Pd-catalyzed De Novo Assembly of Diversely Substituted Indole-Fused Polyheterocycles

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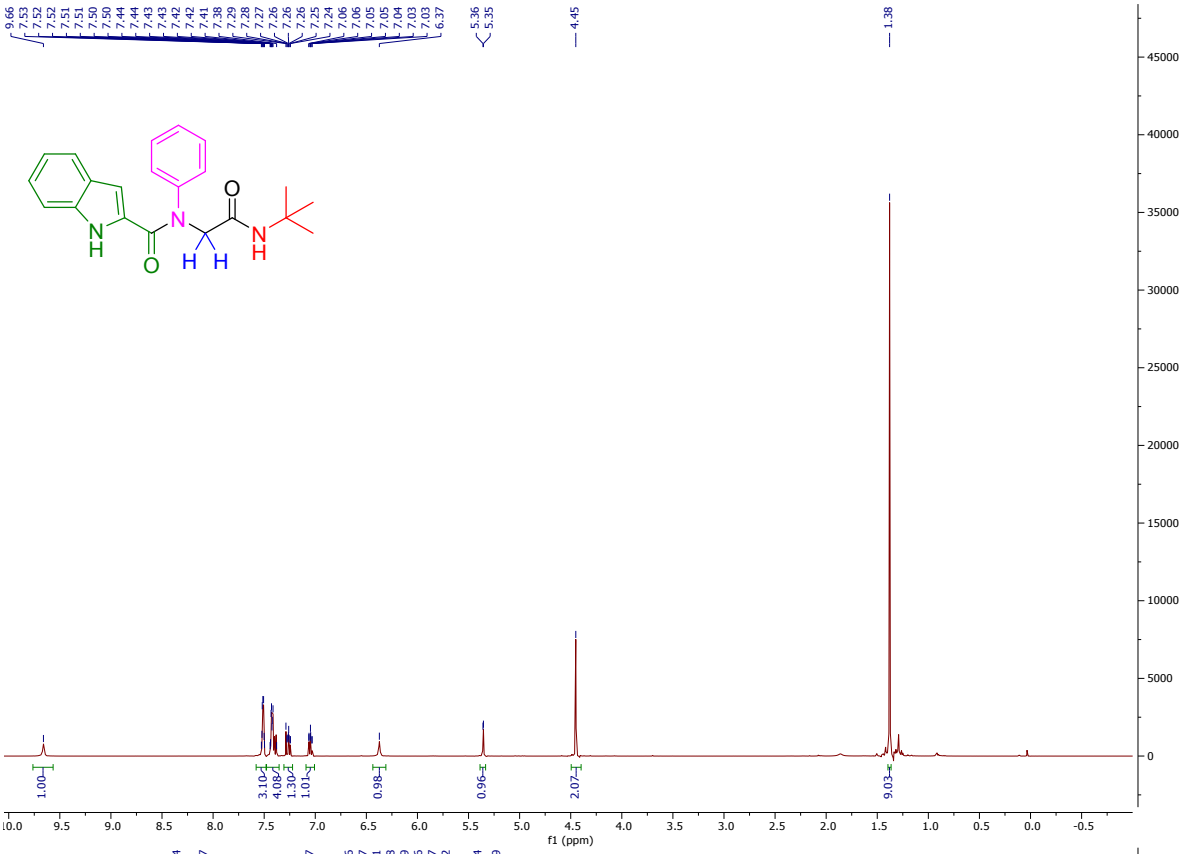
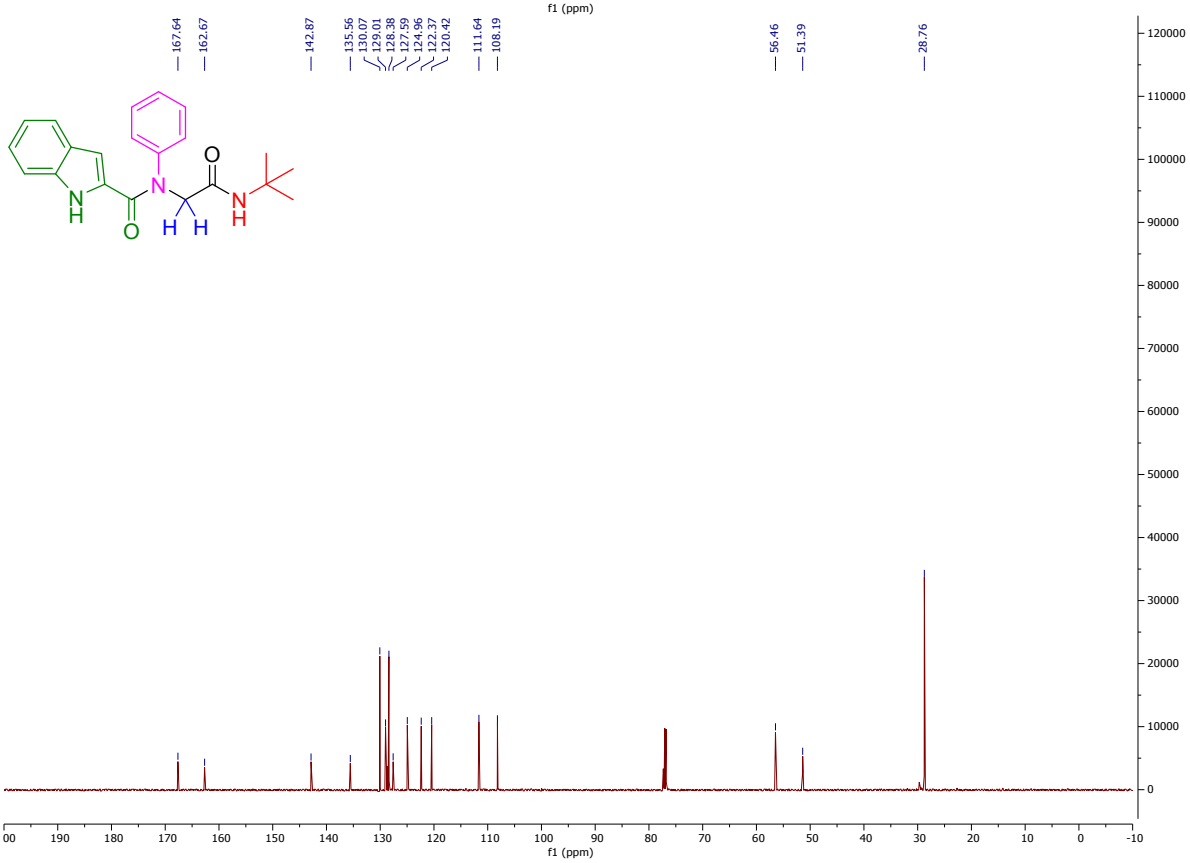
5a: *N*-(2-(*tert*-butylamino)-2-oxoethyl)-*N*-phenyl-*1H*-indole-2-carboxamide





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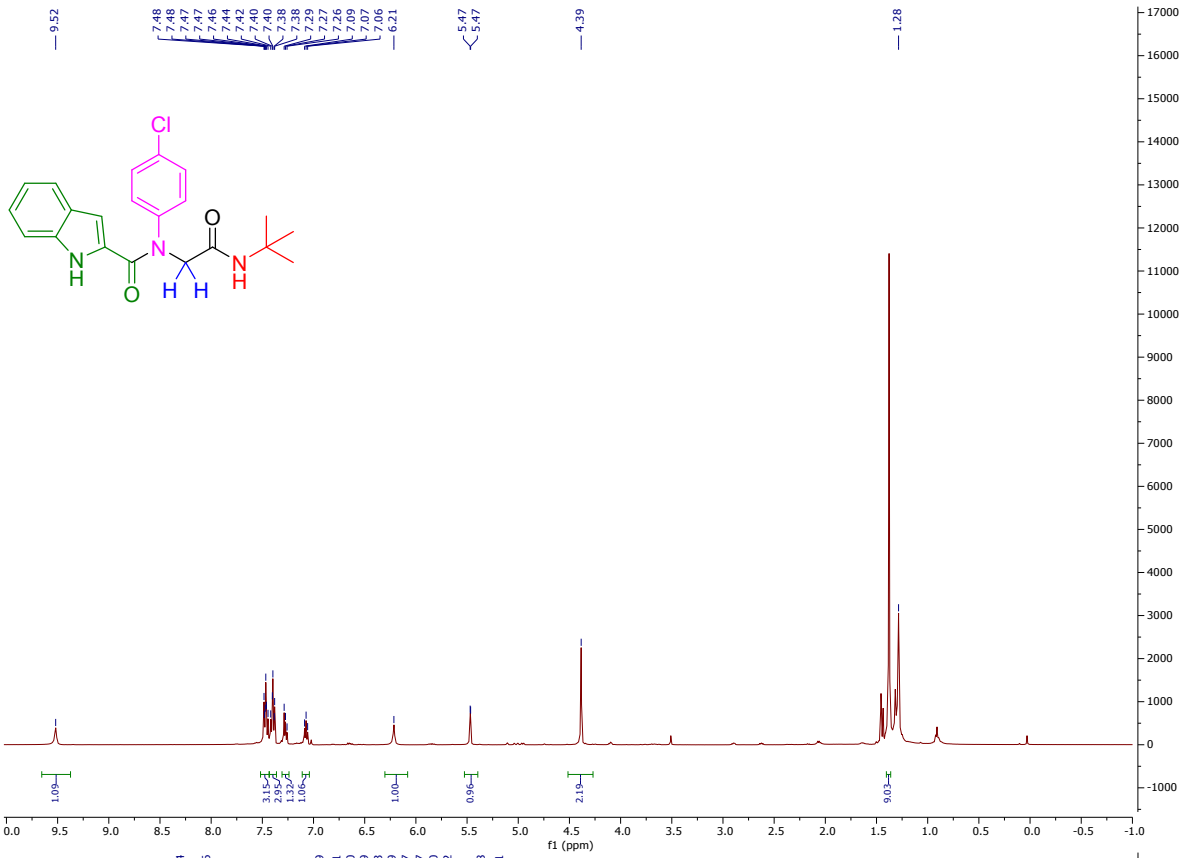

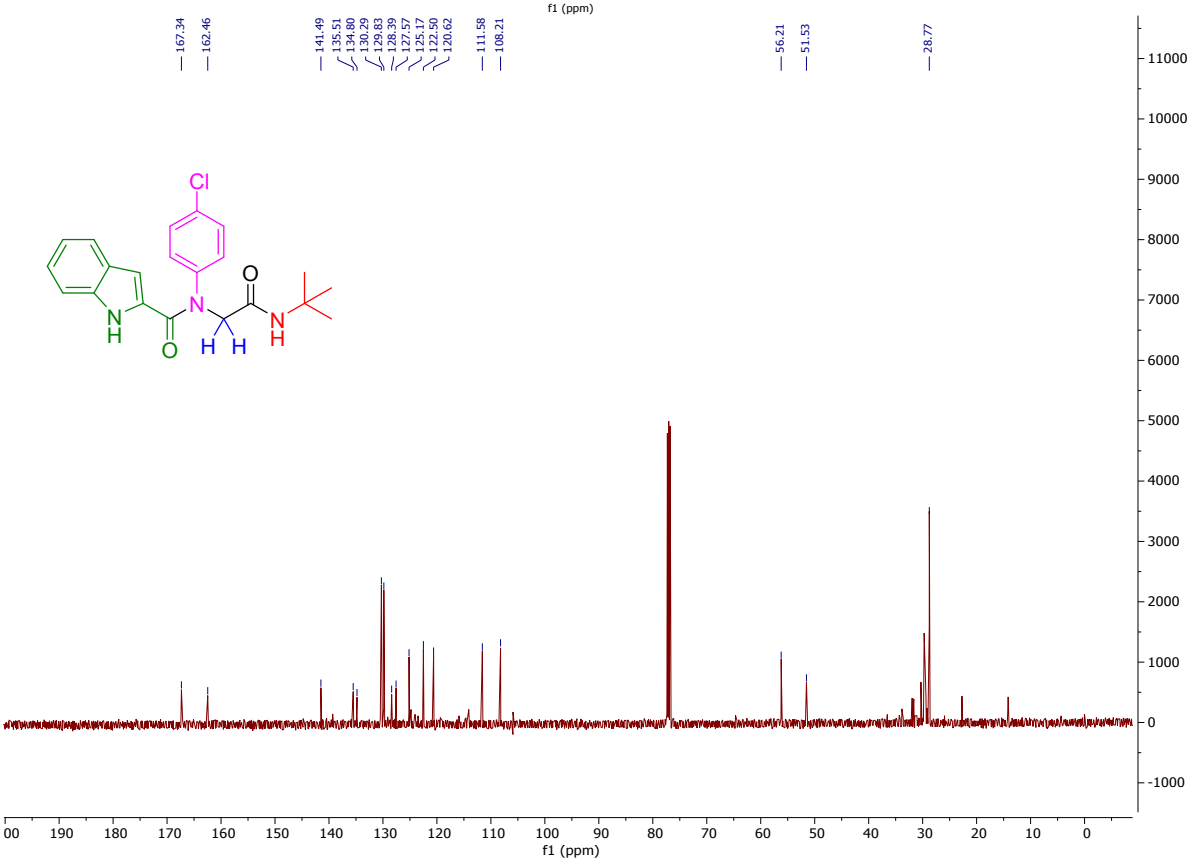

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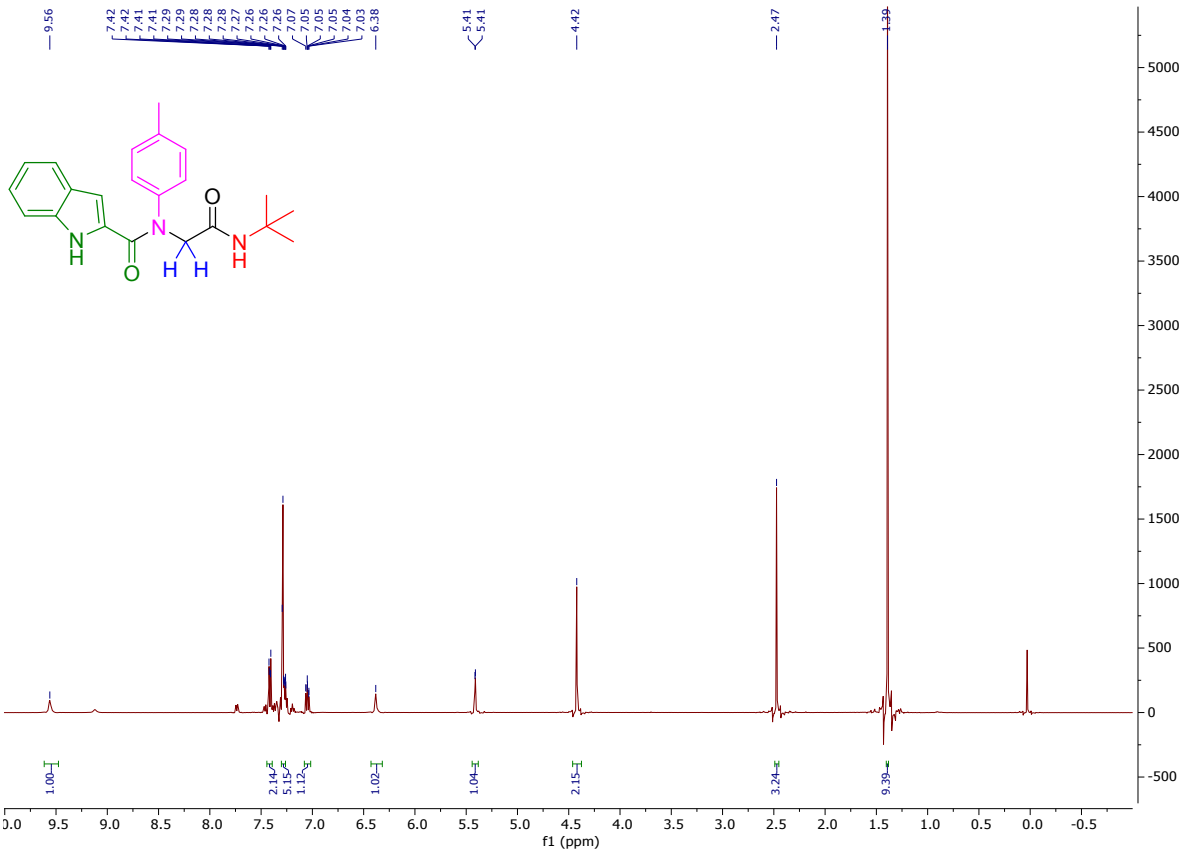

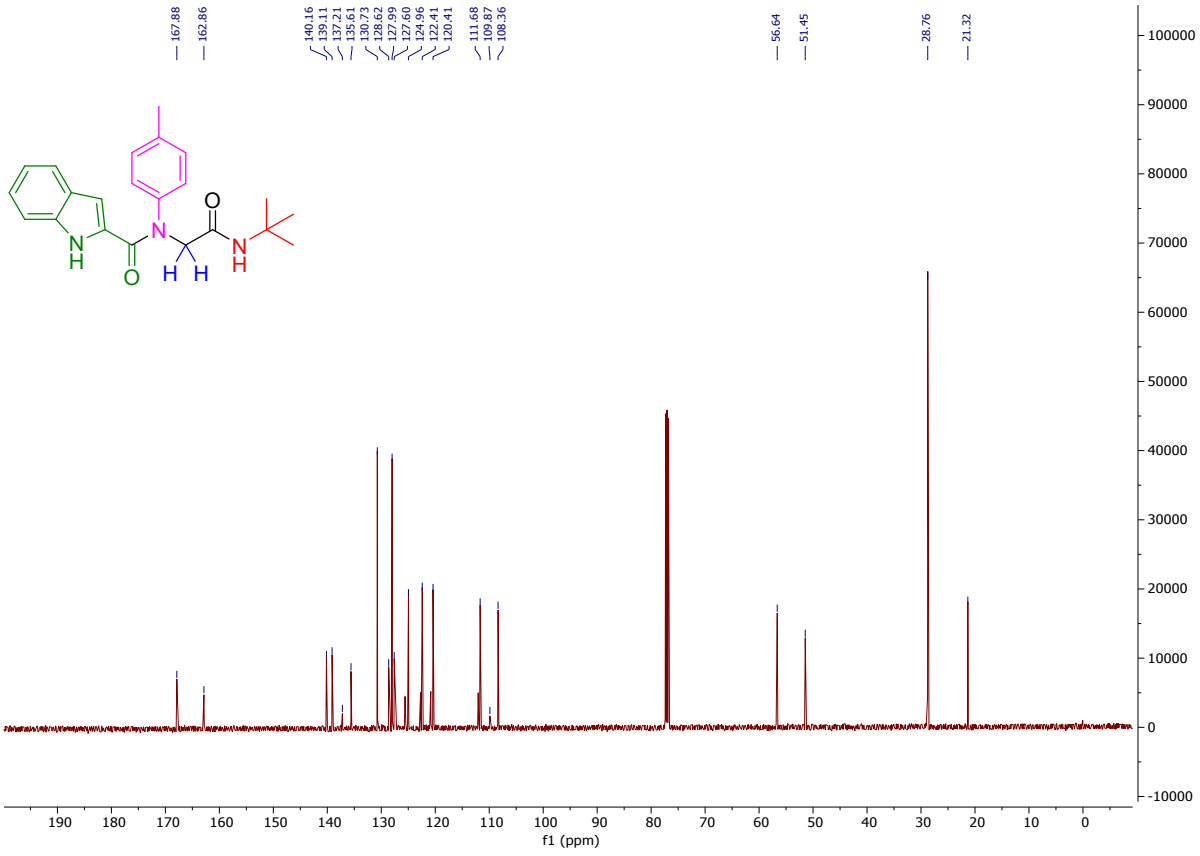

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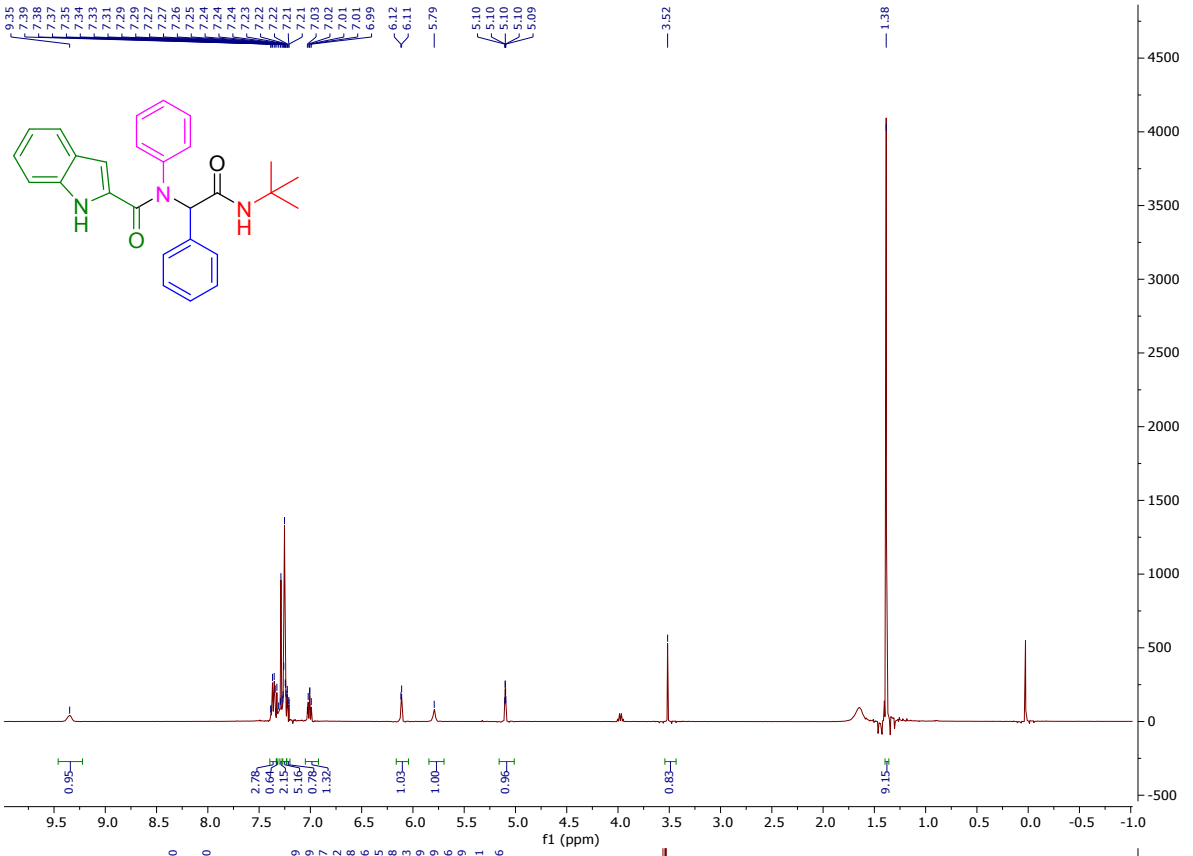

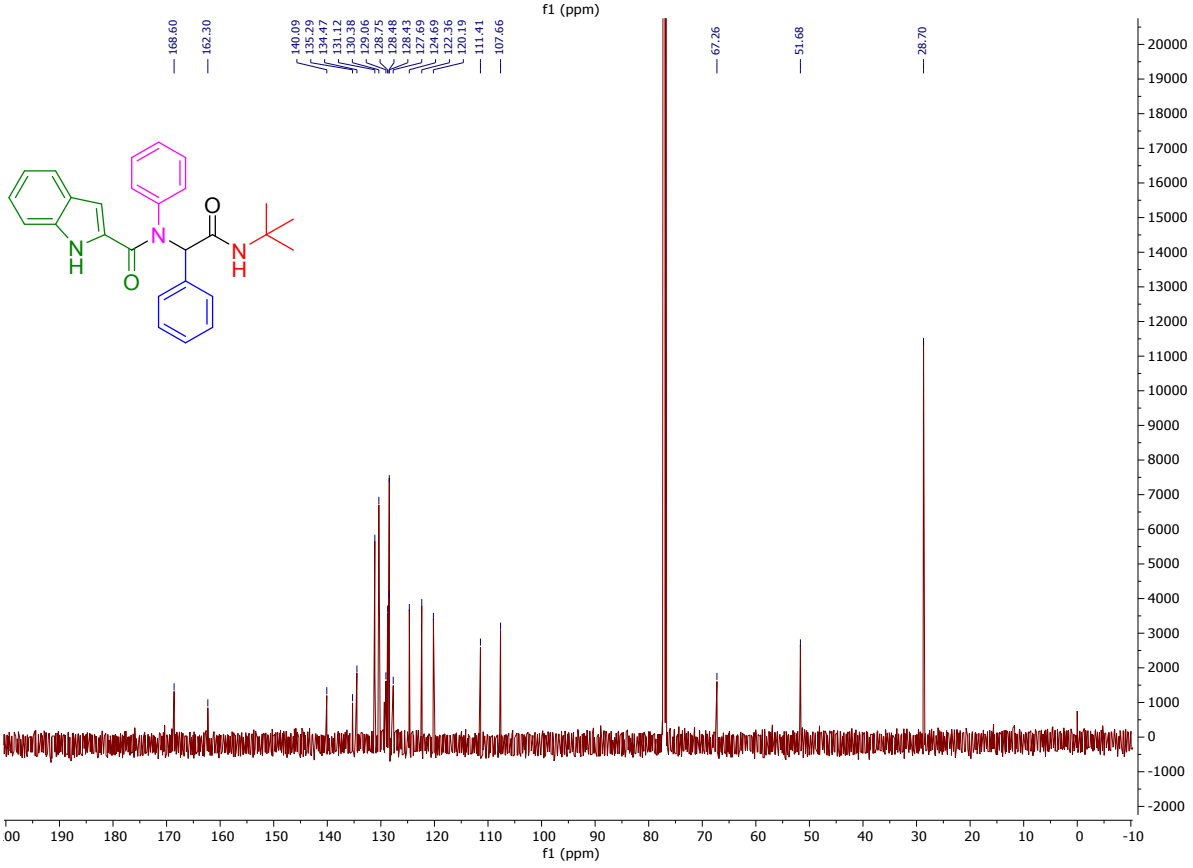

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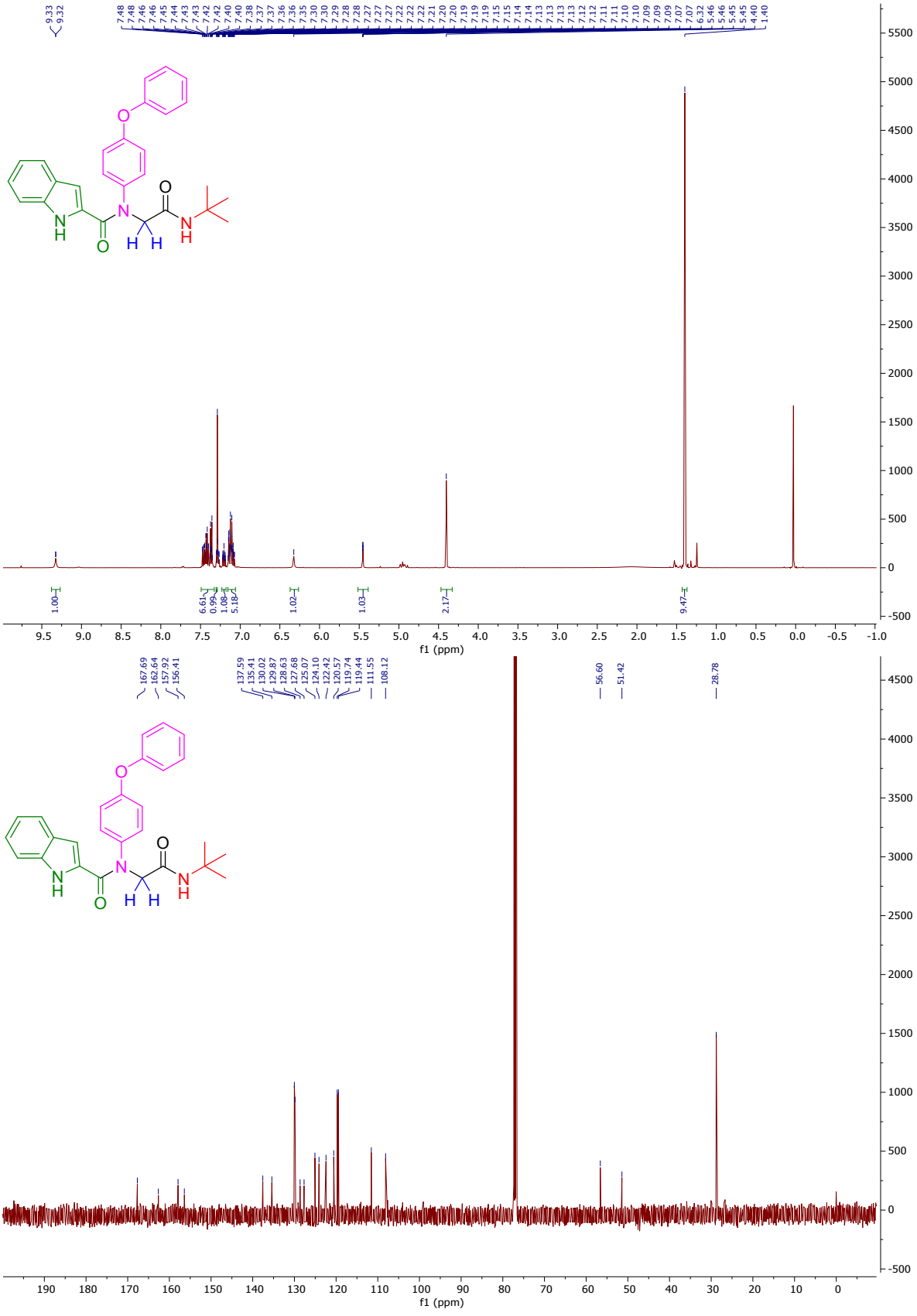

