Reaction of heterocyclic enamines with nitrile-oxide and nitrilimine precursors

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Experimental Section

General Experimental Points

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1600 FTIR spectrophotometer. Mass spectra were recorded on a Fisons VG Platform II spectrometer and on a Micromass Q-TOF Micro spectrometer. NMR spectra were recorded on a Bruker DPX 400 spectrometer operating at 400 MHz for ^{1}H and at 100 MHz for ^{13}C at 25 °C. All chemical shifts are reported in ppm downfield from TMS. Coupling constants (*J*) are reported in Hz. Crystallographic data were recorded on a Nonius KappaCCD diffractometer equipped with an Oxford Cryosystem cryostat. The structures were solved by direct methods with additional light atoms found by Fourier methods. Hydrogen atoms were added at calculated positions and refined using a riding model. Anisotropic displacement parameters were used for all non-H atoms; H-atoms were given isotropic displacement parameters equal to 1.2 or 1.5 times the equivalent isotropic displacement parameter of the atom to which the H-atom is attached. Alkylidenepyrrolidines **1** and **24** were prepared according to a literature procedure;[1] compound **21** was prepared by a similar method. The nitrolic acids,[2] α-chlorooximes[3] and α-chlorohydrazones[4] used in this study were all prepared by standard methods.

Ethyl ester achiral + nitrolic acids

3-(6-Chloropyridin-3-yl)-7a-[3-(6-chloropyridin-3-yl)-1,2,4-oxadiazol-5-yl]-5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazole (3a)

6-Chloropyridin-3-nitrolic acid (**2a**) (2.0 eq., 201 mg, 1.0 mmol) was added to ethyl 2-pyrrolidin-2-ylidene acetate (**1**) (77.5 mg, 0.5 mmol) in dry benzene (10 mL) and the mixture was heated to reflux for 2 h. The reaction was concentrated in vacuo, and the crude residue was purified by flash column chromatography (eluent 1:1 petroleum ether/ethyl acetate) to give the *title compound* (154 mg, 76%) as a yellow solid, m.p. 162 – 163 °C ($CDCl_3$); $\nu_{max.}$ (KBr) 3060, 2980, 1597, 1584, 1382, 1134, 1113, 840 and 740 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 9.03 (1 H, dd, *J* 2.4, 0.6, pyridine 2-H), 8.71 (1 H, d, *J* 2.4, 0.6, pyridine 2-H), 8.27 (1 H, dd, *J* 8.4, 2.4, pyridine 4-H), 8.02 (1 H, dd, *J* 8.4, 2.4, pyridine 4-H), 7.40 (1 H, dd, *J* 8.4, 0.6, pyridine 5-H), 7.38 (1 H, dd, *J* 8.4, 0.6, pyridine 5-H), 3.43 – 3.40 (2 H, m, CH_2N), 2.88 (1 H, ddd, *J* 14.2, 10.7, 6.9, one of CH_2C), 2.72 (1 H, ddd, *J* 14.2, 7.1, 3.3, one of CH_2C), 2.15 – 2.07 (1 H, m, one of C*H*$_2$CH$_2$N) and 2.05 – 1.98 (1 H, m, one of C*H*$_2$CH$_2$N); δ_C (100 MHz; $CDCl_3$) 178.2 (C), 166.3 (C), 156.8 (C), 154.7 (C), 154.5 (C), 149.3 (CH), 149.2 (CH), 138.3 (CH), 137.9 (CH), 125.2 (CH), 125.1 (CH), 122.0 (C), 121.1 (C), 104.4 (C), 54.1 (CH_2), 37.7 (CH_2) and 25.6 (CH_2); *m/z* (TOF ES$^+$) 446 (MH^+ + CH_3CN, 67%), 444 (MH^+ + CH_3CN, 100), 405 (M^+, 16) and 403.0 (M^+, 25). Selected crystallographic data: $C_{17}H_{12}Cl_2N_6O_2$, FW =403.23, T = 150(2) K, λ = 0.71073 Å, Monoclinic, $P2_1/c$, *a* = 6.8900(3) Å, *b* = 13.7810(5) Å, *c* = 18.1120(9), β = 94.5030(10)°, V = 1714.45(13) Å^3, Z = 4, ρ(calc) = 1.562 Mg/m^3 , crystal size = 0.50 x 0.12 x 0.12 mm^3, reflections collected = 6624, independent reflections =3885, R(int)= 0.0569, parameters = 244, R_1 [$I > 2\sigma(I)$] = 0.0848, wR_2 [$I > 2\sigma(I)$] = 0.188, R_1 (all data) = 0.117, wR_2 (all data) = 0.205. Full crystallographic data for this compound have been deposited with the CCDC, reference number 731459, and can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif

3-(Pyridin-4-yl)-7a-(3-(pyridin-4-yl)-1,2,4-oxadiazol-5-yl)-5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazole (3b)

Pyridine-4-nitrolic acid (**2b**) (334 mg, 2 mmol) was added to ethyl 2-pyrrolidin-2-ylidene acetate (**1**) (155 mg, 1 mmol) in dry toluene (4 mL) and the mixture was heated in a CEM Discover microwave reactor for 10 min (100 W, 110 °C, 240 Psi). The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (eluent 20:20:1 petroleum ether/ethyl acetate/methanol) to give the *title compound* (193 mg, 58%) as a pale oil (Found: M^+, 334.1183; $C_{17}H_{14}N_6O_2$ requires M, 334.1178); $\nu_{max.}$ (neat) 2924, 1679, 1599, 1375, 1257, 835 and 799 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.73 - 8.67 (4 H, m), 7.92 (2 H, app. broad d, *J* 6.1), 7.63 – 7.59 (2 H, m), 3.53 – 3.29 (2 H, m, CH_2N), 2.89 (1 H, ddd, *J* 14.2, 10.8, 6.9, one of CH_2C), 2.73 (1 H, ddd, *J* 14.2 7.1, 3.1, one of CH_2C), 2.15 – 2.06 (1 H, m, one of C*H*$_2$CH$_2$N) and 2.05 – 1.99 (1H, m, one of C*H*$_2$CH$_2$N); δ_C (100 MHz; $CDCl_3$) 177.8 (C), 167.0 (C), 157.6 (C), 150.5 (4 x CH), 133.8 (C), 132.8 (C), 121.7 (2 x CH), 121.4 (2 x CH), 104.3 (C), 53.7 (CH_2), 37.2 (CH_2) and 25.0 (CH_2); *m/z* (TOF AP$^+$) 376 (MH^+ + CH_3CN, 100%) and 335 (MH^+, 45).

3-Methyl-7a-(3-methyl-1,2,4-oxadiazol-5-yl)-5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazole (3c)

Acetonitrolic acid (**2c**) (208 mg, 2 mmol) was added to ethyl 2-pyrrolidin-2-ylidene acetate (**1**) (155 mg, 1 mmol) in dry toluene (10 mL) and the mixture was heated under reflux for 2 h. The reaction mixture was concentrated *in vacuo* and the crude residue purified by flash column chromatography (eluent 1:1 petroleum ether/ethyl acetate) to give the

1. M. C. Elliott and S. V. Wordingham, *Synthesis*, 2006, 1162.
2. L. Oresmaa, H. Kotikoski, M. Haukka, J. Salminen, O. Oksala, E. Pohjala, E. Moilanen, H. Vapaatalo, P. Vainiotalo and P. Aulaskari, *J. Med. Chem.*, 2005, **48**, 4231.
3. K.C. Liu, B. R. Shelton and R. K. Howe, *J. Org. Chem.,* 1980, **45** , 3916.
4. H. V. Patel, K. A. Vyas, S. P. Pandey and P. S. Fernandes, *Tetrahedron*, 1996, **52**, 661.

title compound (135 mg, 65%) as a yellow oil; $\nu_{max.}$ (neat) 2982, 1622, 1561, 1436, 1396, 1302, 1105 and 853 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.45 (1 H, ddd, *J* 11.3, 6.9, 3.5, one of CH_2N), 3.18 (1 H, ddd, *J* 11.3, 9.5, 6.1, one of CH_2N), 2.62 (1 H, ddd, *J* 14.0, 9.4, 7.1, one of CH_2C), 2.46 (1 H, ddd, *J* 14.0, 7.5, 4.4, one of CH_2C), 2.36 (3 H, s, CH_3), 2.08 – 1.84 (2 H, m, CH_2CH_2N) and 1.96 (3 H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 177.4 (C), 167.3 (C), 155.7 (C), 102.4 (C), 50.9 (CH_2), 37.3 (CH_2), 24.8 (CH_2), 11.6 (CH_3) and 10.2 (CH_3); *m/z* (TOF EI^+) 208 (M^+, 22%), 178 (100), 111 (38) and 85 (95).

Ethyl 2-(3,4-dihydro-2H-pyrrol-5-yl)-2-(hydroxyimino)acetate (5)

Pyridine-4-nitrolic acid (**2b**) (334 mg, 2 mmol) was added to ethyl (2-pyrrolidin-2-ylidene acetate (**1**) (155 mg, 1 mmol) in dry benzene (10 mL) and the mixture was heated under reflux for 2 h. The reaction was concentrated in vacuo, and the crude residue was purified by flash column chromatography (2 : 1 petroleum ether : ethyl acetate) to give the *title compound* (65 mg, 35%) as a yellow oil; $\nu_{max.}$ (neat) 3546, 2988, 1739, 1608, 1291, 1205, 1029 and 946 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 4.33 (2 H, q, *J* 7.1, OCH_2), 3.89 (2 H, t, *J* 7.7, NCH_2), 3.14 (2 H, t, *J* 8.1, CH_2), 1.97 (2 H, app. quintet, *J* 7.9, CH_2) and 1.33 (3 H, t, *J* 7.1, CH_3); δ_C (100 MHz; $CDCl_3$) 167.8 (C), 164.5 (C), 143.1 (C), 61.3 (CH_2), 54.5 (CH_2), 36.0 (CH_2), 19.6 (CH_2) and 14.2 (CH_3); *m/z* (TOF AP^+) 248 ($MNa^+ + CH_3CN$, 61%), 185 (MH^+, 100) and 152 (38).

General Experimental Procedure – isoxazoles (10)

The alkylidenepyrrolidine **1** (155 mg, 1 mmol) in CH_2Cl_2 (5 mL) was added to a solution of α-chlorooxime **9** (2 mmol) in CH_2Cl_2 (5 mL). Triethylamine (250 mg, 2.5 mmol) was added dropwise and reaction mixture stirred at ambient temperature for 18 h. The crude reaction mixture was filtered through a short plug of silica gel to remove triethylamine hydrochloride, then concentrated *in vacuo* and purified as described below.

Ethyl 5-(3-(*N*'-hydroxybenzimidamido)propyl)-3-phenylisoxazole-4-carboxylate (10a)

The crude product was purified by flash column chromatography (eluent 2:1 petroleum ether/ethyl acetate) to give the *title compound* (267 mg, 68%) as a yellow oil (Found: M^+, 393.1690. $C_{22}H_{23}N_3O_4$ requires M, 393.1689); $\nu_{max.}$ (neat) 3372, 3063, 2980, 1722, 1627, 1447, 1306, 767 and 698 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.49 (2 H, dd, *J* 7.8, 1.7), 7.38 – 7.25 (8 H, m), 5.45 (1 H, broad s, NH), 4.09 (2 H, q, *J* 7.1, OCH_2), 3.09 – 2.94 (4 H, m, $CH_2CH_2CH_2N$), 1.79 (2 H, app. quintet, *J* 7.2, $CH_2CH_2CH_2N$) and 1.05 (3 H, t, *J* 7.1, OCH_2CH_3); δ_C (100 MHz; $CDCl_3$) 178.0 (C), 162.5 (C), 161.7 (C), 156.2 (C), 131.1 (C), 129.7 (CH), 129.6 (CH), 129.3 (2 x CH), 128.4 (2 x CH), 128.4 (2 x CH), 128.3 (C), 127.9 (2 x CH), 108.2 (C), 60.8 (CH_2), 42.7 (CH_2), 28.8 (CH_2), 24.5 (CH_2) and 13.8 (CH_3); *m/z* (TOF ES^+) 393 (M^+, 3%), 245 (12), 144 (26) and 104 (100).

Ethyl 5-(3-(2,6-dichloro-*N*'-hydroxybenzimidamido)propyl)-3-(2,6-dichlorophenyl)isoxazole-4-carboxylate (10b)

The crude product was purified by flash column chromatography (eluent 2:1 petroleum ether/ethyl acetate) to give the *title compound* (366 mg, 69%) as a colourless solid, m.p. 122 – 123 °C (Found: MH^+, 530.0182. $C_{22}H_{20}N_3O_4{}^{35}Cl_4$ requires M, 530.0208); $\nu_{max.}$ (neat) 3372, 2922, 1721, 1644, 1457, 1377, 1297, 910, 784 and 732 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.39 – 7.11 (6 H, m, aromatic CH), 5.57 (1 H, broad s, NH), 4.01 (2 H, q, *J* 7.1, OCH_2), 3.13 (2 H, t, *J* 7.4, $CH_2CH_2CH_2N$), 2.88 (2 H, poorly resolved app. q, *J* 5.1, $CH_2CH_2CH_2N$), 1.88 (2 H, app. quintet, *J* 7.0, $CH_2CH_2CH_2N$) and 0.90 (3 H, t, *J* 7.1, CH_2CH_3); δ_C (100 MHz; $CDCl_3$) 177.9 (C), 160.7 (C), 158.3 (C), 150.2 (C), 135.7 (2 x C-Cl), 135.0 (2 x C-Cl), 131.0 (CH), 130.8 (CH), 129.4 (C), 127.9 (C), 127.8 (2 x CH), 127.4 (2 x CH), 109.0 (C), 60.5 (CH_2), 41.7 (CH_2), 27.8 (CH_2), 24.1 (CH_2) and 13.4 (CH_3); *m/z* (TOF ES^+) 532 (MH^+, 100%) (isotopic distribution consistent with 4 x Cl).

Ethyl 5-(3-(2,4-dichloro-*N*'-hydroxybenzimidamido)propyl)-3-(2,4-dichlorophenyl)isoxazole-4-carboxylate (10c)

The crude residue was purified by flash column chromatography (eluent 2:1 petroleum ether/ethyl acetate) to give the *title compound* (179 mg, 67% using 0.5 mmol of compound **1**) as an orange oil (Found: MH^+, 530.0205. $C_{22}H_{20}N_3O_4{}^{35}Cl_4$ requires M, 530.0208); $\nu_{max.}$ (neat) 3383, 3090, 2980, 1723, 1634, 1594, 1433, 1372, 1308, 1246, 1102 and 825 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.43 (1 H, d, *J* 1.3), 7.39 (1 H, d, *J* 1.8), 7.31 – 7.21 (4 H, m), 5.52 (1 H, app. broad t, *J* 5.7, NH), 4.07 (2 H, q, *J* 7.1, OCH_2), 3.09 (2 H, t, *J* 7.4, $CH_2CH_2CH_2N$), 2.93 (2 H, app. q, *J* 6.5, CH_2N), 1.87 (2 H, app. quintet, *J* 7.2, $CH_2CH_2CH_2N$) and 1.01 (3 H, t, *J* 7.1, CH_2CH_3); δ_C (100 MHz; $CDCl_3$) 177.7 (C), 161.3 (C), 160.0 (C), 152.5 (C), 136.3 (C), 136.3 (C), 134.9 (C), 134.8 (C), 132.4 (CH), 131.8 (CH), 129.6 (CH), 129.3 (CH), 129.0 (C), 127.4 (CH), 127.2 (C), 127.0 (CH), 109.6 (C), 61.0 (CH_2), 42.1 (CH_2), 28.5 (CH_2), 24.3 (CH_2) and 13.7 (CH_3); *m/z* (TOF ES^+) 532 (MH^+, 100%) (isotopic distribution consistent with 4 x Cl).

Ethyl 5-(3-(*N*'-hydroxy-2-nitrobenzimidamido)propyl)-3-(2-nitrophenyl)isoxazole-4-carboxylate (10d)

The crude product was purified by flash column chromatography (eluent 2:1 petroleum ether/ethyl acetate) to give the *title compound* (135 mg, 56% using 0.5 mmol of compound **1**) as a yellow oil (Found: MH^+, 484.1479. $C_{22}H_{22}N_5O_8$ requires M, 484.1468); $\nu_{max.}$ (neat) 3382, 2980, 1718, 1637, 1529, 1348, 1315, 912 and 855 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.16 (1 H, dd, *J* 8.0, 1.3), 7.96 (1 H, dd, *J* 8.1, 1.0), 7.66 (1 H, app. td, *J* 7.5, 1.5), 7.62 – 7.57 (2 H, m), 7.52 (1 H, app. td, *J* 7.7, 1.5), 7.47 (1 H, dd, *J* 7.5, 1.4), 7.44 (1 H, dd, *J* 7.5, 1.4), 5.53 (1 H, broad s, NH), 4.04 (2 H, q, *J*

7.1, OCH_2), 3.10 (2 H, t, *J* 7.4, C*H*$_2$CH$_2$CH$_2$N), 2.95 (2 H, app. q, *J* 6.4, CH$_2$CH$_2$C*H*$_2$N), 1.89 (2 H, app. quintet, *J* 7.1, CH$_2$C*H*$_2$CH$_2$N) and 0.95 (3 H, t, *J* 7.1, OCH$_2$C*H*$_3$); δ_C (100 MHz; $CDCl_3$) 177.6 (C), 161.0 (C), 160.7 (C), 152.6 (C), 148.7 (C), 148.2 (C), 133.4 (CH), 133.2 (CH), 132.1 (CH), 131.8 (CH), 130.7 (CH), 130.5 (CH), 126.3 (C), 124.7 (C), 124.5 (CH), 124.4 (CH), 108.6 (C), 60.9 (CH_2), 42.5 (CH_2), 28.0 (CH_2), 24.2 (CH_2) and 13.5 (CH_3); *m/z* (TOF ES$^+$) 506 (MNa$^+$, 46%) and 484 (MH$^+$, 100).

3-(3-Nitrophenyl)-4-(pyrrolidin-2-ylidene)isoxazol-5(4*H*)-one (11)

The alkylidenepyrrolidine **1** (155 mg, 1 mmol) in CH_2Cl_2 (5 mL) was added to a solution of *N*-hydroxy-3-nitrobenzimidoyl chloride (**9e**) (400 mg, 2 mmol) in CH_2Cl_2 (5 mL). Triethylamine (250 mg, 2.5 mmol) was added dropwise and reaction mixture stirred at ambient temperature for 18 h. The crude reaction mixture was filtered through a short plug of silica gel to remove triethylamine hydrochloride, then concentrated *in vacuo* and purified by flash column chromatography (eluent 1:1 petroleum ether/ethyl acetate) to give *title compound* (193 mg, 41%) as a yellow solid, m.p. 144 – 146 °C (Found: M$^+$, 273.0750; $C_{13}H_{11}N_3O_4$ requires M, 273.0750); $\nu_{max.}$ (KBr disk) 3284, 2926, 1691, 1599 and 1351 cm^{-1}; δ_H (400 MHz; d$_6$-DMSO) 10.11 (1 H, broad s, NH), 8.38 (1 H, dd, *J* 8.2, 2.3), 8.31 (1 H, app. broad s), 8.00 (1 H, d, *J* 7.6), 7.80 (1 H, app. t, *J* 8.0), 3.62 (2 H, t, *J* 7.0, CH_2N), 2.53 – 2.47 (2 H, m, CH_2C) and 1.89 (2 H, app. quintet, *J* 7.2, C*H*$_2$CH$_2$N); δ_C (100 MHz; d$_6$-DMSO) 173.4 (C), 169.5 (C), 160.7 (C), 147.7 (C), 135.3 (CH), 132.1 (C), 130.2 (CH), 124.5 (CH), 123.4 (CH), 84.6 (C), 49.1 (CH_2), 33.3 (CH_2) and 20.3 (CH_2); *m/z* (TOF EI$^+$) 273 (M$^+$, 58%), 230 (100), 200 (93) and 184 (73).

Reactions with α-chlorohydrazones

General Experimental Procedure – Alkyl 3-aryl-3-(2-arylhydrazono)-2-(pyrrolidin-2-ylidene)propanoate

The alkylidenepyrrolidine **1** (39 mg, 0.25 mmol) in CH_2Cl_2 (5 mL) was added to a solution of α-chlorohydrazone **16** (0.5 mmol) in CH_2Cl_2 (5 mL). Triethylamine (75 mg, 0.75 mmol) was added dropwise and reaction mixture stirred at ambient temperature for 18 h. The crude reaction mixture was filtered through a short plug of silica gel to remove triethylamine hydrochloride, then concentrated *in vacuo* and purified as described below.

Ethyl 3-phenyl-3-(2-phenylhydrazono)-2-(pyrrolidin-2-ylidene)propanoate (17a)

The crude product was purified by flash column chromatography (eluent 2:1 petroleum ether/ethyl acetate) to give the *title compound* (32 mg, 37%) as a pale yellow solid, m.p. 122 – 124 °C (lit.[5] 127 - 129 °C) (Found: MH$^+$, 350.1854; $C_{21}H_{24}N_3O_2$ requires M, 350.1869); $\nu_{max.}$ (KBr) 3362, 3273, 1649, 1601, 1501, 1234, 1057 and 748 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.67 (1 H, broad s, NH), 7.84 (1 H, broad s, NH), 7.73 (2 H, app. broad d, *J* 7.1, aromatic CH), 7.32 (2 H app. broad t, *J* 7.4, aromatic CH), 7.29 – 7.24 (3 H, m, aromatic CH), 7.17 (2 H, app. broad d, *J* 7.5, aromatic CH), 6.84 (1 H, app. tt, *J* 7.4, 1.1, aromatic CH), 4.10 – 4.01 (2 H, m, OCH_2), 3.64 (2 H, app. td, *J* 7.2, 3.6, CH_2N), 2.42 (1 H, app. dt, *J* 17.2, 7.8, one of CH_2), 2.31 (1 H, app. dt, *J* 17.2, 7.9, one of CH_2), 1.93 (2 H, app. quintet, *J* 7.4, CH_2) and 1.03 (3 H, t, *J* 7.1, CH_3); *m/z* (TOF ES$^+$) 350 (MH$^+$, 100%).

Ethyl 3-(2-(4-chlorophenyl)hydrazono)-3-(4-nitrophenyl)-2-(pyrrolidin-2-ylidene)propanoate (17b) and ethyl [2-{1-(4-chlorophenyl)-3-(4-nitrophenyl)-5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]triazol-7a-yl}acetate (18b)

The crude product was purified by flash column chromatography (eluent 2:1 petroleum ether/ethyl acetate) to give compound **17b** (63 mg, 59%) as an orange solid and compound **18b** (10 mg, 10%) as a pale oil.

