Chemoenzymatic synthesis of chiral 4,4'-bipyridyls and their metal-organic frameworks

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Supplementary information

1. Synthesis and characterisation

(i) Biotransformation of 4-chloroquinoline **1** to yield (5*R*,6*S*)-4-Chloro-5,6 dihydroquinoline-5,6-diol **2**

Biotransformation of 4-chloroquinoline **1** (19 g, 0.12 mol) by *S. yanoikuyae* B8/36, and work up was carried out using a similar method to that reported earlier using 2-chloroquinoline.[7] Purification of the resulting crude bioproduct by column chromatography (50% EtOAc/hexane) followed by multi-elution PLC (EtOAc), yielded a single metabolite, *cis*-(5*R*,6*S*)-4-chloro-5,6-dihydroquinoline-5,6-diol **2** (7.6 g, 33%). Colourless crystalline solid, mp 138-139 ºC (from EtOAc/hexane); $[\alpha]_D$ +172 (*c* 0.58, MeOH); HRMS (EI) Found: M^+ 197.0264, $C_9H_8ClNO_2$ requires 197.0244; ^{1}H NMR δ_H (300 MHz, CD_3OD, D_2O exchange) 4.47 (1 H, m, H-6), 4.92 (1 H, d, $J_{5,6}$ 5.0, H-5), 6.17 (1 H, m, H-7), 6.42 (1 H, dd, $J_{8,7}$ 9.9, $J_{8,6}$ 2.8, H-8), 7.24 (1 H, d, $J_{3,2}$ 6.5, H-3); 8.22 (1 H, d, $J_{2,3}$ 6.5, H-2); ^{13}C NMR δ_C (125 MHz, CD_3OD) 69.96, 73.63, 127.67, 130.47, 133.62, 143.42, 149.36, 153.56, 157.58; MS *m/z* (EI) 197 (M^+, ^{35}Cl, 17%), 179 (100), 168 (80), 163 (29), 151 (41),140 (38), 128 (22), 116 (44), 104 (12), 89 (30), 63 (21).

(ii)-(5*R*,6*S*)-4-Chloro-5,6,7,8-tetrahydroquinoline-5,6-diol **4**

A solution of the *cis*-dihydrodiol **2** (2 g, 10 mmol) in methanol (30 cm^3) was stirred for 4 days in the presence of PtO_2 (0.23 g, 8 mol %) under an atmosphere of hydrogen at ambient temperature. The catalyst was filtered off and the filtrate concentrated to give the crude hydrogenated product. Purification by column chromatography (EtOAc) afforded the hydrogenated product **4** as a white crystalline solid (1.8 g, 89%); mp 183-184 ºC (from MeOH/EtOAc); $[\alpha]_D$ -81 (*c* 1.02, MeOH); Anal. Found: C, 54.2; H, 4.75; N, 7.0;

$C_9H_{10}ClNO_2$ requires C, 54.15; H, 5.05; N, 7.0; ^{1}H NMR δ_H (300 MHz, CD_3OD, D_2O exchange) 1.82 (1 H, m, H-7), 2.05 (1 H, m, H-7'), 2.78-2.93 (2 H, m, H-8, H-8'), 3.73 (1 H, m, H-6), 4.86 (1 H, d, $J_{5,6}$ 4.8, H-5), 7.27 (1 H, d, $J_{3,2}$ 5.4, H-3), 8.22 (1 H, d, $J_{2,3}$ 5.4, H-2); ^{13}C NMR δ_C (125 MHz, CD_3OD) 25.85, 32.87, 67.56, 70.95, 124.63, 132.61, 148.64, 150.54, 160.36; MS *m/z* (EI) 199 (M^+, ^{35}Cl, 57%), 170 (51), 152 (75), 127 (68), 117 (28), 92 (8).

