

Supporting Information *for*

A rhodium-catalyzed [4 + 2] annulation strategy to synthesize pyranone-mounted tyrosines with anti-neuroinflammatory activity

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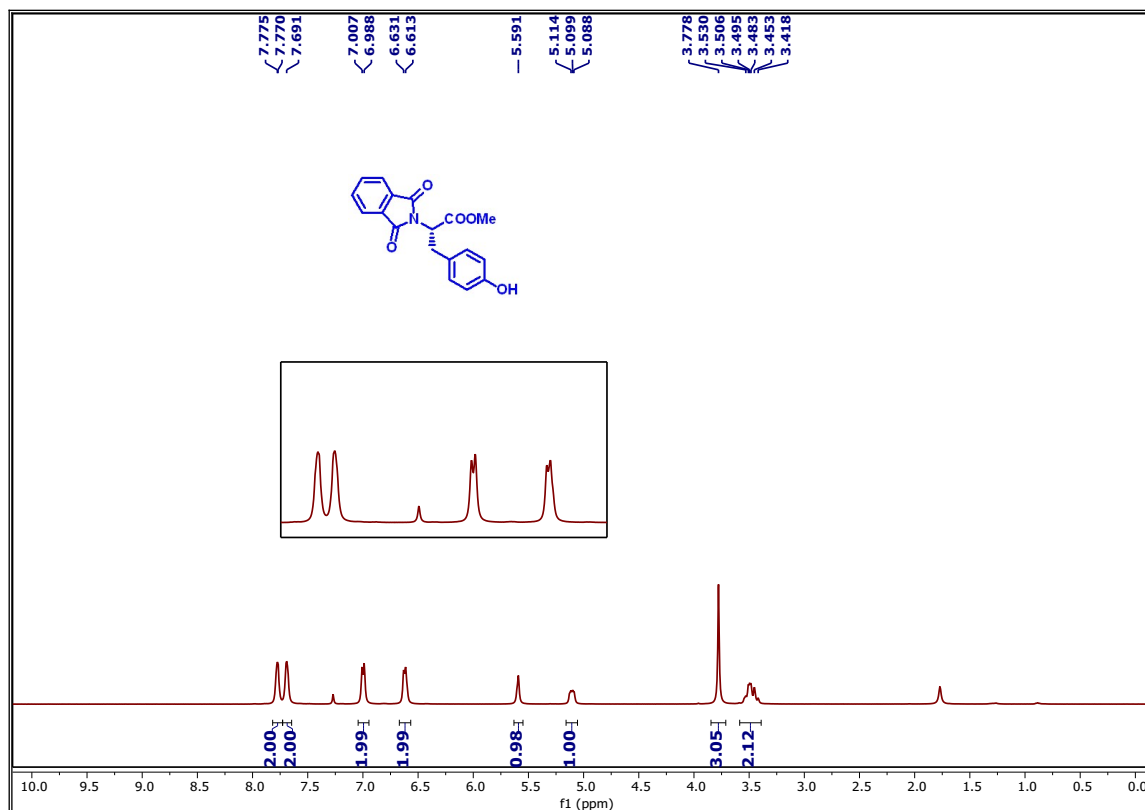
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1. Preparation of unsymmetrical internal alkynes

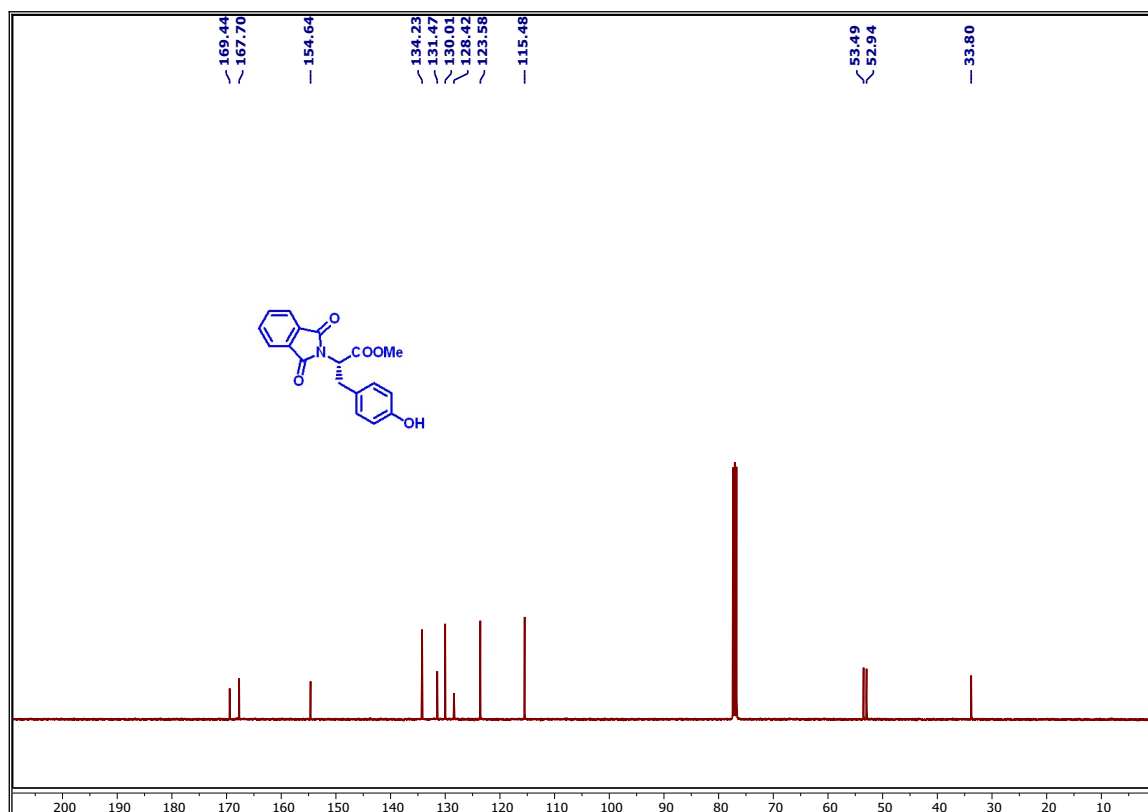
Internal alkynes (**2j**),¹ (**2l-o**),² (**2p-q**)³⁻⁴ and (**2r-s**)⁵ were prepared by the reported procedures.

2. Original NMR spectra of *N*-phthalimido tyrosine methyl ester

¹H NMR of *N*-Phthalimido tyrosine methyl ester (400 MHz, CDCl₃)

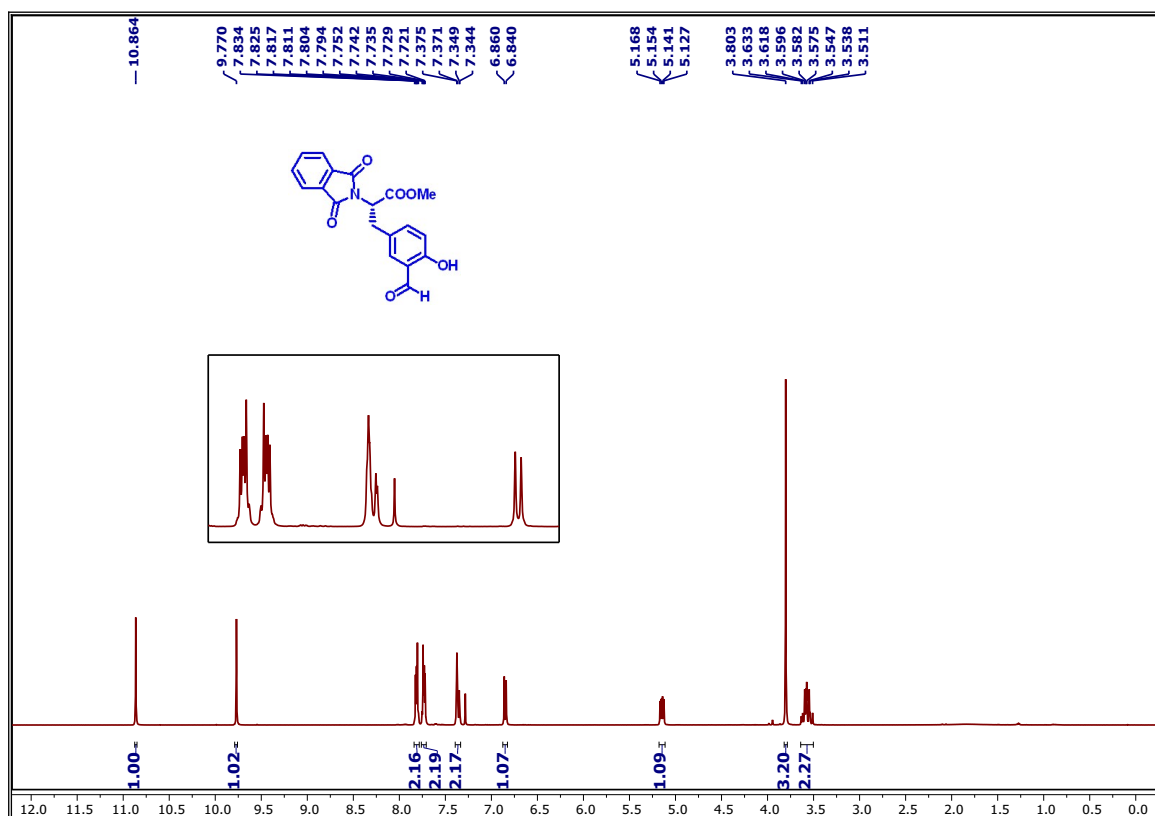


¹³C NMR of *N*-Phthalimido tyrosine methyl ester (100 MHz, CDCl₃)

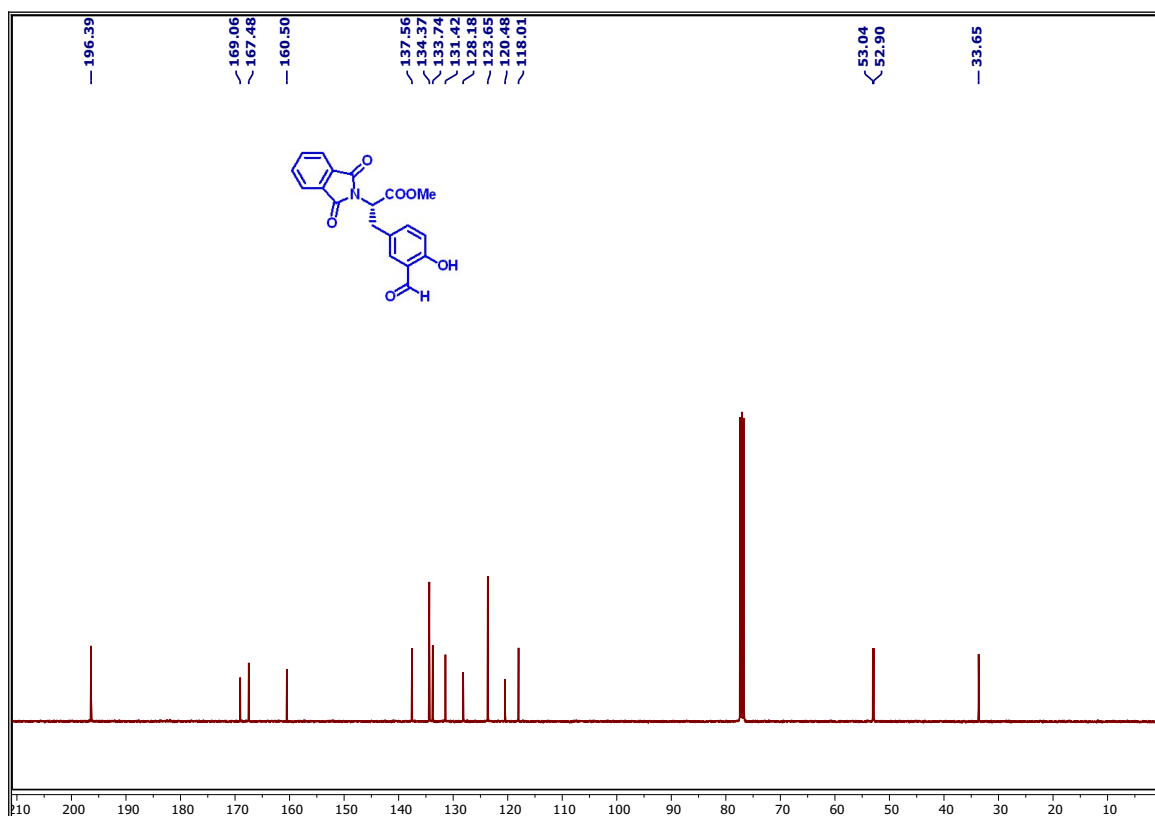


3. Original NMR spectra of *N*-phthalimido C3_{Ar}-formyl tyrosine methyl ester (1a)

¹H NMR of 1a (400 MHz, CDCl₃)

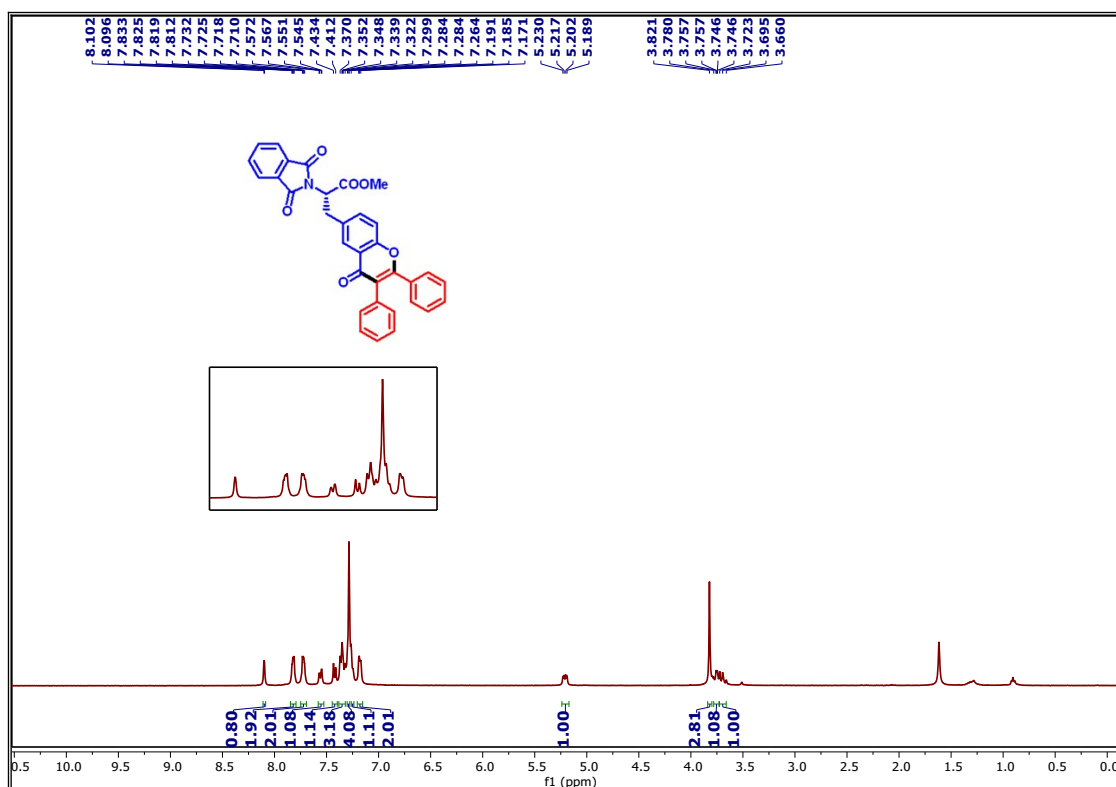


¹³C NMR of 1a (100 MHz, CDCl₃)

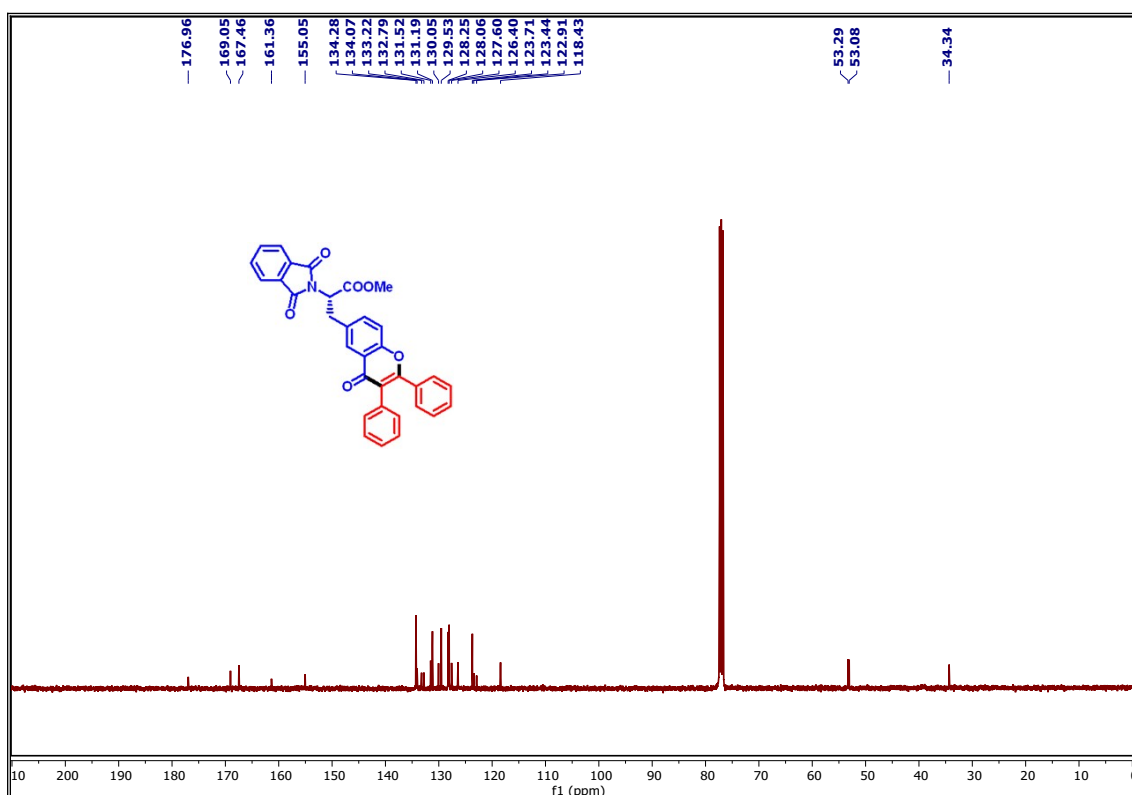


4. Original NMR spectra of 3

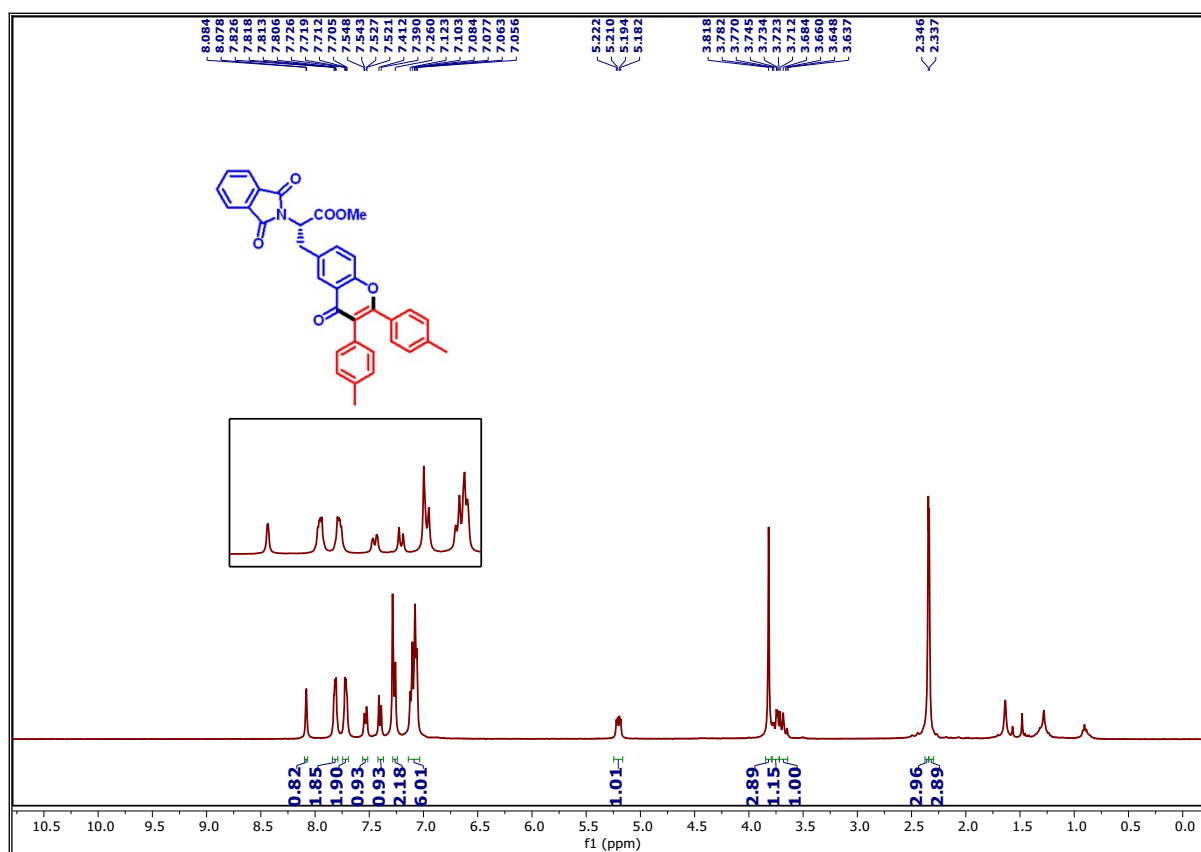
¹H NMR of 3aa (400 MHz, CDCl₃)



