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Synthesis and antioxidant activity of bis unsaturated sulfones, bis pyrroles, and bis pyrazoles

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Abstract The Michael acceptor 1,4-bis-(*E*)-2-(arylsulfonylvinyl)benzene was exploited to prepare a new series of bis heterocycles-(1,4-phenylene)bis(arylsulfonylpyrrole) and (1,4-phenylene)bis(arylsulfonyl pyrazole). All of the compounds were tested for antioxidant activity. Amongst the tested compounds, 1,4-bis-(*E*)-2-(arylsulfonylvinyl)benzene (**5**) was found to be the best potential antioxidant agent.

Keywords Bis unsaturated sulfones · Bis pyrroles · Bis pyrazolines · Bis pyrazoles · Antioxidant activity

Introduction

α,β-Unsaturated sulfones are valuable intermediates in a variety of synthetic transformations and are useful as building blocks in the synthesis of biologically active heterocycles [1–3], cytotoxic, antimicrobial, analgesic, and antipyretic. The synthetic utility of the 1,3-dipolar cycloaddition reaction stems from its wide scope and from the relevance of numerous targets achievable by this chemistry [4], especially heterocycles. In particular, nitrogen-containing heterocycles have attracted widespread attention in the field of synthetic organic chemistry as well as in medicinal chemistry [5]. Among them, pyrroles, pyrazoles, and their derivatives are present in a plethora of natural and synthetic compounds that are of considerable importance. Pyrroles possesses antibacterial, antifungal, antiviral, anti-inflammatory, antitumor, and antioxidant activities [6–11]. The recent success of pyrazole-based COX-2 inhibitors has highlighted the importance of these heterocycles in medicinal chemistry [12]. Pyrazole and its derivatives show a variety of pharmaceutical activities such as antimicrobial [13, 14], antiviral [15, 16],

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anxiolytic [17, 18], anti-inflammatory, [19] and antioxidant [1]. In fact, pyrazole moiety makes the core structure of various drugs, namely difenamizole [20, 21], celecoxib [22], and tepoxalin [23]. Motivated by these findings and in continuation of our studies towards the synthesis and bioassay of different bis heterocycles [24–27], the present work is formulated.

Experimental

Apparatus and analysis

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, 1:3). The IR spectra were recorded on a Thermo Nicolet IR200 FT-IR spectrometer as KBr pellets and the wave numbers were given in cm^{-1}. The ^{1}H NMR spectra were recorded in DMSO-d_6 on a Brucker-400 spectrometer (400 MHz). The ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker spectrometer operating at 100 MHz. All chemical shifts are reported in δ (ppm) using TMS as an internal standard. The mass spectra were recorded on Agilent 1200 series LC-MC/Agilent 6310 Ion trap electron spray ionization mode. The elemental analyses were carried out on a Perkin-Elmer 240C elemental analyzer. The antioxidant property was carried out by using Shimadzu UV-2450 spectrophotometer. The starting compound arylsulfonylacetic acid (**3**) was prepared according to literature procedure [28].

General procedure for the synthesis of 1, 4-bis((*E*)-2-(arylsulfonyl)vinyl)benzene (5)

To a solution of arylsulfonylacetic acid (**1**) (1 mmol) in glacial acetic acid (10 ml), terephthaldehyde (**2**) (0.5 mmol) followed by a catalytic amount of benzylamine (0.20 ml) were added and refluxed for 6–8 h. The reaction mixture was cooled, treated with dry ether (50 ml), and left overnight in a refrigerator. Any product that formed was filtered off. The filtrate was diluted with ether and washed successively with a saturated solution of sodium bicarbonate, sodium bisulfate, dilute hydrochloric acid, and water. The organic layer was dried over anhydrous Na_2SO_4. In many cases, a solid product was obtained on removal of ether under reduced pressure. However, in some instances, a syrupy substance was obtained, which was solidified on treatment with 2-propanol. The crude product was recrystallized from 2-propanol.

*Spectral data for compounds (**5a–e**)*

*1,4-Bis ((E)-2-(phenylsulfonyl)vinyl)benzene (**5a**)* White solid; Mp. 236–238 °C. IR (KBr) (cm^{-1}): 1,625 (C=C), 1,299, 1,134 (SO_2); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.19 (d, 2H, C–H_B, J = 15.3 Hz), 7.46–7.77 (m, 14H, Ar–H), 7.63 (d, 2H, C–H_A, J = 15.3 Hz) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 113.2 (C–H_B), 135.2

(C–H_A), 125.7, 126.3, 129.7, 132.5, 134.1, 136.3, 138.3 ppm (aromatic carbons). MS: (*m/z*) 411.51 $[M + H]^+$. Anal. Calcd. for $C_{22}H_{18}O_4S_2$:C, 64.37; H, 4.42 %. Found: C, 64.45; H, 4.45 %.

1,4-Bis((E)-2-(p-methylphenylsulfonyl)vinyl)benzene ***(5b)*** White solid; Mp. 220–222 °C. IR (KBr) (cm^{-1}): 1,620 (C=C), 1,297, 1,128 (SO_2); ^1H NMR (400 MHz, DMSO-d_6): δ 2.38 (s, 6H, Ar–CH_3), 7.16 (d, 2H, C–H_B, $J = 15.2$ Hz), 7.50–7.79 (m, 12H, Ar–H), 7.60 (d, 2H, C–H_A, $J = 15.2$ Hz) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 24.8 (Ar–CH_3), 112.9 (C–H_B), 133.7 (C–H_A), 126.5, 128.8, 130.3, 131.8, 134.2, 137.5, 142.6 ppm (aromatic carbons). MS: (*m/z*) 439.56 $[M + H]^+$. Anal. Calcd. for $C_{22}H_{22}O_4S_2$:C, 65.73; H, 5.06 %. Found: C, 65.83; H, 5.05 %.

