Synthesis and biological activity of a new class of sulfone linked bis(heterocycles)

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Abstract
Novel sulfone linked bis(heterocycles) having two different heterocyclic rings viz., oxazoline / thiazoline in combination with pyrrole are prepared from *E*-aroylethenesulfonylacetic acid methyl ester exploiting ester and olefin functionalities. The compounds having pyrrole and thiazoline rings exhibited greater antimicrobial activity.

Keywords: 2-Oxazolines, 2-thiazolines, $SmCl_3$, pyrrole, tosylmethyl isocyanide

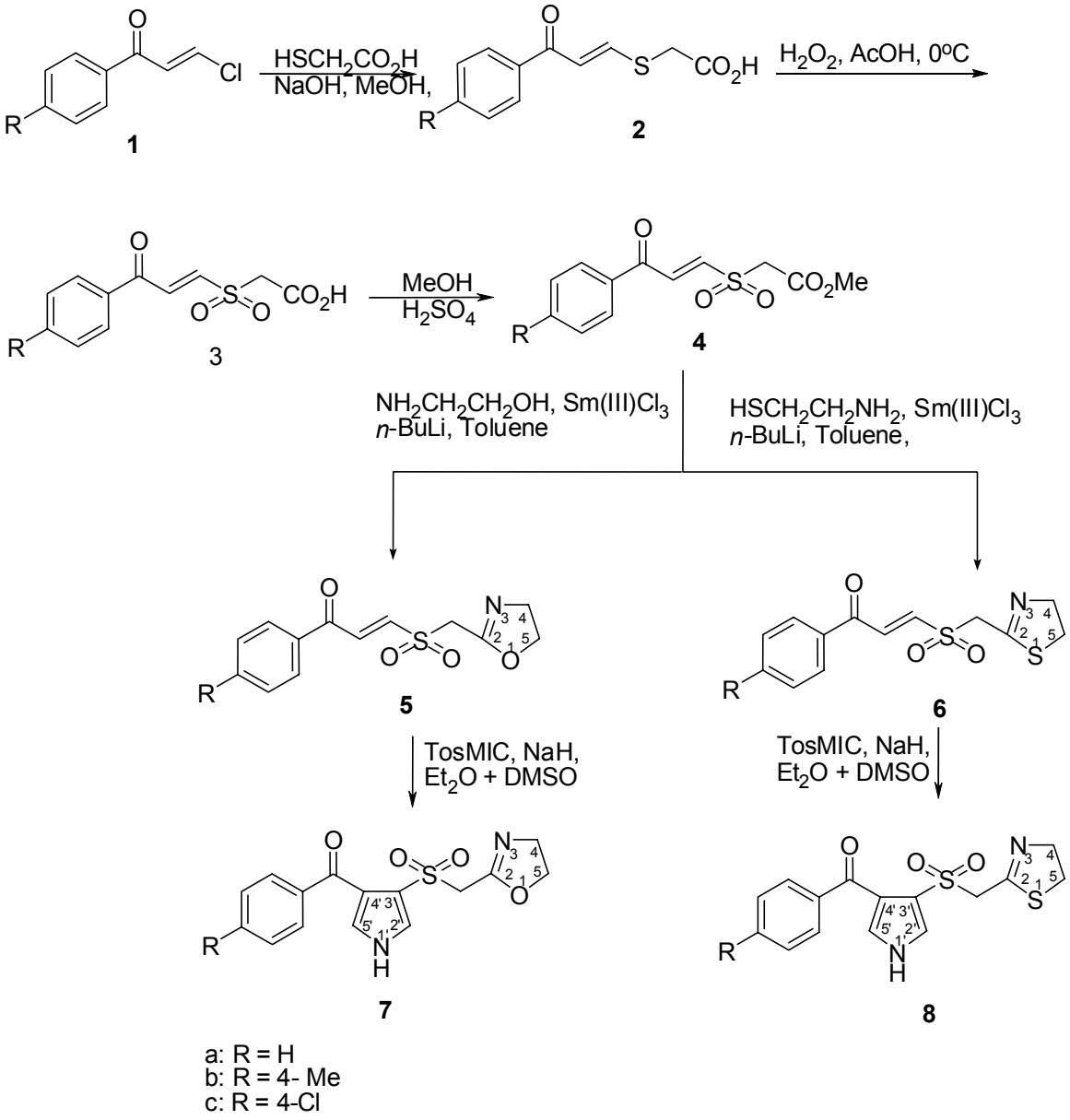
Introduction

The chemistry of heterocyclic compounds has attracted attention in recent times due to its increasing importance in the field of pharmaceuticals and industries. In fact, the development of simple, elegant and facile methodologies for the synthesis of five membered heterocycles is one of the important aspects in organic synthesis. Among five membered heterocycles, pyrroles, oxazoles and thiazoles have gained attention because of their varied physiological activities. 4-Aminopyrrole-2-carboxylate exhibits antibiotic, antiviral and oncolytic activities.[1] Several 2-oxazolines have been used as therapeutic agents. Because of their structural relationship to procaine, the aminophenyl-2-oxazolines have local anaesthetic properties and at the same time have a lower toxicity than procaine.[2] Besides, the oxazoline and thiazoline rings are important constituents of bioactive natural products and pharmaceuticals.[3] The use of oxazoline and thiazoline rings as building blocks in pharmaceutical drug discovery is continually increasing. Hence, it is thought that a worthwhile programme would be to prepare molecules having both pyrrole and oxazole / thiazole rings. Multistep synthetic routes for 3,4-disubstituted pyrroles have been reported in the literature either by coupling of imines and nitroalkanes or using Friedel-Crafts acylation with an electron withdrawing group on the pyrrole nitrogen or 3,4-silylated precursors.[4] However, these synthetic routes are often complicated and limited to only

