Supplementary Material (ESI) for Organic and Biomolecular Chemistry

Tether influence on the binding properties of $tRNA^{Lys}_3$ ligands designed by a fragment based approach.

Roba Moumné,[a] Valéry Larue,[b] Bili Seijo,[b] Thomas Lecourt,[a] Laurent Micouin*[a] and Carine Tisné*[b]

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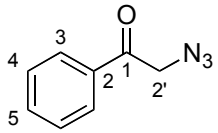
1. Chemistry

1.1. General Procedure for 2-Azido-Ketone Synthesis

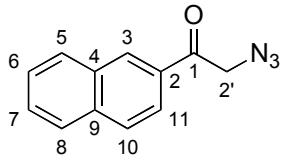
NaN_3 (2 eq) was added to a solution of the α-bromo-ketone in acetone (0.5 mol/L) at room temperature. The reaction was stirred for one hour. After addition of water the product was extracted with EtOAc, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by FC column chromatography on silica gel (Cyclohexane-AcOEt, 9:1).

2-azido-1-Phenylethanone 2a



(oil, 322 mg, 80%); Rf (Cy/ EtOAc, 9:1) 0.31; **2a** was identified by comparison of its spectral data to the literature,[1] δ_H (300 MHz, $CDCl_3$): 7.90 (m, 2H, H_3); 7.62 (1H, m, H_5); 7.49 (2H, t, *J* 9 Hz, H_4); 4.56 (2H, s, $H_{2'}$); δ_C (75 MHz, $CDCl_3$): 193.3 (s, C_1); 134.3 (s, C_2); 134.2 (d, C_5); 129.0 (d, C_3 or C_4); 127.9 (d, C_3 or C_4); 54.9 (t, $C_{2'}$).

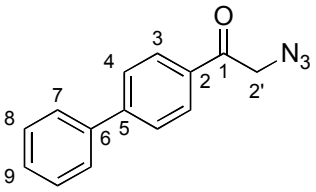
2-azido-1-(naphtalen-2-yl)ethanone 2b



(white powder, 300 mg, 71%); Rf (Cy/ EtOAc, 9:1) 0.30; mp 60-62°C; ν_{max}(KBr, nujol) /cm^{-1} 3103s, 1677s, 1628w, 1421w, 1356s, 1296w, 1275w, 1257w, 1218w, 1190m, 1123w, 912w, 898m, 859m; δ_H (300 MHz, $CDCl_3$): 8.40 (s, 1H, H_3); 7.88-7.97 (4H, m, H_5, H_8, H_{10}, H_{11}); 7.57-7.67 (2H, m, H_6, H_7); 4.71 (2H, s, $H_{2'}$); δ_C (75 MHz, $CDCl_3$): 193.2 (s, C_1); 136.0 (s, C_2); 132.4 (s, C_4 or C_9); 131.7 (s, C_4 or C_9); 129.8 (d, C_3); 129.6 (d, C_5); 129.1 (d, C_7); 129.0 (d, C_{10}); 127.9 (d, C_8); 127.2 (d, C_6); 123.3 (d, C_{11}); 55.0 (t, $C_{2'}$); *m/z* (ESI): 234 (MNa^+), calculated for $C_{12}H_9N_3O$ 211.

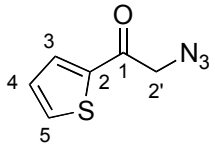
[1] K. Edegger, C. C. Gruber, T. M. Poessl, S. R. Wallner, I. Lavandera, K. Faber, F. Niehaus, J. Eck, R. Oehrlein, A. Hafner, W. Kroutil, *Chem. Comm*. 2006, **22**, 2402.

2-azido-1-(biphenyl-4-yl)ethanone 2c



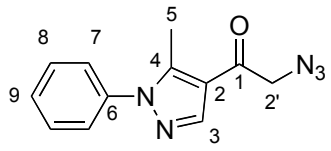
(white powder, 502 mg, 85%); Rf (Cy/ EtOAc, 9:1) 0.22; mp 92-93°C; ν_{max}(KBr, nujol) /cm^{-1} 2139m, 2100s, 1684s, 1604s, 1581w, 1460w, 1447w, 1420w, 1276s, 1226m, 1191w, 1116w, 1075w, 911m, 847m, 832m, 809w; δ_H (300 MHz, $CDCl_3$): 7.98 (2H, d, *J* 6 Hz, H_3); 7.72 (2H, d, *J* 9 Hz, H_4); 7.63 (2H, d, *J* 9 Hz, H_7); 7.26-7.52 (3H, m, H_8, H_9); 4.59 (2H, s, $H_{2'}$); δ_C (75 MHz, $CDCl_3$): 192.8 (s, C_1); 146.7 (s, C_5); 139.4 (s, C_6); 133 (s, C_2); 129.1 (d, C_8); 128.9 (d, C_9); 128.5 (d, C_3); 127.5 (d, C_4); 127.2 (d, C_7); 54.9 (t, $C_{2'}$); *m/z* (ESI): 260 (MNa^+), calculated for $C_{14}H_{11}N_3O$ 237.

2-azido-1-(thiophen-2yl)ethanone 2d



(brown powder, 144 mg, 72%); Rf (Cy/ EtOAc, 9:1) 0.30; mp 62-64°C; ν_{max}(KBr, nujol) /cm^{-1} 2107s, 1658s, 1516w, 1413m, 1305w, 1234w, 1059w, 892m, 851m; δ_H (300 MHz, $CDCl_3$): 7.74 (1H, dd, *J* 3 Hz, *J* 1 Hz, H_5); 7.72 (1H, dd, *J* 2 Hz, *J* 1 Hz, H_3); 7.17 (1H, dd, *J* 4.9 Hz, *J* 4 Hz, H_4); 4.46 (2H, s, $H_{2'}$); δ_C (75 MHz, $CDCl_3$): 186.3 (s, C_1); 140.0 (s, C_2); 135.0 (d, C_5); 132.5 (d, C_4); 128.5 (d, C_3); 54.9 (t, $C_{2'}$); *m/z* (ESI): 190 (MNa^+), calculated for $C_6H_5N_3OS$ 167.

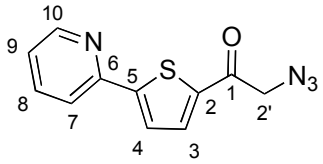
2-azido-1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone 2e



(white powder, 167 mg, 77%); Rf (Cy/ EtOAc, 9:1) 0.30; mp 88-89°C; ν_{max}(KBr, nujol) /cm^{-1} 2128m, 2105s, 1677s, 1600w, 1551m, 1504m, 1407w, 1331w, 1264m, 1221m, 1193w, 1173w, 995w, 938w, 908m, 871w; δ_H (300 MHz, $CDCl_3$): 7.96 (1H, s, H_3); 7.46-7.55 (3H, m); 7.38-7.44 (2H, m); 7.35 (2H, m, $H_{2'}$); 2.60 (3H, s, H_5); δ_C (75 MHz, $CDCl_3$): 188.7 (s,

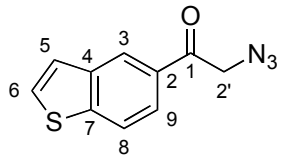
C_1); 144.2 (s, C_2); 140.4 (d, C_3); 138.2 (s, C_6); 129.4 (d); 129 (d); 125.5 (d); 117.9 (s, C_4); 55.7 (t, $C_{2'}$); 12.5 (q, C_5); *m/z* (ESI): 264 (MNa^+), calculated for $C_{12}H_{11}N_5O$ 241.

2-azido-1-(5-(pyridin-2-yl)thiophen-2-yl)ethanone 2f



(white powder, 191 mg, 88%); mp 151-155°C; δ_H (300 MHz, $CDCl_3$): 8.63 (1H, d, *J* 4.2 Hz, H_{10}); 7.61-7.79 (4H, m, H_3, H_4, H_7, H_8); 7.35 (1H, m, H_9); 4.46 (2H, m, $H_{2'}$); 2.60 (3H, s, H_5); δ_C (75 MHz, $CDCl_3$): δ_C (75 MHz, $CDCl_3$)*:* 188.7 (s, C_1); 144.2 (s, C_2); 140.4 (d, C_3); 138.2 (d, C_6); 129.4 (d); 129.0 (d); 125.5 (d); 117.9 (s, C_4); 55.7 (t, $C_{2'}$); 12.5 (q, C_5); *m/z* (ESI): 267 (MNa^+), calculated for $C_{11}H_8N_4OS$ 244.

2-azido-1-(benzothiophen-yl)ethanone 2g



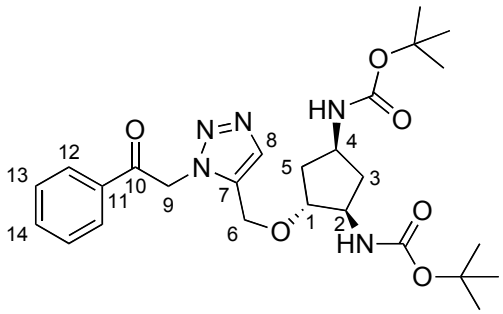
(white powder, 189 mg, 89%); Rf (Cy/ EtOAc, 8:2) 0.64; mp 113-115°C; ν_{max}(KBr, nujol) /cm^{-1} 2097s, 1685s, 1587w, 1417w, 1341w, 1317w, 1278w, 1221m, 1170w, 1154m, 1094w, 1057m, 931w, 920m, 908m, 882w, 820m, 800w; δ_H (300 MHz, $CDCl_3$): 8.34 (1H, s, H_3); 7.97 (1H, d, *J* 8.9 Hz, H_8); 7.87 (1H, d, *J* 8.9 Hz, H_9); 7.56 (1H, d, *J* 5.9 Hz, H_6); 7.45 (1H, d, *J* 4.9 Hz, H_5); 4.65 (3H, s, $H_{2'}$); δ_C (75 MHz, $CDCl_3$): 193.1 (s, C_1); 145.2 (s, C_7); 139.5 (s, C_4); 130.9 (s, C_2); 128.5 (d, C_9); 124.6, 124.0, 123.1, 122.9 (d, C_3, C_5, C_6, C_8); 55.0 (t, $C_{2'}$); *m/z* (ESI): 240 (MNa^+), calculated for $C_{10}H_7N_3OS$ 217.

1.2. General Procedure for RuAAC

Cp*RuCl(COD) (5 mg, 4 mol%) was introduced into a two-necked flask and the flask was evacuated under vacuum and filled with nitrogen three times. After addition of dried THF (1 mL), a solution of DACP (100 mg, 0.29 mmol) in THF (2 mL) and a solution of the azido-ketone (0.29 mmol) in THF (2 mL) were added successively. The reaction was stirred for one

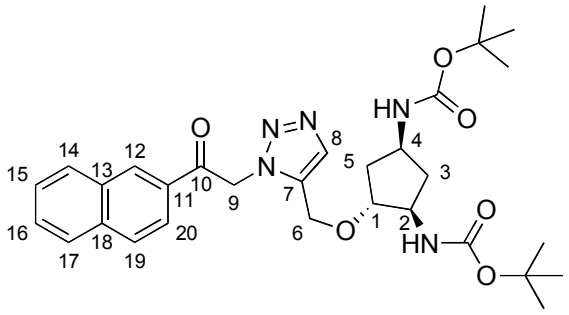
hour. The solution was concentrated *in vacuo* and the crude product was purified by FC column chromatography on silica gel (Cyclohexane-AcOEt, 4:6).

tert-butyl-4-((1-(2-oxo-2-phenylethyl)-1*H*-1,2,3-triazol-5-yl)methoxy)cyclopentane-1,3-dicarbamate 4a



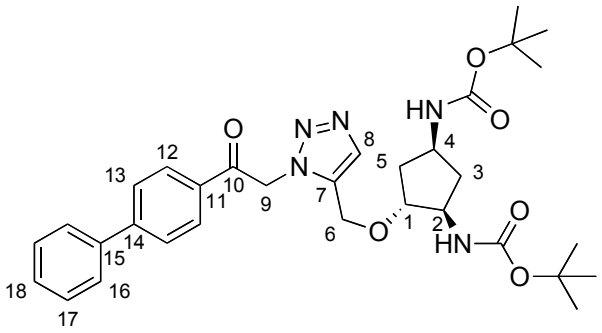
(powder, 116 mg, 80%); Rf (Cy/ EtOAc, 4:6) 0.33; mp 68-72°C; ν_{max}(KBr, nujol) /cm^{-1} 3334br, 1694s, 1598w, 1515s, 1298w, 1250w, 1165m, 1071w, 1001w, 861w; δ_H (300 MHz, $CDCl_3$): 8.03 (2H, dd, *J* 1.3 Hz, 7 Hz, H_{12}); 7.68 (1H, s, H_8); 7.66 (1H, tt, *J* 2 Hz, 7 Hz, H_{14}); 7.54 (2H, t, *J* 7 Hz, H_{13}); 6.04 (1H, d (AB), *J* 18 Hz, H_9); 5.92 (1H, d (AB), *J* 18 Hz, H_9); 5 (1H, br s, NH); 4.73 (1H, br s, NH); 4.67 (1H, d (AB), *J* 11 Hz, H_6); 4.59 (1H, d (AB), *J* 11 Hz, H_6); 3.86 (1H, m, H_4); 3.78-3.80 (1H, m, H_2); 3.69 (1H, dt, *J* 3 Hz, *J* 6 Hz, H_1); 2.39 (1H, dt, *J* 8 Hz, *J* 15 Hz, H_3); 1.84 (1H, ddd, *J* 3 Hz, *J* 7 Hz, *J* 13 Hz, H_5); 1.69-1.76 (1H, m, H_5); 1.43 (18H, s); 1.29 (1H, dt, *J* 7 Hz, *J* 15 Hz, H_3); δ_C (75 MHz, $CDCl_3$): 190.8 (s, C_{10}); 155.3 (s, CO_{Boc}); 134.7 (s, C_7); 134.4 (d, C_{14}); 134.2 (d, C_{11}); 134.0 (d, C_8); 129.2 (d, C_{12} or C_{13}); 128.3 (d, C_{12} or C_{13}); 83.7 (d, C_1); 79.6 (s, $C_{iv\ Boc}$); 59.3 (t, C_6); 55.6 (d, C_2); 54.7 (t, C_9); 49.4 (d, C_4); 37.3 (t, C_3 and C_5); 26.9 (q, C_{tBu}); *m/z* (ESI): 538 (MNa^+), calculated for $C_{26}H_{37}N_5O_6$ 515.

tert-butyl-4-((1-(2-oxo-2-naphtylethyl)-1*H*-1,2,3-triazol-5-yl)methoxy)cyclopentane-1,3-dicarbamate 4b



(powder, 104 mg, 66%); Rf (Cy/ EtOAc, 4:6) 0.45; mp 90-92°C; ν_{max}(KBr, nujol) /cm^{-1} 3333br, 1694s, 1515s, 1366m, 1297w, 1276w, 1254w, 1167m, 1125w, 1072w, 1008w, 861w, 823w; δ_H (300 MHz, $CDCl_3$): 8.60 (1H, s, H_{12}); 8.02-8.06 (2H, m, H_{14}, H_{20}); 7.89-7.97 (2H, m, H_{17}, H_{19}); 7.71 (1H, s, H_8); 7.66 (1H, td, *J* 3 Hz, *J* 9 Hz, H_{16}); 7.60 (1H, td, *J* 3 Hz, *J* 6 Hz, H_{15}); 6.20 (1H, d (AB), *J* 18 Hz, H_9); 6.06 (1H, d (AB), *J* 18 Hz, H_9); 4.96 (1H, br s, NH); 4.75 (2H, d (AB) + br s, *J* 13 Hz, H_6, NH); 4.66 (1H, d (AB), *J* 13 Hz, H_6); 3.87 (1H, m, H_4); 3.73-3.78 (1H, m, H_2); 3.71 (1H, dt, *J* 3 Hz, 6 Hz, H_1); 2.38 (1H, dt, *J* 8 Hz, 14 Hz, H_3); 1.86 (1H, ddd, *J* 3 Hz, 8 Hz, 14 Hz, H_5); 1.60-1.69 (1H, m, H_5); 1.42 (18H, s); 1.29 (1H, dt, *J* 7 Hz, 14 Hz, H_3); δ_C (75 MHz, $CDCl_3$): 190.8 (s, C_{10}); 155.3 (s, CO_{Boc}); 136.1 (s, C_{11}); 134.8 (s, C_7); 133.9 (d, C_8); 132.4 (s, C_{13} or C_{18}); 131.4 (s, C_{13} or C_{18}); 130.4 (d, C_{12}); 129.8 (d, C_{14}); 129.2 (d, C_{16} or C_{19}); 129.1 (d, C_{16} or C_{19}); 127.9 (d, C_{17}); 127.2 (d, C_{15}); 123.3 (d, C_{20}); 83.8 (d, C_1); 79.5 (s, $C_{iv\ Boc}$); 59.3 (t, C_6); 55.5 (d, C_2); 54.7 (t, C_9); 49.3 (d, C_4); 37.2 (2 x t, C_3 and C_5); 28.4 (q, C_{tBu}); *m/z* (ESI): 588 (MNa^+), calculated for $C_{30}H_{39}N_5O_6$ 565.

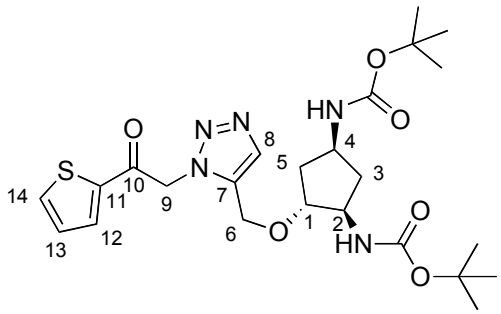
tert-butyl-4-((1-(2-oxo-2-(1,1'-biphenyl-4-yl)ethyl)-1*H*-1,2,3-triazol-5-yl)methoxy) cyclo pentane -1,3-dicarbamate 4c



(powder, 105 mg, 63%); Rf (Cy/ EtOAc, 4:6) 0.33; mp 96-98°C; ν_{max}(KBr, nujol) /cm^{-1} 3334br, 1694s, 1604w, 1515m, 1505m, 1297w, 1234w, 1164w, 1073w, 998w, 843w; δ_H (300 MHz, $CDCl_3$): 8.12 (2H, d, *J* 6 Hz, H_{12}); 7.77 (2H, d, *J* 9 Hz, H_{13}); 7.71 (1H, s, H_8); 7.62-7.67 (2H, m, H_{16}); 7.42-7.53 (3H, m, H_{17}, H_{18}); 6.09 (1H, d (AB), *J* 18 Hz, H_9); 5.97 (1H, d (AB), *J* 18 Hz, H_9); 4.97-4.99 (1H, br s, NH); 4.75 (1H, d (AB), *J* 15 Hz, H_6); 4.66 (2H, d (AB) + br s, *J* 15 Hz, H_6, NH); 3.89 (1H, m, H_4); 3.79-3.81 (1H, m, H_2); 3.72 (1H, dt, *J* 3 Hz, 6 Hz, H_1); 2.42 (1H, dt, *J* 7.5 Hz, 15 Hz, H_3); 1.84-1.91 (1H, m, H_5); 1.60-1.79 (1H, m, H_5); 1.43 (18H, s); 1.33 (1H, dt, *J* 6 Hz, 15 Hz, H_3); δ_C (75 MHz, $CDCl_3$): 190.4 (s, C_{10}); 155.2 (s, CO_{Boc}); 147.1 (s, C_{14}); 139.5 (s, C_{15}); 134.6 (s, C_7); 134.0 (d, C_8); 132.8 (s, C_{11}); 129.1 (d, C_{12} or C_{17}); 128.8 (d, C_{12} or C_{17}); 128.6 (d, C_{18}); 127.7 (d, C_{13} or C_{16}); 127.3 (d, C_{13} or C_{16}); 83.7 (d, C_1);

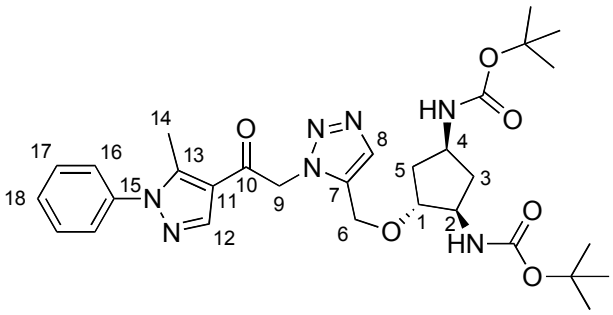
79.7 (s, $C_{iv\ Boc}$); 59.3 (t, C_6); 55.6 (d, C_2); 54.7 (t, C_9); 49.3 (d, C_4); 37.3 (t, C_3 and C_5); 28.4 (q, C_{tBu}); *m/z* (ESI): 614 (MNa^+), calculated for $C_{32}H_{41}N_5O_6$ 591.

tert-butyl-4-((1-(2-oxo-2-thienylethyl)-1*H*-1,2,3-triazol-5-yl)methoxy)cyclopentane-1,3-dicarbamate 4d



(powder, 74 mg, 51%); Rf (Cy/ EtOAc, 4:6) 0.31; mp 88-90°C; δ_H (300 MHz, $CDCl_3$): 7.87 (1H, d, *J* 4 Hz, H_{14}); 7.74 (1H, d, *J* 4.8 Hz, H_{12}); 7.63 (1H, s, H_8); 7.19 (1H, dd, *J* 4.8 Hz, *J* 4 Hz, H_{13}); 5.93 (1H, d (AB), *J* 17.5 Hz, H_9); 5.83 (1H, d (AB), *J* 17.5 Hz, H_9); 5.21 (1H, br s, NH); 4.98 (1H, br s, NH); 4.69 (1H, d (AB), *J* 13 Hz, H_6); 4.62 (1H, d (AB), *J* 13 Hz, H_6); 3.78-3.88 (2H, m, H_4, H_2); 3.67-3.69 (1H, m, H_1); 2.37 (1H, dt, *J* 8 Hz, 13.8 Hz, H_3); 1.79-1.82 (1H, m, H_5); 1.70-1.75 (1H, m, $H_{5'}$); 1.26-1.42 (19H, m, CH_3 (tBu), $H_{3'}$); δ_C (75 MHz, $CDCl_3$): 183.8 (s, C_{10}); 155.2 (s, CO_{Boc}); 140.4 (s, C_{11}); 135.4 (d, C_{14}); 134.7 (s, C_7); 133.9 (d, C_8); 133.2 (d, C_{13}); 128.7 (d, C_{12}); 83.8 (d, C_1); 79.5 (s, $C_{iv\ Boc}$); 59.3 (t, C_6); 55.5 (d, C_2); 54.5 (t, C_9); 49.3 (d, C_4); 37.2 (t, C_3 and C_5); 28.4 (q, C_{tBu}); *m/z* (ESI): 544 (MNa^+), calculated for $C_{24}H_{35}N_5O_6S$ 521.