(iii)-(5*R*,6*S*)-4-Chloro-5,6,7,8-tetrahydro-5,6-dimethoxyquinoline **5**

Sodium hydride (60 % dispersion in mineral oil, 0.6 g, 15 mmol) was added to a solution of tetrahydrodiol **4** (1.5 g, 7.5 mmol) in dry THF (20 cm^3) at 0 °C. Methyl iodide (1 cm^3, 15 mmol) was added to the mixture after 10 min and it was stirred for a further 15 min at 0 °C and then overnight.at room temperature. The reaction mixture was cooled in an ice bath and quenched with THF:H_2O (2 cm^3). The solvents were removed *in vacuo* and the crude product purified by column chromatography (75% EtOAc/hexane) to give dimethoxy derivative **5** as a pale yellow oil (1.2 g, 72%); $[\alpha]_D$ -107 (*c* 1.09, $CHCl_3$); HRMS (EI) Found: M^+, 227.0726, $C_{11}H_{14}ClNO_2$ requires 227.0713; ^{1}H NMR δ_H (300 MHz, $CDCl_3$) 2.08 (1 H, m, H-7), 2.25 (1 H, m, H-7'), 2.92 (1 H, m, H-8), 3.21 (1 H, m, H-8'), 3.48 (1 H, m, H-6), 3.52 (3 H, s, OCH_3), 3.68 (3 H, s, OCH_3), 4.84 (1 H, d, $J_{5,6}$ 4.2, H-5), 7.20 (1 H, d, $J_{3,2}$ 5.3, H-3), 8.35 (1 H, d, $J_{2,3}$ 5.3, H-2); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 21.84, 32.08, 57.22, 60.52, 73.35, 80.80, 122.77, 129.36, 146.35, 150.00, 159.53; MS *m/z* (EI) 227 (M^+, ^{35}Cl, 10%), 212 (100), 180 (12), 164 (10), 152 (23).

(iv) (3a*S*,9b*R*)-9-Chloro-2,2-dimethyl-3a,4,5,9b-tetrahydro-[1,3] dioxolo[4,5*f*]quinoline **7**

The *cis*-tetrahydrodiol **4** (1.0g, 5 mmol) was dissolved in a mixture of acetone (5 cm^3) and 2,2'-dimethoxypropane (5 cm^3). To this solution, a catalytic amount of trifluoroacetic acid was added at 0 ºC. The reaction mixture was left stirring at ice temperature for 20 min and then at room temperature until the starting material had reacted completely (TLC analysis). The solvent was removed under reduced pressure, after adding a few drops of triethylamine, the residue extracted with ethyl acetate (2 x 50 cm^3) and the combined

extract washed with water (2 x 25 cm^3). The extract was dried over Na_2SO_4, concentrated, and the residue purified by flash chromatography (25% EtOAc/hexane), to yield the acetonide derivative **7** as a pale yellow oil (1.03 g, 86%); $[\alpha]_D$ +95 (*c* 0.61, $CHCl_3$); HRMS (EI) Found: M^+-CH_3, 224.0478, $C_{11}H_{11}ClNO_2$ requires 224.0478; ^1H NMR δ_H (300 MHz, $CDCl_3$) 1.34 (3 H, s, CH_3), 1.48 (1 H, s, CH_3), 1.84 (1 H, m, H-4), 2.27 (1 H, m, H-4'), 2.80 (1 H, ddd, $J_{5,4}$ =$J_{5,4'}$ 2.8, $J_{5,5'}$ 9.8, H-5), 3.13 (1 H, ddd, $J_{5',4}$ 2.6, $J_{5',4'}$ 7.2, $J_{5',5}$ 9.8, H-5'), 4.64 (1 H, m, H-3a), 5.45 (1 H, d, $J_{9b,3a}$ 3.8, H-9b), 7.23 (1 H, d, $J_{8,7}$ 3.2, H-8), 8.34 (1 H, d, $J_{7,8}$ 3.2, H-7) ; ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 24.78, 26.66, 26.90, 27.24, 71.60, 72.48, 108.22, 122.82, 127.76, 145.84, 148.66, 160.27; MS *m/z* (EI) 224 (M^+-CH_3, 68%), 213 (3), 182 (100), 164 (18), 152 (21).

