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Article

Synthesis and Antioxidant Activity of 1,4-[Bis(3-arylmethanesulfonyl pyrrolyl and pyrazolyl)]benzenes

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Uma variedade de (1,4-fenileno)bis(arilmetanossulfonilpirrois e pirazois) foram preparados através da cicloadição de reagentes 1,3-dipolares (isocianeto de tosilmetila e diazometano) com 1,4-bis(*E*)-2-[(arilmetanossulfonil)vinil]benzenos, como receptores de Michael. Todos os compostos sintetizados foram avaliados como antioxidantes. Entre os compostos testados, um deles exibiu excelente atividade seqüestradora de radicais nos três métodos avaliados, quando comparado com o ácido ascórbico padrão. Por outro lado, os 1,4-[bis(3-arilmetanossulfonil)-1*H*-pirazol-4-il]benzenos exibiram, comparativamente, maior atividade antioxidante do que os 1,4-[bis (3-arilmetanossulfonil)-1*H*-pirrol-4-il]benzenos. Em geral, foi observado que compostos que possuem um substituinte metoxila no anel aromático, exibem maior atividade antioxidante do que os outros substituintes.

A variety of (1,4-phenylene)bis(arylmethanesulfonylpyrroles and pyrazoles) were prepared by the cycloaddition of 1,3-dipolar reagents, tosylmethyl isocyanide and diazomethane to the Michael acceptor, 1,4-bis(*E*)-2-((arylmethanesulfonyl)vinyl)benzene. All the compounds were evaluated for antioxidant activity. Amongst the tested compounds, one of them displayed excellent radical scavenging activity in all the three methods evaluated when compared with the standard Ascorbic acid. On the other hand, 1,4-(bis(3-arylmethanesulfonyl)-1*H*-pyrazol-4-yl)benzenes exhibited comparatively higher antioxidant activity than 1,4-(bis(3-arylmethanesulfonyl)-1*H*-pyrrol-4-yl) benzenes. In general, it was observed that compounds having methoxy substitutent on aromatic ring displayed greater antioxidant activity than the other substituents.

Keywords: Michael acceptor, pyrrole, pyrazoline, pyrazole, antioxidant activity

Introduction

The chemistry of activated olefins has gained importance because of their utility as valuable intermediates in a variety of synthetic transformations and useful as building blocks in the synthesis of biologically potent heterocycles.[1] The α,β-unsaturated sulfones possess many biological properties including anticancer,[2] antimalarial,[3] anti-inflammatory,[4] antioxidant,[5] antibacterial, anti-HIV,[6] and antifungal.[7] They are also excellent leading skeletons for modification of drug design and development. Pyrroles and their derivatives represent one of the most pharmaceutically important class of *N*-heterocyclic compounds because of their remarkable antibacterial, antiviral, anti-inflammatory, antitumoral, and antioxidant activities.[8] Apart from these, pyrroles are the core units of many natural products and serve as building blocks for porphyrin synthesis.[9] Besides the Paal-Knorr[10] type condensation reaction, various synthetic methods have been developed to synthesize pyrroles, including Hantzsch synthesis,[11] [3+2] cycloaddition of 1,3-dipolar reagents to alkynes,[12] and olefin cross-metathesis.[13] Pyrazole and its derivatives have been attracting a great deal of interest due to their various pharmaceutical applications.[14] Pyrazoles display antimicrobial,[15] antidepressant,[16] immunosuppressive,[17] anticonvulsant,[18] antitumor,[19] and anti-inflammatory[20] activities. In fact, various pyrazoles were used as molecular scaffolds in several drugs such as metamizole,[21] difenamizole,[22] lonazolac,[23] phenidone,[24] and mepirizole.[25] The general methods for the synthesis of pyrazoles are Pechmann synthesis[26] of 1,3-dipolar cycloaddition of diazo compounds to alkenes[27] or alkynes[28] and the Knorr synthesis[29] between hydrazines and 1,3-difunctional compounds. We have reported the 1,3-dipolar cycloaddition of dipolar reagents to a variety of activated mono and bis(olefins) and studied their antimicrobial and antioxidant activities.[30,31] With this

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background and in our continued interest on the synthesis of biologically potent heterocycles, it was thought of exploiting the Michael acceptor, 1,4-bis(*E*)-2-((arylmethanesulfonyl) vinyl)benzene to build pyrrole and pyrazole rings and to investigate their antioxidant potentiality.

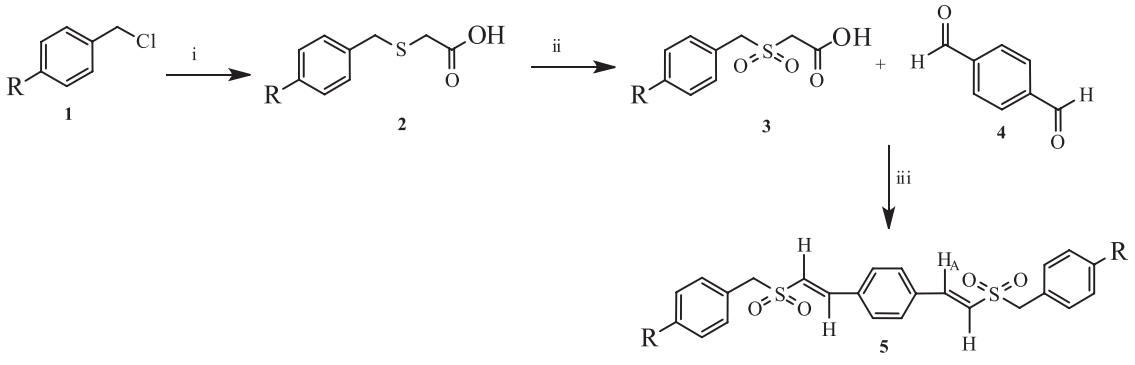
Results and Discussion

The synthetic pathway to achieve the target molecules is depicted in schemes 1 and 2. The Michael acceptor, 1,4-bis(*E*)-2-((arylmethanesulfonyl)vinyl)benzenes (**5a-d**) were prepared by the Knoevenagel reaction of arylmethanesulfonylacetic acids (**3a-d**) with terephthaldehyde (**4**). The compounds **3a-d** were obtained by the treatment of arylmethane chloride with thioglycolic acid followed by oxidation with hydrogen peroxide and glacial acetic acid. The ^{1}H NMR spectrum of compound **5a** displayed a singlet at 4.55 ppm due to methylene protons and two doublets at 7.52, and 7.48 ppm due to olefin protons H_A and H_B, respectively. The coupling constant value J_{AB} = 15.5 Hz indicated that they are in *trans* geometry (Scheme 1).

The olefin functional group present in compounds **5a-d** was utilized to develop pyrrole and pyrazole rings. Treatment of compounds **5a-d** with tosylmethyl isocyanide in the presence of sodium hydride in a solvent mixture of dimethylsulfoxide and ether gave 1,4-(bis(3-arylmethanesulfonyl)-1*H*-pyrrol-4-yl)benzenes (**6a-d**). The ^{1}H NMR spectrum of **6a** exhibited a singlet at 4.23 ppm due to methylene protons. However, the singlets corresponding to 2CH of pyrrole ring were merged with aromatic protons and appeared as a multiplet. In addition to these, a broad singlet was observed at 11.85 ppm due to NH which disappeared on deuteration. Furthermore, the 1,3-dipolar cycloaddition of diazomethane to compounds **5a-d** at –20 °C to –15 °C in the presence of triethylamine in ether produced 1,4-(bis(3-arylmethanesulfonyl)-4,5-dihydro-(1*H*-pyrazol-4-yl))benzenes (**7a-d**). The ^{1}H NMR spectrum of compound **7a** showed an AMX splitting pattern for methine and methylene protons of pyrazoline ring. The three double doublets observed at 4.46, 4.17, and 3.75 ppm were assigned to H_A, H_M and H_X, respectively. The coupling constant J_{AM} 12.2, J_{Mx} 11.6, and J_{Ax} 6.4 Hz indicated that H_A, H_M are *cis*, H_A, H_X are *trans* and H_M, H_X are *geminal*. The compound **7a** was also exhibited a singlet at 4.09 ppm for methylene protons. Apart from these, a broad singlet was observed at 6.53 ppm due to NH which disappeared on deuteration. Thus, in the ^{1}H NMR spectrum of **7a** the two pyrazoline ring protons displayed signals in the same region indicating that the molecule is highly symmetric. This was further evidenced by the appearance of 10 carbon signals in its ^{13}C NMR spectrum. The reaction of compounds **7a-d** with chloranil in xylene resulted in aromatized compounds 1,4-(bis(3-arylmethanesulfonyl)-1*H*-pyrazol-4-yl)benzenes (**8a-d**) (Scheme 2). The absence of an AMX splitting pattern in the ^{1}H NMR spectrum of **8a** confirmed its formation. Moreover in **8a**, a singlet at 4.62 ppm, and another singlet at 6.92 ppm were observed due to methylene and CH protons, respectively. A broad singlet due to NH was also appeared at 10.40 ppm, and disappeared when D_2O was added. The structures of the compounds were further established by IR, ^{13}C NMR spectra and elemental analyses.