1,4-Bis((E)-2-(p-chlorophenylsulfonyl)vinyl)benzene ***(5c)*** White solid; Mp. 243–245 °C. IR (KBr) (cm^{-1}): 1,630 (C=C), 1,302, 1,146 (SO_2); ^1H NMR (400 MHz, DMSO-d_6): δ 7.23 (d, 2H, C–H_B, $J = 15.4$ Hz), 7.66 (d, 2H, C–H_A, $J = 15.4$ Hz), 7.71–7.93 (m, 12H, Ar–H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 113.5 (C–H_B), 135.9 (C–H_A), 126.2, 128.5, 133.8, 135.1, 136.9, 138.7, 139.4 ppm (aromatic carbons). MS: (*m/z*) 480.41 $[M + H]^+$. Anal. Calcd. for $C_{22}H_{16}Cl_2O_4S_2$:C, 55.12; H, 3.36 %. Found: C, 55.18; H, 3.38 %.

1,4-Bis((E)-2-(p-methoxyphenylsulfonyl)vinyl)benzene ***(5d)*** White solid; Mp. 272–274 °C. IR (KBr) (cm^{-1}): 1,628 (C=C), 1,295, 1,139 (SO_2); ^1H NMR (400 MHz, DMSO-d_6): δ 3.85 (s, 6H, Ar–OCH_3), 7.18 (d, 2H, C–H_B, $J = 15.6$ Hz), 7.54–7.82 (m, 12H, Ar–H), 7.62 (d, 2H, C–H_A, $J = 15.6$ Hz) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 54.6 (Ar–OCH_3), 112.5 (C–H_B), 133.2 (C–H_A), 126.1, 126.5, 129.5, 129.7, 131.4, 136.2, 138.1 ppm (aromatic carbons). MS: (*m/z*) 471.56 $[M + H]^+$. Anal. Calcd. for $C_{24}H_{22}O_6S_2$:C, 61.26; H, 4.71 %. Found: C, 61.32; H, 4.74 %.

1,4-Bis((E)-2-(p-hydroxyphenylsulfonyl)vinyl)benzene ***(5e)*** White solid; Mp. 266–268 °C. IR (KBr) (cm^{-1}): 1,632 (C=C), 1,306, 1,141 (SO_2); ^1H NMR (400 MHz, DMSO-d_6): δ 5.27 (s, 2H, Ar–OH), 7.14 (d, 2H, C–H_B, $J = 15.1$ Hz), 7.52–7.81 (m, 12H, Ar–H), 7.58 (d, 2H, C–H_A, $J = 15.1$ Hz) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 111.7 (C–H_B), 132.4 (C–H_A), 125.6, 126.7, 131.2, 133.8, 134.2, 136.1, 139.3 ppm (aromatic carbons). MS: (*m/z*) 445.52 $[M + H]^+$. Anal. Calcd. for $C_{22}H_{20}O_6S_2$:C, 59.53; H, 4.56 %. Found: C, 59.44; H, 4.53 %.

General procedure for the synthesis of 1,4-(bis(3-arylsulfonyl)-1*H*-pyrrol-4-yl)benzene (6)

To a suspension of sodium hydride (0.05 g) in dry ether (10 ml), compound **5** (1 mmol) and tosylmethyl isocyanide (2 mmol) in Et_2O–DMSO (2:1) (15 ml) was added while stirring at room temperature and stirring was continued for 5–7 h. The reaction mixture was diluted with water and extracted with ether. The ethereal layer

was dried over anhydrous Na_2SO_4 and filtered. The solvent was removed *in vacuo*. The resultant residue was purified by column chromatography (silica gel, 60–120 mesh) using hexane, and ethyl acetate (3:1) as eluent.

*Spectral data for compounds (**6a–e**)*

*1,4-(Bis(3-phenylsulfonyl)-1H-pyrrol-4-yl)benzene (**6a**)* Pale yellow solid; Mp. 230–232 °C. IR (KBr) (cm^{-1}): 3,245 (NH), 1,325, 1,136 (SO_2); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.81–7.55 (m, 18H, C_2–H, C_5–H and Ar–H), 11.53 (bs, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 110.2 (C-3), 116.9 (C-5), 122.4 (C-2), 126.6 (C-4), 128.4, 129.9, 132.1, 134.6, 136.3, 141.7 ppm (aromatic carbons). MS: (*m/z*) 489.58 $[M + H]^+$. Anal. Calcd. for $C_{26}H_{20}N_2O_4S_2$:C, 63.92; H, 4.13; N, 5.73 %. Found: C, 64.05; H, 4.18; N, 5.93 %.

*1,4-(Bis(3-(p-methylphenylsulfonyl)-1H-pyrrol-4-yl)benzene (**6b**)* Pale yellow solid; Mp. 238–240 °C. IR (KBr) (cm^{-1}): 3,241 (NH), 1,334, 1,138 (SO_2); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.38 (s, 6H, Ar–CH_3), 6.90–7.52 (m, 16H, C_2–H, C_5–H and Ar–H), 11.76 (bs, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 24.3 (Ar–CH_3), 113.5 (C-3), 117.8 (C-5), 123.7 (C-2), 127.9 (C-4), 128.2, 132.3, 135.6, 137.4, 138.7, 143.2 ppm (aromatic carbons). MS: (*m/z*) 517.63 $[M + H]^+$. Anal. Calcd. for $C_{28}H_{24}N_2O_4S_2$:C, 65.09; H, 4.68; N, 5.42 %. Found: C, 65.25; H, 4.75; N, 5.64 %.

