Supplementary Information

Sulfamides and sulfamide polymers directly from sulfur dioxide

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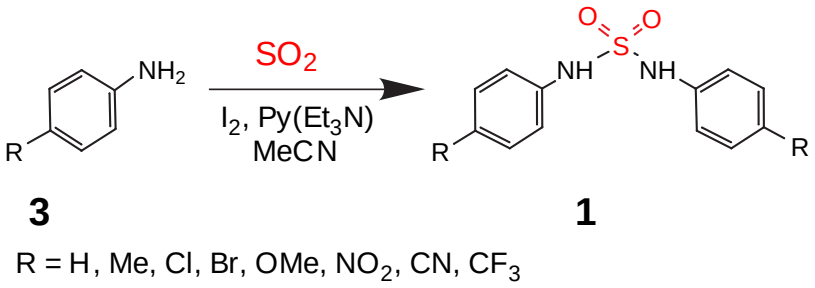
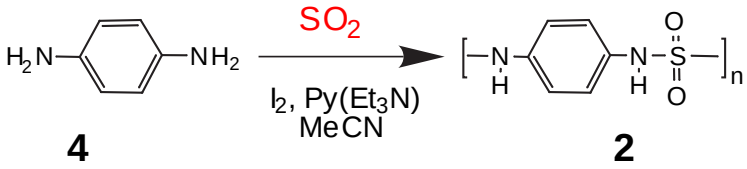
General

X-ray analysis was performed on a Bruker Smart Apex CCD based X-ray diffractometer with the Oxford Cryosystem low temperature setup. FTIR spectra were measured on Bruker Vector 22 spectrometer in KBr. ^{1}H and ^{13}C NMR spectra were recorded at 295K on JEOL 300 and 500 MHz spectrometers in $CDCl_3$ or DMSO-d_6. Chemical shifts were measured relative to residual non-deuterated solvents resonances. SO_2 was purchased from AirGas, Inc. and dried prior the use by passing through P_2O_5. MS analyses were performed on an Agilent ESI-TOF spectrometer. CHN and Cl elemental analyses were done at QTI, Inc. Melting points were measured on a Mel-Temp II apparatus and are uncorrected.





General procedure for preparation of sulfamides 1a-o: SO_2 gas was bubbled through the ice-cold MeCN solution (5 mL) of Py or Et_3N (3 mmol) for 10 min. I_2 (1 mmol) was then added, and after it dissolved, arylamines **3a-o** (1 mmol) were added. The reaction mixture was stirred for 2 h at rt and then poured into 10% aq NaOH (20 mL). The pH of the solution was adjusted up to ~6 using citric acid and the product was extracted with CH_2Cl_2 (3 × 10 mL). Combined organic layers were washed with 2M aq HCl (3 × 10 mL) and brine (3 × 10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave sulfamides **1a-o**, which were purified by recrystallization from $CHCl_3$-hexane. In cases when the product was not soluble in CH_2Cl_2, the solid material was collected by filtration, washed with 2N aq HCl, water and dried in vacuo.

Table S1. Conversion of Arylamines **3** to *N,N'*-diarylsulfamides **1**

Amine	Yield of **1a-o**, %[a]		m.p. [°C]	Lit. m.p. [°C]
	Pyridine	Et_3N		
Aniline **3a**	60	79	110-112	109-110 [1]
4-Me-aniline **3b**	51	79	97-98	98-100 [1]
4-NO_2-aniline **3c**	20	22	187-196 (dec)	195-197 (dec) [2]
2,4,6-Me_3-aniline[d] **3d**	60	87	152-160	164-166 [3]
4-Br-aniline **3e**	75	69	122-124	122-123 [4]
2,4,6-*t*-Bu_3-aniline **3f**	n.d.[c]	n.d.[c]		
2-(CO_2Et)-aniline[b] **3g**	43	62	97-99	