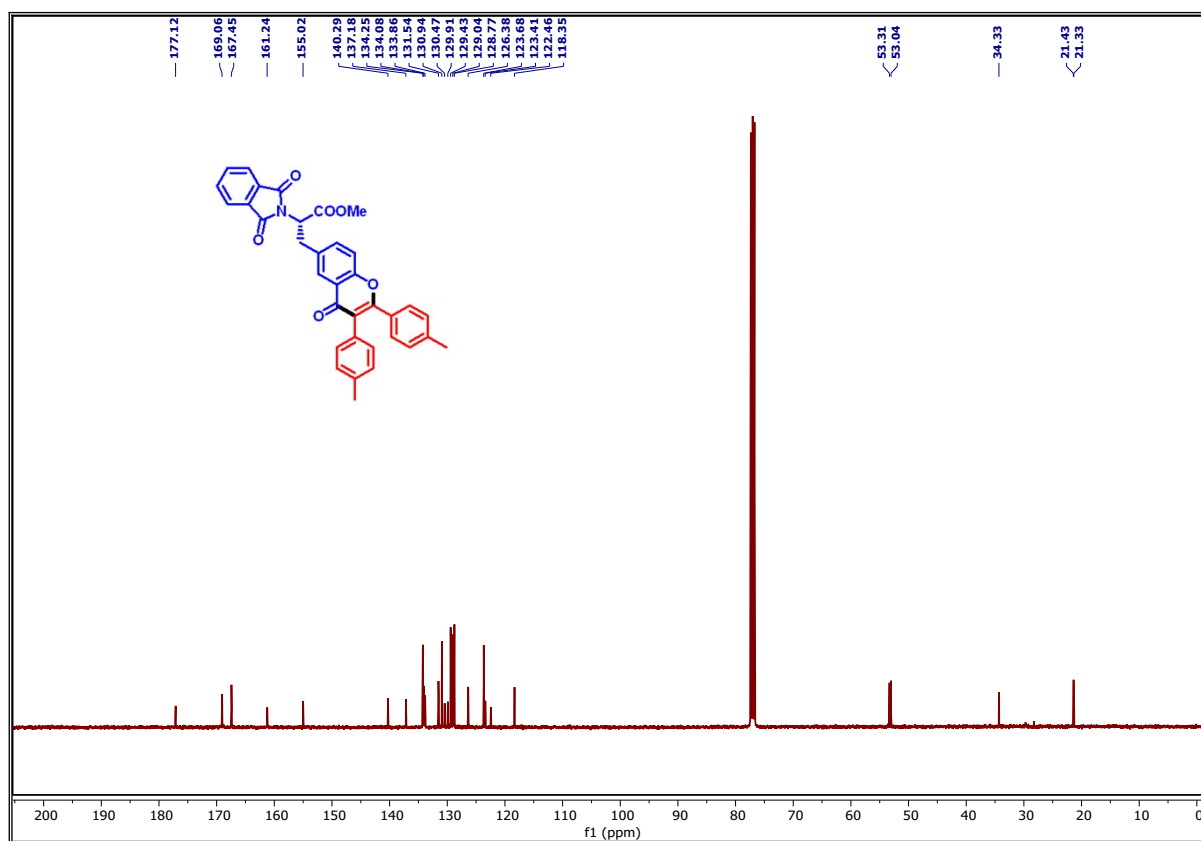
¹³C NMR of 3aa (100 MHz, CDCl₃)



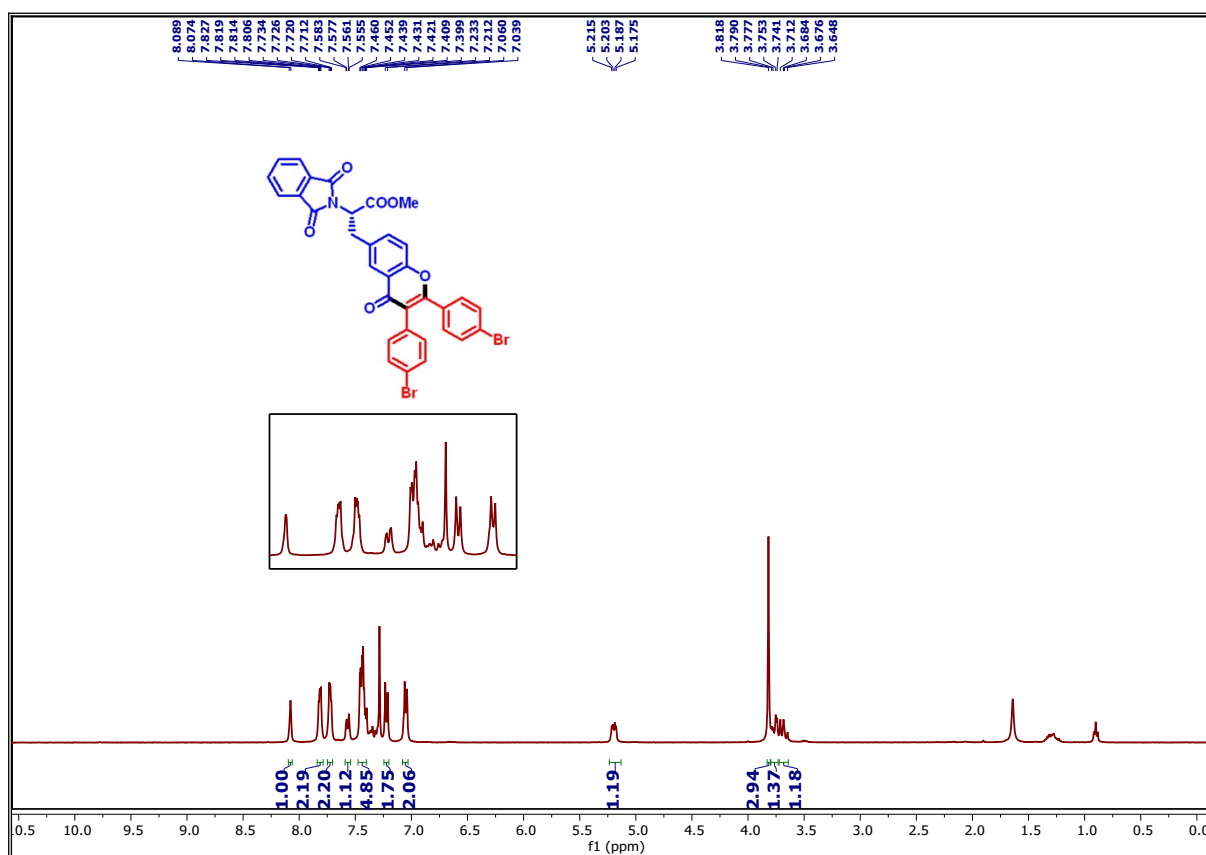
¹H NMR of 3ab (400 MHz, CDCl₃)



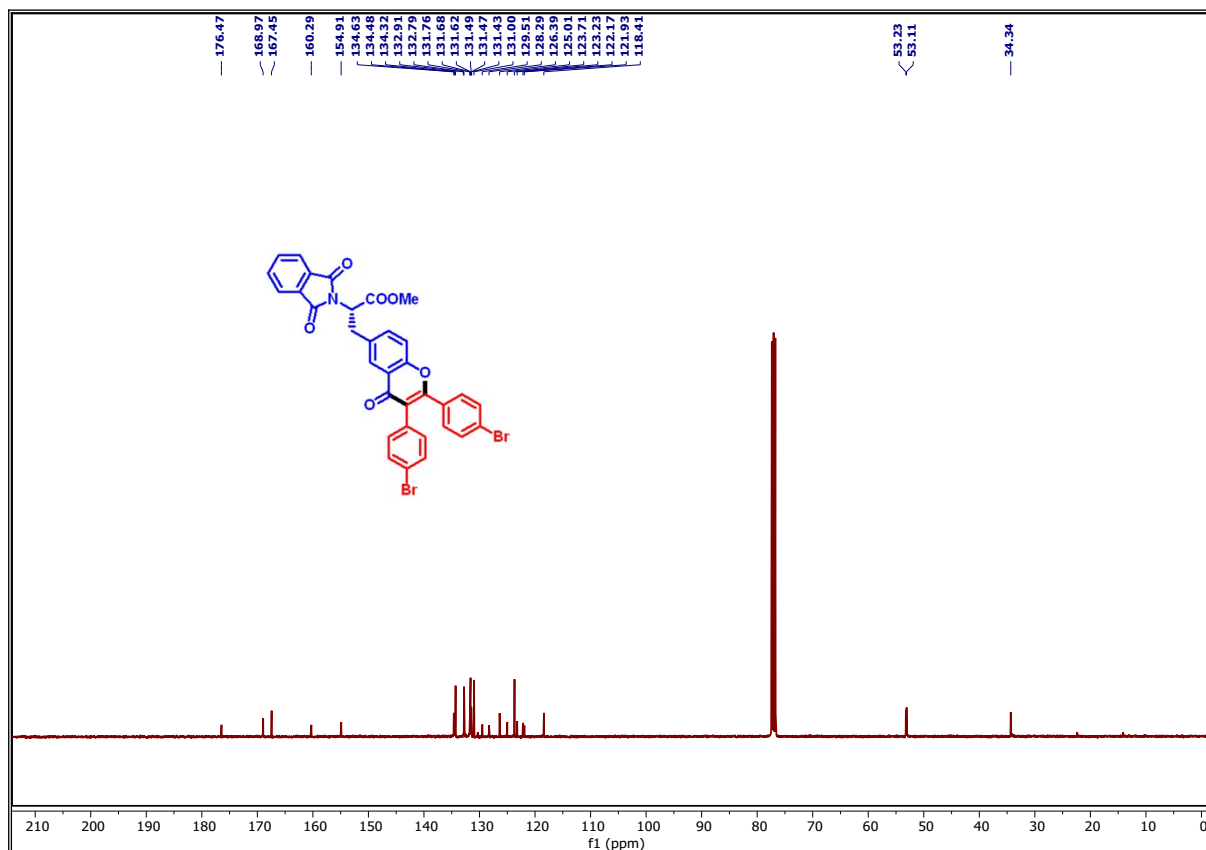
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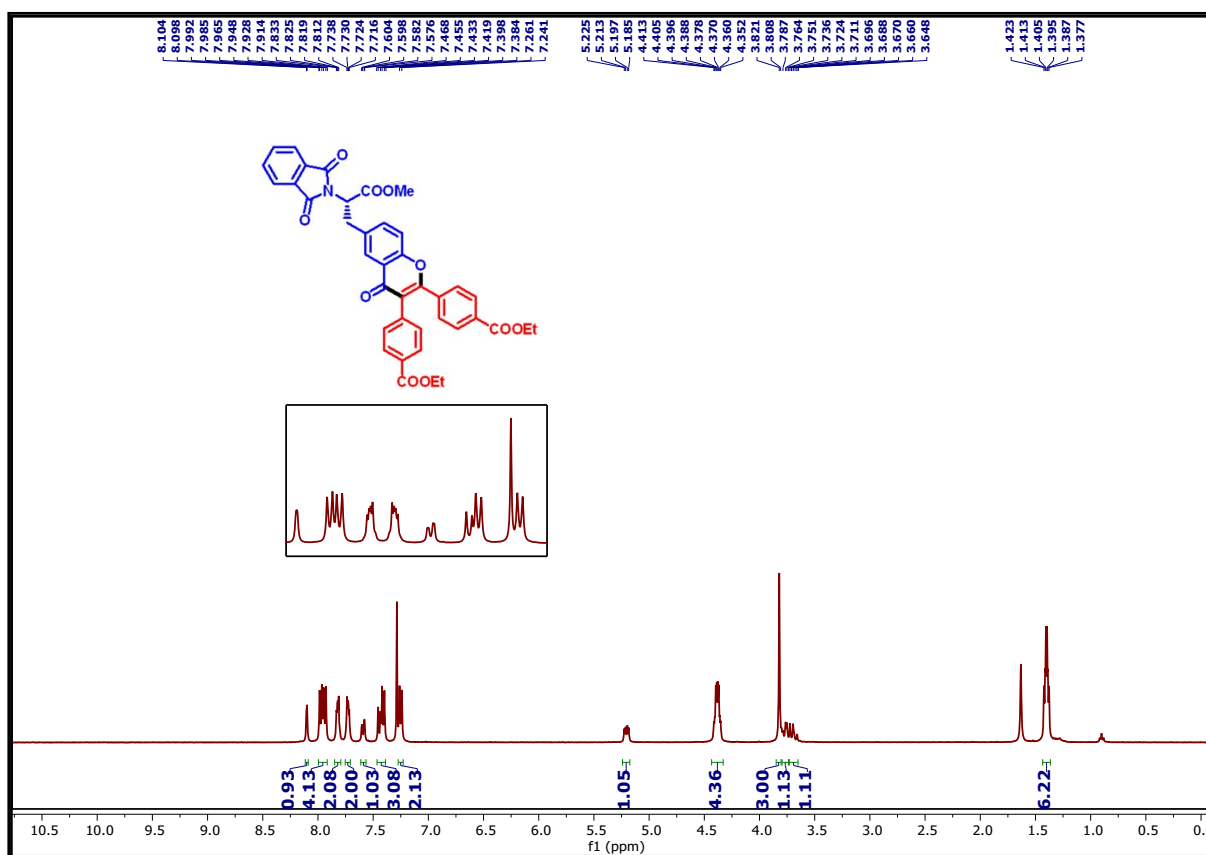
¹H NMR of 3ac (400 MHz, CDCl₃)



