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Original article

Synthesis and bioassay of pyrrolyl oxazolines and thiazolines

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ABSTRACT

A new class of sulfone linked pyrrolyl oxazolines and thiazolines were synthesized from *E*-arylsulfonylethenesulfonylacetic acid methyl ester and studied their antimicrobial and antioxidant activities.

1. Introduction

Oxazolines, thiazolines and pyrroles are important naturally occurring five membered heterocycles. The 2-oxazoline ring system [1], a simple cyclic imino ester, is of great interest in modern organic chemistry because it can be used as a masked carboxylic acid [2], versatile synthetic intermediate [3], and therapeutic agent [4]. A number of reliable preparative methods are known in the literature which includes cyclodehydration of carboxylic acids and β-amino alcohol, treatment of β-hydroxyamide with suitable cyclization reagents such as thionyl chloride [5], phosphorotris-(1,2,4)-triazolide [6], Mitsunobu conditions (DEAD/PPh_3) [7] and phosphorous mediated Appel reaction conditions [8]. In addition, thiazoline derivatives possess anti HIV-1 [9], antimitotic [10] and bioluminescent activities and have recently found applications as building blocks in pharmaceutical drug discovery [11–13]. Thiazolines have been prepared by the condensation of aminothiols with nitriles [9], esters [14], iminoethers [15] or iminotriflates [16] and also by cyclization of *N*-acyl-2-aminoethanols [17,18] or β-hydroxythioamides [19–21]. Netropsin and distamycin are pyrrole polyamides and are naturally occurring anticancer antibiotics [22]. Multistep synthetic routes for 3,4-disubstituted pyrroles have been reported either by coupling of imines and nitroalkanes or using Friedel–Craft's acylation with an electron withdrawing group on pyrrole nitrogen or 3,4-silylated precursors [23]. Pyrroles have also been prepared from Michael acceptors and tosylmethyl isocyanide (TosMIC) [24,25]. Recently we have reported the synthesis, antimicrobial and cyctotoxic activities of a variety of bis heterocycles pyrrolyl oxadiazoles, thiadiazoles and triazoles [26]. In continuation of our interest on the synthesis and pharmacological properties of sulfone linked bis heterocycles, the present work has been taken up.

2. Chemistry

The synthetic method involves the articulation of pyrrole in combination with oxazoline and thiazoline rings from an intermediate *trans*-arylsulfonylethenesulfonyl-acetic acid methyl ester (**1**). This compound was prepared by the reaction of 1-arylsulfonyl-2-chloroethene with mercaptoacetic acid followed by oxidation and esterification [26]. Earlier we have reported the synthesis of 2-arylsulfonylmethyl oxazolines/thiazolines and 2-arylmethanesulfonylmethylsulfonyl oxazolines/thiazolines by the traditional four-step three-intermediate route from arylsulfonylacetic acid methyl ester [27]. We have also reported one pot methodology to develop these heterocycles exploiting lanthanide amino alkoxide complexes as reagents [28]. Encouraged by the results, the ester and olefin functionalities in **1** were appropriately functionalized to develop bis heterocycles. The reaction of compound **1** with 2-aminoethanol and n-butyllithium complexed with a suspension of 5–10% mol. equivalents of anhydrous $SmCl_3$ in toluene resulted

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in 2-(arylsulfonylethenesulfonylmethyl)-4,5-dihydrooxazole (**2**). Adopting similar methodology, 2-(arylsulfonylethenesulfonylmethyl)-4,5-dihydrothiazole (**3**) was prepared by treating **1** with 2-aminoethanethiol and n-butyllithium in the presence of anhydrous $SmCl_3$ in toluene (Scheme 1). The olefin moiety in **2** and **3** was used to develop pyrrole ring. Treatment of **2** and **3** with TosMIC in the presence of sodium hydride in a solvent mixture of ether and DMSO produced 2-(4′-arylsulfonyl-1′*H*-pyrrol-3′-sulfonylmethyl)-4,5-dihydrooxazole (**4**) and 2-(4′-arylsulfonyl-1′*H*-pyrrol-3′-sulfonylmethyl)-4,5-dihydrothiazole (**5**) (Scheme 1).

