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Original article

Synthesis and biological property of some novel 1,3,4-oxadiazoles☆

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ABSTRACT

A series of biphenyl-1,3,4-oxadiazoles namely 5-[substituted-(1,1′-biphenyl)-3-yl]-1,3,4-oxadiazole-2(3H)-thiones and its S-alkyl derivatives have been synthesized by multi step organic synthesis involving Suzuki-Miyaura coupling using palladium catalyst. The synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, IR and LCMS spectroscopic properties. They were tested for their antimicrobial and analgesic activities. Some of them showed significant activity.

1. Introduction

Palladium catalyzed cross-coupling between a formal electrophile C-X (X=Br, I etc.) and an organometallic species C-M (M = Mg, Zn, Sn and B) is a versatile synthetic route for making C–C bonds [1]. The discovery by Suzuki and Miyaura [2] that arylboronic acids undergo palladium catalyzed cross-coupling with aryl halides in the presence of a base has stimulated enormous interest in the application of the Suzuki reaction and variants developed subsequently, to the synthesis of unsymmetrical biaryls and related compounds.

It has been reported in the literature that compounds bearing 1,3,4-oxadiazole ring possess significant biological properties such as anti-inflammatory [3,4,5], hypoglycemic [6], antifungal [7], antibacterial [8a–c], anticancer [9], antitubercular [10], analgesic [11], antiviral [12] activities. Some of the oxadiazole derivatives act as muscle relaxants [13], hypnotic, sedatives [14], and show antimitotic activities [15]. Some material applications of oxadiazole derivatives in the fields of photosensitizers [16] and liquid crystals have also been reported [17].

Further sulphur and fluorine containing molecules are known for their interesting bioactivities and have attracted considerable attention in the pesticide and medicinal formulation [18].

In view of these findings and as a part of our general search for biologically active nitrogen, sulphur and oxygen containing heterocycles, we have employed the Suzuki-Miyaura reaction with palladium catalyst and to synthesize a series of 5-[substituted-(1,1′-biphenyl)-3-yl]-1,3,4-oxadiazole-2(3H)-thione **5a–d** and its S-alkyl derivative **6a–9d**.

2. Results and discussion

2.1. Chemistry

The synthesis of hitherto unreported title compounds was performed as outlined in Scheme 1. Ethyl 3-bromobenzoate (**2**) was prepared from its acid derivative. This underwent palladium catalyzed Suzuki reaction with various boronic acids to form the substituted biphenyl compounds **3a–d** in good yield [2]. The esters **3a–d** on hydrazinolysis with hydrazine hydrate yielded the corresponding hydrazides **4a–d** [19]. Intramolecular cyclization of **4a–d** with carbon disulfide resulted in 5-[substituted-(1,1′-biphenyl)-3-yl]-1,3,4-oxadiazole-2(3H)-thiones **5a–d** [3,20]. Compounds **5a–d** were regioselectively S-alkylated with alkyl halides having interesting functional groups, to give compounds **6a–9d** in good yield [4,21]. The structures of the newly synthesized compounds have been established on the basis of ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, IR and mass spectral studies.

In the IR spectra of compounds **5a–d** the C–O–C, C=S and C=N absorption bands were observed in the region of 1167–1180, 1245–1255 and 1599–1618 cm^{-1} respectively. For compounds

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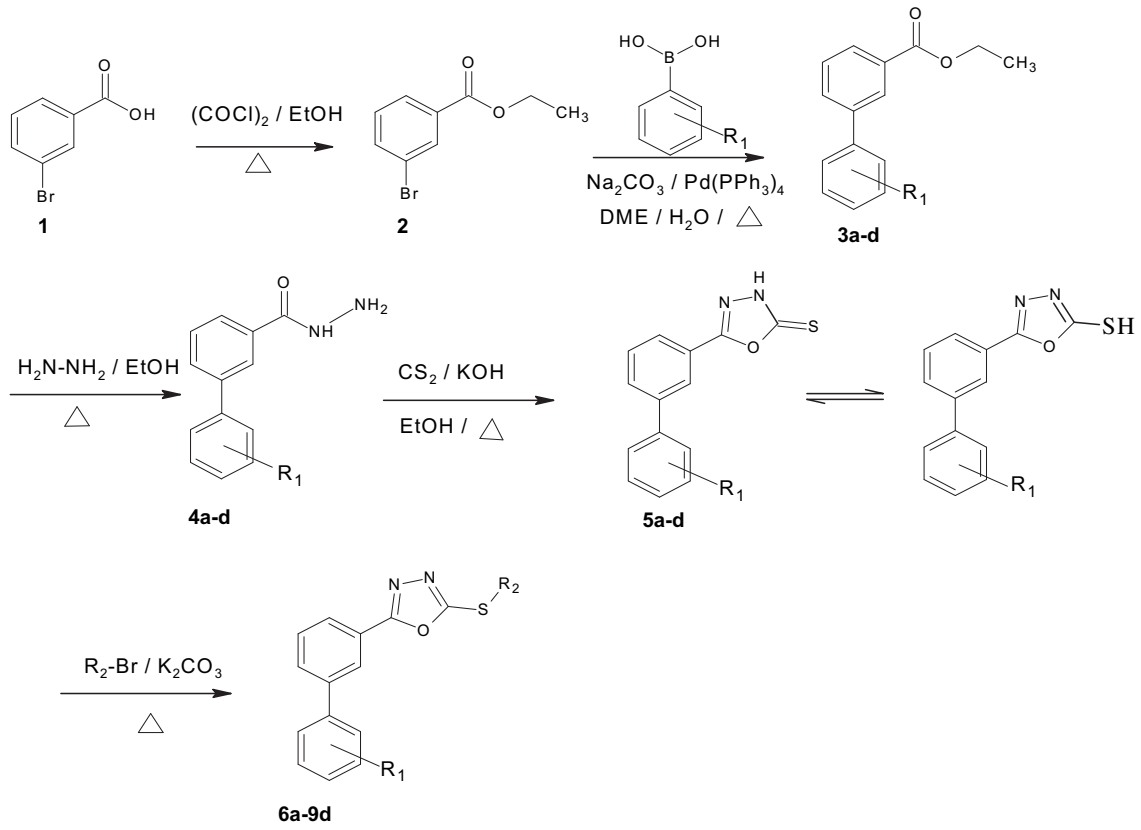

	R_1	R_2		R_1	R_2
6a:	5'-F, 2'-OMe	$-(CH_2)_3COOMe$	**8a:**	5'-F, 2'-OMe	$-(CH_2)_3CN$
6b:	2'-OMe	$-(CH_2)_3COOMe$	**8b:**	2'-OMe	$-(CH_2)_3CN$
6c:	2'-F	$-(CH_2)_3COOMe$	**8c:**	2'-F	$-(CH_2)_3CN$
6d:	3'-Cl	$-(CH_2)_3COOMe$	**8d:**	3'-Cl	$-(CH_2)_3CN$
7a:	5'-F, 2'-OMe	$-(CH_2)_4F$	**9a:**	5'-F, 2'-OMe	$-C_2H_5$
7b:	2'-OMe	$-(CH_2)_4F$	**9b:**	2'-OMe	$-C_2H_5$
7c:	2'-F	$-(CH_2)_4F$	**9c:**	2'-F	$-C_2H_5$
7d:	3'-Cl	$-(CH_2)_4F$	**9d:**	3'-Cl	$-C_2H_5$

Scheme 1.

