Electronic Supplementary Information (ESI)

Palladium-catalyzed cyclization of *o*-alkynyltrifluoroacetanilides followed by isocyanide insertion: synthesis of 2-substituted 1*H*-indole-3-carboxamides

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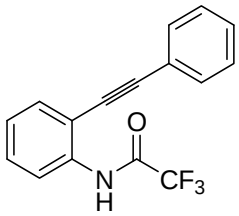
1. General Information

DMSO was used without desiccation. For flash column chromatography, silica gel (200-300 mesh) was applied. Reactions were monitored using thin-layer chromatography (TLC) on commercial silica gel plates (GF 254). Visualization of the developed plates was performed under UV lights (GF 254 nm). Flash column chromatography was performed on silica gel (200-300 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a 400 or 500 MHz spectrometer. Chemical shifts (δ) were reported in ppm referenced to an internal tetramethylsilane standard or the DMSO-d_6 residual peak (δ 2.50) for ^{1}H NMR. Chemical shifts of ^{13}C NMR were reported relative to $CDCl_3$ (δ 77.0) or DMSO-d_6 (δ 39.5). The following abbreviations were used to describe peak splitting patterns when appropriate: br s = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constant, *J*, was reported in Hertz unit (Hz). High resolution mass spectra (HRMS) were obtained on an ESI-LC-MS/MS spectrometer.

2. Preparation of the Substrates 1

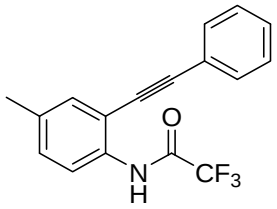
o-Alkynyltrifluoroacetanilides **1** were prepared according to the reported procedure. [1]

_N_-(2-(phenylethynyl)phenyl)-2,2,2-trifluoroacetamide 1a



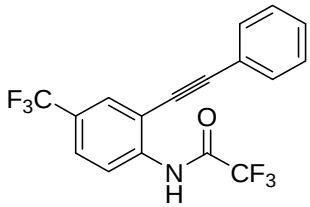
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (br s, 1H), 8.38 (d, *J* = 8.3 Hz, 1H), 7.57 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.53 (m, 2H), 7.42 (m, 4H), 7.22 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4 (q, *J* = 37 Hz), 136.1, 131.7, 131.5, 129.9, 129.3, 128.7, 125.5, 121.7, 119.6, 115.7 (q, *J* = 287 Hz), 113.5, 98.1, 82.9.

_N_-(4-methyl-2-(phenylethynyl)phenyl)-2,2,2-trifluoroacetamide 1b



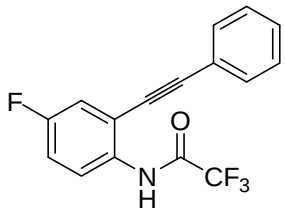
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (br s, 1H), 8.24 (d, *J* = 8.5 Hz, 1H), 7.52 (m, 2H), 7.40 (m, 4H), 7.22 (d, *J* = 8.4 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.3 (q, *J* = 37 Hz), 135.4, 133.7, 132.0, 131.4, 130.6, 129.2, 128.7, 121.8, 119.6, 115.8 (q, *J* = 287 Hz), 113.4, 97.6, 83.1, 20.8.

_N_-(2-(phenylethynyl)-4-(trifluoromethyl)phenyl)-2,2,2-trifluoroacetamide 1c



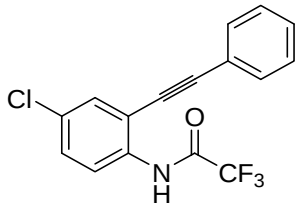
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (br s, 1H), 8.54 (d, *J* = 8.7 Hz, 1H), 7.84 (m, 1H), 7.67 (d, *J* = 8.6 Hz, 1H), 7.54 (m, 2H), 7.44 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7 (q, *J* = 38 Hz), 138.7, 131.6, 129.9, 128.8, 128.7 (q, *J* = 4 Hz), 127.7 (q, *J* = 33 Hz), 126.6 (q, *J* = 4 Hz), 123.3 (q, *J* = 270 Hz), 121.0, 119.6, 115.5 (q, *J* = 287 Hz), 114.0, 99.6, 81.5.

_N_-(4-fluoro-2-(phenylethynyl)phenyl)-2,2,2-trifluoroacetamide 1d



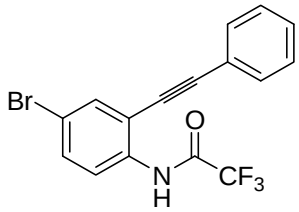
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.31 (br s, 1H), 7.56 (dd, *J* = 9.0, 2.9 Hz ,1H), 7.47 (m, 6H), 7.37 (t, *J* = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.4 (d, *J* = 244 Hz), 155.3 (q, *J* = 37 Hz), 132.3 (d, *J* = 3 Hz), 131.2, 129.4, 129.1 (d, *J* = 9 Hz), 128.9, 121.9 (d, *J* = 11 Hz), 121.6, 118.6 (d, *J* = 24 Hz), 116.7 (d, *J* = 22 Hz), 116.0 (q, *J* = 287 Hz), 95.2, 84.4 (d, *J* = 3 Hz).

_N_-(4-chloro-2-(phenylethynyl)phenyl)-2,2,2-trifluoroacetamide 1e



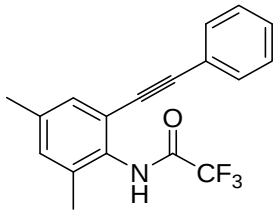
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (br s, 1H), 8.33 (d, *J* = 8.9 Hz, 1H), 7.53 (m, 3H), 7.43 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4 (q, *J* = 38 Hz), 134.6, 131.6, 131.2, 130.8, 129.9, 129.7, 128.8, 121.2, 120.8, 115.6 (q, *J* = 287 Hz), 115.1, 99.1, 81.7.

_N_-(4-bromo-2-(phenylethynyl)phenyl)-2,2,2-trifluoroacetamide 1f



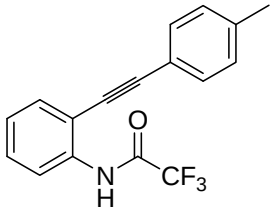
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (br s, 1H), 8.28 (d, *J* = 8.9 Hz, 1H), 7.71 (d, *J* = 2.2 Hz, 1H), 7.52 (m, 3H), 7.43 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4 (q, *J* = 37 Hz), 135.1, 134.1, 132.8, 131.6, 129.7, 128.8, 121.2, 120.9, 118.2, 115.7 (q, *J* = 287 Hz), 115.4, 99.3, 81.5.

_N_-(4,6-dimethyl-2-(phenylethynyl)phenyl)-2,2,2-trifluoroacetamide 1g



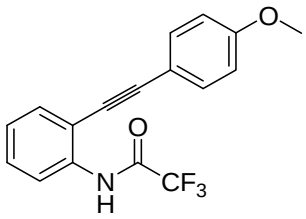
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (br s, 1H), 7.48 (m, 2H), 7.37 (m, 3H), 7.27 (s, 1H), 7.08 (s, 1H), 2.33 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3 (q, *J* = 37 Hz), 138.1, 135.3, 132.2, 131.5, 130.5, 130.4, 128.8, 128.5, 122.5, 120.5, 116.1 (q, *J* = 287 Hz), 95.3, 84.9, 20.8, 18.3.

_N_-(2-(_p_-tolylethynyl)phenyl)-2,2,2-trifluoroacetamide 1h



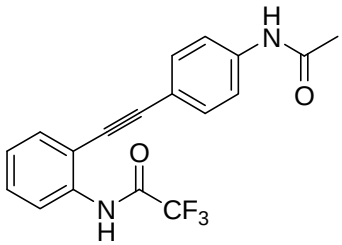
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (br s, 1H), 8.37 (d, *J* = 8.3 Hz, 1H), 7.55 (d, *J* = 7.7 Hz, 1H), 7.41 (m, 3H), 7.22 (m, 3H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4 (q, *J* = 38 Hz), 139.7, 136.0, 131.6, 131.4, 129.6, 129.5, 125.5, 119.6, 118.6, 115.8 (q, *J* = 287 Hz), 113.7, 98.3, 82.3, 21.6.

_N_-(2-((4-methoxyphenyl)ethynyl)phenyl)-2,2,2-trifluoroacetamide 1i



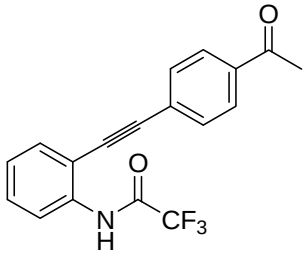
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (br s, 1H), 8.36 (d, *J* = 8.3 Hz, 1H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.48 (m, 1H), 7.46 (m, 1H), 7.40 (m, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 6.94 (m, 1H), 6.91 (m, 1H), 3.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.4, 154.4 (q, *J* = 37 Hz), 135.9, 133.0, 131.4, 129.5, 125.5, 119.5, 115.7 (q, *J* = 287 Hz)114.4, 113.9, 113.7, 98.2, 81.7, 55.4.

_N_-(2-((4-acetamidophenyl)ethynyl)phenyl)-2,2,2-trifluoroacetamide 1j



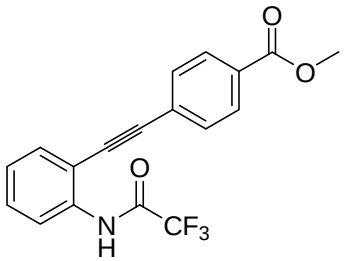
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.26 (br s, 1H), 10.22 (br s, 1H), 7.65 (m, 3H), 7.42 (m, 5H), 2.07 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.6, 155.1 (q, *J* = 36 Hz), 140.0, 135.7, 132.1, 131.8, 129.2, 127.7, 126.8, 120.1, 118.9, 116.1, 116.0 (q, *J* = 287 Hz), 94.7, 84.6, 24.0.

_N_-(2-((4-acetylphenyl)ethynyl)phenyl)-2,2,2-trifluoroacetamide 1k



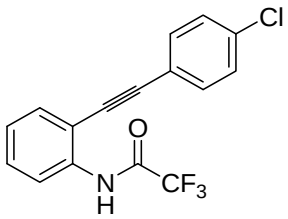
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (br s, 1H), 8.38 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.58 (m, 3H), 7.46 (t, *J* = 7.9 Hz, 1H), 7.24 (m, 1H), 2.63 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.0, 154.4 (q, *J* = 37 Hz), 137.1, 136.2, 131.9, 131.6, 130.5, 128.5, 126.4, 125.7, 119.8, 115.7 (q, *J* = 287 Hz), 112.9, 97.0, 85.9, 26.6.

methyl 4-((2-(2,2,2-trifluoroacetamido)phenyl)ethynyl)benzoate 1l



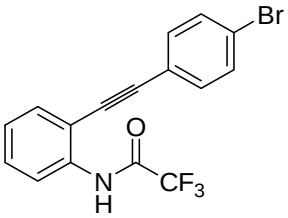
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (br s, 1H), 8.38 (d, *J* = 8.4 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 3H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.24 (m, 1H), 3.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 154.3 (q, *J* = 38 Hz), 136.2, 131.9, 131.4, 130.5, 130.4, 129.8, 126.2, 125.6, 119.8, 115.7 (q, *J* = 287 Hz), 113.0, 97.0, 85.6, 52.4

***N*-(2-((4-chlorophenyl)ethynyl)phenyl)-2,2,2-trifluoroacetamide 1m**



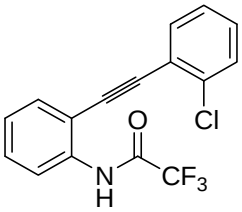
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (br s, 1H), 8.36 (d, *J* = 8.3 Hz, 1H), 7.56 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.45 (m, 3H), 7.39 (m, 2H), 7.23 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.3 (q, *J* = 37 Hz), 136.1, 135.5, 132.6, 131.7, 130.1, 129.1, 125.6, 120.1, 119.7, 115.7 (q, *J* = 287 Hz), 113.2, 96.8, 83.8.

***N*-(2-((4-bromophenyl)ethynyl)phenyl)-2,2,2-trifluoroacetamide 1n**



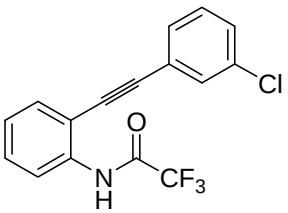
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (br s, 1H), 8.37 (d, *J* = 8.4 Hz, 1H), 7.53 (m, 3H), 7.46 (m, 1H), 7.39 (m, 2H), 7.21 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.3 (q, *J* = 37 Hz), 136.1, 132.8, 132.0, 131.7, 130.1, 125.6, 123.8, 120.6, 119.7, 115.7 (q, *J* = 287 Hz), 113.2, 96.9, 84.0.

_N_-(2-((2-chlorophenyl)ethynyl)phenyl)-2,2,2-trifluoroacetamide 1o



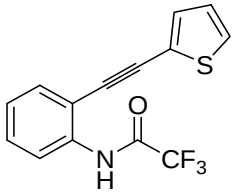
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (br s, 1H), 8.42 (d, *J* = 8.4 Hz, 1H), 7.60 (m, 2H), 7.46 (m, 2H), 7.32 (m, 2H), 7.23 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7 (q, *J* = 38 Hz), 136.3, 135.6, 133.1, 132.2, 130.24, 130.22, 129.4, 126.8, 125.5, 122.0, 119.9, 115.6 (q, *J* = 287 Hz), 113.1, 94.3, 88.1.

_N_-(2-((3-chlorophenyl)ethynyl)phenyl)-2,2,2-trifluoroacetamide 1p



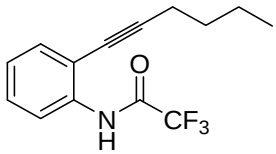
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (br s, 1H), 8.37 (d, *J* = 8.3 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.52 (m, 1H), 7.45 (m, 1H), 7.40 (m, 2H), 7.34 (m, 1H), 7.23 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4 (q, *J* = 37 Hz), 136.2, 134.6, 131.9, 131.3, 130.3, 129.9, 129.59, 129.56, 125.6, 123.4, 119.8, 115.7 (q, *J* = 287 Hz), 113.0, 96.4, 84.0.

_N_-(2-(thiophen-2-ylethynyl)phenyl)-2,2,2-trifluoroacetamide 1q



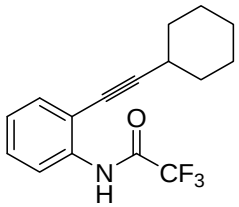
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (br s, 1H), 8.36 (d, *J* = 8.3 Hz, 1H), 7.55 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.39 (dd, *J* = 5.2, 1.0 Hz, 1H), 7.34 (dd, *J* = 3.6, 0.9 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.07 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4 (q, *J* = 37 Hz), 136.0, 132.9, 131.5, 130.0, 128.6, 127.5, 125.6, 121.4, 119.7, 115.7 (q, *J* = 287 Hz), 113.3, 91.2, 86.5.

_N_-(2-(hex-1-yn-1-yl)phenyl)-2,2,2-trifluoroacetamide 1r



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (br s, 1H), 8.33 (d, *J* = 8.4 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.35 (t, *J* = 7.9 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 2.52 (t, *J* = 7.0 Hz, 2H), 1.63 (m, 2H), 1.49 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4 (q, *J* = 37 Hz), 136.2, 131.6, 129.0, 125.3, 119.3, 115.7 (q, *J* = 287 Hz), 114.1, 99.7, 74.7, 30.6, 22.0, 19.2, 13.5.

_N_-(2-(cyclohexylethynyl)phenyl)-2,2,2-trifluoroacetamide 1s



^{1}H NMR (400 MHz, DMSO-d_6) δ 10.99 (br s, 1H), 7.48 (d, *J* = 7.4 Hz, 1H), 7.39 (m, 2H), 7.33 (m, 1H), 2.65 (m, 1H), 1.78 (m, 2H), 1.67 (m, 2H), 1.46 (m, 3H), 1.32 (m, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.9 (q, *J* = 36 Hz), 135.7, 132.2, 128.5, 127.5, 126.5, 120.8, 116.0 (q, *J* = 287 Hz), 99.8, 76.5, 31.9, 28.8, 25.3, 24.0.

3. General Procedures and Product Characterization

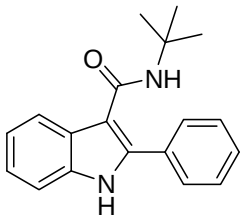
General Procedures

Procedure A for the synthesis of **3**: A mixture of *o*-ethynyltrifluoroacetanilide **1** (0.2 mmol), $PdCl_2$ (1.8 mg, 0.01 mmol, 5.0 mol %), Na_2CO_3 (22 mg, 0.2 mmol, 1.0 equiv) and isocyanide **2** (0.3 mmol, 1.5 equiv) in DMSO (1.0 mL) was stirred at room temperature for 12-48 h under air. After complete consumption of **1** as monitored by TLC analysis, the reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine and concentrated. The residue was purified by chromatography on silica gel using petroleum ether/ethyl acetate as eluent to afford the product **3**.

Procedure B for the synthesis of **4**: A mixture of *o*-ethynyltrifluoroacetanilide **1** (0.2 mmol), $PdCl_2$ (1.8 mg, 0.01 mmol, 5.0 mol %), KOAc (24 mg, 0.24 mmol, 1.2 equiv) and *tert*-butylisocyanide **2a** (34 μL, 0.3 mmol, 1.5 equiv) in DMSO (1.0 mL) was stirred at room temperature for 12-18 h under air. EtOAc (20 mL) and water (20 mL) were added to the reaction mixture. The organic layer was separated, and the aqueous layer was extracted with EtOAc (20 mL × 2). The combined organic layers was washed with brine and concentrated under reduced pressure. The residue was purified by chromatography on silica gel using petroleum ether/ethyl acetate as eluent to afford the desired product **4**.

Product characterization

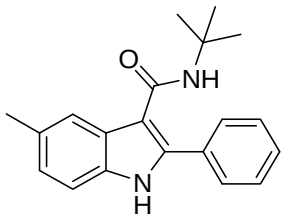
N-*tert*-butyl-2-phenyl-1*H*-indole-3-carboxamide 3aa[2]



White solid, 54 mg, 92% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.61 (br s, 1H), 7.71 (m, 3H), 7.50 (m, 2H), 7.41 (m, 2H), 7.15 (m, 1H), 7.08 (m, 1H), 7.06 (br s, 1H), 1.31 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.9, 136.6, 135.3, 131.8, 128.4,

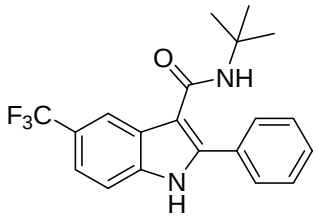
128.3, 128.2, 127.3, 122.0, 119.9, 119.8, 111.3, 110.9, 50.3, 28.5; HRMS (ESI): Exact mass calcd for $C_{19}H_{21}N_2O$ $[M+H]^+$ 293.1648, found 293.1649.

N-tert-butyl-5-methyl-2-phenyl-1_H_-indole-3-carboxamide 3ba



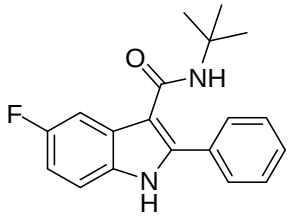
White solid, 54 mg, 88% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.49 (br s, 1H), 7.70 (m, 2H), 7.49 (m, 3H), 7.40 (m, 1H), 7.29 (d, J = 8.2 Hz, 1H), 6.98 (dd, J = 8.3, 1.3 Hz, 1H), 6.94 (br s, 1H), 2.40 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.1, 136.7, 133.8, 131.9, 128.5, 128.4, 128.3, 128.2, 127.6, 123.7, 119.4, 111.0, 110.4, 50.3, 28.5, 21.3; HRMS (ESI): Exact mass calcd for $C_{20}H_{23}N_2O$ $[M+H]^+$ 307.1805, found 307.1805.

N-tert-butyl-2-phenyl-5-trifluoromethyl-1_H_-indole-3-carboxamide 3ca



White solid, 55 mg, 77% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.12 (br s, 1H), 8.05 (s, 1H), 7.74 (m, 1H), 7.73 (m, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.54 (m, 2H), 7.47 (m, 2H), 7.12 (br s, 1H), 1.30 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.2, 139.0, 136.9, 131.0, 128.9, 128.6, 126.8, 125.4 (q, J = 269 Hz), 120.8 (q, J = 31 Hz), 118.4 (d, J = 3 Hz), 117.3 (d, J = 4 Hz), 112.2, 111.4, 50.5, 28.4; HRMS (ESI): Exact mass calcd for $C_{20}H_{20}F_3N_2O$ $[M+H]^+$ 361.1522, found 361.1525.

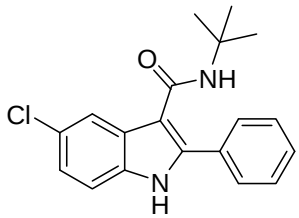
N-tert-butyl-5-fluoro-2-phenyl-1_H_-indole-3-carboxamide 3da



White solid, 54 mg, 88% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.77 (br s, 1H),

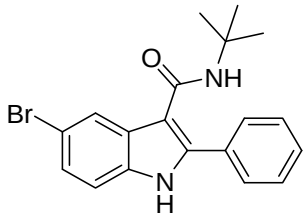
7.70 (m, 2H), 7.51 (m, 2H), 7.45 (m, 1H), 7.40 (m, 2H), 7.00 (m, 1H), 6.97 (br s, 1H), 1.29 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.5, 157.4 (d, J = 231 Hz), 138.9, 132.0, 131.4, 128.6, 128.58, 128.50, 127.7 (d, J = 11 Hz), 112.5 (d, J = 10 Hz), 110.8 (d, J = 5 Hz), 110.2 (d, J = 26 Hz), 104.5 (d, J = 2Hz), 50.3, 28.4; HRMS (ESI): Exact mass calcd for $C_{19}H_{20}FN_2O$ $[M+H]^+$ 311.1554, found 311.1557.

N-tert-butyl-5-chloro-2-phenyl-1_H_-indole-3-carboxamide 3ea



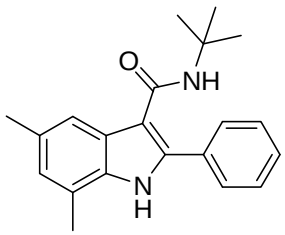
White solid, 55 mg, 85% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.86 (br s, 1H), 7.70 (m, 2H), 7.68 (m, 1H), 7.52 (m, 2H), 7.45 (m, 1H), 7.41 (d, J = 8.6 Hz, 1H), 7.16 (dd, J = 8.6, 2.0 Hz, 1H), 7.06 (br s, 1H), 1.29 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.3, 138.5, 133.8, 131.2, 128.7, 128.50, 128.47, 128.45, 124.6, 122.0, 118.9, 112.9, 110.4, 50.4, 28.4; HRMS (ESI): Exact mass calcd for $C_{19}H_{20}ClN_2O$ $[M+H]^+$ 327.1259, found 327.1260.

N-tert-butyl-5-bromo-2-phenyl-1_H_-indole-3-carboxamide 3fa



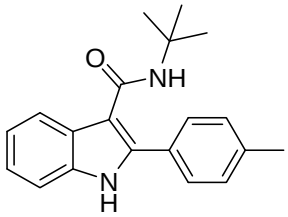
White solid, 63 mg, 84% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.87 (br s, 1H), 7.83 (d, J = 1.8 Hz, 1H), 7.70 (m, 2H), 7.52 (m, 2H), 7.45 (m, 1H), 7.37 (m, 1H), 7.27 (dd, J = 8.6, 1.9 Hz, 1H), 7.05 (br s, 1H), 1.29 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.4, 138.3, 134.1, 131.2, 129.2, 128.7, 128.53, 128.51, 124.6, 122.0, 113.4, 112.6, 110.3, 50.4, 28.4; HRMS (ESI): Exact mass calcd for $C_{19}H_{20}BrN_2O$ $[M+H]^+$ 371.0754, found 371.0755.

N-tert-butyl-5,7-dimethyl-2-phenyl-1_H_-indole-3-carboxamide 3ga



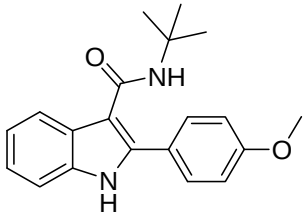
White solid, 44 mg, 69% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.23 (br s, 1H), 7.71 (m, 2H), 7.50 (m, 2H), 7.43 (m, 1H), 7.36 (s, 1H), 6.78 (s, 1H), 6.72 (br s, 1H), 2.47 (s, 3H), 2.36 (s, 3H), 1.27 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.1, 137.1, 133.3, 132.0, 128.9, 128.7, 128.22, 128.17, 127.3, 124.4, 120.4, 117.1, 110.8, 50.2, 28.5, 21.3, 16.8; HRMS (ESI): Exact mass calcd for $C_{21}H_{25}N_2O$ $[M+H]^+$ 321.1961, found 321.1965.

_N_-*tert*-butyl-2-*p*-tolyl-1*H*-indole-3-carboxamide 3ha



White solid, 58 mg, 94% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.55 (br s, 1H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.61 (d, *J* = 7.9 Hz, 2H), 7.38 (d, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 7.9 Hz, 2H), 7.13 (m, 1H), 7.07 (m, 1H), 7.03 (br s, 1H), 2.37 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.1, 137.7, 136.7, 135.2, 128.9, 128.2, 127.4, 121.8, 119.9, 119.7, 111.2, 110.5, 50.3, 28.5, 20.8; HRMS (ESI): Exact mass calcd for $C_{20}H_{23}N_2O$ $[M+H]^+$ 307.1805, found 307.1807.

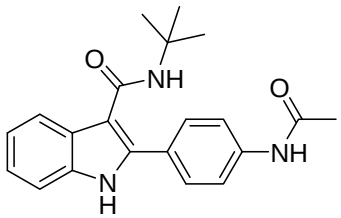
_N_-*tert*-butyl-2-(4-methoxylphenyl)-1*H*-indole-3-carboxamide 3ia



White solid, 59 mg, 91% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.52 (br s, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 8.7 Hz, 2H), 7.38 (d, *J* = 7.9 Hz, 1H), 7.13 (t, *J* = 6.9 Hz, 1H), 7.06 (m, 3H), 6.97 (br s, 1H), 3.82 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.1, 159.4, 136.9, 135.2, 129.7, 127.5, 124.1, 121.7, 119.9,

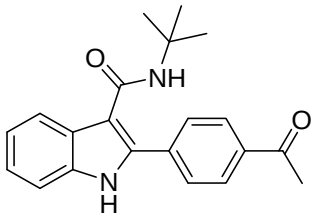
119.7, 113.9, 111.1, 109.9, 55.3, 50.3, 28.5; HRMS (ESI): Exact mass calcd for $C_{20}H_{23}N_2O_2$ $[M+H]^+$ 323.1754, found 323.1754.

_N_-*tert*-butyl-2-(4-acetamidophenyl)-1*H*-indole-3-carboxamide 3ja



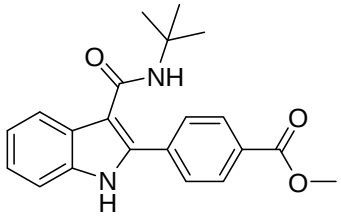
White solid, 57 mg, 82% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.54 (br s, 1H), 10.10 (br s, 1H), 7.68 (m, 3H), 7.65 (m, 2H), 7.38 (d, *J* = 7.9 Hz, 1H), 7.13 (m, 1H), 7.07 (m, 1H), 7.02 (br s, 1H), 2.08 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.4, 165.0, 139.3, 136.7, 135.2, 128.8, 127.4, 126.3, 121.8, 119.9, 119.7, 118.6, 111.2, 110.3, 50.3, 28.5, 24.0; HRMS (ESI): Exact mass calcd for $C_{21}H_{24}N_3O_2$ $[M+H]^+$ 350.1863, found 350.1864.

_N_-*tert*-butyl-2-(4-acetylphenyl)-1*H*-indole-3-carboxamide 3ka



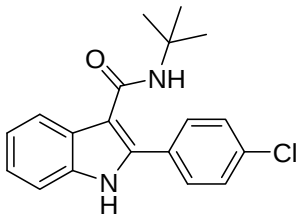
The reaction was performed at 50 ^{o}C. White solid, 51 mg, 76% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.77 (br s, 1H), 8.05 (d, *J* = 8.4 Hz, 2H), 7.87 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.55 (br s, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.19 (m, 1H), 7.11 (m, 1H), 2.62 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 197.4, 165.0, 136.1, 135.73, 135.69, 134.6, 128.3, 127.8, 127.2, 122.7, 120.1, 119.8, 112.9, 111.5, 50.5, 28.5, 26.7; HRMS (ESI): Exact mass calcd for $C_{21}H_{23}N_2O_2$ $[M+H]^+$ 335.1754, found 335.1756.

methyl 4-(3-(*tert*-butylcarbamoyl)-1*H*-indol-2-yl)benzoate 3la



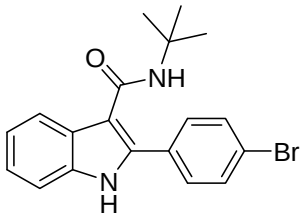
The reaction was performed at 50 °C. White solid, 47 mg, 68% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.77 (br s, 1H), 8.05 (d, *J* = 8.4 Hz, 2H), 7.87 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.49 (br s, 1H), 7.43 (d, *J* = 8.1 Hz, 1H), 7.19 (m, 1H), 7.11 (m, 1H), 3.89 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.9, 164.9, 136.3, 135.7, 134.6, 129.1, 128.6, 128.0, 127.2, 122.7, 120.1, 119.8, 112.8, 111.5, 52.2, 50.5, 28.5; HRMS (ESI): Exact mass calcd for $C_{21}H_{23}N_2O_3$ $[M+H]^+$ 351.1703, found 351.1708.

N-tert-butyl-2-(4-chlorophenyl)-1_H_-indole-3-carboxamide 3ma



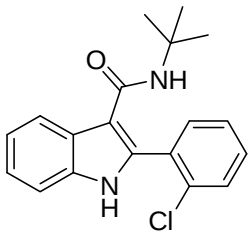
White solid, 50 mg, 76% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.68 (br s, 1H), 7.74 (m, 2H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.57 (m, 2H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.33 (br s, 1H), 7.17 (m, 1H), 7.09 (m, 1H), 1.34 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.9, 135.4, 135.2, 132.7, 130.7, 129.8, 128.4, 127.2, 122.3, 120.1, 119.8, 111.6, 111.4, 50.5, 28.5; HRMS (ESI): Exact mass calcd for $C_{19}H_{20}ClN_2O$ $[M+H]^+$ 327.1259, found 327.1260.

N-tert-butyl-2-(4-bromophenyl)-1_H_-indole-3-carboxamide 3na



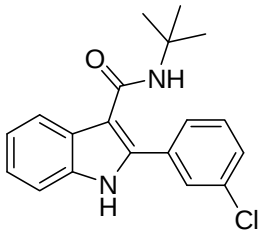
White solid, 64 mg, 86% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.68 (br s, 1H), 7.69 (m, 5H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.34 (br s, 1H), 7.17 (m, 1H), 7.09 (m, 1H), 1.34 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.9, 135.4, 135.2, 131.3, 131.1, 130.1, 127.2, 122.3, 121.3, 120.1, 119.7, 111.7, 111.4, 50.5, 28.5; HRMS (ESI): Exact mass calcd for $C_{19}H_{20}BrN_2O$ $[M+H]^+$ 371.0754, found 371.0755.

N-tert-butyl-2-(2-chlorophenyl)-1_H_-indole-3-carboxamide 3oa



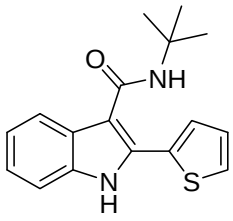
White solid, 52 mg, 79% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.76 (br s, 1H), 7.94 (d, *J* = 7.7 Hz, 1H), 7.67 (m, 1H), 7.60 (m, 1H), 7.53 (m, 2H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.19 (m, 1H), 7.13 (m, 1H), 6.01 (br s, 1H), 1.18 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.9, 135.4, 135.2, 133.3, 132.5, 131.4, 130.8, 129.6, 127.2, 126.3, 122.2, 120.6, 120.3, 111.4, 111.2, 49.9, 28.4; HRMS (ESI): Exact mass calcd for $C_{19}H_{20}ClN_2O$ $[M+H]^+$ 327.1259, found 327.1259.

_N_-*tert*-butyl-2-(3-chlorophenyl)-1*H*-indole-3-carboxamide 3pa



White solid, 50 mg, 76% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.72 (br s, 1H), 7.79 (s, 1H), 7.69 (d, *J* = 7.7 Hz, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.52 (t, *J* = 7.9 Hz, 1H), 7.45 (m, 3H), 7.18 (t, *J* = 7.3 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 1.36 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.9, 135.5, 134.4, 133.8, 133.1, 130.3, 127.7, 127.6, 127.1, 126.4, 122.5, 120.1, 119.8, 112.1, 111.4, 50.5, 28.5; HRMS (ESI): Exact mass calcd for $C_{19}H_{20}ClN_2O$ $[M+H]^+$ 327.1259, found 327.1260.

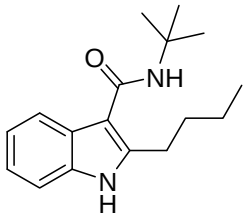
_N_-*tert*-butyl-2-(thiophen-2-yl)-1*H*-indole-3-carboxamide 3qa



White solid, 45 mg, 75% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.65 (br s, 1H), 7.62 (m, 3H), 7.42 (br s, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.17 (m, 2H), 7.08 (m, 1H), 1.38 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.5, 135.2, 133.3, 130.6, 127.4, 127.2, 127.0, 126.8, 122.3, 120.1, 119.7, 111.12, 111.11, 50.4, 28.6; HRMS (ESI):

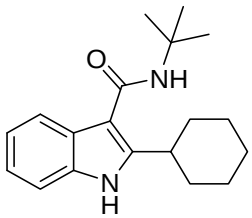
Exact mass calcd for $C_{17}H_{19}N_2OS$ $[M+H]^+$ 299.1213, found 299.1213.

N-tert-butyl-2-butyl-1_H_-indole-3-carboxamide 3ra



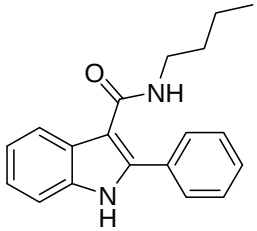
White solid, 47 mg, 88% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.30 (br s, 1H), 7.63 (m, 1H), 7.32 (m, 1H), 7.05 (m, 2H), 6.87 (br s, 1H), 2.98 (t, J = 7.6 Hz, 2H), 1.66 (m, 2H), 1.41 (s, 9H), 1.31 (m, 2H), 0.90 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.2, 142.8, 134.6, 126.1, 120.8, 119.7, 119.2, 110.9, 109.1, 50.3, 31.3, 28.9, 26.2, 21.9, 13.7; HRMS (ESI): Exact mass calcd for $C_{17}H_{25}N_2O$ $[M+H]^+$ 273.1961, found 273.1963.

N-tert-butyl-2-cyclohexyl-1_H_-indole-3-carboxamide 3sa



White solid, 53 mg, 87% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.21 (br s, 1H), 7.58 (m, 1H), 7.33 (m, 1H), 7.04 (m, 2H), 6.88 (br s, 1H), 3.41 (m, 1H), 1.66 (m, 10H), 1.40 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.2, 147.2, 134.7, 125.7, 120.7, 119.7, 119.0, 111.1, 108.0, 50.3, 35.6, 32.0, 28.9, 26.2, 25.6; HRMS (ESI): Exact mass calcd for $C_{19}H_{27}N_2O$ $[M+H]^+$ 299.2118, found 299.2120.

