Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.


# Supporting information

## Open-Resorcinarenes, a New Family of Multivalent Scaffolds

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## General Index

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## Experimental Methods

All reagents and solvents for synthesis were commercial and used without further purification. NMR spectra were recorded at 293 K, unless otherwise stated, using a 400 MHz Bruker Spectrometer. Shifts are referenced relative to deuterated solvent residual peaks. Melting points were recorded using open capillary tubes on a Mel-Temp electrothermal melting point apparatus. Infra-red spectra were recorded using a PerkinElmer Spectrum BX with ATR attachment. High resolution MS were recorded by the EPSRC Mass Spectrometry National facility in Swansea. Thin-layer chromatography (TLC) was carried out on aluminum sheets coated with silica gel 60 $F_{254}$ (Merck). TLC plates were inspected by UV light (λ = 254 nm). Silica gel column chromatography was performed with silica gel Si 60 (40–63 μm).

## Crystal structure analyses of compounds 7a, 7b, 7c and 9

Crystal data and results from structure refinement for the four compounds are collated in **Table 1**.

A crystal of each compound was mounted in oil on a glass fibre and fixed in the cold nitrogen stream on an Oxford Diffraction Xcalibur-3/Sapphire3-CCD diffractometer, equipped with Mo-Kα radiation and graphite monochromator. Intensity data were measured by thin-slice ω- and ϕ-scans.

Data were processed using the CrysAlisPro-CCD and –RED[1] programs. The structures were determined by the direct methods routines in the SHELXS program[2a] and refined by full-matrix least-squares methods, on $F^2$'s, in SHELXL[2b].

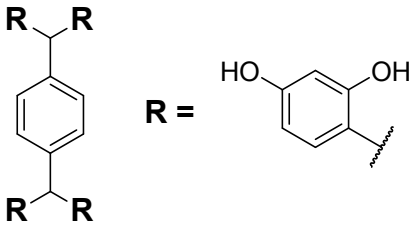
The non-hydrogen atoms of the principal molecule in each structure were refined with anisotropic thermal parameters. There are solvent molecules (ether and/or methanol) in all the crystals; in some cases, **7a** and **9**, these are fully ordered but, in **7b** and **7c**, there is disorder with varying degrees of resolution; except for those of low site occupancy (which were refined isotropically), the non-hydrogen atoms were refined anisotroically. Generally, the phenolic and hydroxyl hydrogen atoms were identified in difference maps and were refined freely; all other hydrogen atoms were added in idealised positions and set to ride on the parent carbon atoms. In compound **7a**, however, all the hydrogen atoms were located in difference maps and refined freely.

Scattering factors for neutral atoms were taken from reference[3]. Computer programs used in this analysis have been noted above, and were run through WinGX[4] on a Dell Optiplex GX620 PC at the University of East Anglia.

**Table 1**. Crystal data and structure refinement details for the four compounds **7a**, **7b**, **7c** and **9**.

| Compound | **7a** | **7b** | **7c** | **9** |
|---|---|---|---|---|
| Elemental formula | $C_{32}$ $H_{22}$ $Cl_4$ $O_8$, 6($C_4$ $H_{10}$ O) | $C_{32}$ $H_{22}$ $Cl_4$ $O_8$, *ca* 7.5(C $H_4$ O) | $C_{32}$ $H_{22}$ $Cl_4$ $O_8$, *ca* 2(C $H_4$ O), *ca* 5($C_4$ $H_{10}$ O) | $C_{20}$ $H_{12}$ $Cl_2$ $O_4$, $C_4$ $H_{10}$ O |
| Formula weight | 1121.02 | 916.61 | 1111.0 | 461.32 |
| Crystal system, space group | Monoclinic, I2/a | Triclinic, P-1 | Triclinic, P-1 | Monoclinic, $P2_1/n$ |
| Unit cell dimensions | | | | |
| a (Å) | 19.5798(5) Å | 11.5190(3) | 13.6713(5) | 12.3214(6) |
| b (Å) | 10.5855(2) Å | 12.8094(5) | 13.6859(4) | 11.6802(5) |
| c (Å ) | 30.2255(8) Å | 15.5844(4) | 15.8507(5) | 15.2837(6) |
| α (°) | 90 | 79.044(3) | 87.748(3) | 90 |
| β (°) | 100.449(2) | 77.462(2) | 71.565(3) | 107.433(4) |
| γ (°) | 90 ° | 71.732(3) | 84.007(3) | 90 |
| Volume ($Å^3$) | 6160.7(3) | 2112.99(11) | 2798.10(17) | 2098.54(17) |
| Z, Calculated density ($Mg/m^3$ ) | 4, 1.209 | 2, 1.441 | 2, 1.319 | 4, 1.460 |
| F(000) | 2392 | 962 | 1184 | 960 |
| Absorption coefficient ($mm^{-1}$ ) | 0.251 | 0.350 | 0.277 | 0.345 mm |
| Crystal colour, shape | pale brown block | colourless prism | pale yellow prism | colourless plate |
| Crystal size (mm) | 0.36 x 0.24 x 0.18 | 0.40 x 0.12 x 0.10 | 0.32 x 0.13 x 0.12 | 0.12 x 0.10 x 0.05 |
| Theta range for data collection (°) | 3.03 to 27.50 | 2.99 to 22.50 | 3.09 to 22.50 | 3.07 to 25.00 |
| Completeness to theta-max (%) | 99.8 | 99.2 | 99.7 | 99.8 |
| Max. and min. transmission | 1.0 and 0.918 | 1.0 and 0.935 | 1.0 and 0.883 | 1.0 and 0.914 |
| Reflections collected | 50395 | 20695 | 30403 | 29087 |
| No. of unique reflections, R(int) | 7083, 0.040 | 5493, 0.054 | 7299, 0.060 | 3688, 0.071 |
| No. of 'observed' reflections ($I > 2\sigma_I$) | 5801 | 3401 | 5321 | 2842 |
| Data / restraints / parameters | 7083 / 0 / 498 | 5493 / 0 / 600 | 7299 / 0 / 768 | 3688 / 0 / 288 |
| Goodness-of-fit on $F^2$, S | 1.027 | 1.041 | 1.046 | 1.028 |
| Final R indices ('observed' data) | $R_1 = 0.038$, $wR_2 = 0.093$ | $R_1 = 0.074$, $wR_2 = 0.191$ | $R_1 = 0.067$, $wR_2 = 0.156$ | $R_1 = 0.038$, $wR_2 = 0.078$ |
| Final R indices (all data) | $R_1 = 0.051$, $wR_2 = 0.099$ | $R_1 = 0.138$, $wR_2 = 0.240$ | $R_1 = 0.095$, $wR_2 = 0.172$ | $R_1 = 0.058$, $wR_2 = 0.083$ |
| Largest diff. peak and hole ($e.Å^{-3}$ ) | 0.32 and -0.24 | 1.11 and -0.37 | 0.40 and -0.39 | 0.24 and -0.23 |

## Platform 6a




*Palladium over carbon* (catalytic) was added to a solution of **7a** (3.18 mmol) and *triethylamine* (12.37 mL, 88.72 mmol) in 150 mL of methanol. A hydrogen atmosphere was applied and the mixture was stirred at 40°C for 18 h. The catalyst was removed by filtration and the solution was dried under reduced pressure. The product was suspended in $HCl_{aq}$ 1.2 M and extracted with ethyl acetate three times. The organic layers were combined, washed with $HCl_{aq}$ 1.2 M, brine and dried over $Na_2SO_4$. Upon evaporation of the solvent the product was obtained as an orange powder (1.9341 g).

Yield: 96% (calculated from NMR to account for solvent of crystallisation)

$[M-H]^-$ = 537.1553 (Calculated: 537.1555)

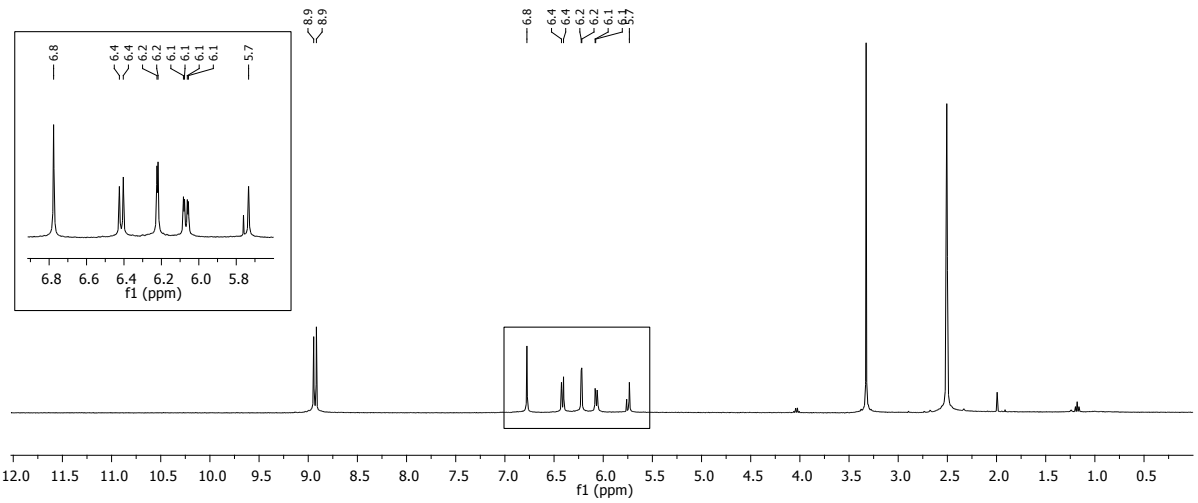
MP: 178-180°C

$^1$H NMR (400 MHz, DMSO) δ 8.94 (s, 4H), 8.92 (s, 4H), 6.78 (s, 4H), 6.41 (d, *J* = 8.3 Hz, 4H), 6.22 (d, *J* = 2.3 Hz, 4H), 6.07 (dd, *J* = 8.3, 2.3 Hz, 4H), 5.73 (s, 2H).

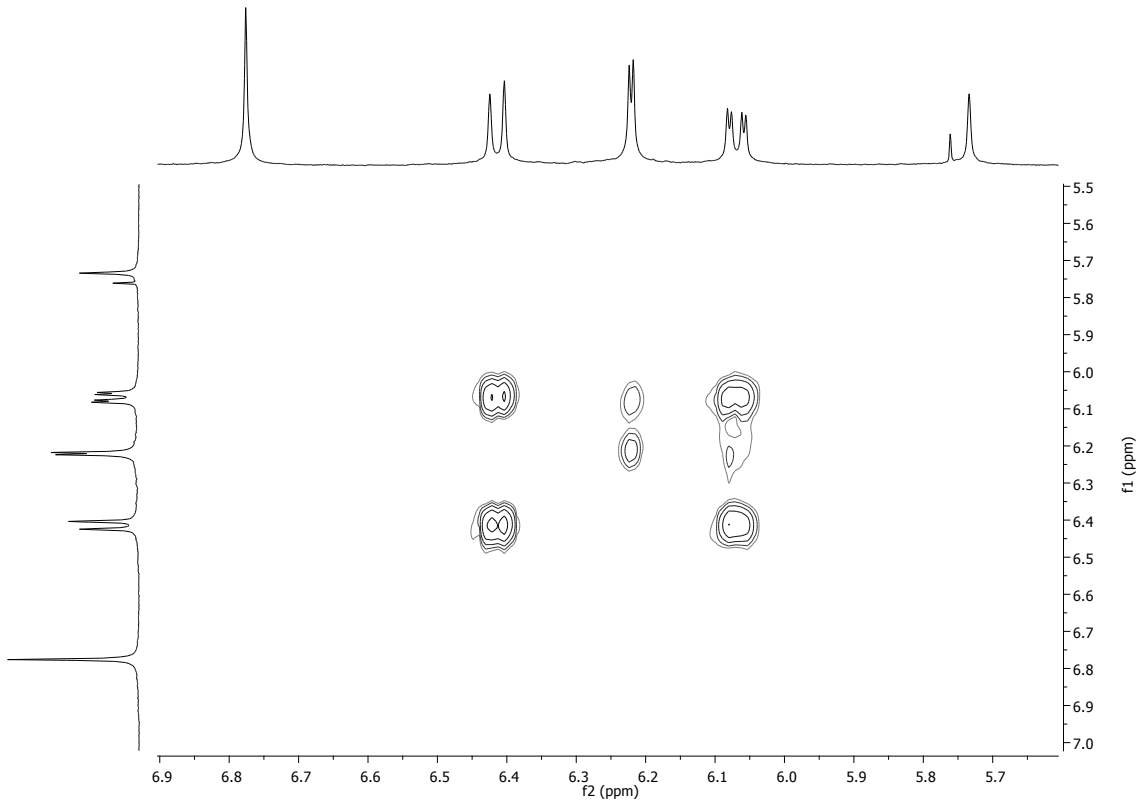
$^{13}$C NMR (101 MHz, DMSO) δ 156.52, 155.74, 142.49, 130.49, 128.62, 122.10, 105.80, 102.79, 41.21.

IR ($\nu_{max}$, $cm^{-1}$): 3291, 1601, 1512.5, 1504.5, 1452, 1374.5, 1298.5, 1248, 1197, 1158.5, 1091, 972, 834.5.

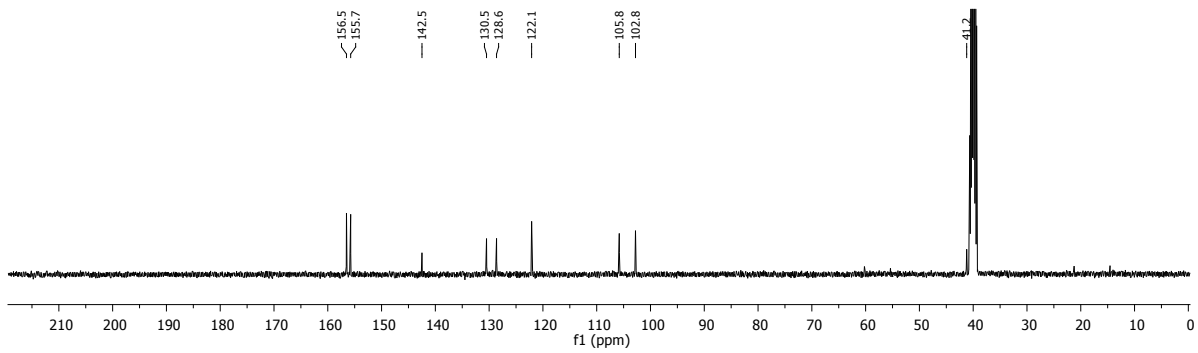
$^{1}$H NMR



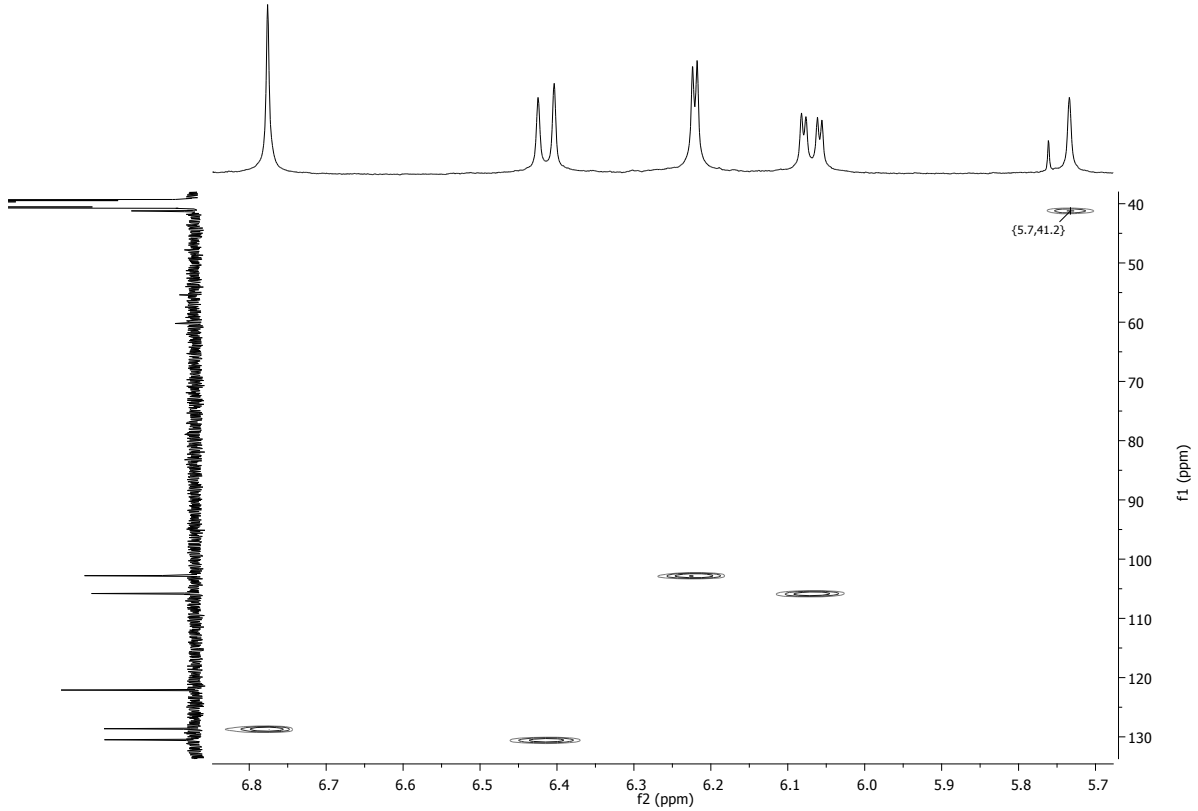

COSY



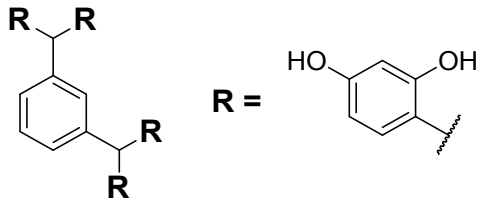
$^{13}$C NMR


156.5
155.7
142.5
130.5
128.6
122.1
105.8
102.8
41.2
f1 (ppm)

HSQC


{5.7,41.2}
f2 (ppm)
f1 (ppm)

## Platform 6b




*Palladium over carbon* (catalytic) was added to a solution of **7b** (0.34 mmol) and *triethylamine* (1.24 mL, 8.87 mmol) in 20mL of ethanol. A hydrogen atmosphere was applied and the mixture was stirred at 50°C for 18 h. The catalyst was removed by filtration and the solution was dried under reduced pressure. The product was suspended in $HCl_{aq}$ 1.2 M and extracted with ethyl acetate three times. The organic layers were combined, washed with $HCl_{aq}$ 1.2 M, brine and dried over $Na_2SO_4$. Upon evaporation of the solvent the product was obtained as an orange powder (160.9 mg).

Yield: 62% (calculated from NMR to account for solvent of crystallisation)

$[M+NH_4]^+$ = 556.1962 (Calculated: 556.1966)

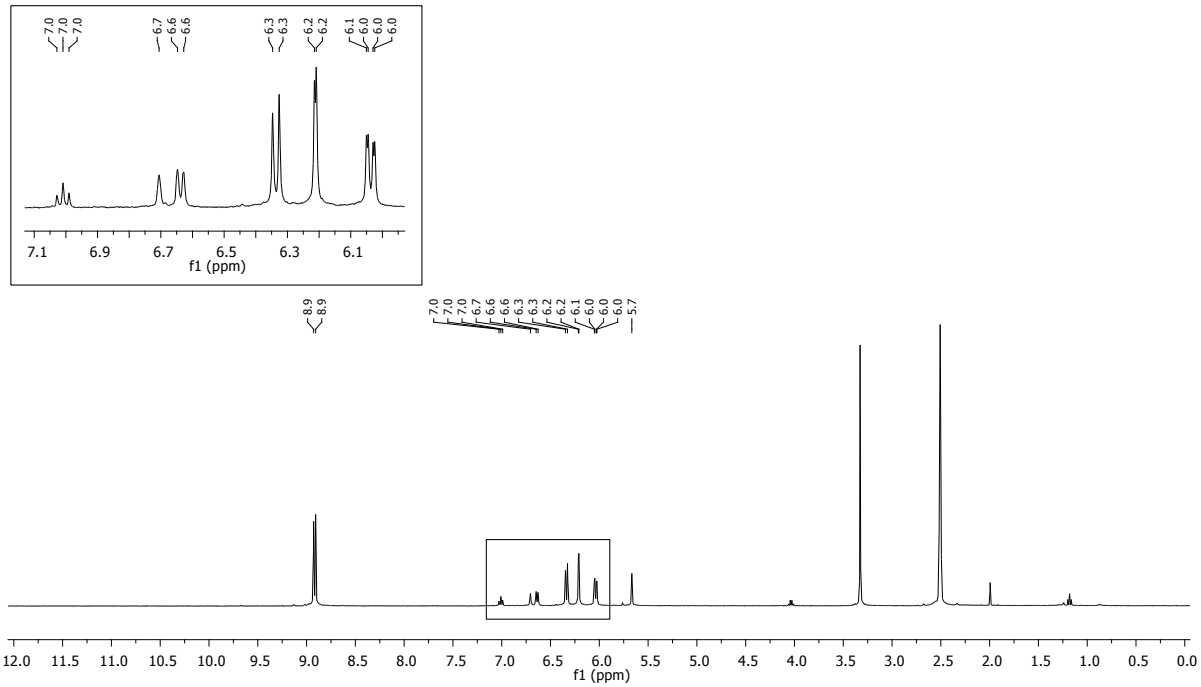
MP: 165-167°C

$^1$H NMR (400 MHz, DMSO) δ 8.98 (d, 4H), 8.91 (s, 4H), 7.01 (t, *J* = 7.8 Hz, 1H), 6.71 (s, 1H), 6.64 (d, *J* = 7.8 Hz, 2H), 6.34 (d, *J* = 8.3 Hz, 4H), 6.21 (d, *J* = 2.2 Hz, 4H), 6.04 (dd, *J* = 8.3, 2.2 Hz, 4H), 5.67 (s, 2H).

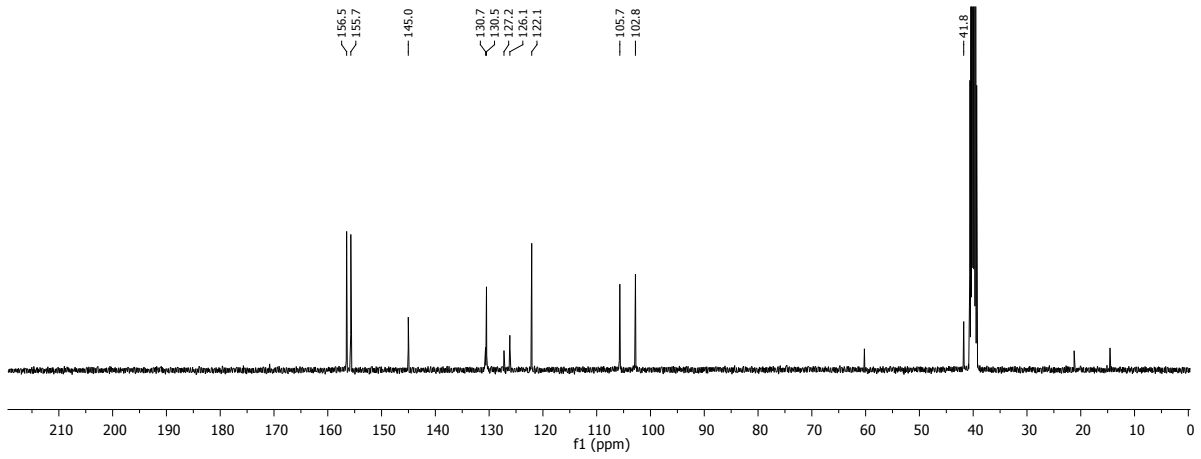
$^{13}$C NMR (101 MHz, DMSO) δ 156.49, 155.72, 145.03, 130.66, 130.49, 127.24, 126.15, 122.08, 105.70, 102.80, 41.77.

IR ($\nu_{max}$, $cm^{-1}$): 3302.5, 1600.5, 1515.5, 1506, 1451.5, 1297.5, 1246.5, 1155.5, 1090.5, 972, 833.5.

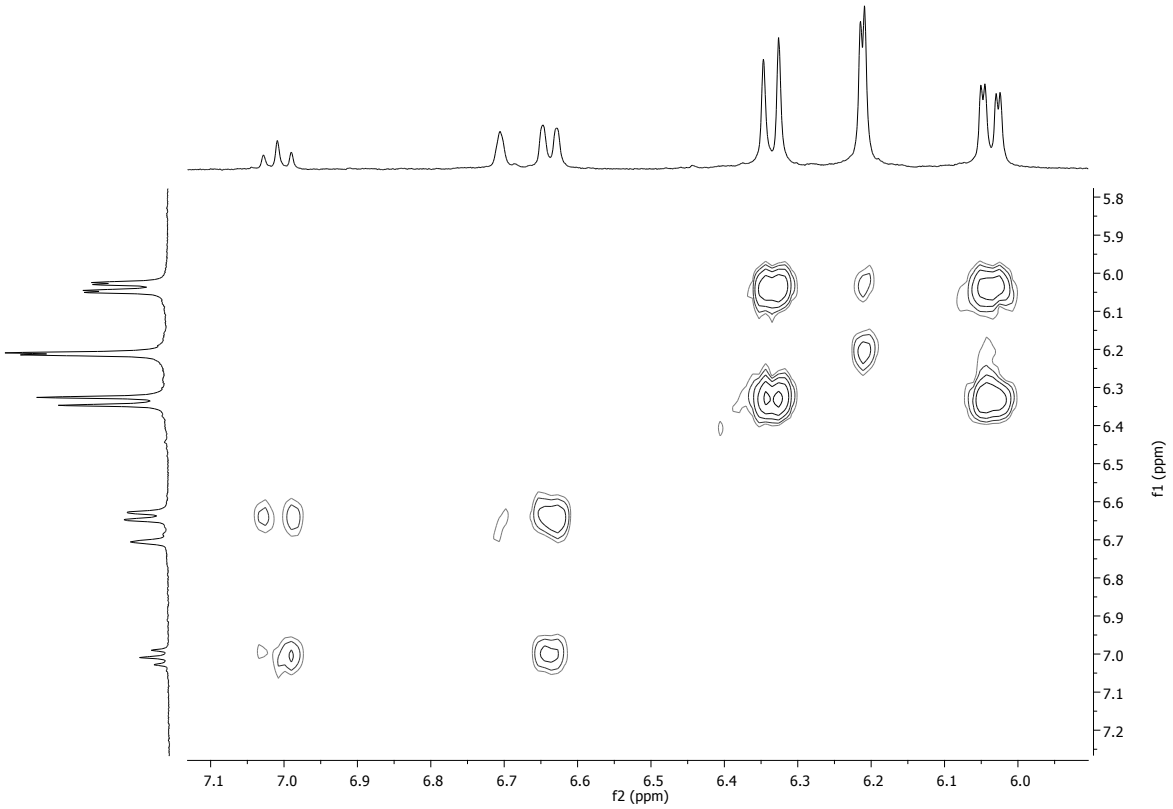
$^{1}$H NMR



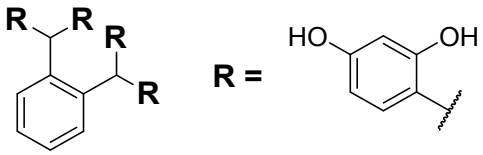

$^{13}$C NMR



COSY


5.8
5.9
6.0
6.1
6.2
6.3
6.4
6.5
6.6
6.7
6.8
6.9
7.0
7.1
7.2
f1 (ppm)
7.1
7.0
6.9
6.8
6.7
6.6
6.5
6.4
6.3
6.2
6.1
6.0
f2 (ppm)

## Platform 6c




*Palladium over carbon* (catalytic) was added to a solution of **7c** (0.23 mmol) and *triethylamine* (0.99 mL, 7.10 mmol) were dissolved in 12 mL of ethanol. A hydrogen atmosphere was applied and the mixture was stirred at 50°C for 18 h. The catalyst was removed by filtration and the solution was dried under reduced pressure. The product was suspended in $HCl_{aq}$ 1.2 M and extracted with ethyl acetate three times. The organic layers were combined, washed with $HCl_{aq}$ 1.2 M, brine and dried over $Na_2SO_4$. Upon evaporation of the solvent the product was obtained as an orange powder (101.6 mg).

