Identification of BACE-1 inhibitors through directed C(sp^3)-H activation on 5-oxo-pyrrolidine-3-carboxylic acid derivatives

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Electronic Supplementary Information

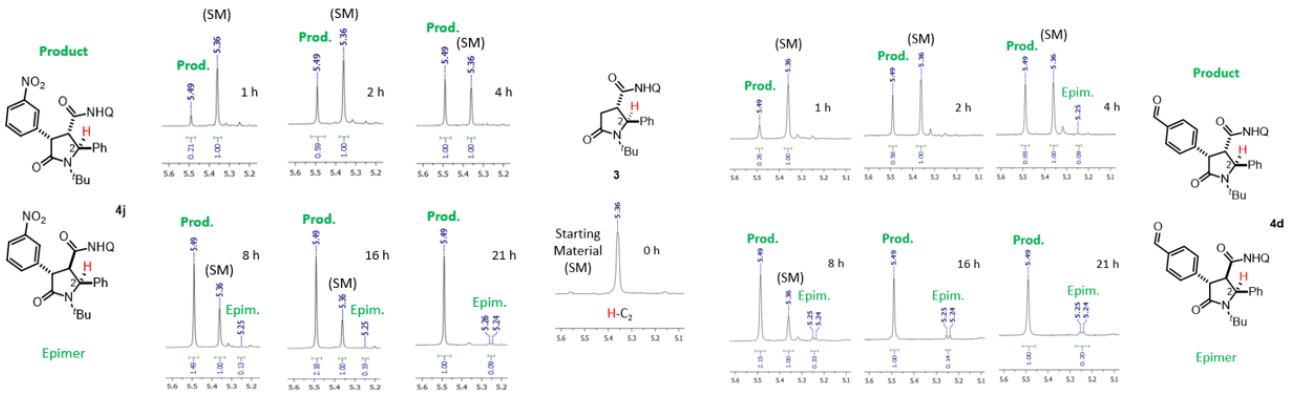

Figure S1. NMR spectra at different time (1, 2, 4, 8, 16, 21 hours) of the reaction mixture of the C(sp^3)-H bond activation reaction, employing 1-iodo-3-nitrobenzene (A) and 4-iodobenzaldehyde (B) as aryl iodides. The reaction conversion trend as well as the epimerization trend can be followed by analyzing the NMR signals of the proton linked to C(2) of the 5-pyrrolidone central scaffold.

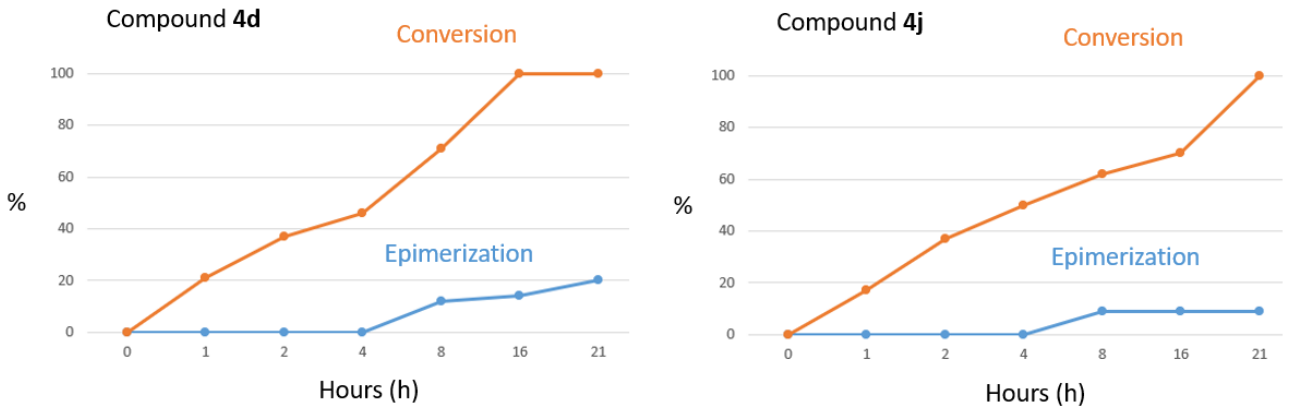

Figure S2. Plots of reaction conversion and epimerization degree as a function of reaction time for the C(sp^3)-H bond activation reaction to achieve compound **4d** (left) and compound **4j** (right).

Crystallographic data for 4g (LB162)

Table 1. Crystal data and structure refinement for LB162.

Identification code	LB162
Empirical formula	2x(C30 H28 Br N3 O2)
Formula weight	1084.92
Temperature	100(2) K
Wavelength	1.54178 A
Crystal system, space group	Triclinic, P -1
Unit cell dimensions	a = 9.6503(2)A alpha = 81.658(1)deg.

	b = 12.2687(2)A beta = 84.899(1)deg. c = 22.1064(4)A gamma = 77.132(1)deg.
Volume	2520.25(8) A^3
Z, Calculated density	2, 1.430 Mg/m^3
Absorption coefficient	2.483 mm^-1
F(000)	1120
Crystal size	0.150 x 0.080 x 0.040 mm
Theta range for data collection	2.023 to 68.556 deg.
Limiting indices	-10<=h<=11, -14<=k<=14, -26<=l<=26
Reflections collected / unique	43937 / 9157 [R(int) = 0.0415]
Completeness to theta = 67.679	98.7 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	9157 / 0 / 658
Goodness-of-fit on F^2	1.087
Final R indices [I>2sigma(I)]	R1 = 0.0365, wR2 = 0.1093
R indices (all data)	R1 = 0.0497, wR2 = 0.1143
Extinction coefficient	0.00110(11)
Largest diff. peak and hole	0.802 and -0.448 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for cu_baldini_20220311_0m_a. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
N(1A)	2529(2)	1301(1)	8760(1)	13(1)
N(2A)	2363(2)	2132(1)	6608(1)	15(1)
N(3A)	1705(2)	1244(1)	5679(1)	21(1)
O(1A)	3970(2)	-480(1)	8806(1)	23(1)
O(2A)	2748(2)	3361(1)	7217(1)	18(1)
Br(1A)	9401(1)	480(1)	6726(1)	22(1)
C(1A)	1743(2)	2162(1)	8307(1)	12(1)
C(2A)	2059(2)	1638(1)	7699(1)	11(1)
C(3A)	3245(2)	556(1)	7823(1)	13(1)
C(4A)	3291(2)	375(2)	8521(1)	14(1)
C(5A)	4731(2)	590(1)	7544(1)	13(1)
C(6A)	5444(2)	1426(2)	7631(1)	15(1)
C(7A)	6824(2)	1410(2)	7386(1)	16(1)
C(8A)	7498(2)	540(2)	7056(1)	15(1)
C(9A)	6822(2)	-303(2)	6963(1)	18(1)
C(10A)	5440(2)	-270(2)	7209(1)	16(1)
C(11A)	2657(2)	1477(2)	9411(1)	16(1)
C(12A)	2086(2)	577(2)	9853(1)	22(1)
C(13A)	4230(2)	1420(2)	9504(1)	28(1)
C(14A)	1814(2)	2645(2)	9532(1)	22(1)
C(15A)	141(2)	2431(1)	8455(1)	12(1)
C(16A)	-586(2)	1588(1)	8690(1)	14(1)
C(17A)	-2057(2)	1839(2)	8802(1)	18(1)
C(18A)	-2820(2)	2942(2)	8674(1)	20(1)
C(19A)	-2105(2)	3782(2)	8431(1)	21(1)
C(20A)	-628(2)	3532(2)	8322(1)	17(1)
C(21A)	2425(2)	2476(1)	7159(1)	11(1)
C(22A)	2681(2)	2661(2)	6021(1)	16(1)
C(23A)	3275(2)	3591(2)	5892(1)	24(1)
C(24A)	3529(2)	4040(2)	5273(1)	30(1)
C(25A)	3204(3)	3571(2)	4799(1)	29(1)
C(26A)	2580(2)	2621(2)	4915(1)	20(1)
C(27A)	2175(2)	2096(2)	4450(1)	26(1)
C(28A)	1554(2)	1187(2)	4605(1)	30(1)
C(29A)	1356(2)	780(2)	5231(1)	28(1)
C(30A)	2314(2)	2159(2)	5530(1)	15(1)
N(1B)	2512(2)	6299(1)	8766(1)	13(1)
N(2B)	2348(2)	7142(1)	6615(1)	16(1)
N(3B)	1460(2)	6493(2)	5650(1)	21(1)
O(1B)	3960(2)	4522(1)	8813(1)	23(1)
O(2B)	2858(2)	8305(1)	7233(1)	18(1)
Br(1B)	9354(1)	5460(1)	6704(1)	24(1)
C(1B)	1718(2)	7159(1)	8313(1)	12(1)
C(2B)	2043(2)	6635(1)	7704(1)	11(1)
C(3B)	3219(2)	5548(1)	7831(1)	13(1)
C(4B)	3276(2)	5375(2)	8528(1)	15(1)
C(5B)	4702(2)	5573(1)	7546(1)	12(1)
C(6B)	5443(2)	6382(2)	7647(1)	15(1)
C(7B)	6817(2)	6368(2)	7393(1)	16(1)

C(8B)	7455(2)	5526(2)	7042(1)	16(1)
C(9B)	6750(2)	4711(2)	6931(1)	19(1)
C(10B)	5374(2)	4744(2)	7184(1)	16(1)
C(11B)	2640(2)	6481(2)	9415(1)	16(1)
C(12B)	2069(2)	5583(2)	9859(1)	21(1)
C(13B)	4213(2)	6421(2)	9508(1)	28(1)
C(14B)	1798(2)	7649(2)	9535(1)	22(1)
C(15B)	125(2)	7428(1)	8460(1)	13(1)
C(16B)	-608(2)	6583(1)	8693(1)	14(1)
C(17B)	-2077(2)	6835(2)	8806(1)	17(1)
C(18B)	-2837(2)	7940(2)	8681(1)	19(1)
C(19B)	-2120(2)	8782(2)	8442(1)	21(1)
C(20B)	-646(2)	8529(2)	8333(1)	17(1)
C(21B)	2448(2)	7460(1)	7168(1)	12(1)
C(22B)	2804(2)	7620(2)	6036(1)	16(1)
C(23B)	3696(2)	8364(2)	5938(1)	27(1)
C(24B)	4149(3)	8745(2)	5335(1)	33(1)
C(25B)	3697(3)	8411(2)	4835(1)	30(1)
C(26B)	2767(2)	7647(2)	4921(1)	21(1)
C(27B)	2240(2)	7255(2)	4437(1)	26(1)
C(28B)	1331(2)	6544(2)	4563(1)	31(1)
C(29B)	972(2)	6187(2)	5179(1)	30(1)
C(30B)	2333(2)	7236(2)	5527(1)	15(1)

Table 3. Bond lengths [A] and angles [deg] for cu_baldini_20220311_0m_a.

N(1A)-C(4A)	1.358(2)
N(1A)-C(1A)	1.471(2)
N(1A)-C(11A)	1.505(2)
N(2A)-C(21A)	1.356(2)
N(2A)-C(22A)	1.403(2)
N(2A)-HN1A	0.81(3)
N(3A)-C(29A)	1.313(3)
N(3A)-C(30A)	1.366(3)
O(1A)-C(4A)	1.226(2)
O(2A)-C(21A)	1.222(2)
Br(1A)-C(8A)	1.9043(18)
C(1A)-C(15A)	1.523(2)
C(1A)-C(2A)	1.552(2)
C(1A)-H(1A)	1.0000
C(2A)-C(21A)	1.528(2)
C(2A)-C(3A)	1.556(2)
C(2A)-H(2A)	1.0000
C(3A)-C(5A)	1.516(3)
C(3A)-C(4A)	1.530(2)
C(3A)-H(3A)	1.0000
C(5A)-C(10A)	1.395(3)
C(5A)-C(6A)	1.399(3)
C(6A)-C(7A)	1.389(3)
C(6A)-H(6A)	0.9500
C(7A)-C(8A)	1.388(3)
C(7A)-H(7A)	0.9500
C(8A)-C(9A)	1.388(3)
C(9A)-C(10A)	1.388(3)
C(9A)-H(9A)	0.9500
C(10A)-H(10A)	0.9500
C(11A)-C(14A)	1.529(3)
C(11A)-C(12A)	1.530(3)
C(11A)-C(13A)	1.535(3)
C(12A)-H(12A)	0.9800
C(12A)-H(12B)	0.9800
C(12A)-H(12C)	0.9800
C(13A)-H(13A)	0.9800
C(13A)-H(13B)	0.9800
C(13A)-H(13C)	0.9800
C(14A)-H(14A)	0.9800
C(14A)-H(14B)	0.9800
C(14A)-H(14C)	0.9800
C(15A)-C(16A)	1.392(3)
C(15A)-C(20A)	1.393(2)
C(16A)-C(17A)	1.391(3)
C(16A)-H(16A)	0.9500
C(17A)-C(18A)	1.391(3)
C(17A)-H(17A)	0.9500
C(18A)-C(19A)	1.385(3)
C(18A)-H(18A)	0.9500
C(19A)-C(20A)	1.396(3)
C(19A)-H(19A)	0.9500
C(20A)-H(20A)	0.9500
C(22A)-C(23A)	1.371(3)
C(22A)-C(30A)	1.430(3)

C(23A)-C(24A)	1.420(3)
C(23A)-H(23A)	0.9500
C(24A)-C(25A)	1.358(3)
C(24A)-H(24A)	0.9500
C(25A)-C(26A)	1.409(3)
C(25A)-H(25A)	0.9500
C(26A)-C(27A)	1.414(3)
C(26A)-C(30A)	1.420(3)
C(27A)-C(28A)	1.368(3)
C(27A)-H(27A)	0.9500
C(28A)-C(29A)	1.413(3)
C(28A)-H(28A)	0.9500
C(29A)-H(29A)	0.9500
N(1B)-C(4B)	1.356(2)
N(1B)-C(1B)	1.475(2)
N(1B)-C(11B)	1.504(2)
N(2B)-C(21B)	1.355(2)
N(2B)-C(22B)	1.404(2)
N(2B)-HN1B	0.80(3)
N(3B)-C(29B)	1.315(3)
N(3B)-C(30B)	1.359(3)
O(1B)-C(4B)	1.225(2)
O(2B)-C(21B)	1.219(2)
Br(1B)-C(8B)	1.9050(19)
C(1B)-C(15B)	1.515(3)
C(1B)-C(2B)	1.552(2)
C(1B)-H(1B)	1.0000
C(2B)-C(21B)	1.526(2)
C(2B)-C(3B)	1.556(2)
C(2B)-H(2B)	1.0000
C(3B)-C(5B)	1.517(3)
C(3B)-C(4B)	1.530(2)
C(3B)-H(3B)	1.0000
C(5B)-C(10B)	1.395(2)
C(5B)-C(6B)	1.398(3)
C(6B)-C(7B)	1.390(3)
C(6B)-H(6B)	0.9500
C(7B)-C(8B)	1.384(3)
C(7B)-H(7B)	0.9500
C(8B)-C(9B)	1.388(3)
C(9B)-C(10B)	1.389(3)
C(9B)-H(9B)	0.9500
C(10B)-H(10B)	0.9500
C(11B)-C(14B)	1.528(3)
C(11B)-C(12B)	1.530(3)
C(11B)-C(13B)	1.534(3)
C(12B)-H(12D)	0.9800
C(12B)-H(12E)	0.9800
C(12B)-H(12F)	0.9800
C(13B)-H(13D)	0.9800
C(13B)-H(13E)	0.9800
C(13B)-H(13F)	0.9800
C(14B)-H(14D)	0.9800
C(14B)-H(14E)	0.9800
C(14B)-H(14F)	0.9800
C(15B)-C(20B)	1.392(2)
C(15B)-C(16B)	1.395(3)
C(16B)-C(17B)	1.390(3)
C(16B)-H(16B)	0.9500

C(17B)-C(18B)	1.391(3)
C(17B)-H(17B)	0.9500
C(18B)-C(19B)	1.385(3)
C(18B)-H(18B)	0.9500
C(19B)-C(20B)	1.394(3)
C(19B)-H(19B)	0.9500
C(20B)-H(20B)	0.9500
C(22B)-C(23B)	1.371(3)
C(22B)-C(30B)	1.425(3)
C(23B)-C(24B)	1.412(3)
C(23B)-H(23B)	0.9500
C(24B)-C(25B)	1.371(3)
C(24B)-H(24B)	0.9500
C(25B)-C(26B)	1.418(3)
C(25B)-H(25B)	0.9500
C(26B)-C(27B)	1.411(3)
C(26B)-C(30B)	1.422(3)
C(27B)-C(28B)	1.355(4)
C(27B)-H(27B)	0.9500
C(28B)-C(29B)	1.407(3)
C(28B)-H(28B)	0.9500
C(29B)-H(29B)	0.9500

C(4A)-N(1A)-C(1A)	113.88(14)
C(4A)-N(1A)-C(11A)	121.80(14)
C(1A)-N(1A)-C(11A)	123.80(14)
C(21A)-N(2A)-C(22A)	128.65(16)
C(21A)-N(2A)-HN1A	117.0(17)
C(22A)-N(2A)-HN1A	114.4(17)
C(29A)-N(3A)-C(30A)	118.11(18)
N(1A)-C(1A)-C(15A)	113.51(14)
N(1A)-C(1A)-C(2A)	104.41(13)
C(15A)-C(1A)-C(2A)	109.25(14)
N(1A)-C(1A)-H(1A)	109.8
C(15A)-C(1A)-H(1A)	109.8
C(2A)-C(1A)-H(1A)	109.8
C(21A)-C(2A)-C(1A)	112.52(14)
C(21A)-C(2A)-C(3A)	114.15(14)
C(1A)-C(2A)-C(3A)	106.40(13)
C(21A)-C(2A)-H(2A)	107.8
C(1A)-C(2A)-H(2A)	107.8
C(3A)-C(2A)-H(2A)	107.8
C(5A)-C(3A)-C(4A)	108.71(14)
C(5A)-C(3A)-C(2A)	117.69(14)
C(4A)-C(3A)-C(2A)	103.42(14)
C(5A)-C(3A)-H(3A)	108.9
C(4A)-C(3A)-H(3A)	108.9
C(2A)-C(3A)-H(3A)	108.9
O(1A)-C(4A)-N(1A)	126.47(17)
O(1A)-C(4A)-C(3A)	123.28(16)
N(1A)-C(4A)-C(3A)	110.21(14)
C(10A)-C(5A)-C(6A)	118.50(17)
C(10A)-C(5A)-C(3A)	118.91(16)
C(6A)-C(5A)-C(3A)	122.54(16)
C(7A)-C(6A)-C(5A)	121.08(17)
C(7A)-C(6A)-H(6A)	119.5
C(5A)-C(6A)-H(6A)	119.5
C(8A)-C(7A)-C(6A)	118.85(17)
C(8A)-C(7A)-H(7A)	120.6