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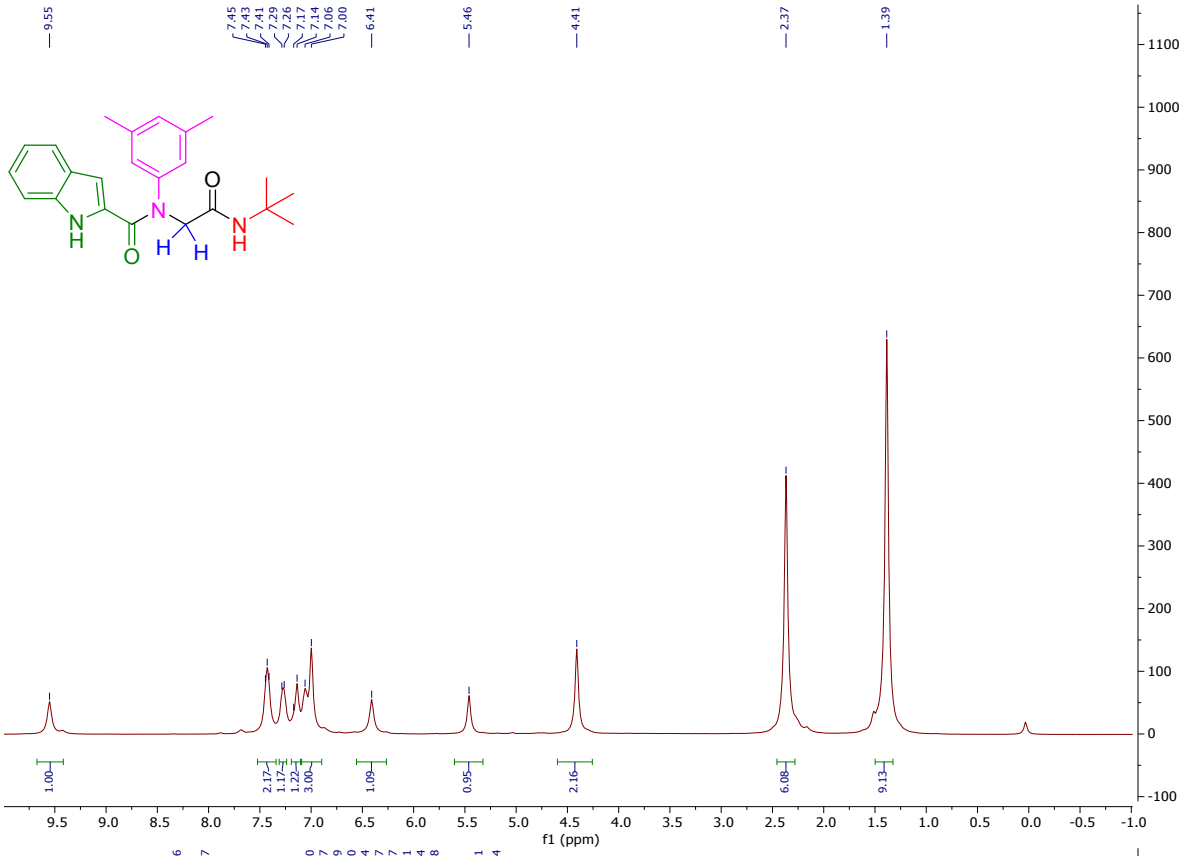

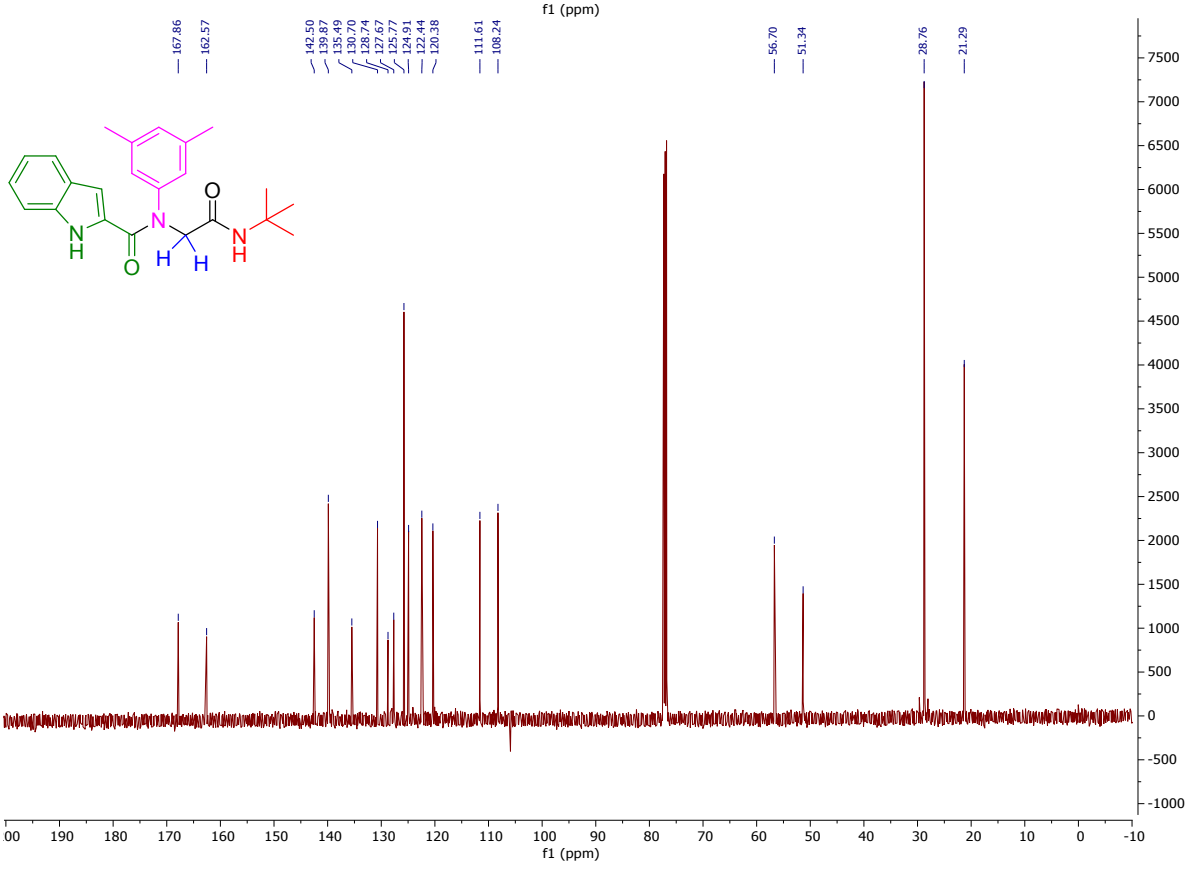

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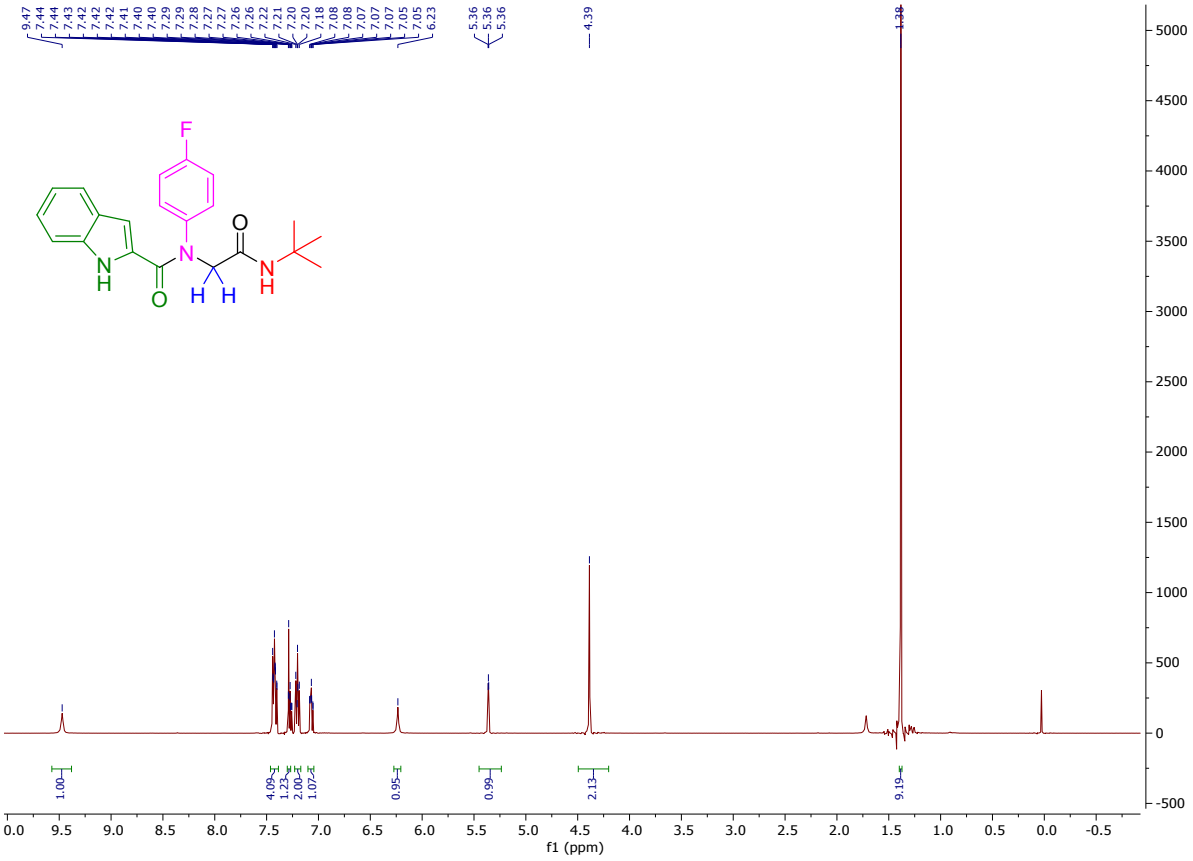

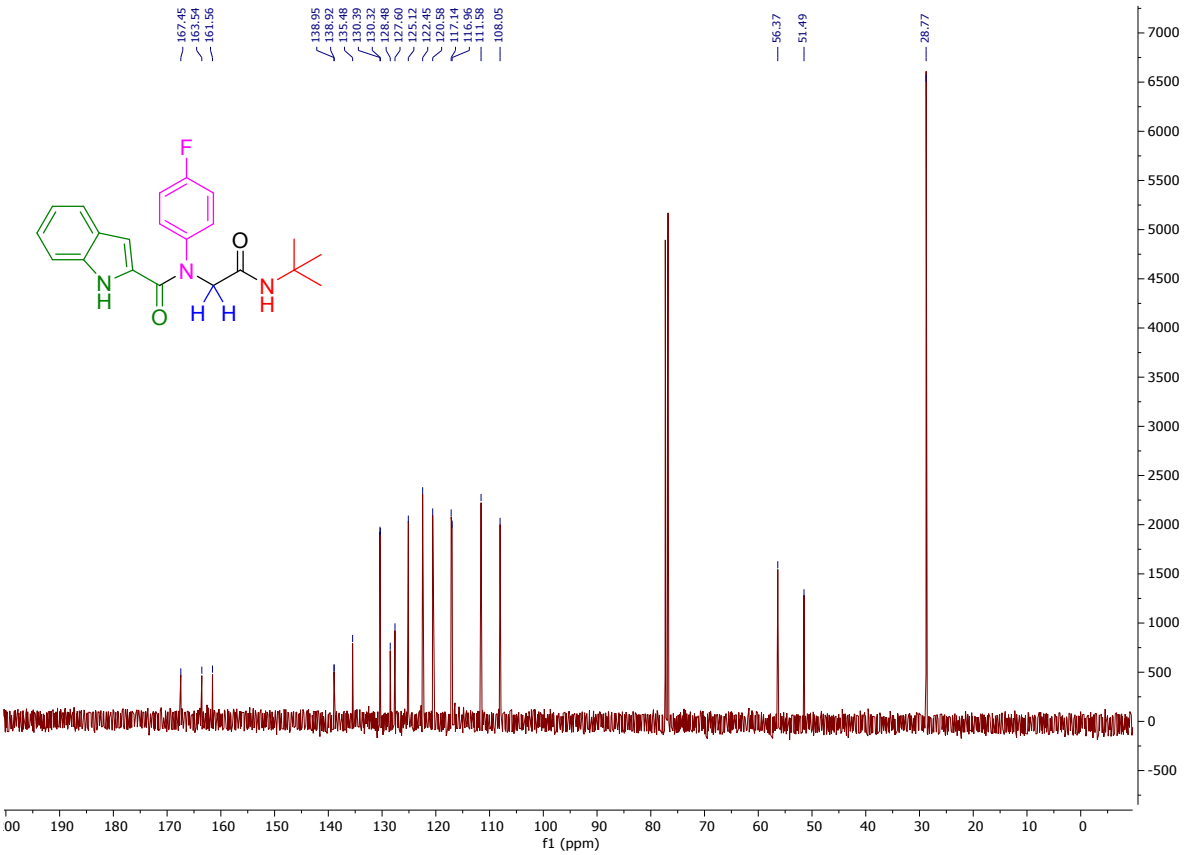

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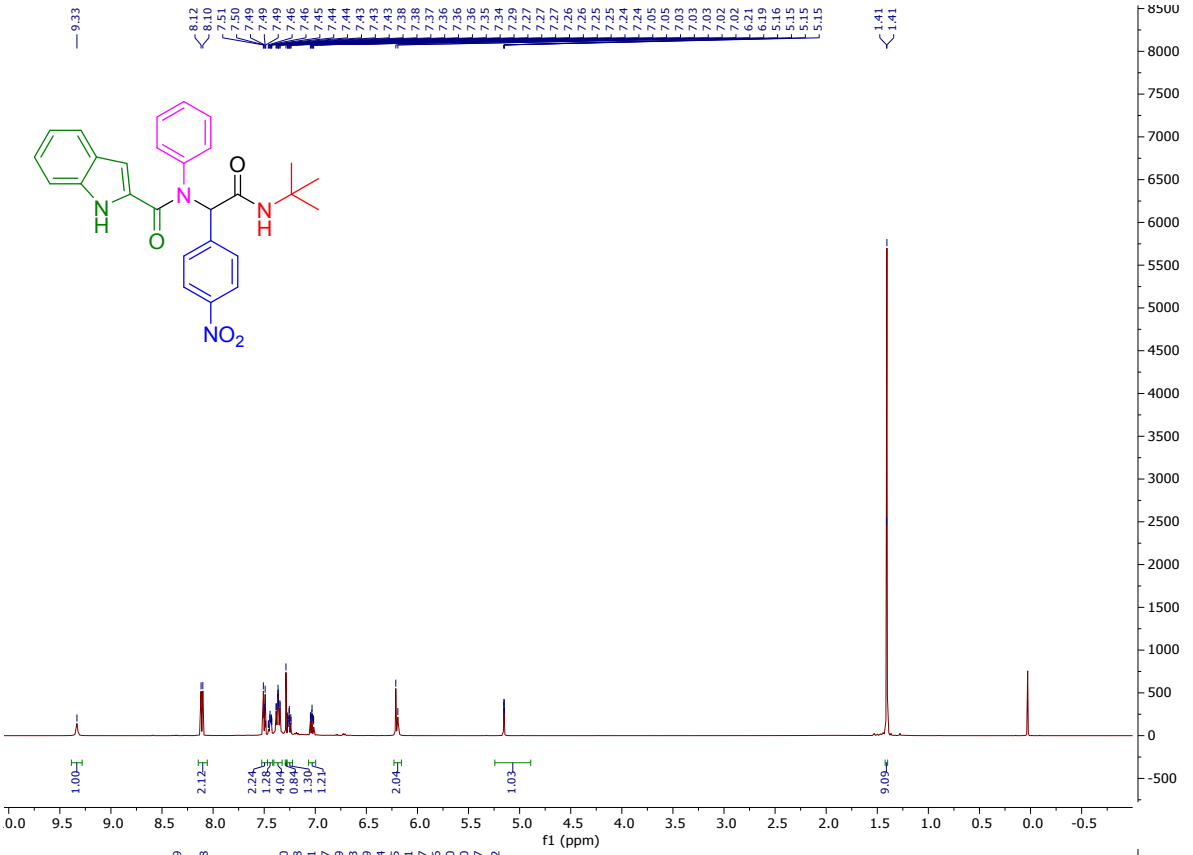

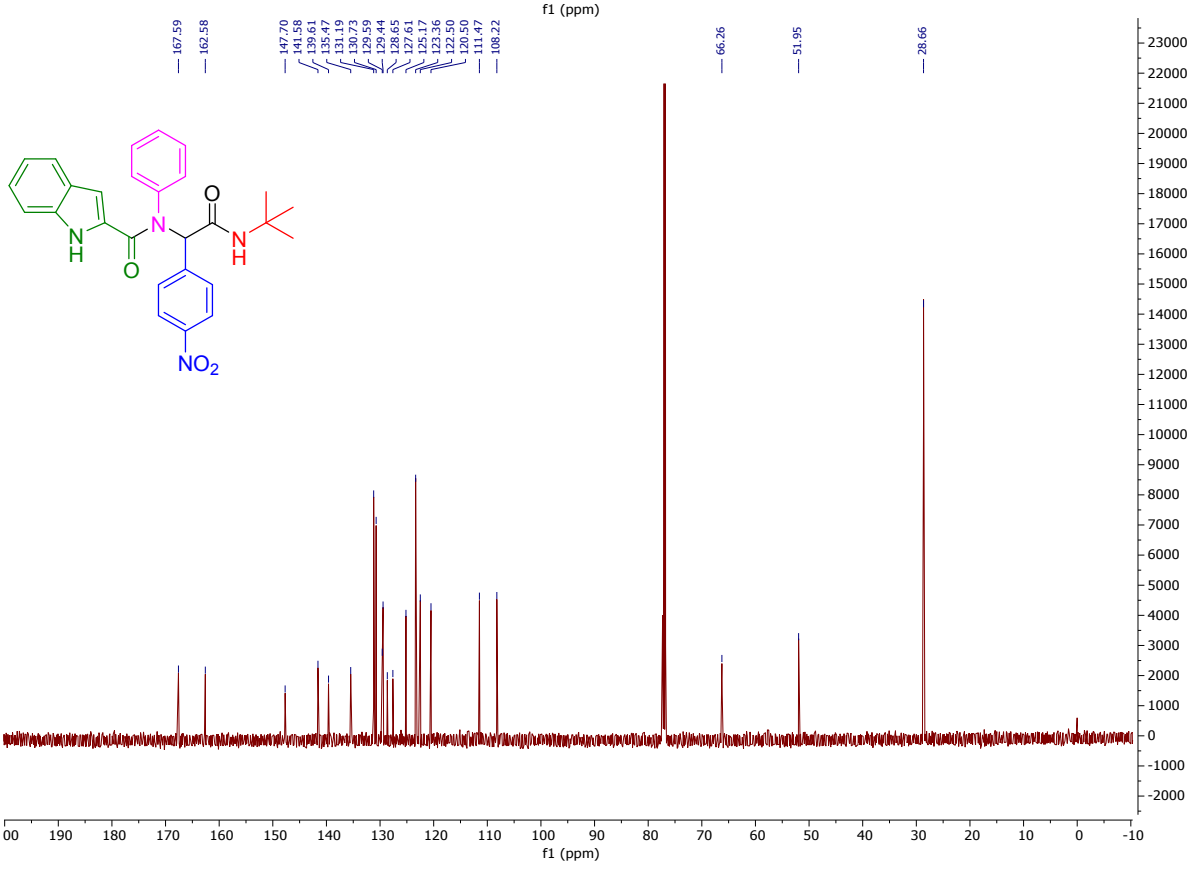

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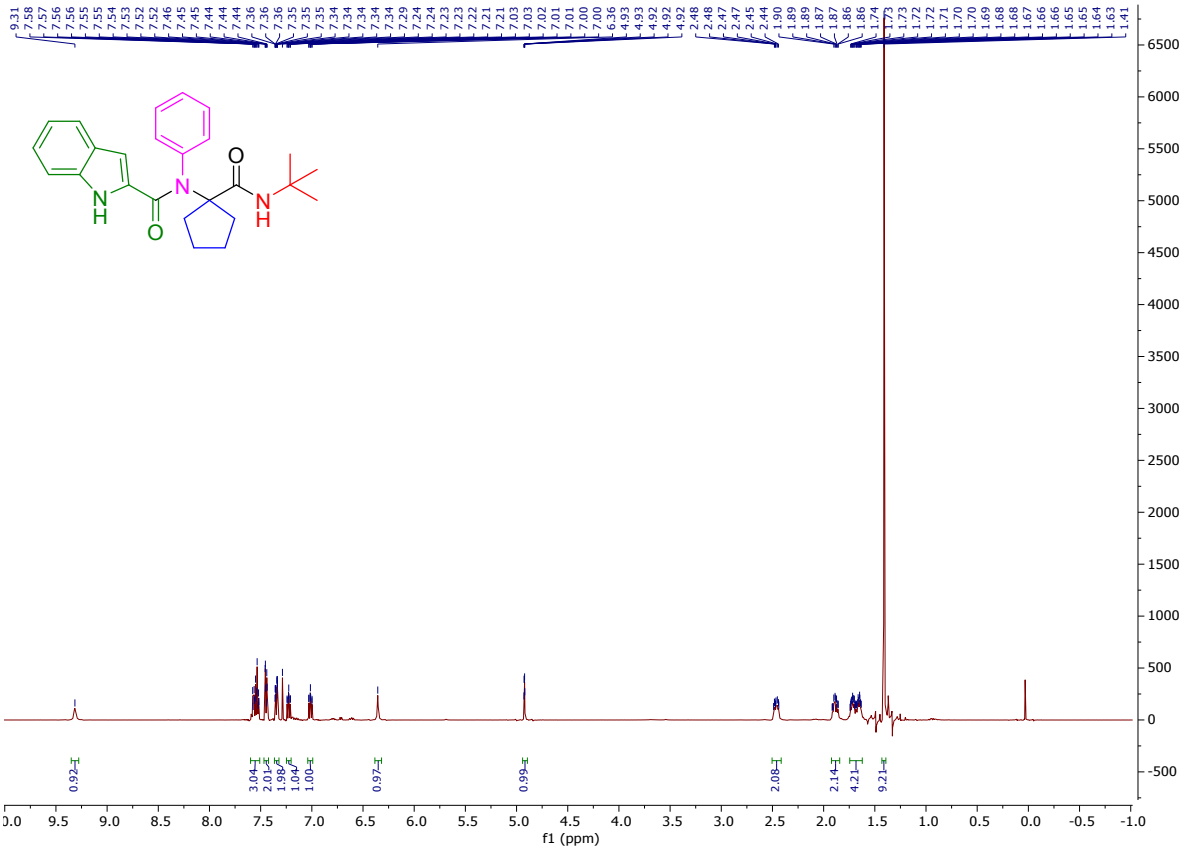
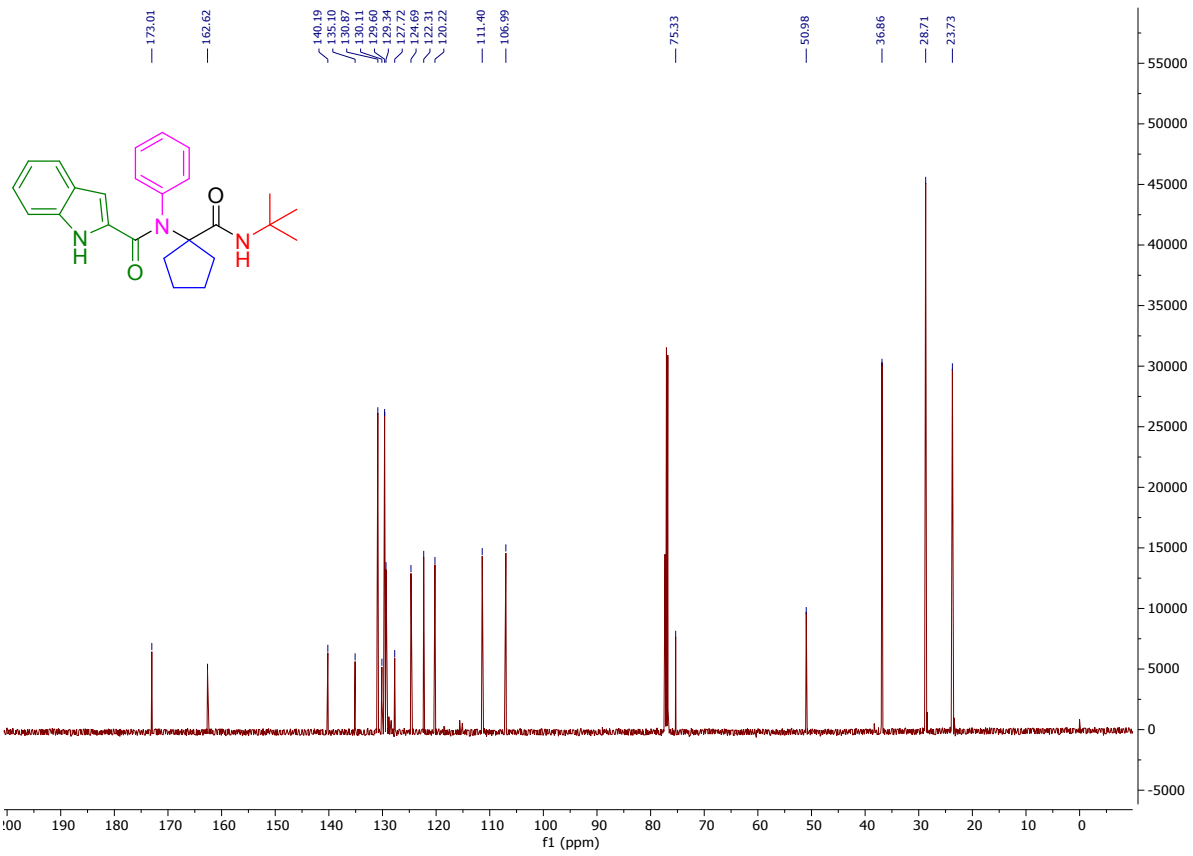
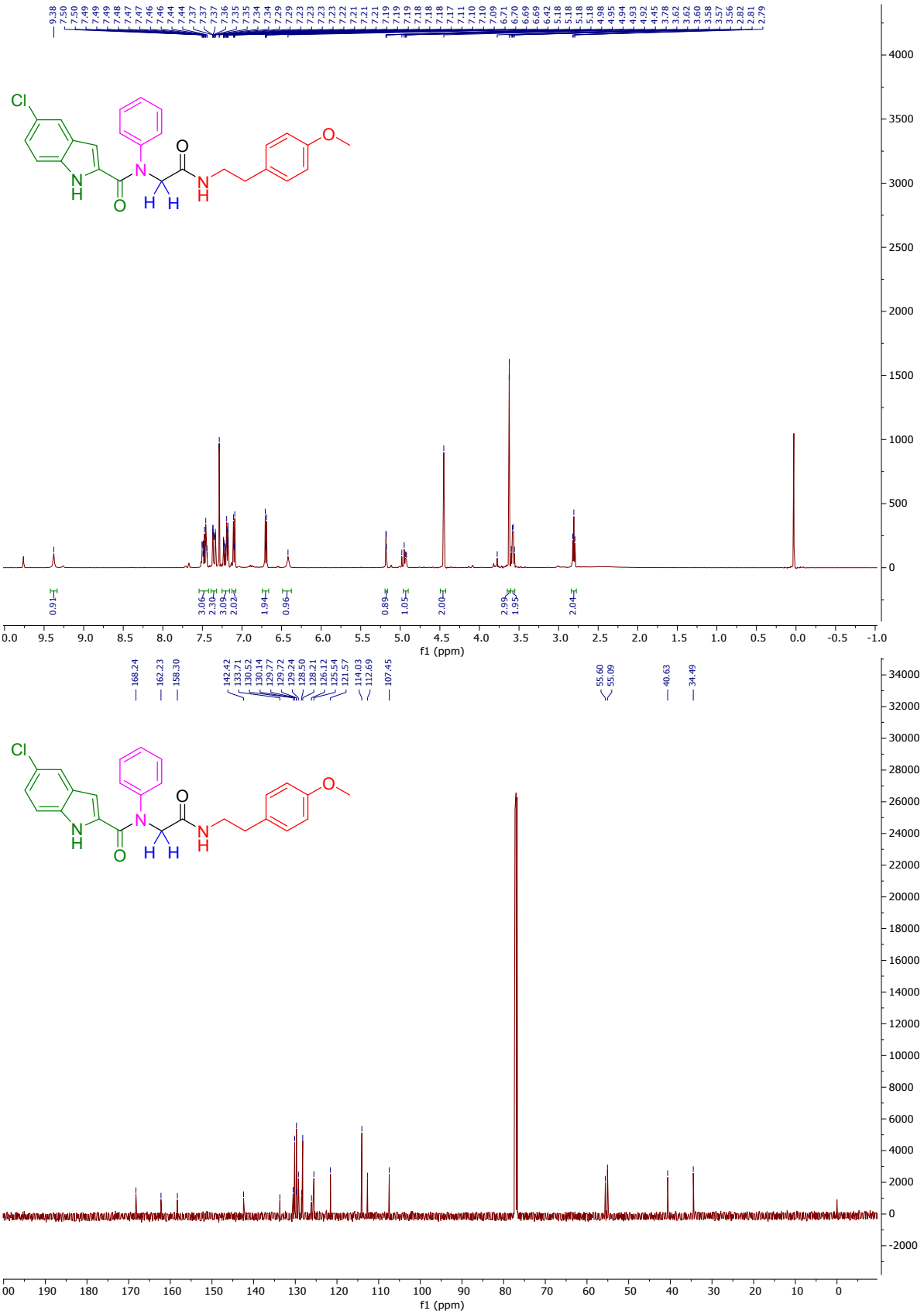




