Supporting Information

Synthesis and Evaluation of Tetrahydroisoquinolines with Pendent Aromatics as Sigma-2 Selective Ligands

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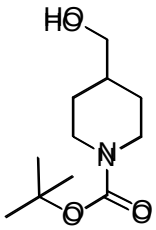
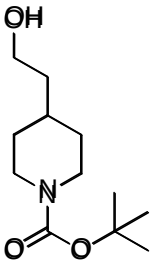
Contents

1-(*tert*-Butoxycarbonyl)-4-hydroxymethylpiperidine[S1] [10]



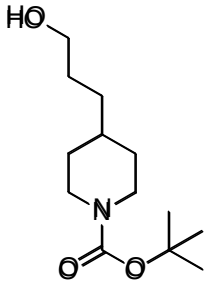
Solid, (6.70 g, 96 %) mp 70-72 °C, (lit[55] 73 °C); ^{1}H NMR ($CDCl_3$) δ 1.11-1.21 (m, 2H), 1.47 (s, 9H), 1.61-1.75 (m, 3H), 2.69-2.75 (m, 2H), 3.00 (d, 2H, *J* = 8.0 Hz), 4.12 (bs, 2H). MS-ES$^+$ *m/z* 216 (MH^+, 73), 160 (100%).

4-(2-Hydroxyethyl)-piperidine-1-carboxylic acid *tert*-butyl ester[S2] [11]



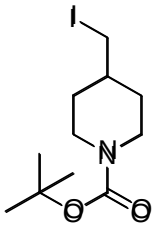
Clear oil, (4.13 g, 93 %); ^{1}H NMR ($CDCl_3$): δ 1.08-1.12 (m, 2H), 1.43 (s, 9H), 1.47-1.67 (m, 5H), 2.67 (t, 2H, *J* = 12.2 Hz), 3.68 (t, 2H, *J* = 6.5 Hz), 4.04-4.09 (m, 2H). MS-EI *m/z* 229 (M^+, 4), 128 (100%).

4-(3-Hydroxypropyl)piperidine-1-carboxylic acid *tert*-butyl ester[S3] [12]



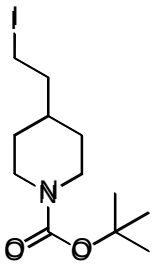
Clear oil, (17.52 g, 64 %); ^{1}H NMR ($CDCl_3$) δ 1.06-1.12 (m, 2H), 1.30-1.40 (m, 3H), 1.45 (s, 9H), 1.51-1.62 (m, 2H), 1.65 (bs, 2H), 2.65 (m, 2H), 3.61 (t, 2H, *J* = 7.0 Hz), 4.06 (bd, 2H, *J* = 12.5 Hz). MS-ES$^+$ *m/z* 244 (MH^+, 27), 229 (100 %).

1-(*tert*-Butoxycarbonyl)-4-(iodomethyl)piperidine[S4] [13]



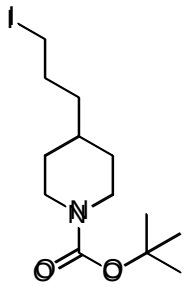
Clear oil, (5.58 g, 88 %); ^{1}H NMR ($CDCl_3$) δ 1.05-1.16 (m, 2H), 1.42 (s, 9H), 1.51-1.63 (m, 1H), 1.78 (bd, 2H, *J* = 12.8 Hz), 2.65 (bt, 2H, *J* = 12.8 Hz), 3.08 (d, 2H, *J* = 7.0 Hz), 4.05-4.11 (m, 2H). MS-ES$^+$ *m/z* 326 (MH^+, 2), 270 (100 %).

4-(2-Iodoethyl)piperidine-1-carboxylic acid *tert*-butyl ester[S5] [14]



Clear oil (730 mg, 56 %); ^{1}H NMR ($CDCl_3$) δ 1.07-1.15 (m, 2H), 1.44 (s, 9H), 1.57-1.66 (m, 3H), 1.76 (q, 2H, *J* = 7.1 Hz), 2.69 (bt, 2H, *J* = 12.6 Hz), 3.20 (t, 2H, *J* = 7.2 Hz), 4.07-4.12 (m, 2H). MS-EI *m/z* 339 (M^+, 8), 156 (100%).

4-(3-Iodoethyl)piperidine-1-carboxylic acid *tert*-butyl ester[S3] [15]



Clear oil (8.62 g, 59 %); ^{1}H NMR δ 1.05-1.13 (m, 2H), 1.29-1.38 (m, 3H) 1.43 (s, 9H), 1.58-1.63 (m, 2H), 1.78-1.86 (m, 2H), 2.64 (bt, *J* = 12.2 Hz), 3.16 (t, 2H, *J* = 7.0 Hz), 4.02 (bs, 2H). MS-EI *m/z* 353 (M^{+}, 12), 143 (100%).

7-Methoxy-1,2,3,4-tetrahydroisoquinoline

To a solution of 7-methoxyisoquinoline[S6] **[53]** (700 mg, 4.40 mmol) in freshly distilled and dried liquid ammonia (30 mL) and EtOH (5 mL) was added Na (700 mg, 30.4 mmol) in small pieces over 5 min. The reaction was allowed to proceed for 1 h. The ammonia solution was then allowed to evaporate and to the residue was added ice H_2O (200 mL) and extracted with EtOAc (150 mL). The organic layer was further washed with H_2O (20 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$) and the organic solvent removed to yield a dark yellow oil. The oil was suspended in Et_2O (50 mL) and made acidic by the addition of a solution of 4 M HCl in dioxane. The resulting suspension was filtered to yield **[54]** (585 mg, 81%) as an off-yellow solid, mp 250-253 ^{o}C. ^{1}H NMR (DMSO) δ 2.91 (t, 2H, *J* = 6.1 Hz), 3.27 (t, *J* = 6.1 Hz), 3.72 (s, 3H), 4.16 (s, 2H), 6.80-8.83 (m, 2H), 7.10 (bd, 1H, *J* = 8.2 Hz). ^{13}C NMR (DMSO) δ 23.9, 40.7, 43.4, 55.1, 111.3, 113.8, 123.9, 129.7, 130.0, 157.7. MS-EI *m/z* 163 (M^{+} free base, 43), 134 (100%); HRMS-EI $C_{10}H_{13}NO$: 163.0997, found 163.0993.

References

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S3 Egbertson, M. S., Chang, C. T.-C., Duggan, M. E., Gould, R. J., Halczenko, W., Hartman, G. D., Laswell, W. L., Lynch, Jr, J. J., Lynch, R. J., Manno, P. D., Naylor, A. M., Prugh, J. D., Ramjit, D. R., Sitko, G. R., Smith, R. S., Turchi, L. M., Zhang, G. *J. Med. Chem.* **1994**, *37*, 2537.

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S5 Askew, B. C.; Bednar, R. A.; Bednar, B.; Claremon, D. A.; Cook, J. J.; McIntyre, C. J.; Hunt, C. A.; Gould, R. J.; Lynch, R. J.; Lynch, J. J.; Gaul, S. L.; Stranieri, M. T.; Sitko, G. R.; Holahan, M. A.; Glass, J. D.; Hamill, T.; Gorham, L. M.; Prueksaritanont, T.; Baldwin, J. J.; Hartman, G. D. *J. Med. Chem.* **1997**, *40*, 1779.

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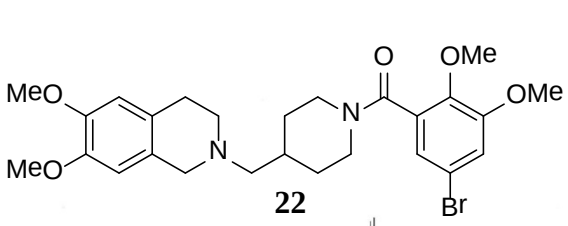
4. ^{1}H and ^{13}C spectra for final compounds 22-39 and 54-63



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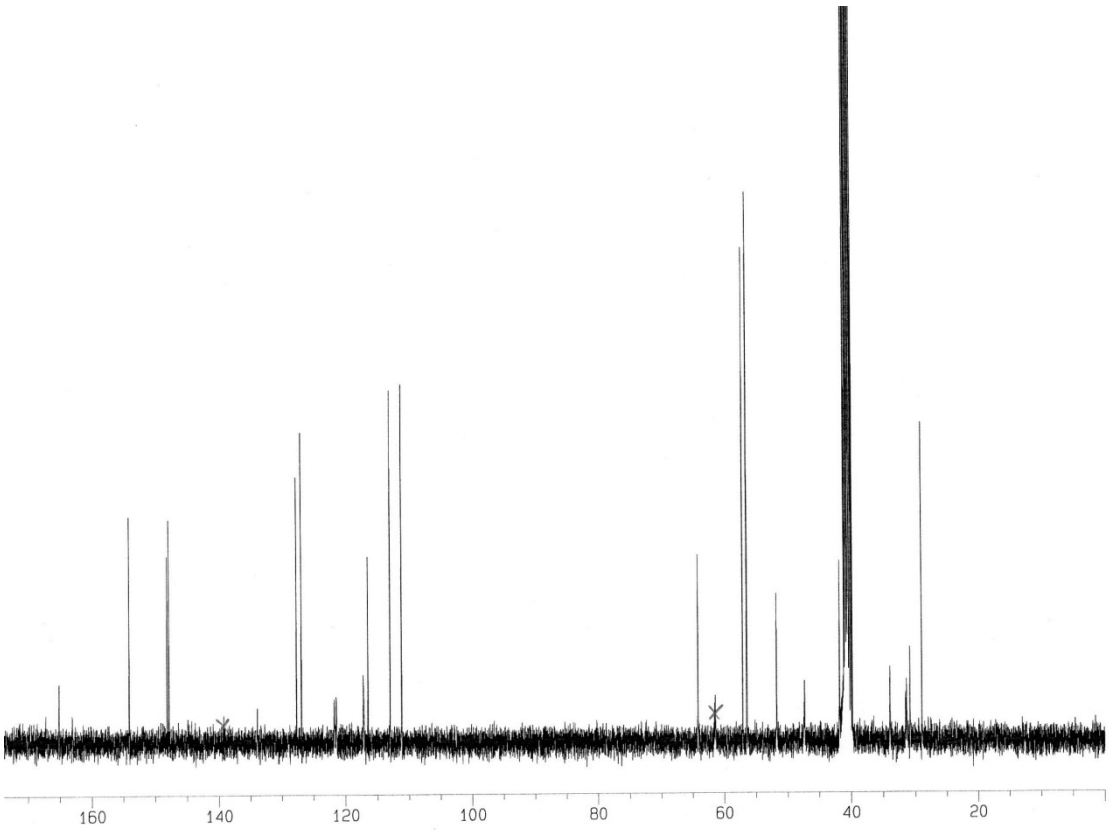

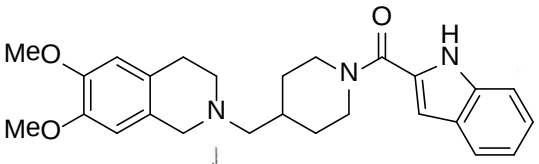

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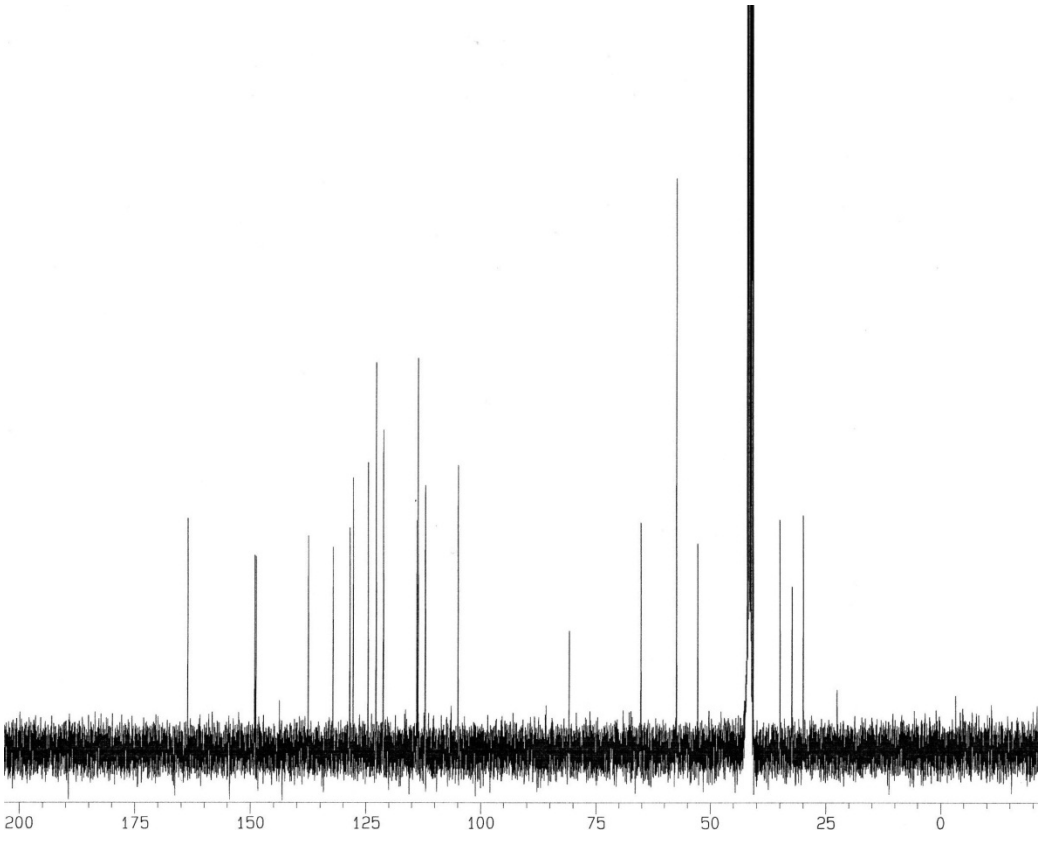