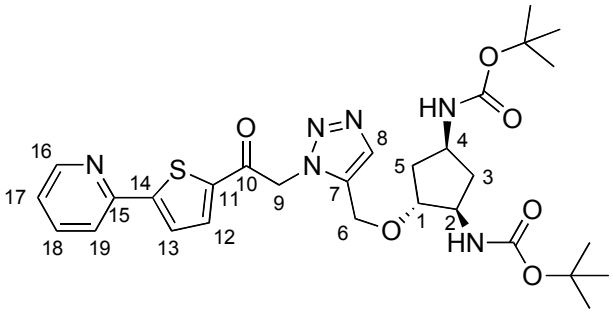
tert-butyl-4-((1-(2-oxo-2-(5-methyl-1-phenylpyrazol-4-yl)ethyl)-1*H*-1,2,3-triazol-5-yl) methoxy)cyclopentane-1,3-dicarbamate 4e



(Powder, 100 mg, 60%); Rf (Cy/ EtOAc, 4:6) 0.26; mp 86-90°C; δ_H (300 MHz, $CDCl_3$): 8.15 (1H, s, H_{12}); 7.67 (1H, s, H_8); 7.42-7.55 (5H, m, H_{16}, H_{17}, H_{18}); 5.84 (1H, d (AB), *J* 17 Hz, H_9); 5.73 (1H, d (AB), *J* 17 Hz, H_9); 5.08 (1H, br s, NH); 4.81 (1H, br s, NH); 4.73 (1H, d

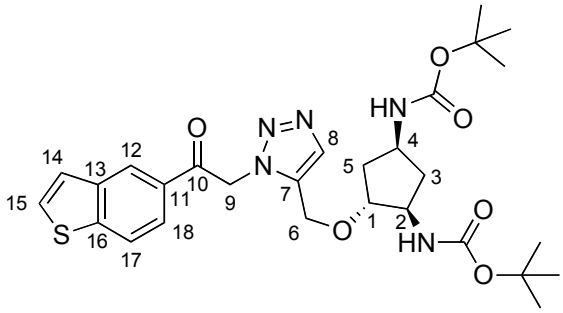
(AB), *J* 13.6 Hz, H_6); 4.65 (1H, d (AB), *J* 13.6 Hz, H_6); 3.81-3.95 (2H, m, H_4, H_2); 3.71-3.73 (1H, m, H_1); 2.60 (3H, s, H_{14}); 2.44 (1H, dt, *J* 8 Hz, *J* 13.6 Hz, H_3); 1.87-1.94 (1H, m, H_5); 1.70-1.79 (1H, m, $H_{5'}$); 1.24-1.42 (19H, m, CH_3 (tBu), $H_{3'}$); δ_C (75 MHz, $CDCl_3$): 186.0 (s, C_{10}); 155.2 (s, CO_{Boc}); 144.5 (s, C_{11}); 140.7 (s, C_{13}); 138.2 (s, C_{15}); 134.7 (s, C_7); 134.0 (d, C_8); 129.4 (d, C_{16} or C_{17}); 129.2 (d, C_{18}); 125.6 (d, C_{16} or C_{17}); 117.8 (d, C_{12}); 83.7 (d, C_1); 79.6 (s, $C_{iv\ Boc}$); 59.3 (t, C_6); 55.6 (d, C_2); 55.4 (t, C_9); 49.5 (d, C_4); 37.2 (t, C_3 and C_5); 28.4 (q, C_{tBu}); 12.5 (q, C_{14}); *m/z* (ESI): 618 (MNa^+), calculated for $C_{30}H_{41}N_7O_6$ 595.

tert-butyl-4-((1-(2-oxo-2-(5-(pyridin-2-yl)thiophen-2-yl)ethyl)-1*H*-1,2,3-triazol-5-yl) methoxy) cyclopentane-1,3-dicarbamate 4f



(powder, 73 mg, 44%); Rf (Cy/ EtOAc, 4:6) 0.25; mp 113-115°C; ν_{max}(KBr, nujol) /cm^{-1} 3327br, 1686s, 1583w, 1510m, 1430m, 1365m, 1295w, 1243m, 1164m, 1076w, 995w; δ_H (300 MHz, $CDCl_3$): 8.61 (1H, dt, *J* 7.5 Hz, 1.5 Hz, H_{16}); 7.86 (1H, d, *J* 7.5 Hz, H_{12}); 7.71-7.79 (2H, m, $H_{17,}$ H_{18}); 7.66 (1H, s, H_8); 7.63 (1H, d, *J* 7.5 Hz, H_{13}); 7.27 (1H, ddd, *J* 7.5 Hz, 7.5 Hz, 1.5 Hz, H_{17}); 5.92 (1H, d (AB), *J* 15 Hz, H_9); 5.84 (1H, d (AB), *J* 15 Hz, H_9); 5.1 (1H, br s, NH); 4.82-4.84 (1H, br s, NH); 4.73 (1H, d (AB), *J* 15 Hz, H_6); 4.65 (1H, d (AB), *J* 15 Hz, H_6); 3.79-3.91 (2H, m, H_4, H_2); 3.69-3.73 (1H, m, H_1); 2.40 (1H, dt, *J* 9 Hz, 12 Hz, H_3); 1.71-1.89 (2H, m, H_5); 1.29-1.43 (19H, m, CH_3 (tBu), $H_{3'}$); δ_C (75 MHz, $CDCl_3$): 183.8 (s, C_{10}); 155.3 (s, CO_{Boc}); 154 (s, C_{14}); 151 (s, C_{15}); 150 (d, C_{16}); 140.6 (d, C_{11}); 137.1 (d, C_{18}); 134.7 (s, C_7); 134 (d, C_8 and C_{12}); 125.4 (d, C_{13}); 123.7 (d, C_{17}); 119.8 (d, C_{19}); 83.9 (d, C_1); 79.5 (s, $C_{iv\ Boc}$); 59.4 (t, C_6); 55.6 (d, C_2); 55.5 (t, C_9); 49.4 (d, C_4); 37.3 (t, C_3 and C_5); 28.4 (q, C_{tBu}); *m/z* (ESI): 621 (MNa^+), calculated for $C_{29}H_{38}N_6O_6S$ 598.

tert-butyl-4-((1-(2-(benzothiophen-5-yl)-2-oxoethyl)-1_H_-1,2,3-triazol-5-yl)methoxy) cyclopentane-1,3-dicarbamate 4g

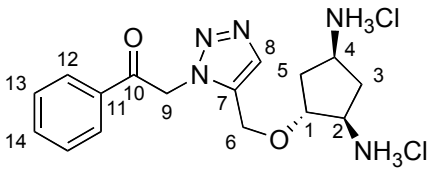


(powder, 123 mg, 74%); Rf (Cy/ EtOAc, 4:6) 0.36; mp 132-136°C; δ_H (300 MHz, $CDCl_3$): 8.53 (1H, s, H_{12}); 7.95-8.02 (2H, m, H_{17}, H_{18}); 7.7 (1H,s, H_8); 7.58 (1H, d, *J* 5.3 Hz, H_{15}); 7.49 (1H, d, *J* 5.3 Hz, H_{14}); 6.15 (1H, d (AB), *J* 18 Hz, H_9); 6.01 (1H, d (AB), *J* 18 Hz, H_9); 5.1 (1H, br s, NH); 4.62-4.71 (3H, m, NH and H_6); 3.69-3.90 (2H, m, H_4, H_2, H_1); 2.38 (1H, dt, *J* 8 Hz, *J* 14 Hz, H_3); 1.71-1.88 (2H, m, H_5); 1.27-1.43 (19H, m, CH_3 (tBu), H_3); δ_C (75 MHz, $CDCl_3$): 190.7 (s, C_{10}); 155.3 (s, CO_{Boc}); 145.3 (s, C_{16}); 139.6 (s, C_{13}); 134.7 (s, C_7); 134 (d, C_8); 130.7 (s, C_{11}); 128.5 (d, C_{15}); 124.8 (d, C_{14}); 124.4 (d, C_{12}); 123.3 (d, C_{17} or C_{18}); 123 (d, C_{17} or C_{18}); 83.7 (d, C_1); 79.7 (s, $C_{iv\ Boc}$); 59.4 (t, C_6); 55.6 (d, C_2); 54.8 (t, C_9); 49.5 (d, C_4); 37.4 (t, C_3 and C_5); 28.4 (q, C_{tBu}); *m/z* (ESI): 594 (MNa^+), calculated for $C_{28}H_{37}N_5O_6S$ 571.

1.3. General Procedure for Boc-Deprotection

A solution of the Boc-protected triazole derivative was cooled in an ice-bath and HCl (*g*) was bubbled inside until the formation of a white precipitate (few minutes). The solution was concentrated *in vacuo*.

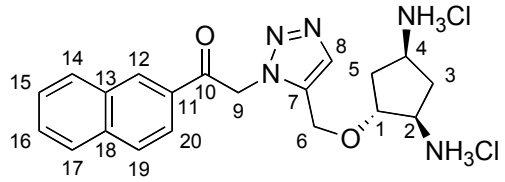
4-((1-(2-oxo-2-phenylethyl)-1_H_-1,2,3-triazol-5-yl)methoxy)cyclopentane-1,3-diamine chloride 5a



(Powder, 60 mg); Rf (BuOH/ AcOH/ H_2O, 4:1:5) 0.12; mp 162-164°C; UV absorptions: $\lambda_{max}(H_2O)$/nm 250 and 290; δ_H (300 MHz, CD_3OD): 8.15-8.17 (2H, m, H_{12}); 8.05 (1H, s, H_8); 7.73-7.77 (1H, m, H_{14}); 7.62 (2H, m, H_{13}); 6.26 (2H, s, H_9); 4.79 (2H, s, H_6); 4.26 (1H, m, H_1); 3.58-3.62 (1H, m, H_4); 3.46 (1H, m, H_2); 2.56 (1H, m, H_3); 2.14 (2H, m, H_5); 1.80 (1H,

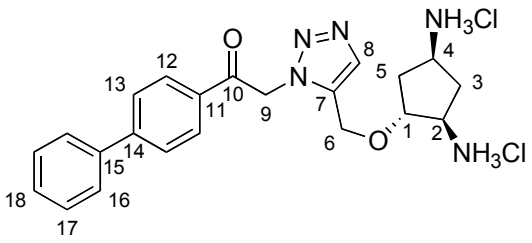
m, H_3); δ_C (75 MHz, CD_3OD): 193.1 (s, C_{10}); 136.0 (d, C_{14}); 135.5 (s, C_{11}); 130.5 (d, C_{12} or C_{13}); 129.8 (d, C_{12} or C_{13}); 81.9 (d, C_1); 61.4 (t, C_6); 56.5 (d and t, C_2 and C_9); 48.6 (d, C_4); 35.5 (t, C_5); 34.2 (t, C_3); *m/z* (HRMS ESI): 316.1768 (MH^+), calculated for $C_{16}H_{22}N_5O_2$ 316.1768.

4-((1-(2-oxo-2-naphtylethyl)-1*H*-1,2,3-triazol-5-yl)methoxy)cyclopentane-1,3-damine chloride 5b



(Powder, 58 mg); Rf (BuOH/ AcOH/ H_2O, 4:1:5) 0.2; mp 176-179°C; UV absorptions: $\lambda_{max}(H_2O)$/nm 290 and 350; δ_H (300 MHz, CD_3OD): 8.86 (1H, s, H_{12}); 7.99-8.17 (5H, m, H_8, H_{14}, H_{17}, H_{19}, H_{20}); 7.64-7.74 (2H, m, H_{15}, H_{16}); 6.39 (2H, s, H_9); 4.81 (2H, s, H_6); 4.25 (1H, dt, *J* 5.8 Hz, *J* 11.5 Hz, H_1); 3.62-3.67 (1H, m, H_4); 3.42-3.50 (1H, m, H_2); 2.55 (1H, dt, *J* 7.1 Hz, *J* 13.2 Hz, H_3); 2.11-2.16 (2H, m, H_5); 1.78 (1H, dt, *J* 10 Hz, *J* 13.1 Hz, $H_{3'}$); δ_C (75 MHz, CD_3OD): 193 (s, C_{10}); 137.8 (s); 134.1 (d (C_8) and s); 132.7 (s); 132.4 (d); 131.1 (d); 130.8 (d); 130.3 (d); 129.2 (d); 128.6 (d); 124.4 (d); 81.9 (d, C_1); 61.3 (t, C_6); 56.6 (d, C_9); 56.4 (t, C_2); 48.4 (d, C_4); 35.4 (t, C_5); 34.1 (t, C_3); *m/z* (HRMS ESI): [MH^+] 366.1925 (Calculated for $C_{20}H_{24}N_5O_2$ 366.1925).

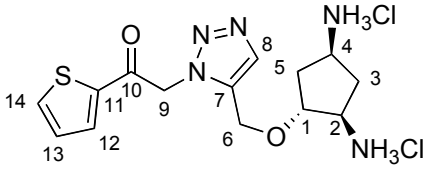
4-((1-(2-oxo-2-(1,1'-biphenyl-4-yl)ethyl)-1*H*-1,2,3-triazol-5-yl)methoxy)cyclopentane-1,3-diamine chloride 5c



(Powder, 37 mg); Rf (BuOH/ AcOH/ H_2O, 4:1:5) 0.28; mp 169-171°C; UV absorptions: $\lambda_{max}(H_2O)$/nm 290; δ_H (300 MHz, CD_3OD): 8.24 (2H, d, *J* 8 Hz, H_{12}); 8.23 (1H, s, H_8); 7.89 (2H, d, *J* 7 Hz, H_{13}); 7.73 (2H, d, *J* 7 Hz, H_{16}); 7.41-7.53 (3H, m, H_{17}, H_{18}); 6.36 (2H, s, H_9); 4.85 (2H, s, H_6); 4.30 (1H, m, H_1); 3.68 (1H, m, H_4); 3.51 (1H, m, H_2); 2.59 (1H, m, H_3); 2.18 (2H, m, H_5); 1.80-1.84 (1H, m, H_3); δ_C (75 MHz, CD_3OD): 192.5 (s, C_{10}); 148.7 (s, C_{14}); 140.7 (s, C_{15}); 134.0 (s, C_{11}); 130.5 (d, C_{12} or C_{17}); 130.3 (d, C_{12} or C_{17}); 129.9 (d, C_{18}); 128.8

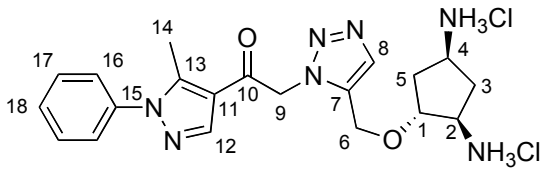
(d, C_{13} or C_{16}); 128.4 (d, C_{13} or C_{16}); 81.9 (d, C_1); 61.3 (t, C_6); 56.9 (t, C_9); 56.4 (d, C_2); 48.5 (d, C_4); 35.4 (t, C_5); 34.2 (t, C_3); *m/z* (HRMS ESI): $[MH]^+$ 392.2081 (Calculated for $C_{22}H_{26}N_5O_2$ 392.2081).

4-((1-(2-oxo-2-(thiophenyl-2-yl)ethyl)-1*H*-1,2,3-triazol-5-yl)methoxy)cyclopentane-1,3-diamine chloride 5d



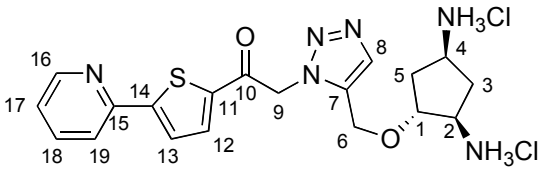
(Powder, 36 mg); Rf (BuOH/ AcOH/ H_2O, 4:1:5) 0.05; mp 176°C; UV absorptions: $\lambda_{max}(H_2O)$/nm 265 and 295; δ_H (300 MHz, CD_3OD): 8.21 (1H, d, *J* 3.7 Hz, H_{14}); 8.06 (1H, s, H_8); 8.04 (1H, d, *J* 5.4 Hz, H_{12}); 7.34 (1H, dd, *J* 3.8 Hz, *J* 5 Hz, H_{13}); 6.2 (2H, s, H_9); 4.81 (2H, s, H_6); 4.26 (1H, m, H_1); 3.58-3.66 (1H, m, H_4); 3.43-3.50 (1H, m, H_2); 2.57 (1H, dt, *J* 6.8 Hz, *J* 13.8 Hz, H_3); 2.13-2.17 (2H, m, H_5); 1.81 (1H, dt, *J* 9.4 Hz, *J* 13.4 Hz, $H_{3'}$); δ_C (75 MHz, CD_3OD): 186.1 (s, C_{10}); 141.6 (s, C_{11}); 137.6 (d, C_{14}); 137.4 (s, C_7); 136.0 (d, C_{13}); 134.0 (d, C_8); 130.4 (d, C_{12}); 82.9 (d, C_1); 61.1 (t, C_6); 56.4 (d, C_2); 56.1 (t, C_9); 48.7 (d, C_4); 35.3 (d, C_5); 34.2 (t_2, C_3); *m/z* (HRMS ESI): $[MH]^+$ 322.1327 (Calculated for $C_{14}H_{20}N_5O_2S$: 322.1321).

4-((1-(2-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-oxoethyl)-1*H*-1,2,3-triazol-5-yl)methoxy) cyclopentane-1,3-diamine chloride 5e



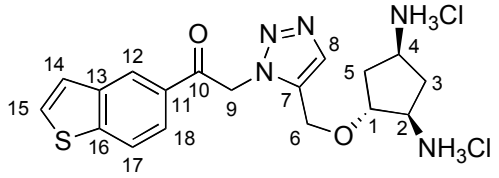
(Powder, 34 mg); Rf (BuOH/ AcOH/ H_2O, 4:1:5) 0.16; mp 182°C; UV absorptions: $\lambda_{max}(H_2O)$/nm 255; δ_H (300 MHz, CD_3OD): 8.47 (1H, s, H_{12}); 8.30 (1H, s, H_8); 7.52-7.61 (5H, m, H_{16}, H_{17}, H_{18}); 6.16 (2H, s, H_9); 4.87 (2H, s, H_9); 3.34 (1H, m, H_1); 3.76 (1H, m, H_4); 3.60 (1H, m, H_2); 2.66 (1H, m, H_3); 2.58 (3H, s, H_{14}); 2.22 (2H, m, H_5); 1.87 (1H, m, $H_{3'}$); δ_C (75 MHz, CD_3OD): 187.8 (s, C_{10}); 146.3 (s, C_{11}); 142.8 (s, C_{13}); 139.5 (s, C_{15}); 130.8 (d, C_{16} or C_{17}); 130.7 (d, C_{18}); 127.1 (d, C_{16} or C_{17}); 119.0 (d, C_{12}); 81.8 (d, C_1); 61.2 (t, C_6); 57.4 (t, C_9); 56.5 (d, C_2); 48.9 (d, C_4); 35.4 (t, C_5); 34.2 (t, C_3); 12.8 (q, C_{14}); *m/z* (HRMS ESI): $[MH]^+$ 396.2142 (Calculated for $C_{20}H_{26}N_7O_2$ 396.2142).

4-((1-(2-oxo-2-(5-(pyridin-2-yl)thiophen-2-yl)ethyl)-1*H*-1,2,3-triazol-5-yl) methoxy) cyclopentane-1,3-diamine chloride 5f



(Powder, 31 mg); Rf (BuOH/ AcOH/ H_2O, 4:1:5) 0.13; mp 194-195°C; UV absorptions: $\lambda_{max}(H_2O)$/nm 336; δ_H (300 MHz, CD_3OD): 8.83 (1H, d, *J* 5 Hz, H_{16}); 8.57 (1H, t, *J* 8 Hz, H_{18}); 8.42 (1H, d, *J* 8 Hz, H_{19}); 8.37 (1H, d, *J* 4 Hz, H_{12}); 8.18 (1H, d, *J* 4 Hz, H_{13}); 8.12 (1H, s, H_8); 7.97 (1H, t, *J* 6 Hz, H_{17}); 6.34 (2H, s, H_9); 4.86 (2H, s, H_6); 4.30-4.32 (1H, m, H_1); 3.68-3.71 (1H, m, H_4); 3.53-3.58 (1H, m, H_2); 2.61-2.66 (1H, m, H_3); 2.17-2.21 (2H, m, H_5); 1.80-1.85 (1H, m, H_3); δ_C (75 MHz, CD_3OD): 186.2 (s, C_{10}); 147.6 (s, C_{14}); 147.1 (d, C_{16}); 145.5 (s, C_{15}); 145.1 (d, C_{18}); 144.6 (s, C_{11}); 137.9 (s, C_7); 136.7 (d, C_{12}); 133.8 (d, C_8); 132.5 (d, C_{13}); 127.5 (d, C_{17}); 126.4 (d, C_{19}); 82.1 (d, C_1); 62.1 (t, C_6); 56.4 (d, C_2); 56.4 (t, C_9); 49 (d, C_4); 35.5 (t, C_5); 34.2 (t, C_3); *m/z* (HRMS ESI): $[MH]^+$ 399.1598 (Calculated for $C_{19}H_{23}N_6O_2S$ 399.1598).

4-((1-(2-(benzothiophen-5-yl)-2-oxoethyl)-1*H*-1,2,3-triazol-5-yl)methoxy) cyclopentane-1,3-diamine chloride 5g

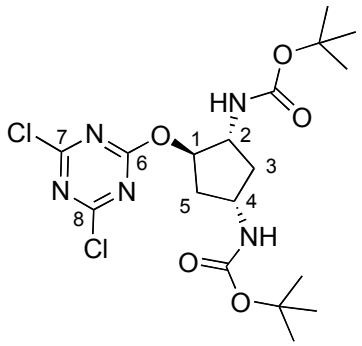


(Powder, 89 mg); Rf (BuOH/ AcOH/ H_2O, 4:1:5) 0.19; mp 142-146°C; UV absorptions: $\lambda_{max}(H_2O)$/nm 255 and 295; δ_H (400 MHz, CD_3OD): 8.74 (1H, s, H_{12}); 8.30 (1H, s, H_8); 8.12 (1H, d, *J* 8.8 Hz, H_{17} or H_{18}); 8.05 (1H, d, *J* 8.4 Hz, H_{17} or H_{18}); 7.78 (1H, d, *J* 5.3 Hz, H_{15}); 7.62 (1H, d, *J* 5.3 Hz, H_{14}); 6.45 (2H, s, H_9); 4.87 (2H, s, H_6); 4.30-4.32 (1H, m, H_1); 3.64-3.68 (1H, m, H_4); 3.50-3.52 (1H, m, H_2); 2.56-2.62 (1H, m, H_3); 2.17-2.20 (2H, m, H_5); 1.78-1.86 (1H, m, $H_{3'}$); δ_C (100 MHz, CD_3OD): 192.5 (s, C_{10}); 147.3 (s, C_{16}); 141.2 (s, C_{13}); 133 (d, C_8); 131.7 (s, C_{11}); 130.3 (d, C_{15}); 126.2 (d, C_{12} or C_{14}); 126.1 (d, C_{12} or C_{14}); 124.5 (d, C_{17} or C_{18}); 124.2 (d, C_{17} or C_{18}); 82.0 (d, C_1); 61.1 (t, C_6); 57.4 (t, C_9); 56.3 (d, C_2); 48.5 (d, C_4);

35.4 (t, C_5); 34.1 (t, C_3); *m/z* (HRMS ESI): $[MH]^+$ 372.1489 (Calculated for $C_{18}H_{22}N_5O_2S$ 372.1489).

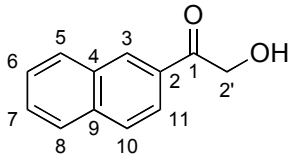
1.4. Synthesis of 2-[4-chloro-6(2,4-diaminocyclopentyloxy)1,3,5-triazin-2-yloxy)-1-naphthalen-2-yl) ethanone 10

Tert-Butyl-4-[4,6-dichloro-1,3,5-triazin-2-yloxy) cyclopentane-1,3-diyldicarbamate 7



To a solution of cyanuric chloride (369 mg, 2 mmol) in freshly distilled dichloroethane (5 mL) are successively added DACP (316 mg, 1 mmol) and K_2CO_3 (276 mg, 2 mmol). The reaction mixture is refluxed for 24 h. After addition of brine solution, the mixture is extracted with DCM. The combined organic layers are washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude mixture is submitted to FC on silica gel (Cyclohexane-AcOEt, 8:2) giving compound **7** as a white powder (36% yield); Rf (Cy/ EtOAc, 6:4) 0.63; mp 104-106°C; δ_H (300 MHz, $CDCl_3$): 5.51-5.52 (1H, m, H_1); 5.29 (1H, br s, NH); 4.99 (1H, br s, NH); 3.97-4.1 (2H, m, H_2, H_4); 2.60 (1H, dt, *J* 8.3 Hz, *J* 13.8 Hz, H_3); 2.14-2.22 (2H, m, H_5); 1.62-1.65 (1H, m, H_3); 1.42 (18H, s, CH_3 (tBu)); δ_C (75 MHz, $CDCl_3$): 172.5 (s, C_7 and C_8); 170.5 (s, C_6); 155.3 (s, CO_{Boc}); 84.4 (d, C_1); 79.8 (s, $C_{iv\ Boc}$); 55.9 (d, C_2); 48.6 (d, C_4); 36.8 (t, C_3 and C_5); 28.4 (q, C_{tBu}); *m/z* (ESI): 464 (MH^+), 486 (MNa^+), calculated for $C_{18}H_{27}Cl_2N_5O_5$ 463.

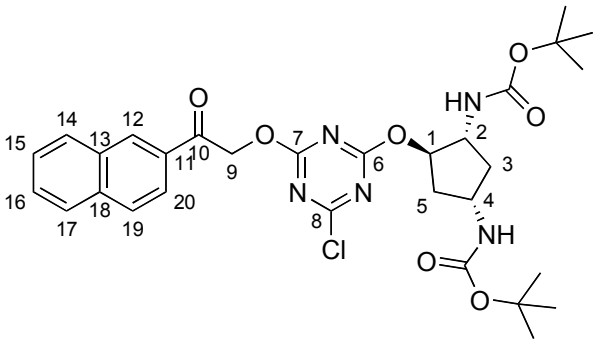
2-Hydroxy-1-(naphtalen-2-yl)ethanone 8



To a mixture of TFA (930 µL, 12 mmol), H_2O (6 mL) and acetonitrile (30 mL) was added acetophenone (1 g, 5.9 mmol) and $PhI(CF_3O_2)_2$ (5.2 g, 12 mmol). The mixture was refluxed

for 3h. After addition of water and extraction with DCM, the combined organic layers are washed with an aqueous saturated solution of $NaHCO_3$, and then water. The solution is dried ($MgSO_4$) and concentrated *in vacuo*. The pure product is obtained as a white powder by precipitation in hexane from the crude mixture (55%); **8** was identified by comparison of its spectral data to the literature [2], Rf (Cy/ EtOAc, 8:2) 0.24; mp 108-110°C; δ_H (300 MHz, $CDCl_3$): 8.43 (1H, s, H_3); 7.88-8.07 (4H, m); 7.56-7.69 (2H, m); 5.02 (2H, s, $H_{2'}$); δ_C (75 MHz, $CDCl_3$): 198.3 (s, C_1); 136.1 (s, C_2); 132.4 (s, C_4 or C_9); 130.7 (s, C_4 or C_9); 129.64 (d, C_3 or C_5); 129.57 (d, C_3 or C_5); 129.2 (d, C_7 or C_{10}); 129 (d, C_7 or C_{10}); 127.9 (d, C_8); 127.2 (d, C_6); 123.1 (d, C_{11}); 65.6 (d, $C_{2'}$).

tert-butyl-4-[4-chloro-6(2-naphthalen-2-yl)-2-oxoethoxy)-1,3,5-triazin-2-yloxy) cyclopentane-1,3-diyldicarbamate 9

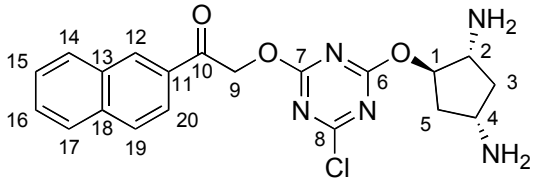


To a suspension of NaH (18 mg, 0.4 mmol) in THF (2 mL) was added a solution of alcohol **8** (80 mg, 0.4 mmol) in anhydrous THF (5 mL). The solution was stirred for 5 min at room temperature. Then, a solution of compound **7** (166 mg, 0.36 mmol) in THF (5 mL) was added. After stirring for 2h, the reaction is quenched with a saturated aqueous solution of NH_4Cl and extracted with DCM. The combined organic layers are dried ($MgSO_4$) and concentrated *in vacuo*. The crude mixture is submitted to FC on silica gel (Cyclohexane, AcOEt, 8:2) giving compound **9** as a white powder (26%); Rf (Cy/ EtOAc, 6:4) 0.43; mp 113-116°C; δ_H (300 MHz, $CDCl_3$): 8.47 (1H, s, H_{12}); 7.89-8.01 (4H, m, H_{14}, H_{17}, H_{19}, H_{20}); 7.57-7.68 (2H, m, H_{15}, H_{16}); 5.93 (1H, d (AB), *J* 16.2 Hz, H_9); 5.83 (1H, d (AB), *J* 16.2 Hz, H_9); 5.37 (2H, m, H_1, NH); 4.77 (1H, br s, NH); 3.93-4.06 (2H, m, H_2, H_4); 2.57 (1H, dt, *J* 8.2 Hz, *J* 13.8 Hz, H_3); 2.14-2.17 (2H, m, H_5); 1.42 (19H, m, CH_3 (tBu), H_3); δ_C (75 MHz, $CDCl_3$): 191.2 (s, C_{10}); 172.9 (s, C_8); 172.1 (s, C_6 or C_7); 171.6 (s, C_6 or C_7); 155.2 (s, CO_{Boc}); 136.1 (s, C_{11}); 132.5 (s, C_{13} or C_{18}); 131.3 (s, C_{13} or C_{18}); 129.8 (d); 129.7 (d); 129.2 (d); 129.1 (d); 128 (d); 127.3

[2] B. M. Trost, J. Xu, T. Schmidt *J. Am. Chem. Soc.* 2008, **130**, 11852.

