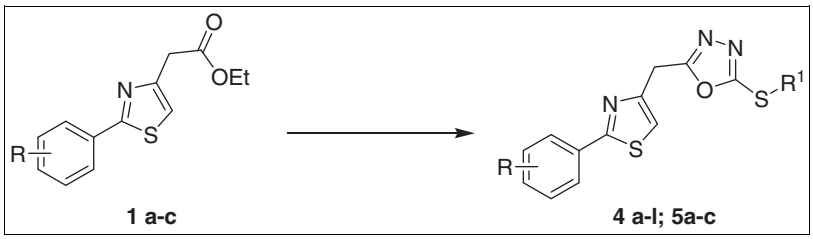
# Synthesis and Pharmacological Evaluation of a Novel Series of 2-((2-Aryl thiazol-4-yl)methyl)-5-(alkyl/alkylnitrile thio)-1,3,4-oxadiazole Derivatives as Possible Antifungal Agents



Shivaji H. Shelke,[a] Pravin C. Mhaske,[b] Sridhar Kumar Kasam,[b] and Vivek D. Bobade[a]*

[a]Department of Chemistry, H. P. T. Arts and R. Y. K. Science College, College Road, Nashik 422005, India
[b]Department of Chemistry, Sir Parshurambhau College, Tilak Road, Pune 411030, India
*E-mail: v_bobade31@rediffmail.com

Received August 10, 2012
DOI 10.1002/jhet.1910
Published online 21 April 2014 in Wiley Online Library (wileyonlinelibrary.com).




In the present investigation, a novel series of 2-[(2-arylthiazol-4-yl)methyl]-5-(alkyl/alkylnitrile thio)-1,3,4-oxadiazole derivatives were synthesized by cyclo-condensation of 2-(2-substituted thiazol-4-yl)aceto hydrazide with carbon disulfide followed by S-alkylation with alkyl halide in dry acetone. All the newly synthesized compounds were characterized by spectral (IR, $^1$H NMR, $^{13}$C NMR, mass, and elemental analysis) methods. The title compounds were screened for *in vitro* antifungal activity and most of the synthesized compounds show moderate to good antifungal activity.

*J. Heterocyclic Chem.*, **51**, 1893 (2014).

## INTRODUCTION

Five-member heterocycles are privileged structures with utility in synthetic and medicinal chemistries. The heterocyclic compounds hold a special place among pharmaceutically active products and development of simple and efficient synthesis of compounds incorporating multi heterocyclic rings has given a new dimension to the drug discovery. Thiazole and oxadiazoles are an important class of five-member heterocyclic compounds, which have been the subject of great interest because of its wide range of biological activities.

Thiazole compounds have attracted continuing interest over the years because of their varied biological activities [1–10]. The presence of oxadiazole nucleus in diverse types of compounds proves its importance in the field of medicinal chemistry. Oxadiazole possesses a wide spectrum of biological activities such as antimicrobial [11–15], anti-tubercular [16–19], anti-inflammatory [20–24], antiviral [25,26], tyrosianse inhibitor activity [27], EGFR PTK inhibitor [28], anticancer [29,30], anticonvulsant [31,32], and protoporphyrinogen oxidase inhibitor [33] activities.

Concurring with previous reports, 2-(4-isopropylthiazol-2-yl)-5-substituted-1,3,4-oxadiazoles [34], 2,3-dihydrothiazoline substituted 1,3,4-oxadiazole [35] 1,2,4-triazolo [1,5-a]-pyrimidine substituted-1,3,4-oxadiazoles [36], thiazole substituted-1,3,4-oxadiazoles [37], 5-dithiazolyl-2-R-1,3,4-Δ4-oxadiazoline [38] derivatives have shown antimicrobial, antitumor, and antifungal activities. In view of these observations, it was thought to synthesize new thiazole-based 2-alkyl/alkylnitrile thio-1,3,4-oxadiazole by the condensation of 2-(2-arylthiazol-4-yl)acetohydrazide with carbon disulfide followed by nucleopholic substitution with alkyl halide.

## RESULTS AND DISCUSSION

The synthetic route of the compounds 4a–l and 5a–c is outlined in Figure 1. Ethyl 2-(2-aryl thiazol-4-yl)acetate 1a–c was prepared by cyclo-condensation of substituted thioamides with ethyl 4-chloro-3-oxobutanoate in dry ethanol. Ester 1a–c on nucleopholic substitution reaction with hydrazine hydrate gave 2-(2-aryl thiazol-4-yl)aceto-hydrazide 2a–c. Carbazide 2a–c on reaction with carbon disulphide and KOH in dry methanol furnished 5-((2-aryl thiazol-4-yl)methyl)-1,3,4-oxadiazole-2-thiol 3a–c. Thiol 3a–c on nucleopholic substitution reaction with alkyl halide/chloroacetonitrile in dry acetone furnished target compounds 2-((2-aryl thiazol-4-yl)methyl)-5-(alkyl thio)-1,3,4-oxadiazole 4a–l and 2-(5-((2-aryl thiazol-4-yl)methyl)-1,3,4-oxadiazol-2-ylthio)acetonitrile 5a–c in good yield.