5j: 5-Chloro-*N*-(2-((4-methoxyphenethyl)amino)-2-oxoethyl)-*N*-phenyl-1*H*-indole-2-carboxamide



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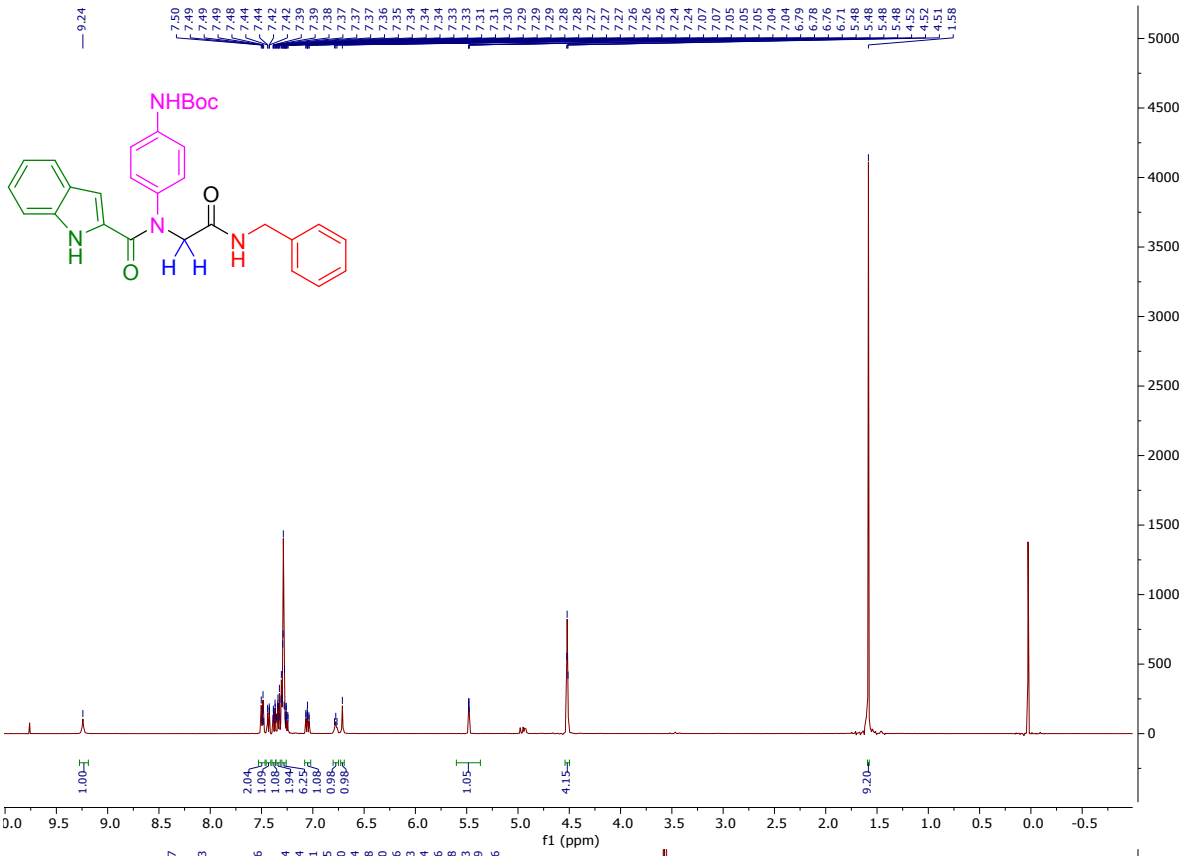
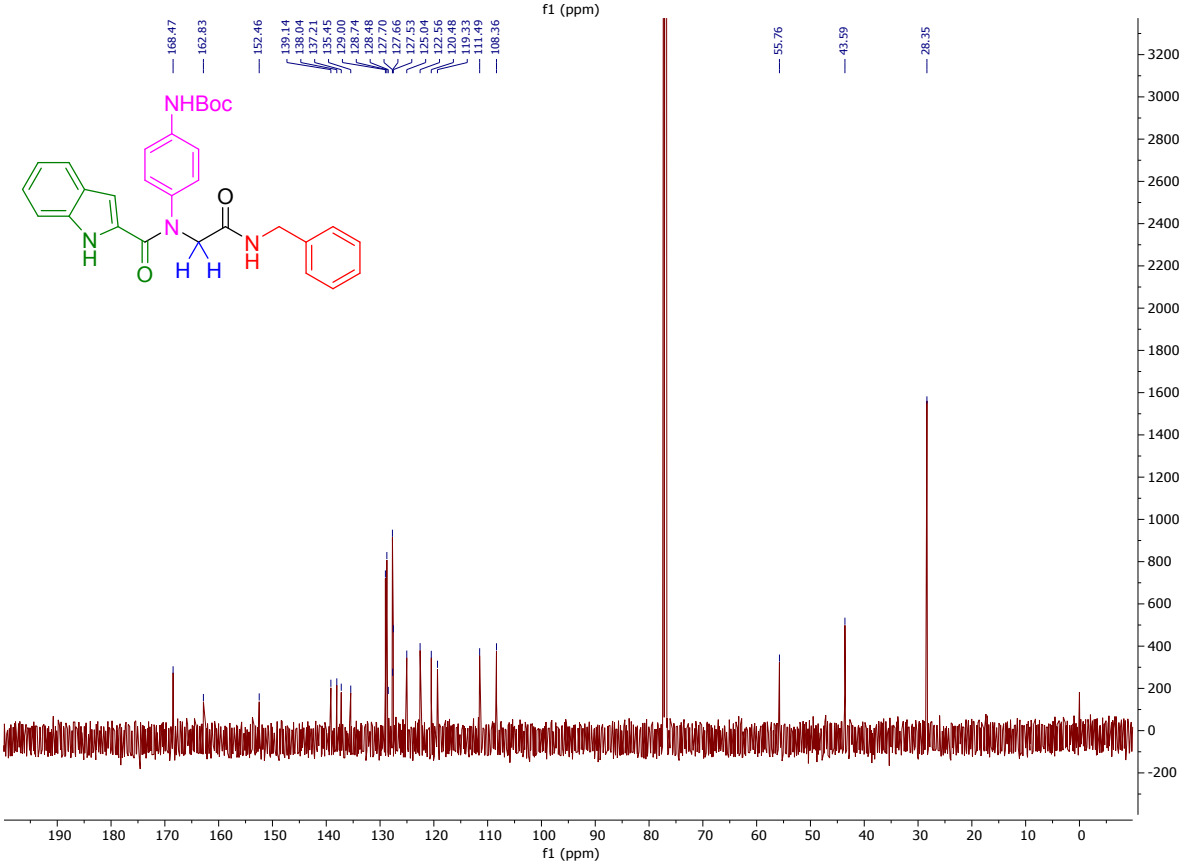
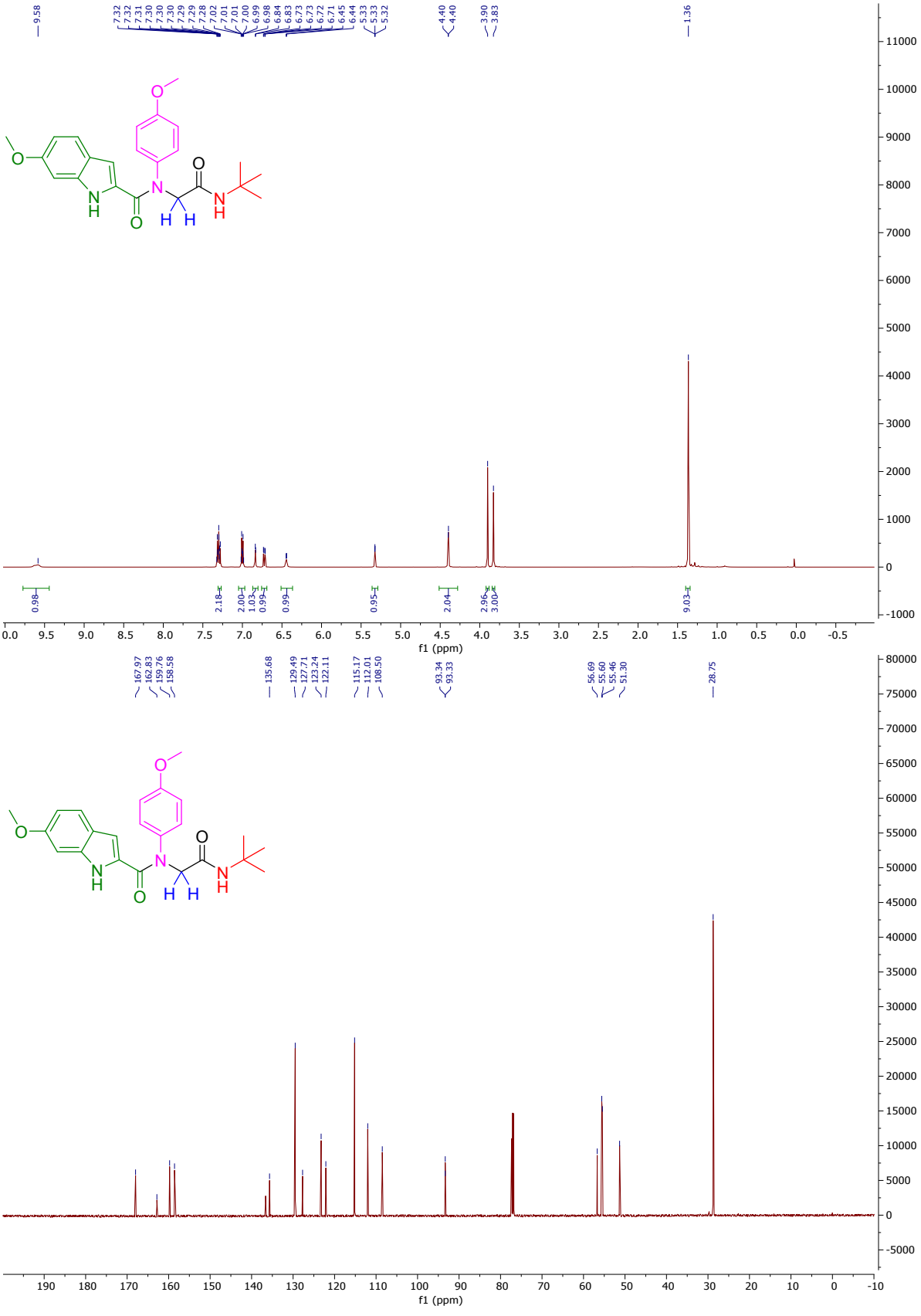




5l: N-(2-(*tert*-butylamino)-2-oxoethyl)-6-methoxy-*N*-(4-methoxyphenyl)-1*H*-indole-2-carboxamide



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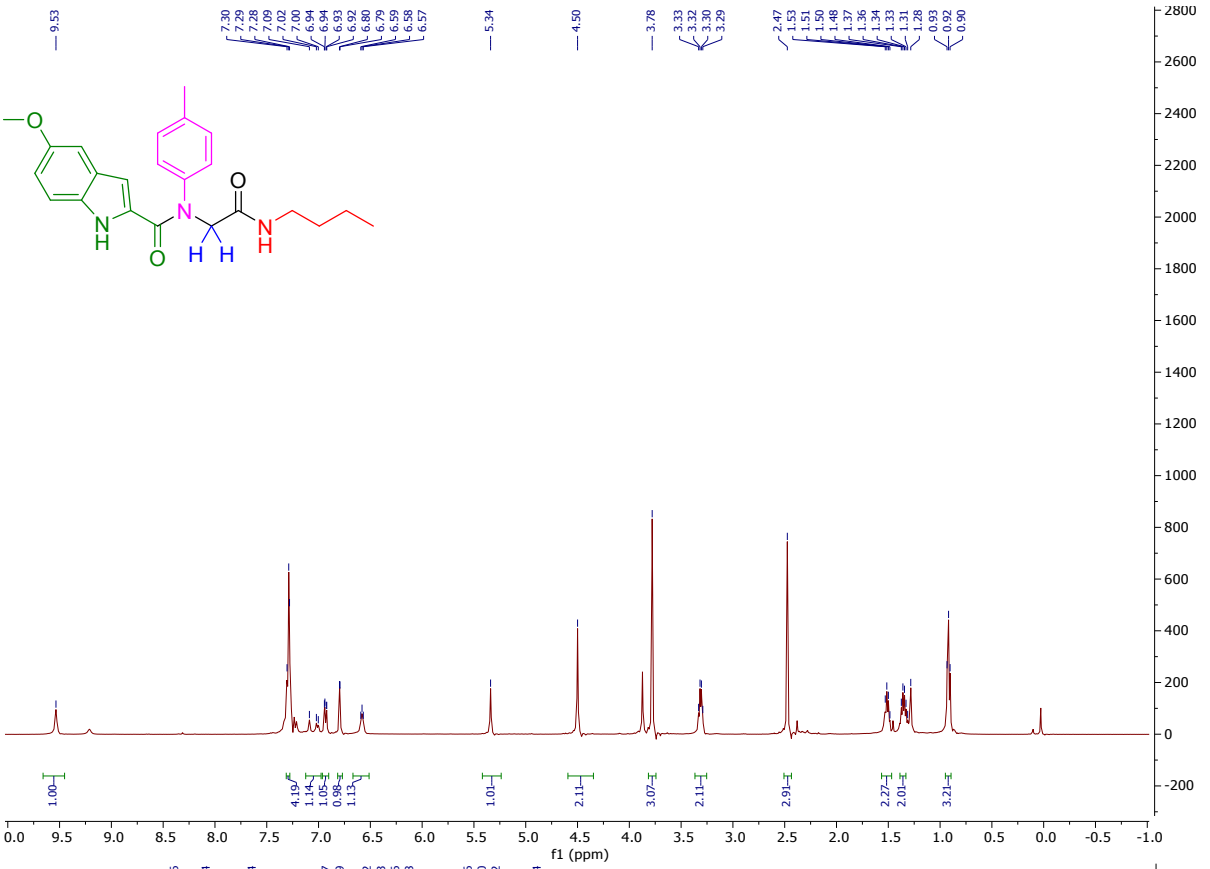

