

Exploring a new, connective Pummerer reaction: Formation of oxindoles by the reaction of thiols with glyoxamides

Marc Miller,^a William Tsang,^a Andrew Merritt^b and David J. Procter*^a

^a School of Chemistry, University of Manchester, Oxford Rd., Manchester, M13 9PL, UK. Email: david.j.procter@manchester.ac.uk

^b GlaxoSmithKline, Gunnelswood Rd., Stevenage, SG1 2NY, UK.

Supporting Information

- S2 General considerations**
- S3 Representative procedure for the connective Pummerer cyclisation with *mono*–glyoxamides – preparation of 12**
- S4 Representative procedure for the connective Pummerer cyclisation with 1,3–*bis*–glyoxamides – preparation of 19**
- S5 Representative procedure for the connective Pummerer cyclisation with 1,4–*bis*–glyoxamides – preparation of 29**
- S7 Selected ¹H and ¹³C NMR spectra**

General considerations

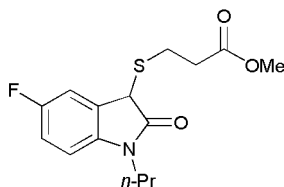
All experiments were performed under an atmosphere of N₂ using anhydrous solvents unless otherwise stated. Reactions were carried out using oven dried glassware. THF was distilled from sodium/benzophenone, CH₂Cl₂ was distilled from CaH₂, NEt₃ was distilled from CaH₂ and stored over KOH under N₂. DMSO was distilled from CaH₂, stored over molecular sieves and under N₂. DMPU was distilled from CaH₂, stored over molecular sieves and under N₂.

¹H NMR and ¹³C NMR were recorded on a Fourier transform spectrometer, with chemical shift values being reported in ppm relative to residual chloroform (δ_{H} 7.27 or δ_{C} 77.2) as an internal standard unless otherwise stated. NMR signals were assigned using DEPT – 135, HMQC and COSY spectra. All coupling constants are reported in Hertz (Hz). Mass spectra were recorded using a Waters Trio 2000 and a Thermo Finnigan MAT 95 XP at the University of Manchester. IR spectra were recorded using a Bio-Rad Excalibur.

Column chromatography was carried using Fischer Matrix silica gel 60 and FluoroFlash silica. Macherey-Nagel aluminium backed plates, precoated with silica gel 60 (UV₂₅₄) were used for thin-layer chromatography and were visualised by UV or staining with KMnO₄.

Representative procedure for the connective Pummerer cyclisation with *mono*-glyoxamides

Methyl 3-(5-fluoro-2-oxo-1-proplindolin-3-ylthio) propanoate **12**



To a solution of oxalyl chloride (203 μ l, 2.13 mmol, 1.1 eq) in CH_2Cl_2 (6 ml) was added DMSO (302 μ l, 4.25 mmol, 2 eq) in CH_2Cl_2 (3 ml) at -78°C . After 0.5 h, *N*-(4-fluorophenyl)-*N*-propyl-2-hydroxyacetamide (449 mg, 2.13 mmol, 1 eq) in CH_2Cl_2 (5 ml) was added. After a further 1 h, Et_3N (1.48 ml, 10.62 mmol, 5 eq) was added and reaction allowed to warm to room temp. After 1 h, CH_2Cl_2 (15 ml) was added to reaction mixture. Organic layer was washed with NaHCO_3 (3×15 ml) then dried (MgSO_4), filtered and concentrated *in vacuo* to give the crude glyoxamide, which was used without further purification. CH_2Cl_2 (8 ml) was added to crude glyoxamide (197 mg, 0.93 mmol, 1 eq) followed by thiol ester (101 μ l, 0.93 mmol, 1 eq) and reaction allowed to stir at room temp for 18 h. TFAA (1.19 ml, 8.39 mmol, 9 eq) was then added and after a further 1 h $\text{BF}_3\cdot\text{OEt}_2$ (574 μ l, 4.66 mmol, 5 eq). After stirring for 1 h, reaction was quenched with NaHCO_3 (15 ml), the organic layer was washed with NaHCO_3 (2×15 ml), dried (MgSO_4), filtered and concentrated *in vacuo* to give an orange oil. The crude mixture was then purified by column chromatography using 20% EtOAc in petroleum ether as eluant to give methyl 3-(5-fluoro-2-oxo-1-proplindolin-3-ylthio) propanoate **12** (197 mg, 0.62 mmol, 67% for 2 steps) as a light orange oil.

^1H NMR (300 MHz, CDCl_3) δ 0.98 (3H, t, $J = 7.4$ Hz, CH_3), 1.53 (2H, sextet, $J = 7.4$ Hz, CH_2), 2.63 (3H, t, $J = 7.1$ Hz, $\text{SCH}_2\text{CH}_2\text{C}=\text{O}$), 2.77-2.86 (1H, m, 1H of CH_2S), 2.98-3.07 (1H, m, 1H of CH_2S), 3.58-3.69 (2H, m, CH_2N), 3.67 (3H, s, CO_2CH_3), 4.30 (1H, s, CHS), 6.74 (1H, dd, $J = 4.1, 8.5$ Hz, ArCH), 6.85 (1H, dt, $J = 2.6, 8.5$ Hz, ArCH), 7.15 (1H, ddd, $J = 0.9, 2.6, 7.8$ Hz, ArCH).

