Ligand-Controlled Switch in Diastereoselectivities: Catalytic Asymmetric Construction of Spirocyclic Pyrrolidine-azetidine/oxe(thie)tane Derivatives

Hua Deng,† Renmeng Jia,† Wu-Lin Yang, Xingxin Yu* and Wei-Ping Deng*

Shanghai Key Laboratory of New Drug Design & School of Pharmacy, East China University of Science and Technology, 130 Meilong Road, Shanghai, 200237, China

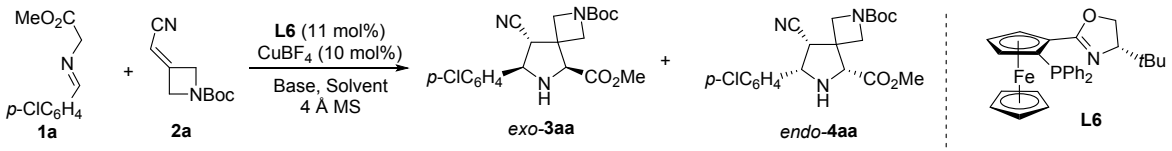
Table of Contents

General information

^{1}H NMR spectrum were recorded on a Bruker AVANCE III 400 MHz spectrometer in $CDCl_3$. Chemical shifts were reported in ppm with the internal TMS signal at 0.0 ppm as a standard. The spectrums are interpreted as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, brs = broad singlet, coupling constant(s) *J* are reported in Hz and relative integrations are reported. ^{13}C NMR (100 MHz) spectrums were recorded on a Bruker AVANCE III 400 MHz spectrometer in $CDCl_3$. Chemical shifts were reported in ppm with the internal chloroform signal at 77.06 ppm as a standard. Optical rotations were measured on an AUTOPOL V. Diastereomeric ratios and enantiomeric excesses were determined from crude ^{1}H NMR spectroscopy interpretation or by analysis of HPLC traces, obtained by using chiralpak AD-H columns with *n*-hexane and *i*-propanol or ethanol as solvents. (Chiralpak AD-H columns were purchased from Daicel Chemical Industries, LTD.) Melting points were obtained in open capillary tubes using SGW X-4 micro melting point apparatus which were uncorrected. Mass spectrums were recorded on TOF mass Waters GCT Premier and Xevo G2 spectrometer. Solvents were dried and distilled following usual protocols. Commercially available materials purchased from Adamas-beta, TCI or Energy Chemical and were used as received.

Imino esters[1] and exocyclic alkenes: *tert*-butyl 3-(2-methoxy-2-oxoethylidene)azetidine-1-carboxylate (**2b**),[2] *tert*-butyl 3-(2-ethoxy-2-oxoethylidene)azetidine-1-carboxylate (**2c**)[2] and 2-(1-tosylazetidin-3-ylidene)acetonitrile (**2d**),[2] 2-(oxetan-3-ylidene)acetonitrile (**2e**),[2] methyl 2-(oxetan-3-ylidene)acetate (**2f**),[2] 2-(thietan-3-ylidene)acetonitrile (**2g**),[3] ethyl 2-(thietan-3-ylidene)acetate (**2h**)[2], *tert*-butyl 4-(cyanomethylene)piperidine-1-carboxylate (**2i**)[4] were prepared according to the literature procedure, *tert*-butyl 3-(cyanomethylene)azetidine-1-carboxylate (**2a**) were purchased from Bidepharm and were used as received.

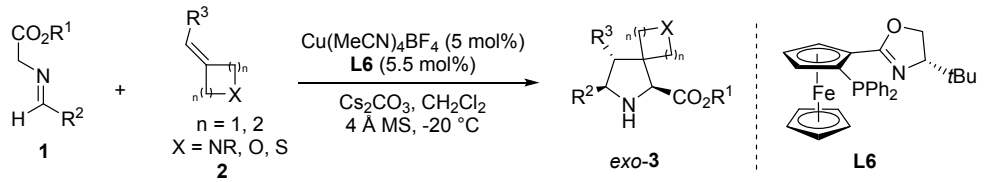
Table S1. Optimization of the reaction conditions



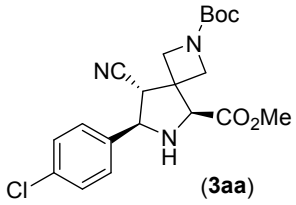
Entry	Solvent	Base	Metal	Yield(%)[b]	*exo*/*endo*[c]	ee(%)[c]
1	CH_2Cl_2	Cs_2CO_3	$CuBF_4$	96	8:1	97
2	THF	Cs_2CO_3	$CuBF_4$	94	7:1	97
3	Et_2O	Cs_2CO_3	$CuBF_4$	95	7:1	96
4	TBME	Cs_2CO_3	$CuBF_4$	96	7:1	96
5	$(CH_2Cl)_2$	Cs_2CO_3	$CuBF_4$	97	6:1	97
6	toluene	Cs_2CO_3	$CuBF_4$	95	4:1	95
7	CH_3CN	Cs_2CO_3	$CuBF_4$	95	4:1	95
8	$CHCl_3$	Cs_2CO_3	$CuBF_4$	96	8:1	96
9	Dioxane	Cs_2CO_3	$CuBF_4$	97	8:1	96
10	2-MeTHF	Cs_2CO_3	$CuBF_4$	89	8:1	95
11	CH_3OH	Cs_2CO_3	$CuBF_4$	trace	-	-
12	THF/CH_3OH	Cs_2CO_3	$CuBF_4$	trace	-	-
13[d]	CH_2Cl_2	DBU	$CuBF_4$	96	4:1	97
14[d]	CH_2Cl_2	Et_3N	$CuBF_4$	93	8:1	93
15[e]	CH_2Cl_2	K_2CO_3	$CuBF_4$	96	7:1	96
16[d]	CH_2Cl_2	LiHMDS	$CuBF_4$	92	7:1	95
17[d]	CH_2Cl_2	DIPEA	$CuBF_4$	trace	-	-
18[d]	CH_2Cl_2	TMG	$CuBF_4$	84	4:1	95
19[d]	CH_2Cl_2	DABCO	$CuBF_4$	60	8:1	97
20[d]	CH_2Cl_2	*t*BuOK	$CuBF_4$	92	6:1	97
21[d]	CH_2Cl_2	DMAP	$CuBF_4$	NR	-	-
22[e]	CH_2Cl_2	Na_2CO_3	$CuBF_4$	94	8:1	96
23[d]	CH_2Cl_2	NaOH	$CuBF_4$	94	9:1	95
24[d]	CH_2Cl_2	KOH	$CuBF_4$	94	8:1	96
25	CH_2Cl_2	Cs_2CO_3	$CuPF_6$	70	4:1	94
26	CH_2Cl_2	Cs_2CO_3	$Cu(OTf)_2$	93	9:1	96
27	CH_2Cl_2	Cs_2CO_3	CuOAc	86	4:1	95
28	CH_2Cl_2	Cs_2CO_3	$AgSbF_6$	88	1.3:1	76/81
29	CH_2Cl_2	Cs_2CO_3	AgF	91	1.6:1	73/84
30	CH_2Cl_2	Cs_2CO_3	$AgBF_4$	79	1.3:1	73/85
31	CH_2Cl_2	Cs_2CO_3	$AgClO_4{\cdot}H_2O$	NR	-	-
32	CH_2Cl_2	Cs_2CO_3	Ag_2CO_3	94	1.3:1	73/77

[a] Unless otherwise stated, the reactions were performed with **1a** (0.12 mmol), **2a** (0.10 mmol) in 1.0 mL of solvent, under an N_2 atmosphere at rt, 1 equiv of base was used, $CuBF_4$ = $Cu(MeCN)_4BF_4$, $CuPF_6$ = $Cu(MeCN)_4PF_6$, TMG = Tetramethylguanidine. [b] Isolated yield. [c] The ratio of *exo*/*endo* was determined by ^1H NMR spectroscopy or/and chiral HPLC analysis, and the ee was determined by chiral HPLC analysis. [d] 20 mol% of base was used. [e] 2 equiv of base was used.

General procedure

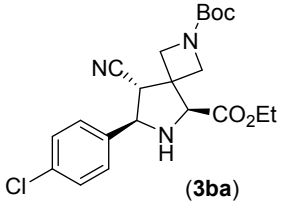


At a nitrogen atmosphere, $Cu(CH_3CN)_4BF_4$ (3.1 mg, 0.01 mmol) and **L6** (5.8 mg, 0.011mmol) were dissolved in 2.0 mL dry CH_2Cl_2, subsequently add 4Å Ms (100 mg), and stirred at room temperature for about 1 h. Then, iminoester **1** (0.24 mmol) and Cs_2CO_3 (65.2 mg, 0.2 mmol) were added, the mixture was cooled to -20 °C and alkene **2** (0.2 mmol) was added. Once starting material was consumed (about 0.5-1 h, monitored by TLC), the mixture was concentrated and the residue was purified by column chromatography (petroleum ether/ethyl acetate 6:1 to 2:1) on silica gel to afford the corresponding product **3**.



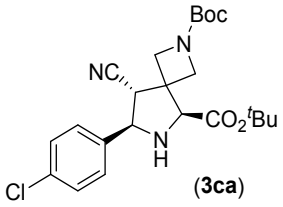
(**3aa**)

2-(*tert*-Butyl) 5-methyl (5*S*,7*R*,8*R*)-7-(4-chlorophenyl)-8-cyano-2,6-diazaspiro[3.4]octane-2,5-dicarboxylate White solid, yield: 98%; m.p.: 165-167 °C; $[\alpha]_D^{25}$ = +134.5 (*c* 1.00, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 – 7.42 (m, 2H), 7.39 – 7.33 (m, 2H), 4.35 (d, *J* = 9.3 Hz, 1H), 4.29 (d, *J* = 9.1 Hz, 1H), 4.13 (s, 1H), 4.05 (d, *J* = 9.2 Hz, 1H), 3.94 (d, *J* = 9.7 Hz, 1H), 3.86 (d, *J* = 9.8 Hz, 1H), 3.83 (s, 3H), 3.22 (d, *J* = 9.3 Hz, 1H), 2.52 (brs, 1H), 1.45 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.4, 155.8, 137.5, 134.6, 129.2 (2C), 128.1 (2C), 116.9, 80.4, 66.2, 63.5, 58.2, 54.2, 52.7, 46.0, 45.3, 28.3 (3C). **HRMS** (ESI-TOF) calcd for $[C_{20}H_{24}ClN_3O_4+H]^+$: 406.1528, found: 406.1532; **HPLC** (Chiralpak AD-H, *n*-hexane/*i*-propanol = 80/20, 1.0 mL/min, 220 nm) t_R = 10.40 min, 16.03 min.



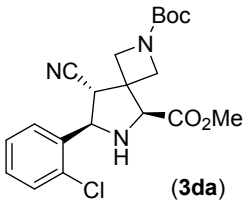
(**3ba**)

2-(*tert*-Butyl) 5-ethyl (5*S*,7*R*,8*R*)-7-(4-chlorophenyl)-8-cyano-2,6-diazaspiro[3.4]octane-2,5-dicarboxylate White solid, yield: 97%; m.p.: 169-171 °C; $[\alpha]_D^{25}$ = +141.3(*c* 1.00, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), δ 4.52 (d, *J* = 7.1 Hz, 1H, minor), 4.41 – 4.23 (m, 4H), 4.17 (d, *J* = 8.9 Hz, 1H, minor), 4.13 – 4.03 (m, 2H), 3.97 (d, *J* = 9.4 Hz, 1H), 3.85 (d, *J* = 9.7 Hz, 1H), 3.48 (d, *J* = 7.1 Hz, 1H, minor), 3.21 (d, *J* = 9.1 Hz, 1H), 2.54 (s, 1H), 1.45 (s, 9H,), 1.35 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (major + minor) 171.8, 171.1, 170.8, 155.7, 137.6, 134.5, 129.1 (2C), 129.0, 128.4, 128.0 (2C), 117.0, 80.3, 66.2, 63.5, 62.1, 61.9, 61.1, 60.4, 58.1, 54.4, 46.3, 46.1, 45.2, 45.0, 28.3 (3C), 21.0, 14.2. **HRMS** (ESI-TOF) calcd for $[C_{21}H_{26}ClN_3O_4+H]^+$: 420.1685, found: 420.1689; **HPLC** (Chiralpak AD-H, *n*-hexane/*i*-propanol = 80/20, 1.0 mL/min, 220 nm) t_R = 10.15 min, 17.21 min.



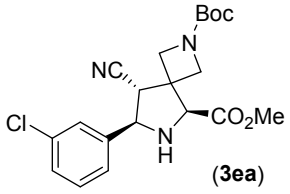
(**3ca**)

2-*tert*-Butyl (5*S*,7*R*,8*R*)-7-(4-chlorophenyl)-8-cyano-2,6-diazaspiro[3.4]octane-2,5-dicarboxylate White solid, yield: 96%; m.p.: 174-176 °C; $[\alpha]_D^{25}$ = +174.2(*c* 1.00, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.5 Hz, 2H), 77.39 – 7.33 (m, 2H), 7.37 – 7.32 (m, 1H, minor), 4.52 (d, *J* = 7.5 Hz, 1H, minor), 4.35 (d, *J* = 8.6 Hz, 1H), 4.27 (d, *J* = 9.1 Hz, 1H), 4.17 (d, *J* = 8.8 Hz, 1H, minor), 4.09 (d, *J* = 9.2 Hz, 1H), 4.06 – 3.98 (m, 1H), 3.97 (s, 1H), 3.94 – 3.89 (m, 2H, minor), 3.86 (s, 1H, minor), 3.79 (d, *J* = 9.6 Hz, 1H), 3.48 (d, *J* = 7.5 Hz, 1H, minor), 3.16 (d, *J* = 8.6 Hz, 1H), 2.51 (brs, 1H), 1.56 (s, 9H, minor), 1.53 (s, 9H), 1.45 (s, 9H), 1.43 (s, 9H, minor). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (major + minor) 170.7, 169.7, 155.6, 155.4, 137.8, 136.8, 134.5, 129.2 (2C), 129.0, 128.4, 128.0 (2C), 117.3, 116.1, 83.6, 83.2, 80.3, 66.8, 66.6, 63.5, 61.1, 57.5, 54.6, 46.6, 46.3, 45.0, 44.6, 28.4 (3C), 28.1 (3C), 28.0. **HRMS** (ESI-TOF) calcd for $[C_{23}H_{30}ClN_3O_4+H]^+$: 448.1998, found: 448.2002; **HPLC** (Chiralpak AD-H, *n*-hexane/*i*-propanol = 80/20, 1.0 mL/min, 220 nm) t_R = 8.63 min, 15.91 min.



(**3da**)

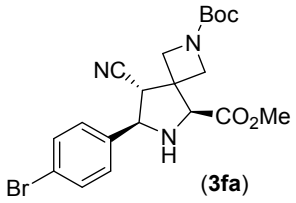
2-(*tert*-Butyl) 5-methyl (5*S*,7*R*,8*R*)-7-(2-chlorophenyl)-8-cyano-2,6-diazaspiro[3.4]octane-2,5-dicarboxylate White solid, yield: 96%; m.p.: 156-158 °C; $[\alpha]_D^{25}$ = +215.4(*c* 1.00, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 7.6, 1.9 Hz, 1H), 7.38 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.35 – 7.21 (m, 2H), 4.98 (d, *J* = 5.3 Hz, 1H), 4.88 (d, *J* = 7.0 Hz, 1H, minor), 4.31 – 4.19 (m, 3H), 4.06 (s, 2H, minor), 4.02 (s, 1H, minor), 3.96 (d, *J* = 9.0 Hz, 1H, , minor), 3.86 (s, 3H), 3.79 (d, *J* = 9.8 Hz, 1H), 3.74 (d, *J* = 7.1 Hz, 1H, minor), 3.46 (d, *J* = 9.8 Hz, 1H), 3.35 (d, *J* = 5.3 Hz, 1H), 2.61 (brs, 1H), 1.42 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.8, 155.8, 137.6, 132.9, 129.8, 129.6, 127.8, 127.5, 117.7, 80.3, 65.4, 60.0, 56.0, 56.0, 52.6, 45.8, 44.6, 28.3 (3C). **HRMS** (ESI-TOF) calcd for $[C_{20}H_{24}ClN_3O_4+H]^+$: 406.1528, found: 406.1533; **HPLC** (Chiralpak AD-H, *n*-hexane/*i*-propanol = 80/20, 1.0 mL/min, 220 nm) t_R = 8.36 min, 17.57 min.



(**3ea**)

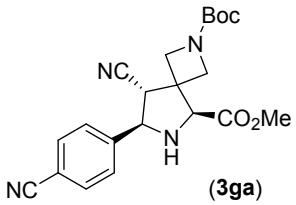
2-(*tert*-Butyl) 5-methyl (5*S*,7*R*,8*R*)-7-(3-chlorophenyl)-8-cyano-2,6-diazaspiro[3.4]octane-2,5-dicarboxylate White solid, yield: 98%; m.p.: 165-167 °C; $[\alpha]_D^{25}$ = +181.4(*c* 1.00, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.40 – 7.35 (m, 1H), 7.34 – 7.31 (m, 2H), 4.50 (d, *J* = 7.2 Hz, 1H, minor), 4.35 (d, *J* = 9.2 Hz, 1H), 4.29 (d, *J* = 9.2 Hz, 1H), 4.13 (s, 1H), 4.06 (d, *J* = 9.2 Hz, 1H), 3.94 (d, *J* = 9.7 Hz, 1H), 3.90 – 3.87 (m, 1H), 3.84 (s, 3H), 3.49 (d, *J* = 6.9 Hz, 1H, minor), 3.25 (d, *J* = 9.2 Hz, 1H), 2.57 (brs, 1H), 1.46 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.2, 155.8, 141.1, 135.0, 130.3,

129.0, 126.8, 125.0, 116.9, 80.4, 66.2, 63.6, 58.1, 54.3, 52.7, 45.9, 45.2, 28.3 (3C). **HRMS** (ESI-TOF) calcd for $[C_{20}H_{24}ClN_3O_4+H]^+$: 406.1528, found: 406.1532; **HPLC** (Chiralpak AD-H, *n*-hexane/*i*-propanol = 80/20, 1.0 mL/min, 220 nm) t_R = 8.18 min, 24.12 min.



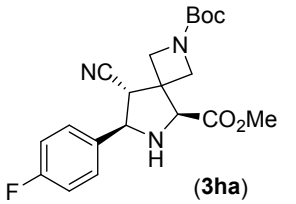
(**3fa**)

2-(*tert*-Butyl) 5-methyl (5*S*,7*R*,8*R*)-7-(4-bromophenyl)-8-cyano-2,6-diazaspiro[3.4]octane-2,5-dicarboxylate White solid, yield: 98%; m.p.: 169-171°C; $[\alpha]_D^{25}$ = +152.7(*c* 1.00, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H, minor), 4.49 (d, *J* = 6.9 Hz, 1H, minor), 4.33 (d, *J* = 9.5 Hz, 1H), 4.29 (d, *J* = 9.1 Hz, 1H), 4.13 (s, 1H), 4.05 (d, *J* = 9.1 Hz, 1H), 4.04 – 3.96 (m, 3H, minor), 3.93 (d, *J* = 9.8 Hz, 1H), 3.90 – 3.85 (m, 1H), 3.83 (s, 3H), 3.48 (d, *J* = 6.9 Hz, 1H, minor), 3.22 (d, *J* = 9.2 Hz, 1H), 2.55 (brs, 1H), 1.45 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.4, 155.8, 138.0, 132.1 (2C), 128.4 (2C), 122.8, 116.9, 80.4, 66.2, 63.6, 58.4, 54.2, 52.7, 46.0, 45.3, 28.3 (3C). **HRMS** (ESI-TOF) calcd for $[C_{20}H_{24}{}^{79}BrN_3O_4+H]^+$: 450.1023, found: 450.1027, $[C_{20}H_{24}{}^{81}BrN_3O_4+H]^+$: 452.1002, found: 452.1006; **HPLC** (Chiralpak AD-H, *n*-hexane/*i*-propanol = 80/20, 1.0 mL/min, 220 nm) t_R = 10.99 min, 17.97 min.



(**3ga**)

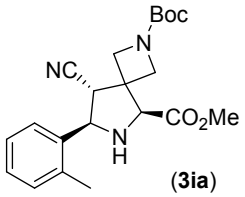
2-(*tert*-Butyl) 5-methyl (5*S*,7*R*,8*R*)-8-cyano-7-(4-cyanophenyl)-2,6-diazaspiro[3.4]octane-2,5-dicarboxylate White solid, yield: 97%; m.p.: 164-166°C; $[\alpha]_D^{25}$ = +185.3(*c* 1.00, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 (s, 4H), 4.62 (d, *J* = 7.2 Hz, 1H, minor), 4.46 (d, *J* = 9.3 Hz, 1H), 4.29 (d, *J* = 9.1 Hz, 1H), 4.18 (s, 1H), 4.05 (d, *J* = 9.2 Hz, 1H), 3.96 – 3.85 (m, 2H), 3.84 (s, 3H), 3.55 (d, *J* = 7.2 Hz, 1H, minor) 3.28 (d, *J* = 9.3 Hz, 1H), 2.66 (brs, 1H), 1.45 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.3, 155.7, 144.7, 132.7 (2C), 127.5 (2C), 118.4, 116.6, 112.6, 80.5, 66.0, 63.4, 58.2, 53.9, 52.7, 45.7, 45.3, 28.3 (3C). **HRMS** (ESI-TOF) calcd for $[C_{21}H_{24}N_4O_4+H]^+$: 397.1870, found: 397.1874; **HPLC** (Chiralpak AD-H, *n*-hexane/*i*-propanol = 80/20, 1.0 mL/min, 220 nm) t_R = 14.13 min, 25.44 min.



(**3ha**)

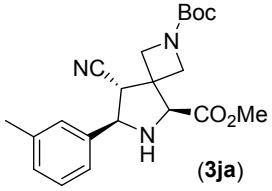
2-(*tert*-Butyl) 5-methyl (5*S*,7*R*,8*R*)-8-cyano-7-(4-fluorophenyl)-2,6-diazaspiro[3.4]octane-2,5-dicarboxylate White solid, yield: 96%; m.p.: 151-153 °C; $[\alpha]_D^{25}$ = +162.5(*c* 1.00, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 – 7.44 (m, 2H), 7.14 – 6.95 (m, 2H), 4.52 (d, *J* = 7.0 Hz, 1H, minor), 4.35 (d, *J* = 9.4 Hz, 1H), 4.30 (d, *J* = 9.2 Hz, 1H), 4.12 (s, 1H) , 4.06 (d, *J* = 9.2 Hz, 1H), 3.95 (d, *J* = 9.7 Hz, 1H), 3.87 (d, *J* = 9.1 Hz, 1H), 3.83 (s, 3H), 3.47 (d, *J* = 7.0 Hz, 1H, minor), 3.22 (d, *J* = 9.3 Hz, 1H), 2.54 (brs,

1H), 1.46 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.5, 162.9 (d, *J* = 247.4 Hz), 155.8, 134.6, 128.4 (d, *J* = 8.2 Hz, 2C), 117.0, 115.9 (d, *J* = 21.6 Hz, 2C), 80.4, 66.2, 63.5, 58.4, 54.3, 52.6, 46.1, 45.2, 28.3 (3C). **HRMS** (ESI-TOF) calcd for $[C_{20}H_{24}FN_3O_4+H]^+$: 390.1824, found: 390.1830; **HPLC** (Chiralpak AD-H, *n*-hexane/*i*-propanol = 80/20, 1.0 mL/min, 220 nm) t_R = 10.30 min, 16.31 min.



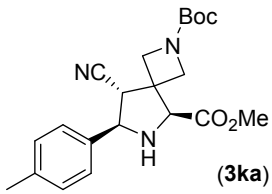
(**3ia**)

2-(*tert*-Butyl) 5-methyl (5*S*,7*R*,8*R*)-8-cyano-7-(*o*-tolyl)-2,6-diazaspiro[3.4]octane-2,5-dicarboxylate White solid, yield: 97%; m.p.: 139-141 °C; $[\alpha]_D^{25}$ = +153.6(*c* 1.00, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.5 Hz, 1H, minor), 7.60 (dd, *J* = 7.2, 1.9 Hz, 1H), 7.33 – 7.11 (m, 3H), 4.69 (d, *J* = 8.0 Hz, 1H), 4.29 (d, *J* = 9.2 Hz, 1H), 4.15 (d, *J* = 9.5 Hz, 1H), 4.13 (s, 1H), 4.06 (s, 2H, minor), 3.95 (d, *J* = 9.8 Hz, 1H), 3.88 (s, 3H, minor), 3.85 (s, 3H), 3.77 (d, *J* = 9.7 Hz, 1H), 3.52 (d, *J* = 7.1 Hz, 1H, minor), 3.23 (d, *J* = 8.0 Hz, 1H), 2.44 (s, 4H), 2.35 (s, 3H, minor), 1.45 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.1, 155.8, 137.1, 136.1, 130.9, 128.4, 126.9, 125.5, 117.6, 80.3, 66.2, 60.0, 57.4, 55.1, 52.7, 45.4, 45.2, 28.3 (3C), 19.5. **HRMS** (ESI-TOF) calcd for $[C_{21}H_{27}N_3O_4+H]^+$: 386.2074, found: 386.2078; **HPLC** (Chiralpak AD-H, *n*-hexane/*i*-propanol = 80/20, 1.0 mL/min, 220 nm) t_R = 8.90 min,13.61 min.



(**3ja**)

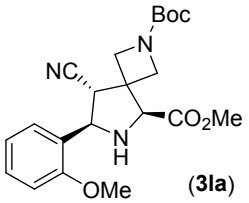
2-(*tert*-Butyl) 5-methyl (5*S*,7*R*,8*R*)-8-cyano-7-(*m*-tolyl)-2,6-diazaspiro[3.4]octane-2,5-dicarboxylate White solid, yield: 97%; m.p.: 142-144 °C; $[\alpha]_D^{25}$ = +174.5(c 1.00, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 3H), 7.20 – 7.13 (m, 1H), 4.47 (d, *J* = 6.8 Hz, 1H, minor), 4.31 (d, *J* = 9.0 Hz, 2H), 4.15 (d, *J* = 9.0 Hz, 1H, minor), 4.11 (s, 1H), 4.08 (d, *J* = 9.2 Hz, 1H), 3.96 (d, *J* = 9.7 Hz, 1H), 3.91 – 3.83 (m, 1H), 3.84 (s, 3H), 3.47 (d, *J* = 6.8 Hz, 1H, minor), 3.23 (d, *J* = 9.1 Hz, 1H), 2.37 (s, 3H), 1.46 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.3, 155.8, 138.7, 138.6, 129.5, 128.9, 127.3, 123.6, 117.2, 80.3, 66.4, 64.4, 58.2, 54.6, 52.6, 46.1, 45.3, 28.3 (3C), 21.4. **HRMS** (ESI-TOF) calcd for $[C_{21}H_{27}N_3O_4+H]^+$: 386.2074, found: 386.2079; **HPLC** (Chiralpak AD-H, *n*-hexane/*i*-propanol = 80/20, 1.0 mL/min, 220 nm) t_R = 9.27 min, 22.53 min.



(**3ka**)

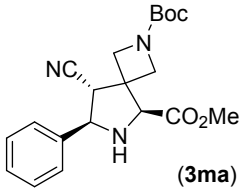
2-(*tert*-Butyl) 5-methyl (5*S*,7*R*,8*R*)-8-cyano-7-(*p*-tolyl)-2,6-diazaspiro[3.4]octane-2,5-dicarboxylate White solid, yield: 97%; m.p.: 171-173 °C; $[\alpha]_D^{25}$ = +192.7(*c* 1.00, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.9 Hz, 2H), 7.19 (d, *J* = 7.8 Hz, 2H), 4.48 (d, *J* = 6.9 Hz, 1H, minor), 4.31 (dd, *J* = 9.4, 2.6 Hz, 2H), 4.15 (d, *J* = 9.0 Hz, 1H, minor), 4.10 (s, 1H), 4.07 (d, *J* = 9.2 Hz, 1H), 4.02 (d, *J* = 6.2 Hz,

2H, minor), 3.95 (d, *J* = 9.7 Hz, 1H), 3.90 – 3.85 (m, 1H), 3.83 (s, 3H), 3.46 (d, *J* = 6.8 Hz, 1H, minor), 3.21 (d, *J* = 9.2 Hz, 1H), 2.51 (brs, 1H), 2.35 (s, 3H), 1.45 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.4, 155.8, 138.7, 135.6, 129.7 (2C), 126.5 (2C), 117.2, 80.3, 66.5, 64.2, 57.9, 54.5, 52.6, 46.2, 45.3, 28.3 (3C), 21.2. **HRMS** (ESI-TOF) calcd for $[C_{21}H_{27}N_3O_4+H]^+$: 386.2074, found: 386.2079; **HPLC** (Chiralpak AD-H, *n*-hexane/*i*-propanol = 80/20, 1.0 mL/min, 220 nm) t_R = 9.56 min, 11.74 min.



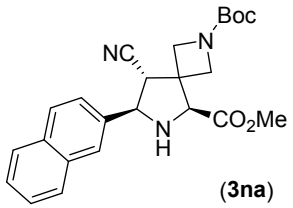
(**3la**)

2-(*tert*-Butyl) 5-methyl (5*S*,7*R*,8*R*)-8-cyano-7-(2-methoxyphenyl)-2,6-diazaspiro[3.4]octane-2,5-dicarboxylate White solid, yield: 97%; m.p.: 145-147 °C; $[\alpha]_D^{25}$ = +234.7(*c* 1.00, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.36 – 7.26 (m, 1H), 7.02 – 6.93 (m, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 4.73 (d, *J* = 7.5 Hz, 1H, minor), 4.64 (d, *J* = 6.6 Hz, 1H), 4.29 (d, *J* = 9.4 Hz, 1H), 4.18 (d, *J* = 9.4 Hz, 1H), 4.08 (s, 1H), 4.02 (d, *J* = 8.6 Hz, 1H, minor), 3.89 – 3.78 (m, 7H), 3.62 (d, *J* = 9.7 Hz, 1H), 3.36 (d, *J* = 6.7 Hz, 1H), 2.86 (brs, 1H), 1.44 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.4, 156.8, 155.9, 129.7, 128.0, 126.6, 121.0, 118.5, 110.6, 80.2, 66.4, 61.1, 56.7, 55.3 (2C), 52.6, 45.6, 45.3, 28.3 (3C). **HRMS** (ESI-TOF) calcd for $[C_{21}H_{27}N_3O_5+H]^+$: 402.2023, found: 402.2027; **HPLC** (Chiralpak AD-H, *n*-hexane/*i*-propanol = 80/20, 1.0 mL/min, 220 nm) t_R = 12.22 min, 27.45 min.



