

Supporting Information: Gaywood and McNab

Synthesis and Chemistry of 4,5-Dihydrothieno[3,2-*b*]pyrrol-6-one – the First Heteroindoxy

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General experimental conditions. Routine ^1H and ^{13}C NMR spectra were recorded at 250 (or 200) and 63 (or 50) MHz respectively for solutions in $[\text{}^2\text{H}]$ chloroform unless otherwise stated. Chemical shift values are quoted in ppm relative to tetramethylsilane (TMS) at 0 ppm and coupling constants are quoted in Hz. ^{13}C NMR data refer to one CH resonance unless otherwise stated. Mass spectra were obtained under electron impact conditions.

Mecrcptoacetone.¹ Chloroacetone (17.2 g, 0.19 mol) was added to a solution of sodium hydrosulfide hydrate (16.00 g, 0.19 mol) in water (50 cm³) at 0 °C and the mixture was mechanically stirred for 2 h at 0 °C. The resulting precipitate was collected and washed with water, ethanol and then ether to yield mecaptoacetone (10.5 g, 63%); mp 109-111 °C (from toluene) (lit.,¹ 112-114 °C); δ_{H} ($[\text{}^2\text{H}_6]$ -acetone, 200 MHz) 1.53 (3H, s, CH₃), 2.89 (2H, s, CH₂) and 4.97 (1H, s, SH).

2-Acetyl-3-aminothiophene 5.² Mercaptoacetone (10.5 g, 0.12 mol) was added in portions to a solution of sodium methoxide [from sodium (5.11 g, 0.22 mol) and methanol (110 cm³)]. A solution of 2-chloroacrylonitrile (10.3 g, 0.117 mol) in methanol (60 cm³) was added to this solution, keeping the temperature below 4 °C. The mixture was stirred for 2 h at room temperature, after which the methanol was removed by rotary evaporation. Water (100 cm³) was added, the mixture was extracted with ether (8 × 100 cm³), the combined organic extracts were dried (MgSO₄), and the solvent was removed. The residue was purified by Kugelrohr distillation to yield 2-acetyl-3-aminothiophene **5** (7.26 g, 44%); bp 120 °C, (9 Torr) (lit.,² mp 82-83 °C); δ_{H} 2.36 (3H, s, acetyl), 6.15 (2H, br s, NH₂), 6.52 [1H, d, *J* 5.1, H(4)] and 7.25 [1H, d, *J* 5.1 H(3)]; δ_{C} 28.2 (CH₃), 111.5 (quat), 119.8, 131.7, 150.1 (quat), and 191.3 (quat).

2-Acetyl-3-azidothiophene 6.³ A cooled solution of sodium nitrite (4.3 g, 62 mmol) in the minimum amount of water was added dropwise, with cooling to a solution of 2-acetyl-3-aminothiophene **5** (6.00 g, 43 mmol) in conc. hydrochloric acid (42 cm³). The mixture was stirred at 0 °C for 30 min. A solution of sodium azide (6.18 g, 95 mmol) in the minimum amount of water was added dropwise with cooling. The solution was stirred for 30 min, and the resulting precipitate collected and washed with water to give 2-acetyl-3-azidothiophene **6** (4.46 g, 61%); mp 56-57 °C (lit.,³ 57-58 °C); δ_{H} 2.57 (3H, s, CH₃), 6.94 [1H, d, $J_{4,3}$ 5.4, H(4)] and 7.51 [1H, d, $J_{3,4}$ 5.4, H(3)]; δ_{C} 29.1 (CH₃), 121.1, 129.2 (quat), 132.6, 140.0 (quat) and 189.9 (quat); m/z 167 (M⁺, 15%), 139 (100), 111 (82), 110 (61), 87 (24), 70 (84) and 58 (51).

Temperature profile of 2-acetyl-3-azidothiophene 6 pyrolysis. CAUTION Azides are potentially explosive – see precautions outlined in the paragraph describing the FVP experiments in the main paper. The pyrolyses were carried out (typically 20 mg, 0.12 mmol; T_i 45 °C; P_i 3.4 × 10⁻² Torr; t 5 min) at the temperatures listed in the following table. To differentiate between 2-acetyl-3-azidothiophene **6** and 3-methylthieno[3,2-*c*]isoxazole **7** the spectra were recorded in [2H₆]DMSO, with the following peaks in the ¹H NMR spectra of the product mixtures used to calculate the product ratio: 2-acetyl-3-azidothiophene **6** {7.32 [1H, d, H(4)] and 8.03 [1H, d, H(3)]}, 3-methylthieno[3,2-*c*]isoxazole **7** {7.11 [1H, d, H(6)] and 7.94 [1H, d, H(5)]} and 4,5-dihydrothieno[3,2-*b*]pyrrol-6-one **3** {6.80 [1H, d, $J_{6,5}$ 5.1, H(6)] and 8.21 [1H, d, $J_{5,6}$ 5.1 H(5)]}.

Furnace temperature / °C	200	250	300	350	400	500	550
2-Acetyl-3-azidothiophene 6 / %	98	92	32	0	0	0	0
3-Methylthieno[3,2- <i>c</i>]isoxazole 7 / %	2	6	45	65	48	18	0
4,5-Dihydrothieno[3,2- <i>b</i>]pyrrol-6-one 3 / %	0	2	23	35	52	82	100

Table 1. Temperature profile of 2-acetyl-3-azidothiophene pyrolysis.

Solvent	3K : 3E ratio	2K : 2E ratio ⁸	9K : 9E ratio ¹¹
C[² H]Cl ₃	>95:5	>95:5	90:10
[² H ₆]Acetone	>95:5	>95:5	25:75
[² H ₄]Methanol	>95:5	92:8	74:26
[² H ₃]Acetonitrile	>95:5	82:18	
[² H ₆]DMSO	80:20	<5:95	5:95

Table 2. Solvent dependence of keto:enol tautomer ratio for **3**, **2** and **9**.

Attempted FVP of 2,2-dimethyl-5-(6-oxo-5,6-dihydrothieno[3,2-*b*]pyrrol-4-ylmethylene)-1,3-dioxane-4,6-dione **17.** FVP of **17** using diffusion pump pressure (60 mg, 0.20 mmol; T_f 650 °C; T_i 200 °C; P_i 3.0 × 10⁻⁶ Torr, t 40 min), yielded a pyrolysate (7 mg) which gave a complex ¹H NMR spectrum with no identifiable resonances. The low recovery from the pyrolysis is due to the large amount of decomposition in the inlet tube of the FVP apparatus.

Competitive deuterium exchange reaction of **2 and **3** in [²H₄]methanol.** A solution of 4,5-dihydrothieno[3,2-*b*]pyrrol-6-one **3** [(from 3-acetyl-2-azidothiophene (15 mg)], and indoxyl **2** [from a corresponding simultaneous pyrolysis of 2-azidoacetophenone (15

mg)]⁴ in [²H₄]methanol was monitored by ¹H NMR spectroscopy at 25 °C. The decline of the CH₂ peaks of both **2** and **3** was measured relative to the signal of *p*-dinitrobenzene (5 mg) as internal standard. Because very little precipitate was observed during the period of the reaction, amounts of oxidation to indigotin species were thought to be small under these conditions.