The structure of compounds 4a–l and 5a–c were confirmed by spectral method. The IR spectrum of 4a–l - displayed absorption bands between 3128 and 2852 $cm^{-1}$ corresponding to C–H, 1599–1481 $cm^{-1}$ corresponding to C=C and C=N and 1245–933 $cm^{-1}$ corresponding to C–O stretching frequency. The $^1$H NMR spectrum of 4e in $CDCl_3$ displayed a triplet at δ 1.47 and a quartet at δ 3.26 that corresponds to S–$CH_2CH_3$ functionality, singlet at δ 4.43 integrating for two protons was assigned to

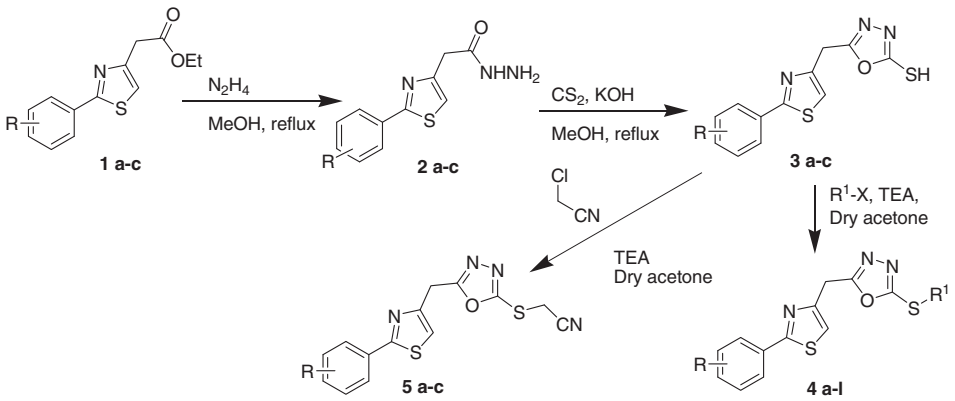



**Figure 1.** Synthetic scheme for compounds **4a-l** and **5a-c**.

methylene protons of thiazole–$CH_2$–oxadiazole. A singlet that appeared at δ 7.25 was attributed to thiazole proton, whereas the aromatic protons resonated at δ 7.34–7.95. It was noteworthy that the thiazole proton appeared downfield (δ 7.73) in DMSO-$d_6$ solvent. The $^{13}C$ NMR spectrum of 4e showed three peaks in the aliphatic region that corresponds to S–$CH_2CH_3$ and methylene carbon of thiazole–$CH_2$–oxadiazole. The aromatic, thiazole, and oxadiazole carbons appeared between δ116.8 and 168.7. The LCMS spectrum of 4e showed $(M+H)^+$ peak at 338.1. The physical properties and yield of synthesized compounds 4a–l and 5a–c are reported in Table 1.

**Antifungal testing.** All the synthesized compounds were quantitatively evaluated for their *in vitro* antifungal activity against *Candida albicans*, *Candida tropicalis, Aspergillus niger* and *Aspergillus flavus*. Fluconazole was used as positive control and DMSO as negative control. The minimum inhibitory concentration (MIC) value is defined as the lowest concentration of the antifungal agent exhibiting no fungal growth. The *in vitro* antimicrobial MIC screening results of synthesized compounds 4a–l and 5a–c are given in Table 2.

**Table 1**

The physical properties and yield of synthesized compounds **4a–l** and **5a–c**.

| Compound | R | $R^1$ | MP[a] | Yield[a] |
|---|---|---|---|---|
| 4a | H | $C_2H_5$ | 86–88 | 80 |
| 4b | H | *n*-$C_3H_7$ | 74–76 | 76 |
| 4c | H | *i*-$C_3H_7$ | 66–67 | 69 |
| 4d | H | *n*-$C_7H_{15}$ | 72–74 | 82 |
| 4e | 3-Cl | $C_2H_5$ | 68–70 | 84 |
| 4f | 3-Cl | *n*-$C_3H_7$ | 86–88 | 79 |
| 4g | 3-Cl | *i*-$C_3H_7$ | 68–70 | 66 |
| 4h | 3-Cl | *n*-$C_7H_{15}$ | 68–70 | 78 |
| 4i | 4-Cl | $C_2H_5$ | 75–77 | 80 |
| 4j | 4-Cl | *n*-$C_3H_7$ | 80–81 | 76 |
| 4k | 4-Cl | *i*-$C_3H_7$ | 64–66 | 65 |
| 4l | 4-Cl | *n*-$C_7H_{15}$ | 78–80 | 80 |
| 5a | H | $CH_2CN$ | 65–66 | 75 |
| 5b | 3-Cl | $CH_2CN$ | 70–72 | 73 |
| 5c | 4-Cl | $CH_2CN$ | 84–86 | 70 |

[a]Isolated yield.
[a°]C.