(**3ma**)

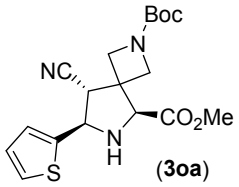
2-(*tert*-Butyl) 5-methyl (5*S*,7*R*,8*R*)-8-cyano-7-phenyl-2,6-diazaspiro[3.4]octane-2,5-dicarboxylate White solid, yield: 96%; m.p.: 154-156 °C; $[\alpha]_D^{25}$ = +183.8(*c* 1.00, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 – 7.46 (m, 2H), 7.45 – 7.32 (m, 3H), 4.52 (d, *J* = 6.4 Hz, 1H, minor), 4.48 (s, 1H, minor), 4.36 (d, *J* = 9.2 Hz, 1H), 4.31 (d, *J* = 9.2 Hz, 1H), 4.12 (s, 1H), 4.08 (d, *J* = 9.2 Hz, 1H), 3.96 (d, *J* = 9.7 Hz, 1H), 3.91 – 3.83 (m, 1H), 3.84 (s, 3H), 3.49 (d, *J* = 6.9 Hz, 1H, minor), 3.25 (d, *J* = 9.2 Hz, 1H), 2.56 (brs, 1H), 1.46 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.4, 155.8, 138.7, 129.0 (2C), 128.8, 126.6 (2C), 117.2, 80.3, 66.4, 64.3, 58.0, 54.5, 52.6, 46.1, 45.3, 28.3 (3C). **HRMS** (ESI-TOF) calcd for $[C_{20}H_{25}N_3O_4+H]^+$: 372.1918.2074, found: 372.1922; **HPLC** (Chiralpak AD-H, *n*-hexane/*i*-propanol = 80/20, 1.0 mL/min, 220 nm) t_R = 9.35 min, 16.26 min.



(**3na**)

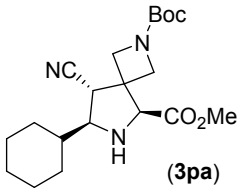
2-(*tert*-Butyl) 5-methyl (5*S*,7*R*,8*R*)-8-cyano-7-(naphthalen-2-yl)-2,6-diazaspiro[3.4]octane-2,5-dicarboxylate White solid, yield: 98%; m.p.: 158-160 °C; $[\alpha]_D^{25}$ = +221.4(*c* 1.00, CH_2Cl_2); **^{1}H NMR**

(400 MHz, $CDCl_3$) δ 7.96 – 7.90 (m, 1H), 7.91 – 7.80 (m, 3H), 7.61 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.55 – 7.46 (m, 2H), 4.67 (d, *J* = 7.1 Hz, 1H, minor), 4.53 (d, *J* = 9.1 Hz, 1H), 4.35 (d, *J* = 9.1 Hz, 1H), 4.17 (s, 1H), 4.11 (d, *J* = 9.2 Hz, 1H), 4.10 – 4.02 (m, 2H, minor), 3.98 (d, *J* = 9.7 Hz, 1H), 3.94 – 3.87 (m, 1H), 3.87 (s, 3H), 3.56 (d, *J* = 6.9 Hz, 1H, minor), 3.35 (d, *J* = 9.1 Hz, 1H), 2.65 (brs, 1H), 1.46 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.4, 155.8, 136.0, 133.5, 133.2, 129.1, 128.1, 127.8, 126.6, 126.5, 126.2, 123.9, 117.2, 80.4, 66.4, 64.5, 58.2, 54.5, 52.7, 46.0, 45.3, 28.3 (3C). **HRMS** (ESI-TOF) calcd for $[C_{24}H_{27}N_3O_4+H]^+$: 422.2074, found: 422.2078; **HPLC** (Chiralpak AD-H, *n*-hexane/*i*-propanol = 80/20, 1.0 mL/min, 220 nm) t_R = 14.71 min, 24.49 min.



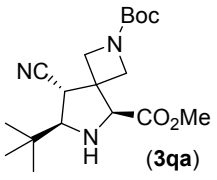
(**3oa**)

2-(*tert*-Butyl) 5-methyl (5*S*,7*R*,8*R*)-8-cyano-7-(thiophen-2-yl)-2,6-diazaspiro[3.4]octane-2,5-dicarboxylate White solid, yield: 97%; m.p.: 119-121 °C; $[\alpha]_D^{25}$ = +173.5(*c* 1.00, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 5.2, 1.3 Hz, 1H), 7.15 (d, *J* = 3.5 Hz, 1H), 6.99 (dd, *J* = 5.1, 3.5 Hz, 1H), 4.78 (d, *J* = 7.2 Hz, 1H, minor), 4.68 (d, *J* = 8.6 Hz, 1H), 4.28 (d, *J* = 9.2 Hz, 1H), 4.17 (d, *J* = 9.0 Hz, 1H, minor), 4.09 (s, 1H), 4.06 (d, *J* = 9.3 Hz, 1H), 3.94 (d, *J* = 9.8 Hz, 1H), 3.91 – 3.84 (m, 1H), 3.83 (s, 3H), 3.50 (d, *J* = 7.1 Hz, 1H, minor), 3.34 (d, *J* = 8.6 Hz, 1H), 2.71 (brs, 1H), 1.45 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.8, 155.8, 143.1, 127.3, 125.7, 125.3, 117.0, 80.4, 66.2, 60.0, 57.6, 54.6, 52.6, 46.7, 45.2, 28.3 (3C). **HRMS** (ESI-TOF) calcd for $[C_{18}H_{23}N_3O_4S+H]^+$: 378.1482, found: 378.1486; **HPLC** (Chiralpak AD-H, *n*-hexane/*i*-propanol = 80/20, 1.0 mL/min, 220 nm) t_R = 10.98 min, 26.59 min.



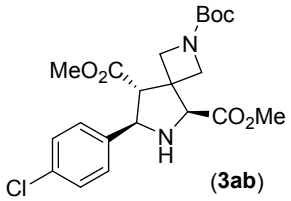
(**3pa**)

2-(*tert*-Butyl) 5-methyl (5*S*,7*S*,8*R*)-8-cyano-7-cyclohexyl-2,6-diazaspiro[3.4]octane-2,5-dicarboxylate White solid, yield: 92%; m.p.: 132-134°C; $[\alpha]_D^{25}$ = +138.5(*c* 1.00, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.24 (d, *J* = 9.2 Hz, 1H), 4.01 (d, *J* = 9.3 Hz, 1H), 3.92 – 3.85 (m, 2H), 3.86 – 3.79 (m, 1H), 3.79 (s, 3H), 3.13 – 3.04 (m, 1H), 2.97 (d, *J* = 8.6 Hz, 1H), 2.17 (s, 1H), 1.86 – 1.65 (m, 6H), 1.45 (s, 9H), 1.32 – 1.01 (m, 5H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.8, 155.8, 118.5, 80.2, 66.4, 66.3, 57.4, 55.4, 52.5, 45.2, 42.5, 41.2, 29.9, 29.7, 28.3 (3C), 26.1, 25.8, 25.7. **HRMS** (ESI-TOF) calcd for $[C_{20}H_{31}N_3O_4+H]^+$: 378.2387, found: 378.2391; **HPLC** (Chiralpak AD-H, *n*-hexane/*i*-propanol = 80/20, 1.0 mL/min, 220 nm) t_R = 7.55 min, 9.55 min.



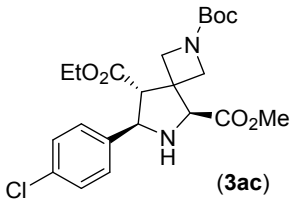
(**3qa**)

2-(*tert*-Butyl) 5-methyl (5*S*,7*R*,8*R*)-7-(*tert*-butyl)-8-cyano-2,6-diazaspiro[3.4]octane-2,5-dicarboxylate White solid, yield: 91%; m.p.: 142-144°C; $[\alpha]_D^{25}$ = +178.6(*c* 1.00, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.24 (d, *J* = 9.4 Hz, 1H), 4.05 (d, *J* = 9.3 Hz, 1H), 3.88 (s, 1H), 3.86 – 3.80 (m, 2H), 3.78 (s, 3H), 3.16 (d, *J* = 8.2 Hz, 1H), 3.03 (d, *J* = 8.3 Hz, 1H), 2.23 (s, 1H), 1.44 (s, 9H), 0.97 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.1, 155.8, 119.0, 80.1, 70.4, 65.9, 56.5, 56.1, 52.4, 45.0, 39.0, 33.6, 28.3 (3C), 26.1 (3C). **HRMS** (ESI-TOF) calcd for $[C_{18}H_{29}N_3O_4+H]^+$: 352.2231, found: 352.2236; **HPLC** (Chiralpak AD-H, *n*-hexane/*i*-propanol = 80/20, 1.0 mL/min, 220 nm) t_R = 8.78 min, 9.36 min.



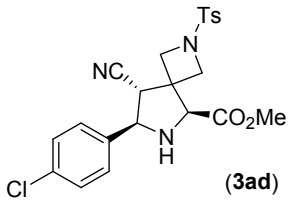
(**3ab**)

2-(*tert*-Butyl) 5,8-dimethyl (5*S*,7*R*,8*R*)-7-(4-chlorophenyl)-2,6-diazaspiro[3.4]octane-2,5,8-tricarboxylate White solid, yield: 94%; m.p.: 153-155 °C; $[\alpha]_D^{25}$ = +156.4 (*c* 1.00, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 4.48 (d, *J* = 7.9 Hz, 1H), 4.13 (s, 1H), 4.08 (d, *J* = 8.3 Hz, 1H, minor), 4.06 – 3.94 (m, 2H), 3.94 – 3.84 (m, 2H), 3.83 (s, 3H), 3.73 (s, 3H), 3.41 (d, *J* = 6.8 Hz, 1H, minor), 3.34 (s, 2H, minor), 3.12 (d, *J* = 8.0 Hz, 1H), 2.46 (brs, 1H), 1.43 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (minor + major) 172.6, 171.8, 171.5, 170.6, 156.0, 140.1, 133.6, 128.8, 128.6, 128.3, 127.9, 79.9, 68.6, 67.3, 63.2, 62.6, 59.2, 57.2, 55.4, 52.5, 52.4, 52.3, 51.5, 45.5, 28.3 (3C). **HRMS** (ESI-TOF) calcd for $[C_{21}H_{27}ClN_2O_6+H]^+$: 439.1630, found: 439.1634; **HPLC** (Chiralpak AD-H, *n*-hexane/*i*-propanol = 80/20, 1.0 mL/min, 220 nm) t_R = 28.26 min, 32.83 min.



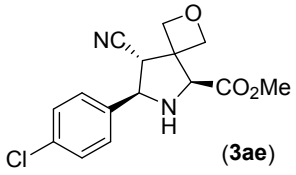
(**3ac**)

2-(*tert*-Butyl) 8-ethyl 5-methyl (5*S*,7*R*,8*R*)-7-(4-chlorophenyl)-2,6-diazaspiro[3.4]octane-2,5,8-tricarboxylate White solid, yield: 99%; m.p.: 156-158 °C; $[\alpha]_D^{25}$ = +164.4 (*c* 1.00, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 6.7 Hz, 2H), 4.48 (d, *J* = 7.9 Hz, 1H), 4.29 – 4.19 (m, 1H), 4.17 – 4.05 (m, 2H), 4.07 – 3.94 (m, 2H), 3.93 – 3.85 (m, 2H), 3.83 (s, 3H), 3.39 (d, *J* = 6.7 Hz, 1H, minor), 3.10 (d, *J* = 8.2 Hz, 1H), 2.44 (brs, 1H), 1.42 (s, 9H), 1.25 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (minor + major) δ 172.8, 171.7, 170.9, 170.2, 156.1, 155.9, 140.2, 133.6, 133.5, 128.8 (2C), 128.5, 128.4 (2C), 128.0, 79.9, 79.8, 68.8, 67.4, 63.2, 62.5, 61.3, 60.7, 59.8, 59.0, 52.5, 52.4, 46.9, 45.5, 28.4 (3C), 28.4 (3C), 14.2, 13.8. **HRMS** (ESI-TOF) calcd for $[C_{22}H_{29}ClN_2O_6+H]^+$: 453.1787, found: 453.1791; **HPLC** (Chiralpak AD-H, *n*-hexane/*i*-propanol = 80/20, 1.0 mL/min, 220 nm) t_R = 14.30 min, 16.99 min.



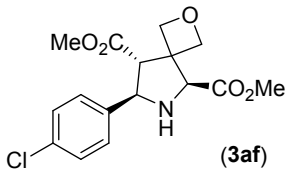
(**3ad**)

Methyl (5*S*,7*R*,8*R*)-7-(4-chlorophenyl)-8-cyano-2-tosyl-2,6-diazaspiro[3.4]octane-5-carboxylate White solid, yield: 75%; m.p.: 173-175 °C; $[\alpha]_D^{25}$ = +170.4 (*c* 1.00, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$)) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.38 (dd, *J* = 8.5, 2.5 Hz, 4H), 7.36 – 7.29 (m, 2H), 4.27 (d, *J* = 9.0 Hz, 1H), 4.05 (s, 1H), 4.02 – 3.97 (m, 2H), 3.87 (d, *J* = 9.0 Hz, 1H), 3.77 (s, 3H), 3.61 (d, *J* = 9.0 Hz, 1H), 3.07 (d, *J* = 9.0 Hz, 1H), 2.45 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.0, 144.9, 137.3, 134.6, 131.0, 130.0 (2C), 129.1 (2C), 128.3 (2C), 127.9 (2C), 116.4, 65.6, 63.4, 58.2, 55.2, 52.7, 45.5, 44.7, 21.6. **HRMS** (ESI-TOF) calcd for $[C_{22}H_{22}ClN_3O_4S+H]^+$: 460.1092, found: 460.1096; **HPLC** (Chiralpak AD-H, *n*-hexane/*i*-propanol = 80/20, 1.0 mL/min, 220 nm) t_R = 17.85 min, 21.31 min.



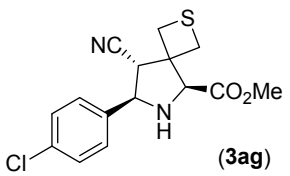
(**3ae**)

Methyl (5*S*,7*R*,8*R*)-7-(4-chlorophenyl)-8-cyano-2-oxa-6-azaspiro[3.4]octane-5-carboxylate White solid, yield: 86%; m.p.: 144-146 °C; $[\alpha]_D^{25}$ = +188.0 (*c* 1.00, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 – 7.40 (m, 2H), 7.38 – 7.30 (m, 2H), 5.00 (d, *J* = 6.8 Hz, 1H), 4.79 (d, *J* = 6.9 Hz, 1H), 4.67 (d, *J* = 7.5 Hz, 1H), 4.59 (d, *J* = 7.5 Hz, 1H), 4.29 (d, *J* = 9.4 Hz, 1H), 4.24 (s, 1H), 3.85 (s, 3H), 3.21 (d, *J* = 9.4 Hz, 1H), 2.55 (brs, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.4, 137.3, 134.6, 129.2 (2C), 128.0 (2C), 117.1, 79.0, 75.5, 65.6, 63.5, 52.7, 50.8, 45.5. **HRMS** (ESI-TOF) calcd for $[C_{15}H_{15}ClN_2O_3+H]^+$: 307.0844, found: 307.0848; **HPLC** (Chiralpak AD-H, *n*-hexane/*i*-propanol = 80/20, 1.0 mL/min, 220 nm) t_R = 31.21 min, 37.76 min.



(**3af**)

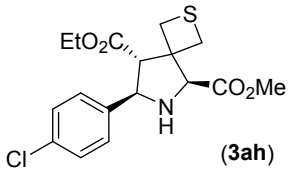
Dimethyl (5*S*,7*R*,8*R*)-7-(4-chlorophenyl)-2-oxa-6-azaspiro[3.4]octane-5,8-dicarboxylate White solid, yield: 91%; m.p.: 154-156 °C; $[\alpha]_D^{25}$ = +156.3 (*c* 1.00, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 4.75 (d, *J* = 6.9 Hz, 1H), 4.71 (d, *J* = 6.8 Hz, 1H), 4.65 (d, *J* = 7.0 Hz, 1H), 4.54 (d, *J* = 7.0 Hz, 1H), 4.44 (d, *J* = 8.2 Hz, 1H), 4.20 (s, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 3.14 (d, *J* = 8.2 Hz, 1H), 2.26 (brs, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.7, 171.6, 139.9, 133.6, 128.8 (2C), 128.2 (2C), 78.1, 77.4, 66.7, 62.7, 58.8, 52.5, 52.4, 51.4. **HRMS** (ESI-TOF) calcd for $[C_{16}H_{18}ClNO_5+H]^+$: 340.0946, found: 340.0951; **HPLC** (Chiralpak AD-H, *n*-hexane/*i*-propanol = 80/20, 1.0 mL/min, 220 nm) t_R = 18.84 min, 23.48 min.



(**3ag**)

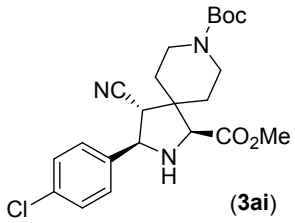
Methyl (5*S*,7*R*,8*R*)-7-(4-chlorophenyl)-8-cyano-2-thia-6-azaspiro[3.4]octane-5-carboxylate White solid, yield: 93%; m.p.: 140-142 °C; $[\alpha]_D^{25}$ = +163.4 (*c* 1.00, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ

7.48 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 4.38 (d, *J* = 9.3 Hz, 1H), 4.27 (s, 1H), 4.13 (s, 1H, minor) , 3.85 (s, 3H), 3.67 (d, *J* = 9.8 Hz, 1H), 3.49 – 3.39 (m, 2H, minor), 3.31 – 3.21 (m, 2H), 3.17 (dd, *J* = 9.8, 6.3 Hz, 2H), 2.54 (brs, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.7, 137.8, 134.5, 129.1 (2C), 128.2 (2C), 117.4, 67.9, 62.9, 55.0, 52.6, 47.9, 34.1, 30.5. **HRMS** (ESI-TOF) calcd for $[C_{15}H_{15}ClN_2O_2S+H]^+$: 323.0616, found: 323.0620; **HPLC** (Chiralpak AD-H, *n*-hexane/*i*-propanol = 80/20, 1.0 mL/min, 220 nm) t_R = 23.89 min, 27.14 min.



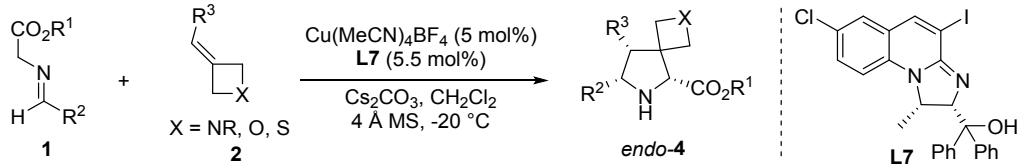
(**3ah**)

8-Ethyl 5-methyl (5*S*,7*R*,8*R*)-7-(4-chlorophenyl)-2-thia-6-azaspiro[3.4]octane-5,8-dicarboxylate White solid, yield: 93%; m.p.: 148-150 °C; $[\alpha]_D^{25}$ = +136.4 (*c* 1.00, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 4.51 (d, *J* = 9.1 Hz, 1H), 4.32 – 4.16 (m, 2H), 4.16 (s, 1H), 3.84 (s, 3H), 3.48 (d, *J* = 9.8 Hz, 1H), 3.36 (d, *J* = 9.9 Hz, 1H), 3.26 (d, *J* = 9.8 Hz, 1H), 3.21 (d, *J* = 9.9 Hz, 1H), 3.05 (d, *J* = 9.2 Hz, 1H), 2.36 (brs, 1H), 1.29 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.1, 170.9, 140.2, 133.4, 128.7 (2C), 128.5 (2C), 69.3, 62.0, 61.4, 59.9, 56.0, 52.3, 33.5, 31.4, 14.2. **HRMS** (ESI-TOF) calcd for $[C_{17}H_{20}ClNO_4S+H]^+$: 370.0880, found: 370.0884; **HPLC** (Chiralpak AD-H, *n*-hexane/*i*-propanol = 80/20, 1.0 mL/min, 220 nm) t_R = 14.03 min, 15.88 min.



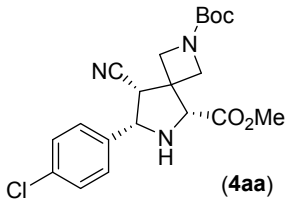
(**3ai**)

8-(*tert*-Butyl) 1-methyl (1*S*,3*R*,4*R*)-3-(4-chlorophenyl)-4-cyano-2,8-diazaspiro[4.5]decane-1,8-dicarboxylate White solid, yield: 86%; m.p.: 168-170 °C; $[\alpha]_D^{25}$ = +157.5 (*c* 1.00, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 4.49 (d, *J* = 10.1 Hz, 1H), 4.02 (s, 2H), 3.79 (s, 3H), 3.77 – 3.66 (m, 1H), 3.34 – 3.09 (m, 2H), 3.00 (d, *J* = 10.1 Hz, 1H), 2.52 (s, 1H), 2.01 – 1.65 (m, 4H), 1.47 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.6, 154.6, 138.4, 134.3, 129.0 (2C), 128.4 (2C), 117.7, 80.1, 65.0, 63.3, 52.2, 48.4, 47.7, 40.6, 39.9, 31.5, 31.3, 28.4 (3C). **HRMS** (ESI-TOF) calcd for $[C_{22}H_{28}ClN_3O_4+H]^+$: 434.1841, found: 434.1846; **HPLC** (Chiralpak AD-H, *n*-hexane/*i*-propanol = 80/20, 1.0 mL/min, 220 nm) t_R = 8.05 min, 11.87 min.



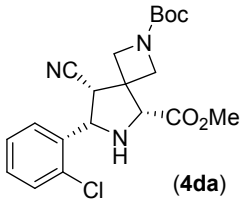
At a nitrogen atmosphere, $Cu(CH_3CN)_4BF_4$ (3.1 mg, 0.01 mmol), Cs_2CO_3 (65.2 mg, 0.2 mmol) and **L7** (5.8 mg, 0.011mmol) were dissolved in 2.0 mL dry CH_2Cl_2, subsequently add 4Å Ms (100 mg), and stirred at room temperature for about 1-2 h. Then, iminoester **1** (0.24 mmol) were added, the mixture was

cooled to -20 °C and alkene **2** (0.2 mmol) was added. Once starting material was consumed (monitored by TLC), the mixture was concentrated and the residue was purified by column chromatography (petroleum ether/ethyl acetate 6:1 to 2:1) on silica gel to afford the corresponding product **4**.



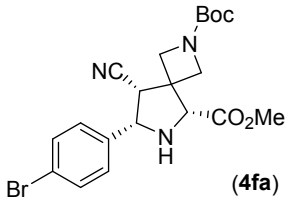
(**4aa**)

2-(*tert*-Butyl) 5-methyl (5*R*,7*S*,8*R*)-7-(4-chlorophenyl)-8-cyano-2,6-diazaspiro[3.4]octane-2,5-dicarboxylate White solid, yield: 88%; m.p.: 176-178°C; $[\alpha]_D^{25}$ = +175.3(*c* 1.00, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.32 (m, 4H), 4.51 (d, *J* = 6.9 Hz, 1H), 4.16 (d, *J* = 8.9 Hz, 1H), 4.05 – 3.92 (m, 4H), 3.88 (s, 3H), 3.48 (d, *J* = 6.9 Hz, 1H), 2.69 (s, 1H), 1.44 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.3, 155.9, 136.3, 134.6, 129.0 (2C), 128.4 (2C), 116.0, 80.4, 66.1, 61.2, 58.5, 54.6, 52.8, 46.4, 45.3, 28.3 (3C). **HRMS** (ESI-TOF) calcd for $[C_{20}H_{24}ClN_3O_4+H]^+$: 406.1528, found: 450.1533; **HPLC** (Chiralpak AD-H, *n*-hexane/ethanol= 80/20, 0.8 mL/min, 220 nm) t_R = 15.81 min, 19.45 min.



(**4da**)

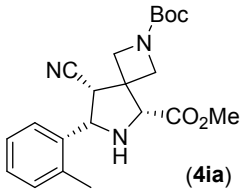
2-(*tert*-Butyl) 5-methyl (5*R*,7*S*,8*R*)-7-(2-chlorophenyl)-8-cyano-2,6-diazaspiro[3.4]octane-2,5-dicarboxylate White solid, yield: 91%; m.p.: 167-169 °C; $[\alpha]_D^{25}$ = +216.2(*c* 1.00, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.44 – 7.34 (m, 2H), 7.33 – 7.27 (m, 1H), 4.88 (d, *J* = 7.0 Hz, 1H), 4.17 (d, *J* = 8.8 Hz, 1H), 4.07 (s, 2H), 4.02 (s, 1H), 3.96 (d, *J* = 8.9 Hz, 1H), 3.87 (s, 3H), 3.74 (d, *J* = 7.0 Hz, 1H), 2.61 (brs, 1H), 1.45 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.1, 155.9, 135.3, 132.9, 129.8, 129.5, 128.0, 127.4, 115.9, 80.3, 65.7, 59.0, 58.1, 54.7, 52.7, 45.2, 44.8, 28.3 (3C). **HRMS** (ESI-TOF) calcd for $[C_{20}H_{24}ClN_3O_4+H]^+$: 406.1528, found: 406.1533; **HPLC** (Chiralpak AD-H, *n*-hexane/ethanol= 80/20, 0.8 mL/min, 220 nm) t_R = 14.22 min, 15.82 min.



(**4fa**)

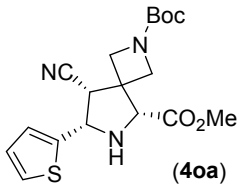
2-(*tert*-Butyl) 5-methyl (5*R*,7*S*,8*R*)-7-(4-bromophenyl)-8-cyano-2,6-diazaspiro[3.4]octane-2,5-dicarboxylate White solid, yield: 80%; m.p.: 156-158 °C; $[\alpha]_D^{25}$ = +153.4(*c* 1.00, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 4.49 (d, *J* = 7.0 Hz, 1H), 4.15 (d, *J* = 8.9 Hz, 1H), 4.05 – 3.95 (m, 3H), 3.94 (d, *J* = 8.9 Hz, 1H), 3.88 (s, 3H), 3.48 (d, *J* = 7.0 Hz, 1H), 2.69 (s, 1H), 1.44 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.3, 155.9, 136.9, 132.0 (2C), 128.7 (2C), 122.8, 116.0, 80.4, 66.1, 61.2, 58.5, 54.7, 52.8, 46.3, 45.2, 28.3 (3C). **HRMS** (ESI-TOF) calcd for $[C_{20}H_{24}{}^{79}BrN_3O_4+H]^+$: 450.1023, found: 450.1027; for $[C_{20}H_{24}{}^{81}BrN_3O_4+H]^+$: 452.1002, found:

452.1006; **HPLC** (Chiralpak AD-H, *n*-hexane/ethanol= 80/20, 0.8 mL/min, 220 nm) t_R = 17.61 min, 21.48 min.



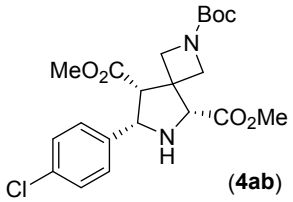
(**4ia**)

2-(*tert*-Butyl) 5-methyl (5*R*,7*S*,8*R*)-8-cyano-7-(o-tolyl)-2,6-diazaspiro[3.4]octane-2,5-dicarboxylate White solid, yield: 85%; m.p.: 151-153 °C; $[\alpha]_D^{25}$ = +152.8(*c* 1.00, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 – 7.63 (m, 1H), 7.35 – 7.25 (m, 1H), 7.28 – 7.16 (m, 2H), 4.72 (d, *J* = 7.2 Hz, 1H), 4.29 (d, *J* = 9.5 Hz, 1H, minor), 4.19 (d, *J* = 8.9 Hz, 1H), 4.13 (s, 1H, minor), 4.06 (s, 2H), 3.99 (s, 1H), 3.94 (d, *J* = 8.9 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H, minor), 3.52 (d, *J* = 7.2 Hz, 1H), 3.23 (d, *J* = 8.1 Hz, 1H, minor), 2.64 (brs, 1H), 2.44 (s, 3H, minor), 2.34 (s, 3H), 1.45 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.2, 156.0, 135.8, 135.3, 130.7, 128.4, 126.7, 125.8, 116.1, 80.3, 66.0, 58.4, 57.9, 55.1, 52.7, 45.4, 45.2, 28.3 (3C), 19.6. **HRMS** (ESI-TOF) calcd for $[C_{21}H_{27}N_3O_4+H]^+$: 386.2074, found: 386.2078; **HPLC** (Chiralpak AD-H, *n*-hexane/ethanol= 80/20, 0.8 mL/min, 220 nm) t_R = 14.43 min, 19.30 min.



