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

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Supporting Information

General considerations

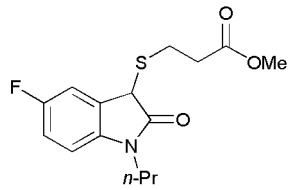
All experimients were performed under an atmosphere of N_2 using anhydrous solvents unless overwise stated. Reactions were carried out using oven dried glassware. THF was distilled from sodium/benzophenone, CH_2Cl_2 was distilled from CaH_2, NEt_3 was distilled from CaH_2 and stored over KOH under N_2. DMSO was distilled from CaH_2, stored over molecular sieves and under N_2. DMPU was distilled from CaH_2, stored over molecular sieves and under N_2.

^{1}H NMR and ^{13}C 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 (UV_{254}) were used for thin-layer chromatography and were visualised by UV or staining with $KMnO_4$.

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 µl, 2.13 mmol, 1.1 eq) in CH_2Cl_2 (6 ml) was added DMSO (302 µl, 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 µl, 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 $BF_3{\cdot}OEt_2$ (574 µl, 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.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (3H, t, J = 7.4 Hz, C*H*$_3$), 1.53 (2H, sextet, J = 7.4Hz, C*H*$_2$), 2.63 (3H, t, J = 7.1 Hz, SCH$_2$C*H*$_2$C=O), 2.77-2-86 (1H, m, 1H of C*H*$_2$S), 2.98-3.07 (1H, m, 1H of C*H*$_2$S), 3.58-3.69 (2H, m, C*H*$_2$N), 3.67 (3H, s, CO$_2$C*H*$_3$), 4.30 (1H, s, C*H*S), 6.74 (1H, dd, J = 4.1, 8.5 Hz, ArC*H*), 6.85 (1H, dt, J = 2.6, 8.5 Hz, ArC*H*), 7.15 (1H, ddd, J = 0.9, 2.6, 7.8 Hz, ArC*H*).

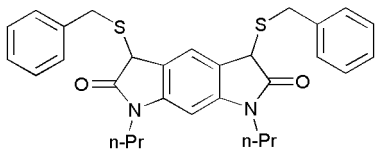
^{13}C NMR (75 MHz, $CDCl_3$) δ 11.6 (*C*H$_3$), 20.9 (*C*H$_2$), 25.2 (*C*H$_2$S), 34.5 (*C*H$_2$C=O), 42.1 (*C*H$_2$N), 45.0 (*C*HS), 52.1 (CO$_2$*C*H$_3$), 109.3 (Ar*C*H, d, J = 8.1 Hz), 113.5 (Ar*C*H, d, J = 25.0 Hz), 115.6 (Ar*C*H, d, J = 23.3 Hz), 127.6 (Ar*C*, d, J = 8.3 Hz), 139.6 (Ar*C*, d, J = 2.0 Hz), 159.4 (Ar*C*F, d, J = 243.6 Hz), 172.2 (*C*=O amide), 175.1 (*C*=O ester).

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

MS *m/z* (CI^+ mode) 312 ((M^+ + H), 24%), 194 (100%), 136 (14%), 108 (15%), 72 (19%), 60 (42%); $C_{15}H_{19}O_3NFS$ 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, $BF_3 \bullet Et_2O$ (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 × C*H*$_3$), 1.60-1.66 (4H, m, 2 × C*H*$_2$), 3.53- 3.58 (4H, m, 2 × NC*H*$_2$), 3.65 (1H, d, J = 13.2 Hz, 1H of C*H*$_2$S), 3.69 (1H, d, J = 13.1 Hz, 1H of C*H*$_2$S), 4.01 (1H, s, C*H*S), 4.03 (1H, s, C*H*S), 4.13 (1H, d, J = 13.2 Hz, 1H of C*H*$_2$S), 4.14

(1H, d, J = 13.1 Hz, 1H of C*H*$_2$S), 6.14 (1H, s, Ar*H*), 7.14-7.31 (11H, m, 1H Ar*H* and 10*H* of benzyl groups).

^{13}C NMR (75 MHz, $CDCl_3$) δ 11.7 (2 × *C*H_3), 21.2 (2 × *C*H_2), 34.6 (2 × *C*H_2S), 42.1 (2 × *C*H_2N), 43.0 (2 × *C*HS), 91.0 (Ar*C*H), 118.9 (2 × Ar*C*), 122.5 (2 × Ar*C*H), 127.5 (Ar*C*H), 127.6 (Ar*C*H), 128.7 (2 × Ar*C*H), 128.8 (2 × Ar*C*H), 129.5 (2 × Ar*C*H), 129.6 (Ar*C*H), 137.5 (Ar*C*), 137.6 (Ar*C*), 144.8 (Ar*C*), 144.9 (Ar*C*), 176.3 (2 x *C*=O),

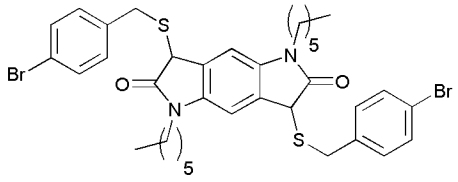
IR υ_{max}/(cm^{-1}) 3410, 3061, 2966, 1714 (C=O), 1614, 1487, 1372, 1208, 1129.

