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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and bioassay of a new class of disubstituted 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazoles

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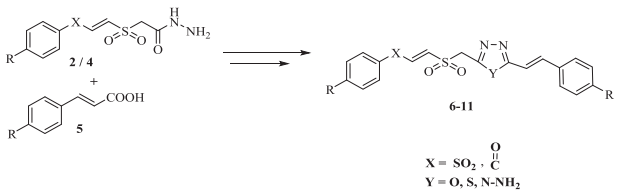
Abstract

A new class of aroylethenesulfonylmethyl styryl oxadiazoles/thiadiazoles/triazoles and arylsulfonylethenesulfonylmethyl styryl oxadiazoles/thiadiazoles/triazoles were synthesized from the synthetic intermediates *E*-aroylethenesulfonylacetic acid methyl ester, *E*-arylsulfonylethenesulfonylacetic acid methyl ester and substituted cinnamic acids adopting conventional and ultrasonication methodologies. All the synthesized compounds were obtained in higher yields and in shorter reaction times in ultrasound irradiation method when compared with conventional method. The structures of all the compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectra. All the title compounds were tested for antimicrobial activity. The arylsulfonylethenesulfonylmethyl styryl azoles displayed higher antimicrobial activity than the aroylethenesulfonylmethyl styryl azoles. The compounds having triazole moiety showed greater activity than those with oxadiazole and thiadiazole. Amongst all the tested compounds unsubstituted and chloro substituted arylsulfonylethenesulfonyl methyl styryl triazoles are identified as potential antimicrobial agents particularly against *B. subtilis* and *P.chrysogenum*.

Graphical Abstract



Keywords Oxadiazole · Thiadiazole · Triazole · Ultrasonication · Antimicrobial activity

Introduction

Drug resistance has become a growing problem in the treatment of infectious diseases caused by micro-organisms. The serious medical problem of bacterial and fungal resistance and the rapid rate at which it develops has led to increasing levels of resistance to classical antibiotics. The development of effective antibacterial and antifungal drugs has become an urgent task for infectious disease research programs. Novel azoles are the candidates for potent and effective antimicrobial agents.

The nitrogen containing five membered heterocycles particularly 1,3,4-oxadiazoles, 1,3,4-thiadiazoles, and 1,2,4-triazoles received considerable attention because of their applications in drug discovery (Wang et al. 2016; Karabanovich et al. 2016; Cai et al. 2016). Moreover, these molecules are used as pharmacophores due to their favorable metabolic profile and ability to form hydrogen bonds

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(Bajaj et al. 2015; Yang et al. 2015; Anand et al. 2015). 1,3,4-oxadiazoles are exhibit antimicrobial (Wang et al. 2016), antitubercular (Desai et al. 2016), antimalarial (Ladani and Patel 2015), analgesic (Fioravanti et al. 2010), anti-inflammatory (Bekhit et al. 2008), and anticonvulsant (Ahmad et al. 2010). Potent pharmacological activity of 1,3,4-oxadiazoles can be attributed to the presence of toxophoric –N=C–O– linkage which may react with the nucleophilic centers of the microbial cell (Zhou et al. 2008). Furamizole (antibiotic drug) (Yadagiri et al. 2015), raltegravir (antiretiroviral drug) (Breunig et al. 2016), fenadiazole (antibiotic drug) (Khan et al. 2017) and zibotentan (anticanser agent) (Kamal et al. 2016) are some of the drugs which contain oxadiazole nucleus. Literature survey reveals that 2,5-disubstituted 1,3,4-oxadiazoles have been synthesized either by thermal/acid catalyzed cyclization of 1,2-diacylhydrazines (Liras et al. 2000) or by oxidative cyclization of semicarbazone/hydrazone in the presence of an oxidant (Gaonkar et al. 2006) or by microwave irradiation of hydrazide and carboxylic acid mixture (Khan et al. 2004).

1,3,4-Thiadiazole and its derivatives possess a broad spectrum of biological activities such as.antioxidant (Hamama et al. 2013), antimicrobial (Patel et al. 2014; Chandrakantha et al. 2014), antidepressant (Khan et al. 2016), anti-diabetic (Pattn et al. 2011), antifungal (Er et al. 2017; Ulusoy et al. 2013), anticonvulsant (Harish et al. 2014), anti-inflammatory (Shkair et al. 2016). Moreover, the sulfur atom of 1,3,4-thiadiazole imparts improved liposolubility, and the mesoionic nature of 1,3,4-thiadiazole makes this class of compounds show good tissue permeability. 1,3,4-thiadiazole fragment appears in a number of clinically used drugs such as acetazolamide; methazolamide; butazolamide (diuretic); sulfamethiazole (antibacterial); cefazolin, cefazedone (antibiotic); atibeprone (anti-depressant); glybuthiazole, glybuzole (antidiabetic); and tebuthiuron (insecticide) (Wilson and Gisvold 1991; Abrahum 2003; Supran et al. 2003). Most frequently used methods for the synthesis of thiadiazoles include the reaction of acylthiosemicarbazides with acid reagents such as trifluoroacetic acid (Palaska et al. 2002) and methanesulfonic acid (Lutwick et al. 1979).

On the other hand, 1,2,4-triazoles attract considerable attention in organic chemistry owing to their pharmacological properties viz., antibacterial (Plech et al. 2015), antifungal (Sun et al. 2007), anti-inflammatory (Abdel-Megeed et al. 2009). In fact 1,2,4-triazole is a core moiety in. ribavirin, rizatriptan, alprazolam, vorozole, letrozole, and anastrozole (Sahin et al. 2012). Among azole-based drugs, conazoles, such as itraconazole, fluconazole, voriconazole, and ravuconazole constitute a major class being used for thetreatment fungal infections (Sahin et al. 2012). One of the synthetic methods for the preparation of triazoles involves the use of *N,N′*-dimethyl formamide dimethyl acetals (Stocks et al. 2004). Replacement of –O– by –S– or –NH– in some heterocycles was reported viz., Bordners (Bordner 1953) preparation of pyrroles from furan and the transformation of epoxide to episulfides by the action of thiocyanates or thiourea (Van Tamelen 1951; Price and Kirk 1953; Culvenor et al. 1952). However, reports about the conversion of 1,3,4-oxadiazoles to 1,3,4-thiadiazoles, and 1,2,4-triazoles are relatively less (Linganna and Lokanatharai 1998; Kiyoshi and Senji 1960).The sulfonyl moiety is an important motif in organic synthesis (Murtaza et al. 2016) and especially in medicinal chemistry (Pan et al. 2015). Aryl sulfones are building blocks in many drugs, such as the antibacterial dapsone (antibiotic) (Rojo et al. 2015), laropiprant (hypolidimic) (McKenney et al. 2015), a prostaglandin D2 antagonist, or the COX-2 inhibitor vioxx (Sturino et al. 2006). Therefore, more general and eco-friendly procedures for the synthesis of heterocycles from easily available starting materials are still highly desirable.

Application of ultrasound in synthetic organic chemistry has received great attention in recent times. A number of organic reactions could be successfully performed under the influence of ultrasonic radiation in substantial yields with short span of reaction time and mild conditions (Rouhani et al. 2015; Saleh and Mady 2009). Compared with conventional methods, sonochemistry is more convenient, easily controlled and appropriate in the view of green chemistry concepts (Vahid and Ali 2012).

Motivated by the above findings and in continuation of our efforts to synthesize simple and novel molecules of biological importance, the present work addresses the ultrasound promoted synthesis of a new class of disubstituted 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazoles.

Materials and methods

Chemistry

Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The homogeneity of the compounds was checked by thin layer chromatography (TLC) (silica gel H, BDH, hexane/ethyl acetate, 3:1). The infra-red (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 nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$/DMSO-d_6 on a Jeol JNM λ-400 MHz spectrometer. The ^{13}C NMR spectra were recorded in $CDCl_3$/DMSO-d_6 on a Jeol JNM spectrometer operating at λ-100 MHz. High-resolution mass spectra were recorded on Micromass Q-TOF

micromass spectrometer using electrospray ionization. All chemical shifts were reported in δ (ppm) using TMS as an internal standard. The microanalyses were performed on a Perkin-Elmer 240 C elemental analyzer. The temperature was measured by flexible probe throughout the reaction. Ultrasonication performed in a Bandelin Sonorex RK 102H ultrasonic bath operating at frequency of 35 KHz. The starting compounds *E*-aroylethenesulfonylacetic acid methyl ester (**1**) and *E*-arylsulfonylethenesulfonylacetic acid methyl ester (**3**) were prepared according to literature procedure (Padmavathi et al. 2008, 2009).

General procedure for the synthesis of *E*-aroylethenesulfonylacetic acid hydrazides (2a–c) and E-arylsulfonylethenesulfonylacetic acid hydrazides (4a–c)

Conventional method: The compound **1/3** (1 mmol), hydrazine hydrate (1 mmol), methanol (6 ml) and 3 drops of pyridine were refluxed for 4–6 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled and the solid separated was collected by filtration. It was dried and recrystallized from methanol.

Ultrasonication method: A mixture of **1/3** (1 mmol), hydrazine hydrate (1 mmol), methanol (3 ml) and 3 drops of pyridine was subjected to ultrasound irradiation at 60 °C for 20–30 min. The reaction mixture was cooled and the solid separated was collected by filtration, dried and recrystallized from methanol.

