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SUPPORTING INFORMATION

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Title: Single-Step Radiosynthesis of “^{18}F-Labeled Click Synthons” from Azide-Functionalized Diaryliodonium Salts
Author(s): Joong-Hyun Chun, Victor W. Pike*

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Synthesis of halobenzyl azides

Reference iodobenzyl azides and fluorobenzyl azides were prepared by known procedures. Analytical data obtained for these compounds agreed with those previously reported in the literature.[1,2]

4-Iodobenzyl azide.[3] NaN_3 (1.37 g, 21 mmol) was added to a stirred solution of 4-iodobenzyl bromide (2.08g, 7 mmol) in DMF (10 mL) at r.t. The reaction mixture was stirred at r.t. for 3 h. Water (20 mL) was added to quench the reaction, and product was extracted with CH_2Cl_2 (20 mL × 3). Combined organic layers were washed with water (50 mL × 3), dried over $MgSO_4$, then concentrated to an oil. Column chromatogrphy of crude product (silica using 10% EtOAc/hexane; R_f = 0.57) gave the 4-iodobenzyl azide as a white solid (1.59 g, 87%). mp = 29−30 °C; ^{1}H-NMR ($CDCl_3$) δ 7.71 (dd, J = 1.6, 8 Hz, 2H), 7.06 (d, J = 8 Hz, 2H), 4.29 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ 137.9, 135.0, 130.0, 93.9, 54.2.

The following compounds were prepared similarly. Fluoroarenes were obtained from corresponding fluorobenzyl bromides.

3-Iodobenzyl azide.[4] Colorless oil (2.46 g, 94%), R_f = 0.55 (10% EtOAc/hexane); ^{1}H-NMR ($CDCl_3$) δ 7.66−7.64 (m, 2H), 7.26 (d, J = 7.6 Hz, 1H), 7.10 (t, J = 9.6 Hz, 1H), 4.27 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ 137.6, 137.2, 136.9, 130.4, 127.2, 94.5, 53.8.

2-Iodobenzyl azide.[5] Pale yellow oil (0.52 g, 96%), R_f = 0.50 (10% EtOAc/hexane); ^{1}H-NMR ($CDCl_3$) δ 7.86 (d, J = 7.6 Hz, 1H), 7.36 (d, J = 4 Hz, 2H), 7.04−6.98 (m, 1H), 4.43 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ 139.6, 138.0, 129.8, 129.4, 128.5, 98.9, 58.9.

4-Fluorobenzyl azide.[2] Colorless oil (0.10 g, 32%, volatile), R_f = 0.5 (10% EtOAc/hexane); ^{1}H-NMR ($CDCl_3$) δ 7.31−7.25 (m, 2H), 7.09−7.05 (m, 2H), 4.31 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ 162.6 (d, J_{C-F} = 246 Hz), 131.2 (d, J_{C-F} = 3 Hz), 130.0 (d, J_{C-F} = 8 Hz), 115.8 (d, J_{C-F} = 21 Hz), 54.0; ^{19}F-NMR ($CDCl_3$) δ −113.5.

3-Fluorobenzyl azide.[6] Colorless oil (0.27 g, 72%, volatile), R_f = 0.52 (10% EtOAc/hexane); ^{1}H-NMR ($CDCl_3$) δ 7.38−7.33 (m, 1H), 7.11−7.09 (m, 1H), 7.06−7.02 (m, 2H), 4.35 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ 163.1 (d, J_{C-F} = 246 Hz), 137.8, 130.4 (d, J_{C-F} = 8 Hz), 123.6 (d, J_{C-F} = 3 Hz), 115.2 (d, J_{C-F} = 21 Hz), 114.9, 54.2; ^{19}F-NMR ($CDCl_3$) δ −112.3.

2-Fluorobenzyl azide.[7] Colorless oil (0.39 g, 65%, volatile), R_f = 0.2 (hexane); ^{1}H-NMR ($CDCl_3$) δ 7.37−7.31 (m, 2H), 7.19−7.08 (m, 2H), 4.41 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ 163.1 (d, $J_{C\text{-}F}$ = 247 Hz), 130.4 (d, $J_{C\text{-}F}$ = 4 Hz), 130.3 (d, $J_{C\text{-}F}$ = 8 Hz), 124.4 (d, $J_{C\text{-}F}$ = 3 Hz), 122.7 (d, $J_{C\text{-}F}$ = 15 Hz), 115.7 (d, $J_{C\text{-}F}$ = 22 Hz), 48.5 (d, $J_{C\text{-}F}$ = 4 Hz); ^{19}F-NMR ($CDCl_3$) δ −118.0.

Synthesis of azidohaloarenes

Azidohaloarenes were prepared by known procedures. Analytical data for these compounds have been reported in the literature.[1,2]

1-Azido-3-iodobenzene.[8]

$NaNO_2$ (0.69 g, 10 mmol) in H_2O (10 mL) was added dropwise with vigrous stirring to an ice-cold solution of 3-iodoaniline (1.53 g, 7 mmol) and *conc.* HCl (5 mL) in H_2O (5 mL) and held at 0 ^{o}C for 1 h. NaN_3 (1.04 g, 16 mmol) in H_2O (10 mL) was then added dropwise. The reaction mixture was kept below 5 ^{o}C and after 1 h product was extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were washed with water (50 mL × 3). The organic layer was dried over $MgSO_4$ and concentrated to a yellow crude oil. Column chromatogrphy of this crude oil (silica, hexane; R_f = 0.52) gave the product as a pale yellow oil (1.37 g, 80%); ^{1}H-NMR ($CDCl_3$) δ 7.43 (dt, J = 1.2, 5.2 Hz, 1H), 7.36 (t, J = 2 Hz, 1H), 7.02 (t, J = 8 Hz, 1H), 6.96-6.93 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ 141.2, 133.8, 130.9, 127.8, 118.3, 94.6.

The following compounds were prepared similarly. Fluoro compounds were prepared from the corresponding fluoroanilines.

1-Azido-4-iodobenzene.[1] Pale yellow solid (1.83 g, 75%), R_f = 0.53 (hexane), mp = 31−32 ^{o}C; ^{1}H-NMR ($CDCl_3$) δ 7.64 (d, J = 8.4 Hz, 2H), 6.78 (d, J = 8.4 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ 140.0, 138.7, 121.0, 88.2.

1-Azido-3-fluorobenzene.[9] Pale yellow solid (0.45 g, 66%), R_f = 0.5 (hexane); ^{1}H-NMR ($CDCl_3$) δ 7.32−7.26 (m, 1H), 6.86−6.80 (m, 2H), 6.72 (dt, J = 2, 5.2 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 163.5 (d, $J_{C\text{-}F}$ =

247 Hz), 141.9 (d, $J_{C\text{-}F}$ = 10 Hz), 130.9 (d, $J_{C\text{-}F}$ = 10 Hz), 114.7 (d, $J_{C\text{-}F}$ = 3 Hz), 111.8 (d, $J_{C\text{-}F}$ = 21 Hz), 106.7 (d, $J_{C\text{-}F}$ = 24 Hz); ^{19}F-NMR ($CDCl_3$) δ −110.8.

1-Azido-4-fluorobenzene.[9] Yellow oil (0.25 g, 45%, volatile), R_f = 0.45 (hexane); ^{1}H-NMR ($CDCl_3$) δ 7.07-7.026 (m, 2H), 6.99−6.96 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 160.0 (d, $J_{C\text{-}F}$ = 244 Hz), 135.8 (d, $J_{C\text{-}F}$ = 3 Hz), 120.3 (d, $J_{C\text{-}F}$ = 9 Hz), 116.6 (d, $J_{C\text{-}F}$ = 23 Hz); ^{19}F-NMR ($CDCl_3$) δ −117.7.

References

[1] W. Qu, M.-P. Kung, C. Hou, S. Oya, H. F. Kung, *J. Med. Chem.* **2007**, *50*, 3380−3387.

[2] L. Verduyn-Campbell, P. H. Elsinga, L. Mirfeizi, R. A. Dierckx, B. L. Feringa, *Org. Biomol. Chem.* **2007**, *50*, 3461−3463.

[3] K. D. Park, P. Morieux, C. Salomé, S. W. Cotten, O. Reamtong, C. Eyers, S. J. Gaskell, J. P. Stables, R. Liu, H. Kohn, *J. Med. Chem.* **2009**, *52*, 6897−6911.

[4] L. Díaz, J. Cases, J. Bujons, A. Llebaria, A. Delgado, *J. Med. Chem.* **2011**, *54*, 2069−2079.

[5] F. Shi, J. P. Waldo, Y. Chen, R. C. Larock, *Org. Lett.* **2008**, *10*, 2409−2412.

[6] L. Hu, S. Zhang, X. He, Z. Luo, X. Wang, W. Liu, X. Qin, *Bioorg. Med. Chem.* **2012**, *20*, 177−182.

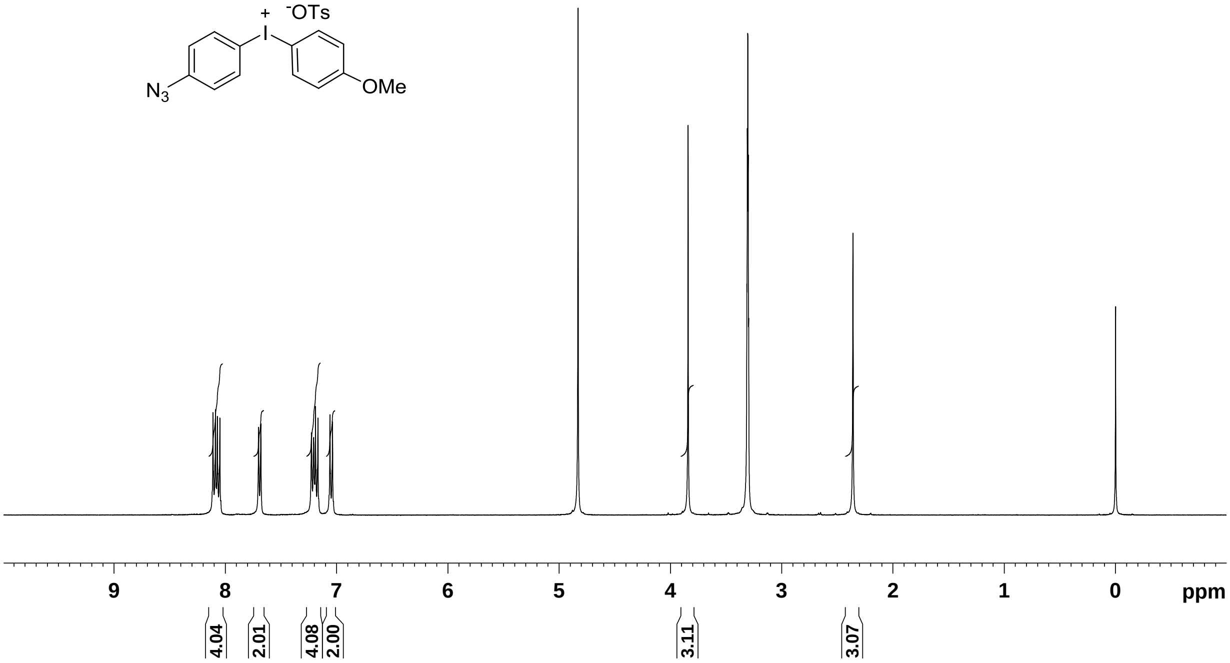
[7] X. Wang, T.-S. Mei, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 7520−7521.