Yield: 69% (calculated from NMR to account for solvent of crystallisation)

$[M+NH_4]^+$ = 556.1961 (Calculated: 556.1966)

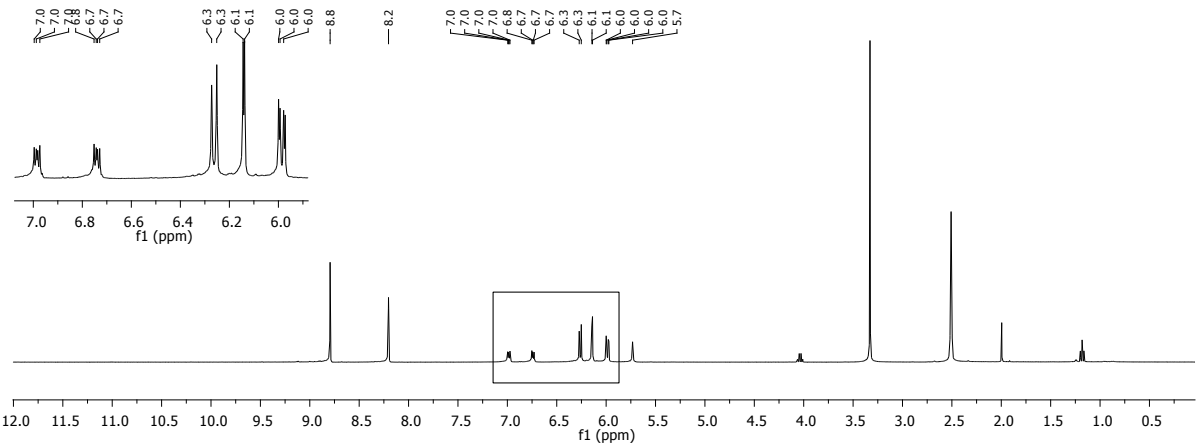
MP: 216-218°C

$^1$H NMR (400 MHz, DMSO) δ 8.79 (s, 4H), 8.20 (s, 4H), 6.98 (dd, *J* = 5.7, 3.5 Hz, 2H), 6.74 (dd, *J* = 5.7, 3.5 Hz, 2H), 6.26 (d, *J* = 8.3 Hz, 4H), 6.14 (d, *J* = 2.4 Hz, 4H), 5.99 (dd, *J* = 8.3, 2.4 Hz, 4H), 5.73 (s, 2H).

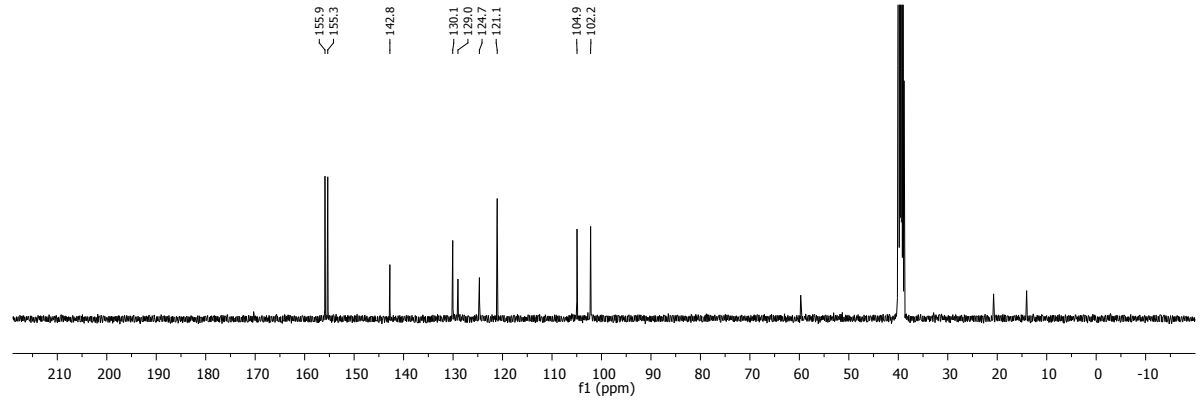
$^{13}$C NMR (101 MHz, DMSO) δ 155.89, 155.33, 142.77, 130.07, 129.01, 124.67, 121.08, 104.95, 102.20, 38.8. (The peak at 38.8 is overlaid with DMSO and was assigned by HSQC)

IR ($\nu_{max}$, $cm^{-1}$): 3501.5, 3306.5, 1599, 1516.5, 1505.5, 1454, 1373.5, 1336.5, 1291.5, 1249.5, 1214.5, 1182, 1168, 1150.5, 1092.5, 970.5, 834.

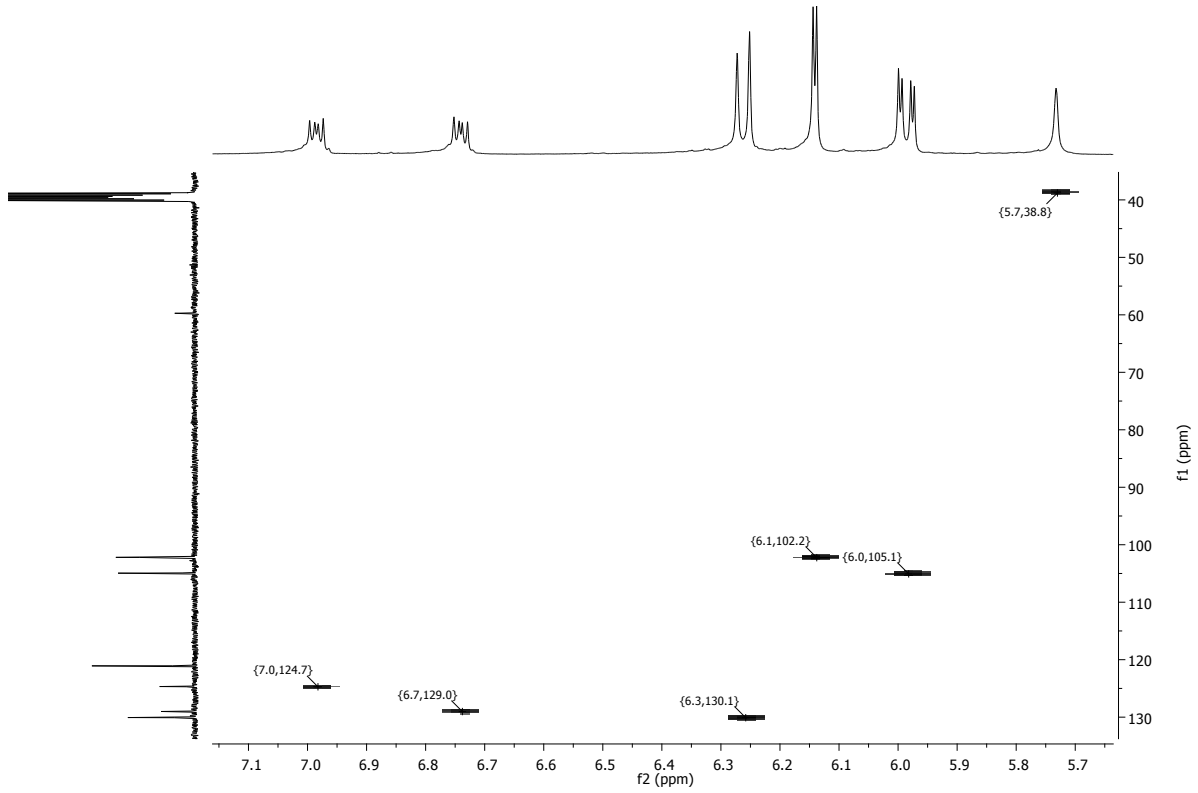
$^{1}$H NMR



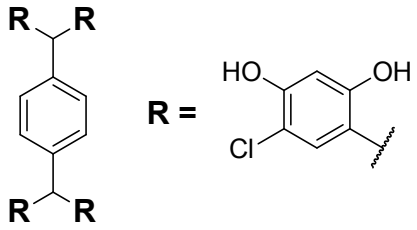

$^{13}$C NMR



HSQC



## Platform 7a




**Method 1**

A mixture of *terephthalaldehyde* (500 mg, 3.73 mmol) and *4-chlororesorcinol* (2.425 g, 16.78mmol) was dissolved in 15 ml of ethanol/HCl 37% (1/1, v/v) and stirred at 70°C for 5 h. The solvent was evaporated and the resulting orange solid obtained was suspended in water, collected by filtration and washed with water. To remove trace *3-chlororesorcinol*, the solid was suspended in dichloromethane, stirred for 15 minutes, collected by filtration and washed with dichloromethane. The orange powder was dried in the desiccator for one week to give 1.6505 g of product.

Yield: 66% (calculated from NMR to account for solvent of crystallisation)

**Method 2**

1.2 mL of *methanesulfonic acid* was added to a pre-cooled (0°C) mixture of *terephthalaldehyde* (500 mg, 3.73 mmol) and *4-chlororesorcinol* (2.425 g, 16.78 mmol) in 15 ml of $Et_2O$/DCM (1/1, v/v). The reaction vessel was sealed and the reaction stirred for 5 h. The mixture was poured into 75 mL of $Et_2O$ and cooled for 18 h at 4°C. The resulting solid was collected and washed with diethyl ether to give the orange crystalline product (2.8132 g).

Yield: 86% (calculated from NMR to account for solvent of crystallisation)

$[M-H]^-$ = 674.9956 (Calculated: 674.9972)

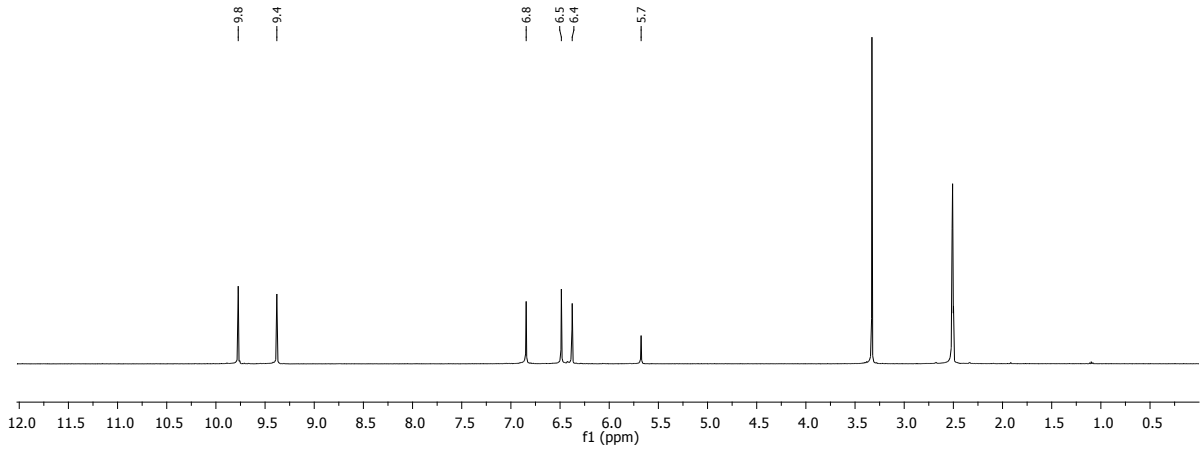
MP: 225-256°C

$^1$H NMR (400 MHz, DMSO) δ 9.77 (s, 4H), 9.38 (s, 4H), 6.84 (s, 4H), 6.49 (s, 4H), 6.38 (s, 4H), 5.68 (s, 2H).

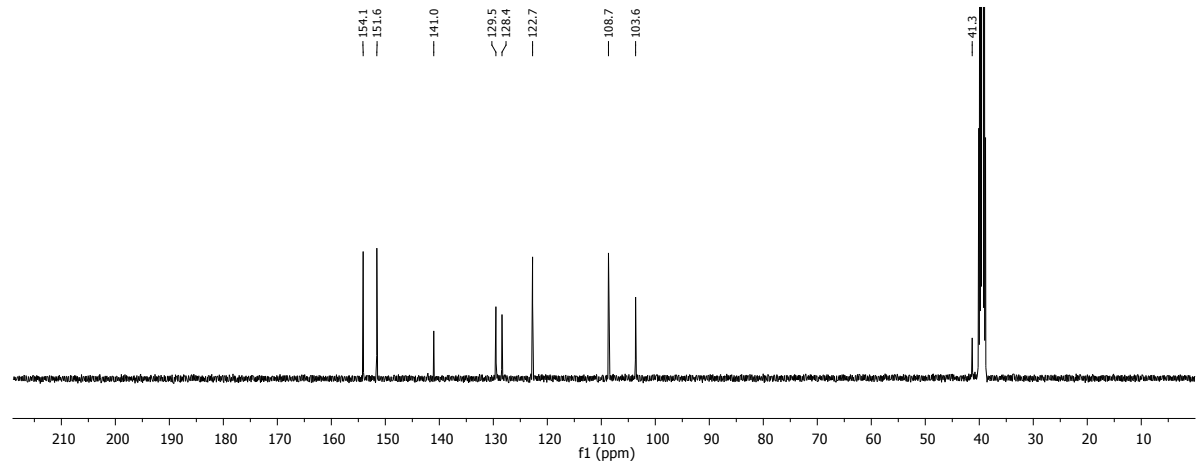
$^{13}$C NMR (101 MHz, DMSO) δ 154.10, 151.57, 141.03, 129.52, 128.39, 122.73, 108.67, 103.65, 41.31.

IR ($\nu_{max}$, $cm^{-1}$): 3498.5, 3424.5, 3209.5, 1613, 1505, 1428.5, 1355.5, 1322, 1283.5, 1266.5, 1245, 1224, 1209, 1194.5, 1169.5, 1121.5, 1029, 905,889.5, 840.5.

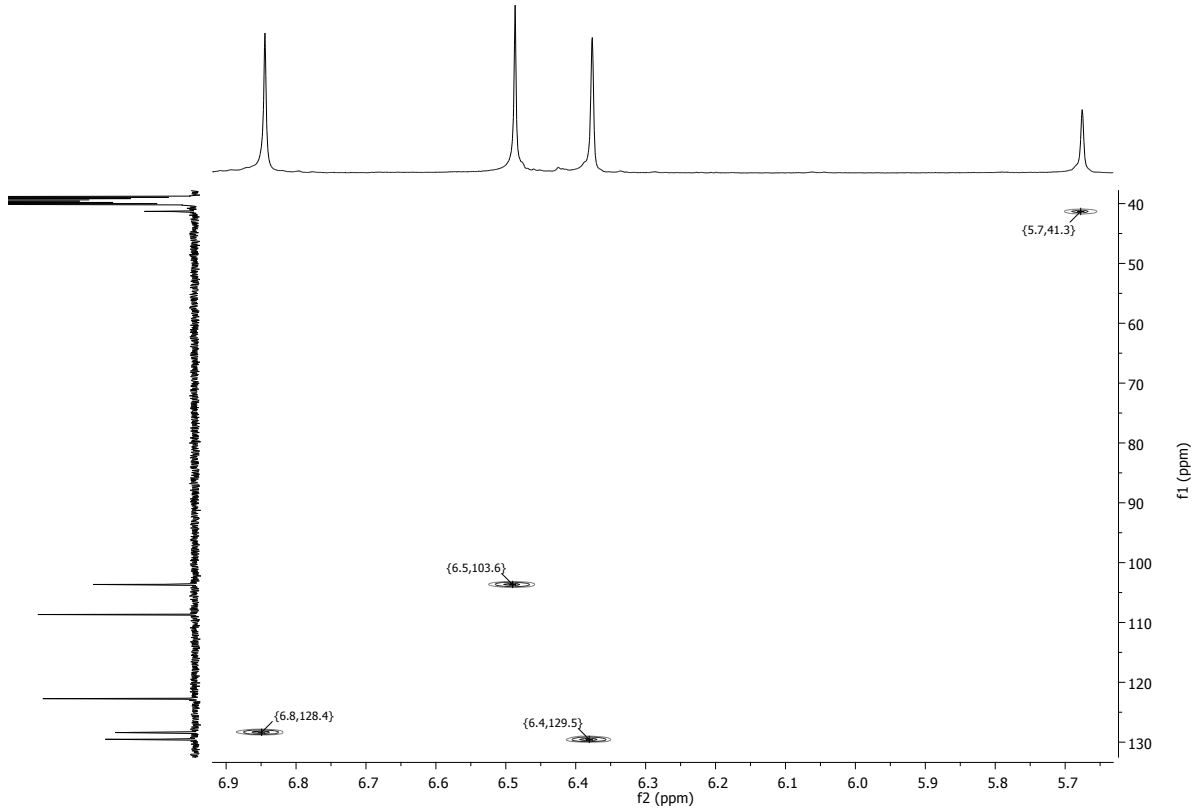
$^{1}$H NMR



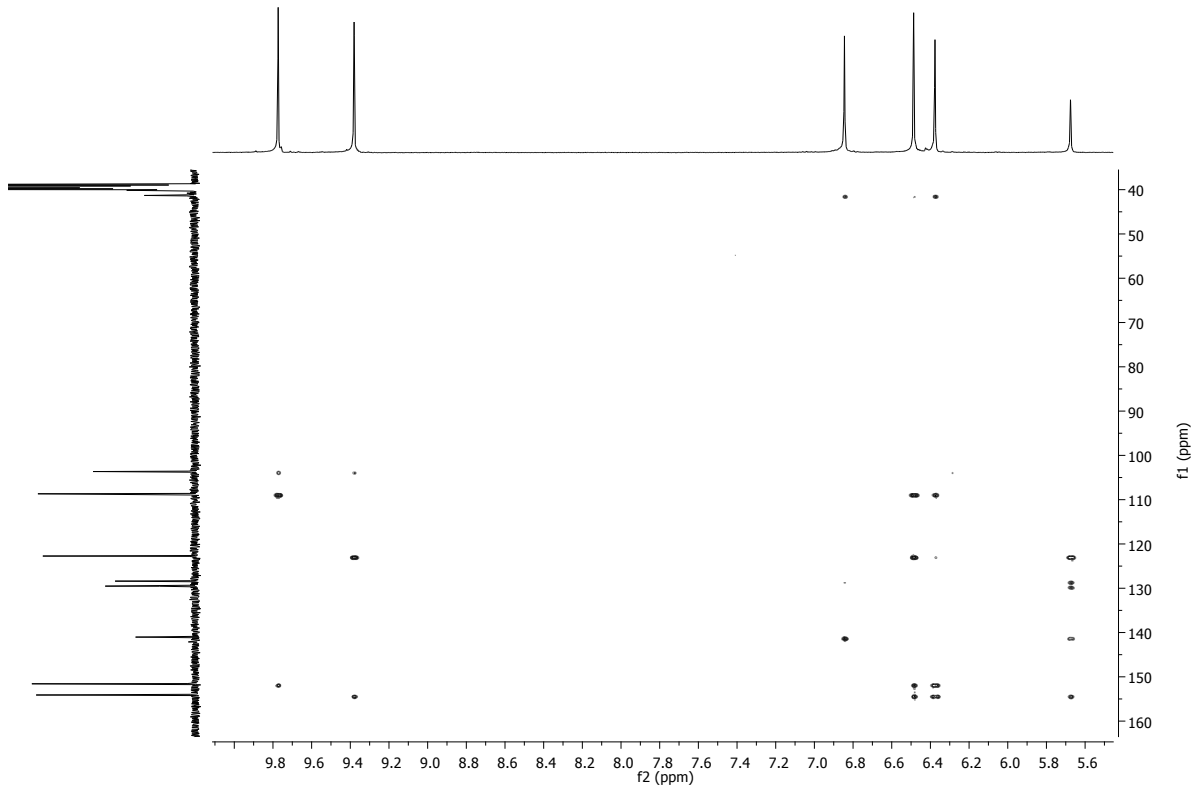

$^{13}$C NMR



HSQC




HMBC



**Crystallisation procedure**

During preparation according to **Method 2**: the mixture obtained after 5 hours was poured in 75mL of diethyl ether: the solid initially dissolved and then recrystallised after one night in the fridge at 4°C. Crystals were taken directly from the solution.

Platform **7a** (**Figure 1**) lies about a twofold symmetry axis, normal to the central $C_6$ ring and through the centre of that ring.

Each of the hydroxyl groups in this molecule is a hydrogen-bond donor, three (and the symmetry-related three) linked to ether (solvent) molecules, and the fourth (and its equivalent) forming a bond with an adjacent **7a** molecule. These molecules thus form chains which run parallel to the crystallographic *b*-axis (**Figure 2**) in the form of columns of **7a** molecules padded out by ether molecules.

**Figure 1.** View of a molecule of **7a**, indicating the atom numbering scheme and hydrogen-bonded atoms of neighbouring molecules. Thermal ellipsoids are drawn at the 50% probability level.

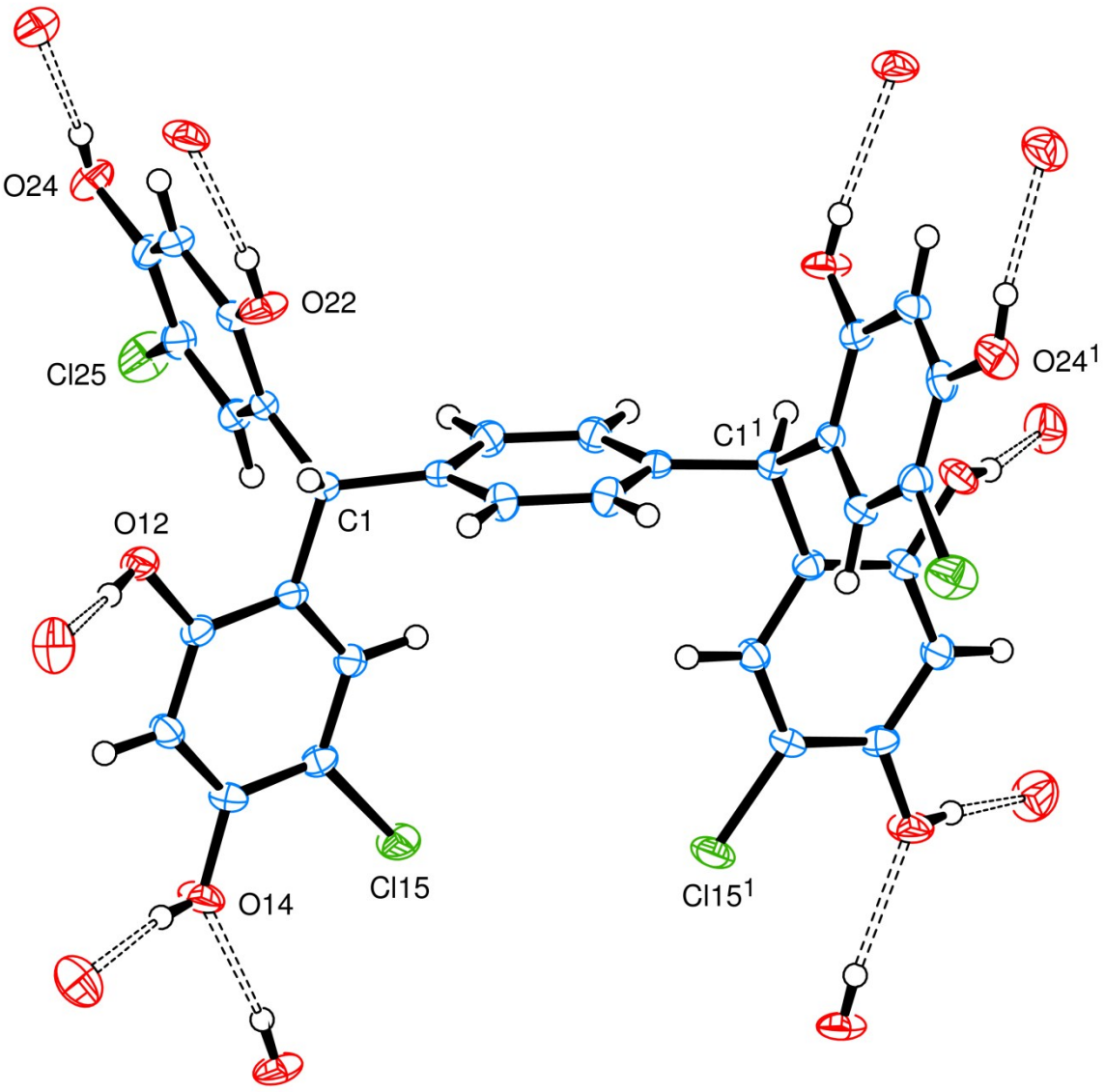
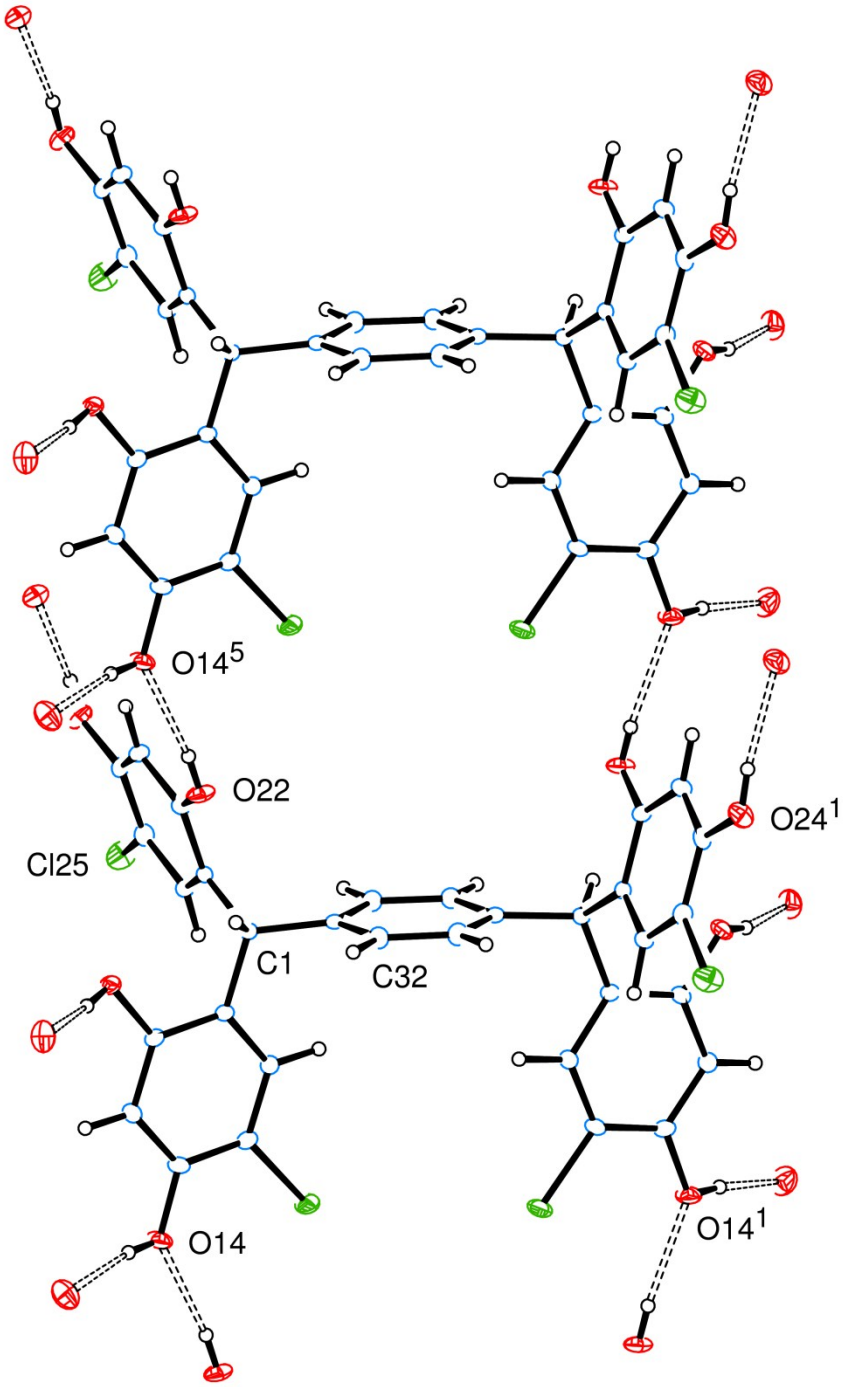
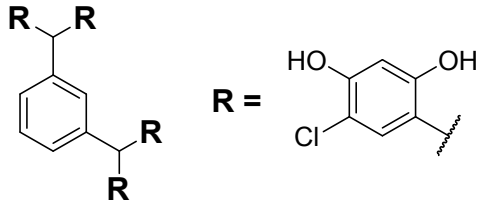


**Figure 2**. **7a** molecules linked through hydrogen bonds in chains. The oxygen atoms of the hydrogen-bonded ether molecules are also included.



## Platform 7b




**Method 1**

A mixture of *isophthalaldehyde* (500 mg, 3.73 mmol) and *4-chlororesorcinol* (2.425 g, 16.78 mmol) was dissolved in 15 ml of ethanol/HCl 37% (1/1, v/v) and stirred at 70°C for 5 h. The solvent was evaporated and the resulting orange solid obtained was suspended in water, collected by filtration and washed with water. To remove trace *3-chlororesorcinol*, the solid was suspended in dichloromethane, stirred for 15 minutes, collected by filtration and washed with dichloromethane. The orange powder was dried in the desiccator for one week to give 2.4721 g of product.