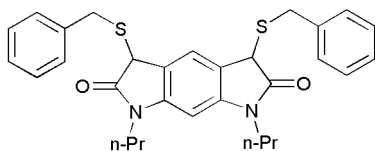
^{13}C NMR (75 MHz, CDCl_3) δ 11.6 (CH_3), 20.9 (CH_2), 25.2 (CH_2S), 34.5 ($\text{CH}_2\text{C}=\text{O}$), 42.1 (CH_2N), 45.0 (CHS), 52.1 (CO_2CH_3), 109.3 (ArCH , d, $J = 8.1$ Hz), 113.5 (ArCH , d, $J = 25.0$ Hz), 115.6 (ArCH , d, $J = 23.3$ Hz), 127.6 (ArC , d, $J = 8.3$ Hz), 139.6 (ArC , d, $J = 2.0$ Hz), 159.4 (ArCF , d, $J = 243.6$ Hz), 172.2 ($\text{C}=\text{O}$ amide), 175.1 ($\text{C}=\text{O}$ ester).

$\nu_{\max}/(\text{cm}^{-1})$ 2938, 1715 (C=O), 1613, 1448, 1345, 1165, 981

MS m/z (CI^+ mode) 312 ($(\text{M}^+ + \text{H})$, 24%), 194 (100%), 136 (14%), 108 (15%), 72 (19%), 60 (42%); $\text{C}_{15}\text{H}_{19}\text{O}_3\text{NFS}$ requires 312.1064, found 312.1066.

Representative procedure for the connective Pummerer cyclisation with a 1,3-bis-glyoxamides

3,5-Bis benzylsulfonyl-1,7-dipropyl-5,7-dihydro-1*H*, 3*H*-pyrrolo[3,2-*f*] indole-2,6-dione **19**



To a solution of oxalyl chloride (120 μl , 1.37 mmol, 2.2 eq) in CH_2Cl_2 (2 ml) at -78°C was added a solution of DMSO (177 μl , 2.50 mmol, 4 eq) in CH_2Cl_2 (2 ml). After stirring for 30 min a solution of 2-hydroxy-*N*-[3-(hydroxy acetyl-propyl amine)-phenyl]-*N*-propyl acetamide (194 mg, 0.62 mmol, 1 eq) in CH_2Cl_2 (3 ml) was added. After stirring for a further 1 h at -78°C , NEt_3 (863 μl , 6.20 mmol, 10 eq) was added and the reaction allowed to stir at room temperature for 1.5 h. CH_2Cl_2 (15 ml) was added to the reaction mixture and the organic layer washed with NaHCO_3 (3×20 ml), dried (MgSO_4) and concentrated *in vacuo* to give the crude *bis*-glyoxamide, which was used without further purification. CH_2Cl_2 (4 ml) was added to the crude *bis*-glyoxamide (90 mg) followed by benzyl mercaptan (48 μl , 0.41 mmol, 1.4 eq) and the reaction was allowed to stir at room temperature for 18 h. TFAA (761 μl , 5.27 mmol, 18 eq) was then added and after a further 1 h, $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (410 μl , 2.93 mmol, 10 eq). After stirring for 1 h the reaction was quenched with NaHCO_3 (20 ml), the organic layer was washed with NaHCO_3 (2×30 ml), dried (MgSO_4), filtered and concentrated *in vacuo* to give a blue oil. The crude reaction mixture was then purified by flash chromatography using 30 % EtOAc in petroleum ether as eluant to give 3,5-bis benzylsulfonyl-1,7, dipropyl-5,7-dihydro 1*H*, 3*H*-pyrrolo[3,2-*f*] indole-2,6-dione **19** (769 mg, 0.15 mmol, 51% over 2 steps) as a dark purple oil.

^1H NMR (500 MHz, CDCl_3) δ 0.92 (6H, t, $J = 7.4$ Hz, $2 \times \text{CH}_3$), 1.60-1.66 (4H, m, $2 \times \text{CH}_2$), 3.53- 3.58 (4H, m, $2 \times \text{NCH}_2$), 3.65 (1H, d, $J = 13.2$ Hz, 1H of CH_2S), 3.69 (1H, d, $J = 13.1$ Hz, 1H of CH_2S), 4.01 (1H, s, CHS), 4.03 (1H, s, CHS), 4.13 (1H, d, $J = 13.2$ Hz, 1H of CH_2S), 4.14

(1H, d, J = 13.1 Hz, 1H of CH₂S), 6.14 (1H, s, ArH), 7.14-7.31 (11H, m, 1H ArH and 10H of benzyl groups).

¹³C NMR (75 MHz, CDCl₃) δ 11.7 (2 × CH₃), 21.2 (2 × CH₂), 34.6 (2 × CH₂S), 42.1 (2 × CH₂N), 43.0 (2 × CHS), 91.0 (ArCH), 118.9 (2 × ArC), 122.5 (2 × ArCH), 127.5 (ArCH), 127.6 (ArCH), 128.7 (2 × ArCH), 128.8 (2 × ArCH), 129.5 (2 × ArCH), 129.6 (ArCH), 137.5 (ArC), 137.6 (ArC), 144.8 (ArC), 144.9 (ArC), 176.3 (2 × C=O),

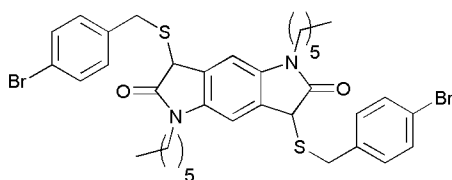
IR ν_{max}/(cm⁻¹) 3410, 3061, 2966, 1714 (C=O), 1614, 1487, 1372, 1208, 1129.

