chemistry proceedings

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Proceeding Paper

Synthesis and Antimicrobial Screening of Some New Thiazole Substituted 1,3,4-Oxadiazole Derivatives †

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† Presented at the 25th International Electronic Conference on Synthetic Organic Chemistry, 15–30 November 2021; Available online: https://ecsoc-25.sciforum.net/.

Abstract: In the present work, the synthesis and antimicrobial activity of new thiazole substituted 1,3,4-oxadiazole derivatives was achieved. The reaction of different thioamides with ethyl 4-chloro-3-oxobutanoate (4-chloro ethyl acetoacetate) provided ethyl 2-(2-arylthiazol-4yl)acetate, which on subsequent reaction with hydrazine hydrate in absolute ethanol afforded 2-(2-arylthiazol-4-yl)acetohydrazide. 2-(2-arylthiazol-4-yl)acetohydrazide, on reaction with CS_2 and KOH in aqueous ethanol, cyclized to form 5-((2-arylthiazol-4-yl)methyl)-1,3,4-oxadiazole-2-thiol. Finally, 5-((2-arylthiazol-4-yl)methyl)-1,3,4-oxadiazole-2-thiol was further treated with α-halo ketones at room temperature to achieve the target compounds. Most of the compounds showed good antibacterial activity, as well as antifungal activity.

Keywords: thiazole substituted 1,3,4-oxadiazole derivatives; thioamides; ethyl 4-chloro-3-oxobutanoate; α-halo ketones; antibacterial and antifungal activity

Citation: Kokate, S.V.; Patil, S.V. Synthesis and Antimicrobial Screening of Some New Thiazole Substituted 1,3,4-Oxadiazole Derivatives. *Chem. Proc.* **2022**, *8*, 12. https://doi.org/10.3390/ecsoc-25-11662

Academic Editor: Julio A. Seijas

Published: 15 November 2021

1. Introduction

It is observed from the relevant literature that thiazole heterocycle is an important moiety accompanied by numerous remarkable biological activities t with thiazole derivatives. Large uses of thiazole originated during the development of drugs for the treatment of allergies [1], inflammation [2], HIV infections [3], and, more recently, for the treatment of pain [4]. Thiazole has also been used as a new inhibitor of bacterial DNA gyrase B [5], as well as for the following purposes: antitumor [6], antibiotic [7–10], anti-inflammatory [11], antibacterial [12], antifungal [13], antitubercular [14–16], and antiviral [17]. It has also been used as a peroxisome proliferator-activated receptor (PPAR) $\alpha/\gamma/\delta$ pan agonist [18].

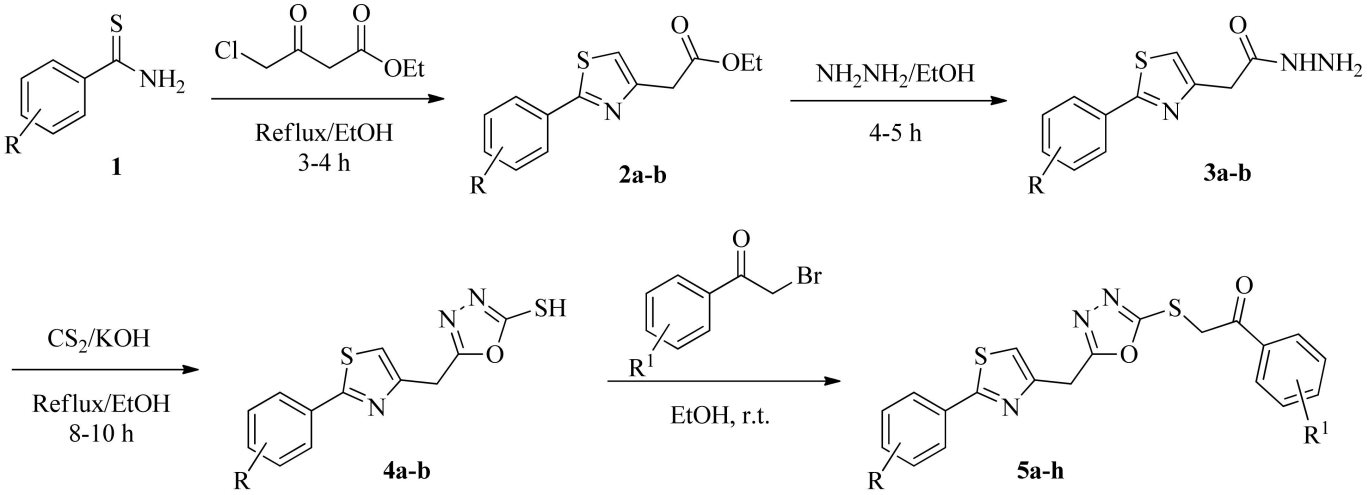
Furthermore, thiazole heterocycles are a noteworthy class of heterocyclic compounds that are present in several important biologically dynamic drug molecules, such as Ritonavir as an antiretroviral drug, Sulfathiazole as an antimicrobial drug, Tiazofurin as an antineoplastic drug, and Abafungin as an antifungal drug [19]. Thiazole-containing heterocycles perform various biological activities, such as antihypertensive, antimicrobial, antifungal, anti-HIV, anticonvulsant, and anti-inflammatory activities [20–24]. Derivatives of thiazole are also well-known to carry out anticancer activities [25–27]. Thiazole derivatives also perform anti-inflammatory [28,29], antibacterial [30], antihypertensive [31], antituberculosis [32], analgesic [33], and anticonvulsant activities [34].