In vitro antioxidant activity

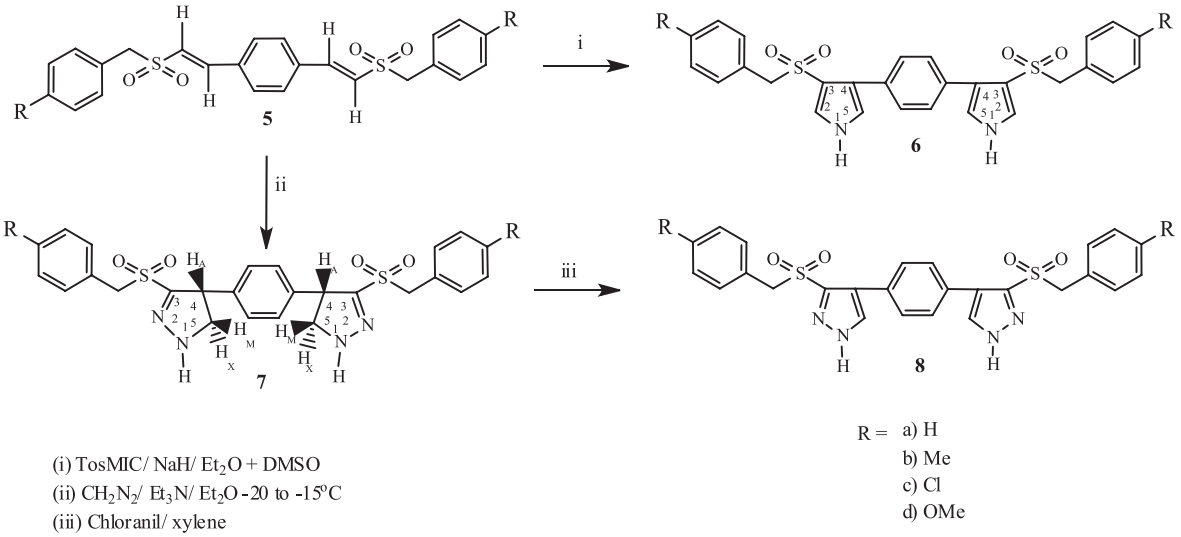
The compounds **5a-d**-**8a-d** were evaluated for antioxidant property by 2,2'-diphenyl-1-picrylhydrazyl (DPPH),[32,33] nitric oxide (NO),[34,35] and hydrogen peroxide (H_2O_2)[36] methods. The observed data on the antioxidant activity of the compounds and control drug are shown in Table 1 and Figure 1. The aim of this study is to identify



(i) $SHCH_2COOH$ / NaOH / MeOH
(ii) H_2O_2 / AcOH
(iii) $BzNH_2$ / AcOH

R = a) H
b) Me
c) Cl
d) OMe

Scheme 1.



Scheme 2.

the potential heterocyclic compound for antioxidant activity. Amongst the tested compounds 1,4-bis(*E*)-2-((arylmethanesulfonyl)-vinyl)benzenes (**5a-d**) were found to be potential antioxidant agents.This may be due to effective conjugation. On the other hand, the 1,4-(bis(3-arylmethanesulfonyl)-1*H*-pyrazol-4-yl)benzenes (**8a**-**d**) exhibited comparatively higher antioxidant activity than 1,4-(bis(3-arylmethanesulfonyl)-1*H*-pyrrol-4-yl)benzenes (**6a**-**d**). The presence of methoxy substitutent on the aromatic ring enhanced the activity which may be due to +M effect. This was evidenced that the compounds **5d** and **8d** showed excellent radical scavenging activity in all the three methods evaluated when compared with the standard ascorbic acid. It was also perceived that the compounds **5b**, **6d**, and **8b** exhibited good activity. However, the compound **7d** displayed least activity, whereas compounds **7a**-**c** showed no activity. The IC_{50} value of the standard drug ascorbic acid in DPPH method was found to be 59.65 at 100 μg mL^{-1} whereas IC_{50} values of the compounds **5d** and **8d** were found to be 56.45 and 57.08 μg mL^{-1}, respectively (Table 2). Besides, the perusal of Table 1 and Figure 1 indicated that radical scavenging activity in all the three

Table 1.The *in vitro* antioxidant activity of compounds **5a-d**–**8a-d** in all three methods

Compd. No.	Concentration / μg mL^{-1} (%)								
	DPPH Method			NO Method			H_2O_2 Method		
	50	75	100	50	75	100	50	75	100
5a	66.20 ± 0.31	70.75 ± 0.27	72.69 ± 0.24	65.45 ± 0.37	71.91 ± 0.29	73.82 ± 0.25	68.04 ± 0.30	71.26 ± 0.24	73.48 ± 0.23
5b	72.18 ± 0.09	76.67 ± 0.08	79.35 ± 0.06	74.76 ± 0.08	78.95 ± 0.06	80.02 ± 0.04	73.30 ± 0.12	77.19 ± 0.07	70.88 ± 0.02
5c	57.72 ± 0.54	62.24 ± 0.45	64.23 ± 0.39	60.80 ± 0.45	64.06 ± 0.43	66.53 ± 0.32	59.73 ± 0.52	63.89 ± 0.46	65.92 ± 0.42
5d	82.12 ± 0.07	85.79 ± 0.04	88.56 ± 0.02	84.15 ± 0.03	88.68 ± 0.09	90.85 ± 0.07	83.52 ± 0.04	86.97 ± 0.01	89.62 ± 0.09
6a	50.26 ± 0.48	53.06 ± 0.46	55.11 ± 0.38	52.41 ± 0.43	54.93 ± 0.34	56.78 ± 0.28	51.73 ± 0.38	53.94 ± 0.32	55.29 ± 0.25
6b	54.15 ± 0.42	57.36 ± 0.34	60.54 ± 0.30	57.70 ± 0.39	59.76 ± 0.30	63.14 ± 0.29	56.09 ± 0.44	58.83 ± 0.35	62.21 ± 0.27
6c	48.07 ± 0.63	50.12 ± 0.56	52.37 ± 0.40	50.32 ± 0.56	54.19 ± 0.49	56.81 ± 0.48	49.44 ± 0.64	52.27 ± 0.59	54.58 ± 0.49
6d	69.83 ± 0.32	71.69 ± 0.26	73.24 ± 0.22	71.26 ± 0.24	74.57 ± 0.18	77.61 ± 0.14	70.12 ± 0.23	72.45 ± 0.19	75.24 ± 0.14
7a	-	-	-	-	-	-	-	-	-
7b	-	-	-	-	-	-	-	-	-
7c	-	-	-	-	-	-	-	-	-
7d	39.48 ± 0.79	41.05 ± 0.73	44.76 ± 0.71	48.14 ± 0.63	51.63 ± 0.52	54.03 ± 0.49	46.39 ± 0.73	49.83 ± 0.69	51.32 ± 0.64
8a	62.40 ± 0.43	65.81 ± 0.48	69.72 ± 0.27	64.28 ± 0.29	68.53 ± 0.23	72.36 ± 0.14	66.62 ± 0.48	65.35 ± 0.39	70.34 ± 0.29
8b	70.31 ± 0.24	73.64 ± 0.18	75.46 ± 0.15	73.75 ± 0.19	75.10 ± 0.16	79.25 ± 0.09	72.85 ± 0.18	74.70 ± 0.16	77.42 ± 0.11
8c	55.53 ± 0.57	57.75 ± 0.52	61.80 ± 0.47	57.65 ± 0.50	61.64 ± 0.45	64.09 ± 0.39	56.10 ± 0.50	59.23 ± 0.42	63.37 ± 0.33
8d	78.48 ± 0.16	82.18 ± 0.11	87.59 ± 0.12	80.12 ± 0.15	83.01 ± 0.08	89.36 ± 0.06	79.54 ± 0.14	81.13 ± 0.09	87.70 ± 0.06
Ascorbic acid	77.15 ± 0.42	80.95 ± 0.39	83.82 ± 0.81	78.23 ± 0.17	81.46 ± 1.37	82.79 ± 0.80	77.68 ± 0.51	79.27 ± 1.29	83.16 ± 0.44
Blank	-	-	-	-	-	-	-	-	-

(-) Showed no scavenging activity. Values were the means of three replicates ± SD.