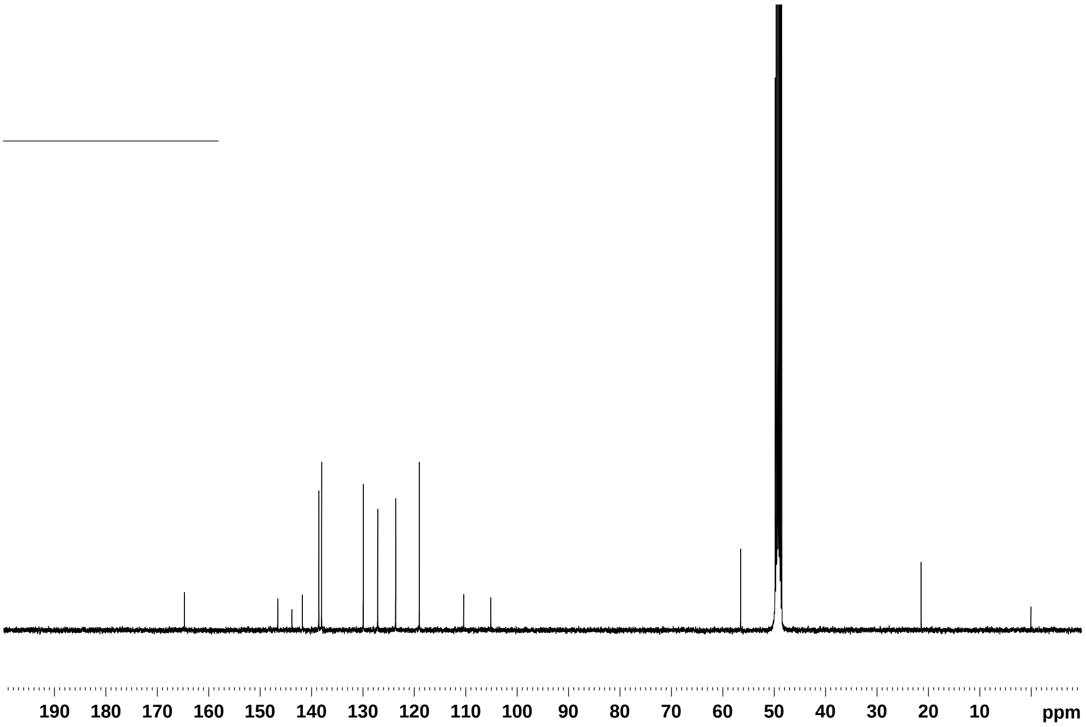
[8] N. Faucher, Y. Ambroise, J.-C. Cintrat, E. Doris, F. Pillon, B. Rousseau, *J. Org. Chem.* **2002**, *67*, 932−934.

[9] E. Leyva, D. Munoz, M. S. Platz, *J. Org. Chem.* **1989**, *54*, 5938−5945.

Appendix 1. ^{1}H and ^{13}C spectra of azide-functionalized diaryliodonium salts

Compound **3**





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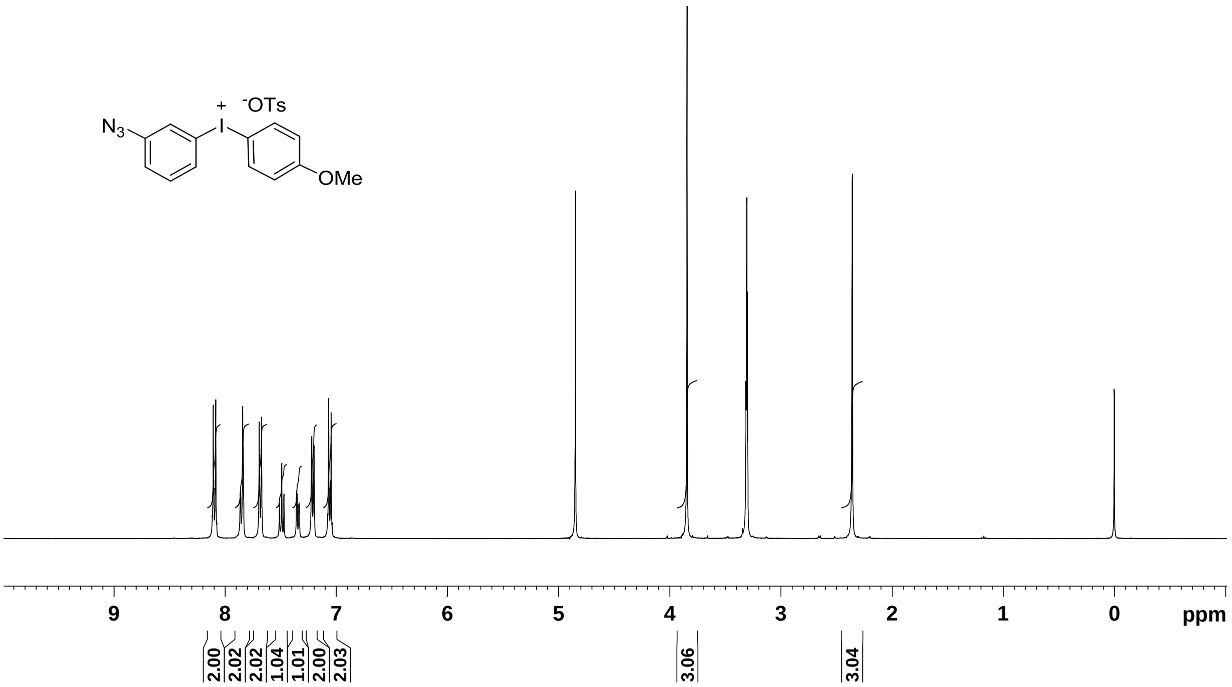

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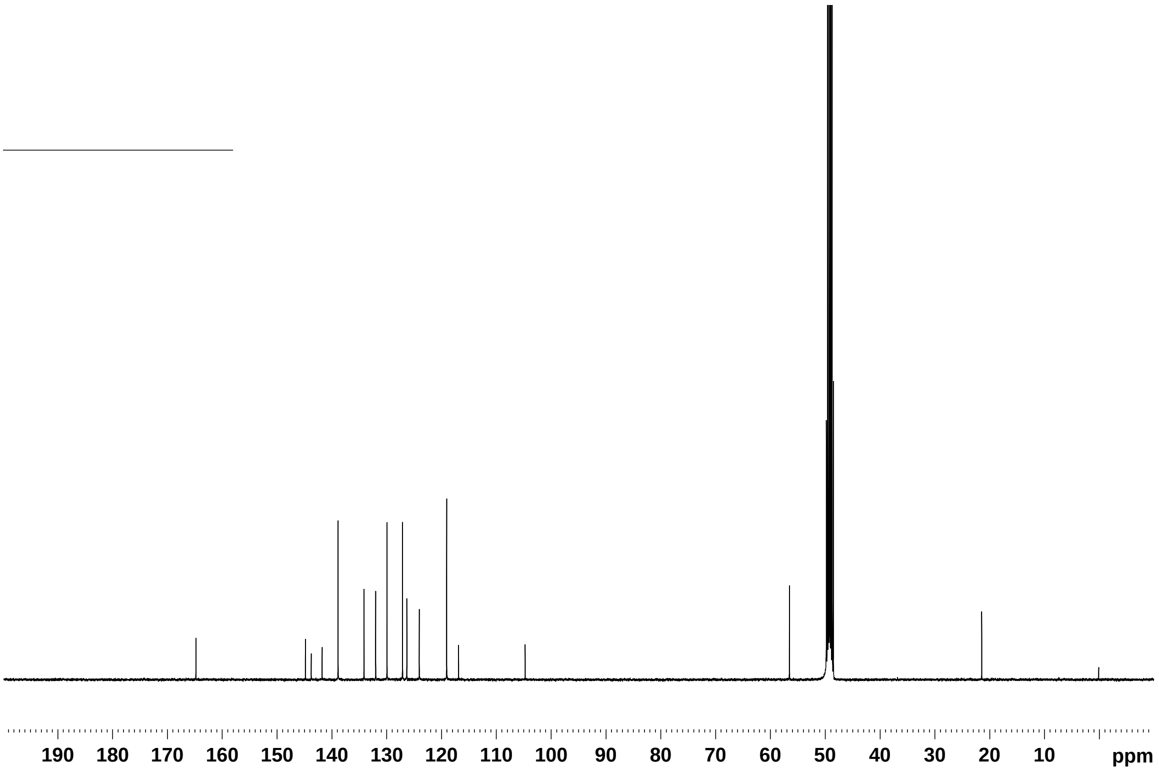