Yield: 91% (calculated from NMR to account for solvent of crystallisation)

$[M-H]^-$ = 674.9954 (Calculated: 674.9972)

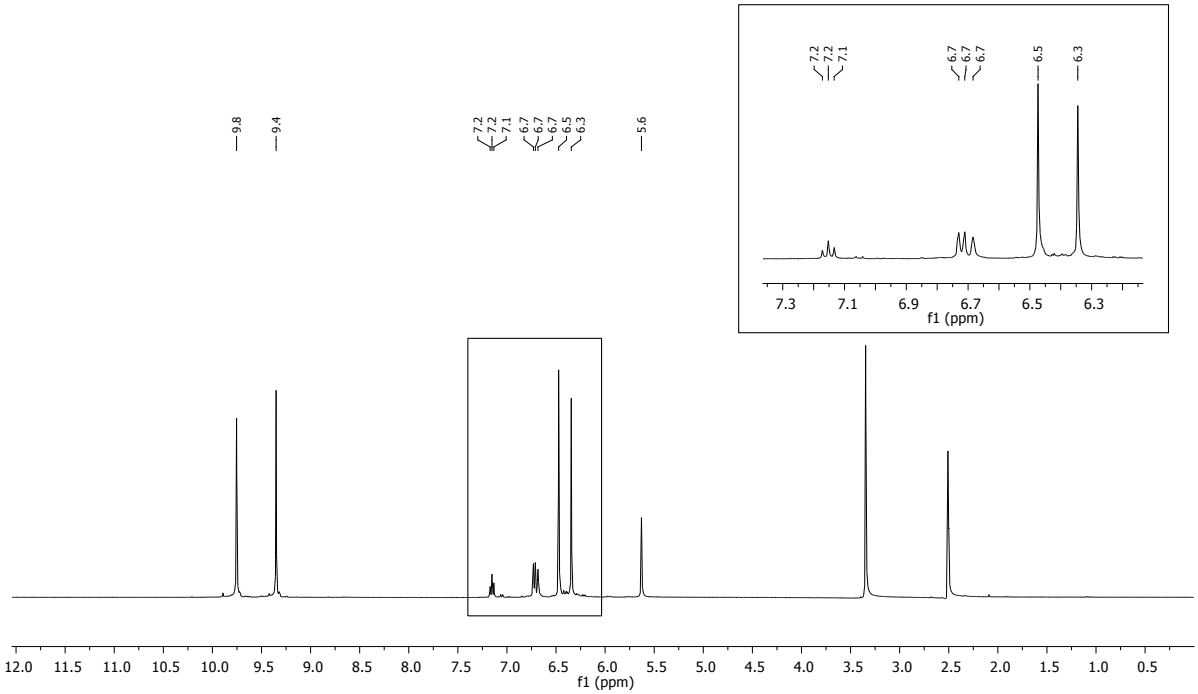
MP: 172-174°C

$^1$H NMR (400 MHz, DMSO) δ 9.75 (s, 4H,), 9.35 (s, 4H), 7.15 (t, *J* = 7.6 Hz, 1H), 6.72 (d, *J* = 7.6 Hz, 2H), 6.47 (s, 4H), 6.34 (s, 4H), 5.63 (s, 2H).

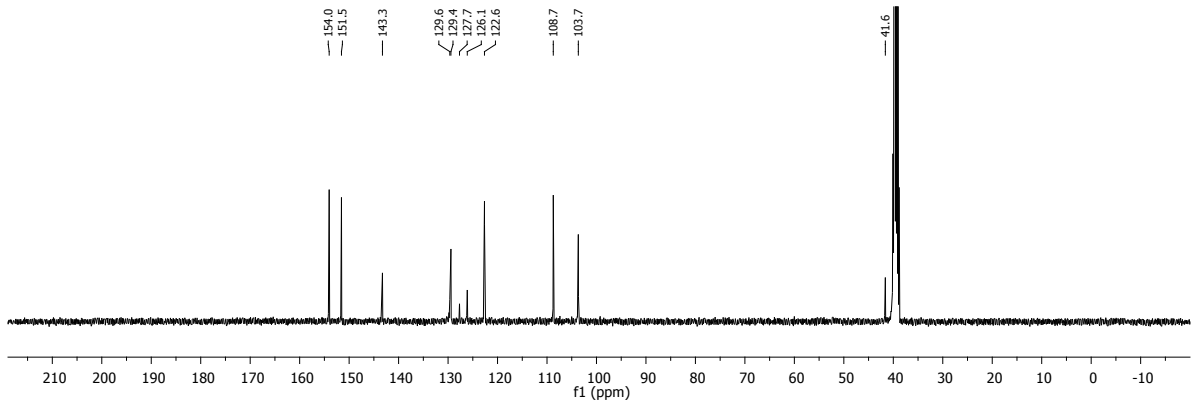
$^{13}$C NMR (101 MHz, DMSO) δ 154.03, 151.55, 143.26, 129.65, 129.42, 127.69, 126.12, 122.64, 108.73, 103.67, 41.61.

IR ($\nu_{max}$, $cm^{-1}$): 3477.5, 3420.5, 3061, 1617, 1602, 1500, 1430, 1381, 1360.5, 1319.5, 1295.5, 1281.5, 1263, 1232, 1208.5, 1194.5, 1179, 1159.5, 1128, 1119, 1089, 1029.5, 900,889.5, 839.5.

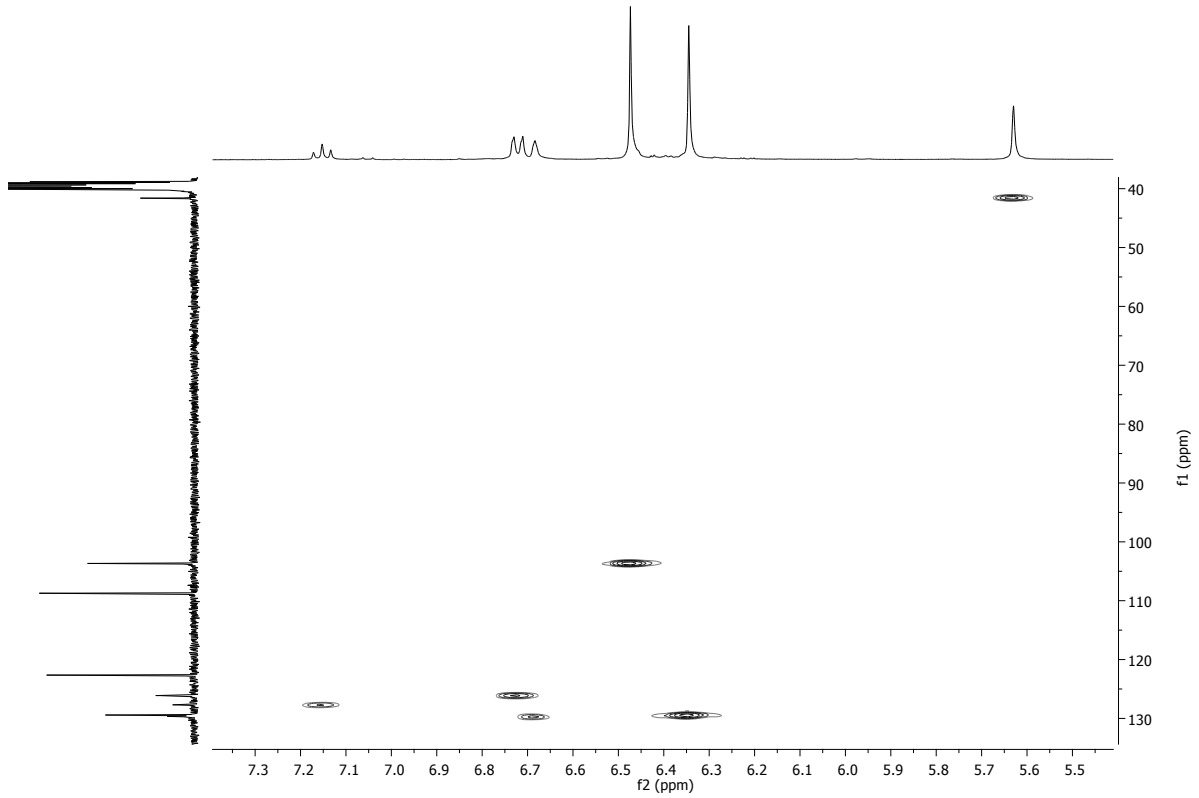
$^{1}$H NMR



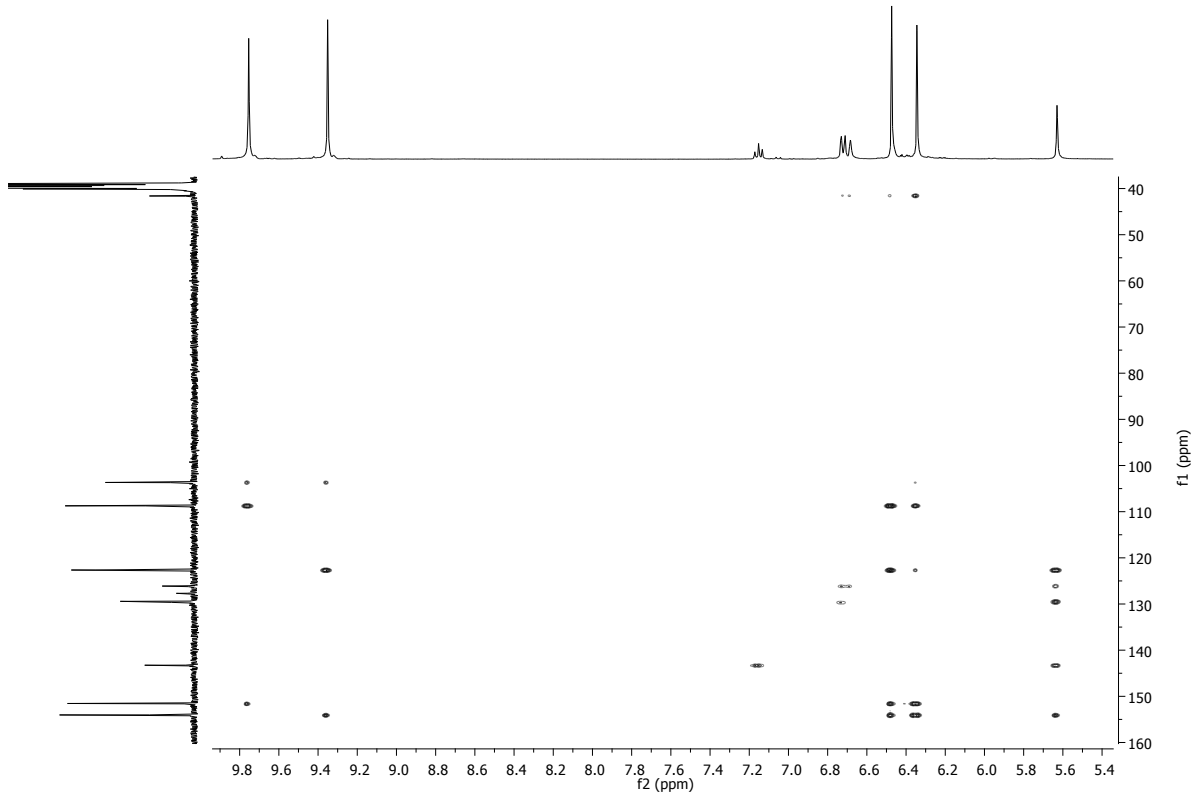

$^{13}$C NMR



HSQC




HMBC



**Crystallisation procedure**

A sample of compound was suspended in a solution 1:1 of DCM:$Et_2O$ and heated to reflux. The minimum amount of methanol necessary to obtain complete dissolution was added; the clear solution obtained was sealed in the tube and left at room temperature to obtain transparent needles.

**Platform 7b** molecules are linked, directly and through bridging methanol molecules, in an extensive hydrogen-bonded network. Principally, the octa-phenols are linked in ladder-like chains through O(24$^3$)-H…O(14) and O(34)-H…O(44$^3$) hydrogen bonds; there are also O(32)-H…O(42$^1$) hydrogen bonds, about centres of symmetry, that link these chains into double-ladder chains. These chains are linked through one or more bridging methanol molecules.

**Figure 3.** View of a molecule of **7b**. Thermal ellipsoids are drawn at the 50% probability level.

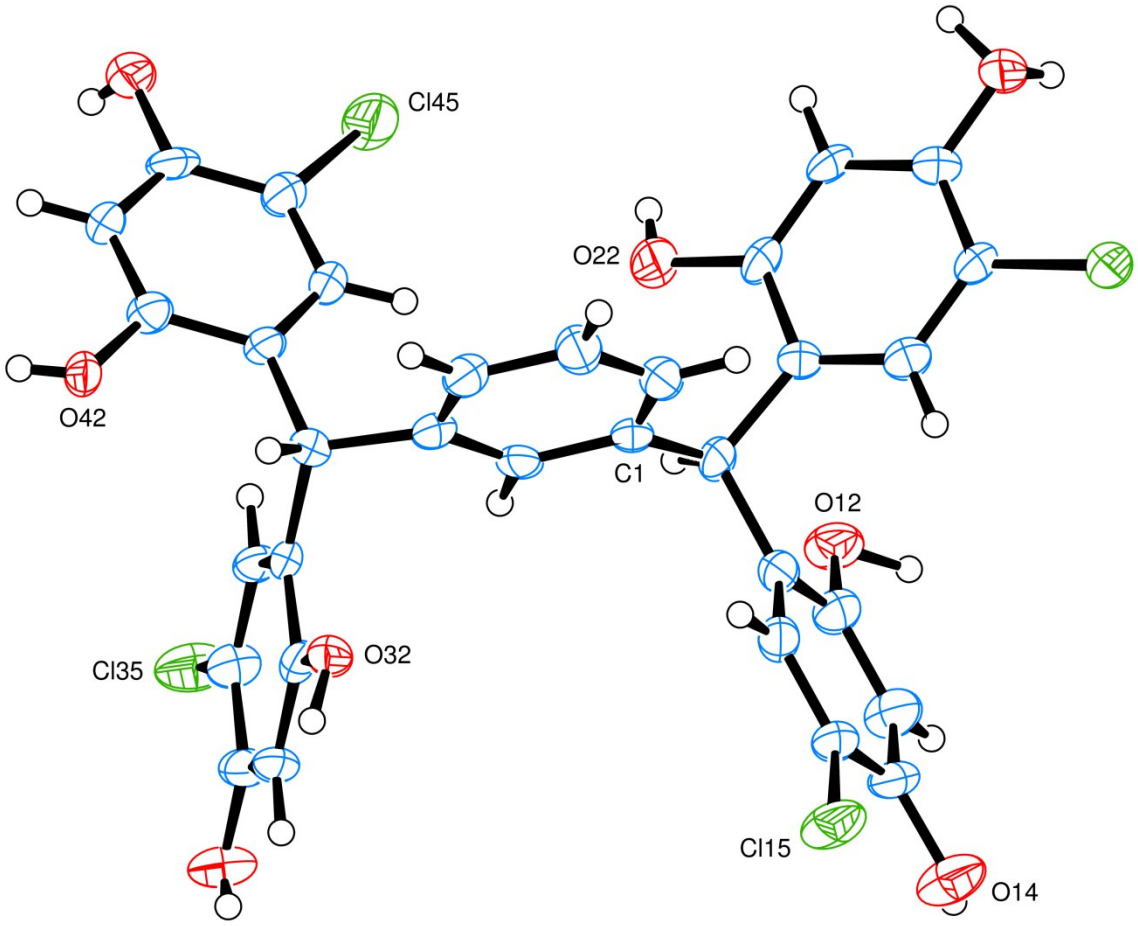
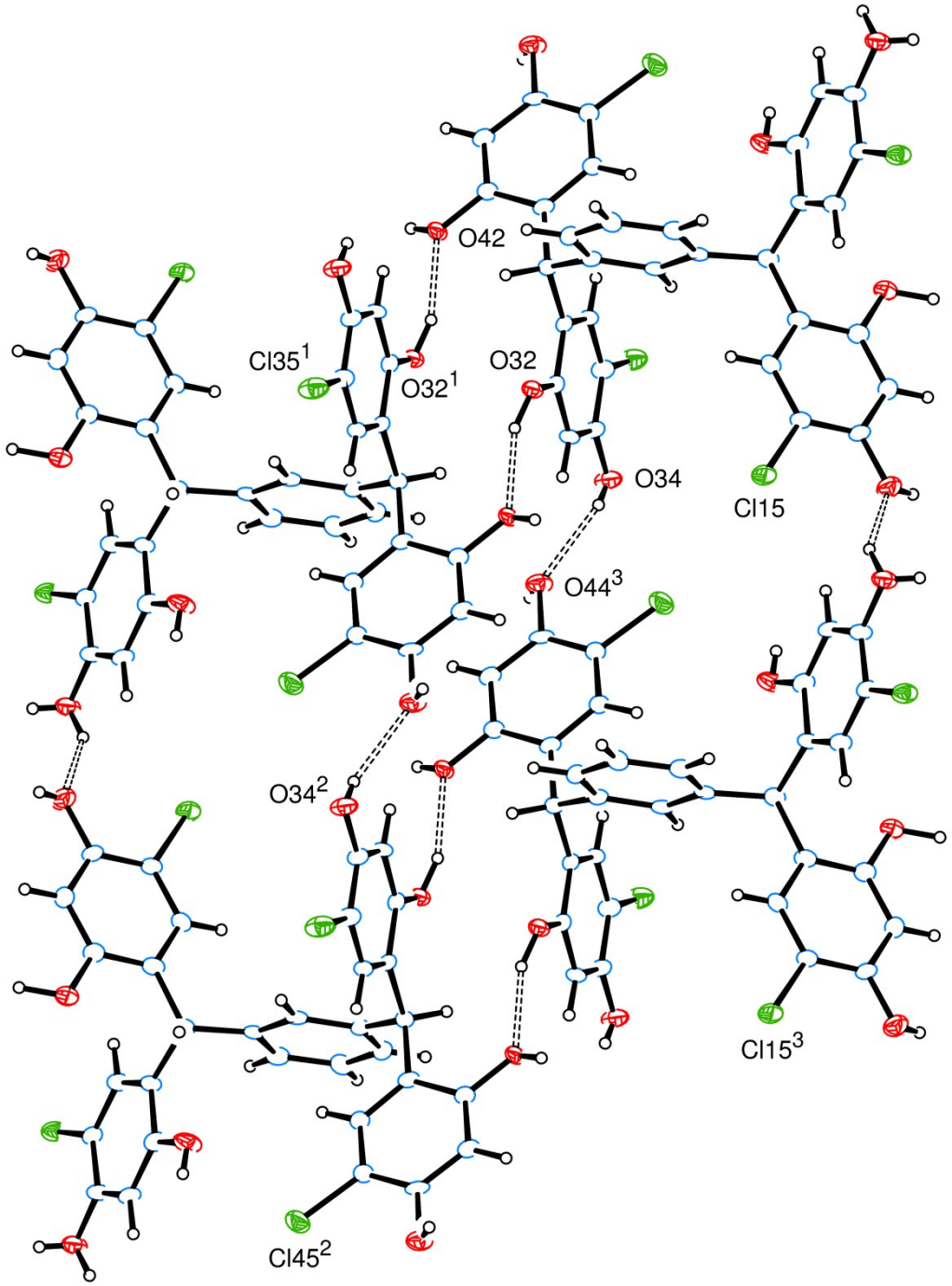
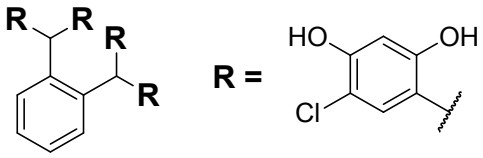


**Figure 4.** Linking, through hydrogen bonds, of the **7b** molecules, showing the ladder formation and the linking of pairs of ladders about centres of symmetry.



## Platform 7c




**Method 1**

A mixture of *phthaldialdehyde* (500 mg, 3.73 mmol) and *4-chlororesorcinol* (2.425 g, 16.78 mmol) was dissolved in 15 ml of ethanol/HCl 37% (1/1, v/v).and stirred at 70°C for 6.5 h. The solvent was evaporated and the resulting orange solid obtained was suspended in water, collected by filtration and washed with water. To remove trace *3-chlororesorcinol*, the solid was suspended in dichloromethane, stirred for 15 minutes, collected by filtration and washed with dichloromethane. The orange powder was dried in the desiccator for one week to give 2.4915 g of product.

Yield: 80.33% (calculated from NMR to account for solvent of crystallisation)

**Method 2**

1.2 mL of *methanesulfonic acid* was added to a pre-cooled (0°C) mixture of *phthaldialdehyde* (500 mg, 3.73mmol) and *4-chlororesorcinol* (2.425 g, 16.78 mmol) in 15 ml of $Et_2O$/DCM (1/1, v/v). The reaction vessel was sealed and the reaction stirred vigorously for 6 h. The mixture was poured into 75 mL of $Et_2O$ and cooled for 18 h at 4°C. The resulting solid was collected and washed with diethyl ether to give a pale yellow powder (398.1 mg).

*Note* stirring must be vigorous, the amount of precipitate formed can give uneven stirring and isolation of **9**; use of reaction tubes is discouraged.

Yield: 94% (calculated from NMR to account for solvent of crystallisation)

$[M-H]^-$ = 674.9954 (Calculated: 674.9972)

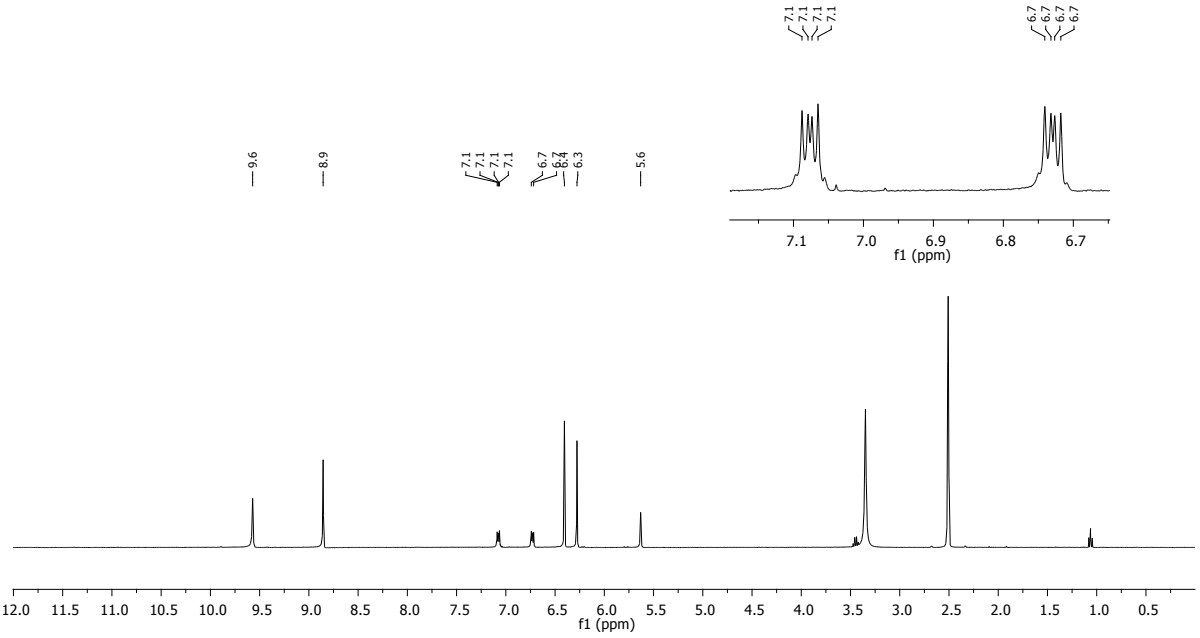
MP: 282-283°C

$^1$H NMR (400 MHz, DMSO) δ 9.57 (s, 4H), 8.86 (s, 4H), 7.08 (dd, *J* = 5.7, 3.5 Hz, 2H), 6.73 (dd, *J* = 5.7, 3.5 Hz, 2H), 6.41 (s, 4H), 6.28 (s, 4H), 5.63 (s, 2H).

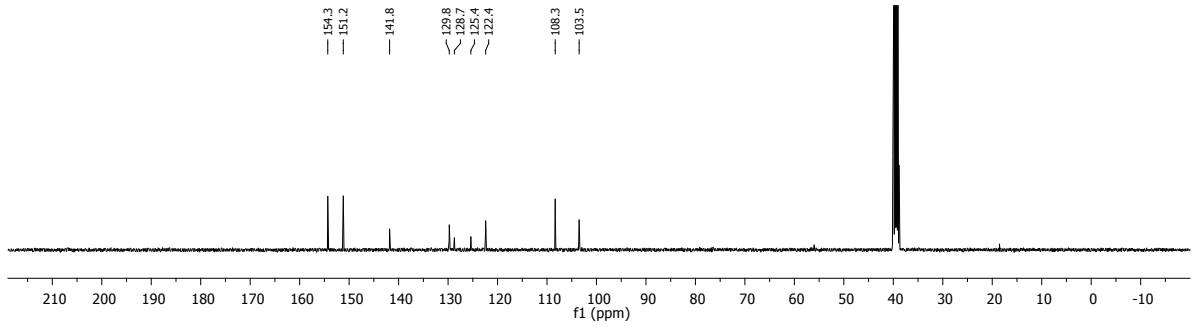
$^{13}$C NMR (101 MHz, DMSO) δ 154.32, 151.18, 141.82, 129.76, 128.72, 125.39, 122.41, 108.34, 103.50, 39.1. (The peak at 39.6 is overlaid with DMSO and was assigned by HSQC)

IR ($\nu_{max}$, $cm^{-1}$): 3492, 3397, 1614, 1598.5, 1502.5, 1424, 1367.5, 1334, 1248, 1191.5, 1126.5, 1029, 905, 895, 876.5, 864, 836.5, 822.

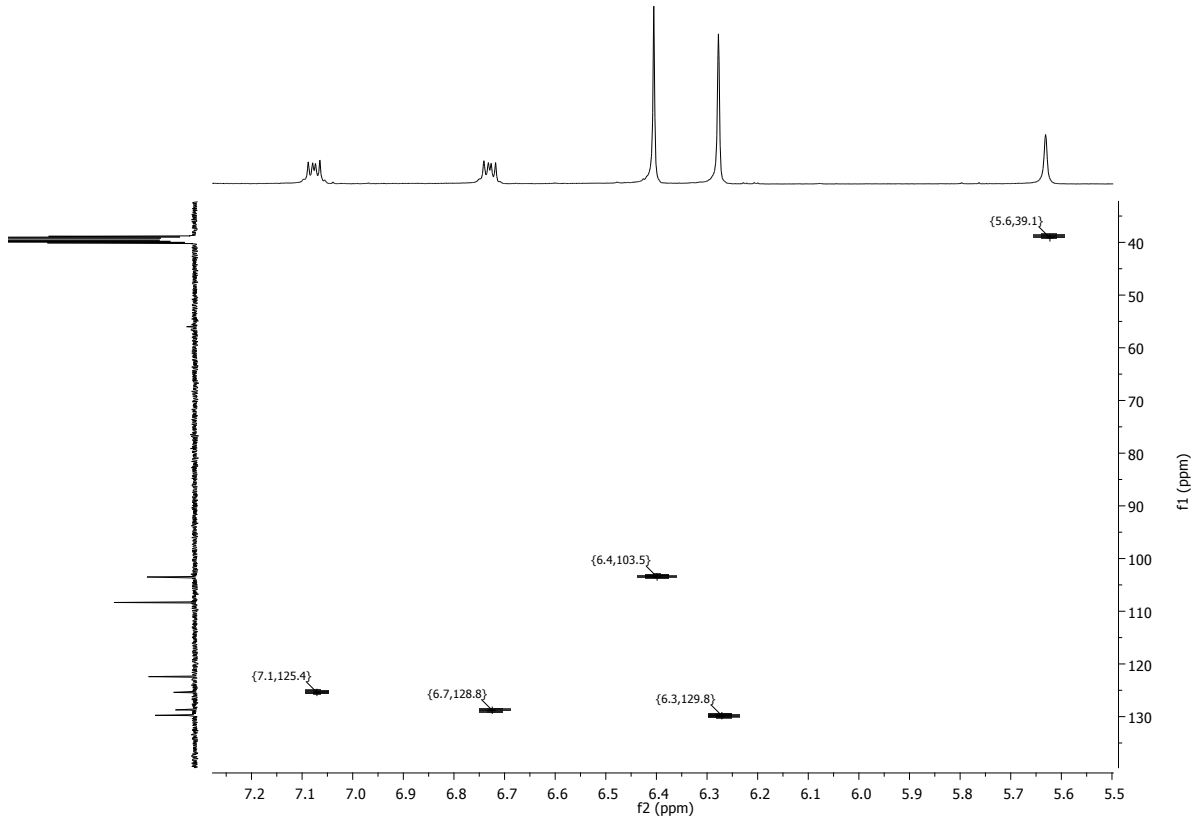
$^{1}$H NMR



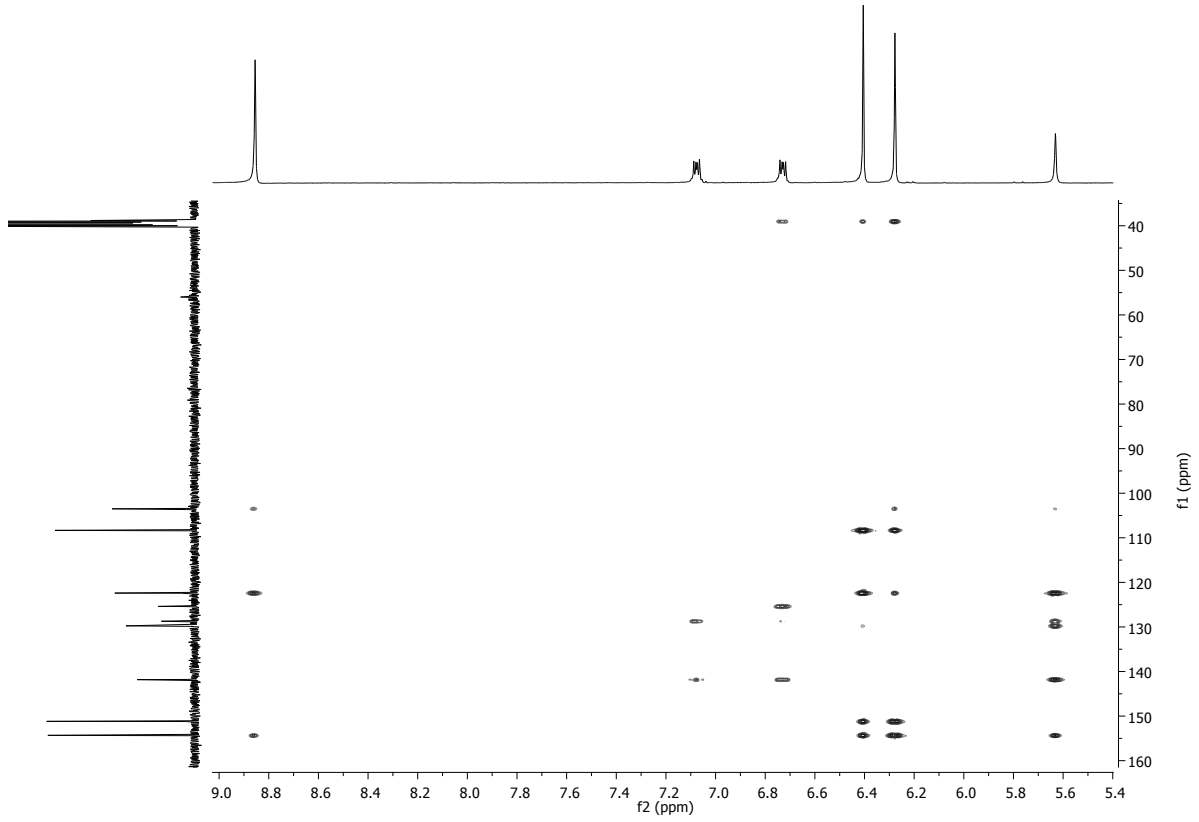

$^{13}$C NMR



HSQC




HMBC



**Crystallisation procedure**

A sample of compound was suspended in diethyl ether and heated to reflux. The minimum amount of methanol necessary to obtain complete dissolution was added; the clear solution obtained was sealed in the tube and left at room temperature to obtain transparent needles.

