Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry
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Ruthenium-catalyzed C–H/O–H and C–H/N–H bonds functionalization: oxidative annulation of cyclopropyl-substituted alkynes

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Electronic Supplementary Material

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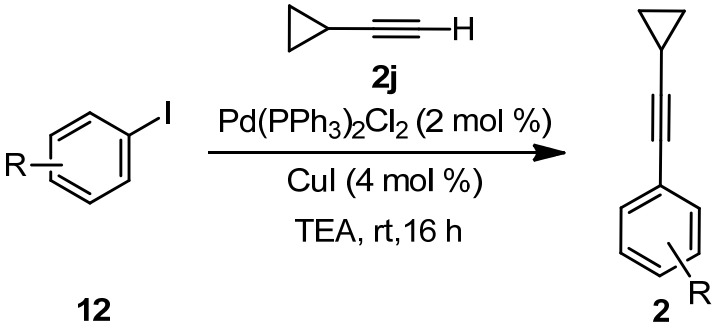
Chemicals and Instrumentation

Catalytic reactions were carried out using pre-dried glassware. Triethylamine and *t*AmOH were distilled over CaH_2 and sodium, respectively. Anhydrous THF was obtained by distillation over sodium benzophenone ketyl. (Cyclopropylethynyl)benzene (**2a**),[1,2a] 1-(cyclopropylethynyl)-3-methylbenzene (**2b**),[2] methyl 4-(cyclopropylethynyl)benzoate (**2c**),[3] 1-(cyclopropylethynyl)naphthalene (**2d**),[3b] 1-(cyclopropylethynyl)-4-methoxylbenzene (**2f**)[3] and previously unknown 1-(cyclopropylethynyl)-3-(trifluoromethyl)benzene (**2e**) were prepared by Sonogashira coupling[4] applying the published procedure[1b] (Table 1). (Pent-1-ynyl)cyclopropane (**2h**) was prepared by alkylation of cyclopropylacetylene (**j**) adopting the slightly modified published procedures[5] (Scheme 1). 1,2-Dicyclopropylethyne (**2g**),[6] $[RuCl_2(p\text{-cymene})]_2$[7], *N*-cyclopropylbenzamide (**5e**),[8a] *N*,3-dimethylbenzamide (**5f**),[8b] 4-chloro-*N*-methylbenzamide (**5g**),[8b] 4-methoxy-*N*-methylbenzamide (**5h**)[8c] and 4-fluoro-*N*-methylbenzamide (**5i**)[8a] were synthesized employing the published protocols. Other chemicals were obtained from commercial sources and were used without further purification. Yields refer to isolated compounds, estimated to be >95 % pure as determined by ^{1}H-NMR and GC. TLC: Macherey-Nagel, TLC plates Alugram® Sil G/UV_{254}. Detection under UV light at 254 nm. Chromatography: Separations were carried out on Merck Silica 60 (0.040–0.063 mm, 70–230 mesh ASTM). All IR spectra were recorded on a BRUKER ALPHA-P spectrometer. MS: EI-MS: Finnigan MAT 95, 70 eV; ESI-MS: Finnigan LCQ. High resolution mass spectrometry (HRMS): APEX IV 7T FTICR, Bruker Daltonic. M.p.: Stuart® Melting Point Apparatus SMP3 melting point apparatus, values are uncorrected. ^{1}H, ^{13}C, ^{19}F NMR-spectra were recorded at 300 (^{1}H) and at 600 (^{1}H), 75.5 {^{13}C, APT (Attached Proton Test)} and 283 MHz (^{19}F), respectively, on Varian Unity-300 instrument.

Experimental details

1. Starting materials

Table 1 Synthesis of cyclopropyl-substituted arylalkynes **2** by Sonogashira coupling



12 **2**

Entry	R (Ar–I)	Product **2**	Yield (%)
1	H	**2a**	84
2	3-Me	**2b**	94
3	4-CO_2Me	**2c**	98
4	(1-Naphthyl iodide)	**2d**	92
5	3-CF_3	**2e**	98
6	4-OMe	**2f**	91

1-(Cyclopropylethynyl)-3-(trifluoromethyl)benzene (2e): To a solution of 1-iodo-3-(trifluoromethyl)benzene (10 g, 5.3 mL, 37 mmol) in anhydrous Et_3N (60 mL) were added in one portion $Pd(PPh_3)_2Cl_2$ (516 mg, 0.7 mmol, 2 mol %) and CuI (280 mg, 1.5 mmol, 4 mol %). Under vigorous stirring, ethynylcyclopropane (**2j**) (2.4 g, 3.1 mL, 37 mmol) was added dropwise at ambient temperature for the period of 20 min, and the reaction mixture was stirred for an additional 16 h at the same temperature. The reaction mixture was washed with saturated NH_4Cl (1 × 200 ml), the aqueous layer was extracted with *n*-hexane (3 × 50 mL) and the combined organic layers were dried over $MgSO_4$. After filtration and concentration of the solution under reduced pressure, the crude product was purified by column chromatography on silica gel eluting with *n*-hexane to yield **2e** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.63 (s, 1H), 7.56–7.45 (m, 2H), 7.41–7.34 (m, 1H), 1.46 (tt, J = 8.2, 5.1 Hz, 1H), 0.95–0.79 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 134.8 (CH), 130.9 (q, J = 32.6 Hz, C), 128.8 (CH), 128.5 (q, J = 3.8 Hz, CH), 125.1 (C), 124.1 (q, J = 3.8 Hz, CH),

123.9 (q, J = 272.5 Hz, C), 95.5 (C), 74.6 (C), 8.8 (CH_2), 0.2 (CH); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -63.01 (s); IR (ATR): 3015, 2236, 1243, 1165, 1070, 798, 694 cm^{-1}; MS (EI) *m/z* (%): 210 (M^+, 100), 209 (25), 183 (20), 141 (90), 115 (30); HRMS (EI) *m/z* calcd for $C_{12}H_9F_3$ (M^+) 210.0656; found: 210.0693.

(Cyclopropylethynyl)benzene (2a): ^1H NMR (300 MHz, $CDCl_3$) δ = 7.40–7.34 (m, 2H), 7.28–7.22 (m, 3H), 1.49–1.39 (m, 1H), 0.91–0.74 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 131.7 (CH), 128.3 (CH), 127.6 (CH), 124.0 (C), 93.5 (C), 75.9 (C), 8.7 (CH_2), 0.3 (CH).

1-(Cyclopropylethynyl)-3-methylbenzene (2b): ^1H NMR (300 MHz, $CDCl_3$) δ = 7.26–7.10 (m, 3H), 7.08–7.02 (m, 1H), 2.30 (s, 3H), 1.48–1.38 (m, 1H), 0.89–0.73 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.9 (C), 132.4 (CH), 128.8 (CH), 128.5 (CH), 128.2 (CH), 123.8 (C), 93.1 (C), 76.0 (C), 21.3 (CH_3), 8.7 (CH_2), 0.3 (CH).

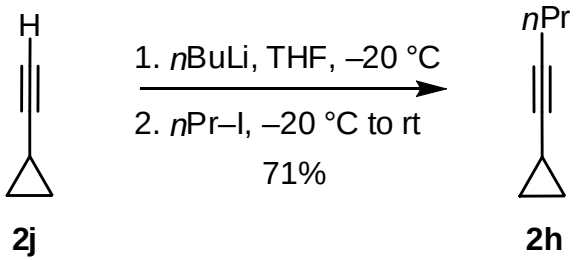
Methyl 4-(Cyclopropylethynyl)benzoate (2c): ^1H NMR (300 MHz, $CDCl_3$) δ = 7.96–7.89 (m, 2H), 7.44–7.38 (m, 2H), 3.89 (s, 3H), 1.51–1.41 (m, 1H), 0.94–0.79 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.8 (C), 131.6 (CH), 129.5 (CH) , 129.0 (C), 128.9 (C), 97.2 (C), 75.5 (C), 52.3 (CH_3), 8.9 (CH_2), 0.4 (CH).

1-(Cyclopropylethynyl)naphthalene (2d): ^1H NMR (300 MHz, $CDCl_3$) δ = 8.35–8.29 (m, 1H), 7.85–7.80 (m, 1H), 7.78 (d, J = 8.3, 1H), 7.64 (dd, J = 7.2, 1.2 Hz, 1H), 7.59–7.46 (m, 2H), 7.42–7.38 (m, 1H), 1.67–1.57 (m, 1H), 1.01–0.89 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 133.5 (C), 133.1 (C), 130.0 (CH), 128.1 (CH), 127.8 (CH), 126.4 (CH), 126.2 (CH), 126.2 (CH), 125.2 (CH), 121.5 (C), 98.5 (C), 73.7 (C), 8.9 (CH_2), 0.6 (CH).

1-(Cyclopropylethynyl)-4-methoxylbenzene (2f): ^1H NMR (300 MHz, $CDCl_3$) δ = 7.28 (dd, J = 8.8, 2.1 Hz, 1H), 6.77 (dd, J = 8.8, 2.1 Hz, 2H), 6.76 (d, J = 2.1 Hz, 1H), 3.79 (s, 3H), 1.4 (m, 1H), 0.89–0.76 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 158.9 (C), 132.9 (CH), 116.0 (C), 113.8 (CH), 91.7 (C), 75.4 (C), 55.2 (CH_3), 8.5 (CH_2), 0.1 (CH)

These spectral data were identical to the previously published ones.[1–3]

(Pent-1-ynyl)cyclopropane (**2h**)[9] was prepared by alkylation of cyclopropylacetylene (**2j**) adopting the modified published procedures[5] (Scheme 1).



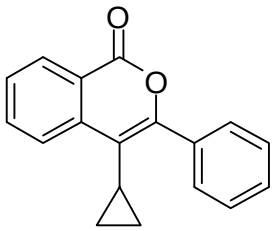
Scheme 1 Synthesis of (pent-1-ynyl)cyclopropane (1-cyclopropyl-2-*n*-propylacetylene, **2h**).

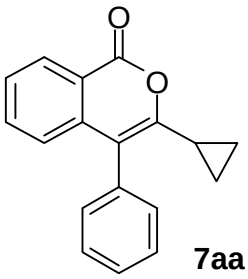
To a cold (–20°C), stirred solution of ethynylcyclopropane (**2j**) (6.61 g, 8.50 mL, 100 mmol), in anhydrous THF (250 mL) was added dropwise *n*BuLi (2.5 M in hexanes, 95 mmol) for the period of 0.5 h. The reaction mixture was stirred for 15 min and then the *n*PrI (14.45 g, 9.8 mL, 85 mmol) was added dropwise for the period of 10 min. Under stirring, the reaction mixture was allowed to warm up to ambient temperature overnight. The THF was distilled off by "bulb to bulb distillation", and the product was purified by fractionated distillation (b.p. 75–78 °C at 125 mbar) to yield **2h** as a colorless oil (6.53 g, 71%): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.06 (td, J = 7.3, 2.0 Hz, 2H), 1.45 (sext, J = 7.3 Hz, 2H), 1.20–1.09 (m, 1H), 0.92 (t, J = 7.3 Hz, 3H), 0.69–0.61 (m, 2H), 0.59–0.51 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 83.4 (C), 75.6 (C), 22.6 (CH_2), 20.9 (CH_2), 13.5 (CH_3), 8.0 (CH_2), –0.4 (CH). IR (ATR):3014, 2934, 2873, 1458, 1049, 895, 872 cm^{-1}; MS (EI) *m/z* (%): 210 (M^+, 5), 108 (30), 91 (40), 79 (55), 77 (100); HRMS (EI) *m/z* calcd for C_8H_{12} $(M)^+$ 108.0939; found: 108.0935.

Synthesis of cyclopropyl-substituted isocoumarins 6 and 7

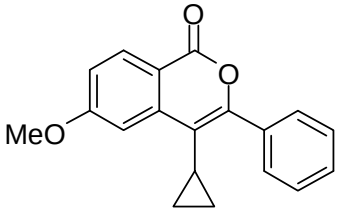
General procedure for ruthenium-catalyzed C–H/O–H bond functionalizations in benzoic acids 4 with ethynylbenzenes 2

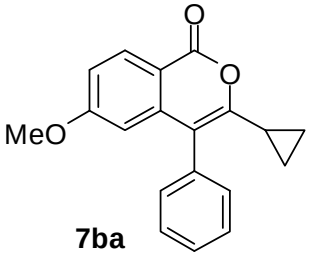
A suspension of acid **4** (2.00 mmol), alkyne **2** (1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.5 mg, 2.5 mol %), KPF_6 (37.0 mg, 20 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (300 mg, 1.50 mmol) in *t*AmOH (3.0 mL) was stirred at 120 °C for 16 h. After cooling to ambient temperature, the reaction mixture was diluted with sat. aq. NH_4Cl/NH_3 solution (1:1, 50 mL) and extracted with EtOAc (4 × 25 mL). The combined organic layers were washed with NH_4Cl/NH_3 solution (1:1, 2 × 20 mL) and dried over $MgSO_4$. After filtration and concentration of the solution under reduced pressure, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc 25:1) to yield **6** and **7** as colorless solids.


6aa


7aa

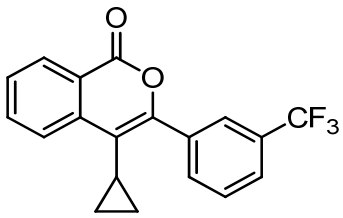
4-Cyclopropyl-3-phenyl-1*H*-isochromen-1-one (6aa) and 3-Cyclopropyl-4-phenyl-1*H*-isochromen-1-one (7aa): According to the general procedure, benzoic acid (**4a**) (490 mg, 4.0 mmol), alkyne (**2a**) (284 mg, 2.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (62.0 mg, 100 μmol), KPF_6 (73.0 mg, 0.4 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (599 mg, 3.0 mmol) yielded **6aa** (351 mg, 67%) and **7aa** (57 mg, 11 %) as colorless solids. **6aa**: m.p. = 115–117 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.33 (dd, J = 8.0, 1.4 Hz, 1H), 8.12 (d, J = 8.2, 1H), 7.78 (td, J = 7.7, 1.4 Hz, 1H), 7.76–7.72 (m, 2H), 7.50 (td, J = 7.7, 1.1 Hz, 1H), 7.46–7.37 (m, 3H), 1.91 (tt, J = 8.1, 5.5 Hz, 1H), 1.00–0.87 (m, 2H), 0.26–0.06 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.5 (C), 153.6 (C), 139.8 (C), 134.6 (CH), 133.3 (C), 129.6 (CH), 129.6 (CH), 129.5 (CH), 127.9 (CH), 127.9 (CH), 124.7 (CH), 120.7 (C), 114.6 (C), 10.0 (CH_2), 9.2 (CH); IR (ATR): 3084, 3049, 3008, 2984, 1727, 1604, 1075, 672 cm^{-1}; UV (MeOH): λ = 340,284,234, 210 nm; MS (EI) *m/z* (relative intensity): 262 (M^+, 50), 217 (45), 185 (40), 105 (55), 77 (100); HRMS (EI) calcd for $C_{18}H_{14}O_2$ (M^+) 262.0994, found: 262.0996. **7aa**: m.p. = 100–102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.20 (dd, J = 7.9, 1.6 Hz, 1H), 7.57–7.33 (m, 7H), (ddd, J = 8.1, 1.1, 0.5 Hz, 1H), 1.58 (m, 1H), 1.21–1.12 (m, 2H), 0.81–0.70 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.2 (C), 154.4 (C), 139.0 (C), 134.6 (CH), 134.4 (C), 131.1 (CH), 129.5 (CH), 129.0 (CH), 128.1 (CH), 126.9 (CH), 124.1 (CH), 119.7 (C), 115.2 (C), 12.1 (CH), 7.8 (CH_2); IR (ATR): 3011, 2961, 2922, 2855, 1718, 1629, 1078, 700 cm^{-1}, MS (EI) *m/z* (relative intensity): 262 (M^+,100), 247 (50), 234 (38), 165 (64), 69 (25), 41 (20); HRMS (EI) calcd for $C_{18}H_{14}O_2$ (M^+) 262.0994, found: 262.0988. UV (Hexane): λ =333, 289, 278,244, 224. The structures of compounds **6aa** and **7aa** were established by X-ray crystal structure analysis.[10]


6ba


7ba

4-Cyclopropyl-6-methoxy-4-phenyl-1*H*-isochromen-1-one (6ba) and 3-Cyclopropyl-6-methoxy-3-phenyl-1*H*-isochromen-1-one (7ba): According to the general procedure, *p*-anisic acid (**4b**) (608 mg, 4.0 mmol), alkyne (**2a**) (284 mg, 2.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (31 mg, 50 μmol), KPF_6 (73 mg, 0.4 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (599 mg, 3.0 mmol) yielded **6ba** (309 mg, 53%) and **7ba** (23

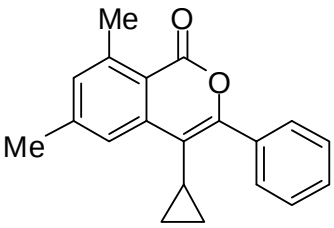
mg, 4%) after column chromatography as colorless solids. **6ba**: m.p. = 144–146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.27 (d, J = 8.8 Hz, 1H), 7.75–7.71 (m, 2H), 7.50 (d, J = 2.5 Hz, 1H), 7.46–7.40 (m, 3H), 7.06 (dd, J = 8.8, 2.5 Hz, 1H), 3.97 (s, 3H), 1.88 (tt, J = 8.1, 5.5 Hz, 1H), 0.98–0.88 (m, 2H), 0.23–0.15 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 164.6 (C), 162.3 (C), 154.2 (C), 142.2 (C), 133.4 (C), 132.0 (CH), 129.6 (CH), 129.6 (CH), 129.5 (CH), 127.9 (CH), 115.5 (CH), 114.4 (C), 113.9 (C), 107.7 (CH), 55.7 (CH_3), 10.0 (CH_2), 9.2 (CH); IR (ATR): 3005, 2956, 2856, 1711, 1600, 1444, 1226, 831 cm^{-1}; MS (EI) *m/z* (%): 292 (M^+, 95), 217 (36), 215 (77), 105 (90), 77 (100); HRMS (EI) calcd for $C_{19}H_{16}O_3$ (M^+) 292.1099; found: 292.1099. **7ba**: m.p. = 126–128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.22 (d, J = 8.8 Hz, 1H), 7.54–7.34 (m, 5H), 6.94 (dd, J = 8.8, 2.5 Hz, 1H), 6.35 (d, J = 2.5 Hz, 1H), 3.72 (s, 3H), 1.67–1.55 (m, 1H), 1.23–1.13 (m, 2H), 0.85–0.74 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 164.6 (C), 162.0 (C), 155.0 (C), 141.4 (C), 134.5 (C), 131.9 (CH), 131.1 (CH), 129.0 (CH), 128.0 (C), 115.1 (C), 114.6 (CH), 113.0 (C), 107.1 (CH), 55.6 (CH_3), 12.2 (CH), 7.8 (CH_2); IR (ATR): 3009, 2925, 1713, 1600, 1231, 1044, 849, 723 cm^{-1}; MS (EI) *m/z* (%): 292 (M^+, 100), 277 (32), 264 (55), 195 (35), 152 (50); HRMS (EI) calcd for $C_{19}H_{16}O_3$ (M^+) 292.1099, found: 292.1105.



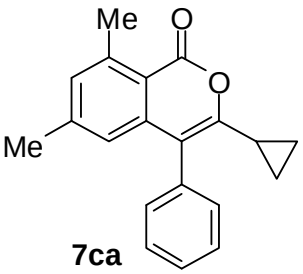
6ae

4-Cyclopropyl-3-(3-(trifluoromethyl)phenyl)-1*H*-isochromen-1-one (6ae): According to the general procedure, benzoic acid (**4a**) (488 mg, 4.0 mmol), alkyne (**2e**) (420 mg, 2.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (31 mg, 50 μmol), KPF_6 (73 mg, 0.4 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (599 mg, 3.0 mmol) yielded **6ae** (137 mg, 21%) after column chromatography as a colorless solid, m.p. = 117–119 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.34 (ddd, J = 7.9, 1.4, 0.6 Hz, 1H), 8.13 (d, J = 8.3 Hz, 1H), 8.03 (s, 1H), 7.95 (d, J = 7.8 Hz, 1H), 7.82 (ddd, J = 8.3, 7.3, 1.4 Hz, 1H), 7.6 (d, J = 7.8, 1H), 7.61–7.51 (m, 2H), 1.94 (tt, J = 8.1, 5.5 Hz, 1H), 1.02–0.93 (m, 2H), 0.21–0.13 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.0 (C), 151.6 (C), 139.2 (C), 134.7 (CH), 133.9 (C), 132.5 (CH), 130.3 (q, J_{C-F}= 32.6 Hz, C), 129.6 (CH), 128.4 (CH), 128.3 (CH), 126.4 (q, J_{C-F} = 3.8 Hz, CH), 125.9 (q, J_{C-F} = 3.8 Hz, CH), 124.7 (CH), 123.9 (q, J_{C-F} = 272 Hz, C), 120.7 (C), 115.6 (C), 10.0 (CH_2), 8.9 (CH); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -62.68. IR (ATR): 3080, 3013, 2926, 1724, 1602, 1332, 1226, 801 cm^{-1}; MS (EI) *m/z* (%): 330 (M^+, 77), 274 (43), 217 (67), 185 (98), 173 (90), 145 (100); HRMS (EI) calcd for $C_{19}H_{13}F_3O_2$ (M^+)

330.0868; found: 330.0868. The structure of compound **6ae** was established by X-ray crystal structure analysis.[10]

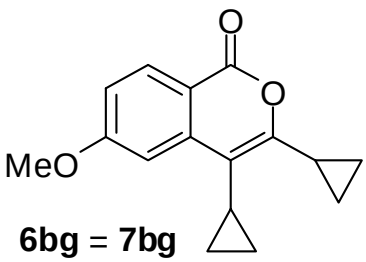


6ca



7ca

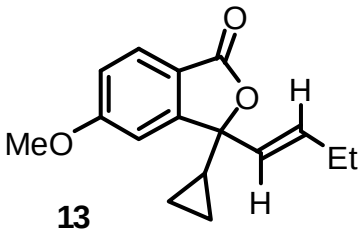
4-Cyclopropyl-6,8-dimethyl-3-phenyl-1*H*-isochromen-1-one (6ca) and 3-Cyclopropyl-6,8-dimethyl-4-phenyl-1*H*-isochromen-1-one (7ca): According to the general procedure, 2,4-dimethylbenzoic acid (**4c)** (601 mg, 4.0 mmol) alkyne (**2a)** (284 mg, 2.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (31 mg, 50 μmol), KPF_6 (73 mg, 0.4 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (599 mg, 3.0 mmol) yielded **6ca** (412 mg, 71%) and **7ca** (69 mg, 12%) after column chromatography as colorless solids. **6ca**: m.p. = 153–155 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.74 (s, 1H), 7.73–7.68 (m, 2H), 7.45–7.35 (m, 3H), 7.11 (s, 1H), 2.80 (s, 3H), 2.47 (s, 3H), 1.83 (tt, J = 8.1, 5.5 Hz, 1H), 0.94–0.85 (m, 2H), 0.17–0.10 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 161.4 (C), 153.1 (C), 144.2 (C), 142.9 (C), 141.2 (C), 133.3 (C), 131.9 (CH), 129.4 (CH), 129.0 (CH), 127.6 (CH), 122.6 (CH), 116.6 (C), 114.3 (C), 23.3 (CH_3), 22.2 (CH_3), 10.2 (CH_2), 9.5 (CH); IR (ATR): 2964, 2922, 2854, 1715, 1602, 1444, 712 cm^{-1}; MS (EI) *m/z* (%): 290 (M^+, 100), 275 (30), 262 (48), 193 (46), 178 (27), 69 (38), 41 (45); HRMS (EI) calcd for $C_{20}H_{18}O_2$ (M^+) 290.1307; found: 290.1310. **7ca**: m.p. = 131–133 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.53–7.38 (m, 3H), 7.36–7.29 (m, 2H), 6.99 (s, 1H), 6.53 (s, 1H), 2.77 (s, 3H), 2.23 (s, 3H), 1.51 (m, 1H), 1.18–1.08 (m, 2H), 0.77–0.67 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 161.4 (C), 153.9 (C), 144.4 (C), 143.1 (C), 140.5 (C), 135.1 (C), 131.1 (CH), 131.0 (CH), 128.8 (CH), 127.7 (CH), 122.3 (CH), 115.7 (C), 115.0 (C), 23.4 (CH_3), 21.9 (CH_3), 11.8 (CH), 7.3 (CH_2); IR (ATR): 3000, 2923, 1719, 1605, 1029, 694, 667 cm^{-1}; MS (EI) *m/z* (%): 290 (M^+, 100), 275 (72), 231 (64), 213 (40), 105 (85), 77 (83); HRMS (EI) calcd for $C_{20}H_{18}O_2$ (M^+) 290.1307; found: 290.1306.



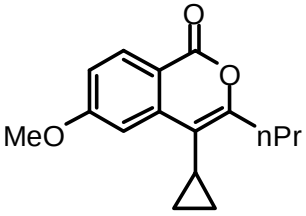
6bg = 7bg

3,4-Dicyclopropyl-6-methoxy-1*H*-isochromen-1-one (6bg = 7bg): According to the general procedure, *p*-anisic acid (**4b**) (608 mg, 4.0 mmol), alkyne (**2g**) (212 mg, 2.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (31 mg, 50 μmol), KPF_6 (73 mg, 0.4 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (599 mg, 3.0 mmol) yielded **6bg = 7bg** (138 mg,

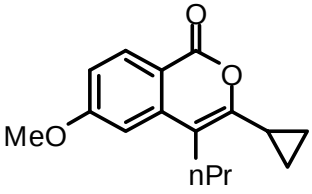
27%) after column chromatography as a colorless solid, m.p. = 91–93 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.11 (d, J = 8.8 Hz, 1H), 7.30 (d, J = 2.5 Hz, 1H), 6.91 (dd, J = 8.8, 2.5 Hz, 1H), 3.90 (s, 3H), 2.40 (tt, J = 8.4, 5.1 Hz, 1H), 1.67 (m, 1H), 1.17–1.05 (m, 4H), 0.94–0.86 (m, 2H), 0.67–0.60 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 164.3 (C), 162.0 (C), 157.0 (C), 141.8 (C), 131.7 (CH), 114.2 (CH), 113.0 (C), 112.0 (C), 106.1 (CH), 55.4 (CH_3), 11.6 (CH), 7.9 (CH_2), 7.3 (CH), 7.2 (CH_2); IR (ATR): 3011, 2982, 2923, 2849, 1712, 1600, 1401, 678 cm^{-1}; MS (ESI): m/z (%) = 535 $[2M + Na]^+$ (100), 513 $[2M + H]^+$ (40), 279 $[M + Na]^+$ (20), 257 $[M + H]^+$) (60); HRMS (ESI) calcd for $C_{16}H_{17}O_3$ $[M+H]^+$ 257.1172; found: 257.1176. In the NMR spectra of crude **6bg = 7bg**, traces of a by-product with the same molecular mass as the one of product **7bg** were observed. Partial NMR spectra of this by-product, i. e. the signals which were not overlapped with the signals of **6bg = 7bg** [^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.93 (dt, J = 15.6, 6.3 Hz, 1H), 5.59 (dt, J = 15.6, 1.5 Hz, 1H), 2.05 (td J = 6.8, 1.5 Hz, 3H), 1.93 (d, J = 6.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 135.0 (CH), 127.2 (CH), 25.3 (CH_2), 18.7 (CH_3), 1.7 (CH_2), 0.8 (CH_2)], indicate **13** as the possible structure. However, **13** was not isolated by column chromatography.



13



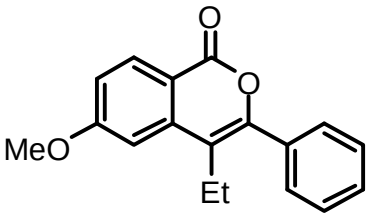
6bh



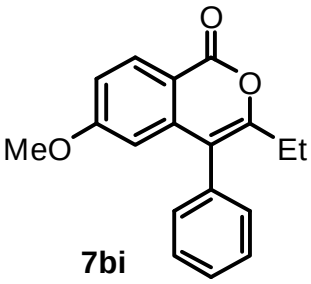
7bh

4-Cyclopropyl-6-methoxy-3-propyl-1*H*-isochromen-1-one (6bh) and 3-Cyclopropyl-6-methoxy-4-propyl-1*H*-isochromen-1-one (7bh): According to the general procedure, *p*-anisic acid (**4b**) (608 mg, 4.0 mmol), alkyne (**2h**) (216 mg, 2.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (31 mg, 50 µmol), KPF_6 (73 mg, 0.4 mmol) and $Cu(OAc)_2 \cdot H_2O$ (599 mg, 3.0 mmol) yielded 274 mg (53%) of **6bh** and **7bh** as an 1:1 unseparable mixture after column chromatography as a colorless solid. **6bh/7bh 1:1 mixture**: m.p. = 153–155 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.18 (d, J = 8.8 Hz, 1H), 8.18 (d, J = 8.8 Hz, 1H), 7.36 (d, J = 2.5 Hz, 1H), 6.97 (dd, J = 8.8, 2.5 Hz, 1H), 6.93 (dd, J = 8.8, 2.4 Hz, 1H), 6.85 (d, J = 2.4 Hz, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 2.73 (ddd, J = 8.6, 6.4, 0.8 Hz, 2H), 2.68–2.64 (m, 2H), 1.97 (tt, J = 8.3, 5.0 Hz, 1H), 1.76–1.69 (m, 2H), 1.67–1.57 (m, 3H),

1.17–1.12 (m, 2H), 1.11–1.06 (m, 2H), 1.02 (t, J = 7.4 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H), 0.91–0.87 (m, 2H), 0.54 (td, J = 6.0, 4.3 Hz, 2H); ^{13}C NMR (76 MHz, $CDCl_3$) δ = 164.6 (C), 164.3 (C), 162.6 (C), 162.1 (C), 157.9 (C), 153.9 (C), 141.6 (C), 140.5 (C), 132.2 (CH), 131.7 (CH), 114.7 (CH), 113.7 (CH), 113.6 (C), 113.5 (C), 112.9 (C), 111.2 (C), 106.0 (CH), 105.5 (CH), 55.5 (CH_3), 33.0 (CH_2), 27.7 (CH_2), 22.4 (CH_2), 20.9 (CH_2), 14.1 (CH_3), 13.9 (CH_3), 11.1 (CH), 7.9 (CH_2), 7.8 (CH), 7.1 (CH_2); IR (ATR): 2954, 2931, 2872, 1708, 1600, 1227, 776 cm^{-1}; MS (EI) *m/z* (%): 258 (M^+ 68), 229 (100), 215 (78), 201 (35), 187 (40), 159 (43), 43 (33); HRMS (EI) calcd for $C_{16}H_{18}O_3$ (M^+) 258.1256; found: 258.1259.



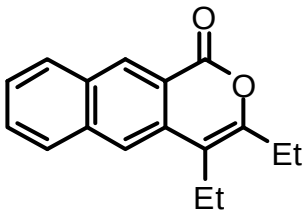
6bi



7bi

4-Ehyl-6-methoxy-3-phenyl-1*H*-isochromen-1-one (6bi) and 3-Ehyl-6-methoxy-4-phenyl-1*H*-isochromen-1-one (7bi): According to the general procedure, *p*-anisic acid (**4b**) (913 mg, 6.0 mmol), alkyne (**2i**) (260 mg, 2.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (31 mg, 50 µmol), KPF_6 (73 mg, 0.4 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (599 mg, 3.0 mmol) yielded **6bi** (263 mg, 47%) and **7bi** (28 mg, 5%) after column chromatography as colorless solids. **6bi**: m.p. = 140–142 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.30 (d, J = 8.7 Hz, 1H), 7.57–7.50 (m, 2H), 7.47–7.40 (m, 3H), 7.06 (dd, J = 8.7, 2.4 Hz, 1H), 7.02 (d, J = 2.4 Hz, 1H), 3.93 (s, 3H), 2.66 (q, J = 7.5 Hz, 2H), 1.26 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 164.7 (C), 162.1 (C), 151.9 (C), 139.9 (C), 133.5 (C), 132.3 (CH), 129.3 (CH), 128.9 (CH), 128.3 (CH), 115.0 (CH), 115.0 (C), 114.5 (C), 106.9 (CH), 55.6 (CH_3), 20.2 (CH_2), 14.6 (CH_3); IR (ATR): 2964, 2936, 2877, 1705, 1601, 1230, 774 cm^{-1}; MS (EI) *m/z* (%): 280 (M^+, 88), 237 (100), 265 (40), 238 (18), 105 (34), 77 (40); HRMS (EI) calcd for $C_{18}H_{16}O_3$ (M^+) 280.1099; found: 280.1099. **7bi**: m.p. = 88–91 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.27 (d, J = 8.8 Hz, 1H), 7.52–7.43 (m, 3H), 7.29–7.24 (m, 2H), 6.99 (dd, J = 8.8, 2.5 Hz, 1H), 6.33 (d, J = 2.5 Hz, 1H), 3.72 (s, 3H), 2.36 (q, J = 7.5 Hz, 2H), 1.18 (dd, J = 7.8, 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 164.5 (C), 162.5 (C), 156.8 (C), 141.2 (C), 134.4 (C), 131.8 (CH), 130.5 (CH), 128.9 (CH), 128.1 (CH), 115.6 (C), 114.9 (CH), 113.4 (C), 107.8 (CH), 55.4 (CH_3), 25.1 (CH_2), 12.4 (CH_3); IR (ATR): 3057, 2962, 2920, 2849, 1719, 1600, 763 cm^{-1}; MS (EI) *m/z* (%): 280 (M^+, 100), 251 (92), 224 (38),

223 (30), 195 (32), 152 (44), 135 (26); HRMS (EI) calcd for $C_{18}H_{16}O_3$ (M^+) 280.1099; found: 280.1103.

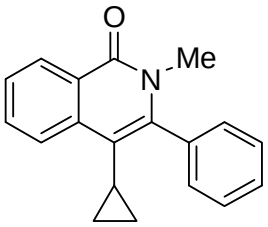


3,4-Diethyl-1*H*-benzo[*g*]isochromen-1-one (6dk): According to the general procedure, 2-naphthoic acid (**4d)** (688 mg, 4.0 mmol) diethylethyne (164 mg, 2.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (31 mg, 50 µmol), KPF_6 (73 mg, 0.4 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (599 mg, 3.0 mmol) yielded **6dk** (158 mg, 31%) after column chromatography as a colorless solid, m.p. = 82–84 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.94 (s, 1H), 8.00 (dd, J = 8.3, 1.4 Hz, 1H), 7.97 – 7.90 (m, 2H), 7.63 (ddd, J = 8.3, 6.7, 1.4 Hz, 1H), 7.53 (ddd, J = 8.1, 6.7, 1.2 Hz, 1H), 2.76 (q, J = 7.5 Hz, 2H), 2.65 (q, J = 7.5 Hz, 2H), 1.32 (t, J = 7.5 Hz, 3H), 1.29 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 163.2 (C), 153.4 (C), 136.5 (C), 132.6 (C), 132.0 (CH), 131.5 (C), 129.4 (CH), 129.1 (CH), 127.9 (CH), 126.4, (CH) 120.9 (CH), 119.5 (C), 112.8 (C), 24.1 (CH_2), 19.6 (CH_2), 14.3 (CH_3), 12.5 (CH_3); IR (ATR): 2959, 2924, 1719, 1626, 1105, 753, 472 cm^{-1}; MS (EI) *m/z* (%): 252 (M^+, 100), 237 (58), 181 (60), 165 (60), 155 (75), 152 (40), 127 (38); HRMS (EI) calcd for $C_{17}H_{16}O_2$ (M^+) 252.1150; found: 252.1159.

Synthesis of Cyclopropyl Substituted Isoquinolones 8 and 9

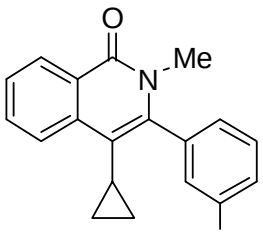
General Procedure for Ruthenium-Catalyzed C–H/N–H Bonds Functionalizations of Benzamides 5 with (Cyclopropylethynyl)benzenes 2

A mixture of *N*-alkylbenzamide **5** (0.50 mmol), disubstituted acetylene (2.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 25 µmol, 5.0 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (200 mg, 1.00 mmol) in *t*AmOH (2.0 mL) was stirred at 100 °C under nitrogen atmosphere for 22 h. After cooling the mixture to ambient temperature, the reaction mixture was diluted with aq. NH_3 solution (75 mL, 1.0 wt %) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with brine (50 mL) and dried over Mg_2SO_4. After filtration and concentration of the solution under reduced pressure, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc 4/1) to yield **8** and **9** as colorless solids.

