A Two-sites Reactive Platform in the Synthesis of Amino-functionalized Amphiphilic Molecules via Sulfenic Acids

Paola Bonaccorsi,[a] Chiara Maria Antonietta Gangemi,[a] Valentina Greco,[b] Giuseppe Gattuso[a] and Anna Barattucci[a]*

[a] Dipartimento di Scienze Chimiche Biologiche Farmaceutiche ed Ambientali (CHIBIOFARAM), Università degli Studi di Messina, Sicily, Italy
[b] Dipartimento di Scienze Chimiche, Università degli studi di Catania, Sicily, Italy

TABLE OF CONTENTS

Chemicals. Solvents were purified according to standard procedures. All the syntheses were monitored by TLC on commercially available precoated plates (silica gel 60 F254), and the products were visualized with vanillin [1 g dissolved in MeOH (60 mL) and conc. H_2SO_4 (0.6 mL)] and UV lamp. Silica gel 60 was used for column chromatography.

Instrumentation. Proton (^1H) and carbon (^{13}C) NMR spectra were recorded on a Varian 500 spectrometer (at 500 MHz for ^1H; and 125 MHz for ^{13}C) using $CDCl_3$ or DMSO-d_6 as solvents. Chemical shifts are given in parts per million (ppm) (δ relative to residual solvent peak for ^1H and ^{13}C), coupling constants (J) are given in Hertz, and the attributions are supported by heteronuclear single-quantum coherence (HSQC) and correlation spectroscopy (COSY) experiments. Chemical shifts are reported in ppm to residual $CHCl_3$ peak (7.26 ppm) or residual DMSO *peak* (2.49 ppm). Combustion analyses were carried out on a FISONS EA1108 elemental analyzer, mass analysis for final products (**1a**, **1b**) were performed with a TSQ-Quantum access Triple Quadrupole Mass Spectrometer (Thermo Fisher Scientific, Waltham, MA, USA), equipped with a HESI (Heated ElectroSpray Ionization) source; analyses were run in positive mode. Mass spectrometer parameters were: sheath gas flow rate, 30 (arbitrary units); aux gas flow rate, 15 (arbitrary units); spray voltage, 5.00 kV; capillary temperature, 250° C; tube lens voltage, 55 V; heater temperature, 270°C; scan mode: full scan.

Computational Studies

The conformational analysis of compound **7a** was carried out with the classical molecular mechanics force field (MMFF) by using the Monte Carlo method to randomly sample the conformational space. The equilibrium geometries were then calculated at the density functional level of theory (DFT, B3LYP functional) using the 6-311++G(d,p) basis set. All quantum mechanical calculations were performed using Spartan ’10 (Wavefunction, Inc., Irvine, CA, USA).

Conformer A (Energy: –2177.66315 au):			**Conformer B (Energy: –2177.62679 au):**		
H	0.220481	-2.437090	H	0.241572	1.644994
C	0.121491	-1.369581	C	0.120836	0.927016
C	-0.121491	1.369581	C	-0.168425	-0.942816
C	-1.033932	-0.697384	C	0.749478	1.148972
C	1.140760	-0.677068	C	-0.640627	-0.217268
C	1.033932	0.697384	C	-0.797472	-1.164487
C	-1.140760	0.677068	C	0.592980	0.201544
H	2.027625	-1.214938	H	-1.121366	-0.374068
H	-2.027625	1.214938	H	1.073841	0.357874
H	-0.220481	2.437090	H	-0.288588	-1.661395
C	-2.136840	-1.424155	C	1.563938	2.386042
H	-2.872531	-0.743748	H	1.807876	2.542422
H	-1.766324	-2.085256	H	1.073746	3.286798
C	2.136840	1.424155	C	-1.612988	-2.400683
H	1.766324	2.085256	H	-1.124063	-3.302055
H	2.872531	0.743748	H	-1.856823	-2.556607
S	-3.112825	-2.591381	S	3.184031	2.492021
O	-2.180266	-3.549646	O	2.970612	2.117260
O	-4.207796	-3.083627	O	3.715624	3.820886
S	3.112825	2.591381	S	-3.233620	-2.504566
O	4.207796	3.083627	O	-3.766599	-3.833069
O	2.180266	3.549646	O	-3.020575	-2.129168
C	3.814849	1.551300	C	-4.336148	-1.261891
C	-3.814849	-1.551300	C	4.287993	1.250060
C	-3.441593	-1.866279	C	5.280564	1.765279
H	-3.844094	-1.326456	H	6.024461	1.116148
H	-2.740265	-2.672255	H	5.381985	2.834787
C	3.441593	1.866279	C	-5.329903	-1.776785
H	3.844094	1.326456	H	-6.073539	-1.127313
H	2.740265	2.672255	H	-5.432409	-2.846388
C	4.716787	0.436117	C	-4.092912	0.184436
C	6.446459	-1.724931	C	-3.728066	2.966600
C	5.785528	0.593942	C	-4.245630	1.058330
C	4.523596	-0.820832	C	-3.752264	0.726346
C	5.374061	-1.884123	C	-3.576065	2.094701
C	6.636910	-0.470072	C	-4.069737	2.425822
H	5.952144	1.557533	H	-4.486127	0.655686
H	3.690428	-0.959356	H	-3.624365	0.069793
H	5.216023	-2.847924	H	-3.319696	2.501000
H	7.467772	-0.332268	H	-4.184597	3.084931
C	-4.716787	-0.436117	C	4.045968	-0.196265
C	-6.446459	1.724931	C	3.681468	-2.978263
C	-5.785528	-0.593942	C	4.198174	-1.071114
C	-4.523596	0.820832	C	3.705912	-0.737119
C	-5.374061	1.884123	C	3.530038	-2.105342
C	-6.636910	0.470072	C	4.022329	-2.438500
H	-5.952144	-1.557533	H	4.438354	-0.669261
H	-3.690428	0.959356	H	3.578218	-0.079815
H	-5.216023	2.847924	H	3.274060	-2.510810
H	-7.467772	0.332268	H	4.136395	-3.098216
C	7.320217	-2.818275	C	-3.532137	4.370690
H	8.702308	-4.573264	H	-3.216348	6.602173
C	8.053127	-3.753110	C	-3.363024	5.556194
C	-7.320217	2.818275	C	3.484752	-4.382087
H	-8.702308	4.573264	H	3.166121	-6.612635
C	-8.053127	3.753110	C	3.314331	-5.567152

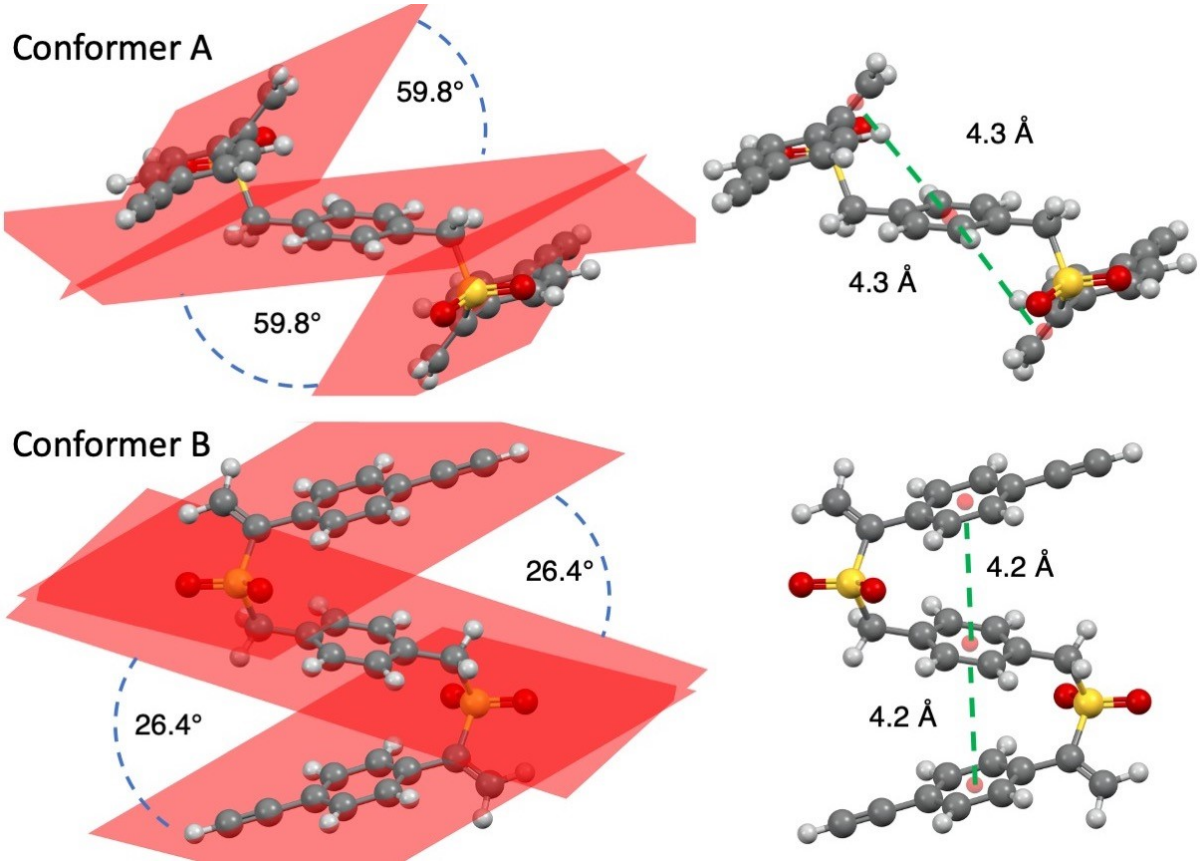
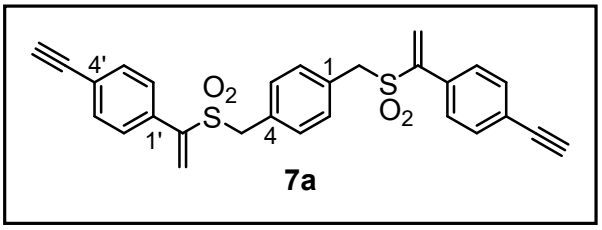


Figure S1 Additional views of conformers A (top) and B (bottom) of compound **7a** highlighting interplanar angles and centroid-centroid distances.

General procedure for the synthesis of compounds **7**

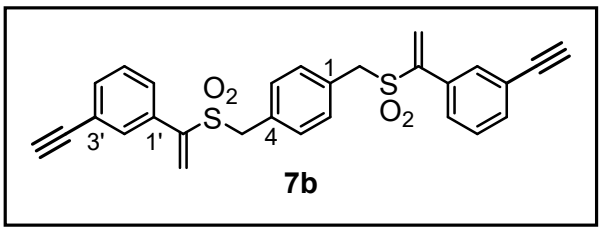
To a solution of the diastereomeric mixtures of **6a** or **6b** (1 eq.) in DCM, a solution of *m*-CPBA (2.5 eq. 80 wt %) in DCM was slowly added at 0°C and under argon atmosphere. The reaction mixture was warmed at r. t. and monitored by TLC (*n*-Hexane/DCM 10:90) until the disappearance of the reagent. The reaction was quenched with the addition of an equal volume of aqueous solution of $Na_2S_2O_3$ (10%w/w) and the organics washed with sat. solution of $NaHCO_3$ (3 times) and brine (twice). The organic phase was dried with Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (n-Hexane/DCM 10:90) and **7a** or **7b** obtained as a white solid.



7a

1,4-Bis{[1-(4-ethynylphenyl)ethenylsulfonyl]methyl}-benzene (**7a**)

Yield: 98%. White solid. TLC: R_f 0.72 (*n*-Hexane/Ethyl Acetate 50:50). δH (500 MHz; $CDCl_3$) 7.55 (8H, m, 2x H-2', 2x H-3', 2x H-5',2x H-6'), 7.12 (4H, s, H-2, H-3, H-5, H-6), 6.32 and 6.00 (4H, two s, 2x $=CH_2$), 4.10 (4H, s, 2x SCH_2), 3.21 (2H, s, 2x ≡CH). δC (125 MHz; $CDCl_3$) 147.3 (q), 132.6 (q), 132.5 and 128.6 (C-2', C-3', C-5', C-6'), 131.1 (C-2, C-3, C-5, C-6), 128.7 and 123.9 (q), 128.2 ($=CH_2$), 82.6 (q), 79.4 (≡CH), 58.5 (SCH_2). Anal. Calcd. for $C_{28}H_{22}O_4S_2$ (486,60): C, 69.11; H, 4.56. Found: C, 69.07; H, 4.55.