(**4oa**)

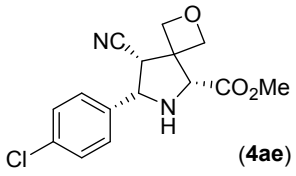
2-(*tert*-Butyl) 5-methyl (5*R*,7*S*,8*R*)-8-cyano-7-(thiophen-2-yl)-2,6-diazaspiro[3.4]octane-2,5-dicarboxylate White solid, yield: 78%; m.p.: 151-153 °C; $[\alpha]_D^{25}$ = +152.8(*c* 1.00, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 5.1 Hz, 1H), 7.18 – 7.11 (m, 1H), 7.08 – 6.99 (m, 1H), 4.79 (d, *J* = 7.0 Hz, 1H), 4.17 (d, *J* = 9.0 Hz, 1H), 4.08 – 3.92 (m, 4H), 3.87 (s, 3H), 3.51 (d, *J* = 6.9 Hz, 1H), 2.61 (brs, 1H), 1.44 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.8, 155.9, 142.0, 127.4, 125.8, 125.5, 115.9, 80.3, 66.1, 57.6, 57.4, 54.8, 52.8, 46.6, 45.1, 28.3 (3C). **HRMS** (ESI-TOF) calcd for $[C_{18}H_{23}N_3O_4S+H]^+$: 378.1482, found: 378.1487; **HPLC** (Chiralpak AD-H, *n*-hexane/ethanol= 80/20, 0.8 mL/min, 220 nm) t_R = 15.89 min, 22.61 min.



(**4ab**)

2-(*tert*-Butyl) 5,8-dimethyl (5*R*,7*S*,8*R*)-7-(4-chlorophenyl)-2,6-diazaspiro[3.4]octane-2,5,8-tricarboxylate White solid, yield: 87%; m.p.: 163-165 °C; $[\alpha]_D^{25}$ = +155.9 (*c* 1.00, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 – 7.25 (m, 4H), 4.48 (d, *J* = 6.8 Hz, 1H), 4.15 – 4.05 (m, 2H), 4.02 (d, *J* = 8.8 Hz, 1H), 3.97 (s, 1H), 3.88 (s, 3H), 3.84 – 3.77 (m, 1H), 3.73 (s, 3H, minor), 3.41 (d, *J* = 6.8 Hz, 1H), 3.34 (s, 3H), 3.13 (d, *J* = 7.8 Hz, 1H, minor), 1.45 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.8, 170.7, 156.1, 136.6, 133.6, 128.6 (2C), 127.9 (2C), 79.9, 68.6, 63.2, 61.5, 59.7, 54.5, 52.5, 51.6, 46.7, 28.4 (3C).

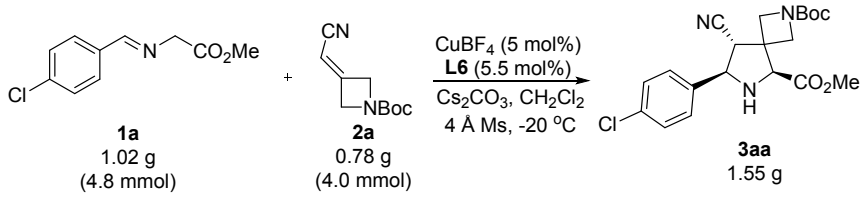
HRMS (ESI-TOF) calcd for $[C_{21}H_{27}ClN_2O_6+H]^+$: 439.1630, found: 439.1634; **HPLC** (Chiralpak AD-H, *n*-hexane/*i*-propanol = 90/10, 1.0 mL/min, 220 nm) t_R = 25.82 min, 28.76 min.



(**4ae**)

Methyl (5*R*,7*S*,8*R*)-7-(4-chlorophenyl)-8-cyano-2-oxa-6-azaspiro[3.4]octane-5-carboxylate White solid, yield: 85%; m.p.: 162-164 °C; $[\alpha]_D^{25}$ = +187.6(*c* 1.00, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 5.00 (d, *J* = 6.9 Hz, 1H, minor), 4.92 – 4.80 (m, 2H), 4.69 (d, *J* = 7.8 Hz, 1H), 4.60 (d, *J* = 6.6 Hz, 1H), 4.43 (d, *J* = 6.4 Hz, 1H), 4.25 (s, 1H, minor), 4.07 (s, 1H), 3.90 (s, 3H), 3.61 (d, *J* = 6.4 Hz, 1H), 3.21 (d, *J* = 9.5 Hz, 1H, minor), 2.67 (brs, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.5, 136.0, 134.7, 129.1 (2C), 128.4 (2C), 116.1, 80.2, 75.4, 65.4, 61.4, 52.9, 51.4, 46.2. **HRMS** (ESI-TOF) calcd for $[C_{15}H_{15}ClN_2O_3+H]^+$: 307.0844, found: 307.0848; **HPLC** (Chiralpak AD-H, *n*-hexane/*i*-propanol = 90/10, 1.0 mL/min, 220 nm) t_R = 41.67 min, 43.80 min.

Gram scale procedure

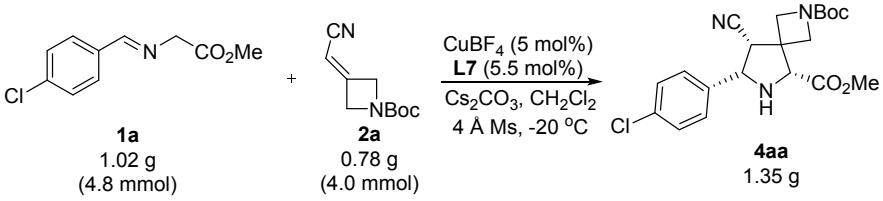


1a
1.02 g
(4.8 mmol)

2a
0.78 g
(4.0 mmol)

3aa
1.55 g

Under a nitrogen atmosphere, $Cu(CH_3CN)_4BF_4$ (62.9 mg, 0.20 mmol) and **L6** (115.6 mg, 0.22 mmol) were dissolved in dry CH_2Cl_2 (40 mL), subsequently add 4Å Ms (800 mg), and stirred at room temperature for about 1 h. Then, glycine imine **1a** (1.02 g, 4.8 mmol) and Cs_2CO_3 (1.30 g, 4.0 mmol) were added, the mixture was cooled to -20 °C and alkene **2a** (0.78 g, 4.0 mmol) was added. Once starting material was consumed (monitored by TLC, about 2 h), the mixture was filtered through celite and the filtrate was concentrated, then the residue was purified by column chromatography (petroleum ether/ethyl acetate 4:1) on silica gel to afford the corresponding product **3aa** in 96% yield.



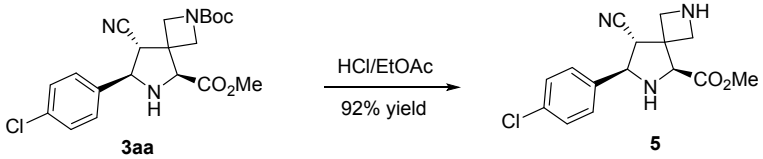
1a
1.02 g
(4.8 mmol)

2a
0.78 g
(4.0 mmol)

4aa
1.35 g

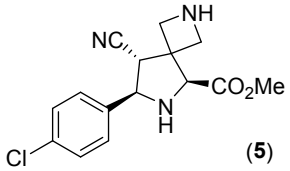
Under a nitrogen atmosphere, $Cu(CH_3CN)_4BF_4$ (62.9 mg, 0.20 mmol), Cs_2CO_3 (1.30 g, 4.0 mmol) and **L7** (115.9 mg, 0.22 mmol) were dissolved in dry CH_2Cl_2 (40 mL), subsequently add 4Å Ms (800 mg), and stirred at room temperature for about 1 h. Then, the mixture was cooled to -20 °C, glycine imine **1a** (1.02 g, 4.8 mmol) and alkene **2a** (0.78 g, 4.0 mmol) was added. Once starting material was consumed (monitored by TLC, about 3.5 h), the mixture was filtered through celite and the filtrate was concentrated, then the residue was purified by column chromatography (petroleum ether/ethyl acetate 4:1) on silica gel to afford the corresponding product **4aa** in 83% yield.

Synthetic transformations of the cycloadduct 3aa



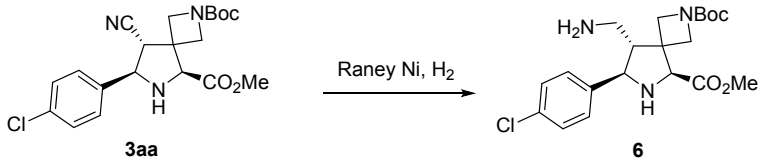
3aa **5**

To a solution of **3aa** (40.6 mg, 0.1 mmol) in EtOAc (1 mL) was added hydrogen chloride (0.5 mL of a 4 M solution in EtOAc) and the mixture was stirred for 3 h, after which time the solvent was removed under reduced pressure. The crude product was purified by column chromatography (CH_2Cl_2/MeOH 10:1) on silica gel to afford the corresponding product **5** in 92% yield



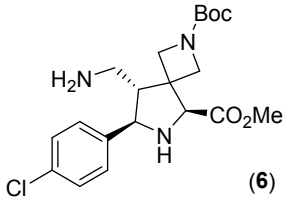
(**5**)

Methyl (5*S*,7*R*,8*R*)-7-(4-chlorophenyl)-8-cyano-2,6-diazaspiro[3.4]octane-5-carboxylate White solid, yield: 92%; m.p.: 121-123 °C; $[\alpha]_D^{25}$ = +223.5(*c* 1.00, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 4.30 (d, *J* = 9.9 Hz, 1H), 4.24 (s, 1H), 4.05 (dd, *J* = 8.5, 1.7 Hz, 1H), 3.82 (s, 3H), 3.75 – 3.64 (m, 2H), 3.61 (d, *J* = 9.0 Hz, 1H), 3.17 (d, *J* = 9.9 Hz, 1H), 2.12 (brs, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.3, 137.7, 134.4, 129.1 (2C), 128.2 (2C), 117.8, 66.5, 63.5, 56.1, 52.5, 51.8, 50.9, 45.9. **HRMS** (ESI-TOF) calcd for $[C_{15}H_{16}ClN_3O_2+H]^+$: 306.1004, found: 306.1007. **HPLC** (Chiralpak AD-H, *n*-hexane/ethanol = 70/30, 1.0 mL/min, 220 nm) t_R = 9.12 min, 21.32 min.



3aa **6**

To a solution of **3aa** (40.6 mg, 0.1 mmol) in EtOH (1 mL) was added Raney Ni (8 mg) and the mixture was stirred at room temperature under H_2 atmosphere (bubble) for 4 h. The conversion was monitored by TLC. The resulting solution was filtered over Celite, and washed with EtOH and ethyl acetate. The solvent was removed under reduced pressure and the residue was purified by column chromatography (CH_2Cl_2/MeOH 10:1) to afford the desired product **6** in 89% yield.



(**6**)

2-(*tert*-Butyl) 5-methyl (5*S*,7*R*,8*S*)-8-(aminomethyl)-7-(4-chlorophenyl)-2,6-diazaspiro[3.4]octane-2,5-dicarboxylate White solid, yield: 89%; m.p.: 155-157 °C; $[\alpha]_D^{25}$ = +176.5(*c* 1.00, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 7.6, 1.9 Hz, 1H), 7.38 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.33 – 7.22 (m, 2H), 4.98 (d, *J* = 5.3 Hz, 1H), 4.88 (d, *J* = 7.0 Hz, 1H, minor), 4.28 – 4.17 (m, 3H), 4.06 (s, 2H, minor), 4.02 (s, 1H, minor), 3.96 (d, *J* = 9.0 Hz, 1H, minor), 3.86 (s, 3H), 3.79 (d, *J* = 9.8 Hz, 1H), 3.74 (d, *J* = 7.1 Hz, 1H, minor), 3.46 (d, *J* = 9.8 Hz, 1H), 3.35 (d, *J* = 5.3 Hz, 1H), 2.61 (s, 1H), 1.42 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.4, 156.4, 141.2, 133.4, 128.9 (2C), 128.6 (2C), 79.9, 67.6, 64.8, 56.8, 55.9, 55.0, 52.3, 45.6, 40.5, 28.4 (3C). **HRMS** (ESI-TOF) calcd for $[C_{20}H_{28}ClN_3O_4+H]^+$: 410.1841, found: 410.1845. **HPLC** (Chiralpak AD-H, *n*-hexane/ethanol = 85/15, 1.0 mL/min, 220 nm) t_R = 35.65 min, 37.76 min.

Proposed transition states of the diastereodivergent asymmetric 1,3-dipolar cycloaddition

The diastereodivergent observed in this asymmetric 1,3-DC cycloaddition can be rationalized by the proposed transition state shown in Figure S1. With the ferrocene *P,N*-ligands **L6**, the *in situ*-formed azomethine ylide is coordinated to the metallic center and oriented in such way because of the steric repulsion between the phenyl group of the ylide and the phenyl ring on the phosphorus atom of the chiral ligand, and the highly steric congestion formation by the cyanogroup leads the dipolarophile (**2a**) approach azomethine ylide through *Re* (C=N) face attack and forms the *exo*-(5*S*,7*R*,8*R*)-**3aa** (**TS1**). With the *N,O*-ligands **L7**, the cyanogroup of **2a** could coordinate with the Cu(I) center, which can stabilize the negatively charged nitrogen atom in the proposed transition states (**TS2**).[5] An *exo* approach of dipolarophile (**2a**) to the copper(I) complex occurred which is compatible with the experimental results.

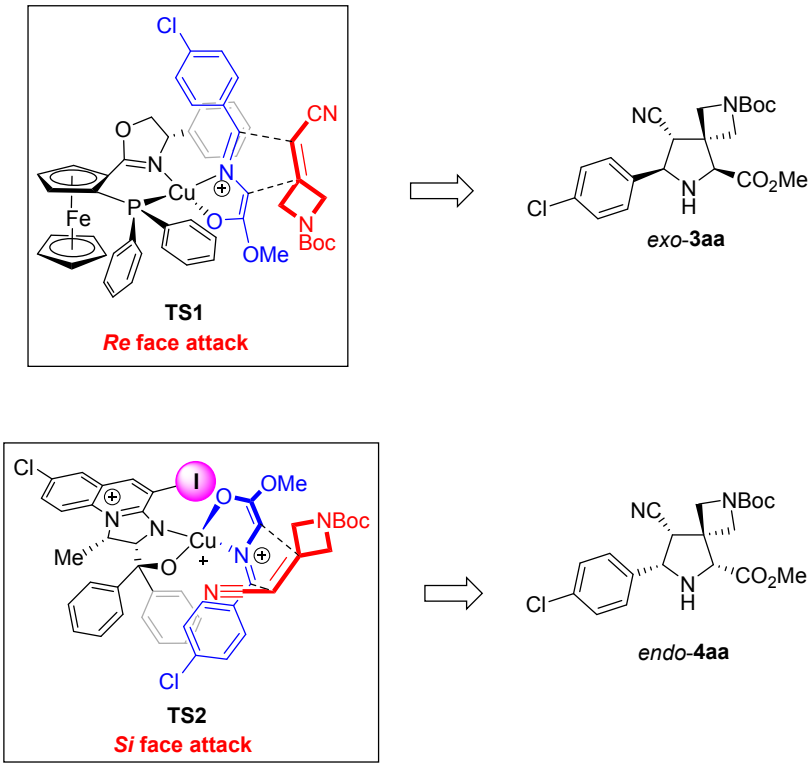


Fig S1. Proposed transition states.

References

(1) (a) A. López-Pérez, J. Adrio, J. C. Carretero, *J. Am. Chem. Soc*. 2008, **130**, 10084. (b) C.-J. Wang, G. Liang, Z.-Y. Xue, F. Gao, *J. Am. Chem. Soc*. 2008, **130**, 17250.

(2) B. A. Chalyk, A. A. Isakov, M. V. Butko, K. V. Hrebeniuk, O. V. Savych, O. V. Kucher, K. S. Gavrilenko, T. V. Druzhenko, V. S. Yarmolchuk, S. Zozulya, and P. K. Mykhailiuk, *Eur. J. Org. Chem*. 2017, 4530.

(3) J. Y. Cassayre, P. Renold, T. Pitterna, M. El Qacemi, WO2013026931A1, 2013.

(4) E. Forcellini, S. Boutin, C.-A. Lefebvre, E. E. Shayhidin, M.-C. Boulanger, G. Rheaume, X. Barbeau, P. Lagüe, P. Mathieu, J.-F. Paquin, *Eur. J. Med. Chem*. 2018, **147**, 130.

(5) (a) X.-X. Yan, Q. Peng, Y. Zhang, K. Zhang, W. Hong, X.-L. Hou, Y.-D. Wu, *Angew. Chem., Int. Ed*. 2006, **45**, 1979. (b) H. Y. Kim, H.-J. Shih, W. E. Knabe, K. Oh, *Angew. Chem., Int. Ed*. 2009, **48**, 7420. (c) T.-L. Liu, Z.-L. He, H.-Y. Tao, Y.-P. Cai and C.-J. Wang, *Chem. Commun*., 2011, **47**, 2616-2618.

The absolute configuration determination of 3fa and 4fa

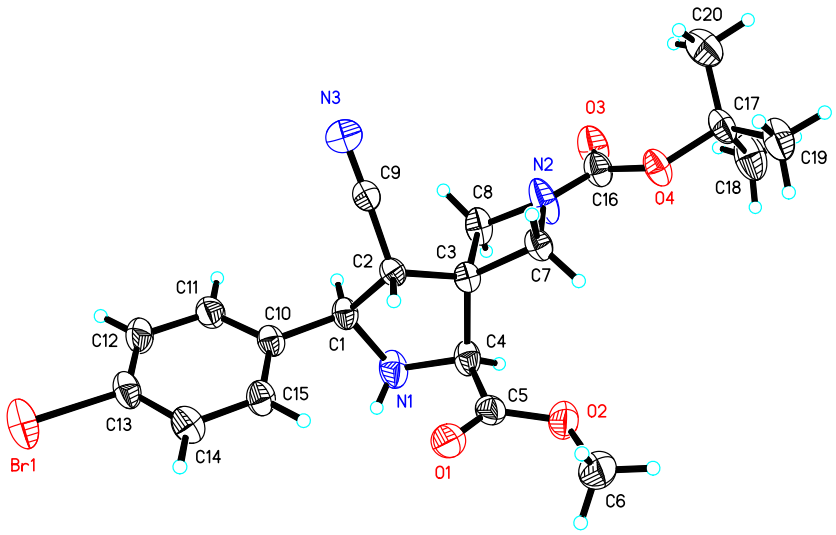


Fig S2. X-ray structure of (5*S*,7*R*,8*R*)-**3fa**

Ellipsoids are drawn at the 30% probability level.

Crystal data and structure refinement for CCDC 1914517

(CCDC **1914517** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html.)

Table S2. Crystal data and structure refinement for (5*S*,7*R*,8*R*)-**3fa**.

Identification code	(5*S*,7*R*,8*R*)-**3fa**	
Empirical formula	$C_{20}H_{24}BrN_3O_4$	
Formula weight	450.33	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 2	
Unit cell dimensions	a = 10.2024(3) Å	α= 90°.
	b = 31.7463(10) Å	β= 90°.
	c = 6.5544(2) Å	γ = 90°.
Volume	2122.89(11) Å^3	
Z	4	
Density (calculated)	1.409 Mg/m^3	
Absorption coefficient	1.966 mm^{-1}	
F(000)	928	
Crystal size	0.200 x 0.170 x 0.130 mm^3	
Theta range for data collection	2.373 to 25.990°.	

Index ranges	-12<=h<=12, -39<=k<=35, -8<=l<=7
Reflections collected	11503
Independent reflections	4090 [R(int) = 0.0271]
Completeness to theta = 25.242°	98.6 %
Absorption correction	Mutli-scan
Max. and min. transmission	0.7456 and 0.5520
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4090 / 1 / 262
Goodness-of-fit on F^2	1.034
Final R indices [I>2sigma(I)]	R1 = 0.0369, wR2 = 0.0832
R indices (all data)	R1 = 0.0552, wR2 = 0.0905
Absolute structure parameter	0.004(6)
Largest diff. peak and hole	0.496 and -0.532 e.Å^{-3}

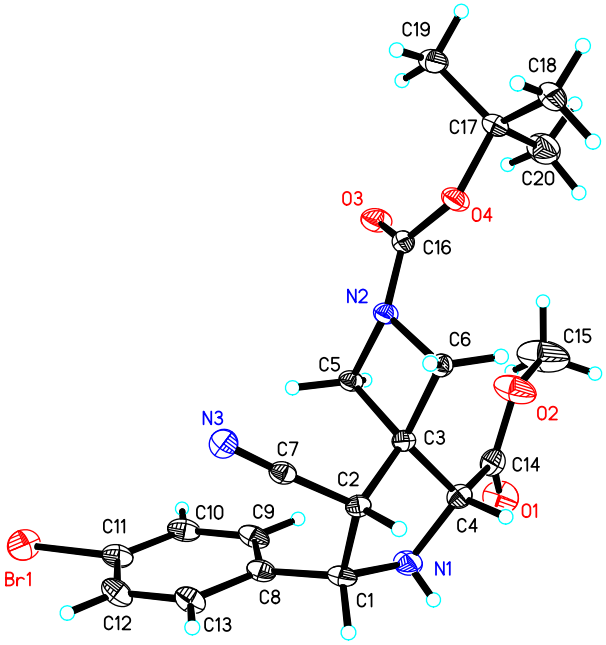


Fig S3. X-ray structure of (5*R*,7*S*,8*R*)-**4fa**
Ellipsoids are drawn at the 30% probability level.

Crystal data and structure refinement for CCDC 1914518

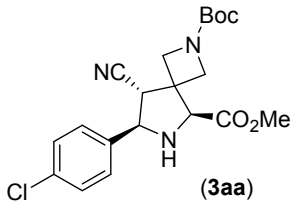
(CCDC **1914518** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html.)

Table S3. Crystal data and structure refinement for (5*R*,7*S*,8*R*)-**4fa**.

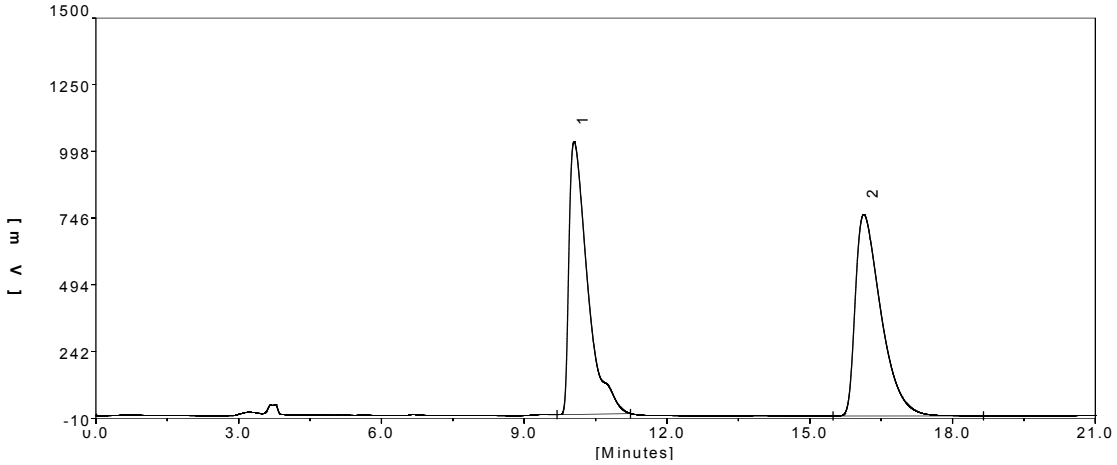
Identification code	(5*R*,7*S*,8*R*)-**4fa**
Empirical formula	C_{20} H_{24} Br N_3 O_4

Formula weight	450.33	
Temperature	193(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 6.4829(2) Å	α= 90°.
	b = 12.2525(3) Å	β= 90°.
	c = 26.9553(7) Å	γ = 90°.
Volume	2141.11(10) $Å^3$	
Z	4	
Density (calculated)	1.397 Mg/m^3	
Absorption coefficient	1.949 mm^{-1}	
F(000)	928	
Crystal size	0.170 x 0.140 x 0.100 mm^3	
Theta range for data collection	3.023 to 25.994°.	
Index ranges	-7<=h<=7, -15<=k<=13, -33<=l<=28	
Reflections collected	10450	
Independent reflections	4108 [R(int) = 0.0299]	
Completeness to theta = 25.242°	99.1 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7456 and 0.3565	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4108 / 1 / 262	
Goodness-of-fit on F^2	1.042	
Final R indices [I>2sigma(I)]	R1 = 0.0322, wR2 = 0.0731	
R indices (all data)	R1 = 0.0389, wR2 = 0.0760	
Absolute structure parameter	0.021(6)	
Largest diff. peak and hole	0.541 and -0.487 $e.Å^{-3}$	

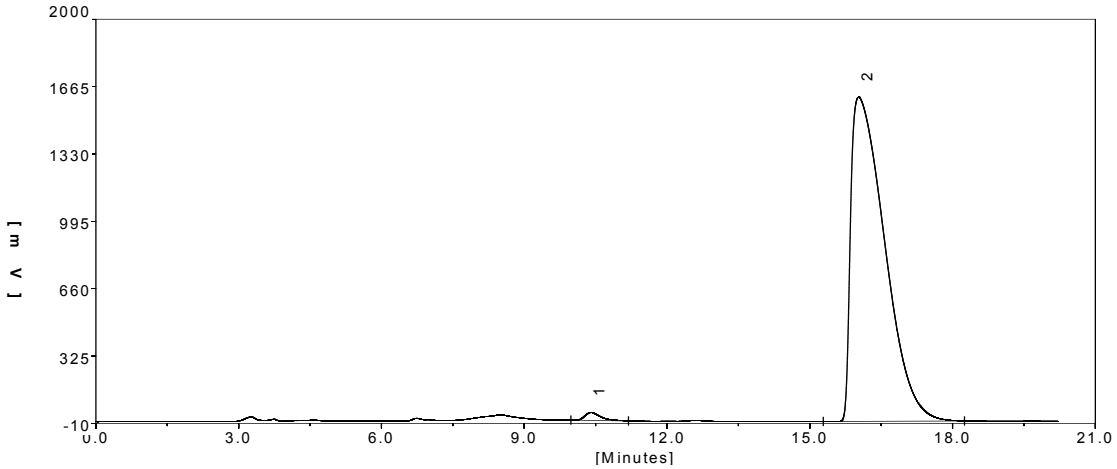
Chiral HPLC Chromatograms



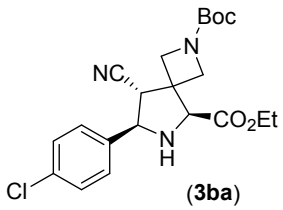
(**3aa**)



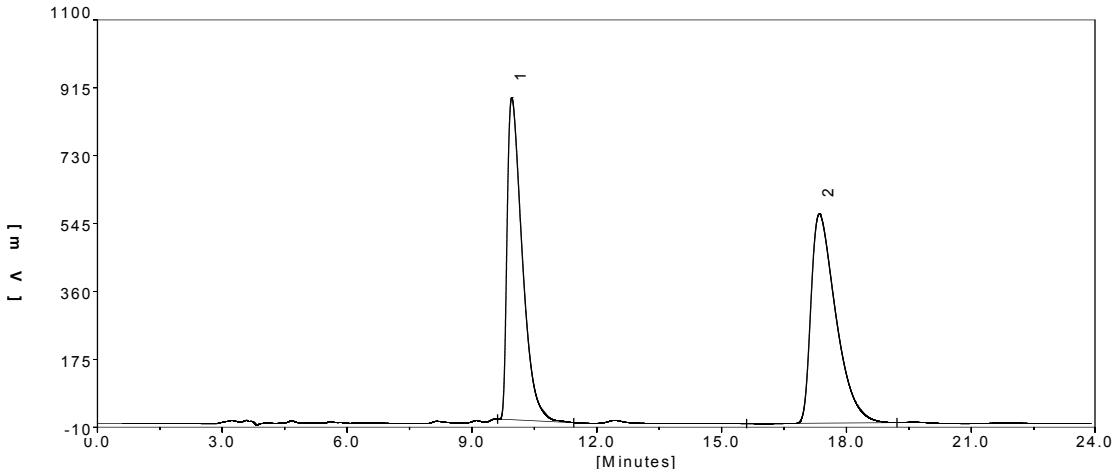
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	10.05000	1029.96	27807.20	49.4381
2	16.13667	760.49	28439.24	50.5619



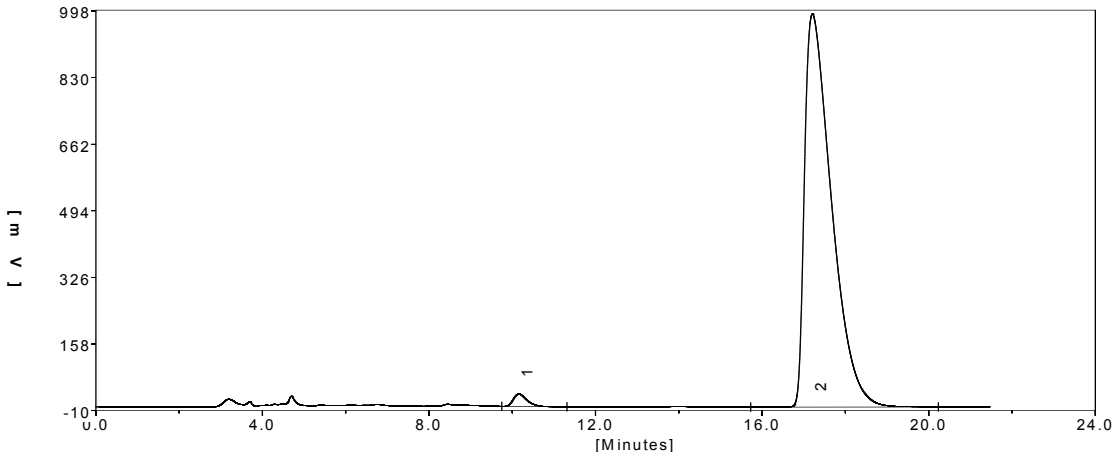
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	10.39667	39.03	886.00	1.1011
2	16.03000	1612.69	79577.32	98.8989



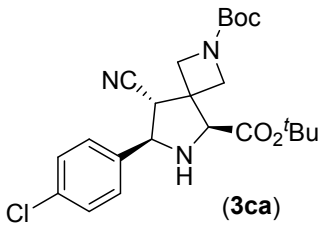
(**3ba**)