The phenyl rings of **Platform 7c** lie in three essentially orthogonal planes, **Figure 5**.

All eight phenolic groups are donors in hydrogen bonds, and several are also acceptor atoms. The O(12) and O(32) each form pairs of links about centres of symmetry with neighbouring **7c** molecules and thus form ladder-like chains through the crystal, (horizontally in **Figure 6**).

The two principal methanol molecules combine in a double bridging link between chains, forming a 'square' hydrogen bonding cycle, **Figure 6**, thus forming sheets of linked molecules.

**Figure 5.** View of a molecule of **7c**. Thermal ellipsoids are drawn at the 50% probability level.

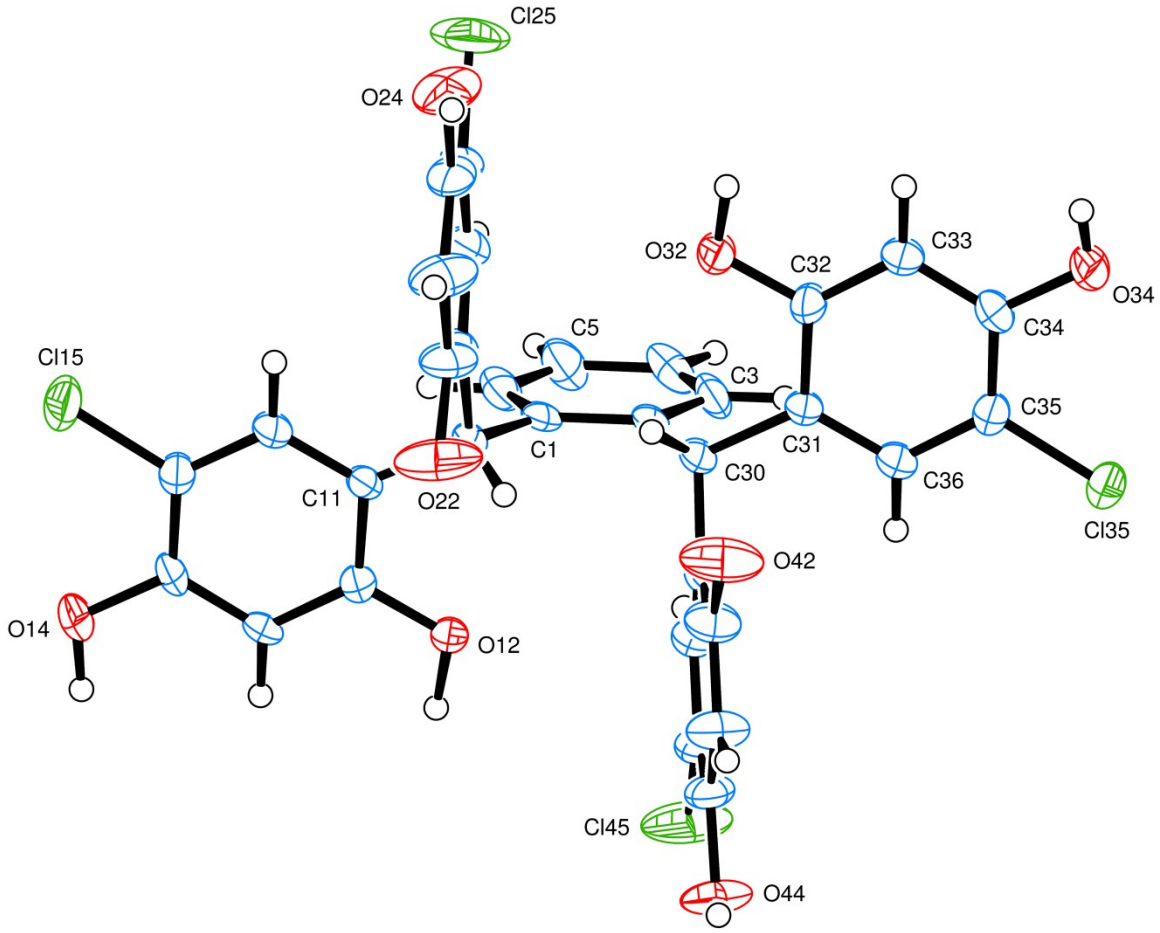
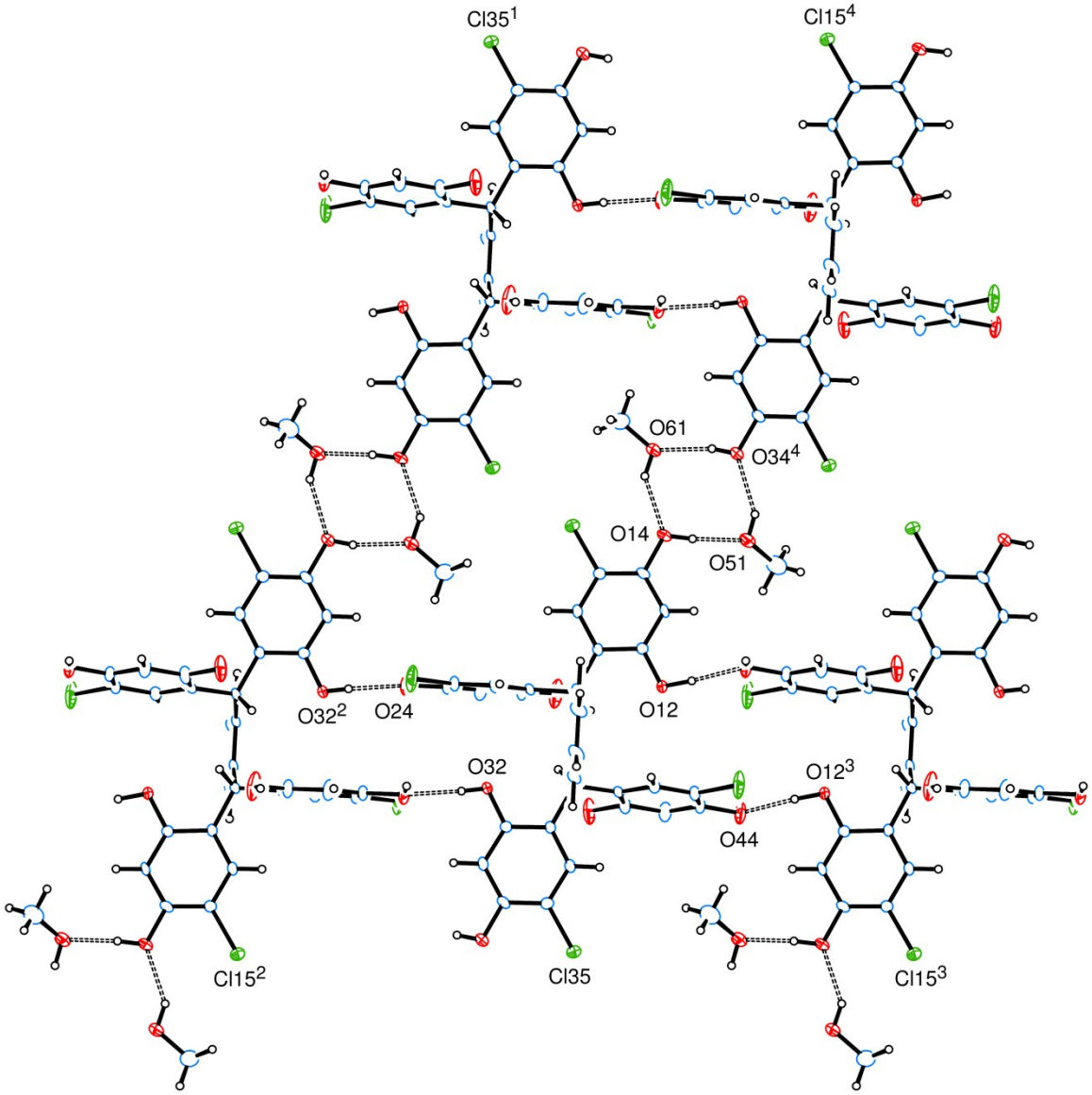
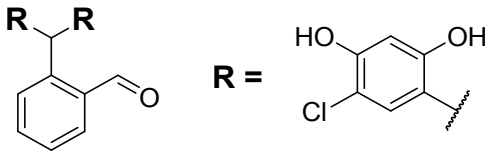


**Figure 6.** The molecules are linked through hydrogen bonds in chains (horizontally) about centres of symmetry, and in sheets and through methanol bridges.



## Synthesis of 8 and 9

Note: **9** can also be isolated from the reaction mixture for **7c** if insufficient stirring occurs




1.2 mL of *methanesulfonic acid* was added to a pre-cooled (0°C) mixture of *phthaldialdehyde* (500 mg, 3.73 mmol) and *4-chlororesorcinol* (1.0778 g, 7.46 mmol) in 15 ml of $Et_2O$/DCM (1/1, v/v). The reaction vessel was sealed and the reaction stirred vigorously for 6 h. The mixture was poured into 75 mL of $Et_2O$ and cooled for 18 h at 4°C. The resulting solid was collected and washed with diethyl ether. The product was dried in the oven at 60°C for 18 h to give 773.2 mg of **8** as a white powder

Yield: 44% (calculated from NMR to account for solvent of crystallisation)

To isolate **9**: after collecting the solid **8**, the remaining liquor was washed with a solution of 1.55 g of $NaHCO_3$ in 20 mL of water and then with brine. The organic layer was dried over $MgSO_4$ and the product was crystallised by solvent evaporation.

Yield: 10.82%

## Aldehyde 8

$[M+NH_4]^+$ = 422.0556 (Calculated: 422.0557)

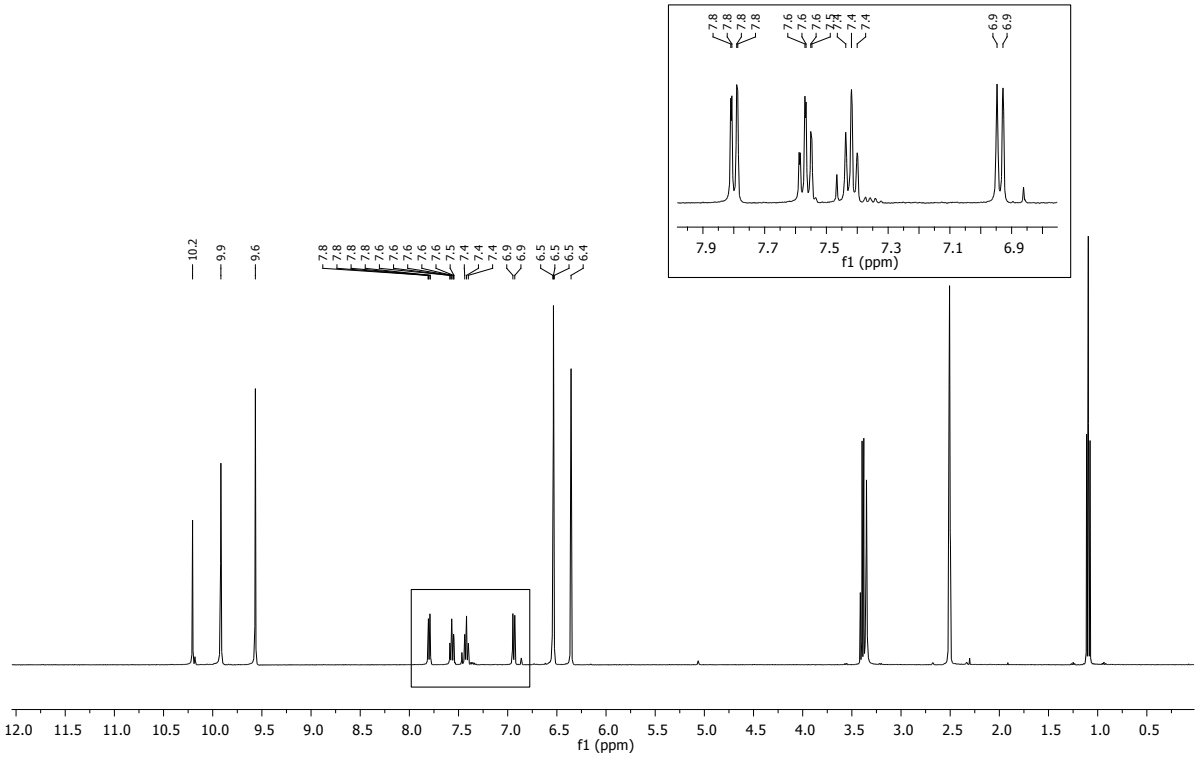
MP: 214-216°C

$^1$H NMR (400 MHz, DMSO) δ 10.20 (s, 1H), 9.92 (s, 2H), 9.57 (s, 2H), 7.80 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.56 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.42 (adt, *J* = 7.6 Hz, 1H), 6.94 (add, *J* = 7.7 Hz, 1H), 6.55 – 6.53 (m, 3H), 6.36 (s, 2H).

$^{13}$C NMR (101 MHz, DMSO) δ 191.70, 153.88, 152.05, 146.41, 133.80, 132.95, 129.76, 129.39, 128.92, 126.67, 121.67, 108.95, 103.79, 37.06.

IR ($\nu_{max}$, $cm^{-1}$): 3420.5, 3366, 3168, 1649, 1613.5, 1594.5, 1521, 1420.5, 1366, 1274, 1251.5, 1217.5, 1194.5, 1174, 1132.5, 1090, 1030.5, 903.5, 895, 866.5, 832.5.

$^{1}$H NMR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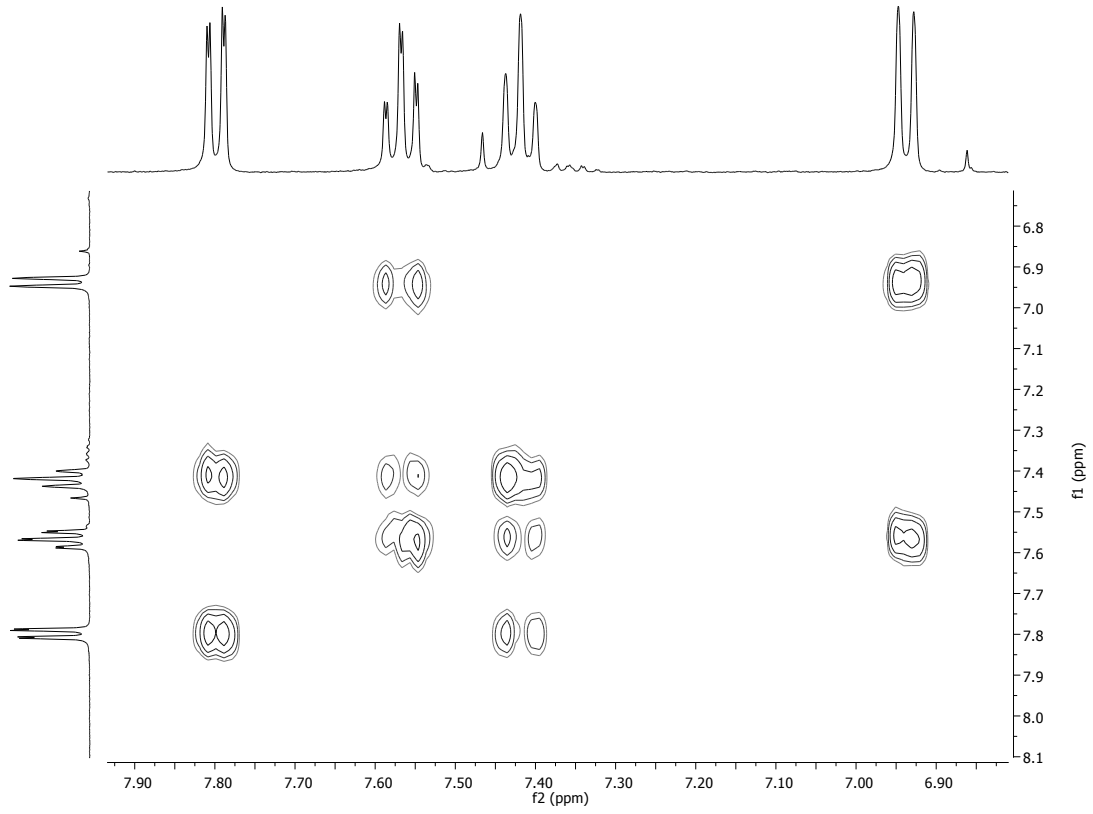
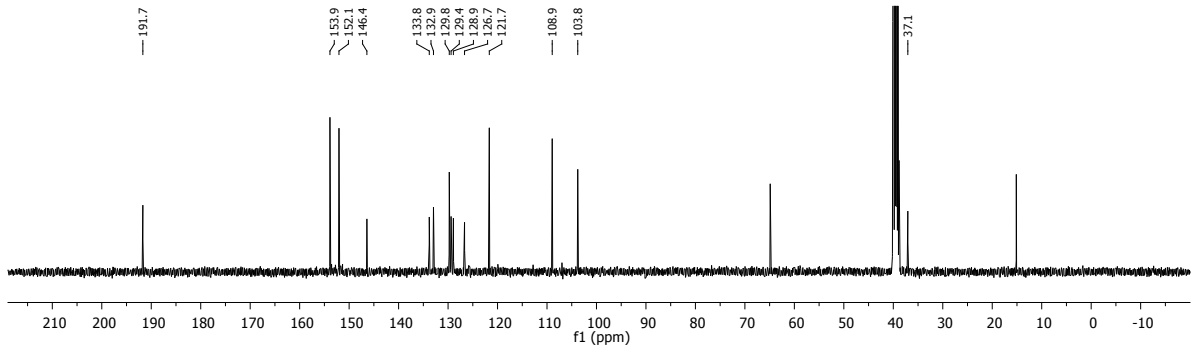
9.9
9.6
7.8
7.8
7.8
7.8
7.6
7.6
7.6
7.6
7.5
7.4
7.4
7.4
6.9
6.9
6.5
6.5
6.5
6.4
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)
7.9 7.7 7.5 7.3 7.1 6.9
f1 (ppm)

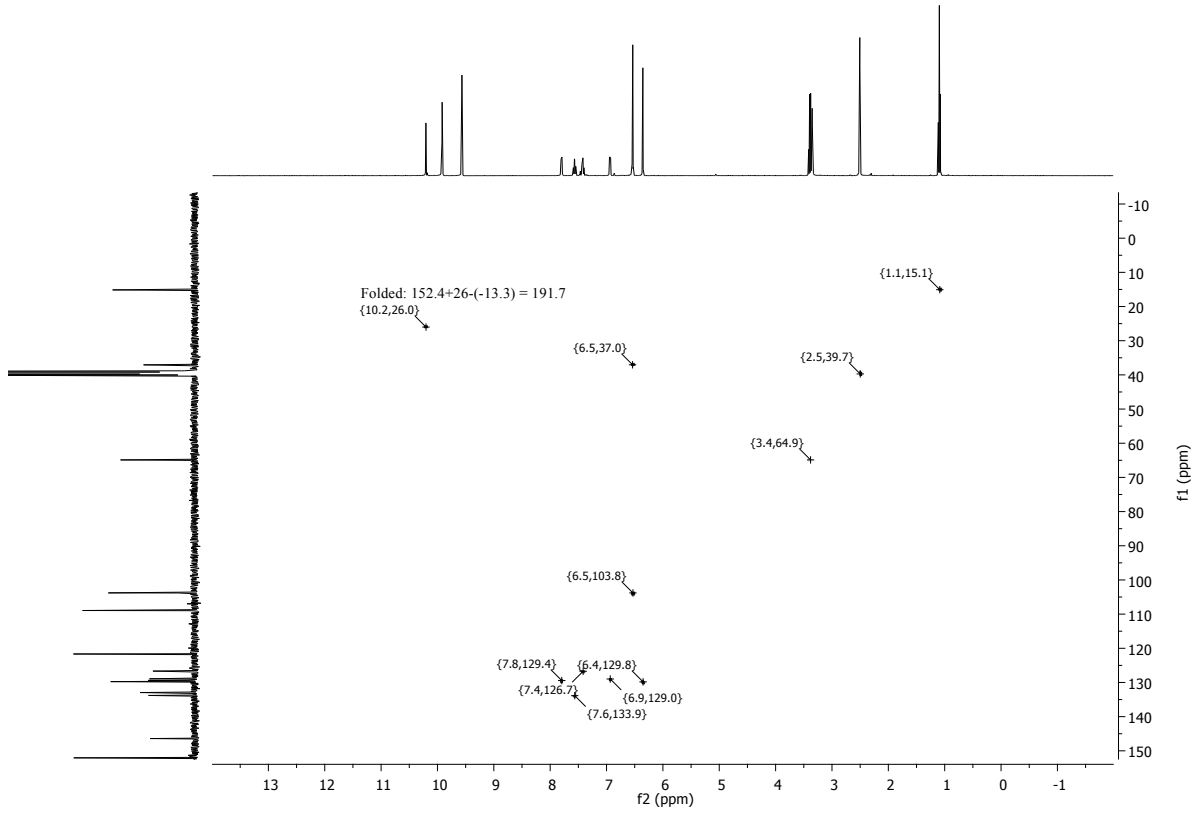
COSY


7.90 7.80 7.70 7.60 7.50 7.40 7.30 7.20 7.10 7.00 6.90
f2 (ppm)
6.8 6.9 7.0 7.1 7.2 7.3 7.4 7.5 7.6 7.7 7.8 7.9 8.0 8.1
f1 (ppm)

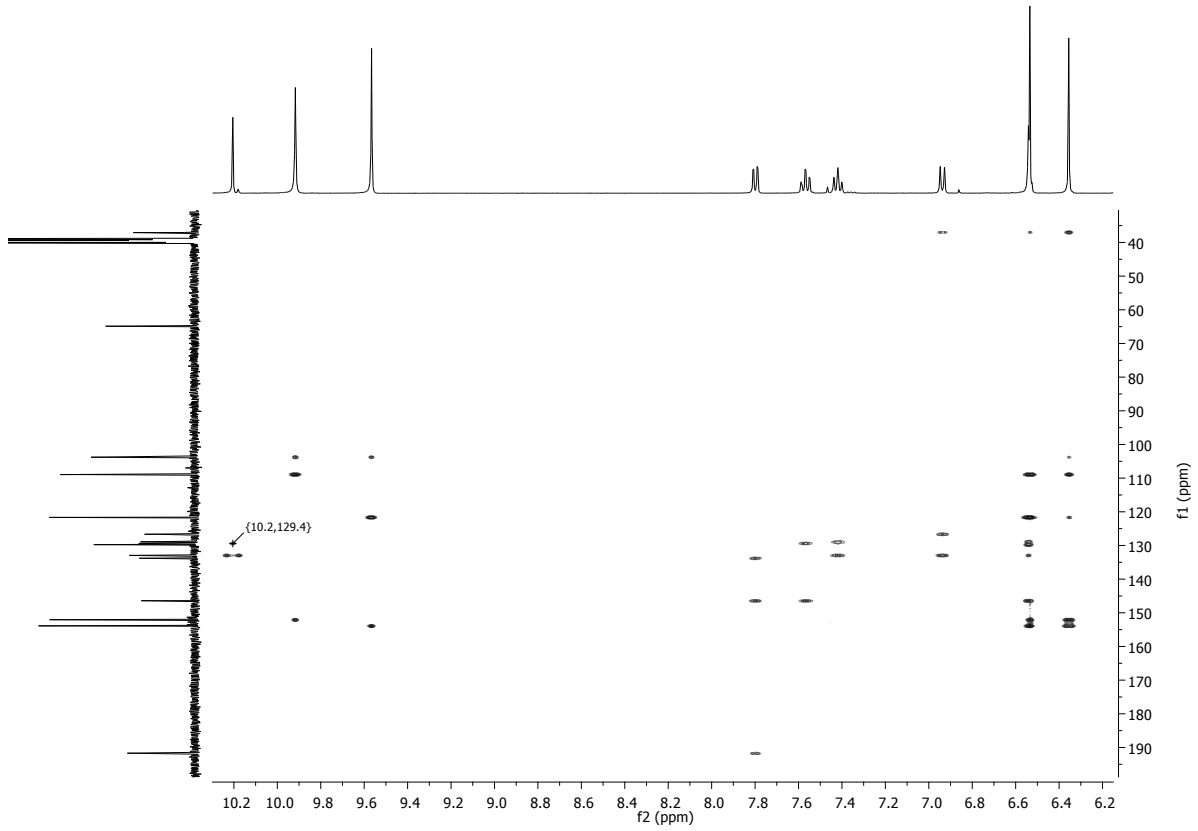
$^{13}$C NMR


191.7
153.9
152.1
146.4
133.8
132.9
129.8
129.4
128.9
126.7
121.7
108.9
103.8
37.1
f1 (ppm)

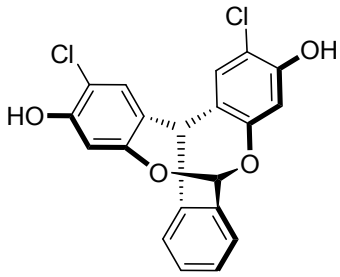
HSQC


Folded: 152.4+26-(-13.3) = 191.7
{10.2,26.0}
{1.1,15.1}
{6.5,37.0}
{2.5,39.7}
{3.4,64.9}
{6.5,103.8}
{7.8,129.4}
{6.4,129.8}
{7.4,126.7}
{6.9,129.0}
{7.6,133.9}
f2 (ppm)
f1 (ppm)

HSQC


{10.2,129.4}
10.2 10.0 9.8 9.6 9.4 9.2 9.0 8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2
f2 (ppm)
40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190
f1 (ppm)

## Acetal 9




$[M+H]^+$ = 387.0188 (Calculated: 387.0185)

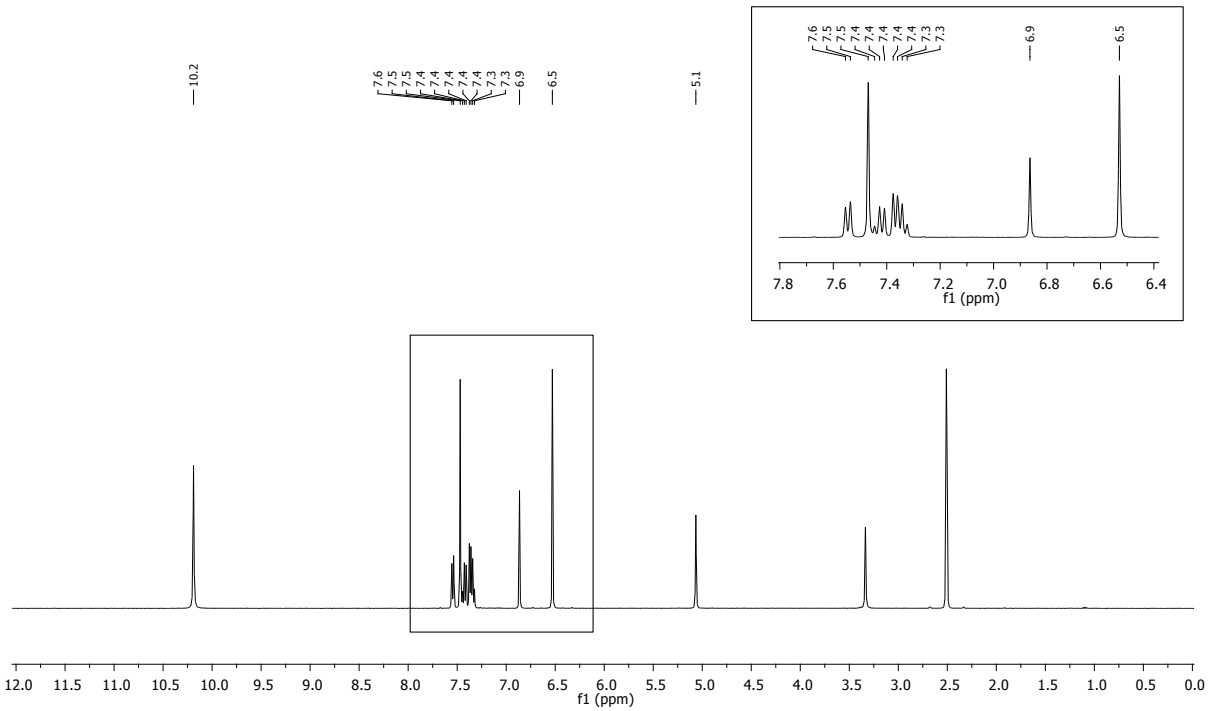
MP: 259-260°C

$^1$H NMR (400 MHz, DMSO) δ 10.19 (s, 2H), 7.55 (d, *J* = 7.3 Hz, 1H), 7.47 (s, 2H), 7.45 – 7.31 (m, 3H), 6.86 (s, 1H), 6.53 (s, 2H), 5.07 (s, 1H).