C(6A)-C(7A)-H(7A)	120.6
C(7A)-C(8A)-C(9A)	121.52(17)
C(7A)-C(8A)-Br(1A)	119.92(14)
C(9A)-C(8A)-Br(1A)	118.56(14)
C(8A)-C(9A)-C(10A)	118.77(17)
C(8A)-C(9A)-H(9A)	120.6
C(10A)-C(9A)-H(9A)	120.6
C(9A)-C(10A)-C(5A)	121.27(17)
C(9A)-C(10A)-H(10A)	119.4
C(5A)-C(10A)-H(10A)	119.4
N(1A)-C(11A)-C(14A)	110.33(14)
N(1A)-C(11A)-C(12A)	109.91(15)
C(14A)-C(11A)-C(12A)	109.27(16)
N(1A)-C(11A)-C(13A)	108.33(16)
C(14A)-C(11A)-C(13A)	107.91(17)
C(12A)-C(11A)-C(13A)	111.06(16)
C(11A)-C(12A)-H(12A)	109.5
C(11A)-C(12A)-H(12B)	109.5
H(12A)-C(12A)-H(12B)	109.5
C(11A)-C(12A)-H(12C)	109.5
H(12A)-C(12A)-H(12C)	109.5
H(12B)-C(12A)-H(12C)	109.5
C(11A)-C(13A)-H(13A)	109.5
C(11A)-C(13A)-H(13B)	109.5
H(13A)-C(13A)-H(13B)	109.5
C(11A)-C(13A)-H(13C)	109.5
H(13A)-C(13A)-H(13C)	109.5
H(13B)-C(13A)-H(13C)	109.5
C(11A)-C(14A)-H(14A)	109.5
C(11A)-C(14A)-H(14B)	109.5
H(14A)-C(14A)-H(14B)	109.5
C(11A)-C(14A)-H(14C)	109.5
H(14A)-C(14A)-H(14C)	109.5
H(14B)-C(14A)-H(14C)	109.5
C(16A)-C(15A)-C(20A)	118.97(17)
C(16A)-C(15A)-C(1A)	121.33(15)
C(20A)-C(15A)-C(1A)	119.62(16)
C(17A)-C(16A)-C(15A)	120.79(16)
C(17A)-C(16A)-H(16A)	119.6
C(15A)-C(16A)-H(16A)	119.6
C(18A)-C(17A)-C(16A)	120.02(18)
C(18A)-C(17A)-H(17A)	120.0
C(16A)-C(17A)-H(17A)	120.0
C(19A)-C(18A)-C(17A)	119.51(18)
C(19A)-C(18A)-H(18A)	120.2
C(17A)-C(18A)-H(18A)	120.2
C(18A)-C(19A)-C(20A)	120.50(17)
C(18A)-C(19A)-H(19A)	119.7
C(20A)-C(19A)-H(19A)	119.7
C(15A)-C(20A)-C(19A)	120.20(18)
C(15A)-C(20A)-H(20A)	119.9
C(19A)-C(20A)-H(20A)	119.9
O(2A)-C(21A)-N(2A)	123.40(16)
O(2A)-C(21A)-C(2A)	123.52(16)
N(2A)-C(21A)-C(2A)	113.07(15)
C(23A)-C(22A)-N(2A)	126.02(18)
C(23A)-C(22A)-C(30A)	119.49(18)
N(2A)-C(22A)-C(30A)	114.48(17)
C(22A)-C(23A)-C(24A)	119.75(19)

C(22A)-C(23A)-H(23A)	120.1
C(24A)-C(23A)-H(23A)	120.1
C(25A)-C(24A)-C(23A)	121.9(2)
C(25A)-C(24A)-H(24A)	119.0
C(23A)-C(24A)-H(24A)	119.0
C(24A)-C(25A)-C(26A)	119.8(2)
C(24A)-C(25A)-H(25A)	120.1
C(26A)-C(25A)-H(25A)	120.1
C(25A)-C(26A)-C(27A)	123.70(19)
C(25A)-C(26A)-C(30A)	119.26(18)
C(27A)-C(26A)-C(30A)	117.03(19)
C(28A)-C(27A)-C(26A)	119.76(19)
C(28A)-C(27A)-H(27A)	120.1
C(26A)-C(27A)-H(27A)	120.1
C(27A)-C(28A)-C(29A)	118.81(19)
C(27A)-C(28A)-H(28A)	120.6
C(29A)-C(28A)-H(28A)	120.6
N(3A)-C(29A)-C(28A)	123.6(2)
N(3A)-C(29A)-H(29A)	118.2
C(28A)-C(29A)-H(29A)	118.2
N(3A)-C(30A)-C(26A)	122.66(17)
N(3A)-C(30A)-C(22A)	117.59(17)
C(26A)-C(30A)-C(22A)	119.75(18)
C(4B)-N(1B)-C(1B)	113.94(14)
C(4B)-N(1B)-C(11B)	121.92(14)
C(1B)-N(1B)-C(11B)	123.63(14)
C(21B)-N(2B)-C(22B)	128.10(16)
C(21B)-N(2B)-HN1B	116.8(18)
C(22B)-N(2B)-HN1B	115.0(18)
C(29B)-N(3B)-C(30B)	117.03(19)
N(1B)-C(1B)-C(15B)	113.73(14)
N(1B)-C(1B)-C(2B)	104.33(13)
C(15B)-C(1B)-C(2B)	109.64(14)
N(1B)-C(1B)-H(1B)	109.7
C(15B)-C(1B)-H(1B)	109.7
C(2B)-C(1B)-H(1B)	109.7
C(21B)-C(2B)-C(1B)	112.71(14)
C(21B)-C(2B)-C(3B)	113.28(14)
C(1B)-C(2B)-C(3B)	106.52(13)
C(21B)-C(2B)-H(2B)	108.0
C(1B)-C(2B)-H(2B)	108.0
C(3B)-C(2B)-H(2B)	108.0
C(5B)-C(3B)-C(4B)	108.77(14)
C(5B)-C(3B)-C(2B)	117.35(14)
C(4B)-C(3B)-C(2B)	103.53(14)
C(5B)-C(3B)-H(3B)	109.0
C(4B)-C(3B)-H(3B)	109.0
C(2B)-C(3B)-H(3B)	109.0
O(1B)-C(4B)-N(1B)	126.55(17)
O(1B)-C(4B)-C(3B)	123.14(16)
N(1B)-C(4B)-C(3B)	110.28(14)
C(10B)-C(5B)-C(6B)	118.45(17)
C(10B)-C(5B)-C(3B)	119.16(16)
C(6B)-C(5B)-C(3B)	122.37(16)
C(7B)-C(6B)-C(5B)	121.17(17)
C(7B)-C(6B)-H(6B)	119.4
C(5B)-C(6B)-H(6B)	119.4
C(8B)-C(7B)-C(6B)	118.77(17)
C(8B)-C(7B)-H(7B)	120.6

C(6B)-C(7B)-H(7B)	120.6
C(7B)-C(8B)-C(9B)	121.61(18)
C(7B)-C(8B)-Br(1B)	119.83(14)
C(9B)-C(8B)-Br(1B)	118.56(14)
C(8B)-C(9B)-C(10B)	118.79(17)
C(8B)-C(9B)-H(9B)	120.6
C(10B)-C(9B)-H(9B)	120.6
C(9B)-C(10B)-C(5B)	121.20(17)
C(9B)-C(10B)-H(10B)	119.4
C(5B)-C(10B)-H(10B)	119.4
N(1B)-C(11B)-C(14B)	110.48(14)
N(1B)-C(11B)-C(12B)	109.74(15)
C(14B)-C(11B)-C(12B)	109.25(16)
N(1B)-C(11B)-C(13B)	108.32(15)
C(14B)-C(11B)-C(13B)	108.05(17)
C(12B)-C(11B)-C(13B)	110.97(16)
C(11B)-C(12B)-H(12D)	109.5
C(11B)-C(12B)-H(12E)	109.5
H(12D)-C(12B)-H(12E)	109.5
C(11B)-C(12B)-H(12F)	109.5
H(12D)-C(12B)-H(12F)	109.5
H(12E)-C(12B)-H(12F)	109.5
C(11B)-C(13B)-H(13D)	109.5
C(11B)-C(13B)-H(13E)	109.5
H(13D)-C(13B)-H(13E)	109.5
C(11B)-C(13B)-H(13F)	109.5
H(13D)-C(13B)-H(13F)	109.5
H(13E)-C(13B)-H(13F)	109.5
C(11B)-C(14B)-H(14D)	109.5
C(11B)-C(14B)-H(14E)	109.5
H(14D)-C(14B)-H(14E)	109.5
C(11B)-C(14B)-H(14F)	109.5
H(14D)-C(14B)-H(14F)	109.5
H(14E)-C(14B)-H(14F)	109.5
C(20B)-C(15B)-C(16B)	118.73(17)
C(20B)-C(15B)-C(1B)	119.81(16)
C(16B)-C(15B)-C(1B)	121.38(15)
C(17B)-C(16B)-C(15B)	120.82(16)
C(17B)-C(16B)-H(16B)	119.6
C(15B)-C(16B)-H(16B)	119.6
C(16B)-C(17B)-C(18B)	120.01(18)
C(16B)-C(17B)-H(17B)	120.0
C(18B)-C(17B)-H(17B)	120.0
C(19B)-C(18B)-C(17B)	119.57(18)
C(19B)-C(18B)-H(18B)	120.2
C(17B)-C(18B)-H(18B)	120.2
C(18B)-C(19B)-C(20B)	120.37(17)
C(18B)-C(19B)-H(19B)	119.8
C(20B)-C(19B)-H(19B)	119.8
C(15B)-C(20B)-C(19B)	120.49(18)
C(15B)-C(20B)-H(20B)	119.8
C(19B)-C(20B)-H(20B)	119.8
O(2B)-C(21B)-N(2B)	123.51(17)
O(2B)-C(21B)-C(2B)	123.22(16)
N(2B)-C(21B)-C(2B)	113.23(15)
C(23B)-C(22B)-N(2B)	124.79(18)
C(23B)-C(22B)-C(30B)	119.83(18)
N(2B)-C(22B)-C(30B)	115.31(17)
C(22B)-C(23B)-C(24B)	120.0(2)

C(22B)-C(23B)-H(23B)	120.0
C(24B)-C(23B)-H(23B)	120.0
C(25B)-C(24B)-C(23B)	121.7(2)
C(25B)-C(24B)-H(24B)	119.1
C(23B)-C(24B)-H(24B)	119.1
C(24B)-C(25B)-C(26B)	119.5(2)
C(24B)-C(25B)-H(25B)	120.2
C(26B)-C(25B)-H(25B)	120.2
C(27B)-C(26B)-C(25B)	123.82(19)
C(27B)-C(26B)-C(30B)	117.0(2)
C(25B)-C(26B)-C(30B)	119.14(19)
C(28B)-C(27B)-C(26B)	119.77(19)
C(28B)-C(27B)-H(27B)	120.1
C(26B)-C(27B)-H(27B)	120.1
C(27B)-C(28B)-C(29B)	118.6(2)
C(27B)-C(28B)-H(28B)	120.7
C(29B)-C(28B)-H(28B)	120.7
N(3B)-C(29B)-C(28B)	124.6(2)
N(3B)-C(29B)-H(29B)	117.7
C(28B)-C(29B)-H(29B)	117.7
N(3B)-C(30B)-C(26B)	122.89(18)
N(3B)-C(30B)-C(22B)	117.38(17)
C(26B)-C(30B)-C(22B)	119.72(18)

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for cu_baldini_20220311_0m_a.

The anisotropic displacement factor exponent takes the form:

-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
N(1A)	14(1)	17(1)	8(1)	0(1)	-1(1)	-2(1)
N(2A)	21(1)	16(1)	10(1)	1(1)	1(1)	-10(1)
N(3A)	20(1)	28(1)	16(1)	-5(1)	3(1)	-10(1)
O(1A)	22(1)	22(1)	18(1)	6(1)	6(1)	5(1)
O(2A)	27(1)	17(1)	13(1)	-2(1)	2(1)	-10(1)
Br(1A)	15(1)	37(1)	18(1)	-6(1)	6(1)	-12(1)
C(1A)	15(1)	12(1)	8(1)	1(1)	-1(1)	-4(1)
C(2A)	12(1)	14(1)	9(1)	-2(1)	1(1)	-4(1)
C(3A)	13(1)	13(1)	12(1)	-1(1)	1(1)	-4(1)
C(4A)	13(1)	17(1)	12(1)	2(1)	4(1)	-3(1)
C(5A)	14(1)	15(1)	8(1)	1(1)	1(1)	-4(1)
C(6A)	17(1)	15(1)	13(1)	-1(1)	0(1)	-3(1)
C(7A)	17(1)	18(1)	13(1)	1(1)	-2(1)	-8(1)
C(8A)	14(1)	23(1)	9(1)	2(1)	2(1)	-7(1)
C(9A)	20(1)	22(1)	13(1)	-6(1)	4(1)	-6(1)
C(10A)	17(1)	19(1)	13(1)	-3(1)	2(1)	-8(1)
C(11A)	17(1)	25(1)	9(1)	-1(1)	-2(1)	-8(1)
C(12A)	30(1)	27(1)	10(1)	1(1)	1(1)	-11(1)
C(13A)	19(1)	49(1)	20(1)	-1(1)	-5(1)	-14(1)
C(14A)	32(1)	26(1)	11(1)	-6(1)	0(1)	-10(1)
C(15A)	15(1)	14(1)	7(1)	-2(1)	0(1)	-2(1)
C(16A)	15(1)	13(1)	13(1)	-2(1)	-3(1)	-1(1)
C(17A)	18(1)	25(1)	12(1)	-3(1)	1(1)	-7(1)
C(18A)	12(1)	32(1)	13(1)	-6(1)	-1(1)	2(1)
C(19A)	23(1)	20(1)	15(1)	-2(1)	-3(1)	7(1)
C(20A)	23(1)	15(1)	12(1)	0(1)	1(1)	-3(1)
C(21A)	10(1)	14(1)	10(1)	-1(1)	2(1)	-3(1)
C(22A)	17(1)	18(1)	10(1)	-1(1)	2(1)	-2(1)
C(23A)	33(1)	23(1)	19(1)	-3(1)	4(1)	-12(1)
C(24A)	40(1)	24(1)	27(1)	0(1)	7(1)	-13(1)
C(25A)	45(1)	23(1)	17(1)	2(1)	8(1)	-8(1)
C(26A)	24(1)	21(1)	11(1)	0(1)	2(1)	1(1)
C(27A)	30(1)	34(1)	10(1)	-3(1)	-1(1)	2(1)
C(28A)	31(1)	46(1)	16(1)	-11(1)	-1(1)	-10(1)
C(29A)	29(1)	38(1)	22(1)	-10(1)	3(1)	-15(1)
C(30A)	10(1)	19(1)	12(1)	-1(1)	1(1)	1(1)
N(1B)	14(1)	17(1)	8(1)	1(1)	0(1)	-2(1)
N(2B)	21(1)	17(1)	11(1)	0(1)	0(1)	-11(1)
N(3B)	19(1)	30(1)	17(1)	-6(1)	2(1)	-8(1)
O(1B)	21(1)	22(1)	18(1)	6(1)	5(1)	4(1)
O(2B)	25(1)	16(1)	14(1)	-2(1)	2(1)	-10(1)
Br(1B)	15(1)	43(1)	18(1)	-7(1)	6(1)	-13(1)
C(1B)	16(1)	12(1)	7(1)	0(1)	-1(1)	-4(1)
C(2B)	12(1)	12(1)	10(1)	-1(1)	0(1)	-4(1)
C(3B)	14(1)	13(1)	12(1)	-1(1)	2(1)	-5(1)
C(4B)	13(1)	17(1)	12(1)	2(1)	3(1)	-3(1)
C(5B)	14(1)	14(1)	9(1)	1(1)	1(1)	-4(1)
C(6B)	17(1)	14(1)	13(1)	0(1)	1(1)	-4(1)
C(7B)	17(1)	19(1)	13(1)	2(1)	-2(1)	-9(1)

C(8B)	14(1)	25(1)	10(1)	2(1)	2(1)	-8(1)
C(9B)	20(1)	22(1)	14(1)	-6(1)	3(1)	-6(1)
C(10B)	16(1)	18(1)	13(1)	-3(1)	3(1)	-7(1)
C(11B)	15(1)	26(1)	9(1)	0(1)	-1(1)	-8(1)
C(12B)	27(1)	27(1)	11(1)	1(1)	2(1)	-11(1)
C(13B)	20(1)	49(1)	19(1)	-2(1)	-5(1)	-14(1)
C(14B)	33(1)	24(1)	13(1)	-6(1)	-1(1)	-9(1)
C(15B)	16(1)	14(1)	8(1)	-2(1)	-1(1)	-2(1)
C(16B)	16(1)	14(1)	12(1)	-2(1)	-2(1)	-2(1)
C(17B)	16(1)	24(1)	13(1)	-3(1)	0(1)	-6(1)
C(18B)	12(1)	31(1)	13(1)	-6(1)	-1(1)	1(1)
C(19B)	23(1)	19(1)	14(1)	-3(1)	-4(1)	7(1)
C(20B)	23(1)	14(1)	12(1)	0(1)	1(1)	-2(1)
C(21B)	11(1)	14(1)	10(1)	0(1)	1(1)	-3(1)
C(22B)	19(1)	17(1)	11(1)	1(1)	2(1)	-3(1)
C(23B)	40(1)	24(1)	20(1)	-1(1)	4(1)	-15(1)
C(24B)	47(1)	23(1)	30(1)	3(1)	8(1)	-15(1)
C(25B)	41(1)	22(1)	20(1)	5(1)	9(1)	-4(1)
C(26B)	24(1)	19(1)	13(1)	2(1)	2(1)	5(1)
C(27B)	29(1)	32(1)	11(1)	-2(1)	-1(1)	8(1)
C(28B)	29(1)	45(1)	18(1)	-13(1)	-4(1)	-1(1)
C(29B)	28(1)	43(1)	24(1)	-14(1)	2(1)	-11(1)
C(30B)	13(1)	17(1)	12(1)	0(1)	0(1)	3(1)

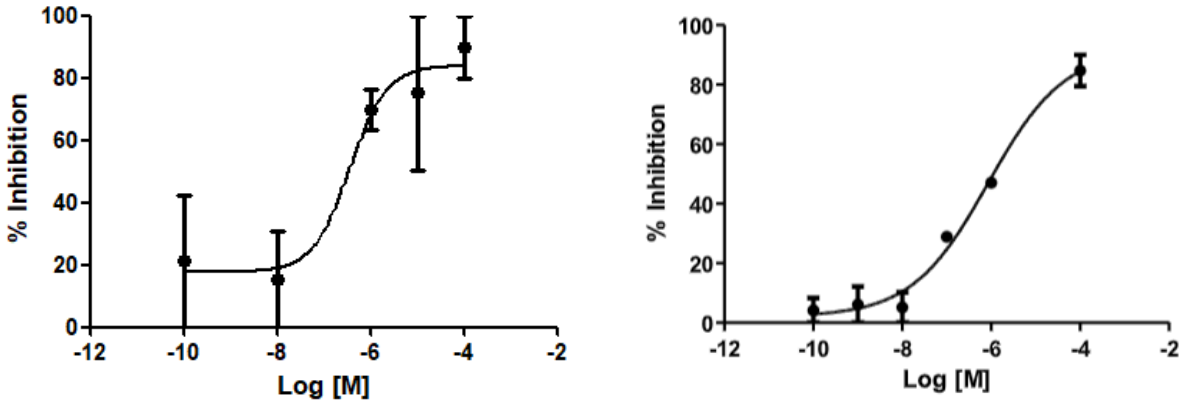

Figure S3. Inhibition curve of **4g** (left, IC_{50}=340 nM) and **5b** (right, IC_{50}=853 nM) on BACE-1 enzyme. Experiments were conducted in triplicate. Data are presented as means ± SD from three independent experiments