Table 2.The IC_{50} of compounds **5a-d**-**8a-d**

Comp. No.	IC_{50} / μmol mL^{-1}
5a	0.156 ± 0.63
5b	0.135 ± 0.47
5c	0.153 ± 0.89
5d	0.111 ± 0.51
6a	0.175 ± 0.78
6b	0.151 ± 0.65
6c	0.163 ± 0.94
6d	0.118 ± 0.42
7a	-
7b	-
7c	-
7d	0.191 ± 0.38
8a	0.138 ± 0.54
8b	0.121 ± 0.71
8c	0.097 ± 0.45
8d	0.098 ± 0.29
Ascorbic acid	0.124 ± 0.64
Blank	-

methods increases with increase in concentration.

Experimental

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 IR 200 FT–IR spectrometer as KBr pellets and the wave numbers were given in cm^{-1}. The ^1H NMR spectra were recorded in DMSO-d_6 on a Bruker-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 elemental analyses were carried out on a Perkin-Elmer 240C elemental analyzer. The antioxidant property was performed by using Shimadzu UV-2450 spectrophotometer. The arylmethanesulfonylacetic acids (**3a-d**) were prepared as per the literature procedure.[37]

General procedure for the synthesis of 1,4-bis(*E*)-2-((arylmethanesulfonyl)vinyl)benzenes (**5a–d**)

To a solution of arylmethanesulfonylacetic acids (**3a-d**) (2 mmol) in glacial acetic acid (10 mL^{-1}), terephthaldehyde (**4**) (1 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^{-1}) and left overnight in a refrigerator. The separated solid was collected and washed with methanol. The filtrate was diluted with ether and washed successively with a saturated solution of sodium bicarbonate, sodium bisulfite, dilute hydrochloric acid and water. The organic layer was dried over anhydrous sodium sulfate. 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.

1,4-Bis(*E*)-2-((phenylmethanesulfonyl)vinyl)benzene (**5a**)

mp 226-228 °C; IR (KBr) ν_{max}/cm^{-1} 1620, 1336, 1136; ^1H NMR (400 MHz, DMSO-d_6) δ 4.55 (s, 4H, CH_2), 7.48 (d, 2H, J_{AB} 15.5, CH), 7.52 (d, 2H, J_{AB} 15.5, CH), 7.30–7.73 (m, 14H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 60.3,

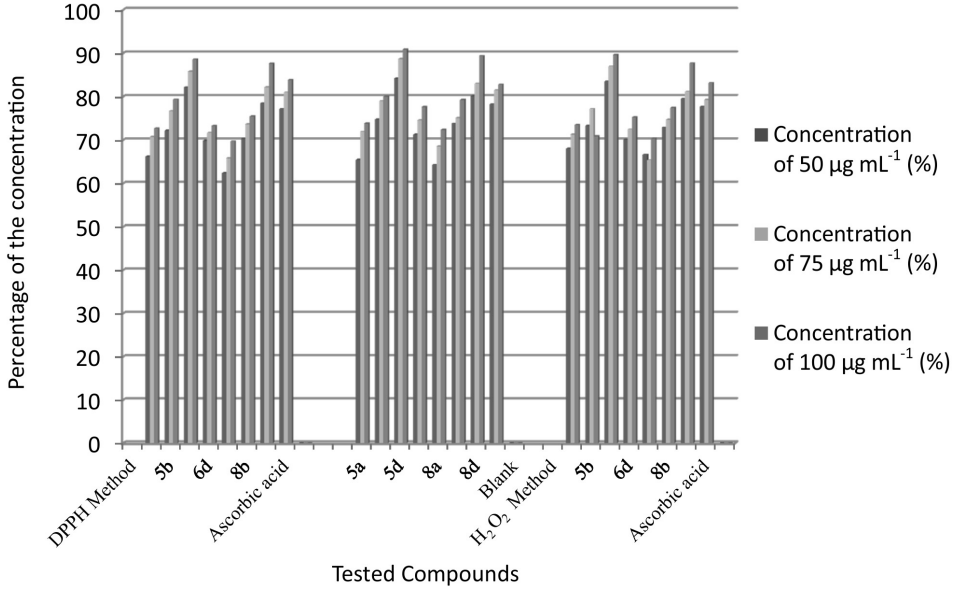


Figure1. The *in-vitro* antioxidant activity of compounds **5a-d**-**8a-d** in all three methods.

128.0, 128.8, 129.1, 129.6, 131.5, 135.1, 142.5; calcd. for $C_{24}H_{22}O_4S_2$: *m/z* 438.56; C, 65.73; H, 5.06.

1,4-Bis(*E*)-2-((p-methylphenylmethanesulfonyl)vinyl) benzene (**5b**)

mp 243-245 °C; IR (KBr) ν_{max}/cm^{-1} 1615, 1329, 1143; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.41 (s, 6H, CH_3), 4.52 (s, 4H, CH_2), 7.45 (d, 2H, J_{AB} 15.6, CH), 7.51 (d, 2H, J_{AB} 15.6, CH), 7.28–7.71 (m, 12H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.7, 59.5, 128.3, 129.0, 129.5, 129.8, 131.6, 135.4, 142.7; calcd. for $C_{26}H_{26}O_4S_2$: *m/z* 466.61; C, 66.92; H, 5.52.

1,4-Bis(*E*)-2-((p-chlorophenylmethanesulfonyl)vinyl) benzene (**5c**)

mp 260-262 °C; IR (KBr) ν_{max} /cm^{-1} 1627, 1346, 1138; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.60 (s, 4H, CH_2), 7.52 (d, 2H, J_{AB} 15.9, CH), 7.58 (d, 2H, J_{AB} 15.9, CH), 7.46-7.83 (m, 12H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 60.5, 128.4, 129.9, 130.2, 130.9, 131.8, 135.3, 143.1; calcd. for $C_{24}H_{20}Cl_2O_4S_2$: *m/z* 507.45; C, 56.81; H, 3.97.

1,4-Bis(*E*)-2-((p-methoxyphenylmethanesulfonyl)vinyl) benzene (**5d**)

mp 259-261 °C; IR (KBr) ν_{max}/cm^{-1} 1625, 1338, 1140; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.92 (s, 6H, OCH_3), 4.58 (s, 4H, CH_2), 7.50 (d, 2H, J_{AB} 15.7, CH), 7.55 (d, 2H, J_{AB} -15.7, CH), 7.42-7.78 (m, 12H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 55.3, 59.2, 128.5, 129.3, 129.7, 130.0, 131.4, 135.6, 142.9; calcd. for $C_{26}H_{26}O_6S_2$: *m/z* 498.61; C, 62.63; H, 5.26.

General procedure for the synthesis of 1,4-(bis(3-arylmethanesulfonyl)-1*H*-pyrrol-4-yl)benzenes (**6a-d**)

The compounds **5a-d** (1 mmol) and tosylmethyl isocyanide (2 mmol) in ether-dimethylsulfoxide (2:1) was added dropwise under stirring to a stirred suspension of sodium hydride (50 mg) in ether (20 mL^{-1}) at room temperature and stirring was continued for 8-10 h. Then, water was added to the reaction mixture and extracted with ether. The ethereal layer was dried over anhydrous sodium sulfate and filtered. Evaporation of the solvent under vacuum gave a crude product which was purified by column chromatography (silica gel, 60-120 mesh) using hexane and ethyl acetate (4:1) as eluent.

1,4-(Bis(3-phenylmethanesulfonyl)-1*H*-pyrrol-4-yl)benzene (**6a**)

mp 245–247 °C; IR (KBr) ν_{max}/cm^{-1} 3258, 1624, 1339, 1145; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.23 (s, 4H, CH_2), 7.01-7.75 (m, 18H, 2CH, Ar-H), 11.85 (bs, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 60.9, 118.6, 120.0, 122.5, 126.3, 128.0, 128.6, 129.1, 130.5, 131.9; calcd. for $C_{28}H_{24}N_2O_4S_2$: *m/z* 516.63; C, 65.09; H, 4.68; N, 5.42. Found: C, 65.18; H, 4.71; N, 5.36.