Careful analysis of the MICs in Table 2 provides some lead molecules with good antifungal activity. Of the compounds 4a–l tested, compounds with S–$CH(CH_3)_2$ expressed a moderate to good antifungal activity against all of the tested pathogens. It was observed that in compounds 4a, 4b, and 4c, the phenyl group at two-position of thiazole ring and $R^1 = –C_2H_5$, *n*-$C_3H_7$ and –$CH(CH_3)_2$, respectively, showed good to moderate activity against most of the fungi species with MIC values 3.125–12.5 μg/mL. Introduction of the chlorine at three-position of the phenyl ring of thiazole nucleus, compounds 4g ($R^1 = –CH(CH_3)_2$) and 4h ($R^1 = n$-$C_7H_{15}$) inhibited the growth of all the tested species, where as compounds 4e ($R^1 = –C_2H_5$) and 4f ($R^1 = n$-$C_3H_7$ ) registered a moderate to good activity against *A. niger* and *A. flavus*. If the 3-chloro phenyl group is replaced by 4-chloro phenyl group, compound 4k ($R^1 = –CH(CH_3)_2$) recorded good activity against *C. albicans*, *C. tropicalis*, and *A. niger* with MICs (3.125–6.25 μg/mL) and compound 4j ($R^1 = n$-$C_3H_7$ ) showed good activity against *A. niger* (MIC 3.125 μg/mL) and moderate activity against *A. flavus* (MIC 12.5 μg/mL). Compound 5c (R = 4–Cl and $R^1 = –CH_2CN$) recorded good activity against *C. albicans*, *C. tropicalis*, and *A. niger* with MICs (3.125–12.5 μg/mL) and compound 5b (R = 3–Cl and $R^1 = –CH_2CN$) registered the MIC at 6.25 μg/mL against *A. flavus*. Thus, it is concluded that compound 4g registered the MIC at 3.125 μg/mL against *C. tropicalis*, compounds 4b, 4j, 4k, and 5c showed significant activity at MIC 3.125 μg/mL against *A. niger*, and compounds 4a and 4c recorded excellent activity at MIC 3.125 μg/mL against *A. flavus*.

## CONCLUSIONS

In summary, the antifungal screening result showed that 2-[(2-R-1,3-thiazol-4-yl)methyl]-5-($R^1$-thio)-1,3,4-oxadiazoles 4a (R = $C_6H_5$, $R^1 = C_2H_5$), 4b (R = $C_6H_5$, $R^1 = n$-$C_3H_7$), 4c (R = $C_6H_5$, $R^1 = –CH(CH_3)_2$, 4g (R = 3-$ClC_6H_4$, $R^1 = –CH$

**Table 2**

Antifungal activity of 2-[(2-aryl-1,3-thiazol-4-yl)methyl]-5-(alkylthio)-1,3,4-oxadiazole **4a–l** and 2-[5-((2-aryl-1,3-thiazol-4-yl)methyl]-1,3,4-oxadiazol-2-ylthio]acetonitrile **5a–c**.

| | | MIC μg/mL (μM) | | | |
|---|---|---|---|---|---|
| Compound | MW | *Candida albicans* | *Candida tropicalis* | *Aspergillus niger* | *Aspergillus flavus* |
| 4a | 303.40 | 12.5 (41.20) | 12.5 (41.20) | 50 (164.80) | 3.125 (10.54) |
| 4b | 317.43 | 6.25 (19.69) | 12.5 (39.37) | 3.125 (9.84) | 25 (78.75) |
| 4c | 317.43 | 12.5 (39.37) | 12.5 (39.37) | 6.25 (19.69) | 3.125 (9.84) |
| 4d | 373.54 | 25 (66.93) | >100 | 25 (66.93) | 50 (133.85) |
| 4e | 337.85 | 50 (133.74) | >100 | 25 (66.87) | 12.5 (33.43) |
| 4f | 351.87 | >100 | 25 (71.05) | 12.5 (35.52) | 6.25 (17.76) |
| 4g | 351.87 | 6.25 (17.76) | 3.125 (8.88) | 6.25 (17.76) | 12.5 (35.52) |
| 4h | 407.98 | 12.5 (30.63) | 25 (61.25) | 6.25 (15.31) | 12.5 (30.63) |
| 4i | 337.85 | 25 (66.87) | 50 (133.74) | >100 | 50 (133.74) |
| 4j | 351.87 | 25 (71.05) | 50 (142.09) | 3.125 (8.88) | 12.5 (35.52) |
| 4k | 351.87 | 6.25 (17.76) | 6.25 (17.76) | 3.125 (8.88) | 25 (71.05) |
| 4l | 407.98 | 25 (61.27) | >100 | 25 (61.27) | 50 (122.55) |
| 5a | 314.39 | 25 (79.51) | 25 (79.51) | 25 (79.51) | 50 (159.03) |
| 5b | 348.83 | 50 (143.33) | 25 (71.68) | 25 (71.68) | 6.25 (17.91) |
| 5c | 348.83 | 6.25 (17.91) | 12.5 (35.83) | 3.25 (8.96) | 25 (71.68) |
| Fluconazole | | 1.56 (5.09) | 3.125 (10.18) | 1.56 (5.09) | 3.125 (10.18) |

$(CH_3)_2$, 4h (R = 4-$ClC_6H_4$, $R^1 = n$-$C_7H_{15}$), 4k (R = 4-$ClC_6H_4$, $R^1$ = –$CH(CH_3)_2$ and 5c (R = 4-$ClC_6H_4$, $R^1$ = $CH_2CN$) displayed good antifungal activity at a level of MIC from 3.125 to 12.5 μg/mL against most of the strains. It is also concluded that the S–$CH(CH_3)_2$ group is more effective against all tested strains. The results also reveal that compounds with $R^1$ = alkyl, phenyl or 3-chlorophenyl group at 2 position of thiazole ring show good activity against most of the tested species as compared with 4-chlorophenyl group.