3. Biology

3.1. Antimicrobial activity

The compounds **2a**–**c** to **5a**–**c** were tested for *in vitro* antimicrobial activity against the Gram-positive bacteria *Staphylococcus aureus* (NCIM No. 5021), *Bacillus subtilis* (NCIM No. 2063), the Gram-negative bacteria *Klebsiella pneumoniae* (NCIM No. 2957), *Proteus vulgaris* (NCIM No. 2027) and fungi *Fusarium solani* (NCIM No. 1330), *Curvularia lunata* (NCIM No. 716) and *Aspergillus niger* (NCIM No. 596). The preliminary screening was carried out by agar disc-diffusion method [29] using nutrient agar medium. The minimum inhibitory concentration for the most active compounds **3c**, **5a**, and **5c** against the same microorganisms used in the preliminary screening was carried out using microdilution susceptibility method [30]. Chloramphenicol and Ketoconazole were used as control drugs. The observed data on the antimicrobial activity of the compounds and control drugs are given in Tables 1–3.

3.2. Antioxidant testing

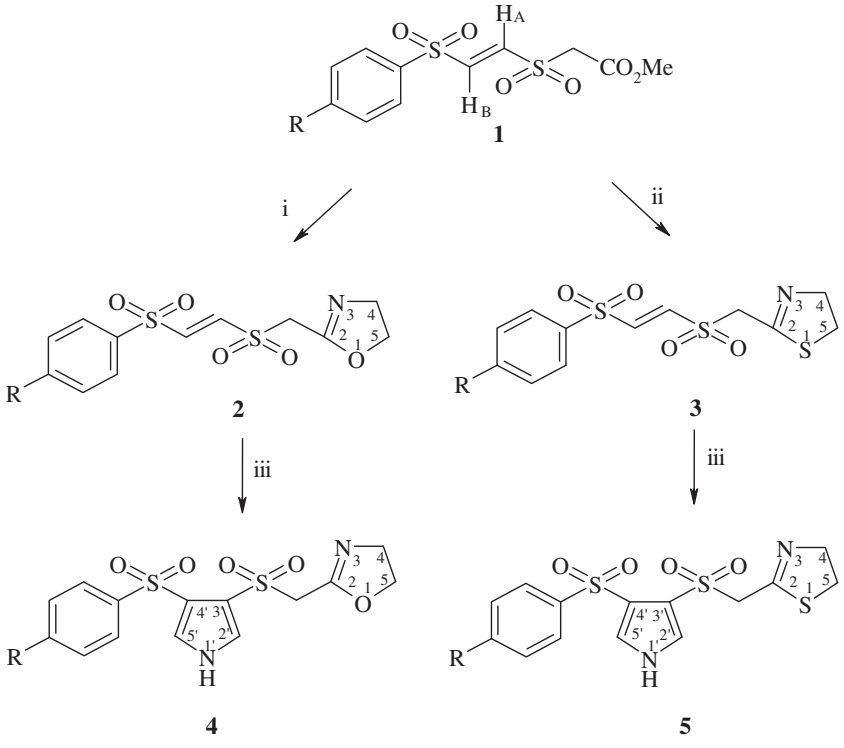
The compounds **2a**–**c** to **5a**–**c** were tested for antioxidant property by nitric oxide [31,32] and DPPH [33] methods. The observed data on the antioxidant activity is given in Table 4.

4. Results and discussion

We have synthesized a new class of heterocycles, 2-(arylsulfonylethenesulfonylmethyl)-4,5-dihydrooxazole (**2**) 2-(arylsulfonylethenesulfonylmethyl)-4,5-dihydrothiazole (**3**), 2-(4′-arylsulfonyl-1′*H*-pyrrol-3′-sulfonylmethyl)-4,5-dihydrooxazole (**4**) and 2-(4′-arylsulfonyl-1′*H*-pyrrol-3′-sulfonylmethyl)-4,5-dihydrothiazole (**5**) as depicted in Scheme 1. Structures of all the compounds were established on the basis of elemental analyses, IR, ^{1}H NMR and ^{13}C NMR spectral data.

4.1. Biological results

The results of preliminary antimicrobial testing of the compounds are shown in Tables 1–3. The results revealed that, the inhibitory activity against Gram-positive bacteria was higher than Gram-negative bacteria. The oxazoline derivatives **2a**–**c** were displayed least activity. The compounds **3c**, **5a** and **5c** showed excellent activity against Gram-positive (inhibitory zone > 27 mm) and good activity against Gram-negative (inhibitory zone > 20 mm) bacteria. The compounds having pyrrole in combination with oxazoline unit displayed moderate activity **4a**–**c** when compared with compounds having only oxazoline moiety **2a**–**c**. All the test compounds showed moderate to high inhibitory effect towards tested fungi. The presence



Scheme 1.

Table 1
Antibacterial activity of **5**–**8**.