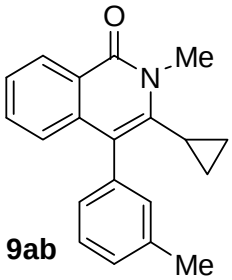


8aa

4-Cyclopropyl-2-methyl-3-phenylisoquinolin-1(2*H*)-one (8aa): According to the general procedure, *N*-methylbenzamide (**5a**) (135 mg, 1.0 mmol), alkyne **2a** (284 mg, 2.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (31 mg, 50 μmol), and $Cu(OAc)_2{\cdot}H_2O$ (399 mg, 2.0 mmol), yielded **8aa** (195 mg, 71%) after column chromatography as a colorless solid, m.p. = 139–141°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.49 (ddd, J = 8.0, 1.5, 0.6 Hz, 1H), 8.19 (ddd, J = 8.3, 1.2, 0.6 Hz, 1H), 7.68 (ddd, J = 8.4, 7.1, 1.5 Hz, 1H), 7.51–7.39 (m, 4H), 7.31–7.27 (m, 2H), 3.28 (s, 3H), 1.62 (tt, J = 8.3, 5.6 Hz, 1H), 0.69–0.55 (m, 2H), 0.17–0.05 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.8 (C), 142.9 (C), 138.0 (C), 135.7 (C), 131.7 (CH), 129.9 (CH), 128.4 (CH), 128.4 (CH), 127.9 (CH), 126.2 (CH), 125.1 (C), 124.4 (CH), 115.0 (C), 34.2 (CH_3), 10.5 (CH), 8.7 (CH_2); IR (ATR): 3081, 2994, 2957, 2924, 1643, 1587, 1025, 759 cm^{-1}; MS (EI) *m/z* (relative intensity): 275 (M^+ 32), 274 (100), 246 (15), 198 (27), 77 (30); HRMS (EI) calcd for $C_{19}H_{17}NO$ (M^+) 275.1310, found: 275.1298. The structure of compound **8aa** was established by X-ray crystal structure analysis.[10]



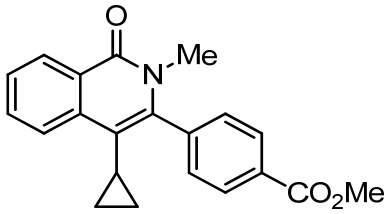
8ab



9ab

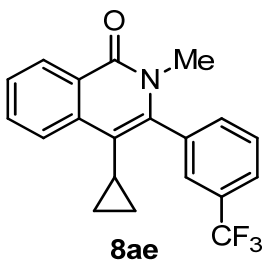
4-Cyclopropyl-2-methyl-3-(*m*-tolyl)-isoquinolin-1(2*H*)-one (8ab) and 3-Cyclopropyl-2-methyl-4-(*m*-tolyl)isoquinolin-1(2*H*)-one (9ab): According to the general procedure, *N*-methylbenzamide (**5a**) (135 mg, 1.0 mmol), alkyne (**2b**) (312 mg, 2.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (31 mg, 50 μmol), $Cu(OAc)_2{\cdot}H_2O$ (399 mg, 2.0 mmol) yielded **8ab** (176 mg, 61%) as a brown oil and **9ab** (49 mg, 17%) as colorless solids after column chromatography. **8ab**: ^{1}H NMR (300 MHz,$CDCl_3$) δ = 8.49 (ddd, J = 8.1, 1.5, 0.6 Hz, 1H), 8.19 (d, J = 8.3 Hz, 1H), 7.68 (ddd, J = 8.3, 7.1, 1.5 Hz, 1H), 7.48 (ddd, J = 8.1, 7.1, 1.2 Hz, 1H), 7.35 (m, 1H), 7.24 (d, J = 7.6 Hz, 1H), 7.14–7.03 (m, 2H), 3.28 (s, 3H), 2.41 (br. s, 3H), 1.62 (tt, J = 8.3, 5.6 Hz, 1H), 0.65–0.57 (m, 2H), 0.15–0.08 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.8 (C), 143.1 (C), 138.1 (C), 138.0 (C), 135.6 (C), 131.7 (CH), 130.5 (CH), 129.1 (CH), 128.3 (CH), 127.9 (CH), 127.0 (CH), 126.2 (CH), 125.1 (C), 124.3 (CH), 114.9 (C), 34.2 (CH_3), 21.4 (CH_3),

10.5 (CH), 8.7 (CH_2); IR (ATR): 3007, 2952, 2920, 1641, 1607, 1480, 1028, 701 cm^{-1}; MS (EI) *m/z* (%): 289 (M^+ 60), 288 (100), 274 (20), 259 (18), 246 (13), 198 (30); HRMS (EI) calcd for $C_{20}H_{19}NO$ (M^+) 289.1467; found: 289.1456. **9ab**: m.p. = 123–125 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.46 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.50–7.37 (m, 2H), 7.32 (m, 1H), 7.23–7.15 (m, 2H), 7.10–7.03 (m, 2H), 3.84 (s, 3H), 2.39 (s, 3H), 1.74 (tt, *J* = 8.4, 5.8 Hz, 1H), 0.78–0.68 (m, 2H), 0.34 (td, *J* = 6.2, 4.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCL_3$) δ = 163.0 (C), 140.0 (C), 137.7 (C), 137.0 (C), 136.9 (C), 132.1 (CH), 131.7 (CH), 128.5 (CH), 128.1 (CH), 127.8 (CH), 127.7 (CH), 126.1 (CH), 124.8 (CH), 124.6 (C), 119.8 (C), 32.2 (CH_3), 21.5 (CH_3), 13.9 (CH), 10.1 (CH_2); IR (ATR): 2954, 2823, 2853, 1630, 1583, 1023, 704 cm^{-1}; MS (EI) *m/z* (%): 289 (M^+, 100), 288 (38), 274 (70), 261 (35), 246 (20), 77 (30); HRMS (EI) calcd for $C_{20}H_{19}NO$ (M^+) 289.1467; found: 289.1464.



8ac

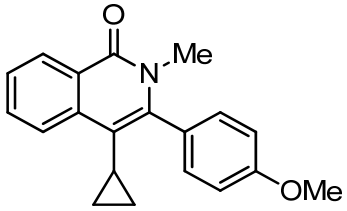
Methyl 4-(4-Cyclopropyl-2-methyl-1-oxo-1,2-dihydro-isoquinolin-3-yl)benzoate (8ac): According to the general procedure, *N*-methylbenzamide (**5a**) (135 mg, 1.0 mmol), alkyne **2c** (400 mg, 2.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (31 mg, 50 µmol), $Cu(OAc)_2{\cdot}H_2O$ (399 mg, 2.0 mmol) yielded **8ac** (136 mg, 41%) after column chromatography as a colorless solid. **8ac**: m.p. = 203–205 °C; ^{1}H NMR (300 MHz,$CDCl_3$) δ = 8.48 (ddd, *J* = 8.0, 1.5, 0.6 Hz, 1H), 8.20–8.13 (m, 3H), 7.69 (ddd, *J* = 8.3, 7.1, 1.5 Hz, 1H), 7.50 (ddd, *J* = 8.0, 7.1, 1.2 Hz, 1H), 7.48 (d, *J* = 8.1 Hz, 2H), 3.96 (s, 3H), 3.26 (s, 3H), 1.63 (tt, *J* = 8.3, 5.6 Hz, 1H), 0.66–0.59 (m, 2H), 0.13–0.04 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 166.4 (C), 162.5 C), 141.7 (C), 140.2 (C), 137.7 (C), 131.8 (CH), 130.1 (C), 130.1 (CH), 129.6 (CH), 127.9 (CH), 126.5 (CH), 125.2 (C), 124.4 (CH), 115.2 (C), 52.4 (CH_3), 34.3 (CH_3), 10.5 (CH), 9.0 (CH_2); IR (ATR): 3003, 2951, 1718, 1640, 1586, 1273, 1059, 779, 703 cm^{-1}; MS (EI) *m/z* (%): 333 (M^+, 42), 332 (100), 274 (15), 273 (18), 259 (12),198 (23); HRMS (EI) calcd for $C_{21}H_{19}NO_3$ (M^+) 333.1365; found: 333.1352.



8ae

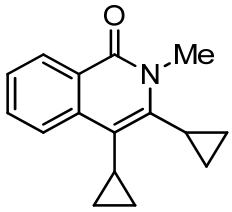
4-Cyclopropyl-2-methyl-3-[3-(trifluoromethyl)phenyl]isoquinolin-1(2*H*)-one (8ae): According to the general procedure, *N*-methylbenzamide (**5a**) (135 mg, 1.0 mmol), alkyne **2e** (420 mg, 2.0

mmol), $[RuCl_2(p\text{-cymene})]_2$ (31 mg, 50 µmol), $Cu(OAc)_2{\cdot}H_2O$ (399 mg, 2.0 mmol) yielded **8ae** (130 mg, 38%) after column chromatography as a colorless solid, m.p. = 136–138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.49 (dd, J = 8.0, 1.4 Hz, 1H), 8.18 (dt, J = 8.3, 0.8 Hz, 1H), 7.75–7.59 (m, 4H), 7.50 (ddd, J = 8.2, 7.1, 1.2 Hz, 2H), 3.27 (s, 3H), 1.64 (tt, J = 8.3, 5.6 Hz, 1H), 0.76–0.52 (m, 2H), 0.16–-0.06 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.6 (C), 141.2 (C), 137.7 (C), 136.5 (C), 133.3 (CH), 131.9 (CH), 131.1 (q, J_{C-F} = 32.7 Hz, C), 129.0 (CH), 128.0 (CH), 126.9 (q, J_{C-F} = 3.8 Hz, CH), 126.7 (CH), 125.3 (C), 125.3 (q, J_{C-F} = 3.8 Hz, CH), 124.5 (CH), 123.8 (q, J_{C-F} = 272.5 Hz, C), 115.6 (C), 34.3 (CH_3), 10.4 (CH), 9.0 (CH_2), 8.8 (CH_2); IR (ATR): 3063, 2996, 2945, 1644, 1594, 1311, 1130, 769, 703 cm^{-1}; MS (EI) *m/z* (%): 343 (M^+, 50), 342 (100), 314 (10), 198 (30), 186 (23),145 (21); HRMS (EI) calcd for $C_{20}H_{16}F_3NO$ (M^+) 343.1184; found: 343.1184.



8af

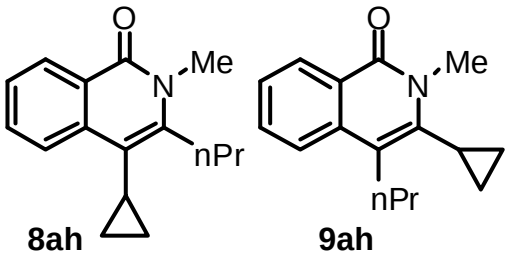
4-Cyclopropyl-3-(4-methoxyphenyl)-2-methylisoquinolin-1(2*H*)-one (8af): According to the general procedure, *N*-methylbenzamide (**5a**) (135 mg, 1.0 mmol), alkyne **2f** (344 mg, 2.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (31 mg, 50 µmol), $Cu(OAc)_2{\cdot}H_2O$ (399 mg, 2.0 mmol) yielded **8af** (198 mg, 65%) after column chromatography as a colorless solid, m.p. = 125–127 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.49 (dd, J = 8.0, 1.4 Hz, 1H), 8.17 (d, J = 8.3 Hz, 1H), 7.66 (ddd, J = 8.3, 7.1, 1.4 Hz, 1H), 7.46 (ddd, J = 8.0, 7.1, 1.1 Hz, 1H), 7.19 (d, J = 7.5 Hz, 2H), 6.97 (d, J = 7.5 Hz, 2H), 3.86 (s, 3H), 3.28 (s, 3H), 1.61 (tt, J = 8.3, 5.6 Hz, 1H), 0.68–0.58 (m, 2H), 0.15–0.06 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.8 (C), 159.4 (C), 142.7 (C), 138.0 (C), 131.6 (CH), 131.1 (CH), 128.0 (C), 127.8 (CH), 126.1 (CH), 125.0 (C), 124.3 (CH), 115.2 (C), 113.7 (CH), 55.2 (CH_3), 34.2 (CH_3), 10.5 (CH), 8.8 (CH_2); IR (ATR): 2998, 2942, 2843, 1642, 1603, 1509, 1217, 1024, 709 cm^{-1}; MS (EI) *m/z* (%): 305 (M^+, 63), 304 (100), 275 (15), 247 (12), 198 (68),155 (15); HRMS (EI) calcd for $C_{20}H_{19}NO_2$ (M^+) 305.1416; found: 305.1405.



8ag

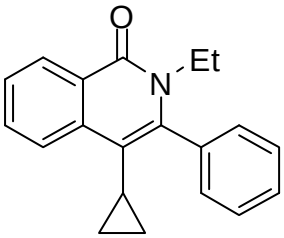
3,4-Dicyclopropyl-2-methylisoquinolin-1(2*H*)-one (8ag): According to the general procedure, *N*-methylbenzamide (**5a**) (135 mg, 1.0 mmol), alkyne **2g** (212 mg, 2.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (31 mg, 50 µmol), $Cu(OAc)_2{\cdot}H_2O$ (399 mg, 2.0 mmol) yielded **8ag** (199 mg, 83%) after

column chromatography as a colorless solid, m.p. = 100–102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.39 (dd, J = 8.0, 1.4 Hz, 1H), 8.06 (d, J = 8.3, 1H), 7.61 (ddd, J = 8.3, 7.0, 1.5 Hz, 1H), 7.40 (ddd, J = 8.0, 7.0, 1.2 Hz, 1H), 3.74 (s, 3H), 1.88–1.70 (m, 1H), 1.22–1.15 (m, 2H), 1.14–1.06 (m, 1H), 1.14–1.13 (m, 2H), 0.86–0.75 (m, 2H), 0.64–0.52 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.8 (C), 143.1 (C), 138.0 (C), 131.5 (CH), 127.6 (CH), 125.8 (CH), 124.6 (C), 123.9 (CH), 117.9 (C), 32.1 (CH_3), 13.8 (CH), 10.8 (CH), 10.2 (CH_2), 9.3 (CH_2); IR (ATR): 3080, 3003, 2976, 2920, 1641, 1587, 1024, 771, 704 cm^{-1}; MS (EI) *m/z* (%): 239 (M^+, 21), 238 (28), 198 (100), 196 (14), 128 (13), 43 (18); HRMS (EI) calcd for $C_{16}H_{17}NO$ (M^+) 239.1310; found: 239.1298.

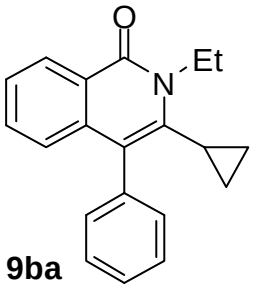


8ah **9ah**

4-Cyclopropyl-2-methyl-3-propylisoquinolin-1(2*H*)-one (8ah) and 3-Cyclopropyl-2-methyl-4-propylisoquinolin-1(2*H*)-one (9ah): According to the general procedure, *N*-methylbenzamide (**5a**) (135 mg, 1.0 mmol), alkyne **2h** (217 mg, 2.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (31 mg, 50 µmol), $Cu(OAc)_2{\cdot}H_2O$ (399 mg, 2.0 mmol) yielded **8ah** (39 mg, 16%) as a colorless solid and **9ah** (106 mg, 44%) as a brown oil and after column chromatography. **8ah**: ^{1}H NMR (300 MHz, $CDCL_3$) δ = 8.42 (ddd, J = 8.1, 1.5, 0.6 Hz, 1H), 8.15 (ddd, J = 8.4, 1.2, 0.7 Hz, 1H), 7.63 (ddd, J = 8.4, 7.0, 1.5 Hz, 1H), 7.41 (ddd, J = 8.1, 7.0, 1.2 Hz, 1H), 3.64 (s, 3H), 3.08 (ddd, J = 7.9, 6.4, 2.2 Hz, 2H), 1.75 (tt, J = 8.2, 5.6 Hz, 1H), 1.62 (dq, J = 15.8, 7.4 Hz, 2H), 1.21–1.14 (m, 2H), 1.05 (t, J = 7.4 Hz, 3H), 0.62–0.55 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 163.2 (C), 143.7 (C), 137.9 (C), 131.4 (CH), 127.9 (CH), 125.5 (CH), 124.4 (C), 124.0 (CH), 114.6 (C), 31.8 (CH_2), 31.4 (CH_3), 22.3 (CH_2), 14.2 (CH_3), 9.6 (CH), 9.3 (CH_2). The connectivity of compound **8ah** was established by X-ray crystal structure analysis.[10] **9ah**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.29 (ddd, J = 8.8, 1.2, 0.7 Hz, 1H), 7.67–7.55 (m, 2H), 7.45–7.38 (m, 1H), 3.75 (s, 3H), 3.03–2.84 (m, 2H), 1.77 (tt, J = 8.3, 5.8 Hz, 1H), 1.65–1.51 (m, 2H), 1.26–1.15 (m, 2H), 1.01 (t, J = 7.3 Hz, 3H), 0.79–0.69 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.8 (C), 139.9 (C), 136.4 (C), 131.7 (CH), 128.1 (CH), 125.9 (CH), 125.3 (C), 122.9 (CH), 117.4 (C), 33.1 (CH_3), 29.6 (CH_2), 23.6 (CH_2), 14.3 (CH), 12.4 (CH), 10.0 (CH_2); IR (ATR): 3084, 3003, 2957, 2872, 1636, 1586, 1335, 1034, 767, 702 cm^{-1}; MS (EI) *m/z* (%): 241 (M^+, 32), 212 (100), 197 (38), 128 (16), 115 (13),43 (10); HRMS (EI) calcd for $C_{16}H_{19}NO$ (M^+) 241.1467; found: 241.1469.

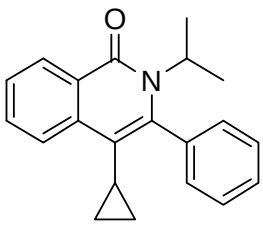


8ba



9ba

4-Cyclopropyl-2-ethyl-3-phenylisoquinolin-1(2*H*)-one (8ba) and 3-Cyclopropyl-2-ethyl-3-phenylisoquinolin-1(2*H*)-one (9ba): According to the general procedure, *N*-ethylbenzamide (**5b**) (149 mg, 1.0 mmol), alkyne **2a** (284 mg, 2.0 mmol), $RuCl_2$(*p*-cymene)]$_2$ (31 mg, 50 µmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol) yielded **8ba** (101 mg, 35%) and **9ba** (11 mg, 4%) after column chromatography as colorless solids. **8ba**: m.p. = 116–117 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.49 (ddd, J = 8.1, 1.5, 0.5 Hz, 1H), 8.18 (dt, J = 8.4, 0.8 Hz, 1H), 7.66 (ddd, J = 8.4, 7.0, 1.5 Hz, 1H), 7.50–7.41 (m, 4H), 7.35–7.27 (m, 2H), 3.89 (q, J = 7.0 Hz, 2H), 1.54 (tt, J = 8.3, 5.6 Hz, 1H), 1.08 (t, J = 7.0 Hz, 3H), 0.64–0.54 (m, 2H), 0.14 (td, J = 6.1, 4.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.0 (C), 142.8 (C), 137.9 (C), 135.4 (C), 131.6 (CH), 130.0 (CH), 128.3 (CH), 128.1 (CH), 127.8 (CH), 126.1 (CH), 125.3 (C), 124.2 (CH), 115.0 (C), 40.8 (CH_2), 14.0 (CH_3), 10.5 (CH), 8.6 (CH_2); IR (ATR): 3066, 2982, 2873, 1634, 1584, 1443, 1276, 1032, 766, 703 cm^{-1}; MS (EI) *m/z* (%): 289 (M^+, 55), 288 (100), 260 (24), 212 (23), 128 (15), 104 (18), 77 (21); HRMS (EI) calcd for $C_{20}H_{19}NO$ (M^+) 289.1467; found: 289.1456. **9ba**: m.p. = 131–133 °C; ^{1}H NMR (301 MHz, $CDCl_3$) δ = 8.46 (ddd, 7.6, 1.5, 0.8 Hz, 1H), 7.50–7.34 (m, 5H), 7.29–7.18 (m, 3H), 4.60 (q, J = 7.0 Hz, 2H), 1.75 (tt, J = 8.3, 5.8 Hz, 1H), 1.40 (t, J = 7.0 Hz, 3H), 0.78–0.68 (m, 2H), 0.40–0.32 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 162.4 (C), 139.6 (C), 137.3 (C), 136.7 (C), 131.6 (CH), 131.5 (CH), 128.1 (CH), 127.7 (CH), 127.0 (CH), 126.1 (CH), 125.0 (C), 124.7 (CH), 119.7 (C), 39.5 (CH_2), 14.4 (CH_3), 13.3 (CH), 10.2 (CH); IR (ATR): 3058, 2927, 1639, 1585, 1443, 1025, 776, 701 cm^{-1}; MS (EI) *m/z* (%): 289 (M^+, 100), 288 (16), 274 (35), 274 (32), 165 (20), 41 (5); HRMS (EI) calcd for $C_{20}H_{19}NO$ (M^+) 289.1467; found: 289.1466.



8ca

4-cyclopropyl-2-isopropyl-3-phenylisoquinolin-1(2*H*)-one (8ca): According to general procedure, *N*-isopropylbenzamide (**5c**) (163 mg, 1.0 mmol), alkyne (**2a**) (284 mg, 2.0 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (31 mg, 50 µmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol) yielded **8ca** (70 mg, 23%) as a yellow oil after column chromatography,^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.47 (dd, J = 8.1, 1.5 Hz, 1H), 8.17 (d, J = 8.2 Hz, 1H), 7.68 (ddd, J = 8.4, 7.1, 1.5 Hz, 1H), 7.51–7.44 (m, 4H), 7.35–7.29 (m, 2H), 4.09 (sept, J = 6.8

Hz, 1H), 1.55 (m, 1H), 1.52 (d, J = 6.8 Hz, 6H), 0.64–0.55 (m, 2H), 0.17–0.10 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 162.8(C), 143.7 (C), 137.8 (C), 136.6 (C), 131.6 (CH), 129.7 (CH), 128.5 (CH), 128.4 (CH), 127.7 (CH), 126.8 (C), 126.2 (CH), 124.3 (CH), 115.0 (C), 53.1 (CH), 19.7 (CH_3), 11.2 (CH), 9.1 (CH_2); IR (ATR): 3348, 2971, 1648, 1247, 1220, 694 cm^{-1}; MS (EI) *m/z* (relative intensity): 303 (M^+,41), 302 (46), 260 (100), 246 (36), 184 (27), 77 (18), 43 (24); HRMS (EI) calcd for $C_{21}H_{20}NO$ $[M-H]^+$ 302.1545, found: 302.1540.

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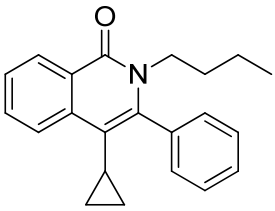
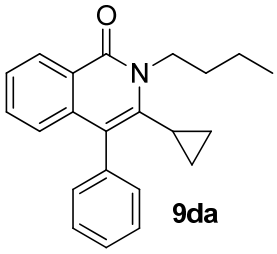
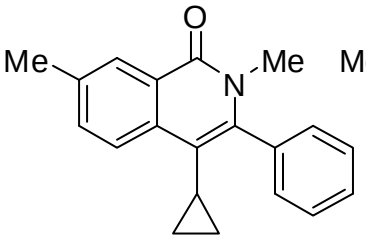


8da

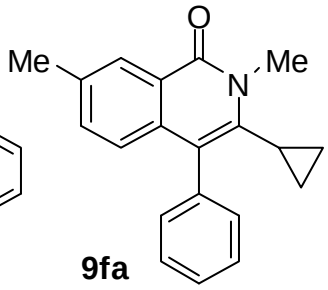


9da

2-butyl-4-cyclopropyl-3-phenylisoquinolin-1(2*H*)-one (8da) and 2-butyl-3-cyclopropyl-4-phenylisoquinolin-1(2*H*)-one (9da): According to general procedure, *N*-butylbenzamide (**5d**) (177 mg, 1.0 mmol), alkyne (**2a**) (284 mg, 2.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (31 mg, 50 µmol), $Cu(OAc)_2{\cdot}H_2O$ (399 mg, 2.0 mmol) yielded **8da** (111 mg, 35%) as a brown viscous oil and **9da** (13 mg, 4%) as a brown viscous oil after column chromatography. **8da**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.49 (dd, *J* = 8.1, 1.4 Hz, 1H), 8.19 (d, *J* = 8.3 Hz, 1H), 7.67 (ddd, *J* = 8.3, 7.1, 1.5 Hz, 1H), 7.52–7.41 (m, 4H), 7.34–7.28 (m, 2H), 3.85–3.77 (m, 2H), 1.59–1.51 (m, 1H), 1.53–1.43 (m, 2H), 1.08 (sex, *J* = 7.4 Hz, 2H), 0.69 (t, *J* = 7.4 Hz, 3H), 0.63–0.56 (m, 2H), 0.18–0.11 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 162.3 (C), 143.0 (C), 138.0 (C), 135.6 (C), 131.7 (CH), 130.3 (CH), 128.5 (CH), 128.2 (CH), 128.0 (CH), 126.3 (CH), 125.5 (C), 124.4 (CH), 115.1 (C), 45.8 (CH_2), 30.9 (CH_2), 20.2 (CH_2), 13.7 (CH_3), 10.9 (CH), 9.0 (CH_2); IR (ATR): 2958, 1642, 1585, 1083, 702 cm^{-1}; MS (EI) *m/z* (relative intensity): 317 (M^+,50), 316 (100), 260 (50), 246 (35), 128 (20), 77 (23), 41 (32); HRMS (EI) calcd for $C_{22}H_{23}NO$ (M^+) 317.1780, found: 317.1774. **9da**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.50–8.46 (m, 1H), 7.52–7.39 (m, 5H), 7.31–7.26 (m, 2H), 7.25–7.21 (m, 1H), 4.58–4.51 (m, 2H), 1.86–1.71 (m, 3H), 1.48 (sex, *J* = 7.3 Hz, 2H), 1.00 (t, *J* = 7.3 Hz, 3H), 0.78–0.70 (m, 2H), 0.41–0.33 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.7 (C), 140.0 (C), 137.6 (C), 137.0 (C), 131.8 (CH), 131.7 (CH), 128.4 (CH), 128.0 (CH), 127.2 (CH), 126.3 (CH), 125.1 (C), 124.9 (CH), 120.0 (C), 44.5 (CH_2), 31.4 (CH_2), 20.8 (CH_2), 14.0 (CH), 13.5 (CH_3), 10.43 (CH_2); IR (ATR): 2957, 2870, 1640, 1586, 1326, 775, 702 cm^{-1}; MS (ESI) *m/z* (relative intensity): 657 $[2M + Na]^+$ (100), 340 $[M + Na]^+$ (68). HRMS (ESI) calcd for $C_{22}H_{24}NO$ $[M+H]^+$ 318,1858, found: 318.1859.

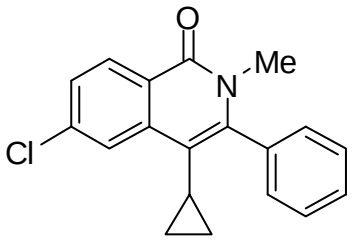


8fa

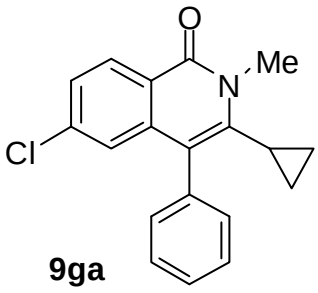


9fa

4-Cyclopropyl-2,7-dimethyl-3-phenylisoquinolin-1(2*H*)-one (8fa) and 3-Cyclopropyl-2,7-dimethyl-4-phenylisoquinolin-1(2*H*)-one (9fa): According to the general procedure, *N*,3-dimethylbenzamide (**5f**) (149 mg, 1.0 mmol), alkyne **2a** (284 mg, 2.0 mmol), $RuCl_2(p\text{-cymene})]_2$ (31 mg, 50 μmol), $Cu(OAc)_2{\cdot}H_2O$ (399 mg, 2.0 mmol) yielded **8fa** (159 mg, 55%) and **9fa** (20 mg, 7%) after column chromatography as colorless solids. **8fa**: m.p. = 113–115 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.29 (d, J = 1.7 Hz, 1H), 8.08 (d, J = 8.3 Hz, 1H), 7.54–7.41 (m, 4H), 7.33–7.26 (m, 2H), 3.27 (s, 3H), 2.50 (s, 3H), 1.62 (tt, J = 8.3, 5.6 Hz, 1H), 0.64–0.55 (m, 2H), 0.09 (td, J = 6.2, 4.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.7 (C) , 141.9 (C), 136.2 (C), 135.8 (C), 135.7 (C), 133.2 (CH), 130.0 (CH), 128.4 (CH), 128.3 (CH), 127.4 (CH), 125.0 (C), 124.4 (CH), 115.0 (C), 34.2 (CH_3), 21.3 (CH_3), 10.5 (CH), 8.7 (CH_2); IR (ATR): 2993, 2957, 1643, 1586, 1444, 1038, 828, 735, 706 cm^{-1}; MS (EI) *m/z* (%): 289 (M^+, 62), 288 (100), 247 (58), 212 (35), 169 (13),115 (15), 77 (35); HRMS (EI) calcd for $C_{20}H_{19}NO$ (M^+) 289.1467; found: 289.1459. **9fa**: m.p. = 126–128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.27 (d, J = 1.7 Hz, 1H), 7.46–7.34 (m, 3H), 7.31–7.24 (m, 3H), 7.12 (d, J = 8.3 Hz, 1H), 3.84 (s, 3H), 2.44 (s, 3H), 1.79–1.66 (m, 1H), 0.77–0.66 (m, 2H), 0.36–0.24 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 162.8 (C), 139.1 (C), 137.2 (C), 136.1 (C), 134.5 (C), 133.1 (CH), 131.4 (CH), 128.1 (CH), 127.2 (CH), 127.0 (CH), 124.7 (CH), 124.5 (C), 119.6 (C), 32.3 (CH_3), 21.3 (CH_3), 13.9 (CH), 10.2 (CH_2); IR (ATR): 3066, 2922, 2853, 1645, 1500, 1340, 823, 703 cm^{-1}; MS (EI) *m/z* (%): 289 (M^+, 100), 274 (50), 210 (18), 178 (10), 115 (5), 41 (8); HRMS (EI) calcd for $C_{20}H_{19}NO$ (M^+) 289.1467; found: 289.1463.



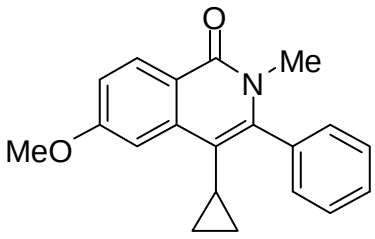
8ga



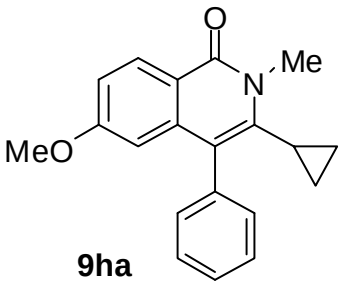
9ga

6-Chloro-4-cyclopropyl-2-methyl-3-phenylisoquinolin-1(2*H*)-one (8ga) and 6-Chloro-3-cyclopropyl-2-methyl-4-phenylisoquinolin-1(2*H*)-one (9ga): According to the general procedure, 4-chloro-*N*-methylbenzamide (**5g**) (169 mg, 1.0 mmol), alkyne **2a** (284 mg, 2.0 mmol), $RuCl_2(p\text{-cymene})]_2$ (31 mg,

50 μmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol) yielded **8ga** (226 mg, 73%) and **9ga** (25 mg, 8%) after column chromatography as colorless solids. **8ga**: m.p. = 157–159 °C; ^{1}H NMR (301 MHz, $CDCl_3$) δ = 8.41 (d, J = 8.6 Hz, 1H), 8.14 (d, J = 2.0 Hz, 1H), 7.54–7.38 (m, 4H), 7.30–7.25 (m, 2H), 3.26 (s, 3H), 1.57 (tt, J = 8.3, 5.6 Hz, 1H), 0.68–0.57 (m, 2H), 0.14–0.04 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.2 (C), 144.4 (C), 139.4 (C), 138.4 (C), 135.3 (C), 129.8 (CH), 129.8 (CH), 128.7 (CH), 128.5 (CH), 126.8 (CH), 123.9 (CH), 123.5 (C), 114.2 (C), 34.3 (CH_3), 10.4 (CH), 8.8 (CH_2); IR (ATR): 3055, 3002, 2948, 1636, 1598, 1335, 1037, 770, 711 cm^{-1}. MS (EI) *m/z* (%): 309 (M^+, 33), 308 (100), 274 (35), 232 (38), 189 (18), 77 (42); HRMS (EI) calcd for $C_{19}H_{16}ClNO$ (M^+) 309.0920; found: 309.0927. **9ga**: m.p. = 200–202 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.41 (dd, J = 8.6, 1.3 Hz, 1H), 7.51–7.40 (m, 3H), 7.37 (dt, J = 8.6, 1.7 Hz, 1H), 7.30–7.22 (m, 2H), 7.20 (d, J = 2.0 Hz, 1H), 3.84 (d, J = 1.1 Hz, 3H), 1.80–1.69 (m, 1H), 0.83–0.70 (m, 2H), 0.39–0.29 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.4 (C), 141.7 (C), 138.4 (C), 138.2 (C), 136.4 (C), 131.3 (CH), 129.6 (CH), 128.5 (CH), 127.4 (CH), 126.7 (CH), 124.0 (CH), 122.9 (C), 118.9 (C), 32.3 (CH_3), 14.0 (CH), 10.2 (CH_2); IR (ATR): 3065, 2998, 2850, 1645, 1584, 1441, 1329, 777, 709 cm^{-1}; MS (EI) *m/z* (%): 309 (M^+, 68), 294 (45), 259 (20), 59 (29), 43 (100); HRMS (EI) calcd for $C_{19}H_{16}ClNO$ (M^+) 309.0920; found: 309.0920.



