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Synthesis and antimicrobial activity of oxadiazole nucleus containing 2,5-substituted 1,3,4-oxadiazole derivatives

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ABSTRACT

In this study, we report the synthesis of 2,5-substituted 1,3,4-oxadiazole derivatives using condensation of cyclohexanecarbohydrazide derivatives and carbon disulfide. In present study, we have prepared total seven derivatives based on 1,3,4-oxadiazole core further functionalized with thiol moieties. The structures of synthesized compounds (C_1-C_9) were confirmed by the ^{1}H NMR, and Mass spectrometry. These synthesized molecules were subjected to antibacterial and fungal activity against selected microbial and fungal strains. Some of derivatives showed good biological behaviour against gram positive and gram negative bacteria.

Keywords: 1,3,4-oxadiazole, cyclohexanecarbohydrazide, antibacterial, antifungal

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1. INTRODUCTION

In recent decades, chemists have focused on heterocyclic compounds and their various derivatives, as well as their applications in the pharmaceutical and chemical fields.[1] Further, the development of biologically active molecules based on molecular recognition is an attractive and challenging research topic in medicinal and supramolecular chemistry. Specially 1,3,4-Oxadiazole Analogs are essentially applied in medicine for the treatment of different kinds of fungal and promising antimicrobial agents, antifungal[1], anti-inflammatory[2], anticancer[3] and anti-HIV[4]. Compounds of this structure often exhibit greater activity than conventional antibiotics, namely penicillin G, ampicillin, and gentamicin. On the other hand, various reports show that the introduction of halogen atoms into the pharmacophore structure could be beneficial for antimicrobial activity if it improves the solubility of drugs in lipids. The vital essential for new antibiotics is mainly due to the increased incidence of bacterial infections by resistant strains, especially Gram-positive organisms, both in the hospital and in the community. 1,3,4-Oxadiazole derivatives are a relatively new class of antibiotics that inhibit bacterial protein synthesis by preventing the binding of aminoacyl t-RNA to the ribosome A site.[5]

1,3,4-Oxadiazole is a bioactive motif in medicinal chemistry.[6] The general use of this motif as a core moiety in medicinal chemistry establishes it as a member of the privileged structures. Substituted 1,3,4-oxadiazoles are some of the most important heterocyclic compounds, and they have gained attention because of their remarkable biological and pharmacological properties.[7–15] They have also attracted interest in medicinal chemistry as bioisosteres for carboxylic acids, esters, and carboxamides, which contribute substantially to increasing pharmacological activity by participating in hydrogen bonding interactions with receptors.[16]

A number of molecules based upon this monocyclic heterocyclic template have been investigated for their anti-inflammatory activity.[17-20] Addition to this, oxadiazole based molecules showed good light emitting properties and liquid crystalline nature with good temperature range of mesophase.[21-27] Further, gelation behaviour of oxadiazole linked calixarene based compounds is also well reported in literature.[28-30]

In present investigation, we have prepared total nine derivatives of oxadiazole linked thiol based moieties and characterized by using various spectroscopic methods. Further, these compounds showed good antibacterial and antifungal activity against various pathogens. We have compared our results with standard drugs for more understanding the structure activity relationship of target oxadiazole linked compounds respectively.

2. EXPERIMENTAL

The required raw materials are purchased from a lab-scale reagent supplier. And all raw materials used without further purification or any treatment. All the solvents were used in dry conditions or nitrogen atmosphere. In-process check TLC has performed aluminum plates with 0.2 mm of silica gel purchased from Merck aluminum. And visualized with UV light or other TLC stains. Melting points were done by the classical method using one end open capillary tube and are uncorrected. Purification was carried out using flash column chromatography with the silica gel 60-120 mesh. NMR spectroscopy was performed over Brucker AMX 300 MHz,

^{1}H FT-NMR using Acetonitrile/D_2O, Chloroform-d, DMSO as a solvent. MASS spectra were done by use of Shimadzu LCMS.