MS *m/z* (EI⁺ mode) 516 (M⁺, 7%), 393 (16%), 124 (8%), 91 (100%), 77 (16%), 65 (43%).

C₃₀H₃₃O₂N₂S₂ requires 517.1987. Found 517.1978.

Representative procedure for the connective Pummerer cyclisation with a 1,4-bis-glyoxamides

3,7-Bis-(4-bromo-benzylsulfanyl)-1,5-dihexyl-5,7-dihydro-1*H*,3*H*-pyrrolo[2,3-*f*]indole-2,6-dione 29



To a solution of oxalyl chloride (223 μl, 2.56 mmol, 2.2 eq) in CH₂Cl₂ (6 ml) at -78 °C was added DMSO (330 μl, 4.65 mmol, 4 eq) in CH₂Cl₂ (5 ml). After stirring for 30 min a solution of *N,N'*-(1,4-phenylene)*bis*(*N*-hexyl-2-hydroxyacetamide) (456 mg, 1.16 mmol, 1 eq) in CH₂Cl₂ (5 ml) was added. After a further 1 h at -78 °C, NEt₃ (1.62 ml, 11.62 mmol, 10 eq) was added and the reaction allowed to stir at room temperature for 1 h. CH₂Cl₂ (10 ml) was added to the reaction mixture and the organic layer washed with aqueous saturated NaHCO₃ (3 × 25 ml), dried (Na₂SO₄), filtered and concentrated *in vacuo* to give the crude *bis*-glyoxamide, which was used without further purification. CH₂Cl₂ (6 ml) was added to a portion of crude *bis*-glyoxamide (227 mg, 0.58 mmol, 1 eq) followed by 4-bromobenzyl mercaptan (236 mg, 1.16 mmol, 2 eq) in CH and the reaction was allowed to stir at room temperature for 18 h. TFAA (1.47 ml, 10.44 mmol, 18 eq) was then added and after a further 1 h BF₃•OEt₂ (713 μl, 5.80 mmol, 10 eq) was also added. After stirring for 1 h, the reaction mixture was quenched with aqueous saturated NaHCO₃.

(20 ml) and CH_2Cl_2 (15 ml) added and the organic layer separated. The organic fraction was washed with aqueous saturated NaHCO_3 (2×20 ml), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude mixture as a red solid. The crude reaction mixture was then purified by flash chromatography using 15% EtOAc in petroleum ether as eluant to afford 3,7-bis-(4-bromobenzylsulfanyl)-1,5-dihexyl-5,7-dihydro-1*H*,3*H*-pyrrolo[2,3-*f*]indole-2,6-dione **29** as a 1:1 mixture of diastereoisomers (238 mg, 0.31 mmol, 54%).

^1H NMR (500 MHz, CDCl_3) δ 0.81 (12H, t, $J = 7.2$ Hz, $4 \times \text{CH}_3$ of both diastereoisomers), 1.18-1.29 (24H, m, $4 \times \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ of both diastereoisomers), 1.67-1.69 (4H, quin, $J = 7.2$ Hz, $4 \times \text{NCH}_2\text{CH}_2$ of both diastereoisomers), 3.46-3.53 (2H, m, $2 \times 1\text{H}$ from CH_2N of both diastereoisomers), 3.55-3.61 (2H, m, $2 \times 1\text{H}$ from CH_2N of both diastereoisomers), 3.59 (1H, d, $J = 13.2$ Hz, 1H from CH_2S of one diastereoisomer), 3.62 (1H, d, $J = 13.2$ Hz, 1H from CH_2S of one diastereoisomer), 4.04 (1H, s, *CHS* of one diastereoisomer), 4.05 (1H, d, $J = 13.2$ Hz, 1H from CH_2S of one diastereoisomer), 4.07 (1H, s, *CHS* of one diastereoisomer), 4.13 (1H, d, $J = 13.2$ Hz, 1H from CH_2S of one diastereoisomer), 6.57 (4H, s, $4 \times \text{ArH}$ of both diastereoisomers), 7.12-7.16 (8H, m, $8 \times \text{ArH}$ of both diastereoisomers), 7.29-7.34 (8H, m, $8 \times \text{ArH}$ of both diastereoisomers).