CNS MPO calculations

Calculated physicochemical properties were obtained using standard commercial packages. cLogP, tPSA, HBD and MW values were obtained using the web-based public tool SwissADME, whereas pKa and cLogD values, were calculated with ACD Labs Software v 6.0. The CNS MPO scores were calculated using the method published by Wagner and coworkers. For each physicochemical properties, a value T0 = 1.0 is assigned if the property is in the more desirable range, and a value T0 = 0 when the value is in the less desirable range. A linear transformation is applied between the two inflection points. The most desirable and least desirable ranges for each physicochemical property are given as follows:

More desirable range (T0 = 1)	Less desirable range (T0 = 0)
cLogP ≤ 3	cLogP > 5
cLogD ≤ 2	cLogD > 4
MW ≤ 360	MW > 500
40 < tPSA ≤ 90	tPSA ≤ 20; tPSA > 120
HBD ≤ 0.5	HBD > 3.5
pKa ≤ 8	pKa > 10

Cmpd	**cLogP**		**cLogD**		**pTSA**		**MW**		**pKa**		**HBD**		**CNS MPO**
	Value	T0	Value	T0	Value	T0	Value	T0	Value	T0	Value	T0	
2	1.48	1	-0.79	1	57.61	1	261.14	1	4.42	1	1	0.83	**5.83**
3	3.05	0.98	4.35	0	62.3	1	387.19	0.8	3.34	1	1	0.83	**4.61**
4a	4.75	0.13	6.19	0	62.3	1	463.23	0.26	3.34	1	1	0.83	**3.22**
4b	5.11	0	6.65	0	62.3	1	477.24	0.16	3.34	1	1	0.83	**3**
4c	5.11	0	6.65	0	62.3	1	477.24	0.16	3.34	1	1	0.83	**3**
4d	4.21	0.4	5.61	0	79.37	1	491.22	0.06	3.34	1	1	0.83	**3.3**
4e	4.72	0.14	6.11	0	71.53	1	493.24	0.05	3.34	1	1	0.83	**3.02**
4f	4.72	0.14	6.11	0	71.53	1	493.24	0.05	3.34	1	1	0.83	**3.02**
4g	5.44	0	6.96	0	62.3	1	541.14	0	3.34	1	1	0.83	**2.83**
4h	5.38	0	6.79	0	62.3	1	497.19	0.01	3.34	1	1	0.83	**2.84**
4i	4.85	0.08	6.24	0	62.3	1	481.22	0.14	3.34	1	1	0.83	**3.05**
4j	4.58	0.21	5.92	0	108.12	0.4	508.21	0	3.34	1	1	0.83	**2.44**
5a	3.14	0.93	0.99	1	66.84	1	367.18	0.95	4.27	1	1	0.83	**5.71**
5b	3.86	0.57	1.80	1	57.61	1	415.08	0.6	4.22	1	1	0.83	**4**

The overall CNS MPO score is then obtained by the sum of each component T0. The CNS MPO score can range between 0 to 6, and desirable compounds for CNS drug discovery development are defined as having CNS MPO > 4