6a–**9d** the band at 1245–1255 cm^{-1} disappeared indicating the S-alkylation. Further in the IR spectra of compounds **6a**–**d** the ester carbonyl appeared as a strong band in the region of 1731–1742 cm^{-1}. In compounds **8a**–**d** the carbon-nitrogen triple bond appeared around 2242–2246 cm^{-1}.

In the ^1H NMR spectra of **4a**–**d** the NH proton were seen around 9.80–9.91 ppm, whereas in compounds **5a**–**d** the NH signal was shifted to 14.80 ppm, indicating the thiol-thione tautomerism. For compounds **6a**–**9d** the formation of S-alkyl derivative was indicated by the presence of a peak around 3.32–3.42 ppm for the S–CH_2 group. Similarly in the ^{13}C NMR of **5a**–**d** the C=S signal was observed at around 177–182 ppm. However in compounds **6a**–**9d** this signal was absent which is a strong evidence for S-alkylation.

In ^{19}F NMR of compounds **6a** and **6c** the signals observed at −123.2 and −128.2 ppm were due to fluorines at the aromatic ring. In compounds **7b** and **7d** having fluorine attached to an aliphatic system the signals were seen at −218.5 and −220.9 ppm respectively.

2.2. Biological activity

The antibacterial activities of compounds **5a**–**d** and **6a**–**9d** were evaluated against four bacterial strains namely *Staphylococcus aureus, Pseudomonas aeruginosa, Eschericia coli, Bascillus subtilis* by cup-plate method.

The results indicated that the compounds having a fluoro substituent in the biphenyl ring showed maximum activity (**5c, 6c,**

7c, **8c**). The results are summarized in Table 1. None of the tested compounds showed any significant antifungal activity.

The compounds were tested for their analgesic activity using Eddy's hot plate method. The results are summarized in Table 2. Analgesic results showed that compounds **5a–b, 5d, 6a–b, 6d, 7b, 7d** and **8b** had high activity, whereas compounds **5c, 6c**, **7a, 7c**, **8a, 8c** and **8d** had moderate activity.

3. Conclusion

A series of 1,3,4-oxadiazoles, namely 5-[substituted-(1,1′-biphenyl)-3-yl]-1,3,4-oxadiazole-2(3H)-thiones **5a–d** and its S-alkyl derivatives **6a–9d** have been synthesized in good yield and screened for their antibacterial, antifungal and analgesic activities. The antibacterial screening showed that among the tested compounds, the fluoro substituted compound **7c** exhibited the highest activity against all the tested microorganisms.

Analgesic activity screening indicated that the compounds bearing ester functional group in the S-alkylated derivatives **6a–b** and **6d** gave the highest activities.

4. Experimental

4.1. Chemistry

Thin layer chromatography was used to analyse the reaction progress and purity of the compounds synthesized. Melting points were determined in open glass capillary methods and were uncorrected. IR spectra were obtained in KBr discs on a Shimadzu-8400 FTIR spectrophotometer, ^{1}H NMR spectra were recorded on Brucker spectrometer (400 MHz) in DMSO-d_6/$CDCl_3$ using TMS as an internal standard, Mass spectra were recorded on Agilent 6320 Ion Trap method, ^{13}C NMR spectra were recorded on Brucker spectrometer (100 MHz) in DMSO-d_6/$CDCl_3$. ^{19}F NMR spectra were recorded on 376 MHz in $CDCl_3$ as solvent.

4.1.1. Procedure for synthesis of ethyl 3-bromobenzoate: (**2**)

Oxalyl chloride (50.5 g, 398 mmol) and catalytic amount of *N,N*-dimethylformamide were added to a solution of 3-bromobenzoic acid (**1**) (20.0 g, 99.5 mmol) in ethyl alcohol (200 mL) and the resulting mixture was heated to 95 °C for 3 h. The solvent was removed and the compound was taken in ethyl acetate (500 mL), washed with water (200 mL), saturated sodium bicarbonate solution (100 mL), saturated sodium chloride solution (100 mL), dried over sodium sulphate, concentrated to afford compound **2** (20.5 g, 89.51 mmol, 90%) as colorless liquid.

^{1}H NMR (DMSO-d_6) δ: 1.21 (t, 3H, J = 7.2, CH_3), 4.23 (q, 2H, J = 7.1, OCH_2), 7.58–7.65 (m, 1H, Ar–H), 7.78 (d, 1H, J = 8.1, Ar–H), 7.90 (d, 1H, J = 8.1, Ar–H), 8.08 (s, 1H, Ar–H); GCMS: (m/z) 229.

4.1.2. Procedure for synthesis of ethyl 5′-fluoro-2′-methoxy-(1,1′-biphenyl)-3-carboxylate: (**3a**)

To a degassed mixture of compound **2** (20.0 g, 87.33 mmol), 5-fluoro-2-methoxy boronic acid (17.8 g, 104.8 mmol), sodium carbonate (37.0 g, 349.32 mmol), in 1,2-dimethoxy ethane (100 mL) and water (40 mL), palladium tetrakis (1.0 g, 0.87 mmol) was added and resulting mixture was heated to 85 °C for 10 h. The solvents were removed and the compound was taken in ethyl acetate (500 mL), washed with water (200 mL), saturated sodium bicarbonate solution (100 mL), saturated sodium chloride solution (100 mL), dried over sodium sulphate. The contents were concentrated and purified by column chromatography [3–5% ethyl acetate in petroleum ether] to afford compound **3a** (14.3 g, 51.09 mmol, 58%) as colorless liquid.