(iv) (5*R*,6*S*)-5,6,7,8-Tetrahydro-5,6-dimethoxy-4(pyridin-4-yl)quinoline **6** and (3a*S*,9b*R*)-2,2-dimethyl-3a,4,5,9b-tetrahydro-9-(pyridin-4-yl)-[1,3]-dioxolo[4,5*f*]quinoline **8**

General procedure:- A 25 cm^3 Schlenk flask with a small stirring bar was charged with 4-pyridine boronic acid (1.10 mmol), tris(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$] (initially 9.2 mg, 0.010 mmol and subsquently the same amount three times every 6 h), and tricyclohexyl phosphine (PCy_3) (6.7 mg, 0.024 mmol). The flask was repeatedly evacuated and refilled with nitrogen and finally sealed under nitrogen atmosphere. A mixture of dioxane (2.67 cm^3), 4-chloroquinoline derivatives **5** or **7** (1 mmol), and aqueous K_3PO_4 (1.27 M, 1.33 cm^3, 1.70 mmol) was introduced into the flask using a syringe needle. The reaction mixture was heated, with vigorous stirring in an oil bath, at 100 ºC for 18 h. It was then filtered through a pad of silica gel (using EtOAc as eluant). The organic solvents were removed, from the filtrate, under reduced pressure and the aqueous concentrate extracted with EtOAc (3 x 5 cm^3). The extract was dried over anhydrous $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified either by column chromatography (silica gel) or by PLC (EtOAc).

(5*R*,6*S*)-5,6,7,8-Tetrahydro-5,6-dimethoxy-4(pyridin-4-yl)quinoline **6**

Following the general cross-coupling procedure, compound **5** (1 g, 4.4 mmol), 4,4'-bipyridine **6** was obtained, after PLC purification (EtOAc), as a pale yellow crystalline solid (0.67 g, 57%); mp 74-76 ºC (from EtOAc/hexane); $[\alpha]_D$ -99 (*c* 1.15, $CHCl_3$); Anal. Found: C, 70.6; H, 6.5; N, 10.0; $C_{16}H_{18}N_2O_2$ requires C, 71.1; H, 6.7; N, 10.4; HRMS (EI) Found: M^+, 270.1364, $C_{16}H_{18}N_2O_2$ requires 270.1368; ^{1}H NMR δ_H (500 MHz, $CDCl_3$) 2.12 (1 H, m, H-7), 2.30 (1 H, m, H-7'), 3.03 (1 H, m, H-8), 3.19 (3 H, s, OCH_3), 3.31 (1 H, m, H-8'), 3.43 (3 H, s, OCH_3), 3.59 (1 H, ddd, $J_{6,7}$ 2.9, $J_{6,7'}$ 6.7, $J_{6,5}$ 18.3, H-6), 4.35 (1 H, m, H-5), 7.00 (1 H, d, $J_{3,2}$ 8.1, H-3), 7.28-7.32 (2 H, m, Ar*H*), 8.54 (1 H, d, $J_{2,3}$ 8.1, H-2), 8.72-8.74 (2 H, m, Ar*H*); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 21.69, 31.77, 57.06, 59.33, 74.07, 80.70, 122.10, 123.95, 128.46, 147.30, 149.19, 149.52, 150.19, 157.91; MS *m/z* (EI) 270 (M^+,18%), 255 (100), 223 (11), 195 (49), 168 (8), 115 (7), 71 (5), 61 (12).

(3a*S*,9b*R*)-2,2-Dimethyl-3a,4,5,9b-tetrahydro-9-(pyridin-4-yl)-[1,3]-dioxolo[4,5*f*]quinoline **8**