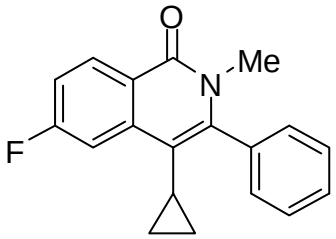
8ha



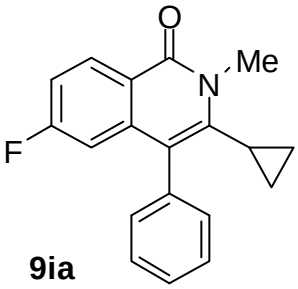
9ha

4-Cyclopropyl-6-methoxy-2-methyl-3-phenylisoquinolin-1(2*H*)-one (8ha) and 3-cyclopropyl-6-methoxy-2-methyl-4-phenylisoquinolin-1(2*H*)-one (9ha): According to the general procedure, 4-methoxy-*N*-methylbenzamide (**5h**) (165 mg, 1.0 mmol), alkyne **2a** (284 mg, 2.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (31 mg, 50 μmol), and $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol), yielded **8ha** (173 mg, 56%) and **9ha** (9mg, 3%) after column chromatography as colorless solids. **8ha**: m.p. = 135–137 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.39 (d, J = 8.9 Hz, 1H), 7.53 (d, J = 2.5 Hz, 1H), 7.48–7.37 (m, 3H), 7.29–7.23 (m, 2H), 7.04 (dd, J = 8.9, 2.5 Hz, 1H), 3.91 (d, J = 1.5 Hz, 3H), 3.24 (d, J = 1.4 Hz, 3H), 1.57 (tt, J = 8.2, 5.6 Hz, 1H), 0.63–0.54 (m, 2H), 0.13–0.05 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.3 (C), 162.2 (C), 143.5 (C), 140.0 (C), 135.6 (C), 129.9 (CH), 129.8 (CH), 128.3 (CH), 119.0 (C), 115.1 (C),

114.4 (C), 109.1 (C), 106.9 (CH), 55.2 (CH_3), 33.9 (CH_3), 10.4 (CH), 8.6 (CH_2); IR (ATR): 2991, 2939, 2914, 1639, 1604, 1275, 1027, 779, 725, 687 cm^{-1}; MS (EI) *m/z* (%): 305 (M^+, 52), 304 (84), 274 (100), 228 (68),185 (20),118 (30), 84 (40), 77 (46); HRMS (EI) calcd for $C_{20}H_{19}NO_2$ (M^+) 305.1416; found: 305.1416. **9ha**: m.p. = 145–147 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.39 (d, J = 8.9 Hz, 1H), 7.47–7.33 (m, 3H), 7.28 (d, J = 1.7 Hz, 1H), 7.25 (t, J = 1.5 Hz, 1H), 6.99 (dd, J = 8.9, 2.5 Hz, 1H), 6.59 (d, J = 2.5 Hz, 1H), 3.81 (s, 3H), 3.68 (s, 3H), 1.72 (tt, J = 8.3, 5.7 Hz, 1H), 0.75–0.66 (m, 2H), 0.34–0.25 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.6 (C), 162.3 (C), 140.8 (C), 138.9 (C), 137.3(C), 131.4 (CH_2), 129.9 (CH), 128.3 (CH), 127.1 (CH), 119.4 (C), 118.7 (C), 115.0 (CH), 106.5 (CH), 55.2 (CH_3), 32.1 (CH_3), 14.0 (CH), 10.2 (CH_2); IR (ATR): 3057, 2974, 2939, 2914, 1643, 1586, 1225, 1025, 781, 705 cm^{-1}; MS (EI) *m/z* (%): 305 (M^+, 94), 290 (100), 277 (33), 152 (21), 82 (13), 41 (10); HRMS (EI) calcd for $C_{20}H_{19}NO_2$ (M+) 305.1416; found: 305.1417.



8ia



9ia

4-Cyclopropyl-6-fluoro-2-methyl-3-phenylisoquinolin-1(2*H*)-one (8ia) and 3-Cyclopropyl-6-fluoro-2-methyl-4-phenylisoquinolin-1(2*H*)-one (9ia): According to the general procedure, 4-fluoro-*N*-methylbenzamide (**5i**) (153 mg, 1.0 mmol), alkyne **2a** (284 mg, 2.0 mmol), $RuCl_2$(*p*-cymene)]$_2$ (31 mg, 50 µmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol) yielded **8ia** (197 mg, 67%) and **9ia** (26 mg, 9%) after column chromatography as colorless solids. **8ai**: m.p. = 158–160 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.49 (m, 1H), 7.79 (dd, J = 10.9, 2.5 Hz, 1H), 7.51–7.42 (m, 3H), 7.30–7.26 (m, 2H), 7.17 (ddd, J = 8.8, 8.2, 2.6 Hz, 1H), 3.26 (s, 3H), 1.57 (tt, J = 8.3, 5.6 Hz, 1H), 0.66–0.56 (m, 2H), 0.14–0.04 (m, 2H); ^{13}C NMR (76 MHz, $CDCl_3$) δ = 165.1 (d, J_{C-F} = 250.6 Hz, C), 162.1 (C), 144.3 (C), 140.6 (d, J_{C-F} = 10.0 Hz, C), 135.4 (C), 131.1 (d, J_{C-F} = 10.0 Hz, CH), 129.8 (CH), 128.6 (CH), 128.5 (CH), 121.8 (d, J_{C-F} = 1.7 Hz, C), 114.9 (d, J_{C-F} = 23.7 Hz, CH), 114.5 (d, J_{C-F} = 3.4 Hz, C), 109.5 (d, J_{C-F} = 23.0 Hz, CH), 34.2 (CH_3), 10.5 (CH), 8.7 (CH_2); ^{19}F NMR (283 MHz, $CDCl_3$) δ = -106.4 (ddd, J = 10.9, 8.2, 6.1 Hz); IR (ATR): 3057, 3010, 1645, 1600, 1561, 1339, 1167, 1048, 775, 733, 705 cm^{-1}; MS (EI) *m/z* (%): 293 (M^+, 45), 292 (75), 216 (35), 77 (24), 58 (23), 44 (35), 43 (100); HRMS (ESI) calcd for $C_{19}H_{17}FNO$ $[M + H]^+$ 294.1289, found: 294.1289. **9ia**: m.p. = 128–130 °C; ^{1}H NMR (300

MHz, $CDCl_3$) δ = 8.47 (m, 1H), 7.50–7.34 (m, 3H), 7.28–7.21 (m, 2H), 7.10 (ddd, J = 8.8, 8.1, 2.5 Hz, 1H), 6.84 (dd, J = 10.9, 2.5 Hz, 1H), 3.83 (s, 3H), 1.73 (tt, J = 8.4, 5.8 Hz, 1H), 0.79–0.70 (m, 2H), 0.37–0.29 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.0 (d, J_{C-F} = 250.9 Hz, C), 162.3 (C), 141.6 (C), 139.3 (d, J_{C-F} = 9.6 Hz, C), 136.6 (C), 131.3 (CH), 131.0 (d, J_{C-F} = 9.9 Hz, CH), 128.4 (CH), 127.4 (CH), 121.3 (d, J_{C-F} = 1.7 Hz, C), 119.2 (d, J_{C-F} = 3.3 Hz, C), 114.8 (d, J_{C-F} = 23.6 Hz, CH), 109.8 (d, J_{C-F} = 23.4 Hz, CH), 32.2 (CH_3), 14.0 (CH), 10.2 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -106.6 (ddd, J = 10.8, 8.0, 6.0 Hz); IR (ATR): 3057, 2924, 1644, 1607, 1590, 1378, 1149, 1058, 776, 702 cm^{-1}; MS (EI) *m/z* (%): 293 (M^+, 100), 278 (70), 265 (30), 183 (18), 98 (13), 57(15), 43 (21); HRMS (EI) calcd for $C_{19}H_{16}FNO$ (M^+) 293.1216; found: 293.1211.

Spectroscopic criteria for cyclopropyl-substituted heterocycles of the type 6–9

The regiochemistry in the pair of 3-aryl-4-cyclopropyl- (**6**, **8**) and 4-aryl-3-cyclopropyl-substituted (**7**, **9**) isocoumarins and isoquinolones can easily be determined on the basis of chemical shifts of the methyne group in the cyclopropyl substituents (Table 2; regiochemistries of the key compounds were established by X-ray crystal structure analysis).[10]

Table 2 Chemical shifts in ^{1}H and ^{13}C NMR spectra of the CH fragments in cyclopropane moieties in compounds of the type **6–9**

Compound	**6aa**	**7aa**	**6ae**	**6ba**
δ_H/δ_C	1.91/9.0	1.63/12.0	1.94/8.9	1.88/9.2
Compound	**7ca**	**8aa**	**7ba**	**6ca**
δ_H/δ_C	1.51/11.6	1.62/10.5	1.61/12.2	1.83/9.5
Compound	**8ab**	**9ab**	**8ac**	**8ae**
δ_H/δ_C	1.62/10.5	1.74/13.9	1.63/10.5	1.64/10.4
Compound	**8af**	**8ah**	**9ah**	**8ba**
δ_H/δ_C	1.61/10.5	1.75/9.6	1.77/12.4	1.54/10.5
Compound	**9ba**	**8ca**	**8da**	**9da**
δ_H/δ_C	1.75/13.3	1.55/11.2	1.57/10.9	1.75/14.0
Compound	**8fa**	**9fa**	**8ga**	**9ga**
δ_H/δ_C	1.62/10.5	1.73/13.9	1.57/10.4	1.75/14.0
Compound	**8ha**	**9ha**	**8ia**	**9ia**
δ_H/δ_C	1,57/10.4	1.72/14.0	1.57/10.5	1.73/14.0

According to the Table 2, in the ^{1}H NMR spectra, the resonances of these methyne protons of the 3-aryl-4-cyclopropyl-substituted isocoumarins **6** exhibit a downfield shift relative to the signals of 4-aryl-3-cyclopropyl-substituted regioisomers **7**, while the signals in isoquinolones

8 demonstrate an upfield shift in comparison with those of **9**. In the ^{13}C NMR spectra, the signals of methyne carbon atoms of 3-aryl-4-cyclopropyl-substituted heterocycles **6**, **8** shows an upfield shift in comparison with those of 4-aryl-3-cyclopropyl-substituted ones **7**, **9** for both isocoumarins and isoquinolones families.

Crystal Structure Analysis: Crystals suitable for X-ray diffractometry of all compounds were obtained by slow evaporation of their solutions in *n*-octane/Et_2O. The single crystal X-ray data were collected on a Bruker SMART-CCD 6000 diffractometer at 120.0(2)K using graphite monochromated Mo-K_α radiation (λ = 0.71073 Å).

Table 2 Crystal and data collection parameters for compounds **6aa**, **7aa**, **7ae**, **8aa** and **8ah**

Compound	**6aa**	**6ae**	**7aa**	**8aa**	**8ah**
Formula	$C_{18}H_{14}O_2$	$C_{19}H_{13}F_3O_2$	$C_{18}H_{14}O_2$	$C_{19}H_{17}NO$	$C_{16}H_{19}NO$
Molecular mass	262.29	330.29	262.29	275.34	241.32
Crystal system	Monoclinic	Monoclinic	Triclinic	Monoclinic	Triclinic
Space group	*C* 2/c	*P* 2_1/c	*P*-1	*P* 2_1/c	*P*-1
Crystal size [mm]	0.44 × 0.44 × 0.40	0.44 × 0.20 × 0.18	0.22 × 0.14 × 0.08	0.38 × 0.32 × 0.25	0.14 × 0.14 × 0.11
a [Å]	21.7506(12)	13.3582(7)	8.5382(7)	8.6979(3)	7.9056(4)
b [Å]	10.3408(6)	14.6219(8)	9.1292(8)	16.6842(5)	8.8734(5)
c [Å]	14.2419(8)	7.6852(4)	35.608(3)	10.4505(3)	9.7298(5)
α [°]	90	90.00	87.430(2)	90.00	96.304(2)
β [°]	124.719(1)	90.502(2)	86.668(2)	113.293(1)	100.043(2)
γ [°]	90	90.00	75.652(2)	90.00	108.110(2)
V [$Å^3$]	2632.9(3)	1501.03(14)	2683.1(4)	1392.94(8)	628.90(6)
Z	8	4	8	4	2
F(000)	1104.0	680.0	1104.0	584.0	260.0
D [g cm^{-3}]	1.323	1.462	1.299	1.313	1.274
μ [mm^{-1}]	0.085	0.119	0.084	0.081	0.079
Θ_{max} [°]	30.00	29.00	27.00	29.50	29.00
Refl. collected	14905	22487	23605	17011	10556
Refl. independent	3844	3608	11558	3877	3344
R_{int}	0.0498	0.0286	0.0816	0.0272	0.0518
R_1 [$I \geq 2\sigma(I)$]	0.0389	0.0754	0.0591	0.0460	0.0582
wR_2(all data)	0.1170	0.2099	0.1136	0.1353	0.1688
No. of parameters refined	237	278	721	258	239
GOOF	1.036	1.086	0.931	1.063	0.980
Largest diff. peak and hole, e·$Å^{-3}$	0.35, –0.19	0.99, –1.06	0.81, –0.47	0.43, –0.22	0.53, –0.24

All structures were solved by direct method and refined by full-matrix least squares on F^2 for all data. All non-hydrogen atoms were refined with anisotropic displacement parameters, H-atoms were located on the difference map and refined isotropically.[10] Crystal and data collection parameters are summarized in Table 2. For isocoumarine **6ae** only major component of disordered CF_3-group is shown, and for isocoumarine **7aa** one of four independent molecules is shown.

In the crystal, 4-cyclopropyl-3-phenylisocoumarin **6aa** adopts the conformations with the dihedral angle C1–C2–C3–center (C4–C5) equal to –99.5°. In contrast to this, in **7aa** the dihedral angles C1–C2–C3–center (C4–C5) = 179.4° with the angle between aromatic planes of 66.5°, i. e. with almost ideal conditions for the conjugation of cyclopropyl and isocoumarin fragments (Fig. 1). Probably because of this compound **7aa** on silica gel (i. e. in the solid state) can be seen in UV light λ = 365 nm, while compound **6aa** only at λ = 254 nm. However, no essential differences were found: in UV spectra of the compounds **6aa** and **7aa** in their solutions (see above).

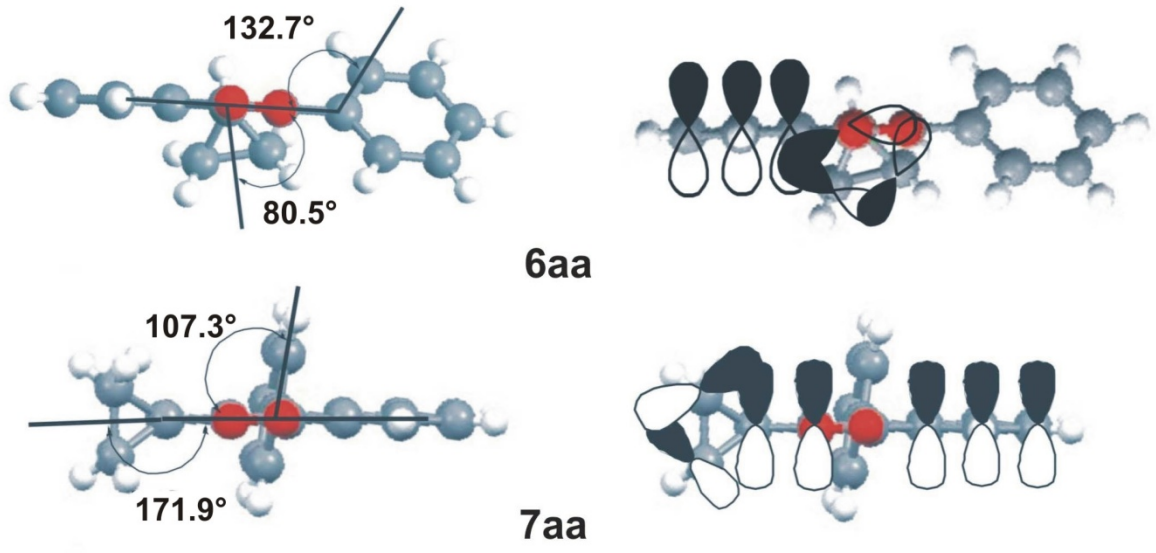


Fig. 1 Conjugation in cyclopropylisocoumarins **6aa** and **7aa**.

Notes and references

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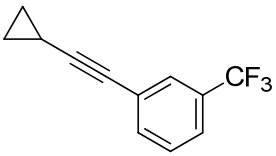
8 (*a*) V. C. Agwada, *J. Chem. Eng. Data*, 1984, **29**, 231–235; (*b*) L. Ackermann, A. V. Lygin and N. Hofmann, *Angew. Chem*., 2011, **123**, 6503–6506; *Angew. Chem., Int. Ed.,* 2011, **50**, 6379–6382; (*c*) T. K. Hyster, and T. Rovis, Tomislav, *J. Am. Chem. Soc*., 2010, **132**, 10565–10569.

9 For the alternative preparation, however, without experimental and spectral details see: J. K. Crandall and D. J. Keyton, *Chem. Commun. (London)*, 1968, 1069–1070.

CCDC-901337 (**6aa**), -901338 (**7aa**), -901339 (**7ae**), -901340 (**9aa**) and -901341 (**9ah**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

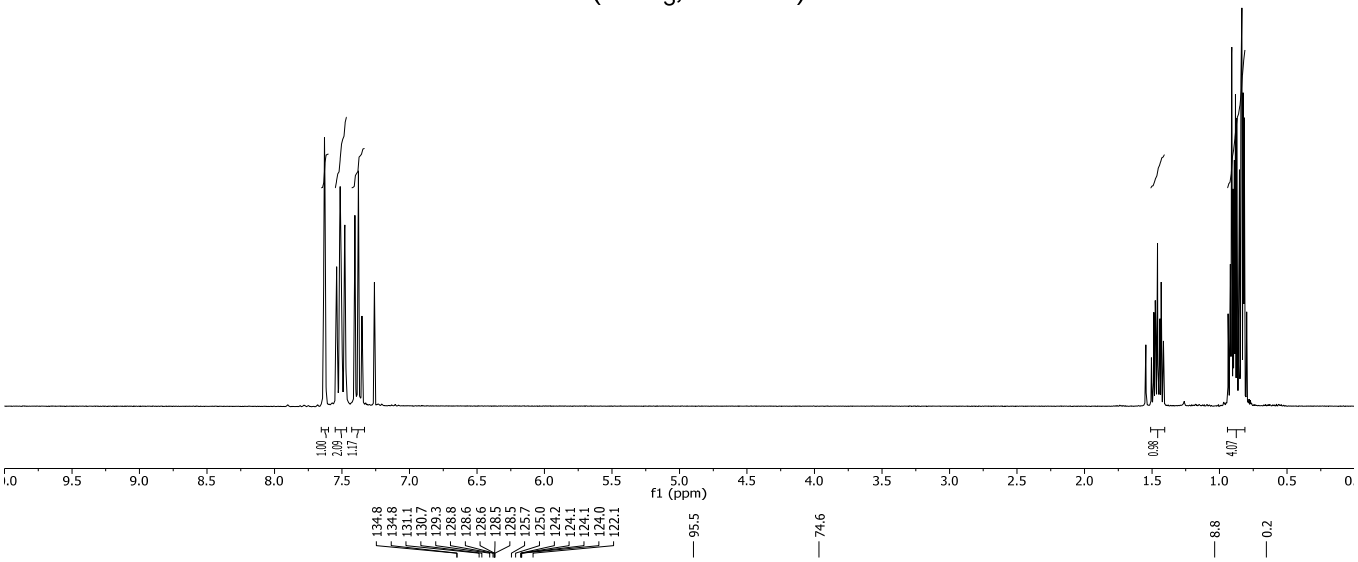
^{1}H and ^{13}C NMR Spectra of new Compounds

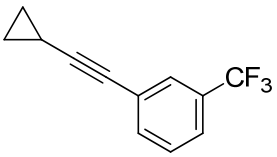
1-(Cyclopropylethynyl)-3-(trifluoromethyl)benzene (2e)



2e

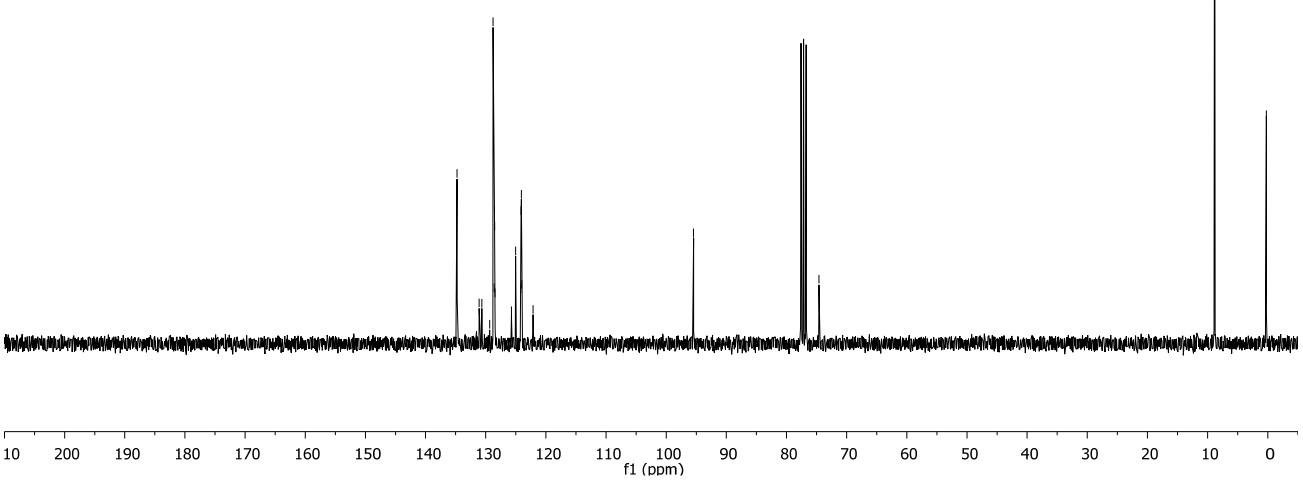
($CDCl_3$, 300 MHz)



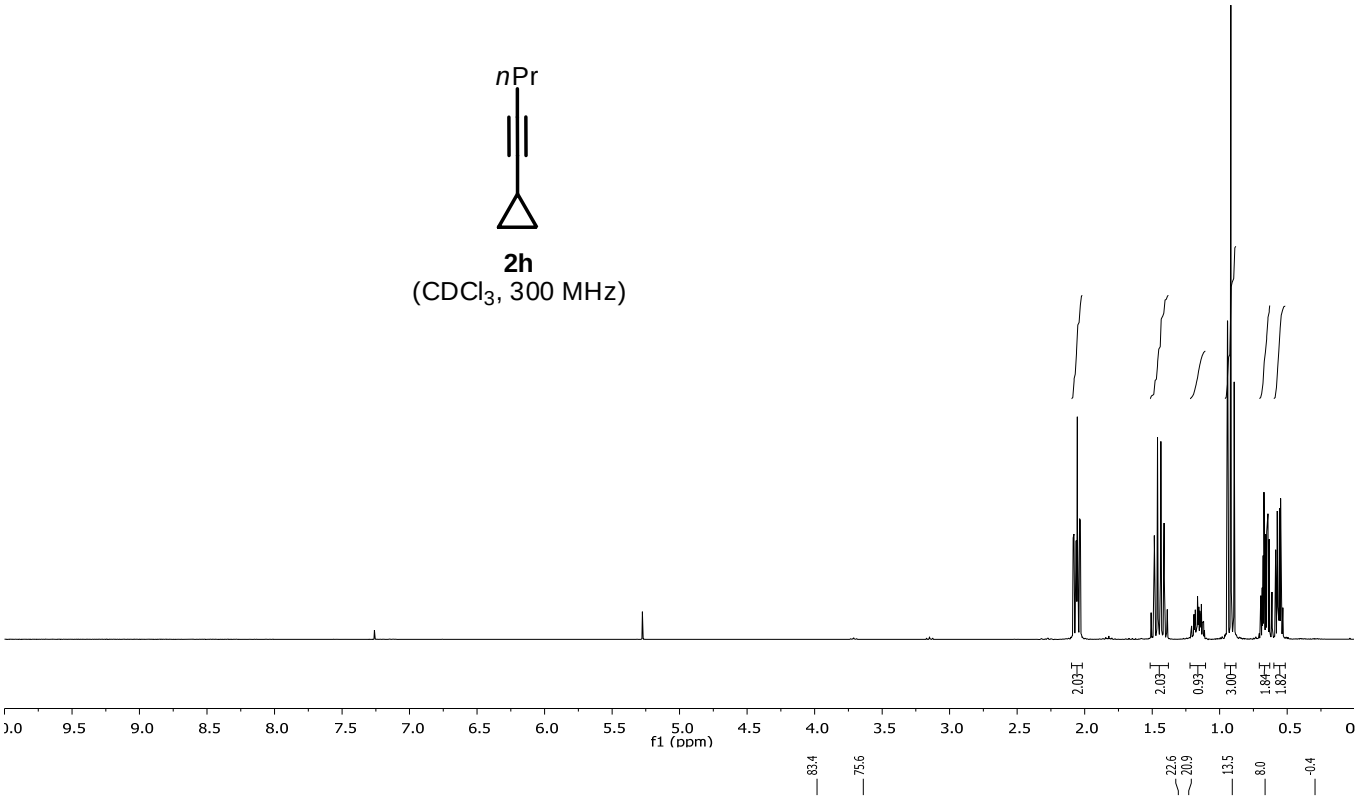


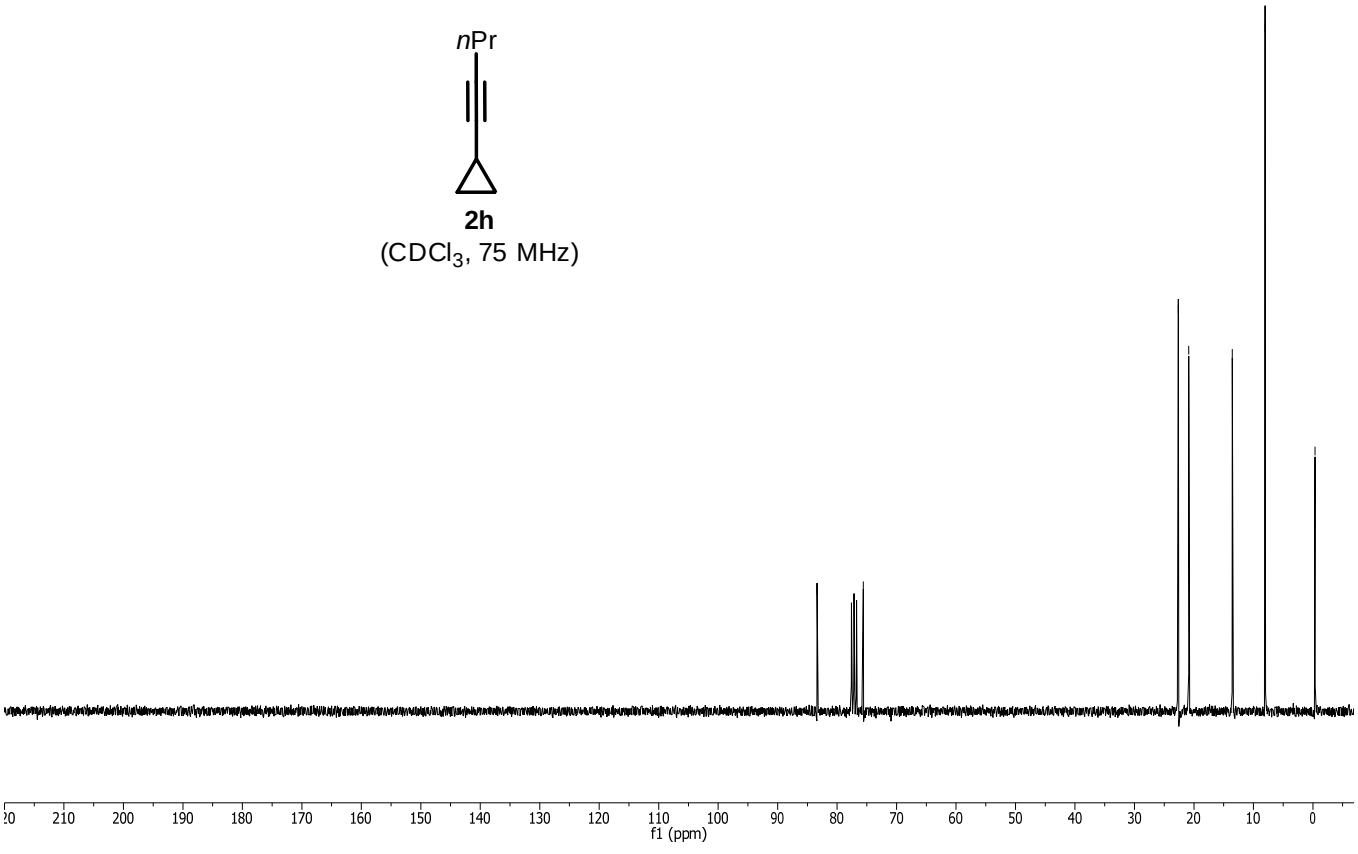
2e

($CDCl_3$, 75 MHz)

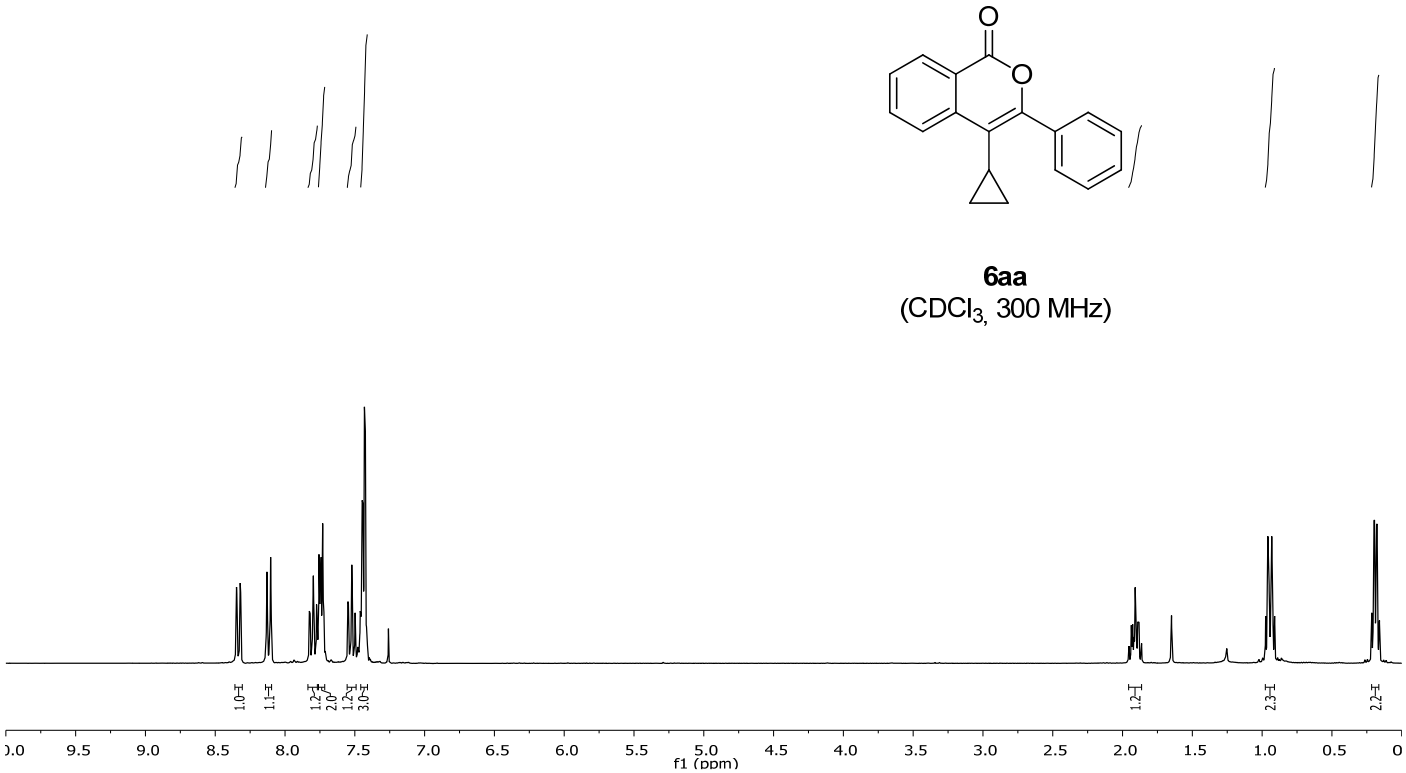


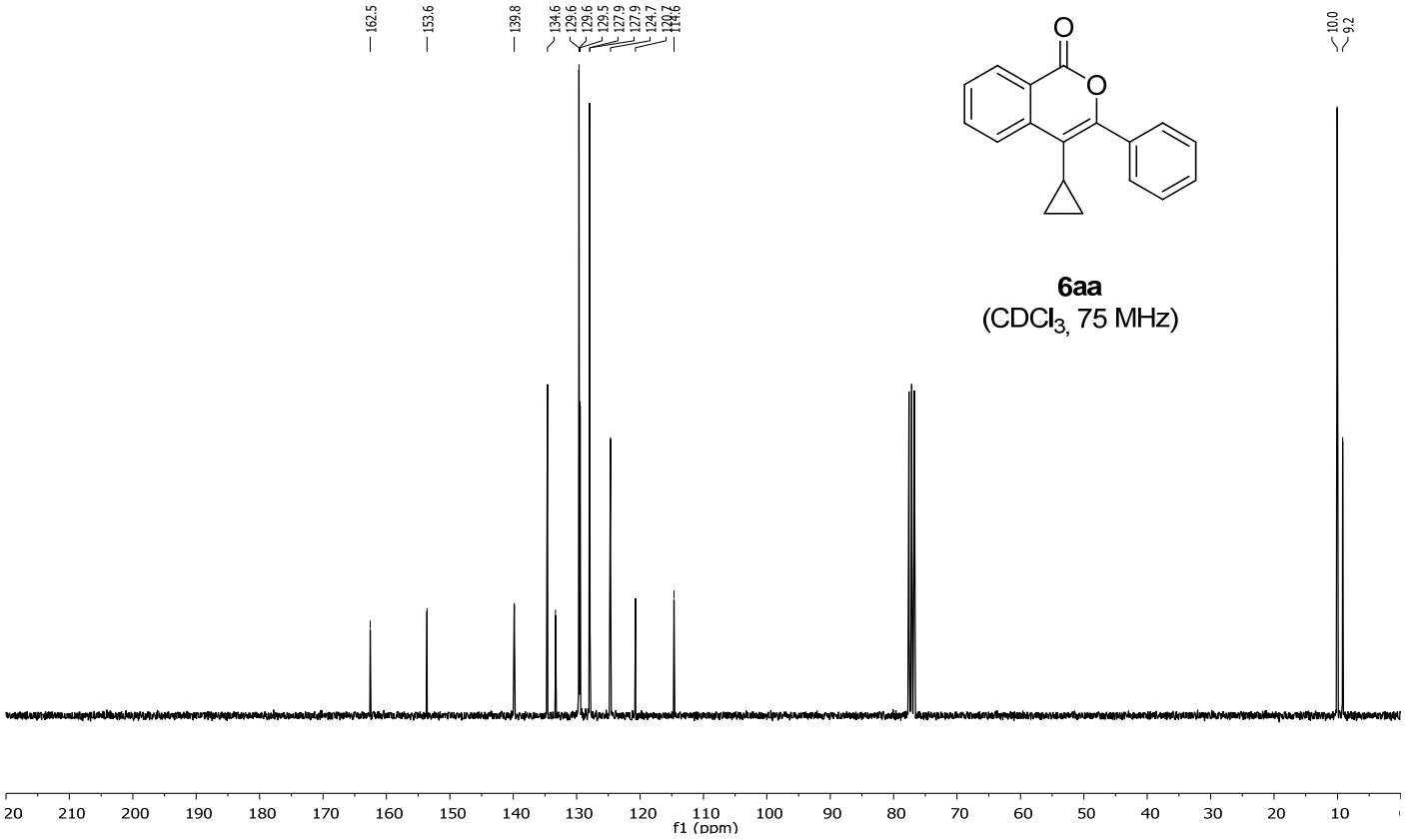
(Pent-1-ynyl)cyclopropane (1-cyclopropyl-2-*n*-propylacetylene) (2h)



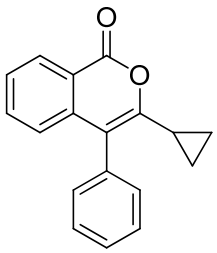


4-Cyclopropyl-3-phenyl-1*H*-isochromen-1-one (6aa)