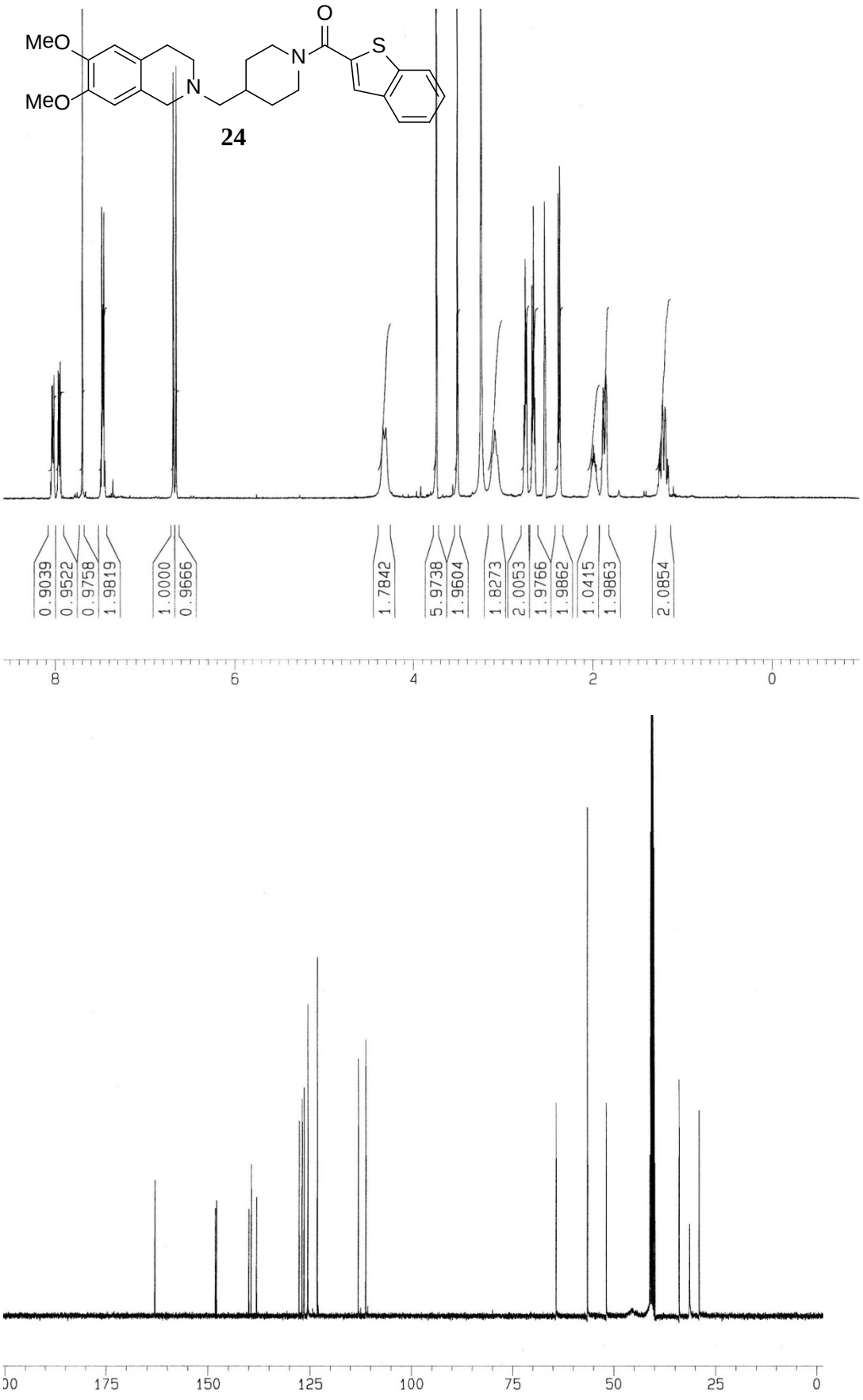

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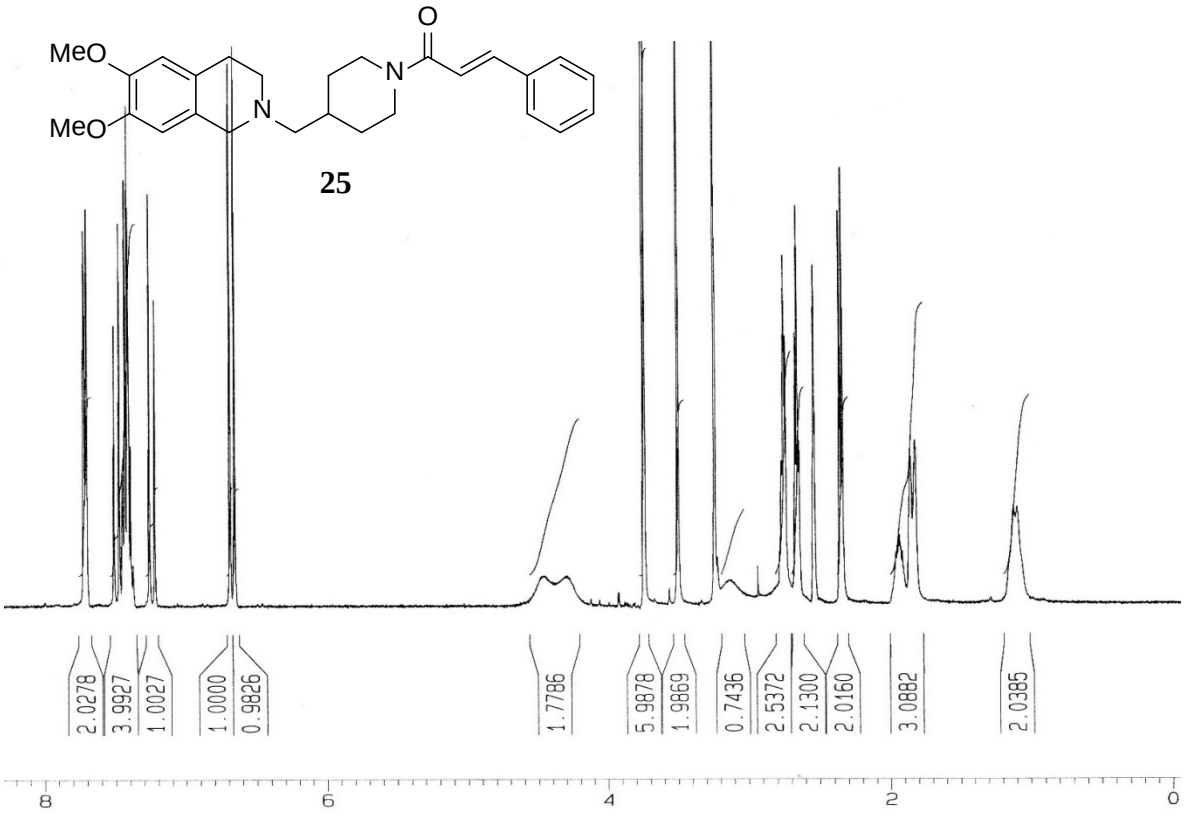
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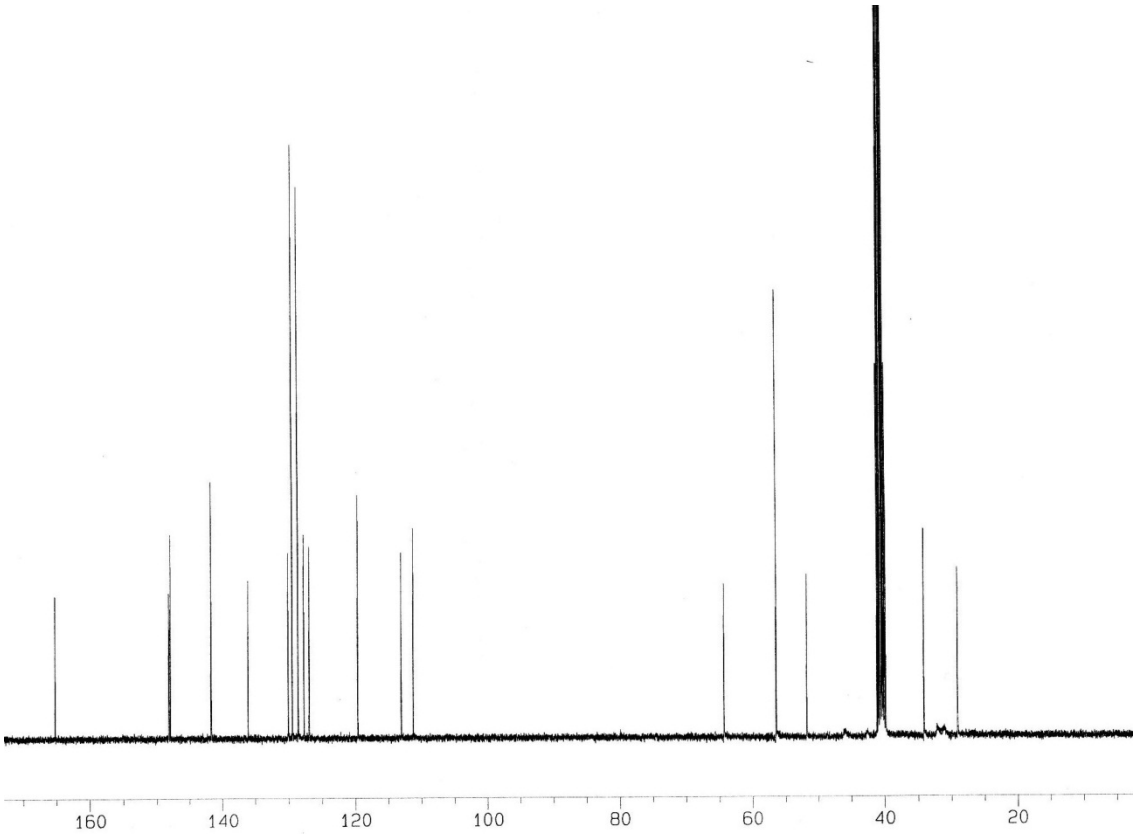
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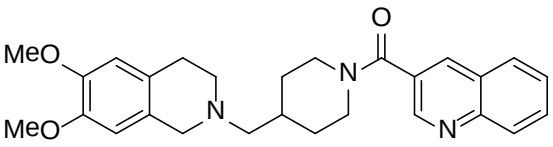
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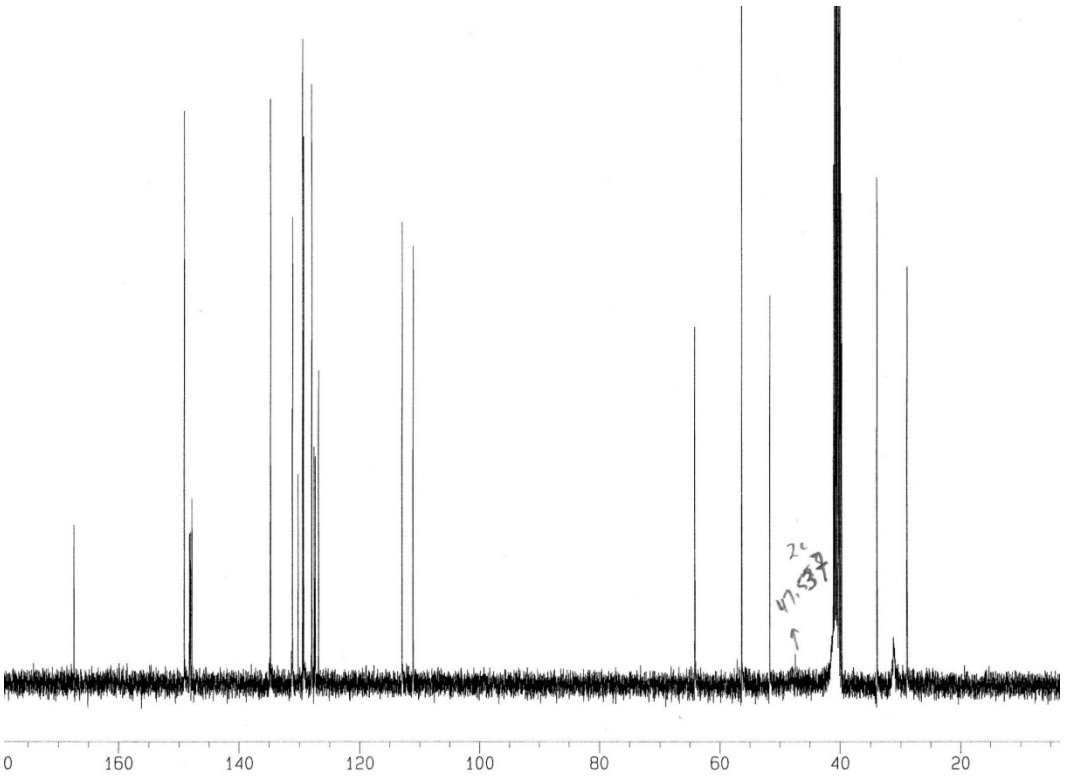
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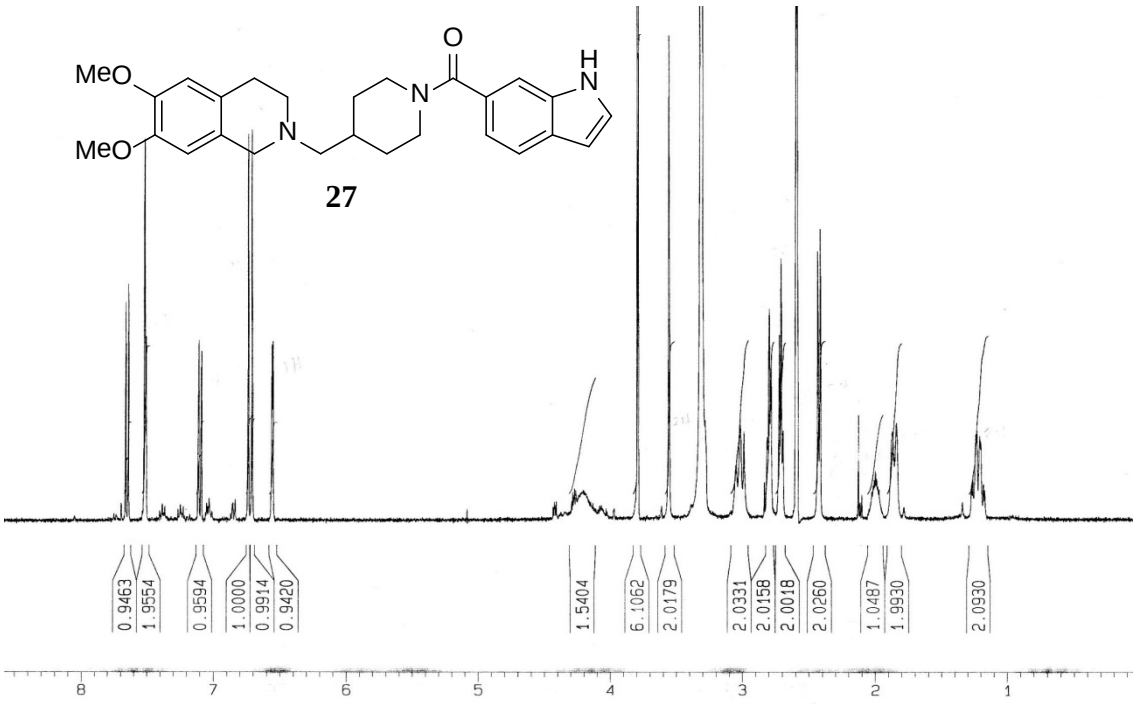

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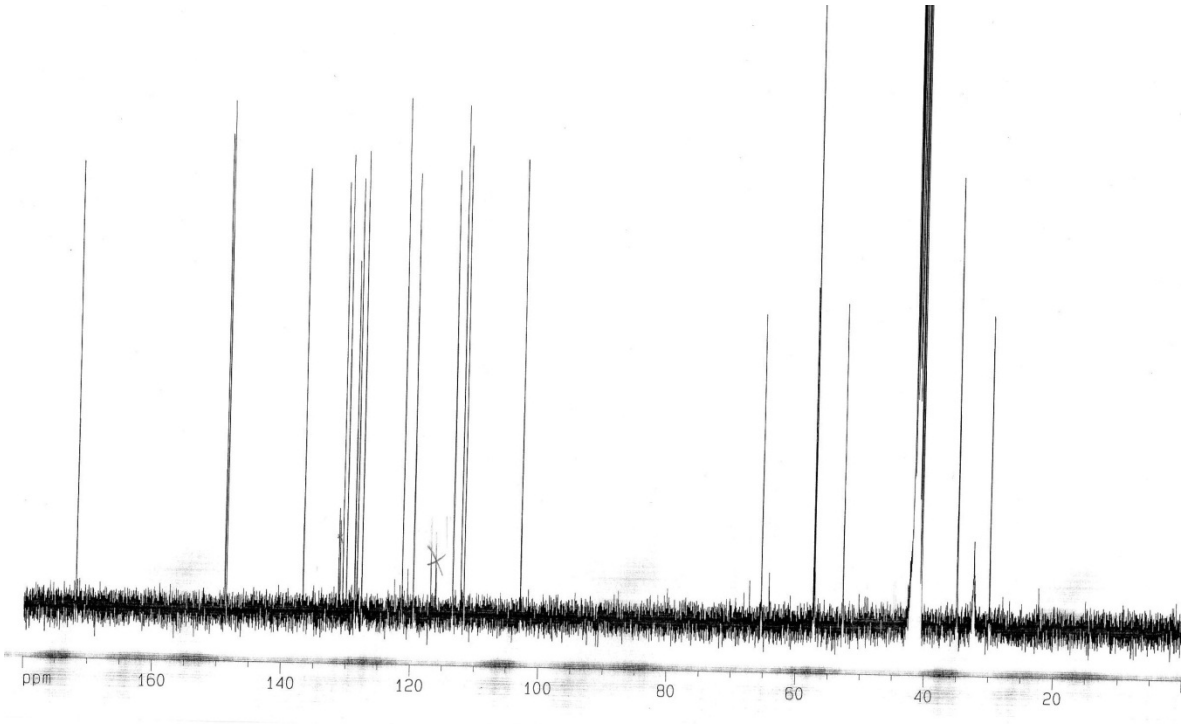

