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Laboratory note

Synthesis and bioassay of a new class of heterocycles pyrrolyl oxadiazoles/thiadiazoles/triazoles

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Abstract

A new class of heterocycles pyrrolyl thiadiazoles, pyrrolyl oxadiazoles and pyrrolyl triazoles were prepared from arylsulfonylethenesulfonyl-acetic acid methyl ester and tested for their antimicrobial and cytotoxic activities.

Keywords: Pyrroles; 1,3,4-Thiadiazoles; 1,3,4-Oxadiazoles; Antimicrobial activity; Cytotoxic activity

1. Introduction

Among different five-membered heterocyclic systems pyrrole, oxadiazole, thiadiazole, triazole and their derivatives have gained importance as they constitute the structural features of many bioactive compounds. 1,3,4-Oxadiazoles are of significant interest in medicinal chemistry in a number of biological targets including benzodiazepine receptor agonists [1], 5-HT receptor agonists [2], muscarinic agonists [3], 5-HT antagonists [4], human NK_1 antagonists [5], antirhinoviral compounds [6] and anti-inflammatory agents [7]. They have been used as peptide mimetics due to their particular geometric and electrostatic properties [8,9]. Apart from these, 1,2,3-substituted thiadiazole derivatives were associated with diverse biological activities [10,11]. Various substituted 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles and their dihydro analogues possess diverse pharmacological activities such as antimicrobial [12], antibacterial [13], antitubercular [14], anti-inflammatory [15–17], and antifungal [18,19]. A number of pyrrole derivatives *viz*., tolmetin, ketorolac, etc., were of pharmacological relevance due to their anti-inflammatory and analgesic properties [20]. Hence, it is considered worthwhile to prepare a new class of heterocycles from synthetically vulnerable intermediate arylsulfonylethenesulfonylacetic acid methyl ester (**4**).

2. Chemistry

The compound, *E*-arylsulfonylethenesulfonylacetic acid methyl ester (**4**) was obtained by the condensation of 1-arylsulfonyl-2-chloroethene with mercaptoacetic acid followed by oxidation and esterification (Scheme 1 and Table 1). Earlier, we have studied the reactivity of phenacylsulfonylacetic acid methyl ester and aroylethenesulfonylacetic acid methyl ester towards the development of heterocycles. When phenacylsulfonylacetic acid methyl ester was treated with hydrazine hydrate instead of the expected acid hydrazide, 1,1-dioxo-6-phenyl-1,2,4,7-tetrahydro-1λ^6-1,4,5-thiadiazepin-3-one was obtained [21]. In order to get the desired heterocycles, keto group in phenacylsulfonylacetic acid methyl ester was protected by oximation. The ester functionality was exploited for oxadiazoles, thiadiazoles and triazoles. The deoximation of keto group was affected by β-cyclodextrin in the presence of oxidizing agent [22]. However,

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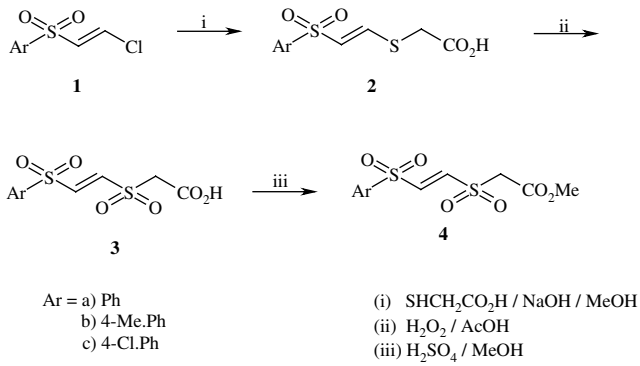
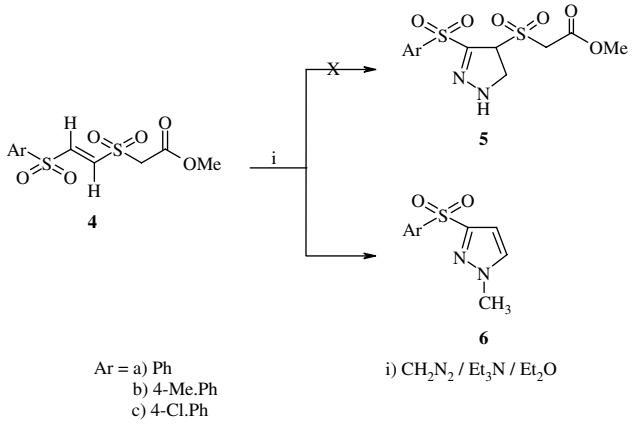


Scheme 1.

aroylethenesulfonylacetic acid methyl ester on treatment with hydrazine hydrate produced 1,1-dioxo-6-phenacyl-[1,4,5]thiadiazinan-3-one and (3-aryl-4,5-dihydro-1*H*-pyrazole-5-sulfonyl)acetic acid methyl ester instead of acid hydrazide [23]. As such, first the olefinic moiety in the former was utilized to develop pyrazole ring by 1,3-dipolar cycloaddition methodology with diazomethane. The resultant pyrazolyl ester was used to construct oxadiazoles, thiadiazoles and triazoles [23]. As unexpected products were obtained in both the cases when a molecule having two different functional groups was treated with hydrazine hydrate, we thought of exploiting olefin moiety in **4** to construct pyrazole ring. When **4** was treated with diazomethane in the presence of Et_3N at −20 to −15 °C for 48 h a solid was obtained and identified as *N*-methyl-3-arylsulfonylpyrazole (**6**) by spectral parameters (Scheme 2). It seems the 1-pyrazoline formed during the course of the reaction in the presence of carbene generated from diazomethane led to a bicyclic compound which was ultimately aromatized by the elimination of sulfonylacetic ester moiety (mechanism). In our interest to develop heterocycles from **4**, it was treated with tosylmethyl isocyanide (TosMIC) in the presence of sodium hydride in a solvent mixture of ether and DMSO. The compound obtained was identified as (4-arylsulfonyl-1*H*-pyrrole-3-sulfonyl)acetic acid methyl ester (**7**). The articulation of oxadiazole, thiadiazole and triazole rings was made by the use of ester moiety in **7**. The compound **7** on reaction with hydrazine hydrate gave the corresponding acid hydrazide **8**. The potassium dithiocarbazate of acid hydrazide **9** was prepared from **8** on treatment with carbon disulfide in the presence of potassium hydroxide under ultrasonic conditions. This on refluxing in acetic acid cyclized to 5′-(4-arylsulfonyl-1*H*-pyrrole-3-sulfonylmethyl)-[1′,3′,4′]thiadiazole-2′-thiol (**10**). Acid catalysed hydrolysis of **9** resulted in 5′-(4-arylsulfonyl-1*H*-pyrrole-3-sulfonylmethyl)-[1′,3′,4′]oxadiazole-2′-thiol (**11**). Further, the compound **9** on treatment with hydrazine hydrate produced 4′-amino-5′-(4-arylsulfonyl-1