4-Chloroquinoline derivative **8** (1 g, 4.18 mmol) was obtained using the same cross-coupling procedure. Purification by flash chromatography (50% EtOAc/hexane) gave the 4,4'-bipyridine **8** as a white solid (0.66 g, 56%); mp 123-125 ºC (from EtOAc/hexane); $[\alpha]_D$ +74 (*c* 1.03, $CHCl_3$); Anal. Found: C, 71.8; H, 6.4; N, 10.0; $C_{17}H_{18}N_2O_2$ requires C, 72.3; H, 6.4; N, 9.9; ^{1}H NMR δ_H (300 MHz, $CDCl_3$) 1.36 (3 H, s, CH_3), 1.48 (1 H, s, CH_3), 1.71 (1 H, m, H-4), 2.23 (1 H, m, H-4'), 2.88 (1 H, m, H-5), 3.15 (1 H, ddd, $J_{5',4}$ 2.1, $J_{5',4'}$ 7.5, $J_{5',5}$ 9.6, H-5'), 4.53 (1 H, m, H-3a), 5.02 (1 H, d, $J_{9b,3a}$ 4.2, H-9b), 7.11 (1 H, d, $J_{8,7}$ 3.4, H-8), 7.50 (2 H, m, Ar*H*), 8.54 (1 H, d, $J_{7,8}$ 3.4, H-7), 8.72 (2 H, m, Ar*H*); ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 23.96, 26.16, 26.35, 26.99, 28.13, 29.30, 71.58, 73.15, 107.59, 122.39, 124.04, 126.01, 145.74, 148.41, 148.69, 149.72, 161.11; MS *m/z* (EI) 267 (M^+-CH_3, 52%), 225 (100), 207 (16), 195 (19).

(v) (5*R*,6*S*)-5,6,7,8-Tetrahydro-4(pyridin-4-yl)quinoline-5,6-diol **9**

A solution of acetonide **8** (0.5 g, 1.77 mmol) in a mixture of THF:H_2O:TFA (8:2:1) (5 cm^3) was heated at 50 °C for 3 h. When the starting material had reacted completely, the mixture was treated with excess of NH_4OH solution and the solvents were removed under reduce pressure. The crude product obtained was crystallised from MeOH/$CHCl_3$ to give a pure sample of 4,4'-bipyridine **9**, a white solid (0.35 g, 82%); mp 258 ºC (d) (from EtOAc/MeOH); $[\alpha]_D$ -52 (*c* 0.5, MeOH); Anal. Found: C, 68.9; H, 5.9; N, 11.4; $C_{14}H_{14}N_2O_2$ requires C, 69.4; H, 5.8; N, 11.6; ^{1}H NMR δ_H (300 MHz, $CDCl_3$) 1.83 (1 H, m, H-7), 2.16 (1 H, m, H-7'), 2.92 (1 H, m, H-8), 3.15 (1 H, ddd, $J_{8',7}$ 2.0, $J_{8',7'}$ 6.5, $J_{8',8}$ 18.3, H-8'), 3.21 (2 H, m, 2 x OH), 3.76 (1 H, m, H-6), 4.42 (1 H, m, H-5), 7.11 (1 H, d, $J_{3,2}$ 5.07, H-3), 7.54 (2 H, m, Ar*H*), 8.39 (1 H, d, $J_{2,3}$ 5.07, H-2), 8.53 (2 H, m, Ar*H*); ^{13}C NMR δ_C (125 MHz, CD_3OD) 25.51, 32.57, 68.01, 70.92, 124.12, 126.11, 131.41, 149.04, 149.93, 150.44, 151.56, 158.96; MS *m/z* (ES) 243 (M^++H, 100%), 231 (27), 215 (10), 177 (3), 133 (5).

Synthesis of [Zn_2(fumarate)$_2$(**6**)] (method I)

To a solution of DMF (12 cm^3), ethanol (1 cm^3) and water (1 cm^3), contained in a 25 cm^3 flask, was added $Zn(NO_3)_2 \cdot 6H_2O$ (0.030 g, 0.1 mmol), fumaric acid (FMA) **5.17** (0.012 g, 0.1 mmol), and chiral bipyridine **5.4** (0.0135 g, 0.05 mmol). The flask containing the reaction mixture was sealed and heated in an oil bath at 60 °C for 48 h. The reaction mixture was then cooled to room temperature and small white crystals determined to be Zn_5(fumarate)$_4$(DMF)$_2$(OH)$_2$ were collected. The mother liquor was diluted with ethanol (~2 cm^3) and the solution left undisturbed for one week. A second crop of crystals determined to be [Zn_2(fumarate)$_2$(**6**)] were formed (0.008 mg, 27%, after desolvation). Microanalysis**,** found: C, 43.8; H, 4.0; N, 6.0; $C_{24}H_{22}N_2O_{10}Zn_2$ requires C, 45.8; H, 3.5; N, 4.45.