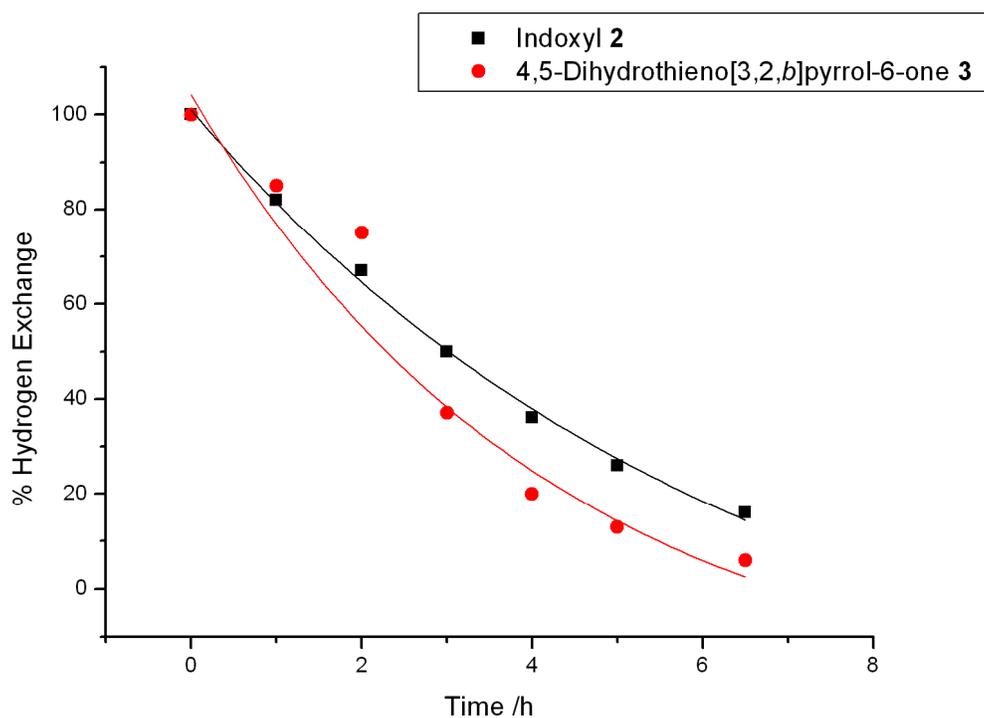
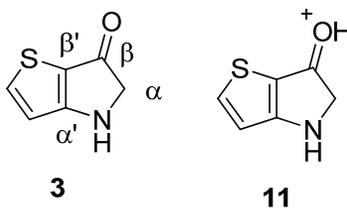


Figure 1. Plot of deuterium exchange for the competitive exchange of indoxyl **2** and 4,5-dihydrothieno[3,2-*b*]pyrrol-6-one **3** in [²H₄]methanol. Black line represents indoxyl **2** and red line represents 4,5-dihydrothieno[3,2-*b*]pyrrol-6-one **3**.

Effect of *O*-protonation on NMR spectra of **3**

Peak Assignment	CH ₂	H(2)	H(3)
δ_{H} (CDCl ₃)	4.24	7.85	6.68
δ_{H} (TFA)	5.05 (+0.81)	8.56 (+0.71)	6.88 (+0.20)

Table 3. Comparison of ¹H chemical shifts for protonated (in TFA) and non-protonated (in [²H]chloroform) forms of 4,5-dihydrothieno[3,2-*b*]pyrrol-6-one **3**, with differences upon protonation shown in parentheses.



Peak Assignment	C(2)	C(3)	C(α')	C(α)	C(β)	C(β')
δ_{C} (CDCl ₃)	143.9	113.7	175.0	61.0	196.2	116.3
δ_{C} (TFA)	163.7 (+19.8)	114.7 (+1.0)	182.3 ^a (+7.3)	62.1 (+1.1)	183.5 ^a (-12.7)	115.8 (-0.5)

Table 4. Comparison of ¹³C chemical shifts for protonated (in TFA) and non-protonated (in [²H]chloroform) forms of 4,5-dihydrothieno[3,2-*b*]pyrrol-6-one **3**, with differences upon protonation shown in parentheses.

^aAssignments may be reversed.