*1,4-(Bis(3-(p-chlorophenylsulfonyl)-1H-pyrrol-4-yl)benzene (**6c**)* Pale yellow solid; Mp. 277–279 °C. IR (KBr) (cm^{-1}): 3,256 (NH), 1,340, 1,145 (SO_2); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.08–7.62 (m, 16H, C_2–H, C_5–H and Ar–H), 12.02 (bs, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 114.8 (C–3), 119.2 (C–5), 125.6 (C–2), 129.4 (C-4), 127.2, 129.8, 134.5, 137.3, 139.4, 140.3 ppm (aromatic carbons). MS: (*m/z*) 558.47 $[M + H]^+$. Anal. Calcd. for $C_{26}H_{18}Cl_2N_2O_4S_2$: C, 56.02; H, 3.25; N, 5.03 %. Found: C, 56.14; H, 3.21; N, 5.21 %.

*1,4-(Bis(3-(p-methoxyphenylsulfonyl)-1H-pyrrol-4-yl)benzene (**6d**)* Pale yellow solid; Mp. 268–271 °C. IR (KBr) (cm^{-1}): 3,251 (NH), 1,336, 1,130 (SO_2); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.87 (s, 6H, Ar–OCH_3), 7.05–7.57 (m, 16H, Ar–H, C_5–H and C_2–H),11.83 (bs, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 54.8 (Ar–OCH_3), 114.3 (C–3), 118.5 (C–5), 124.7 (C–2), 128.4 (C–4), 115.1, 128.3, 129.5, 133.2, 136.8, 165.0 ppm (aromatic carbons). MS: (*m/z*) 549.63 $[M + H]^+$. Anal. Calcd. for $C_{28}H_{24}N_2O_6S_2$:C, 61.30; H, 4.41; N, 5.11 %. Found: C, 61.20; H, 4.44; N, 5.26 %.

*1,4-(Bis(3-(p-hydroxyphenylsulfonyl)-1H-pyrrol-4-yl)benzene (**6e**)* Pale yellow solid; Mp. 241-243 °C. IR (KBr) (cm^{-1}): 3,249 (NH), 1,332, 1,126 (SO_2); ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.29 (s, 2H, Ar–OH), 6.89–7.64 (m, 16H, Ar–H, C_5–H and C_2–H), 11.68 (bs, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 112.7 (C–3), 117.6 (C–5), 122.1 (C–2), 127.5 (C–4), 116.8, 128.5, 129.7, 134.3,

136.9, 163.2 ppm (aromatic carbons). MS: (*m/z*) 521.58 $[M + H]^+$. Anal. Calcd. for $C_{26}H_{20}N_2O_6S_2$:C, 59.99; H, 3.87; N, 5.38 %. Found: C, 60.17; H, 3.97; N, 5.62 %.

General procedure for the synthesis of 1,4-(bis(3-arylsulfonyl)-4,5-dihydro-(1*H*-pyrazol-4-yl))benzene (7)

A well-cooled ethereal solution of diazomethane (40 ml, 4 mmol) and a catalytic amount of triethylamine (2 ml) were added to a solution of compound **5** (1 mmol) in dichloromethane (10 ml). The reaction mixture was kept at −20 to −15 °C for 48–56 h. The solvent was removed under reduced pressure. The resultant solid was purified by column chromatography (silica gel, 60–120 mesh) using ethyl acetate, and hexane (1:4) as eluent.

*Spectral data for new compounds (**7a–e**)*

*1,4-(Bis(3-phenylsulfonyl)-4,5-dihydro-(1H-pyrazol-4-yl))benzene(**7a**)* Yellow solid; Mp. 232–234 °C. IR (KBr) (cm^{-1}): 3,253 (NH), 1,565 (C=N), 1,326, 1,132 (SO_2); ^{1}H NMR (400 MHz, DMSO-d_6): 3.32 (dd, 2H, H_X, $J_{AX} = 5.8$ Hz, $J_{MX} = 10.9$ - Hz), 3.87 (dd, 2H, H_M, $J_{AM} = 12.5$ Hz), 4.35 (dd, 2H, H_A), 6.63 (bs, 2H, NH), 7.12–7.98 (m, 14H, Ar–H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 35.7 (C–4), 56.8 (C–5), 157.1 (C–3), 127.9, 130.6, 132.4, 134.7, 136.0, 141.2 ppm (aromatic carbons). MS: (*m/z*) 495.59 $[M + H]^+$. Anal. Calcd. for $C_{24}H_{22}N_4O_4S_2$:C, 58.28; H, 4.48; N, 11.33 %. Found: C, 58.39; H, 4.50; N, 11.49 %.

*1,4-(Bis(3-(p-methylphenylsulfonyl)-4,5-dihydro-(1H-pyrazol-4-yl))benzene (**7b**)* Yellow solid; Mp. 244–246 °C. IR (KBr) (cm^{-1}): 3,265 (NH), 1,578 (C=N), 1,338, 1,146 (SO_2); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.32 (s, 6H, Ar–CH_3), 3.43 (dd, 2H, H_X, $J_{AX} = 6.2$ Hz, $J_{MX} = 11.1$ Hz), 3.97 (dd, 2H, H_M, $J_{AM} = 12.7$ Hz), 4.45 (dd, 2H, H_A), 6.72 (bs, 2H, NH), 6.98–7.85 (m, 12H, Ar–H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.7 (Ar–CH_3), 35.3 (C–4), 57.6 (C–5), 158.2 (C–3), 128.1, 135.4, 132.7, 137.2, 138.0, 143.8 ppm (aromatic carbons). MS: (*m/z*) 523.64 $[M + H]^+$. Anal. Calcd. for $C_{26}H_{26}N_2O_4S_2$:C, 59.75; H, 5.01; N, 10.72 %. Found: C, 59.83; H, 5.00; N, 10.85 %.

