ 6.9 (d, 1H, C_5-H of phenyl moiety $J = 6.1$), δ 7.29 (d, 2H, C_2, C_6-H of phenoxy moiety $J = 9{,}0$), δ 8.03 (d, 2H, C_5-H, C_6-H of phenyl moiety $J = 8.2$), δ 8.4 (s, C_2-H of phenyl moiety), 13.41 (s, 1 H, OH of phenyl moiety); ^{13}C NMR δ: 28.66 (SCH_3), 13.97 (SCH_2), 22.31 (C_7H_2), 58.94 (OCH_2), 113.52 (C_8), 115.27 (C_2H and C_6H), 118.66 (C_3H), 122.67 (C_5), 127.51 (C_4), 128.33 (C_6H), 131.82 (C_3H and C_5H), 132.11 (C_3 and C_5), 153.28 (C_3 and C_5), 154.88 (C_2), 156.56 (C_1), 164.73 (C_1), 171.43 (amide carbon); DEPT: CH and CH_3 δ: 14.09, 115.38, 118.77, 128.44, 131.93, 132.23, CH_2 δ: 22.43, 28.77, 59.06; MS FAB$^+$ (*m/z*, %): ($M^+ + 1$) 442 (100%), M^+ 441 (50%), 288 (40%), 271 (10%), 107 (8%), 105 (5%).

*6.6.3. 2-Hydroxy-5-(3-{[4-(Methyl sulphonyl) phenoxy] methyl}-7H-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazin-6-yl) benzamide (**7i**)*

IR: 3350 cm^{-1} (NH_2), 3024, 2927 cm^{-1} (S–CH_3), 1672 cm^{-1} (C=O), 1599 cm^{-1} (C=N), 1462 cm^{-1} (aromatic skeleton), 1237 cm^{-1} (N–N=C), 694 cm^{-1} (C–S–C). MS FAB^+ (*m/z*, %): ($M^+ + 1$) 460 (80%), M^+ 459 (30%), 289 (10%), 105 (30%).

Characterization data of **7a–l** are given in Table 1.

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Appendix. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejmech.2006.10.010.

References

[1] B.N. Goswami, J.C.S. Kataky, J.N. Baruah, J. Heterocycl. Chem. 21 (1984) 1225.
[2] R.H. Khan, R.A.K. Srivastava, R.C. Rastogi, Indian J. Chem. 24B (1985) 883.
[3] J. Heeres, L.J. Backx, J. Med. Chem. 27 (1984) 894.
[4] M.D. Mullican, M.W. Wilson, D.T. Connor, C.R. Kostlan, d.J. Schrier, R.D. Dyer, J. Med. Chem. 36 (1993) 1090.
[5] A. Czarnocka, Janowicz, H. Foks, A. Nasal, J. Petrusewicz, B. Damasiewicz, A. Radwanska, R. Kaliszan, Pharmazie 46 (1991) 109.
[6] R.W. Sidwell, L.B. Allen, J.H. Hoffman, J.T. Witkowshi, L.N. Simon, Proc. Soc. Exp. Biol. Med. 148 (1975) 854; Chem. Abstr. 118 (1993) 11961z.
[7] K. Singh, A. Hasan, R. Pratap, P.Y. Guru, D.S. Bhakuni, J. Indian Chem. Soc. 66 (1989) 686.
[8] C. Hart, Drugs for migraine, in: Modern Drug Discovery, American Chemical Society, 1999.
[9] M.E. Deason, K.R. Whitten, US 5,962,725, Oct. 5, 1999.
[10] A.S. Bell, D. Brown, N.K. Terrett, US 5,250,534, Oct. 5, 1993.
[11] A.L. Rawlins, G.P. Woods, US 2,589,211, March 18, 1952.
[12] J.M. Sprague, D.H. Pa, US 2,407,966, Sept. 17, 1946.
[13] B. Camerino, G.P. Milan, US 3,098,069, July 16, 1963.
[14] D.H. Boschelli, D.T. Connor, C.R. Kostlan, J.B. Kramer, M.D. Mullican, J.C. Sircar, US 5,102,897, April 7, 1992.
[15] A.R. Farghaly, E.D. Clercq, H. El-Kashef, ARKIVOC 10 (2006) 137.
[16] Z.Y. Zhang, M. Li, L. Zhao, Z.M. Li, R.A. Liao, Chin. J. Org. Chem. 13 (1993) 397.
[17] R. Gupta, S. Sudan, V. Mengi, P.L. Kachroo, Indian J. Chem., Sect. B 35 (1996) 621.
[18] A.L. Barry, Procedure for testing antimicrobial agents in agar media, in: V.L. Corian (Ed.), Antibiotics in Laboratory Medicine, Williams and Wilkins, Baltimore, MD, 1991, p. 1.
[19] D. James, Mac. Lowry, Marry J. Jaqua, Sally T. Selepak, Appl. Microbiol. 20 (1970) 46.
[20] B.A. Arthington-Skaggs, M. Motley, D.W. Warnock, C.J. Morrison, J. Clin. Microbiol. 38 (2000) 2254.
[21] R.S. Verma, Z.K. Khan, A.P. Singh (Eds.), Antifungal Agents: Past, Present and Future Prospects, National Academy of Chemistry and Biology, Lucknow, India, 1998, p. 55.
[22] Christine H. Fenlon, Michael H. Cynamon, Antimicrob. Agents Chemother. 29 (1986) 386.
[23] R. Davis, A. Markham, J.A. Balfour, Ciprofloxacin, An updated review of its pharmacology, therapeutic efficacy and tolerability, Drugs 51 (6) (1996) 1019.