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

$C_{30}H_{33}O_2N_2S_2$ 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 CH_2Cl_2 (6 ml) at -78°C was added DMSO (330 µl, 4.65 mmol, 4 eq) in CH_2Cl_2 (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 CH_2Cl_2 (5 ml) was added. After a further 1 h at –78 °C, NEt_3 (1.62 ml, 11.62 mmol, 10 eq) was added and the reaction allowed to stir at room temperature for 1 h. CH_2Cl_2 (10 ml) was added to the reaction mixture and the organic layer washed with aqueous saturated $NaHCO_3$ (3 × 25 ml), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude *bis*–glyoxamide, which was used without further purification. CH_2Cl_2 (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 BF_3•OEt_2 (713 µl, 5.80 mmol, 10 eq) was also added. After stirring for 1 h, the reaction mixture was quenched with aqueous saturated $NaHCO_3$

(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-bromo-benzylsulfanyl)-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%).

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

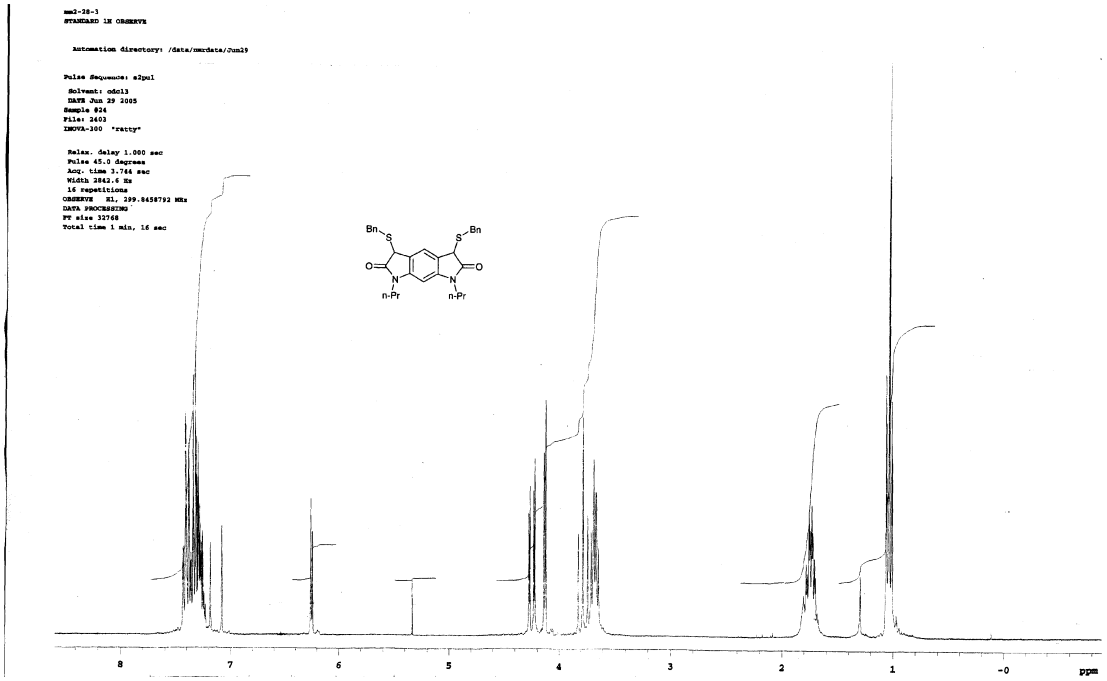
^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1 (4 × *C*H$_3$), 22.6 (4 × *C*H$_2$), 26.5 (4 × *C*H$_2$), 27.4 (4 × *C*H$_2$), 29.7 (4 × *C*H$_2$), 33.6 (4 × *C*H$_2$S), 40.4 (4 × *C*H$_2$N), 43.5 (4 × *C*HS), 106.9 (4 × Ar*C*H), 121.2 (4 × Ar*C*), 126.0 (4 × Ar*C*), 130.9 (4 × Ar*C*H), 131.5 (4 × Ar*C*H), 136.3 (4 × Ar*C*), 139.1 (4 × Ar*C*), 174.2 (4 × *C*=O).