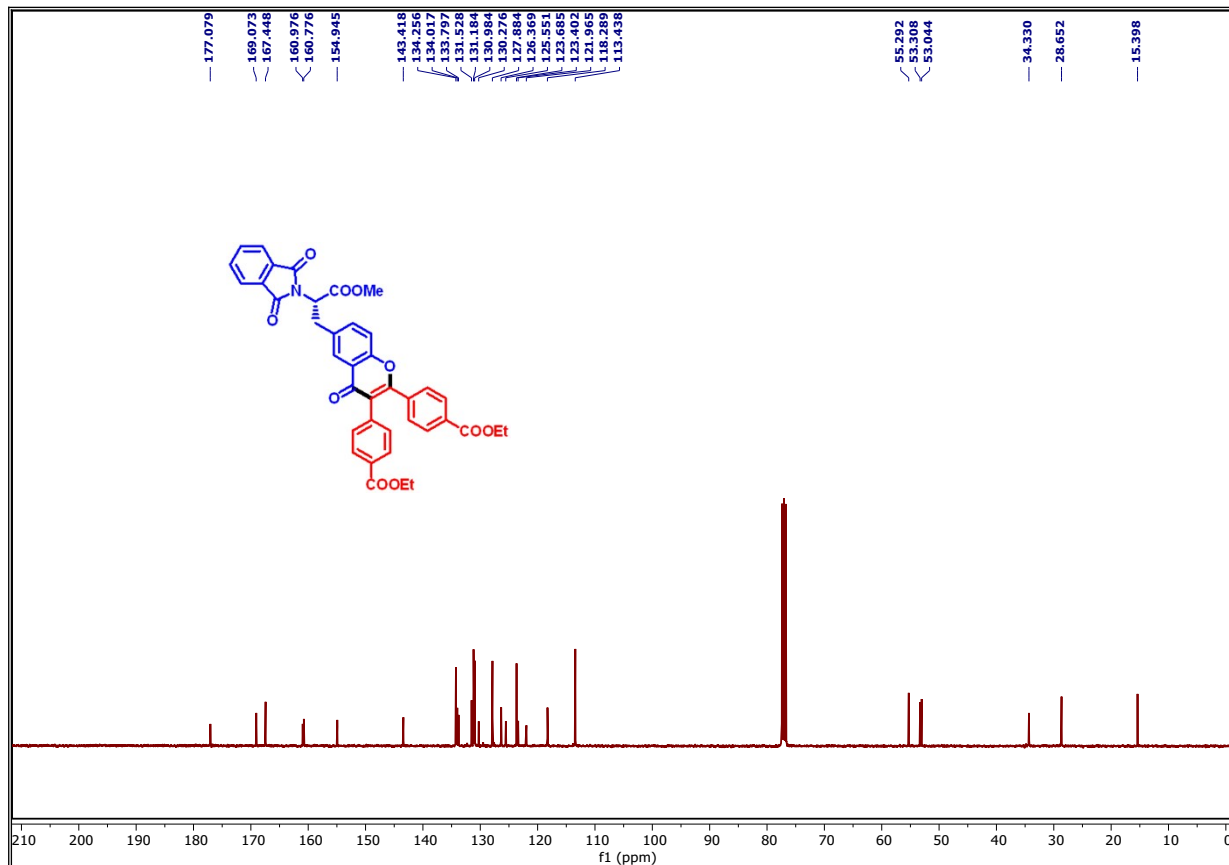
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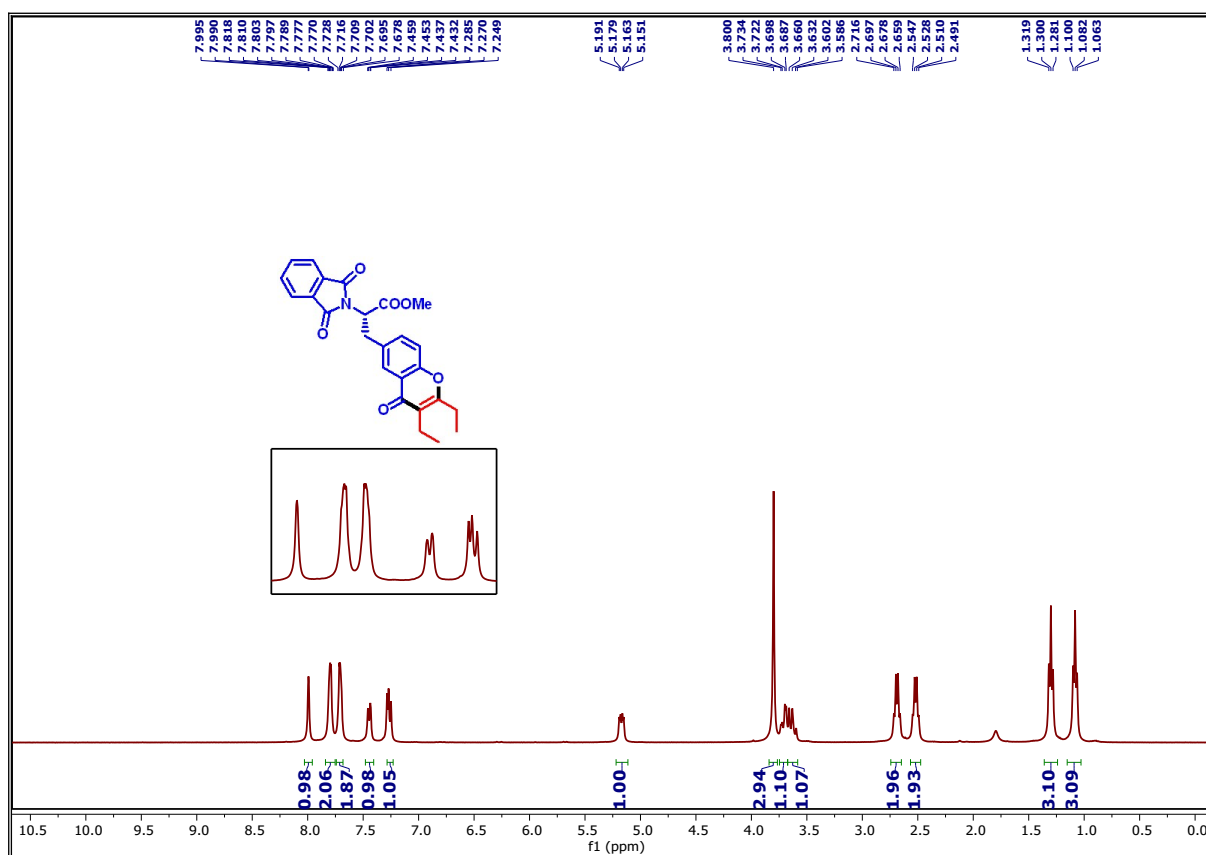
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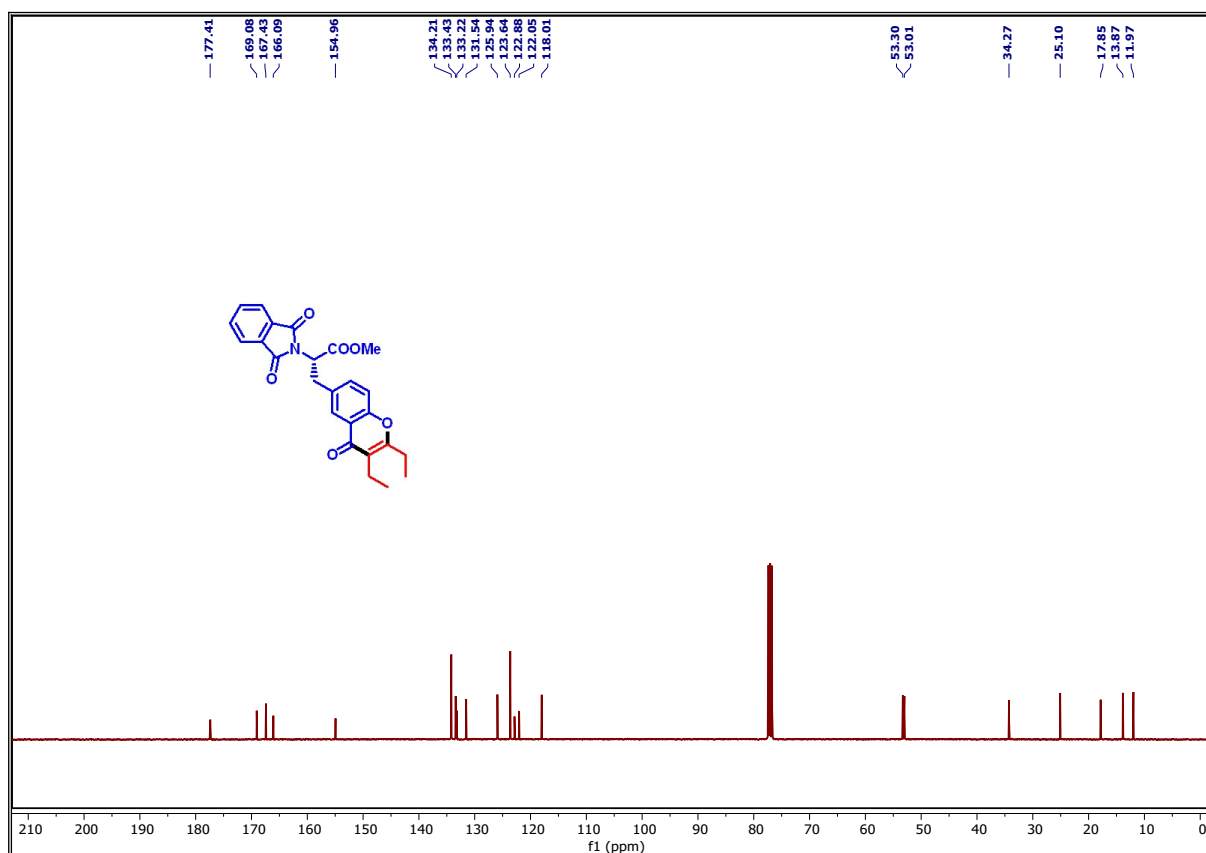
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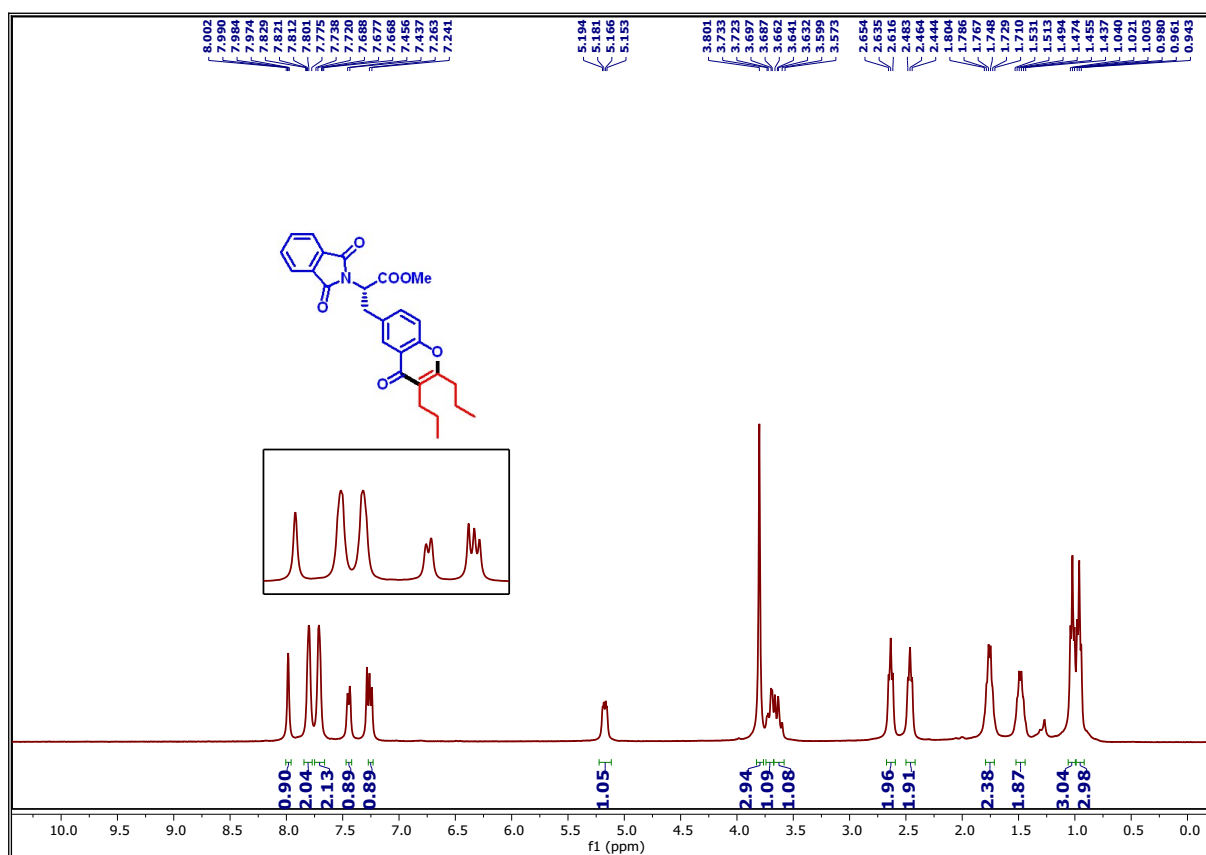
¹H NMR of 3ae (400 MHz, CDCl₃)



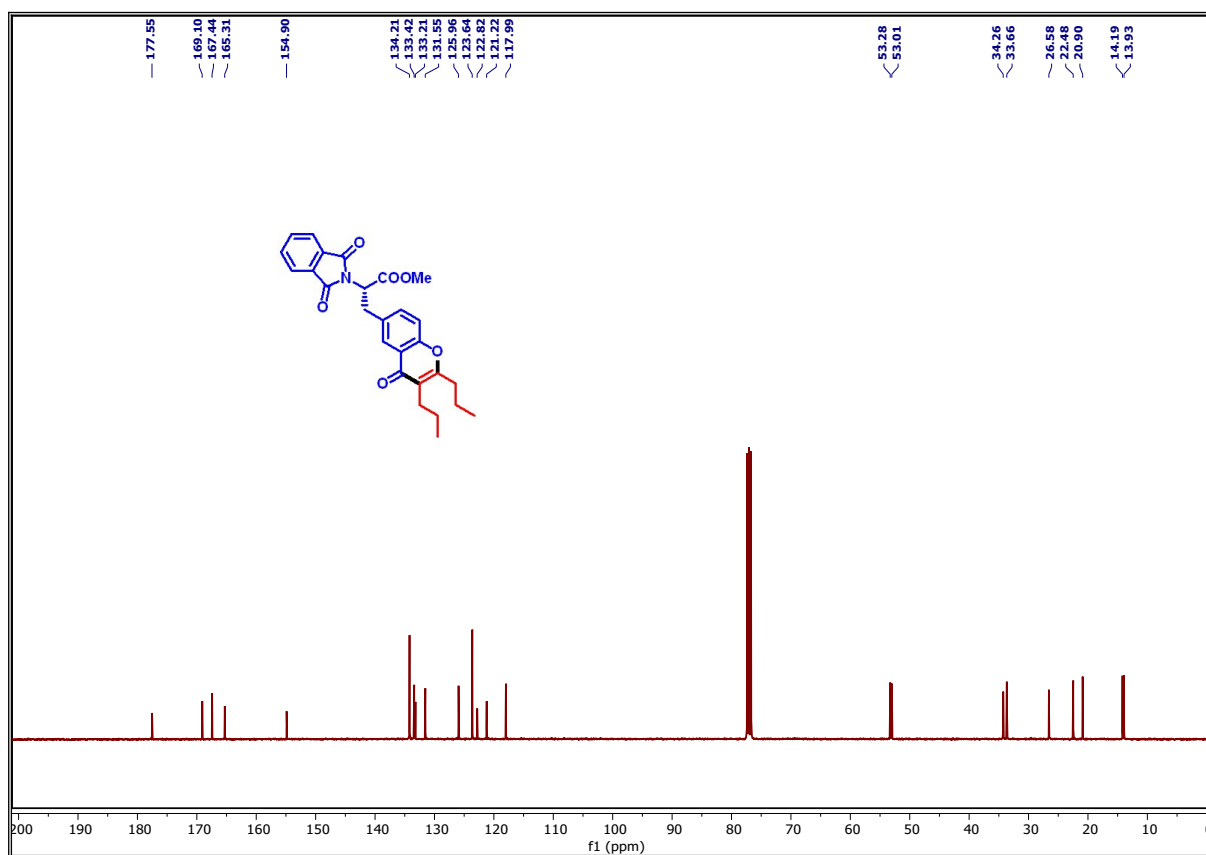
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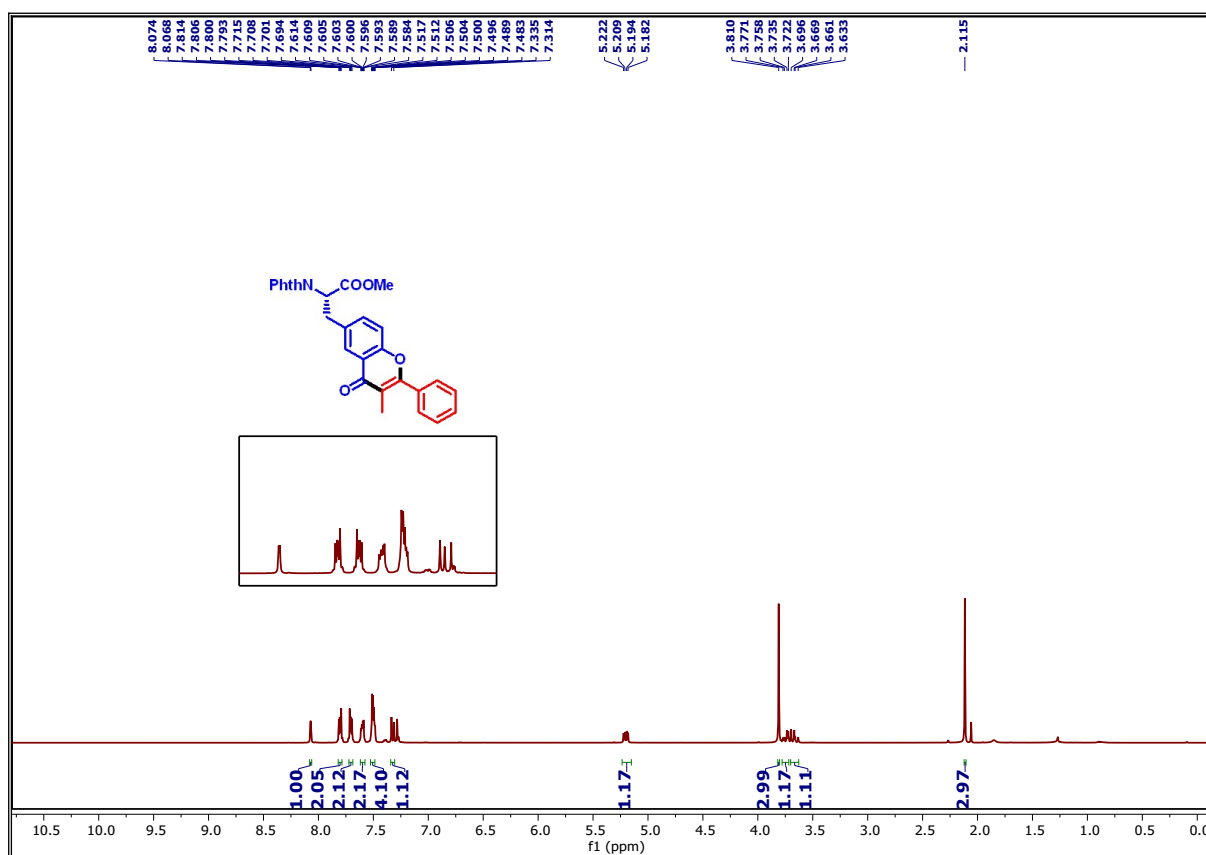
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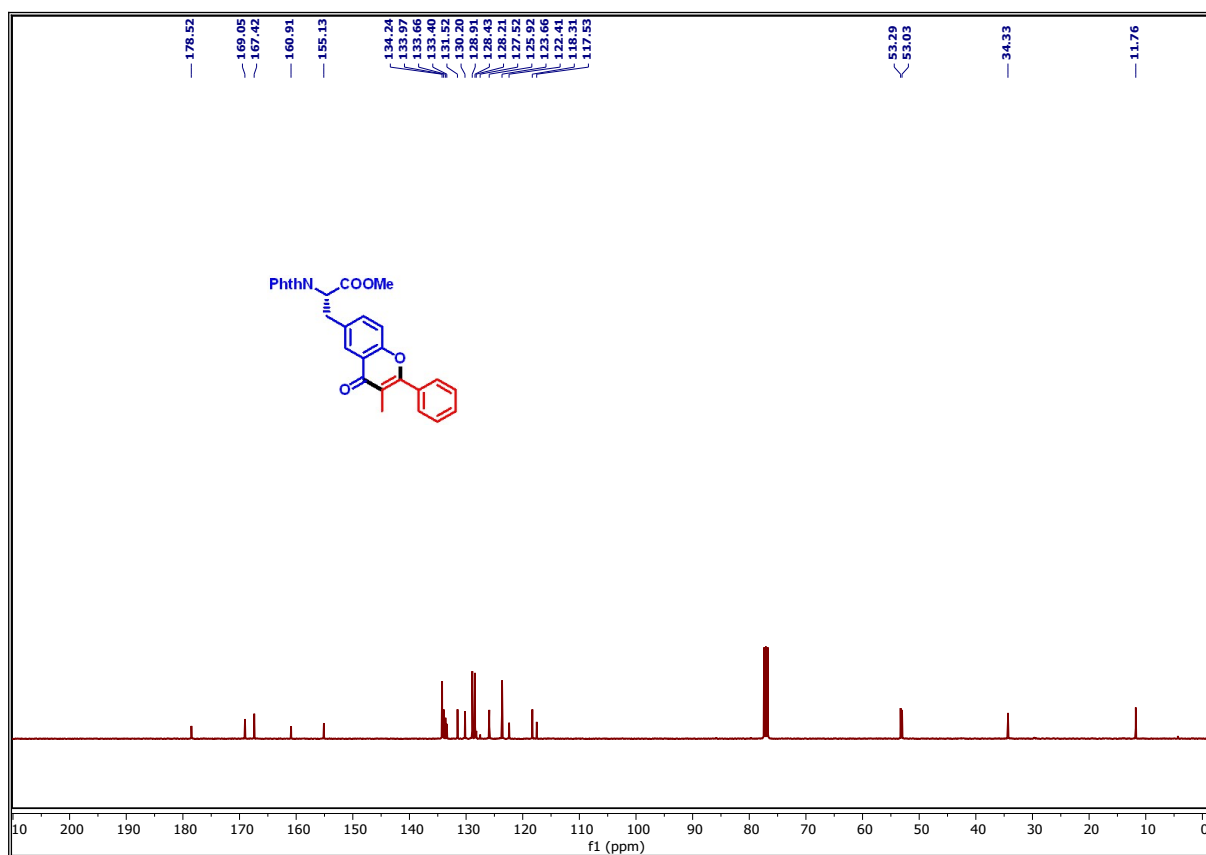
¹³C NMR of 3af (100 MHz, CDCl₃)