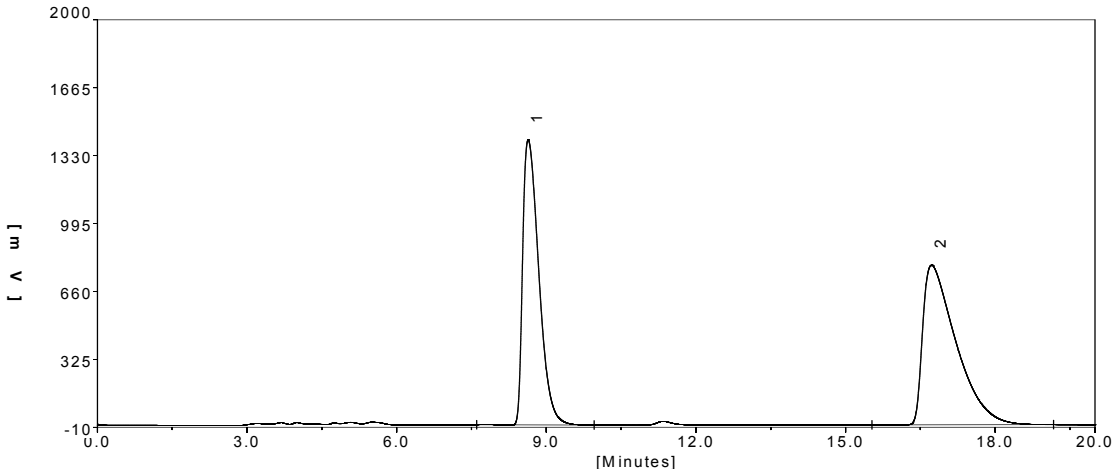
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	9.98750	878.14	22126.60	48.4710
2	17.37833	570.14	23522.51	51.5290



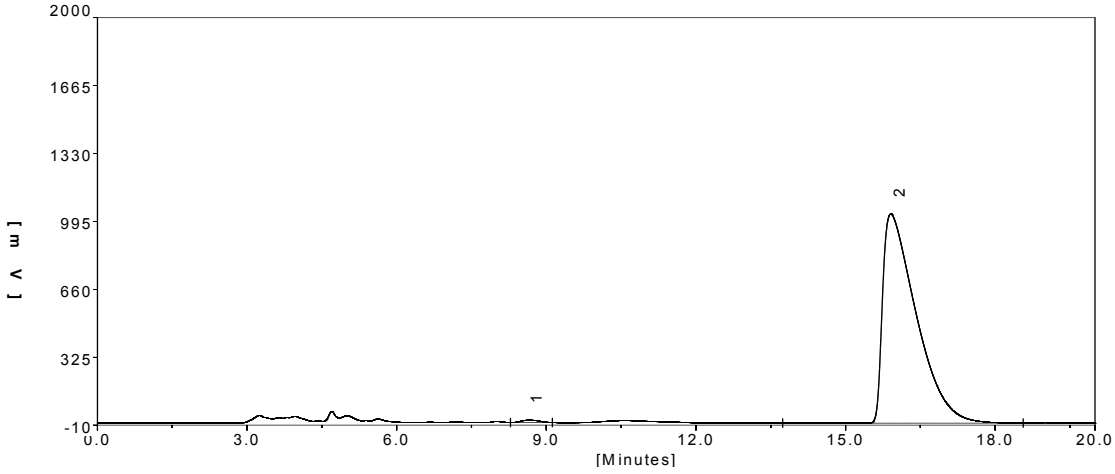
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	10.15333	31.54	711.39	1.5740
2	17.20750	991.40	44484.49	98.4260



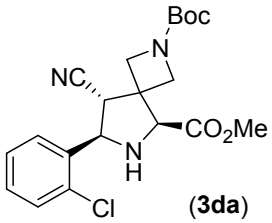
(**3ca**)



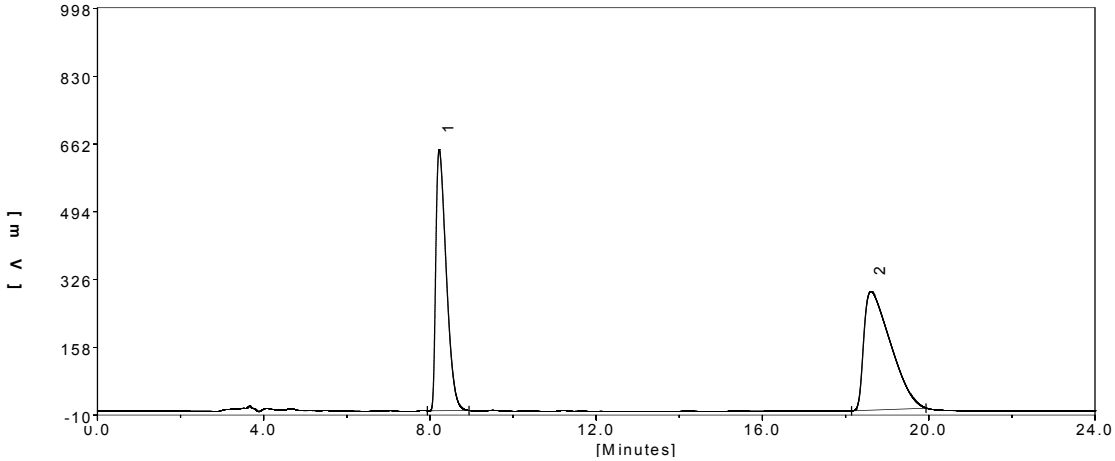
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	8.63667	1406.54	31639.78	46.4025
2	16.72500	788.32	36545.69	53.5975



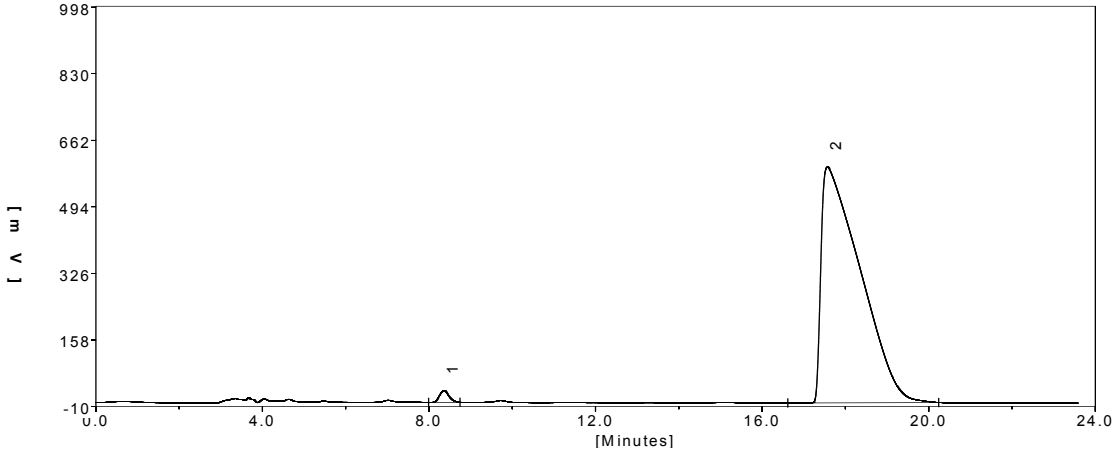
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	8.63083	11.46	287.23	0.5931
2	15.90750	1032.13	48141.43	99.4069



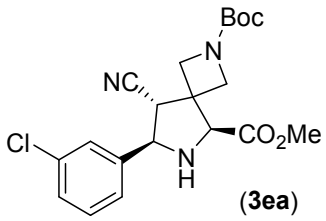
(**3da**)



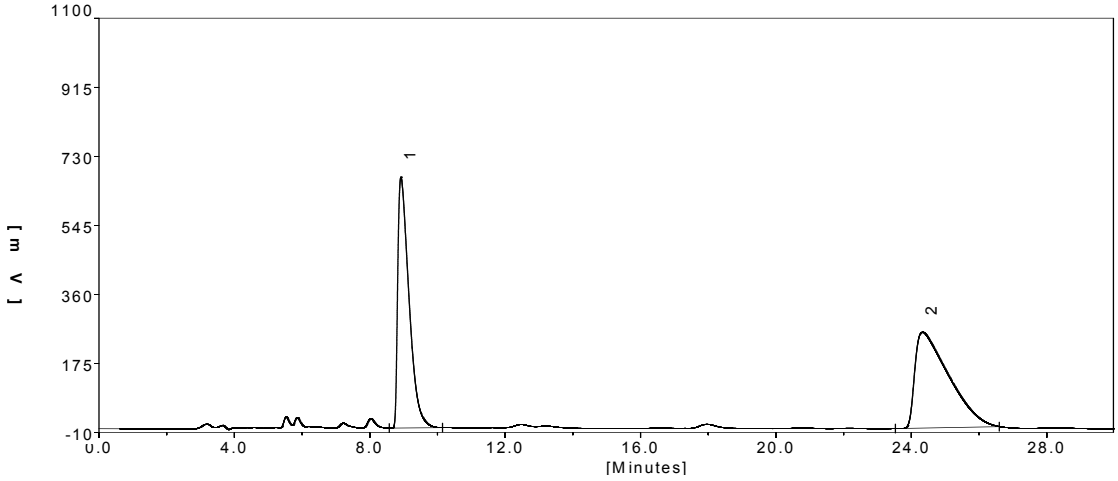
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	8.22500	647.35	11266.32	46.1355
2	18.61083	294.46	13153.77	53.8645



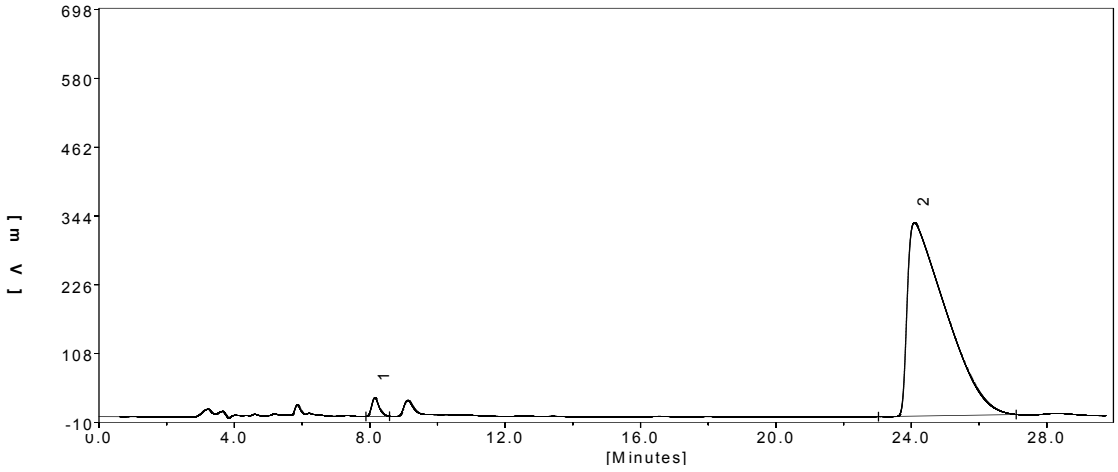
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	8.35667	29.99	468.44	1.1959
2	17.56667	595.18	38701.35	98.8041



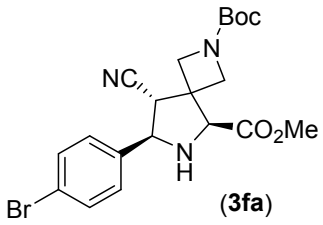
(**3ea**)



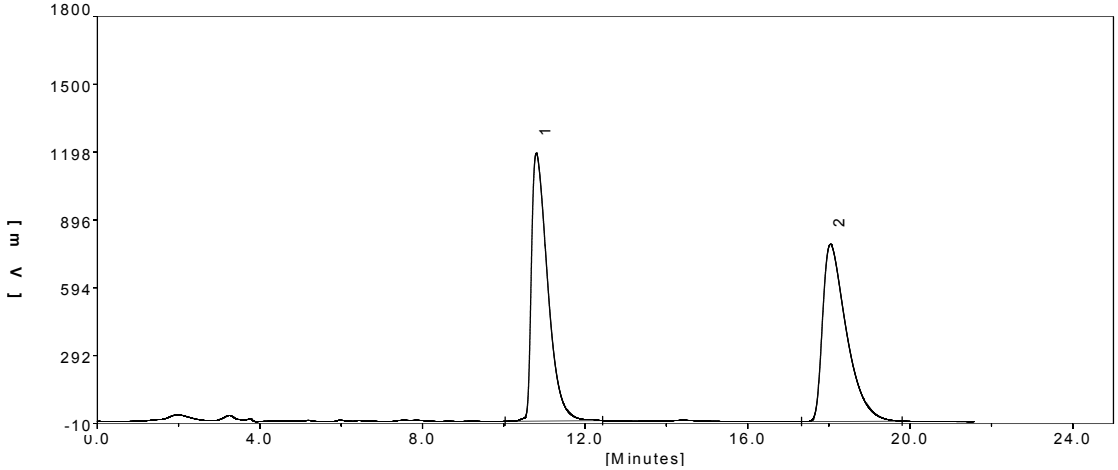
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	8.95333	672.19	15452.12	46.6247
2	24.35833	257.06	17689.40	53.3753



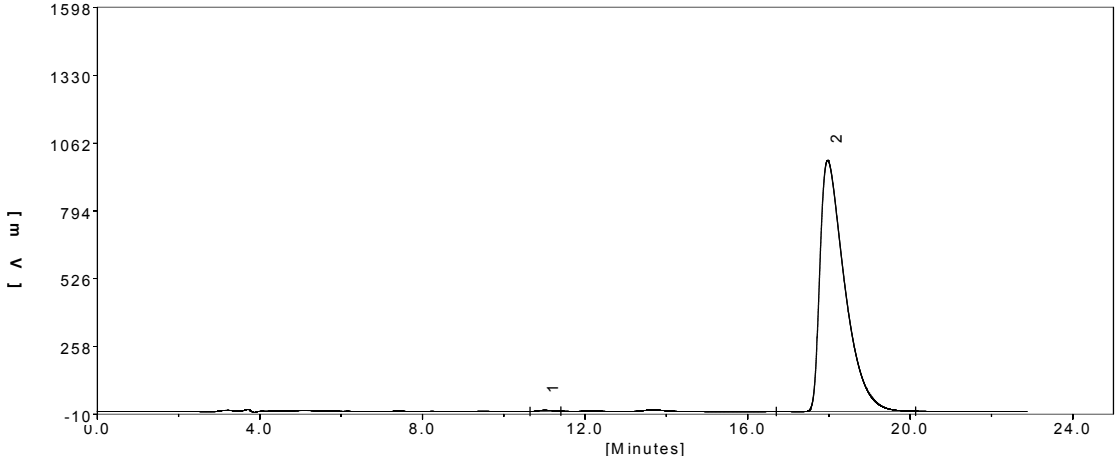
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	8.18167	31.91	482.95	1.8138
2	24.12167	331.50	26142.56	98.1862



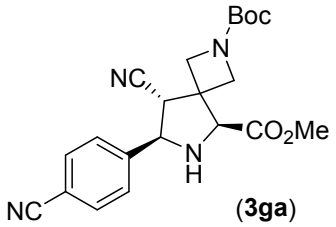
(**3fa**)



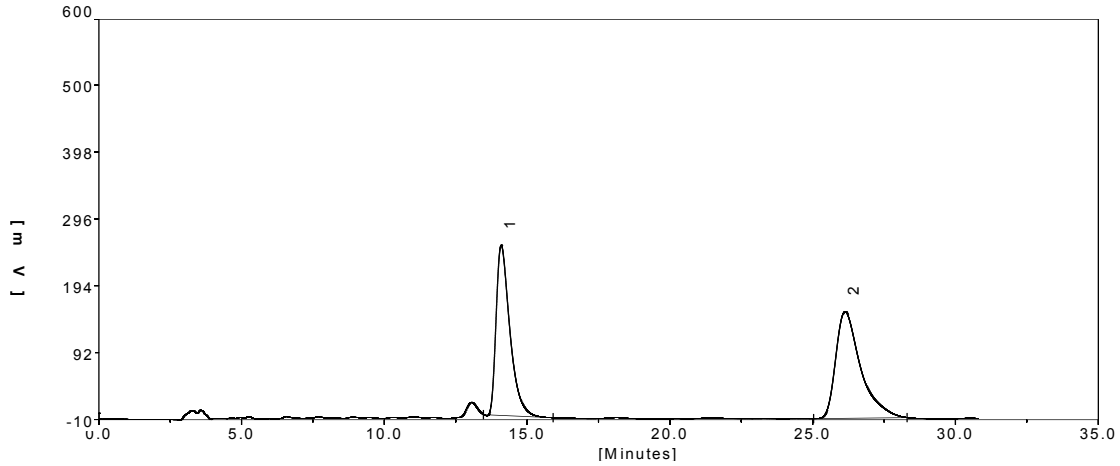
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	10.80167	1191.65	32962.23	50.7590
2	18.03833	788.28	31976.44	49.2410



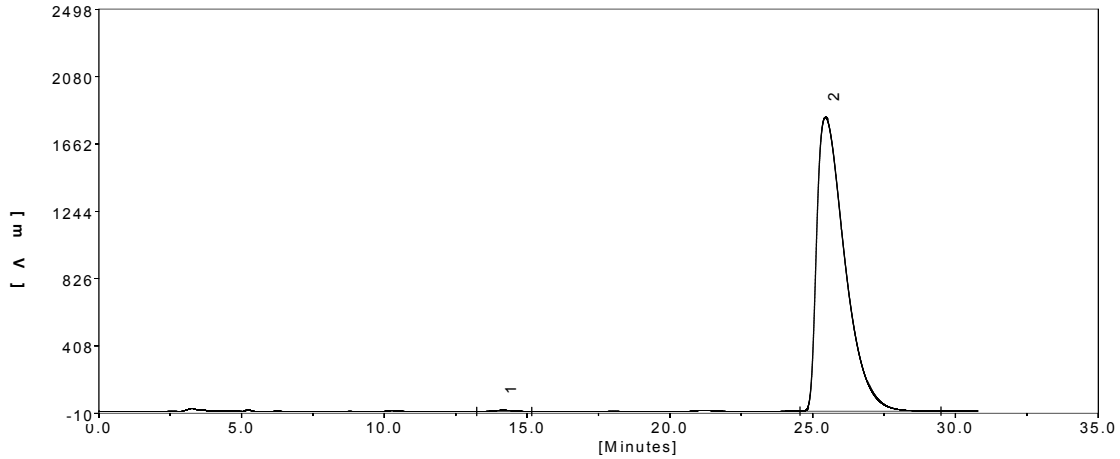
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	10.98917	4.40	95.42	0.2286
2	17.96917	993.55	41640.82	99.7714



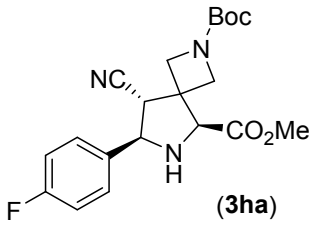
(**3ga**)



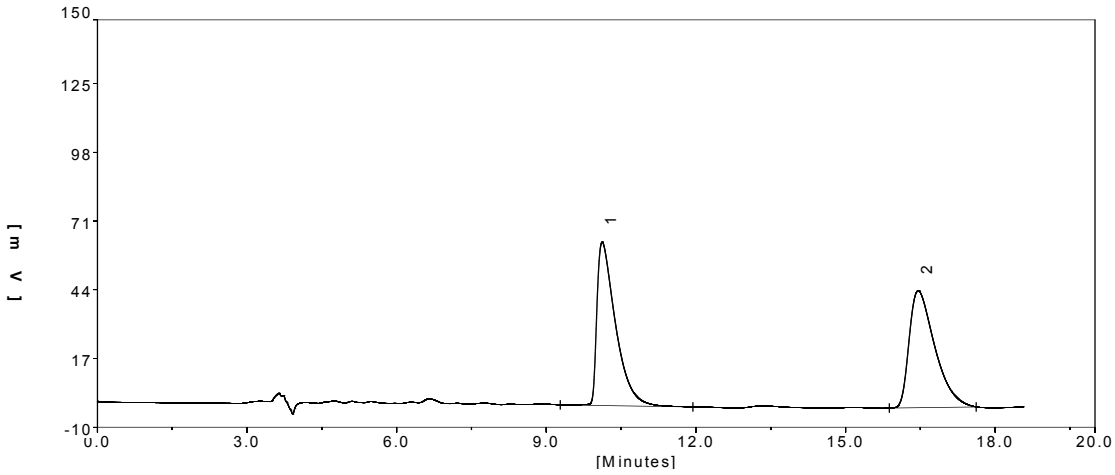
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	14.09167	259.51	8671.15	46.9495
2	26.13333	162.65	9797.96	53.0505



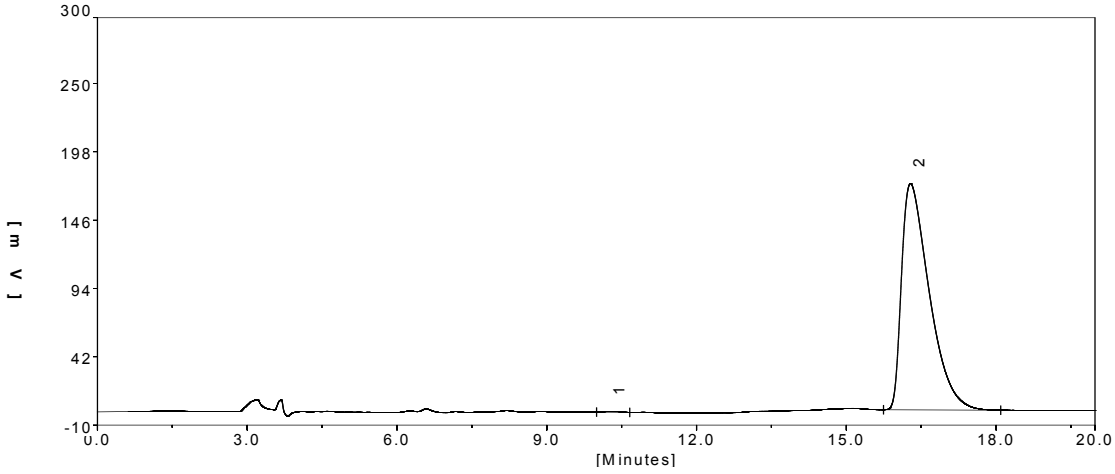
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	14.13000	8.38	351.24	0.2829
2	25.44417	1826.17	123795.03	99.7171



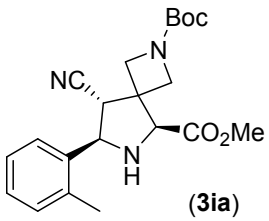
(**3ha**)



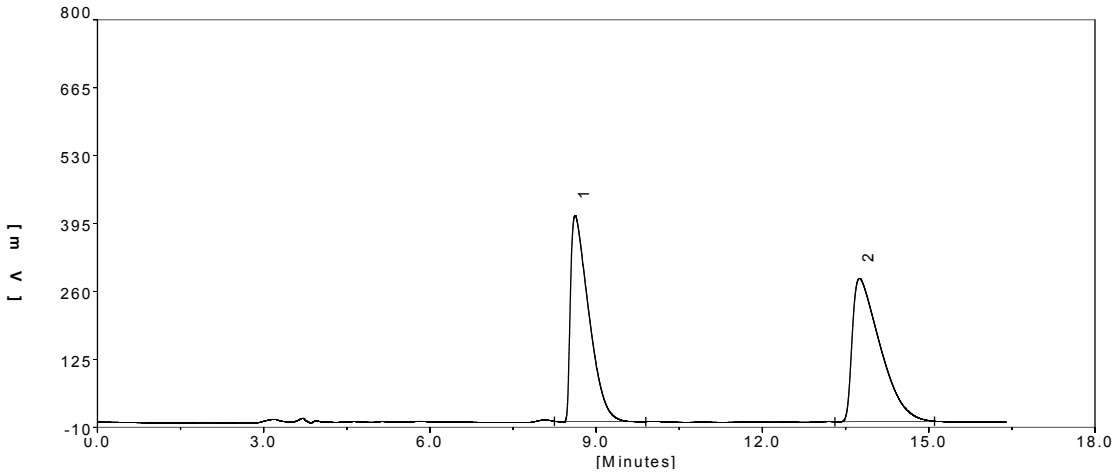
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	10.12083	64.22	1664.14	50.3584
2	16.45500	45.98	1640.45	49.6416



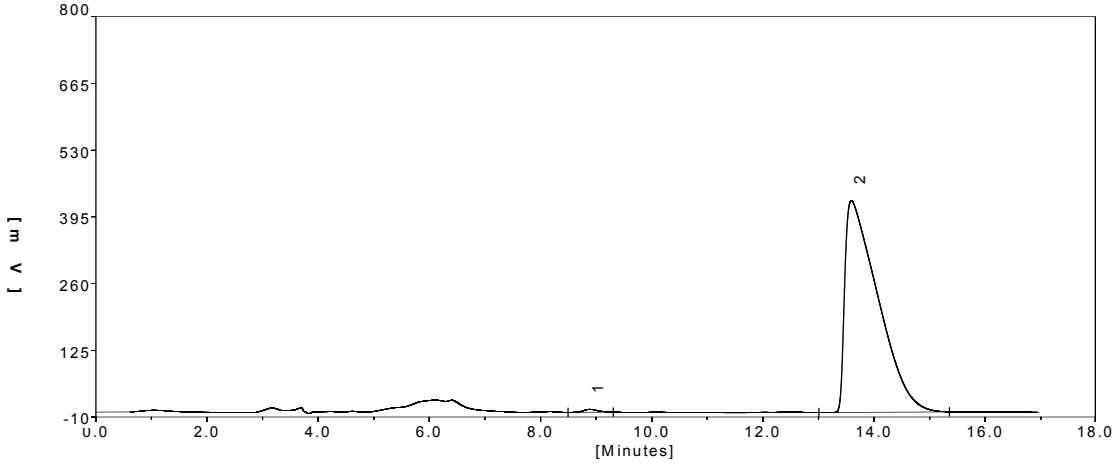
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	10.29500	0.66	13.12	0.1973
2	16.30667	172.25	6636.29	99.8027



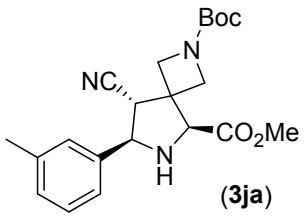
(**3ia**)



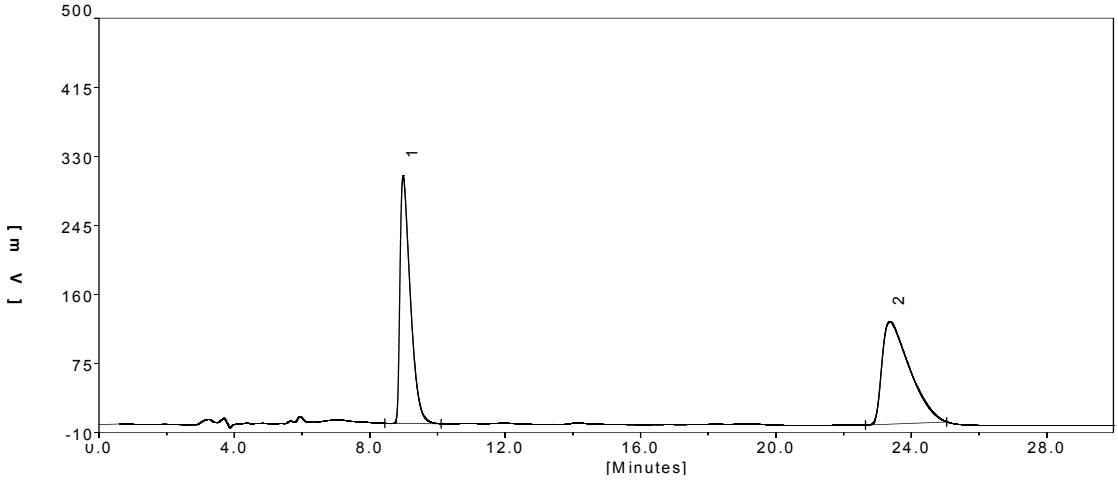
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	8.62000	409.75	9356.18	48.5388
2	13.75083	284.85	9919.50	51.4612



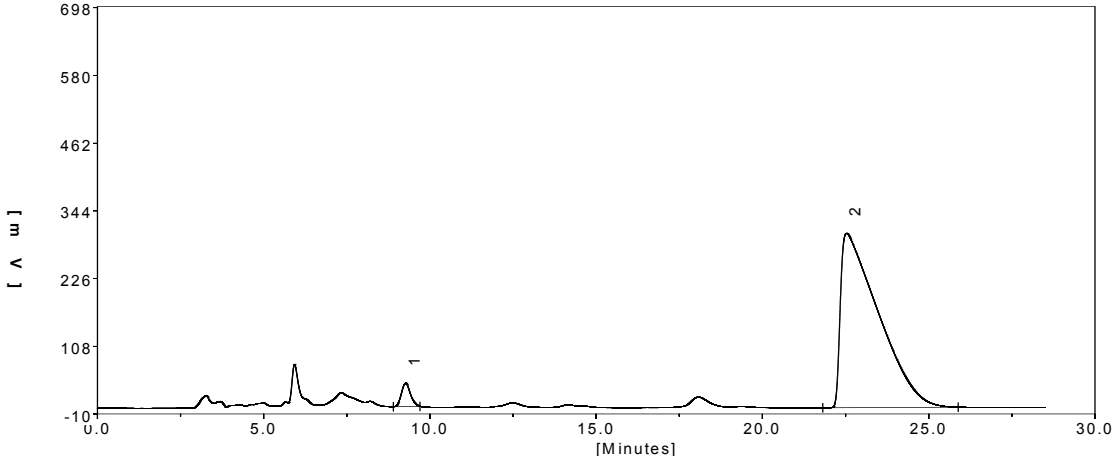
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	8.90000	6.00	106.11	0.5972
2	13.61167	428.76	17663.63	99.4028



