*Supporting Information*

# Ugi-derived Dehydroalanines as a Pivotal Template in the Diversity Oriented Synthesis of Aza-polyheterocycles

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## 1. Materials and Methods

**spectra** were measured on a Nicolet Magna 750 FT-IR spectrometer; absorptions are given in wavenumbers ($cm^{-1}$). **Mass spectra** were obtained on a JEOL JMS-AX505HA spectrometer. **NMR spectroscopy**: $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Varian Gemini-200 and JEOL Eclipse-300 spectrometers, Measurements were carried out at RT. Chemical shifts (δ) are reported in parts per million (ppm) relative to $Si(CH_3)_4$ for $^{1}H$ and $^{13}C$ NMR experiments were carried out in $CDCl_3$. Coupling constants (*J*) are reported in hertz (Hz), peak multiplicity is indicated as follows: s= singlet, d= doublet, t= triplet, m= multiplet, bs: broad signal for proton spectra. **X-ray diffraction**: X-ray diffraction studies were realized on a Bruker AXS diffractometer with an area detector, Mo Kα radiation, λ=0.71078 Å. Solution and refinement have been carried out by Simon Hernández. Full crystallographic data were submitted as CIF files with the Cambridge Crystallographic Data Center, CCDC Nos. 912003, 912004 and 912005.

## 2. Experimental section

Ugi adducts were prepared as described in the literature,[1] from 2-benzoyloxyacetaldehyde,[2] the corresponding amines, the appropriate carboxylic acid and an isonitrile, all Ugi products were used without further purification. The elimination procedure also was synthesized according the previous report.[1] The amines were synthesized according literature procedure,[3] carboxylic acid were prepared from oxidation of corresponding aldehydes.[4] The substituted 2-bromobenzylamines were synthesized according to a previously two-step protocol.[5]

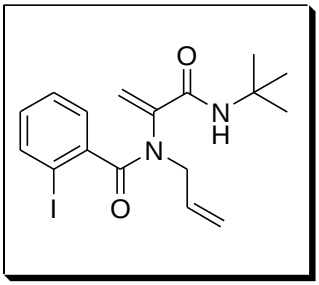
**Heck reaction**

**Method A.** To a mixture of the corresponding dehydroalanine (1.0 equiv) in degassed DMA, $PdCl_2(PPh_3)_2$ (10% mol) and NaOAc (2 equiv), was added. The resulting solution was refluxed under an argon atmosphere and stirred until TLC indicated full conversion. The mixture was extracted with ethyl acetate (3X20 mL). The organic layers were dried over $Na_2SO_4$ and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel with a mixture of hexanes:EtOAc as eluent, affording the corresponding compound.

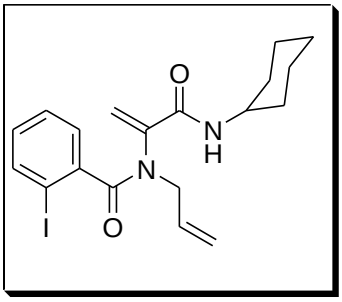
**Method B.** To a round flask with stir bar was charged with corresponding dehydroalanine (0.108 mmol), $PdCl_2(PPh_3)_2$ ( 0.0108 mmol), $Cu(OAc)_2$ (0.0216 mmol), NaOAc (0.216 mmol) in 3 ml of DMA, previously degassed. Then the mixture reaction was stirred and heated to 162 °C until starting materials have disappeared. The reaction mixture was diluted with EtOAc and washed with water (3X10 mL). The organic layer was then washed with brine and dried with $Na_2SO_4$. Organic solvent was removed and the crude product was purified by flash chromatographic on silica gel, to afford pure compound cyclic.

***One-pot*** **synthesis of pyrazinoisoquinolines.** To a solution of 0.46 mmol of the corresponding Ugi adduct in 7.5 mL of acetonitrile, 1.378 mmol of $Cs_2CO_3$ were added. The mixture was refluxed under argon atmosphere and monitored by TLC. After 2 h of stirring, the solvent was evaporated under reduced pressure and the residue was diluted with ethyl acetate (20 mL); the solution was washed with water (2 x 10 mL), and saturated NaCl solution (2 x 10 mL), dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The crude DKP was then dissolved in 15 mL of toluene and 0.069 mmol of $Pd(AcO)_2$, 0.138 mmol of $PPh_3$, and 0.92 mmol of $K_2CO_3$ were added. The solution was degasificated by bubbling argon for 30 min. After that, the mixture was allowed to reflux for

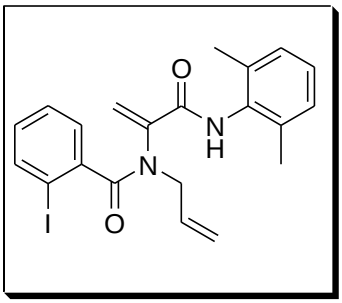
6–12 h until the completion of the reaction. Then, the mixture was diluted with 20 mL of AcOEt and sequentially washed with water (2 x 15 mL) and with a saturated NaCl solution (2 x 10 mL). The organic layer was evaporated and the product was finally purified by silica gel flash column chromatography silica gel with a mixture of hexanes:EtOAc as eluent, affording the corresponding compound.



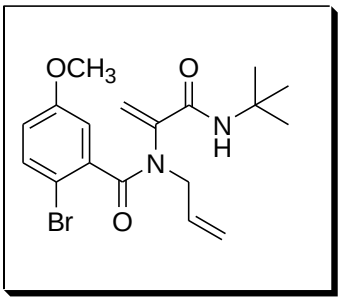
**Compound 9a, *N*-allyl-*N*-(1-*tert*-butylcarbamoyl-vinyl)-2-iodo-benzamide**, was purified by flash column chromatography (eluent 80:20 hexane/EtOAc). The product was obtained as a white solid (55%, two steps), m.p. 120–121 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.78 (d, *J* =7.8 Hz, 1H), 7.42–7.29 (m, 2H), 7.02 (t, *J* =7.8 Hz, 1H), 6.10–5.99 (m, 1H), 5.77 (s, 1H), 5.65 (s, 1H), 5.55 (s, 1H), 5.35–5.13 (m, 2H), 4.31 (d, *J* =6.0 Hz, 2H), 1.31 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 169.7, 162.7, 142.7, 141.5, 139.4, 132.4, 130.4, 127.8, 127.7, 120.4, 119.4, 94.1, 51.7, 51.3, 28.6. **HRMS** (FAB+, M+) calculated for $C_{17}H_{22}N_2O_2I$ [M+1], 413.0722; found 413.0726. **IR** *v* ($cm^{-1}$): 3357, 2975, 1646, 1624, 1518, 1389.



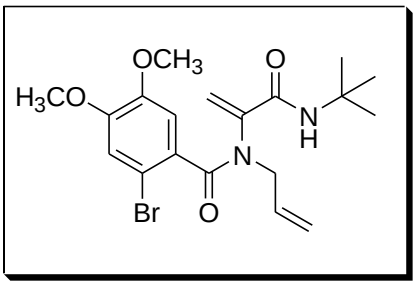
**Compound 9b, *N*-allyl-*N*-(1-cyclohexylcarbamoyl-vinyl)-2-iodo-benzamide,** was purified by flash column chromatography (eluent 85:15 hexane/EtOAc). The product was obtained as a white solid (57 %, two steps), m.p. 102–104 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.77 (d, *J* =7.8 Hz, 1H), 7.25–7.21 (m, 2H), 7.13–6.98 (m, 1H), 6.09–5.98 (m, 2H), 5.86 (s, 1H), 5.57 (s, 1H), 5.28–5.25 (m, 1H), 4.29 (d, *J* =3.0 Hz, 2H), 3.77–3.71 (m, 1H), 1.85–1.61 (m, 5H), 1.37–1.13 (m, 5H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 169.9, 162.4, 141.6, 141.5, 139.3, 132.1, 130.4, 127.7, 127.6, 121.7, 119.5, 94.0, 50.9, 48.9, 32.8, 25.3, 24.9. **HRMS** (FAB+, M+) calculated for $C_{19}H_{23}N_2O_2I$ [M], 438.0807; found 438.0804. **IR** *v* ($cm^{-1}$): 3352, 2926, 1673, 1623, 1527, 1397.



**Compound 9c**, ***N*-allyl-*N*-[1-(2,6-dimethyl-phenylcarbamoyl)-vinyl]-2-iodo-benzamide**, was purified by flash column chromatography (eluent 70:30 hexane/EtOAc). The product was obtained as a white solid (65 %, two steps), m.p. 153–155 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.85–7.78 (m, 1H), 7.59–7.55 (m, 1H), 7.42–7.31 (m, 2H), 7.09–7.05 (m, 3H), 6.27 (s, 1H), 6.01 (s, 1H), 5.65 (s, 1H), 5.33–5.17 (m, 3H), 4.35 (s, 1H), 4.02 (d, *J* =6.0 Hz, 1H), 2.30 (s, 3H), 2.11 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 170.9, 162.7, 142.1, 141.0, 139.4, 135.7, 133.3, 132.0, 130.8, 128.4, 127.8, 123.6, 119.8, 119.4, 119.0, 94.2, 50.3, 18.6. **HRMS** (FAB+) calculated for $C_{21}H_{21}N_2O_2I$ [M+], 460.0643; found 460.0648. **IR** *v* ($cm^{-1}$): 3269, 1654, 1625, 1523, 1383.

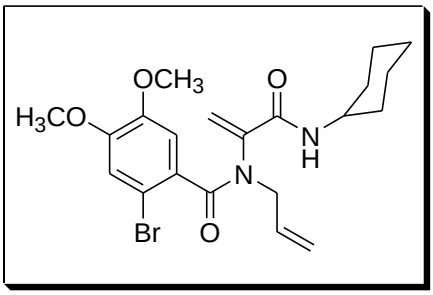


**Compound 9d, *N*-allyl-2-bromo-*N*-(1-*tert*-butylcarbamoyl-vinyl)-5-methoxy-benzamide**, was purified by flash column chromatography (eluent 70:30 hexane/EtOAc). The product was obtained as a white solid (52 %, two steps), m.p. 123–125 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.36 (d, *J* =8.7 Hz, 1H), 6.84 (d, *J* =3.0 Hz, 1H), 6.74 (dd, *J* =3.0, 8.7 Hz, 1H), 6.08–5.94 (m, 1H), 5.77 (s, 1H), 5.71 (s, 1H), 5.51 (s, 1H), 5.34–5.08 (m, 2H), 4.29 (s, 2H), 3.73 (s, 3H), 1.31 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 168.3, 162.7, 158.5, 142.6, 133.5, 132.3, 120.3, 119.2, 116.8, 113.9, 110.1, 99.0, 55.5, 51.7, 51.1, 28.5. **HRMS** (FAB+, M+) calculated for $C_{18}H_{24}N_2O_3Br$ [M+1], 395.0981; found 395.0970. **IR** *v* ($cm^{-1}$): 3360, 2970, 1651, 1619, 1516, 1393.

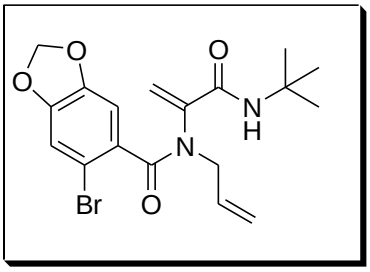


**Compound 9e, *N*-allyl-2-bromo-*N*-(1-*tert*-butylcarbamoyl-vinyl)-4,5-dimethoxy-benzamide**, was purified by flash column chromatography (eluent 60:40 hexane/EtOAc). The product was obtained as a white solid (58 %, two steps), m.p. 104–106 °C. **$^{1}$H NMR** (200 MHz, $CDCl_3$) δ: 6.92 (s, 1H), 6.90 (s, 1H), 5.97 (bs, 1H), 5.77 (s, 1H), 5.65 (s, 1H), 5.40 (s, 1H), 5.32–5.22 (m, 2H), 4.29 (s, 2H), 3.86 (s, 3H), 3.79 (s, 3H), 1.30 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 168.3, 163.0, 150.0, 147.9, 143.0, 132.5, 129.7, 118.7 (2C), 115.0, 111.6, 110.5, 56.1, 55.9, 51.5, 50.8, 28.4. **HRMS** (FAB+,

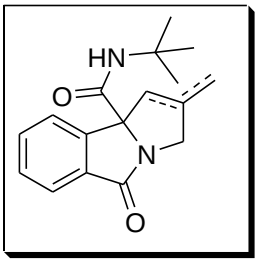
M+) calculated for $C_{19}H_{26}N_2O_4Br$ [M+1], 425.1068; found 425.1076. **IR** *v* ($cm^{-1}$): 3357, 2966, 1645, 1622, 1506, 1210.



**Compound 9f, *N*-allyl-2-bromo-*N*-(1-cyclohexycarbamoyl-vinyl)-4,5-dimethoxy-benzamide,** was purified by flash column chromatography (eluent 65:35 hexane/EtOAc) the product was obtained as a white solid (64 %, two steps), m.p. 124–126 °C. **$^1$H NMR** (300 MHz, $CDCl_3$) δ: 6.92 (s, 1H), 6.85 (s, 1H), 5.98 (s, 2H), 5.75 (s, 1H), 5.43 (s, 1H), 5.30–5.23 (m, 2H), 4.28 (s, 1H), 3.90–3.85 (m, 4H), 3.75 (s, 3H), 1.80–1.60 (m, 5H), 1.37–1.13 (m, 5H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 168.5, 162.8, 150.1, 148.0, 142.2, 132.3, 130.0, 120.0, 119.0, 115.1, 111.3, 110.6, 56.2, 56.0, 50.7, 48.8, 32.9, 25.4, 24.8. **HRMS** (FAB+, M+) calculated for $C_{21}H_{27}N_2O_4Br$ [M], 450.1160; found 450.1154. **IR** *v* ($cm^{-1}$): 3318, 2929, 1625, 1506, 1400, 1256, 1212.

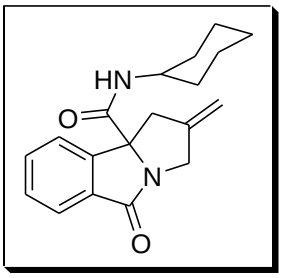


**Compound 9g, 6-bromo-benzo[1,3]dioxole-5-carboxylic acid allyl-(1-*tert*-butylcarbamoyl-vinyl)-amide**, was purified by flash column chromatography (eluent 70:30 hexane/EtOAc). The product was obtained as a white solid (78 %, two steps), m.p. 147–149 °C. **$^1$H NMR** (300 MHz, $CDCl_3$) δ: 6.92 (s, 1H), 6.73 (s, 1H), 6.02 (s, 1H), 5.97 (s, 2H), 5.84 (s, 1H), 5.73 (s, 1H), 5.50 (s, 1H), 5.33–5.24 (m, 2H), 4.28 (d, *J*= 6.0 Hz, 2H), 1.32 (s 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 168.1, 162.7, 149.0, 147.0, 142.7, 132.3, 130.7, 120.0, 119.3, 112.7, 111.3, 108.6, 102.1, 51.7, 51.5, 28.5. **HRMS** (FAB+, M+) calculated for $C_{18}H_{22}N_2O_4Br$ [M+1], 409.0762; found 409.0763. **IR** *v* ($cm^{-1}$): 3396, 2974, 1669, 1620, 1525, 1441, 1242.

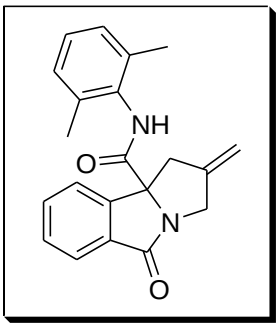


**Compound 10a**, was purified by flash column chromatography (eluent 95:5 hexane/EtOAc). The product was obtained as a white solid (85 %), m.p. 155–158 °C. **$^1$H NMR** (300 MHz, $CDCl_3$) δ: 7.90–7.73 (m, 3H), 7.60–7.44 (m, 3H), 6.20 (s, 1H), 5.11 (dd, *J* =1.2, 10.8 Hz, 2H), 4.48 (t, *J* = 15.9 Hz, 1H), 3.99–3.86 (m, 1H), 3.52 (dd, *J* =1.2, 15.3 Hz, 1H), 2.27 (dd, *J* =1.8, 15.0 Hz, 1H), 1.78 (d, *J* =1.2 Hz,

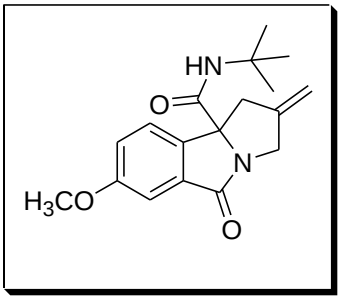
2H), 1.25 (d, *J* =4.2 Hz, 14H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 176.7, 173.1, 169.1, 168.7, 147.9, 146.8, 146.6, 140.6, 133.3, 133.1, 130.4, 129.2, 129.1, 124.5, 124.2, 123.5, 123.1, 109.7, 82.7, 76.3, 55.1, 51.4, 51.3, 47.8, 41.3, 28.6, 28.5, 14.5. **HRMS** (FAB+, M+) calculated for $C_{17}H_{21}N_2O_2$ [M+1], 285.1611; found 285.1603. **IR** *v* ($cm^{-1}$): 3316, 2925, 1708, 1662, 1520, 1358, 1221, 703.




**Compound 10b**, **2-methylene-5-oxo-2,3-dihydro-1*H*,5*H*-pyrrolo[2,1-*a*]isoindole-9b-carboxilic acid cyclohexylamide**, was purified by flash column chromatography (eluent 80:20 hexane/EtOAc). The product was obtained as a white solid (81 %), m.p. 148–151 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.82–7.75 (m, 2H), 7.61–7.48 (m, 2H), 6.44–6.11 (m, 1H), 5.11 (d, *J* =11.1 Hz, 1H), 4.50 (t, *J* =16.3 Hz, 1H), 3.92 (t, *J* =16.3 Hz, 1H), 3.56 (s, 1H), 3. 54 (d, *J* =14.7 Hz, 1H), 2.32 (d, *J* =15.6 Hz, 1H), 1.58–0.89 (m, 10H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 173.1, 168.7, 146.5, 133.3, 133.1, 129.3, 124.5, 124.2, 123.6, 123.2, 109.8, 55.1, 48.6, 47.8, 41.3, 33.1, 32.6, 25.3, 24.8, 24.7. **HRMS** (FAB+, M+) calculated for $C_{19}H_{23}N_2O_2$ [M+1], 311.1770; found 311.1760. **IR** *v* ($cm^{-1}$): 3318, 2931, 1709, 1665, 1525, 1321.

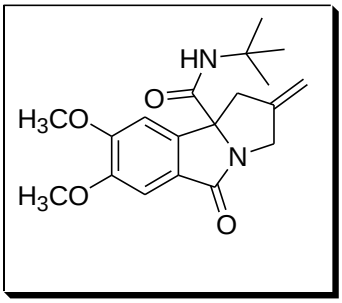



**Compound 10c, 2-methylene-5-oxo-2,3-dihydro-1*H*,5*H*-pyrrolo[2,1-*a*]isoindole-9b-carboxilic acid (2,6-dimethyl-phenyl)-amide**, was purified by flash column chromatography (eluent 70:30 hexane/EtOAc). The product was obtained as a white solid (75 %), m.p. 189–193 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.80–7.78 (m, 3H), 7.61–7.53 (m, 2H), 7.07–6.98 (m, 3H), 5.19 (dd, *J* =3, 9 Hz, 2H), 4.60 (d, *J* =15 Hz, 1H), 4.07 (dd, *J* =1.8, 15 Hz, 1H), 3.64 (dd, *J* =0.9, 15 Hz, 1H), 2.38 (d, *J* = 15 Hz, 1H), 1.95 (s, 6H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 172.9, 168.2, 146.4, 146.3, 135.3, 133.2, 132.7, 130.6, 129.5, 128.2, 127.5, 124.4, 123.3, 110.3, 76.4, 48.0, 41.2, 17.9. **HRMS** (FAB+, M+) calculated for $C_{21}H_{21}N_2O_2$ [M+1], 333.1594; found 333.1603. **IR** *v* ($cm^{-1}$): 3277, 2920, 1702, 1677, 1497, 1365.

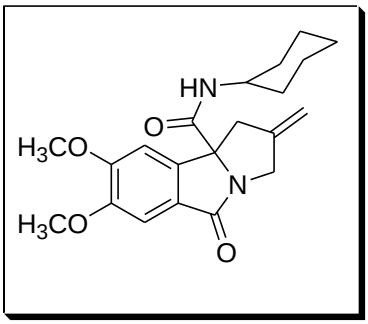



**Compound 10d, 7-methoxy-2-methylene-5-oxo-2,3-dihydro-1*H*,5*H*-pyrrolo[2,1-*a*]isoindole-9b-carboxilic acid *tert*-butyl-amide**, was purified by flash column chromatography (eluent 70:30 hexane/EtOAc). The product

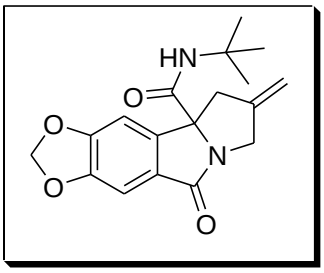
was obtained as a white solid (76 %), m.p. 113–116 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.63 (dd, *J* =0.6, 8.4 Hz, 1H), 7.26 (d, *J* =2.7 Hz, 1H), 7.12 (dd, *J* =2.7, 8.4 Hz, 1H), 6.17 (s, 1H), 5.10 (dd, *J* = 2.4, 10.8 Hz, 2H), 4.49 (d, *J* = 15.6 Hz, 1H), 3.91–3.85 (m, 4H), 3.49 (dd, *J* =1.2, 15 Hz, 1H), 2.24 (d, *J* = 15 Hz, 1H), 1.24 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 173.1, 169.0, 160.8 146.7, 139.3, 131.9, 124.1, 121.1, 109.7, 106.9, 76.0, 55.7, 51.4, 47.8, 41.4, 28.5. **HRMS** (FAB+, M+) calculated for $C_{18}H_{23}N_2O_3$ [M+1], 315.1715; found 315.1709. **IR** *v* ($cm^{-1}$): 3327, 2967, 1708, 1673, 1489.



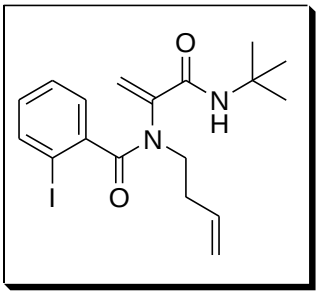

**Compound 10e, 7,8-dimethoxy-2-methylene-5-oxo-2,3-dihydro-1*H*,5*H*-pyrrolo[2,1-*a*]isoindole-9b-carboxilic acid *tert*-butylamide**, was purified by flash column chromatography (eluent 60:40 hexane/EtOAc). The product was obtained as a white solid (72 %), m.p. 161–164 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.23 (s, 1H), 7.20 (s, 1H), 6.27 (s, 1H), 5.10 (dd, *J* =1.6, 10.9 Hz, 2H), 4.47 (d, *J* =15.6 Hz, 1H), 3.97 (s, 1H), 3.93 (s, 1H), 3.64 (d, *J* =1.2 Hz, 1H), 2.26 (d, *J* =15.0 Hz, 1H), 1.25 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 173.8, 169.1, 153.8, 150.6, 146.8, 141.4, 122.3, 109.6, 105.3, 105.0, 75.9, 56.5, 56.2, 51.4, 47.9, 41.5, 28.5. **HRMS** (FAB+, M+) calculated for $C_{19}H_{25}N_2O_4$ [M+1], 345.1808; found 345.1814. **IR** *v* ($cm^{-1}$): 3335, 2937, 1705, 1672, 1501, 1461, 1323.



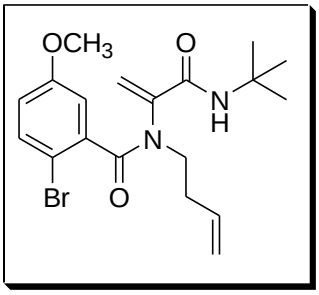

**Compound 10f, 7,8-dimethoxy-2-methylene-5-oxo-2,3-dihydro-1*H*,5*H*-pyrrolo[2,1-*a*]isoindole-9b-carboxilic acid cyclohexylamide,** was purified by flash column chromatography (eluent 65:35 hexane/EtOAc). The product was obtained as a white solid (86 %), m.p. 170–172 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.23 (s, 1H), 7.20 (s, 1H), 6.32 (d, *J* =6.0 Hz, 1H), 5.10 (d, *J* =9.0 Hz, 2H), 4.48 (d, *J* =15.0 Hz, 1H), 3.97 (s, 3H), 3.93 (s, 3H), 3.64 (s, 1H), 3.48 (d, *J* =15.0 Hz, 1H), 2.31(d, *J* =15.0 Hz), 1.89–1.60 (m, 6H), 1.34–0.91 (m, 5H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 173.8, 169.1, 153.8, 150.6, 146.8, 141.2, 122.4, 109.7, 105.3, 105.1, 75.7, 56.5, 56.3, 48.6, 48.0, 41.6, 33.1, 32.7, 25.4, 24.8, 24.7. **HRMS** (FAB+, M+) calculated for $C_{21}H_{27}N_2O_4$ [M+1], 371.1963; found 371.1971. **IR** *v* ($cm^{-1}$): 3388, 2933, 1707, 1668, 1501, 1329, 1190, 1002.




**Compound 10g, 2-methylene-9-oxo-2,3-dihydro-1*H*,9*H*-5,7-*dioxa*-9*a*-*aza*-*cyclopenta*[*a*]indacene-3a-carboxilic acid *tert*-butylamide,** was purified by flash column chromatography (eluent 75:25 hexane/EtOAc). The product was obtained as a white solid (73 %), m.p. 185–188 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.16 (s, 1H), 7.14 (s, 1H), 6.25 (s, 1H), 6.08 (s, 2H), 5.09 (d, *J* =12.0 Hz, 2H), 4.46 (d, *J* =15.0 Hz, 1H), 3.85 (dd, *J* =1.8, 15.0 Hz, 1H), 3.45 (dd, *J* =1.2, 15.0 Hz, 1H), 2.25 (d, *J* =15.0 Hz, 1H), 1.26 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 173.0, 168.8, 152.4, 149.2, 146.6, 143.2, 124.2, 109.7, 103.5, 103.4, 102.2, 75.7, 51.4, 48.0, 41.5, 28.5. **HRMS** (FAB+, M+) calculated for $C_{18}H_{21}N_2O_4$ [M+1], 329.1497; found 329.1501. **IR** *v* ($cm^{-1}$): 3336, 2968, 1696, 1672, 1521, 1465, 1344, 1290, 1149, 1038.

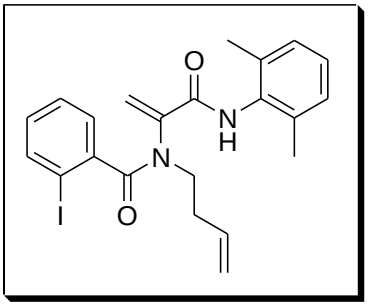



**Compound 11a'**, ***N*-but-3-enyl-*N*-(1-*tert*-butylcarbamoyl-vinyl)-2-iodo-benzamide**, was purified by flash column chromatography (eluent 75:25 hexane/EtOAc). The product was obtained as a white solid (77 %), m.p. 110–113 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.78 (d, *J* =8.1 Hz, 1H), 7.30–7.20 (m, 2H), 7.04–6.98 (m, 1H), 5.94–5.85 (m, 1H), 5.82 (s, 1H), 5.73 (s, 1H), 5.56 (s, 1H), 5.24–4.93 (m, 2H), 3.77 (t, *J* =6.8 Hz, 2H), 2.51 (q, *J* =6.9 Hz, 2H), 1.32 (s, 9H).**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 169.9, 162.6, 142.8, 141.6, 139.4, 134.8, 130.3, 128.3, 127.7, 120.6, 117.3, 94.1, 51.8, 47.4, 31.7, 28.6. **HRMS** (FAB+, M+) calculated for $C_{18}H_{23}N_2O_2I$ [M], 426.0796; found 426.0804. **IR** *v* ($cm^{-1}$): 3360, 2975, 1669, 1644, 1625, 1517, 1396, 1363, 1319, 1219, 911, 743, 638.

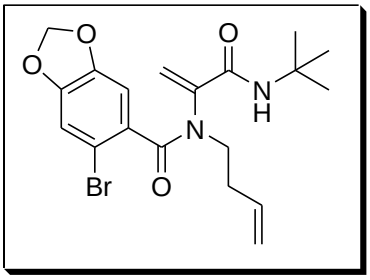



**Compound 11b', 2-bromo-*N*-but-3-enyl-*N*-(1-*tert*-butylcarbamoyl-vinyl)-5-methoxy-benzamide**, was purified by flash column chromatography (eluent 80:20 hexane/EtOAc). The product was obtained as a white solid (62 %), m.p. 115–117 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.36 (d, *J*=9.0 Hz, 1H), 6.80 (d, *J*=3.0 Hz, 1H), 6.73 (dd, *J*=3.0, 9.0 Hz, 1H), 5.93–5.80 (m, 3H), 5.20–4.96 (m, 2H), 3.81 (s, 1H), 3.72 (s, 3H), 3.39 (t, *J*=7.5 Hz, 1H), 2.48 (q, *J*=7.2 Hz, 2H), 1.32 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 168.4, 162.6, 158.5, 142.5, 134.8, 133.5, 120.6, 117.2, 116.7, 113.8, 110.1, 99.9, 55.4, 51.7, 41.1, 31.7, 28.5. **HRMS** (FAB+, M+)

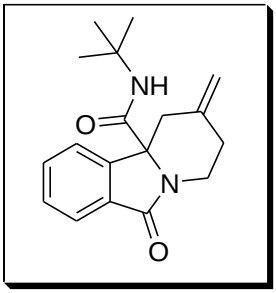
calculated for $C_{19}H_{25}N_2O_3Br$ [M], 408.1051; found 408.1049. **IR** v ($cm^{-1}$): 3343, 2945, 1655, 1617, 1514, 1216.



**Compound 11c', *N*-but-3-enyl-*N*-[1-(2,6-dimethyl-phenylcarbamoyl)-vinyl]-2-iodo-benzamide**, was purified by flash column chromatography (eluent 75:25 hexane/EtOAc). The product was obtained as a white solid (67 %), m.p. 152–154 °C. **$^1$H NMR** (300 MHz, $CDCl_3$) δ: 7.86–7.79 (m, 1H), 7.51–7.34 (m, 2H), 7.16–7.04 (m, 4H), 6.36 (s, 1H), 6.06–5.87 (m, 1H), 5.70 (d, *J*=1.2 Hz, 1H), 5.20–4.95 (m, 2H), 3.83 (s, 1H), 3.65 (d, *J*=6.0 Hz, 1H), 3.46 (s, 1H), 2.55 (d, *J*=6.0 Hz, 1H), 2.32 (s, 3H), 2.16 (s, 3H), 1.62 (s, 1H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 170.1, 161.5, 141.5, 141.1, 139.3, 135.2, 134.6, 133.2, 130.3, 128.2, 127.6, 127.5, 127.2, 123.7, 117.2, 94.1, 46.4, 31.4, 18.5. **HRMS** (FAB+, M+) calculated for $C_{22}H_{23}N_2O_2I$ [M], 475.0881; found 475.0883. **IR** *v* ($cm^{-1}$): 3268, 2945, 1652, 1623, 1523, 1391, 1321, 767, 738, 656.

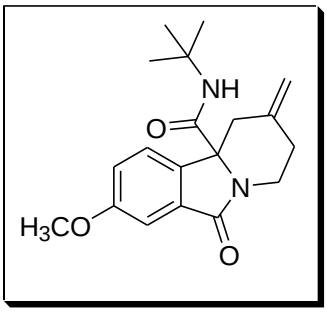


**Compound 11d', 6-bromo-benzo[1,3]dioxole-5-carboxylic acid but-3-enyl-(1-*tert*-butylcarbamoyl-vinyl)amide**, was purified by flash column chromatography (eluent 80:20 hexane/EtOAc). The product was obtained as a white solid (54 %), m.p. 134–135 °C. **$^1$H NMR** (300 MHz, $CDCl_3$) δ: 6.91 (s, 1H), 6.71 (s, 1H), 5.97 (s, 2H), 5.91–5.80 (m, 3H), 5.23–5.04 (m, 2H), 3.73 (s, 2H), 2.46 (q, *J*=6.0 Hz, 2H), 1.33 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 168.1, 162.5, 148.9, 146.8, 142.5, 134.8, 130.8, 120.1, 117.1, 112.6, 108.4, 102.0, 99.8, 51.7, 47.3, 31.6, 28.5. **HRMS** (FAB+, M+) calculated for $C_{19}H_{24}N_2O_4Br$ [M+1], 423.0912; found 423.0919. **IR** v ($cm^{-1}$): 3399, 1668, 1620, 1526, 1484, 1420, 1241, 1033, 908.608.

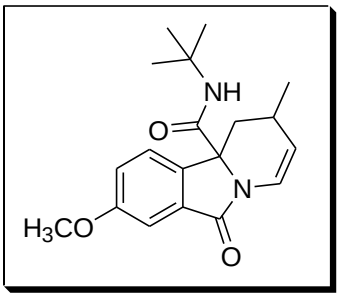


**Compound 11a, 2-methylene-6-oxo-1,2,3,4-tetrahydro-6*H*-pyrido[2,1-*a*]isoindole-10b-carboxylic acid *tert*-butylamide**, was purified by flash column chromatography (eluent 80:20 hexane/EtOAc). The product was obtained as a white solid (74 %), m.p. 208–210 °C. **$^1$H NMR** (300 MHz, $CDCl_3$) δ: 7.86 (d, *J* =7.2 Hz, 1H), 7.67–7.48 (m, 3H), 5.60–5.48 (m, 1H), 5.03 (d, *J* =29 Hz, 1H),

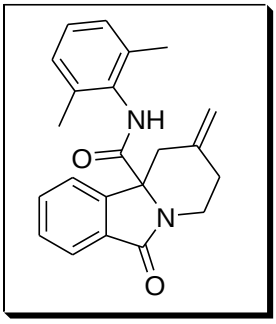
4.74–4.63 (m, 1H), 3.75–3.43 (m, 2H), 2.36–2.04 (m, 1H), 1.94–1.67 (m, 3H), 1.21 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$, mixture) δ: 167.8, 166.9, 140.3, 132.5, 132.4, 128.9, 124.0, 123.9, 121.7, 121.6, 115.7, 113.0, 51.5, 42.1, 40.1, 39.0, 36.5, 33.7, 28.5, 28.4, 23.2. **HRMS** (FAB+, M+) calculated for $C_{18}H_{23}N_2O_2$ [M], 299.1763; found 299.1760. **IR** *v* ($cm^{-1}$): 3313, 2966, 1698, 1666, 1526, 1451, 1391, 1224.



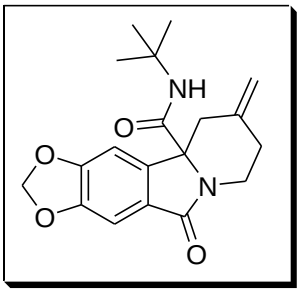

**Compound 11b, 8-methoxy-2-methylene-6-oxo-1,2,3,4-tetrahydro-6*H*-pyrido[2,1-*a*]isoindole-10b-carboxylic acid *tert*-butylamide**, was purified by flash column chromatography (eluent 85:15 hexane/EtOAc). The product was obtained as a white solid (72 %), m.p. 193–196 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.53 (d, *J*=8.4 Hz, 1H), 7.30 (d, *J*=2.4 Hz, 1H), 7.11 (dd, *J*=2.4, 8.4 Hz, 1H), 5.62 (s, 1H), 5.06 (d, *J*=1.5 Hz, 1H), 4.96 (d, *J*=1.5 Hz, 1H), 4.68–4.61 (m, 1H), 3.86 (s, 3H), 3.70 (dd, *J*=1.5, 12.9 Hz, 1H), 2.96 (ddd, *J*=3.9, 12.6, 16.8 Hz, 1H), 2.37–2.31 (m, 1H), 2.17–2.04 (m, 1H), 1.77 (d, *J*=11.4 Hz, 1H), 1.21 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 168.4, 167.1, 160.5, 140.4, 139.2, 122.6, 120.5, 112.9, 106.7, 99.9, 69.9, 55.7, 51.5, 42.3, 40.1, 33.6, 28.5. **HRMS** (FAB+, M+) calculated for $C_{19}H_{25}N_2O_3$ [M+1], 329.1857; found 329.1865. **IR** v ($cm^{-1}$): 3301, 2952, 1695, 1668, 1528, 1486, 1391, 1274, 1026.



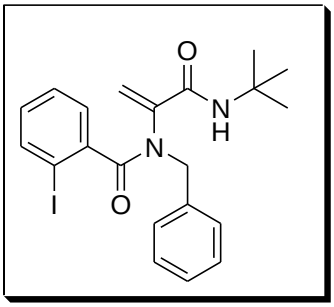

**Compound 11b isomer, 8-methoxy-2-methyl-6-oxo-1,2-dihydro-6*H*-pyrido[2,1-*a*]isoindole-10b-carboxylic acid *tert*-butylamide,** was purified by flash column chromatography (eluent 85:315 hexane/EtOAc). The product was obtained as a white solid (17 %), m.p. 170–1732 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.68 (d, *J*=8.4 Hz, 1H), 7.30 (d, *J*=2.4 Hz, 1H), 7.15 (dd, *J*=2.7, 8.4 Hz, 1H), 7.03 (dd, *J*=2.7, 8.1 Hz, 1H), 5.80 (s, 1H), 5.15 (d, *J*=8.1 Hz, 1H), 3.87 (s, 3H), 3.10 (dd, *J*=3.9, 11.1 Hz, 1H), 2.53–2.45 (m, 1H), 1.62 (s, 1H), 1.22 (s, 9H), 1.07 (d, *J*=6.9 MHz, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 168.8, 167.2, 160.8, 138.5, 130.8, 124.0, 121.4, 120.0, 118.2, 106.6, 68.4, 55.7, 51.6, 38.9, 28.4, 27.2, 20.5. **HRMS** (FAB+, M+) calculated for $C_{19}H_{25}N_2O_3$ [M+1], 329.1870; found 329.1865. **IR** v ($cm^{-1}$): 3337, 2922, 1699, 1663, 1527, 1487, 1348, 1256, 1024.



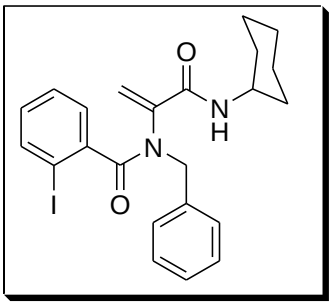
**Compound 11c, 2-methylene-6-oxo-1,2,3,4-tetrahydro-6*H*-pyrido[2,1-*a*]isoindole-10b-carboxylic acid (2,6-dimethyl-phenyl-amide,** was purified by flash column chromatography (eluent 85:15 hexane/EtOAc). The product was obtained as a white solid (71 %), m.p. 218–220 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.78 (d, *J* =7.5 Hz, 1H), 7.70 (dd, *J* =0.9, 7.5 Hz, 1H), 7.62–7.48 (m, 2H), 7.07–7.97 (m, 3H), 5.12 (s, 1H), 5.05 (S, 1H), 4.72 (dd, *J* =6.0, 13.0 Hz, 1H), 3.85 (d, *J* = 13.0 Hz, 1H), 3.27 (ddd, *J* =4.2, 13.0, 17.0 Hz, 1H), 2.45–2.18 (m, 2H), 1.90 (s, 6H), 1.70 (s, 1H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 168.5, 166.8, 146.4, 140.6, 135.6, 133.1, 132.7, 129.6, 129.3, 128.3, 127.6, 124.1, 122.2, 113.7, 70.9, 41.9, 40.6, 33.9, 18.3. **HRMS** (FAB+, M+) calculated for $C_{22}H_{23}N_2O_4$ [M+1], 347.1761; found 347.1760. **IR** *v* ($cm^{-1}$): 3265, 2921, 1676, 1501, 1468, 1395.



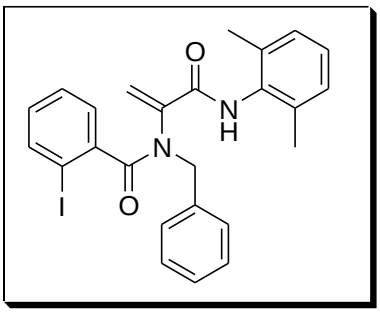
**Compound 11d, 6-methylene-9-oxo-5,6,7,8-tetrahydro-9*H*-1,3-dioxa-8a-aza-cyclopenta[b]fluorene-4b-carboxylic acid *tert*-butylamide,** was purified by flash column chromatography (eluent 80:20 hexane/EtOAc). The product was obtained as a white solid (60 %), m.p. 181–184 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.20 (s, 1H), 7.05 (s, 1H), 6.06 (s, 2H), 5.59 (d, *J*=1.8 Hz, 1H), 5.03 (s, 1H), 4.95 (s, 1H), 4.63-4.56 (m, 1H), 3.64 (d, *J*=1.5 Hz, 1H), 2.97-2.87 (m, 1H), 2.31 (d, *J*=1.2 Hz, 1H), 1.78-1.74 (m, 2H), 1.22 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 168.2, 167.0, 151.9, 148.9, 142.9, 140.4, 123.3, 112.9, 103.4, 102.2, 102.1, 69.8, 51.5, 42.4, 40.2, 33.7, 28.5. **HRMS** (FAB+, M+) calculated for $C_{19}H_{23}N_2O_4$ [M+1], 343.1661; found 343.1658**. IR** v ($cm^{-1}$): 3286, 2922, 1664, 1525, 1466, 1293, 1140, 1033.



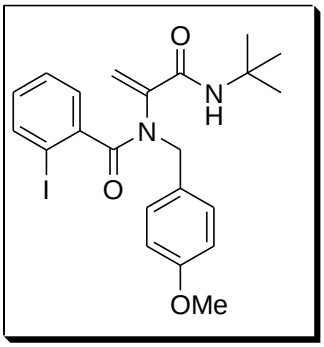
**Compound 12a,** the spectroscopy characterization has been previously reported.[1]



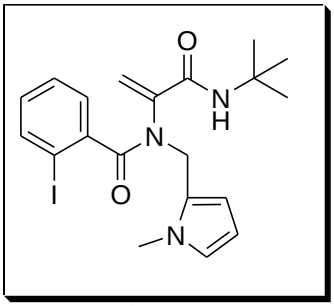
**Compound 12b, *N*-benzyl-*N*-(1-cyclohexylcarbamoyl-vinyl)-2-iodo-benzamide.** The product was obtained as a white solid (68 %), m.p. 160–162 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.76 (d, *J*=6 Hz, 2H), 7.48-7.22(m, 6H), 7.03-6.97(m, 1H), 6.09(s, N-H), 5.76(s, 1H), 5.38(s, 1H), 4.94(s, 2H), 3.63-3.57(m, 1H), 2.04-0.91 (m, 10H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 170.0, 162.4, 141.7, 141.4, 139.3, 136.6, 130.4, 129.4, 128.7, 128.0, 127.7 (2C), 121.9, 94.1, 51.6, 48.8, 32.7, 25.7, 25.3, 25.0, 24.9. **HRMS** (FAB+, M+) calculated for $C_{23}H_{25}IN_2O_2$ [M], 489.1039; found 489.1044. **IR** *v* ($cm^{-1}$): 3343, 2927, 2854, 1666, 1619, 1524, 695.



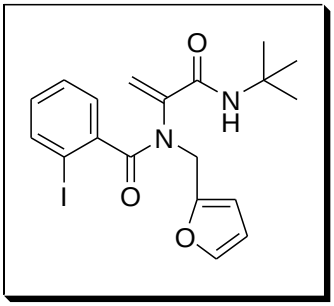
**Compound 12c, *N*-benzyl-*N*-[1-(2,6-dimethyl-phenylcarbamoyl)-vinyl)-2-iodo-benzamide**. The product was obtained as a white solid (45 %), m.p. 210–212 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$ + DMSO) δ: 9.20(bs, 1H), 7.79 (d, *J*=9 Hz, 1H), 7.53-7.25(m, 8H), 7.09-7.06 (m, 4H), 5.92 (s, 1H), 5.35(s, 1H), 5.01 (bs, 2H), 2.17 (s. 6H). **$^{13}$C NMR** (75 MHz, $CDCl_3$ +DMSO) δ: 169.7, 161.3, 141.6, 140.1, 138.7, 136.2, 135.1, 133.7, 129.8, 128.5, 128.0, 127.6, 127.3, 127.1, 127.0, 126.8, 123.3, 93.9, 49.5, 18.0. **HRMS** (FAB+, M+) calculated for $C_{25}H_{23}IN_2O_2$ [M], 511.0883; found 511.0884. **IR** *v* ($cm^{-1}$): 3280, 2921, 1656, 1623, 1522, 771.



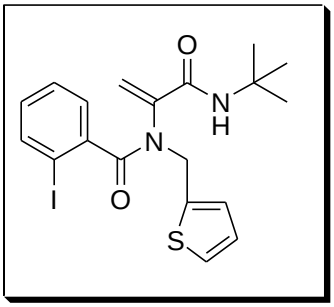
**Compound 12d, *N*-(1-*tert*-butylcarbamoyl-vinyl)-2-iodo-*N*-(4-methoxy-benzyl)-benzamide**. The product was obtained as a white solid (59 %), m.p. 115–118 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.75 (d, *J*=9 Hz, 1H), 7.55 (dd, 1H, *J*=3 Hz, *J*= 9 Hz, 1H), 7.42-7.24 (m, 4H), 7.03-6.97 (m, 1H), 6.88 (d, *J*=9 Hz, 1H), 5.83 (s, 1H), 5.45 (s, 1H), 5.33 (bs, 1H), 4.89 (s, 2H), 3.81 (s, 3H), 1.17 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 169.9, 162.7, 159.7, 142.8, 141.5, 139.5, 131.0, 130.6, 129.1, 128.6, 127.8, 121.8, 114.3, 94.3, 55.5, 51.8, 51.3, 28.5. **HRMS** (FAB+, M+) calculated for $C_{22}H_{25}IN_2O_3$ [M], 493.0988; found 493.0998. **IR** *v* ($cm^{-1}$): 3300, 2969, 1665, 1629, 1513, 685.



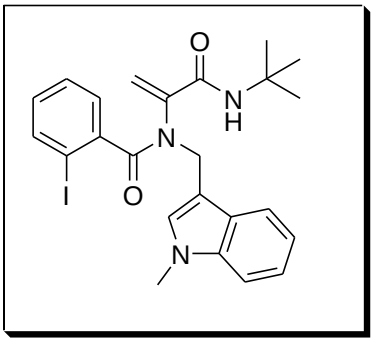
**Compound 12e, *N*-(1-*tert*-butylcarbamoyl-vinyl)-2-iodo-*N*-(1-methyl-1*H*-pyrrol-2-ylmethyl)-benzamide**. The product was obtained as a white solid (58 %), m.p. 170–172 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.74 (d, *J*= 9 Hz, 1H), 7.28-7.26 (m, 1H), 7.01-6.99 (m, 1H), 6.62(s, 1H), 6.14-6.04 (m, 2H), 5.75 (s, 1H), 5.47 (s, 1H), 5.23 (bs, 1H), 4.99 (s, 2H), 3.75 (s, 3H), 1.20 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 169.4, 163.0, 142.7, 141.6, 139.4, 130.4, 128.2, 127.8, 127.2, 123.6, 121.2, 111.6, 107.6, 94.1, 51.5, 42.8, 34.6, 28.4. **HRMS** (FAB+, M+) calculated for $C_{20}H_{24}IN_3O_2$ [M], 465.0913; found 465.0917. **IR** *v* ($cm^{-1}$): 3366, 2966, 1667, 1618, 1519, 735.



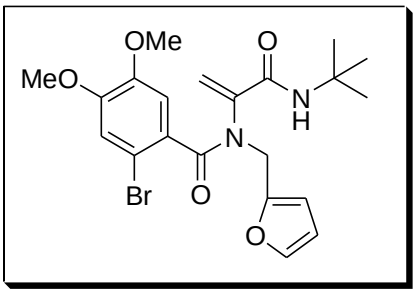
**Compound 12f, *N*-(1-*tert*-butylcarbamoyl-vinyl)-*N*-furan-2-ylmethyl-2-iodo-benzamide**. The product was obtained as a yellow solid (51 %), m.p. 118–120 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.76 (d, *J*=9 Hz, 1H), 7.59-7.55 (m, 1H), 7.40-7.23 (m, 3H), 7.04-6.99 (m, 1H), 6.45-6.35 (m, 2H), 5.90 (s, 1H), 5.33 (s, 1H), 4.94 (s, 2H), 1.25 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 169.8, 162.6, 150.1, 142.5, 139.6, 130.7, 128.7, 128.3, 127.8, 121.4, 111.0, 110.4, 109.9, 94.1, 51.7, 45.4, 28.6. **HRMS** (FAB+, M+) calculated for $C_{19}H_{21}IN_2O_3$ [M], 453.0675; found 453.0669. **IR** *v* ($cm^{-1}$): 3373, 2962, 1665, 1619, 1521, 748.



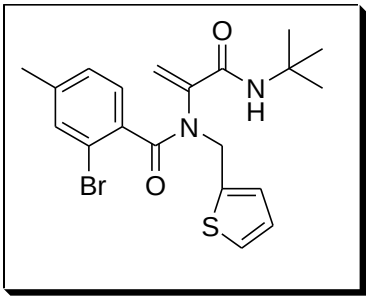
**Compound 12g, *N*-(1-*tert*-butylcarbamoyl-vinyl)-2-iodo-*N*-thiophen-2-ylmethyl-benzamide**. The product was obtained as a yellow solid (55 %), m.p. 113–115 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.75 (d, *J*=9 Hz, 1H), 7.58-7.02 (m, 4H), 7.11-6.96 (m, 2H),5.89 (s, 1H), 5.55 (s, 1H), 5.32(bs, 1H), 5.07 (s, 2H), 1.18 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 197.7, 162.6, 145.0, 142.8, 141.1, 139.6, 138.7, 130.7, 128.8, 128.6, 128.2, 127.8, 127.1, 126.7, 121.8, 94.2, 51.7, 47.3, 28.4. **HRMS** (FAB+, M+) calculated for $C_{19}H_{21}IN_2O_2S$ [M], 469.0447; found 469.0441. **IR** *v* ($cm^{-1}$): 3394, 2963, 1666, 1616, 1518, 724.



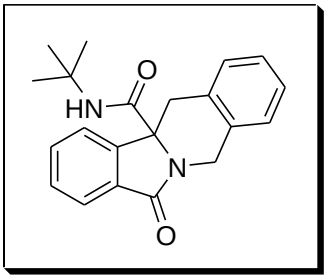
**Compound 12h, *N*-(1-*tert*-butylcarbamoyl-vinyl)-2-iodo-*N*-(1-methyl-1*H*-indol-3-ylmethyl)-benzamide**. The product was obtained as a pale oil (65 %). **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.84 (d, *J*=7.8 Hz, 1H), 7.74 (d, J=7.8 Hz, 1H), 7.35-7.14 (m, 6H), 7.00-6.94 (m, 1H), 6.12 (s, 1H), 5.79 (s, 1H), 5.16 (s, 2H), 3.77 (s. 3H), 0.74 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 169.5, 162.6, 143.5, 141.5, 139.5, 137.1, 130.6, 129.9, 128.2, 127.6, 127.2, 122.7, 122.4, 120.4, 119.9, 109.6, 94.2, 51.0, 44.5, 33.0, 27.7. **HRMS** (FAB+, M+) calculated for $C_{24}H_{26}IN_3O_2$ [M], 515.1070; found 515.1066. **IR** *v* ($cm^{-1}$): 3380, 1653, 1617, 1511, 740.



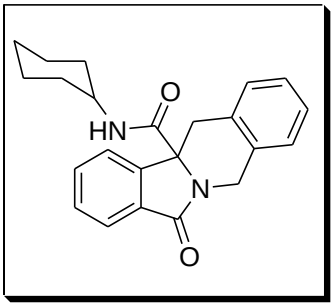
**Compound 12i, 2-bromo-*N*-(1-*tert*-butylcarbamoyl-vinyl)-*N*-furan-2-ylmethyl-4,5-dimethoxy-benzamide**. The product was obtained as a pail oil (80 %). **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.38 (s, 1H), 6.92-6.88 (m, 2H), 6.41-6.36 (m, 2H), 5.76 (s, 1H), 5.63 (bs, 1H), 5.44 (s, 1H), 4.91 (s, 2H), 3.85 (s, 3H), 3.80 (s, 3H), 1.25 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 168.5, 162.9, 150.4, 148.1, 143.2, 142.4, 129.3, 119.9, 115.4, 112.2, 110.9, 109.9, 56.3, 56.2, 51.7, 45.0, 28.5. **HRMS** (FAB+, M+) calculated for $C_{21}H_{25}BrN_2O_5$ [M], 465.1025; found 465.1022. **IR** *v* ($cm^{-1}$): 3355, 2968, 1664, 1624, 1508, 754.



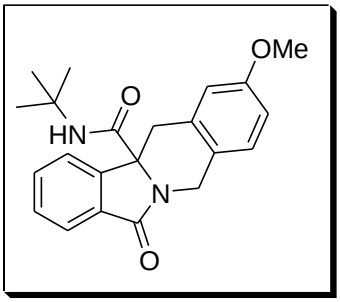
**Compound 12j, 2-bromo-*N*-(1-*tert*-butylcarbamoyl-vinyl)-4-methyl-*N*-thiophen-2-ylmethyl-benzamide**. The product was obtained as a pail oil (71 %). **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.59-7.56 (m, 1H), 7.39-7.26 (m, 3H), 7.13-6.96(m, 3H), 6.00 (s, 1H), 5.51 (s, 1H), 5.07 (s, 2H), 2.29 (s, 3H), 1.16 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 168.7, 162.4, 145.1, 142.8, 141.5, 138.7, 134.2, 133.5, 131.0, 128.6, 128.3, 127.9, 127.1, 122.0, 120.1, 51.6, 47.4, 28.3, 21.1. **HRMS** (FAB+, M+) calculated for $C_{20}H_{23}BrN_2O_2S$ [M], 435.0742; found 435.0746. **IR** *v* ($cm^{-1}$): 3359, 2969, 1667, 1622, 1516, 755.




**Compound 14a, 7-oxo-5,12-dihydro-7*H*-isoindolo[2,1-*b*]isoquinoline-11b-carboxylic acid *tert*-butylamide**, was purified by flash column chromatography (eluent 90:10 hexane/EtOAc). The product was obtained as a white solid (61 %), m.p. 208–210 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.89 (d, *J* =9 Hz, 1H), 7.79 (d, *J* =9 Hz, 1H),7.62 (t, *J* = 9 Hz, 1H), 7.53 (t, *J* = 9 Hz, 1H), 7.23 (s, 4H), 5.65 (s, 1H, NH), 5.34 (d, *J* =18 Hz, 1H), 4.55 (d, *J* =18 Hz, 1H), 4.14 (d, *J* =15 Hz, 1H), 2.61 (d, *J* =15 Hz, 1H), 1.06 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 169.4, 167.6, 146.8, 132.7, 131.3, 130.3, 130.0, 129.5, 129.0, 127.4, 127.1, 126.3, 123.9, 122.1, 68.1, 51.5, 42.3, 37.4, 28.3. **HRMS** (FAB+, M+) calculated for $C_{21}H_{22}N_2O_2$ [M], 335.1758; found 335.1760. **IR** *v* ($cm^{-1}$): 3324, 2968, 1698, 1672, 1526, 1361, 740.

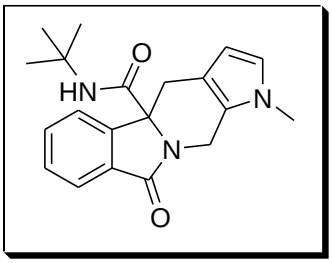



**Compound 14b, 7-oxo-5,12-dihydro-7*H*-isoindolo[2,1-*b*]isoquinoline-11b-carboxylic acid cyclohexylamide,** was purified by flash column chromatography (eluent 70:30 hexane/EtOAc). The product was obtained as a white solid (27 %), m.p. 220–222 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.87 (d, *J*= 6 Hz, 1H), 7.77 (d, *J*= 9Hz, 1H), 7.64-7.49 (m, 2H), 7.26-7.22 (m, 4H), 5.76 (d, *J*= 9 Hz, 1H), 5.35 (d, *J*= 18 Hz, 1H), 4.55 (d, *J*=18 Hz, 1H), 4.17 (d, *J*=15 Hz, 1H), 3.55-3.48 (m, 1H), 2.64 (d, *J*=15 Hz, 1H), 1.59-0.82 (m, 10H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 169.5, 167.7, 146.9, 132.8, 131.3, 130.4, 130.2, 129.6, 129.4, 127.6, 127.4, 126.6, 124.1, 122.3, 67.9, 48.8, 42.3, 37.3, 33.0, 32.6, 29.9, 25.4, 24.8. **HRMS** (FAB+, M+) calculated for $C_{23}H_{24}N_2O_2$ [M], 361.1916; found 361.1915. **IR** *v* ($cm^{-1}$): 3317, 2929, 1693, 1666, 1530, 742.

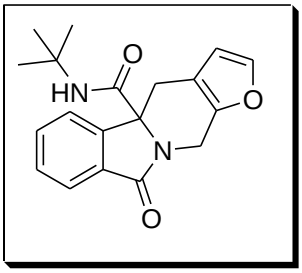



**Compound 14d, 2-methoxy-7oxo-5,12-dihydro-7*H*-isoindolo[2,1-*b*]isoquinoline-11b-carboxylic acid *tert*-butylamide,** was purified by flash column chromatography (eluent 70:30 hexane/EtOAc). The product was obtained as a white solid (33 %), m.p. 175–178 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.88 (d, *J*= 6Hz, 1H), 7.77 (d, *J*=*9* Hz, 1H), 7.65-7.51 (m, 2H), 7.13 (d, *J*= 9Hz, 1H), 6.84-6.75 (m, 2H), 5.66 (bs, 1H) 5.27 (d, *J*=15 Hz, 1H), 4.49 (d, *J*=15 Hz, 1H), 4.08 (d, *J*=15 Hz, 1H), 3.80 (s, 3H), 2.58 (d, *J*= 15 Hz, 1H), 1.08 (s, 9H).

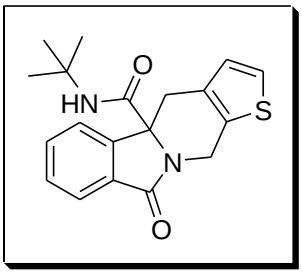
**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 169.5, 167.7, 158.8, 146.9, 132.8, 132.7, 130.2, 129.3, 127.5, 124.1, 122.4, 122.2, 114.1, 113.8, 68.2, 55.4, 51.7, 41.9, 37.7, 28.5. **HRMS** (FAB+, M+) calculated for $C_{22}H_{24}N_2O_3$ [M+], 365.1865; found 365.1867. **IR** *v* ($cm^{-1}$): IR: 3315, 2967, 1696, 1674, 1507, 756.