*1,4-(Bis(3-(p-chlorophenylsulfonyl)-4,5-dihydro-(1H-pyrazol-4-yl))benzene (**7c**)* Yellow solid; Mp. 283–285 °C. IR (KBr) (cm^{-1}): 3,268 (NH), 1,584 (C=N), 1,345, 1,139 (SO_2); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.50 (dd, 2H, H_X, $J_{AX} = 6.4$ Hz, $J_{MX} = 11.6$ Hz), 4.08 (dd, 2H, H_M, $J_{AM} = 12.8$ Hz), 4.52 (dd, 2H, H_A), 6.78 (bs, 2H, NH), 7.04–7.95 (m, 12H, Ar–H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 37.4 (C–4), 58.5 (C–5), 159.3 (C–3), 126.8, 129.2, 133.6, 137.1,139.5, 140.7 ppm (aromatic carbons). MS: (*m/z*) 564.48 $[M + H]^+$. Anal. Calcd. for $C_{24}H_{20}Cl_2N_4O_4S_2$:C, 51.16; H, 3.58; N, 9.94 %. Found: C, 51.02; H, 3.62; N, 10.14 %.

*1,4-(Bis(3-(p-methoxyphenylsulfonyl)-4,5-dihydro-(1H-pyrazol-4-yl))benzene (**7d**)* Yellow solid; Mp. 278–280 °C. IR (KBr) (cm^{-1}): 3,256 (NH), 1,570 (C=N),

1,339, 1,125 (SO_2); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.45 (dd, 2H, H_X, $J_{AX} = 6.3$ Hz, $J_{MX} = 11.4$ Hz), 3.81 (s, 6H, Ar–OCH_3), 4.02 (dd, 2H, H_M, $J_{AM} = 12.7$ Hz), 4.48 (dd, 2H, H_A), 6.74 (bs, 2H, NH), 7.01–7.89 (m, 12H, Ar–H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 36.8 (C–4), 54.3 (Ar–OCH_3), 58.2 (C–5), 158.6 (C–3), 114.7, 127.3, 128.0, 133.5, 136.2, 164.6 ppm (aromatic carbons). MS: (*m/z*) 555.64 $[M + H]^+$. Anal. Calcd. for $C_{26}H_{26}N_4O_6S_2$:C, 56.30; H, 4.72; N, 10.10 %. Found: C, 56.37; H, 4.74; N, 10.22 %.

*1,4-(Bis(3-(p-hydroxyphenylsulfonyl)-4,5-dihydro-(1H-pyrazol-4-yl))benzene (**7e**)* Yellow solid; Mp. 258–260 °C. IR (KBr) (cm^{-1}): 3,252 (NH), 1,572 (C=N), 1,331, 1,134 (SO_2); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.38 (dd, 2H, H_X, $J_{AX} = 6.0$ Hz, $J_{MX} = 10.9$ Hz), 3.93 (dd, 2H, H_M, $J_{AM} = 11.7$ Hz), 4.41 (dd, 2H, H_A), 5.23 (s, 2H, Ar–OH), 6.68 (bs, 2H, NH), 6.95–7.82 (m, 12H, Ar–H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 35.9 (C–4), 57.4 (C–5), 157.5 (C–3), 115.8, 126.5, 129.1, 133.4, 136.0, 162.9 ppm (aromatic carbons). MS: (*m/z*) 527.58 $[M + H]^+$. Anal. Calcd. for $C_{24}H_{22}N_4O_6S_2$:C, 54.74; H, 4.21; N, 10.64 %. Found: C, 54.90; H, 4.24; N, 10.89 %.

General procedure for the synthesis of 1,4-(bis(3-phenylsulfonyl)-1*H*-pyrazol-4-yl)benzene (8)

A mixture of compound **7** (1 mmol), chloranil (2.4 mmol) and xylene (20 ml) was refluxed for 23–26 h. Then, it was treated with 5 % sodium hydroxide solution. The organic extract was separated, washed with water, and dried (an. Na_2SO_4). The solvent was removed on a rotary evaporator. The resultant solid was recrystallized from 2-propanol.

*Spectral data for compounds (**8a–e**)*

*1,4-(Bis(3-phenylsulfonyl)-1H-pyrazol-4-yl)benzene (**8a**)* White solid; Mp. 257–259 °C. IR (KBr) (cm^{-1}): 3,257 (NH), 1,560 (C=N), 1,327, 1,137 (SO_2); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.61 (s, 2H, C_5–H), 7.32–8.01 (m, 14H, Ar–H), 10.62 (bs, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 127.5 (C–4), 131.3 (C–3), 135.0 (C–5), 128.6, 129.4, 133.5, 134.8, 136.5, 141.3 ppm (aromatic carbons). MS: (*m/z*) 491.55 $[M + H]^+$. Anal. Calcd. for $C_{24}H_{18}N_4O_4S_2$:C, 58.76; H, 3.70; N, 11.42 %. Found: C, 58.87; H, 3.76; N, 11.20 %.

*1,4-(Bis(3-(p-methylphenylsulfonyl)-1H-pyrazol-4-yl)benzene (**8b**)* White solid; Mp. 246–248 °C. IR (KBr) (cm^{-1}): 3,261 (NH), 1,575 (C=N), 1,335, 1,140 (SO_2); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.41 (s, 6H, Ar–CH_3), 6.68 (s, 2H, C_5–H),7.43–8.07 (m, 12H, Ar–H), 10.73 (bs, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.4 (Ar–CH_3), 128.4 (C–4), 132.6 (C–3), 136.2 (C–5), 128.8, 132.6, 135.1, 137.8, 138.6, 143.0 ppm (aromatic carbons). MS: (*m/z*) 519.61 $[M + H]^+$. Anal. Calcd. for $C_{26}H_{22}N_4O_4S_2$:C, 60.21; H, 4.28; N, 10.28 %. Found: C, 60.38; H, 4.38; N, 10.53 %.