Benzoylethenesulfonylacetic acid hydrazide (2a) M.p. 100–102 °C; IR (KBr cm^{-1}): 1330, 1136 (SO_2), 1627 (C=C), 1670 (CO), 3243 (NH), 3450, 3331 (NH_2). ^{1}H NMR (DMSO-d_6): δ 3.85 (s, 2H, CH_2), 4.33 (bs, 2H, NH_2), 7.39–7.56 (m, 5H, Ar–H), 7.81 (d, 1H, H_B, $J = 14.0$ Hz), 8.24 (d, 1H, H_A, $J = 14.0$ Hz), 9.28 (bs, 1H, CO–NH) ppm. ^{13}C NMR (DMSO-d_6): δ 58.4 (CH_2), 138.6 (C–H_A), 142.0 (C–H_B), 163.6 (CO–NH), 178.4 (ArCO), 128.2 (Ar–C), 131.6 (Ar–C), 135.6 (Ar–C), 137.7 (Ar–C) ppm. HRMS (*m/z*): 291.2788 [M+Na]; Anal. calcd. for $C_{11}H_{12}N_2O_4S$: C49.24, H4.51, N10.44: Found: C49.36, H4.55, N10.69.

4-Methylbenzoylethenesulfonylacetic acid hydrazide (2b) M.p. 119–121 °C; IR (KBr cm^{-1}): 1321, 1133 (SO_2), 1626 (C=C), 1640 (CO), 3239 (NH), 3442, 3328 (NH_2). ^{1}H NMR (DMSO-d_6): δ 2.26 (s, 3H, Ar–CH_3), 3.81 (s, 2H, CH_2), 4.31 (bs, 2H, NH_2), 7.14–7.30 (m, 4H, Ar–H), 7.73 (d, 1H, H_B, $J = 13.7$ Hz), 8.21 (d, 1H, H_A, $J = 13.7$ Hz), 9.25 (bs, 1H, CO–NH) ppm. ^{13}C NMR (DMSO-d_6): δ 23.4 (Ar–CH_3), 58.0 (CH_2), 138.4 (C–H_A) 143.2 (C–H_B), 162.2 (CO–NH), 180.9 (ArCO) 128.6 (Ar–C), 130.8 (Ar–C), 135.0 (Ar–C), 137.3 (Ar–C) ppm. HRMS (*m/z*): 305.3038 [M+Na]; Anal. calcd. for $C_{12}H_{14}N_2O_4S$: C51.05, H5.00, N9.92: Found: C51.17, H5.06, N10.11.

4-Chlorobenzoylethenesulfonylacetic acid hydrazide (2c) M.p. 132–134 °C. IR (KBr cm^{-1}): 1335, 1139 (SO_2), 1632 (C=C), 1669 (CO), 3248 (NH), 3455, 3340 (NH_2). ^{1}H NMR (DMSO-d_6): δ 3.90 (s, 2H, CH_2), 4.35 (bs, 2H, NH_2), 7.21–7.35 (m, 4H, Ar–H), 7.76 (d, 1H, H_B, $J = 14.0$ Hz), 8.29 (d, 1H, H_A, $J = 14.0$ Hz), 9.33 (bs, 1H, CO–NH) ppm. ^{13}C NMR (DMSO-d_6): δ 58.9 (CH_2), 138.1 (C–H_A), 143.7 (C–H_B), 163.5 (CO–NH), 181.6 (ArCO) 127.8 (Ar–C), 130.2 (Ar–C), 134.6 (Ar–C), 136.5 (Ar–C) ppm. HRMS (*m/z*): 325.7188 [M+Na]; Anal. calcd. for $C_{11}H_{11}ClN_2O_4S$: C43.64, H3.66, N9.25. Found: C43.73, H3.70, N9.34.

Phenylsulfonylethenesulfonylacetic acid hydrazide (4a) M.p. 136–138 °C; IR (KBr cm^{-1}): 1332, 1141 (SO_2), 1630 (C=C), 1665 (C=O), 3236 (NH), 3445, 3339 (NH_2). ^{1}H NMR (DMSO-d_6): δ 3.94 (s, 2H, CH_2), 4.38 (bs, 2H, NH_2), 7.40–7.58 (m, 5H, Ar–H), 7.92 (d, 1H, H_B, $J = 13.7$ Hz), 8.35 (d, 1H, H_A, $J = 13.7$ Hz), 9.26 (bs, 1H, CO–NH) ppm. ^{13}C NMR (DMSO-d_6): δ 57.4 (CH_2), 137.2 (C–H_A), 142.9 (C–H_B), 164.3 (CO–NH), 127.8 (Ar–C), 129.2 (Ar–C), 134.5 (Ar–C), 136.9 (Ar–C) ppm. HRMS (*m/z*): 327.3248 [M+Na]; Anal. calcd. for $C_{10}H_{12}N_2O_5S_2$: C39.47, H3.97, N9.20. Found: C39.63, H4.00, N9.27.

4-Methylphenylsulfonylethenesulfonylacetic acid hydrazide (4b) M.p. 144–146 °C. IR (KBr cm^{-1}): 1319, 1131 (SO_2), 1625 (C=C), 1660 (C=O), 3222 (NH), 3438, 3332 (NH_2). ^{1}H NMR (DMSO-d_6): δ 2.26 (s, 3H, Ar–CH_3), 3.87 (s, 2H, CH_2), 4.32 (bs, 2H, NH_2), 7.15–7.32 (m, 4H, Ar–H), 7.86 (d, 1H, H_B, $J = 13.9$ Hz), 8.20 (d, 1H, H_A, $J = 13.9$ Hz), 9.24 (bs, 1H, CO–NH) ppm. ^{13}C NMR (DMSO-d_6): δ 22.5 (Ar–CH_3), 57.1 (CH_2), 137.6 (C–H_A), 142.3 (C–H_B), 163.7 (CO–NH), 127.2 (Ar–C), 130.7 (Ar–C), 131.4 (Ar–C), 135.8 (Ar–C) ppm. HRMS (*m/z*): 341.3518 [M+Na]; Anal. calcd. for $C_{11}H_{14}N_2O_5S_2$: C41.50, H4.43, N8.80. Found: C41.61, H4.46, N9.04.

4-Chlorophenylsulfonylethenesulfonylacetic acid hydrazide (4c) M.p. 153–155 °C. IR (KBr cm^{-1}): 1339, 1150 (SO_2), 1632 (C=C), 1672 (C=O), 3234 (NH), 3452, 3344 (NH_2). ^{1}H NMR (DMSO-d_6): δ 3.93 (s, 2H, CH_2), 4.36 (bs, 2H, NH_2), 7.37–7.54 (m, 4H, Ar–H), 7.84 (d, 1H, H_B, $J = 14.5$ Hz), 8.23 (d, 1H, H_A, $J = 14.5$ Hz), 9.30 (bs, 1H, CO–NH) ppm. ^{13}C NMR (DMSO-d_6): δ 57.8 (CH_2), 137.0 (C–H_A), 142.0 (C–H_B), 164.8 (CO–NH), 128.0 (Ar–C), 130.6 (Ar–C), 131.6 (Ar–C), 135.4 (Ar–C) ppm. HRMS (*m/z*): 361.7668 [M+Na]; Anal. calcd. for $C_{10}H_{11}ClN_2O_5S_2$: C33.45, H3.27, N8.27. Found: C33.55, H3.28, N8.11.

General procedure for the preparation of 2-(*E*-aroylethenesulfonylmethyl)-5-styryl-1,3,4-oxadiazoles (6a–c)/2-(*E*-arylsulfonylethenesulfonylmethyl)-5-styryl-1,3,4-oxadiazoles (9a–c)

Conventional method: To an equimolar (1 mmol) mixture of **2/4** and cinnamic acid (**5**), phosphorus oxychloride(7 ml) was added and heated to reflux for 3–5 h. After completion of the reaction (monitored by TLC), the excess phosphorus oxychloride was removed under vacuum and the residue was poured onto crushed ice. The separated solid was collected by filtration and washed with saturated sodium bicarbonate solution followed by water. It was dried and recrystallized from ethanol.

Ultrasonication method: A mixture of **2/4** (1 mmol), cinnamic acid (**5**) (1 mmol) and phosphorus oxychloride (5 ml) was subjected to ultrasound irradiation at a frequency of 35 KHz for 20–25 min at room temperature. After completion of the reaction, the excess phosphorus oxychloride was removed under reduced pressure and the residue was poured onto crushed ice. The separated solid was collected by filtration. It was washed with saturated sodium bicarbonate solution followed by water, dried and recrystallized from ethanol.

2-(Benzoylethenesulfonylmethyl)-5-styryl-1,3,4-oxadiazole (6a) M.p. 158–160 °C. IR (KBr cm^{-1}): 1327, 1139 (SO_2), 1570 (C=N), 1625 (C=C), 1674 (CO). ^{1}H NMR (DMSO-d_6): δ 4.64 (s, 2H, CH_2), 7.19–7.58 (m, 12H, H_C, H_D & Ar–H), 8.01 (d, 1H, H_B, $J = 14.0$ Hz), 8.28 (d, 1H, H_A, $J = 14.0$ Hz) ppm. ^{13}C NMR (DMSO-d_6): δ 58.5 (CH_2), 123.5 (C–H_D), 133.5 (C–H_C), 136.9 (C–H_A), 141.9 (C–H_B), 158.6 (C-5), 161.6 (C-2), 180.5 (C=O), 127.0 (Ar–C), 128.3 (Ar–C), 128.8 (Ar–C), 129.1 (Ar–C), 130.2 (Ar–C), 130.6 (Ar–C), 138.6 (Ar–C), 140.7 (Ar–C) ppm. HRMS (*m/z*): 403.4078 [M+Na]; Anal. calcd. for $C_{20}H_{16}N_2O_4S$: C, 63.15; H, 4.24; N, 7.36. Found: C63.26, H4.26, N7.61.