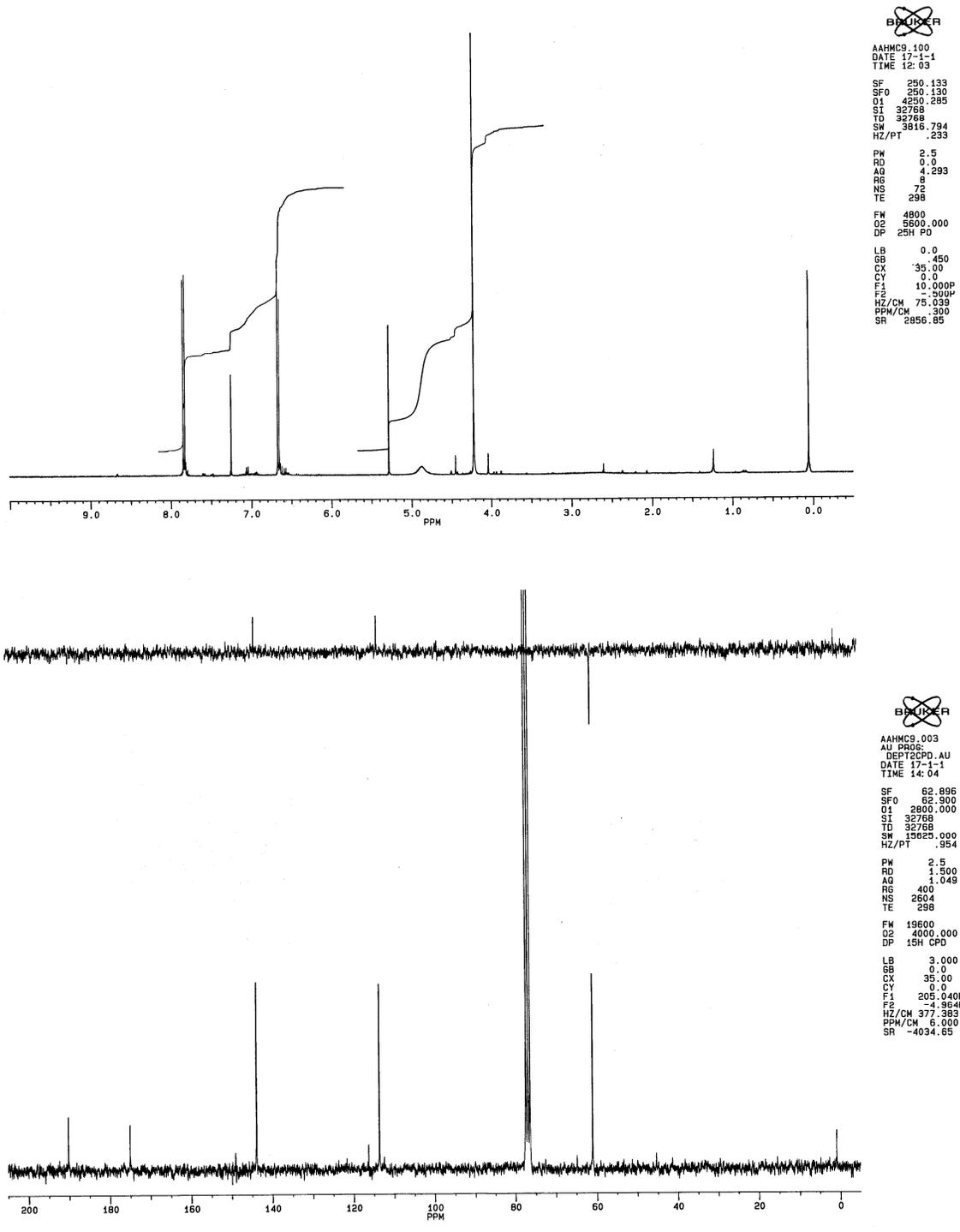


Figure 2. ¹H and ¹³C NMR (BB and DEPT-135) spectra of **3K**

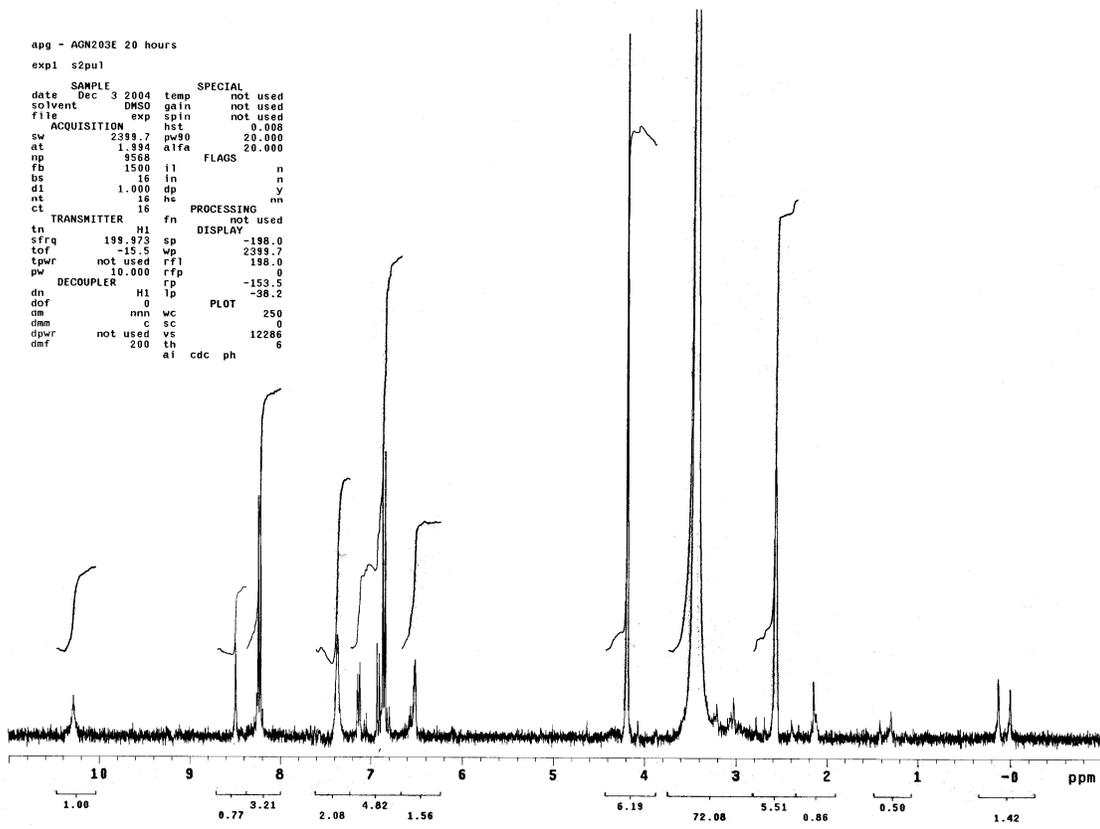


Figure 3. DMSO spectrum of **3** showing enol tautomer signals at $\delta_{\text{H}}(\mathbf{3E})$ 10.30 (1H, br, s), 8.49 (1H, s), 7.13 (1H, d), 6.92 (1H, d) and 6.51 (1H, s).

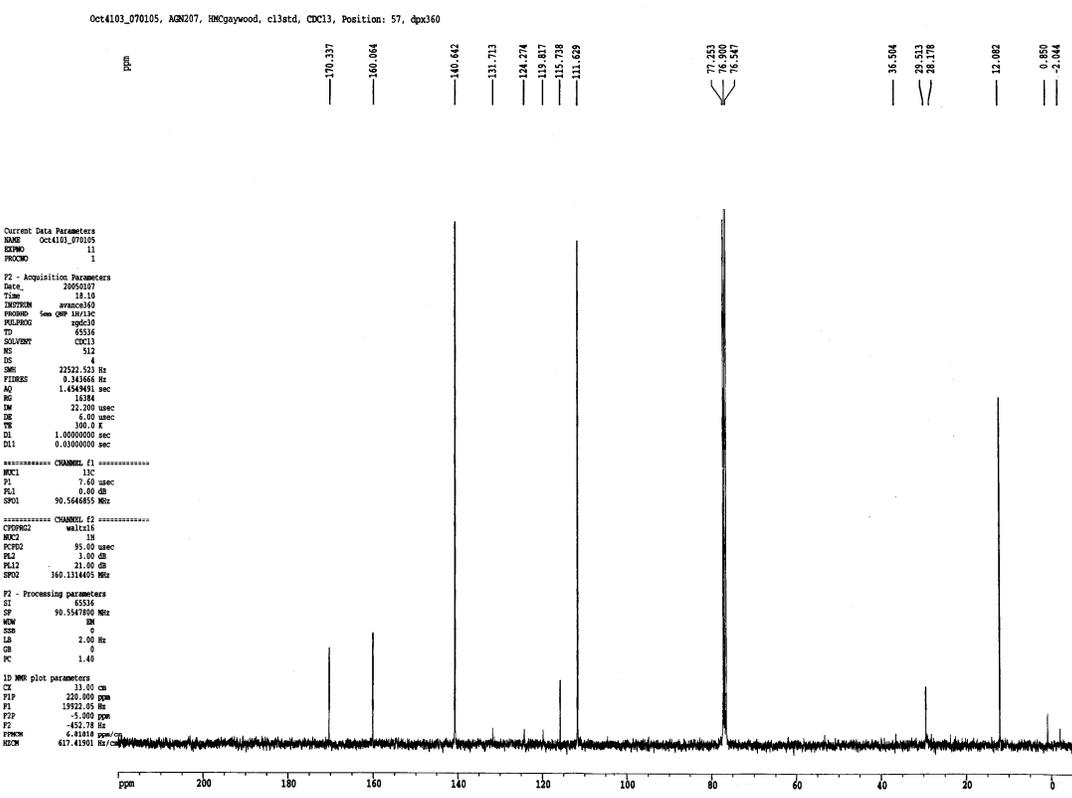
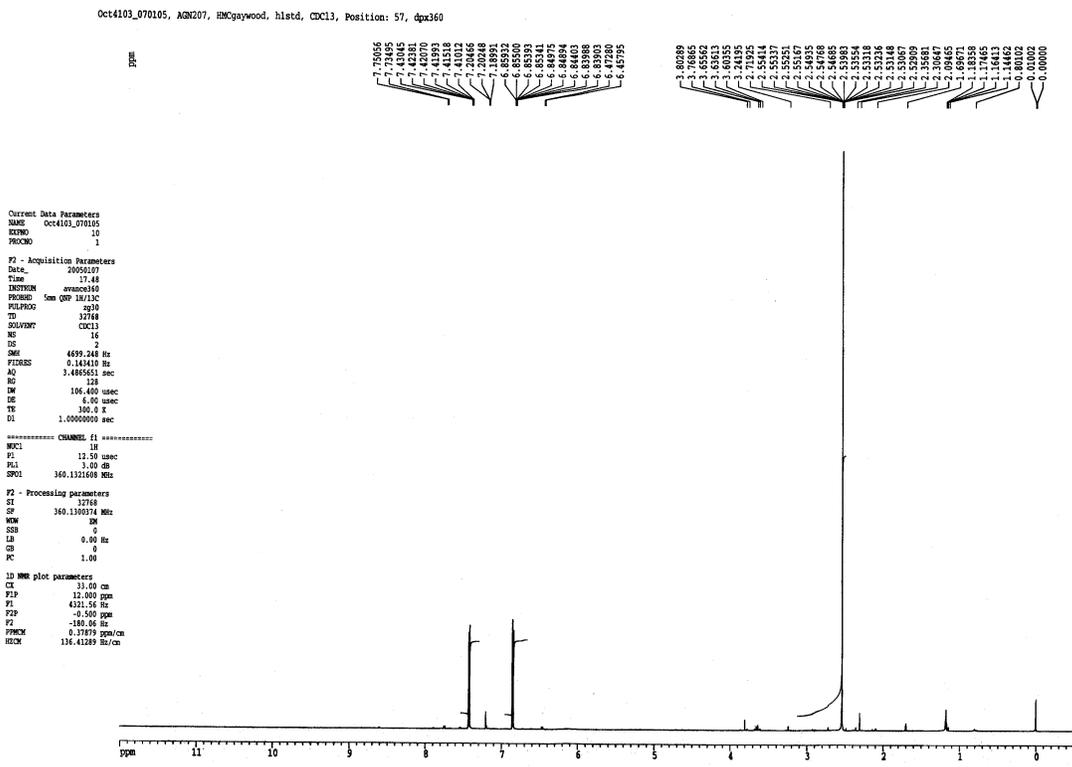


Figure 4. ¹H and ¹³C NMR spectra of 7.