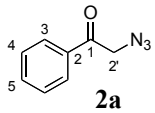
(d); 123.3 (d); 83.2 (d, C_1); 79.8 (s, $C_{iv\ Boc}$); 69.8 (t, C_9); 55.9 (d, C_2); 48.7 (d, C_4); 36.8 (t, C_3 and C_5); 28.4 (q, C_{tBu}).

2-[4-chloro-6(2,4-diaminocyclopentyloxy)1,3,5-triazin-2-yloxy)-1-naphthalen-2-yl) ethanone 10



A solution of **9** (16 mg, 0.026 mmol) was cooled in an ice-bath and HCl (*g*) was bubbled inside until the formation of a white precipitate (few minutes). The solution was concentrated *in vacuo* (13 mg); UV absorptions: $\lambda_{max}(H_2O)$/nm 290 and 350; δ_H (300 MHz, CD_3OD): 8.68 (1H, s, H_{12}); 8.11 (1H, d, *J* 8 Hz); 8.01 (2H, m); 7.97 (1H, d, *J* 8 Hz); 7.60-7.71 (2H, m); 6.12 (1H, d (AB), *J* 16.5 Hz, H_9); 6.02 (1H, d (AB), *J* 16.5 Hz, H_9); 5.64-5.71 (1H, m, H_1); 3.86-3.95 (2H, m, H_2, H_4); 2.72-2.76 (1H, m, H_3); 2.48-2.55 (1H, m, H_5); 2.35-2.42 (1H, m, H_5); 1.99-2.03 (1H, m, H_3); δ_C (75 MHz, CD_3OD): 193.6 (s, C_{10}); 174 (s, C_6 or C_7); 173.8 (s, C_6 or C_7); 172.9 (s, C_8); 137.7 (s, C_{11}); 134.1 (s, C_{13} or C_{18}); 132.5 (s, C_{13} or C_{18}); 131.5 (d); 131 (d); 130.4 (d); 130.1 (d); 129.1 (d); 128.4 (d); 124.2 (d); 80.4 (d, C_1); 71.8 (t, C_9); 55.9 (d, C_2); 36 (t, C_5); 34.6 (t, C_3); *m/z* (HRMS ESI): $[MH]^+$ 414.1327 (Calculated for $C_{20}H_{21}ClN_5O_3$ 414.1327).

2. ^{1}H and ^{13}C NMR spectra of compounds 2, 4, 5, 7, 9 and 10



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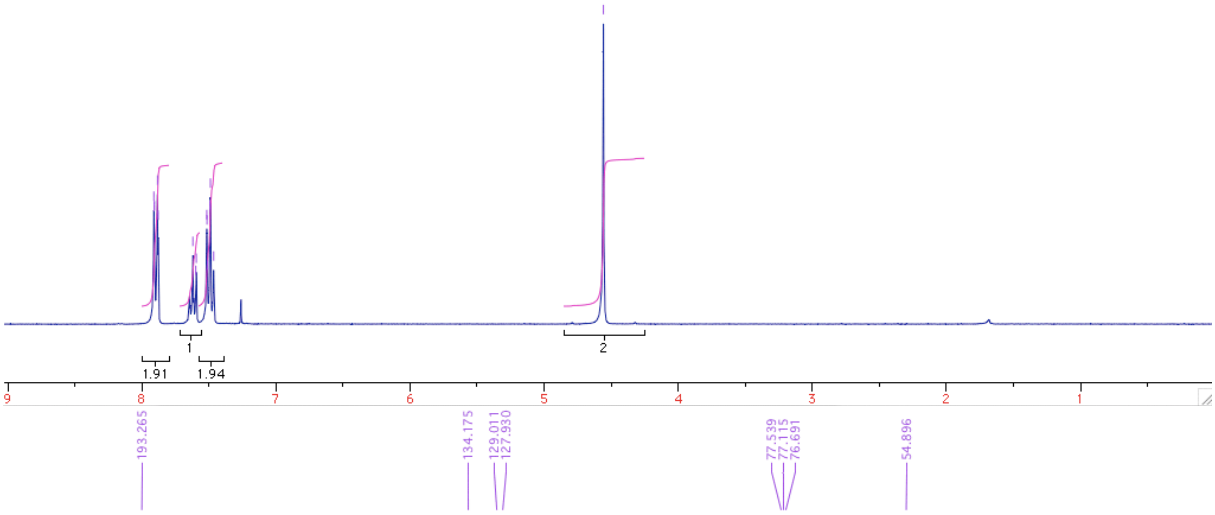

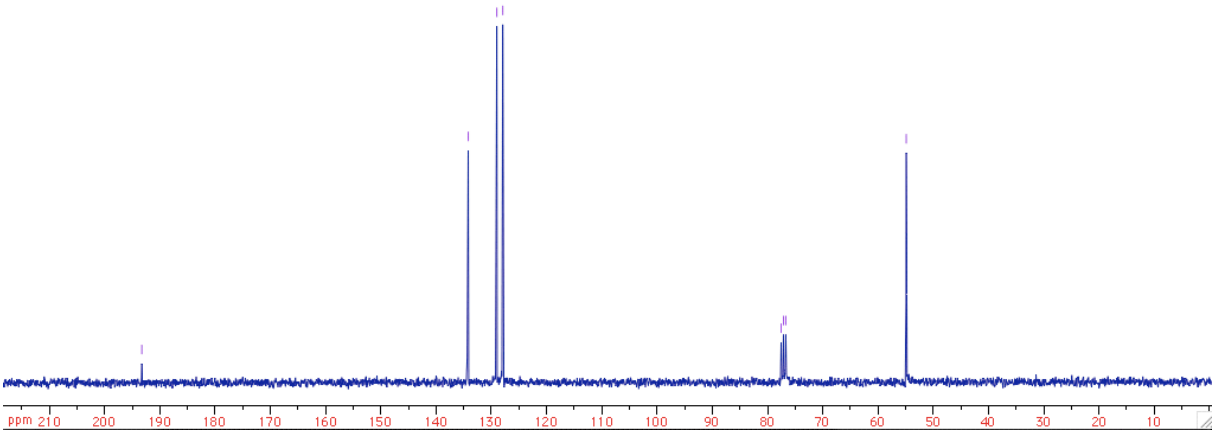


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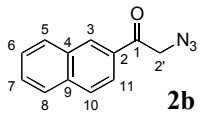
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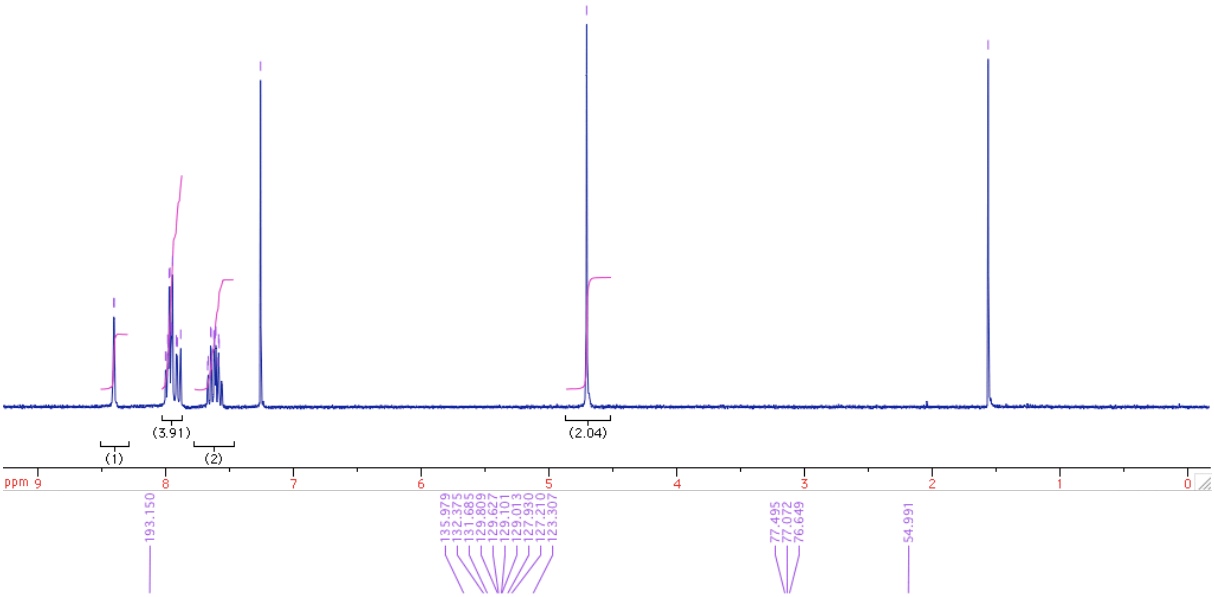
2b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(1)
(2)
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2
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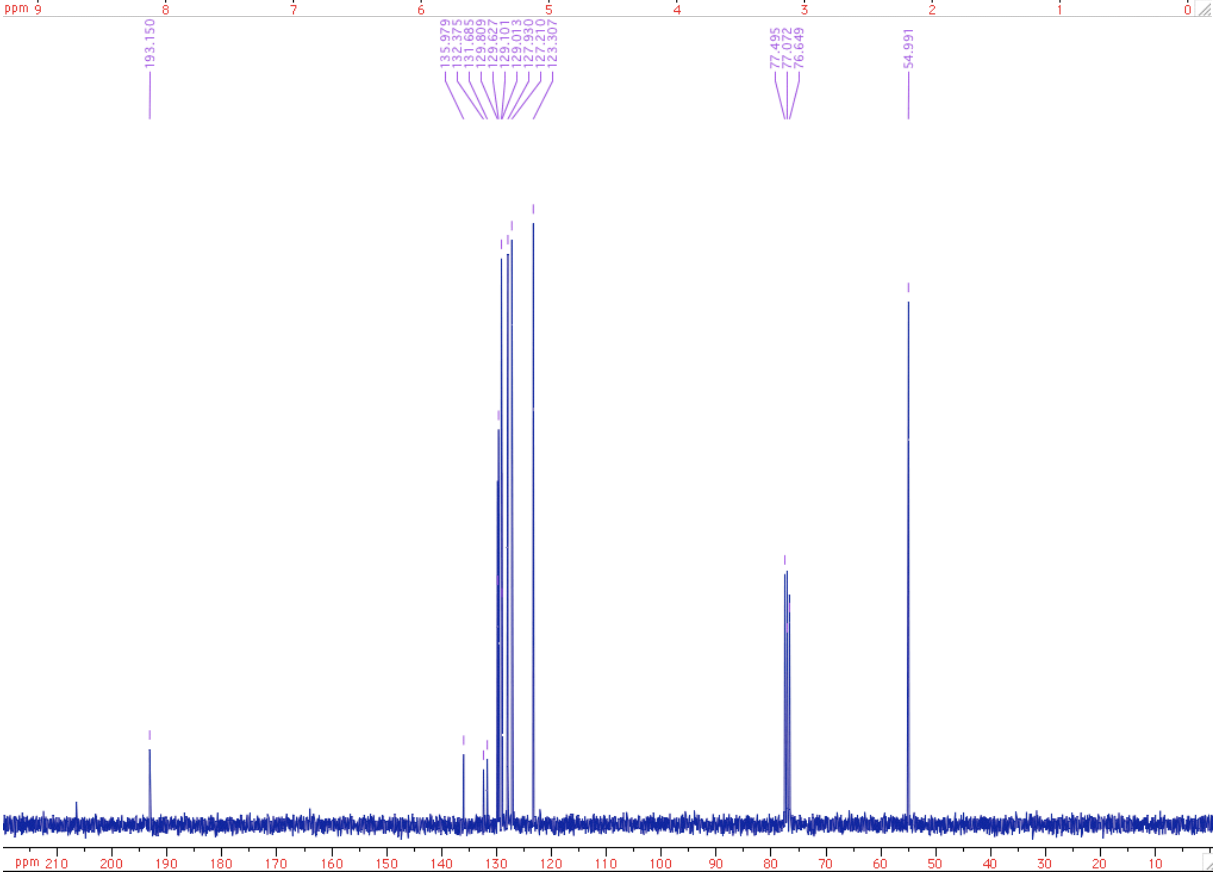
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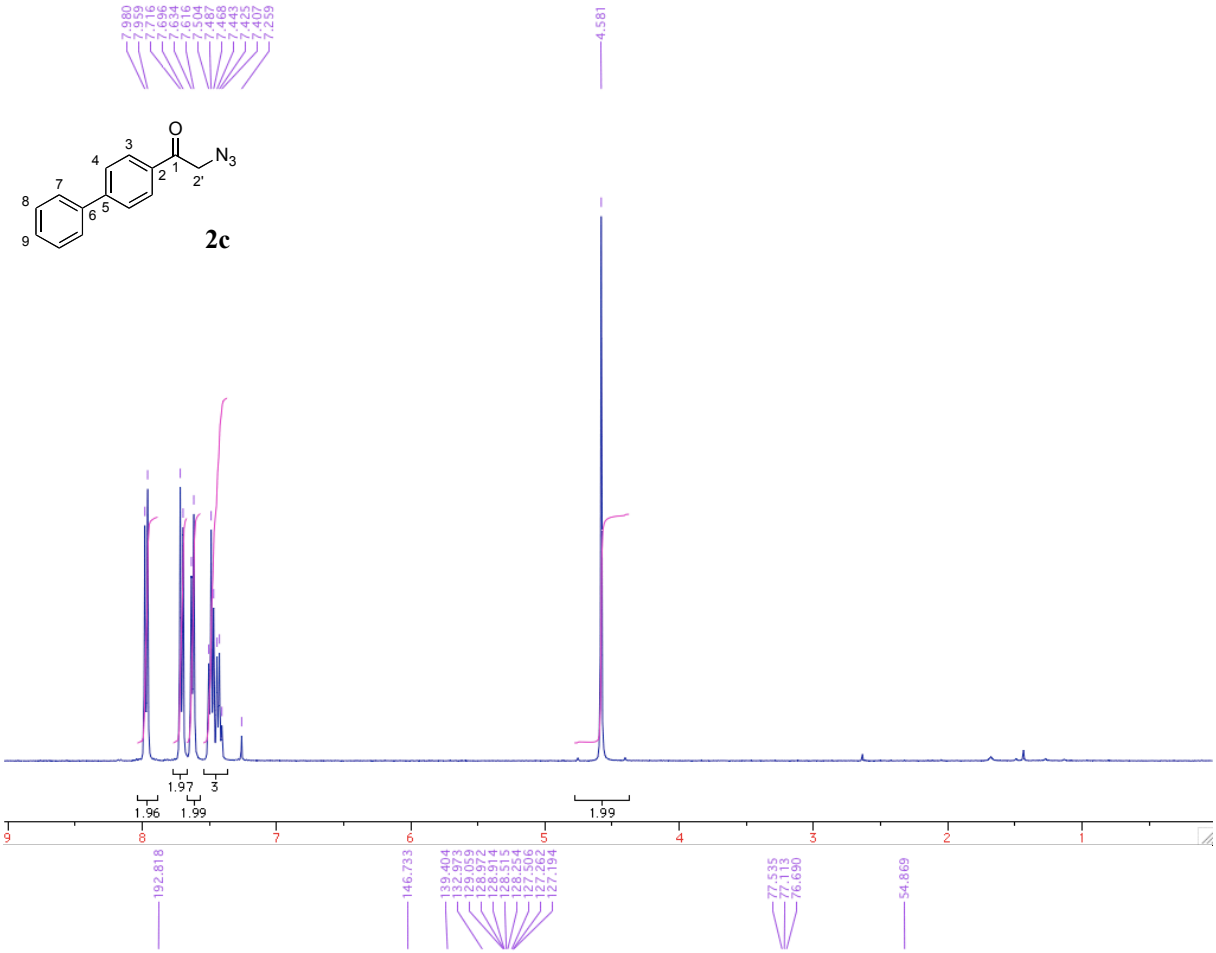
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4.581
O
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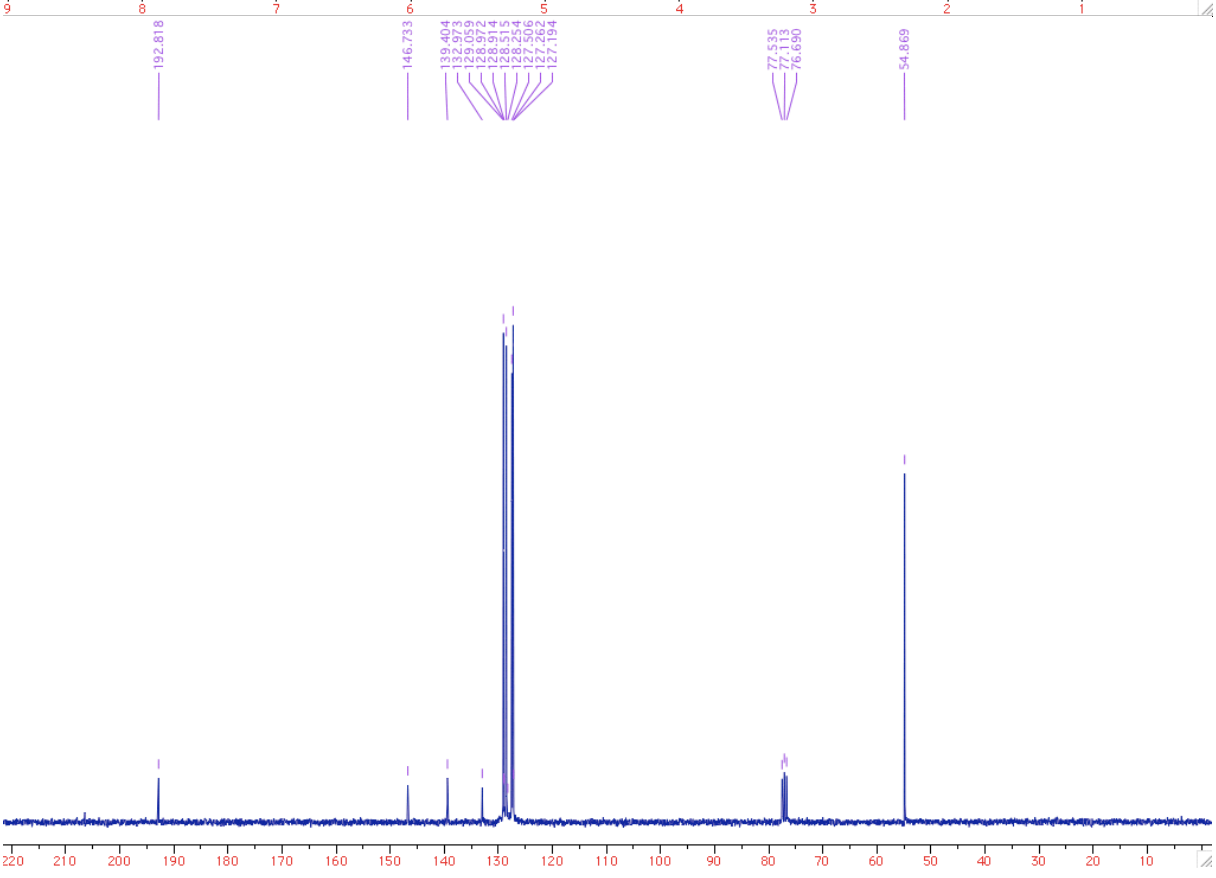
1.97
3
1.99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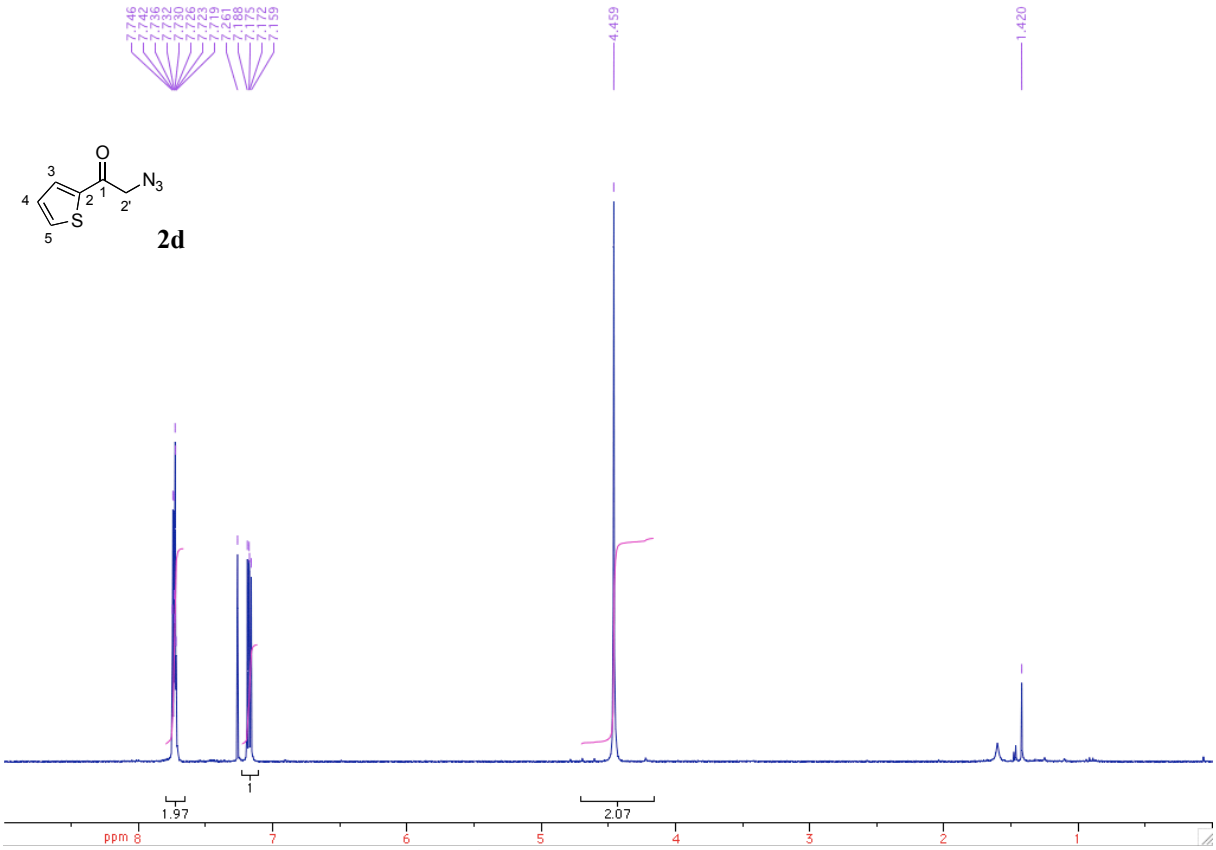
54.869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2
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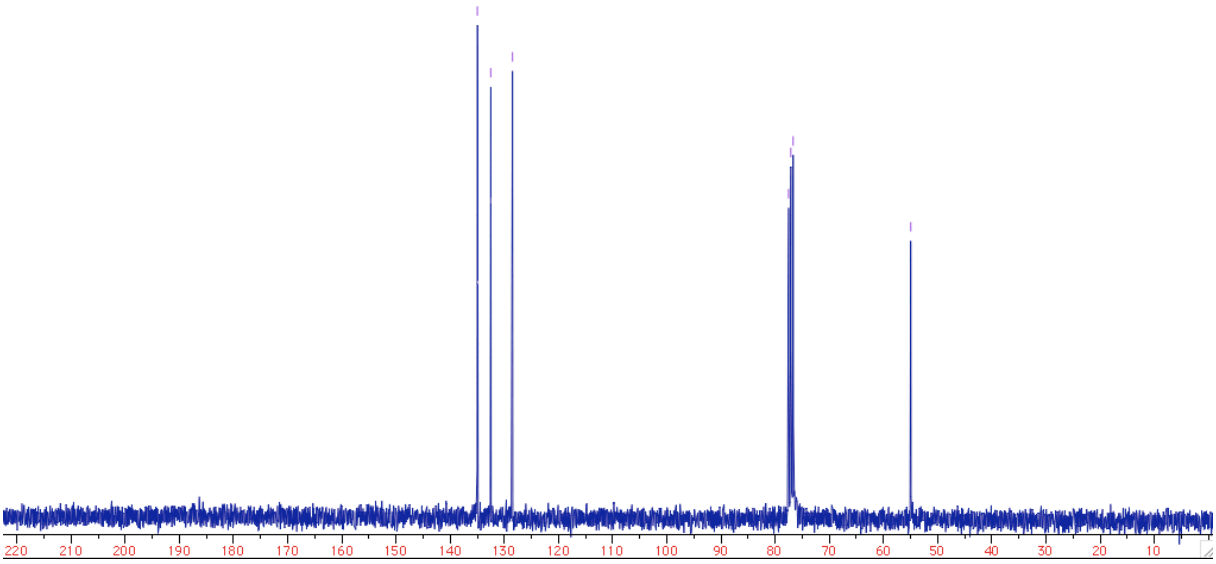
2d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20
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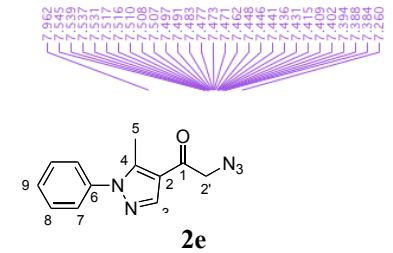
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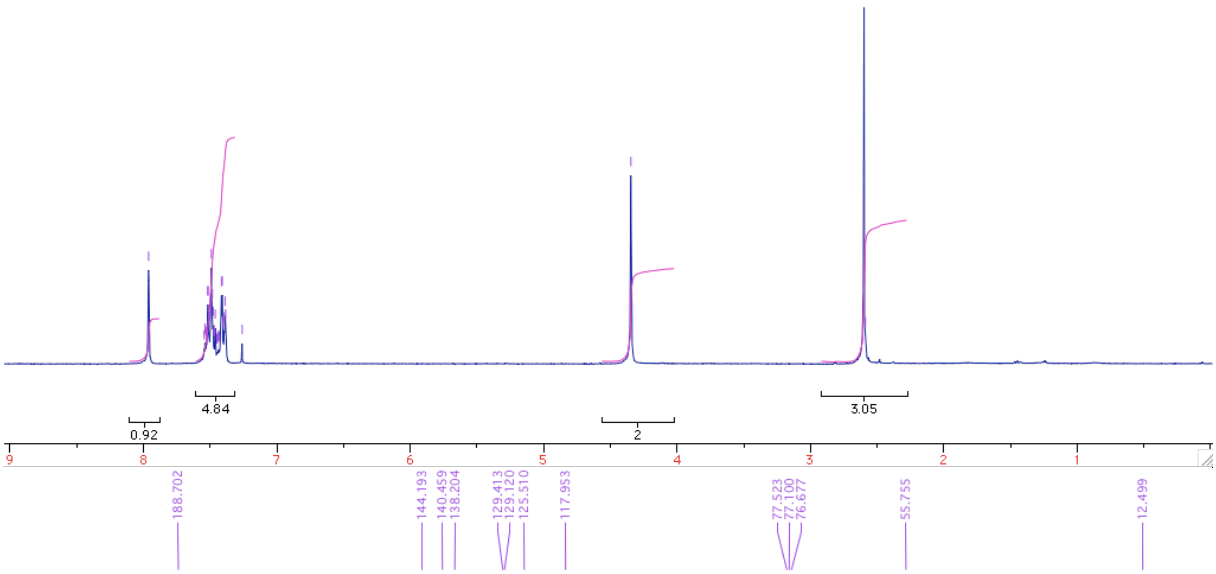
N
8
7