2-(4-Methylbenzoylethenesulfonylmethyl)-5-(4-methylstyryl)-1,3,4-oxadiazole (6b) M.p. 167–169 °C. IR (KBr cm^{-1}): 1326, 1140 (SO_2), 1567 (C=N), 1624 (C=C), 1669 (CO). ^{1}H NMR (DMSO-d_6): δ 2.34, 2.37 (s, 6H, Ar–CH_3), 4.57 (s, 2H, CH_2), 7.09–7.43 (m, 10H, H_C, H_D & Ar–H), 7.87 (d, 1H, H_B, $J = 14.8$ Hz), 8.25 (d, 1H, H_A, $J = 14.8$ Hz) ppm. ^{13}C NMR (DMSO-d_6): δ 24.5, 25.2 (Ar–CH_3), 57.1 (CH_2), 123.0 (C–H_D), 134.2 (C–H_C), 137.5 (C–H_A), 141.2 (C–H_B), 158.2 (C-5), 161.3 (C-2), 179.4 (C=O), 127.4 (Ar–C), 128.3 (Ar–C), 129.5 (Ar–C), 130.0 (Ar–C), 130.8 (Ar–C), 131.7 (Ar–C), 133.2 (Ar–C), 143.6 (Ar–C) ppm. HRMS (*m/z*): 431.4618 [M+Na]; Anal. calcd. for $C_{22}H_{20}N_2O_4S$: C64.69, H4.94, N6.86. Found: C64.79, H4.95, N7.00.

2-(4-Chlorobenzoylethenesulfonylmethyl)-5-(4-chlorostyryl)-1,3,4-oxadiazole (6c) M.p. 188–190 °C. IR (KBr cm^{-1}): 1337, 1142 (SO_2), 1579 (C=N), 1629 (C=C), 1676 (CO). ^{1}H NMR (DMSO-d_6): δ 4.69 (s, 2H, CH_2), 6.81–7.39 (m, 10H, H_C, H_D & Ar–H), 7.75 (d, 1H, H_B, $J = 14.2$ Hz), 8.34 (d, 1H, H_A, $J = 14.2$ Hz) ppm. ^{13}C NMR (DMSO-d_6): δ 57.0 (CH_2), 124.2 (C–H_C), 133.9 (C–H_D), 137.5 (C–H_A), 141.6 (C–H_B), 159.4 (C-5), 162.0 (C-2), 180.8 (C=O), 127.6 (Ar–C), 128.2 (Ar–C), 129.0 (Ar–C), 129.9 (Ar–C), 130.7 (Ar–C), 132.4 (Ar–C), 135.8 (Ar–C), 140.6 (Ar–C) ppm. HRMS (*m/z*): 472.2918 [M+Na]; Anal. calcd. for $C_{20}H_{14}Cl_2N_2O_4S$: C53.47, H3.14, N6.24. Found: C53.40, H3.13, N6.41.

2-(Phenylsulfonylethenesulfonylmethyl)-5-styryl-1,3,4-oxadiazole (9a) M.p. 170–172 °C. IR (KBr cm^{-1}): 1336, 1138 (SO_2), 1580 (C=N), 1626 (C=C). ^{1}H NMR (DMSO-d_6): δ 4.63 (s, 2H, CH_2), 7.19–7.60 (m, 12H, H_C, H_D & Ar–H), 7.82 (d, 1H, H_B, $J = 14.0$ Hz), 8.32 (d, 1H, H_A, $J = 14.0$Hz) ppm. ^{13}C NMR (DMSO-d_6): δ 57.9 (CH_2), 123.4 (C–H_D), 133.6 (C–H_C), 135.6 (C–H_A), 141.9 (C–H_B), 158.3 (C-5), 161.2 (C-2), 127.3 (Ar–C), 128.5 (Ar–C), 129.1 (Ar–C), 129.8 (Ar–C), 130.3 (Ar–C), 131.9 (Ar–C), 135.6 (Ar–C), 137.9 (Ar–C) ppm. HRMS (*m/z*): 439.4605 [M+Na]; Anal. calcd. for $C_{19}H_{16}N_2O_5S_2$: C54.79, H3.87, N6.73. Found: C54.84, H3.91, N6.89.

2-(4-Methylphenylsulfonylethenesulfonylmethyl)-5-(4-methylstyryl)-1,3,4-oxadiazole (9b) M.p. 198–200 °C. IR (KBr cm^{-1}): 1324, 1129 (SO_2), 1574 (C=N), 1630 (C=C). ^{1}H NMR (DMSO-d_6): δ 2.23, 2.26 (s, 6H, Ar–CH_3), 4.60 (s, 2H, CH_2), 6.87–7.56 (m, 10H, H_C, H_D, and Ar–H), 7.74 (d, 1H, H_B, $J = 13.8$ Hz), 8.22 (d, 1H, H_A, $J = 13.8$ Hz) ppm. ^{13}C NMR (DMSO-d_6): δ 23.2, 23.6 (Ar–CH_3), 57.5 (CH_2), 124.8 (C–H_D), 134.7 (C–H_C), 135.8 (C–H_A), 140.3 (C–H_B), 158.7 (C-5), 160.7 (C-2), 126.2 (Ar–C), 127.6 (Ar–C), 129.4 (Ar–C), 130.5 (Ar–C), 131.8 (Ar–C), 132.3 (Ar–C), 133.8 (Ar–C), 139.4 (Ar-C) ppm; HRMS (*m/z*): 467.5098 [M+Na]; Anal. calcd. for $C_{21}H_{20}N_2O_5S_2$: C56.74, H4.54, N6.30. Found: C56.84, H4.65, N6.53.

2-(4-Chlorophenylsulfonylethenesulfonylmethyl)-5-(4-chlorostyryl)-1,3,4-oxadiazole (9c) M.p. 210–212 °C. IR (KBr cm^{-1}): 1340, 1150 (SO_2), 1585 (C=N), 1635 (C=C). ^{1}H NMR (DMSO-d_6): δ 4.71 (s, 2H, CH_2), 7.18–7.50 (m, 10H, H_C, H_D, and Ar–H), 7.93 (d, 1H, H_B, $J = 14.5$ Hz), 8.37 ppm (d, 1H, H_A, $J = 14.5$ Hz). ^{13}C NMR (DMSO-d_6): δ 58.3 (CH_2), 123.5 (C–H_D), 134.5 (C–H_C), 135.6 (C–H_A), 141.8 (C–H_B), 159.1 (C-5), 161.9 (C-2), 126.4 (Ar–C), 127.3n (Ar–C), 128.5 (Ar–C), 129.0 (Ar–C), 130.2 (Ar–C), 132.6 (Ar–C), 138.8 (Ar–C), 139.2 (Ar–C) ppm. HRMS (*m/z*): 508.3398 [M+Na]; Anal. calcd. for $C_{19}H_{14}Cl_2N_2O_5S_2$: C47.02, H2.91, N5.77. Found: C46.97, H2.90, N5.60.

General procedure for the preparation of 2-(*E*-aroylethenesulfonylmethyl)-5-styryl-1,3,4-thiadiazoles (7a–c)/2-(*E*-arylsulfonylethenesulfonylmethyl)-5-styryl-1,3,4-thadiazoles (10a–c)

Conventional method: The compounds **6/9** (1 mmol), thiourea (4 mmol) and tetrahydrofuran (8 ml) was taken in a sealed tube. It was heated at reflux conditions for 13–16 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the contents of the flask were extracted with dichloromethane. The dichloromethane layer was washed with water and brine solution. It was and dried over anhydrous Na_2SO_4 and the solvent was removed on a rotary evaporator. The resultant residue was purified by column chromatography (silica gel, 60–120 mesh) using ethyl acetate-hexane (1:3) as eluent.

Ultrasonciation method: In a sealed test tube, a mixture of **6/9** (1 mmol), thiourea (4 mmol) and tetrahydrofuran (4 ml) was taken and heated at reflux conditions under ultrasonication at a frequency of 35 KHz for 40–50 min. After completion of the reaction, the reaction mixture extracted with dichloromethane and was washed with water followed by brine solution. It was dried over anhydrous Na_2SO_4 and the solvent was removed in vacuo. The resultant residue was purified by column chromatography (silica gel, 60–120 mesh) using ethyl acetate-hexane (1:3) as eluent.

2-(Benzoylethenesulfonylmethyl)-5-styryl-1,3,4-thiadiazole (7a) M.p. 164–166 °C. IR (KBr cm^{-1}): 1340, 1150 (SO_2), 1585 (C=N), 1623 (C=C), 1672 (C=O). ^{1}H NMR (DMSO-d_6): δ 4.67 (s, 2H, CH_2), 7.23–7.65 (m, 12H, H_C, H_D, and Ar–H), 7.94 (d, 1H, H_B, $J = 14.6$ Hz), 8.26 (d, 1H, H_A, $J = 14.6$ Hz) ppm. ^{13}C NMR (DMSO-d_6): δ 57.3 (CH_2), 123.9 (C–H_D), 132.4 (C–H_C), 139.8 (C–H_A), 141.5 (C–H_B), 157.7 (C-5), 166.0 (C-2), 180.4 (C=O), 127.9 (Ar–C), 128.7 (Ar–C), 129.6 (Ar–C), 130.0 (Ar–C), 131.8 (Ar–C), 133.2 (Ar–C), 135.5 (Ar–C), 142.0 (Ar–C) ppm. HRMS (*m/z*): 419.4695 [M+Na]; Anal. calcd. for $C_{20}H_{16}N_2O_3S_2$: C60.59, H4.07, N7.07. Found: C60.70, H4.10, N7.30.