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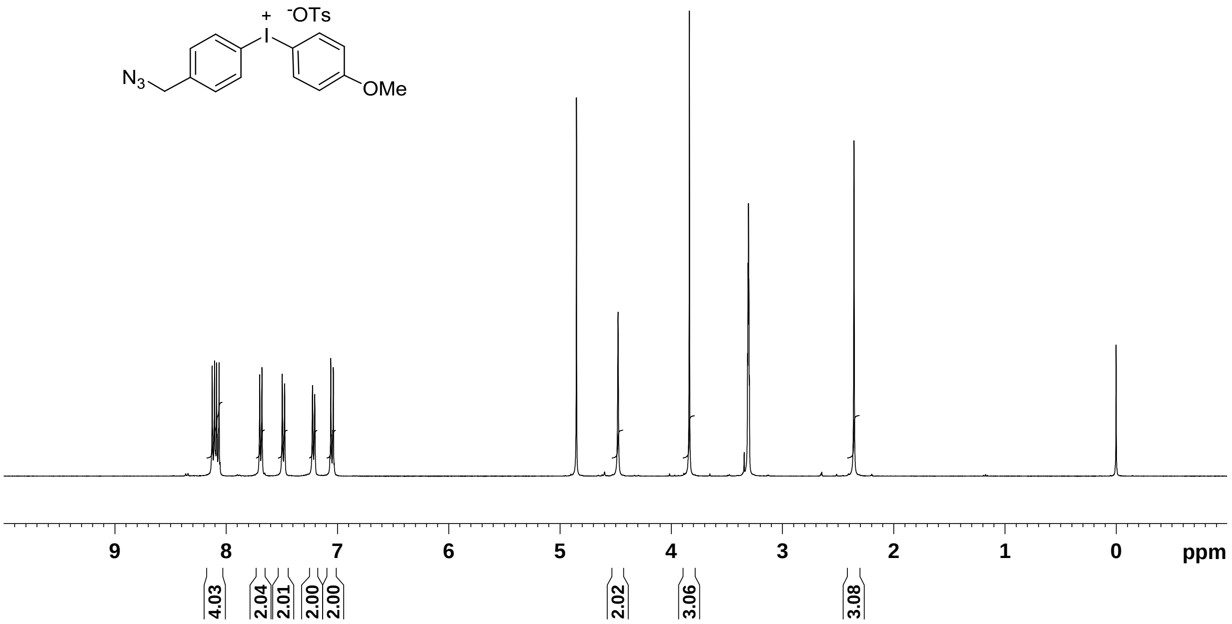
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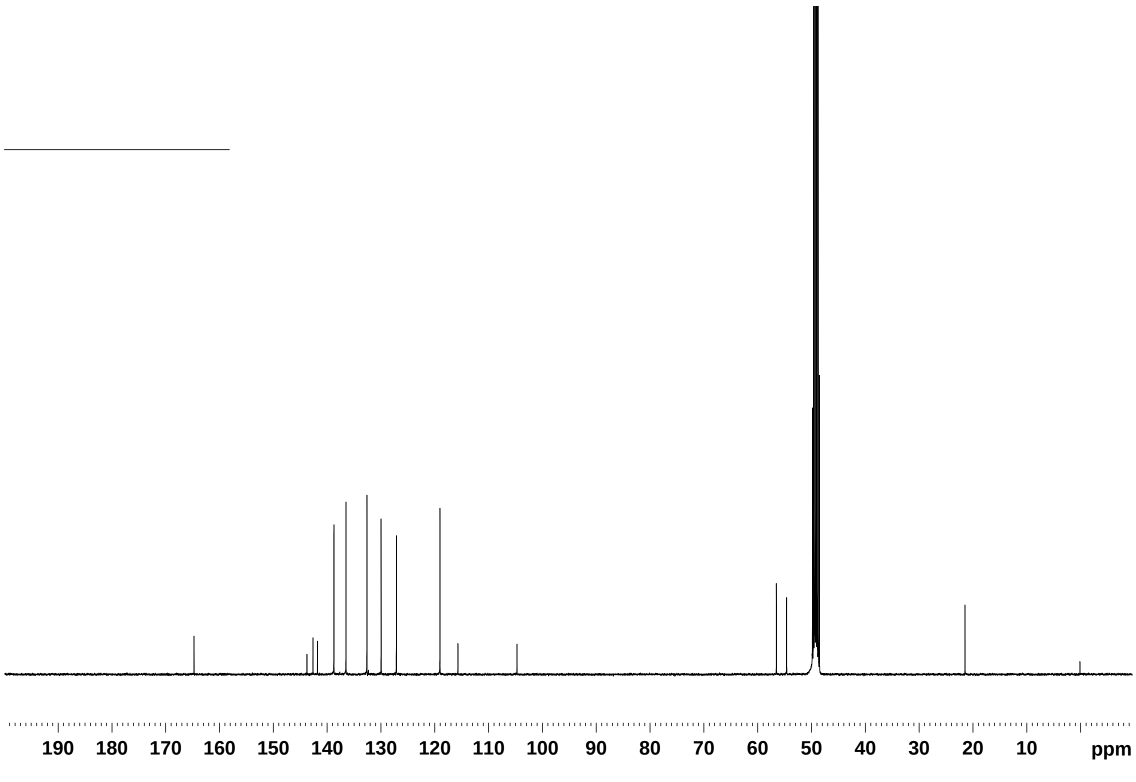
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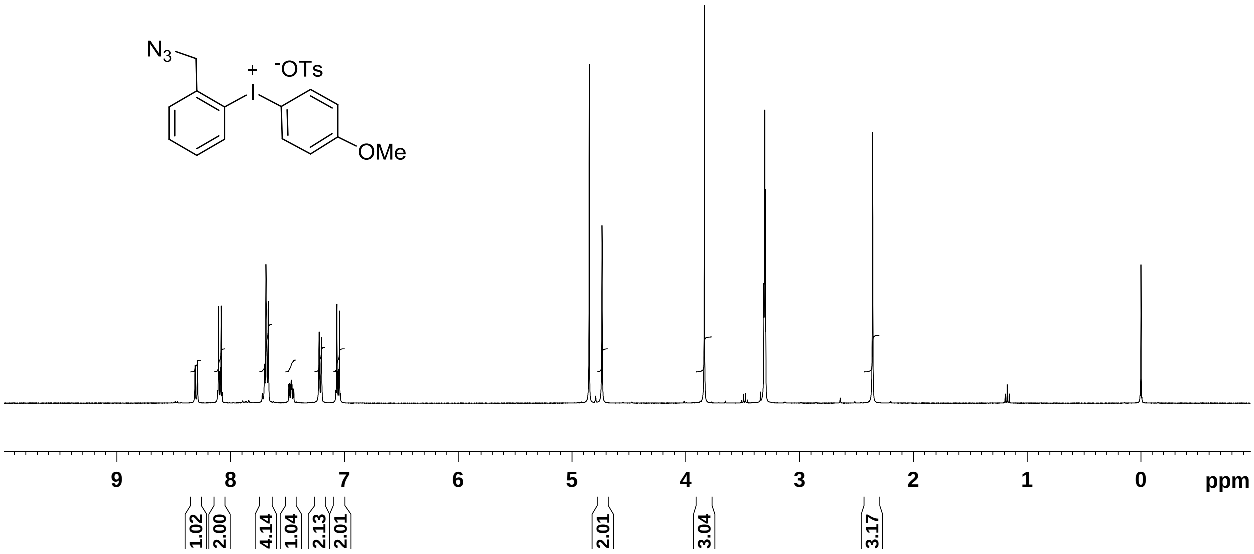
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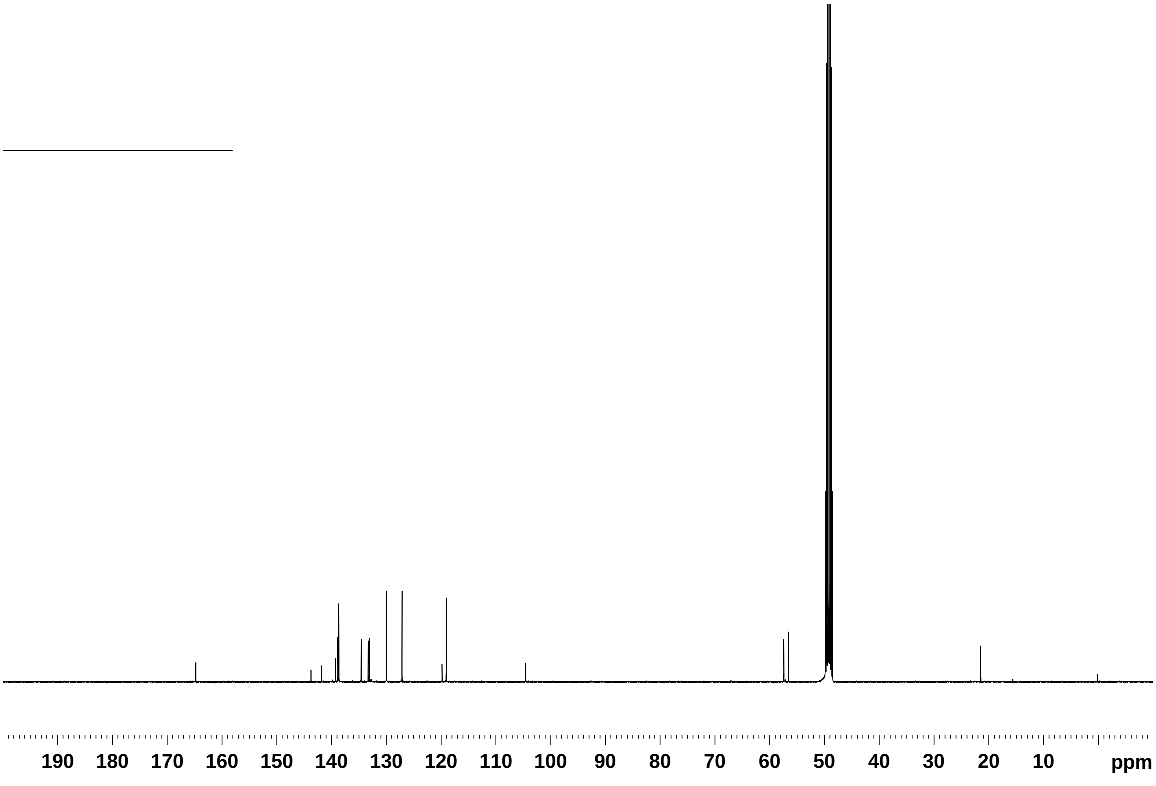
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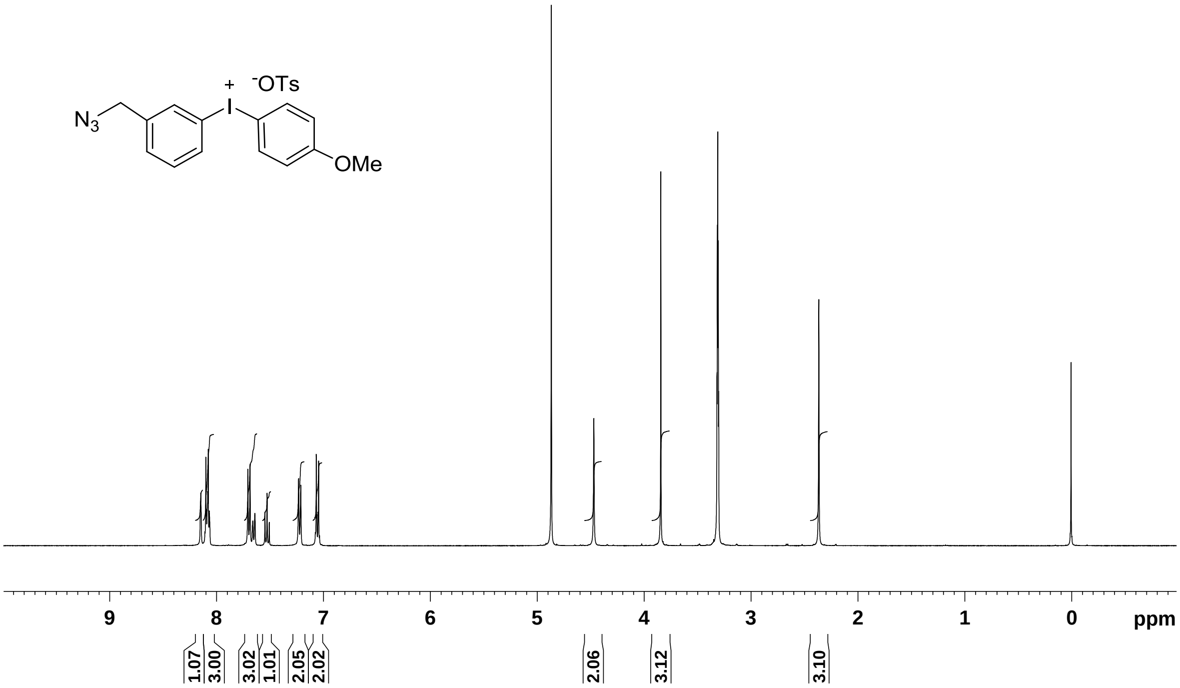

