Synthesis of Symmetrical Bis(5-substituted oxadiazolyl/thiadiazolyl/triazolylmethyl)sulfones

Padmaja Adivireddy,* Pedamalakondaiah Devanaboina, Lavanya Gopala, and Rajasekhar Chittoor

Department of Chemistry, Sri Venkateswara University, Tirupati 517 502, Andhra Pradesh, India
*E-mail: adivireddyp@yahoo.co.in

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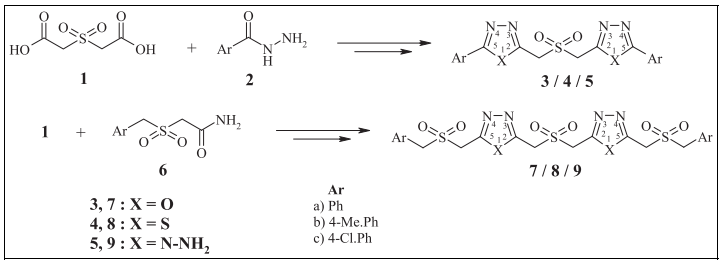

A new class of bis(oxadiazolyl/thiadiazolyl/triazolylmethyl)sulfones were prepared by the cyclocondensation of sulfonyldiacetic acid with aryl acid hydrazide and arylmethanesulfonylacetic acid hydrazide.

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INTRODUCTION

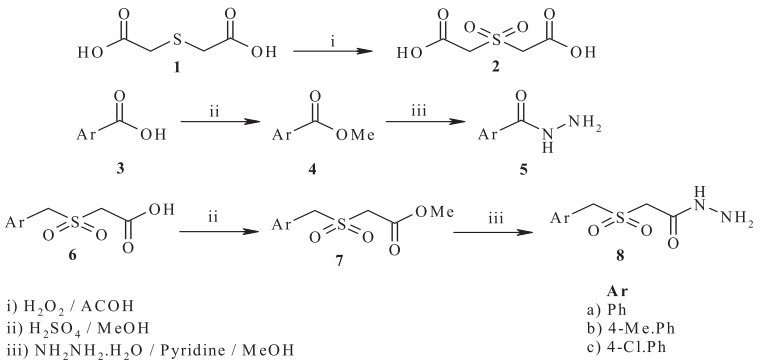
Aryl sulfones are widely used in medicinal chemistry and found in several drugs including the recently developed selective COX-2 inhibitor Vioxx [1]. The five-membered heterocycles particularly 1,3,4-oxadiazole, 1,3,4-thiadiazole, and 1,2,4-triazoles are prominent compounds that possess various pharmacological activities. Some 1,3,4-oxadiazole sulfones exhibit antibacterial and antifungal activities [2,3]. The important method for the synthesis of 1,3,4-oxadiazoles involves cyclization of diacylhydrazines prepared by the reaction of acyl chlorides and hydrazine. Several cyclodehydrating agents $Et_2O{\cdot}BF_3$ [4], triflic anhydride [5], polyphosphoric acid [6], and so on, have been used. One-pot synthesis of 1,3,4-oxadiazoles from hydrazine and carboxylic acids has also been reported [7,8]. 1,3,4-Thiadiazole nucleus constitutes the active part of several compounds including antibacterial, antimycotic, and anti-inflammatory agents [9,10]. Most frequently used methods for the synthesis of thiadiazoles include the reaction of acylthiosemicarbazides with acidic reagents such as trifluoroacetic acid [11] and methanesulfonic acid [9]. Besides, 1,2,4-triazole and their derivatives show insecticidal [12], antifungal [13], antimicrobial [14], and anti-inflammatory [15] properties. One of the synthetic methods for the preparation of triazoles involves the use of *N*,*N*′-dimethyl formamide dimethyl acetals [16]. Replacement of –O– by –S– or –NH– in some heterocycles was reported viz., Bordner's [17] preparation of pyrroles from furan and the transformation of epoxides to episulfides by the action of thiocyanates or thiourea [18–20]. However, reports about the conversion of 1,3,4-oxadiazoles to 1,3,4-thiadiazoles and 1,2,4-triazoles are relatively less [21,22]. Thus, there is a quest for the synthesis of a variety of azoles linked by different pharmacophoric units. In fact, we have reported the synthesis of multifunctional 1,3,4-oxadiazoles, 1,3,4-thiadiazoles, and 1,2,4-triazoles via potassium salt of different acid hyrazides [23]. We have also reported these heterocycles from various acids and acid hydrazides followed by interconversion in the presence of appropriate nucleophiles [24]. Encouraged by these results and our continued interest in the development of a variety of heterocycles with different pharmacophore unit, the present work has been taken up.