2-(4-Methylbenzoylethenesulfonylmethyl)-5-(4-methylstyryl)-1,3,4-thiadiazole (7b) M.p. 173–175 °C. IR (KBr cm^{-1}): 1319, 1136 (SO_2), 1580 (C=N), 1618 (C=C), 1668 (CO). ^{1}H NMR (DMSO-d_6): δ 2.36, 2.39 (s, 6H, Ar–CH_3), 4.62 (s, 2H, CH_2), 7.17–7.47 (m, 10H, H_C, H_D, and Ar–H), 7.72 (d, 1H, H_B, $J = 14.4$ Hz), 8.30 (d, 1H, H_A, $J = 14.4$ Hz) ppm. ^{13}C NMR (DMSO-d_6): δ 24.2, 25.0 (Ar–CH_3), 56.7 (CH_2), 123.6 (C–H_D), 133.2 (C–H_C), 137.0 (C–H_A), 141.8 (C–H_B), 156.4 (C-5), 165.6 (C-2), 181.2 (C=O), 126.6 (Ar–C), 127.5 (Ar–C), 128.6 (Ar–C), 129.4 (Ar–C), 130.7 (Ar–C), 132.4 (Ar–C), 134.6 (Ar–C), 142.5 (Ar–C) ppm. HRMS (*m/z*): 447.5228 [M+Na]; Anal. calcd. for $C_{22}H_{20}N_2O_3S_2$: C62.24, H4.75, N6.60. Found: C62.37, H4.78, N6.87.

2-(4-Chlorobenzoylethenesulfonylmethyl)-5-(4-chlorostyryl)-1,3,4-thiadiazole (7c) M.p. 186–188 °C. IR (KBr cm^{-1}): 1337, 1149 (SO_2), 1585 (C=N), 1626 (C=C), 1675 (CO). ^{1}H NMR (DMSO-d_6): δ 4.70 (s, 2H, CH_2), 7.22–7.52 (m, 10H, H_C, H_D, and Ar–H), 7.88 (d, 1H, H_B, $J = 14.1$ Hz), 8.22 (d, 1H, H_A, $J = 14.1$ Hz) ppm. ^{13}C NMR (DMSO-d_6): δ 57.8 (CH_2), 124.7 (C–H_D), 134.5 (C–H_C), 135.9 (C–H_A), 141.2 (C–H_B), 156.5 (C-5), 166.3 (C-2), 180.7 (C=O), 128.9 (Ar–C), 129.7 (Ar–C), 130.8 (Ar–C), 131.4 (Ar-C), 132.3 (Ar-C), 132.9 (Ar-C), 136.2 (Ar–C), 137.8 (Ar–C) ppm. HRMS (*m/z*): 488.3528 [M+Na]; Anal. calcd. for $C_{20}H_{14}Cl_2N_2O_3S_2$: C51.62, H3.03, N6.02. Found: C51.71, H3.04, N6.22.

2-(Phenylsulfonylethenesulfonylmethyl)-5-styryl-1,3,4-thadiazole (10a) M.p. 187–189 °C. IR (KBr cm^{-1}): 1336, 1138 (SO_2), 1582 (C=N), 1632 (C=C). ^{1}H NMR (DMSO-d_6): δ 4.68 (s, 2H, CH_2), 7.02–7.43 (m, 12H, H_C, H_D, and Ar–H), 7.71 (d, 1H, H_B, $J = 14.3$ Hz), 8.12 (d, 1H, H_A, $J = 14.3$ Hz) ppm. ^{13}C NMR (DMSO-d_6): δ 57.2 (CH_2), 123.9 (C–H_D), 132.6 (C–H_C), 136.2 (C–H_A), 141.5 (C–H_B), 157.4 (C-5), 166.5 (C-2), 126.5 (Ar–C), 127.1 (Ar–C), 128.5 (Ar–C), 129.6 (Ar–C), 130.5 (Ar–C), 132.6 (Ar–C), 135.4 (Ar–C), 138.6 (Ar–C) ppm. HRMS (*m/z*): 455.5168 [M+Na]; Anal. calcd. for $C_{19}H_{16}N_2O_4S_3$: C52.76, H3.73, N6.48. Found: C52.89, H3.77, N6.72.

2-(4-Methylphenylsulfonylethenesulfonylmethyl)-5-(4-methylstyryl)-1,3,4-thadiazole (10b) M.p. 206–208 °C. IR (KBr cm^{-1}): 1325, 1141 (SO_2), 1580 (C=N), 1629 (C=C). ^{1}H NMR (DMSO-d_6): δ 2.36, 2.39 (s, 6H, Ar–CH_3), 4.61 (s, 2H, CH_2), 7.07–7.45 (m, 10H, H_C, H_D, and Ar–H), 7.85 (d, 1H, H_B, $J = 13.9$ Hz), 8.18 (d, 1H, H_A, $J = 13.9$ Hz) ppm. ^{13}C NMR (DMSO-d_6): δ 24.1, 25.4 (Ar–CH_3), 56.9 (CH_2), 124.0 (C–H_D), 134.1 (C–H_C), 135.0 (C-H_A), 140.5 (C–H_B), 156.8 (C-5), 166.0 (C-2), 128.2 (Ar–C), 129.0 (Ar–C), 129.7 (Ar–C), 131.4 (Ar–C), 132.9 (Ar–C), 133.7 (Ar–C), 135.8 (Ar–C), 138.3 (Ar–C) ppm. HRMS (*m/z*): 483.5708 [M+Na]; Anal. Calcd. for $C_{21}H_{20}N_2O_4S_3$: C54.76, H4.38, N6.08. Found: C54.87, H4.39, N6.22.

2-(4-Chlorophenylsulfonylethenesulfonylmethyl)-5-(4-chlorostyryl)-1,3,4-thadiazole (10c) M.p. 225–227 °C. IR (KBr cm^{-1}): 1341, 1145 (SO_2), 1586 (C=N), 1633 (C=C). ^{1}H NMR (DMSO-d_6): δ 4.72 (s, 2H, CH_2), 6.99–7.61 (m, 10H, H_C, H_D, and Ar–H), 7.91 (d, 1H, H_B, $J = 14.6$ Hz), 8.27 (d, 1H, H_A, $J = 14.6$ Hz) ppm. ^{13}C NMR (DMSO-d_6): δ 57.6 (CH_2), 124.6 (C–H_D), 133.0 (C–H_C), 137.6 (C–H_A), 141.9 (C–H_B), 159.3 (C-5), 166.8 (C-2), 127.4 (Ar–C),

128.8 (Ar–C), 130.0 (Ar–C), 130.9 (Ar–C), 131.6 (Ar–C), 134.8 (Ar–C), 135.4 (Ar–C), 140.7 (Ar–C) ppm; HRMS (*m/z*): 524.4008 [M+Na]; Anal. calcd. for $C_{19}H_{14}Cl_2N_2O_4S_3$: C45.51, H2.81, N5.59. Found: C45.59, H2.85, N5.67.

General procedure for the preparation of 3-(*E*-aroylethenesulfonylmethyl)-4-amino-5-styryl-1,2,4-triazoles (8a–c)/3-(*E*-arylsulfonylethenesulfonylmethyl)-4-amino-5-styryl-1,2,4-triazoles (11a–c)

Conventional method: A solution of **6/9** (1 mmol) and hydrazine hydrate (4 mmol) in *n*-butanol (5 ml) was refluxed for 5–8 h. Then, potassium hydroxide (10 mmol) was added to the reaction media and the precipitate formed was filtered. The solid obtained was acidified with conc. HCl to pH ≈ 3 and washed with water. It was dried and purified by column chromatography (silica gel, 160–120 mesh) using ethyl acetate-hexane (1:3) as eluent.

Ultrasonciation method: To a solution of **6/9** (1 mmol) in *n*-butanol (3 ml), hydrazine hydrate (4 mmol) was added and kept under ultrasonication at a frequency of 35 KHz for 30–40 min. Then, potassium hydroxide (10 mmol) was added to the reaction media. The precipitate formed was filtered and acidified with conc. HCl to pH ≈ 3. It was washed with water, dried and purified by column chromatography (silica gel, 160–120 mesh) using ethyl acetate-hexane (1:3) as eluent.

3-(Benzoylethenesulfonylmethyl)-4-amino-5-styryl-1,2,4-triazole (8a) M.p. 161–163 °C. IR (KBr cm^{-1}): 1329, 1140 (SO_2), 1575 (C=N), 1632 (C=C), 1679 (CO), 3448, 3330 (NH_2). ^{1}H NMR (DMSO-d_6): δ 4.58 (s, 2H, CH_2), 5.62 (bs, 2H, NH_2), 6.97–7.42 (m, 12H, H_C, H_D, and Ar–H), 7.70 (d, 1H, H_B, $J = 14.7$ Hz), 8.33 (d, 1H, H_A, $J = 14.7$ Hz) ppm. ^{13}C NMR (DMSO-d_6): δ 56.6 (CH_2), 112.6 (C–H_D), 134.0 (C–H_C), 137.5 (C–H_A), 142.4 (C–H_B), 147.8 (C-5), 156.9 (C-3), 181.5 (C=O), 126.1 (Ar–C), 126.8 (Ar–C), 127.4 (Ar–C), 128.2 (Ar–C), 129.6 (Ar–C), 132.4 (Ar–C), 135.7 (Ar–C), 139.2 (Ar–C) ppm; HRMS (*m/z*): 417.4388 [M+Na]; Anal. calcd. for $C_{20}H_{18}N_4O_3S$ (394.44): C60.90, H4.60, N14.20. Found: C61.02, H4.63, N14.46.