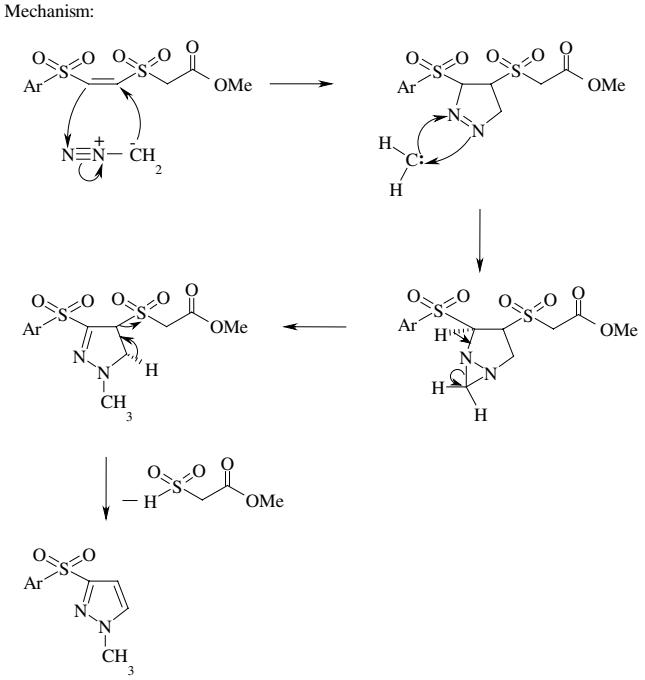
Table 1
Characterization data of compounds **2–4** and **6–12**

Compound	Mp (°C)/(colour)	Ar	Yield (%)	Molecular formula (M.Wt)	Analysis % calcd./(found)		
					C	H	N
2a	43–45 (white crystals)	Ph	72	$C_{10}H_{10}O_4S_2$ (258.31)	46.50 (46.74)	3.90 (3.87)	–
2b	40–42 (white crystals)	4-MePh	68	$C_{11}H_{12}O_4S_2$ (272.34)	48.51 (48.61)	4.44 (4.46)	–
2c	51–53 (white solid)	4-ClPh	76	$C_{10}H_9ClO_4S_2$ (292.76)	41.03 (40.95)	3.10 (3.05)	–
3a	146–148 (white solid)	Ph	84	$C_{10}H_{10}O_6S_2$ (290.31)	41.37 (41.32)	3.47 (3.52)	–
3b	163–165 (white solid)	4-MePh	85	$C_{11}H_{12}O_6S_2$ (304.34)	43.41 (43.50)	3.97 (4.00)	–
3c	157–159 (white solid)	4-ClPh	82	$C_{10}H_9ClO_6S_2$ (324.76)	36.98 (37.04)	2.79 (2.81)	–
4a	118–120 (white crystals)	Ph	86	$C_{11}H_{12}O_6S_2$ (304.34)	43.41 (43.36)	3.97 (4.01)	–
4b	124–126 (white crystals)	4-MePh	87	$C_{12}H_{14}O_6S_2$ (318.37)	45.27 (45.31)	4.43 (4.39)	–
4c	131–133 (white crystals)	4-ClPh	85	$C_{11}H_{11}ClO_6S_2$ (338.78)	39.00 (38.92)	3.27 (3.29)	–
6a	78–80 (yellow solid)	Ph	68	$C_{10}H_{10}N_2O_2S$ (222.26)	54.04 (54.00)	4.53 (4.50)	12.60 (12.71)
6b	66–68 (yellow solid)	4-MePh	64	$C_{11}H_{12}N_2O_2S$ (236.29)	55.91 (55.97)	5.12 (5.00)	11.86 (11.94)
6c	87–89 (Yellow solid)	4-ClPh	67	$C_{10}H_9ClN_2O_2S$ (256.71)	46.79 (46.83)	3.53 (3.57)	10.91 (10.83)
7a	141–143 (yellow solid)	Ph	69	$C_{13}H_{13}NO_6S$ (343.38)	45.47 (45.51)	3.82 (3.80)	4.08 (4.05)
7b	158–160 (yellow solid)	4-MePh	71	$C_{14}H_{15}NO_6S_2$ (357.4)	47.05 (47.01)	4.23 (4.20)	3.92 (3.98)
7c	164–166 (yellow solid)	4-ClPh	74	$C_{13}H_{12}ClNO_6S_2$ (377.82)	41.33 (41.37)	3.20 (3.22)	3.71 (3.77)
8a	156–158 (yellow solid)	Ph	72	$C_{12}H_{13}N_3O_5S_2$ (343.38)	41.97 (41.93)	3.82 (3.84)	12.24 (12.21)
8b	163–165 (Yellow solid)	4-MePh	70	$C_{13}H_{15}N_3O_5S_2$ (357.41)	43.69 (43.72)	4.23 (4.26)	11.76 (11.71)
8c	172–174 (yellow solid)	4-ClPh	75	$C_{12}H_{12}ClN_3O_5S_2$ (377.82)	38.15 (38.12)	3.20 (3.23)	11.12 (11.16)
9a	– (white solid)	Ph	82	$C_{13}H_{12}KN_3O_5S_4$ (457.61)	–	–	–
9b	– (white solid)	4-MePh	79	$C_{14}H_{14}KN_3O_5S_4$ (471.64)	–	–	–
9c	– (white solid)	4-ClPh	81	$C_{13}H_{11}ClKN_3O_5S_4$ (492.05)	–	–	–
10a	196–198 (yellow solid)	Ph	73	$C_{13}H_{11}N_3O_4S_4$ (401.5)	38.89 (38.86)	2.76 (2.75)	10.47 (10.54)
10b	189–191 (yellow solid)	4-MePh	69	$C_{14}H_{13}N_3O_4S_4$ (415.53)	40.47 (40.51)	3.15 (3.17)	10.11 (10.20)
10c	206–208 (yellow solid)	4-ClPh	68	$C_{13}H_{10}ClN_3O_4S_4$ (435.95)	35.82 (35.85)	2.31 (2.29)	9.64 (9.69)
11a	167–169 (yellow solid)	Ph	67	$C_{13}H_{11}N_3O_5S_3$ (385.44)	40.51 (40.47)	2.88 (2.92)	10.90 (10.97)
11b	180–182 (Yellow solid)	4-MePh	68	$C_{14}H_{13}N_3O_5S_3$ (399.47)	42.09 (42.04)	3.28 (3.30)	10.52 (10.45)
11c	174–176 (yellow solid)	4-ClPh	71	$C_{13}H_{10}ClN_3O_5S_3$ (419.88)	37.19 (37.22)	2.40 (2.39)	10.01 (10.05)
12a	212–214 (yellow solid)	Ph	67	$C_{13}H_{13}N_5O_4S_3$ (399.47)	39.09 (39.06)	3.28 (3.26)	17.53 (17.49)
12b	209–211 (yellow solid)	4-MePh	70	$C_{14}H_{15}N_5O_4S_3$ (413.5)	40.67 (40.65)	3.66 (3.68)	16.94 (16.98)
12c	234–236 (yellow solid)	4-ClPh	72	$C_{13}H_{12}ClN_5O_4S_3$ (433.91)	35.98 (36.01)	2.79 (2.80)	16.14 (16.20)