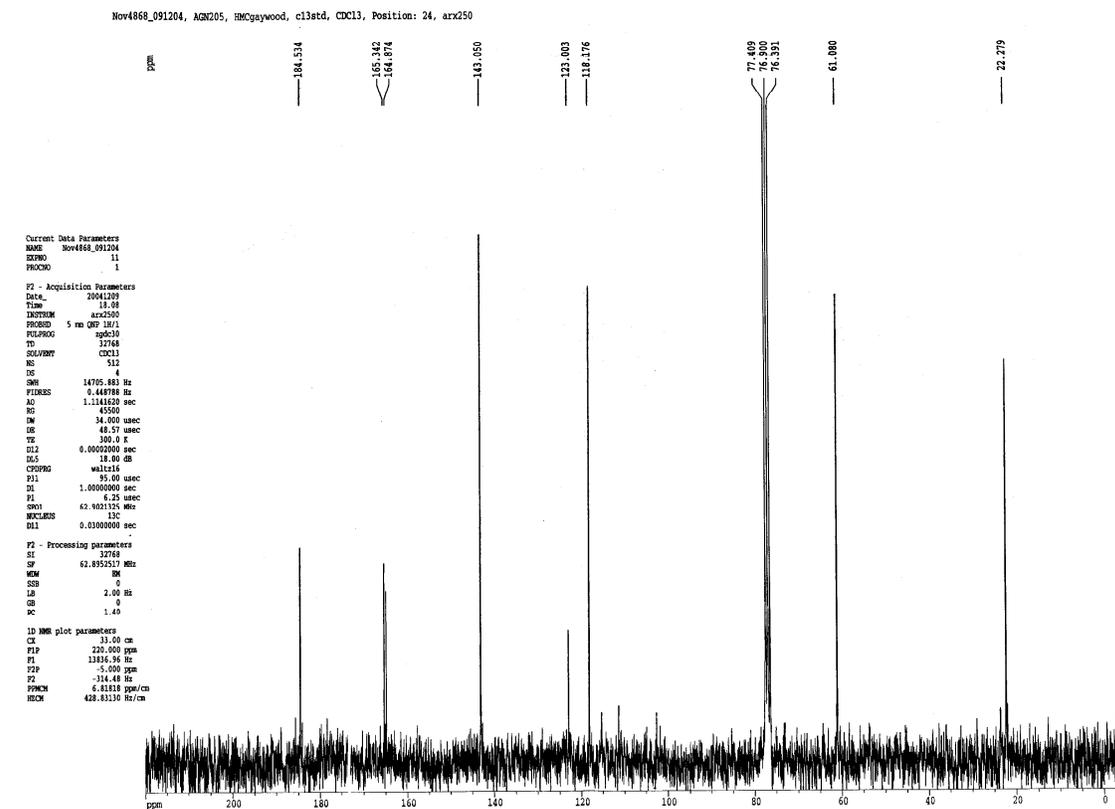
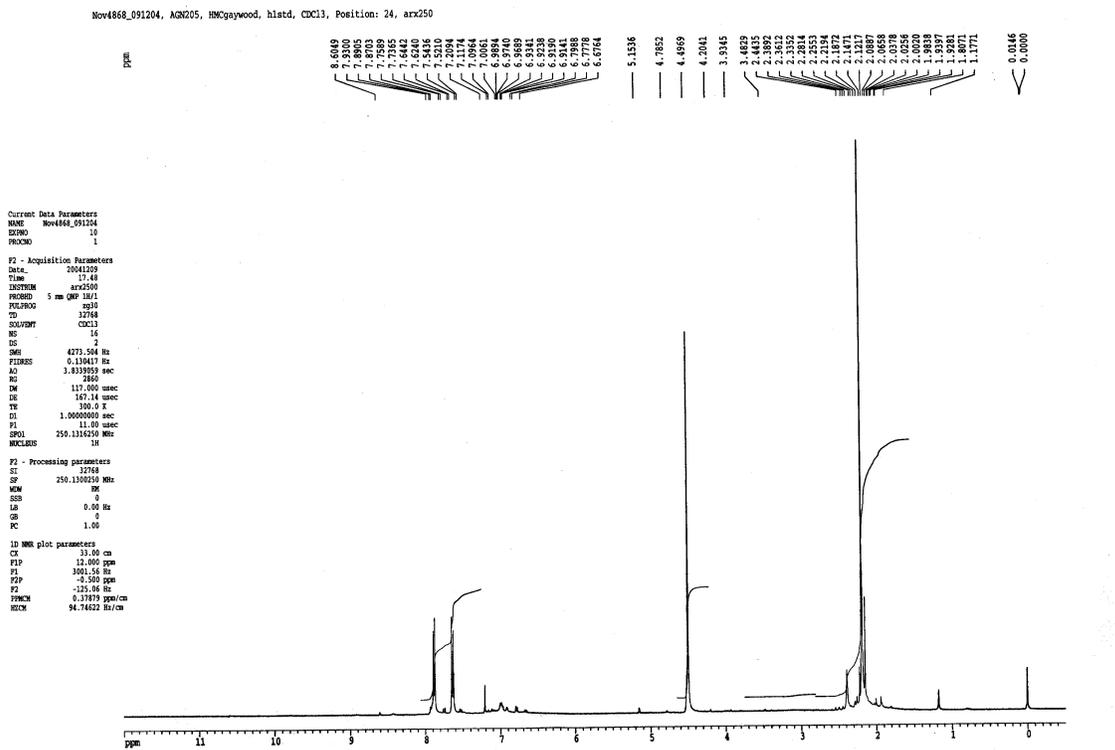


Figure 5. ¹H and ¹³C NMR spectra of **12**.