2. 1. Methyl 4-(trifluoromethyl)cyclohexane-1-carboxylate (2)

The slurry of methyl 4-(trifluoromethyl)benzoate **1** (204 g, 1.0 mole) in methanol (200 mL, 1 rel vol) charged in autoclave reactor followed by the addition of 5% Rhodium on alumina (4.0 g, 0.02 rel vol) catalyst. The vessel was pressurized with hydrogen at 10 Kg/cm^2 and heated at 60 °C for 12 h with vigorous stirring. Reaction monitored by TLC/HPLC/GC. After the reaction, cooled to RT and release the hydrogen pressure. The reaction mixture filtered through a celite bed, the filtrate concentrated to get crude oil. Purified by high vacuum distillation at boiling 110-120 °C/1-2 mmHg to get methyl 4-(trifluoromethyl)cyclohexane-1-carboxylate **2** as a liquid. Yield 72%, colorless liquid. ^{1}H NMR (300 MHz, Chloroform-d) δ 3.64 (s, 3H), 2.56 – 2.31 (m, 2H), 1.96 – 1.58 (m, 8H).

2. 2. 4-(trifluoromethyl)cyclohexane-1-carbohydrazide (3)

To the stirred solution of methyl 4-(trifluoromethyl)cyclohexane-1-carboxylate **2** in methanol (10 rel vol) was added hydrazine hydrate (1 rel vol) at RT in a single lot. The reaction mixture was heated at reflux for 12 h. TLC monitoring shows the completion of reaction conversion. The reaction mixture concentrates to dryness in vacuum to get residue which was suspended in water (5 rel vol) and stirred for 1 h. the slurry was filtered and washed with water, dried in a vacuum to get 4-(trifluoromethyl)cyclohexane-1-carbohydrazide **3**. Yield 88%, white solid. ^{1}H NMR (300 MHz, Chloroform-d) δ 8.71 (bs, 1H), 4.06 (d, *J* = 6.0 Hz, 2H), 2.50 – 2.44 (m, 1H), 2.44 – 2.31 (m, 1H), 1.91 – 1.60 (m, 8H). LCMS (MM-ES+APCI): 209.1 [M - H]$^-$.

2. 3. Potassium 2-(4-(trifluoromethyl)cyclohexane-1-carbonyl)hydrazine-1-carbodithioate (3A)

To a stirred solution of 4-(trifluoromethyl)cyclohexane-1-carbohydrazide **3** in isopropyl alcohol (20 rel vol) was added a solution of potassium hydroxide (2 eq) in isopropyl alcohol at below 5 °C. Carbon disulfide (1.1 eq) was added dropwise with vigorous stirring, during addition precipitation started. Stirred for 2 h at the same temperature. Filtered the solid, wash with cooled IPA, and ether under dry nitrogen condition. Dried in vacuum to get potassium 2-(4-(trifluoromethyl)cyclohexane-1-carbonyl)hydrazine-1-carbodithioate **3A.** yield 55%, white solid. ^{1}H NMR (300 MHz, Acetonitrile/D_2O) δ 2.67 – 2.51 (m, 1H), 2.50 – 2.32 (m, 1H), 2.01 – 1.68 (m, 9H). LCMS (MM-ES+APCI): 285.1 [M - H]$^-$.

2. 4. 5-(4-(trifluoromethyl)cyclohexyl)-1,3,4-oxadiazole-2-thiol (4)

To the stirred solution of potassium 2-(4-(trifluoromethyl)cyclohexane-1-carbonyl)hydrazine-1-carbodithioate **3A** in IPA (10 rel vol) was heated at reflux for 12 h. TLC monitoring shows the completion of reaction conversion. The reaction mixture concentrates on dryness in vacuum to get residue which was dissolved in water (5 rel vol) and adjust pH of 4 to 5 with dilute HCl. The reaction mixture extracted with ether (5 rel vol), separate organic, dried over sodium sulfate, and concentrated to get crude, which was purified by crystallization in a mixture of ether/Hexane (1:1) to afford solid 5-(4-(trifluoromethyl)cyclohexyl)-1,3,4-oxadiazole-2-thiol **4**. Yield 62%, crystalline pale yellow solid. ^{1}H NMR (300 MHz,

Chloroform-d) δ 5.57 (s, 1H), 3.14 - 3.05 (m, 1H), 2.49 - 2.28 (m, 1H), 2.23 – 2.17 (m, 2H), 1.89 - 1.54 (m, 6H). LCMS (MM-ES+APCI): 253.2 $[M + H]^+$.