## EXPERIMENTAL

Melting points were determined in an open capillary on Veego melting point apparatus (Mumbai, India) and are uncorrected. All reactions were monitored by thin layer chromatography on 0.25 mm E. Merck silica gel plates (F-254) using UV light or iodine vapors as the visualizing methods. Infrared (IR) spectra ($cm^{-1}$) were recorded in KBr on a Shimadzu Model FTIR-435 spectrophotometer (Kyoto, Japan). $^1$H NMR and $^{13}$C NMR spectra were recorded in $CDCl_3$ and DMSO-$d_6$ solution on a Varian Mercury YH-300 spectrometer (Darmstadt, Germany) operating at 300 MHz for $^1$H or 75 MHz for $^{13}$C respectively. Chemical shifts are expressed relative to tetramethylsilane and are reported as δ (ppm). LCMS measurements were made on a Jeol-JMS-DX 303 mass spectrometer (Tokyo, Japan). The elemental analysis was performed on FLASH EA 1112 analyzer (Thermo Scientific, Cambridge, UK) and results were found within the ±0.4% of theoretical values.

**General procedure for synthesis of compounds 4a–l.** The solution of thiol 3a–c (10 mmol), triethyl amine (11 mmol), and alkyl halide (11 mmol) in dry acetone was refluxed for 1 h. After completion of the reaction (TLC), the solvent was evaporated under reduced pressure; residue was dissolved in ethyl acetate and extracted with 5% HCl. Organic layer was washed with water and distilled on rotary evaporator to furnish target compounds. All the compounds were purified by column chromatography using ethyl acetate: hexane (9:1) as eluent.

***2-[(2-phenyl-1,3-thiazol-4-yl)methyl]-5-(ethylthio)-1,3,4-oxadiazole 4a.*** IR: 3120, 2931, 2854, 1599, 1516, 1481, 1417, 1381, 1244, 1151, 1074, 976, 933 785, 688 $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): δ 1.46 (t, $J$ = 7.2 Hz, 3H),3.25 (q, $J$ = 7.2 Hz, 2H), 4.42 (s, 2H), 7.18 (s, 1H), 7.40–7.44 (m, 3H), 7.89–7.94 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 14.5, 26.8, 29.6, 116.5, 126.6, 128.8, 130.0, 133.2, 149.1, 164.3, 164.8, 169.0; LCMS: 304.1 $(M+H)^+$. *Anal*. Calcd. for $C_{14}H_{13}N_3OS_2$: C, 55.42; H, 4.32; N, 13.85. Found: C, 55.46; H, 4.28; N, 13.79.

***2-[(2-Phenyl-1,3-thiazol-4-yl)methyl]-5-(propylthio)-1,3,4-oxadiazole 4b.*** IR: 3118, 2930, 2850, 1594, 1518, 1483, 1420, 1379, 1240, 1149, 1074, 975, 938, 688 $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): δ 1.44 (t, $J$ = 7.2 Hz, 3H),1.83 (m, 2H), 3.21 (t, $J$ = 7.2 Hz, 2H), 4.42 (s, 2H), 7.18 (s, 1H), 7.42–7.44 (m, 3H), 7.91–7.94 (m, 2H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 13.2, 22.5, 28.0, 34.3, 116.1, 126.5, 129.0, 130.1, 133.2, 149.0, 164.2, 164.7, 168.9; LCMS: 318.1 $(M+H)^+$. *Anal*. Calcd. for $C_{15}H_{15}N_3OS_2$: C, 56.76; H, 4.76; N, 13.24. Found: C, 56.68; H, 4.71; N, 13.18.

***2-[(2-phenyl-1,3-thiazol-4-yl)methyl]-5-(2-propylthio)-1,3,4-oxadiazole 4c.*** IR: 3122, 2933, 2850, 1597, 1518, 1483, 1417, 1382, 1245, 1150, 1075, 977, 785, 685 $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): δ 1.47 (d, $J$ = 6.8 Hz, 6H), 3.84–3.93 (m, 1H), 4.42 (s, 2H), 7.17 (s, 1H), 7.41–7.43 (m, 3H), 7.91–7.93 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 23.2, 28.2, 38.8, 116.1, 126.4, 128.9, 130.1, 133.2, 149.2, 164.4, 164.8, 169.0; LCMS: 318.1 $(M+H)^+$. *Anal.*

Calcd. for $C_{15}H_{15}N_3OS_2$: C, 56.76; H, 4.76; N, 13.24. Found: C, 56.62; H, 4.70; N, 13.16.