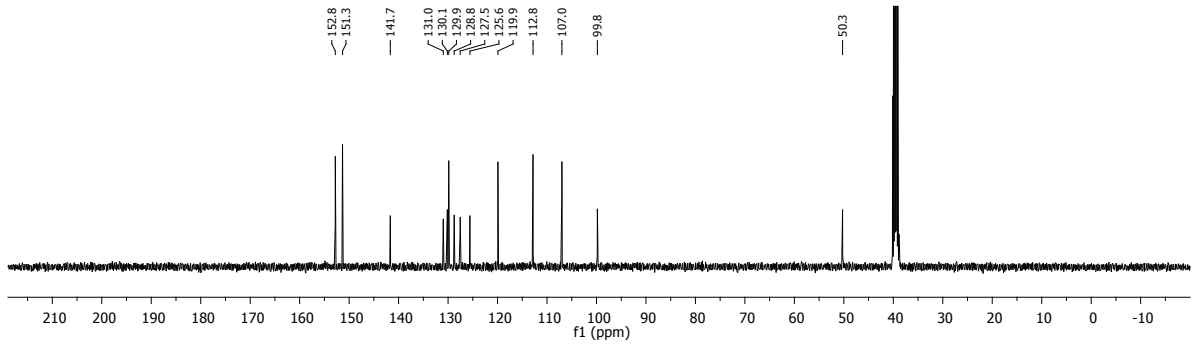
$^{13}$C NMR (101 MHz, DMSO) δ 152.80, 151.33, 141.67, 130.97, 130.15, 129.86, 128.76, 127.55, 125.58, 119.92, 112.82, 106.99, 99.82, 50.26.

IR ($\nu_{max}$, $cm^{-1}$): 3476.5, 3427.5, 1612, 1486.5, 1431, 1319, 1278, 1240, 1218.5, 1210, 1145, 1122.5, 1067.5, 1042, 978.5, 953.5, 940.5, 923, 901, 870.5, 858.5, 840.5, 822.5.

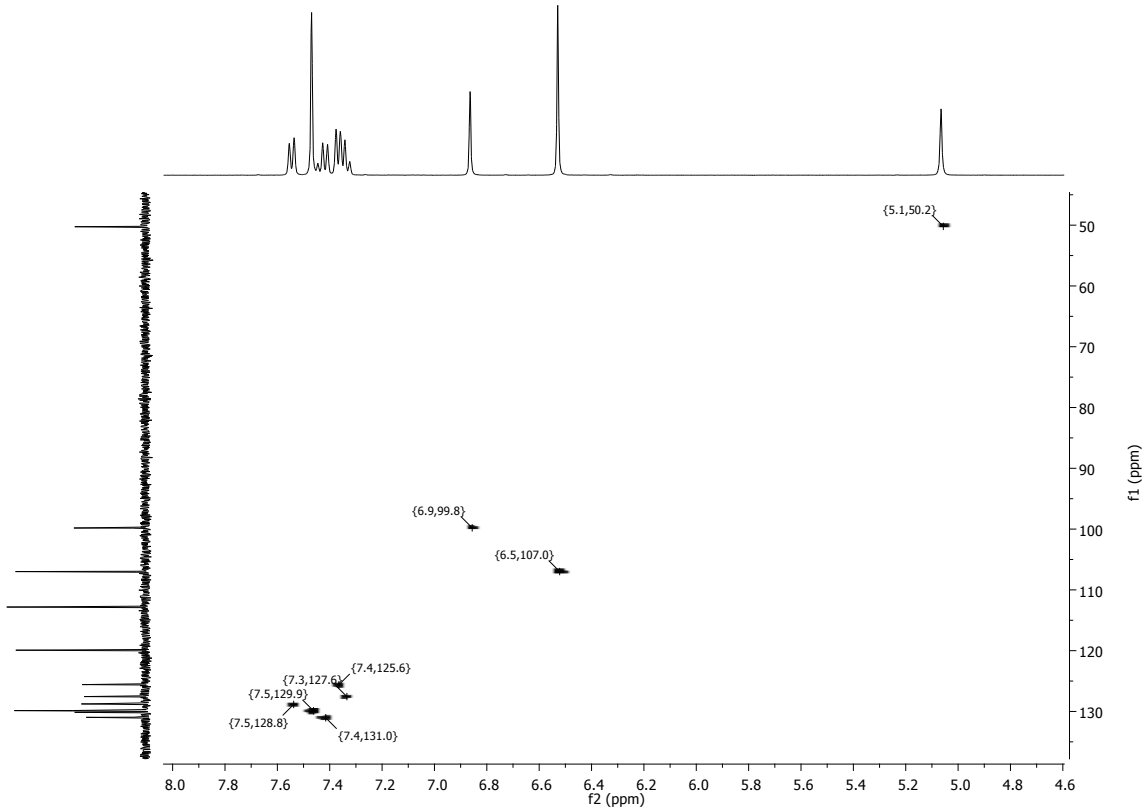
$^1$H NMR



$^{13}$C NMR


152.8
151.3
141.7
131.0
130.1
129.9
128.8
127.5
125.6
119.9
112.8
107.0
99.8
50.3
f1 (ppm)

HSQC


{5.1,50.2}
{6.9,99.8}
{6.5,107.0}
{7.4,125.6}
{7.3,127.6}
{7.5,129.9}
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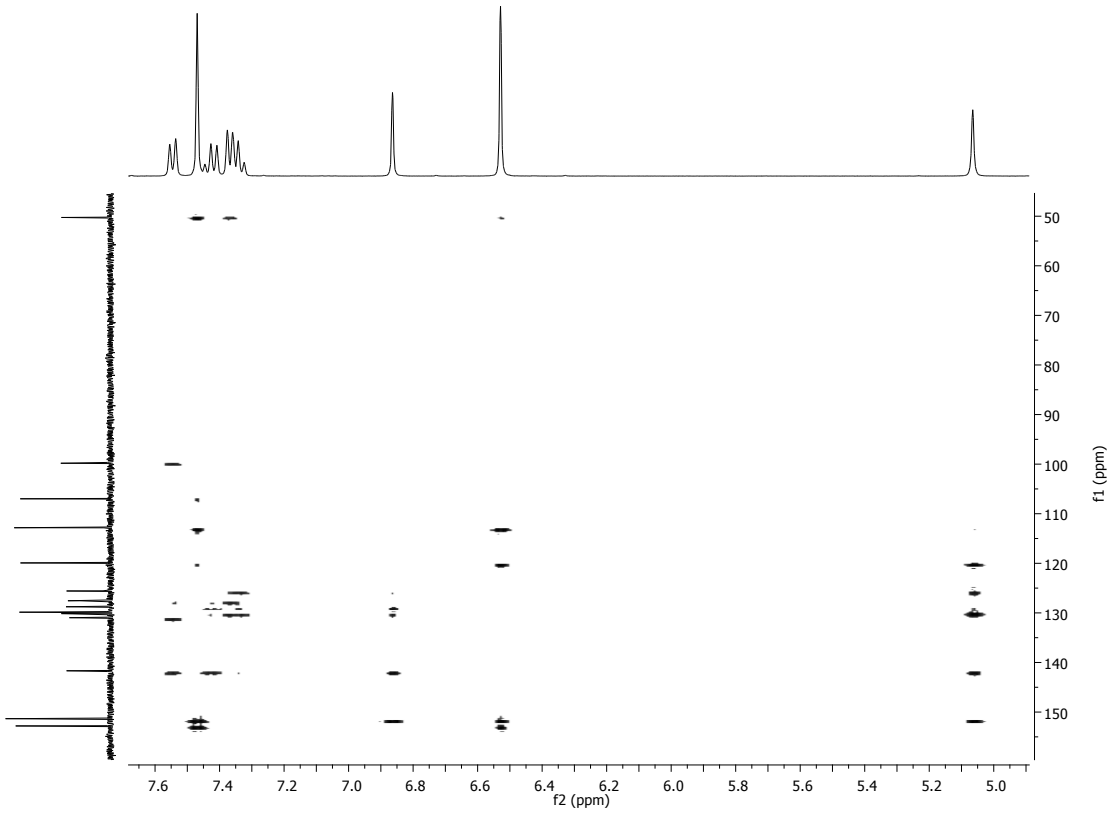
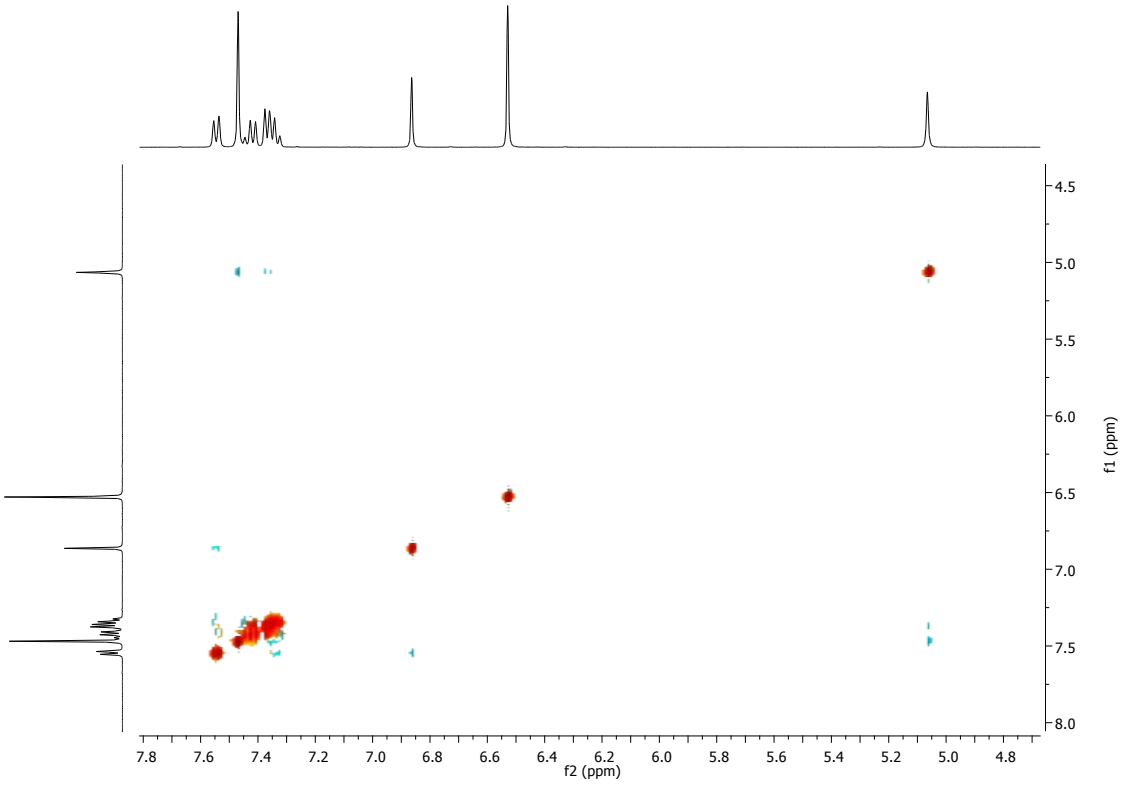
{7.4,131.0}
f2 (ppm)
f1 (ppm)

HMBC




NOESY



The compound forms a rigid triplanar molecule which crystallises with an ether (solvent) molecule.

The only atoms that do not lie on one of the three planes are the phenolate hydrogen atoms which are directed in forming hydrogen bonds which link the diphenolate molecules in chains and to the ether molecules.

**Figure 7.** View of a molecule of **9** and hydrogen-bonded solvent ($Et_2O$) molecule, indicating the atom numbering scheme. Thermal ellipsoids are drawn at the 50% probability level.

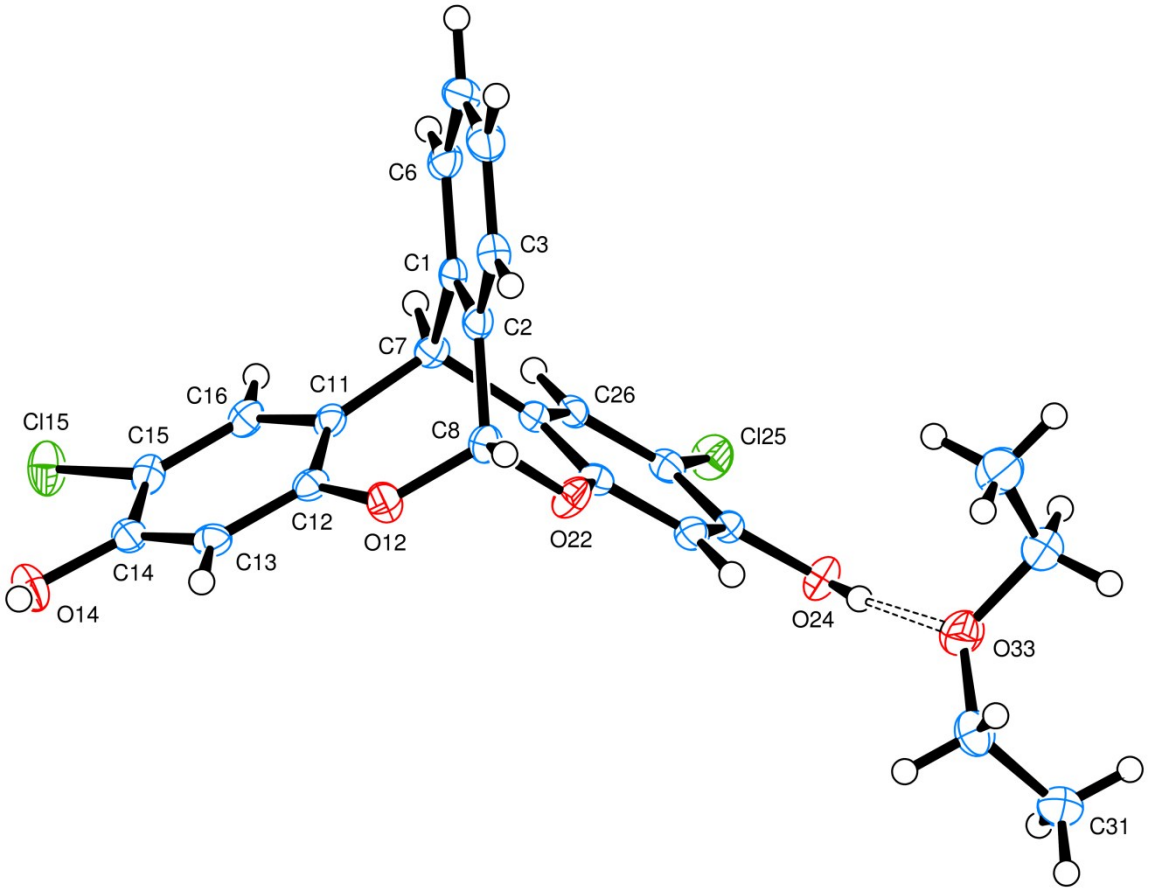
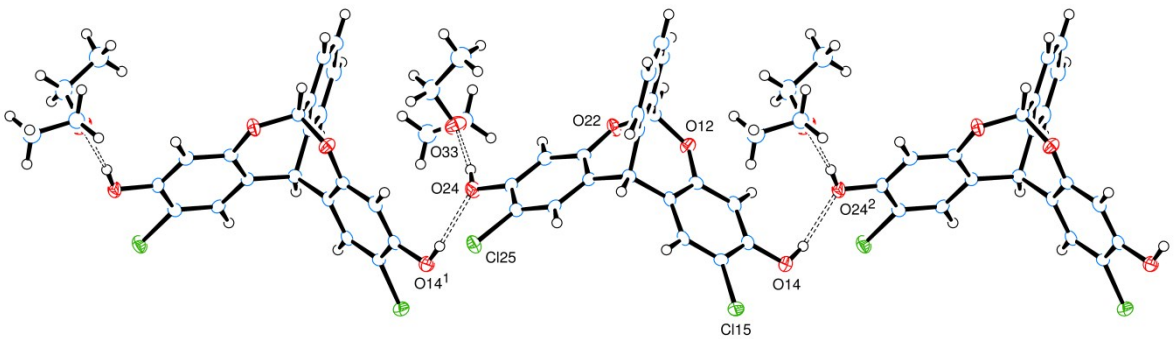
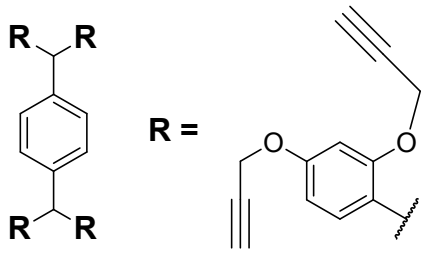



**Figure 8.** A chain of hydrogen-bond linked **9** and ether molecules.



## Platform 10




A mixture of **6a** (3.26 mmol), *anhydrous potassium carbonate* (10.4236 g, 75,42 mmol), and *propargyl bromide* (5.5446 g, 57.46 mmol) in 100 ml of DMF was stirred at 70°C for 5 h and then for 18 h at 80°C. The solvent was evaporated under reduced pressure and the resulting solid suspended in water and extracted three times with diethyl ether. The organic layers were combined, washed with $NaHCO_3$, brine and then dried over $MgSO_4$. The crude product obtained upon evaporation of the solvent was purified via flash chromatography on silica gel (DCM as eluent) and dried in the oven at 120°C. A pale yellow solid was obtained (1.6239 g).

Yield: 59%

$[M+NH_4]^+$ = 860.3217 (Calculated: 860.3218)

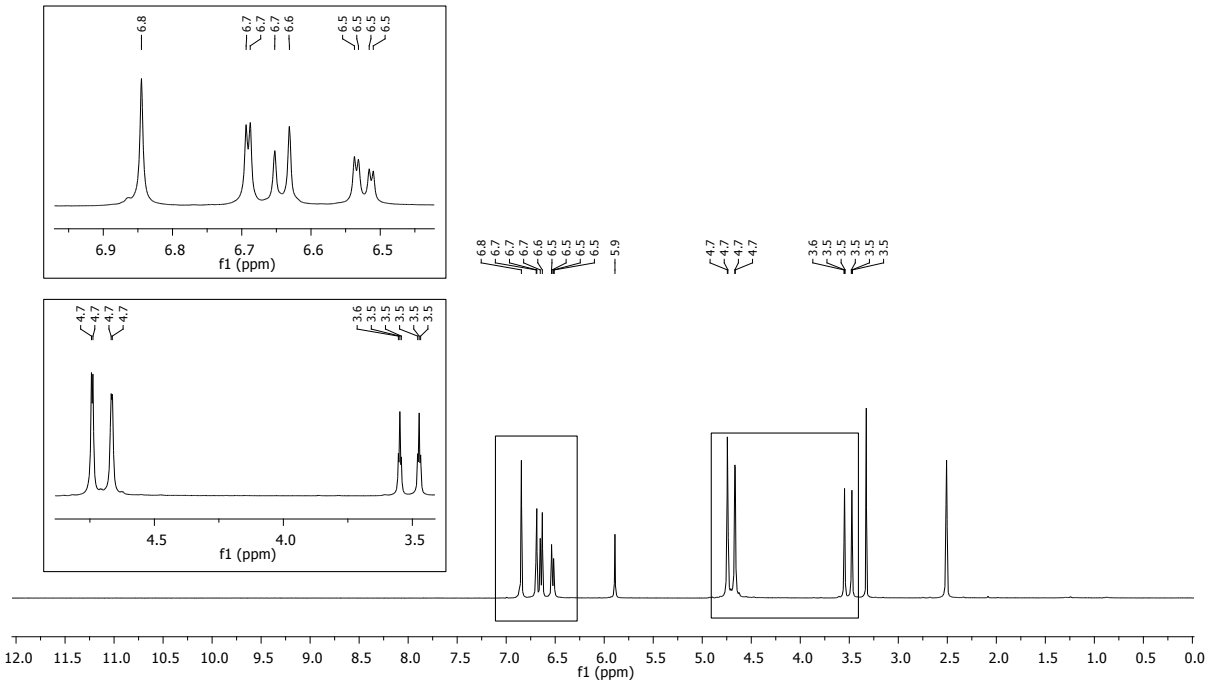
MP: 135-137°C

$^1$H NMR (400 MHz, DMSO) δ 6.84 (s, 4H), 6.69 (d, *J* = 2.3 Hz, 4H), 6.64 (d, *J* = 8.5 Hz, 4H), 6.52 (dd, *J* = 8.5, 2.3 Hz, 4H), 5.89 (s, 2H), 4.74 (d, *J* = 2.3 Hz, 8H), 4.67 (d, *J* = 2.3 Hz, 8H), 3.55 (t, *J* = 2.3 Hz, 4H), 3.47 (t, *J* = 2.3 Hz, 4H).

$^{13}$C NMR (101 MHz, DMSO) δ 156.61, 155.46, 140.93, 129.91, 128.42, 125.55, 105.94, 101.22, 79.24, 79.16, 78.18, 78.00, 56.07, 55.50, 41.01.

IR ($\nu_{max}$, $cm^{-1}$): 3286, 1607.5, 1586, 1498, 1451, 1428, 1370.5, 1285, 1247, 1162.5, 1109, 1025, 941.5, 920.5, 832, 800.

$^{1}$H NMR


6.8
6.7
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6.5
6.5
6.5
6.5
6.9
6.8
6.7
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6.5
f1 (ppm)
4.7
4.7
4.7
4.7
3.6
3.5
3.5
3.5
3.5
4.5
4.0
3.5
f1 (ppm)
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11.5
11.0
10.5
10.0
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8.5
8.0
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7.0
6.5
6.0
5.5
5.0
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4.0
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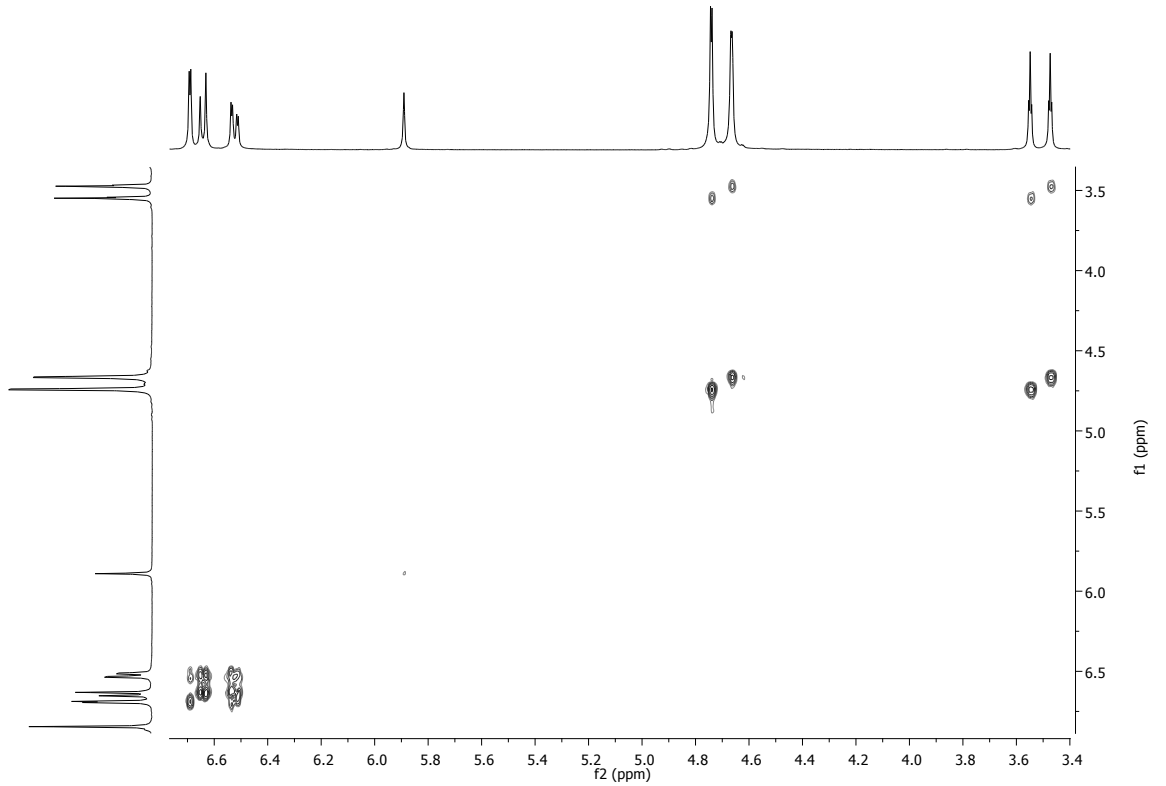
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

COSY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4.8
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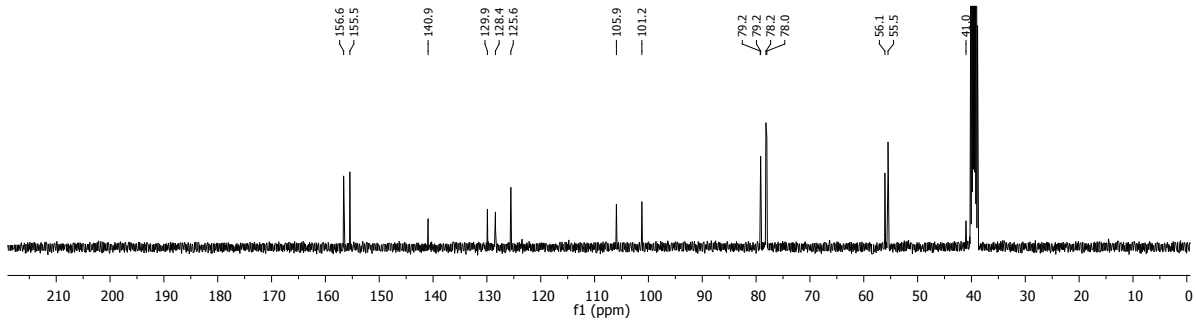
4.4
4.2
4.0
3.8
3.6
3.4
f2 (ppm)
3.5
4.0
4.5
5.0
5.5
6.0
6.5
f1 (ppm)

$^{13}$C NMR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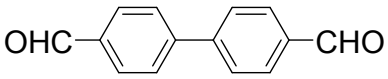
128.4
125.6
105.9
101.2
79.2
79.2
78.2
78.0
56.1
55.5
41.0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

## Platform 11[5]




To a stirred solution of 4-formylphenylboronic acid (1.0 g, 6.669 mmol), 4-bromobenzaldehyde (1.3 g, 6.8 mmol), DMF (160 mL) and $Na_2CO_3$ (4.3 g, 0.04 mol) in water (16 mL), a catalytic amount of 5% $Pd(dppf)Cl_2$ (0.033 mmol) was added. The flask was flushed with argon and the reaction mixture was allowed to stir for 18 hours at 40 °C. The solvent was removed under reduced pressure and the product was purified by column chromatography (DCM/Hexane 1:1) to give **11** as white solid.