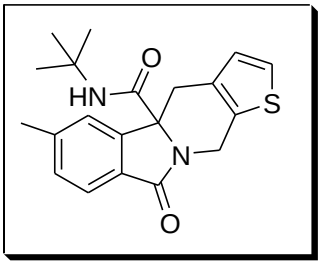
**Compound 14e, 1-methyl-9-oxo-4,10-dihydro-1*H*,9*H*-1,9a-diaza-cyclopenta[*b*]fluorene-4a-carboxylic acid *tert*-butylamide,** was purified by flash column chromatography (eluent 70:30 hexane/EtOAc). The product was obtained as a white solid (52 %), m.p. 215–218 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.84 (d, *J*= 6 Hz, 1H), 7.68 (d, *J*= 6 Hz, 1H), 7.49-7.61 (m, 2H), 6.54 (d, *J*=2.7 Hz, 1H), 5.96 (d, *J*= 2.7 Hz, 1H), 5.58 (bs, 1H), 5.29 (d, *J*=15 Hz, 1H), 4.26 (d, *J*= 15 Hz, 1H), 4.06 (d, *J*=15 Hz, 1H), 3.56 (s, 3H), 2.42 (d, *J*=15 Hz, 1H), 1.14 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 169.2, 167.8, 147.2, 132.8, 129.6, 129.1, 124.0, 122.3, 121.9, 121.7, 113.8, 106.5, 69.4, 51.7, 37.1, 33.4, 30.7, 28.7. **HRMS** (FAB+, M+) calculated for $C_{20}H_{24}N_3O_2$ [M+1], 338.1869; found 338.1867. **IR** *v* ($cm^{-1}$): 3316, 2922, 1690, 1665, 1522, 730.



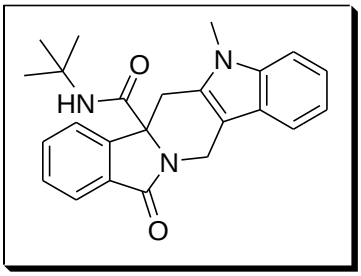
**Compound 14f, 9-oxo-4,10-dihydro-9*H*-1-oxa-9a-aza-cyclopenta[*b*]fluorene-4a-carboxylic acid *tert*-butylamide,** was purified by flash column chromatography (eluent 70:30 hexane/EtOAc). The product was obtained as a white solid (62 %), m.p. 204–206 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.82 (d, *J*=7.5 Hz, 1H), 7.70-7.48 (m, 3H), 7.35 (d, *J*=18 Hz, 1H), 6.29 (d, *J*=18 Hz, 1H), 5.72 (bs, 1H), 5.31 (d, *J*=18 Hz, 1H), 4.30 (d, *J*=18 Hz, 1H), 4.08 (d, *J*=15 Hz, 1H) , 2.38(d, *J*=15 Hz, 1H), 1.17 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 169.0, 167.4, 146.6, 144.3, 142.9, 133.04, 129.4, 129.3, 124.1, 121.8, 114.7, 110.4, 69.1, 51.9, 38.0, 29.6, 28.6. **HRMS** (FAB+, M+) calculated for $C_{19}H_{20}N_2O_3$ [M], 325.1552; found 325.1552. **IR** *v* ($cm^{-1}$): 3329, 2962, 1697, 1667, 1523, 730.



**Compound 14g, 9-oxo-4,10-dihydro-9*H*-1-thia-9a-aza-cyclopenta[*b*]fluorene-4a-carboxylic acid *tert*-butylamide,** was purified by flash column chromatography (eluent 70:30 hexane/EtOAc). The product was obtained as a white solid (56 %), m.p. 228–230 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.84 (d, *J*= 6Hz, 1H), 7.71 (d, *J*= 6 Hz, 1H), 7.64- 7.49 (m, 2H), 7.21 (d, *J*= 5.1 Hz, 1H), 6.83 (d, *J*=5.1, 1H), 5.69 (bs, 1H), 5.47 (d, J=17.7 Hz), 4.51 (d, *J*= 16.8 Hz, 1H), 4.25 (d, *J*=15 Hz, 1H), 2.44 (d, *J*=15 Hz, 1H), 1.14 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 168.8, 167.5, 146.8, 132.9, 132.1, 129.7, 129.4, 129.3, 127.2, 124.5, 124.2, 121.9, 68.5, 51.8, 39.4, 33.2, 28.6. **HRMS** (FAB+, M+) calculated for $C_{19}H_{20}N_2O_2S$ [M], 340.1245; found 340.1251. **IR** *v* ($cm^{-1}$): 3322, 2955, 1695, 1667, 1524, 690.

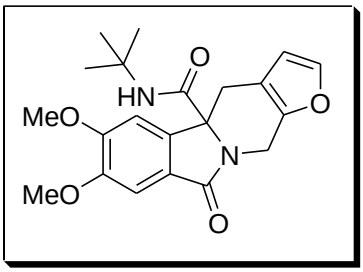


**Compound 14h, 6-methyl-9-oxo-4,10-dihydro-9*H*-1-thia-9a-aza-cyclopenta[*b*]fluorene-4a-carboxylic acid *tert*-butylamide,** was purified by flash column chromatography (eluent 70:30 hexane/EtOAc). The product was obtained as a white solid (68 %), m.p. 233–235 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.70 (d, *J*= 6 Hz,1H), 7.51(s, 1H), 7.31 (d, *J*= 6Hz, 1H), 7.20 (d, *J*= 6 Hz, 1H), 6.83 (d, *J*=6 Hz, 1H), 5.78 (bs, 1H), 5.45 (d, *J*=18 Hz, 1H), 4.49 (d, *J*=15 Hz, 1H), 4.22 (d, *J*=15 Hz, 1H), 2.48 (s, 3H), 2.42 (d, *J*=15 Hz, 1H), 1.15 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 168.9, 167.6, 147.2, 143.9, 132.1, 130.3, 129.5, 127.2, 127.1, 124.4, 123.9, 122.2, 68.3, 51.8, 39.3, 33.3, 28.6, 22.1. **HRMS** (FAB+, M+) calculated for $C_{20}H_{22}N_2O_2S$ [M], 355.1480; found 355.1486. **IR** *v* ($cm^{-1}$): IR: 3327, 2966, 2921, 1693, 1667, 1520, 694.

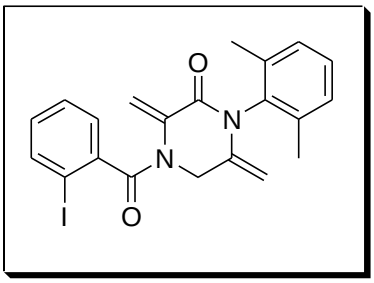


**Compound 14i, 12-methyl-6-oxo-11,12-dihydro-5*H*-6*H*-5a,12-diaza-indeno[1,2-*b*]fluorene-10b-carboxylic acid *tert*-butylamide,** was purified by flash column chromatography (eluent 70:30 hexane/EtOAc). The product was obtained as a white solid (61 %), m.p. 238–240 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.88 (d, *J*=9 Hz, 1H), 7.73 (d, *J*= 6Hz, 1H), 7.60-7.50 (m, 3H), 7.31-7.10 (m, 3H), 5.77 (bs, 1H), 5.52 (d, *J*= 15 Hz, 1H), 4.51 (d, *J*=15 Hz, 1H), 4.43 (d, *J*= 15 Hz, 1H), 3.68 (s, 3H), 2.60 (d, *J*=18 Hz, 1H), 1.12 (s, 9H).

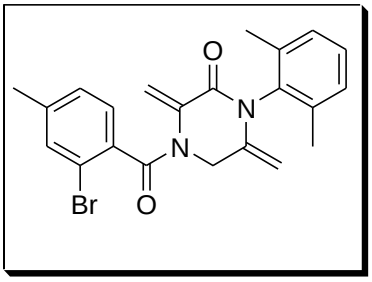
**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 168.8, 167.4, 146.7, 137.9, 132.8, 131.2, 129.9, 129.4, 124.8, 124.1, 121.7, 121.5, 119. 4, 117.8, 109.3, 104.2, 68.7, 51.8, 36.9, 29.4, 29.2, 28.5. **HRMS** (FAB+, M+) calculated for $C_{24}H_{25}N_3O_2$ [M], 387.1947; found 387.1946. **IR** *v* ($cm^{-1}$): 3332, 2973, 1694, 1669, 1522, 742.



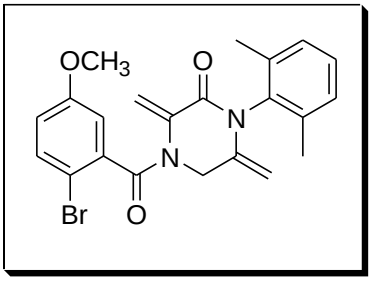

**Compound 14j, 6,7-dimethoxy-9-oxo-4,10-dihydro-9*H*-1-oxa-9a-aza-cyclopenta[*b*]fluorene-4a-carboxylic acid *tert*-butylamide,** was purified by flash column chromatography (eluent 70:30 hexane/EtOAc). The product was obtained as a white solid (39 %), m.p. 243–245 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.36 (d, *J*= 3Hz, 1H), 7.26 (s, 1H), 7.11 (s, 1H), 6.28 (d, *J*= 3 Hz, 1H), 5.86 (bs, 1H), 5.26(d, *J*= 18 Hz, 1H), 4.28(d, J=18 Hz, 1H), 4.03 (d, *J*=18 Hz, 1H), 3.97 (s, 3H), 3.93(s, 3H), 2.36 (d, *J*=15 Hz, 1H), 1.18 (s, 9H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 168.8, 167.4, 153.3, 150.2, 144.3, 142.5, 140.4, 121.2, 114.2, 110.1, 106.0, 103.4, 68.2, 56.4, 56.1, 51.4, 37.6, 29.4, 28.3. **HRMS** (FAB+, M+) calculated for $C_{21}H_{24}N_2O_5$ [M], 385.1763; found 385.1768. **IR** *v* ($cm^{-1}$): IR: 3314, 2924, 1692, 1668, 1500.



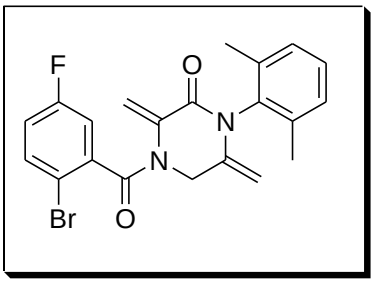

**Compound 17a**, **1-(2,6-dimethyl-phenyl)-4-(2-iodo-benzoyl)-3,6-dimethylene-piperazin-2-one**, was purified by flash column chromatography (eluent 96:14 hexane/EtOAc). The product was obtained as a yellow solid (79 %), m.p. 147–150 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.85 (d, *J* =8 Hz, 1H), 7.40 (t, *J* =5.1, 6.9 Hz, 1H), 7.25–7.09 (m, 5H), 6.17 (s, 1H), 4.87 (s, 2H), 4.41 (s, 1H), 3.87 (s, 1H), 2.16 (s, 6H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 168.5, 157.7, 140.9, 139.6, 137.8, 135.4, 135.3, 130.9, 128.8, 128.7 (2C), 128.5, 128.4, 118.1, 94.7, 44.1, 17.7. **HRMS** (FAB+, M+) calculated for $C_{21}H_{20}IN_2O_2$ [M+1], 459.0581; found 459.0570. **IR** v (cm-1): 1679, 1654, 1628, 1404, 1350, 1299, 1163, 988, 774.



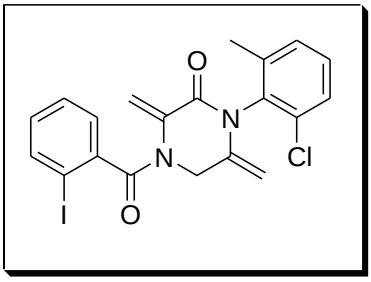

**Compound 17b, 4-(2-bromo-4-methyl-benzoyl)-1-(2,6-dimethyl-phenyl)-3,6-dimethylene-piperazin-2-one,** was purified by flash column chromatography (eluent 8:2 hexane/EtOAc). The product was obtained as light yellow oil (39 %). **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.39 (s, 1H), 7.24–7.14 (m, 5H), 6.12 (s, 1H), 4.86 (s, 2H), 4.38 (s, 1H), 3.86 (s, 1H), 2.36 (s, 3H), 2.15 (s, 6H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 166.9, 159.5, 141.9, 141.7, 137.9, 136.2, 135.3, 135.1, 133.6, 133.5, 128.9, 128.8, 128.7, 128.6, 128.4, 119.2, 112.8, 106.2, 29.7, 21.1, 17.8, 16.4. **HRMS** (FAB+, M+) calculated for $C_{22}H_{22}N_2O_2Br$ [M+1], 425.0874; found 425.0865. **IR** ν ($cm^{-1}$): 1662, 1640, 1357, 1309, 1165.



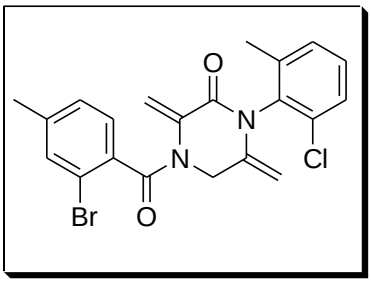

**Compound 17c, 4-(2-bromo-5-methoxy-benzoyl)-1-(2,6-dimethyl-phenyl)-3,6-dimethylene-piperazin-2-one,** was purified by flash column chromatography (eluent 80:20 hexane/EtOAc). The product was obtained as a light yellow solid (59 %), m.p. 106–110 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.42 (d, *J* =8.1 Hz, 1H), 7.24–7.14 (m, 3H), 6.87–6.82 (m, 2H), 6.13 (s, 1H), 4.94 (s, 1H), 4.67 (s, 1H), 4.42 (s, 1H), 3.87 (s, 1H), 3.78 (s, 3H), 2.15 (s, 6H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 166.6, 159.0, 157.6, 137.7, 137.2, 135.7, 135.2, 133.9, 128.8, 128.7, 128.5, 127.0, 117.4, 117.2, 114.2, 94.7, 55.5, 44.0, 17.5. **HRMS** (FAB+, M+) calculated for $C_{22}H_{22}N_2O_3Br$ [M+1], 441.0816; found 441.0814. **IR** ν (cm-1): 1688, 1624, 1569, 1471, 1415, 1308, 782.



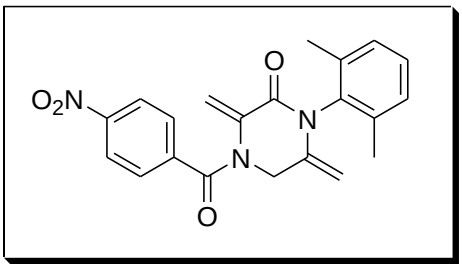

**Compound 17d**, **4-(2-bromo-5-fluoro-benzoyl)-1-(2,6-dimethyl-phenyl)-3,6-dimethylene-piperazin-2-one,** was purified by flash column chromatography (eluent 80:20 hexane/EtOAc). The product was obtained as a white solid (54 %), m.p. 133–136°C. **$^{1}$H NMR** (200 MHz, $CDCl_3$) δ: 7.51 (s, 1H), 7.27–7.03 (m, 5H), 6.16 (s, 1H), 4.91 (s, 2H), 4.67 (s, 1H), 4.43 (s, 1H), 3.90 (s, 1H), 2.15 (s, 6H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 165.5, 163.4, 160.1, 157.5, 137.6, 135.2, 134.8, 134.7, 128.8, 128.7, 128.5, 118.6, 118.4, 117.6, 99.9, 95.1, 44.1, 17.6. **HRMS** (FAB+, M+) calculated for $C_{21}H_{19}N_2O_2BrF$ [M+1], 429.0609; found 429.0614. **IR** ν ($cm^{-1}$): 1681, 1644, 1617, 1464, 1425, 1307, 1211, 778.



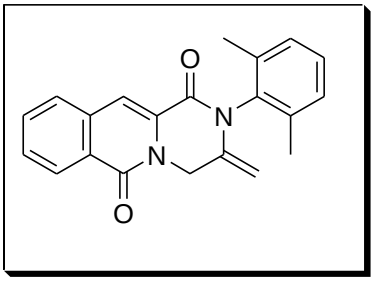

**Compound 17e**, **1-(2-chloro-6-methyl-phenyl)-4-(2-iodo-benzoyl)-3,6-dimethylene-piperazin-2-one,** was purified by flash column chromatography (eluent 80:20 hexane/EtOAc). The product was obtained as a light yellow solid (66 %), m.p. 157–160 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.85 (d, *J* =7.2 Hz, 1H), 7.38 (dd, *J* =1.8, 7.2 Hz, 2H), 7.30–7.25 (m, 3H), 7.11 (t, *J* =7.5 Hz, 1H), 6.15 (s, 1H), 4.91 (s, 2H), 4.47 (s, 1H), 3.88(s, 1H), 2.23 (s, 3H). **HRMS** (FAB+, M+) calculated for $C_{20}H_{17}N_2O_2ICl$ [M+1], 479.0026; found 479.0023. **IR** ν ($cm^{-1}$): 1684, 1655, 1631, 1405, 1298, 1164, 988, 772, 737.



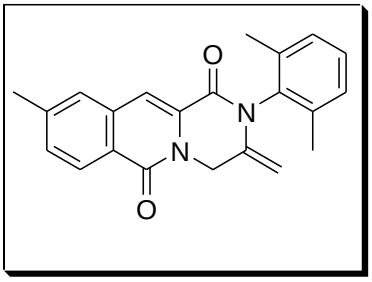

**Compound 17f**, **4-(2-bromo-4-methyl-benzoyl)-1-(2-chloro-6-methyl-phenyl)-3,6-dimethylene-piperazin-2-one,** was purified by flash column chromatography (eluent 75:25 hexane/EtOAc). The product was obtained as a light yellow oil (69 %). **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.39–7.36 (m, 2H), 7.24–7.15 (m, 4H), 6.13 (s, 1H), 4.97–4.61 (m, 3H), 4.43 (s, 1H), 3.86 (s, 1H), 2.36 (s, 3H), 2.22 (s, 3H). **HRMS** (FAB+, M+) calculated for $C_{21}H_{18}N_2O_2ClBr$ [M], 444.0239; found 444.0240. **IR** ν ($cm^{-1}$): 1636, 1454, 1353, 1301, 1164, 772.



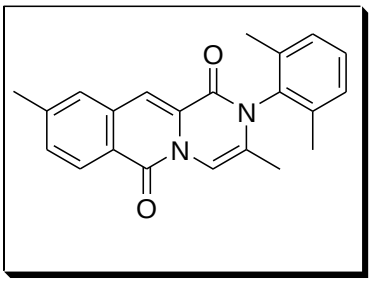

**Compound 17g, 1,-(2,6-dimethyl-phenyl)-3,6-dimethylene-4-(4-nitro-benzoyl)-piperazin-2-one**, was purified by flash column chromatography (eluent 75:25 hexane/EtOAc). The product was obtained as a yellow solid (64 %), m.p. 142–144 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 8.41 (t, *J* =2.4 Hz, 1H), 8.35–8.30 (m, 1H), 7.84–7.80 (m, 1H), 7.62 (t, *J* =8.0 Hz, 1H), 7.27–7.17 (m, 3H), 6.22 (s, 1H), 4.93 (s, 1H), 4.75 (s, 2H), 4.36 (d, *J* =1.5 Hz, 1H), 3.90 (d, *J* =1.5 Hz, 1H), 2.21 (s, 6H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 166.7, 157.5, 148.1, 137.8, 136.9, 135.6, 135.4, 134.8, 134.1, 129.7, 128.9 (2C), 125.6, 123.7, 118.7, 94.5, 45.7, 17.4. **HRMS** (FAB+, M+) calculated for $C_{21}H_{20}N_3O_4$ [M+1], 378.1454; found 378.1454. **IR** ν ($cm^{-1}$): 1662, 1622, 1526, 1347, 1305, 854, 771, 702.



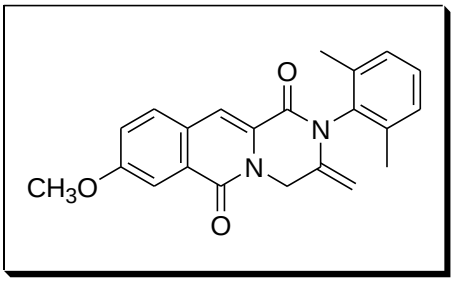
**Compound 18a**, **2-(2,6-dimethyl-phenyl)-3-methylene-3,4-dihydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,6-dione,** was purified by flash column chromatography (eluent 95:5 hexane/EtOAc). The product was obtained as a yellow solid (87 %), m.p. 165–168 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 8.48 (d, *J* =9 Hz, 1H), 7.73–7.59 (m, 3H), 7.25–7.16 (m, 4H), 5.06 (s, 2H), 4.63 (s, 1H), 4.08 (s, 1H), 2.16 (s, 6H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 160.6, 156.8, 136.6, 135.6, 135.4, 135.1, 132.9, 130.0, 129.2, 128.9, 128.2, 128.0, 127.0, 111.3, 97.7, 43.1, 17.7. **HRMS** (FAB+, M+) calculated for $C_{21}H_{19}N_2O_2$ [M+1], 331.1452; found 331.1447. **IR** v (cm-1): 1647, 1629, 1455, 1431, 1373, 1309, 864, 758.



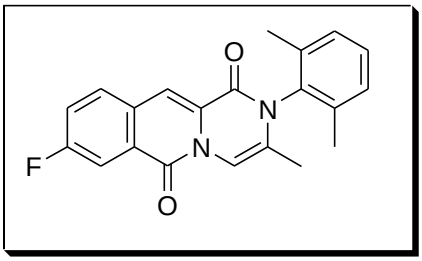
**Compound 18b-exo**, **2-(2,6-dimethyl-phenyl)-9-methyl-3-methylene-3,4-dihydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,6-dione,** was purified by flash column chromatography (eluent 9:1 hexane/EtOAc). The product was obtained as a yellow solid (78 %), m.p. 240–243 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 8.37 (d, *J* =8.1 Hz, 1H), 7.61 (s, 1H), 7.50 (s, 1H), 7.45 (d, *J* =8.4 Hz, 1H), 7.28–7.18 (m, 3H), 5.05 (s, 2H), 4.62 (d, *J* =1.0 Hz, 1H), 4.08 (d, *J* =1.0 Hz, 1H), 2.52 (s, 3H), 2.17 (s, 6H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 160.6, 156.9, 143.7, 136.7, 135.6, 135.4, 135.2, 130.8, 130.0, 128.9, 128.8, 128.0, 127.9, 124.8, 113.3, 97.7, 43.0, 21.8, 17.7. **HRMS** (FAB+, M+) calculated for $C_{22}H_{21}N_2O_2$ [M+1], 345.1601; found 345.1603. **IR** v ($cm^{-1}$): 1649, 1629, 1467, 1324, 1301, 827, 765.



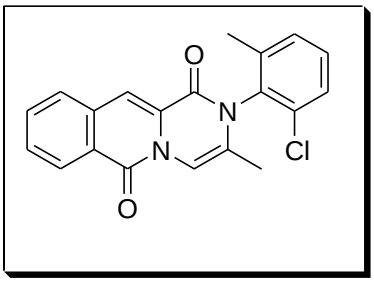
**Compound 18b-endo**, **2-(2,6-dimethyl-phenyl)-3,9-dimethyl-2*H*-pyrazino[1,2-*b*]isoquinoline-1,6-dione,** was purified by flash column chromatography (eluent 9:1 hexane/EtOAc). The product was obtained as a yellow solid (5 %), m.p. 219–222 °C. **$^{1}$H NMR** (200 MHz, $CDCl_3$) δ: 8.46 (d, *J* =8.4 Hz, 1H), 7.75 (d, *J* =3.6 Hz, 2H), 7.56 (s, 1H), 7.47 (d, *J* =12.3 Hz, 1H), 7.29–7.17 (m, 3H), 2.54 (s, 3H), 2.16 (s, 6H), 1.77 (s, 3H). **$^{13}$C NMR** (50 MHz, $CDCl_3$) δ: 158.5, 157.4, 143.6, 135.8, 135.1, 130.4, 129.2, 129.0, 128.7, 128.2, 127.6, 123.4, 123.0, 108.2, 103.4, 21.9, 17.8, 17.2. **HRMS** (FAB+, M+) calculated for $C_{22}H_{20}N_2O_2$ [M], 344.1531; found 344.1525. **IR** v ($cm^{-1}$): 1641, 1472, 1395, 1346, 1326, 905, 769,726.



**Compound 18c**, **2-(2,6-dimethyl-phenyl)-8-methoxy-3-methylene-3,4-dihydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,6-dione,** was purified by flash column chromatography (eluent 85:15 hexane/EtOAc). The product was obtained as a yellow solid (69 %), m.p. 215–218 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 7.87 (d, *J* =2.7 Hz, 1H), 7.66–7.63 (m, 2H), 7.33(dd, *J* =2.7, 8.7 Hz, 1H), 7.26–7.17 (m, 3H), 5.08 (s, 2H), 4.63 (*J* =1.5 Hz, 1H), 4.08 (*J* =1.5 Hz, 1H), 3.98 (s, 3H), 2.17 (s, 6H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 160.7, 160.2, 156.9, 136.7, 135.6, 135.4, 129.9, 129.0, 128.8, 128.6, 127.8, 123.4, 111.5, 108.1, 99.9, 97.5, 55.8, 43.3, 17.7. **HRMS** (FAB+, M+) calculated for $C_{22}H_{20}N_2O_3$ [M], 360.1469; found 360.1474. **IR** ν ($cm^{-1}$): 1673, 1627, 1500, 1429, 1305, 1019.

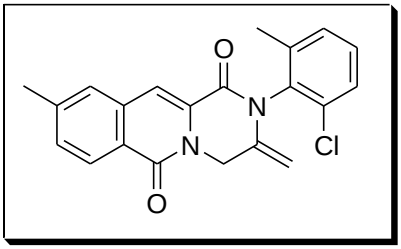


**Compound 18d**, **2-(2,6-dimethyl-phenyl)-8-fluoro-3-methylene-3-methyl-2*H*-pyrazino[1,2-*b*]isoquinoline-1,6-dione**, was purified by flash column chromatography (eluent 90:10 hexane/EtOAc). The product was obtained as a yellow solid (85 %), m.p. 230–233 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 8.21 (dd, *J* =3.3, 9.3 Hz, 1H), 7.83–7.78 (m, 2H), 7.72 (d, *J* =1.8 Hz, 1H), 7.50 (ddd, *J* =3.0, 8.4, 11.4 Hz, 1H), 7.31–7.19 (m, 3H), 2.15 (s, 6H), 1.79 (d, *J* =1.8 Hz, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 164.1, 160.8, 157.2, 135.8, 135.0, 131.6, 130.7, 130.6, 129.3, 128.8, 124.3, 122.2, 121.9, 113.4, 113.1, 107.9, 107.9, 103.2, 17.7, 17.3. **HRMS** (FAB+, M+) calculated for $C_{21}H_{17}N_2O_2F$ [M], 348.1282; found 348.1274**. IR** ν ($cm^{-1}$): 1687, 1645, 1494, 1332, 763.

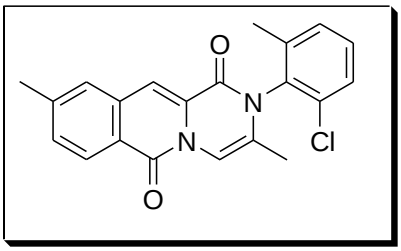


**Compound 18e**, **2-(2chloro-6-methyl-phenyl)-3-methyl-2*H*-pyrazino[1,2-*b*]isoquinoline-1,6-dione,** was purified by flash column chromatography (eluent 80:20 hexane/EtOAc). The product was obtained as a yellow solid (84 %), m.p. 174–176 °C. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ: 8.57 (d, *J* =8.1 Hz, 1H), 7.83–7.74 (m, 4H), 7.68–7.62 (m, 1H), 7.41–7.29 (m, 3H), 2.23 (s, 3H), 1.84 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 160.5, 156.8, 138.5, 136.4, 135.0, 134.1, 132.9, 132.7, 130.2, 129.9, 129.8, 129.5, 129.3, 128.2, 128.1, 128.0,

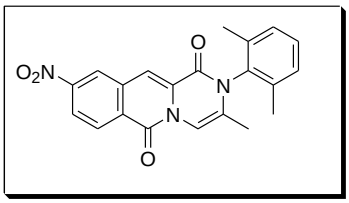
111.6, 98.1, 43.2, 18.1. **HRMS** (FAB+, M+) calculated for $C_{20}H_{15}N_2O_2Cl$ [M+1], 350.0822; found 350.0822. **IR** v ($cm^{-1}$): 1643, 1596, 1462, 1409, 1332, 1147, 864, 762, 689.




**Compound 18f-exo**, **2-(2chloro-6-methyl-phenyl)-9-methyl-3-methylene-3,4-dihydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,6-dione,** was purified by flash column chromatography (eluent 80:20 hexane/EtOAc). The product was obtained as a yellow solid (52 %), m.p. 244–246 °C. **$^1$H NMR** (300 MHz, $CDCl_3$) δ: 8.37 (d, *J* =8.4 Hz, 1H), 7.62 (s, 1H), 7.50-7.40 (m, 3H), 7.34-7.28 (m, 2H), 5.15 (d, *J* =15.3 Hz, 1H), 5.01 (d, *J* =15.3 Hz, 1H), 4.68 (d, *J* =1.8 Hz, 1H), 4.11 (d, *J* =1.8 Hz, 1H), 2.52 (s, 3H), 2.24 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 160.5, 156.9, 143.7, 138.5, 136.5, 135.1, 134.1, 132.8, 130.9, 129.8 (2C), 129.5, 128.2, 128.0, 127.9, 124.9, 111.6, 98.0, 43.1, 21.8, 18.1. **HRMS** (FAB+, M+) calculated for $C_{21}H_{18}N_2O_2Cl$ [M+1], 365.1048; found 365.1057. **IR** v ($cm^{-1}$): 1674, 1634, 1462, 1323, 1299, 910, 768.

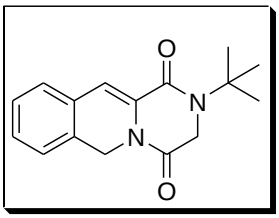



**Compound 18f-endo**, **2-(2chloro-6-methyl-phenyl)-3,9-dimethyl-2*H*-pyrazino[1,2-*b*]isoquinoline-1,6-dione**, was purified by flash column chromatography (eluent 80:20 hexane/EtOAc). The product was obtained as a yellow solid (46 %), m.p. 239–243 °C. **$^1$H NMR** (300 MHz, $CDCl_3$) δ: 8.45 (d, *J* =8.4 Hz, 1H), 7.76 (s, 1H), 7.73 (d, *J* =1.2 Hz, 1H), 7.56 (s, 1H), 7.49–7.40 (m, 2H), 7.36–7.29 (m, 2H), 2.54 (s, 3H), 2.22 (s, 3H), 1.83 (d, *J* =1.2 Hz, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 158.4 157.3, 143.6, 138.7, 135.0, 133.7, 133.3, 130.5, 130.2, 129.4, 128.7, 128.3, 127.9, 127.6, 123.2, 123.1, 108.6, 103.4, 21.9, 18.1, 17.0**. HRMS** (FAB+, M+) calculated for $C_{21}H_{17}N_2O_2Cl$ [M], 364.0982; found 364.0979**. IR** v ($cm^{-1}$): 1648, 1619, 1457, 1395, 1347, 1322, 905, 770.

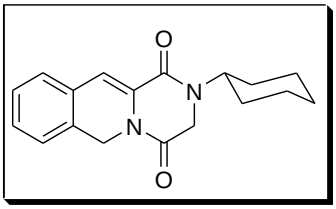



**Compound 18g, 2-(2,6-dimethyl-phenyl)-3-methyl-9-nitro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,6-dione**, was purified by flash column chromatography (eluent 90:10 hexane/EtOAc). The product was obtained as a white solid (82 %), m.p. 243–245 °C. **$^1$H NMR** (300 MHz, $CDCl_3$) δ: 8.21 (dd, *J* = 2.7, 9.0 Hz, 1H), 7.83 (m, 2H), 7.72 (s, 1H), 7.50 (ddd, *J* =2.7, 8.1, 8.7 Hz, 1H), 7.29 (t, *J* = 6.3 Hz, 1H), 7.22–7.19 (m, 2H), 2.15

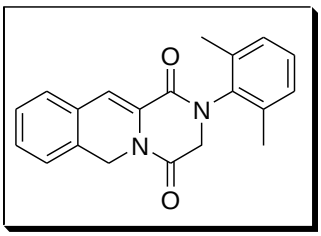
(s, 6H), 1.79 (d, *J* =1.5 Hz, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ: 164.1, 160.8, 157.2, 135.7, 130.6, 130.5, 129.3, 128.7, 124.3, 122.2, 121.9, 113.4, 113.1, 107.9, 107.8, 103.1, 17.7, 17.3. **IR** ν ($cm^{-1}$): 1645, 1601, 1412, 1348, 1333, 947, 763.



**Compound 22a, 2-*tert*-butyl-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione** was purified by flash column chromatography (eluent 70:30 hexane/EtOAc). The product was obtained as a white solid (64 %), m.p. 104–106 °C. **$^{1}$H-NMR** (400 MHz, $CDCl_3$) δ:1.51 (s, 9H, $CH_3$), 4.13 (s, 2H, $COCH_2N$), 5.01 (s, 2H, $ArCH_2$), 6.98 (s, 1H, C=CH), 7.16–7.13 (m, 1H, ArH), 7.21–7.19 (m, 1H, ArH), 7.27–7.24 (m, 2H, ArH). **$^{13}$C-NMR** (100 MHz, $CDCl_3$) δ: 27.7, 44.0, 47.0, 58.2, 115.1, 125.7, 127.1, 128.2, 128.9, 129.0, 129.1, 129.8, 159.2, 162.7. **IR** ν ($cm^{-1}$): 3367, 3063, 2978, 2928, 1677, 1622, 1421, 1199. **MS (DART+)** m/z: 271 (M+H); **HRMS** m/z calcd for $C_{16}H_{19}N_2O_2$ [M+H], 271.14465; found 271.14407.

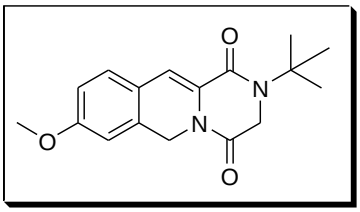


**Compound 22b, 2-cyclohexyl-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione** was purified by flash column chromatography (eluent 70:30 hexane/EtOAc). The product was obtained as a white solid (71 %), m.p. 58–60 °C. **$^{1}$H-NMR** (300 MHz, $CDCl_3$) δ: 1.46–1.36 (m, 7H, $CH_2$), 1.85-1.69 (m, 3H, $CH_2$) , 4.04 (s, 2H, $COCH_2N$), 4.51 (br s, 1H, NCH), 5.03 (s, 2H, $ArCH_2$), 7.00 (s, 1H, C=CH), 7.15–7.13 (m, 1H, ArH), 7.28–7.23 (m, 3H, ArH). **$^{13}$C-NMR** (75.5 MHz, $CDCl_3$) δ: 25.5, 25.6, 29.3, 44.2, 45.2, 52.9, 115.7, 125.9, 127.2, 128.1, 128.3, 129.3, 129.4, 129.7, 157.8, 162.2. **IR** ν ($cm^{-1}$): 2930, 2855, 1678, 1617, 1309, 1239, 1197, 1044, 758, 728. **MS (DART+)** m/z: 297 (M+H); **HRMS** m/z calcd for $C_{18}H_{21}N_2O_2$ [M+H], 297.16030; found 297.16023.

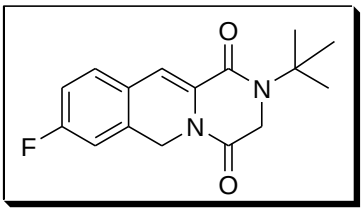


**Compound 22c, 2-(2,6-dimethylphenyl)-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione** was purified by flash column chromatography (eluent 85:15 hexane/EtOAc). The product was obtained as a colorless oil (72 %). **$^{1}$H-NMR** (400 MHZ, $CDCl_3$) δ: 2.24 (s, 6H, $CH_3$), 4.25 (s, 2H, $COCH_2N$), 5.15 (s, 2H, $ArCH_2$), 7.11 (s 1H, C=CH), 7.21–7.16 (m, 4H, ArH), 7.32–7.26 (m, 3H, ArH). **$^{13}$C-NMR** (100 MHz, $CDCl_3$) δ: 17.7, 44.4, 51.3, 116.4, 125.9, 127.3, 127.5, 128.3, 128.8, 129.0, 129.3, 129.4,

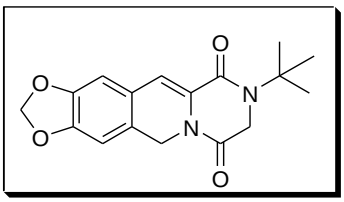
129.5, 135.2, 137.1, 157.3, 161.6. **IR** ν ($cm^{-1}$): 3332, 3009, 2923, 1682, 1625, 1478, 1401. **MS (DART+)** m/z: 319 (M+H); **HRMS** m/z calcd for $C_{20}H_{19}N_2O_2$ [M+H], 319.14465; found 319.14454.



**Compound *22*d, 2-*tert*-butyl-8-methoxy–2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione** was purified by flash column chromatography (eluent 70:30 hexane/EtOAc). The product was obtained as a yellow solid (63 %). **$^1$H-NMR** (300 MHZ, $CDCl_3$) δ: 1.51 (s, 9H, $CH_3$), 3.81 (s, 3H, $CH_3O$), 4.12 (s, 2H, $COCH_2N$), 4.99 (s, 2H, $ArCH_2$), 6.69 (d, *J* = 2.4 Hz, 1H, ArH), 6.78 (dd, *J* = 8.4 and 2.4 Hz, 1H, ArH), 6.95 (s, 1H, C=CH), 7.14 (d, *J* = 8.4 Hz, 1H, ArH). **$^{13}$C-NMR** (75.5 MHz, $CDCl_3$) δ: 27.9, 44.2, 47.1, 55.5, 58.2, 112.0, 113.3, 115.3, 122.7, 127.0, 128.8, 131.1, 159.7, 160.6, 162.8. **IR** ν ($cm^{-1}$): 3368, 2970, 2933, 1675, 1618, 1418, 1198. **MS (DART+)** m/z: 300 (M+H); **HRMS m/z** calcd for $C_{17}H_{20}N_2O_3$ [M+H], 300.1474; found 300.1476.

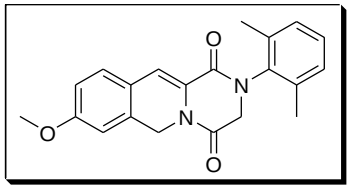


**Compound *22*e, 2-*tert*-butyl-8-fluoro–2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione** was purified by flash column chromatography (eluent 70:30 hexane/EtOAc). The product was obtained as an off-white solid (63 %); m.p. 141–143 °C. **$^1$H-NMR** (300 MHz, $CDCl_3$) δ: 1.51 (s, 9H, $CH_3$), 4.14 (s, 2H, $COCH_2N$), 5.00 (s, 2H, $ArCH_2$), 6.86 (d, *J* = 8.7 Hz, 1H, ArH), 6.97–6.97 (comp, 2H, ArH and C=CH), 7.17 (dd, *J* = 8.25 and 5.4 Hz, 1H, ArH). **$^{13}$C-NMR** (75.5 MHz, $CDCl_3$) δ: 27.8, 43.92 (d, *J* = 2.8 Hz), 47.1, 58.3, 113.4 (d, *J* = 30.7 Hz), 114.0 (d, *J* = 2.1 Hz), 115.2 (d, *J* = 29 Hz), 126.1 (d, *J* = 4.3 Hz), 128.5 (d, *J* = 3.9 Hz), 128.9 (d, *J* = 11.1 Hz), 131.5 (d, *J* = 10.7 Hz), 159.1, 162.7, 163.0 (d, *J* = 331.3). **IR** ν ($cm^{-1}$):3308, 3064, 2971, 2921, 1675, 1618, 1404, 1198, 728. **MS (DART+)** m/z: (M+H) 289; **HRMS m/z** calcd for $C_{16}H_{18}FN_2O_2$ [M+H], 289.13523; found 289.13453.



**Compound 22f, 9-(*tert*-butyl)-8,9-dihydro-5*H*-[1,3]dioxolo[4,5-*g*]pyrazino[1,2-*b*]isoquinoline-7,10-dione** was purified by flash column chromatography (eluent 80:20 hexane/EtOAc). The product was obtained as a yellowish solid (63%); m.p. 103–105 °C. **$^1$H-NMR** (300 MHz, $CDCl_3$) δ: 1.51 (s, 9H, $CH_3$), 4.12 (s, 2H,

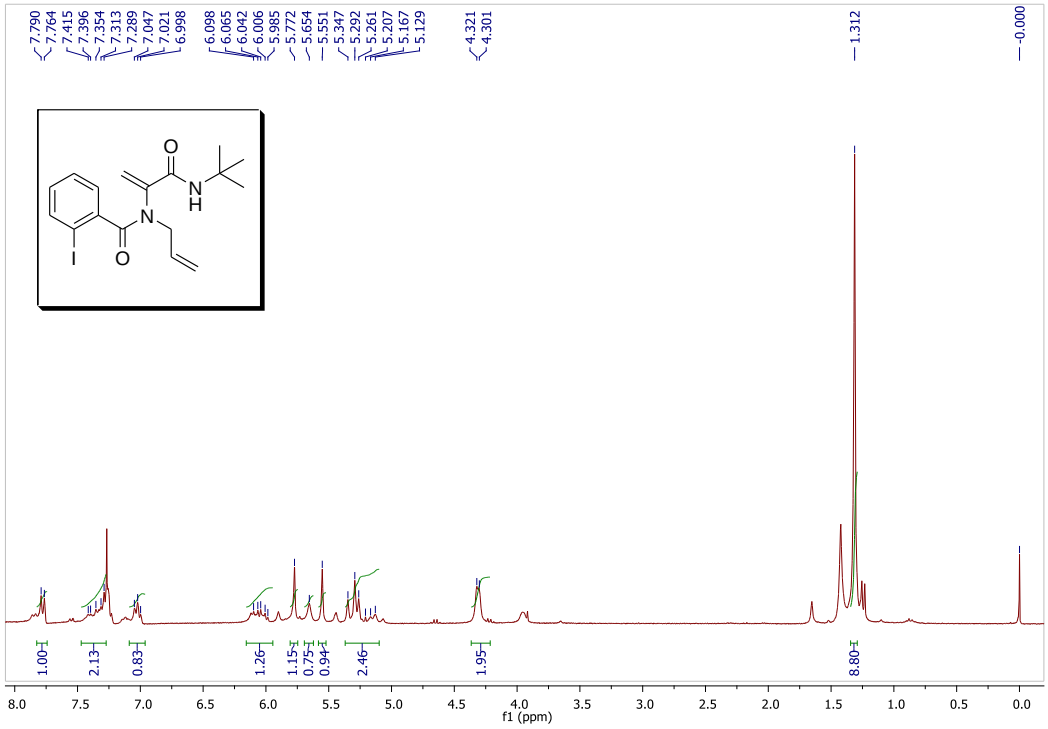
$COCH_2N$), 4.92 (s, 2H, $ArCH_2$), 5.97 (s, 2H, $OOCH_2$), 6.62 (s, 1H, ArH), 6.67 (s, 1H, ArH), 6.85 (s, 1H, C=CH). **$^{13}$C-NMR** (75.5 MHz, $CDCl_3$) $\delta$: 27.8, 44.1, 47.1, 58.2, 101.5, 106.7, 107.3, 115.4, 123.6, 123.9, 127.5, 147.5, 148.5, 159.5, 162.8. **IR** $\nu$ ($cm^{-1}$) 2963, 2912, 1678, 1630, 1599, 1399, 1242, 1194, 1030, 928. **MS (DART+)** m/z: (M+H) 315; **HRMS m/z** calcd for $C_{17}H_{19}N_2O_4$ [M+H], 315.13448 ; found 315.13529.

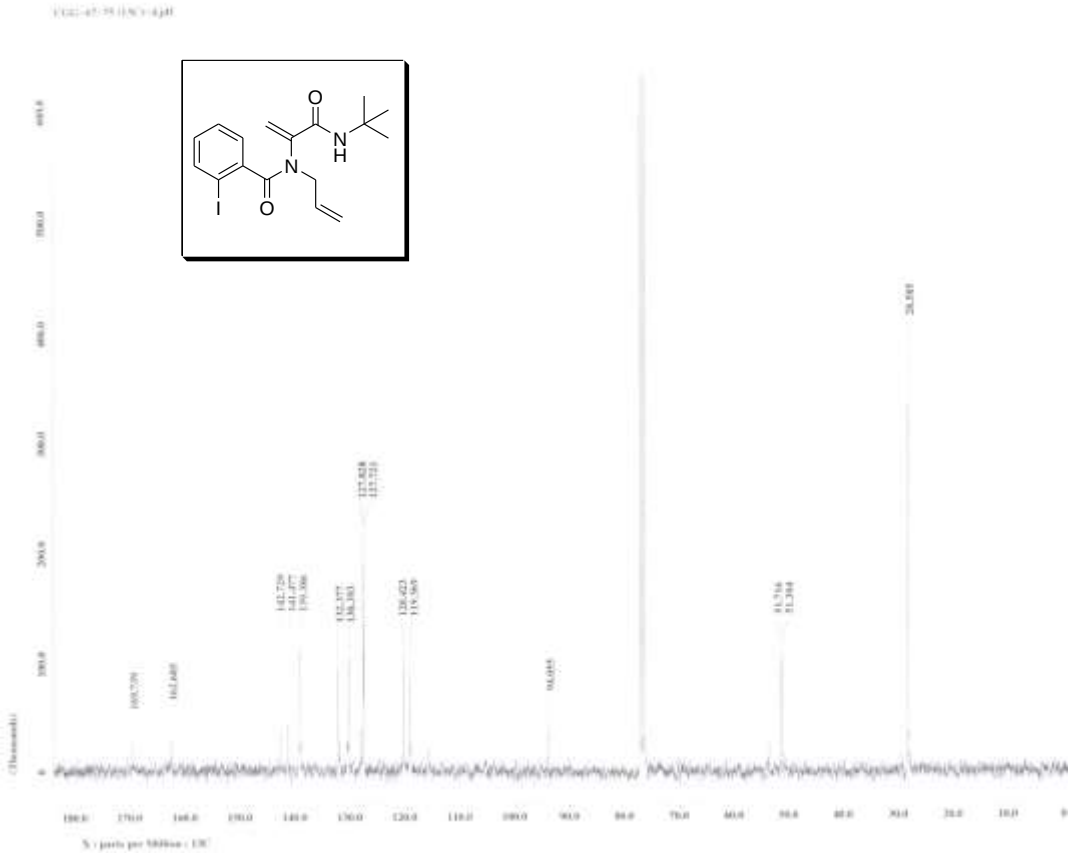



**Compound *22*g, 2-(2,6-dimethylphenyl)-8-methoxy-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione** was purified by flash column chromatography (eluent 80:20 hexane/EtOAc). The product was obtained as a yellow oil (50%).**$^{1}$H-NMR** (300 MHz ,$CDCl_3$) $\delta$:2.42 (s, 6H, $CH_3Ar$), 4.01 (s, 3H, $CH_3O$), 4.42 (s, 2H, $COCH_2N$), 5.29 (s, 2H, $ArCH_2$), 6.93 (s, 1H, C=CH), 6.99 (dd, *J* = 8.4 and 2.4 Hz, 1H, ArH), 7.41–7.31 (m, 5H, ArH). **$^{13}$C-NMR** (75.5 MHz ,$CDCl_3$) $\delta$: 17.8, 44.7, 51.4, 55.6, 112.1, 113.5, 116.6, 122.2, 125.4, 128.8, 129.0, 129.1, 131.4, 135.3, 137.3, 157.7, 161.0, 161.6. **IR** $\nu$ ($cm^{-1}$): 2921, 2852, 1725, 1673, 1620, 1463, 1398, 1265, 1027, 910, 728. **MS (DART+)** m/z: 349 (M+H); **HRMS m/z** calcd for $C_{21}H_{21}N_2O_3$ [M+H], 349.15522 ;found 349.15438.

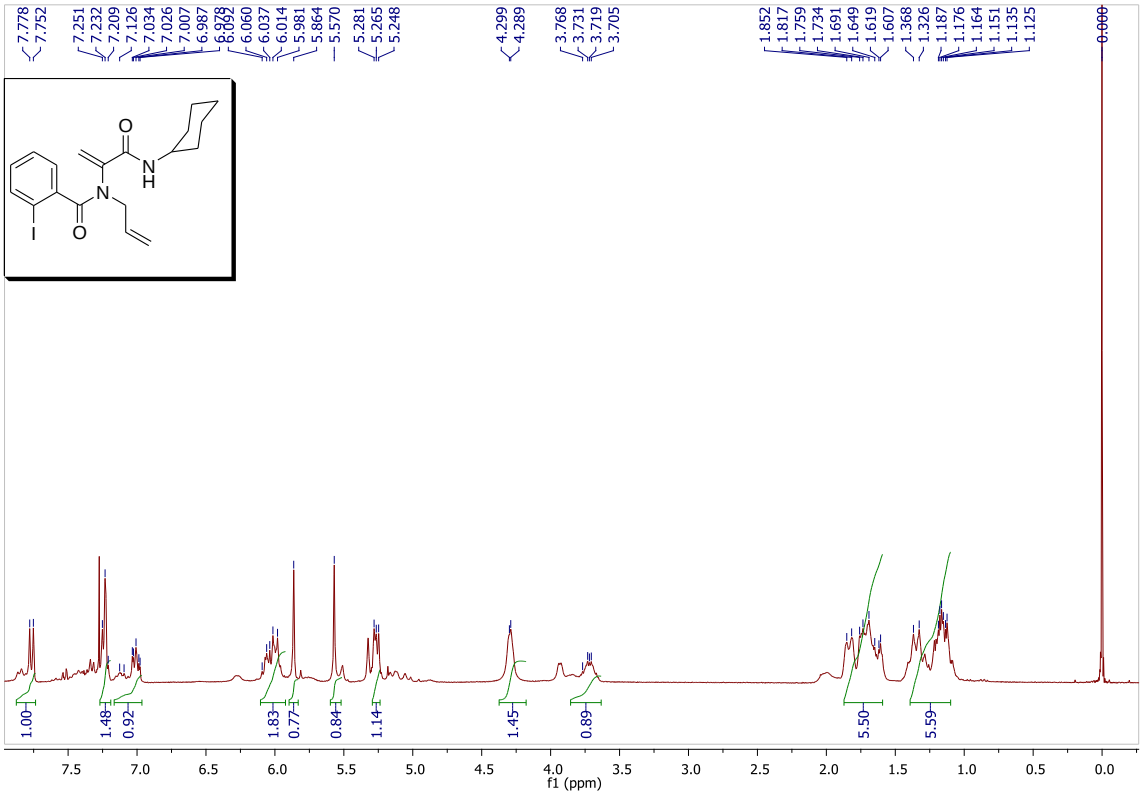
## 3. NMR Spectra

**Compound 9a,** *N*-allyl-*N*-(1-*tert*-butylcarbamoyl-vinyl)-2-iodo-benzamide

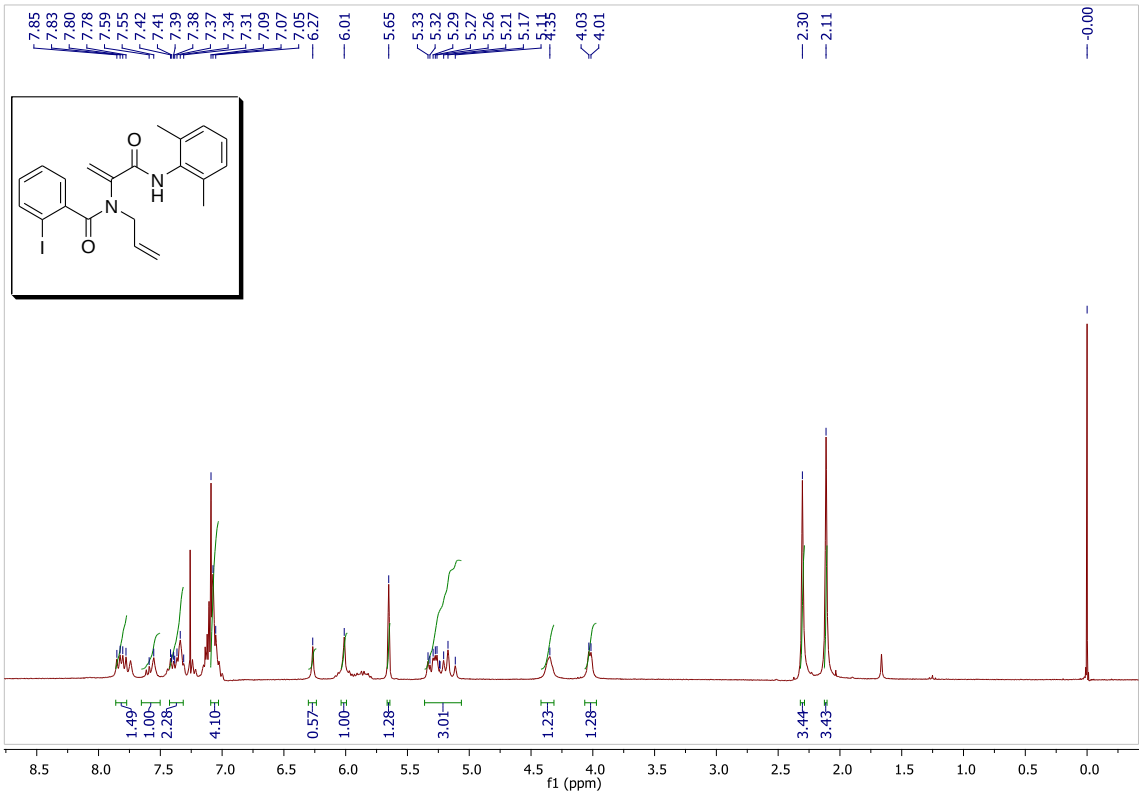


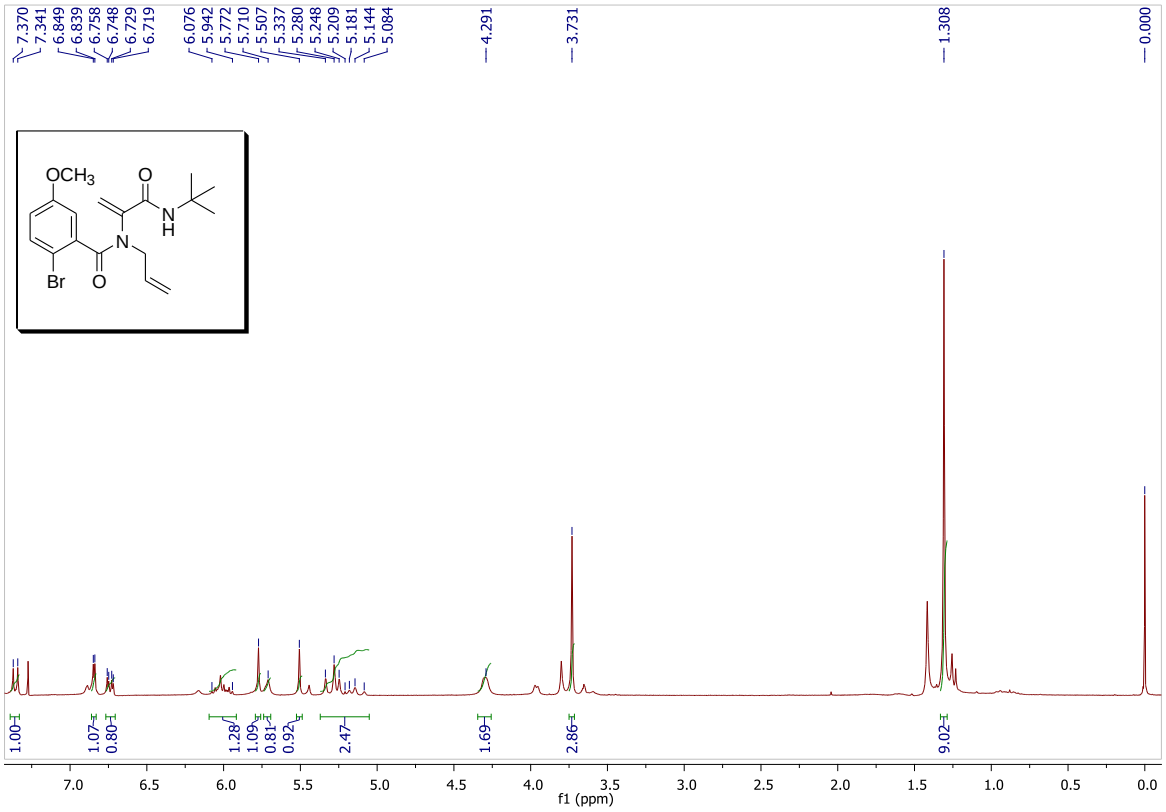
**Compound 9b,** *N*-allyl-*N*-(1-cyclohexylcarbamoyl-vinyl)-2-iodo-benzamide