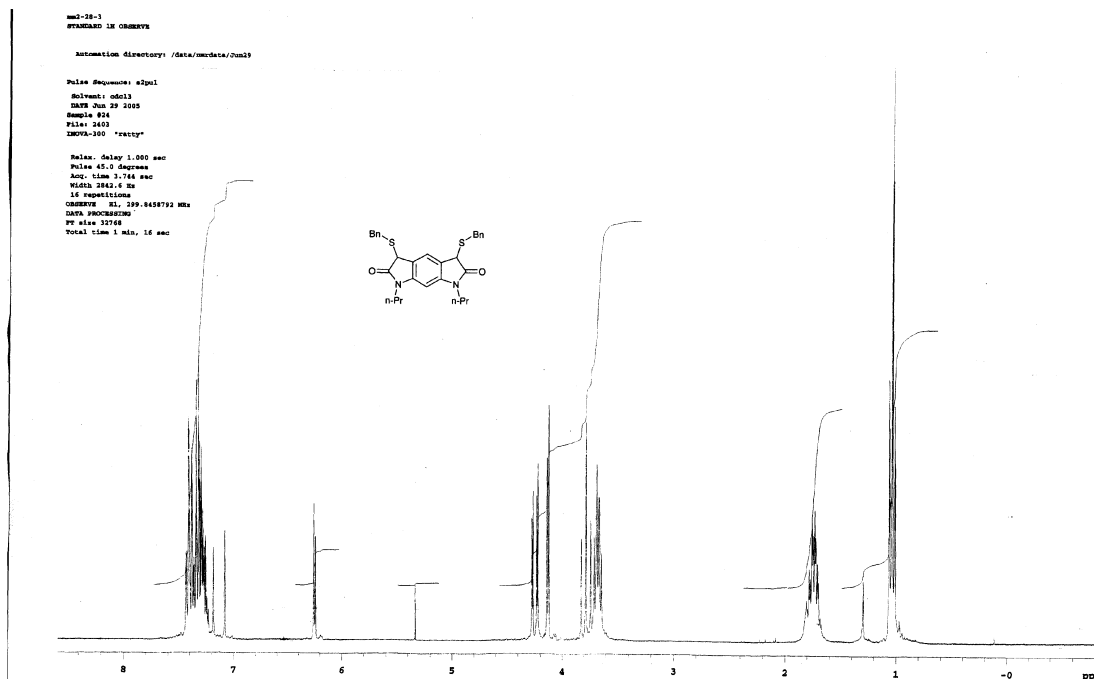
^{13}C NMR (125 MHz, CDCl_3) δ 14.1 ($4 \times \text{CH}_3$), 22.6 ($4 \times \text{CH}_2$), 26.5 ($4 \times \text{CH}_2$), 27.4 ($4 \times \text{CH}_2$), 29.7 ($4 \times \text{CH}_2$), 33.6 ($4 \times \text{CH}_2\text{S}$), 40.4 ($4 \times \text{CH}_2\text{N}$), 43.5 ($4 \times \text{CHS}$), 106.9 ($4 \times \text{ArCH}$), 121.2 ($4 \times \text{ArC}$), 126.0 ($4 \times \text{ArC}$), 130.9 ($4 \times \text{ArCH}$), 131.5 ($4 \times \text{ArCH}$), 136.3 ($4 \times \text{ArC}$), 139.1 ($4 \times \text{ArC}$), 174.2 ($4 \times \text{C=O}$).

IR $\nu_{\text{max}}/(\text{cm}^{-1})$ 2924, 1681, 1465, 1346, 1226, 1124, 1095, 1009, 987

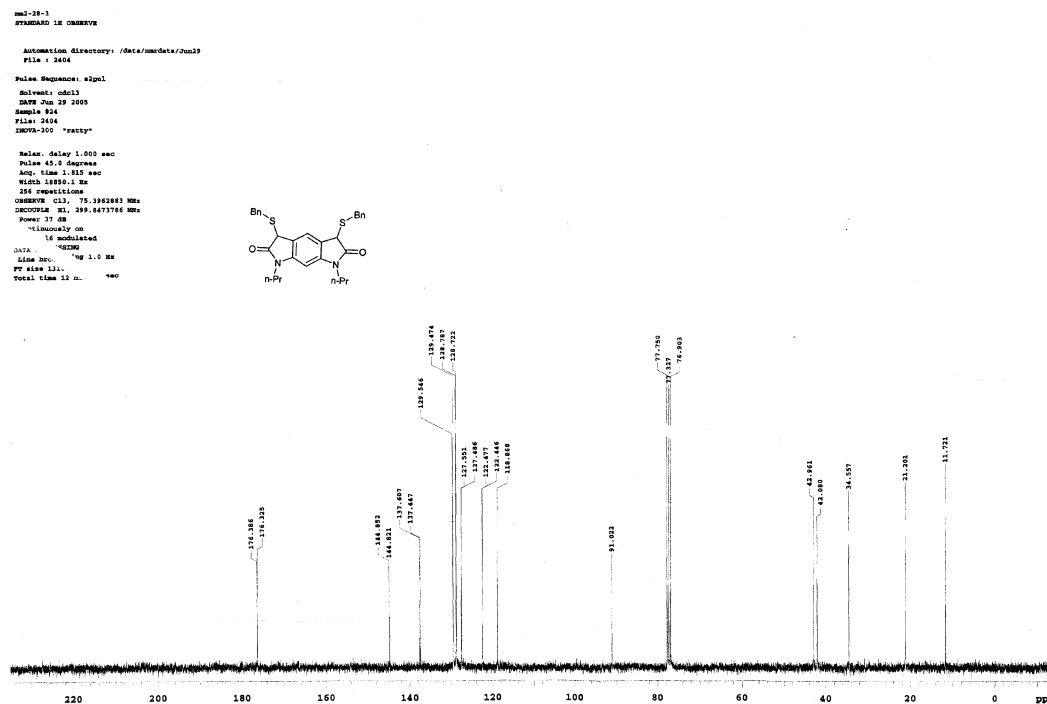
MS m/z (ES^- mode) 757 ($(\text{M}+\text{H})^+$, 43%), 569 (100%), 415.2 (35%), 339.7 (18%), 273 (10%).