PDB coordinates of top-ranked pose of cmpd 4g

```
ATOM      1  C   UNK  0001      73.893  49.935   6.406  1.00  0.00
ATOM      2  C   UNK  0001      73.483  50.372   7.661  1.00  0.00
ATOM      3  C   UNK  0001      73.014  49.217   5.612  1.00  0.00
ATOM      4  C   UNK  0001      68.894  42.189   8.054  1.00  0.00
ATOM      5  C   UNK  0001      70.899  42.077   6.724  1.00  0.00
ATOM      6  C   UNK  0001      72.202  50.080   8.115  1.00  0.00
ATOM      7  C   UNK  0001      71.733  48.918   6.070  1.00  0.00
ATOM      8  C   UNK  0001      65.368  48.355   6.855  1.00  0.00
ATOM      9  C   UNK  0001      66.803  46.687   7.809  1.00  0.00
ATOM     10  C   UNK  0001      64.439  46.564   8.130  1.00  0.00
ATOM     11  C   UNK  0001      69.891  41.438   7.488  1.00  0.00
ATOM     12  C   UNK  0001      71.968  41.393   6.106  1.00  0.00
ATOM     13  C   UNK  0001      64.254  47.722   7.397  1.00  0.00
ATOM     14  C   UNK  0001      65.703  46.035   8.350  1.00  0.00
ATOM     15  C   UNK  0001      72.904  42.090   5.417  1.00  0.00
ATOM     16  C   UNK  0001      69.116  51.481   8.440  1.00  0.00
ATOM     17  C   UNK  0001      68.852  43.594   7.914  1.00  0.00
ATOM     18  C   UNK  0001      71.316  49.343   7.329  1.00  0.00
ATOM     19  C   UNK  0001      67.813  51.750   9.194  1.00  0.00
ATOM     20  C   UNK  0001      70.291  51.323   9.413  1.00  0.00