Scheme 2.

H-pyrrole-3-sulfonylmethyl)-[1′,2′,4′]-triazole-3′-thiol (**12**) (Scheme 3 and Table 1).



3. Biology

3.1. Antimicrobial activity

The synthesized compounds were tested for their *in vitro* antimicrobial activity against the Gram-positive bacteria *Staphylococcus aureus*, *Bacillus subtilis*, the Gram-negative bacteria *Escherichia coli*, *Klebsiella pneumoniae* and fungi *Fusarium solani*, *Curvularia lunata* and *Aspergillus niger*. The primary screening was carried out by agar disc-diffusion method [24] using nutrient agar medium. The minimal inhibitory concentration for the most active compounds **10c**, **12a** and **12c** against the same microorganisms used in the preliminary screening was carried out using microdilution susceptibility method [25]. Ciprofloxacin and ketoconazole were used as control drugs.

3.2. MTT assay for cell viability

Toxicity of compounds in different cell lines in the presence of 10 and 0.2% FBS, respectively, was determined using 3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyltetrazolium bromide reduction assay [26,27]. The compounds were dissolved in DMSO at 10 mM concentration and stored at −20 °C. The dilutions were made in culture medium before treatment.

Nearly 8000 cells/well were plated in 96-well plates. After 3–4 h, the compounds were added to the cells at different concentrations. After 72 h of incubation, 20 μl of MTT solution was added and the cells were incubated further for 4 h. Blue formazan crystals were seen at well when checked under microscope. Media was removed and 200 μl of DMSO was added per well. The absorbance was measured using microtiter plate reader. Control treatments were performed with DMSO. The % viability was then calculated as $[\{A_{590}$ (treated cells)−background]/$[A_{590}$ (untreated cells)−background$\}] \times 100$.