4-Cl-aniline **3i**	58	66	120-121	120-121 [2]
4-MeO-aniline **3j**	39	70	98-100	99-101 [1]
4-CF_3-aniline[b] **3k**	53	58	150-152	
4-CN-aniline **3l**	24	54	260-262 (dec)	168-170 (dec) [2]
2-aminopyridine **3m**	17	41	218-220	218-220 [5]
1-naphthylamine•HCl[b] **3n**	32	35	167-168 (dec)	
N-Me aniline **3o**	n.d.[c]	n.d.[c]		

[a]Isolated yields. [b]All new compounds were characterized by high-resolution ^{1}H and ^{13}C NMR spectroscopy and CHN elemental microanalyses. [c]Not detected. [d]According to [3] the direct reaction between the sulfuryl chloride and 2,4,6 trimethylaniline did not yield 2,4,6,2',4',6'-hexamethylsulfanilide.

(2-(CO_2Et)-C_6H_4-NH)$_2SO_2$ (1g): mp 97-99 °C (from $CHCl_3$/hexane); ^{1}H NMR (500 MHz; $CDCl_3$): δ 10.9 (2 H, s, NH), 7.87 (2 H, dd, *J* = 8.3, *J* = 2.0, Ar), 7.71 (2 H, dd, *J* = 8.7, *J* = 1.0, Ar), 7.48 (2 H, ddd, *J* = 8.3, *J* = 8.7, *J* = 2.0, Ar), 7.00 (2 H, ddd, *J* = 8.3, *J* = 8.7, *J* = 1.0, Ar), 4.27 (4 H, q, *J* = 7.3, CH_2), 1.34 (6 H, t, *J* = 7.3, CH_3); ^{13}C NMR (125 MHz; $CDCl_3$): δ 167.7, 140.2, 134.6, 131.1, 122.6, 118.4, 115.6, 61.6, 14.2; Found: C, 55.02; H, 5.05; N, 7.07. Calcd. for $C_{18}H_{20}N_2O_6S$: C, 55.09; H, 5.14; N, 7.14.

(4-CF_3-C_6H_4-NH)$_2SO_2$ (1k): mp 150-152 °C (from $CHCl_3$/hexane); ^{1}H NMR (500 MHz; DMSO-d_6): δ 11.1 (2 H, s, NH), 7.63 (4 H, d, *J* = 8.7, Ar), 7.29 (4 H, d, *J* = 8.7, Ar); ^{13}C NMR (125 MHz; DMSO-d_6): δ 142.0, 127.0, 124.9, 123.6, 118.1; Found: C, 43.62; H, 2.49; N, 7.18. Calcd. for $C_{14}H_{10}F_6N_2O_2S$: C, 43.76; H, 2.62; N, 7.29.

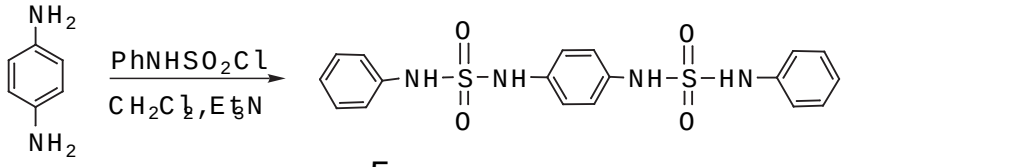
(4-CN-C_6H_4-NH)$_2SO_2$ (1l): mp 260-262 °C (decomp., from THF/hexane); ^{1}H NMR (300 MHz; DMSO-d_6): δ 11.2 (2 H, s, NH), 7.73 (4 H, d, *J* = 8.6, Ar), 7.23 (4 H, d, *J* = 8.6, Ar); ^{13}C NMR (75 MHz; DMSO-d_6): δ 142.5, 134.2, 119.3, 117.9, 105.3; Found: C, 55.73; H, 3.33; N, 18.48. Calcd. for $C_{14}H_{10}N_4O_2S$: C, 56.37; H, 3.38; N, 18.78.