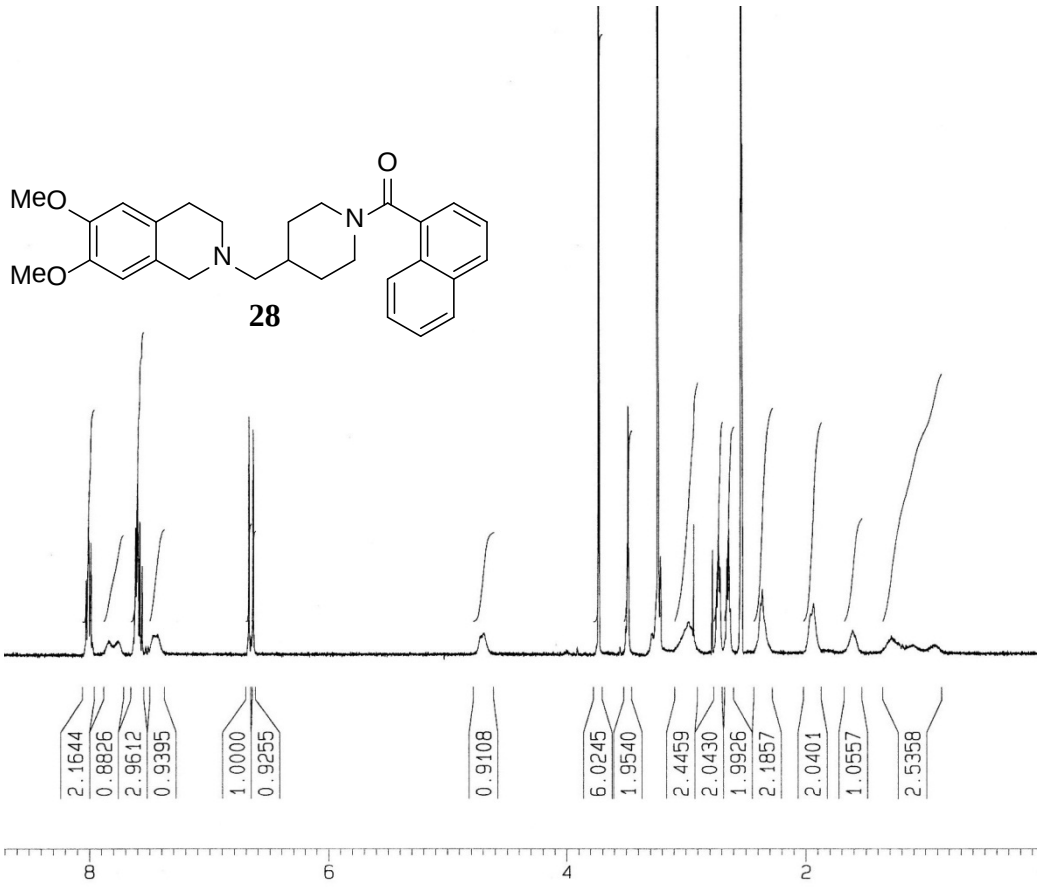

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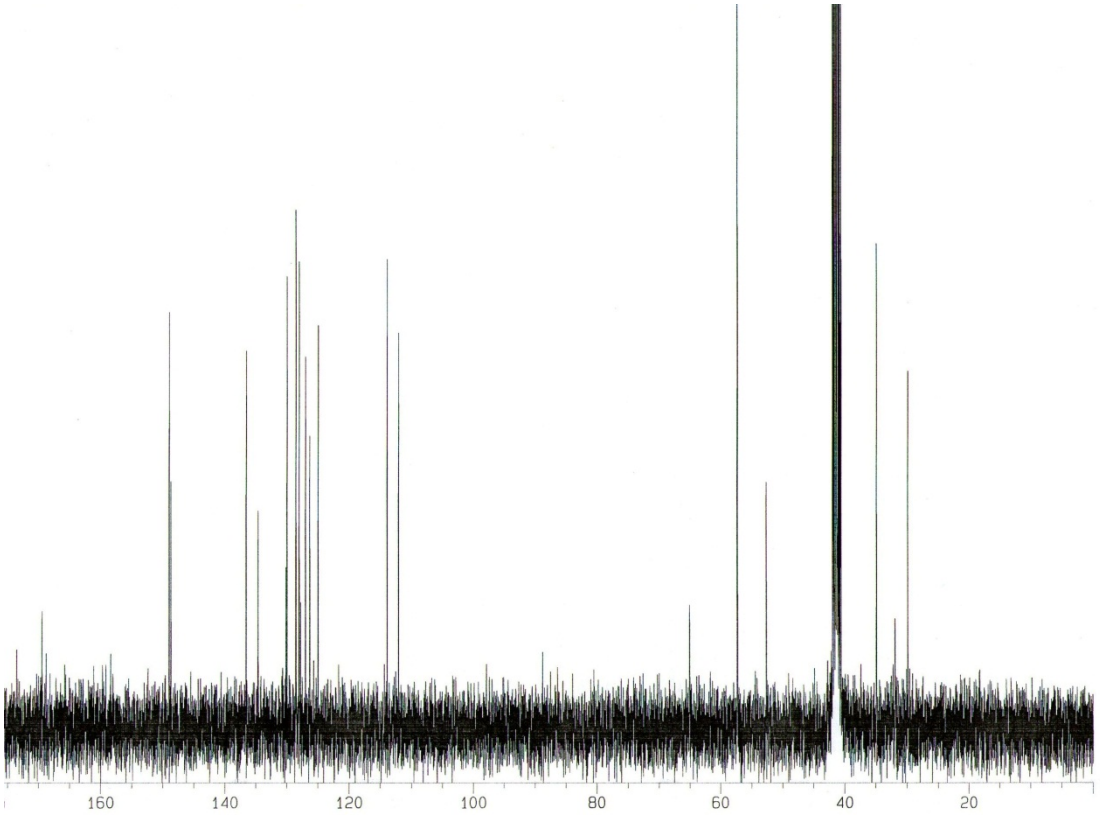

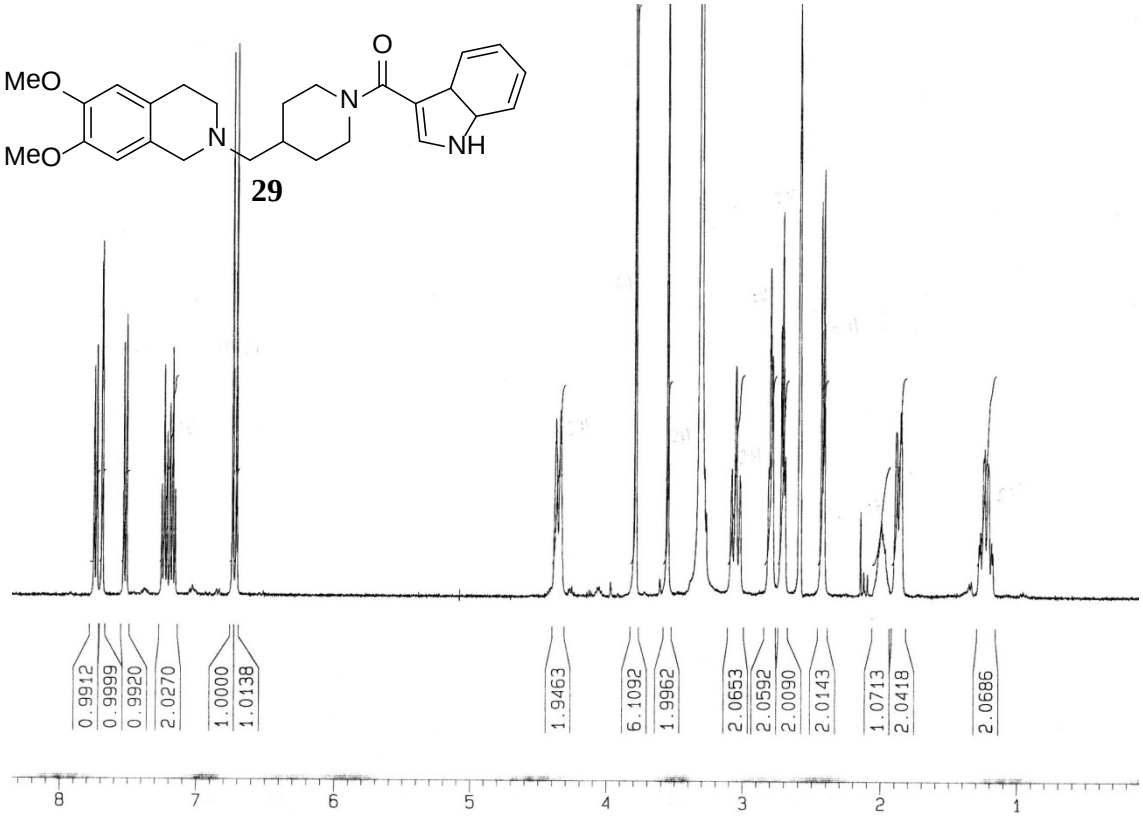

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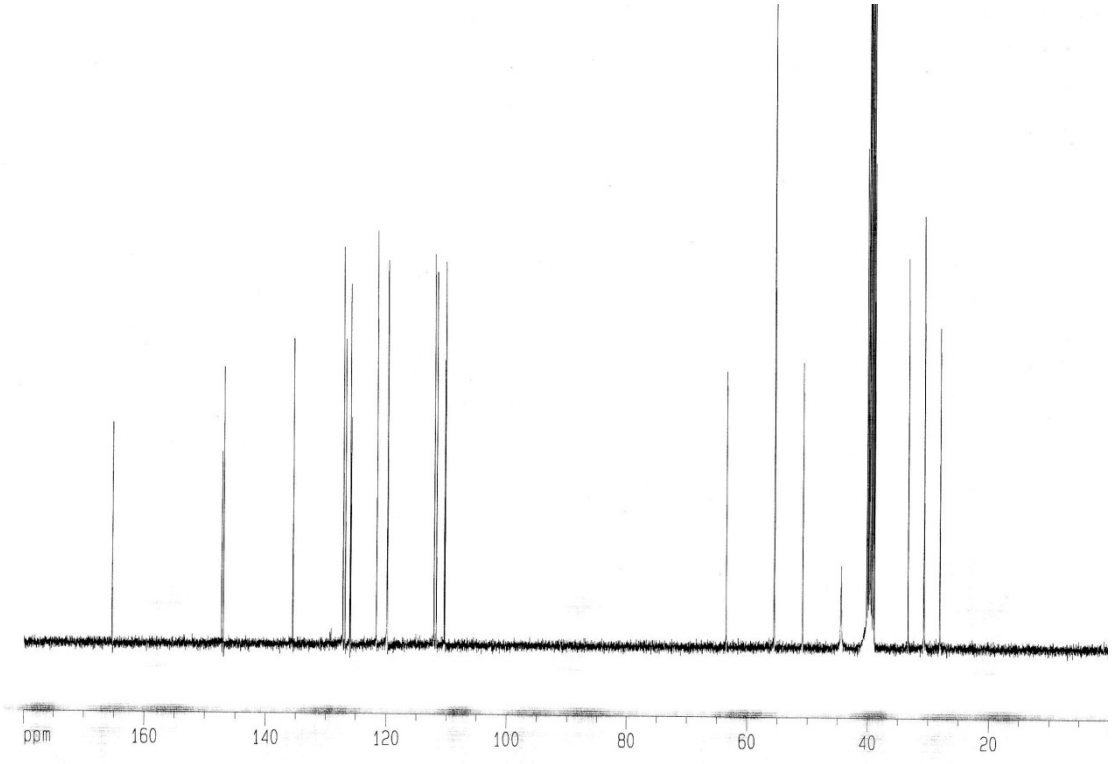

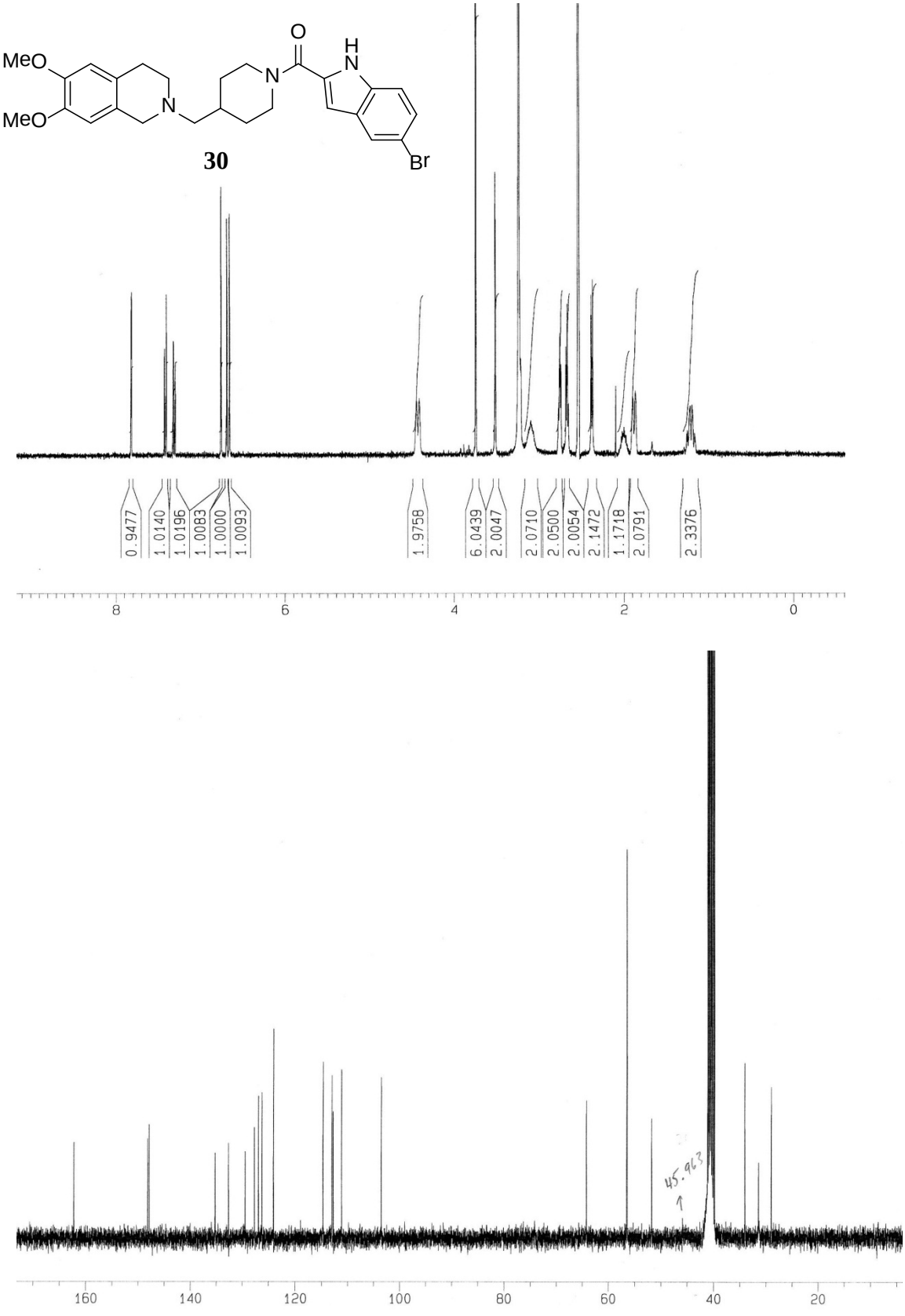

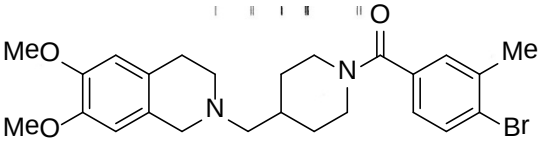

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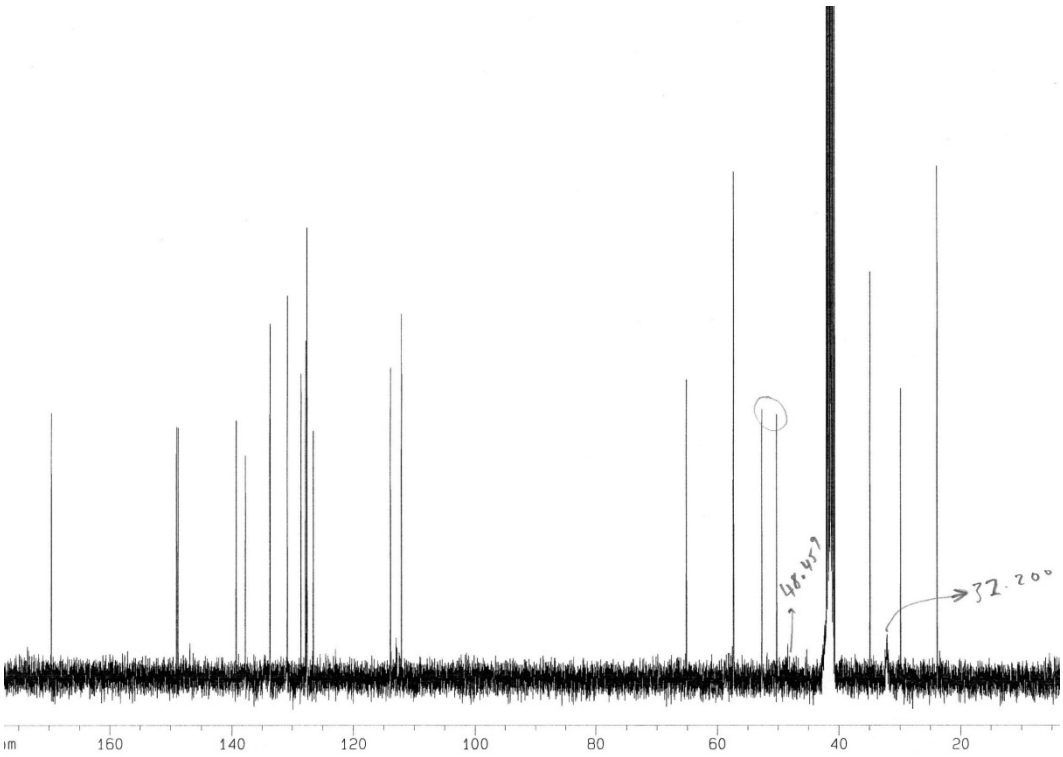