1,4-(Bis(3-p-methylphenylmethanesulfonyl)-1*H*-pyrrol-4-yl) benzene (**6b**)

mp 252-254 °C; IR (KBr) ν_{max}/cm^{-1} 3255, 1621, 1332, 1144; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.39 (s, 6H, CH_3), 4.21 (s, 4H, CH_2), 6.98-7.72 (m, 16H, 2CH, Ar-H), 11.82 (bs, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.5, 60.6, 118.2, 119.7, 121.5, 126.0, 127.6, 128.2, 130.1, 131.7, 132.4; calcd. for $C_{30}H_{28}N_2O_4S_2$: 544.68; C, 66.15; H, 5.18; N, 5.14. Found: C, 66.26; H, 5.23; N, 5.30.

1,4-(Bis(3-p-chlorophenylmethanesulfonyl)-1*H*-pyrrol-4-yl) benzene (**6c**)

mp 275-277 °C; IR (KBr) ν_{max}/cm^{-1} 3269, 1632, 1345, 1150; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.36 (s, 4H, CH_2), 7.09-7.83 (m, 16H, 2CH, Ar-H), 11.91 (bs, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 61.8, 119.4, 120.7, 123.2, 127.8, 127.5, 130.8, 131.3, 132.7, 133.4; calcd. for $C_{28}H_{22}Cl_2N_2O_4S_2$: *m/z* 585.52; C, 57.44; H, 3.79; N, 4.78. Found: C, 57.50; H, 3.80; N, 4.88.

1,4-(Bis(3-p-methoxyphenylmethanesulfonyl)-1*H*-pyrrol-4-yl)benzene (**6d**)

mp 268-270 °C; IR (KBr) ν_{max}/cm^{-1} 3253, 1637, 1341, 1142; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.89 (s, 6H, OCH_3), 4.34 (s, 4H, CH_2), 7.06-7.80 (m, 16H, 2CH, Ar-H), 11.89 (bs, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 55.1, 61.5, 119.2, 120.4, 122.8, 127.1, 130.4, 131.0, 132.2, 132.6, 133.5; calcd. for $C_{30}H_{28}N_2O_6S_2$: *m/z* 576.68, found: 576.69; C, 62.48; H, 4.89; N, 4.86. Found: C, 62.55; H, 4.93; N, 4.97.

General procedure for the synthesis of 1,4-(bis(3-arylmethanesulfonyl)-4,5-dihydro-(1*H*-pyrazol-4-yl)) benzenes (**7a-d**)

To a well cooled solution of compounds **5a-d** (0.25 mmol) in dichloromethane (20 mL^{-1}), an ice-cold ethereal solution of diazomethane (40 mL^{-1}, 0.4 mol L^{-1}) and triethylamine (0.2 g) were added. The reaction mixture was kept at –20 ºC to –15 ºC for 40-48 h. The solvent was removed under reduced pressure and the resultant solid was purified by column chromatography (silica gel, 60-120 mesh) using ethyl acetate and hexane (1:4) as eluent.

1,4-(Bis(3-phenylmethanesulfonyl)-4,5-dihydro-(1*H*-pyrazol-4-yl))benzene (**7a**)

mp 237-239 °C; IR (KBr) ν_{max}/cm^{-1} 3267, 1576, 1331, 1141; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.75 (dd, 2H, J_{AX} 6.4, H_X, CH_2), 4.58 (s, 4H, CH_2), 4.17 (dd, 2H, J_{MX} 11.6, H_M, CH_2), 4.46 (dd, 2H, J_{AM} 12.2, H_A, CH), 6.53 (bs, 2H, NH), 7.16-7.85 (m, 14H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 37.4, 57.6, 58.3, 124.8, 125.5, 126.9, 127.3, 132.3, 134.2, 156.9; calcd. for $C_{26}H_{26}N_4O_4S_2$: *m/z* 522.64; C, 59.75; H, 5.01; N, 10.72. Found: C, 59.86; H, 4.99; N, 10.97.

1,4-(Bis(3-p-methylphenylmethanesulfonyl)-4,5-dihydro-(1*H*-pyrazol-4-yl))benzene (**7b**)

mp 252-254 °C; IR (KBr) ν_{max}/cm^{-1} 3268, 1574, 1346, 1152; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.36 (s, 6H, CH_3), 3.72 (dd, 2H, J_{AX} 6.1, H_X, CH_2), 4.57 (s, 4H, CH_2), 4.12 (dd, 2H, J_{MX} 11.2, H_M, CH_2), 4.34 (dd, 2H, J_{AM} 12.0, H_A, CH), 6.54 (bs, 2H, NH), 7.09-7.78 (m, 12H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.1, 37.2, 57.2, 57.4, 125.1, 125.9, 126.7, 127.4, 130.5, 132.8, 155.7; calcd. for $C_{28}H_{30}N_4O_4S_2$: *m/z* 550.69; C, 61.07; H, 5.49; N, 10.17. Found: C, 61.16; H, 5.54; N, 10.29.

1,4-(Bis(3-p-chlorophenylmethanesulfonyl)-4,5-dihydro-(1*H*-pyrazol-4-yl))benzene (**7c**)

mp 258-260 °C; IR (KBr) ν_{max}/cm^{-1} 3272, 1582, 1349, 1135; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.85 (dd, 2H, J_{AX} 6.7, H_X, CH_2), 4.51 (s, 4H, CH_2), 4.23 (dd, 2H, J_{MX} 11.9, H_M, CH_2), 4.56 (dd, 2H, J_{AM} 12.5, H_A, CH), 6.53 (bs, 2H, NH), 7.23-7.92 (m, 12H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 37.7, 57.1 (C-5), 58.5, 125.2, 126.5, 127.7, 132.1, 133.8, 134.4, 156.8; calcd. for $C_{26}H_{24}Cl_2N_4O_4S_2$: *m/z* 591.53; C, 52.79; H, 4.09; N, 9.47. Found: C, 57.79; H, 5.21; N, 9.75.

1,4-(Bis(3-p-methoxyphenylmethanesulfonyl)-4,5-dihydro-(1*H*-pyrazol-4-yl))benzene (**7d**)

mp 279-281 °C; IR (KBr) ν_{max}/cm^{-1} 3265, 1569, 1342, 1133; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.78 (dd, 2H, J_{AX} 6.5, H_X, CH_2), 3.86 (s, 6H, OCH_3), 4.55 (s, 4H, Ph-CH_2), 4.21 (dd, 2H, J_{MX} 11.8, H_M, CH_2), 4.51 (dd, 2H, J_{AM} 12.3, H_A, CH), 6.57 (bs, 2H, NH), 7.19-7.88 (m, 12H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 37.5, 54.8, 58.0, 58.1, 125.8, 126.4, 127.0, 132.9, 133.7, 134.5, 156.3; calcd. for $C_{28}H_{30}N_4O_6S_2$: *m/z* 582.69; C, 57.71; H, 5.19; N, 9.62. Found: C, 57.79; H, 5.21; N, 9.75.

General procedure for the synthesis of 1,4-(bis(3-arylmethanesulfonyl)-1*H*-pyrazol-4-yl)benzenes (**8a-d**)

A solution of compounds **7a-d** (1 mmol) and chloranil (2.4 mmol) in xylene (10 mL^{-1}) was refluxed for 24-27 h. Then, it was treated with 5% sodium hydroxide solution. The organic extract was separated, repeatedly washed with water and dried anhydrous sodium sulfate. The solvent was removed *in vaccuo*. The resultant solid was recrystallized from 2-propanol.

1,4-(Bis(3-phenylsulfonyl)-1*H*-pyrazol-4-yl)benzene (**8a**)

mp 264-266 °C; IR (KBr) ν_{max}/cm^{-1} 3266, 1618, 1580, 1328, 1149; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.62 (s, 4H, CH_2), 6.92 (s, 2H, CH), 7.63-8.09 (m, 12H, Ar-H), 10.40 (bs, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 58.4, 129.6, 132.0, 133.8, 133.9, 134.3, 135.5, 136.7, 137.1, 137.7; calcd. for $C_{26}H_{22}N_4O_4S_2$: *m/z* 518.61; C, 60.21; H, 4.28; N, 10.80. Found: C, 60.32; H, 4.34; N, 10.96.

1,4-(Bis(3-p-methylphenylsulfonyl)-1*H*-pyrazol-4-yl) benzene (**8b**)

mp 251-253 °C; IR (KBr) ν_{max}/cm^{-1} 3272, 1614, 1578, 1339, 1152; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.43 (s, 6H, CH_3), 4.60 (s, 4H, CH_2), 6.87 (s, 2H, CH), 7.55-8.01 (m, 12H, Ar-H), 10.36 (bs, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.7, 57.9, 129.4, 123.6, 124.9, 125.4, 126.1, 133.3, 133.7, 134.8, 137.3; calcd. for $C_{28}H_{26}N_4O_4S_2$: *m/z* 546.66; C, 61.52; H, 4.79; N, 10.25. Found: C, 61.48; H, 4.80; N, 10.38.