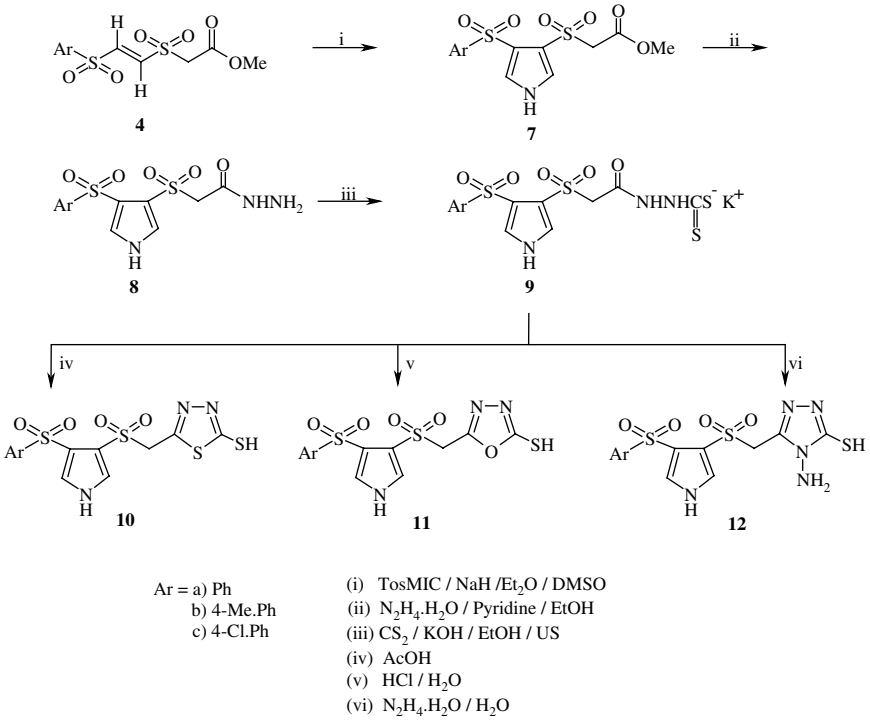
4. Results, discussion and conclusion

The structures of the compounds synthesized in the present work were established by spectral parameters. The ^{1}H NMR spectrum of **4a** showed two doublets at δ 7.93 and 7.41 ppm for H_A and H_B. The coupling constant value $J = 14.7$ Hz indicates that it possess *trans* geometry. Besides, two singlets were observed at δ 4.15 and 3.78 ppm for methylene and methoxy protons of carbomethoxy group. The ^{1}H NMR spectrum of **6a** displayed a singlet and two doublets at δ 3.94, 6.78 and 7.39 ppm which were accounted for N−CH_3, C_5−H and C_4−H, respectively. The mass spectrum of **6a** exhibited a molecular ion peak at *m*/*z* 222 corresponding to its molecular formula. The ^{1}H NMR spectrum of **7a** showed two singlets at δ 6.96 and 7.09 ppm for pyrrole ring protons, C_2−H and C_5−H. In addition two singlets were observed at δ 3.72 and 4.21 ppm due to methoxy and methylene protons. A broad singlet observed at δ 10.21 ppm due to NH disappeared on deuteration. The ^{1}H NMR spectrum of **8a** displayed broad signals in the regions δ 9.46 and 5.10 ppm for NH and NH_2 which disappeared on deuteration in addition to signals due to other protons.

The ^{1}H NMR spectra of **10–12** displayed a singlet in the region δ 10.18–10.28 ppm for SH besides signals due to pyrrole ring and methylene protons. In addition to these, **12a** showed a broad singlet at δ 5.42 ppm for NH_2 which disappeared on deuteration. The structures of **10–12** were further confirmed by ^{13}C NMR spectra (Table 2).

4.1. Biological results

The results on preliminary antibacterial testing of the final compounds (**10–12**) are shown in Table 3. The results revealed that in general, the inhibitory activity against the Gram-positive bacteria was higher than that of the Gram-



Scheme 3.

negative bacteria. The compounds **10c**, **12a** and **12c** showed excellent activity against Gram-positive bacteria (inhibitory zone > 28 mm) and good activity against Gram-negative bacteria (inhibitory zone > 22 mm). All the tested compounds showed moderate (**11a–c**) to high (**10a–c** and **12a–c**) inhibitory effect towards tested fungi. The presence of chloro substituent at position 4 of arylsulfonyl group caused good antimicrobial activity (Table 4).

The MIC values were determined as the lowest concentration that completely inhibited visible growth of the microorganisms (Table 5). The structure–antimicrobial activity relationship of the synthesized compounds revealed that the compounds having pyrrole in combination with oxadiazole moiety exhibited least activity when compared with compounds having pyrrole with thiadiazole and triazole moieties. Among the substituents on the aryl group, 4-chlorophenyl derivatives were the most active. The maximum activity was attained with compound **12c**.

The cytotoxic activity of the compounds **10a**, **11a** and **12a** in A_{549} and CCl_{64} cell lines in the presence of 10 and 0.2% FBS, respectively, was determined using 3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyltetrazolium bromide reduction assay. The compounds were dissolved in DMSO at 10 μM concentration and stored at −20 °C. The dilutions were made in culture medium before treatment. The compounds tested did not exhibit cytotoxic activity up to 100 μM concentration.

In conclusion, a new class of heterocycles, pyrrole in combination with thiadiazole, oxadiazole and triazole are developed adopting simple, elegant and well-versed methodologies from a vulnerable substrate, arylsulfonylethenesulfonylacetic acid methyl ester. The *in vitro* antimicrobial activity of lead compounds showed that all compounds tested are more active towards fungi than bacteria. The compound pyrrole in combination with triazole showed greater antimicrobial activity.

5. Experimental

5.1. 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 Varian EM-360 spectrometer (300 MHz). The ^{13}C NMR spectra were recorded in $CDCl_3$/DMSO-d_6 on a Varian VXR 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 starting compound 1-arylsulfonyl-2-chloroethene was prepared according to literature procedure [28].

5.1.1. General procedure for the synthesis of E-arylsulfonylethenemercapto acetic acid *2a–c*

To a solution of sodium hydroxide (2 mmol) in methanol (10 ml), mercaptoacetic acid (1 mmol) was added dropwise. To this compound **1** (1 mmol) was added in portions and the reaction mixture was stirred at 0 °C for 3 h. The contents