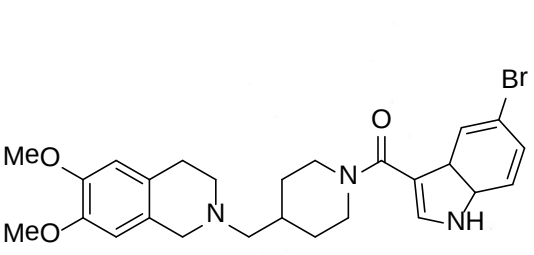

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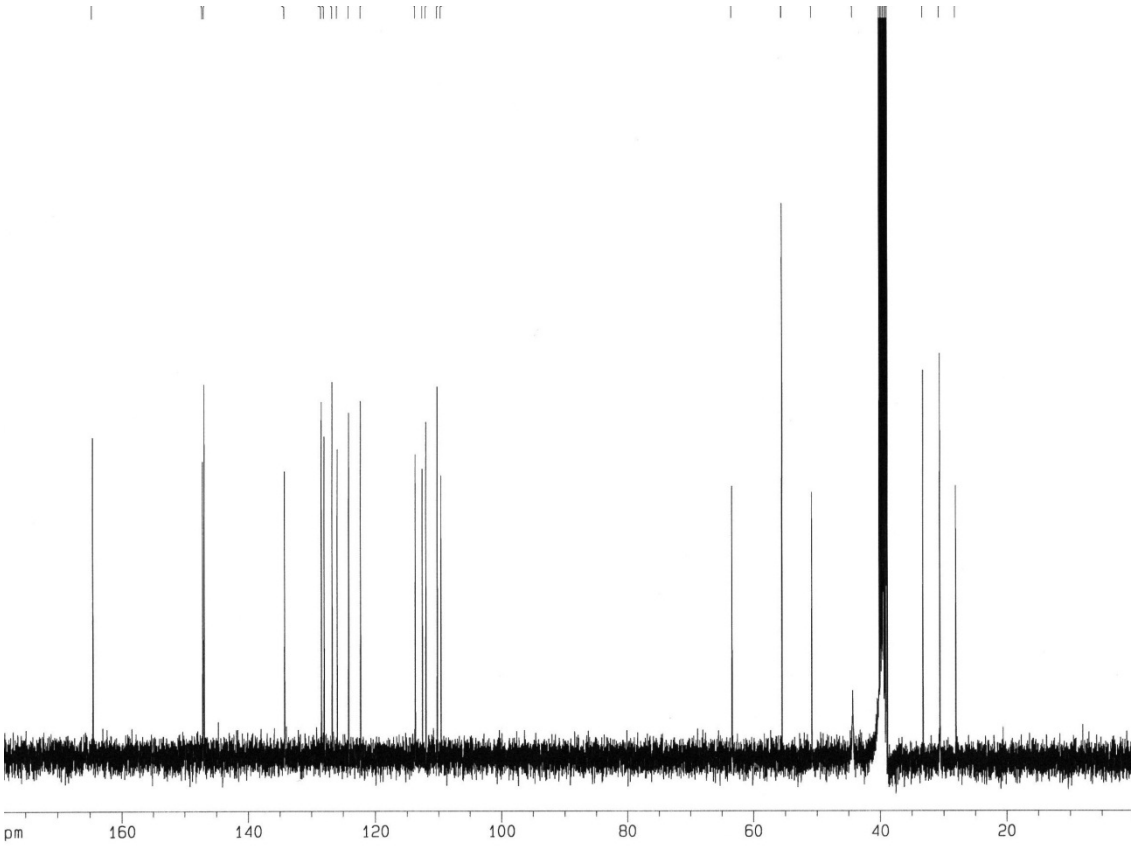

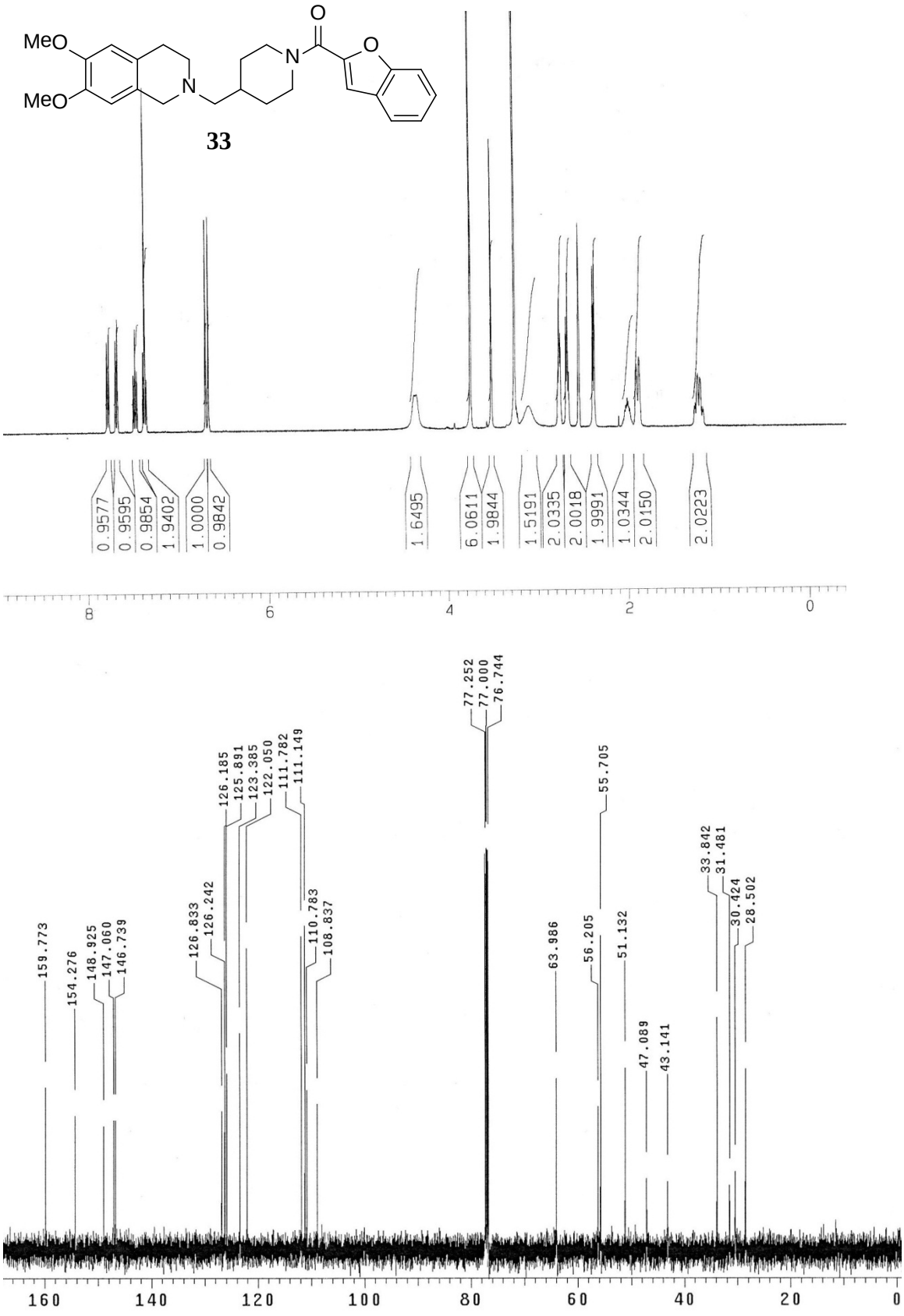

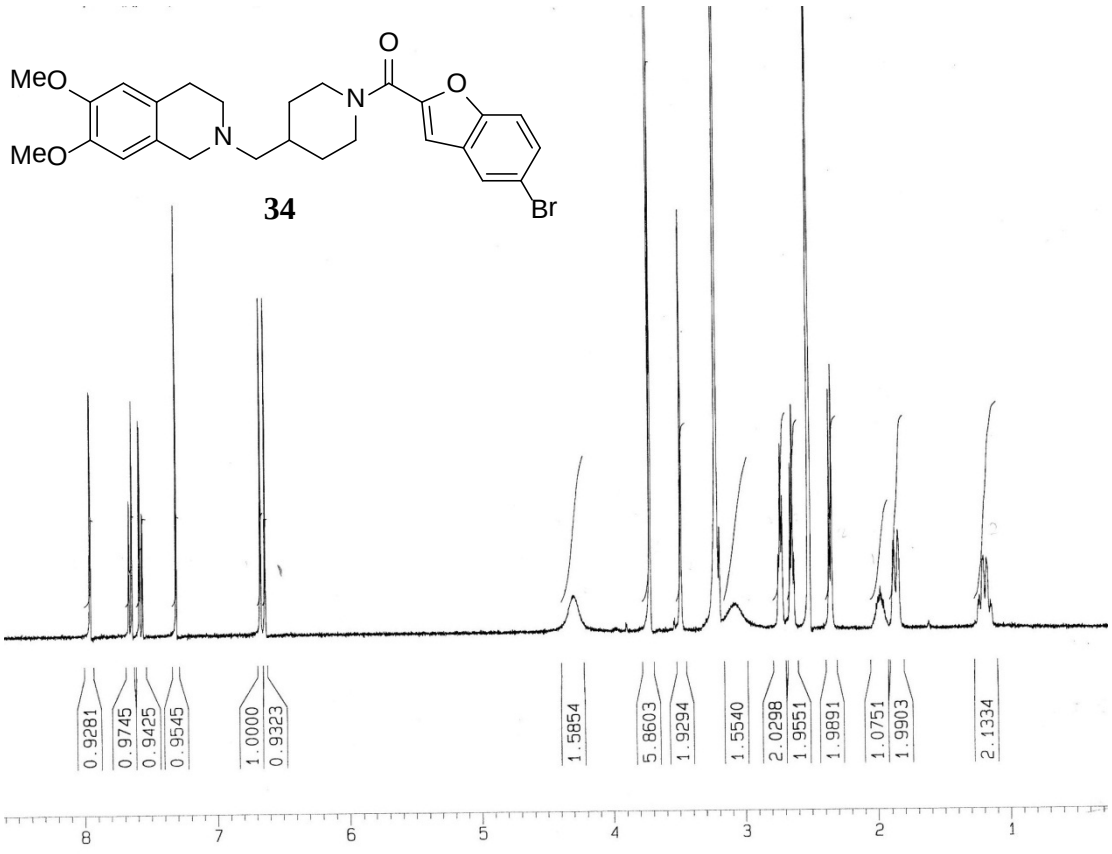

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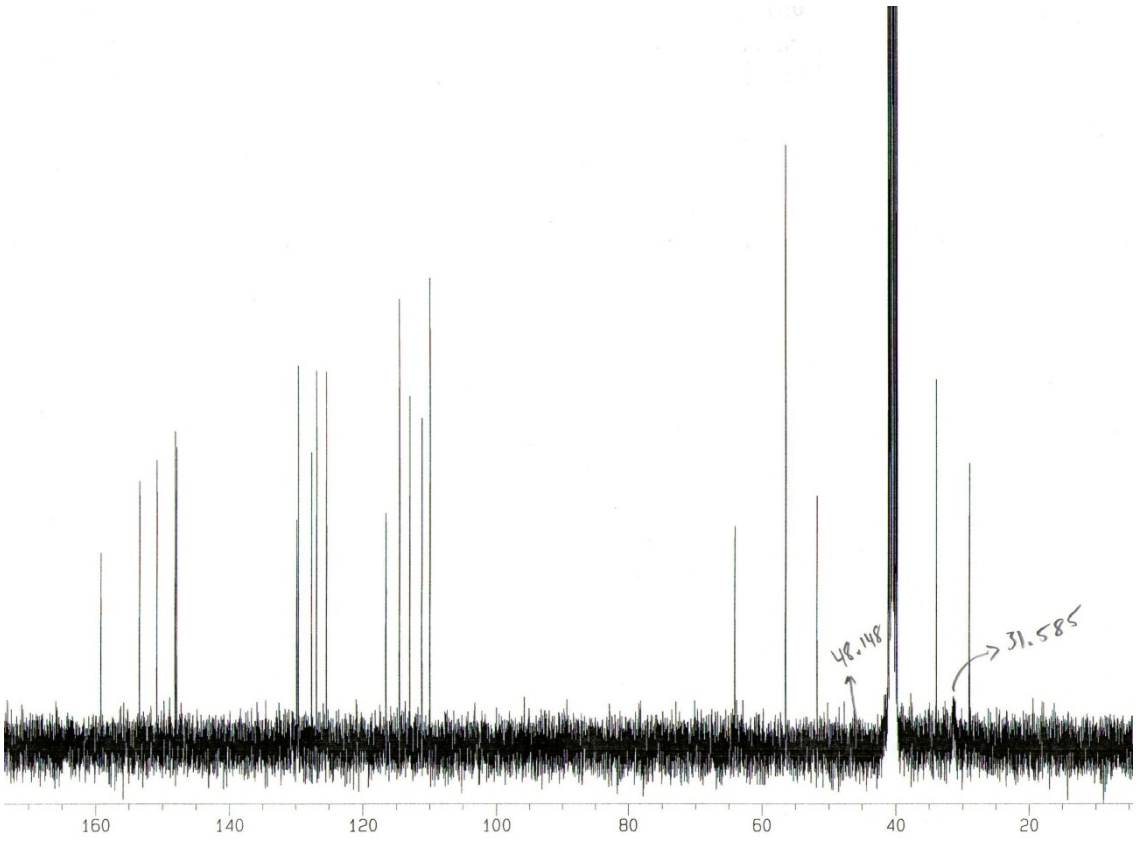