some substituents. 3,4-Disubstitued pyrroles have also been synthesized from Michael acceptors with tosylmethyl isocyanide (TosMIC).[5,6] A variety of methods have been reported for the synthesis of oxazolines viz., cyclodehydration of amidoalcohols,[7] condensation of imidate hydrochlorides,[8] carboxylic acids,[9] orthoesters,[10] imino ether hydrochlorides,[11] and nitriles[12] with aminoalcohols. Similarly, syntheses of thiazolines are reported by the coupling of imidate esters with 2-aminothiols,[13] cyclodehydration of hydroxy thioamides[14] and heterocyclic inter conversions from oxazolines[15] or oxazolidines.[16] However, lanthanide amino alkoxide complexes as reagents for the preparation of oxazolines and thiazolines are sparsely reported.[17] Herein we wish to report our results pertaining to the development of bis heterocycles from aroylethenesulfonylacetic acid methyl ester by exploiting ester moiety using lanthanide 2-aminoalkoxide complexes to get 2-oxazolines and 2-thiazolines and olefin moiety using 1,3-dipolar cycloaddition of TosMIC to develop pyrrole unit.

Results and Discussion

The synthetic intermediate aroylethenesulfonylacetic acid methyl ester (**4**) is prepared by the condensation of 1-aroyl-2-chloroethene (**1**) with mercaptoacetic acid followed by oxidation and esterification (Scheme 1) Treatment of **4** with 2-aminoethanol in the presence of *n*-butyllithium complexed with a suspension of 5-10% mol. equiv. of anhydrous $SmCl_3$ in toluene produced 2-(aroylethenesulfonylmethyl)-4,5-dihydrooxazole (**5**) (Scheme1). Adopting similar methodology, the reaction of **4** is carried out with 2-aminoethanethiol and *n*-butyllithium in the presence of anhydrous $SmCl_3$ in toluene. The compound obtained is found to be 2-(aroylethenesulfonylmethyl)-4,5-dihydrothiazole (**6**) (Scheme 1). The ^{1}H-NMR spectra of **5a** and **6a** displayed two triplets for C_4-H and C_5-H of 2-oxazoline and 2-thiazoline rings at δ 3.78, 4.88 and 3.91, 3.38. Besides, two doublets and a singlet are observed at δ 7.96, 7.62 and 4.29 in **5a** and at δ 7.89, 7.61 and 4.23 in **6a** which are assigned to olefin protons H_A, H_B and methylene protons, respectively. The *J* value (*J* = 14.4, 14.4 Hz) indicates that H_A and H_B possess *trans* geometry. The ^{13}C-NMR spectrum of **5a** displayed signals at 52.4 (C-4), 57.8 (C-5), 55.2 (SO_2-CH_2), 137.1 (CO-*C*H), 144.4 (*C*H-SO_2), 158.9 (C-2), 182.4 (C=O) where as **6a** at 37.8 (C-5), 54.2 (C-4), 56.8 (SO_2-CH_2), 136.8 (CO-*C*H), 143.9 (*C*H-SO_2), 162.3 (C-2), 181.7 (C=O) besides signals due to aromatic carbons.



Scheme 1

The olefin moiety present in **5** and **6** is utilized to develop pyrrole ring. The reaction of **5** with tosylmethyl isocyanide in the presence of sodium hydride in a mixture of ether and dimethyl sulfoxide gave a solid which is identified as 2-(4′-aroyl-1′*H*-pyrrol-3′-sulfonylmethyl)-4,5-dihydrooxazole (**7**). Similarly treatment of **6** with tosylmethyl isocyanide in the presence of sodium hydride furnished 2-(4′-aroyl-1′*H*-pyrrol-3′-sulfonylmethyl)-4,5-dihydrothiazole (**8**) (see Scheme 1). The ^{1}H-NMR spectra of **7a** and **8a** exhibited two singlets at δ 6.48, 6.56 and 6.96, 6.78 which are assigned to C_2′-H and C_5′-H of pyrrole ring. Apart from these two triplets are observed at δ 3.73, 4.94 (**7a**) and at 3.95, 3.36 (**8a**) due to C_4-H and C_5-H of oxazoline and

thiazoline rings. A sharp singlet is observed at 4.21 (**7a**) and 4.17 (**8a**) for methylene protons. Besides a broad singlet is appeared at 9.21 (**7a**) and 9.13 (**8a**) for NH which disappeared on deuteration. The ^{13}C-NMR spectra of **7a** and **8a** displayed signals at 52.4 (C-4), 58.2 (C-5), 55.9 (SO_2-CH_2), 102.4 (C-4′), 105.2 (C-3′), 116.8 (C-2′), 119.6 (C-5′), 159.7 (C-2), 180.2 (C=O) and at 37.4 (C-5), 53.2 (C-4), 56.6 (SO_2-CH_2), 103.6 (C-4′), 104.8 (C-3′), 115.1 (C-2′), 119.8 (C-5′), 163.3 (C-2), 181.1 (C=O).