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

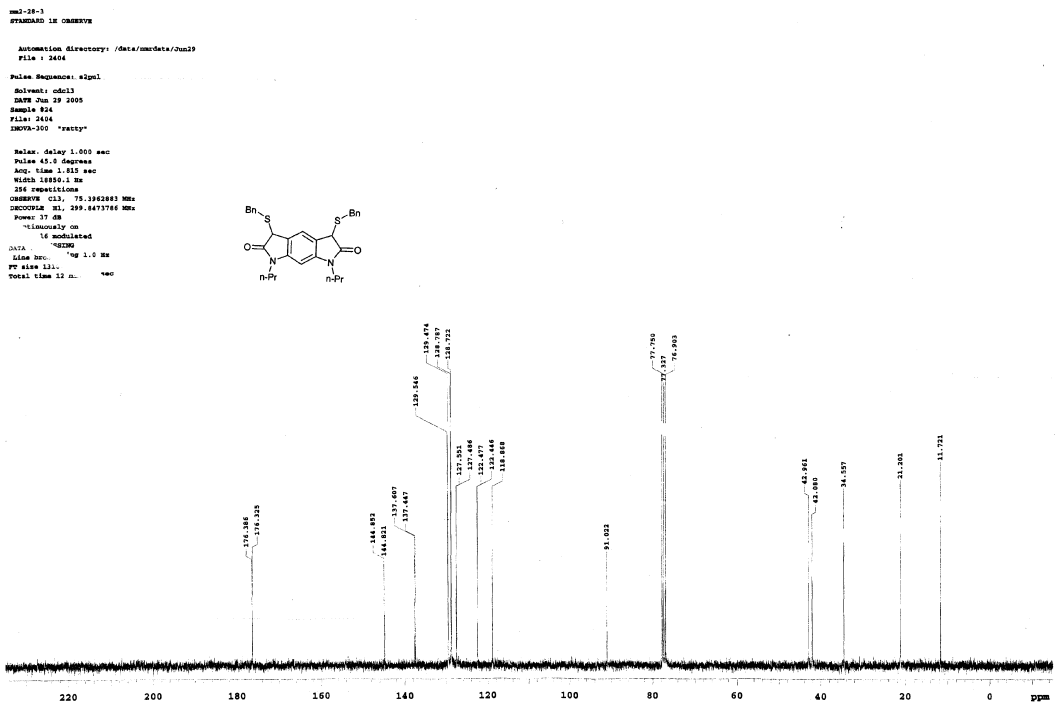
MS *m/z* (ES$^-$ mode) 757 ((M+H)$^+$, 43%), 569 (100%), 415.2 (35%), 339.7 (18%), 273 (10%).