3-(4-Methylbenzoylethenesulfonylmethyl)-4-amino-5-(4-methylstyryl)-1,2,4-triazole (8b) M.p. 168–170 °C. IR (KBr cm^{-1}): 1325, 1138 (SO_2), 1625 (C=C), 1586 (C=N), 1674 (CO), 3440, 3326 (NH_2). ^{1}H NMR (DMSO-d_6): δ 2.29, 2.34 (s, 6H, Ar–CH_3), 4.52 (s, 2H, CH_2), 5.60 (bs, 2H, NH_2), 7.03–7.47 (m, 10H, H_C, H_D, and Ar–H), 7.78 (d, 1H, H_B, $J = 14.9$ Hz), 8.31 (d, 1H, H_A, $J = 14.9$ Hz) ppm. ^{13}C NMR (DMSO-d_6): δ 23.4, 23.8 (Ar–CH_3), 57.0 (CH_2), 112.7 (C–H_D), 133.9 (C–H_C), 137.0 (C–H_A), 142.7 (C–H_B), 147.8 (C-5), 156.9 (C-3), 182.7 (C=O), 126.2 (Ar–C), 126.9 (Ar–C), 127.5 (Ar–C), 128.6 (Ar–C), 129.5 (Ar–C), 132.2 (Ar–C), 136.6 (Ar–C), 140.6 (Ar–C) ppm; HRMS (*m/z*): 445.4928 [M+Na]; Anal. calcd. for $C_{22}H_{22}N_4O_3S$: C62.54; H5.25; N13.26. Found: C62.66, H5.24, N13.45.

3-(4-Chlorobenzoylethenesulfonylmethyl)-4-amino-5-(4-chlorostyryl)-1,2,4-triazole (8c) M.p. 182–184 °C. IR (KBr cm^{-1}): 1339, 1142 (SO_2), 1584 (C=N), 1636 (C=C), 1672 (CO), 3451, 3338 (NH_2). ^{1}H NMR (DMSO-d_6): δ 4.66 (s, 2H, CH_2), 5.72 (bs, 2H, NH_2), 6.92–7.40 (m, 10H, H_C, H_D, and Ar–H), 8.05 (d, 1H, H_B, $J =$ 13.6 Hz), 8.36 (d, 1H, H_A, $J = 13.6$ Hz) ppm. ^{13}C NMR (DMSO-d_6): δ 56.5 (CH_2), 113.0 (C–H_D), 133.0 (C–H_C), 137.2 (C–H_A), 142.8 (C–H_B), 148.6 (C-5), 157.2 (C-3), 183.2 (C=O), 127.5 (Ar–C), 128.9 (Ar–C), 129.7 (Ar–C), 130.6 (Ar–C), 131.4 (Ar–C), 133.5 (Ar–C), 134.8 (Ar–C), 139.6 (Ar–C) ppm. HRMS (*m/z*): 486.3228; Anal. calcd. for $C_{20}H_{16}Cl_2N_4O_3S$ (463.33): C51.85, H3.48, N12.09. Found: C51.93, H3.51, N12.23.

3-(Phenylsulfonylethenesulfonylmethyl)-4-amino-5-styryl-1,2,4-triazole (11a) M.p. 191–193 °C. IR (KBr cm^{-1}): 1336, 1143 (SO_2), 1584 (C=N), 1634 (C=C), 3445 and 3329 (NH_2). ^{1}H NMR (DMSO-d_6): δ 4.54 (s, 2H, CH_2), 5.65 (bs, 2H, NH_2), 7.12–7.65 (m, 12H, H_C, H_D, nd Ar–H), 7.89 (d, 1H, H_B, $J = 14.2$ Hz), 8.15 (d, 1H, H_A, $J =$ 14.2 Hz) ppm. ^{13}C NMR (DMSO-d_6): δ 52.4 (CH_2), 112.2 (C–H_D), 133.1 (C–H_C), 135.8 (C–H_A), 142.0 (C–H_B), 148.4 (C-5), 157.0 (C-3), 127.5 (Ar–C), 128.9 (Ar–C), 129.7 (Ar–C), 130.7 (Ar–C), 132.4 (Ar–C), 133.9 (Ar–C), 136.5 (Ar–C), 140.1 (Ar–C) ppm. HRMS (*m/z*): 453.4904; Anal. calcd. for $C_{19}H_{18}N_4O_4S_2$: C53.01, H4.21, N13.01. Found: C53.09, H4.25, N13.21.

3-(4-Methylphenylsulfonylethenesulfonylmethyl)-4-amino-5-(4-methylstyryl)-1,2,4-triazole (11b) M.p. 203–205 °C. IR (KBr cm^{-1}): 1328, 1136 (SO_2); 1572 (C=N), 1629 (C=C), 3440, 3324 (NH_2). ^{1}H NMR (DMSO-d_6): δ 2.29, 2.34 (s, 6H, Ar–CH_3), 4.51 (s, 2H, CH_2), 5.52 (bs, 2H, NH_2), 7.04–7.60 (m, 10H, H_C, H_D, and Ar–H), 7.76 (d, 1H, H_B, $J = 14.2$ Hz), 8.29 (d, 1H, H_A, $J = 14.2$ Hz) ppm.^{13}C NMR (DMSO-d_6): δ 23.5, 23.2 (Ar–CH_3), 56.3 (CH_2), 113.2 (C–H_D), 133.6 (C–H_C), 136.2 (C–H_A), 141.4 (C–H_B), 147.5 (C-5), 156.4 (C-3), 127.0 (Ar–C), 128.4 (Ar–C), 129.9 (Ar–C), 130.2 (Ar–C), 131.4 (Ar–C), 132.8 (Ar–C), 134.6 (Ar–C), 138.3 (Ar–C) ppm; HRMS (*m/z*): 481.5408; Anal. calcd. for $C_{21}H_{22}N_4O_4S_2$ (458.55): C55.01, H4.84, N12.22. Found: C55.10, H4.82, N12.36.

3-(4-Chlorophenylsulfonylethenesulfonylmethyl)-4-amino-5-(4-chlorostyryl)-1,2,4-triazole (11c) M.p. 220–222 °C. IR (KBr cm^{-1}): 1345, 1149 (SO_2), 1591 (C=N), 1640 (C=C), 3450, 3335 (NH_2). ^{1}H NMR (DMSO-d_6): δ 4.65 (s, 2H,

CH_2), 5.69 (bs, 2HH, NH_2), 6.91–7.52 (m, 10H, H_C, H_D, and Ar–H), 7.83 (d, 1H, H_B, $J = 14.4$ Hz), 8.19 (d, 1H, H_A, $J = 14.4$ Hz) ppm. ^{13}C NMR (DMSO-d_6): δ 58.7 (CH_2), 112.1 (C–H_D), 134.4 (C–H_C), 135.9 (C–H_A), 142.3 (C–H_B), 148.2 (C-5), 157.4 (C-3), 126.0 (Ar–C), 127.6 (Ar–C), 128.6 (Ar–C), 129.4 (Ar–C), 130.7 (Ar–C), 133.6 (Ar–C), 138.8 (Ar–C), 142.0 (Ar–C) ppm; HRMS (*m/z*): 522.3708; Anal. calcd. for $C_{19}H_{16}Cl_2N_4O_4S_2$ (499.38): C45.70, H3.23, N11.22. Found: C45.84, H3.24, N11.38.

Biological activity

The compounds **6–11** were dissolved in DMSO at different concentrations 12.5, 25, 50, and 100 µg/well.

Cells

Bacterial strains *Staphylococcus aureus* (ATCC No. 25923), *Bacillus subtilis* (ATCC No. 6051) (Gram-positive bacteria), *Pseudomonas aeruginosa* (ATCC No. 15442), *Klebsiella pneumoniae* (ATCC No. 2342), (Gram-negative bacteria) and fungi *Aspergillus niger*, (ATCC No. 6275), *Penicillium chrysogenum* (ATCC No. 10106) are obtained from the Department of Botany, S.V.University, Tirupati.

Antibacterial and antifungal assays

The in vitro antimicrobial activity of the newly synthesized compounds was determined by agar well diffusion method against test organisms. (Chung et al. 1990; Kumari et al 2011). Nutrient broth (NB) plates are swabbed with 24 h old broth culture (100 µl) of test bacteria. For this, inoculum containing 106 cfu/ml of each tested bacterial culture was spread on nutrient agar plates with a sterile swab moistened with the bacterial suspension. Using the sterile cork borer, wells (6 mm) are made into each petriplate. Various concentrations of DMSO dissolved compounds (12.5, 25, 50, and 100 µg/well) were added into the wells by using sterile pipettes. Simultaneously the standard antibiotics, Chloramphenicol for antibacterial activity and Ketoconazole for antifungal activity (as positive control) are tested against the pathogens. The samples are dissolved in DMSO which showed no zone of inhibition acts as negative control. All the synthesized compounds, positive control and negative control were tested at the same concentrations to see the effectiveness of the test compounds. The plates are incubated at 37 °C for 24 h for bacteria and at 28 °C for 48 h for fungi. After appropriate incubation, the diameter of zone of inhibition of each well is measured in mm. Duplicates are maintained and the average values are calculated for eventual antibacterial activity. Data were expressed as mean ± standard deviation.

Minimum inhibitory concentration (MIC) assay

Broth dilution test is used to determine of the above mentioned samples. (Janovska et al. 2003; Joshi et al. 2009) Freshly prepared nutrient broth is used as diluents. The 24 h old culture of the test bacteria *S. aureus, B. subtilis, P. aeruginosa, K. pneumoniae* and fungi *A. niger, P. chrysogenum* are diluted 100-folds in nutrient broth (100 µl bacterial cultures in 10 ml NB). Increasing concentrations of the test samples (1.25, 2.5, 5, 10, 20, 40 µl of stock solution contains 6.25, 12.5, 25, 50, 100, 200 µg/ml of the compounds) are added to the test tubes containing the bacterial and fungal cultures. All the tubes are incubated at 37 °C for 24 h for bacteria and at 28 °C for 48 h for fungi. The tubes are examined for visible turbidity and using NB as control. Control without test samples and with solvent is assayed simultaneously. The lowest concentration that inhibited visible growth of the tested organisms is recorded as MIC. To determine the minimum bactericidal concentration (MBC) (Clinical and Laboratory Standards Institute 2006) and minimum fungicidal concentration (MFC) (Clinical and Laboratory Standards Institute 2008) for each set of test tubes in the MIC determination, a loopful of broth is collected from those tubes which did not show any growth and inoculated on sterile nutrient broth (for bacteria) and PDA (for fungi) by streaking. Plates inoculated with bacteria and fungi are incubated at 37 °C for 24 h and at 28 °C for 48 h, respectively. After incubation, the lowest concentration is noted as MBC (for bacteria) or MFC (for fungi) at which no visible growth is observed.