A literature search revealed that an oxadiazole heterocycle clubbed with thiazole showed different biological activities, such as antimicrobial, antitumor, and antifungal activities [35–38], stearyl-CoA desaturase inhibition activity [39], antimicrobial and antitubercular activity [36,40], anti-proliferative, anti-mitotic, and microtubule destabilizing activities [41], and anti-micobacterial activity [42]. These results encouraged us to consider new thiazole-containing 1,3,4-oxadiazole derivatives and to monitor them for antibacterial

and antifungal activities. In the present work, we report the synthesis and antimicrobial activity of new thiazole-substituted 1,3,4-oxadiazole derivatives.

2. Results and Discussion

The structure of ethyl-2(2-arylthiazol-4yl) acetate **2a–b** was confirmed by the appearance of a band at 1725–30 cm^{-1}, due to C=O stretching of the ester functional group. The structures of compounds **3a–b** were confirmed by absorption bands in the regions of 3180–3320 cm^{-1} and 1680–1690 cm^{-1}, due to C=O and $NHNH_2$. The cyclization reaction of compounds **3a–b** with CS_2 in the presence of KOH to form 1,3,4-oxadiazoles **4a–b** was confirmed by the disappearance of bands at 3180–3320 cm^{-1} and 1680–1690 cm^{-1} and by the appearance of a new band at 2450–2510 cm^{-1}, due to SH stretching. The structures of **4a–b** were also confirmed by ^1H NMR spectra that showed a broad singlet at 11 ppm, due to SH, a singlet at 7.1–7.2 ppm, due to a thiazolyl proton, a singlet at 4.4–4.5 ppm, due to CH_2, and a multiplet at 7.4–8.2 ppm, due to aromatic protons. The conversion of **4a–b** to the target compounds **5a–h** (Scheme 1) was also confirmed by elemental analysis, IR, ^1H NMR, ^{13}C NMR, and MS. The IR spectra of these compounds showed bands at 1690–1700 cm^{-1}, due to C=O. The ^1H NMR spectra of compounds **5a–h** showed two singlets at 4.4–4.5 ppm and 4.8–4.9 ppm, due to two CH_2 groups, and one singlet in the region of 7.1–7.2 ppm, due to a thiazolyl proton, while the aromatic protons appeared as a multiplet at 7.4–8.2 ppm. The molecular ion peaks of all the title compounds were obtained from EI-MS. The presence of M+2 peaks were characteristic for the compounds, with chlorine and bromine atoms.



Compound	5a	5b	5c	5d	5e	5f	5g	5h
R	H	H	H	H	4-Cl	4-Cl	4-Cl	4-Cl
R^1	4-F	4-Cl	4-Br	H	4-F	4-Cl	4-Br	H

Scheme 1. Synthetic route for synthesis of **5a–h**.