1,4-(Bis(3-p-chlorophenylsulfonyl)-1*H*-pyrazol-4-yl)benzene (**8c**)

mp 287-289 °C; IR (KBr) ν_{max}/cm^{-1} 3274, 1621, 1591, 1347, 1155; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.64 (s, 4H, CH_2), 6.96 (s, 2H, CH), 7.69-8.16 (m, 12H, Ar-H), 10.45 (bs, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 58.6, 130.3, 133.0, 134.5, 134.6, 135.2, 136.8, 137.3, 138.1, 139.7; calcd. for $C_{26}H_{20}Cl_2N_4O_4S_2$: *m/z* 587.50; C, 53.15; H, 3.43; N, 9.54. Found: C, 53.22; H, 3.41; N, 9.65.

1,4-(Bis(3-p-methoxyphenylsulfonyl)-1*H*-pyrazol-4-yl) benzene (**8d**)

mp 272-274 °C; IR (KBr) ν_{max}/cm^{-1} 3278, 1626, 1575, 1340, 1148; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.83 (s, 6H, OCH_3), 4.66 (s, 4H, CH_2), 6.94 (s, 2H, CH), 7.66-8.12 (m, 12H, Ar-H), 10.42 (bs, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 55.7, 58.2, 129.9, 133.1, 134.2, 134.5, 135.7, 136.4, 137.2, 137.9, 138.8; calcd. for $C_{28}H_{26}N_4O_6S_2$: *m/z* 578.66; C, 58.12; H, 4.53; N, 9.68. Found: C, 58.21; H, 4.56; N, 9.82.

Antioxidant testing

The compounds **5a-d**-**8a-d** were tested for antioxidant property by DPPH, NO, and H_2O_2 methods.

Antioxidant assays

DPPH radical scavenging activity

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 radical (DPPH). The spectrophotometric assay uses the stable radical DPPH as a reagent. To 4 mL^{-1} of 0.004% w/v methanol solution of DPPH, 1 mL^{-1} of various concentrations of the test compounds (50, 75, and 100 μg mg L^{-1}) in methanol were added. After a 30 min incubation period at room temperature, the absorbance was read against blank at 517 nm. Ascorbic acid was used as the standard. The percentage of inhibition (I%) of free radical production from DPPH was calculated by the following equation

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

where $A_{control}$ is the absorbance of the control reaction (containing methanolic DPPH and ascorbic acid), A_{sample} is the absorbance of the test compound (containing methanolic DPPH and test compound), and A_{blank} is 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} in μg mL^{-1} = 50 × 100 / % Inhibition
IC_{50} in μm mL^{-1}= % of the IC_{50} / M.Wt. of the compound.

Nitric oxide (NO) radical scavenging activity

Nitric oxide scavenging activity was measured by slightly modified methods of Green *et al.* and Marcocci *et al.*, Nitric oxide radicals (NO) were generated from sodium nitroprusside.[34,35] 1 mL of sodium nitroprusside (10 mmol L^{-1}) and 1.5 mL^{-1} of phosphate buffer saline (0.2 M, pH 7.4) were added to different concentrations (50, 75, and 100 μg mg L^{-1}) 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^{-1} of Griess reagent (1% sulfanilamide, 2% H_3PO_4, and 0.1% naphthylethylenediamine dihydrochloride). The absorbance of the chromatophore was measured at 546 nm. Ascorbic acid was used as standard. Nitric oxide scavenging activity was calculated by the following equation

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

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

Hydrogen peroxide (H_2O_2) radical scavenging activity

The H_2O_2 scavenging ability of the test compound was determined according to the method of Ruch *et al.*[36] A solution of H_2O_2 (40 mmol L^{-1}) was prepared in phosphate buffer (pH 7.4). The different concentrations of the test compounds 50, 75, and 100 μg mg L^{-1} in 3.4 mL^{-1} phosphate buffer were added to H_2O_2 solution (0.6 mL, 40 mmol L^{-1}). 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

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

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

Conclusions

A variety of (1,4-phenylene)bis(arylmethanesulfonyl-pyrroles and pyrazoles) were prepared by the cycloaddition of 1,3-dipolar reagents, tosylmethyl isocyanide and diazomethane to 1,4-bis(*E*)-2-((arylmethanesulfonyl) vinyl)benzenes (**5a-d**). All the compounds were evaluated for antioxidant activity. Amongst the tested compounds **5d** displayed excellent radical scavenging activity in all the three methods evaluated when compared with the standard ascorbic acid. On the other hand, 1,4-(bis(3-arylmethanesulfonyl)-1*H*-pyrazol-4-yl)benzenes (**8a-d**) exhibited comparatively higher antioxidant activity than 1,4-(bis(3-arylmethanesulfonyl)-1*H*-pyrrol-4-yl)benzenes (**6a-d**). In general, it was observed that compounds having methoxy substitutent on aromatic ring displayed greater antioxidant activity than the other substituents.

Supplementary Information

Supplementary data (NMR spectra) are available free of charge at http://jbcs.sbq.org.br as PDF file.

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References

1. Helder, R.; Doornbos, T.; Strating, J.; Zwanenburg, B.; *Tetrahedron* **1973**, *29*, 1375.
2. Xia, Y.; Yang, Z. Y.; Xia, P.; Bastow, K. F.; Nakanishi, Y.; Lee, K. H.; *Bioorg. Med. Chem. Lett.* **2000**, *10*, 699.
3. Liu, M.; Wilairat, P.; Go, M. L.; *J. Med. Chem.* **2001**, *44*, 4443.
4. Hsieh, H. K.; Tsao, L. T.; Wang, J. P.; Lin, C. N.; *J. Pharm. Pharmacol*. **2000**, *52*, 163.
5. Maria, K.; Dimitra, H. L.; Maria, G.; *Med. Chem.* **2008**, *4*, 586.
6. Cheenpracha, S.; Karalai, C.; Ponglimanont, C.; Subhadhirasakul, S.; Tewtrakul, S.; *Bioorg. Med. Chem.* **2006**, *14*, 1710.
7. Svetaz, L.; Tapia, A.; Lopez, S. N.; Furlan, R. L. E.; Petenatti, E.; Pioli, R.; Schmeda Hirschmann, G.; Zacchino, S. A.; *J. Agric. Food Chem.* **2004**, *52*, 3297.
8. Jacobi, P. A.; Coults, L. D.; Guo, J. S.; Leung, S. I. J.; *Org. Chem.* **2000**, *65*, 205.
9. Jones, R. A.; Bean, G. P.; *The Chemistry of Pyrroles*, Academic Press: London, 1977.
10. Knorr, L. B.; *Named Reactions* **1884**, *17*, 2863; Paal, C. B.; *Named Reactions* **1884**, *17*, 2756.
11. Estevez, V.; Villacampa, M.; Menendez, J. C.; *Chem. Commun.* **2013**, *49*, 591.
12. Marie, S. T. M.; Daniel, J. S.; Bruce, A. A.; *Org. Lett.* **2010**, *12*, 4916.
13. Timothy, J. D.; John, F. B.; Louis, K. M. C.; *Org. Biomol. Chem.* **2012**, *10*, 1322.
14. Gursoy, A.; Demirayak, S.; Capan, G.; Erol, K.; Vural, K.; *Eur. J. Med. Chem.* **2000**, *35*, 359.
15. Ramalingham, K.; Thyvekikakath, G. X.; Berlin, K. D.; Chesnut, R. W.; Brown, R. A.; Durham, N. N. ; Ealick, A. E.; Vender, H. D.; *J. Med. Chem.* **1977**, *20*, 847.
16. Rajendra, P. Y.; Lakshmana, R. A.; Prasoona, L.; Murali, K.; Ravi, K. P.; *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5030.
17. Lombardino, J. G.; Otterness, I. G.; *J. Med. Chem.* **1981**, *24*, 830.
18. Ozdemir, Z.; Kandilici, H. B.; Gumusel, B.; Calis, U.; Bilgin, A. A.; *Eur. J. Med. Chem.* **2007**, *42*, 373.
19. Taylor, E. C.; Patel, H. H.; *Tetrahedron* **1992**, *48*, 8089.
20. Fathalla, O. A.; Zaki, M. E.; Swelam, S. A.; Nofal, S. M.; El Eraky, W. I.; *Acta Pol. Pharm.* **2003**, *60*, 51.
21. McQuay, H. J.; Moore, R. A. In *Wall and Melzack's Textbook of Pain*, McMahon, S.; Koltzenburg, M., eds.; Elsevier Churchill Livingstone: Edinburgh, 2005, pp. 471.
22. Kameyama, T.; Ukai, M.; Nabeshima, T.; *Chem. Pharm. Bull.* **1978**, *26*, 3265.
23. Vinge, E.; Bjorkman, S. B.; *Acta Pharmacol. Toxicol.* **1986**, *59*, 165.
24. Bragt, P. C.; Bansberg, J. I.; Bonta, I. L.; *Inflammation* **1980**, *4*, 289.
25. Takabatake, E.; Kodama, R.; Tanaka, Y.; Dohmori, R.; Tachizawa, H.; Naito, T.; *Chem. Pharm. Bull.* **1970**, *18*, 1900.
26. Molteni, G.; *Arkivoc.* **2007**, 224.
27. Bao Xiang, Z.; Yang, Y.; Shoji, E.; *Tetrahedron* **1996**, *52*, 12049.
28. Conti, P.; Pinto, A.; Tamborini, L.; Rizzo, V.; De Micheli, C.; *Tetrahedron* **2007**, *63*, 5554.
29. Snyder, N. L.; Adams, T. P. In *Name Reactions in Heterocyclic Chemistry II*, Li, J. J.; Corey, E. J., eds.; John Wiley & Sons, Inc.: New York, 2011, pp. 572.
30. Padmavathi, V.; Mahesh, K.; Dinneswara Reddy, D.; Padmaja, A.; *Eur. J. Med. Chem.* **2010**, *45*, 3178.
31. Padmavathi, V.; Radha Lakshmi, T.; Mahesh, K.; Padmaja, A.; *Chem. Pharm. Bull.* **2009**, *57*, 1200.
32. Burits, M.; Bucar, F.; *Phytother. Res.* **2000**, *14*, 323.
33. Cuendet, M.; Hostettmann, K.; Potterat, O.; *Helv. Chim. Acta* **1997**, *80*, 1144.
34. Green, L. C.; Wagner, D. A.; Glogowski, J.; Skipper, P. L.; Wishnok, J. S.; Tannenbaum, S. R.; *Anal. Biochem*. **1982**, *126*, 131.
35. Marcocci, L.; Maguire, J. J.; Droy Lefaix, M. T.; Packer, L.; *Biochem. Biophys. Res. Commun.* **1994**, *201*, 748.
36. Ruch, R. J.; Cheng, S. J.; Klaunig, J. E.; *Carcinogensis* **1989**, *10*, 1003.
37. Bhaskar Reddy, D.; Reddy, N. S.; Reddy, S. M.; Reddy, V. R.; Balasubramanyam, S.; *Org. Prep. Proceed. Int.* **1988**, *20*, 83.