RESULTS AND DISCUSSION

The synthetic routes adopted to prepare the target molecules are outlined in Schemes 1 and 2. The cyclocondensation of one mole of sulfonyldiacetic acid (**2**) with two moles aryl acid hydrazide (**5**) in the presence of $POCl_3$ led to the formation of bis(5-aryl-1,3,4-oxadiazolylmethyl)sulfone (**9**). Interconversion of oxadiazole to thiadiazole was effected by treating compound **9** with thiourea in tetrahydrofuran to obtain bis(5-aryl-1,3,4-thiadiazolylmethyl)sulfone (**10**). On the other hand, the reaction of compound **9** with hydrazine hydrate in the presence of KOH in *n*-butanol furnished bis (5-aryl(4-amino)-1,2,4-triazol-3-ylmethyl)sulfone (**11**) (Scheme 1 and Table 1). The ^{1}H NMR spectra of **9a** and **10a** exhibited a singlet at δ 4.92 and 5.15 because of methylene protons attached to C-2 while **11a** at 5.01 ppm because of methylene protons attached to C-3 in addition to aromatic protons. Moreover, in compound **11a**, a broad singlet appeared at δ 5.62 ppm was attributed to NH_2, which disappeared on deuteration. The 70-eV mass spectra of **9a**, **10a**, and **11a** displayed molecular ion peaks at 382.07, 414.03, and 410.13 corresponding to their molecular formulae $C_{18}H_{14}N_4O_4S$, $C_{18}H_{14}N_4O_4S$, and $C_{18}H_{18}N_8O_2S$.

Adopting similar methodology, the reaction of sulfonyldiacetic acid (**2**) with two moles of arylmethanesulfonylacetic acid