Data for compound 17b: Orange solid (63 mg, 59%), m.p. 151 – 153 °C (Found: MH$^+$, 429.1337. $C_{21}H_{22}N_4O_4{}^{35}Cl$ requires M, 429.1300); $\nu_{max.}$ (KBr) 3368, 3248, 1649, 1572, 1336, 1238, 852 and 821 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.69 (1 H, broad s, NH), 8.11 (2 H, d, *J* 8.9, aromatic CH), 7.97 (1 H, broad s, NH), 7.77 (2 H, d, *J* 8.9, aromatic CH), 7.18 (2 H, d, *J* 9.1, aromatic CH), 7.06 (2 H, d, *J* 9.1, aromatic CH), 4.04 – 3.92 (2 H, m, OCH_2), 3.61 (2 H, app. broad t, *J* 6.6, CH_2N), 2.32 (1 H, app. dt, *J* 17.2, 7.8, one of CH_2C), 2.20 (1 H, app. dt, *J* 17.2, 7.8, one of CH_2C), 1.91 (2 H, app. quintet, *J* 7.5, CH_2) and 0.96 (3 H, t, *J* 7.1, CH_3); *m/z* (TOF ES$^+$) 470 (MH$^+$ + CH_3CN, 68%) and 429 (MH$^+$, 100).

Data for compound 18b: Pale oil (10 mg, 10%) (Found: MH$^+$, 429.1346. $C_{21}H_{22}N_4O_4{}^{35}Cl$ requires M, 429.1300); $\nu_{max.}$ (KBr) 2924, 1726, 1591, 1489, 1340, 1091, and 856 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.24 (2 H, d, *J* 9.0, aromatic CH), 7.93 (2 H, d, *J* 9.0, aromatic CH), 7.23 (2 H, d, *J* 9.1, aromatic CH), 7.12 (2 H, d, *J* 9.0, aromatic CH), 4.09 – 3.96 (2 H, m, CH_2O), 3.44 (1 H, ddd, *J* 10.2, 7.5, 6.4, one of CH_2N), 3.26 (1 H, ddd, *J* 10.2, 6.8, 5.5, one of CH_2N), 3.06 (1 H, d, *J* 14.5, one of CH_2), 2.91 (1 H, d, *J* 14.5, one of CH_2), 2.65 – 2.52 (2 H, m, CH_2), 2.09 – 1.99 (1 H, m, one of CH_2), 1.93 – 1.82 (1 H, m, one of CH_2) and 1.18 (3 H, t, *J* 7.1, CH_3); δ_C (100 MHz; $CDCl_3$) 169.3 (C), 150.5 (C), 147.7 (C), 140.5 (C), 135.0 (C), 129.1 (CH), 127.3 (CH), 124.9 (C), 123.9 (CH), 115.6 (CH), 92.2 (C), 60.7 (CH_2), 53.2 (CH_2), 42.9 (CH_2), 37.2 (CH_2), 26.0 (CH_2) and 14.1 (CH_3); *m/z* (TOF ES$^+$) 429 (MH$^+$, 95%), 391 (100) and 341 (94).

Ethyl 3-(4-bromophenyl)-3-(2-(4-chlorophenyl)hydrazono)-2-(pyrrolidin-2-ylidene)propanoate 17c)

The crude product was purified by flash column chromatography (eluent 2:1 petroleum ether/ethyl acetate) to give the

title compound (59 mg, 51%) as a pale yellow solid, m.p. 134 – 136 °C (Found: MH^+, 462.0561. $C_{21}H_{22}N_3O_3{}^{35}Cl^{79}Br$ requires M, 462.0584); $\nu_{max.}$ (KBr) 3356, 3267, 1657, 1595, 1497, 1483, 1244, 1086, 824 and 783 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.68 (1 H, broad s, NH), 7.83 (1 H, broad s, NH), 7.58 (2 H, d, *J* 8.7, aromatic CH), 7.44 (2 H, d, *J* 8.7, aromatic CH), 7.21 (2 H, d, *J* 8.9, aromatic CH), 7.08 (2 H, d, *J* 8.9, aromatic CH), 4.11 – 4.00 (2 H, m, OCH_2), 3.65 (2 H, app. td, *J* 7.3, 2.4, CH_2N), 2.41 – 2.21 (2 H, m, CH_2), 1.94 (2 H, app. quintet, *J* 7.3, CH_2) and 1.03 (3 H, t, *J* 7.1, CH_3); δ_C (100 MHz; $CDCl_3$) 168.5 (C), 167.6 (C), 143.2 (C), 141.0 (C), 138.0 (C), 131.2 (CH), 129.0 (CH), 127.4 (CH), 124.3 (C), 121.6 (C), 114.1 (CH), 79.8 (C), 59.3 (CH_2), 47.7 (CH_2), 31.5 (CH_2), 21.5 (CH_2) and 14.5 (CH_3); *m/z* (TOF ES^+) 505 ($MH^+ + CH_3CN$, 41%) and 464 (MH^+, 100) (isotopic distribution consistent with 1 x Br and 1 x Cl).

Methyl 3-phenyl-3-(2-phenylhydrazono)-2-(pyrrolidin-2-ylidene)propanoate (22)

The crude product was purified by flash column chromatography (eluent 2:1 petroleum ether/ethyl acetate) to give the *title compound* (20 mg, 21% from 0.28 mmol of alkylidenepyrrolidine **21**) as a pale yellow solid, m.p. 165 – 170 °C (hexane/Et_2O) (Found: MH^+, 336.1718; $C_{20}H_{22}N_3O_2$ requires M, 336.1712); $\nu_{max.}$ (Nujol) 3389, 3273, 1653, 1601, 1575 and 1505 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.66 (1 H, broad s, NH), 7.86 (1 H, broad s, NH), 7.74 (2 H, d, *J* 7.3, aromatic CH), 7.33 (2 H app. t, *J* 7.5, aromatic CH), 7.29 – 7.23 (3 H, m, aromatic CH), 7.17 (2 H, d, *J* 7.6, aromatic CH), 6.84 (1 H, app. t, *J* 7.2, aromatic CH), 3.69 – 3.60 (2 H, m, CH_2N), 3.56 (3 H, s, OCH_3), 2.47 – 2.26 (2 H, m, CH_2), and 1.93 (2 H, app. quintet, *J* 7.6, CH_2); δ_C (100 MHz; $CDCl_3$) 169.7 (C), 168.1 (C), 145.3 (C), 141.5 (C), 139.5 (C), 129.6 (2 x CH), 128.7 (2 x CH), 128.0 (CH), 126.2 (2 x CH), 120.1 (CH), 113.5 (2 x CH), 80.4 (C), 51.4 (CH_3), 48.2 (CH_2), 31.9 (CH_2) and 22.0 (CH_2); *m/z* (TOF ES^+) 336 (MH^+, 100%) and 304 (20). Selected crystallographic data: $C_{20}H_{21}N_3O_2$, FW = 335.40, T = 150(2) K, λ = 0.71073 Å, Monoclinic, $P2_1/n$, *a* = 10.4390(7) Å, *b* = 8.2177(7) Å, *c* = 20.2299(13) Å, β = 102.142(4)°, V = 1696.6(2) $Å^3$, Z = 4, ρ(calc) = 1.313 Mg/m^3 , crystal size = 0.35 x 0.15 x 0.04 mm^3, reflections collected = 3780, independent reflections =2266, R(int)= 0.0557, parameters = 227, R_1 [$I > 2\sigma(I)$] = 0.059, wR_2 [$I > 2\sigma(I)$] = 0.124, R_1 (all data) = 0.092, wR_2 (all data) = 0.139. The low data to parameter ratio for this compound is due to the weakness of the data from the crystals which could only be obtained as thin plates. Full crystallographic data for this compound have been deposited with the CCDC, reference number 776572, and can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif

Achiral phenylsulfonylmethyl compounds

General Procedure 25a – h

Triethylamine (30 mg, 0.3 mmol) was added to a solution of (*Z*)-2-(phenylsulfonylmethylene)pyrrolidine (**24**) (56 mg, 0.25 mmol) and α-chlorooxime **9** (0.25 mmol) in dry CH_2Cl_2 (5 mL). The reaction mixture was heated under reflux for 18 h. The solution was then washed with water (3 x 15 mL), dried over magnesium sulfate and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (eluent 3:1 petroleum ether/ethyl acetate) to give compounds **25a** – **25h** as described below.

General Procedure 25i – j

A solution of the nitrolic acid (**2b** or **2d**) (0.25 mmol) and (*Z*)-2-(phenylsulfonylmethylene) pyrrolidine (**24**) (0.25 mmol) in dry toluene (5 mL) was heated under reflux for 2 h. The solvent was removed *in vacuo* and crude product purified by flash column chromatography on silica gel (eluent 2:1 petroleum ether/ethyl acetate) to give compounds **25i** or **25j**.

3-Phenyl-7a-(phenylsulfonylmethyl)-5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazole (25a)

The general procedure above gave the *title compound* (59 mg, 69%) as a yellow oil (Found: MH^+, 343.1121. $C_{18}H_{19}N_2SO_3$ requires M, 343.1116); $\nu_{max.}$(neat) 2974, 1593, 1562, 1447, 1371, 1308, 1143, 1082, 751 and 690 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.87 (2 H, d, *J* 7.1, aromatic CH), 7.56 (1 H, app. tt, *J* 7.4, 2.1, aromatic CH), 7.47 (2 H, app. t, *J* 7.6, aromatic CH), 7.36 – 7.30 (3 H, m, aromatic CH), 7.24 (2 H, app. broad tt, *J* 7.4, 1.3, aromatic CH), 3.69 (1 H, d, *J* 14.8, one of CH_2SO_2), 3.67 (1 H, d, *J* 14.8, one of CH_2SO_2), 3.21 – 3.01 (2 H, m, CH_2N), 2.73 (1 H, ddd, *J* 14.1, 11.7, 7.0, one of CH_2C), 2.38 (1 H, ddd, *J* 14.1, 7.1, 1.0, one of CH_2C), 1.89 – 1.79 (1 H, m, one of CH_2CH_2N) and 1.78 – 1.67 (1 H, m, one of CH_2CH_2N); δ_C (100 MHz; $CDCl_3$) 159.4 (C), 140.8 (C), 133.5 (CH), 130.9 (CH), 129.1 (2 x CH), 128.5 (2 x CH), 127.7 (2 x CH), 127.6 (2 x CH), 125.5 (C), 105.5 (C), 60.9 (CH_2), 52.8 (CH_2), 36.5 (CH_2) and 24.8 (CH_2); *m/z* (TOF ES^+) 343 (MH^+, 100%) and 224 (7).

3-(2,6-Dichlorophenyl)-7a-(phenylsulfonylmethyl)-5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazole (25b)

The general procedure above gave the *title compound* (76 mg, 75%) as a colourless oil (Found: M^+, 410.0271. $C_{18}H_{16}N_2SO_3{}^{35}Cl_2$ requires M, 410.0259); $\nu_{max.}$(neat) 2975, 1606, 1574, 1431, 1351, 1307, 1156, 1083 and 747 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.91 (2 H, app. broad d, *J* 7.1, aromatic CH), 7.59 (1 H, app. tt, *J* 7.4, 1.3, aromatic CH), 7.51 (2 H, app. broad t, *J* 7.5, aromatic CH), 7.31 – 7.24 (3 H, m, aromatic CH), 3.88 (1 H, d, *J* 14.6, one of CH_2SO_2), 3.56 (1 H, d, *J* 14.6, one of CH_2SO_2), 3.24 – 3.17 (1 H, m, one of CH_2N), 2.92 – 2.84 (1 H, m, one of CH_2N), 2.68 (1 H, d, *J* 14.4, 10.7, 8.0, one of CH_2C), 2.56 – 2.49 (1 H, m, one of CH_2C) and 1.97 – 1.88 (2 H, m, CH_2CH_2N); δ_C (100 MHz; $CDCl_3$) 153.9 (C), 140.5 (C), 136.3 (C), 133.8 (CH), 132.1 (CH), 129.1 (2 x CH), 128.3 (2 x CH), 128.0 (2 x

CH), 125.0 (C), 106.1 (C), 62.5 (CH_2), 50.8 (CH_2), 36.8 (CH_2) and 25.5 (CH_2); *m/z* (TOF ES^+) 410 (M^+, 2%), 375 (8), 255 (36) and 173 (100) (isotopic distribution of peaks with *m/z* > 254 consistent with 2 x Cl).

3-(2,4-Dichlorophenyl)-7a-(phenylsulfonylmethyl)-5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazole (25c)

The general procedure above gave the *title compound* (45 mg, 44%) as a colourless oil (Found: MH^+, 411.0320. $C_{18}H_{16}N_2SO_3{}^{35}Cl_2$ requires M, 411.0337); $\nu_{max.}$(neat) 2974, 1584, 1480, 1447, 1359, 1157, 1083, 883 and 830 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.89 (2 H, app. broad d, *J* 7.2, aromatic CH), 7.60 (1 H, app. tt, *J* 7.4, 1.2, aromatic CH), 7.51 (2 H, app. broad t, *J* 7.6, aromatic CH), 7.39 (1 H, d, *J* 1.8, aromatic CH), 7.16 (1 H, dd, *J* 8.4, 1.8, aromatic CH), 7.13 (1 H, d, *J* 8.4, aromatic CH), 3.71 (1 H, d, *J* 14.7, one of CH_2SO_2), 3.64 (1 H, d, *J* 14.7, one of CH_2SO_2), 3.03 – 2.99 (2 H, m, CH_2N), 2.68 (1 H, ddd, *J* 14.2, 11.5, 7.0, one of CH_2C), 2.41 (1 H, ddd, *J* 14.2, 7.3, 2.1, one of CH_2C) and 1.92 – 1.70 (2 H, m, CH_2CH_2N); δ_C (100 MHz; $CDCl_3$) 156.5 (C), 140.8 (C), 137.2 (C), 134.7 (C), 133.7 (CH), 132.5 (CH), 130.7 (CH), 129.2 (2 x CH), 127.9 (2 x CH), 127.2 (CH), 123.3 (C), 105.5 (C), 61.7 (CH_2), 52.0 (CH_2), 37.1 (CH_2) and 24.9 (CH_2); *m/z* (TOF ES^+) 411 (MH^+, 100%) (isotopic distribution consistent with 2 x Cl).

3-(3-Nitrophenyl)-7a-(phenylsulfonylmethyl)-5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazole (25e)

The general procedure above gave the *title compound* (74 mg, 76%) as a yellow oil (Found: M^+, 387.0886. $C_{18}H_{17}N_3O_5S$ requires M, 387.0889); $\nu_{max.}$ (neat) 2974, 1593, 1531, 1350, 1308, 1142, 1084, 739 and 688 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.19 (1 H, ddd, *J* 8.2, 2.3, 1.0, aromatic CH), 8.06 (1 H, app. t, *J* 1.9, aromatic CH), 7.88 (2 H, app. broad d, *J* 7.1, aromatic CH), 7.81 (1 H, app. dt, *J* 7.8, 1.3, aromatic CH), 7.58 (1 H, app. tt, *J* 7.4, 1.3, aromatic CH), 7.54 – 7.46 (3 H, m, aromatic CH), 3.69 (2 H, app. s, CH_2SO_2), 3.19 – 3.07 (2 H, m, CH_2N), 2.78 (1 H, ddd, *J* 14.2, 11.8, 6.9, one of CH_2C), 2.41 (1 H, ddd, *J* 14.2, 7.3, 1.2, one of CH_2C), 1.95 – 1.86 (1 H, m, one of CH_2CH_2N) and 1.82 – 1.71 (1 H, m, one of CH_2CH_2N); δ_C (100 MHz; $CDCl_3$) 157.8 (C), 148.3 (C), 140.7 (C), 133.9 (CH), 133.4 (CH), 130.0 (CH), 129.4 (2 x CH), 127.7 (2 x CH), 125.5 (CH), 122.4 (CH), 106.8 (C), 60.8 (CH_2), 53.2 (CH_2), 36.7 (CH_2) and 25.0 (CH_2); *m/z* (TOF EI^+) 387 (M^+, 7%), 346 (25), 232 (100), 185 (98) and 102 (99).

3-(4-Fluorophenyl)-7a-(phenylsulfonylmethyl)-5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazole (25f)

The general procedure above gave the *title compound* (76 mg, 73% from 0.29 mmol of **24**) as a colourless solid, m.p. 134 – 136 °C (Found: MH^+, 361.1035. $C_{18}H_{18}N_2SO_3F$ requires M, 361.1022); $\nu_{max.}$ (Nujol) 1587, 1447, 1373, 1306, 1143, 838 and 752 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.87 (2 H, app. broad d, *J* 7.1, aromatic CH), 7.58 (1 H, app. tt, *J* 7.4, 1.3, aromatic CH), 7.48 (2 H, app. broad t, *J* 7.6, aromatic CH), 7.35 (2 H, app. dd, *J* 8.8, 5.4, aromatic CH), 6.95 (2 H, app. t, *J* 8.8, aromatic CH), 3.66 (2 H, app. s, CH_2SO_2), 3.13 – 3.07 (2 H, m, CH_2N), 2.73 (1 H, ddd, *J* 14.1, 11.7, 7.0, one of CH_2C), 2.38 (1 H, ddd, *J* 14.1, 7.2, 1.6, one of CH_2C), 1.89 – 1.82 (1 H, m, one of CH_2CH_2N) and 1.80 – 1.70 (1 H, m, one of CH_2CH_2N); δ_C (100 MHz; $CDCl_3$) 164.2 (C, $^1J_{C\text{-}F}$ 252), 158.6 (C), 140.8 (C), 133.5 (CH), 129.9 (2 x CH, $^3J_{C\text{-}F}$ 8.6), 129.1 (2 x CH), 127.6 (2 x CH), 121.8 (C, $^4J_{C\text{-}F}$ 3.3), 115.7 (2 x CH, $^2J_{C\text{-}F}$ 22.0), 105.6 (C), 60.8 (CH_2), 52.8 (CH_2), 36.5 (CH_2) and 24.9 (CH_2); *m/z* (TOF ES^+) 361 (MH^+, 100%).

3-(4-Bromophenyl)-7a-(phenylsulfonylmethyl)-5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazole (25g)

The general procedure above gave the *title compound* (61 mg, 66% from 0.22 mmol of **24**) as a waxy oil (Found: MH^+, 421.0242. $C_{18}H_{18}N_2SO_3{}^{79}Br$ requires M, 421.0222); $\nu_{max.}$(neat) 2976, 1604, 1510, 1308, 1157, 845 and 688 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.87 (2 H, app. broad d, *J* 7.2, aromatic CH), 7.9 (1 H, app. tt, *J* 7.4, 1.2, aromatic CH), 7.49 (2 H, app. broad t, *J* 7.7, aromatic CH), 7.40 (2 H, d, *J* 8.5, aromatic CH), 7.21 (2 H, d, *J* 8.5, aromatic CH), 3.66 (2 H, app. s, CH_2SO_2), 3.09 (2 H, app. dd, *J* 9.7, 4.0, CH_2N), 2.74 (1 H, ddd, *J* 14.2, 11.7, 7.0, one of CH_2C), 2.38 (1 H, ddd, *J* 14.2, 7.0, 1.6, one of CH_2C), 1.91 – 1.82 (1 H, m, one of CH_2CH_2N) and 1.81 – 1.71 (1 H, m, one of CH_2CH_2N); δ_C (100 MHz; $CDCl_3$) 158.8 (C), 140.9 (C), 133.7 (CH), 132.0 (2 x CH), 129.3 (2 x CH), 129.3 (2 x CH), 127.7 (2 x CH), 125.5 (C), 124.7 (C), 106.0 (C), 60.9 (CH_2), 53.0 (CH_2), 36.6 (CH_2) and 25.0 (CH_2); *m/z* (TOF ES^+) 423 (MH^+, 100%), 421 (MH^+, 92).

7a-(Phenylsulfonylmethyl)-3-(thien-2-yl)-5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazole (25h)

The general procedure above gave the *title compound* (56 mg, 78%) as a yellow oil (Found: M^+, 348.0590. $C_{16}H_{16}N_2S_2O_3$ requires M, 348.0602); $\nu_{max.}$(neat) 2952, 1585, 1513, 1440, 1367, 1307, 1156 and 1082 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.87 (2 H, app. broad d, *J* 7.1, aromatic CH), 7.56 (1 H, app. tt, *J* 7.4, 1.3, aromatic CH), 7.48 (2 H, app. tt, *J* 7.5, 1.7, aromatic CH), 7.32 (1 H, dd, *J* 5.0, 1.2, thiophene 5-H), 7.06 (1 H, dd, *J* 3.7, 1.2, thiophene 3-H), 6.95 (1 H, dd, *J* 5.0, 3.7, thiophene 4-H), 3.69 (1 H, d, *J* 14.9, one of CH_2SO_2), 3.63 (1 H, d, *J* 14.9, one of CH_2SO_2), 3.34 – 3.26 (1 H, m, one of CH_2N), 3.12 (1 H, app. dt, *J* 11.2, 5.7, one of CH_2N), 2.72 (1 H, ddd, *J* 14.2, 11.6, 7.0, one of CH_2C), 2.39 (1 H, app. broad dd, *J* 14.2, 6.9, one of CH_2C) and 1.90 – 1.71 (2 H, m, CH_2CH_2N); δ_C (100 MHz; $CDCl_3$) 155.2 (C), 140.8 (C), 133.7 (CH), 129.6 (CH), 129.3 (CH), 129.2 (2 x CH), 127.8 (2 x CH), 127.6 (CH), 127.4 (C), 105.9 (C), 61.1 (CH_2), 53.3 (CH_2), 36.5 (CH_2) and 25.1 (CH_2); *m/z* (TOF EI^+) 348 (M^+, 8%), 193 (99), 158 (98), 108 (99) and 77 (100).

7a-(Phenylsulfonylmethyl)-3-(pyridin-4-yl)-5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazole (25i)

The general procedure above gave the *title compound* (58 mg, 68%) as a pale oil (Found: MH^+, 343.1074.

$C_{17}H_{18}N_3SO_3$ requires M, 344.1069); $\nu_{max.}$ (neat) 3059, 1590, 1447, 1374, 1307 and 1143 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.56 (2 H, d, *J* 6.0, pyridine 2-H and 6-H), 7.87 (2 H, broad app. d, *J* 7.3, aromatic CH), 7.59 (1 H, app. tt, *J* 7.4, 1.9, aromatic CH), 7.50 (2 H, app. t, *J* 7.6, aromatic CH), 7.26 (2 H, d, *J* 6.0, pyridine 3-H and 5-H), 3.69 (1 H, d, *J* 14.8, one of CH_2SO_2), 3.64 (1 H, d, *J* 14.8, one of CH_2SO_2), 3.20 – 3.10 (2 H, m, CH_2N), 2.75 (1 H, ddd, *J* 14.2, 11.7, 6.9, one of CH_2C), 2.42 (1 H, ddd, *J* 14.2, 7.3, 1.7, one of CH_2C), 1.95 – 1.86 (1 H, m, one of CH_2CH_2N) and 1.82 – 1.68 (1 H, m, one of CH_2CH_2N); δ_C (100 MHz; $CDCl_3$) 157.8 (C), 150.3 (2 x CH), 140.8 (C), 133.8 (CH), 133.4 (C), 129.3 (2 x CH), 127.7 (2 x CH), 121.5 (2 x CH), 106.9 (C), 61.0 (CH_2), 53.1 (CH_2), 36.7 (CH_2) and 25.0 (CH_2); *m/z* (TOF ES^+) 385 ($MH^+ + CH_3CN$, 41%) and 344 (MH^+, 100%).