(1-Napthyl-NH)$_2SO_2$ (1n): mp 167-168 °C (decomp., from acetone/hexane); ^{1}H NMR (500 MHz; DMSO-d_6): δ 10.0 (2 H, s, NH), 8.00 (2 H, d, *J* = 8.7, Ar), 7.8 (2 H, d, *J* = 7.8, Ar), 7.73 (2 H, d, *J* = 7.8, Ar), 7.59 (2 H, d, *J* = 7.3, Ar), 7.46 (4 H, m, Ar), 7.34 (2 H, ddd, *J* = 7.8, *J* = 7.3, *J* = 1.0, Ar); ^{13}C NMR (125 MHz; DMSO-d_6): δ 134.4, 133.9, 128.7, 128.4, 126.6, 126.2, 126.1, 126.0, 123.5, 120.8; Found: C, 68.18; H, 4.51; N, 7.96. Calcd. for $C_{20}H_{16}N_2O_2S$: C, 68.95; H, 4.63; N, 8.04.

Preparation of poly(phenylenesulfamide) 2: SO_2 gas was bubbled through the ice-cold MeCN solution (10 mL) of Et_3N (12 mmol, 1.69 mL, 1.21 g) for 20 min. I_2 (4 mmol, 1.05 g) was then added, and after it dissolved, *p*-phenylenediamine **4** (2 mmol, 0.22 g) was added. The reaction mixture was stirred for 2 h at rt and then poured

into 10% aq NaOH (40 mL). The pH of the solution was adjusted up to ~6 using citric acid and the solid material was collected by filtration. The light brown product was dissolved in 1M NaOH and reprecipitated then with 1M HCl twice. The polymer was washed with water in a centrifuge tube until washing were eventually neutral. Drying in vacuo at 60 °C gave the polymer **2** (0.125 g, 35%): mp 190-205 °C (decomp.); ^{1}H NMR (300 MHz; DMSO-d_6): δ 8.96 (m, NH), 6.96 (m, Ar); FTIR (KBr, cm^{-1}): ν 3277 (NH), 1325 and 1152 (S=O); Found: C, 39.96; H, 3.63; N, 14.15; Cl, 3.96. Calcd. for $C_{66}H_{70}N_{22}O_{20}S_{10}Cl_2$: C, 42.10; H, 3.75; N, 16.36; Cl, 3.77.

Method A



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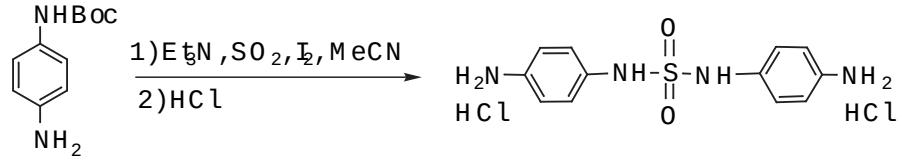

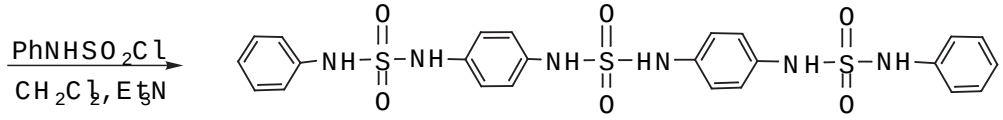

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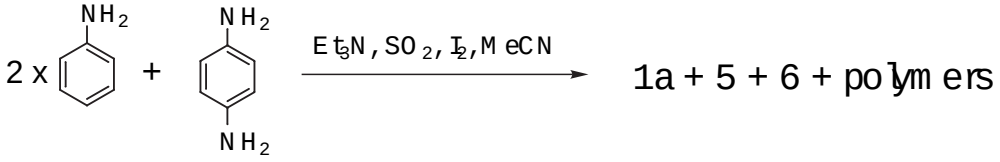
Method B