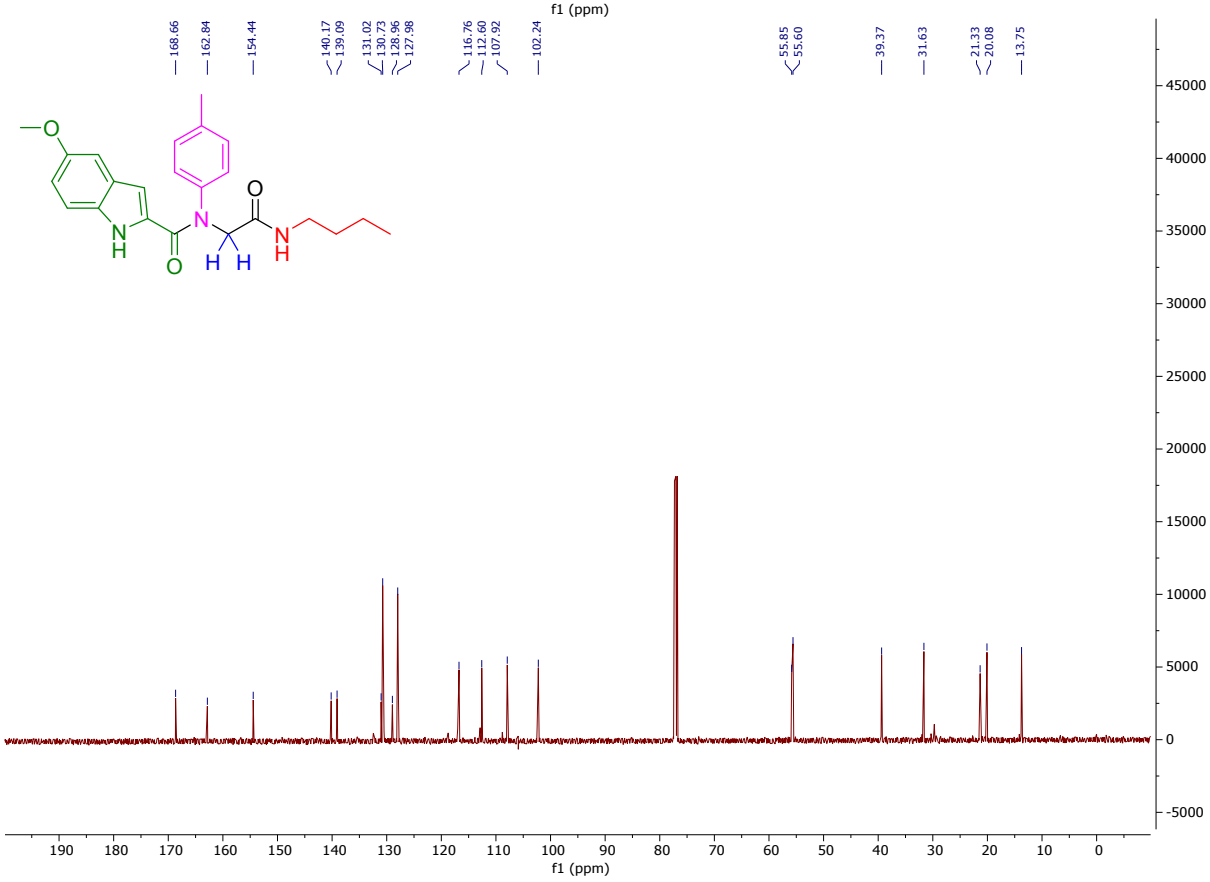

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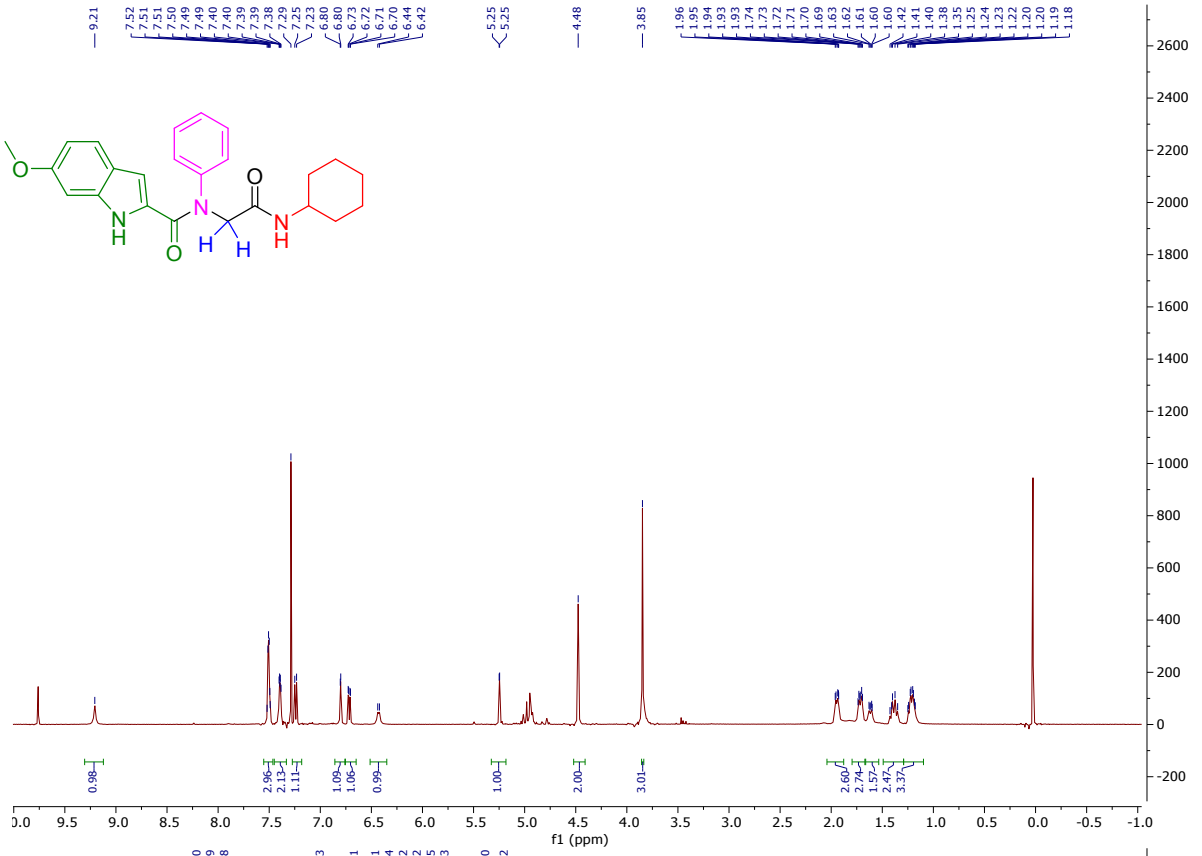
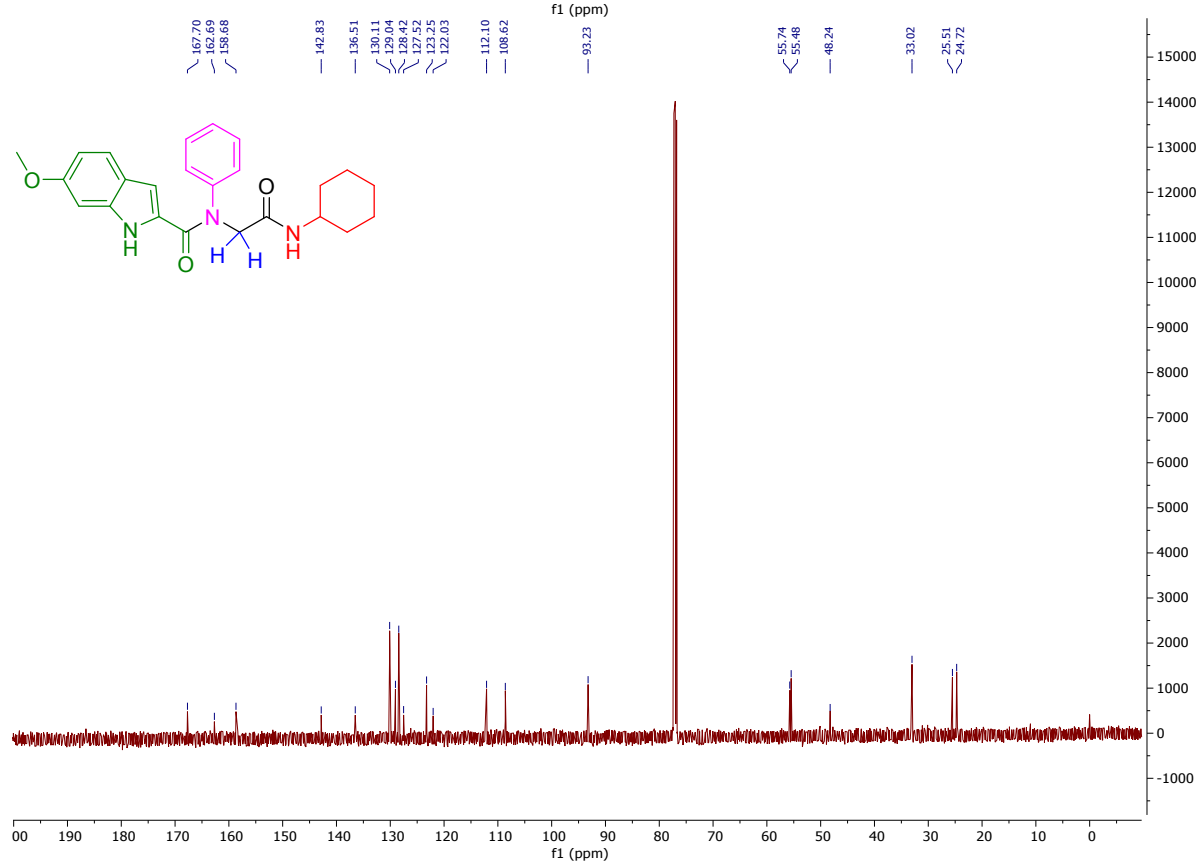
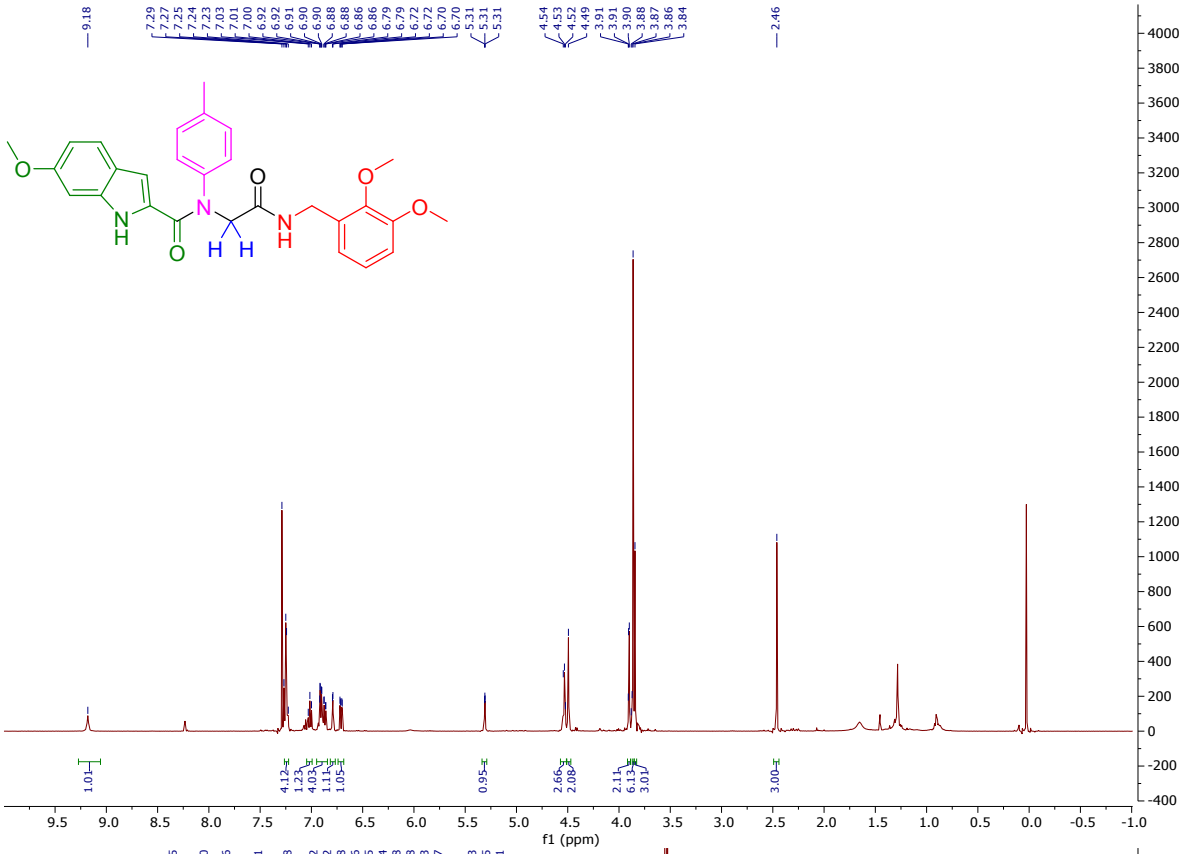
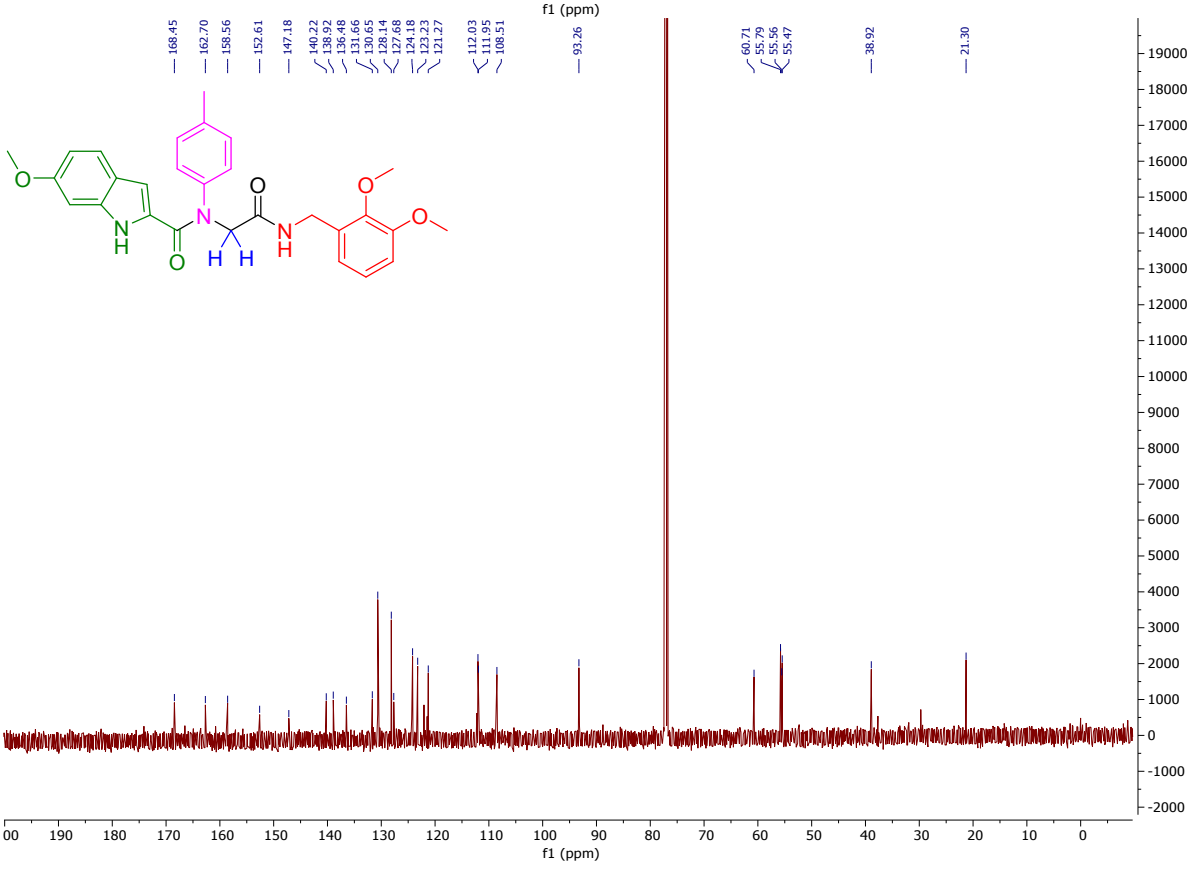


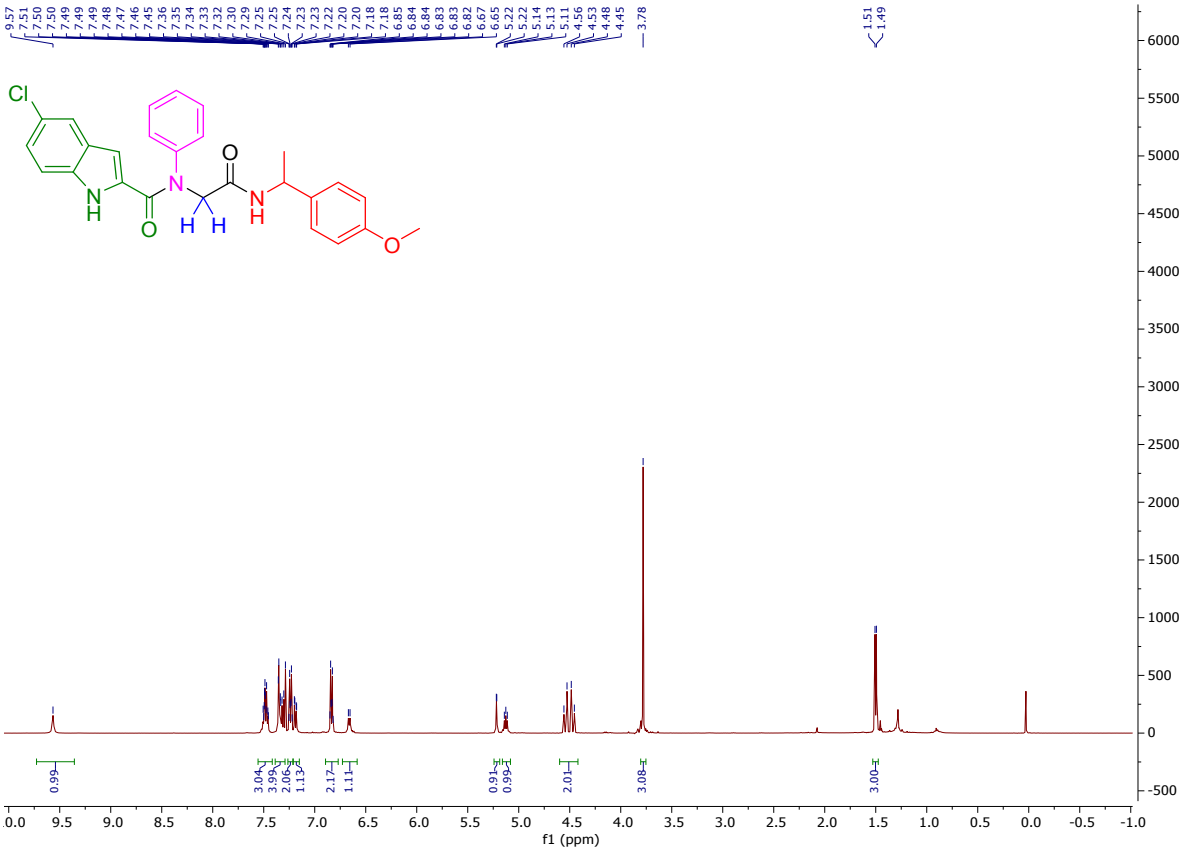


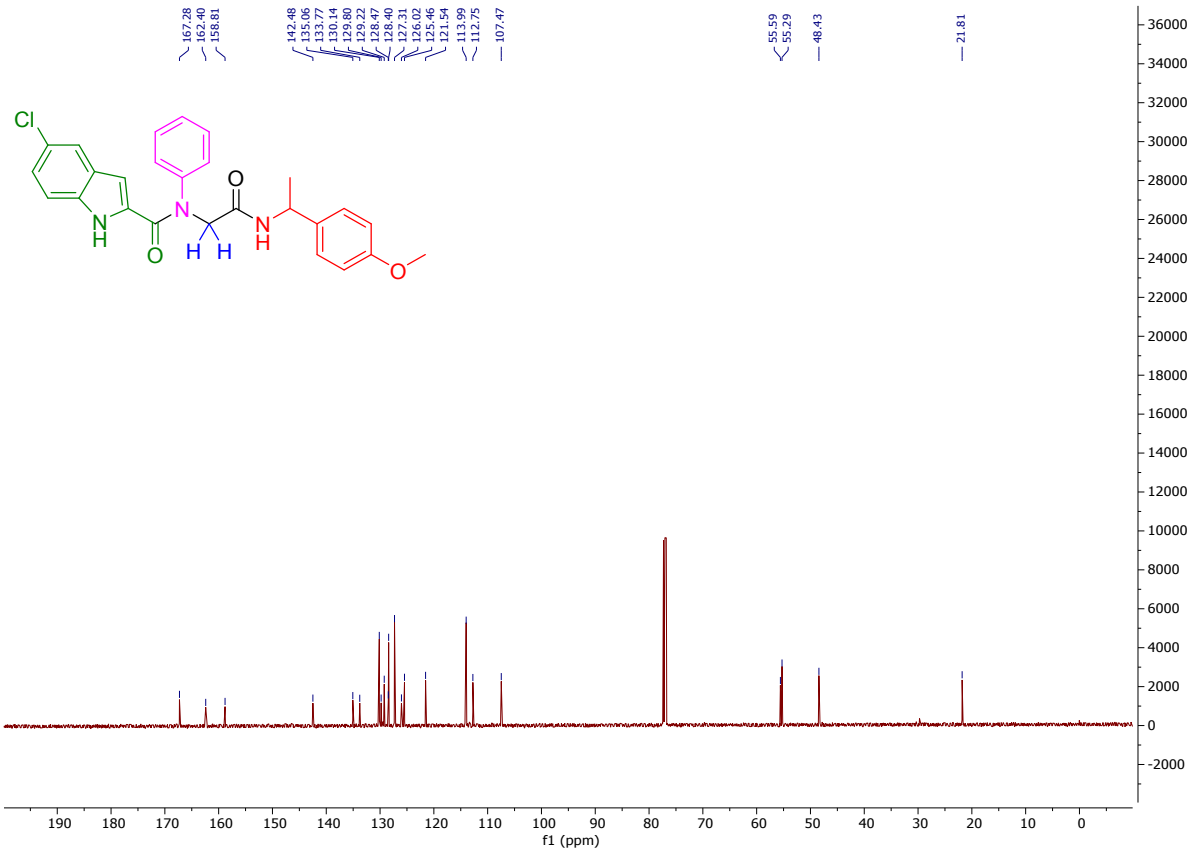
5o: *N*-(2-((2,3-dimethoxybenzyl)amino)-2-oxoethyl)-6-methoxy-*N*-(*p*-tolyl)-1*H*-indole-2-carboxamide





5p: 5-Chloro-*N*-(2-((1-(4-methoxyphenyl)ethyl)amino)-2-oxoethyl)-*N*-phenyl-1*H*-indole-2-carboxamide





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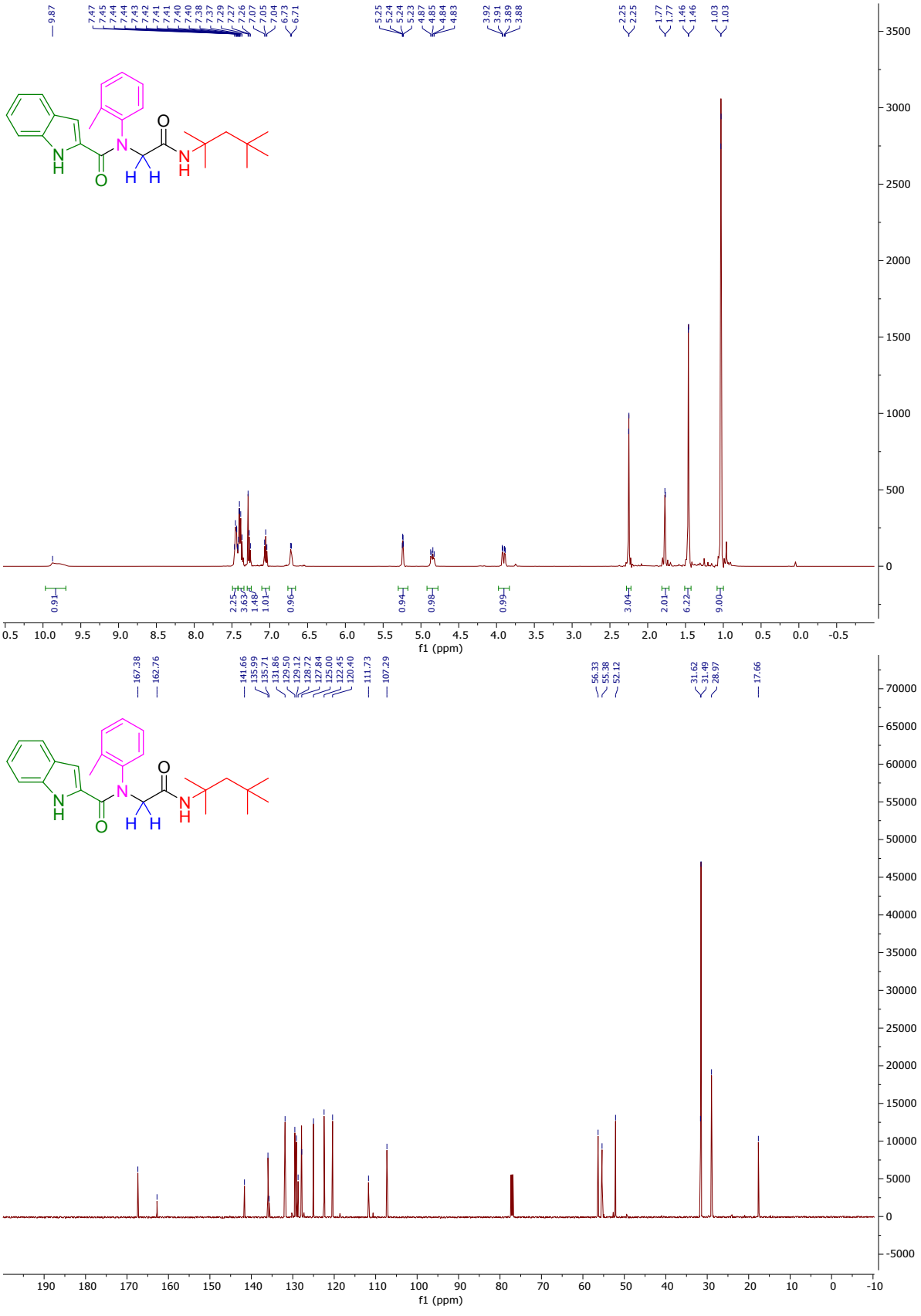
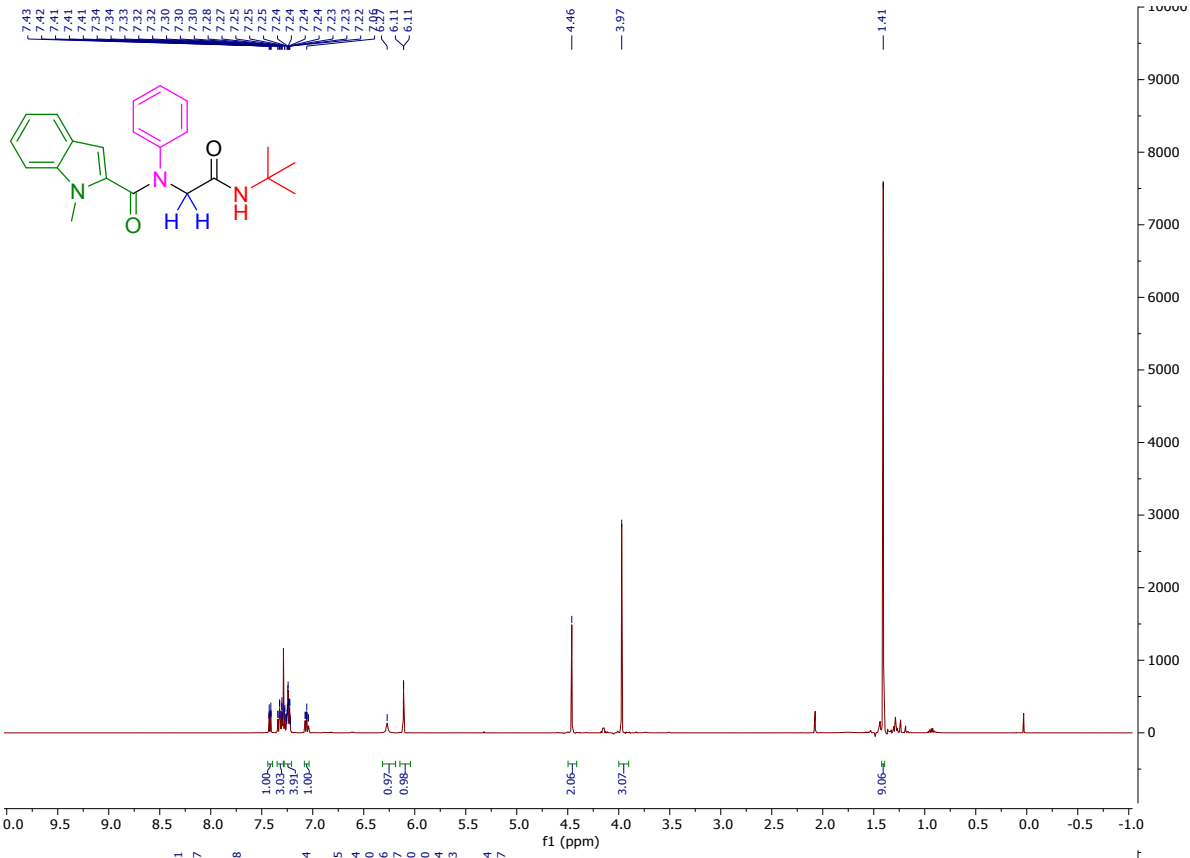
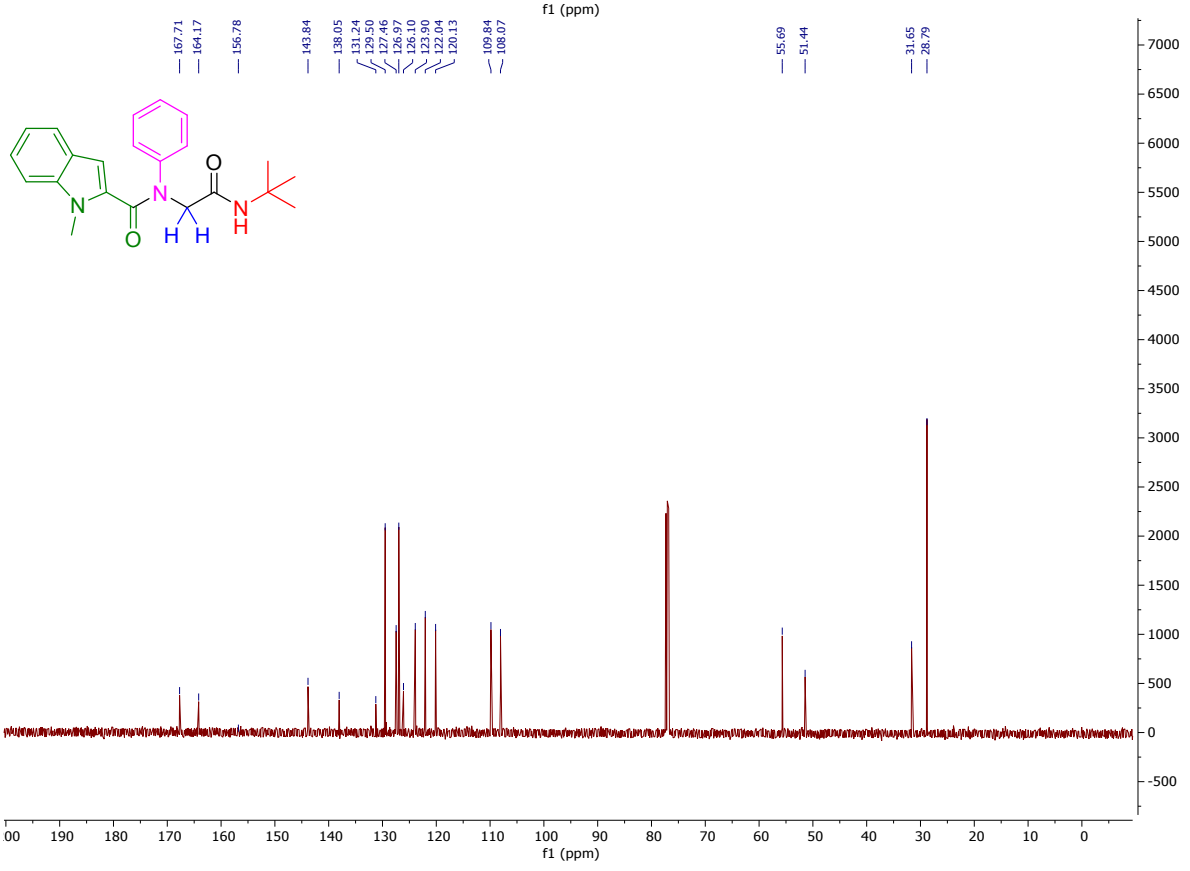
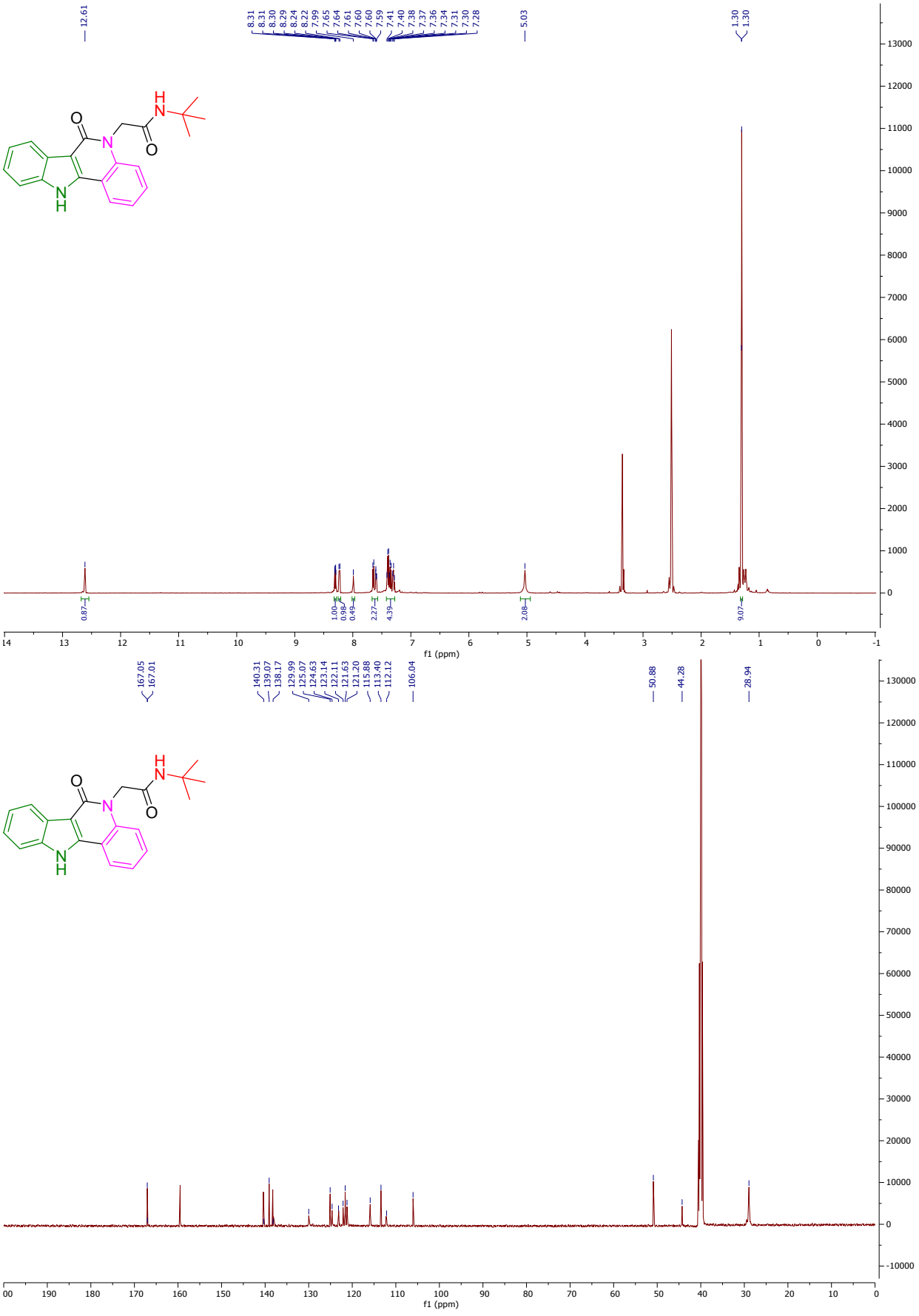