7a-(Phenylsulfonylmethyl)-3-(pyridin-3-yl)-5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazole (25j)

The general procedure above gave the *title compound* (49 mg, 58%) as a pale oil (Found: M^+, 343.0994. $C_{17}H_{17}N_3SO_3$ requires M, 343.0991); $\nu_{max.}$ (neat) 2962,, 2926, 1550, 1447, 1378, 1261, 1083, 1020, 800 and 687 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.58 (1 H, app. broad d, *J* 4.9, pyridine 6-H), 8.47 (1 H, d, *J* 1.2, pyridine 2-H), 7.88 (2 H, d, *J* 7.2, aromatic CH), 7.75 (1 H, app. dt, *J* 7.9, 1.6, pyridine 4-H), 7.61 (1 H, t, *J* 7.4, aromatic CH), 7.51 (2 H, app. t, *J* 7.3, aromatic CH), 7.23 (1 H, dd, *J* 7.9, 4.9, pyridine 5-H), 3.68 (2 H, app. s, CH_2SO_2), 3.13 (2 H, app. dd, *J* 10.4, 4.3, CH_2N), 2.77 (1 H, ddd, *J* 14.2, 11.8, 6.9, one of CH_2C), 2.41 (1 H, ddd, *J* 14.2, 7.1, 1.7, one of CH_2C), 1.95 – 1.86 (1 H, m, one of CH_2CH_2N) and 1.84 – 1.70 (1 H, m, one of CH_2CH_2N); δ_C (100 MHz; $CDCl_3$) 157.5 (C), 151.8 (CH), 148.7 (CH), 140.9 (C), 135.1 (CH), 133.8 (CH), 129.3 (2 x CH), 127.7 (2 x CH), 123.5 (CH), 122.0 (C), 106.2 (C), 60.9 (CH_2), 53.0 (CH_2), 36.6 (CH_2) and 25.0 (CH_2); *m/z* (TOF EI^+) 343 (M^+, 57%), 302 (47), 160 (100) and 105 (95).

Chiral phenylsulfonylmethyl compounds

(*S*,*Z*)-Ethyl 5-(phenylsulfonylmethylene)pyrrolidine-2-carboxylate (26)

A solution of *n*-BuLi (1.6M in Hexanes, 3.8 mL, 6.1 mmol was added to a solution of diisopropylamine (0.84 mL, 6 mmol) in THF (40 mL) at 0 °C. A solution of phenyl methyl sulfone (925 mg, 6 mmol) in THF (5 mL) was added dropwise over 30 min. and the solution allowed to stir for a further 30 min. (2*S*)-1-*tert*-butyl 2-ethyl 5-oxopyrrolidine-1,2-dicarboxylate (1.54 g, 6 mmol) in THF (5 mL) was added over 30 min and the solution allowed to warm to 25 °C and stirred for 18 h. Saturated aqueous NH_4Cl solution (25 mL) was added and the organic layer extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were washed with brine (2x50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The resulting oil was dissolved in CH_2Cl_2 (5 mL) and trifluoroacetic acid (1.37 g, 12 mmol) added. The resulting solution was stirred for 18 h at 25 °C before being concentrated *in vacuo*. Saturated aqueous sodium bicarbonate solution (20 mL) was and the organic materials extracted into CH_2Cl_2 (3 x 25 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. Purification by flash column chromatography (eluent 2:1 petroleum ether/ethyl acetate) gave the *title compound* (885 mg, 51 %) as a pale oil (Found: MH^+, 296.0945. $C_{14}H_{18}NO_4S$ requires M, 296.0957); $\nu_{max.}$ (neat) 3395, 2981, 1735, 1607, 1446, 1279, 1199, 1078, 847 and 717 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.83 (2 H, broad d, *J* 7.0), 7.53 – 7.37 (3 H, m), 4.68 (1 H, s, alkene CH), 4.30 (1 H, dd, *J* 8.4, 4.8, CHN), 4.14 (2 H, q, *J* 7.1, OCH_2), 2.64 – 2.49 (2 H, m, CH_2C), 2.27 – 2.16 (1 H, m, one of CH_2CHN), 2.06 – 1.96 (1 H, m, one of CH_2CHN) and 1.22 (3 H, t, *J* 7.1, CH_3CH_2); δ_C (100 MHz; $CDCl_3$) 171.6 (C), 160.4 (C), 144.8 (C), 131.9 (CH), 128.8 (2 x CH), 125.7 (2 x CH), 85.3 (CH), 61.6 (CH_2), 60.5 (CH), 31.7 (CH_2), 25.7 (CH_2) and 14.1 (CH_3); *m/z* (TOF MS AP^+) 296 (MH^+, 100%).

General Procedure for 27a-c,f,g

Triethylamine (30 mg, 0.3 mmol) was added to a solution of (*S*,*Z*)-ethyl 5-(phenylsulfonylmethylene)pyrrolidine-2-carboxylate (**26**) (74 mg, 0.25 mmol) and α-chlorooxime **9** (0.25 mmol) in dry CH_2Cl_2 (5 mL). The reaction mixture was heated under reflux for 18 h. The solution was then washed with water (3 x 15 mL), dried over magnesium sulfate and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (eluent 3:1 petroleum ether/ethyl acetate) to give compounds **27a-c,f,g** as described below.

(5*S*,7a*S*)-Ethyl 3-phenyl-7a-(phenylsulfonylmethyl)-5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazole-5-carboxylate (27a)

The general procedure above gave the *title compound* (48 mg, 46%) as a yellow oil (Found: MH^+, 415.1338. $C_{21}H_{23}N_2SO_5$ requires M, 415.1328); $\nu_{max.}$ (neat) 2980, 1732, 1608, 1447, 1370, 1309, 1084, 750 and 688 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.91 (2 H, app. broad d, *J* 7.1), 7.60 – 7.54 (3 H, m), 7.48 (2 H, app. broad t, *J* 7.5), 7.38 (1 H, app. tt, *J* 7.4, 1.4), 7.31 (2 H, app. broad t, *J* 7.3), 4.18 (2 H, q, *J* 7.1, OCH_2), 3.98 (1 H, dd, *J* 7.2, 2.2, CHN), 3.88 (1 H, d, *J* 14.7, one of CH_2SO_2), 3.62 (1 H, d, *J* 14.7, one of CH_2SO_2), 2.65 – 2.60 (2 H, m, CH_2C), 2.15 – 2.04 (2 H, m, CH_2CHN) and 1.25 (3 H, t, *J* 7.1, CH_3CH_2); δ_C (100 MHz; $CDCl_3$) 171.2 (C), 158.2 (C), 140.4 (C), 133.8 (CH), 131.5 (CH), 129.1 (2 x CH), 129.0 (2 x CH), 128.3 (2 x CH), 128.0 (2 x CH), 125.1 (C), 106.2 (C), 64.5 (CH), 63.2 (CH_2), 61.8 (CH_2), 35.7 (CH_2), 29.1 (CH_2) and 14.2 (CH_3); *m/z* (TOF MS ES^+) 415 (MH^+, 64%) and 296 (100).

(5*S*,7a*S*)-Ethyl 3-(2,6-dichlorophenyl)-7a-(phenylsulfonylmethyl)-5,6,7,7a-tetrahydropyrrolo [1,2-*d*][1,2,4]oxadiazole-5-carboxylate (27b)

The general procedure above gave the *title compound* (62 mg, 51%) as a yellow oil (Found: MH^+, 483.0534. $C_{21}H_{21}N_2SO_5{}^{35}Cl_2$ requires M, 483.0534); $\nu_{max.}$ (neat) 2980, 1740, 1434, 1322, 1157 and 790 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.94 (2 H, app. dd, *J* 8.2, 1.5), 7.62 – 7.47 (3 H, m), 7.31 – 7.27 (3 H, m), 4.09 – 3.97 (2 H, m, OCH_2), 4.04 (1 H, d, *J* 14.8, one of CH_2SO_2), 3.95 (1 H, dd, *J* 7.6, 2.1, CHN), 3.70 (1 H, d, *J* 14.8), 2.79 – 2.56 (2 H, m, CH_2C), 2.34 – 2.09 (2 H, m, C*H*$_2$CHN) and 1.15 (3 H, t, *J* 7.1, C*H*$_3$CH$_2$); δ_C (100 MHz; $CDCl_3$) 170.5 (C), 152.3 (C), 140.2 (C), 136.0 – 137.0 (broad resonance, C), 133.7 (CH), 132.4 (CH), 129.0 (2 x CH), 128.4 (broad, 2 x CH), 128.2 (2 x CH), 124.1 (C) 106.5 (C), 63.2 (CH_2), 62.5 (CH_2), 61.5 (CH), 35.4 (CH_2), 29.6 (CH_2) and 14.0 (CH_3); *m/z* (TOF AP^+) 505 (MNa^+, 100%) and 483 (MH^+, 69) (isotopic distribution consistent with 2 x Cl).

(5*S*,7a*S*)-Ethyl 3-(2,4-dichlorophenyl)-7a-(phenylsulfonylmethyl)-5,6,7,7a-tetrahydropyrrolo [1,2-*d*][1,2,4]oxadiazole-5-carboxylate (27c)

The general procedure above gave the *title compound* (78 mg, 65%) as a colourless oil (Found: MH^+, 483.0528. $C_{21}H_{21}N_2SO_5{}^{35}Cl_2$ requires M, 483.0548); $\nu_{max.}$ (neat) 2926, 1739, 1584, 1447, 1308, 1153, 1085 and 687 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.91 (2 H, broad d, *J* 7.2), 7.63 – 7.48 (4 H, m), 7.40 (1 H, d, *J* 2.0), 7.22 (1 H, dd, *J* 8.4, 2.0), 4.11 (2 H, q, *J* 7.1, OCH_2), 3.92 (1 H, d, *J* 14.8, one of CH_2SO_2), 3.81 (1 H, dd, *J* 5.3, 4.2, CHN), 3.74 (1 H, d, *J* 14.8, one of CH_2SO_2), 2.69 – 2.54 (2 H, m, CH_2C), 2.12 – 2.04 (2 H, m, C*H*$_2$CHN) and 1.21 (3 H, t, *J* 7.1, C*H*$_3$CH$_2$); δ_C (100 MHz; $CDCl_3$) 170.7 (C), 155.2 (C), 140.4 (C), 137.8 (C), 134.8 (C), 133.8 (CH), 132.8 (CH), 130.9 (CH), 129.1 (2 x CH), 128.3 (2 x CH), 122.7 (C), 106.4 (C), 63.9 (CH), 63.3 (CH_2), 61.7 (CH_2), 36.0 (CH_2), 29.1 (CH_2) and 14.1 (CH_3); *m/z* (TOF AP^+) 485 (MH^+, 52%), 483 (MH^+, 67), 296 (100) and 198 (60) (isotopic distribution of MH^+ peaks consistent with 2 x Cl).

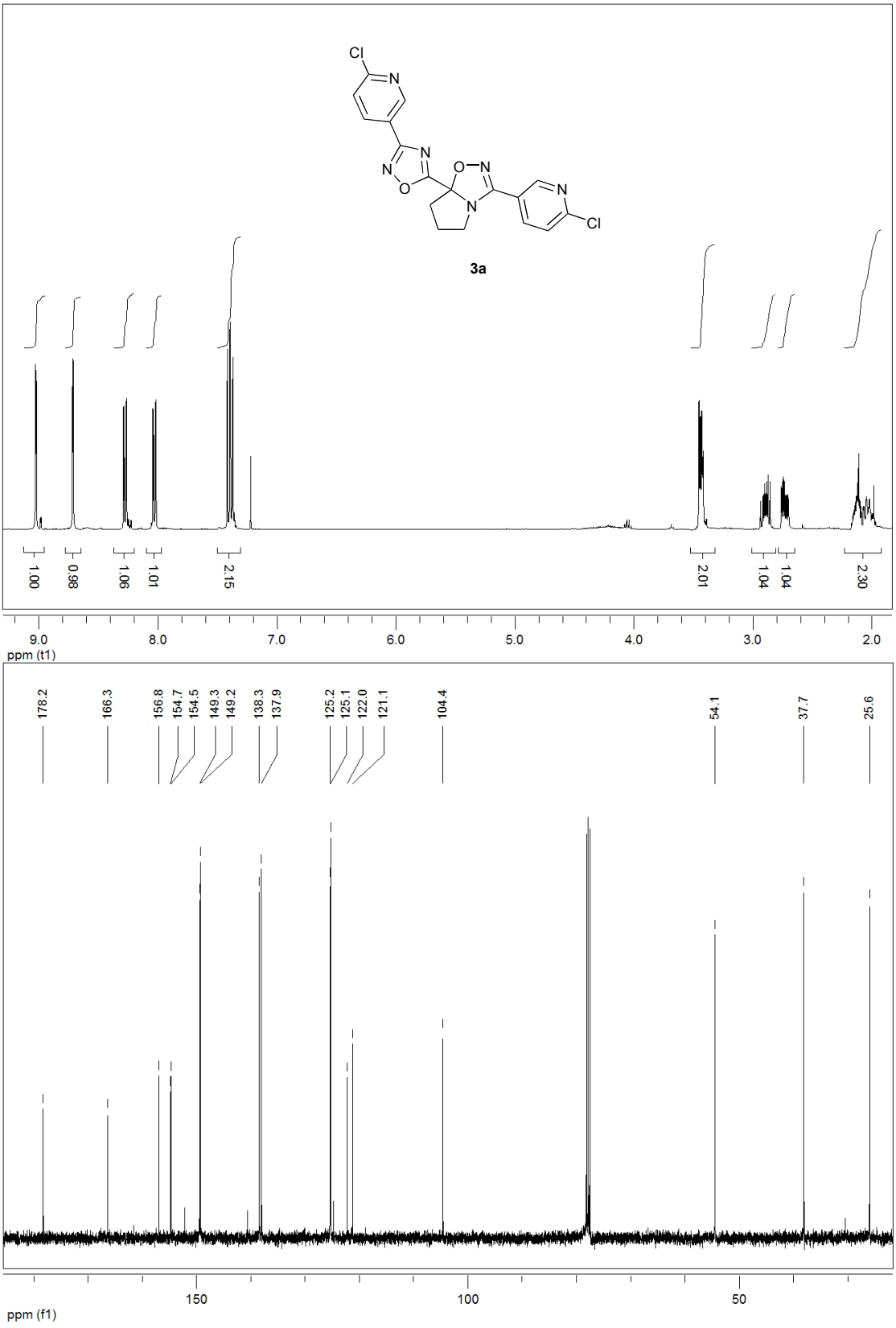
(5*S*,7a*S*)-Ethyl 3-(4-fluorophenyl)-7a-(phenylsulfonylmethyl)- -5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazole-5-carboxylate (27f)

The general procedure above gave the *title compound* (108 mg, 56% from 0.45 mmol of compound **26**) as a pale yellow oil (Found: MH^+, 433.1216. $C_{21}H_{22}N_2SO_5F$ requires M, 433.1233); $\nu_{max.}$ (neat) 1737, 1604, 1510, 1447, 1369, 1309 and 1156 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.90 (2 H, app. dd, *J* 7.2, 1.4), 7.62 – 7.54 (3 H, m), 7.49 (2 H, app. broad t, *J* 7.6), 7.01 (2 H, app. t, *J* 8.7), 4.18 (2 H, app. dq, *J* 7.1, 0.8, OCH_2), 3.94 (1 H, dd, *J* 7.9, 1.5, CHN), 3.86 (1 H, d, *J* 14.3, one of CH_2SO_2), 3.60 (1 H, d, *J* 14.3, one of CH_2SO_2), 2.64 – 2.59 (2 H, m, CH_2C) and 2.18 – 2.04 (2 H, m, C*H*$_2$CHN); δ_C (100 MHz; $CDCl_3$) 171.0 (C), 157.4 (C), 140.4 (C), 133.8 (CH), 130.2 (2 x CH, $^3J_{C\text{-}F}$ 8.7), 129.1 (2 x CH), 128.2 (2 x CH), 121.4 (C, $^4J_{C\text{-}F}$ 3.3), 116.3 (2 x CH, $^2J_{C\text{-}F}$ 22.2), 106.3 (C), 64.6 (CH), 63.0 (CH_2), 61.8 (CH_2), 35.7 (CH_2), 29.0 (CH_2) and 14.2 (CH_3); *m/z* (TOF AP^+) 433 (MH^+, 100%).

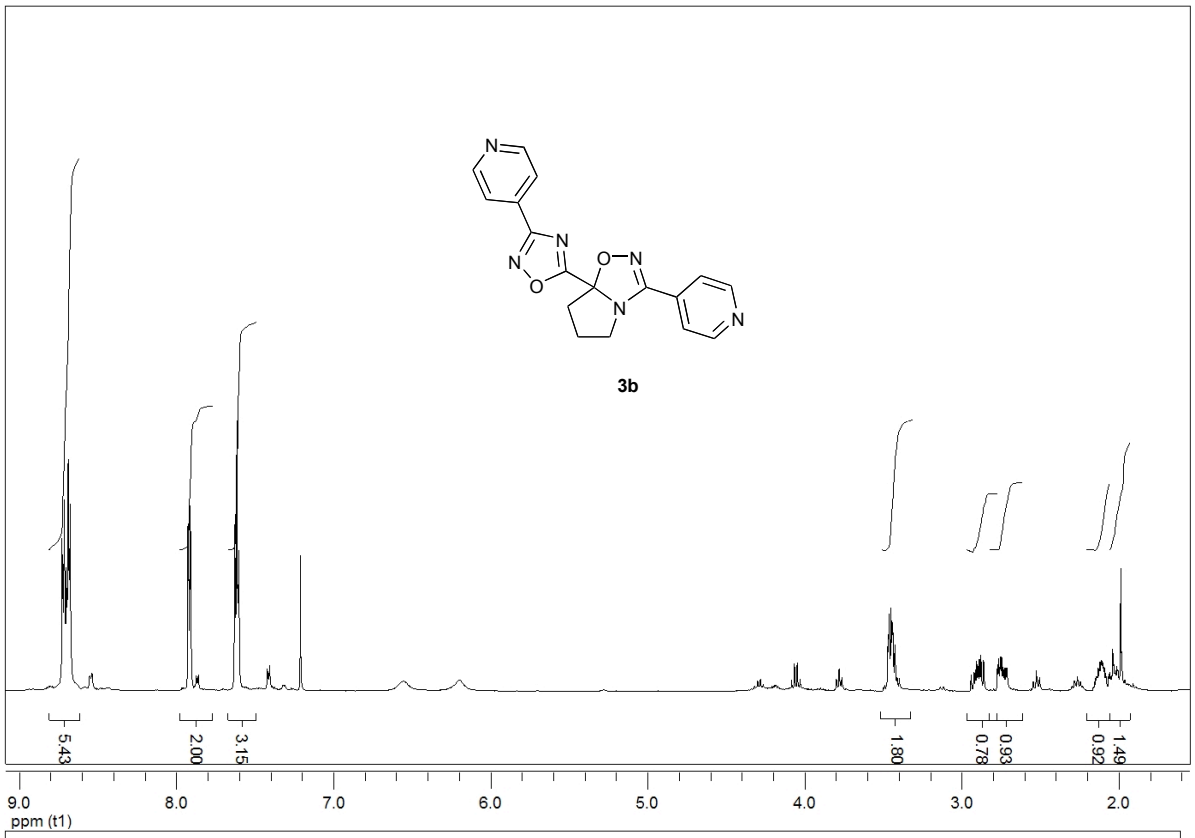
(5*S*,7a*S*)-Ethyl 3-(4-bromophenyl)-7a-(phenylsulfonylmethyl)- -5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazole-5-carboxylate (27g)

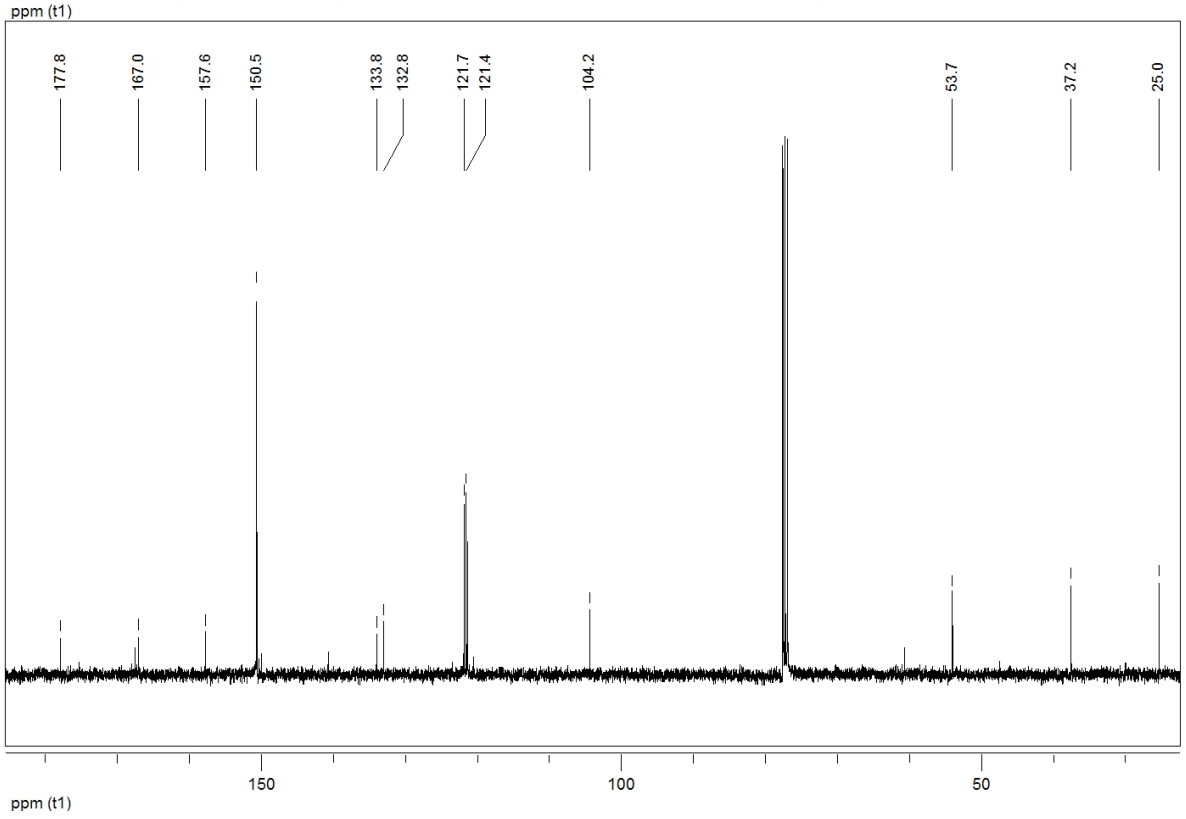
According to the general procedure above, alkylidenepyrrolidine **26** (50 mg, 0.17 mmol) gave recovered **26** (19 mg, 38%) and the *title compound* (24 mg, 29%) as a colourless oil (Found: MH^+, 493.0438. $C_{21}H_{22}N_2SO_5{}^{79}Br_2$ requires M, 493.0433); $\nu_{max.}$ (neat) 2977, 1739, 1589, 1447, 1321, 1156 and 1084 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.90 (2 H, app. broad d, *J* 7.2), 7.58 (1 H, app. tt, *J* 7.4, 1.2), 7.48 (2 H, app. broad t, *J* 7.9), 7.46 (4 H, app. s), 4.18 (2 H, q, *J* 7.1, OCH_2), 3.92 (1 H, dd, *J* 8.0, 1.4, CHN), 3.85 (1 H, d, *J* 14.7, one of CH_2SO_2), 3.60 (1 H, d, *J* 14.7, one of CH_2SO_2), 2.65 – 2.59 (2 H, m, CH_2C), 2.18 – 2.03 (2 H, m, C*H*$_2$CHN) and 1.25 (3 H, t, *J* 7.1, CH_3CH_2); δ_C (100 MHz; $CDCl_3$) 170.9 (C), 157.6 (C), 140.4 (C), 133.8 (CH), 132.3 (2 x CH), 129.4 (2 x CH), 129.1 (2 x CH), 128.2 (2 x CH), 126.0 (C), 124.1 (C), 106.6 (C), 64.6 (CH_2), 63.0 (CH), 61.9 (CH_2), 35.7 (CH_2), 29.0 (CH_2) and 14.2 (CH_3); *m/z* (TOF ES^+) 495 (MH^+, 100%) and 493 (MH^+, 98).