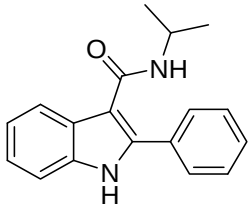
_N_-butyl-2-phenyl-1_H_-indole-3-carboxamide 3ab



$PdCl_2$ (3.6 mg, 10 mol %) and Cs_2CO_3 (65 mg, 1 equiv) instead of Na_2CO_3 were employed. White solid, 30 mg, 51% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.67 (br

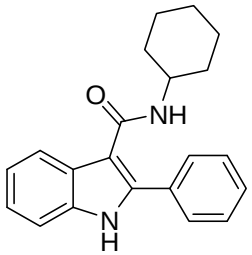
s, 1H), 7.72 (m, 4H), 7.48 (m, 2H), 7.40 (m, 2H), 7.16 (m, 1H), 7.09 (m, 1H), 7.24 (m, 2H), 1.47 (m, 2H), 1.31 (m, 2H), 0.90 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.2, 136.9, 135.4, 131.8, 128.4, 128.2, 128.1, 127.1, 122.1, 120.0, 119.8, 111.4, 110.1, 38.5, 31.2, 19.7, 13.7; HRMS (ESI): Exact mass calcd for $C_{19}H_{21}N_2O$ $[M+H]^+$ 293.1648, found 293.1649.

_N_-isopropyl-2-phenyl-1_H_-indole-3-carboxamide 3ac



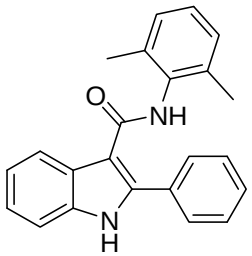
$PdCl_2$ (3.6 mg, 10 mol %) and Cs_2CO_3 (65 mg, 1 equiv) instead of Na_2CO_3 were employed. White solid, 35 mg, 63% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.65 (br s, 1H), 7.73 (m, 1H), 7.71 (m, 1H), 7.65 (d, J = 7.9 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.48 (m, 2H), 7.40 (m, 2H), 7.16 (m, 1H), 7.09 (m, 1H), 4.12 (m, 1H), 1.10 (d, J = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.5, 136.7, 135.4, 131.8, 128.4, 128.20, 128.15, 127.2, 122.1, 120.0, 119.8, 111.4, 110.2, 40.5, 22.3; HRMS (ESI): Exact mass calcd for $C_{18}H_{19}N_2O$ $[M+H]^+$ 279.1492, found 279.1490.

_N_-cyclohexyl-2-phenyl-1_H_-indole-3-carboxamide 3ad



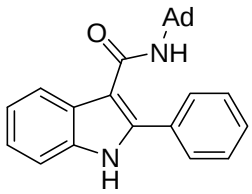
$PdCl_2$ (3.6 mg, 10 mol %) and Cs_2CO_3 (65 mg, 1 equiv) instead of Na_2CO_3 were employed. White solid, 39 mg, 61% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.65 (br s, 1H), 7.73 (m, 1H), 7.71 (m, 1H), 7.66 (d, J = 7.9 Hz, 1H), 7.52 (m, 1H), 7.48 (m, 2H), 7.40 (m, 2H), 7.16 (m, 1H), 7.08 (m, 1H), 3.79 (m, 1H), 2.20 (m, 10H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.3, 136.7, 135.4, 131.8, 128.4, 128.2, 128.1, 127.2, 122.1, 119.9, 119.8, 111.3, 110.1, 47.6, 32.3, 25.2, 24.6; HRMS (ESI): Exact mass calcd for $C_{21}H_{23}N_2O$ $[M+H]^+$ 319.1805, found 319.1804.

_N_-(2,6-dimethylphenyl)-2-phenyl-1_H_-indole-3-carboxamide 3ae



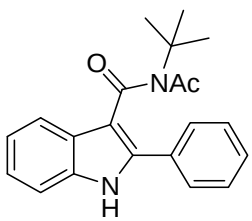
The reaction was performed in the presence of $PdCl_2$ (3.6 mg, 10 mol %) and Cs_2CO_3 (65 mg, 1 equiv) instead of Na_2CO_3 at 50 ^oC. White solid, 39 mg, 57% yield. ^1H NMR (400 MHz, DMSO-d_6) δ 11.82 (br s, 1H), 9.25 (br s, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.80 (m, 2H), 7.49 (m, 3H), 7.42 (m, 1H), 7.21 (m, 1H), 7.16 (m, 1H), 7.10 (m, 3H), 2.25 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.2, 137.9, 135.7, 135.50, 135.45, 131.9, 128.5, 128.4, 128.3, 127.7, 127.1, 126.3, 122.2, 120.2, 119.9, 111.6, 109.8, 18.6; HRMS (ESI): Exact mass calcd for $C_{23}H_{21}N_2O$ $[M+H]^+$ 341.1648, found 341.1645.

_N_-(adamantan-1-yl)-2-phenyl-1_H_-indole-3-carboxamide 3af



White solid, 73 mg, 98% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (br s, 1H), 8.16 (m, 1H), 7.64 (m, 2H), 7.48 (m, 3H), 7.35 (m, 1H), 7.22 (m, 2H), 5.28 (br s, 1H), 2.04 (m, 3H), 1.95 (m, 6H), 1.66 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 137.9, 135.3, 131.7, 129.3, 128.9, 127.8, 123.1, 121.45, 121.42, 110.8, 110.7, 51.9, 41.7, 36.4, 29.5; HRMS (ESI): Exact mass calcd for $C_{25}H_{27}N_2O$ $[M+H]^+$ 371.2118, found 371.2118.

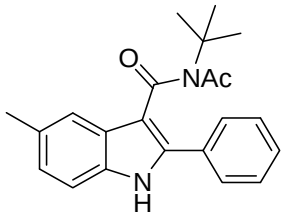
_N_-acetyl-_N_-_tert_-butyl-2-phenyl-1_H_-indole-3-carboxamide 4a



White solid, 58 mg, 86% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 9.02 (br s, 1H), 8.13

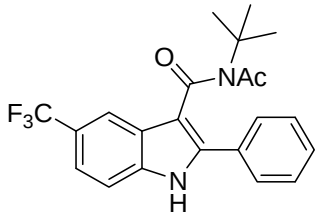
(m, 1H), 7.61 (m, 2H), 7.50 (m, 3H), 7.45 (m, 1H), 7.35 (m, 2H), 2.05 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 169.6, 147.2, 135.2, 131.6, 130.0, 129.3, 128.6, 126.9, 124.0, 123.3, 121.4, 111.9, 111.5, 58.8, 28.5, 25.7; HRMS (ESI): Exact mass calcd for $C_{21}H_{22}N_2NaO_2$ $[M+Na]^+$ 357.1573, found 357.1574.

_N_-acetyl-_N-tert_-butyl-5-methyl-2-phenyl-1_H_-indole-3-carboxamide 4b



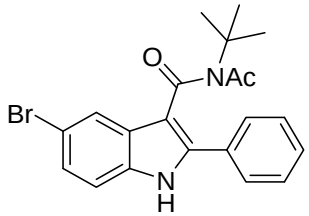
White solid, 59 mg, 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (br s, 1H), 7.95 (s, 1H), 7.58 (m, 2H), 7.46 (m, 3H), 7.34 (d, J = 8.2 Hz, 1H), 7.15 (d, J = 8.3 Hz, 1H), 2.50 (s, 3H), 2.03 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 169.8, 147.2, 133.6, 132.9, 131.8, 129.8, 129.3, 128.5, 127.3, 125.4, 121.1, 111.4, 111.2, 58.7, 28.4, 25.6, 21.8; HRMS (ESI): Exact mass calcd for $C_{22}H_{24}N_2NaO_2$ $[M+Na]^+$ 371.1730, found 371.1732.

_N_-acetyl-_N-tert_-butyl-2-phenyl-5-trifluoromethyl-1_H_-indole-3-carboxamide 4c



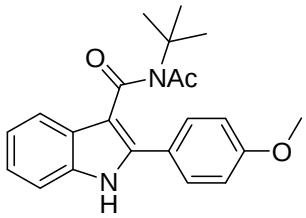
White solid, 65 mg, 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (br s, 1H), 8.52 (s, 1H), 7.57 (m, 3H), 7.55 (m, 1H), 7.50 (m, 3H), 2.00 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 169.8, 148.4, 136.8, 131.0, 130.3, 129.3, 128.7, 126.7, 120.88, 120.85, 119.20, 119.17, 112.4, 112.0, 59.0, 28.3, 25.8; HRMS (ESI): Exact mass calcd for $C_{22}H_{21}F_3N_2NaO_2$ $[M+Na]^+$ 425.1447, found 425.1448.

_N_-acetyl-_N-tert_-butyl-5-bromo-2-phenyl-1_H_-indole-3-carboxamide 4d



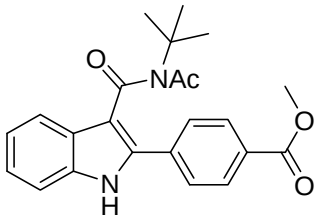
White solid, 61 mg, 73% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (br s, 1H), 8.34 (d, *J* = 1.7 Hz, 1H), 7.56 (m, 2H), 7.49 (m, 3H), 7.42 (d, *J* = 8.6 Hz, 1H), 7.32 (d, *J* = 8.6 Hz, 1H), 2.01 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 171.2, 169.8, 147.8, 134.0, 131.1, 130.1, 129.3, 128.8, 128.6, 127.1, 124.1, 116.8, 113.0, 111.4, 58.9, 28.3, 25.7; HRMS (ESI): Exact mass calcd for $C_{21}H_{21}BrN_2NaO_2$ $[M+Na]^+$435.0679, found 435.0680.

_N_-acetyl-_N_-_tert_-butyl-2-(4-methoxylphenyl)-1_H_-indole-3-carboxamide 4e



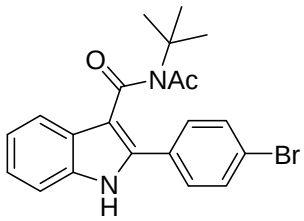
White solid, 55 mg, 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (br s, 1H), 8.09 (m, 1H), 7.59 (m, 2H), 7.43 (m, 1H), 7.35 (m, 2H), 7.03 (m, 2H), 3.87 (s, 3H), 2.06 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 169.6, 161.0, 147.5, 135.1, 130.7, 127.0, 123.8, 123.6, 123.2, 121.3, 114.1, 111.4, 58.8, 55.4, 28.6, 25.6; HRMS (ESI): Exact mass calcd for $C_{22}H_{24}N_2NaO_3$ $[M+Na]^+$ 387.1679, found 387.1682.

methyl 4-(3-(acetyl(_tert_-butyl)carbamoyl)-1_H_-indol-2-yl)benzoate 4f



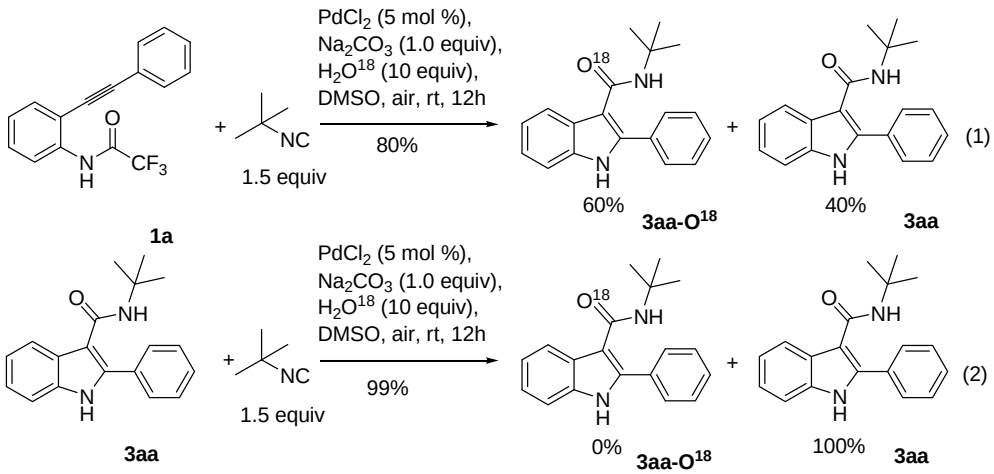
The reaction was performed at 50 °C. White solid, 43 mg, 56% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (br s, 1H), 8.11 (m, 2H), 8.06 (m, 1H), 7.69 (m, 2H), 7.48 (m, 1H), 7.37 (m, 2H), 3.95 (s, 3H), 2.03 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 169.7, 166.5, 145.9, 136.1, 135.6, 131.1, 129.6, 129.4, 126.7, 124.2, 123.4, 121.1, 112.1, 111.9, 59.0, 52.4, 28.6, 25.6; HRMS (ESI): Exact mass calcd for $C_{23}H_{24}N_2NaO_{24}$ $[M+Na]^+$ 415.1628, found 415.1630.

_N_-acetyl-_N_-_tert_-butyl-2-(4-bromophenyl)-1_H_-indole-3-carboxamide 4g



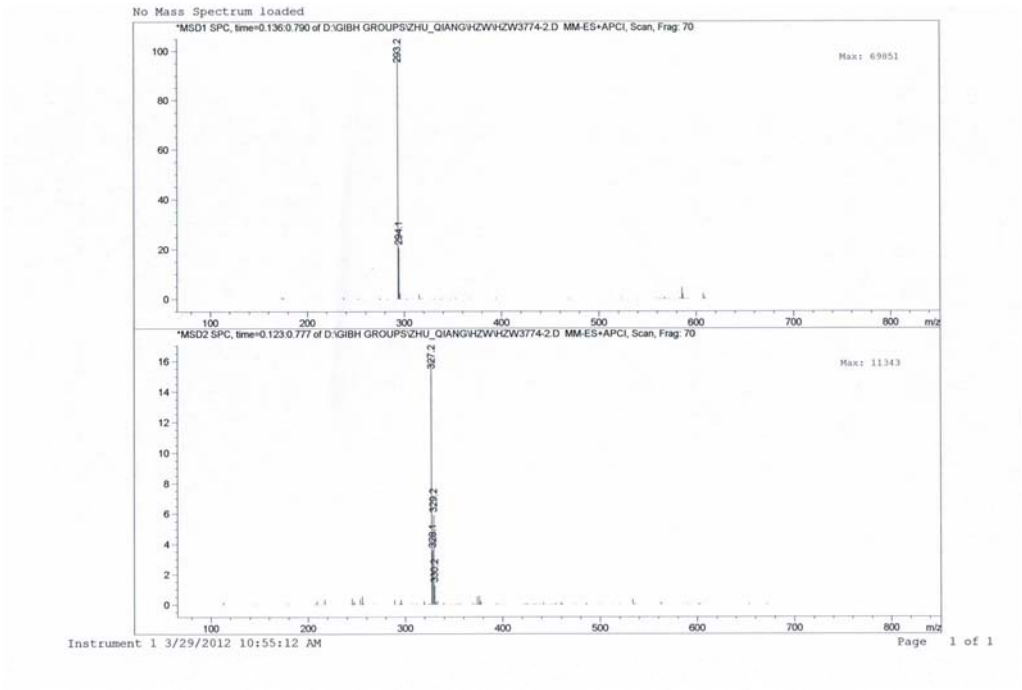
White solid, 42 mg, 55% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (br s, 1H), 8.05 (m, 1H), 7.63 (m, 2H), 7.52 (m, 2H), 7.46 (m, 1H), 7.35 (m, 2H), 2.02 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 169.6, 146.0, 135.3, 131.8, 130.9, 130.4, 126.7, 124.5, 124.2, 123.4, 121.1, 111.9, 111.7, 59.0, 28.6, 25.6; HRMS (ESI): Exact mass calcd for $C_{21}H_{21}BrN_2NaO_2$ $[M+Na]^+$ 435.0679, found 435.0680.

4. Determination of the Oxygen Source in Product 3aa

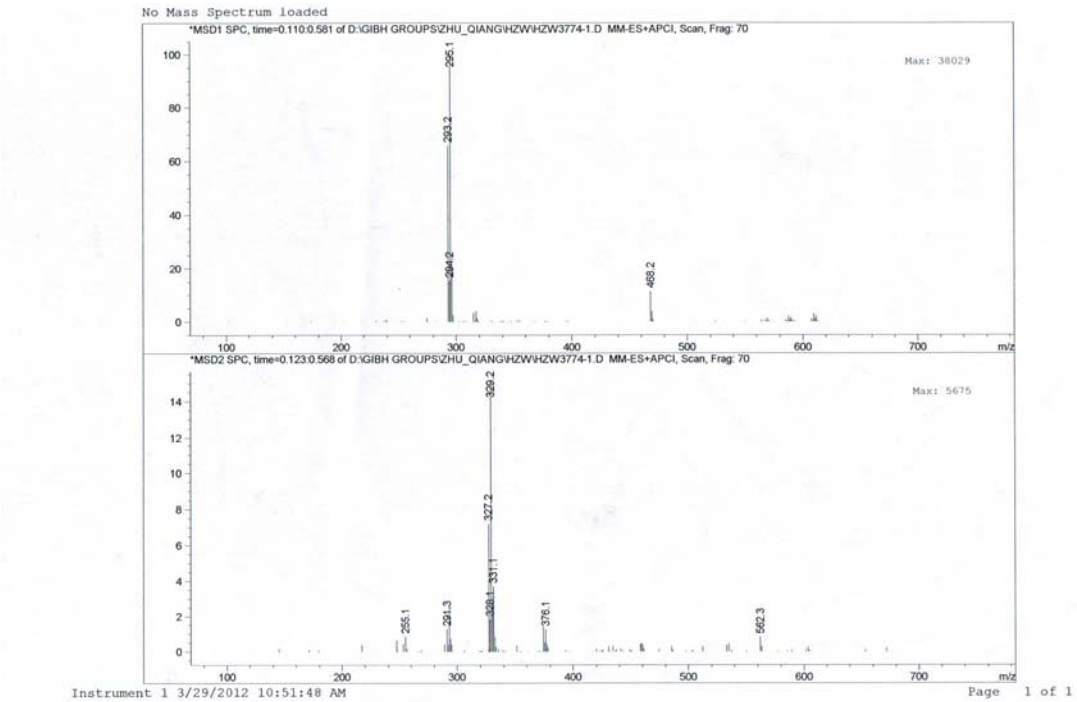


When the reaction was performed in the presence of 10 equiv of H_2O^{18} under otherwise identical conditions described for the synthesis of **3**, **3aa** was obtained in 80% yield, in which about 60% of the product was O^{18} incorporated (eq 1). In a control experiment (eq 2), **1a** was replaced by **3aa**, and no oxygen exchange was detected in the recovered **3aa**. The result suggested that water was involved during the amide bond formation, not after that.

MS (ES+APCI) of **3aa**



MS (ES+APCI) of **3aa-O^{18} and 3aa**

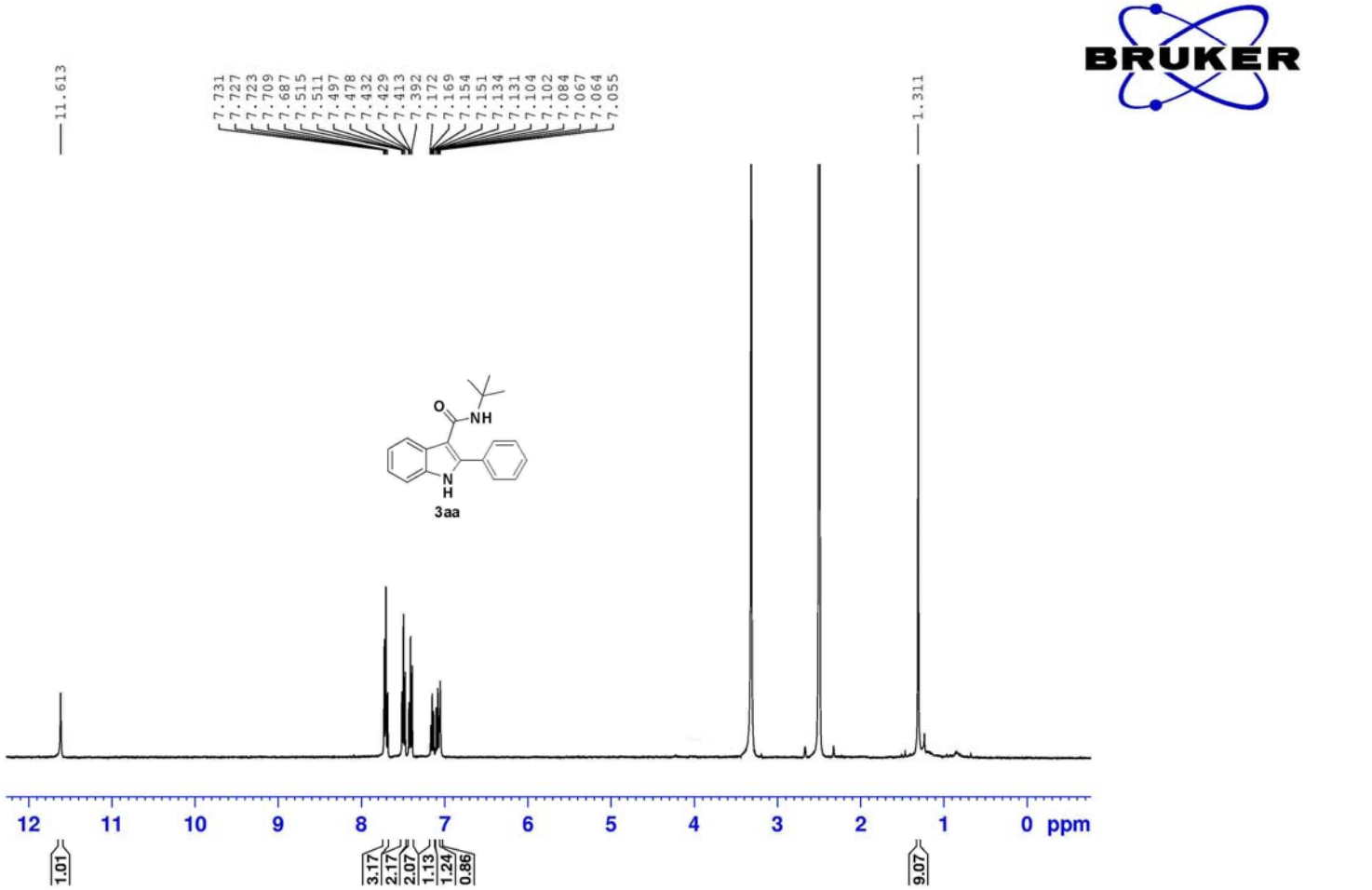


5. References

(1) S. Cacchi, G. Fabrizi and P. Pace, *J. Org. Chem.*, 1998, **63**, 1001.

(2) J. Peng, L. Liu, Z. Hu, J. Huang and Q. Zhu, *Chem. Commun.*, 2012, **48**, 3772.

6. Copies of NMR Spectra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7.687
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7.432
7.429
7.413
7.392
7.172
7.169
7.154
7.151
7.134
7.131
7.104
7.102
7.084
7.067
7.064
7.055
1.311
O
NH
N
H
3aa
12
11
10
9
8
7
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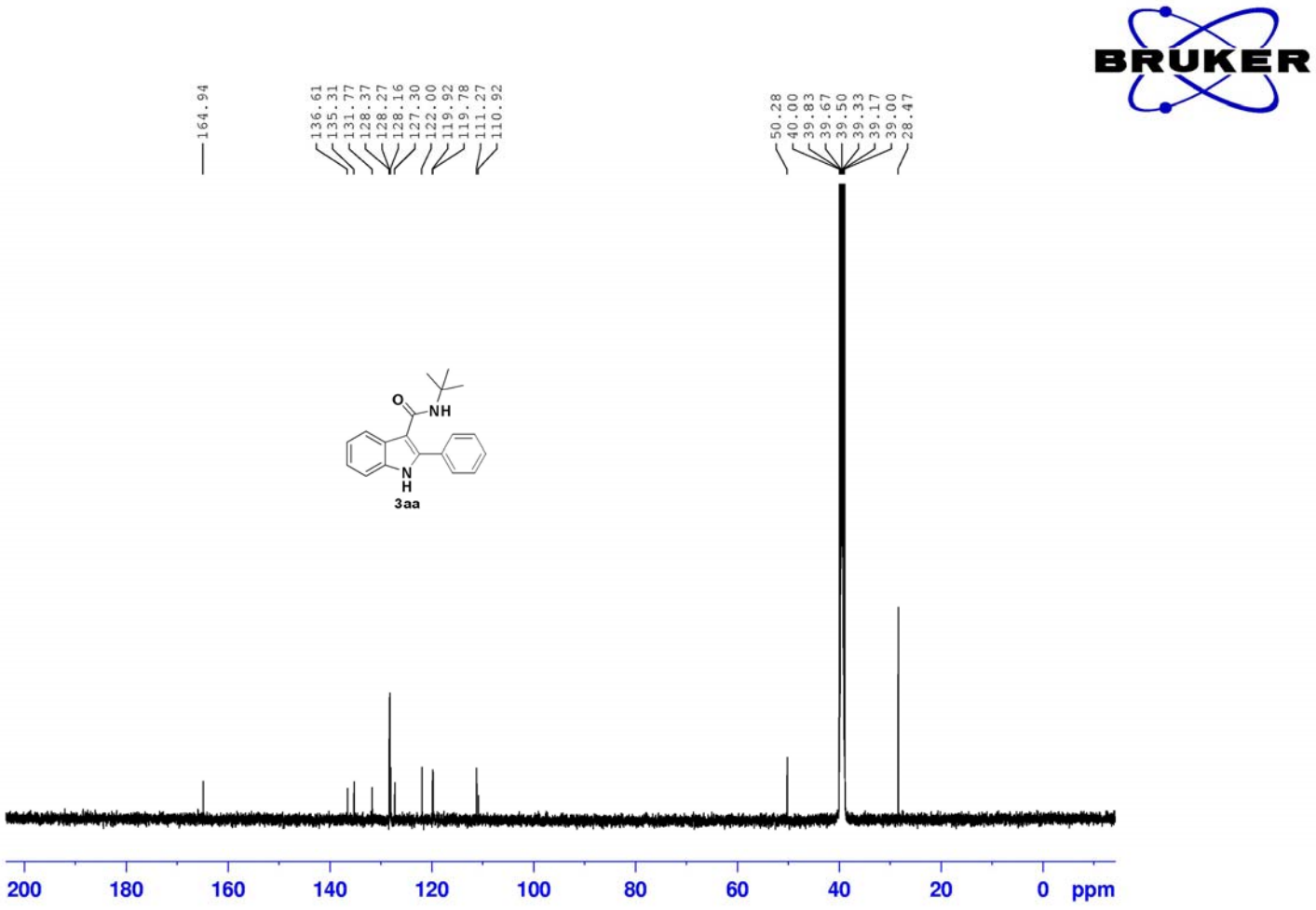
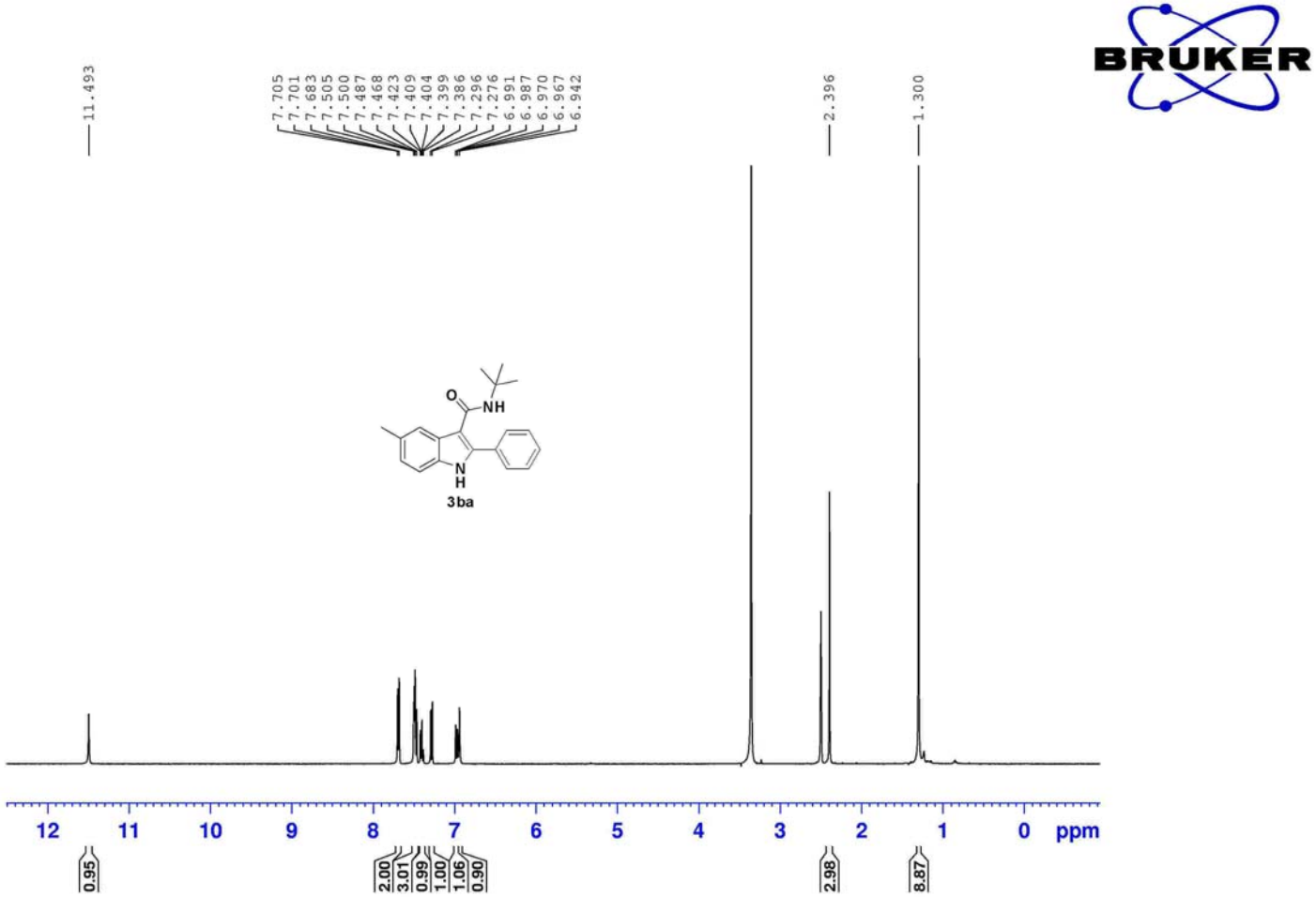
2.17
2.07
1.13
1.24
0.86
9.07

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7.276
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N
H
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11
10
9
8
7
6
5
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1.00
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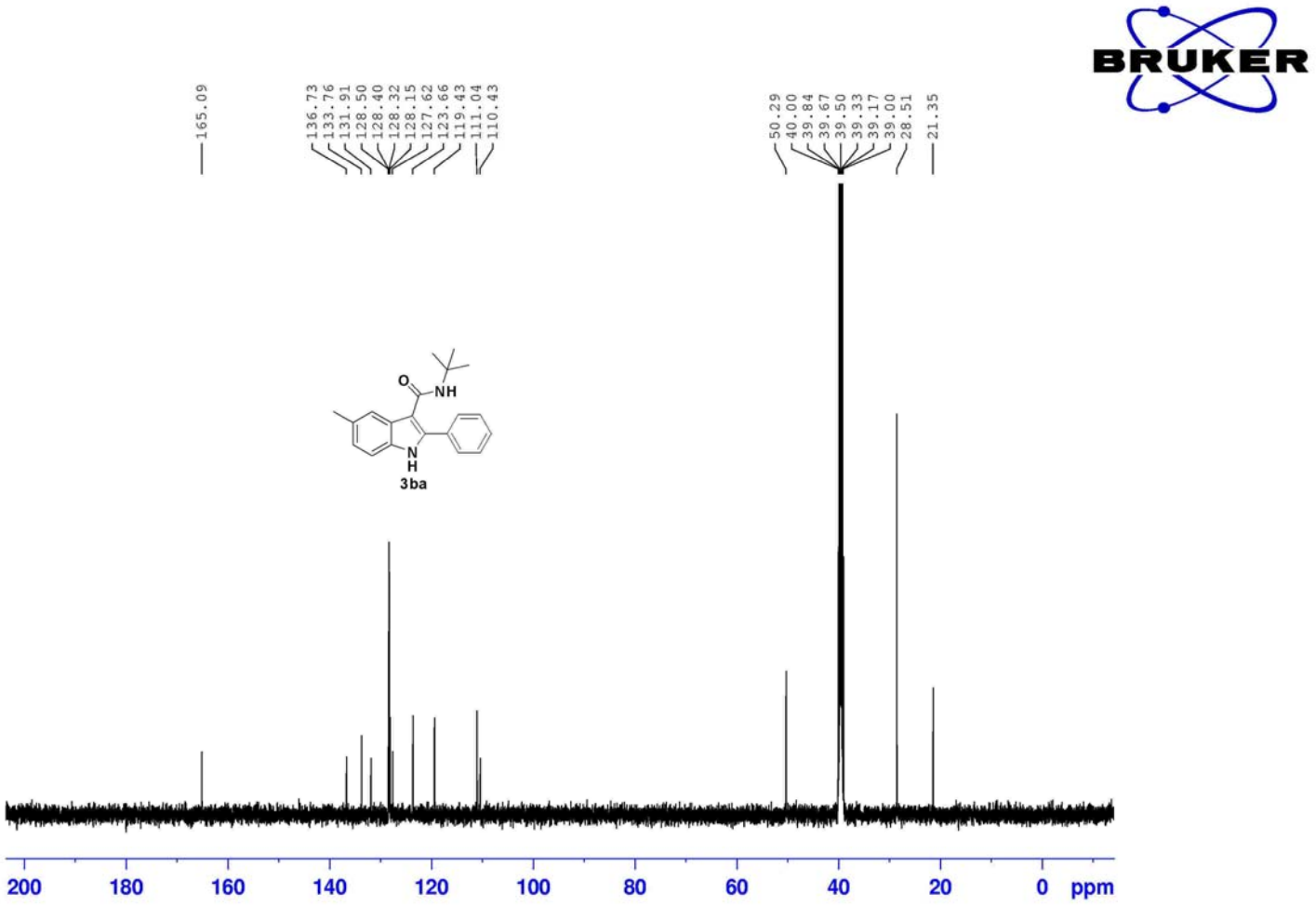
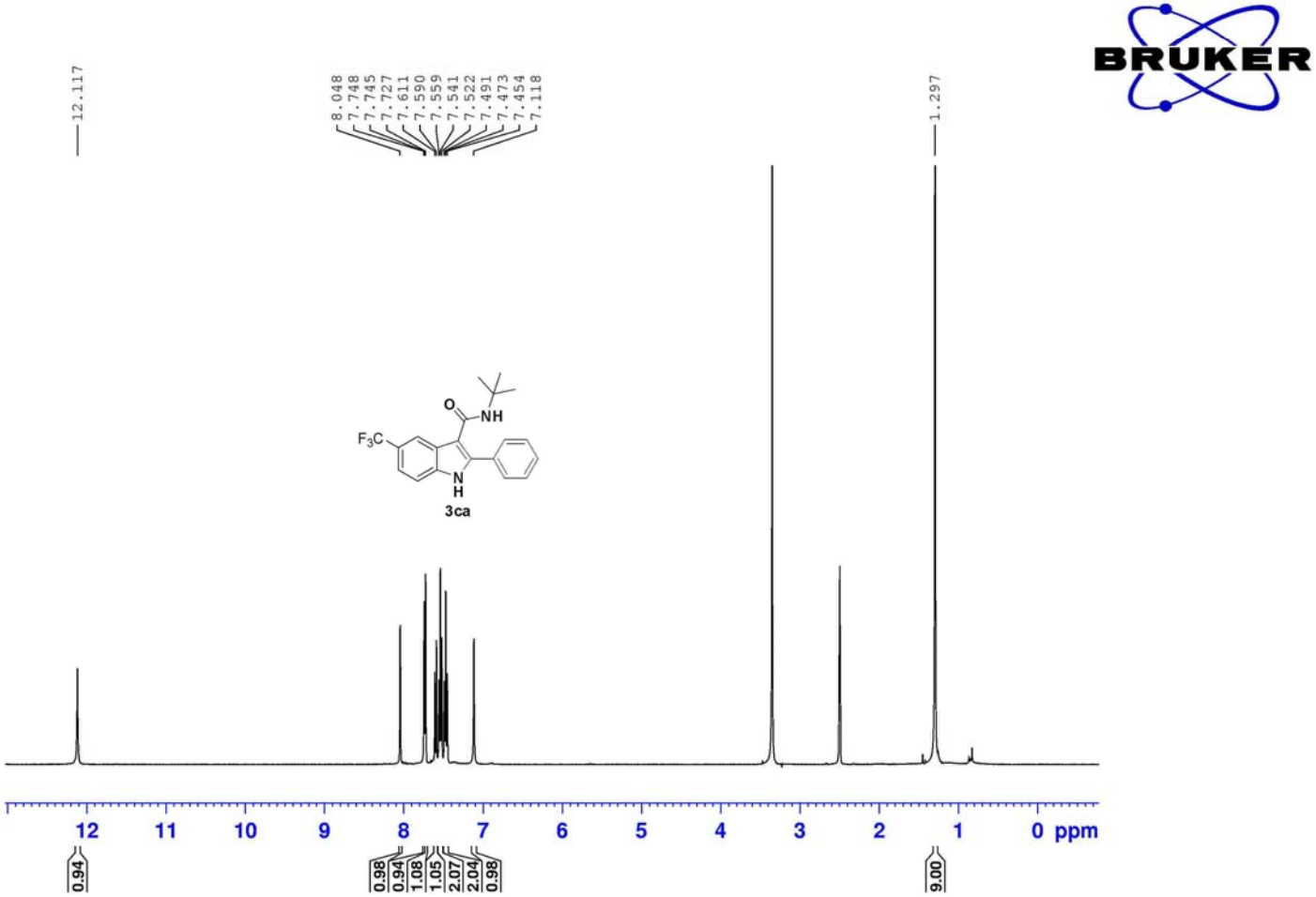
8.87