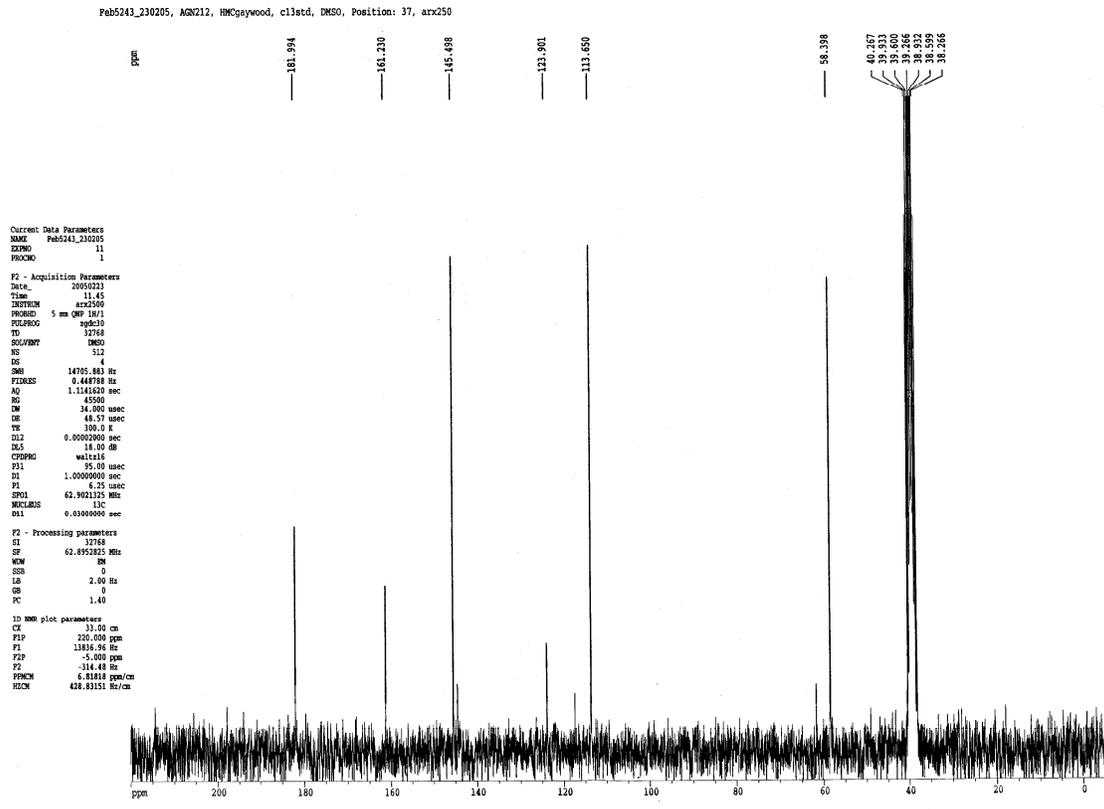
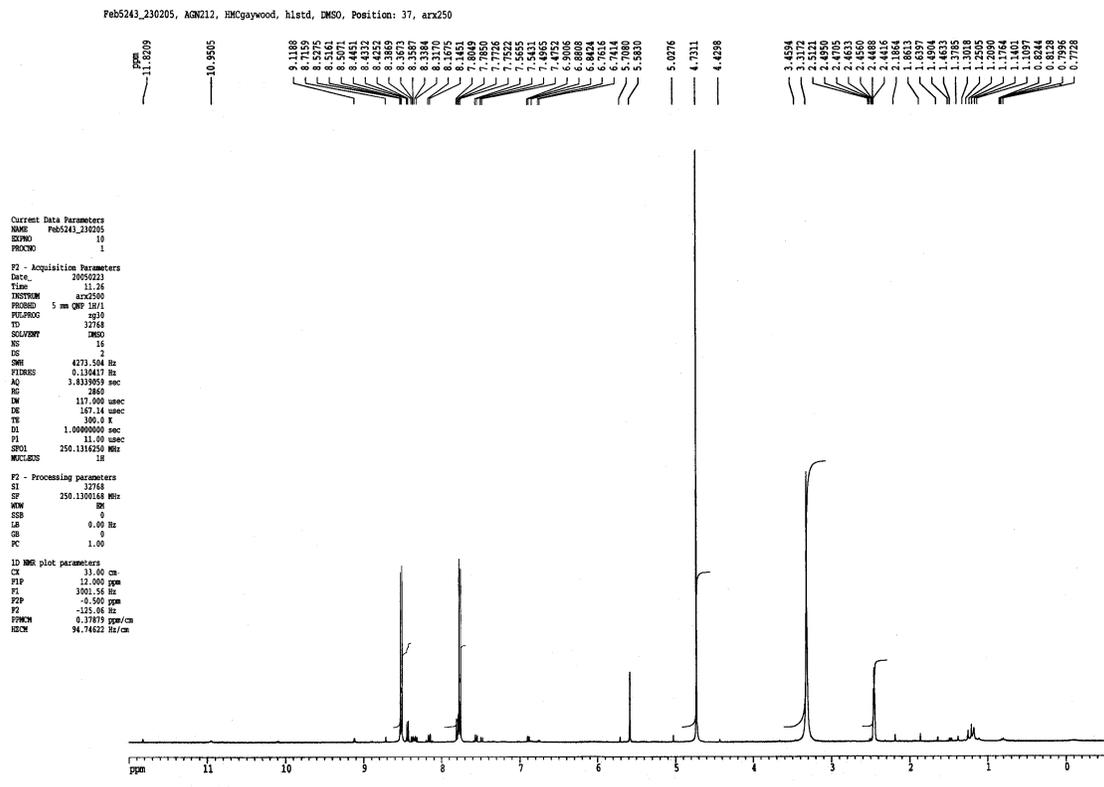


Figure 6. ¹H and ¹³C NMR spectra of 14.

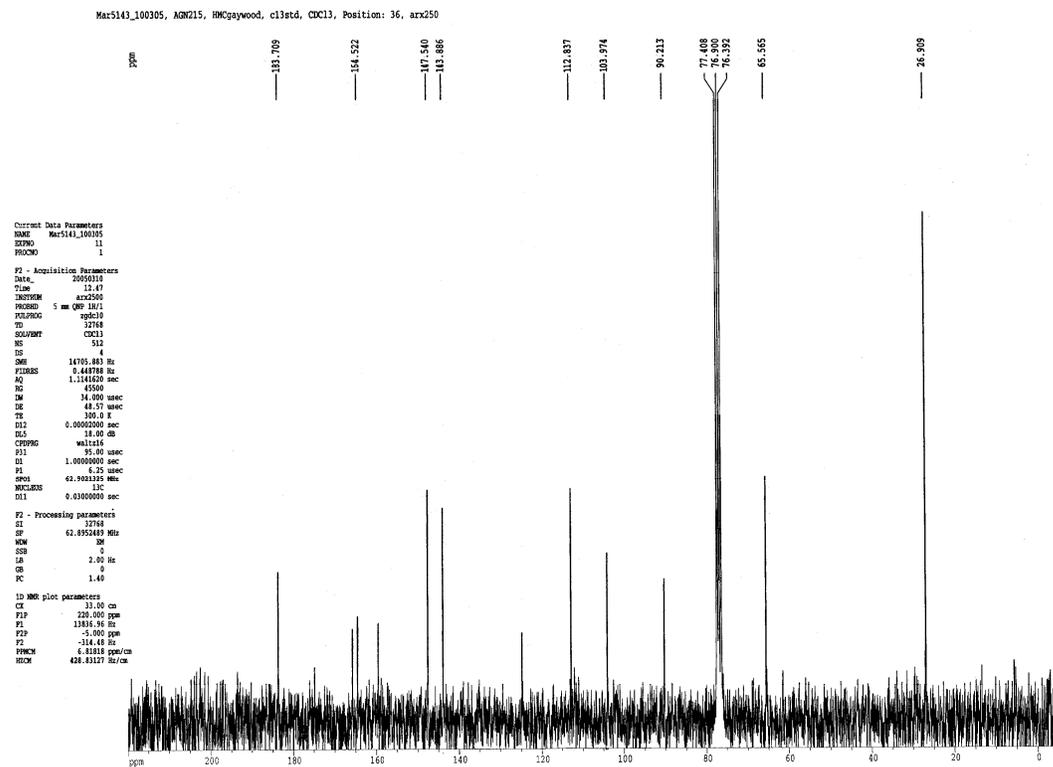
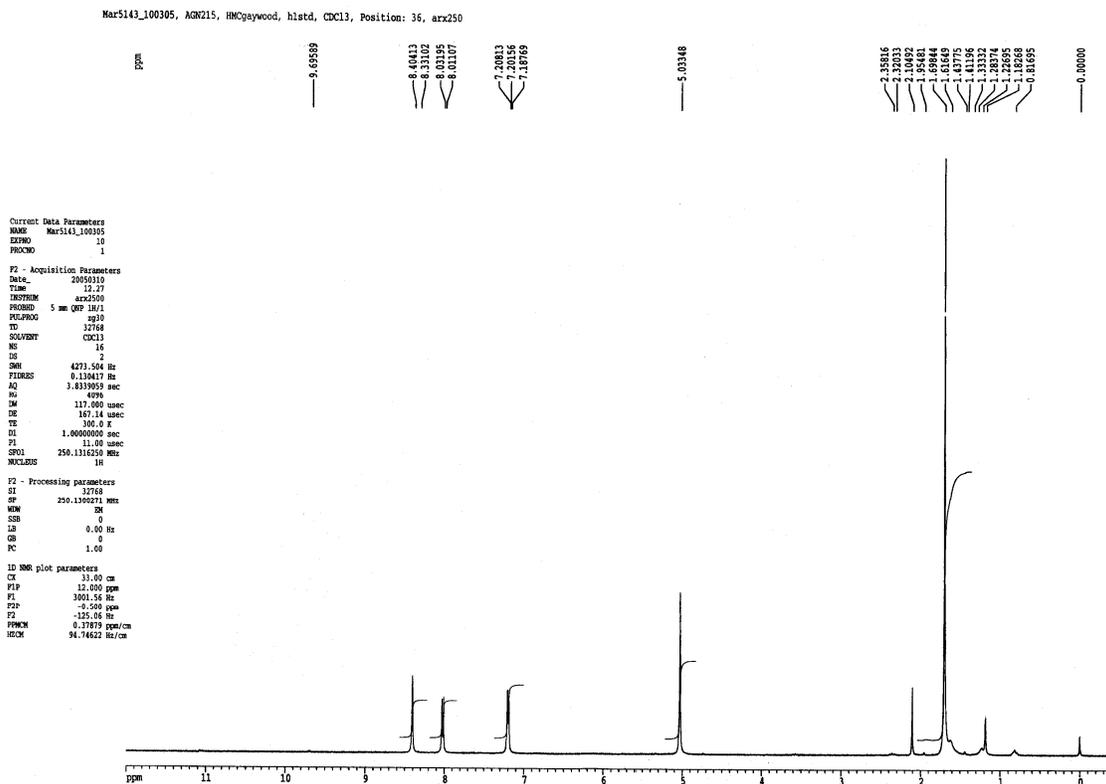


Figure 7. ¹H and ¹³C NMR spectra of 17.