ATOM     21  C   UNK  0001      69.419  52.663   7.520  1.00  0.00
ATOM     22  C   UNK  0001      66.655  47.850   7.053  1.00  0.00
ATOM     23  Br  UNK  0001      62.930  45.649   8.851  1.00  0.00
ATOM     24  C   UNK  0001      69.809  44.238   7.173  1.00  0.00
ATOM     25  C   UNK  0001      70.847  43.487   6.549  1.00  0.00
ATOM     26  C   UNK  0001      72.757  43.484   5.302  1.00  0.00
ATOM     27  C   UNK  0001      69.272  47.960   6.893  1.00  0.00
ATOM     28  C   UNK  0001      67.883  48.495   6.441  1.00  0.00
ATOM     29  C   UNK  0001      69.900  49.062   7.788  1.00  0.00
ATOM     30  C   UNK  0001      67.918  49.970   6.848  1.00  0.00
ATOM     31  C   UNK  0001      69.198  46.606   7.592  1.00  0.00
ATOM     32  N   UNK  0001      71.764  44.175   5.819  1.00  0.00
ATOM     33  O   UNK  0001      67.060  50.777   6.512  1.00  0.00
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ATOM     36  N   UNK  0001      68.990  50.213   7.642  1.00  0.00
ATOM     37  H   UNK  0001      74.911  50.159   6.045  1.00  0.00
ATOM     38  H   UNK  0001      74.175  50.951   8.297  1.00  0.00
ATOM     39  H   UNK  0001      73.331  48.880   4.610  1.00  0.00
ATOM     40  H   UNK  0001      68.104  41.683   8.634  1.00  0.00
ATOM     41  H   UNK  0001      71.882  50.435   9.109  1.00  0.00