Procedure for preparation of sulfamide oligomers 5 and 6. Method A. Ph-NHSO$_2$NH-C$_6$H$_4$-NHSO$_2$NH-Ph (5): To the ice-cold solution of phenylsulfamoyl chloride[6] PhNHSO$_2$Cl (2.2 mmol, 0.42 g) in CH_2Cl_2 (5 mL) the CH_2Cl_2 solution (5 mL) of *p*-phenylenediamine **4** (1 mmol, 0.11 g) and Et_3N (2.4 mmol, 0.34 mL, 0.24 g) was added dropwise. The reaction mixture was stirred for overnight at rt and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (10 mL) and washed with 1N HCl (3 × 3 mL) and brine (3 × 3 mL) and dried over anhydrous Na_2SO_4. Evaporation of solvent leaved a solid which was purified by column chromatography (SiO_2, AcOEt/hexane = 2/1, R_f = 0.5) to give the triphenyldisulfamide **5** (0.19 g, 45%); mp. 190-

194 °C (decomp., from AcOEt/hexane); ^{1}H NMR (500 MHz; DMSO-d_6): δ 10.07 (2 H, s, NH), 10.00 (2 H, s, NH), 7.24 (4 H, dd, *J* = 7.3, *J* = 7.3, Ar), 7.10 (4 H, dd, *J* = 7.3, *J* = 2.0, Ar), 6.98 (2 H, m, Ar), 6.97 (4 H, s, Ar); ^{13}C NMR (125 MHz; DMSO-d_6): δ 138.8, 134.1, 129.5, 123.3, 120.7, 118.8; FTIR (KBr, cm^{-1}): ν 3279 (NH), 1319 and 1147 (S=O); ESI-TOF, *m/z* 441.0652 (calcd. for $C_{18}H_{18}N_4O_4S_2Na$, 441.0662); Found: C, 50.75; H, 4.33; N, 12.89; Calcd. for $C_{18}H_{18}N_4O_4S_2$: C, 51.66; H, 4.34; N, 13.39.

(Ph-NHSO$_2$NH-C$_6$H$_4$-NH)$_2$SO$_2$ (6): Step 1 (BocNH-C$_6$H$_4$-NH)$_2$SO$_2$: SO_2 gas was bubbled through the ice-cold MeCN solution (5 mL) of Et_3N (3 mmol, 0.43 mL, 0.31 g) for 10 min. I_2 (1 mmol, 0.25 g) was then added, and after it dissolved, monoprotected Boc phenylenediamine[7] (1 mmol, 0.21 g) was added. The reaction mixture was stirred for 2 h at rt and then poured into 10% aq NaOH (20 mL). The pH of the solution was adjusted up to ~6 using citric acid and the product was extracted with CH_2Cl_2 (3 × 10 mL). Combined organic layers were washed with 10% citric acid solution (3 × 10 mL) and brine (3 × 10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave light brown solid material, which were purified by column chromatography (SiO_2, AcOEt/hexane = 2/1) to give the product (0.101 g, 42%); mp. 124-130 °C (from AcOEt/hexane); ^{1}H NMR (500 MHz; DMSO-d_6): δ 9.78 (2 H, s, NH,), 9.19 (2 H, s, NH), 7.29 (4 H, d, *J* = 9.1, Ar), 6.96 (4 H, d, *J* = 9.1, Ar), 1.45 (18 H, s, CH_3); ^{13}C NMR (125 MHz; DMSO-d_6): δ 153.4, 135.7, 133.0, 120.4, 119.4, 79.4, 28.7; FTIR (KBr, cm^{-1}): ν 3287 (NH), 1699 (C=O); 1369 and 1154 (S=O); Found: C, 55.24; H, 6.38; N, 10.59; Calcd. for $C_{22}H_{30}N_4O_6S$: C, 55.22; H, 6.32; N, 11.71.