3-(6-Chloropyridin-3-yl)-7a-[3-(6-chloropyridin-3-yl)-1,2,4-oxadiazol-5-yl]-5,6,7,7a-tetrahydropyrrolo[1,2-d][1,2,4]oxadiazole (3a)

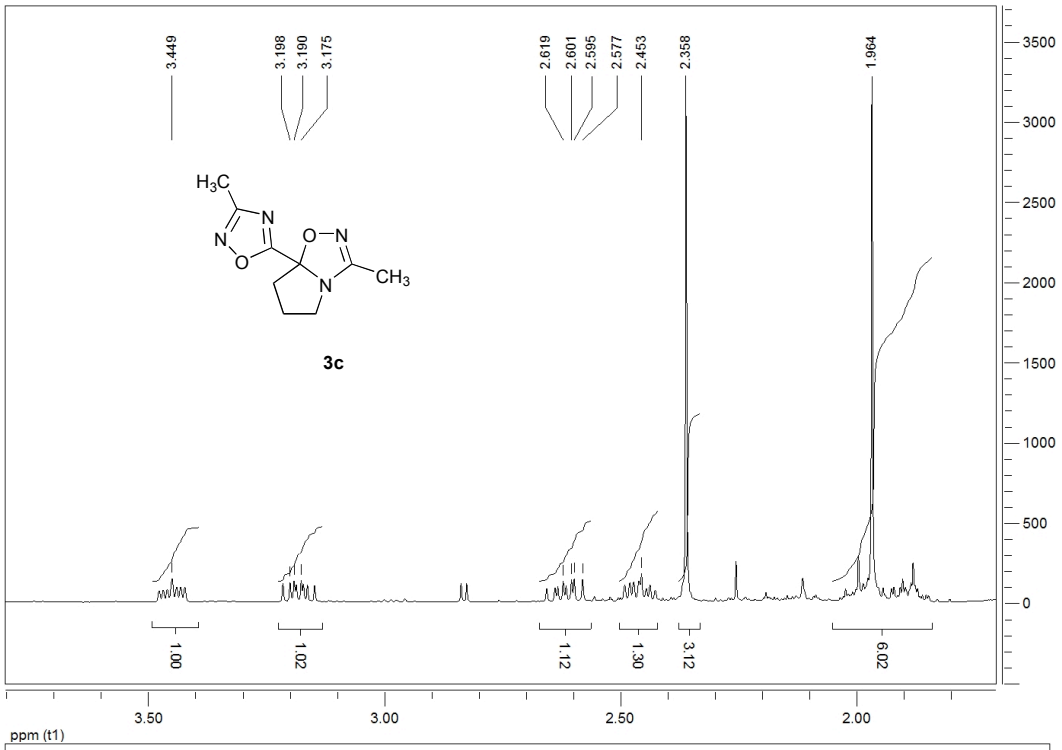


3-(Pyridin-4-yl)-7a-(3-(pyridin-4-yl)-1,2,4-oxadiazol-5-yl)-5,6,7,7a-tetrahydropyrrolo[1,2-d][1,2,4]oxadiazole (3b)

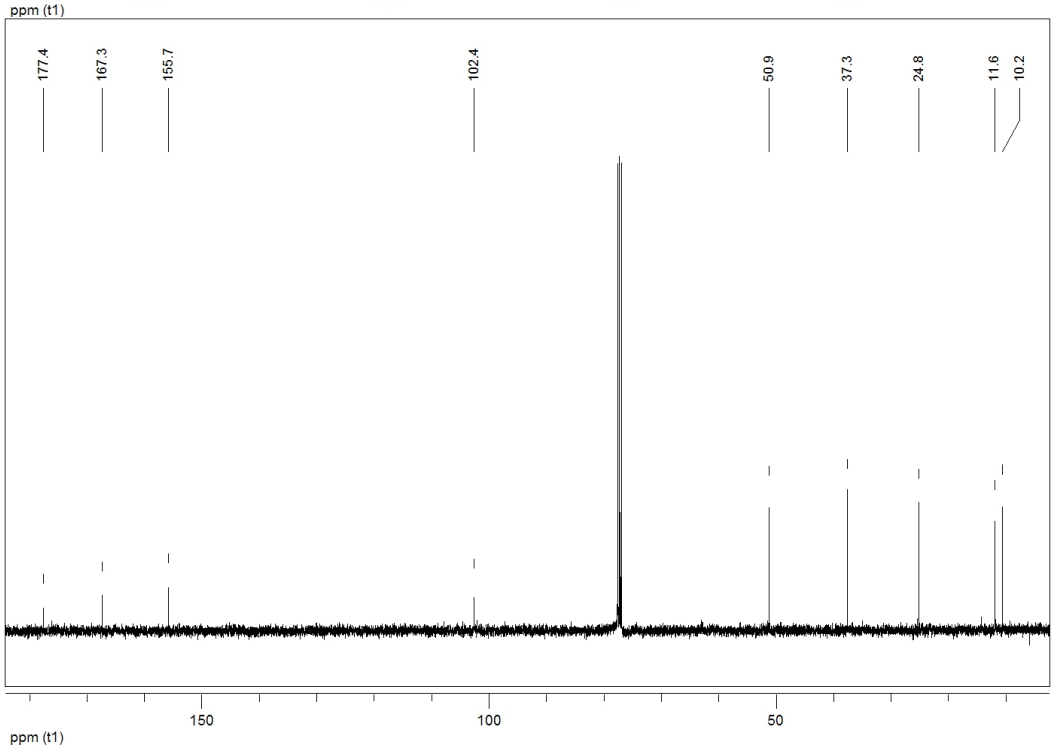




3-Methyl-7a-(3-methyl-1,2,4-oxadiazol-5-yl)-5,6,7,7a-tetrahydropyrrolo[1,2-d][1,2,4]oxadiazole (3c)

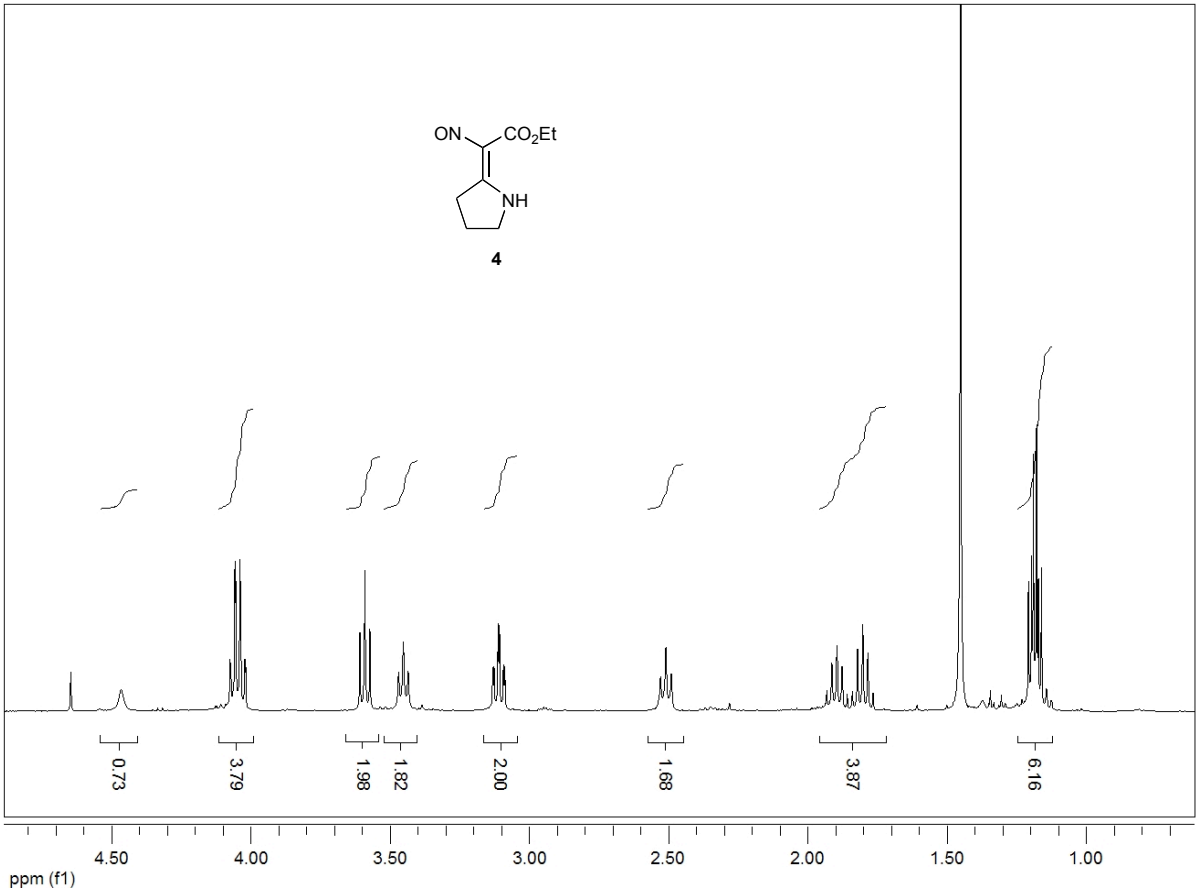


3c

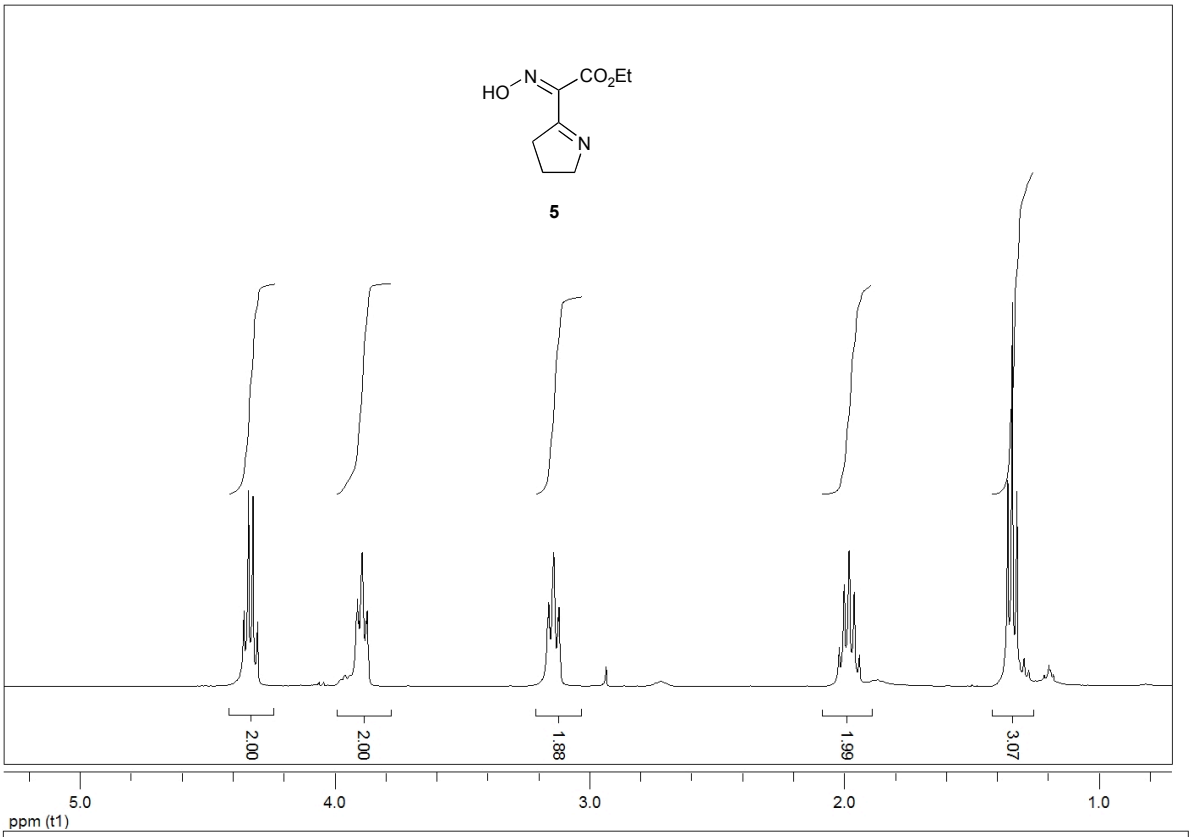


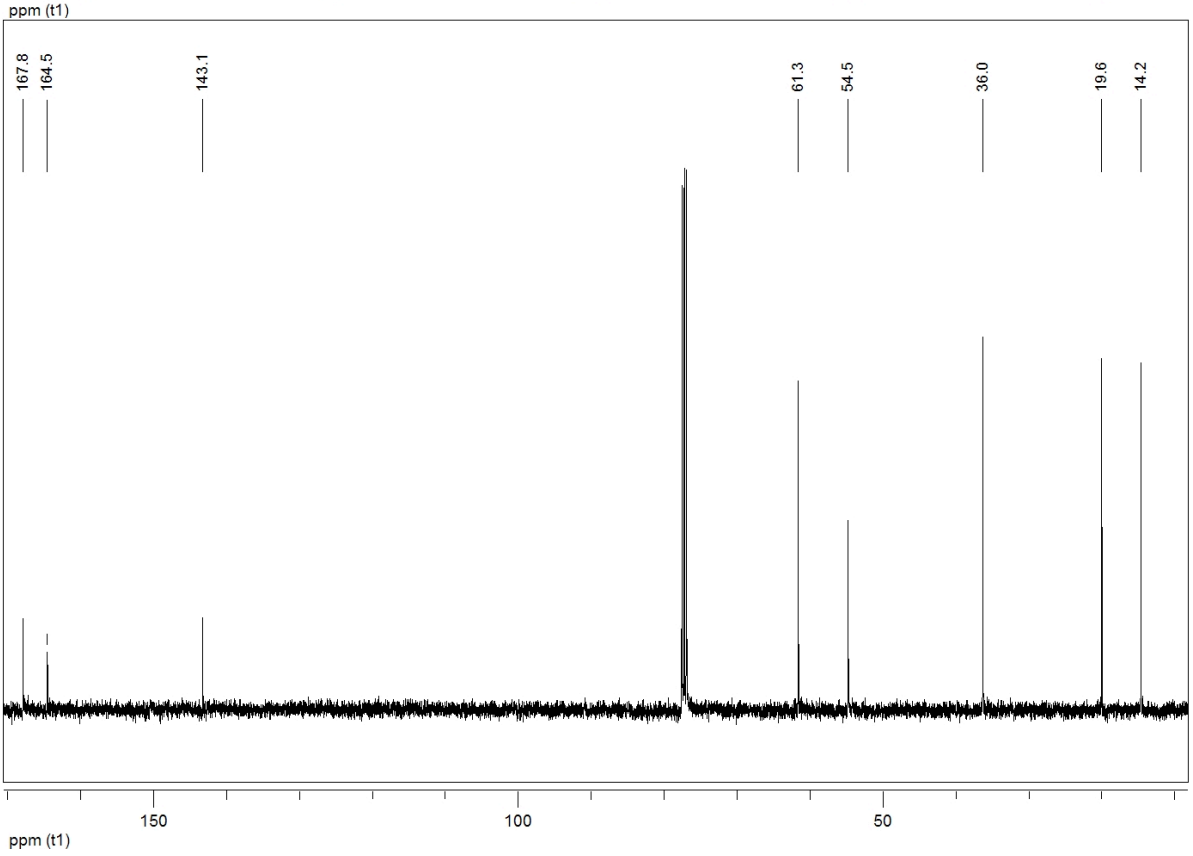
(*E*)-Ethyl 2-nitroso-2-(pyrrolidin-2-ylidene)acetate (4)

Expansion of the ^{1}H NMR spectrum of the crude reaction mixture from which compound **5** was isolated.

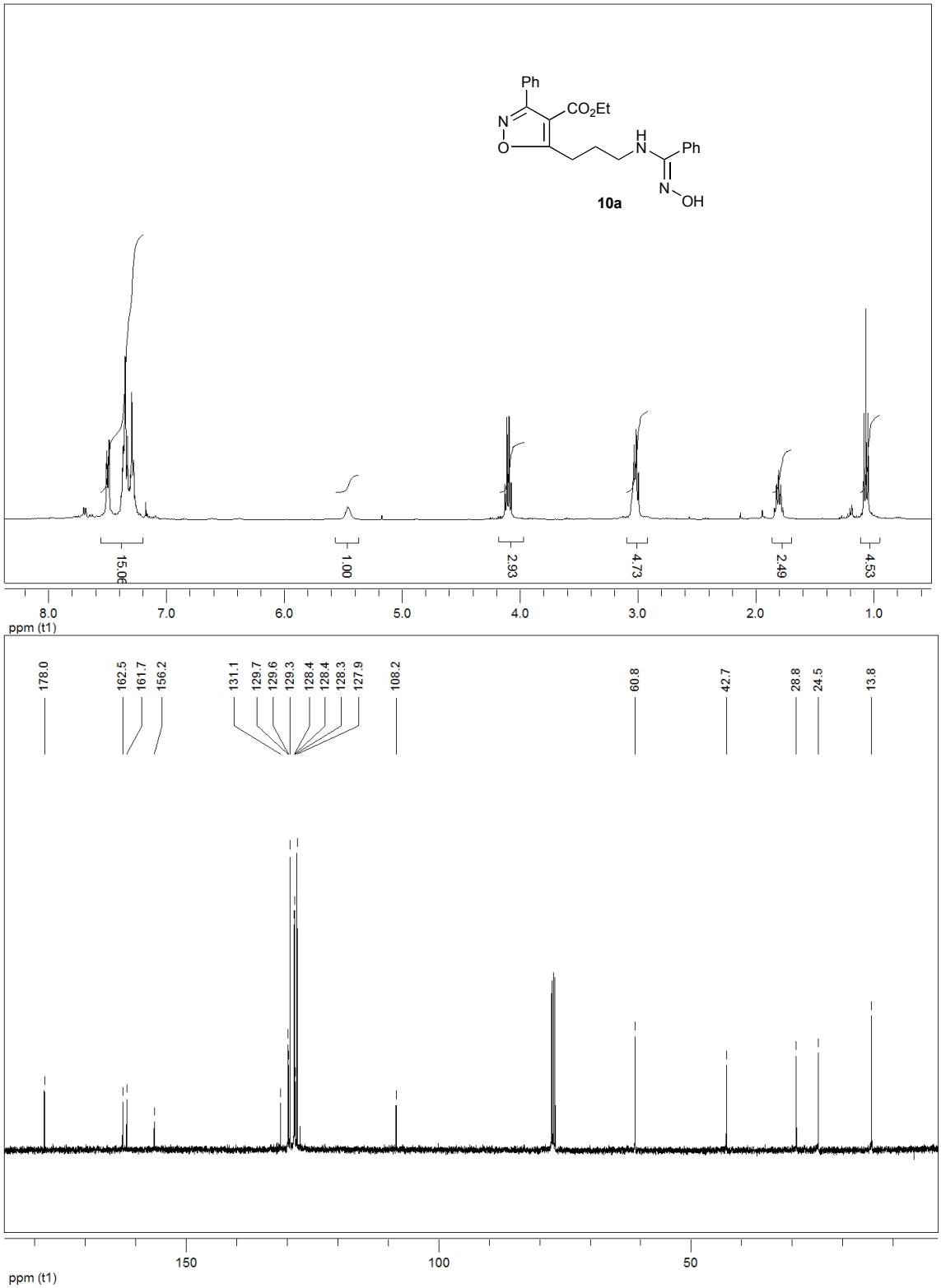


Ethyl 2-(3,4-dihydro-2H-pyrrol-5-yl)-2-(hydroxyimino)acetate (5)