Synthesis of [Zn_2(fumarate)$_2$(**6**)] (method II)

To a solution of DMF (30 cm^3), ethanol (3 cm^3) and water (3 cm^3), contained in a 50 cm^3 flask, was added $Zn(NO_3)_2 \cdot 6H_2O$ (0.179 g, 0.6 mmol), fumaric acid (FMA) (0.070 g, 0.6

mmol), and chiral bipyridine **6** (0.243 g, 0.9 mmol). The flask containing the reaction mixture was sealed and heated in an oil bath at 60 °C for 48 h. After cooling the reaction mixture to room temperature, white crystals of of a material determined to be [Zn_2(fumarate)$_2$(**6**)] from XRPD (0.11 g, 58% after desolvation) were collected.

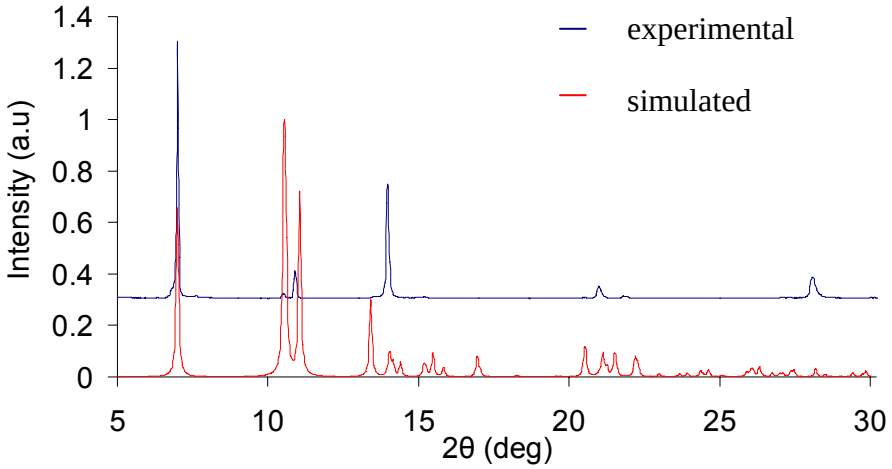
Desolvation:

Desolvated framework [Zn_2(fumarate)$_2$(**6**)] is obtained on heating framework [Zn_2(fumarate)$_2$(**6**)].2DMF at 140 °C for 2 h under a stream of nitrogen. Complete loss of solvent was confirmed by digestion in D_2O and ^{1}H NMR spectroscopy.