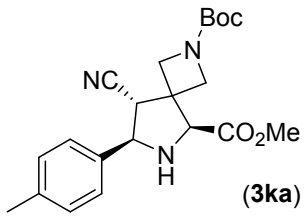
(**3ja**)



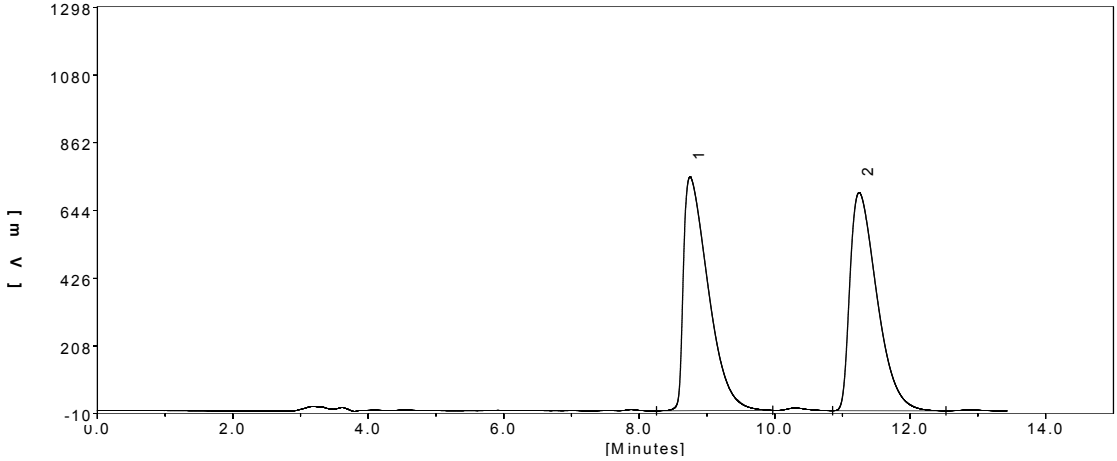
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	9.01750	305.11	6448.96	47.4705
2	23.39167	126.18	7136.23	52.5295



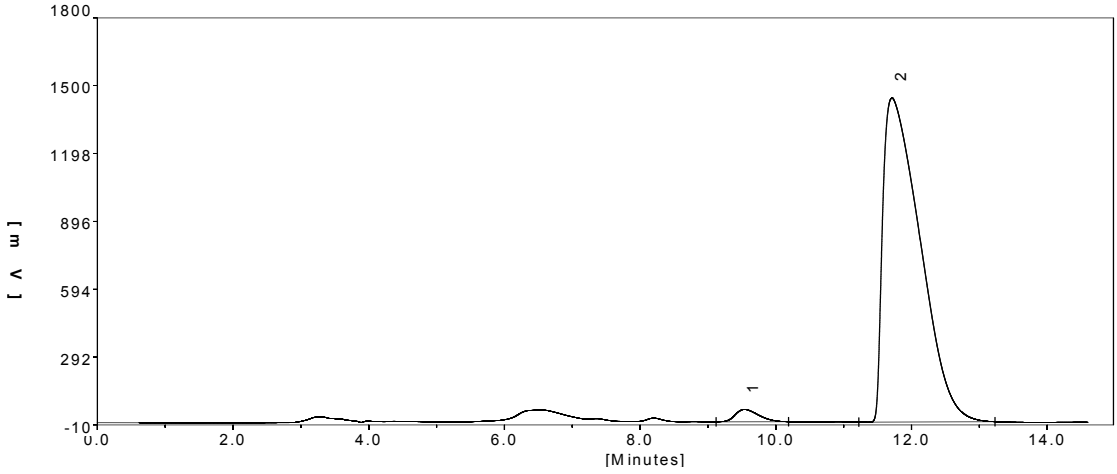
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	9.26917	40.93	771.11	3.1142
2	22.53083	303.99	23990.40	96.8858



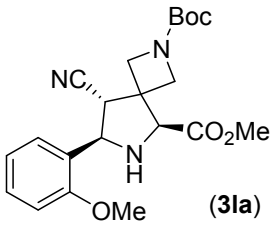
(**3ka**)



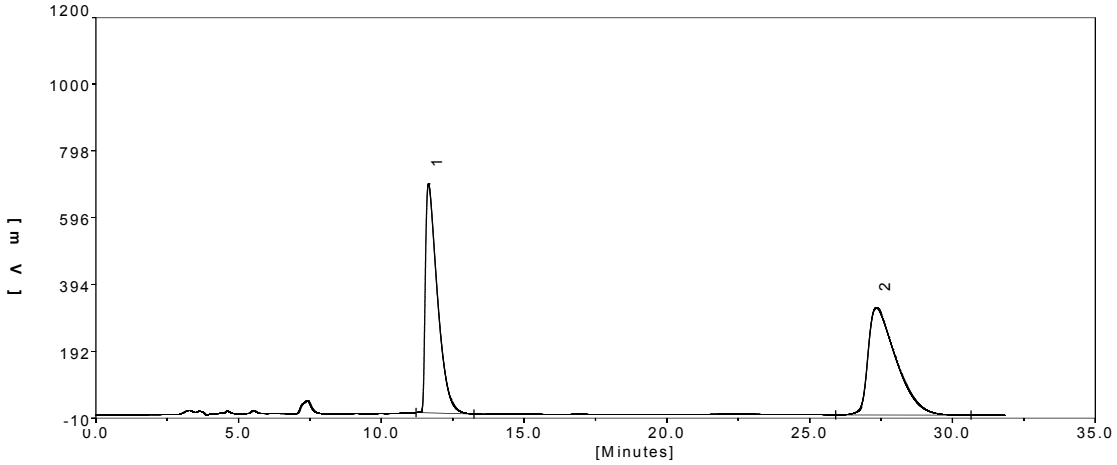
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	8.75000	752.58	19047.87	49.5488
2	11.24667	702.45	19394.81	50.4512



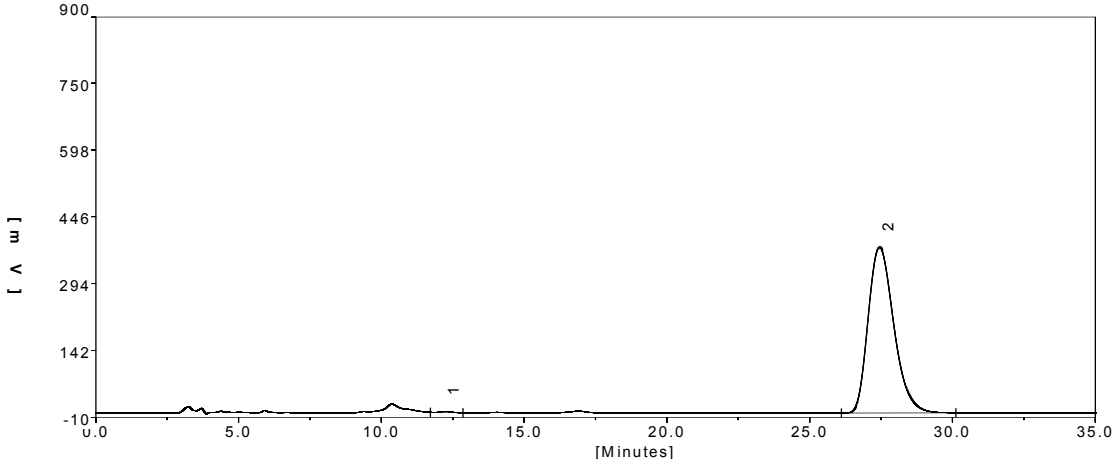
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	9.55667	55.01	1313.01	2.3403
2	11.73667	1441.24	54791.27	97.6597



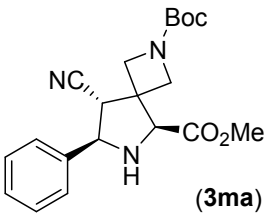
(**3la**)



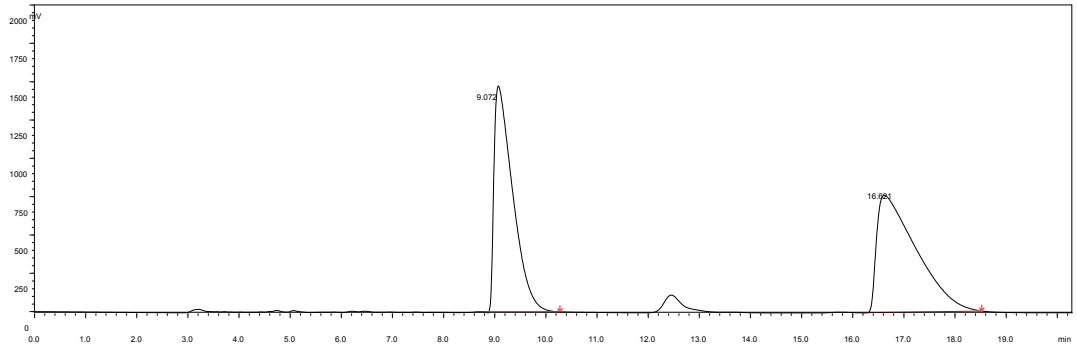
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	11.65083	692.28	20271.43	48.0362
2	27.32917	324.76	21928.86	51.9638



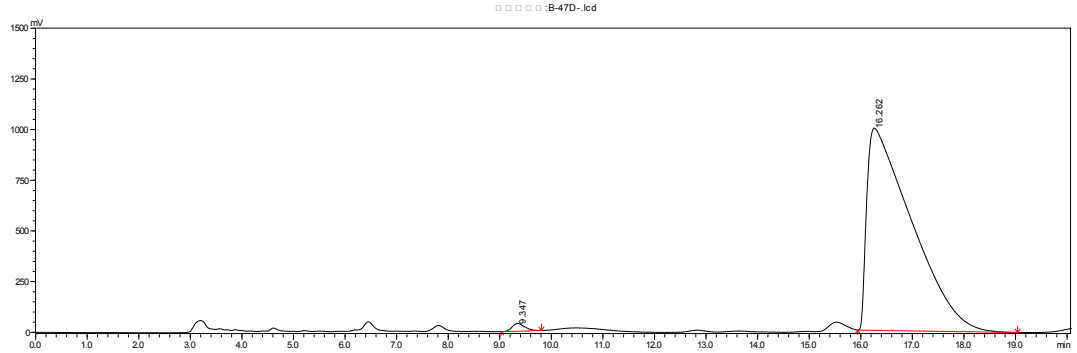
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	12.22167	2.65	58.78	0.2492
2	27.44500	377.09	23523.86	99.7508



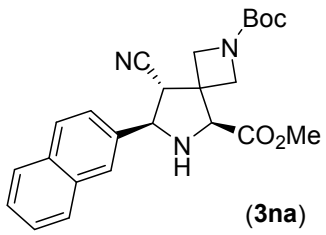
(**3ma**)



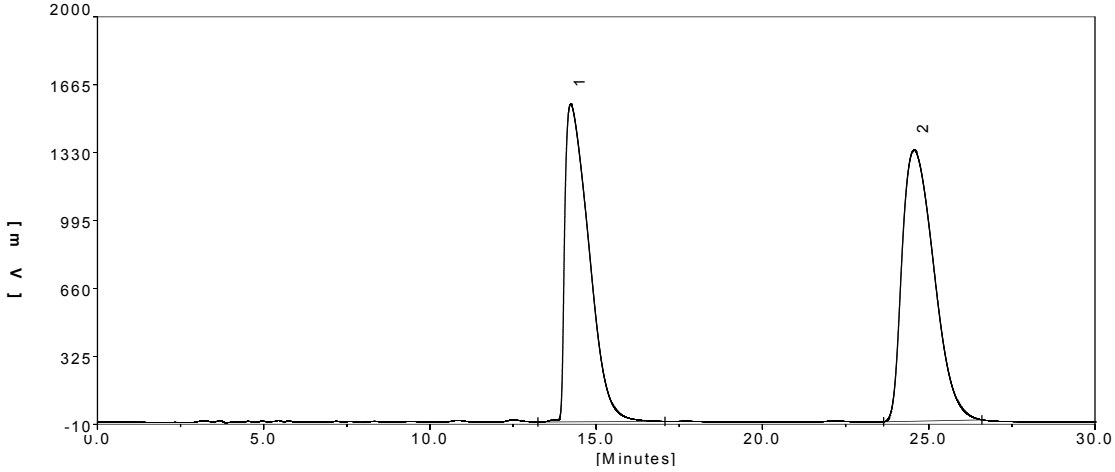
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	9.072	1472555	37536555	47.808
2	16.621	764461	40978638	52.192



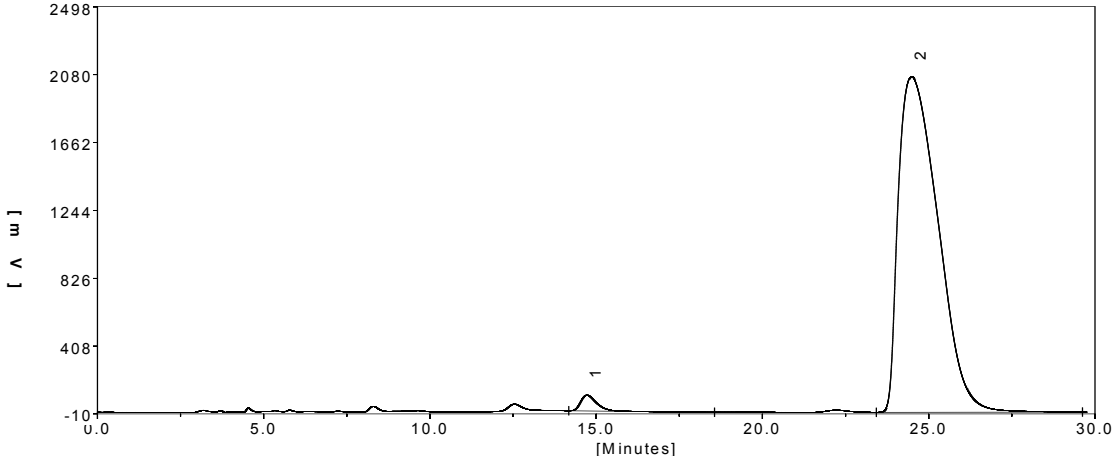
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	9.347	38359	662721	1.085
2	16.262	997112	60445147	98.915



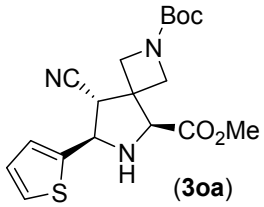
(**3na**)



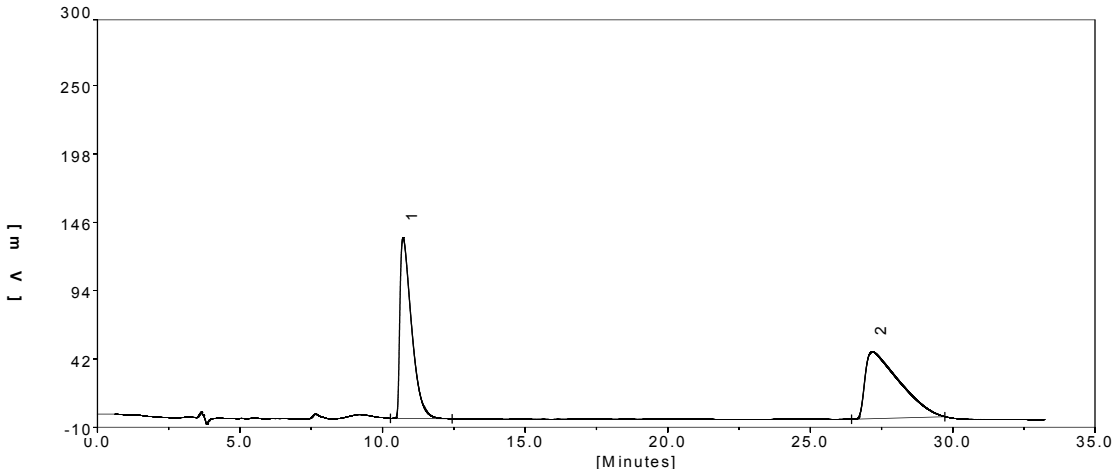
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	14.23417	1568.20	78130.62	46.8003
2	24.56000	1338.35	88813.95	53.1997



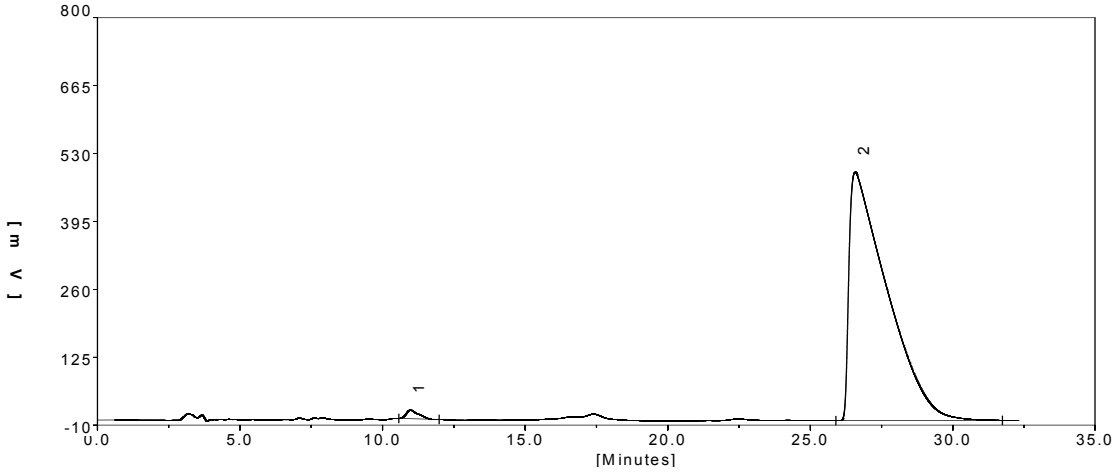
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	14.71417	97.45	3133.46	1.8031
2	24.48750	2068.03	170646.90	98.1969



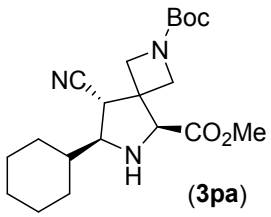
(**3oa**)



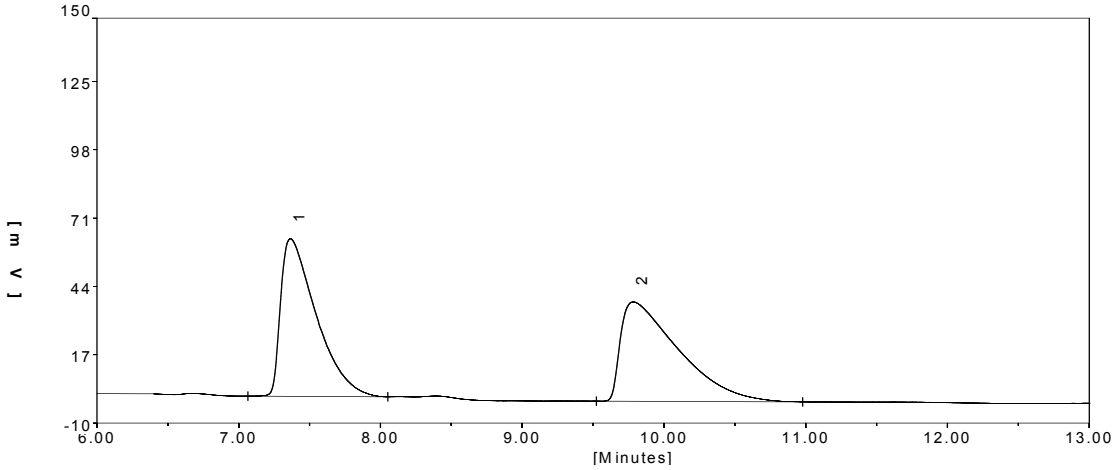
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	10.74000	137.61	3882.58	48.1475
2	27.19167	50.92	4181.35	51.8525



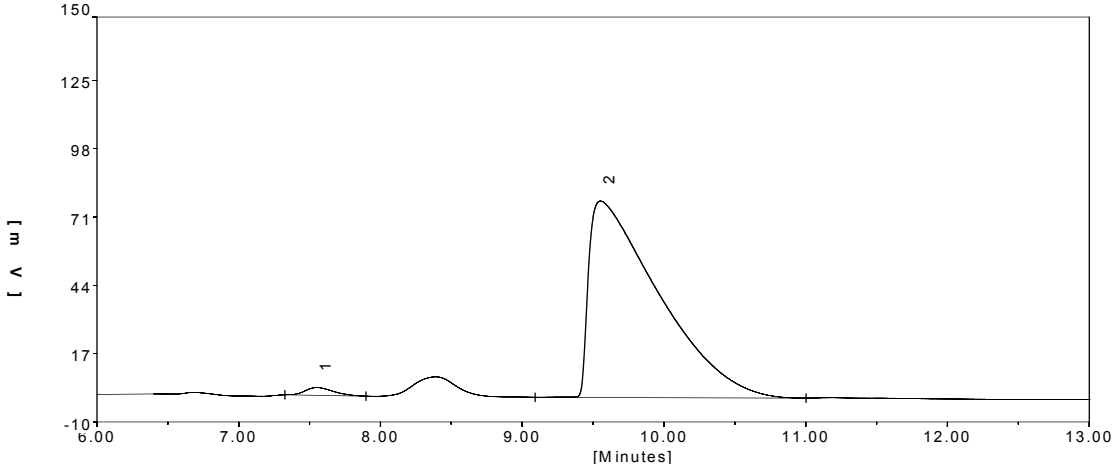
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	10.98167	17.32	502.08	1.0875
2	26.59167	494.09	45668.48	98.9125



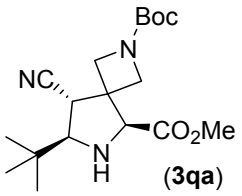
(**3pa**)



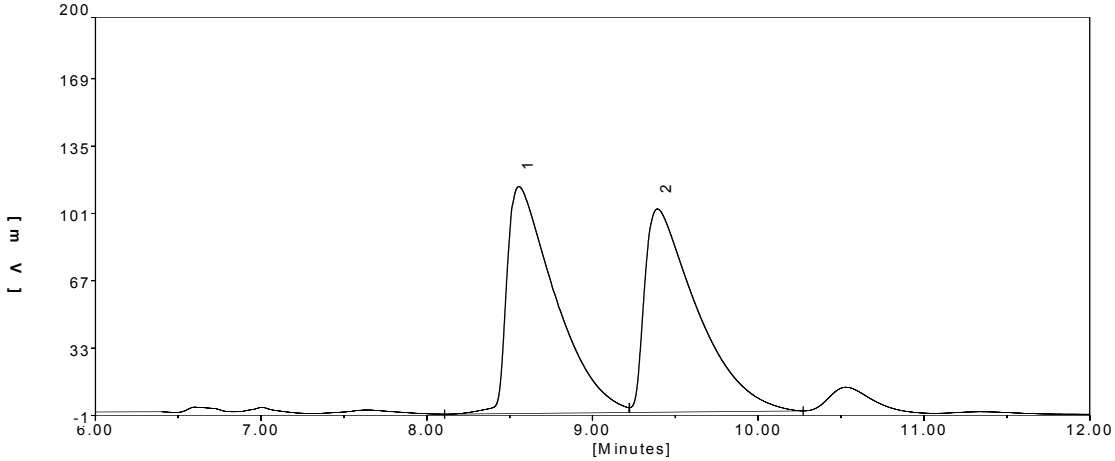
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	7.36500	62.26	1085.80	49.3937
2	9.78333	39.27	1112.46	50.6063



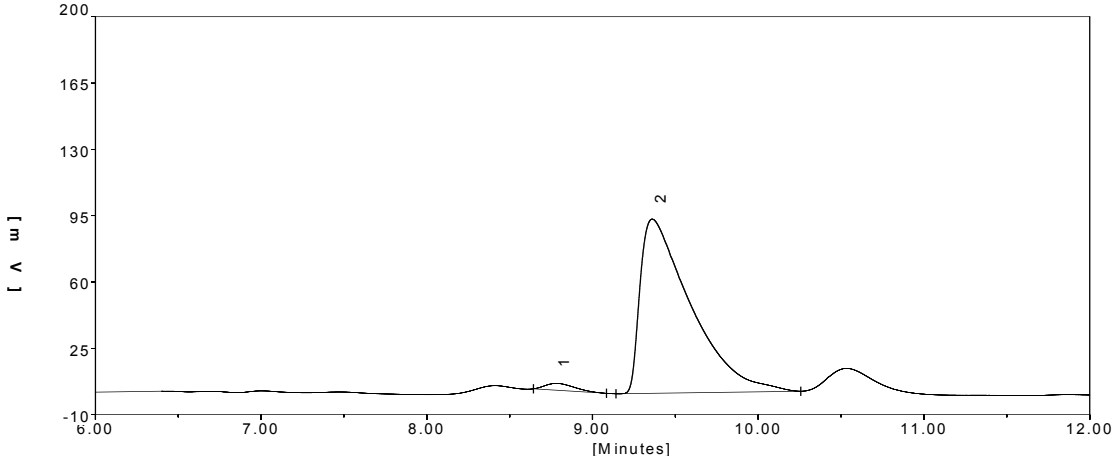
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	7.55083	3.08	42.07	1.5548
2	9.55250	77.63	2663.81	98.4452



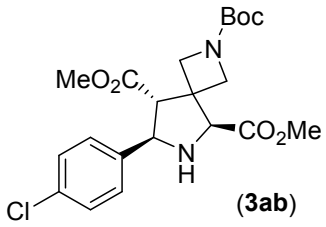
(**3qa**)



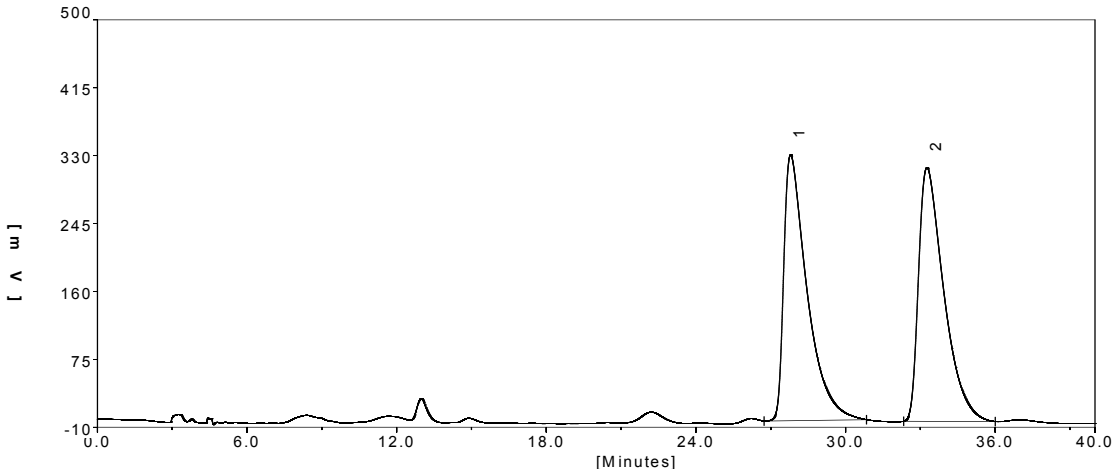
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	8.55583	114.61	2328.06	50.8149
2	9.39167	102.65	2253.39	49.1851



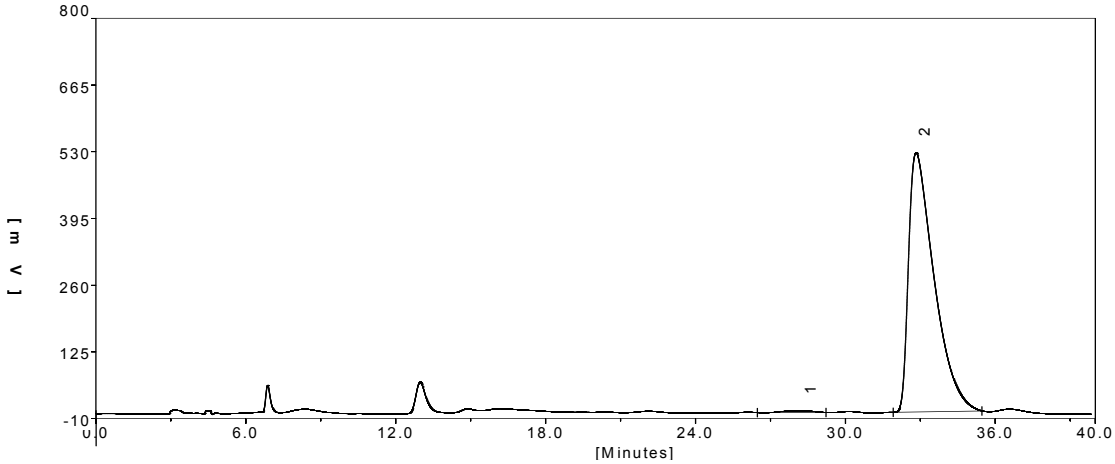
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	8.77500	3.58	44.41	2.2264
2	9.36000	91.93	1950.45	97.7736



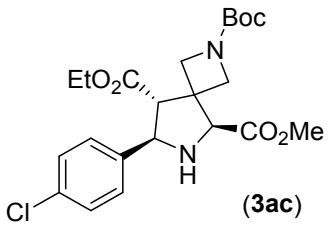
(**3ab**)