7b

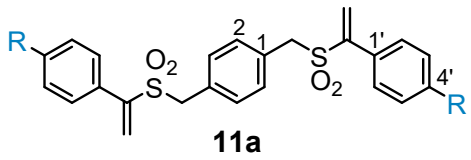
1,3-Bis{[1-(4-ethynylphenyl)ethenylsulfonyl]methyl}-benzene (**7b**)

Yield: 98%. White solid. TLC: R_f 0.70 (*n*-Hexane/Ethyl Acetate 50:50). δH (500 MHz; $CDCl_3$) 7.64 (2H, s, 2x H-2'), 7.59 and 7.56 (4H, dd, $J_{4',5'}$= $J_{5',6'}$ =7.9, 2x H-4', 2x H-6'), 7.39 (2H, t, $J_{2',3'}$= $J_{3',4'}$ =7.9, 2x H-5'), 7.13 (4H, s, H-2, H-3, H-5, H-6), 6.32 and 5.99 (4H, two s, 2x $=CH_2$), 4.10 (4H , s, 2x SCH_2), 3.15 (2H, s, 2x ≡CH). δC (125 MHz; $CDCl_3$) 147.2 (q), 133.4 and 129.0 (C-4', C-5', C-6'), 132.7 (q), 132.2 (C-2'), 131,1 (C-2, C-3, C-5, C-6), 129.0 and 123.0 (q), 128.2($=CH_2$), 82.6 (q), 79.4 (≡CH), 58.5 (SCH_2). Anal. Calcd. for $C_{28}H_{22}O_4S_2$ (486,60): C, 69.11; H, 4.56. Found: C, 68.98; H, 4.54.

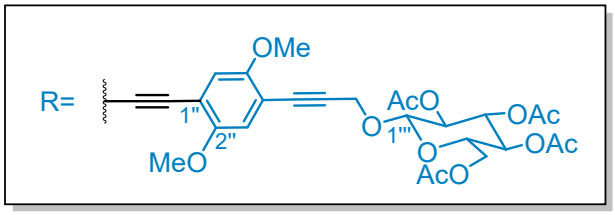
General procedure for the synthesis of compounds **11**

A solution of compound **11a** or **11b** (1 eq.), compound **10** (2.5 eq.) and $[Pd(PPh_3)]_4$ (0.1 eq.) in dry DMF and NEt_3 (1:1 *ratio*) was stirred at 60°C, under argon atmosphere for 2h, until the disappearance of the reagent by TLC (*n*-Hexane/Ethyl Acetate 25:75). The solvent was removed under reduced pressure, the crude product was purified by column chromatography (DCM 100) and the desired product was obtained as a white solid.

Compound 11a

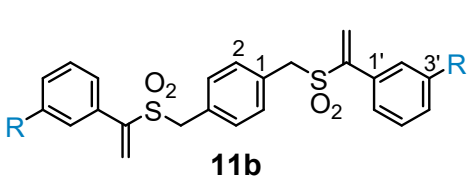


11a

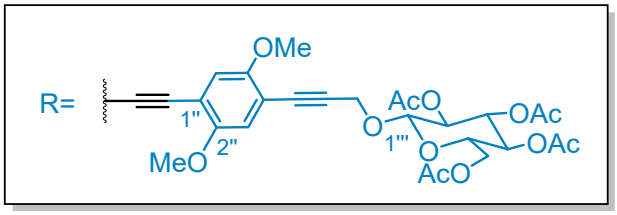


Yield: 49%. White solid. R_f 0.65 (DCM/Ethyl Acetate 80:20). δH (500 MHz; $CDCl_3$) 7.59 (8H, m, 2x H-2', 2x H-3', 2x H-5', 2x H-6'), 7.10 (4H, s, H-2, H-3, H-5, H-6), 7.02 and 6.95 (4H, two s, 2x H-3'', 2x H-6''), 6.30 e 6.01 (4H, two s, 2x $=CH_2$), 5.25 (2H, t, $J_{2''',3'''}$= $J_{3''',4'''}$ =9.8, 2x H-3'''), 5.11 (2H, t, $J_{3''',4'''}$= $J_{4''',5'''}$ =9.8, 2x H-4'''), 5.04 (2H, dd, $J_{1''',2'''}$= 8.3, $J_{2''',3'''}$= 9.8, 2x H-2'''), 4.90 (2H, d, $J_{1''',2'''}$ =8.3, 2x H-1'''), 4.65 (4H, s, 2x $CH_2C\equiv$), 4.26 and 4.16 (2H, split AB system, $J_{5''',6'''A}$ =4.4, $J_{6'''A,6'''B}$ =12.8, 2x H_2-6'''), 4.10 (4H, s, 2x SCH_2), 3.89 and 3.88 (12H, two s, 4x -OCH_3), 3.75 (2H, m, 2x H-5'''), 2.07, 2.04, 2.02, and 2.01 (24H, four s, 8x CH_3CO). δC (125 MHz; $CDCl_3$) 170.6, 170.3, 169.4 and 169.3 (4x CO), 154.1 (q), 147.3 (q), 132.1 (q), 132.0 and 128.6 (C-2', C-3', C-5', C-6'), 131,0 (C-2, C-3, C-5, C-6), 128,4 and 124.9 (q), 128.2 ($=CH_2$), 115.7 and 115.5 (C-3'', C-6''), 113.3 and 112.7 (q), 98.3 (C-1'''), 94.0, 89.2, 87.6 and 83.3 (q), 72.8 (C-3'''), 71.9 (C-5'''), 71.1 (C-2'''), 68.3 (C-4'''), 61.8 (C-6'''), 58.5 (SCH_2), 57.0 ($CH_2C\equiv$), 56.4 and 56.3 (-OCH_3), 20.7, 20.6 and 20.5 (CH_3CO). Anal. Calcd. for $C_{78}H_{78}O_{28}S_2$ (1527,57): C, 61.33; H, 5.15. Found: C, 61.27; H, 5.17.

Compound 11b



11b



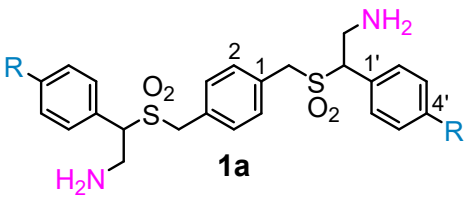
Yield: 46%. White solid. R_f 0.65 (DCM/Ethyl Acetate 80:20). δH (500 MHz; $CDCl_3$) 7.74 (2H, s, 2x H-2'), 7.62 and 7.52 (4H, two d, $J_{4',5'}$= $J_{5',6'}$ =7.5, 2x H-4', 2x H-6'), 7.40 (2H, t, $J_{4',5'}$= $J_{5',6'}$ =7.5, 2x H-5'), 7.13 (4H, s, H-2, H-3, H-5, H-6), 7.04 and 6.96

(4H, two s, 2x H-3'', 2x H-6''), 6.34 and 6.02 (4H, two s, 2x =CH_2), 5.27 (2H, t, $J_{2''',3'''} = J_{3''',4'''}$ =9.5, 2x H-3'''), 5.12 (2H, t, $J_{3''',4'''} = J_{4''',5'''}$ =9.6, 2x H-4'''), 5.05 (2H, dd, $J_{1''',2'''}$ =8.0, $J_{2''',3'''}$ =9.8, 2x H-2'''), 4.91 (2H, d, $J_{1''',2'''}$ =8.0, 2x H-1'''), 4.66 (4H, s, 2x $CH_2C{\equiv}$), 4.29 and 4.17 (2H, split AB system, $J_{5''',6'''A}$ = 4.5, $J_{6'''A,6'''B}$ =12.5, 2x H_2-6'''), 4.13 (4H, s, 2x SCH_2), 3.89 (12H, s, 4x OCH_3), 3.76 (2H, m, 2x H-5'''), 2.08, 2.05, 2.03, and 2.01 (24H, four s, 8x CH_3CO). δC (125 MHz; $CDCl_3$) 170.7, 170.3, 169.5 and 169.4 (4 x CO), 154.1 and 153.9 (q), 147.4 (q), 132.9, 128.9 and 128.8 (C-4', 5', 6'), 132.7 (q), 131.6 (C-2'), 131,1 (C-2, C-3, C-5, C-6), 128,7 and 124.0 (q), 128.2 (=CH_2), 115.7 and 115.6 (C-3'', C-6''), 113.3 and 112.6 (q), 98.3 (C-1'''), 93.9, 89.2, 86.6 and 83.3 (q), 72.8 (C-3'''), 71.9 (C-5'''), 71.1 (C-2'''), 68.3 (C-4'''), 61.8 (C-6'''), 58.6 (SCH_2), 57.0 ($CH_2C{\equiv}$), 56.5 and 56.4 (-OCH_3), 20.7, 20.6 and 20.5 (CH_3CO). Anal. Calcd. for $C_{78}H_{78}O_{28}S_2$ (1527,57): C, 61.33; H, 5.15. Found: C, 61.55; H, 5.13.

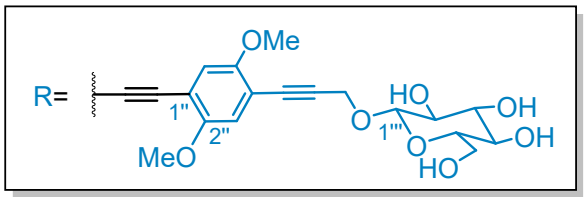
General procedure for the synthesis of compounds **1**

Compound **11a** or **11b** (0.2 mmol) was dissolved in THF-MeOH (1:1, 40 mL). A large excess of aqueous ammonia (12 mL) was added, and the reaction was maintained under continuous stirring at r.t. overnight, until the disappearance of the starting product by TLC (*n*-Hexane/Ethyl Acetate 40:60). Solvents were removed under reduced pressure and several washings with Et_2O were performed to purify the product from the undesired acetamide.[1]

Compound 1a



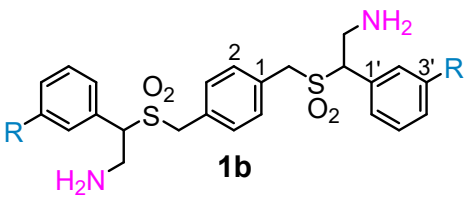
1a



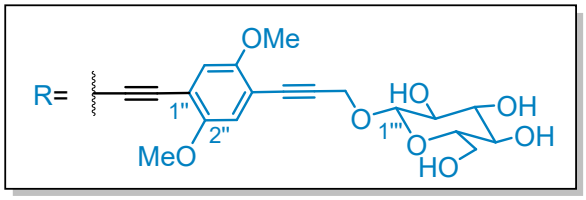
Yield: 98%. White solid. R_f 0.01 (Ethyl Acetate 100). δH (500 MHz; DMSO-d_6) 7.57 and 7.44 (8H, two d, *J*= 8.4, 2x H-2', 2x H-3', 2x H-5', 2x H-6'), 7.33 (4H, s, H-2, H-3, H-5, H-6), 7.16 and 7.08 (4H, two s, 2x H-3'', 2x H-6''), 5.12 (2H, d, *J* =4.8, 2x -OH), 4.96 (2H, d, *J* =4.4, 2x -OH), 4.91 (2H, d, *J* =5.4, 2x -OH), 4.67 (2H, part A of AB system, d, *J* =15.5, 2x $CH_2C{\equiv}$), 4.6-4.5 (6H, m, 2x $CH_2C{\equiv}$, 2x CH_2S; 2x -OH-6'''), 4.44 (2H, dd, J_{vic} =5.5, J_{vic} =4.1, 2x -$CHCH_2NH_2$), 4.38-4.32 (4H, m, 2x -CH_2S and 2x H-1'''), 3.82 and 3.81 (12H, two s, 4x -OCH_3), 3.71-2.95 (16H, m, 2x H_2-6''', 2x H-5''', 2x H-4''', 2x H-3''', 2x H-2''', 2x -$CHCH_2NH_2$). δC (125 MHz; DMSO-d_6) 154.1 and 153.9 (q), 133.3 (q), 131.9 and 130.9 (C-2', C-3', C-5', C-6'), 131.7 (C-2, C-3, C-5, C-6), 128.4 and 123.0 (q), 116.3 and 116.0 (C-3'', C-6''), 112.9 and 112.7 (q), 101.6 (C-1'''), 94.6, 91.7, 87.1 and 82.5 (q), 77.5, 77.1, 73.7 and 70.5 (C-2''', C-

3’’’, C-4’’’, C-5’’’), 69.9 (-CHCH$_2$NH$_2$), 61.6 (C-6’’’), 57.6 (-CH$_2$S), 56.6 and 56.2 (-OCH$_3$), 56.2 (-CH$_2$C≡), 41.8 (-CHCH$_2$NH$_2$). Anal. Calcd. for $C_{62}H_{68}N_2O_{20}S_2$ (1225,34): C, 60.77; H, 5.59; N, 2.29. Found: C, 60.82; H, 5.60; N, 2.29. ESI(+)-MS m/z calcd. for $C_{62}H_{68}N_2O_{20}S_2$ ([M+H]$^+$) 1226.35, found 1226.32 and 613.23 ([M+2H]$^{2+}$).