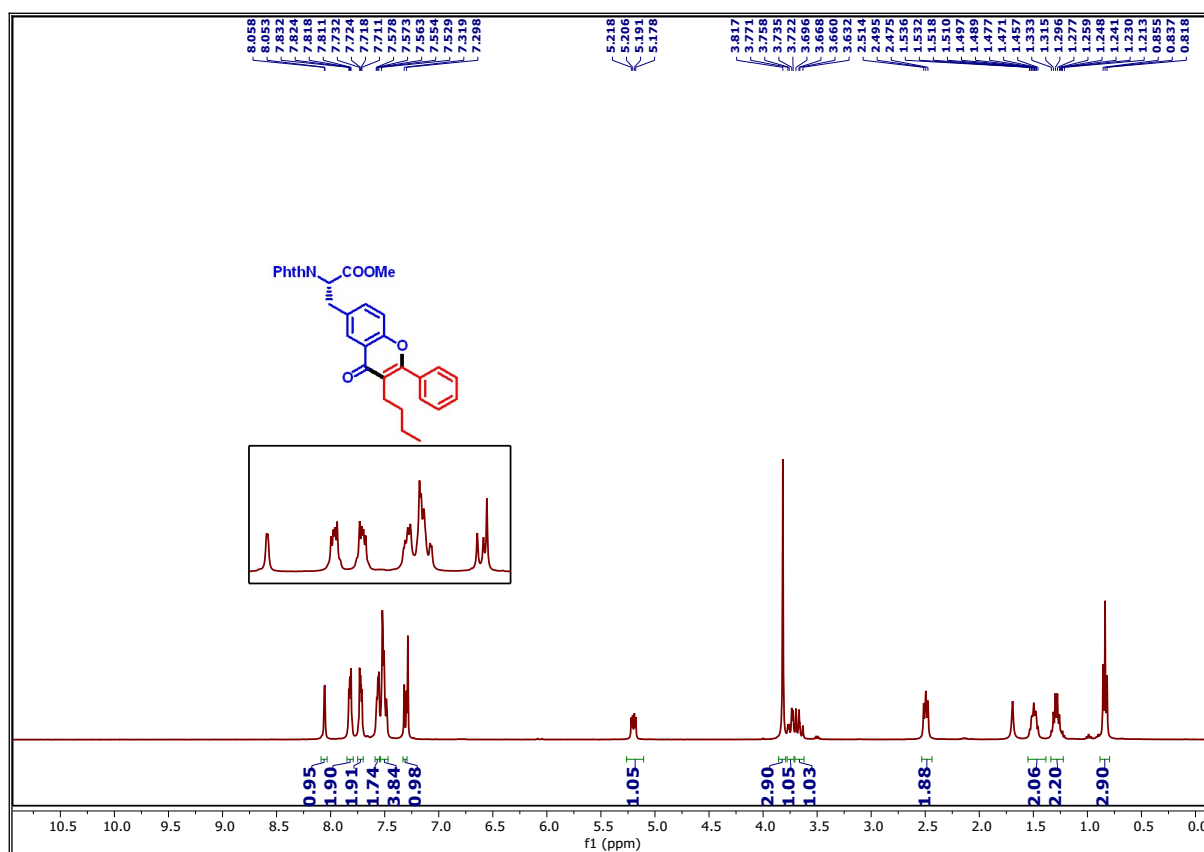
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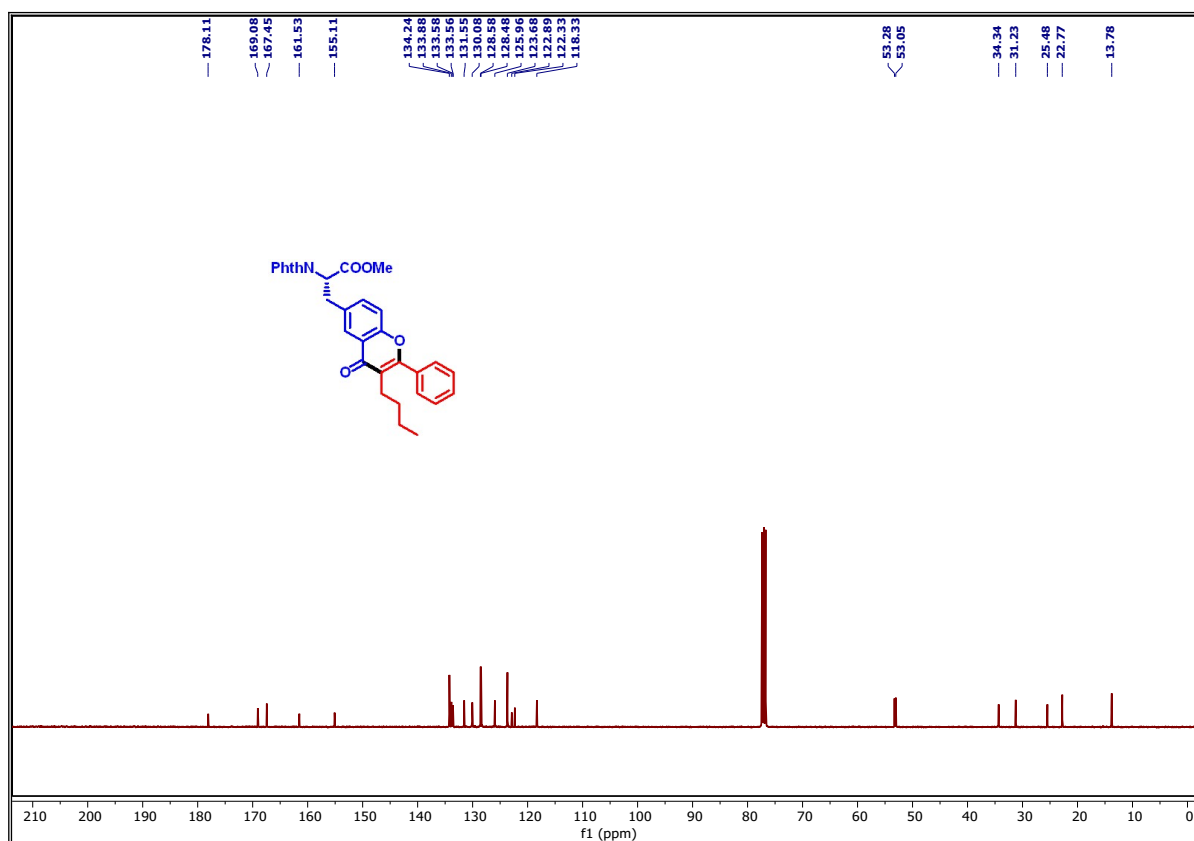
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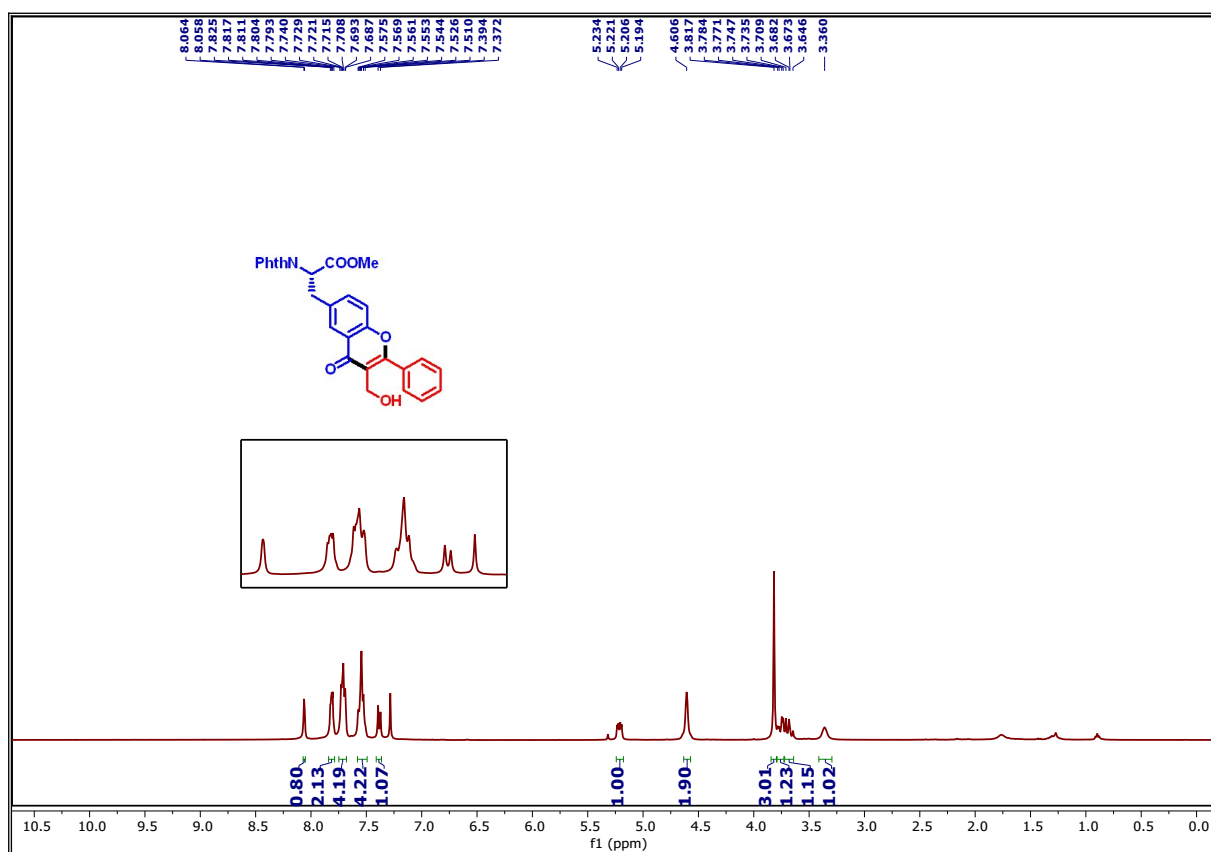
¹H NMR of 3ah (400 MHz, CDCl₃)