Compound **3a**: ^{1}H NMR (DMSO-d_6) δ: 1.31 (t, 3H, J = 7.1, CH_3), 3.74 (s, 3H, OMe), 4.33 (q, 2H, J = 7.1, OCH_2), 7.13–7.23 (m, 3H, Ar–H), 7.54–7.59 (m, 1H, Ar–H), 7.76 (d, 1H, J = 7.9, Ar–H), 7.94 (d, 1H, J = 7.8, Ar–H), 8.04 (s, 1H, Ar–H); ^{13}C NMR (DMSO-d_6) δ: 14.1, 55.2, 60.9, 112.0, 115.7, 115.8, 122.0, 123.0, 124.0, 127.0, 128.0, 131.0, 133.0, 151.6 (d, J = 230.1), 159.0, 166.0; ^{19}F NMR ($CDCl_3$) δ: -123.3 (m, 1F); GCMS: (m/z) 274.

Compound **3b**: yield: 10.1 g, 39.06 mmol, 55%, colorless oil; ^{1}H NMR (DMSO-d_6) δ: 1.41 (t, 3H, J = 7.1, CH_3), 3.83 (s, 3H, OMe), 4.11 (q, 2H, J = 7.0, OCH_2), 7.01–7.08 (m, 2H, Ar–H), 7.33–7.39 (m, 2H, Ar–H), 7.45–7.51 (m, 1H, Ar–H), 7.73 (d, 1H, J = 9.1, Ar–H), 8.01 (d, 1H, J = 9.1, Ar–H), 8.21 (s, 1H, Ar–H); ^{13}C NMR (DMSO-d_6) δ: 14.0, 55.0, 60.9, 108.0, 118.0, 122.0, 124.1, 126.4, 127.0, 128.0, 129.0, 129.9, 132.0, 136.7, 157.9, 166.2; GCMS: (m/z) 256.

Compound **3c**: yield: 11.2 g, 45.08 mmol, 50%, colorless oil; ^{1}H NMR ($CDCl_3$) δ: 1.42 (t, 3H, J = 7.1, CH_3), 4.44 (q, 2H, J = 7.1, OCH_2), 7.16–7.26 (m, 2H, Ar–H), 7.35–7.37 (m, 1H, Ar–H), 7.45 (d, 1H, J = 8.0, Ar–H), 7.51–7.55 (m, 1H, Ar–H), 7.75 (d, 1H, J = 9.0, Ar–H), 8.07 (d, 1H, J = 9.0, Ar–H), 8.23 (s, 1H, Ar–H); ^{13}C NMR (DMSO-d_6) δ: 14.0, 60.9, 113.0, 122.2, 123.0, 126.0, 127.9, 128.0,

Table 1
Antibacterial activity data (μg/mL) of the compounds **5a–d, 6a–9d**: zone of inhibition in mm.

Compound	Gram-positive bacteria				Gram-negative bacteria			
	S. aureus		*B. subtilis*		*E. coli*		*P. aeruginosa*	
	50 (μg/mL)	100 (μg/mL)	50 (μg/mL)	100 (μg/mL)	50 (μg/mL)	100 (μg/mL)	50 (μg/mL)	100 (μg/mL)
5a	12	17	12	19	08	20	14	19
5b	11	18	10	21	12	18	11	18
5c	15	20	12	19	15	19	18	21
5d	10	11	13	09	11	16	09	14
6a	10	16	13	18	15	18	13	19
6b	09	14	11	15	07	16	18	21
6c	15	17	09	16	09	16	13	21
6d	10	16	11	18	18	19	06	18
7a	12	15	10	17	12	19	07	15
7b	15	21	15	20	12	16	06	15
7c	13	20	20	22	13	19	17	18
7d	05	12	15	20	12	15	15	20
8a	07	13	07	18	10	18	15	18
8b	12	18	17	20	10	20	09	20
8c	11	16	12	18	17	21	16	20
8d	10	15	08	16	10	17	12	16
Streptomycin	–	–	–	–	21	25	21	25
Procaine penicillin	22	27	24	28	–	–	–	–

Table 2
Analgesic activities of the compounds **5a**–**d** and **6a**–**9d**.

Reaction time (s) after drug administration					
Compound	0 h ± SE[a]	0.5 h ± SE[a]	1 h ± SE[a]	2nd h ± SE[a]	4th h ± SE[a]
5a	4.35 ± 0.10	5.22 ± 0.24	5.74 ± 0.21	8.41 ± 0.31	6.35 ± 0.77
5b	4.43 ± 0.08	4.94 ± 0.21	5.84 ± 0.89	7.61 ± 0.71	6.28 ± 0.37
5c	4.46 ± 0.09	4.99 ± 0.15	5.24 ± 0.21	5.38 ± 0.15	5.04 ± 0.02
5d	4.15 ± 0.06	4.71 ± 0.12	4.84 ± 0.21	5.01 ± 0.11	5.08 ± 0.01
6a	4.73 ± 0.11	4.75 ± 0.09	5.11 ± 0.02	6.01 ± 0.18	6.01 ± 0.22
6b	4.91 ± 0.21	5.01 ± 0.19	5.21 ± 0.15	6.58 ± 0.13	6.21 ± 0.16
6c	4.43 ± 0.14	4.53 ± 0.14	4.62 ± 0.15	4.84 ± 0.11	4.49 ± 0.11
6d	4.71 ± 0.13	4.96 ± 0.11	5.36 ± 0.11	6.58 ± 0.15	5.59 ± 0.12
7a	4.31 ± 0.08	4.35 ± 0.09	4.48 ± 0.11	4.72 ± 0.15	4.55 ± 0.14
7b	4.59 ± 0.11	4.9 ± 0.09	5.01 ± 0.98	6.17 ± 0.17	6.01 ± 0.21
7c	4.51 ± 0.19	4.62 ± 0.19	4.69 ± 0.19	4.87 ± 0.25	4.47 ± 0.16
7d	4.48 ± 0.13	5.56 ± 0.22	5.79 ± 0.25	8.35 ± 0.34	6.44 ± 0.72
8a	4.88 ± 0.11	4.92 ± 0.11	4.86 ± 0.04	4.99 ± 0.08	4.74 ± 0.13
8b	5.05 ± 0.11	5.25 ± 0.08	5.40 ± 0.11	6.57 ± 0.22	5.59 ± 0.25
8c	4.44 ± 0.13	4.54 ± 0.15	4.71 ± 0.19	4.92 ± 0.23	4.49 ± 0.09
8d	4.24 ± 0.08	4.51 ± 0.01	4.77 ± 0.81	5.12 ± 0.12	4.71 ± 0.21
Control	4.18 ± 0.04	4.17 ± 0.04	4.38 ± 0.12	4.86 ± 0.18	4.57 ± 0.11
Standard	4.24 ± 0.04	5.58 ± 0.07	5.93 ± 0.09	8.06 ± 0.31	7.85 ± 0.37

[a] SE = Standard Error.