Compound 1b



1b

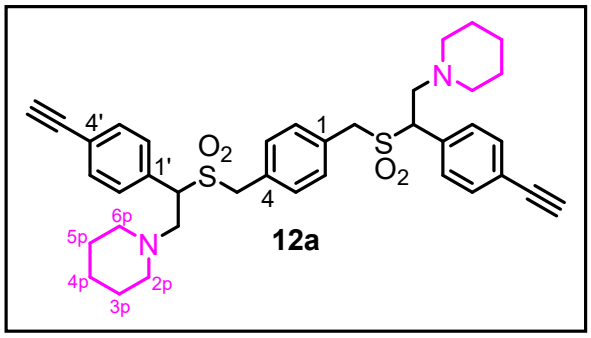


Yield: 98%. White solid. R_f 0.01 (Ethyl Acetate 100). δH (500 MHz; DMSO-d_6) 7.54 (4H, br s, 2x H-2’, 2x H-5’), 7.47-7.43 (4H, m, 2x H-4’, 2x H-6’), 7.34 (4H, s, H-2, H-3, H-5, H-6), 7.17 and 7.09 (4H, two s, 2x H-3”, 2x H-6”), 5.14 (2H, br s, 2x OH), 4.92 (2H, br s, 2x OH), 4.69 (2H, br s, 2x OH), 4.68 (2H, part A of AB system, d, *J* =15.5, 2x C*H*$_2$C≡), 4.60-4.53 (6H, m, 2x C*H*$_2$C≡, 2x C*H*$_2$S; 2x -OH-6’’’), 4.44 (2H, br t, *J* =5.5; 2x -C*H*CH$_2$NH$_2$), 4.38-4.31 (4H, m, 2x -C*H*$_2$S and 2x H-1’’’), 3.82 and 3.81 (two s, 12H, 4x -OCH$_3$), 3.72-2.98 (16H, m, 2x H$_2$-6’’’, 2x H-5’’’, 2x H-4’’’, 2x H-3’’’, 2x H-2’’’, 2x -CHC*H*$_2$NH$_2$). δC (125 MHz; DMSO-d_6) 153.7 and 153.4 (q), 132.7 (q), 131.4 and 131.3 (C-2’, C-5’, C-2, C-5), 129.1 (C-4’, C-6’) 127.9 and 122.6 (q), 115.8 and 115.6 (C-3’’, C-6’’), 112.4 and 112.3 (q), 101.1 (C-1’’’) 94.1, 91.2, 86.3 and 82.0 (q), 77.0, 76.7, 73.3 and 70.1 (C-2’’’, C-3’’’, C-4’’’, C-5’’’), 69.3 (-*C*HCH$_2$NH$_2$), 61.2 (C-6’’’), 57.2 (-*C*H$_2$S), 56.2 and 56.1 (-OCH$_3$), 55.8 (-*C*H$_2$C≡), 41.3 (-CH*C*H$_2$NH$_2$). Anal. Calcd. for $C_{62}H_{68}N_2O_{20}S_2$ (1225,34): C, 60.77; H, 5.59; N, 2.29. Found: C, 60.84; H, 5.57; N, 2.29. ESI(+)-MS m/z calcd. for $C_{62}H_{68}N_2O_{20}S_2$ ([M+H]$^+$) 1226.35, found 1226.26 and 613.24 ([M+2H]$^{2+}$).

General procedure for the synthesis of compounds **12**

To a solution of **7a** or **7b** (1eq.) in MeOH, piperidine (3.2 eq.) was added and the reaction mixture was stirred at r.t., under argon atmosphere, until the disappearance of the starting product by TLC (*n*-Hexane/Ethyl Acetate 50:50). The solvent was evaporated under reduced pressure. The desired product **12a** or **12b** was obtained without needing any further purification, after removing of piperidine excess under vacuum.

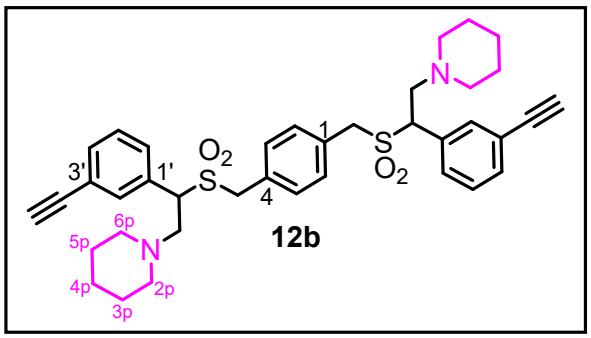
Compound 12a



12a

Yield: 98%. White solid. R_f 0.43 (*n*-Hexane/Ethyl Acetate 50:50). δH (500 MHz; $CDCl_3$) 7.48 and 7,27 ((H, two d, J_{orto} =7.8, 2 x H-2', 2x H-3', 2x H-5', 2x H-6'), 7.41 (4H, s, H-2, H-3, H-5, H-6), 4.47 and 4.38 (4H, AB system, J_{gem} =13.2, 2x SCH_2), 4.19 (2H, part X of ABX system, J_{vic1} =7.3, J_{vic2} =4.4, 2x -C*H*CH_2Pi), 3.50 and 2.84 (4H, part A and B of ABX system, J_{gem} =13.6 J_{vic1} *=7.3* J_{vic2} =4.4, 2x -CHC*H*$_2$Pi), 3.11 (2H, s, 2x ≡CH), 2.47 (8H, m, 2x H_2-2p, 2x H_2-6p), 1.43 (8H, m, 2x H_2-3p, 2x H_2-5p), 1.26 (4H, m, 2x H_2-4p) . δC (125 MHz; $CDCl_3$) 132.8 (q), 132.5 and 129.7 (C-2', C-3', C-5', C-6'), 131.5 (C-2, C-3, C-5, C-6), 128,4 and 122.8 (q), 82.9 (q), 78.3 (≡CH), 65.2 (-*C*HCH_2Pi), 59.2 and 59.1 (SCH_2, -CH*C*H_2Pi), 54.8 (C-2p, C-6p), 26.0 (C-3p, C-5p), 24.0 (C-4p). Anal. Calcd. for $C_{38}H_{44}N_2O_4S_2$ (656,90): C, 69.48; H, 6.75; N, 4.26. Found: C, 69.33; H, 6.73; N, 4.25.

Compound 12b



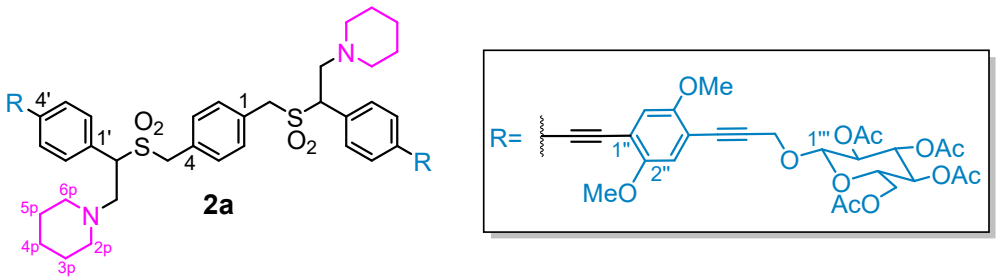
12b

Yield: 98%. White solid. R_f 0.41 (*n*-Hexane/Ethyl Acetate 50:50). δH (500 MHz; $CDCl_3$) δ 7.52-7.20 (8H, m, 2x H-2', 2x H-4', 2x H-5', 2x H-6'), 7.42 (4H, s, H-2, H-3, H-5, H-6), 4.48 and 4.41 (4H, AB system, J_{gem} =14.2, 2x SCH_2), 4.19 (2H, part X of ABX system , J_{vic1} =7.8, J_{vic2} =4.6, 2x -C*H*CH_2Pi), 3.50 and 2.83 (4H, part A and B of ABX system, J_{gem} =13.2, J_{vic1} *=7.8,* J_{vic2} =4.6, 2x -CHC*H*$_2$Pi), 3.17 (2H, s, 2x ≡CH), 2.47 (8H, m, 2x H_2-2p, 2x H_2-6p), 1.43 (8H, m, 2x H_2-3p, 2x H_2-5p), 1.25 (4H, m, 2x H_2-4p). δC (125 MHz; $CDCl_3$) 133.3, 132. 6, 130.1 and 128.8 (C-2', C-4', C-5', C-6'), 132.5 (q), 131.5 (C-2, C-3, C-5, C-6), 128.5 and 122.8 (q), 82.9 (q), 78.0 (≡CH), 65.0 (-CHCH$_2$Pi), 59.4 and 59.2 (SCH_2 and -CHCH$_2$Pi), 54.8 (C-2p, C-6p), 26.0 (C-3p, C-5p), 24.0 (C-4p). Anal. Calcd. for $C_{38}H_{44}N_2O_4S_2$ (656,90): C, 69.48; H, 6.75; N, 4.26. Found: C, 69.55; H, 6.76; N, 4.27.

General procedure for the synthesis of compounds **2**

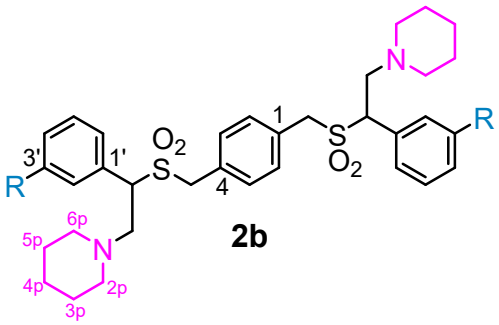
Compounds **2** were obtained following the general procedure for the synthesis of compounds **11**. The mixture was reacted until the disappearance of compounds **12** by TLC (*n*-Hexane/Ethyl Acetate 40:60). The solvents were removed under reduced pressure and the reaction crudes purified by column chromatography (*n*-Hexane/Ethyl Acetate 40:60). The desired products **2** were obtained as white solids.