5r: *N*-(2-(*tert*-butylamino)-2-oxoethyl)-1-methyl-*N*-phenyl-*1H*-indole-2-carboxamide





6a: *N*-(*tert*-butyl)-2-(6-oxo-6,11-dihydro-5*H*-indolo[3,2-*c*]quinolin-5-yl)acetamide



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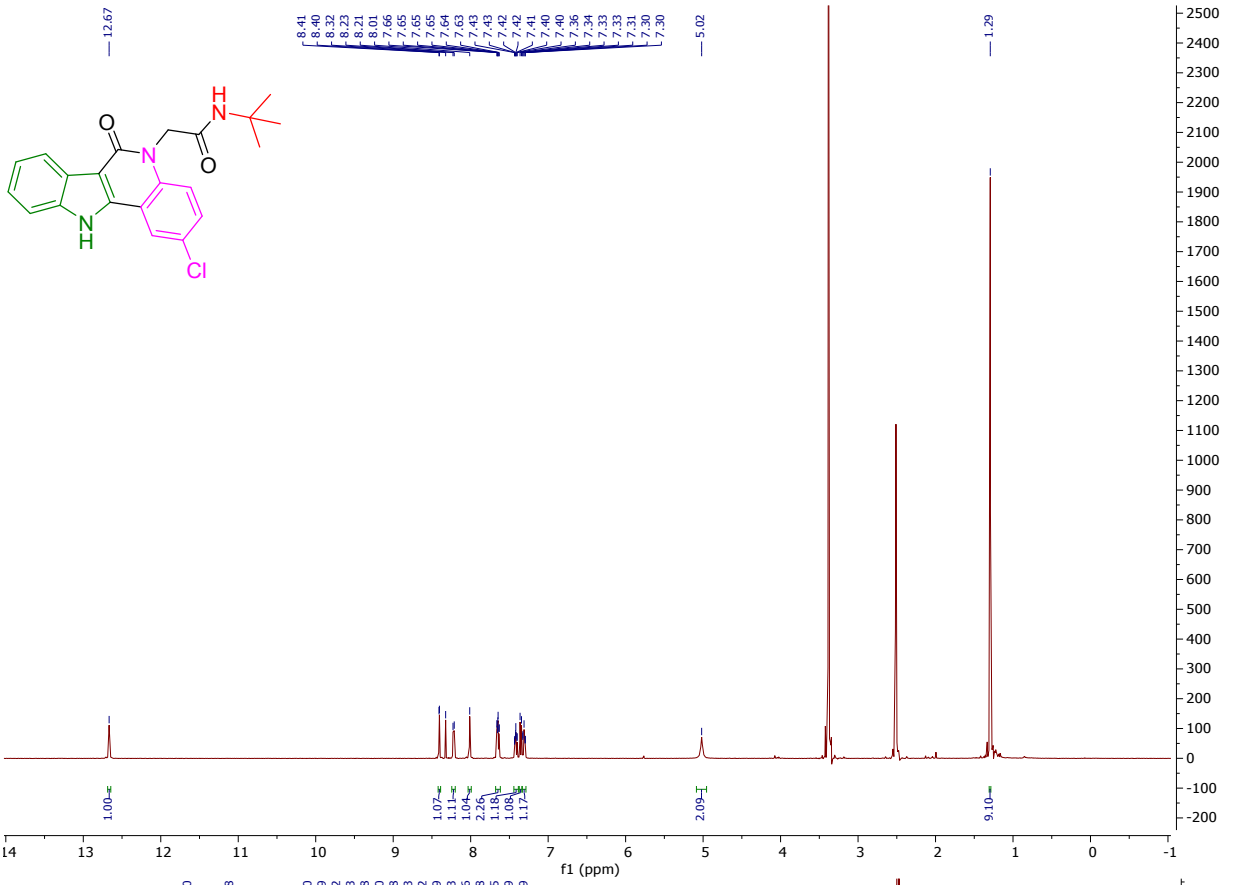
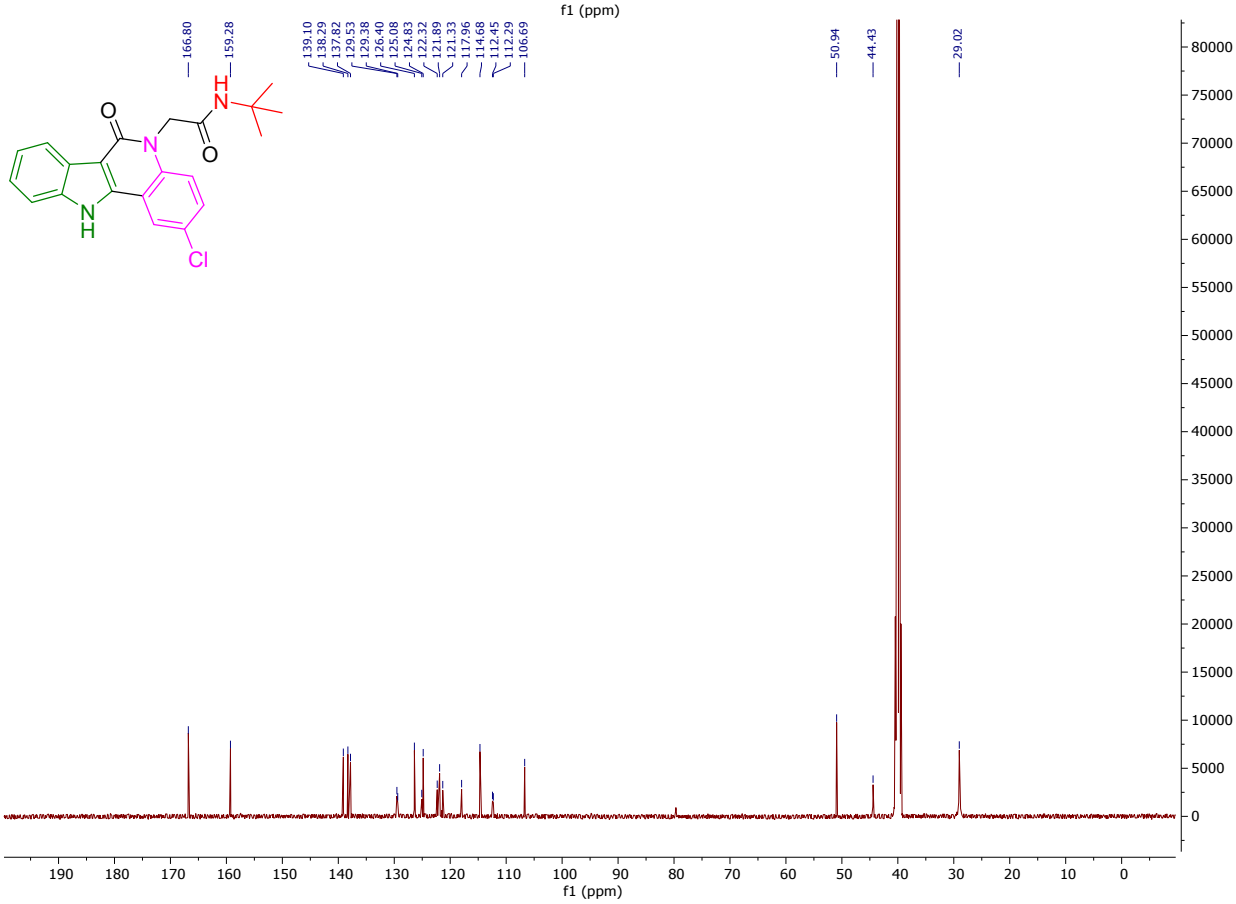
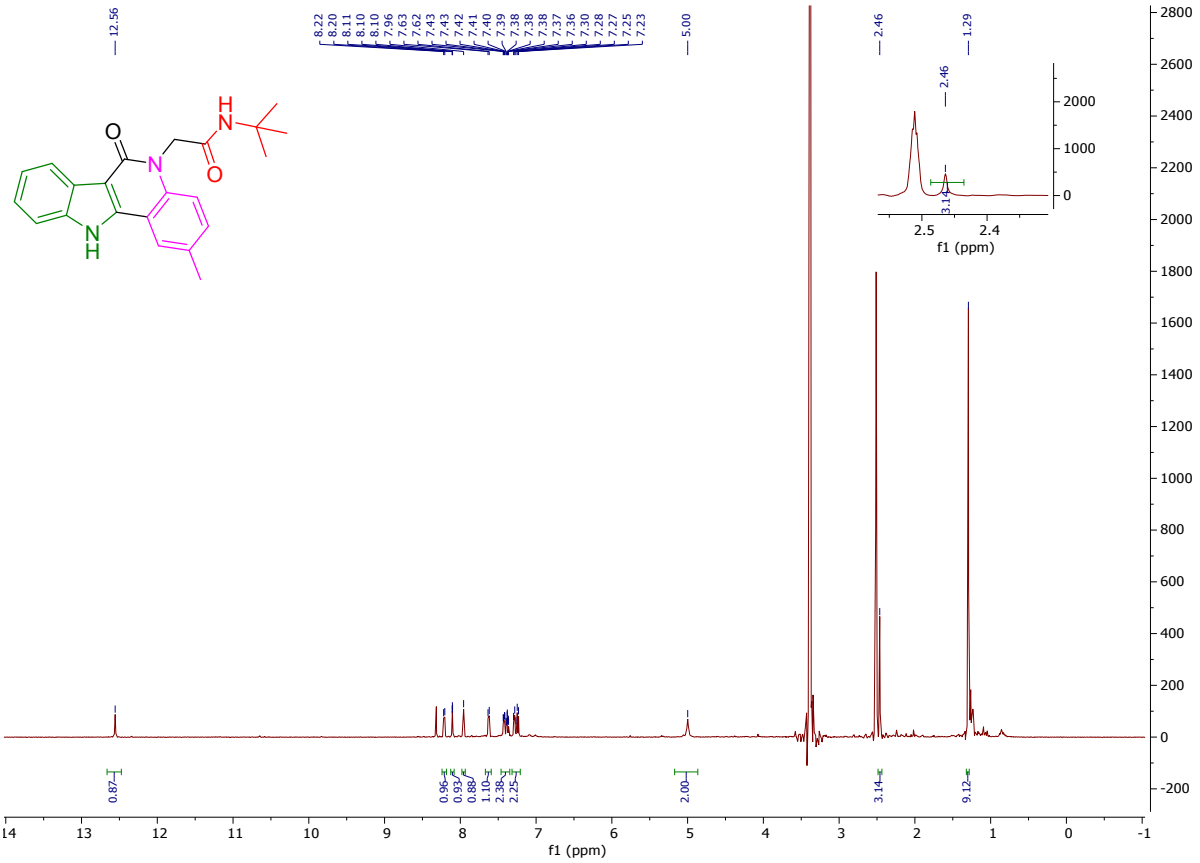
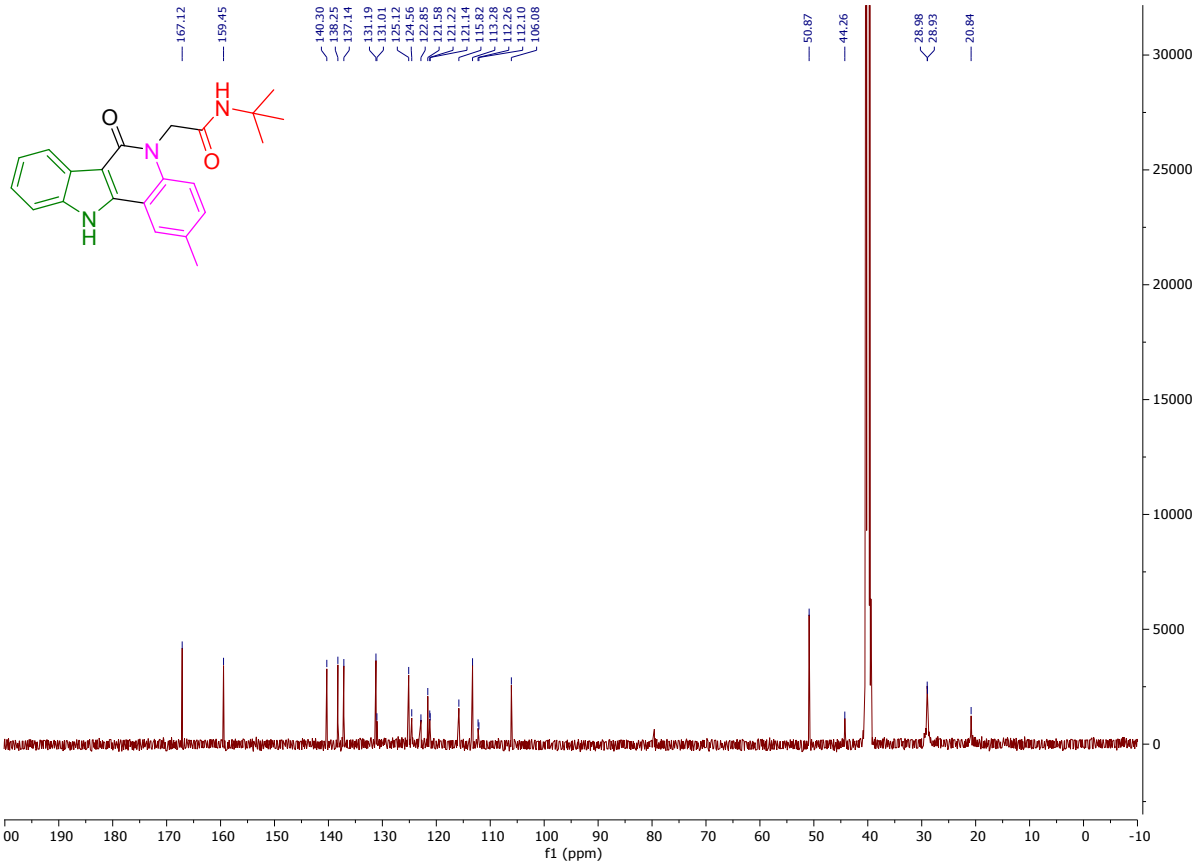


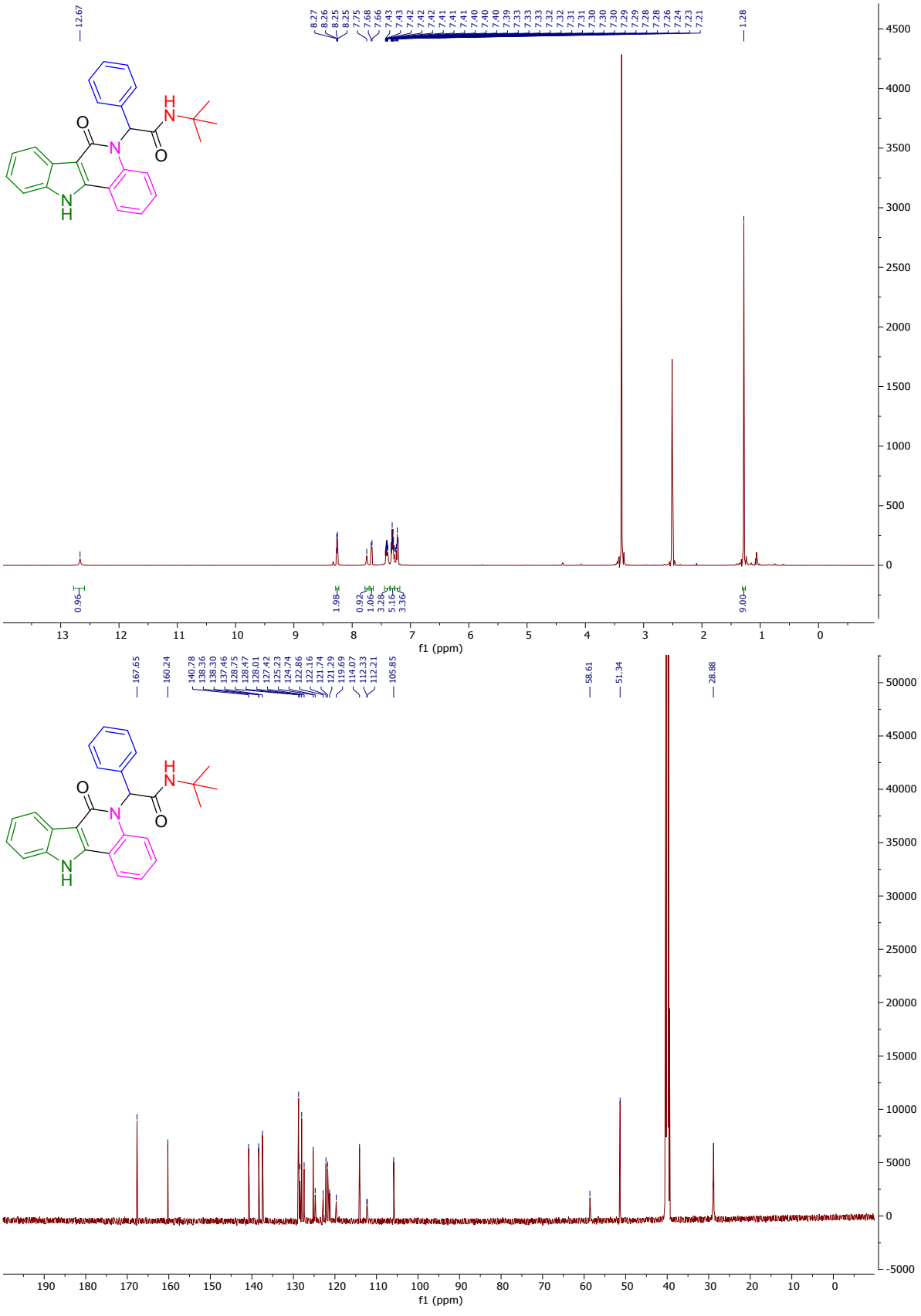


6c:*N*-(*tert*-butyl)-2-(2-methyl-6-oxo-6,11-dihydro-5*H*-indolo[3,2-*c*]quinolin-5-yl)acetamide





6d: *N*-(*tert*-butyl)-2-(6-oxo-6,11-dihydro-5*H*-indolo[3,2-*c*]quinolin-5-yl)-2-phenylacetamide



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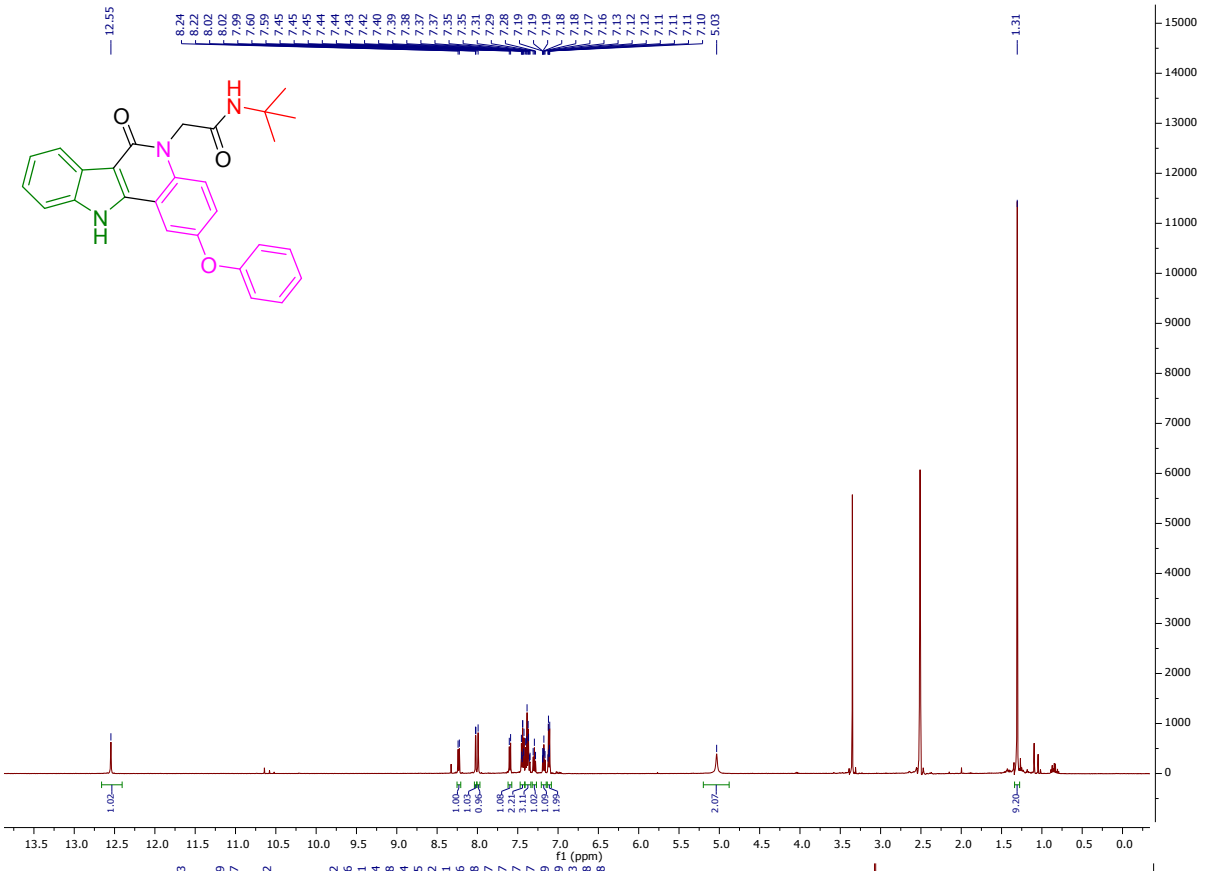

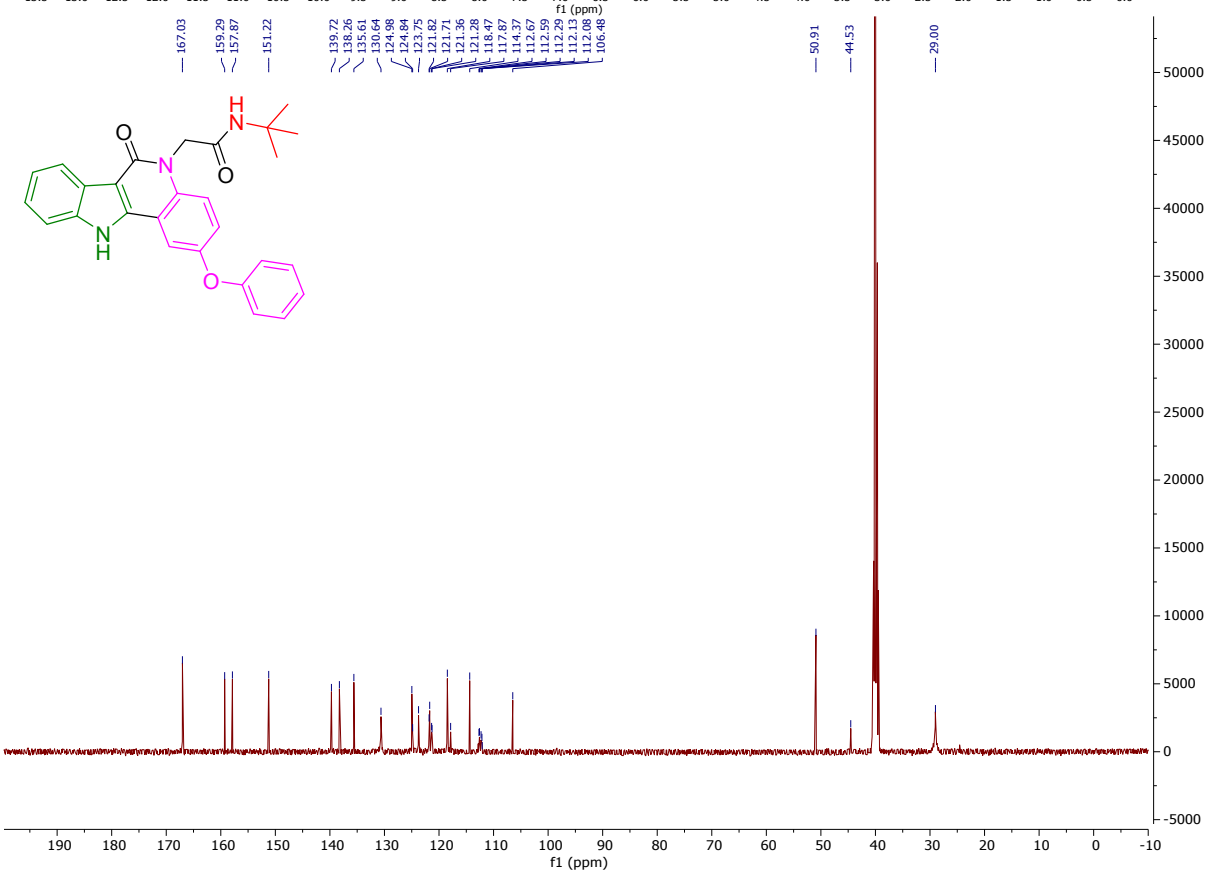

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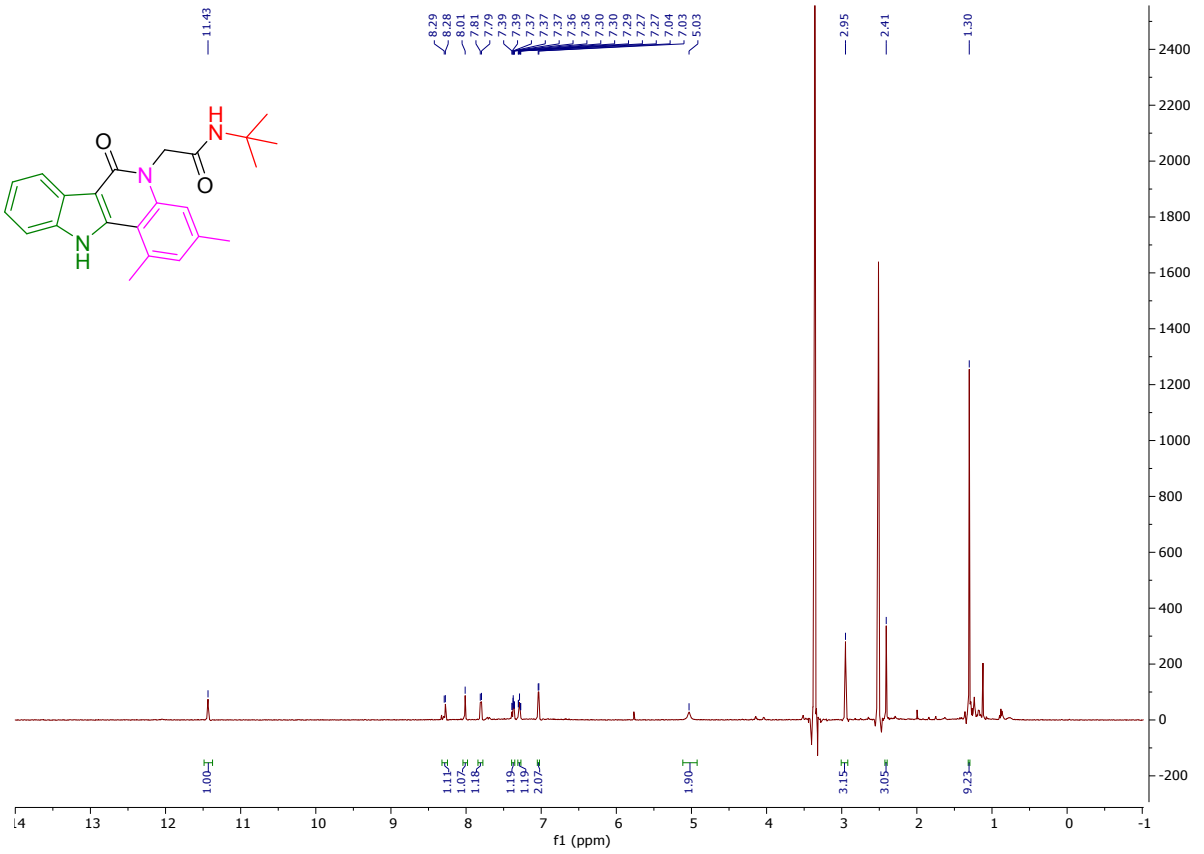