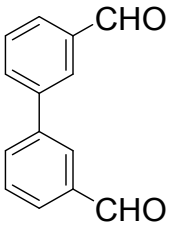
Yield: 86% (calculated from NMR to account for solvent of crystallisation)

MP: 155-158 °C

$^{1}$H NMR (400 MHz, DMSO) δ 10.10 (s, 2H), 8.10 – 7.98 (m, 8H).

$^{13}$C NMR (101 MHz, DMSO) δ 193.29, 144.86, 136.28, 130.67, 128.40.

## Platform 12[6]




To a stirred solution of 3-formylphenylboronic acid (1.0 g, 6.669 mmol), 3-bromobenzaldehyde (0.778 mL, 6.669 mmol), DMF (160 mL) and $Na_2CO_3$ (4.241 g, 40.014 mmol) in water (16 mL), a catalytic amount of 5% Pd(dppf)$Cl_2$ (0.033 mmol) was added. The flask was flushed with argon and the reaction mixture was allowed to stir for 18 hours at 40 °C. The solvent was removed under reduced pressure and the product was purified by column chromatography (DCM/Hexane 1:1) to give **11** as a white solid.

Yield: 69%

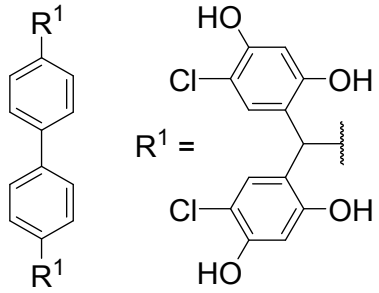
$[M+NH_4]^+$ = 228.1016 (Calculated: 228.1019)

MP: 93-95 °C (lit. 92-94 °C)

$^1$H-NMR (400 MHz, CDCl3) δ 10.14 (s, 1H), 8.18 (s, 1H), 8.04 – 7.86 (m, 2H), 7.69 (t, *J* = 7.7 Hz, 1H).

$^{13}$C-NMR (101 MHz, CDCl3) δ 192.03, 140.71, 137.10, 132.99, 129.80, 129.47, 128.01.

## Platform 13




0.56 mL of methanesulfonic acid was added to a pre-cooled (0 °C) mixture of **11** (0.3 g, 1.2 mmol) and 4-chlororesorcinol (0.8 mg, 5.4 mmol) in 7 ml of $Et_2O$/DCM (1/1, v/v). The reaction vessel was sealed and the reaction allowed to stir for 18 h. The resulting mixture was diluted with diethyl ether, poured into distilled water and allowed to stir vigorously until a suspension was obtained. The product was collected by Büchner filtration, washed with abundant distilled water and dried in a desiccator to give an orange powder.

Yield: 79% (calculated from NMR to account for solvent of crystallisation)

$[M-H]^-$= 751.0258 (Calculated: 751.0286)

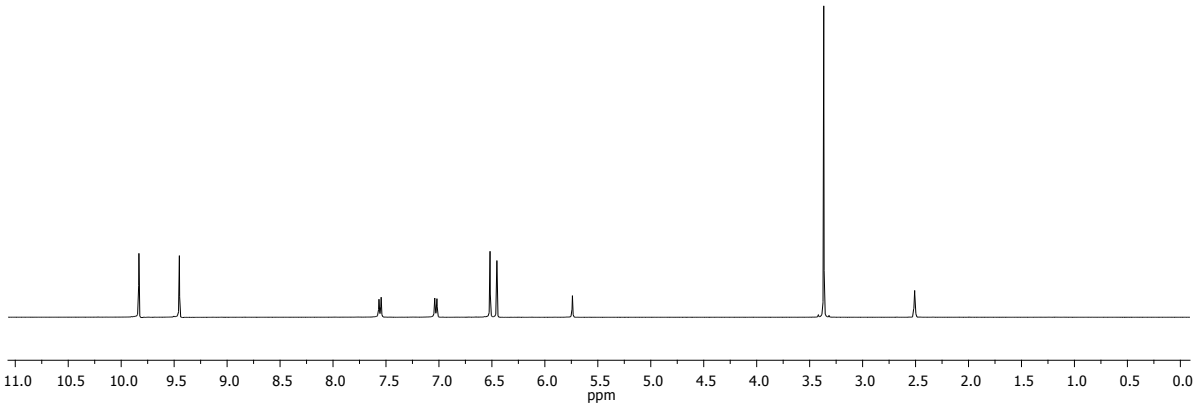
MP: 195-200 °C

$^1$H-NMR (400 MHz, DMSO) δ 9.83 (s, 4H), 9.45 (s, 4H), 7.56 (d, *J* = 8.3 Hz, 4H), 7.03 (d, *J* = 8.3 Hz, 4H), 6.52 (s, 4H), 6.45 (s, 4H), 5.74 (s, 2H).

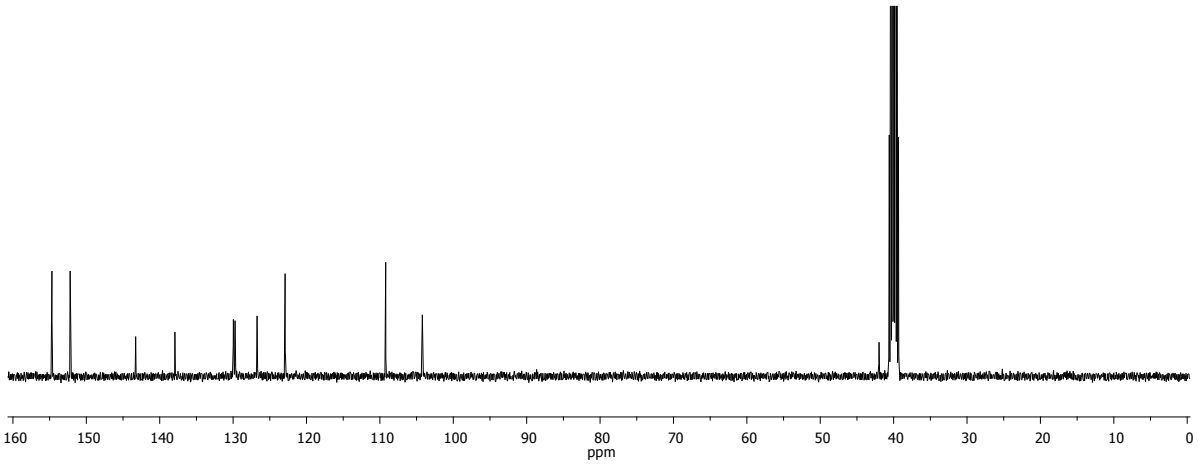
$^{13}$C-NMR (101 MHz, DMSO) δ 154.69, 152.21, 143.28, 137.93, 129.97, 129.73, 126.73, 122.91, 109.21, 104.22, 41.99.

IR ($\nu_{max}$, $cm^{-1}$): 3335, 2359, 2361, 2338, 1612, 1492, 1432, 1330, 1275, 1233, 1169, 1122, 1025, 1007, 896, 882, 867.

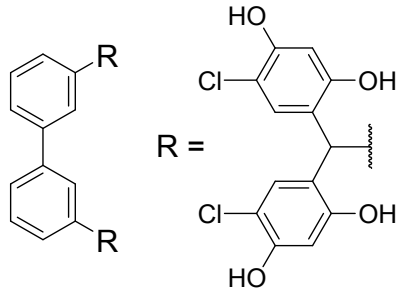
$^1$H NMR



$^{13}$C NMR



## Platform 14




0.16 mL of methanesulfonic acid was added to a pre-cooled (0 °C) mixture of **12** (101.2 mg, 0.48 mmol) and 4-chlororesorcinol (310.5 mg, 2.15 mmol) in 2 ml of $Et_2O$/DCM (1/1, v/v). The reaction vessel was sealed and the reaction allowed to stir for 6 h. The resulting mixture was diluted with diethyl ether, poured into distilled water and allowed to stir vigorously until a suspension was obtained. The product was collected by Büchner filtration, washed with abundant distilled water and dried in a desiccator to give an off yellow powder.

Yield: 99.5% (calculated from NMR to account for solvent of crystallisation)

$[M-H]^-$ = 751.0263 (Calculated: 751.0286)

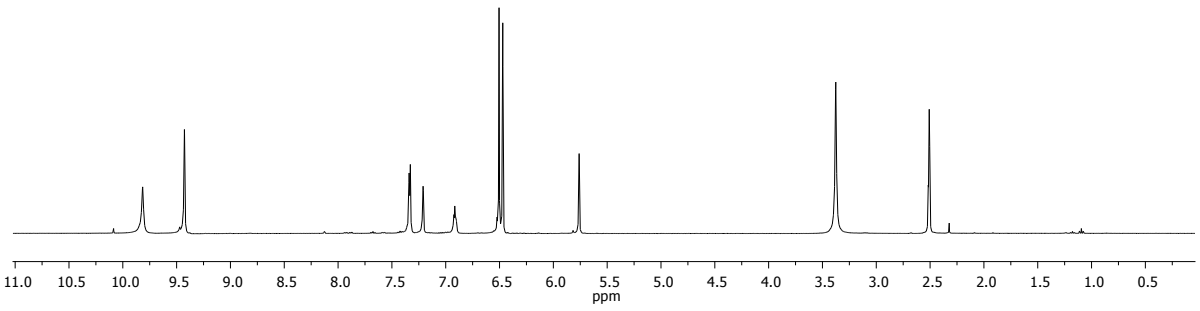
MP: 261-270 °C

$^1$H-NMR (400 MHz, DMSO) δ 9.82 (s, 4H), 9.43 (s, 4H), 7.33 (m, 4H), 7.21 (s, 2H), 7.00 – 6.84 (m, 2H), 6.50 (s, 4H), 6.47 (s, 4H), 5.76 (s, 2H).

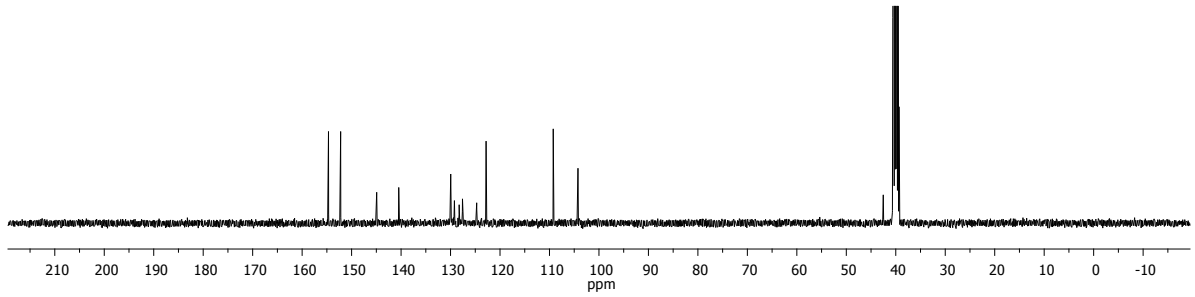
$^{13}$C-NMR (101 MHz, DMSO) δ 154.67, 152.21, 144.93, 140.47, 129.96, 129.22, 128.26, 127.59, 124.71, 122.82, 109.24, 104.24, 42.53.

IR ($\nu_{max}$, $cm^{-1}$): 3526, 3491, 1612, 1595, 1491, 1434, 1335, 1278, 1244, 1226, 1214, 1189, 1160, 1148, 1117, 1023, 905, 859, 836.

$^1$H NMR



$^{13}$C NMR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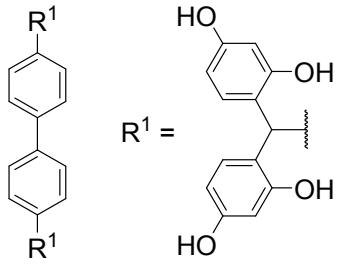
## Platform 15




Palladium over carbon (catalytic) was added to a solution of **13** (300 mg, 0.348 mmol) and triethylamine (1.33 mL, 9.57 mmol) in 20 mL of ethanol. A hydrogen atmosphere was applied and the mixture was allowed to stir at 50 °C for 5 h. The catalyst was removed by filtration and the solution was dried under reduced pressure. The product was suspended in HCl 1.2 M and extracted with ethyl acetate three times. The organic layers were combined, washed with HCl 1.2 M, brine and dried over $Na_2SO_4$. The solvent was removed under reduced pressure and the solid obtained was suspended in water, collected by Büchner filtration and washed thoroughly with water. The product was then dried in a desiccator to give an orange powder.

Yield: 68.7% (calculated from NMR to account for solvent of crystallisation)

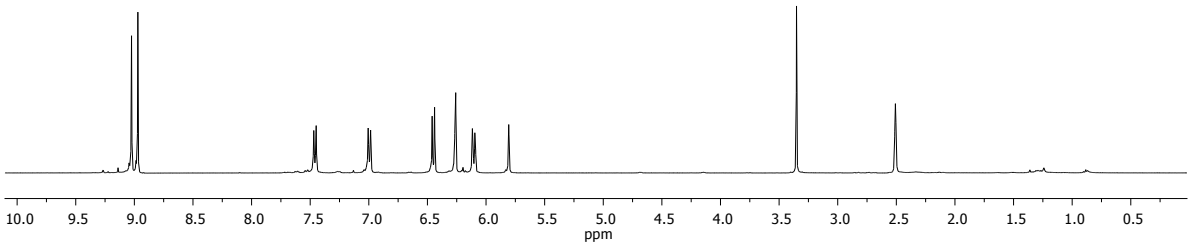
MP: 180-185 °C

$[M+H]^+$= 615.2007 (Calculated: 615.2013)

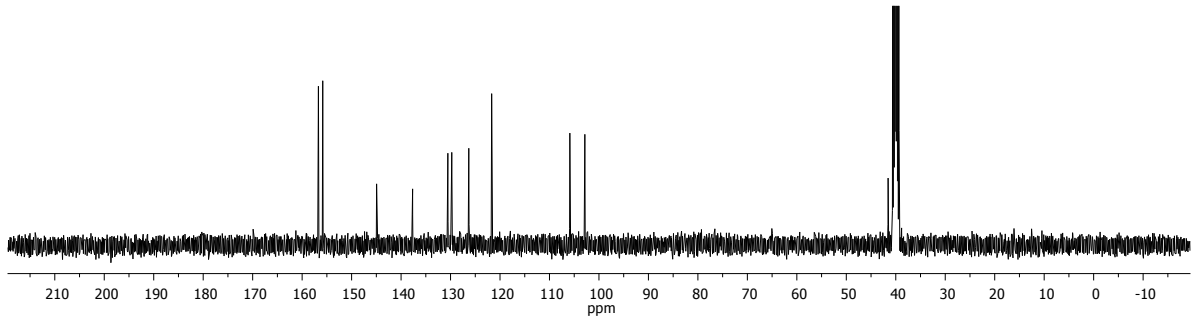
$^1$H NMR (400 MHz, DMSO) δ 9.02 (s, 4H), 8.97 (s, 4H), 7.46 (d, *J* = 8.3 Hz, 4H), 7.00 (d, *J* = 8.3 Hz, 4H), 6.45 (d, *J* = 8.3 Hz, 4H), 6.26 (d, *J* = 2.4 Hz, 4H), 6.10 (dd, *J* = 8.3, 2.4 Hz, 4H), 5.81 (s, 2H).

$^{13}$C NMR (101 MHz, DMSO) δ 156.71, 155.83, 144.95, 137.67, 130.54, 129.75, 126.31, 121.69, 105.88, 102.85, 41.55.

$^1$H NMR



$^{13}$C NMR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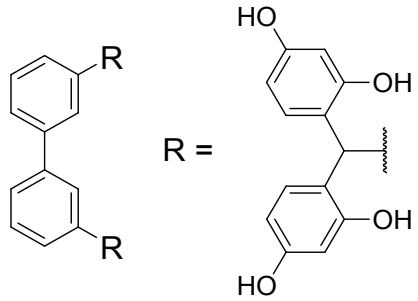
## Platform 16




Palladium over carbon (catalytic) was added to a solution of **14** (0.97 mmol) and triethylamine (3.55 mL, 25.5 mmol) in 48 mL of ethanol. A hydrogen atmosphere was applied and the mixture was allowed to stir at 50 °C for 18 h. The catalyst was removed by filtration and the solution was dried under reduced pressure. The product was suspended in HCl 1.2 M and extracted with ethyl acetate three times. The organic layers were combined, washed with HCl 1.2 M, brine and dried over $Na_2SO_4$. The solvent was removed under reduced pressure and the solid obtained was suspended in water, collected by Büchner filtration and washed thoroughly with water. The product was then dried in a desiccator to give an orange powder.

Yield: 38.8% (calculated from NMR to account for solvent of crystallisation)

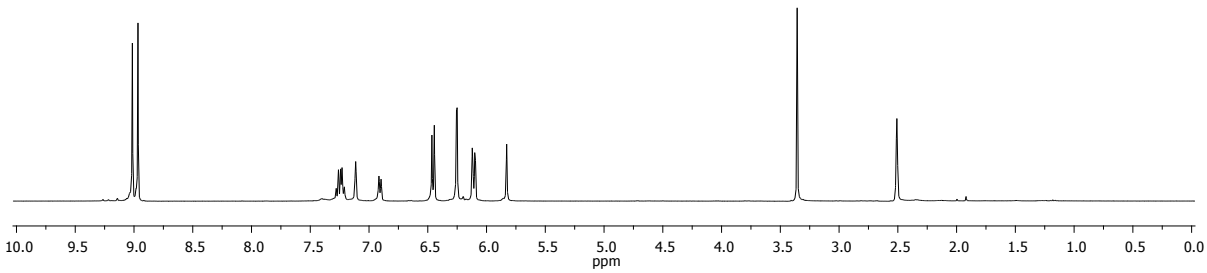
$[M-H]^-$ = 613.1862 (Calculated: 613.1868)

$^1$H-NMR (400 MHz, DMSO) δ 9.01 (s, 4H), 8.97 (s, 4H), 7.31 – 7.19 (m, 4H), 7.11 (s, 2H), 6.91 (d, *J* = 7.3 Hz, 2H), 6.45 (d, *J* = 8.3 Hz, 4H), 6.25 (d, *J* = 2.3 Hz, 4H), 6.11 (dd, *J* = 8.3, 2.3 Hz, 4H), 5.83 (s, 1H).

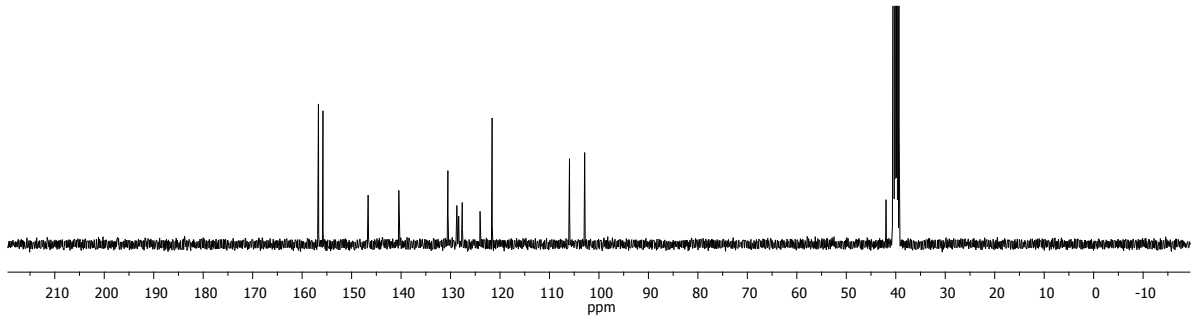
$^{13}$C-NMR (101 MHz, DMSO) δ 156.70, 155.79, 146.66, 140.46, 130.54, 128.72, 128.35, 127.63, 124.03, 121.59, 105.95, 102.89, 41.97.

IR ($\nu_{max}$, $cm^{-1}$): 3307, 1601, 1518, 1506, 1453, 1298, 1157, 1090, 973, 834.

$^1$H NMR



$^{13}$C NMR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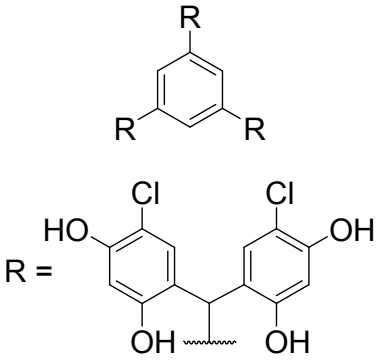
## Platform 17




0.48 mL of methanesulfonic acid was added to a pre-cooled (0 °C) mixture of benzene-1,3,5-tricarboxaldehyde (100 mg, 0.6 mmol) and 4-chlororesorcinol (624 mg, 4.32 mmol) in 6 ml of $Et_2O$/DCM (1/1, v/v). The reaction vessel was sealed and the reaction allowed to stir for 24 h. The resulting mixture was diluted with diethyl ether, poured into distilled water and allowed to stir vigorously until a suspension was obtained and all organic solvent evaporated. The product was collected by Büchner filtration, washed with abundant distilled water and dried in a desiccator to give a yellow powder.

Yield: 68.5% (calculated from NMR to account for solvent of crystallisation)

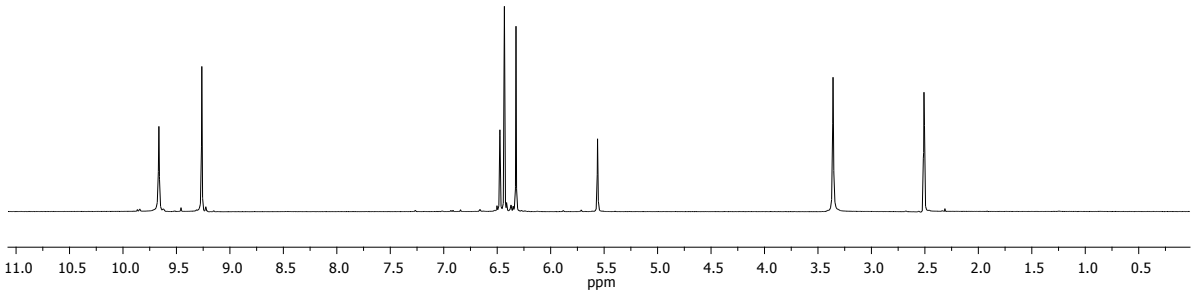
$[M-H]^-$ = 972.9738 (Calculated: 972.9773)

$^1$H-NMR (400 MHz, DMSO) δ 9.66 (s, 6H), 9.26 (s, 6H), 6.47 (s, 3H), 6.43 (s, 6H), 6.32 (s, 6H), 5.56 (s, 3H).

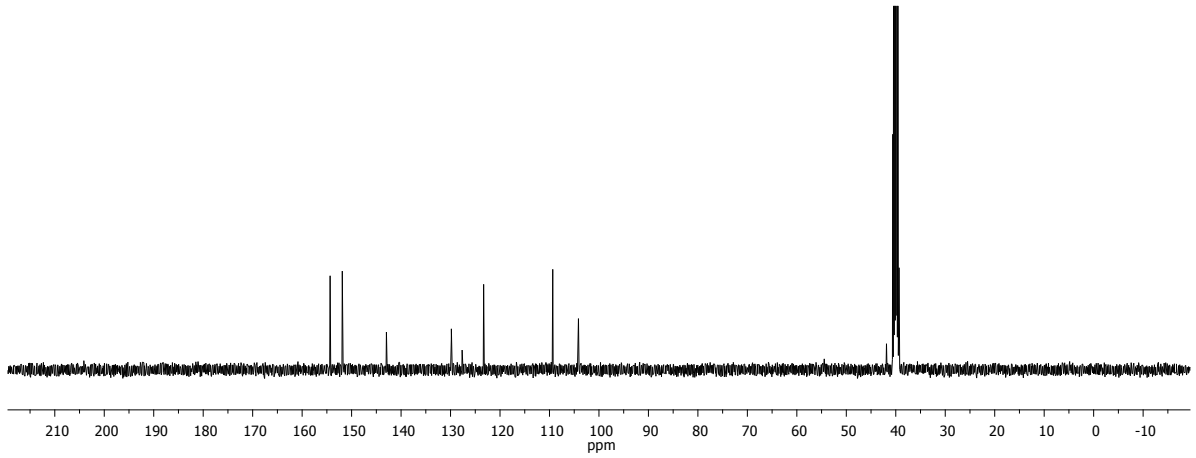
$^{13}$C-NMR (101 MHz, DMSO) δ 154.34, 151.88, 142.96, 129.83, 127.66, 123.31, 109.34, 104.14, 41.88.

IR ($\nu_{max}$, $cm^{-1}$): 3549, 3439, 3347, 3203, 1614, 1506, 1430, 1417, 1338, 1242, 1195, 1176, 1126, 1031, 973, 912, 894, 883, 838, 823.

$^1$H NMR



$^{13}$C NMR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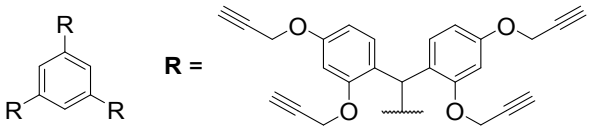
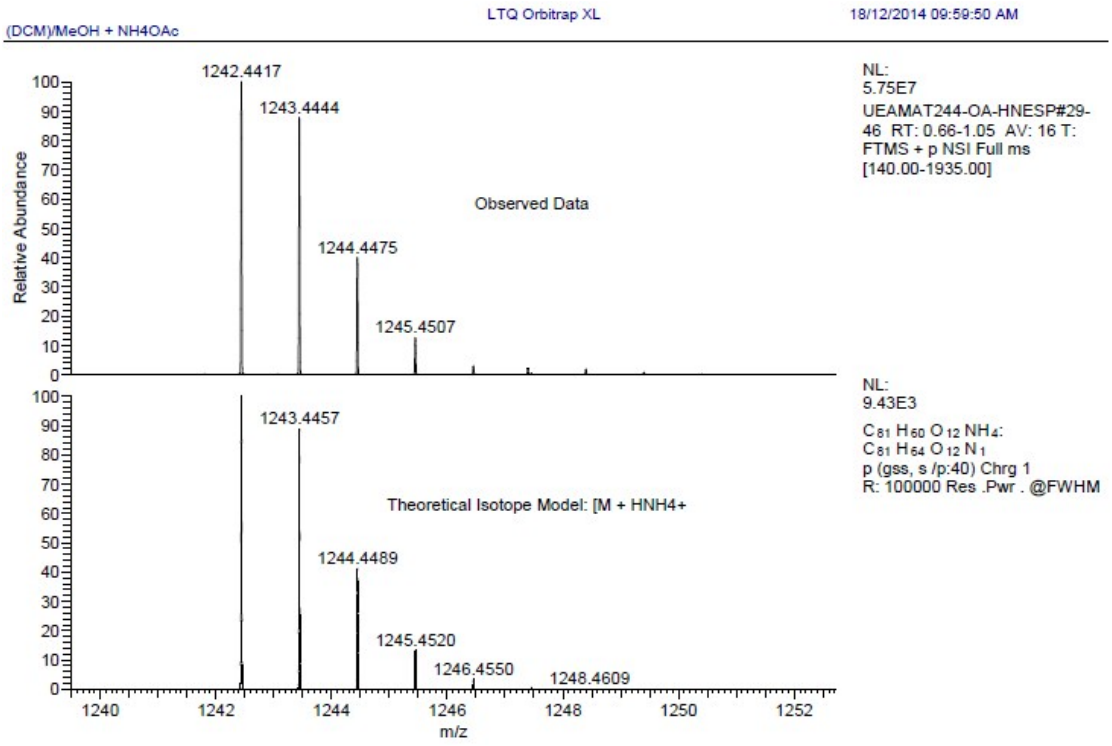
## Platform 18




Palladium over carbon (catalytic) was added to a solution of **17** (0.33 mmol) and triethylamine (1 mL, 7.17 mmol) were dissolved in 24 mL of ethanol. A hydrogen atmosphere was applied and the mixture was allowed to stir at 50 °C for 5 h. The catalyst was removed by filtration and the solution was dried under reduced pressure. The product was suspended in $HCl_{aq}$ 10% v/v and extracted with ethyl acetate three times. The organic layers were combined, washed with $HCl_{aq}$ 10% v/v, brine and dried over $Na_2SO_4$. Upon evaporation, 260 mg of crude, dehalogenated intermediate were obtained as an orange powder.

A mixture of the crude (160 mg), anhydrous potassium carbonate (948.7 mg, 6.86 mmol), and propargyl bromide 80 % in toluene (680.9 mg, 4.58 mmol) in 10 ml of DMF was allowed to stir at 70 °C for 5 h and then for 18 h at 80 °C. The solvent was evaporated under reduced pressure and the resulting solid suspended in water and extracted three times with diethyl ether. The organic layers were combined, washed with $NaHCO_3$, brine and then dried over $MgSO_4$. The crude product obtained upon evaporation of the solvent was purified via flash chromatography on silica gel (DCM as eluent) to give **18**.