Statistical analysis

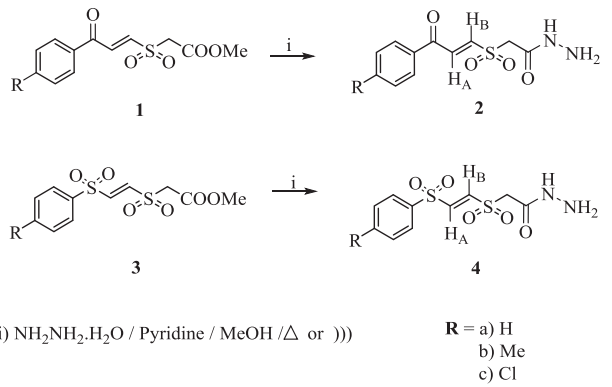
Experiments were carried out in duplicate ($n = 2$) and results are expressed as mean ± standard deviation (SD). Two-way ANOVA (MS-Excel) was used for multiple comparisons and it showed that $P < 0.01$ which represent statistically significant differences.

Results and discussion

Chemistry

A new class of aroylethenesulfonylmethyl styryl azoles and arylsulfonylethenesulfonylmethyl styryl azoles were synthesized from the synthetic intermediates *E*-aroylethenesulfonylacetic acid methyl ester (**1**), *E*--arylsulfonylethe nesulfonylacetic acid methyl ester (**3**) and substituted cinnamic acids The treatment of compounds **1** and **3** with hydrazine hydrate in the presence of pyridine furnished *E*-aroylethenesulfonylacetic acid hydrazide (**2**) and

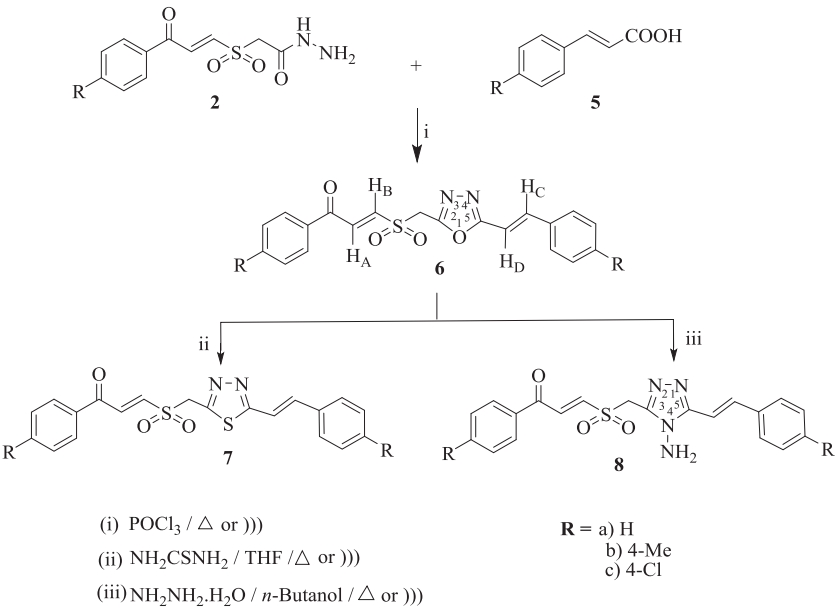
E-arylsulfonylethene-sulfonylacetic acid hydrazide (**4**) (Scheme 1). The ^{1}H NMR spectra of **2a** and **4a** displayed a singlet and two doublets at δ 3.85, 8.24, 7.81 and 3.94, 8.35, 7.92 ppm due to methylene, H_A and H_B (olefin protons) respectively. Besides two broad singlets were observed at δ 9.28, 4.33 and at 9.26, 4.38 ppm were assigned to NH and NH_2.The ester functionality present in compounds **1** and **3** was exploited to develop oxadiazole ring. The cyclo-condensation of compound **2** with cinnamic acid (**5**) in the presence of phosphorus oxychloride gave 2-(*E*-aroylethenesulfonylmethyl)-5-styryl-1,3,4-oxadiazole (**6**). Interconvertion of oxadiazole to thiadiazole was effected by the reaction of compound **6** with thiourea in tetrahydrofuran to obtain 2-(*E*-aroylethenesulfonylmethyl)-5-styryl-1,3,4-thadiazole (**7**). On the other hand, the reaction between compound **6** and hydrazine hydrate in *n*-butanol afforded 3-(*E*-aroylethenesulfonylmethyl)-4-amino-5-styryl-1,2,4-triazole



Scheme 1 Synthesis of *E*-aroylethenesulfonylacetic acid hydrazides and *E*-arylsulfonyl- ethenesulfonylacetic acid hydrazides

(**8**). The compounds **6, 7**, and **8** were also prepared adopting ultrasonication methodology (Scheme 2 and Table 1).

The ^{1}H NMR spectra of **6a**, **7a**, and **8a** displayed a singlet at δ 4.64, 4.67, 4.58 (CH_2), two doublets at 8.28, 8.26, 8.33 (H_A) and 8.01, 7.94, 7.70 ppm (H_B). Another set of two doublets due to olefin protons H_C and H_D adjacent to aryl group appeared at much downfield region and merged with aromatic protons. The coupling constants $J_{AB} = 14.0$, 14.6, and 14.7 Hz indicated that they possess *trans* geometry. Apart from these, a broad singlet observed at δ 5.62 ppm in **8a** was assigned to NH_2. The signal due to NH_2 disappeared when D_2O was added. In a similar way, the reaction of compound **4** with **5** in the presence of phosphorus oxychloride yielded 2-(*E*-arylsulfonylethenesulfonylmethyl)-5-styryl-1,3,4-oxadiazole (**9**). The treatment of compound **9** with thiourea in tetrahydrofuran produced 2-(*E*-arylsulfonylethenesulfonyl-methyl)-5-styryl-1,3,4-thadiazole (**10**). Besides, 3-(*E*-arylsulfonylethenesulfonylmethyl)-4-amino-5-styryl-1,2,4-triazole (**11**) was synthesized by the reaction of compound **9** with hydrazine hydrate in *n*-butanol. Furthermore the compounds **9, 10**, and **11** were prepared adopting ultrasonication methodology (Scheme 3 and Table 1). The ^{1}H NMR spectra of **9a**, **10a**, and **11a** exhibited signals at δ 4.63, 4.68, 4.54; 8.32, 8.12, 8.15 and 7.82, 7.71, 7.89 ppm due to methylene protons, H_A and H_B (olefin protons) respectively. The coupling constants $J_{AB} = 14.0$, 14.3, and 14.2 Hz indicated that they possess *trans* geometry. Furthermore, two doublets due to olefin protons H_C and H_D adjacent to aryl group appeared at much downfield region and merged with aromatic protons. In addition to these, a broad singlet appeared at δ 5.65 ppm due to NH_2 in compound **11a** was disappeared on deuteration. The structures of compounds **6–11** were further



Scheme 2 Synthesis of 2/3-*E*-aroylethenesulfonylmethyl-5-styryl-1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazoles

Table 1 The reaction time and yields of the compounds **6–11** under ultrasonication and conventional methods

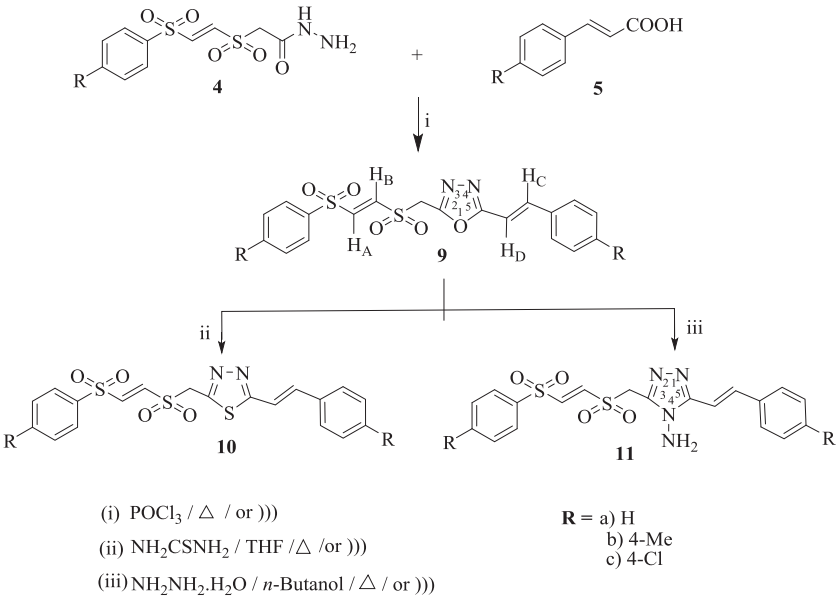
Product	Time (h)	Time (min)	Yield (%)	
	Conventional	Ultrasound	Conventional	Ultrasound
2a	5.5	27	65	86
2b	6	30	63	80
2c	5	25	72	85
4a	4.5	22	70	89
4b	5	25	65	87
4c	4	20	71	90
6a	4	25	64	84
6b	5	23	62	82
6c	3.5	21	70	87
7a	15	47	69	90
7b	16	50	66	88
7c	14	45	72	91
8a	8	40	66	89
8b	6.5	38	64	87
8c	7	34	62	91
9a	3.5	22	66	89
9b	4.5	24	63	90
9c	3	20	68	92
10a	14	42	72	92
10b	15	46	68	90
10c	13	40	69	93
11a	5	37	71	91
11b	6	35	69	90
11c	5	30	67	94

established by IR, ^{13}C NMR, mass spectra, and microanalyses.