2. 5. General Preparation of 2-substituted-5-(4-(trifluoromethyl)cyclohexyl)-1,3,4-oxadiazole derivatives from C1 to C9

To the stirred solution of 5-(4-(trifluoromethyl)cyclohexyl)-1,3,4-oxadiazole-2-thiol **4** and K_2CO_3 (2 eq) in THF (10 rel vol) was added alkyl halide (1.5 eq) dropwise at RT. The reaction mixture was heated at 45 °C for 5-6 h. TLC monitoring shows the completion of reaction conversion. The reaction mixture concentrated to dryness in vacuum to get residue which was suspended in water (5 rel vol) and extracted with ether (5 rel vol), separate organic, dried over sodium sulfate, and concentrated to get crude, which was purified by crystallization in a mixture of ether/Hexane (1:1) to afford following compounds.

2. 5. 1. 2-(methylthio)-5-(4-(trifluoromethyl)cyclohexyl)-1,3,4-oxadiazole (C1)

Yield 48%, pale yellow semi-solid. ^{1}H NMR (300 MHz, Chloroform-d) δ 3.15 – 3.06 (m, 1H), 2.72 (s, 3H), 2.48 – 2.27 (m, 1H), 2.32 – 2.16 (m, 2H), 1.88 – 1.58 (m, 6H). LCMS (MM-ES+APCI): 267.1 $[M + H]^+$.

2. 5. 2. 2-(ethyl thio)-5-(4-(trifluoromethyl)cyclohexyl)-1,3,4-oxadiazole (C2)

Yield 55%, pale yellow semi-solid. ^{1}H NMR (300 MHz, Chloroform-d) δ 3.29 – 3.04 (m, 3H), 2.47 – 2.17 (m, 3H), 1.90 – 1.58 (m, 6H), 1.35 (t, J = 9.0 Hz, 3H). LCMS (MM-ES+APCI): 281.1 $[M + H]^+$.

2. 5. 3. 2-(isopropylthio)-5-(4-(trifluoromethyl)cyclohexyl)-1,3,4-oxadiazole (C3)

Yield 39%, pale yellow solid. ^{1}H NMR (300 MHz, Chloroform-d) δ 4.20 – 4.01 (m, 1H), 3.37 – 3.22 (m, 1H), 2.68 – 2.47 (m, 1H), 2.52 – 2.36 (m, 2H), 2.09 – 1.89 (m, 4H), 1.94 – 1.78 (m, 2H), 1.50 (d, *J* = 6.0 Hz, 6H). LCMS (MM-ES+APCI): 295.1 $[M + H]^+$

2. 5. 4. 2-(cyclopropylthio)-5-(4-(trifluoromethyl)cyclohexyl)-1,3,4-oxadiazole (C4)

Yield 60%, pale yellow solid. ^{1}H NMR (300 MHz, Chloroform-d) δ 4.20 – 4.01 (m, 1H), 3.37 – 3.22 (m, 1H), 2.68 – 2.47 (m, 1H), 2.52 – 2.36 (m, 2H), 2.09 – 1.89 (m, 4H), 1.94 – 1.78 (m, 1H), 1.50 (d, *J* = 6.0 Hz, 4H). LCMS (MM-ES+APCI): 291.0 $[M - H]^-$

2. 5. 5. Ethyl 2-((5-(4-(trifluoromethyl)cyclohexyl)-1,3,4-oxadiazol-2-yl)thio)acetate (C5)