Selected ^1H and ^{13}C NMR spectra

^1H NMR of **19**

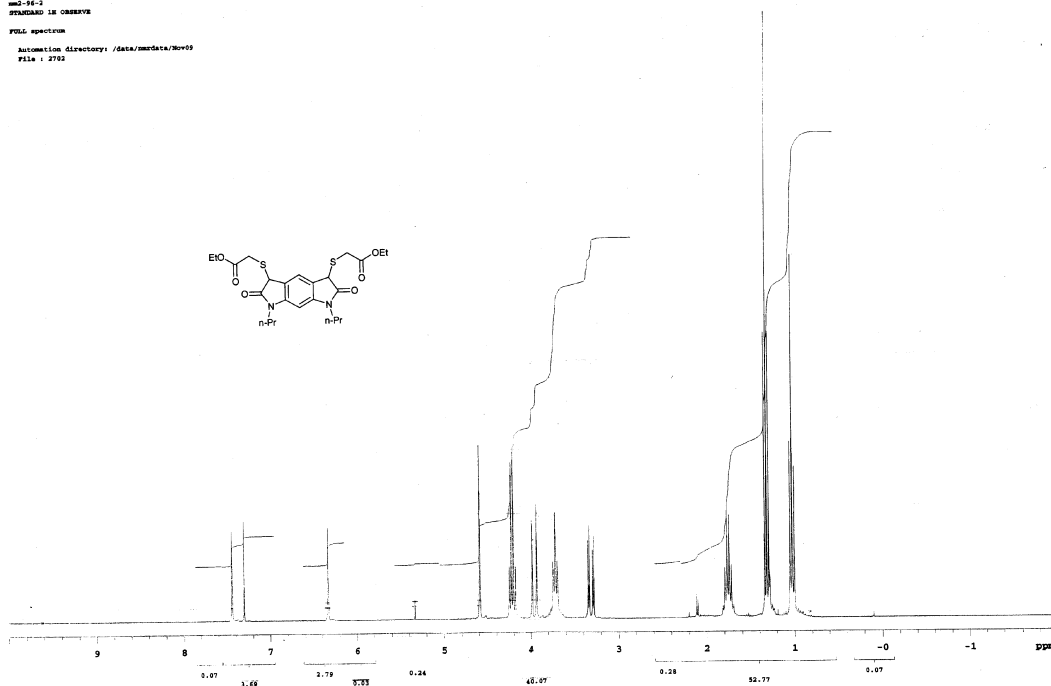


^{13}C NMR of **19**



¹H NMR of 21

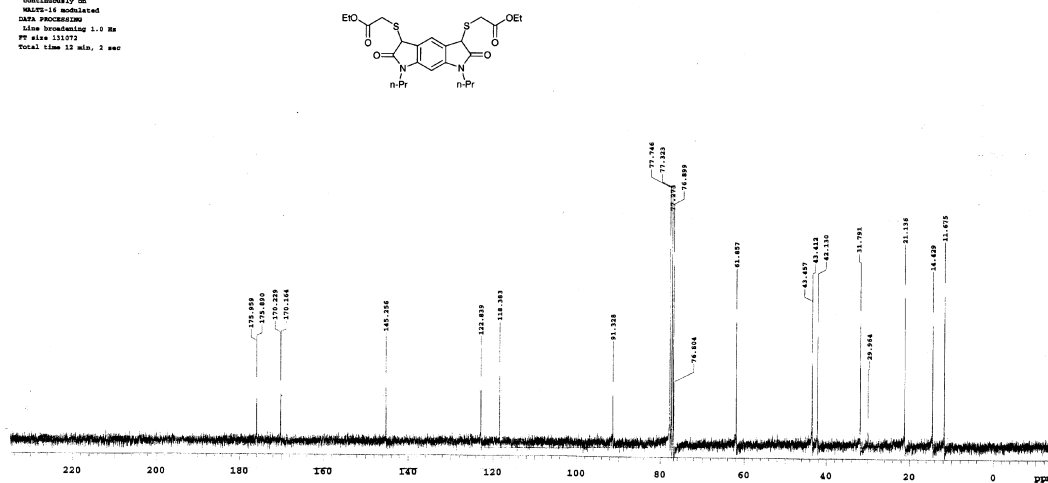
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¹³C NMR of 21

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Date Mon 10 2003
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Pulse 45.0 degree
Acq. time 1.815 sec
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256 repetitions
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DECOUPLE H1, 299.6427868 MHz
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continuously on
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DATA PROCESSING
line broadening 1.0 Hz
PPM scale 131073
Total time 32 min, 2 sec