2e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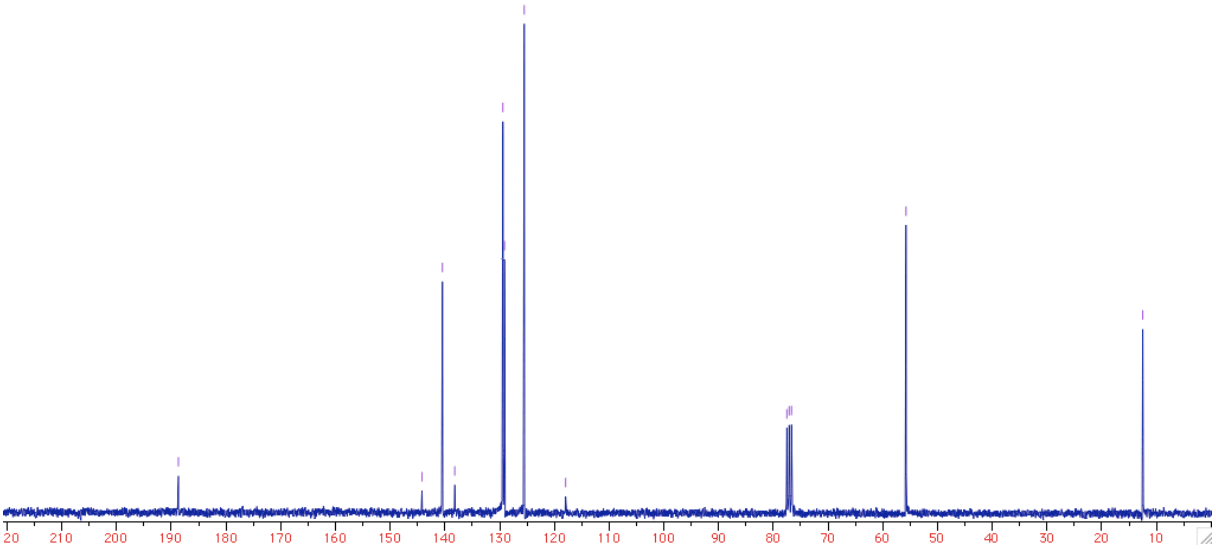
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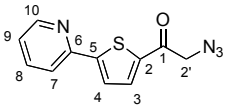
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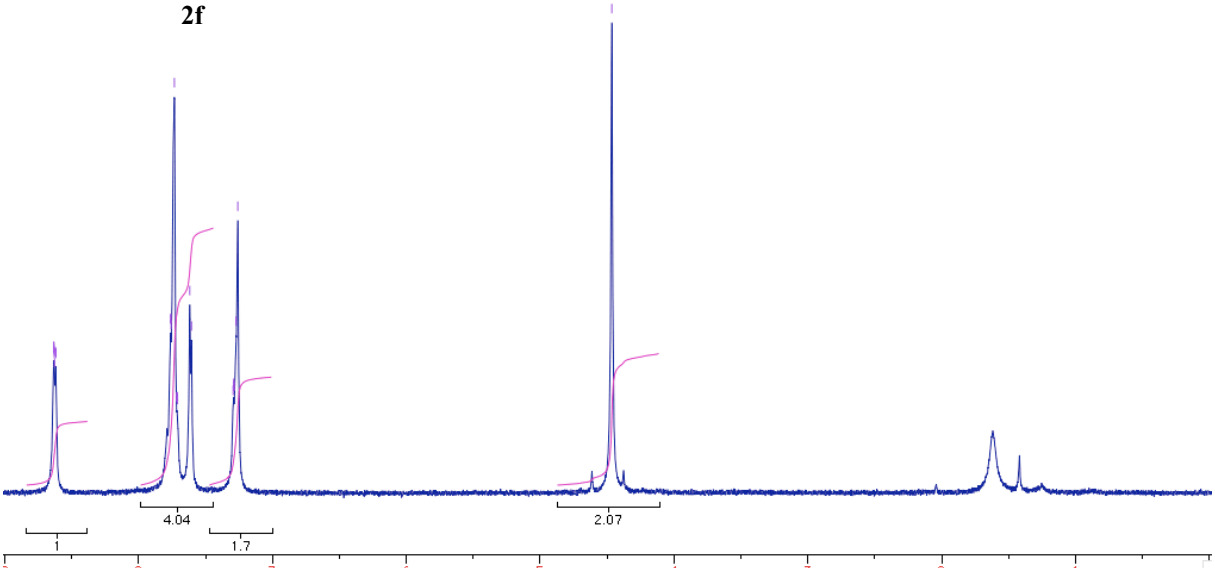
3

2f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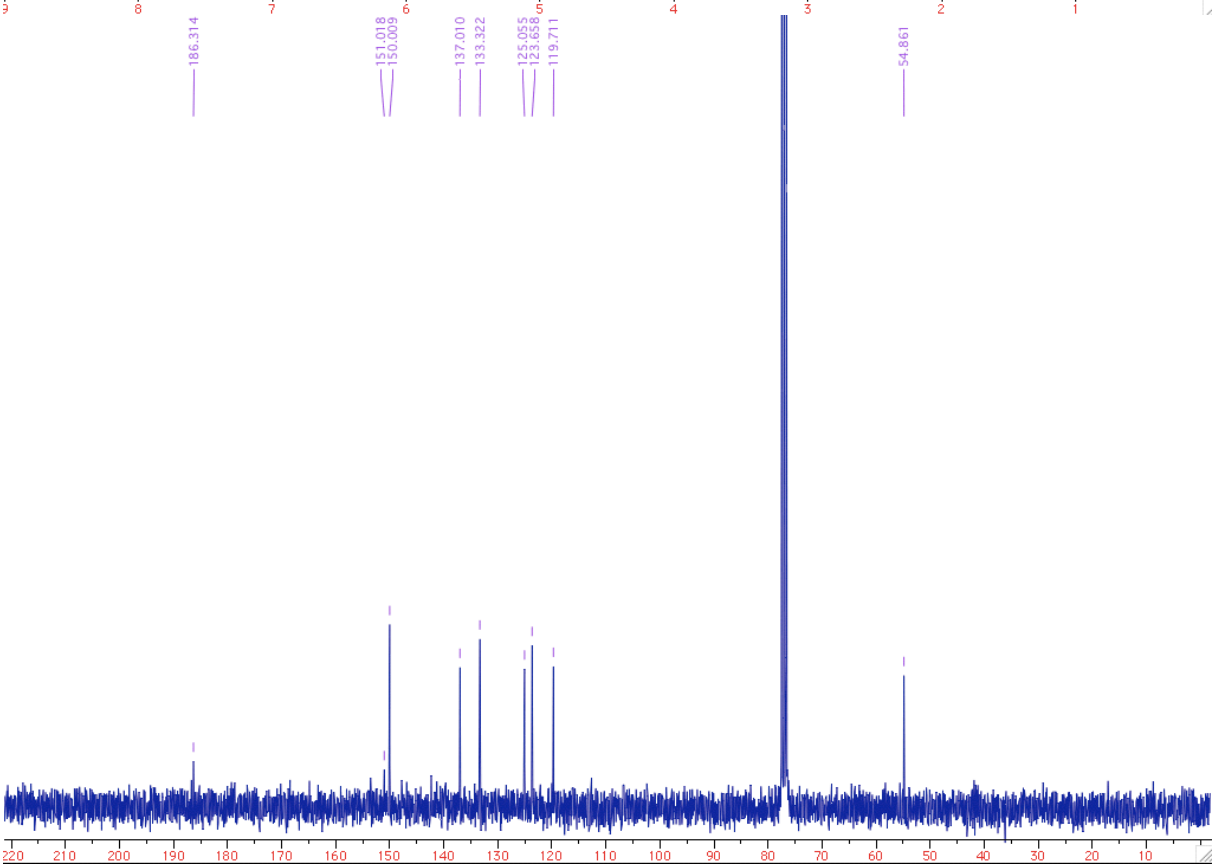
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20
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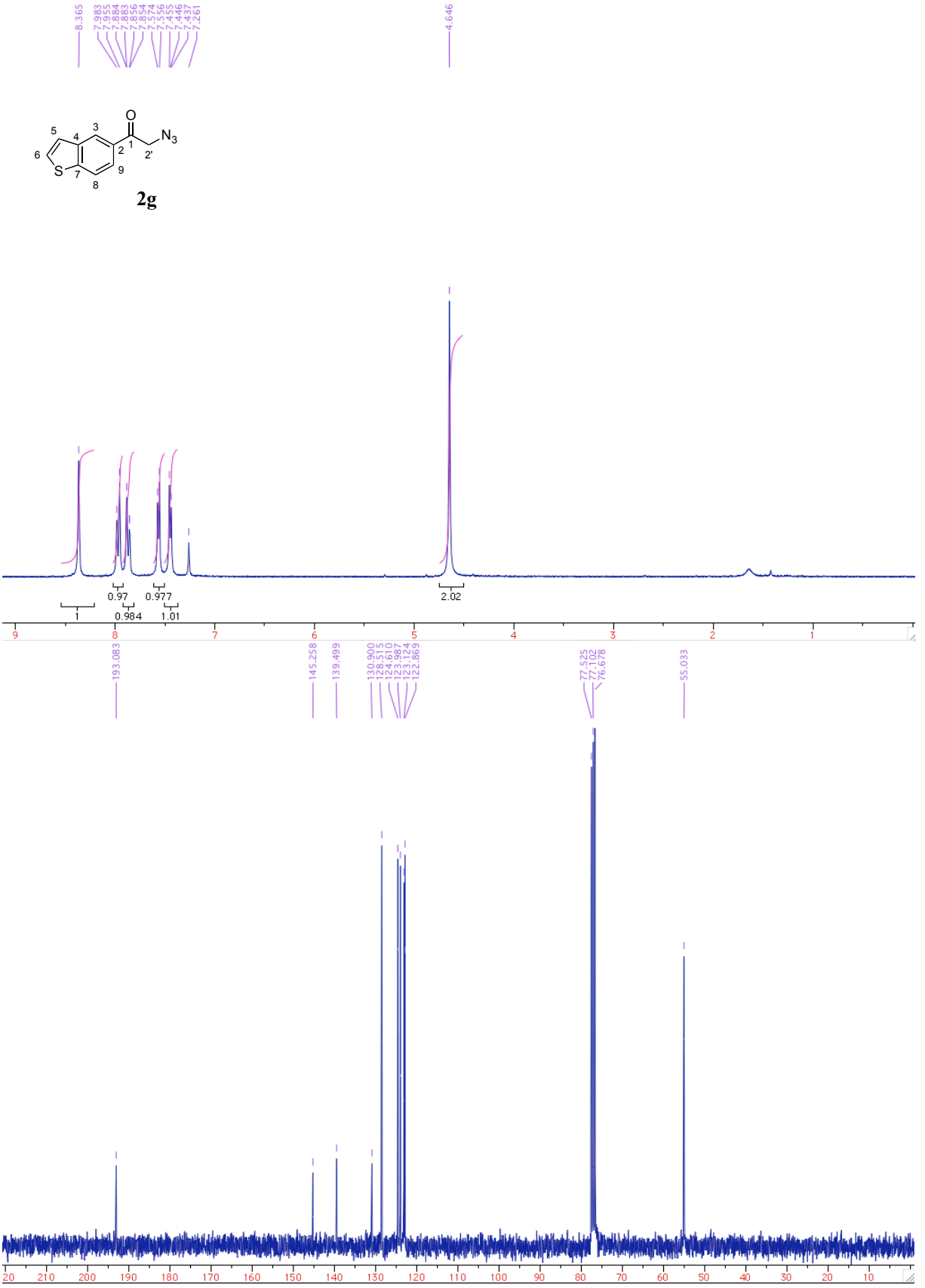
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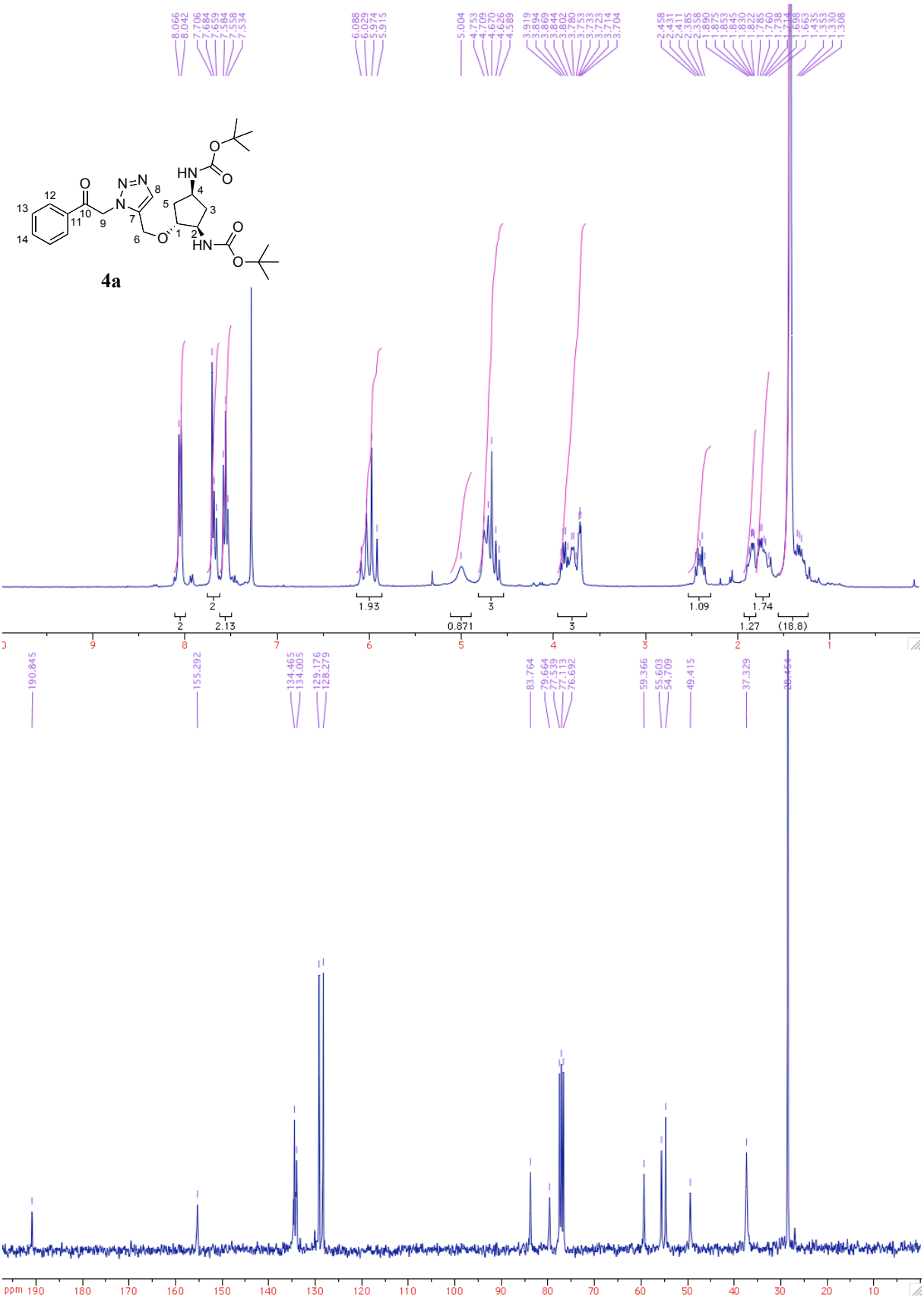
2g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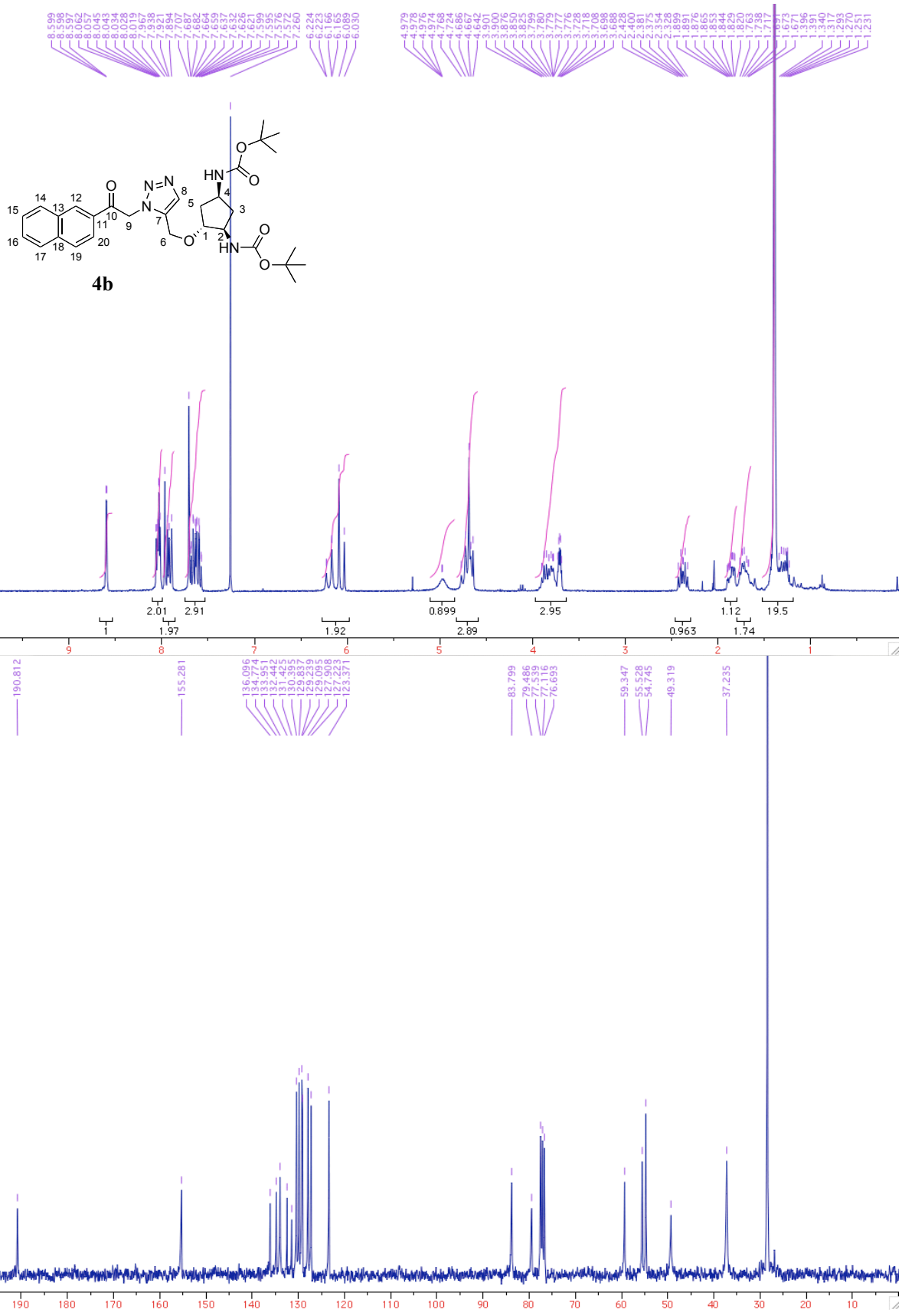
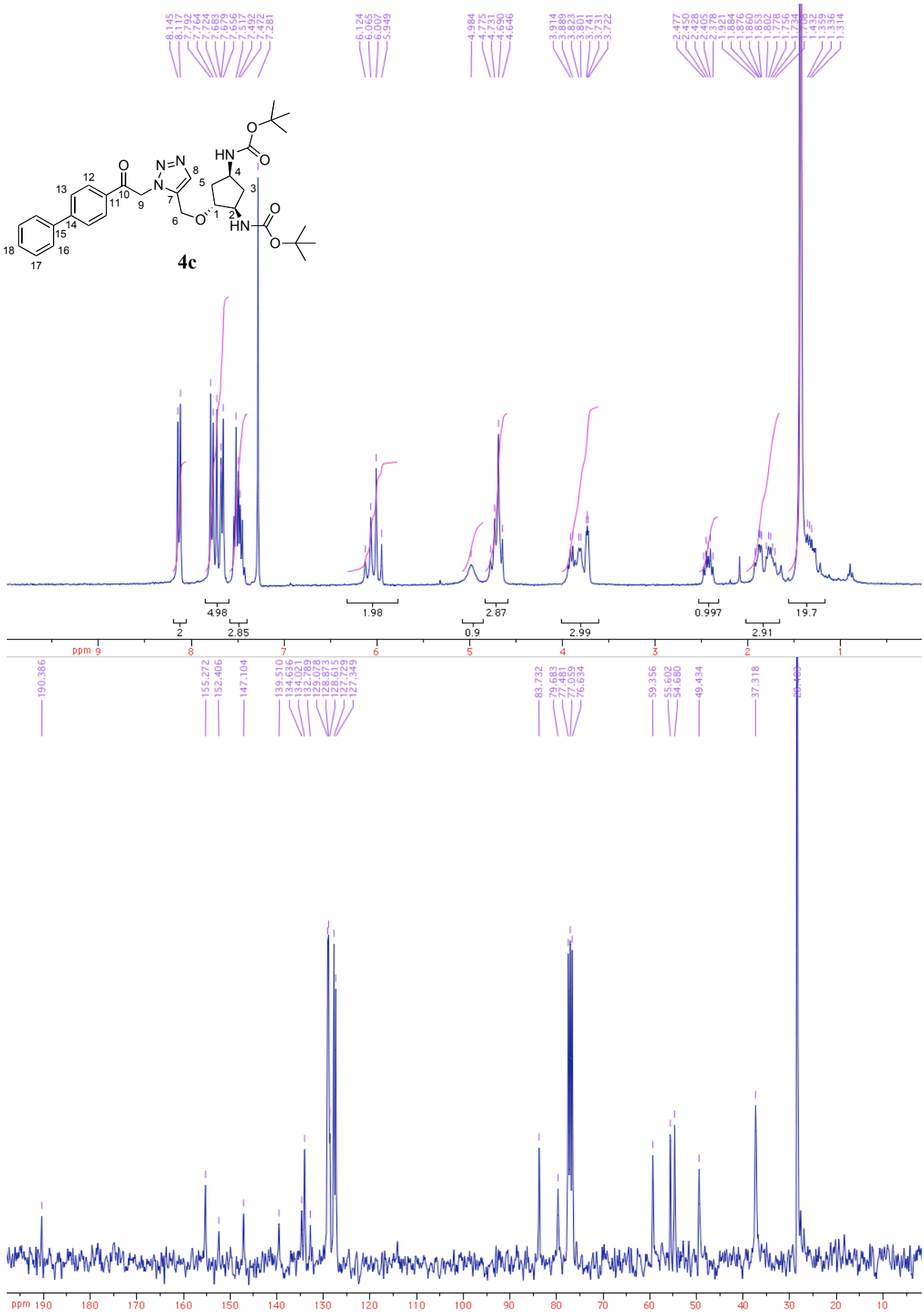