Compound 2a

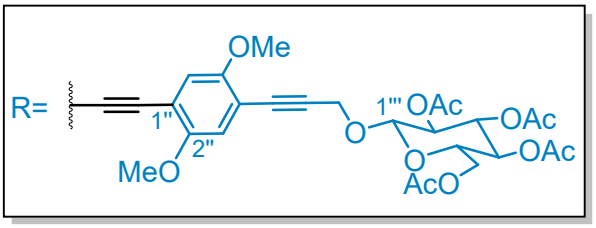


Yield: 55%. White solid. R_f 0.12 (*n*-Hexane/Ethyl Acetate 40:60). δH (500 MHz; $CDCl_3$) 7.55 and 7,33 (8H, AA'XX' system, J_{orto} =8.0, 2x H-2', 2x H-3', 2x H-5', 2x H-6'), 7.41 (4H, s, H-2, H-3, H-5, H-6), 7.00 and 6.93 (4H, two s , 2x H-3'', 2x H-6''), 5.26 (t, $J_{2''',3'''} = J_{3''',4'''}$ =9.0, 2x H-3'''), 5.11 (2H, t, $J_{3''',4'''} = J_{4''',5'''}$ =9.0, 2x H-4'''), 5.04 (2H, t, $J_{1''',2'''} = J_{2''',3'''}$ =9.0, 2x H-2'''), 4.90 (2H, d, $J_{1''',2'''}$ =9, 2x H-1'''), 4.64 (4H, s, 2x $CH_2C{\equiv}$), 4.48-4.15 (10H, m, 2x SCH_2, 2x -$CH$$CH_2$Pi, 2x H_2-6'''), 3.87 (12H, s, 4x OCH_3), 3.76 (2H, m, 2x H-5'''), 3.54 and 2.90 (4H, m AB of an ABX system, 2x -$CHCH_2$Pi), 2.49 (8H, m, 2x H_2-2p, 2x H_2-6p) , 2.07, 2.04, 2.02 and 2.00 (24H, four s, 8x CH_3CO), 1.57 (8H, m, 2x H_2-3p, 2x H_2-5p), 1.42 (4H, m, 2 x H_2-4p). δC (125 MHz; $CDCl_3$) 170.7, 170.3, 169.5 and 169.4 (4 x -CO), 154.1 and 154.0 (q), 132.1 and 129.9 (C-2', C-3', C-5', C-6'), 131.6 (C-2, C-3, C-5, C-6), 128.7, 128.3 and 124.1 (q), 115.7 and 115.6 (C-3'', C-5''), 114.6 and 112.4 (q), 98.2 (C-1'''), 94.3, 89.1, 86,7 and 83.3 (q), 72. 8 (C-3'''), 71.9 (C-5'''), 71.0 (C-2'''), 68.1 (C-4'''), 65.3 (-$C$$HCH_2$Pi), 61.8 (C-6''') 59.0 and 58.9 (SCH_2, -$CHCH_2$Pi), 57.1 (-$CH_2C{\equiv}$), 56.5 and 56.3 (-OCH_3), 54.8 (C-2p, C-6p), 25.5 (C-3p, C-5p), 23.6 (C-4p), 20.8, 20.7, 20.6 and 20.5 (CH_3CO). Anal. Calcd. for $C_{88}H_{100}N_2O_{28}S_2$ (1697,86): C, 62.25; H, 5.94; N, 1.65. Found: C, 62.31; H, 5.93; N, 1.65.

Compound 2b



2b



Yield: 62%. White solid. R_f 0.13 (*n*-Hexane/Ethyl Acetate 40:60). δH (500 MHz; $CDCl_3$) δ 7.67-7.28 (8H, m, 2 x H-2', 2x H-4', 2x H-5', 2x H-6'), 7.45 (4H, s, H-2, H-3, H-5, H-6), 7.01 and 6.94 (4H, two s, 2x H-3'', 2x H-6''), 5.27 (2H, t, $J_{2''', 3'''} = J_{3''', 4'''}$ =9.0, 2x H-3'''), 5.12 (2H, t, $J_{3''', 4'''} = J_{4''', 5'''}$ =9.0, 2x H-4'''), 5.05 (2H, br t, 2x H-2'''), 4.91 (2H, d, $J_{1''', 2'''}$ =8.0, 2x H-1'''), 4.65 (4H, s, 2x $CH_2C\equiv$), 4.53-4.12 (10H, m, 2x S*C*H_2, 2x -*C*HCH_2Pi, 2x H_2-6'''), 3.87 (12H, s, 4x OCH_3), 3.77 (2H, m, 2x H-5'''), 3.57 and 3.1 (4H, m AB of an ABX system, 2x -CHCH_2Pi), 2.53 (8H, m, 2x H_2-2p, 2x H_2-6p) , 2.08, 2.05, 2.03 and 2.01 (24H, four s, 8x CH_3CO), 1.66 (8H, m, 2x H_2-3p, 2x H_2-5p), 1.42 (4H, m, 4H, 2x H_2-4p). δC (125 MHz; $CDCl_3$) 170.8, 170.4, 169.6 and 169.5 (4 x -CO), 154.1 and 153.9 (q), 132.3, 131.8, 128.7 and 128.5 (C-2', C-3', C-5', C-6', C-2, C-3, C-5, C-6), 130.6, 128.4 and 124.3 (q), 115.9 and 115.8 (C-3'', C-6''), 113.6 and 112.6 (q), 98.2 (C-1'''), 94.3, 89.3, 86,6 and 83.5 (q), 72. 9 (C-3'''), 72.0 (C-5'''), 71.3 (C-2'''), 68.4 (C-4'''), 62.0 (-*C*HCH_2Pi), 61.9 (C-6'''), 59.9 (SCH_2), 57.1 (*C*$H_2C\equiv$), 56.6 and 56.5 (-OCH_3), 55.1 (C-2p, C-6p), 46.1 (-CH*C*H_2Pi), 29.6 (C-3p, C-5p), 23.5 (C-4p), 21,1 and 20.1 (*C*H_3CO). Anal. Calcd. for $C_{88}H_{100}N_2O_{28}S_2$ (1697,86): C, 62.25; H, 5.94; N, 1.65. Found: C, 62.49; H, 5.92; N, 1.65.