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7.611
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7.559
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7.522
7.491
7.473
7.454
7.118
1.297
O
NH
F3C
N
H
3ca
12
11
10
9
8
7
6
5
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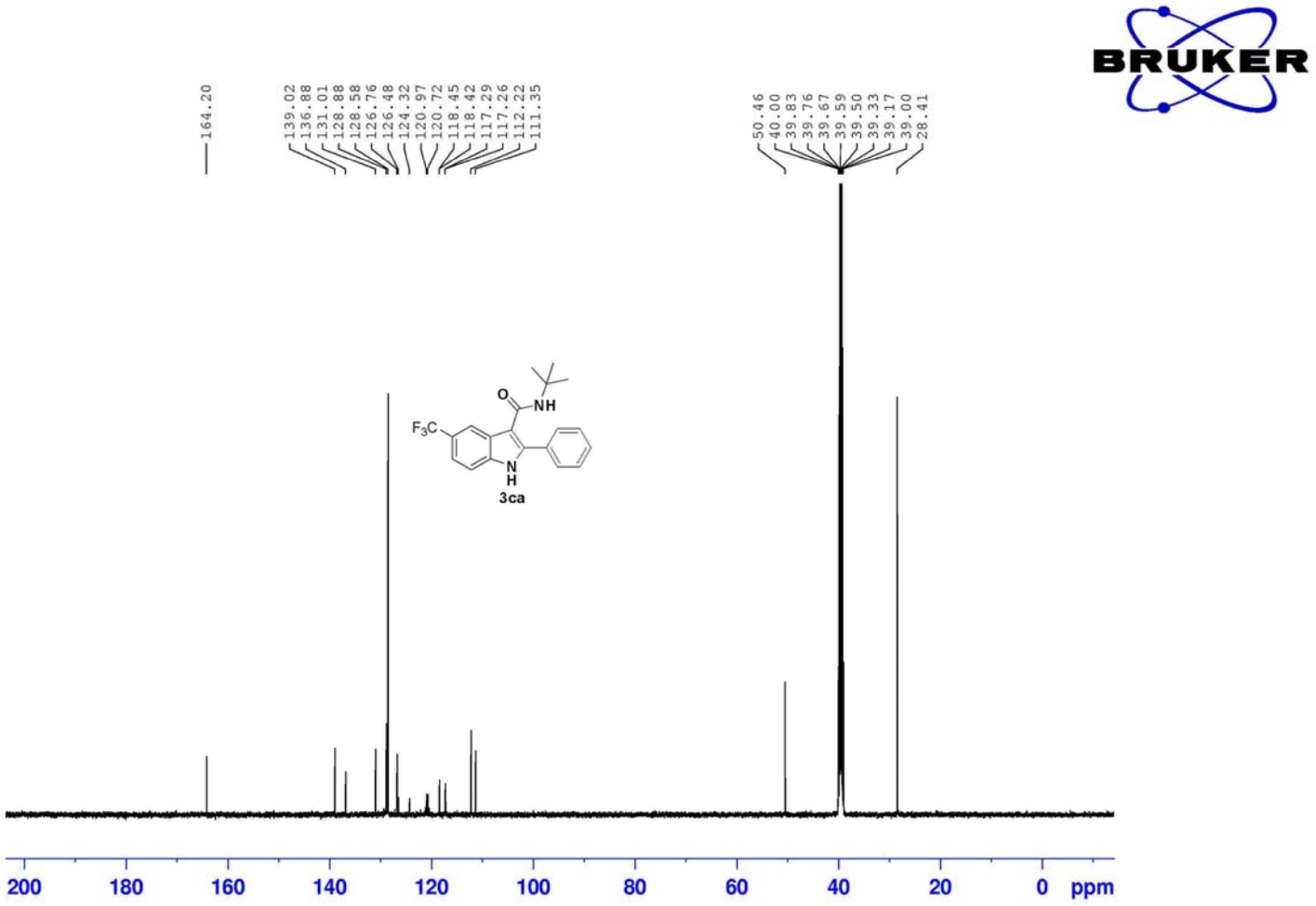
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117.29
117.26
112.22
111.35
50.46
40.00
39.83
39.76
39.67
39.59
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39.33
39.17
39.00
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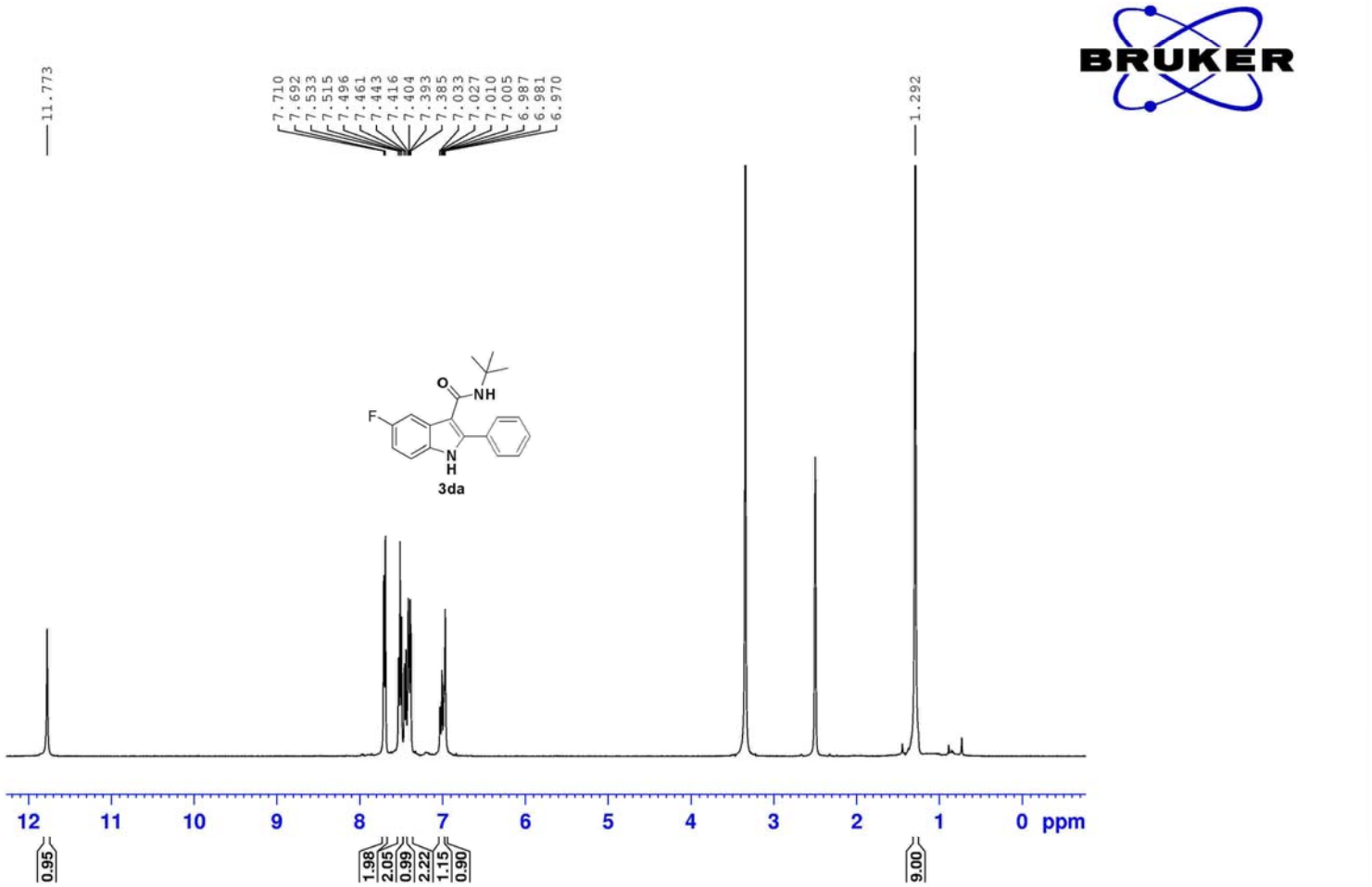
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7.010
7.005
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6.981
6.970
1.292
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F
N
H
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12
11
10
9
8
7
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4
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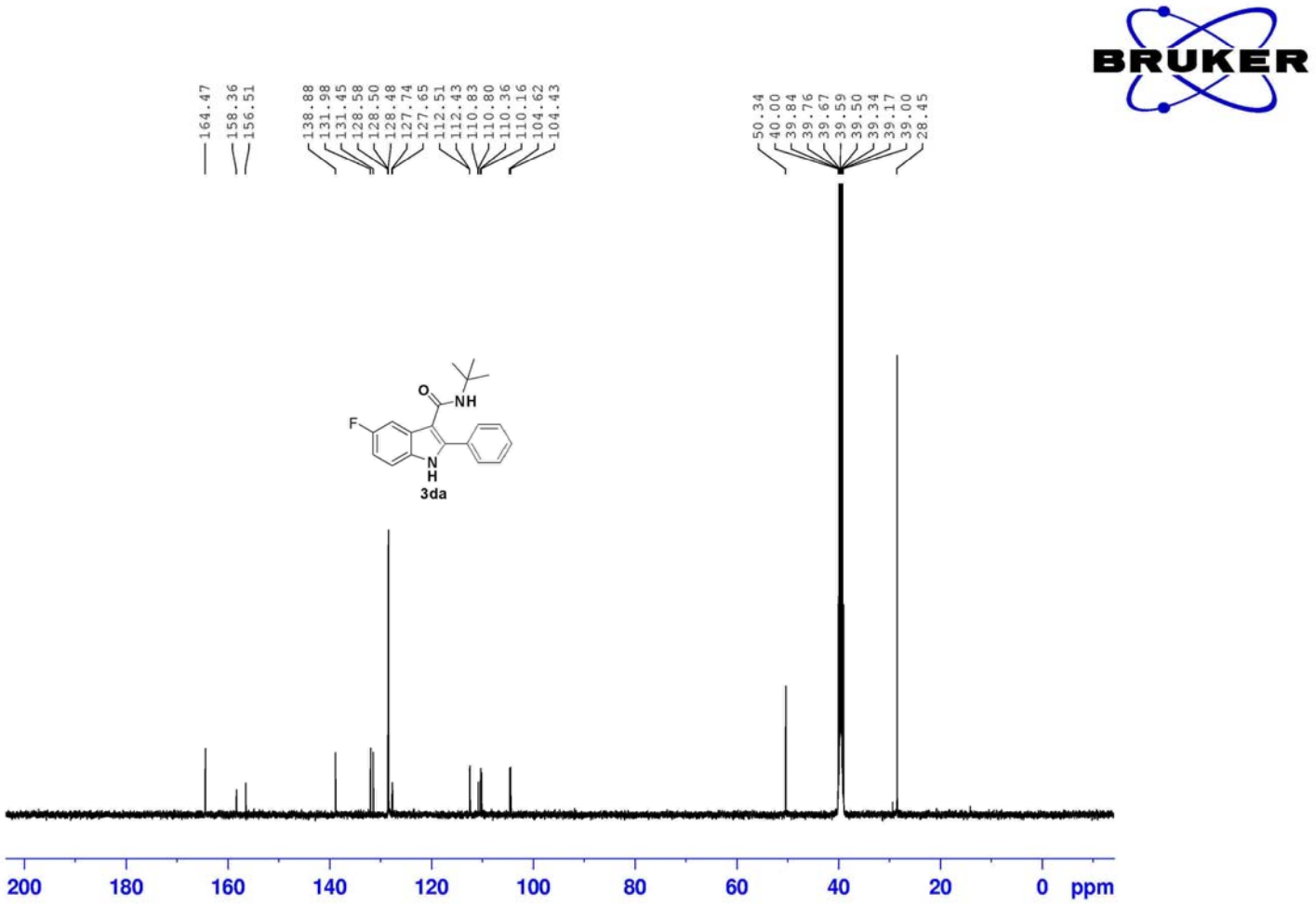
9.00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39.00
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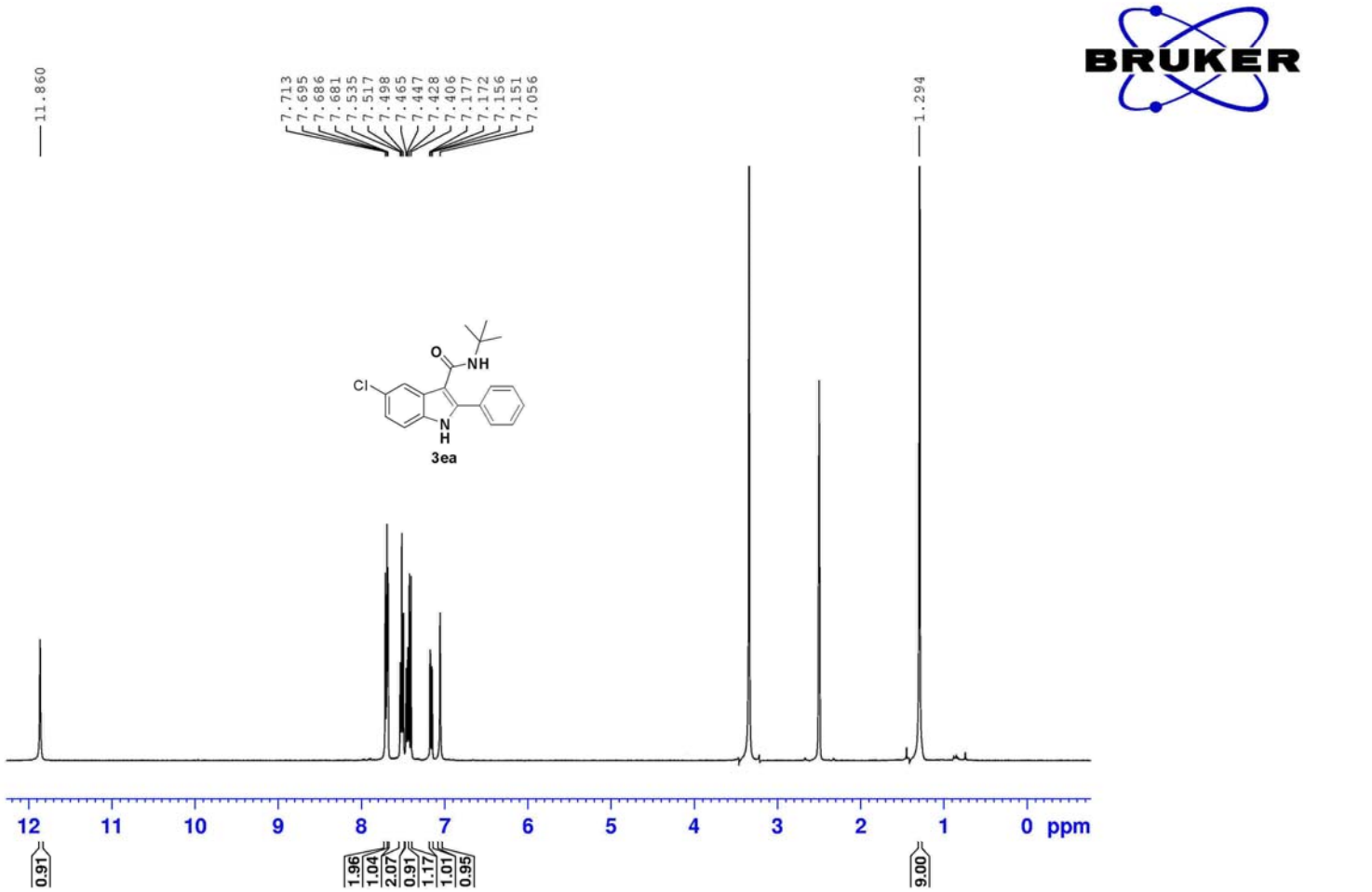
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7.428
7.406
7.177
7.172
7.156
7.151
7.056
1.294
O
NH
Cl
N
H
3ea
12
11
10
9
8
7
6
5
4
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2.07
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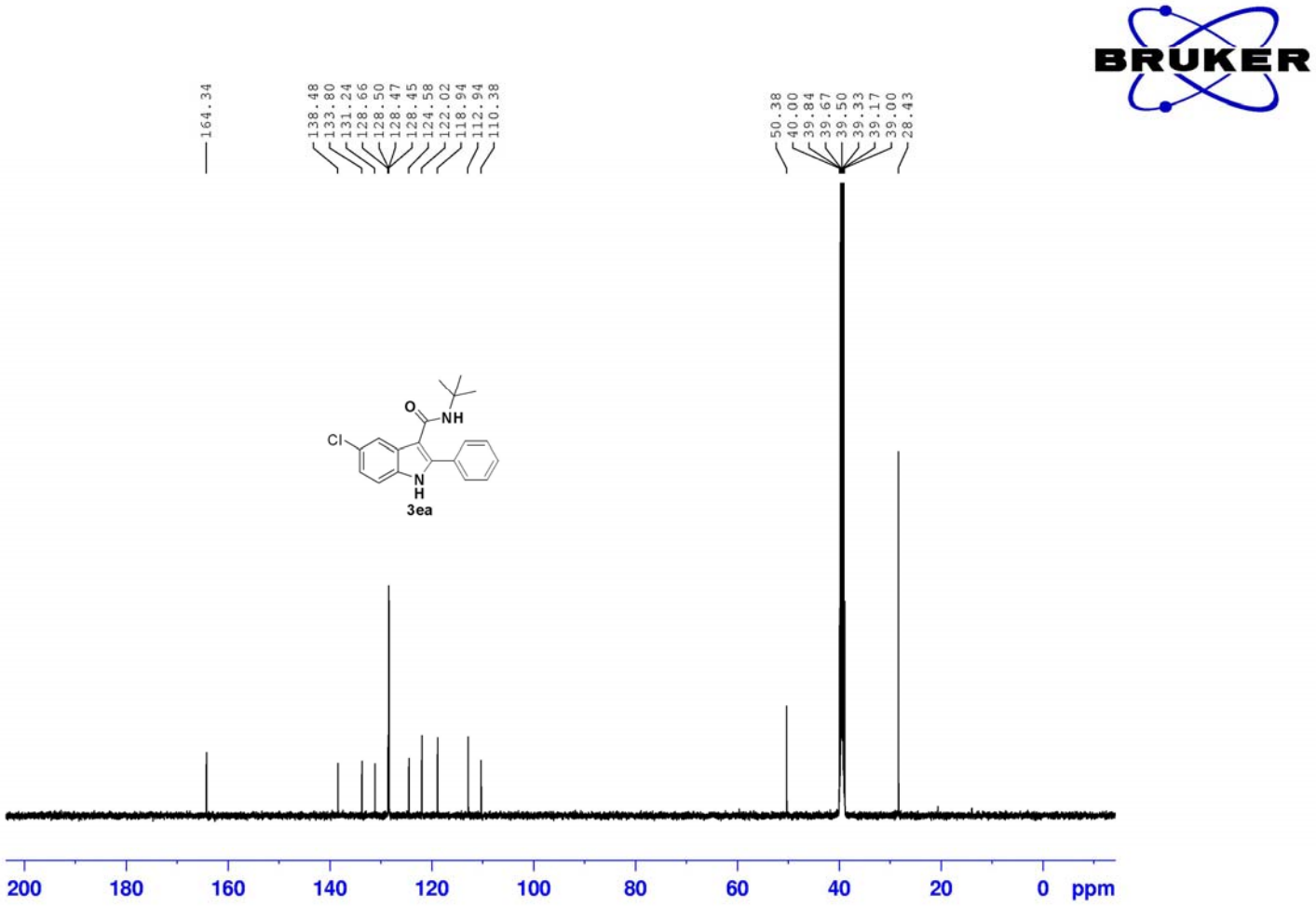
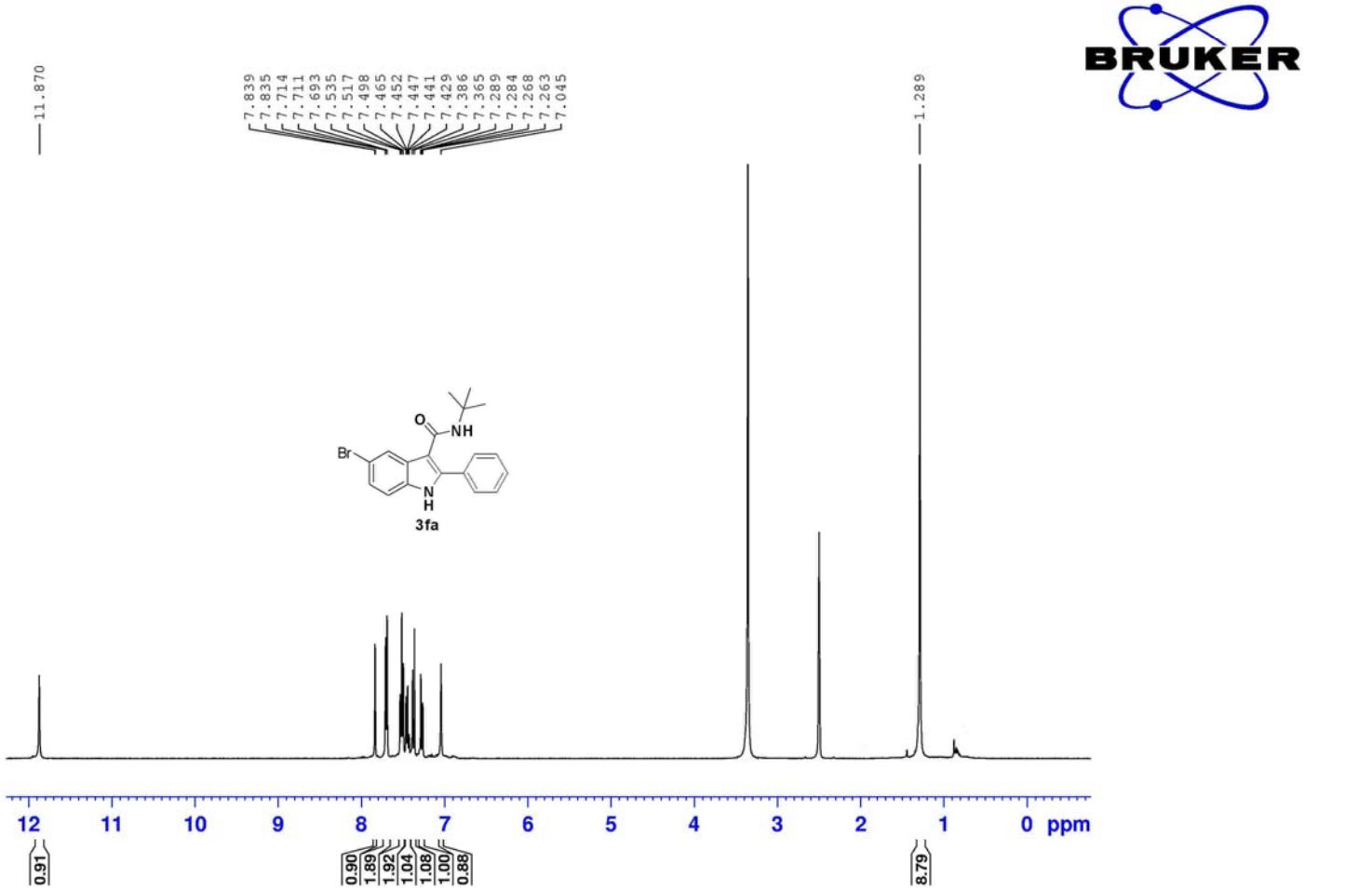
9.00

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7.447
7.441
7.429
7.386
7.365
7.289
7.284
7.268
7.263
7.045
1.289
O
NH
Br
N
H
3fa
12
11
10
9
8
7
6
5
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1.04
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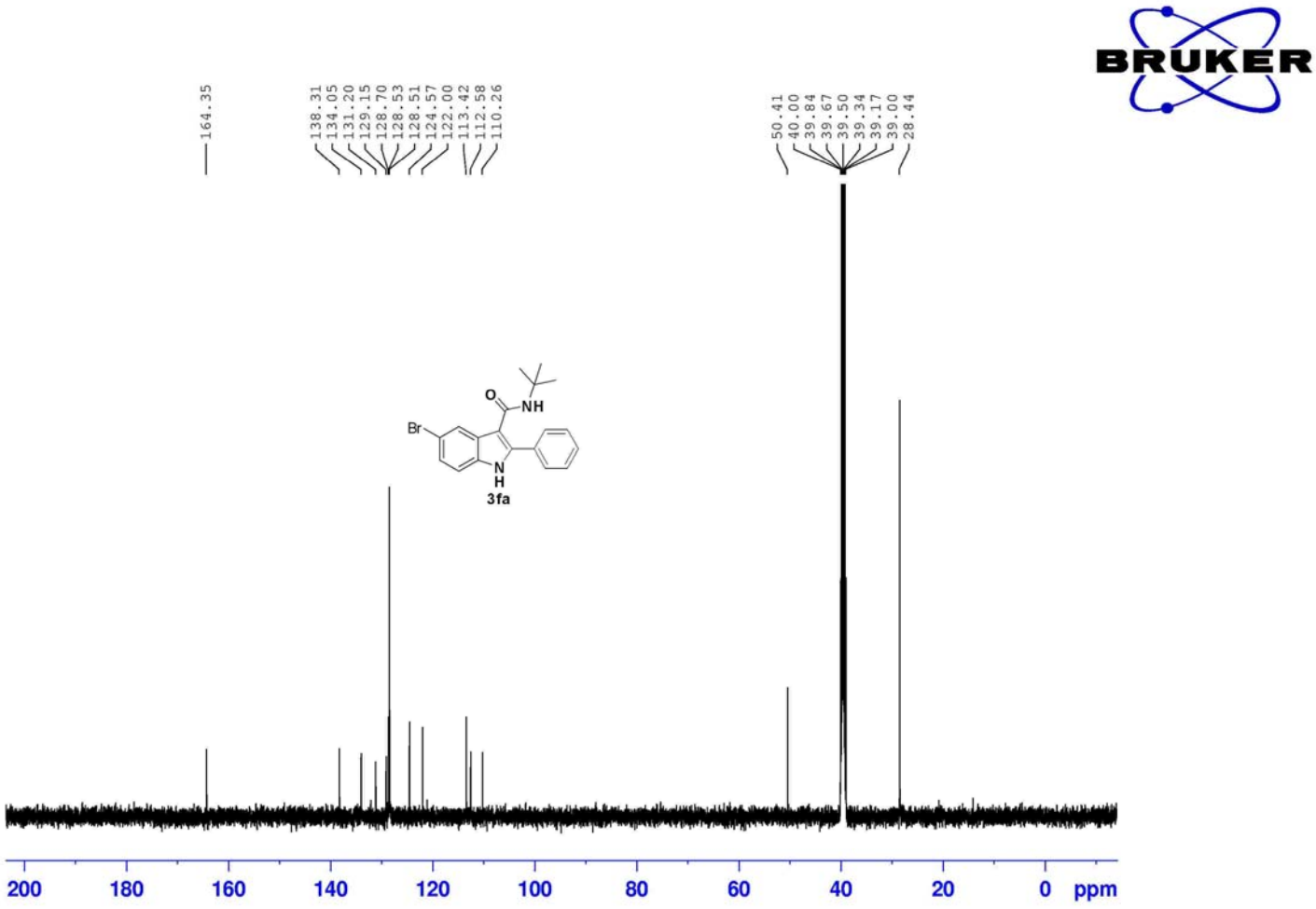
8.79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128.53
128.51
124.57
122.00
113.42
112.58
110.26
50.41
40.00
39.84
39.67
39.50
39.34
39.17
39.00
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Br
N
H
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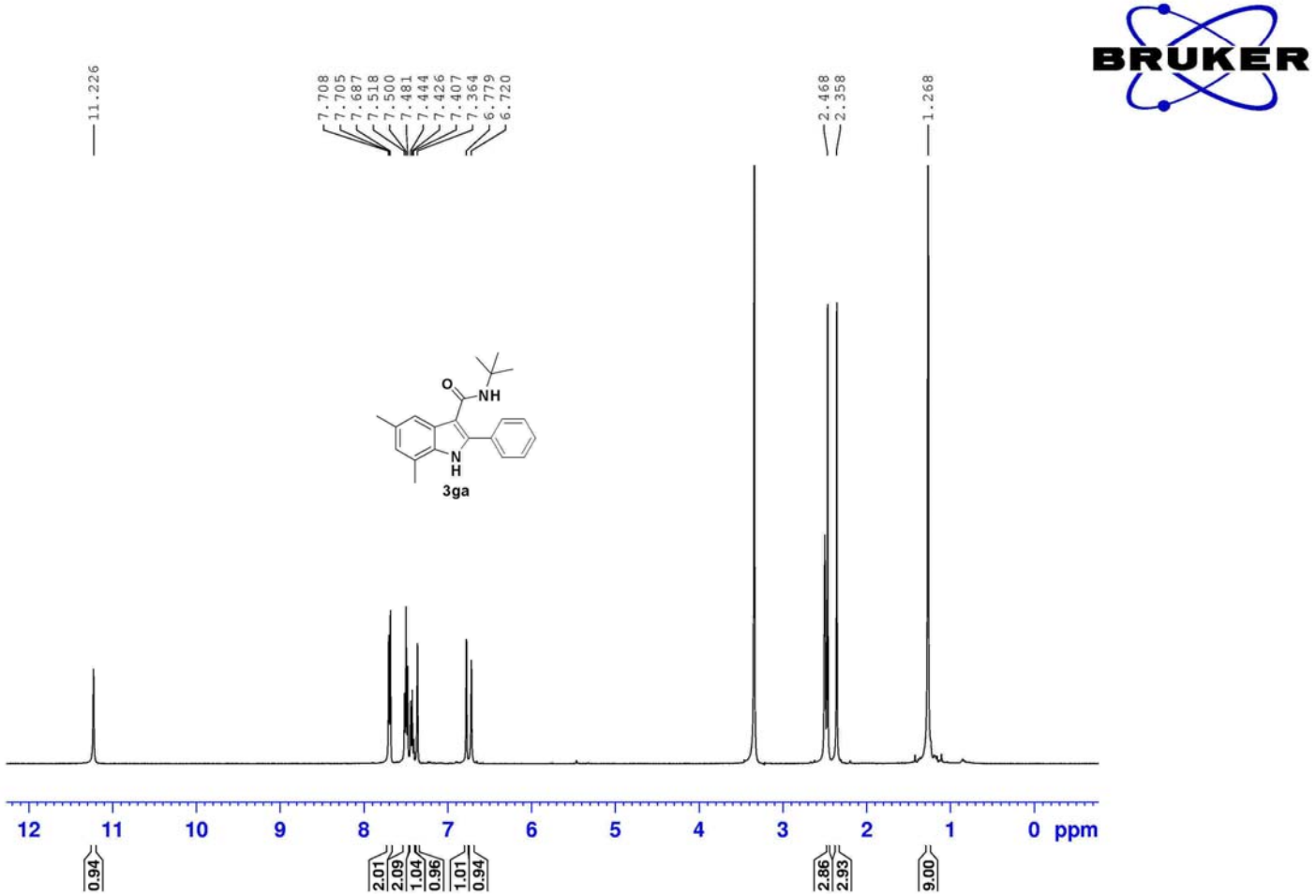
60
40
20
0
ppm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7.481
7.444
7.426
7.407
7.364
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6.720
2.468
2.358
1.268
O
NH
N
H
3ga
12
11
10
9
8
7
6
5
4
3
2
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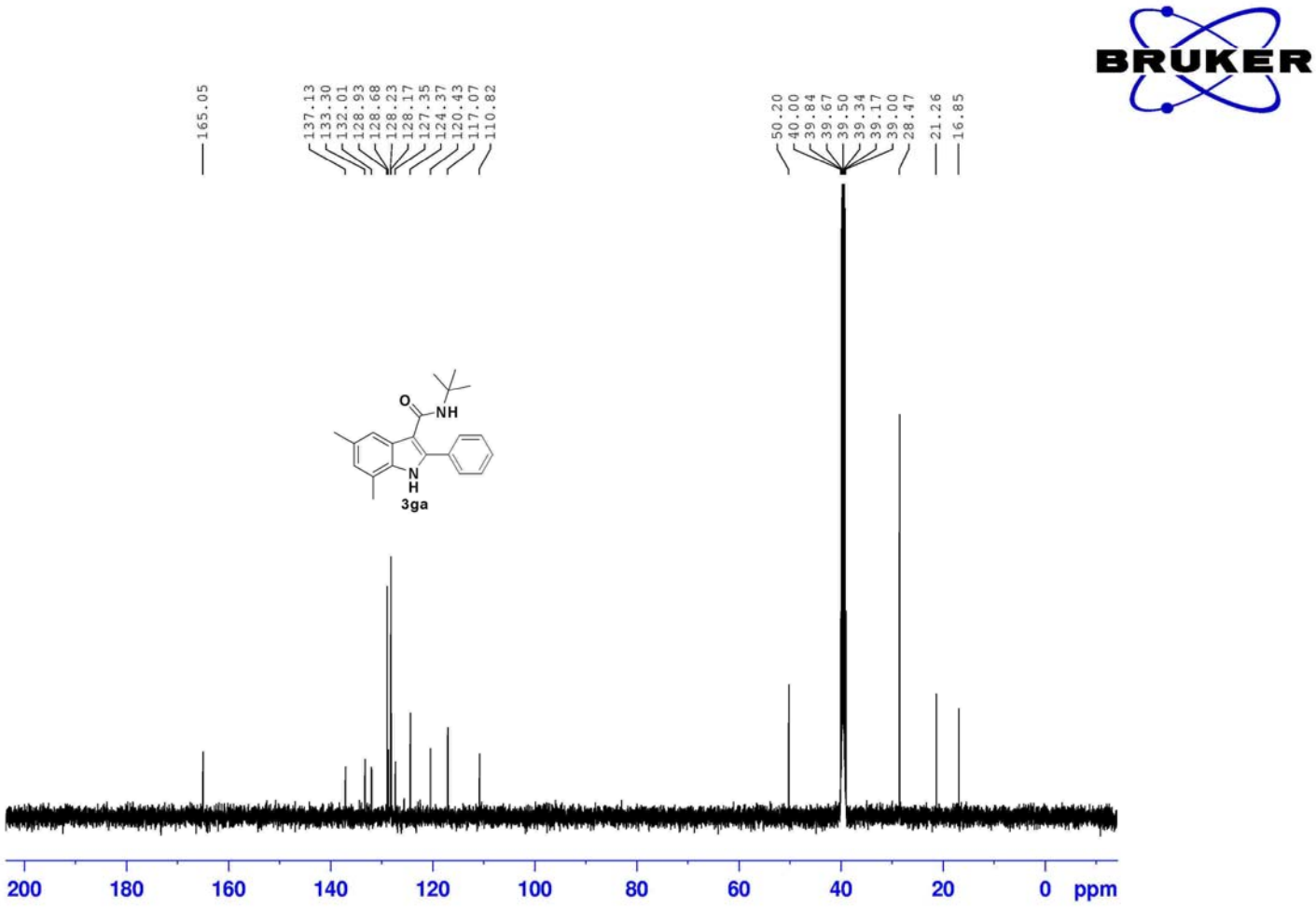
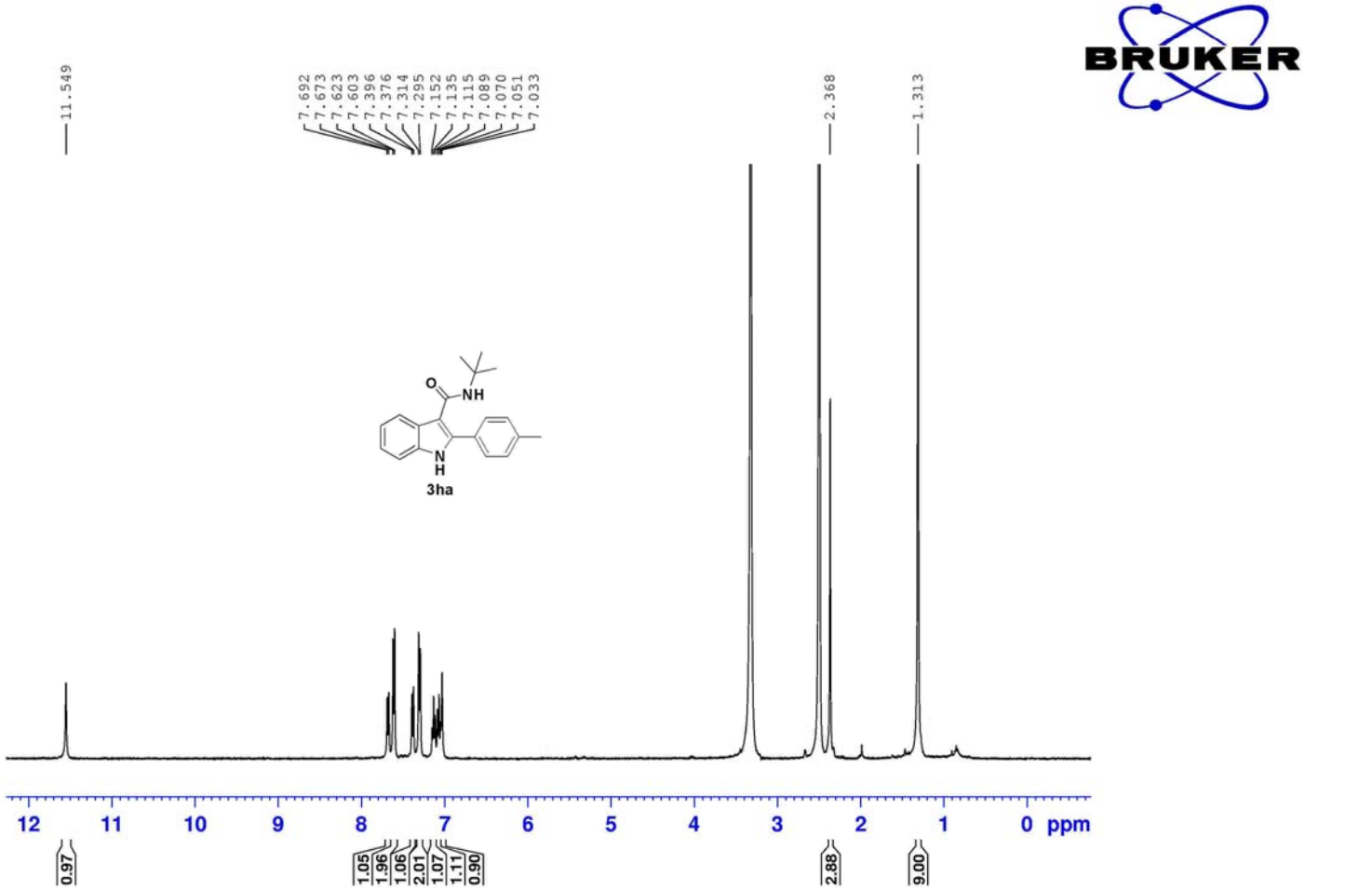
2.01
2.09
1.04
0.96
1.01
0.94
2.86
2.93
9.00