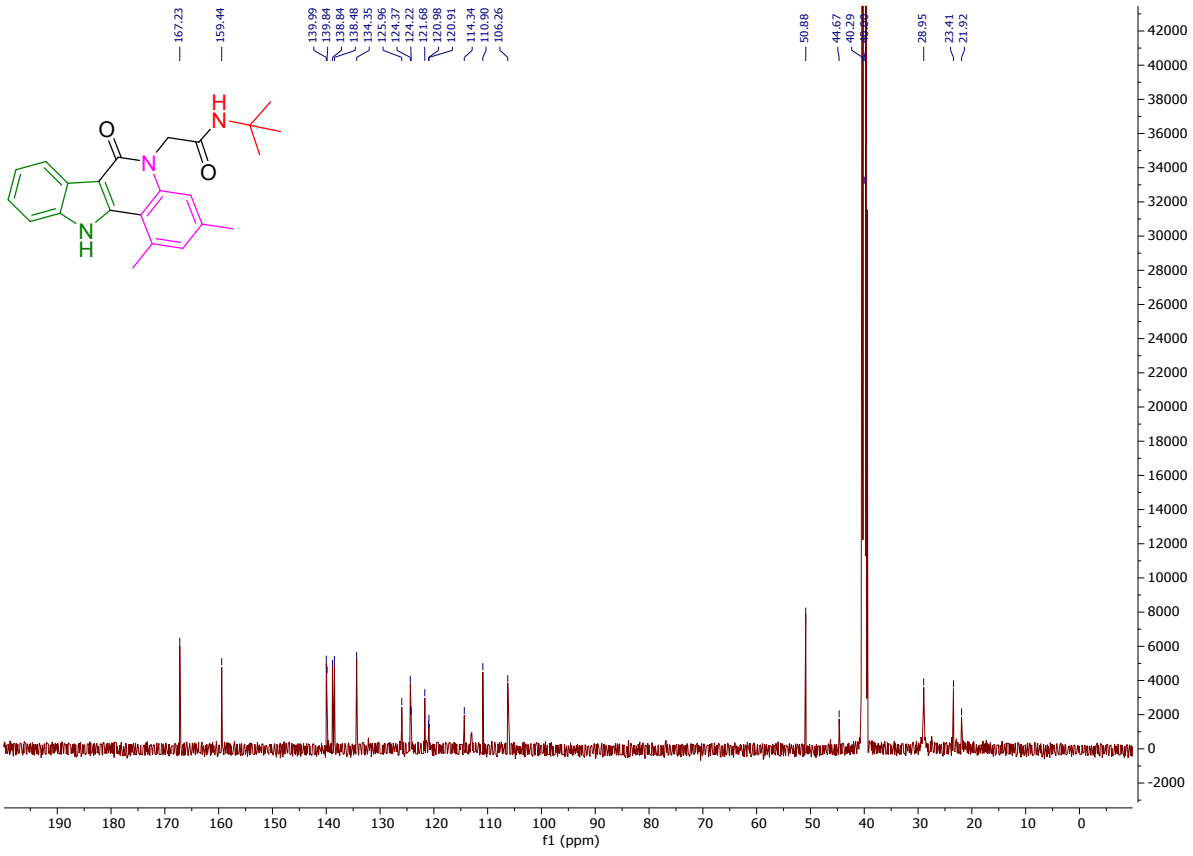

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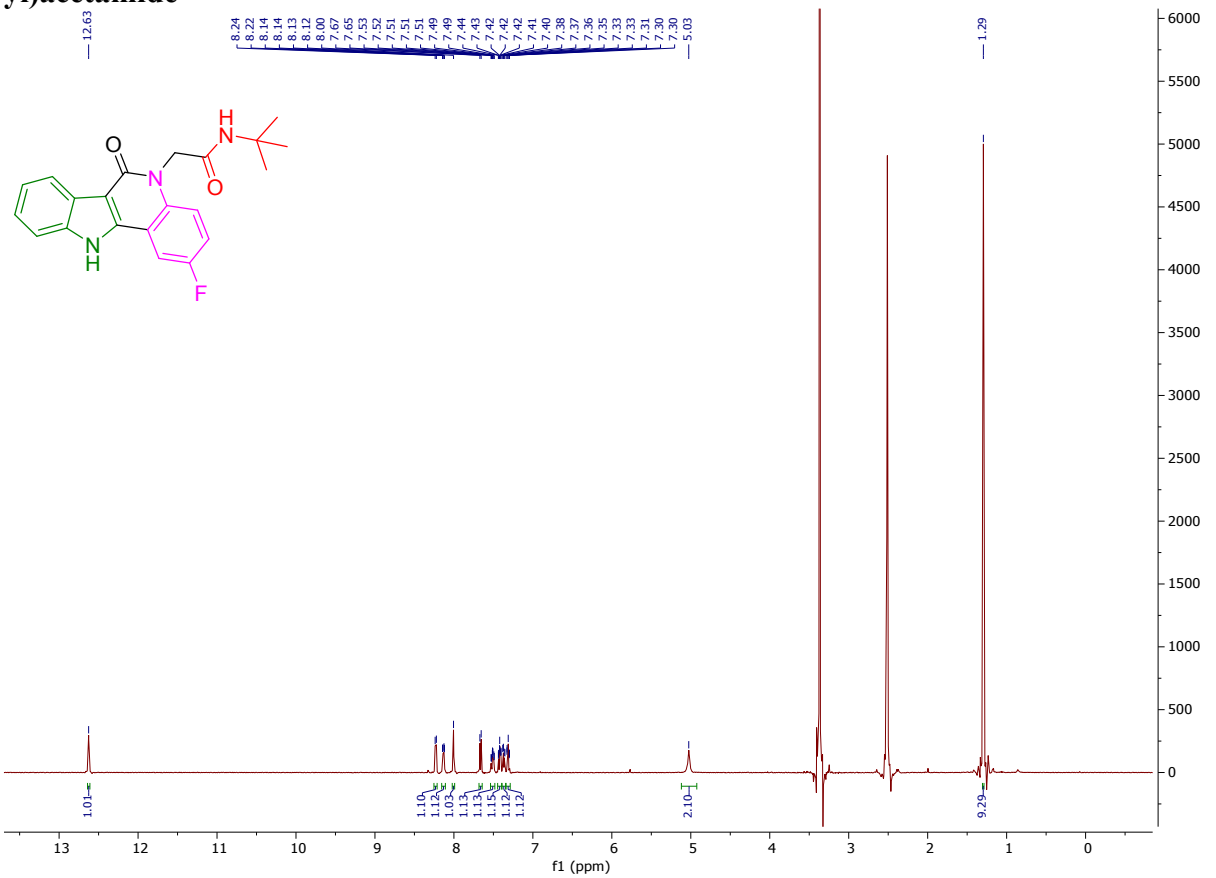
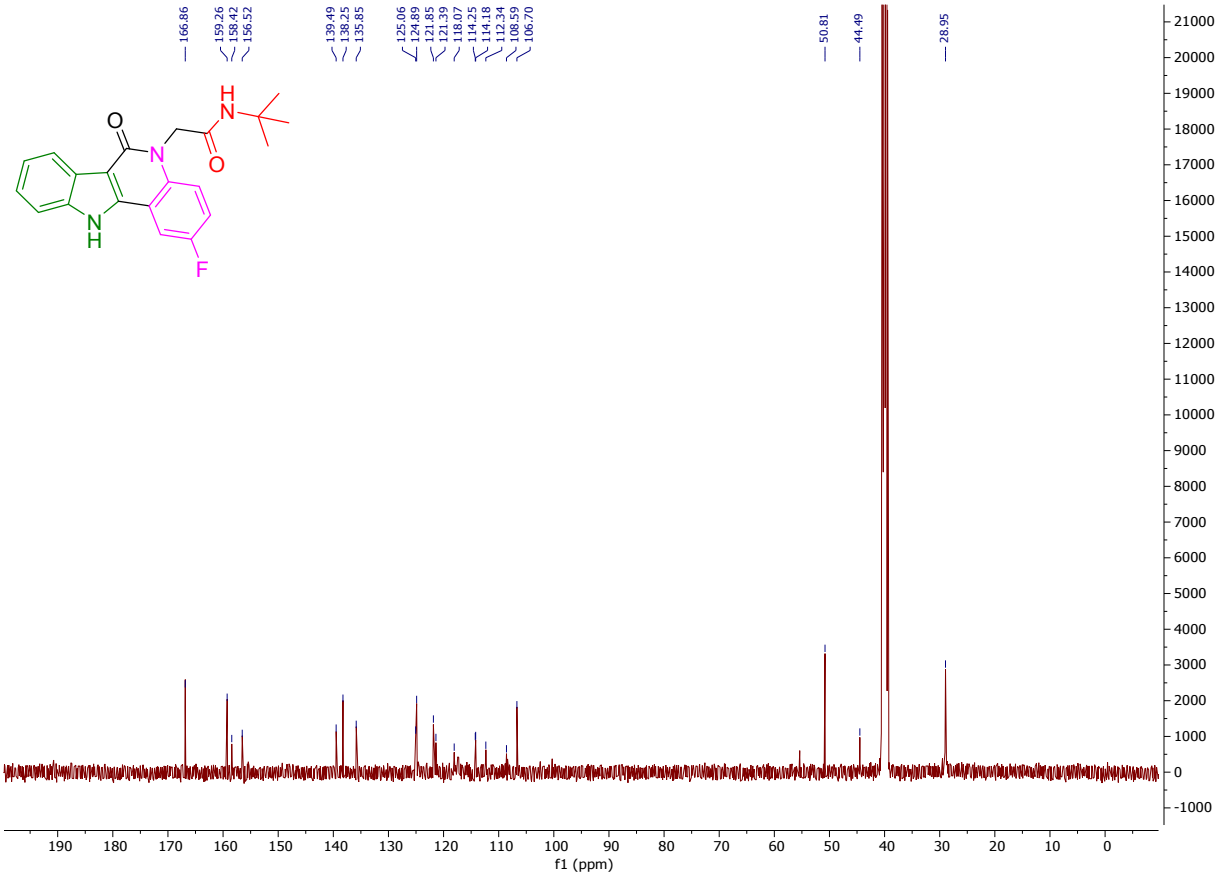
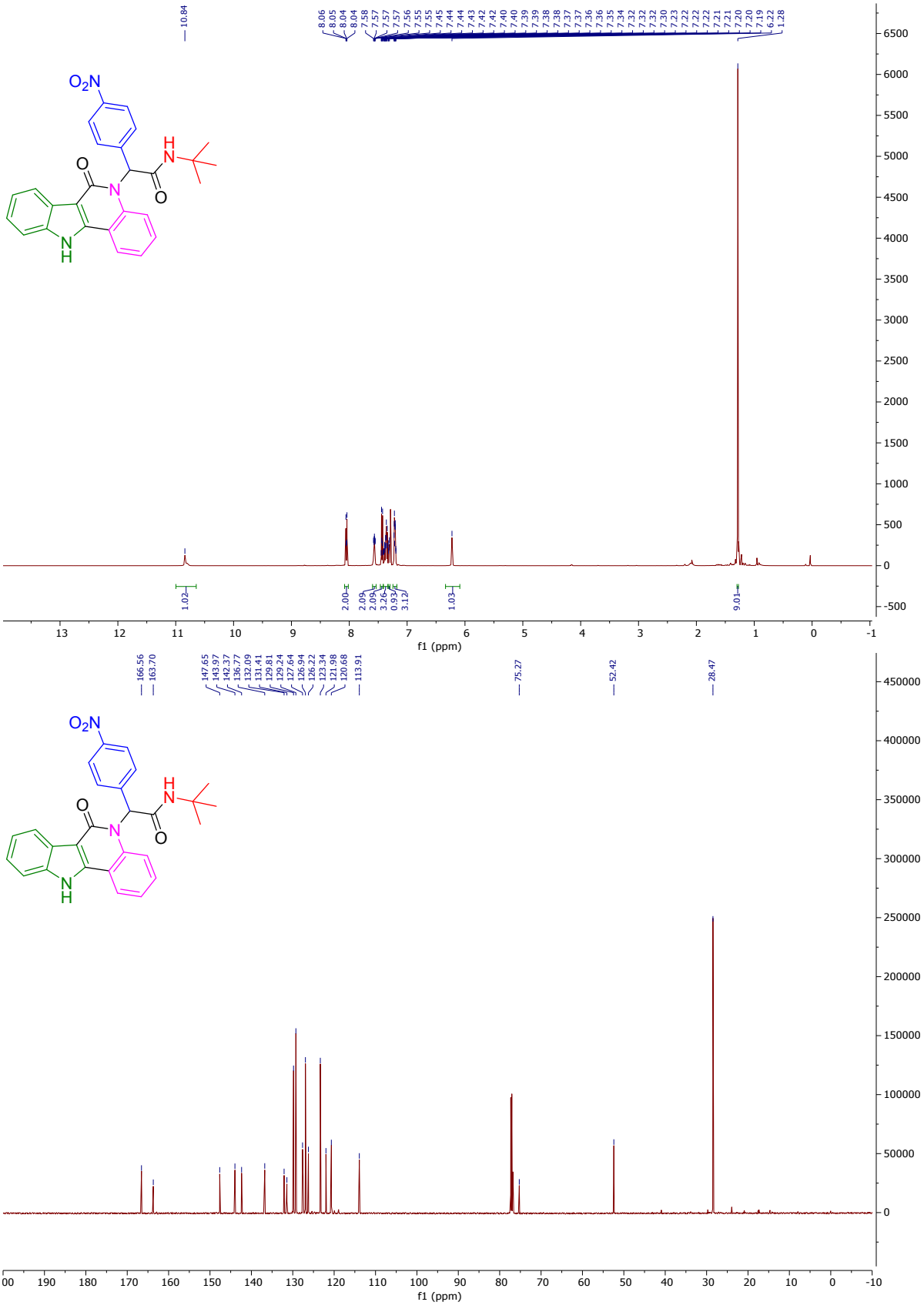




6h: *N*-(*tert*-butyl)-2-(4-nitrophenyl)-2-(6-oxo-6,11-dihydro-5*H*-indolo[3,2-*c*]quinolin-5-yl)acetamide



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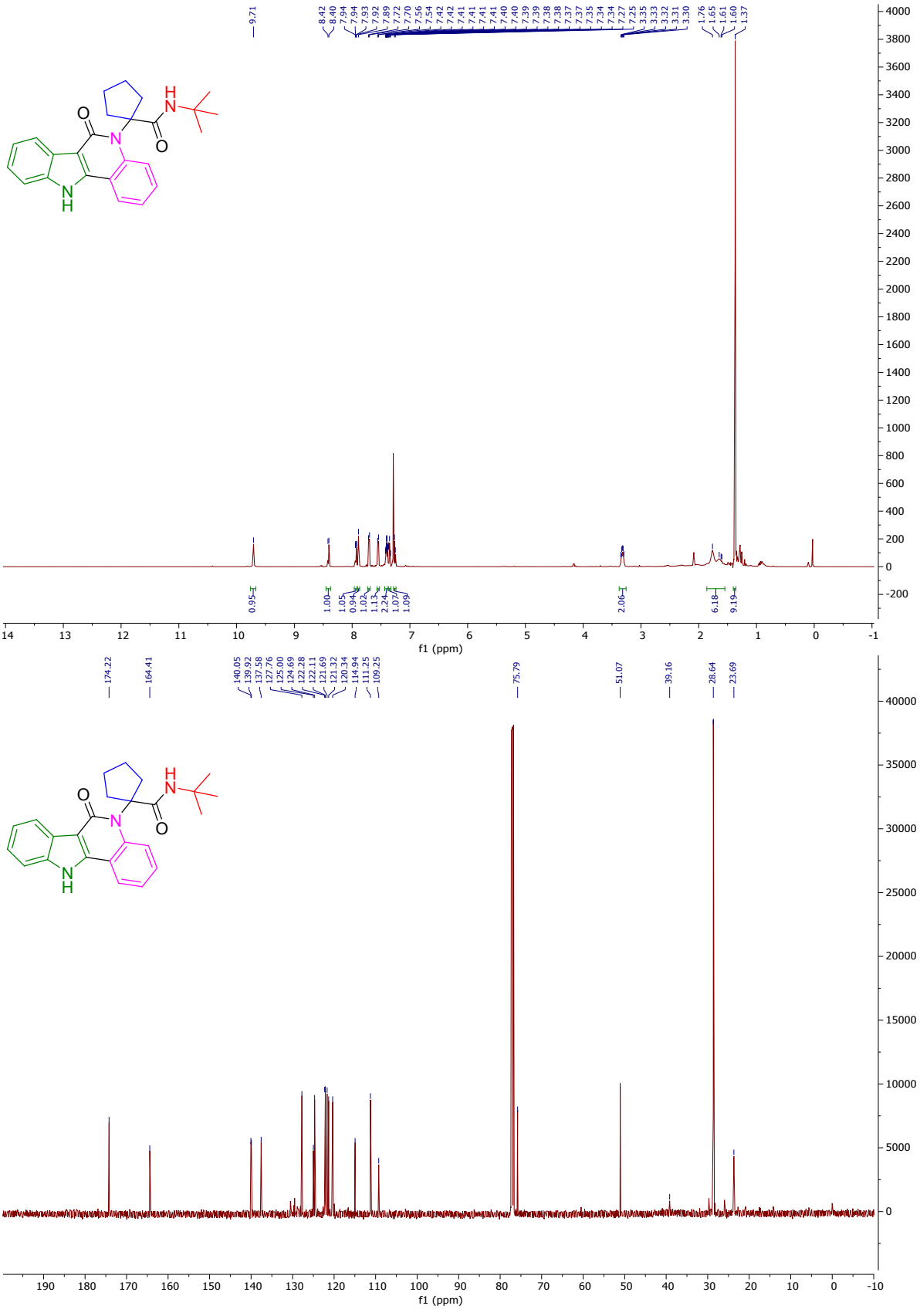
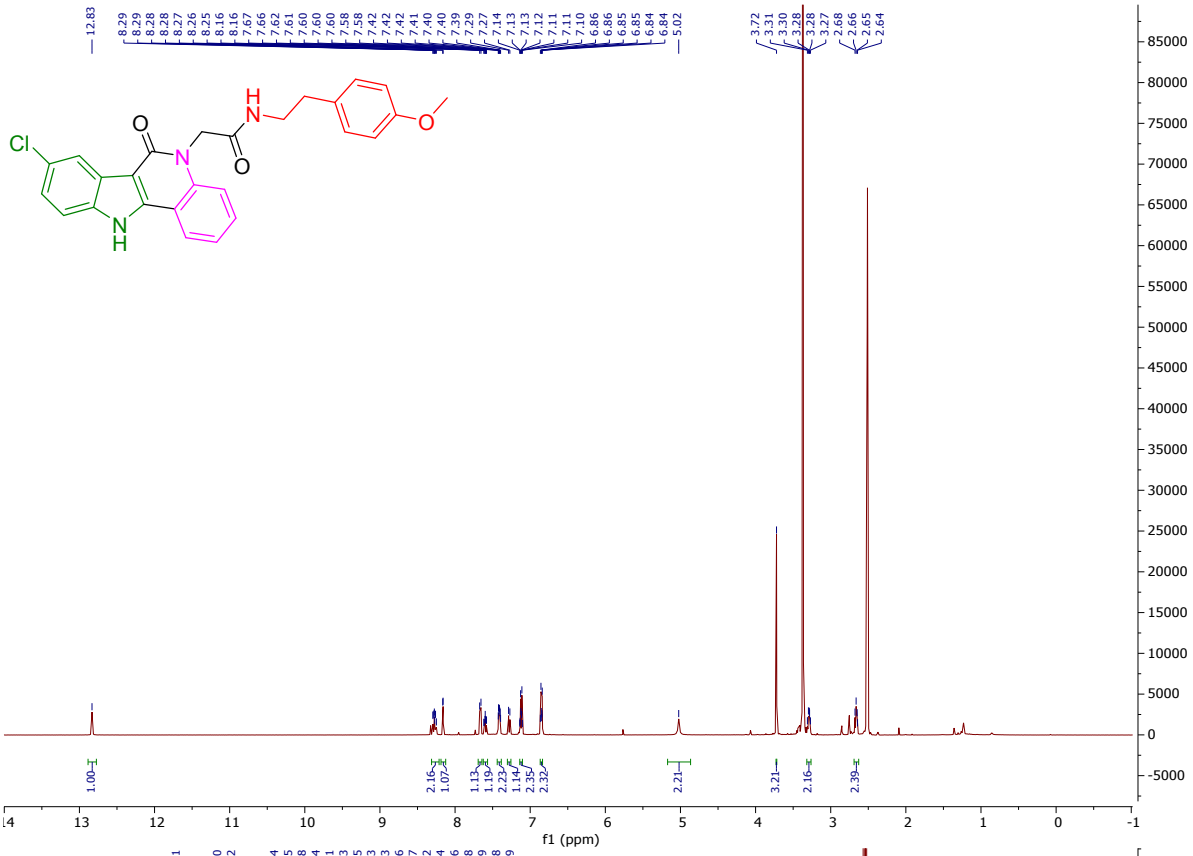
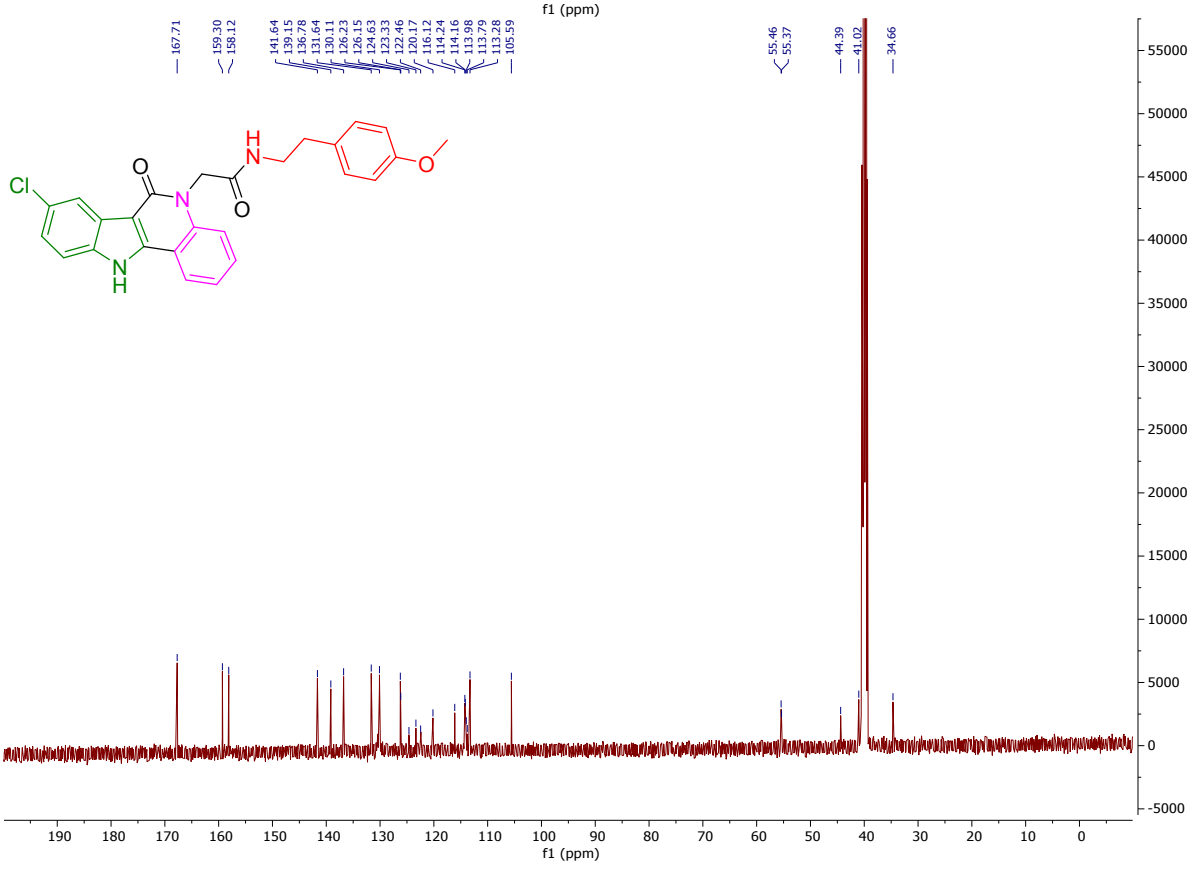
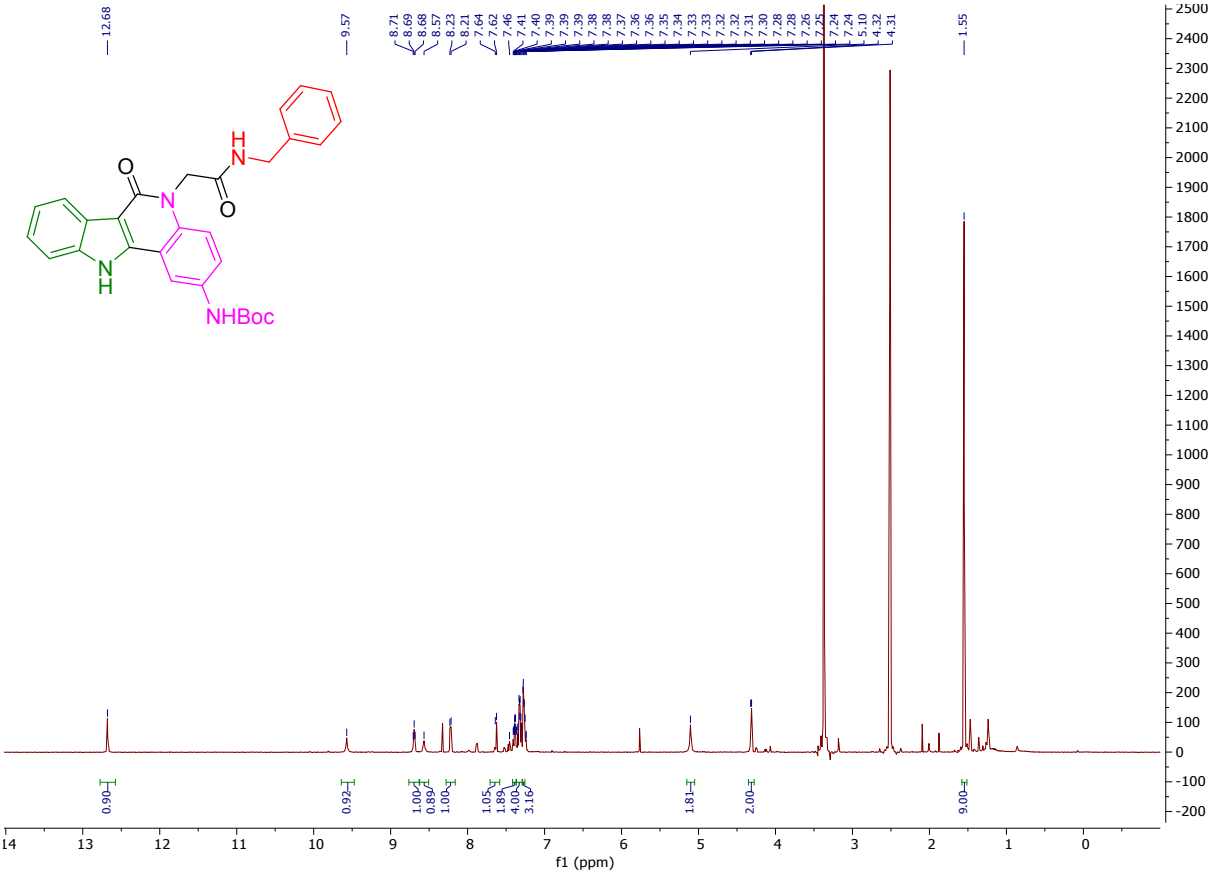