Table 2
Spectral data of the compounds **2–4** and **6–12**

Compound no.	IR (KBr) cm^{-1}	^1H NMR ($CDCl_3$) δ ppm	^{13}C NMR ($CDCl_3$) δ ppm	Mass *m/z* ($M^{+\cdot}$)
2a	1122, 1330 (SO_2), 1704 (C=O), 3242 (OH)	3.61 (s, 2H, CH_2), 7.59 (d, $J = 13.4$ Hz, 1H, H_B), 7.87 (d, $J = 13.4$ Hz, 1H, H_A), 7.38–7.79 (m, 5H, ArH), 9.84 (br s, 1H, OH)	52.2 (CH_2), 135.9 (SO_2CH), 142.4 (CHS), 170.2 (COOH), 128.2, 129.5, 130.2, 132.8 (aromatic carbons)	–
2b	1125, 1333 (SO_2), 1710 (C=O), 3247 (OH)	2.23 (s, 3H, Ar–CH_3), 3.57 (s, 2H, CH_2), 7.62 (d, $J = 13.7$ Hz, 1H, H_B), 7.94 (d, $J = 13.7$ Hz, 1H, H_A), 7.34–7.82 (m, 4H, ArH), 9.89 (br s, 1H, OH)	22.3 (Ar–CH_3), 51.8 (CH_2), 136.4 (SO_2CH), 141.6 (*C*HS), 169.7 (COOH), 127.4, 129.3, 130.7, 131.6 (aromatic carbons)	–
2c	1120, 1338 (SO_2), 1708 (C=O), 3249 (OH)	3.68 (s, 2H, CH_2), 7.56 (d, $J = 14.0$ Hz, 1H, H_B), 7.89 (d, $J = 13.8$ Hz, 1H, H_A), 7.51–7.84 (m, 4H, ArH), 9.82 (br s, 1H, OH)	52.9 (CH_2), 135.4 (SO_2CH), 142.9 (*C*HS), 171.0 (COOH), 128.6, 130.2, 131.6, 134.6 (aromatic carbons)	–
3a	1118, 1334 (SO_2), 1706 (C=O), 3251 (OH)	4.36 (s, 2H, SO_2CH_2), 7.61 (d, $J = 14.3$ Hz, 1H, H_B), 7.84 (d, $J = 14.3$ Hz, 1H, H_A), 7.51–7.79 (m, 5H, ArH), 9.79 (br s, 1H, OH)	58.8 ($-SO_2CH_2$), 135.9 (SO_2CH), 141.4 ($CHSO_2$), 170.7 (COOH), 127.5, 128.8, 130.2, 131.4 (aromatic carbons)	–
3b	1115, 1340 (SO_2), 1714 (C=O), 3254 (OH)	2.26 (s, 3H, $ArCH_3$), 4.31 (s, 2H, CH_2), 7.63 (d, $J = 14.6$ Hz, 1H, H_B), 7.93 (d, $J = 14.6$ Hz, 1H, H_A), 7.37–7.85 (m, 4H, ArH), 9.83 (br s, 1H, OH)	22.6 (Ar–CH_3), 58.4 (SO_2CH_2), 136.2 (SO_2CH), 140.7 ($CHSO_2$), 171.1 (COOH), 127.1, 128.3, 129.4, 130.8 (aromatic carbons)	–
3c	1119, 1339 (SO_2), 1716 (C=O), 3252 (OH)	4.37 (s, 2H, $-SO_2CH_2$), 7.68 (d, $J = 14.8$ Hz, 1H, H_B), 7.99 (d, $J = 14.8$ Hz, 1H, H_A), 7.42–7.88 (m, 4H, ArH), 9.91 (br s, 1H, OH)	57.9 (CH_2), 136.7 (SO_2CH), 142.2 ($CHSO_2$), 172.3 (COOH), 127.8, 128.6, 131.2, 135.2 (aromatic carbons)	–
4a	1124, 1332 (SO_2), 1746 (C=O)	3.78 (s, 3H, OCH_3), 4.15 (s, 2H, $-SO_2CH_2$), 7.41 (d, $J = 14.7$ Hz, 1H, H_B), 7.93 (d, $J = 14.7$ Hz, 1H, H_A), 7.57–7.82 (m, 5H, ArH)	53.5 (OCH_3), 59.0 (CH_2), 137.8 (SO_2CH), 143.6 ($CHSO_2$), 167.6 (CO_2CH_3), 128.6, 129.8, 135.0, 137.3 (aromatic carbons)	304.34
4b	1127, 1334 (SO_2), 1743 (C=O)	2.25 (s, 3H, $ArCH_3$), 3.74 (s, 3H, OCH_3), 4.21 (s, 2H, $-SO_2CH_2$), 7.48 (d, $J = 14.3$ Hz, 1H, H_B), 7.84 (d, $J = 14.3$ Hz, 1H, H_A), 7.42–7.75 (m, 4H, ArH)	22.6 (Ar–CH_3), 52.4 (OCH_3), 58.2 (SO_2CH_2), 136.9 (SO_2CH), 144.3 ($CHSO_2$), 168.5 (CO_2CH_3), 128.4, 130.6, 132.3, 136.4 (aromatic carbons)	318.37