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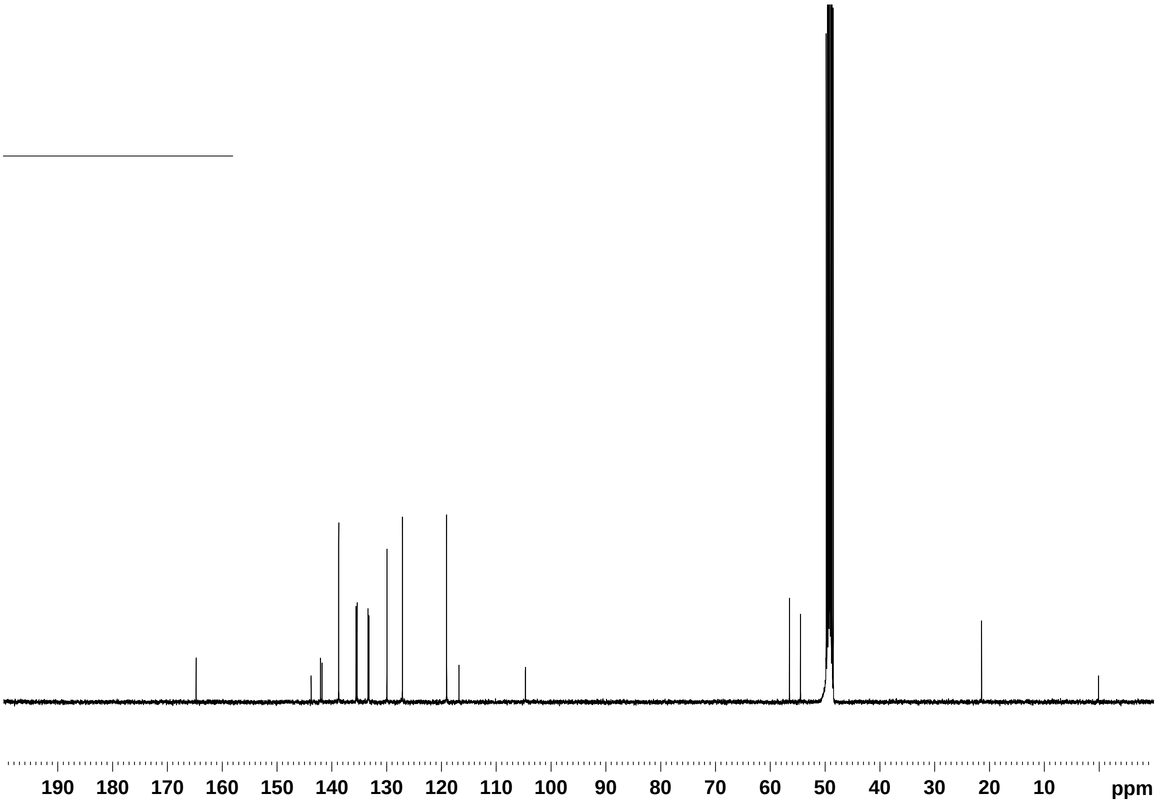