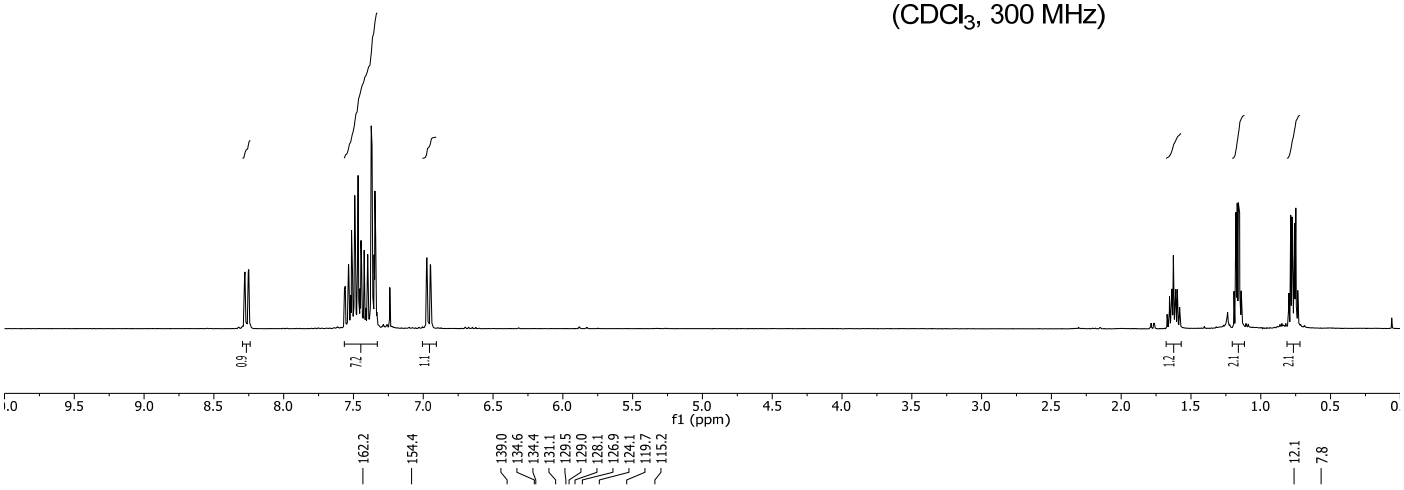


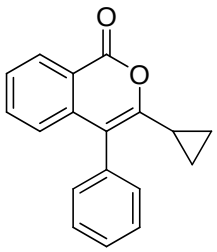


3-Cyclopropyl-4-phenyl-1*H*-isochromen-1-one (7aa)



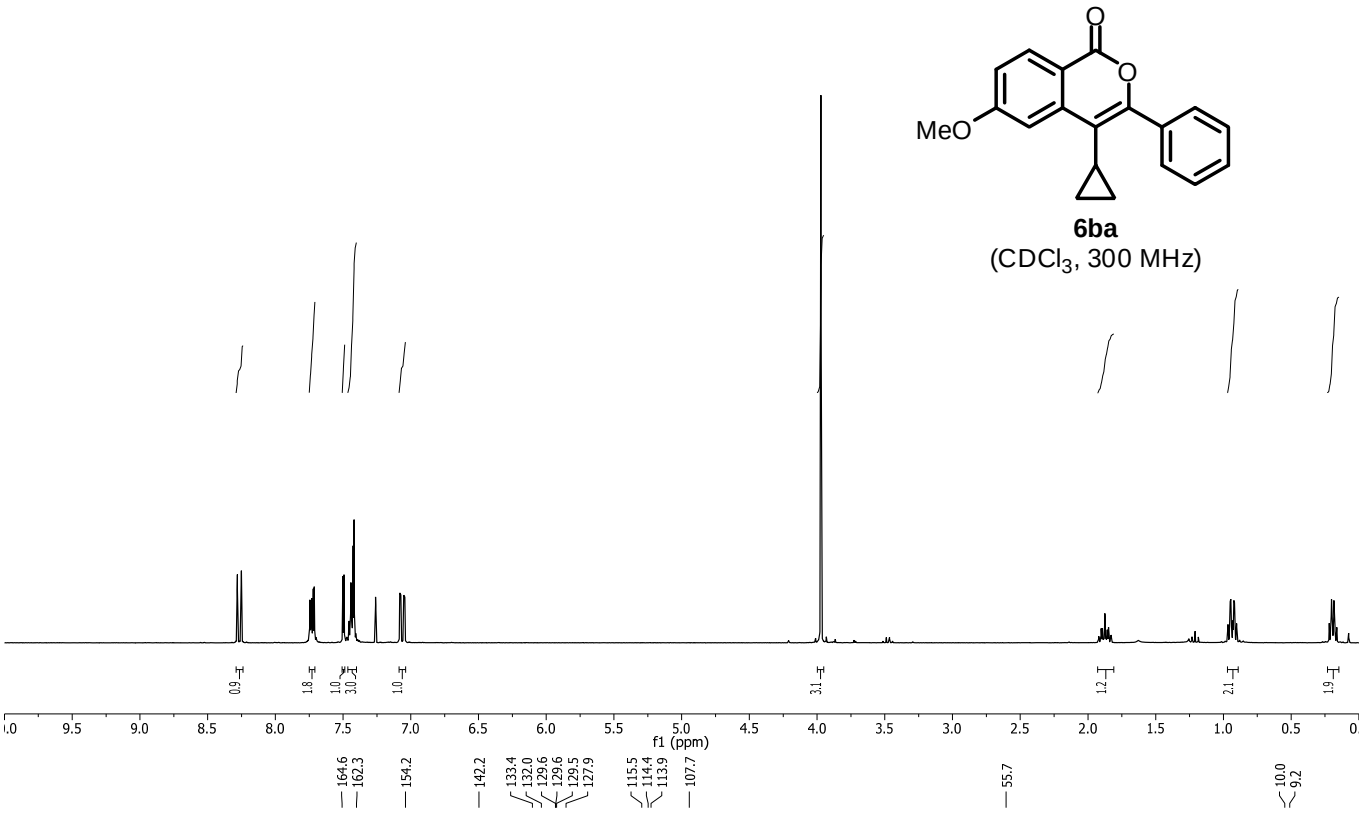
7aa
($CDCl_3$, 300 MHz)

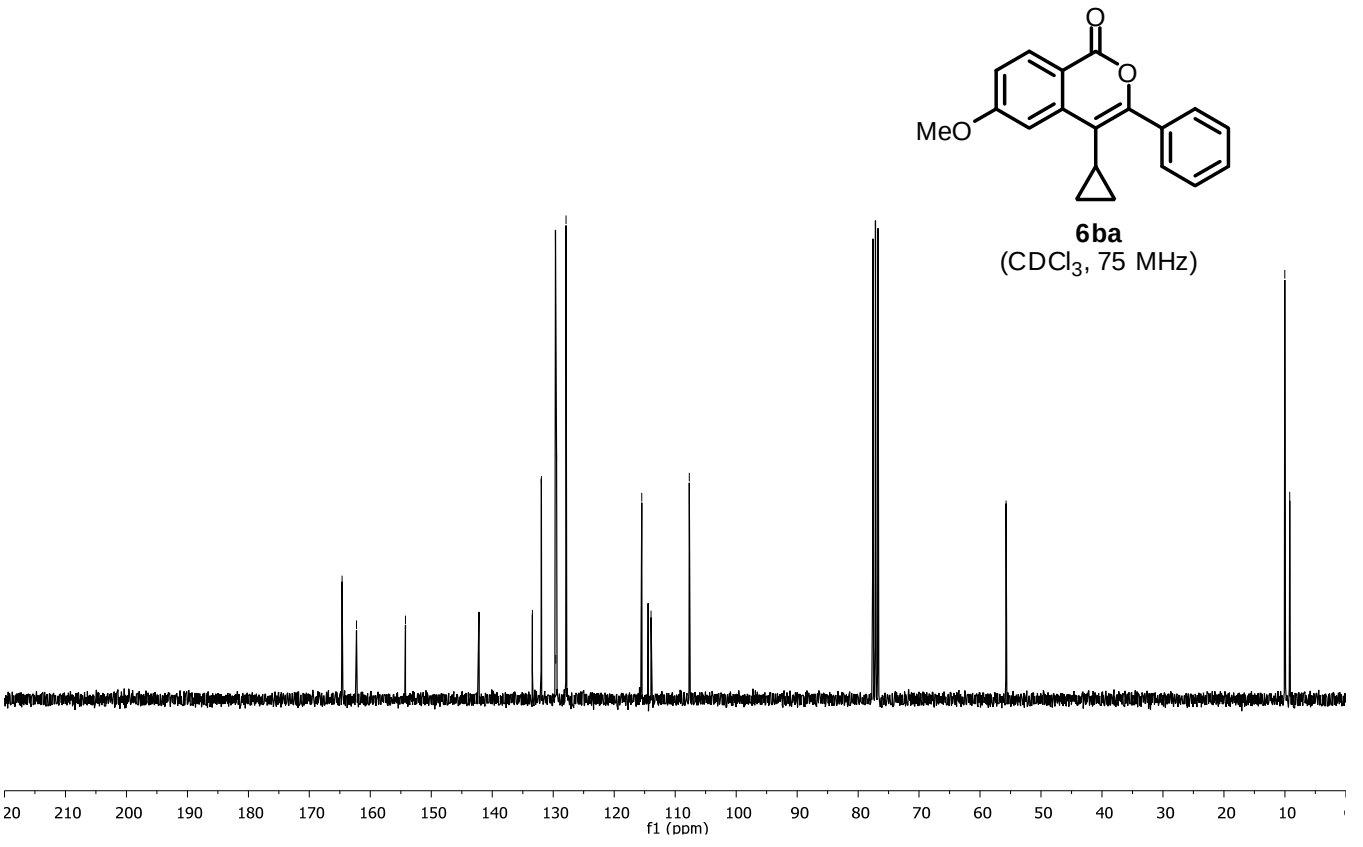




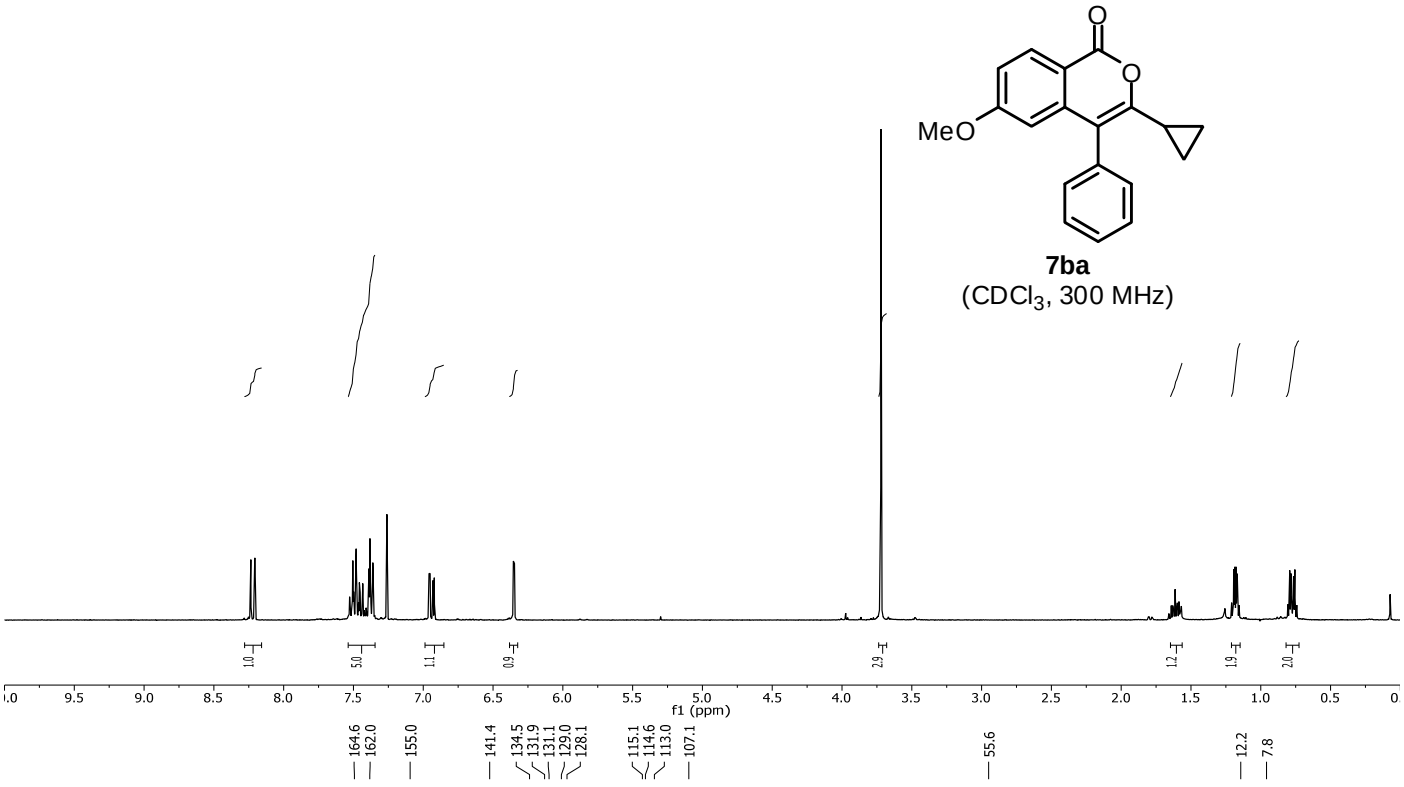
7aa
($CDCl_3$, 75 MHz)

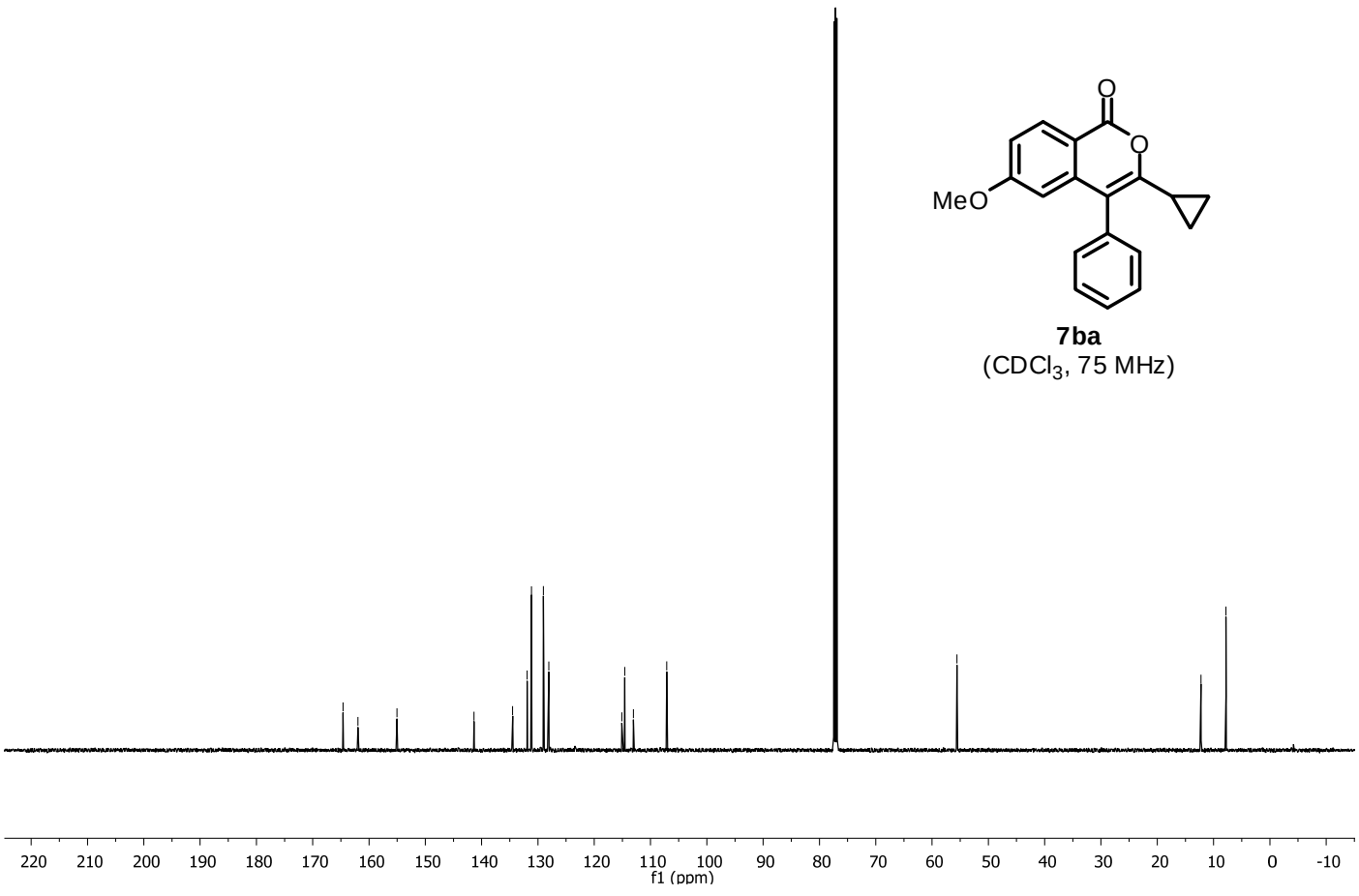
4-Cyclopropyl-6-methoxy-4-phenyl-1H-isochromen-1-one (6ba)



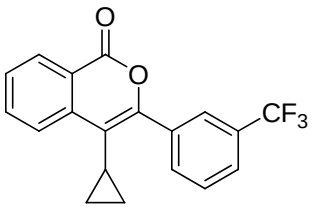


3-Cyclopropyl-6-methoxy-4-phenyl-1*H*-isochromen-1-one (7ba)

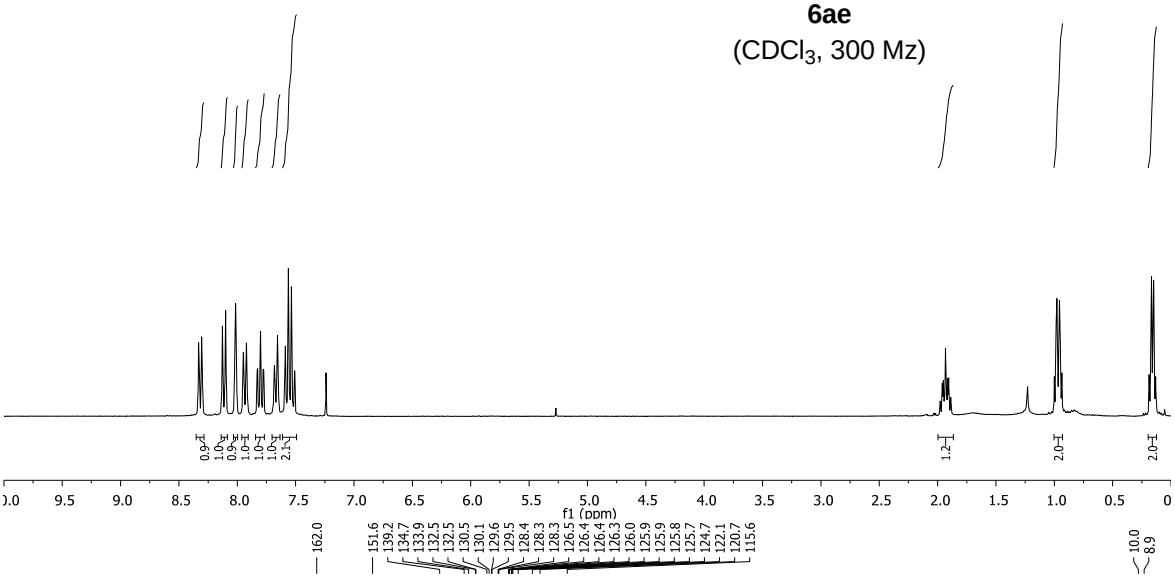


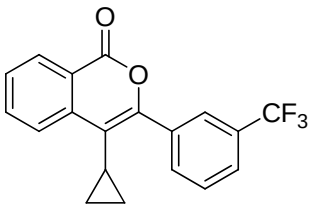


4-Cyclopropyl-3-(3-(trifluoromethyl)phenyl)-1*H*-isochromen-1-one (6ae)

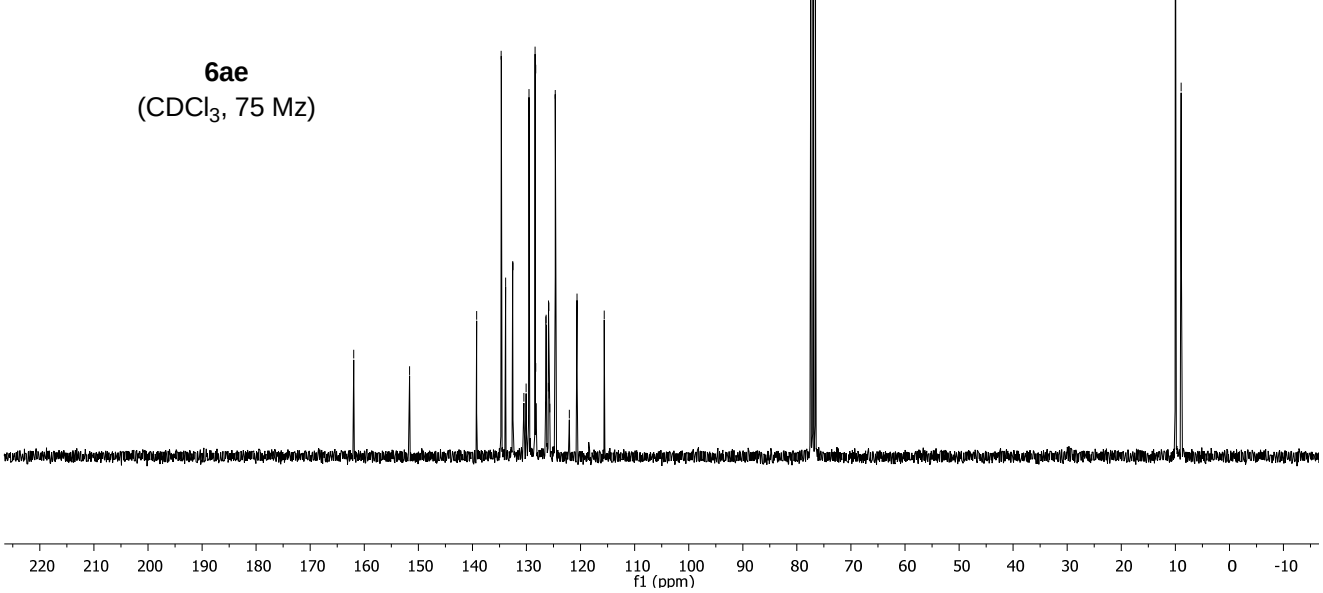


6ae
($CDCl_3$, 300 Mz)

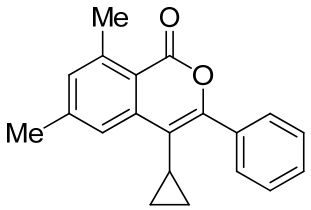




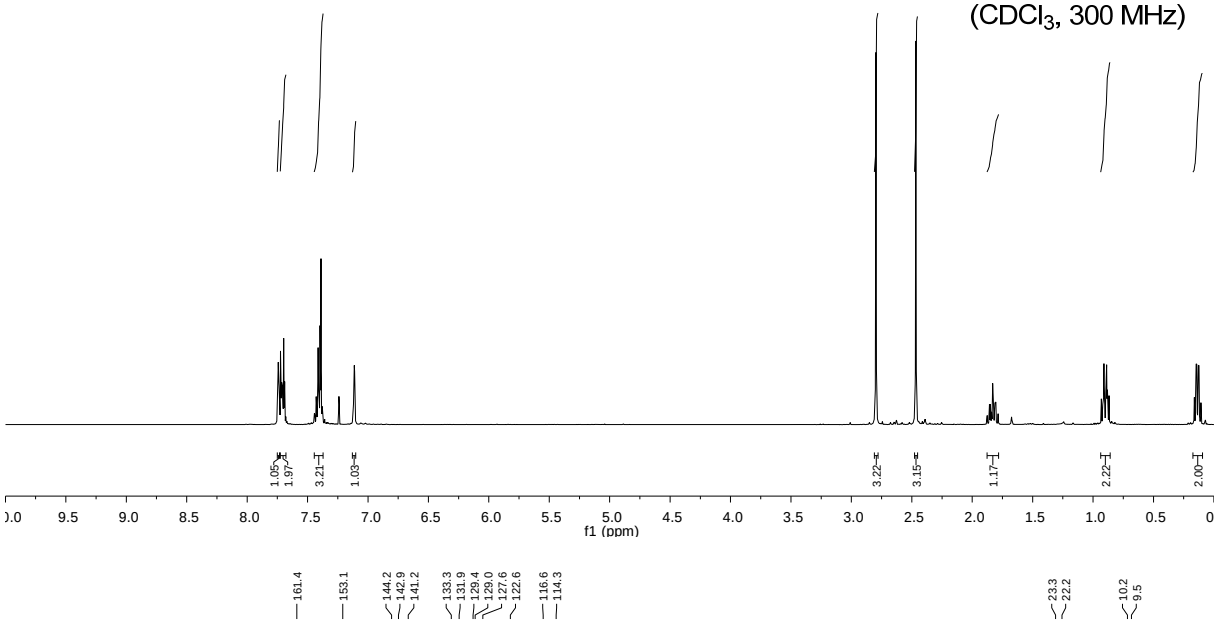
6ae
($CDCl_3$, 75 Mz)

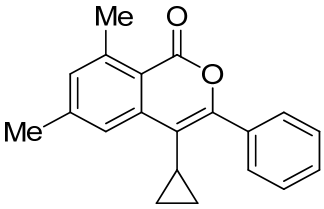


4-Cyclopropyl-6,8-dimethyl-3-phenyl-1*H*-isochromen-1-one (6ca)

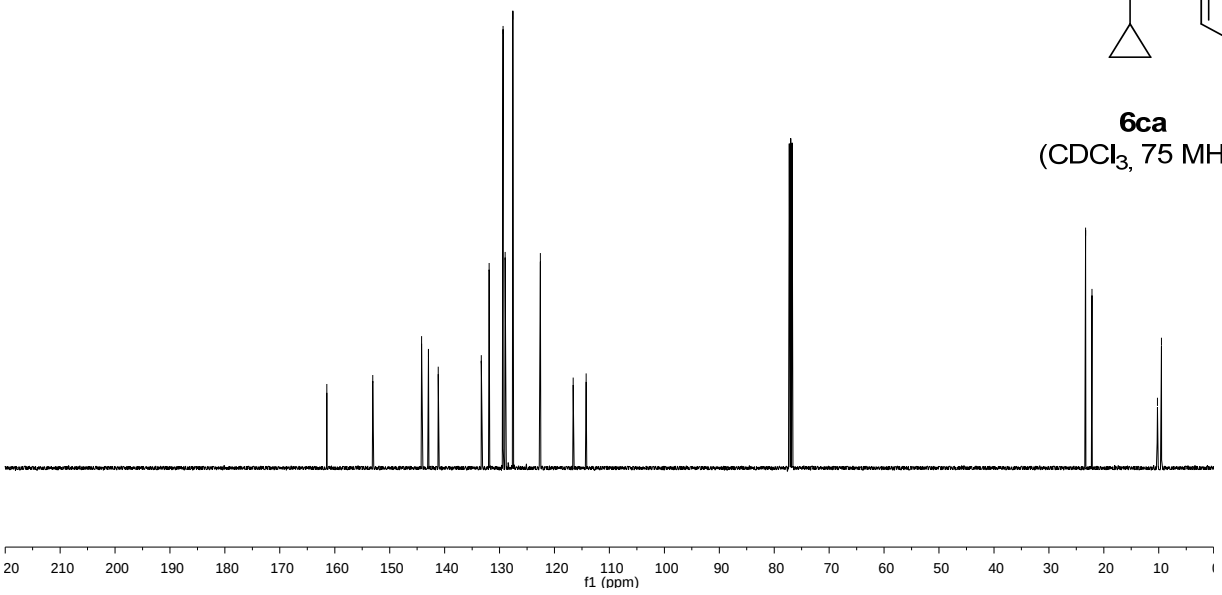


6ca
($CDCl_3$, 300 MHz)

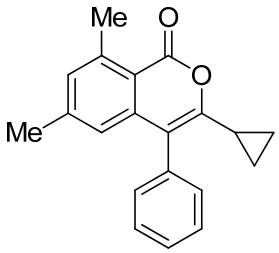




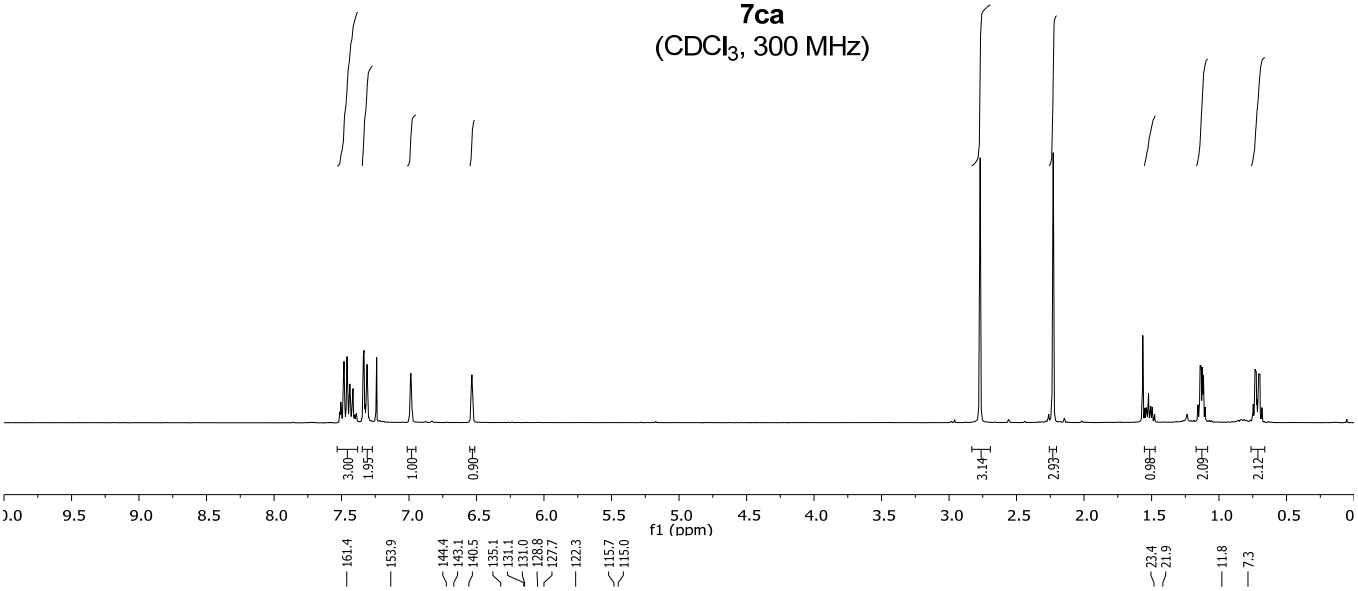
6ca
($CDCl_3$, 75 MHz)

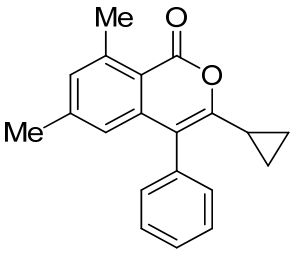


3-Cyclopropyl-6,8-dimethyl-4-phenyl-1*H*-isochromen-1-one (7ca)

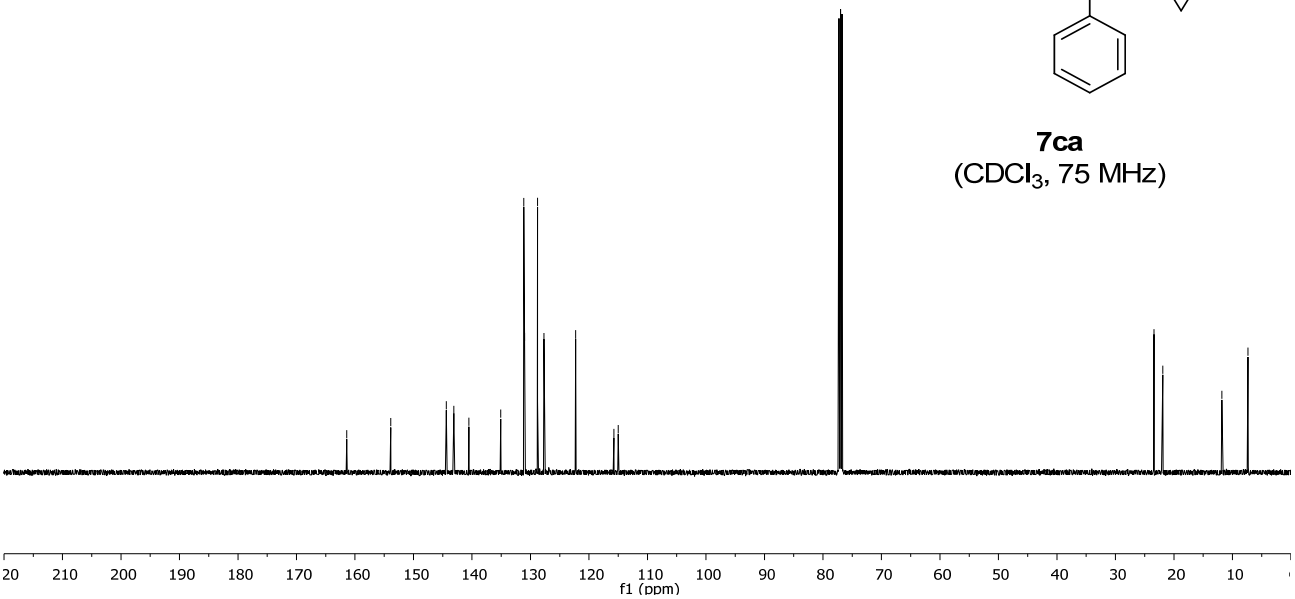


7ca
($CDCl_3$, 300 MHz)

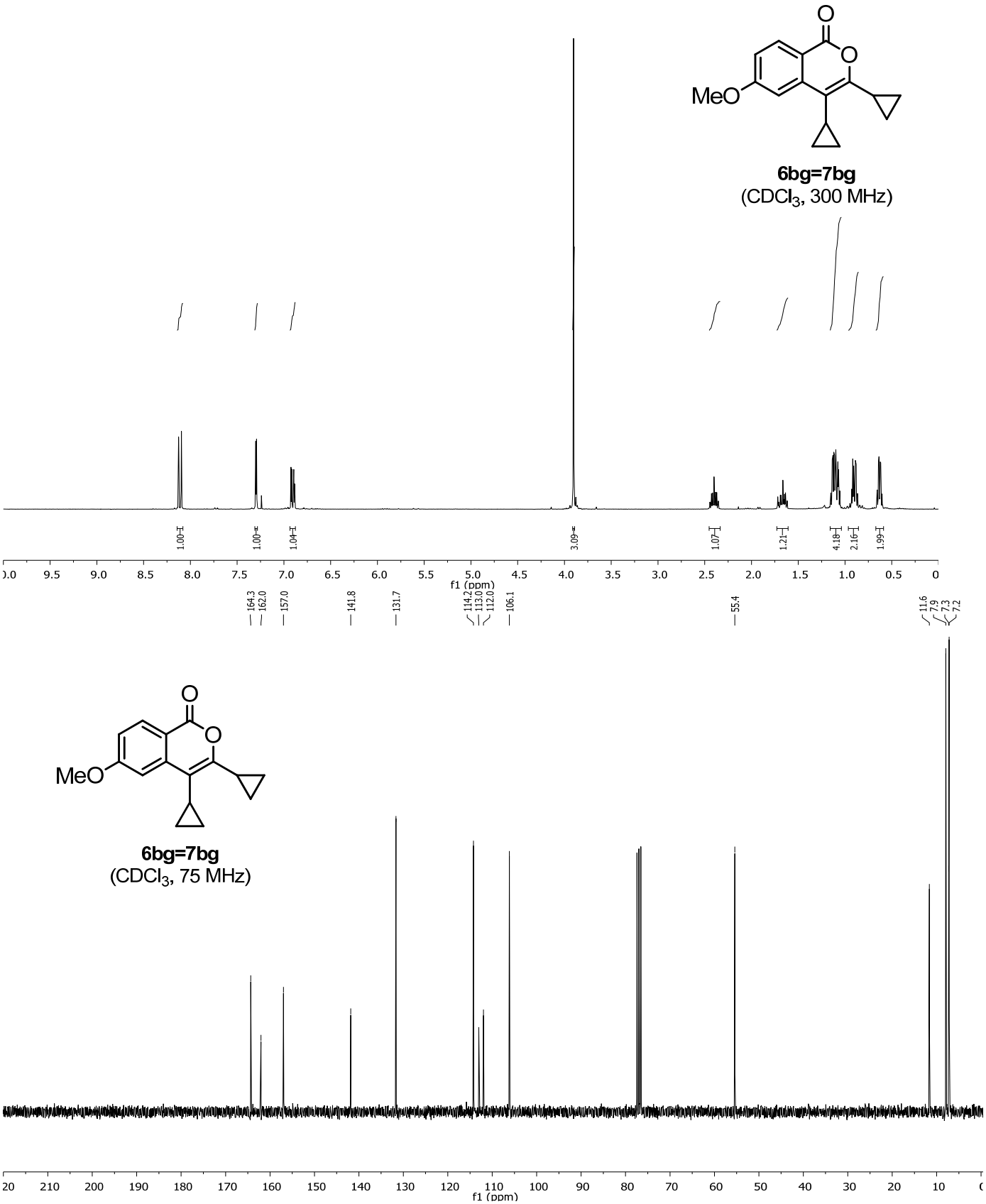




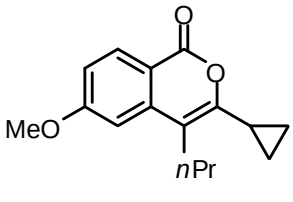
7ca
($CDCl_3$, 75 MHz)