4b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3.823
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3.731
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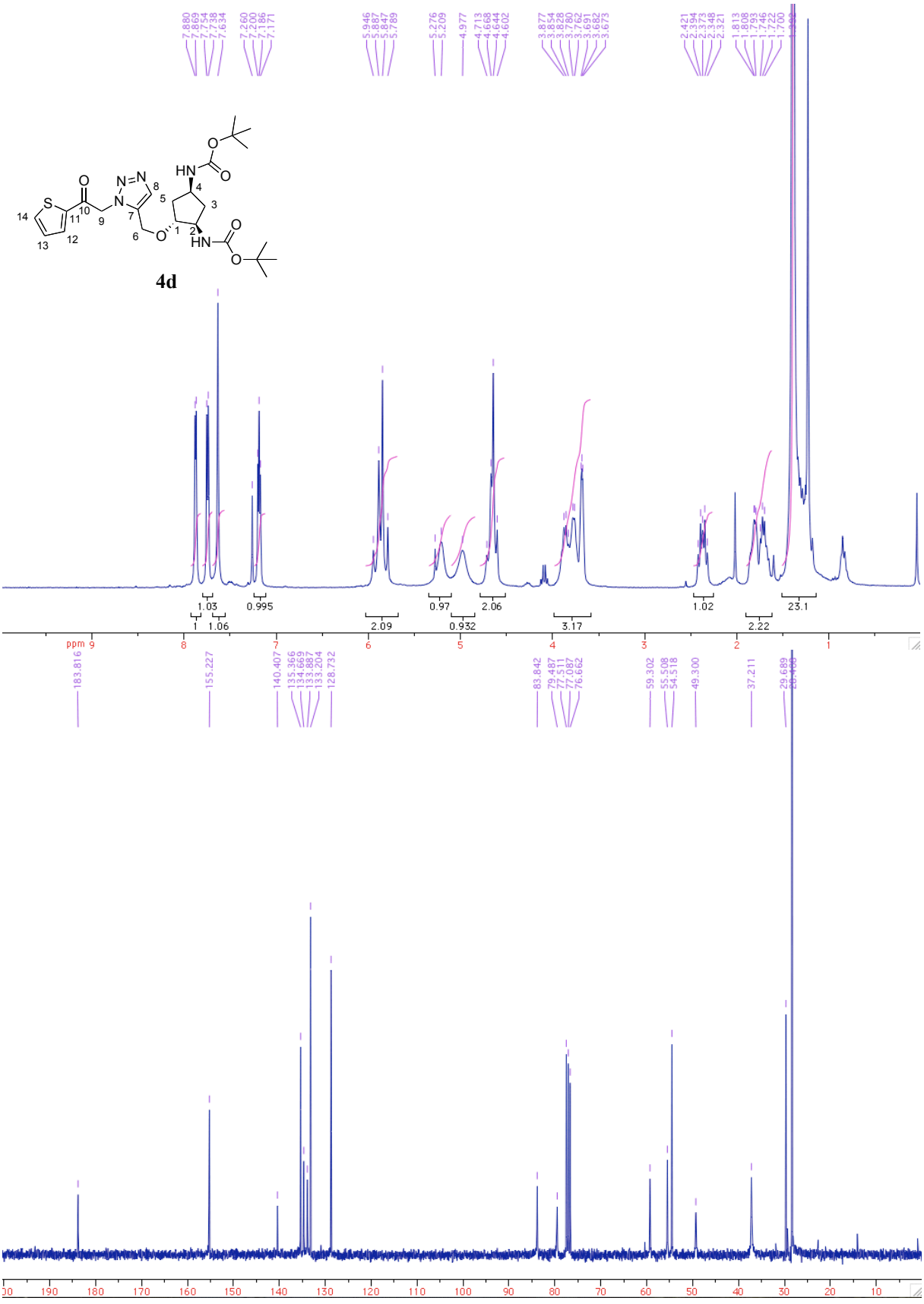
ppm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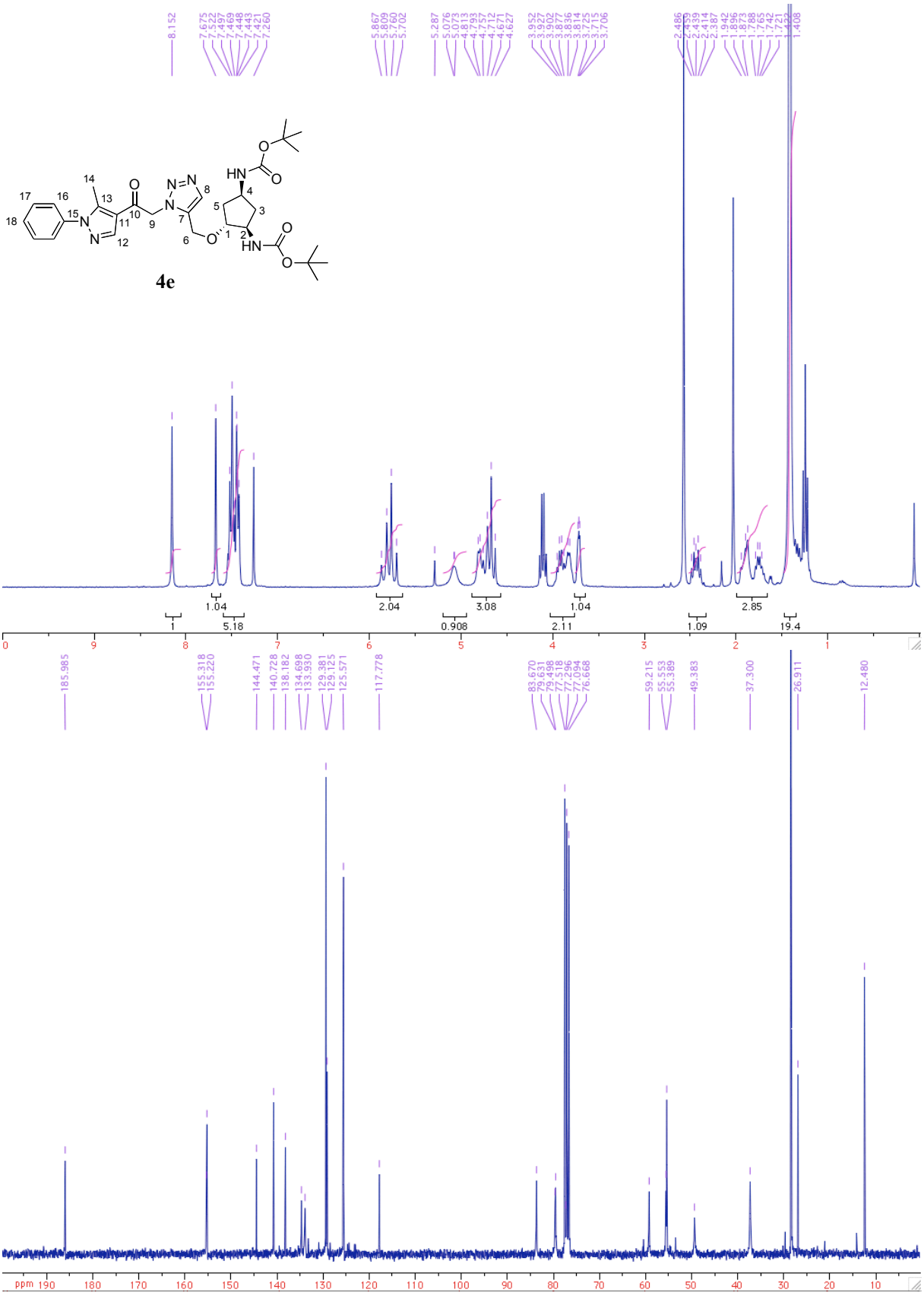
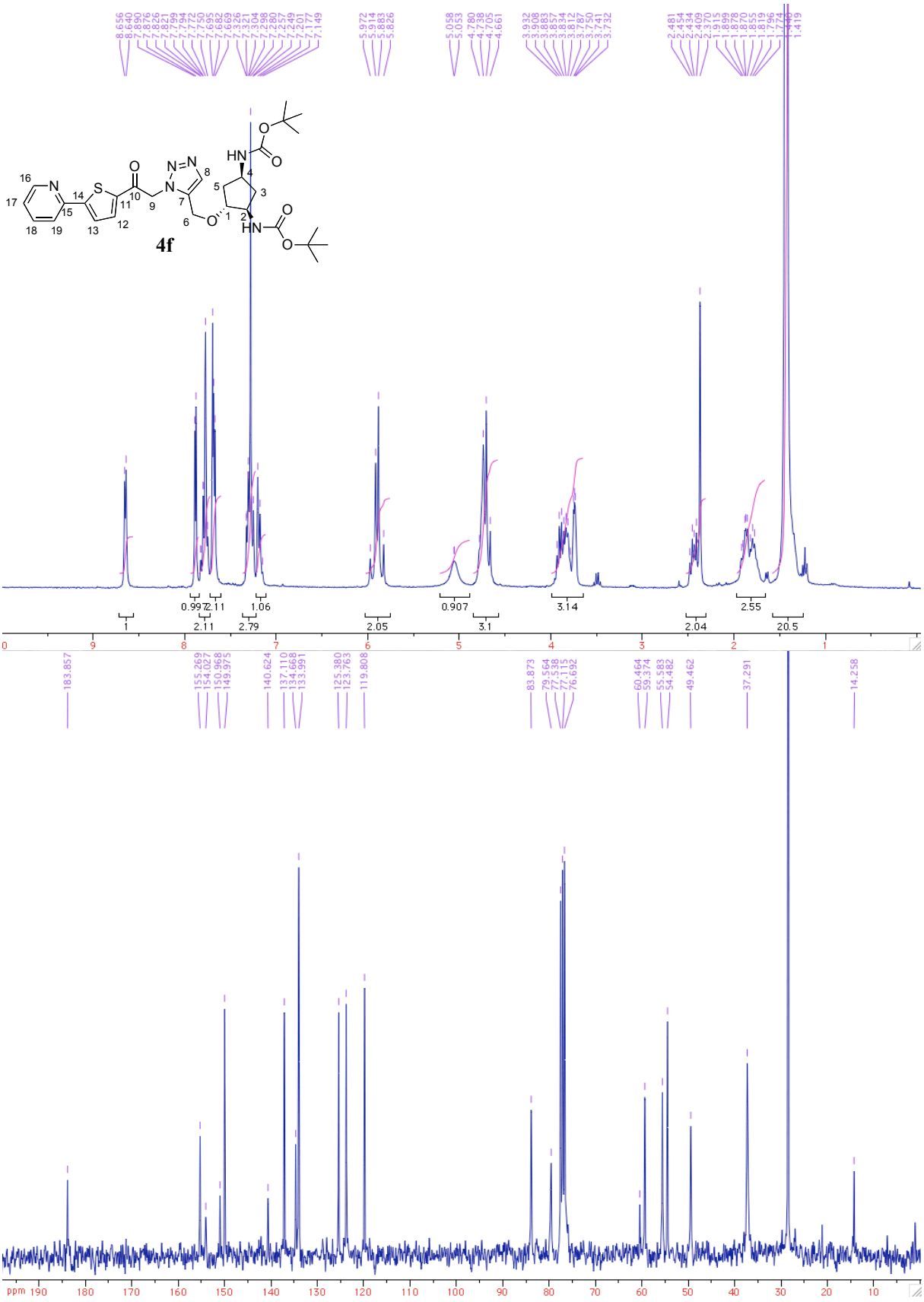


4e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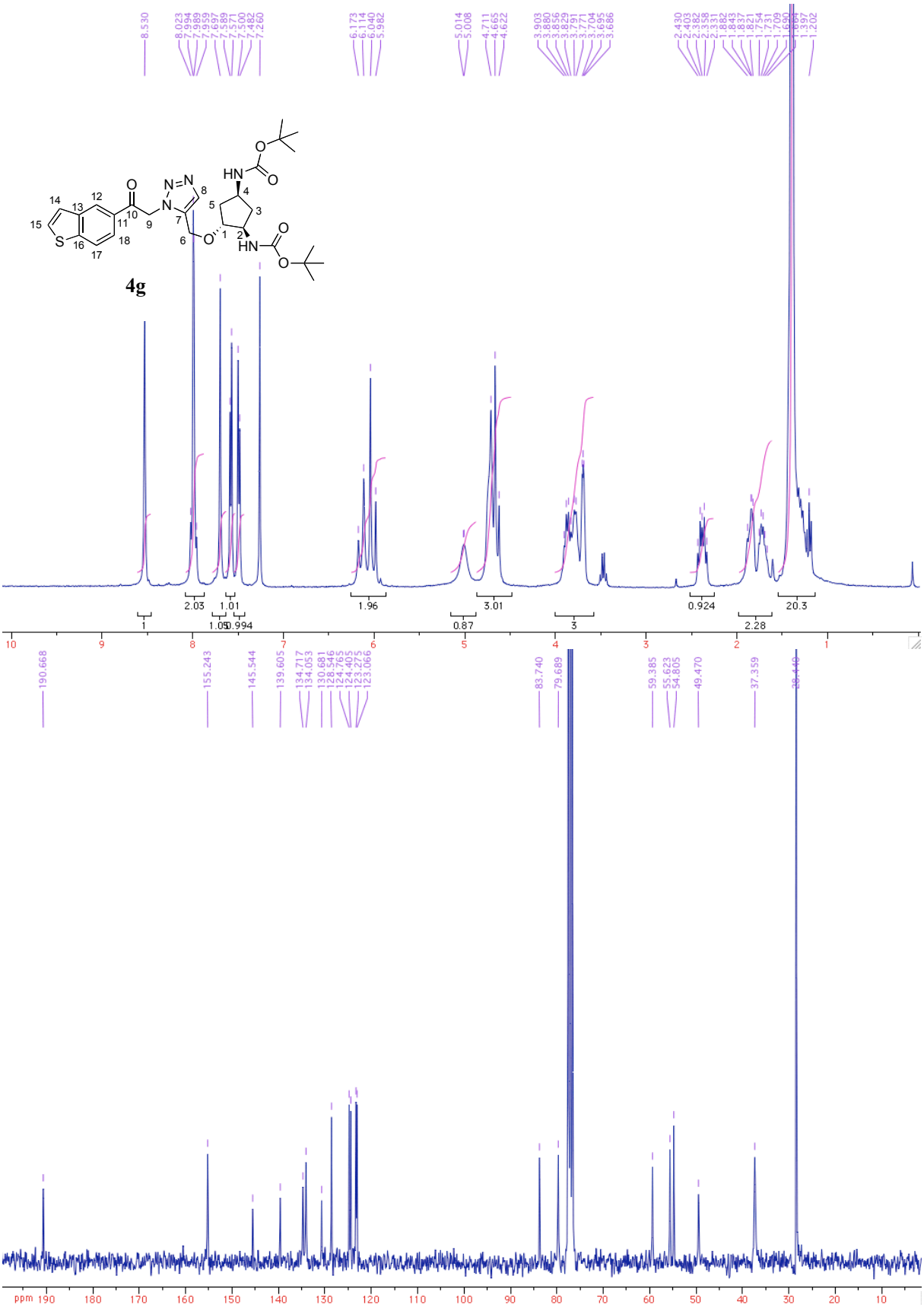

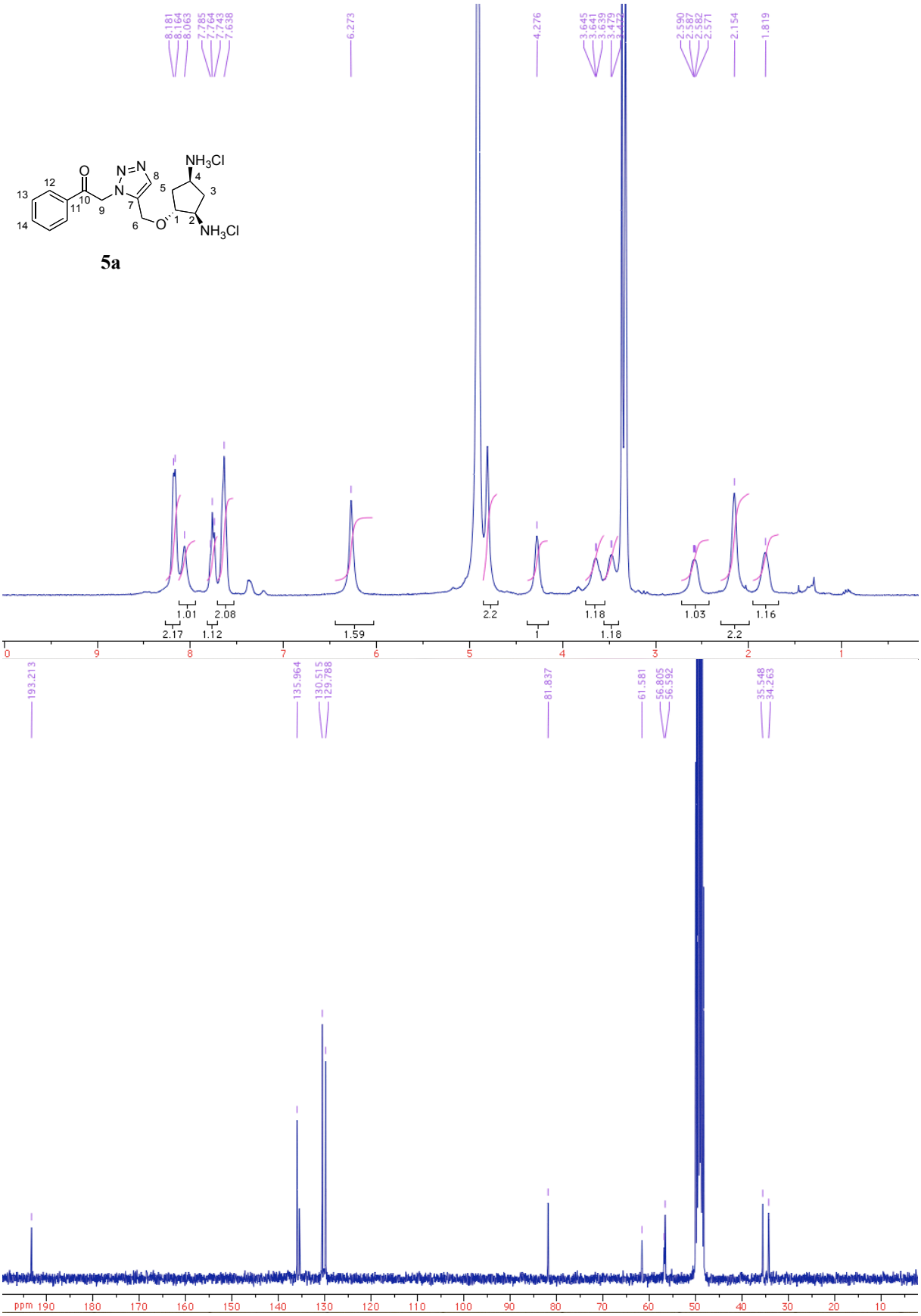
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7.638
6.273
4.276
3.645
3.641
3.479
3.439
3.422
2.590
2.587
2.582
2.571
2.154
1.819
NH3Cl
NH3Cl
1.01
2.08
2.2
1.18
1.03
1.16
2.17
1.12
1.59
1
1.18
2.2
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130.515
129.788
81.837
61.581
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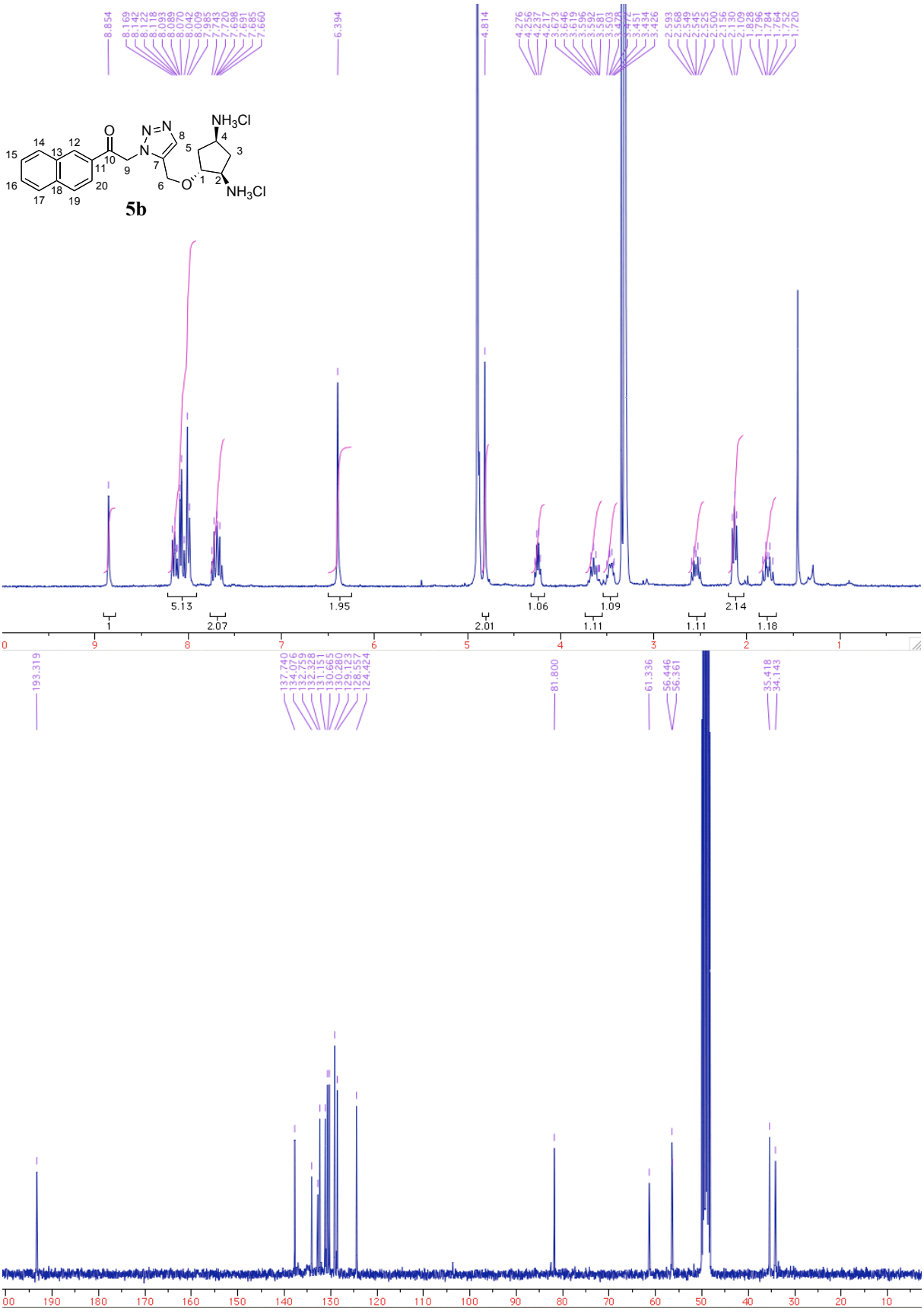
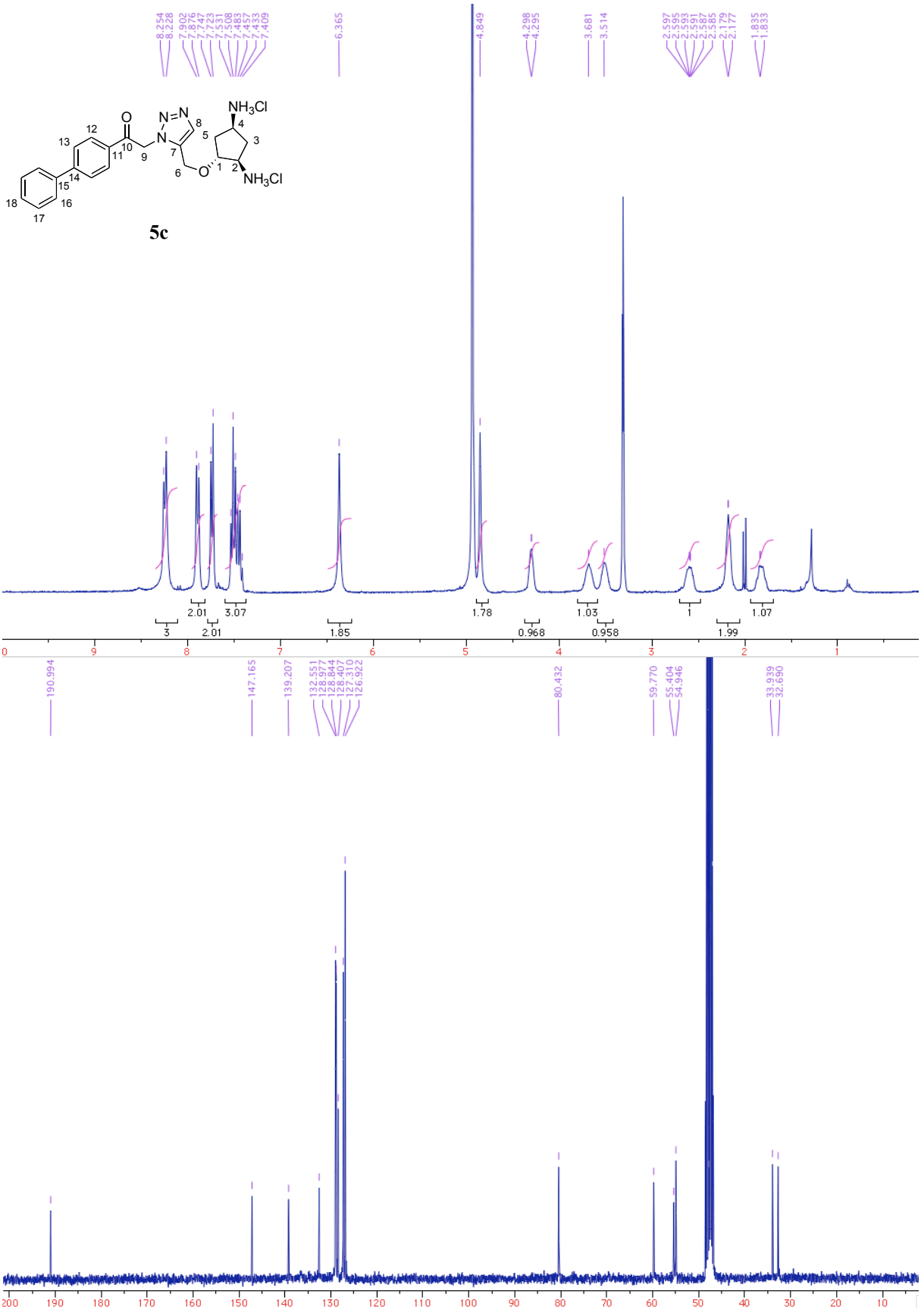
56.592
35.548
34.263
ppm