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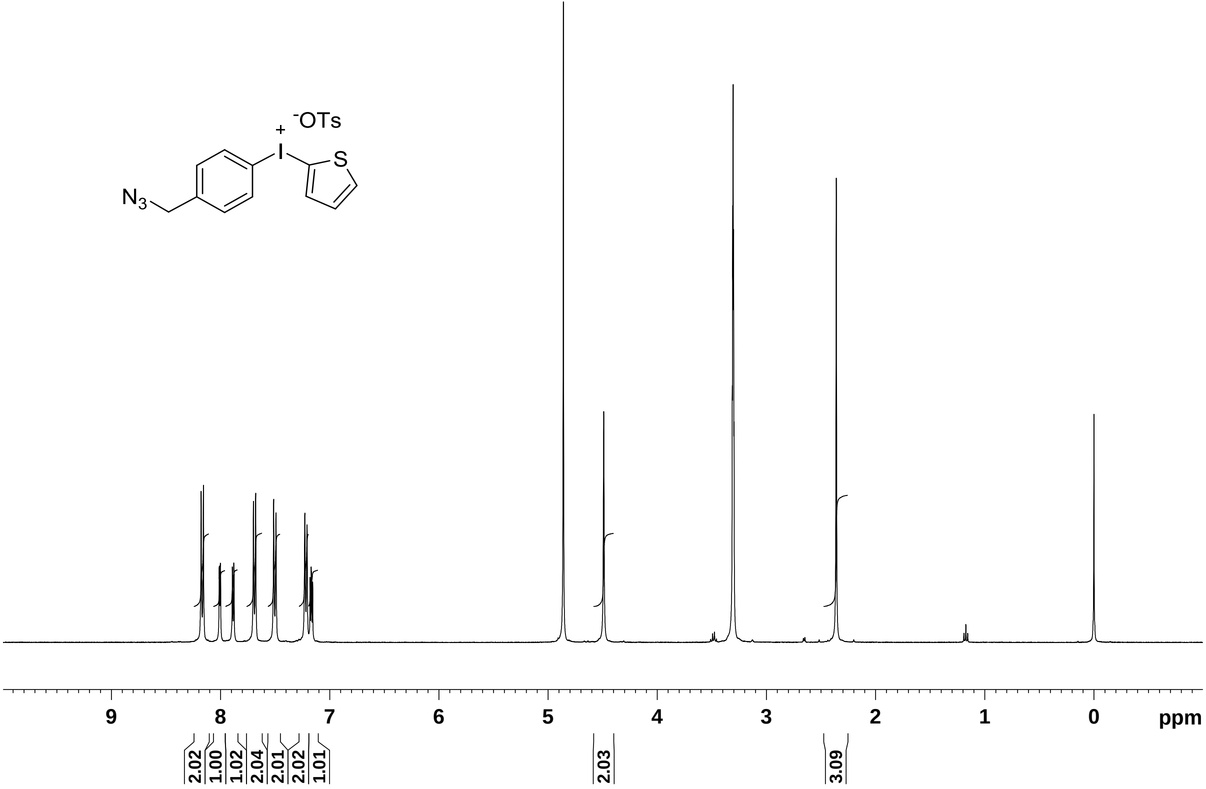
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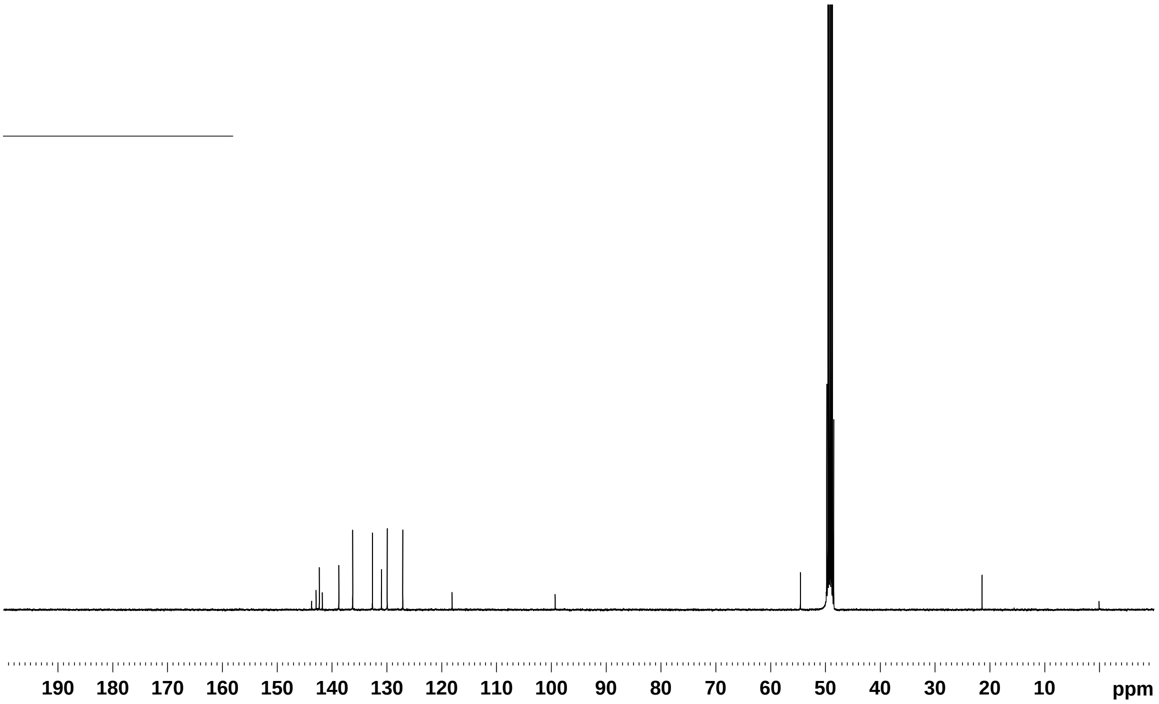
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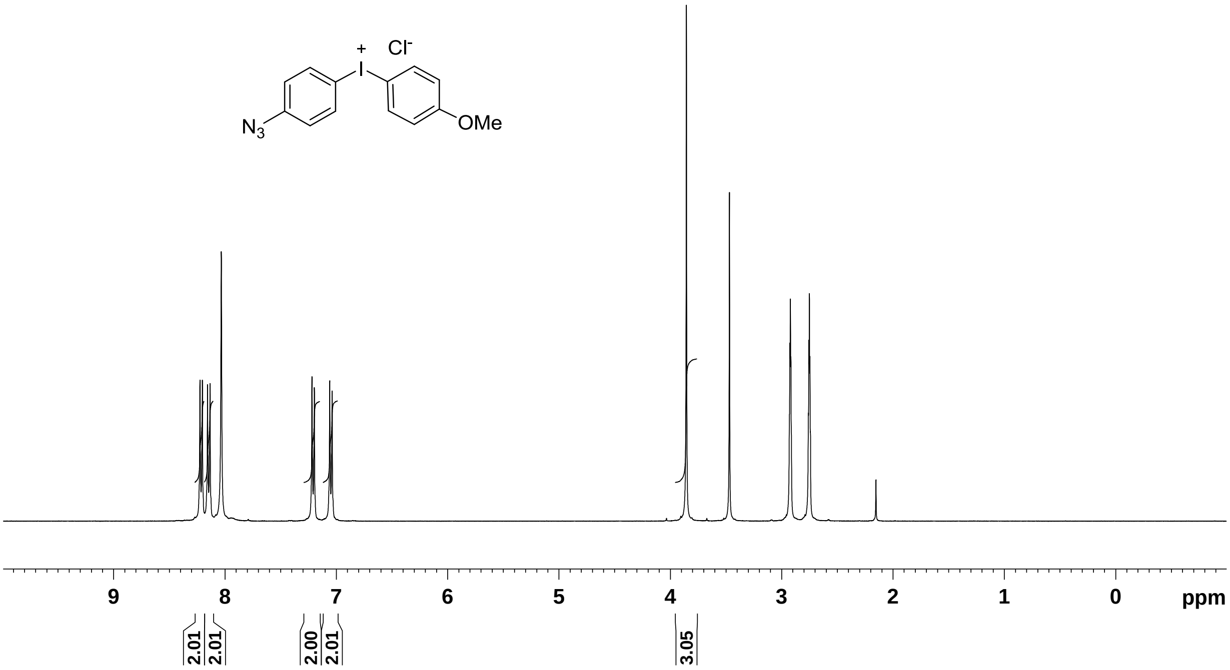
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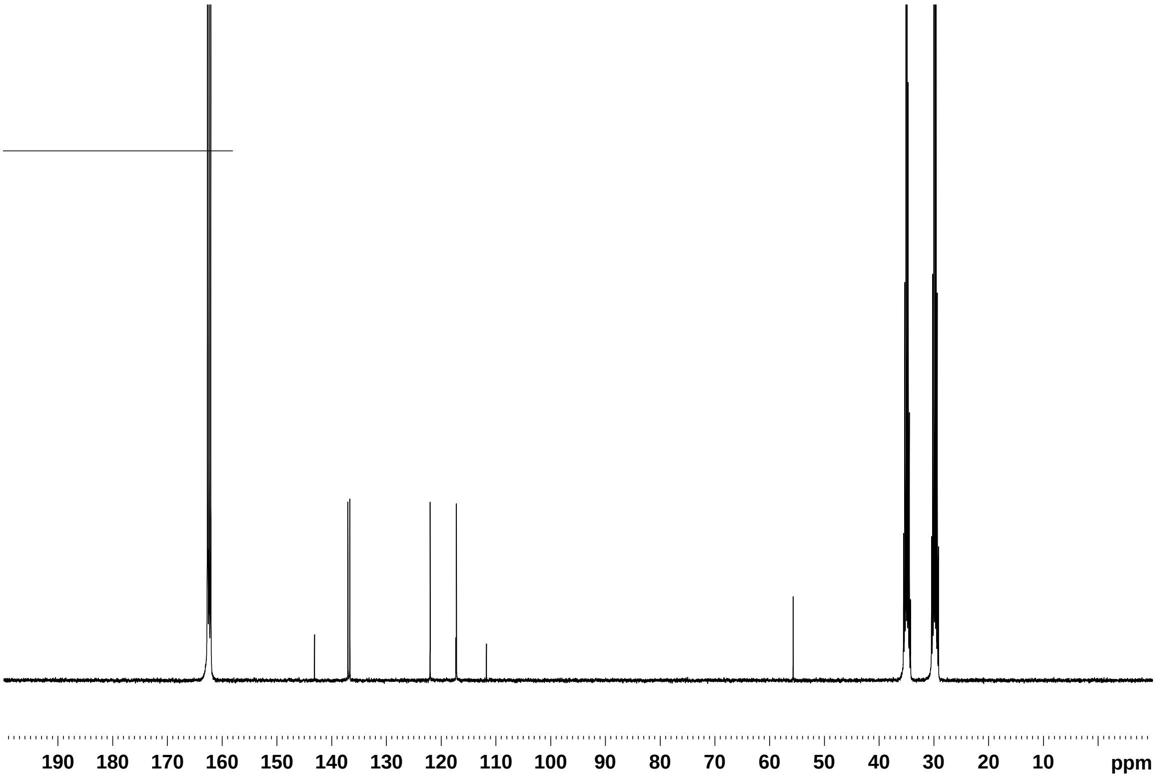
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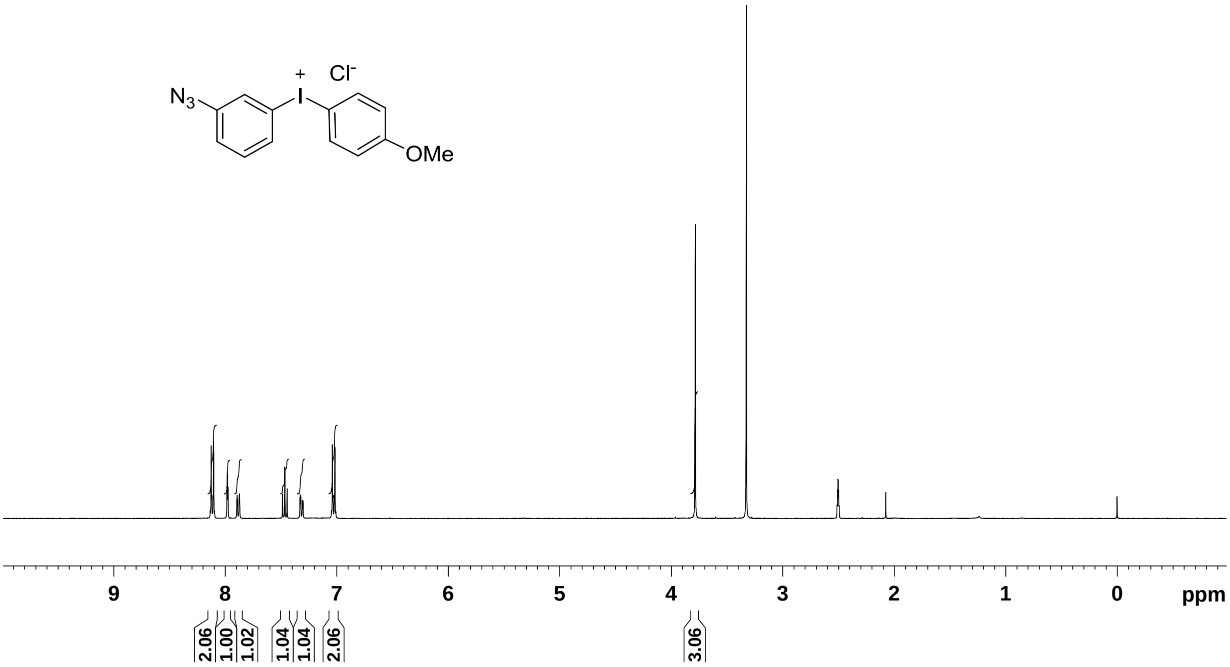
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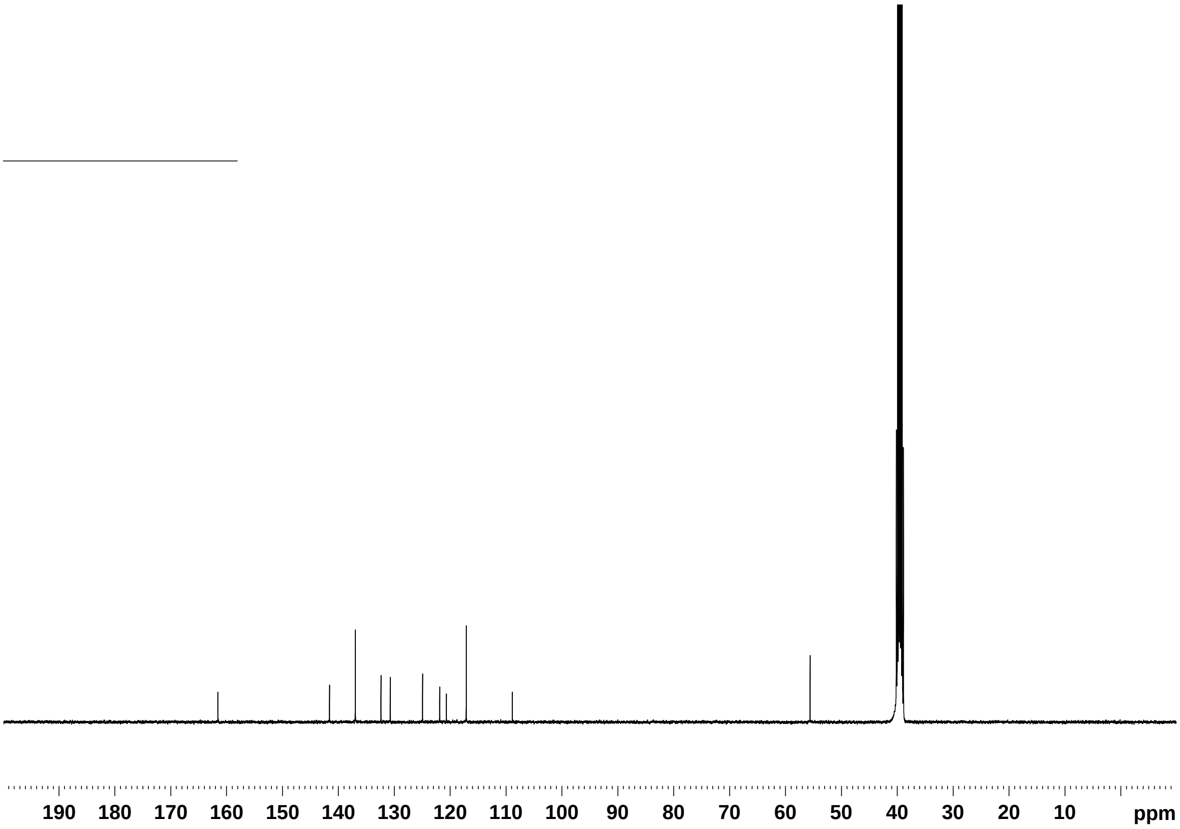
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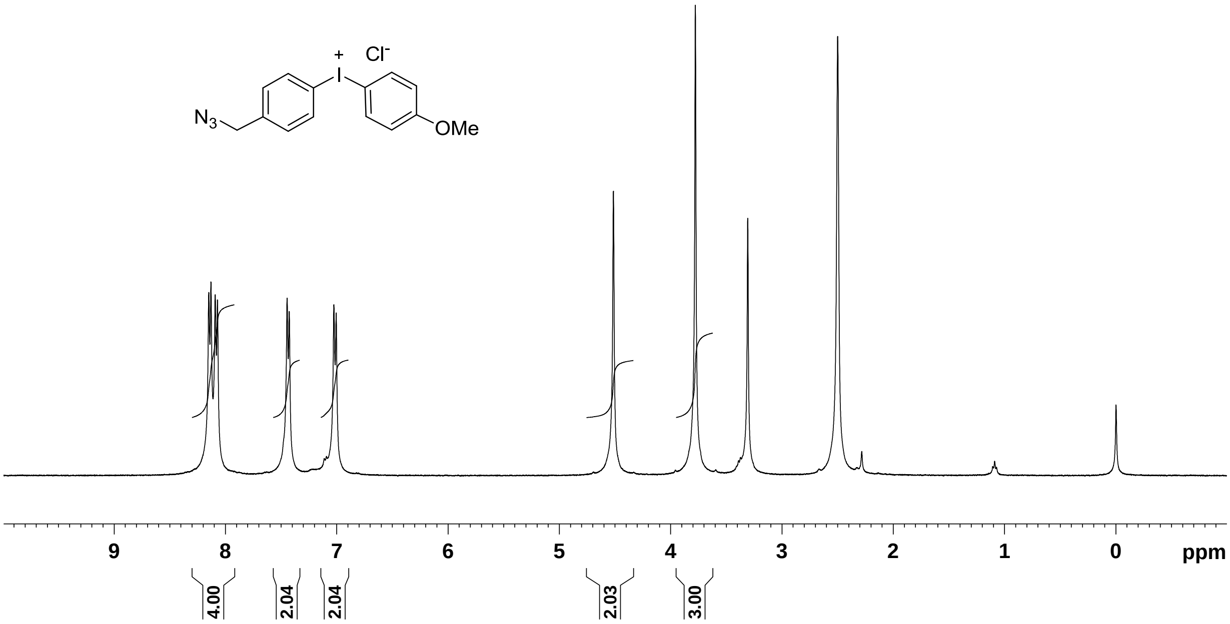