***2-[(2-phenyl-1,3-thiazol-4-yl)methyl]-5-(heptylthio)-1,3,4-oxadiazole 4d.*** IR: 3120, 2931, 2854, 1599, 1516, 1481, 1417, 1381, 1244, 1151, 1074, 976, 933 785, 688 $cm^{-1}$; $^1H$ NMR(400 MHz, DMSO-$d_6$): δ 0.83 (t, $J$ = 7.2 Hz, 3H), 1.20–1.32 (m, 8H), 1.67 (quint, 2H), 3.19 (t, $J$ = 7.2 Hz, 2H), 4.46 (s, 2H), 7.48–7.56 (m, 3H), 7.65 (s, 1H), 7.90 (m, 2H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ 13.8, 21.9, 27.3, 27.7, 29.9, 28.9, 31.0, 31.9, 116.0, 126.5, 128.8, 130.0, 133.1, 149.2, 164.3, 164.8, 168.9; LCMS: 374.0 $(M+H)^+$. *Anal*. Calcd. for $C_{19}H_{23}N_3OS_2$ C, 61.09; H, 6.21; N, 11.25. Found: C, 61.14; H, 6.18; N, 11.20.

***2-[(2-(3-Chlorophenyl)-1,3-thiazol-4-yl)methyl]-5-(ethylthio)-1,3,4-oxadiazole 4e.*** IR: 3091, 2962, 2870, 1579, 1518, 1483, 1408, 1238, 1193, 1151, 1008, 964, 802, 765 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ 1.47 (t, $J$ = 7.6 Hz, 3H), 3.26 (q, $J$ = 7.6 Hz, 2H), 4.43 (s, 2H),7.25 (s, 1H), 7.34–7.41 (m, 2H), 7.78–7.81 (m, 1H), 7.95 (s, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 14.6, 26.9, 28.1, 116.8, 124.7, 126.4, 130.1, 134.7, 135.0, 149.4, 164.9, 166.8, 168.7; LCMS: 338.1 $(M+H)^+$. *Anal*. Calcd. for $C_{14}H_{12}ClN_3OS_2$: C, 49.77; H, 3.58; N, 12.44. Found: C, 49.80; H, 3.55; N, 12.39.

***2-[(2-(3-Chlorophenyl)-1,3-thiazol-4-yl)methyl]-5-(propylthio)-1,3,4-oxadiazole 4f.*** IR: 3091, 2962, 2870, 1579, 1518, 1483, 1408, 1238, 1193, 1151, 1008, 964, 802, 765 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ 1.02 (t, $J$ = 6.9 Hz, 3H), 1.40–1.88 (m, 2H), 3.19 (t, $J$ = 7.2 Hz, 2H), 4.39 (s, 2H), 7.21 (s, 1H), 7.31–7.38 (m, 2H), 7.74–7.77 (m, 1H), 7.92 (m, 1H);$^{13}C$ NMR (75 MHz, $CDCl_3$): δ 13.1, 22.6, 28.1, 34.3, 116.7, 124.6, 126.4, 130.0, 130.1, 134.8, 134.9, 149.5, 164.7, 165.0, 166.6; LCMS: 352.1 $(M+H)^+$. *Anal*. Calcd. for $C_{15}H_{14}ClN_3OS_2$: C, 51.20; H, 4.01; N, 11.94. Found: C, 51.15; H, 3.97; N, 11.89.

***2-[(2-(3-Chlorophenyl)-1,3-thiazol-4-yl)methyl]-5-(isopropylthio)-1,3,4-oxadiazole 4g.*** IR: 3091, 2962, 2870, 1579, 1518, 1483, 1408, 1238, 1193, 1151, 1008, 964, 802, 765 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ 1.42 (d, $J$ = 7.2 Hz, 6H), 3.88–3.92 (m, 1H), 4.43 (s, 1H), 7.24 (s, 1H), 7.33–7.39 (m, 2H), 7.77–7.79 (m, 1H), 7.94 (m, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 23.1, 28.2, 38.8, 116.8, 124.7, 126.5, 130.0, 130.2, 134.8, 134.9, 149.4, 164.7, 165.1, 167.1; LCMS: 352.0 $(M+H)^+$. *Anal*. Calcd. for $C_{15}H_{14}ClN_3OS_2$: C, 51.20; H, 4.01; N, 11.94. Found: C, 51.14; H, 3.98; N, 11.89.

***2-[(2-(3-Chlorophenyl)-1,3-thiazol-4-yl)methyl]-5-(heptylthio)-1,3,4-oxadiazole 4h.*** IR: 3120, 2931, 2854, 1599, 1516, 1481, 1417, 1381, 1244, 1151, 1074, 976, 933 785, 688 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 0.82 (t, $J$ = 7.2 Hz, 3H), 1.19–1.23 (m, 8H), 1.67 (m, 2H), 3.18 (t, $J$ = 7.6 Hz, 2H), 4.46 (s, 2H),7.52–7.54 (m, 2H), 7.73(s, 1H), 7.84 (m, 1H), 7.90 (s, 1H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ 13.8, 21.9, 27.2, 27.6, 27.9, 28.9, 30.9, 31.9, 118.5, 124.8, 125.3, 130.0, 131.2, 133.9, 134.5, 149.7, 163.7, 165,1, 165.4; LCMS: 408.1 $(M+H)^+$. *Anal*. Calcd. for $C_{19}H_{22}ClN_3OS_2$: C, 55.93; H, 5.44; N, 10.30. Found: C, 55.99; H, 5.40; N, 10.27.