Step 2 (HCl•NH$_2$-C$_6$H$_4$-NH)$_2$SO$_2$: To the ice cold solution of MeOH (5 mmol, 0.2 mL, 0.16 g) in 5 mL of CH_2Cl_2 acetyl chloride (1.7 mmol, 0.12 mL, 0.14 g) was added dropwise and the reaction mixture was stirred for 30 min. Then the solution of (BocNH-C_6H_4-NH)$_2$SO$_2$ (0.2 mmol, 0.095 g) in CH_2Cl_2 (5 mL) was added and the reaction mixture was stirred at rt until TLC (AcOEt/hexane = 2/1) showed that starting material disappeared. Solvent was removed under reduced pressure and the residue was recrystallized from MeOH/ether to give white crystals of (HCl•NH$_2$-C_6H_4-NH)$_2$SO$_2$: (0.064 g, 91%); mp. 170-174 °C (decomp., from MeOH/ether; ^{1}H NMR (300 MHz; DMSO-d_6): δ 10.43 (2 H, s, NH,), 9.83 (6 H, br, NH), 7.18 (4 H, d, *J* = 8.9, Ar), 7.12 (4 H, d, *J* = 8.9, Ar); ^{13}C NMR (75 MHz; DMSO-d_6): δ 138.0, 127.4, 124.4, 119.6; FTIR (KBr, cm^{-1}): ν 2862 (NH), 1313 and 1154 (S=O).

Step 3 (Ph-NHSO$_2$NH-C$_6$H$_4$-NH)$_2$SO$_2$ (6): To the ice-cold solution of phenylsulfamoyl chloride $PhNHSO_2Cl$ (0.31 mmol, 0.06 g) in MeCN (3 mL), the MeCN solution (3 mL) of (HCl•NH$_2$-C_6H_4-NH)$_2$SO$_2$ (0.14 mmol, 0.05 g) and Et_3N (0.62 mmol, 0.09 mL, 0.62 g) was added dropwise. The reaction mixture was stirred for overnight at rt, concentrated under reduced pressure, redissolved in EtOAc (10 mL) and then washed with 1N HCl (3 × 3 mL), brine (3 × 3 mL) and dried over anhydrous Na_2SO_4. Evaporation of solvent gave a light brown solid, which was purified by column chromatography (SiO_2, AcOEt/hexane = 2/1, R_f = 0.3) to give the tetraphenyltrisulfamide **6** (0.034 g, 41%): mp. 200-210 °C (decomp., from AcOEt/hexane); ^{1}H NMR (500 MHz; DMSO-d_6): δ 10.07 (2 H,

s, NH), 10.00 (2 H, s, NH), 9.88 (2 H, s, NH), 7.24 (4 H, dd, *J* = 7.8, *J* = 7.8, Ar), 7.09 (4 H, d, *J* = 7.8, Ar), 6.97 (10 H, m, Ar); ^{13}C NMR (125 MHz; DMSO-d_6): δ 138.8, 134.2, 134.0, 129.5, 123.3, 120.7, 120.6, 118.8; FTIR (KBr, cm^{-1}): ν 3301 (NH), 1329 and 1152 (S=O); ESI-TOF, *m/z* 587.0833 (calcd. for $C_{24}H_{23}N_6O_6S_3$, [M-H] 587.0847); Found: C, 48.80; H, 4.18; N, 13.92; Calcd. for. $C_{24}H_{24}N_6O_6S_3$ C, 48.97; H, 4.11; N, 14.28.

Procedure for preparation of sulfamides 5 and 6. Method B: The ice-cold MeCN solution (10 mL) of Et_3N (6.6 mmol, 0.93 mL, 0.66 g), p-phenylenediamine **4** (1 mmol, 0.11 g) and aniline $PhNH_2$ (2.2 mmol, 0.2 mL, 0.21 g) was saturated by SO_2 gas (20 min) and then I_2 (2.2 mmol, 0.56 g) was added. After 2 h of stirring at rt the reaction mixture was poured into 10% aq NaOH (20 mL). Citric acid was used to bring the pH of solution to ~6, which was extracted then by ethyl acetate (3 × 10 mL). Combined organic layers were washed with 2M aq HCl (3 × 10 mL) and brine (3 × 10 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under the reduced pressure the residue was chromatographed (SiO_2, AcOEt/hexane = 2/1) to get diphenylsulfamide **1a** (0.109 g, 40%), triphenyldisulfamide **5** (0.016 g, 4%) and tetraphenyltrisulfamide **6** (0.009 g, 3%).