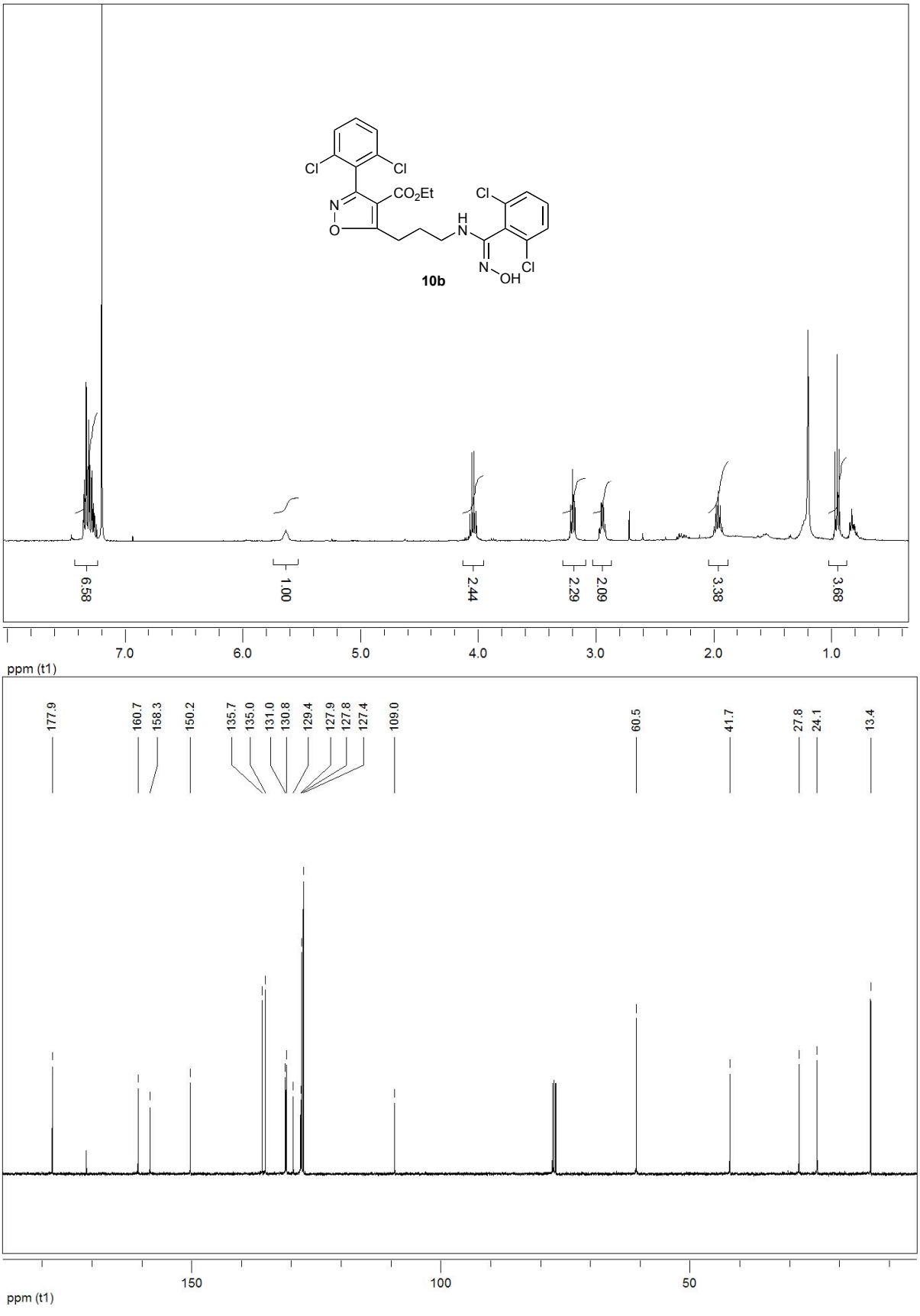




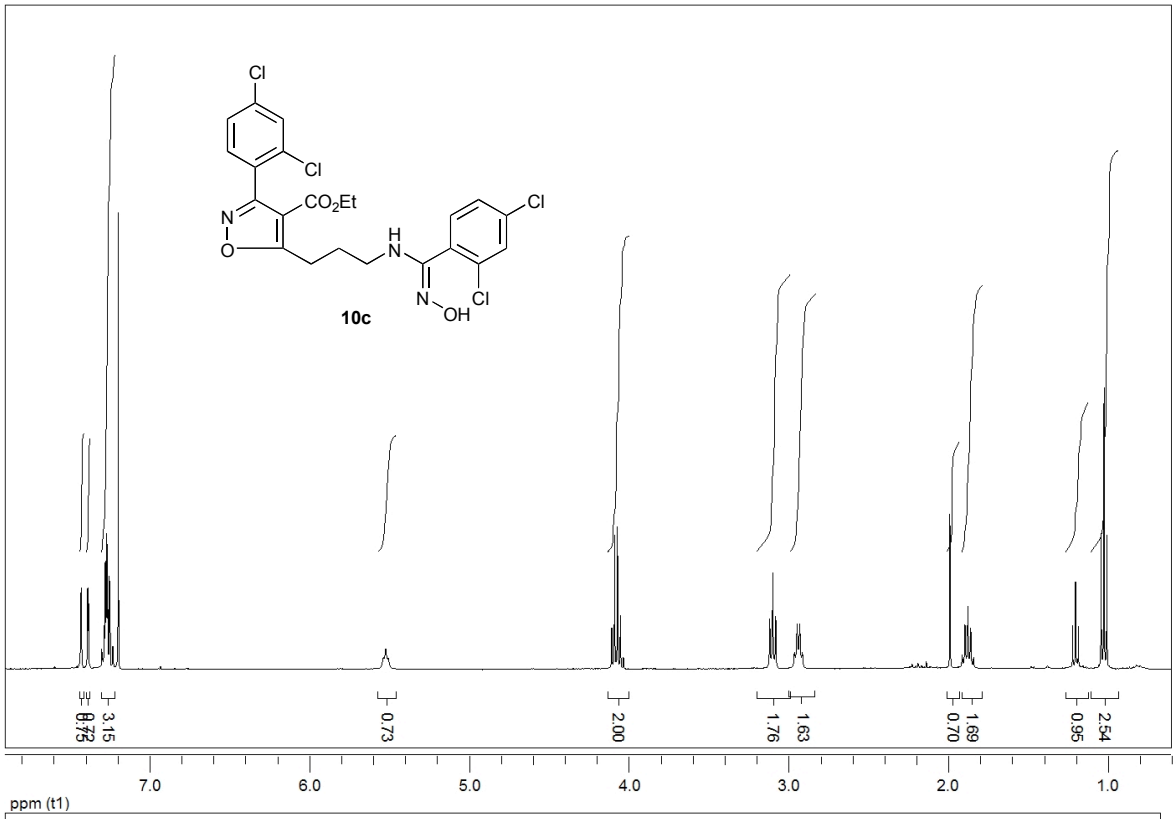
Ethyl 5-(3-(N'-hydroxybenzimidamido)propyl)-3-phenylisoxazole-4-carboxylate (10a)

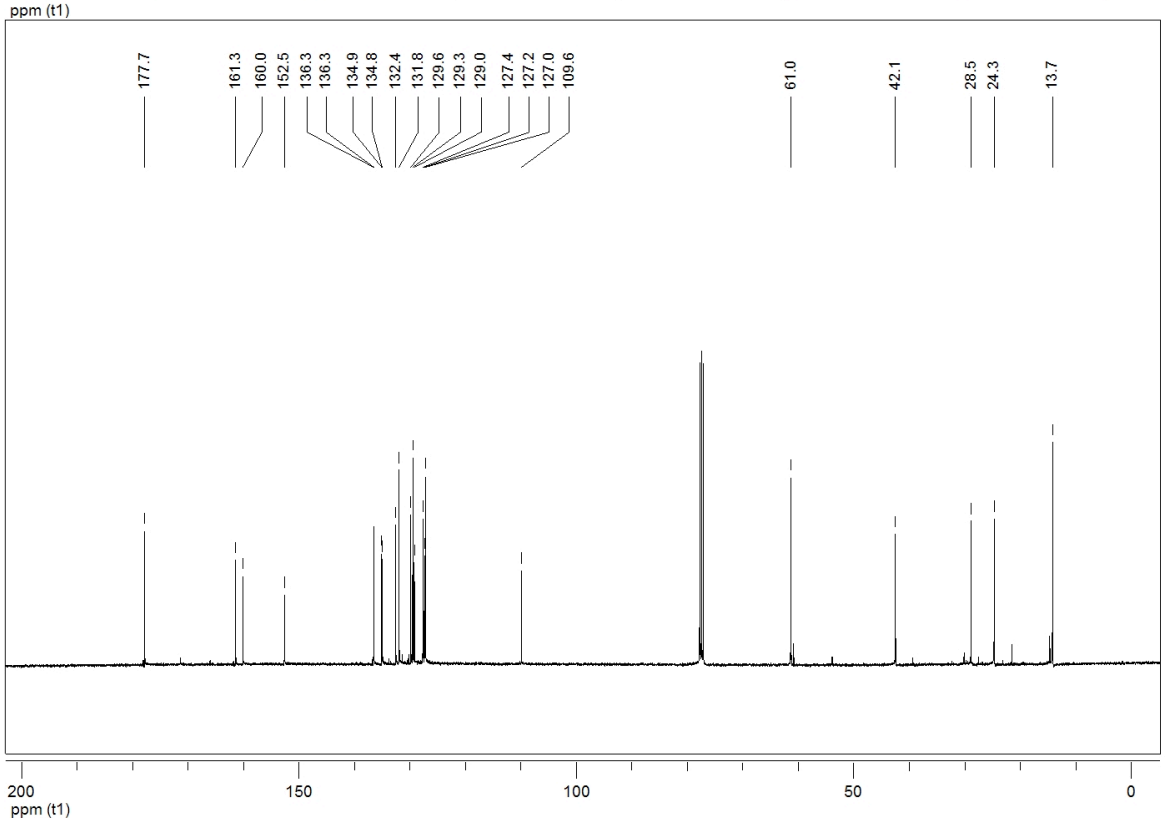


Ethyl 5-(3-(2,6-dichloro-N'-hydroxybenzimidamido)propyl)-3-(2,6-dichlorophenyl)isoxazole-4-carboxylate (10b)

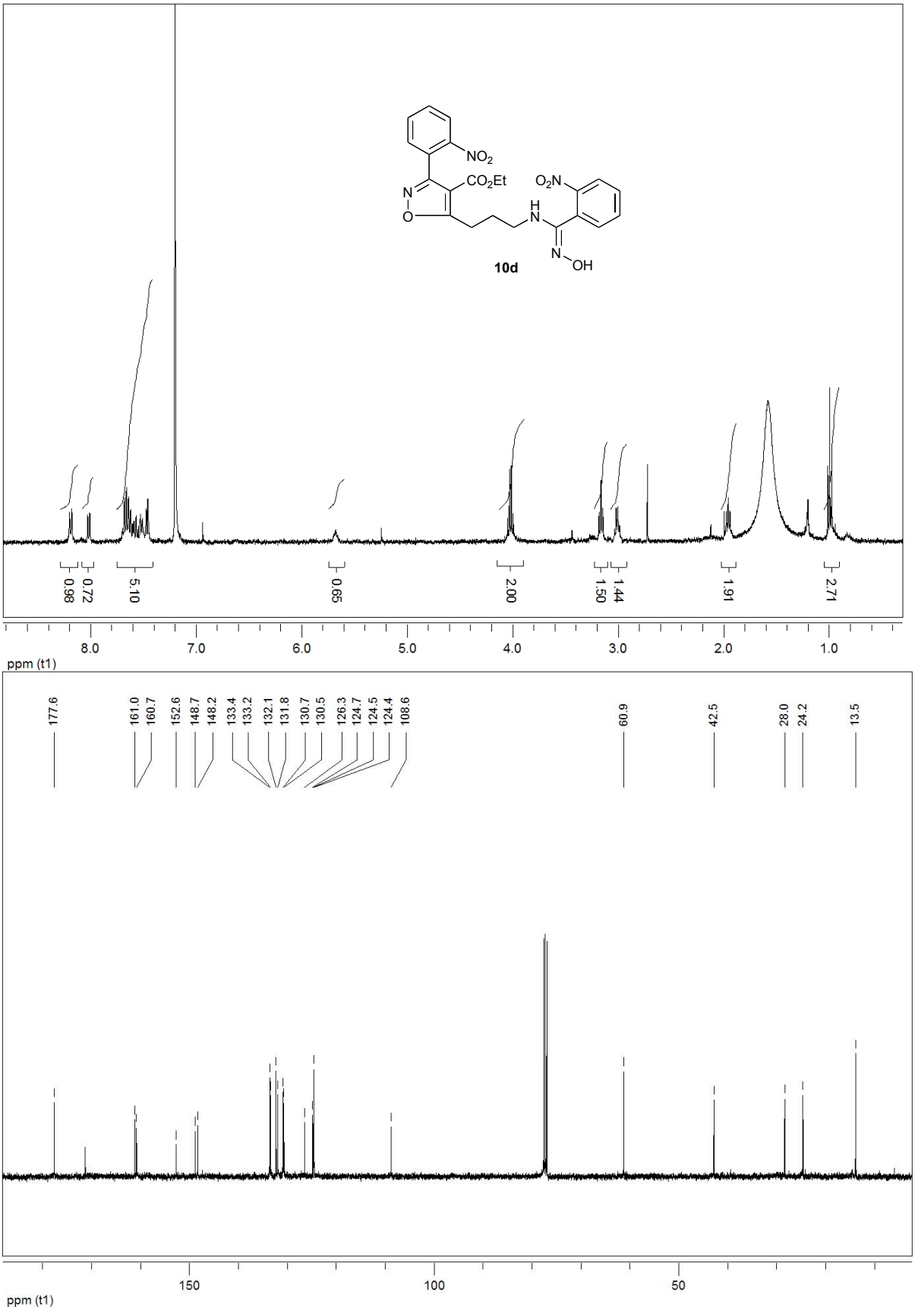


Ethyl 5-(3-(2,4-dichloro-N'-hydroxybenzimidamido)propyl)-3-(2,4-dichlorophenyl)isoxazole-4-carboxylate (10c)

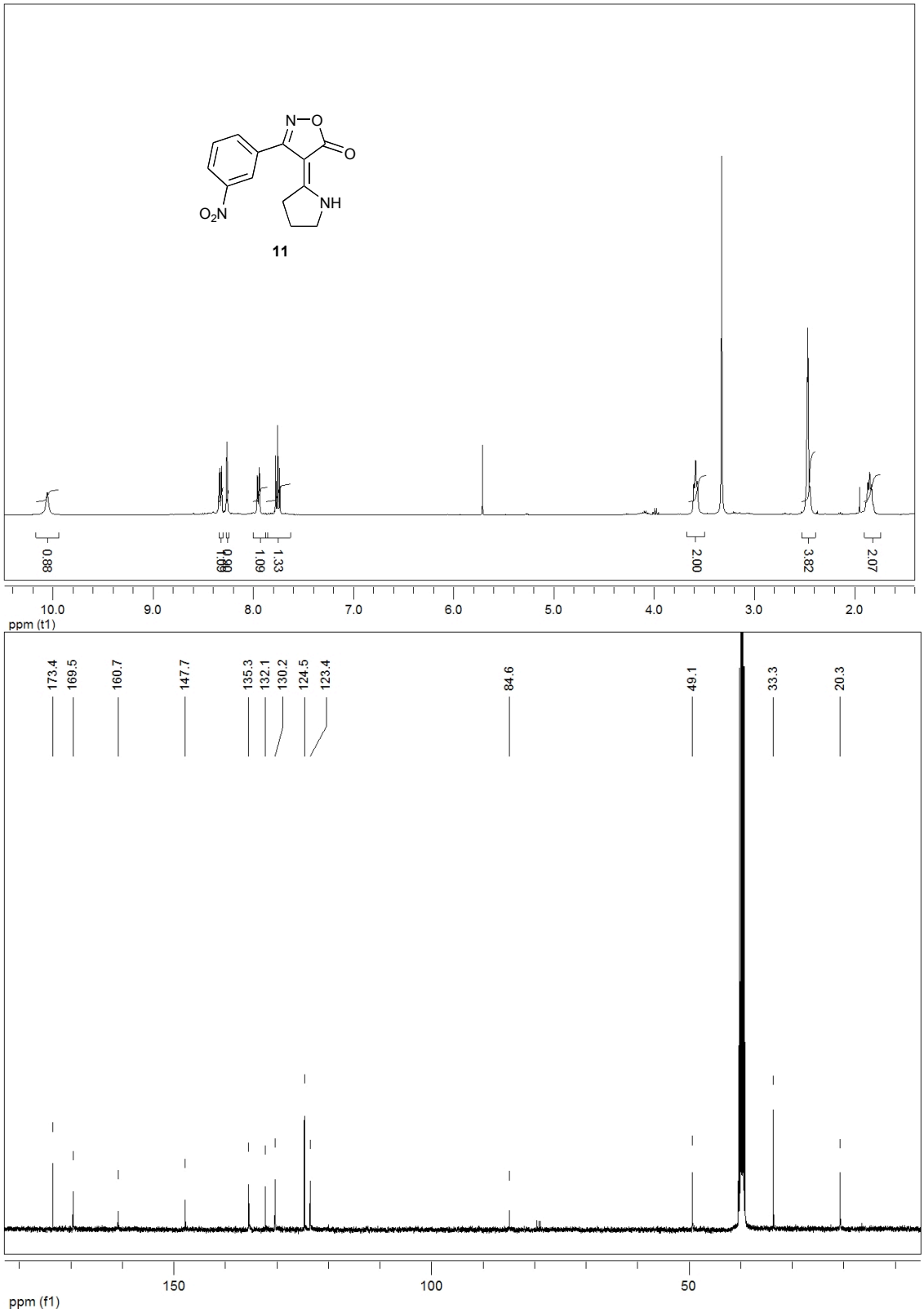




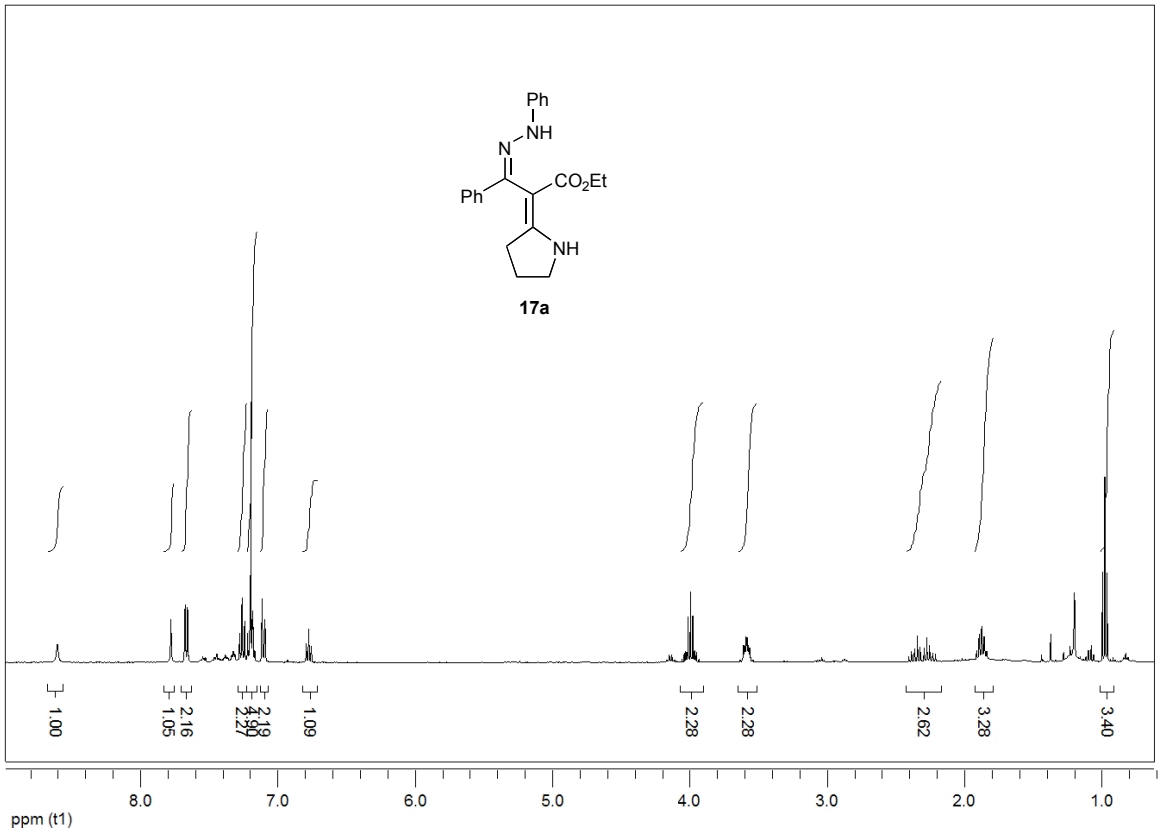
Ethyl 5-(3-(N'-hydroxy-2-nitrobenzimidamido)propyl)-3-(2-nitrophenyl)isoxazole-4-carboxylate (10d)



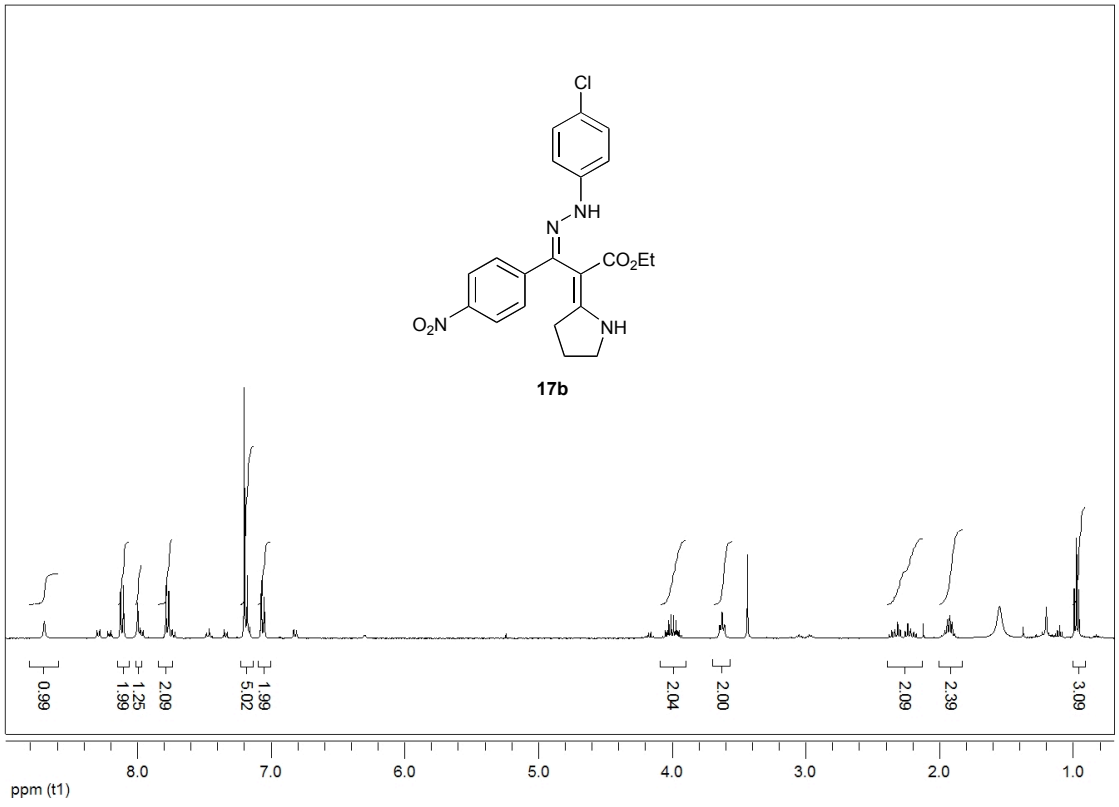
3-(3-Nitrophenyl)-4-(pyrrolidin-2-ylidene)isoxazol-5(4H)-one (11)