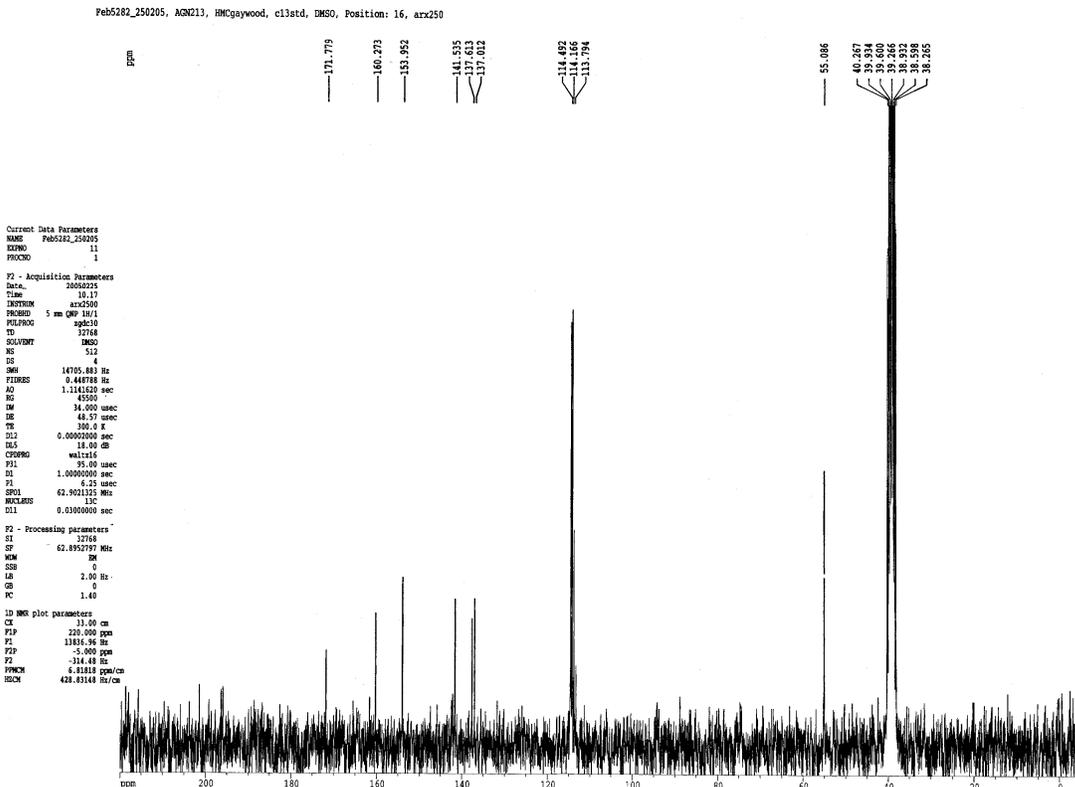
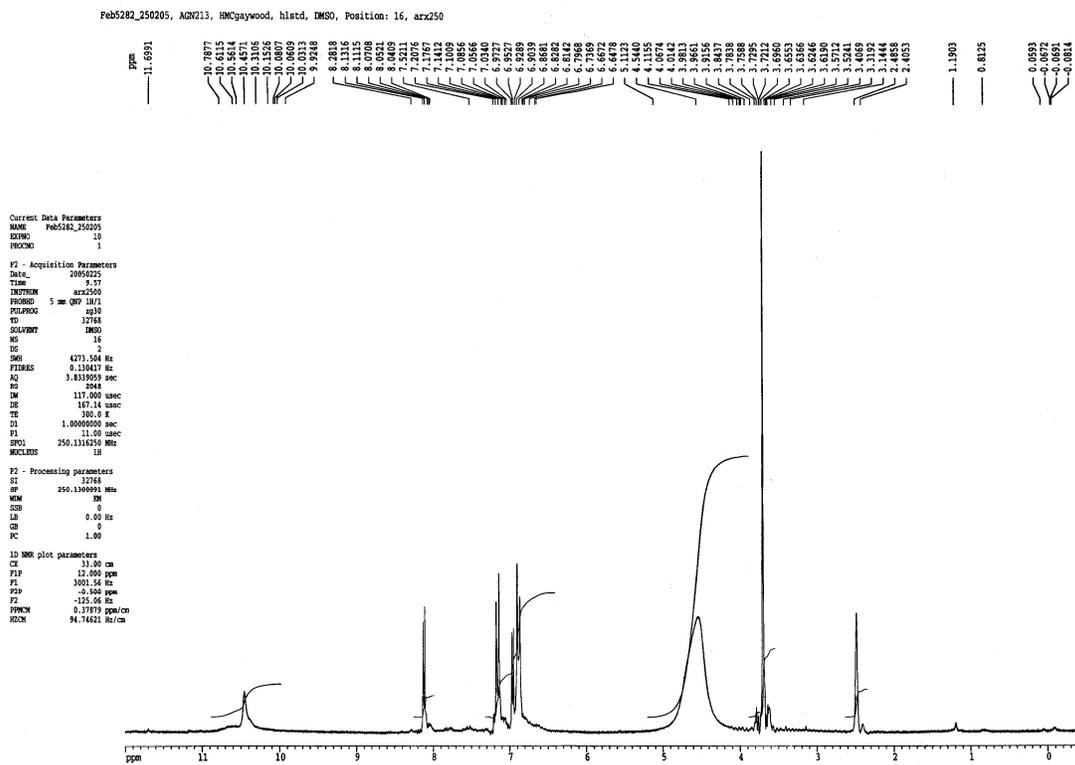


Figure 8. ¹H and ¹³C NMR spectra of 19.