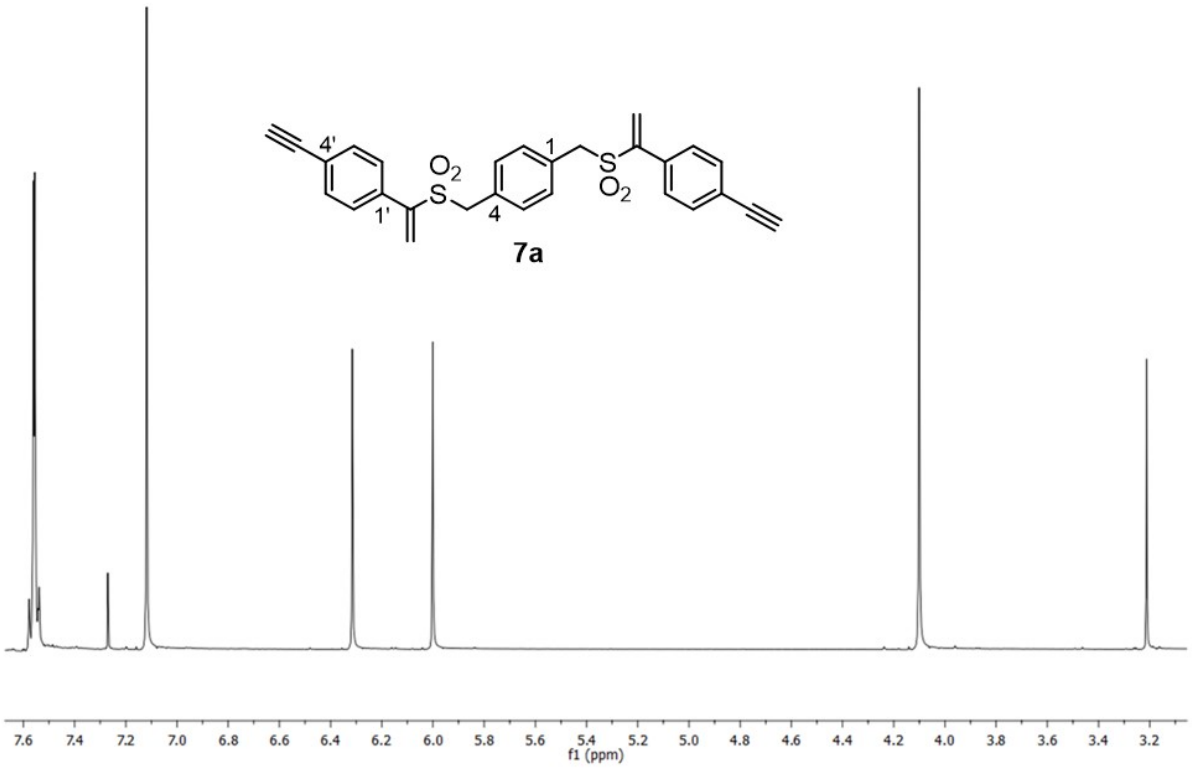


Figure S2. ^{1}H-NMR of compound **7a**

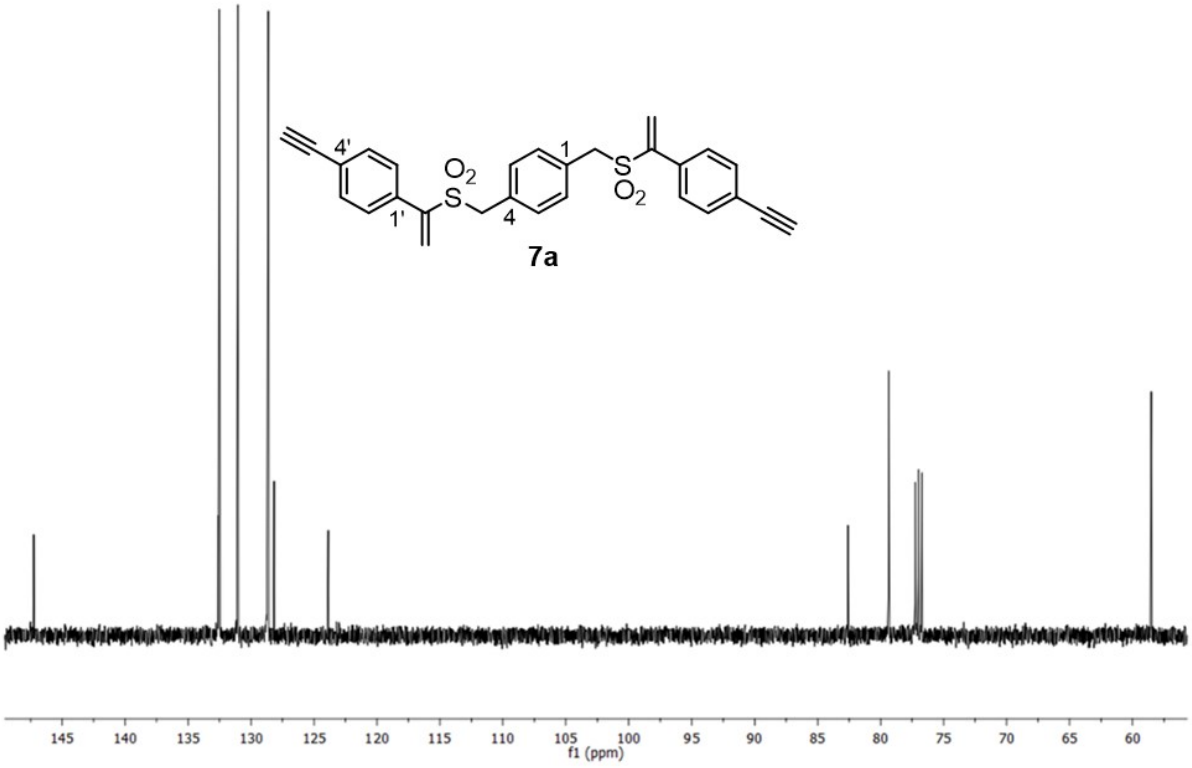


Figure S3. ^{13}C-NMR of compound **7a**

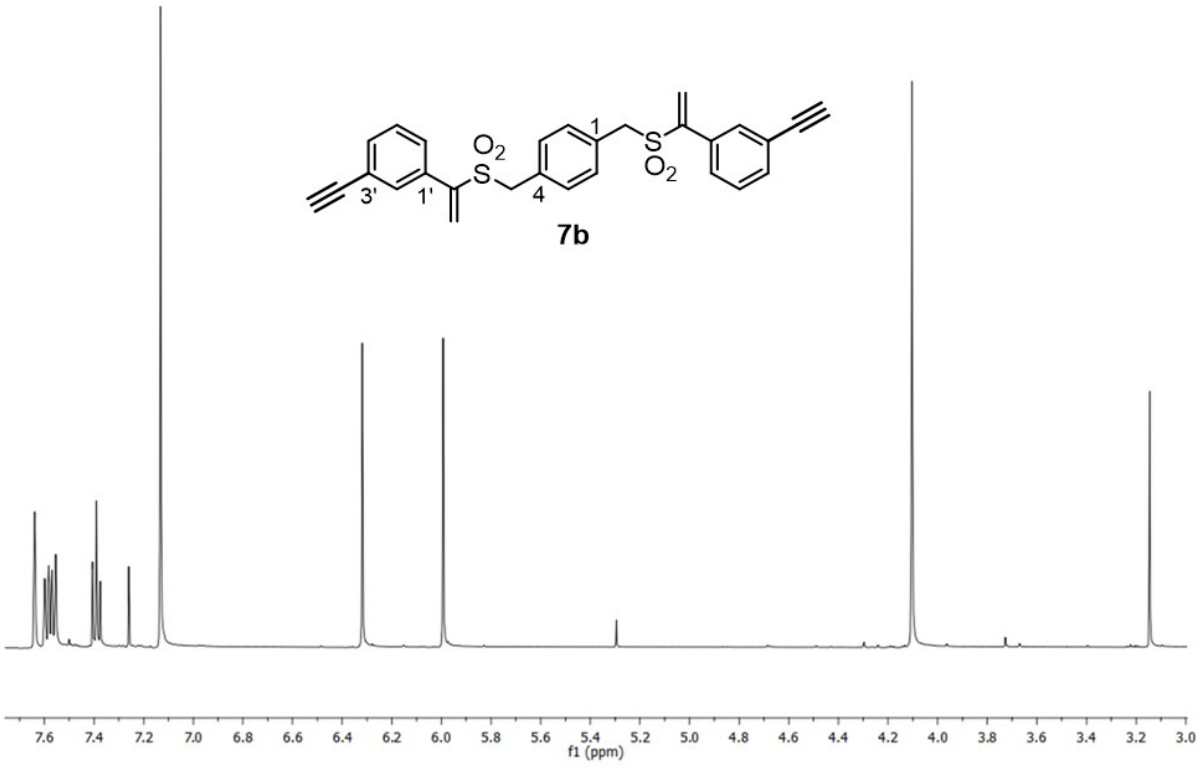


Figure S4. ^{1}H-NMR of compound **7b**

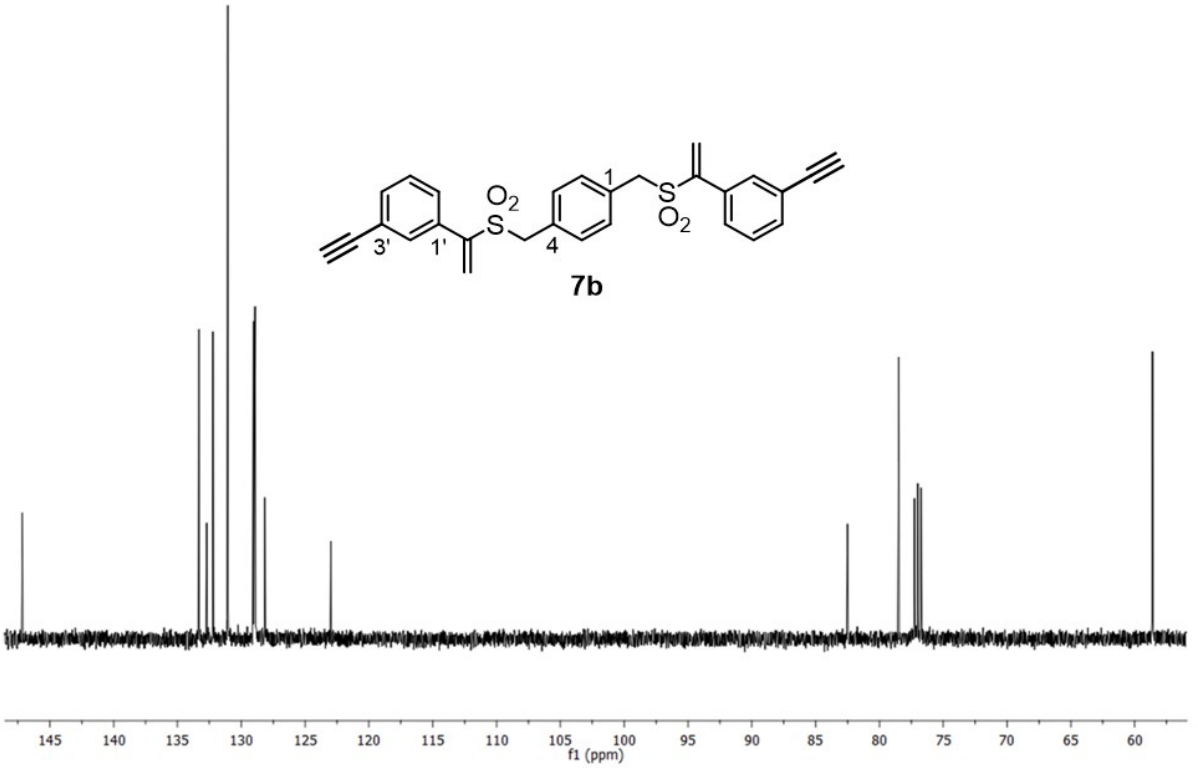


Figure S5. ^{13}C-NMR of compound **7b**

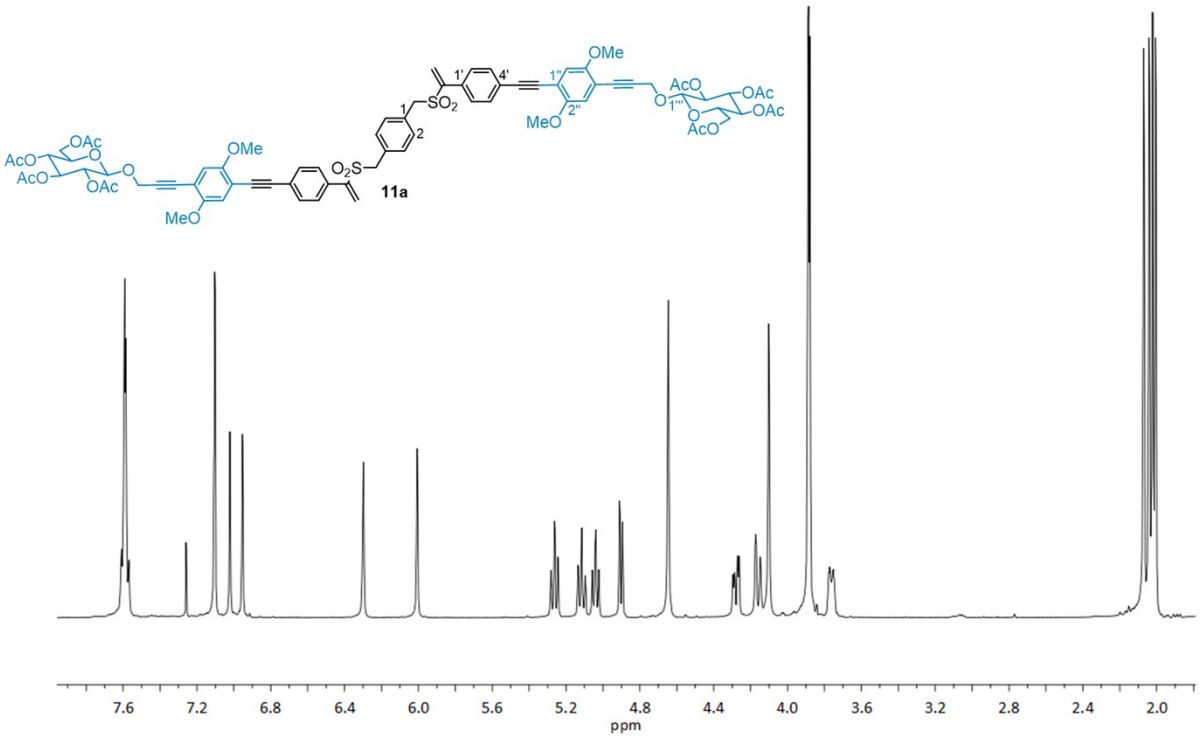


Figure S6. ^{1}H-NMR of compound **11a**

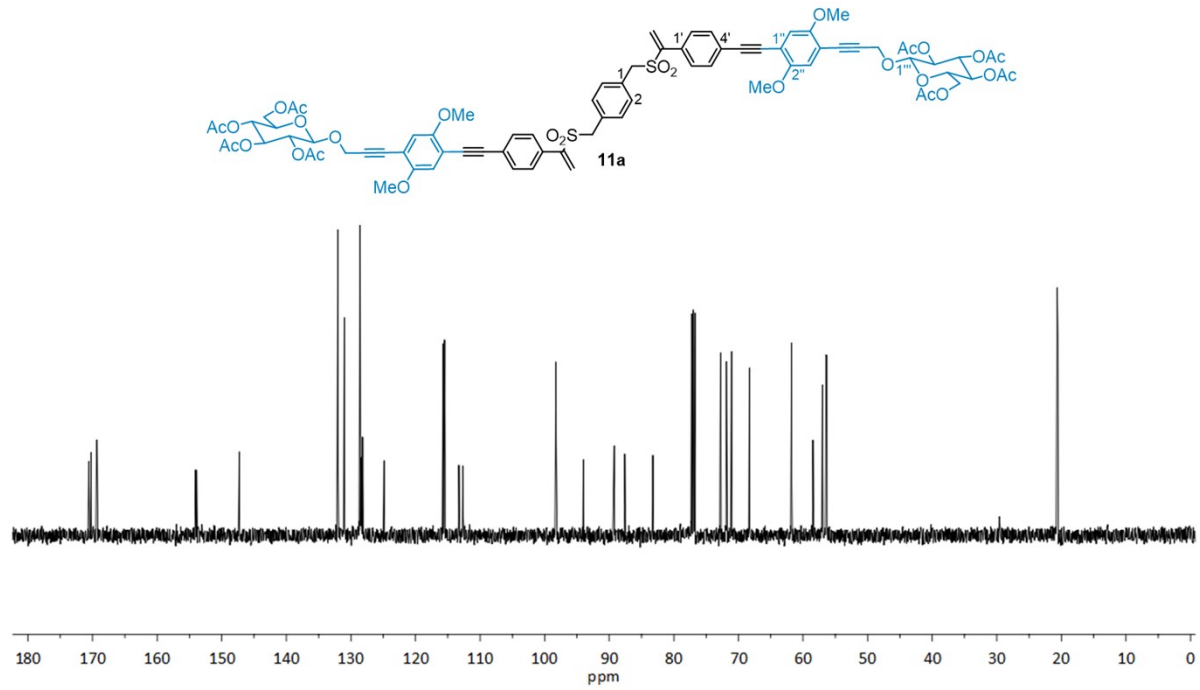


Figure S7. ^{13}C-NMR of compound **11a**

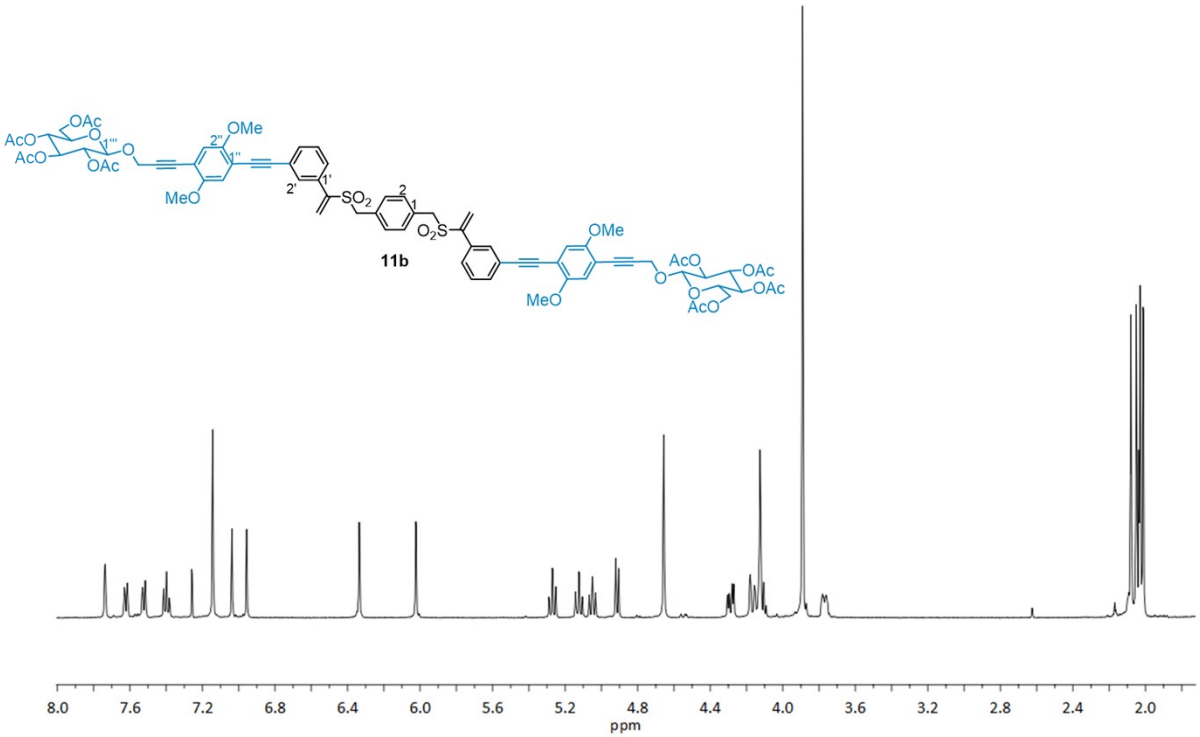