1,4-(Bis(3-(p-chlorophenylsulfonyl)-1H-pyrazol-4-yl)benzene ***(8c)*** White solid; Mp. 281–283 °C. IR (KBr) (cm^{-1}): 3,254 (NH), 1,582 (C=N), 1,343, 1,143 (SO_2); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.83 (s, 2H, C_5–H), 7.51-8.14 (m, 12H, Ar–H), 10.85 (bs, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 129.8 (C–4), 133.5 (C–3), 137.3 (C–5), 127.5, 129.3, 134.2, 137.6, 139.1, 140.6 ppm (aromatic carbons). MS: (*m/z*) 560.44 $[M + H]^+$. Anal. Calcd. for $C_{24}H_{16}Cl_2N_4O_4S_2$:C, 51.53; H, 2.88; N, 10.01 %. Found: C, 51.46; H, 2.86; N, 10.15 %.

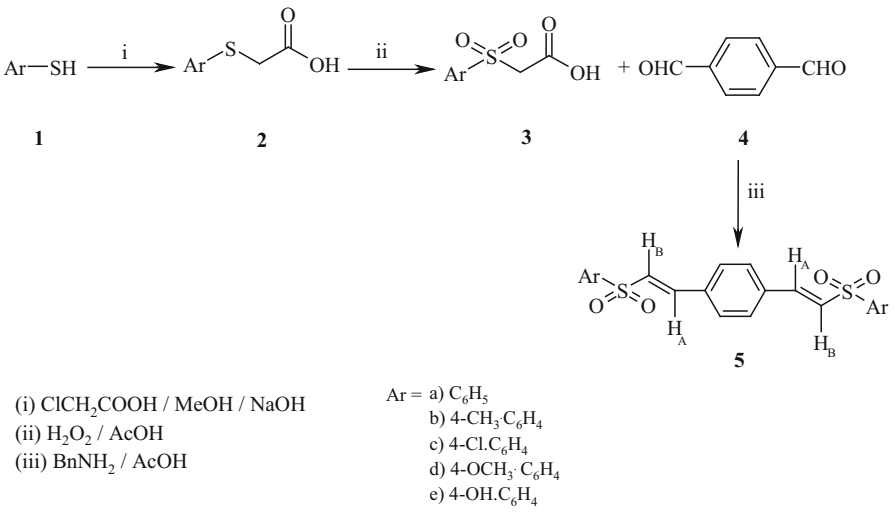
1,4-(Bis(3-(p-methoxyphenylsulfonyl)-1H-pyrazol-4-yl)benzene ***(8d)*** White solid; Mp. 275–277 °C. IR (KBr) (cm^{-1}): 3,258 (NH), 1,580 (C=N), 1,339, 1,136 (SO_2); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.89 (s, 6H, Ar–OCH_3), 6.76 (s, 2H, C_5–H), 7.48–8.12 (m, 12H, Ar–H), 10.79 (bs, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.6 (Ar–OCH_3), 129.2 (C–4), 132.7 (C–3), 136.9 (C–5), 115.4, 128.7, 129.6, 133.9, 137.6, 165.2 ppm (aromatic carbons). MS: (*m/z*) 551.61 $[M + H]^+$. Anal. Calcd. for $C_{26}H_{22}N_4O_6S_2$:C, 56.72; H, 4.03; N, 10.18 %. Found: C, 56.87; H, 4.10; N, 10.46 %.

1,4-(Bis(3-(p-hydroxyphenylsulfonyl)-1H-pyrazol-4-yl)benzene ***(8e)*** White solid; Mp. 249–251 °C. IR (KBr) (cm^{-1}): 3,260 (NH), 1,578 (C=N), 1,330, 1,131 (SO_2); ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.32 (s, 2H, Ar–OH), 6.65 (s, 2H, C_5–H), 7.39–8.05 (m, 12H, Ar–H), 10.64 (bs, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 127.7 (C–4), 131.9 (C–3), 135.4 (C–5), 116.5, 128.9, 129.6, 134.4, 136.7, 163.4 ppm (aromatic carbons). MS: (*m/z*) 523.55 $[M + H]^+$. Anal. Calcd. for $C_{24}H_{18}N_4O_6S_2$:C, 55.16; H, 3.47; N, 10.72 %. Found: C, 55.25; H, 3.50; N, 10.89 %.