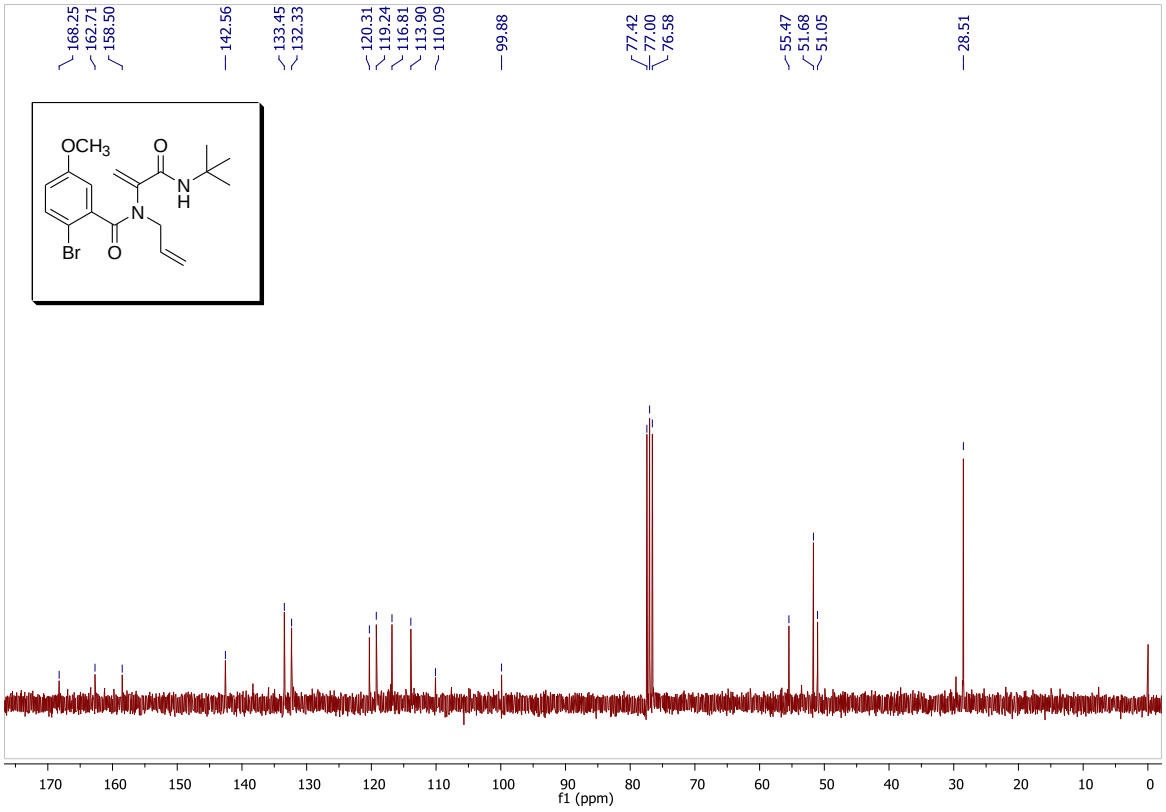



**Compound 9c**, *N*-allyl-*N*-[1-(2,6-dimethyl-phenylcarbamoyl)-vinyl]-2-iodo-benzamide

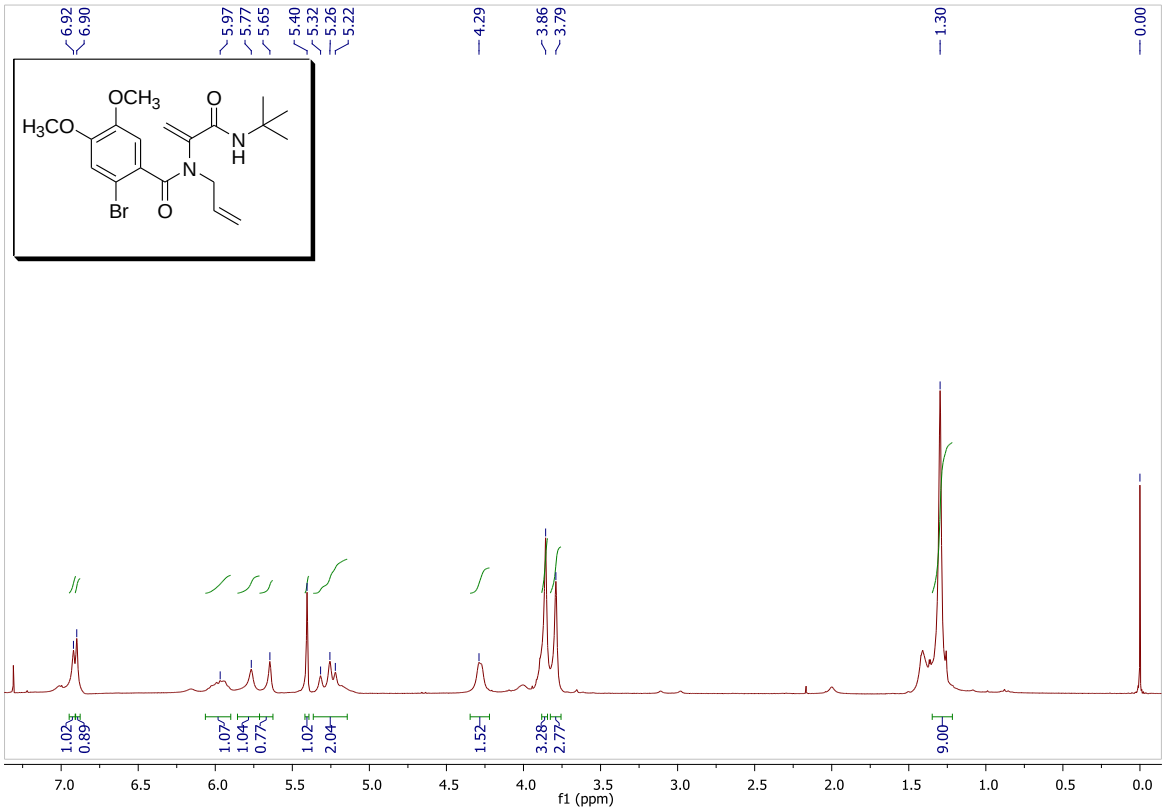


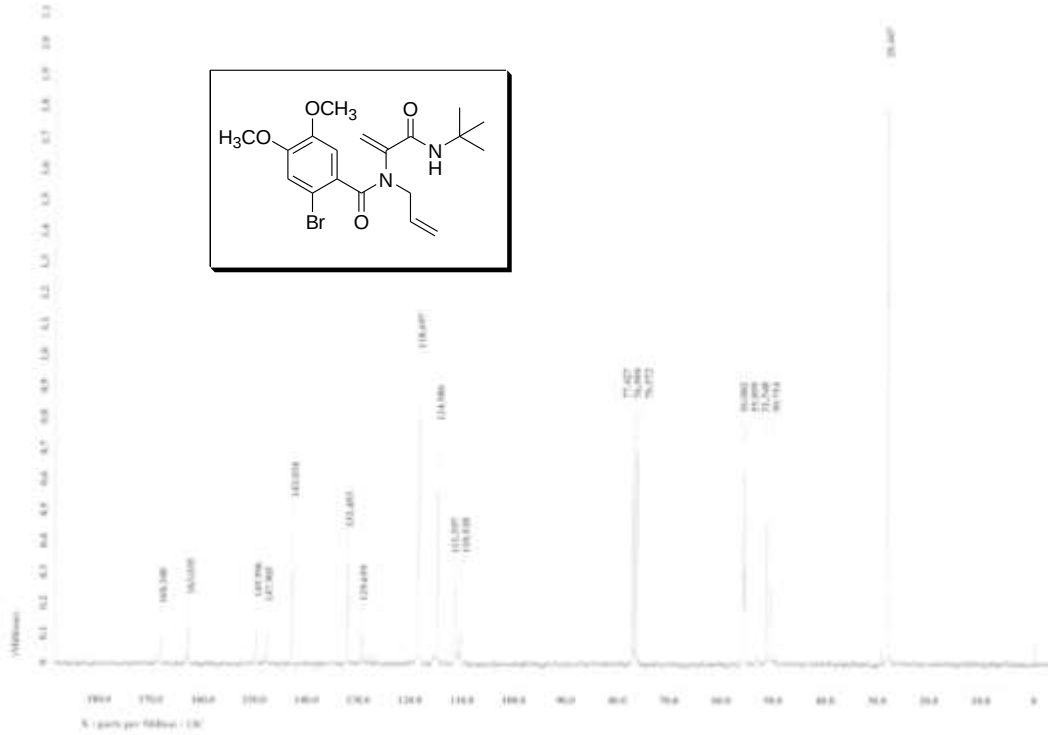
**Compound 9d,** *N*-allyl-2-bromo-*N*-(1-*tert*-butylcarbamoyl-vinyl)-5-methoxy-benzamide



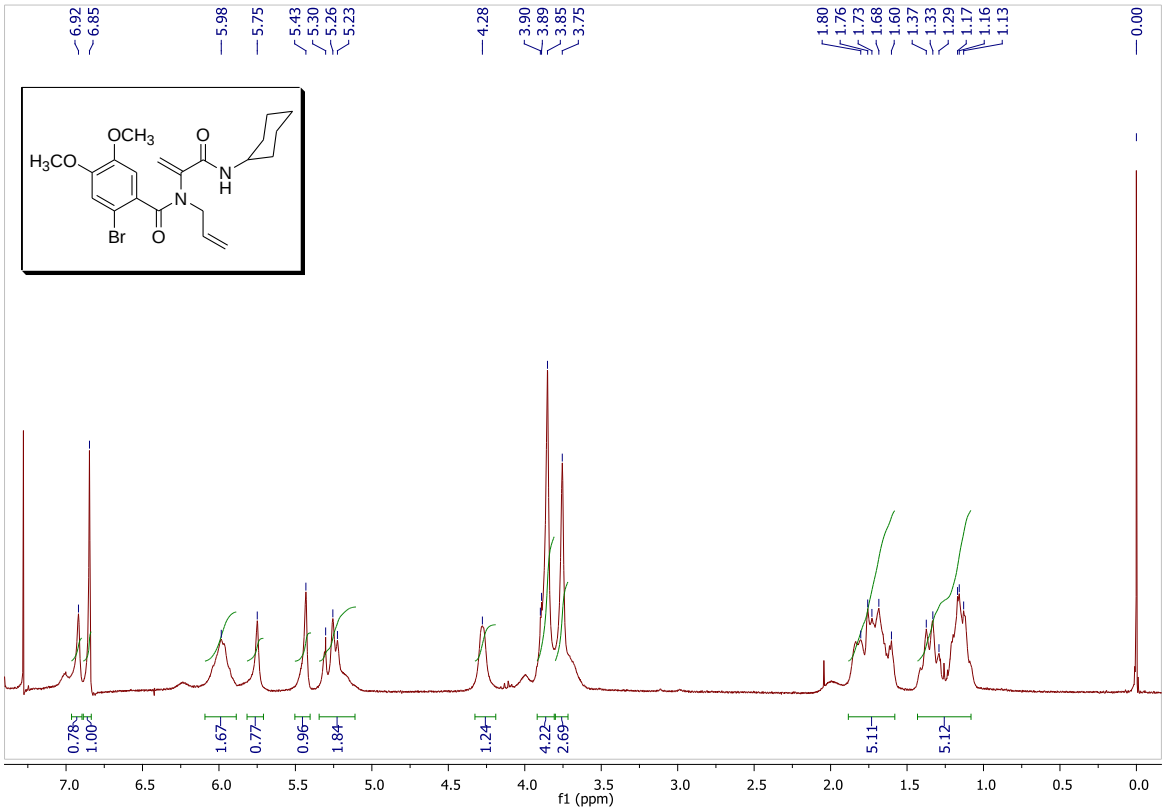



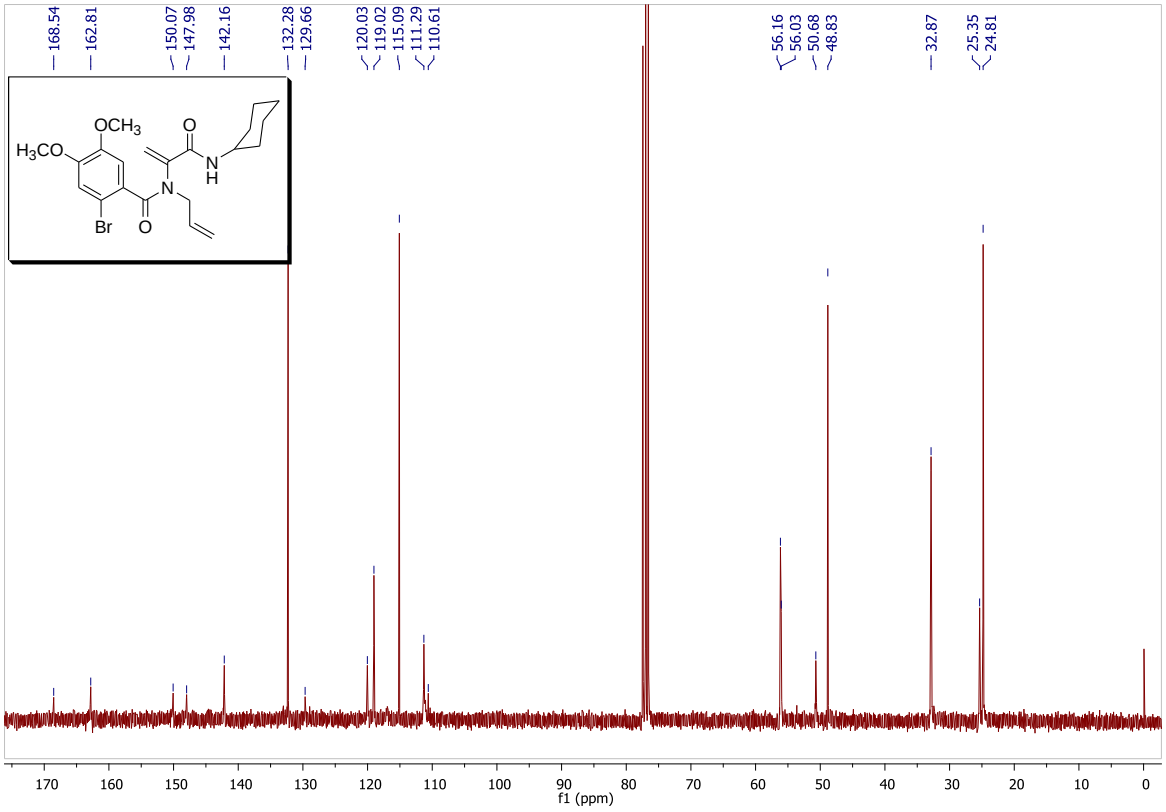
**Compound 9e,** *N*-allyl-2-bromo-*N*-(1-*tert*-butylcarbamoyl-vinyl)-4,5-dimethoxy-benzamide



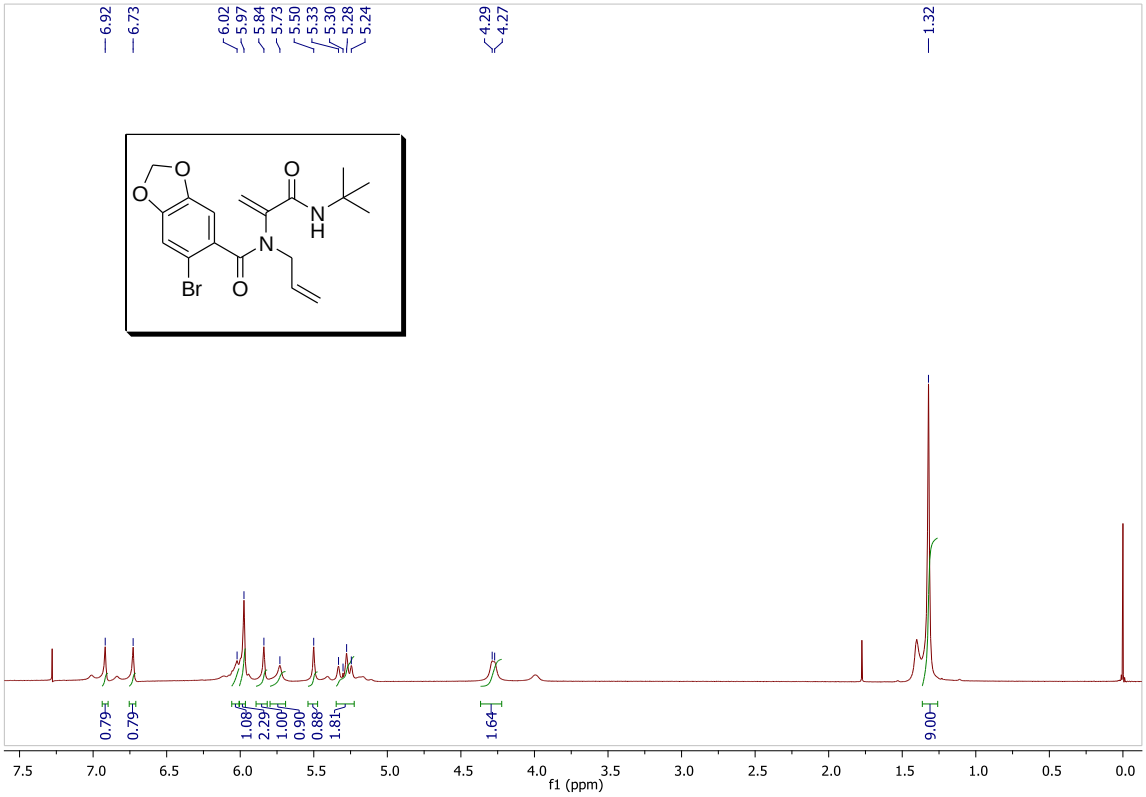



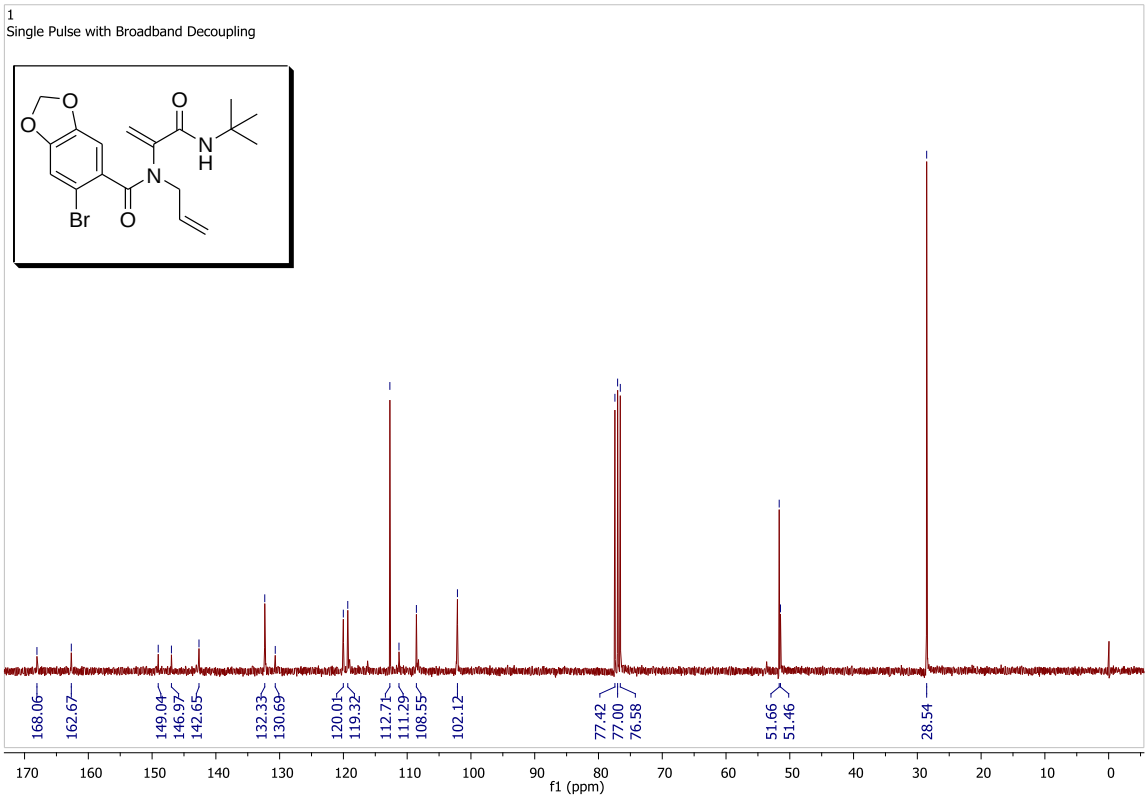
**Compound 9f,** *N*-allyl-2-bromo-*N*-(1-cyclohexycarbamoyl-vinyl)-4,5-dimethoxy-benzamide



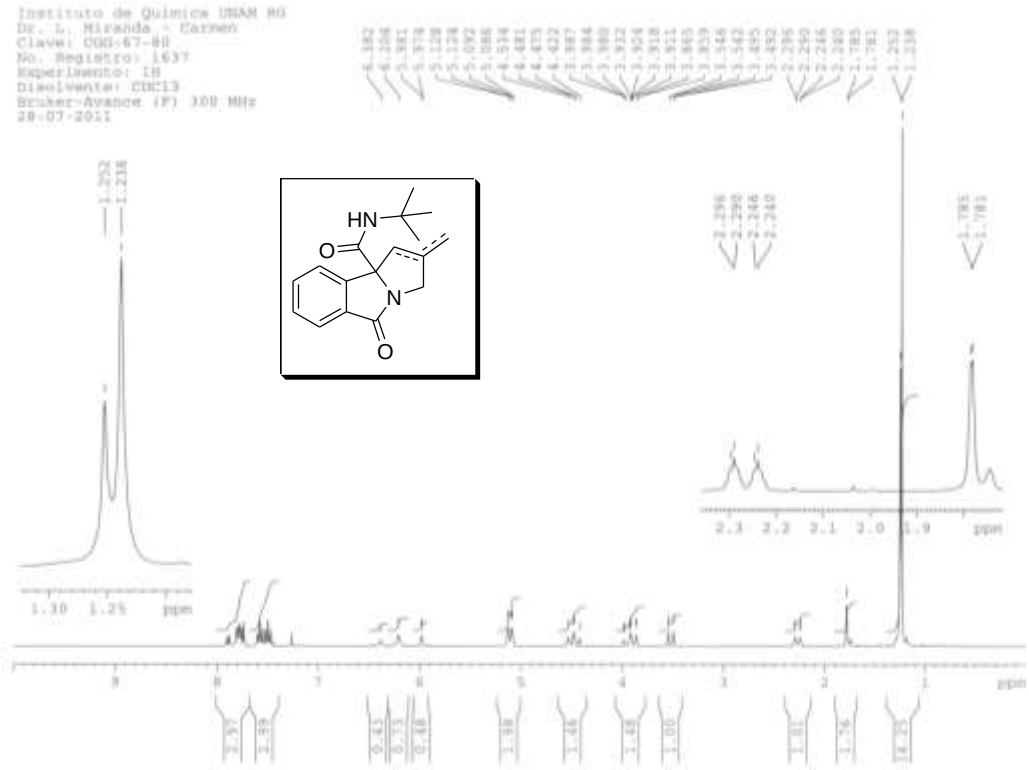



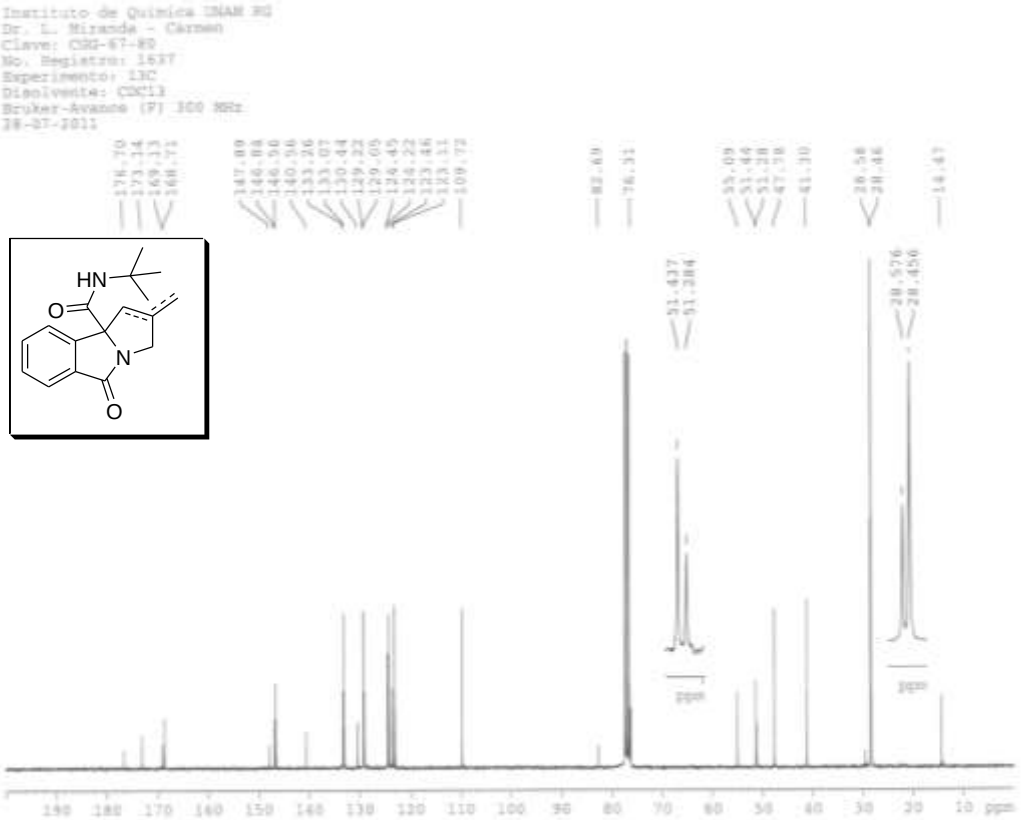
**Compound 9g,** 6-bromo-benzo[1,3]dioxole-5-carboxylic acid allyl-(1-*tert*-butylcarbamoyl-vinyl)-amide



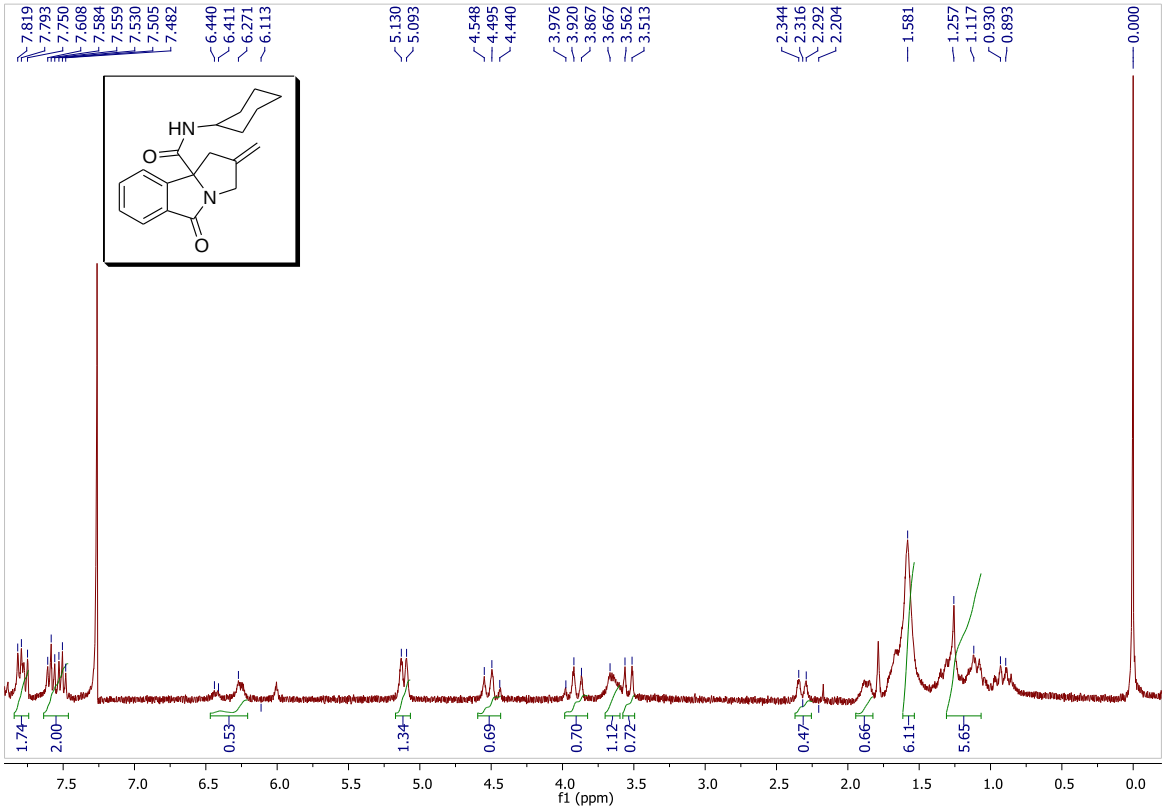



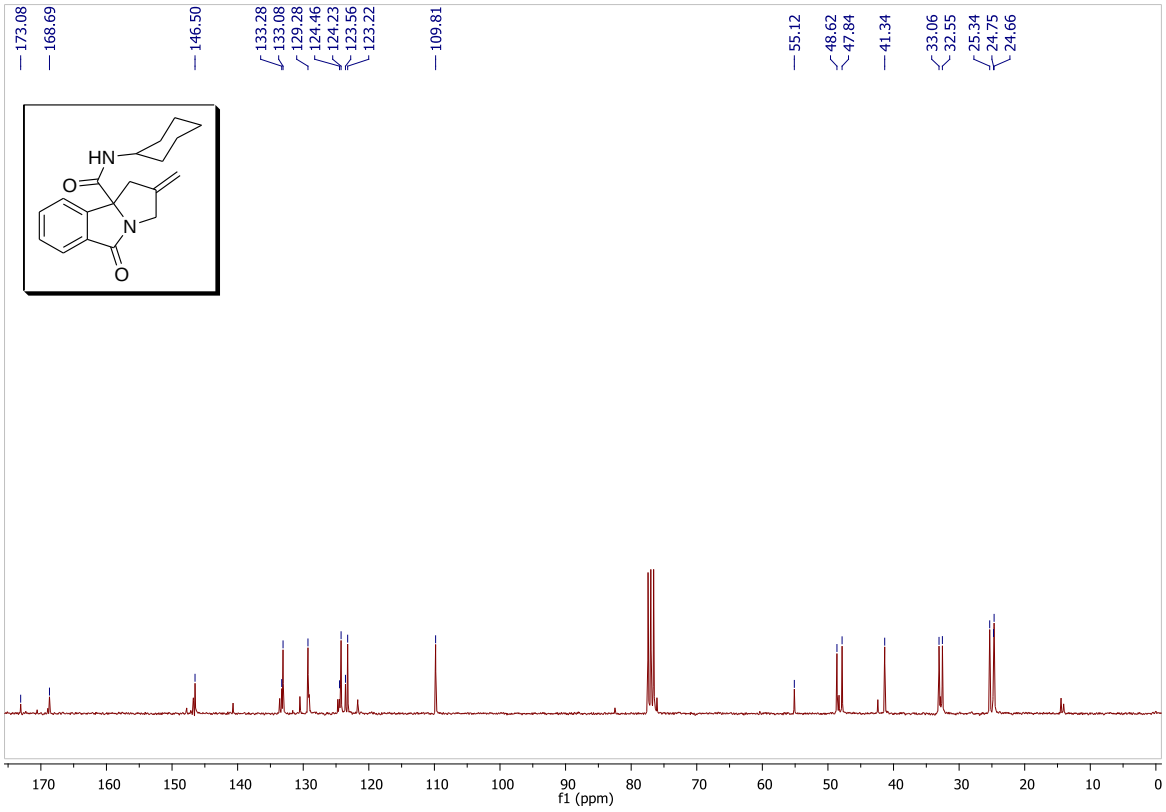
**Compound 10a**, 9b-[1-(*tert*-butylamino)vinyl]-2-methyl-3,9b-dihydro-5*H*-pyrrolo[2,1-*a*]isoindol-5-one



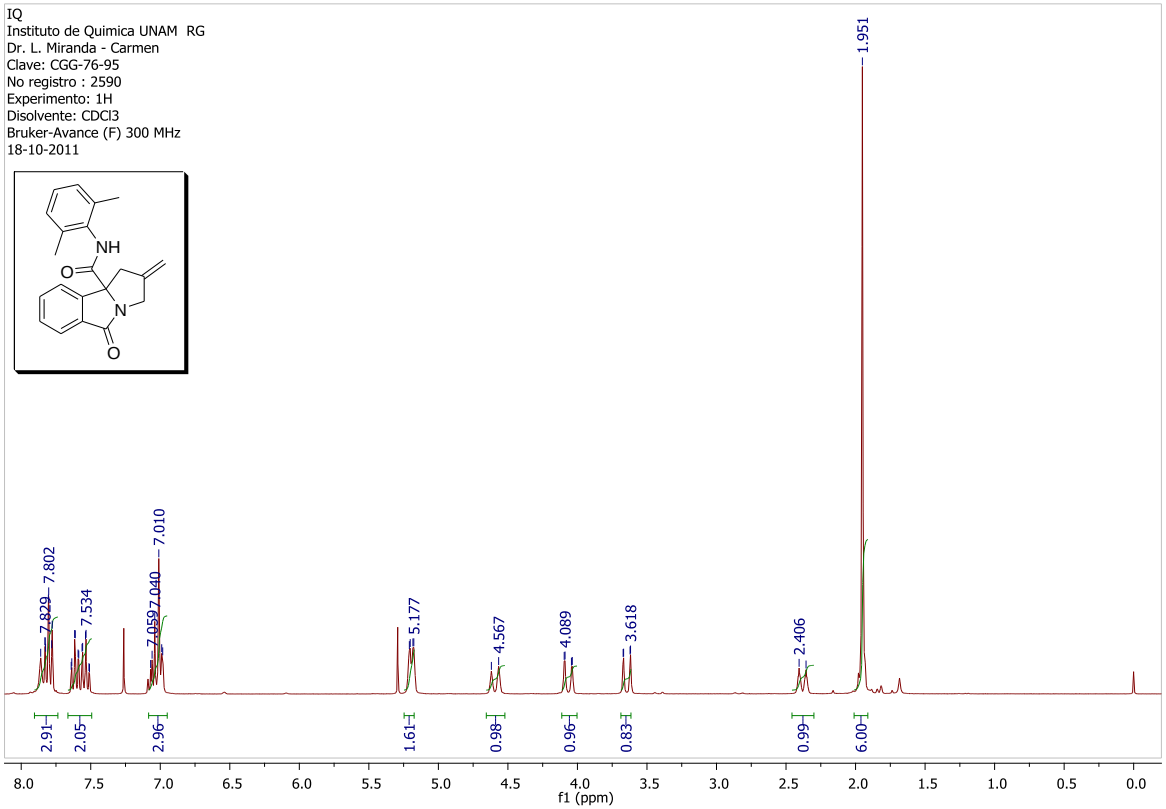



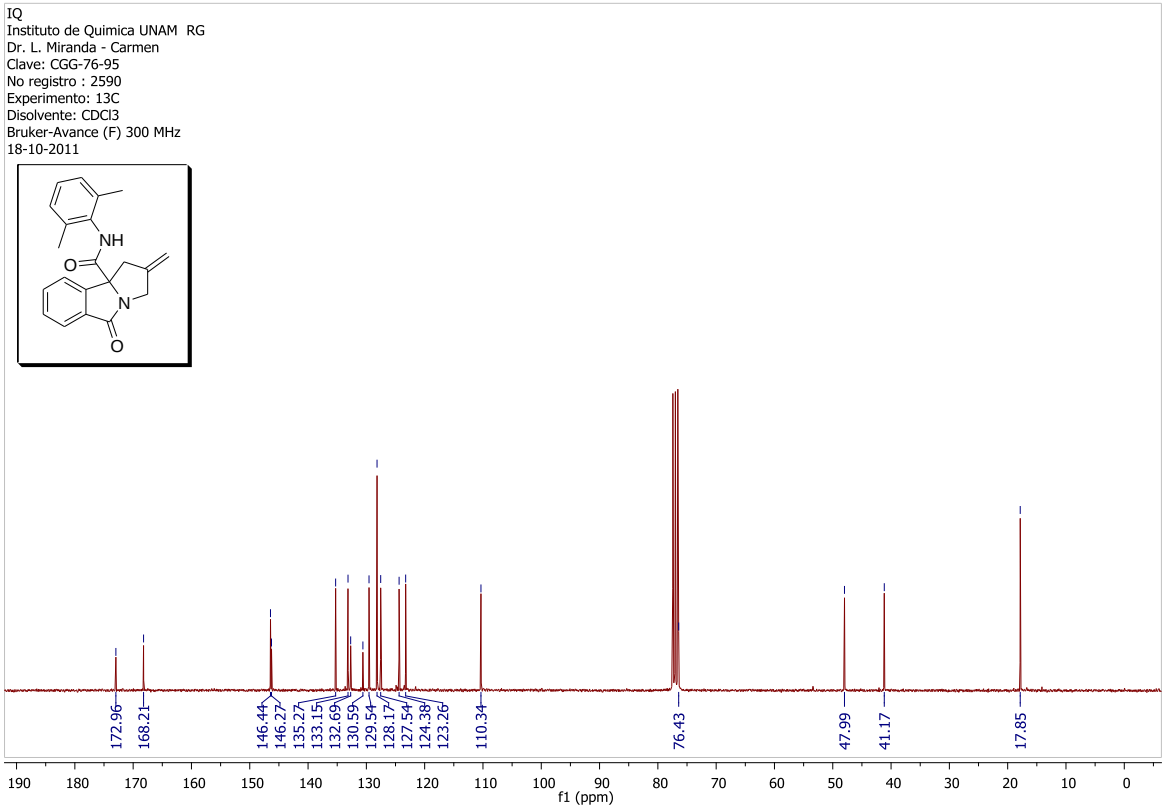
**Compound 10b**, 2-methylene-5-oxo-2,3-dihydro-1*H*,5*H*-pyrrolo[2,1-*a*]isoindole-9b-carboxilic acid cyclohexylamide



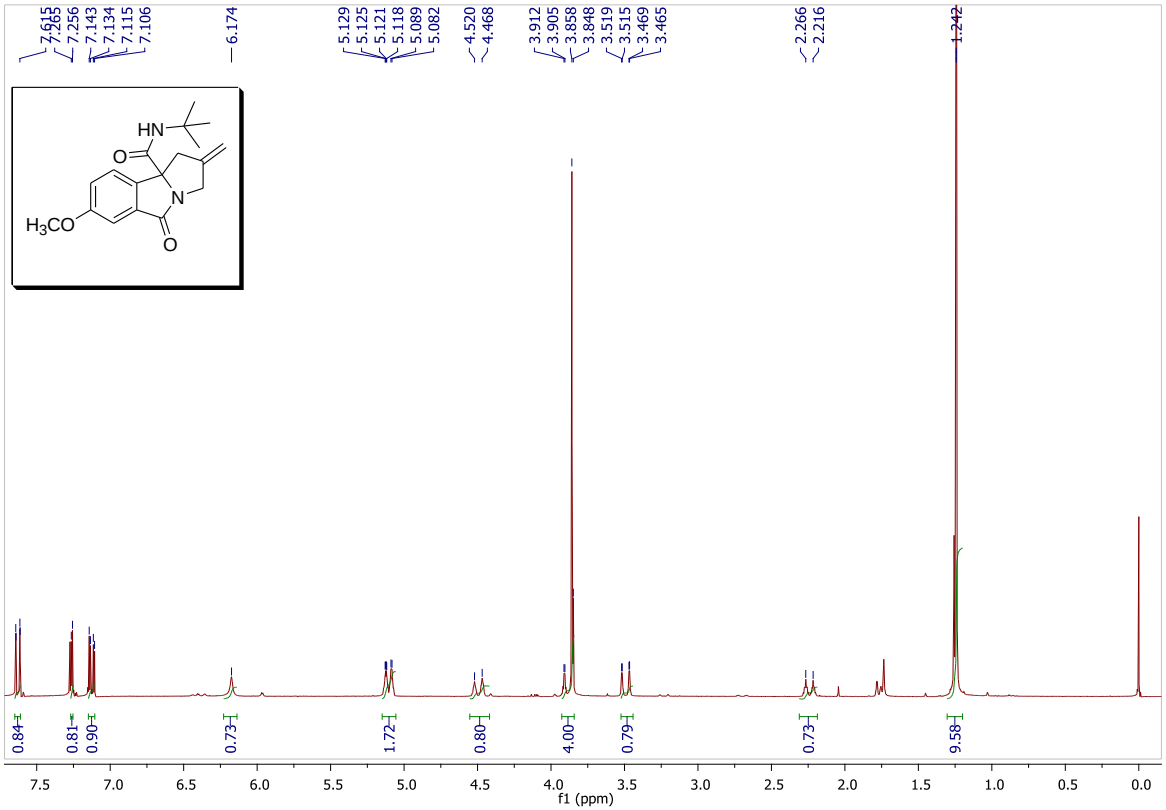



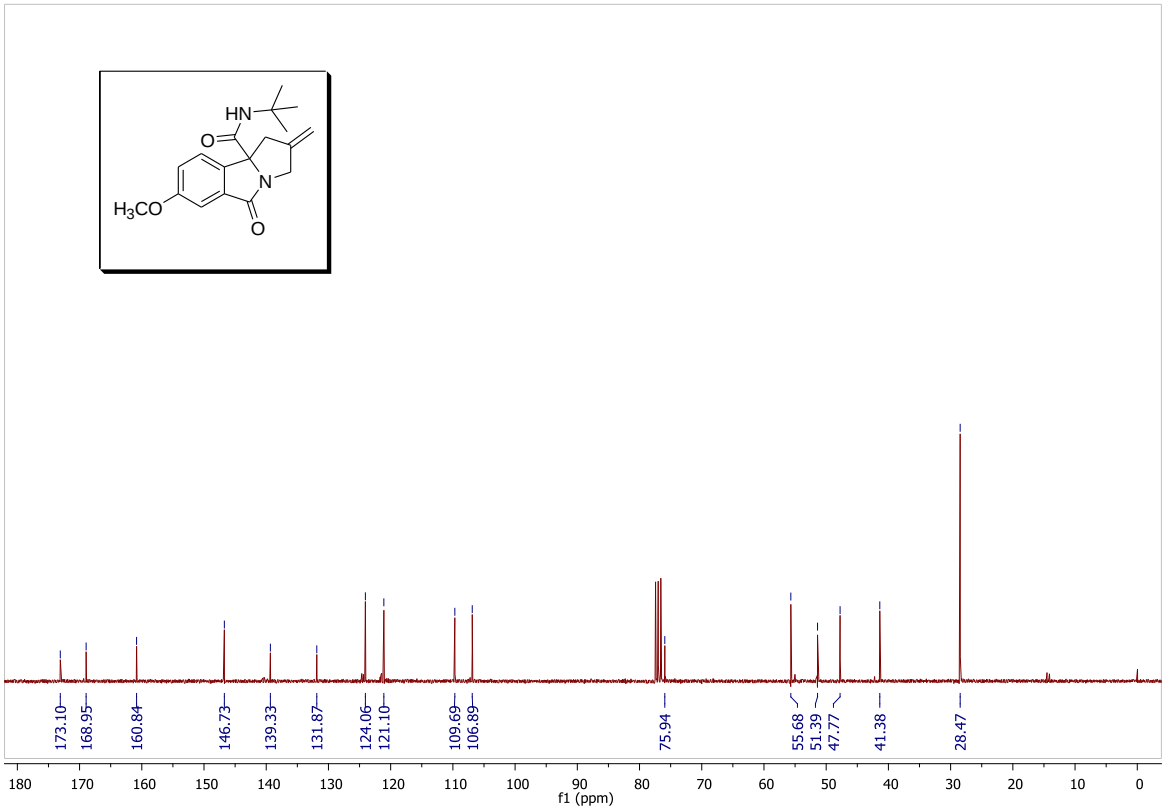
**Compound 10c,** 2-methylene-5-oxo-2,3-dihydro-1*H*,5*H*-pyrrolo[2,1-*a*]isoindole-9b-carboxilic acid (2,6-dimethyl-phenyl)-amide



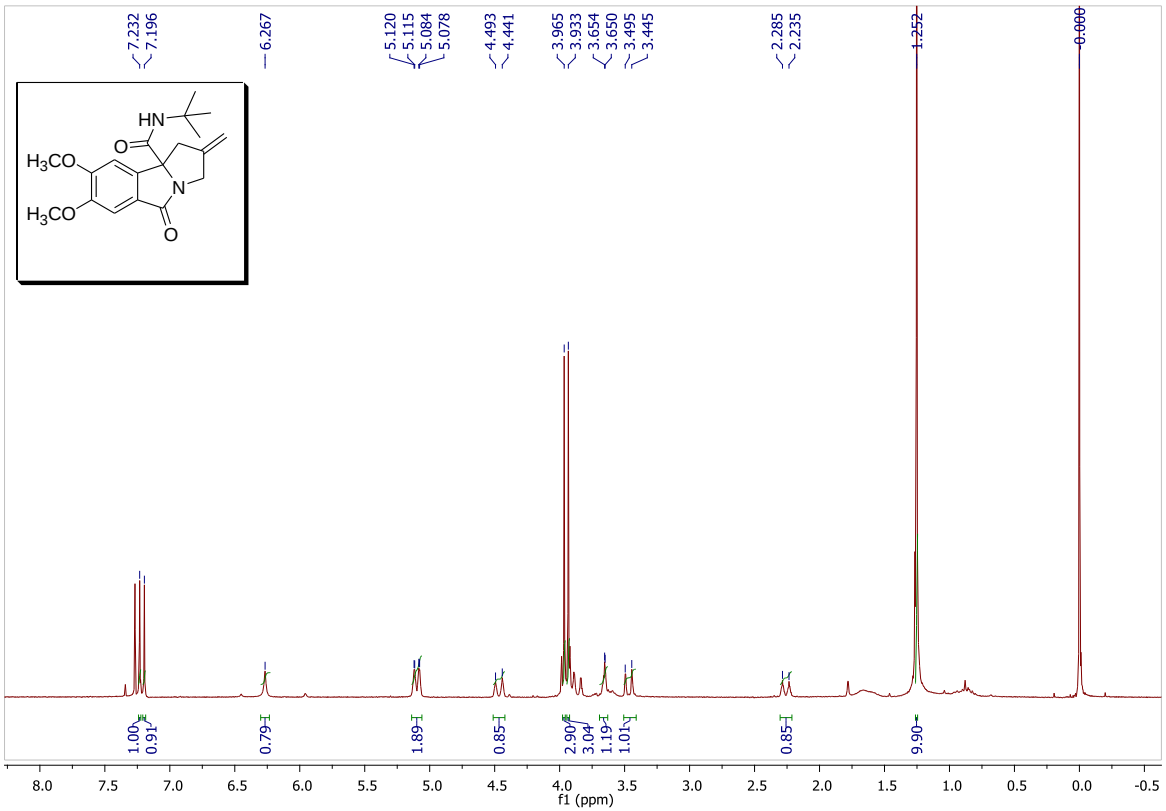



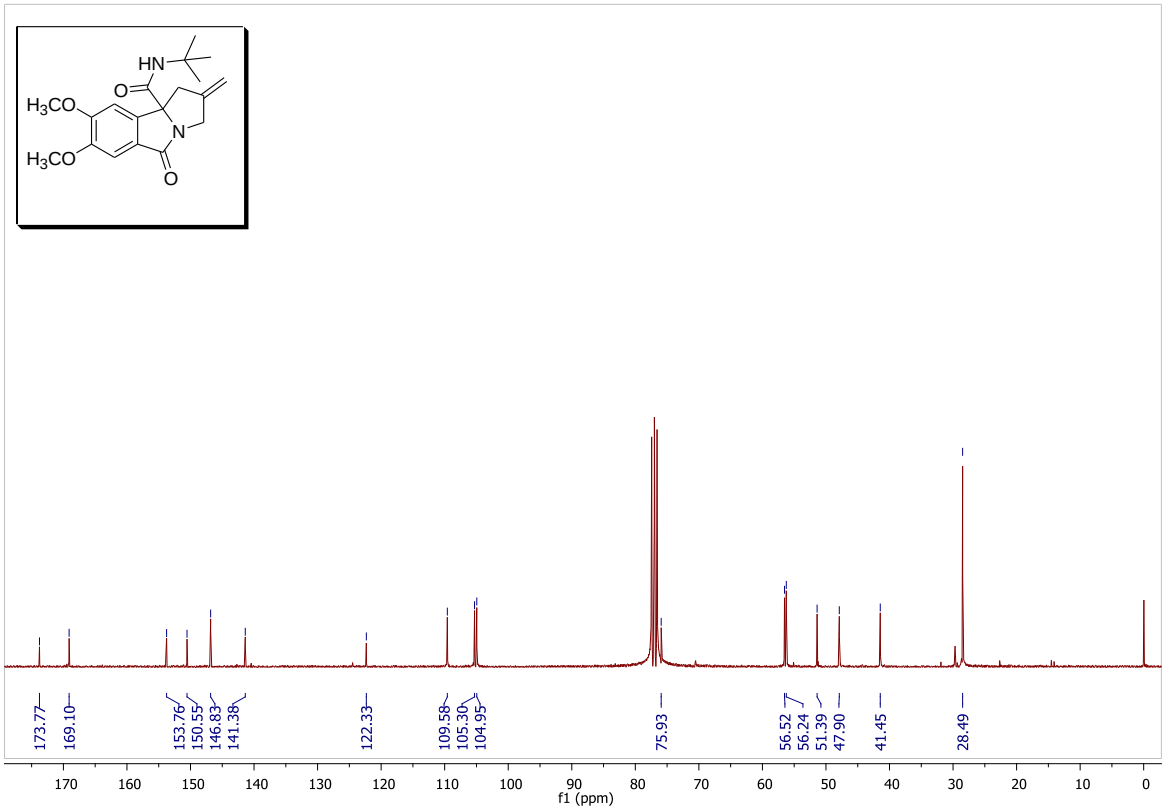
**Compound 10d,** 7-methoxy-2-methylene-5-oxo-2,3-dihydro-1*H*,5*H*-pyrrolo[2,1-*a*]isoindole-9b-carboxilic acid *tert*-butyl-amide



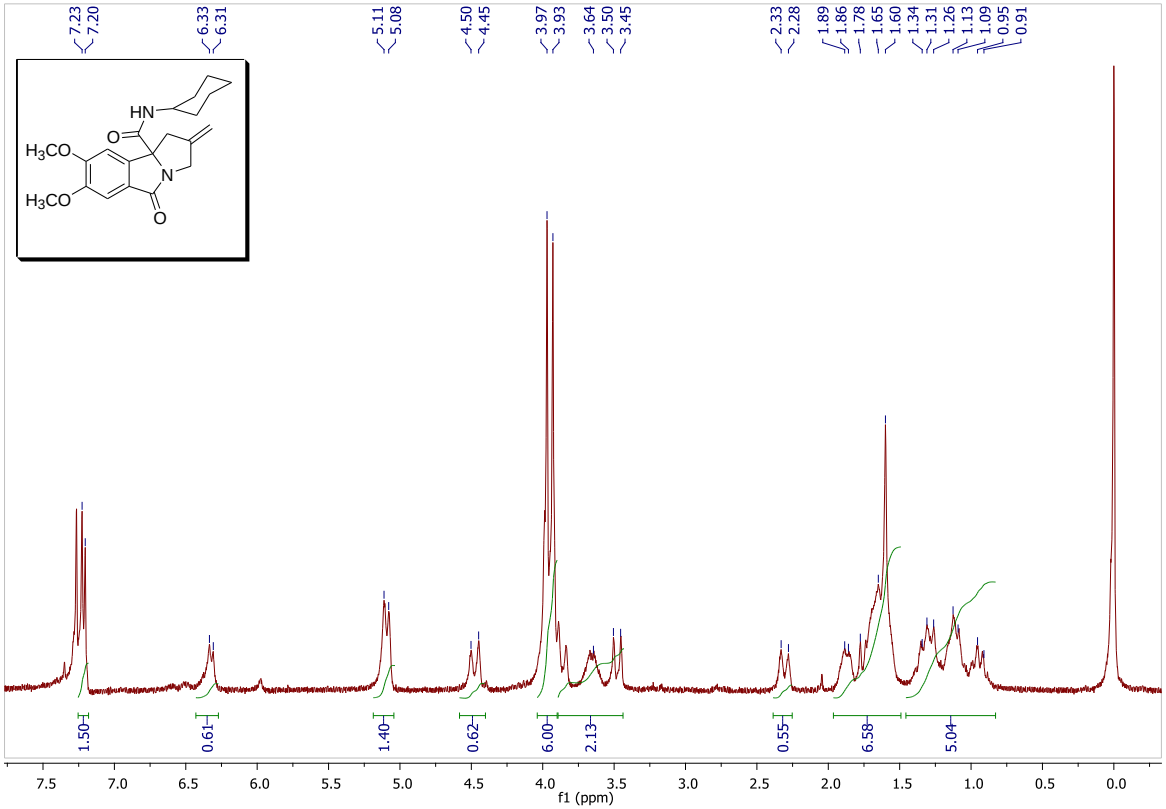



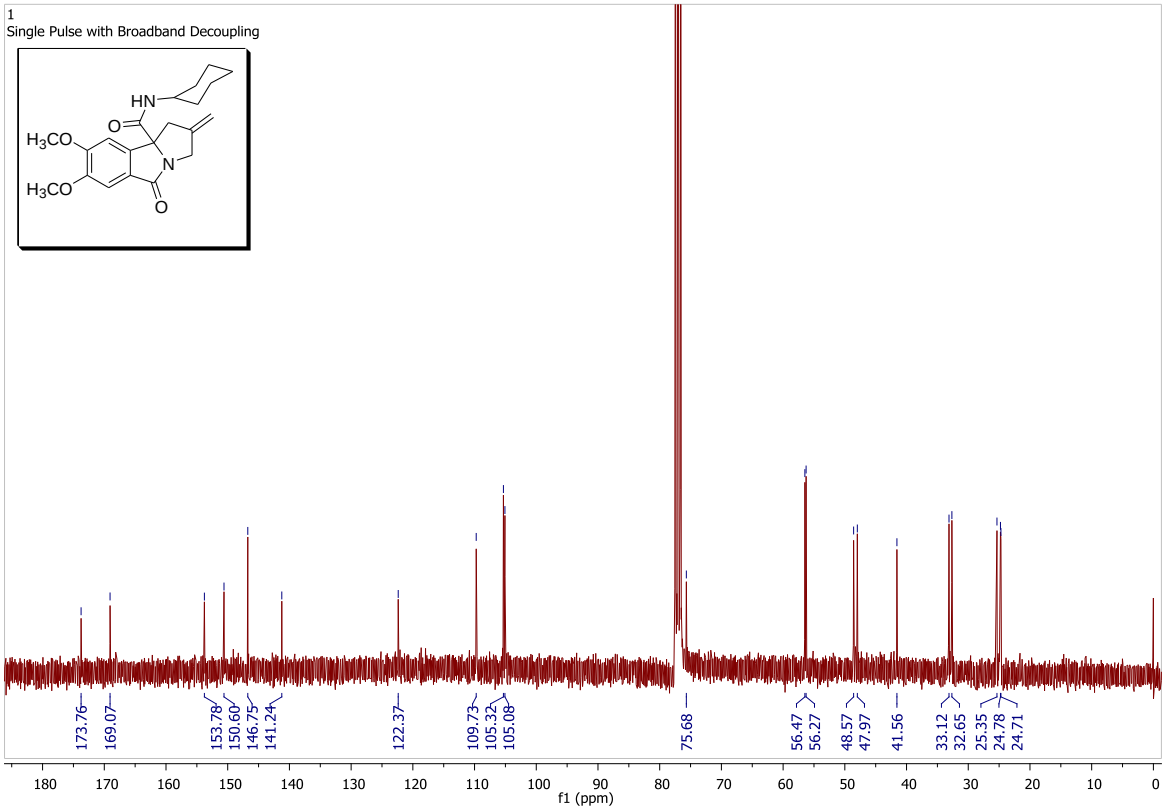
**Compound 10e,** 7,8-dimethoxy-2-methylene-5-oxo-2,3-dihydro-1*H*,5*H*-pyrrolo[2,1-*a*]isoindole-9b-carboxilic acid *tert*-butylamide



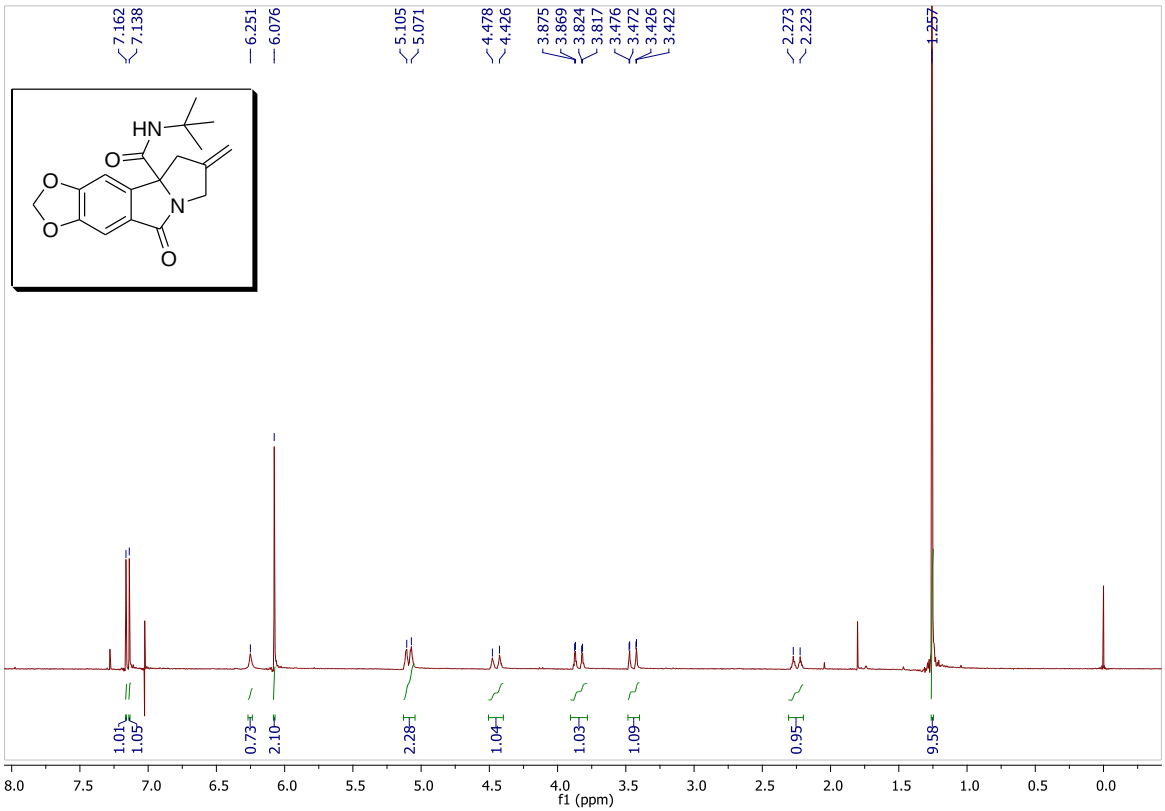



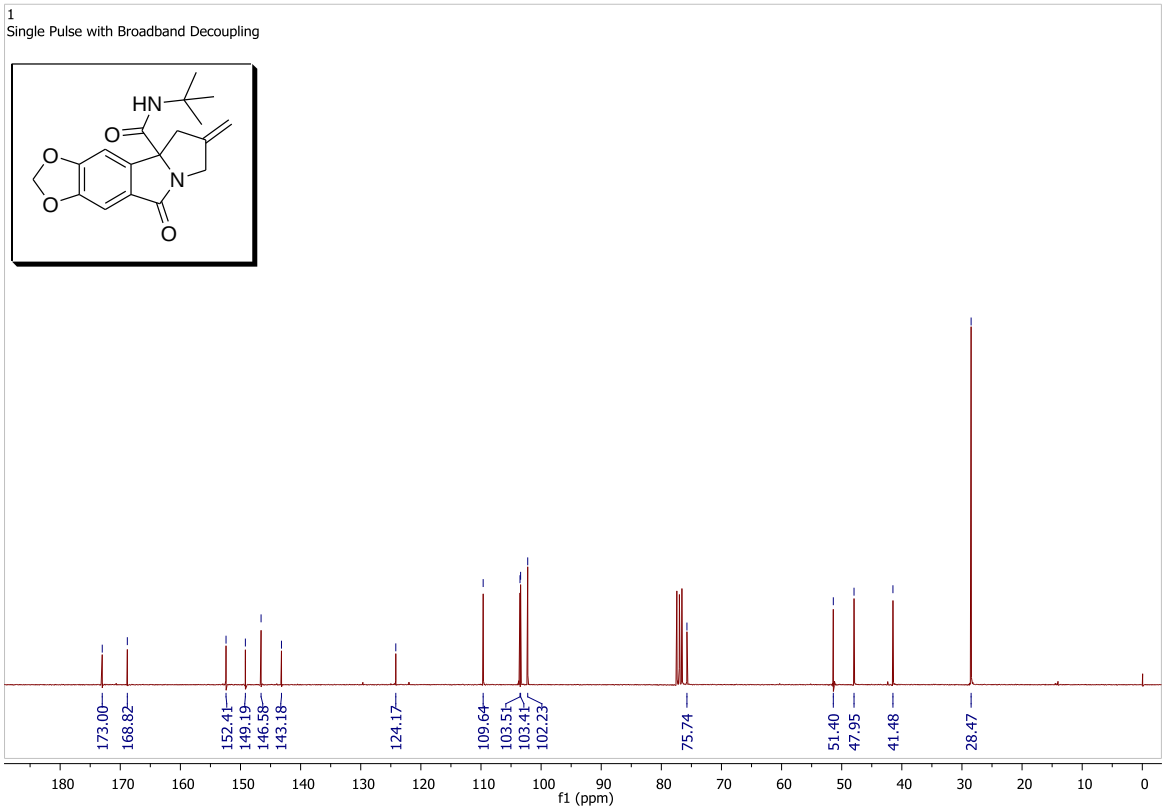
**Compound 10f,** 7,8-dimethoxy-2-methylene-5-oxo-2,3-dihydro-1*H*,5*H*-pyrrolo[2,1-*a*]isoindole-9b-carboxilic acid cyclohexylamide