Figure S8. ^{1}H-NMR of compound **11b**

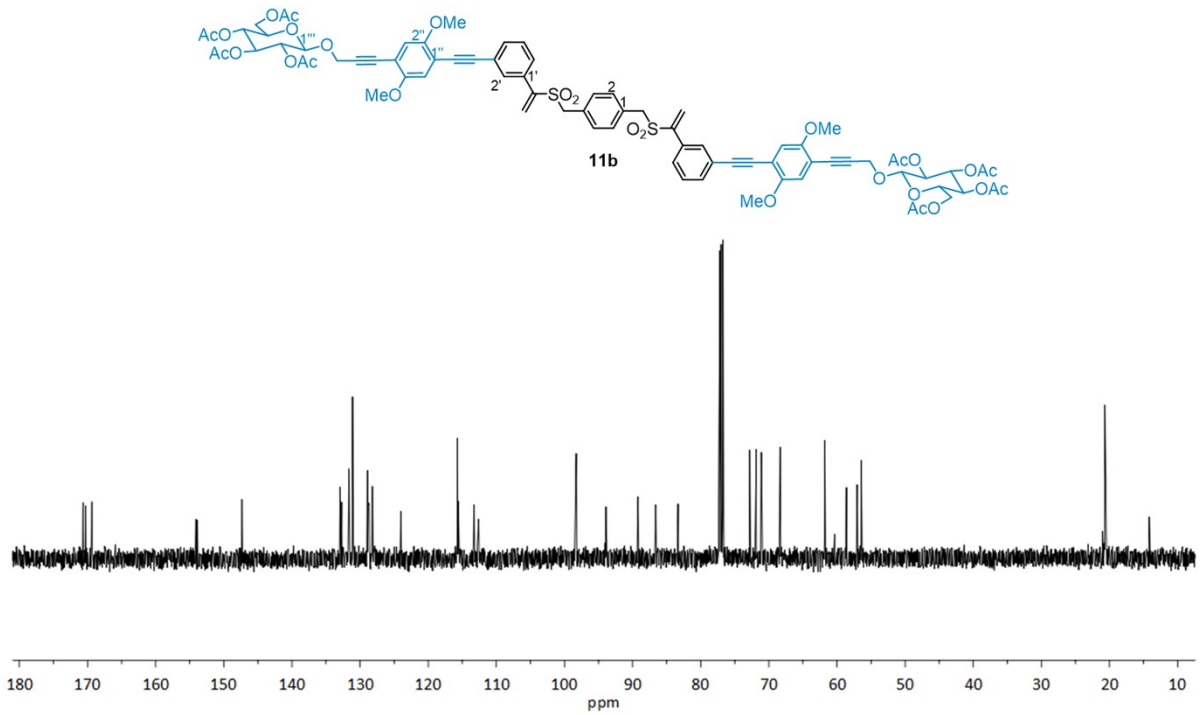


Figure S9. ^{13}C-NMR of compound **11b**

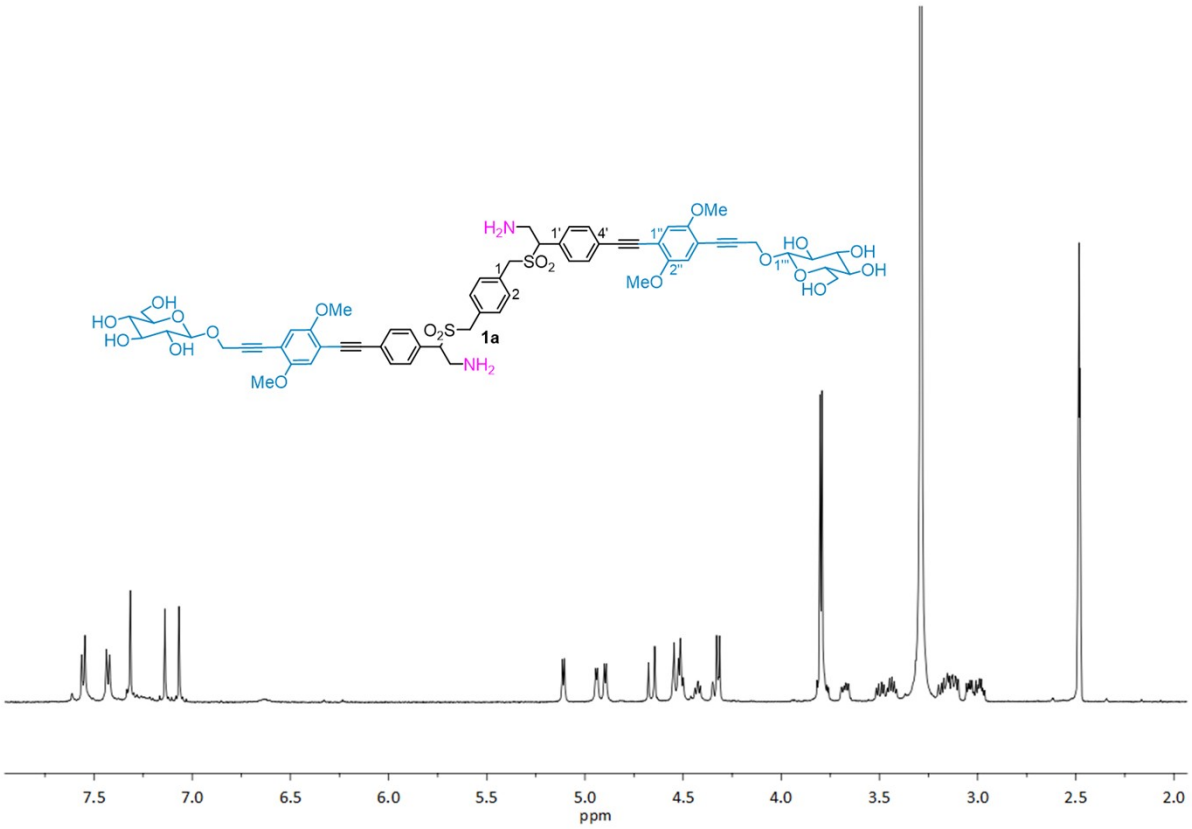


Figure S10. ^{1}H-NMR of compound **1a**

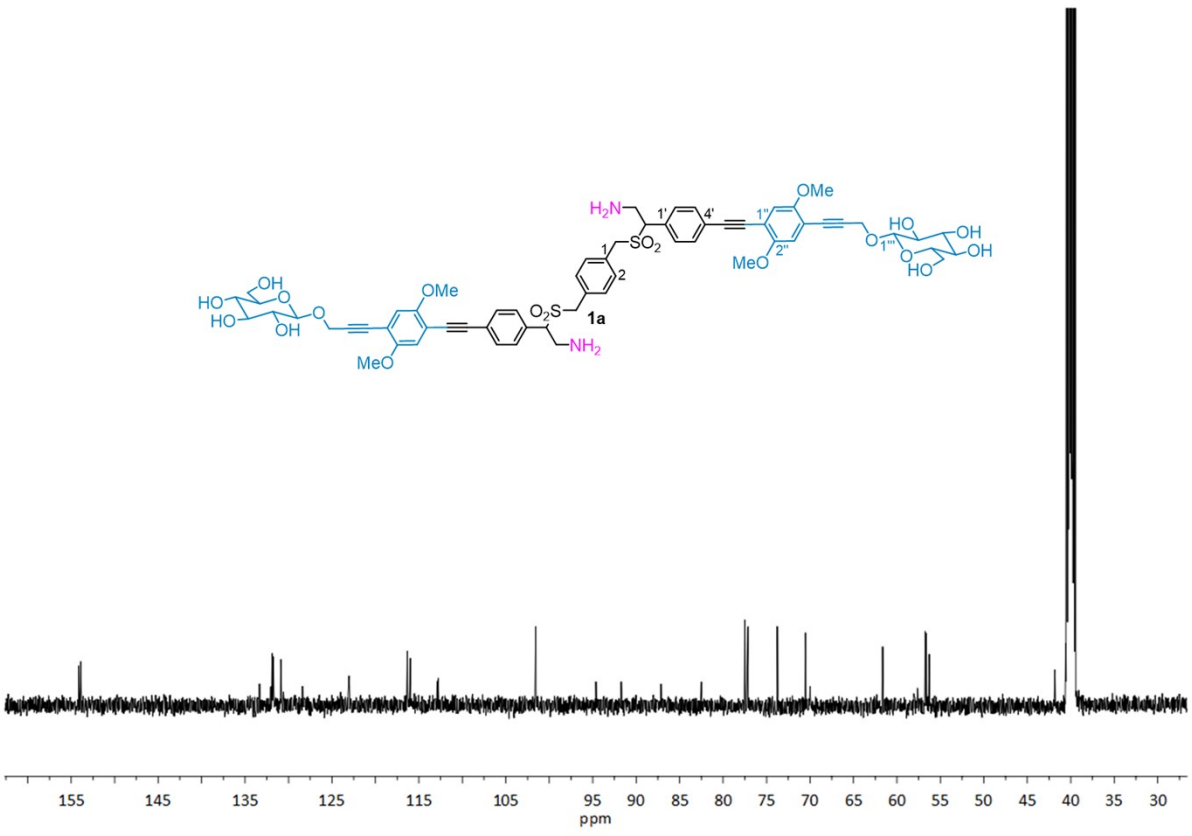


Figure S11. ^{13}C-NMR of compound **1a**

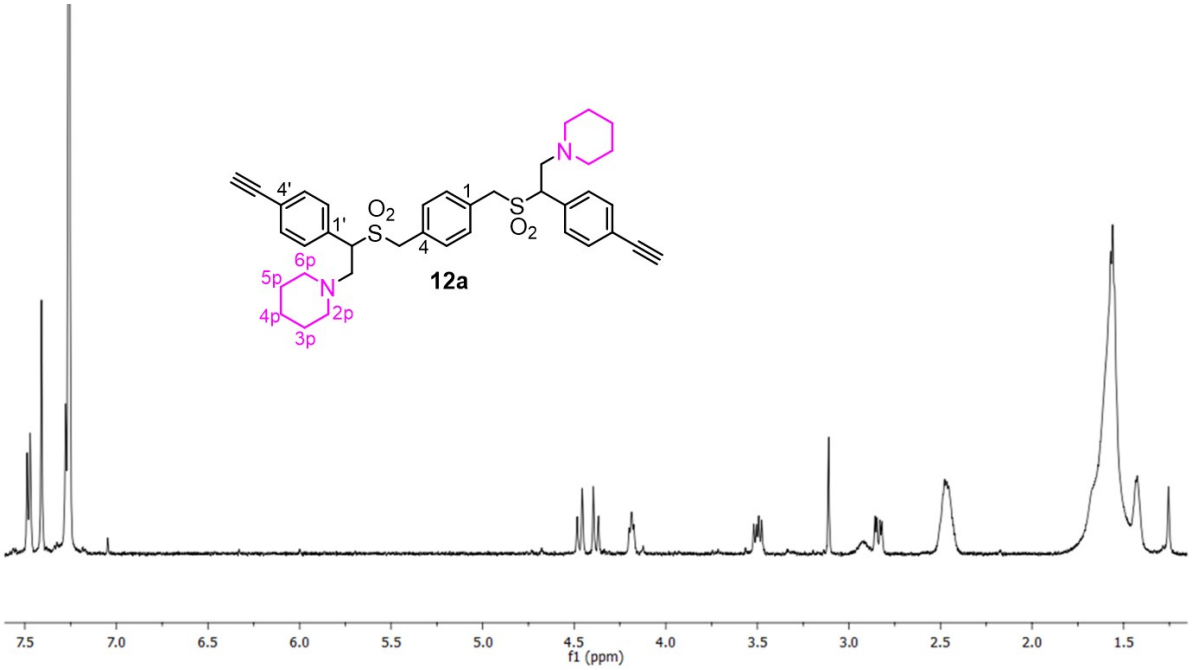


Figure S12. ^{1}H-NMR of compound **12a**

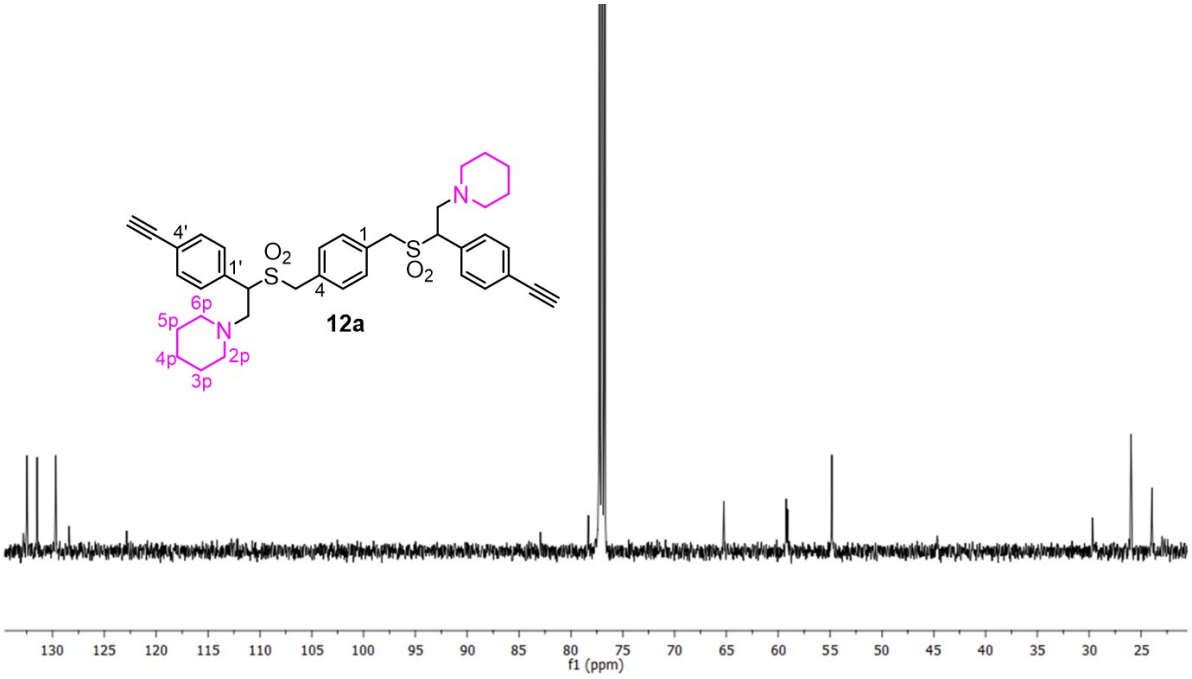


Figure S13. ^{13}C-NMR of compound **12a**

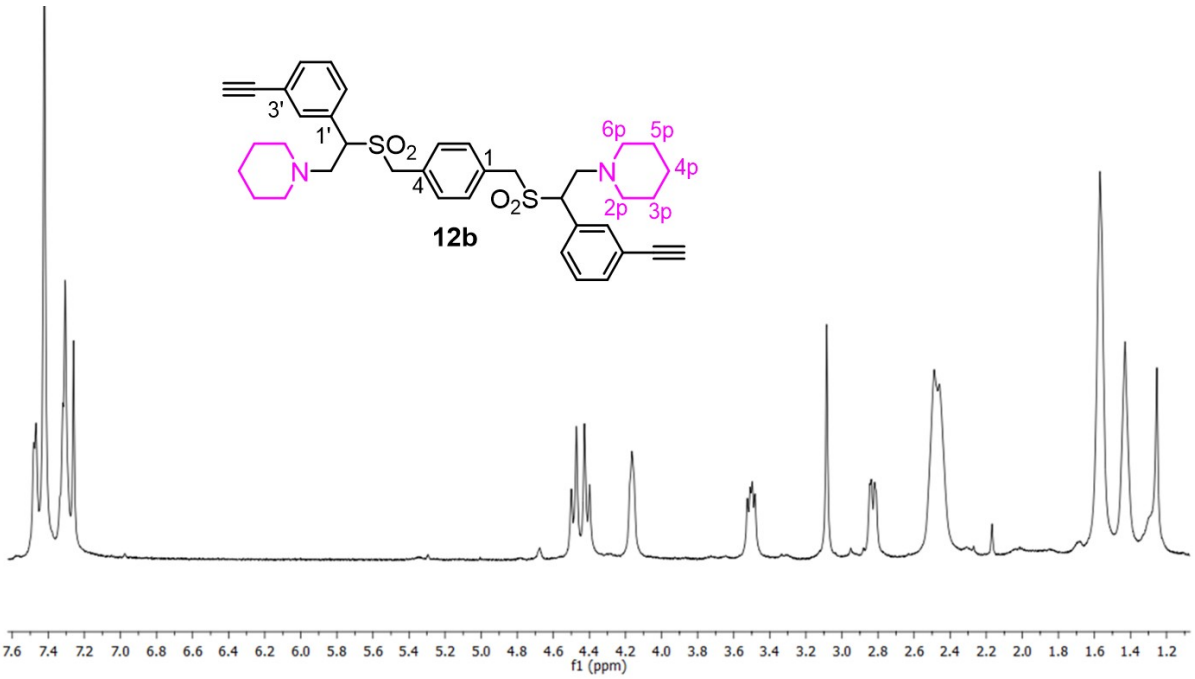