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

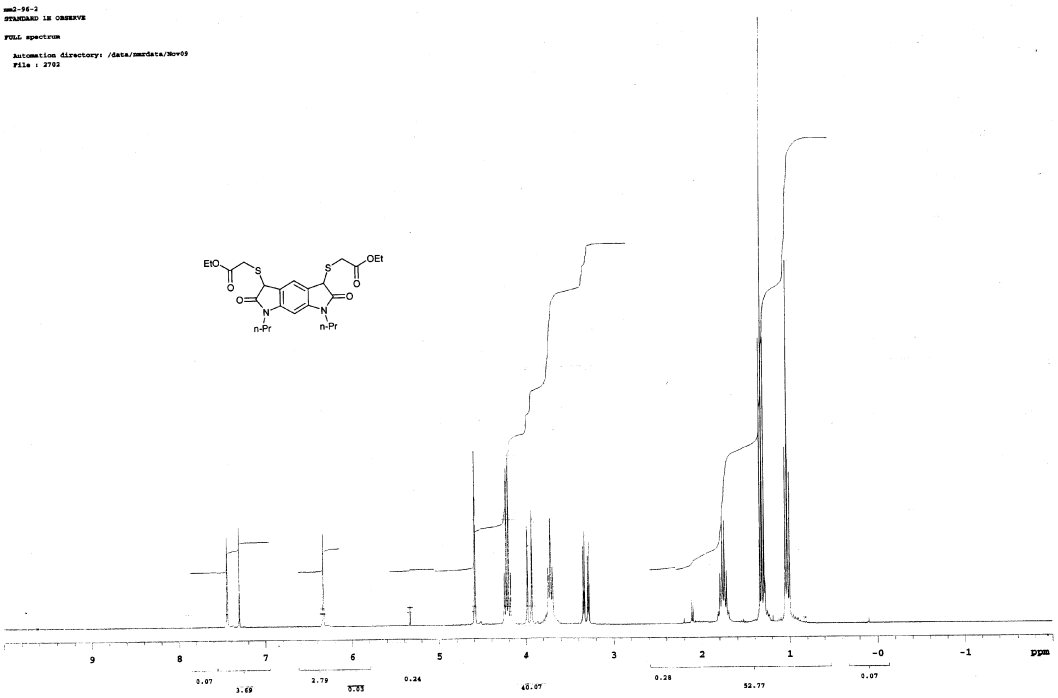
*^{1}H NMR of **19***



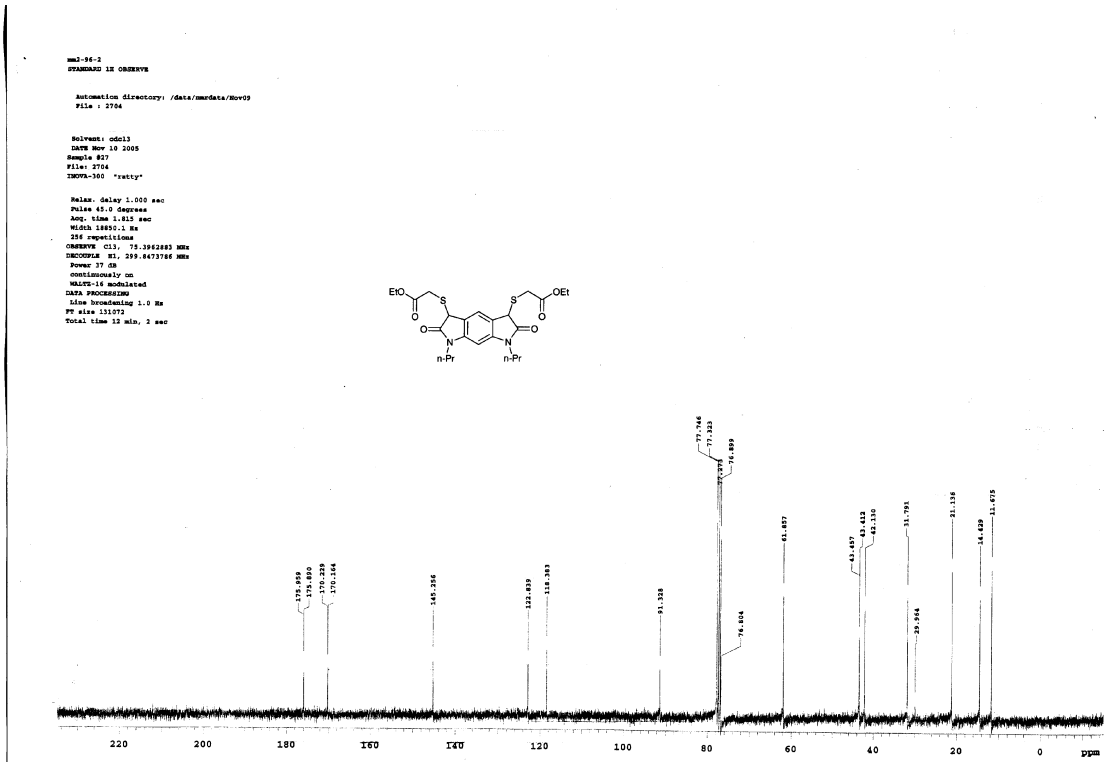
*^{13}C NMR of **19***