X-ray Structure Determinations. A suitable crystal covered with a layer of hydrocarbon oil was selected and mounted with paratone-N oil on a cryo-loop, and immediately placed in the low-temperature nitrogen stream. The X-ray intensity data were measured at 100(2) K on a Bruker SMART APEX CCD area detector system equipped with a Oxford Cryosystems 700 Series Cryostream cooler, a graphite monochromator, and a Mo Kα fine-focus sealed tube (λ = 0.710 73 Å). The detector was placed at a distance of 5.995 cm from the crystal. The data frames were integrated with the Bruker SAINT-Plus software package. Data were corrected for absorption effects using the multi-scan technique (SADABS). Structures were solved and refined using Bruker SHELXTL (Version 6.14) software package. Some details of the data collection and refinement are given in Tables S1-2. Further details are in the cif files.

Table S2. Crystal data and structure refinement for **(Ph-NH)$_2$SO$_2$**.

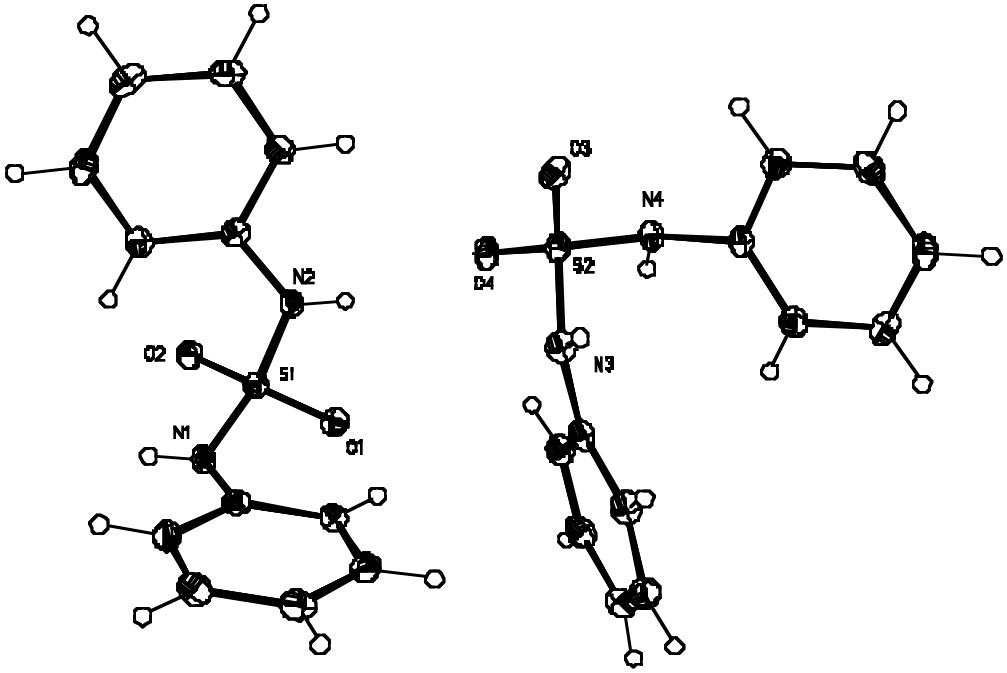
Identification code	dias266s	
Empirical formula	C12 H12 N2 O2 S	
Formula weight	248.30	
Temperature	100(2) K	
Wavelength	0.71073	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 10.0786(6)	α= 78.4390(10)¡.
	b = 11.3145(7)	β= 72.4410(10)¡.
	c = 11.3378(7)	γ = 74.6320(10)¡.
Volume	1178.34(12) ^{3}	
Z	4	