Biological evaluation - Antimicrobial activity. The compounds **5-8** were tested for antimicrobial activity at two different concentrations: 100 and 200μg/mL. The antibacterial activity was screened against *Staphylococcus aureus, Bacillus subtilis* (Gram-positive bacteria) and *Escherichia coli, Klebsiella pneumoniae* (Gram-negative bacteria) on nutrient agar plates at 37 ºC for 24 h using chloramphenicol (25 μg per disc) as reference drug. The compounds were also evaluated for their antifungal activity against *Fusarium solani, Curvularia lunata* and *Aspergillus niger* using ketoconazole (25 μg per disc) as standard drug. Fungi cultures were grown on potato dextrose agar medium (PDA) at 25 ºC for 3 days. The spore suspension was adjusted to 10^6 pores ml^{-1} at an mg ml^{-1} concentration by the Vincent and Vincent method.[18]
The results of the compounds of preliminary antibacterial testing shown in Table 1 revealed that, in general, the inhibitory activity against the Gram-positive bacteria was higher than that of the Gram-negative bacteria. The compounds **6c**, **8a** and **8c** showed excellent activity against Gram-positive bacteria (inhibitory zone > 25 mm) and good activity against Gram-negative bacteria (inhibitory zone > 18 mm). The compounds **5** and **7** displayed least activity against both bacteria. All the test compounds exhibited moderate (**5a-c** and **7a-c**) to high (**6a-c** and **8a-c**) inhibitory effect towards tested fungi (Table 2).

Table 1. Antibacterial activity of compounds **5-8**

Compound	Concentration (μg)	Zone of inhibition (mm)			
		Gram-positive bacteria		Gram-negative bacteria	
		S. aureus	*B. subtilis*	*E. coli*	*K. pneumoniae*
5a	100	10	9	-	-
	200	12	12	-	-
5b	100	9	9	-	-
	200	11	10	-	-
5c	100	12	10	9	8
	200	15	14	11	9
6a	100	22	25	16	16
	200	26	27	20	19

6b	100	19	18	13	11
	200	22	23	16	15
6c	100	23	22	19	20
	200	27	26	23	24
7a	100	12	11	9	8
	200	15	13	11	11
7b	100	9	11	-	-
	200	13	14	-	-
7c	100	11	12	11	9
	200	15	15	13	11
8a	100	25	27	19	20
	200	29	30	25	25
8b	100	20	19	17	14
	200	24	25	20	20
8c	100	30	29	22	23
	200	32	33	26	25
Chloramphenicol	100	35	38	40	42
	200	39	41	44	45

Table 2. Antifungal activity of compounds **5-8**

Compound	Concentration (μg)	Zone of inhibition (mm)		
		F. solani	*C. lunata*	*A. niger*
5a	100	16	16	17
	200	20	18	21
5b	100	17	17	16
	200	19	21	21
5c	100	15	17	15
	200	18	20	18

6a	100	25	26	25
	200	27	28	29
6b	100	24	22	21
	200	26	24	24
6c	100	28	23	26
	200	31	25	29
7a	100	19	18	16
	200	22	23	20
7b	100	18	17	17
	200	20	21	20
7c	100	20	21	18
	200	23	23	20
8a	100	33	33	30
	200	36	35	34
8b	100	29	27	32
	200	33	35	36
8c	100	34	34	33
	200	38	40	37
Ketoconazole	100	38	41	36
	200	42	44	39

The 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 pyrrole in combination with oxazoline moiety exhibited least activity when compared with compounds having pyrrole with thiazoline moiety. Among the substituents on the aryl group, 4-chloro phenyl derivatives were the most active. The maximum activity was observed with compound **8c**.

Table 3. Minimal inhibitory concentrations (MIC, μg / mL) of compounds **6c, 8a and 8c**

Compound	Minimal inhibitory concentration (MIC, μg / mL)						
	S. aureus	*B. subtilis*	*E. coli*	*K. pneumoniae*	*F. solani*	*C. lunata*	*A. niger*
6c	100	200	200	200	100	100	200
8a	25	100	100	100	100	100	100
8c	12.5	50	50	50	50	12.5	25
Chloramphenicol	6.25	6.25	6.25	12.5	-	-	-
Ketoconazole	-	-	-	-	12.5	6.25	6.25

Conclusions

In conclusion, a new class of bis(heterocycles), pyrrole in combination with oxazoline and thiazoline was developed adopting simple, elegant and well-versed methodologies from a vulnerable substrate, *E*-aroylethenesulfonyl acetic acid methyl ester. The antimicrobial activity of lead compounds showed high inhibitory activity towards fungi than bacteria. The compounds pyrrole in combination with thiazoline displayed greater antimicrobial activity.