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7.673
7.623
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7.396
7.376
7.314
7.295
7.152
7.135
7.115
7.089
7.070
7.051
7.033
2.368
1.313
O
NH
N
H
3ha
12
11
10
9
8
7
6
5
4
3
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1.05
1.96
1.06
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1.07
1.11
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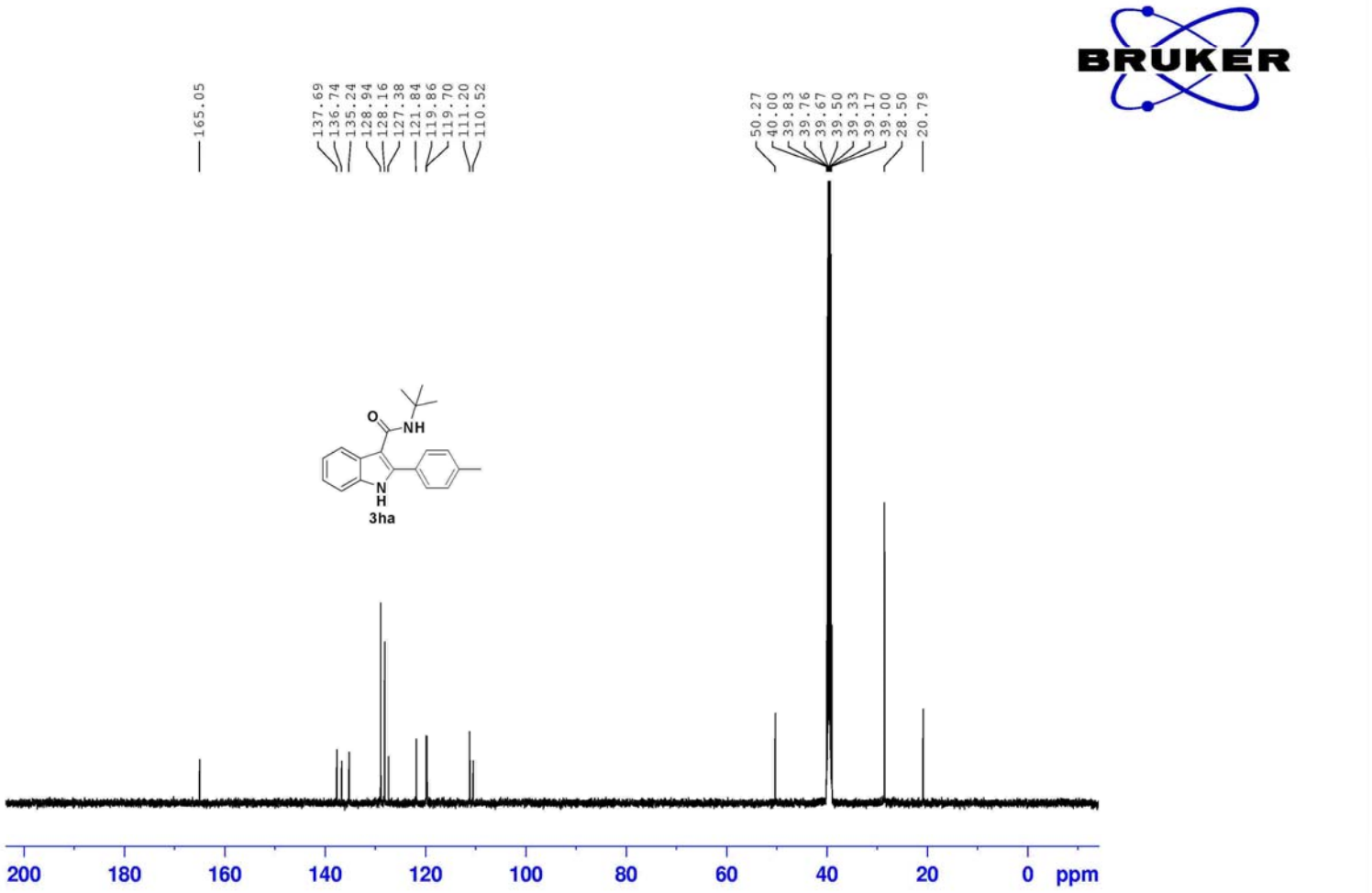
2.88
9.00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128.16
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121.84
119.86
119.70
111.20
110.52
50.27
40.00
39.83
39.76
39.67
39.50
39.33
39.17
39.00
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NH
N
H
3ha
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140
120
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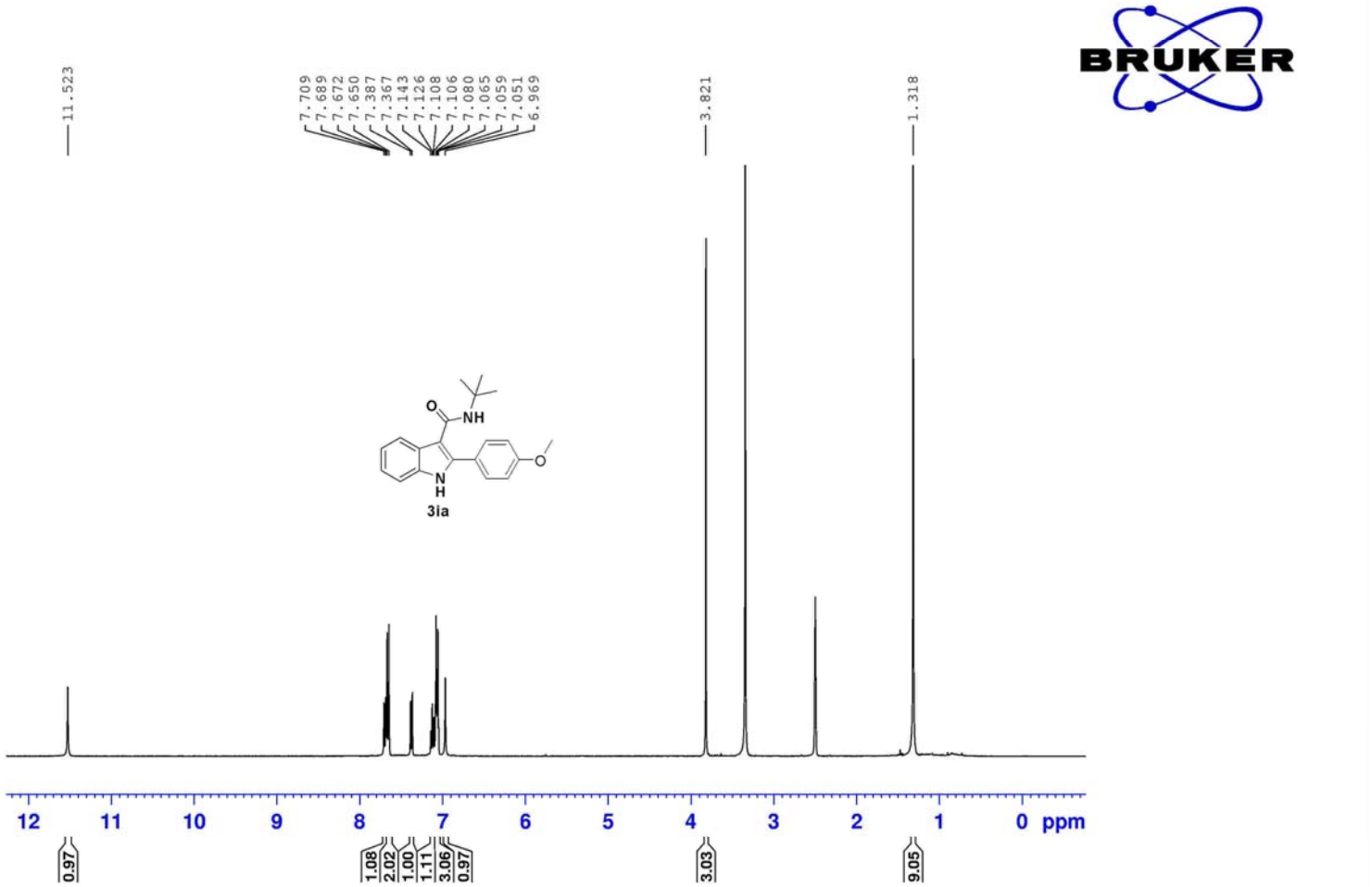
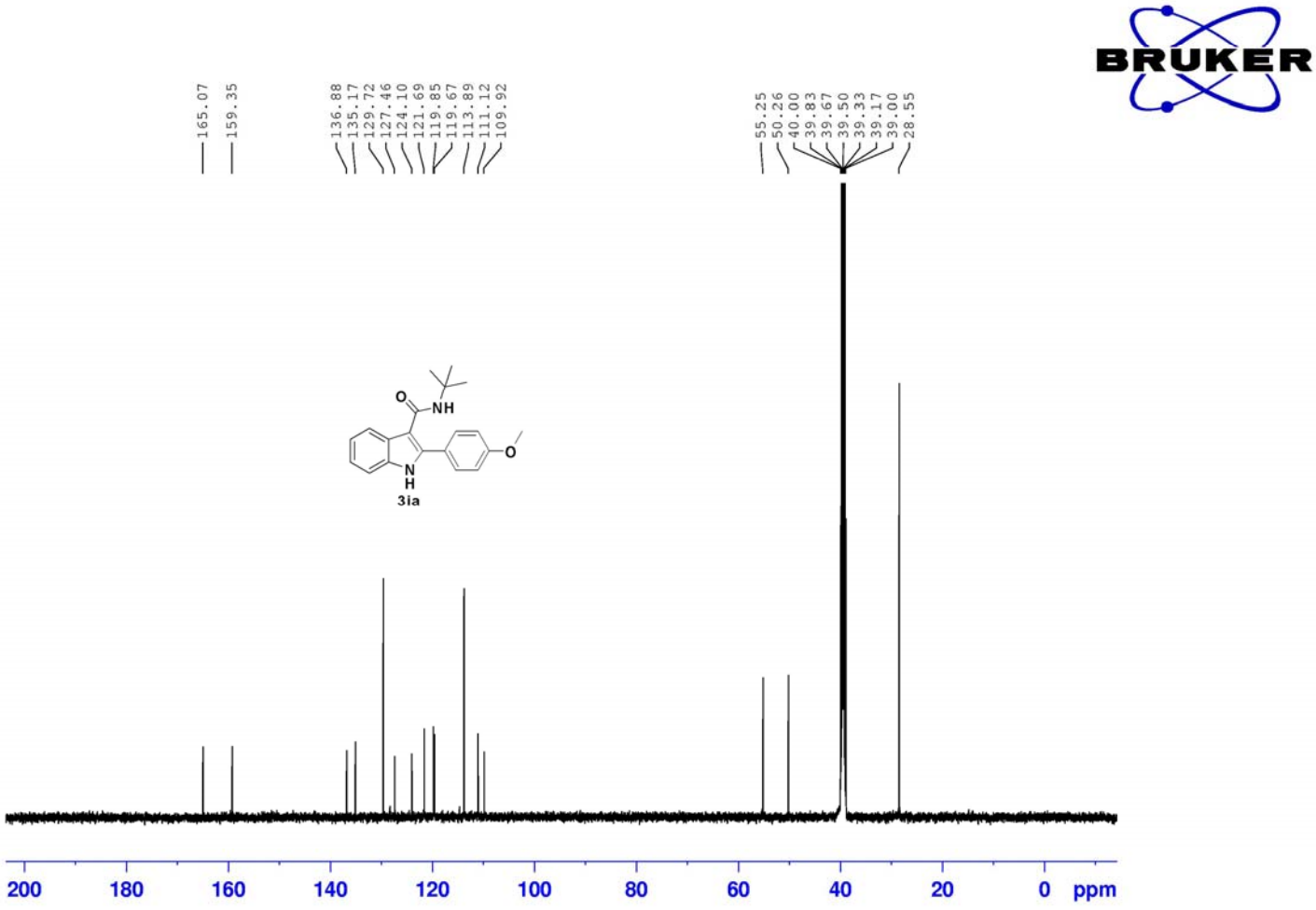
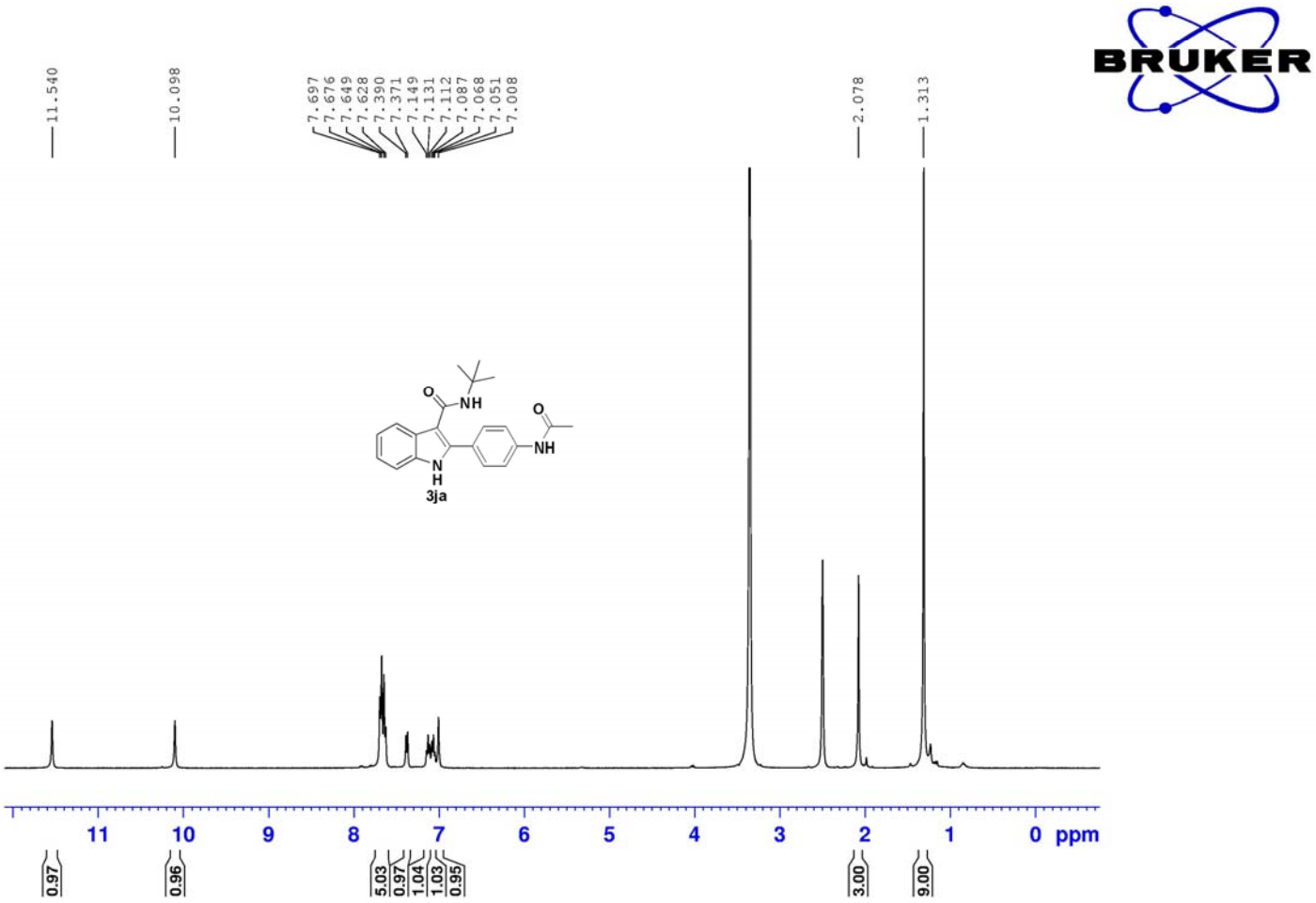
40
20
0
ppm



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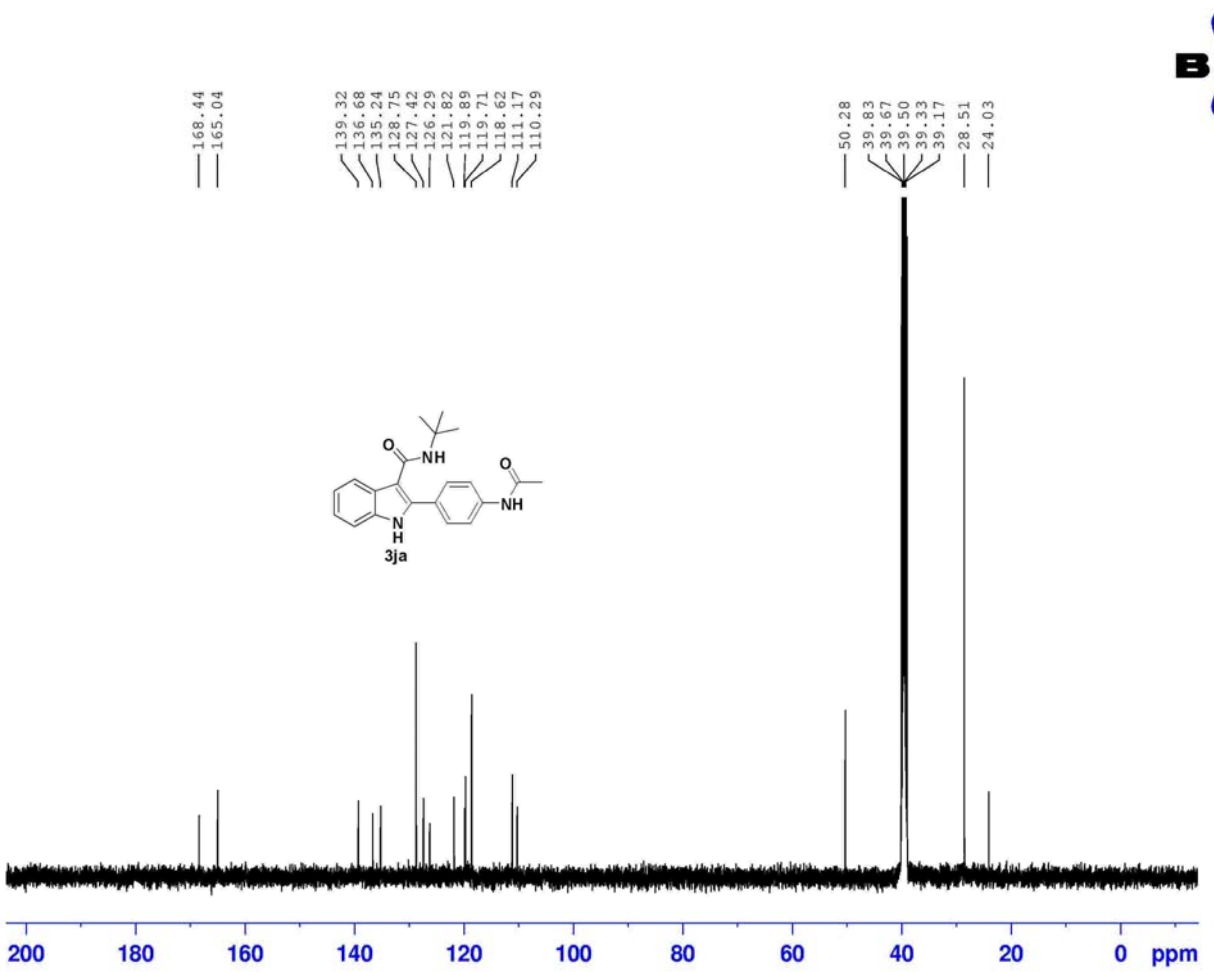
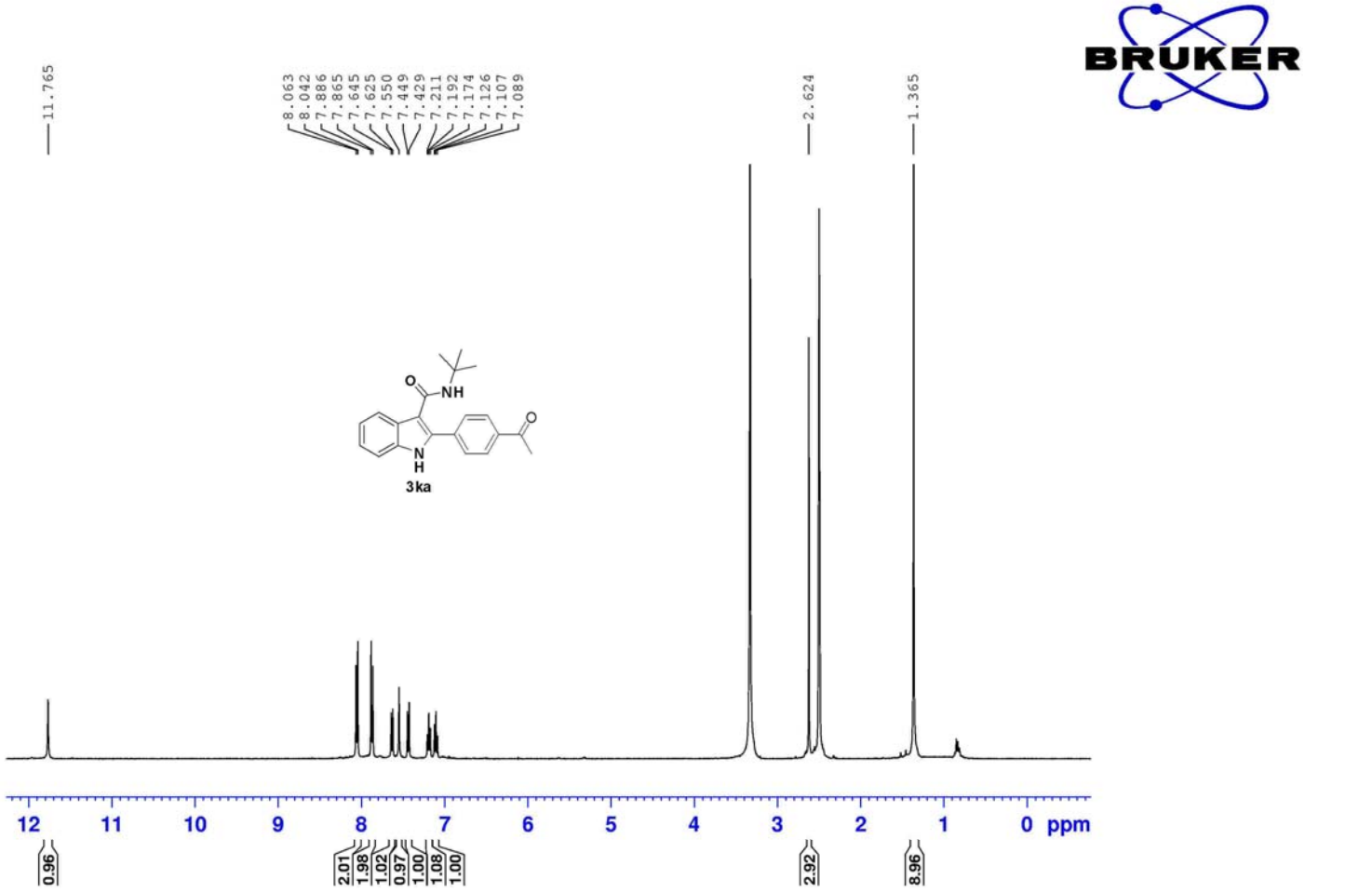
7.676
7.649
7.628
7.390
7.371
7.149
7.131
7.112
7.087
7.068
7.051
7.008
2.078
1.313
O
NH
O
NH
N
H
3ja
11
10
9
8
7
6
5
4
3
2
1
0 ppm
0.97
0.96
5.03
0.97
1.04
1.03
0.95
3.00
9.00

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8.042
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7.645
7.625
7.550
7.449
7.429
7.211
7.192
7.174
7.126
7.107
7.089
2.624
1.365
NH
N
H
3ka
12
11
10
9
8
7
6
5
4
3
2
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0 ppm
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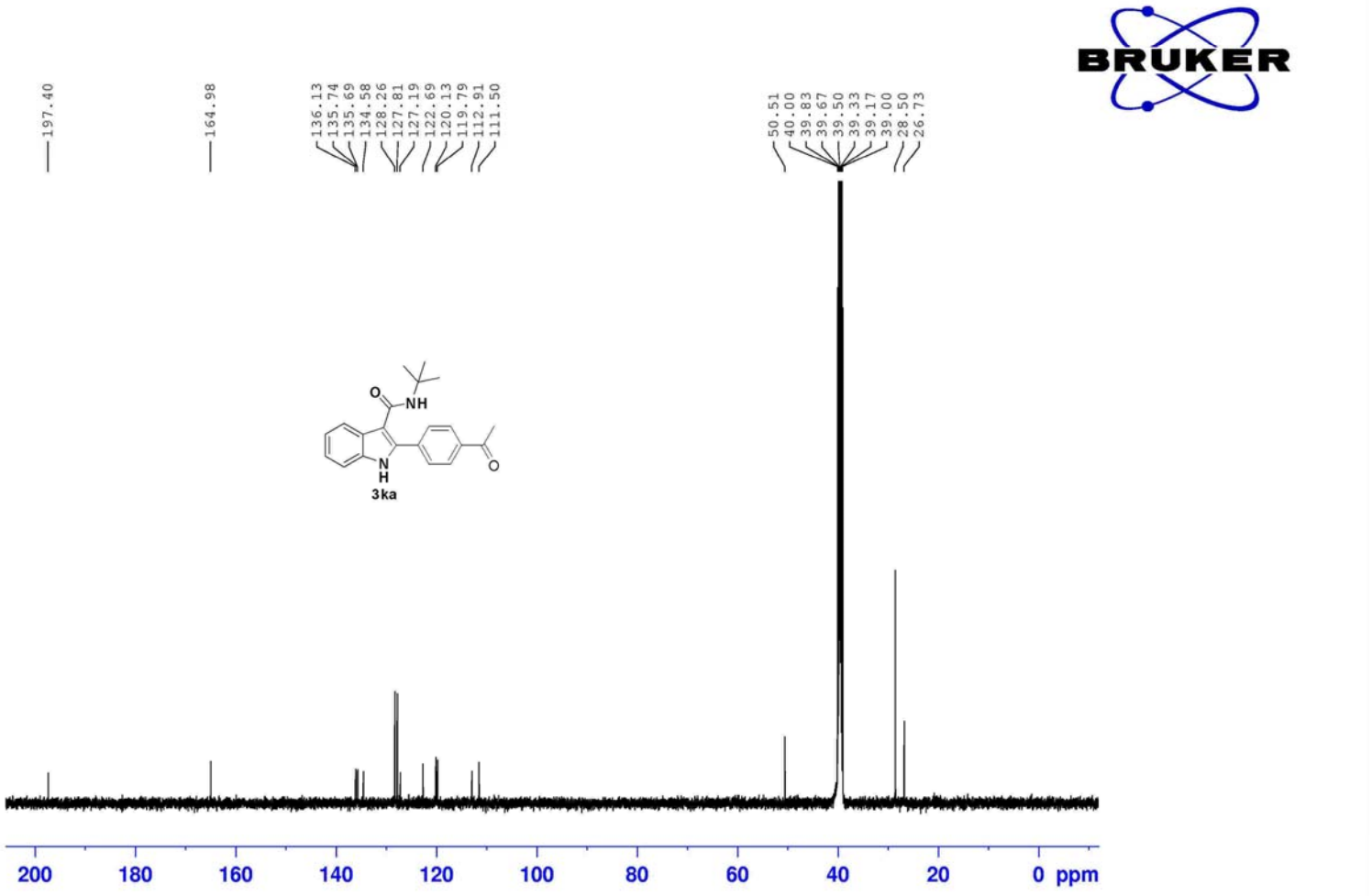
2.01
1.98
1.02
0.97
1.00
1.08
1.00
2.92
8.96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134.58
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127.81
127.19
122.69
120.13
119.79
112.91
111.50
50.51
40.00
39.83
39.67
39.50
39.33
39.17
39.00
28.50
26.73
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NH
N
H
O
3ka
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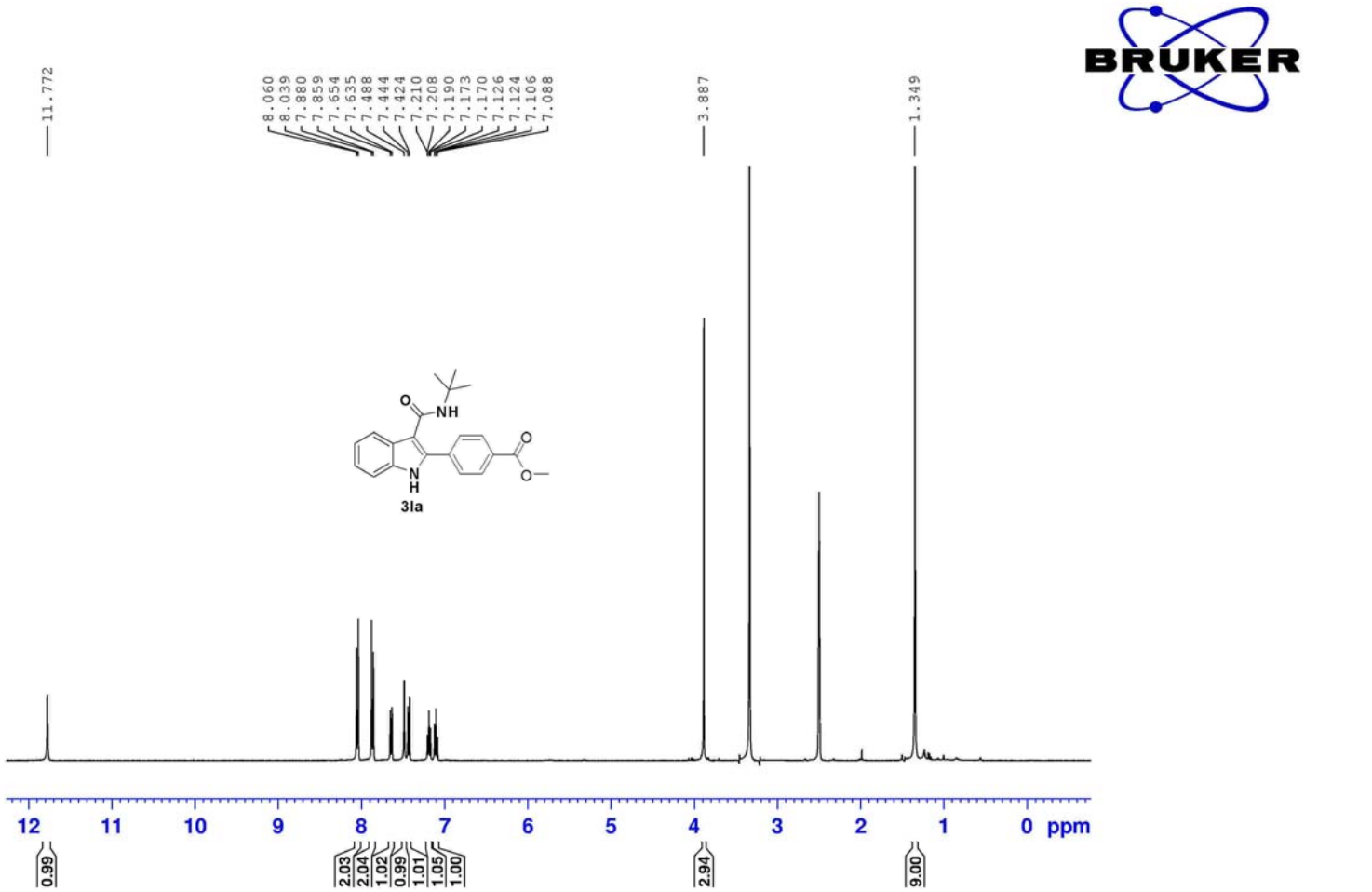
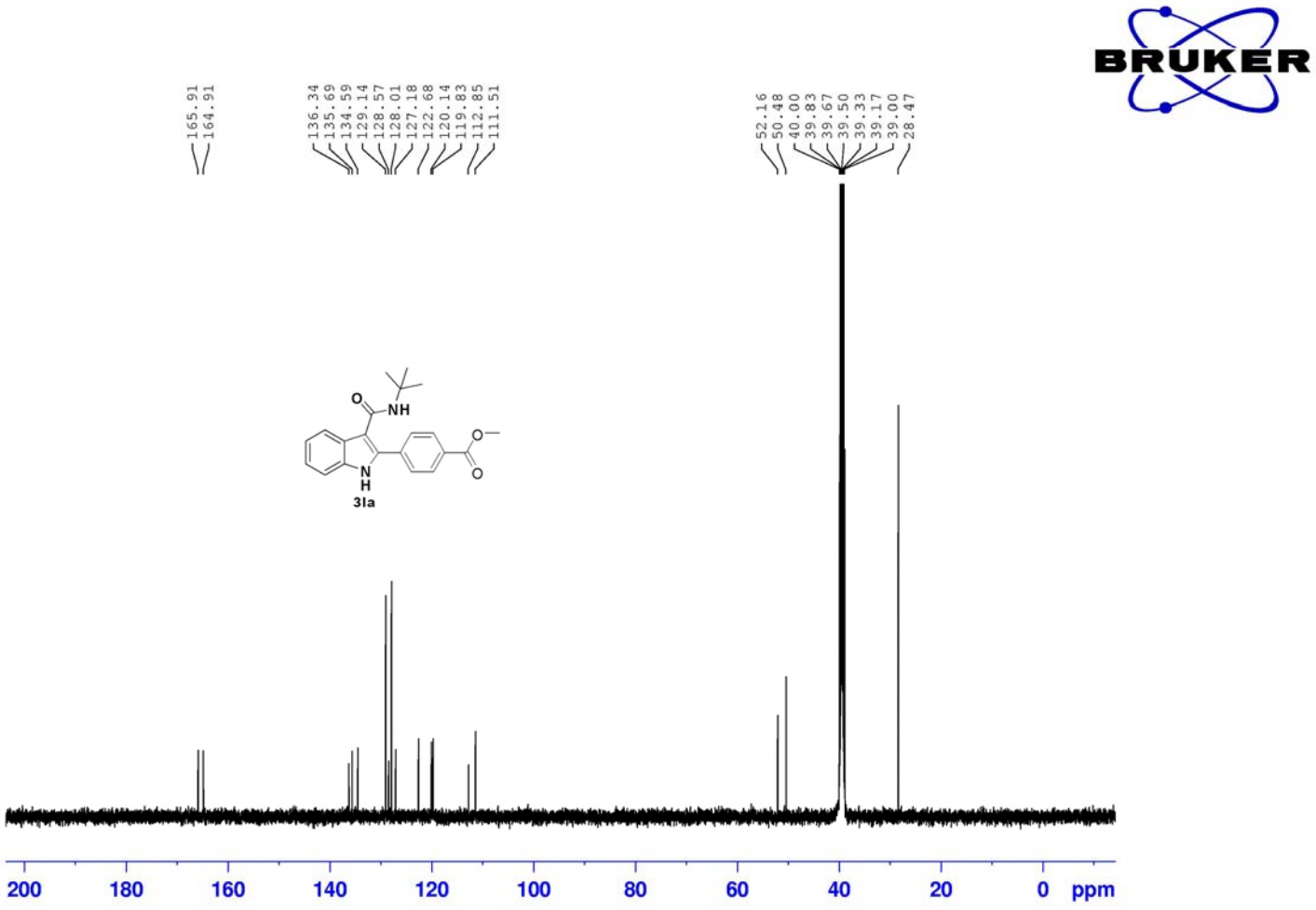
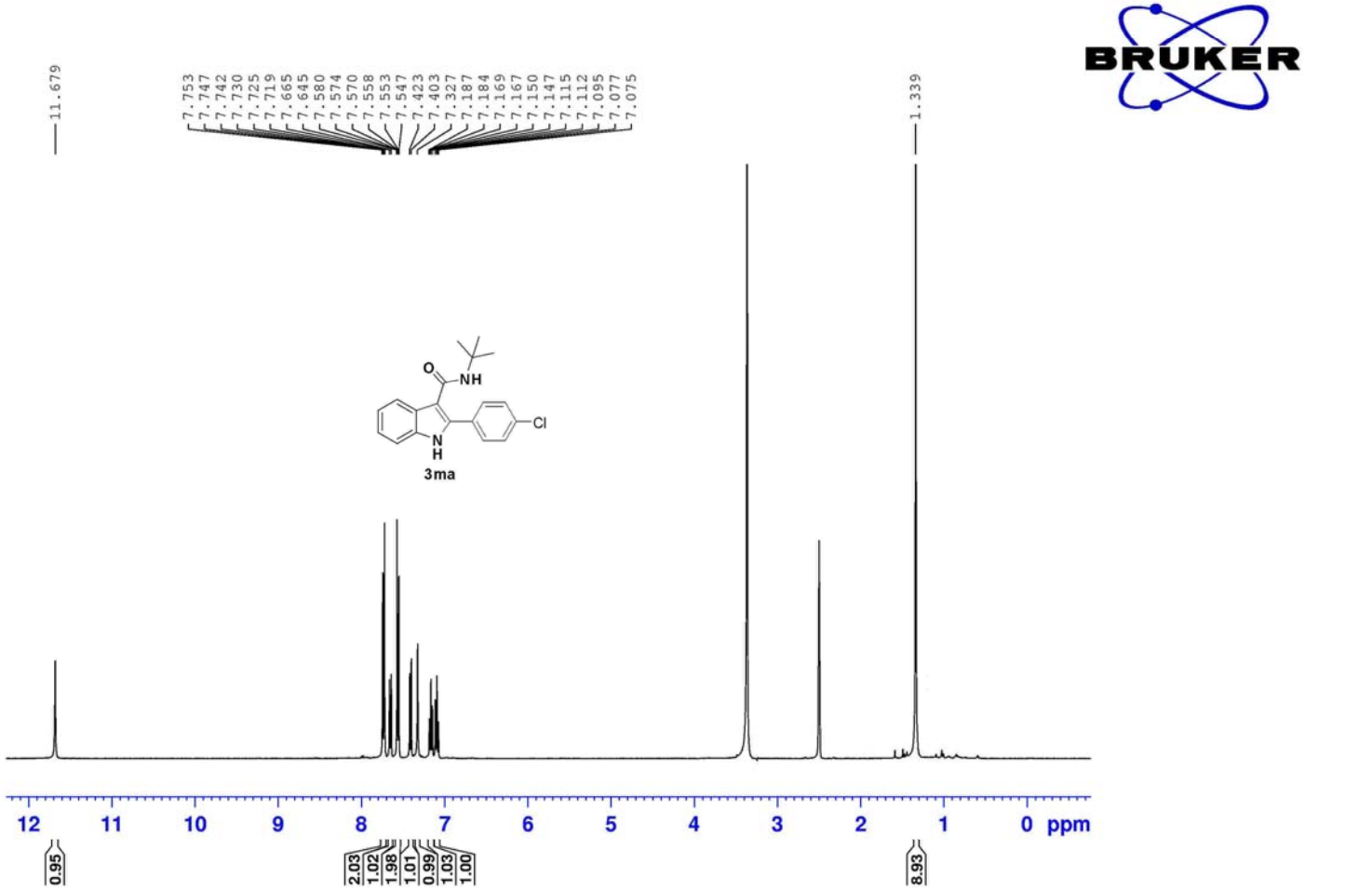
140
120
100
80
60
40
20
0 ppm