3. Biological Results and Discussion

All of the synthesized compounds were screened for their antibacterial and antifungal activities. Most of the compounds **5a–h** showed good antibacterial and antifungal activities, as shown in Table 1. The antimicrobial activity results clearly indicated that S-substituted thiazolyl-1,3,4-oxadiazole derivatives **5a–h** showed enhanced antimicrobial activity, as compared to thiazolyl oxadiazole compound **4a** and **4b** in which the SH group is free. It was further observed that in compounds **5a** and **5e**, in which R^1 is 4-F substituted, showed good antibacterial activity and antifungal activity, irrespective of the R group.

Table 1. Antimicrobial screening of synthesized compounds.

Compound	*S. aureus*	*E. coli*	*B. subtilis*	*P. aeruginosa*	*A. niger*	*C. albicans*
4a	11.5	10	-	9.6	9.65	12.5
4b	10.9	8.85	9.12	-	8.9	11.6
5a	20	19	-	13.1	12.54	14
5b	17.8	-	-	12	-	12.5
5c	15.4	16.1	-	10.5	9.4	12
5d	14.6	14.8	-	10	9	11.5
5e	21.5	-	18.3	-	14.51	16.5
5f	18.5	17.5	15.4	-	-	14.7
5g	-	16	15	-	11.6	-
5h	15.3	14.8	14.6	-	10.3	12.4
Nystatin	NA	NA	NA	NA	21.12	21.96
Chloramphenicol	32.8	29.14	30.11	24.68	NA	NA

Zone diameter of growth inhibition in mm, calculated by digital vernier Caliper. NA = not applicable; (-) = inactive. Chloramphenicol (100 µg/disc) and nystatin (100 µg/disc) were used as references; synthesized compounds (100 µg/disc).

4. Experimental

General procedure for synthesis of (**3a**–**b**)*: synthesized as per reference No. 38.*

General procedure for the synthesis of 5-((2-arylthiazol-4-yl)methyl)-1,3,4-oxadiazole-2-thiol (**4a**–**b**) (Table 2).

Table 2. Physical data of compounds **4a**–**b**.

Compound	Color	M.P. (°C)	R_f Value/Solvent System (Ethyl Acetate/Hexane:s)	Yield (%)
4a	Grey	184–186	0.12/7:3	71
4b	Grey	218–220	0.13/7:3	75

To a mixture of compound **3** (1 mmol) in ethanol (25 mL), carbon disulphide (1.3 mmol) and potassium hydroxide (1 mmol) were added. The reaction mixture was refluxed gently in water bath till evolution of H_2S ceased. The progress of the reaction was monitored by TLC (30% Ethyl acetate/hexanes). After completion of the reaction, the solvent was completely removed and the residue was poured into water and acidified with concentrated HCl to obtain a solid product that was filtered, dried, and recrystallized from ethanol.

General procedure for the synthesis of 2-(5-(2-arylthiazol-4-yl)methyl)2-thiosubstituted-1,3,4-oxadiazole derivatives (**5a**–**h**).

To a stirred solution of compound **4a**–**b** (1 mmol) in ethanol, substituted α-haloketones (1 mmol) were added. The reaction mixture was stirred at room temperature. The reaction progress was monitored by TLC (30% Ethyl acetate/hexanes). After completion, the reaction mixture was poured into crushed ice to obtain a solid product that was filtered, dried, and purified by column chromatography on silica gel using 2% of ethyl acetate/hexanes.

5. Spectral Data

2-(5-((2-Phenylthiazol-4-yl)methyl)-1,3,4-oxadiazol-2-ylthio)-1-(4-fluorophenyl) ethanone (**5a**) Yield: (68%); m.p.: 99–103 °C; IR (KBr, cm^{-1}): 3120, 2931, 2854, 1690, 933 785, 688; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.4–7.6 (m, 5H, Ar-H), 7.1 (s, 1H, thiazolyl-H), 4.4 (s, 2H, CH_2), 4.8 (s, 2H, S-CH_2), 8.1 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.2 (dd, *J* = 11.5 and 8.2 Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 128.8, 129.0, 127.0, 132.0, 169.0, 109.0, 150.0, 32.0, 165.0, 169.0, 35.0, 183.0, 132.0, 130.0, [115.5, 115.8 (d, *J* = 22.5 Hz, 2C)], [165.3, 162.1 (d, *J* = 243 Hz, 1C)];

anal. calcd. for $C_{20}H_{14}FN_3O_2S_2$: C, 58.38; H, 3.43; N, 10.21; found: C, 58.24; H, 3.28; N, 10.42; MS (EI, 70 eV): *m*/*z* (%) 411 (M^+), 412 (M^{+1}).