Figure S14. ^{1}H-NMR of compound **12b**

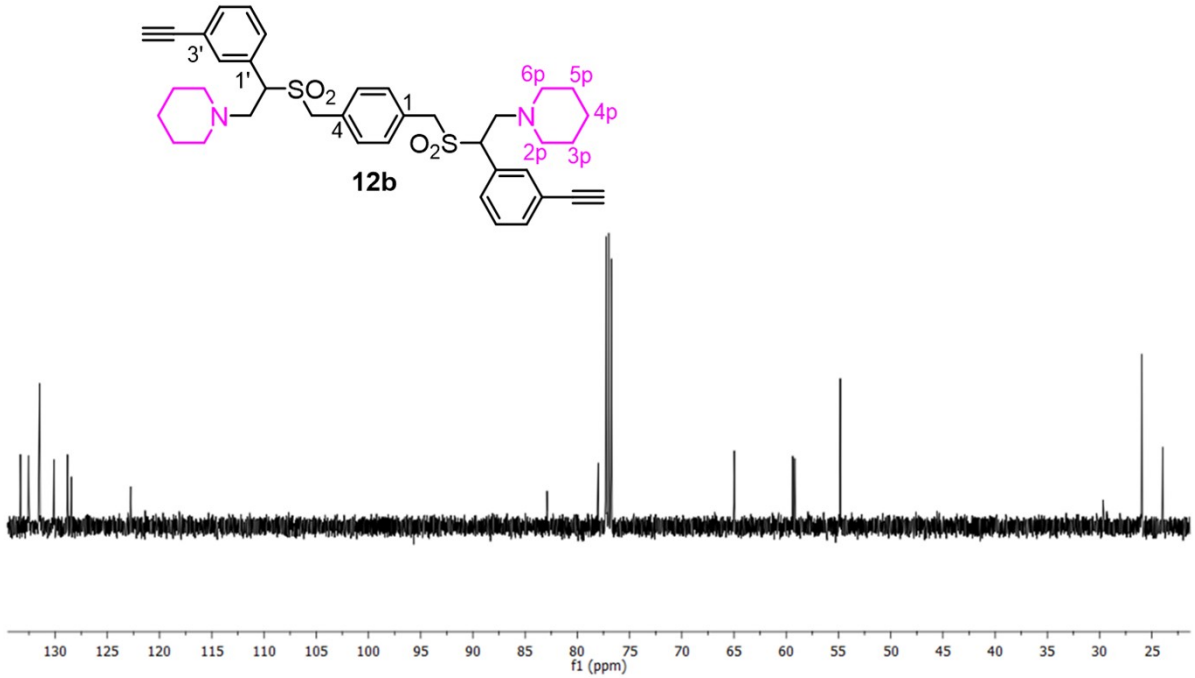


Figure S15. ^{13}C-NMR of compound **12b**

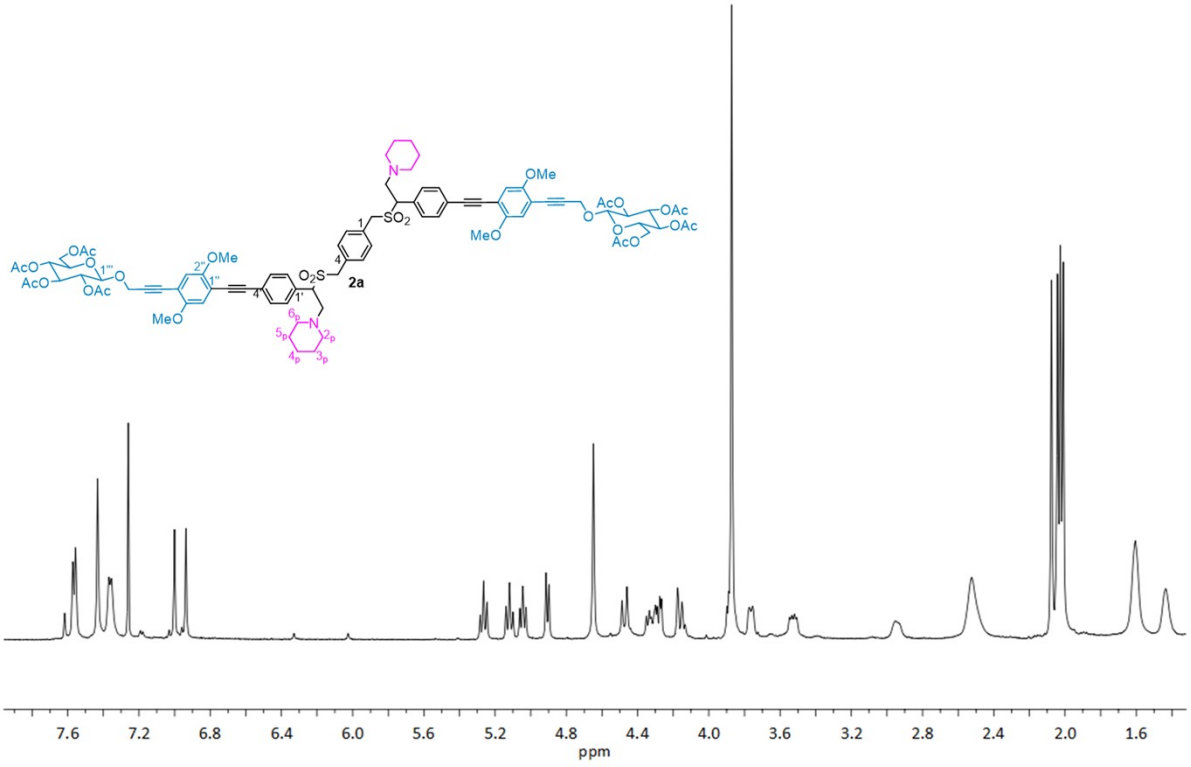


Figure S16. ^{1}H-NMR of compound **2a**

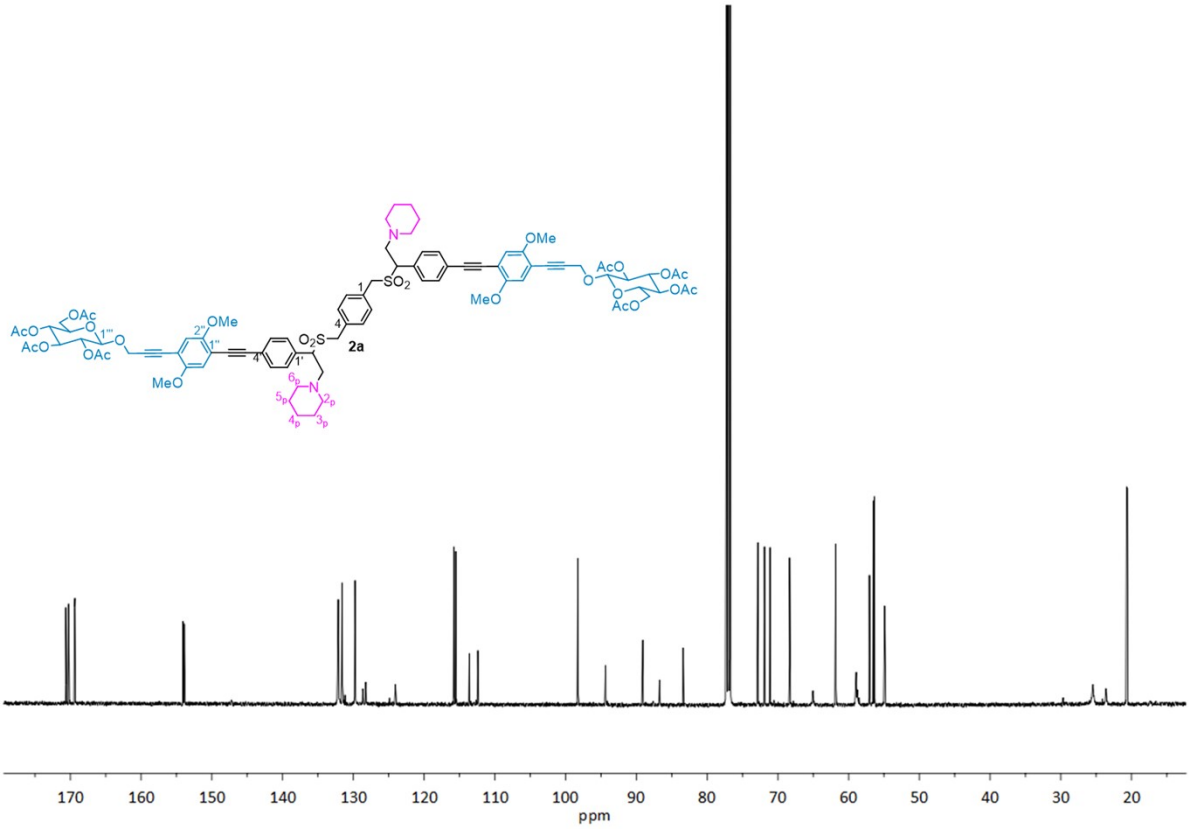


Figure S17. ^{13}C-NMR of compound **2a**

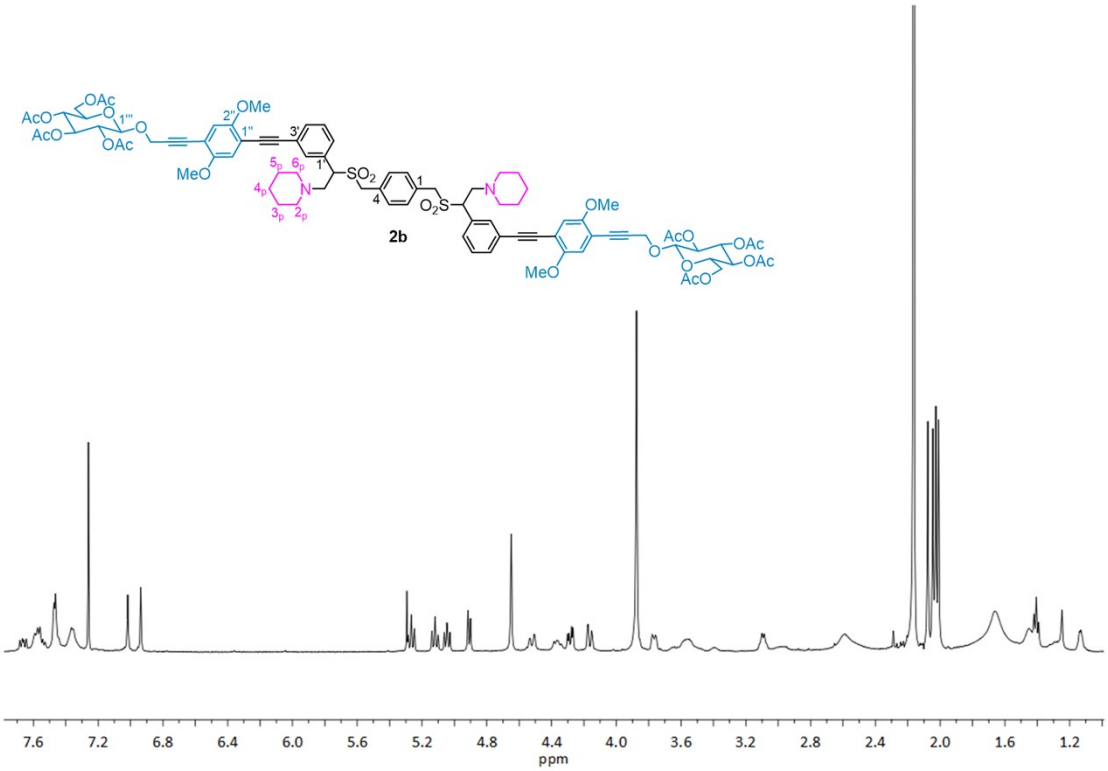


Figure S18. ^{1}H-NMR of compound **2b**

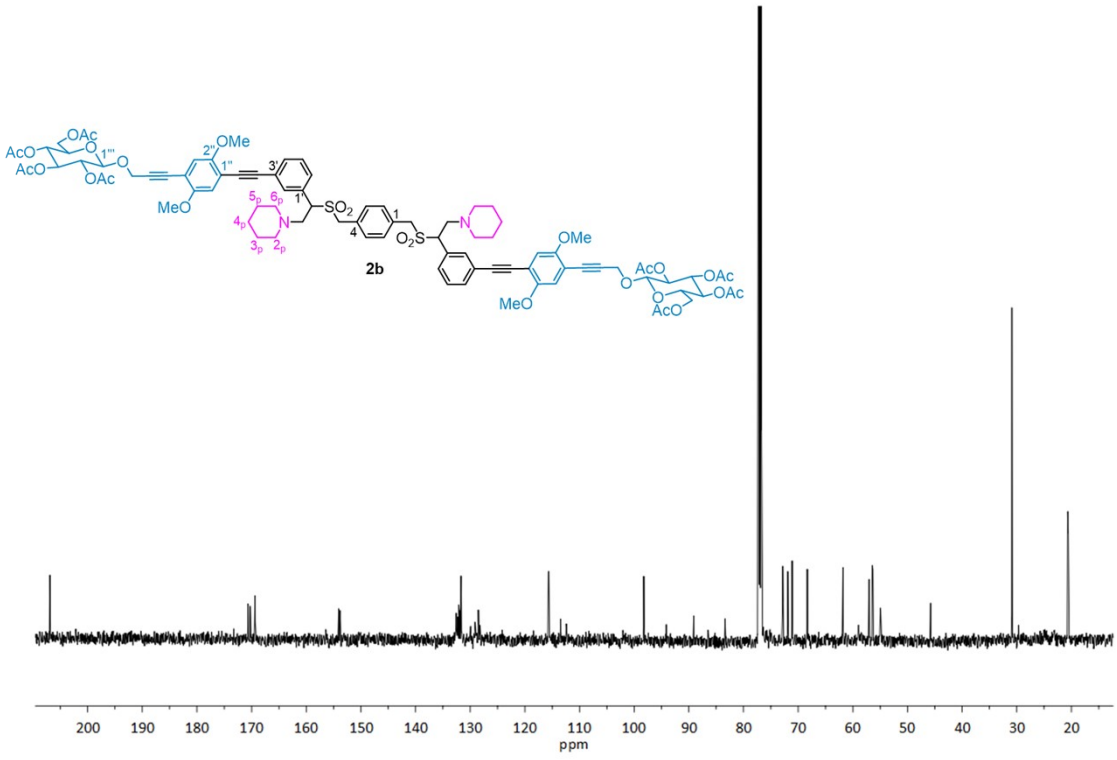


Figure S19. ^{13}C-NMR of compound **2b**

Solubility tests

- Solubility in water