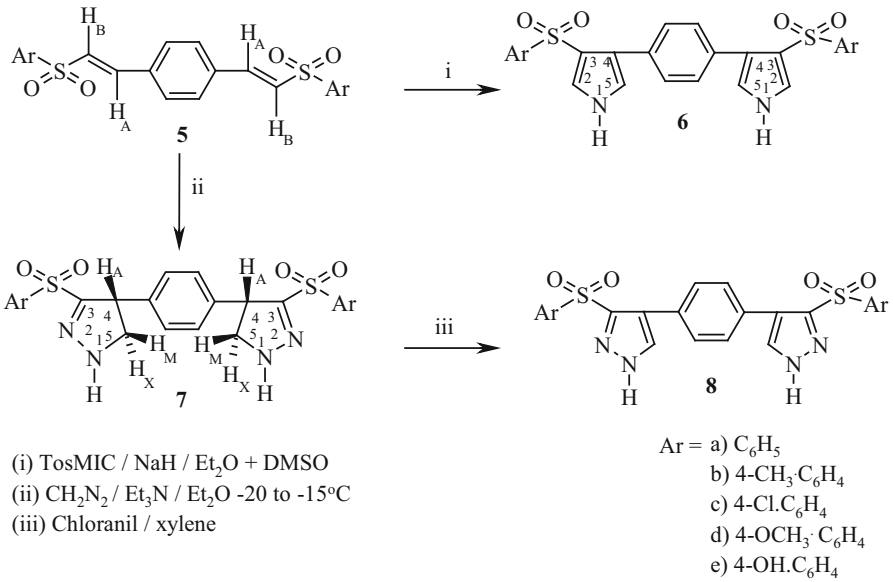
Results and discussion

The synthetic scheme involves the preparation of bis heterocycles viz., 1,4-(bis(3-arylsulfonyl)-1*H*-pyrrol-4-yl)benzene (**6**), 1,4-(bis(3-arylsulfonyl)-4,5-dihydro-(1*H*-pyrazol-4-yl))benzene (**7**) and 1,4-(bis(3-arylsulfonyl)-1*H*-pyrazol-4-yl)benzene (**8**) from the Michael acceptor 1,4-bis-(*E*)-2-(arylsulfonylvinyl)benzene (**5**). The compound **5** was prepared by the Knoevenagel condensation of arylsulfonylacetic acid (**3**) with terephthaldehyde (**4**) in the presence of benzylamine in AcOH. The arylsulfonylacetic acid (**3**) was in turn obtained by the reaction of thiophenol (**1**) with 2-chloroacetic acid followed by oxidation of the resultant arylthioacetic acid (**2**) with hydrogen peroxide in glacial acetic acid (Scheme 1). The ^{1}H NMR spectrum of **5a** exhibited two doublets at δ 7.19 and 7.63 ppm due to olefin protons, H_B and H_A. The downfield signal was assigned to H_A. The coupling constant value $J_{AB} = 15.3$ Hz indicated that they possess *trans* geometry.

1,3-Dipolar cycloaddition of dipolar reagents to dipolarophiles is one of the facile techniques for the preparation of five-membered heterocycles. The olefin functional group moiety present in the synthetic intermediate **5** was exploited to synthesize five-membered heterocycles- pyrroles and pyrazoles. The reaction of compound **5**



Scheme 1 Synthesis of 1,4-bis-(arylsulfonylvinyl)benzenes



Scheme 2 Synthesis of (1,4-phenylene)bis(arylsulfonylpyrroles and pyrazoles)

with tosylmethyl isocyanide (TosMIC) [3] in the presence of sodium hydride in a solvent mixture of DMSO and ether yielded 1,4-(bis(3-arylsulfonyl)-1*H*-pyrrol-4-yl)benzene (**6**) (Scheme 2). In the ^{1}H NMR spectrum of compound **6a**, the singlets due to C_2-H and C_5-H of pyrrole ring appeared at downfield region and merged with aromatic protons. Compound **6a** also showed a broad signal at 11.53 ppm belonging

to NH of pyrrole ring. This signal disappeared upon addition of D_2O. On the other hand, the 1,3-dipolar cycloaddition of ethereal diazomethane (CH_2N_2) [29] to compound **5** in the presence of Et_3N at −20 to −15 °C produced 1,4-(bis(3-arylsulfonyl)-4,5-dihydro-(1*H*-pyrazol-4-yl))benzene (**7**). The ^{1}H NMR spectrum of compound **7a** displayed an AMX splitting pattern for methine and methylene protons of pyrazoline ring. The three double doublets observed at δ 4.35, 3.87, 3.32 ppm were assigned to H_A, H_M, and H_X, respectively. The coupling constant values $J_{AM} = 11.4$, $J_{MX} = 10.6$ and $J_{AX} = 5.8$ Hz indicated that H_A, H_M are *cis*, H_A, H_X are *trans* and H_M, H_X are *geminal*. In addition to these, a broad singlet was observed at δ 6.63 ppm due to NH, which disappeared on deuteration.

The treatment of compound **7** with chloranil in xylene resulted in aromatized compound, 1,4-(bis(3-arylsulfonyl)-1*H*-pyrazol-4-yl)benzene (**8**) (Scheme 2). The absence of an AMX splitting pattern due to pyrazoline ring protons in the ^{1}H NMR spectrum of **8a** confirmed its formation. The structures of the compounds were further confirmed by IR, ^{13}C NMR, mass spectra and microanalyses.

Experimental procedure for antioxidant activity

2,2,-Diphenyl-1-picrylhydrazyl (DPPH) method

The hydrogen atom or electron donation ability of the compounds was measured from the bleaching of the purple colored methanol solution of 2,2,-diphenyl-1-picrylhydrazyl (DPPH) [30, 31]. This property makes it suitable for spectrophotometric studies. One milliliter of various concentrations of the test compounds (50, 75, and 100 μg/ml) in methanol were added to 4 ml of 0.004 % (w/v) methanol solution of DPPH. After a 30-min incubation period at room temperature, the absorbance was read against blank at 517 nm. The percent of inhibition (I %) of free radical production from DPPH was calculated by the following equation

$$I\,\% = \left[(A_{\text{control}} - A_{\text{sample}})/A_{\text{blank}}\right] \times 100$$

where A_{control} was the absorbance of the control reaction (containing methanolic DPPH and ascorbic acid), A_{sample} was the absorbance of the test compound (containing methanolic DPPH and test compound) and A_{blank} was the absorbance of the blank (containing only methanolic DPPH). Tests were carried out in triplicate.

The IC_{50} was calculated by the following equation

$$IC_{50}\,\text{in}\,\mu\text{gml}^{-1} = 50 \times 100/\%\,\text{Inhibition}$$

$$50\,\mu\text{M} = \%\,\text{of the}\,IC_{50}/\text{M.Wt. of the compound.}$$

Nitric oxide (NO) method

Nitric oxide scavenging activity was measured by slightly modified methods of Green et al. and Marcocci et al. [32, 33]. Nitric oxide radicals (NO) were generated from sodium nitroprusside. One milliliter of sodium nitroprusside (10 mm) and

1.5 ml of phosphate buffer saline (0.2 M, pH 7.4) were added to different concentrations (50, 75, and 100 μg/ml) of the test compounds and incubated for 150 min at 25 °C. After incubation, 1 ml of the reaction mixture was treated with 1 ml of Griess reagent (1 % sulfanilamide, 2 % H_3PO_4 and 0.1 % naphthylethylene-diamine dihydrochloride). The absorbance of the chromophore was measured at 546 nm. Ascorbic acid was used as the standard. Nitric oxide scavenging activity was calculated by the following equation

$$\% \text{ of scavenging} = \left[\left(A_{\text{control}} - A_{\text{sample}}\right)/A_{\text{blank}}\right] \times 100$$

where A_{control} was the absorbance of the control reaction (containing all reagents and ascorbic acid), A_{sample} was the absorbance of the test compound (containing all reagents and test compound) and A_{blank} was the absorbance of the blank (containing only reagents). Tests were carried out in triplicate.