Experimental Section

General Procedures. 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, 1:4). 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 ^{1}H 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 were reported in δ (ppm) using TMS as an internal standard. The microanalyses were performed on Perkin-Elmer 240C elemental analyzer. The starting compound 1-aroyl-2-chloroethene (**1**) was prepared by passing vinyl chloride gas into a solution of aroyl chloride in chloroform in the presence of anhydrous $AlCl_3$ at 10-15 ^{o}C.[19]

***E*-Benzoylethenemercaptoacetic acid (2a). Typical procedure.** To a solution of sodium hydroxide (20 mmol) in methanol (10 mL), mercaptoacetic acid (10 mmol) was added dropwise. To this, compound **1** (10 mmol) was added in portions and the reaction mixture was stirred at 0 ^{o}C for 3 h. The contents were poured onto crushed ice and neutralized with dil. HCl. The aqueous layer was extracted with ethyl acetate. The solvent was removed under reduced pressure and the solid obtained was recrystallized from methanol to get **8a**. Yield 1.578 g (71%); white solid; m. p. 34-36 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.74 (s, 2H, S- CH_2), 7.68 (d, J = 13.7 Hz, 1H, H_B), 7.93 (d, J = 13.7 Hz, 1H, H_A), 7.46-7.84 (m, 5H, Ar-H); 9.91 (bs, 1H, OH); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 53.4 (S-CH_2), 137.8 (CO-*C*H), 143.8 (CH-S), 171.9 (CO-OH), 184.1 (C=O), 128.7, 131.1, 132.6, 135.5 (aromatic carbons); IR (KBr): v = 3200 (OH), 1725 (C=O), 1660 (Ar-C=O), 1585 (C=C).

***E*-*p*-Methylbenzoylethenemercaptoacetic acid (2b).** Yield 1.796 g (76%); white solid; m. p. 45-47 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.27 (s, 3H, CH_3), 3.70 (s, 2H, S- CH_2), 7.71 (d, J = 13.9 Hz, 1H, H_B), 7.95 (d, J = 13.9 Hz, 1H, H_A), 7.38-7.82 (m, 4H, Ar-H), 10.1 (bs,1H, OH); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 23.2 (-CH_3), 53.8 (S-CH_2), 137.2 (CO-*C*H), 143.3 (CH-S), 170.5 (COOH), 183.5 (C=O), 127.6, 130.4, 133.1, 139.5 (aromatic carbons); IR (KBr): v = 3214 (OH), 1722 (C=O), 1657 (Ar-C=O), 1581 (C=C).

***E*-*p*-Chlorobenzoylethenemercaptoacetic acid (2c).** Yield 1.899 g (74%); white solid; m. p. 67-69 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.79 (s, 2H, S- CH_2), 7.74 (d, J = 13.5 Hz, 1H, H_B), 7.98 (d, J = 13.5 Hz, 1H, H_A), 7.54-7.89 (m, 4H, Ar-H), 9.82 (bs, 1H, OH); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 54.1 (S-CH_2), 138.1 (CO-*C*H), 144.2 (*C*H-S), 171.4 (COOH), 184.2 (C=O), 128.4, 130.6, 132.4, 141.5 (aromatic carbons); IR (KBr): v = 3218 (OH), 1714 (C=O), 1664 (Ar-C=O), 1574 (C=C).

***E*-Benzoylethenesulfonylacetic acid (3a). Typical procedure.** The compound **2** (10 mmol) was subjected to oxidation with 30% hydrogen peroxide (2 mL) in glacial acetic acid (6.5 mL). The contents were stirred at 0 ^{o}C for 4 h. and kept aside for 36 h. The reaction mixture was poured onto crushed ice. The solid separated was filtered and recrystallized from water to get pure **3a**. Yield 2.237 g (88%); white solid; m. p. 132-134 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.38 (s, 2H, SO_2- CH_2), 7.66 (d, J = 14.2 Hz, 1H, H_B,), 7.96 (d, J = 14.2 Hz, 1H, H_A), 7.56-7.88 (m, 5H, Ar-H), 9.68 (bs, 1H, OH); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 56.8 (SO_2-CH_2), 138.7 (CO-*C*H), 141.8 (*C*H-SO_2), 172.8 (COOH), 182.4 (C=O), 128.4, 129.4, 132.6, 134.4 (aromatic carbons); IR (KBr): v = 3221 (OH), 1727 (C=O), 1662 (Ar-C=O), 1584 (C=C), 1326, 1130 (SO_2).

***E*-(*p*-Methylbenzoyl)ethenesulfonylacetic acid (3b).** Yield 2.280 g (85%); white solid; m. p. 125-127 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.24 (s, 2H, -CH_3), 4.40 (s, 2H, SO_2- CH_2), 7.63 (d, J = 14.4 Hz, 1H, H_B), 7.92 (d, J = 14.4 Hz, 1H, H_A), 7.42-7.80 (m, 4H, Ar-H), 9.92 (bs, 1H, OH); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 24.2 (-CH_3), 57.2 (SO_2-CH_2), 137.6 (CO-*C*H), 142.3 (CH-SO_2), 172.3 (COOH), 181.3 (C=O), 128.2, 129.2, 131.9, 135.4 (aromatic carbons); IR (KBr): v = 3224 (OH), 1714 (C=O), 1658 (Ar-C=O), 1568 (C=C), 1314, 1132 (SO_2).