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Supplementary Information

Synthesis and Antioxidant Activity of 1,4-[Bis(3-arylmethanesulfonyl pyrrolyl and pyrazolyl)]benzenes

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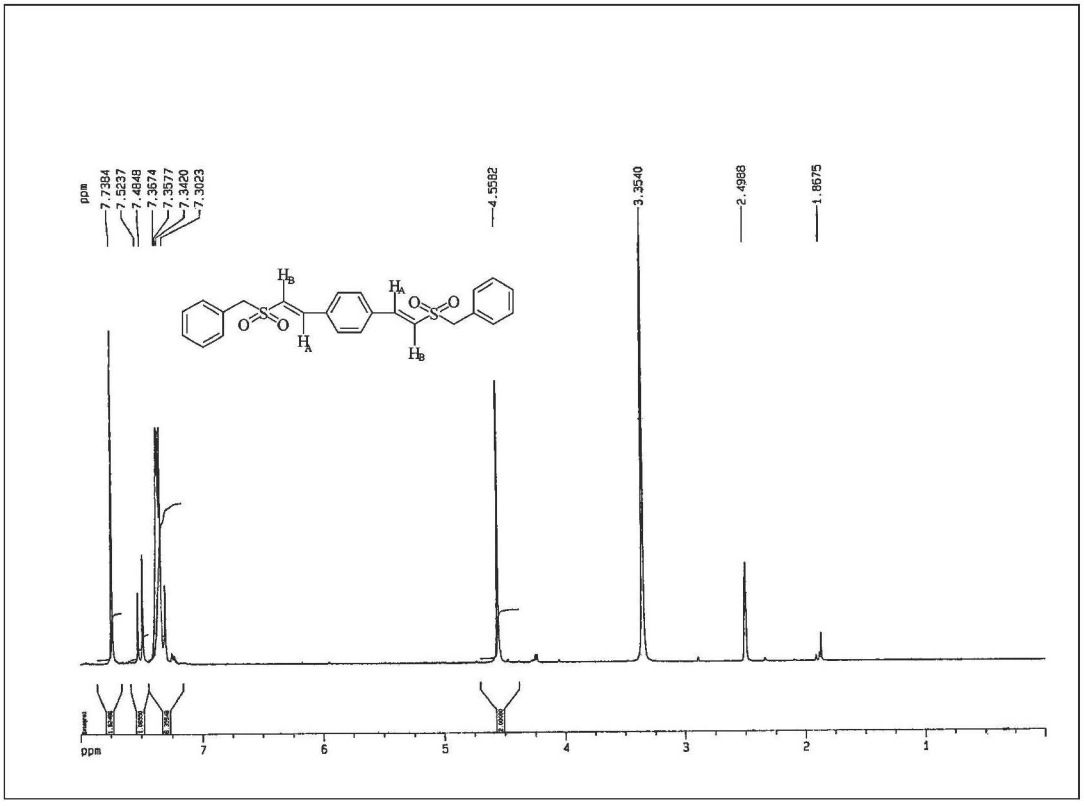

Figure S1. The ^{1}H NMR spectrum (DMSO-d_6, 400 MHz) of compound **5a**.

*e-mail: adivireddyp@yahoo.co.in

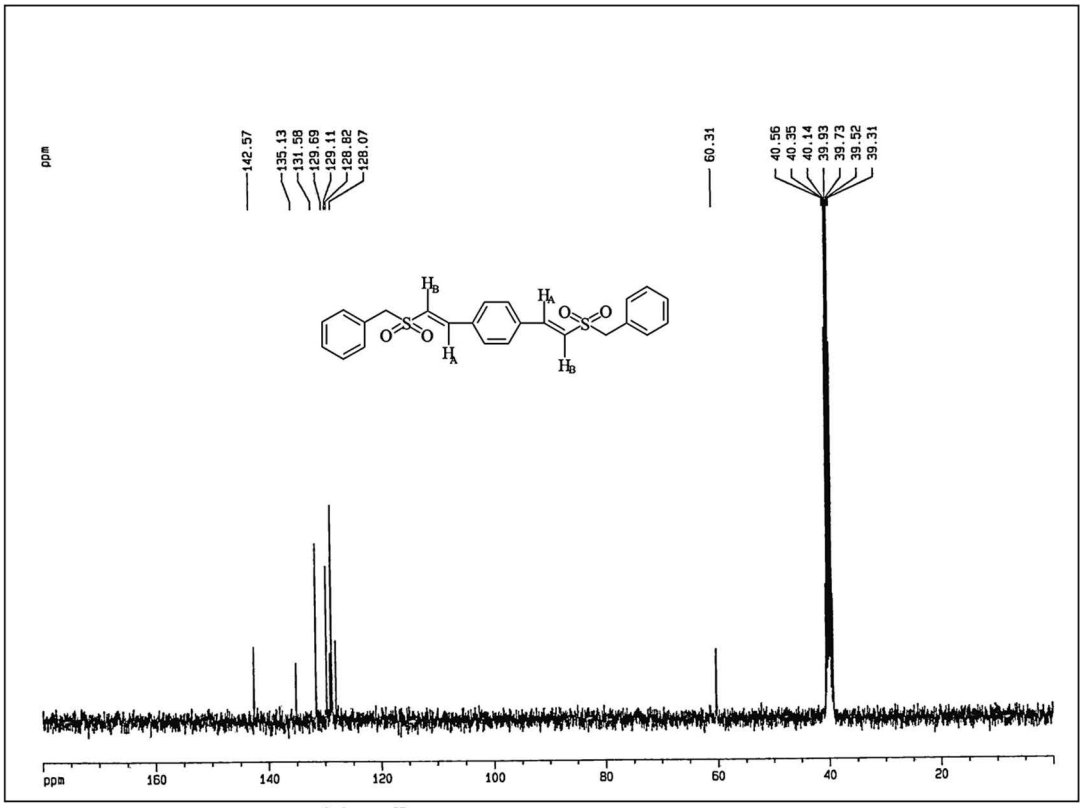

Figure S2. The ^{13}C NMR spectrum (DMSO-d_6, 100 MHz) of compound **5a**.