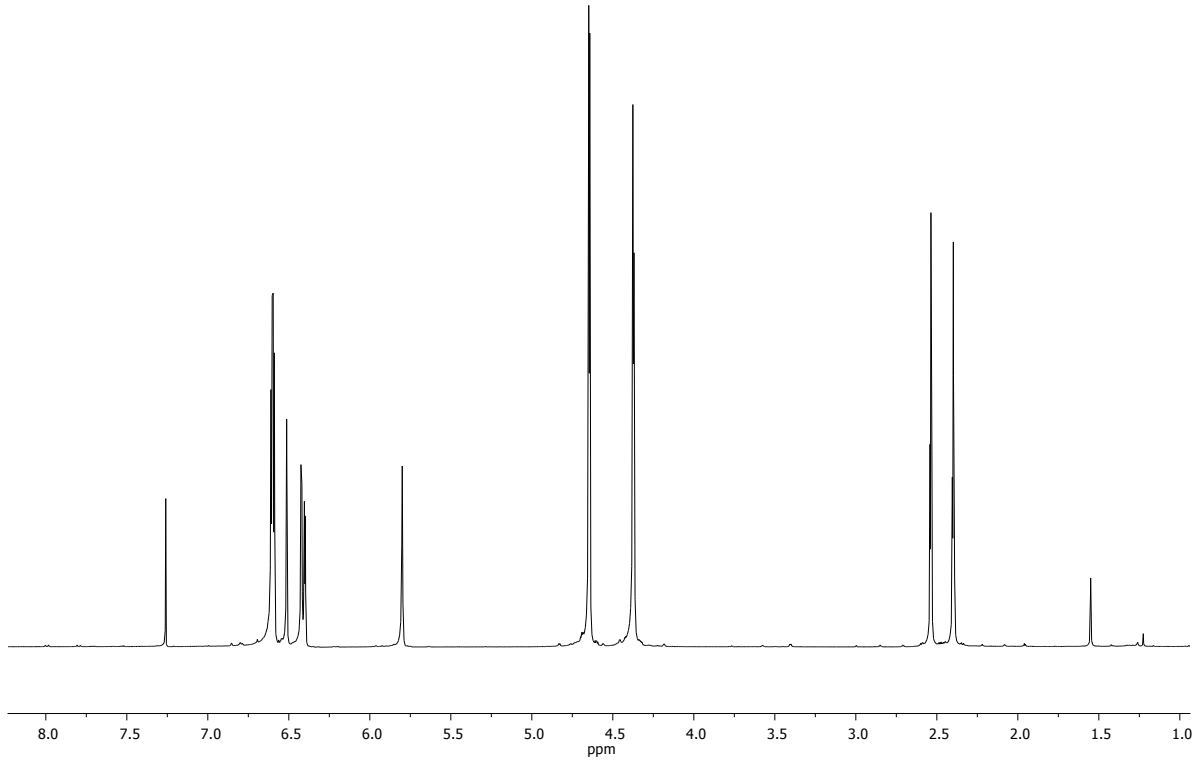
Yield: 31.8% over two steps



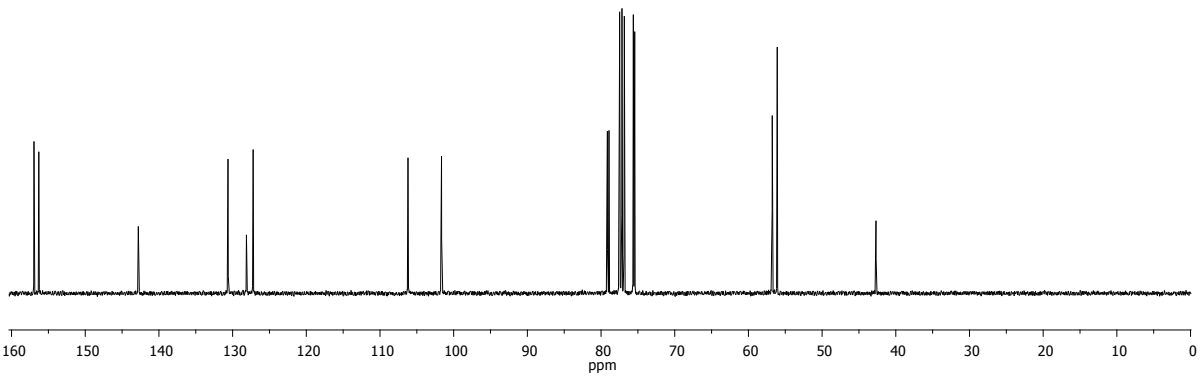

$^1$H-NMR (400 MHz, $CDCl_3$) δ 6.56 – 6.47 (m, 12H), 6.44 (s, 3H), 6.34 (dd, *J* = 8.5, 2.4 Hz, 6H), 5.72 (s, 3H), 4.57 (d, *J* = 2.4 Hz, 12H), 4.30 (d, *J* = 2.4 Hz, 12H), 2.46 (t, *J* = 2.4 Hz, 6H), 2.32 (t, *J* = 2.4 Hz, 6H).

$^{13}$C-NMR (101 MHz, $CDCl_3$) δ 156.85, 156.20, 142.69, 130.52, 128.02, 127.11, 106.09, 101.55, 79.04, 78.82, 75.52, 75.33, 56.66, 55.99, 42.58.

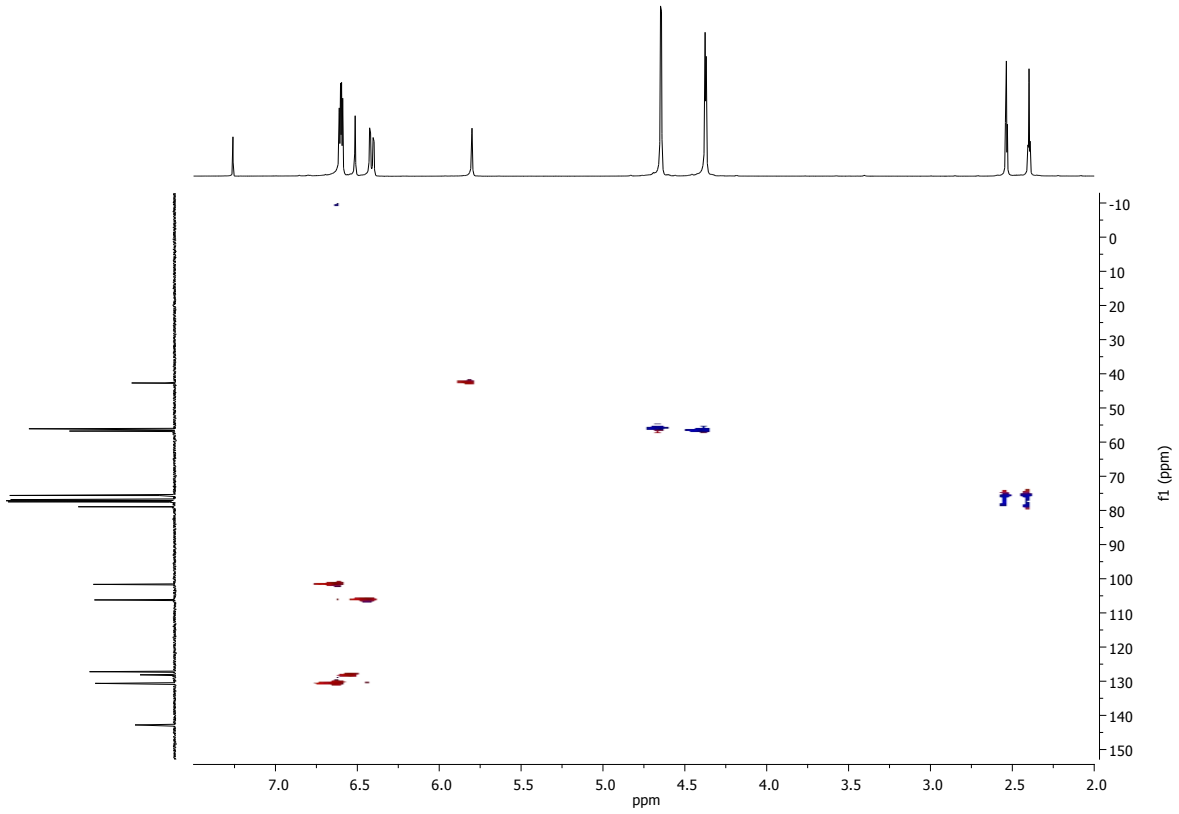
$^{1}$H NMR




$^{13}$C NMR



HSQC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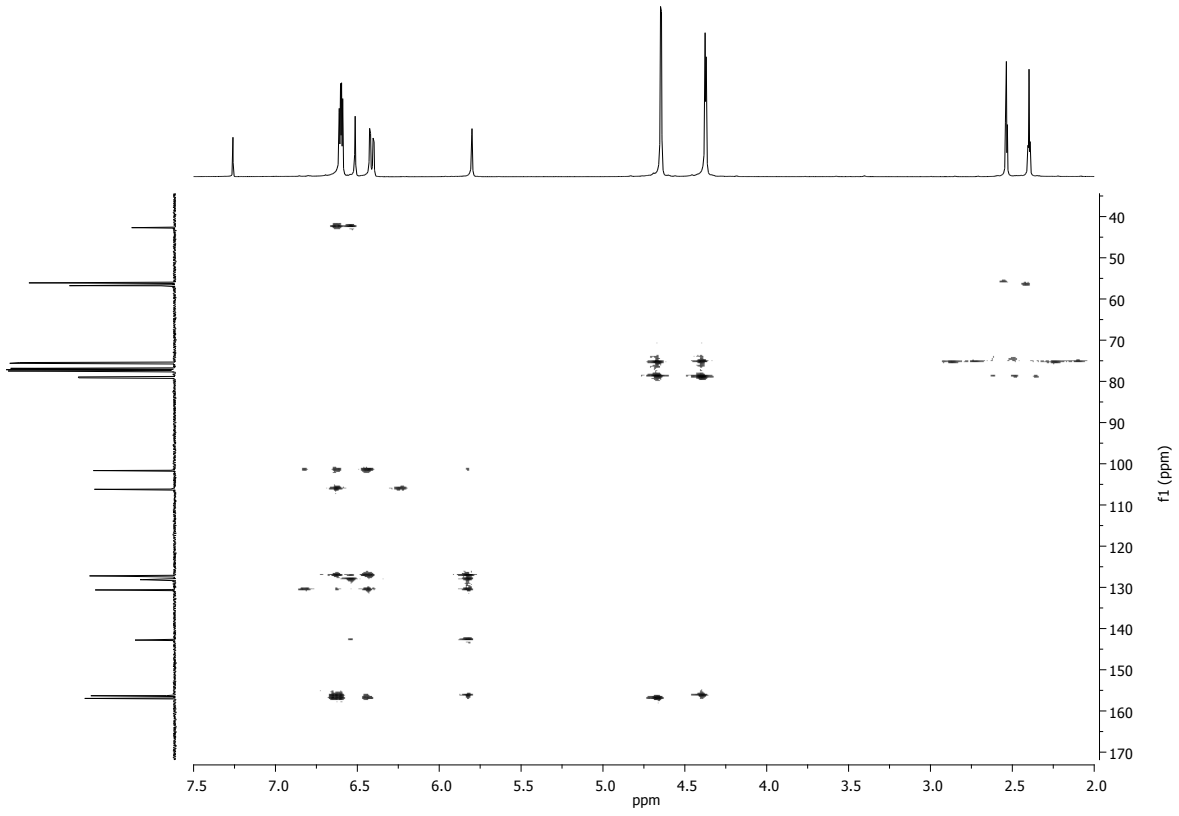
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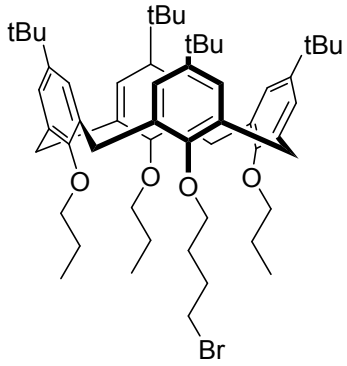
## Platform 19[7]



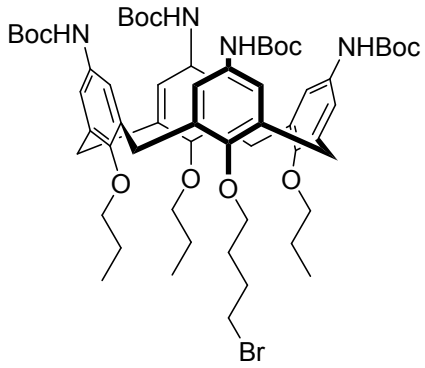

Prepared according to Regayeg.[7]

MP: 184-186 °C (180 °C) [7]

$^{1}$H-NMR (400 MHz CDCl3, ppm): δ 6.80 (s, 4H), 6.74 (m, 4H), 4.39 (t, *J* = 12.4 Hz, 4H), 3.89 (t, *J* = 7.6 Hz, 2H), 3.81 (m, 6H), 3.50 (t, *J* = 6.8, 2H), 3.12 (m, 4H), 2.16 (m, 2H), 2.01 (m, 8H), 1.06 (m, 45H).

$^{13}$C NMR (101 MHz, $CDCl_3$) δ 153.74, 153.60, 153.54, 144.49, 144.24, 144.19, 134.00, 133.93, 133.68, 133.50, 125.02, 124.93, 124.80, 76.90, 74.08, 33.85, 33.84, 33.79, 33.56, 31.50, 31.49, 31.44, 31.08, 31.07, 29.83, 29.06, 23.40, 23.28, 10.39, 10.33.

## Platform 20




To a stirring solution of **19** (2 g, 2.2 mmol) in DCM (138 mL) were added, in sequence, glacial acetic acid (13.8 mL) and concentrated nitric acid (13.8 mL). After 6 hours, the reaction was diluted with 350 mL of distilled water, the organic layer was collected, washed with distilled water (twice), with brine (once) and dried with $MgSO_4$. The solvent was removed under reduced pressure and the residue was triturated with methanol to give a white solid (1.72 g). A mixture of this crude (1.70 g) and tin chloride dihydrate (11.31 g, 50.1 mmol) in ethanol (110 mL) was allowed to stir at reflux for 48 hours. The solvent was removed under reduced pressure and the result was treated with 350 mL of a solution of 10% NaOH in water. The mixture was then extracted with DCM three times. The organic layers were collected, washed with distilled water (twice), brine (once) and dried with $MgSO_4$. The solvent was removed under reduced pressure to give 1.18 g of brown solid. Boc-anhydride (10.83 g, 49.6 mmol) was added to a stirring solution of the previous crude (1.17 g) and DIPEA (6.41 g, 49.6 mmol) in 40 mL of DCM and allowed to stir for 60 hours at room temperature. The resulting mixture was diluted with DCM and the organic layer was washed with water (twice), brine (once) and dried with $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (ethyl acetate/DCM 1/20) to give **20**.

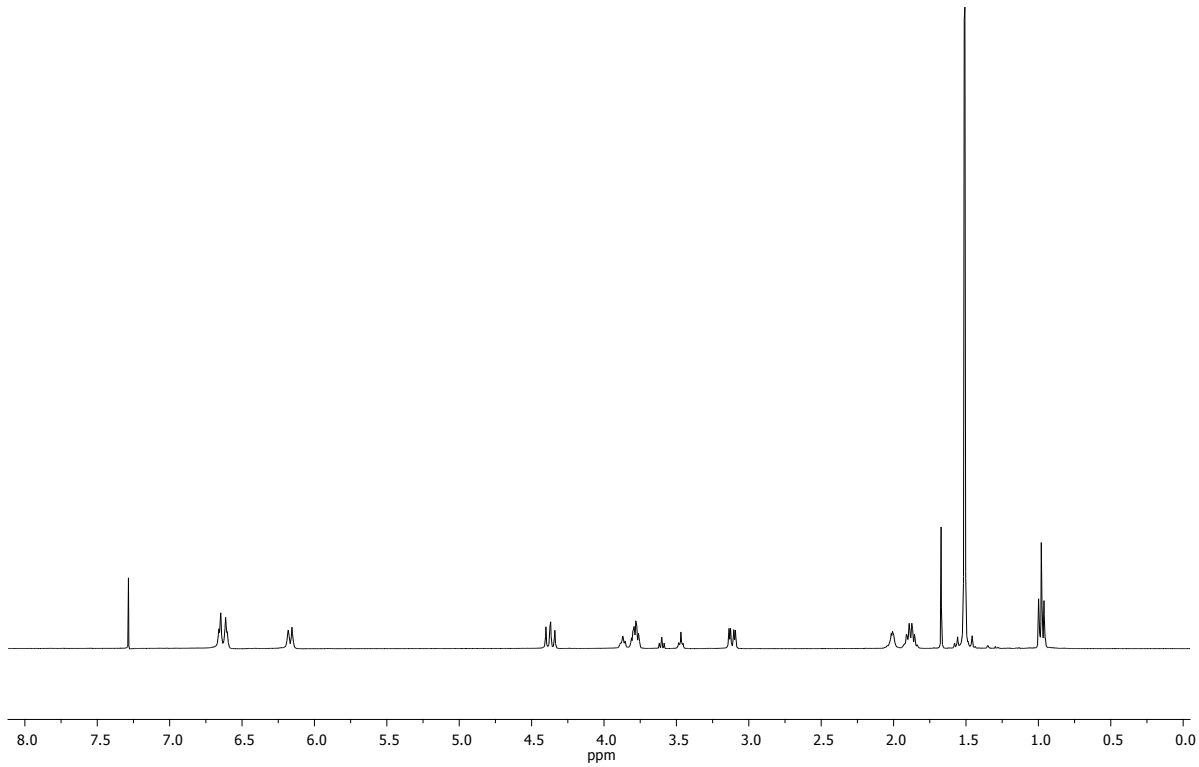
Yield: 29% over three steps, from **19**

$[M+NH_4]^+$ = 1164.5651 (Calculated: 1164.5670)

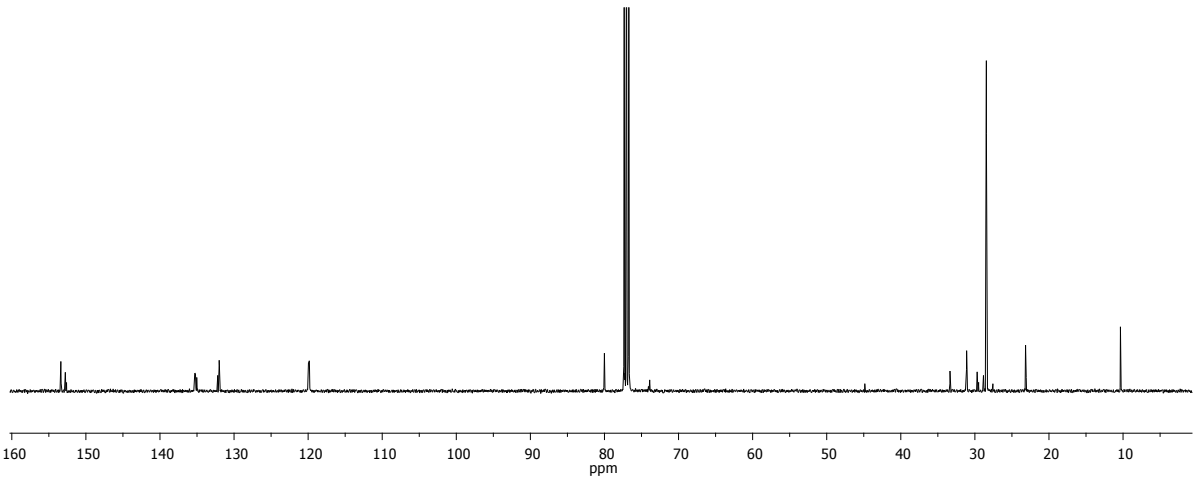
$^1$H NMR (400 MHz, $CDCl_3$) δ 6.69 – 6.56 (m, *8*H), 6.22 – 6.11 (m, 4H), 4.44 – 4.30 (m, 4H), 3.91 – 3.83 (m, 2H), 3.83 – 3.73 (m, 6H), 3.60 (t, *J* = 6.6 Hz, 1H), 3.47 (t, *J* = 6.3 Hz, 1H), 3.18 – 3.06 (m, 4H), 2.08 – 1.96 (m, 4H), 1.96 – 1.81 (m, 6H) 1.60 – 1.41 (m, 36H), 1.03 – 0.93 (m, 9H).

$^{13}$C NMR (101 MHz, $CDCl_3$) δ 153.38, 153.37, 153.35, 152.86, 152.84, 152.78, 152.65, 152.61, 135.30, 135.21, 135.03, 132.20, 132.00, 119.96, 119.91, 119.83, 80.06, 80.01, 77.23, 76.79, 73.90, 44.86, 33.36, 31.11, 29.69, 29.50, 28.84, 28.45, 27.57, 23.16, 23.09, 10.35.

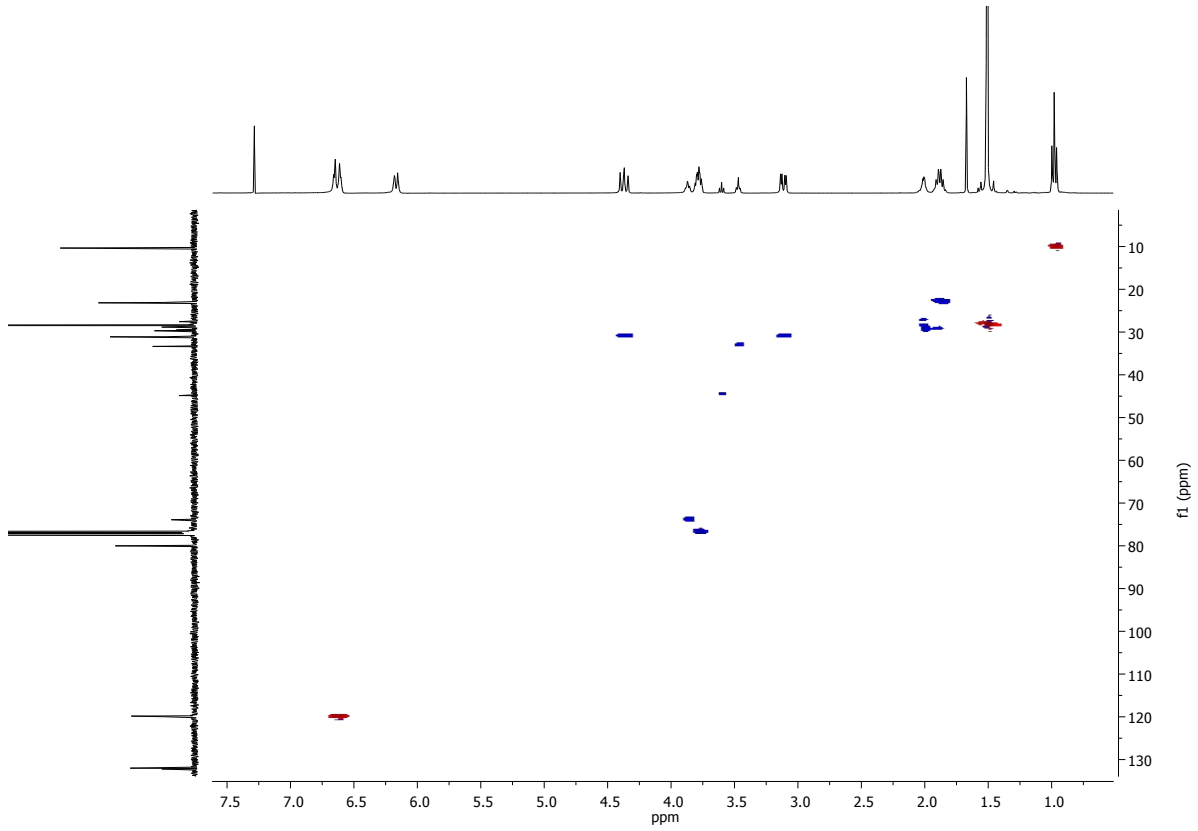
$^{1}$H NMR



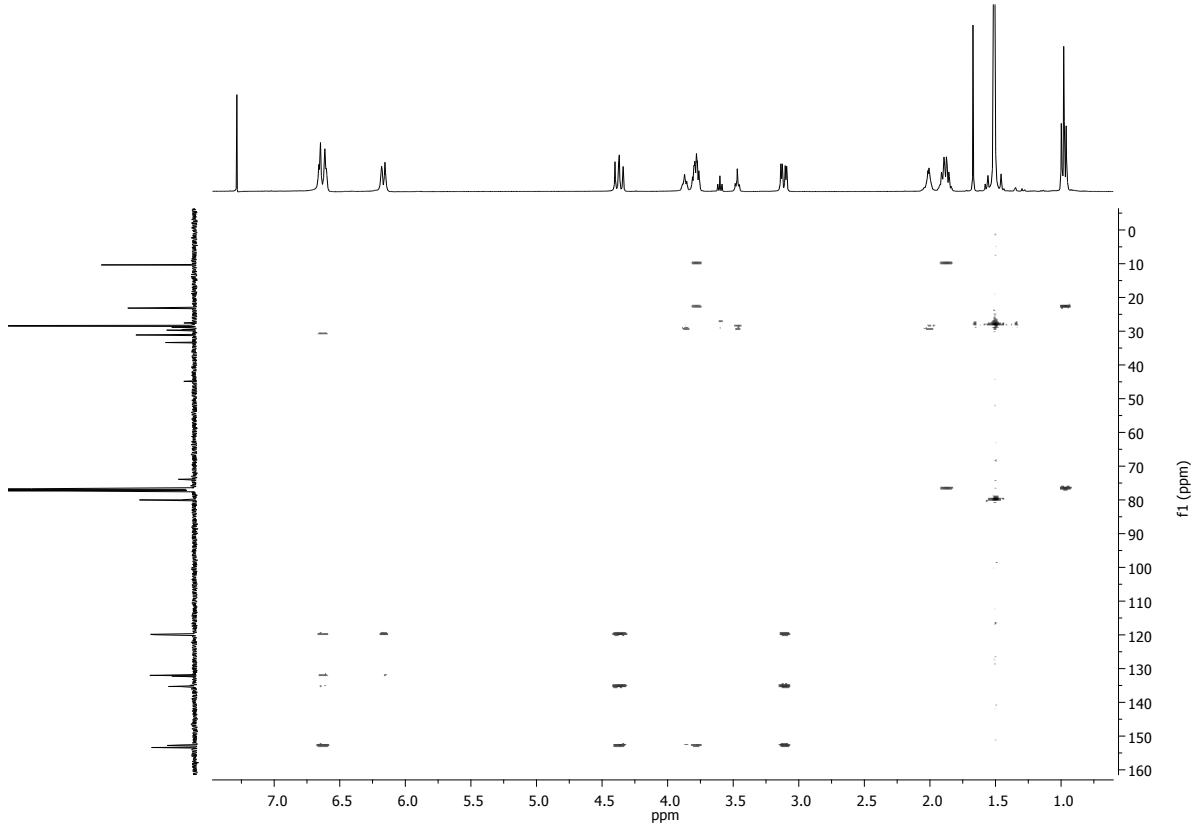

$^{13}$C NMR



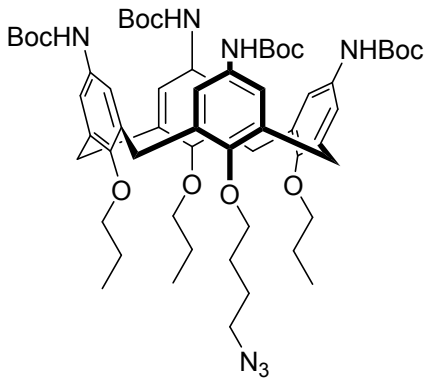
HSQC


10
20
30
40
50
60
70
80
90
100
110
120
130
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

HMBC


0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
f1 (ppm)
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

## Platform 21




Sodium azide (0.12 g, 1.85 mmol) was added to a solution of **20** (0.6 g, 0.52 mmol) in DMF (10 mL) and allowed to stir at 60 °C for 18 hours. The mixture was then diluted with water and the solid was collected by Büchner filtration. The product was washed with abundant distilled water and dried in air.