***E*-(*p*-Chlorobenzoyl)ethenesulfonylacetic acid (3c).** Yield 2.512 g (87%); white solid; m. p. 151-153 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.42 (s, 2H, SO_2-CH_2), 7.69 (d, J = 14.6 Hz, 1H, H_B), 7.98 (d, J = 14.3 Hz, 1H, H_A), 7.52-7.87 (m, 4H, Ar-H), 9.96 (bs, 1H, OH); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 56.5 (SO_2-CH_2), 138.1 (CO-*C*H), 142.6 (*C*H-SO_2), 173.2 (COOH), 179.6 (C=O), 128.1, 129.6, 132.3, 134.2 (aromatic carbons); IR (KBr): v = 3218 (OH), 1724 (C=O), 1666 (Ar-C=O), 1564 (C=C), 1336, 1138 (SO_2).

***E*-Benzoylethenesulfonylacetic acid methyl ester (4a). Typical procedure.** To a solution of compound **3** (10 mmol) in methanol (20 mL), sulfuric acid (4 mL) was added and refluxed for 6-8 h. The contents were cooled and poured onto crushed ice. The solid separated was filtered and recrystallized from methanol to get pure **4a.** Yield 2.280 g (85%); white crystals; m. p. 94-96 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.78 (s, 3H, -OCH_3), 4.36 (s, 2H, SO_2- CH_2), 7.65 (d, J = 13.9 Hz, 1H, H_B), 7.91 (d, J = 13.7 Hz, 1H, H_A), 7.36-7.52 (m, 5H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 53.1 (OCH_3), 59.6 (SO_2-CH_2), 138.4 (CO-*C*H), 145.6 (CH-SO_2), 168.1 (*C*O_2CH_3), 182.4 (C=O), 130.5, 132.3, 137.5, 139.4 (aromatic carbons); IR (KBr): v = 1746 (CO_2Me), 1668 (C=O), 1579 (C=C), 1316, 1142 (SO_2); Anal. Calcd. for $C_{12}H_{12}O_5S$ (268.29): C, 53.72 ; H, 4.51. Found: C, 53.78; H, 4.49.

***E*-(*p*-Methylbenzoyl)ethenesulfonylacetic acid methyl ester (4b).** Yield 2.512 g (89%); white crystals; m. p. 101-103 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.28 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 4.32 (s, 2H, SO_2- CH_2), 7.62 (d, J = 13.7 Hz, 1H, H_B), 7.88 (d, J = 13.7 Hz, 1H, H_A), 7.32-7.54 (m, 4H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 23.1 (CH_3), 53.4 (OCH_3), 58.1 (SO_2-CH_2), 138.1 (CO-*C*H), 146.1 (CH-SO_2), 167.4 (*C*O_2CH_3), 181.3 (C=O), 129.4, 131.6, 136.3, 138.4 (aromatic carbons); IR (KBr): v = 1749 (CO_2Me), 1662 (C=O), 1574 (C=C), 1341, 1128 (SO_2); Anal. Calcd. for $C_{13}H_{14}O_5S$ (282.31): C, 55.31; H, 5.00. Found: C, 55.34; H, 5.02.

***E*-(*p*-Chlorobenzoyl)ethenesulfonylacetic acid methyl ester (4c).** Yield 2.634 g (87%); white crystals; m. p. 124-126 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.75 (s, 3H, OCH_3), 4.38 (s, 2H, SO_2- CH_2), 7.69 (d, J = 14.2 Hz, 1H, H_B), 7.94 (d, J = 14.2 Hz, 1H, H_A), 7.48-7.72 (m, 4H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 53.8 (OCH_3), 58.9 (SO_2-CH_2), 138.9 (CO-*C*H), 147.3 (*C*H-SO_2), 168.6 (*C*O_2CH_3), 181.6 (C=O), 128.9, 131.4, 135.8, 137.4 (aromatic carbons); IR (KBr): v = 1752 (CO_2Me), 1669 (C=O), 1568 (C=C), 1325, 1149 (SO_2); Anal. Calcd. for $C_{12}H_{11}ClO_5S$ (302.73): C, 47.61; H, 3.66. Found: C, 47.55; H, 3.69.

2-(Aroylethenesulfonylmethyl)-4,5-dihydrooxazole (5) / 2-(Aroylethenesulfonyl-methyl)-4,5-dihydrothiazole (6). Typical procedure. To a flask charged with anhydrous samarium chloride (0.1 mmol), dry toluene (10 mL) and 2 mmols of aminoethanol / aminoethanethiol were added followed by 2.2 mmol of *n*-butyllithium at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 30 min. Then the contents were refluxed to 120 ^{o}C and 1mmol of aroylethenesulfonylacetic acid methyl ester (**4**) was added and continued the 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].