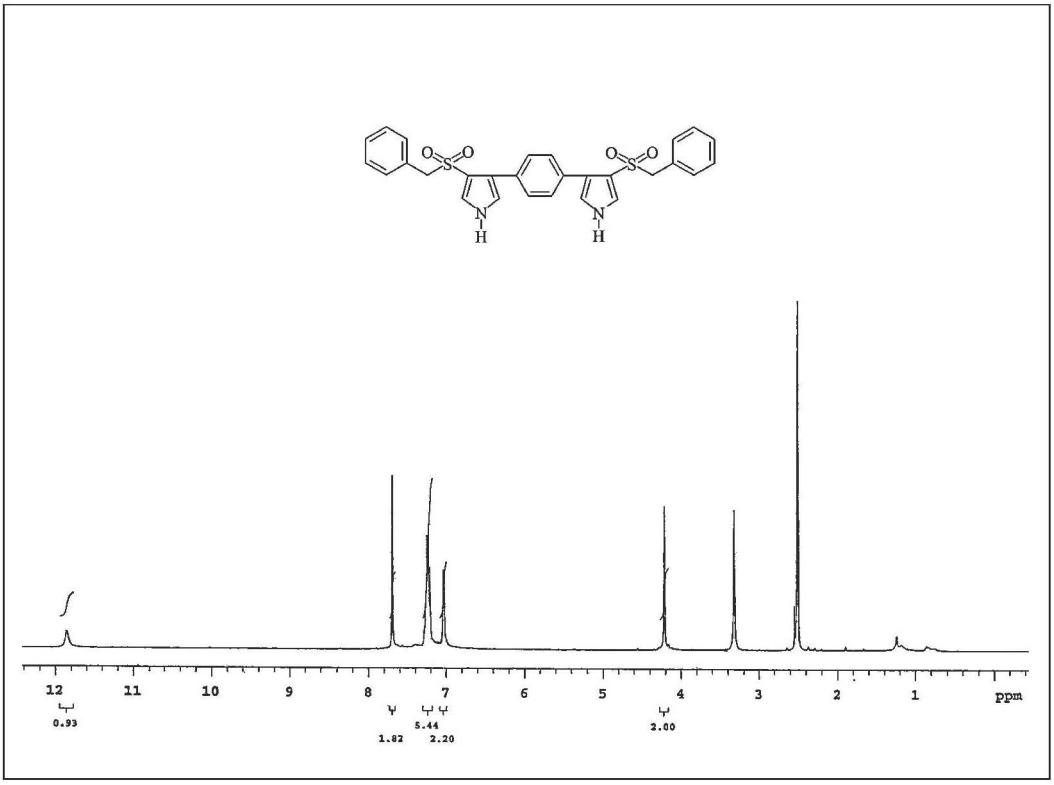

Figure S3. The ^{1}H NMR spectrum (DMSO-d_6, 400 MHz) of compound **6a**.

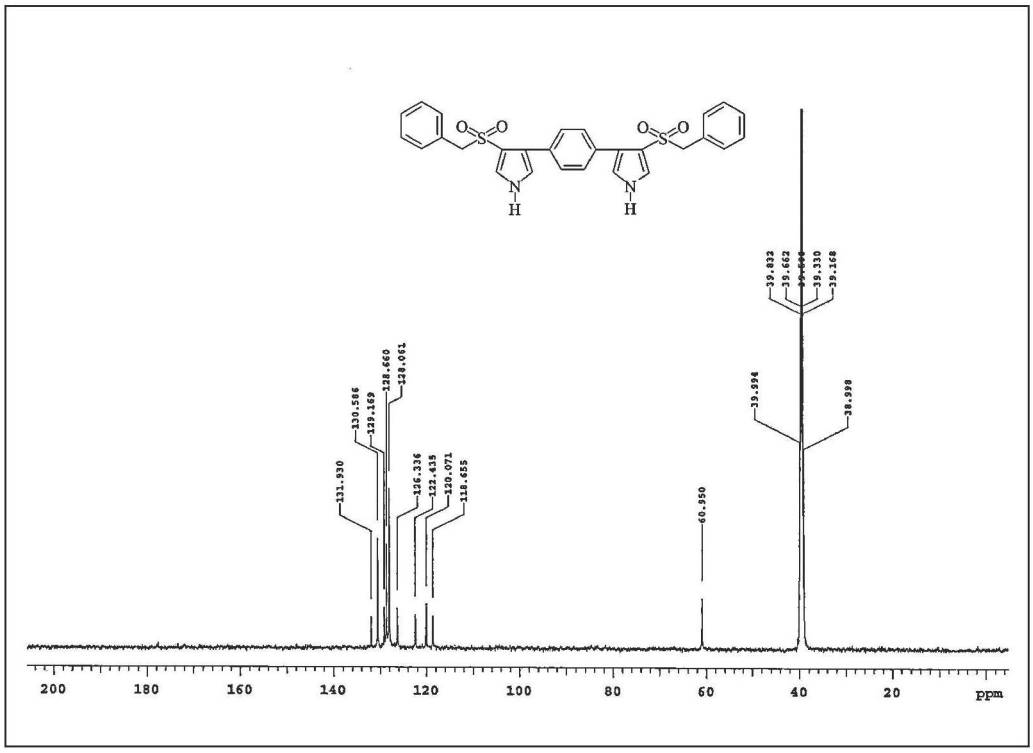

Figure S4. The ^{13}C NMR spectrum (DMSO-d_6, 100 MHz) of compound **6a**.

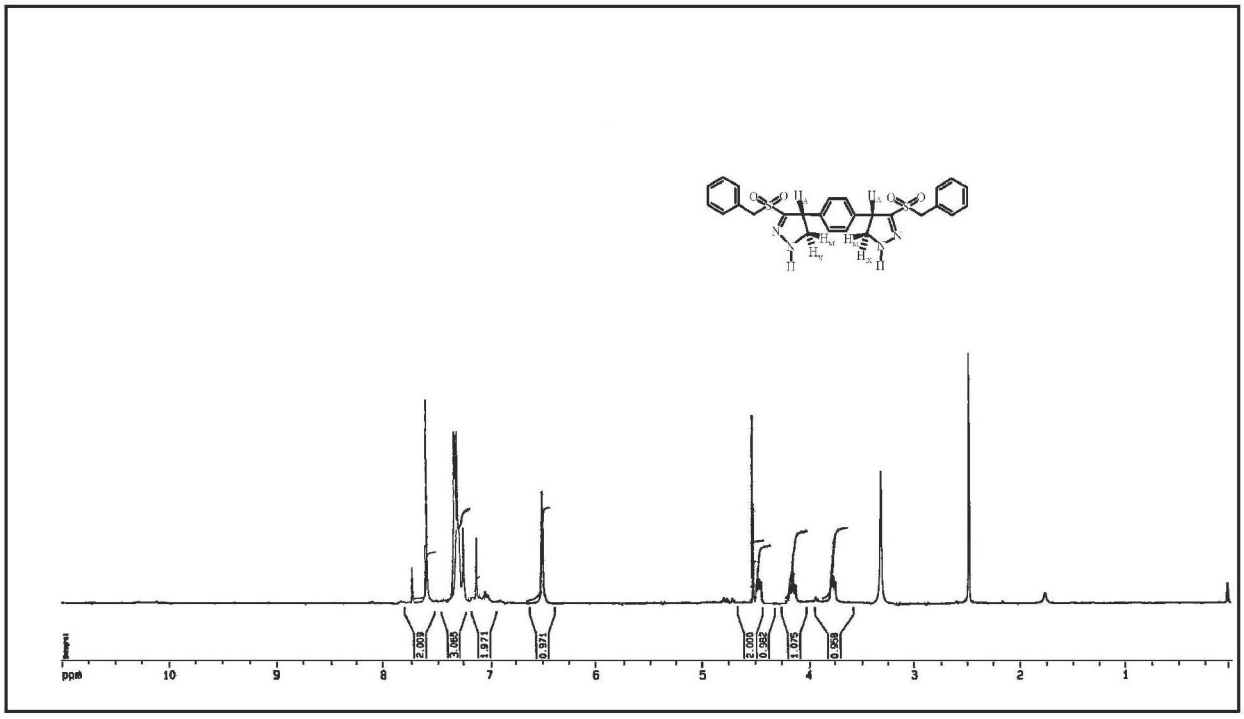

Figure S5. The ^{1}H NMR spectrum (DMSO-d_6, 400 MHz) of compound **7a**.