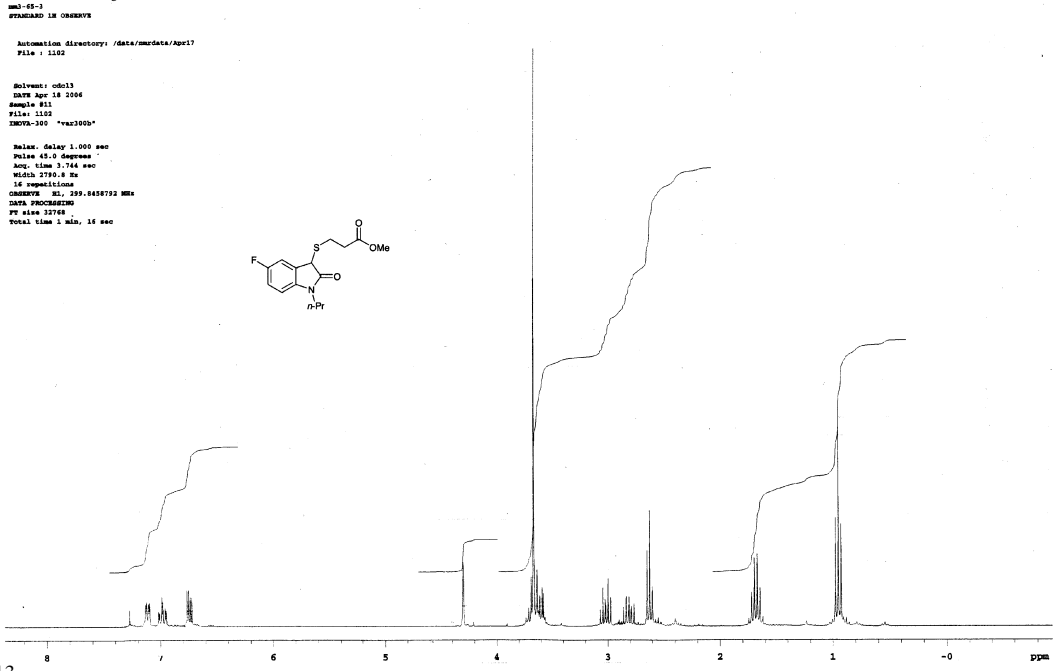
*[1]H NMR of **21***



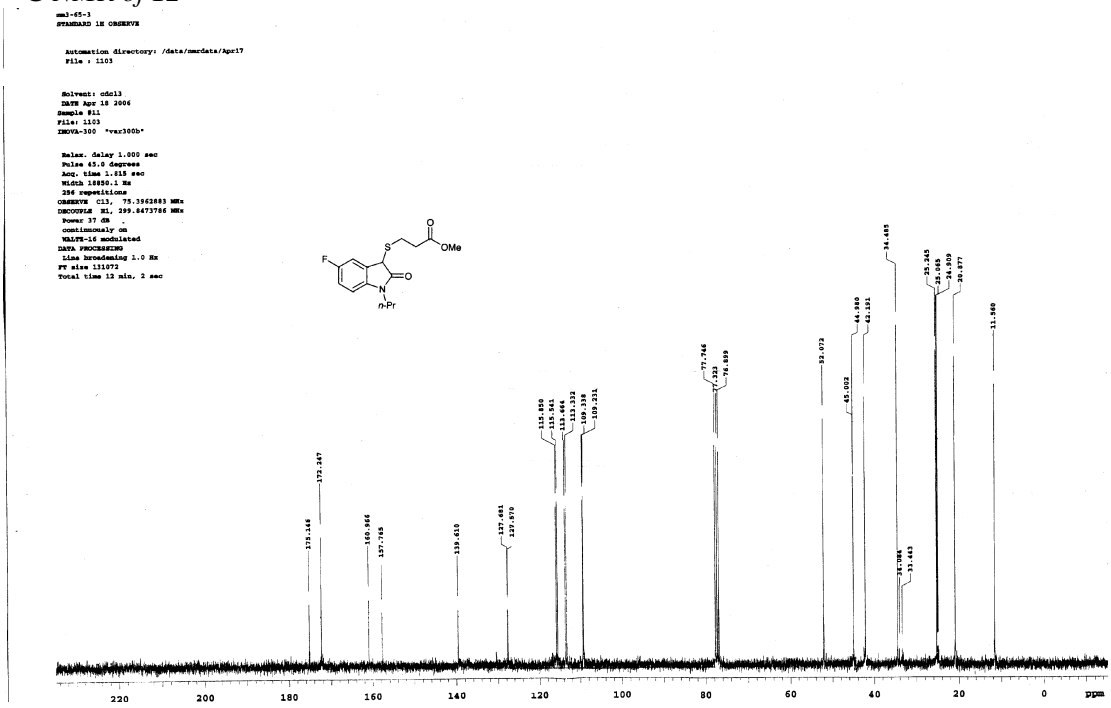
*[13]C NMR of **21***



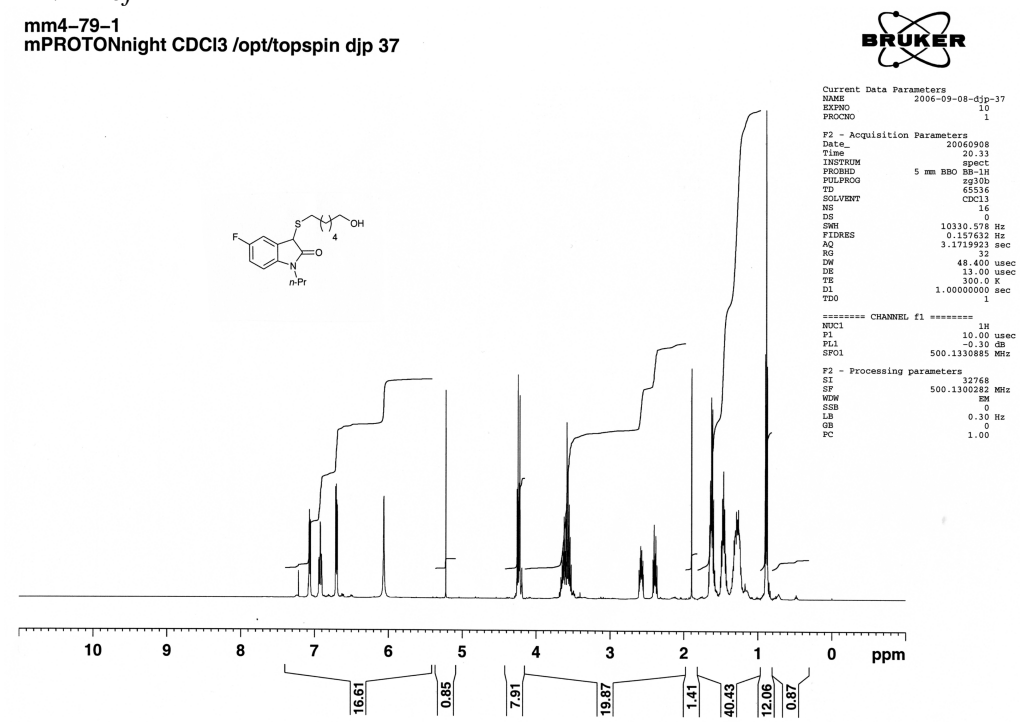
^{1}H NMR of **12**