Scheme 1



Scheme 2

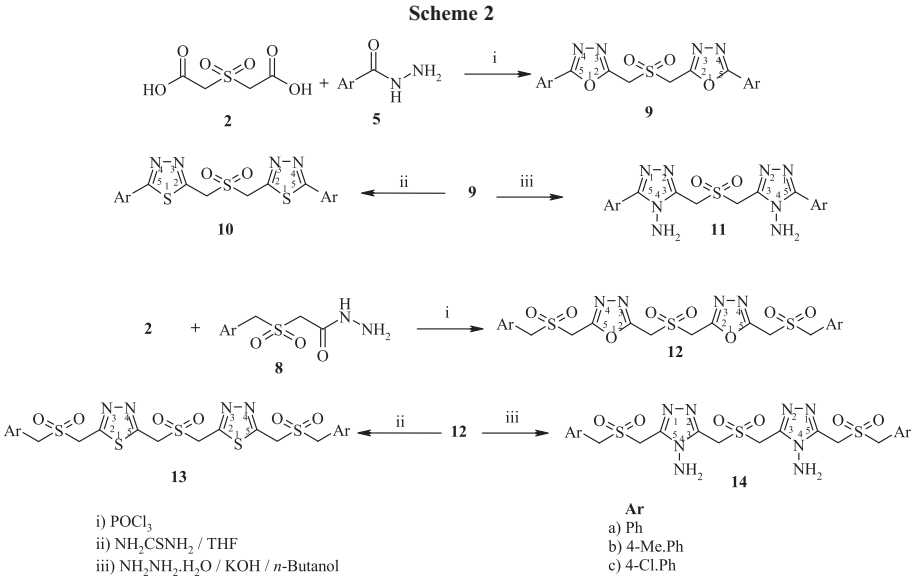


Table 1

Physical and analytical data of compounds **9–14.**

Compound	Mp (°C)	Yield (%)	Molecular formula (mol. wt)	Analysis % calcd. (found)		
				C	H	N
9a	141–143	75	$C_{18}H_{14}N_4O_4S$ (382.39)	56.66 (56.54)	3.74 (3.69)	14.79 (14.65)
9b	134–136	72	$C_{20}H_{18}N_4O_4S$ (410.45)	58.60 (58.53)	4.45 (4.42)	13.75 (13.65)
9c	155–157	80	$C_{18}H_{12}Cl_2N_4O_4S$ (451.28)	48.07 (47.91)	2.74 (2.68)	12.60 (12.41)
10a	150–152	77	$C_{18}H_{14}N_4O_4S$ (414.52)	52.25 (52.15)	3.48 (3.40)	13.68 (13.52)
10b	146–148	74	$C_{20}H_{18}N_4O_2S_3$ (442.58)	54.24 (54.28)	4.12 (4.10)	12.76 (12.66)
10c	162–164	82	$C_{18}H_{12}Cl_2N_4O_2S_3$ (483.41)	44.79 (44.72)	2.49 (2.50)	11.72 (11.59)
11a	159–161	78	$C_{18}H_{18}N_8O_2S$ (410.45)	52.43 (52.27)	4.47 (4.42)	27.51 (27.30)
11b	143–145	76	$C_{20}H_{22}N_8O_2S$ (438.51)	54.87 (54.78)	5.10 (5.06)	25.57 (25.55)
11c	171–173	81	$C_{18}H_{16}Cl_2N_8O_2S$ (479.34)	45.21 (45.10)	3.34 (3.36)	23.53 (23.38)
12a	188–190	84	$C_{22}H_{22}N_4O_8S_3$ (566.63)	44.78 (44.63)	3.96 (3.91)	10.06 (9.89)
12b	167–169	79	$C_{24}H_{26}N_4O_8S_3$ (594.68)	48.53 (48.47)	4.44 (4.41)	9.31 (9.42)
12c	203–205	87	$C_{22}H_{20}Cl_2N_4O_8S_3$ (655.52)	41.66 (41.58)	3.13 (3.17)	8.96 (8.82)
13a	210–212	83	$C_{22}H_{22}N_4O_6S_5$ (598.76)	44.08 (44.13)	3.72 (3.70)	9.48 (9.36)
13b	191–193	78	$C_{24}H_{26}N_4O_6S_5$ (626.81)	46.10 (45.99)	4.16 (4.18)	9.12 (8.94)
13c	218–220	86	$C_{22}H_{20}Cl_2N_4O_6S_5$ (667.65)	39.67 (39.58)	3.03 (3.02)	8.53 (8.39)
14a	207–209	84	$C_{22}H_{26}N_8O_6S_3$ (594.69)	44.54 (44.43)	4.45 (4.41)	19.02 (18.84)
14b	197–199	80	$C_{24}H_{30}N_8O_6S_3$ (622.74)	46.36 (46.29)	4.88 (4.86)	18.11 (17.99)
14c	216–218	88	$C_{22}H_{24}Cl_2N_8O_6S_3$ (663.58)	39.87 (39.82)	3.64 (3.65)	16.98 (16.89)

Table 2

IR data of compounds **9–14.**

Compound	IR (KBr) cm^{-1}				
	NH_2		C=N	SO_2	
9a	—	—	1577	1312	1148
9b	—	—	1576	1310	1142
9c	—	—	1584	1318	1153
10a	—	—	1582	1331	1145
10b	—	—	1579	1342	1140
10c	—	—	1585	1322	1147
11a	3480	3362	1564	1319	1130
11b	3475	3360	1560	1314	1132
11c	3486	3375	1582	1325	1135
12a	—	—	1568	1341	1139
12b	—	—	1565	1334	1137
12c	—	—	1574	1345	1143
13a	—	—	1586	1330	1136
13b	—	—	1583	1339	1131
13c	—	—	1590	1328	1138
14a	3488	3370	1578	1338	1136
14b	3475	3365	1576	1332	1128
14c	3492	3376	1582	1326	1150