Yield 42%, white solid. ^{1}H NMR (300 MHz, Chloroform-d) δ 4.27 – 4.16 (m, 2H), 4.16 (s, 0H), 4.03 (s, 2H), 3.18 – 3.03 (m, 1H), 2.49 – 2.25 (m, 1H), 1.95 – 1.58 (m, 8H), 1.25 (t, *J* = 9.0 Hz, 3H). LCMS (MM-ES+APCI): 337.0 $[M - H]^-$

2. 5. 6. 2-((5-(4-(trifluoromethyl)cyclohexyl)-1,3,4-oxadiazol-2-yl)thio)acetonitrile (C6)

Yield 37%, off white solid. ^{1}H NMR (300 MHz, Chloroform-d) δ 4.17 (s, 2H), 3.15 – 3.04 (m, 1H), 2.49 –2.17 (m, 3H), 1.90 – 1.58 (m, 6H). LCMS (MM-ES+APCI): 292.3 $[M + H]^+$

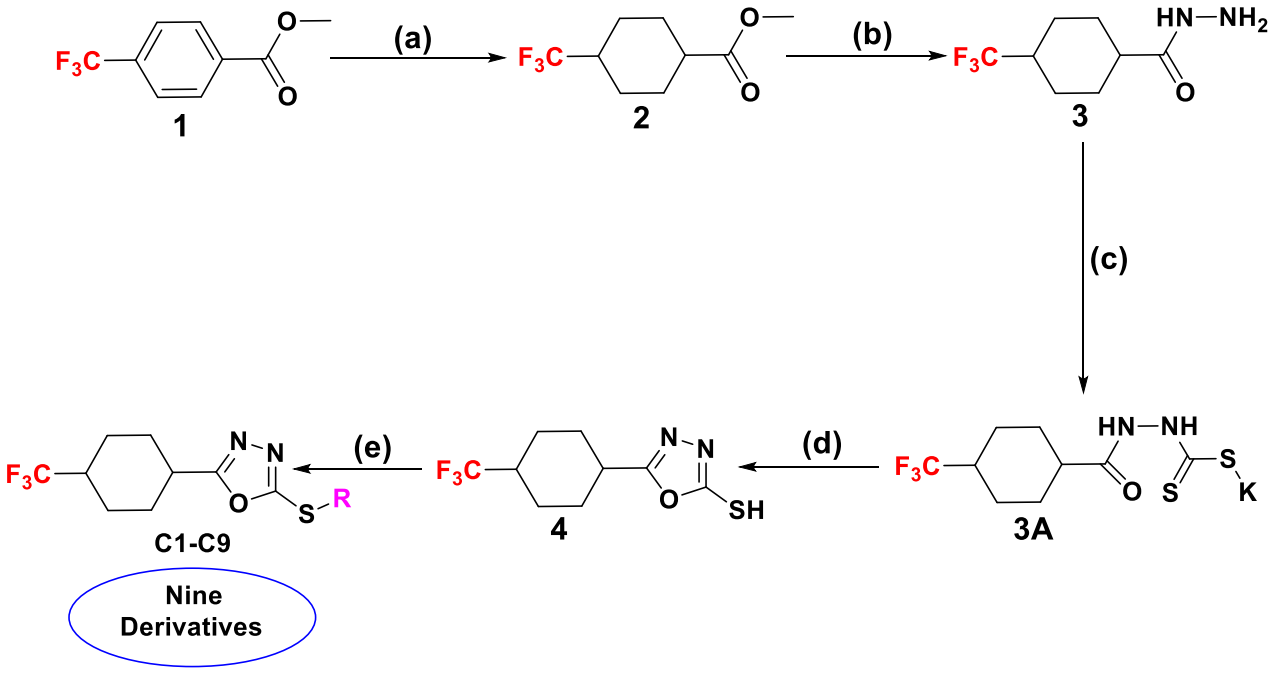
2. 5. 7. 2-((2-methoxyethyl)thio)-5-(4-(trifluoromethyl)cyclohexyl)-1,3,4-oxadiazole (C7)