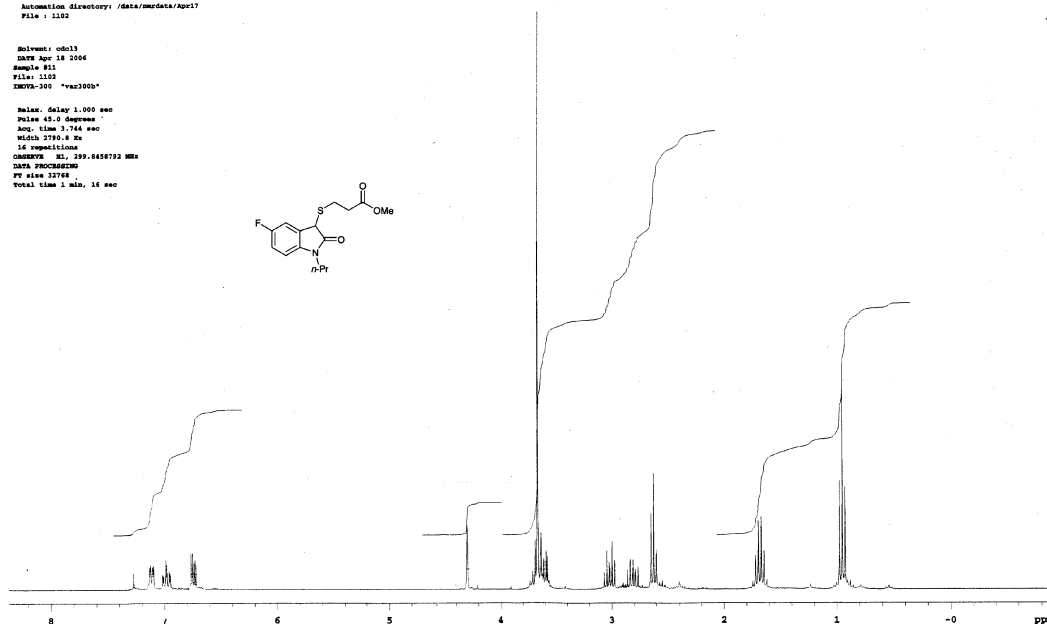
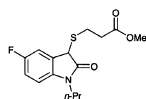
¹H NMR of 12

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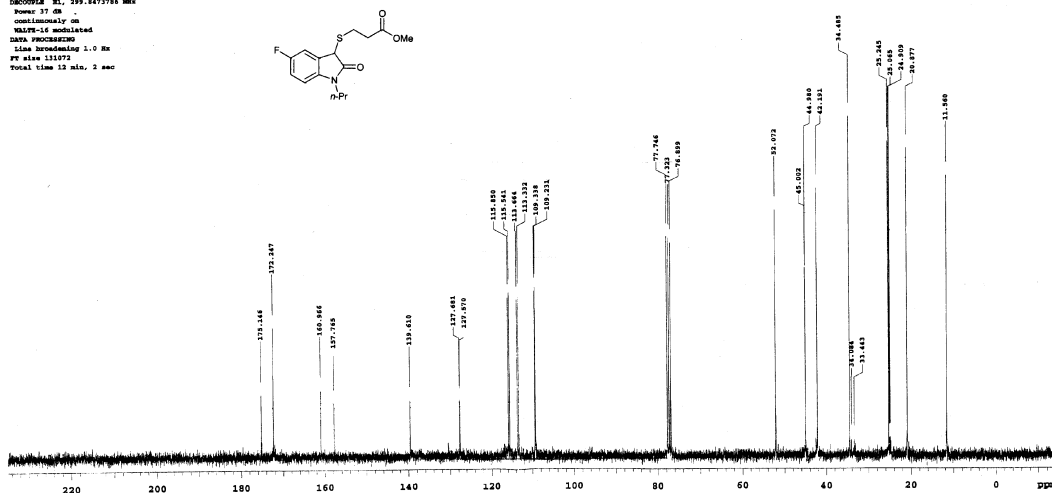
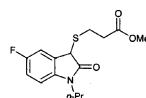
¹³C NMR of 12

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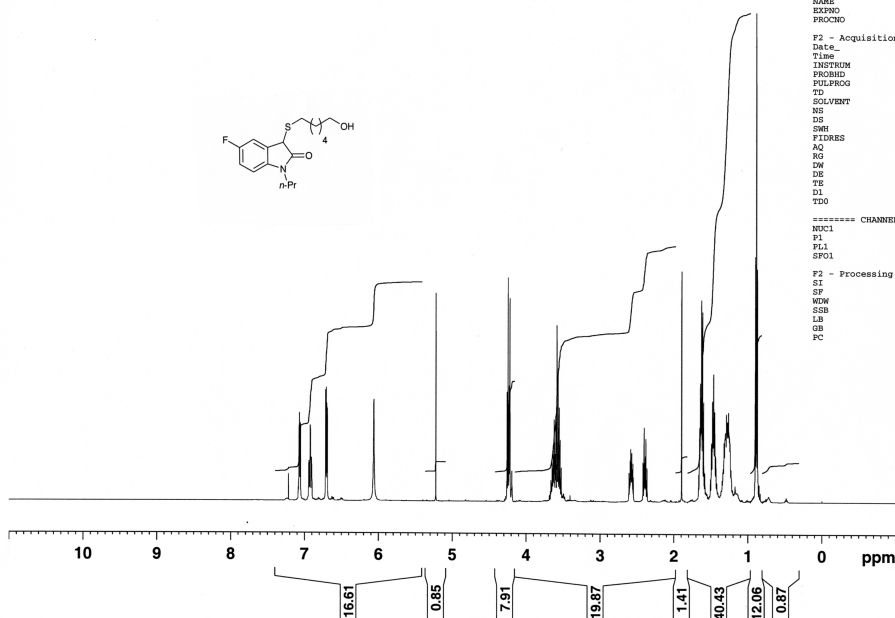
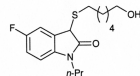
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Total time: 12 min, 2 sec