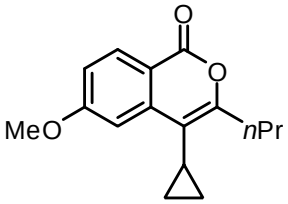
3,4-Dicyclopropyl-6-methoxy-1*H*-isochromen-1-one (6bg = 7bg)



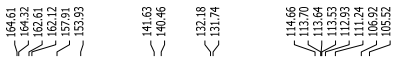
3-Cyclopropyl-6-methoxy-4-propyl-1*H*-isochromen-1-one and 4-Cyclopropyl-6-methoxy-3-propyl-1*H*-isochromen-1-one

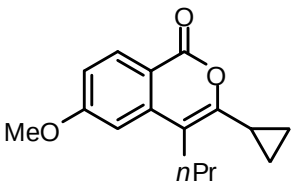


7bh
($CDCl_3$, 300 MHz)

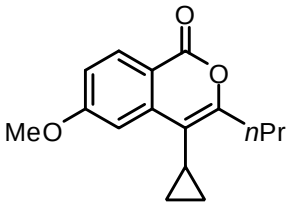


6bh
($CDCl_3$, 300 MHz)



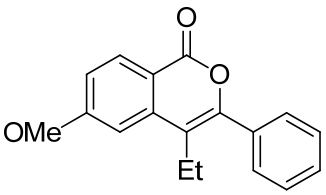


7bh
($CDCl_3$, 75 MHz)

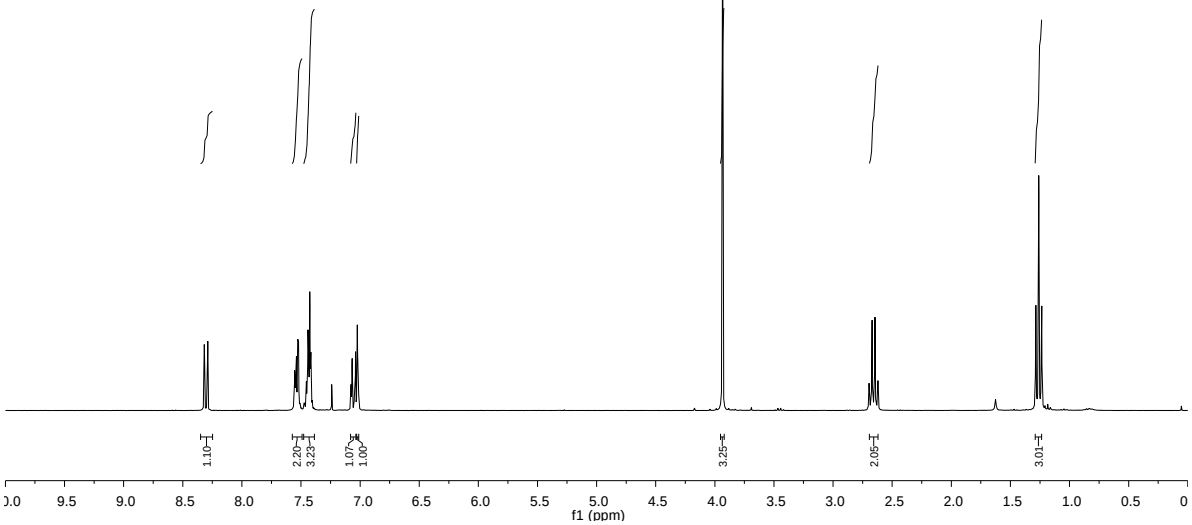


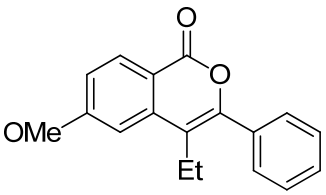
6bh
($CDCl_3$, 75 MHz)

4-Ehyl-6-methoxy-3-phenyl-1*H*-isochromen-1-one (6bi)

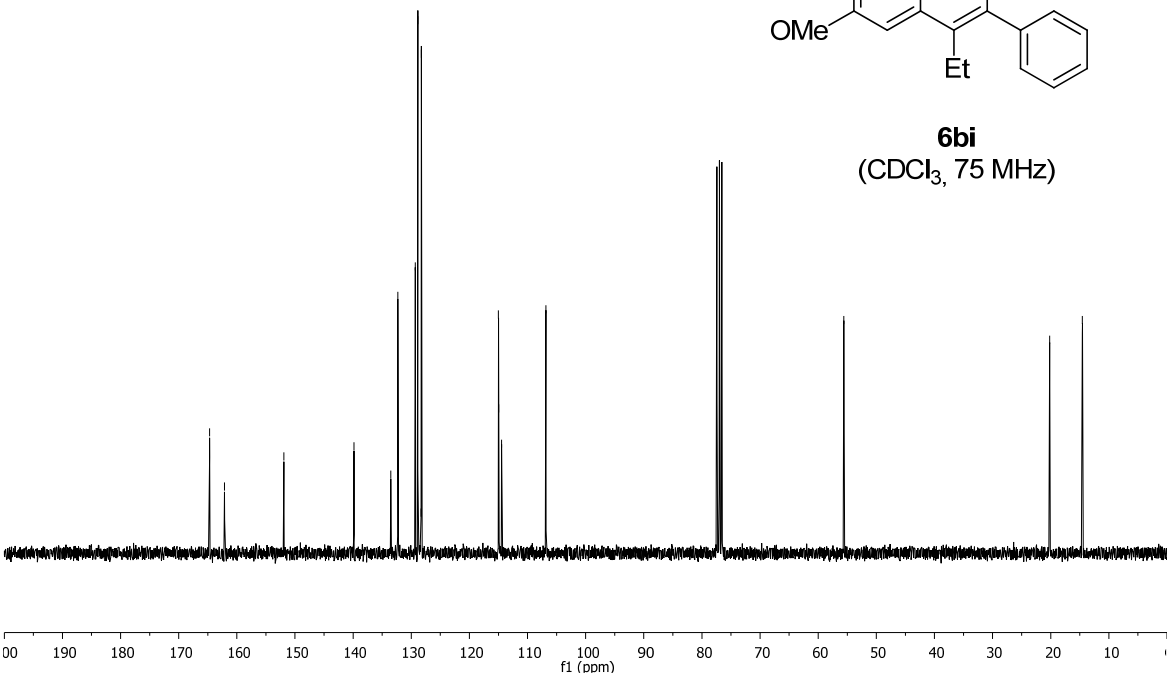


6bi
($CDCl_3$, 300 MHz)

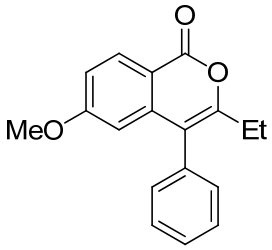




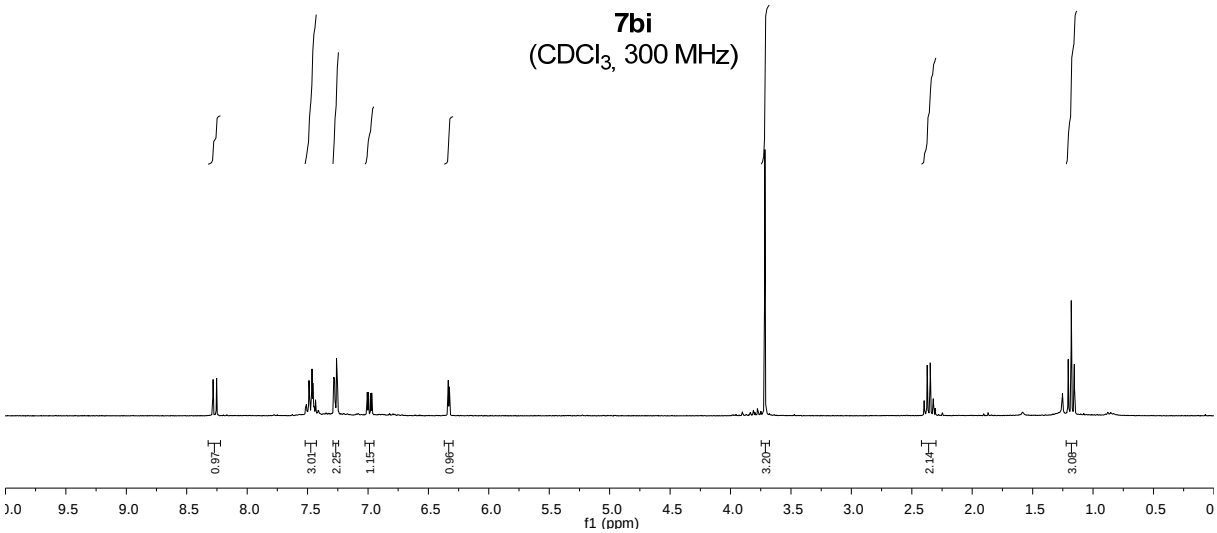
6bi
($CDCl_3$, 75 MHz)

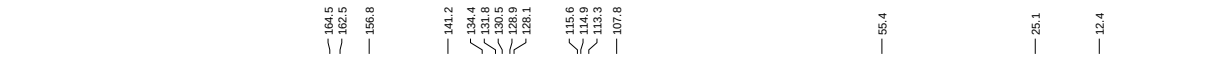


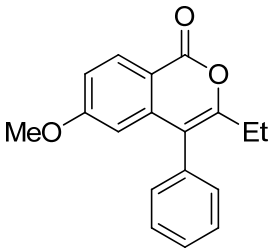
3-Ehyl-6-methoxy-4-phenyl-1*H*-isochromen-1-one (7bi)



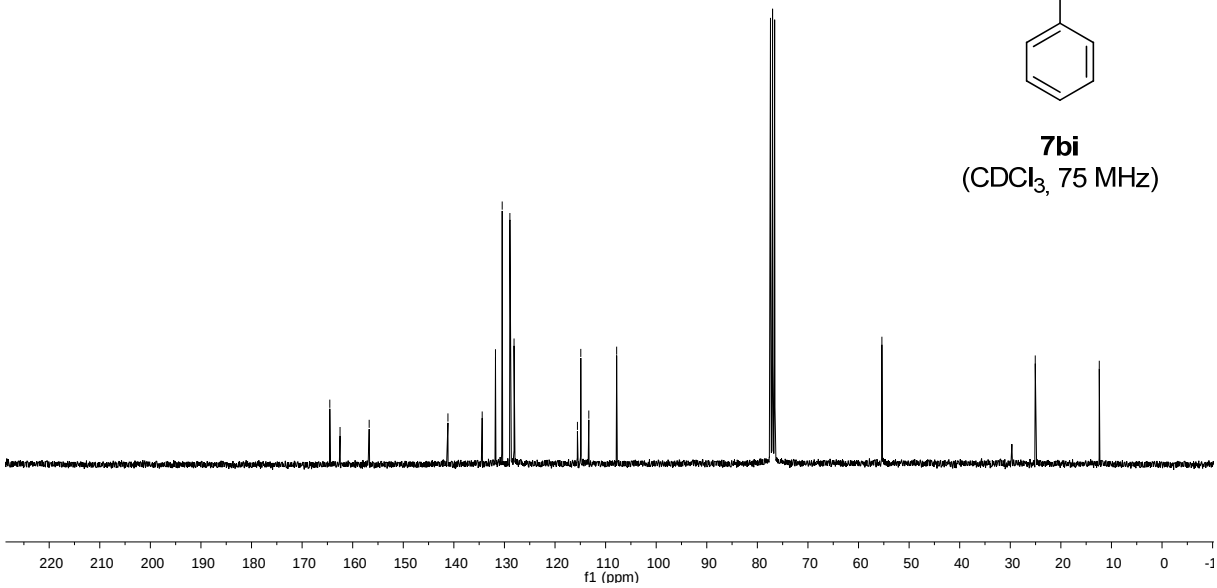
7bi
($CDCl_3$, 300 MHz)



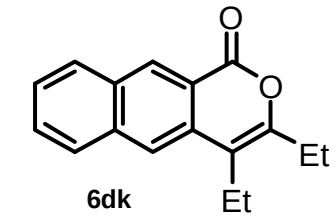




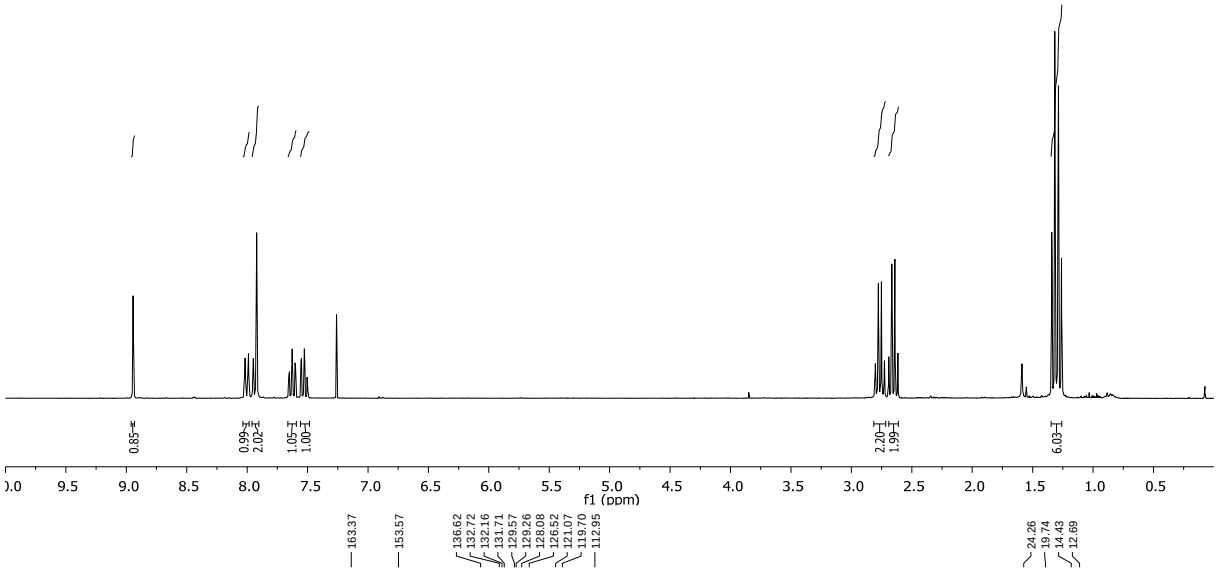
7bi
($CDCl_3$, 75 MHz)

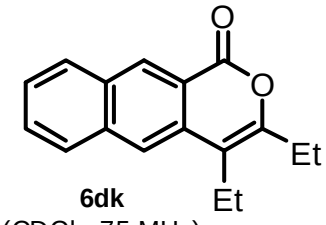


3,4-Diethyl-1*H*-benzo[*g*]isochromen-1-one (6dk)

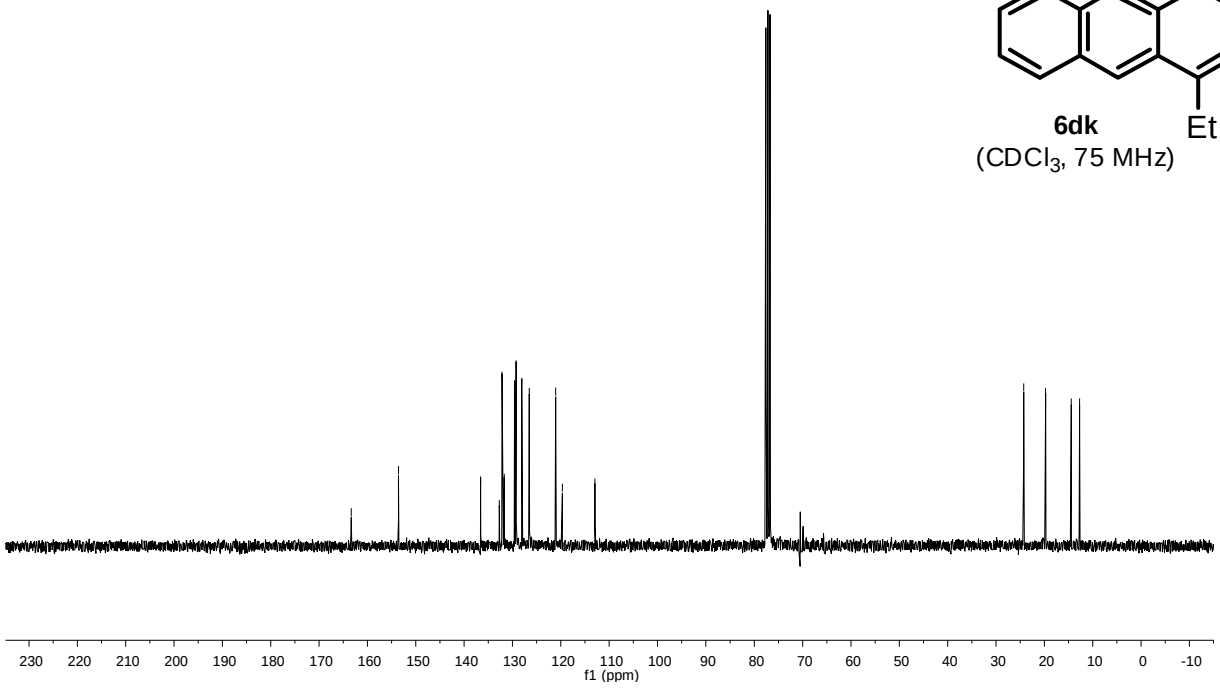


6dk
($CDCl_3$, 300 MHz)

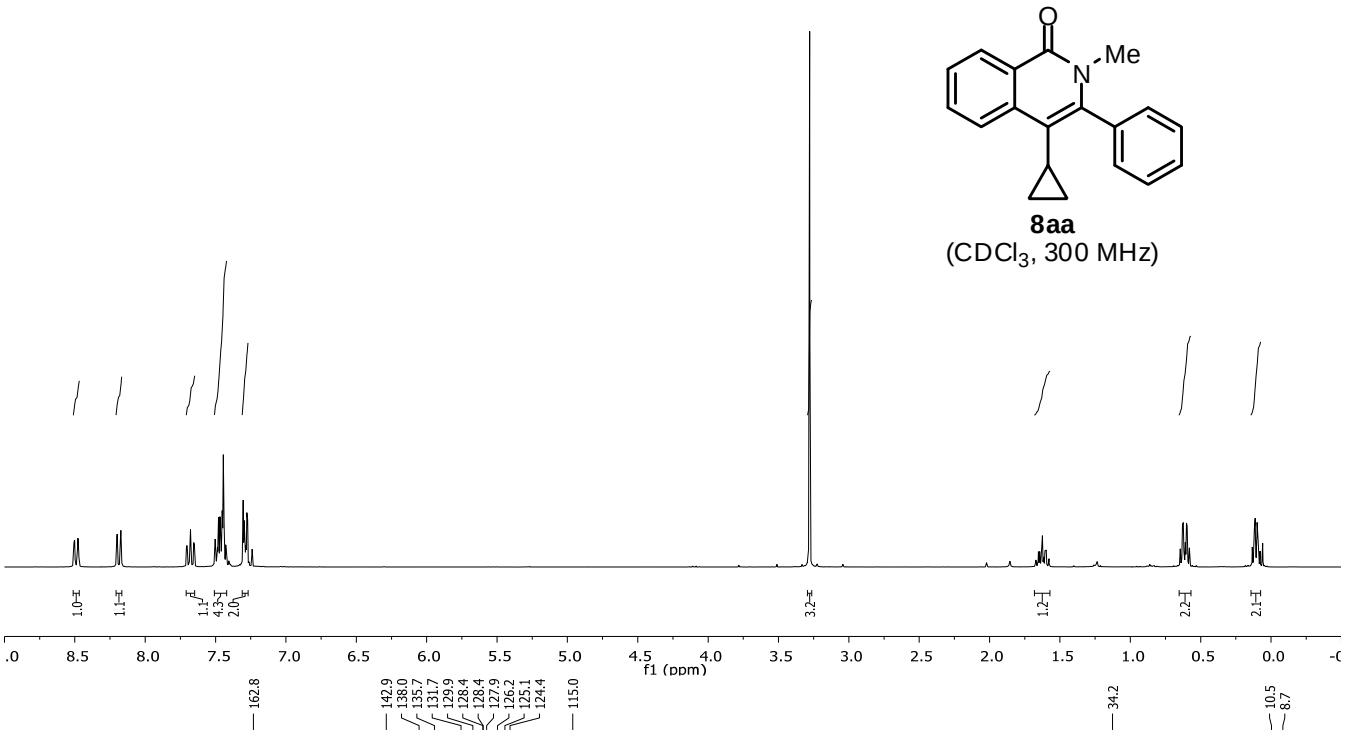


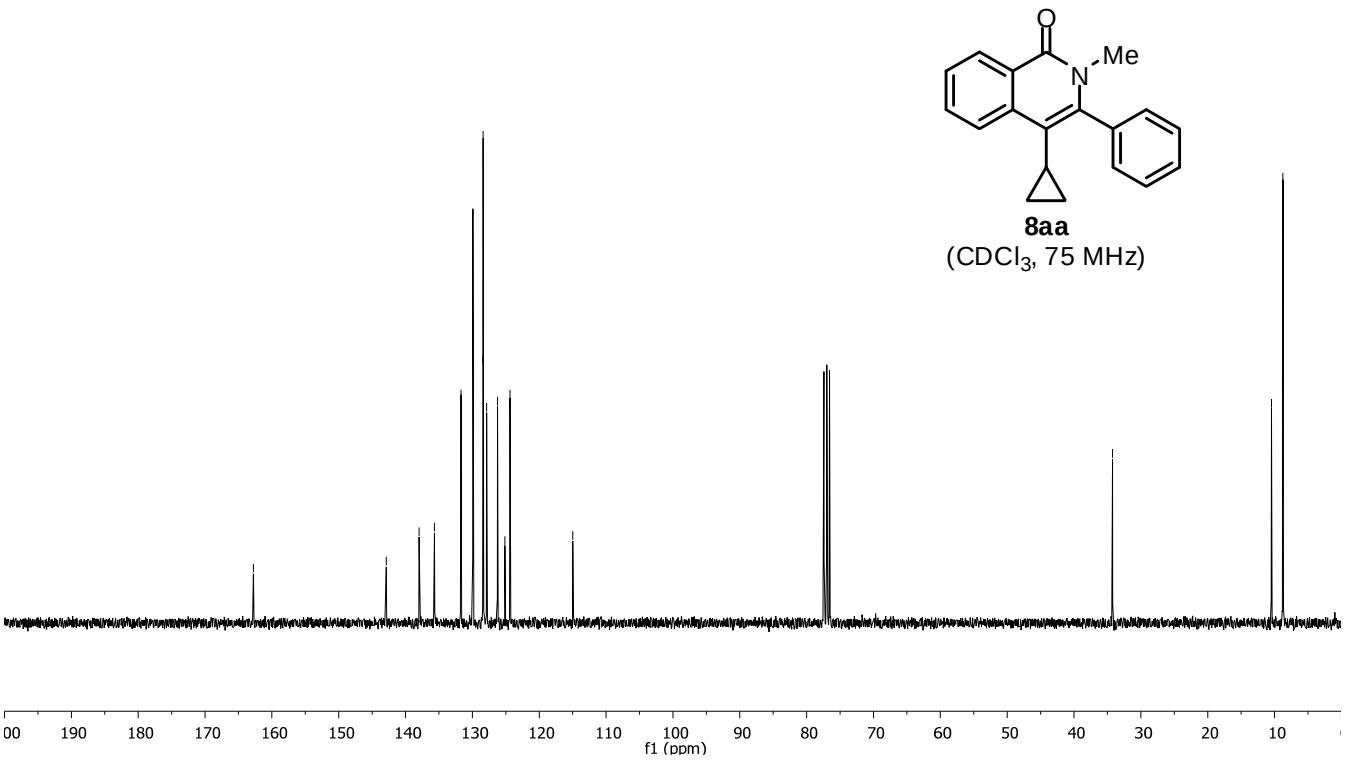


6dk
($CDCl_3$, 75 MHz)

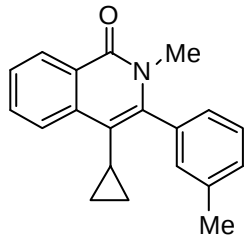


4-Cyclopropyl-2-methyl-3-phenylisoquinolin-1(2H)-one (8aa)

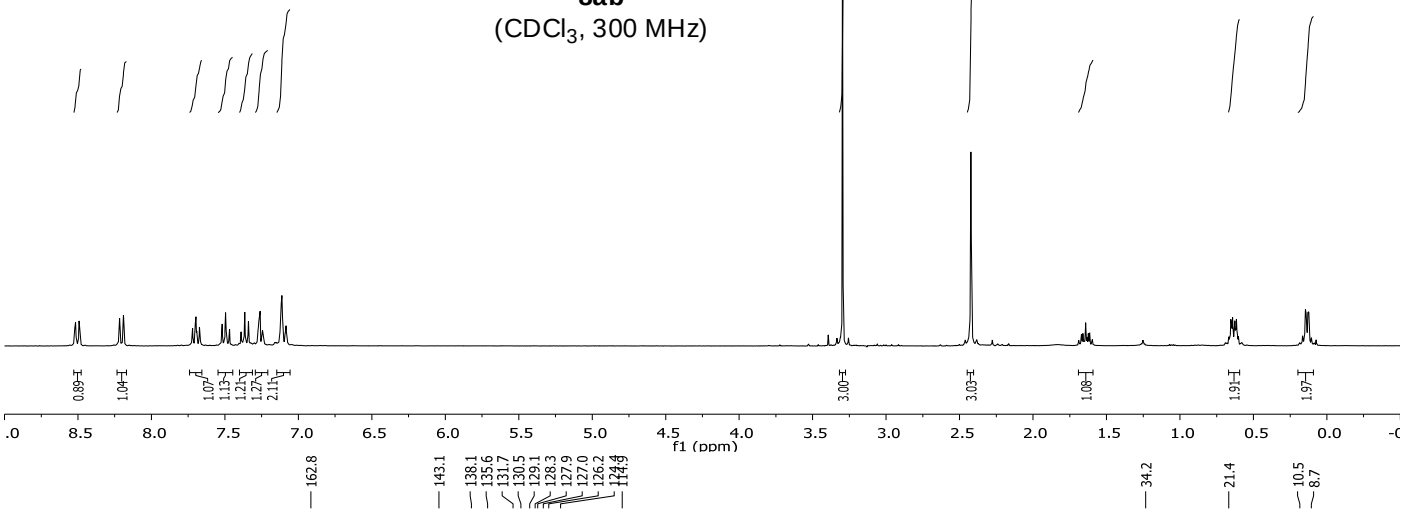


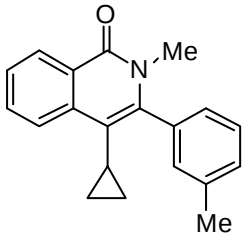


4-Cyclopropyl-2-methyl-3-(*m*-tolyl)isoquinolin-1(2*H*)-one (8ab)



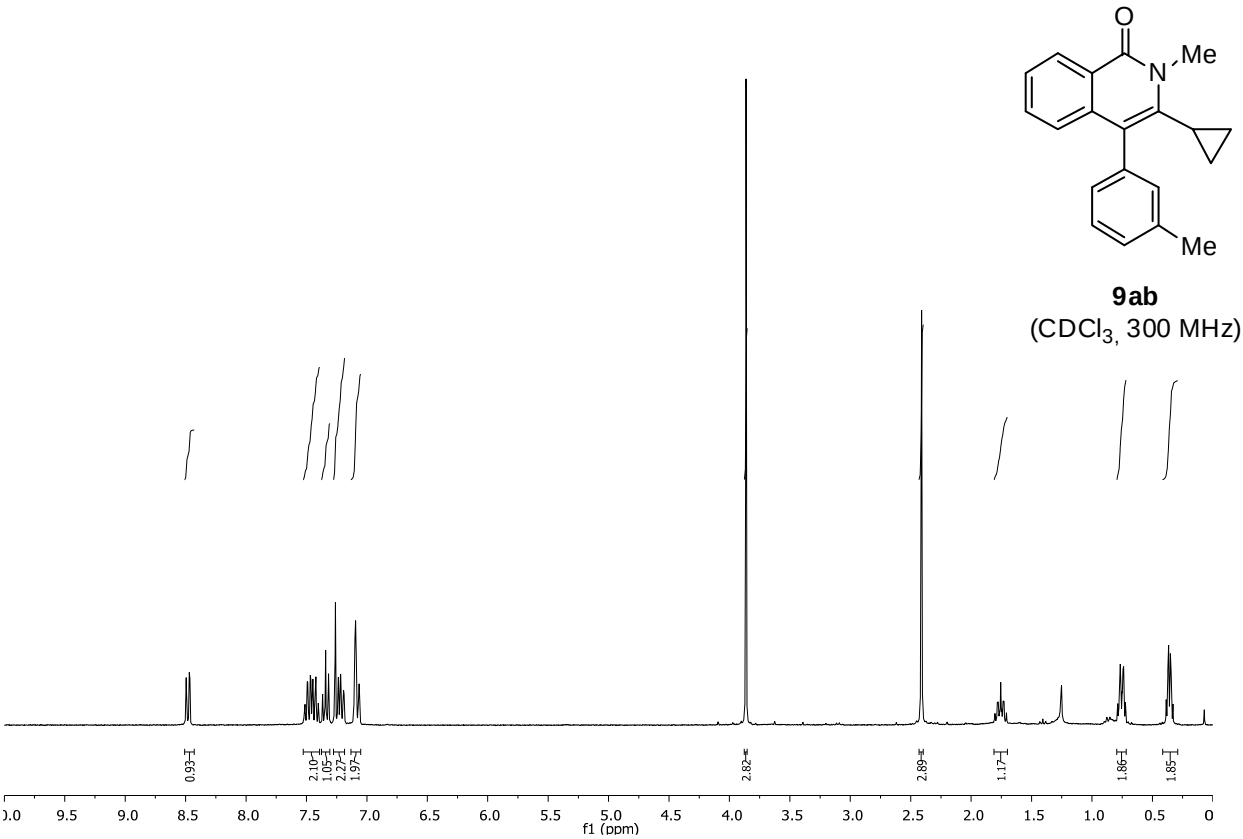
8ab
($CDCl_3$, 300 MHz)



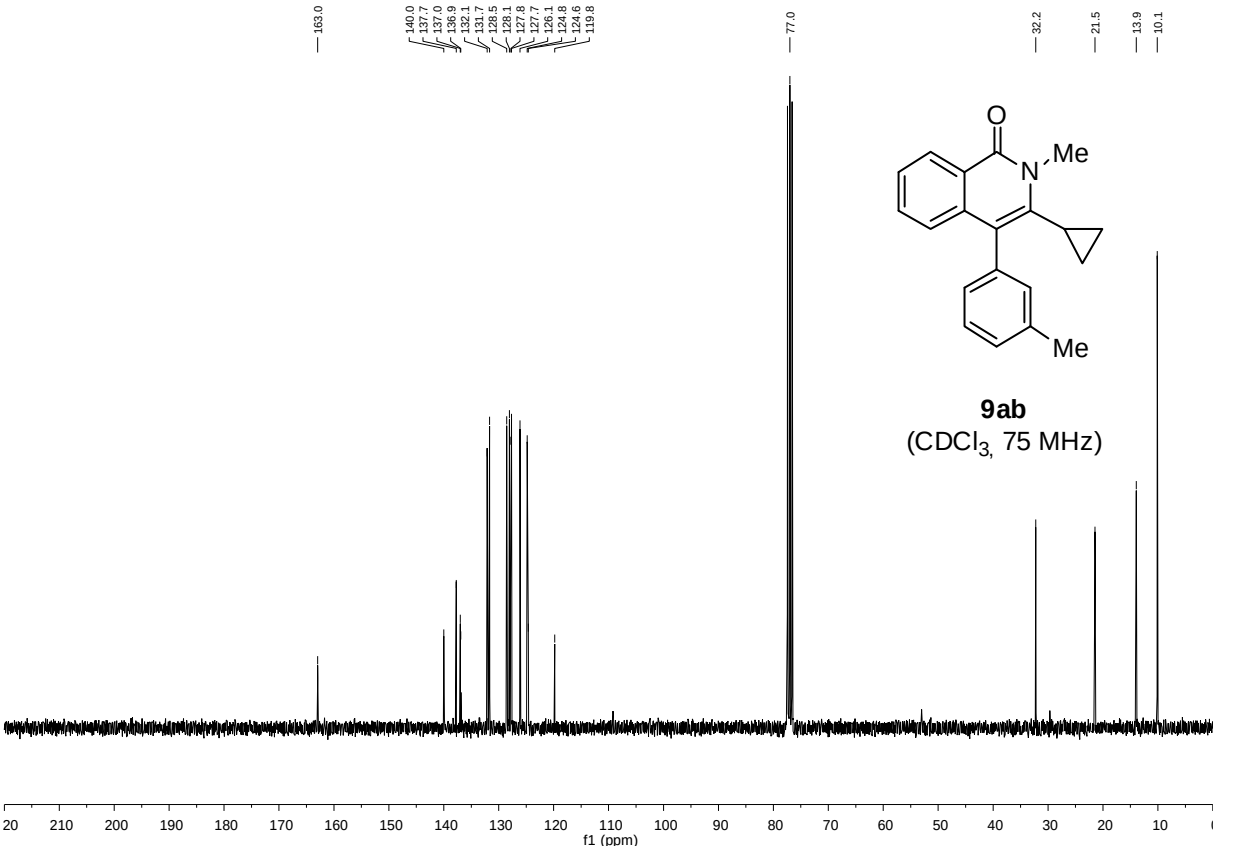


8ab
($CDCl_3$, 75 MHz)

3-Cyclopropyl-2-methyl-4-(*m*-tolyl)isoquinolin-1(2*H*)-one (9ab)