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7.665
7.645
7.580
7.574
7.570
7.558
7.553
7.547
7.423
7.403
7.327
7.187
7.184
7.169
7.167
7.150
7.147
7.115
7.112
7.095
7.077
7.075
1.339
O
NH
N
H
Cl
3ma
12
11
10
9
8
7
6
5
4
3
2
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0 ppm
0.95
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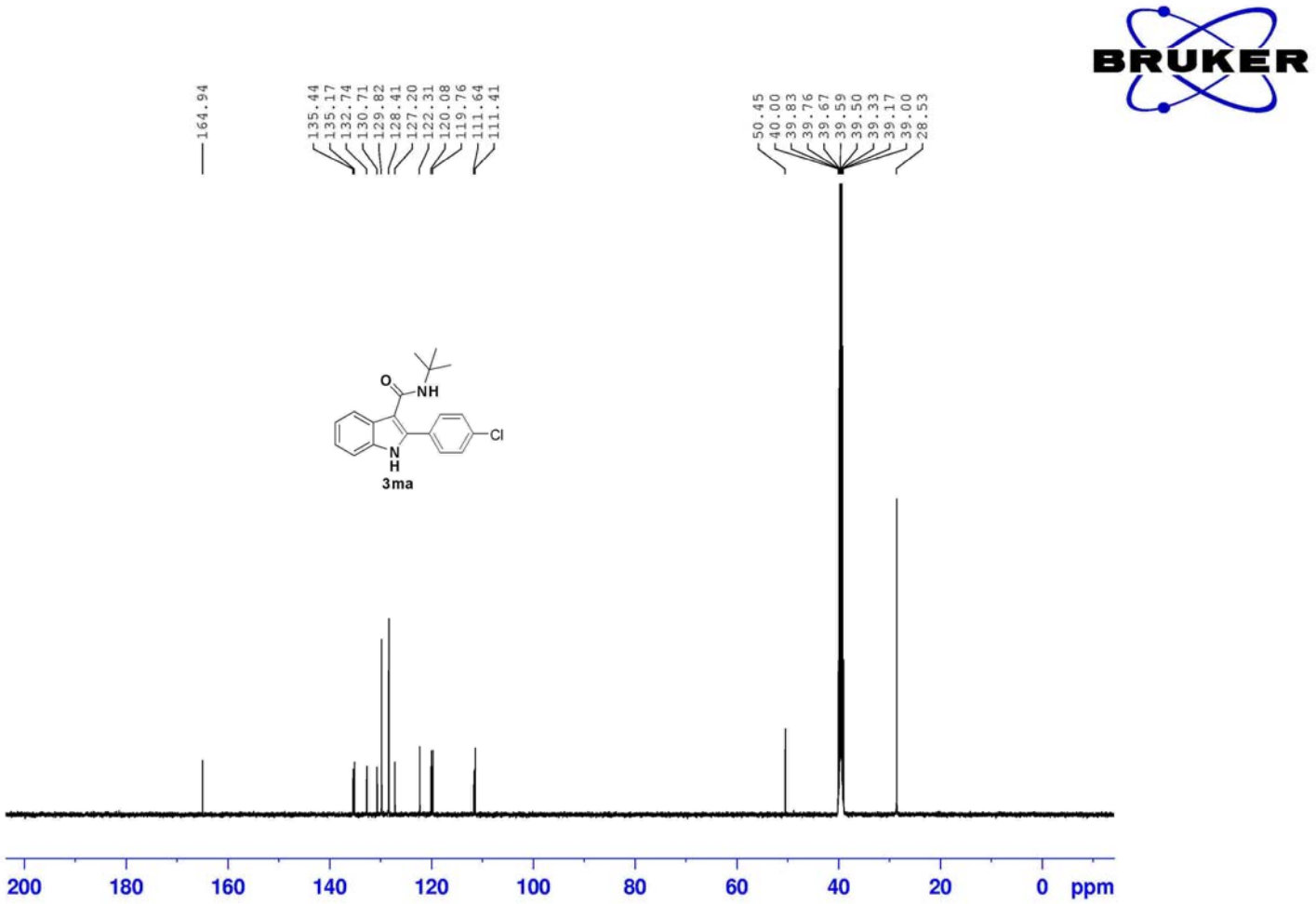
1.02
1.98
1.01
0.99
1.03
1.00
8.93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132.74
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129.82
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127.20
122.31
120.08
119.76
111.64
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50.45
40.00
39.83
39.76
39.67
39.59
39.50
39.33
39.17
39.00
28.53
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NH
N
H
Cl
3ma
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120
100
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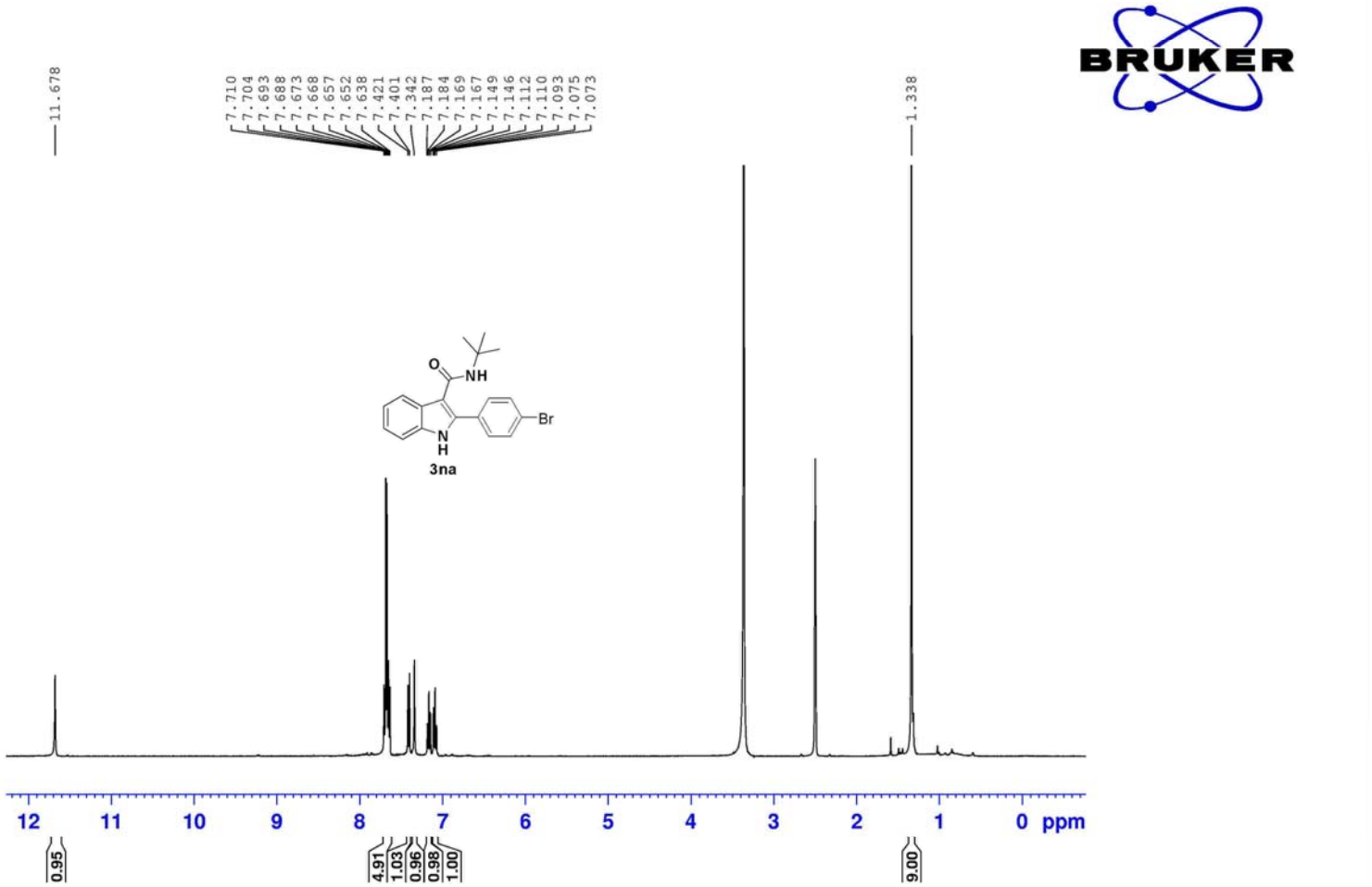
40
20
0
ppm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7.401
7.342
7.187
7.184
7.169
7.167
7.149
7.146
7.112
7.110
7.093
7.075
7.073
1.338
O
NH
Br
N
H
3na
12
11
10
9
8
7
6
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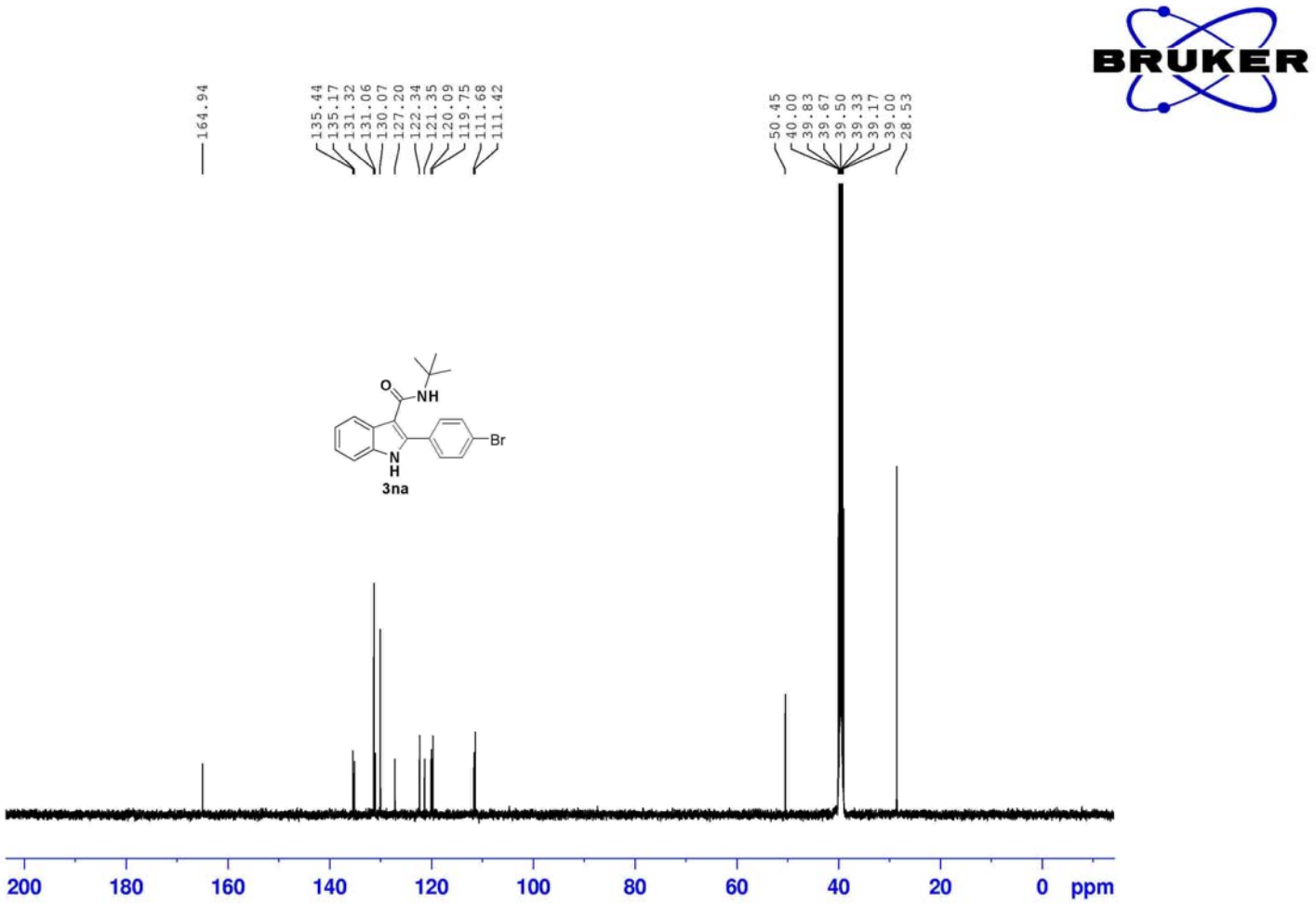
3
2
1
0 ppm
0.95
4.91
1.03
0.96
0.98
1.00
9.00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130.07
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122.34
121.35
120.09
119.75
111.68
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50.45
40.00
39.83
39.67
39.50
39.33
39.17
39.00
28.53
O
NH
Br
N
H
3na
200
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160
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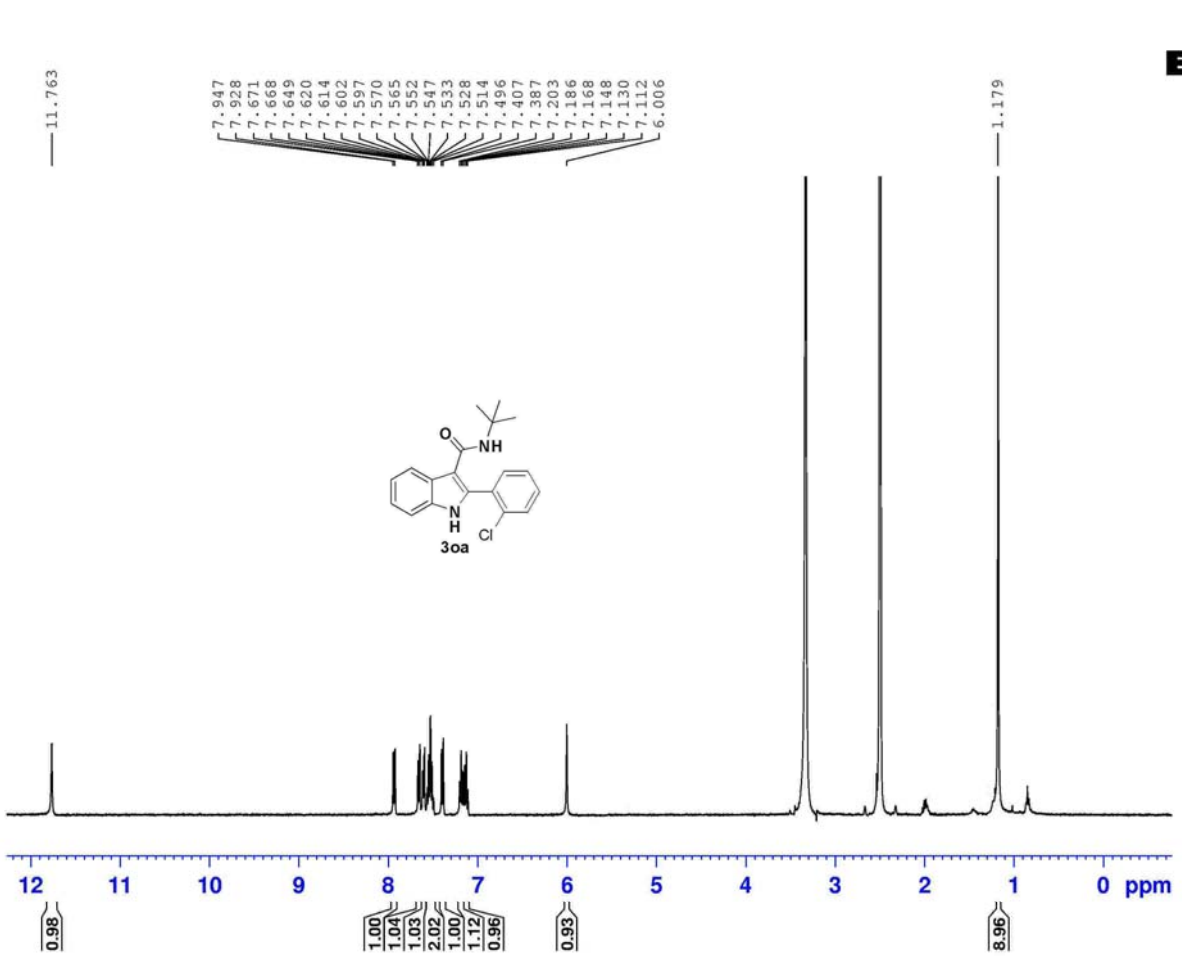
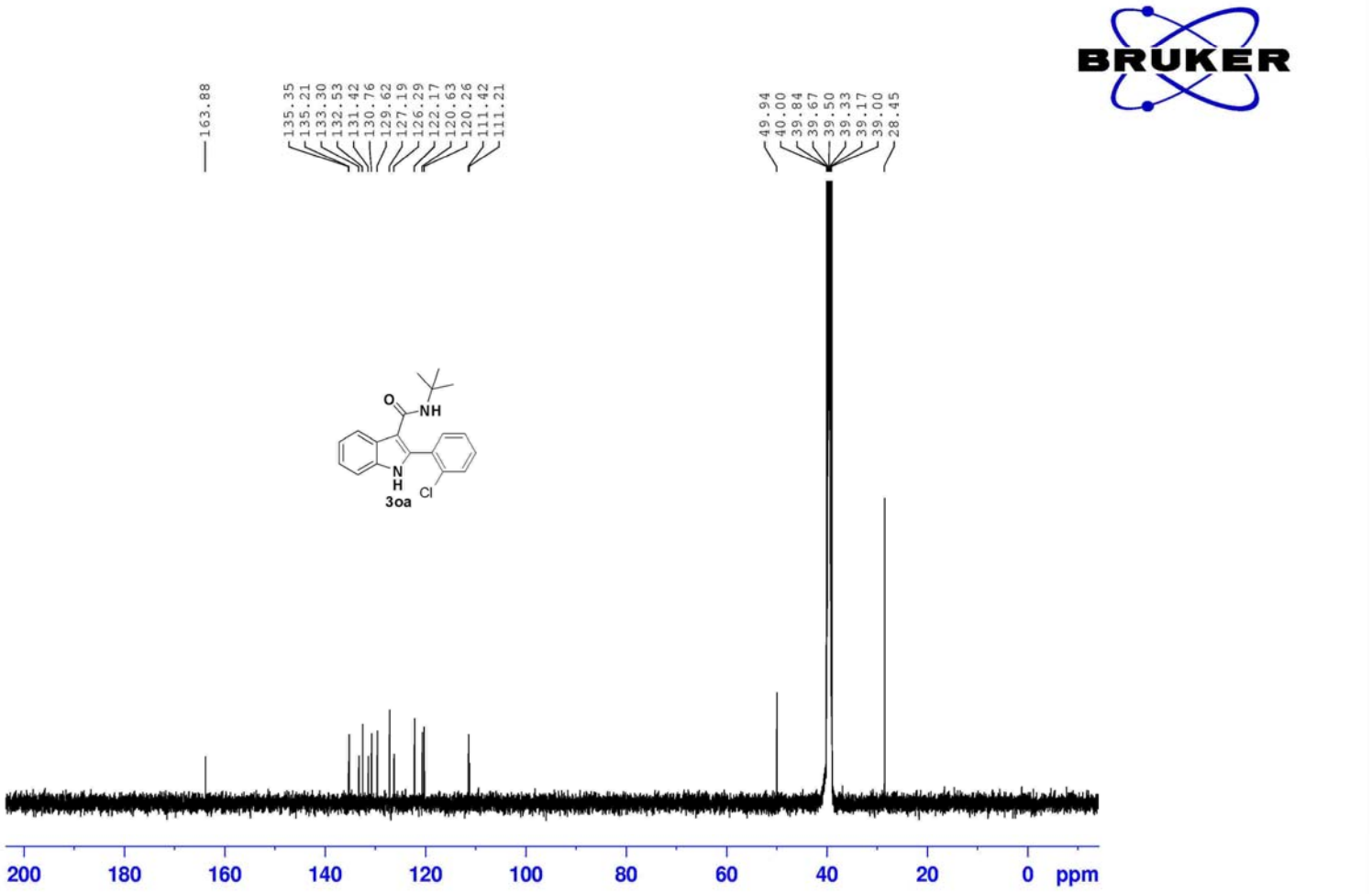
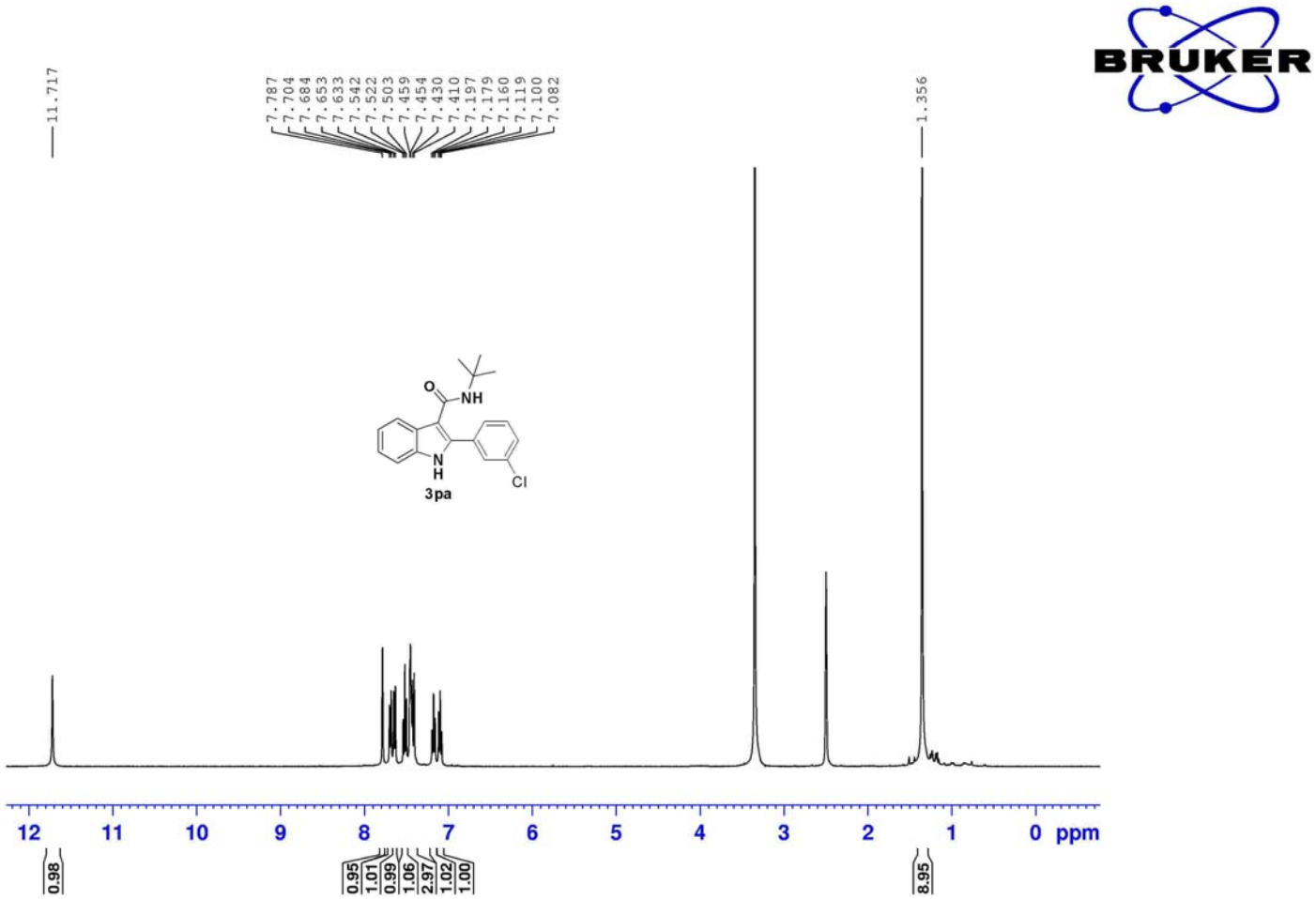
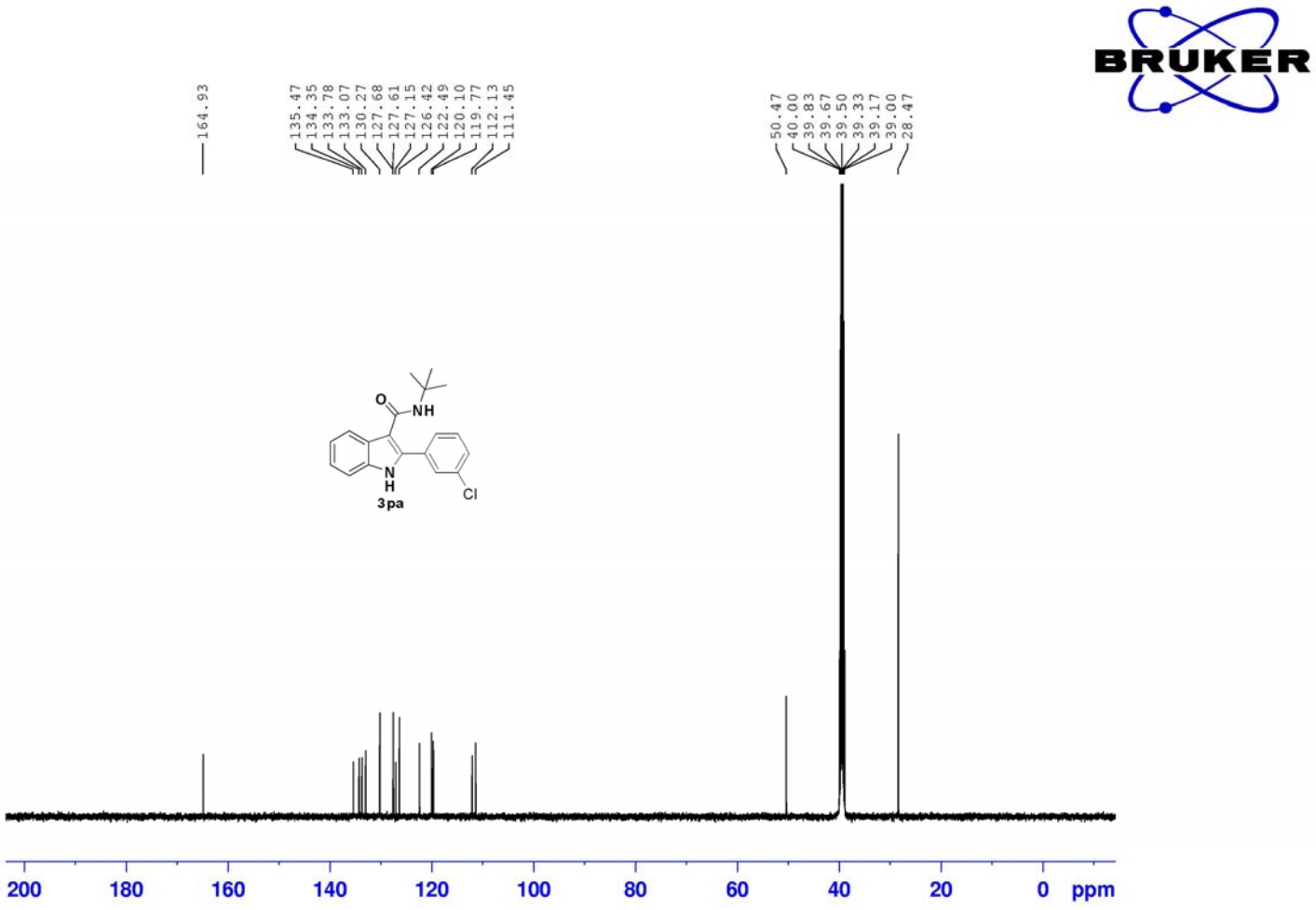
120
100
80
60
40
20
0
ppm