  1a: 2mM; **1b**: 1.5mM; **deacetylated 2a**: 0.8mM; **deacetylated 2b**: 0.7mM
- Solubility in 1-octanol
  1a: 5mM; **1b**: 2.3mM; **deacetylated 2a**: 1.2mM; **deacetylated 2b:** 1.2mM

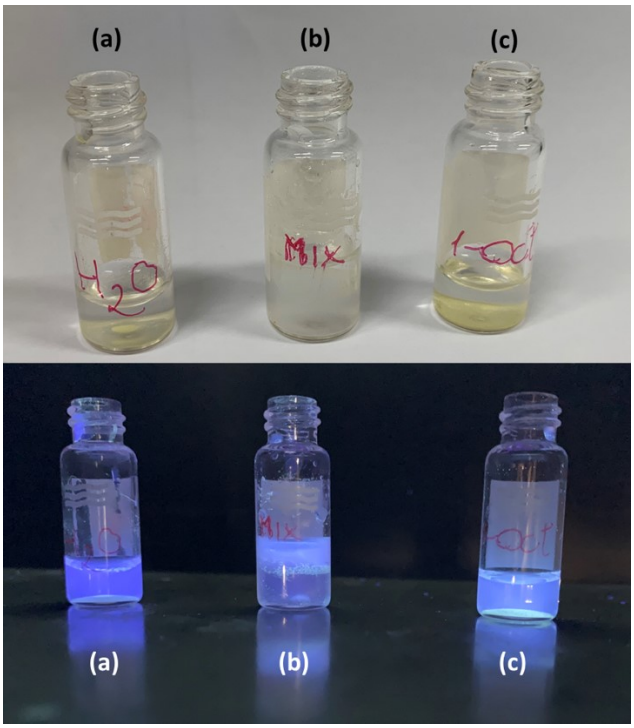


Figure S20. Solutions of **1a**, in water (vial a), in 1-octanol (vial c) and in both the solvents (vial b).

References

[1] G. B. Giovenzana, L. Lay, D. Monti, G. Palmisano and L. Panza, Synthesis of carboranyl derivatives of alkynyl glycosides as potential BNCT agents, *Tetrahedron,* 1999, **55**, 14123–14136.