4c	1123, 1339 (SO_2), 1749 (C=O)	3.68 (s, 3H, OCH_3), 4.17 (s, 2H, CH_2), 7.45 (d, $J = 13.9$ Hz, 1H, H_B), 7.78 (d, $J = 13.9$ Hz, 1H, H_A), 7.49–7.78 (m, 4H, ArH)	22.1 (Ar–CH_3), 52.9 (OCH_3), 59.1 (SO_2CH_2), 138.2 (SO_2CH), 142.9 ($CHSO_2$), 169.7 (CO_2CH_3), 128.2, 130.4, 132.7, 136.8 (aromatic carbons)	338.78
6a	1129, 1341 (SO_2), 1574 (C=N)	3.94 (s, 3H, N–CH_3), 6.78 (d, 1H, C_5–H, $J = 2.7$ Hz), 7.39 (d, 1H, C_4–H, $J = 2.7$ Hz), 7.26–8.04 (m, 5H, Ar–H)	38.4 (N–CH_3), 107. 9 (C-4), 141.1 (C-5), 151.6 (C-3), 127.7, 129.0, 131.9, 133.3 (aromatic carbons)	222.26
6b	1130, 1336 (SO_2), 1579 (C=N)	2.27 (s, 3H, Ar–CH_3), 3.91 (s, 3H, N–CH_3), 6.74 (d, 1H, C_5–H, $J = 2.6$ Hz), 7.36 (d, 1H, C_4–H, $J = 2.6$ Hz), 7.20–7.89 (m, 4H, Ar–H)	22.4 (Ar–CH_3), 39.1 (N–CH_3), 107.4 (C-4), 142.7 (C-5), 151.1 (C-3), 127.2, 128.6, 131.1, 133.6 (aromatic carbons)	236.29
6c	1124, 1338 (SO_2), 1582 (C=N)	3.98 (s, 3H, N–CH_3), 6.80 (d, 1H, C_5–H, $J = 2.9$ Hz), 7.32 (d, 1H, C_4–H, $J = 2.9$ Hz), 7.27–7.86 (m, 4H, Ar–H)	39.6 (N–CH_3), 108.8 (C-4), 143.2 (C-5), 152.6 (C-3), 127.6, 128.4, 131.4, 134.2 (aromatic carbons)	256.71
7a	1122, 1334 (SO_2), 1744 (C=O), 3375 (NH)	3.72 (s, 3H, OCH_3), 4.21 (s, 2H, SO_2–CH_2), 6.96 (s, 1H, C_2–H), 7.09 (s, 1H, C_5–H), 10.21 (br s, 1H, NH), 7.35–7.81 (m, 5H, Ar–H)	53.2 (OCH_3), 59.5 (SO_2–CH_2), 106.8 (C-3), 109.6 (C-4), 115.4 (C-2), 118.3 (C-5), 168.2 (CO_2CH_3), 128.2, 129.4, 132.4, 133.3 (aromatic carbons)	–
7b	1132, 1323 (SO_2), 1743 (C=O), 3368 (NH)	2.31 (s, 3H, Ar–CH_3), 3.65 (s, 3H, OCH_3), 4.18 (s, 2H, SO_2–CH_2), 6.86 (s, 1H, C_2–H), 7.02 (s, 1H, C_5–H), 10.15 (br s, 1H, NH), 7.31–7.78 (m, 4H, Ar–H)	22.7 (Ar–CH_3), 52.7 (OCH_3), 59.2 (SO_2–CH_2), 105.6 (C-3), 108.9 (C-4), 115.8 (C-2), 117.1 (C-5), 168.5 (CO_2CH_3), 128.8, 129.6, 131.2, 132.1 (aromatic carbons)	–
7c	1120, 1332 (SO_2), 1749 (C=O), 3378 (NH)	3.74 (s, 3H, OCH_3), 4.25 (s, 2H, SO_2–CH_2), 6.88 (s, 1H, C_2–H), 7.11 (s, 1H, C_5–H), 10.26 (br s, 1H, NH), 7.24–7.84 (m, 4H, Ar–H)	53.5 (OCH_3), 58.7 (SO_2–CH_2), 104.8 (C-3), 109.1 (C-4), 115.2 (C-2), 117.9 (C-5), 169.3 (CO_2CH_3), 128.4, 129.2, 131.4, 133.8 (aromatic carbons)	–
8a	1132, 1331 (SO_2), 1646 (C=O), 3219 (NH_2), 3381 (NH)	4.24 (s, 2H, SO_2–CH_2), 5.10 (br s, 2H, NH_2), 6.90 (s, 1H, C_2–H), 7.06 (s, 1H, C_5–H), 9.46 (br s, 1H, NH), 10.12 (br s, 1H, NH), 7.29–7.74 (m, 5H, Ar–H)	59.2 (SO_2–CH_2), 103.6 (C-3), 108.2 (C-4), 114.9 (C-2), 117.2 (C-5), 167.4 (CO), 128.1, 129.4, 131.3, 132.8 (aromatic carbons)	–
8b	1128, 1329 (SO_2), 1642 (C=O), 3221 (NH_2), 3374 (NH)	2.35 (s, 3H, Ar–CH_3), 4.20 (s, 2H, SO_2–CH_2), 5.04 (br s, 2H, NH_2), 6.84 (s, 1H, C_2–H), 7.13 (s, 1H, C_5–H), 9.20 (br s, 1H, NH), 10.06 (br s, 1H, NH), 7.22–7.76 (m, 4H, Ar–H)	22.4 (Ar–CH_3), 58.7 (SO_2–CH_2), 103.9 (C-3), 108.4 (C-4), 115.2 (C-2), 116.8 (C-5), 167.7 (CO), 127.8, 128.9, 130.6, 131.4 (aromatic carbons)	–