Compound	Concentration (μg/disc)	Zone of inhibition (mm)			
		Gram-positive bacteria		Gram-negative bacteria	
		Staphylococcus aureus	*Bacillus subtilis*	*Klebsiella pneumoniae*	*Proteus vulgaris*
2a	100	11	10	–	–
	200	13	12	–	–
2b	100	10	9	–	–
	200	13	11	–	–
2c	100	13	12	10	9
	200	15	14	12	10
3a	100	21	22	19	17
	200	24	23	21	18
3b	100	20	19	17	15
	200	23	21	20	18
3c	100	27	29	22	21
	200	28	31	23	22
4a	100	15	16	14	13
	200	19	18	17	15
4b	100	12	13	10	11
	200	15	14	13	13
4c	100	17	16	15	12
	200	19	19	17	14
5a	100	29	30	23	24
	200	30	32	25	28
5b	100	23	22	20	17
	200	26	24	21	19
5c	100	32	33	27	29
	200	34	35	29	30
Chloramphenicol	100	35	38	37	42
	200	41	44	42	45

of chloro substituent in the aromatic ring enhances the antimicrobial activity.

The minimum inhibitory concentration (MIC) values were determined as the lowest concentration that completely inhibited visible growth of the microorganisms (Table 3). The structure-antimicrobial activity relationship of the synthesized compounds revealed that the compounds having oxazoline (**2a**–**c**) showed least activity. However, the compounds having thiazoline (**3a**–**c**) exhibited good activity when compared with compounds having oxazoline and pyrrole units (**4a**–**c**). On the other hand, compounds with thiazoline and pyrrole rings (**5a**–**c**) displayed excellent activity. The maximum activity was observed with the compounds **3c**, **5a** and **5c**.

4.2. Antioxidant testing

The compounds **2a**–**c** to **5a**–**c** were tested for antioxidant property by nitric oxide, DPPH and reducing power methods. The compounds **2a**, **2c**, **4a** and **4c** exhibited high antioxidant property in all the three methods at 100 μM concentration (Table 4). In fact, the compounds having oxazoline and pyrrole units displayed high antioxidant property. The maximum activity was observed with the compound **4c**.

5. Conclusion

A new class of heterocycles 2-(arylsulfonylethenesulfonylmethyl)-4,5-dihydrooxazole (**2**), 2-(arylsulfonylethenesulfonylmethyl)-4,5-dihydrothiazole (**3**), 2-(4′-arylsulfonyl-1′*H*-pyrrol-3′-sulfonylmethyl)-4,5-dihydrooxazole (**4**) and 2-(4′-arylsulfonyl-1′*H*-pyrrol-3′-sulfonylmethyl)-4,5-dihydrothiazole (**5**) were developed by functionalization of ester and olefin moieties in *E*-arylsulfonylethenesulfonylacetic acid methyl ester (**1**) exploiting lanthanide chemistry and 1,3-diploar cycloaddition methodology. The antimicrobial testing showed that the compounds having pyrrole with thiazoline possess excellent antimicrobial activity. However, the compounds having pyrrole with oxazoline showed good antioxidant property.

6. Experimental

6.1. Chemistry

Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The purity of the compounds was checked by TLC (silica gel H, BDH, ethyl acetate–hexane, 0.5:2). The IR spectra were recorded on a Thermo Nicolet IR 200 FT-IR spectrometer as KBr pellets and the wave numbers were given in cm^{-1}. The ^1H NMR spectra were recorded in $CDCl_3$/DMSO-d_6 on a Jeol JNM λ-300 MHz. The ^{13}C NMR spectra were recorded in $CDCl_3$/DMSO-d_6 on a Jeol JNM spectrometer operating at 75.5 MHz. All chemical shifts are reported in δ (ppm) using TMS as an internal standard. The microanalyses were performed on Perkin-Elmer 240C elemental analyzer. The antioxidant property was carried out by using Shimadzu UV-2450 spectrophotometer. The starting compound *trans*-arylsulfonylethenesulfonylacetic acid methyl ester (**1**) was prepared according to literature procedure [26].

Table 2
Antifungal activity of **5**–**8**.