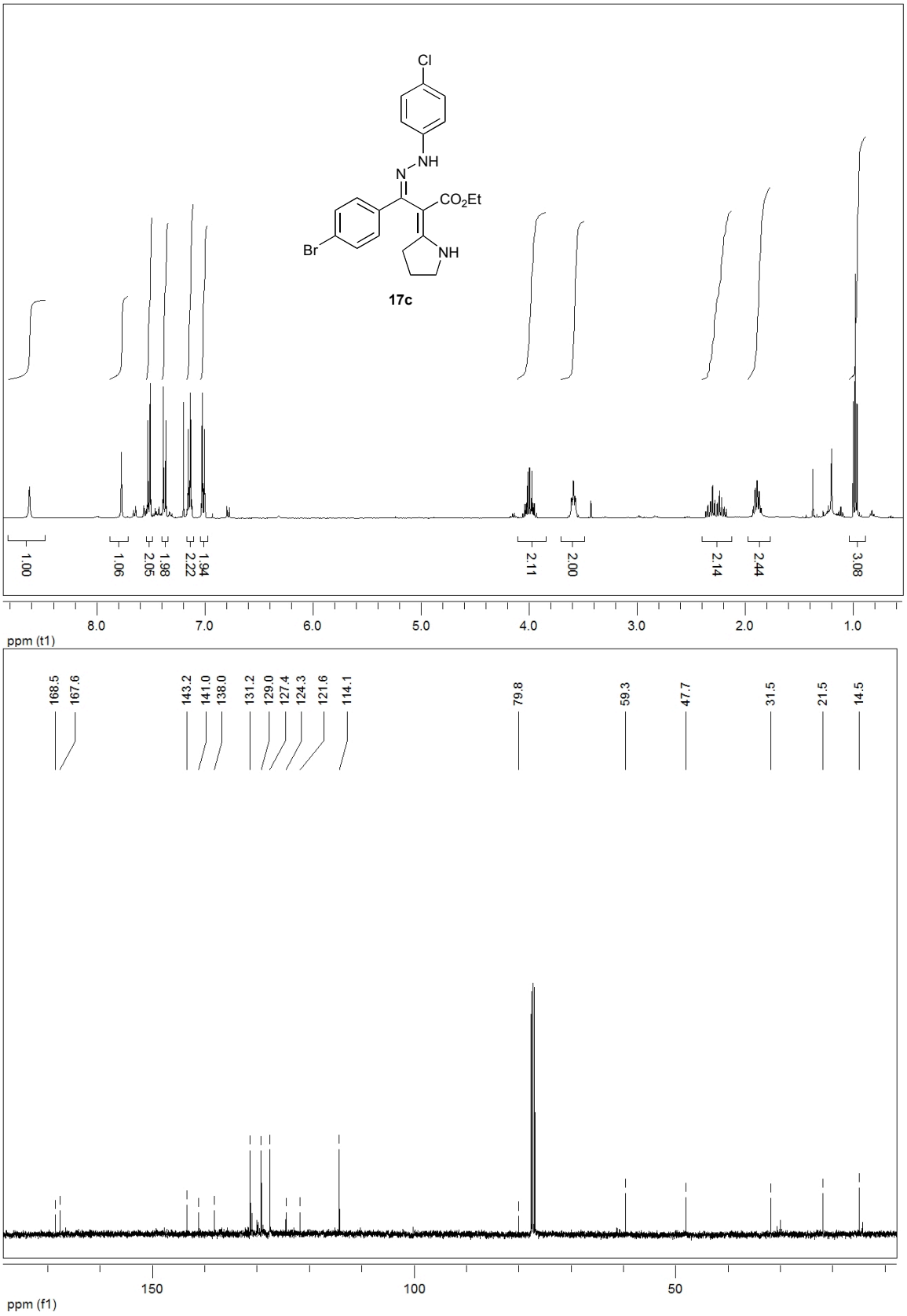
Ethyl 3-phenyl-3-(2-phenylhydrazono)-2-(pyrrolidin-2-ylidene)propanoate (17a)



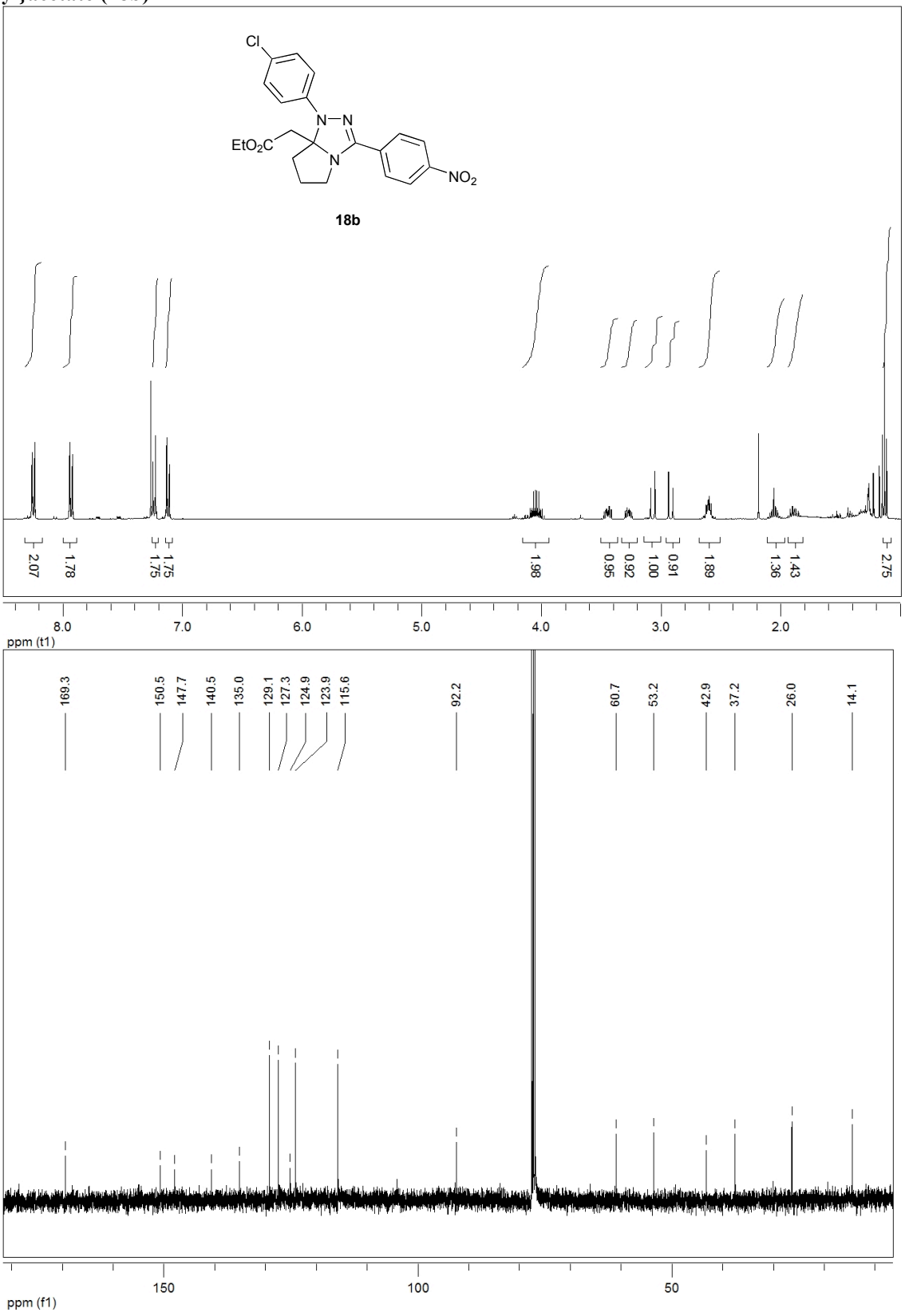
Ethyl 3-(2-(4-chlorophenyl)hydrazono)-3-(4-nitrophenyl)-2-(pyrrolidin-2-ylidene)propanoate (17b)



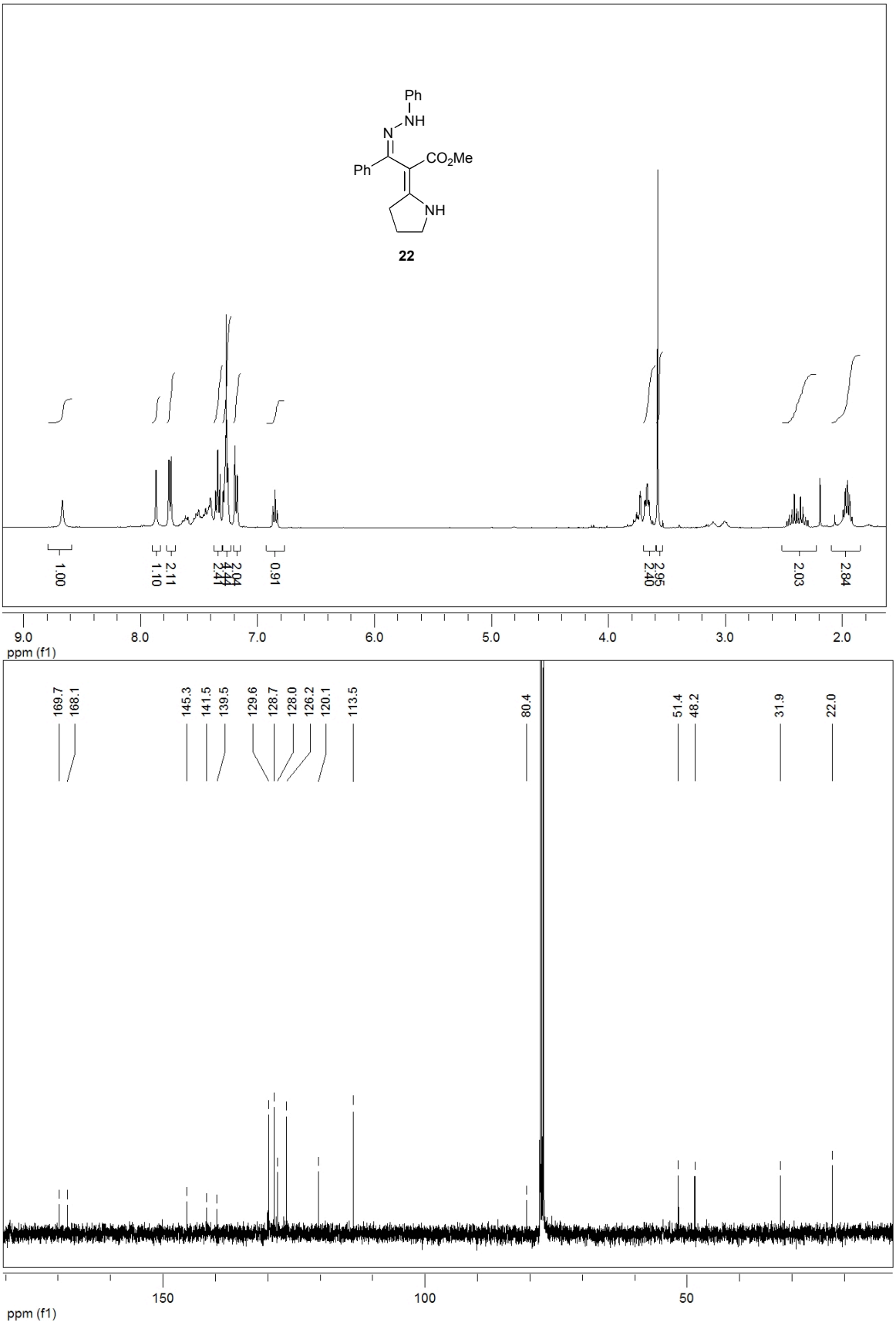
Ethyl 3-(4-bromophenyl)-3-(2-(4-chlorophenyl)hydrazono)-2-(pyrrolidin-2-ylidene)propanoate (17c)



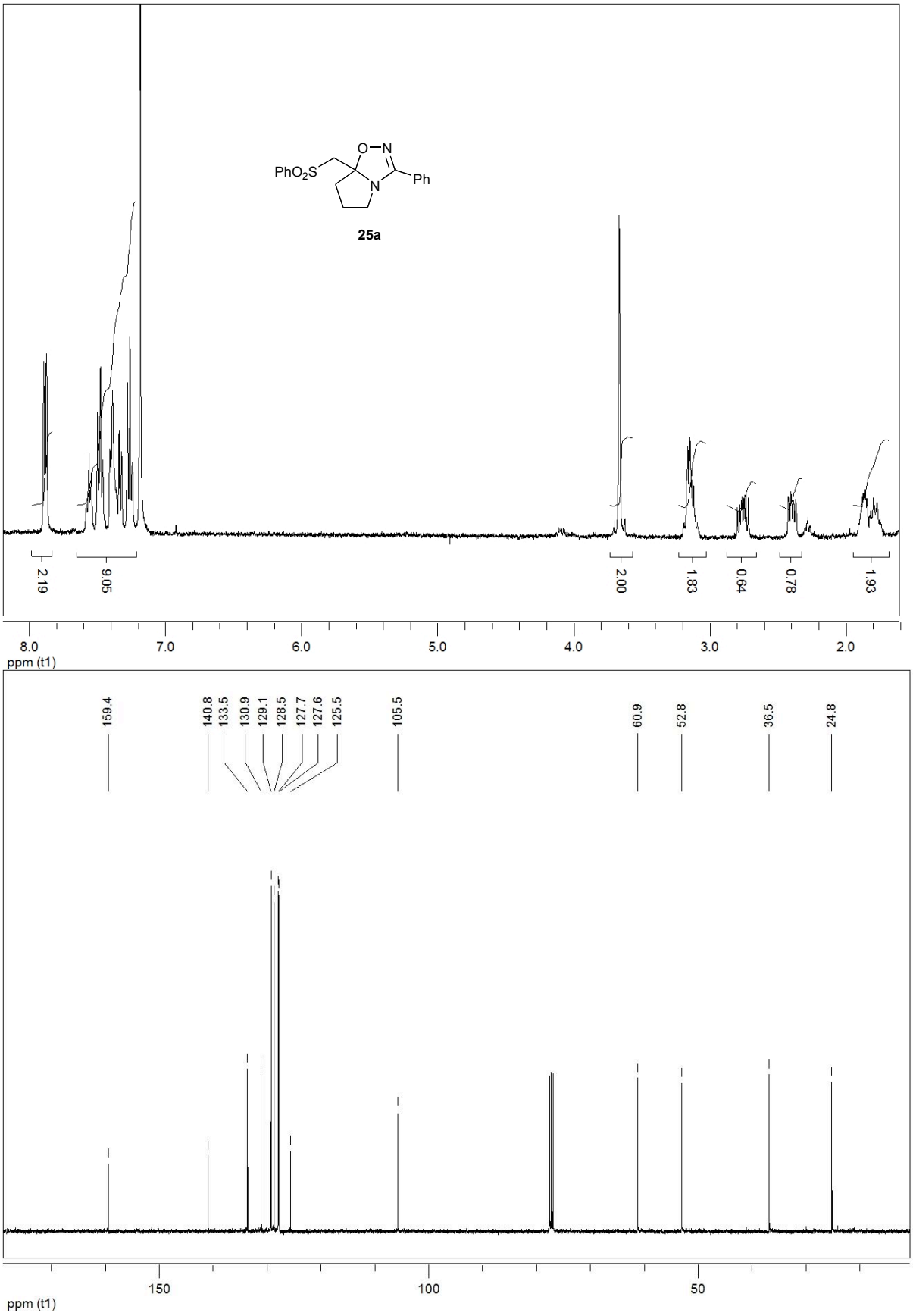
Ethyl [2-{1-(4-chlorophenyl)-3-(4-nitrophenyl)-5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]triazol-7a-yl}acetate (18b)



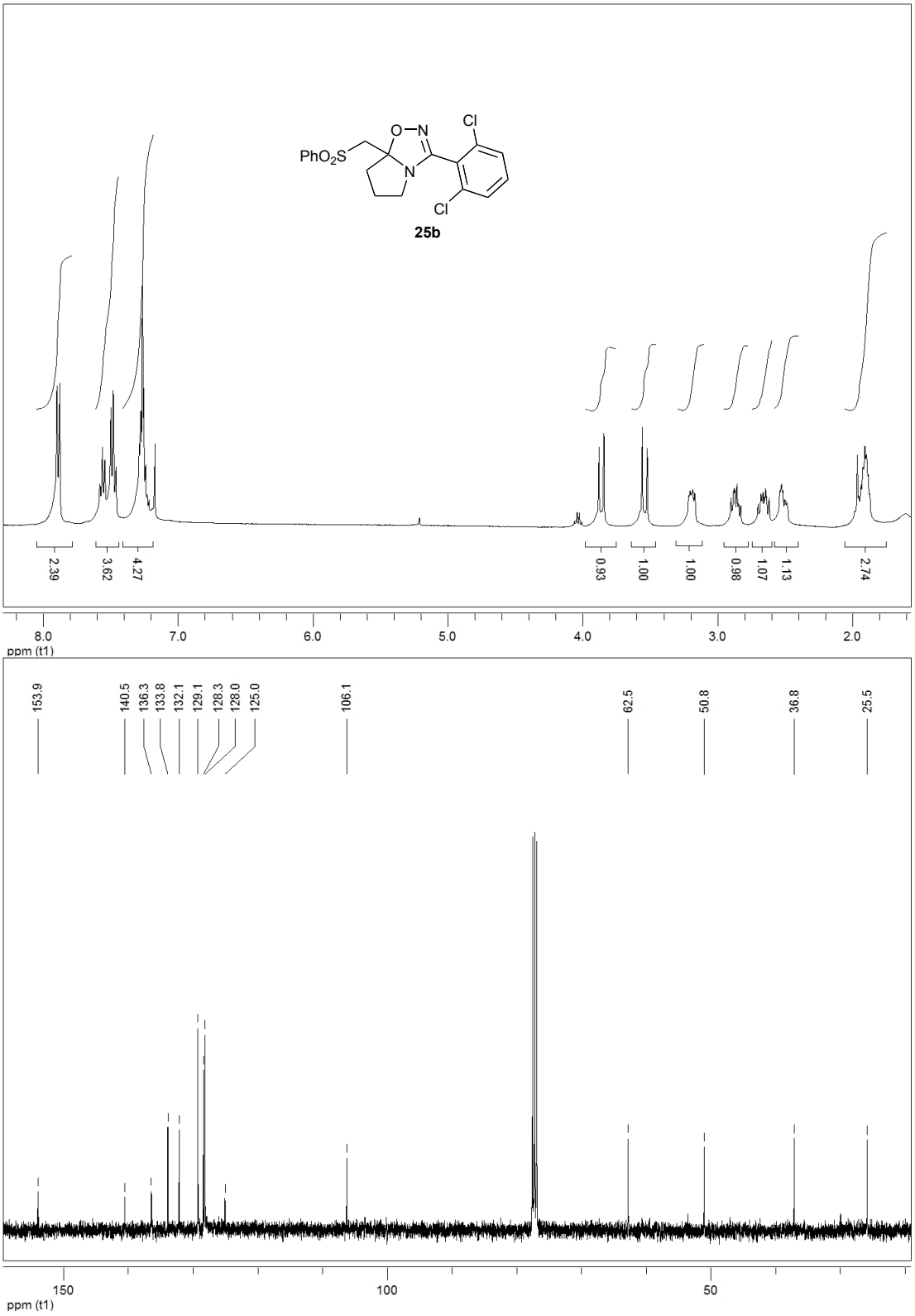
Methyl 3-phenyl-3-(2-phenylhydrazono)-2-(pyrrolidin-2-ylidene)propanoate (22)



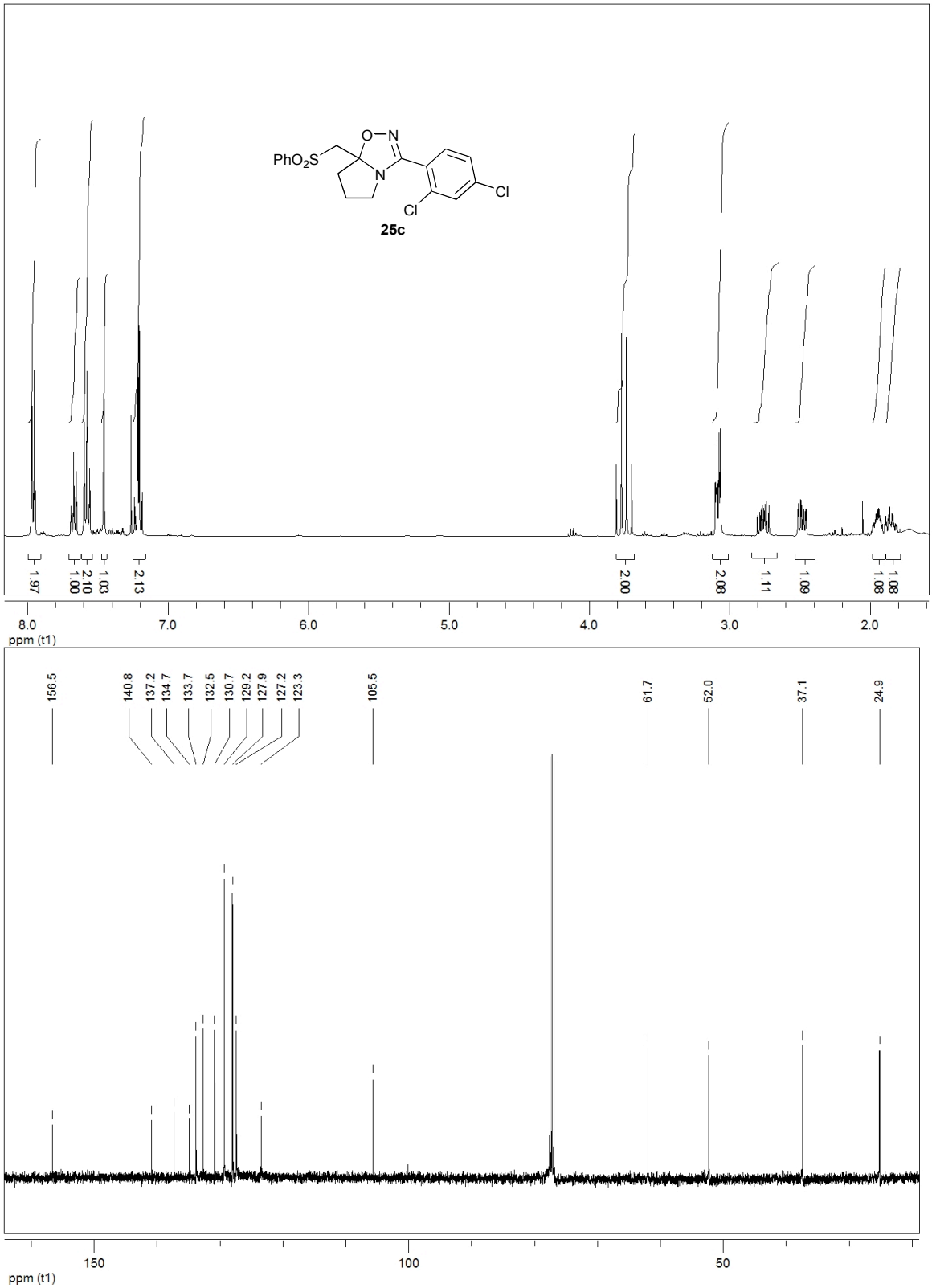
3-Phenyl-7a-(phenylsulfonylmethyl)-5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazole (25a)