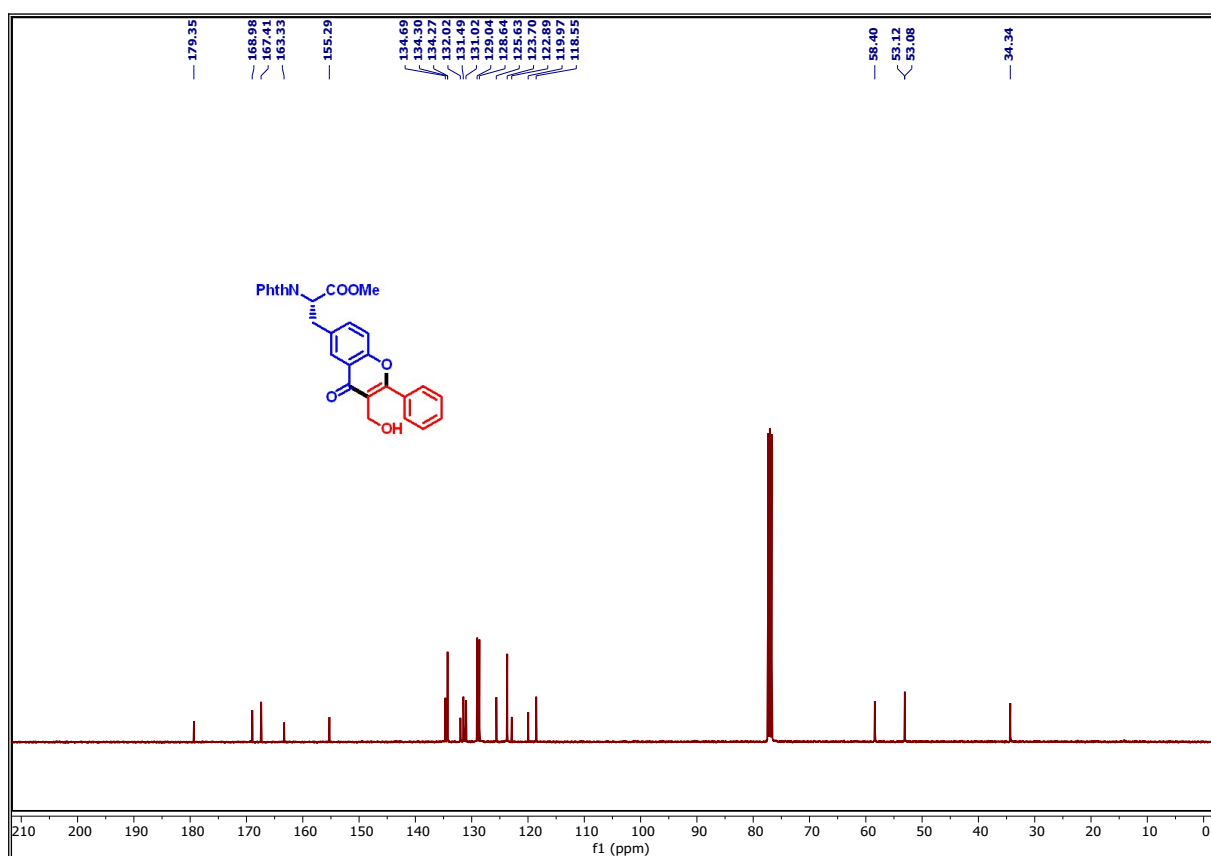
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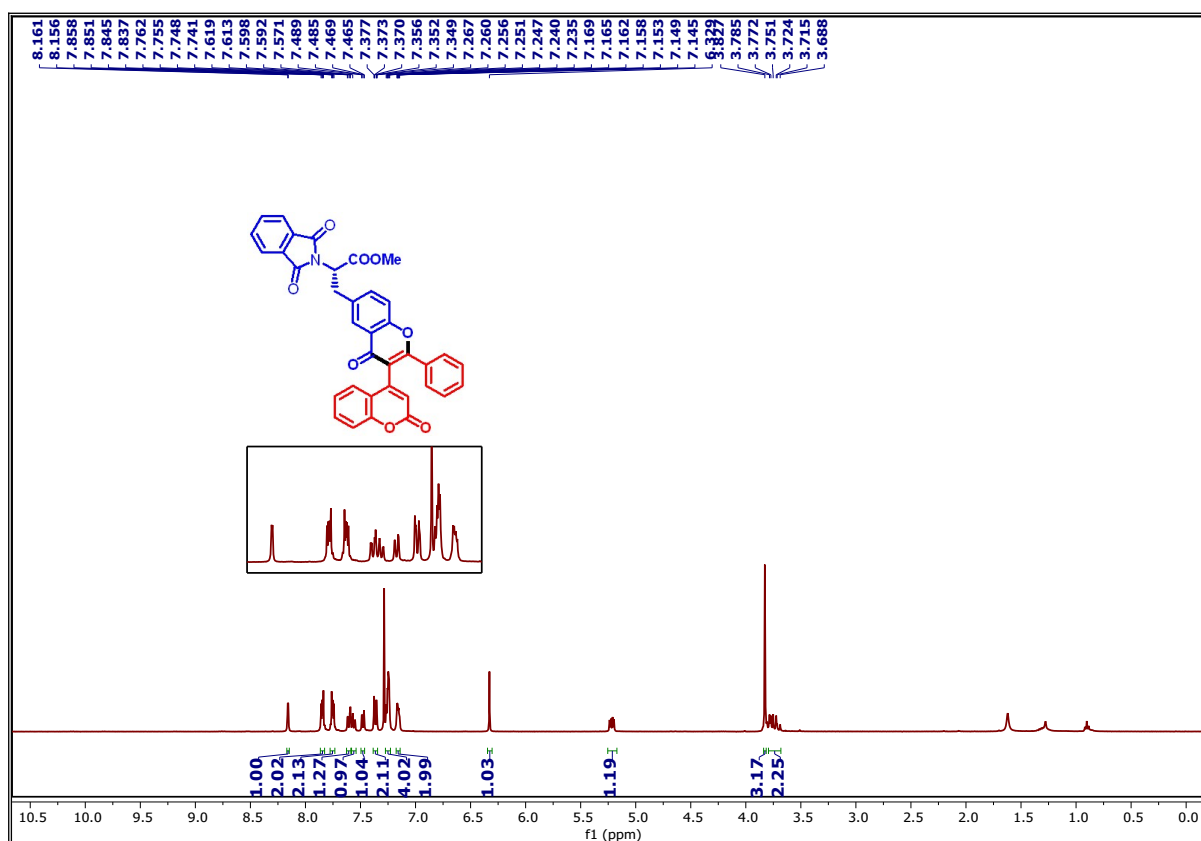
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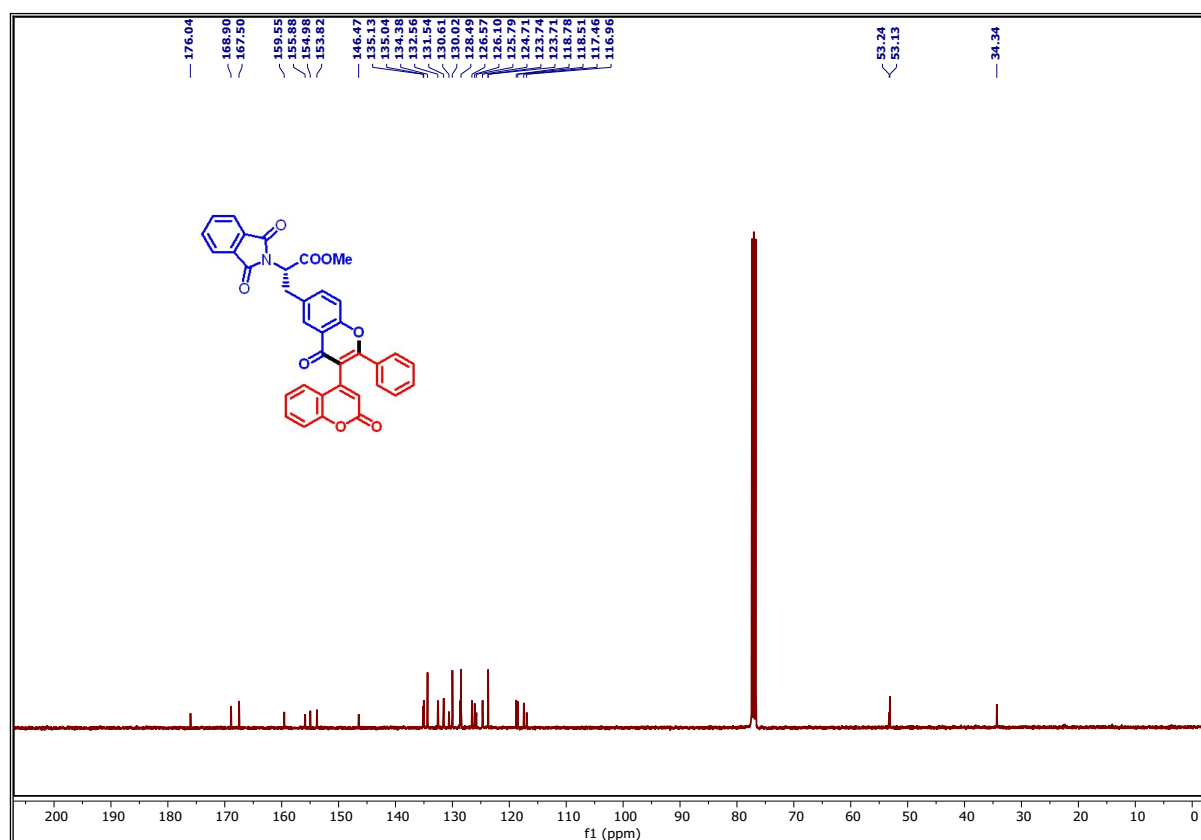
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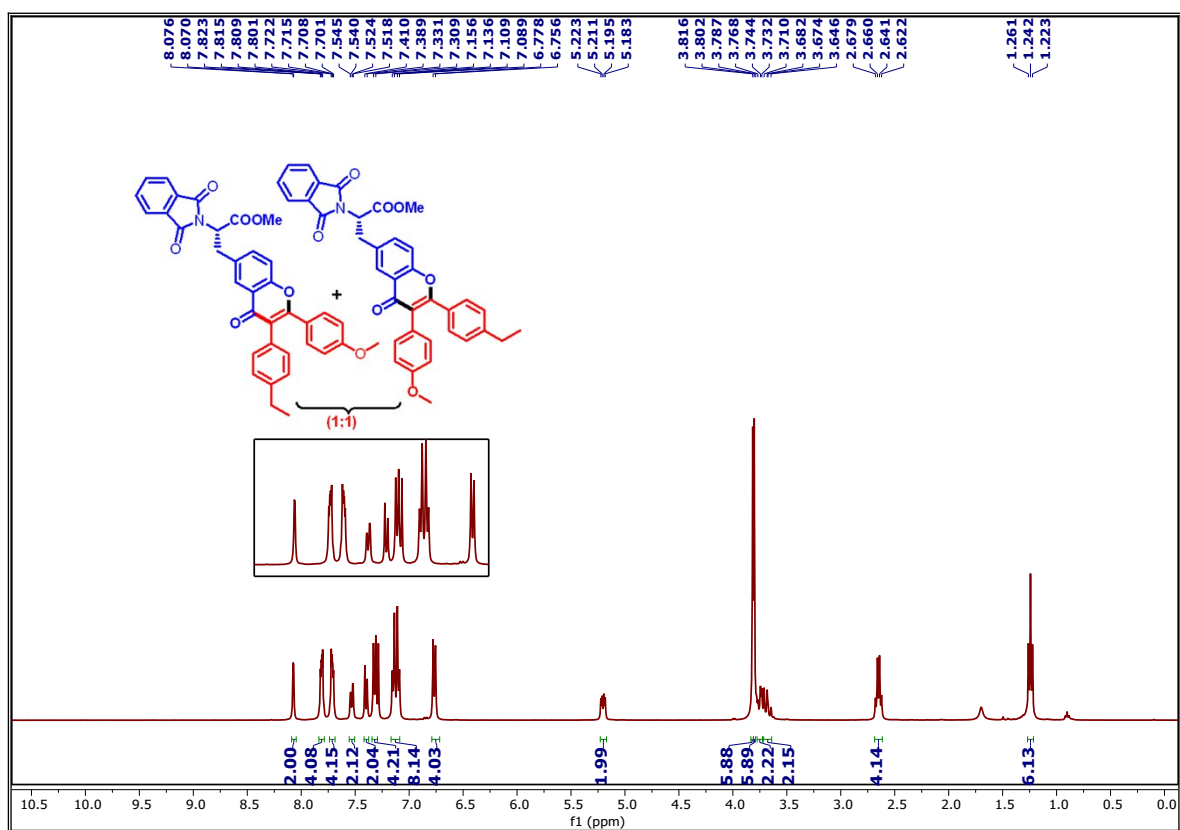
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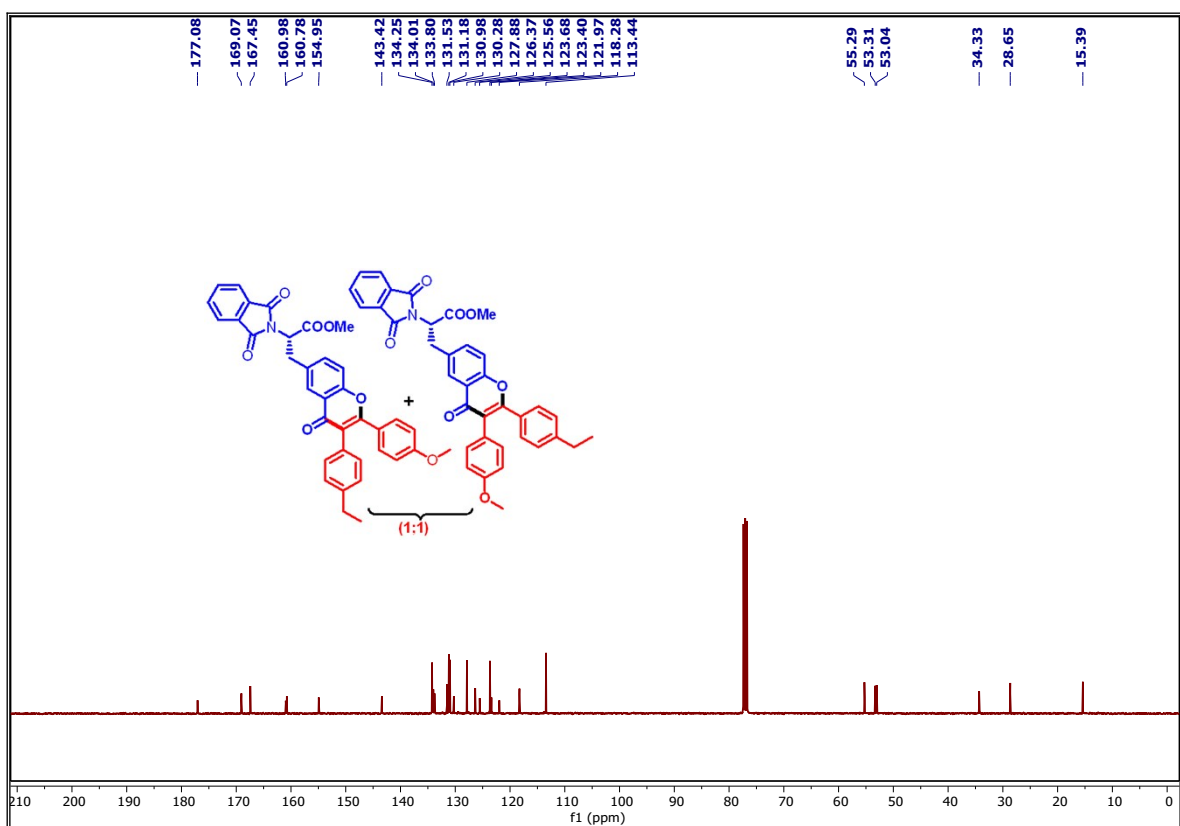
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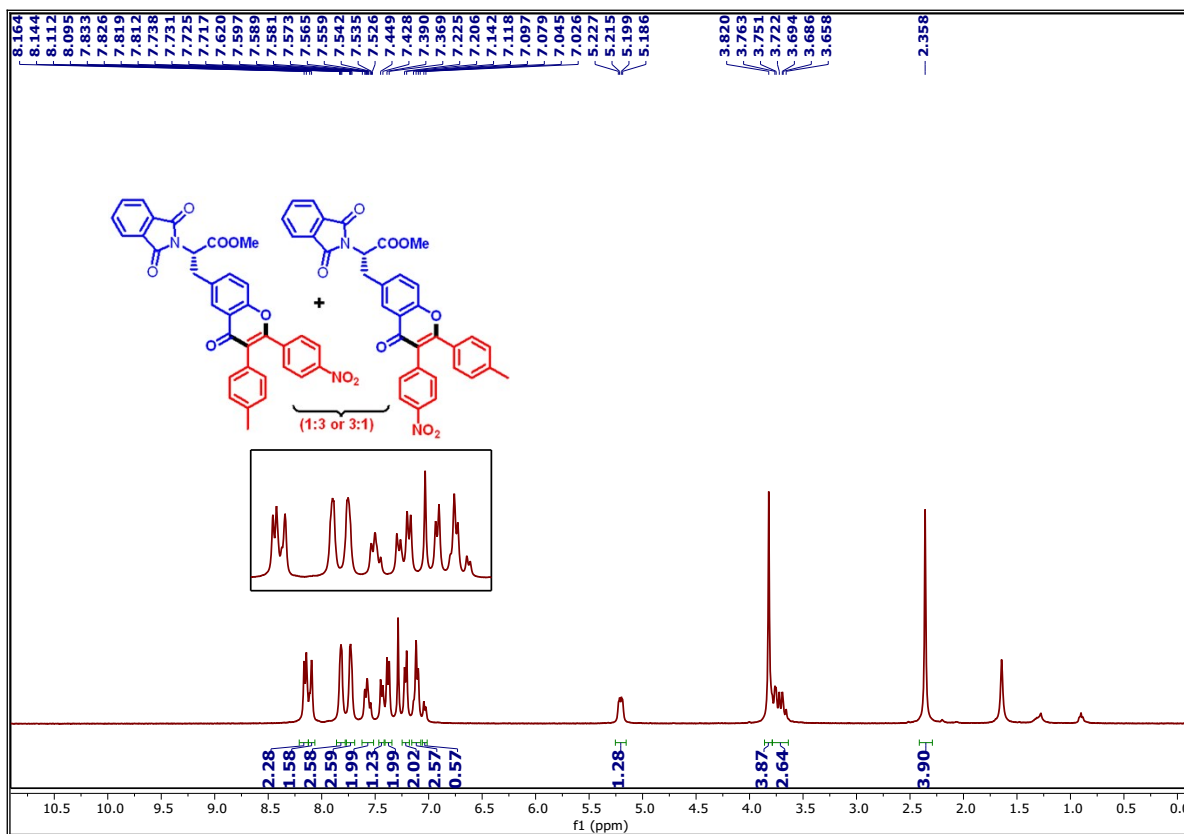
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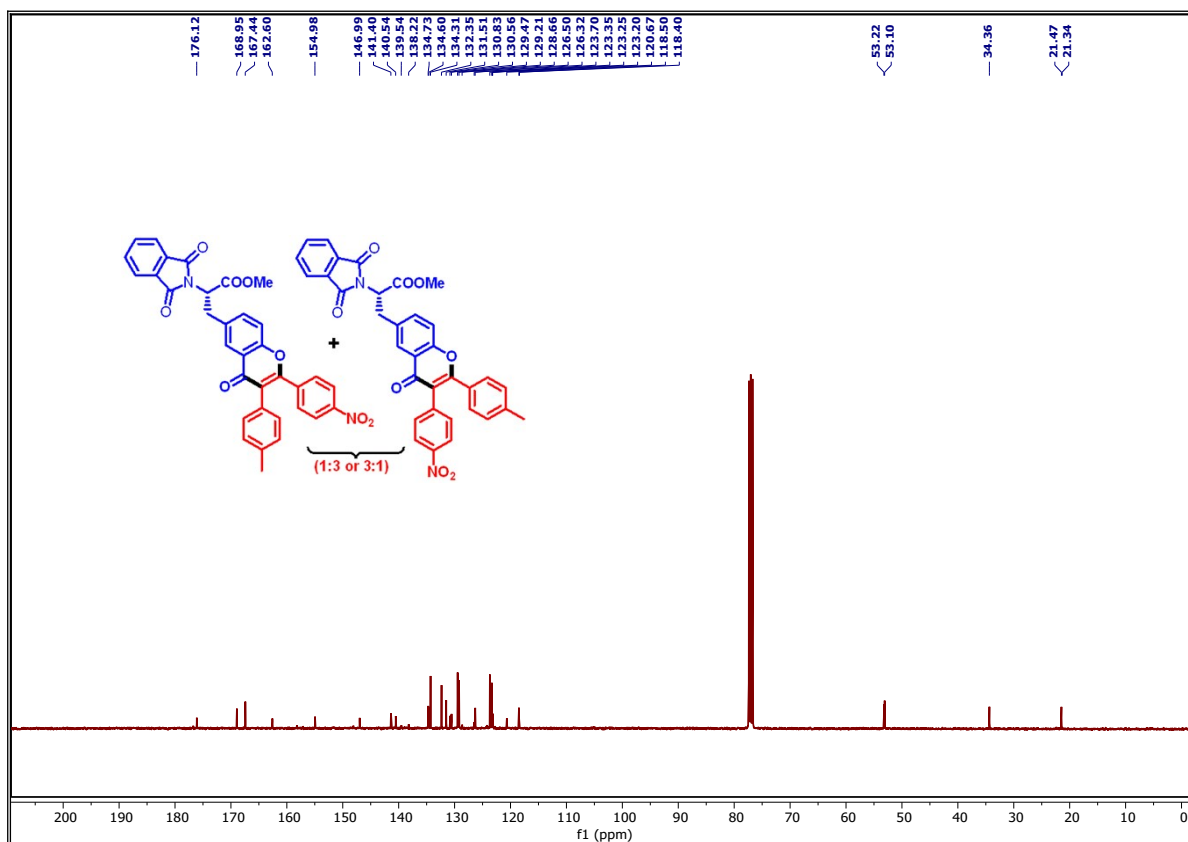
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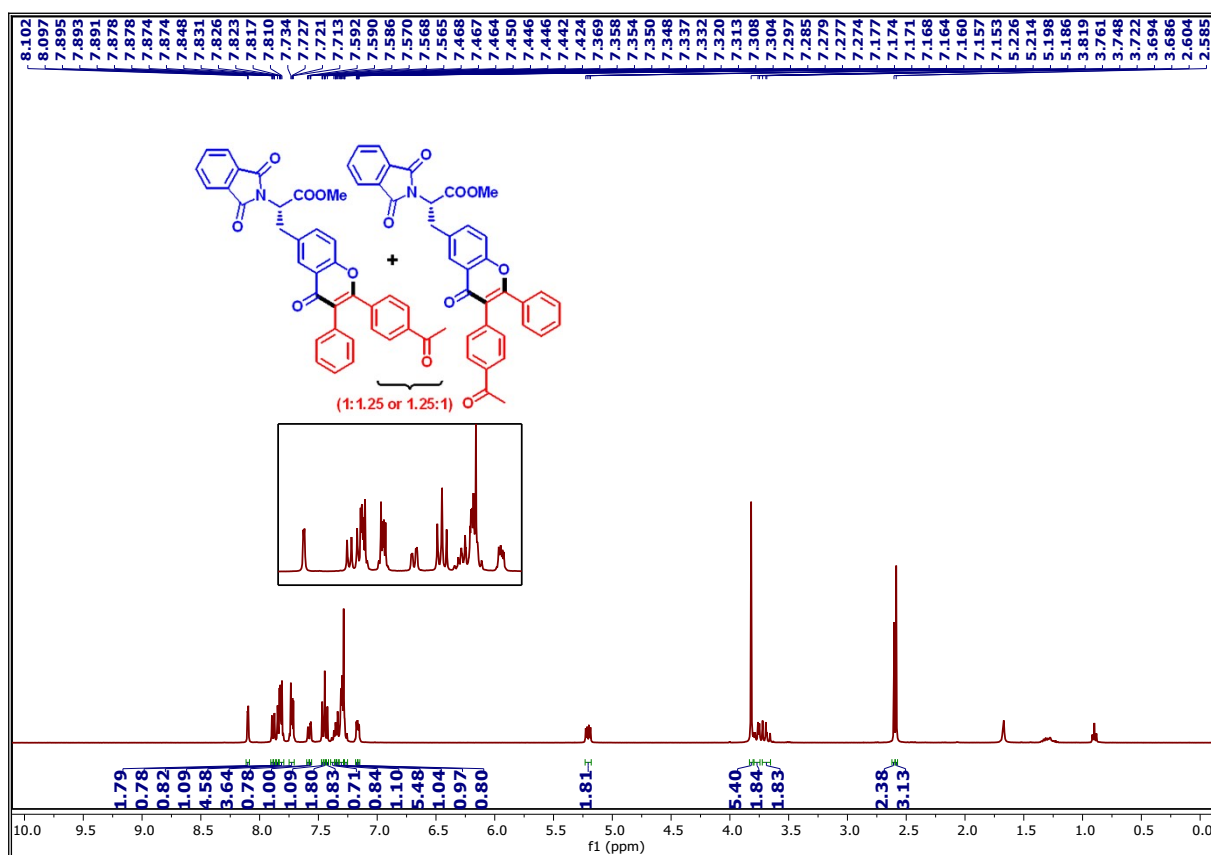
¹H NMR of 3al (400 MHz, CDCl₃)