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127.61
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119.77
112.13
111.45
50.47
40.00
39.83
39.67
39.50
39.33
39.17
39.00
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N
H
Cl
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40
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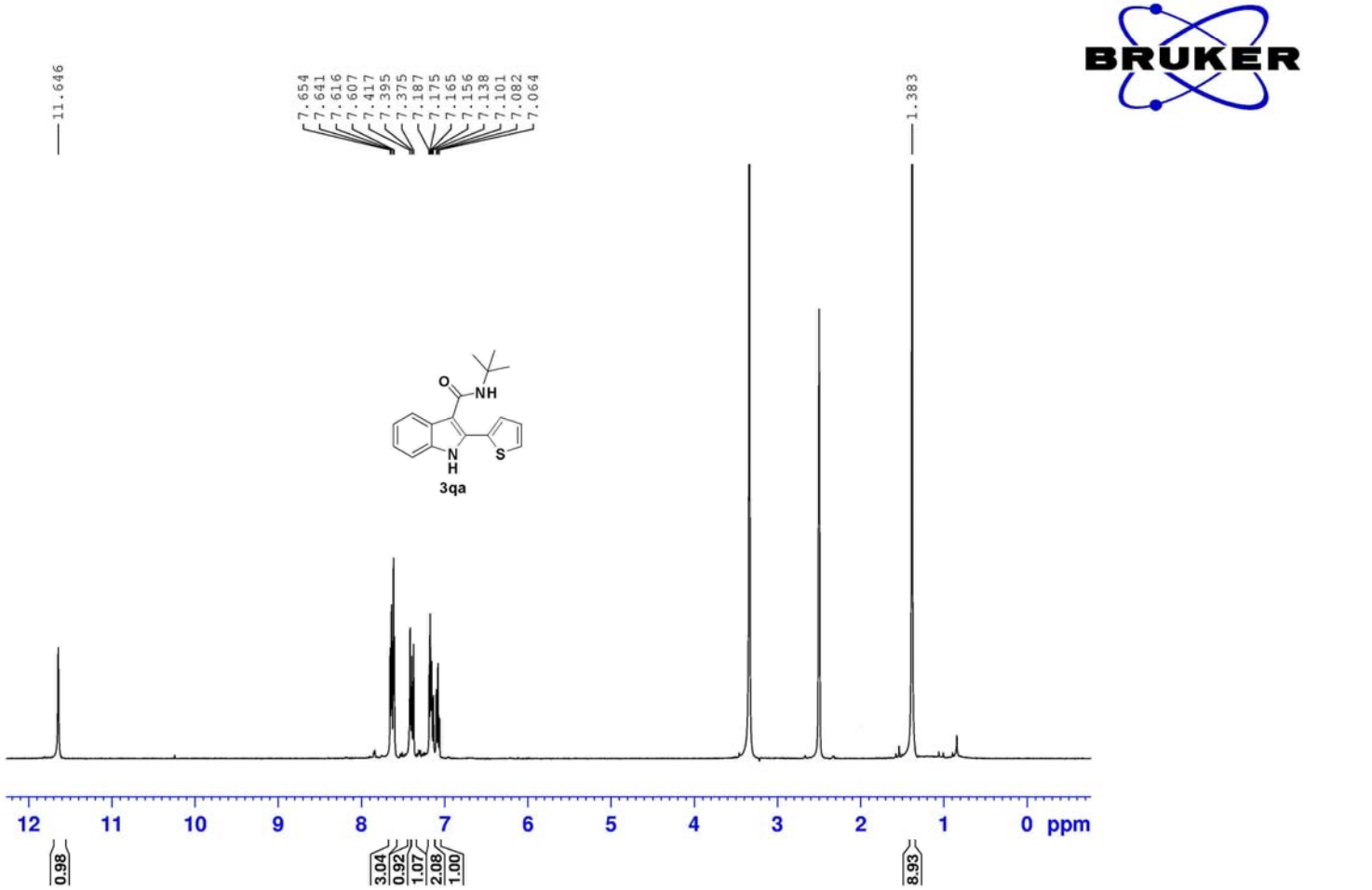
0
ppm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7.156
7.138
7.101
7.082
7.064
1.383
O
NH
N
H
S
3qa
12
11
10
9
8
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2
1
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0.92
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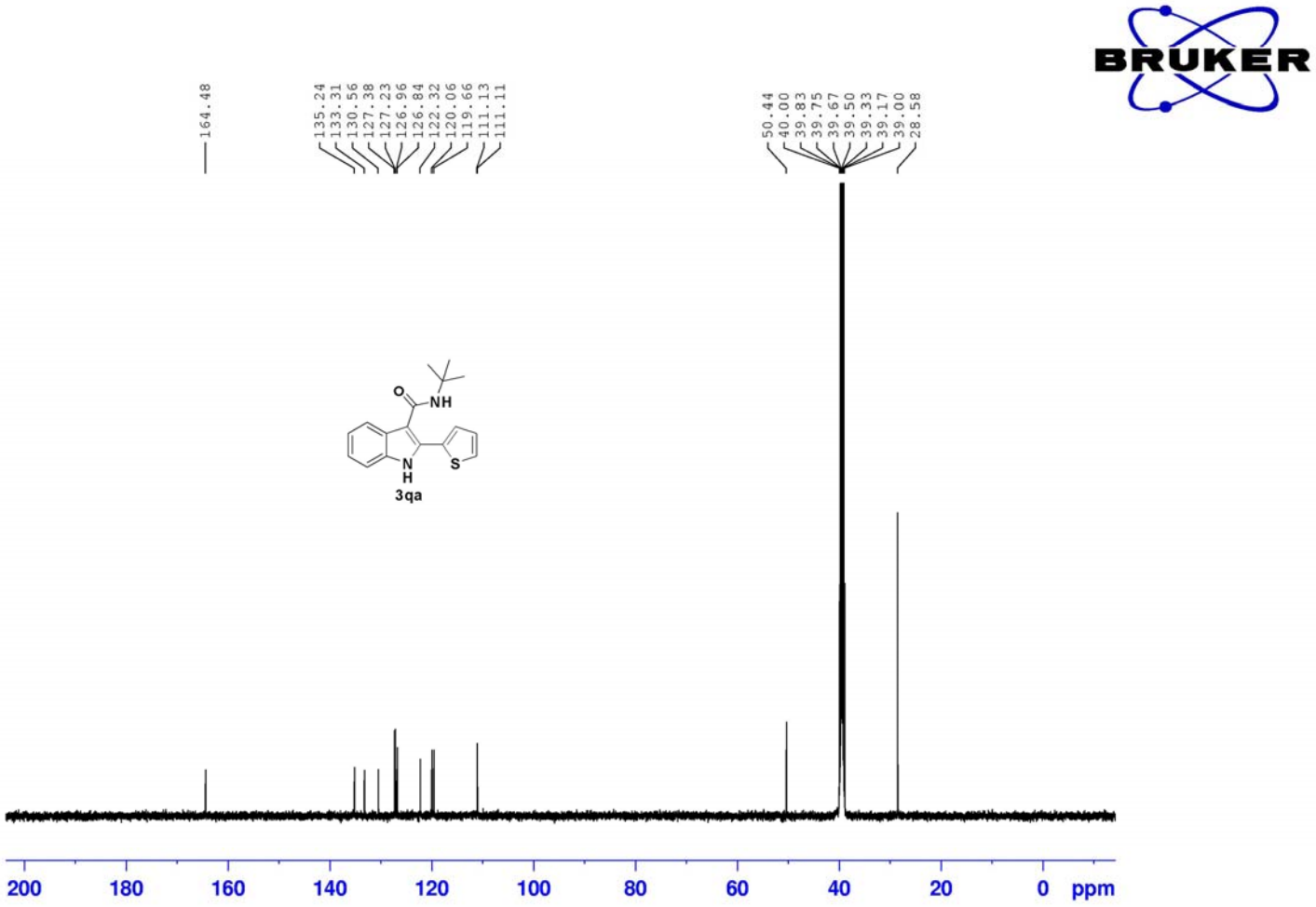
8.93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50.44
40.00
39.83
39.75
39.67
39.50
39.33
39.17
39.00
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N
H
S
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200
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160
140
120
100
80
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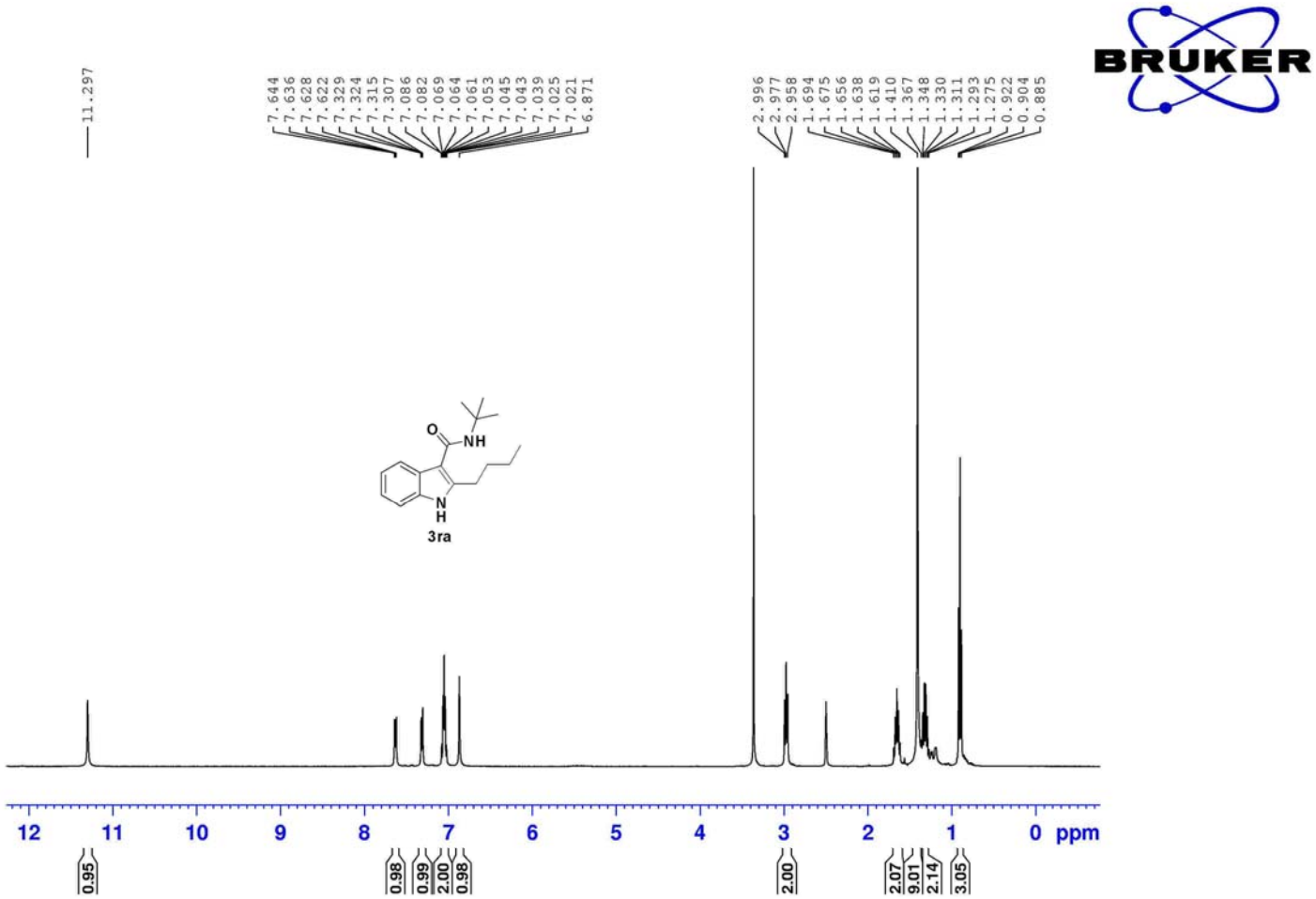
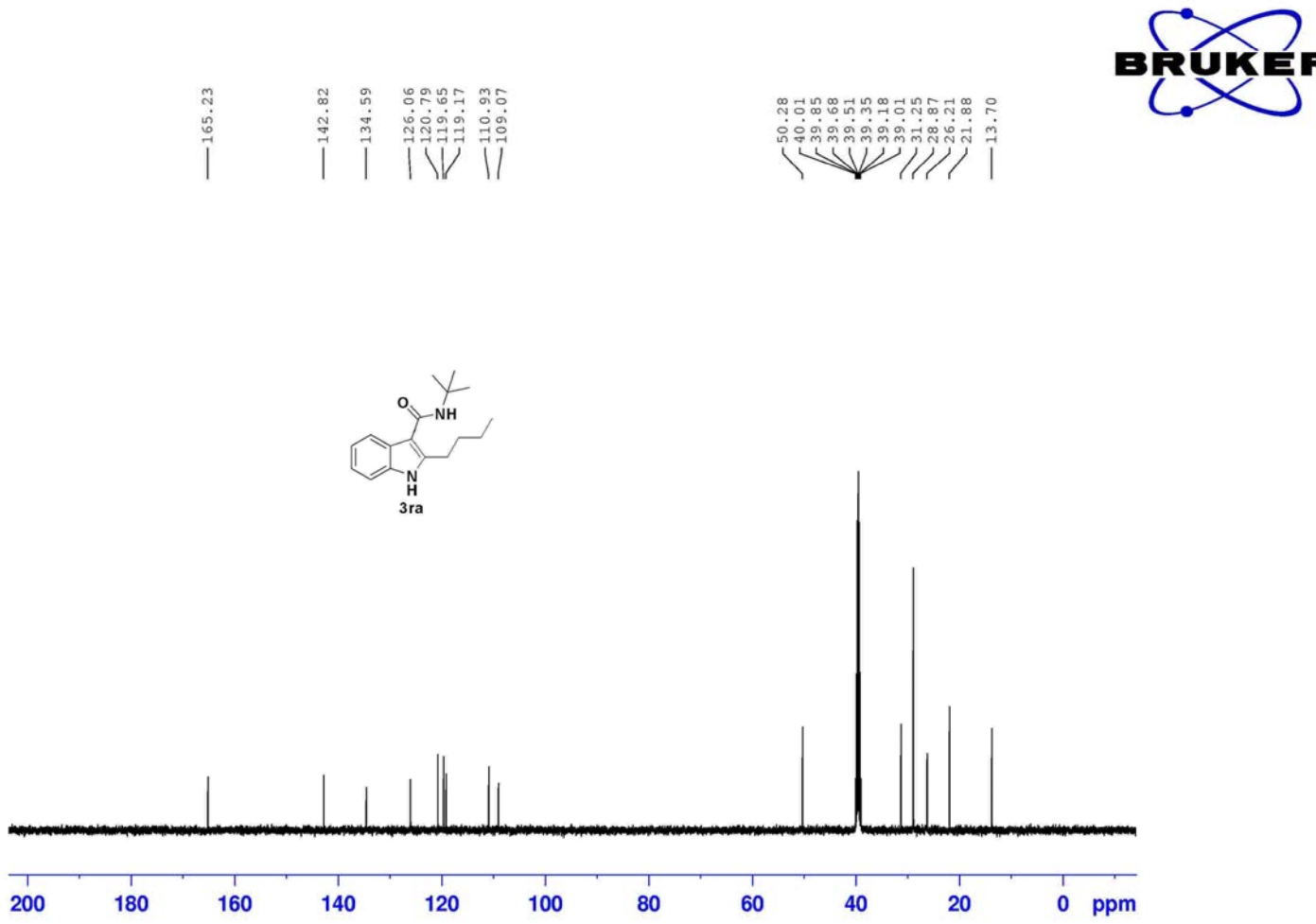
40
20
0
ppm

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39.51
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39.18
39.01
31.25
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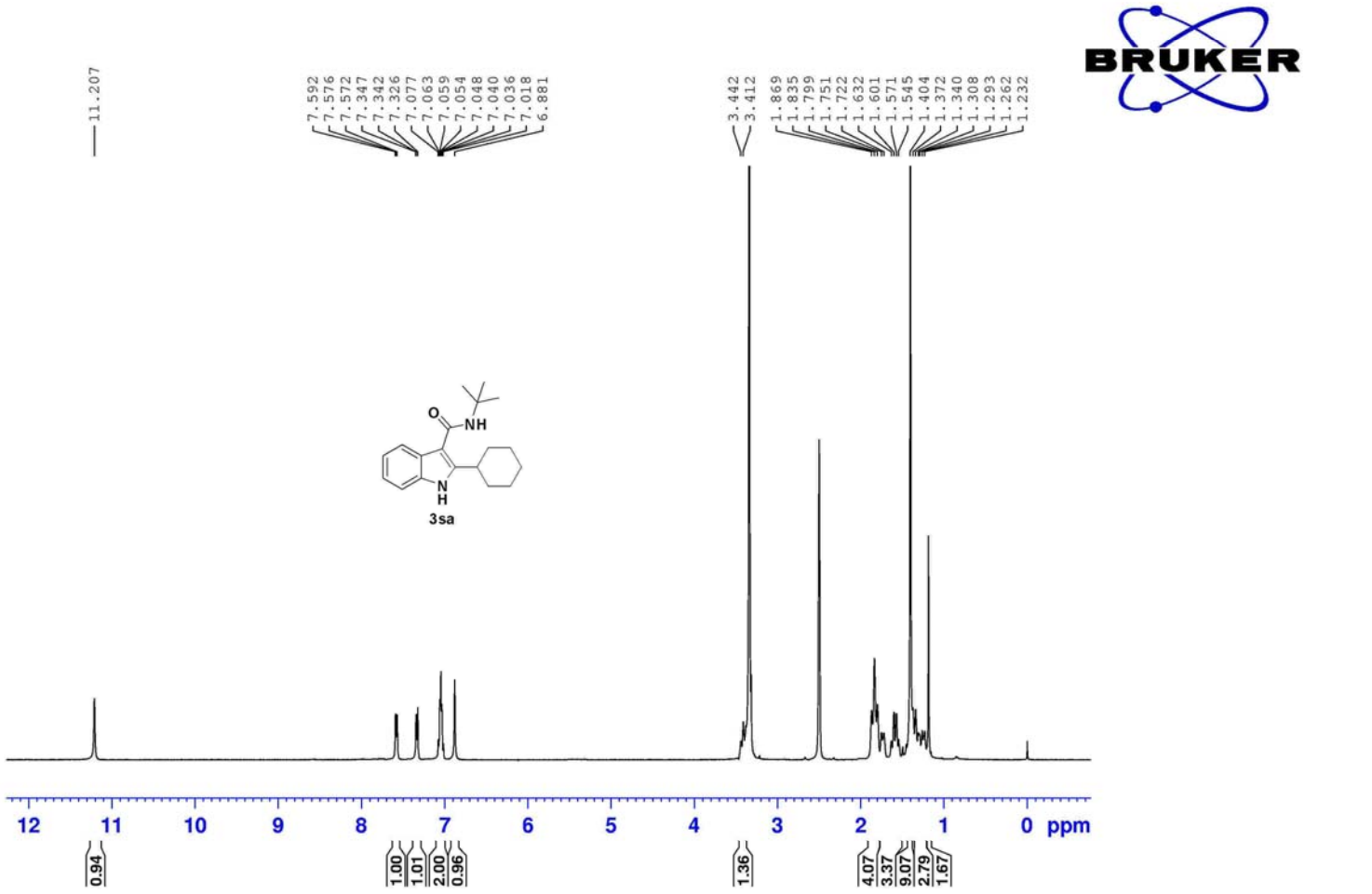
ppm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7.059
7.054
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7.036
7.018
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3.412
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1.835
1.799
1.751
1.722
1.632
1.601
1.571
1.545
1.404
1.372
1.340
1.308
1.293
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1.232
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NH
N
H
3sa
12
11
10
9
8
7
6
5
4
3
2
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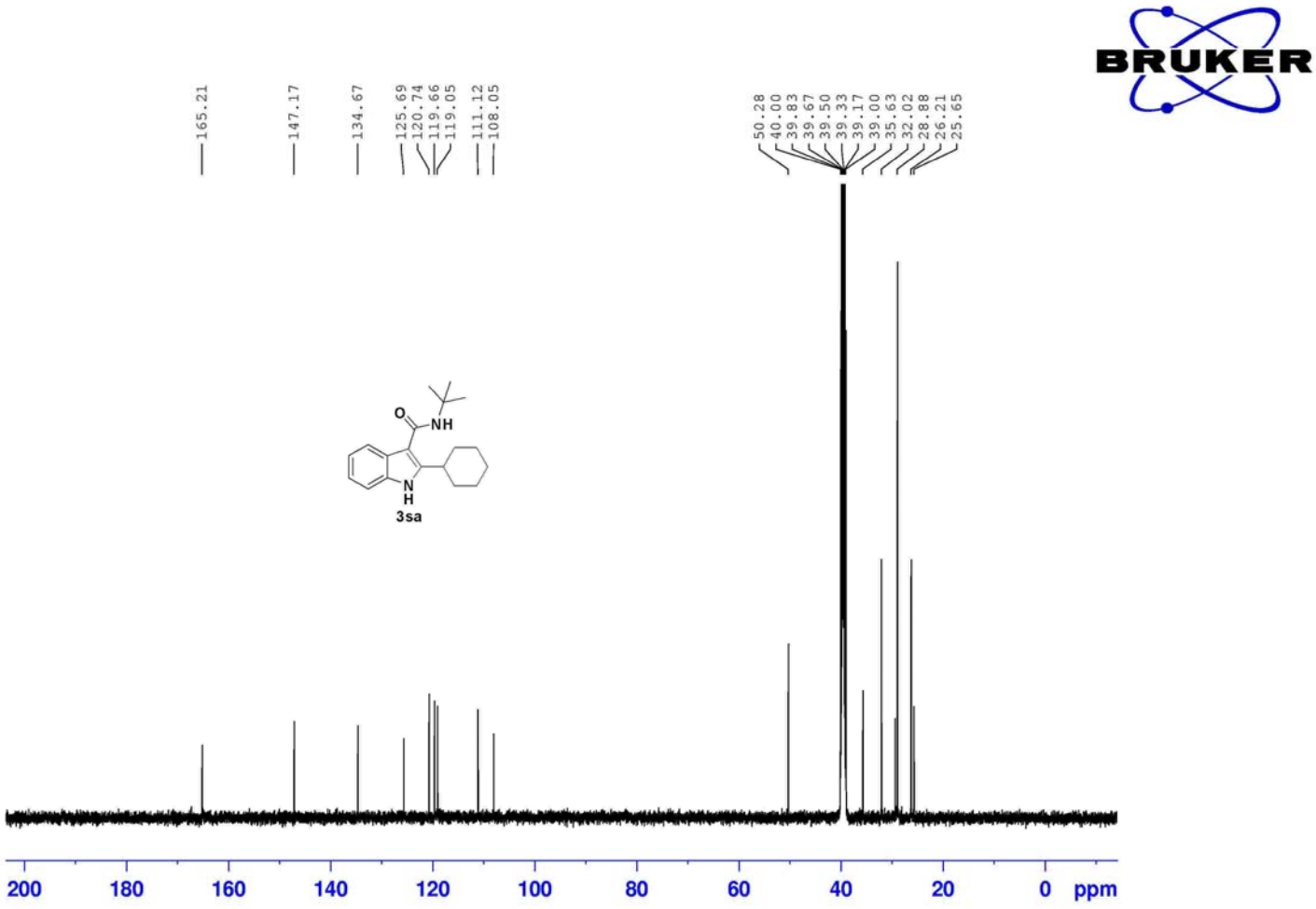
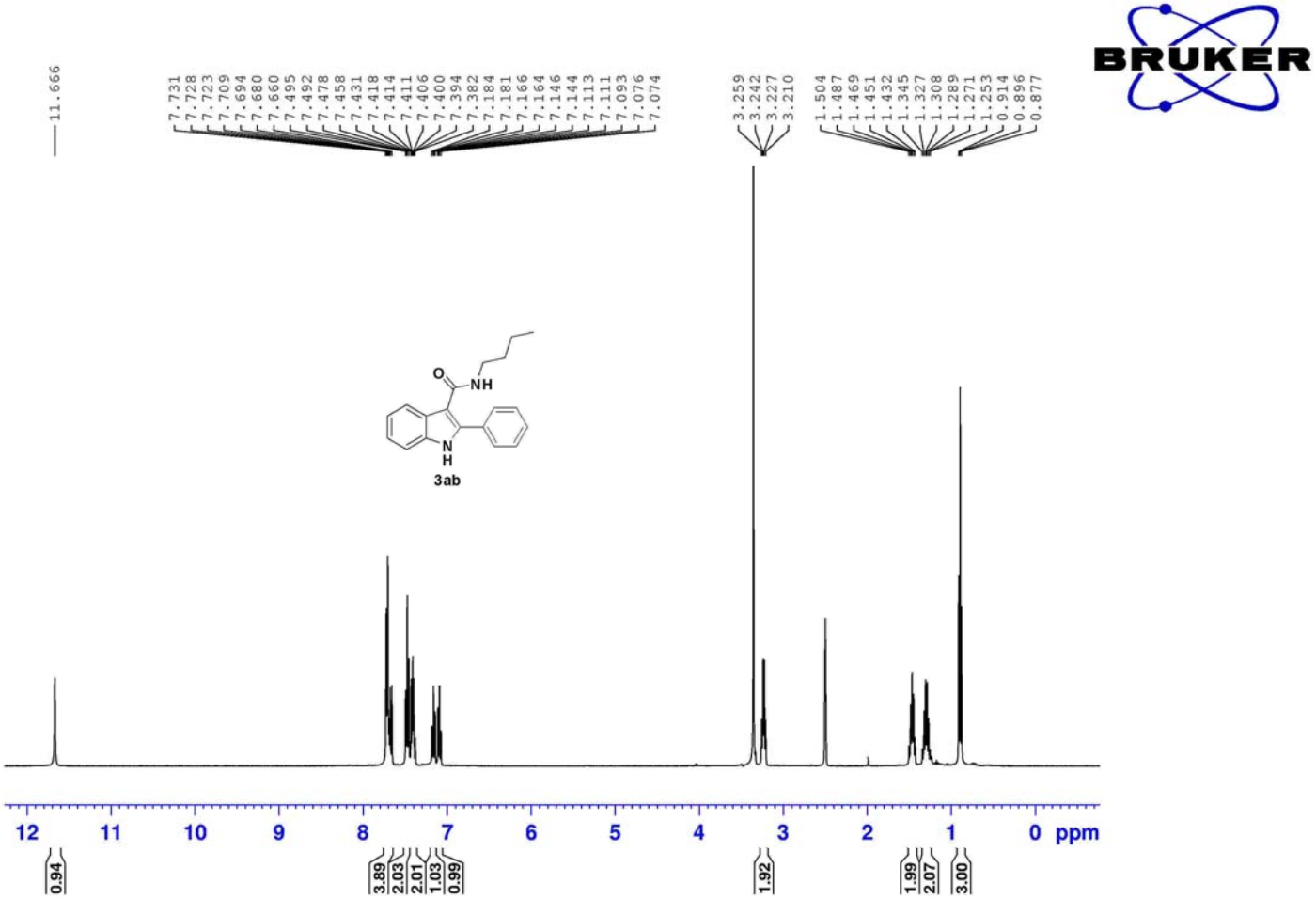
1.67

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7.411
7.406
7.400
7.394
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7.184
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7.144
7.113
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7.076
7.074
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1.432
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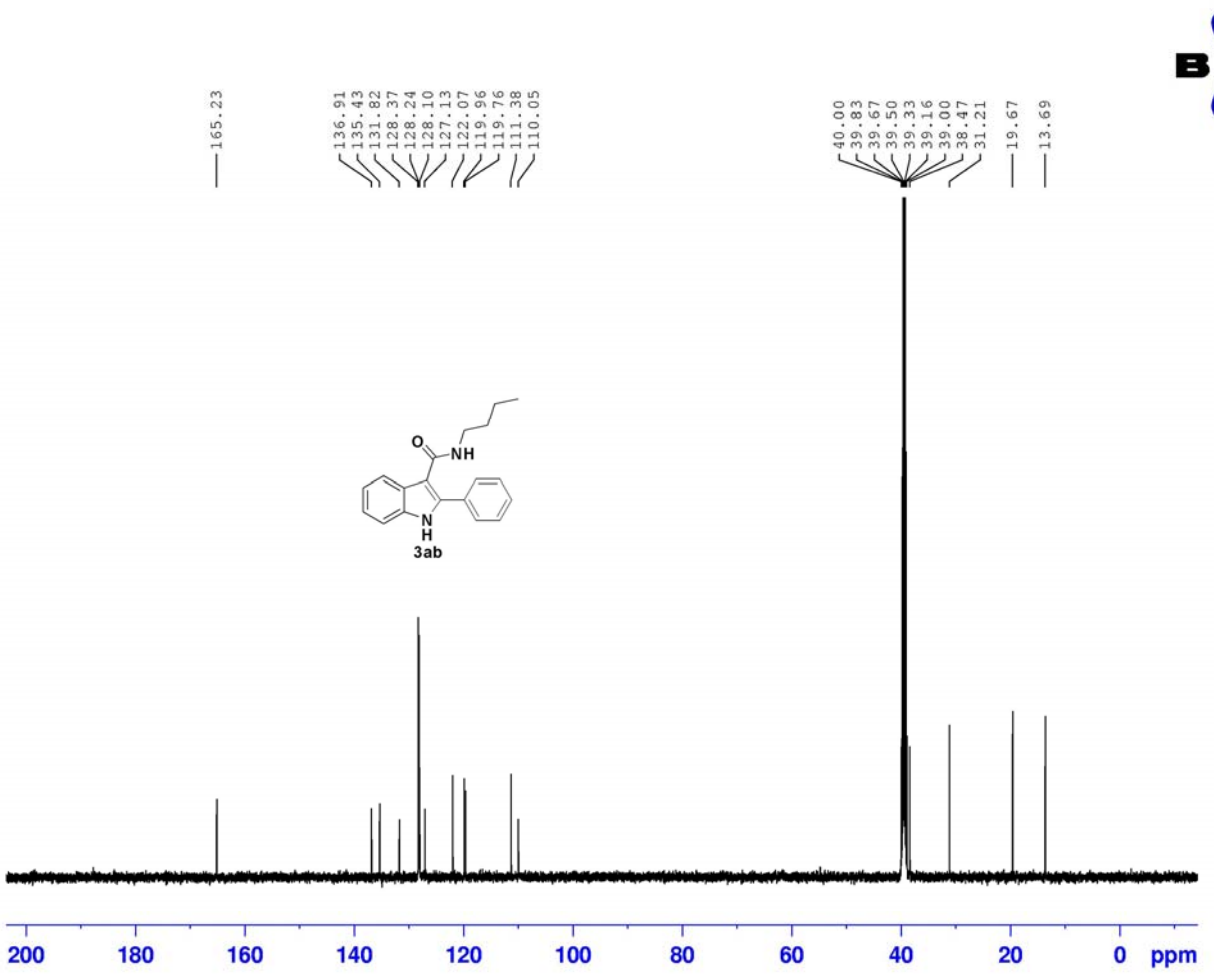
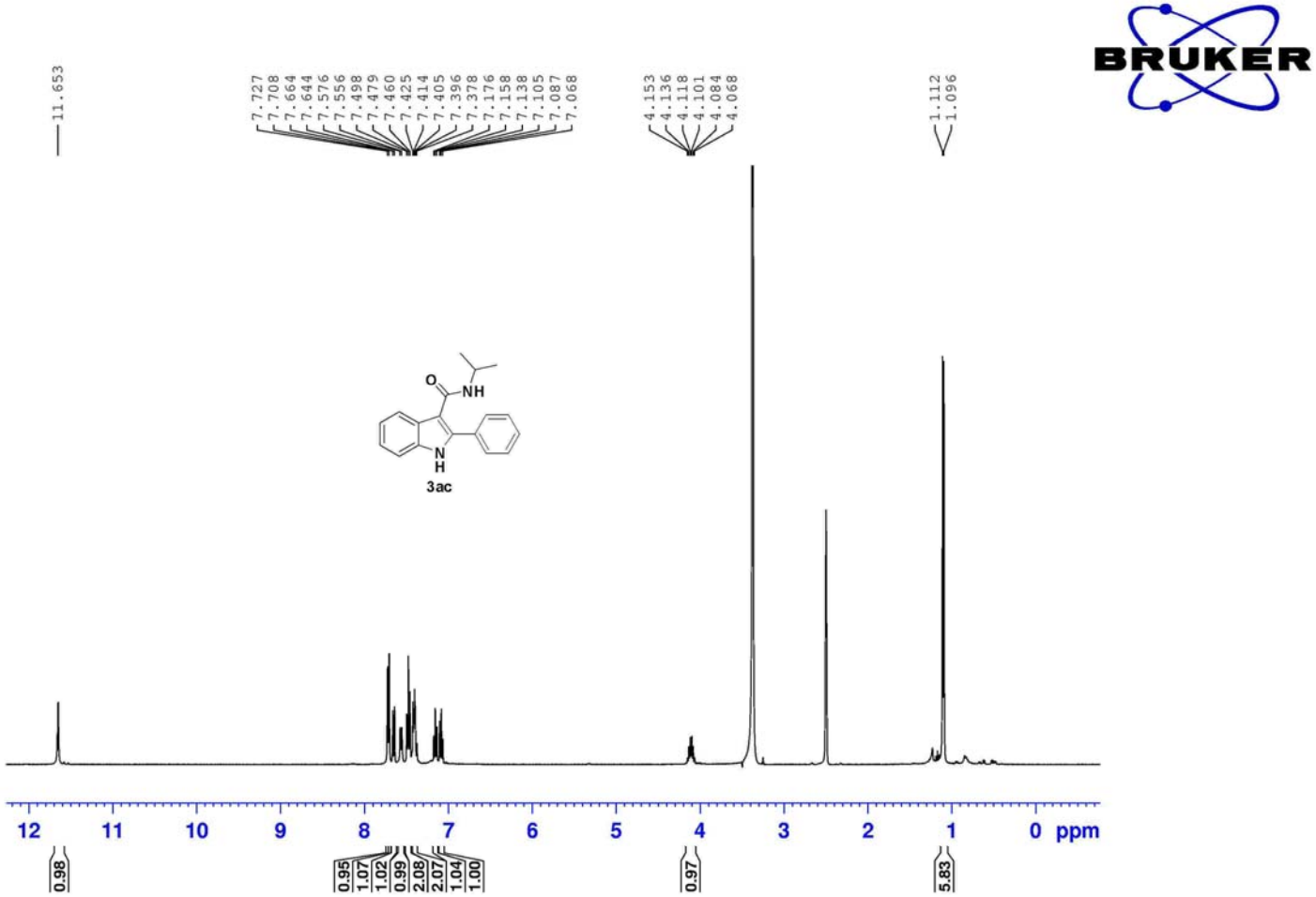
3.00