129.3, 130.0, 133.0, 133.6, 136.2, 162.2 (d, J = 256.1), 166.2; ^{19}F NMR ($CDCl_3$) δ: -127.4 (m, 1F); GCMS: (m/z) 244.

Compound **3d** [22]: yield: 13.1 g, 50.01 mmol, 51%, colorless oil; ^{1}H NMR ($CDCl_3$) δ: 1.43 (t, 3H, J = 7.1, CH_3), 4.44 (q, 2H, J = 7.1, OCH_2), 7.35–7.41 (m, 2H, Ar–H), 7.43–7.57 (m, 2H, Ar–H), 7.61–7.62 (m, 1H, Ar–H), 7.75 (d, 1H, J = 10.8, Ar–H), 8.05 (d, 1H, J = 10.8, Ar–H), 8.24 (1H, s, Ar–H); GCMS: (m/z) 260.

*4.1.3. Procedure for synthesis of 5′-fluoro-2′-methoxy-(1,1′-biphenyl)-3-carbohydrazide: (**4a**)*

To a solution of **3a** (14.3 g, 51.09 mmol) in ethyl alcohol (160 mL), hydrazine hydrate (3.8 g, 76.64 mmol) was added and resulting mixture was heated to 100 °C for 10 h. The mixture was concentrated and to the residue water was added and resulting solid was filtered, washed with water and recrystalized from ethyl alcohol to give compound **4a** (8.3 g, 31.92 mmol, 62%) as a white solid.

Compound **4a**: mp: 199–200 °C; ^{1}H NMR (DMSO-d_6) δ: 3.74 (s, 3H, OCH_3), 4.51 (bs, 2H, NH_2), 7.11–7.25 (m, 3H, Ar–H), 7.45–7.49 (m, 1H, Ar–H), 7.64 (d, 1H, J = 7.7, Ar–H), 7.78 (d, 1H, J = 7.7, Ar–H), 7.90 (s, 1H, Ar–H), 9.81 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 55.2, 112.0, 116.5, 116.8, 124.0, 126.0, 128.1, 129.5, 130.1, 131.1, 136.5, 152.3 (d, J = 230.3), 161.0, 171.0; ^{19}F NMR ($CDCl_3$) δ: -124.1 (m, 1F); LCMS: M+1: 261.

Compound **4b**: yield: 5.6 g, 23.14 mmol, 60%, white solid; mp: 180–181 °C; ^{1}H NMR (DMSO-d_6) δ: 3.75 (s, 3H, OCH_3), 4.61 (bs, 2H, NH_2), 7.11–7.12 (m, 2H, Ar–H), 7.31–7.35 (m, 2H, Ar–H), 7.43–7.48 (m, 1H, Ar–H), 7.59 (d, 1H, J = 7.7, Ar–H), 7.73 (d, 1H, J = 7.6, Ar–H), 7.88 (s, 1H, Ar–H), 9.79 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 56.0, 109.0, 120.1, 125.1, 126.2, 128.1, 128.6, 130.0, 131.0, 134.1, 136.1, 137.3, 159.0, 172.0; LCMS: M+1: 243.

Compound **4c**: yield: 6.0 g, 26.24 mmol, 58%, white solid; mp: 172–174 °C; ^{1}H NMR (DMSO-d_6) δ: 4.91 (bs, 2H, NH_2), 7.29–7.36 (m, 2H, Ar–H), 7.41–7.43 (m, 1H, Ar–H), 7.52–7.61 (m, 2H, Ar–H), 7.69 (d, 1H, J = 7.6, Ar–H), 7.85 (d, 1H, J = 7.7, Ar–H), 7.98 (s, 1H, Ar–H), 9.86 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 113.0, 124.1, 127.1, 128.2, 131.0, 131.5, 133.2, 133.8, 135.2, 135.8, 136.1, 162.1 (d, J = 253.4), 171.2; ^{19}F NMR ($CDCl_3$) δ: -128.1 (m, 1F); LCMS: M+1: 231.

Compound **4d**: yield: 6.8 g, 27.6 mmol, 55%, white solid; mp: 160–162 °C; ^{1}H NMR (DMSO-d_6) δ: 4.51 (bs, 2H, NH_2), 7.42–7.56 (m, 4H, Ar–H), 7.58 (d, 1H, J = 7.7, Ar–H), 7.69–7.85 (m, 2H, Ar–H), 8.11 (s, 1H, Ar–H), 9.91 (bs, 1H, NH); LCMS: M+1: 247.

*4.1.4. Procedure for synthesis of 5-[5′-fluoro-2′-methoxy-(1,1′-biphenyl)3-yl]-1,3,4-oxadiazole-2(3H)-thione: (**5a**)*

To a solution of **4a** (8.2 g, 31.53 mmol) in ethyl alcohol (140 mL), carbon disulfide (4.79 g, 63.07 mmol), and potassium hydroxide (1.76 g, 31.53 mmol) were added and the resulting solution was heated to reflux for 10 h. The reaction mixture was concentrated and the residue was dissolved in water and acidified with hydrochloric acid. The resulting solid was filtered, dried and recrystallized from ethanol to afford compound **5a** (4.3 g, 14.23 mmol, 45%) as a white solid.

Compound **5a**: mp: 176.6–178 °C; IR (KBr): 1178 (C–O–C), 1245 (C=S) 1618 (C=N), 3073 cm^{-1} (=C–H of Ar); ^{1}H NMR (DMSO-d_6) δ: 3.75 (s, 3H, OCH_3), 7.13–7.27 (m, 3H, Ar–H), 7.61–7.65 (m, 1H, Ar–H), 7.73 (d, 1H, J = 9.0, Ar–H), 7.86 (d, 1H, J = 9.0, Ar–H), 7.95 (s, 1H, Ar–H), 14.81 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 56.2, 113.3, 115.5, 116.7, 122.4, 125.1, 126.6, 129.4, 129.5, 133.1, 137.9, 152.4, 156.4 (d, J = 235.1), 160.4, 177.4; ^{19}F NMR ($CDCl_3$) δ: -122.1 (m, 1F) LCMS: M+1: 303.