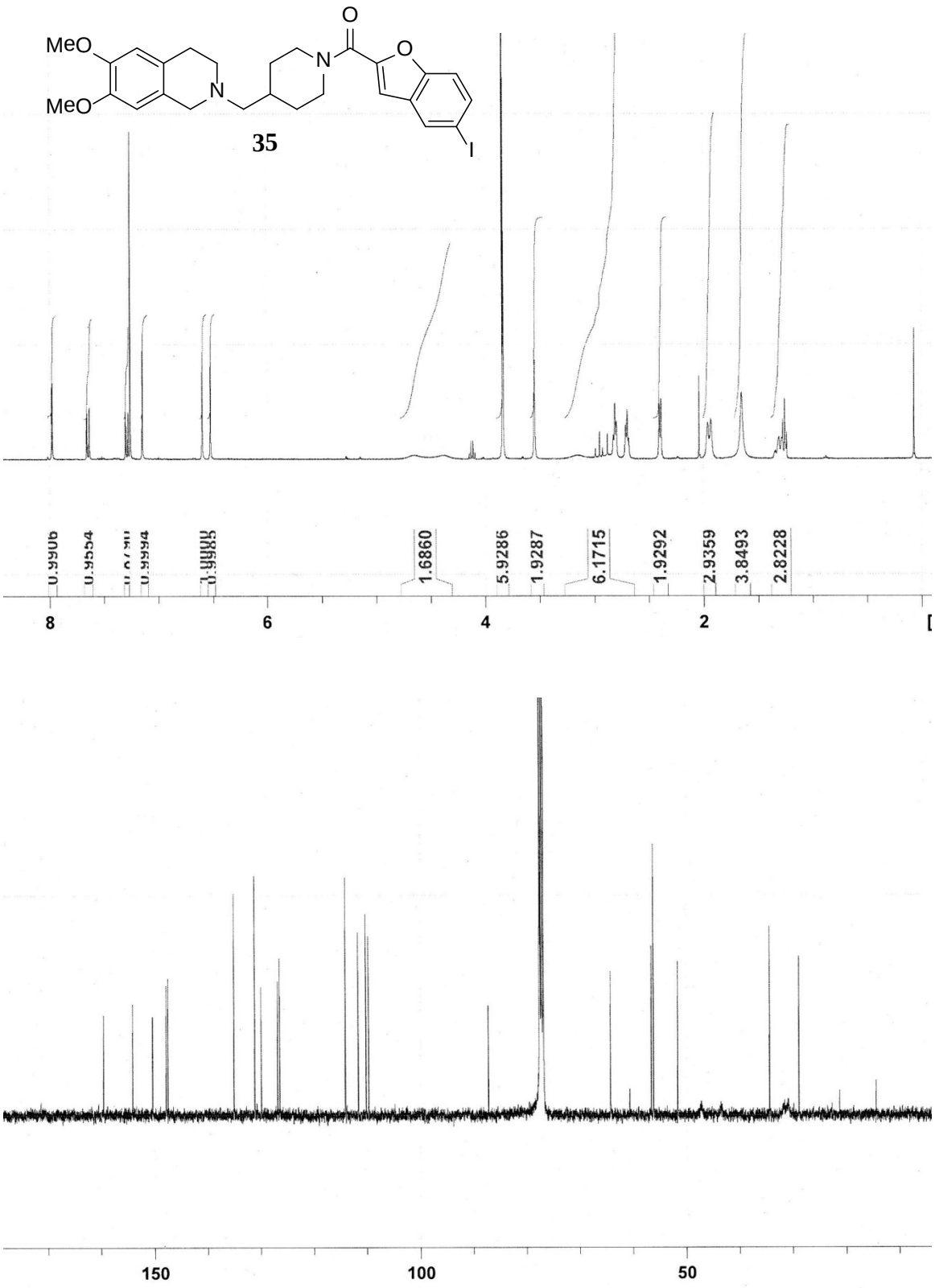

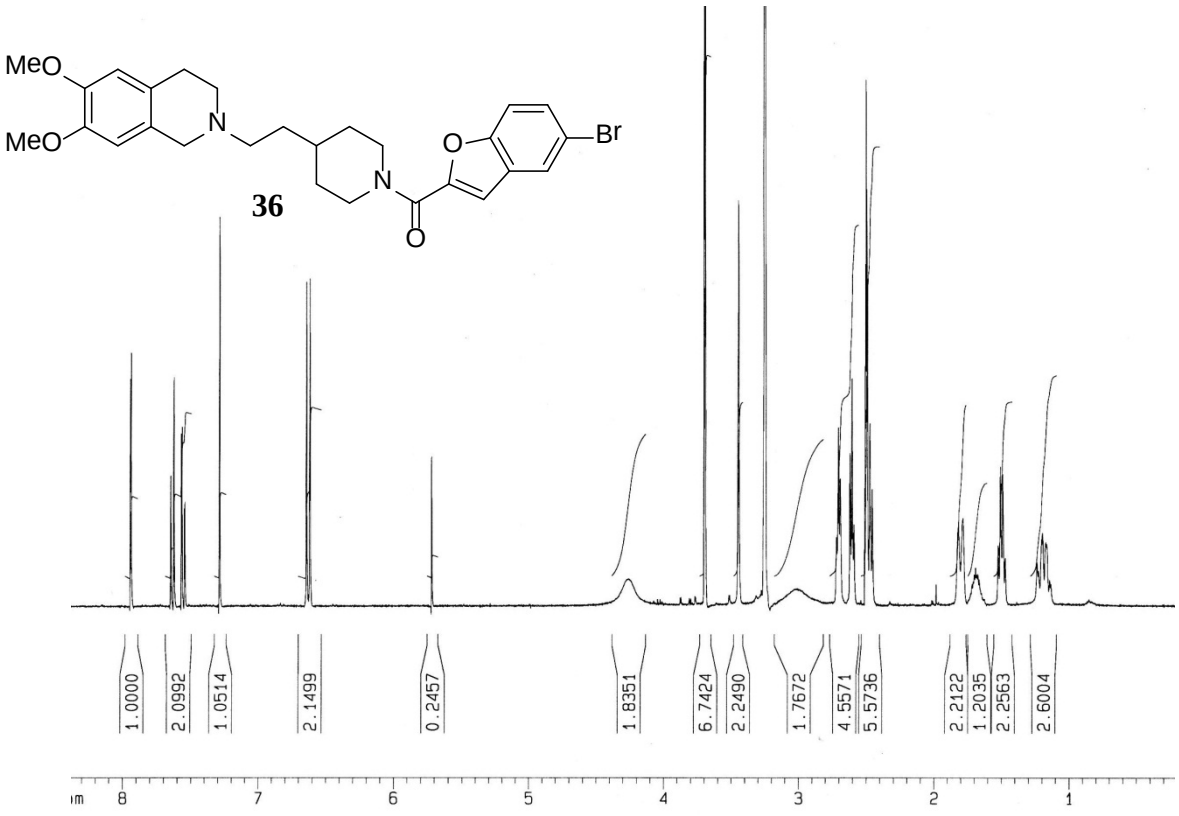

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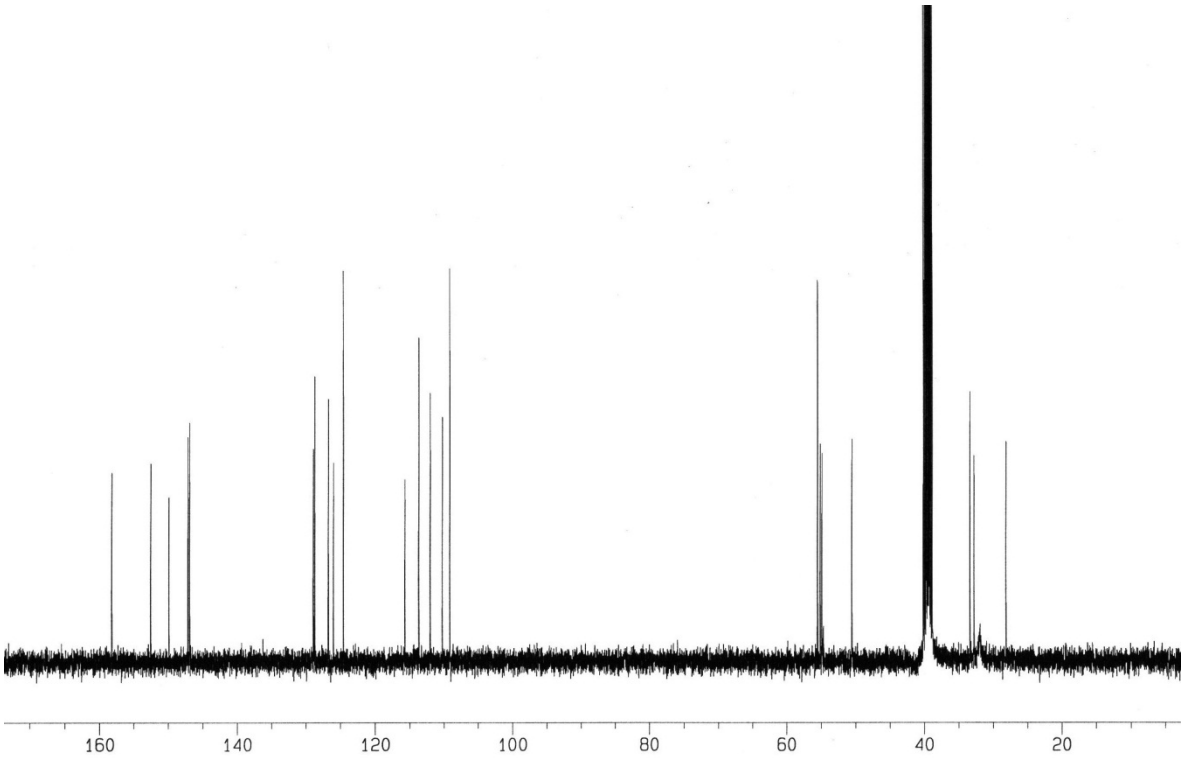