Density (calculated)	1.400 Mg/m^3
Absorption coefficient	0.265 mm^{-1}
F(000)	520
Crystal size	0.37 x 0.32 x 0.07 mm^3
Theta range for data collection	1.88 to 26.00¡.
Index ranges	-12<=h<=12, -13<=k<=13, -13<=l<=13
Reflections collected	9448
Independent reflections	4608 [R(int) = 0.0196]
Completeness to theta = 26.00¡	99.5 %
Absorption correction	None
Max. and min. transmission	0.9814 and 0.9082
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4608 / 0 / 323
Goodness-of-fit on F^2	1.045
Final R indices [I>2sigma(I)]	R1 = 0.0371, wR2 = 0.0929
R indices (all data)	R1 = 0.0442, wR2 = 0.0988
Largest diff. peak and hole	0.426 and -0.441 e. $^{-3}$

Table S3. Crystal data and structure refinement for **Ph-$NHSO_2NH$-C_6H_4-$NHSO_2NH$-Ph**.

Identification code	dias326s	
Empirical formula	C24 H30 N4 O6 S2	
Formula weight	534.64	
Temperature	100(2) K	
Wavelength	0.71073	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 8.8506(6)	α= 90¡.
	b = 9.9988(7)	β= 101.1520(10)¡.
	c = 15.2627(11)	γ = 90¡.
Volume	1325.17(16) ^{3}	
Z	2	
Density (calculated)	1.340 Mg/m^3	
Absorption coefficient	0.246 mm^{-1}	
F(000)	564	
Crystal size	0.38 x 0.24 x 0.11 mm^3	
Theta range for data collection	2.35 to 25.99¡.	
Index ranges	-10<=h<=10, -12<=k<=12, -18<=l<=18	
Reflections collected	9052	
Independent reflections	2571 [R(int) = 0.0211]	

Completeness to theta = 25.99¡	98.7 %
Absorption correction	None
Max. and min. transmission	0.9734 and 0.9126
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2571 / 0 / 173
Goodness-of-fit on F^2	1.075
Final R indices [I>2sigma(I)]	R1 = 0.0362, wR2 = 0.0927
R indices (all data)	R1 = 0.0407, wR2 = 0.0970
Largest diff. peak and hole	0.292 and -0.408 e. $^{-3}$



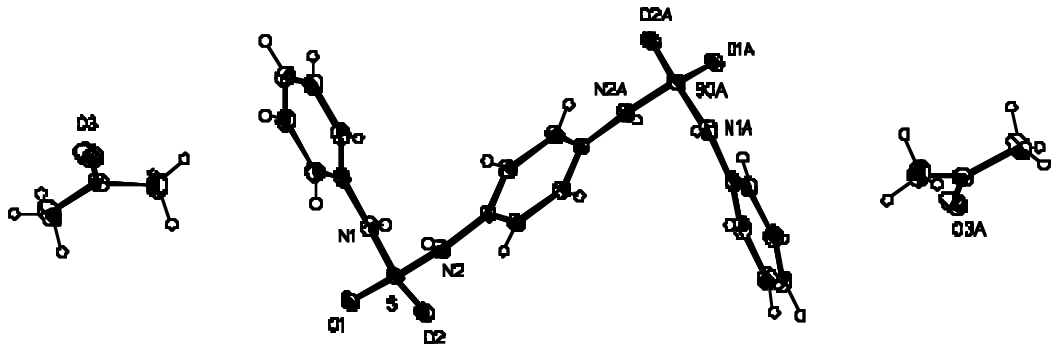


Figure S1: ORTEP diagrams of **1a**, top (two molecules in the symmetric unit) and **5,** bottom (crystallizes with two acetone molecules).