5a





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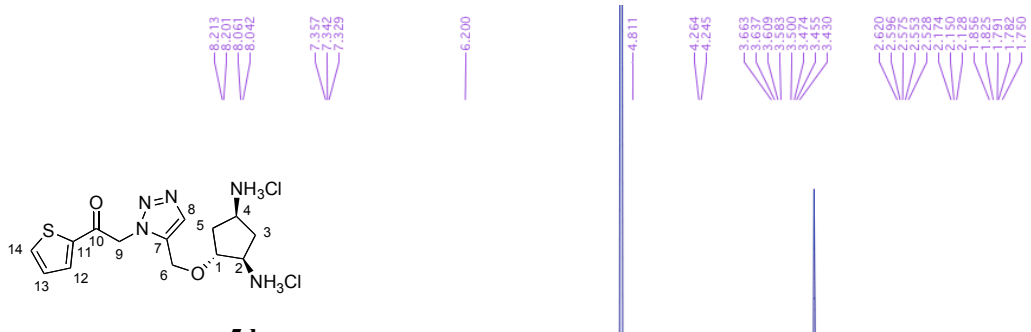
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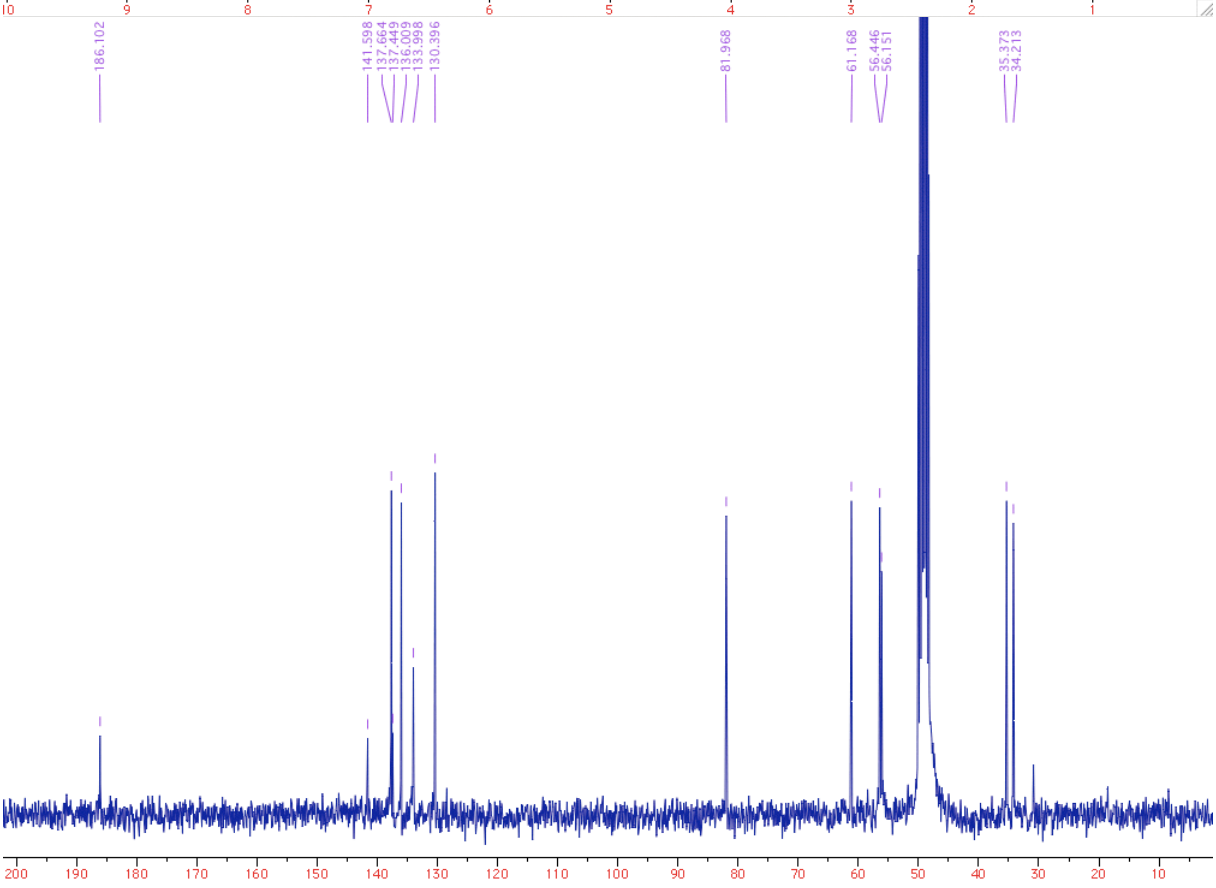
8.061
8.042
7.357
7.342
7.329
6.200
4.811
4.264
4.245
3.663
3.637
3.609
3.583
3.500
3.474
3.455
3.430
2.620
2.596
2.575
2.553
2.528
2.174
2.150
2.128
1.856
1.825
1.791
1.782
1.750

O
S
N
N
N
NH3Cl
NH3Cl
1
2
3
4
5
6
7
8
9
10
11
12
13
14

5d

1.95
0.969
1.96
2.19
1.11
1.1
1.08
1.05
2.02
1.1
1
10
9
8
7
6
5
4
3
2
1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137.449
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133.998
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81.968
61.168
56.446
56.151
35.373
34.213
200
190
180
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160
150
140
130
120
110
100
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80
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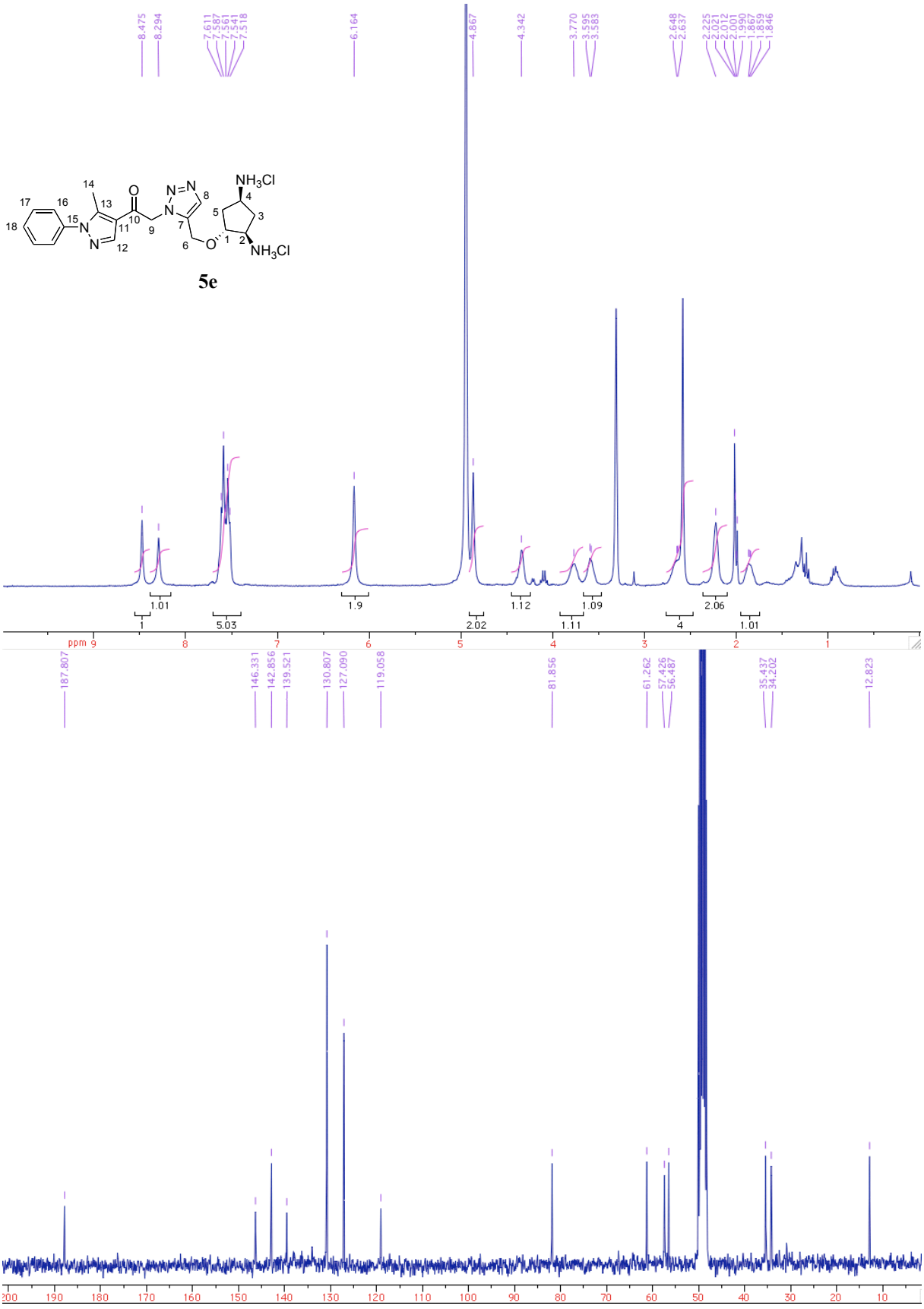
60
50
40
30
20
10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6.164
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4.342
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3.595
3.583
2.648
2.637
2.225
2.021
2.012
2.001
1.990
1.867
1.859
1.846
NH3Cl
NH3Cl
1.01
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1.9
2.02
1.12
1.11
1.09
4
2.06
1.01
ppm
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142.856
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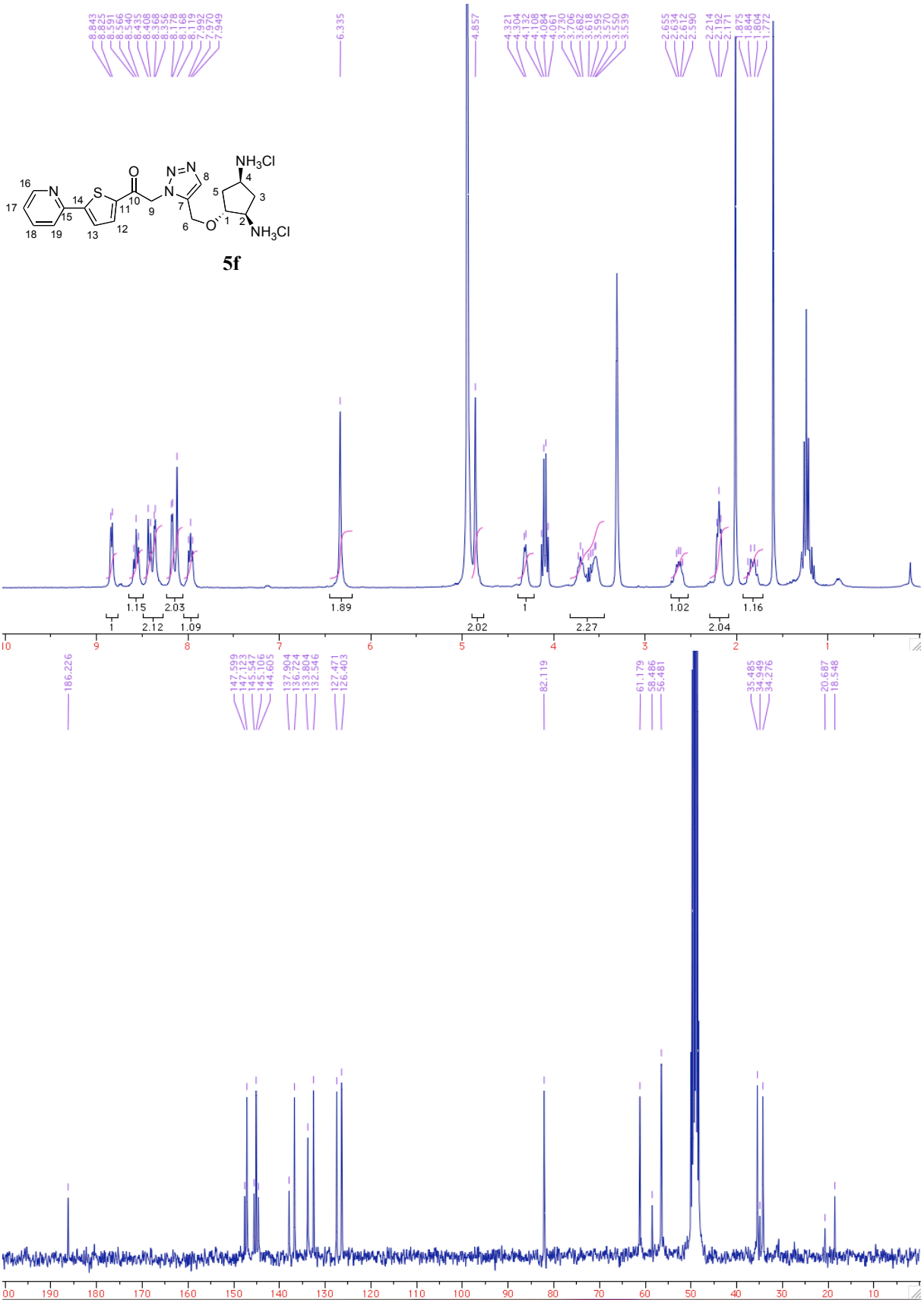
34.202
12.823

5e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8.408
8.356
8.178
8.168
8.119
7.992
7.970
7.949
6.335
4.857
4.321
4.304
4.132
4.108
4.084
4.061
3.730
3.706
3.682
3.618
3.595
3.570
3.550
3.539
2.655
2.634
2.612
2.590
2.214
2.192
2.171
1.875
1.844
1.804
1.772
1.15
2.03
1.89
1
1.02
1.16
1
2.12
1.09
2.02
2.27
2.04
186.226
147.599
147.123
145.147
145.106
144.605
137.904
136.724
135.864
132.946
127.471
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82.119
61.179
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56.481
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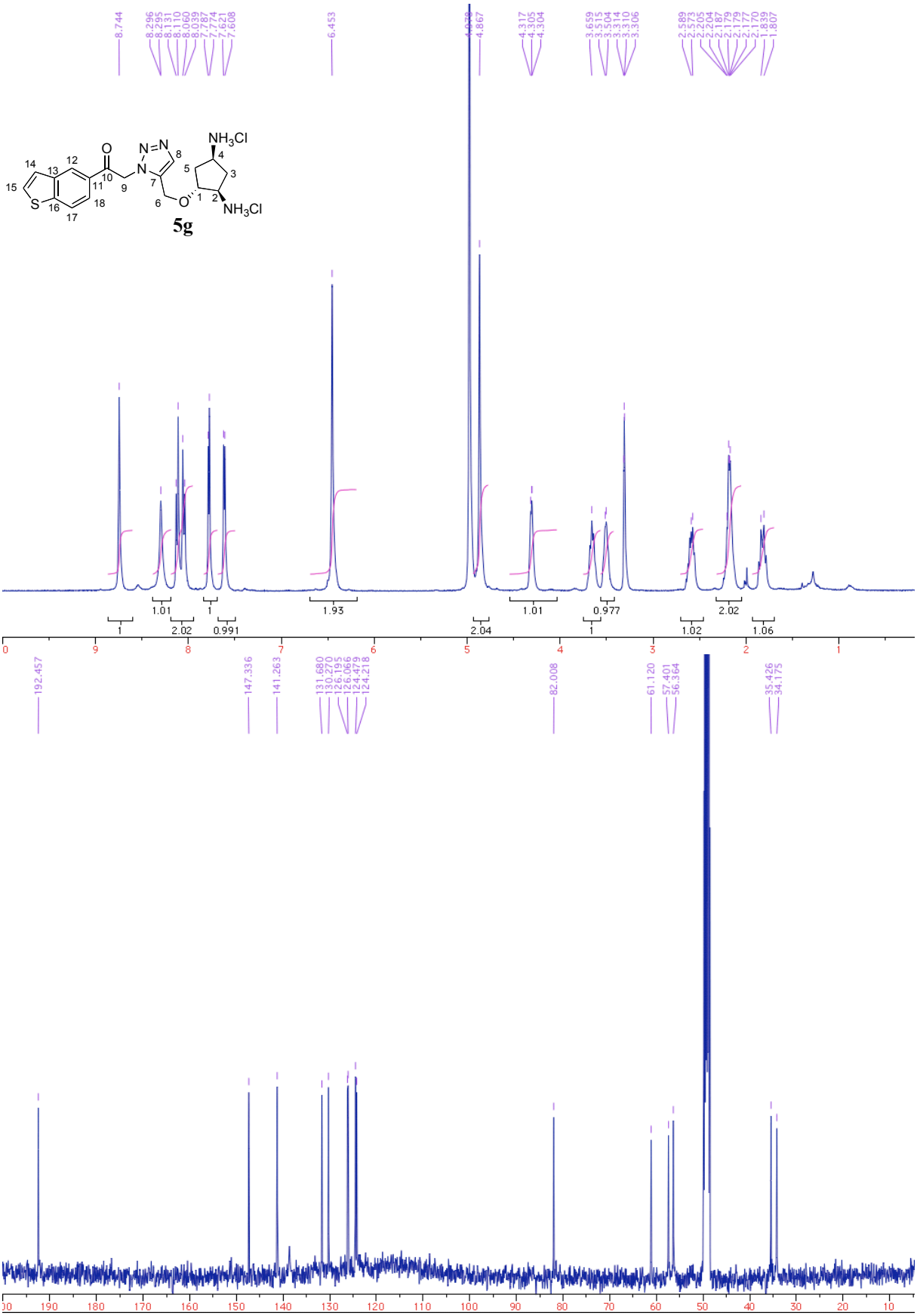
34.949
34.276
20.687
18.548

5f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8.060
8.039
7.787
7.774
7.621
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6.453
4.938
4.867
4.317
4.305
4.304
3.659
3.515
3.504
3.314
3.310
3.306
2.589
2.573
2.205
2.204
2.187
2.179
2.177
2.170
1.839
1.807
NH3Cl
NH3Cl
5g
1.01
2.02
1
0.991
1.93
2.04
1.01
0.977
1
2.02
1.02
1.06
192.457
147.336
141.263
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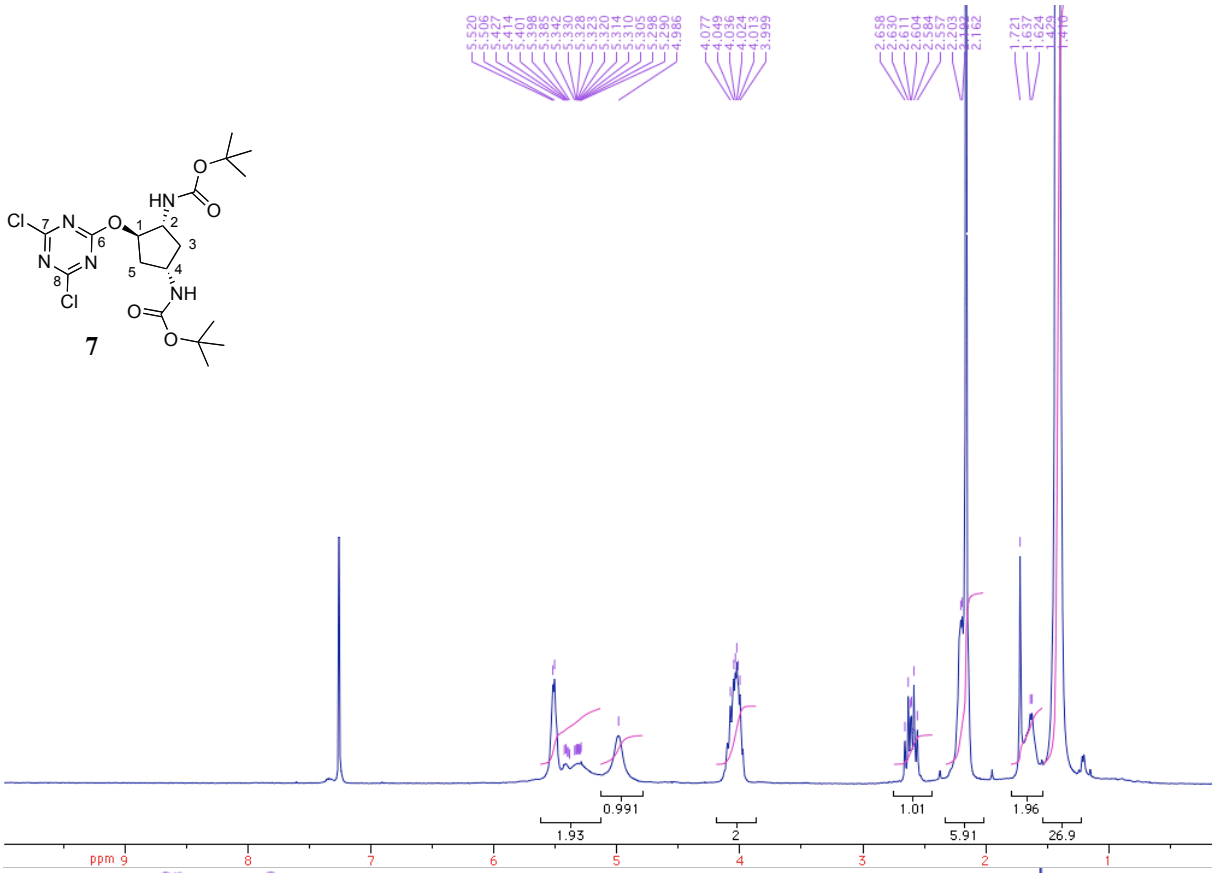
130.270
126.195
126.066
124.478
124.218
82.008
61.120
57.401
56.364
35.426
34.175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5.342
5.340
5.328
5.323
5.320
5.314
5.310
5.305
5.298
5.290
4.986
4.077
4.049
4.036
4.024
4.013
3.999
2.658
2.630
2.611
2.604
2.584
2.557
2.203
2.183
2.162
1.721
1.637
1.624
1.429
1.410
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1.93
2
5.91
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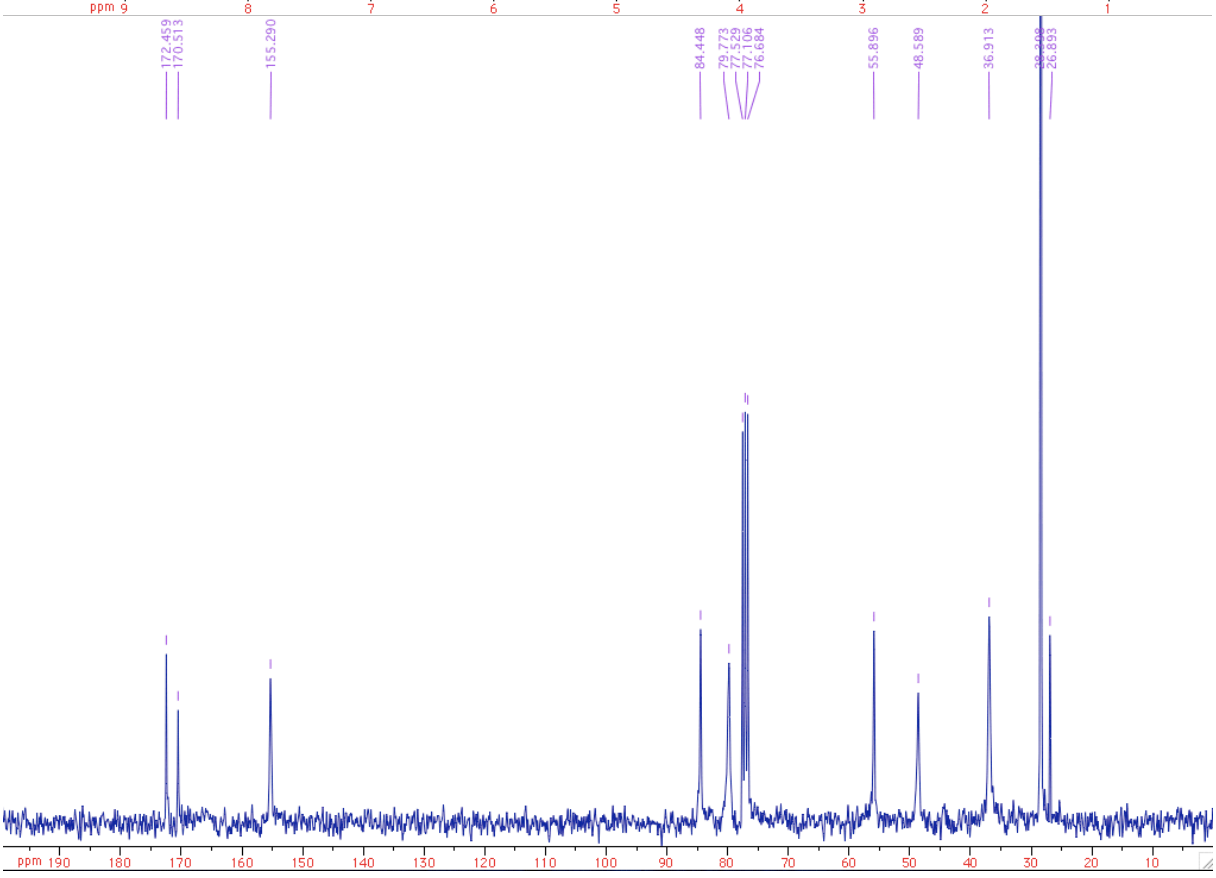
ppm 9
8
7
6
5
4
3
2
1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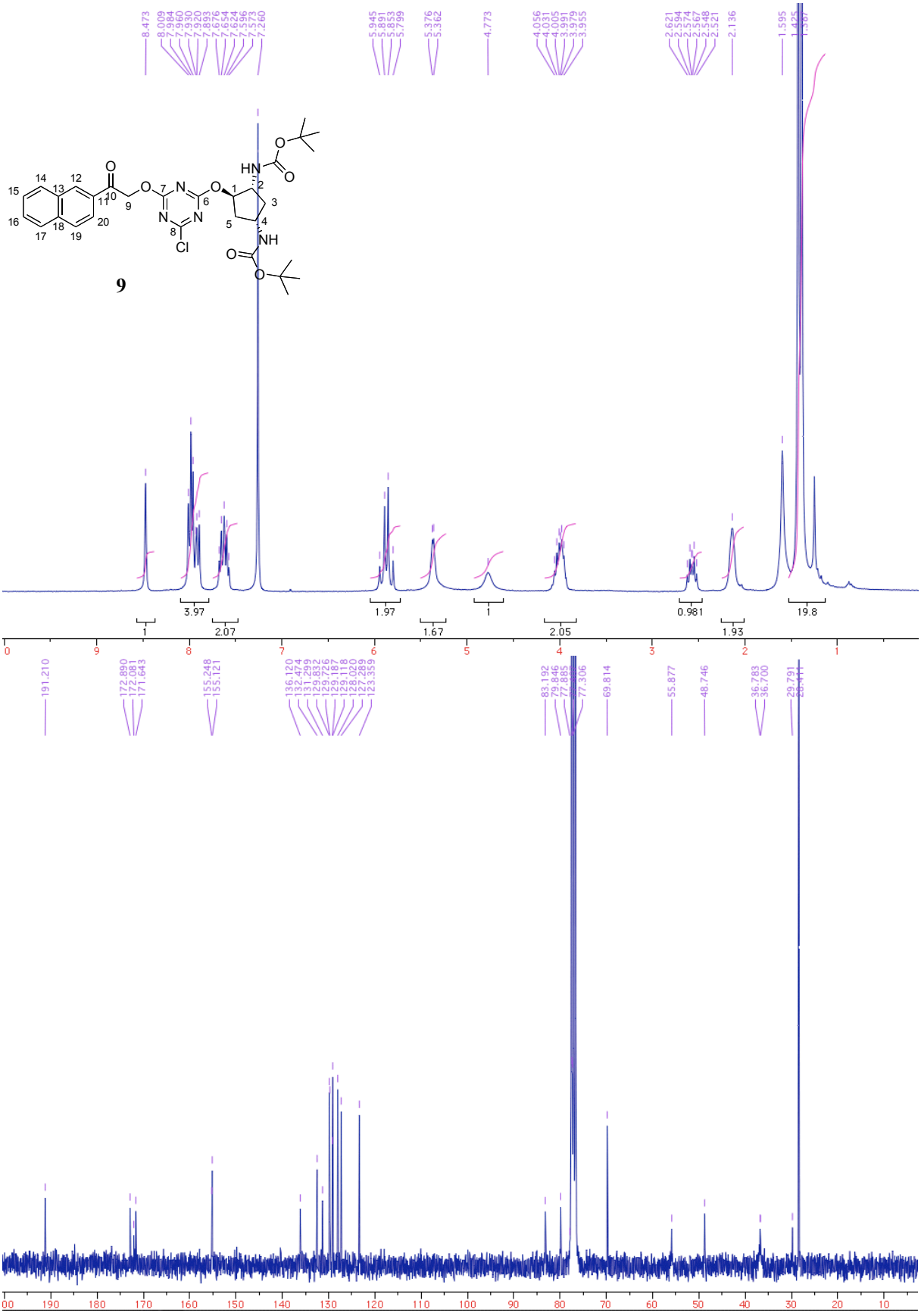
77.529
77.106
76.684
55.896
48.589
36.913
28.298
26.893
ppm 190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