2-(Benzoylethenesulfonylmethyl)-4,5-dihydrooxazole (5a). Yield 0.213 g (77 %); white solid; m. p. 117-119 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.78 (t, J = 5.9 Hz, 2H, H-4), 4.29 (s, 2H, SO_2- CH_2), 4.88 (t, J = 5.9 Hz, 2H, H-5), 7.62 (d, J = 14.4 Hz, 1H, H_B,), 7.96 (d, J = 14.4 Hz, 1H, H_A,), 7.46-7.56 (m, 5H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 52.4 (C-4), 55.2 (SO_2-CH_2), 57.8 (C-5), 137.1 (CO-*C*H), 144.4 (*C*H-SO_2), 158.9 (C-2), 182.4 (C=O), 127.8, 129.8, 131.6, 132.3 (aromatic carbons); IR (KBr): v = 1662 (C=O), 1578 (C=N), 1563 (C=C), 1325, 1149 (SO_2); Anal. Calcd. for $C_{13}H_{11}NO_4S$ (277.30): C, 56.31; H, 4.00; N, 5.05. Found: C, 56.37; H, 3.97; N, 5.09.

2-(*p*-Methylbenzoylethenesulfonylmethyl)-4,5-dihydrooxazole (5b). Yield 0.239 g (82%); white solid; m. p. 132-134 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.24 (s, 3H, CH_3), 3.82 (t, J = 5.7 Hz, 2H, H-4), 4.32 (s, 2H, SO_2- CH_2), 4.79 (t, J = 5.7 Hz, 2H, H-5), 7.68 (d, J = 14.2 Hz, 1H, H_B), 7.85 (d, J = 14.2 Hz, 1H, H_A), 7.34-7.53 (m, 4H,Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 21.8 (CH_3), 52.8 (C-4), 55.8 (SO_2-CH_2), 56.9 (C-5), 137.4 (CO-*C*H), 143.8 (*C*H-SO_2), 161.4 (C-2), 181.7 (C=O), 127.1, 128.4, 129.2, 132.3 (aromatic carbons); IR (KBr): v = 1668 (C=O), 1574 (C=N), 1561 (C=C), 1331, 1138 (SO_2); Anal. Calcd. for $C_{14}H_{13}NO_4S$ (291.32): C, 57.72; H, 4.50; N, 4.81. Found: C, 57.79; H, 4.55; N, 4.86.

2-(*p*-Chlorobenzoylethenesulfonylmethyl)-4,5-dihydrooxazole (5c). Yield 0.206 g (66%); white solid; m. p. 141-142 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.72 (t, J = 5.4 Hz, H-4), 4.35 (s, 2H, SO_2- CH_2), 4.92 (t, J = 5.4 Hz, 2H, H-5), 7.69 (d, J = 14.4 Hz, 1H, H_B), 7.91 (d, J = 14.4 Hz, 1H, H_A), 7.48-7.64 (m, 4H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 53.1 (C-4), 56.2 (SO_2-CH_2), 58.1 (C-5), 138.2 (CO-*C*H), 142.4 (*C*H-SO_2), 160.6 (C-2), 183.6 (C=O), 128.4, 129.2, 129.8, 133.6 (aromatic carbons); IR (KBr): v = 1671 (C=O), 1568 (C=N), 1562 (C=C), 1328, 1142 (SO_2); Anal. Calcd. for $C_{13}H_{10}ClNO_4S$ (311.74): C, 50.09; H, 3.23; N, 4.49. Found: C, 50.02; H, 3.26; N, 4.42.

2-(Benzoylethenesulfonylmethyl)-4,5-dihydrothiazole (6a). Yield 0.201 g (68%); white solid; m. p. 108-110 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.38 (t, J = 8.3 Hz, 2H, H-5), 3.91 (t, J = 8.3 Hz, 2H, H-4), 4.23 (s, 2H, SO_2- CH_2), 7.61 (d, J = 14.3 Hz, 1H, H_B), 7.89 (d, J = 14.3 Hz, 1H, H_A), 7.42-7.74 (m, 5H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 37.8 (C-5), 54.2 (C-4), 56.8 (SO_2-CH_2), 136.8 (CO-*C*H), 143.9 (*C*H-SO_2), 162.3 (C-2), 181.7 (C=O), 127.3, 128.2, 129.1, 131.8 (aromatic carbons); IR (KBr): v = 1677 (C=O), 1573 (C=N), 1564 (C=C), 1331, 1142 (SO_2); Anal. Calcd. for $C_{13}H_{13}NO_3S_2$ (295.38): C, 52.86; H, 4.44; N, 4.74. Found: C, 52.81; H, 4.48; N, 4.70.

2-(*p*-Methylbenzoylethenesulfonylmethyl)-4,5-dihydrothiazole (6b). Yield 0.195 g (63%); white solid; m. p. 120-122 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.34 (s, 3H, CH_3), 3.31 (t, J = 8.3 Hz, 2H, H-5), 3.88 (t, J = 8.3 Hz, 2H, H-4), 4.21 (s, 2H, SO_2- CH_2), 7.64 (d, J = 14.1 Hz, 1H, H_B), 7.88 (d, J = 14.1 Hz, 1H, H_A), 7.36-7.72 (m, 4H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 22.3 (CH_3), 37.3 (C-5), 55.6 (C-4), 56.6 (SO_2-CH_2), 136.1 (CO-*C*H), 143.2 (*C*H-SO_2), 159.2 (C-2), 180.6 (C=O), 126.8, 128.4, 129.6, 130.2 (aromatic carbons); IR (KBr): v = 1681

(C=O), 1574 (C=N), 1559 (C=C), 1328, 1144 (SO_2); Anal. Calcd. for $C_{14}H_{15}NO_3S_2$ (309.40): C, 54.35; H, 4.89 ; N, 4.53. Found: C, 54.39; H, 4.92; N, 4.61.