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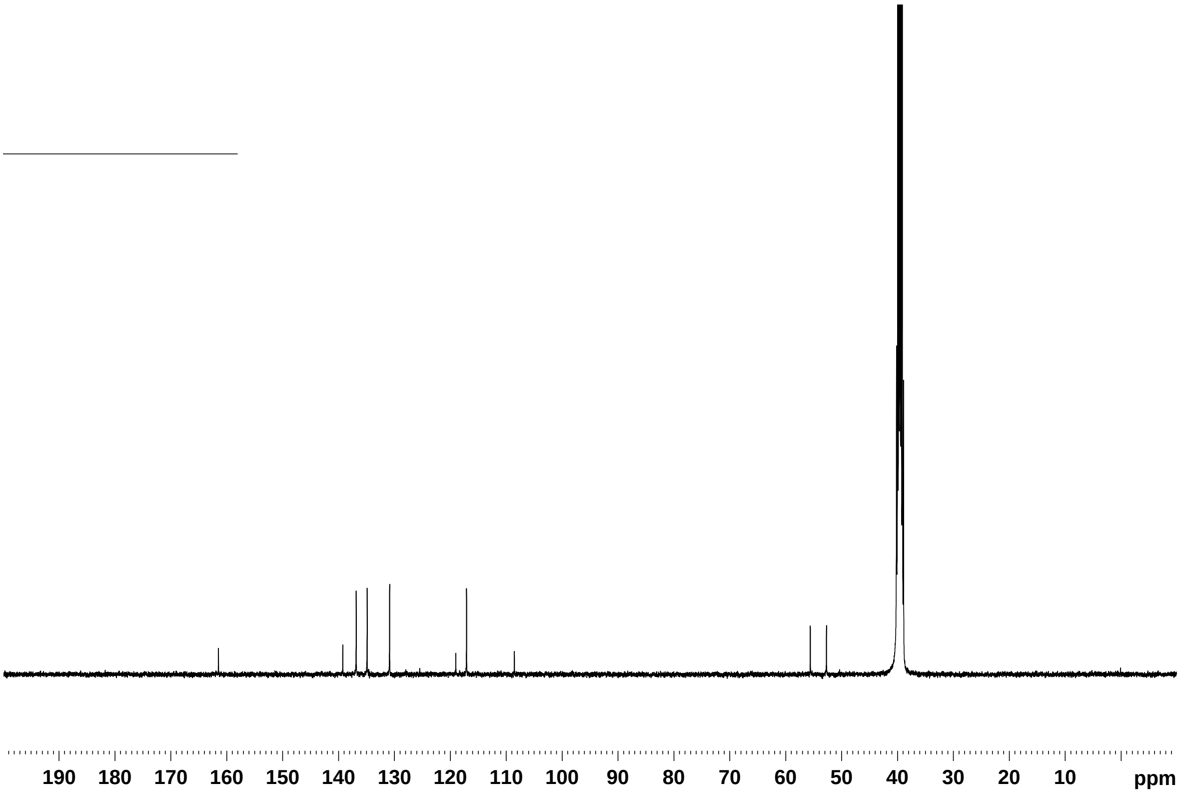
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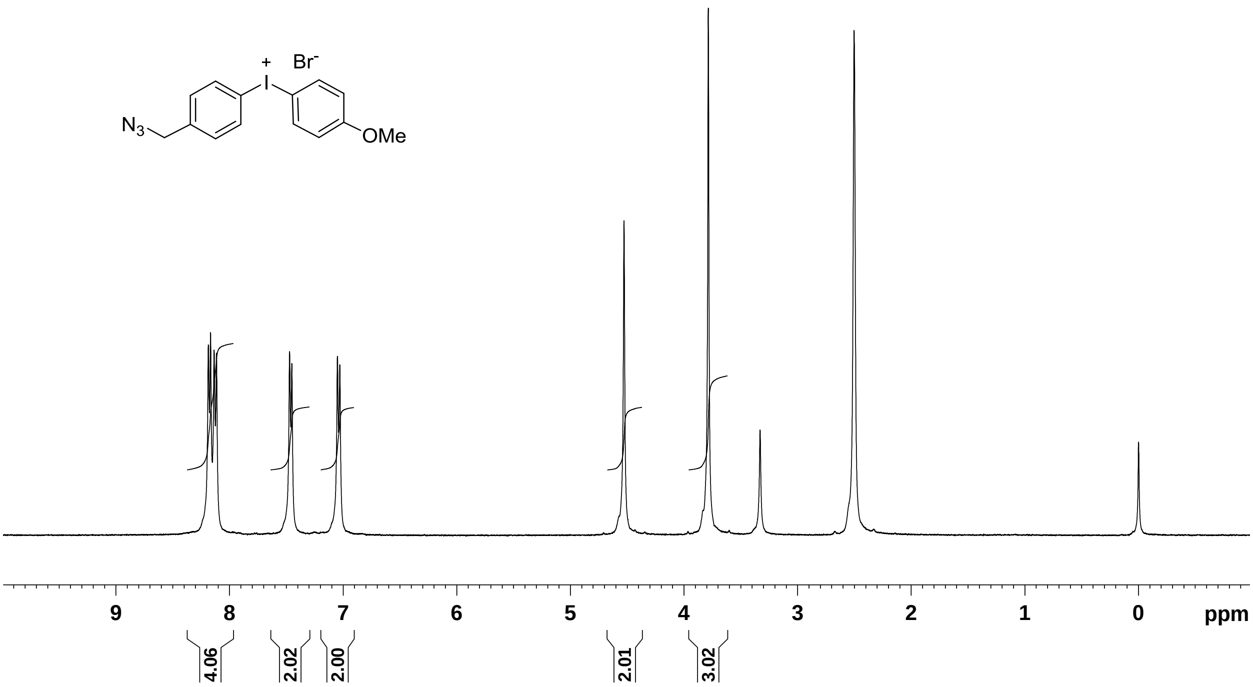
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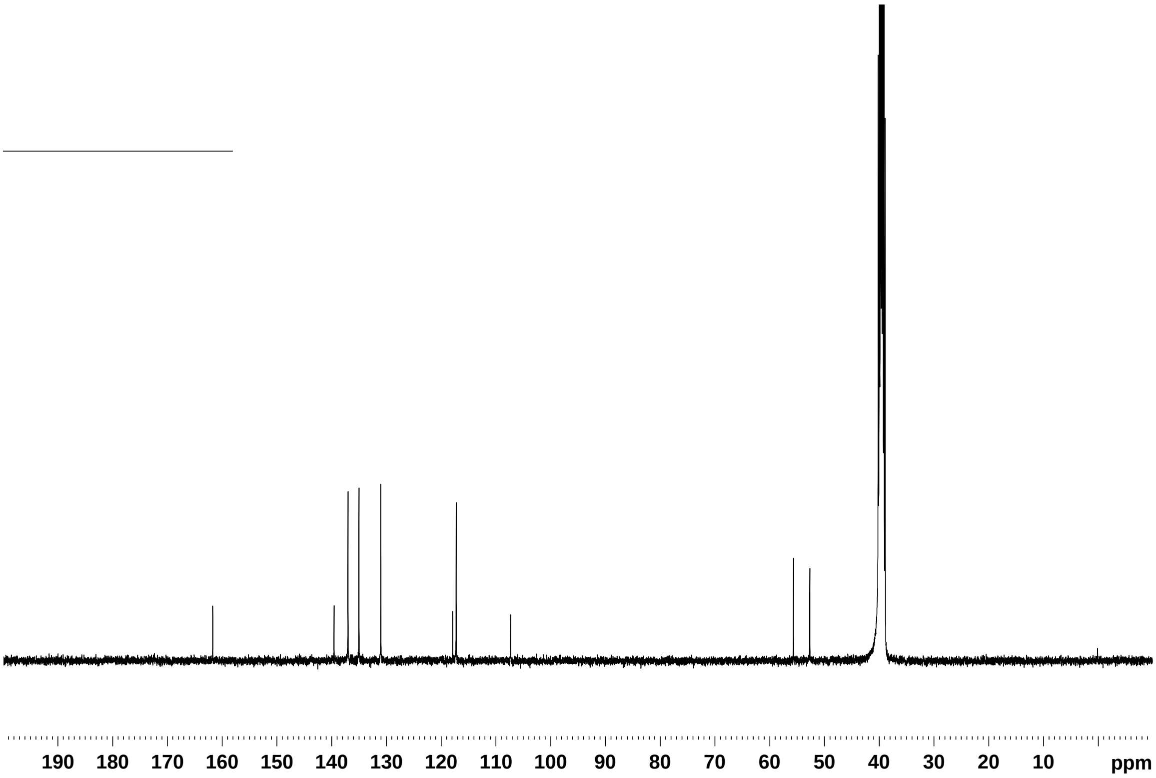
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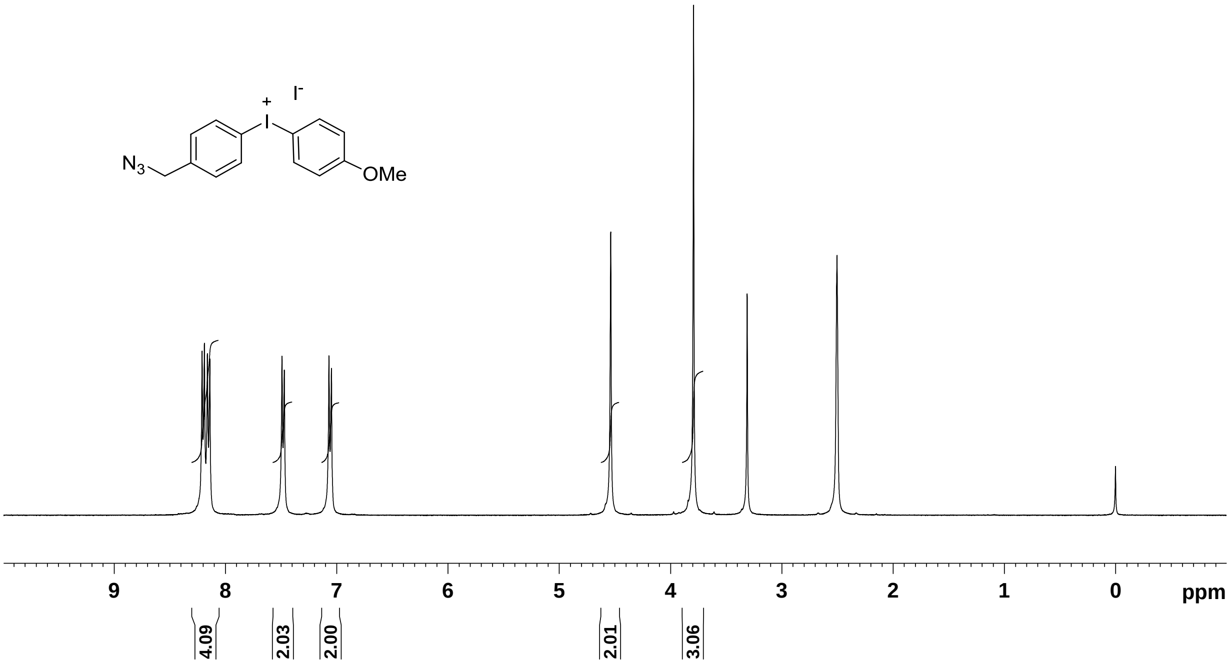
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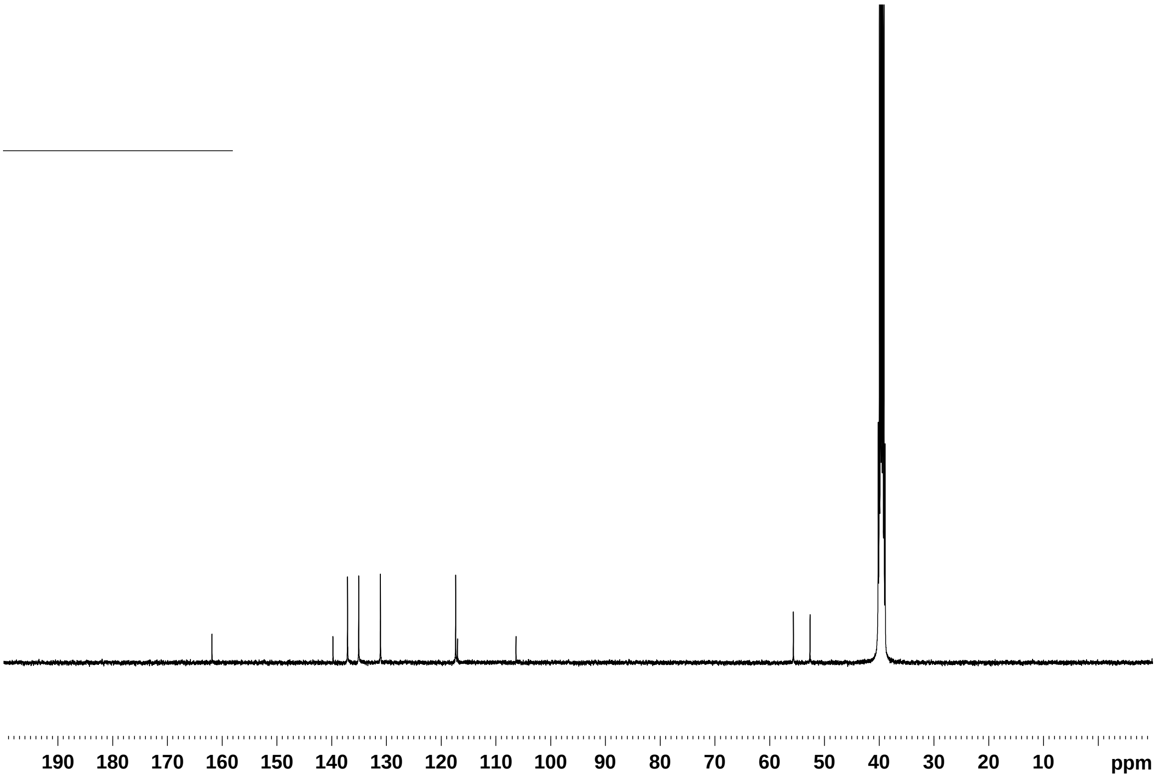
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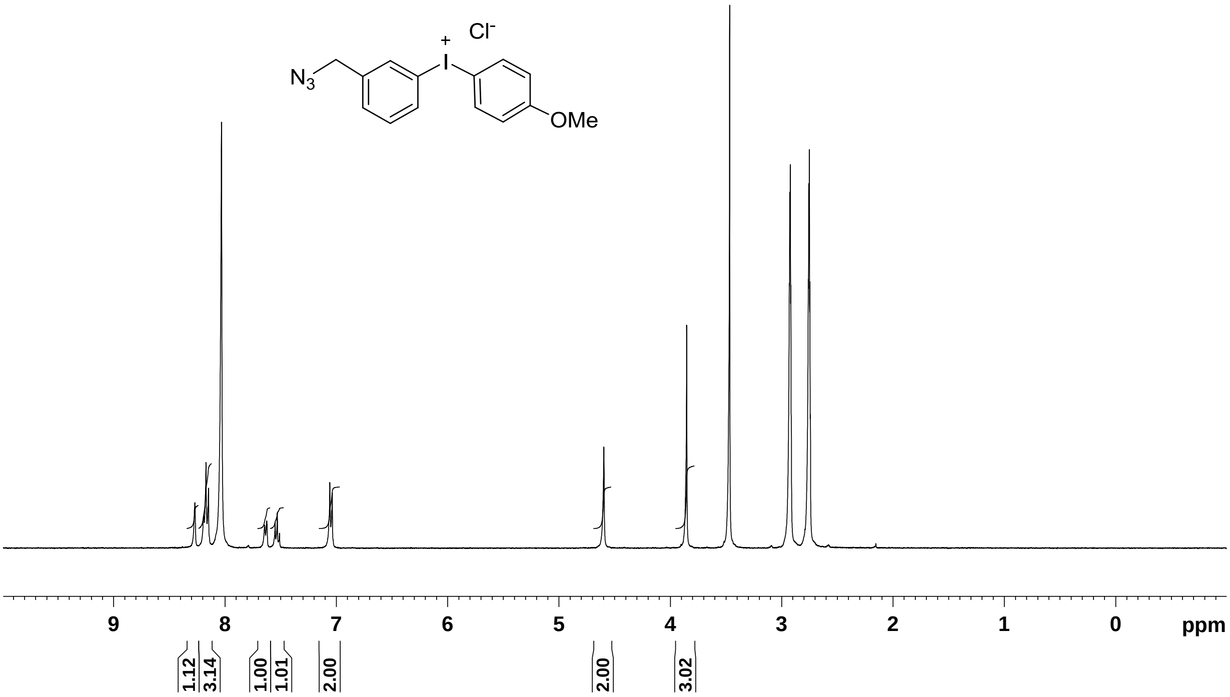