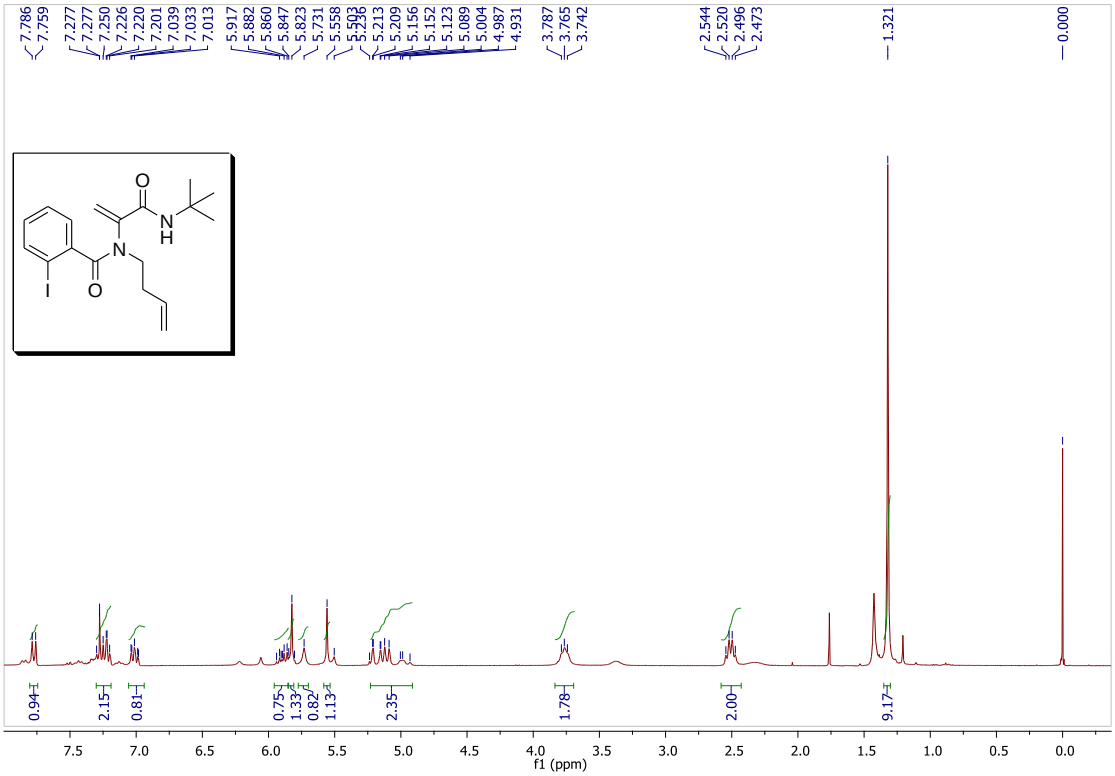



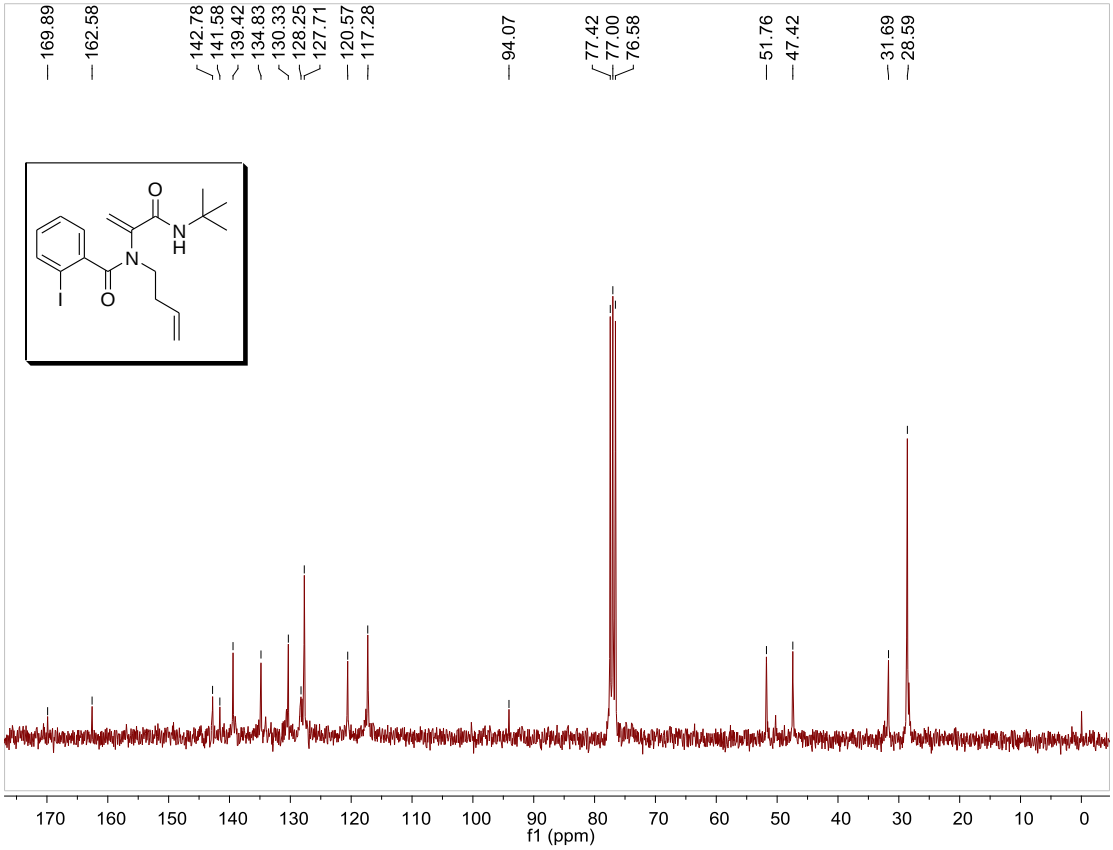
**Compound 10g,** 2-methylene-9-oxo-2,3-dihydro-1*H*,9*H*-5,7-*dioxa*-9*a*-*aza*-*cyclopenta*[*a*]indacene-3a-carboxilic acid *tert*-butylamide



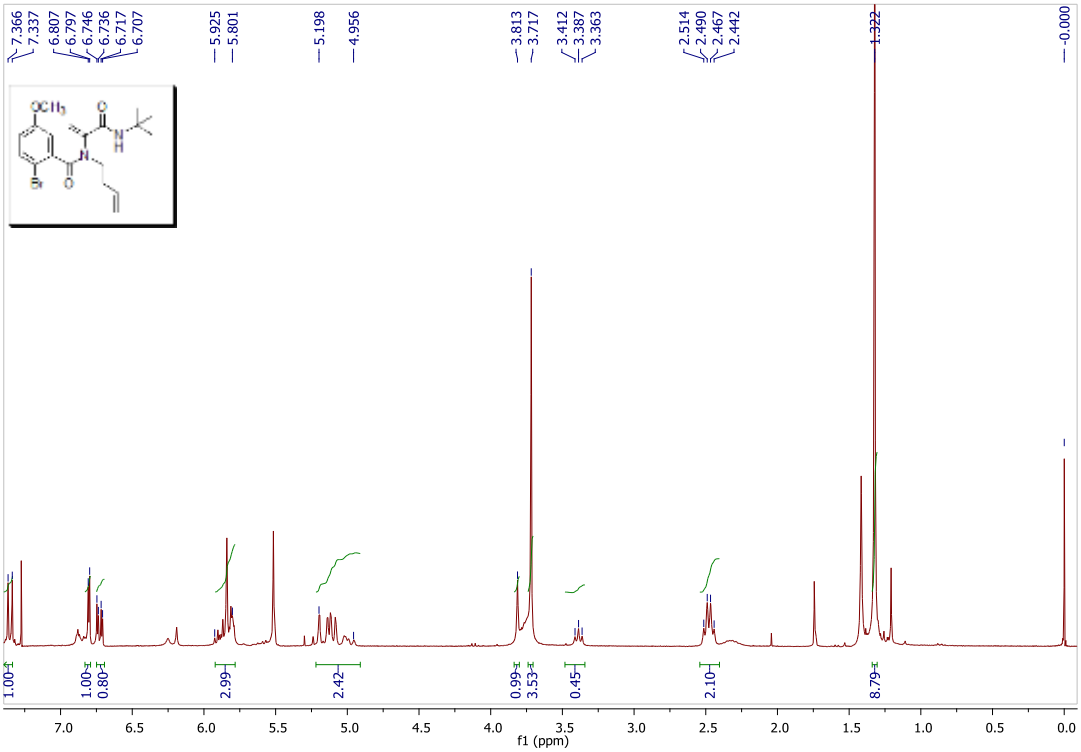



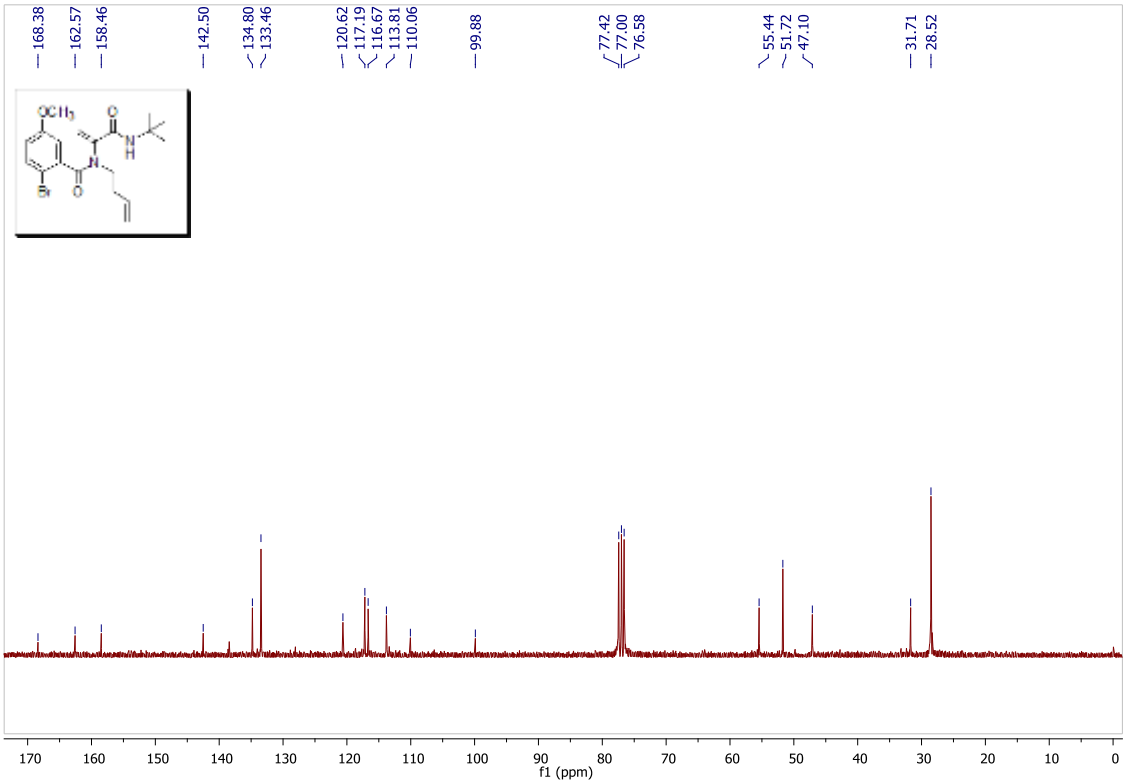
**Compound 11a',** *N*-but-3-enyl-*N*-(1-*tert*-butylcarbamoyl-vinyl)-2-iodo-benzamide



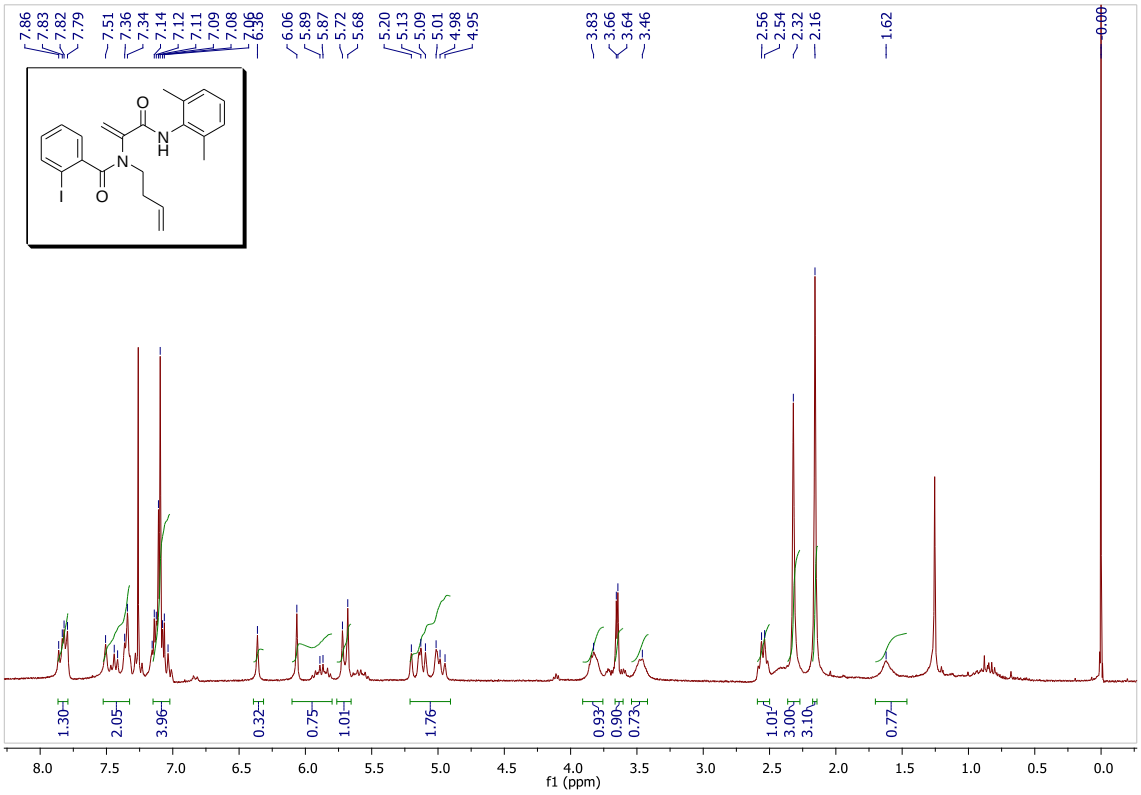



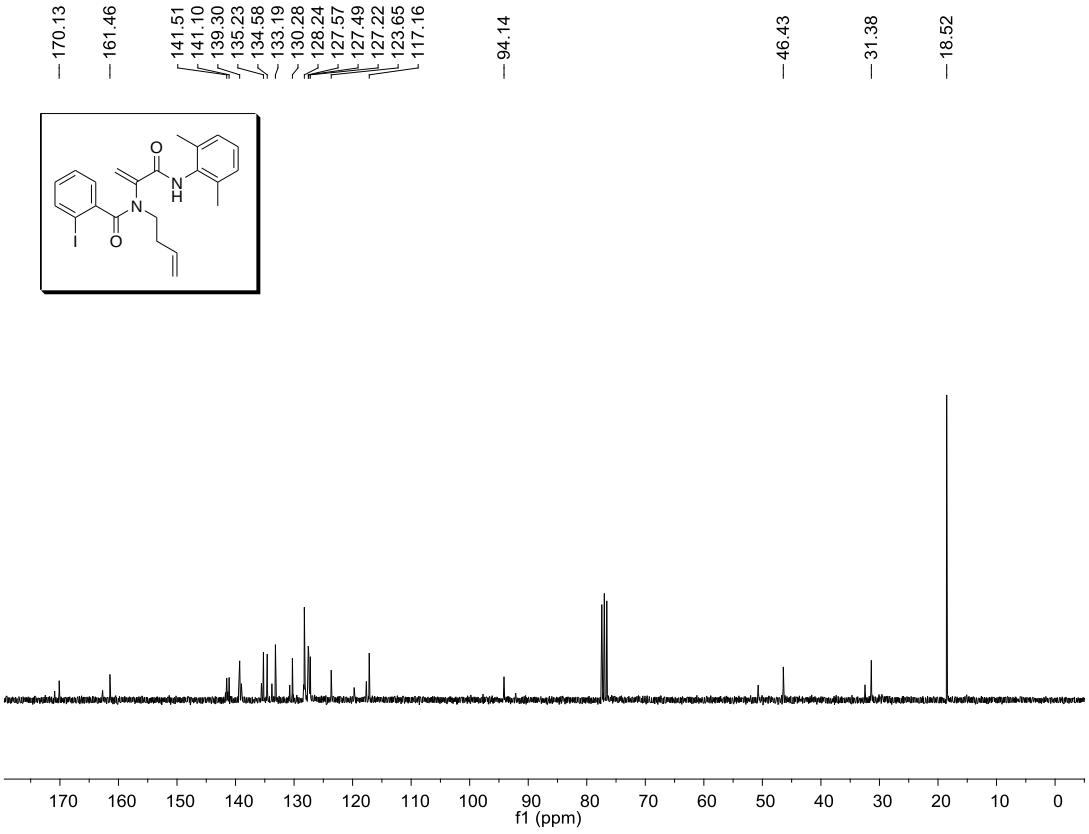
**Compound 11b',** 2-bromo-*N*-but-3-enyl-*N*-(1-*tert*-butylcarbamoyl-vinyl)-5-methoxy-benzamide



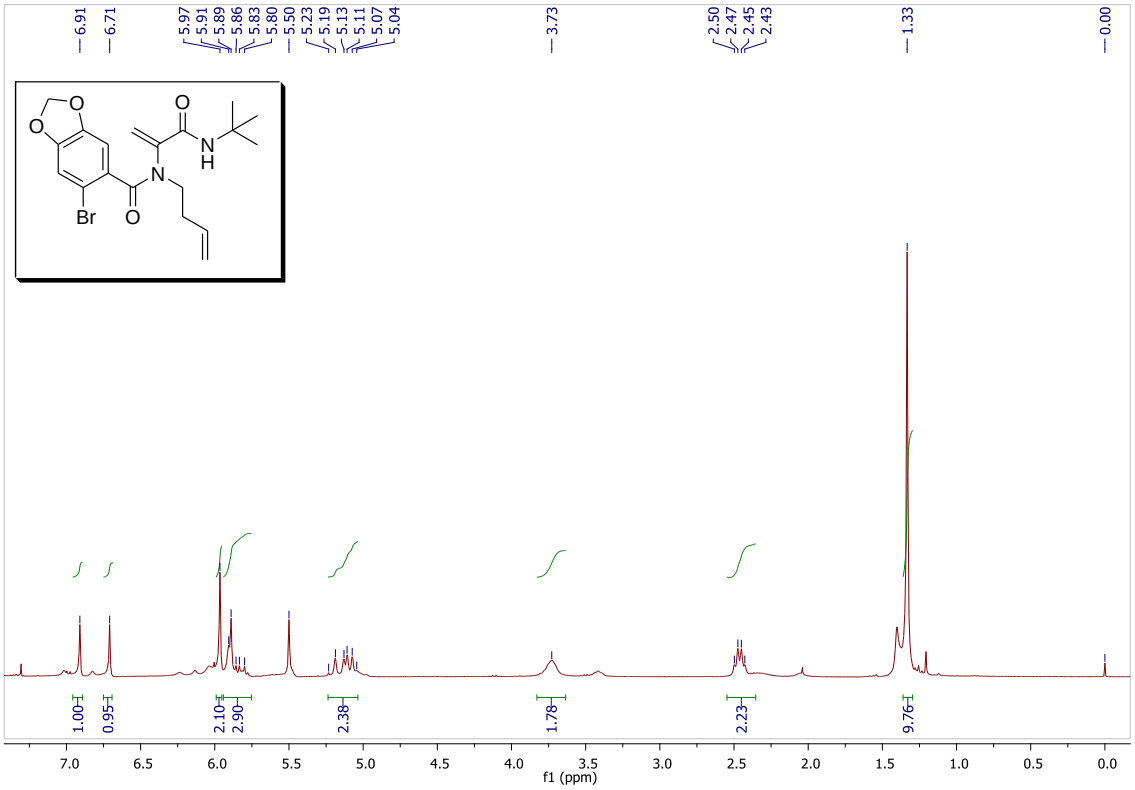



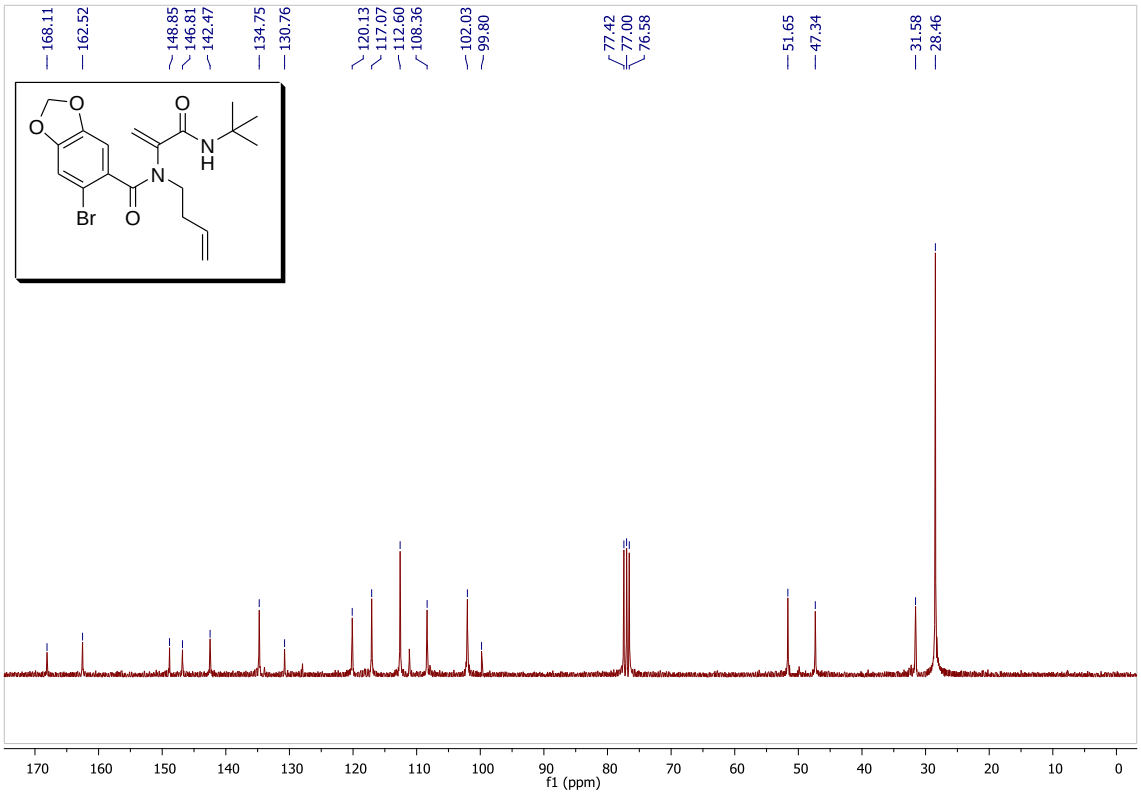
**Compound 11c',** *N*-but-3-enyl-*N*-[1-(2,6-dimethyl-phenylcarbamoyl)-vinyl]-2-iodo-benzamide



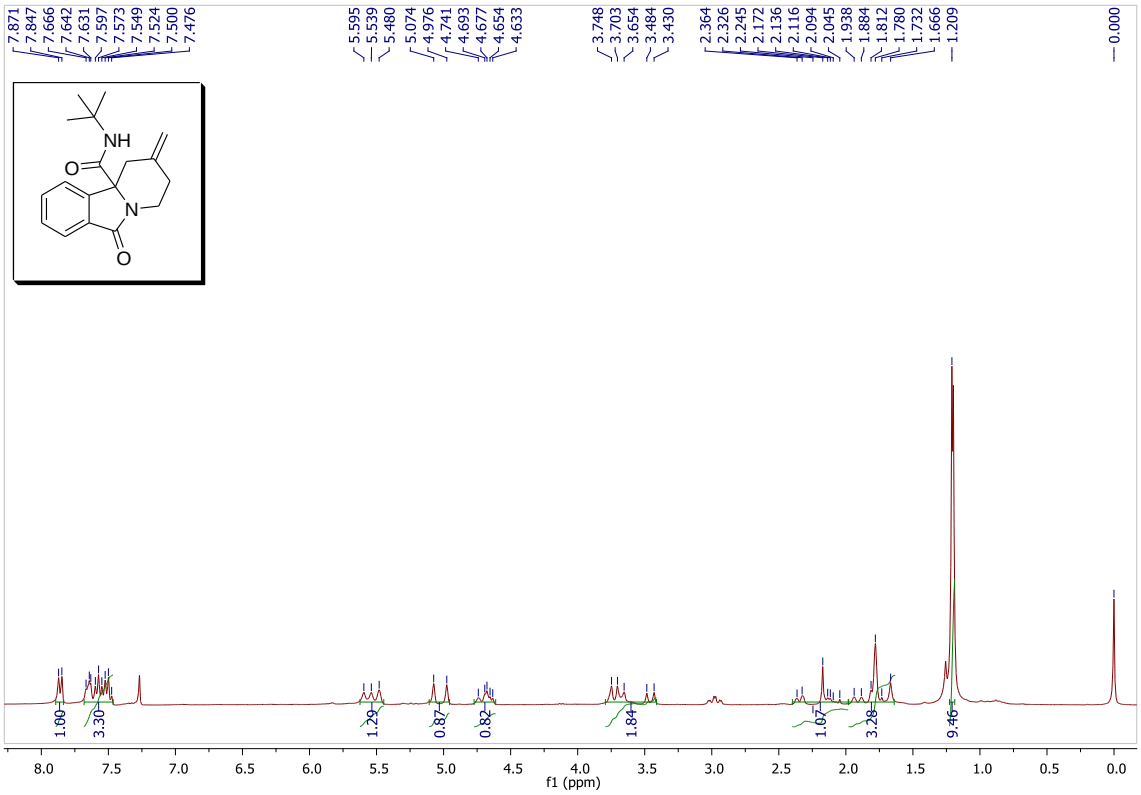



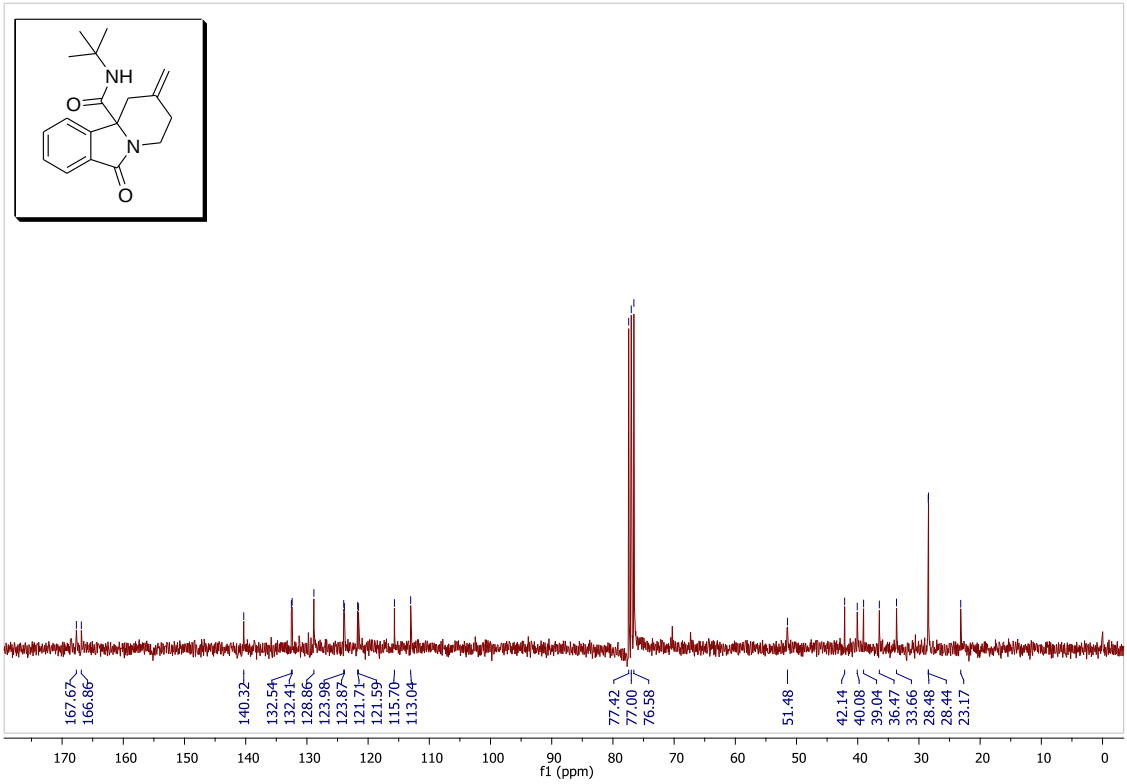
**Compound 11d',** 6-bromo-benzo[1,3]dioxole-5-carboxylic acid but-3-enyl-(1-*tert*-butylcarbamoyl-vinyl)amide



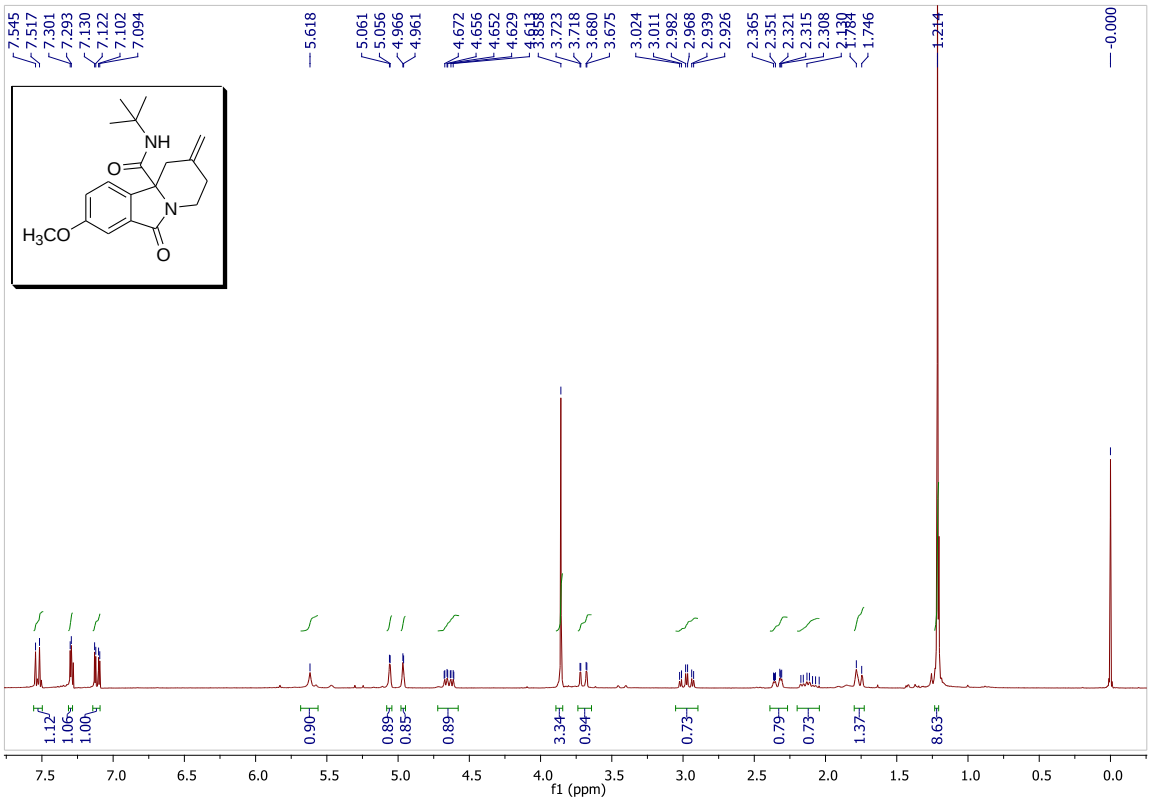



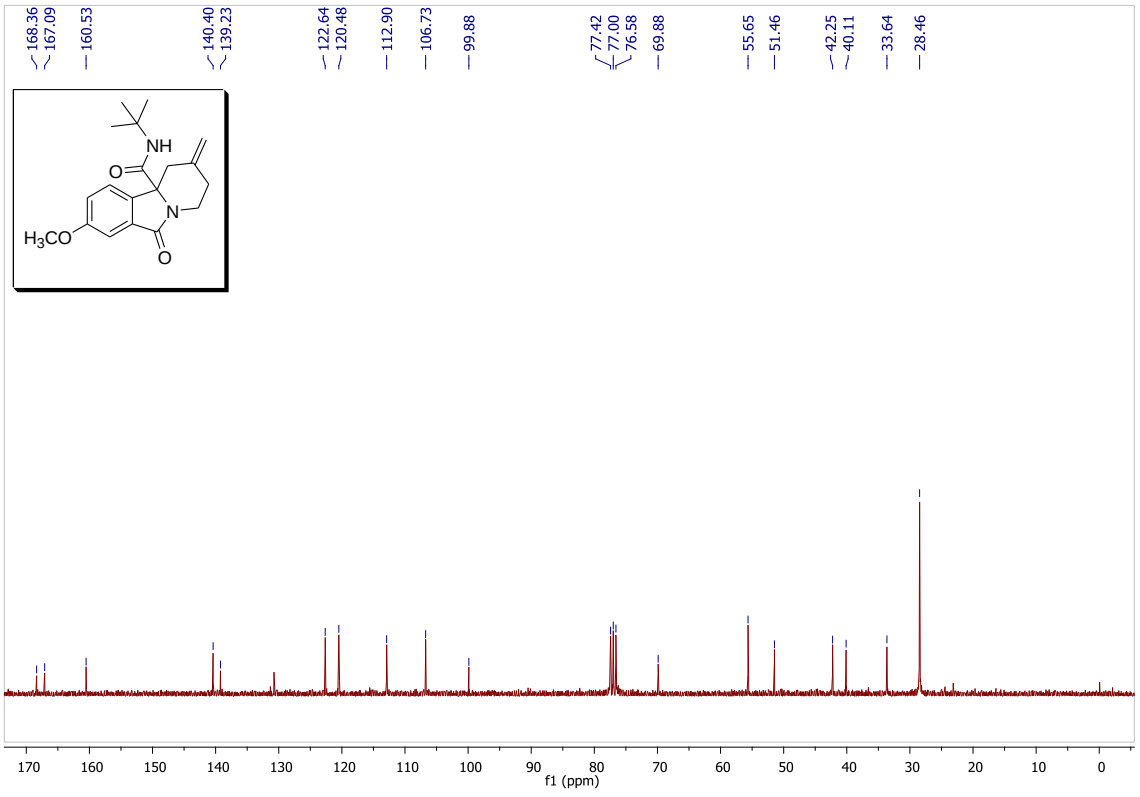
**Compound 11a,** 2-methylene-6-oxo-1,2,3,4-tetrahydro-6*H*-pyrido[2,1-*a*]isoindole-10b-carboxylic acid *tert*-butylamide



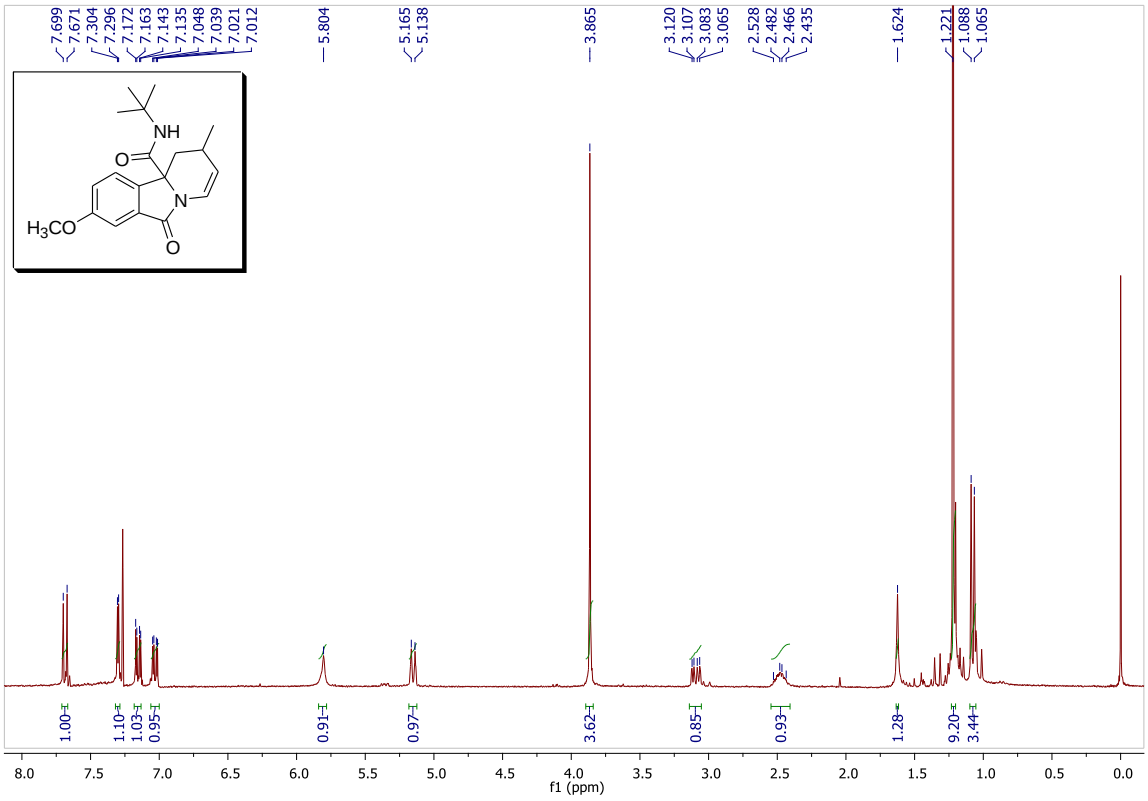



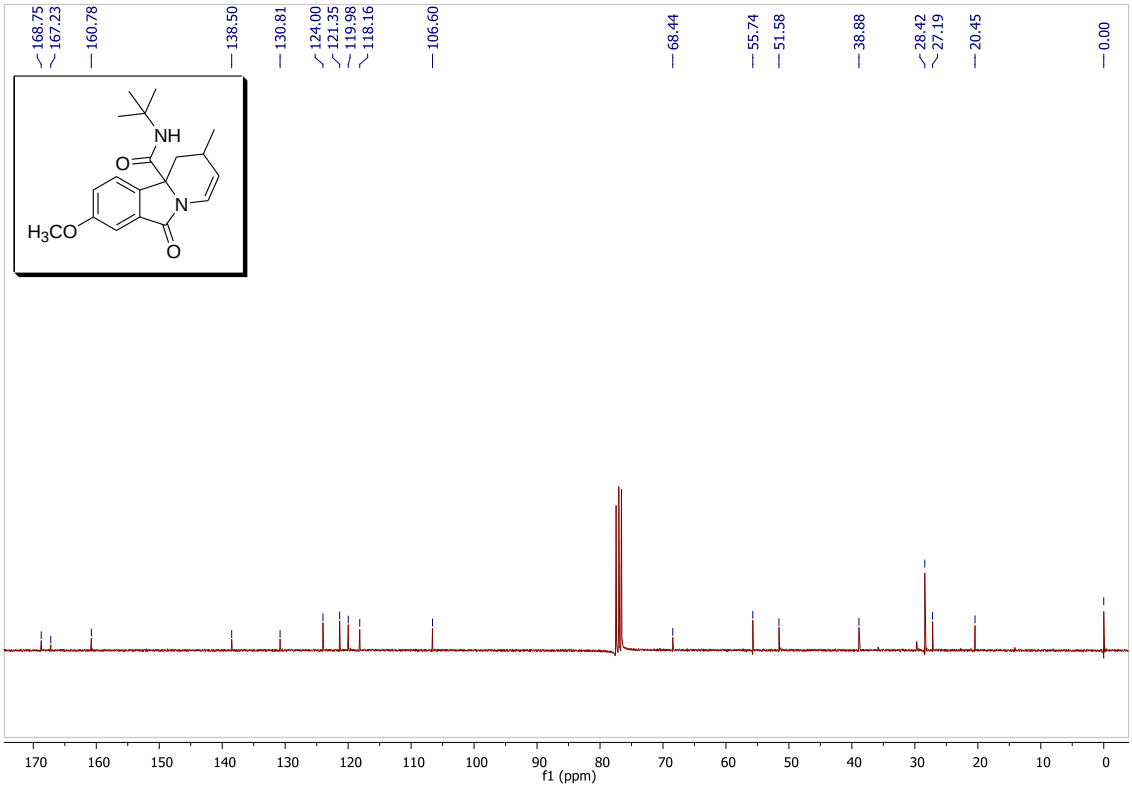
**Compound 11b,** 8-methoxy-2-methylene-6-oxo-1,2,3,4-tetrahydro-6*H*-pyrido[2,1-*a*]isoindole-10b-carboxylic acid *tert*-butylamide



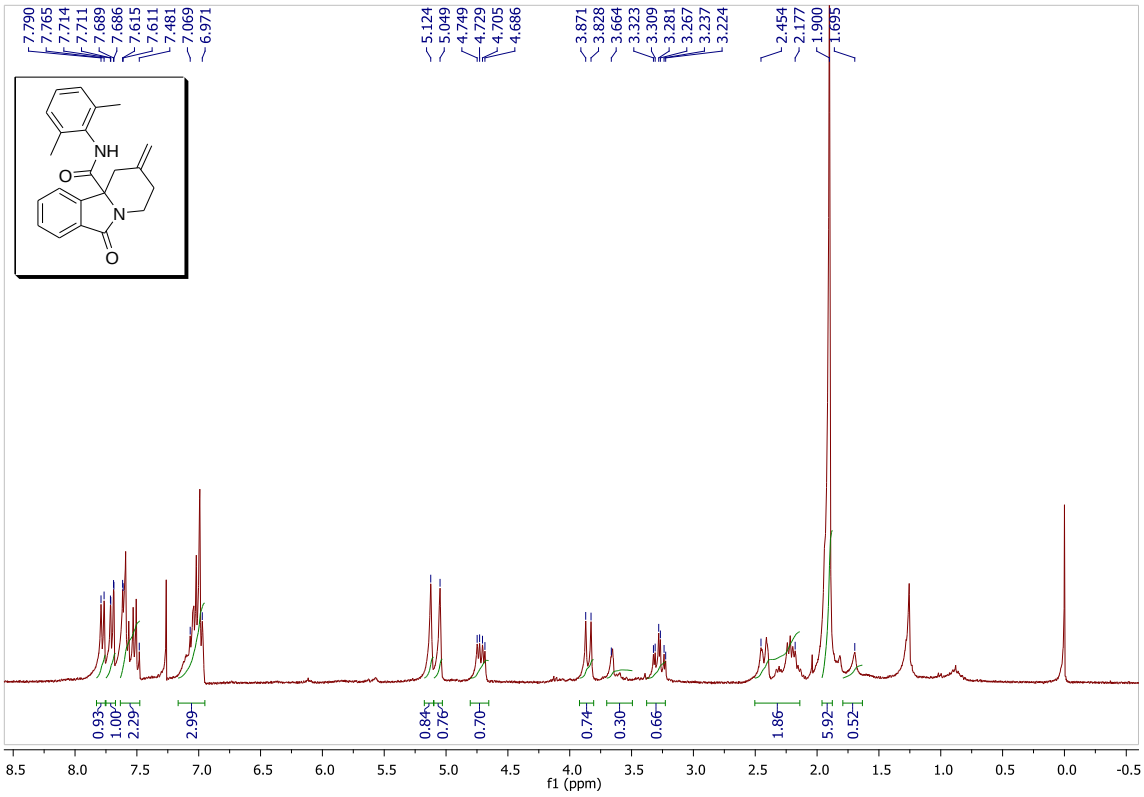



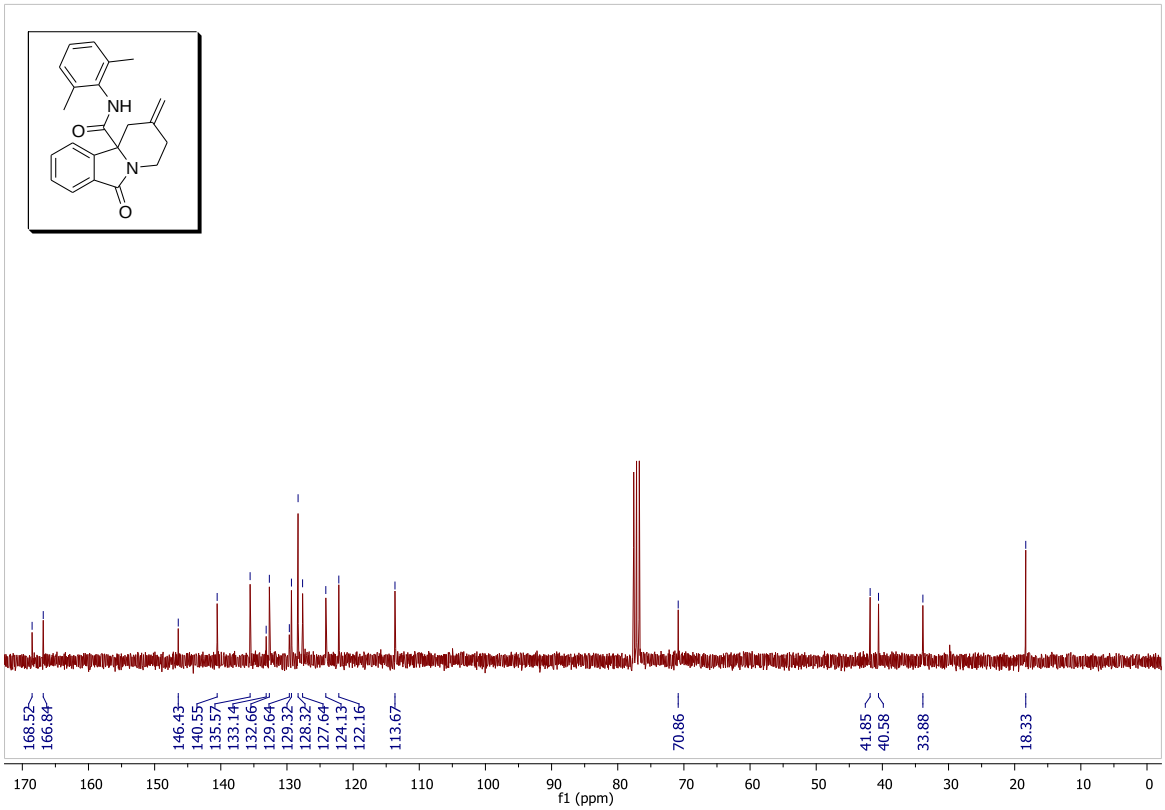
**Compound 11b isomer,** 8-methoxy-2-methyl-6-oxo-1,2-dihydro-6*H*-pyrido[2,1-*a*]isoindole-10b-carboxylic acid *tert*-butylamide



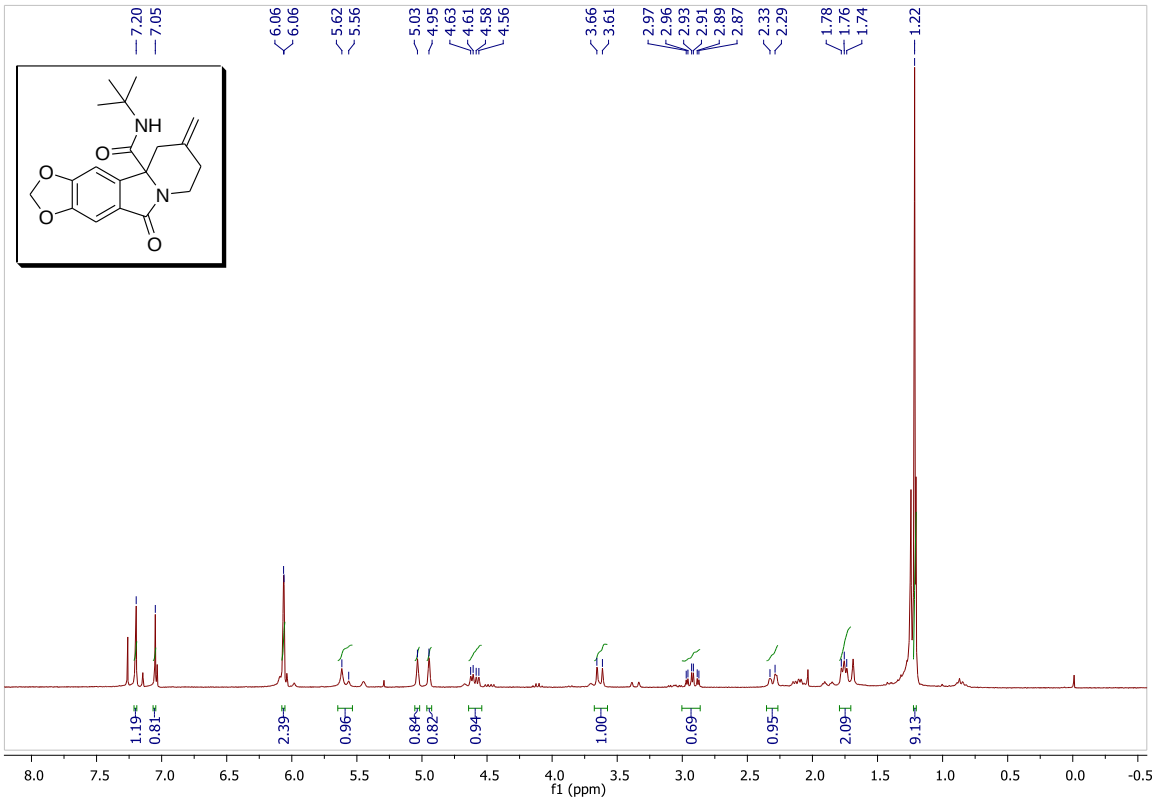



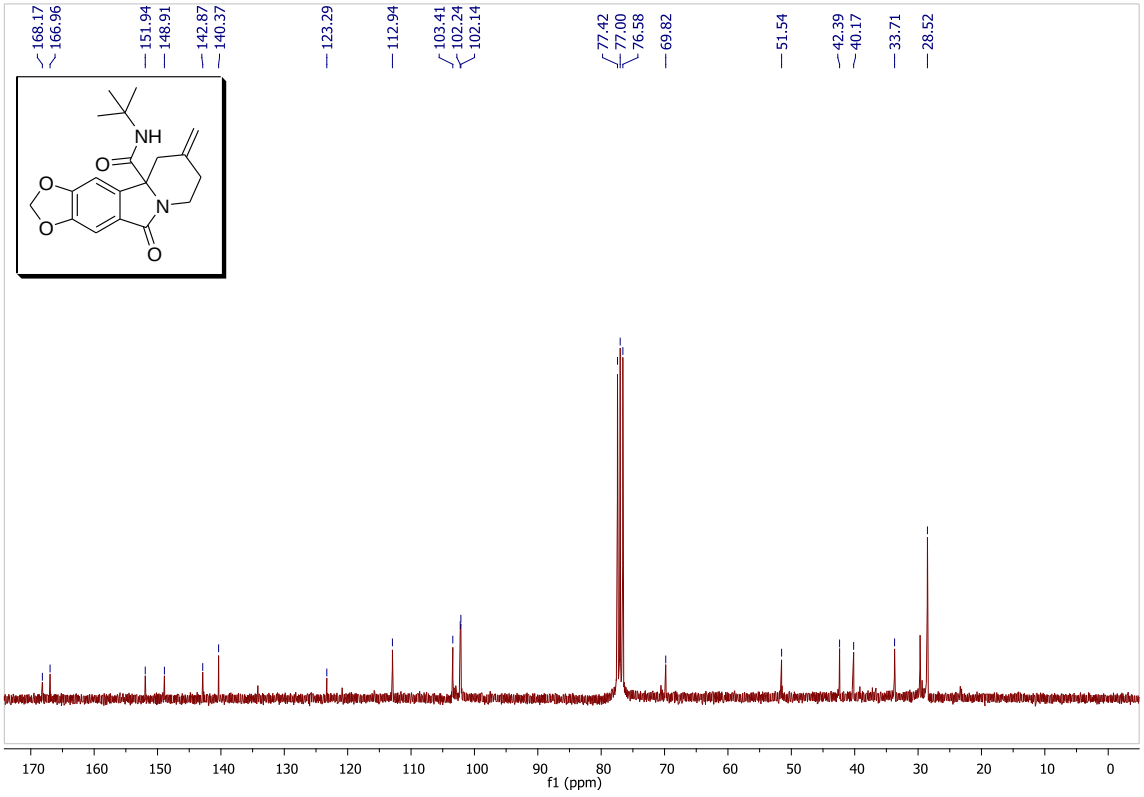
**Compound 11c,** 2-methylene-6-oxo-1,2,3,4-tetrahydro-6*H*-pyrido[2,1-*a*]isoindole-10b-carboxylic acid (2,6-dimethyl-phenyl-amide



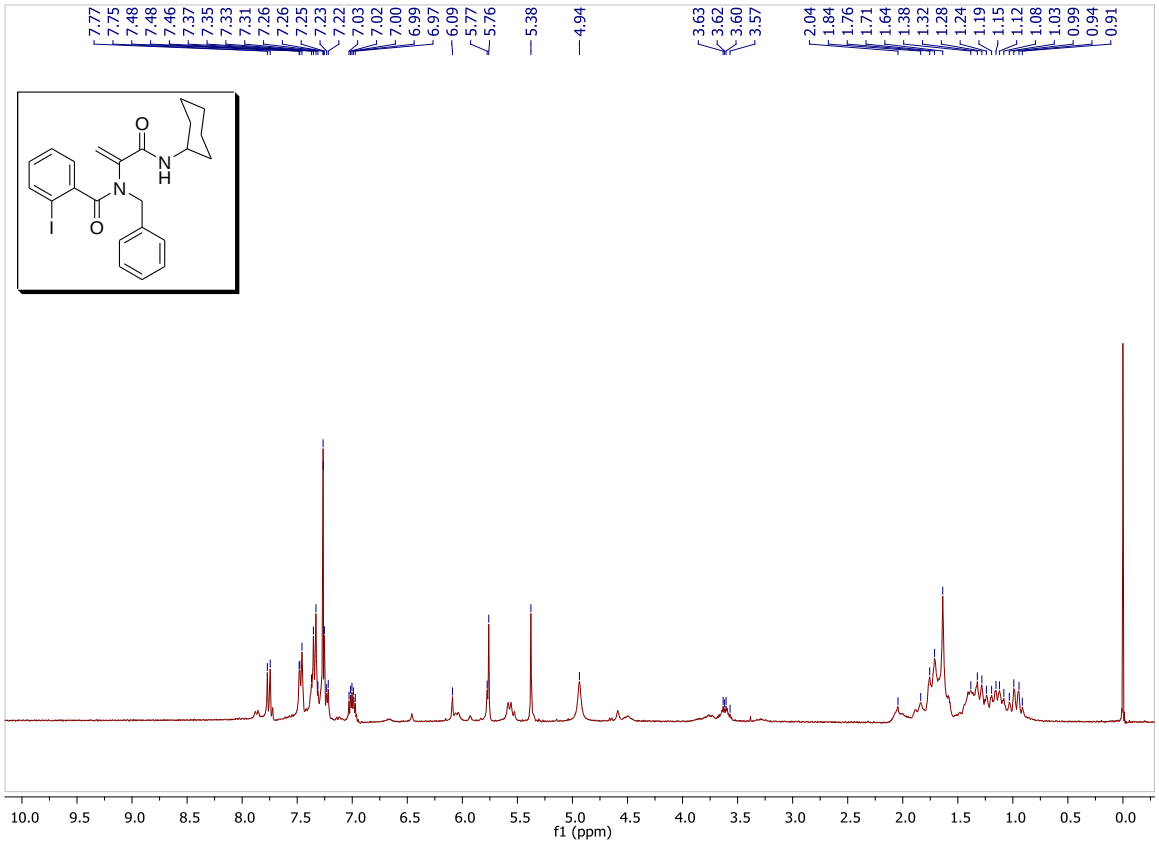



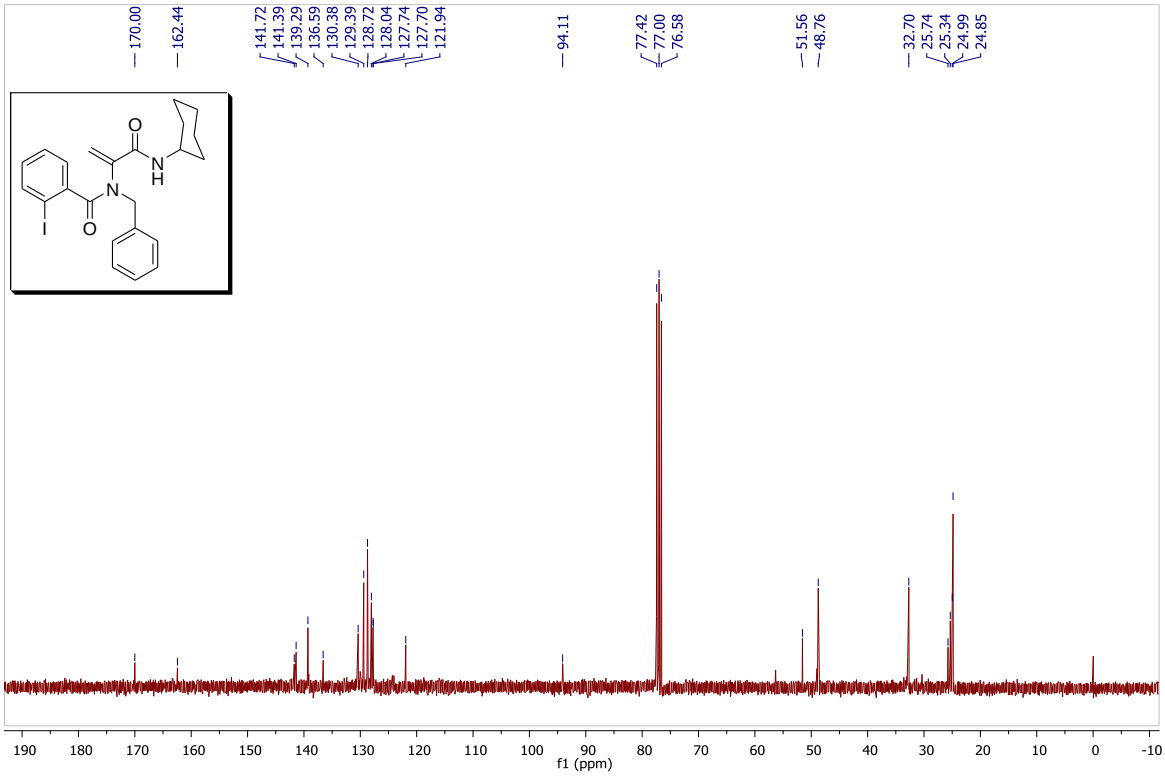
**Compound 11d,** 6-methylene-9-oxo-5,6,7,8-tetrahydro-9*H*-1,3-dioxa-8a-aza-cyclopenta[b]fluorene-4b-carboxylic acid *tert*-butylamide