2-(5-((2-Phenylthiazol-4-yl)methyl)-1,3,4-oxadiazol-2-ylthio)-1-(4-chlorophenyl) ethanone (**5b**) Yield: (65%); m.p.: 105–108 °C; IR (KBr, cm^{-1}): 3118, 2930, 1690, 938, 688; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.4–7.6 (m, 5H, Ar-H), 7.1 (s, 1H, thiazolyl-H), 4.4 (s, 2H, CH_2), 4.8 (s, 2H, S-CH_2), 7.7 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.9 (d, *J* = 8.4, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 128.8, 129.0 (2C), 127.0 (2C), 132.0, 169.0, 109.0, 150.0, 32.0, 165.0, 169.0, 35.0, 183.0, 137.0, 130.0 (2C), 131.0 (2C), 136.3; anal. calcd. for $C_{20}H_{14}ClN_3O_2S_2$: C, 56.13; H, 3.30; N, 9.82; found: C, 56.21; H, 3.28; N, 9.71; MS (EI, 70 eV): *m*/*z* (%) 427 (M^+), 428 (M^{+1}).

2-(5-((2-Phenylthiazol-4-yl)methyl)-1,3,4-oxadiazol-2-ylthio)-1-(4-bromophenyl) ethanone (**5c**) Yield: (70%); m.p.: 110–116 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.4–7.6 (m, 5H, Ar-H), 7.1 (s, 1H, thiazolyl-H), 4.4 (s, 2H, CH_2), 4.8 (s, 2H, S-CH_2), 7.9 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.6 (d, *J* = 8.3 Hz, 2H, Ar-H); anal. calcd. for $C_{20}H_{14}BrN_3O_2S_2$: C, 50.58; H, 2.99; N, 8.90; found: C, 50.49; H, 3.11; N, 8.85; MS (EI, 70 eV): *m*/*z* (%) 471 (M^+), 472 (M^{+1}).

2-(5-((2-Phenylthiazol-4-yl)methyl)-1,3,4-oxadiazol-2-ylthio)-1-phenylethanone (**5d**) Yield: (72%); m.p.: 100–106 °C; IR (KBr, cm^{-1}): 3120, 2931, 1690, 785, 688; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.4–7.9 (m, 10H, Ar-H), 7.1 (s, 1H, thiazolyl-H), 4.4 (s, 2H, CH_2), 4.8 (s, 2H, S-CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 128.8, 129.0 (2C), 127.0 (2C), 132.0, 169.0, 109.0, 150.0. 32.0, 165.0, 169.0, 35.0, 183.0, 135.0, 131.0 (2C), 131.5 (2C), 129.3; anal. calcd. for $C_{20}H_{15}N_3O_2S_2$: C, 61.05; H, 3.84; N, 10.68; found: C, 61.14; H, 3.74; N, 10.56; MS (EI, 70 eV): *m*/*z* (%) 393 (M^+), 394 (M^{+1}).

2-(5-((2-(4-Chlorophenylthiazol-4-yl)methyl)-1,3,4-oxadiazol-2-ylthio)-1-(4-fluoro phenyl)ethanone (**5e**) Yield: (69%); m.p.: 115–118 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.4 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.5 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.2 (s, 1H, thiazolyl-H), 4.4 (s, 2H, CH_2), 4.8 (s, 2H, S-CH_2), 8.1 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.3 (dd, *J* = 11.2 and 8.3 Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.2, 128.7 (2C), 128.3 (2C), 131.0, 170.1, 109.4, 150.1, 32.0 (CH_2), 166.4, 170.2, 35.0 (S-CH_2), 183.1 (C=O), 132.0, 130.0 (2C), [116.2, 115.9 (d, *J* = 22.5 Hz, 2C)], [164.4, 161.2 (d, *J* = 244 Hz, 1C)]; anal. calcd. for $C_{20}H_{13}ClFN_3O_2S_2$: C, 53.87; H, 2.94; N, 9.42; found: C, 53.79; H, 2.79; N, 9.34. MS (EI, 70 eV): *m*/*z* (%) 445 (M^+), 446 (M^{+1}).