Compound	Concentration (μg/ml)	Zone of inhibition (mm)		
		Fusarium solani	*Curvularia* lunata	*Aspergillus niger*
2a	100	14	16	17
	200	15	18	19
2b	100	14	18	14
	200	17	19	16
2c	100	16	18	17
	200	19	20	20
3a	100	26	24	26
	200	29	26	28
3b	100	22	21	20
	200	25	24	23
3c	100	29	24	27
	200	31	28	29
4a	100	18	19	20
	200	22	23	22
4b	100	18	17	17
	200	20	21	21
4c	100	21	20	21
	200	23	23	22
5a	100	34	32	30
	200	37	35	33
5b	100	29	28	31
	200	31	32	35
5c	100	35	36	34
	200	38	41	38
Ketoconazole	100	38	41	36
	200	42	44	39

*6.1.1. General procedure for the synthesis of 2-(arylsulfonylethenesulfonylmethyl)-4,5-dihydrooxazole **2a**–**c**/2-(arylsulfonylethenesulfonylmethyl)-4,5-dihydrothiazole **3a**–**c***

To a flask charged with anhydrous samarium chloride (0.1 mmol), dry toluene (10 ml) and aminoethanol/aminoethanethiol (2 mmol) followed by *n*-butyllithium (2.2 mmol) were added at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. Then the contents were refluxed to 120 °C. To this, arylsulfonylethenesulfonylacetic acid methyl ester (**1**) (1 mmol) was added and continued refluxion for an additional period of 12–14 h. The suspension was cooled to room temperature and filtered. The filtrate was extracted with chloroform, washed with water followed by brine solution. The solvent was removed *in vacuo*. The product was purified by column chromatography [silica gel (60–120 mesh), EtOAc–hexane 1:3].

*6.1.1.1. 2-(Phenylsulfonylethenesulfonylmethyl)-4,5-dihydrooxazole **2a**.* White solid (0.2239 g, 71%); m.p. 125–127 °C; IR (KBr): 1128, 1334 (SO_2), 1572 (C=C), 1581 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 3.62 (t, 2H, C-4, $J = 5.5$ Hz), 4.24 (s, 2H, SO_2CH_2), 4.65 (t, 2H, C-5, $J = 5.5$ Hz), 7.28 (d, $J = 14.1$ Hz, 1H, H_B), 7.66 (d, $J = 14.1$ Hz, 1H, H_A), 7.32–7.83 (m, 5H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 51.4 (C-4), 57.6 (SO_2CH_2), 59.4 (C-5), 137.4 (SO_2CH), 143.9 ($CHSO_2$), 161.8 (C-2), 127.4, 129.4, 130.7, 131.5 ppm (aromatic carbons). Anal. Calcd. for $C_{12}H_{13}NO_5S_2$: C, 45.70; H, 4.15; N, 4.44; Found: C, 45.79; H, 4.19; N, 4.50.

Table 4
Antioxidant property of **2**–**5**.

Compound	% Inhibition at 100 μM		
	Nitric oxide method	DPPH method	Reducing power
2a	82.12	83.72	79.45
2b	74.23	73.88	73.51
2c	85.54	86.61	82.68
3a	30.42	29.31	29.28
3b	21.74	22.18	21.21
3c	32.28	33.46	28.31
4a	87.68	88.32	86.81
4b	78.54	76.14	77.31
4c	92.11	91.46	89.41
5a	34.61	33.84	32.41
5b	23.74	23.21	22.89
5c	41.42	40.51	40.35
Ascorbic acid	96.90	95.37	–
Butylated hydroxy toluene (BHT)	–	–	92.34

*6.1.1.2. 2-(p-Methylphenylsulfonylethenesulfonylmethyl)-4,5-dihydrooxazole **2b**.* White solid (0.2173 g, 66 %); m.p. 152–154 °C; IR (KBr): 1138, 1336 (SO_2), 1580 (C=C), 1595 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 2.23 (s, 3H, Ar-CH_3), 3.71 (t, 2H, C-4, $J = 5.7$ Hz), 4.28 (s, 2H, SO_2CH_2), 4.71 (t, 2H, C-5, $J = 5.7$ Hz), 7.32 (d, $J = 14.3$ Hz, 1H, H_B), 7.69 (d, $J = 14.3$ Hz, 1H, H_A), 7.36–7.74 (m, 4H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 22.1 (Ar-CH_3), 51.9 (C-4), 58.2 (SO_2CH_2), 60.2 (C-5), 138.7 (SO_2CH), 142.6 ($CHSO_2$), 160.1 (C-2), 128.6, 129.9, 130.2, 132.4 ppm (aromatic carbons). Anal. Calcd. for $C_{13}H_{15}NO_5S_2$: C, 47.40; H, 4.59; N, 4.25; Found: C, 47.32; H, 4.64; N, 4.29.