hydrazide (**8**) in the presence of $POCl_3$ yielded bis(5-arylmethanesulfonylmethyl-1,3,4-oxadiazolylmethyl)sulfone (**12**). The compound **12** on treatment with thiourea in tetrahydrofuran produced bis(5-arylmethanesulfonylmethyl-1,3,4-thiadiazolylmethyl)sulfone (**13**). Furthermore, bis(5-arylmethanesulfonylmethyl(4-amino)-1,2,4-triazol-3-ylmethyl) sulfone (**14**) was prepared by the reaction of the compound **12** with hydrazine hydrate in the presence of KOH in *n*-butanol (Scheme 2 and Table 1). The ^{1}H NMR spectra of **12a** displayed three singlets at δ 4.85, 5.49, 5.60 ppm; **13a** at 5.11, 5.58, 5.72 ppm; and **14a** at 5.07, 5.51, 5.55 ppm because of methylene protons attached to C-2/C-3, C-5, and Ar-CH_2, respectively. In addition to these, compound **14a** presented a broad singlet at 5.75 ppm for NH_2. The signals due to highly acidic protons disappeared when D_2O was added. The 70-eV mass spectra of **12a**, **13a**, and **14a** showed molecular ion peaks at 566.06, 598.01, and 594.11 corresponding to their chemical composition $C_{22}H_{22}N_4O_8S_3$, $C_{22}H_{22}N_4O_6S_5$, and $C_{22}H_{26}N_8O_6S_3$. The structures of all the new compounds were further established by IR (Table 2), ^{13}C NMR (Table 3), and elemental analyses.

Table 3

^{1}H and ^{13}C NMR data of compounds **9–14**.