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7.396
7.378
7.176
7.158
7.138
7.105
7.087
7.068
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4.136
4.118
4.101
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1.096
O
NH
N
H
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8
7
6
5
4
3
2
1
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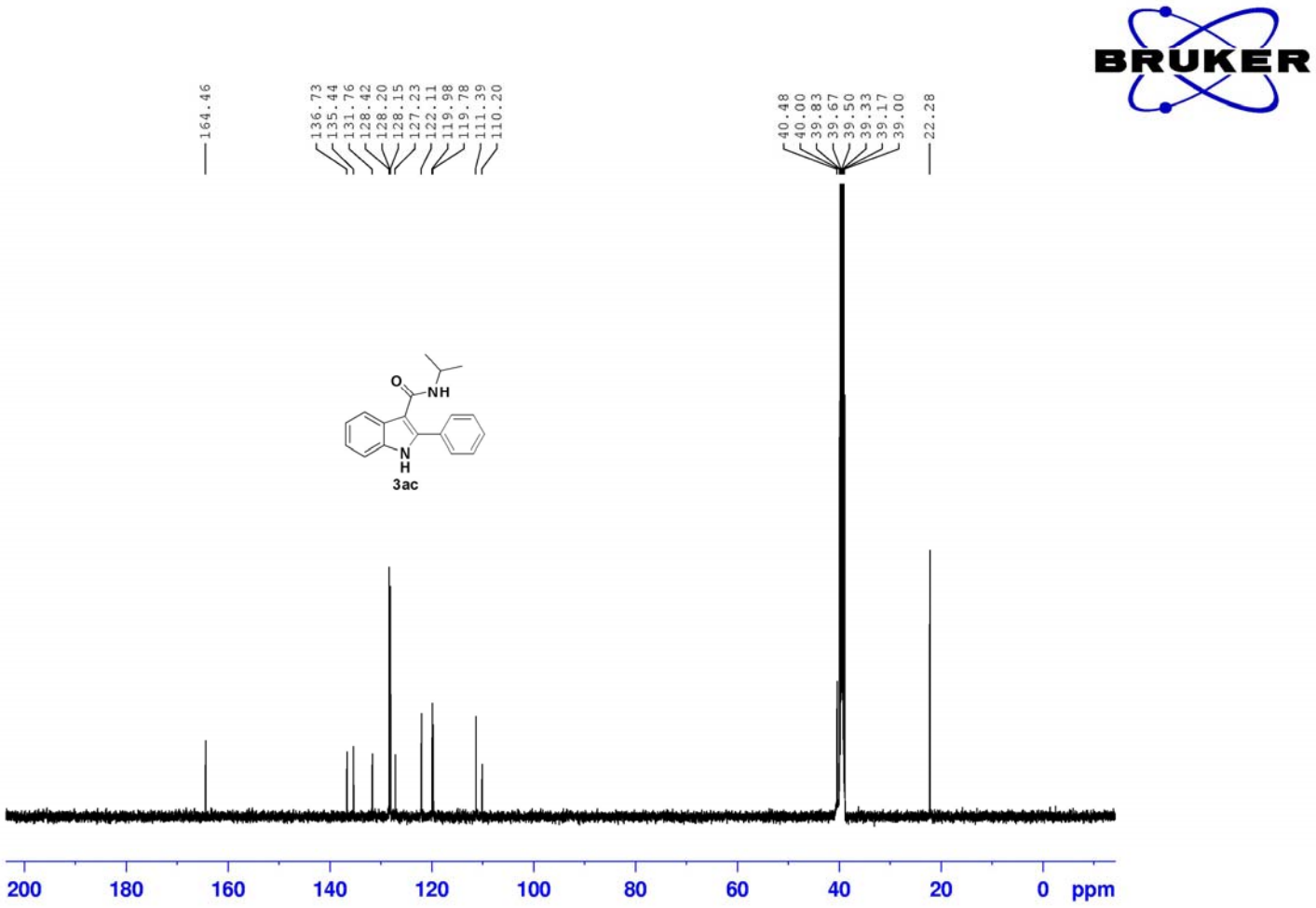
0.95
1.07
1.02
0.99
2.08
2.07
1.04
1.00
0.97
5.83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136.73
135.44
131.76
128.42
128.20
128.15
127.23
122.11
119.98
119.78
111.39
110.20
40.48
40.00
39.83
39.67
39.50
39.33
39.17
39.00
22.28
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NH
N
H
3ac
200
180
160
140
120
100
80
60
40
20
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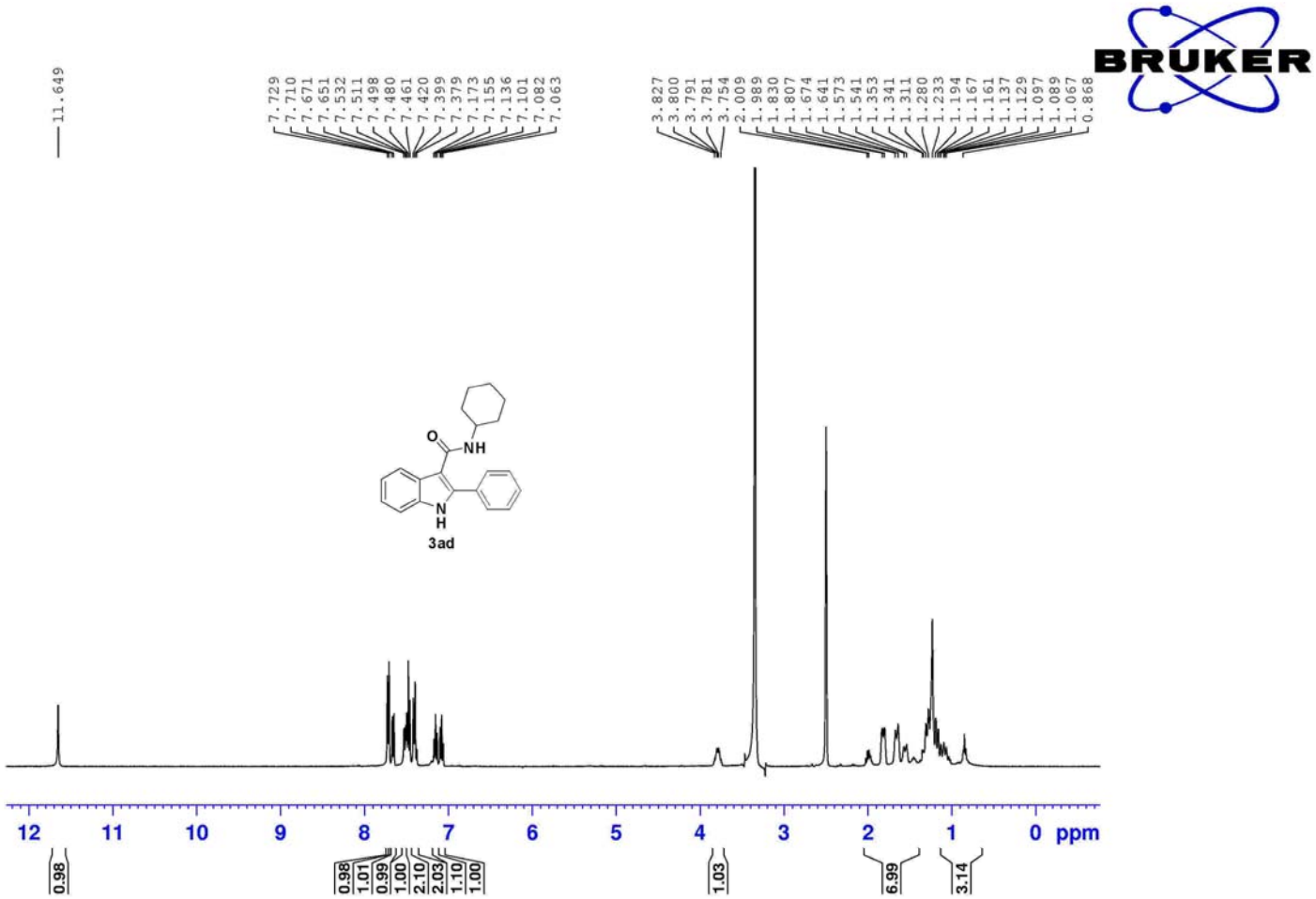
ppm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7.671
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7.532
7.511
7.498
7.480
7.461
7.420
7.399
7.379
7.173
7.155
7.136
7.101
7.082
7.063
3.827
3.800
3.791
3.781
3.754
2.009
1.989
1.830
1.807
1.674
1.641
1.573
1.541
1.353
1.341
1.311
1.280
1.233
1.194
1.167
1.161
1.137
1.129
1.097
1.089
1.067
0.868
O
NH
N
H
3ad
12
11
10
9
8
7
6
5
4
3
2
1
0 ppm
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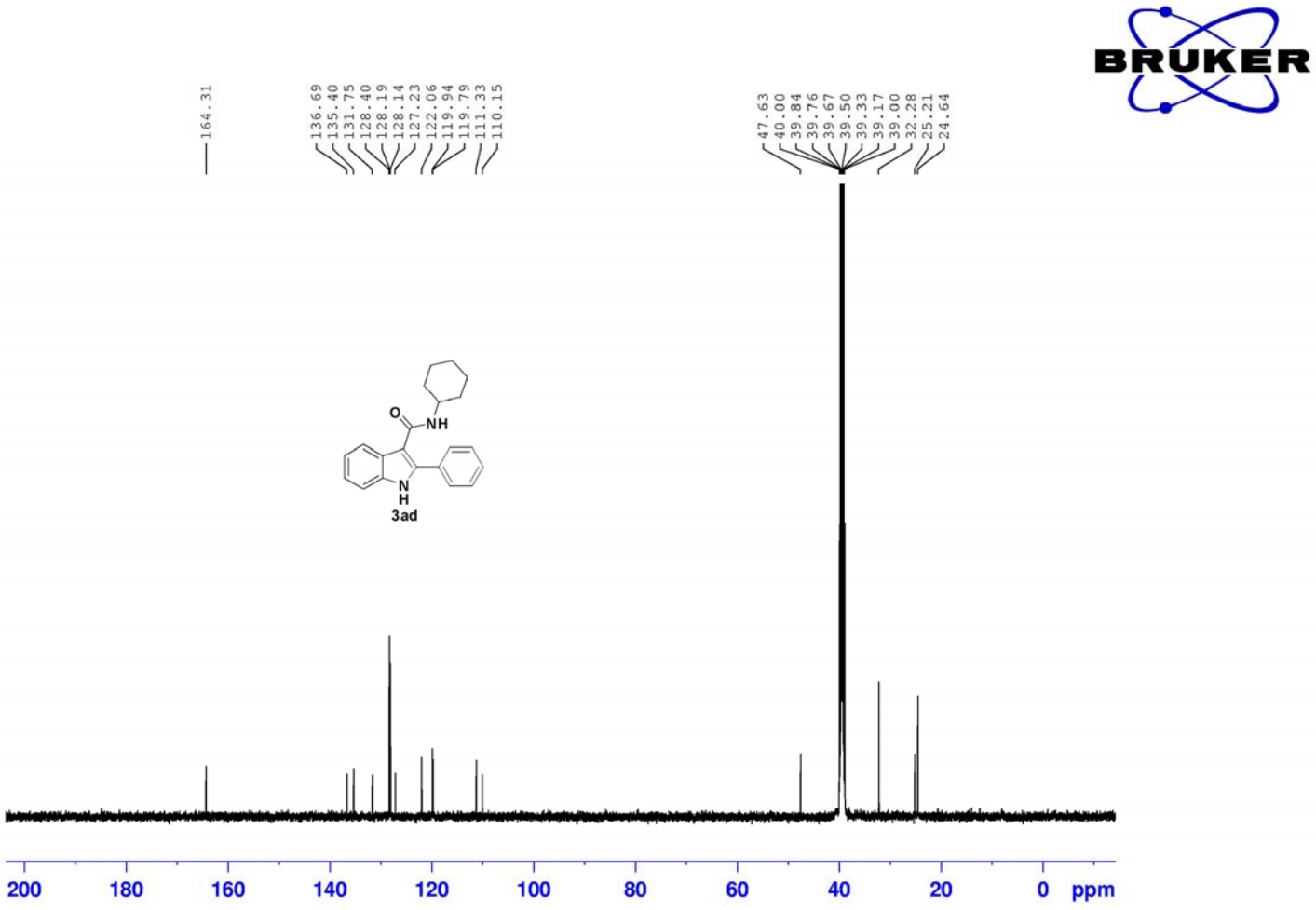
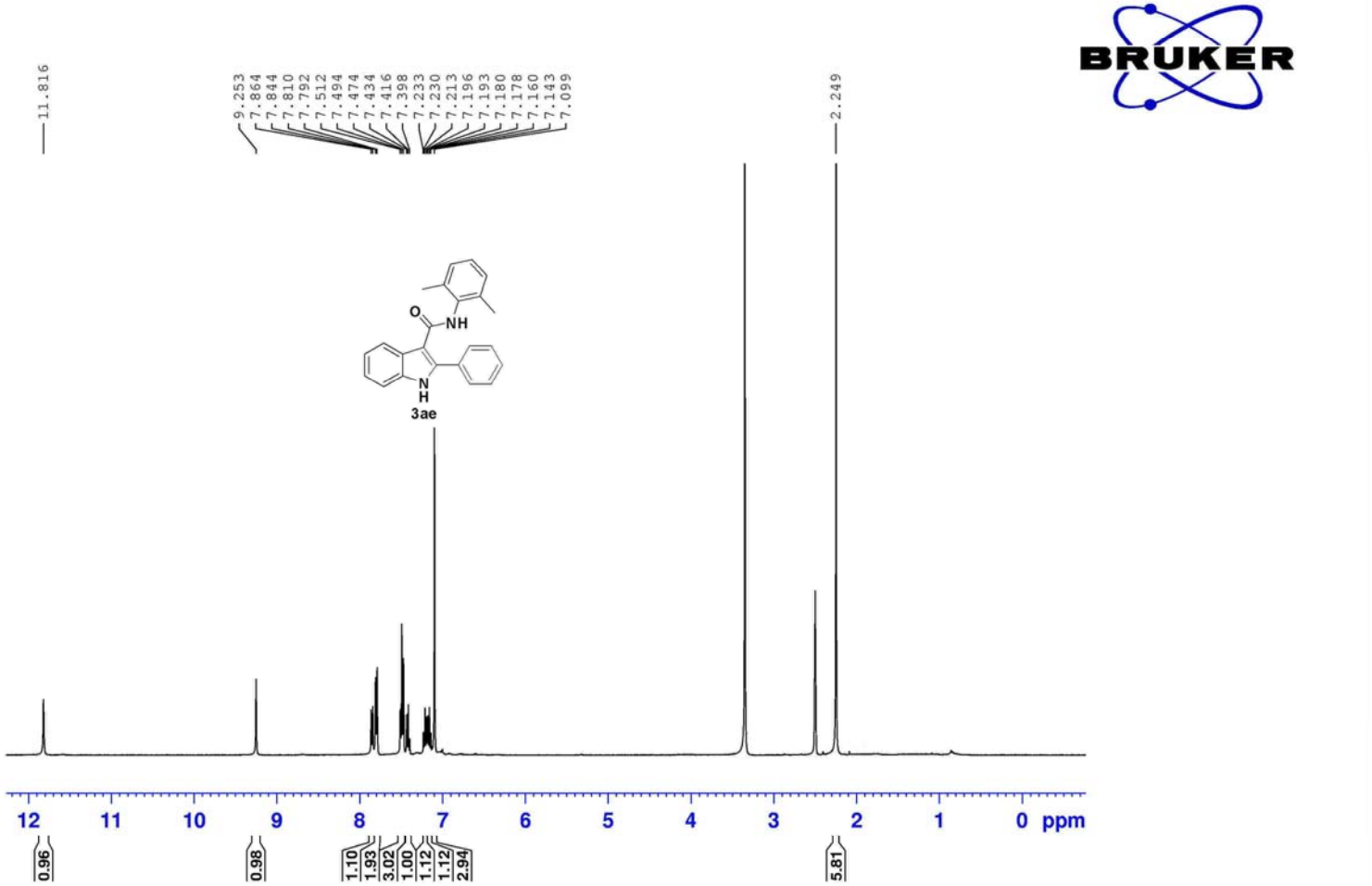
0.99
1.00
2.10
2.03
1.10
1.00
1.03
6.99
3.14

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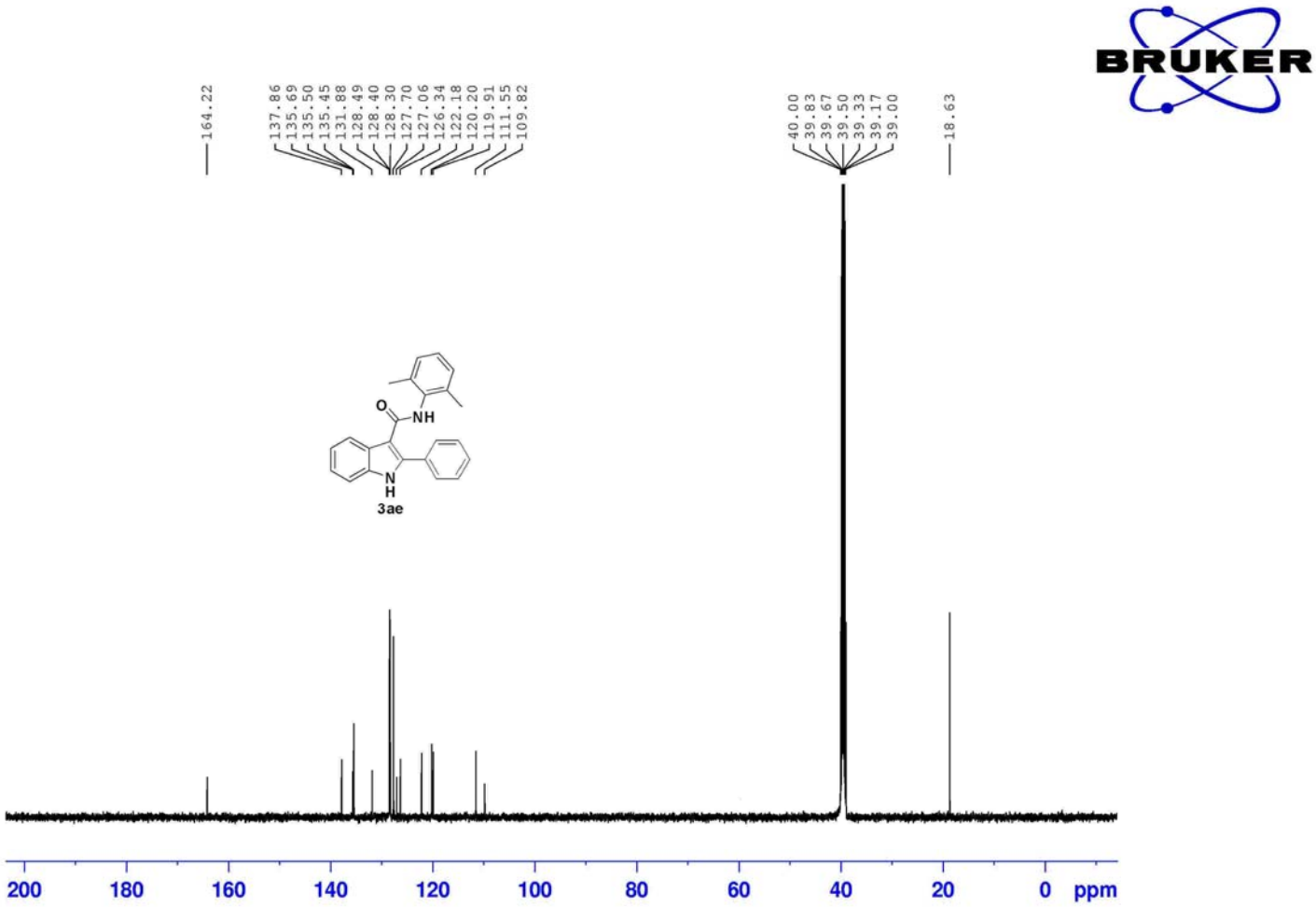
7.864
7.844
7.810
7.792
7.512
7.494
7.474
7.434
7.416
7.398
7.233
7.230
7.213
7.196
7.193
7.180
7.178
7.160
7.143
7.099
2.249
O
NH
N
H
3ae
12
11
10
9
8
7
6
5
4
3
2
1
0 ppm
0.96
0.98
1.10
1.93
3.02
1.00
1.12
1.12
2.94
5.81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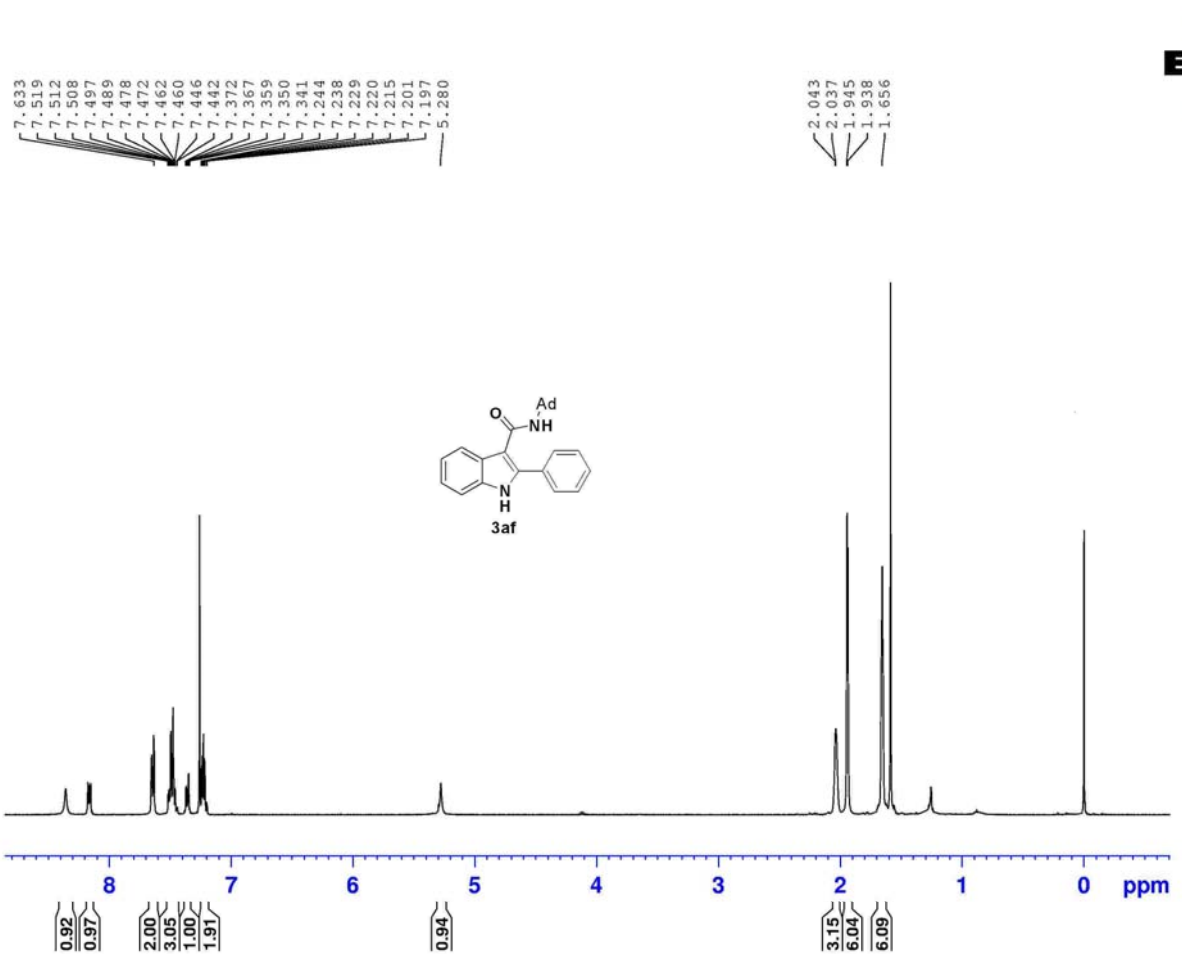
137.86
135.69
135.50
135.45
131.88
128.49
128.40
128.30
127.70
127.06
126.34
122.18
120.20
119.91
111.55
109.82
40.00
39.83
39.67
39.50
39.33
39.17
39.00
18.63
O
NH
N
H
3ae
200
180
160
140
120
100
80
60
40
20
0
ppm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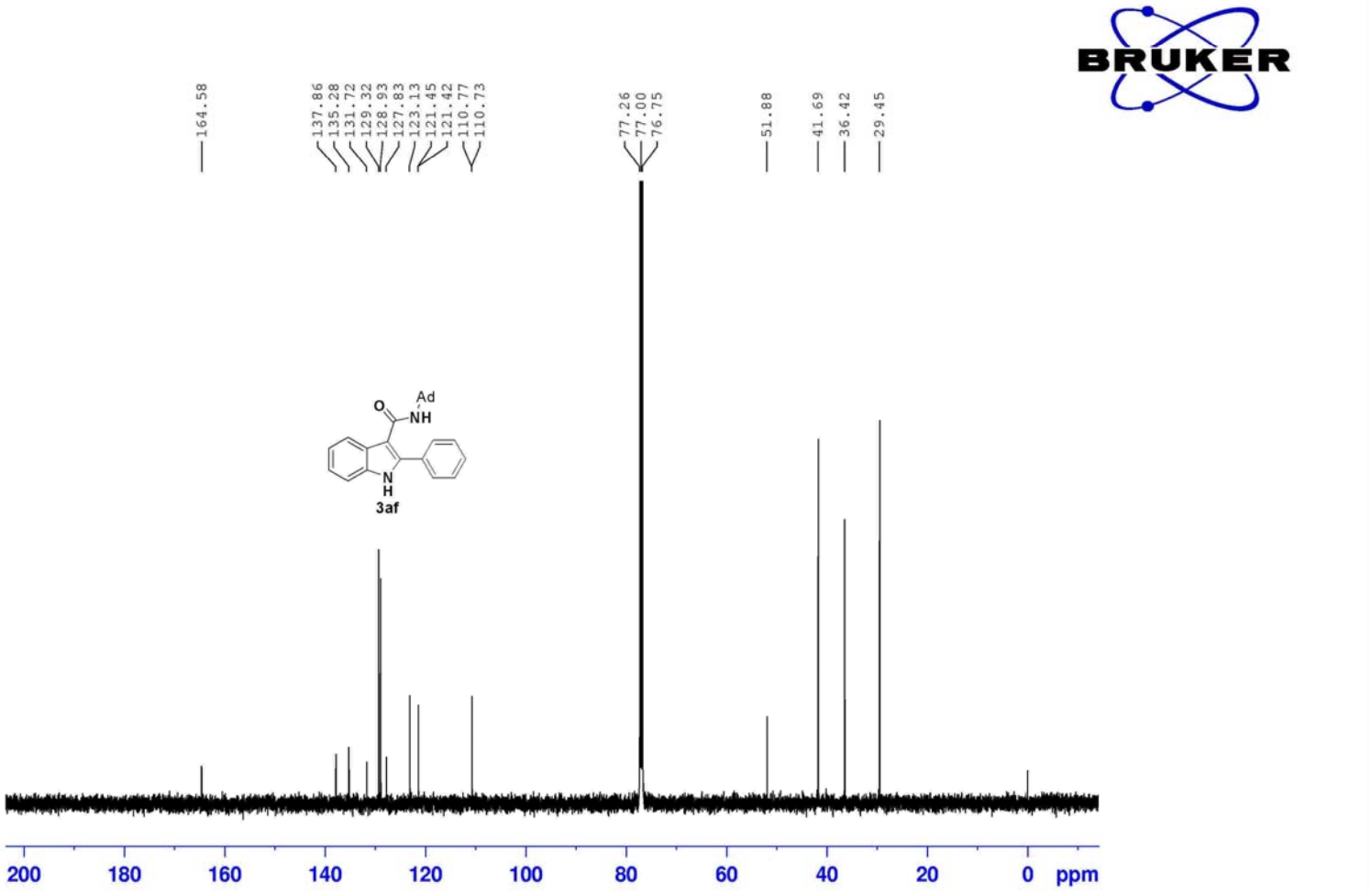
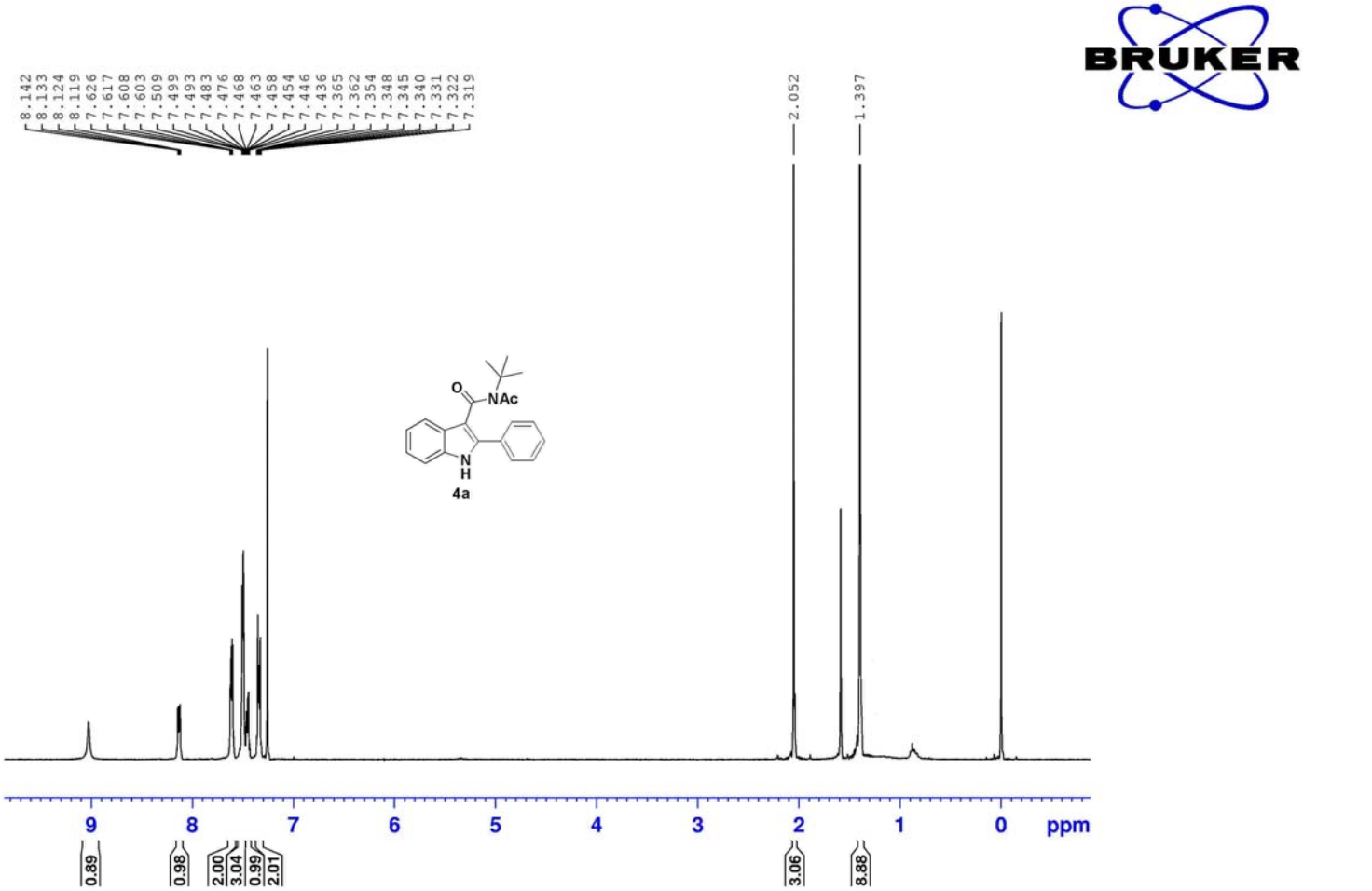
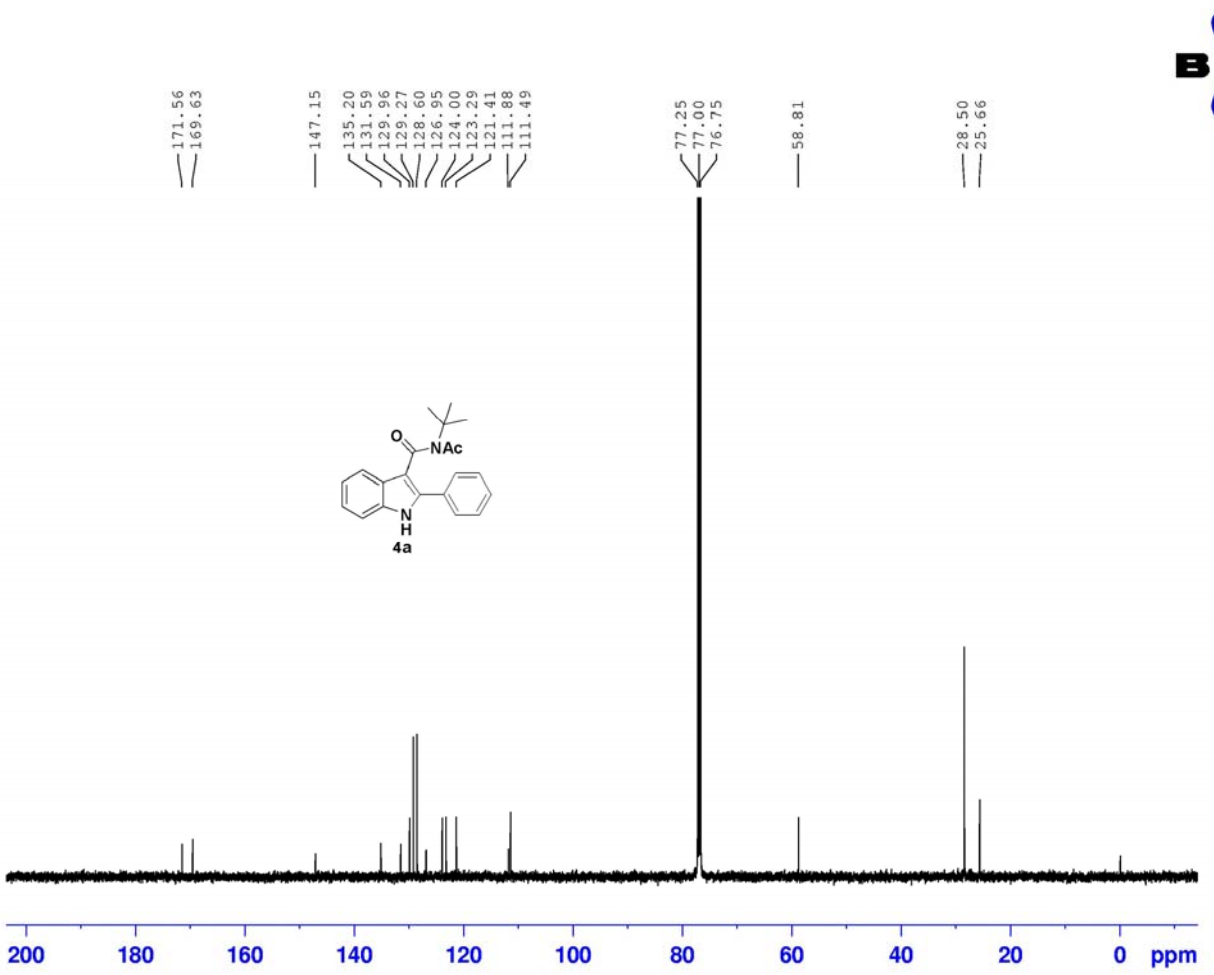
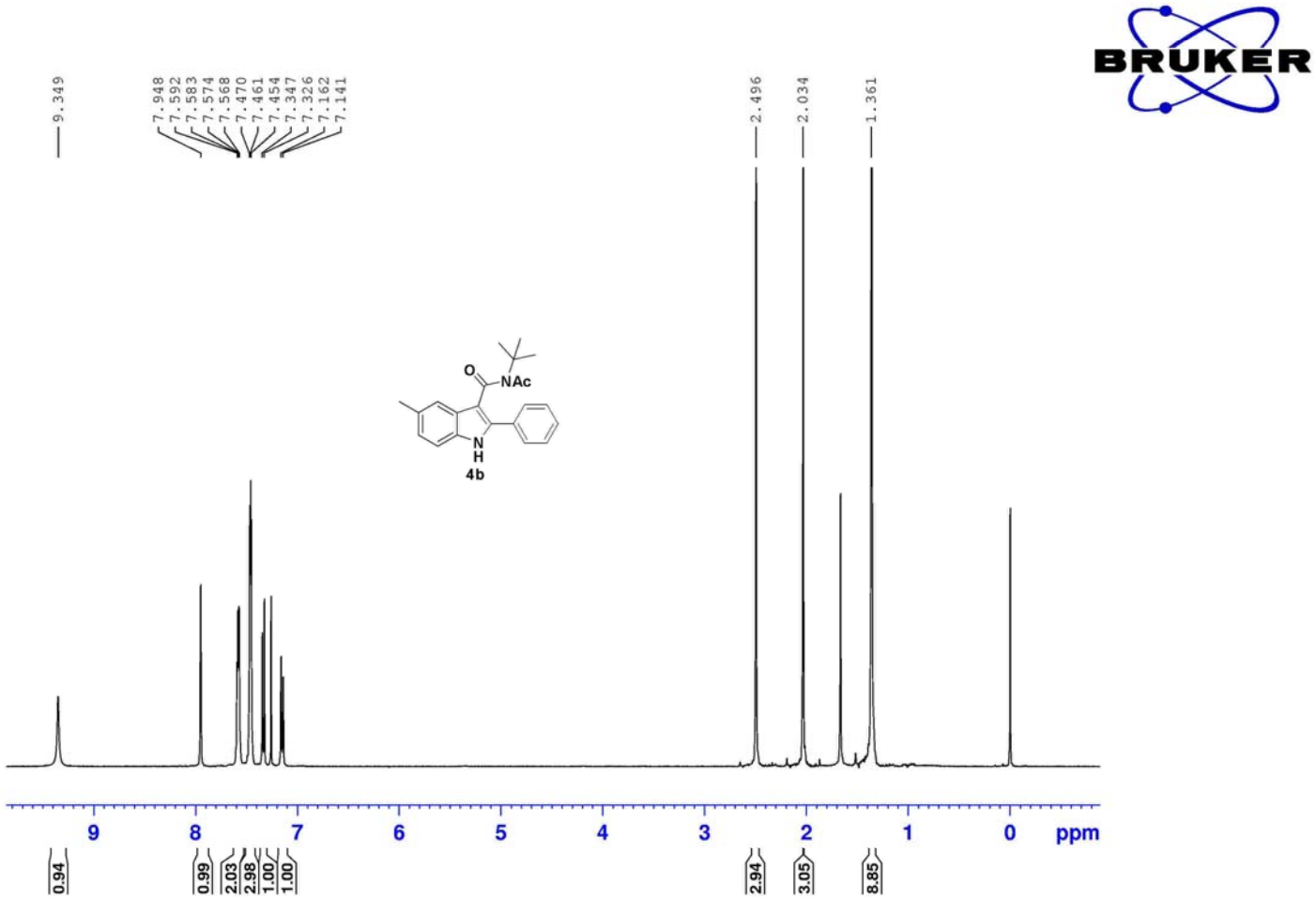
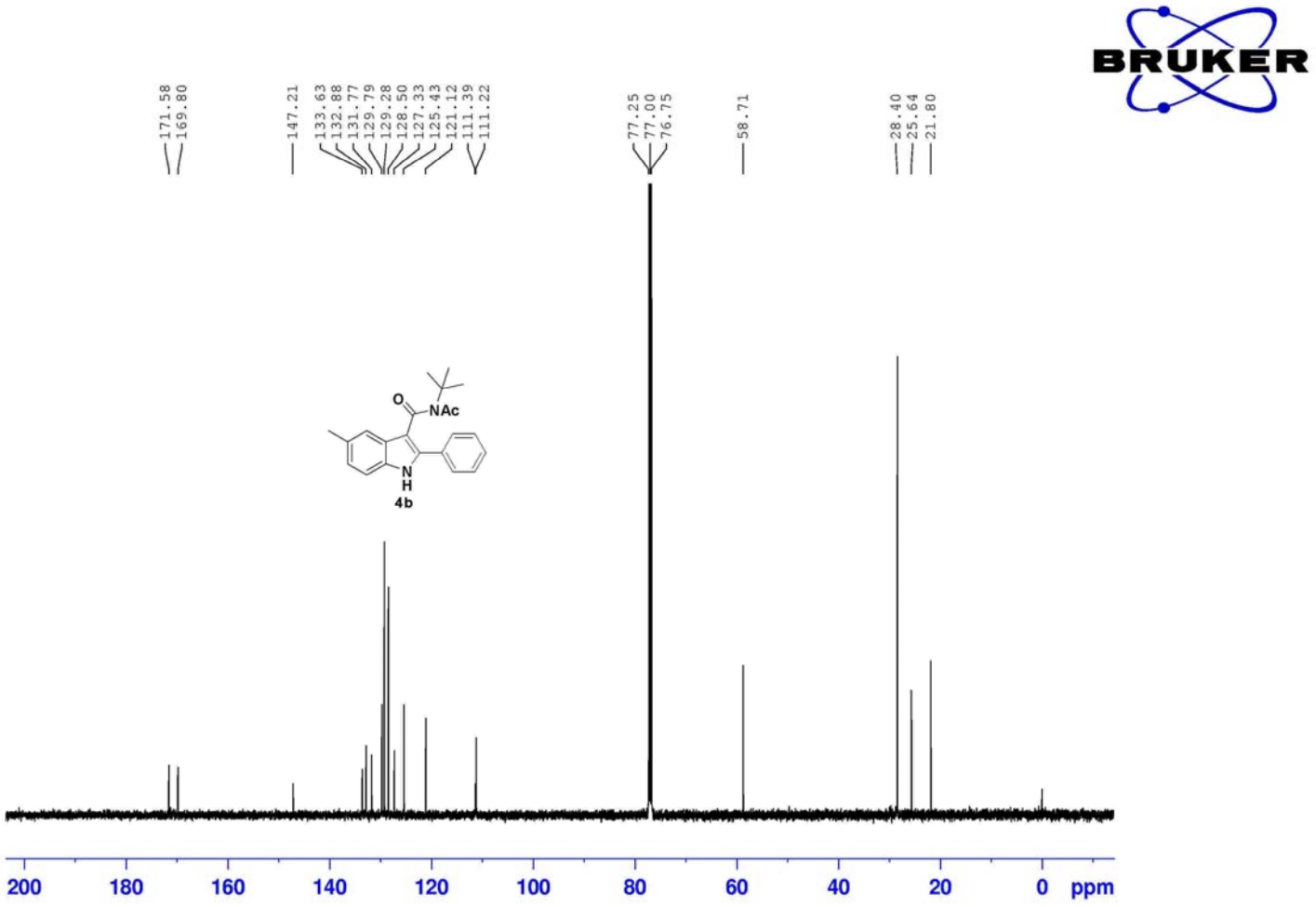
7.519
7.512
7.508
7.497
7.489
7.478
7.472
7.462
7.460
7.446
7.442
7.372
7.367
7.359
7.350
7.341
7.244
7.238
7.229
7.220
7.215
7.201
7.197
5.280
2.043
2.037
1.945
1.938
1.656
Ad
NH
O
N
H
3af
8
7
6
5
4
3
2
1
0
ppm
0.92
0.97
2.00
3.05
1.00
1.91
0.94
3.15
6.04
6.09