Compound **5b**: yield: 3.3 g, 11.61 mmol, 50%, white solid; mp: 144–146.8 °C; IR (KBr): 1180 (C–O–C), 1249 (C=S) 1599 (C=N), 3059 cm^{-1} (=C–H of Ar); ^{1}H NMR (DMSO-d_6) δ: 3.77 (s, 3H, OCH_3), 7.03–7.08 (m, 1H, Ar–H), 7.13 (d, 1H, J = 8.1, Ar–H), 7.33–7.41 (m, 2H, Ar–H), 7.59–7.64 (m, 1H, Ar–H), 7.73 (d, 1H, J = 7.7, Ar–H), 7.83 (d, 1H, J = 7.6, Ar–H), 7.93 (s, 1H, Ar–H), 14.7 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 60.8, 117.1, 126.1, 127.5, 129.7, 131.7, 133.3, 134.5, 134.8, 135.5, 138.2, 144.3, 161.2, 165.7, 182.6; LCMS: M-1: 283.

Compound **5c**: yield: 3.6 g, 13.23 mmol, 51%, white solid; mp: 155–158 °C; IR (KBr): 1178 (C–O–C), 1255 (C=S) 1607 (C=N), 3082 cm^{-1} (=C–H of Ar); ^{1}H NMR (DMSO-d_6) δ: 7.33–7.36 (m, 3H, Ar–H), 7.39–7.51 (m, 1H, Ar–H), 7.60–7.69 (m, 1H, Ar–H), 7.81 (d, 1H, J = 7.6, Ar–H), 7.92 (d, 1H, J = 8.1, Ar–H), 7.99 (s, 1H, Ar–H), 14.81 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 113.1, 116.1, 116.3, 121.5, 124.7, 126.7 128.5, 128.6, 129.8, 133.2, 138.3, 153.9 (d, J = 259.2), 161.7, 179.6; ^{19}F NMR ($CDCl_3$) δ: -128.2 (m, 1F); LCMS: M-1: 271.

Compound **5d**: yield: 3.6 g, 12.51 mmol, 45%, white solid; mp: 146–148 °C; IR (KBr): 1167 (C–O–C), 1251 (C=S) 1618 (C=N), 3057 cm^{-1} (=C–H of Ar); ^{1}H NMR (DMSO-d_6) δ: 7.48–7.57 (m, 2H, Ar–H), 7.63–7.77 (m, 2H, Ar–H), 7.82–8.26 (m, 4H, Ar–H), 14.81 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) 123.7, 124.7, 126.0, 126.1, 127.1, 128.4, 130.7, 131.1, 131.7, 134.3, 140.1, 141.3, 160.7, 177.9; LCMS: M-1: 287.

*4.1.5. Procedure for synthesis of methyl 4-{[5-(5′-fluoro-2′-methoxy-(1,1′-biphenyl)-3-yl)-1,3,4-oxadiazol-2-yl]sulfanyl}butanoate: (**6a**)*

To a solution of **5a** (0.5 g, 1.65 mmol) in dry *N,N*-dimethylformamide (5 mL), dry potassium carbonate (0.27 g, 1.98 mmol) and methyl 4-bromobutanoate (0.35 g, 1.98 mmol) were added and the resulting solution was heated to 85 °C for 1 h. The mixture was concentrated and taken in ethyl acetate (50 mL), washed with water (20 mL), saturated sodium chloride solution (20 mL) and dried over sodium sulphate. The resulting solution was concentrated and purified by column chromatography [20–30% ethyl acetate in petroleum ether] to afford compound **6a** (0.36 g, 0.89 mmol, 55%) as a colorless oil.

Compound **6a**: IR (KBr): 1742, 1080 (C–O–C linkage) 1642, 1473, 1374 cm^{-1} (oxadiazole ring stretch); ^1H NMR ($CDCl_3$) δ: 2.19–2.22 (m, 2H, CH_2), 2.55 (t, 2H, $J = 7.2$, CH_2), 3.39 (t, 2H, $J = 7.2$, SCH_2), 3.69 (s, 3H, ester CH_3), 3.81 (s, 3H, OCH_3), 6.94 (d, 1H, $J = 13.2$, Ar–H), 7.09–7.22 (m, 2H, Ar–H), 7.52–7.56 (m, 1H, Ar–H), 7.68 (d, 1H, $J = 8.0$, Ar–H), 7.99 (d, 1H, $J = 7.6$, Ar–H), 8.15 (s, 1H, Ar–H); ^{13}C NMR ($CDCl_3$) δ: 24.5, 31.7, 32.3, 51.7, 56.2, 112.3, 114.9, 117.4, 123.5, 125.5, 127.6, 128.8, 130.4, 132.6, 138.4, 152.5, 157.1 (d, $J = 237.1$), 164.1, 165.1, 172.9; ^{19}F NMR ($CDCl_3$) δ: -123.2 (m, 1F); LCMS M+1: 403.

Compound **6b**: yield: 0.39 g, 1.02 mmol, 58%, pale yellow oil; IR (KBr): 1731, 1025 (C–O–C linkage), 1598, 1434, 1366 cm^{-1} (oxadiazole ring str.); ^1H NMR ($CDCl_3$) δ: 2.12–2.21 (m, 2H, CH_2), 2.53 (t, 2H, $J = 7.2$, CH_2), 3.34 (t, 2H, $J = 7.2$, SCH_2), 3.69 (s, 3H, ester CH_3), 3.83 (s, 3H, OCH_3), 7.01–7.06 (m, 2H, Ar–H), 7.34–7.36 (m, 2H, Ar–H), 7.51–7.54 (m, 1H, Ar–H), 7.68 (d, 1H, $J = 9.6$, Ar–H), 7.95 (d, 1H, $J = 9.2$, Ar–H), 8.16 (s, 1H, Ar–H); ^{13}C NMR ($CDCl_3$) δ: 24.5, 31.7, 32.4, 51.7, 55.5, 111.2, 120.9, 123.3, 125.1, 127.7, 128.6, 129.2, 129.3, 130.7, 132.8, 139.5, 156.4, 163.9, 165.9, 173.1; LCMS: M+1:385.

Compound **6c**: yield: 0.35 g, 0.94 mmol, 52%, colorless oil; IR (KBr): 1734.5, 1042 (C–O–C linkage), 1554, 1468, 1368 cm^{-1} (oxadiazole ring str.); ^1H NMR ($CDCl_3$) δ: 2.19–2.23 (m, 2H, CH_2), 2.54 (t, 2H, $J = 7.1$, CH_2), 3.38 (t, 2H, $J = 7.1$, SCH_2), 3.69 (s, 3H, ester CH_3), 7.17–7.25 (m, 3H, Ar–H), 7.47–7.51 (m, 1H, Ar–H), 7.56–7.61 (m, 1H, Ar–H), 7.71 (d, 1H, $J = 9.2$, Ar–H), 8.03 (d, 1H, $J = 8.9$, Ar–H), 8.18 (s, 1H, Ar–H); ^{13}C NMR ($CDCl_3$) δ: 24.5, 31.7, 32.4, 51.7, 116.3, 123.9, 124.5, 125.8, 127.1, 127.7, 129.2, 129.7, 129.8, 130.6, 136.8, 159.6 (d, $J = 246.1$), 164.1, 165.6, 173.2; ^{19}F NMR ($CDCl_3$)δ: -128.2 (m, 1F); LCMS: M+1: 373.