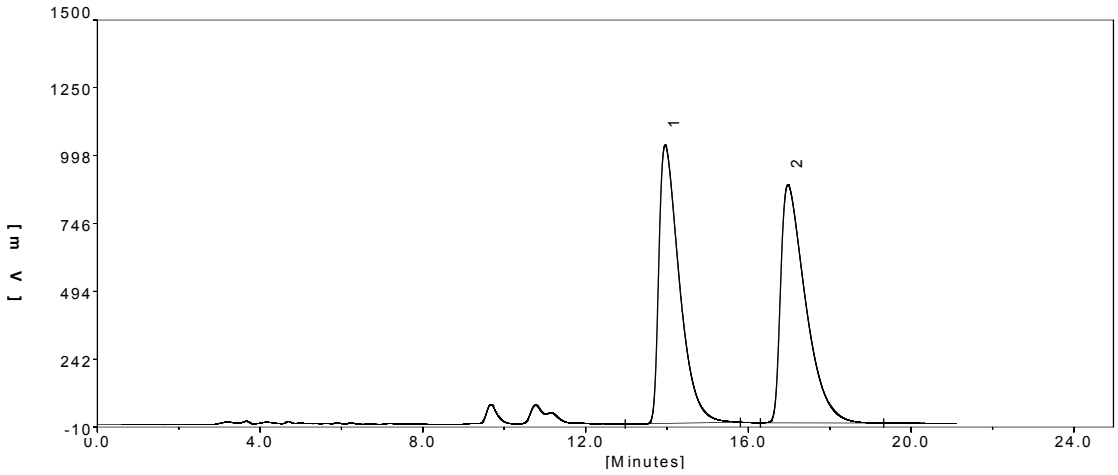
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	27.79500	333.01	21595.62	49.2048
2	33.26500	317.86	22293.65	50.7952



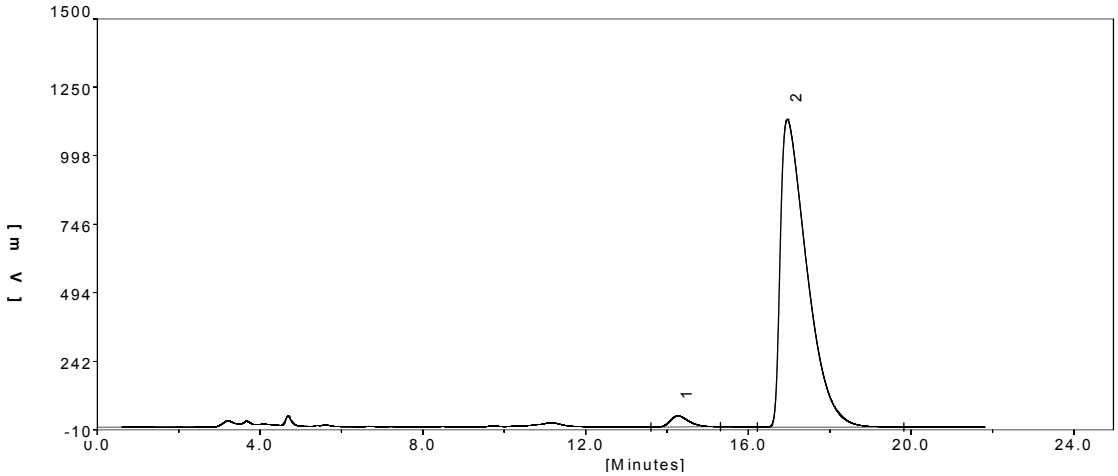
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	28.26083	3.71	285.79	0.7623
2	32.82833	524.58	37203.91	99.2377



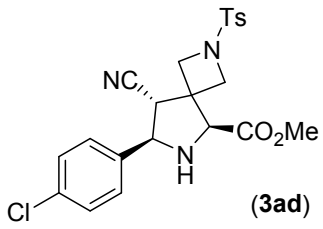
(**3ac**)



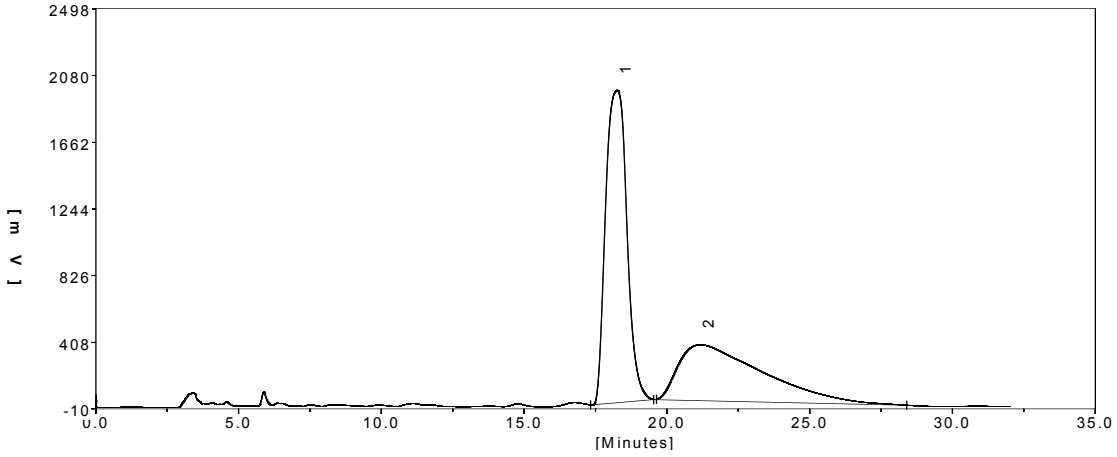
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	13.98583	1032.73	36000.81	49.0847
2	17.00333	883.54	37343.50	50.9153



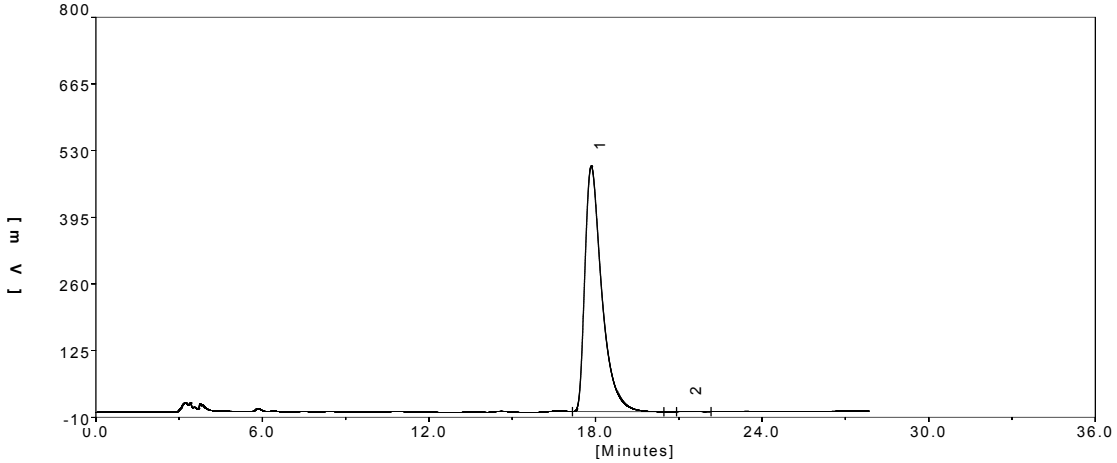
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	14.29000	40.87	1286.32	2.4641
2	16.98833	1131.50	50916.47	97.5359



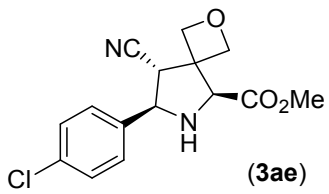
(**3ad**)



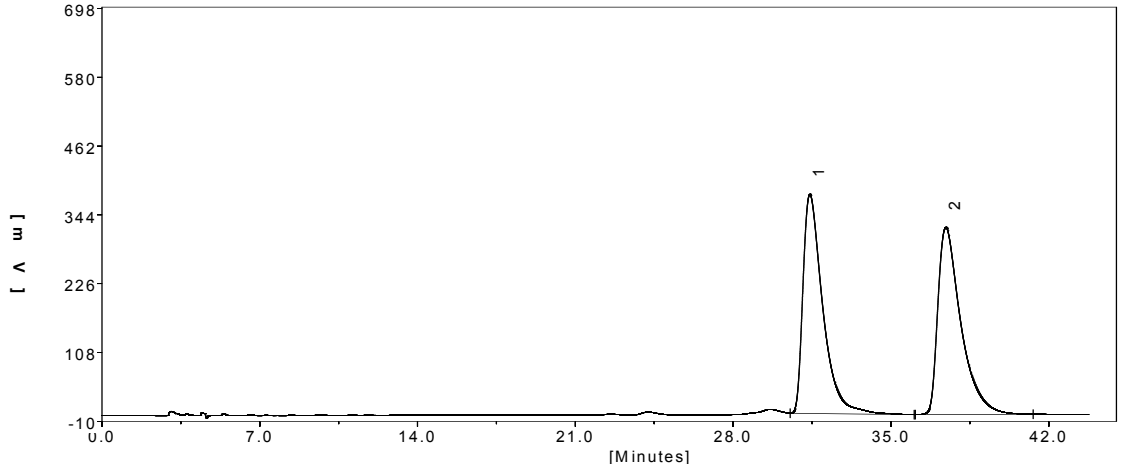
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	18.24500	1959.54	101429.15	58.4469
2	21.15750	350.58	72111.46	41.5531



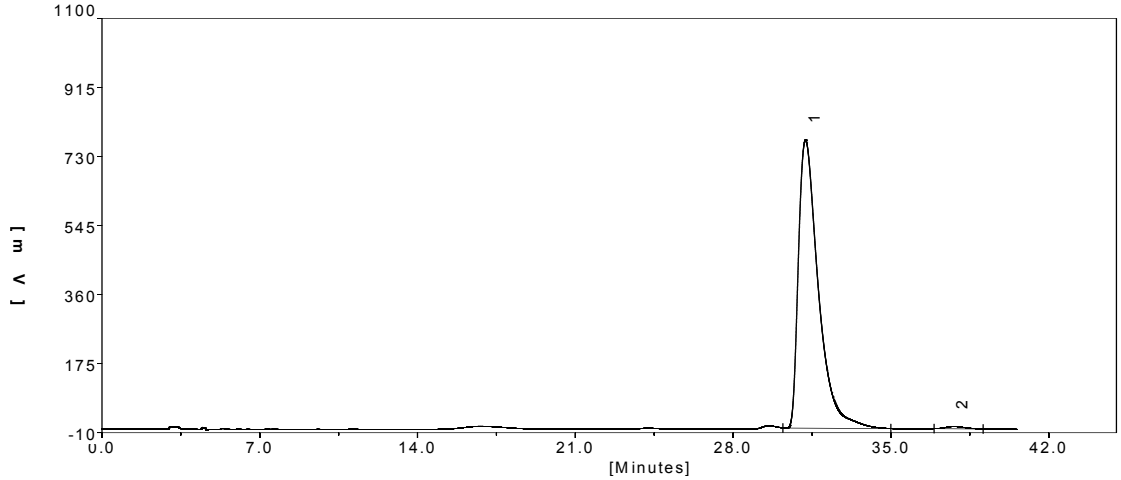
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	17.84667	497.32	20947.34	99.9850
2	21.30917	0.16	3.14	0.0150



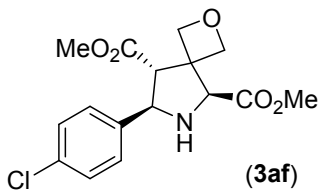
(**3ae**)



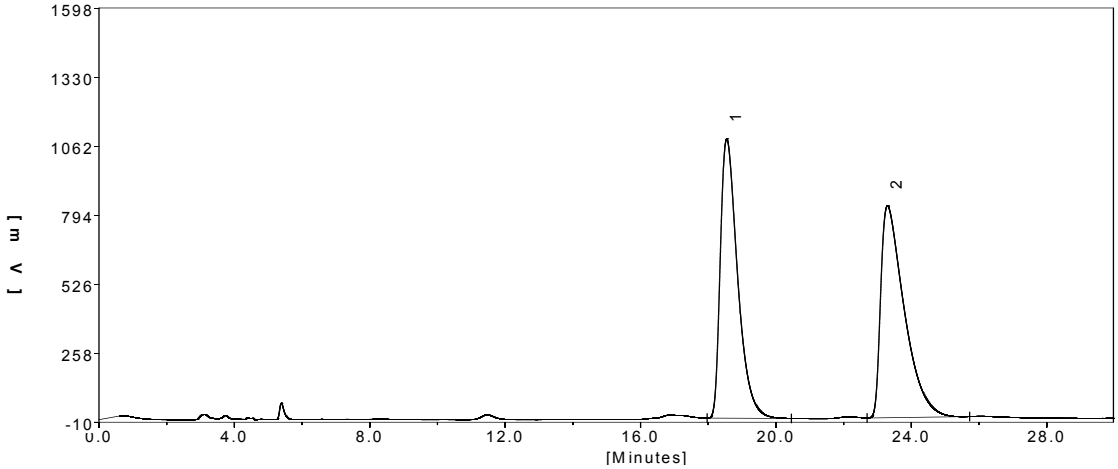
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	31.40333	375.84	22894.99	50.2053
2	37.43583	321.07	22707.74	49.7947



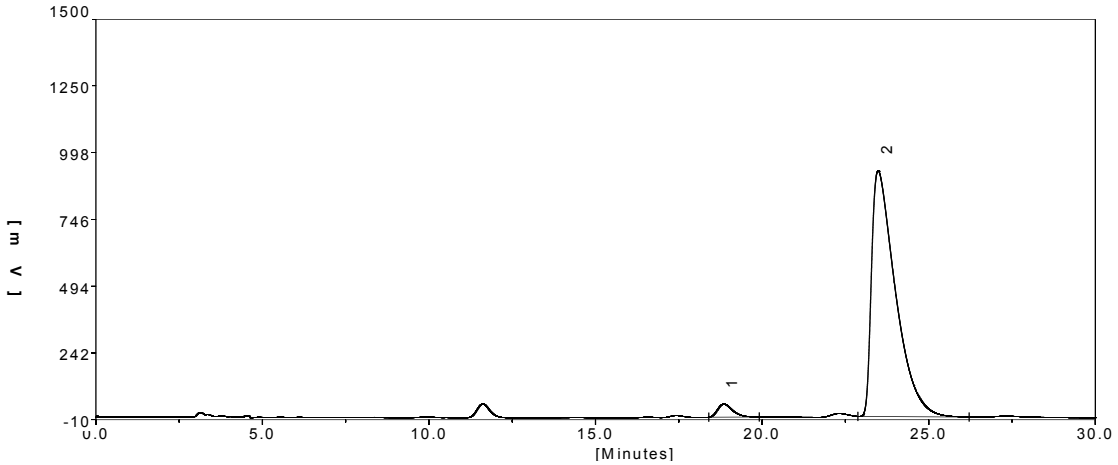
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	31.21000	772.62	47410.28	99.2708
2	37.76250	6.02	348.25	0.7292



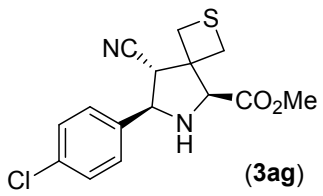
(**3af**)



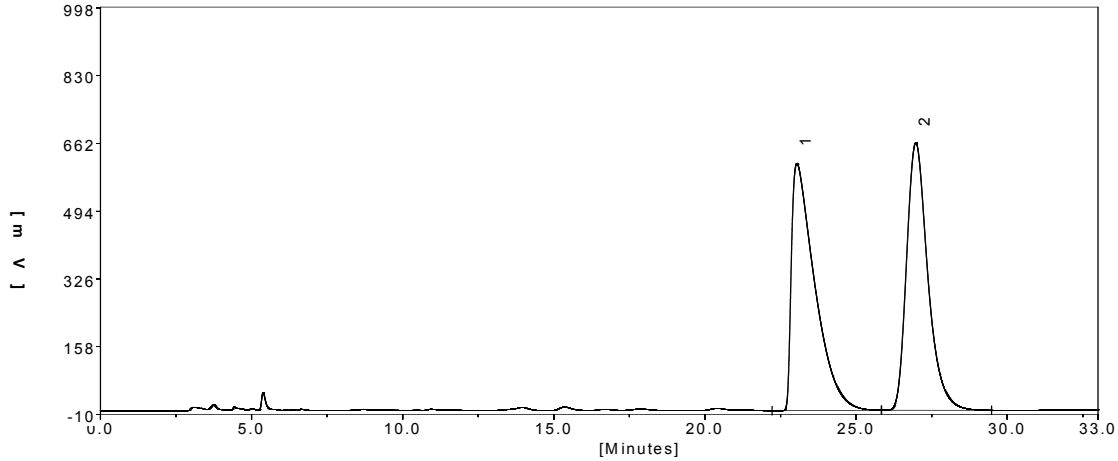
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	18.57750	1085.74	38458.73	49.2855
2	23.32750	823.87	39573.88	50.7145



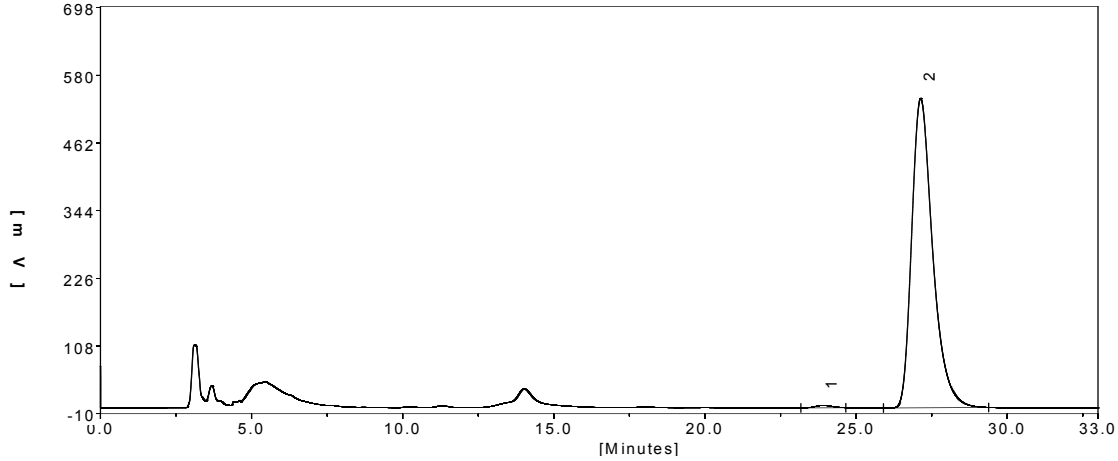
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	18.84000	49.41	1524.40	3.1958
2	23.48333	927.64	46175.09	96.8042



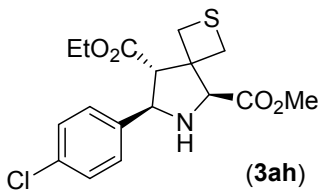
(**3ag**)



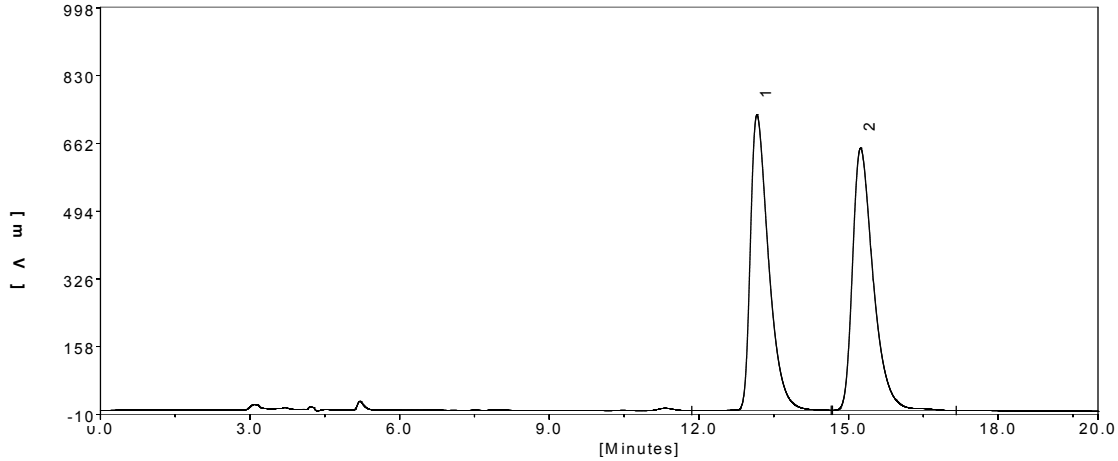
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	23.04167	613.23	32789.51	50.3249
2	26.97583	663.55	32366.09	49.6751



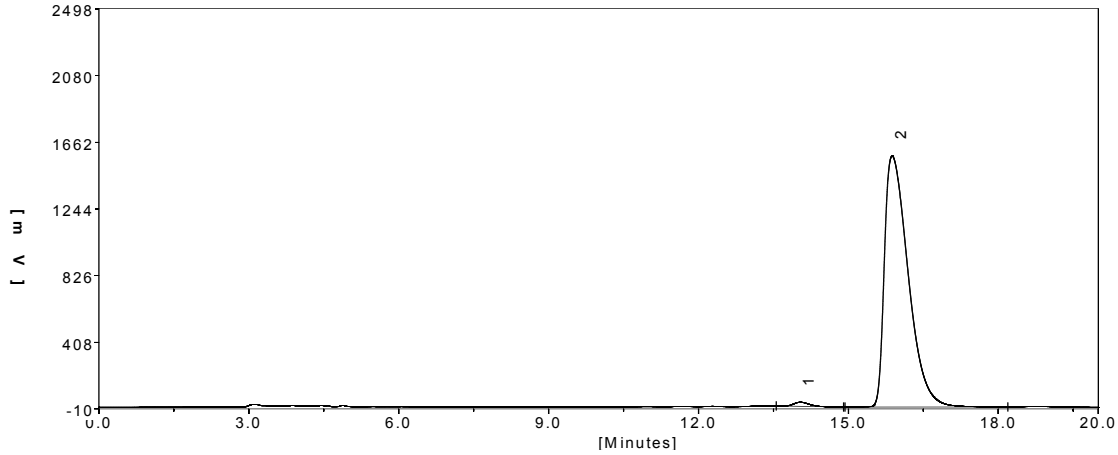
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	23.89083	4.25	163.16	0.6219
2	27.13750	539.58	26071.39	99.3781



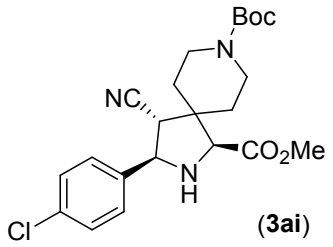
(**3ah**)



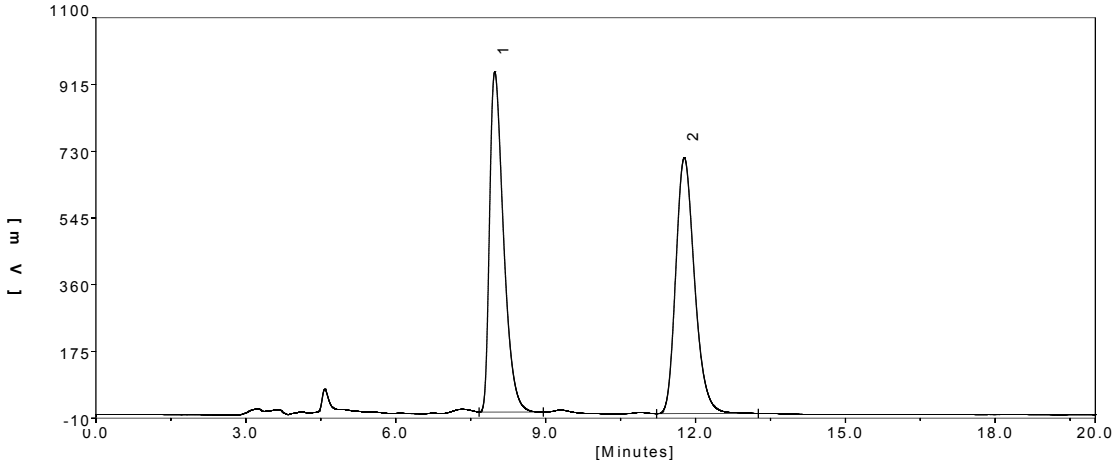
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	13.16417	733.05	18516.86	49.7579
2	15.24167	650.39	18697.03	50.2421



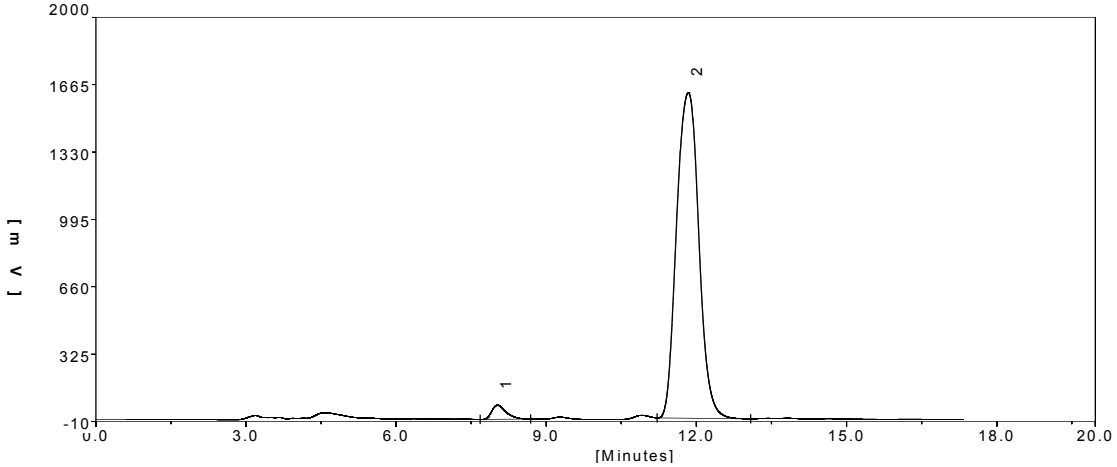
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	14.03000	26.09	536.81	1.0232
2	15.87583	1574.45	51928.11	98.9768



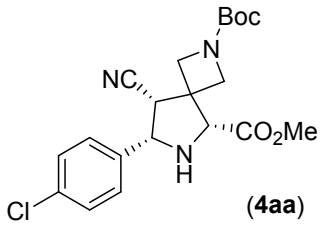
(**3ai**)



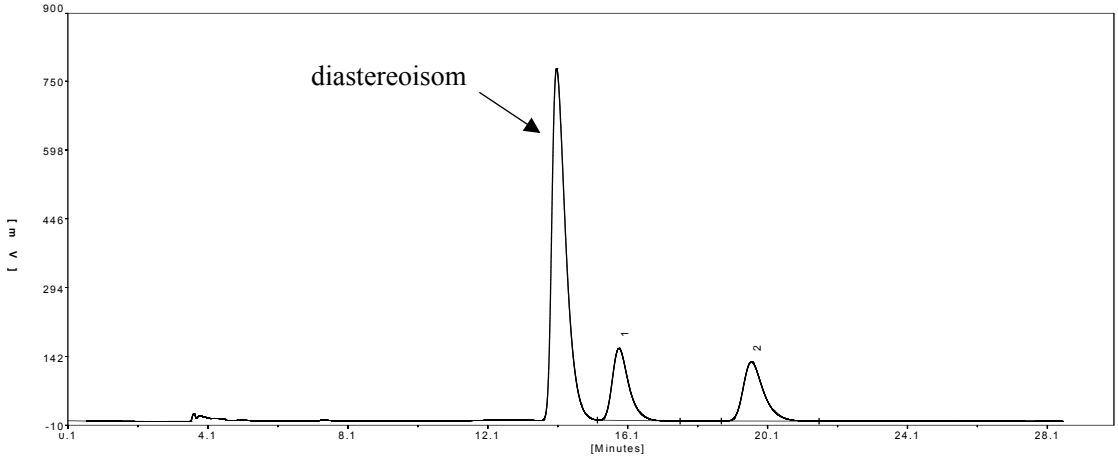
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	7.98167	943.48	18297.42	49.6913
2	11.77667	709.94	18524.78	50.3087



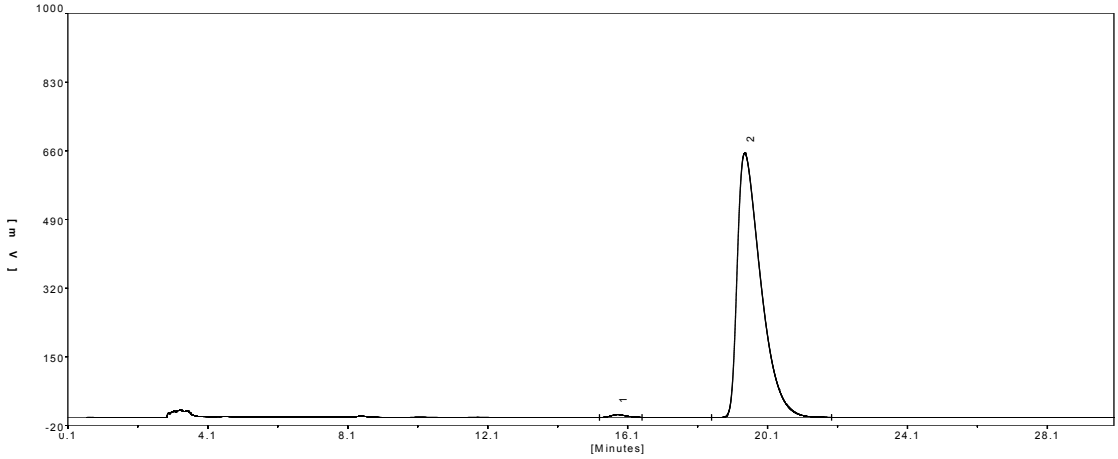
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	8.05083	70.66	1374.90	2.6763
2	11.86833	1619.23	49998.18	97.3237



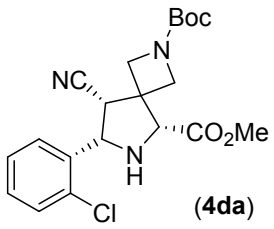
(**4aa**)