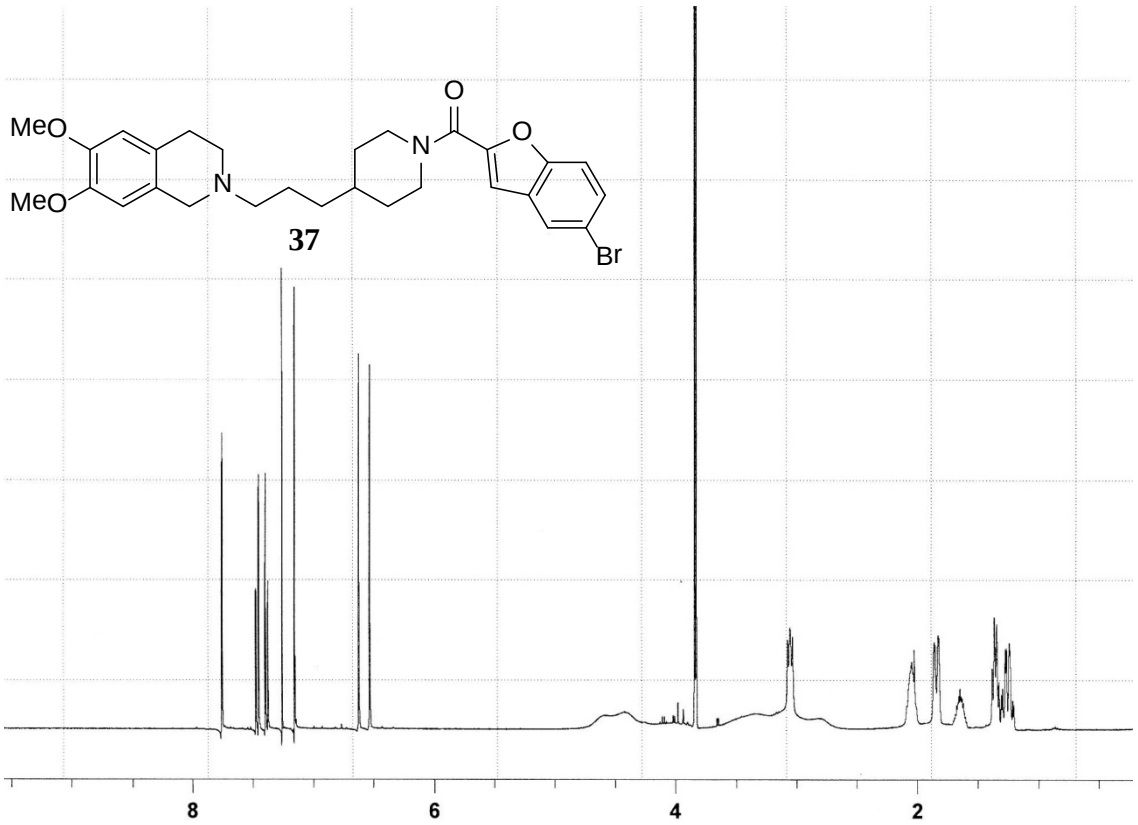

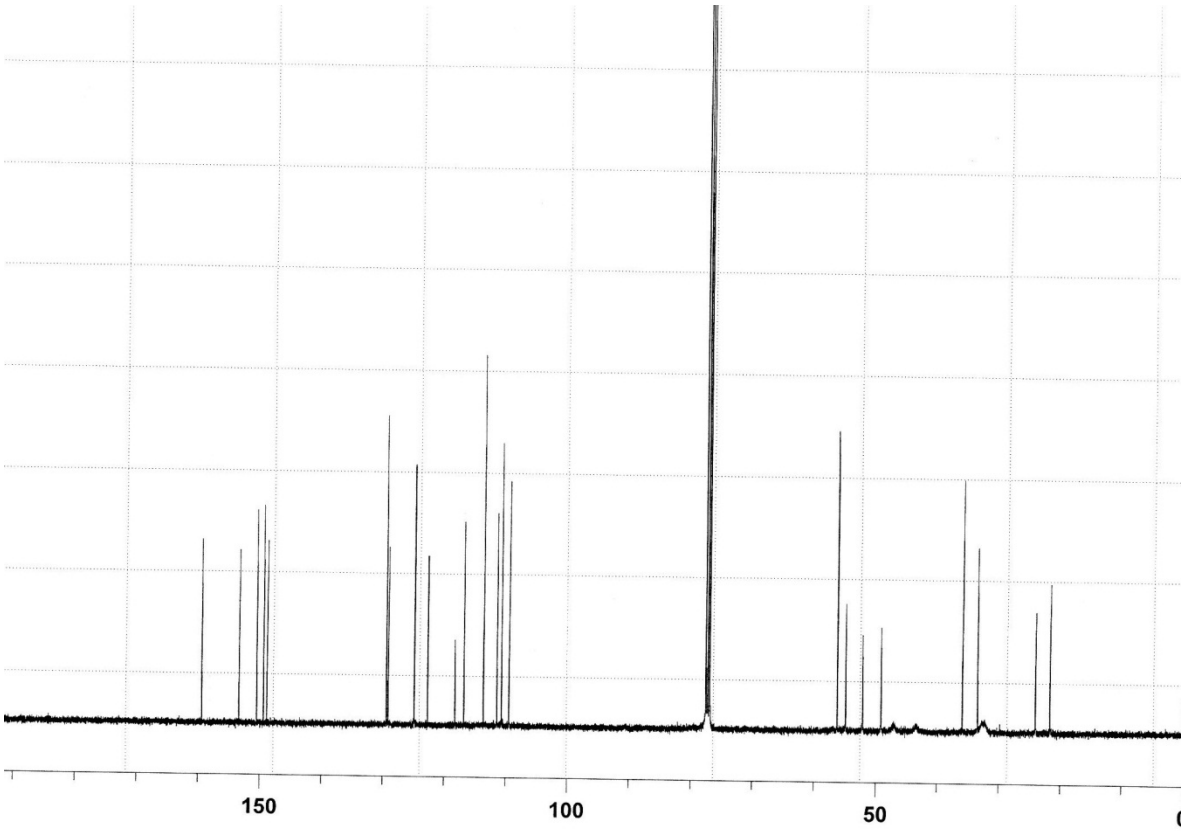

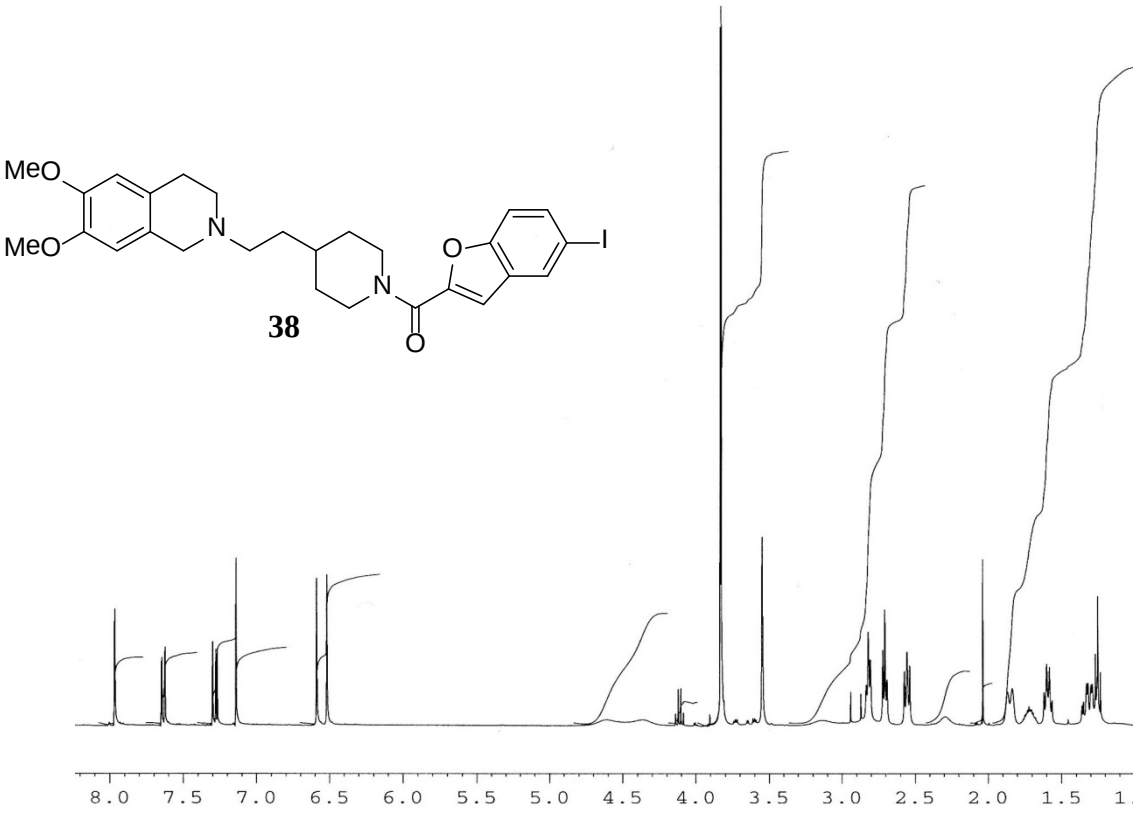

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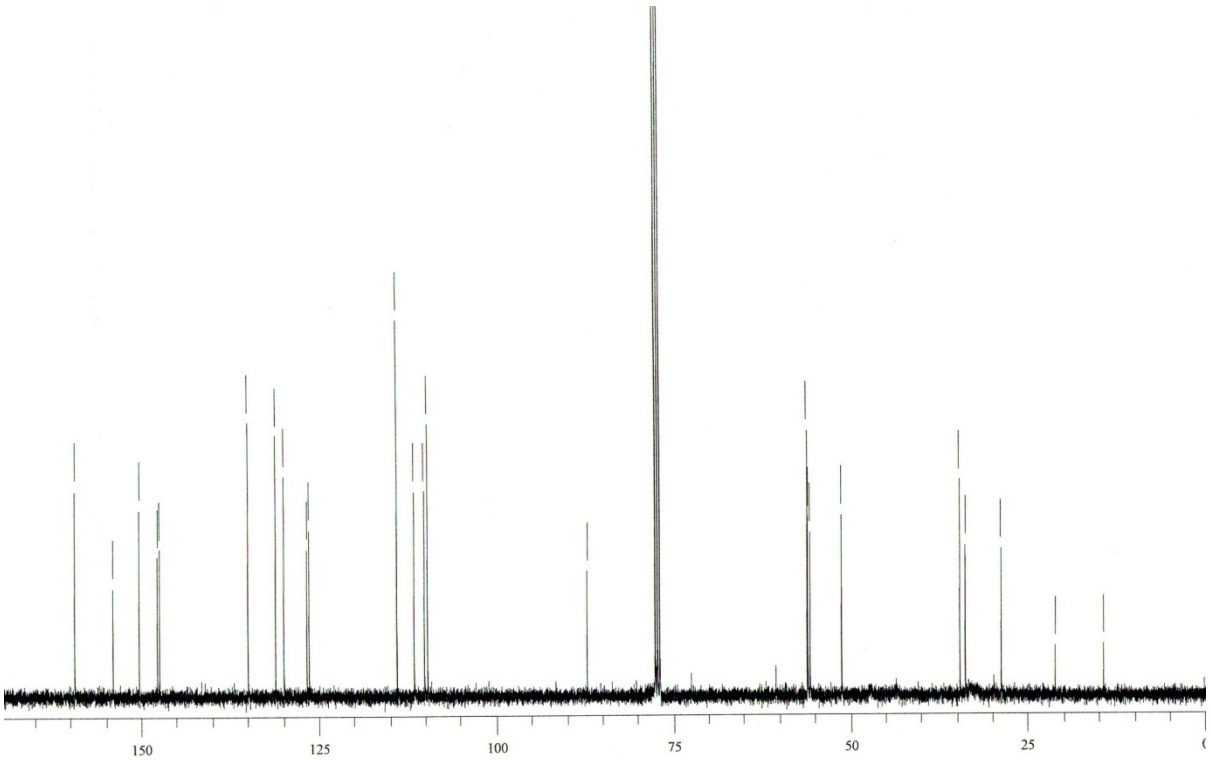

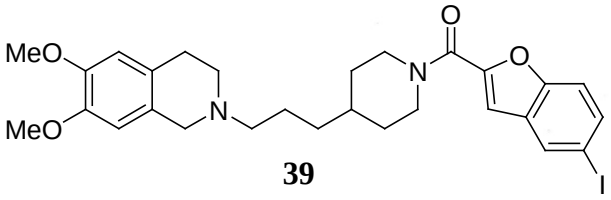

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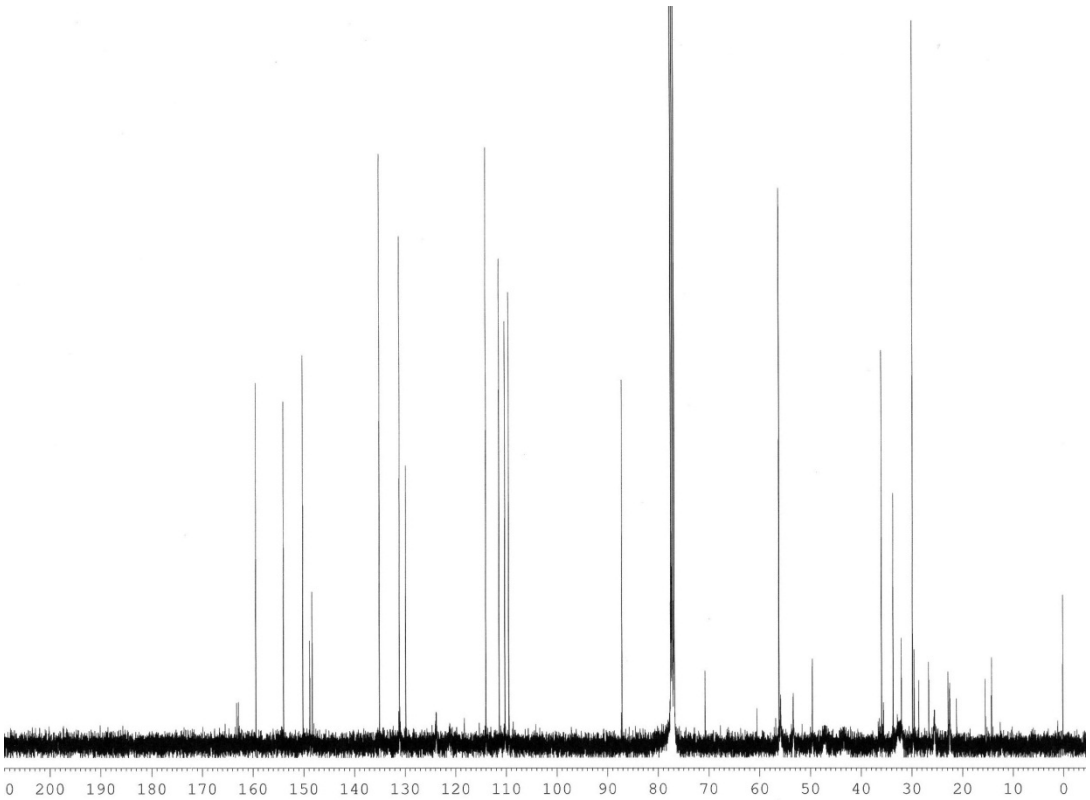

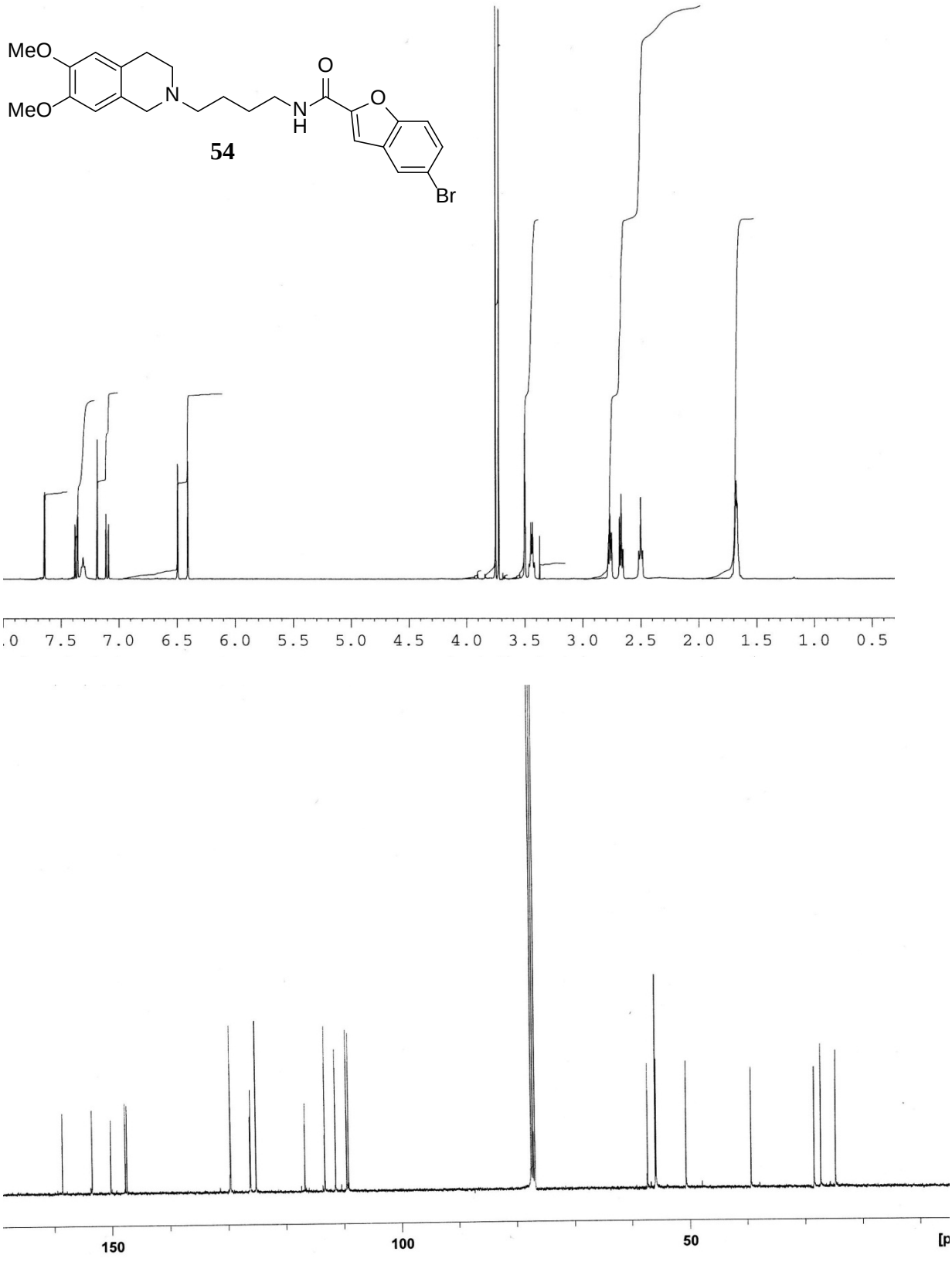

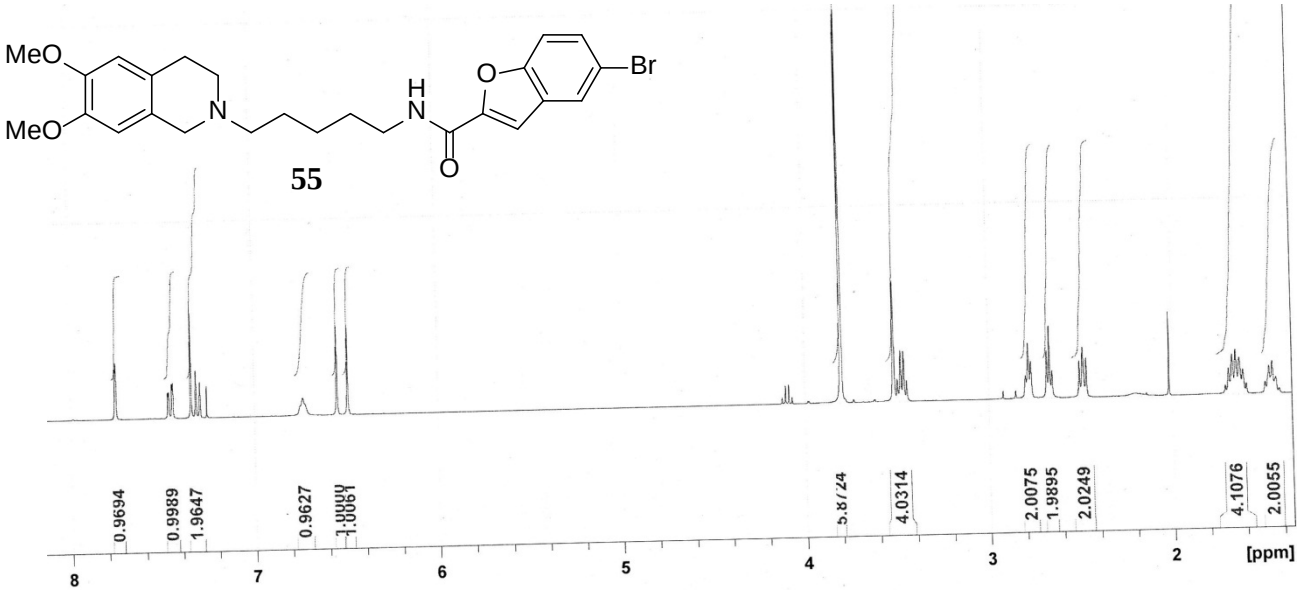
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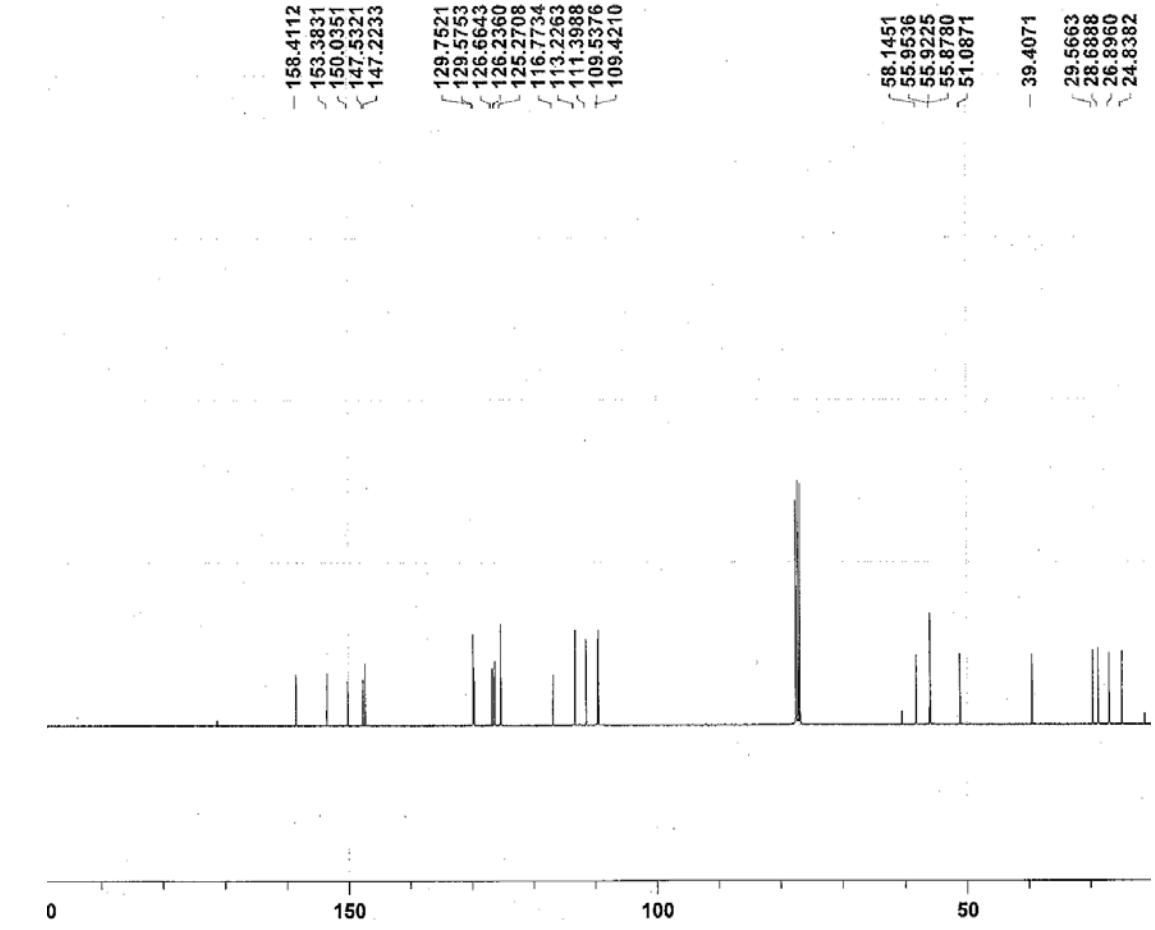
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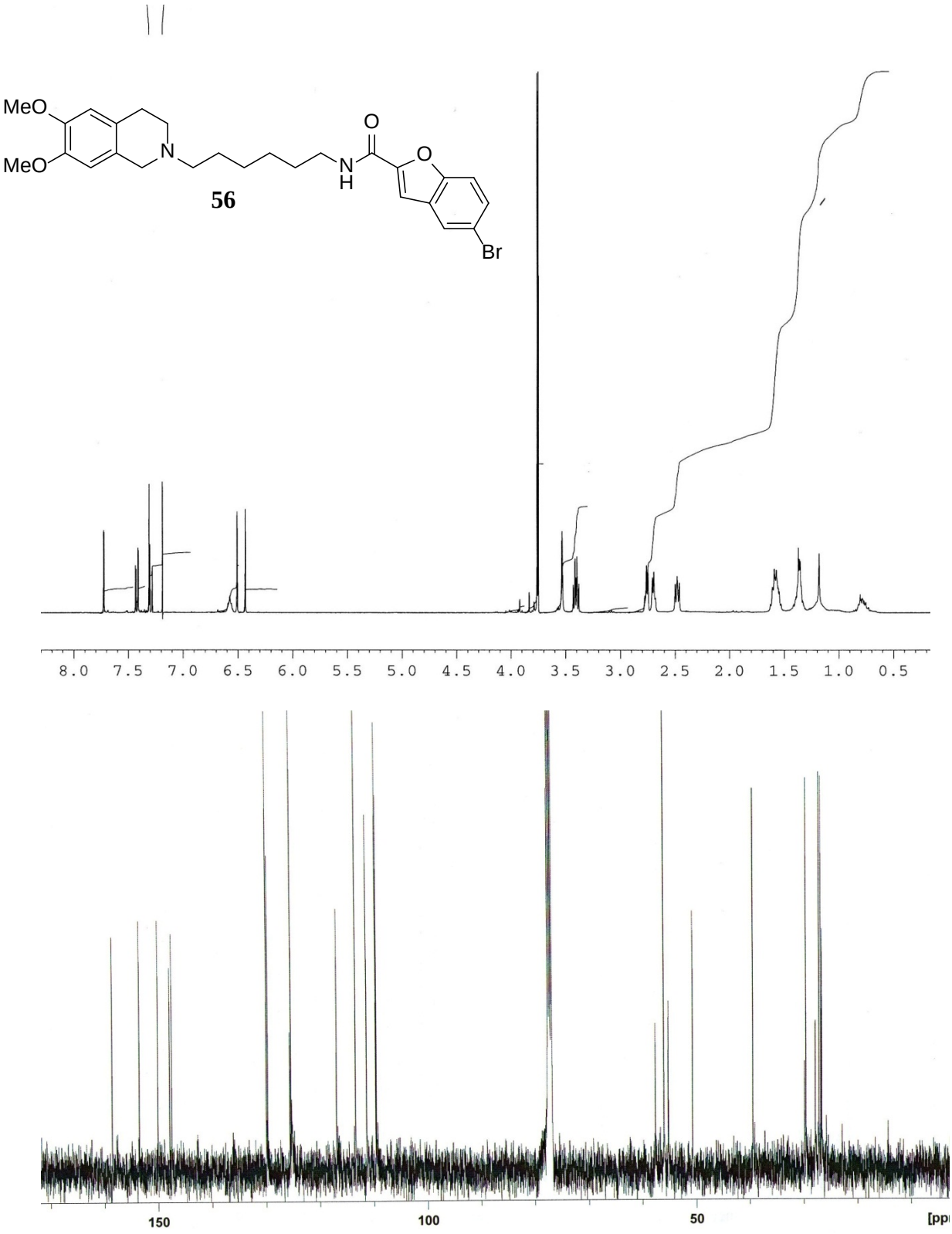