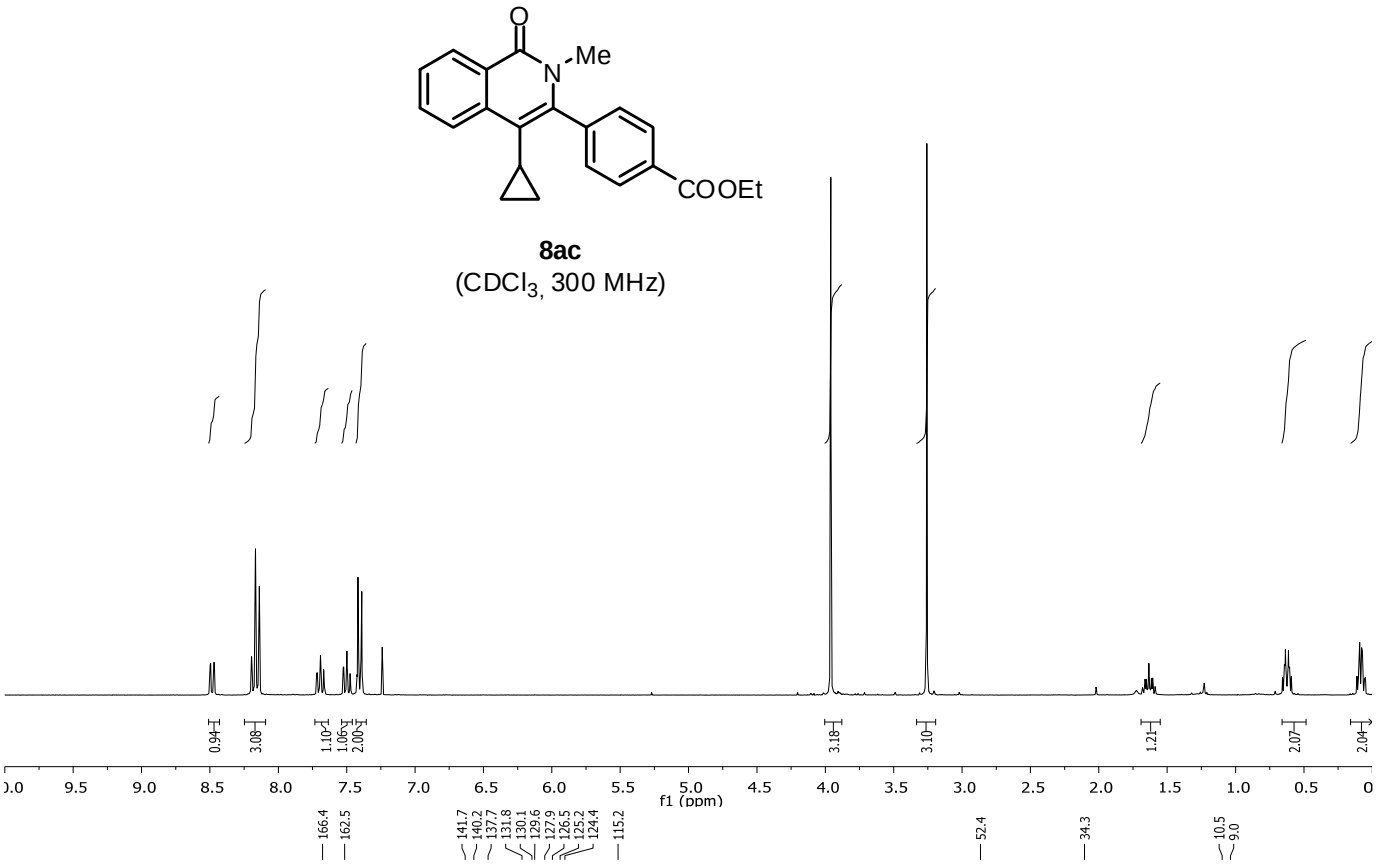


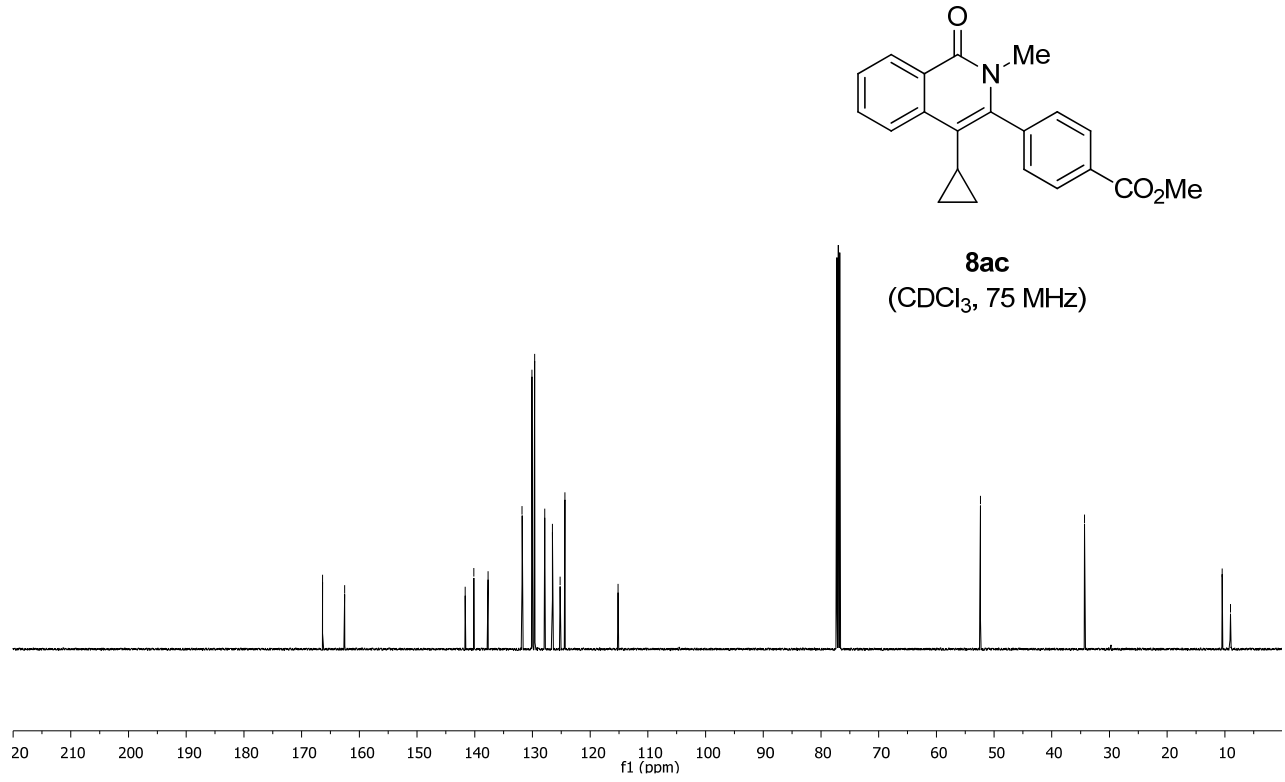
9ab
($CDCl_3$, 300 MHz)



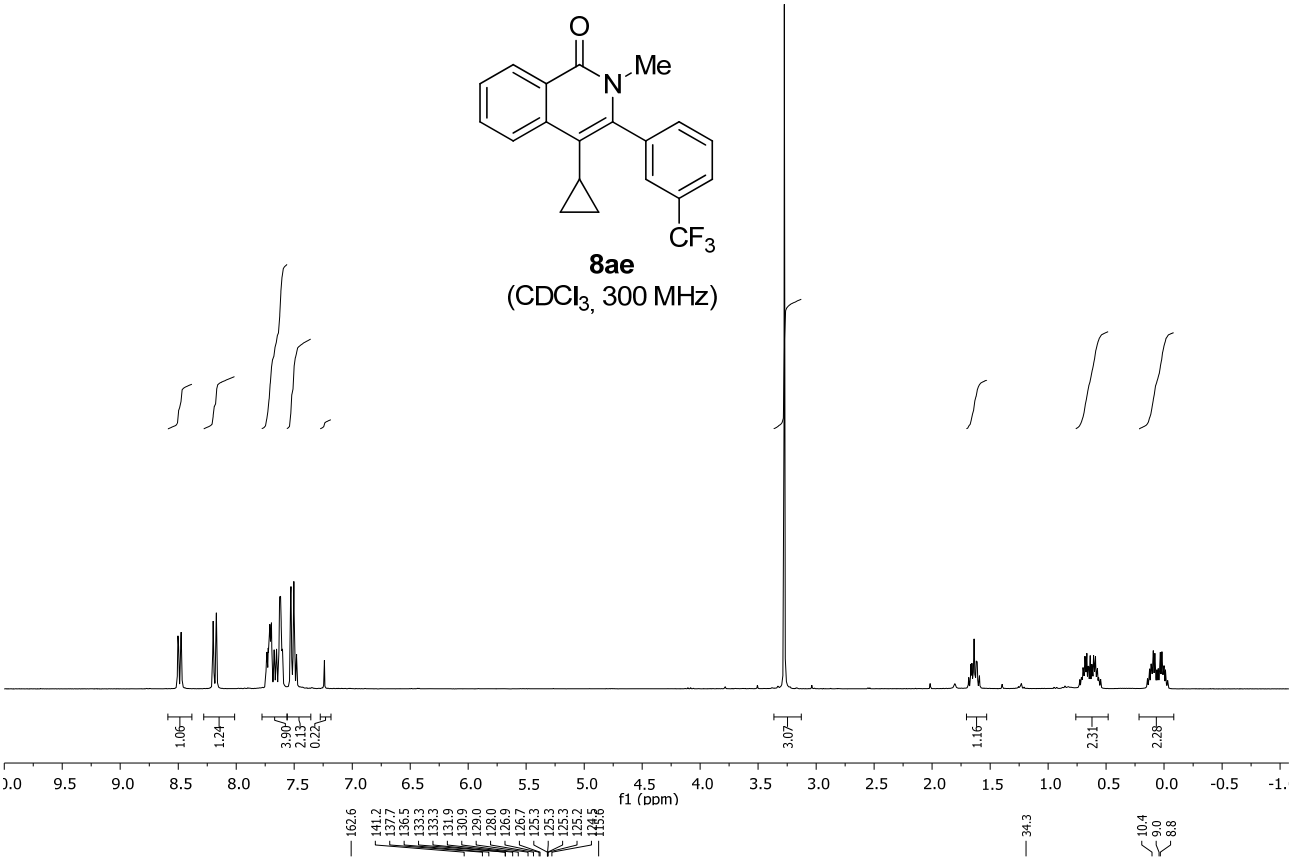
9ab
($CDCl_3$, 75 MHz)

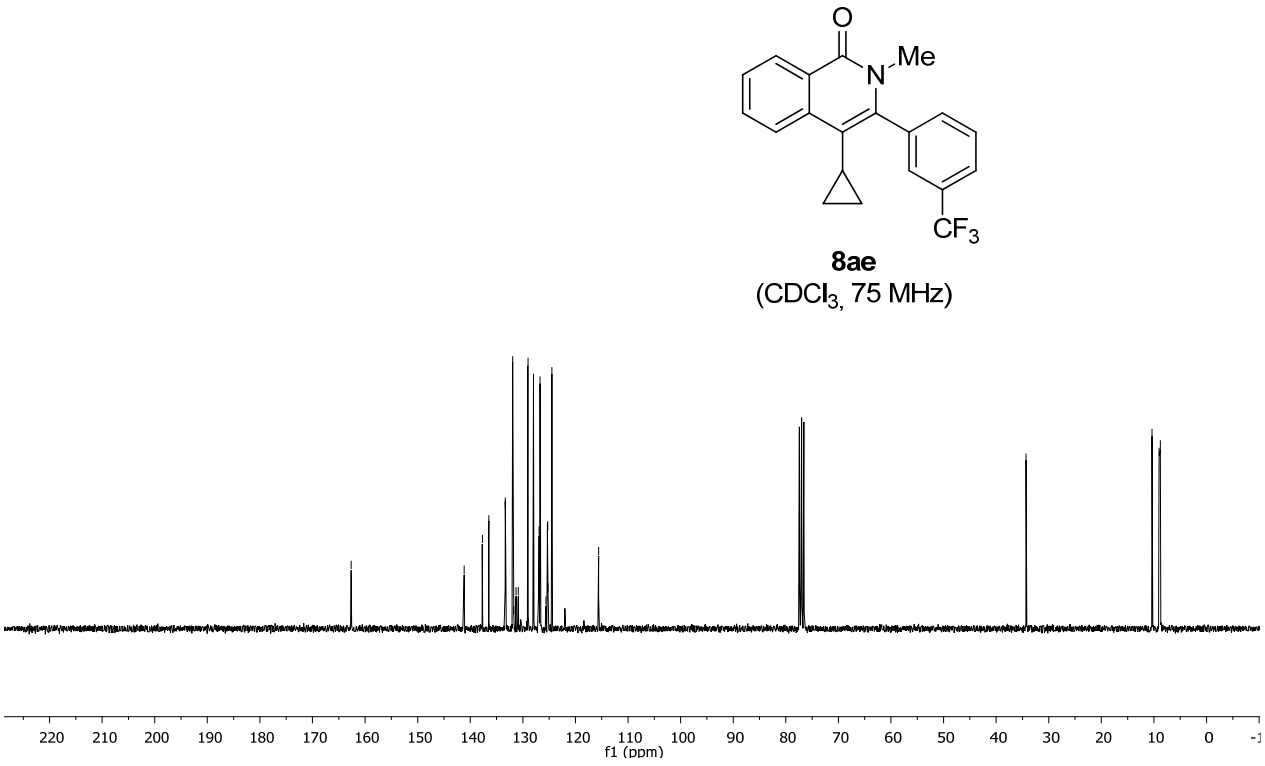
Methyl 4-(4-cyclopropyl-2-methyl-1-oxo-1,2-dihydroisoquinolin-3-yl)benzoate (8ac)



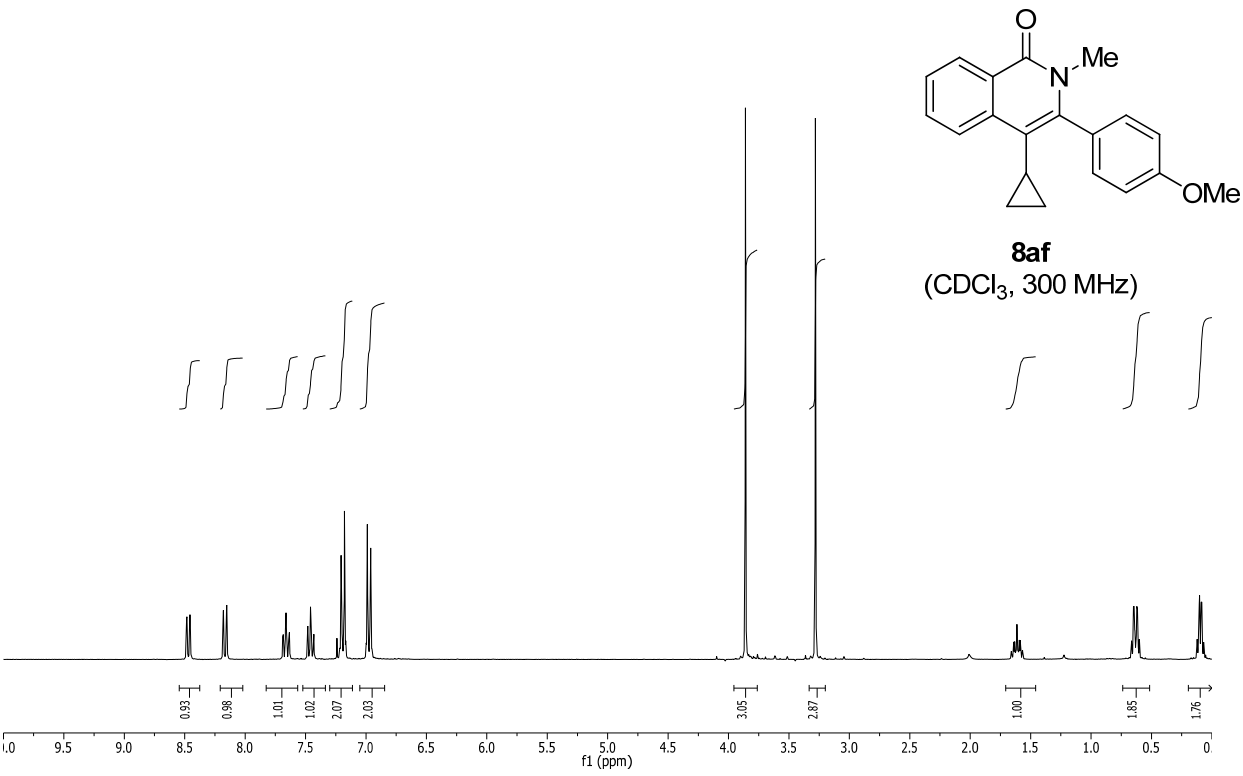


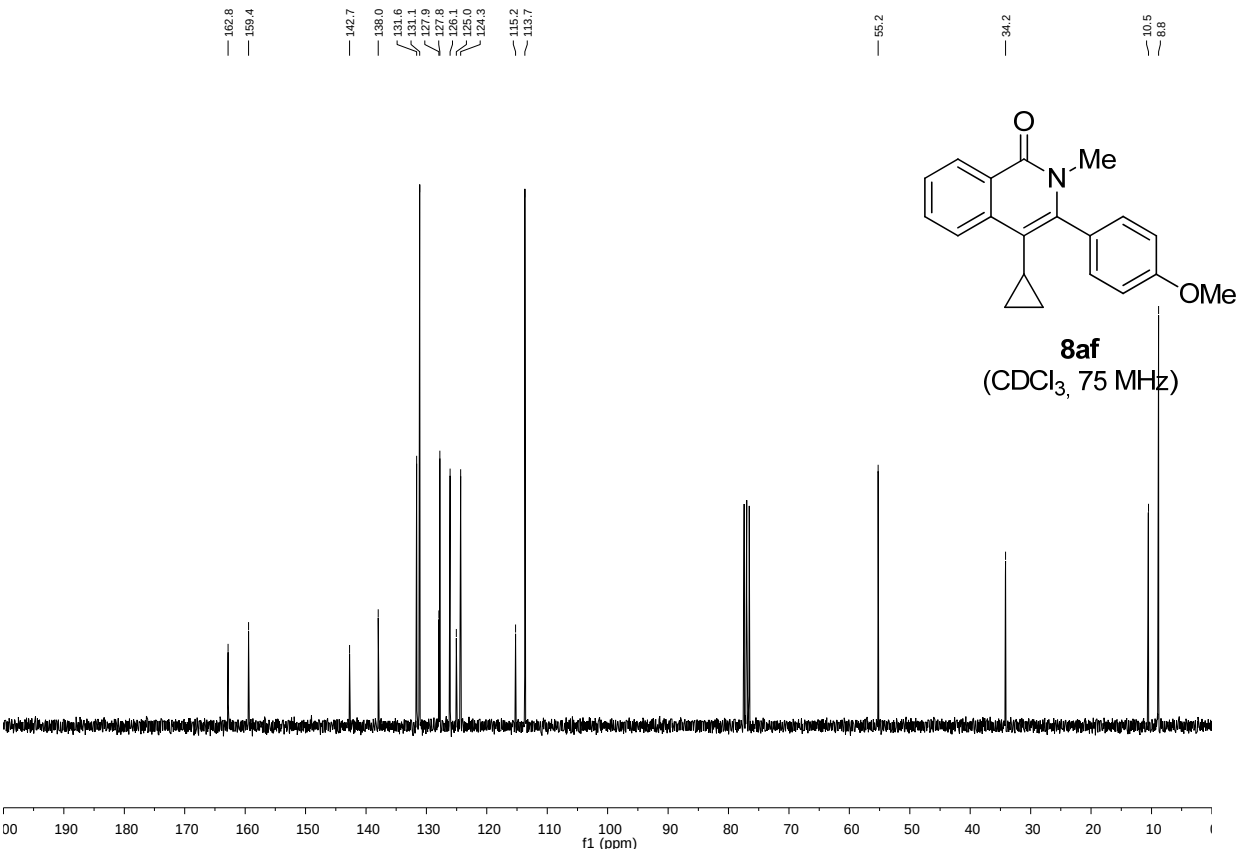
4-Cyclopropyl-2-methyl-3-(3-(trifluoromethyl)phenyl)isoquinolin-1(2*H*)-one (8ae)



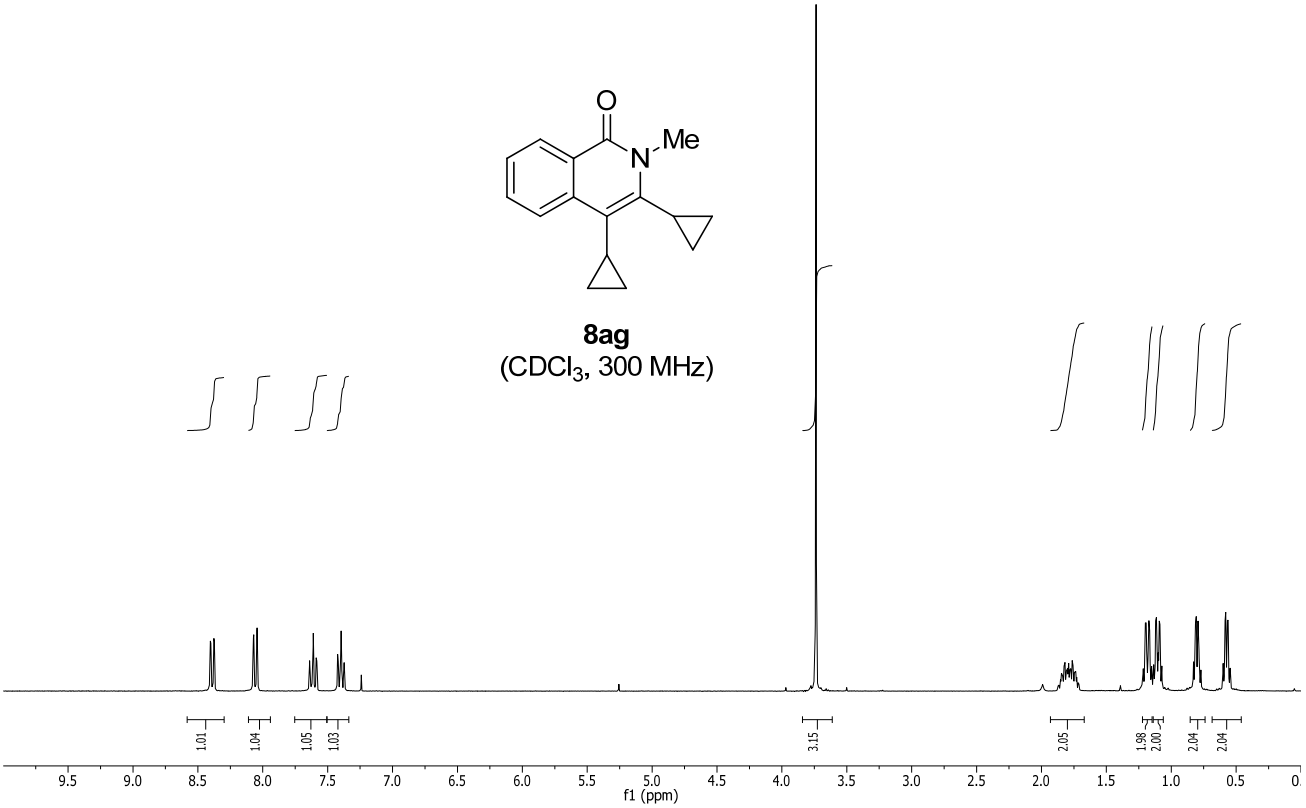


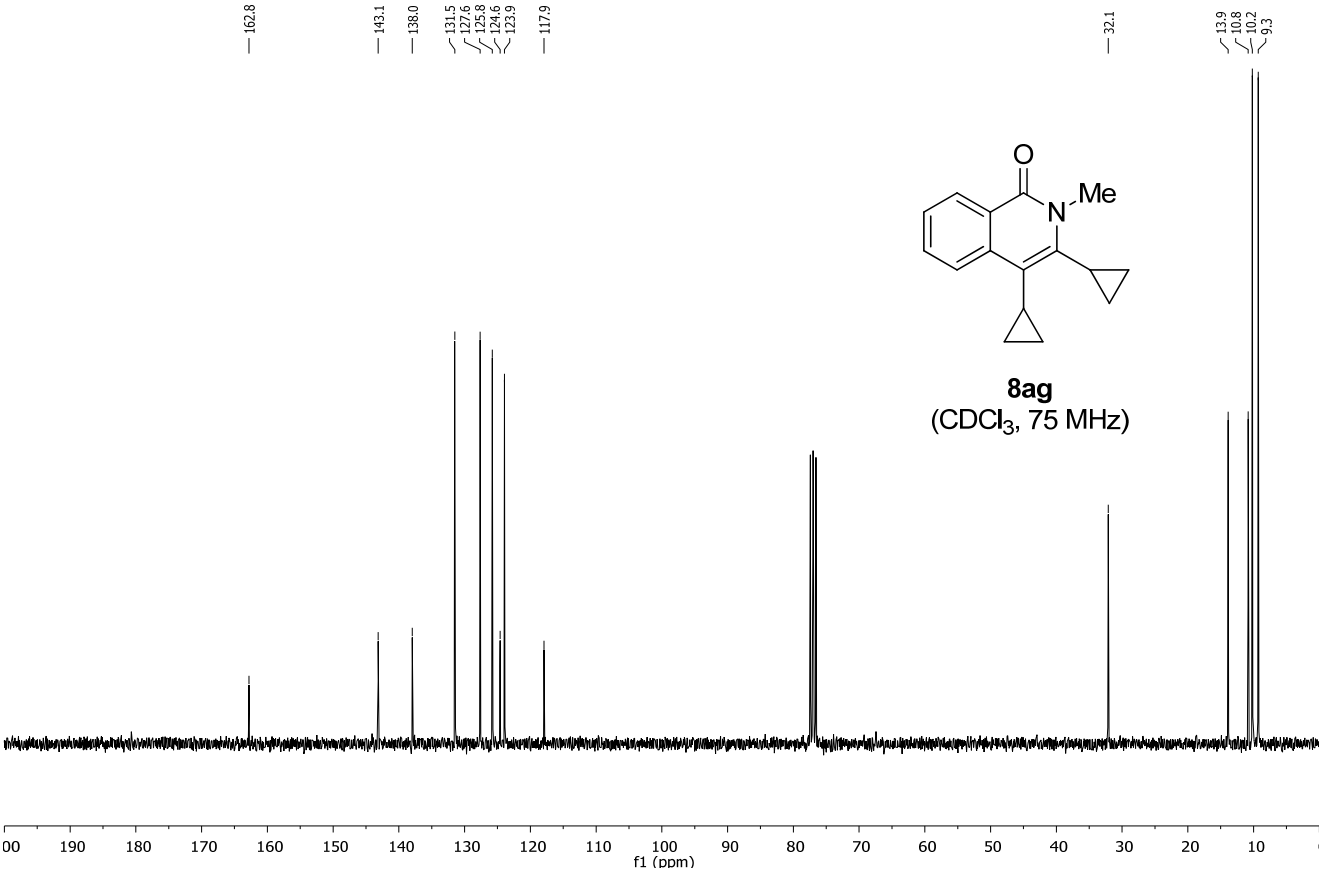
4-Cyclopropyl-3-(4-methoxyphenyl)-2-methylisoquinolin-1(2*H*)-one (8af)



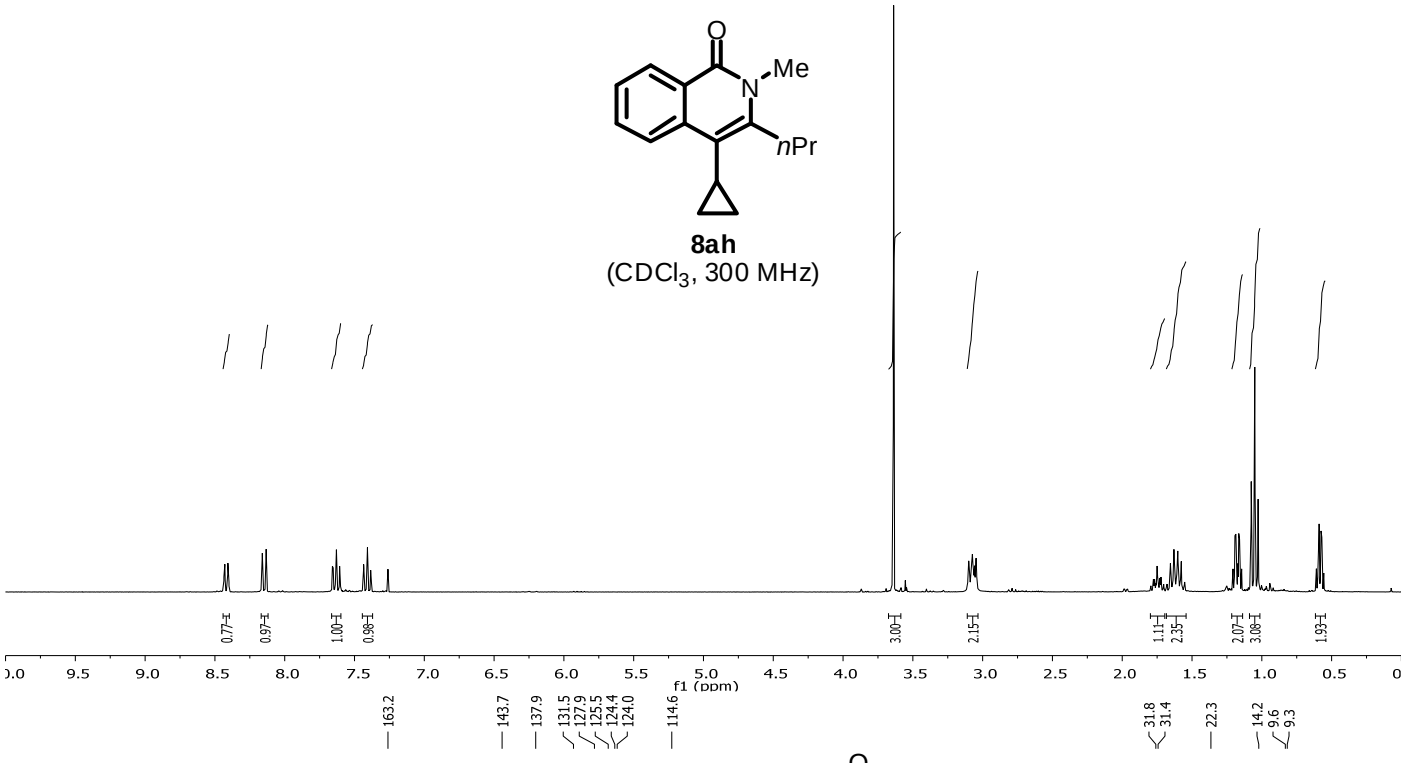


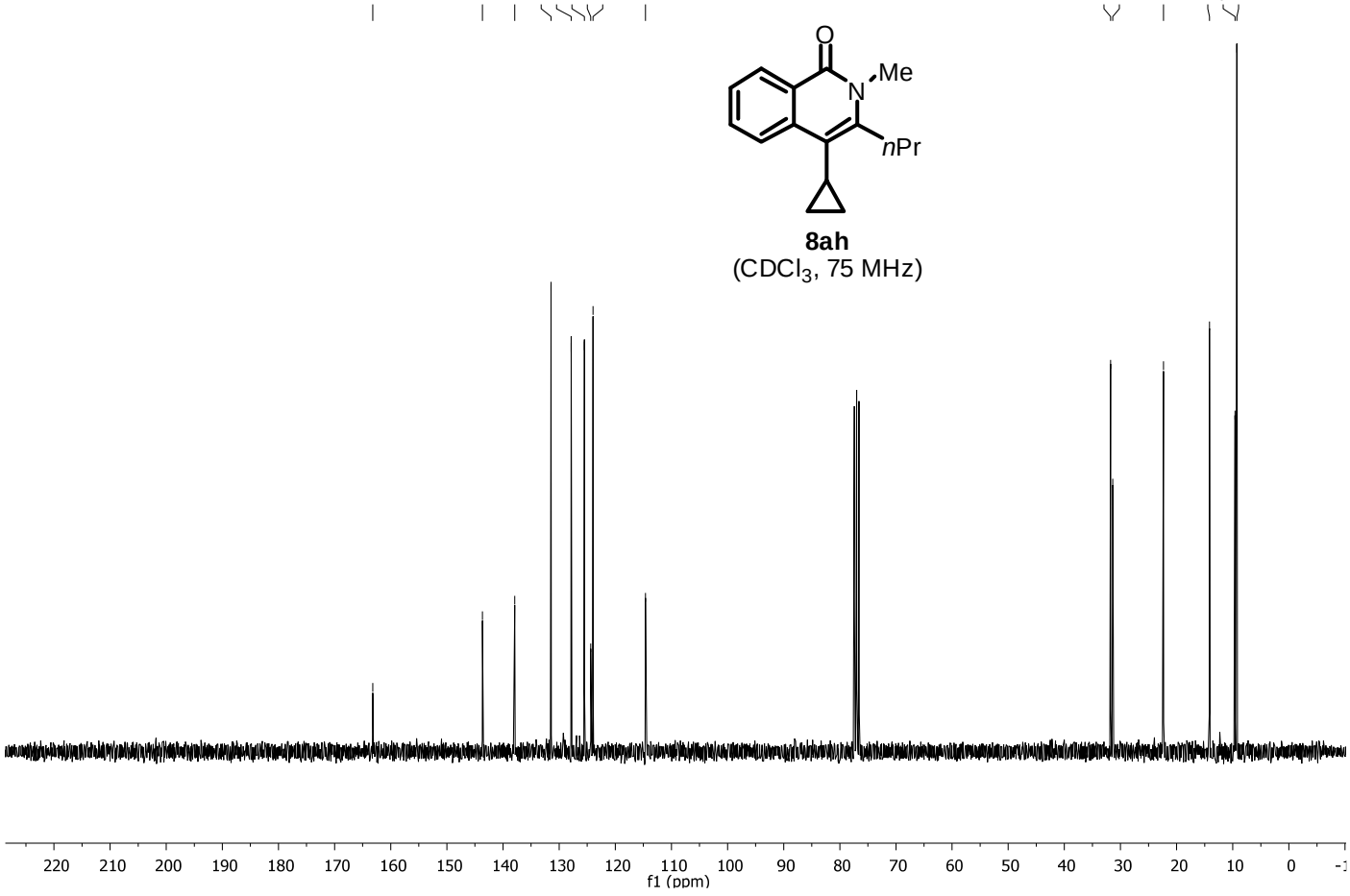
3,4-Dicyclopropyl-2-methylisoquinolin-1(2*H*)-one (8ag)



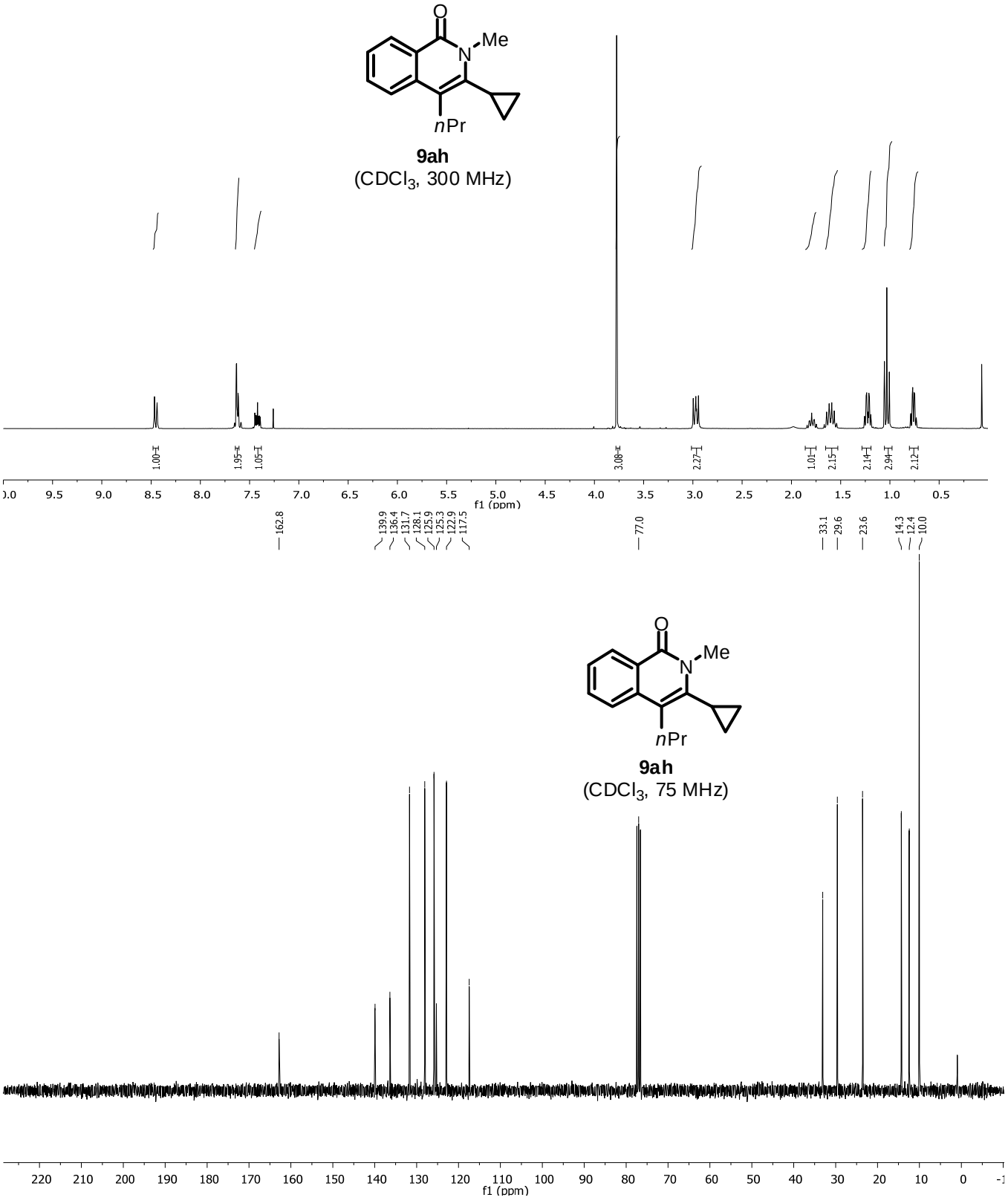


4-Cyclopropyl-2-methyl-3-propylisoquinolin-1(2*H*)-one (8ah)