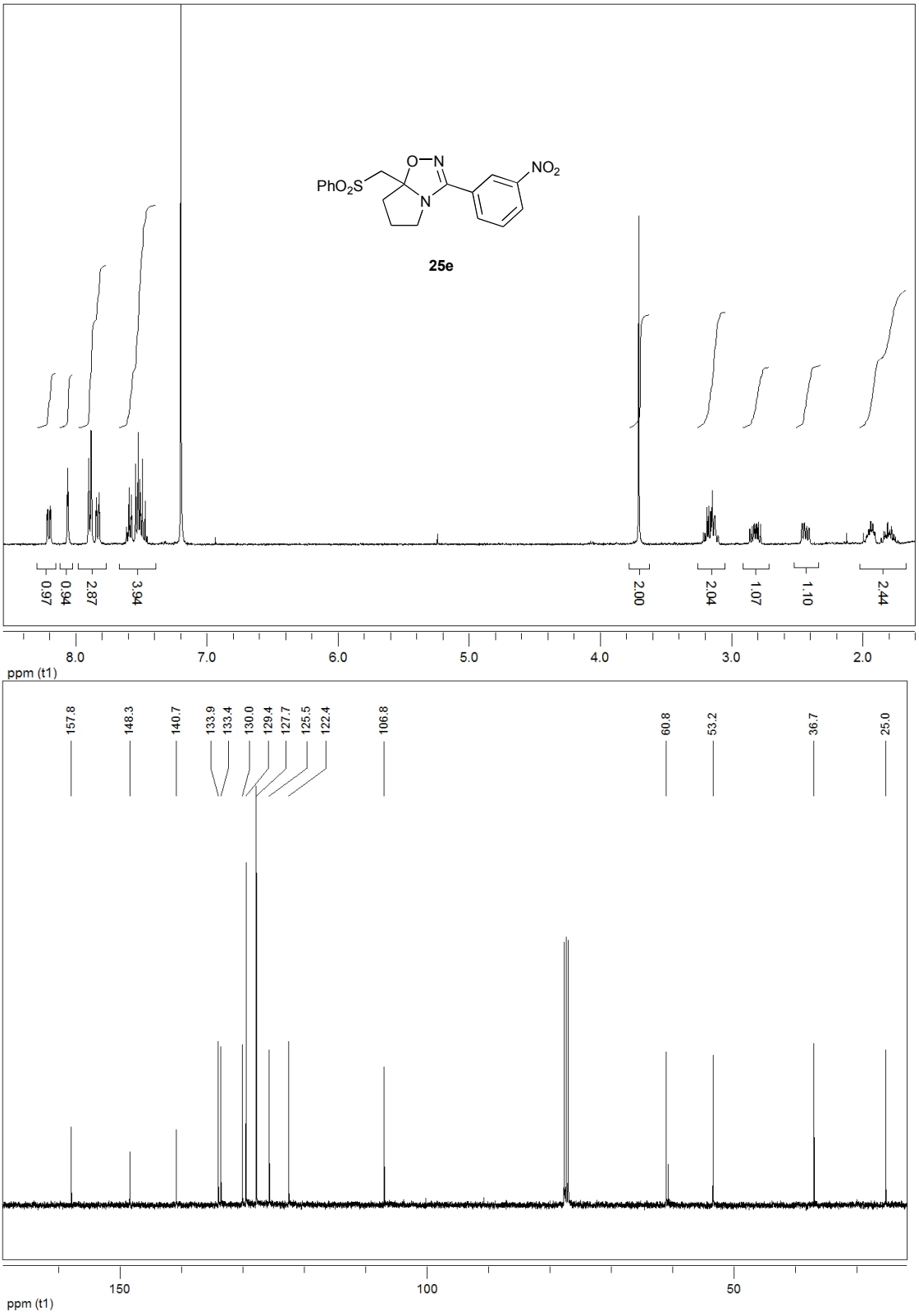
3-(2,6-Dichlorophenyl)-7a-(phenylsulfonylmethyl)-5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazole (25b)



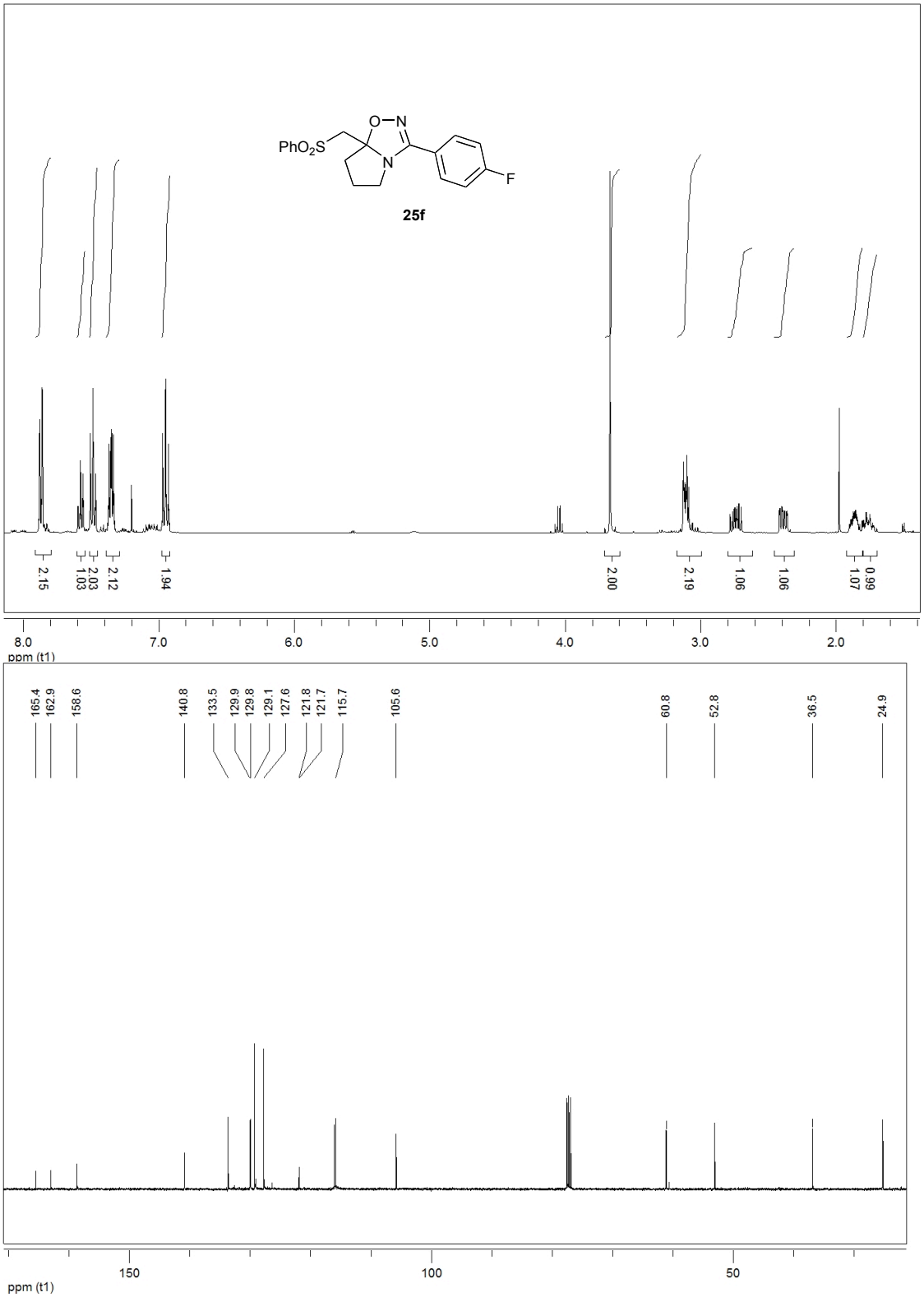
3-(2,4-Dichlorophenyl)-7a-(phenylsulfonylmethyl)-5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazole (25c)



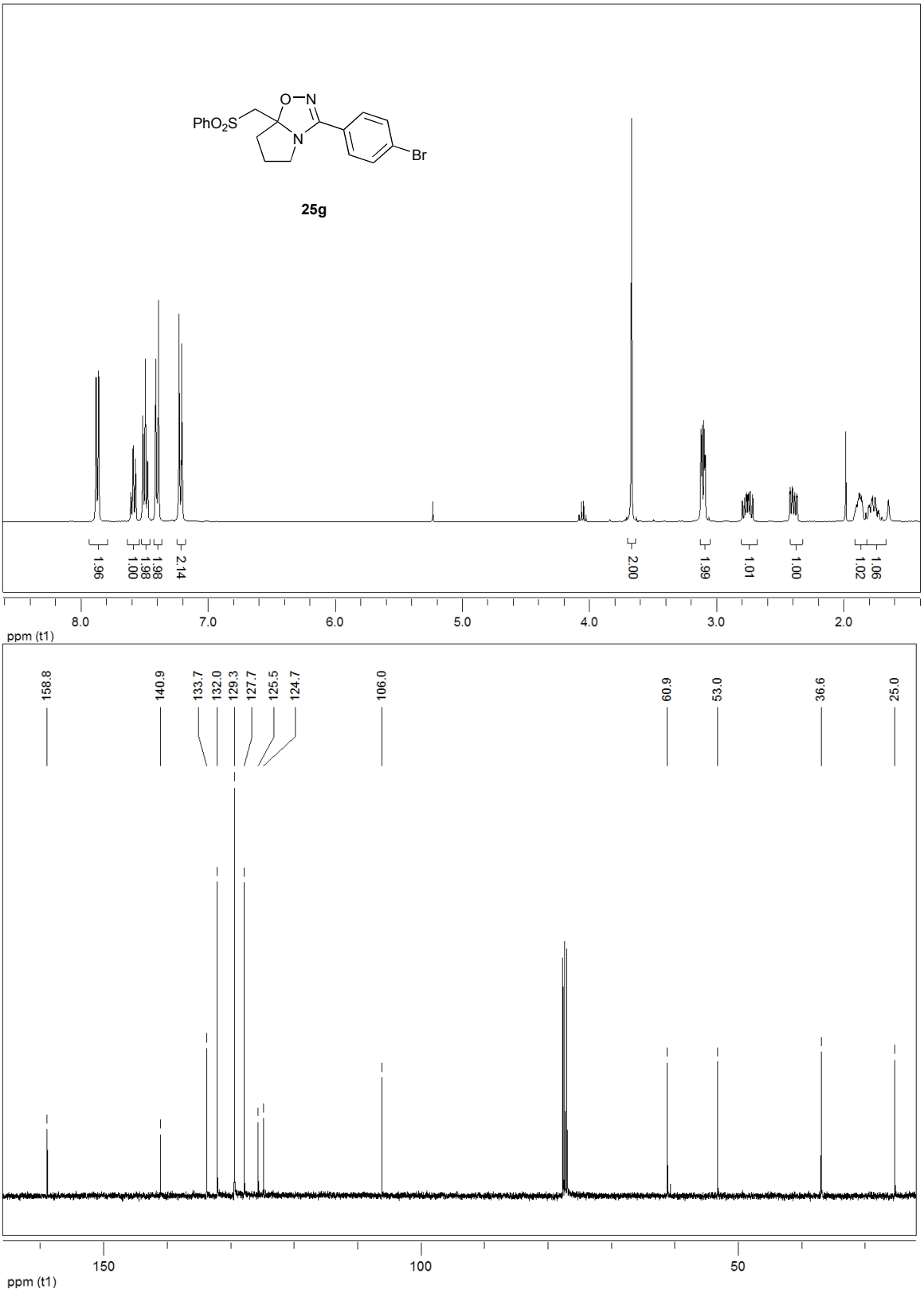
3-(3-Nitrophenyl)-7a-(phenylsulfonylmethyl)-5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazole (25e)



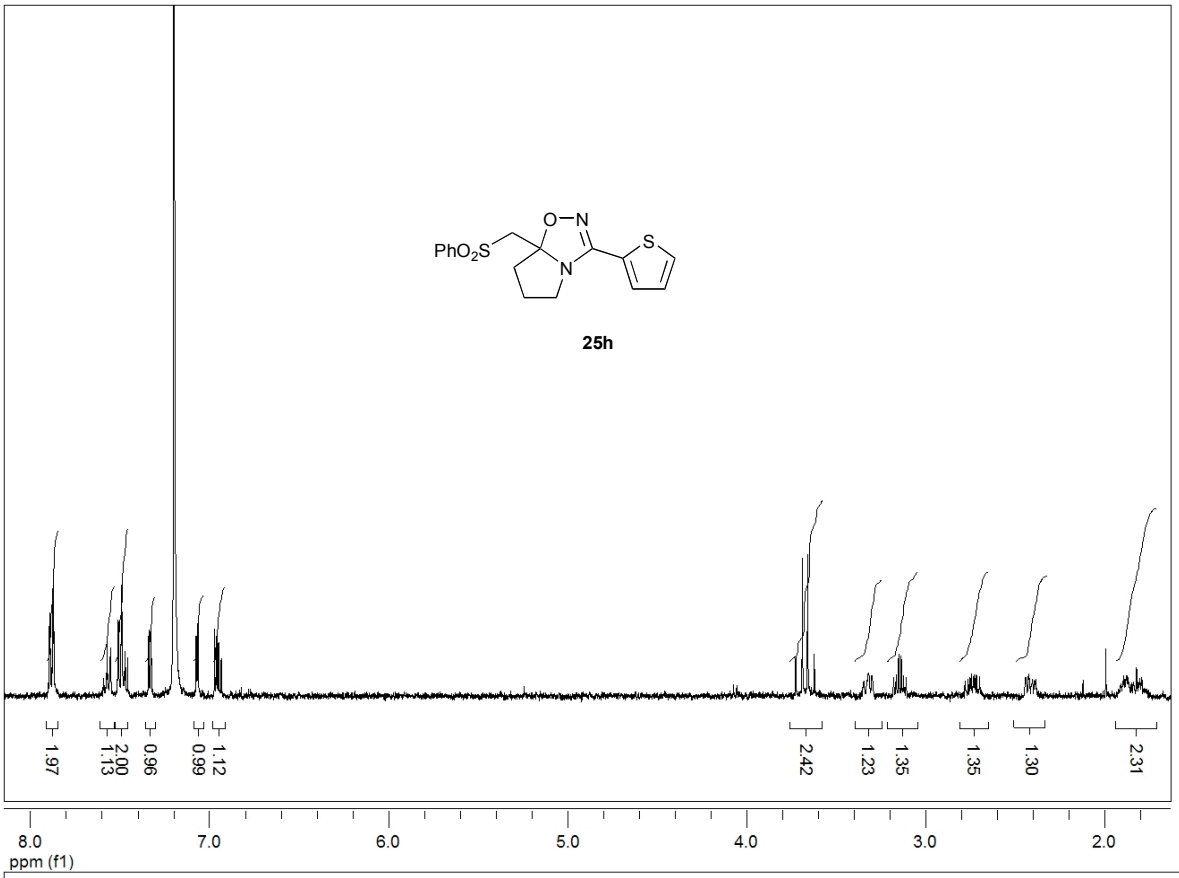
3-(4-Fluorophenyl)-7a-(phenylsulfonylmethyl)-5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazole (25f)

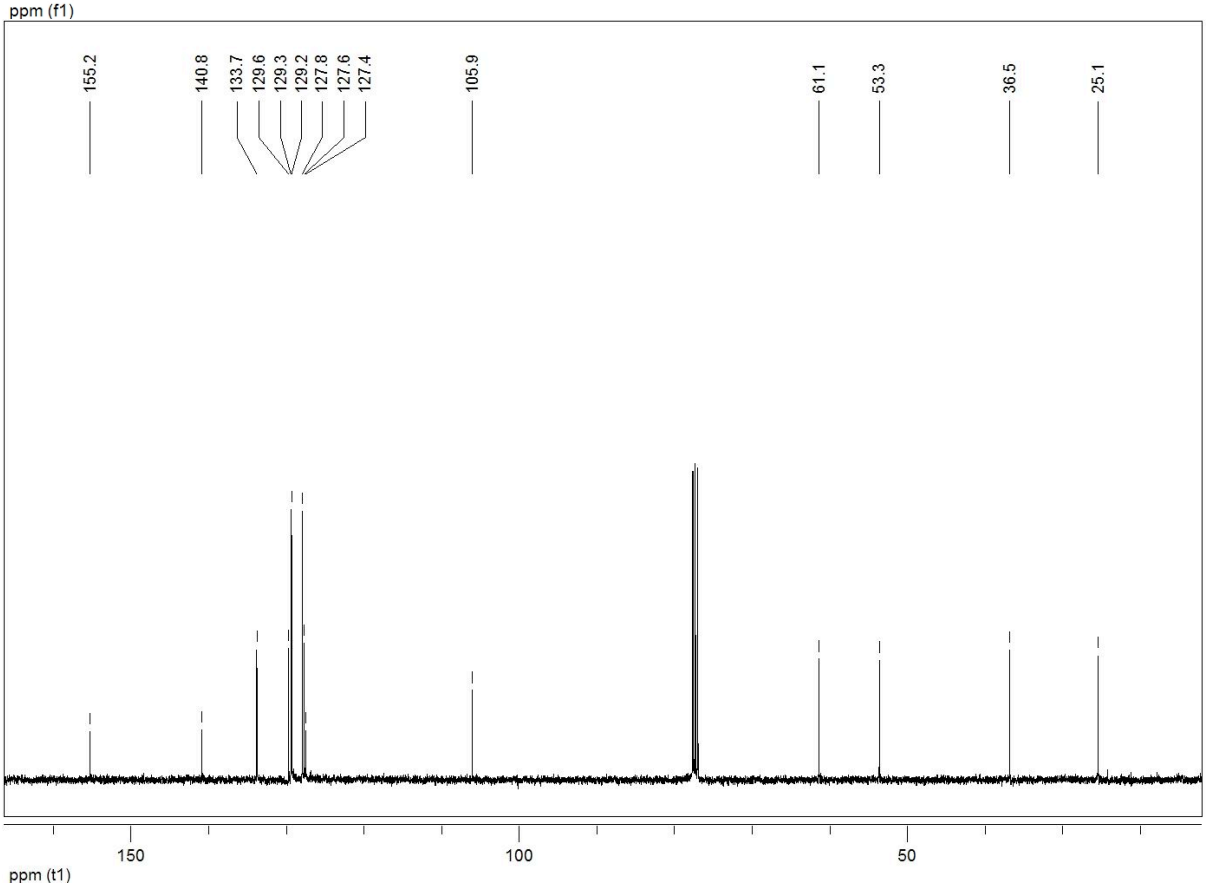


3-(4-Bromophenyl)-7a-(phenylsulfonylmethyl)-5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazole (25g)

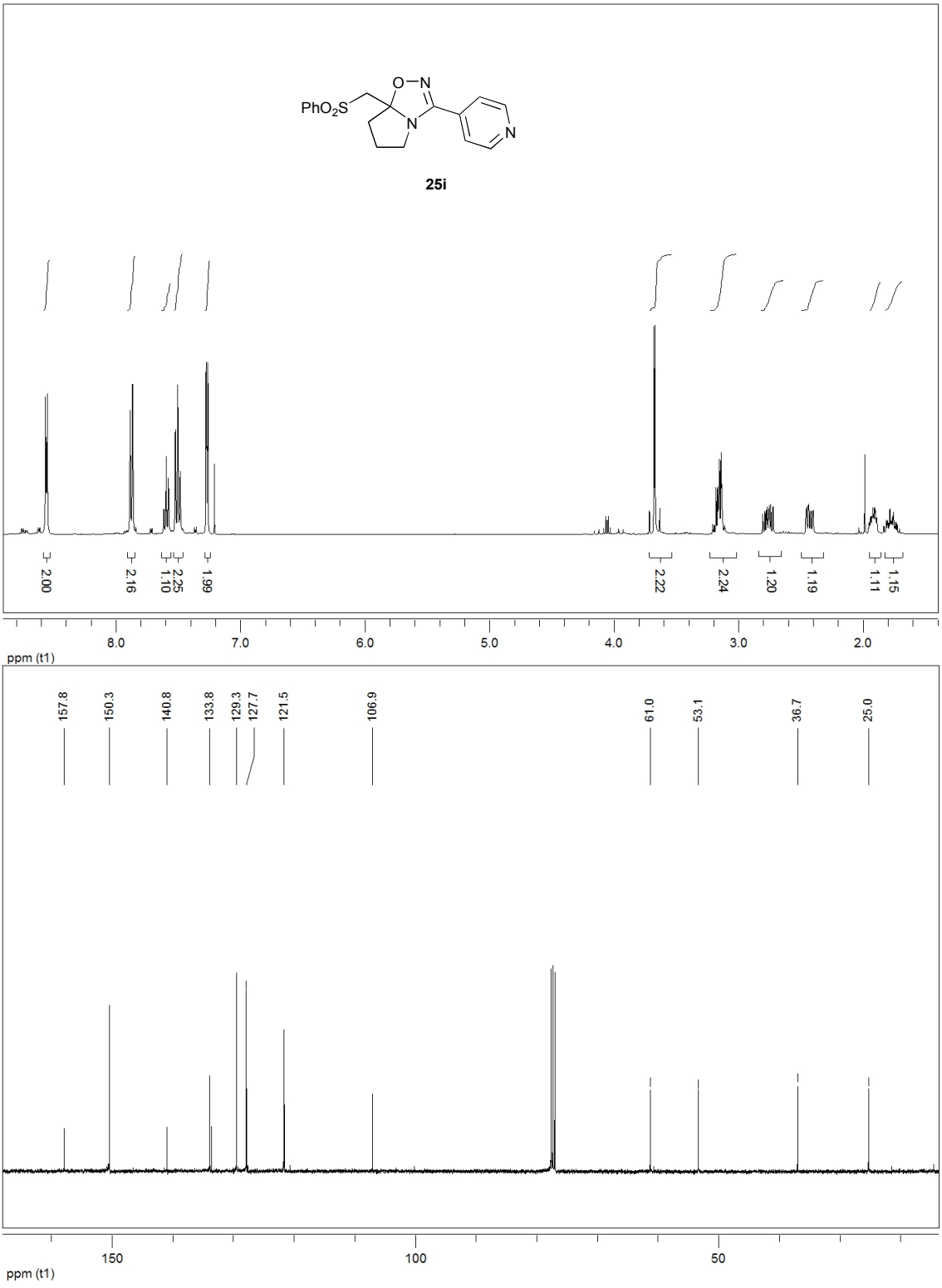


7a-(Phenylsulfonylmethyl)-3-(thien-2-yl)-5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazole (25h)