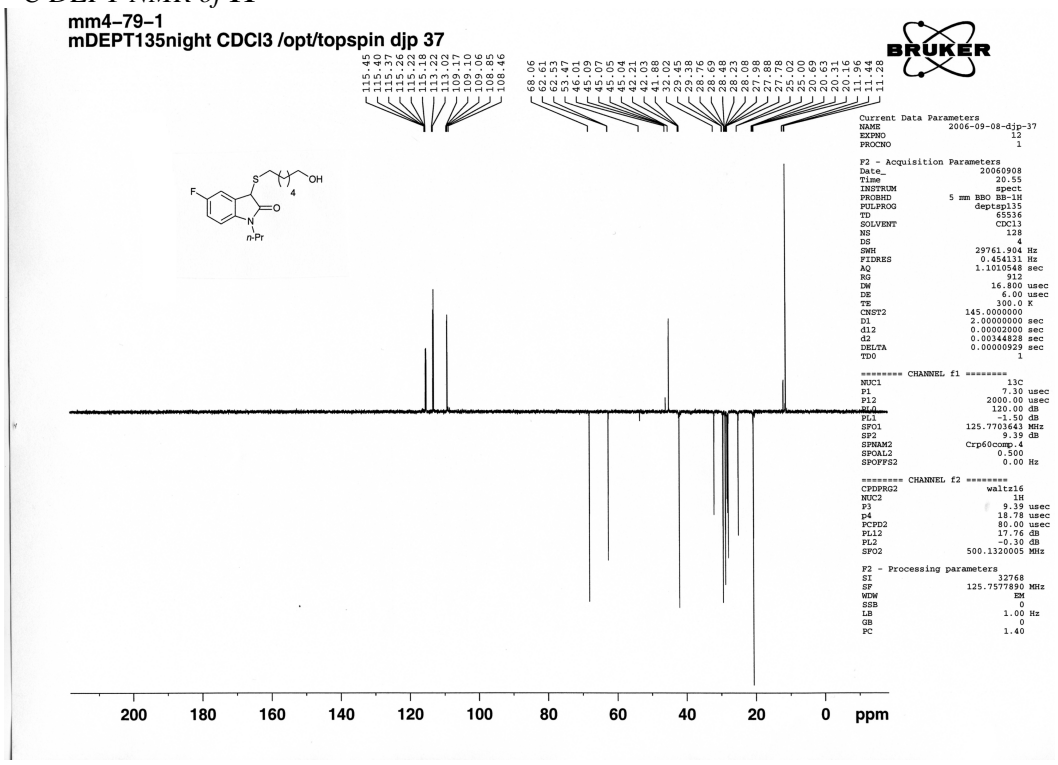
^{13}C NMR of **12**



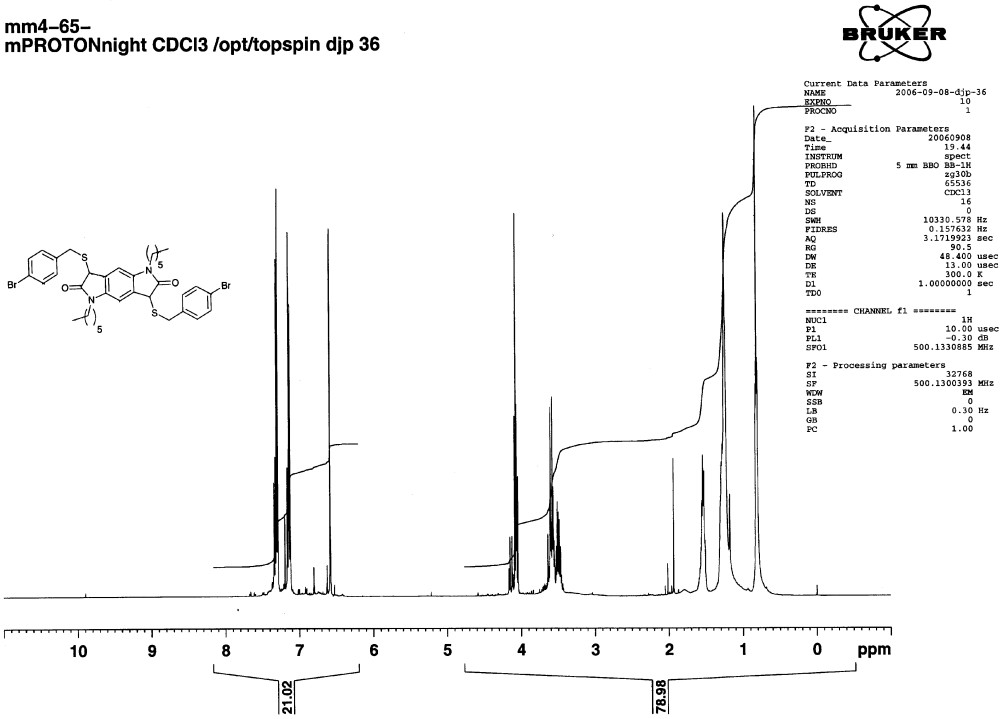
^{1}H NMR of ***11***



^{13}C DEPT NMR of ***11***



^{1}H NMR of ***29***