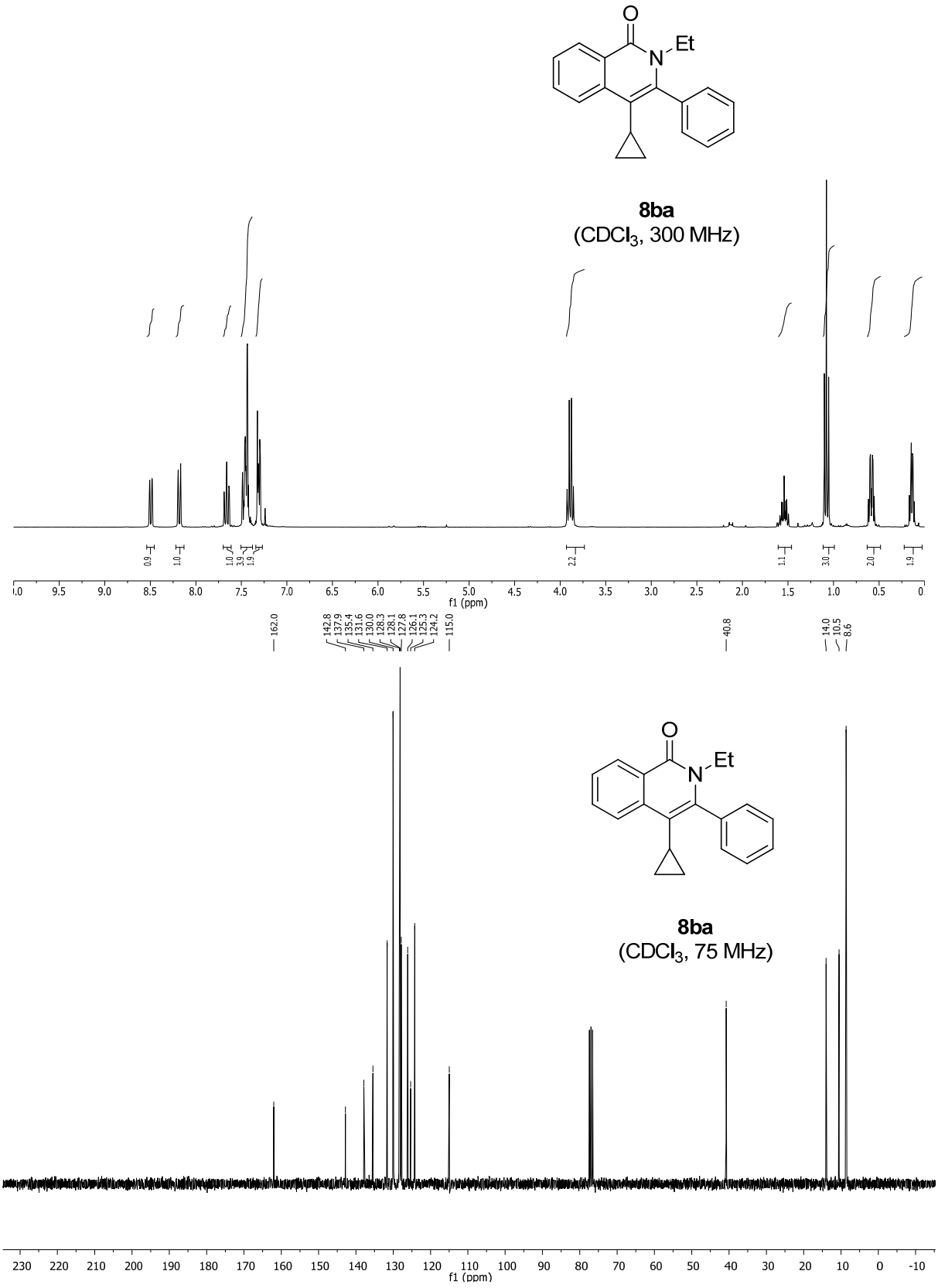




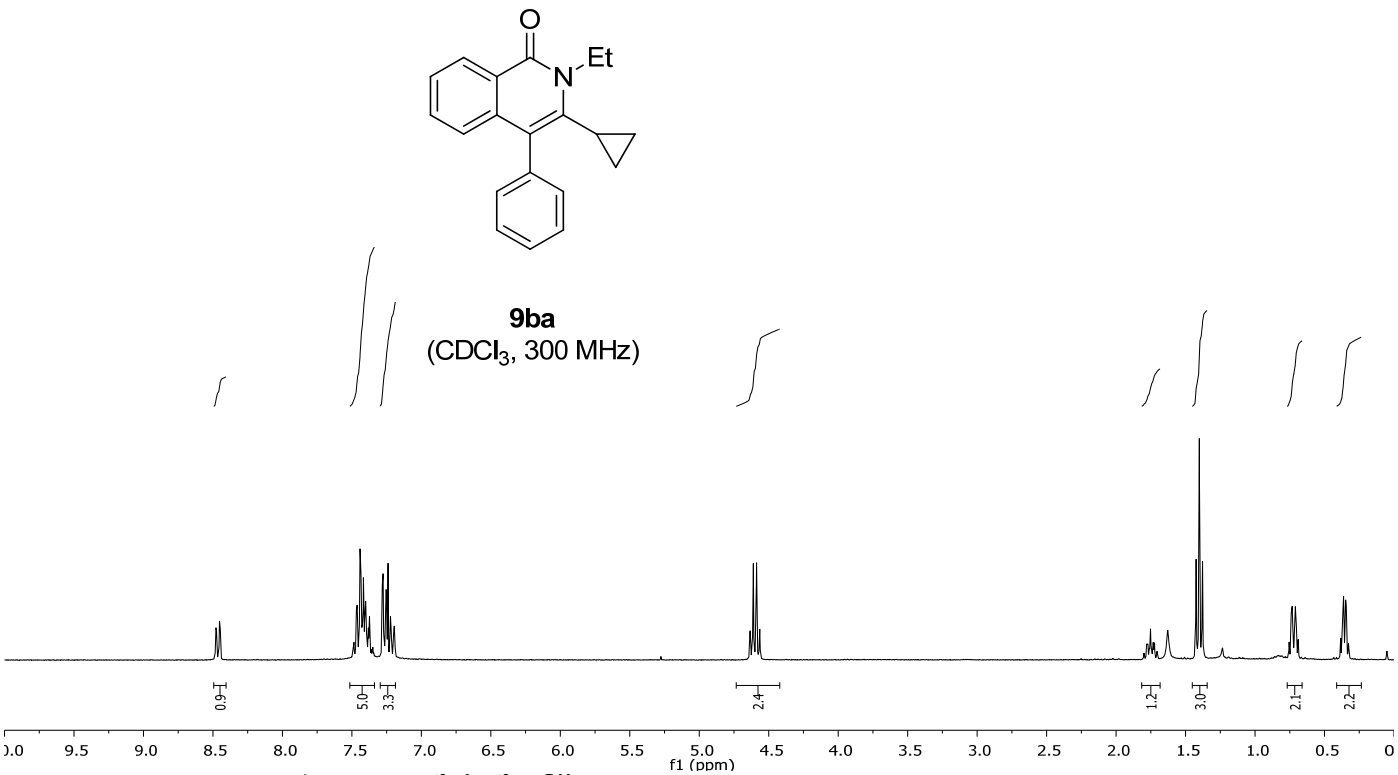
3-Cyclopropyl-2-methyl-4-propylisoquinolin-1(2*H*)-one (9ah)

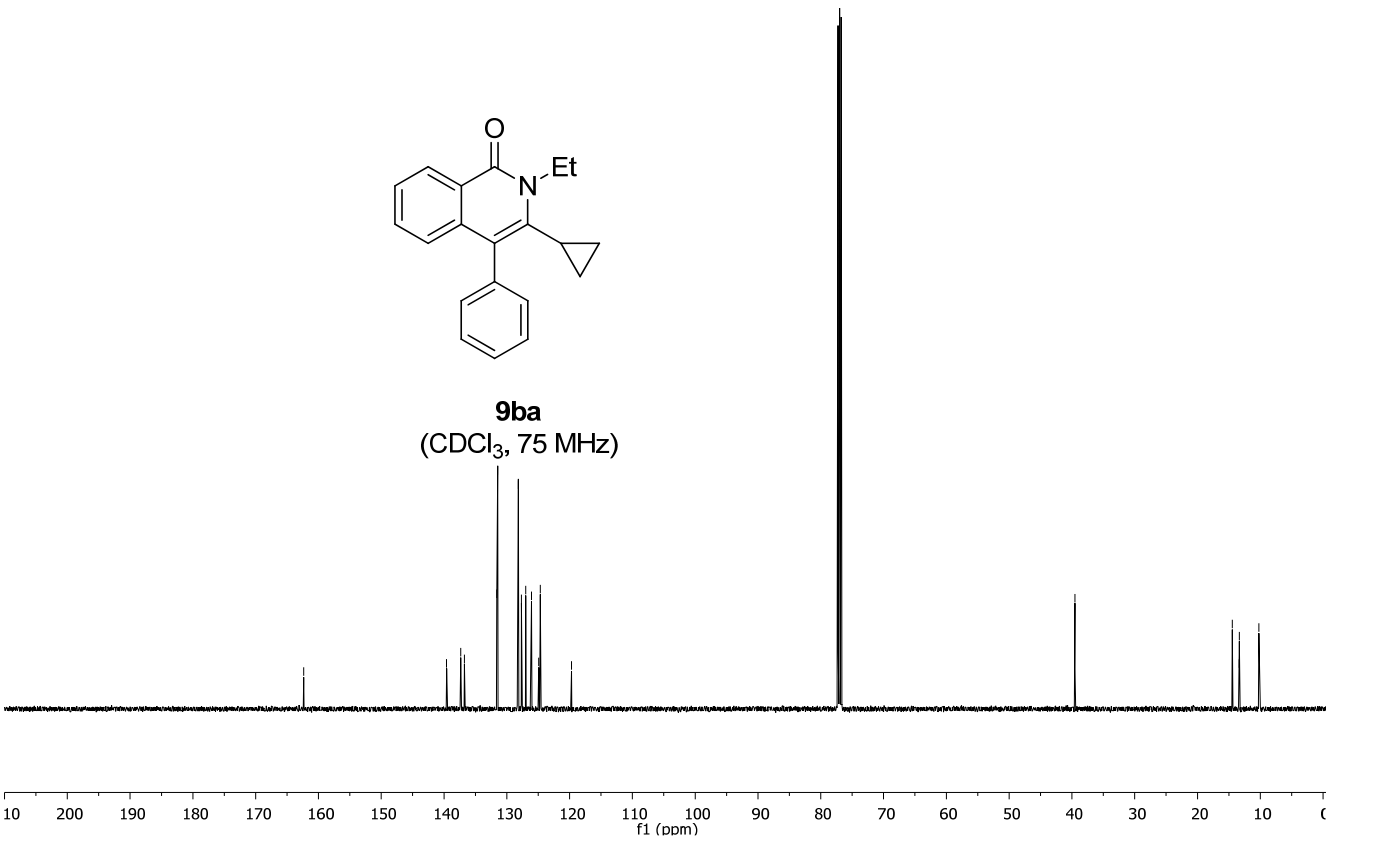


4-Cyclopropyl-2-ethyl-3-phenylisoquinolin-1(2*H*)-one (8ba)

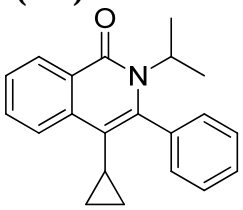


3-Cyclopropyl-2-ethyl-3-phenylisoquinolin-1(2*H*)-one (9ba)

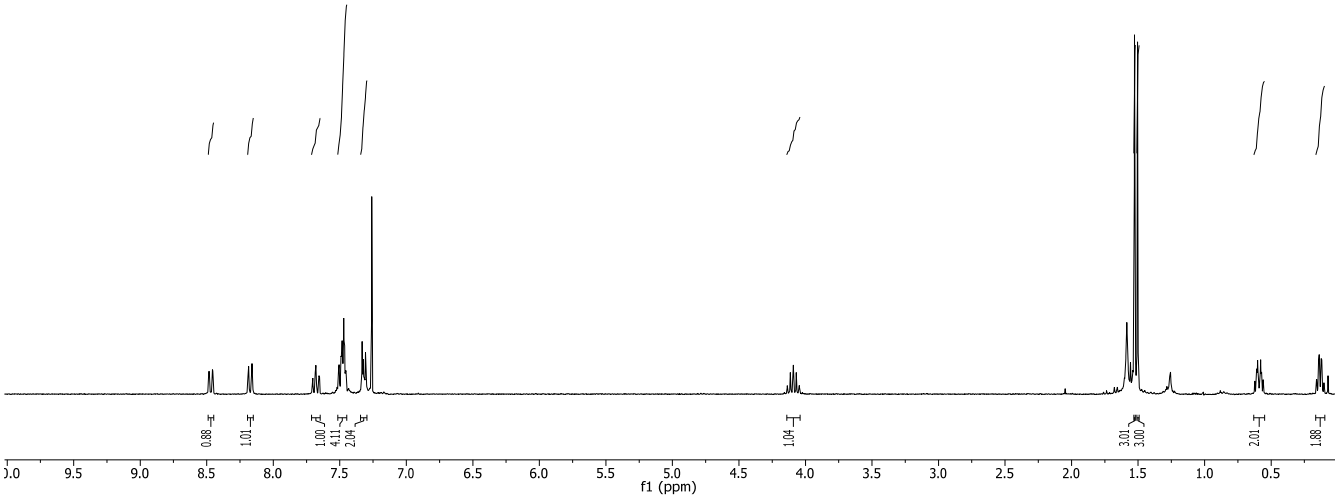


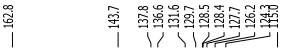


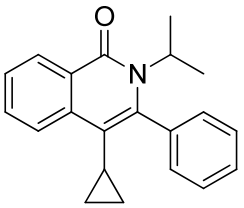
4-Cyclopropyl-2-isopropyl-3-phenylisoquinolin-1(2*H*)-one (8ca)



8ca
($CDCl_3$, 300 MHz)

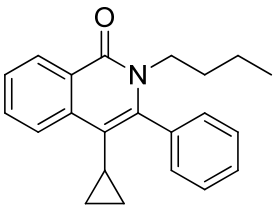




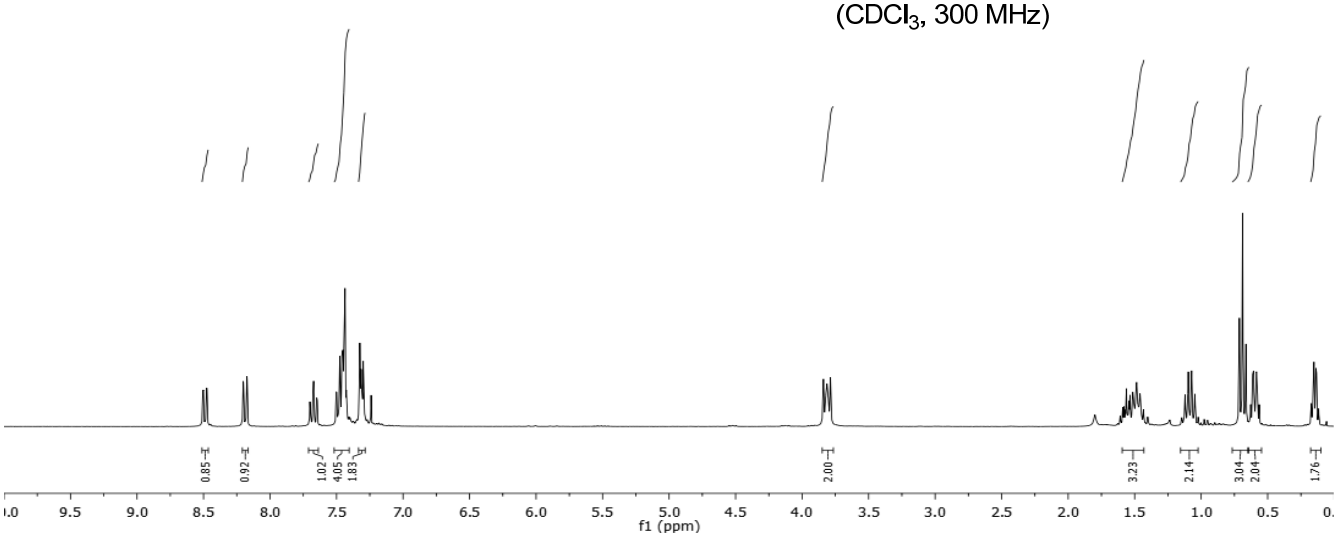


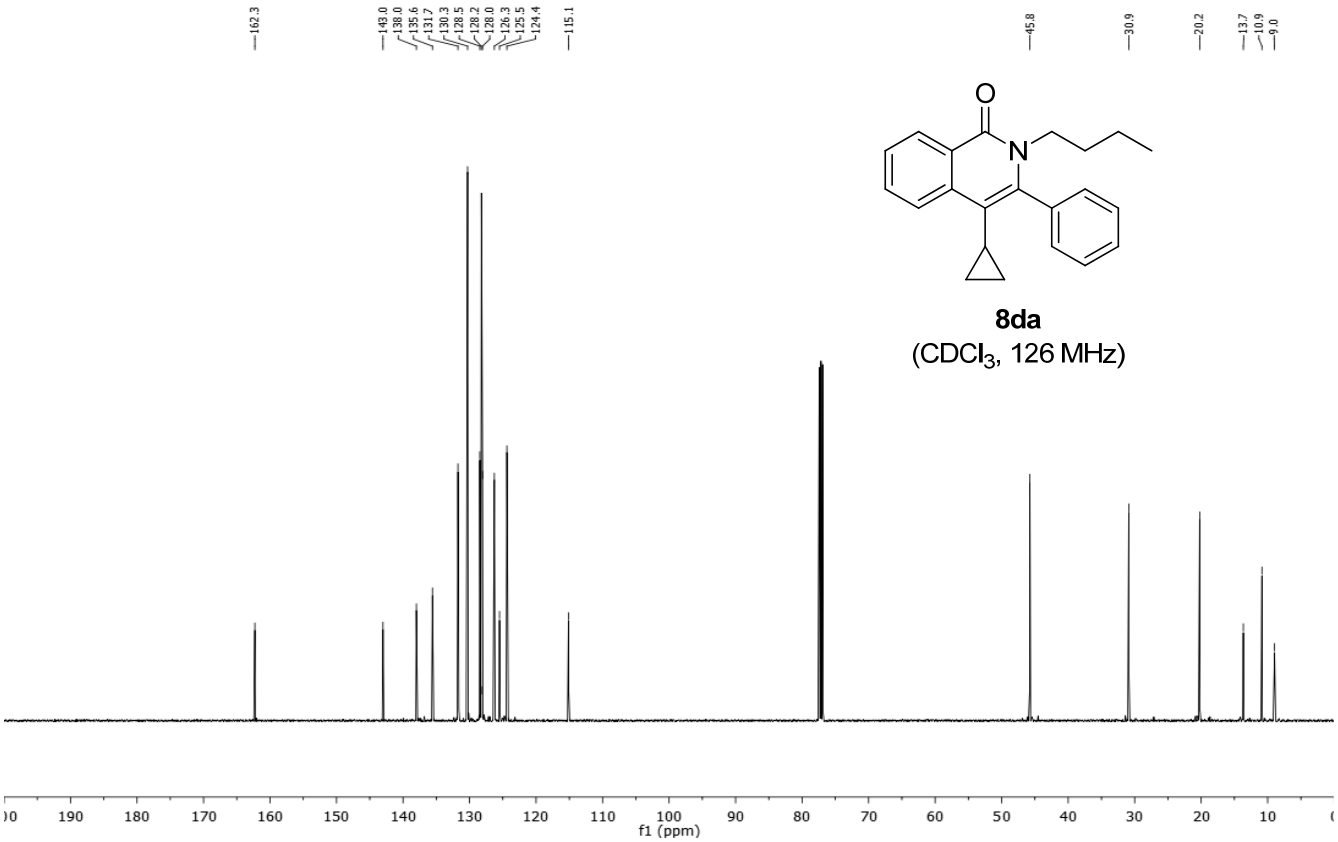
8ca
($CDCl_3$, 126 MHz)

2-butyl-4-cyclopropyl-3-phenylisoquinolin-1(2*H*)-one (8da)



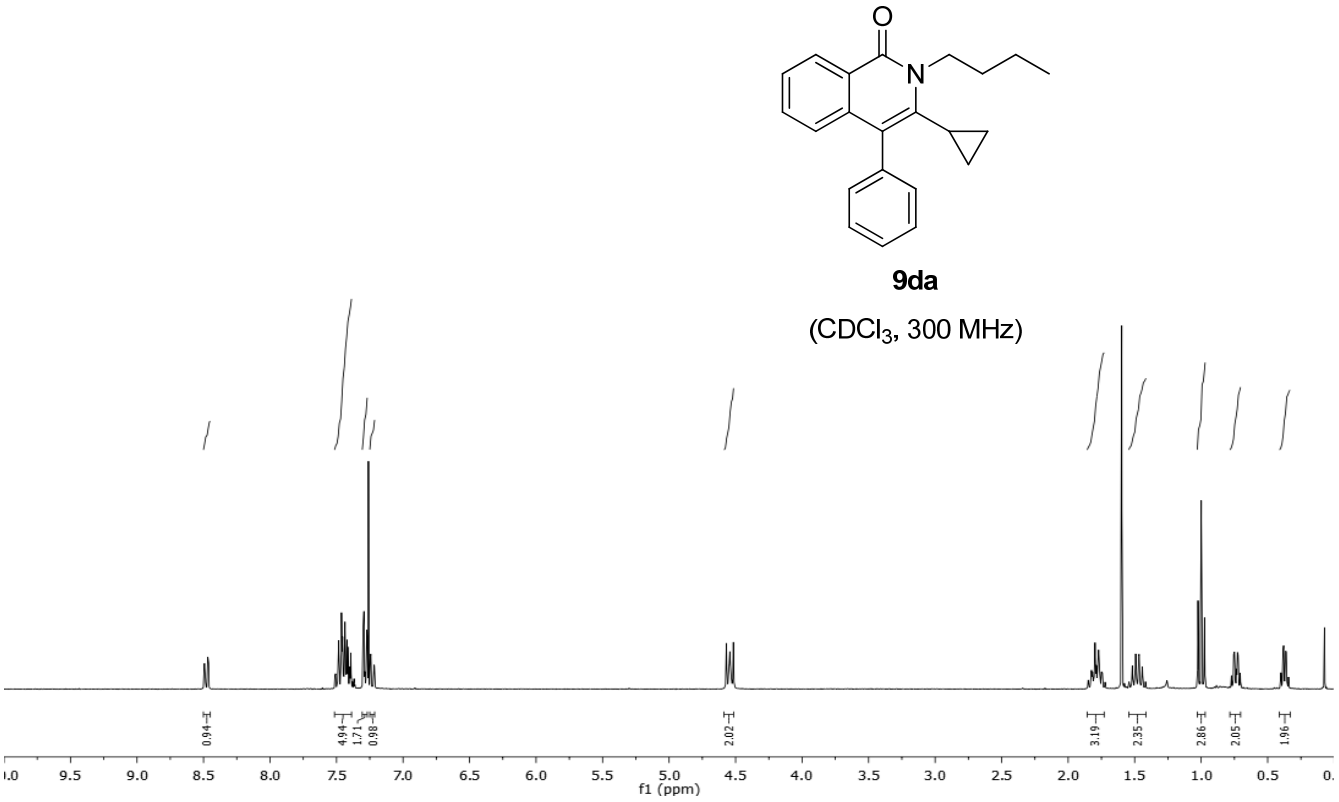
8da
($CDCl_3$, 300 MHz)

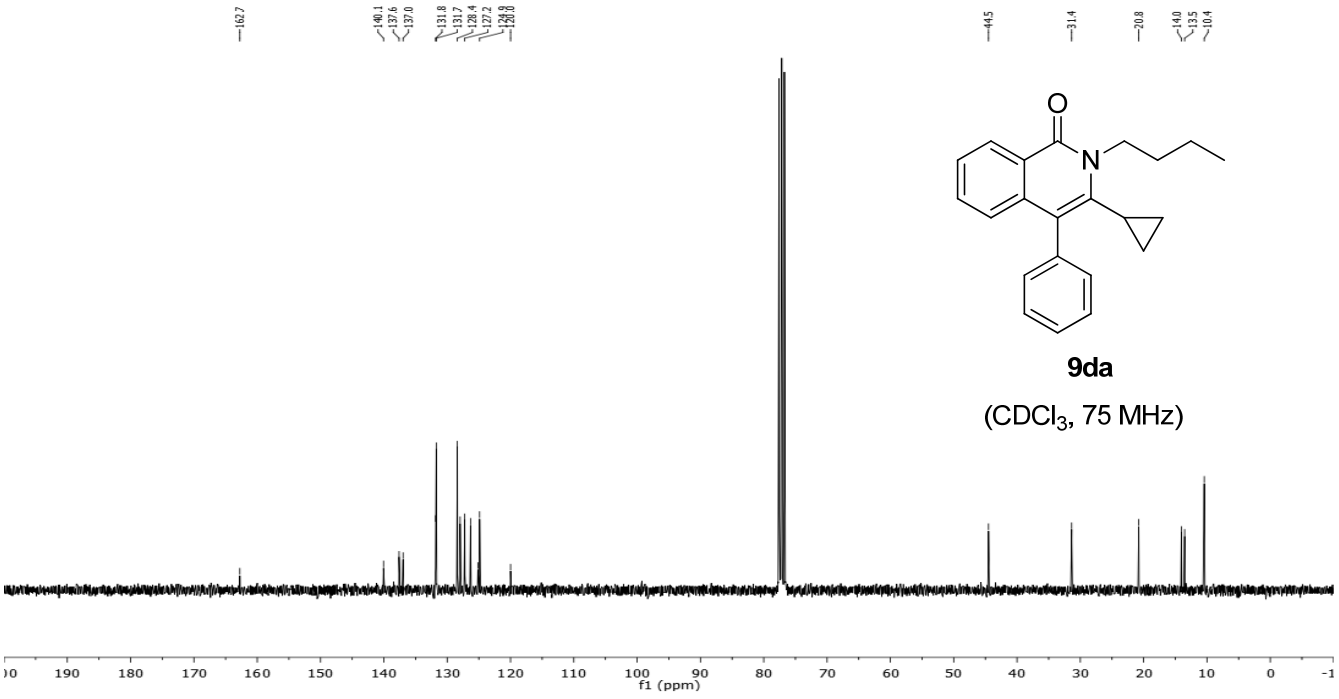




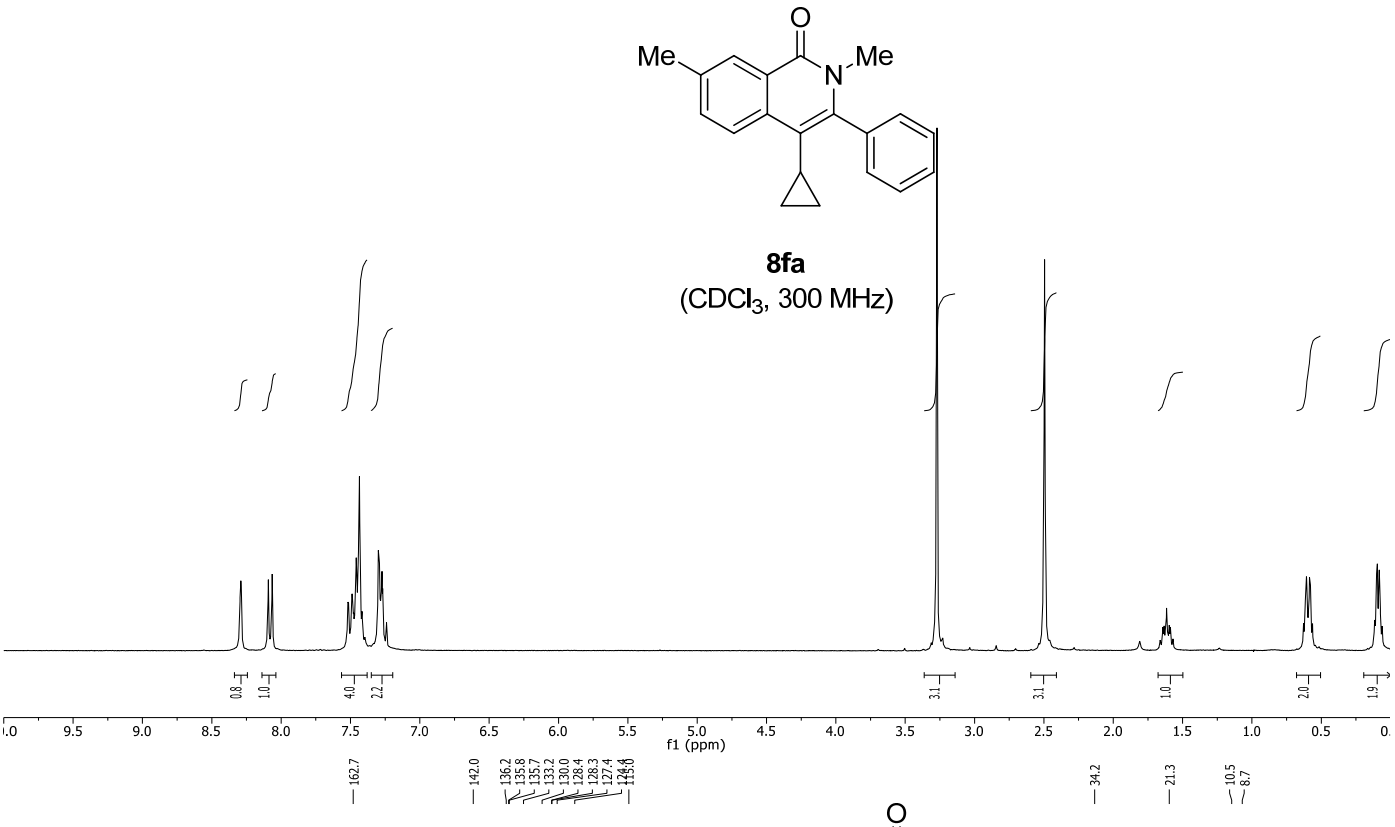
8da
($CDCl_3$, 126 MHz)

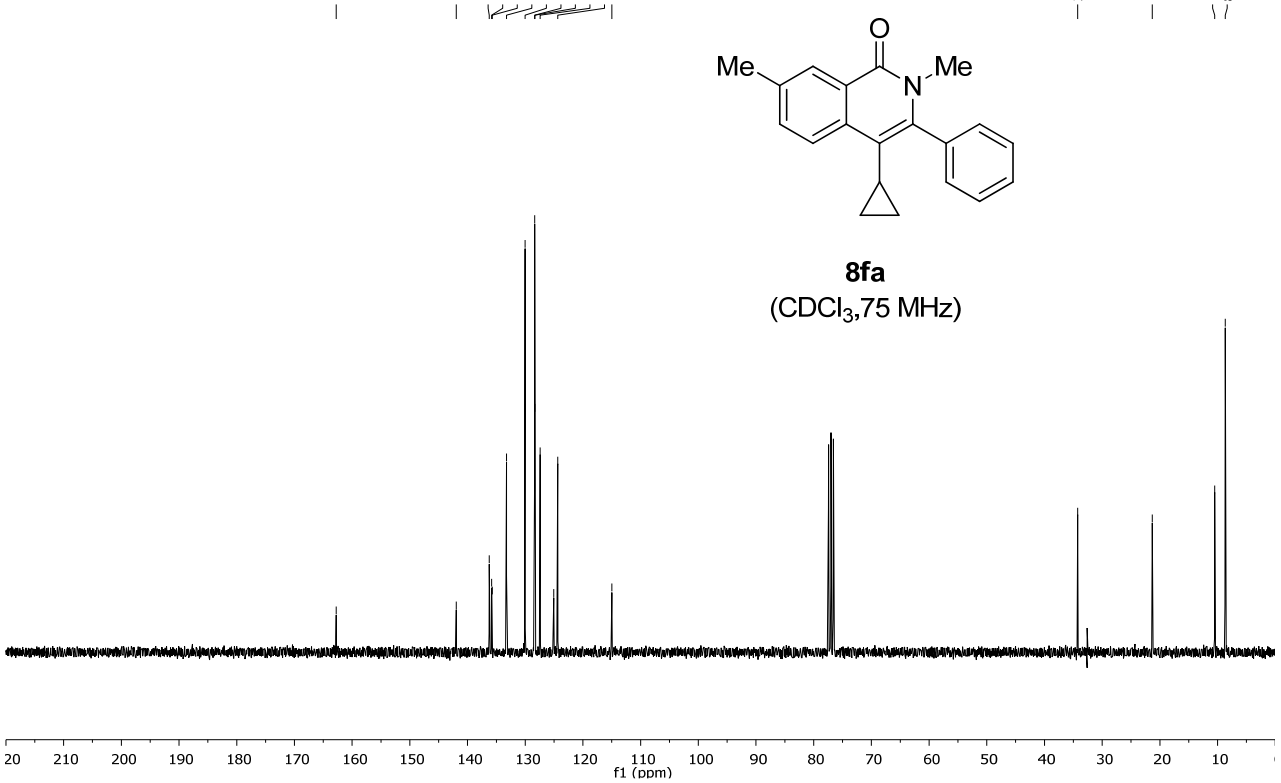
2-Butyl-3-cyclopropyl-4-phenylisoquinolin-1(2*H*)-one (9da)