ATOM     42  H   UNK  0001      71.044  48.341   5.431  1.00  0.00
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ATOM     55  H2  UNK  0001      70.089  50.538  10.178  1.00  0.00
ATOM     56  H3  UNK  0001      70.411  52.292   9.952  1.00  0.00
ATOM     57  H1  UNK  0001      70.369  52.467   6.970  1.00  0.00
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ATOM     58  H2  UNK  0001      69.441  53.633   8.070  1.00  0.00
ATOM     59  H3  UNK  0001      68.599  52.722   6.766  1.00  0.00
ATOM     60  H   UNK  0001      73.528  44.036   4.739  1.00  0.00
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TER      64      UNK  0001
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CONECT    2    1    6   38
CONECT    3    7    1   39
CONECT    4   11   17   40
CONECT    5   11   25   12
CONECT    6   18    2   41
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CONECT    8   13   22   43
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CONECT   15   12   26   49
CONECT   16   19   21   36   20
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CONECT   18   29    7    6
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CONECT   36   29   16   30
CONECT   37    1
CONECT   38    2
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CONECT   44    9
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CONECT   49   15
CONECT   50   17
CONECT   51   19
CONECT   52   19
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CONECT   54   20
CONECT   55   20
CONECT   56   20
CONECT   57   21
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CONECT   59   21
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CONECT   61   27
CONECT   62   29
CONECT   63   35
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END
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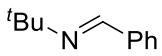
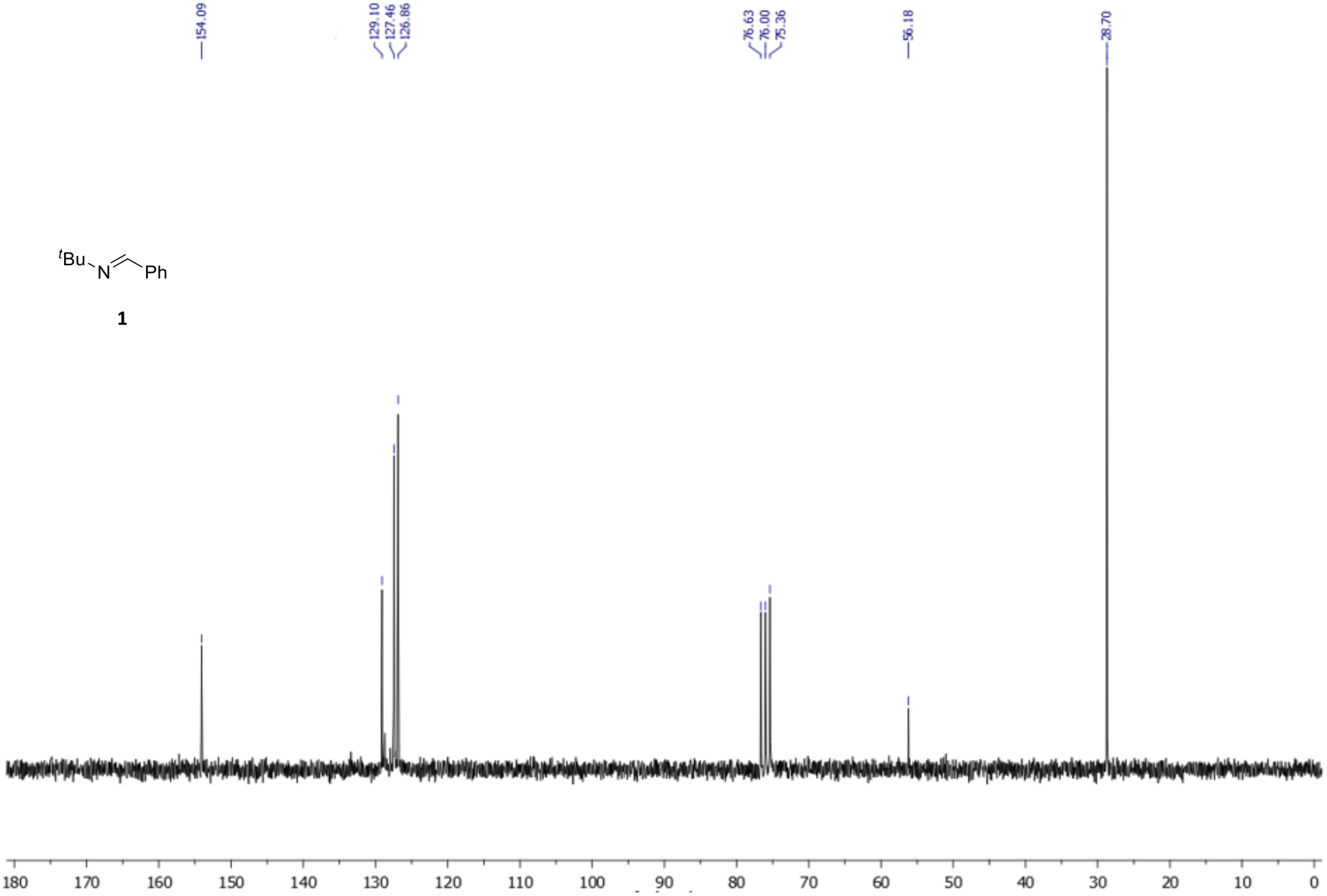
^{1}H NMR (200MHz, $CDCl_3$)



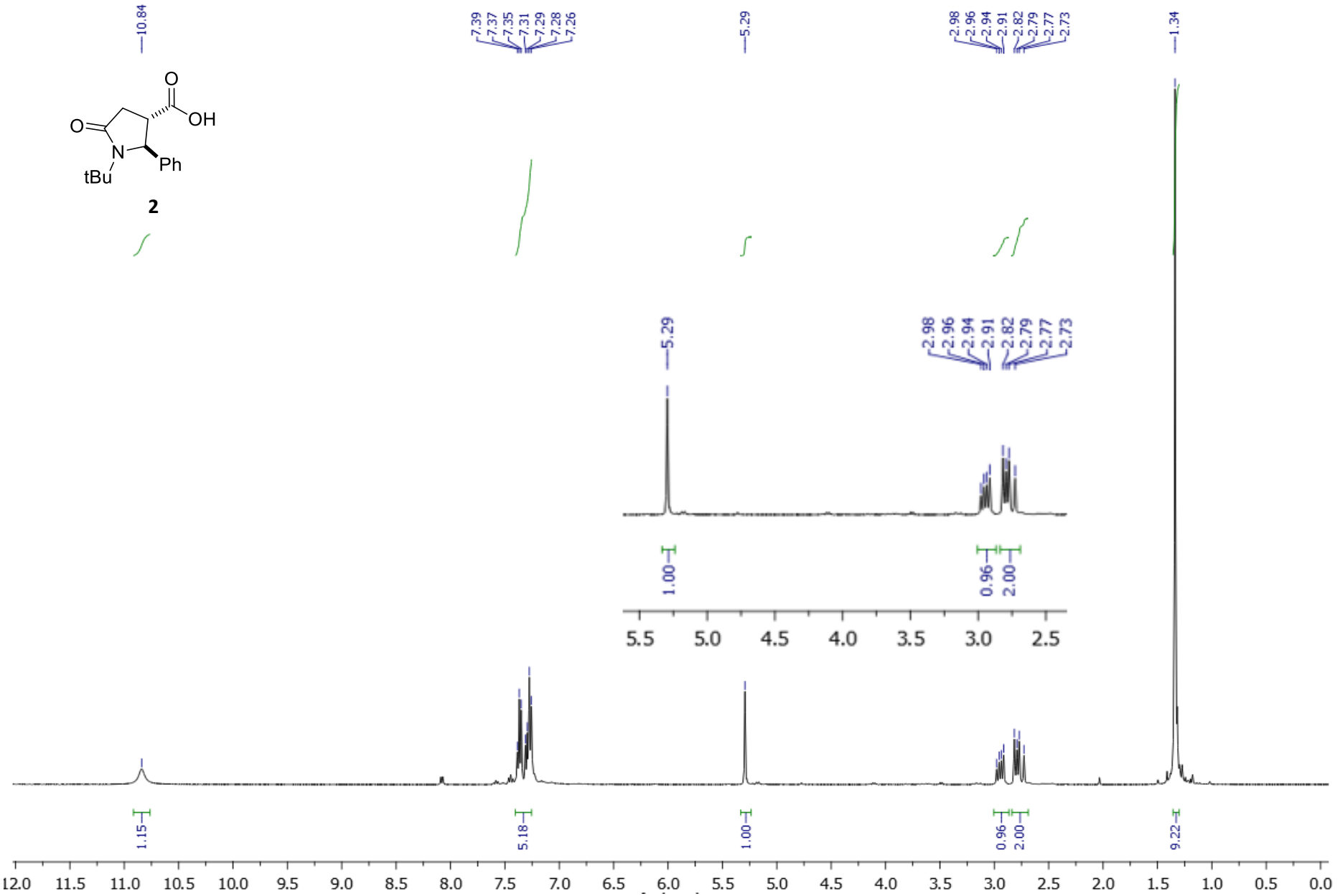
1

^{13}C NMR (50MHz, $CDCl_3$)



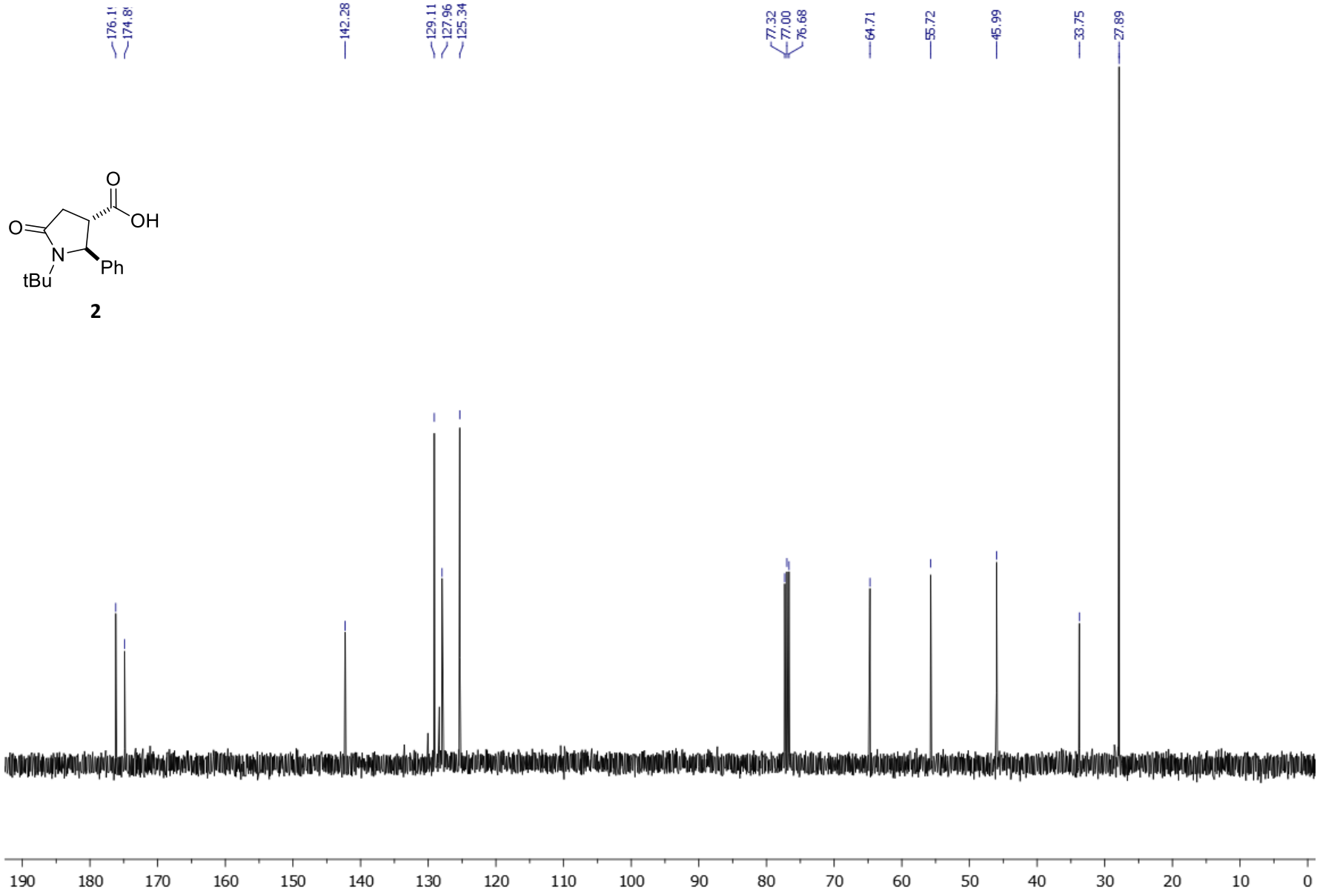
1

^{1}H NMR (400MHz, $CDCl_3$)



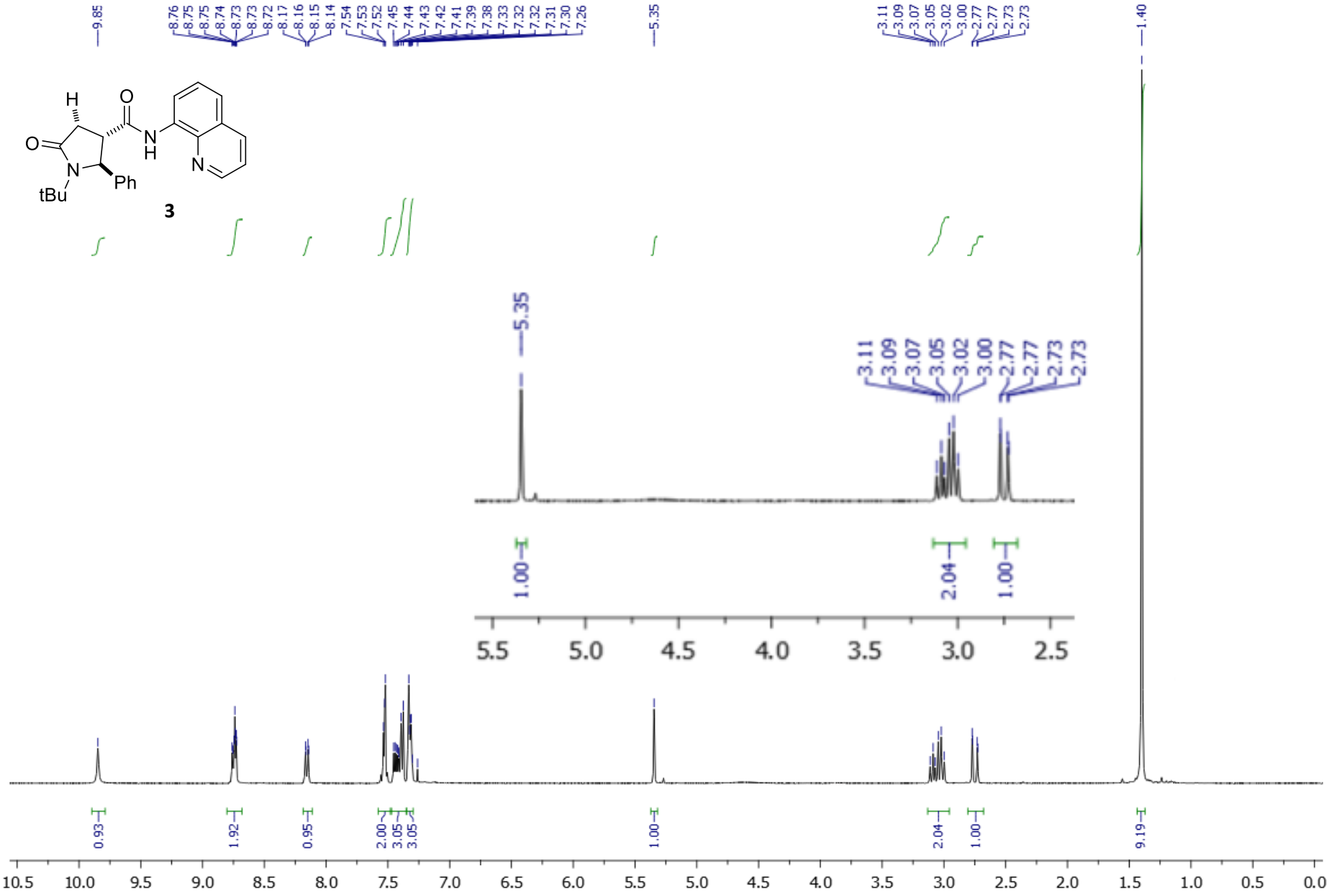
2

^{13}C NMR (100MHz, $CDCl_3$)

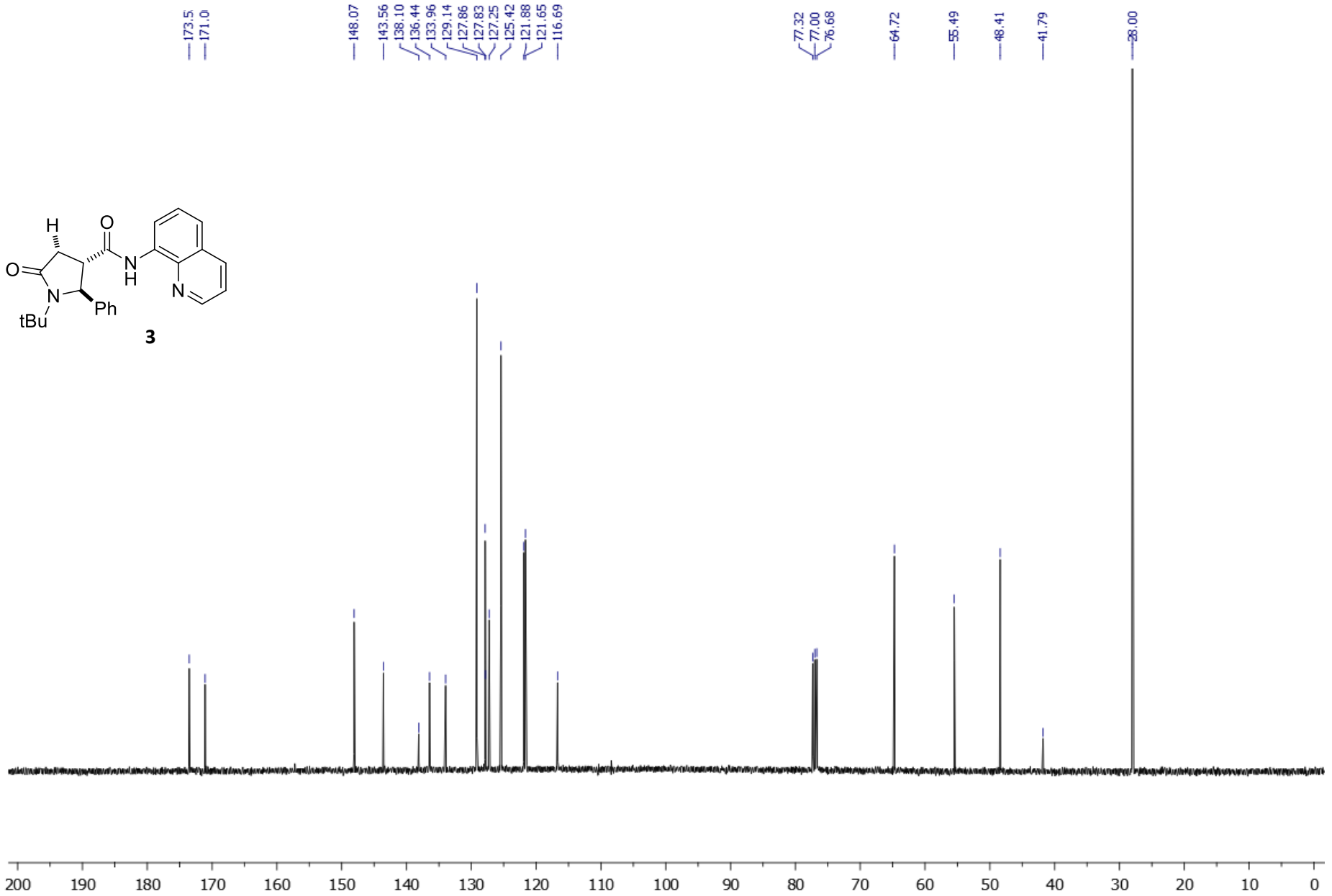


2

^{1}H NMR (400MHz, $CDCl_3$)

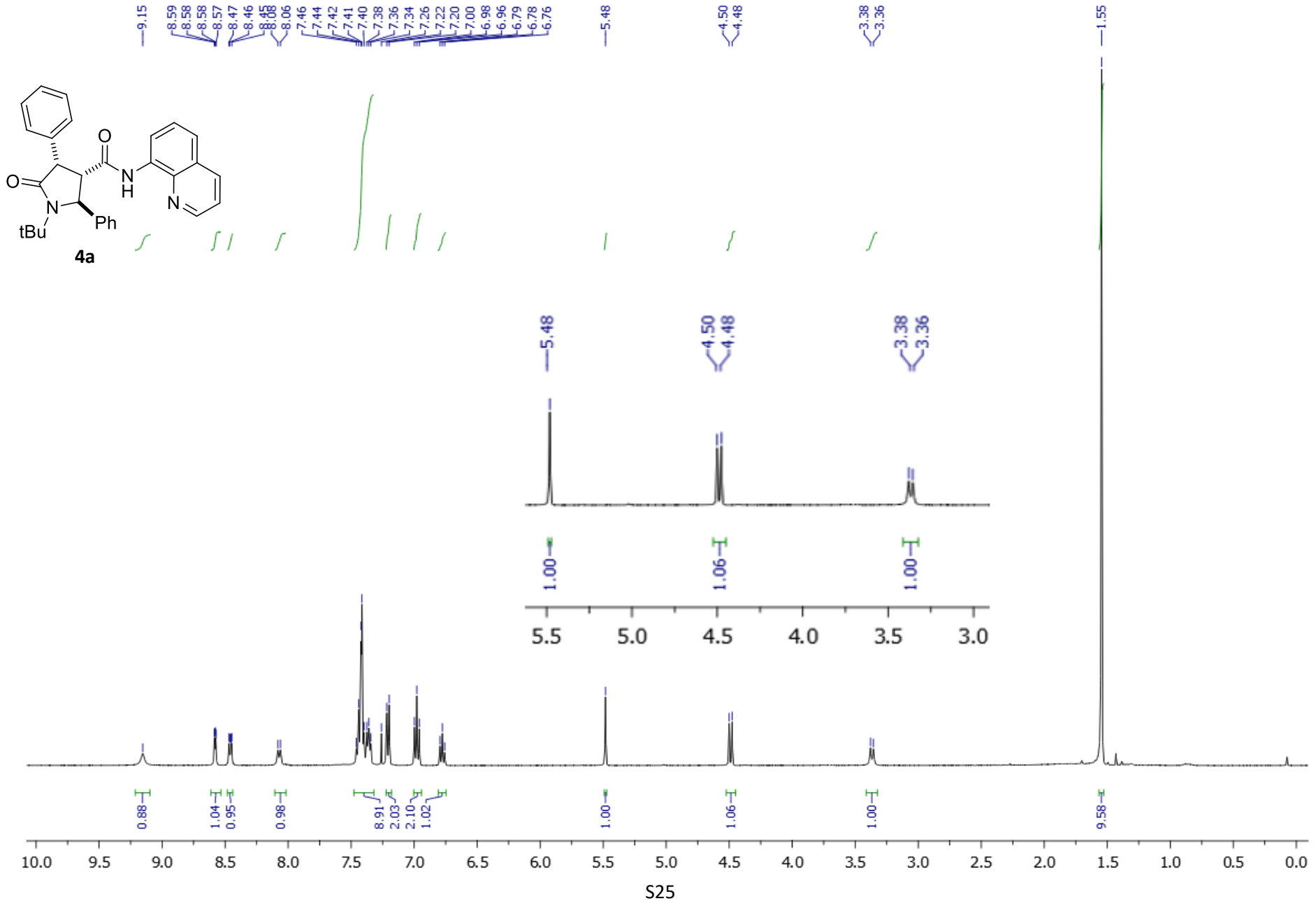


^{13}C NMR (100MHz, $CDCl_3$)

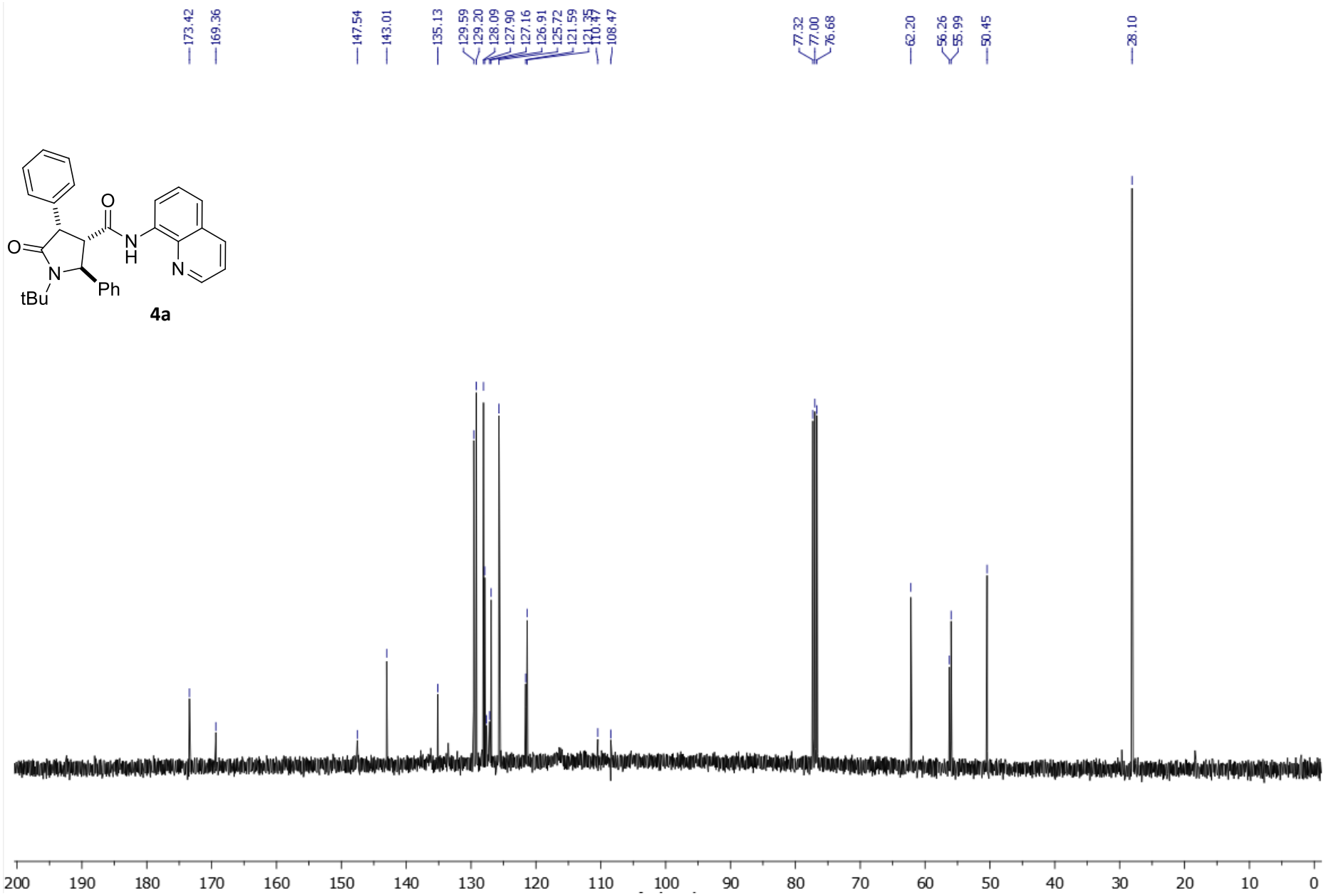


3

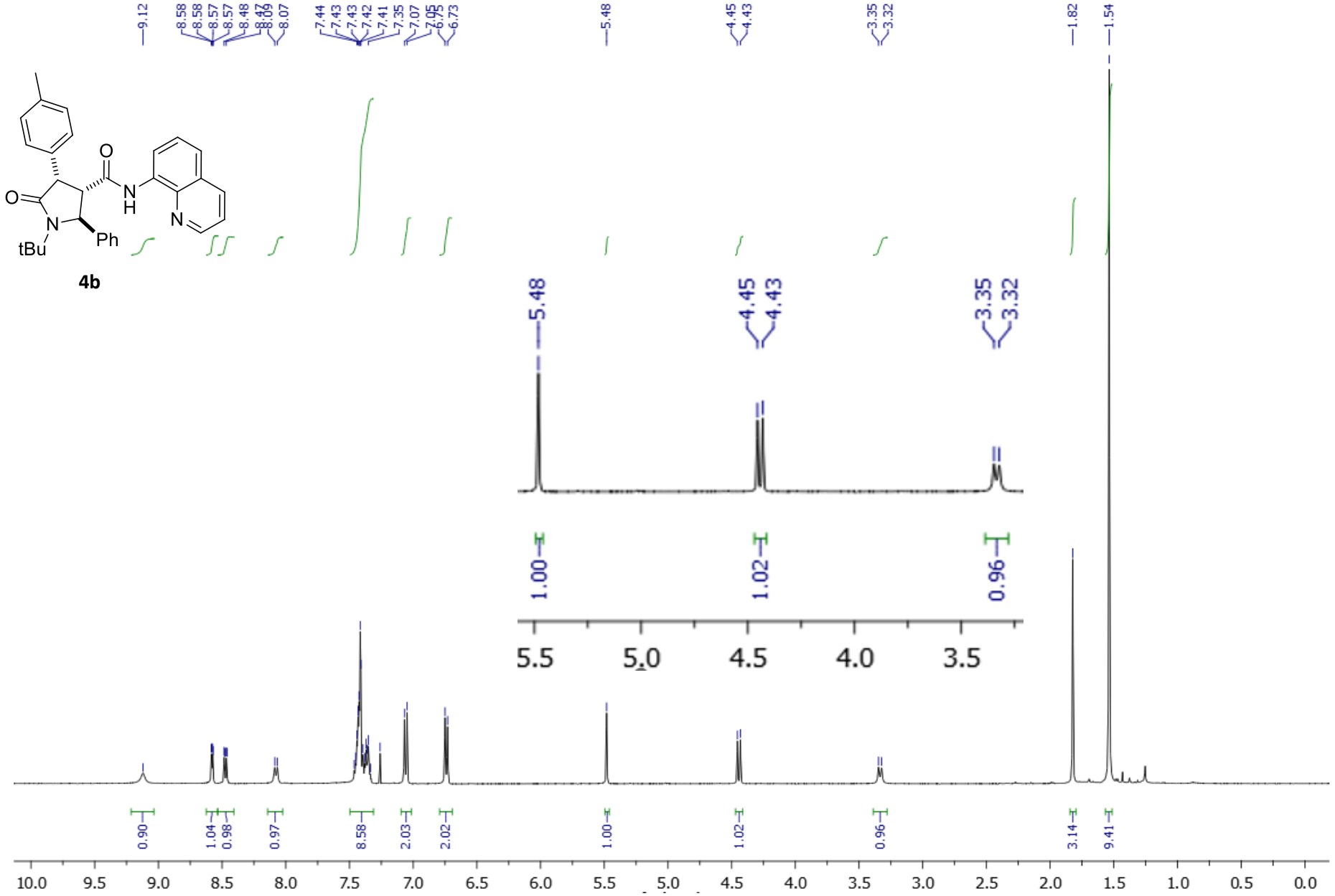
^{1}H NMR (400MHz, $CDCl_3$)



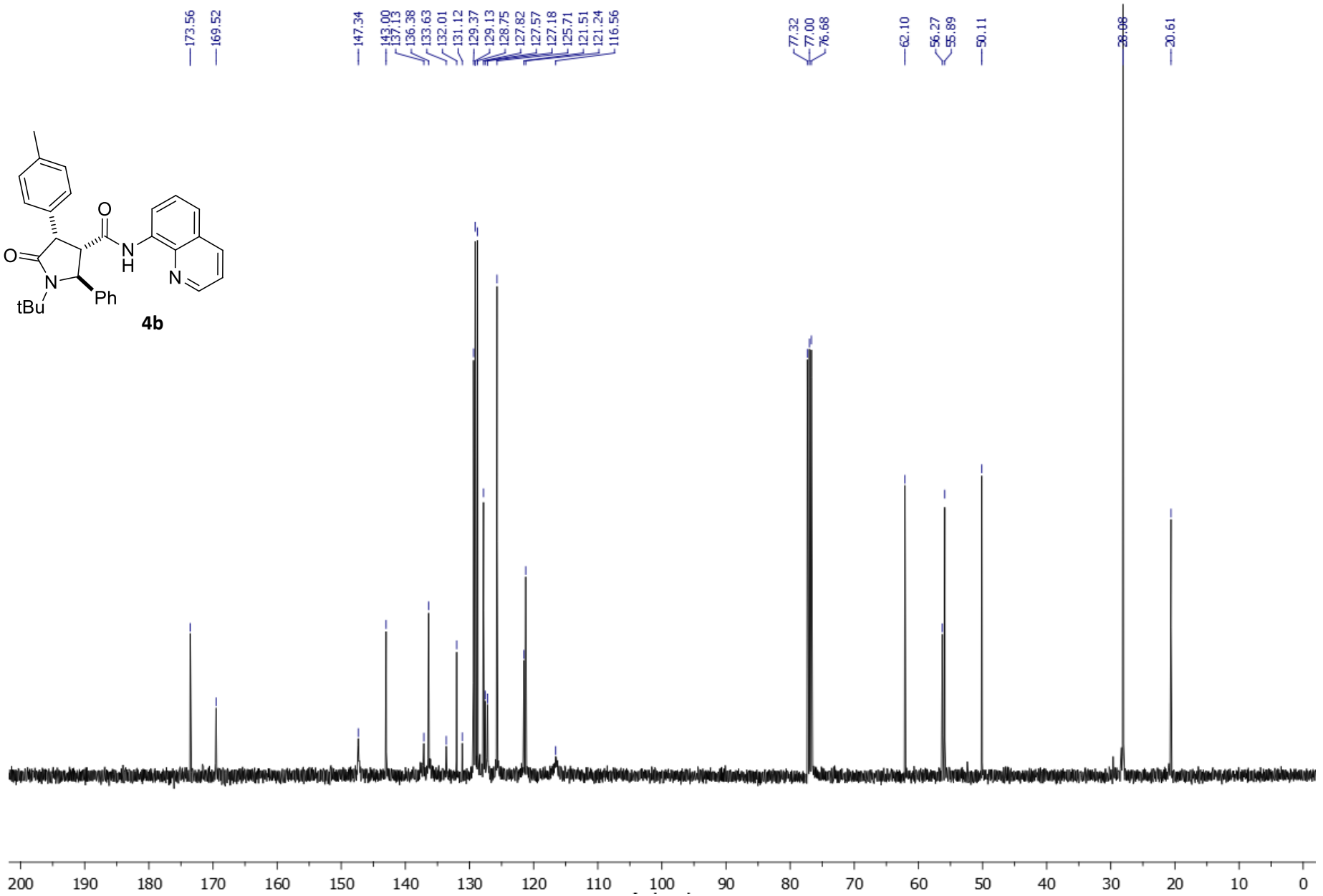
^{13}C NMR (100MHz, $CDCl_3$)



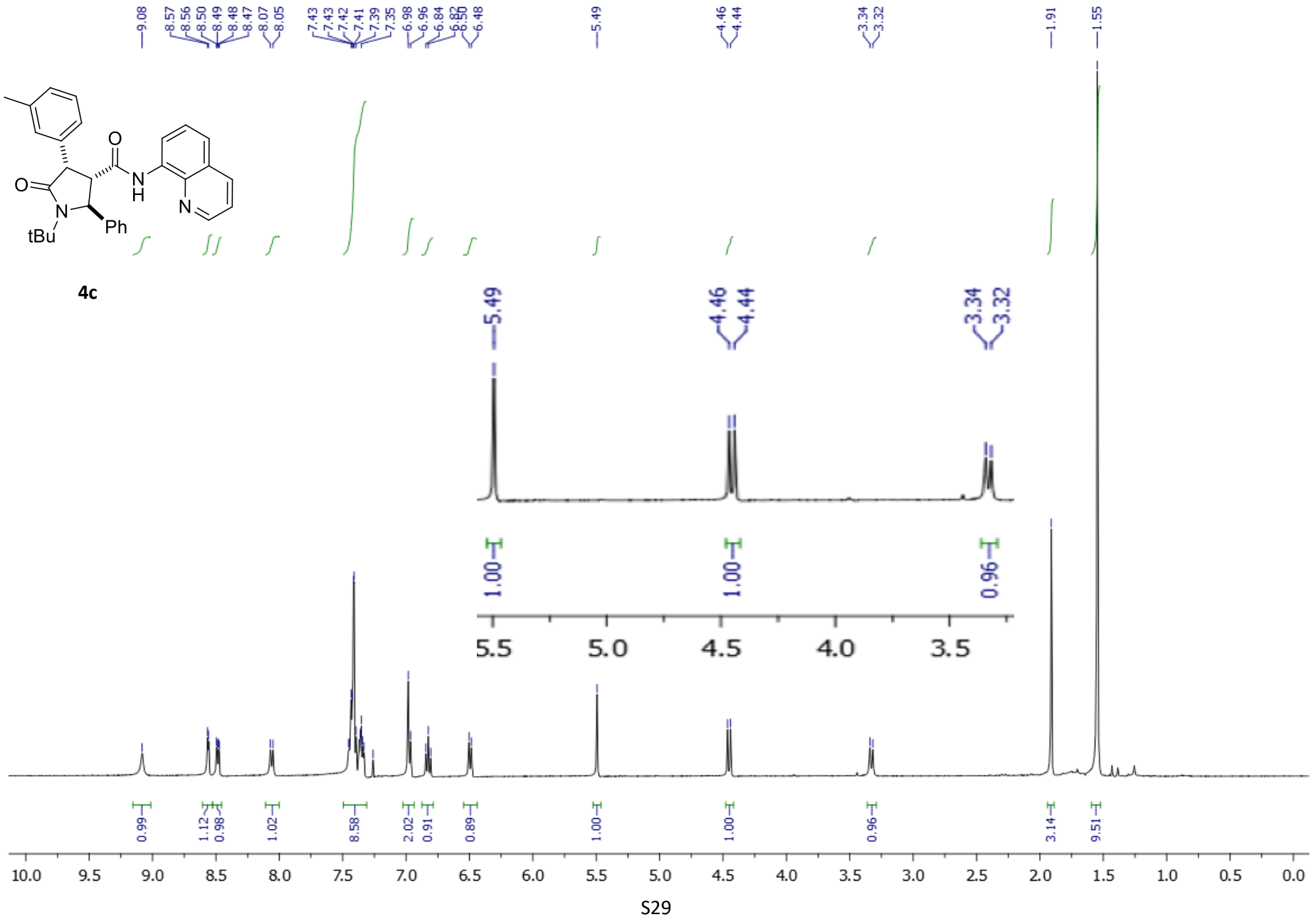
^{1}H NMR (400MHz, $CDCl_3$)



^{13}C NMR (100MHz, $CDCl_3$)

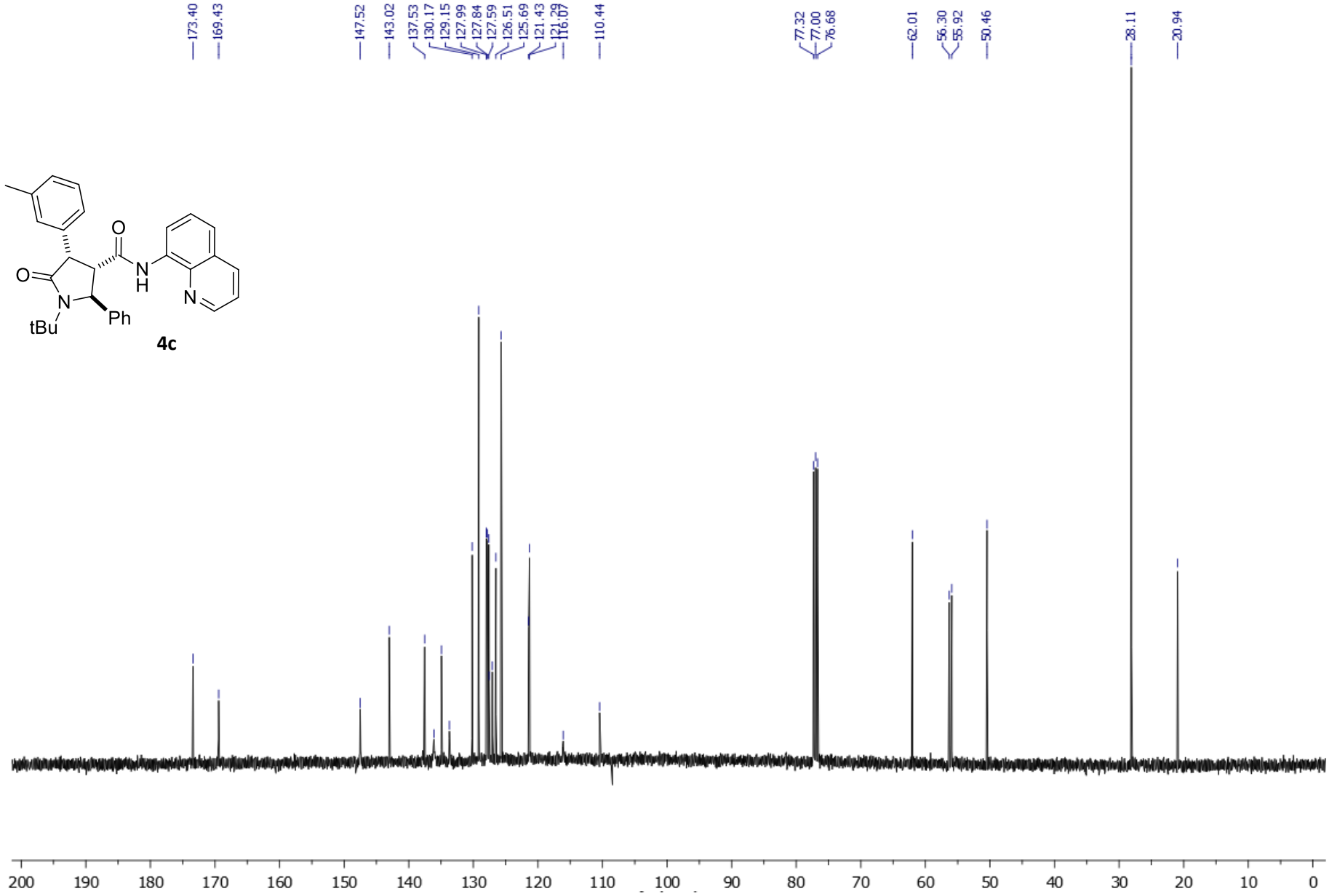


^{1}H NMR (400MHz, $CDCl_3$)



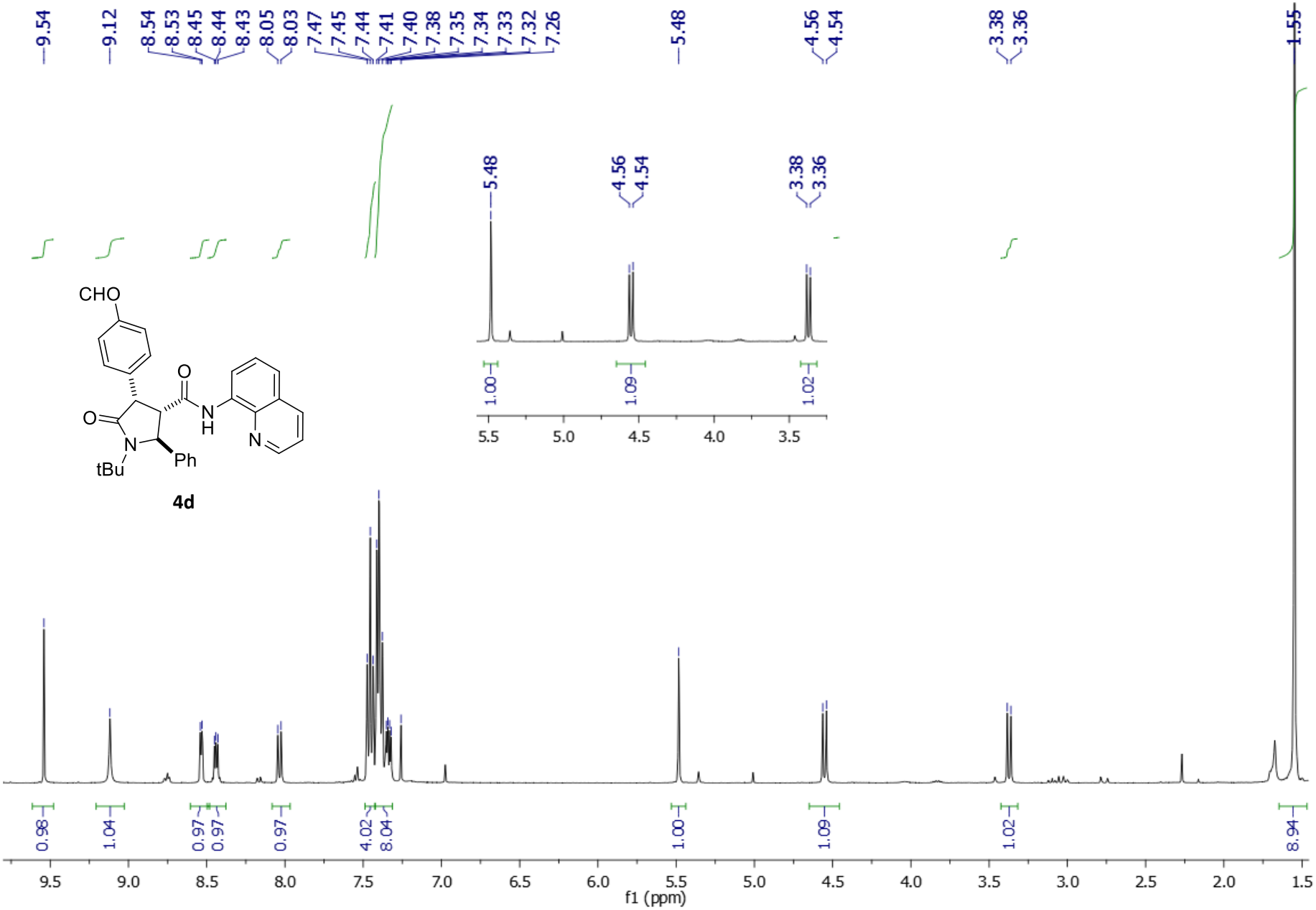
4c