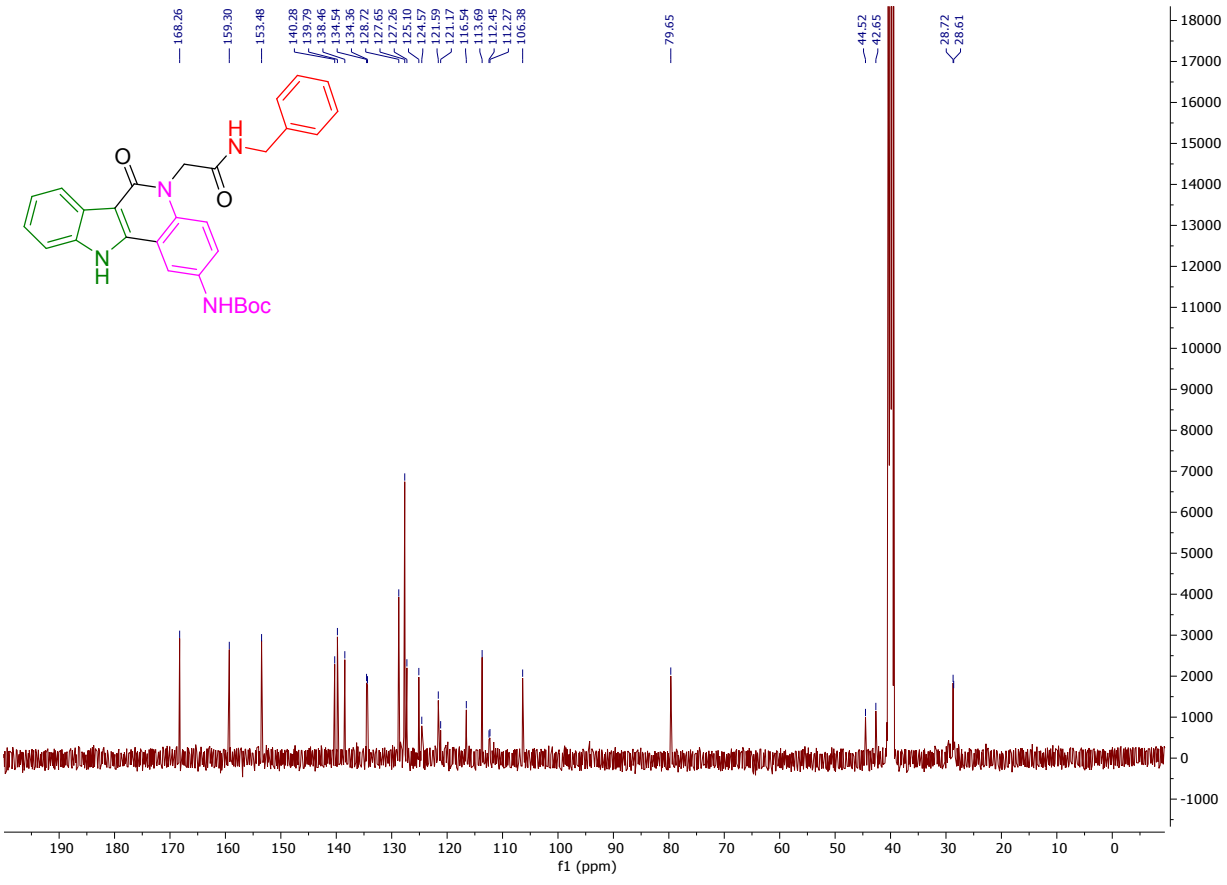
6j: 2-(8-Chloro-6-oxo-6,11-dihydro-5*H*-indolo[3,2-*c*]quinolin-5-yl)-*N*-(4-methoxyphenethyl)acetamide



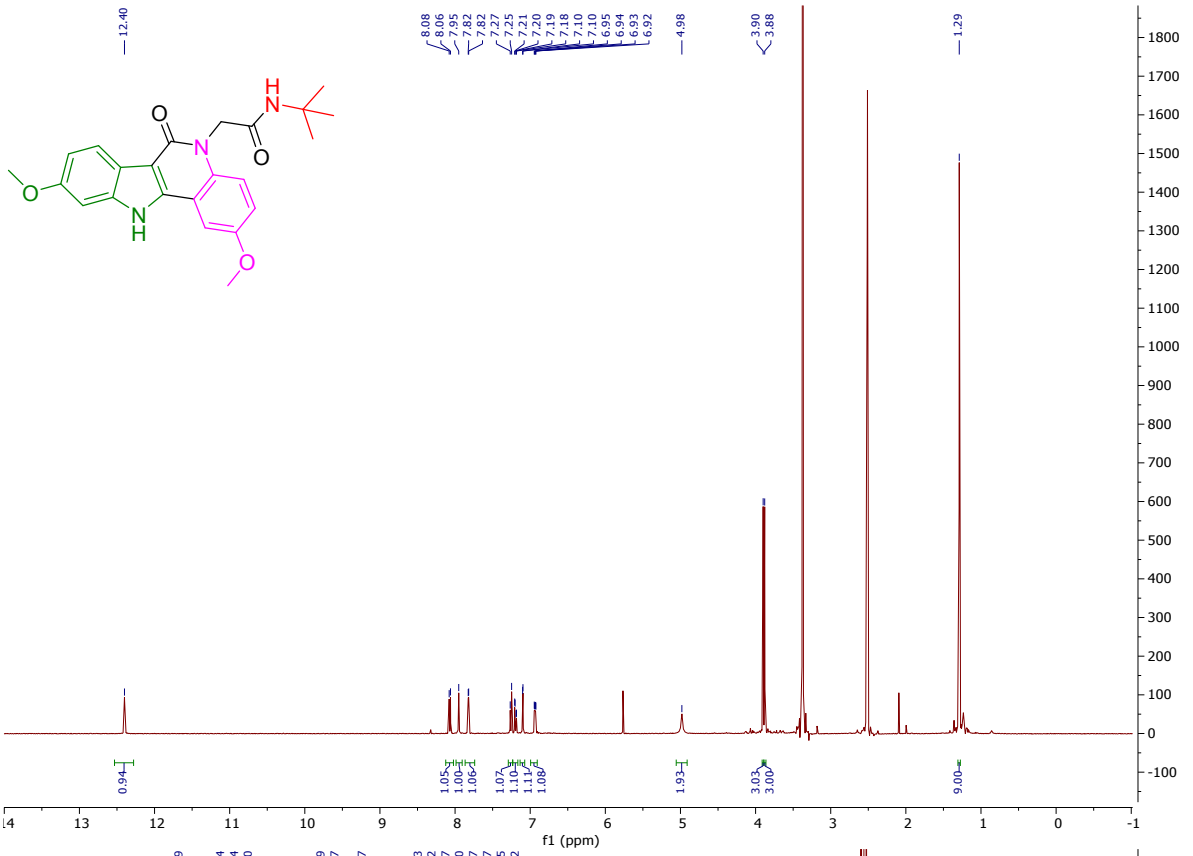


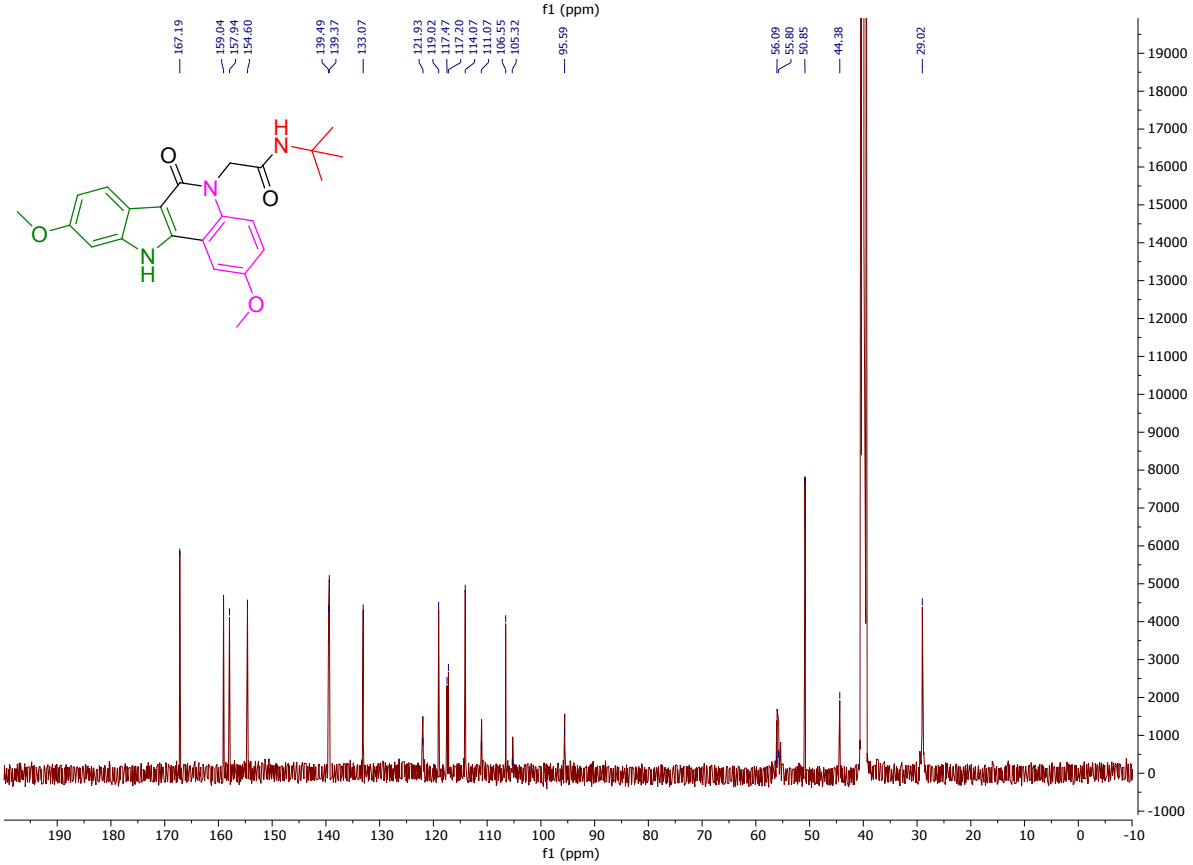
6k: *Tert*-butyl (5-(2-(benzylamino)-2-oxoethyl)-6-oxo-6,11-dihydro-5*H*-indolo[3,2-*c*]quinolin-2-yl)carbamate



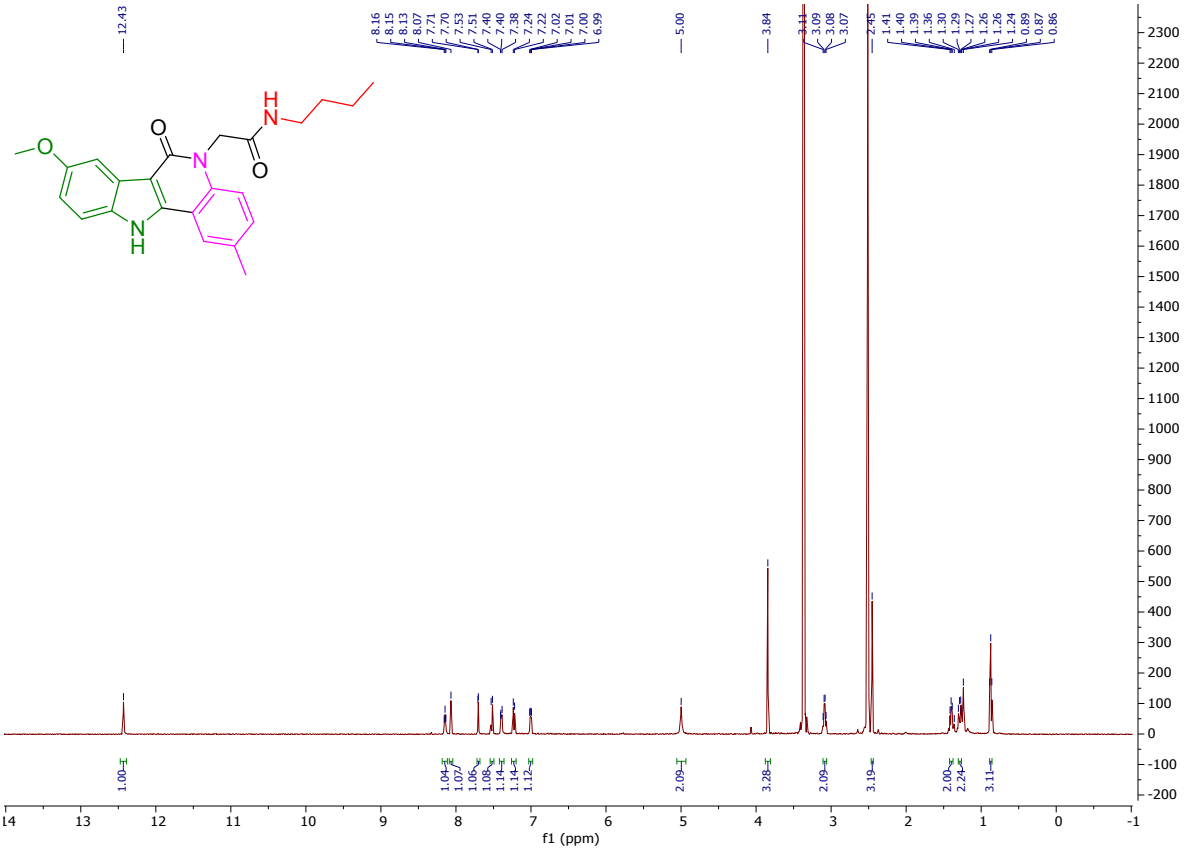


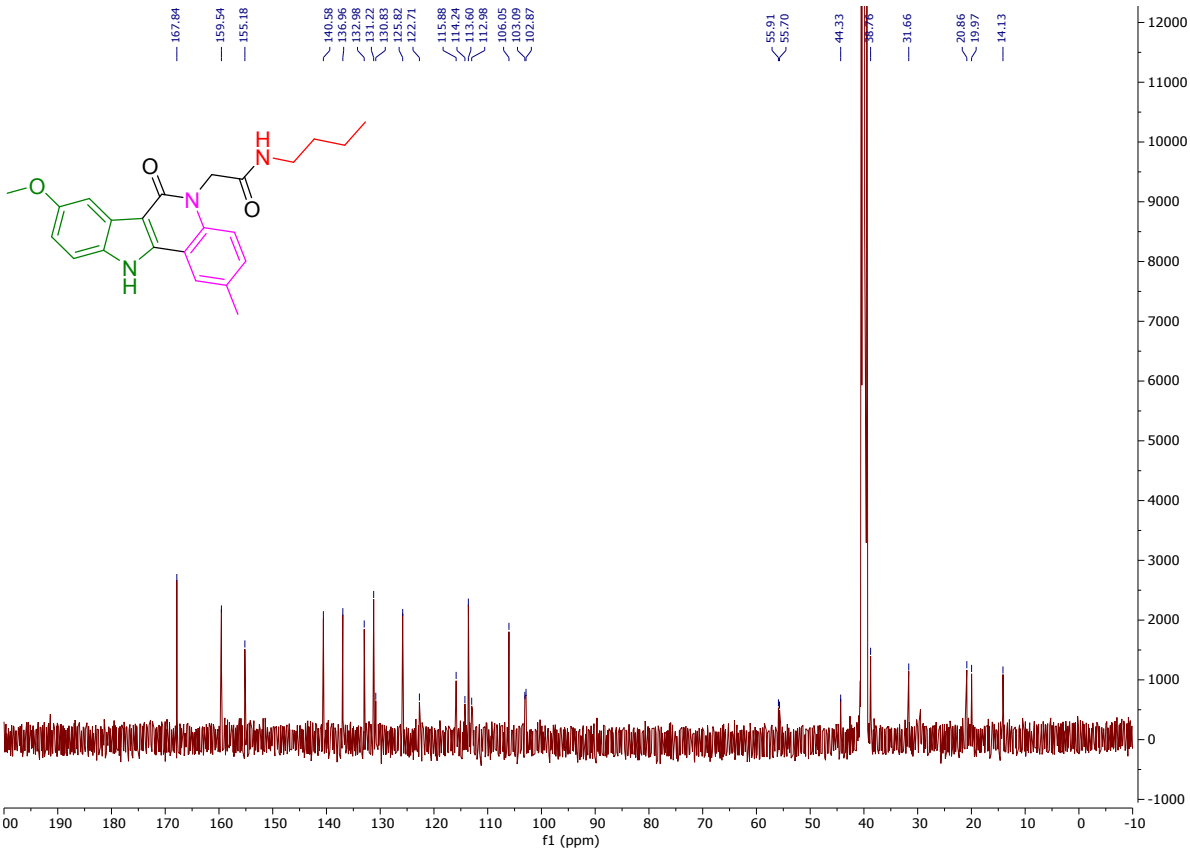
6l: *N*-(*tert*-butyl)-2-(2,9-dimethoxy-6-oxo-6,11-dihydro-5*H*-indolo[3,2-*c*]quinolin-5-yl)acetamide



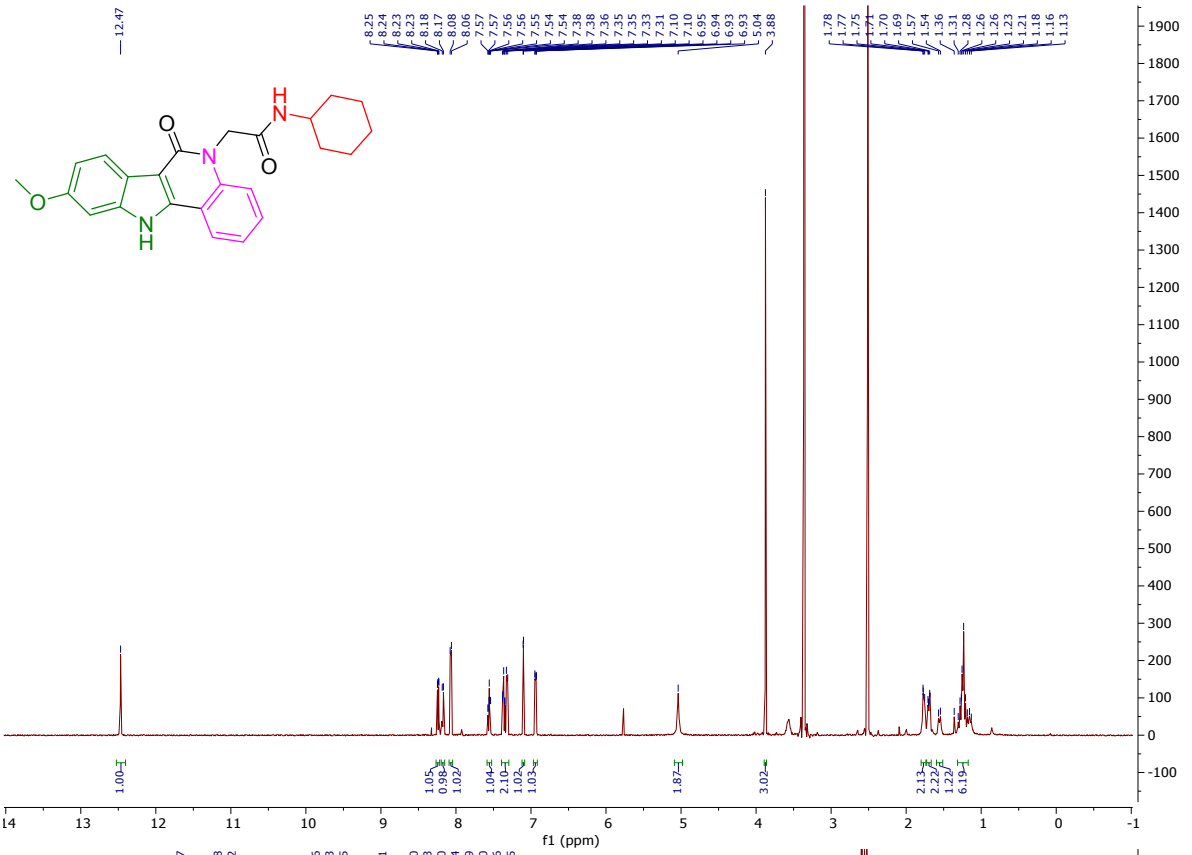


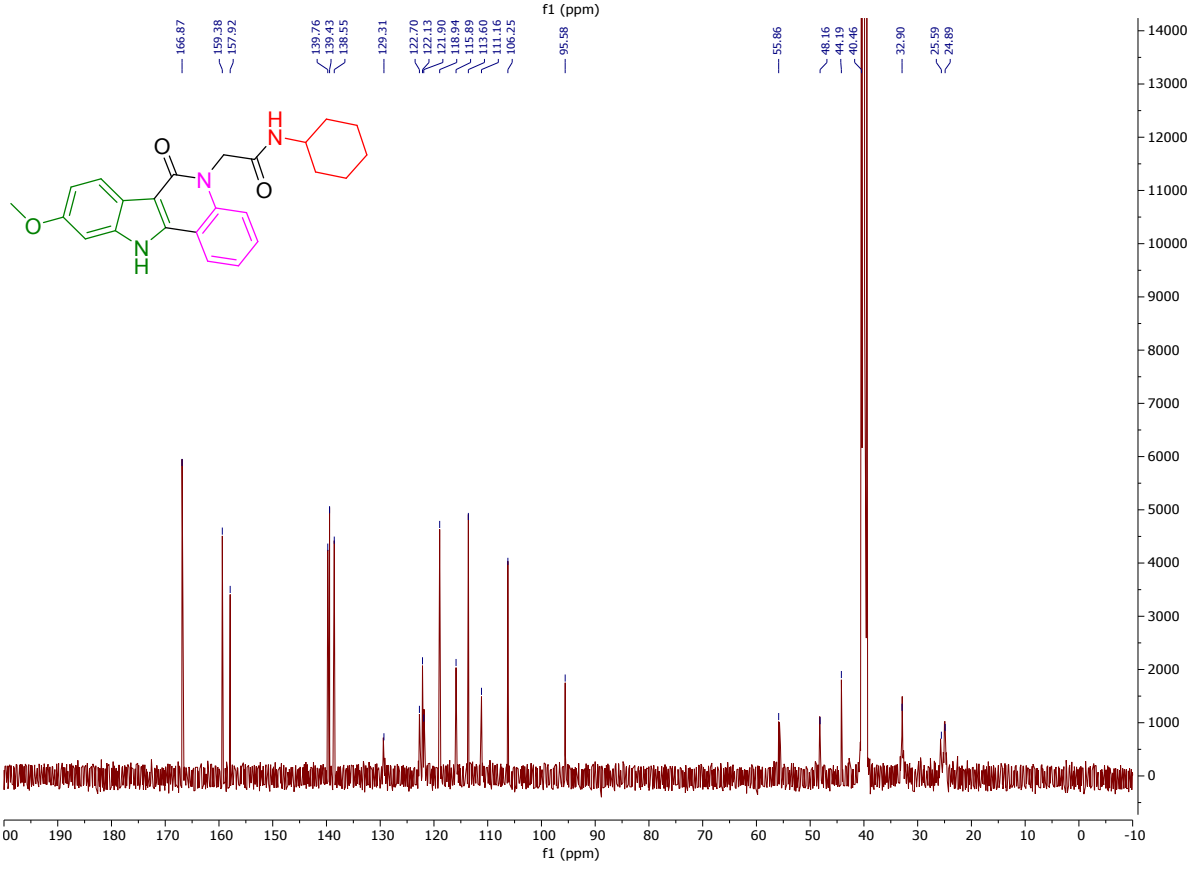
6m: *N*-butyl-2-(9-methoxy-2-methyl-6-oxo-6,11-dihydro-5*H*-indolo[3,2-*c*]quinolin-5-yl)acetamide



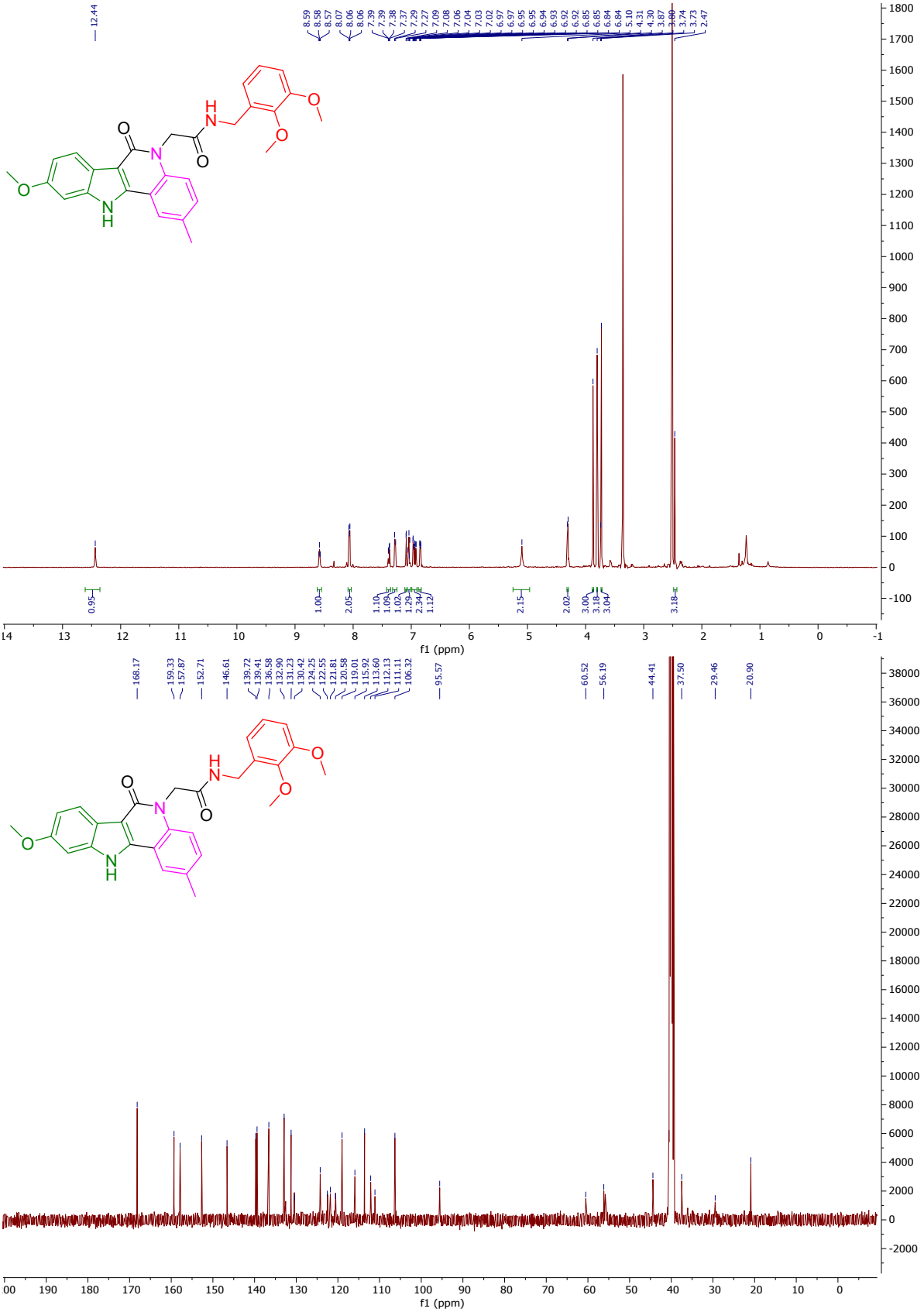


6n: *N*-cyclohexyl-2-(9-methoxy-6-oxo-6,11-dihydro-5*H*-indolo[3,2-*c*]quinolin-5-yl)acetamide