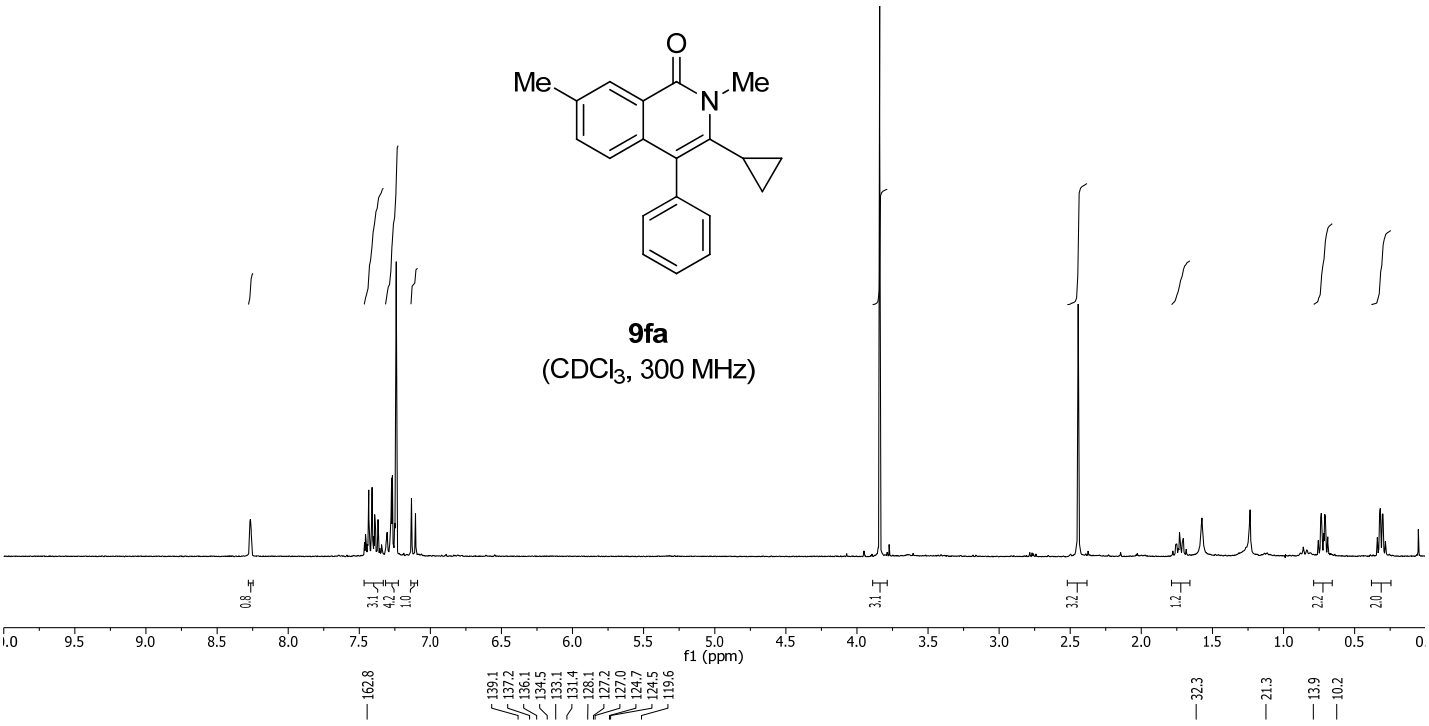


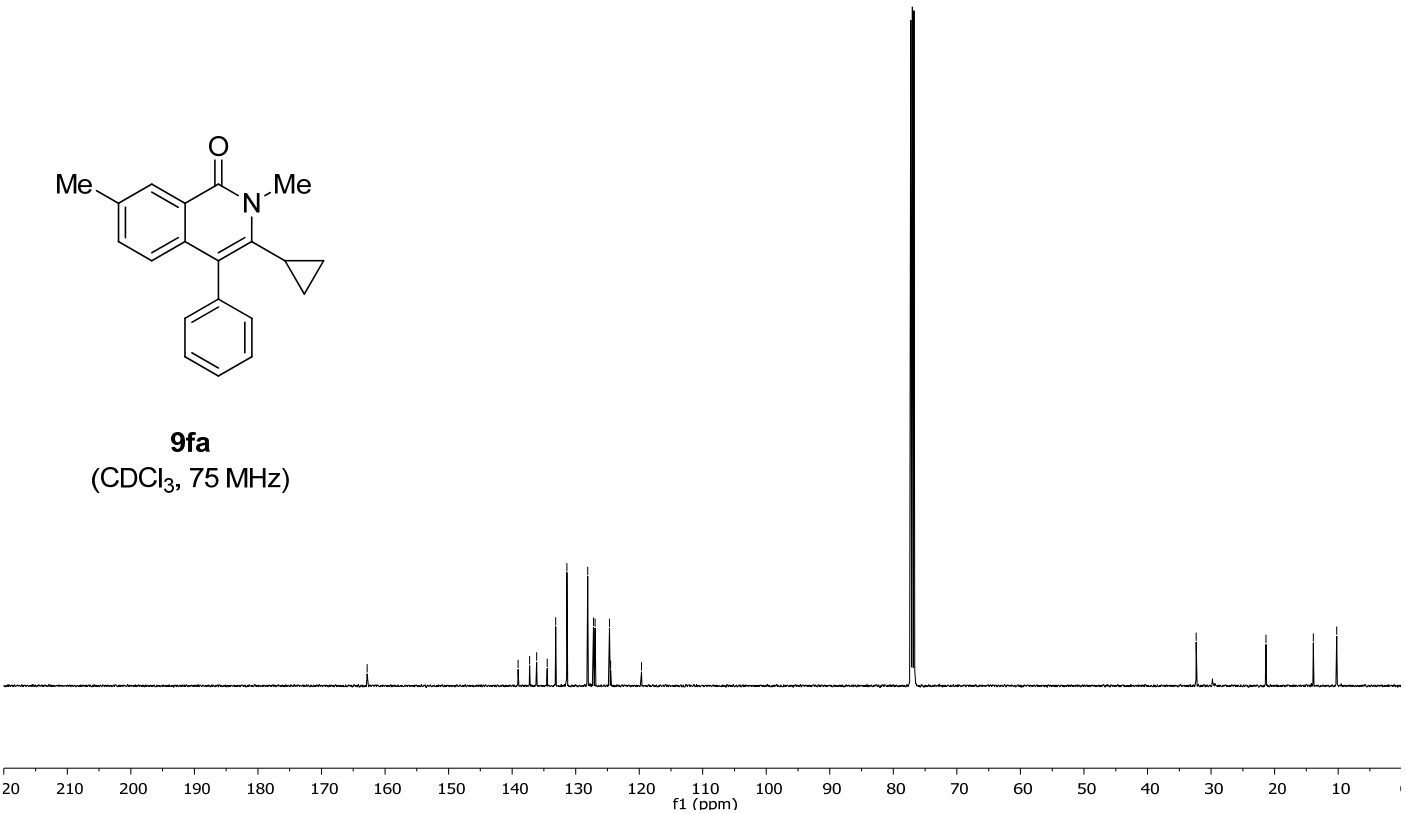
Cyclopropyl-2,7-dimethyl-3-phenylisoquinolin-1(2*H*)-one (8fa)



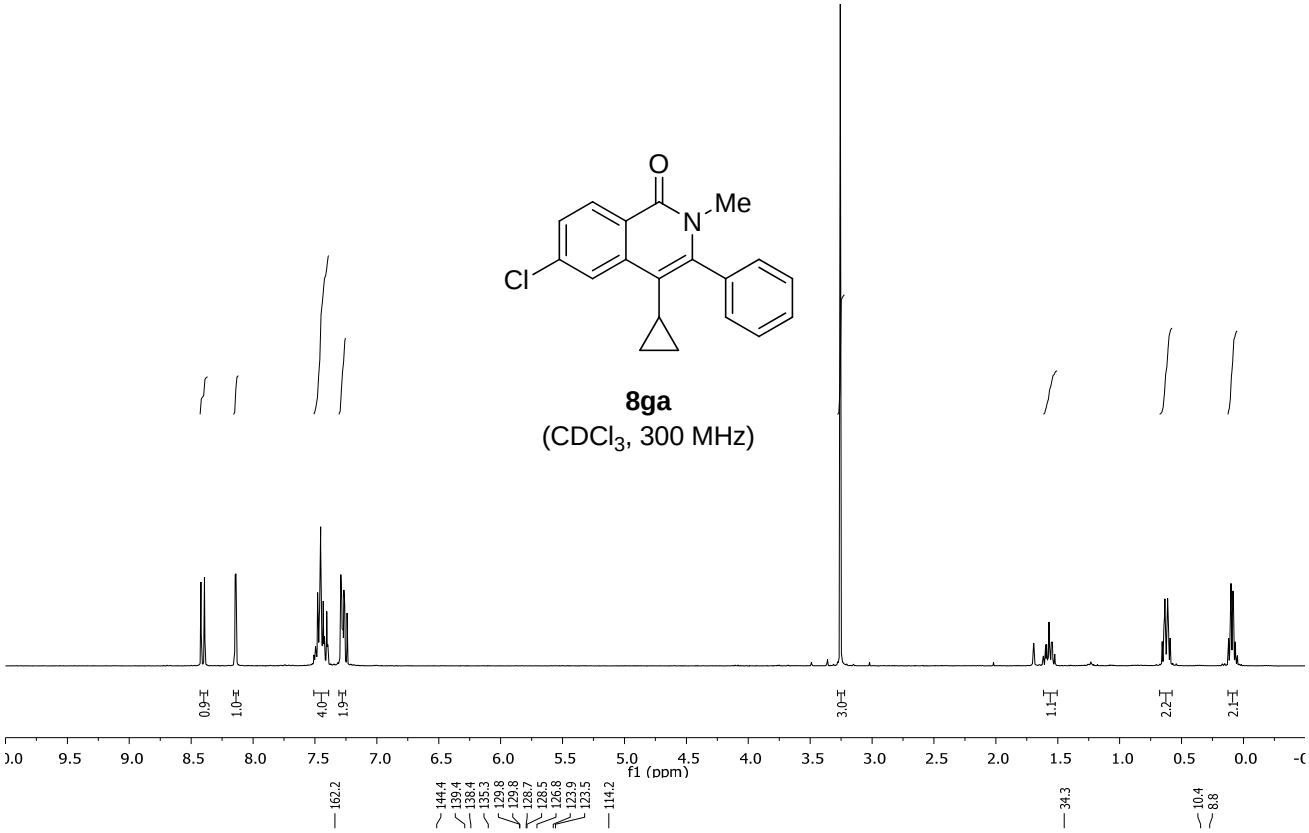


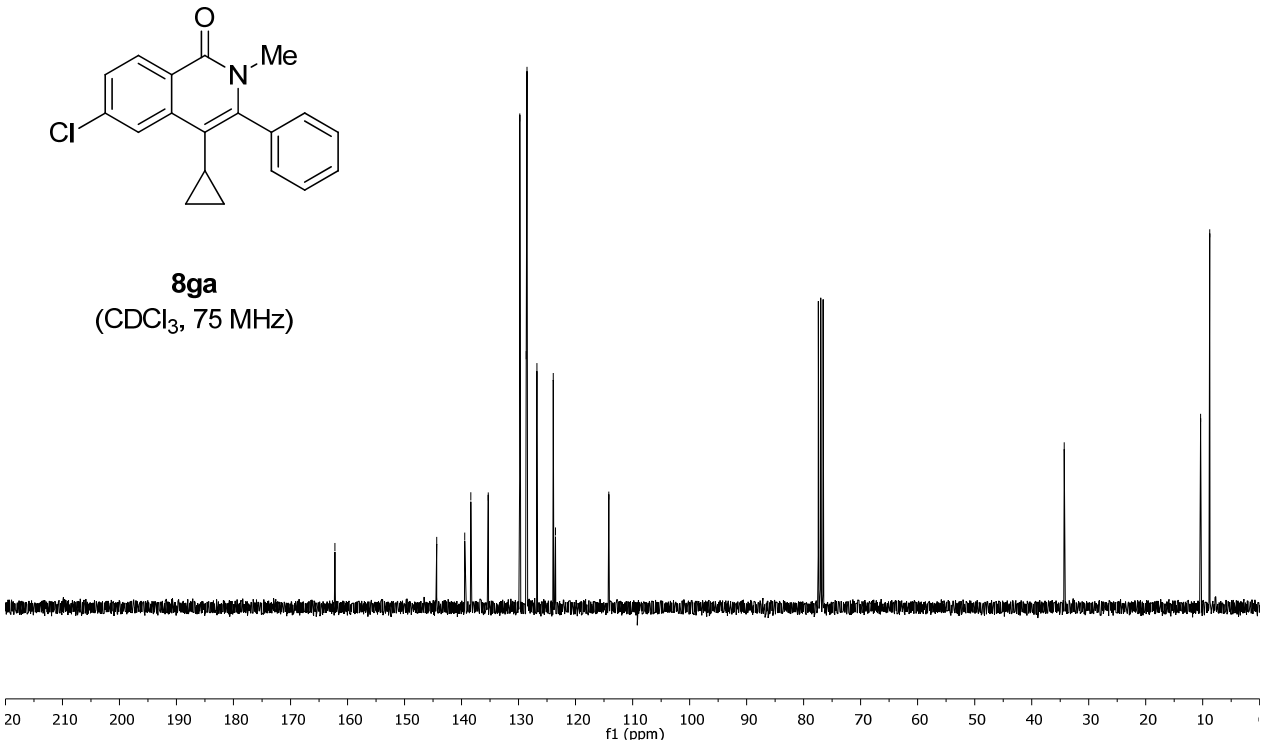
3-Cyclopropyl-2,7-dimethyl-4-phenylisoquinolin-1(2*H*)-one (9fa)



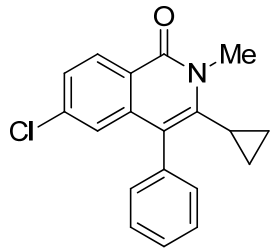


6-Chloro-4-cyclopropyl-2-methyl-3-phenylisoquinolin-1(2*H*)-one (8ga)

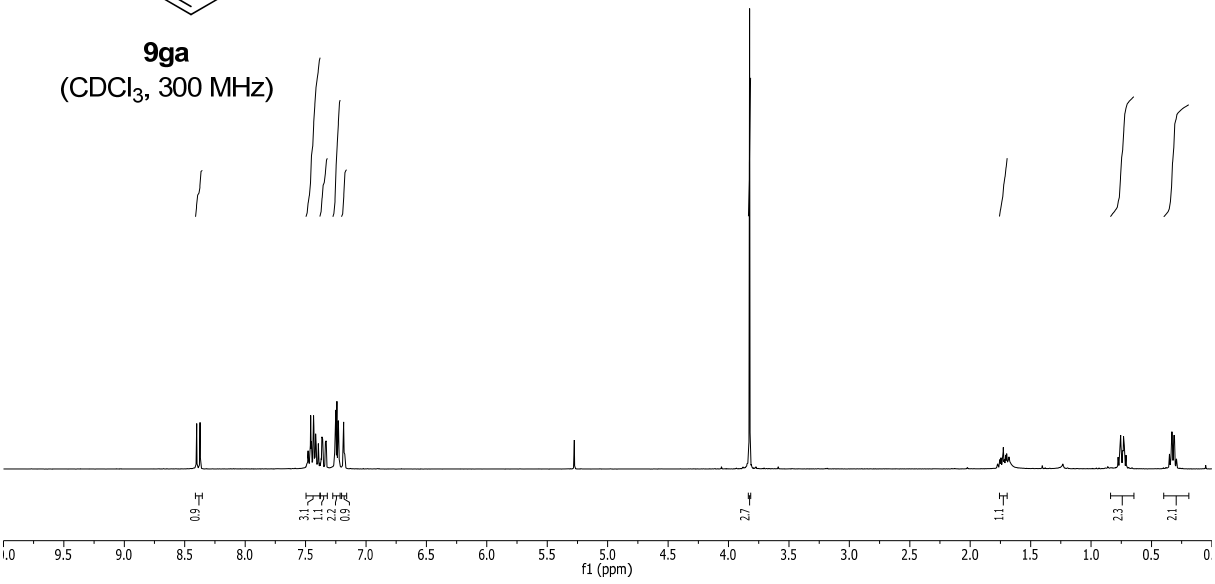


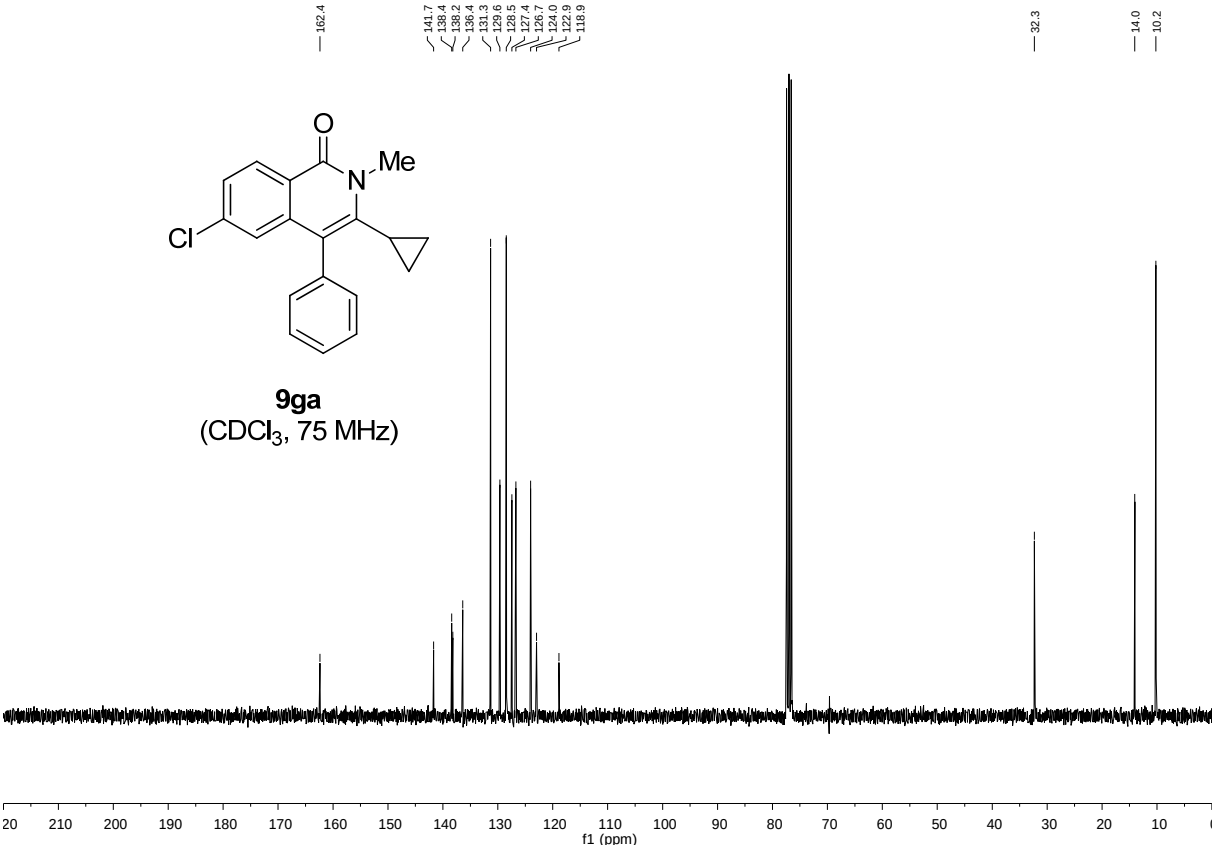


6-Chloro-3-cyclopropyl-2-methyl-4-phenylisoquinolin-1(2*H*)-one (9ga)



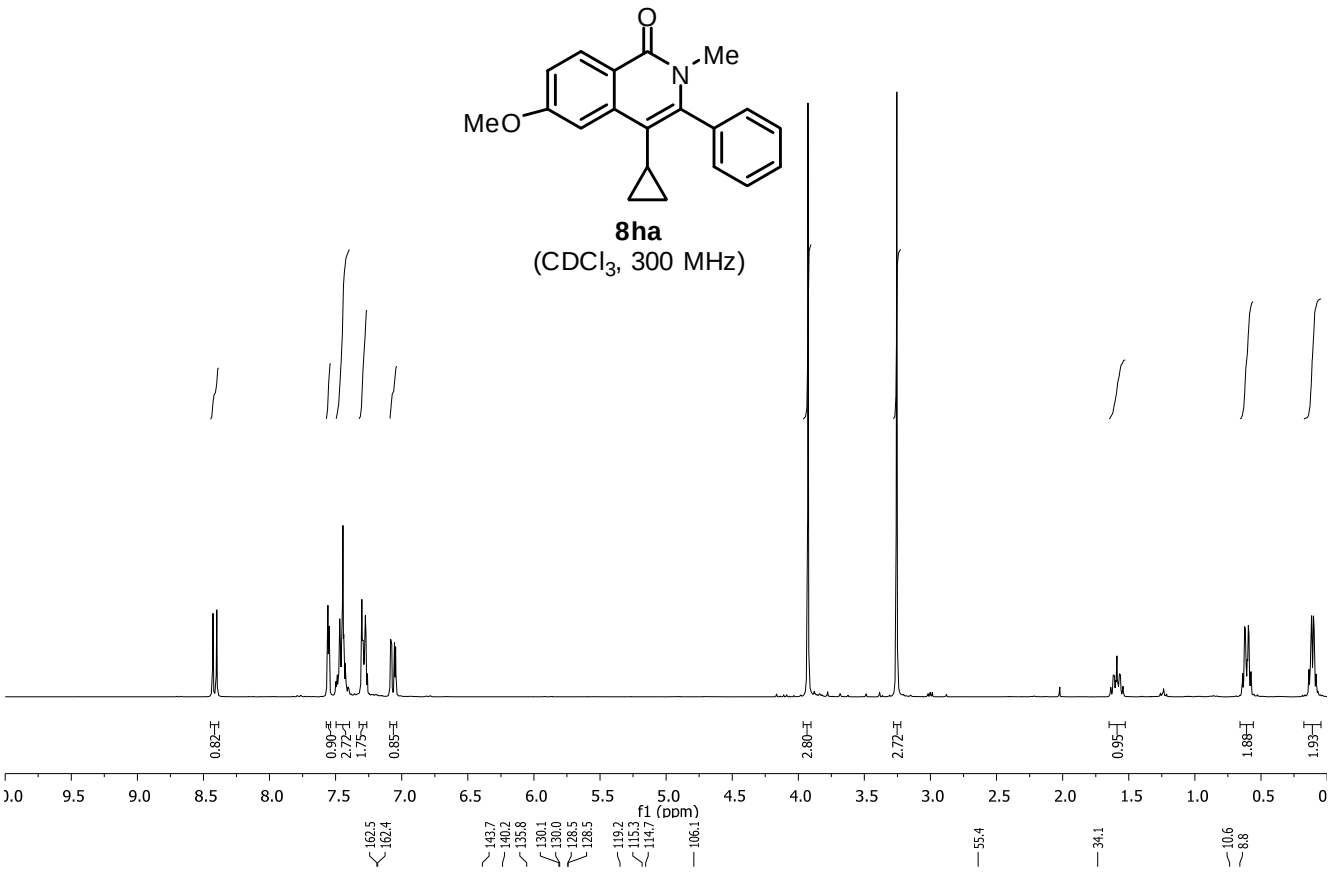
9ga
($CDCl_3$, 300 MHz)

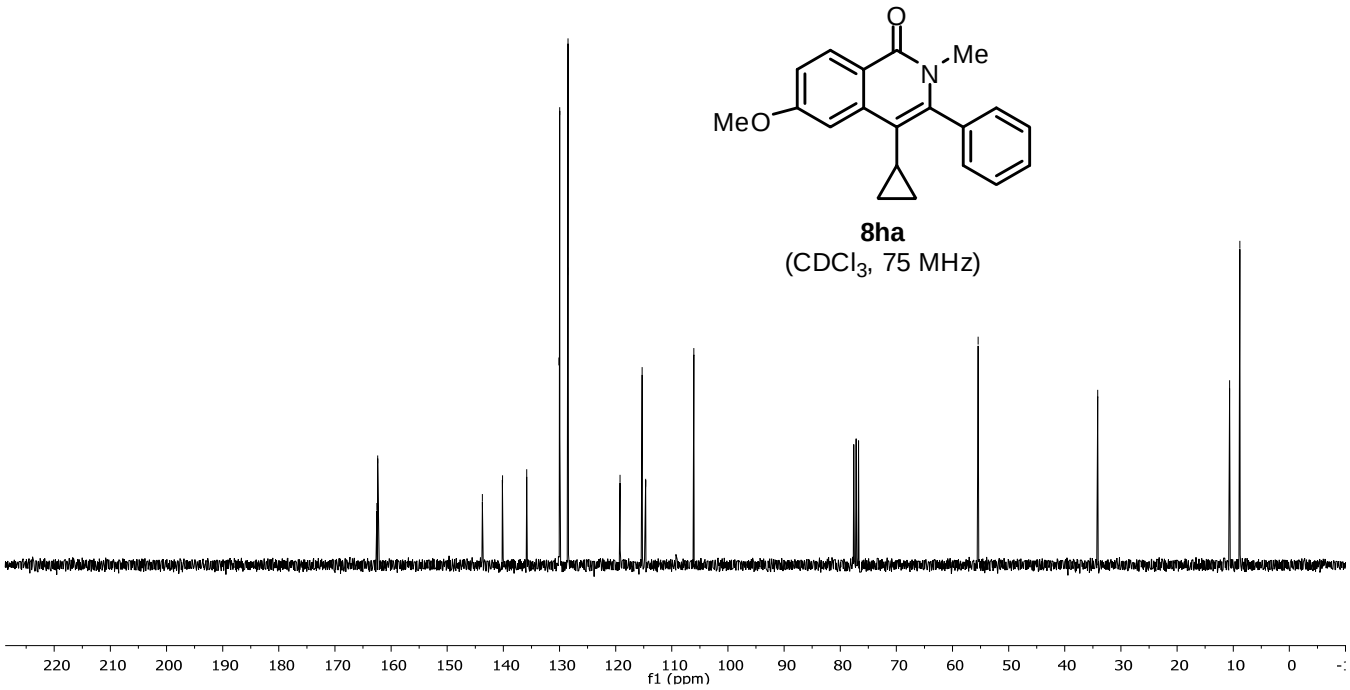




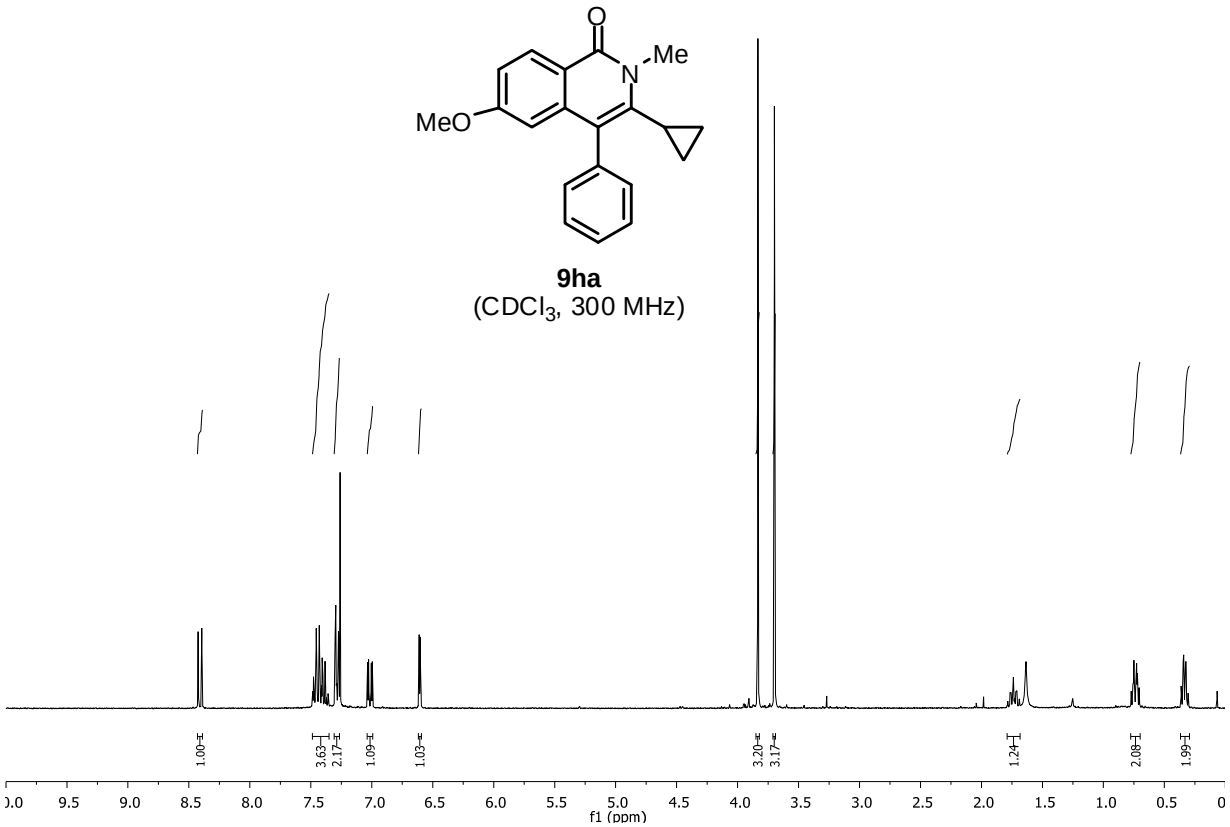
9ga
($CDCl_3$, 75 MHz)

4-Cyclopropyl-6-methoxy-2-methyl-3-phenylisoquinolin-1(2*H*)-one (8ha)

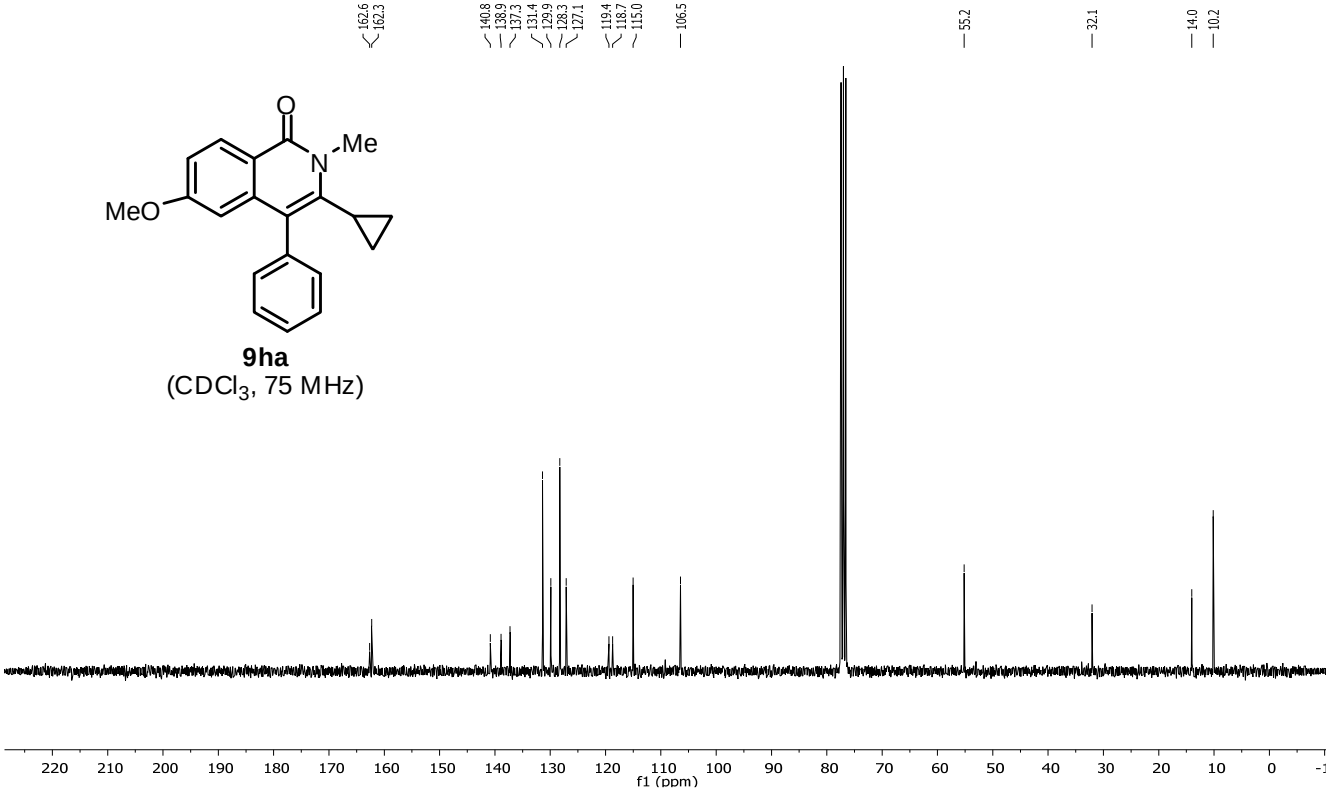




3-Cyclopropyl-6-methoxy-2-methyl-4-phenylisoquinolin-1(2*H*)-one (9ha)

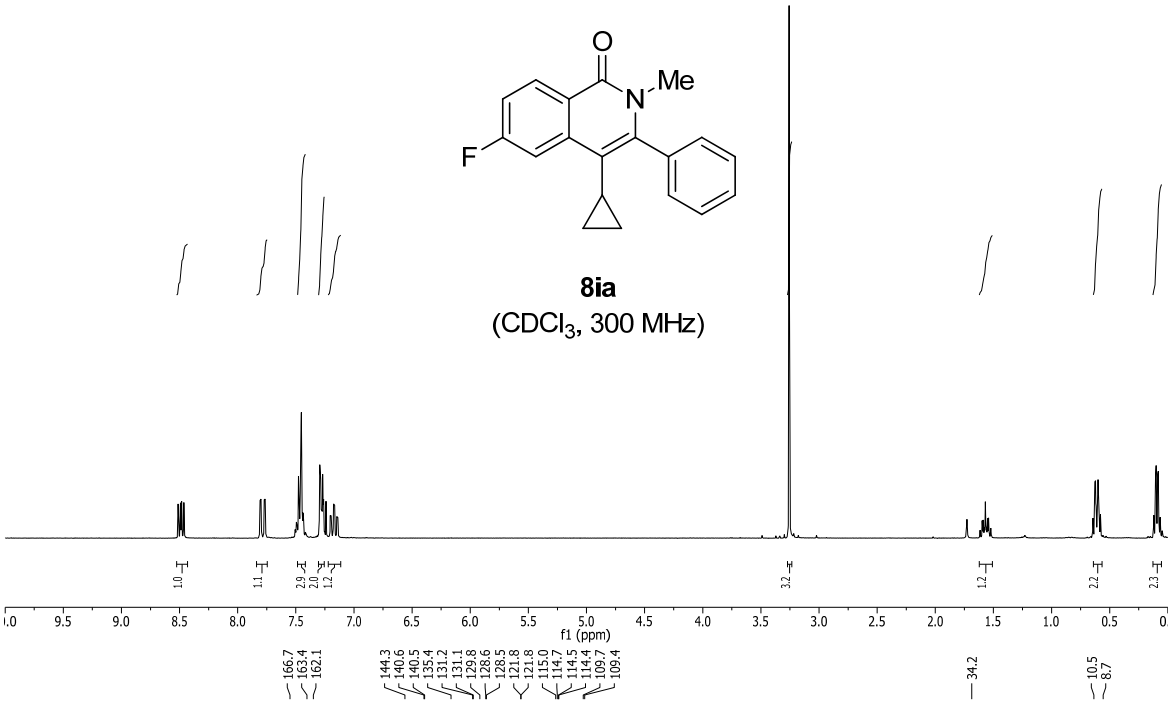


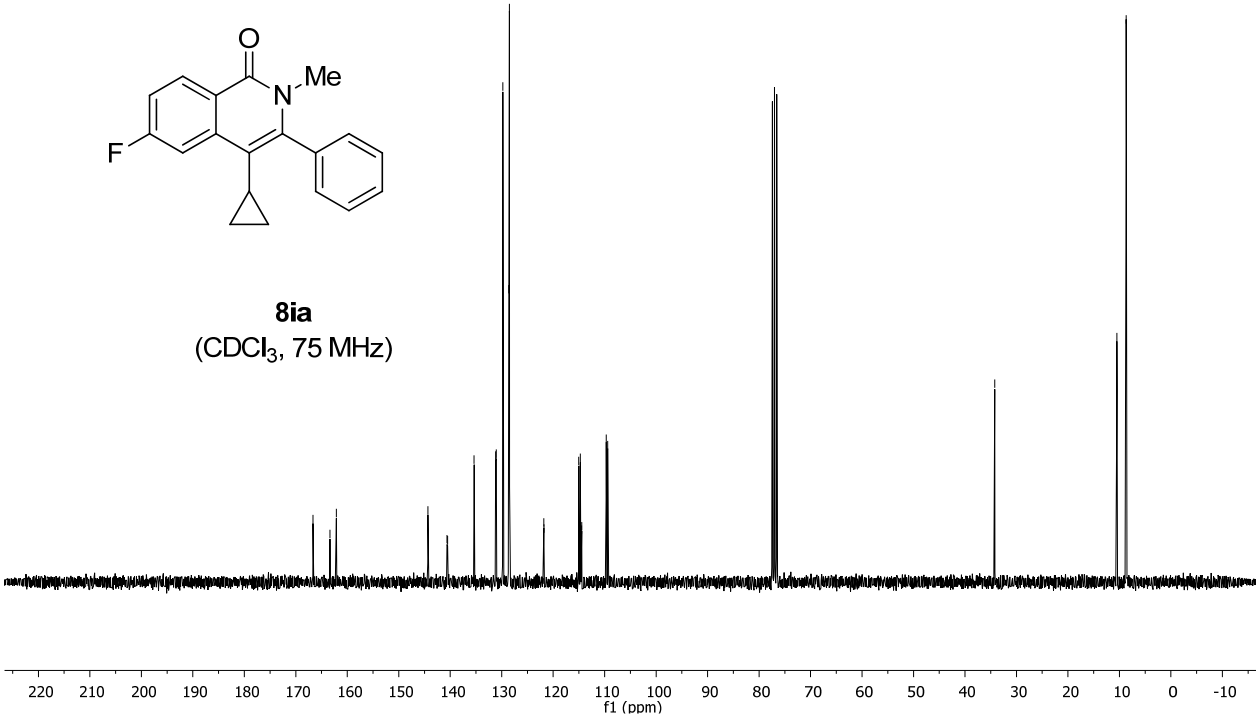
9ha
($CDCl_3$, 300 MHz)



9ha
($CDCl_3$, 75 MHz)

4-Cyclopropyl-6-fluoro-2-methyl-3-phenylisoquinolin-1(2*H*)-one (8ia)





3-Cyclopropyl-6-fluoro-2-methyl-4-phenylisoquinolin-1(2*H*)-one (9ia)