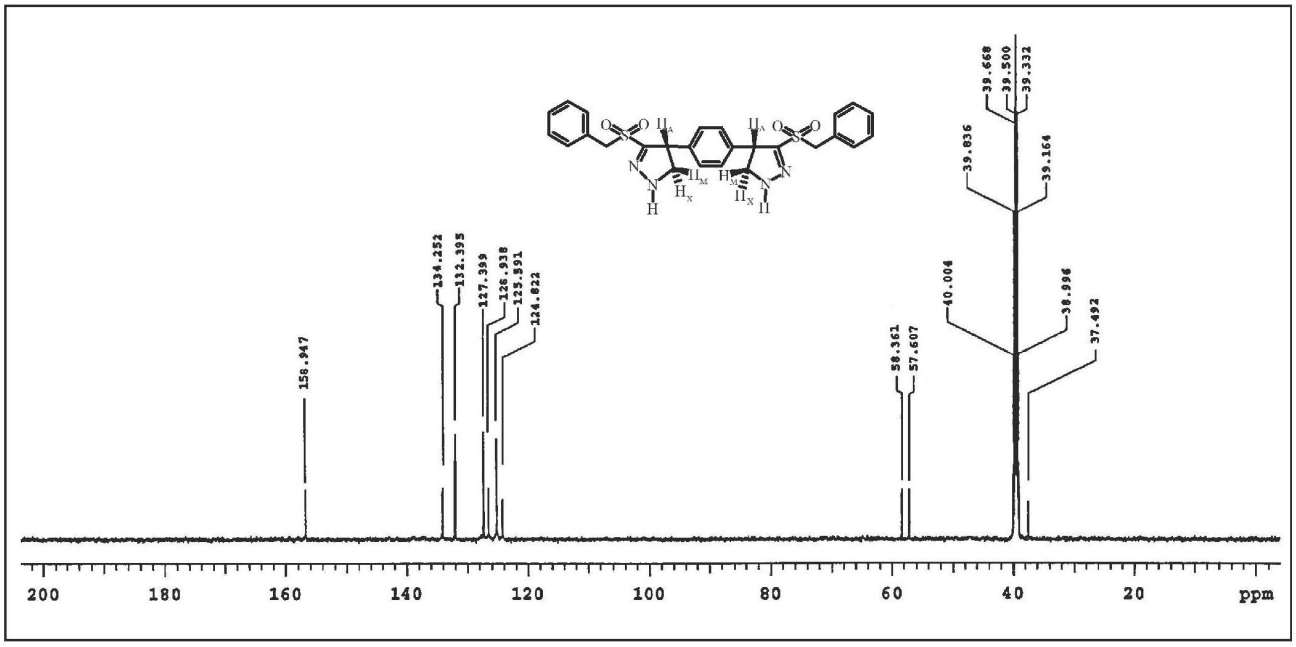

Figure S6. The ^{13}C NMR spectrum (DMSO-d_6, 100 MHz) of compound **7a**.

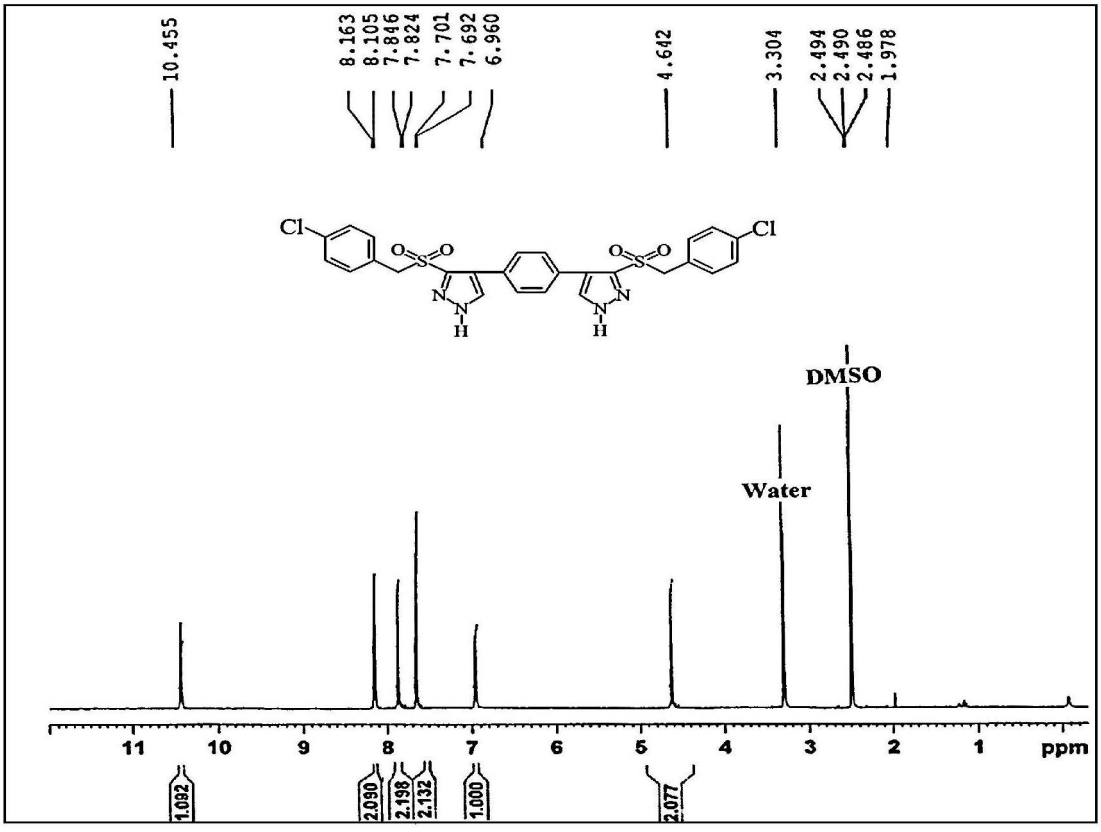

Figure S7. The ^{1}H NMR spectrum (DMSO-d_6, 400 MHz) of compound **8c**.

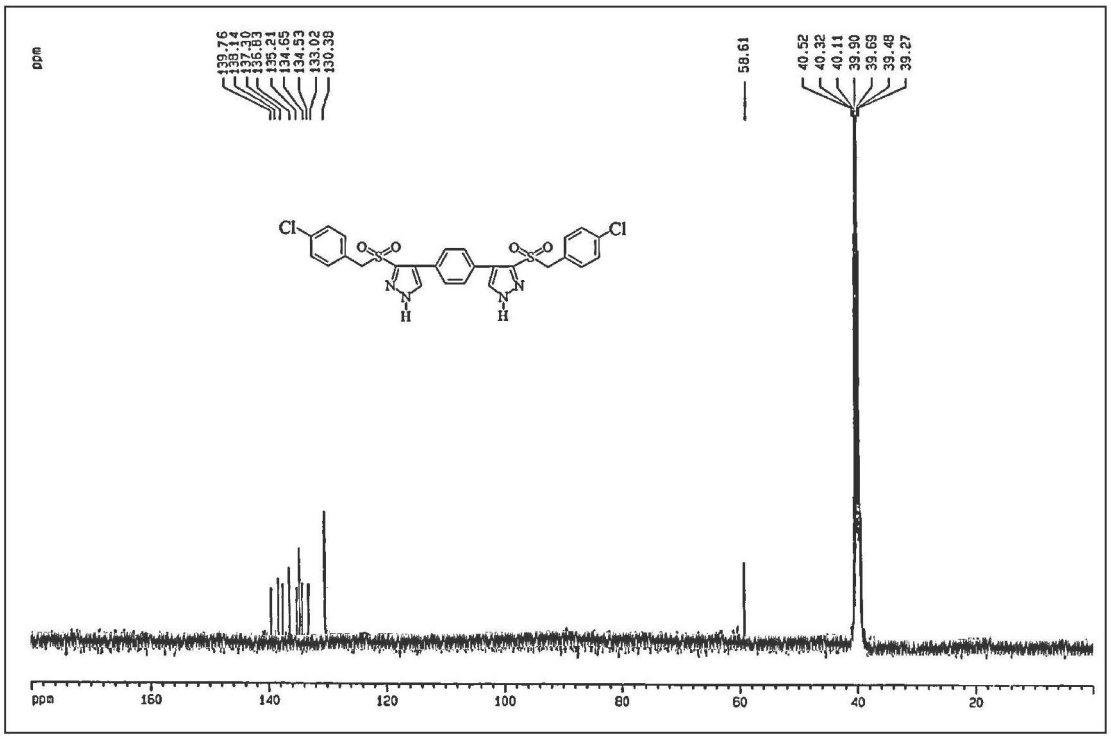

Figure S8. The ^{13}C NMR spectrum (DMSO-d_6, 100 MHz) of compound **8c**.