(*continued on next page*)

Table 2 (*continued*)

Compound no.	IR (KBr) cm^{-1}	^1H NMR ($CDCl_3$) δ ppm	^{13}C NMR ($CDCl_3$) δ ppm	Mass *m/z* ($M^{+\cdot}$)
8c	1135, 1333 (SO_2), 1650 (C=O), 3227 (NH_2), 3389 (NH)	4.22 (s, 2H, SO_2–CH_2), 5.14 (br s, 2H, NH_2), 6.87 (s, 1H, C_2–H), 7.08 (s, 1H, C_5–H), 9.27 (br s, 1H, NH), 10.09 (br s, 1H, NH), 7.27–7.81 (m, 4H, Ar–H)	59.5 (SO_2–CH_2), 103.2 (C-3), 108.9 (C-4), 115.8 (C-2), 117.2 (C-5), 167.9 (CO), 128.2, 131.3, 132.6, 133.9 (aromatic carbons)	–
9a	1125, 1307 (SO_2), 1038 (C=S), 1690 (CO), 3436 (NH)	–	–	–
9b	1120, 1310 (SO_2), 1042 (C=S), 1682 (CO), 3436 (NH)	–	–	–
9c	1128, 1314 (SO_2), 1043 (C=S), 1692 (CO), 3442 (NH)	–	–	–
10a	1125, 1330 (SO_2), 1628 (C=N), 2551 (SH), 3368 (NH)	4.24 (s, 2H, SO_2–CH_2), 6.91 (s, 1H, C_2–H), 7.12 (s, 1H, C_5–H), 10.18 (br s, 1H, NH), 10.21 (s, 1H, SH), 7.22–7.73 (m, 5H, Ar–H)	58.1 (SO_2–CH_2), 102.8 (C-3), 108.2 (C-4), 115.2 (C-2), 116.6 (C-5), 163.7 (C-2′), 168.2 (C-5′), 128.9, 129.3, 131.8, 132.8 (aromatic carbons)	401.5
10b	1132, 1337 (SO_2), 1632 (C=N), 2556 (SH), 3352 (NH)	2.29 (s, 3H, Ar–CH_3), 4.23 (s, 2H, SO_2–CH_2), 6.97 (s, 1H, C_2–H), 7.08 (s, 1H, C_5–H), 10.18 (br s, 1H, NH), 10.23 (s, 1H, SH), 7.24–7.78 (m, 4H, Ar–H)	22.8 (Ar–CH_3), 58.4 (SO_2–CH_2), 102.4 (C-3), 109.4 (C-4), 114.9 (C-2), 118.2 (C-5), 163.4 (C-2′), 168.6 (C-5′), 128.4, 129.7, 131.3, 131.6 (aromatic carbons)	415.53
10c	1137, 1331 (SO_2), 1639 (C=N), 2552 (SH), 3364 (NH)	4.26 (s, 2H, SO_2–CH_2), 6.91 (s, 1H, C_2–H), 7.13 (s, 1H, C_5–H), 10.06 (br s, 1H, NH), 10.27 (s, 1H, SH), 7.28–7.84 (m, 4H, Ar–H)	58.9 (SO_2–CH_2), 101.9 (C-3), 109.7 (C-4), 115.4 (C-2), 119.4 (C-5), 163.2 (C-2′), 168.9 (C-5′), 128.1, 129.9, 131.7, 133.4 (aromatic carbons)	435.95
11a	1131, 1338 (SO_2), 1621 (C=N), 3347 (NH)	4.27 (s, 2H, SO_2–CH_2), 6.87 (s, 1H, C_2–H), 7.09 (s, 1H, C_5–H), 10.02 (br s, 1H, NH), 10.24 (s, 1H, SH), 7.27–7.81 (m, 5H, Ar–H)	58.8 (SO_2–CH_2), 102.4 (C-3), 110.3 (C-4), 114.9 (C-2), 119.5 (C-5), 161.2 (C-2′), 168.6 (C-5′), 128.3, 129.6, 131.7, 132.2 (aromatic carbons)	385.44
11b	1127, 1330 (SO_2), 1633 (C=N), 2634 (SH), 3338 (NH)	2.26 (s, 3H, Ar–CH_3), 4.24 (s, 2H, SO_2–CH_2), 6.84 (s, 1H, C_2–H), 7.12 (s, 1H, C_5–H), 10.07 (br s, 1H, NH), 10.18 (s, 1H, SH), 7.23–7.77 (m, 4H, Ar–H)	22.3 (Ar–CH_3), 58.4 (SO_2–CH_2), 102.8 (C-3), 109.6 (C-4), 114.3 (C-2), 119.1 (C-5), 160.8 (C-2′), 168.2 (C-5′), 128.4, 129.3, 130.9, 131.7 (aromatic carbons)	399.47
11c	1134, 1337 (SO_2), 1622 (C=N), 2631 (SH), 3332 (NH)	4.30 (s, 2H, SO_2–CH_2), 6.89 (s, 1H, C_2–H), 7.16 (s, 1H, C_5–H), 10.08 (br s, 1H, NH), 10.21 (s, 1H, SH), 7.25–7.84 (m, 4H, Ar–H)	58.8 (SO_2–CH_2), 103.3 (C-3), 109.9 (C-4), 114.8 (C-2), 119.7 (C-5), 160.6 (C-2′), 168.5 (C-5′), 128.7, 129.8, 130.4, 132.3 (aromatic carbons)	419.88
12a	1126, 1334 (SO_2), 1632 (C=N), 2571 (SH), 3256 (NH_2), 3328 (NH)	4.23 (s, 2H, SO_2–CH_2), 6.85 (s, 1H, C_2–H), 7.05 (s, 1H, C_5–H), 5.42 (s, 2H, NH_2), 10.03 (br s, 1H, NH), 10.19 (s, 1H, SH), 7.24–7.79 (m, 5H, Ar–H)	58.2 (SO_2–CH_2), 102.6 (C-3), 109.4 (C-4), 114.5 (C-2), 119.5 (C-5), 143.8 (C-3′), 167.3 (C-5′), 128.1, 129.4, 131.2, 132.7 (aromatic carbons)	399.47
12b	1133, 1332 (SO_2), 1637 (C=N), 2564 (SH), 3261 (NH_2), 3321 (NH)	2.25 (s, 3H, Ar–CH_3), 4.26 (s, 2H, SO_2–CH_2), 6.82 (s, 1H, C_2–H), 7.10 (s, 1H, C_5–H), 5.36 (s, 2H, NH_2), 9.98 (br s, 1H, NH), 10.25 (s, 1H, SH), 7.32–7.83 (m, 4H, Ar–H)	22.6 (Ar–CH_3), 58.2 (SO_2–CH_2), 102.4 (C-3), 109.2 (C-4), 114.7 (C-2), 119.2 (C-5), 143.2 (C-3′), 167.9 (C-5′), 128.7, 129.9, 131.7, 132.5 (aromatic carbons)	413.5
12c	1139, 1341 (SO_2), 1643 (C=N), 2579 (SH), 3252 (NH_2), 3334 (NH)	4.21 (s, 2H, SO_2–CH_2), 6.47 (s, 1H, C_2–H), 6.72 (s, 1H, C_5–H), 5.45 (s, 2H, NH_2), 10.06 (br s, 1H, NH), 10.28 (s, 1H, SH), 7.29–7.79 (m, 4H, Ar–H)	58.4 (SO_2–CH_2), 102.9 (C-3), 109.7 (C-4), 114.8 (C-2), 119.8 (C-5), 144.6 (C-3′), 168.4 (C-5′), 128.4, 129.5, 131.1, 132.3 (aromatic carbons)	433.91

were poured onto crushed ice and neutralized with conc. HCl. The aqueous layer was extracted with ethyl acetate and the solvent was removed under reduced pressure. The resultant solid was recrystallized from water.

*5.1.2. General procedure for the synthesis of E-arylsulfonylethenesulfonylacetic acid **3a–c***

The compound **2** (1 mmol) was subjected to oxidation with 30% hydrogen peroxide (4.37 ml) in glacial acetic acid (7 ml). The contents were stirred at 0 °C for 4 h and kept aside for 36 h. Then the reaction mixture was poured onto crushed ice. The solid separated was filtered, dried and recrystallized from water.

*5.1.3. General procedure for the synthesis of E-arylsulfonylethenesulfonylacetic acid methyl ester **4a–c***

To a solution of compound **3** (1 mmol) in methanol (10 ml), sulfuric acid (2 ml) was added and refluxed for 6–8 h. The contents were cooled and poured onto crushed

Table 3
Antibacterial activity of compounds **10–12**

Compound	Concentration (μg/disc)	Zone of inhibition (mm)			
		Gram-positive bacteria		Gram-negative bacteria	
		S. aureus	*B. subtilis*	*E. coli*	*K. pneumoniae*
10a	100	18	21	16	17
	200	20	23	20	21
10b	100	16	17	18	16
	200	17	19	20	19
10c	100	25	28	22	23
	200	30	32	27	28
11a	100	12	11	14	13
	200	15	13	17	16
11b	100	11	12	11	11
	200	14	16	14	13
11c	100	14	14	10	11
	200	17	18	12	13
12a	100	28	31	22	21
	200	32	35	26	22
12b	100	24	25	20	21
	200	28	27	24	23
12c	100	32	34	23	26
	200	35	38	25	28
Ciprofloxacin	100	34	36	40	37
	200	38	42	45	42

ice. The solid separated was filtered, dried and recrystallized from methanol.