Antimicrobial activity evaluation

Investigation of antibacterial screening data presented in Table 2; Fig. 1 indicated that Gram-positive bacteria were more susceptible towards the tested compounds than Gram-negative ones. The compounds having triazole unit **8**, **11** displayed higher inhibitory activity than thiadiazole **7**, **10** and oxadiazole moieties **6**, **9**. The presence of electron withdrawing chloro substituent on the aromatic ring enhanced the activity. In fact, the compounds **11a** and **11c** exhibited higher antibacterial activity particularly on *B. subtilis* (39 mm at 100 µg/well) and (41 mm at 100 µg/well) when compared with the standard drug Chloramphenicol (38 mm at 100 µg/well).

All the tested compounds inhibited the spore germination against tested fungi (Table 3; Fig. 2). It was observed that all the compounds exhibited slightly higher antifungal activity against *P. chrysogenum* than on *A.niger*. The compounds **11a** (40 mm at 100 µg/well) and **11c** (43 mm at 100 µg/well) showed higher antifungal activity particularly against *P. chrysogenum* when compared with the standard drug Ketoconazole (39 mm at 100 µg/well). It was also observed that, the arylsulfonylethenesulfonylmethyl azoles **9–11** displayed higher inhibitory activity than the aroylethenesulfonylmethyl azoles **6–8**. This may be due to the presence of more electronegative atom *viz*., chlorine in the aromatic ring which may enhance the biological potency, bioavailability, metabolic stability and lipophilicity. Enhanced lipophilicity may lead to easier absorption and



Scheme 3 Synthesis of 2/3-*E*-arylsulfonylethenesulfonylmethyl-5-styryl-1,3,4-oxadiazoles /1,3,4 - thiadiazoles and 1,2,4-triazoles

Table 2 The in vitro antibacterial activity of compounds **6–11**

Compd no.	Zone of inhibition (mm)															
	Gram-positive bacteria								Gram-negative bacteria							
	S. aureus				*B. subtilis*				*P. aeruginosa*				*K. pneumoniae*			
	12.5 µg/well	25 µg/well	50 µg/well	100 µg/well	12.5 µg/well	25 µg/well	50 µg/well	100 µg/well	12.5 µg/well	25 µg/well	50 µg/well	100 µg/well	12.5 µg/well	25 µg/well	50 µg/well	100 µg/well
6a	–	–	–	8 ± 0.9	–	–	–	10 ± 1.5	–	–	–	–	–	–	–	–
6b	–	–	–	9 ± 1.2	–	–	–	8 ± 1.2	–	–	–	–	–	–	–	–
6c	–	–	9 ± 1.1	11 ± 1.5	–	9 ± 2.1	12 ± 2.4	15 ± 1.1	–	–	–	8 ± 0.6	–	–	–	10 ± 1.6
7a	8 ± 1.6	11 ± 2.6	14 ± 0.8	17 ± 2.2	14 ± 1.2	16 ± 2.3	18 ± 2.8	21 ± 1.6	–	–	–	9 ± 1.9	11 ± 1.3	8 ± 1.1	10 ± 1.8	13 ± 1.7
7b	–	9 ± 1.8	11 ± 2.4	14 ± 2.3	9 ± 2.8	12 ± 1.1	15 ± 1.4	18 ± 1.2	–	–	–	–	–	–	9 ± 1.7	13 ± 0.8
7c	13 ± 1.9	16 ± 2.1	18 ± 1.4	19 ± 2.3	16 ± 1.8	19 ± 2.4	21 ± 2.5	24 ± 2.2	–	8 ± 1.1	9 ± 1.7	11 ± 2.4	8 ± 1.1	10 ± 1.4	11 ± 1.9	14 ± 1.8
8a	9 ± 1.1	12 ± 2.2	16 ± 2.4	21 ± 2.1	28 ± 1.7	30 ± 1.6	31 ± 1.8	32 ± 1.3	11 ± 2.6	13 ± 1.4	15 ± 1.7	18 ± 1.5	19 ± 2.2	21 ± 2.5	23 ± 1.6	26 ± 0.9
8b	16 ± 2.0	18 ± 1.5	21 ± 1.6	22 ± 1.4	24 ± 2.2	25 ± 2.0	27 ± 2.7	30 ± 2.1	9 ± 1.3	11 ± 1.4	13 ± 2.3	16 ± 2.5	15 ± 2.3	17 ± 1.7	20 ± 1.3	21 ± 1.2
8c	22 ± 1.6	24 ± 2.3	27 ± 2.6	30 ± 1.1	29 ± 2.6	31 ± 1.8	33 ± 2.1	36 ± 2.4	13 ± 2.7	15 ± 2.6	17 ± 1.2	19 ± 1.8	20 ± 1.7	22 ± 1.5	25 ± 0.9	28 ± 1.6
9a	–	–	8 ± 0.9	10 ± 2.7	7 ± 2.1	9 ± 1.2	11 ± 1.6	13 ± 1.5	–	–	–	–	–	–	9 ± 1.6	11 ± 1.7
9b	–	–	–	8 ± 1.0	–	–	8 ± 1.1	10 ± 1.9	–	–	–	–	–	–	–	–
9c	–	–	–	12 ± 1.6	8 ± 1.2	11 ± 2.4	13 ± 2.6	16 ± 1.5	–	–	9 ± 1.8	11 ± 2.1	–	–	9 ± 1.1	12 ± 1.4
10a	10 ± 1.3	13 ± 2.1	16 ± 1.9	19 ± 2.5	16 ± 1.7	18 ± 1.2	20 ± 1.4	22 ± 2.3	–	8 ± 0.9	10 ± 1.9	13 ± 2.7	10 ± 2.1	12 ± 1.3	14 ± 1.6	16 ± 2.2
10b	10 ± 1.4	12 ± 1.9	13 ± 2.2	15 ± 1.4	13 ± 2.1	15 ± 2.5	17 ± 1.7	19 ± 1.8	–	–	8 ± 1.9	10 ± 2.7	–	9 ± 1.2	12 ± 0.9	16 ± 2.1
10c	15 ± 1.5	16 ± 2.4	18 ± 1.2	22 ± 1.8	20 ± 1.1	22 ± 1.7	24 ± 2.3	27 ± 2.5	8 ± 0.8	10 ± 1.6	12 ± 1.3	14 ± 1.7	11 ± 1.6	13 ± 2.4	15 ± 1.5	18 ± 1.9
11a	26 ± 1.8	28 ± 2.5	32 ± 1.0	35 ± 1.2	30 ± 2.4	33 ± 1.4	35 ± 1.7	39 ± 2.3	15 ± 2.5	16 ± 1.2	18 ± 1.5	21 ± 1.6	22 ± 1.8	24 ± 2.6	27 ± 1.4	30 ± 1.3
11b	18 ± 2.5	20 ± 1.3	22 ± 1.8	25 ± 2.7	23 ± 1.9	26 ± 1.4	29 ± 1.5	31 ± 2.9	10 ± 2.1	12 ± 2.7	14 ± 2.4	17 ± 2.6	16 ± 1.7	18 ± 1.9	21 ± 1.6	23 ± 2.3
11c	25 ± 2.3	27 ± 1.2	29 ± 1.7	33 ± 2.5	31 ± 1.4	33 ± 2.6	36 ± 1.8	41 ± 2.7	16 ± 1.1	18 ± 2.3	20 ± 1.4	22 ± 1.2	23 ± 1.8	26 ± 1.6	29 ± 2.6	32 ± 2.9
Chloramphenicol	28 ± 1.2	30 ± 2.4	33 ± 1.3	35 ± 1.8	30 ± 2.1	32 ± 1.4	34 ± 2.3	38 ± 1.7	23 ± 2.5	25 ± 1.5	27 ± 2.2	30 ± 1.9	36 ± 2.6	38 ± 1.6	40 ± 1.1	42 ± 2.7
Control (DMSO)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

(–) No activity, (±) standard devation

The value are expressed as mean ± SD performed in duplicate. $n = 2$ (Expressed is repeated for two times)