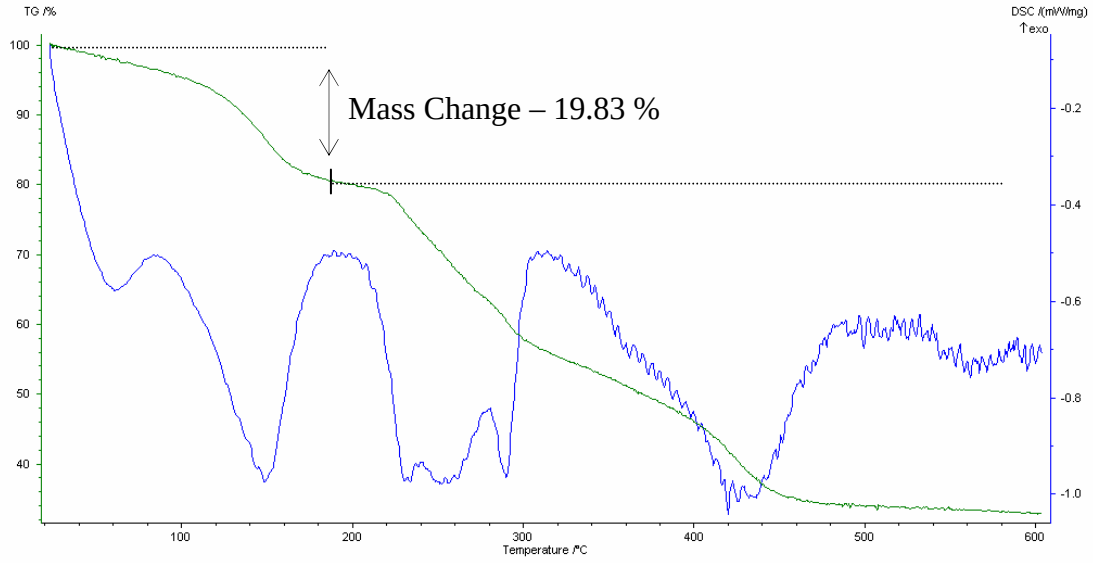
Synthesis of [Zn_2(fumarate)$_2$(**9**)]

To a solution of DMF (12 cm^3), ethanol (1 cm^3) and water (1 cm^3), contained in a 25 cm^3 flask, was added $Zn(NO_3)_2 \cdot 6H_2O$ (0.030 g, 0.1 mmol), fumaric acid (FMA) (0.012 mg, 0.1 mmol), and chiral bipyridine **9** (0.036 g, 0.15 mmol). The flask, containing the reaction mixture, was sealed and heated in an oil bath at 60 °C for 48 h. After cooling the reaction mixture to room temperature, white crystals of [Zn_2(fumarate)$_2$(**9**)] (0.013 g, 46%) were collected.

2. Comparison of the XRPD pattern of bulk [Zn_2(fumarate)$_2$(**6**)].2DMF with the pattern simulated from the single crystal structure.