*6.1.1.3. 2-(P-Chlorophenylsulfonylethenesulfonylmethyl)-4,5-dihydrooxazole **2c**.* White solid (0.2413 g, 69 %); m.p. 166–168 °C; IR (KBr): 1134, 1332 (SO_2), 1577 (C=C), 1587 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.65 (t, 2H, C-4, $J = 5.2$ Hz), 4.31 (s, 2H, SO_2CH_2), 4.62 (t, 2H, C-5, $J = 5.2$ Hz), 7.41 (d, $J = 14.6$ Hz, 1H, H_B), 7.73 (d, $J = 14.6$ Hz, 1H, H_A), 7.45–7.79 (m, 4H, Ar-H) ppm; ^{13}C NMR (DMSO-d_6) δ 52.2 (C-4), 58.9 (SO_2CH_2), 59.7 (C-5), 138.1 (SO_2CH), 143.1 ($CHSO_2$), 159.6 (C-2), 129.2, 130.4, 131.8, 132.6 ppm (aromatic carbons). Anal. Calcd. for $C_{12}H_{12}ClNO_5S_2$: C, 41.20; H, 3.46; N, 4.00; Found: C, 41.26; H, 3.49; N, 4.06.

*6.1.1.4. 2-(Phenylsulfonylethenesulfonylmethyl)-4,5-dihydrothiazole **3a**.* White solid (0.2518 g, 76 %); m.p. 114–116 °C; IR (KBr): 1130, 1339 (SO_2), 1573 (C=C), 1594 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6)

Table 3
Minimum inhibitory concentration (MIC, μg/ml) of **3c**, **5a** and **5c**.

Compound	Minimum inhibitory concentration, MIC, μg/ml						
	S. aureus	*B. subtilis*	*K. pneumoniae*	*P. vulgaris*	*F. solani*	*C. lunata*	*A. niger*
2c	200	100	200	200	100	200	100
5a	100	50	100	100	100	100	100
5c	25	12.5	50	50	50	12.5	25
Chloramphenicol	6.25	6.25	6.25	12.5	–	–	–
Ketoconazole	–	–	–	–	12.5	6.25	6.25

δ 3.37 (t, 2H, C-5, $J = 7.3$ Hz), 3.76 (t, 2H, C-4, $J = 7.3$ Hz), 4.27 (s, 2H, SO_2CH_2), 7.37 (d, $J = 14.3$ Hz, 1H, H_B), 7.68 (d, $J = 14.1$ Hz, 1H, H_A), 7.39–7.73 (m, 5H, Ar-H) ppm; ^{13}C NMR (DMSO-d_6) δ 36.9 (C-5), 51.7 (C-4), 58.0 (SO_2CH_2), 136.9 (SO_2CH), 143.6 ($CHSO_2$), 157.7 (C-2), 128.2, 129.7, 130.2, 131.9 ppm (aromatic carbons). Anal. Calcd. for $C_{12}H_{13}NO_4S_3$: C, 43.49; H, 3.95; N, 4.23; Found: C, 43.54; H, 3.91; N, 4.28.

6.1.1.5. 2-(P-Methylphenylsulfonylethenesulfonylmethyl)-4,5-dihydrothiazole ***3b***. White solid (0.2693 g, 78 %); m.p. 125–127 °C; IR (KBr): 1136, 1343 (SO_2), 1579 (C=C), 1583 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.21 (s, 3H, Ar-CH_3), 3.33 (t, 2H, C-5, $J = 7.0$ Hz), 3.69 (t, 2H, C-4, $J = 7.0$ Hz), 4.34 (s, 2H, SO_2CH_2), 7.35 (d, $J = 13.7$ Hz, 1H, H_B), 7.61 (d, $J = 13.7$ Hz, 1H, H_A), 7.44–7.76 (m, 4H, Ar-H) ppm; ^{13}C NMR (DMSO-d_6) δ 21.6 (Ar-CH_3), 37.3 (C-5), 52.5 (C-4), 59.9 (SO_2CH_2), 136.2 (SO_2CH), 142.9 ($CHSO_2$), 159.3 (C-2), 128.6, 129.9, 130.6, 131.2 ppm (aromatic carbons). Anal. Calcd. for $C_{13}H_{15}NO_4S_3$: C, 45.20; H, 4.38; N, 4.05; Found: C, 45.14; H,; 4.35 N, 4.08.