5.1.4. General procedure for the synthesis of N-methyl-3-arylsulfonylpyrazole *6a–c*

To a cooled solution of arylsulfonylethenesulfonylacetic acid methyl ester **4a–c** (5 mmol) in dichloromethane (20 ml), an ethereal solution of diazomethane (40 ml, 0.4 M) and triethylamine (0.12 g) were added. The reaction mixture was kept at −20 to −15 °C for 40–48 h. The solvent was removed under reduced pressure. The resultant solid was purified by column chromatography (hexane/ethyl acetate, 4:1).

5.1.5. General procedure for the synthesis of (4-arylsulfonyl-1H-pyrrole-3-sulfonyl)-acetic acid methyl ester *7a–c*

An equimolar mixture (1 mmol) of TosMIC and **4a–c** in Et_2O/DMSO (10 ml, 2:1) was added dropwise to a stirred suspension of NaH (50 mg) in dry Et_2O (10 ml) at room temperature. Then stirring was continued for 24 h and diluted with water. It was extracted with Et_2O and the organic layer was dried over anhydrous Na_2SO_4. Removal of the solvent gave crude product which was purified by filtration through a column of silica gel (BDH, 60–120 mesh with hexane/EtOAc, 4:1) as eluent.

Table 4
Antifungal activity of compounds **10–12**

Compound	Concentration (μg/disc)	Zone of inhibition (mm)		
		F. solani	*C. lunata*	*A. niger*
10a	100	25	28	24
	200	27	29	29
10b	100	25	22	21
	200	27	24	24
10c	100	26	23	26
	200	31	25	28
11a	100	18	17	15
	200	20	21	20
11b	100	16	15	17
	200	19	18	21
11c	100	18	17	15
	200	21	20	18
12a	100	33	34	30
	200	36	36	34
12b	100	29	28	34
	200	33	35	36
12c	100	35	38	34
	200	40	41	37
Ketoconazole	100	38	41	36
	200	42	44	39

5.1.6. General procedure for the synthesis of (4-arylsulfonyl-1H-pyrrole-3-sulfonyl)-acetic acid hydrazide *8a–c*

To a solution of **7a–c** (1 mmol) in absolute ethanol (5 ml), hydrazine hydrate (4.5 mmol) and pyridine (0.4 ml) were added and stirred for 6 h at room temperature. The resultant solid was filtered, dried and recrystallized from ethanol.

5.1.7. General procedure for the preparation of potassium (4-arylsulfonyl-1H-pyrrole-3-sulfonylacetyl)-hydrazine-N′-carbodithioate *9a–c*

To a mixture of potassium hydroxide (2 mmol) and **8a–c** (1 mmol) in absolute ethanol (5 ml), carbon disulfide (4 mmol) was added and sonicated for 12 h. The separated solid was filtered and dried.

5.1.8. General procedure for the synthesis of 5′-(4-arylsulfonyl-1H-pyrrole-3-sulfonylmethyl)-[1′,3′,4′]thiadiazole-2′-thiol *10a–c*

A mixture of **9a–c** (1 mmol) and acetic acid (4 ml) was refluxed for 24 h. The contents of the flask were cooled and poured onto crushed ice. The solid obtained was filtered, dried and recrystallized from 2-propanol.

5.1.9. General procedure for the synthesis of 5′-(4-arylsulfonyl-1H-pyrrole-3-sulfonylmethyl)-[1′,3′,4′]oxadiazole-2′-thiol *11a–c*

The compound **9a–c** (1 mmol) was dissolved in 6 ml of water and acidified with conc. HCl (1–2 ml). The regenerated solid was filtered, dried and purified by recrystallization from 2-propanol.

Table 5
The minimal inhibitory concentration (MIC, μg/ml) of compounds **10c**, **12a** and **12c**

Compound	Minimal inhibitory concentration (MIC, μg/ml)						
	S. aureus	*B. subtilis*	*E. coli*	*K. pneumoniae*	*F. solani*	*C. lunata*	*A. niger*
10c	100	200	200	200	100	100	200
12a	25	100	100	100	100	100	100
12c	12.5	50	50	50	50	12.5	25
Ciprofloxacin	6.25	6.25	6.25	6.25	–	–	–
Ketoconazole	–	–	–	–	12.5	6.25	6.25

*5.1.10. General procedure for the preparation of 4′-amino-5′-(4-arylsulfonyl-1H-pyrrole-3-sulfonylmethyl)-[1′,2′,4′]triazole-3′-thiol **12a–c***

To a solution of **9a–c** (1 mmol) in 6 ml of water, hydrazine hydrate (2 mmol) was added and refluxed for 8–9 h. The contents of the flask were cooled, diluted with water and acidified with acetic acid (2 ml). The separated solid was filtered, dried and recrystallized from 2-propanol.

5.2. Biological assays

5.2.1. Compounds

The compounds **10–12** were dissolved in DMSO at different concentrations of 100, 200 and 800 μg/ml.

5.2.2. Cells

Bacterial strains *S. aureus*, *B. subtilis*, *E. coli*, *K. pneumonie* and fungi *F. solani*, *C. lunata* and *A. niger* were obtained from NCIM, Pune, India.

5.2.3. Antibacterial and antifungal assays

Preliminary antimicrobial activities of **10–12** compounds 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 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. Ciprofloxacin was used as reference antibacterial agent. Ketoconazole was used as reference antifungal agent. The test compounds, ciprofloxacin 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 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.

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