2-(*p*-Chlorobenzoylethenesulfonylmethyl)-4,5-dihydrothiazole (6c). Yield 0.214 g (65%); white solid; m. p. 133-135 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.37 (t, J = 7.5 Hz, 2H, H-5), 3.92 (t, J = 7.5 Hz, 2H, H-4), 4.31 (s, 2H, SO_2- CH_2), 7.62 (d, J = 14.1 Hz, 1H, H_B), 7.81 (d, J = 14.1 Hz, 1H, H_A), 7.46-7.75 (m, 4H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 36.9 (C-5), 55.4 (C-4), 57.9 (SO_2-CH_2), 136.8 (CO-*C*H), 142.8 (*C*H-SO_2), 159.4 (C-2), 181.4 (C=O), 127.6, 128.9, 131.4, 137.2 (aromatic carbons); IR (KBr): ν = 1676 (C=O), 1568 (C=N), 1561 (C=C), 1330, 1143 (SO_2); Anal. Calcd. for $C_{13}H_{12}ClNO_3S_2$ (329.82): C, 47.34; H, 3.67; N, 4.25 . Found: C, 47.39; H, 3.64; N, 4.31.

2-(4′-Aroyl-1′*H*-pyrrol-3′-sulfonylmethyl)-4,5-dihydrooxazole (7a) / 2-(4′-Aroyl-1′*H*-pyrrol-3′-sulfonylmethyl)-4,5-dihydrothiazole (8a). Typical procedure. A mixture of 1 mmol of TosMIC and 1 mmol of 2-(aroylethenesulfonylmethyl)-4,5-dihydrooxazole / 2-(aroylethenesulfonylmethyl)-4,5-dihydrothiazole (**5**/**6**) in Et_2O/DMSO (2:1) was added dropwise to a stirred mixture 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 passing through a column chromatography [silica gel (60-120 mesh), EtOAc- hexane 1.5:3] as eluent.

2-(4′-(Benzoyl-1′*H*-pyrrol-3′-sulfonylmethyl)-4,5-dihydrooxazole (7a). Yield 0.197 g (62%); pale yellow solid; m. p. 189-191 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.73 (t, J = 5.3 Hz, 2H, H-4), 4.21 (s, 2H, SO_2- CH_2), 4.94 (t, J = 5.3 Hz, 2H, H-5), 6.48 (s, 1H, H-2′), 6.96 (s, 1H, H-5′), 7.35-7.58 (m, 5H, Ar-H), 9.21 (bs, 1H, NH); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 52.4 (C-4), 55.9 (SO_2-CH_2), 58.2 (C-5), 102.4 (C-4′), 105.2 (C-3′), 116.8 (C-2′), 119.6 (C-5′), 159.7 (C-2), 180.2 (C=O), 127.9, 129.6, 131.4, 132.6 (aromatic carbons); IR (KBr): ν = 3208 (NH), 1678 (C=O), 1573 (C=N), 1330, 1148 (SO_2); Anal. Calcd. for $C_{15}H_{14}N_2O_4S$ (318.35): C, 56.59; H, 4.43; N, 8.80. Found: C, 56.54; H, 4.44; N, 8.69.

2-(4′-(*p*-Methylbenzoyl-1′*H*-pyrrol-3′-sulfonylmethyl)-4,5-dihydrooxazole (7b). Yield 0.236 g (71%); pale yellow solid; m. p. 176-178 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.24 (s, 3H, CH_3), 3.84 (t, J = 5.8 Hz, 2H, H-4), 4.27 (s, 2H, SO_2- CH_2), 4.87 (t, J = 5.8 Hz, 2H, H-5), 6.45 (s, 1H, H-2′), 6.91 (s, 1H, H-5′), 7.27-7.52 (m, 4H, Ar-H), 9.26 (bs, 1H, NH); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 23.5 (CH_3), 52.5 (C-4), 54.8 (SO_2-CH_2), 57.9 (C-5), 101.9 (C-4′), 105.8 (C-3′), 115.9 (C-2′), 119.1 (C-5′), 158.6 (C-2), 181.8 (C=O), 127.2, 127.9, 129.1, 130.7 (aromatic carbons); IR (KBr): ν = 3210 (NH), 1672 (C=O), 1577 (C=N), 1334, 1142 (SO_2); Anal. Calcd. for $C_{16}H_{16}N_2O_4S$ (332.37): C, 57.82; H, 4.85; N, 8.43. Found: C, 57.87; H, 4.82; N, 8.38.