***2-[(2-(4-Chlorophenyl)-1,3-thiazol-4-yl)methyl]-5-(ethylthio)-1,3,4-oxadiazole 4i.*** IR: 3120, 2931, 2854, 1599, 1516, 1481, 1417, 1381, 1244, 1151, 1074, 976, 933 785, 688 $cm^{-1}$; $^1H$ NMR(300 MHz, $CDCl_3$): δ 1.47 (t, $J$ = 7.6 Hz, 3H), 3.25 (q, $J$ = 7.6 Hz, 2H), 4.42 (s, 2H),7.21 (s,1H), 7.40(d, $J$ = 8Hz, 2H), 7.86 (d, $J$ = 8Hz,2H);$^{13}C$ NMR (75 MHz, $CDCl_3$): δ 14.5, 26.9, 28.1, 116.1, 126.4, 129.0, 130.1, 133.3, 149.1, 164.3, 164.8, 169.0; LCMS: 338.0 $(M+H)^+$ *Anal*. Calcd. for $C_{14}H_{12}ClN_3OS_2$: C, 49.77; H, 3.58; N, 12.44. Found: C, 49.72; H, 3.61; N, 12.39.

***2-[(2-(4-Chlorophenyl)-1,3-thiazol-4-yl)methyl]-5-(propylthio)-1,3,4-oxadiazole 4j.*** IR: 3128, 2964, 2933, 1589, 1491, 1454, 1406, 1246, 1145, 1087, 1008, 840, 783 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 0.94 (t, $J$ = 7.2 Hz, 3H), 1.65–1.77 (m, 2H), 3.18 (t, $J$ = 7.2 Hz, 2H), 4.47 (s, 2H), , 7.55 (d, $J$ = 8.4 Hz, 2H), 7.69 (s, 1H), 7.91 (d, $J$ = 8.4 Hz, 2H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ 12.7, 22.3, 27.3, 33.8, 118.2, 127.7, 129.2, 131.5, 134.8, 149.6, 163.7, 165.2, 165.9; LCMS: 352.0 $(M+H)^+$. *Anal*. Calcd. for $C_{15}H_{14}ClN_3OS_2$: C, 51.20; H, 4.01; N, 11.94. Found: C, 51.17; H, 4.02; N, 11.90.

***2-[(2-(4-Chlorophenyl)-1,3-thiazol-4-yl)methyl]-5-(isopropylthio)-1,3,4-oxadiazole 4k.*** IR: 3122, 2933, 2850, 1597, 1518, 1483, 1417, 1382, 1245, 1150, 1075, 977, 785, 685 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ 1.47 (d, $J$ = 7.2 Hz, 6H), 3.85–3.94 (m, 1H), 4.42 (s, 2H),7.20 (s, 1H), 7.40 (d, $J$ = 8.6 Hz, 2H), 7.83 (d, $J$ = 8.6 Hz, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 23.2, 28.2, 38.8, 116.1, 126.4, 128.9, 130.1, 133.2, 149.2, 164.4, 164.8, 169.0; LCMS: 352.1 $(M+H)^+$. *Anal*. Calcd. for $C_{15}H_{14}ClN_3OS_2$: C, 51.20; H, 4.01; N, 11.94. Found: C, 51.17; H, 4.00; N, 11.90.

***2-[(2-(4-Chlorophenyl)-1,3-thiazol-4-yl)methyl]-5-(heptylthio)-1,3,4-oxadiazole 4l.*** IR: 3124, 2926, 2852, 1589, 1516, 1489, 1419, 1381, 1247, 1149, 1095, 1006, 972, 837 781, 688 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 0.82 (t, $J$ = 7.2 Hz, 3H), 1.20–1.33 (m, 8H), 1.65 (quint, 2H), 3.16 (t, $J$ = 7.2 Hz, 2H), 4.46 (s, 2H),7.54 (d, $J$ = 8.4 Hz, 2H), 7.69 (s, 1H), 7.90 (d, $J$ = 8.4 Hz, 2H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ 13.8, 21.9, 27.3, 27.7, 28.0, 28.9, 31.0, 31.9, 118.1, 127.8, 129.2, 131.5, 134.8, 149.7, 163.7, 165.1, 165.9; LCMS: 408.1 $(M+H)^+$. *Anal*. Calcd. for $C_{19}H_{22}ClN_3OS_2$: C, 55.93; H, 5.44; N, 10.30. Found: C, 55.88; H, 5.45; N, 10.33.

***2-[5-((2-Phenyl-1,3-thiazol-4-yl)methyl)-1,3,4-oxadiazol-2-ylthio]acetonitrile 5a.*** 3115, 2977, 2930, 2248, 1584, 1489, 1477, 1430, 1379, 1240, 1139, 1008, 960, 830, $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ 4.42 (s, 2H), 4.51 (s, 2H), 7.18 (s, 1H), 7.40–7.44 (m, 3H), 7.89–7.94 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 17.6, 28.2,, 116.6, 126.6, 128.8, 130.1, 133.2, 149.1, 164.3, 164.7, 169.0; LCMS: 315.1 $(M+H)^+$. *Anal*. Calcd. for $C_{14}H_{10}N_4OS_2$: C, 53.49; H, 3.21; N, 17.82. Found: C, 53.46; H, 3.24; N, 17.78.