6.1.1.6. 2-(P-Chlorophenylsulfonylethenesulfonylmethyl)-4,5-dihydrothiazole ***3c***. White solid (0.2561 g, 70 %); m.p. 133–135 °C; IR (KBr): 1129, 1345 (SO_2), 1574 (C=C), 1588 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.39 (t, 2H, C-5, $J = 7.5$ Hz), 3.73 (t, 2H, C-4, $J = 7.5$ Hz), 4.32 (s, 2H, SO_2CH_2), 7.47 (d, $J = 14.2$ Hz, 1H, H_B), 7.72 (d, $J = 14.2$ Hz, 1H, H_A), 7.49–7.79 (m, 4H, Ar-H) ppm; ^{13}C NMR (DMSO-d_6) δ 36.8 (C-5), 51.9 (C-4), 59.2 (SO_2CH_2), 137.7 (SO_2CH), 143.2 ($CHSO_2$), 158.7 (C-2), 128.1, 129.7, 130.4, 131.6 ppm (aromatic carbons). Anal. Calcd. for $C_{12}H_{12}ClNO_4S_3$: C, 39.39; H, 3.31; N, 3.83; Found: C, 39.43; H, 3.28; N, 3.87.

6.1.2. General procedure for the synthesis of 2-(4′-arylsulfonyl-1′H-pyrrol-3′-sulfonylmethyl)-4,5-dihydrooxazole ***4a–c****/2-(4′-arylsulfonyl-1′H-pyrrol-3′-sulfonylmethyl)-4,5-dihydrothiazole* ***5a–c***

An equimolar mixture of TosMIC and 2-(arylsulfonylethenesulfonylmethyl)-4,5-dihydrooxazole/2-(arylsulfonylethenesulfonylmethyl)-4,5-dihydrothiazole (**2**/**3**) (1 mmol) in Et_2O/DMSO (2:1) was added dropwise to a stirred contents of NaH (50 mg) in dry Et_2O (10 ml) at room temperature and stirring was continued for 12–14 h. Then the reaction mixture was diluted with water and extracted with ether. The ethereal layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The resultant solid was purified by column chromatography using silica gel (60–120 mesh) and EtOAc–hexane (1.5:3) as eluent.

6.1.2.1. 2-(4′-Phenylsulfonyl-1′H-pyrrol-3′-sulfonylmethyl)-4,5-dihydrooxazole ***4a***. Yellow solid (0.2374 g, 67 %); m.p. 202–204 °C; IR (KBr): 1139, 1342 (SO_2), 1576 (C=N), 3224 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.67 (t, 2H, C-4, $J = 5.6$ Hz), 4.21 (s, 2H, SO_2-CH_2), 4.61 (t, 2H, C-5, $J = 5.6$ Hz), 6.89 (s, 1H, C_2'-H), 7.11 (s, 1H, C_5'-H), 7.31–7.72 (m, 5H, Ar-H), 9.98 (bs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 52.1 (C-4), 58.8 (SO_2-CH_2), 60.2 (C-5), 106.4 (C-3′), 109.3 (C-4′), 114.9 (C-2′), 117.8 (C-5′), 160.1 (C-2), 128.4, 129.7, 131.2, 131.9 ppm (aromatic carbons). Anal. Calcd. for $C_{14}H_{14}N_2O_5S_2$: C, 47.45; H, 3.98; N, 7.90; Found: C, 47.50; H, 4.04; N, 7.96.

6.1.2.2. 2-(4′-P-Methylphenylsulfonyl-1′H-pyrrol-3′-sulfonylmethyl)-4,5-dihydrooxazole ***4b***. Yellow solid (0.2652 g, 72 %); m.p. 197–199 °C; IR (KBr): 1135, 1338 (SO_2), 1568 (C=N), 3227 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.24 (s, 3H, Ar-CH_3), 3.65 (t, 2H, C-4, $J = 5.2$ Hz), 4.25 (s, 2H, SO_2-CH_2), 4.65 (t, 2H, C-5, $J = 5.2$ Hz), 6.91 (s, 1H, C_2'-H), 7.17 (s, 1H, C_5'-H), 7.35–7.68 (m, 4H, Ar-H), 10.06 (bs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 22.4 (Ar-CH_3), 51.8 (C-4), 58.2 (SO_2-CH_2), 59.4 (C-5), 106.1 (C-3′), 108.9 (C-4′), 115.1 (C-2′), 116.4 (C-5′), 160.6 (C-2), 128.1, 128.9, 129.6, 130.7 ppm (aromatic carbons). Anal. Calcd. for $C_{15}H_{16}N_2O_5S_2$: C, 48.90; H, 4.38; N, 7.60; Found: C, 48.86; H, 4.43; N, 7.55.