¹H NMR of 11

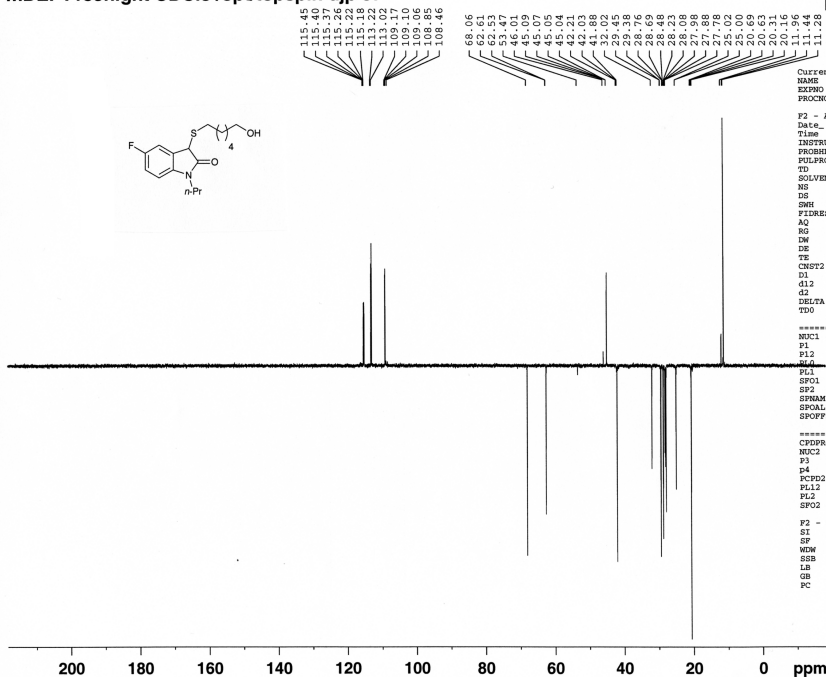
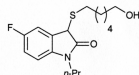
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¹³C DEPT NMR of 11

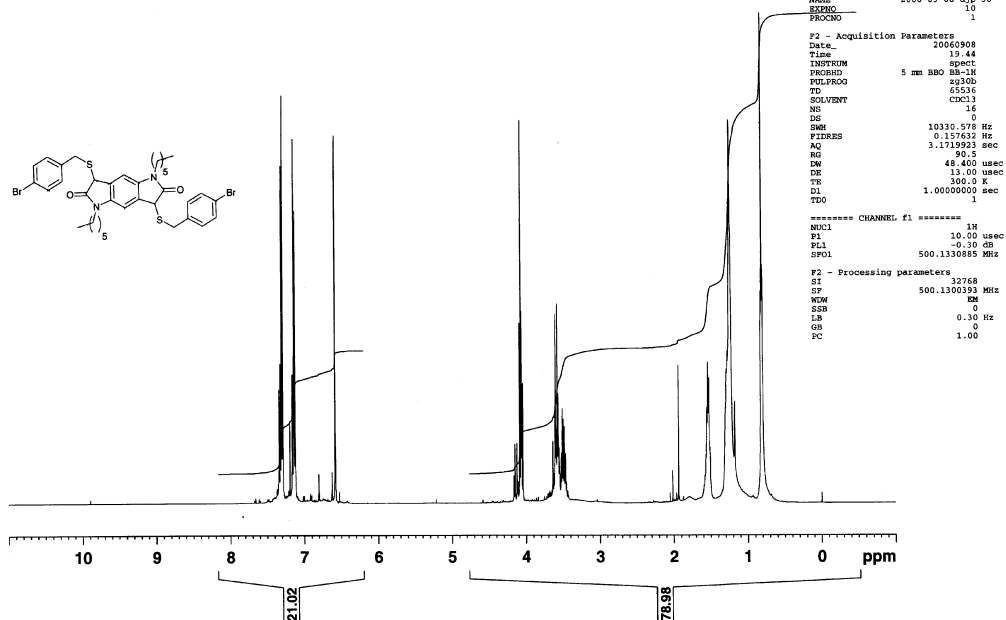
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SFOFFS2 0.00 Hz
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PCPD2 80.00 usec
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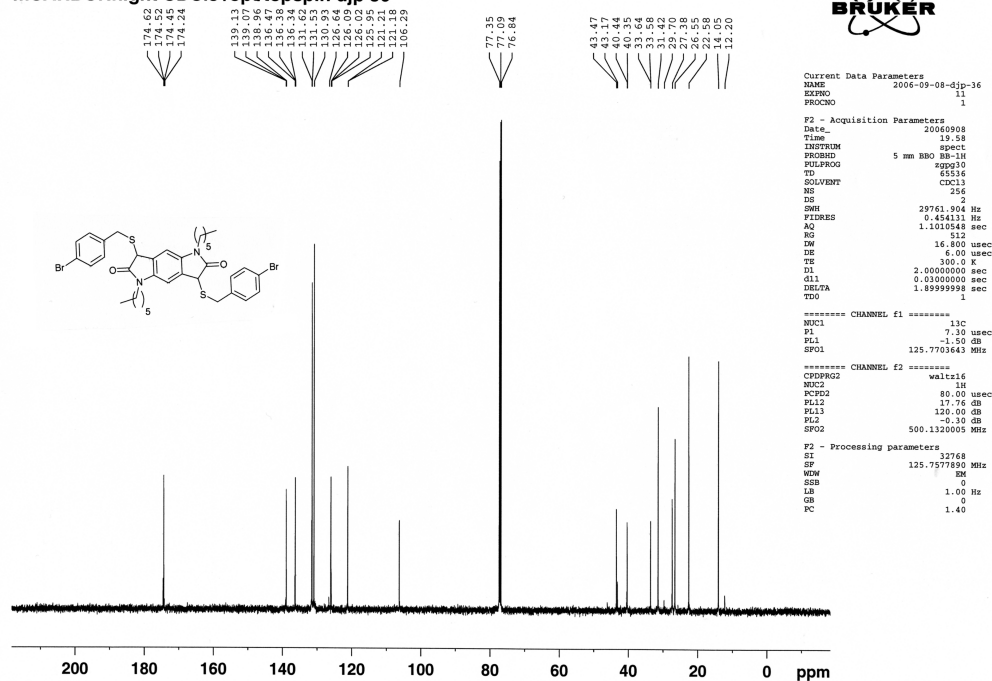
¹H NMR of 29