2-(5-((2-(4-Chlorophenylthiazol-4-yl)methyl)-1,3,4-oxadiazol-2-ylthio)-1-(4-chlororophenyl) ethanone (**5f**) Yield: (64%); m.p.: 112–116 °C; IR (KBr, cm^{-1}): 3090, 2950, 1690, 2835, 964, 802, 765; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.4 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.5 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.2 (s, 1H, thiazolyl-H), 4.4 (s, 2H, CH_2), 4.8 (s, 2H, S-CH_2), 7.8 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.9 (d, *J* = 8.3 Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.2, 128.7 (2C), 128.3 (2C), 131.0, 170.1, 109.4, 150.1, 32.0 (CH_2), 166.4, 170.2, 35.0 (S-CH_2), 183.1 (C=O), 135.7, 130.0 (2C), 130.8 (2C), 136.7; anal. calcd. for $C_{20}H_{13}Cl_2N_3O_2S_2$: C, 51.95; H, 2.83; N, 9.09; found: C, 52.08; H, 2.76; N, 9.18. MS (EI, 70 eV): *m*/*z* (%) 461 (M^+), 462 (M^{+1}).

2-(5-((2-(4-Chlorophenylthiazol-4-yl)methyl)-1,3,4-oxadiazol-2-ylthio)-1-(4-bromo phenyl) ethanone (**5g**) Yield: (71%); m.p.: 101–105 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.4 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.5 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.2 (s, 1H, thiazolyl-H), 4.4 (s, 2H, CH_2), 4.8 (s, 2H, S-CH_2), 7.8 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.6 (d, *J* = 8.1 Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.2, 128.3 (2C), 128.5 (2C), 131.0, 170.0, 109.4, 150.1, 32.0 (CH_2), 166.4, 170.2, 35.0 (S-CH_2), 183.1 (C=O), 135.5, 131.0 (2C), 131.5 (2C), 128.0; anal. calcd. for $C_{20}H_{13}BrClN_3O_2S_2$: C, 47.40; H, 2.59; N, 8.29; found: C, 47.31; H, 5.57; N, 8.92. MS (EI, 70 eV): *m*/*z* (%) 505 (M^+), 506 (M^{+1}).

2-(5-((2-(4-Chlorophenylthiazol-4-yl)methyl)-1,3,4-oxadiazol-2-ylthio)-1-phenyl ethanone (**5h**) Yield: (69%); m.p.: 121–125 °C; IR (KBr, cm^{-1}): 3120, 2930, 1690, 933, 785, 688; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.4 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.5 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.2 (s, 1H, thiazolyl-H), 4.4 (s, 2H, CH_2), 4.8 (s, 2H, S-CH_2), 7.6–7.8 (m, 5H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.2, 128.5 (2C), 128.2 (2C), 131.1, 170.1, 109.5, 150.1, 32.2 (CH_2), 166..0, 170.2, 35.0 (S-CH_2), 183.1 (C=O), 135.8, 128.7 (2C), 128.5 (2C), 129.2; anal. calcd. for $C_{20}H_{14}ClN_3O_2S_2$:

C, 56.13; H, 3.30; N, 9.82; found: C, 56.27; H, 3.21; N, 9.78. MS (EI, 70 eV): m/z (%) 427 (M^+), 428 (M^{+1}).

6. Conclusions

Different S-substituted 1,3,4-oxadiazole derivatives were synthesized and evaluated for their antimicrobial activities. It was interesting to note that compounds with S-substitution were found to be biologically more potent than their respective unsubstituted derivatives. Therefore, our assumption that antimicrobial activity could be modified by incorporating more than one heterocyclic nucleus in the same molecule could possibly lead us to derivatives with enhanced activity. Thus, these molecules could act as lead molecules for further exploration of new drug molecules.

Author Contributions: Literature and spectral analysis, S.V.K.; Designing and synthesis of molecules, S.V.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Acknowledgments: The authors thank the G. E. Society's HPT Arts and RYK Science College, Nashik, for providing laboratory facility. The authors also thank BCUD, Pune University and UGC, New Delhi, for financial support.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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