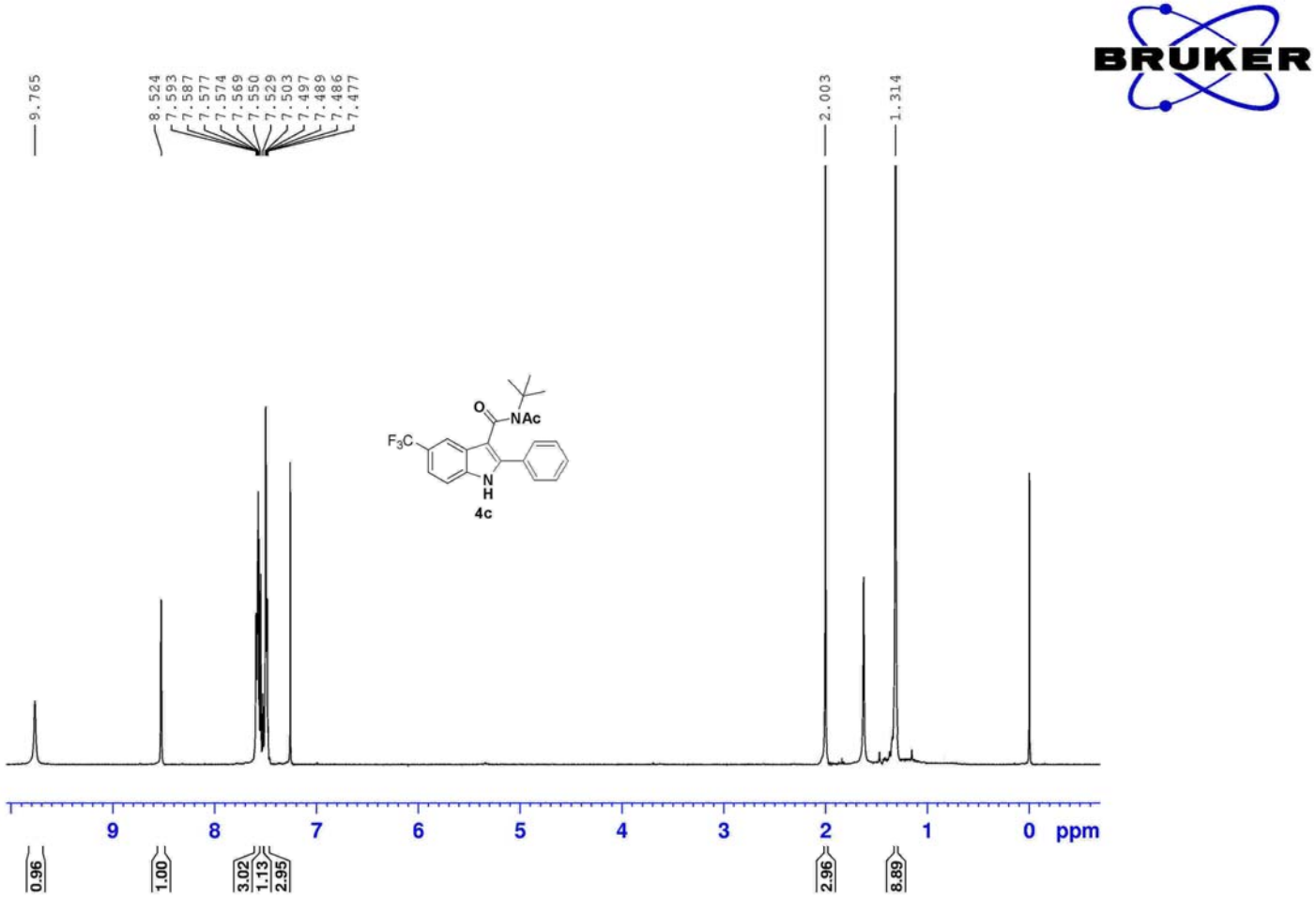








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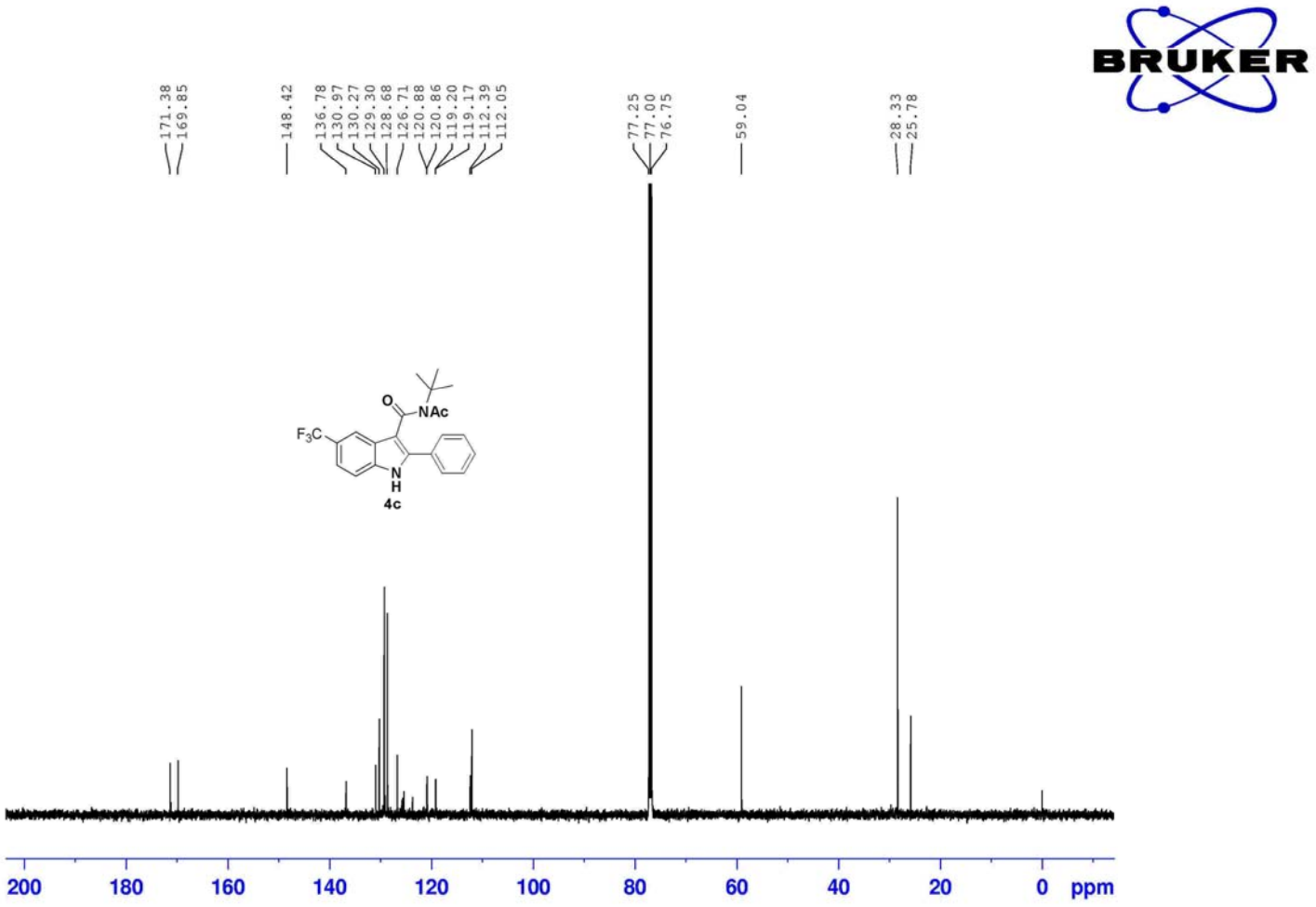
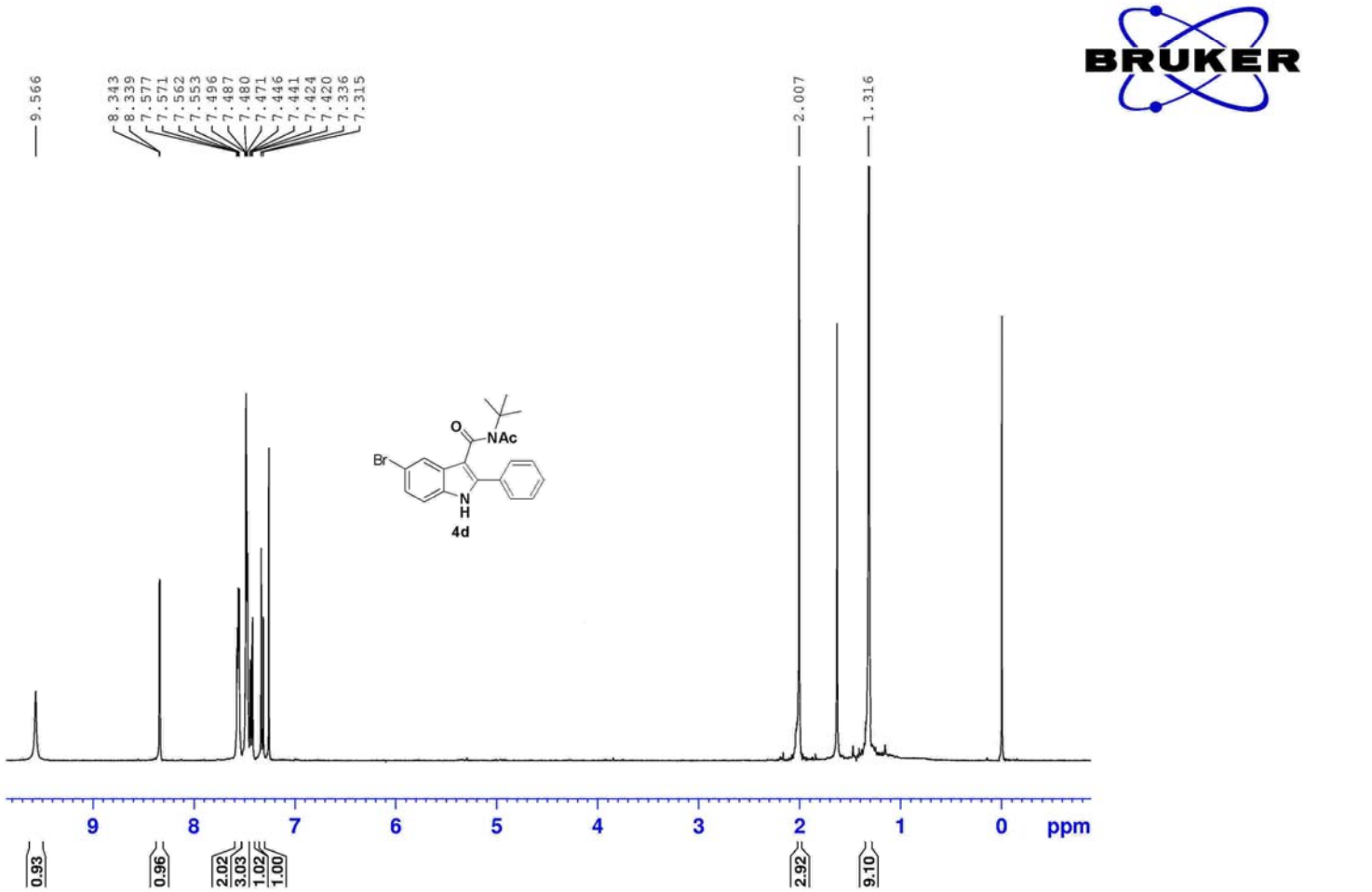
7.593
7.587
7.577
7.574
7.569
7.550
7.529
7.503
7.497
7.489
7.486
7.477
2.003
1.314
O
NAc
F3C
N
H
4c
9
8
7
6
5
4
3
2
1
0
ppm
0.96
1.00
3.02
1.13
2.95
2.96
8.89

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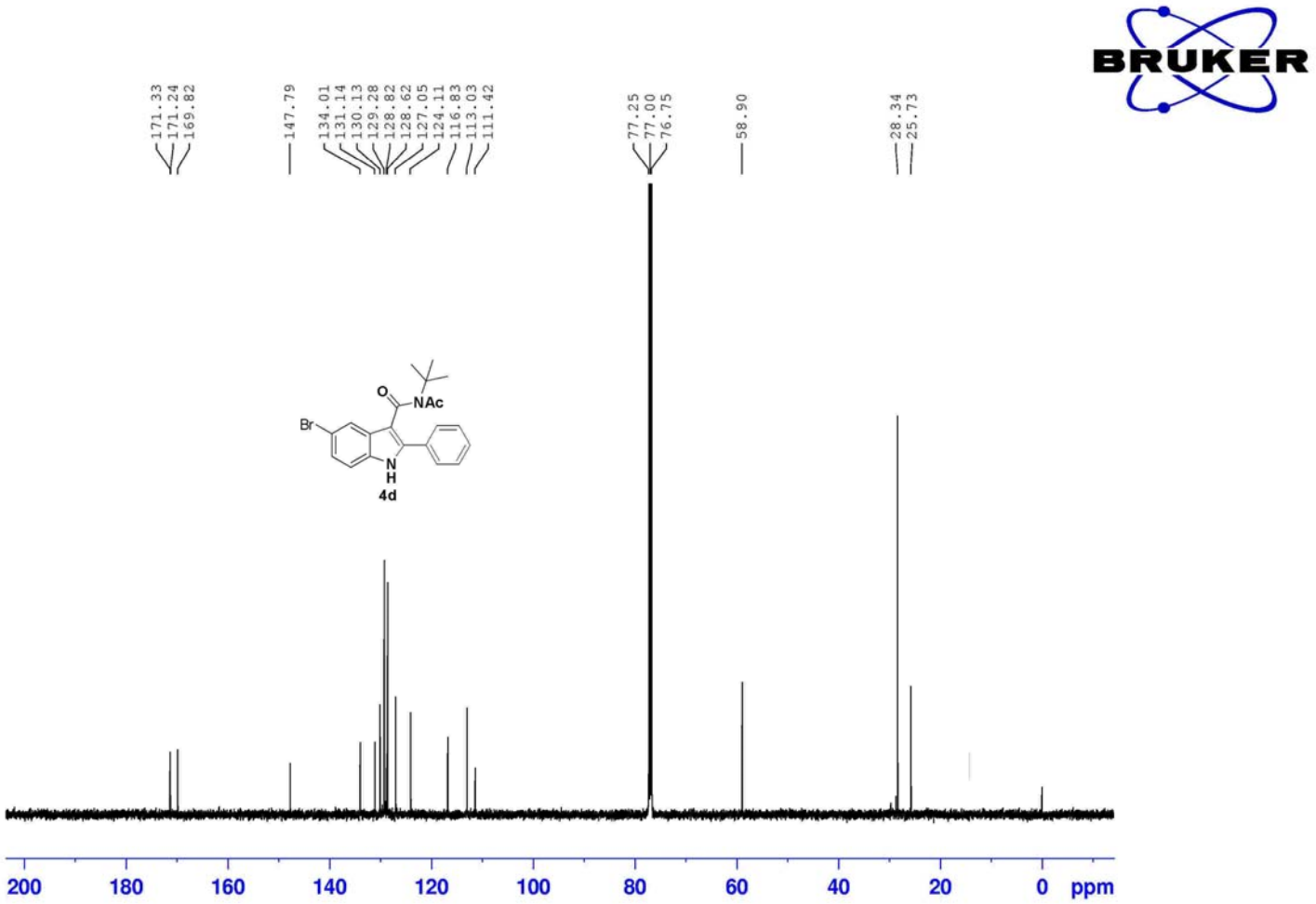
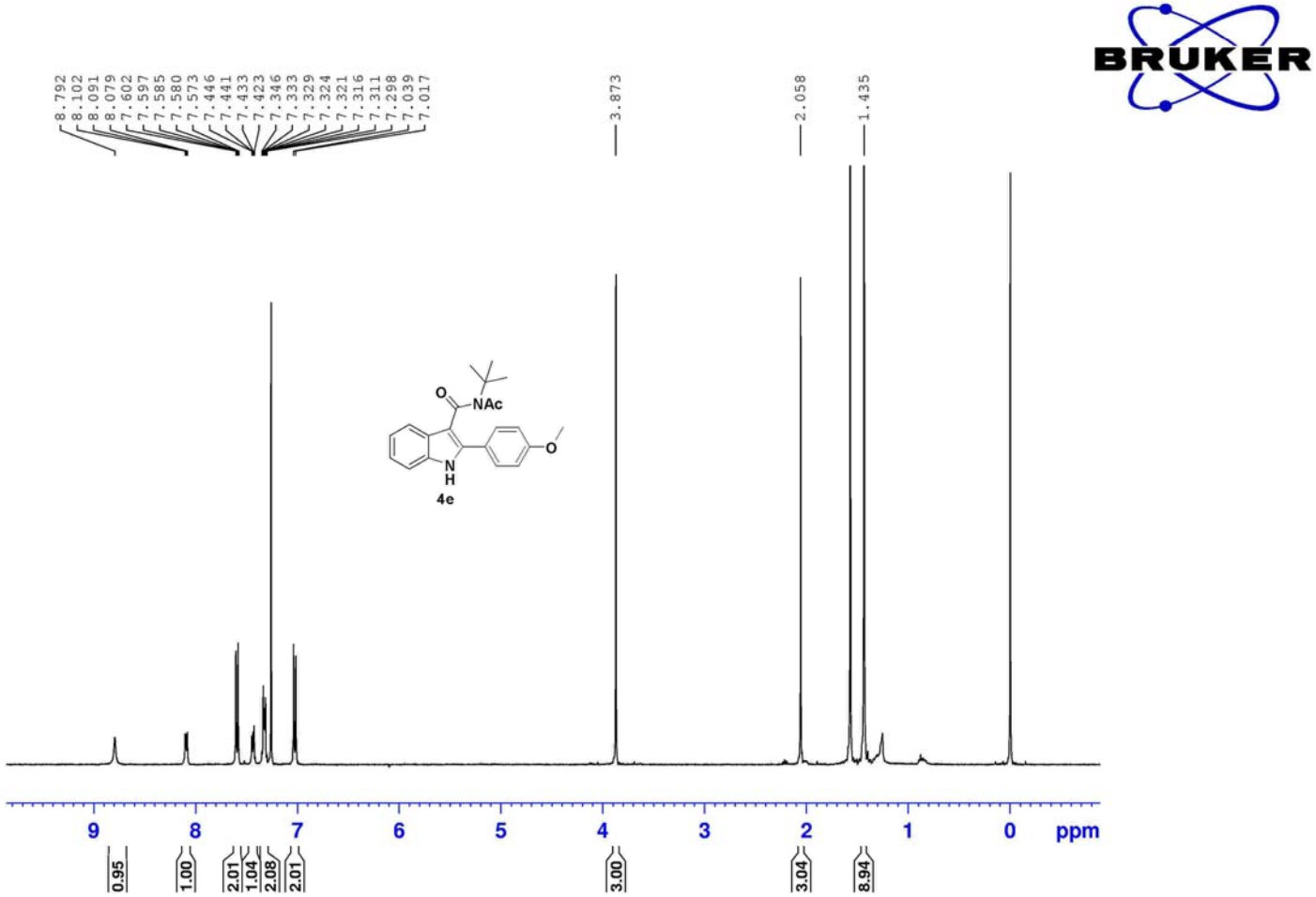
8.343
8.339
7.577
7.571
7.562
7.553
7.496
7.487
7.480
7.471
7.446
7.441
7.424
7.420
7.336
7.315
2.007
1.316
O
NAc
Br
N
H
4d
9
8
7
6
5
4
3
2
1
0
ppm
0.93
0.96
2.02
3.03
1.02
1.00
2.92
9.10


171.33
171.24
169.82
147.79
134.01
131.14
130.13
129.28
128.82
128.62
127.05
124.11
116.83
113.03
111.42
77.25
77.00
76.75
58.90
28.34
25.73
O
NAc
Br
N
H
4d
200
180
160
140
120
100
80
60
40
20
0
ppm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7.597
7.585
7.580
7.573
7.446
7.441
7.433
7.423
7.346
7.333
7.329
7.324
7.321
7.316
7.311
7.298
7.039
7.017
3.873
2.058
1.435
NAc
O
N
H
4e
9
8
7
6
5
4
3
2
1
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ppm
0.95
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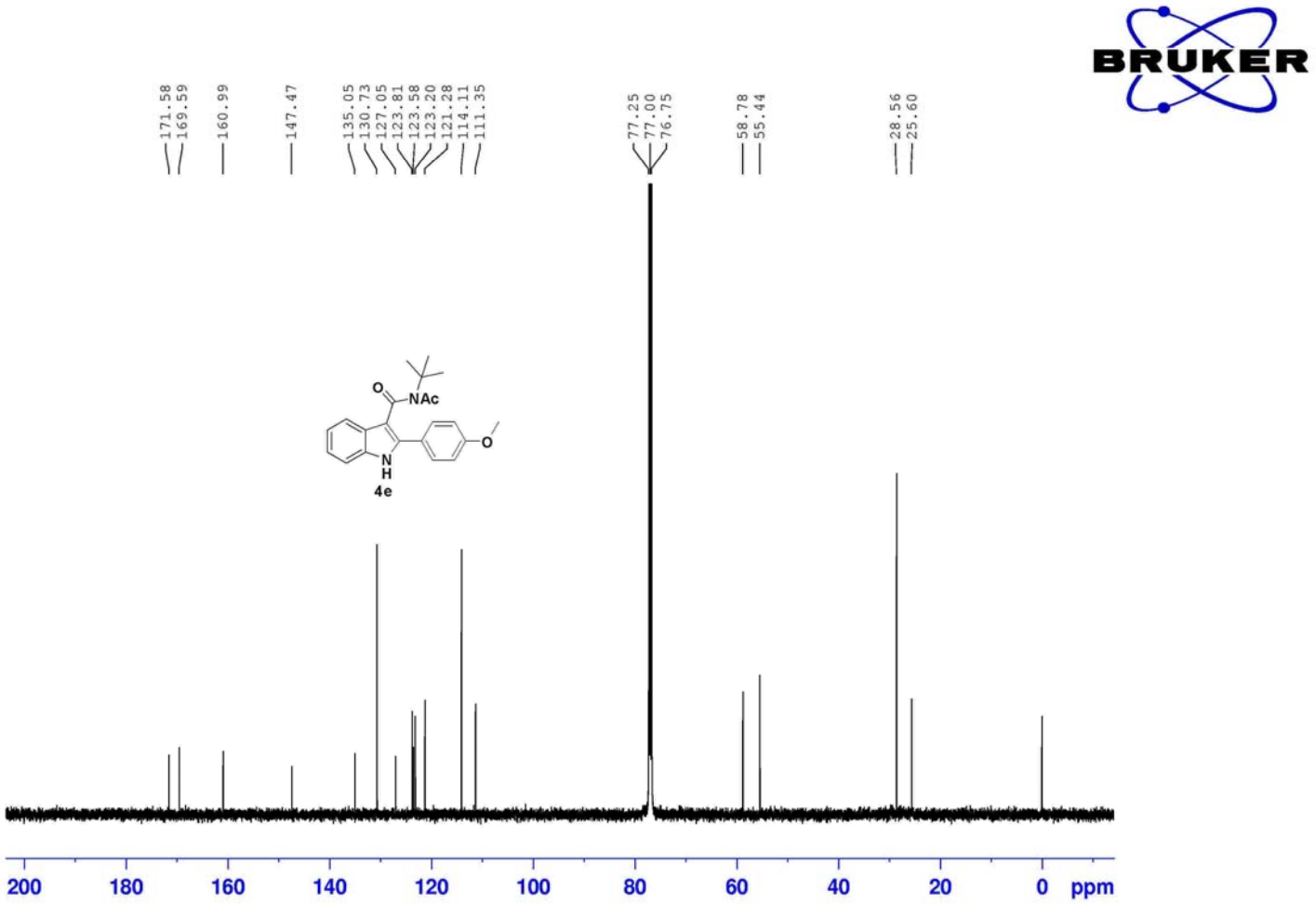
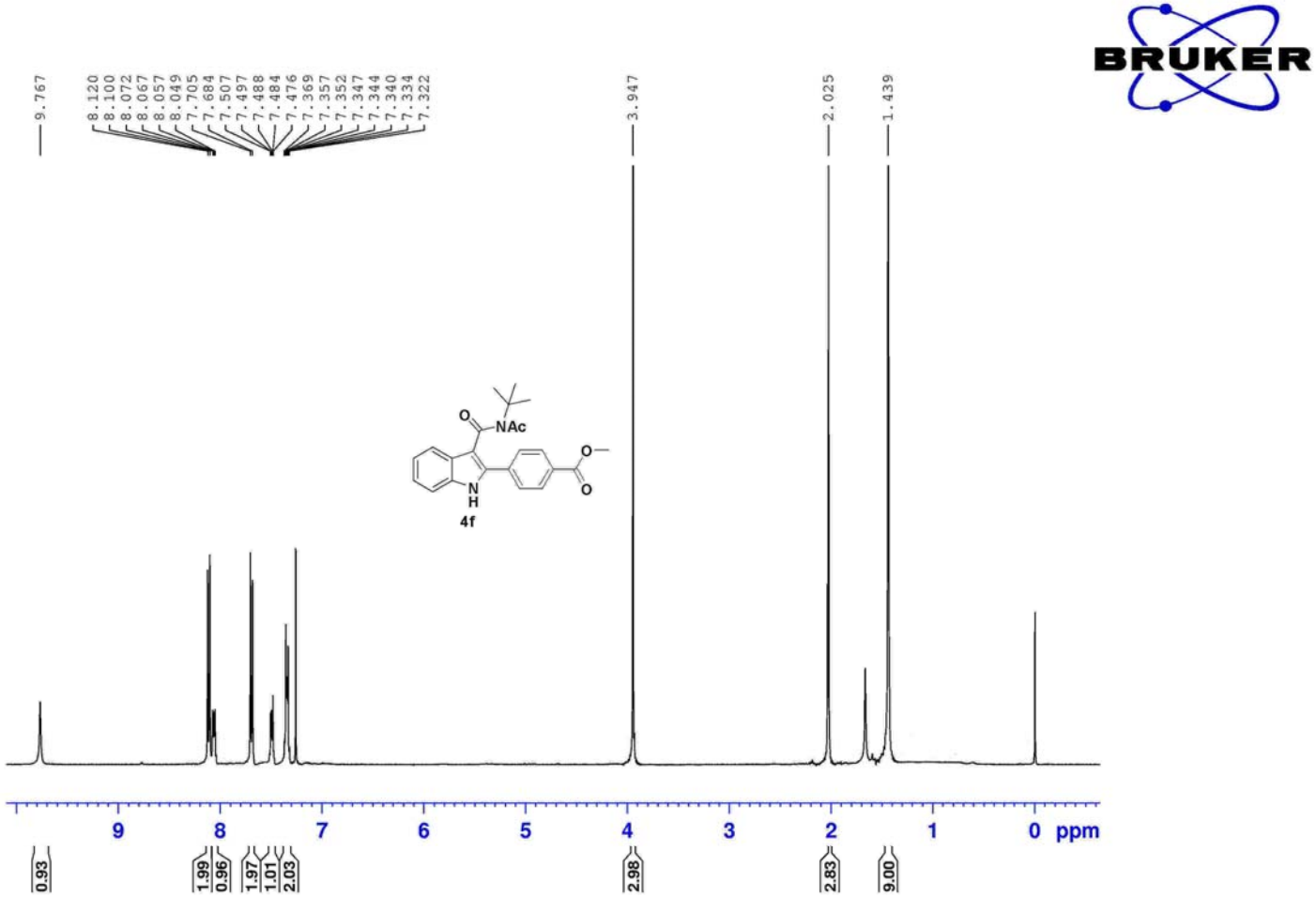
2.01
1.04
2.08
2.01
3.00
3.04
8.94

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8.100
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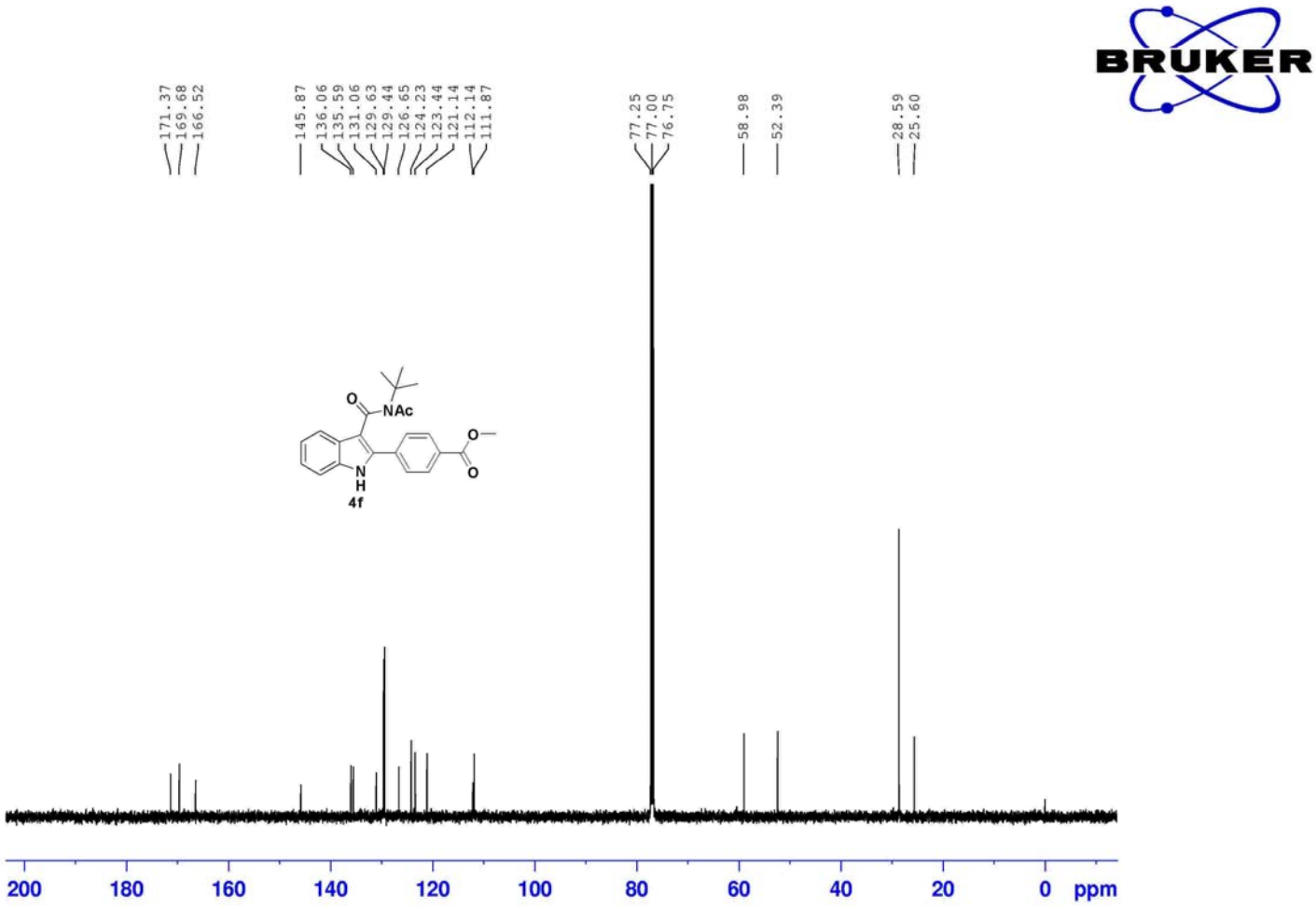
7.684
7.507
7.497
7.488
7.484
7.476
7.369
7.357
7.352
7.347
7.344
7.340
7.334
7.322
3.947
2.025
1.439
NAc
O
O
O
N
H
4f
9
8
7
6
5
4
3
2
1
0 ppm
0.93
1.99
0.96
1.97
1.01
2.03
2.98
2.83
9.00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135.59
131.06
129.63
129.44
126.65
124.23
123.44
121.14
112.14
111.87
77.25
77.00
76.75
58.98
52.39
28.59
25.60
O
NAc
O
O
N
H
4f
200
180
160
140
120
100
80
60
40
20
0
ppm