***2-[5-((2-(3-Chlorophenyl)-1,3-thiazol-4-yl)methyl)-1,3,4-oxadiazol-2-ylthio]acetonitrile 5b.*** 3110, 2979, 2932, 2249, 1588, 1490, 1485, 1433, 1390, 1245, 1176, 1140, 1006, 960, 715, $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ 4.43

(s, 2H), 4.51 (s, 2H), 7.25 (s, 1H), 7.34–7.41 (m, 2H), 7.78–7.81 (m, 1H), 7.95 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 17.6, 28.1, 116.7, 124.8, 126.5, 130.1, 134.6, 134.9, 149.4, 164.9, 166.7, 168.6; LCMS: 349.1 $(M+H)^+$. *Anal*. Calcd. For $C_{14}H_9ClN_4OS_2$: C, 48.20; H, 2.60; N, 16.06. Found: C, 48.15; H, 2.58; N, 16.03.

***2-[5-((2-(4-Chlorophenyl)-1,3-thiazol-4-yl)methyl)-1,3,4-oxadiazol-2-ylthio]acetonitrile 5c.*** 3109, 2980, 2935, 2249, 1589, 1491, 1485, 1433, 1396, 1244, 1176, 1139, 1008, 960, 717, $cm^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 4.43 (s, 2H), 4.52 (s, 2H), 7.54 (d, $J = 8.4$ Hz, 2H), 7.7 (s, 1H), 7.92 (d, $J = 8.4$ Hz, 2H); $^{13}$C NMR (100 MHz, DMSO): δ 17.7, 28.2, 114.6, 116.7, 127.7, 129.1, 131.6, 136.2, 148.8, 161.2, 166.2, 167.3; LCMS: 349.0 $(M+H)^+$. *Anal*. Calcd. for $C_{14}H_9ClN_4OS_2$: C, 48.20; H, 2.60; N, 16.06. Found: C, 48.17; H, 2.57; N, 16.02.

**Antifungal activity.** All the strains were obtained from microbial type culture collection at the NCIM, Pune, India. For the antifungal activity, Sabouraud dextrose broth medium was used. The spores were obtained from 10 days culture of *C. albicans*, *C. tropicalis, A. niger*, and *A. flavus* species. The twofold dilution technique [39–42] was followed to determine the MIC of the synthesized compounds. The test compounds were dissolved in dimethyl sulfoxide (DMSO) and then diluted with culture medium (Mueller Hinton agar medium) at the required final concentration in between 0.2 and 100 μg/mL. A plate containing only the culture medium and DMSO in the same dilution was used as negative control. The MIC values were recorded after incubation at 37 °C for a period of 24 h, the turbidity produced in each tube was recorded by using a UV–visible spectrometer. The lowest concentration of the test substance that completely inhibited the growth of the microorganism was reported as MIC expressed in terms of μg/mL.

**Acknowledgments.** The authors would like to express their sincere thanks to Department of Chemistry, Pune University, IIT, Mumbai for providing spectral analysis and CSIR, New Delhi for financial assistance.

## REFERENCES AND NOTES

[1] Nicolaou, K. C.; Roschanger, F.; Vourloumis, D. Angew Chem Int Ed 1998, 37, 2014.

[2] Ojika, M.; Suzuki, Y.; Tsukamoto, A.; Sakagami, Y.; Fudou, R.; Yoshimura, T.; Yamanaka, S. J Antibiot 1998, 51, 275.

[3] Suzuki, Y.; Ojika, M.; Sakagami, Y.; Fudou, R.; Yamanaka, S. Tetrahedron 1998, 54, 11399.

[4] El-Subbagh, H. I.; Al-Obaid, A. M. Eur J Med Chem 1996, 31, 1017.

[5] Zhang, C.; Zink, D. L.; Ushio, M.; Burgess, B.; Onishi, R.; Masurekar, P.; Barrett, J. F.; Singh, S. B. Bioorg Med Chem 2008, 16, 8818.

[6] Kalkhambkar, R. G.; Kulkarni, G. M.; Shivkumar, H.; Rao, N. R. Eur J Med Chem 2007, 42, 1272.

[7] Franklin, P. X.; Pillai, A. D.; Rathod, P. D.; Yerande, S.; Nivsarkar, M.; Padh, H.; Vasu, K. K.; Sudarsanam V. Eur J Med Chem 2008, 43, 129.

[8] Zitouni, G. T.; Ozdemir, A.; Kaplancikli, Z. A.; Benkli, K.; Chevallet, P.; Akalin, G. Eur J Med Chem 2008, 43, 981.

[9] Bekhit, A. A.; Ashour, H. M. A.; Abdel Ghany, Y. S.; Bekhit, A. E. A.; Baraka A. Eur J Med Chem 2008, 43, 456.

[10] Karegoudar, P.; Karthikeyan, M. S.; Prasad, D. J.; Mahalinga, M.; Holla, B. S.; Kumari, N. S. Eur J Med Chem 2008, 43, 261.

[11] Saini, R.; Rai, A. K.; Kesari, A. N.; Shaharyar, M. Asian J Res Chem 2009, 2, 34.

[12] Ravindra, K. C.; Vagdevi, H. M.; Vaidya, V. P.; Padmashali, B. Ind J Chem 2006, 45B, 2506.

[13] Desai, N. C.; Bhavsar, A. M.; Shah, M. D.; Saxena, A. K. Ind. J. Chem. 2008, 47B, 579.