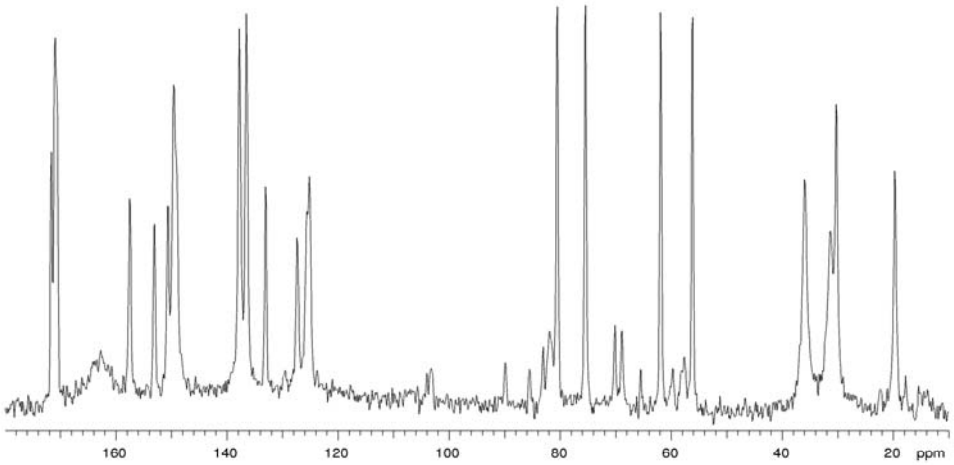


3. TGA and DSC for [Zn_2(fumarate)$_2$(**6**)].2DMF

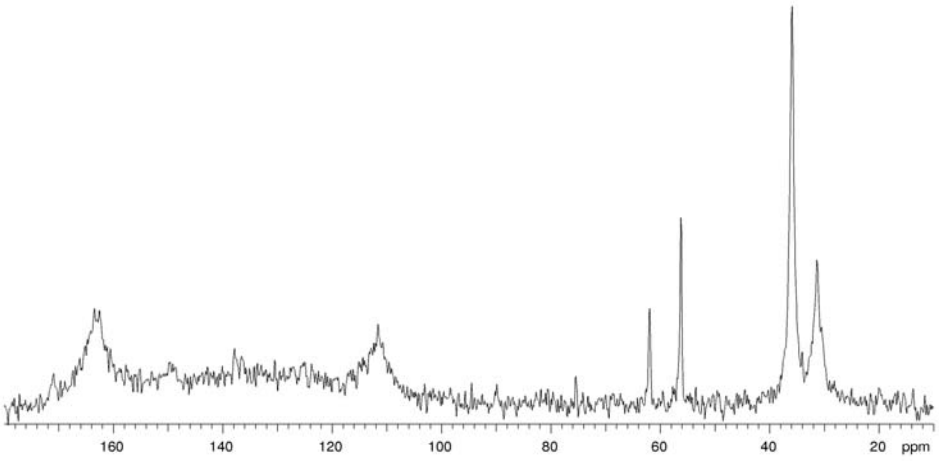


4. Variable-temperature ^{13}C NMR spectra of $[Zn_2(fumarate)_2(\mathbf{6})]\cdot 2DMF$

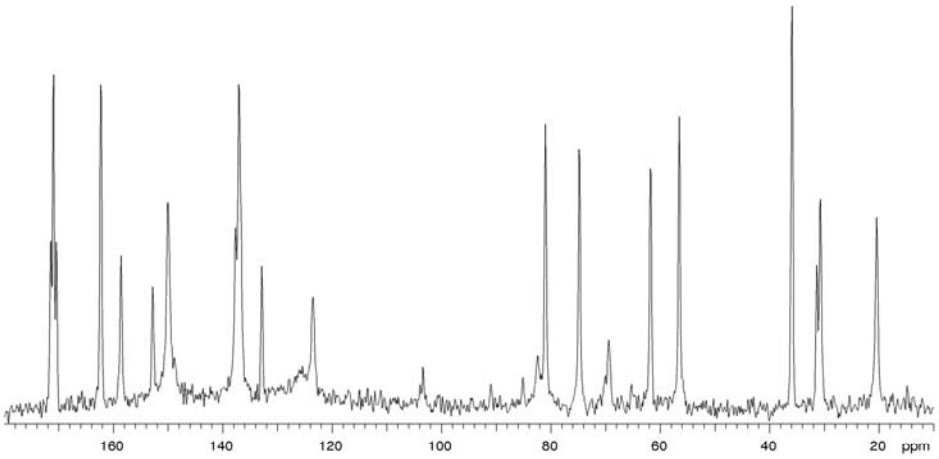
Spectrum 1
Solid state ^{13}C CPMAS spectrum $[Zn_2(fumarate)_2(\mathbf{6})]\cdot 2DMF$ at 25 °C



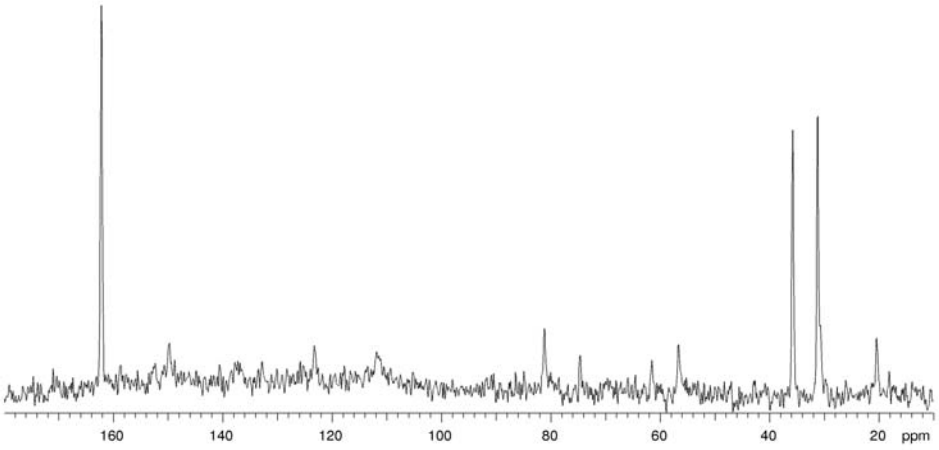
Spectrum 2
Solid state ^{13}C DPMAS spectrum of $[Zn_2(fumarate)_2(\mathbf{6})]\cdot 2DMF$ at 25 °C