Yield 59%, pale yellow solid. ^{1}H NMR (300 MHz, Chloroform-d) δ 3.61 – 3.50 (m, 2H), 3.48 – 3.40 (m, 2H), 3.23 (s, 3H), 3.19 – 3.04 (m, 1H), 2.49 – 2.28 (m, 1H), 2.27 – 2.17 (m, 2H), 1.90 – 1.58 (m, 6H). LCMS (MM-ES+APCI): 311.1 $[M + H]^+$

2. 5. 8. 2-((2,2-diethoxyethyl)thio)-5-(4-(trifluoromethyl)cyclohexyl)-1,3,4-oxadiazole (C8)

Yield 72%, pale yellow solid. ^{1}H NMR (300 MHz, Chloroform-d) δ 4.91 (t, *J* = 7.0 Hz, 1H), 3.66 – 3.50 (m, 4H), 3.48 (d, *J* = 7.0 Hz, 2H), 3.19 – 3.04 (m, 1H), 2.47 – 2.27 (m, 1H), 1.95 – 1.78 (m, 2H), 1.77 – 1.69 (m, 4H), 1.68 – 1.53 (m, 2H), 1.19 (t, *J* = 9.0 Hz, 6H). LCMS (MM-ES+APCI): 369.1 $[M + H]^+$

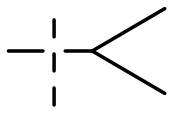
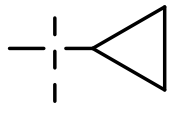
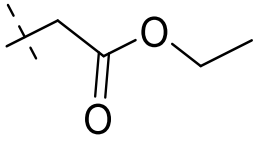
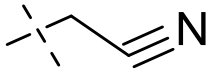
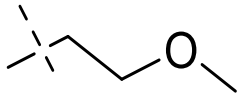
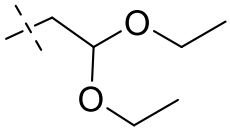
3. REACTION AND SCHEME



Scheme 1. Schematic way for preparation of desired compounds **(C_1-C_9);**

Table 1. Represenation of various - R groups used

	R =
C1	Me
C2	Et

C3	
C4	
C5	
C6	
C7	
C8	

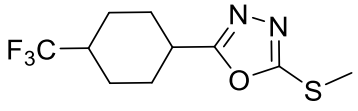
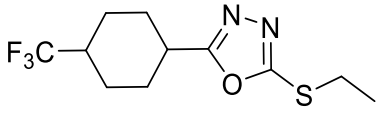
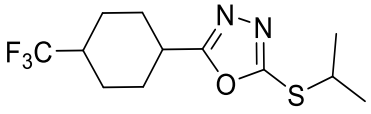
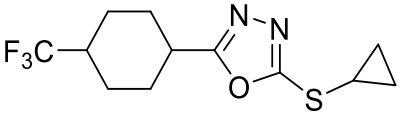
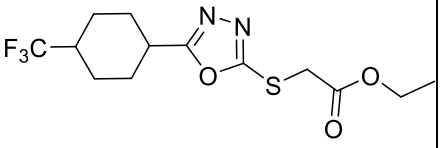
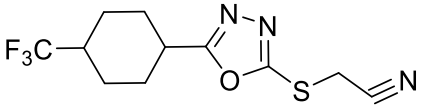
4. BIOLOGICAL ACTIVITY

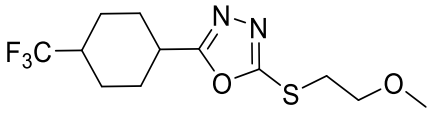
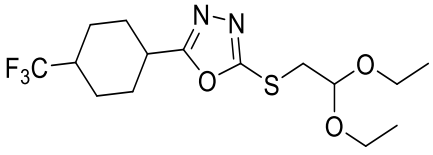
The study of the literature reveals that the 1,3,4-oxadiazole derivatives have an enormous therapeutic activity. The present study aims to synthesize 1,3,4-oxadiazole derivatives in the hope of having a fascinating antimicrobial activity. With these objective and various derivatives of 1,3,4-oxadiazole screened Antibacterial activity and antifungal activity. The purified products were screened for their antibacterial activity. The nutrient agar broth prepared by the usual method was inoculated aseptically with 0.5 ml of 24 hrs. old subcultures of *B. subtilis*, *C. tetani*, *S. typhi,* and *E. coli* in separate conical flasks at 40-50 °C and mixed well by gently shaking. About 25 ml content of the flasks were poured and evenly spread in a Petri-dish (12 cm in diameter) and allowed to set for two hrs.