Compound **6d**: yield: 0.33 g, 0.86 mmol, 50%, colorless oil; IR (KBr): 1732, 1180 (C–O–C linkage), 1593, 1318, 1291 cm^{-1} (oxadiazole ring str.); ^1H NMR ($CDCl_3$) δ: 2.18–2.24 (m, 2H, CH_2), 2.57 (t, 2H, $J = 7.1$, CH_2), 3.38 (t, 2H, $J = 7.1$, SCH_2), 3.71 (s, 3H, ester CH_3), 7.37–7.44 (m, 2H, Ar–H), 7.52 (d, 1H, $J = 7.3$, Ar–H), 7.59 (s, 1H, Ar–H), 7.61–7.63 (m, 1H, Ar–H), 7.72 (d, 1H, $J = 7.7$, Ar–H), 8.01 (d, 1H, $J = 7.8$, Ar–H), 8.22 (s, 1H, Ar–H); ^{13}C NMR ($CDCl_3$) δ: 24.4, 31.7, 32.4, 51.6, 124.2, 125.1, 125.2, 125.8, 127.2, 127.9, 129.6 130.1, 130.2, 134.8, 140.7, 141.5, 164.1, 165.5, 172.8; LCMS: M+1:389.

Compound **7a**: yield: 0.34 g, 0.91 mmol, 56%, colorless oil; IR (KBr): 1018 (C–O–C linkage.) 1596, 1478, 1392 cm^{-1} (oxadiazole ring str.); ^1H NMR ($CDCl_3$) δ: 1.86–1.95 (m, 2H, CH_2), 2.01–2.05 (m, 2H, CH_2), 3.39 (t, 2H, $J = 7.1$, SCH_2), 3.80 (s, 3H, OCH_3), 4.46 (t, 1H, $J = 5.8$, F–CH), 4.57 (t, 1H, $J = 5.7$, F–CH), 6.95–7.11 (m, 3H, Ar–H), 7.55–7.61 (m, 1H, Ar–H), 7.68 (d, 1H, $J = 10.6$, Ar–H), 8.01 (d, 1H, $J = 10.6$, Ar–H), 8.15 (s, 1H, Ar–H); ^{13}C NMR ($CDCl_3$) δ: 25.4, 29.3, 32.1, 56.2, 83.3 (d, $J = 165.1$), 112.3, 115.1, 117.4, 123.5, 125.5, 127.5, 128.8, 130.4, 132.6, 138.4, 152.6, 157.1 (d, $J = 237.1$), 164.2, 165.1; ^{19}F NMR ($CDCl_3$) δ: -124.2 (m, 1F), -218.3 (m, 1F); LCMS M+1: 377.

Compound **7b**: yield: 0.32 g, 0.89 mmol, 51%, colorless oil; IR (KBr): 1023 (C–O–C linkage.) 1579, 1429, 1255 cm^{-1} (oxadiazole ring strech); ^1H NMR ($CDCl_3$) δ: 1.86–1.92 (m, 2H, CH_2), 1.94–2.04 (m, 2H, CH_2), 3.36 (t, 2H, $J = 7.1$, SCH_2), 3.81 (s, 3H, OCH_3), 4.45 (t, 1H, $J = 5.8$, F–CH), 4.57 (t, 1H, $J = 5.7$, F–CH), 7.01–7.08 (m, 2H, Ar–H), 7.35–7.39 (m, 2H, Ar–H), 7.51–7.55 (m, 1H, Ar–H), 7.71 (d, 1H, $J = 10.2$, Ar–H), 7.97 (d, 1H, $J = 8.9$, Ar–H), 8.17 (s, 1H, Ar–H); ^{13}C NMR ($CDCl_3$) δ: 25.4, 29.3, 32.1, 55.2, 83.3 (d, $J = 164.2$), 111.2, 120.9, 123.4, 125.1, 127.7, 128.7, 129.2, 129.3, 130.7, 132.8, 139.5, 156.4, 164.1, 165.9; ^{19}F NMR ($CDCl_3$) δ: -218.5 (m, 1F); LCMS M+1: 359.

Compound **7c**: yield: 0.34 g, 0.98 mmol, 55%, colorless oil; IR (KBr): 1039 (C–O–C linkage.) 1598, 1497, 1255 cm^{-1} (oxadiazole ring strech); ^1H NMR ($CDCl_3$) δ: 1.84–1.88 (m, 2H, CH_2), 1.92–2.01 (m, 2H, CH_2), 3.36 (t, 2H, $J = 7.2$, SCH_2), 4.45 (t, 1H, $J = 6.1$, F–CH), 4.57 (t, 1H, $J = 6.1$, F–CH), 7.16–7.25 (m, 2H, Ar–H), 7.36–7.51 (m, 2H, Ar–H), 7.55–7.59 (m, 1H, Ar–H), 7.72 (d, 1H, $J = 8.8$, Ar–H), 8.02 (d, 1H, $J = 8.8$, Ar–H), 8.17 (s, 1H, Ar–H); ^{13}C NMR ($CDCl_3$) δ: 25.3, 29.1, 32.0, 83.2 (d, $J = 164.2$), 116.1, 123.8, 124.4, 125.7, 127.0, 127.7, 129.1, 129.7, 130.5, 132.2, 136.7, 159.6 (d, $J = 247.1$), 164.3, 165.5; ^{19}F NMR ($CDCl_3$) δ: -127.1 (m, 1F), -218.9 (m, 1F); LCMS M+1: 347.

Compound **7d**: yield: 0.32 g, 0.88 mmol, 51%, colorless oil; IR (KBr): 1026 (C–O–C linkage.), 1553, 1392, 1183 cm^{-1} (oxadiazole ring strech); ^1H NMR ($CDCl_3$) δ: 1.86–1.93 (m, 2H, CH_2), 2.01–2.06 (m, 2H, CH_2), 3.37 (t, 2H, $J = 7.1$, SCH_2), 4.46 (t, 1H, $J = 5.8$, F–CH), 4.58 (t, 1H, $J = 5.7$, F–CH), 7.27–7.51 (m, 2H, Ar–H), 7.53–7.57 (m, 2H, Ar–H), 7.59–7.63 (m, 1H, Ar–H), 7.73 (d, 1H, $J = 10.7$, Ar–H), 8.02 (d, 1H, $J = 10.5$, Ar–H), 8.21 (s, 1H, Ar–H); ^{13}C NMR ($CDCl_3$) δ: 25.4, 29.3, 32.6, 83.3 (d, $J = 165.1$), 124.3, 125.1, 125.3, 125.9, 127.3, 127.7, 128.1, 129.7, 130.2, 134.8, 140.7, 141.6, 164.4, 165.5; ^{19}F NMR ($CDCl_3$) δ: -220.9 (m, 1F) LCMS M+1: 363.