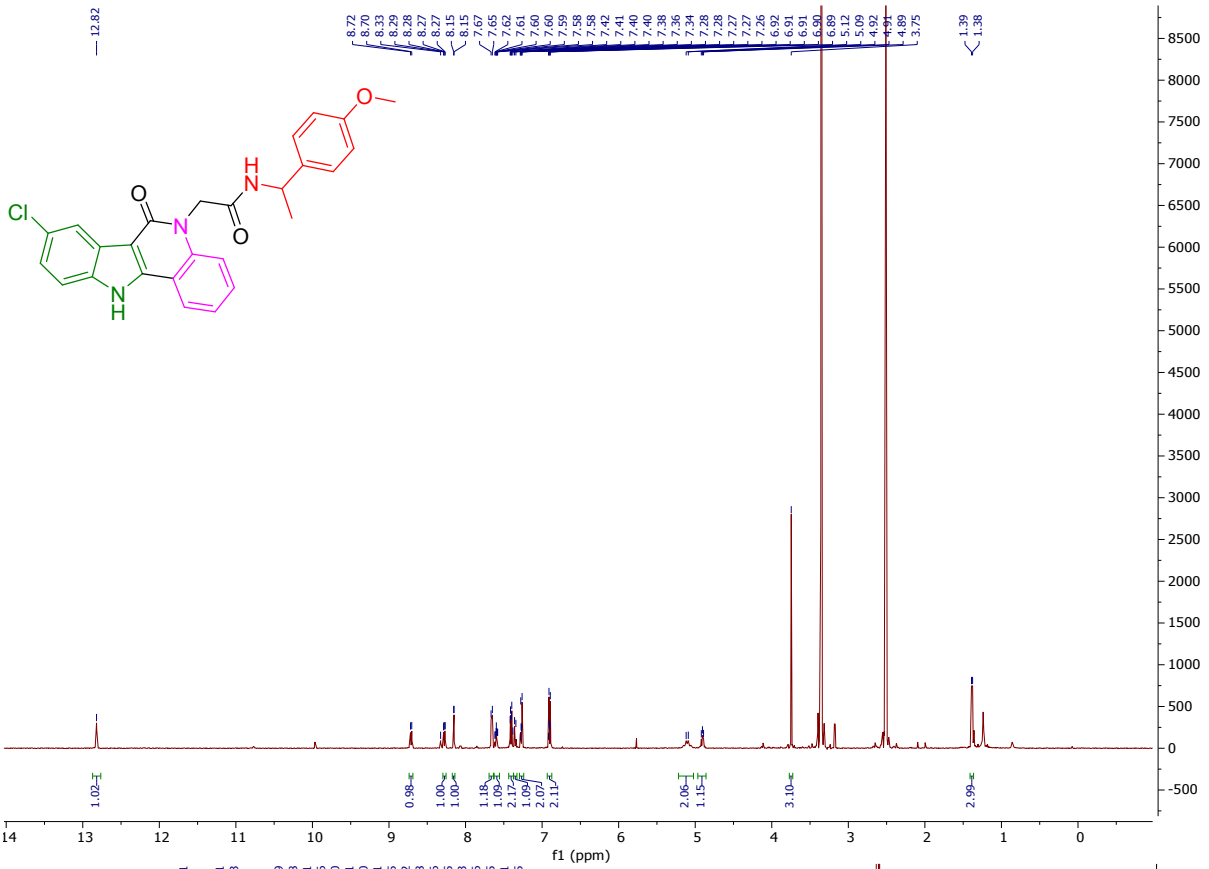


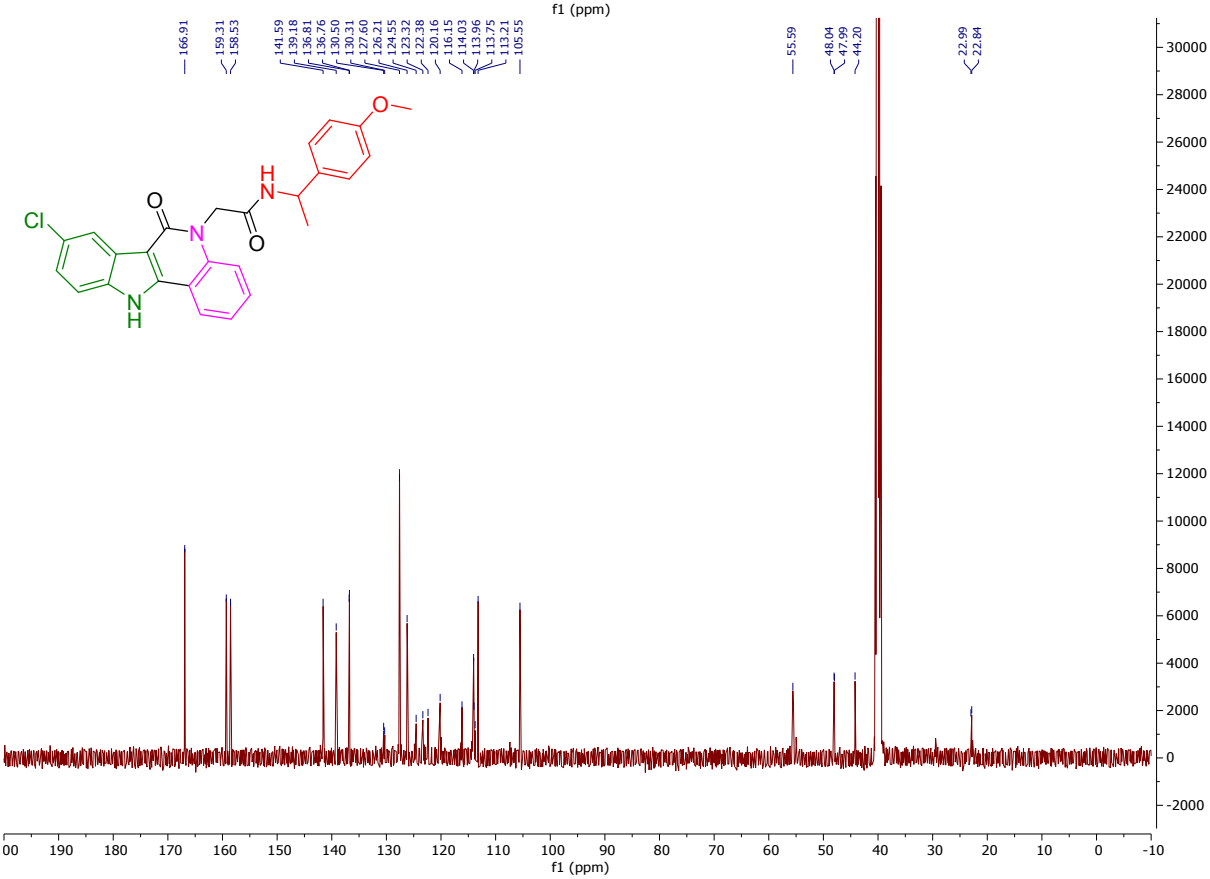


6o: *N*-(2,3-Dimethoxybenzyl)-2-(9-methoxy-2-methyl-6-oxo-6,11-dihydro-5*H*-indolo[3,2-*c*]quinolin-5-yl)acetamide

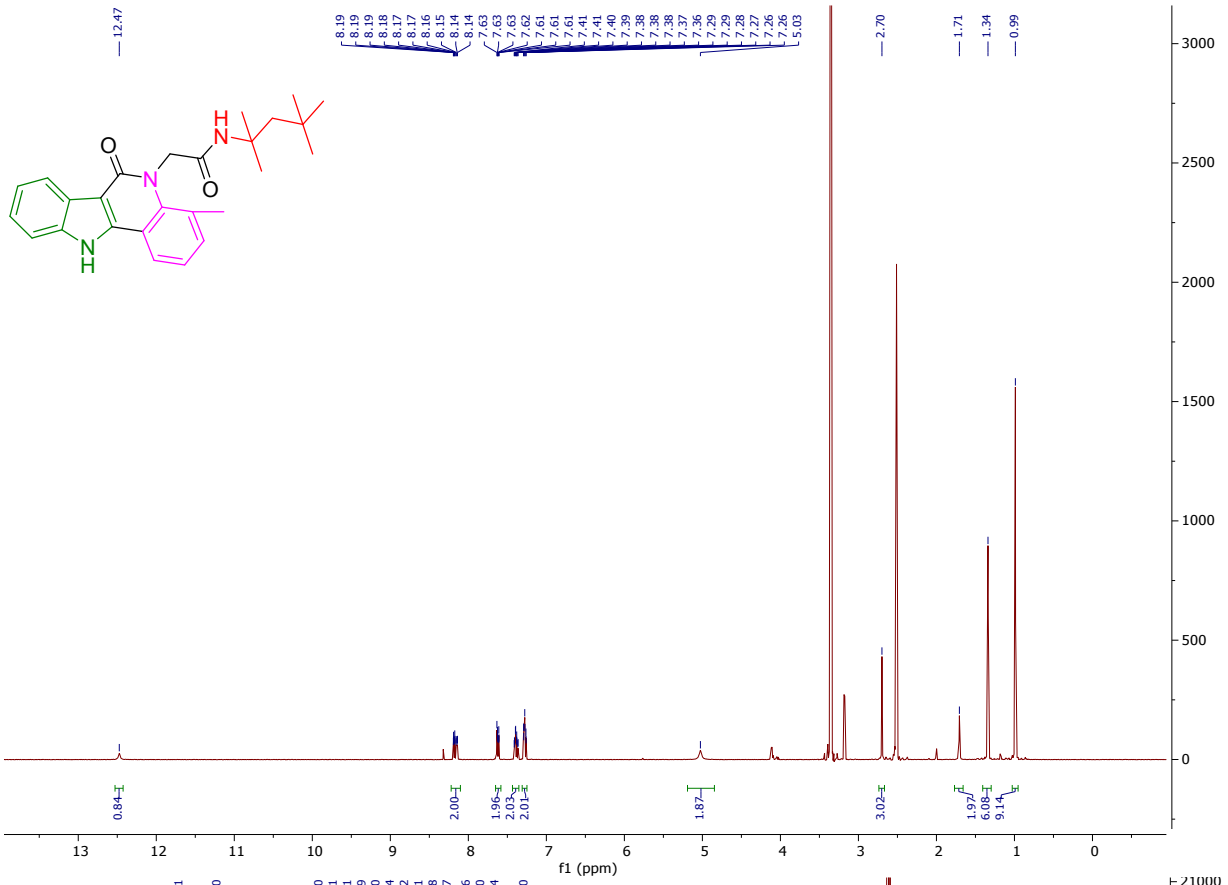


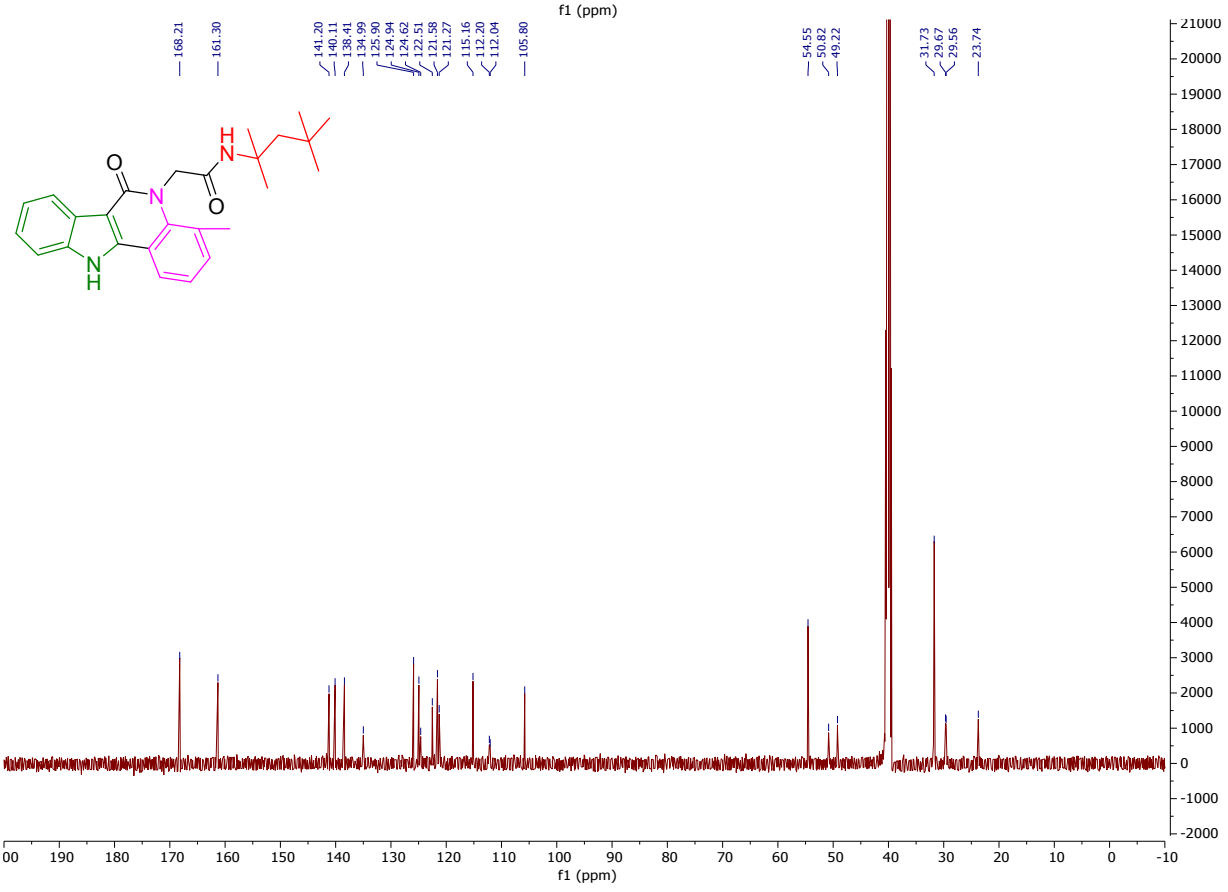
6p: 2-(8-Chloro-6-oxo-6,11-dihydro-5*H*-indolo[3,2-*c*]quinolin-5-yl)-*N*-(1-(4-methoxyphenyl)ethyl)acetamide



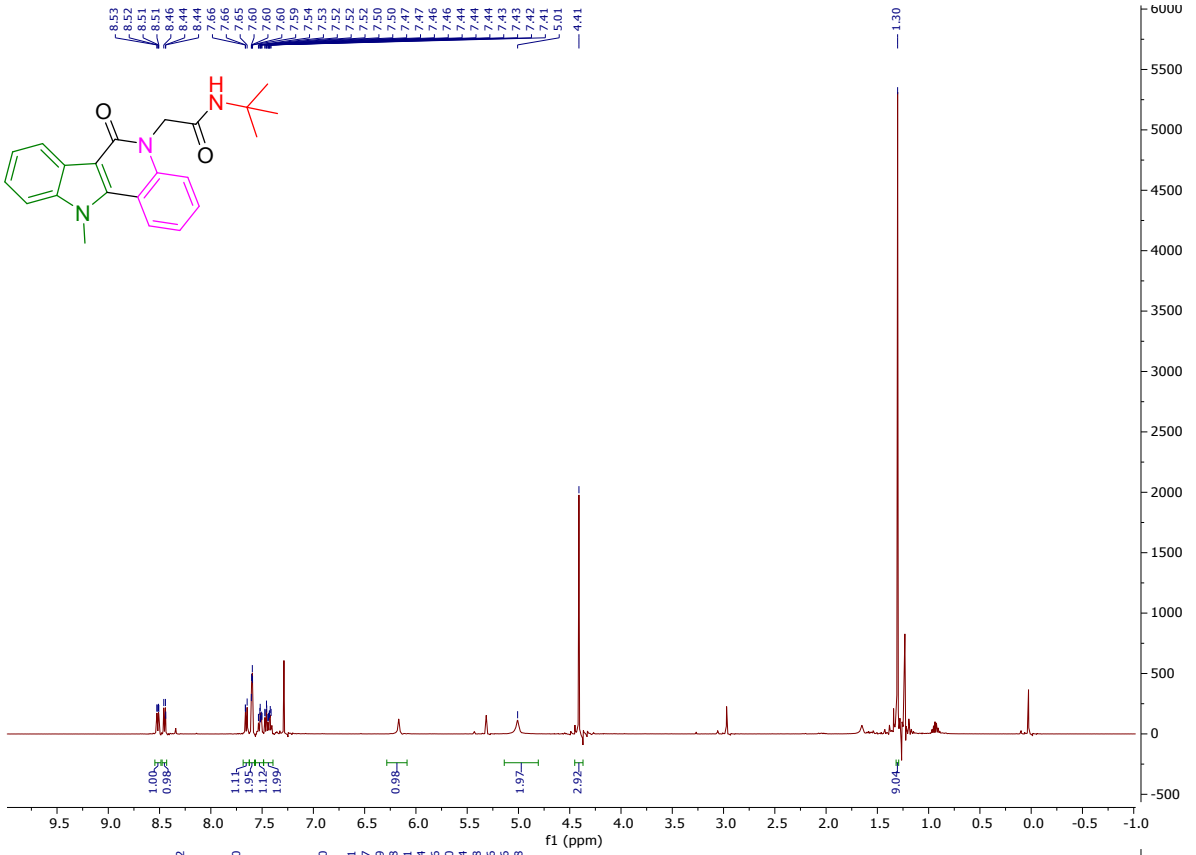


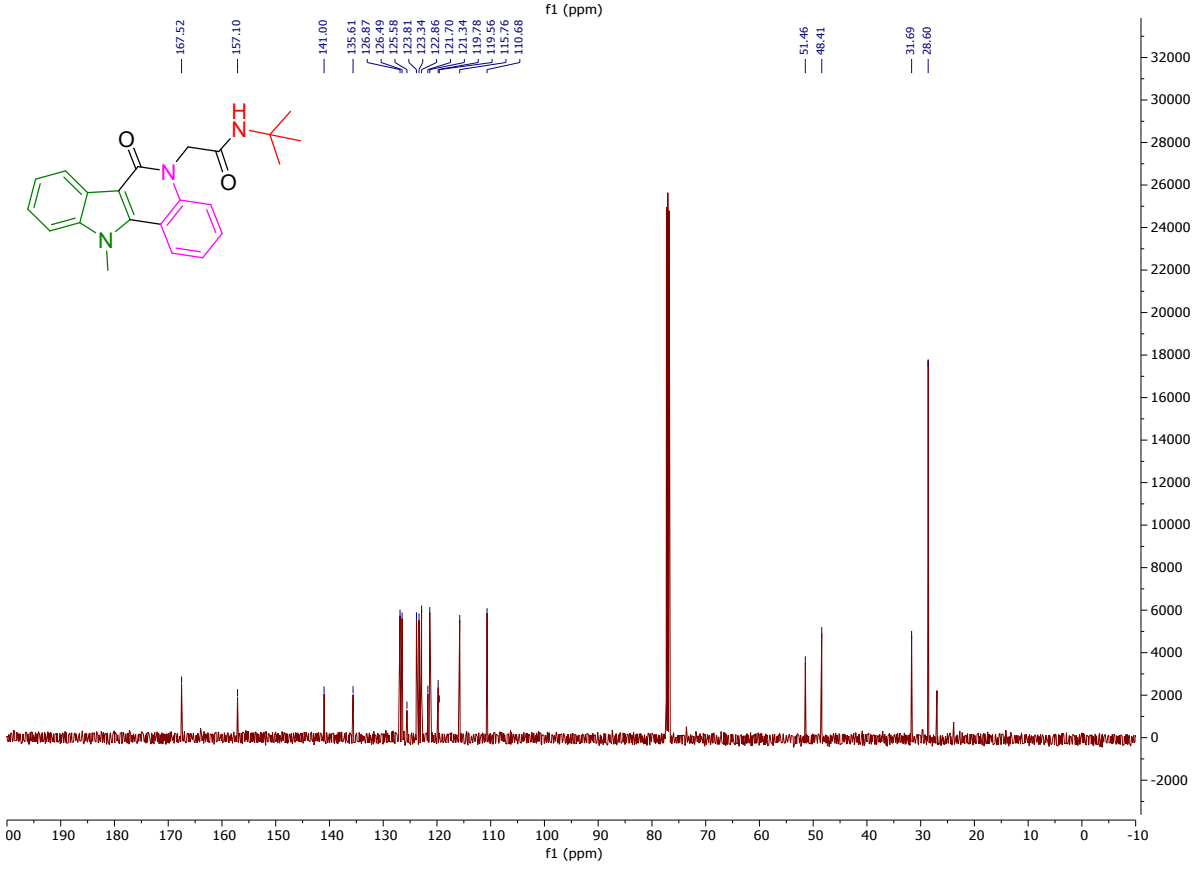
6q: 2-(4-Methyl-6-oxo-6,11-dihydro-5*H*-indolo[3,2-*c*]quinolin-5-yl)-*N*-(2,4,4-trimethylpentan-2-yl)acetamide





6r: *N*-(*tert*-butyl)-2-(11-methyl-6-oxo-6,11-dihydro-5*H*-indolo[3,2-*c*]quinolin-5-yl)acetamide



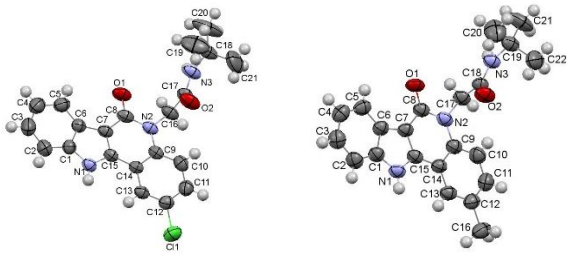


Docking Procedure

All the synthesized compounds were converted to 2D-structures with OpenBabel.[S1] Conformers were generated with Moloc.[S2] The conformers were subsequently docked in the crystal structure with PDB code 3CY2[S3] using Moloc. The poses were visualized with Pymol,[S4] which was also used to create the docking figure.

X-ray structure determination

Single crystals were obtained from EtOH solutions by vapour diffusion in room temperature. A polycyclic fragment is planar with accuracy of 0.05 Å in structure **6b** and 0.02 Å in structure **6c**. The existence of extended π-system results in formation of stacking dimers in the crystal phase (Figure 3). The distance between π-systems is 3.35 Å (C11…C6 contact, 1-x,1-y,1-z symmetry operation) in structure **6b** and 3.51 Å (C12…C6 contact, 1-x,1-y,1-z symmetry operation) in structure **6c**. Stacked molecules are bound additionally by the N1-H…O2' and C13-H…O2' intermolecular hydrogen bonds in both structures (Table S1, Supporting Information). Moreover, the presence of the methyl substituent in compound **6c** causes the additional formation of the C16-H…π (C5) intermolecular hydrogen bond in dimer of molecules **6c**. Stacked dimers are bound by the N3-H…O1' (1-x,-y,1-z) hydrogen bonds (Table S1, Supporting Information).



6b **6c**

Figure S1. Molecular structures of selected compounds according to X-ray diffraction data. Thermal ellipsoids are shown at the 50 % probability level.

Figure S2. Stacking dimers of compounds **6b** (on the left) and **6c** (on the right) in the crystal phase.

The crystals of **6b**($C_{21}H_{20}N_3O_2Cl$) are monoclinic. At 293 K, a = 12.540(2) Å, b = 11.523(2) Å, c = 13.578(2) Å, β = 96.66(1)°, V = 1948.7(5) Å^3, M_r = 381.85, Z = 4, space group $P2_1/n$, d_{calc} = 1.302 g/cm^3, μ(MoK_α) = 0.217 mm^{-1}, F(000) = 800.

The crystals of **6c** ($C_{22}H_{23}N_3O_2$) are monoclinic. At 293 K, a = 7.8798(7) Å, b = 11.5501(8) Å, c = 21.251(2) Å, β = 100.393(8)°, V = 1902.4(3) Å^3, M_r = 361.43, Z = 4, space group $P2_1/c$, d_{calc} = 1.262 g/cm^3, μ(MoK_α) = 0.082 mm^{-1}, F(000) = 768.

Intensities of 19814 reflections (5577 independent, R_{int}=0.097) for **6b** and 20215 reflections (5437 independent, R_{int}=0.071) for **6c** were measured on an Xcalibur 3 diffractometer (graphite monochromated MoK_α radiation, CCD-detector, ω scanning, $2\Theta_{max}$ = 60°).

The structures were solved by direct method using SHELXTL package.[S5] Positions of hydrogen atoms were located from electron density difference maps and refined using riding model with $U_{iso} = nU_{eq}$ (n = 1.5 for methyl groups and 1.2 for other hydrogen atoms). Full-matrix least-squares refinement against F^2 in anisotropic approximation for non-hydrogen atoms was converged to wR_2=0.147 for 5577 reflections (R_1 = 0.065 for 2325 reflections with $F > 4\sigma(F)$, S = 0.872) in the case of **6b**, and wR_2=0.157 for 5437 reflections (R_1 = 0.064 for 2281 reflections with $F > 4\sigma(F)$, S = 0.870) in the case of **6c**.

Final atomic coordinates, geometrical parameters and crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, 11 Union Road, Cambridge, CB2 1EZ, UK (E-mail: deposit@ccdc.cam.ac.uk; fax: +44 1223 336033) and are available on request quoting the deposition numbers 1912181 (**6b**) and 1912182 (**6c**).

Table S1 Intermolecular hydrogen bonds in structures 6b and 6c

Hydrogen bond	Symmetry operation	Geometrical characterisitcs	
		H…A, A	D-H…A, deg
Structure **6b**			
N1-H…O2	1-x,1-y,1-z	1.99	149
C13-H…O2	1-x,1-y,1-z	2.60	144
N3-H…O1	1-x,-y,1-z	2.04	178
Structure **6c**			
N1-H…O2	1-x,1-y,1-z	1.98	154
C13-H…O2	1-x,1-y,1-z	2.66	151
C16-H…C5 (π)	1-x,1-y,1-z	2.74	150
N3-H…O1	1-x,-y,1-z	2.07	156

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(S5) Sheldrick, G. M. A Short History of SHELX. *Acta Cryst.* **2008**, *A64*, 112–122.