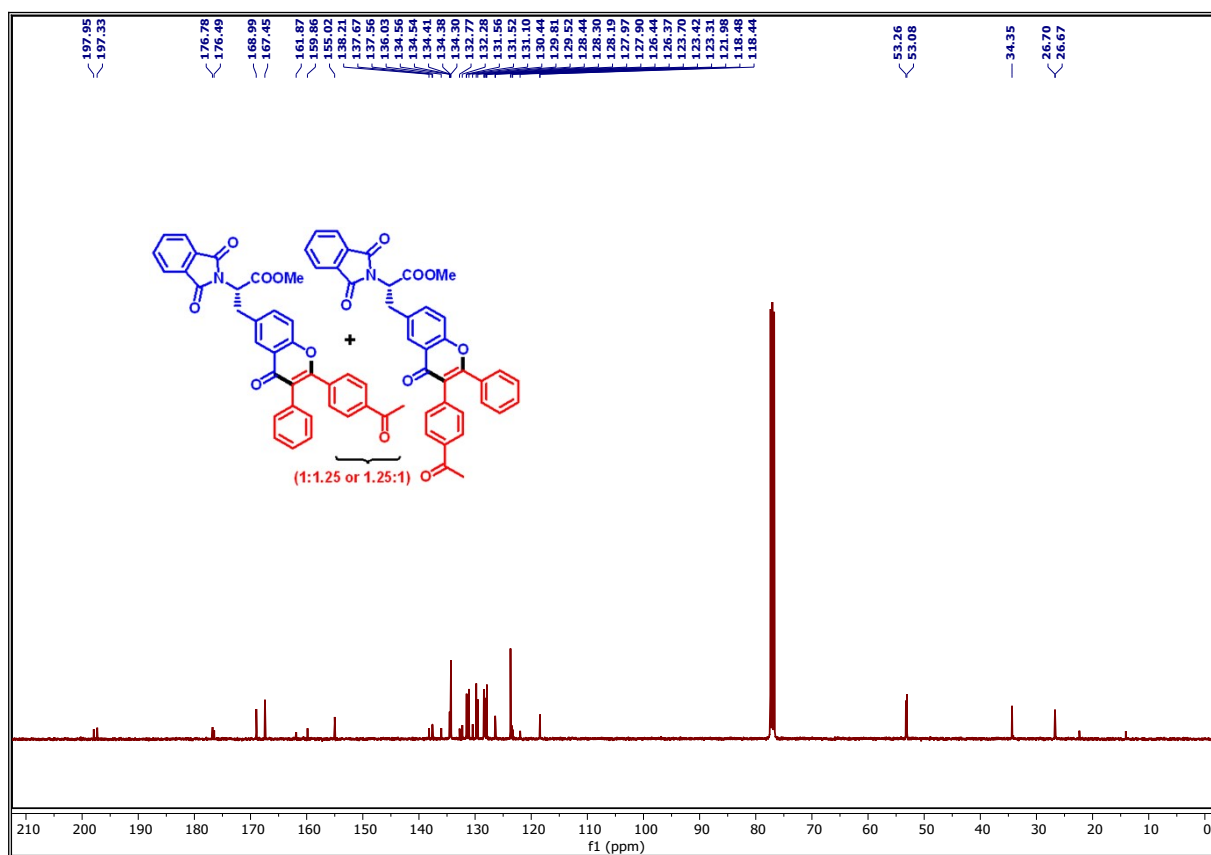
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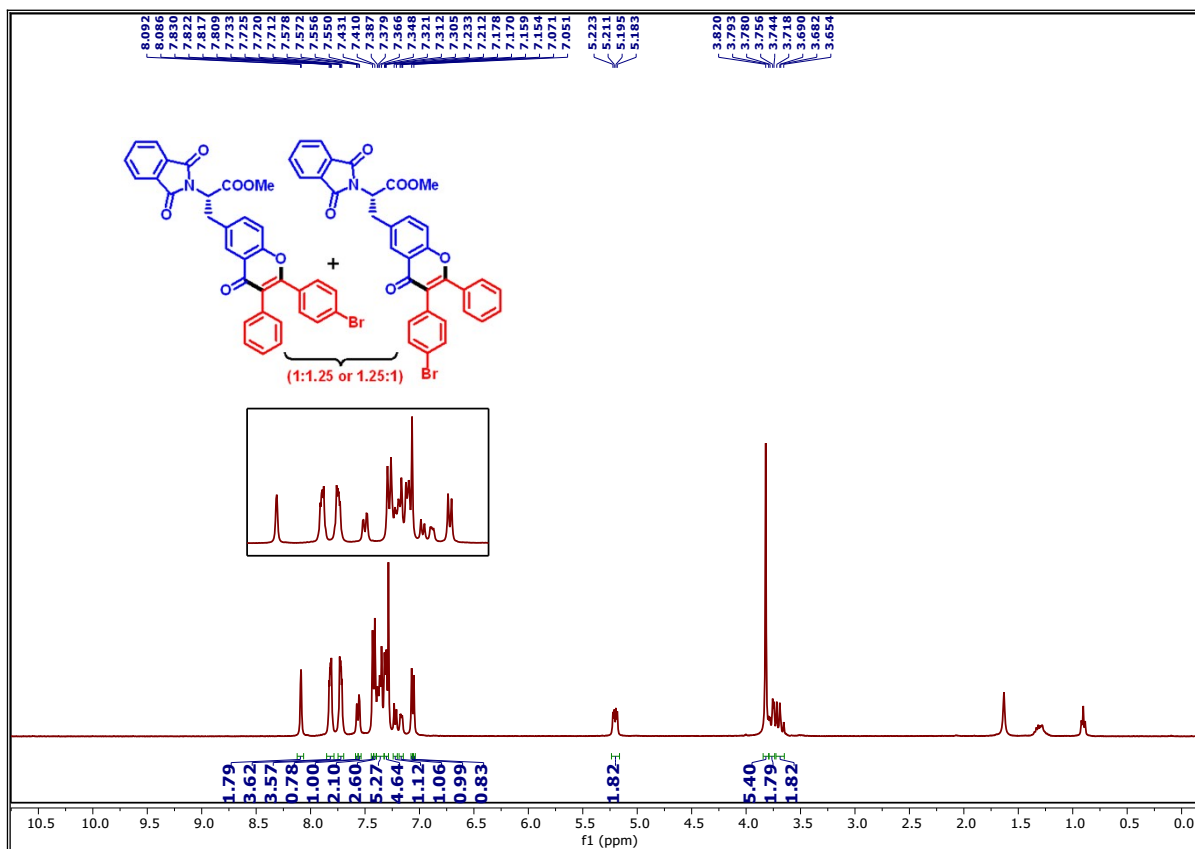
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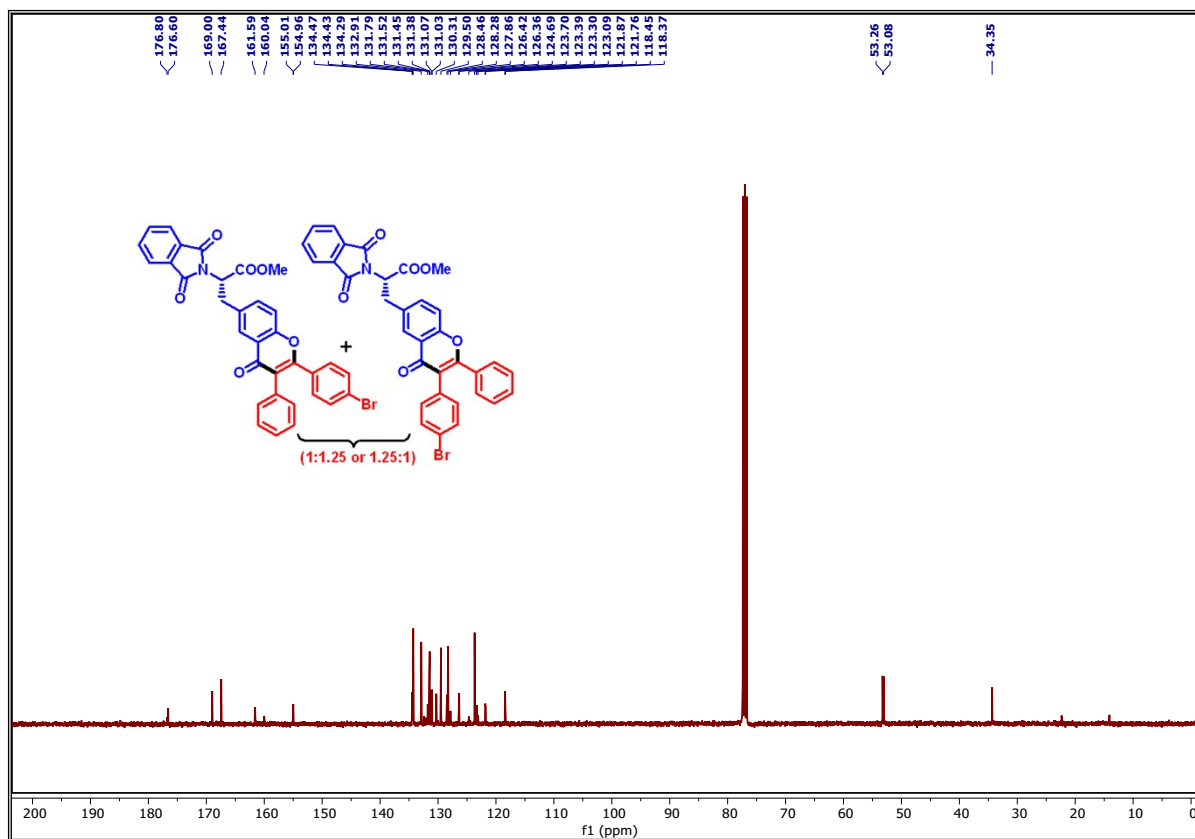
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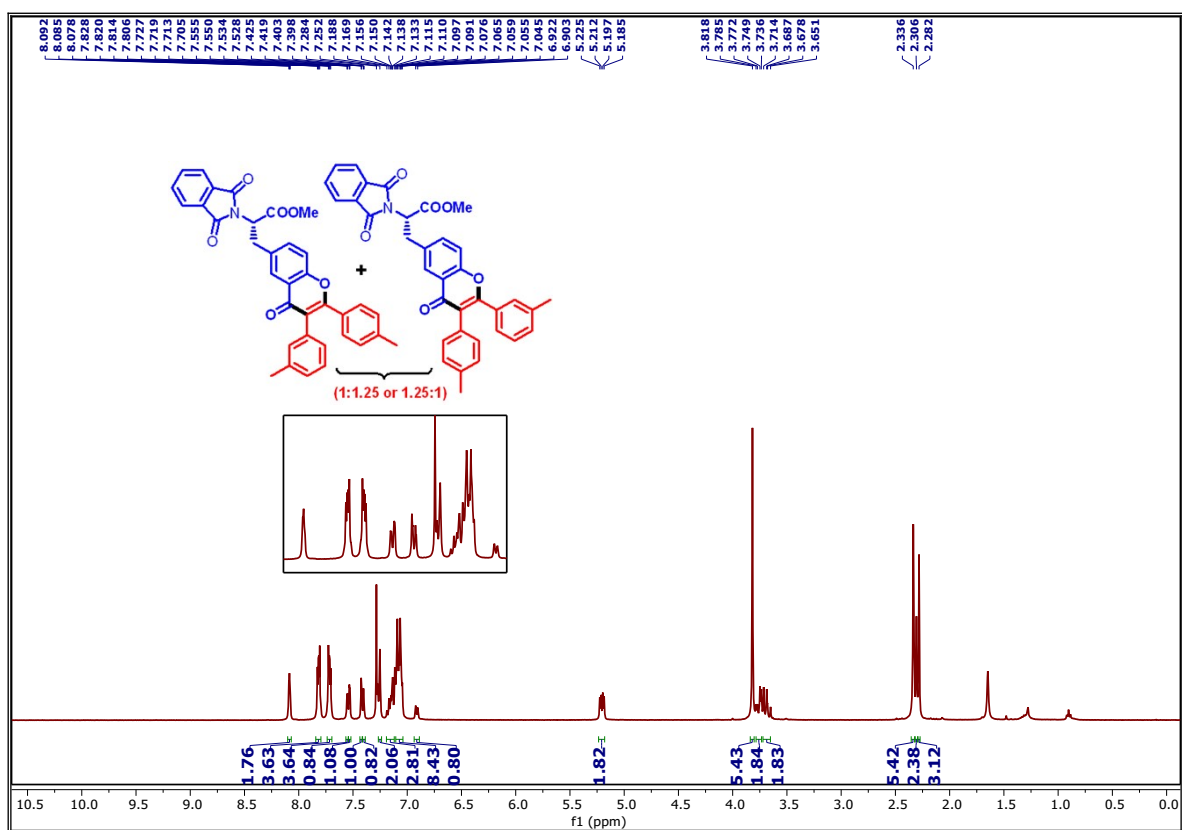
¹H NMR of 3an (400 MHz, CDCl₃)



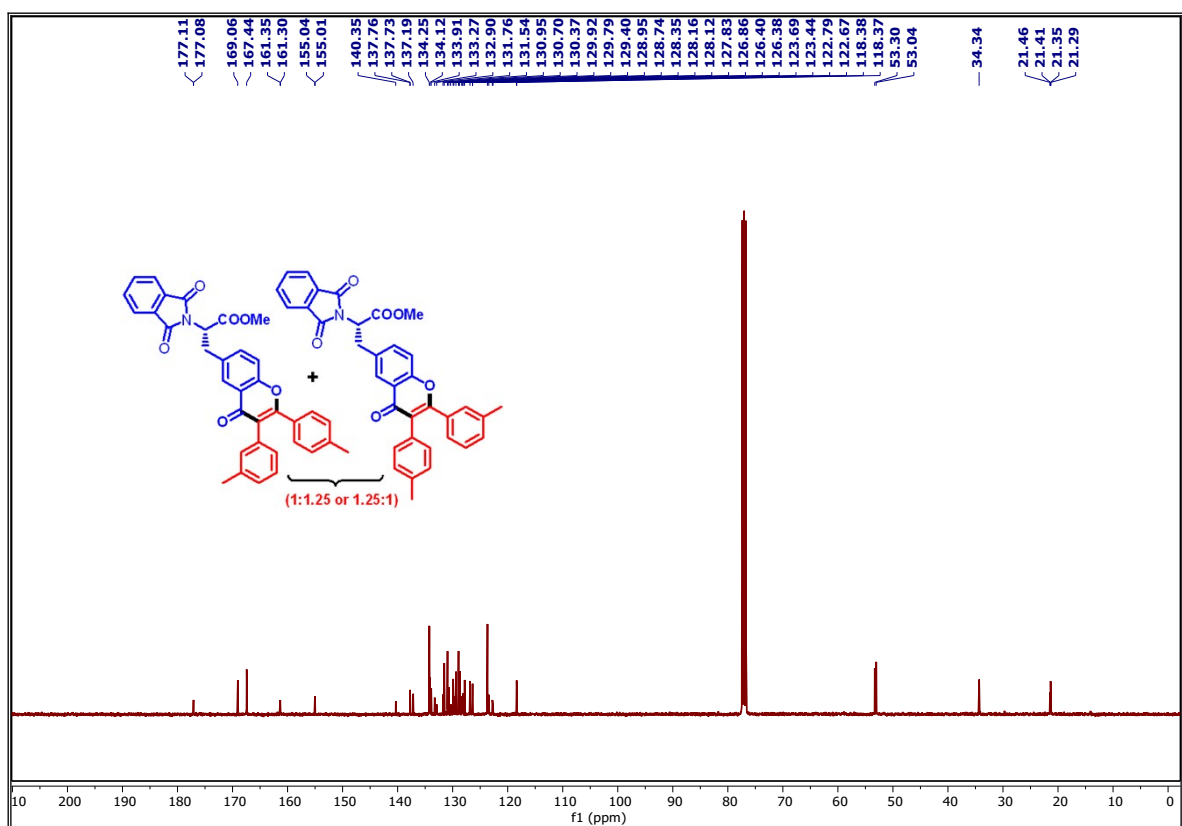
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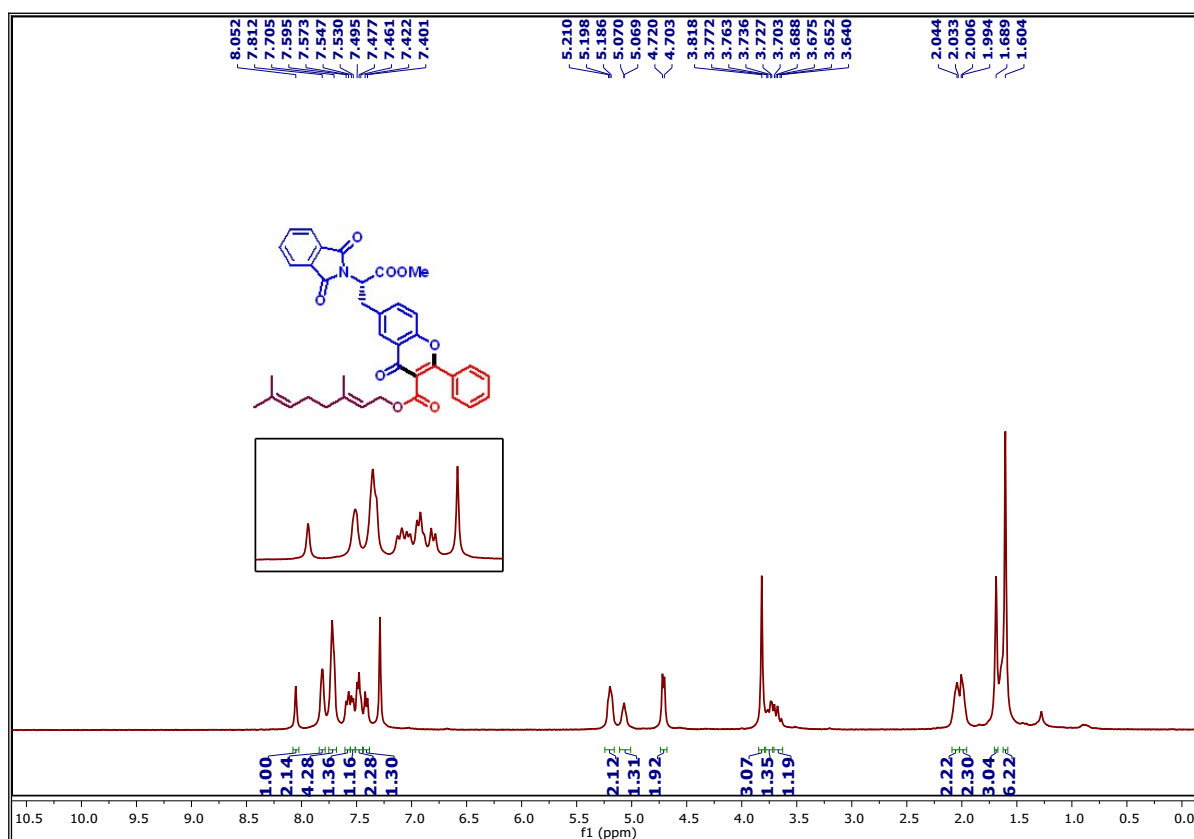
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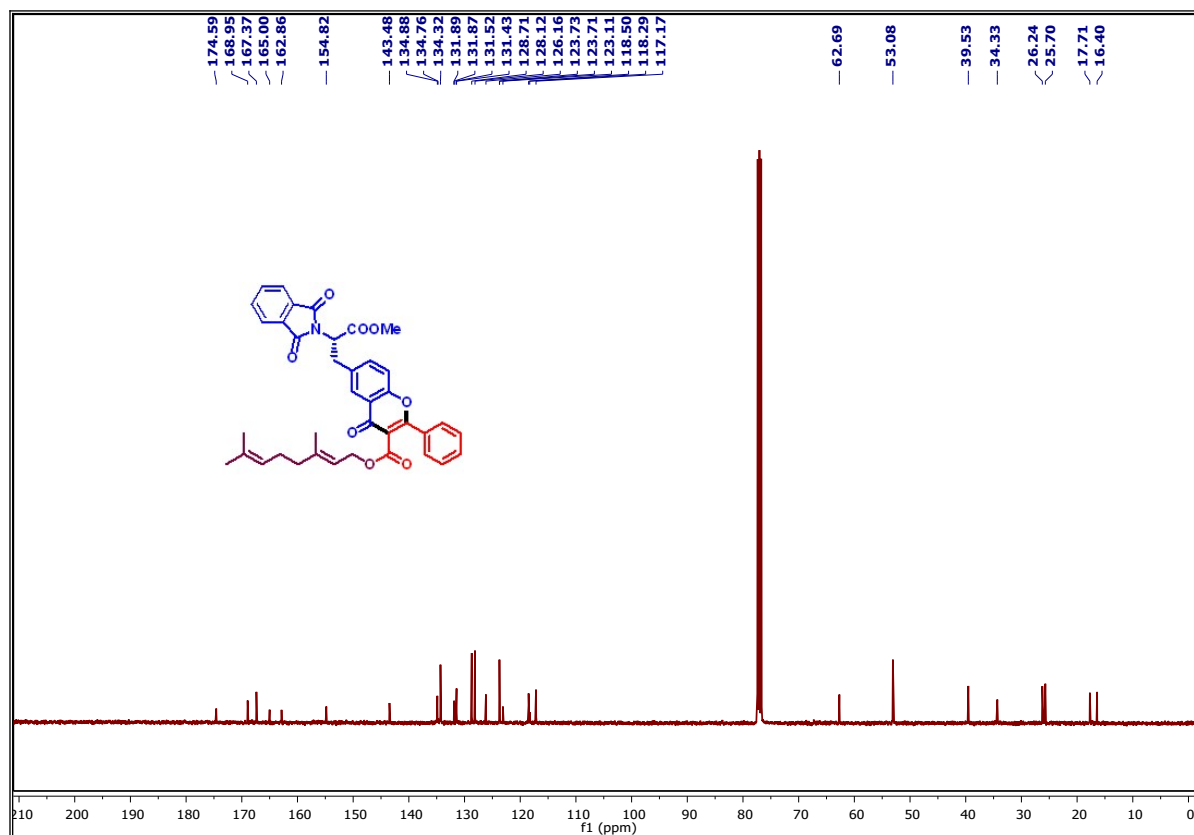
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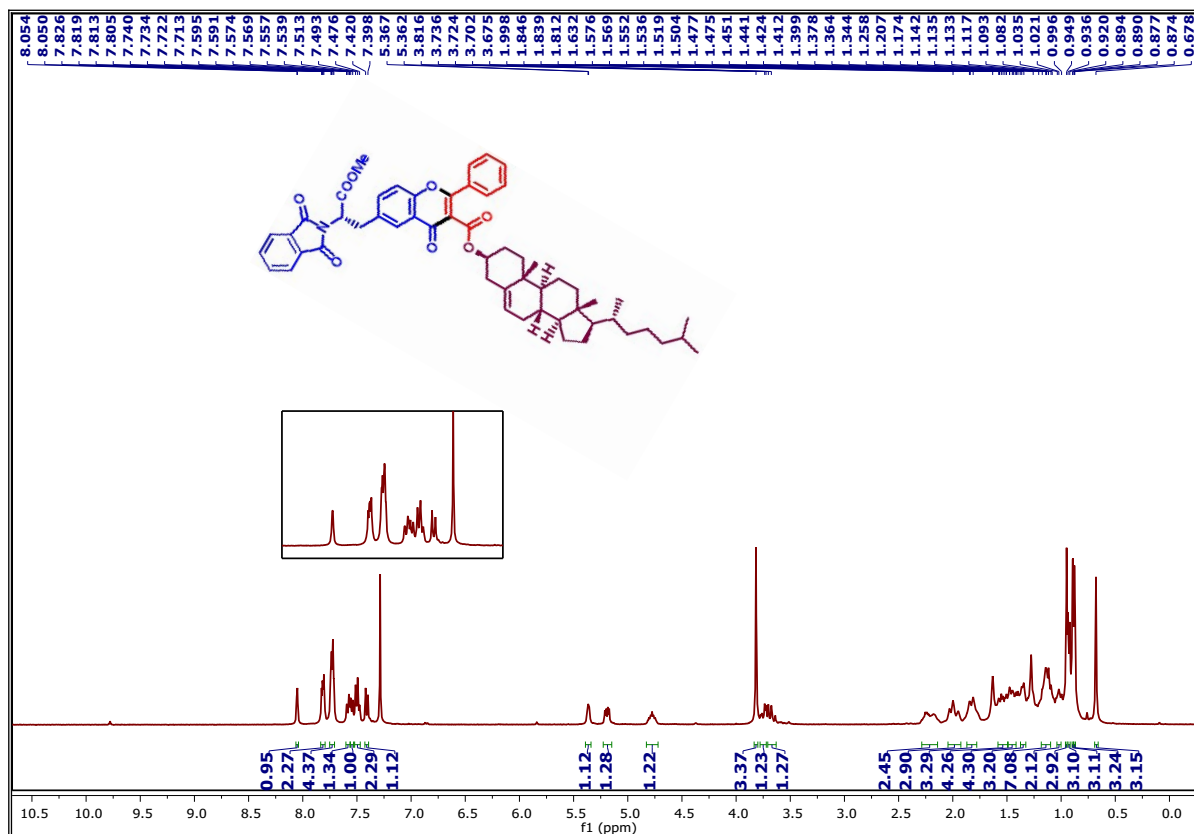
¹H NMR of 3ap (400 MHz, CDCl₃)