Hydrogen peroxide (H_2O_2) method

The H_2O_2 scavenging ability of the test compound was determined according to the method of Ruch et al. [34]. A solution of H_2O_2 (40 mm) was prepared in phosphate

Table 1 The in vitro antioxidant activity of compounds **5a–e** to **8a–e** in DPPH method

Compound	Concentration (μg/ml)		
	50	75	100
5a	59.23 ± 0.40	61.36 ± 0.31	63.98 ± 0.33
5b	67.40 ± 0.25	69.54 ± 0.21	71.43 ± 0.17
5c	47.90 ± 0.66	49.51 ± 0.62	52.65 ± 0.54
5d	69.23 ± 0.23	71.35 ± 0.17	72.86 ± 0.16
5e	68.61 ± 0.24	70.41 ± 0.15	71.92 ± 0.18
6a	50.11 ± 0.60	51.53 ± 0.56	55.16 ± 0.48
6b	55.66 ± 0.48	57.90 ± 0.43	58.04 ± 0.41
6c	45.46 ± 0.71	46.93 ± 0.67	48.82 ± 0.64
6d	63.50 ± 0.35	66.69 ± 0.27	68.93 ± 0.26
6e	62.11 ± 0.38	64.69 ± 0.32	66.04 ± 0.29
7a	42.13 ± 0.79	44.95 ± 0.65	48.20 ± 0.67
7b	43.85 ± 0.75	46.12 ± 0.68	49.46 ± 0.62
7c	41.78 ± 0.86	44.18 ± 0.61	47.85 ± 0.66
7d	49.54 ± 0.63	50.13 ± 0.59	51.97 ± 0.56
7e	48.73 ± 0.62	49.86 ± 0.62	52.10 ± 0.54
8a	52.92 ± 0.54	56.10 ± 0.47	57.23 ± 0.42
8b	57.54 ± 0.44	59.55 ± 0.42	61.52 ± 0.35
8c	46.53 ± 0.69	47.03 ± 0.68	51.18 ± 0.55
8d	65.14 ± 0.29	67.32 ± 0.25	69.41 ± 0.22
8e	63.84 ± 0.32	66.75 ± 0.28	69.71 ± 0.25
Ascorbic acid	61.44 ± 0.37	64.66 ± 0.29	66.05 ± 0.26
Blank	–	–	–

– showed no scavenging activity. Values were the means of three replicates ± SD

buffer (pH 7.4); 50-, 75-, and 100-μg/ml concentrations of the test compounds in 3.4 ml phosphate buffer were added to H_2O_2 solution (0.6 ml, 40 mm). The absorbance value of the reaction mixture was recorded at 230 nm. The percent of scavenging of H_2O_2 was calculated by the following equation

$$\% \text{ of scavenging} = \left[\left(A_{\text{control}} - A_{\text{sample}}\right)/A_{\text{blank}}\right] \times 100$$

where A_{control} was the absorbance of the control reaction (containing all reagents and Ascorbic acid), A_{sample} was the absorbance of the test compound (containing all reagents and test compound) and A_{blank} was the absorbance of the blank (containing only reagents). Tests were carried out in triplicate.

Antioxidant activity

The compounds **5a–e** to **8a–e** were tested for antioxidant properties by DPPH, NO, and H_2O_2 methods at three different concentrations 50, 75, and 100 μg ml^{-1}. The observed data on the antioxidant activity of the compounds and control drug are shown in Tables 1, 2, 3, 4. Amongst all the tested compounds, 1,4-bis((*E*)-2-(*p*-methoxyphenylsulfonyl)vinyl)benzene (**5d**) was found to be the most potential

Table 2 The IC_{50} of the compounds **5a–e** to **8a–e** in DPPH method

Compound	Concentration 50 (μmol ml^{-1})
5a	0.1028 ± 0.0018
5b	0.0845 ± 0.0020
5c	0.1088 ± 0.0011
5d	0.0767 ± 0.0019
5e	0.0819 ± 0.0020
6a	0.1021 ± 0.0012
6b	0.0869 ± 0.0013
6c	0.0986 ± 0.0008
6d	0.0717 ± 0.0016
6e	0.0773 ± 0.0016
7a	0.1199 ± 0.0010
7b	0.1090 ± 0.0011
7c	0.1061 ± 0.0009
7d	0.0909 ± 0.0010
7e	0.0974 ± 0.0010
8a	0.0963 ± 0.0013
8b	0.0837 ± 0.0013
8c	0.0960 ± 0.0009
8d	0.0696 ± 0.0015
8e	0.0749 ± 0.0015
Ascorbic acid	0.2310 ± 0.0065
Blank	–