2-(4′-(*p*-Chlorobenzoyl-1′*H*-pyrrol-3′-sulfonylmethyl)-4,5-dihydrooxazole (7c). Yield 0.215 g (61%); pale yellow solid; m. p. 212-214 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.89 (t, J = 5.6 Hz, 2H, H-4), 4.21 (s, 2H, SO_2- CH_2), 4.96 (t, J = 5.6 Hz, 2H, H-5), 6.39 (s, 1H, H-2′), 6.86 (s, 1H, H-5′), 7.38-7.62 (m, 4H, Ar-H), 9.28 (bs, 1H, NH); ^{13}C NMR (300 MHz, DMSO-

d_6): δ = 52.8 (C-4), 54.4 (SO_2-CH_2), 57.4 (C-5), 102.1 (C-4′), 106.2 (C-3′), 115.1 (C-2′), 120.1 (C-5′), 160.1 (C-2), 181.7 (C=O), 128.2, 129.6, 132.1, 135.7 (aromatic carbons); IR (KBr): v = 3218 (NH), 1673 (C=O), 1571 (C=N), 1339, 1148 (SO_2); Anal. Calcd. for $C_{15}H_{13}ClN_2O_4S$ (352.79): C, 51.07; H, 3.71; N, 7.94. Found: C, 51.14; H, 3.74; N, 8.02.

2-(4′-Benzoyl-1′*H*-pyrrol-3′-sulfonylmethyl)-4,5-dihydrothiazole (8a). Yield 0.214 g (64%); pale yellow solid; m. p. 176-178 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.36 (t, J = 7.3 Hz, 2H, H-5), 3.95 (t, J = 7.3 Hz, 2H, H-4), 4.17 (s, 2H, SO_2- CH_2), 6.56 (s, 1H, H-2′), 6.78 (s, 1H, H-5′), 7.38-7.71 (m, 5H, Ar-H), 9.13 (bs, 1H, NH); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 37.4 (C-5), 53.2 (C-4), 56.6 (SO_2-CH_2), 103.6 (C-4′), 104.8 (C-3′), 115.1 (C-2′), 119.8 (C-5′), 163.3 (C-2), 181.1 (C=O), 127.9, 129.5, 129.8, 131.2 (aromatic carbons); IR (KBr): v = 3216 (NH), 1668 (C=O), 1569 (C=N), 1336, 1145 (SO_2); Anal. Calcd. for $C_{15}H_{14}N_2O_3S_2$ (334.41): C, 53.87; H, 4.22 ; N, 8.38 . Found: C, 53.84; H, 4.20; N, 8.34.

2-(4′-(*p*-Methylbenzoyl-1′*H*-pyrrol-3′-sulfonylmethyl)-4,5-dihydrothiazole (8b). Yield 0.229 g (66%); white solid; m. p. 158-160 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.51 (s, 3H, CH_3), 3.39 (t, J = 8.1 Hz, 2H, H-5), 3.82 (t, J = 8.1 Hz, 2H, H-4), 4.25 (s, 2H, SO_2- CH_2), 6.49 (s, 1H, H-2′), 6.81 (s, 1H, H-5′), 7.36-7.59 (m, 4H, Ar-H), 9.18 (bs, 1H, NH); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 24.2 (CH_3), 37.8 (C-5), 52.9 (C-4), 56.4 (SO_2-CH_2), 102.9 (C-4′), 103.6 (C-3′), 115.7 (C-2′), 118.9 (C-5′), 161.8 (C-2), 182.4 (C=O), 127.4, 129.2, 129.6, 131.1 (aromatic carbons); IR (KBr): v = 3214 (NH), 1663 (C=O), 1564 (C=N), 1331, 1139 (SO_2); Anal. Calcd. for $C_{16}H_{16}N_2O_3S_2$ (348.44): C, 55.15; H, 4.63; N, 8.04. Found: C, 55.11; H, 4.61; N, 8.01.

2-(4′-(*p*-Chlorobenzoyl-1′*H*-pyrrol-3′-sulfonylmethyl)-4,5-dihydrothiazole (8c). Yield 0.254 g (69%); white solid; m. p. 193-195 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.42 (t, J = 8.3 Hz, 2H, H-5), 3.87 (t, J = 8.3 Hz, 2H, H-4), 4.29 (s, 2H, SO_2- CH_2), 6.51 (s, 1H, H-2′), 6.89 (s, 1H, H-5′); 7.44-7.67 (m, 4H, Ar-H), 9.21 (bs, 1H, NH); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 38.8 (C-5), 53.9 (C-4), 55.1 (SO_2-CH_2), 101.4 (C-4′), 104.2 (C-3′), 115.6 (C-2′), 119.4 (C-5′), 163.2 (C-2), 181.1 (C=O), 129.1, 129.8, 131.5, 133.4 (aromatic carbons); IR (KBr): v = 3219 (NH), 1673 (C=O), 1566 (C=N), 1338, 1132 (SO_2); Anal. Calcd. for $C_{15}H_{13}ClN_2O_3S_2$ (368.86): C, 48.84; H, 3.55; N, 7.59. Found: C, 48.72; H, 3.52; N, 7.65.

Antimicrobial activity

Chemistry

The compounds **5-8** were dissolved in DMSO at different concentrations of 100, 200 & 800 µg/mL.

Cells

Bacterial strains *Staphylococcus aureus*, *Bacillus subtilis*, *Klebsiella pneumoniae*, *Proteus vulgaris* and fungi *Aspergillus niger*, *Fusarium solani* & *Curvularia lunata* were obtained from NCIM, Pune, India.

Antibacterial and antifungal assays

Preliminary antimicrobial activities of compounds **5-8** 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 ºC 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. The twofold dilution of the solution was prepared (400, 200, 100, …, 6.25 µg/mL). The microorganism suspensions were incubated at 36ºC 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.

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