The cups (10 mm in diameter) were formed with the help of a borer in agar medium and filled with 0.04 ml (40 μg) solution of the sample in DMSO. The plates were incubated at 37 °C for 24 hrs. and the inhibition of the bacterial growth was measured in millimeters and recorded as shown in respective data Table. *A. niger* and *C. Albicans* were employed for testing antifungal activity using the cup-plate method. The culture was maintained on Sabouraud's agar slants. Sterilized Sabouraud's agar medium was inoculated for 72 hrs. old 0.5 ml suspension of fungal spores in a separate flask. About 25 ml of the inoculated medium was evenly spread in a petri-dish and allowed to set for two hrs [31-41].

The cups (10 mm 34 in diameter) were punched. The plates were incubated at 30 °C for 48 hrs. After the completion of the incubation period, the zone of inhibition of growth in the form of a diameter in mm was measured. Along the test solution in each petri-dish one cup was filled up with solvent which acts as a control. The zones of inhibition are recorded in the data Table 2.

Table 2. Inhibition Zone of Microrganism Tested with Synthesised Compounds.

Compounds	Structure	% Inhibition Activity					
		Bacterial				Fungi	
		B. subtilis	*C. tetani*	*S. typhi*	*E. coli*	*A. niger*	*C. albicans*
C1		15	22	19	26	19	24
C2		18	26	21	22	17	17
C3		17	20	26	19	21	19
C4		14	28	23	22	26	15
C5		22	19	18	17	28	22
C6		17	16	19	15	14	18

C7		24	21	20	19	19	23
C9		11	24	22	23	22	20
Sparfloxacin		100	100	100	100	-	-
Fluconazole		-	-	-	-	100	100
Note: maximum concentration (100 µg/mL)							

5. CONCLUSIONS

The synthesis of 2-substituted-5-(4-(trifluoromethyl)cyclohexyl)-1,3,4-oxadiazole derivatives is discussed in Figure 1. methyl 4-(trifluoromethyl)benzoate is ring reduced by 5% Rhodium on alumina as catalyst using in methanol at 10 Kg/cm^2 and 60 °C for 12 h to get Methyl 4-(trifluoromethyl)cyclohexane-1-carboxylate. Which was treated with hydrazine hydrate at reflux temperature in Methanol as a solvent to get 4-(trifluoromethyl)cyclohexane-1-carbohydrazide. This isolated hydrazide compound reacted with carbon disulfide and potassium hydroxide as a base in isopropyl alcohol at lower temperature yielded Potassium 2-(4-(trifluoromethyl)cyclohexane-1-carbonyl)hydrazine-1-carbodithioate.

This potassium salt was carried forward for cyclization in the same solvent IPA at reflux temperature to get 5-(4-(trifluoromethyl)cyclohexyl)-1,3,4-oxadiazole-2-thiol. Then thiol was undergoing a classical alkylation reaction using potassium carbonate as base and different alkyl halide in THF at a temperature range of 40 to 50 °C to get 2-substituted-5-(4-(trifluoromethyl)cyclohexyl)-1,3,4-oxadiazole derivatives. Synthesized compound C4 showing moderate antibacterial activity against *C. tetani* were as C9 very low against *B. subtilis* and rest of all shows between moderate to low. Compound C5 showing moderate antifungal activity against *A. niger* were as C6 very low against *A. niger* and rest of all shows between moderate to low.

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