Unfortunately, thus far, we have not been able to obtain high quality crystals of compound **6** for detailed X-ray crystallographic work. Nevertheless, the X-ray data collected on the poorly diffracting samples clearly show the basic backbone of the tetramer. It adopts a W-shaped structure as illustrated in Figure S2.

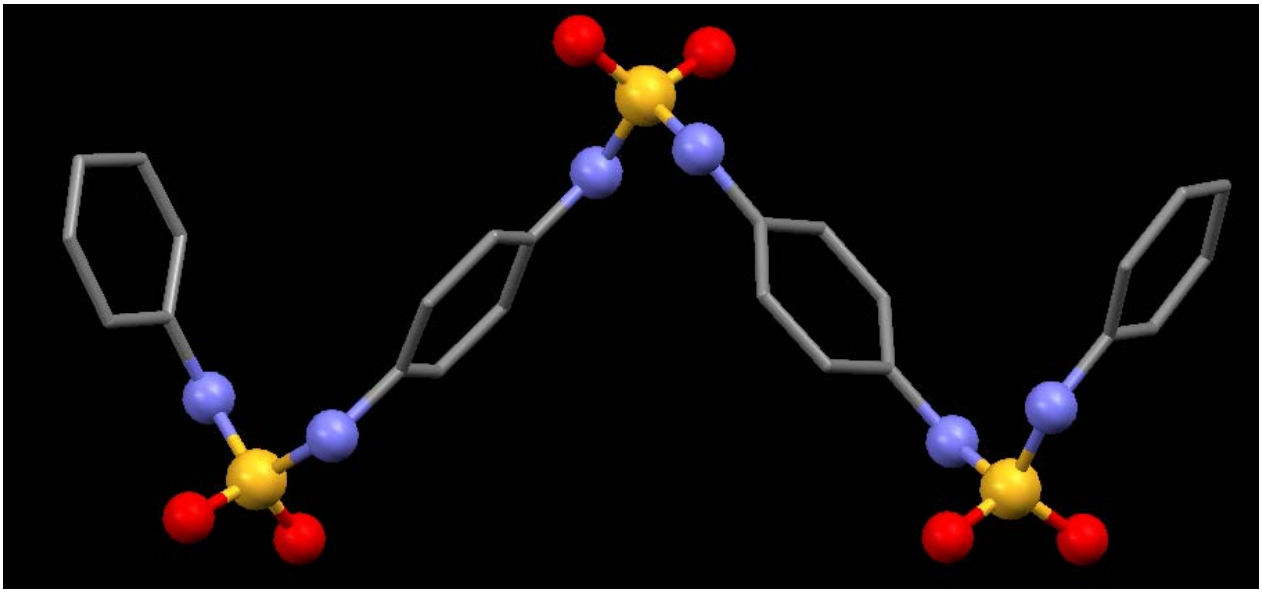


Figure S2. Molecular structure of the tetramer **6** showing the W-shaped backbone

REFERENCES

1 W. J. Spillane, J. A. Barry, F. L. Scott, *J. Chem. Soc., Perkin Trans. 2*, 1973, 481-483.

2 E. W. Parnell, *J. Chem. Soc.,* 1960, 4366-4368.

R. A. Abramovitch, T. Chellathurai, W. D. Holcomb, I. T. McMaster, D. P. Vanderpool, *J. Org. Chem.*, 1977, **42**, 2920-2926.

4 B. H. Chase, W. T. Weller, *J. Pharm. Pharmacol.*, 1964, **16**, 163-173.

5 W. J. Spillane, J. A. Barry, W. A. Heaphy, F. L. Scott, *Z. Naturforsch., Teil B*, 1974, **29**, 702-703.

6 J. A. Kloek, K. L. Leschinsky, *J. Org. Chem.*, 1976, **41**, 4028-4029.

7 A. Renodon-Corniere, S. Dijols, C. Perollier, D. Lefevre-Groboillot, J.-L. Boucher, R. Attias, M.-A. Sari, D. Stuehr, D. Mansuy, *J. Med. Chem.*, 2002, **45**, 944-954.