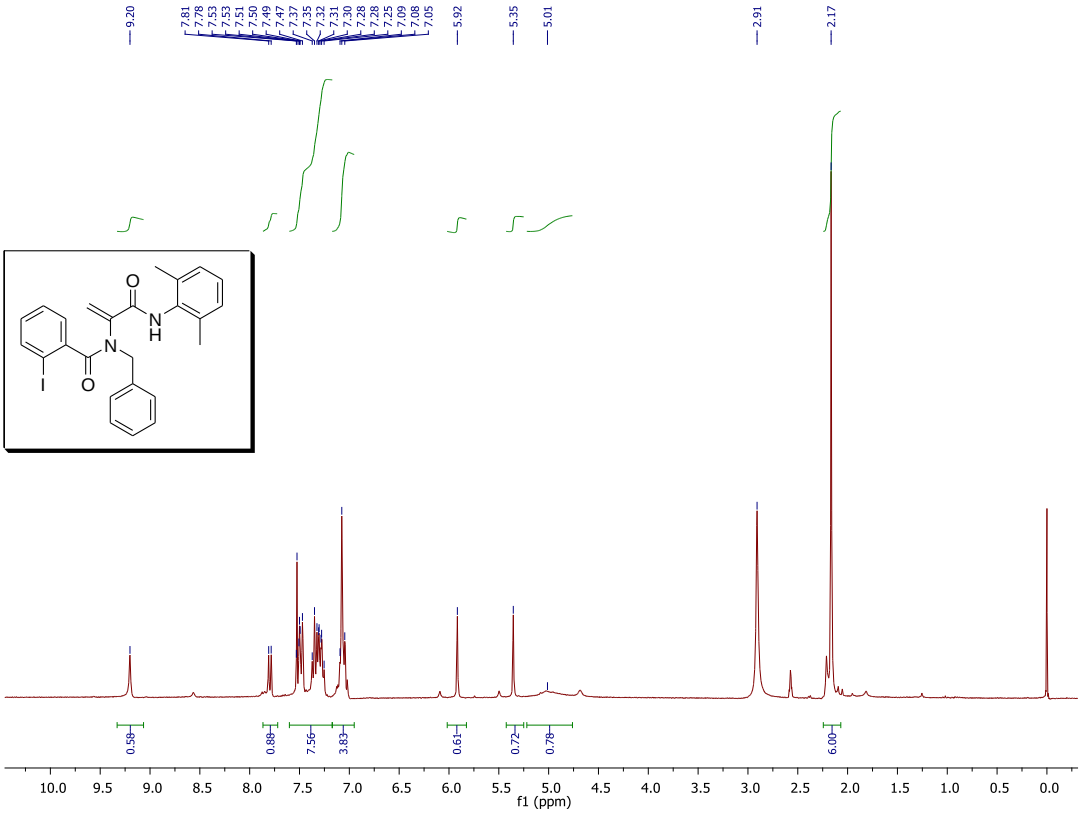



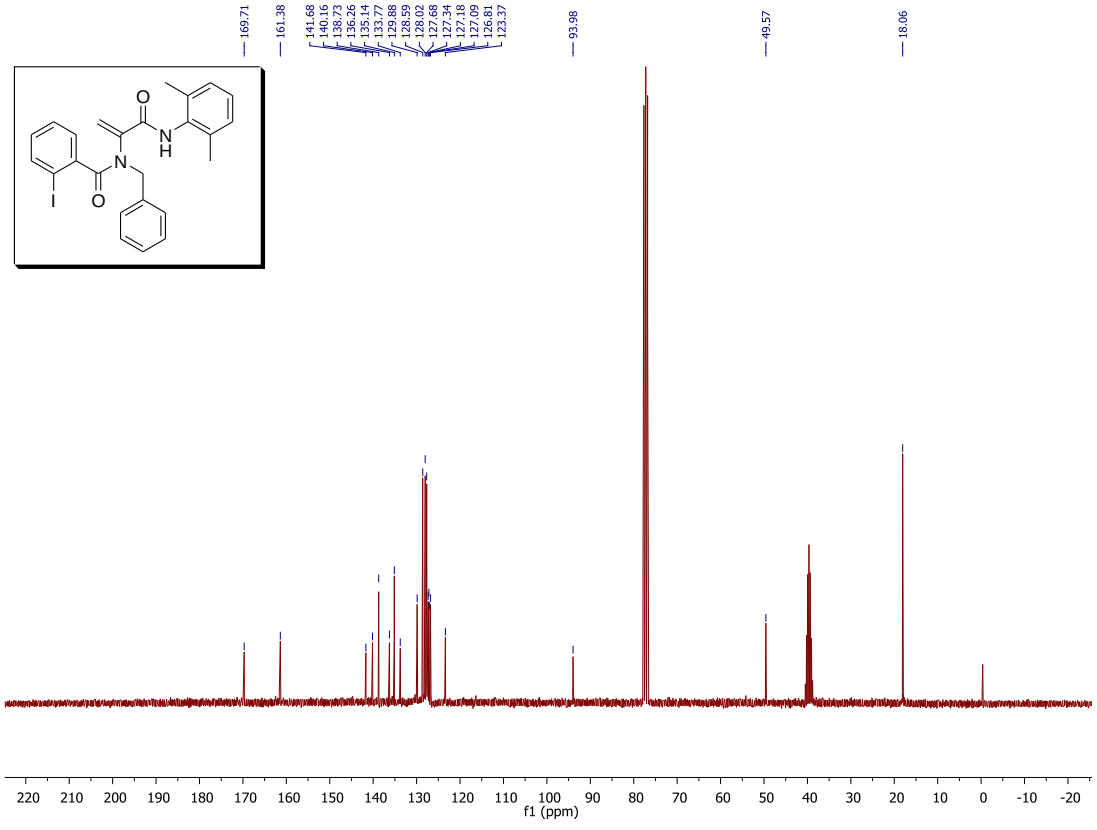
**Compound 12b,** *N*-benzyl-*N*-(1-cyclohexylcarbamoyl-vinyl)-2-iodo-benzamide



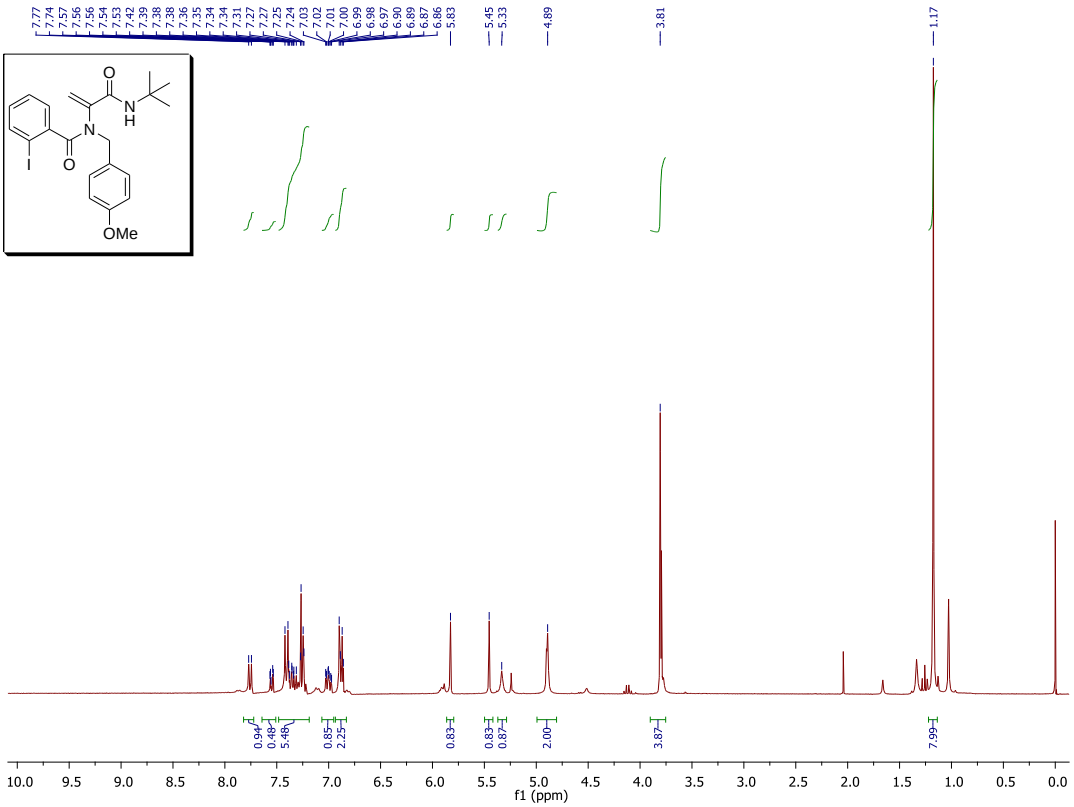



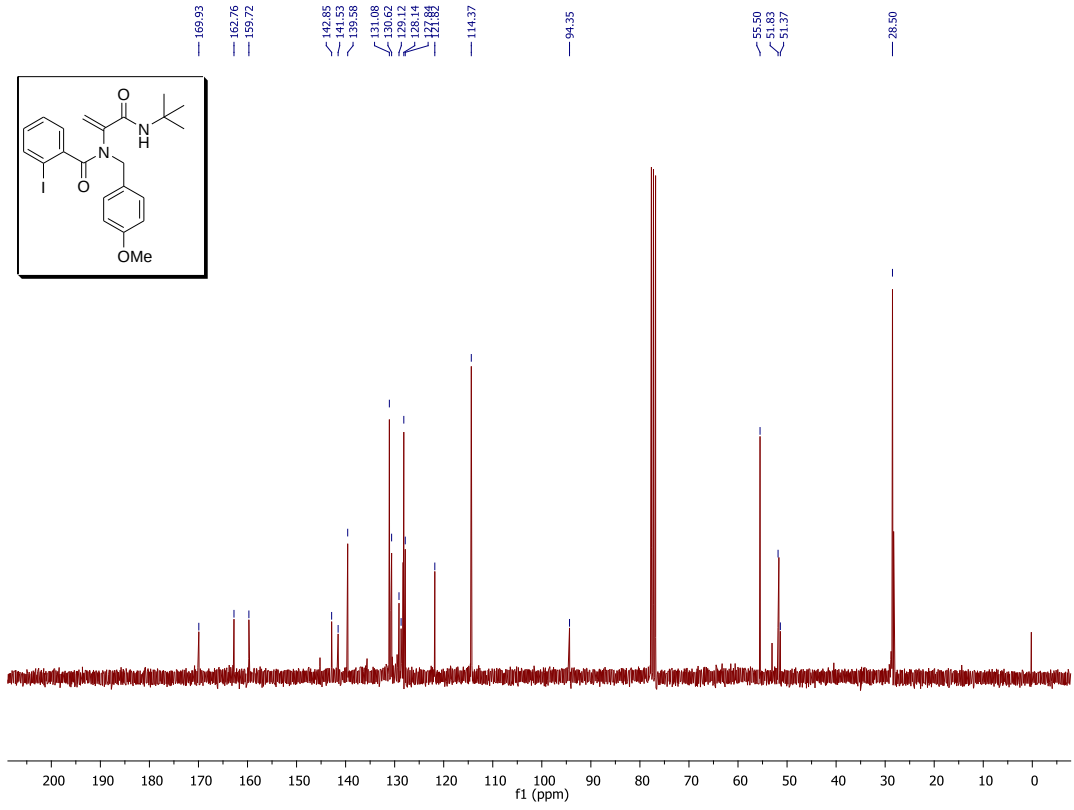
**Compound 12c,** *N*-benzyl-*N*-[1-(2,6-dimethyl-phenylcarbamoyl)-vinyl)-2-iodo-benzamide



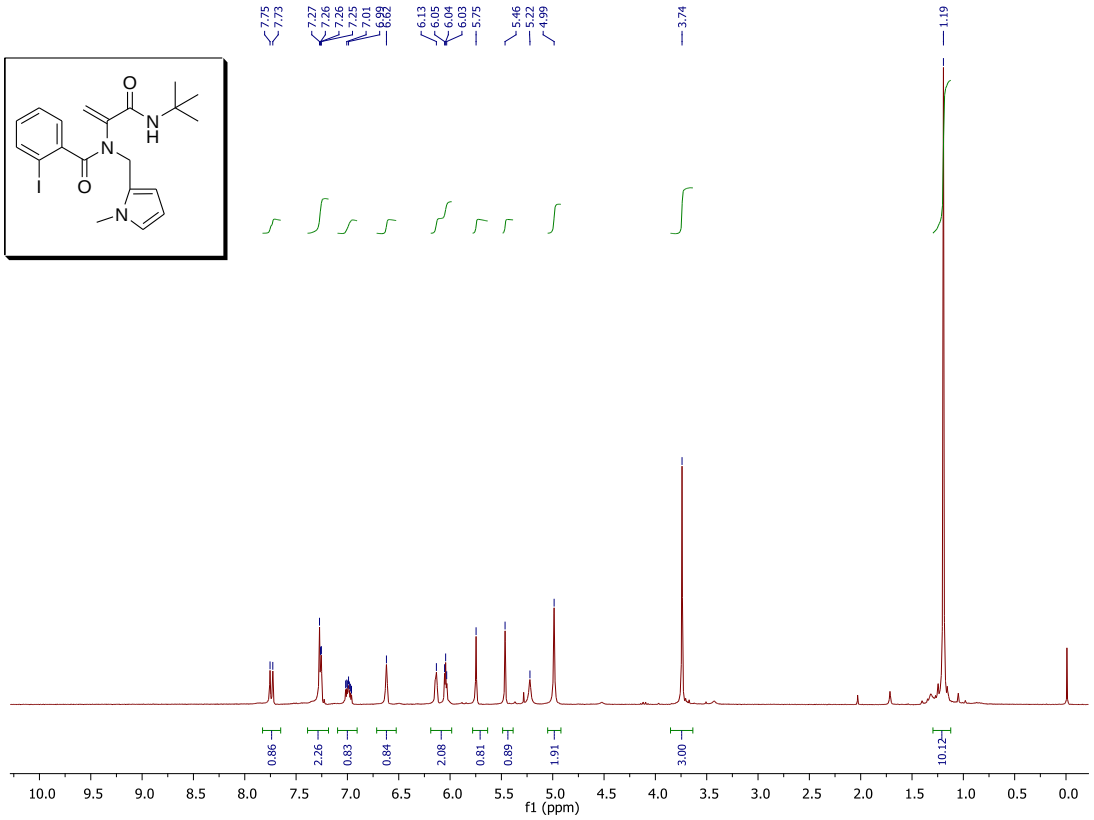



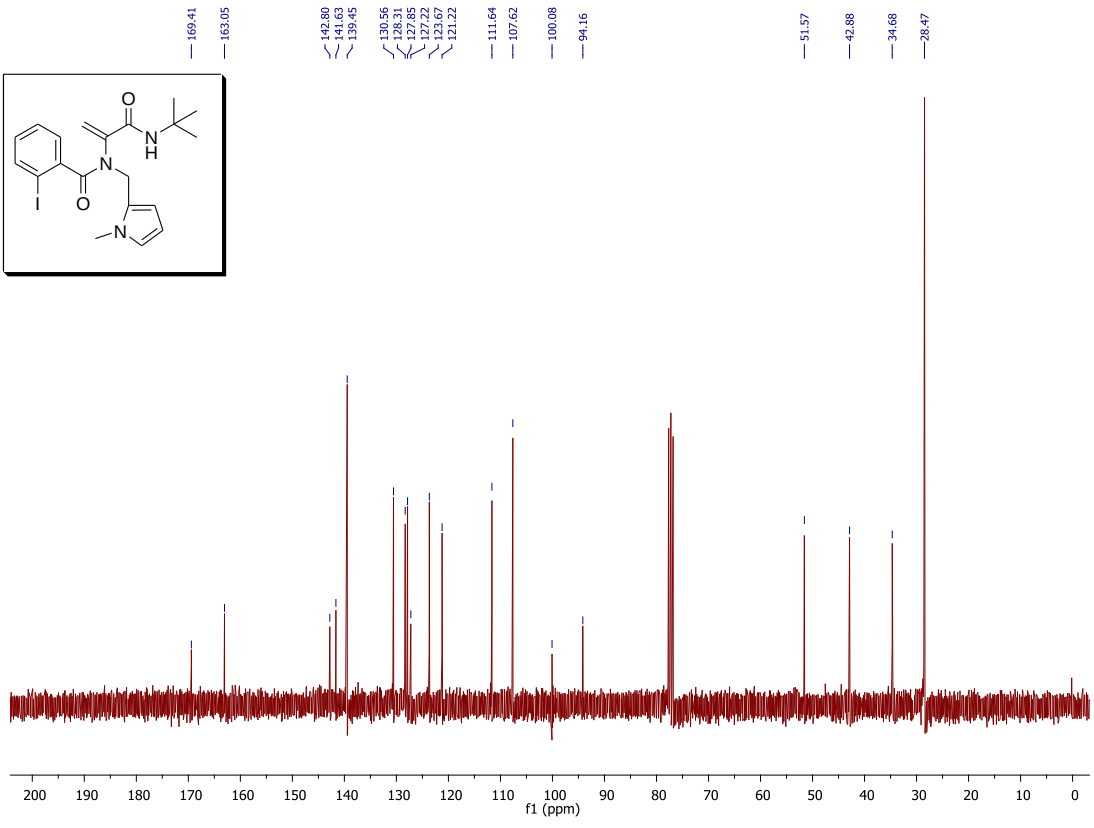
**Compound 12d,** *N*-(1-*tert*-butylcarbamoyl-vinyl)-2-iodo-*N*-(4-methoxy-benzyl)-benzamide



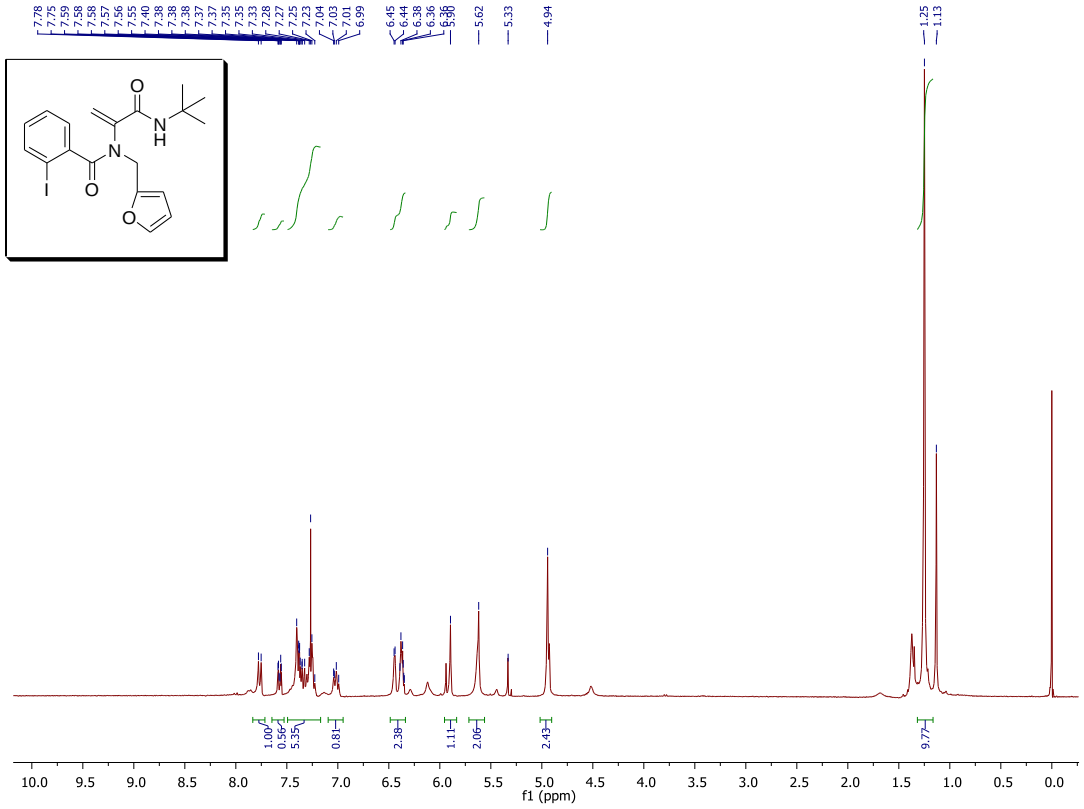



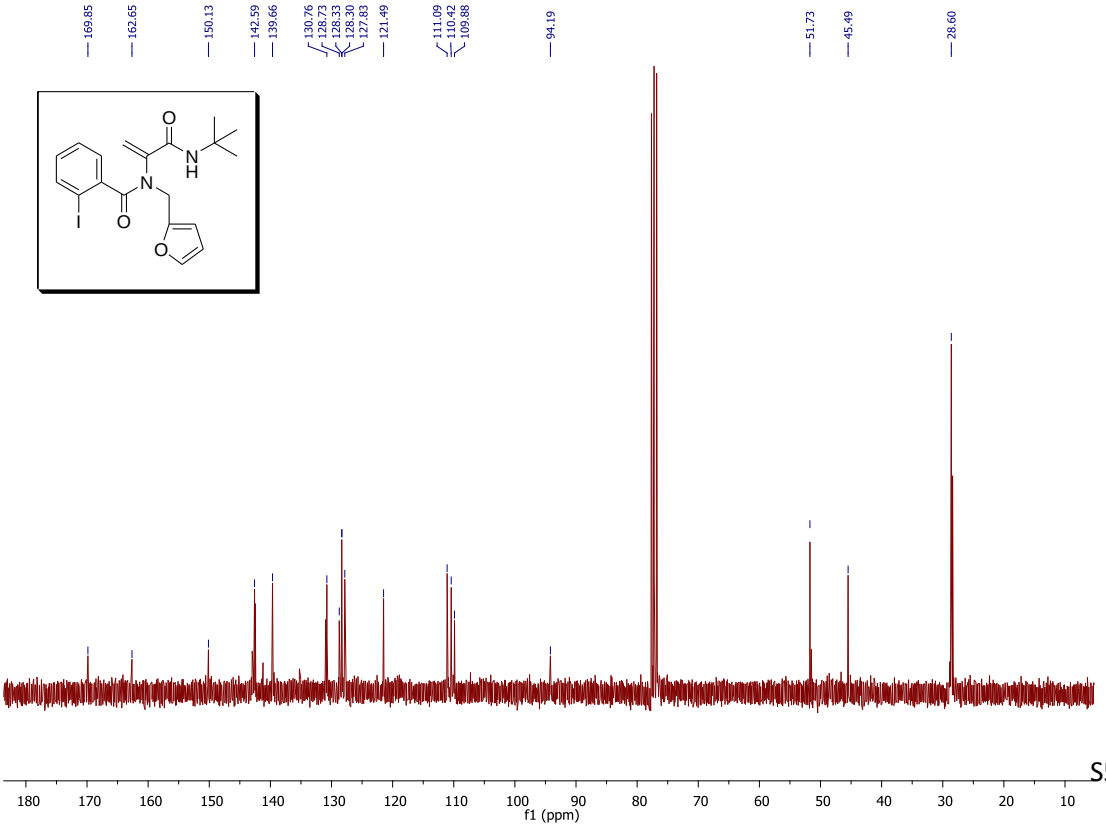
**Compound 12e,** *N*-(1-*tert*-butylcarbamoyl-vinyl)-2-iodo-*N*-(1-methyl-1*H*-pyrrol-2-ylmethyl)-benzamide



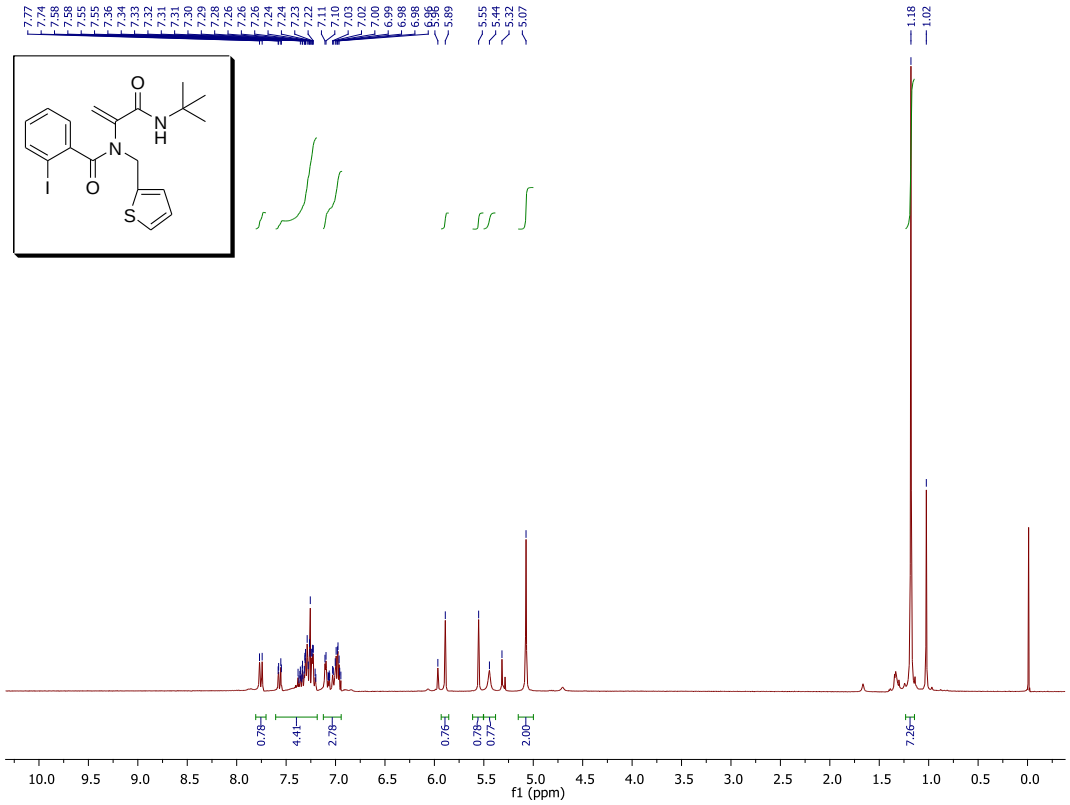



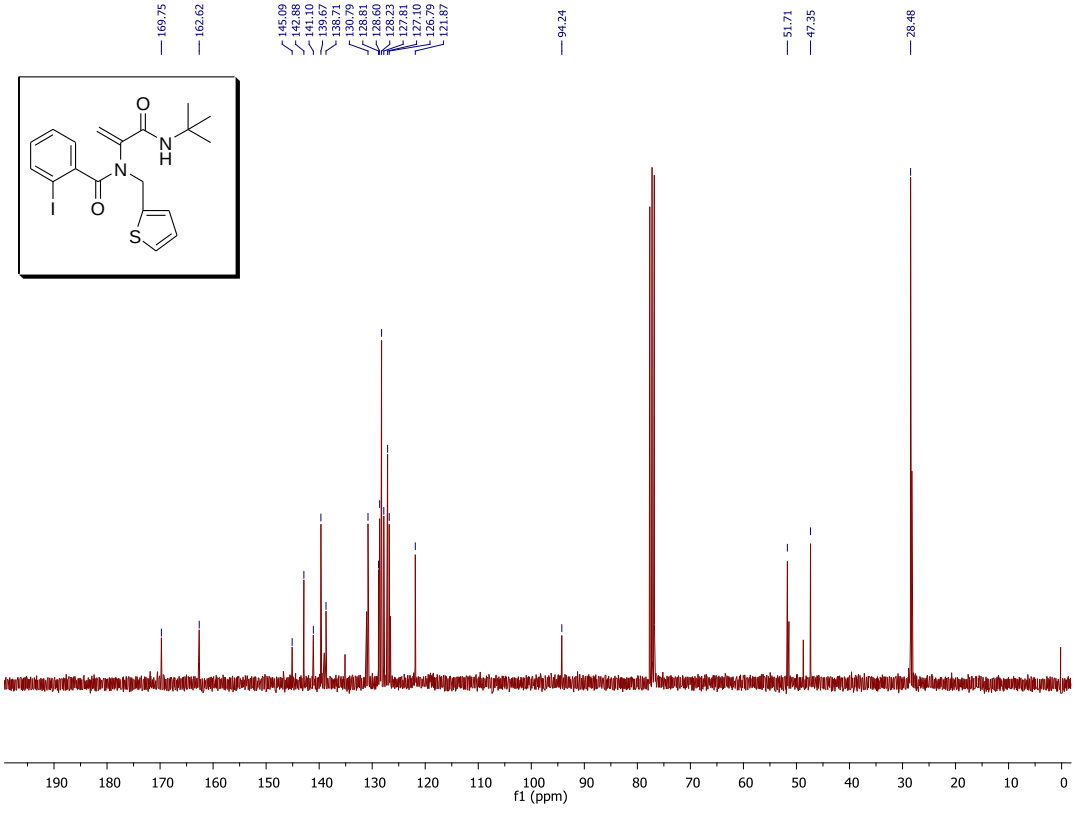
**Compound 12f,** *N*-(1-*tert*-butylcarbamoyl-vinyl)-*N*-furan-2-ylmethyl-2-iodo-benzamide



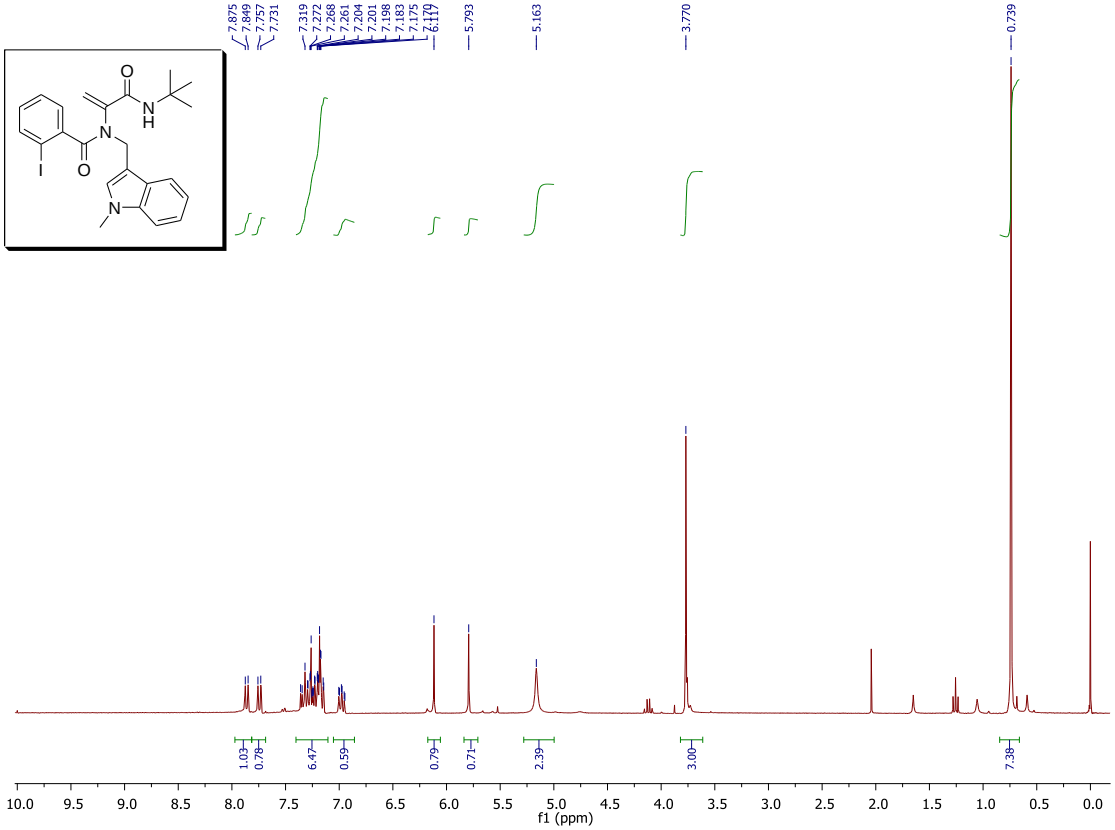



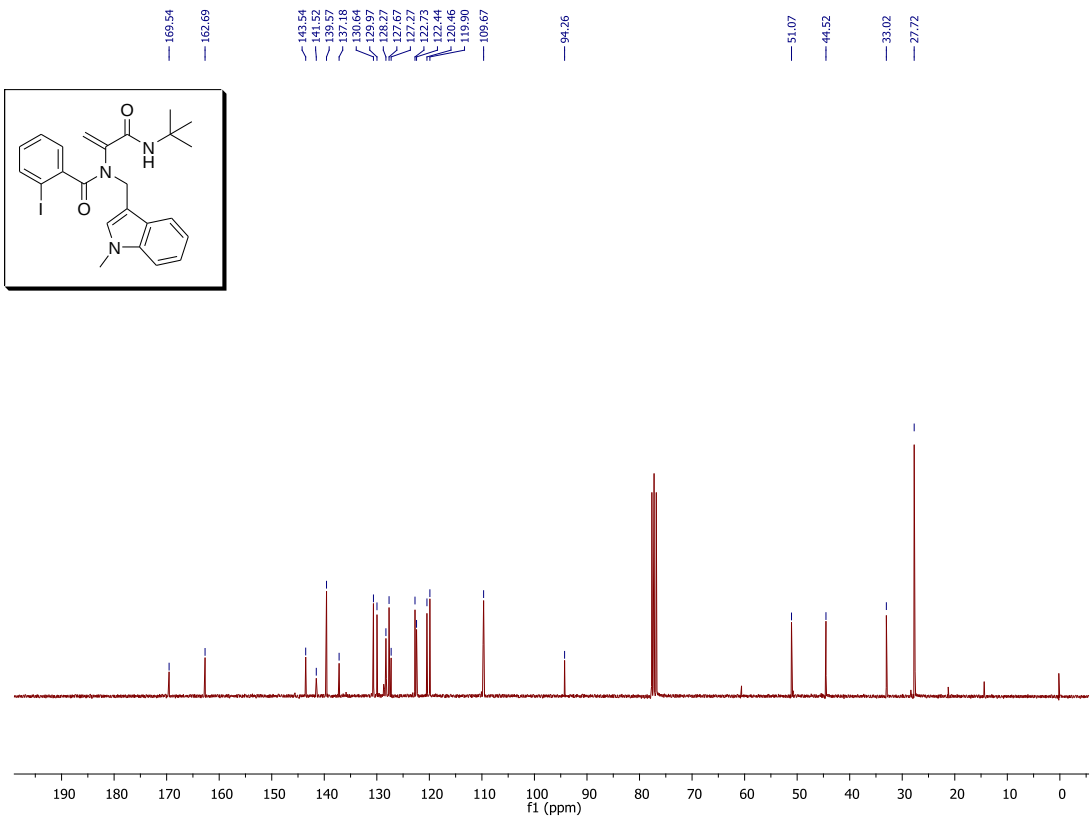
**Compound 12g,** *N*-(1-*tert*-butylcarbamoyl-vinyl)-2-iodo-*N*-thiophen-2-ylmethyl-benzamide



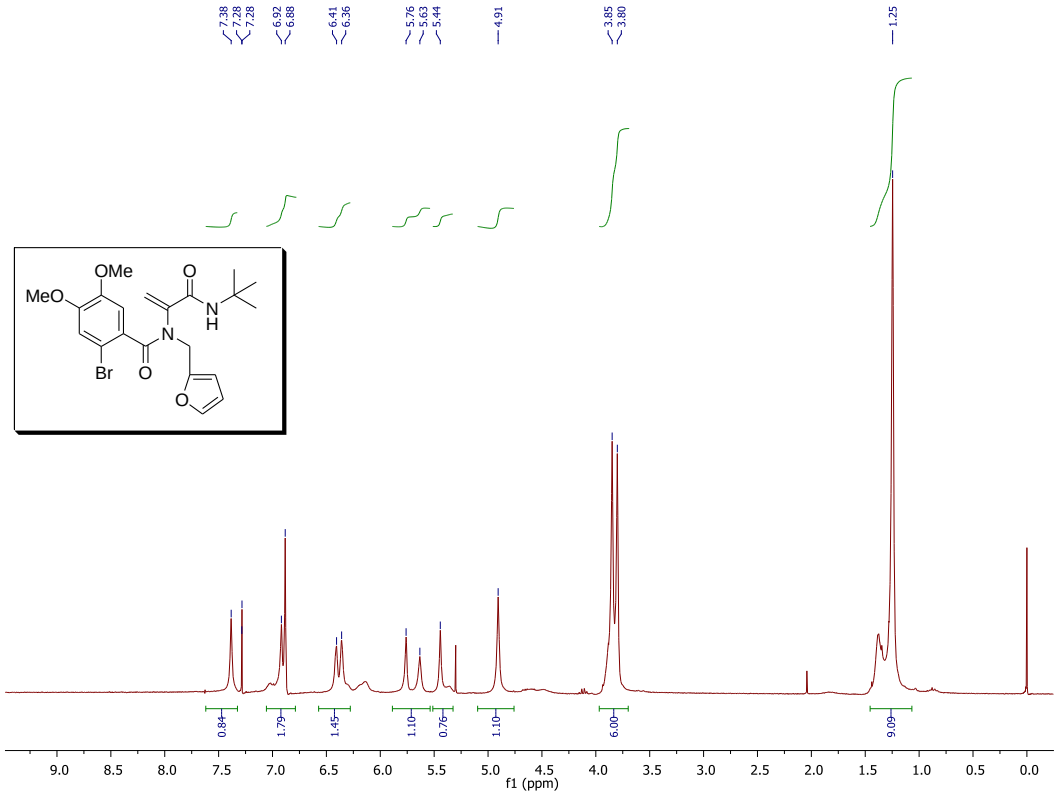



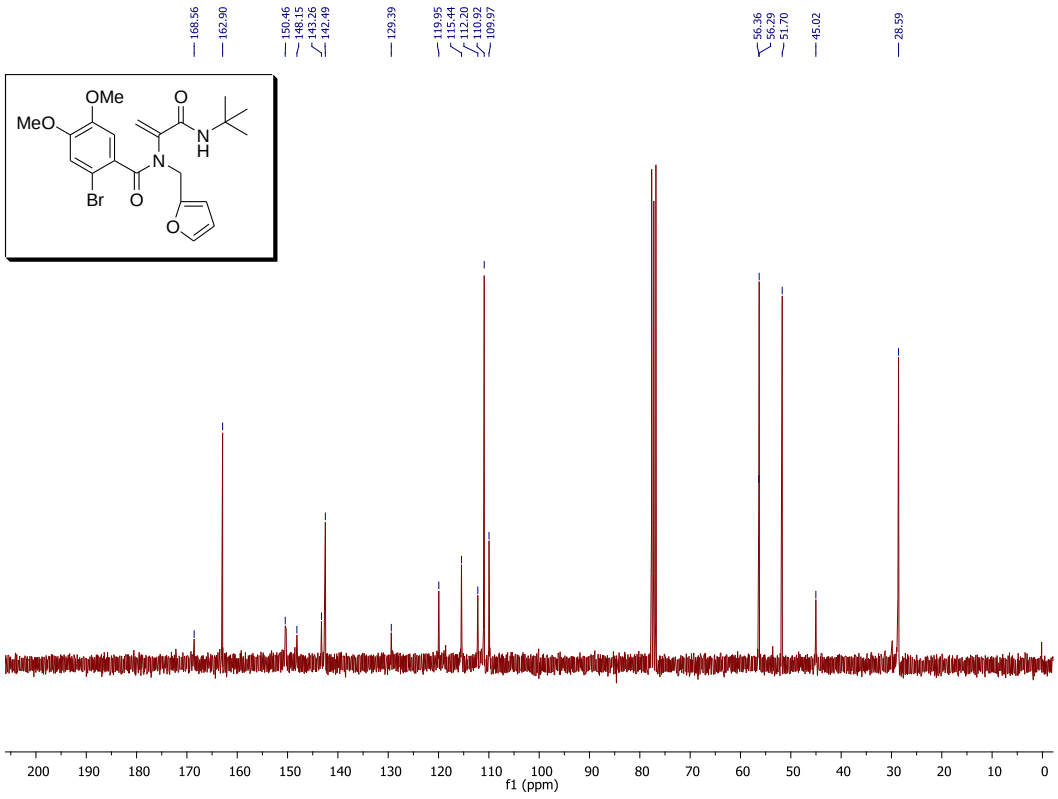
**Compound 12h,** *N*-(1-*tert*-butylcarbamoyl-vinyl)-2-iodo-*N*-(1-methyl-1*H*-indol-3-ylmethyl)-benzamide



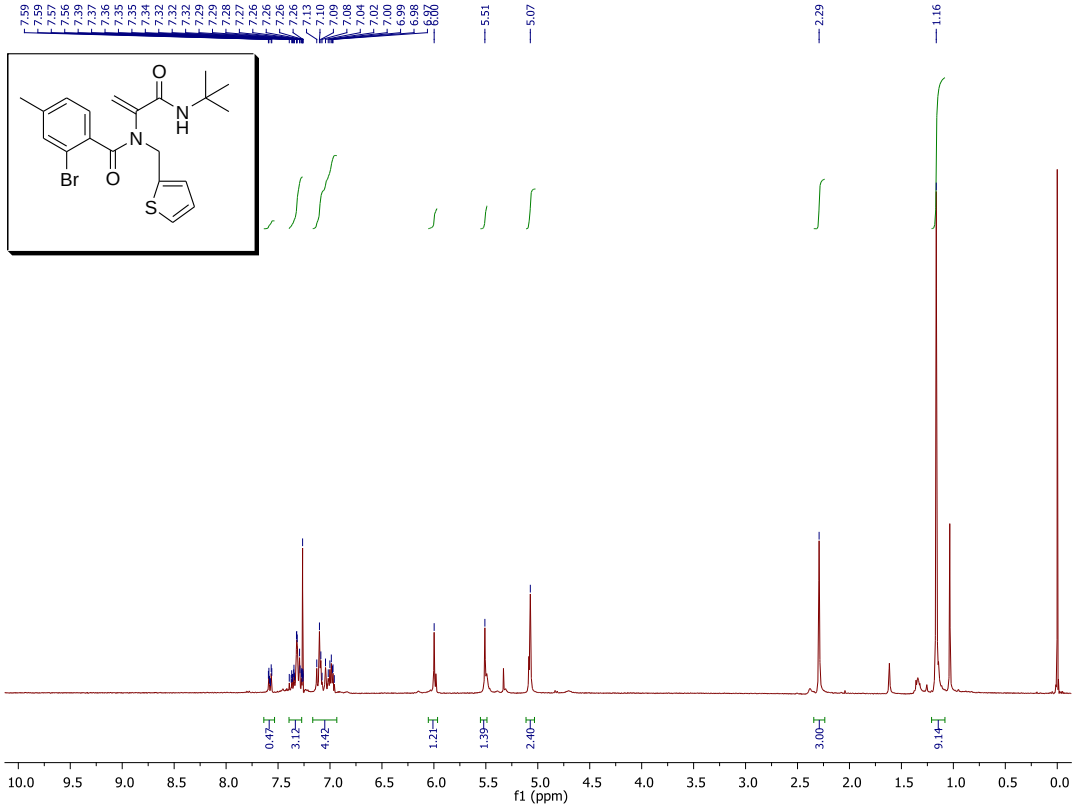



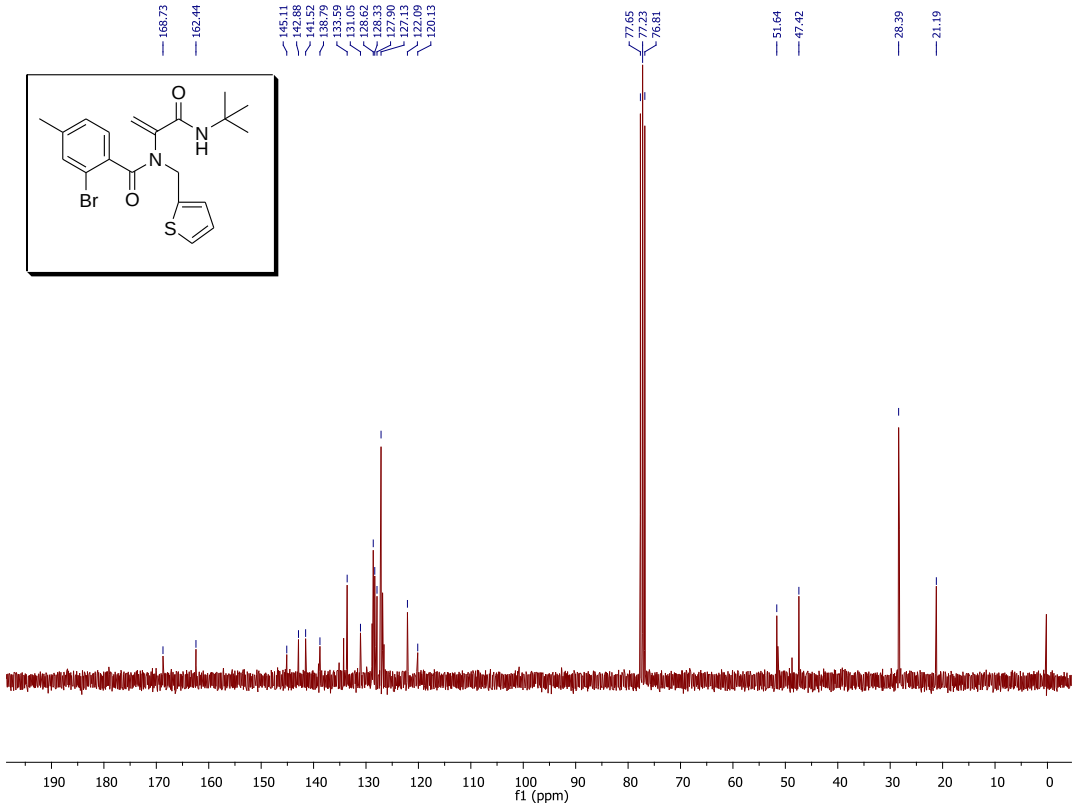
**Compound 12i,** 2-bromo-*N*-(1-*tert*-butylcarbamoyl-vinyl)-*N*-furan-2-ylmethyl-4,5-dimethoxy-benzamide



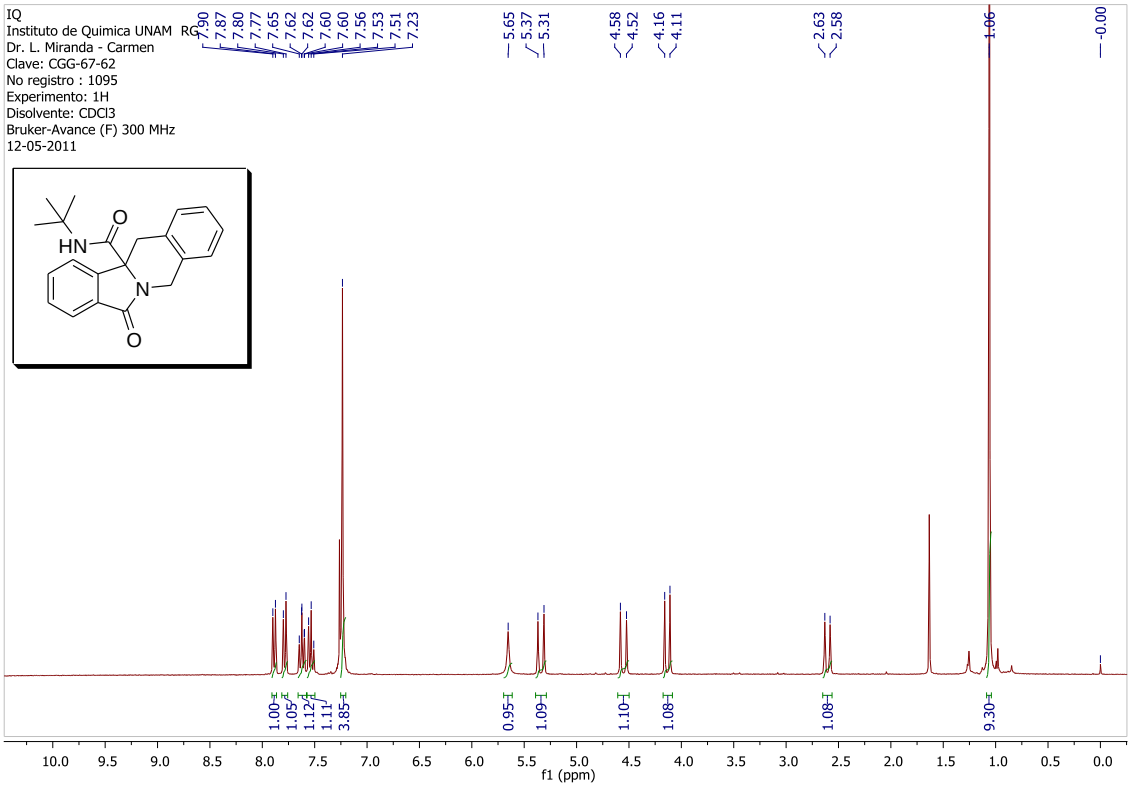



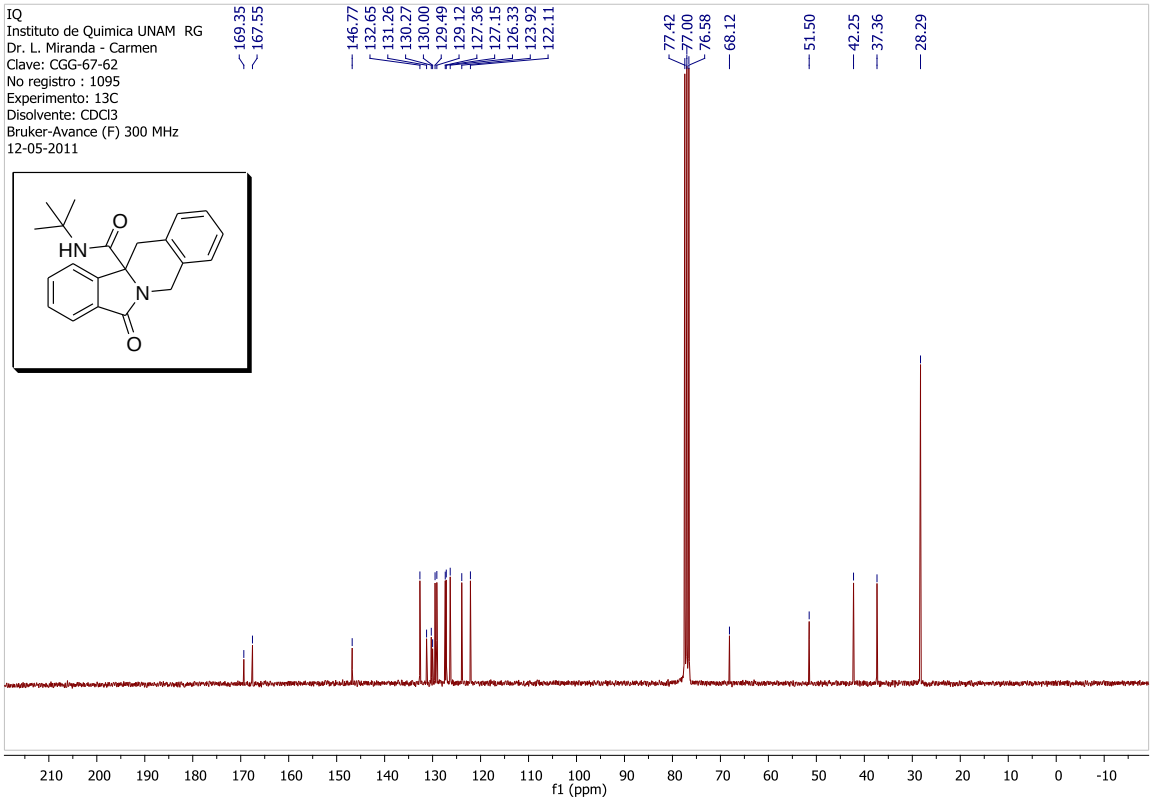
**Compound 12j,** 2-bromo-*N*-(1-*tert*-butylcarbamoyl-vinyl)-4-methyl-*N*-thiophen-2-ylmethyl-benzamide



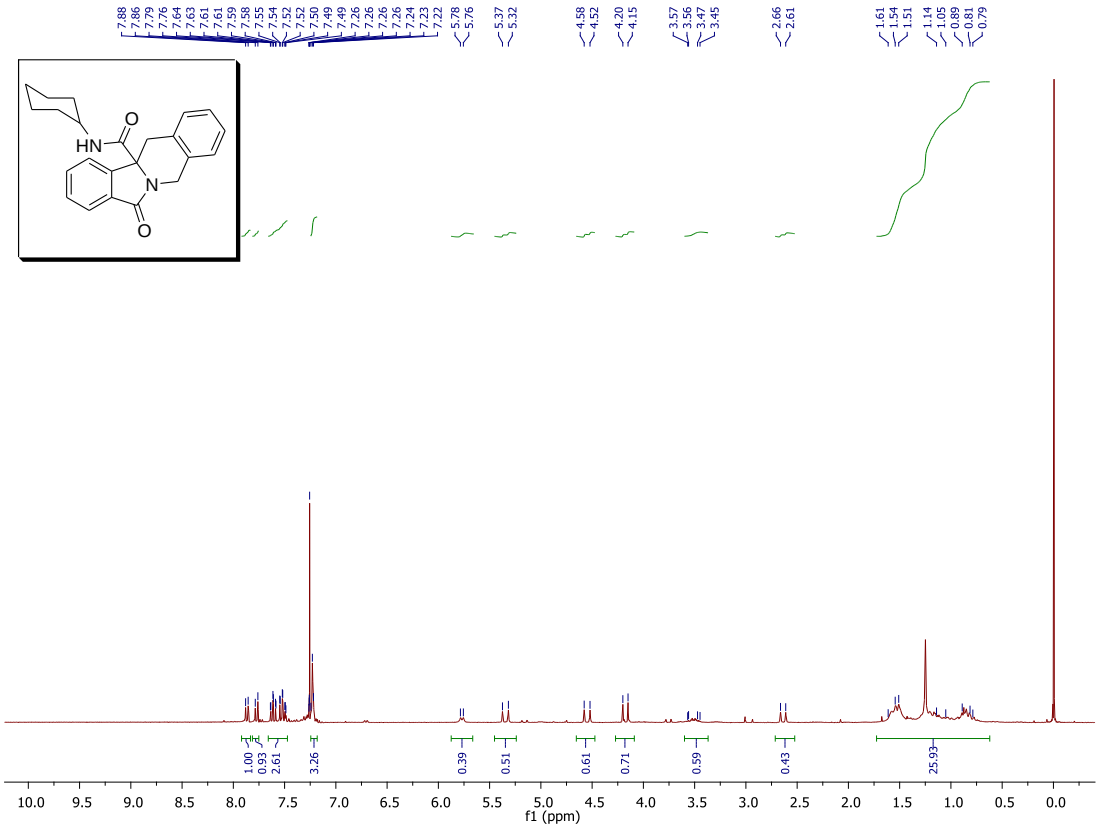



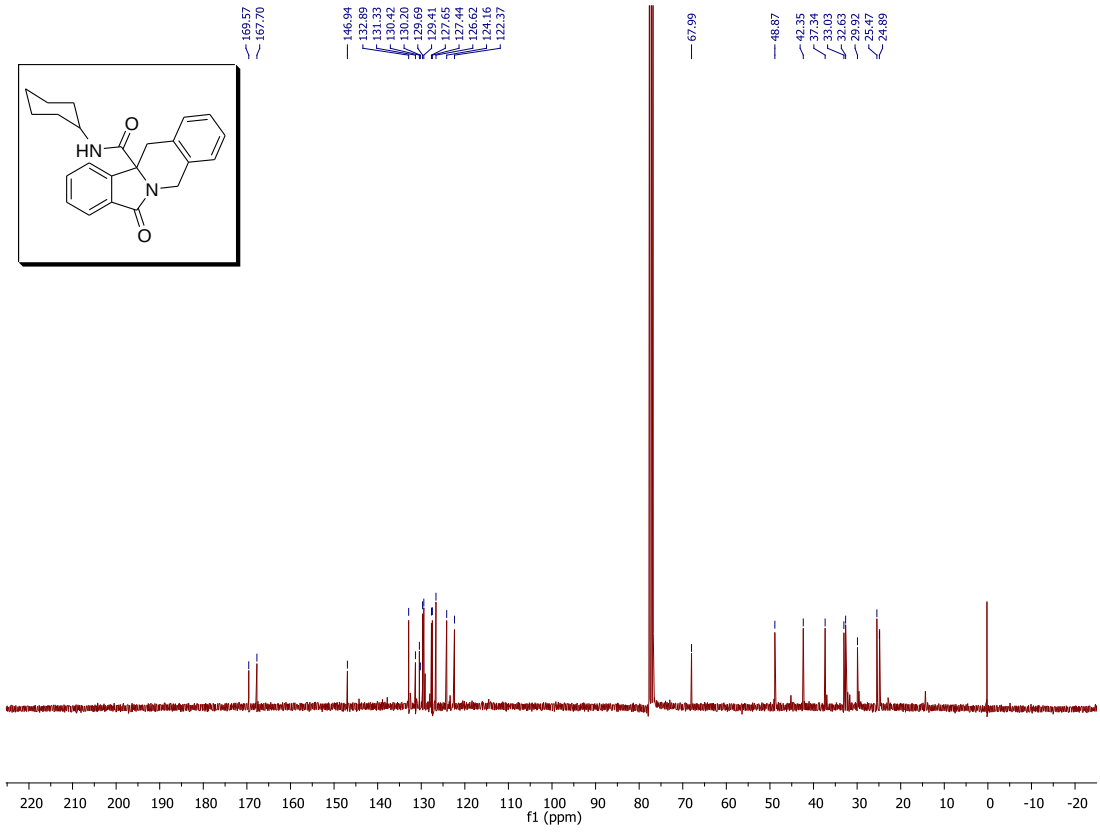
**Compound 14a,** 7-oxo-5,12-dihydro-7*H*-isoindolo[2,1-*b*]isoquinoline-11b-carboxylic acid *tert*-butylamide