Compound	^{1}H NMR ($CDCl_3$/DMSO-d_6)	^{13}C NMR ($CDCl_3$/DMSO-d_6)
9a	4.92 (s, 4H, CH_2-(C-2)), 7.21–7.59 (m, 10H, Ar-H)	50.4 (CH_2-(C-2)), 159.2 (C-5), 161.8 (C-2), 127.3, 128.9, 129.4, 130.1 (aromatic carbons)
9b	2.26 (s, 6H, Ar-CH_3), 4.88 (s, 4H, CH_2-(C-2)), 7.11-7.46 (m, 8H, Ar-H)	23.9 (Ar-CH_3), 49.6 (CH_2-(C-2)), 159.5 (C-5), 161.2 (C-2), 126.3, 128.6, 129.7, 131.2 (aromatic carbons)
9c	4.98 (s, 4H, CH_2-(C-2)), 7.27–7.62 (m, 8H, Ar-H)	51.2 (CH_2-(C-2)), 161.2 (C-5), 163.5 (C-2), 127.8, 129.5, 132.7, 136.5 (aromatic carbons)
10a	5.15 (s, 4H, CH_2-(C-2)), 7.24–7.58 (m, 10H, Ar-H)	51.3 (CH_2-(C-2)), 174.2 (C-5), 175.6 (C-2), 128.2, 129.8, 13.5, 134.2 (aromatic carbons)
10b	2.28 (s, 6H, Ar-CH_3), 5.13 (s, 4H, CH_2-(C-2)), 7.20-7.52 (m, 8H, Ar-H)	24.6 (Ar-CH_3), 51.6 (CH_2-(C-2)), 173.4 (C-5), 175.3 (C-2), 127.8, 129.6, 130.3, 136.2 (aromatic carbons)
10c	5.16 (s, 4H, CH_2-(C-2)), 7.29–7.70 (m, 8H, Ar-H)	52.7 (CH_2-(C-2)), 176.6 (C-5), 178.2 (C-2), 128.4, 129.9, 131.4, 135.2 (aromatic carbons)
11a	5.01 (s, 4H, CH_2-(C-3)), 5.62 (bs, 4H, NH_2), 7.19-7.64 (m, 10H, Ar-H)	51.6 (CH_2-(C-3)), 159.4 (C-5), 162.8 (C-3), 127.4, 129.5, 130.2, 131.3 (aromatic carbons)
11b	2.24 (s, 6H, Ar-CH_3), 5.03 (s, 4H, CH_2-(C-3)), 5.60 (bs, 4H, NH_2), 7.15–7.57 (m, 8H, Ar-H)	24.1 (Ar-CH_3), 50.9 (CH_2-(C-3)), 157.9 (C-5), 161.4 (C-3), 126.8, 128.0, 131.2, 135.6 (aromatic carbons)
11c	5.08 (s, 4H, CH_2-(C-3)), 5.64 (bs, 4H, NH_2), 7.25-7.75 (m, 8H, Ar-H)	51.8 (CH_2-(C-3)), 159.8 (C-5), 163.1 (C-3), 129.9, 131.8, 132.8, 134.5 (aromatic carbons)
12a	4.85 (s, 4H, CH_2-(C-2)), 5.49 (s, 4H, CH_2-(C-5)), 5.60 (s, 4H, Ar-CH_2), 7.13–7.48 (m, 10H, Ar-H)	54.8 (CH_2-(C-2)), 58.5 (CH_2-(C-5)), 60.3 (Ar-CH_2), 161.4 (C-5), 163.4 (C-2), 124.5, 126.4, 128.7, 130.6 (aromatic carbons)
12b	2.29 (s, 6H, Ar-CH_3), 4.78 (s, 4H, CH_2-(C-2)), 5.38 (s, 4H, CH_2-(C-5)), 5.58 (s, 4H, Ar-CH_2), 7.03–7.35 (m, 8H, Ar-H)	25.4 (Ar-CH_3), 54.4 (CH_2-(C-2)), 57.8 (CH_2-(C-5)), 59.8 (Ar-CH_2), 159.3 (C-5), 162.9 (C-2), 122.4, 129.8, 131.5, 136.4 (aromatic carbons)
12c	5.03 (s, 4H, CH_2-(C-2)), 5.52 (s, 4H, CH_2-(C-5)), 5.63 (s, 4H, Ar-CH_2), 7.22–7.51 (m, 8H, Ar-H)	55.8 (CH_2-(C-2)), 59.2 (CH_2-(C-5)), 61.5 (Ar-CH_2), 162.8 (C-5), 163.7 (C-2), 123.4, 128.3, 132.9, 135.7 (aromatic carbons)
13a	5.11 (s, 4H, CH_2- (C-2)), 5.58 (s, 4H, CH_2-(C-5)), 5.72 (s, 4H, Ar-CH_2), 7.16–7.49 (m, 10H, Ar-H)	55.5 (CH_2-(C-2)), 60.4 (CH_2-(C-5)), 63.8 (Ar-CH_2), 176.4 (C-5), 178.6 (C-2), 124.9, 126.9, 130.7, 131.9 (aromatic carbons)
13b	2.31 (s, 6H, Ar-CH_3), 5.09 (s, 4H, CH_2-(C-2)), 5.47 (s, 4H, CH_2-(C-5)), 5.72 (s, 4H, Ar-CH_2), 7.12–7.41 (m, 8H, Ar-H)	26.7 (Ar-CH_3), 55.7 (CH_2-(C-2)), 59.8 (CH_2-(C-5)), 62.7 (Ar-CH_2), 175.3 (C-5), 177.9 (C-2), 124.2, 126.8, 132.9, 137.3 (aromatic carbons)
13c	5.16 (s, 4H, CH_2-(C-2)), 5.62 (s, 4H, CH_2-(C-5)), 5.74 (s, 4H, Ar-CH_2), 7.23–7.53 (m, 8H, Ar-H)	55.9 (CH_2-(C-2)), 61.8 (CH_2-(C-5)), 64.9 (Ar-CH_2), 176.8 (C-5), 178.2 (C-2), 125.6, 127.9, 133.2, 136.8 (aromatic carbons)
14a	5.07 (s, 4H, CH_2-(C-3)), 5.51 (s, 4H, CH_2-(C-5)), 5.55 (s, 4H, Ar-CH_2), 5.62 (bs, 4H, NH_2), 7.10–7.47 (m, 10H, Ar-H)	53.8 (CH_2-(C-3)), 59.5 (CH_2-(C-5)), 62.5 (Ar-CH_2), 153.8 (C-5), 164.2 (C-3), 124.6, 125.4, 131.6, 132.9 (aromatic carbons)
14b	2.27 (s, 6H, Ar-CH_3), 5.04 (s, 4H, CH_2-(C-3)), 5.49 (s, 4H, CH_2- (C-5)), 5.60 (s, 4H, Ar-CH_2), 5.64 (bs, 4H, NH_2), 7.06–7.39 (m, 8H, Ar-H)	25.8 (Ar-CH_3), 52.9 (CH_2-(C-3)), 59.3 (CH_2-(C-5)), 62.2 (Ar-CH_2), 154.7 (C-5), 163.9 (C-3), 123.2, 125.0, 131.0, 137.1 (aromatic carbons)
14c	5.14 (s, 4H, CH_2-(C-3)), 5.54 (s, 4H, CH_2-C-5), 5.62 (s, 4H, Ar-CH_2), 5.66 (bs, 4H, NH_2), 7.17–7.52 (m, 8H, Ar-H)	54.3 (CH_2-(C-3)), 60.2 (CH_2-(C-5)), 63.5 (Ar-CH_2), 154.8 (C-5), 165.0 (C-3), 124.9, 125.7, 132.6, 135.7 (aromatic carbons)