Yield: quantitative

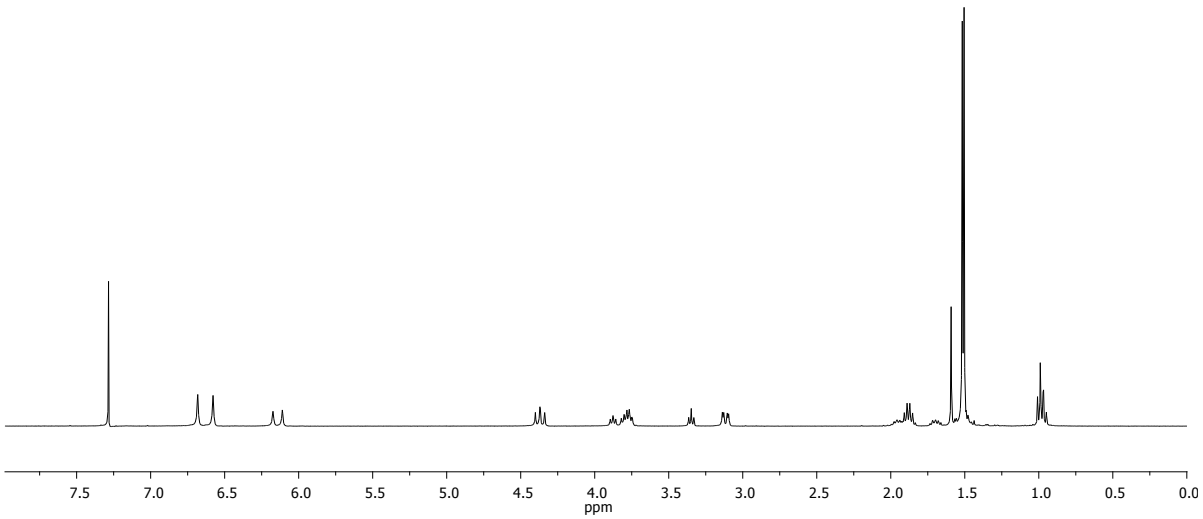
$[M+NH_4]^+$ = 1125.6575 (Calculated: 1125.6594)

$^1$H NMR (400 MHz, $CDCl_3$) δ 6.68 (s, 4H), 6.58 (s, 4H), 6.17 (s, 2H), 6.11 (s, 2H), 4.42 – 4.30 (m, 4H), 3.91 – 3.84 (m, 2H), 3.84 – 3.71 (m, 6H), 3.35 (t, *J* = 6.9 Hz, 2H), 3.17 – 3.05 (m, 4H), 2.03 – 1.79 (m, 8H), 1.77 – 1.63 (m, 2H), 1.50 (dd, *J* = 10.5, 5.0 Hz, 36H), 1.07 – 0.91 (m, 9H).

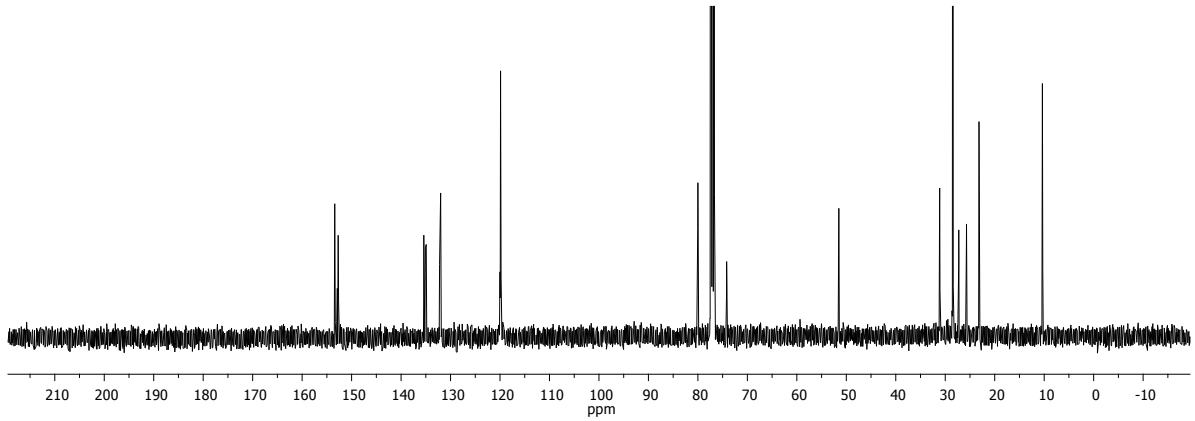
$^{13}$C NMR (101 MHz, $CDCl_3$) δ 153.41, 153.36, 153.35, 152.89, 152.71, 152.64, 135.41, 135.36, 135.08, 134.92, 132.22, 132.04, 132.00, 119.99, 119.89, 119.81, 80.07, 80.03, 80.00, 77.23, 76.80, 74.19, 51.51, 31.13, 31.10, 28.45, 27.26, 25.70, 23.17, 23.07, 10.36, 10.30.

IR ($\nu_{max}$, $cm^{-1}$): 2977, 2931, 2873, 2096, 1700, 1601, 1522, 1472, 1416, 1367, 1291, 1241, 1215, 1149, 1066, 1037, 1004, 964, 872, 770.

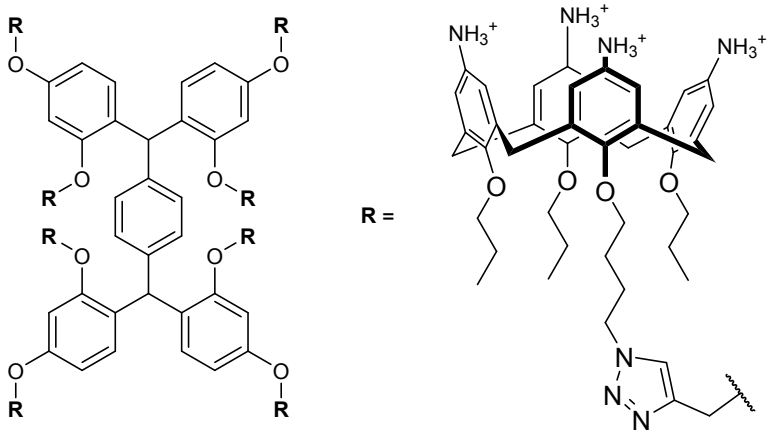
$^1$H NMR



$^{13}$C NMR


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

## Platform 22



Compound **21** (600 mg, 0.541 mmol) was added to a mixture of **10** (28.5 mg, 33.8 µmol), $CuSO_4 \cdot 5H_2O$ (25 mg, 0.1 mmol) and sodium ascorbate (250 mg, 1.26 mmol) in 7 ml of DMF under argon. The mixture was slowly heated to 80 °C. After 4 h at 80 °C, the DMF was evaporated under reduced pressure. The dark yellow product was suspended in DCM, absorbed onto silica and purified by flash chromatography (DCM/ethyl acetate 10/1 until the remaining **20** has been recovered, then DCM/MeOH 20/1 to elute the product).

Yield: 76.8%. Excess of **20** was recovered in 92.5% yield.

$[M+(NH_4)_5]^{5+}$ = 1959.8908 (Calculated: 1959.8962)

$^1$H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 4H), 7.14 (s, 4H), 6.88 (s, 4H), 6.71 – 6.48 (m, 68H), 6.44 (d, *J* = 8.4 Hz, 4H), 6.40 (s, 4H), 6.32 (s, 16H), 6.18 (s, 16H), 5.96 (s, 2H), 5.08 (s, 8H), 4.93 (s, 8H), 4.44 – 4.15 (m, 48H), 3.91 – 3.63 (m, 64H), 3.17 – 2.90 (m, 32H), 2.07 – 1.70 (m, 80H), 1.57 – 1.33 (m, 288H), 1.07 – 0.79 (m, 72H).

$^{13}$C NMR (101 MHz, $CDCl_3$) δ 158.04, 153.49, 153.44, 153.41, 153.39, 152.83, 152.79, 152.75, 152.68, 152.40, 152.30, 143.86, 135.34, 135.31, 135.28, 135.19, 135.11, 135.09, 135.00, 134.86, 132.41, 132.35, 132.08, 131.98, 122.61, 122.60, 120.12, 120.04, 120.02, 119.94, 119.88, 100.88, 80.00, 79.96, 79.89, 77.23, 73.93, 73.79, 62.03, 62.01, 50.30, 50.15, 31.10, 28.47, 28.46, 27.24, 27.16, 27.08, 23.16, 23.12, 23.09, 10.48, 10.42, 10.41, 10.32.

The previous click product (82 mg) was dissolved in DCM (2 mL) and $HCl_{(g)}$ was bubbled into the solution until a white precipitate formed. The mixture was cooled at 0 °C with an ice bath and MeOH was added dropwise to dissolve the precipitate. After one hour the source of $HCl_{(g)}$ was removed and argon was bubbled in the mixture for sixty minutes. The solvent was then removed under reduced pressure. The residue was dissolved in 16 mL of HPLC Solvent A, filtered and purified by preparative RP-HPLC to give **22**.

Yield: 78.8% (Calculated as TFA salt)

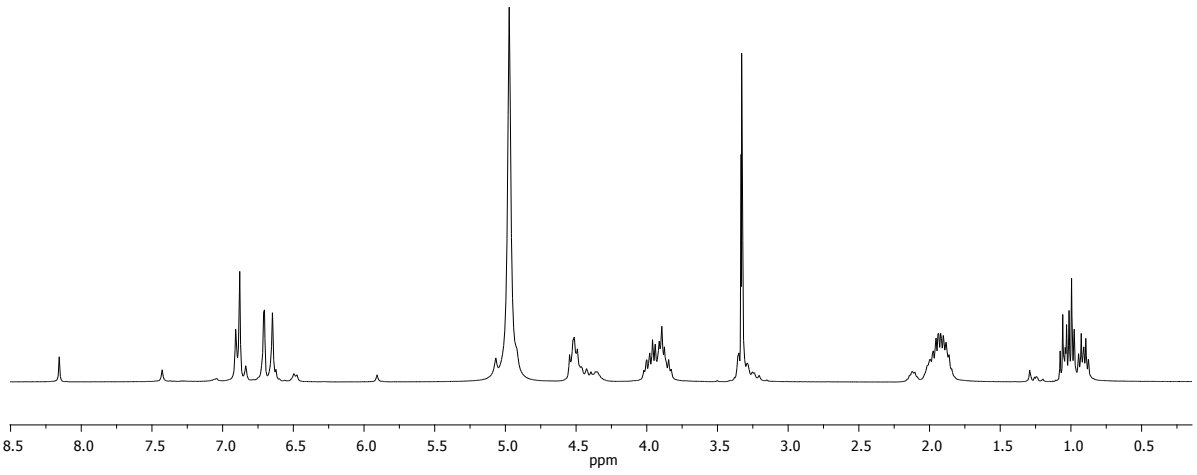
$[M+(NH_4)_5]^{5+}$ = 1302.1327 (Calculated: 1302.1328)

$^{1}$H NMR (400 MHz, MeOD) δ 8.13 (d, *J* = 20.2 Hz, 4H), 7.43 (s, 4H), 7.04 (s, 4H), 6.96 – 6.80 (m, *J* = 14.2 Hz, 34H), 6.79 – 6.57 (m, 38H), 6.49 (d, *J* = 8.5 Hz, 4H), 5.91 (s, 2H), 4.62 – 4.28 (m, 48H), 4.10 – 3.74 (m, 64H), 2.20 – 2.07 (m, 8H), 2.07 – 1.79 (m, 72H), 1.14 – 0.81 (m, 72H).

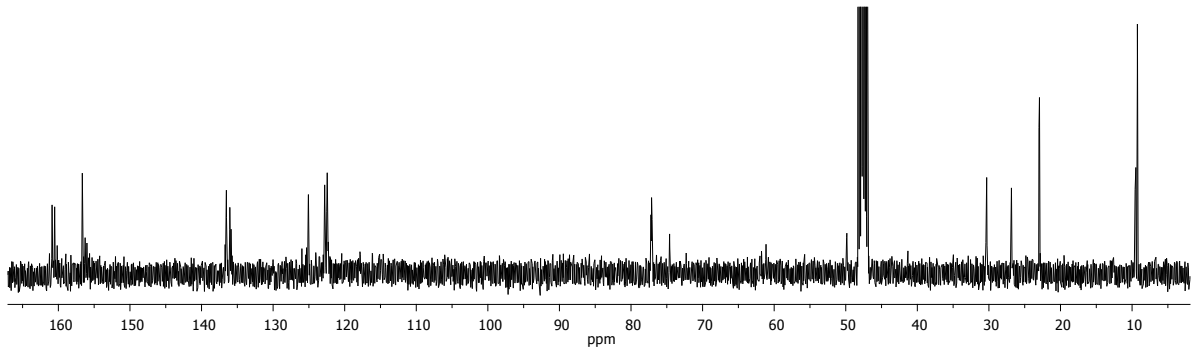
$^{13}$C NMR (101 MHz, MeOD) δ 161.24, 160.88, 160.52, 160.16, 156.65, 156.26, 156.10, 156.01, 136.70, 136.61, 136.53, 136.05, 135.99, 135.88, 135.80, 125.07, 125.04, 122.86, 122.84, 122.80, 122.51, 122.44, 122.35, 77.22, 77.13, 77.07, 74.66, 74.61, 74.59, 61.14, 49.85, 30.36, 30.31, 26.85, 23.00, 22.94, 9.58, 9.47, 9.26.

IR ($v_{max}$, $cm^{-1}$): 2966, 2931, 2873, 2625, 1667, 1467, 1184, 1064, 1036, 999, 959, 839, 798, 721, 703.

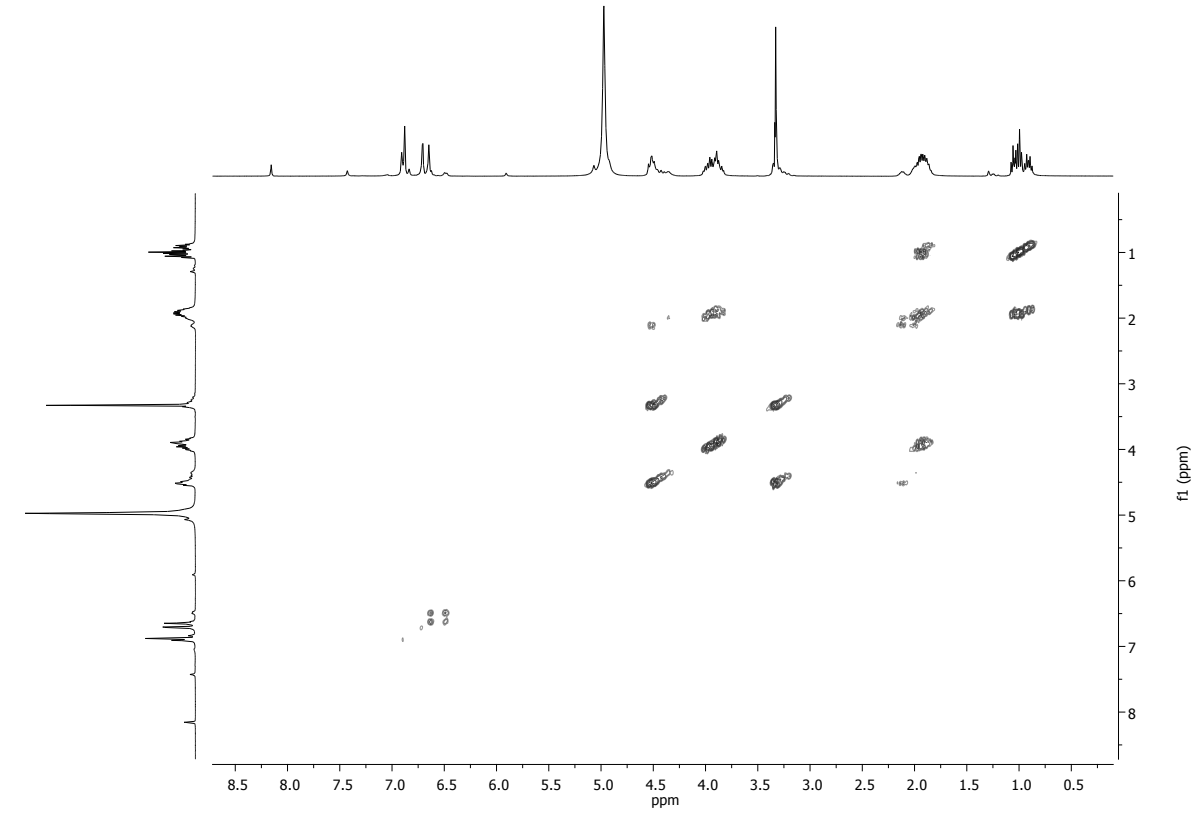
$^{1}$H NMR




$^{13}$C NMR



COSY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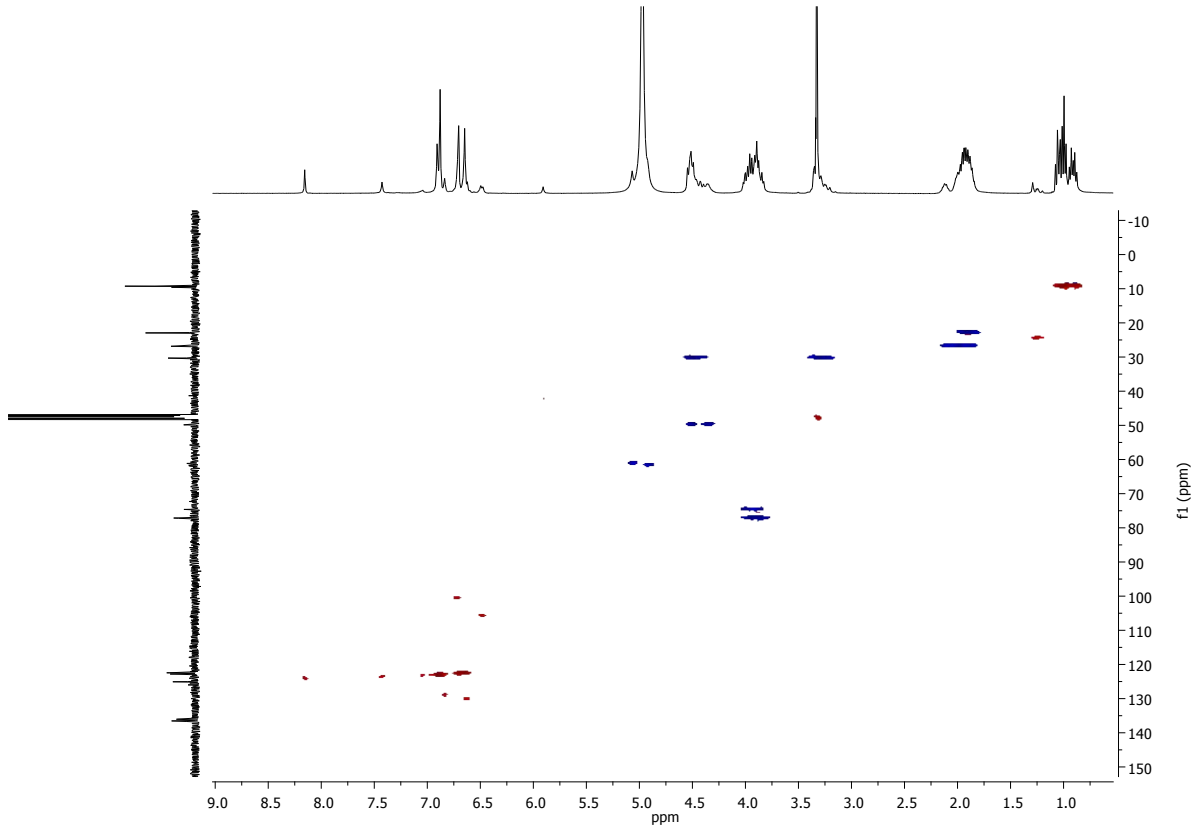
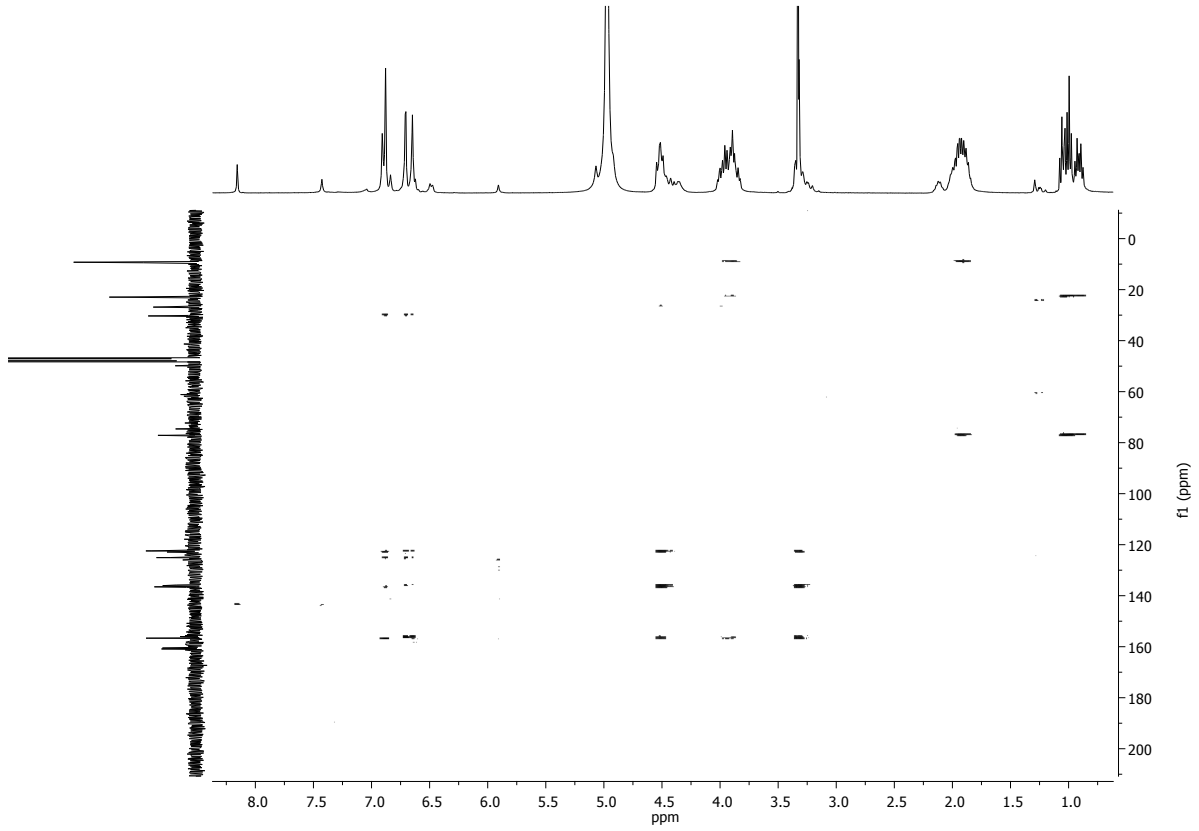
ppm
1 2 3 4 5 6 7 8
f1 (ppm)

HSQC


9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm
-10 0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150
f1 (ppm)

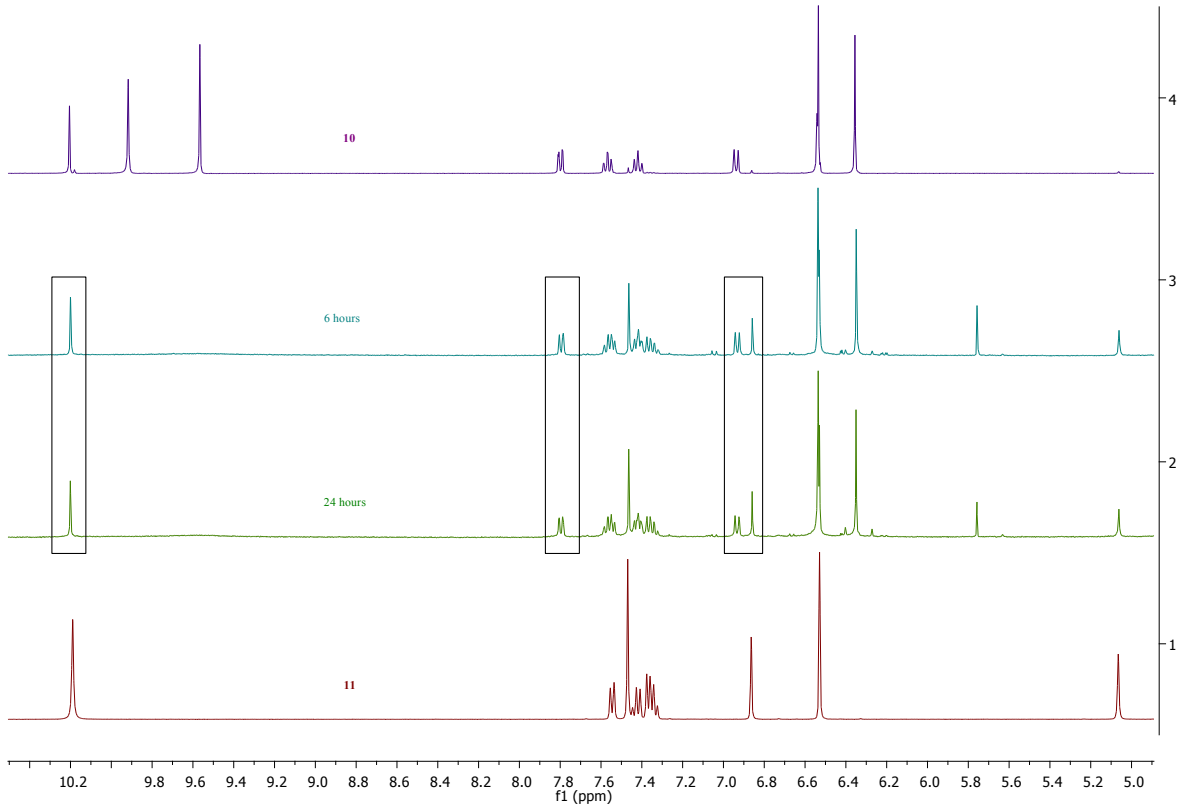
HMBC


0
20
40
60
80
100
120
140
160
180
200
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

## Formation of aldehyde 8 and acetal 9.

The reaction was set up as described for the synthesis of **8** and **9**; samples were taken after 6 and 24 hours and immediately dried with compressed air.

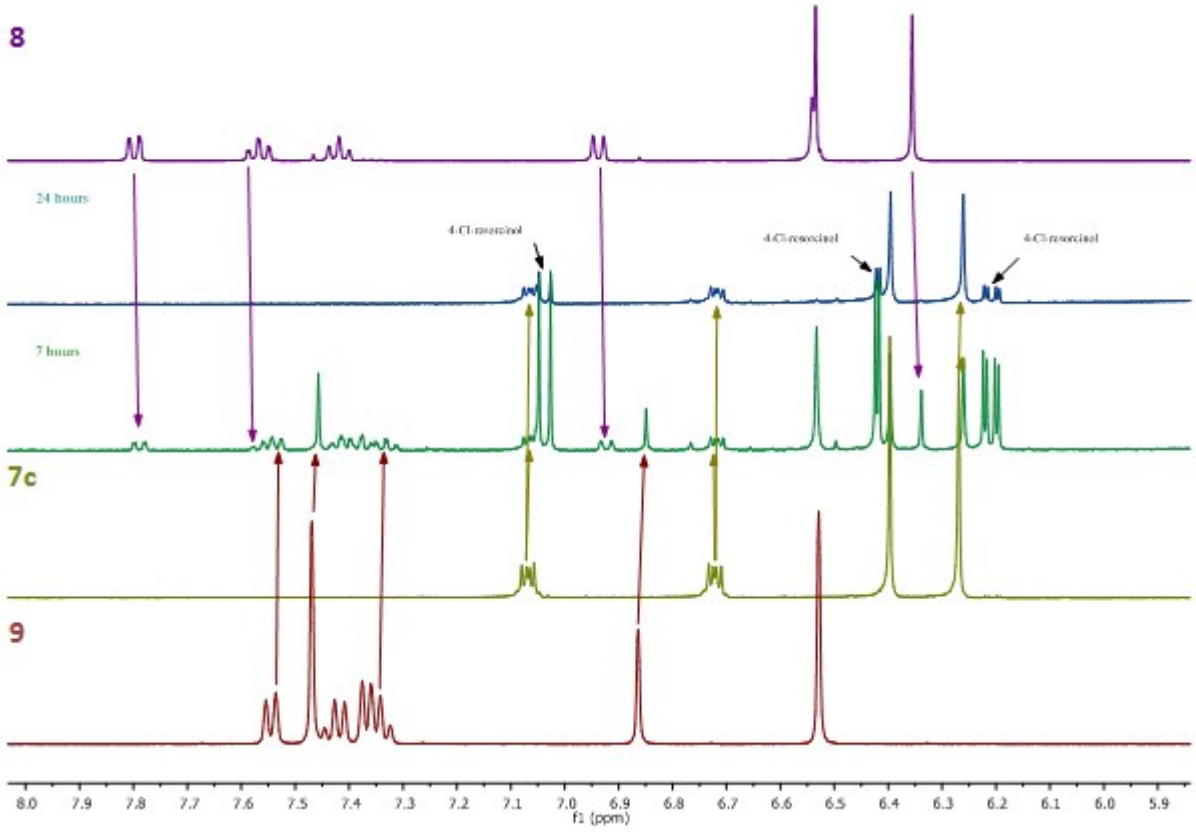
**Figure 9**. Results after 6 and 24 hours and references for **8** and **9**. All spectra were recorded in DMSO-$d_6$ at 400 MHz. The integrals of the peaks indicated with squares were used to calculate the ratio between **8** and **9**.



## Conversion of 9 to 7c

0.08 mL of *methanesulfonic acid* was added to a pre-cooled (0°C) mixture of **9** (11 mg, 0.03 mmol) and *4-chlororesorcinol* (12.3 mg, 0.08 mmol) in 1 ml of $Et_2O$/DCM (1/1, v/v). The reaction vessel was sealed. The mixture was stirred and samples were taken after 7 and 24 hours and immediately dried with compressed air

**Figure 10.** Results and references with characteristic peaks for **8**, **9**, **7c** and *4-chlororesorcinol.* All spectra were recorded in DMSO-$d_6$ at 400 MHz.



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