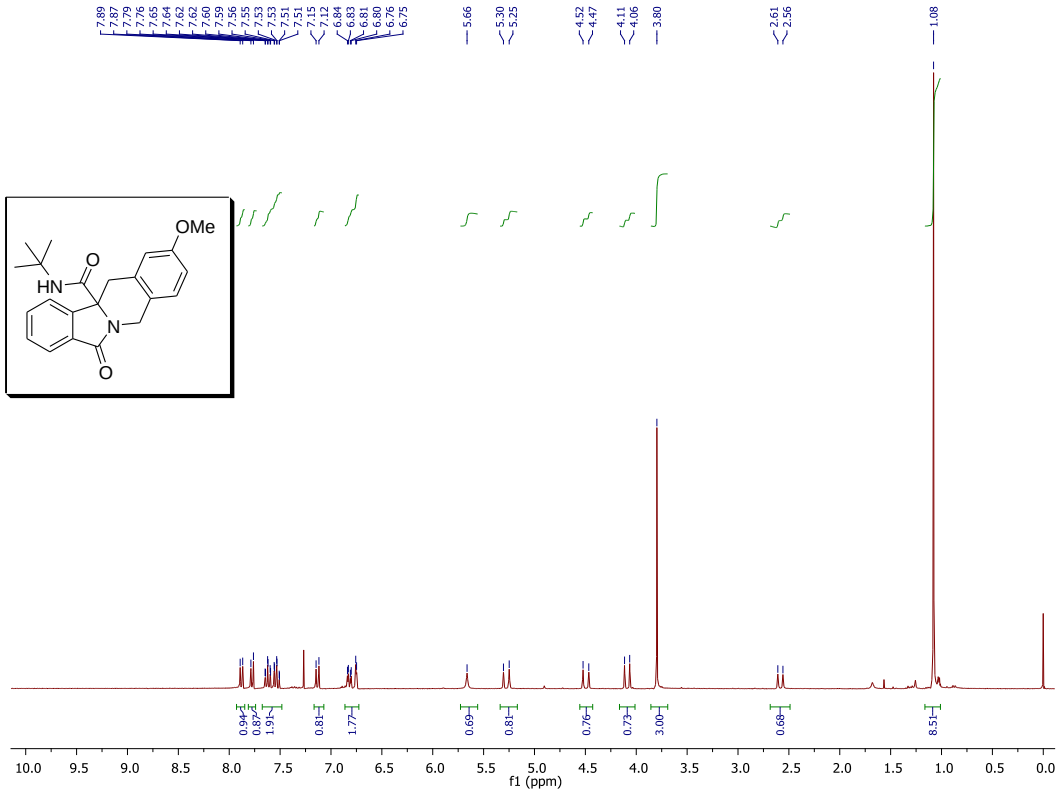



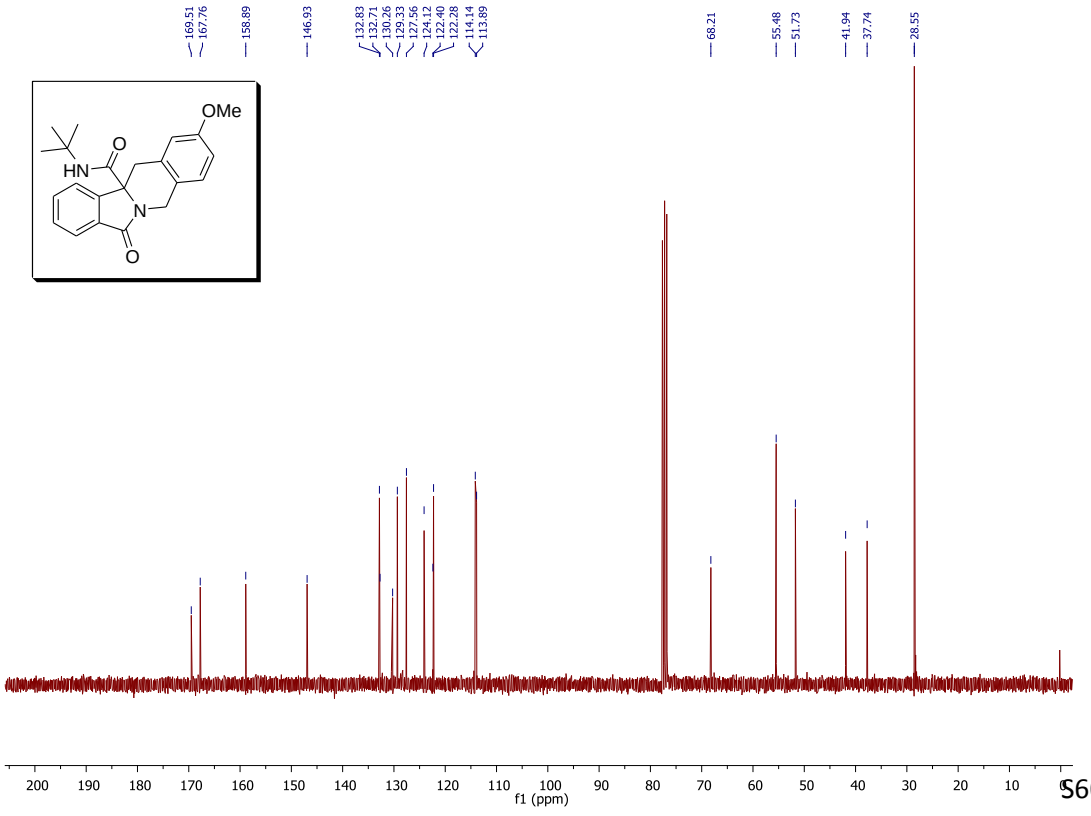
**Compound 14b,** 7-oxo-5,12-dihydro-7*H*-isoindolo[2,1-*b*]isoquinoline-11b-carboxylic acid cyclohexylamide



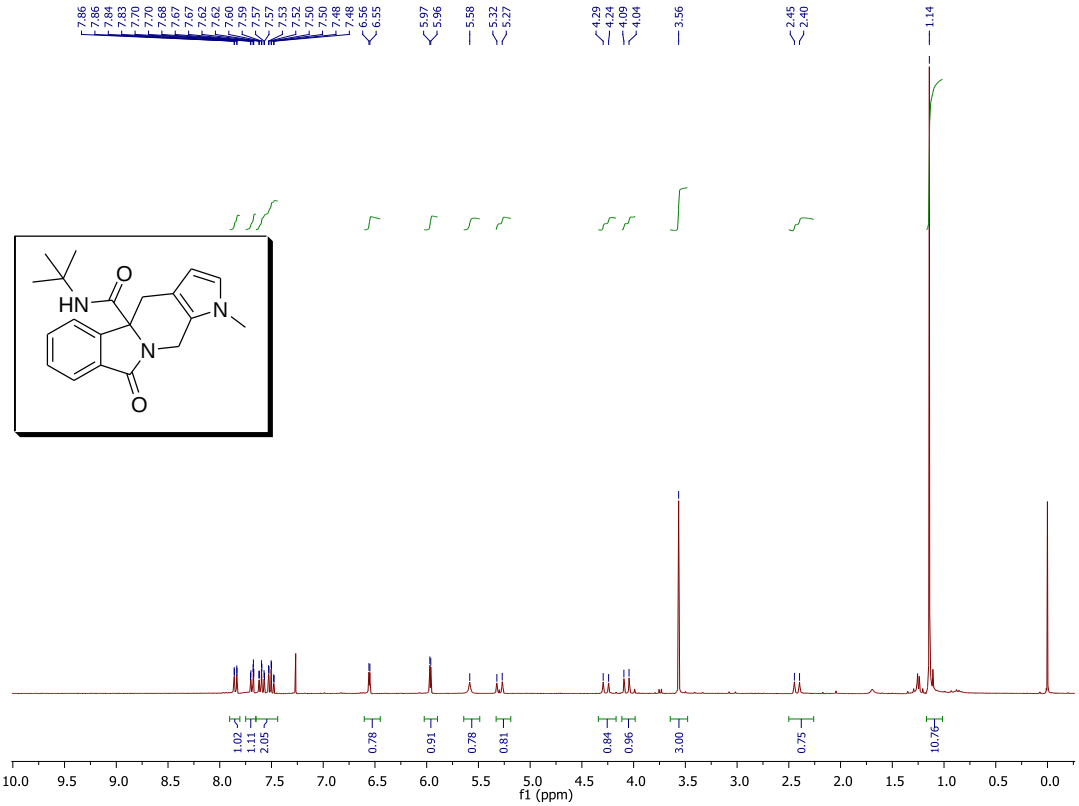



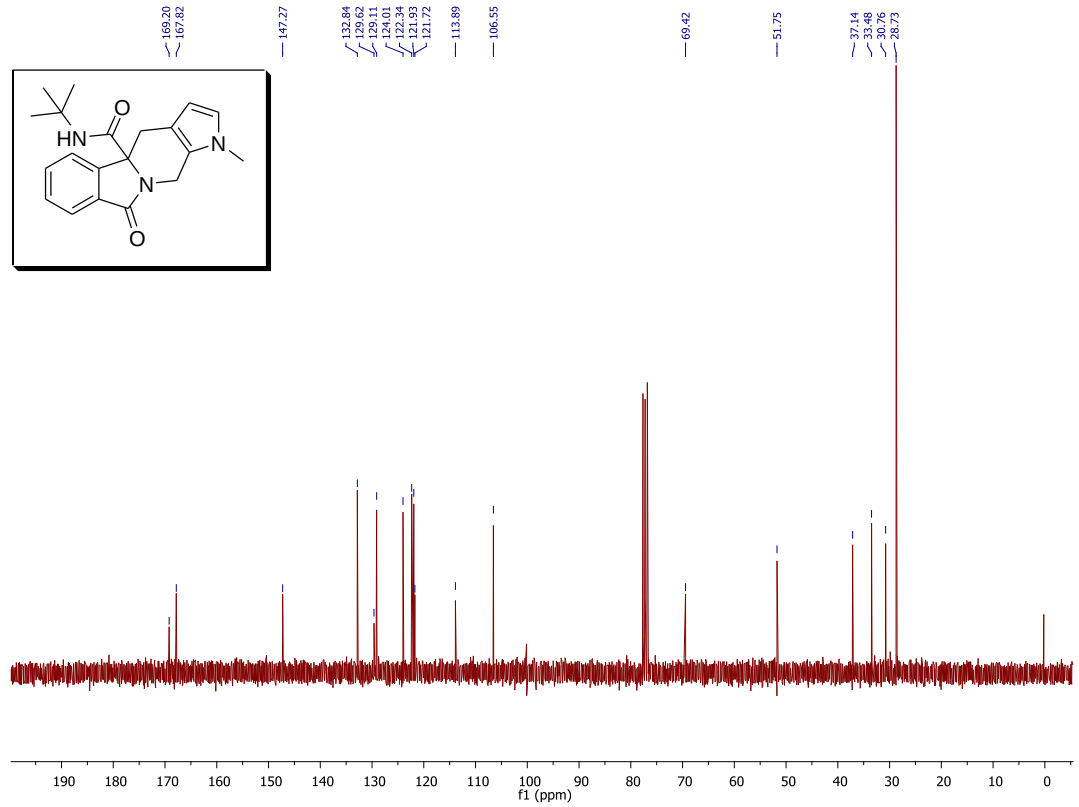
**Compound 14d,** 2-methoxy-7oxo-5,12-dihydro-7*H*-isoindolo[2,1-*b*]isoquinoline-11b-carboxylic acid *tert*-butylamide



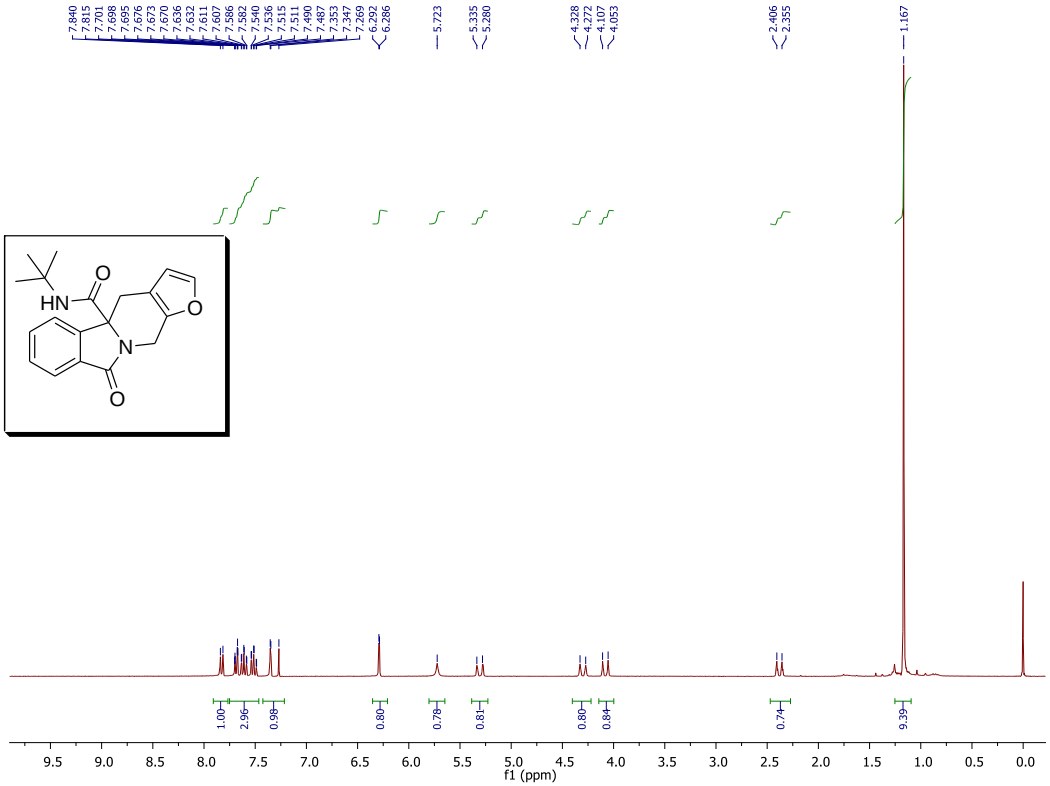



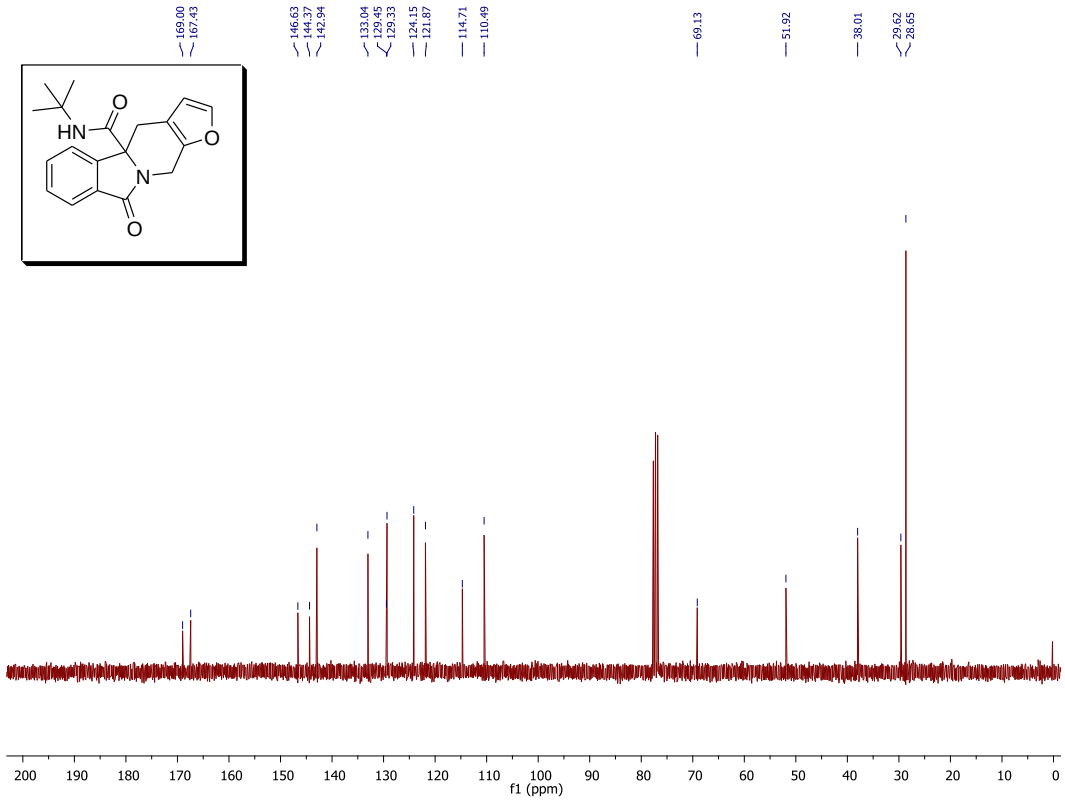
**Compound 14e,** 1-methyl-9-oxo-4,10-dihydro-1*H*,9*H*-1,9a-diaza-cyclopenta[*b*]fluorene-4a-carboxylic acid *tert*-butylamide



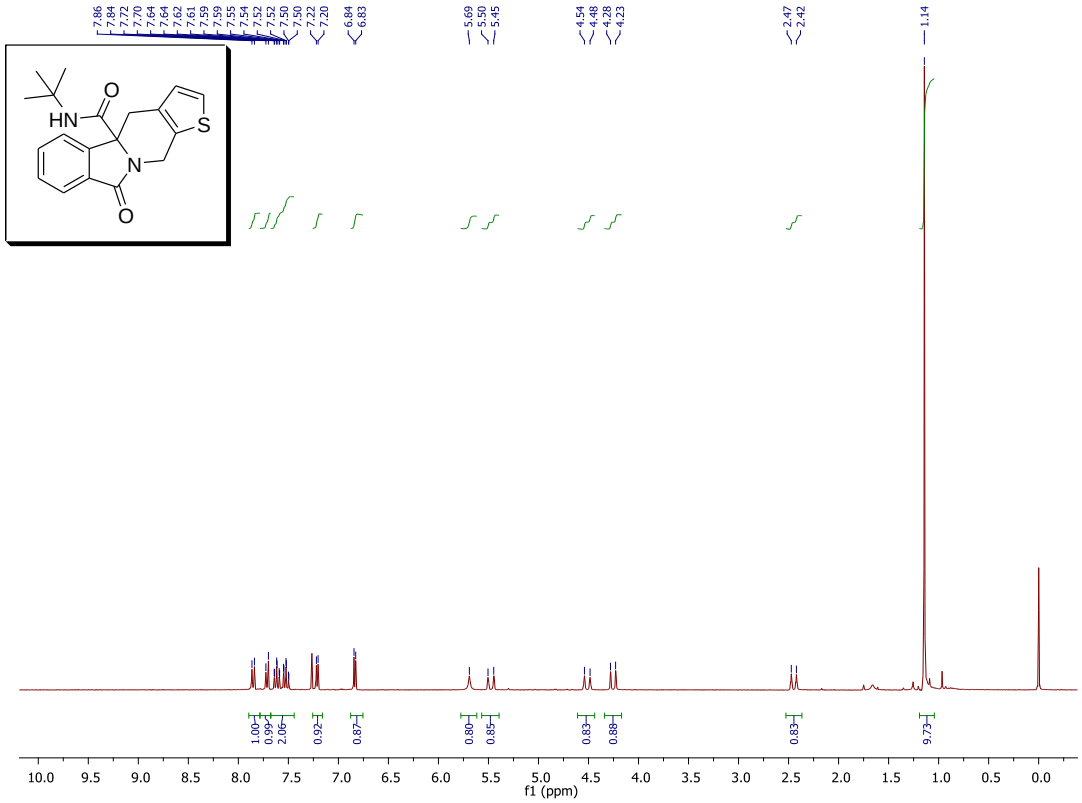



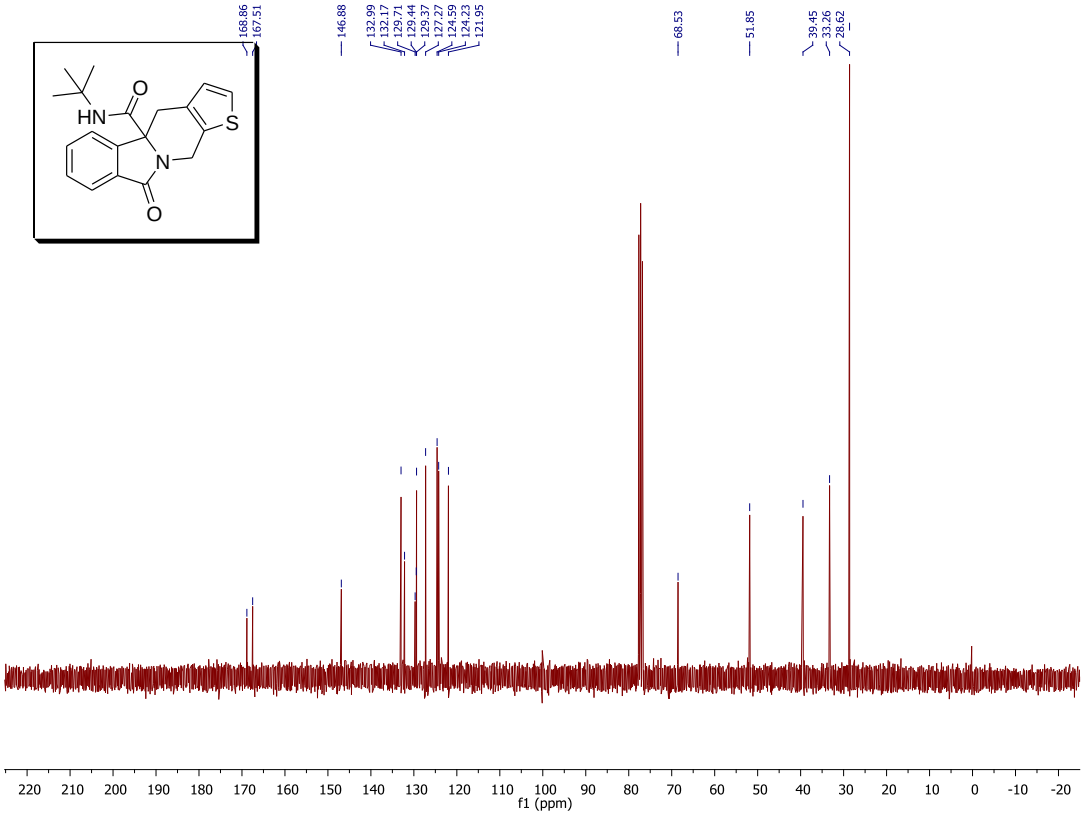
**Compound 14f,** 9-oxo-4,10-dihydro-9*H*-1-oxa-9a-aza-cyclopenta[*b*]fluorene-4a-carboxylic acid *tert*-butylamide



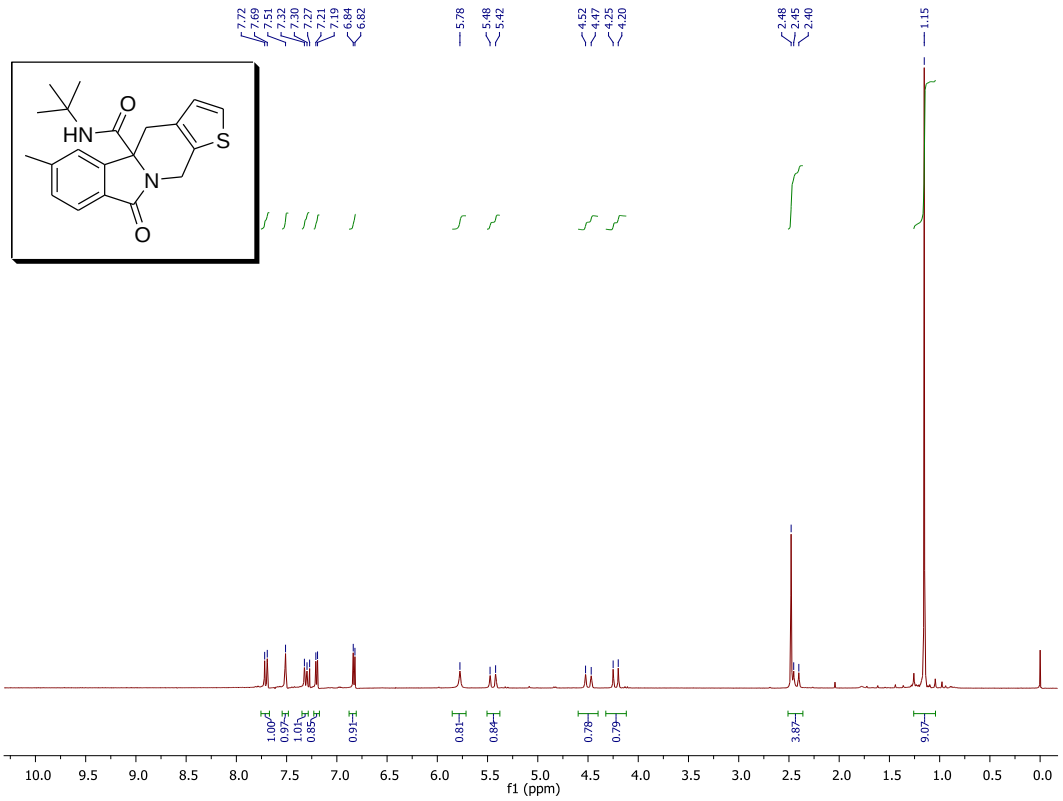



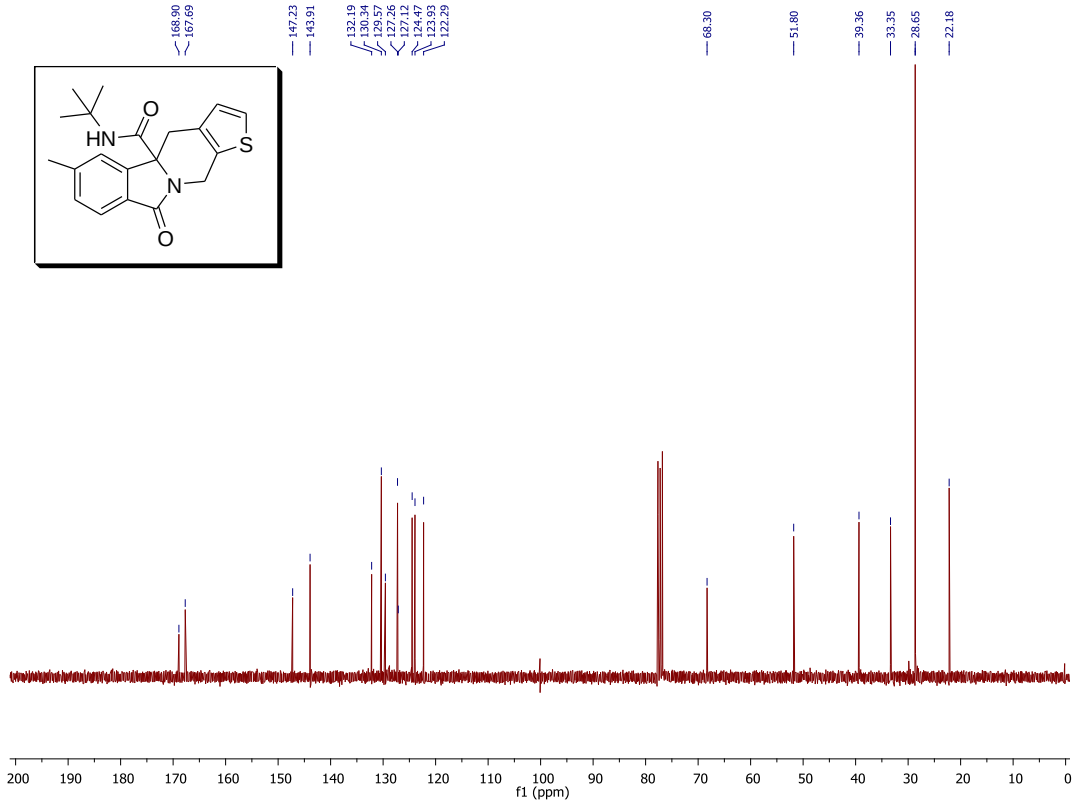
**Compound 14g,** 9-oxo-4,10-dihydro-9*H*-1-thia-9a-aza-cyclopenta[*b*]fluorene-4a-carboxylic acid *tert*-butylamide



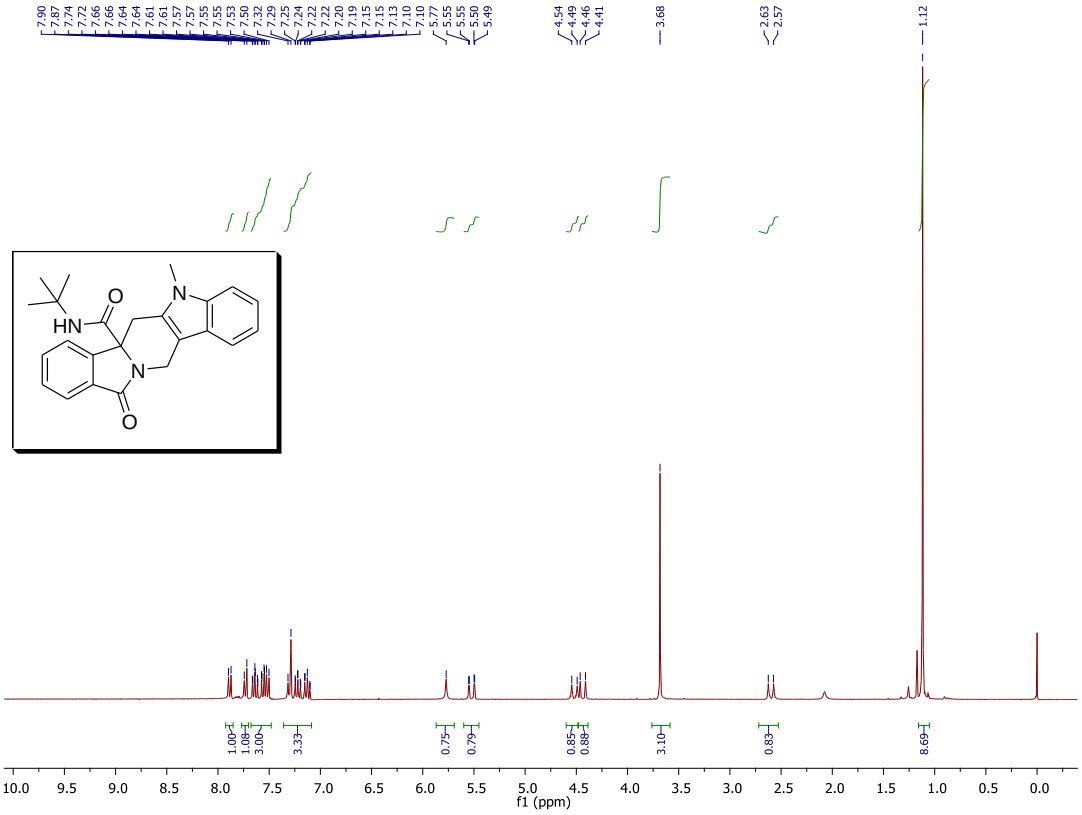



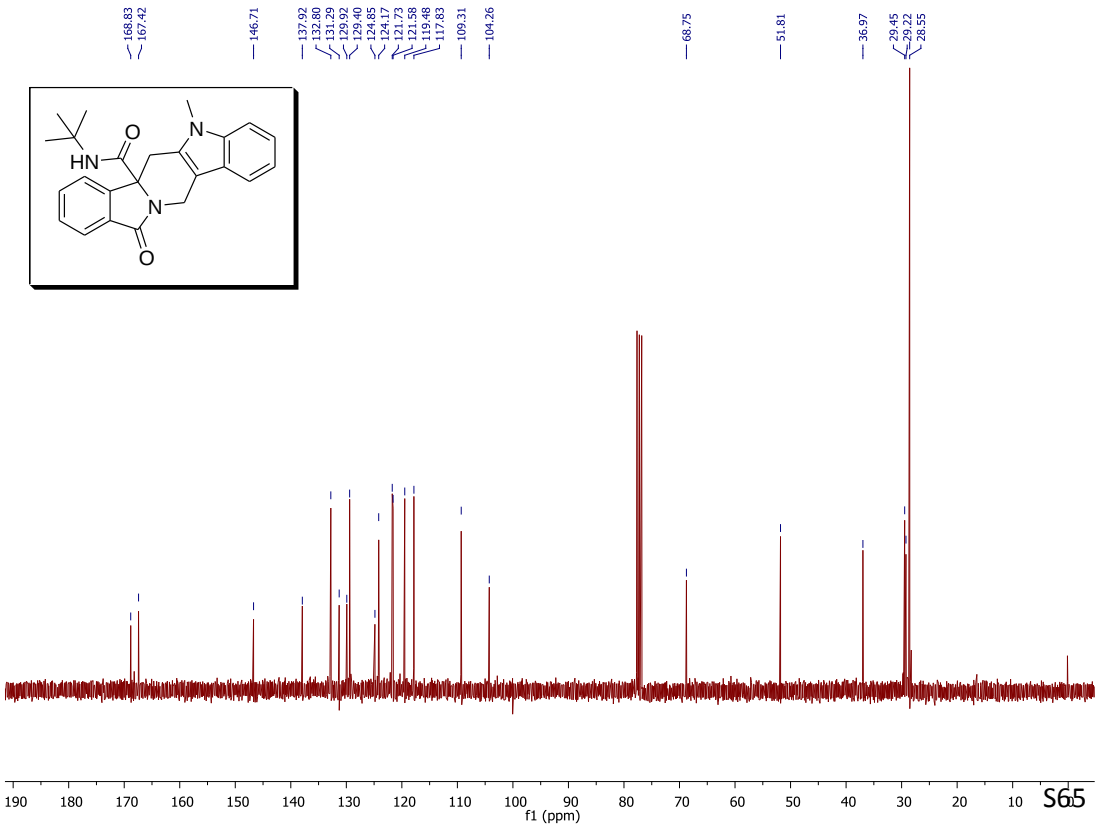
**Compound 14h,** 6-methyl-9-oxo-4,10-dihydro-9*H*-1-thia-9a-aza-cyclopenta[*b*]fluorene-4a-carboxylic acid *tert*-butylamide



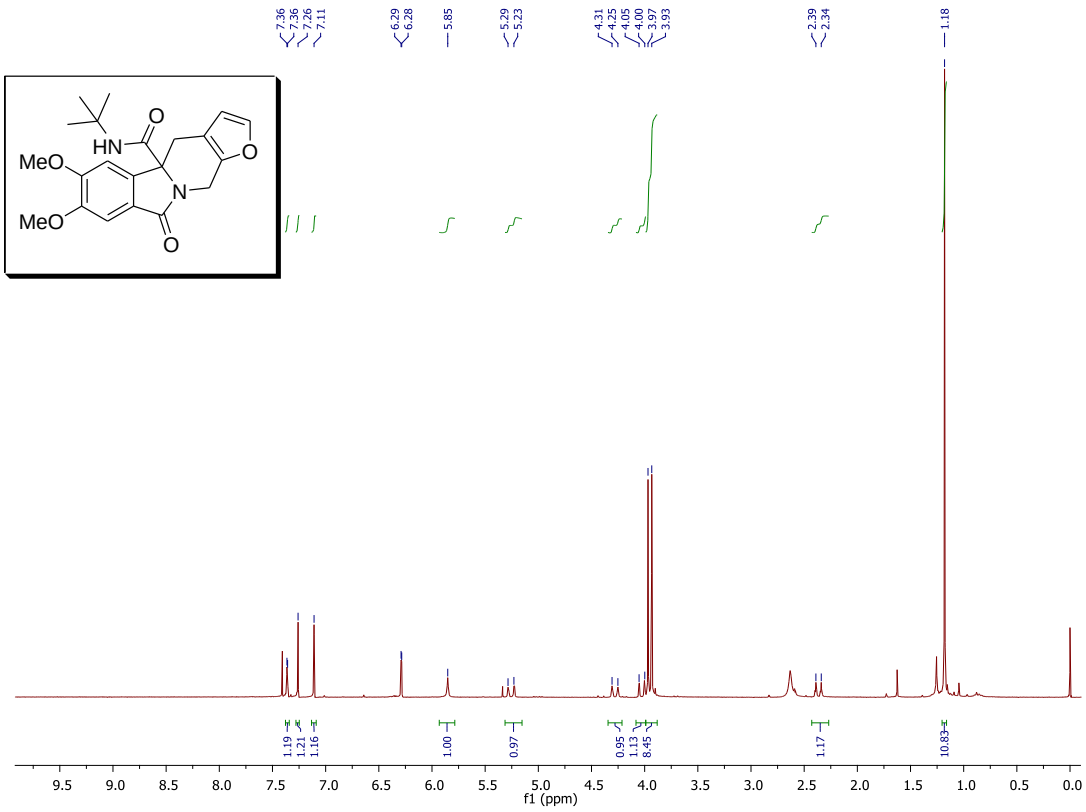



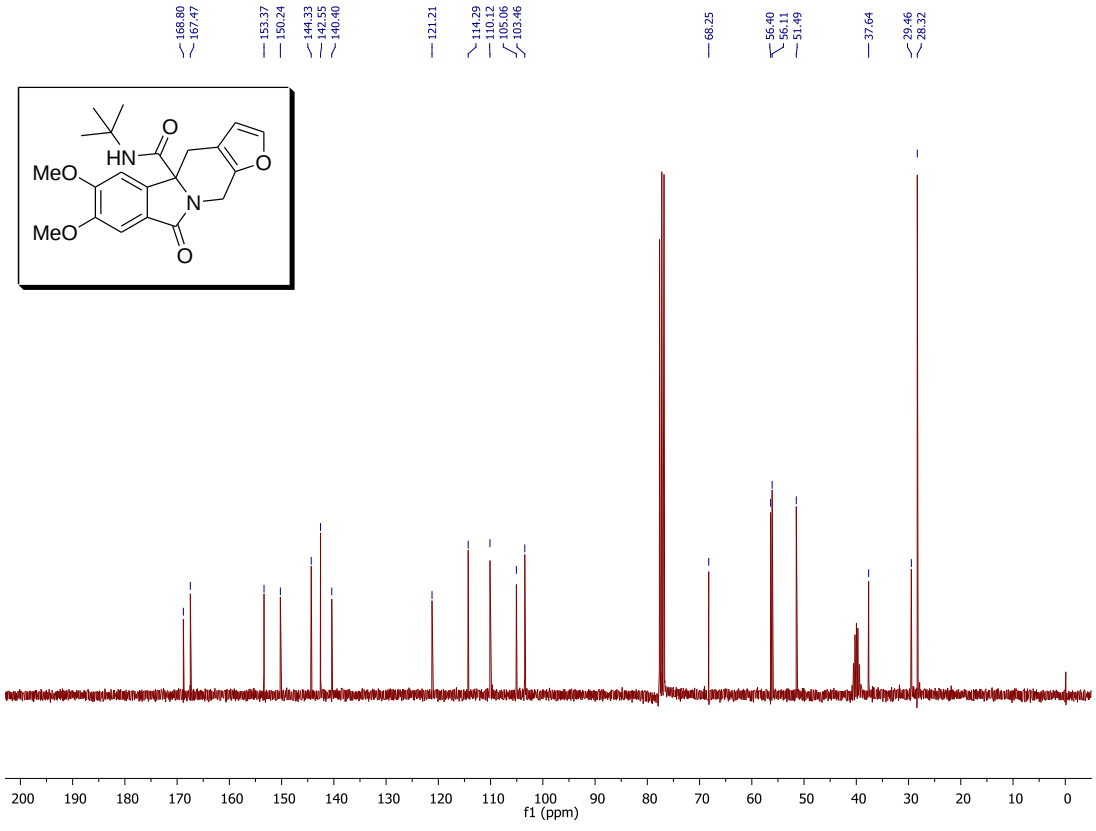
**Compound 14i,** 12-methyl-6-oxo-11,12-dihydro-5*H*-6*H*-5a,12-diaza-indeno[1,2-*b*]fluorene-10b-carboxylic acid *tert*-butylamide



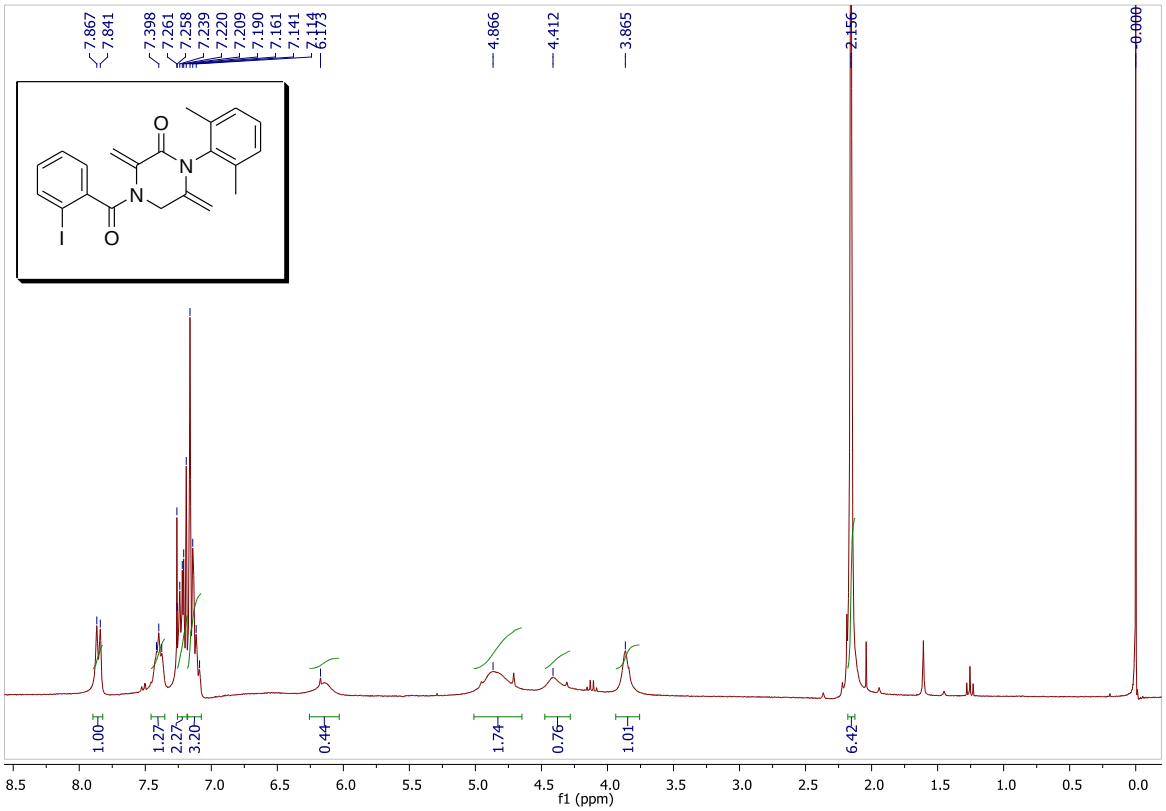



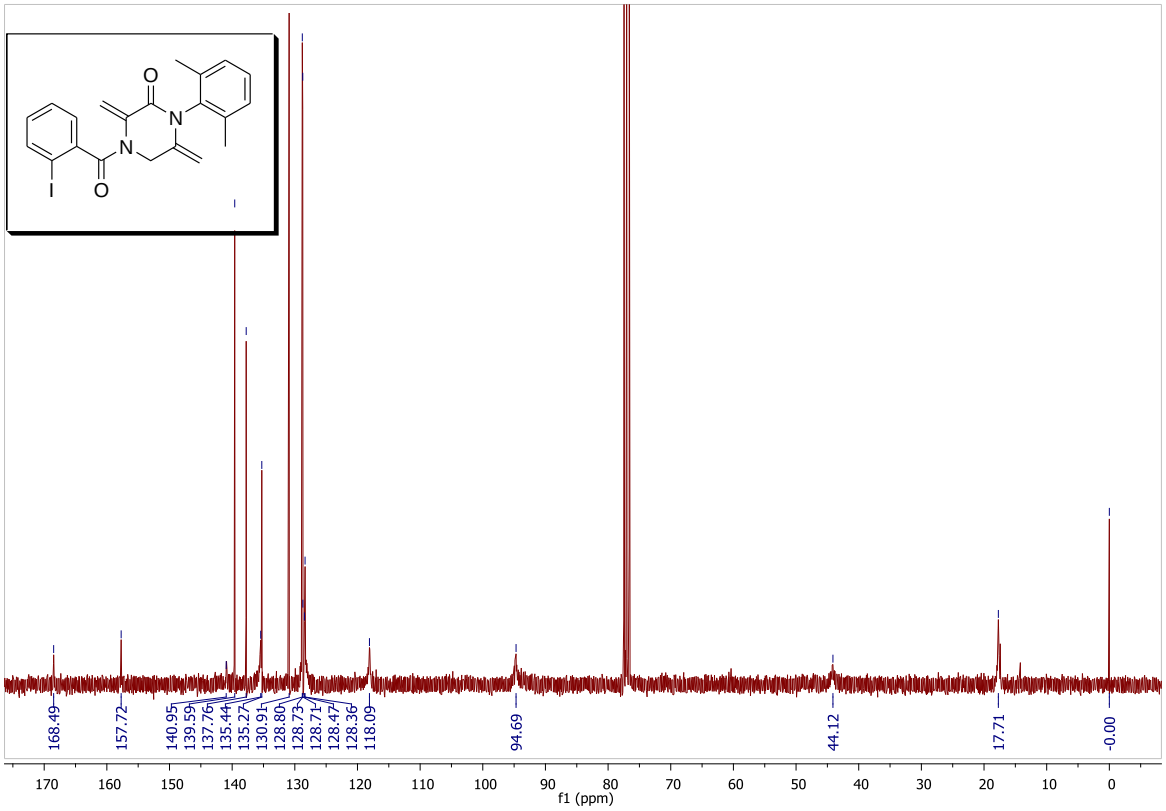
**Compound 14j,** 6,7-dimethoxy-9-oxo-4,10-dihydro-9*H*-1-oxa-9a-aza-cyclopenta[*b*]fluorene-4a-carboxylic acid *tert*-butylamide



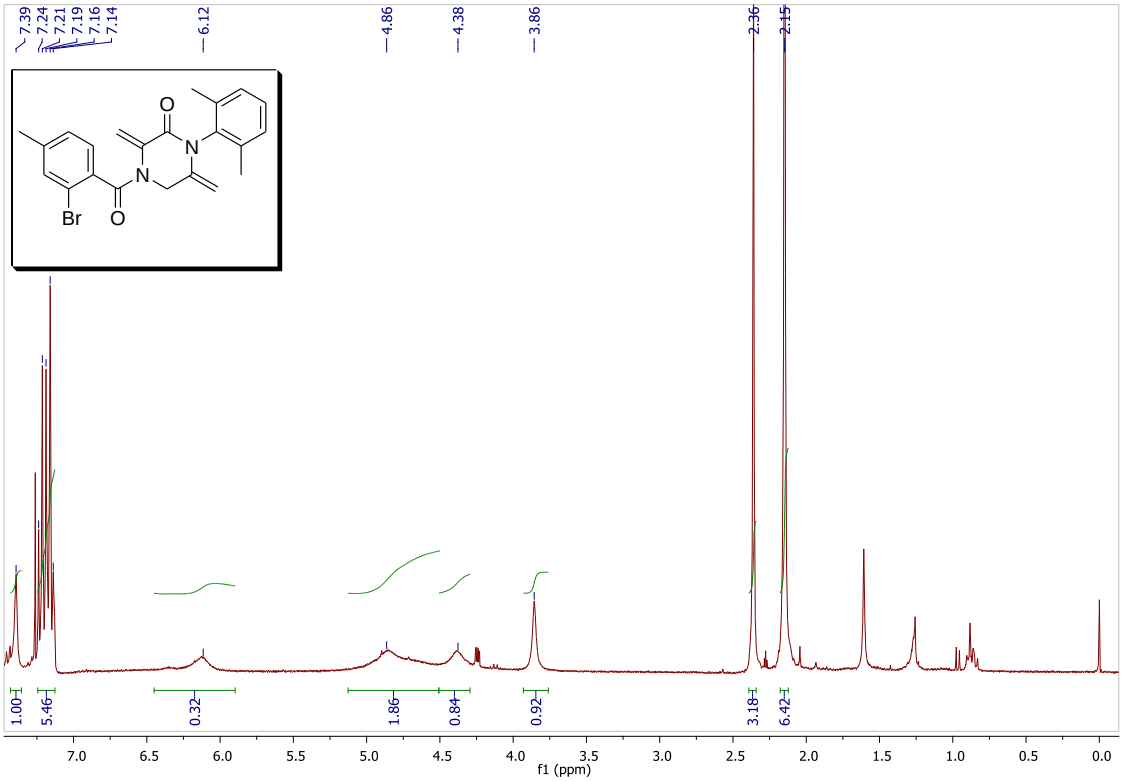



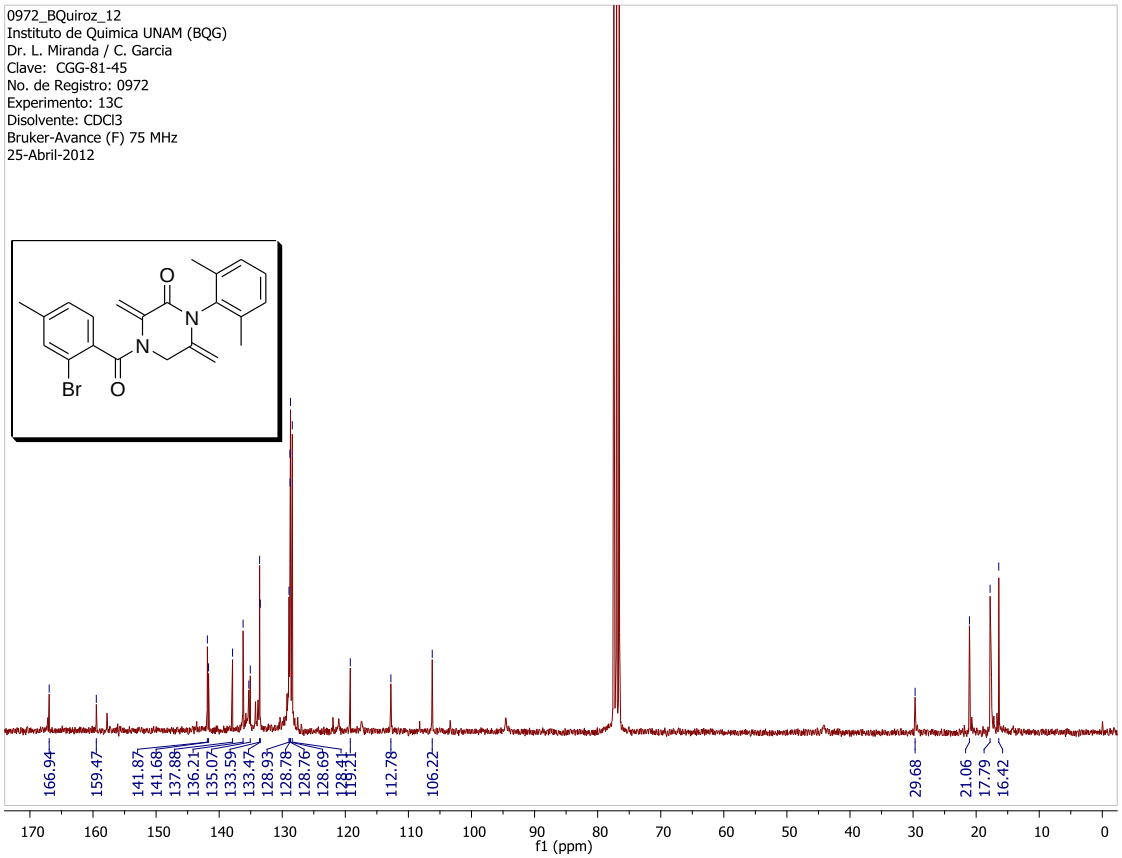
**Compound 17a**, 1-(2,6-dimethyl-phenyl)-4-(2-iodo-benzoyl)-3,6-dimethylene-piperazin-2-one



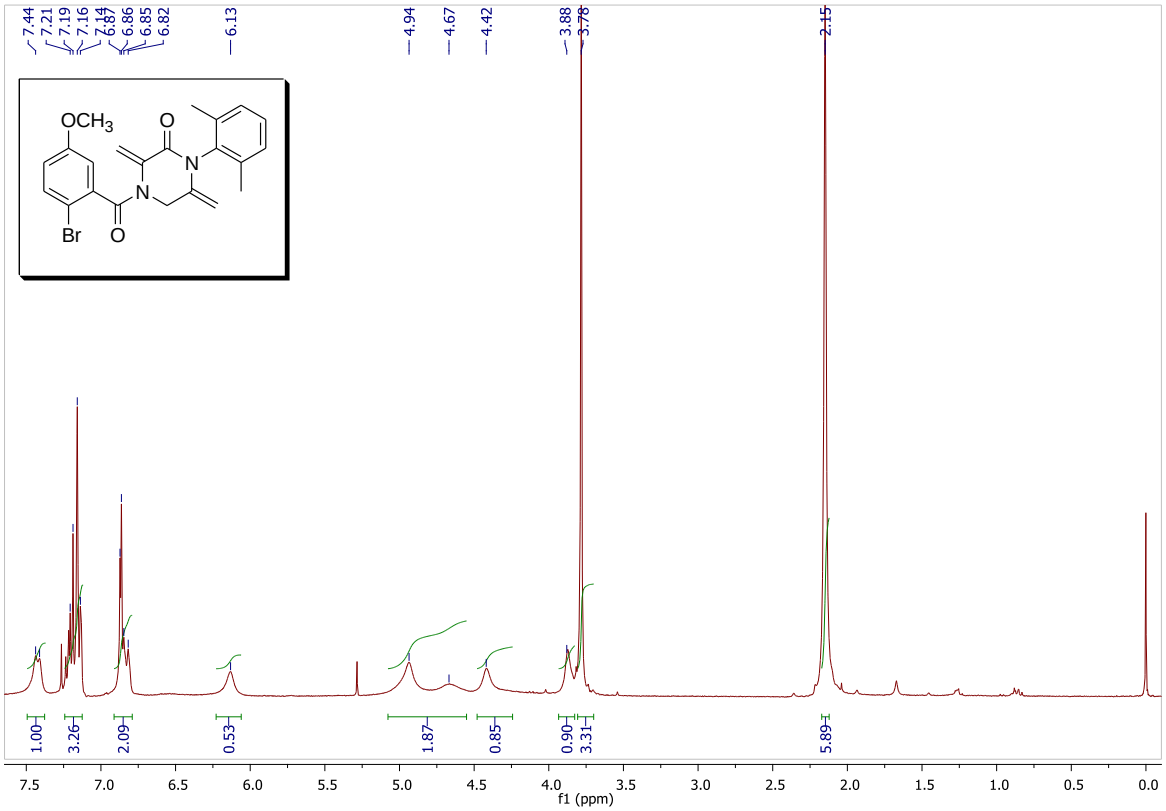



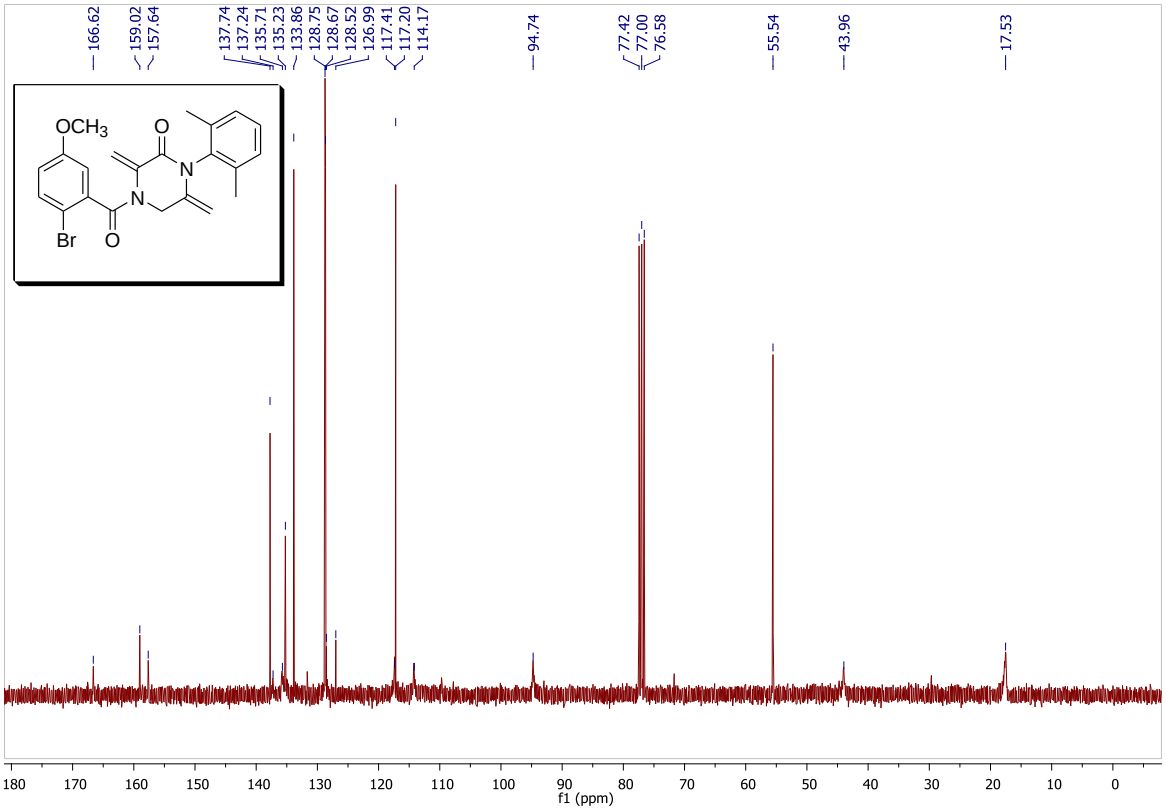
**Compound 17b,** 4-(2-bromo-4-methyl-benzoyl)-1-(2,6-dimethyl-phenyl)-3,6-dimethylene-piperazin-2-one



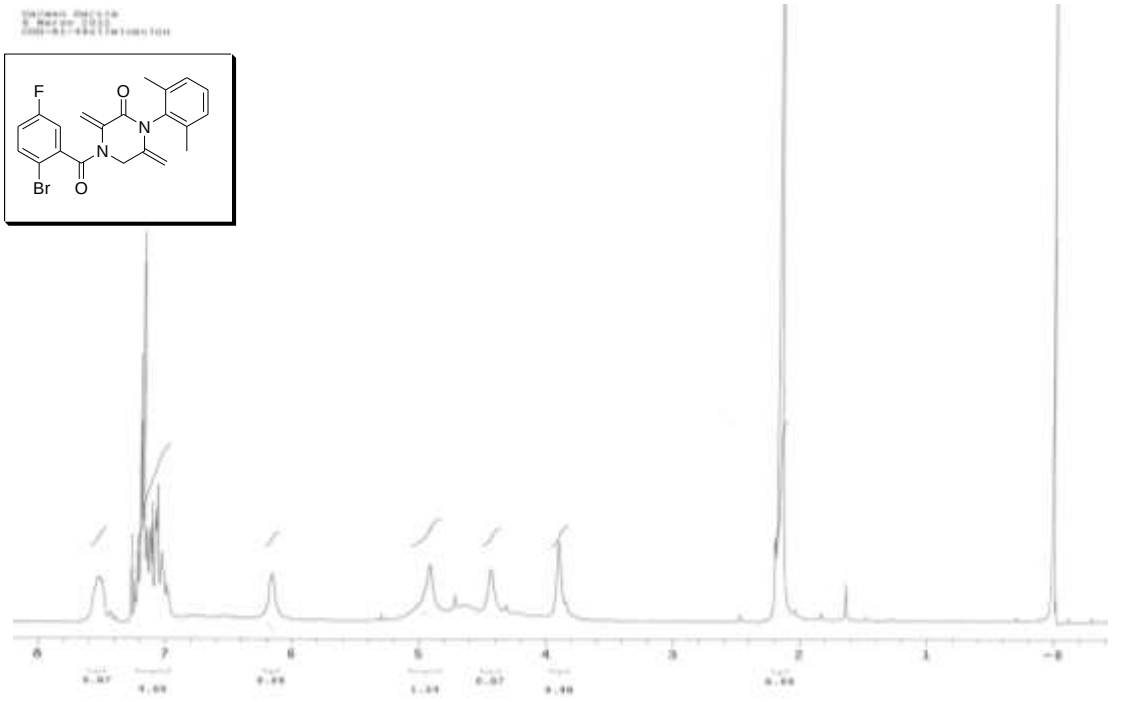



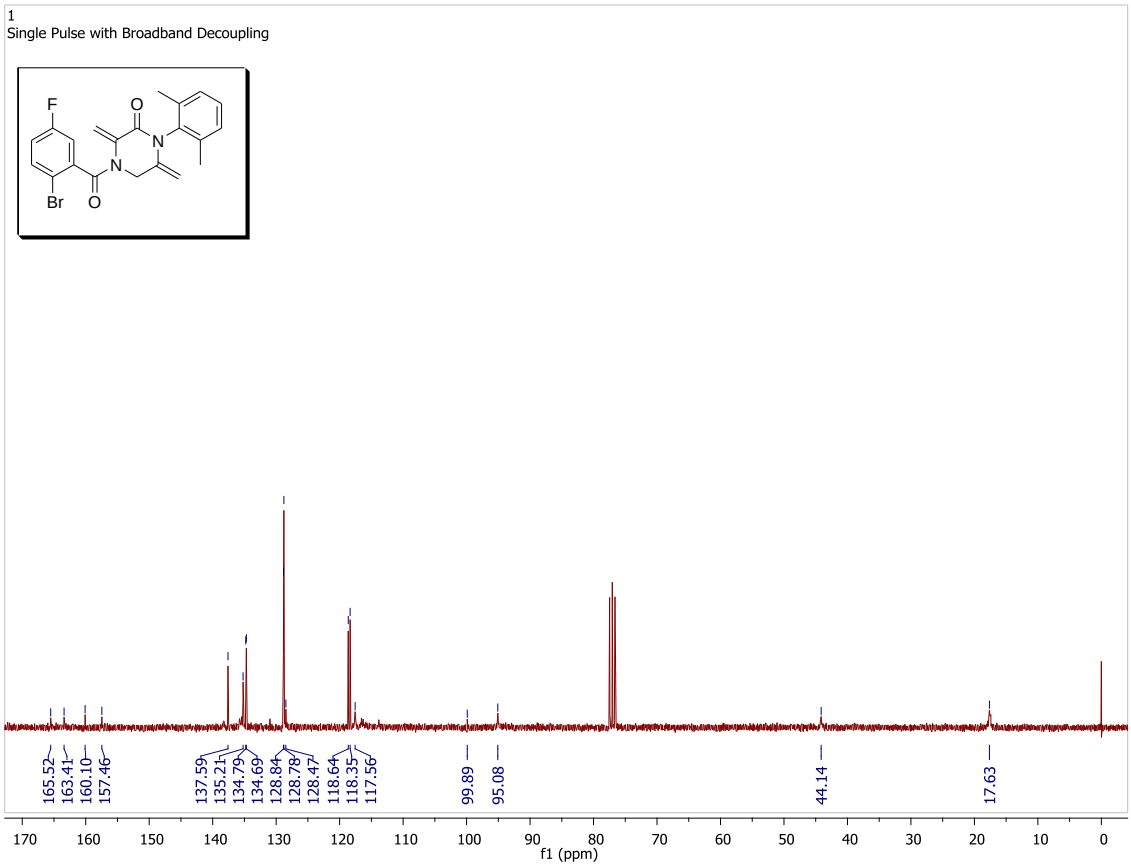
**Compound 17c,** 4-(2-bromo-5-methoxy-benzoyl)-1-(2,6-dimethyl-phenyl)-3,6-dimethylene-piperazin-2-one