Compound **8a**: yield: 0.29 g, 0.79 mmol, 48%, colorless oil; IR (KBr): 2246, 1023 (C–O–C linkage.), 1592, 1499, 1287 cm^{-1} (oxadiazole ring str.); ^1H NMR ($CDCl_3$) δ: 2.25–2.32 (m, 2H, CH_2), 2.59 (t, 2H, $J = 14.4$, CH_2), 3.42 (t, 2H, $J = 11.2$, SCH_2), 3.79 (s, 3H, OCH_3), 6.91–7.08 (m 3H, Ar–H), 7.54–7.58 (m, 1H, Ar–H), 7.67 (d, 1H, $J = 7.6$, Ar–H), 7.97 (d, 1H, $J = 1.2$, Ar–H), 8.21 (s, 1H, Ar–H); ^{13}C NMR ($CDCl_3$) δ: 16.1, 25.1, 30.9, 56.2, 118.5, 112.4, 115.2, 117.4, 123.3, 125.5, 127.6, 128.9, 130.4, 132.8, 138.5, 152.6, 157.1 (d, $J = 237.2$), 163.3, 166.1; ^{19}F NMR ($CDCl_3$) δ: -124.3 (m, 1F); LCMS: M+1: 370.

Compound **8b**: yield: 0.32 g, 0.91 mmol, 52%, colorless oil; IR (KBr): 2245, 1023 (C–O–C linkage.), 1597, 1423, 1255 cm^{-1} (oxadiazole ring str.); ^1H NMR ($CDCl_3$) δ: 2.28–2.33 (m, 2H, CH_2), 2.62 (t, 2H, $J = 7.2$, CH_2), 3.43 (t, 2H, $J = 6.8$, SCH_2), 3.84 (s, 3H, OCH_3), 7.01–7.08 (m 2H, Ar–H), 7.34–7.39 (m, 2H, Ar–H), 7.52–7.56 (m, 1H, Ar–H), 7.72 (d, 1H, $J = 9.2$, Ar–H), 7.97 (d, 1H, $J = 10.0$, Ar–H), 8.16 (s, 1H, Ar–H); ^{13}C NMR ($CDCl_3$) δ: 16.1, 25.1, 32.3, 55.6, 111.3, 118.4, 120.9, 123.1, 125.1, 127.7, 128.7, 129.1, 129.3, 130.7, 133.0, 139.6, 156.4, 163.1, 166.2; LCMS: M+1: 352.

Compound **8c**: yield: 0.35 g, 1.01 mmol, 57%, colorless oil; IR (KBr): 2245, 1068 (C–O–C linkage.), 1585, 1422, 1180 cm^{-1} (oxadiazole ring str.); ^1H NMR ($CDCl_3$) δ: 2.29–2.34 (m, 2H, CH_2), 2.61 (t, 2H, $J = 7.1$, CH_2), 3.44 (t, 2H, $J = 6.9$, SCH_2), 7.17–7.28 (m 2H, Ar–H), 7.38–7.57 (m, 2H, Ar–H), 7.59–7.61 (m, 1H, Ar–H), 7.73 (d, 1H, $J = 9.1$, Ar–H), 8.02 (d, 1H, $J = 9.1$, Ar–H), 8.19 (s, 1H, Ar–H); ^{13}C NMR ($CDCl_3$) δ: 16.1, 25.1, 30.8, 116.1, 118.5, 123.7, 124.6, 125.8, 127.1, 127.7, 129.2, 129.8, 130.6, 132.4, 136.8, 159.6 (d, $J = 246.2$), 163.4, 165.9; ^{19}F NMR ($CDCl_3$) δ: -128.7 (m, 1F); LCMS M+1: 340.

Compound **8d**: yield: 0.35 g, 0.98 mmol, 58%, colorless oil; IR (KBr): 2242, 1087 (C–O–C linkage.), 1547, 1415, 1080 cm^{-1} (oxadiazole ring str.); ^1H NMR ($CDCl_3$) δ: 2.29–2.33 (m, 2H, CH_2), 2.61 (t, 2H, $J = 7.1$, CH_2), 3.46 (t, 2H, $J = 6.9$, SCH_2), 7.27–7.52 (m, 2H, Ar–H), 7.53–7.58 (m, 2H, Ar–H), 7.61–7.63 (m, 1H, Ar–H), 7.75 (d, 1H, $J = 10.7$, Ar–H), 8.01 (d, 1H, $J = 10.2$, Ar–H), 8.20 (s, 1H, Ar–H); ^{13}C NMR ($CDCl_3$) δ: 16.1, 25.2, 30.8, 118.5, 124.1, 125.1, 125.2, 125.9, 127.2, 127.9, 129.6, 130.1, 130.3, 134.8, 140.7, 141.4, 163.4, 165.7; LCMS M+1: 356.5.

Compound **9a**: yield: 0.30 g, 0.91 mmol, 55%, pale yellow oil; IR (KBr): 1024 (C–O–C linkage.), 1593, 1499, 1398 cm^{-1} (oxadiazole ring str.); ^1H NMR ($CDCl_3$) δ: 1.53 (t, 3H, $J = 7.4$, CH_3), 3.34 (q, 2H,

$J = 7.3$, CH_2), 3.81 (s, 3H, OCH_3), 6.92–7.10 (m, 3H, Ar–H), 7.53–7.56 (m, 1H, Ar–H), 7.67 (d, 1H, $J = 9.1$, Ar–H), 8.01 (d, 1H, $J = 10.1$, Ar–H), 8.15 (s, 1H, Ar–H); ^{13}C NMR ($CDCl_3$) δ: 14.7, 27.1, 56.2, 112.3, 115.1, 117.4, 123.6, 125.5, 128.8, 130.4, 130.7, 132.6, 138.4, 152.6, 157.1 (d, $J = 238.2$), 164.3, 165.6; ^{19}F NMR ($CDCl_3$) δ: -124.1 (m, 1F); LCMS: M+1: 331.