6.1.2.3. 2-(4′-P-Chlorophenylsulfonyl-1′H-pyrrol-3′-sulfonylmethyl)-4,5-dihydrooxazole ***4c***. Yellow solid (0.2916 g, 75 %); m.p. 221–223 °C; IR (KBr): 1142, 1345 (SO_2), 1566 (C=N), 3220 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.68 (t, 2H, C-4, $J = 5.4$ Hz), 4.24 (s, 2H, SO_2-CH_2), 4.68 (t, 2H, C-5, $J = 5.4$ Hz), 6.93 (s, 1H, C_2'-H), 7.13 (s, 1H, C_5'-H), 7.32–7.81 (m, 4H, Ar-H), 10.21 (bs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 52.2 (C-4), 58.9 (SO_2-CH_2), 60.9 (C-5), 105.7 (C-3′), 108.1 (C-4′), 114.8 (C-2′), 115.6 (C-5′), 159.4 (C-2), 128.7, 129.2, 130.2, 131.4 ppm (aromatic carbons). Anal. Calcd. for $C_{14}H_{13}ClN_2O_5S_2$: C,43.24; H, 3.37; N, 7.20; Found: C, 43.18; H, 3.33; N, 7.26.

6.1.2.4. 2-(4′-Phenylsulfonyl-1′H-pyrrol-3′-sulfonylmethyl)-4,5-dihydrothiazole ***5a***. Yellow solid (0.2852 g, 77 %); m.p. 176–178 °C; IR (KBr): 1148, 1330 (SO_2), 1570 (C=N), 3228 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.34 (t, 2H, C-5, $J = 7.1$ Hz), 3.71 (t, 2H, C-4, $J = 7.1$ Hz), 4.26 (s, 2H, SO_2-CH_2), 6.88 (s, 1H, C_2'-H), 7.09 (s, 1H, C_5'-H), 7.26–7.71 (m, 5H, Ar-H), 9.59 (bs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 37.4 (C-5), 52.8 (C-4), 58.4 (SO_2CH_2), 106.4 (C-3′), 107.8 (C-4′), 114.2 (C-2′), 115.0 (C-5′), 160.4 (C-2), 128.1, 129.8, 130.9, 131.9 ppm (aromatic carbons). Anal. Calcd. for $C_{14}H_{14}N_2O_4S_3$: C, 45.39; H, 3.81; N, 7.56; Found: C, 45.43; H, 3.75; N, 7.52.

6.1.2.5. 2-(4′-P-Methylphenylsulfonyl-1′H-pyrrol-3′-sulfonylmethyl)-4,5-dihydrothiazole ***5b***. Yellow solid (0.2845 g, 74 %); m.p. 182–184 °C; IR (KBr): 1132, 1334 (SO_2), 1565 (C=N). 3226 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.26 (s, 3H, Ar-CH_3), 3.39 (t, 2H, C-5, $J = 7.4$ Hz), 3.78 (t, 2H, C-4, $J = 7.4$ Hz), 4.22 (s, 2H, SO_2-CH_2), 6.94 (s, 1H, C_2'-H), 7.15 (s, 1H, C_5'-H), 7.31–7.78 (m, 4H, Ar-H), 9.68 (bs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 21.4 (Ar-CH_3), 36.7 (C-5), 51.6 (C-4), 59.1 (SO_2CH_2), 105.9 (C-3′), 108.7 (C-4′), 113.5 (C-2′), 114.7 (C-5′), 161.2 (C-2), 126.7, 128.9, 130.5, 132.4 ppm (aromatic carbons). Anal. Calcd. for $C_{15}H_{16}N_2O_4S_3$: C, 46.86; H, 4.19; N, 7.29; Found: C, 46.92; H, 4.24; N, 7.34.

6.1.2.6. 2-(4′-P-Chlorophenylsulfonyl-1′H-pyrrol-3′-sulfonylmethyl)-4,5-dihydrothiazole ***5c***. Yellow solid (0.2955g, 73 %); m.p. 193–195 °C; IR (KBr): 1140, 1340 (SO_2), 1576 (C=N), 3231 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.32 (t, 2H, C-5, $J = 7.2$ Hz), 3.73 (t, 2H, C-4, $J = 7.2$ Hz), 4.28 (s, 2H, SO_2-CH_2), 6.99 (s, 1H, C_2'-H), 7.12 (s, 1H, C_5'-H), 7.16–7.87 (m, 4H, Ar-H), 9.77 (bs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 37.2 (C-5), 52.3 (C-4), 58.7 (SO_2CH_2), 105.2 (C-3′), 107.5 (C-4′), 112.9 (C-2′), 115.3 (C-5′), 160.8 (C-2), 127.7, 128.1, 133.3, 134.2 ppm (aromatic carbons). Anal. Calcd. for $C_{14}H_{13}ClN_2O_4S_3$: C, 41.53; H, 3.24; N, 6.92; Found: C, 41.47; H, 3.28; N, 6.85.