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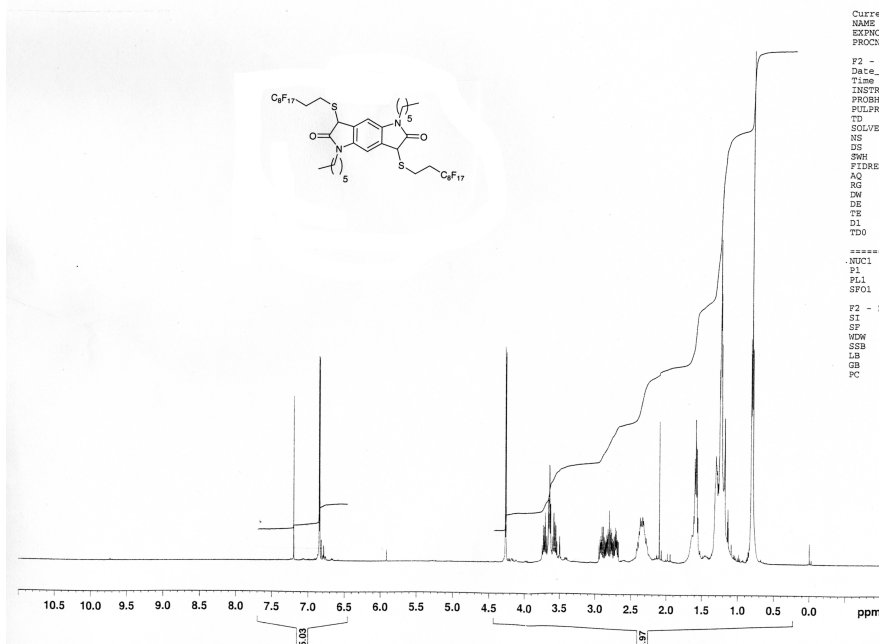
¹³C NMR of 29

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¹H NMR of 30

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BRUKER

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PROCNO 1

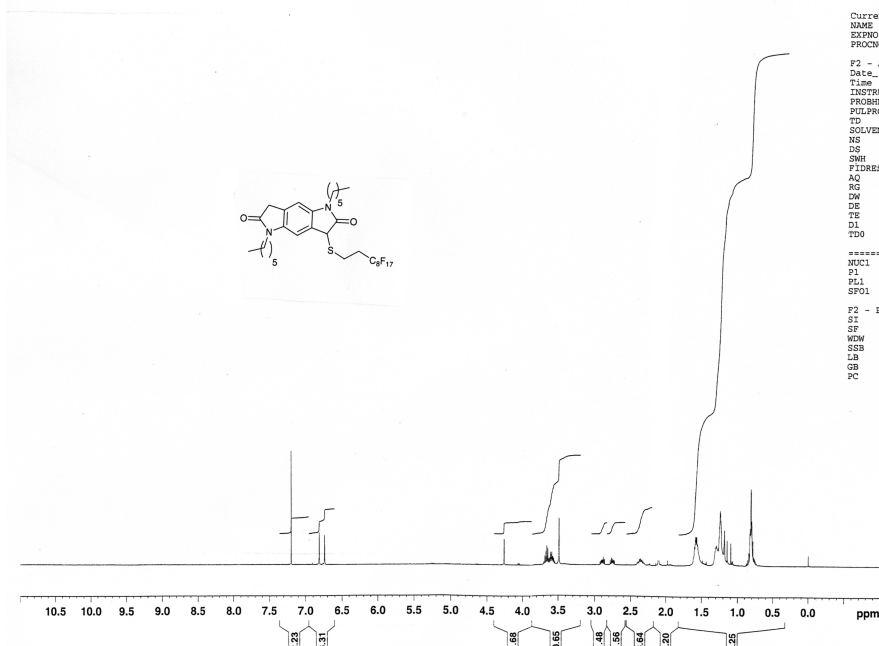
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¹H NMR of 32

mm4-84-2
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BRUKER

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PROCNO 1

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¹H NMR of 31

mm4-74-1
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