Cl
N
O
HN
O
O
1
2
3
4
5
6
7
8
N
N
Cl
NH
O
O

7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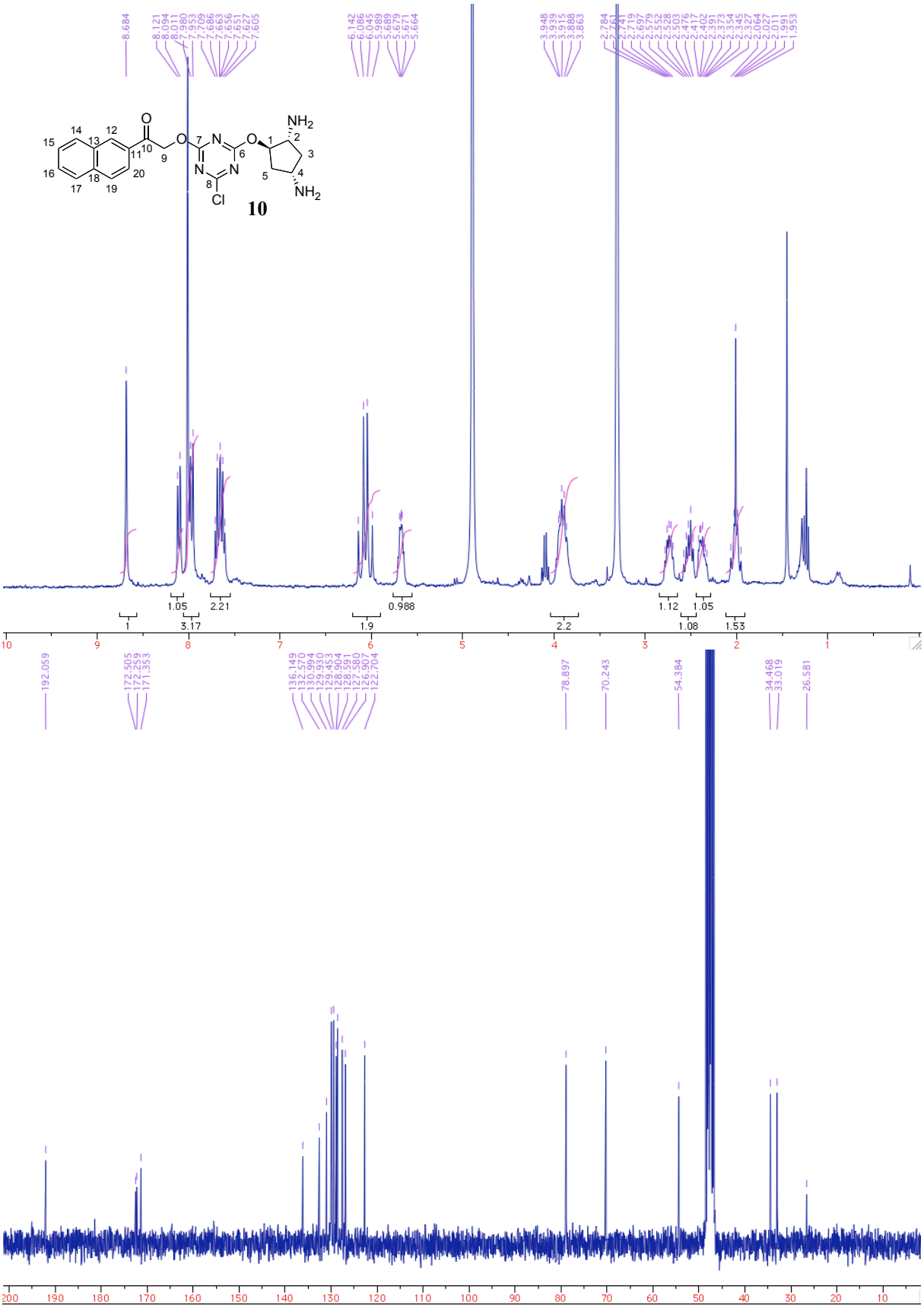
7.676
7.654
7.624
7.596
7.573
7.260
5.945
5.891
5.853
5.799
5.376
5.362
4.773
4.056
4.031
4.005
3.991
3.979
3.955
2.621
2.594
2.574
2.567
2.548
2.521
2.136
1.595
1.425
1.367
3.97
1.97
1
0.981
19.8
1
2.07
1.67
2.05
1.93
0
9
8
7
6
5
4
3
2
1
191.210
172.890
172.081
171.643
155.248
155.121
136.120
132.474
131.299
129.852
129.676
129.187
129.118
128.020
127.289
123.359
83.192
79.846
77.885
77.306
69.814
55.877
48.746
36.783
36.700
29.791
28.411
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

9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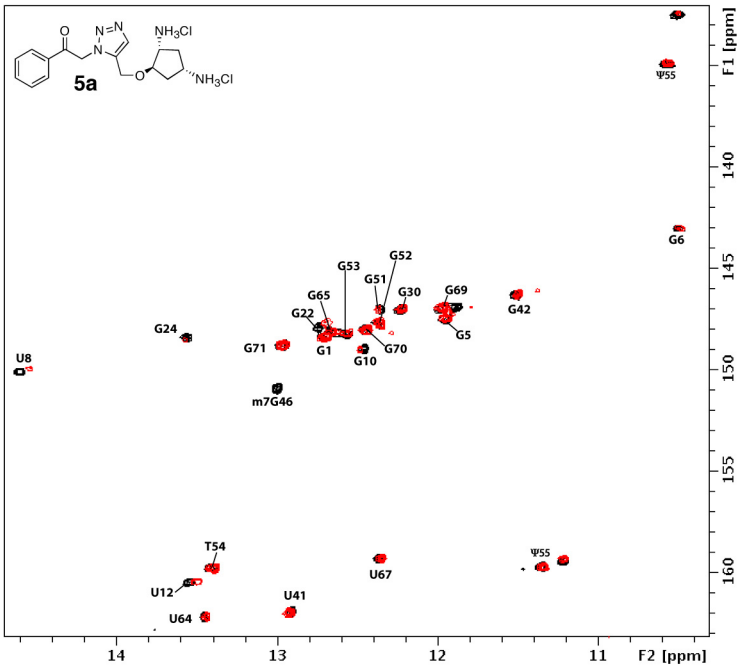
8.094
8.011
7.980
7.953
7.709
7.686
7.663
7.656
7.651
7.627
7.605
6.142
6.086
6.045
5.989
5.689
5.679
5.671
5.664
3.948
3.939
3.915
3.888
3.863
2.784
2.761
2.741
2.719
2.697
2.579
2.552
2.528
2.503
2.476
2.417
2.402
2.391
2.373
2.354
2.345
2.327
2.064
2.027
2.011
1.991
1.953
1.05
3.17
2.21
1.9
0.988
2.2
1.12
1.08
1.05
1.53
192.059
172.505
172.259
171.353
136.149
132.570
130.994
129.930
129.453
128.904
128.591
127.580
126.907
122.704
78.897
70.243
54.384
34.468
33.019
26.581

10

3. Superimposition of TROSY Spectra of $tRNA^{Lys}_3$ (black, 0.2 mM) and $tRNA^{Lys}_3$ (0.2 mM) mixed with compounds 5a-5g and 10 (red)

1:1



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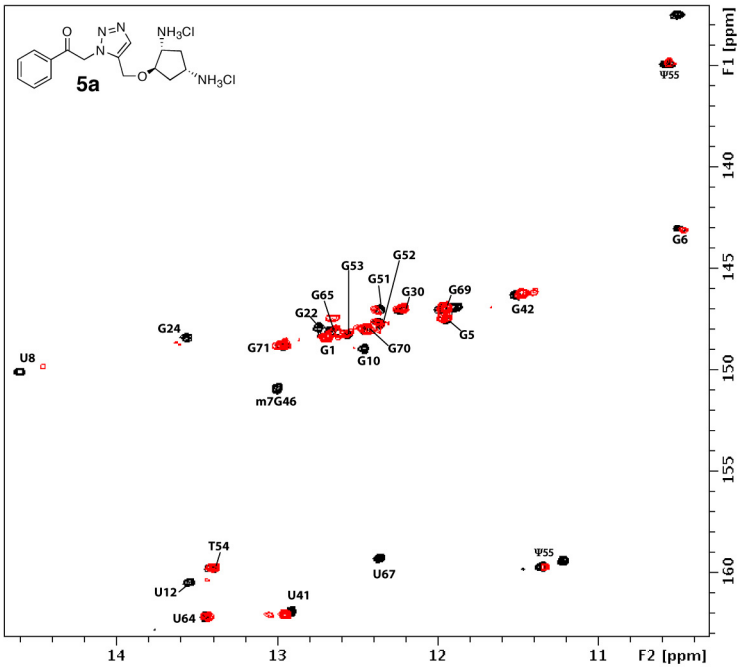

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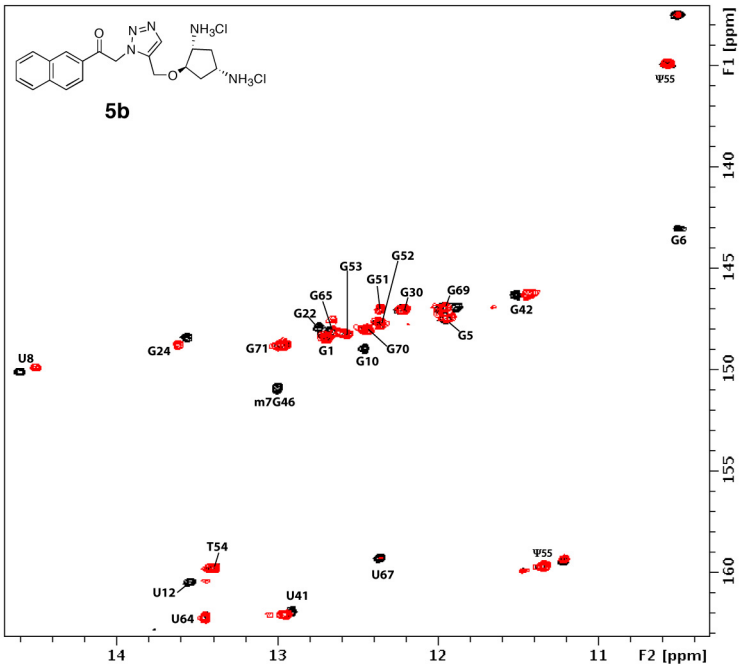
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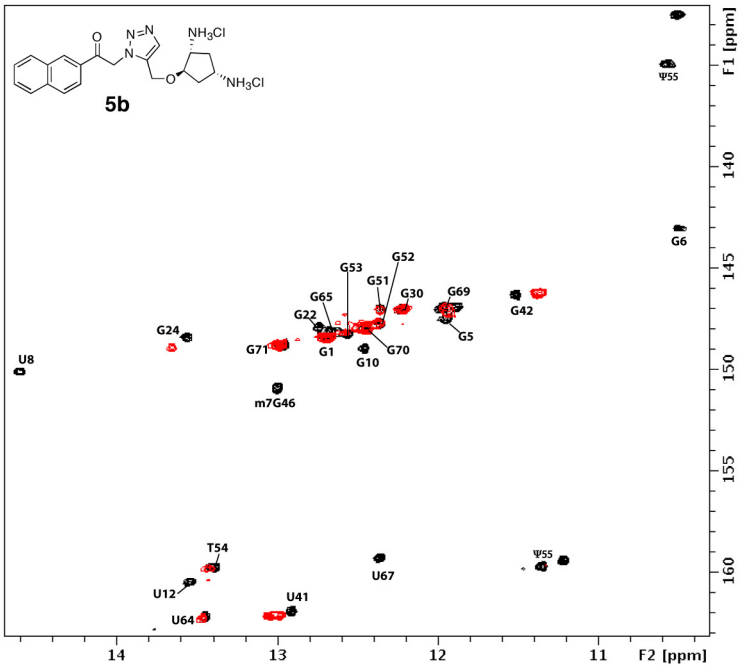
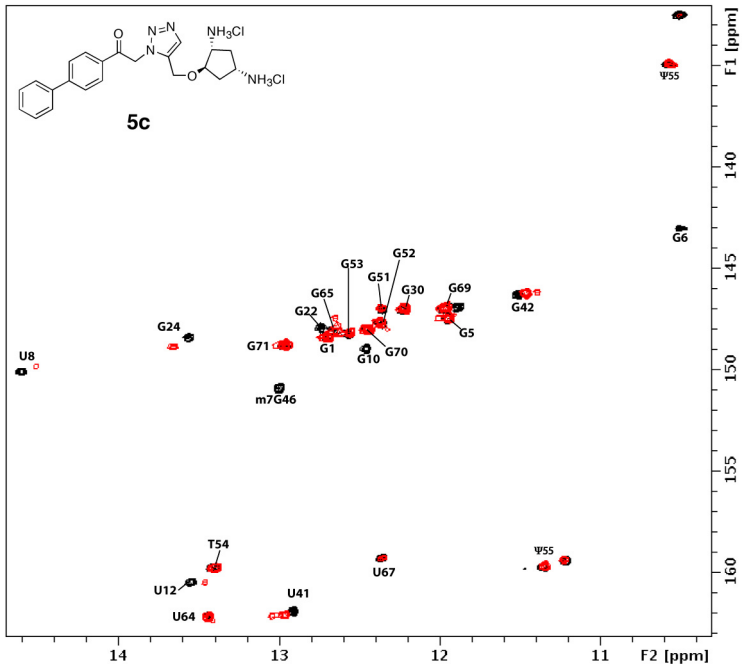
NH3Cl
Ψ55
G6
G53
G52
G51
G65
G30
G69
G22
G42
G5
G24
G71
G1
G70
G10
U8
m7G46
T54
U67
Ψ55
U12
U41
U64
F1 [ppm]
F2 [ppm]
140
145
150
155
160
14
13
12
11

1:4


5b
NH3Cl
NH3Cl
Ψ55
G6
G53
G52
G51
G65
G30
G69
G22
G42
G5
G24
G71
G1
G70
G10
U8
m7G46
T54
U67
Ψ55
U12
U41
U64
F1 [ppm]
F2 [ppm]
140
145
150
155
160
14
13
12
11

1:1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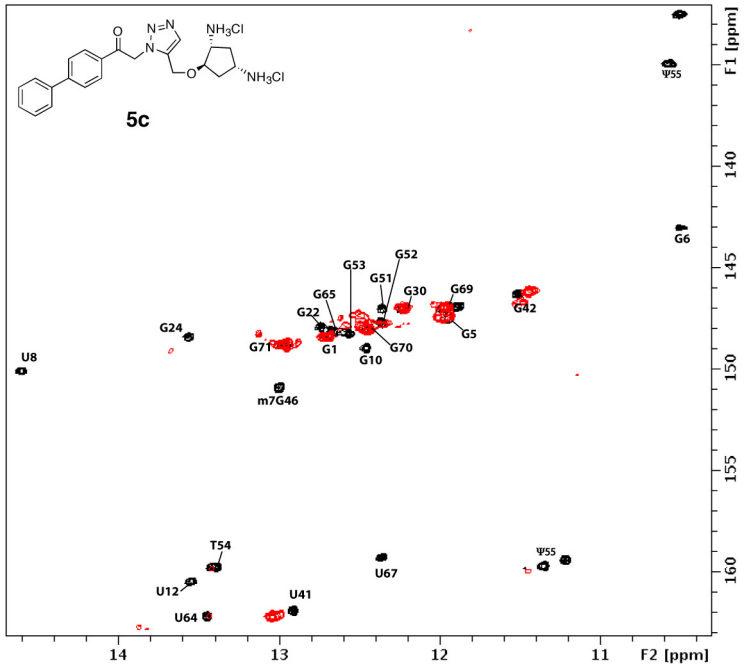
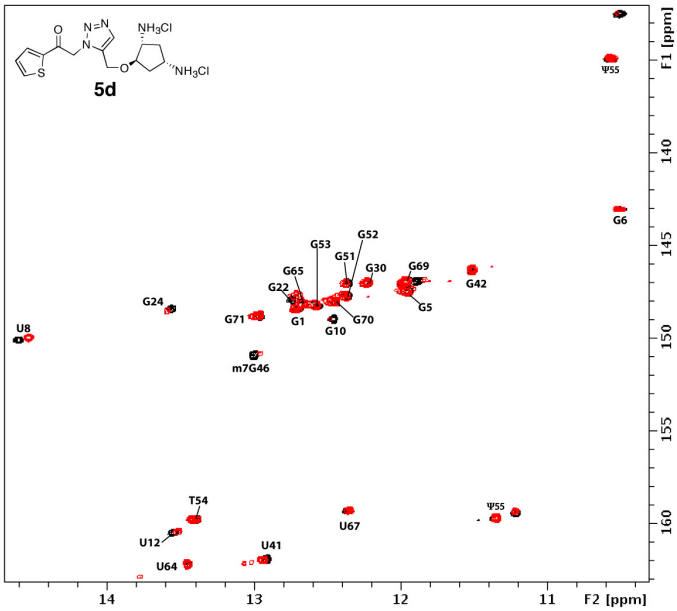
NH3Cl
NH3Cl
Ψ55
G6
G53
G52
G51
G65
G30
G69
G22
G42
G24
G5
G71
G1
G10
G70
U8
m7G46
T54
U67
Ψ55
U12
U41
U64
F1 [ppm]
F2 [ppm]
140
145
150
155
160
14
13
12
11

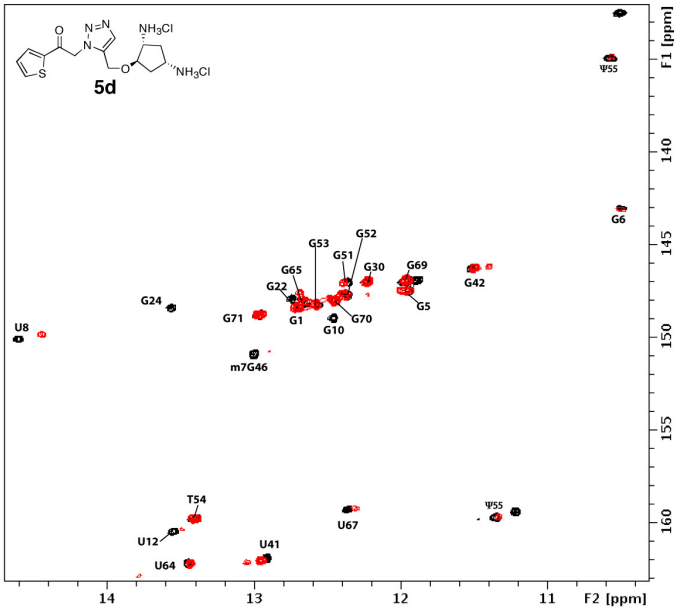
1:4


5c
NH3Cl
NH3Cl
Ψ55
G6
G53
G52
G51
G65
G30
G69
G22
G42
G24
G5
G71
G1
G10
G70
U8
m7G46
T54
U67
Ψ55
U12
U41
U64
F1 [ppm]
F2 [ppm]
140
145
150
155
160
14
13
12
11

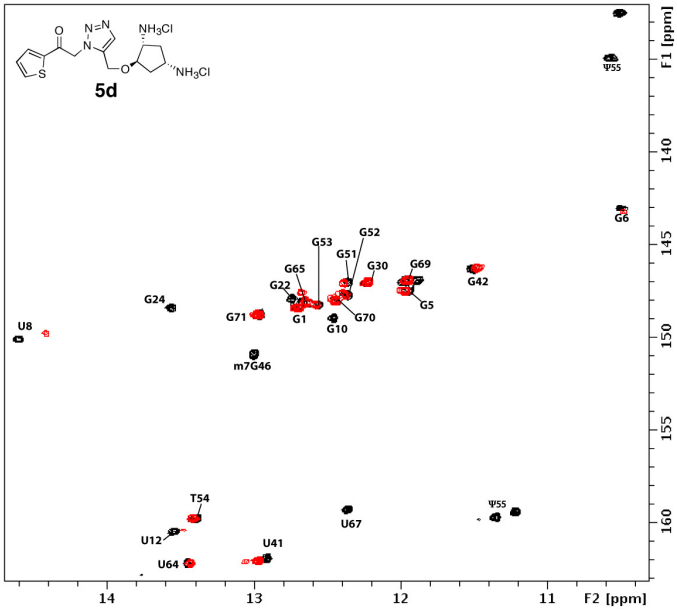
1:1


5d
NH3Cl
NH3Cl
Ψ55
G6
G53
G52
G51
G65
G30
G69
G22
G42
G24
G5
G71
G1
G70
G10
U8
m7G46
T54
U67
Ψ55
U12
U41
U64
F1 [ppm]
F2 [ppm]
14
13
12
11
140
145
150
155
160