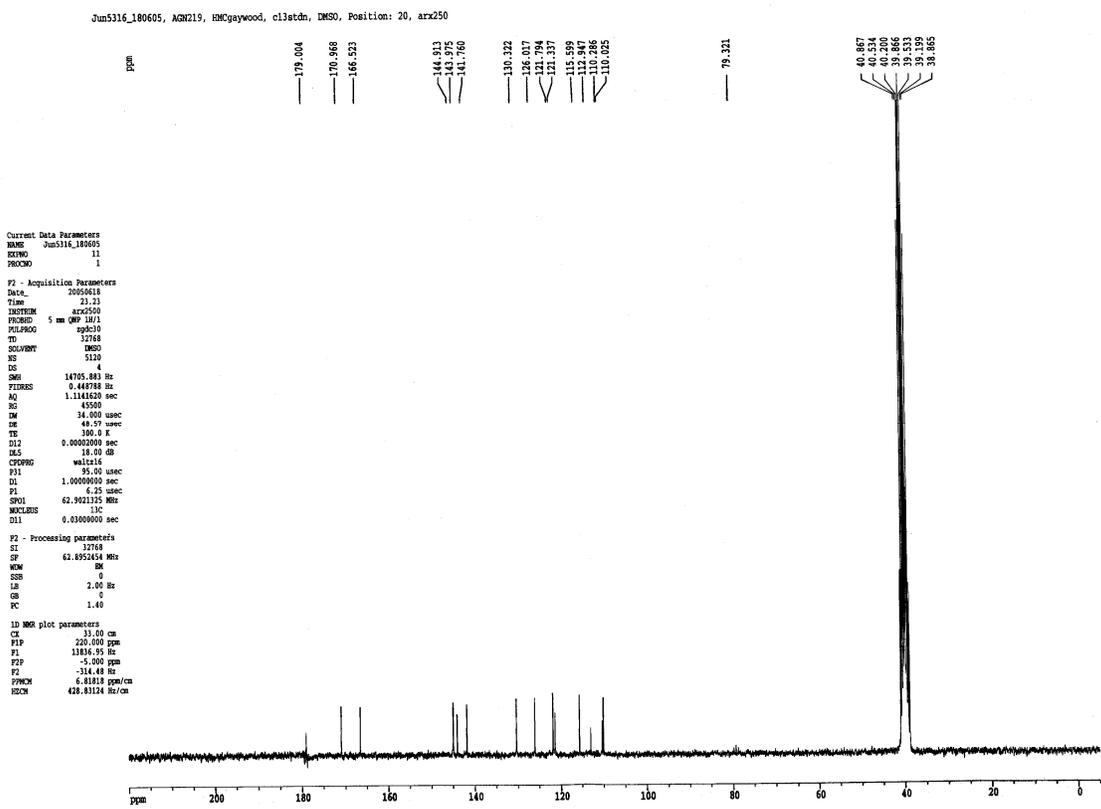
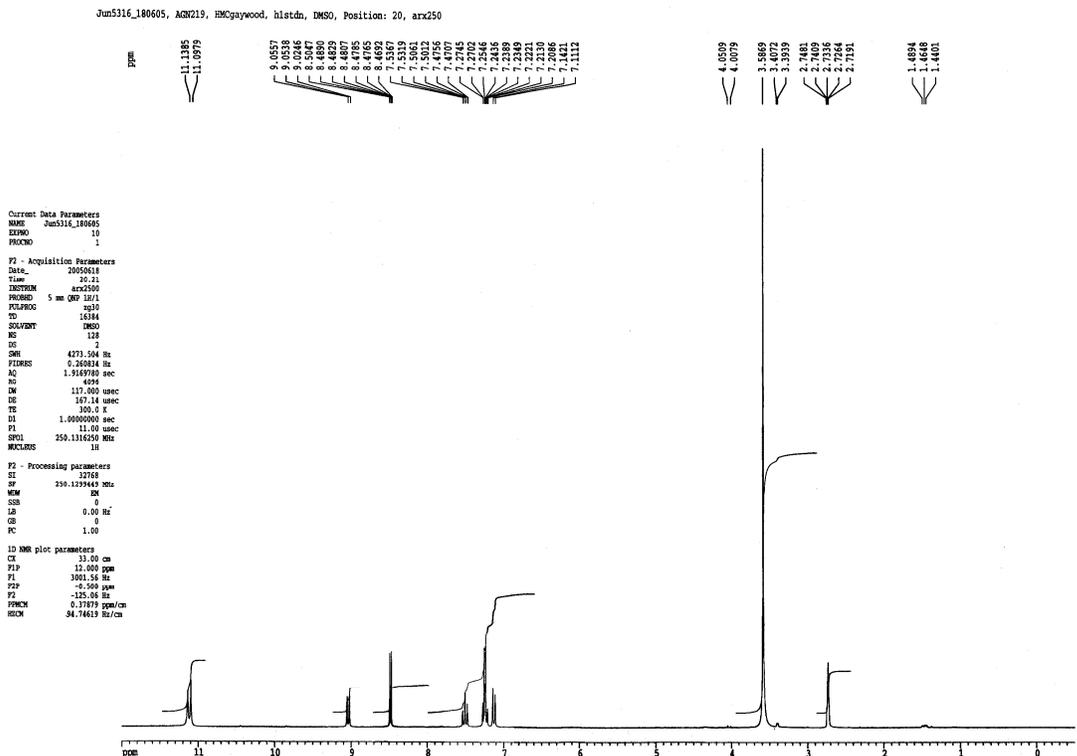


Figure 9. ¹H and ¹³C NMR spectra of 22.

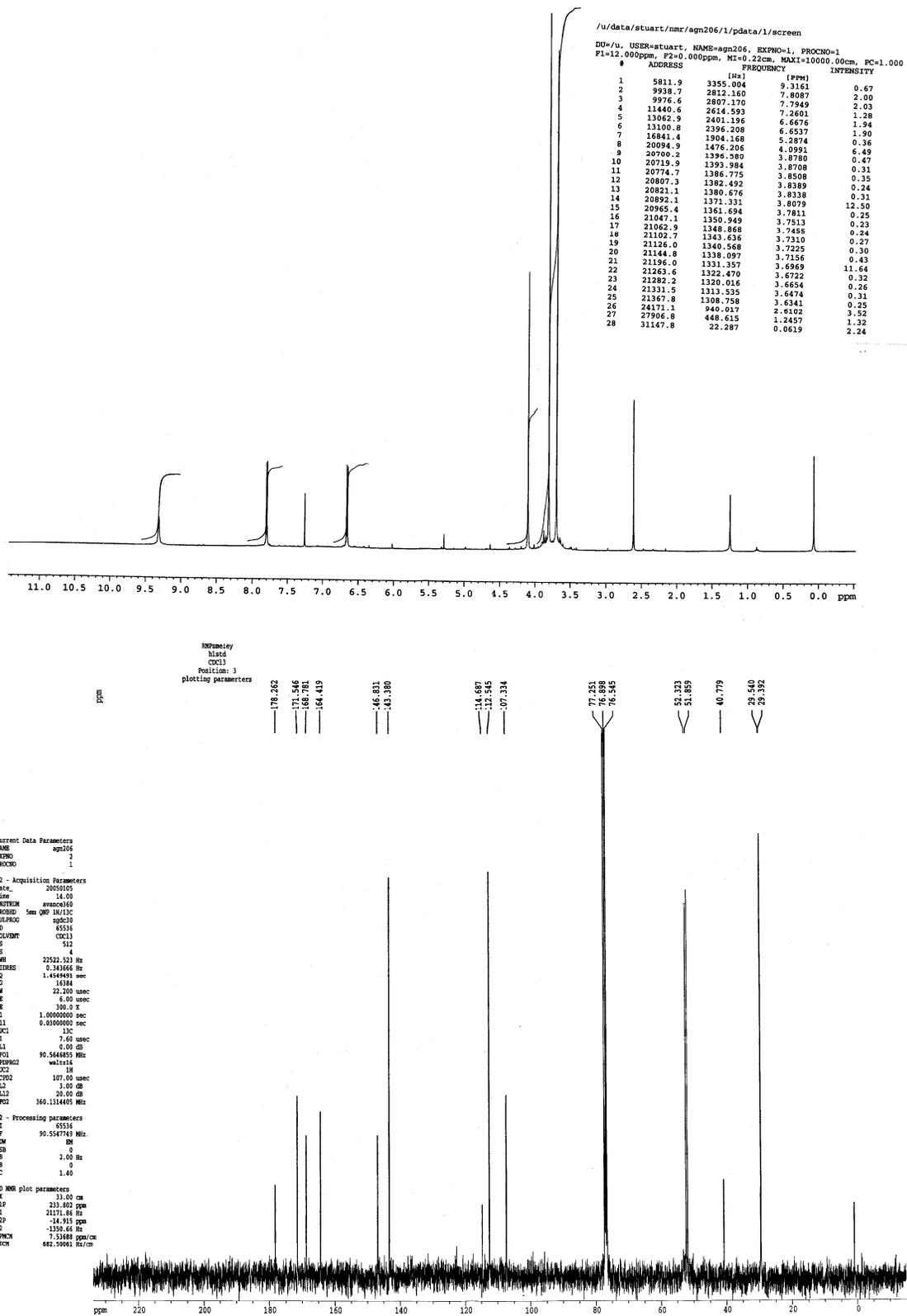


Figure 10. ^1H and ^{13}C NMR spectra of 24.