Compound **9b**: yield: 0.30 g, 0.98 mmol, 56%, pale yellow oil; IR (KBr): 1023 (C–O–C linkage.), 1598, 1497, 1255 cm^{-1} (oxadiazole ring str.); ^{1}H NMR ($CDCl_3$) δ: 1.53 (t, 3H, $J = 7.3$, CH_3), 3.34 (q, 2H, $J = 7.3$, SCH_2), 3.83 (s, 3H, OCH_3), 7.01–7.08 (m, 2H, Ar–H), 7.35–7.39 (m, 2H, Ar–H), 7.51–7.55 (m, 1H, Ar–H), 7.70 (d, 1H, $J = 10.6$, Ar–H), 7.98 (d, 1H, $J = 9.1$, Ar–H), 8.18 (s, 1H, Ar–H); ^{13}C NMR ($CDCl_3$) δ: 14.7, 27.2, 55.5, 111.2, 120.9, 123.6, 125.1, 127.7, 128.6, 129.2, 129.3, 130.7, 132.8, 139.5, 156.4, 164.2, 165.8; LCMS: M+1: 313.

Compound **9c**: yield: 0.28 g, 0.93 mmol, 51%, pale yellow oil; IR (KBr): 1025 (C–O–C linkage.), 1555, 1406, 1110 cm^{-1} (oxadiazole ring str.); ^{1}H NMR ($CDCl_3$) δ: 1.53 (t, 3H, $J = 7.4$, CH_3), 3.32 (q, 2H, $J = 7.3$, SCH_2), 7.16–7.38 (m, 3H, Ar–H), 7.46–7.51 (m, 1H, Ar–H), 7.56–7.61 (m, 1H, Ar–H), 7.71 (d, 1H, $J = 9.1$, Ar–H), 8.02 (d, 1H, $J = 10.6$, Ar–H), 8.18 (s, 1H, Ar–H); ^{13}C NMR ($CDCl_3$) δ: 14.7, 29.3, 116.3, 124.5, 124.6, 125.8, 127.0, 127.8, 129.1, 129.6, 130.6, 132.1, 136.8, 159.6 (d, $J = 247.1$), 164.5, 165.5; ^{19}F NMR ($CDCl_3$) δ: -129.4 (m, 1F); LCMS: M+1: 301.

Compound **9d**: yield: 0.27 g, 0.85 mmol, 50%, pale yellow oil; IR (KBr): 1025(C–O–C linkage.), 1565, 1406, 1120 cm^{-1} (oxadiazole ring str.); ^{1}H NMR ($CDCl_3$) δ: 1.54 (t, 3H, $J = 7.4$, CH_3), 3.36 (q, 2H, $J = 7.3$, SCH_2), 7.26–7.44 (m, 3H, Ar–H), 7.51–7.53 (m, 1H, Ar–H), 7.57–7.64 (m, 1H, Ar–H), 7.73 (d, 1H, $J = 10.8$, Ar–H), 8.03 (d, 1H, $J = 10.5$, Ar–H), 8.21 (s, 1H, Ar–H); ^{13}C NMR ($CDCl_3$) δ: 14.1, 27.2, 124.3, 125.1, 125.3, 125.9, 127.3, 127.4, 127.9, 129.6, 130.2, 134.8, 140.7, 141.2, 164.6, 165.4; LCMS: M+1: 317.

4.2. Biological activity

4.2.1. Antimicrobial activity studies

4.2.1.1. Antibacterial activity. The newly synthesized compounds were screened for their antibacterial activity against four bacterial strains namely *S. aureus, P. aeruginosa, Eschericia coli, Bascillus subtilis* by cup-plate method. The sterilized nutrient agar medium was distributed 100 mL each in two 250 mL conical flasks and allowed to cool to room temperature. To these media, 18–24 h grown sub-cultures were added and shaken thoroughly to ensure uniform distribution of organism's throughout the medium. Then, this agar medium was distributed in equal portions, in sterilized petridishes, ensuring that each petridish contains about 45–50 mL of the medium. The medium was then allowed for solidification. Then, cups were made with the help of a sterile cork borer (6 mm diameter) punching into the set of agar media. The cups were filled with 0.1 mL of two test dilutions. Then, the petridishes were kept for incubation in an inverted position for 24–48 h at 37 °C, in an incubator. When growth inhibition zones were developed surrounding each cup, their diameter in mm was measured and compared with that of the standard drugs Streptomycin, Procaine penicillin.

4.2.1.2. Antifungal activity. The newly synthesized compounds were screened for their antifungal activity against the fungal organism Fusarium oxysporum at the concentration levels of 50 μg/0.1 mL and 100 μg/0.1 mL by cup-plate method, Griseofulvin was used as the standard. To the sterilized potato dextrose agar medium inoculated for 72 h, subculture of fungus were added and shaken thoroughly to ensure uniform distribution. Then, this was poured into previously sterilized and labeled petridishes and allowed to solidify. Then, with the help of a borer four cups were made in each plate. Two cups were filled with 0.1 mL of two test dilutions and the other two cups with respective concentrations of standard dilutions. Then, the plates were left as it is for 2–3 h for diffusion and then they were kept for incubation at 37 °C for 24 h.

4.2.2. Analgesic activity

All the compounds were tested for their analgesic activity using Eddy's hot plate method. In this method heat is used a source of pain. Animals are placed individually on hot plate, maintained at constant temperature (55 ± 1 °C). The reaction time i.e. time taken by the animal to lick its hind paw or to leap out after placing it on the hot plate is taken as the reaction time. Albino mice of either sex were selected and divided into 12 groups, containing 6 animals in each group. These animals were fasted for 24 h, prior to the experiment. Animals of Group-I were considered as control, which are administered with 2% acacia suspension. Where as Group-II was treated with standard drug i.e. Pentazocin (35 mg/kg) which is considered as standard group. (Ref-IP) Similarly Group- III, to XII treated with compounds **5a**–**d** and **6a**–**9d** (100 mg/kg). The reaction time for each mouse was recorded at 0, 30, 60, 120 and 240 min after the administration of test compounds by using Eddy's hot plate.

4.2.3. Determination of acute toxicity (LD_{50})

The acute toxicity of compounds **5a**–**d** and **6a**–**9d** was determined in albino mice of either sex weighing between 18 and 22 g, maintained under standard husbandry conditions. The animals were fasted 3 h prior to the experiment and "up and down" (OECD guidelines NO: 425) method of CPCSEA was adopted for toxicity studies. Animals were administered with single dose of compound and observed for its mortality during 48 h study period (short term) toxicity. Based on the compounds short term toxicity profile the doses of the next animals were determined as per OECD guidelines NO: 425. All the animals were observed for long term toxicity (7days) and then $1/10^{th}$ of the lethal dose of the individual compound was taken as effective dose ED_{50} and was used throughout the experimental studies.

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