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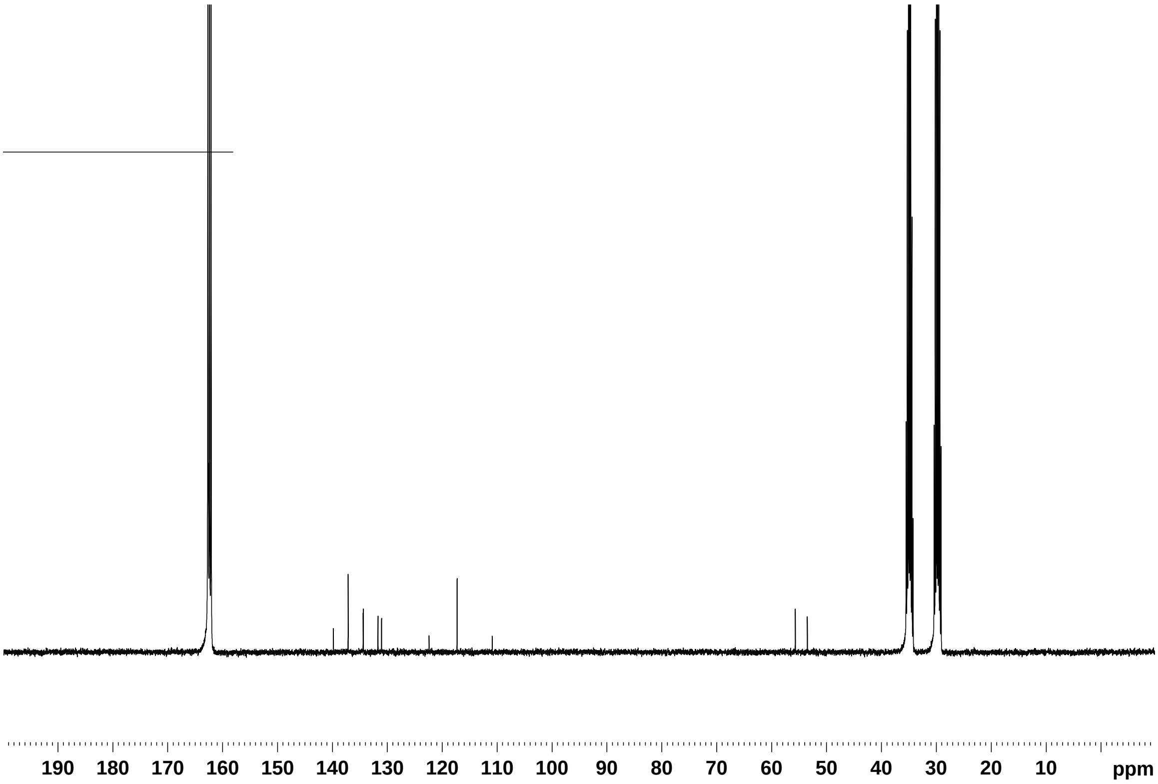