6.2. Biological assays

6.2.1. Compounds

The compounds **2a–c** to **5a–c** were dissolved in DMSO at different concentrations of 100, 200 and 800 μg/ml.

6.2.2. Cells

Bacterial strains *S. aureus*, *B. subtilis*, *K. pneumonie*, *P. vulgaris* and fungi *F. solani*, *C. lunata* and *A. niger* were obtained from National Collection of Industrial Microorganisms (NCIM), National Chemical Laboratory, Pune, India.

6.3. Antibacterial and antifungal assays

Preliminary antimicrobial activities of compounds **2a–c** to **5a–c** were tested by agar disc-diffusion method. Sterile filter paper discs (6 mm diameter) moistened with the test compound solution in

DMSO of specific concentration 100 μg and 200 μg/disc were carefully placed on the agar culture plates that had been previously inoculated separately with the microorganisms. The plates were incubated at 37 °C and the diameter of the growth inhibition zones were measured after 24 h in case of bacteria and after 48 h in case of fungi.

The MICs of the compound assays were carried out using microdilution susceptibility method. Chloramphenicol was used as reference antibacterial agent. Ketoconazole was used as reference antifungal agent. The test compounds, chloramphenicol and ketoconazole were dissolved in DMSO at concentration of 800 μg/ml and two-fold dilution of the solution was prepared (400, 200, 100,…, 6.25 μg/ml). The microorganism suspensions were inoculated to the corresponding wells. The plates were incubated at 36 °C for 24 and 48 h for bacteria and fungi, respectively. The minimum inhibitory concentrations of the compounds were recorded as the lowest concentration of each chemical compounds in the tubes with no turbidity (i.e. no growth) of inoculated bacteria/fungi.

6.3.1. Antioxidant testing

The compounds **2a**–**c** to **5a**–**c** were tested for antioxidant property by nitric oxide, DPPH and reducing power methods.

6.3.2. Assay for nitric oxide (NO) scavenging activity

Sodium nitroprusside (5 μM) in phosphate buffer pH 7.4 was incubated with 100 μM concentration of test compounds dissolved in a suitable solvent (dioxane/ methanol) and tubes were incubated at 25 °C for 120 min. Control experiment was conducted with equal amount of solvent in an identical manner. At intervals, 0.5 ml of incubation solution was taken and diluted with 0.5 ml of Griess reagent (1% Sulfanilamide, 0.1% *N*-naphthylethylenediamine dihydrochloride and 2% *o*-phosphoric acid dissolved in distilled water). The absorbance of the chromophore formed during diazotization of nitrite with sulfanilamide and subsequent *N*-naphthylethylenediamine dihydrochloride was read at λ 546 nm. The experiment was repeated in triplicate.

6.3.3. Reduction of 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical (DPPH method)

The nitrogen centered stable free radical 1,1-diphenyl-2-picrylhydrazyl (DPPH) has often been used to characterize antioxidants. It is reversibly reduced and the odd electron in the DPPH free radical gives a strong absorption maximum at λ 517 nm, which is purple in color. This property makes it suitable for spectrophotometric studies. A radical scavenging antioxidant reacts with DPPH stable free radical and converts into 1,1-diphenyl-2-picrylhydrazine. The resulting decolorization is stoichiometric with respect to the number of electrons captured. The change in the absorbance produced in this reaction has been used to measure antioxidant properties.

The solutions of test compounds (100 μM) were added to DPPH (100 μM) in dioxane/ethanol. The tubes were kept at an ambient temperature for 20 min. and the absorbance was measured at λ 517 nm. The difference between the test and the control experiments was taken and expressed as the per cent scavenging of the DPPH radical.

6.3.4. Reducing power

The reducing power was determined according to the method of Oyaizu [34]. The 100 μM concentration was prepared in methanol were mixed with phosphate buffer (2.5 ml, 0.2M, pH 6.6) and potassium ferricyanide [$K_3Fe(CN)_6$ (2.5 ml, 1%). The mixture was incubated at 50 °C for 20 min and 2.5 ml of trichloroacetic acid (10%) was added to the mixture, which was then centrifuged at 3000 rpm for 10 min. The upper layer of the solution (2.5 ml) was mixed with distilled water (2.5 ml) and $FeCl_3$ (0.5 ml, 0.1%) and the absorbance was measured at 700 nm. Increased absorbance of the reaction mixture indicated increased reducing power. In this method also the compound **4c** showed the highest reducing power.

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