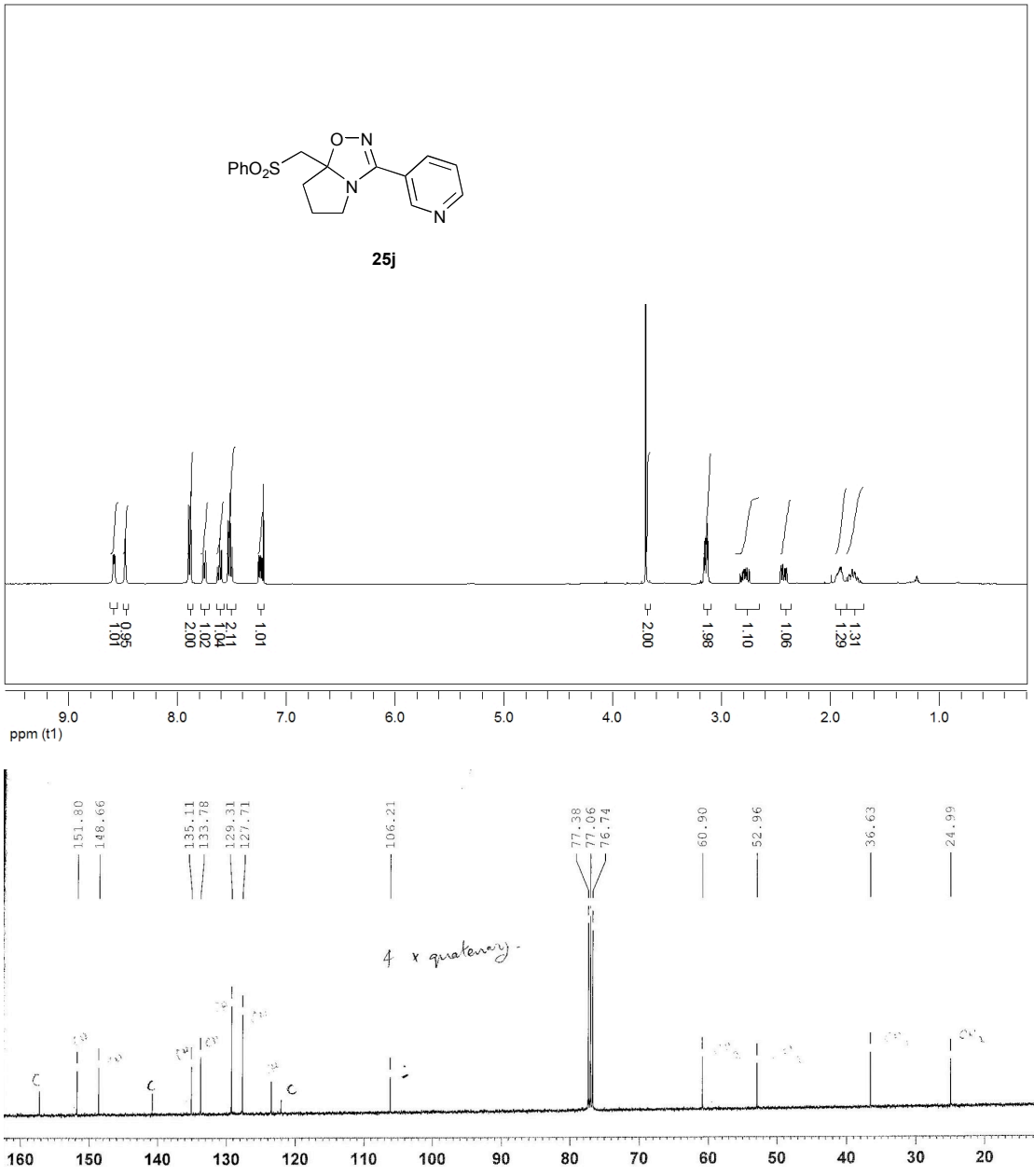




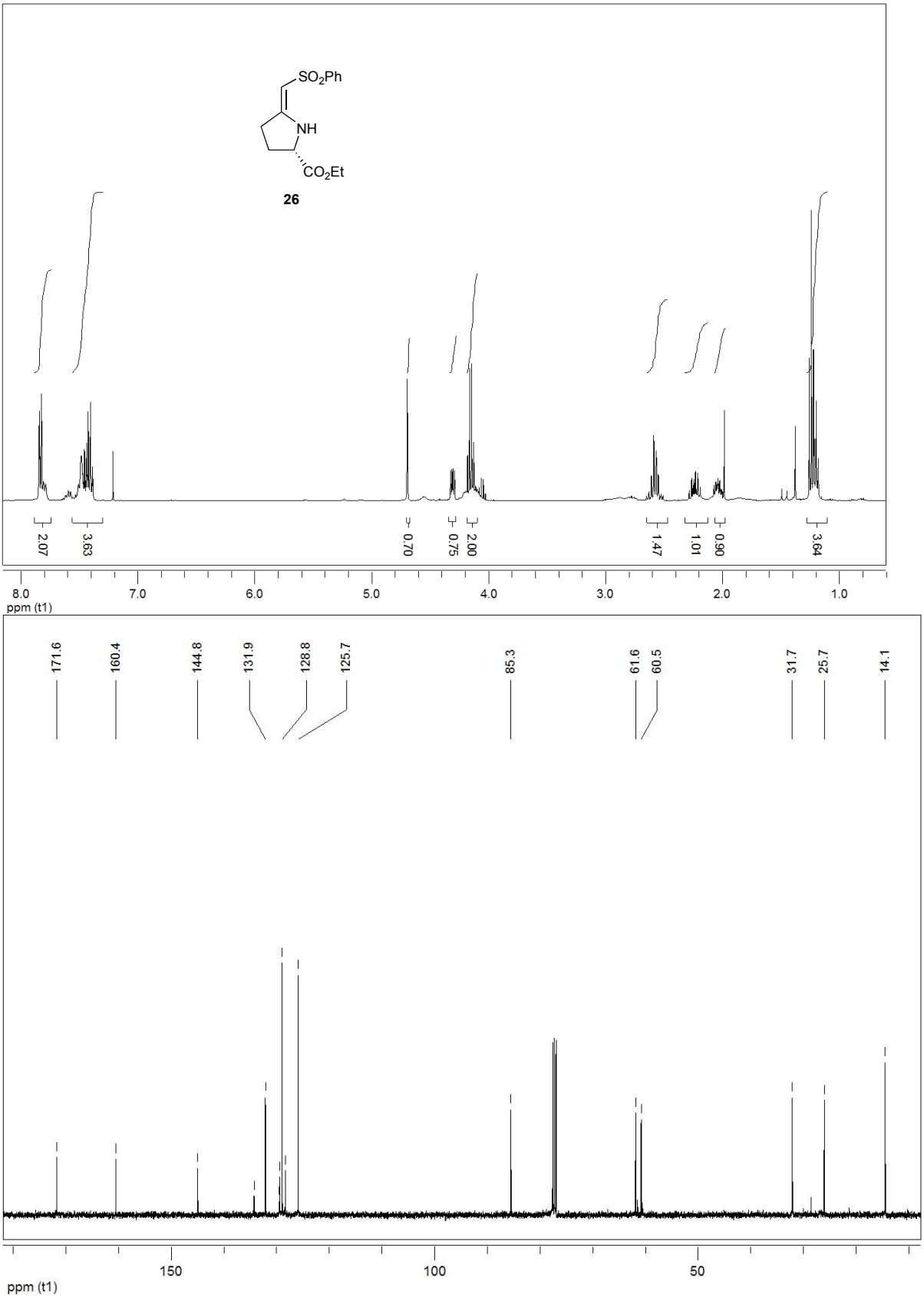
7a-(Phenylsulfonylmethyl)-3-(pyridin-4-yl)-5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazole (25i)



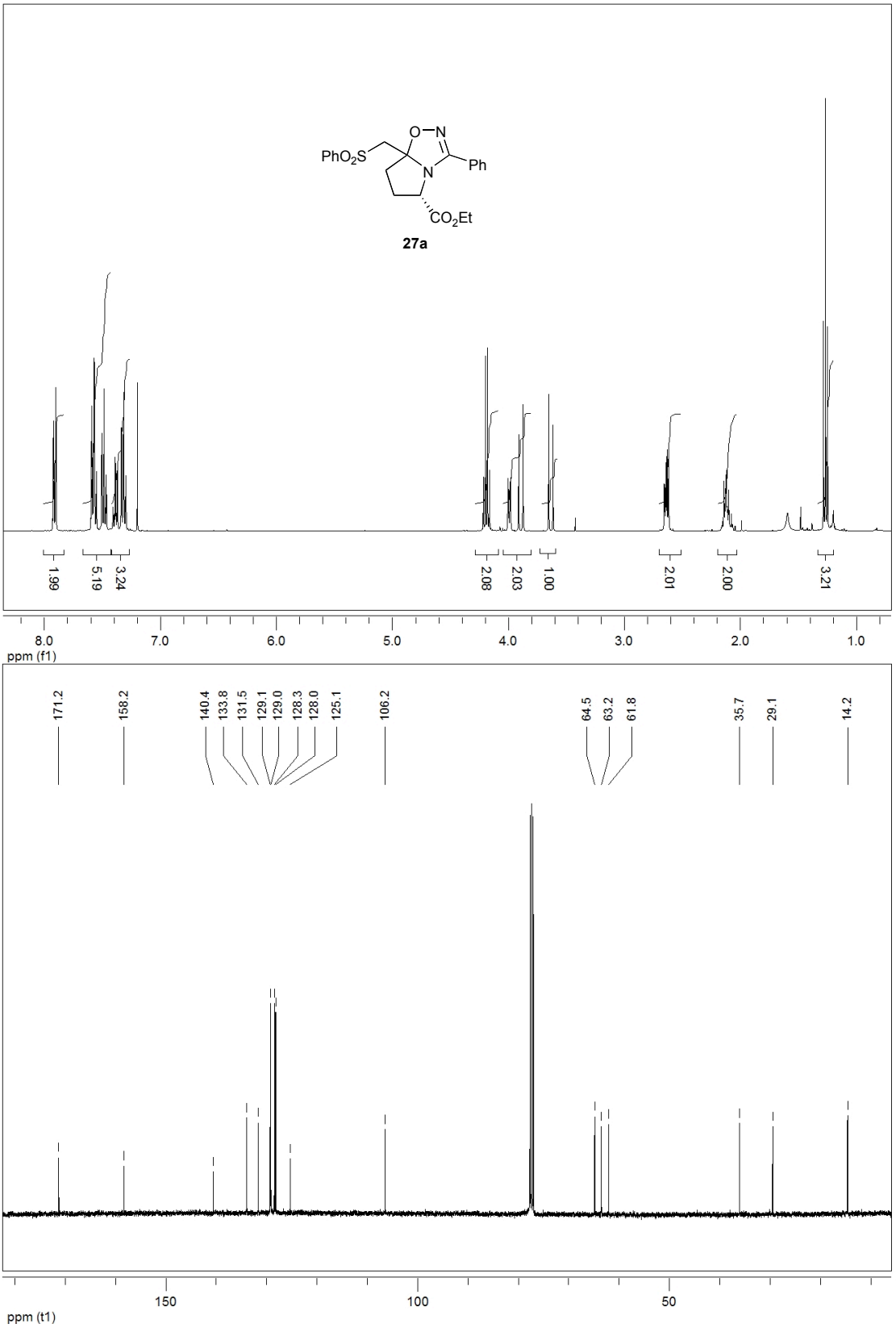
7a-(Phenylsulfonylmethyl)-3-(pyridin-3-yl)-5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazole (25j)



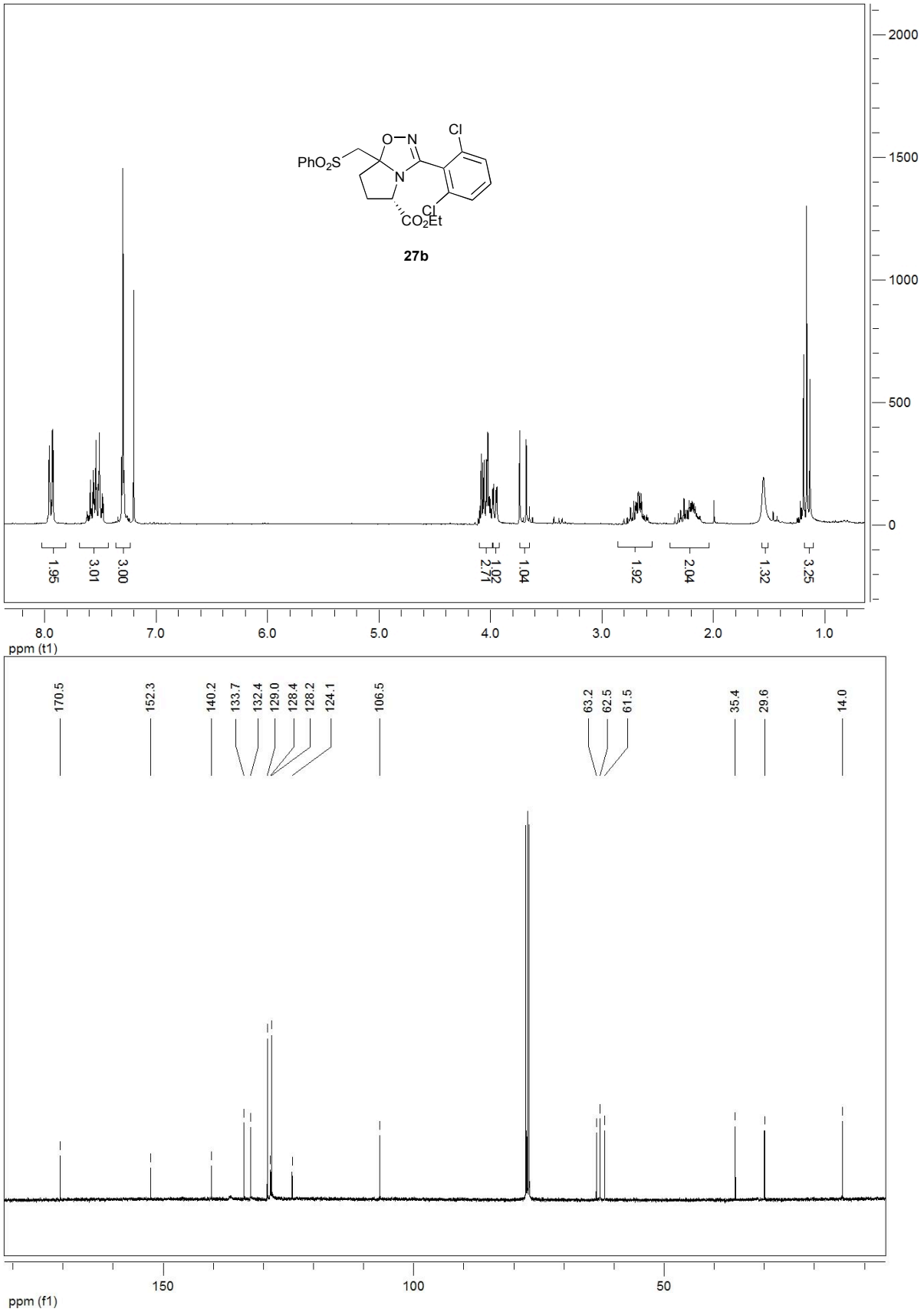
(*S*,*Z*)-Ethyl 5-(phenylsulfonylmethylene)pyrrolidine-2-carboxylate (26)



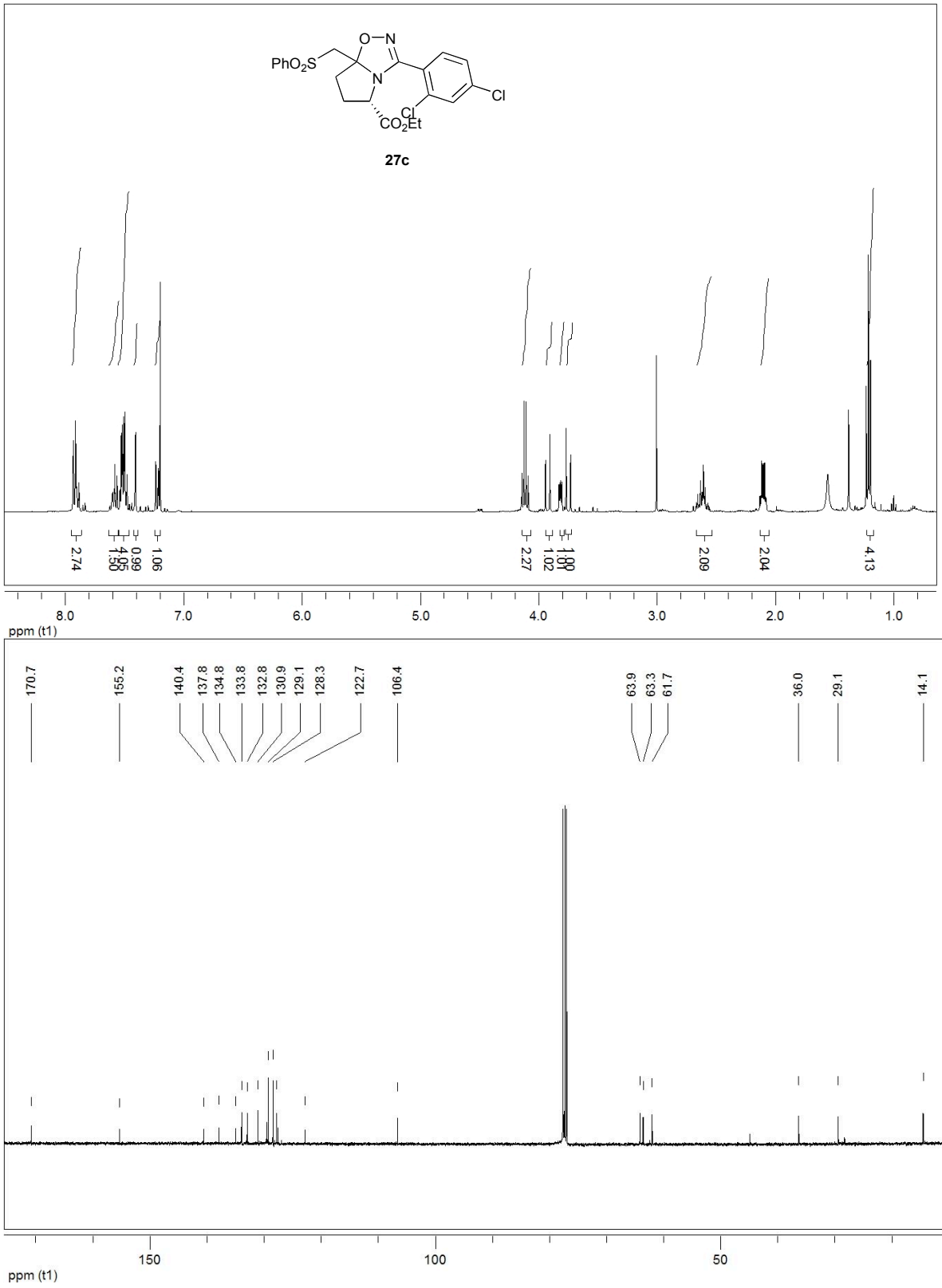
(5*S*,7a*S*)-Ethyl 3-phenyl-7a-(phenylsulfonylmethyl)-5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazole-5-carboxylate (27a)



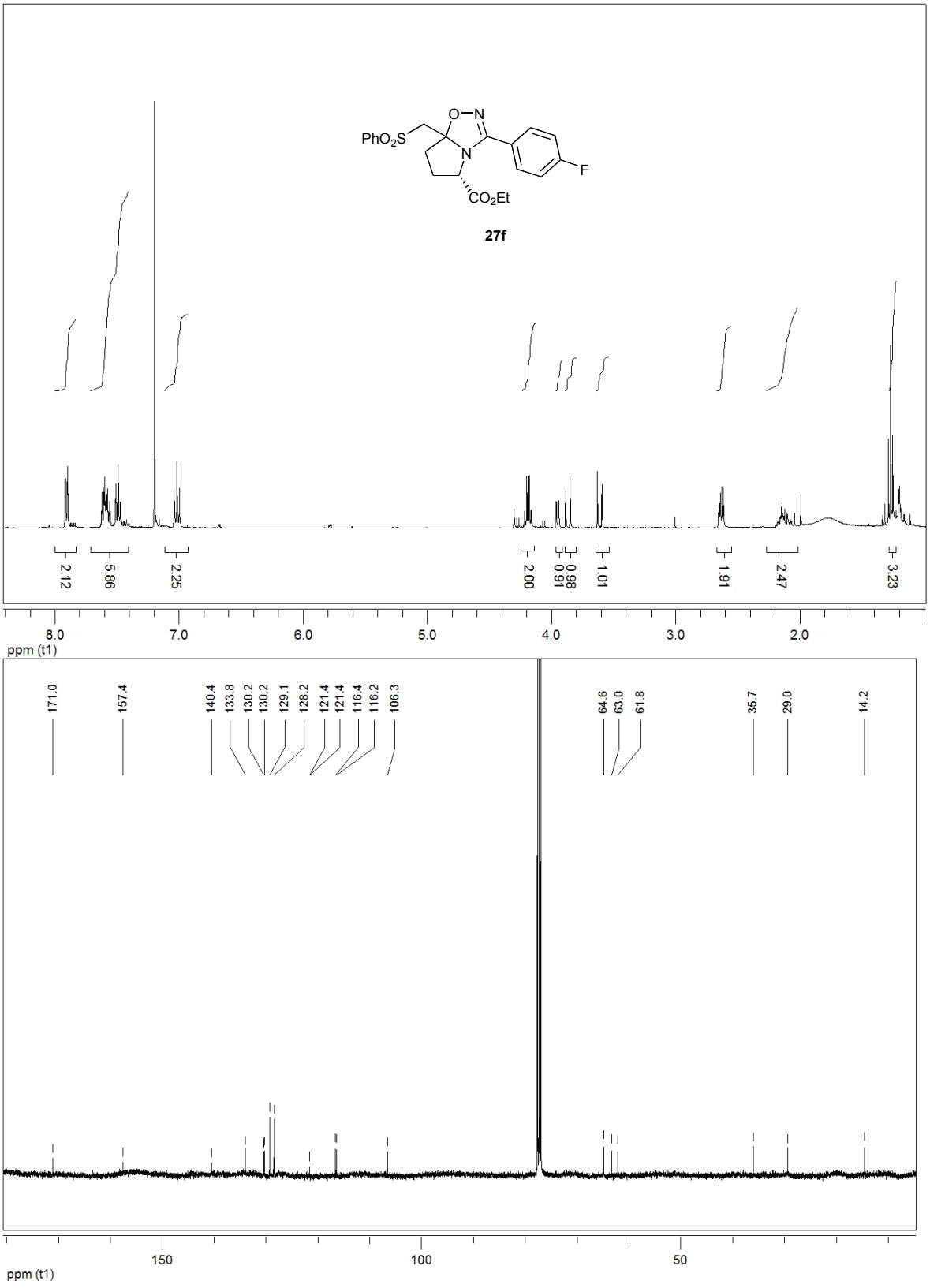
(5*S*,7a*S*)-Ethyl 3-(2,6-dichlorophenyl)-7a-(phenylsulfonylmethyl)-5,6,7,7a-tetrahydropyrrolo [1,2-*d*][1,2,4]oxadiazole-5-carboxylate (27b)



(5*S*,7a*S*)-Ethyl 3-(2,4-dichlorophenyl)-7a-(phenylsulfonylmethyl)-5,6,7,7a-tetrahydropyrrolo [1,2-*d*][1,2,4]oxadiazole-5-carboxylate (27c)



(5*S*,7a*S*)-Ethyl 3-(4-fluorophenyl)-7a-(phenylsulfonylmethyl)- -5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazole-5-carboxylate (27f)



(5*S*,7a*S*)-Ethyl 3-(4-bromophenyl)-7a-(phenylsulfonylmethyl)- -5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazole-5-carboxylate (27g)