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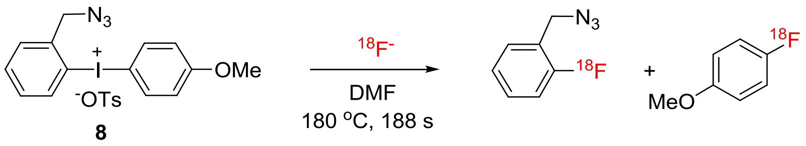
Appendix 2. Selected radio-HPLC chromatograms from analyses of reaction products from the radiofluorination of diaryliodonium salts.



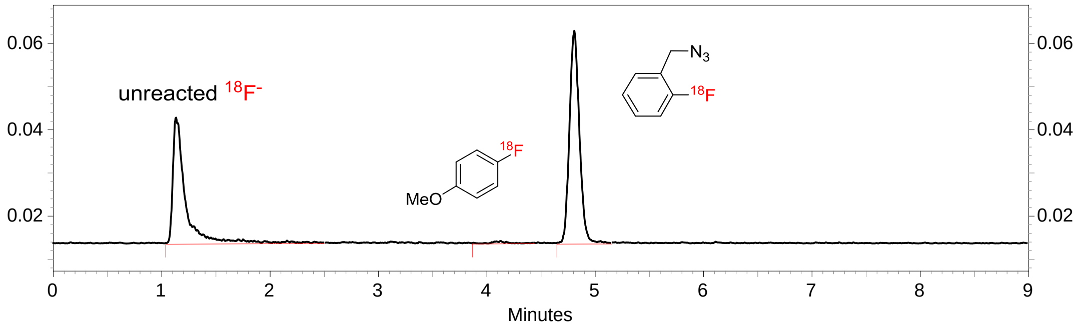
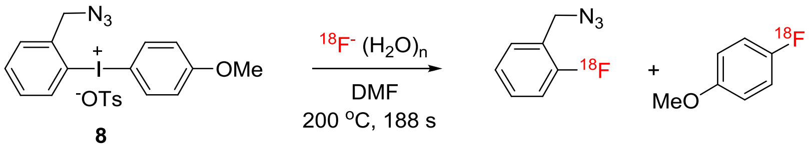


Figure S1. Radiochromatogram from the HPLC analysis of the products from the reaction of $[^{18}F]$fluoride ion with compound **8** at 180 °C for 188 s in DMF.



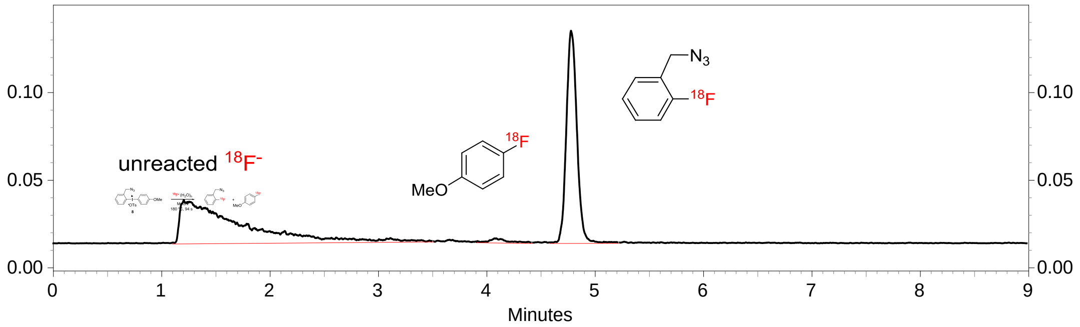
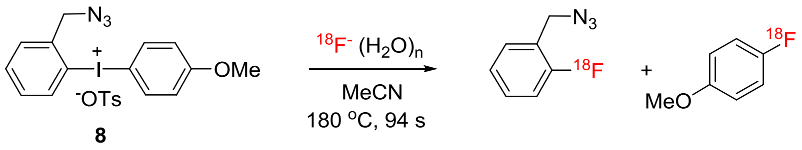


Figure S2. Radiochromatogram from the HPLC analysis of the products from the reaction of $[^{18}F]$fluoride ion with compound **8** at 200 °C for 188 s in DMF.



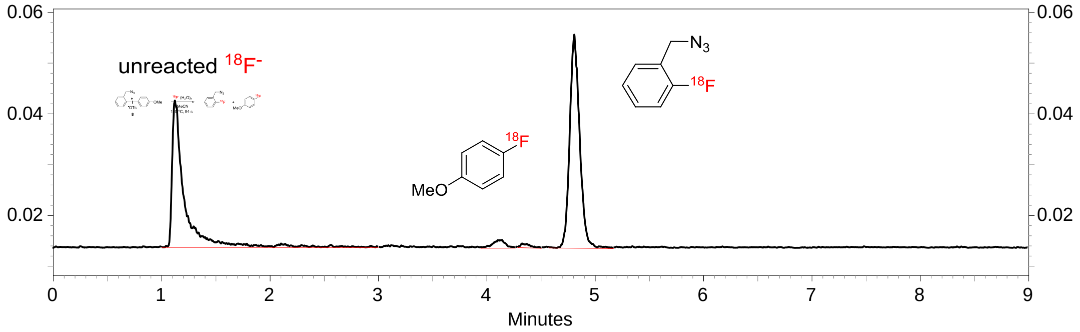


Figure S3. Radiochromatogram from the HPLC analysis of the products from the reaction of $[^{18}F]$fluoride ion with compound **8** at 180 °C for 94 s in MeCN.