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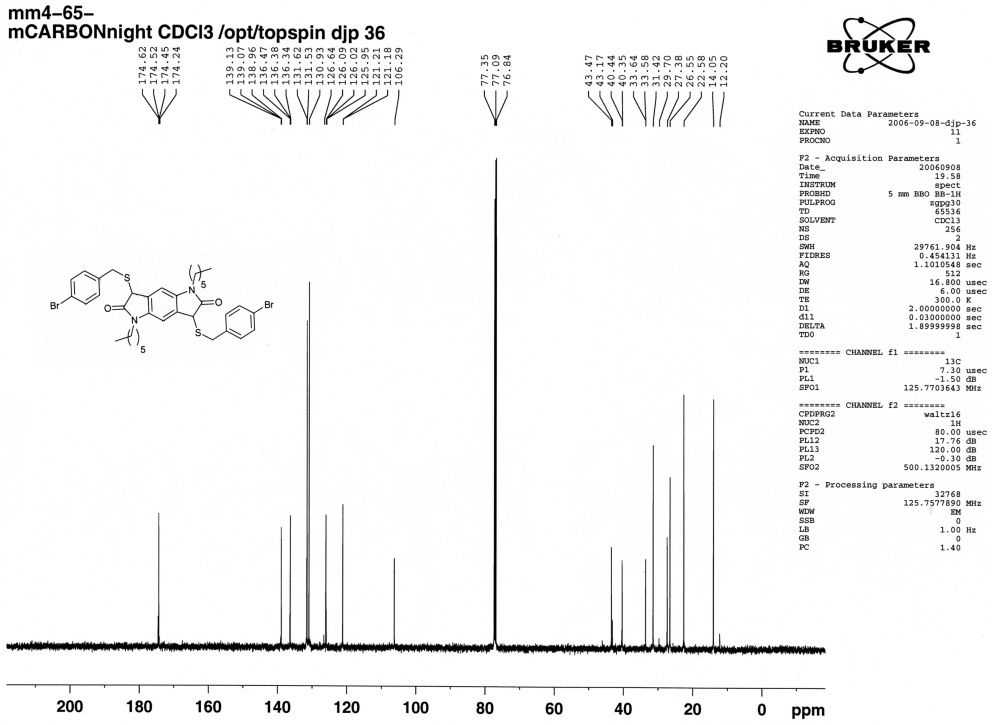
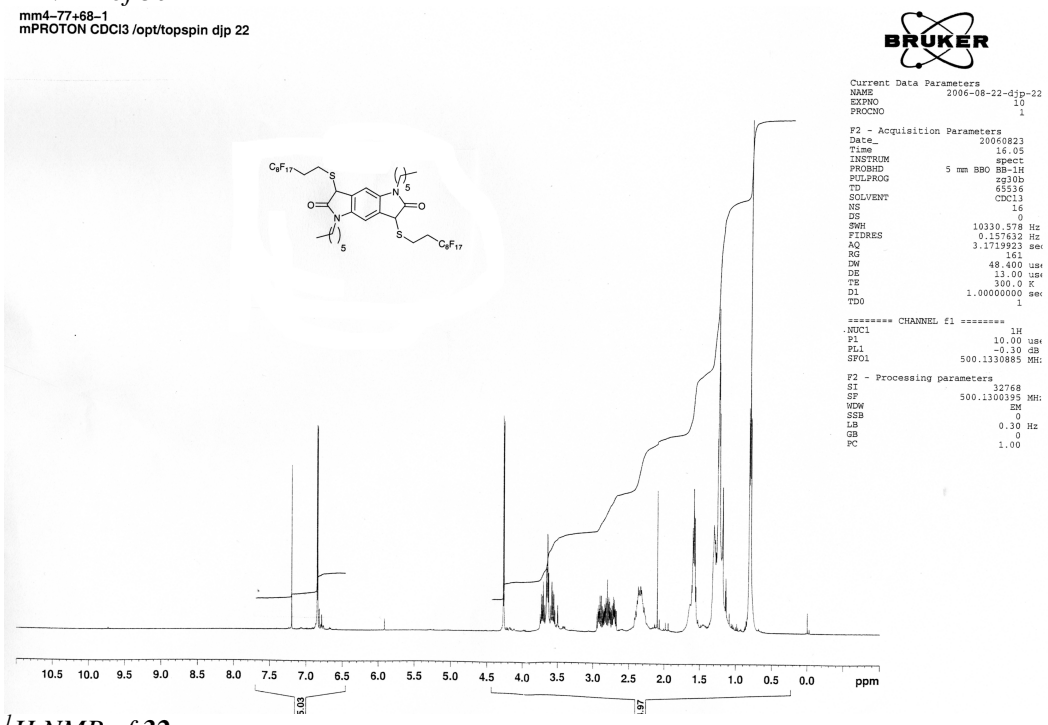
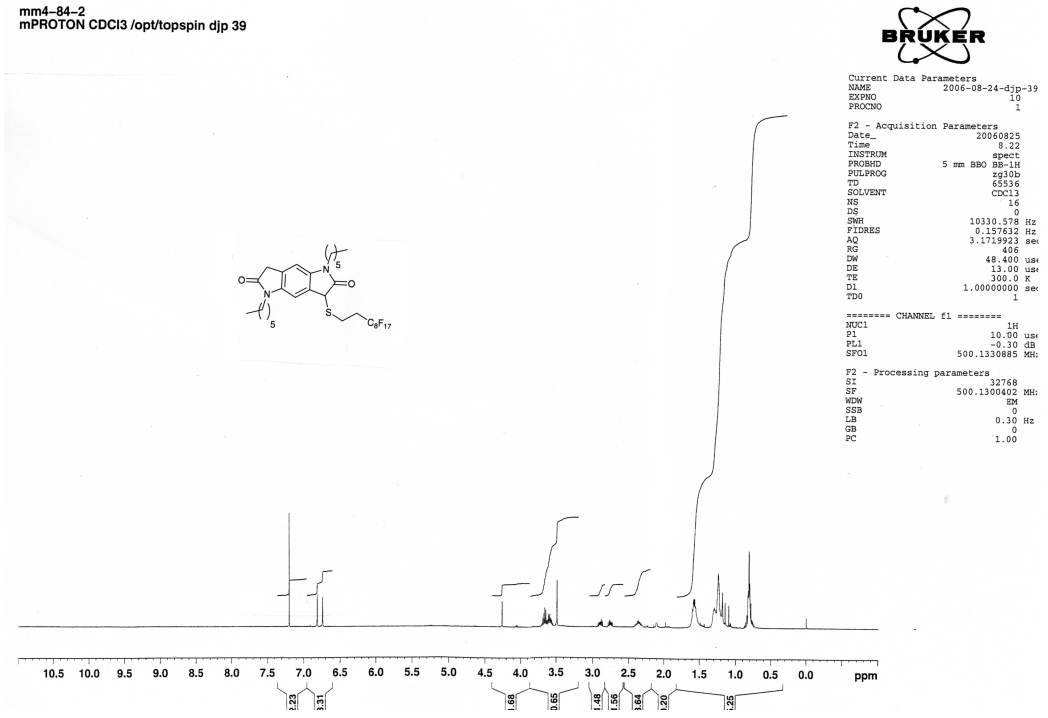