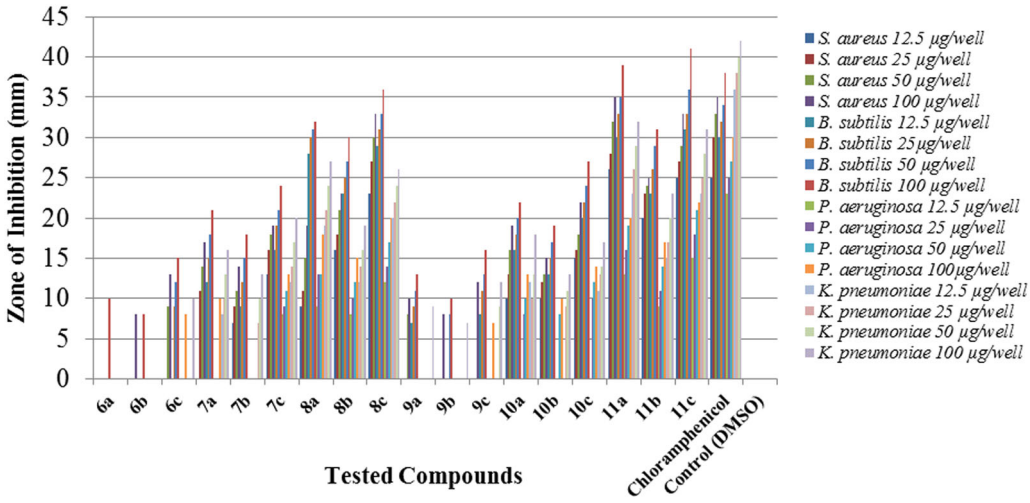


Fig. 1 The in vitro antibacterial activity of compounds **6–11**

Table 3 The in vitro antifungal activity of compounds **6–11**

Compd no.	Zone of inhibition (mm)							
	A. niger				*P.chrysogenum*			
	12.5 µg/well	25 µg/well	50 µg/well	100 µg/well	12.5 µg/well	25 µg/well	50 µg/well	100 µg/well
6a	–	–	–	9 ± 1.3	–	8 ± 1.0	10 ± 2.2	12 ± 1.6
6b	–	–	–	–	–	–	–	10 ± 1.1
6c	–	–	9 ± 1.1	12 ± 1.6	–	8 ± 1.3	11 ± 1.4	14 ± 2.1
7a	9 ± 1.0	12 ± 1.1	14 ± 2.1	16 ± 1.1	18 ± 1.7	20 ± 2.9	22 ± 2.3	24 ± 1.3
7b	–	–	9 ± 1.4	11 ± 1.3	13 ± 1.9	15 ± 1.8	17 ± 1.2	20 ± 2.6
7c	12 ± 1.1	13 ± 2.8	15 ± 1.2	17 ± 2.5	19 ± 1.7	21 ± 1.9	23 ± 2.4	26 ± 2.7
8a	20 ± 2.3	22 ± 1.3	25 ± 1.5	27 ± 1.4	29 ± 1.1	31 ± 1.6	33 ± 2.1	36 ± 2.5
8b	18 ± 2.5	20 ± 1.6	22 ± 2.6	24 ± 1.5	25 ± 2.2	27 ± 1.4	29 ± 1.3	32 ± 1.9
8c	22 ± 1.3	24 ± 2.9	26 ± 1.7	29 ± 2.6	30 ± 1.8	32 ± 2.1	34 ± 1.1	37 ± 1.2
9a	–	–	–	–	9 ± 1.6	11 ± 2.2	14 ± 2.5	16 ± 2.8
9b	–	–	–	9 ± 1.4	–	–	9 ± 1.3	12 ± 1.8
9c	–	–	–	8 ± 1.0	10 ± 2.7	12 ± 1.3	15 ± 1.7	18 ± 2.2
10a	14 ± 1.1	16 ± 2.8	18 ± 1.2	20 ± 2.5	22 ± 1.7	24 ± 1.9	25 ± 2.4	28 ± 2.7
10b	-	9 ± 1.3	11 ± 2.5	13 ± 1.9	14 ± 1.9	16 ± 1.5	18 ± 1.8	21 ± 2.3
10c	16 ± 1.6	18 ± 2.5	20 ± 1.8	22 ± 2.8	23 ± 1.3	24 ± 2.4	26 ± 1.3	29 ± 1.5
11a	24 ± 1.7	26 ± 2.3	28 ± 1.6	31 ± 1.1	33 ± 1.5	36 ± 1.1	38 ± 2.5	40 ± 2.7
11b	19 ± 2.9	21 ± 1.7	24 ± 2.3	26 ± 2.2	28 ± 2.5	29 ± 1.2	31 ± 1.5	34 ± 1.7
11c	28 ± 2.8	30 ± 1.9	32 ± 2.2	34 ± 1.7	35 ± 2.6	37 ± 1.1	40 ± 1.6	43 ± 2.4
Ketocon-azole	29 ± 1.2	31 ± 2.4	34 ± 1.5	37 ± 2.3	33 ± 3.6	35 ± 1.8	37 ± 3.5	39 ± 1.7
Control (DMSO)	–	–	–	–	–	–	–	–

(−) No activity, (±) standard deviation, The value are expressed as mean ± SD performed in duplicate

$n = 2$ (Expressed is repeated for two times)

transportation of molecules within the biological systems (Plech et al. 2013; Almeida de et al. 2010)

The MIC, MBC, and MFC values of the tested compounds are shown in Table 4. MIC is the lowest concentration of an antimicrobial that will inhibit the visible growth of a micro-organism. (But it is not sure that the microorganisms are completely killed.) The MBC/MFC is the lowest concentration of antibiotic required to kill a particular bacterium/fungi. The MBC/MFC involves an additional set of steps performed once the MIC is

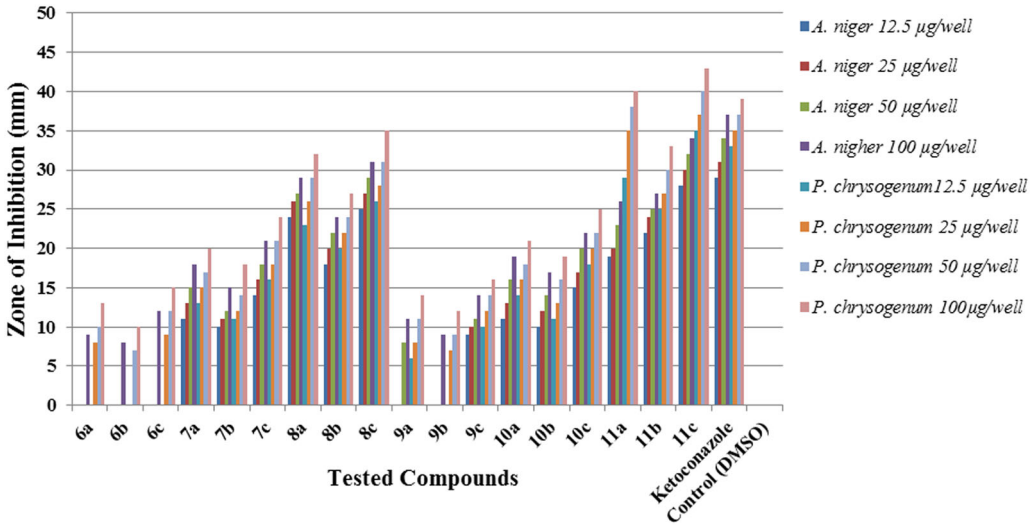


Fig. 2 The in vitro antifungal activity of compounds **6–11**

Table 4 MIC, MBC, and MFC of compounds **11a** and **11c**

Compd no.	Minimum inhibitory concentration MIC (MBC/MFC) µg/well					
	S. aureus	*B. subtilis*	*P. aeruginosa*	*K. pneumoniae*	*A. niger*	*P.chrysogenum*
11a	50 (200)	6.25 (12.5)	50 (200)	100 (>200)	25 (100)	12.5 (25)
11c	25 (>100)	6.25 (12.5)	50 (200)	100 (200)	12.5 (50)	12.5 (25)
Chloram-phenicol	6.25	6.25	6.25	12.5	–	–
Ketoconazole	–	–	–	–	6.25	12.5

(–) No activity

determined. The antimicrobials are usually regarded as bactericidal/fungicidal if the MBC/MFC is not greater than four times the MIC (French 2006). The arylsulfonylethenesulfonylmethyl triazoles **11a** and **11c** exhibited low MIC values. In addition MBC value is 2 × MIC in case of *B. subtills* and MFC value is 2 × MIC in case of *P.chrysogenum*. However, the other compounds showed bactericidal and fungicidal effects greater than 2 × MIC. The structure-activity relationship of the synthesized compounds revealed that the compounds having oxadiazole moiety **6, 9** exhibited least activity whereas the compounds having thiadiazole **7, 10** displayed moderate activity. On the other hand, compounds having triazole moiety **8, 11** exhibited high antimicrobial activity. The unsubstituted and chloro substituted compounds presented higher antimicrobial activity than the methyl substituted ones. It was observed that arylsulfonylethenesulfonylmethyl styryl azoles (**9–10**) exhibited greater antimicrobial activity than aroylethenesulfonylmethyl styryl azoles (**6–8**). Amongst the compounds having arylsulfonylethenesulfonylmethyl triazoles containing compounds **11a** and **11c** exhibited excellent activity against *B. subtills* with an inhibition zone of 39 and 42 mm at 100 mg/well, respectively. The compounds **11a** and **11c** also displayed strong antifungal activity against *P. chrysogenum* with an inhibition zone of 40 and 43 mm at 100 mg/well, respectively.

Conclusions

In summary, a new class of aroylethenesulfonylmethyl/arylsulfonylethenesulfonylmethyl styryl 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazoles were synthesized from the synthetic intermediates *E*-aroylethenesulfonylmethyl acetic acid methyl ester, *E*-arylsulfonylethenesulfonylmethyl acetic acid methyl ester and substituted cinnamic acids adopting conventional and ultrasonication methodologies. All the synthesized compounds were obtained in higher yields and in shorter reaction times in ultrasound irradiation method when compared with the conventional method. The structures of all the compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, and mass spectra. All the lead compounds were evaluated for antimicrobial activity. It was observed that arylsulfonylethenesulfonylmethyl styryl azoles (**9–10**) exhibited greater antimicrobial activity than aroylethenesulfonylmethyl styryl

azoles (**6**–**8**). Besides, compounds having triazole moiety exhibited higher antimicrobial activity than those having thiadiazole and oxadiazole moieties. Moreover, compounds having electron withdrawing chloro substituent enhances the activity. Amongst all the tested compounds unsubstituted and chloro substituted arylsulfonylethenesulfonyl methyl styryl 1,2,4-triazoles (**11a** and **11c**) are found to be potential antimicrobial agents particularly against *B.subtills* and *P. chrysogenum*.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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