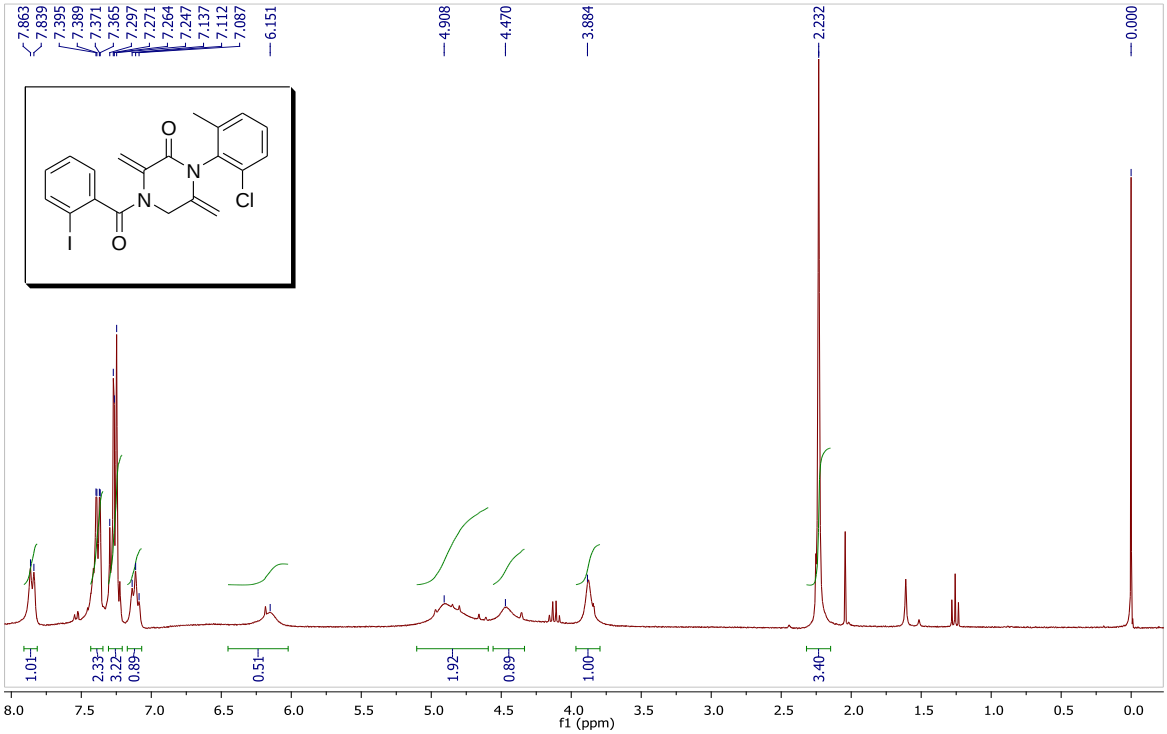



**Compound 17d,** 4-(2-bromo-5-fluoro-benzoyl)-1-(2,6-dimethyl-phenyl)-3,6-dimethylene-piperazin-2-one

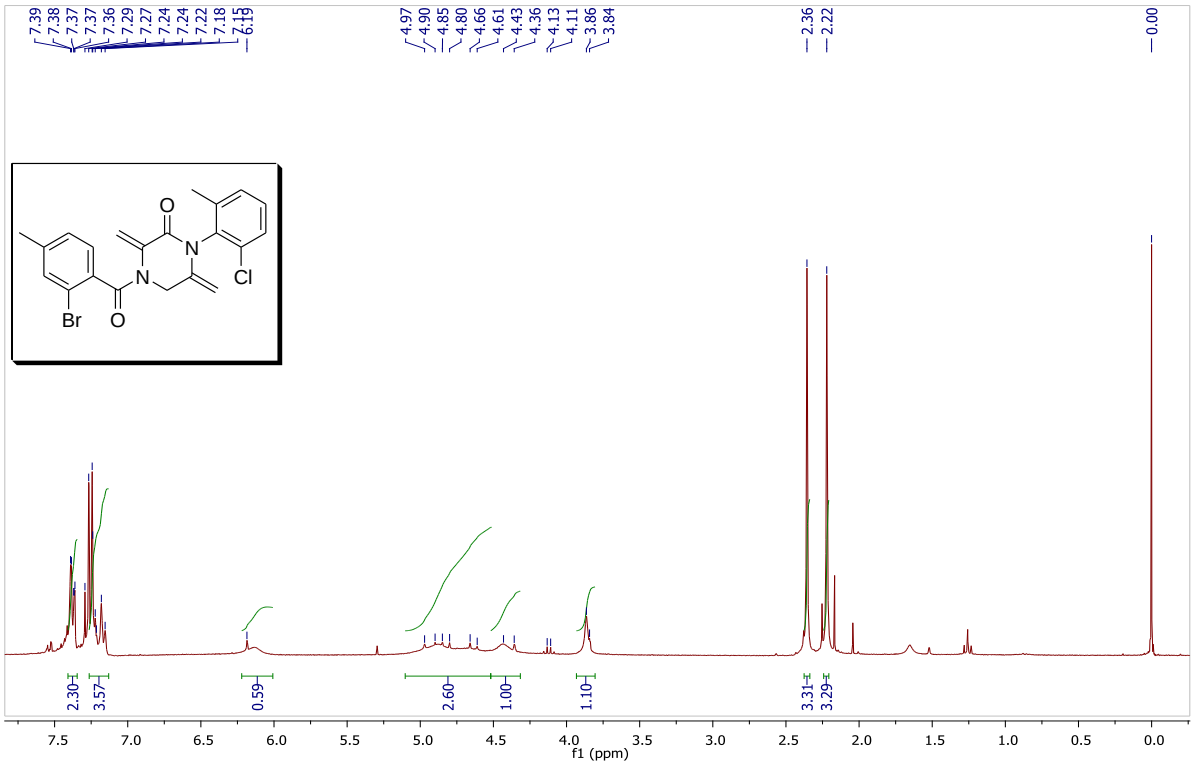


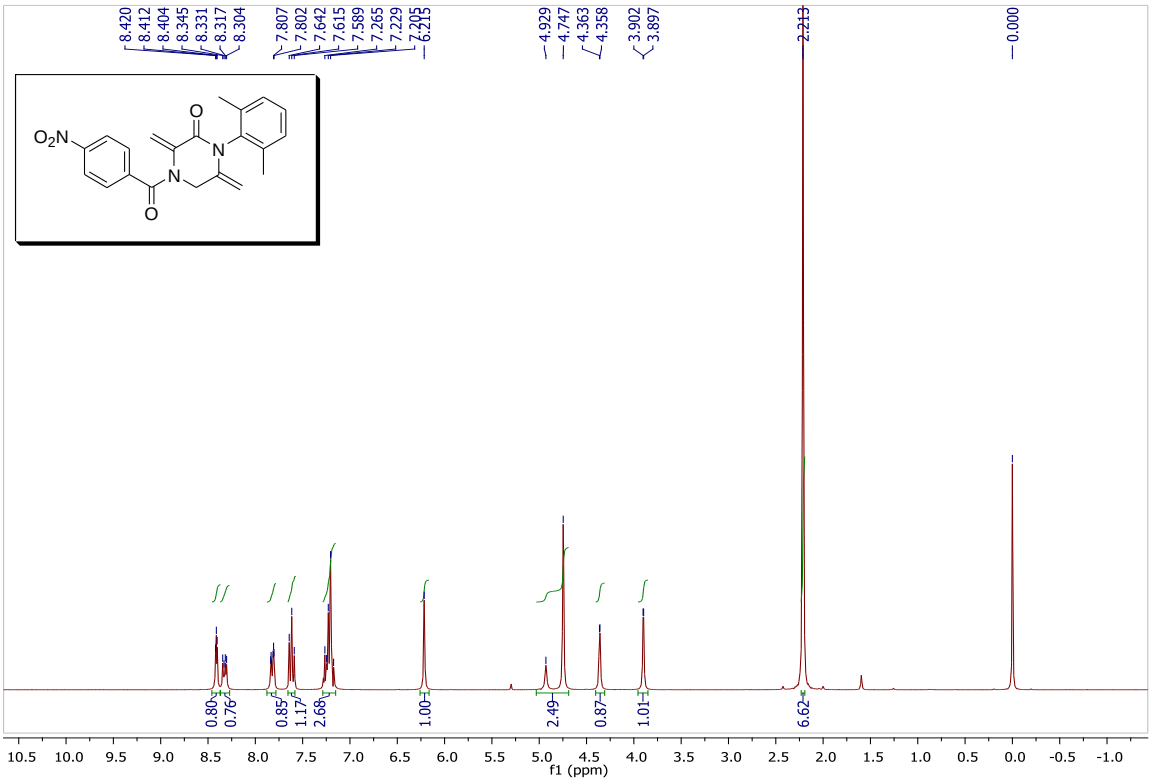
**Compound 17e,** 1-(2-chloro-6-methyl-phenyl)-4-(2-iodo-benzoyl)-3,6-dimethylene-piperazin-2-one

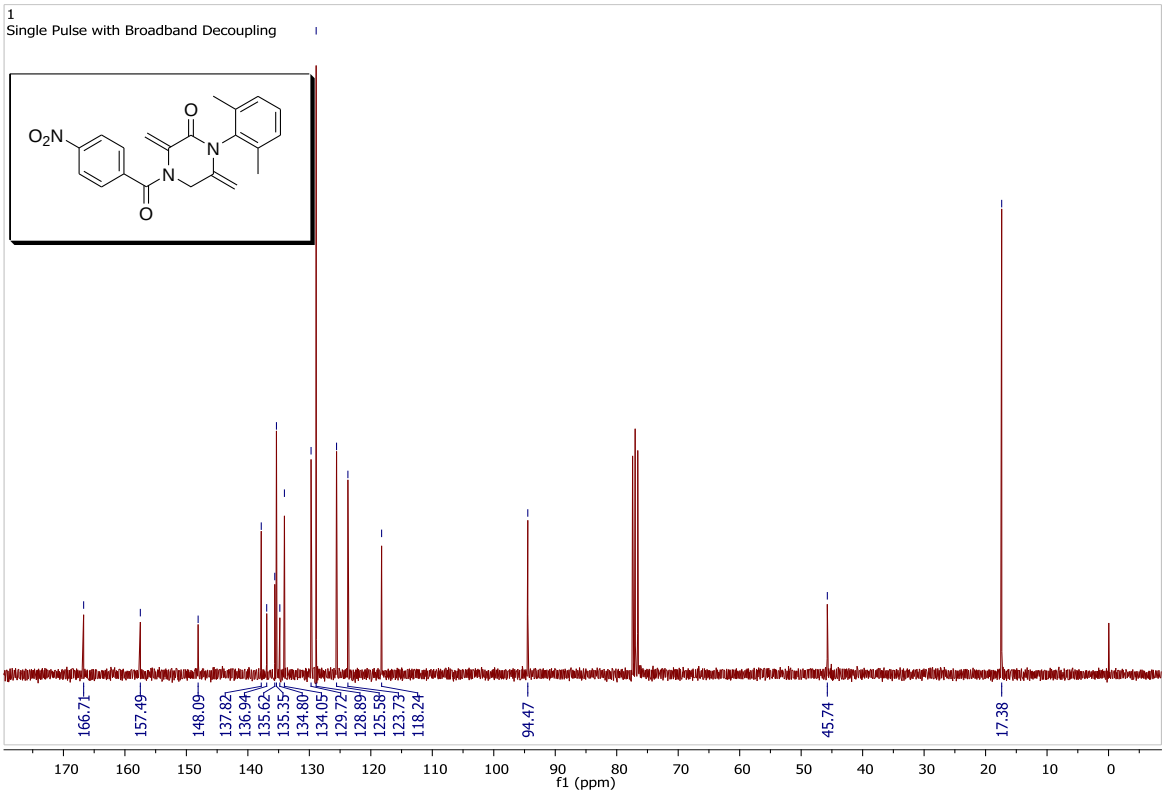



**Compound 17f,** 4-(2-bromo-4-methyl-benzoyl)-1-(2-chloro-6-methyl-phenyl)-3,6-dimethylene-piperazin-2-one

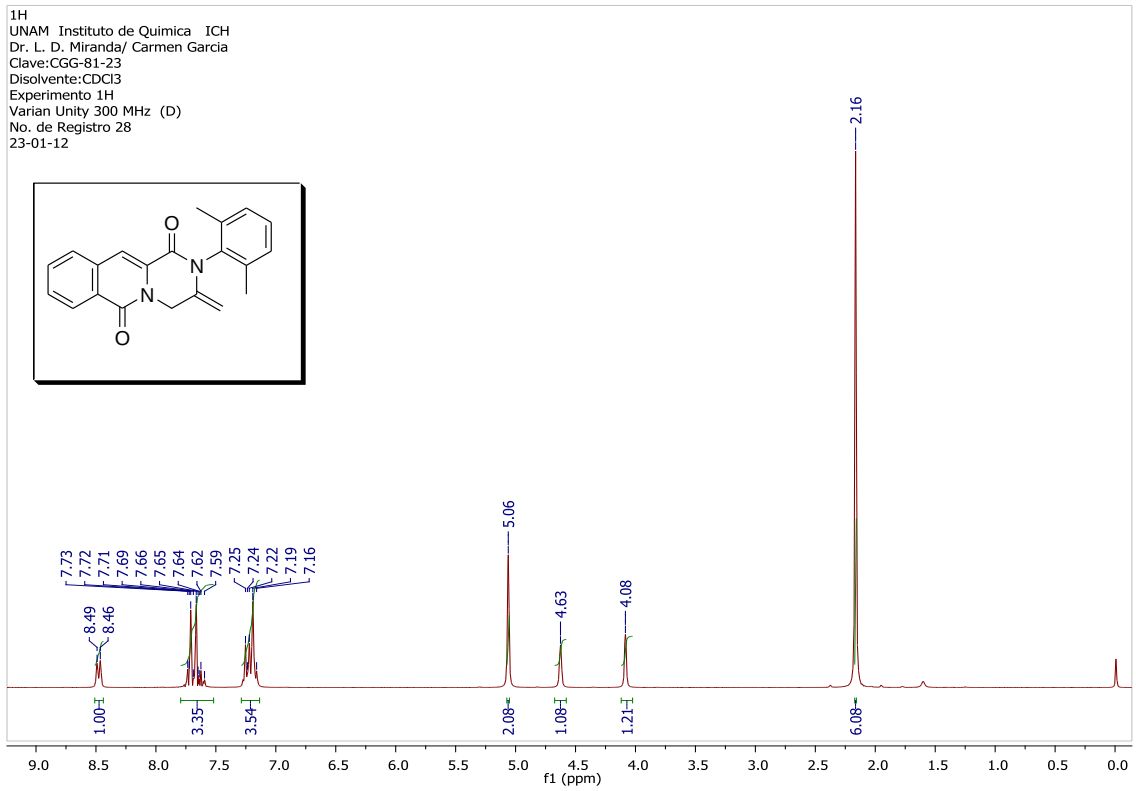


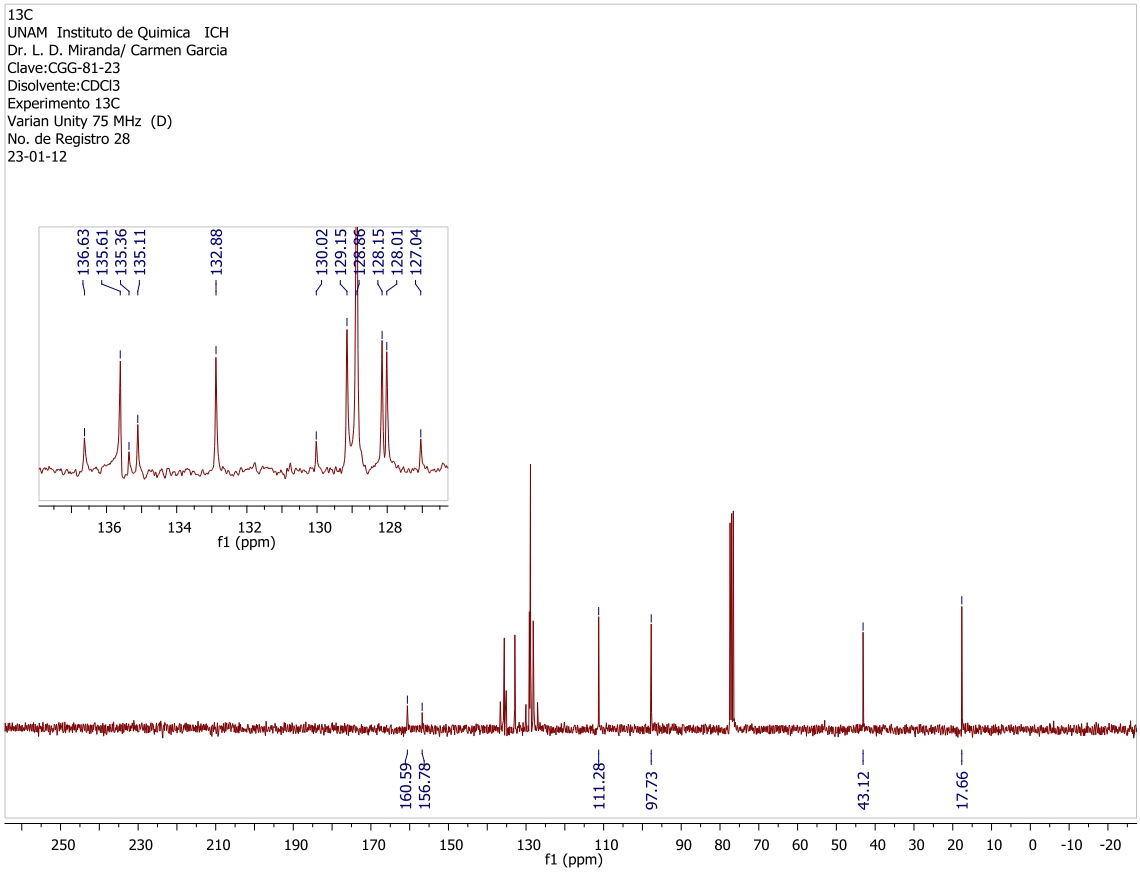
**Compound 17g,** 1,-(2,6-dimethyl-phenyl)-3,6-dimethylene-4-(4-nitro-benzoyl)-piperazin-2-one



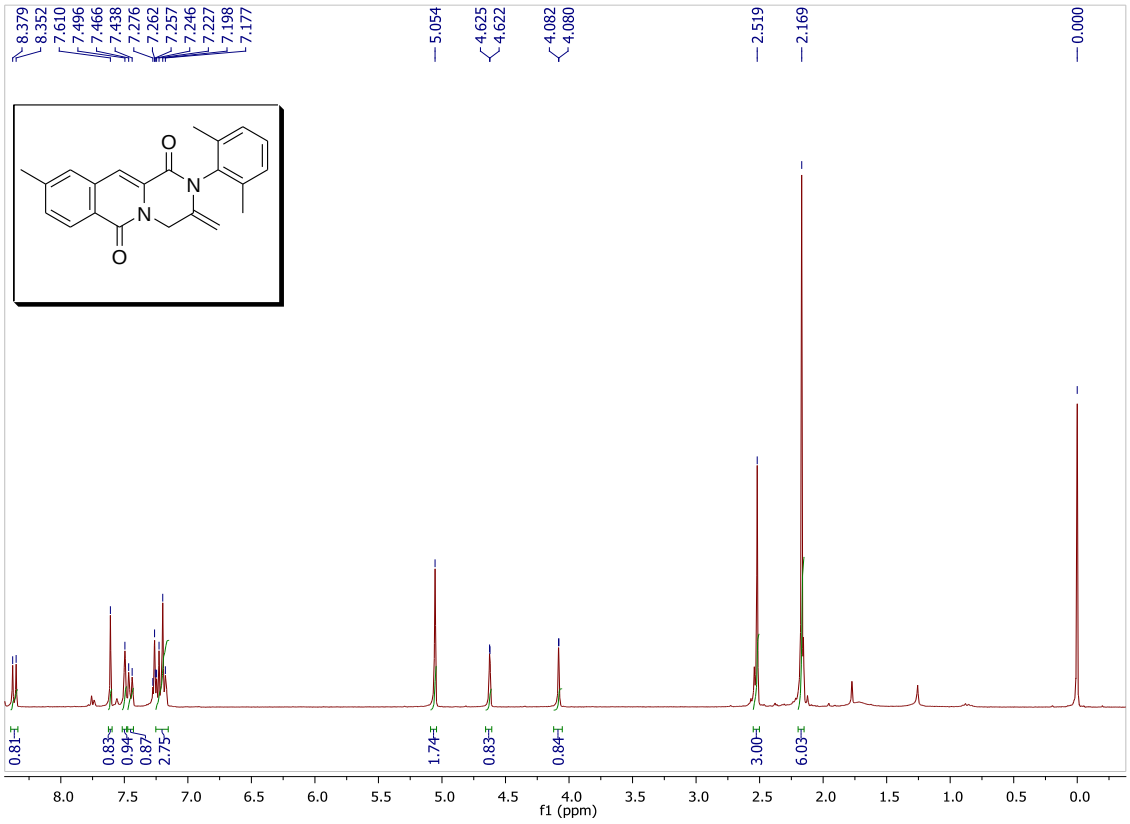



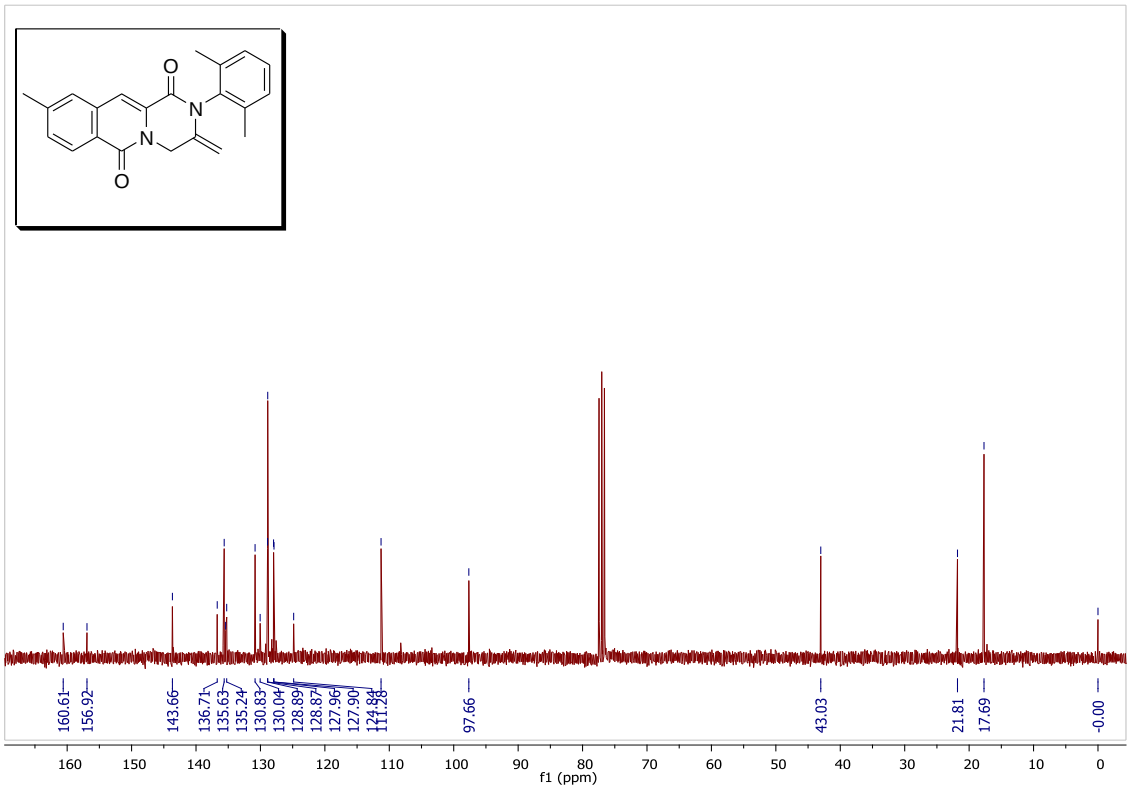
**Compound 18a,** 2-(2,6-dimethyl-phenyl)-3-methylene-3,4-dihydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,6-dione



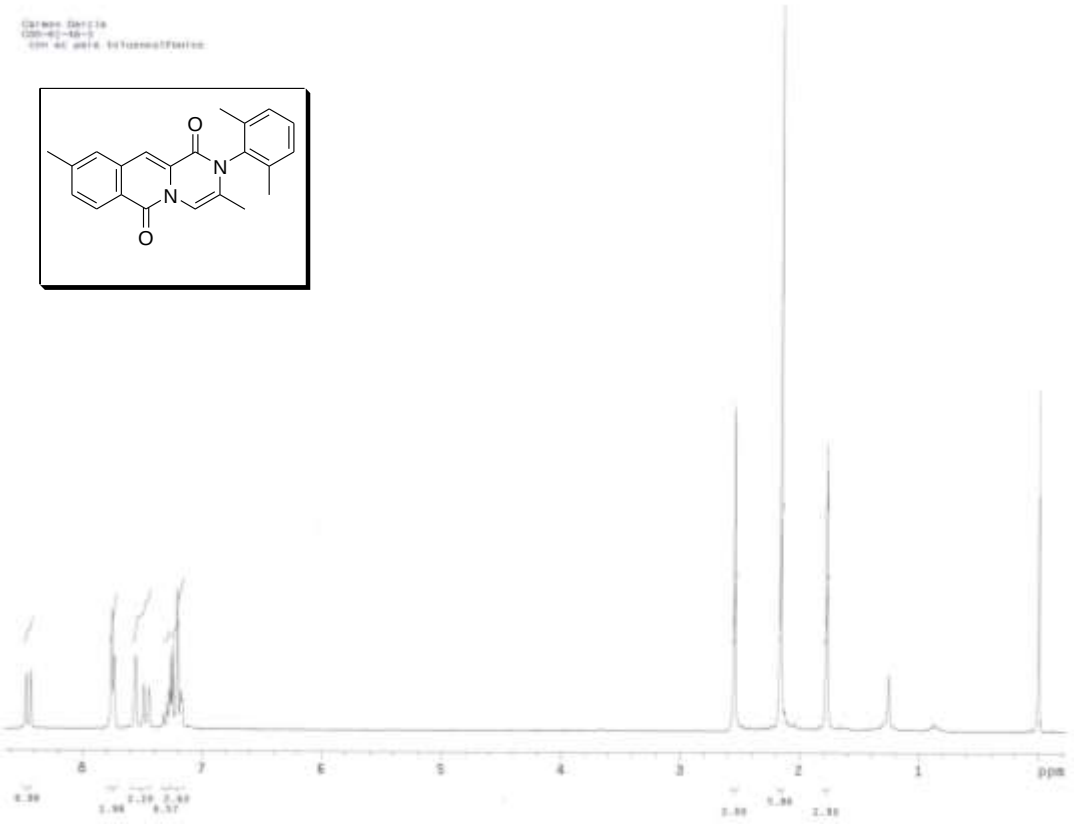



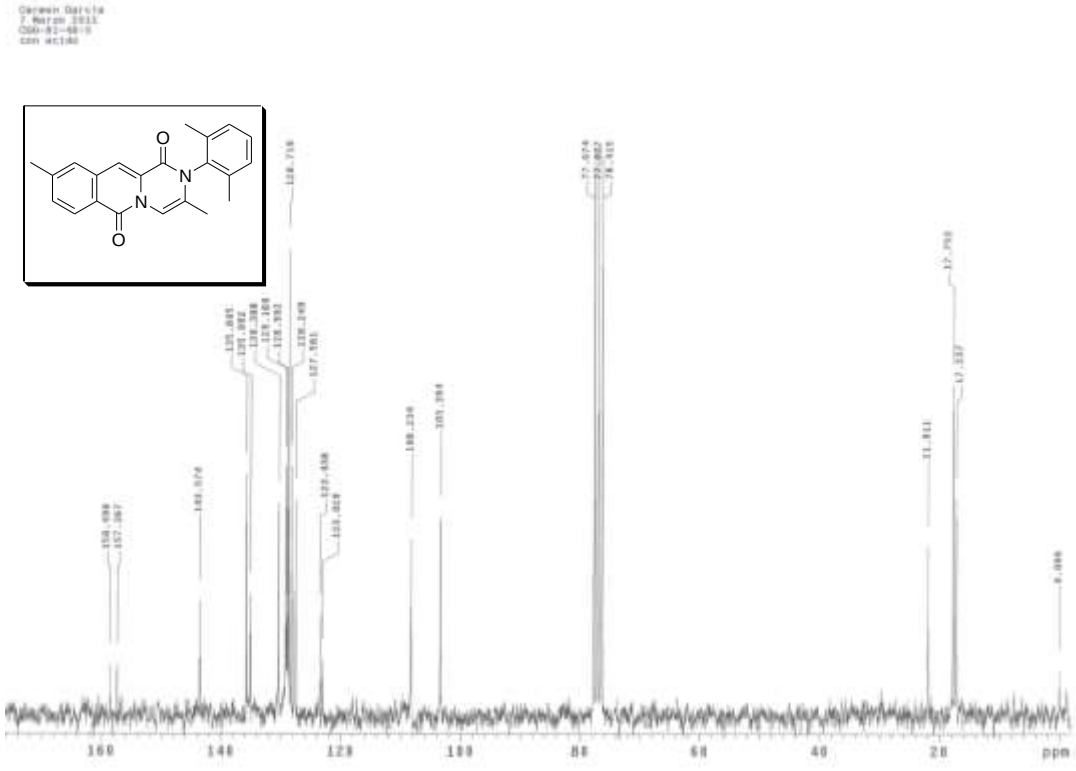
**Compound18b-exo,** 2-(2,6-dimethyl-phenyl)-9-methyl-3-methylene-3,4-dihydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,6-dione



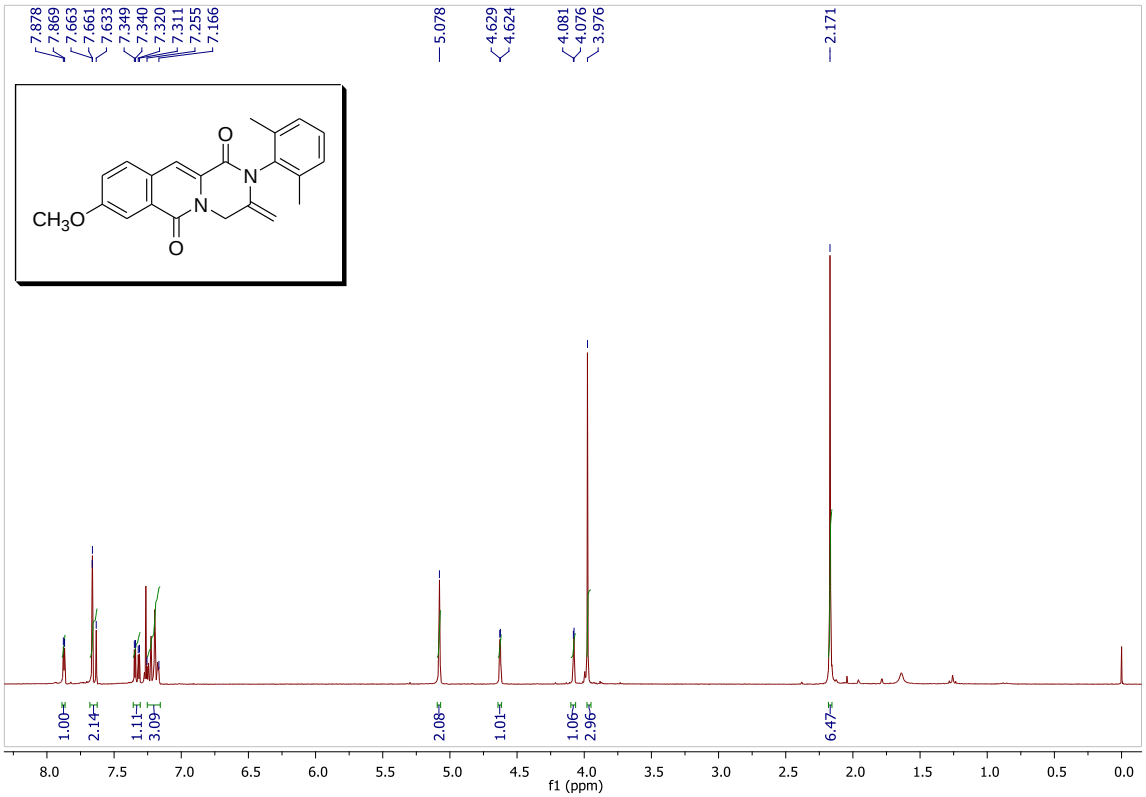



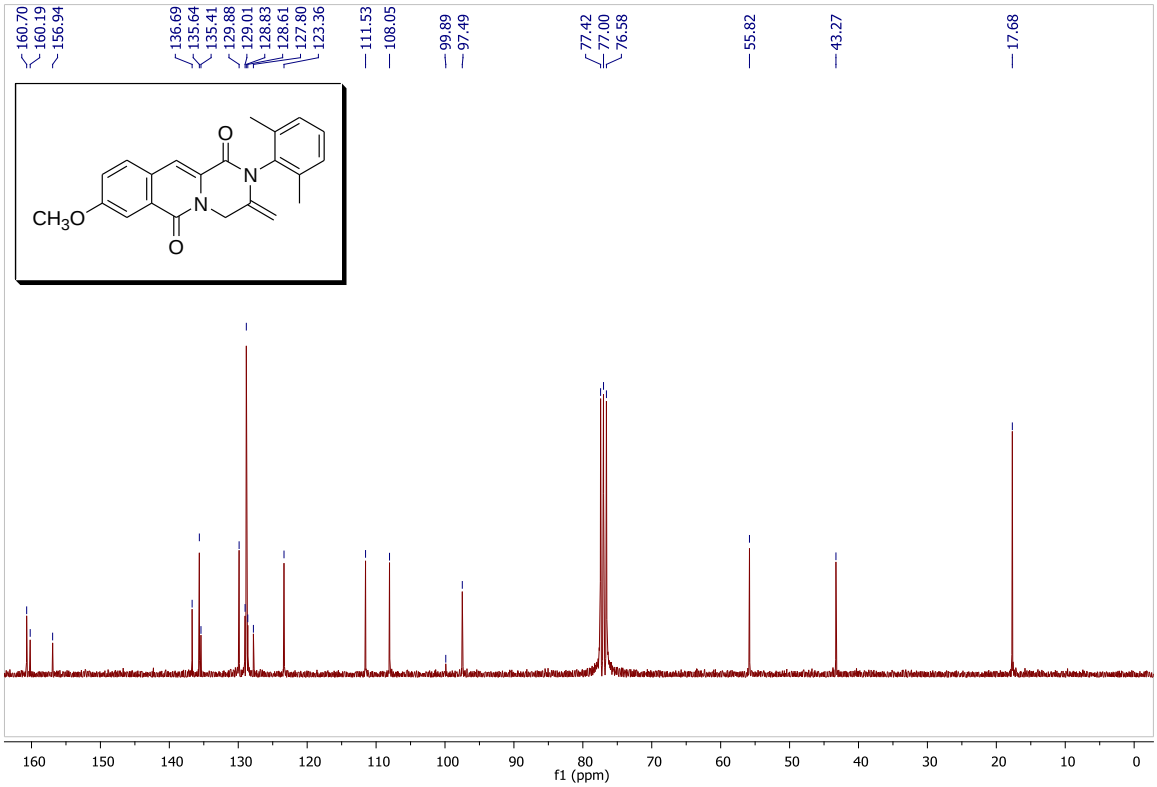
**Compound18b-endo,** 2-(2,6-dimethyl-phenyl)-3,9-dimethyl-2*H*-pyrazino[1,2-*b*]isoquinoline-1,6-dione



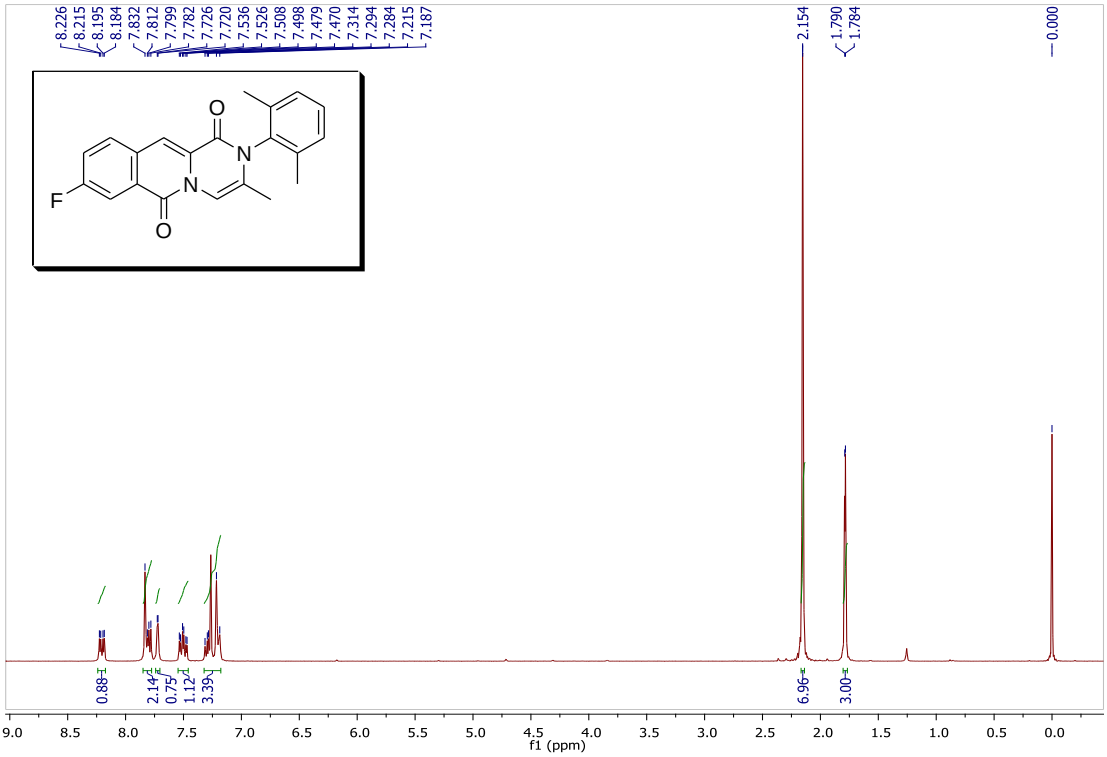


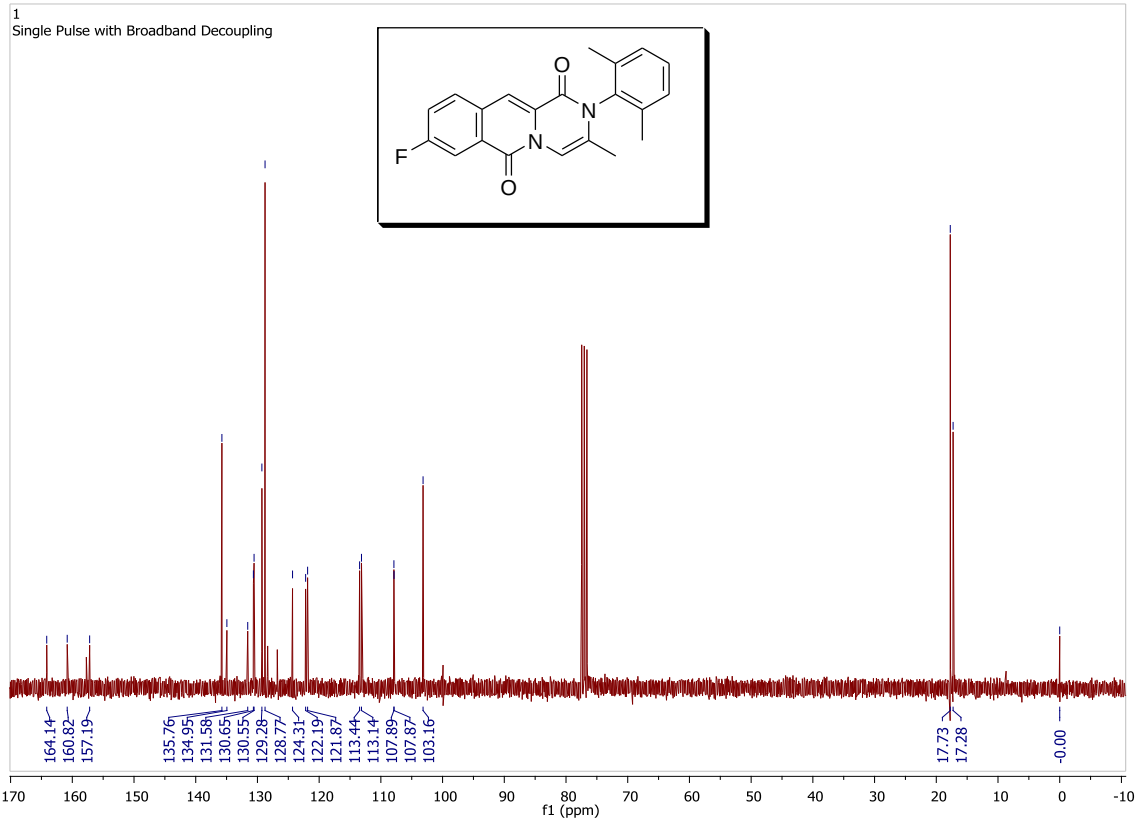
**Compound 18c,** 2-(2,6-dimethyl-phenyl)-8-methoxy-3-methylene-3,4-dihydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,6-dione



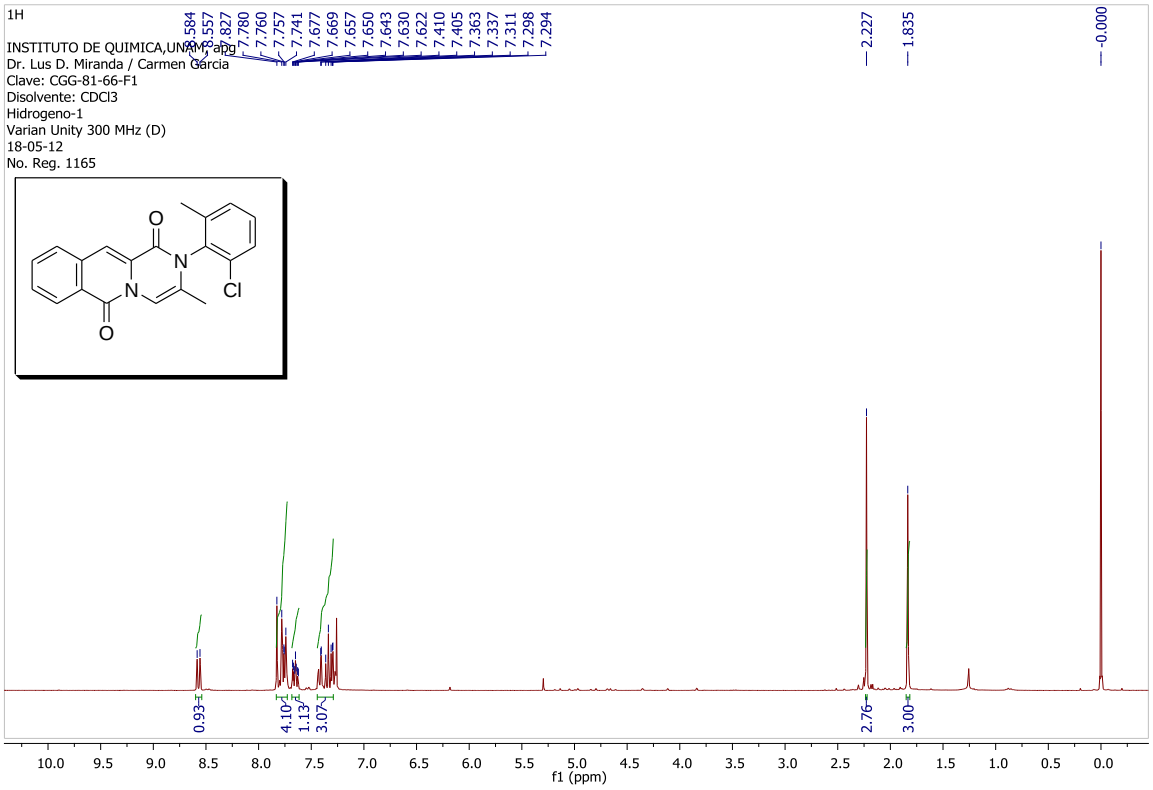



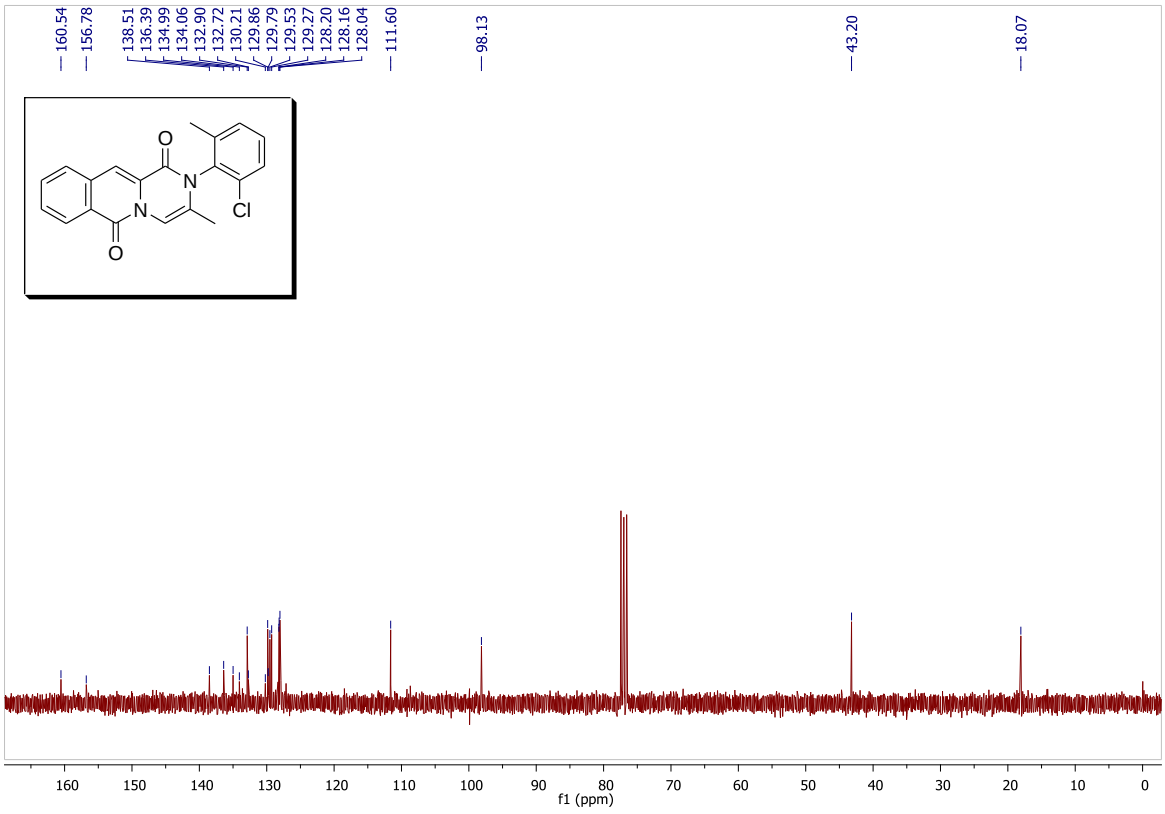
**Compound 18d,** 2-(2,6-dimethyl-phenyl)-8-fluoro-3-methylene-3-methyl-2*H*-pyrazino[1,2-*b*]isoquinoline-1,6-dione



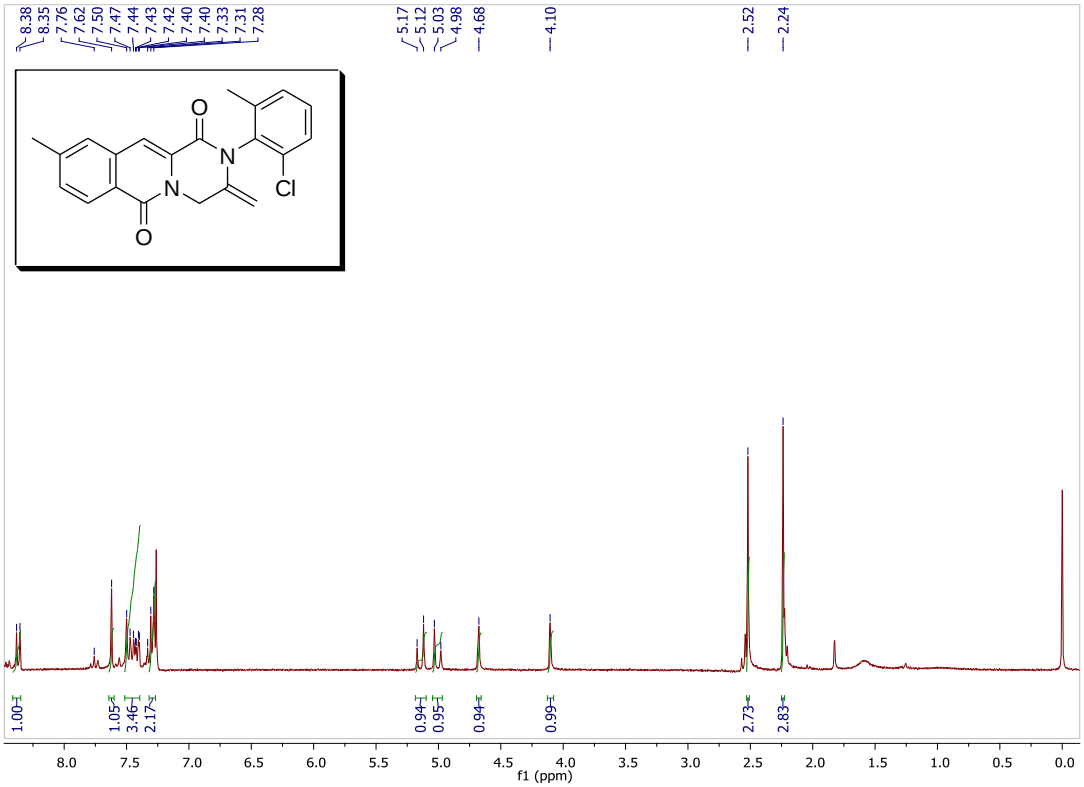



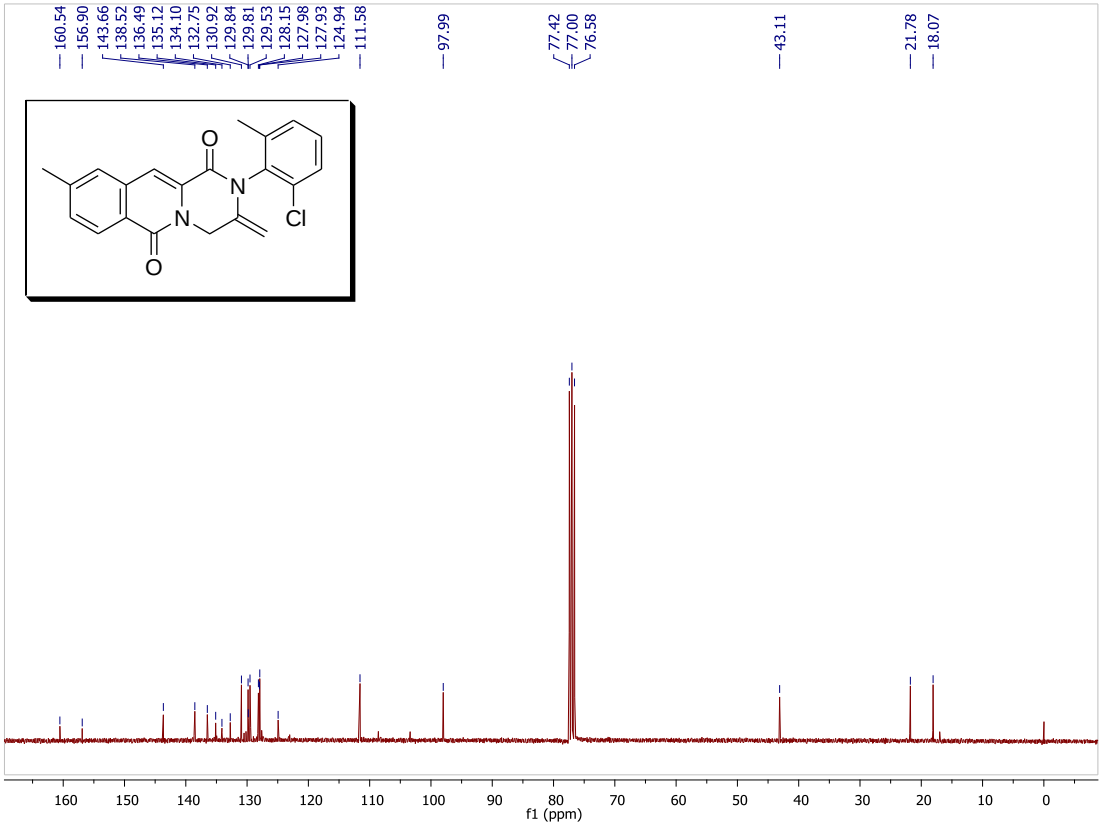
**Compound 18e,** 2-(2chloro-6-methyl-phenyl)-3-methyl-2*H*-pyrazino[1,2-*b*]isoquinoline-1,6-dione



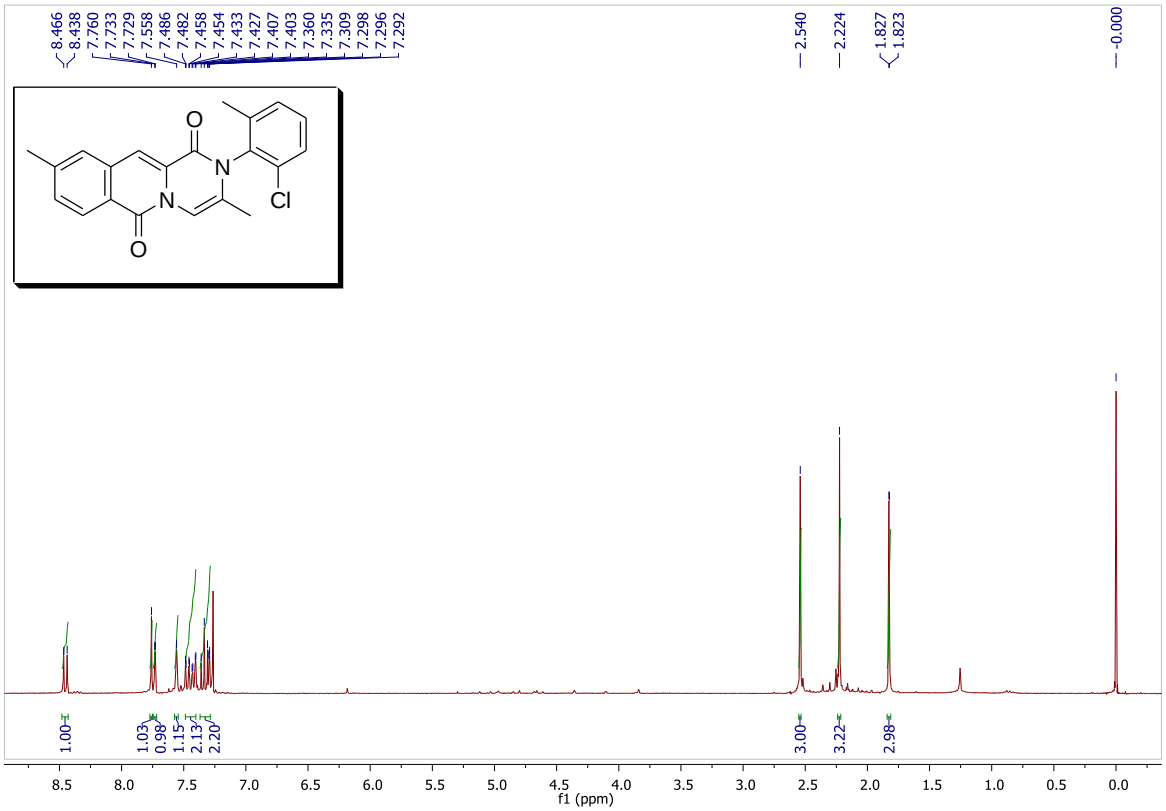



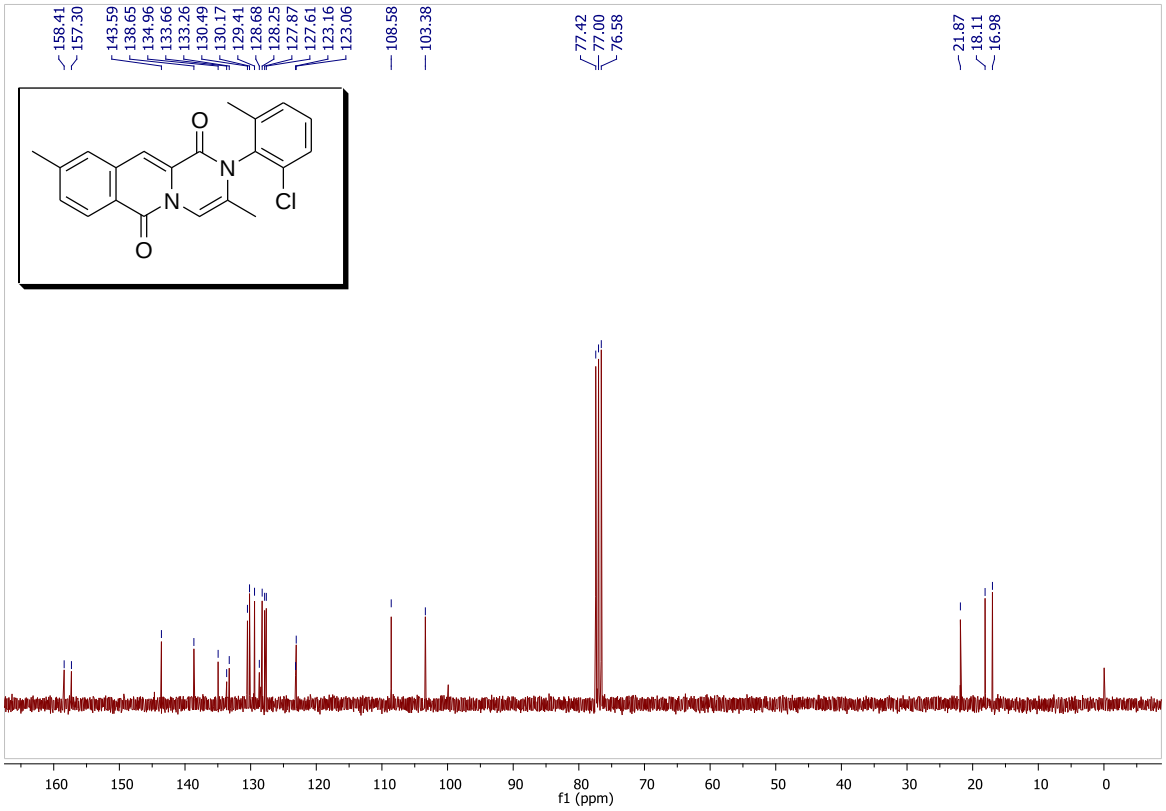
**Compound 18f-exo,** 2-(2chloro-6-methyl-phenyl)-9-methyl-3-methylene-3,4-dihydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,6-dione