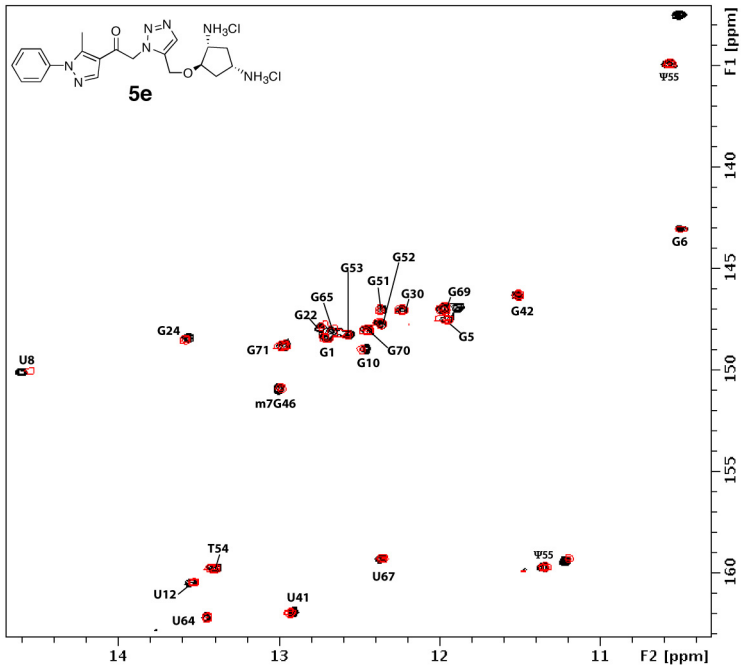
1:4


5d
NH3Cl
NH3Cl
Ψ55
G6
G53
G52
G51
G65
G30
G69
G22
G42
G24
G5
G71
G1
G70
G10
U8
m7G46
T54
U67
Ψ55
U12
U41
U64
F1 [ppm]
F2 [ppm]
14
13
12
11
140
145
150
155
160

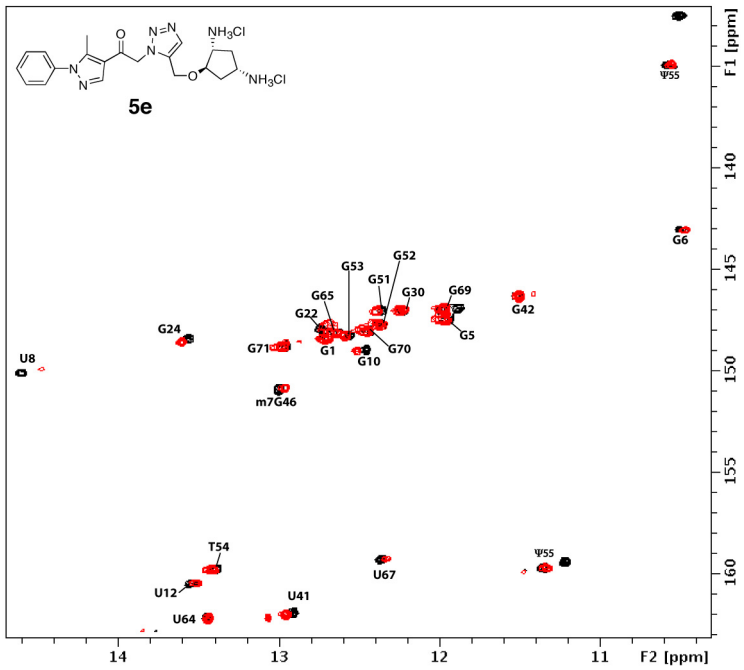
1:7


5d
NH3Cl
NH3Cl
Ψ55
G6
G53
G52
G51
G65
G30
G69
G22
G42
G24
G5
G71
G1
G70
G10
U8
m7G46
T54
U67
Ψ55
U12
U41
U64
F1 [ppm]
F2 [ppm]
14
13
12
11
140
145
150
155
160

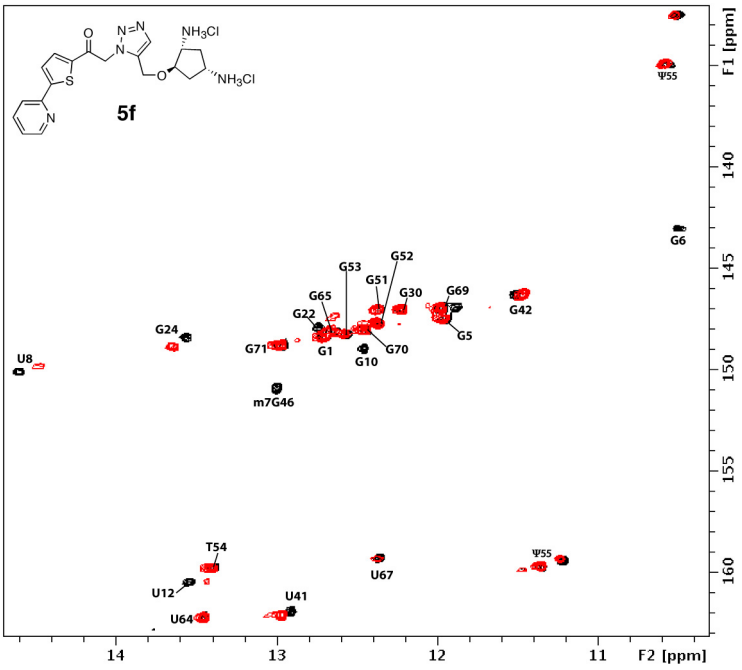
1:1


5e
NH3Cl
NH3Cl
Ψ55
G6
G53
G52
G51
G65
G30
G69
G22
G42
G24
G5
G71
G1
G70
G10
U8
m7G46
T54
U67
Ψ55
U12
U41
U64
F1 [ppm]
F2 [ppm]
140
145
150
155
160
14
13
12
11

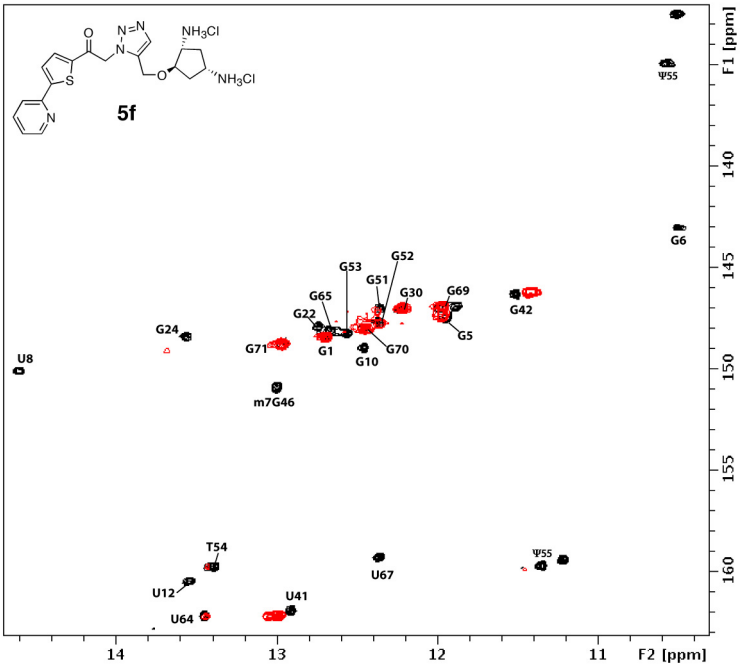
1:4


5e
NH3Cl
NH3Cl
Ψ55
G6
G53
G52
G51
G65
G30
G69
G22
G42
G24
G5
G71
G1
G70
G10
U8
m7G46
T54
U67
Ψ55
U12
U41
U64
F1 [ppm]
F2 [ppm]
140
145
150
155
160
14
13
12
11

1:1


5f
NH3Cl
NH3Cl
Ψ55
G6
G53
G52
G51
G65
G30
G69
G22
G42
G24
G5
G71
G1
G70
G10
U8
m7G46
T54
U67
Ψ55
U12
U41
U64
F1 [ppm]
F2 [ppm]
140
145
150
155
160
14
13
12
11

1:4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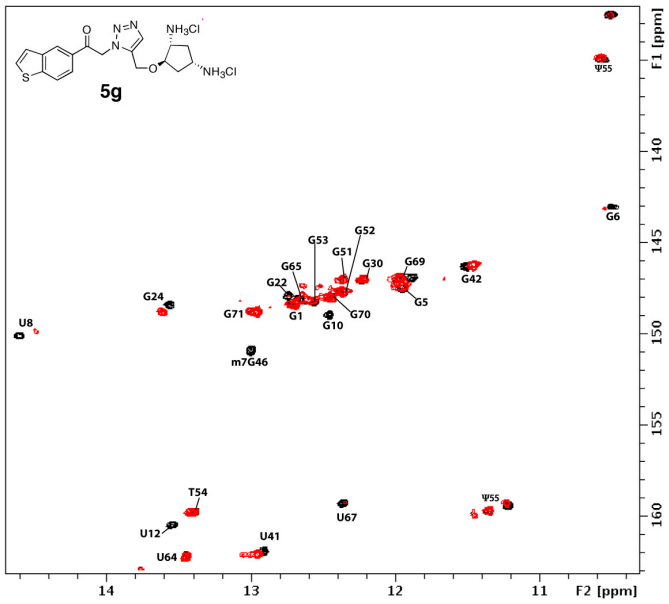
NH3Cl
Ψ55
G6
G53
G52
G51
G65
G30
G69
G22
G42
G24
G5
G71
G1
G70
G10
U8
m7G46
T54
U67
Ψ55
U12
U41
U64
F1 [ppm]
F2 [ppm]
140
145
150
155
160
14
13
12
11

1:1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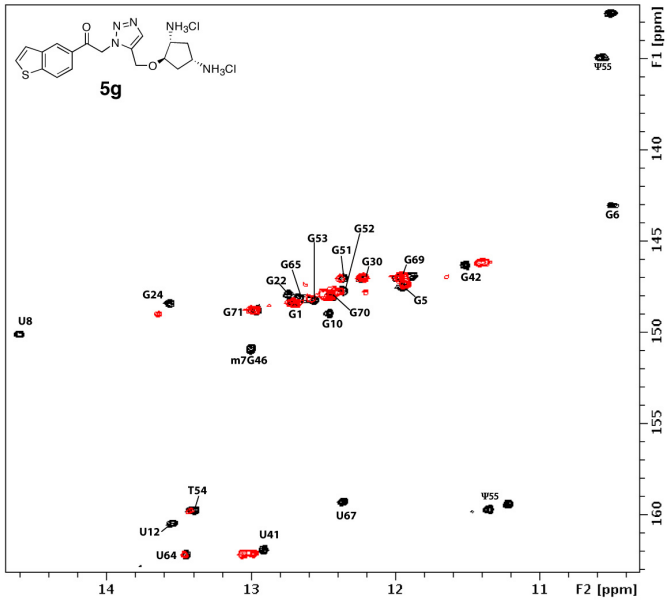
NH3Cl
Ψ55
G6
G53
G52
G51
G65
G30
G69
G22
G42
G24
G5
G71
G1
G70
G10
U8
m7G46
T54
U67
Ψ55
U12
U41
U64
F1 [ppm]
F2 [ppm]
14
13
12
11
140
145
150
155
160

1:4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NH3Cl
Ψ55
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G53
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G5
G71
G1
G70
G10
U8
m7G46
T54
U67
Ψ55
U12
U41
U64
F1 [ppm]
F2 [ppm]
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13
12
11
140
145
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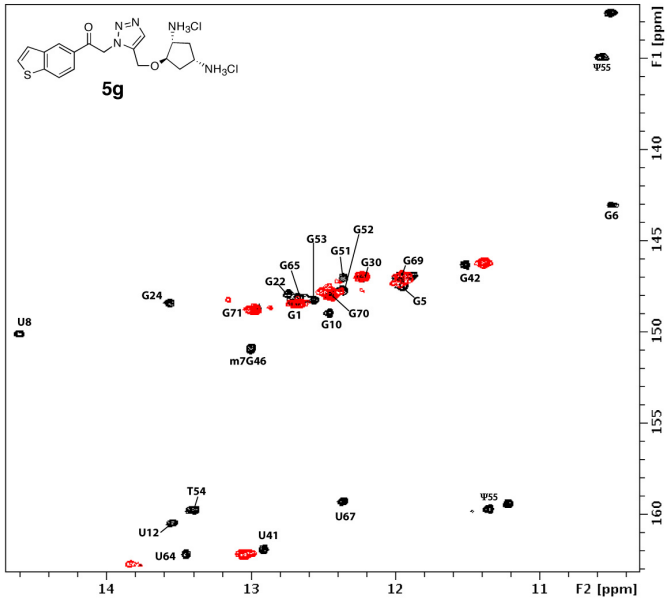
155
160

1:7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NH3Cl
Ψ55
G6
G53
G52
G51
G65
G30
G69
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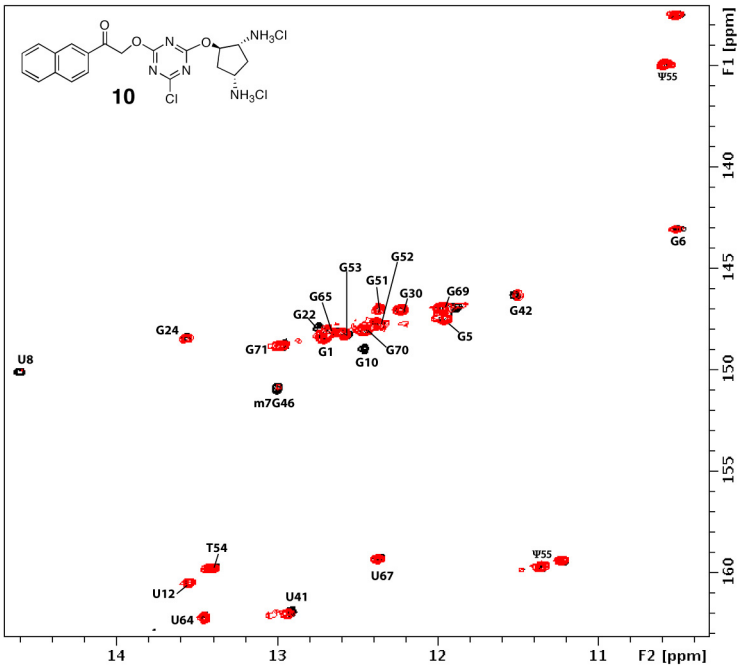
G42
G24
G5
G71
G1
G70
G10
U8
m7G46
T54
U67
Ψ55
U12
U41
U64
F1 [ppm]
F2 [ppm]
14
13
12
11
140
145
150
155
160

1:1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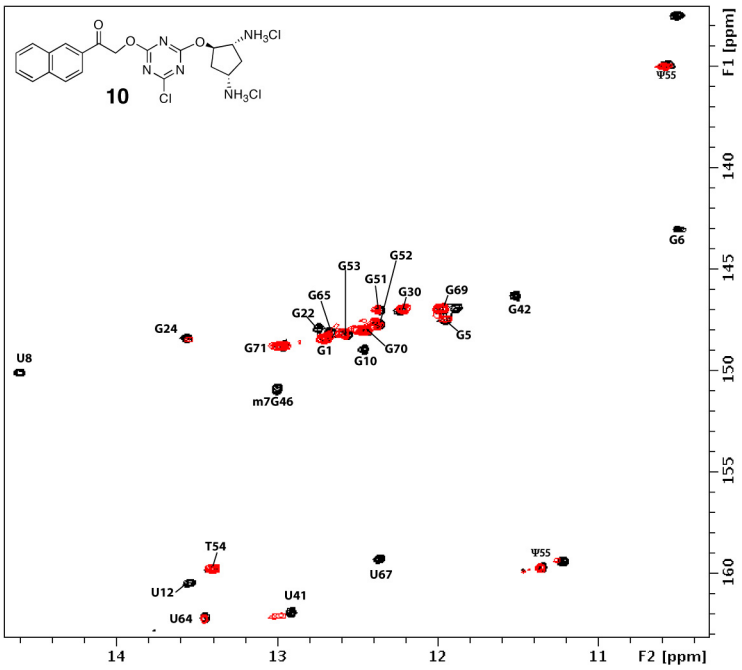
Cl
NH3Cl
Ψ55
G6
G53
G52
G51
G65
G30
G69
G22
G42
G24
G5
G71
G1
G70
G10
U8
m7G46
T54
U67
Ψ55
U12
U41
U64
14
13
12
11
F2 [ppm]
F1 [ppm]
140
145
150
155
160

1:4


10
NH3Cl
Cl
NH3Cl
Ψ55
G6
G53
G52
G51
G65
G30
G69
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G42
G24
G5
G71
G1
G70
G10
U8
m7G46
T54
U67
Ψ55
U12
U41
U64
14
13
12
11
F2 [ppm]
F1 [ppm]
140
145
150
155
160

Additional data: selectivity study of 5b.

$tRNA_m^{Met}$ has a D-arm sequence identical to $tRNA^{Lys}_3$, but differs in its T-arm, in which the G65-C51 base pair is replaced by U65-A51. 1D NMR chemical shift perturbation (CSP) on $tRNA_m^{Met}$ (Figure 1 below) was conducted with compound **5b**. For this tRNA, in 1D spectra, three NMR signals located in the T-arm could be followed during the titration (Figure 1). Contrary to the results obtained with $tRNA^{Lys}_3$ (see Figure 2 bellow), almost no perturbations are observed on the T-arm signals of $tRNA_m^{Met}$ when increasing the concentration of **5b**. Thus, **5b** clearly interacts with the T-arm of $tRNA^{Lys}_3$, and this interaction seems to be specific. Furthermore, no secondary binding site appears at similar (and even greater) concentrations for compounds **1** or **10**.

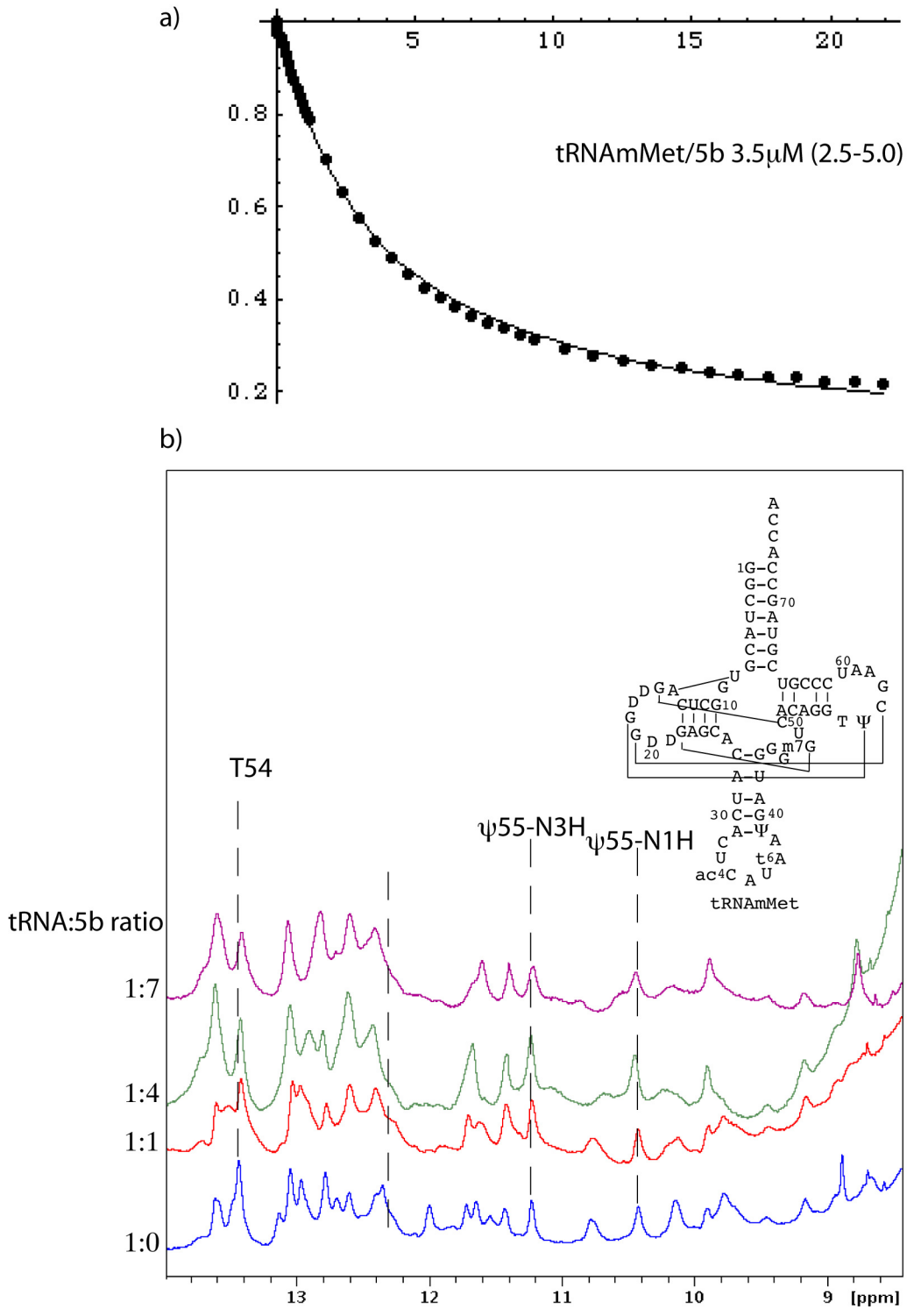

Fig. 1 a) Fluorescence titrations of compounds 5b with $tRNA_m^{Met}$. The value of Kd are indicated with the 95% confidence interval in parenthesis. b) 1D ^1H NMR spectra showing the imino proton resonances of $tRNA_m^{Met}$ (0.4 mM) when increasing concentration of compound **5b** is added. The tRNA:5b ratio are indicated on the left of the spectra.

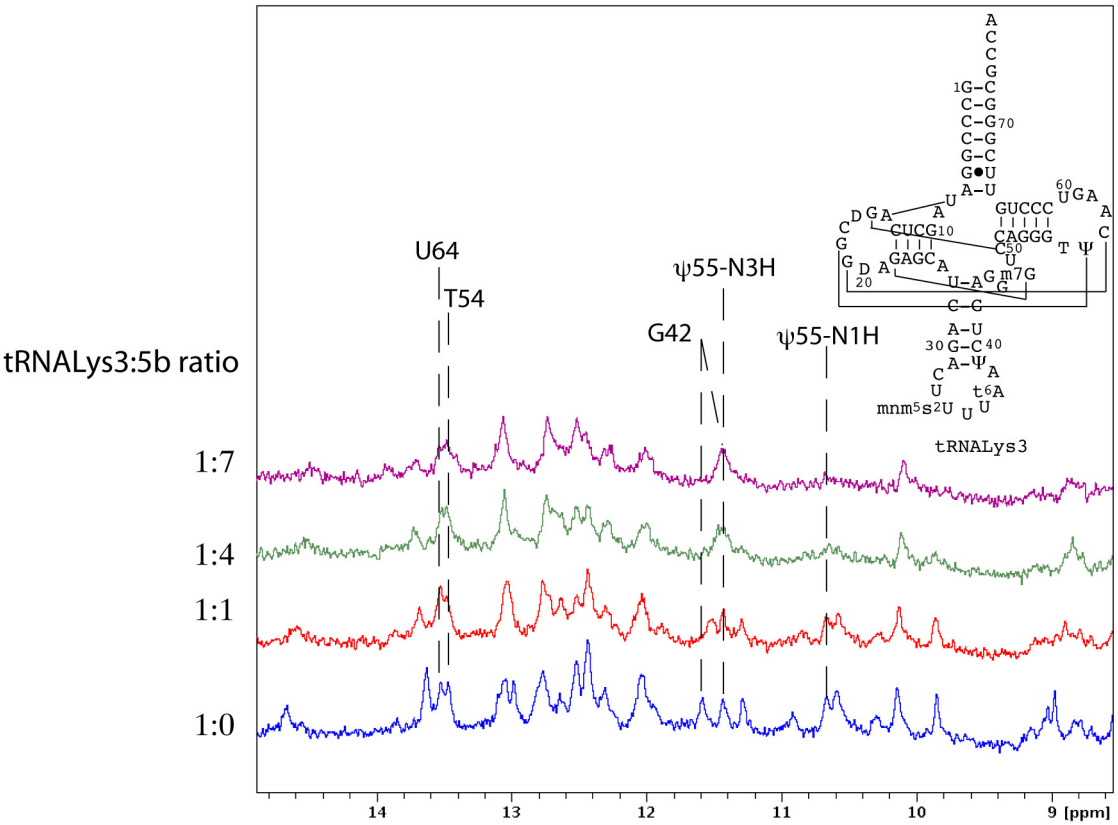

Fig 2 1D ^{1}H NMR spectra showing the imino proton resonances of $tRNA^{Lys}_{3}$ (100 µM) when increasing concentration of compound **5b** is added. The tRNA:5b ratio are indicated on the left of the spectra.