CONCLUSION

A new class of bis(5-aryl-1,3,4-oxadiazolyl/thiadiazolyl/1,2,4-triazolylmethyl)sulfones and bis(5-arylmethanesulfonyl methyl-1,3,4-oxadiazolyl/thiadiazolyl/1,2,4-triazolyl methyl) sulfones were synthesized by exploiting the ester functionalities in aryl acid methyl ester and arylmethanesulfonylacetic acid methyl ester adopting simple and well-versed methodologies. All the new compounds were characterized by spectral parameters and elemental analyses.

EXPERIMENTAL

General. 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, hexane/ethyl acetate, 3:1). The IR spectra were recorded on a Thermo Nicolet IR 200 FT-IR spectrometer as KBr pellets, and the wave numbers were given in cm^{-1}. The ^1H NMR spectra were recorded in $CDCl_3$/DMSO-d_6 on a Brucker-400 spectrometer (400 MHz). The ^{13}C NMR spectra were recorded in $CDCl_3$/DMSO-d_6 on a Brucker 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 Finnigan Mat 1210 B at 70 eV with an emission current of 100 μA. The microanalyses were performed on a Perkin-Elmer 240C elemental analyzer. The starting compound sulfonyldiacetic acid (**2**) was prepared by the literature procedure [25].

Aryl acid hydrazide (5)/arylmethanesulfonylacetic acid hydrazide/(8): general procedure. To a solution of aryl acid methyl ester (**4**)/arylmethanesulfonylacetic acid methyl ester (**7**) (10 mmol) in methanol (6 mL), hydrazine hydrate (11 mmol), and three drops of pyridine were added and refluxed for 4–6 h. The reaction mixture was cooled, and the solid separated was collected by filtration, dried, and recrystallized from methanol.

Bis(5-aryl-1,3,4-oxadiazolylmethyl)sulfone (9)/bis(5-arylmeth anesulfonylmethyl-1,3,4-oxadiazolylmethyl)sulfone (12): general procedure. A mixture of sulfonyldiacetic acid (**2**) (1 mmol), aryl acid hydrazide (**5**)/arylmethanesulfonylacetic acid hydrazide (**8**) (2 mmol), and $POCl_3$ (7 mL) was heated under reflux for 8–10 h . The excess $POCl_3$ was removed under reduced pressure, and the residue was poured onto crushed ice. The solid separated was filtered washed with saturated sodium bicarbonate solution, followed by water. It was dried and recrystallized from ethanol.

Bis(5-aryl-1,3,4-thiadiazolylmethyl)sulfone (10)/bis(5-arylmeth anesulfonylmethyl-1,3,4-thiadiazolylmethyl)sulfone (13): general procedure. In a sealed test tube, the compound bis(5-aryl-1,3,4-oxadiazolylmethyl)sulfone (**9**)/bis(5-arylmethanesulfonylmethyl-1,3,4-oxadiazolylmethyl)sulfone (**12**) (2.5 mmol), thiourea (20 mmol), and tetrahydrofuran (5 mL) were taken and heated at 120–150°C in an oil bath for 22–24 h. After the reaction was completed, it was extracted with dichloromethane. The organic layer was washed with water, brine solution, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the resultant solid was recrystallized from 2-propanol.

Bis(5-aryl(4-amino)-1,2,4-triazol-3-ylmethyl)sulfone (11)/bis (5-arylmethane sulfonylmethyl(4-amino)-1,2,4-triazol-3-ylmethyl) sulfone (14): general procedure. To a solution of **9/12** (1 mmol) in *n*-butanol (10 mL), hydrazine hydrate (6 mmol) was added and refluxed for 9–11 h. Then, KOH (4 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 recrystallized from ethanol.

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