^{13}C NMR (100MHz, $CDCl_3$)

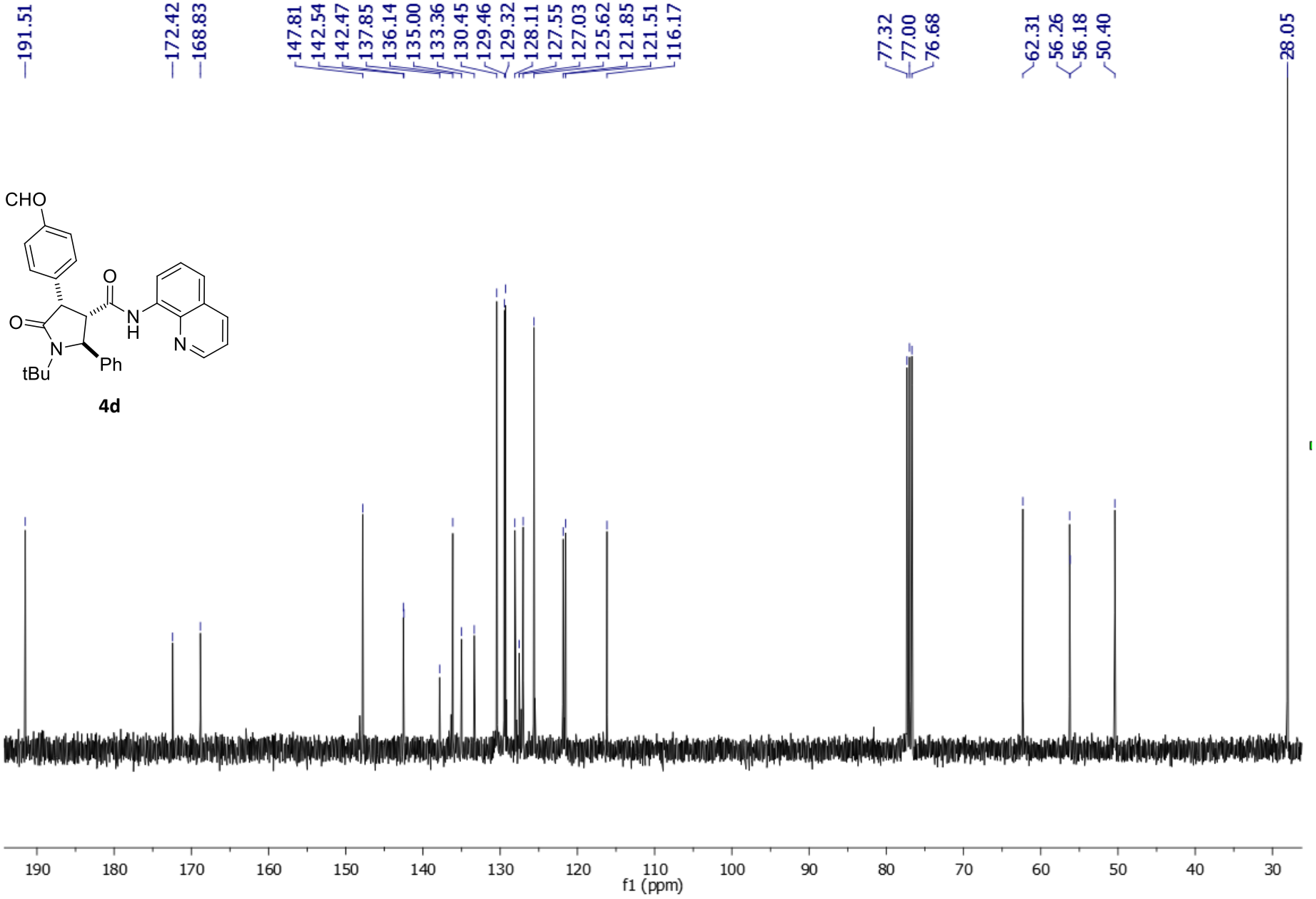


4c

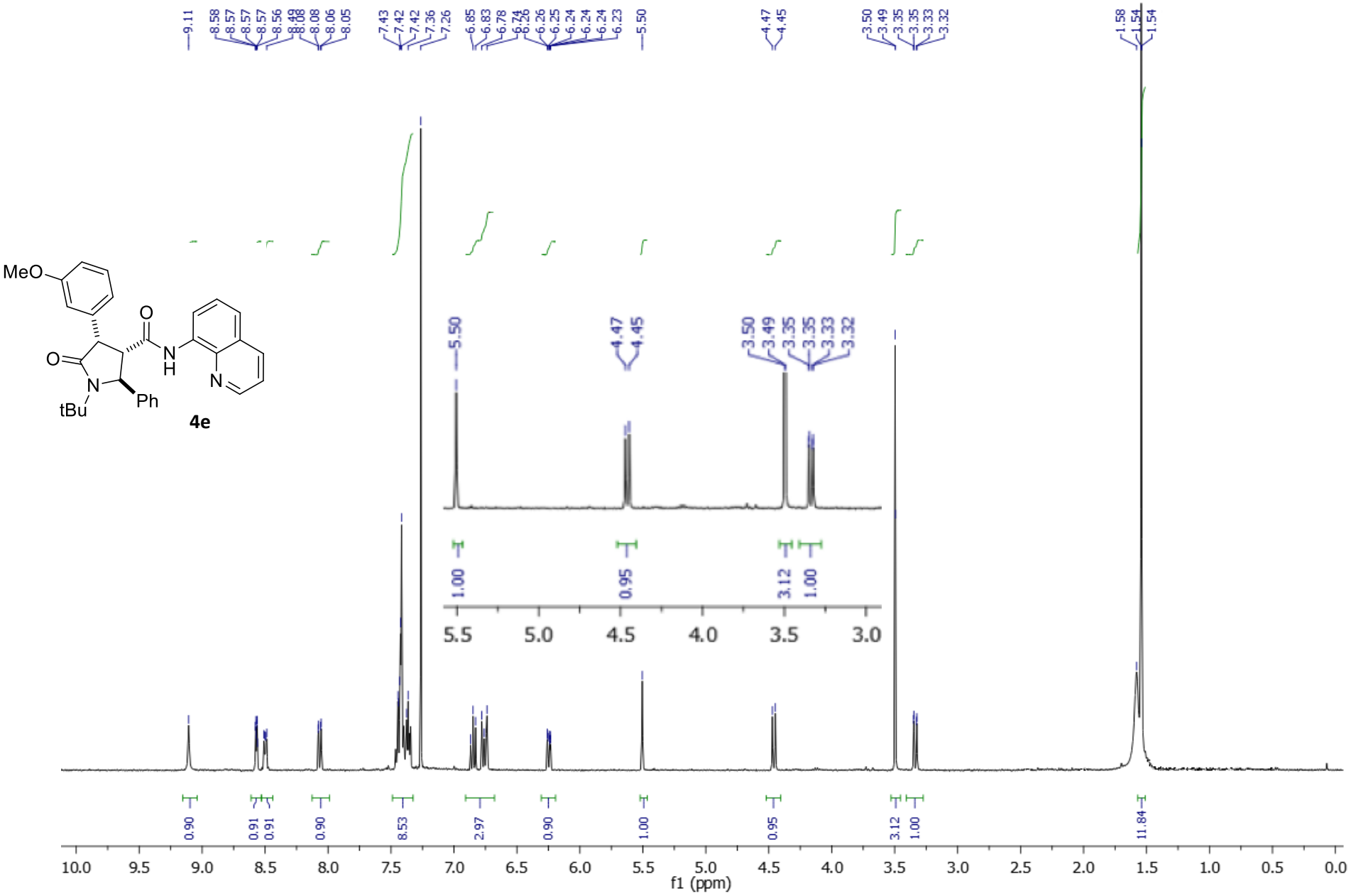
^{1}H NMR (400MHz, $CDCl_3$)



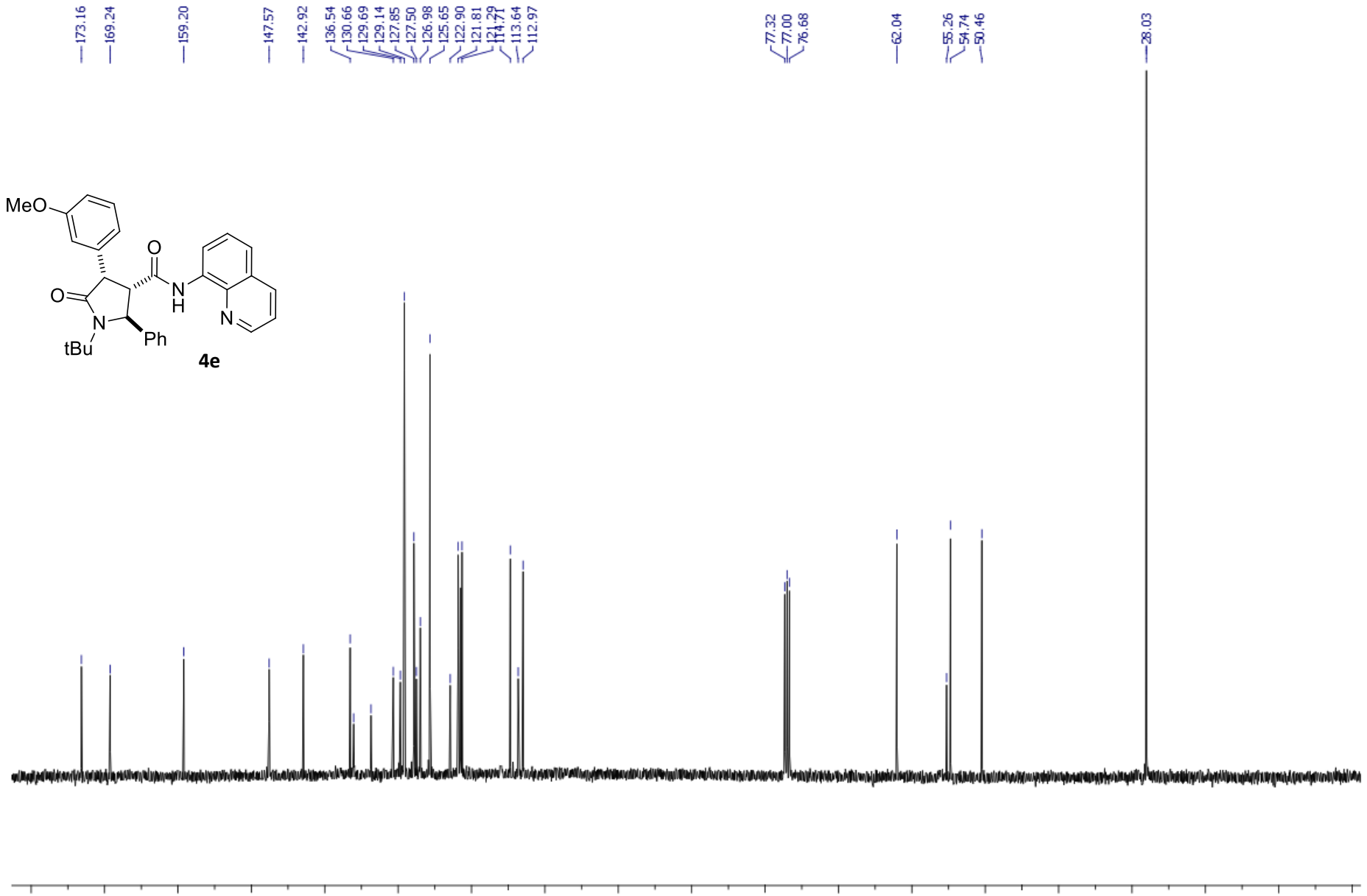
^{13}C NMR (100MHz, $CDCl_3$)



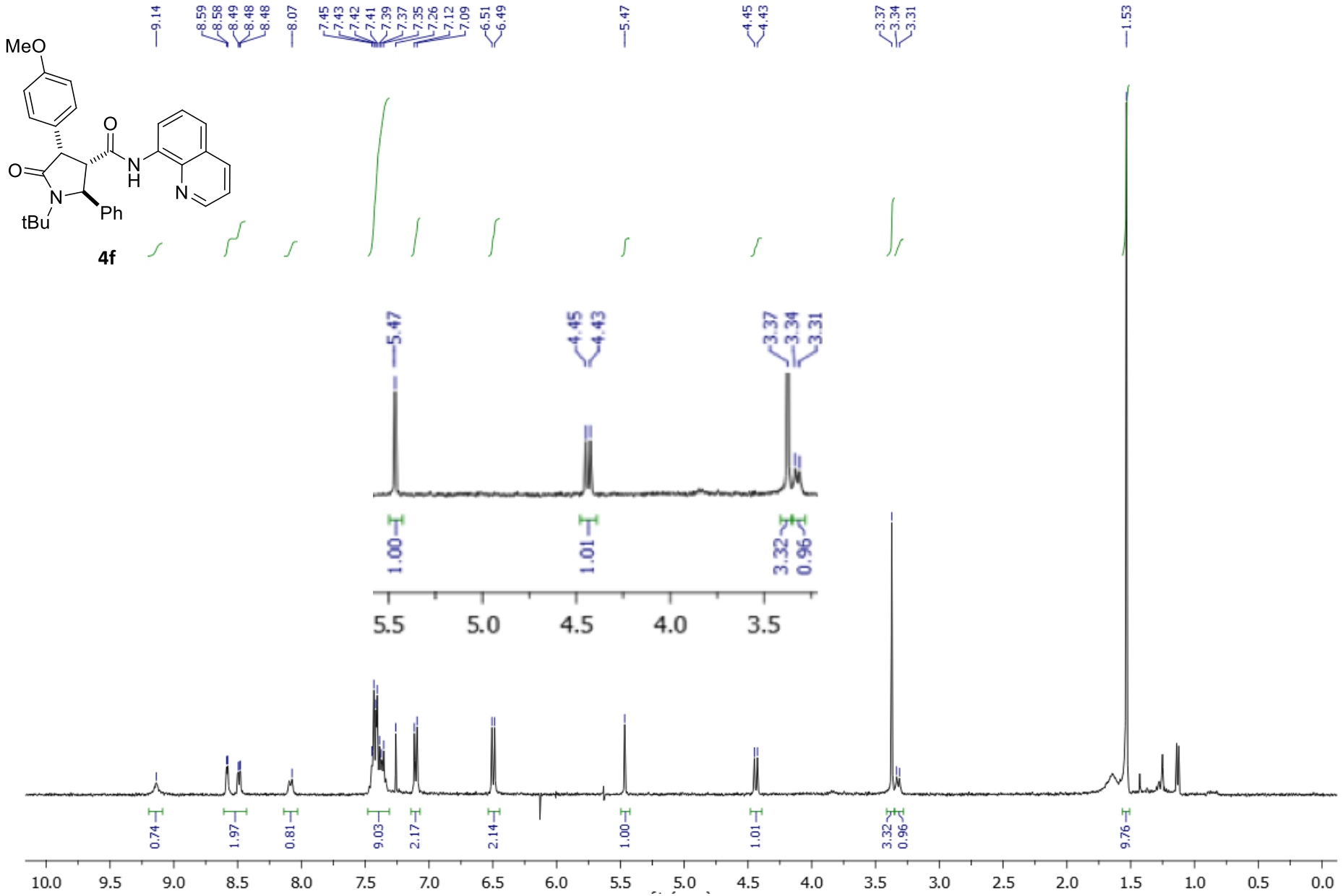
^{1}H NMR (400MHz, $CDCl_3$)



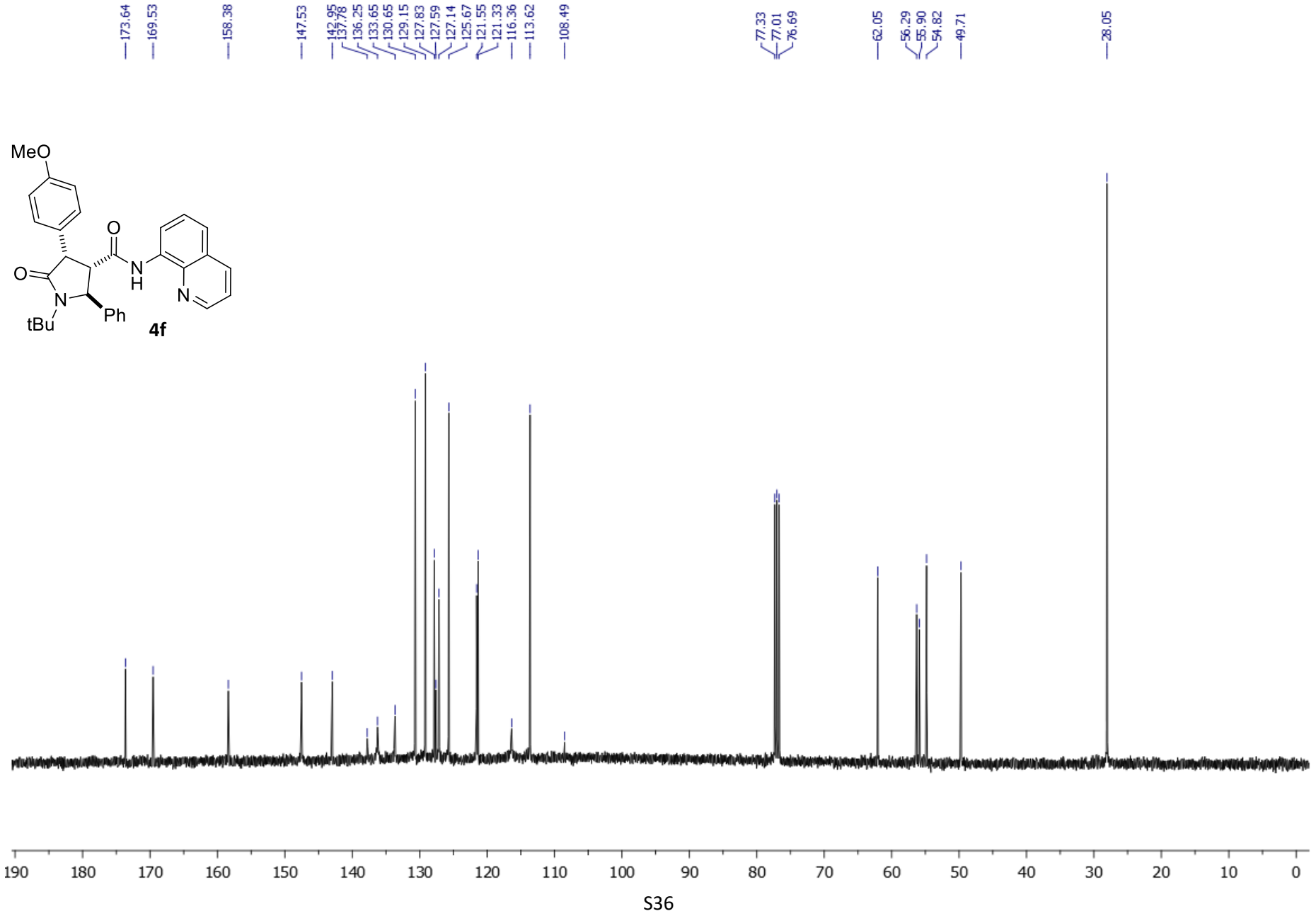
^{13}C NMR (100MHz, $CDCl_3$)



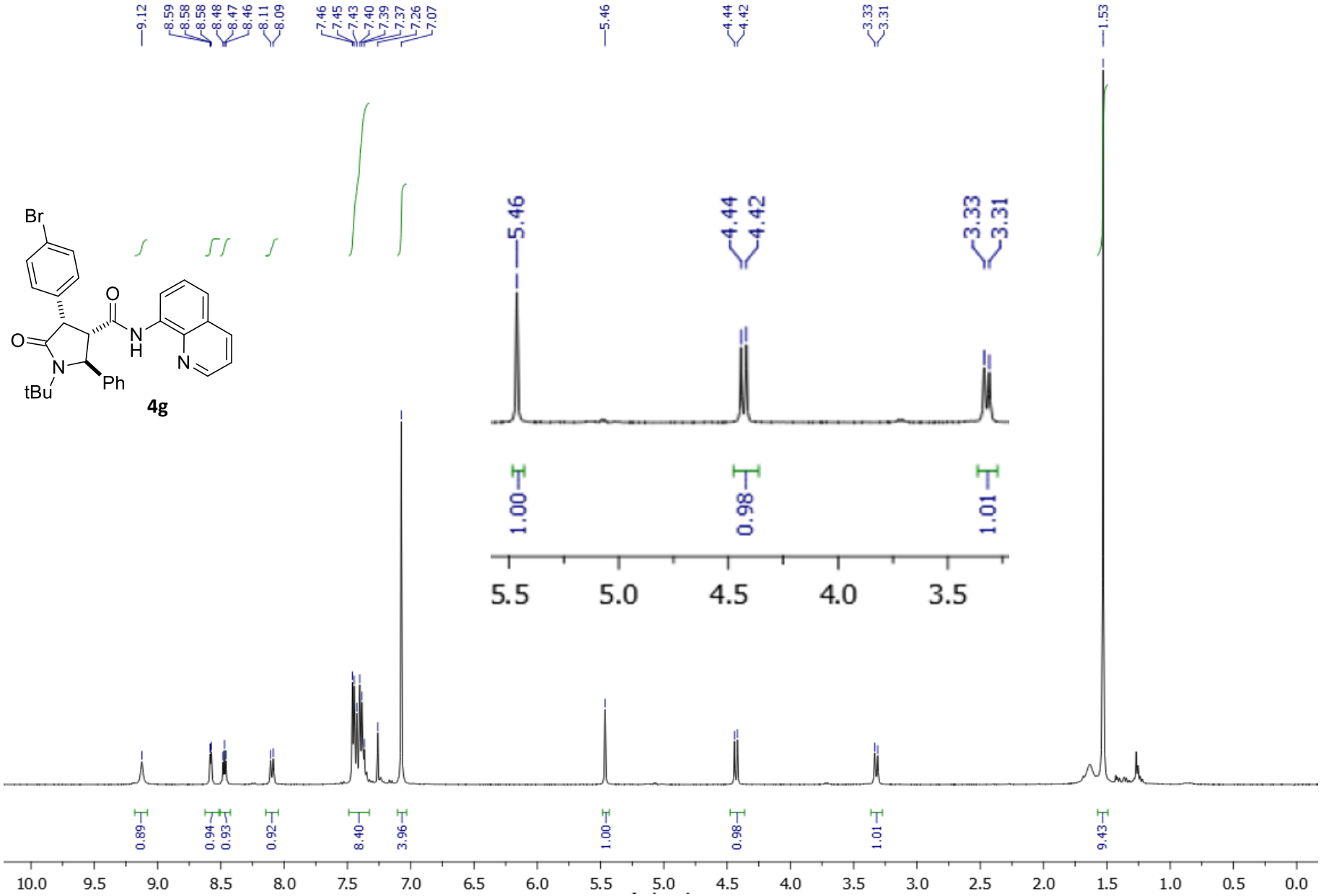
^{1}H NMR (400MHz, $CDCl_3$)



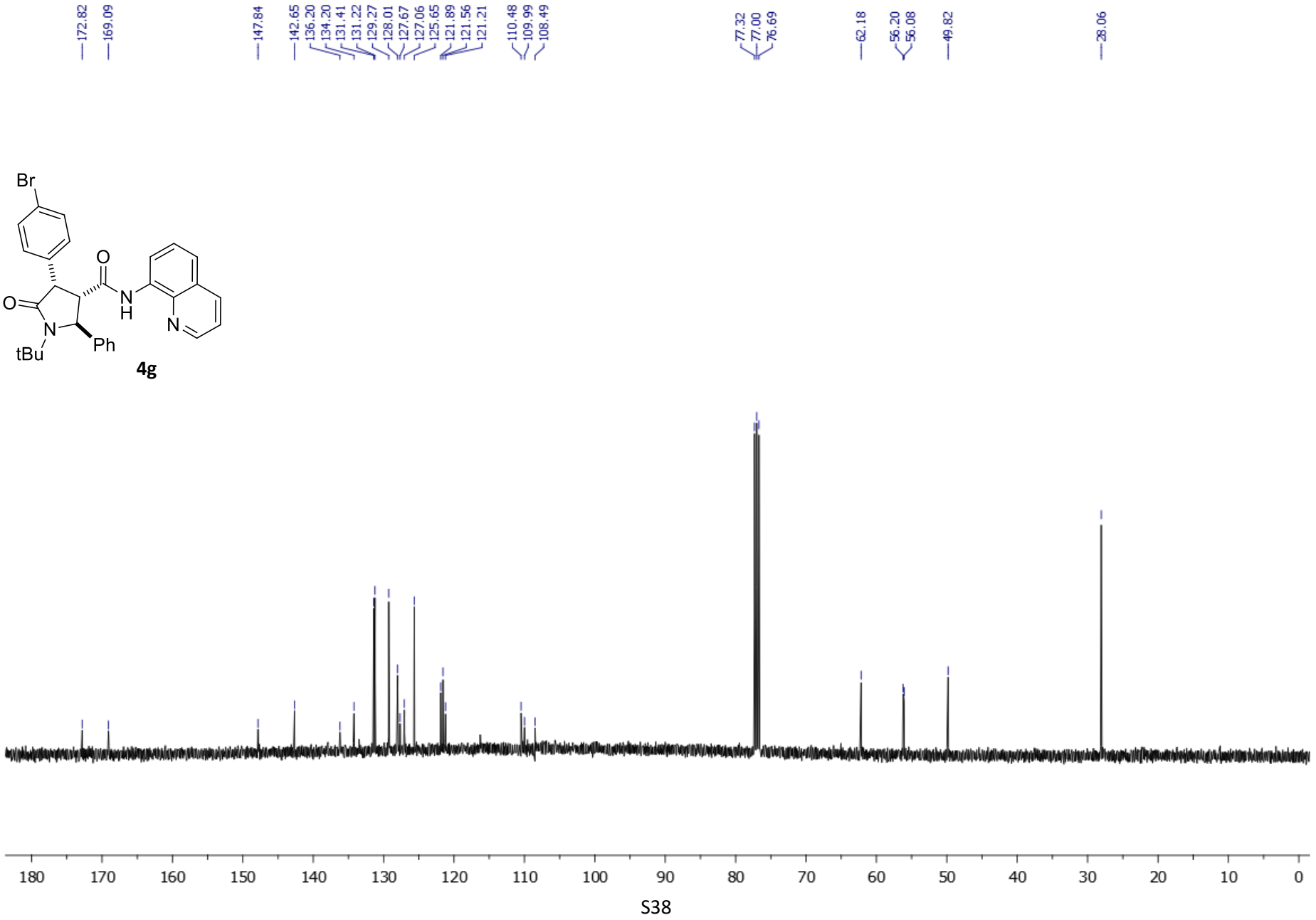
^{13}C NMR (100MHz, $CDCl_3$)



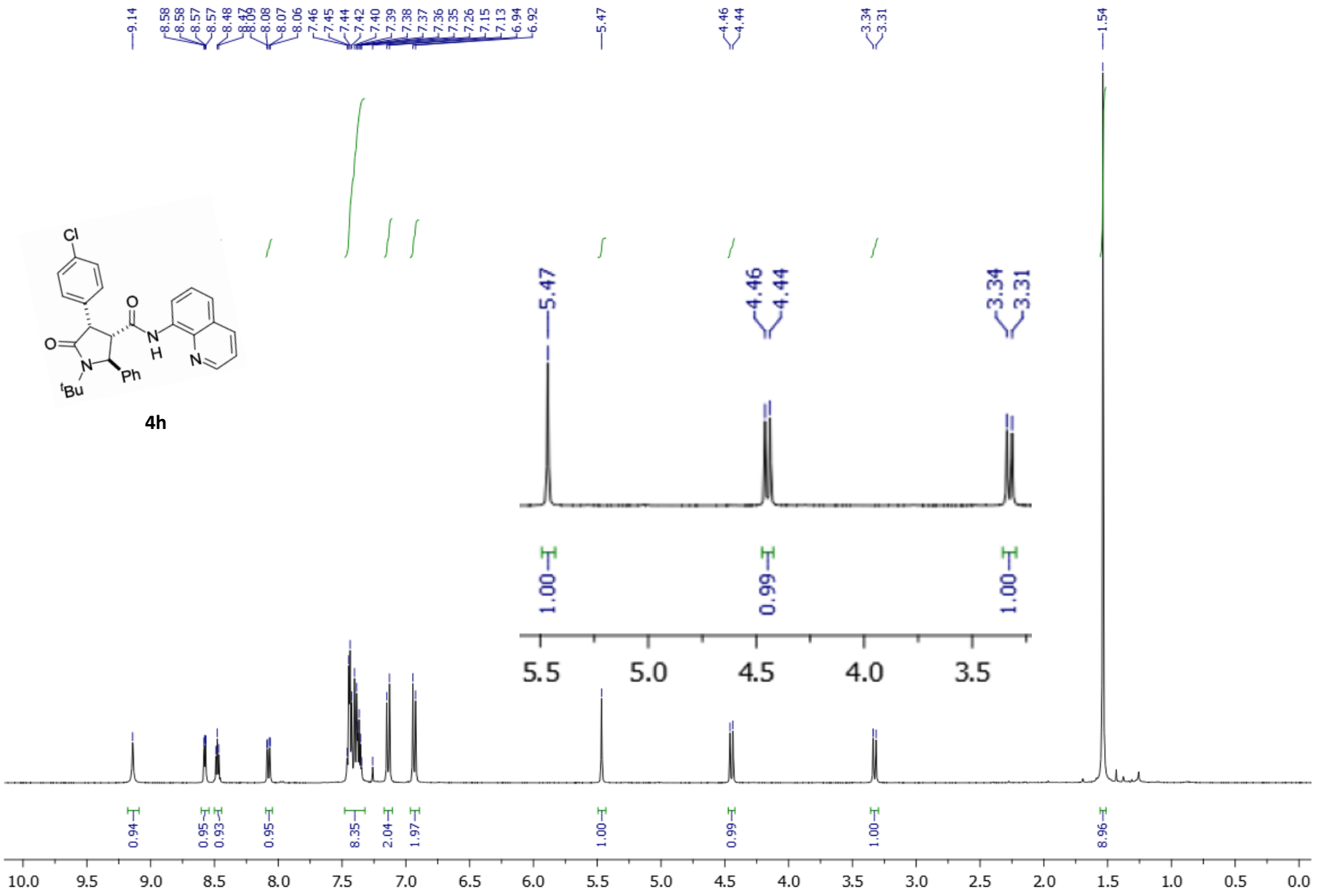
^{1}H NMR (400MHz, $CDCl_3$)



^{13}C NMR (100MHz, $CDCl_3$)

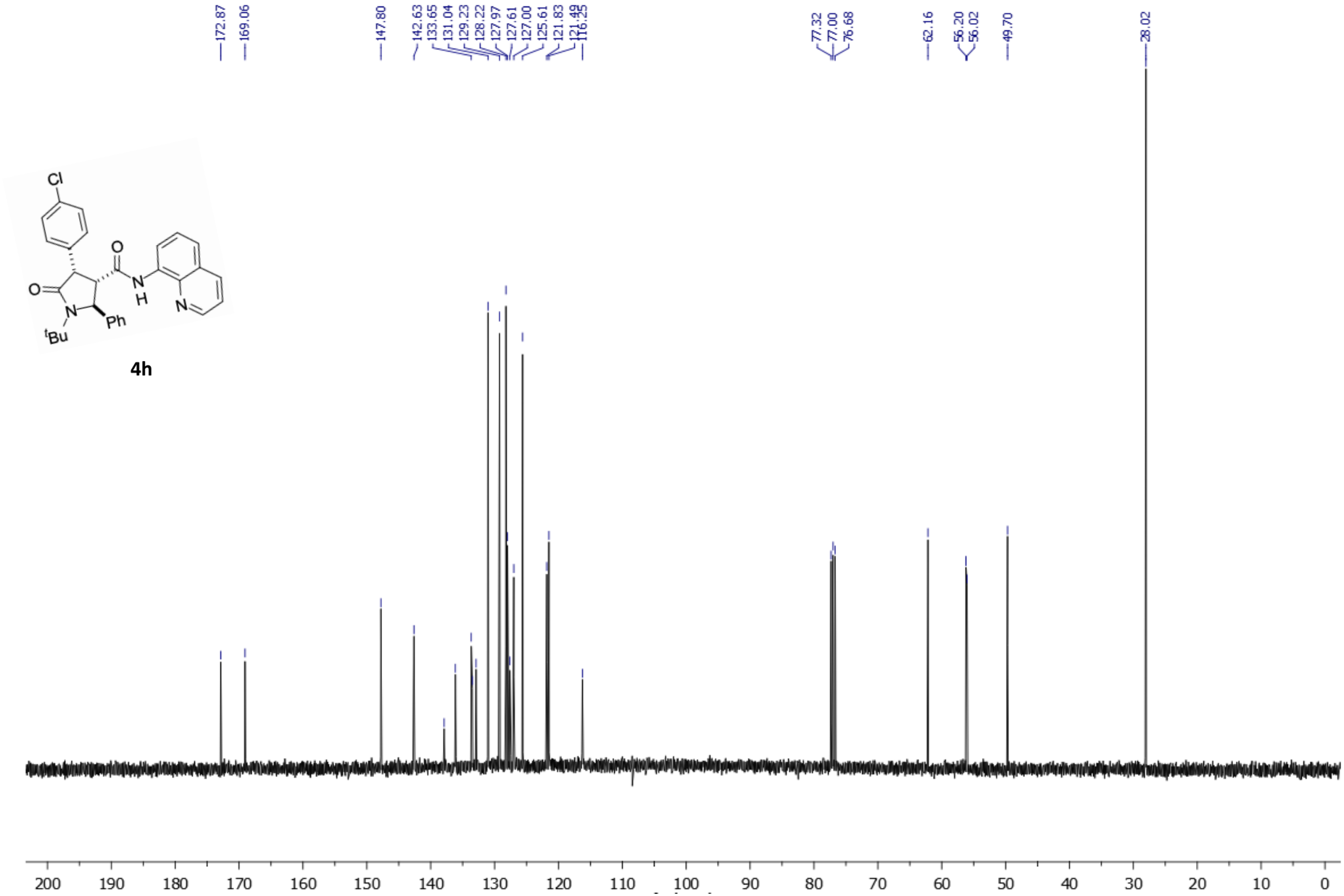


^{1}H NMR (400MHz, $CDCl_3$)



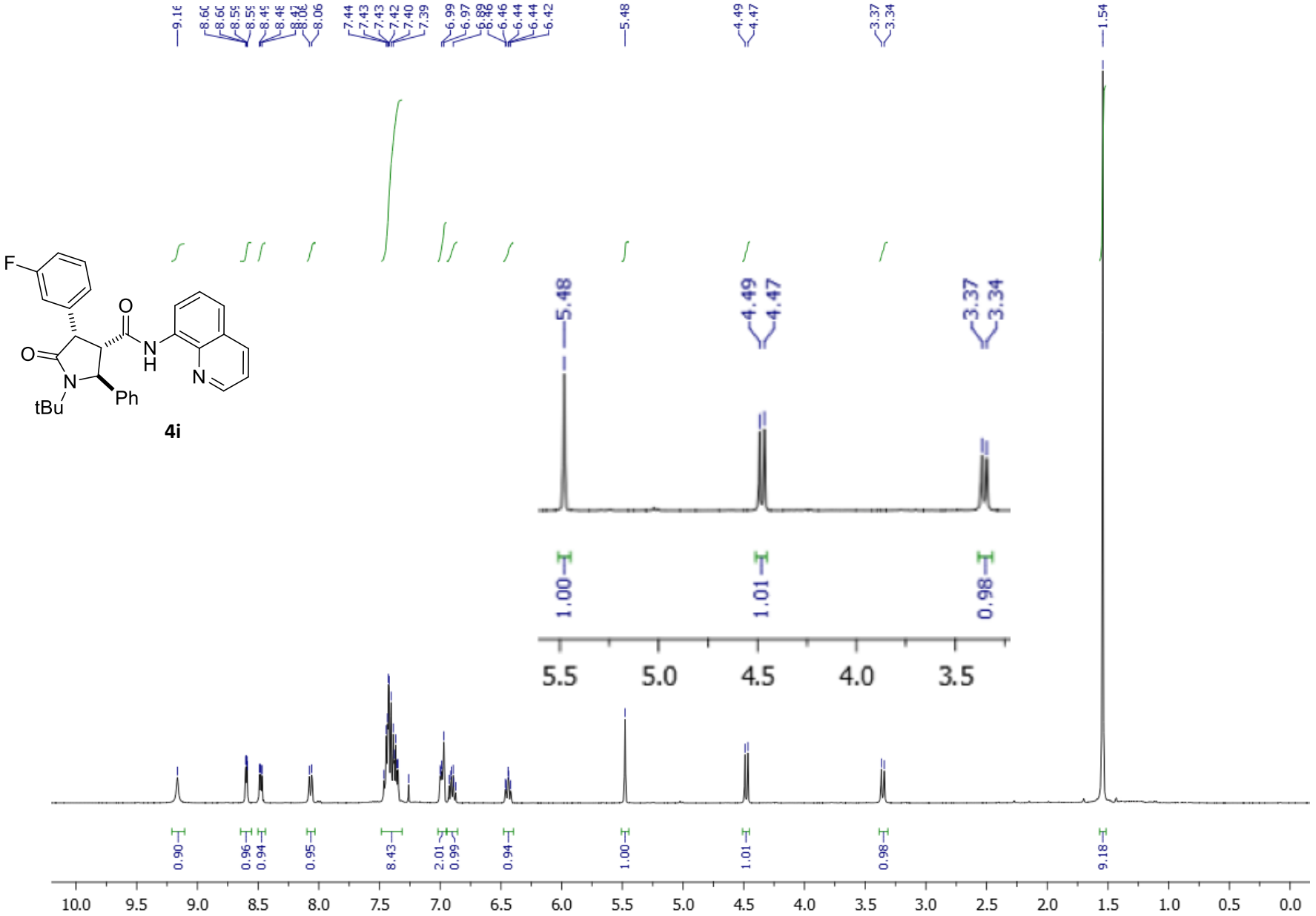
4h

^{13}C NMR (100MHz, $CDCl_3$)

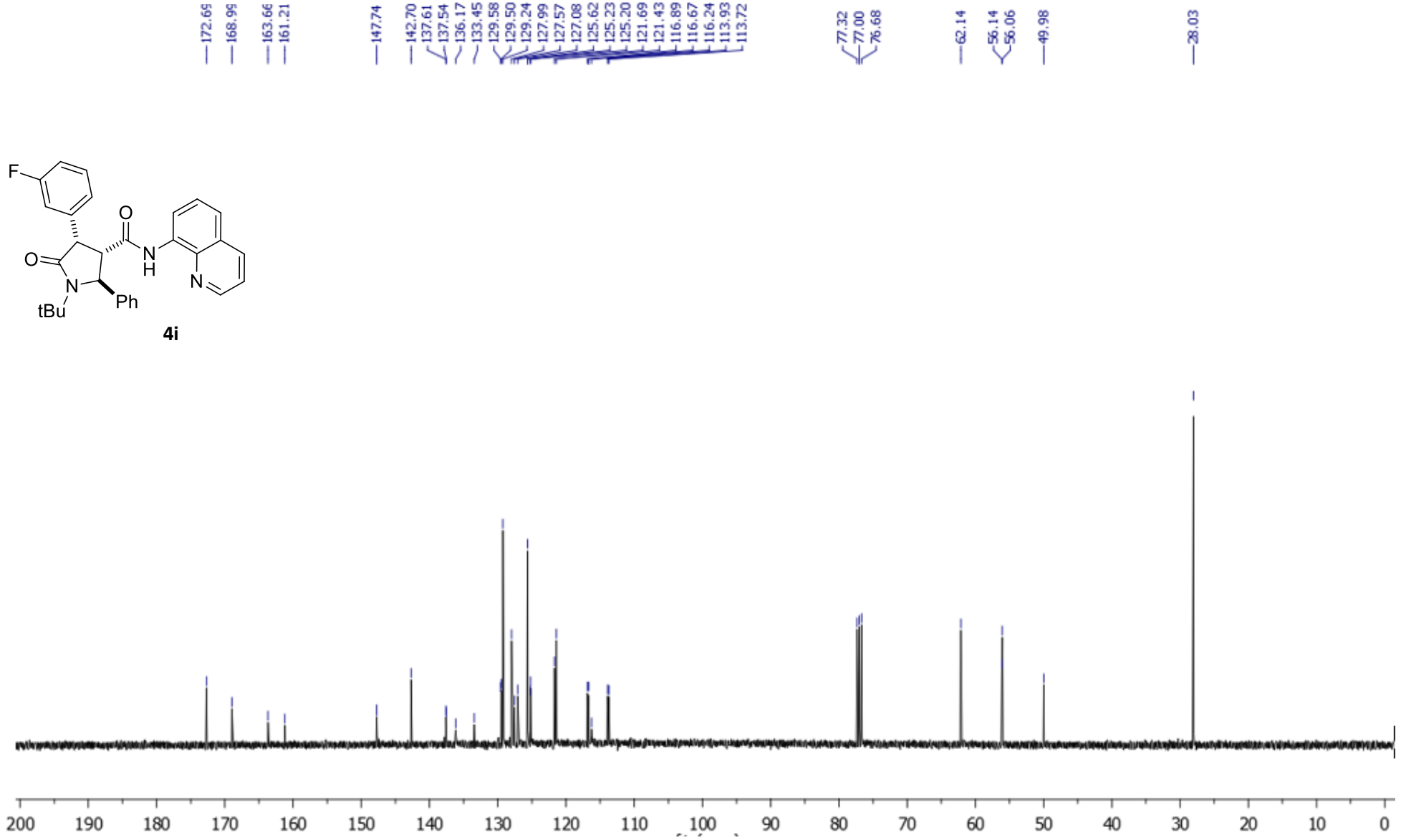


4h

^{1}H NMR (400MHz, $CDCl_3$)

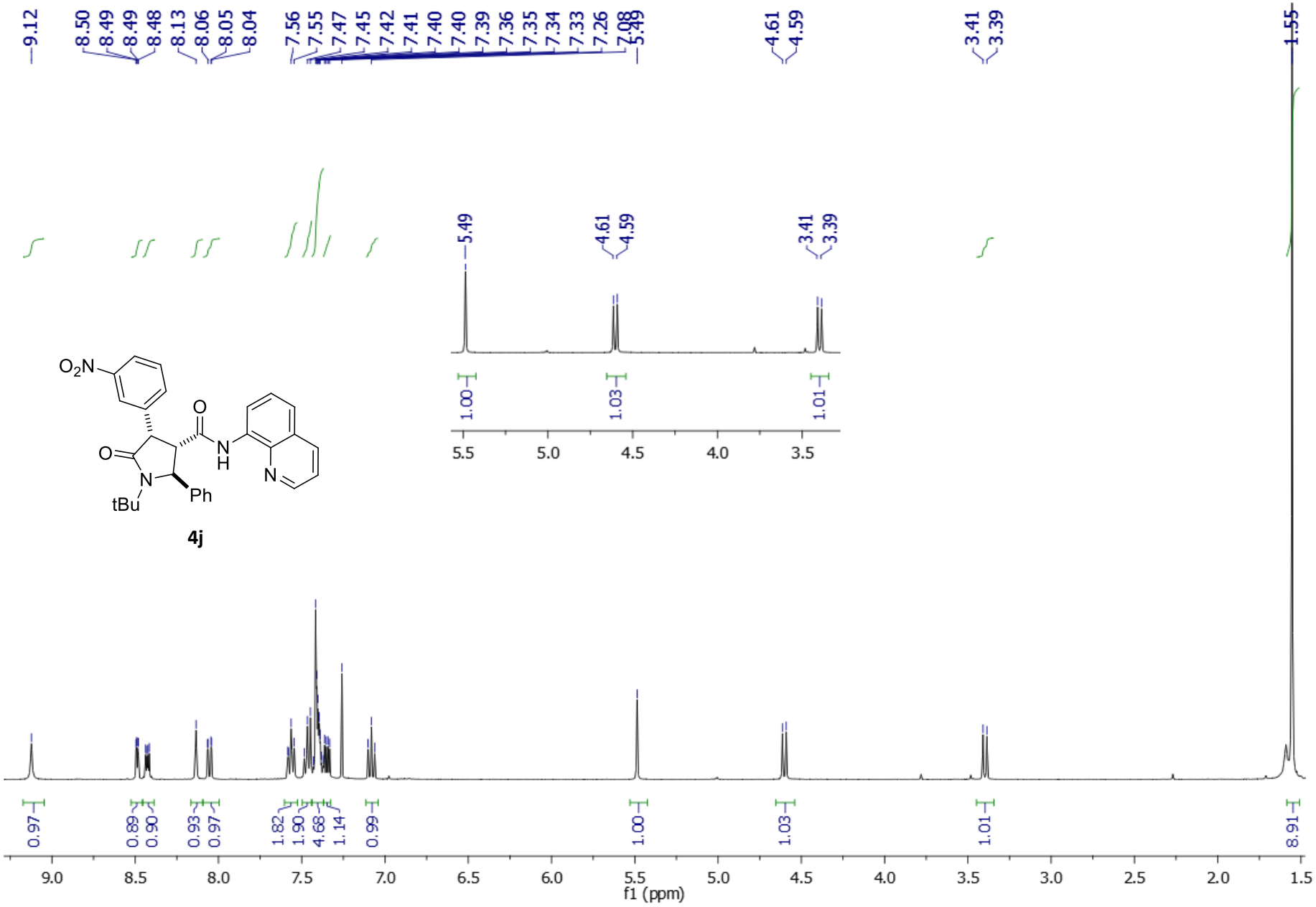


^{13}C NMR (100MHz, $CDCl_3$)



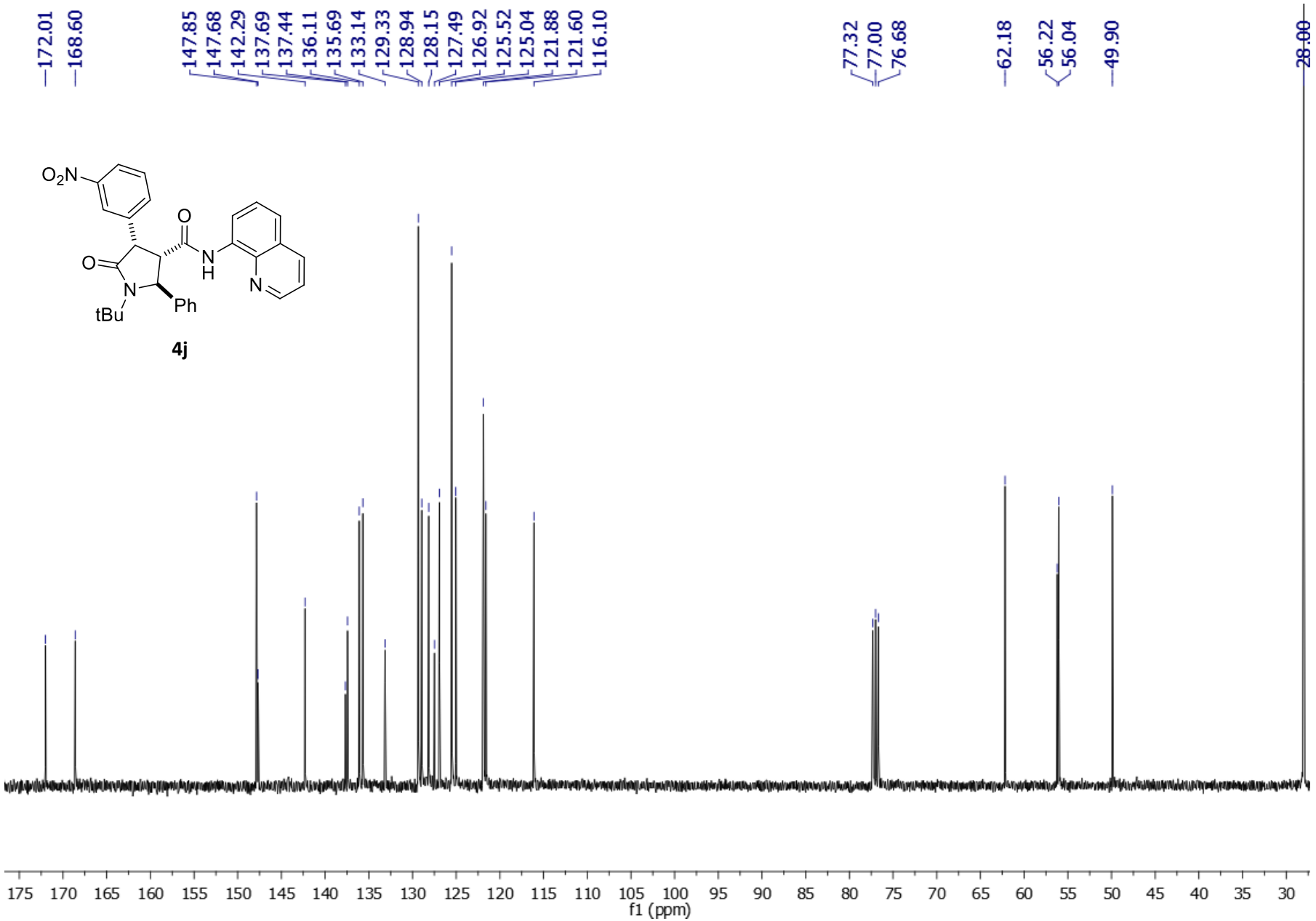
4i

^{1}H NMR (400MHz, $CDCl_3$)

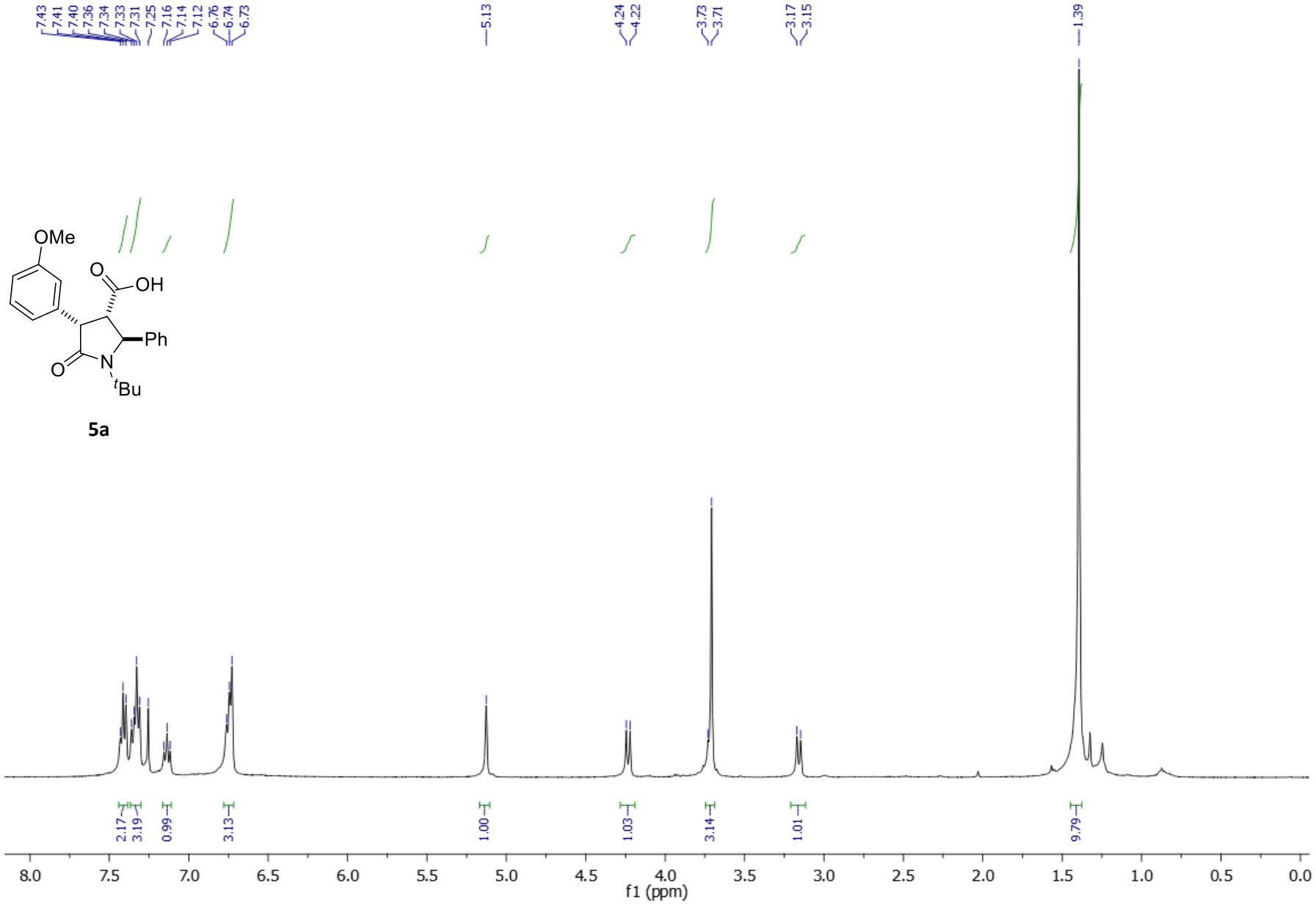


4j

^{13}C NMR (100MHz, $CDCl_3$)

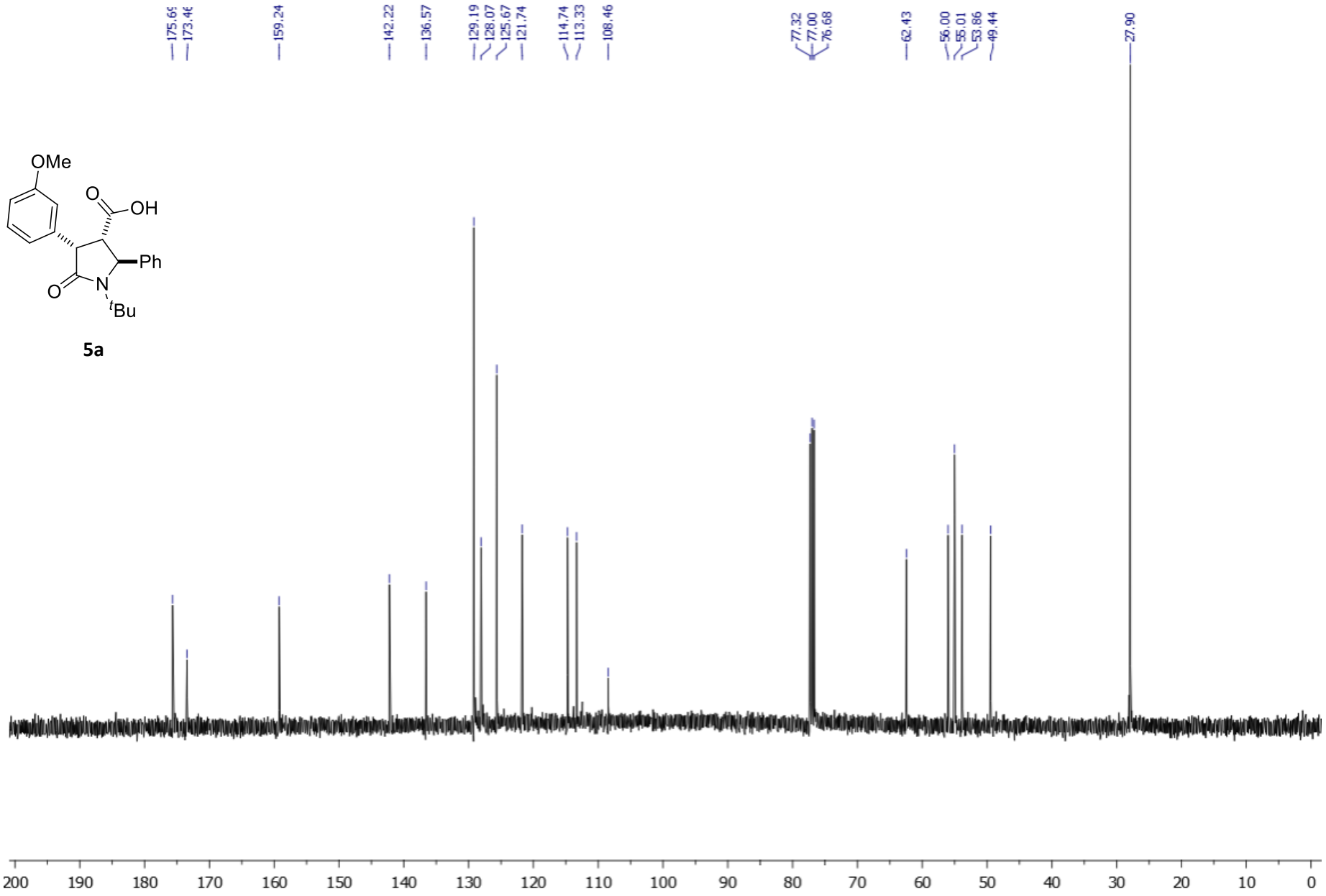


^{1}H NMR (400MHz, $CDCl_3$)



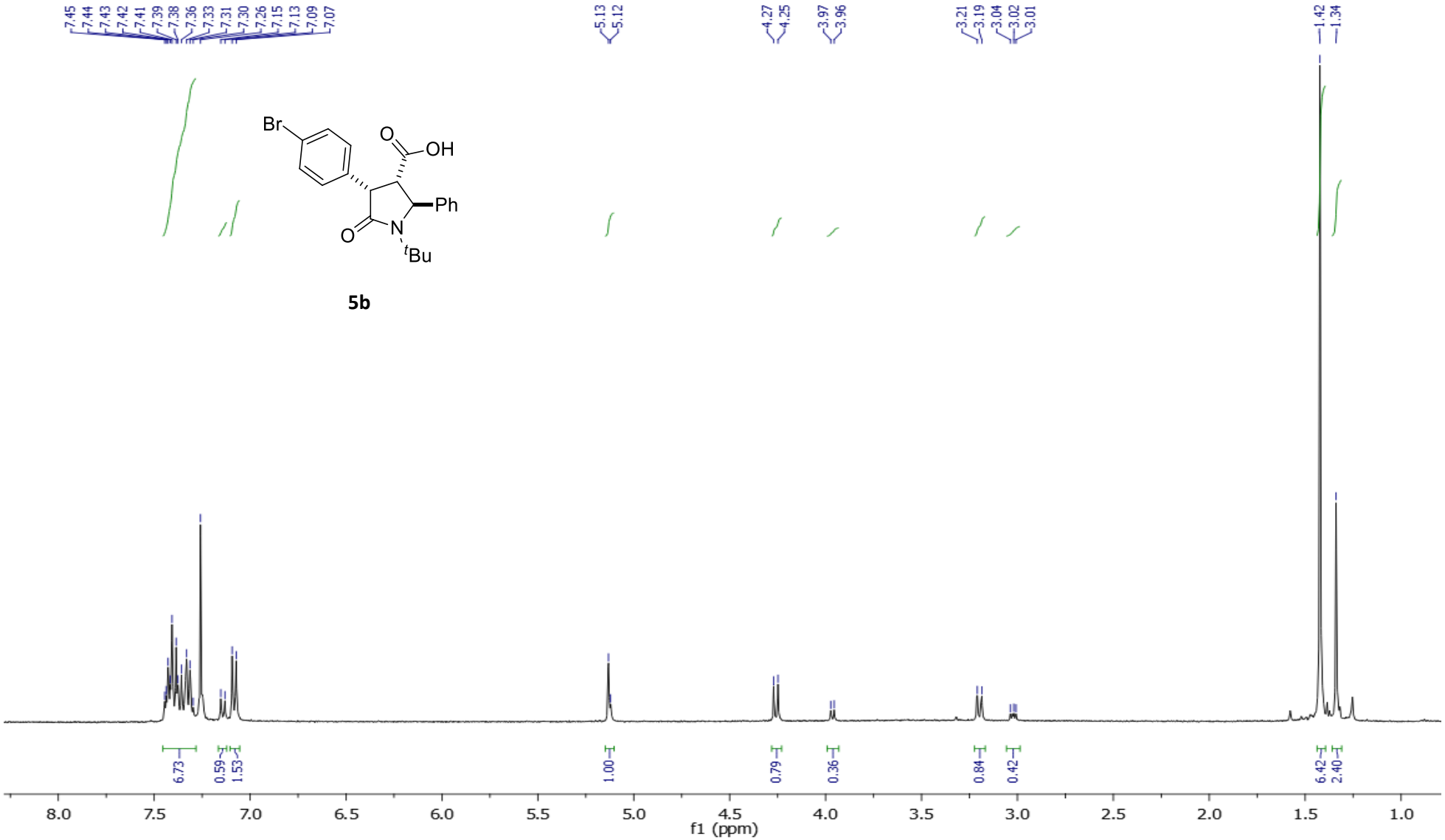
5a

^{13}C NMR (100MHz, $CDCl_3$)



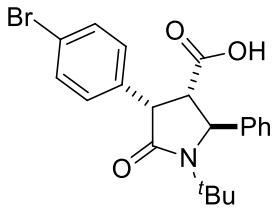
5a

^{1}H NMR (400MHz, $CDCl_3$)



5b

^{13}C NMR (100MHz, $CDCl_3$) – mixture of epimers



5b