– showed no scavenging activity. Values were the means of three replicates ± SD

antioxidant agent. This may be due to effective conjugation. On the other hand, 1,4-(bis(3-arylsulfonyl)-1*H*-pyrrol-4-yl)benzenes **6a–e** and 1,4-(bis(3-arylsulfonyl)-1*H*-pyrazol-4-yl)benzenes **8a–e** exhibited better antioxidant activity than 1,4-(bis(3-arylsulfonyl)-4,5-dihydro-(1*H*-pyrazol-4-yl))benzenes **7a–e**. It was also inferred that those having methyl, methoxy, and hydroxy substituents on the aromatic ring showed higher activity than the other substituents, which may due to +I effect and +M effect. This was evidenced that the compounds **5b**, **5d**, **5e**, **8d**, and **8e** showed excellent radical scavenging activity in all the three methods evaluated when compared with the standard ascorbic acid. Furthermore, it was perceived that the compounds, **5a**, **6b**, **6d**, **6e,** and **8b** exhibited good activity whereas **7a–e** displayed the least activity. Among the aromatized compounds, **8a–e** displayed slightly higher activity than **6a–e**. In general, it was noticed that electron-donating groups enhances the activity. The IC_{50} value of the standard drug ascorbic acid in DPPH method was found to be 40.69 μg ml^{-1} at 50 μg ml^{-1} whereas IC_{50} values of the compounds **5b**, **5d, 5e**, **8d**, and **8e** were found to be 37.09, 36.11, 36.43, 38.37, and 39.16 μg ml^{-1}, respectively (Table 2). It was also observed that radical scavenging activity increases with growing in concentration in all the three methods.

Table 3 The in vitro antioxidant activity of compounds **5a–e** to **8a–e** in NO method

Compound	Concentration (μg/ml)		
	50	75	100
5a	67.04 ± 0.25	68.24 ± 0.24	71.69 ± 0.17
5b	76.71 ± 0.11	77.34 ± 0.10	79.74 ± 0.06
5c	60.93 ± 0.31	62.13 ± 0.39	64.61 ± 0.30
5d	79.54 ± 0.08	80.45 ± 0.06	84.53 ± 0.04
5e	77.12 ± 0.10	78.76 ± 0.09	80.15 ± 0.07
6a	62.71 ± 0.29	63.14 ± 0.30	66.83 ± 0.28
6b	65.73 ± 0.27	66.47 ± 0.26	70.02 ± 0.19
6c	58.15 ± 0.34	60.09 ± 0.32	61.89 ± 0.32
6d	68.16 ± 0.14	72.61 ± 0.14	74.05 ± 0.12
6e	67.78 ± 0.24	69.82 ± 0.23	72.94 ± 0.16
7a	49.12 ± 0.63	50.97 ± 0.42	51.72 ± 0.54
7b	53.80 ± 0.49	55.82 ± 0.37	55.64 ± 0.58
7c	45.26 ± 0.65	47.12 ± 0.66	48.38 ± 0.62
7d	57.53 ± 0.43	59.56 ± 0.33	60.25 ± 0.40
7e	54.34 ± 0.48	56.71 ± 0.36	58.92 ± 0.42
8a	64.15 ± 0.28	65.36 ± 0.27	67.58 ± 0.25
8b	66.48 ± 0.26	67.52 ± 0.25	70.74 ± 0.18
8c	60.13 ± 0.32	61.68 ± 0.34	63.86 ± 0.31
8d	74.58 ± 0.12	75.89 ± 0.13	77.38 ± 0.10
8e	72.63 ± 0.15	73.92 ± 0.15	75.63 ± 0.13
Ascorbic acid	69.21 ± 0.21	72.60 ± 0.16	74.51 ± 0.15
Blank	–	–	–

– showed no scavenging activity. Values were the means of three replicates ± SD

Table 4 The in vitro antioxidant activity of compounds **5a–e** to **8a–e** in H_2O_2 method

Compound	Concentration (μg/ml)		
	50	75	100
5a	65.41 ± 0.29	66.68 ± 0.26	68.56 ± 0.27
5b	74.60 ± 0.13	76.96 ± 0.10	79.47 ± 0.08
5c	59.63 ± 0.39	61.34 ± 0.37	63.38 ± 0.33
5d	77.75 ± 0.10	78.08 ± 0.09	80.58 ± 0.06
5e	75.45 ± 0.13	77.54 ± 0.10	79.65 ± 0.08
6a	60.09 ± 0.38	62.21 ± 0.36	64.32 ± 0.31
6b	63.90 ± 0.32	64.15 ± 0.31	66.14 ± 0.27
6c	57.54 ± 0.42	59.13 ± 0.40	61.75 ± 0.36
6d	68.47 ± 0.24	71.96 ± 0.17	75.84 ± 0.16
6e	66.81 ± 0.27	68.75 ± 0.26	74.93 ± 0.28
7a	50.44 ± 0.53	51.27 ± 0.52	53.58 ± 0.49
7b	51.56 ± 0.49	53.96 ± 0.51	55.14 ± 0.48
7c	48.12 ± 0.56	60.34 ± 0.53	52.45 ± 0.51
7d	54.18 ± 0.45	56.26 ± 0.47	58.42 ± 0.41
7e	53.71 ± 0.48	55.81 ± 0.45	57.38 ± 0.42
8a	62.54 ± 0.34	63.74 ± 0.32	65.08 ± 0.30
8b	64.76 ± 0.30	65.02 ± 0.30	66.91 ± 0.26
8c	58.16 ± 0.41	59.54 ± 0.39	62.11 ± 0.34
8d	74.15 ± 0.12	76.05 ± 0.11	78.85 ± 0.09
8e	71.52 ± 0.17	73.78 ± 0.16	75.61 ± 0.13
Ascorbic acid	67.86 ± 0.25	69.13 ± 0.19	71.34 ± 0.17
Blank	–	–	–

– showed no scavenging activity. Values were the means of three replicates ± SD

Conclusions

The Michael acceptor 1,4-bis(arylsulfonylvinyl)benzene (**5**) was exploited to prepare a new series of (1,4-phenylene)bis(arylsufonylpyrroles) (**6**) and (1,4-phenylene)bis(arylsufonyl pyrazoles) (**8**) adopting simple and versatile 1,3-dipolar cycloaddition methodology. All the compounds were tested for antioxidant activity. Amongst the tested compounds, **5d** was identified as the potential antioxidant agent. It was also noticed that electron-donating groups enhanced the antioxidant activity.

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