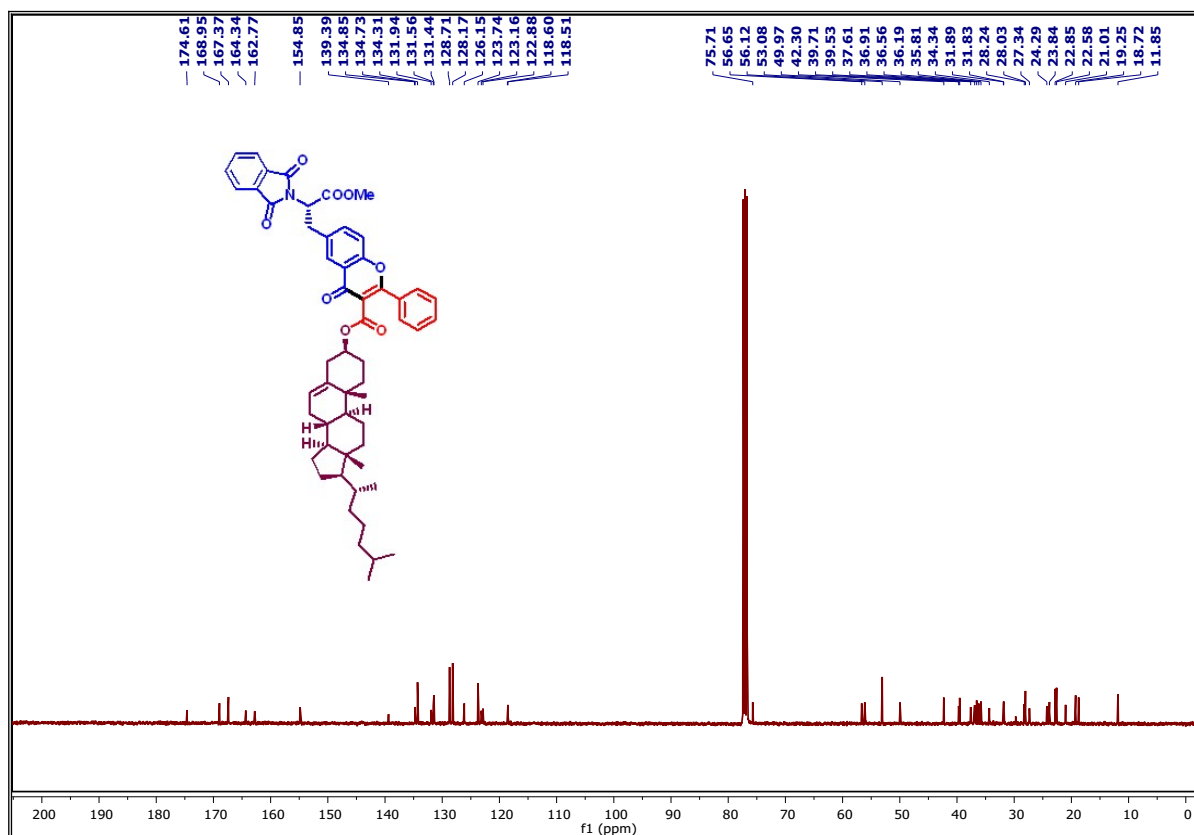
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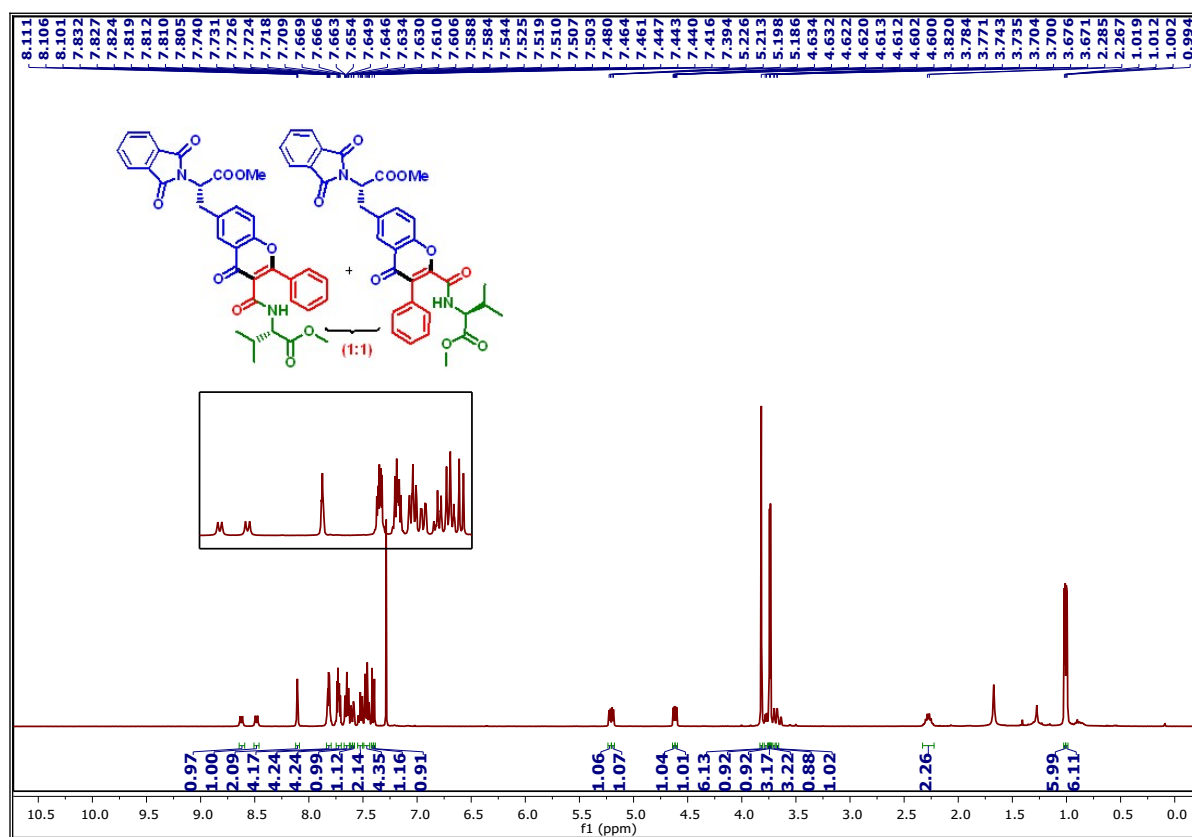
¹H NMR of 3aq (400 MHz, CDCl₃)



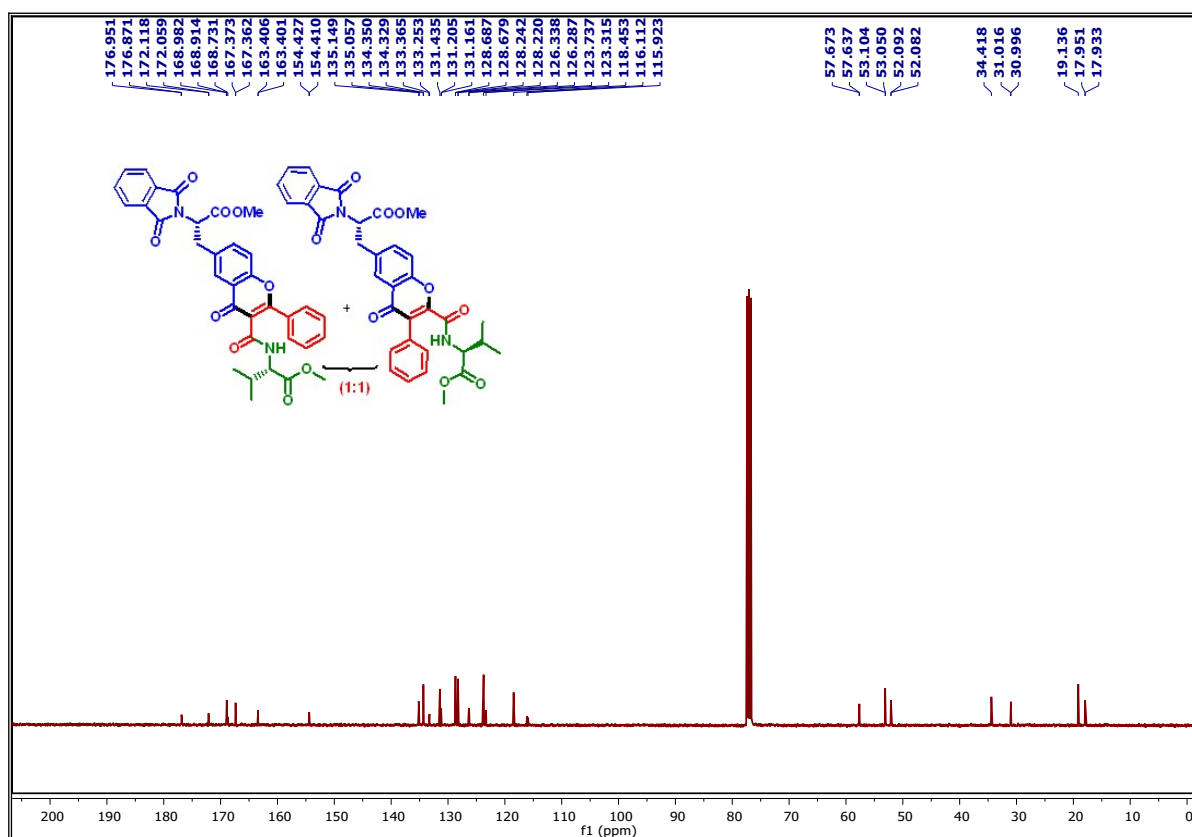
¹³C NMR of 3aq (100 MHz, CDCl₃)



¹H NMR of 3ar (400 MHz, CDCl₃)



¹³C NMR of 3ar (100 MHz, CDCl₃)



Chemical structure of compound 10:

COC(=O)N1Cc2cc3c(cc2O1)C(=O)N(Cc4ccccc4)C(=O)O3

1H NMR spectrum (CDCl₃):

Chemical shift (ppm): 8.588, 8.569, 8.471, 8.453, 8.086, 7.833, 7.825, 7.820, 7.813, 7.738, 7.590, 7.572, 7.540, 7.518, 7.500, 7.457, 7.440, 7.422, 7.399, 7.378, 7.286, 7.285, 7.266, 7.248, 7.152, 7.135, 5.230, 5.218, 5.203, 5.190, 5.003, 5.000, 4.989, 4.972, 4.960, 3.824, 3.785, 3.772, 3.749, 3.736, 3.705, 3.682, 3.646, 3.213, 3.199, 3.178, 3.165, 3.141, 3.124, 3.118, 3.107.

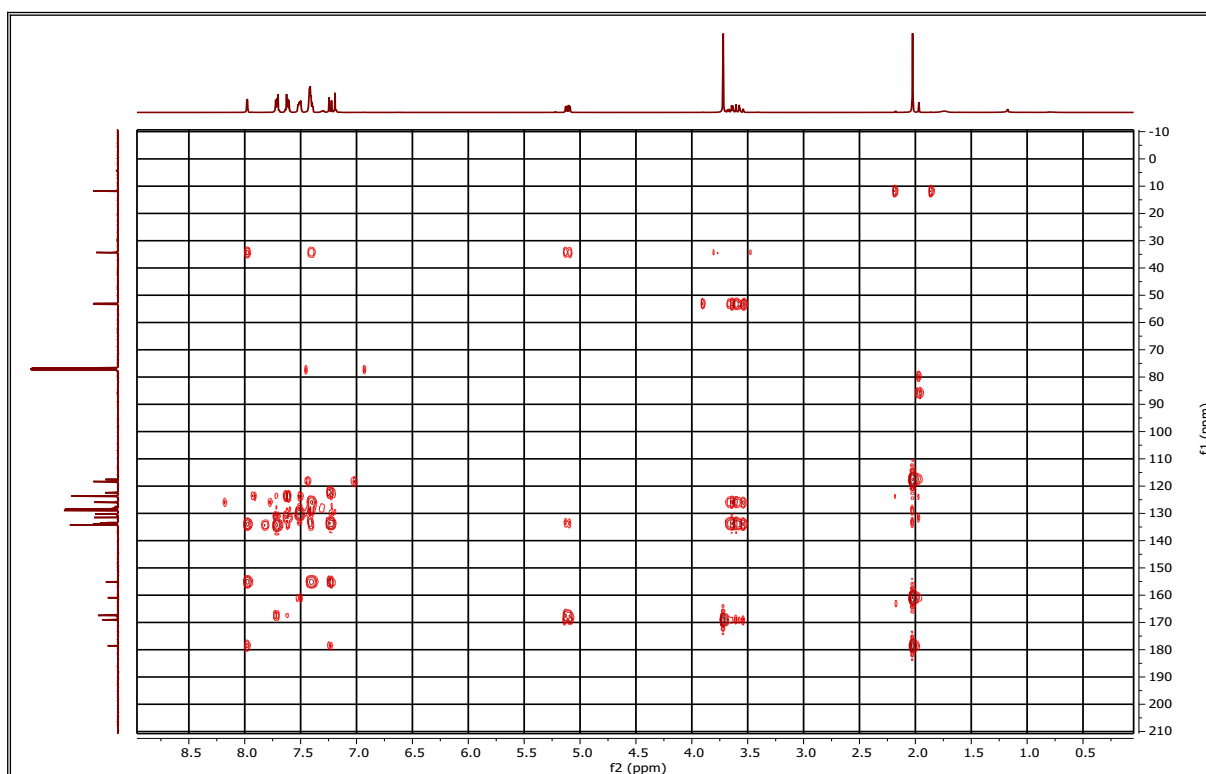
Integration values: 1.00, 0.96, 1.99, 3.99, 4.05, 5.05, 3.32, 4.31, 2.14, 2.94, 3.31, 3.96, 0.99, 0.96, 2.08, 5.95, 0.94, 1.91, 6.10, 1.27, 4.28.

Chemical structure of compound 10 is shown above the spectrum. The structure is a dimer of a chiral molecule, with two units linked by a central carbon-carbon bond. Each unit contains a benzimidazole ring system, a chiral auxiliary (a benzyl group with a chiral auxiliary), and a chiral auxiliary (a benzyl group with a chiral auxiliary). The spectrum shows peaks for the aromatic and heterocyclic carbons (115-177 ppm), the carbonyl carbons (176-177 ppm), and the aliphatic carbons (34-54 ppm). A list of peak chemical shifts is provided on the right side of the spectrum.