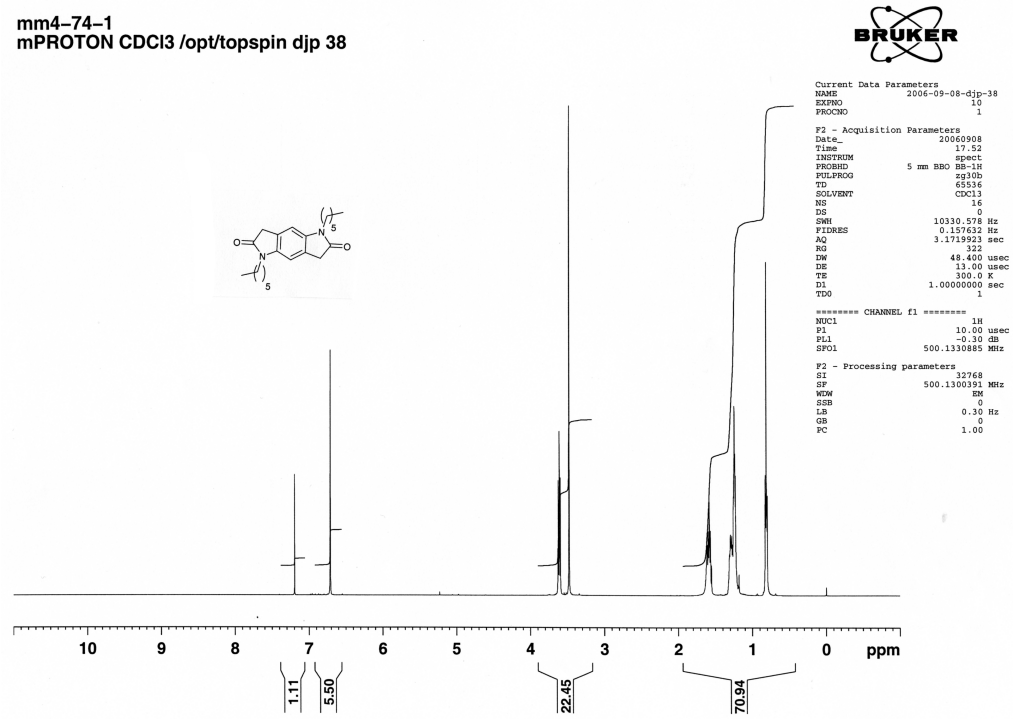
^1H NMR of ***30***



^1H NMR of ***32***



^{1}H NMR of ***31***



^{13}C NMR of ***31***