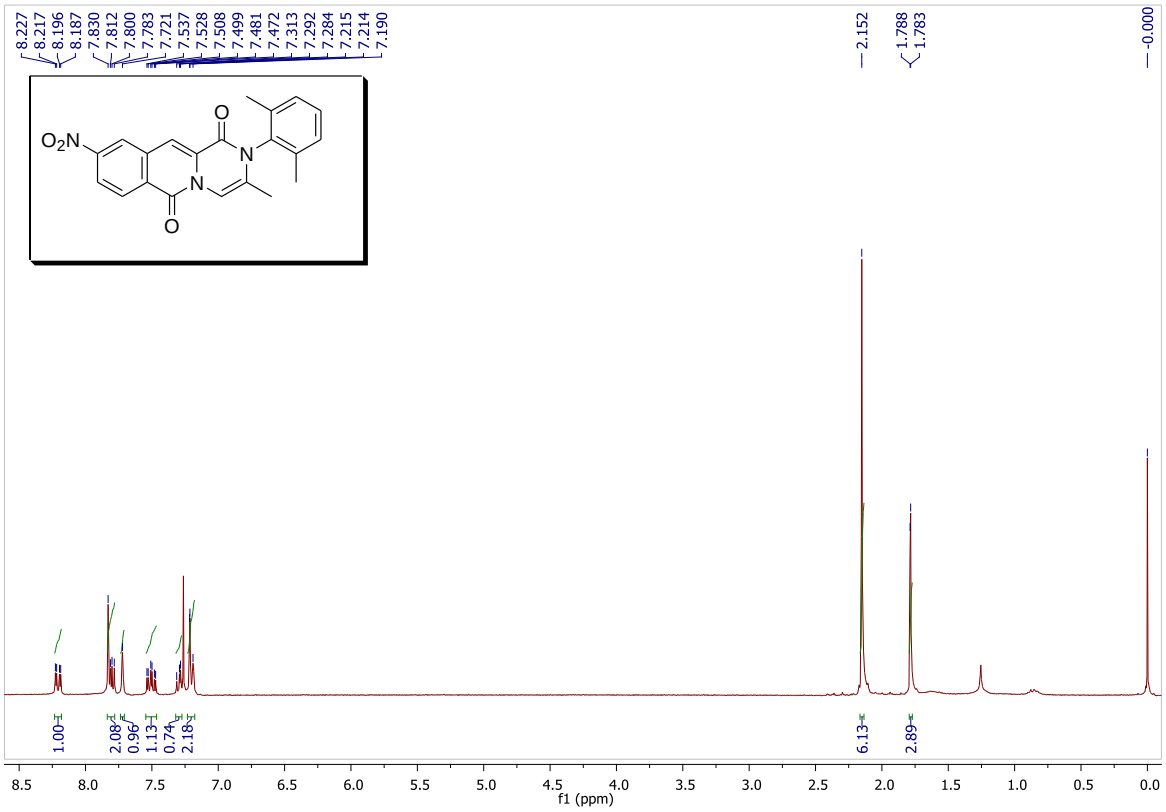



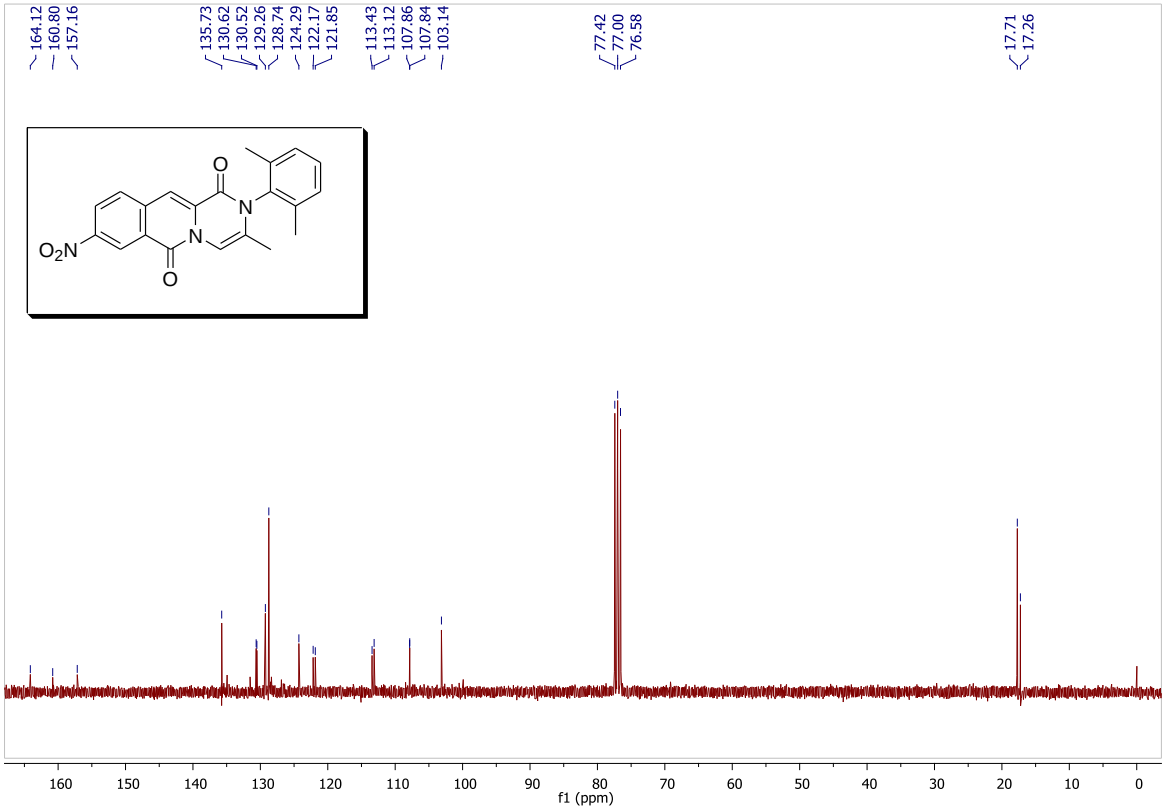
**Compound 18f-endo**, 2-(2chloro-6-methyl-phenyl)-3,9-dimethyl-2*H*-pyrazino[1,2-*b*]isoquinoline-1,6-dione



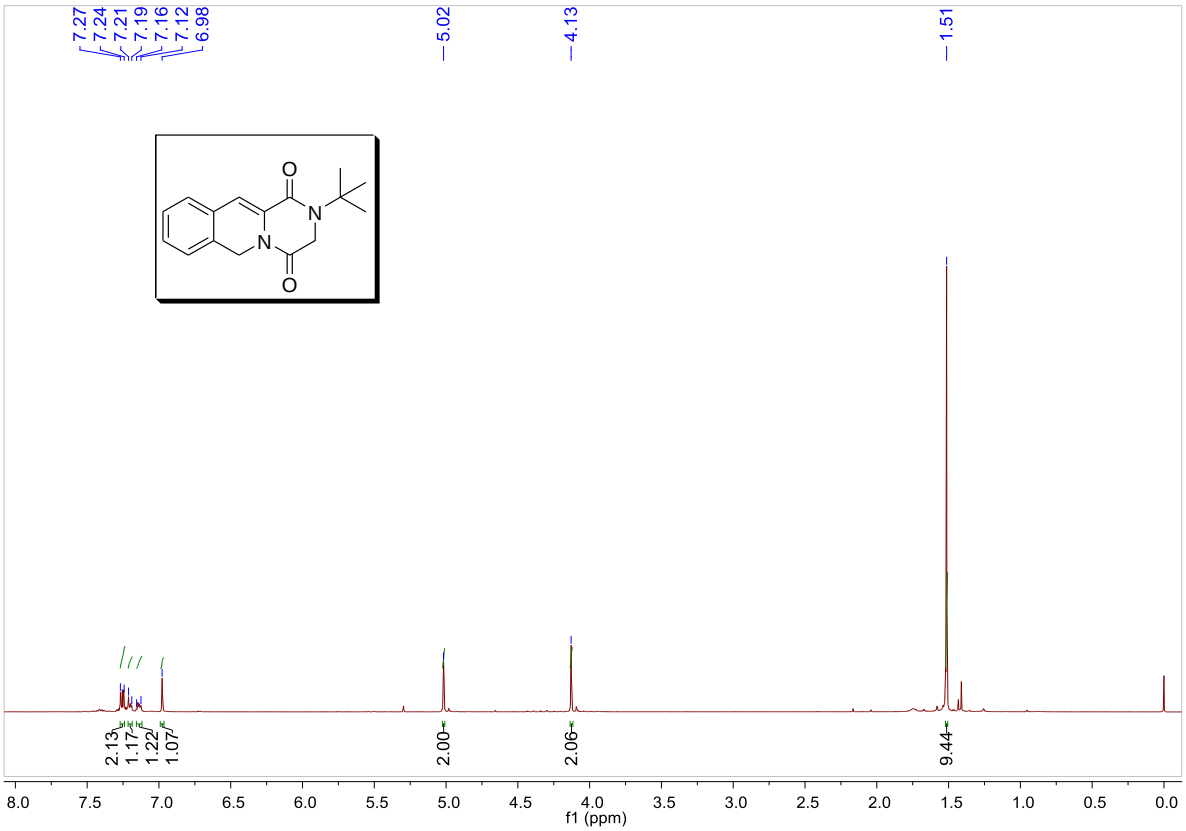



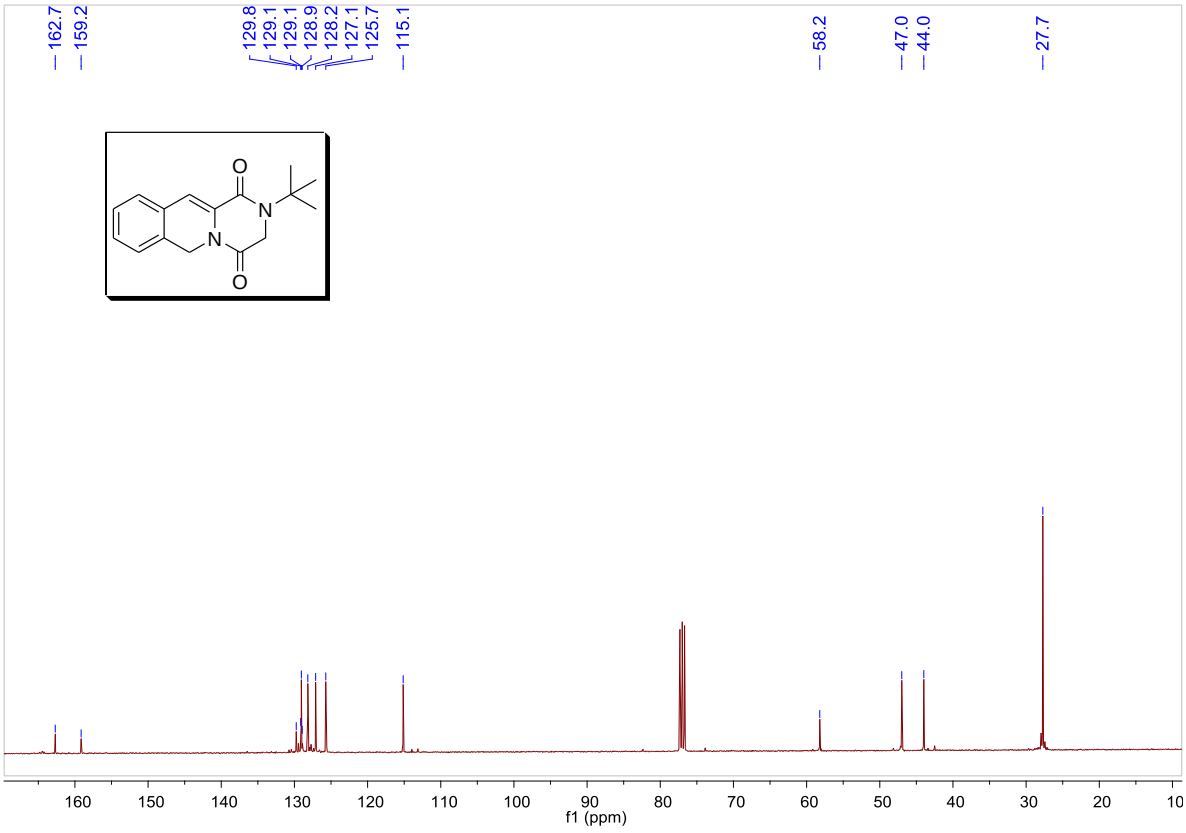
**Compound 18g,** 2-(2,6-dimethyl-phenyl)-3-methyl-9-nitro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,6-dione



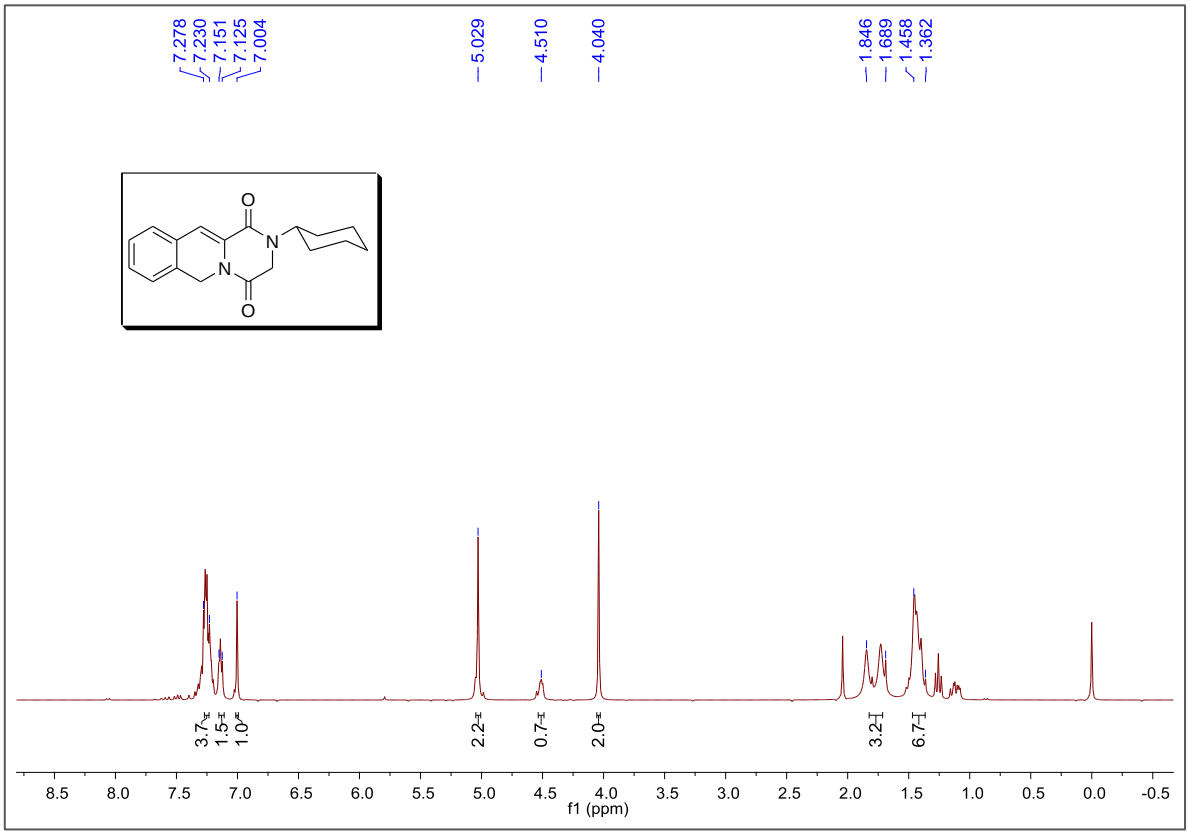



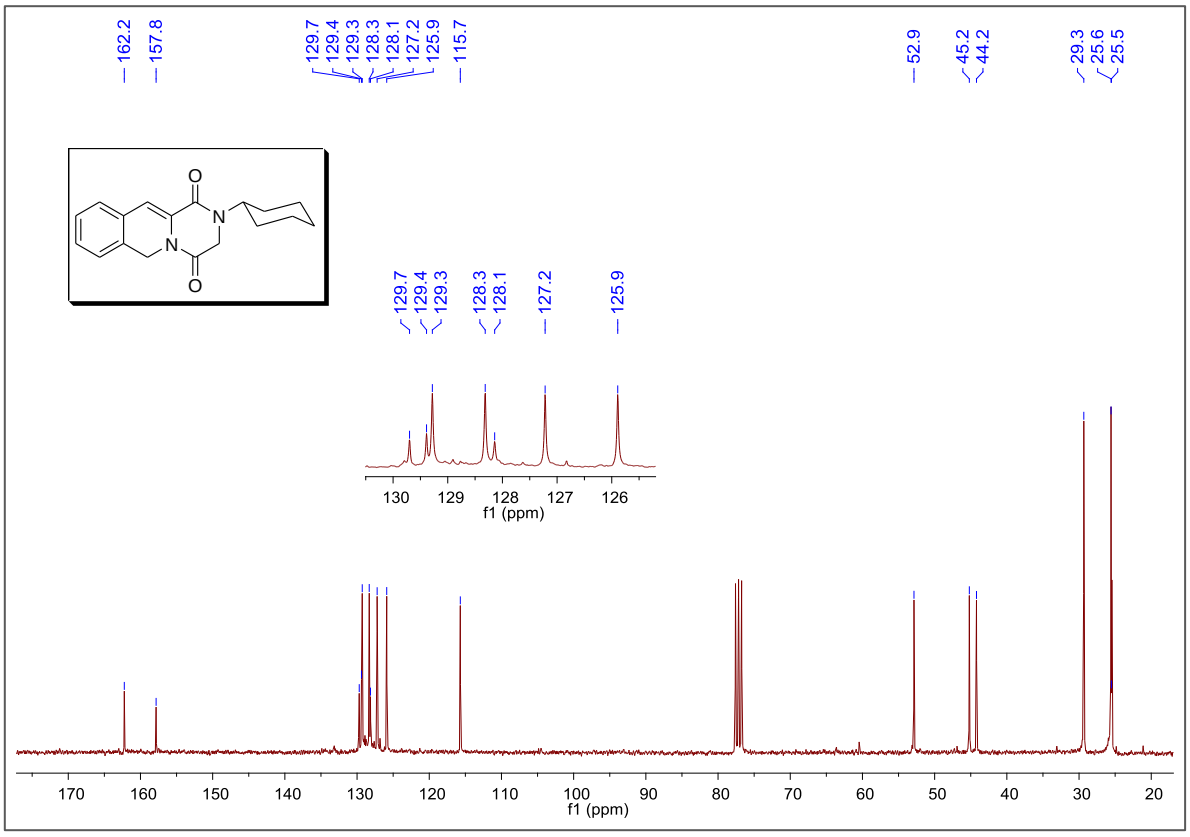
**Compound 22a,** 2-*tert*-butyl-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione



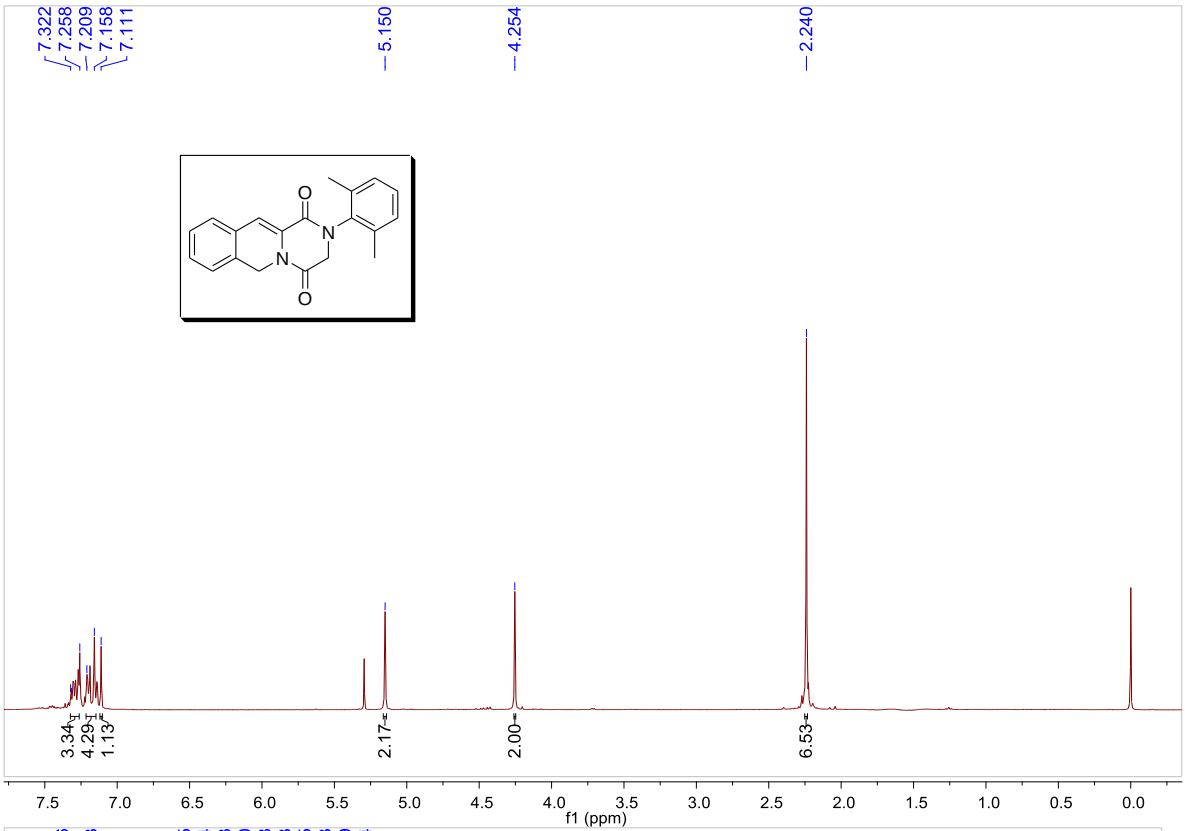



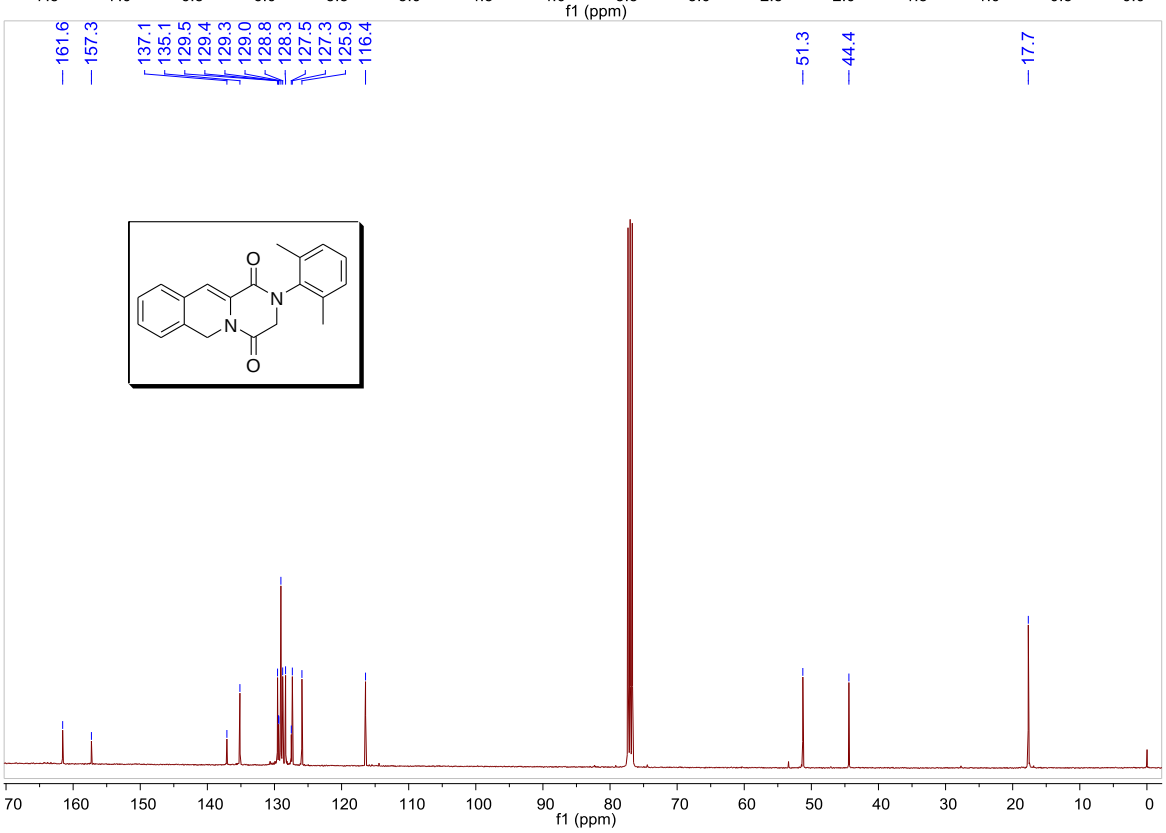
**Compound 22b**, 2-cyclohexyl-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione



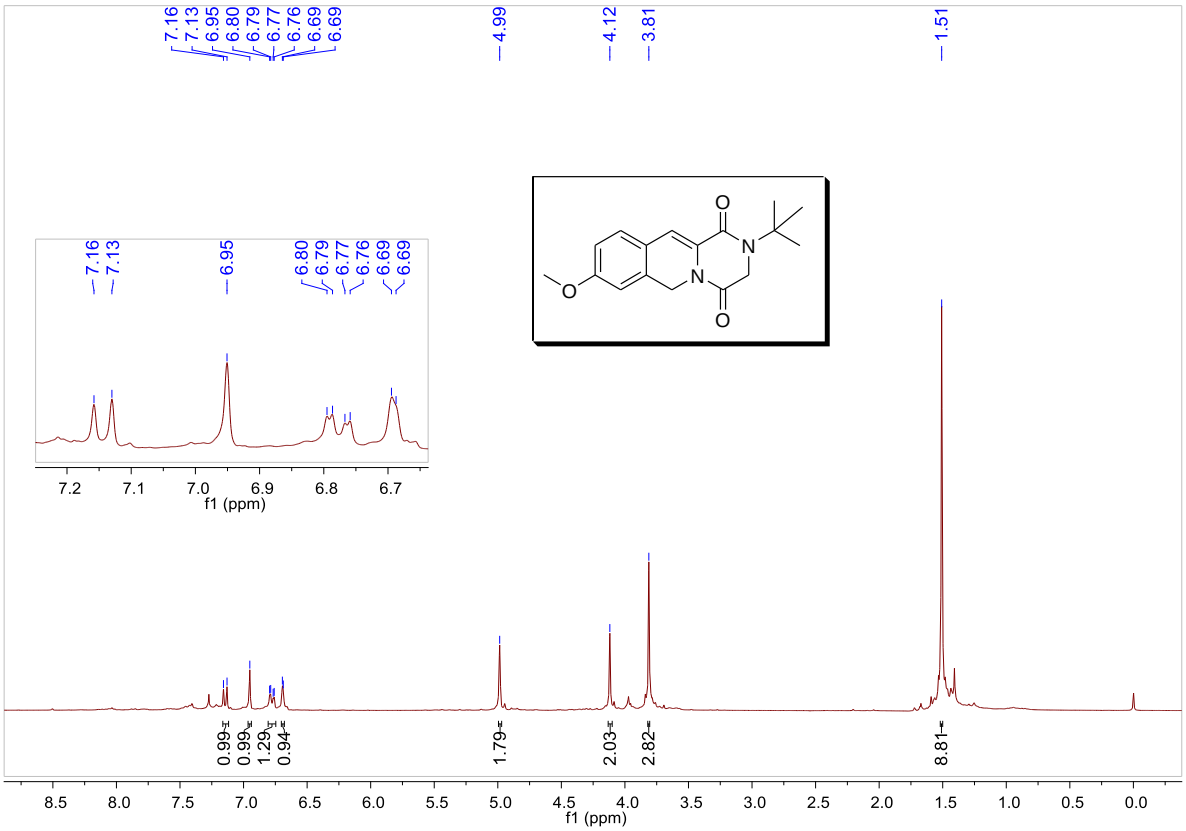



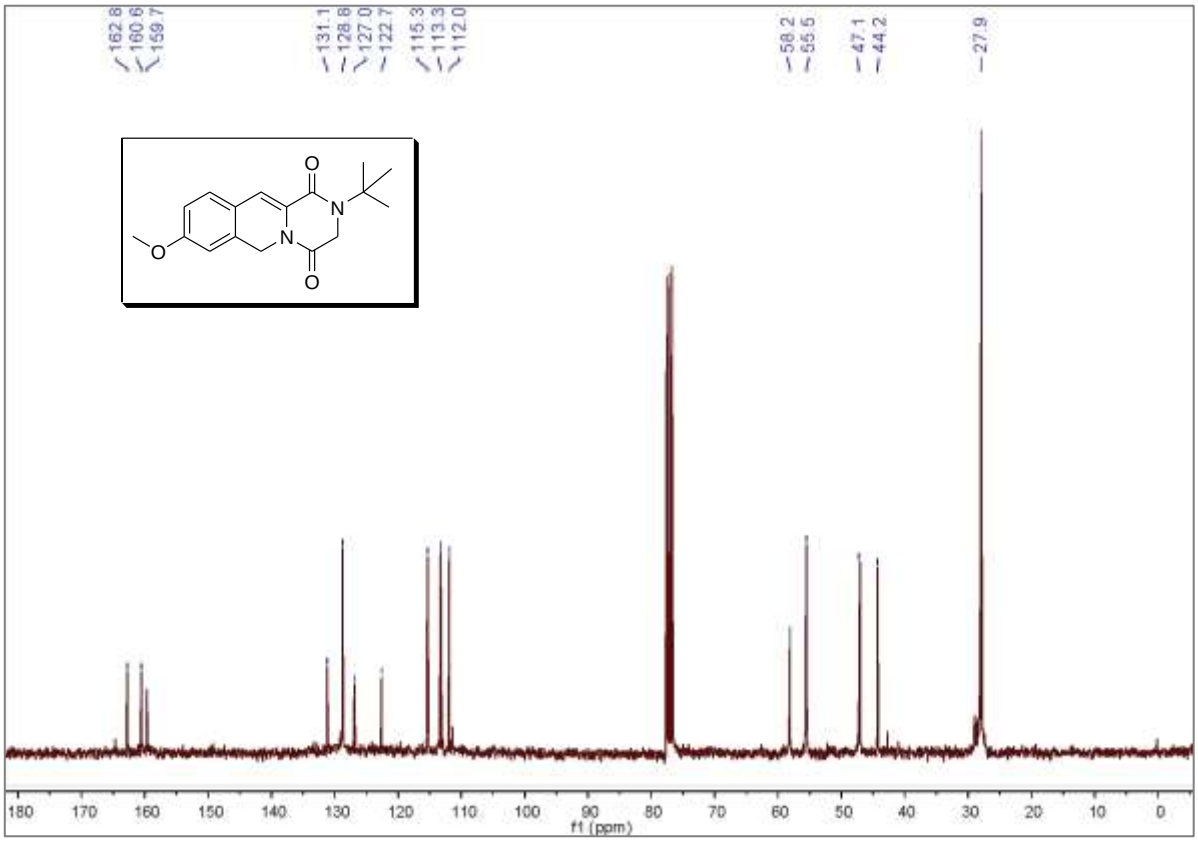
**Compound 22c,** 2-(2,6-dimethylphenyl)-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione



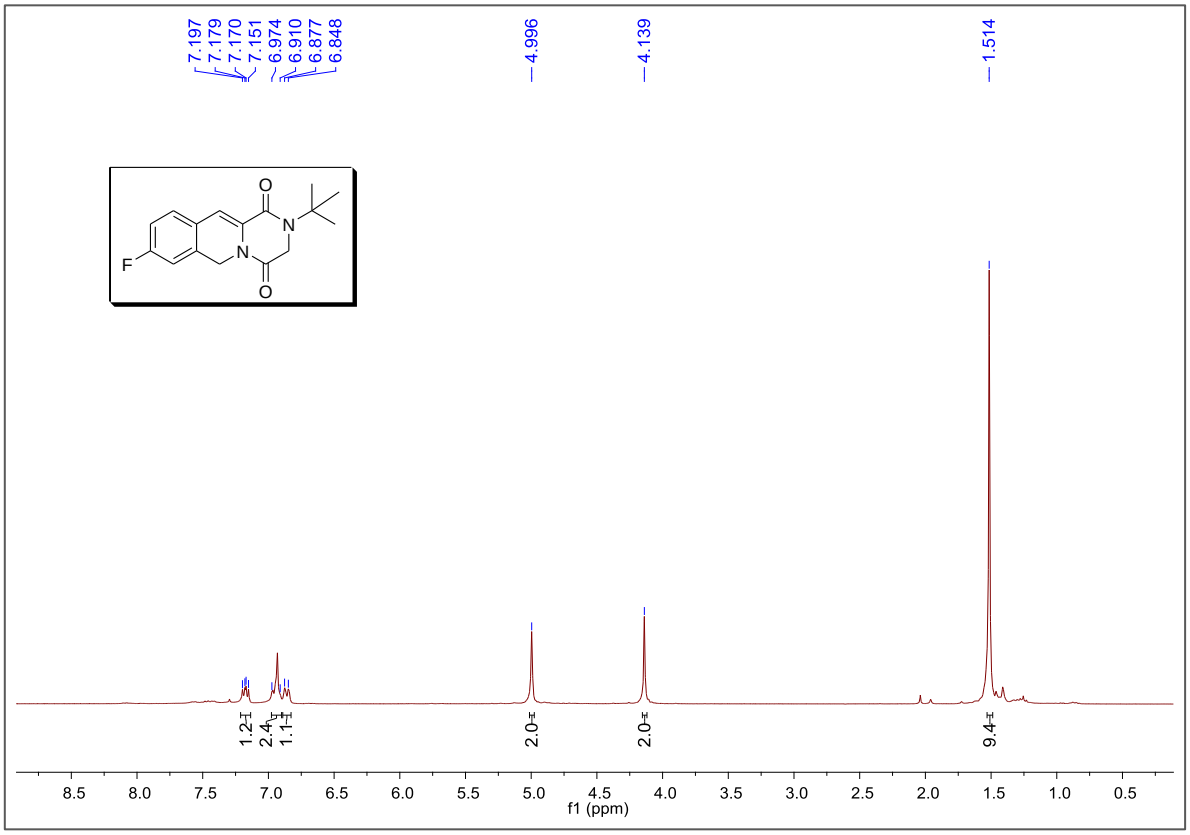



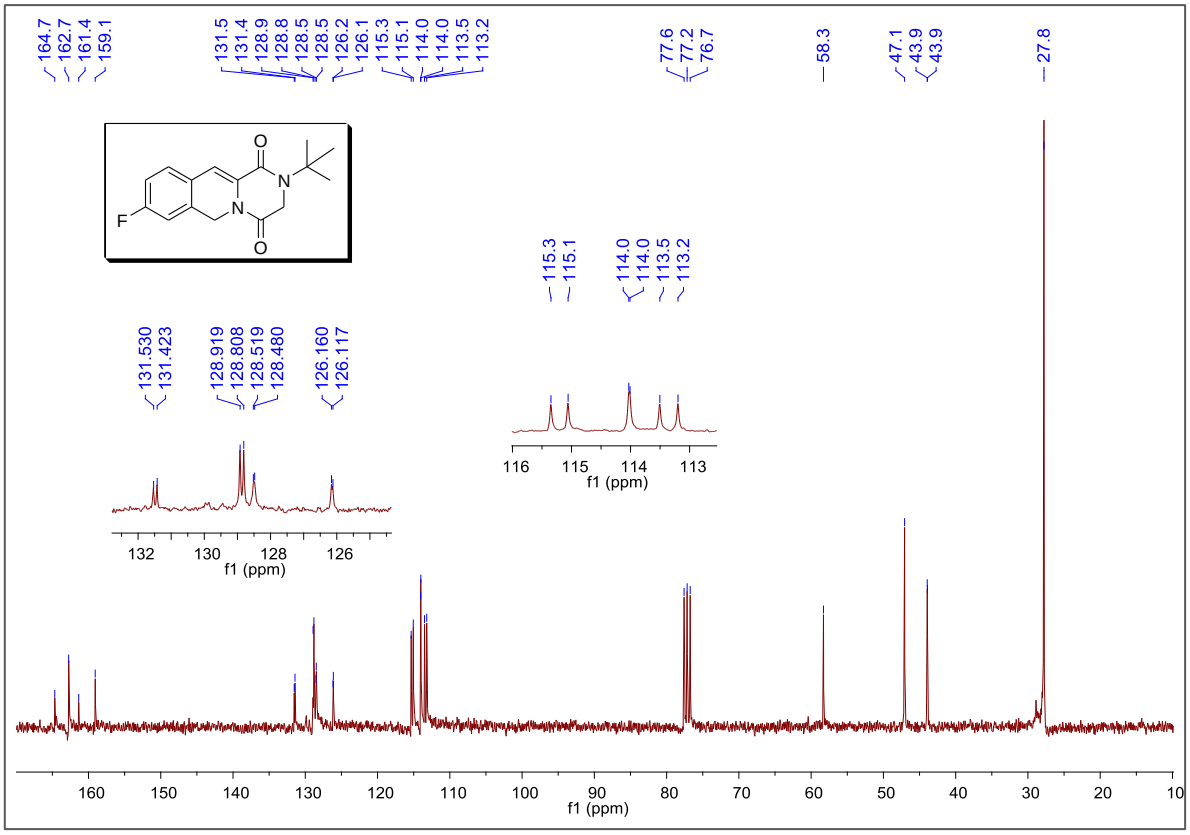
**Compound 22d**, 2-*tert*-butyl-8-methoxy–2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione



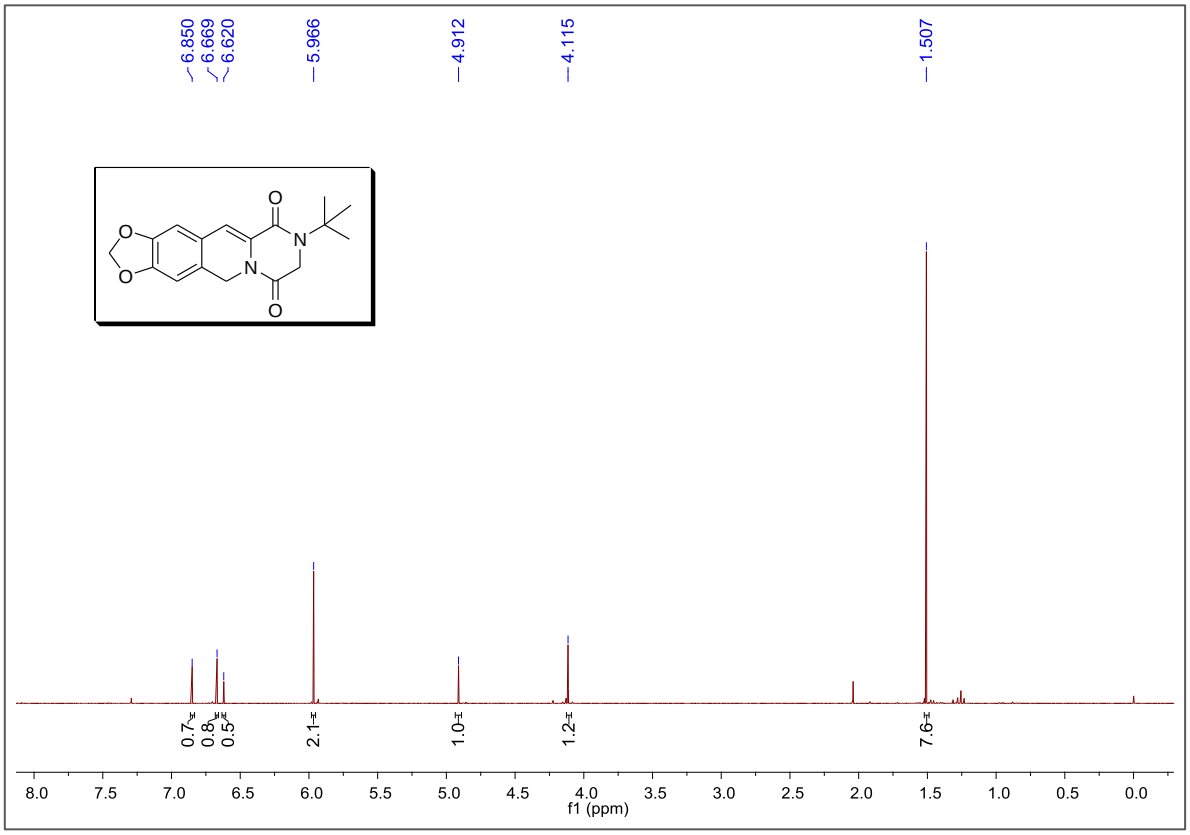



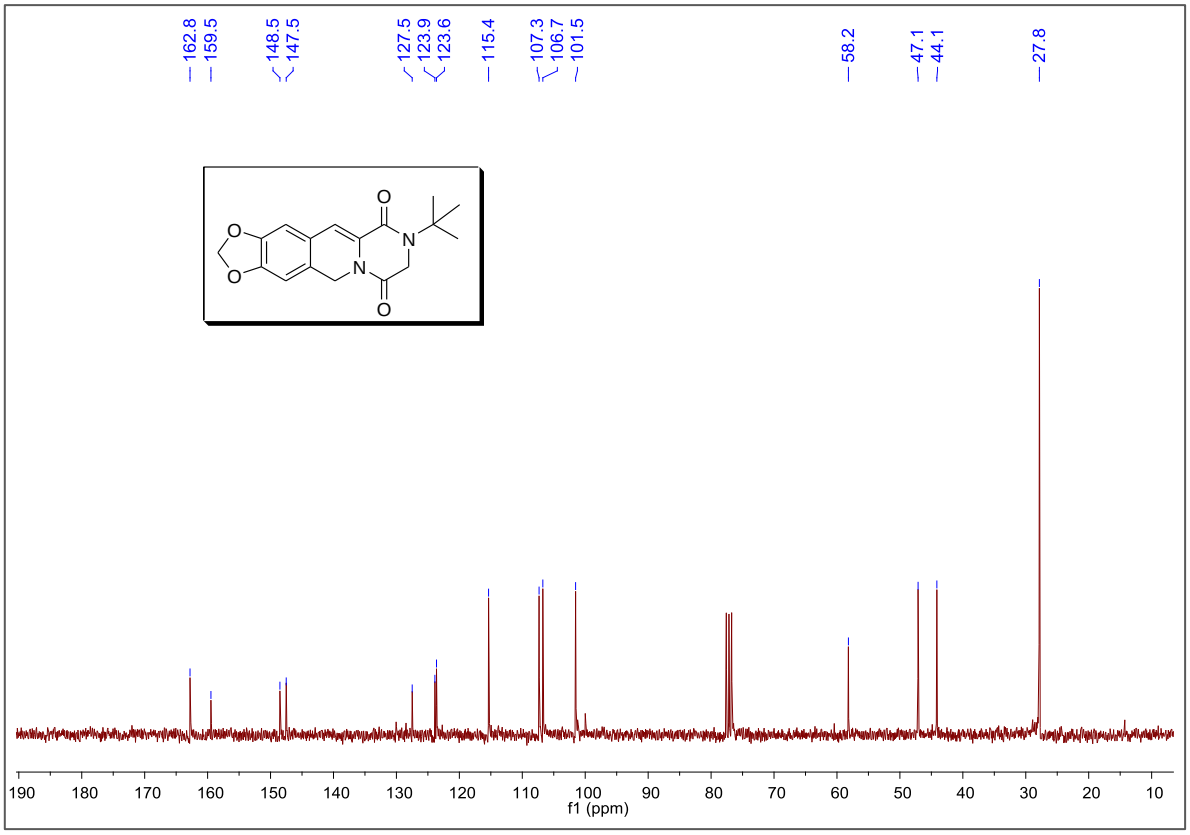
**Compound 22e,** 2-*tert*-butyl-8-fluoro–2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione



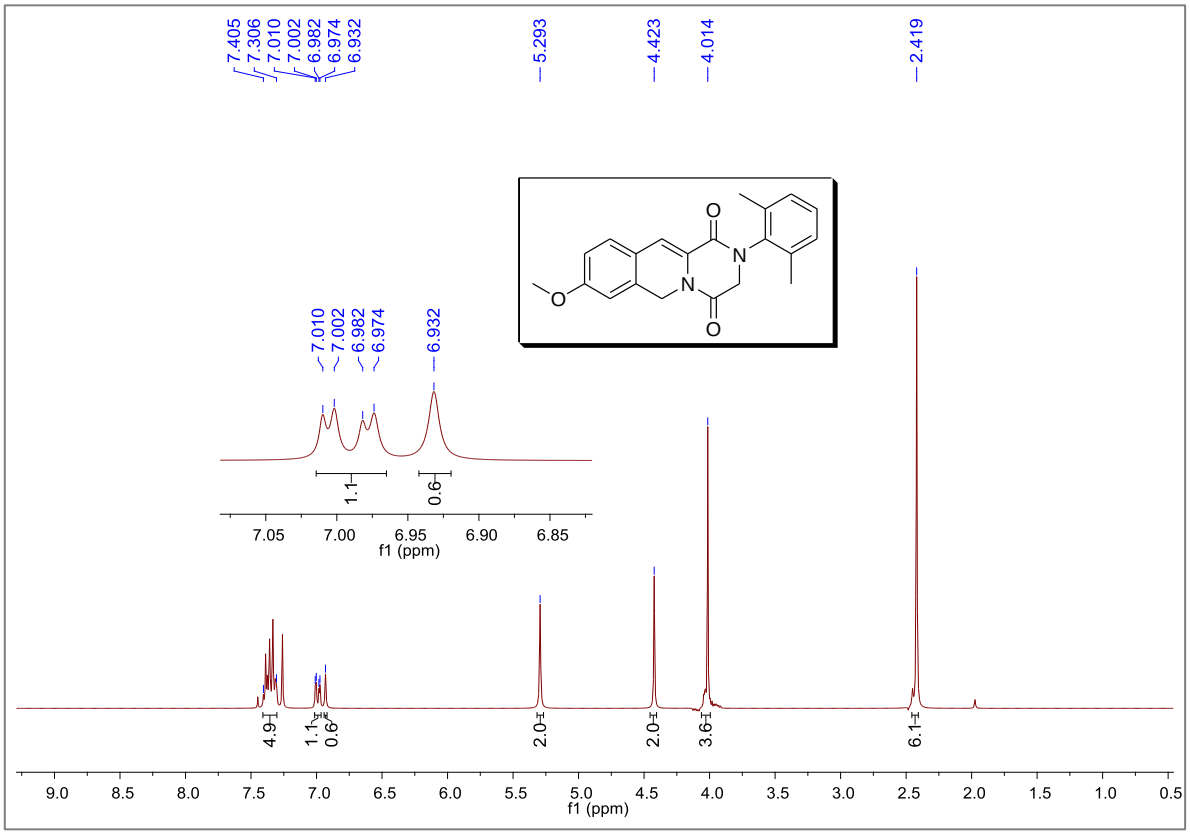



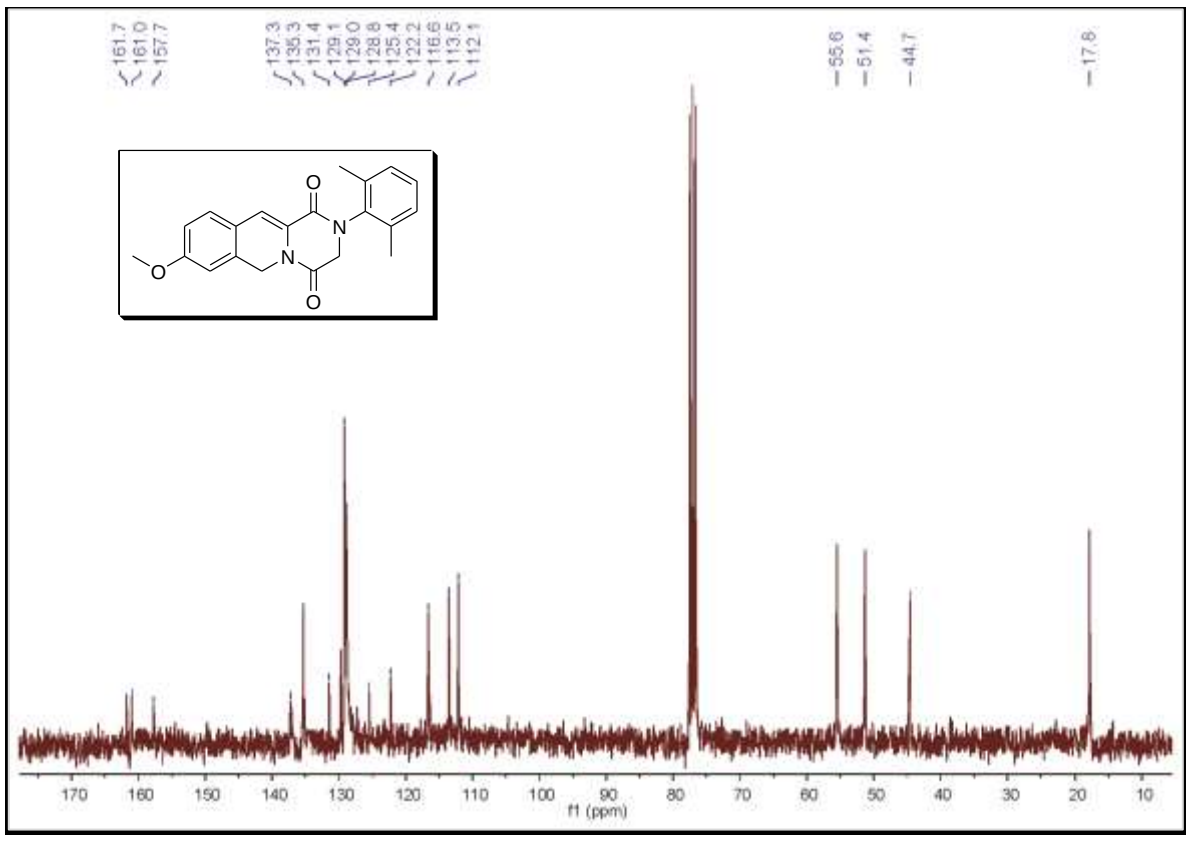
**Compound 22f**, 9-(*tert*-butyl)-8,9-dihydro-5*H*-[1,3]dioxolo[4,5-*g*]pyrazino[1,2-*b*]isoquinoline-7,10-dione



**Compound 22g,** 2-(2,6-dimethylphenyl)-8-methoxy-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione



## 4. X-Ray crystallographic

The X-ray diffraction analysis of **10a**, **11a** and **14a** confirmed the N-heterocyclic structure, full crystallographic data were submitted as CIF files with the Cambridge Crystallograpic Data Center, CCDC Nos. 912003 for **10a**, 912004 for **11a**, and 912005 for **14a**. These data can be obtained free of change from The Cambridge Crystallograpic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

### 4.1. Compound 10a (CCDC 912003)

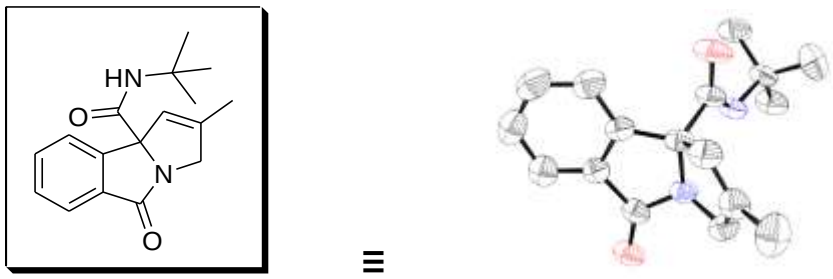



Figure 1. ORTEP diagram of the molecular structure of compound **10a**. Hydrogen atoms were omitted for clarity.

| | | |
|---|---|---|
| Empirical formula | $C_{17}H_{20}N_2O_2$ | |
| Formula weight | 284.35 | |
| Temperature | 298(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Triclinic | |
| Space group | P-1 | |
| Unit cell dimensions | a = 9.074(2) Å | α= 105.491(4)° |
| | b = 9.586(2) Å | β= 97.554(4)° |
| | c = 10.271(2) Å | γ= 108.975(4)° |
| Volume | 790.4(3) $Å^3$ | |
| Z | 2 | |
| Density (calculated) | 1.195 $Mg/m^3$ | |
| Absorption coefficient | 0.079 $mm^{-1}$ | |
| F(000) | 304 | |
| Crystal size / colour / shape | 0.18 x 0.18 x 0.10 mm / Colorless / Prism | |
| Theta range for data collection | 2.12 to 25.39° | |
| Index ranges | -10<=h<=10, -11<=k<=11, -12<=l<=12 | |
| Reflections collected | 6602 | |
| Independent reflections | 2905 [R(int) = 0.0329] | |
| Completeness to theta = 25.39° | 99.7 % | |
| Measurement device | Bruker Smart APEX AXS CCD area detector 01-67 | |
| Absorption correction | None | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 2905 / 97 / 222 | |
| Goodness-of-fit on $F^2$ | 0.828 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0431, wR2 = 0.0977 | |
| R indices (all data) | R1 = 0.0941, wR2 = 0.1110 | |
| Largest diff. peak and hole | 0.123 and -0.118 $e.Å^{-3}$ | |

## 4.2. Compound 11a (CCDC 912004)


Figure 2. ORTEP diagram of the molecular structure of compound **11a**. Hydrogen atoms were omitted for clarity.

| | | |
|---|---|---|
| Empirical formula | $C_{18}H_{22}N_2O_2$ | |
| Formula weight | 298.38 | |
| Temperature | 298(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P 21/c | |
| Unit cell dimensions | a = 9.1496(13) Å | α= 90° |
| | b = 9.3085(13) Å | β= 95.325(2)° |
| | c = 19.945(3) Å | γ= 90° |
| Volume | 1691.3(4) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.172 $Mg/m^3$ | |
| Absorption coefficient | 0.077 mm-1 | |
| F(000) | 640 | |
| Crystal size / colour / shape | 0.36 x 0.22 x 0.15 mm / Colorless / Prism | |
| Theta range for data collection | 2.05 to 25.35° | |
| Index ranges | -10<=h<=11, -11<=k<=11, -23<=l<=24 | |
| Reflections collected | 13090 | |
| Independent reflections | 3088 [R(int) = 0.0645] | |
| Completeness to theta = 25.35° | 99.9 % | |
| Measurement device | Bruker Smart APEX AXS CCD area detector | |
| Absorption correction | None | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3088 / 70 / 222 | |
| Goodness-of-fit on $F^2$ | 0.943 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0540, wR2 = 0.1274 | |
| R indices (all data) | R1 = 0.1136, wR2 = 0.1462 | |
| Largest diff. peak and hole | 0.179 and -0.138 e.$Å^{-3}$ | |

## 4.3. Compound 14a (CCDC-912005)

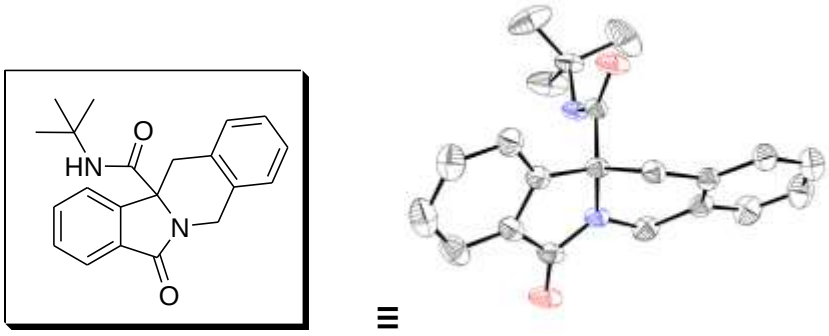



Figure 3. ORTEP diagram of the molecular structure of compound **14a**. Hydrogen atoms were omitted for clarity.

| | | |
|---|---|---|
| Empirical formula | $C_{21}\ H_{22}\ N_2\ O_2$ | |
| Formula weight | 334.41 | |
| Temperature | 298(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Triclinic | |
| Space group | P -1 | |
| Unit cell dimensions | a = 9.2332(15) Å | α = 105.017(3)° |
| | b = 10.3088(17) Å | β = 100.269(3)° |
| | c = 10.7141(18) Å | γ= 102.043(3)° |
| Volume | 933.7(3) $Å^3$ | |
| Z | 2 | |
| Density (calculated) | 1.189 $Mg/m^3$ | |
| Absorption coefficient | 0.077 $mm^{-1}$ | |
| F(000) | 356 | |
| Crystal size / colour / shape | 0.34 x 0.18 x 0.10 mm / Colorless / Prism | |
| Theta range for data collection | 2.03 to 25.38° | |
| Index ranges | -11<=h<=11, -12<=k<=12, -12<=l<=12 | |
| Reflections collected | 7775 | |
| Independent reflections | 3415 [R(int) = 0.0371] | |
| Completeness to theta = 25.38° | 99.5 % | |
| Measurement device | Bruker Smart APEX AXS CCD area detector 01-67 | |
| Absorption correction | None | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3415 / 1 / 232 | |
| Goodness-of-fit on $F^2$ | 0.922 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0462, wR2 = 0.1081 | |
| R indices (all data) | R1 = 0.0707, wR2 = 0.1180 | |
| Largest diff. peak and hole | 0.144 and -0.199 $e.Å^{-3}$ | |

## 5. References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[4] K J. Zhang, Y. Zhang, Y. Shan, W. Li, N. Ma, L. He, *Eur. J. Med. Chem.* **2010**, *45,* 2798-2805.

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