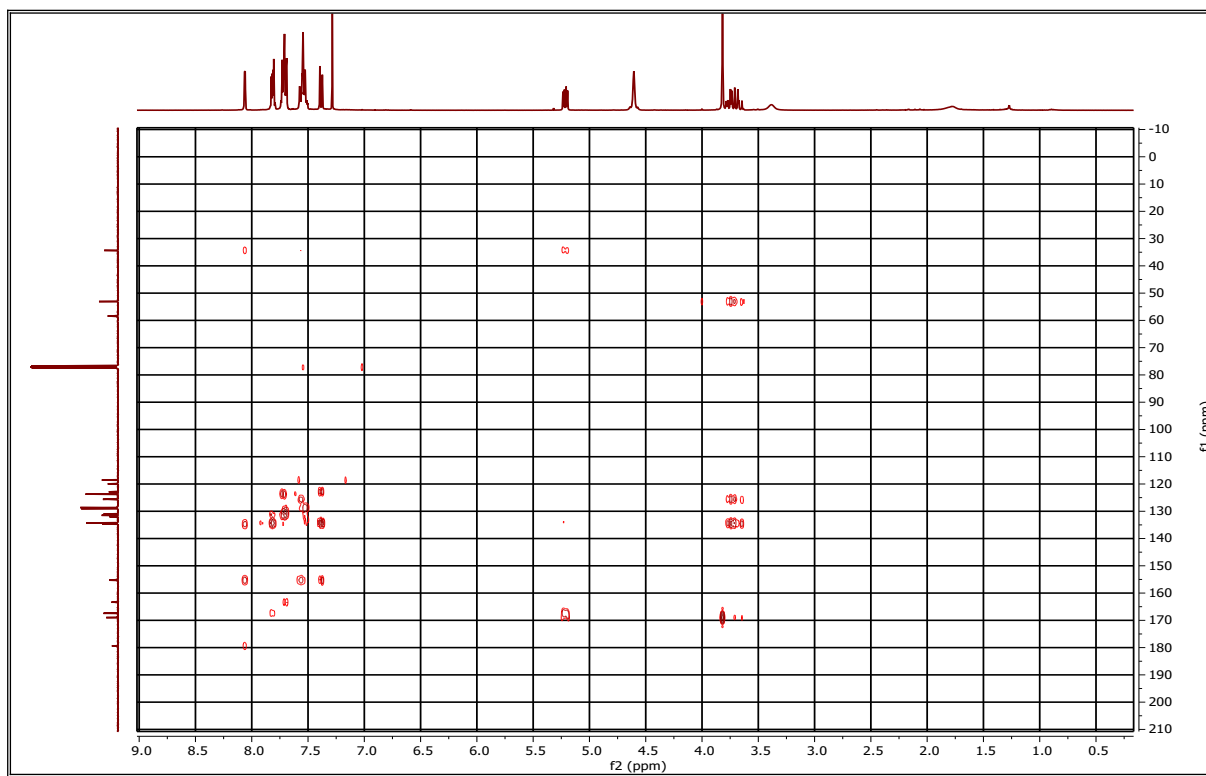
Chemical Shift (ppm)
176.678
176.615
171.701
171.639
168.924
168.624
168.409
167.383
163.193
163.186
154.408
154.388
136.238
136.191
135.109
135.003
134.358
134.340
133.235
133.159
131.447
131.432
131.233
131.203
129.404
128.692
128.682
128.527
128.254
128.240
126.962
126.323
126.299
123.738
123.294
118.418
115.976
115.802
53.661
53.643
53.106
53.036
52.264
38.159
36.103
34.387

5. HMBC of 3ag, 3ai,3aj

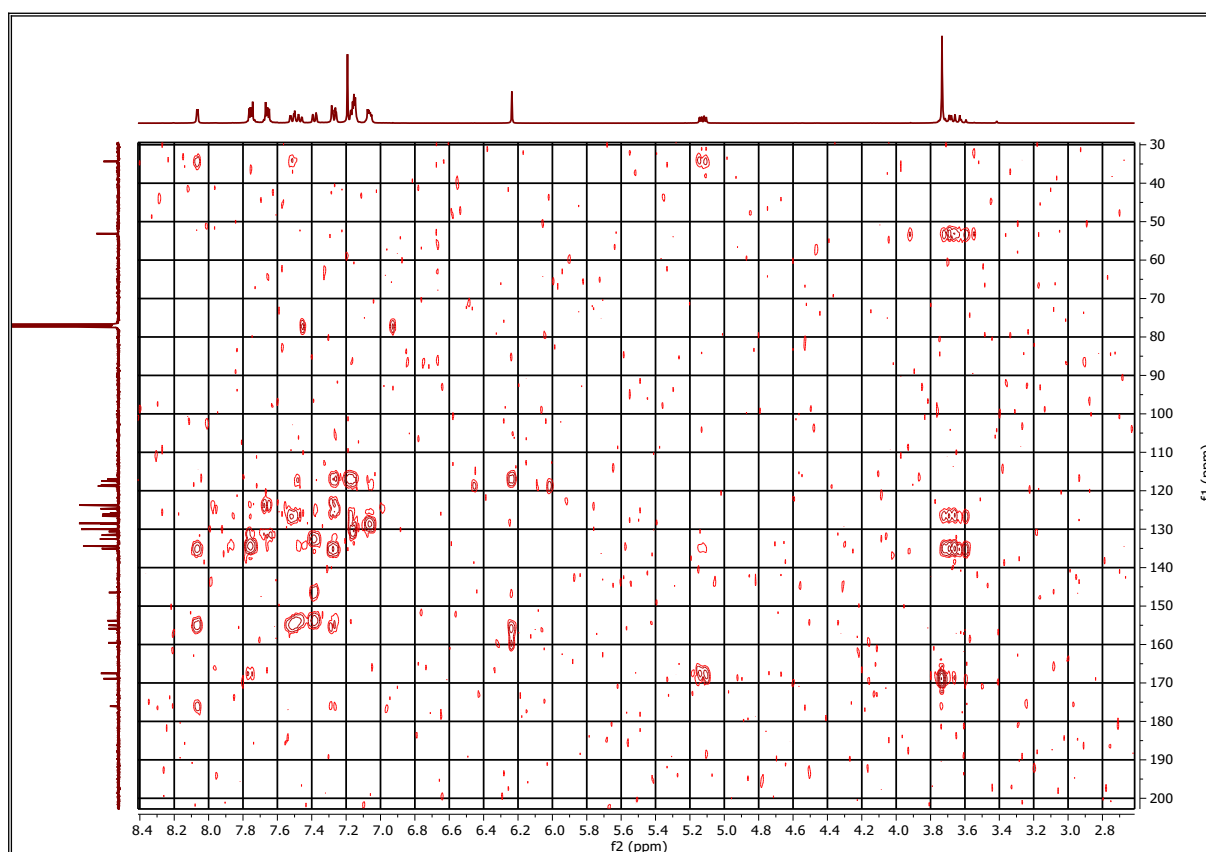
^1H - ^{13}C correlation NMR of 3ag (HMBC)



^1H - ^{13}C correlation NMR of 3ai (HMBC)



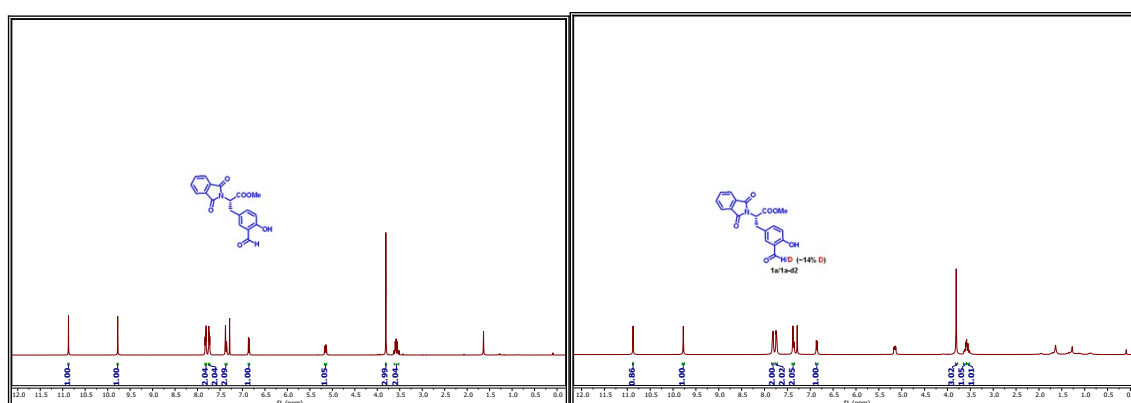
^1H - ^{13}C correlation NMR of 3aj (HMBC)



6. Deuterium labelling study [Refer Scheme 4i]

To an oven-dried 10 mL round bottom flask charged with 3 mL of ACN : D_2O (2:1), **1a** (1 equiv), $[\text{Cp}^*\text{RhCl}_2]_2$ (2.5 mol %), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (0.5 equiv) were added. The reaction was allowed to stir at 80 °C for 4 h. The reaction was cooled to room temperature, quenched with water and extracted with DCM (2×15 mL). The organic layers were combined, dried over anhydrous sodium sulphate and concentrated under reduced pressure. Purification by column chromatography using ethyl acetate/hexanes (2:8) as eluent afforded the desired product (**1a/1a- d_2**); ^1H NMR of this product indicated approximately 14% deuteration scrambling on C3_{Ar} -formly tyrosine proton when compared with the ^1H NMR of **1a**.

^1H NMR of **1a** and **1a/1a- d_2** (400 MHz, CDCl_3)



7. HRMS Analysis of crude reaction mixture[Refer Scheme 4ii]

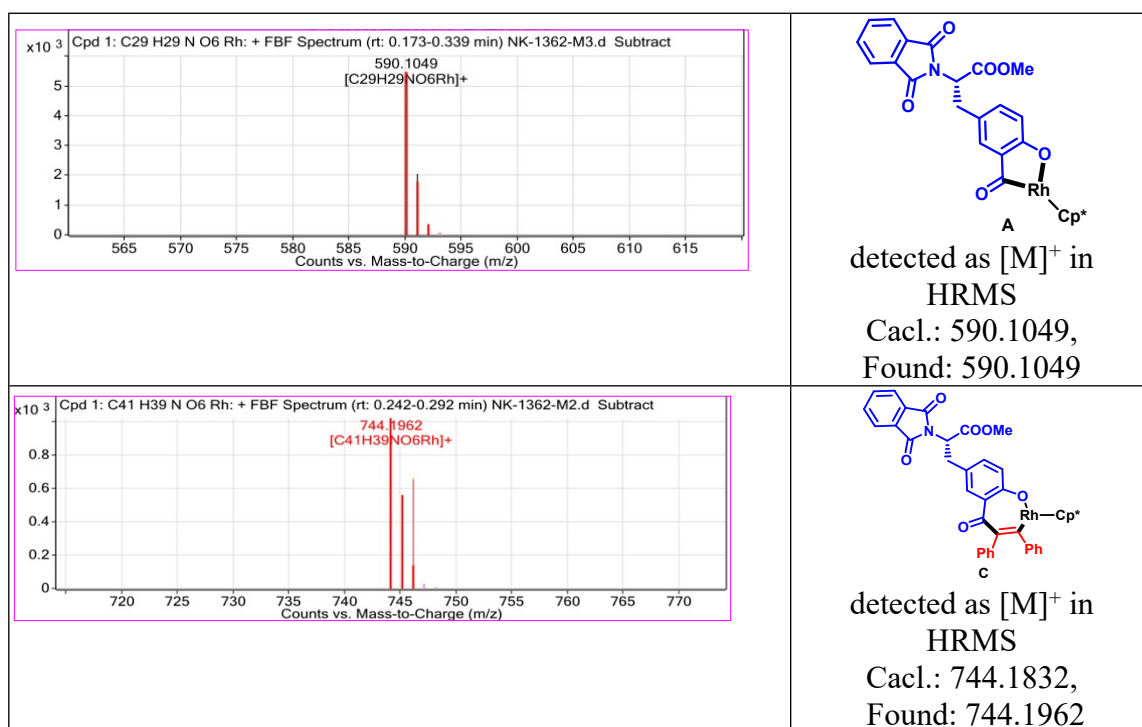
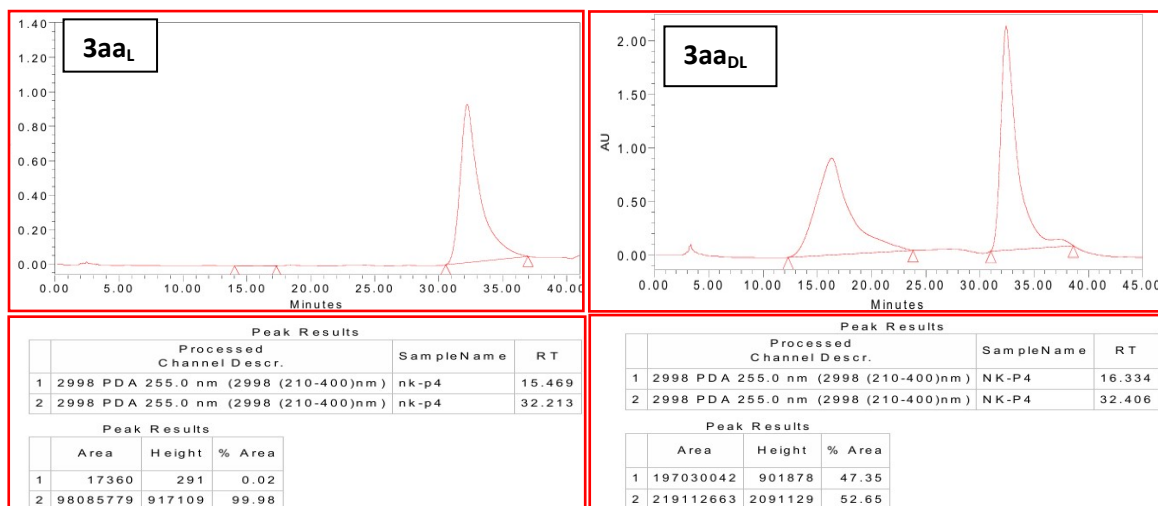


Figure 1. HRMS Data of crude reaction mixture between 1a and 2a

8. HPLC chromatograms of 3aa_L and 3aac_{DL}

HPLC separation of **3aa_L** (Chiralpak[®] IA-3, ⁿhexane/*i*PrOH: 85:15, v/v, Detection wavelength: 255 nm), 1.0 mL/min.): *t_r* (major) = 15.5 min, *t_r* (minor) = 32.2 min, >99% ee.
 HPLC separation of **3aa_{DL}** (Chiralpak[®] IA-3, ⁿhexane/*i*PrOH: 85:15, v/v), 1.0 mL/min., Detection wavelength: 255 nm): *t_r* = 16.3 min, *t_r* = 32.4 min.



9. In cellulo studies of the selected

compounds.

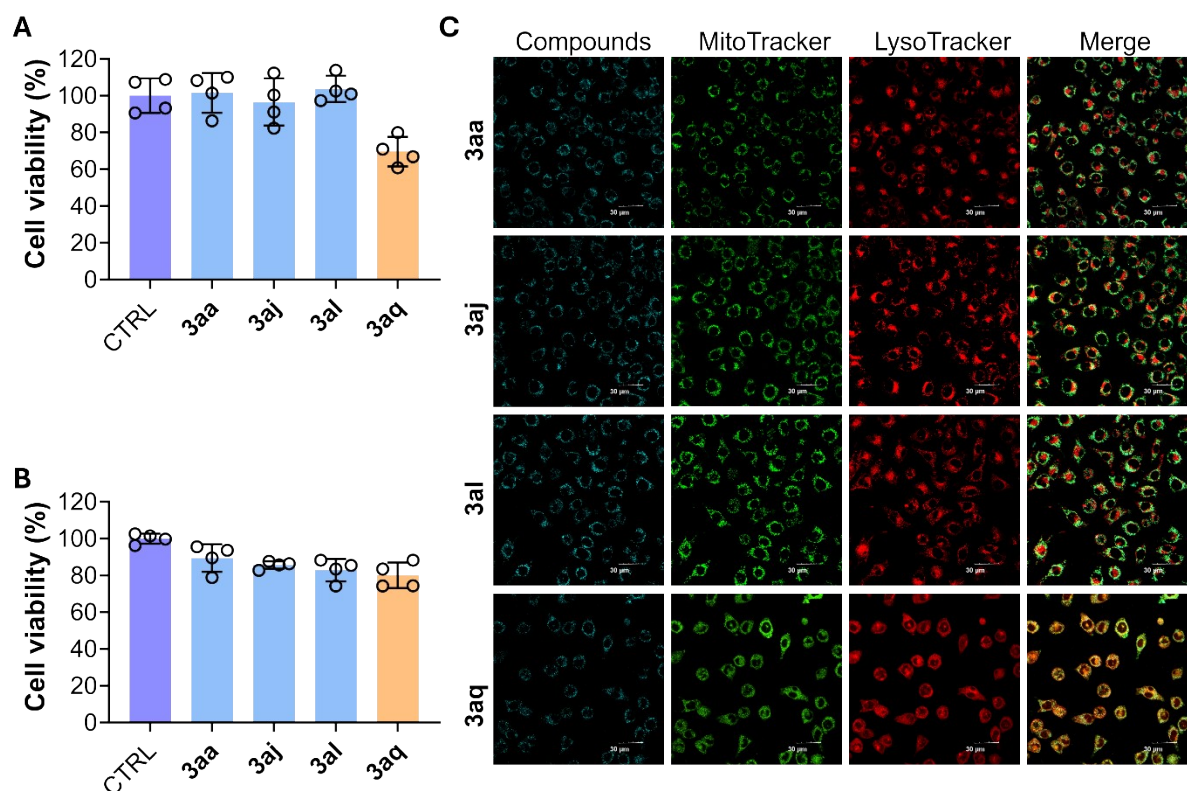


Figure S1. *In cellulo* studies of the tested compounds. The cell viability assay of the molecules in (A) SH-SY5Y human neuroblastoma cells and (B) N9 murine microglial cells. (C) The cellular uptake study of the molecules (Cyan= molecules, Green= MitoTracker green and Red= LysoTracker red). (The experiment was repeated with $n = 3$).

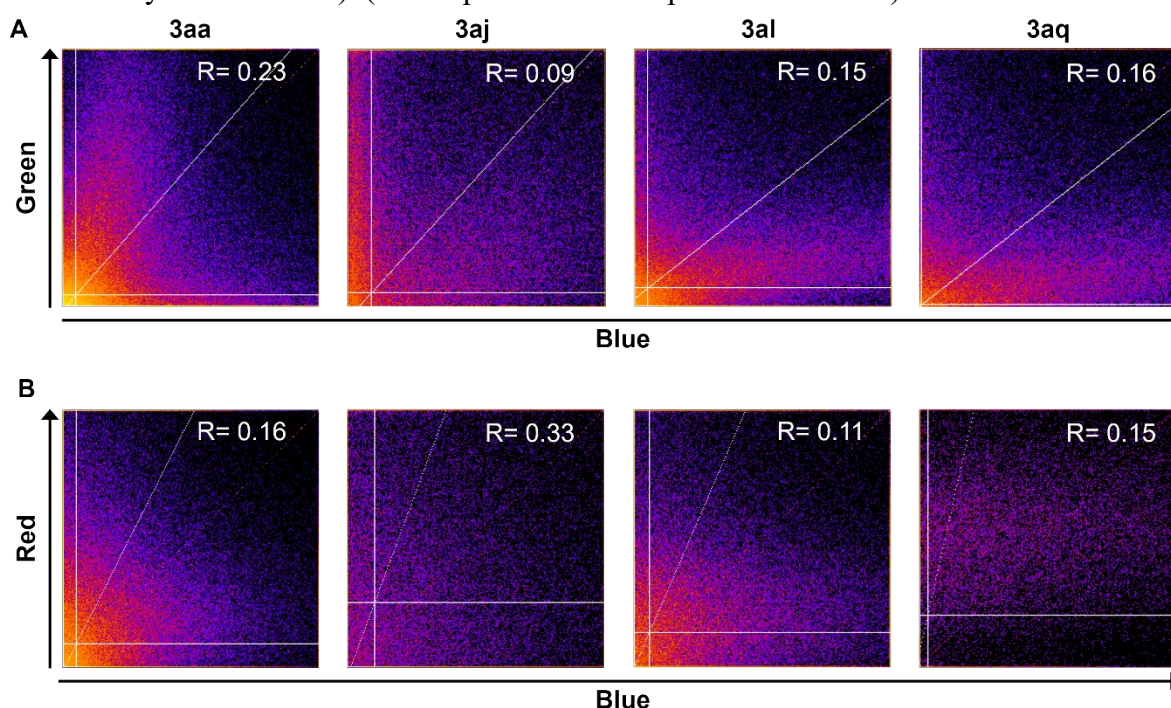


Figure S2. Colocalization of the molecules with mitochondria (A) and lysosome (B). Pearson coefficient is given in each image.

10. References

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2. H.-R. Li, Y.-A. Ran, Y.-Y. Zhu, W. Guo, S.-F. Ni, L.-R. Wen, M. Li and L.-B. Zhang, *Chem. Sci.*, 2024, **15**, 8156-8162.
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5. P. Szuroczki, B. Boros and L. Kollár, *Tetrahedron.*, 2018, **74**, 6129-6136.