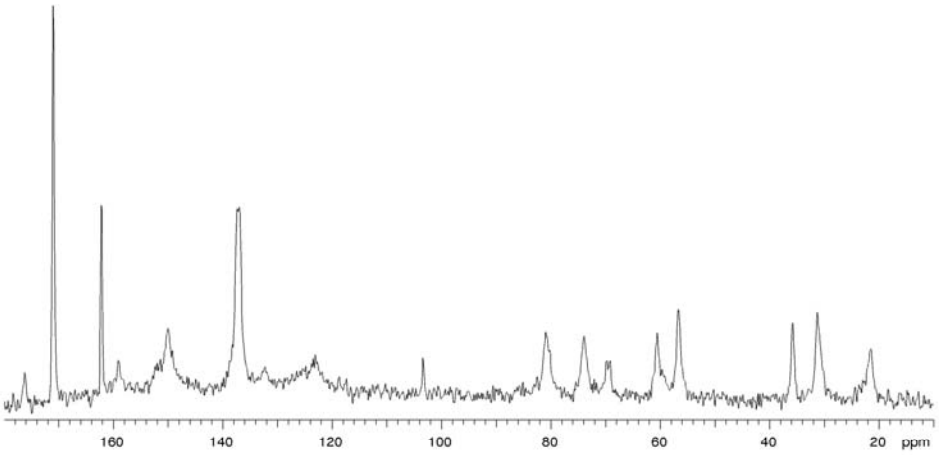
Spectrum 3
Solid state ^{13}C CPMAS spectrum of [Zn_2(fumarate)$_2$(**6**)].2DMF at 100 °C



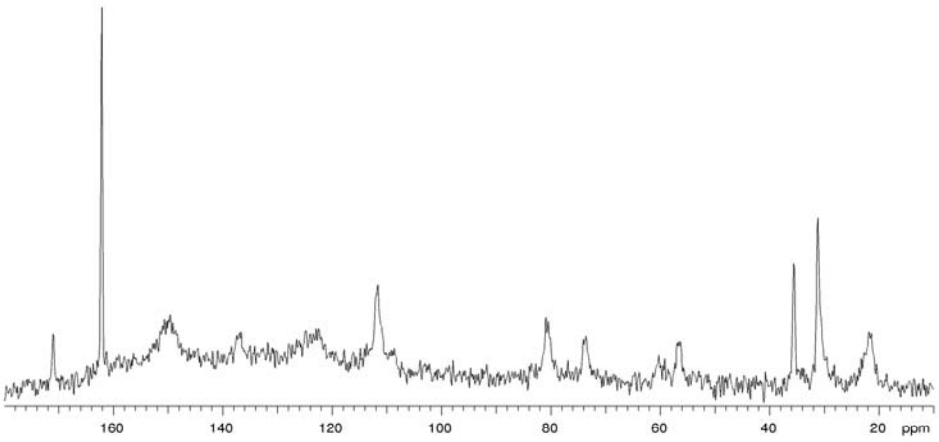
Spectrum 4
Solid state ^{13}C DPMAS spectrum of [Zn_2(fumarate)$_2$(**6**)].2DMF at 100 °C



Spectrum 5
Solid state ^{13}C CPMAS spectrumof $[Zn_2(fumarate)_2(\mathbf{6})]$.2DMF at 150 °C



Spectrum 6
Solid state ^{13}C DPMAS spectrum of $[Zn_2(fumarate)_2(\mathbf{6})]$.2DMF at 150 °C



Spectrum 7
Solid state ^{13}C CPMAS spectrum of [Zn_2(fumarate)$_2$(**6**)].2DMF at 25 °C after heating.