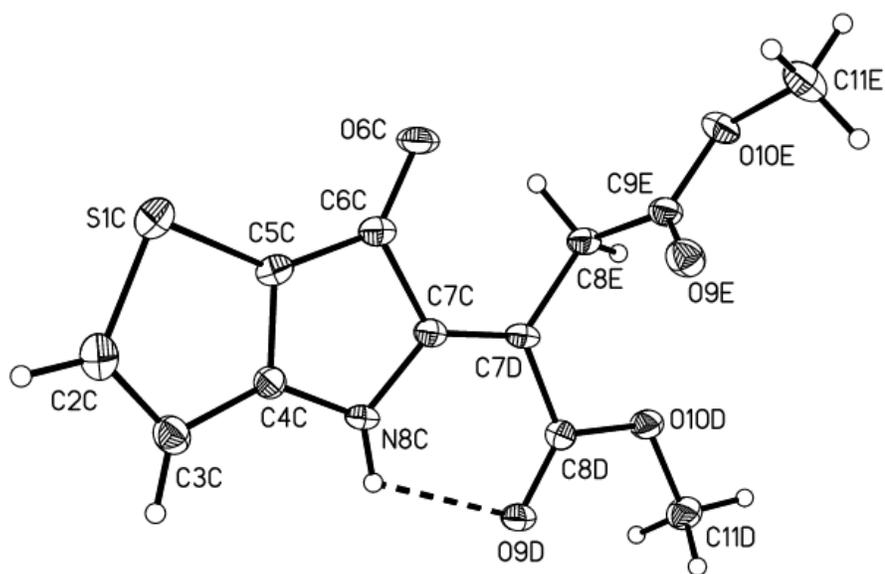
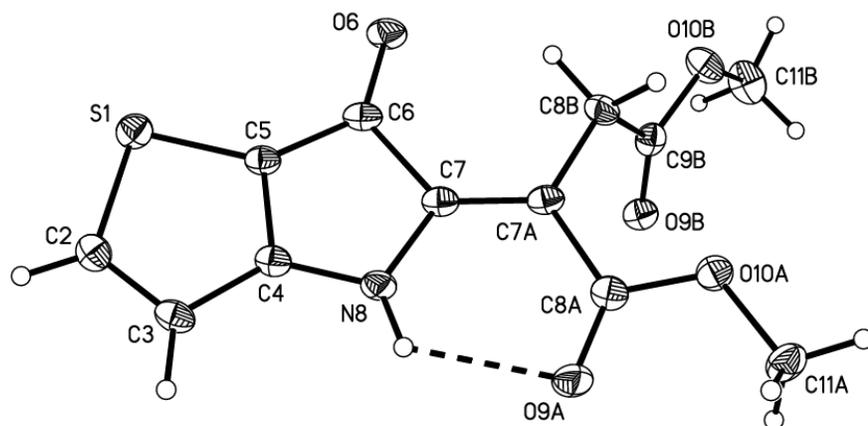


Figure 11. ORTEP plots of **24** showing the first and second molecules and the crystallographic numbering scheme.

Table 4. Selected bond lengths [\AA] and angles [deg] for **24** (hm0501).

S(1)-C(2)	1.714(3)
S(1)-C(5)	1.725(3)
C(2)-C(3)	1.368(4)
C(3)-C(4)	1.406(4)
C(4)-N(8)	1.369(4)
C(4)-C(5)	1.380(4)
C(5)-C(6)	1.420(4)
C(6)-O(6)	1.235(3)
C(6)-C(7)	1.549(4)
C(7)-C(7A)	1.348(4)
C(7)-N(8)	1.387(3)
C(7A)-C(8A)	1.481(4)
C(7A)-C(8B)	1.502(4)
C(8A)-O(9A)	1.214(3)
C(8A)-O(10A)	1.335(3)
O(10A)-C(11A)	1.448(3)
C(8B)-C(9B)	1.508(4)
C(9B)-O(9B)	1.198(3)
C(9B)-O(10B)	1.349(3)
O(10B)-C(11B)	1.446(3)
S(1C)-C(5C)	1.718(3)
S(1C)-C(2C)	1.727(3)
C(2C)-C(3C)	1.360(4)
C(3C)-C(4C)	1.401(4)
C(4C)-C(5C)	1.373(4)

C(4C)-N(8C)	1.387(3)
C(5C)-C(6C)	1.432(4)
C(6C)-O(6C)	1.230(3)
C(6C)-C(7C)	1.539(4)
C(7C)-C(7D)	1.349(4)
C(7C)-N(8C)	1.382(3)
C(7D)-C(8D)	1.474(4)
C(7D)-C(8E)	1.505(3)
C(8E)-C(9E)	1.501(4)
C(9E)-O(9E)	1.206(3)
C(9E)-O(10E)	1.340(3)
O(10E)-C(11E)	1.442(4)
C(8D)-O(9D)	1.218(3)
C(8D)-O(10D)	1.341(3)
O(10D)-C(11D)	1.456(3)
C(2)-S(1)-C(5)	90.34(14)
C(3)-C(2)-S(1)	114.0(2)
C(2)-C(3)-C(4)	110.6(3)
N(8)-C(4)-C(5)	111.2(2)
N(8)-C(4)-C(3)	135.3(3)
C(5)-C(4)-C(3)	113.5(3)
C(4)-C(5)-C(6)	109.1(3)
C(4)-C(5)-S(1)	111.5(2)
C(6)-C(5)-S(1)	139.3(2)
O(6)-C(6)-C(5)	130.5(3)
O(6)-C(6)-C(7)	125.4(3)

C(5)-C(6)-C(7)	104.1(2)
C(7A)-C(7)-N(8)	126.2(3)
C(7A)-C(7)-C(6)	128.2(2)
N(8)-C(7)-C(6)	105.6(2)
C(4)-N(8)-C(7)	109.9(2)
C(7)-C(7A)-C(8A)	119.4(2)
C(7)-C(7A)-C(8B)	122.8(3)
C(8A)-C(7A)-C(8B)	117.9(3)
O(9A)-C(8A)-O(10A)	122.9(3)
O(9A)-C(8A)-C(7A)	124.7(3)
O(10A)-C(8A)-C(7A)	112.4(2)
C(8A)-O(10A)-C(11A)	115.3(2)
C(7A)-C(8B)-C(9B)	112.4(2)
O(9B)-C(9B)-O(10B)	123.9(2)
O(9B)-C(9B)-C(8B)	126.2(3)
O(10B)-C(9B)-C(8B)	109.9(3)
C(9B)-O(10B)-C(11B)	116.3(2)
C(5C)-S(1C)-C(2C)	89.79(14)
C(3C)-C(2C)-S(1C)	114.3(2)
C(2C)-C(3C)-C(4C)	110.1(3)
C(5C)-C(4C)-N(8C)	111.0(2)
C(5C)-C(4C)-C(3C)	114.2(3)
N(8C)-C(4C)-C(3C)	134.8(3)
C(4C)-C(5C)-C(6C)	109.4(2)
C(4C)-C(5C)-S(1C)	111.64(19)
C(6C)-C(5C)-S(1C)	138.7(2)
O(6C)-C(6C)-C(5C)	131.5(3)

O(6C)-C(6C)-C(7C)	124.9(2)
C(5C)-C(6C)-C(7C)	103.6(2)
C(7D)-C(7C)-N(8C)	127.3(2)
C(7D)-C(7C)-C(6C)	125.9(2)
N(8C)-C(7C)-C(6C)	106.7(2)
C(7C)-N(8C)-C(4C)	109.3(2)
C(7C)-C(7D)-C(8D)	118.9(2)
C(7C)-C(7D)-C(8E)	122.2(2)
C(8D)-C(7D)-C(8E)	118.9(2)
C(7D)-C(8E)-C(9E)	112.9(2)
O(9E)-C(9E)-O(10E)	122.5(3)
O(9E)-C(9E)-C(8E)	126.5(2)
O(10E)-C(9E)-C(8E)	110.9(2)
C(9E)-O(10E)-C(11E)	116.1(2)
O(9D)-C(8D)-O(10D)	122.9(3)
O(9D)-C(8D)-C(7D)	124.9(2)
O(10D)-C(8D)-C(7D)	112.2(2)
C(8D)-O(10D)-C(11D)	115.6(2)

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