[14] Mogilaiah, K.; Vidya, K. Ind. J. Chem. 2006, 45B, 1905.

[15] Khanum, S. A.; Sheena, S.; Umesha, S.; Kavitha, R. Eur J Med Chem 2005, 40, 1156.

[16] Ananthan, S.; Faaleolea, E. R.; Goldman, R. C.; Hobrath, J. V.; Kwong, C. D.; Laughon, B. E.; Maddry, J. A.; Mehta, A.; Rasmussen, L.; Reynolds, R. C.; Secrist III, J. A.; Shindo, N.; Showe, D. N.; Sosa, M. I.; Suling, W. J.; White, E. L. Tuberculosis 2009, 89, 334.

[17] Vazquez, G. N.; Salinas, G. M. M.; Fajardo, Z. V. D.; Villarreal, J. V.; Soto, S. E.; Salazar, F. G.; Nunez, E. H.; Fernandez, S. S.. Bioorg Med Chem 2007, 15, 5502.

[18] Pattan, S. R.; Rabara, P. A.; Pattan, J. S.; Bukitagar, A. A.; Wakale, V. S.; Musmade, D. S. Ind J Chem 2009, 48B, 1453.

[19] Mallikarjuna, B. P.; Sastry, B. S.; Kumar, G. V. S.; Rajendraprasad, Y.; Chandrashekar, S. M.; Sathisha, K. Eur J Med Chem 2009, 44, 4739.

[20] Kumar, A.; Rajput, C. S. Eur J Med Chem 2009, 44, 83.

[21] Akhter, M.; Husain, A.; Azad, B.; Ajmal, M. Eur J Med Chem 2009, 44, 2372.

[22] Boschelli, D. H.; Connor, D. T.; Bornemeier, D. A.; Dyer, R. D.; Kennedy, J. A.; Kuipers, P. J.; Okonkwo, G. C.; Schrier, D. J.; Wright, C. D. J. Med Chem 1993, 36, 1802.

[23] Bhandari, S. V.; Bothara, K. G.; Raut, M. K.; Patil, A. A.; Sarkate, A. P.; Mokale, V. J. Bioorg Med Chem 2008, 16, 1822.

[24] Wagle, S.; Adhikari, A. V.; Kumari, N. S. Indian J Chem, Sect B 2008, 47B, 439.

[25] Tan, T. M. C.; Chen, Y.; Kong, K. H.; Bai, J.; Li, Y.; Lim, S. G.; Ang, T. H.; Lama, Y. Antiviral Res 2006, 71, 7.

[26] El-Emam, A. A.; Al-Deeb, O. A.; Al-Omara, M.; Lehmann, J. Bioorg Med Chem 2004, 12, 5107.

[27] Ghani, U.; Ullah, N. Bioorg Med Chem 2010, 18, 4042.

[28] Abou-Seri, S. M. Eur J Med Chem 2010, 45, 4113.

[29] Kumar, D.; Sundaree, S.; Johnson, E. O.; Shah, K. Bioorg Med Chem Lett 2009, 19, 4492.

[30] Zaied, M. A. A.; Telbani, E. M. E.; Elgemeie, G. H.; Nawwar, G. A. M. Eur J Med Chem 2011, 46, 229.

[31] Zarghi, A.; Hamedi, S.; Tootooni, F.; Amini, B.; Sharift, B.; Faizi, M.; Tabatabai, S. A. Shafiee, A. Sci Pharm 2008, 76, 185.

[32] Yar, M. S.; Akhter, M. W. Acta Pol Pharm Drug Res 2009, 66, 393.

[33] Zuo, Y.; Yang, S. G.; Jiang, L. L.; Hao, G. F.; Wang, Z. F.; Wu, Q. Y.; Xi, Z.; Yang, G. F. Bioorg Med Chem 2012, 20, 296.

[34] Suresh Kumar, G. V.; Rajendraprasad, Y.; Mallikarjuna, B. P.; Chandrashekar, S. M.; Kistayya, C. Eur J Med Chem 2010, 45, 2063.

[35] Bondock, S.; Adel, S.; Etman, H. A.; Badria F. A. Eur J Med Chem 2012, 48, 192.

[36] Chen, Q.; Zhu, X. L.; Jiang, L. L.; Liu, Z. M.; Yang, G. F. Eur J Med Chem 2008, 43, 595.

[37] Shiradkar, M.; Suresh Kumar, G. V.; Dasari, V.; Tatikonda, S.; Akula, K. C.; Shah, R. Eur J Med Chem 2007, 42, 807.

[38] Oniga, S.; Oniga, O.; Brimdusa, T.; Mariana, P.; Muresan, A.; Donia, G. Farmacia 2000, XLVIII(3), 65.

[39] Cruickshank, R.; Duguid, J. P.; Marion, B. P.; Swain, R. H. A.. Medicinal Microbiology, 12th edn. Churchil Livingstone: London 1975, Vol 2, pp 196.

[40] Collins, H. A. Microbiological Methods, 2nd edn. Butterworth: London, 1976.

[41] Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically NCCLS Approval Standards. Wayne, PA: USA, 2003.

[42] NCCLS Approval Standard Document M2-A7, National Committee for Clinical Laboratory Standards. Vilanova, PA: USA, 2000.