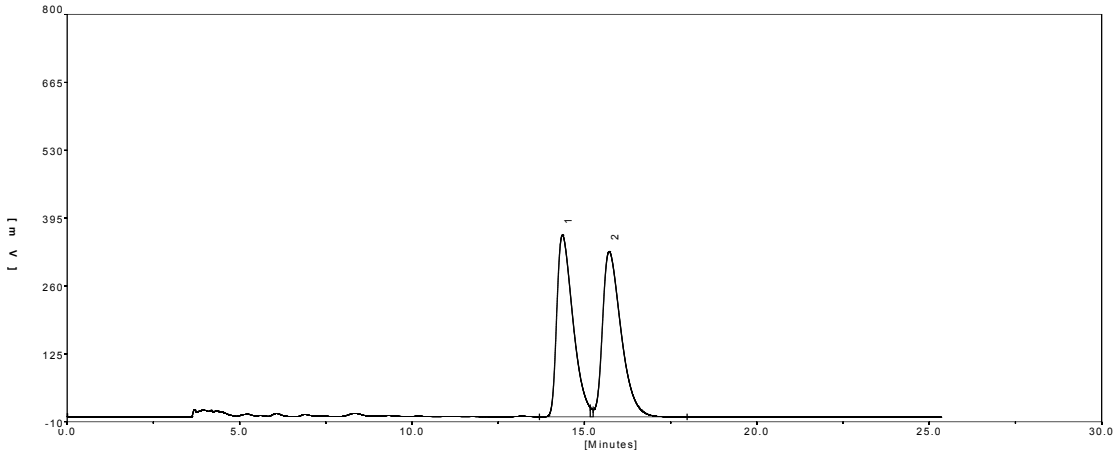
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	15.85583	159.38	5164.50	49.5286
2	19.64083	130.76	5262.82	50.4714



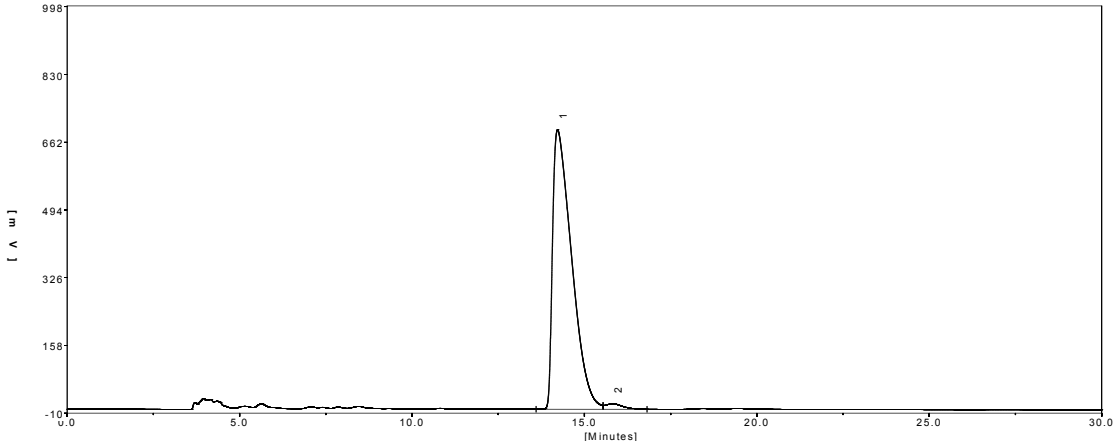
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	15.80583	6.82	204.89	0.6719
2	19.44917	654.49	30290.57	99.3281



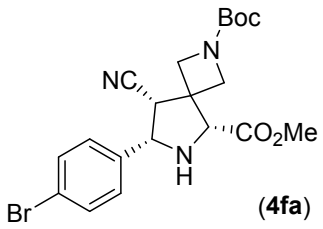
(**4da**)



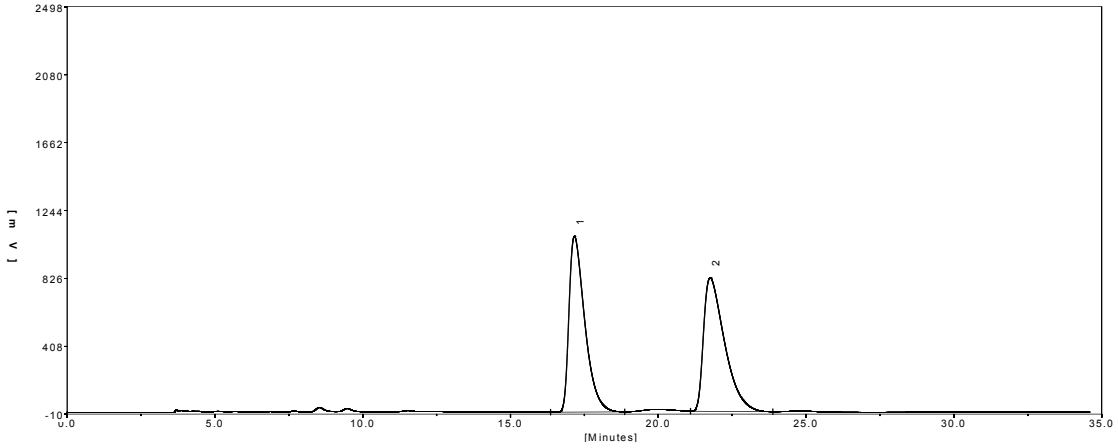
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	14.36417	361.40	11798.68	48.9093
2	15.72083	329.09	12324.90	51.0907



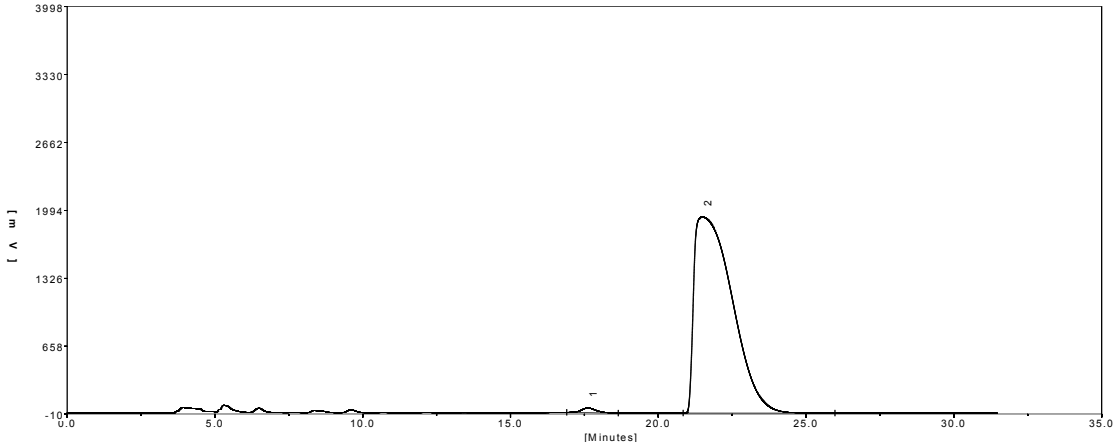
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	14.22250	693.28	26633.60	98.2623
2	15.82000	13.76	471.01	1.7377



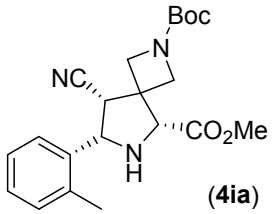
(**4fa**)



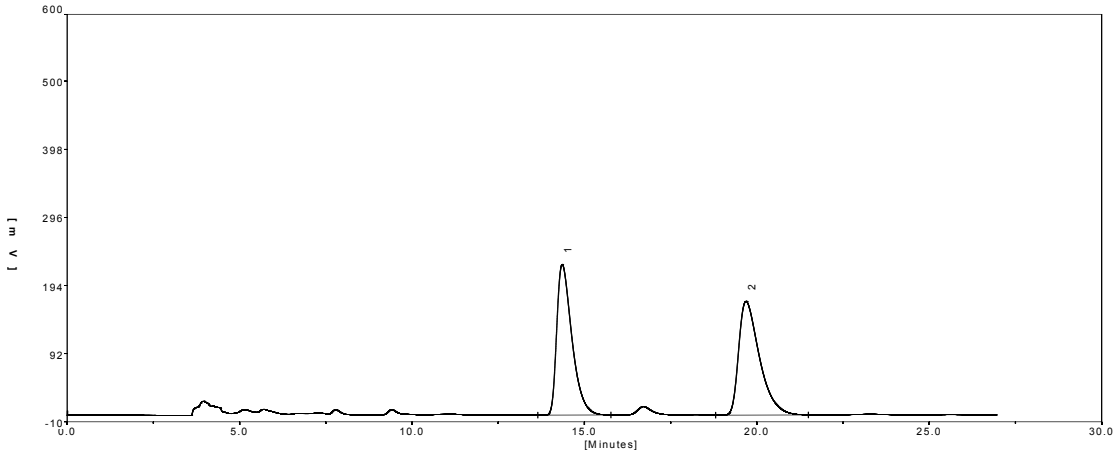
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	17.16417	1083.85	40191.15	49.7581
2	21.75667	823.43	40582.00	50.2419



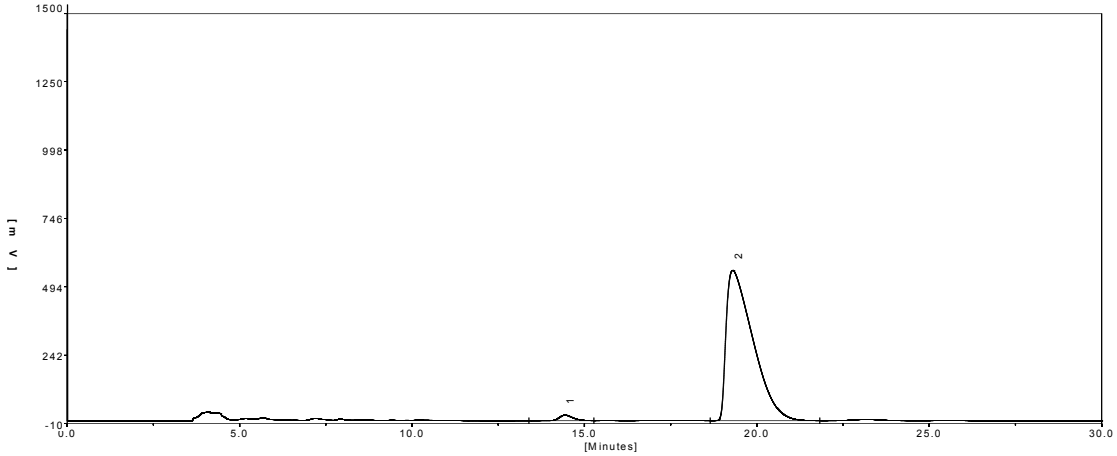
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	17.60917	46.23	1568.65	0.9005
2	21.48250	1930.45	172631.65	99.0995



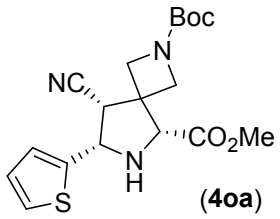
(**4ia**)



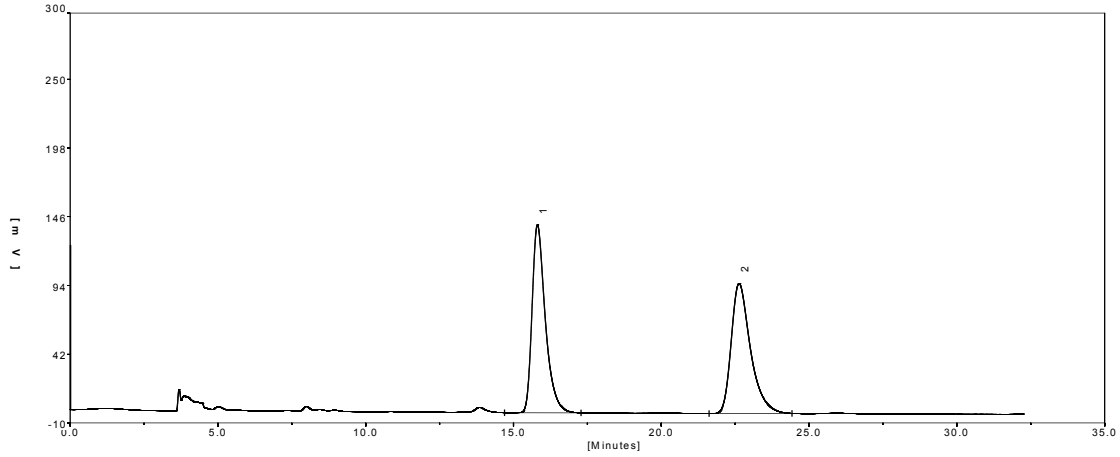
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	14.35750	225.70	6877.22	49.1475
2	19.68833	170.42	7115.81	50.8525



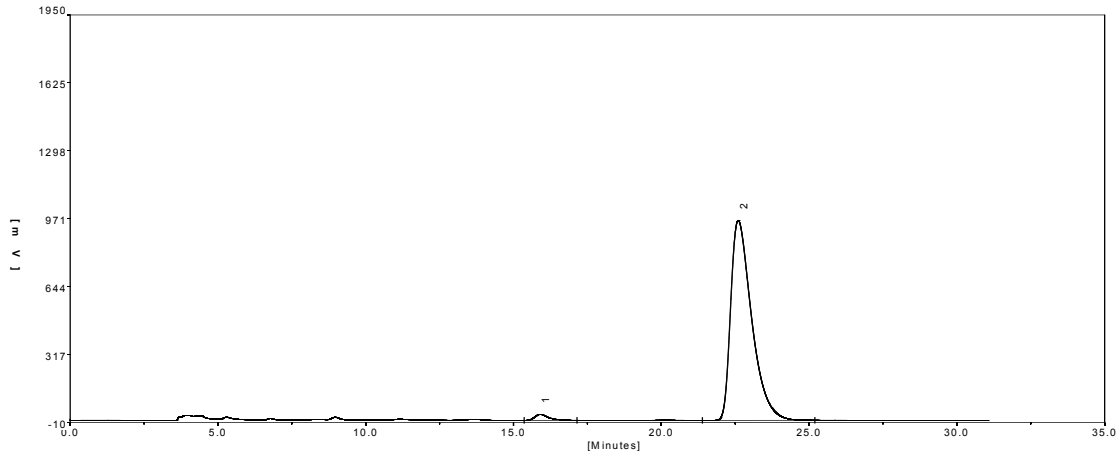
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	14.42750	20.71	566.13	1.8649
2	19.30250	554.13	29791.59	98.1351



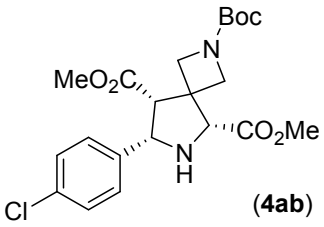
(**4oa**)



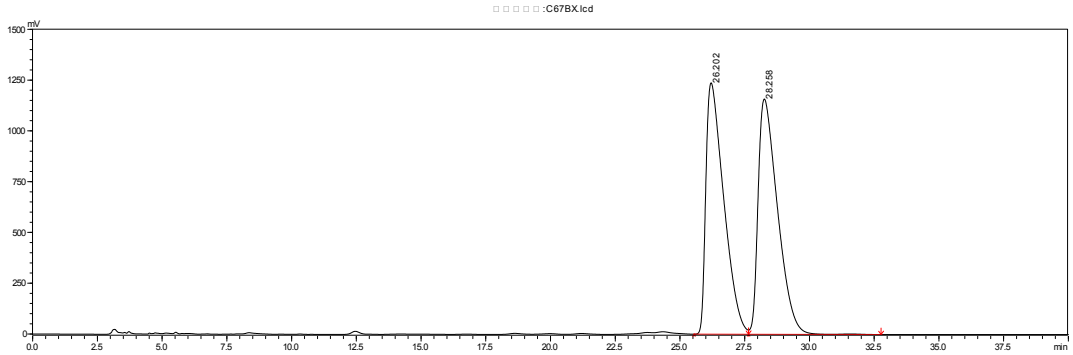
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	15.81083	142.15	4441.21	49.9880
2	22.63000	98.44	4443.34	50.0120



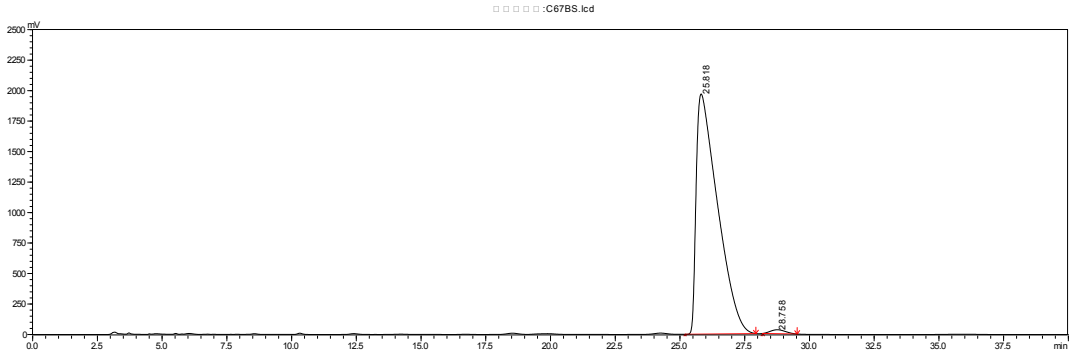
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	15.89083	28.90	923.30	1.9141
2	22.60500	962.15	47313.86	98.0859



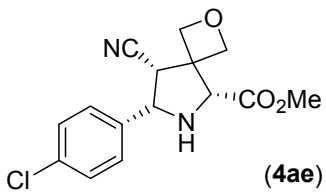
(**4ab**)



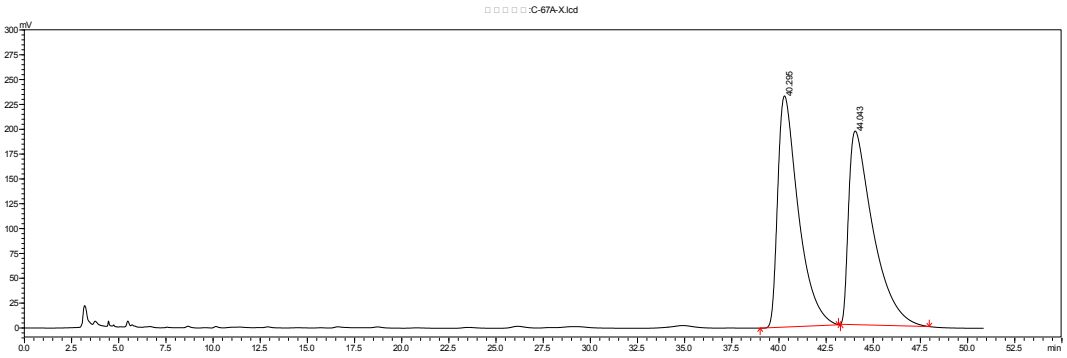
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	26.202	1237.84	59407.12	49.553
2	28.258	1158.74	60479.52	50.447



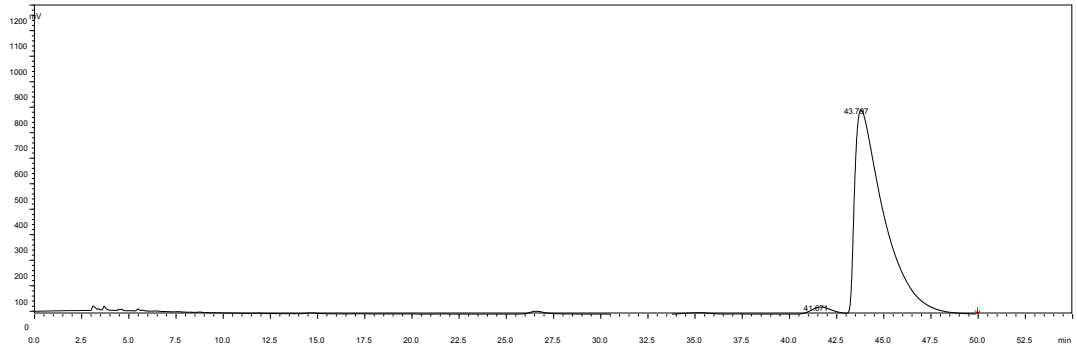
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	25.818	1969.37	112994.68	98.870
2	28.758	32.13	1291.94	1.130



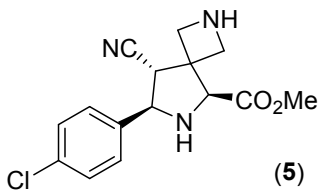
(**4ae**)



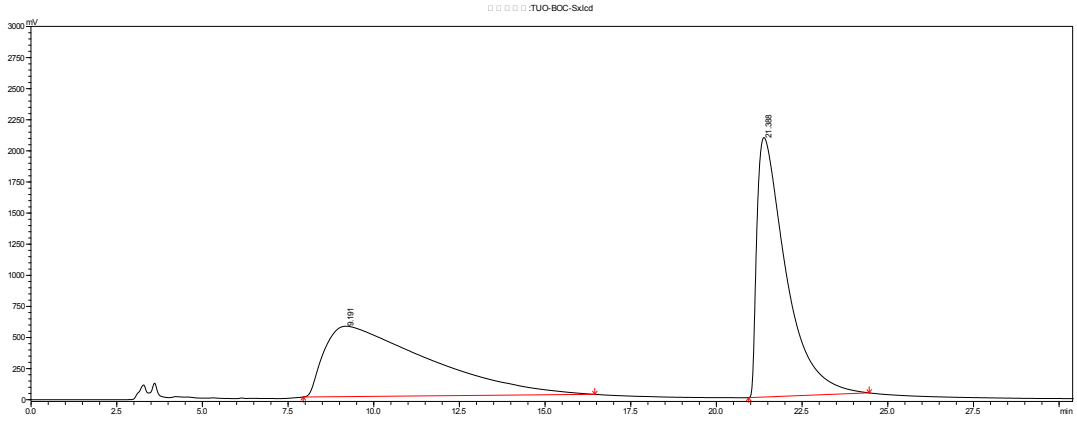
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	40.295	232.73	17716.12	50.313
2	44.043	194.92	17496.03	49.687



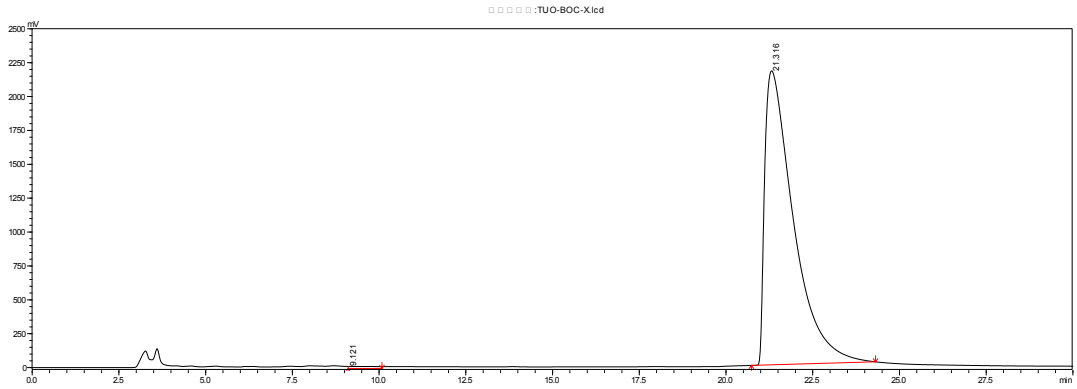
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	41.671	27.27	2083.99	2.375
2	43.797	800.09	85659.71	97.625



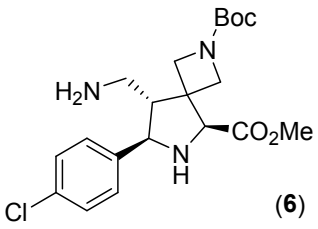
(**5**)



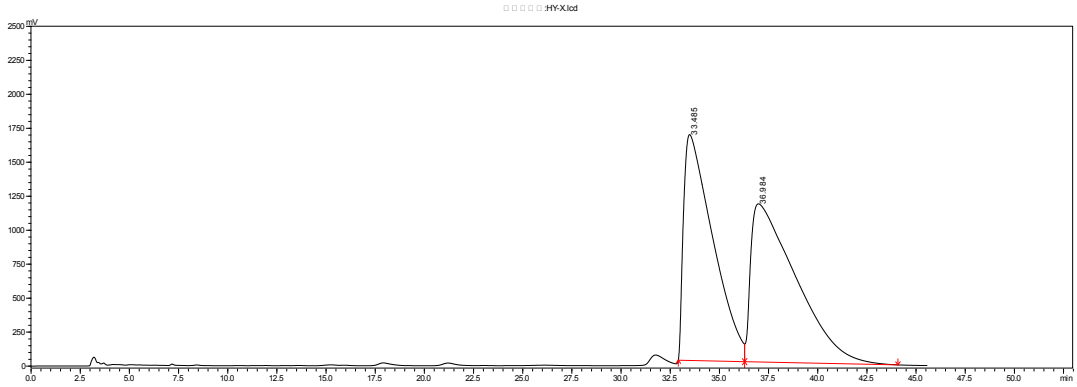
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	9.191	566.06	119590.07	49.243
2	21.388	2085.61	123267.01	50.757



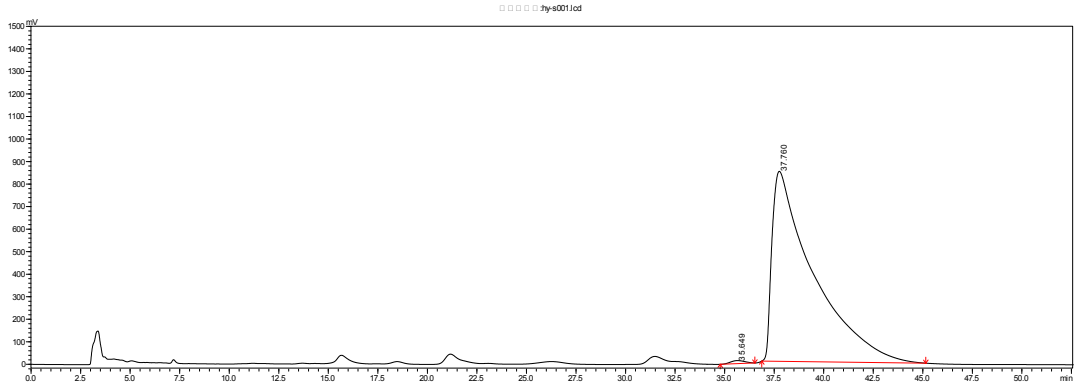
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	9.121	14,75	829.36	0.660
2	21.316	2169.73	124783.23	99.340



(**6**)



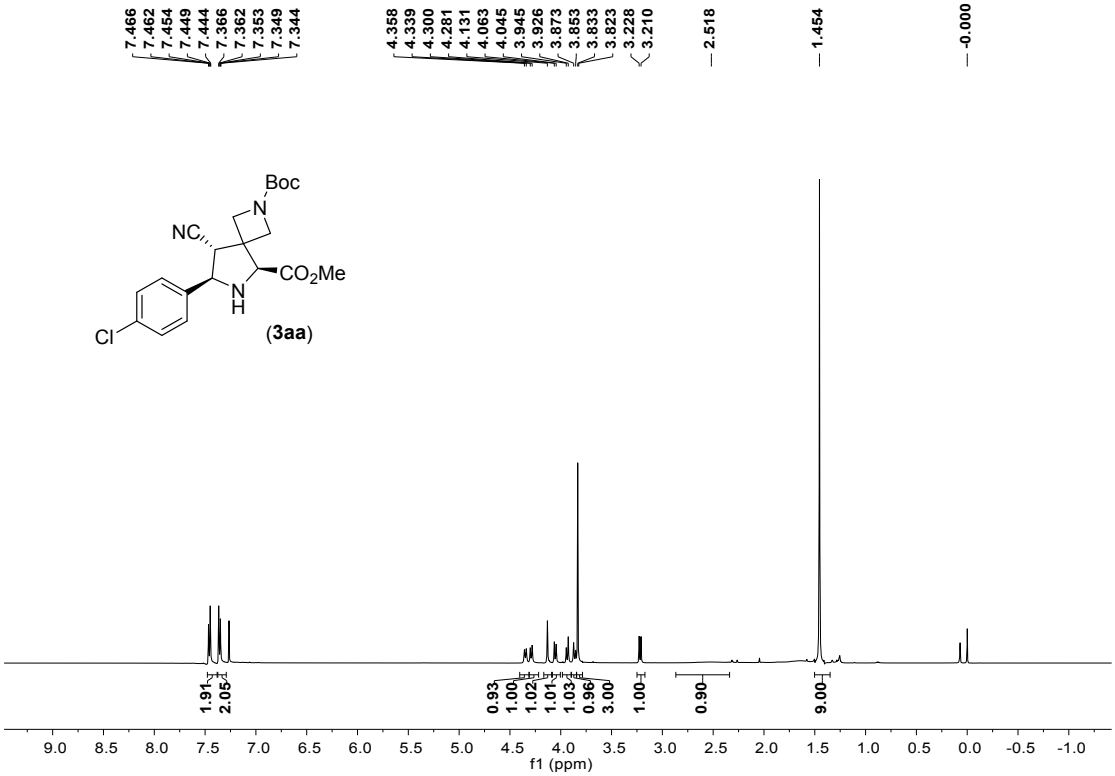
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	33.485	1662.52	171523.78	47.948
2	36.984	1163.49	186205.93	52.052