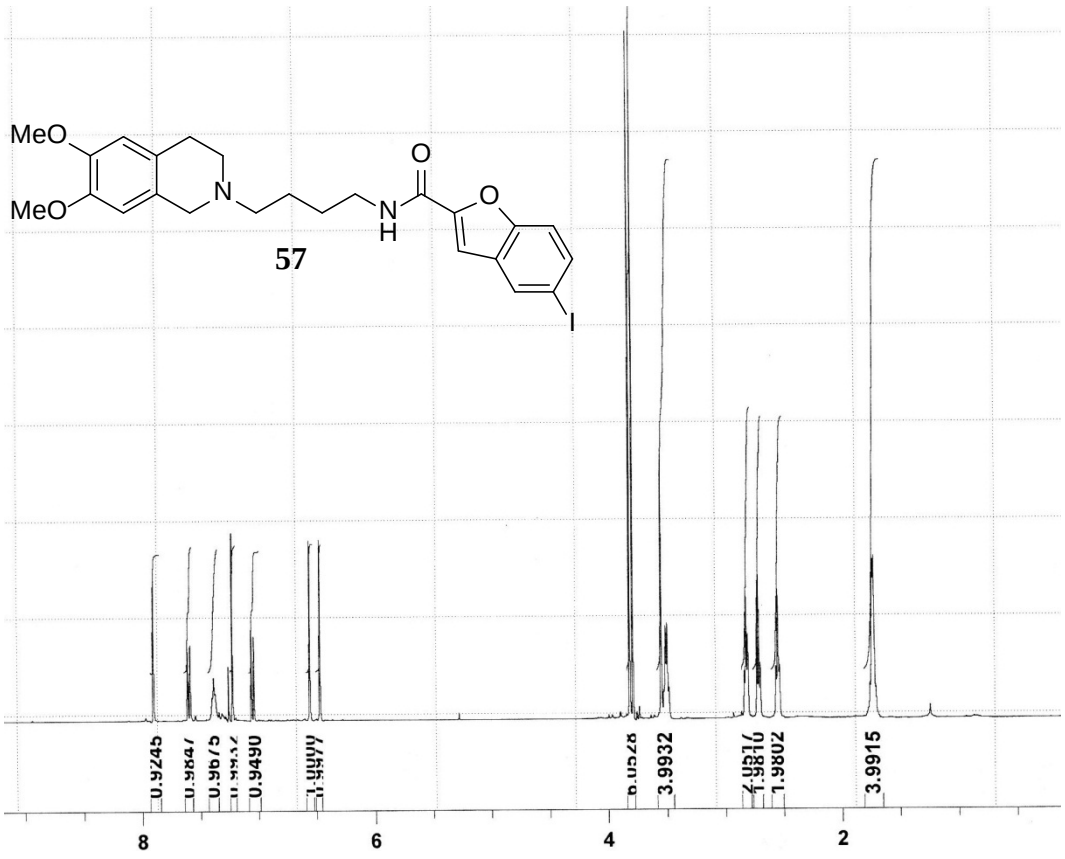

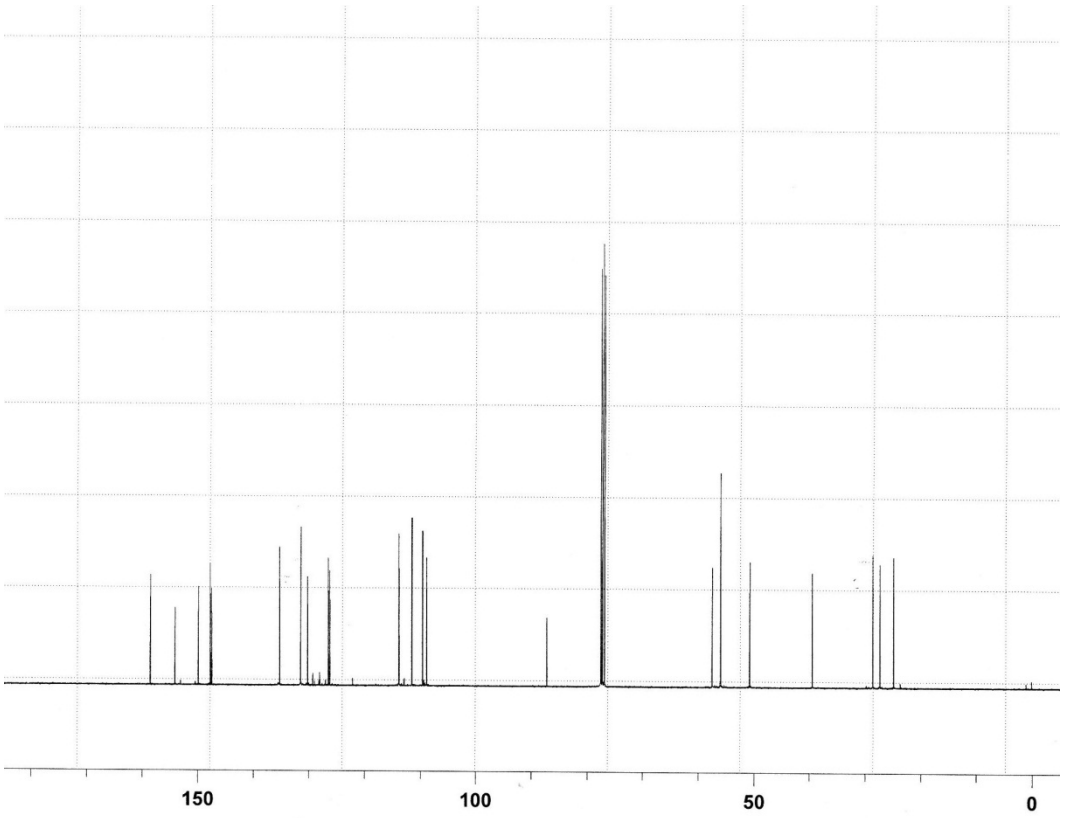

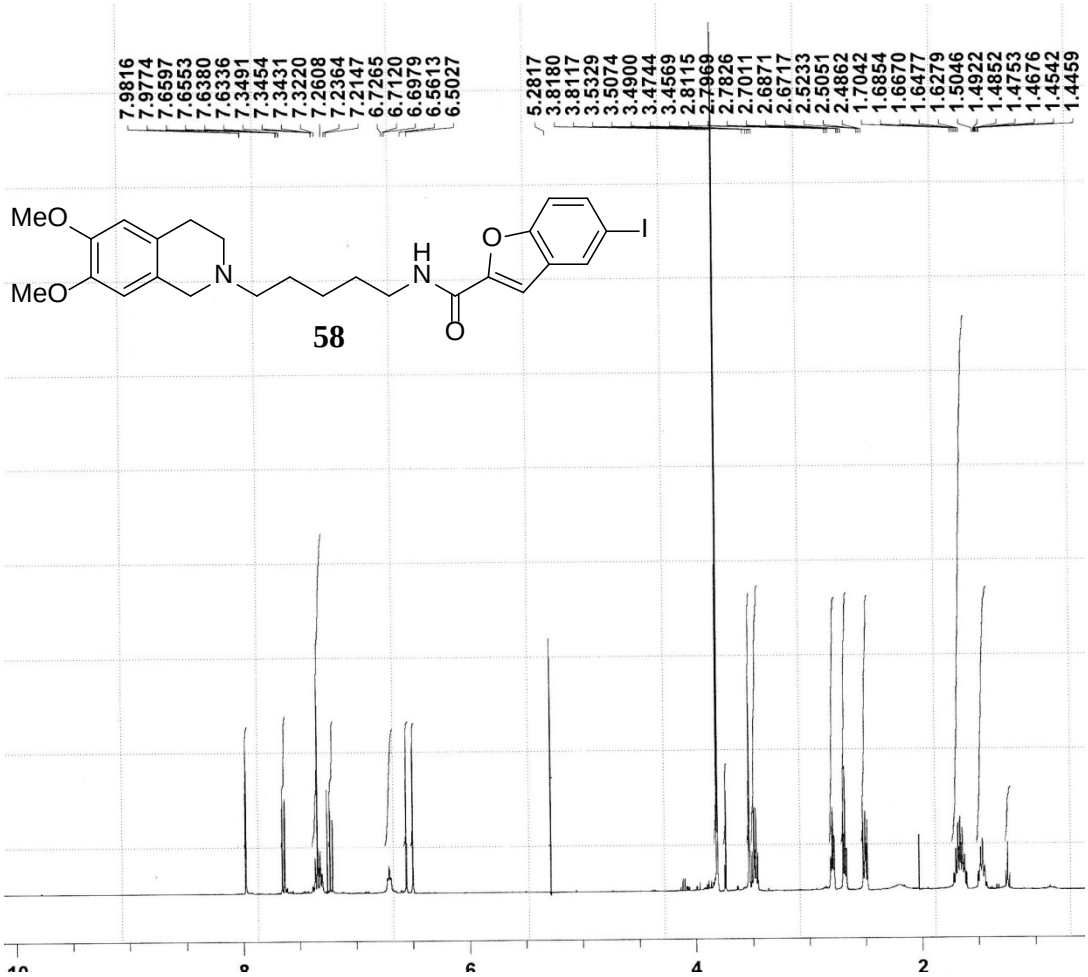

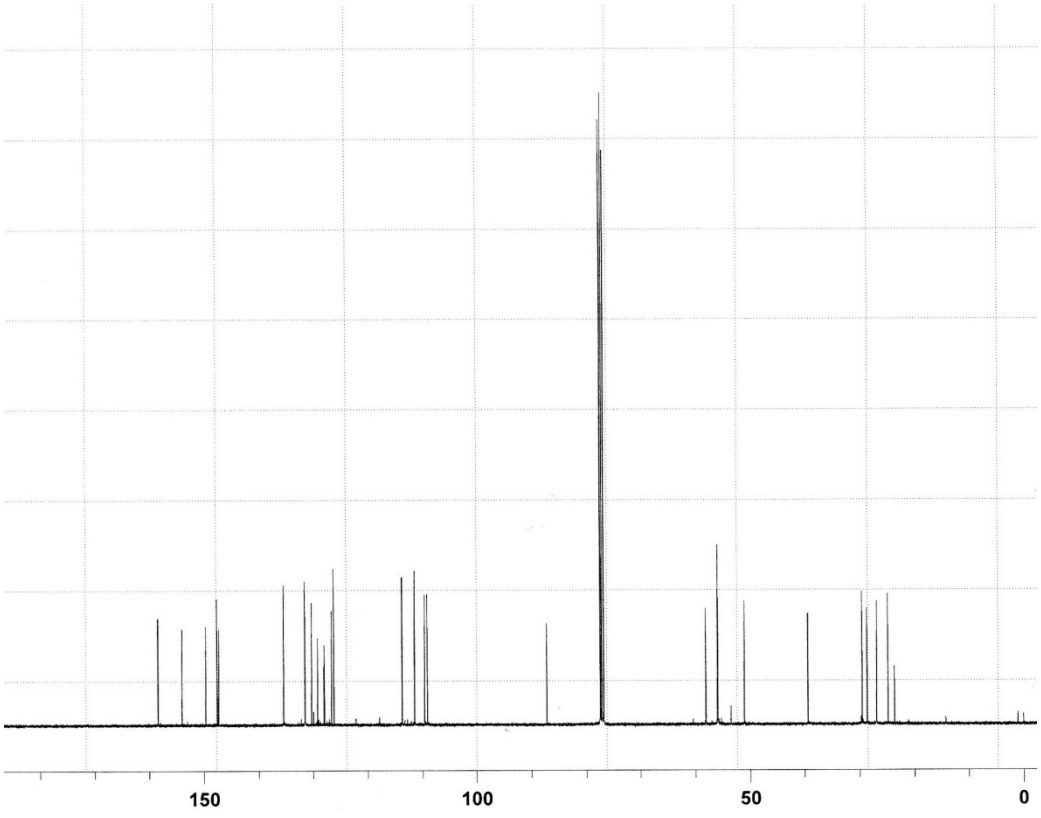

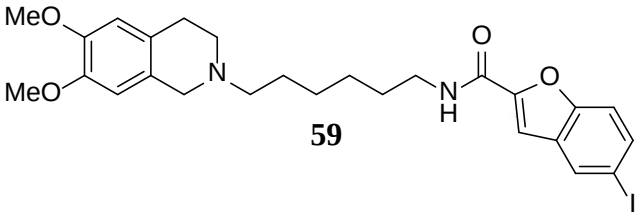

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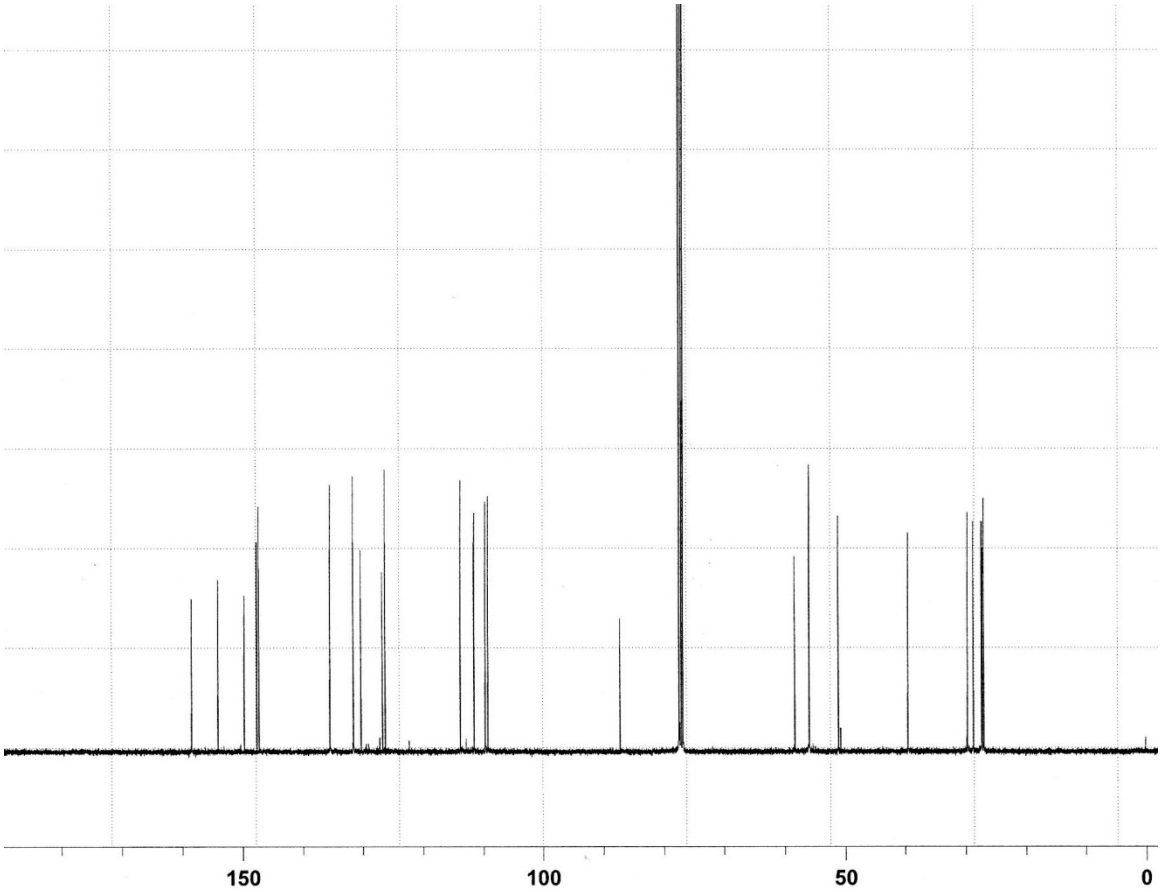

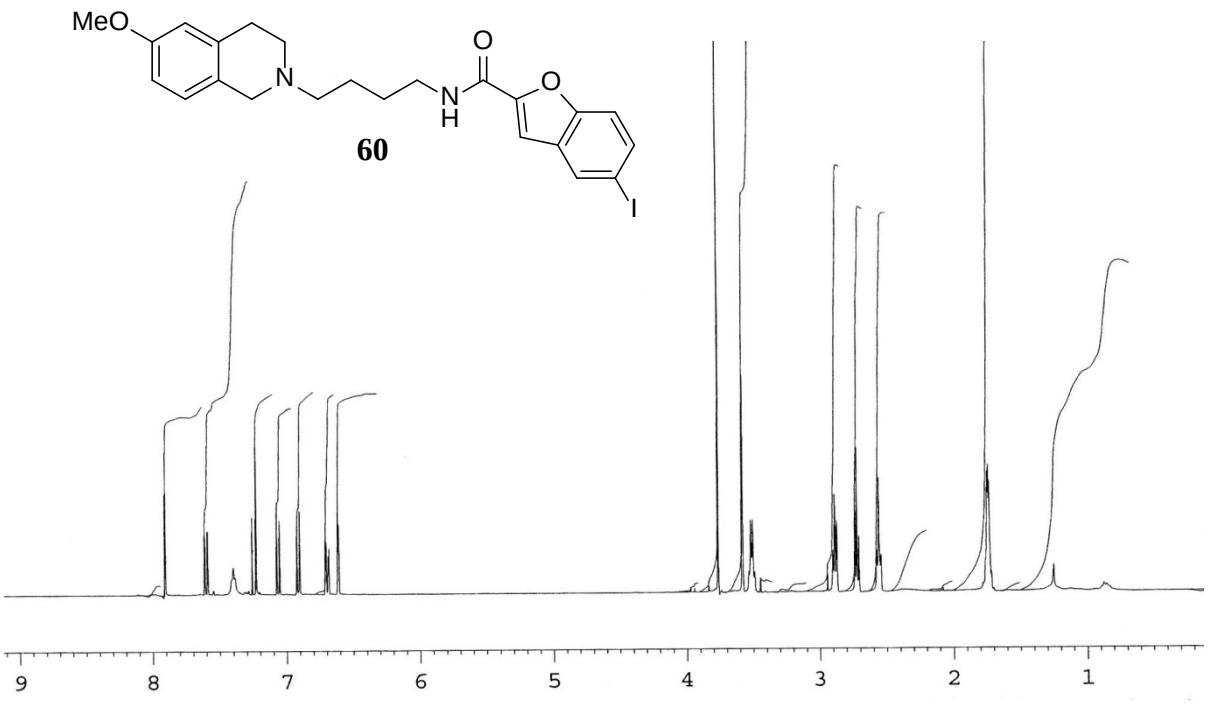

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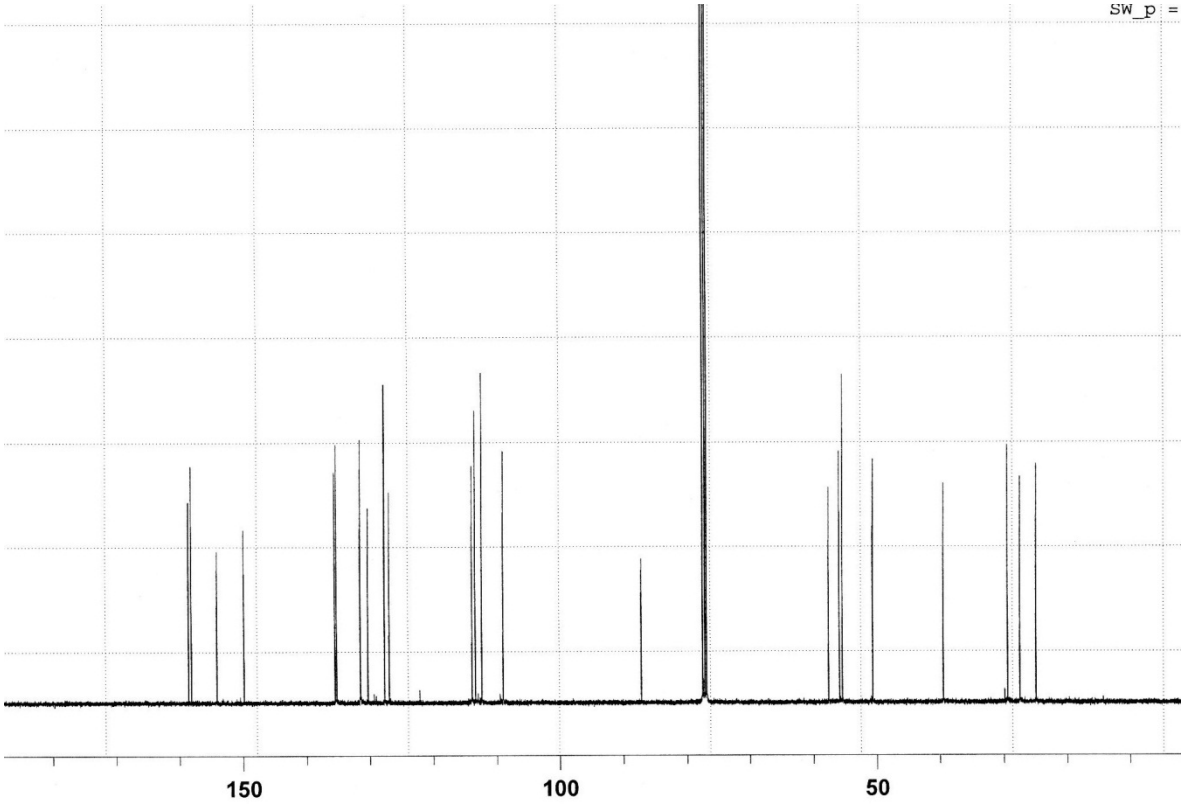

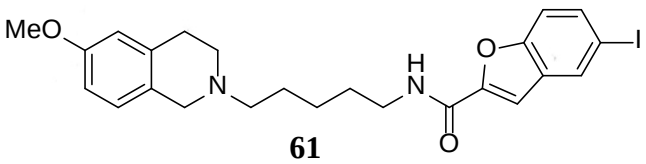

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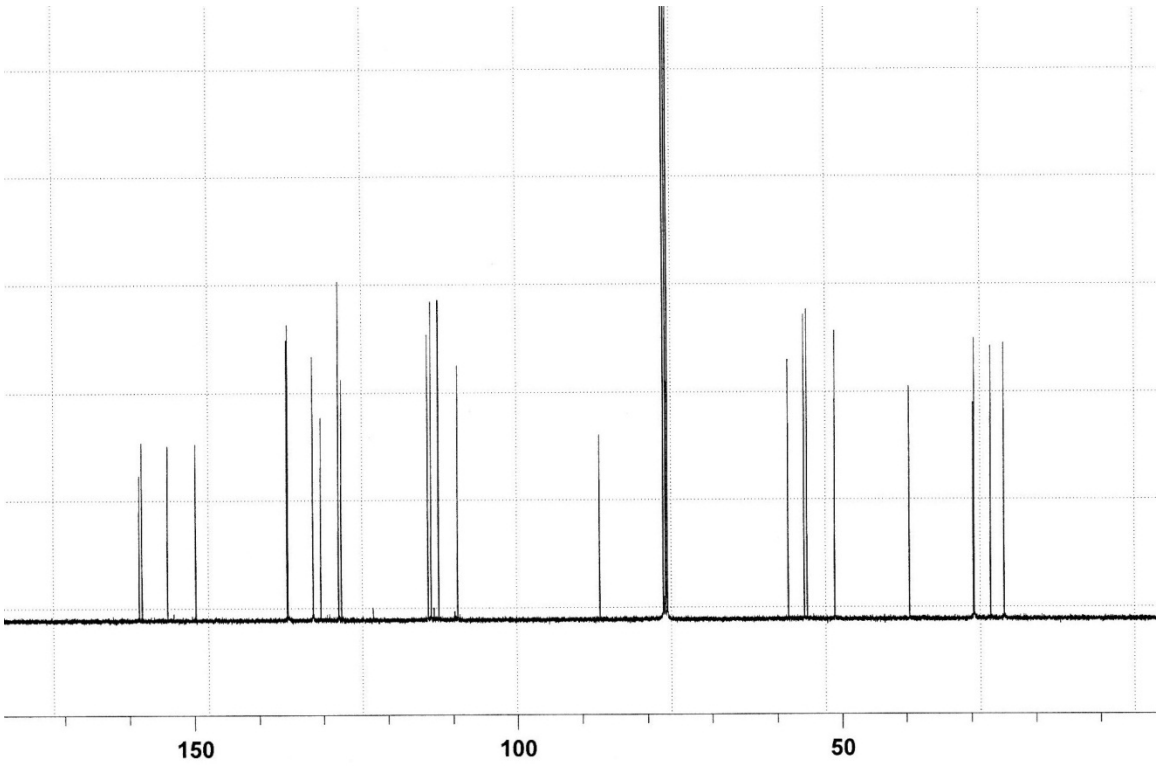

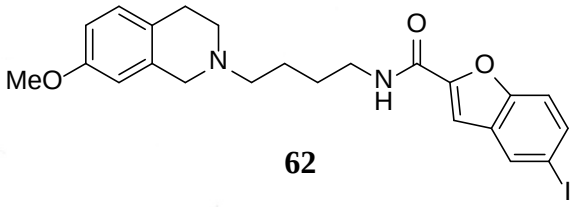

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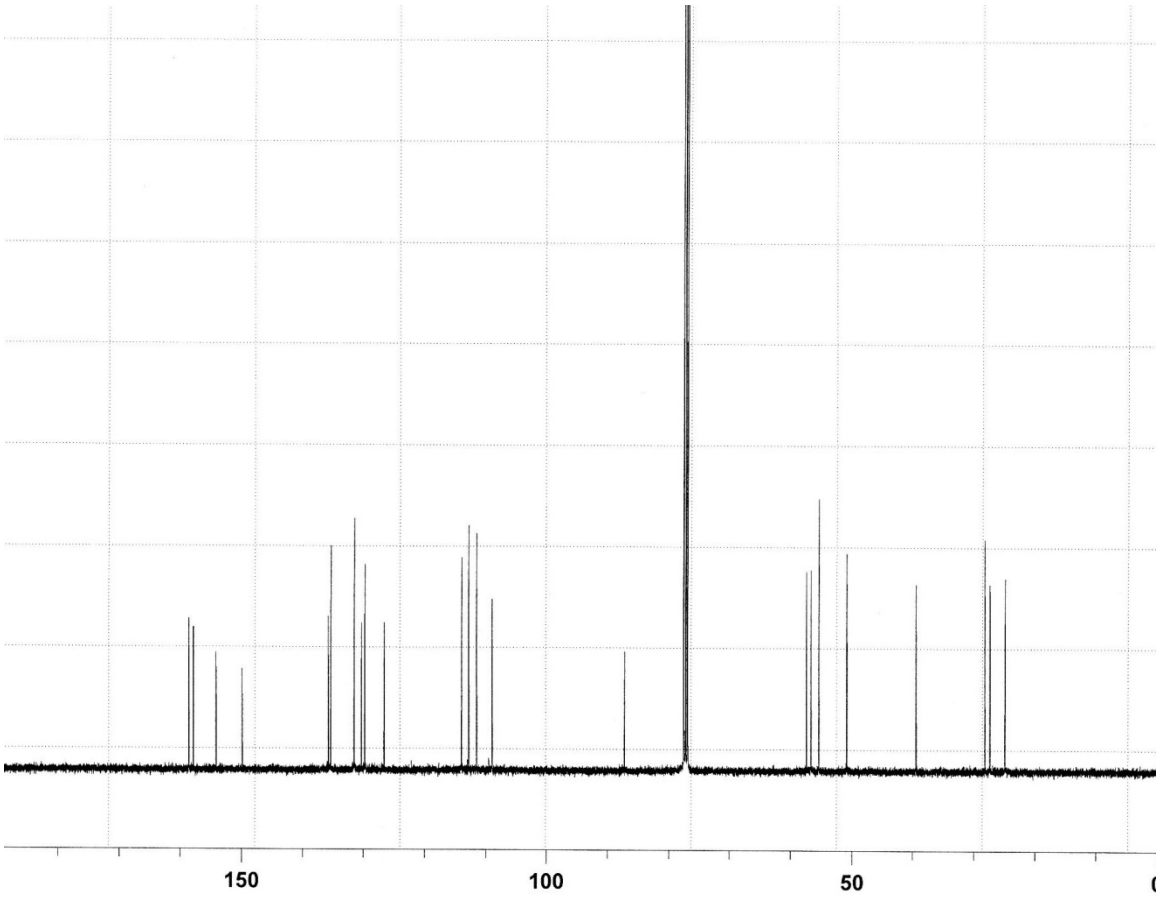

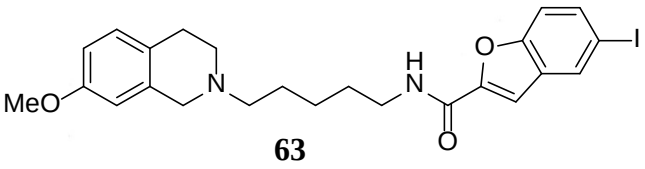

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