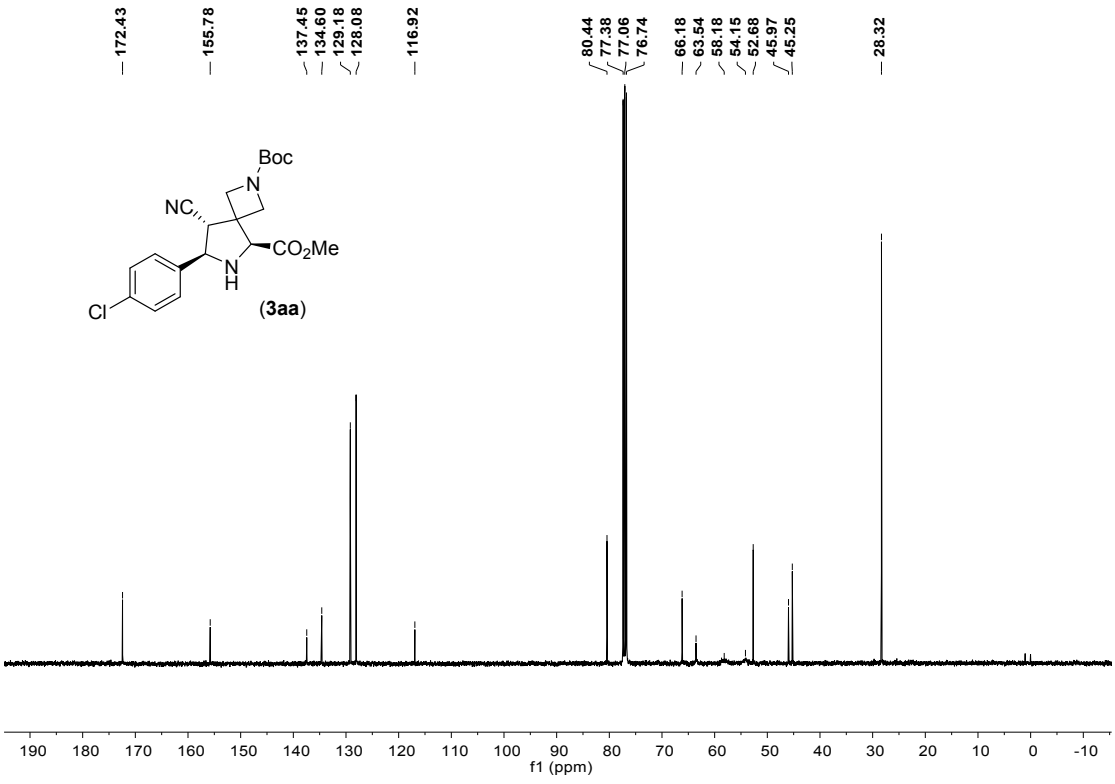
#	Ret Time (min)	Height (mV)	Area (mV.sec)	Area (%)
1	35.649	13.50	676.13	0.549
2	37.760	843.18	122377.18	99.451

^{1}H NMR and ^{13}C NMR spectra

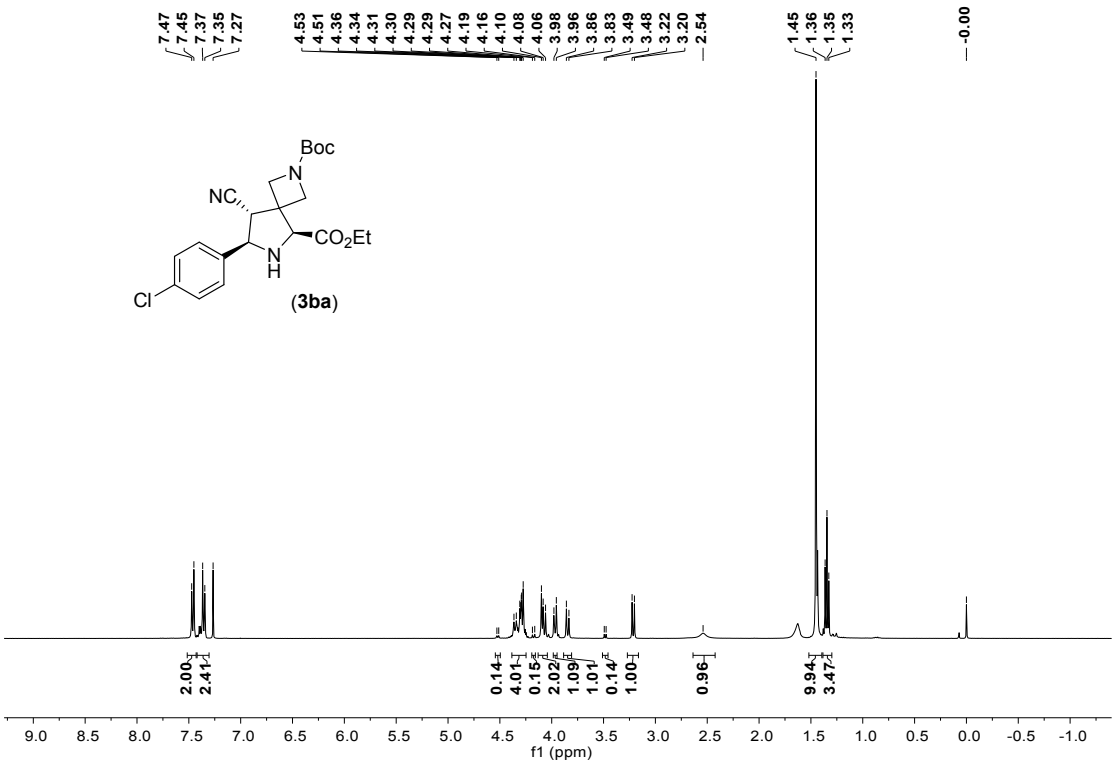
^{1}H NMR spectrum of compound **3aa** ($CDCl_3$)



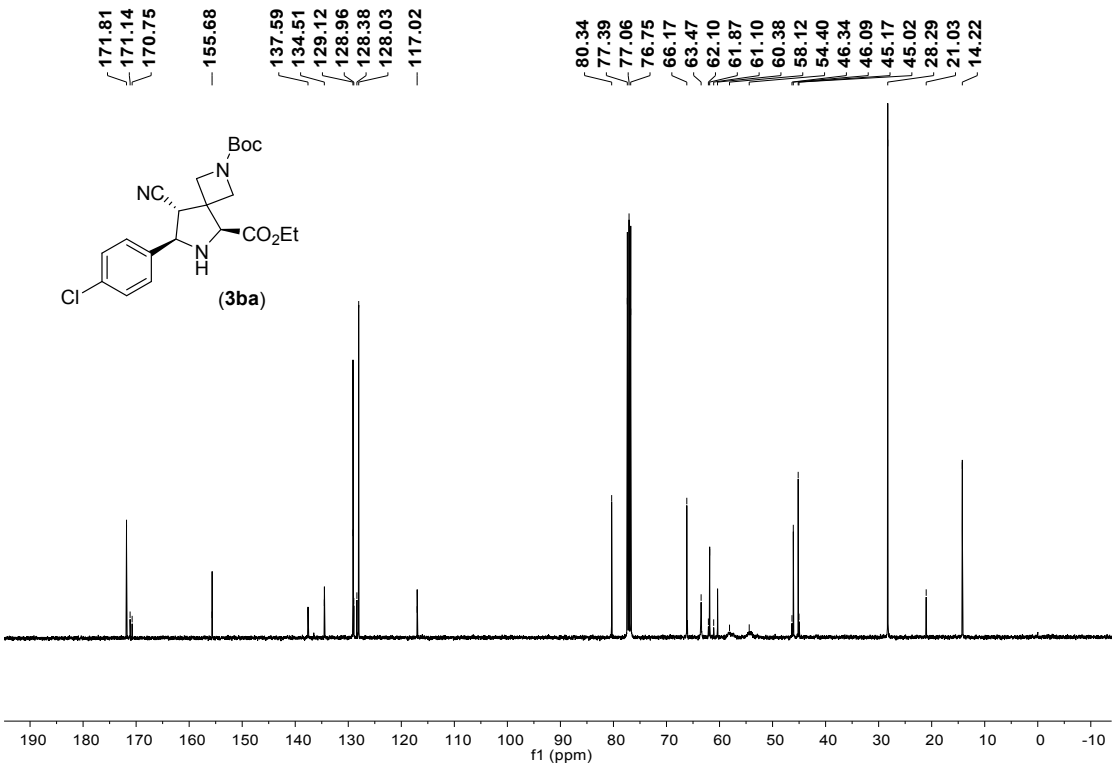
^{13}C NMR spectrum of compound **3aa** ($CDCl_3$)



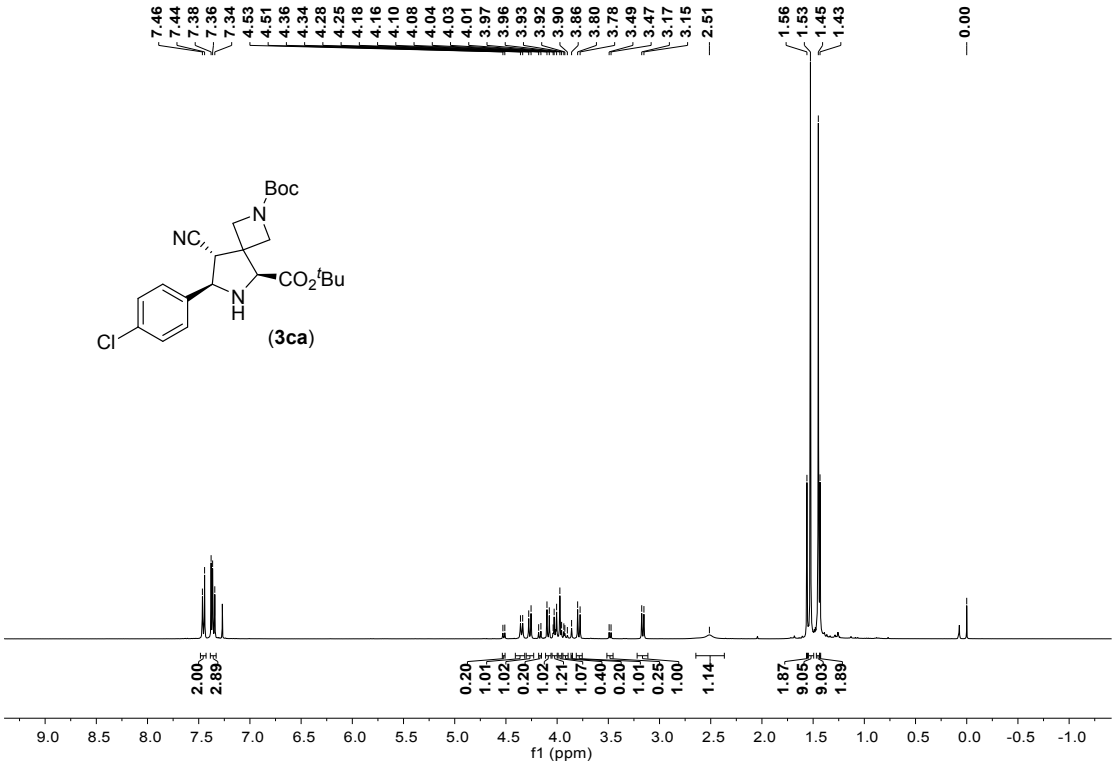
^{1}H NMR spectrum of compound **3ba** ($CDCl_3$)



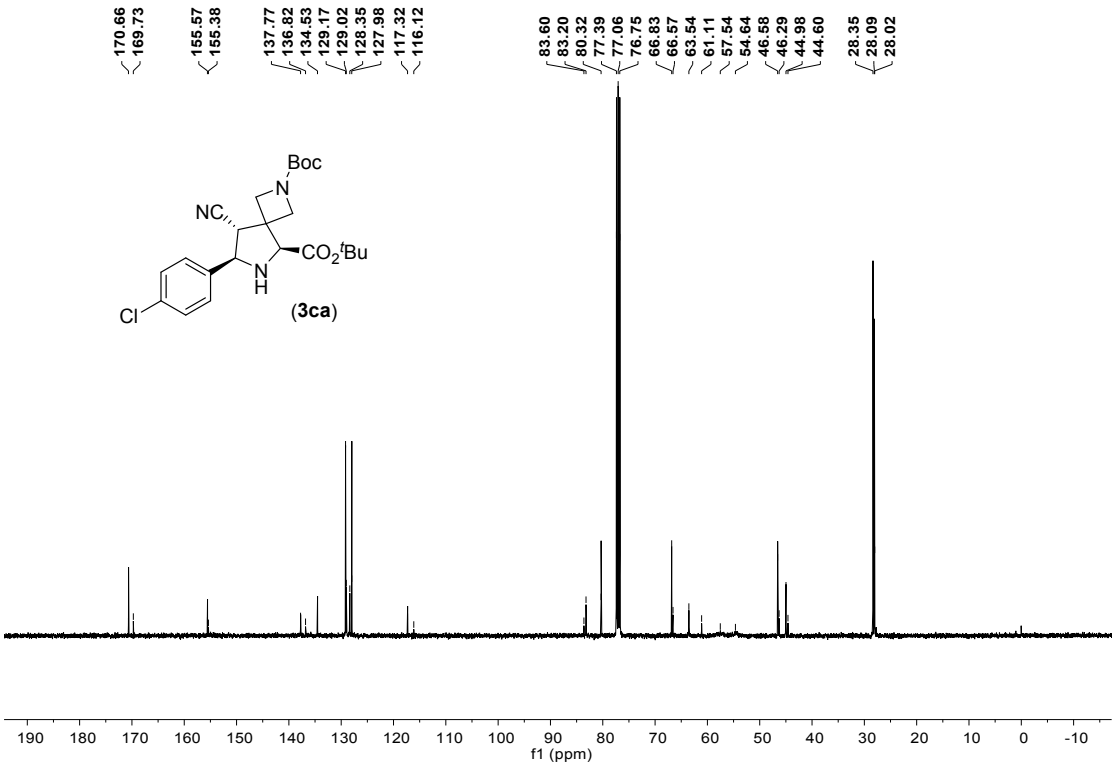
^{13}C NMR spectrum of compound **3ba** ($CDCl_3$)



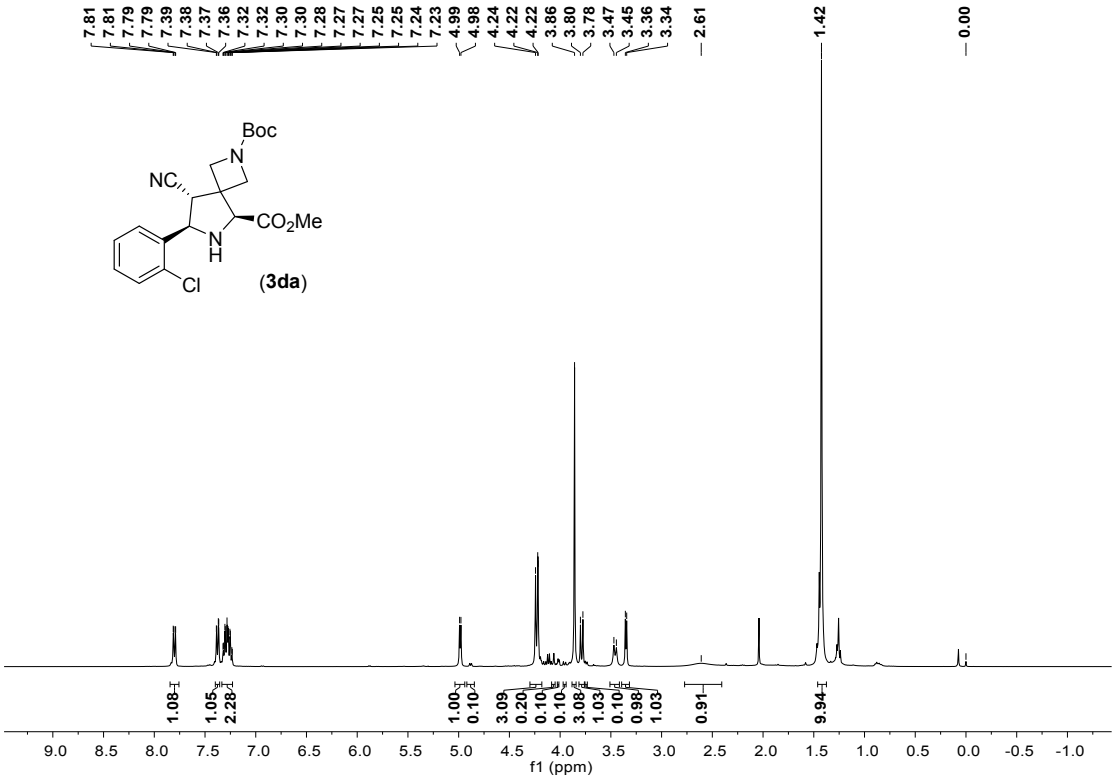
^{1}H NMR spectrum of compound **3ca** ($CDCl_3$)



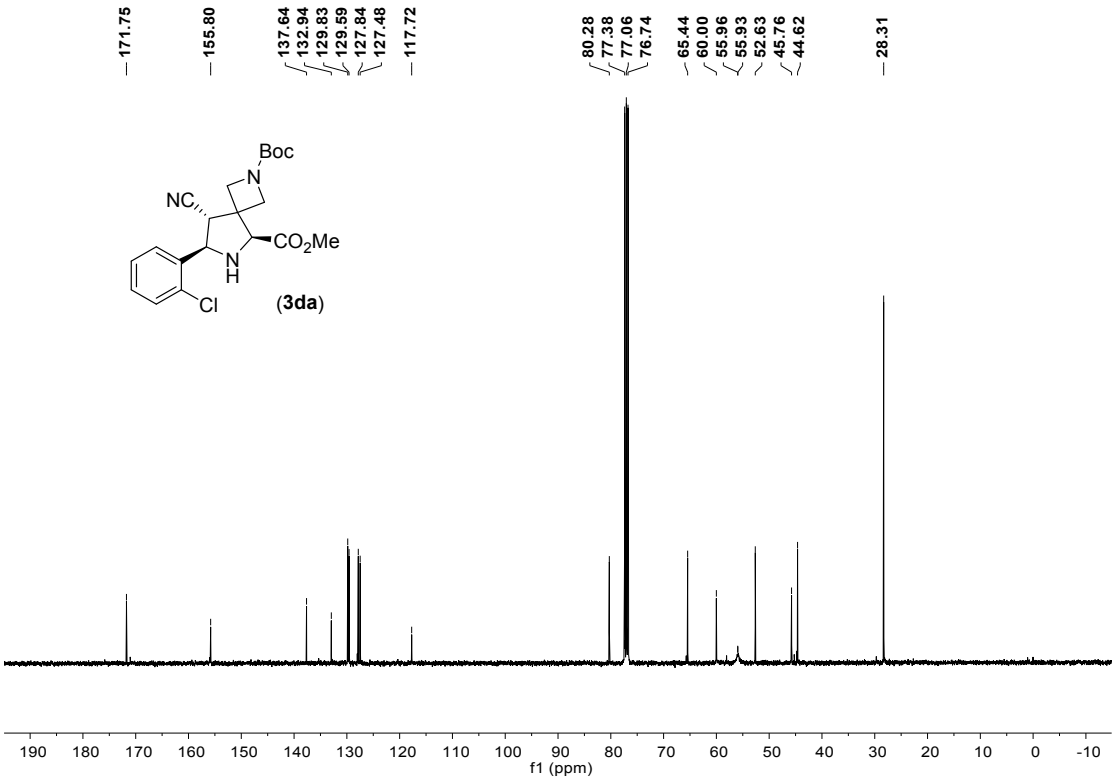
^{13}C NMR spectrum of compound **3ca** ($CDCl_3$)



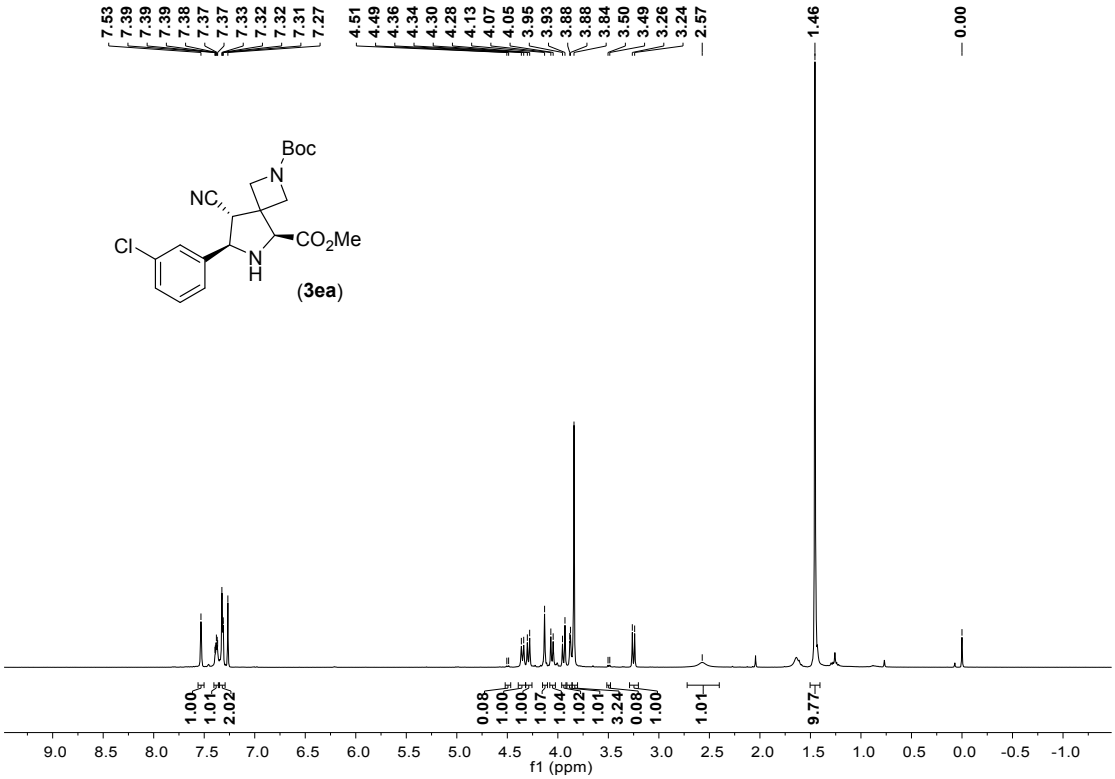
^{1}H NMR spectrum of compound **3da** ($CDCl_3$)



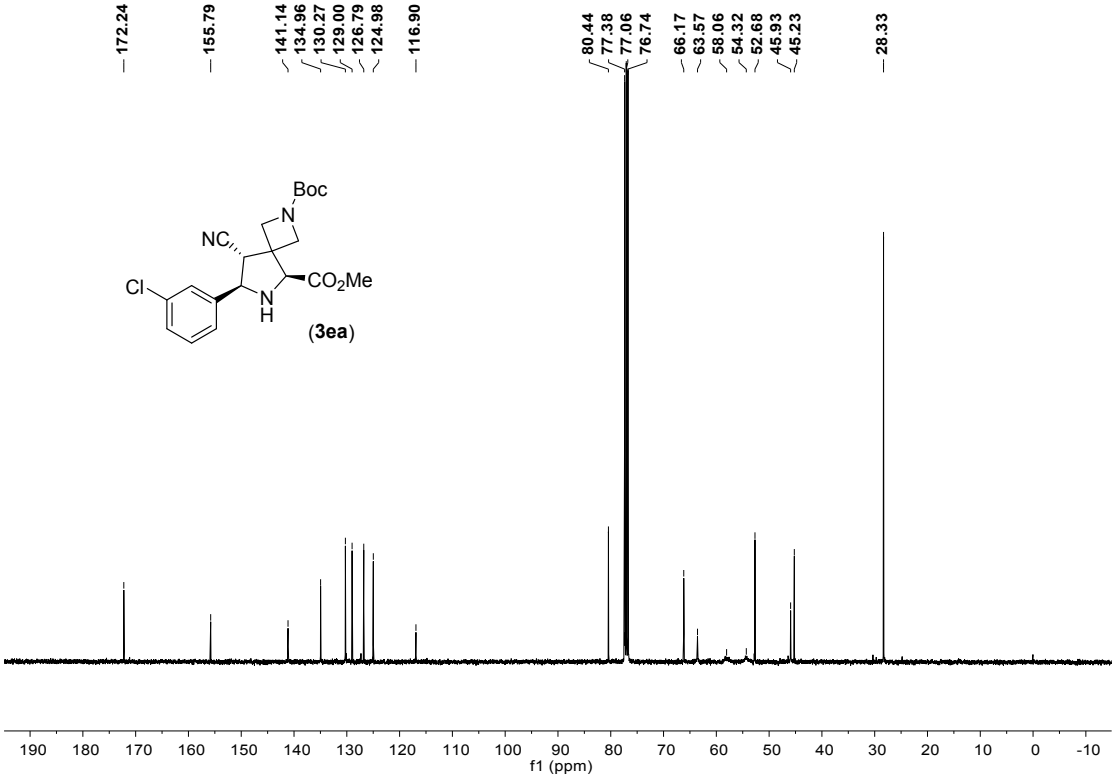
^{13}C NMR spectrum of compound **3da** ($CDCl_3$)



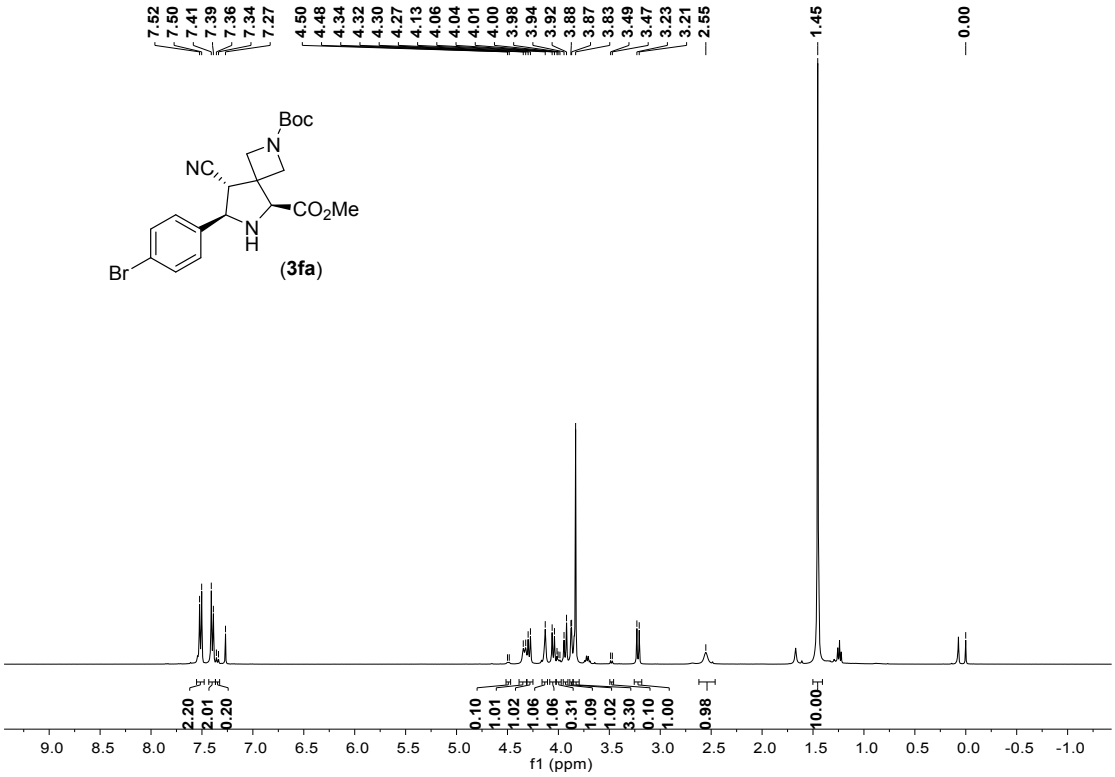
^{1}H NMR spectrum of compound **3ea** ($CDCl_3$)



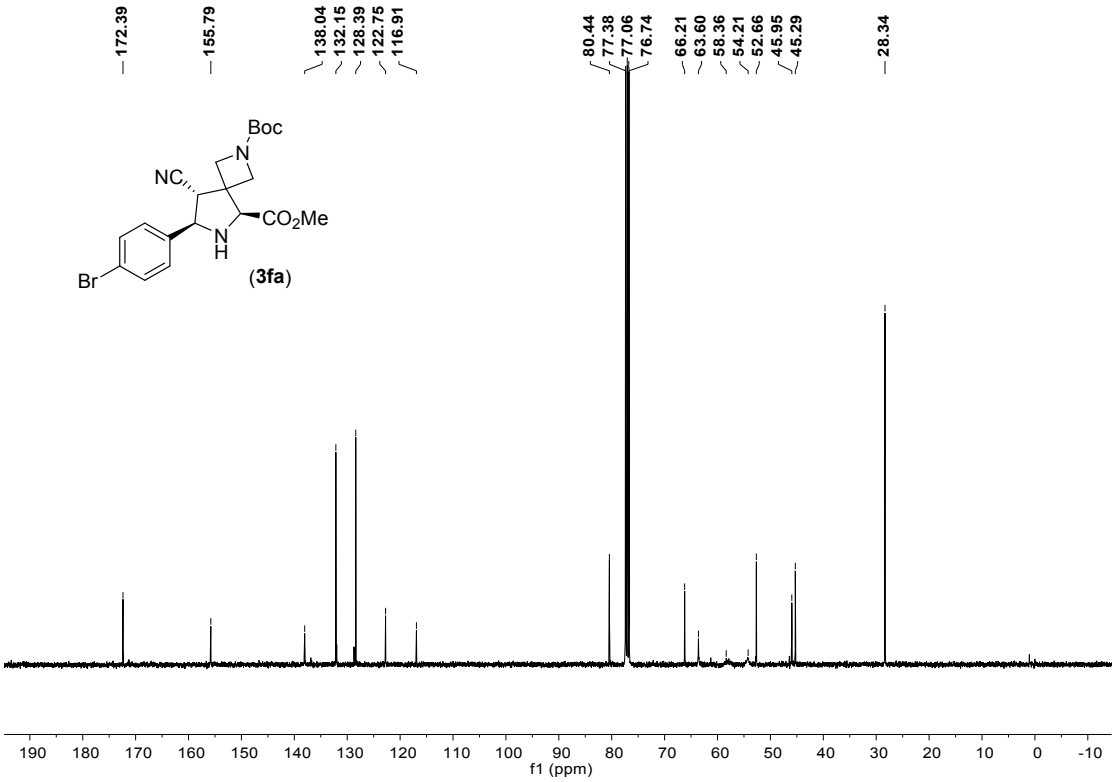
^{13}C NMR spectrum of compound **3ea** ($CDCl_3$)



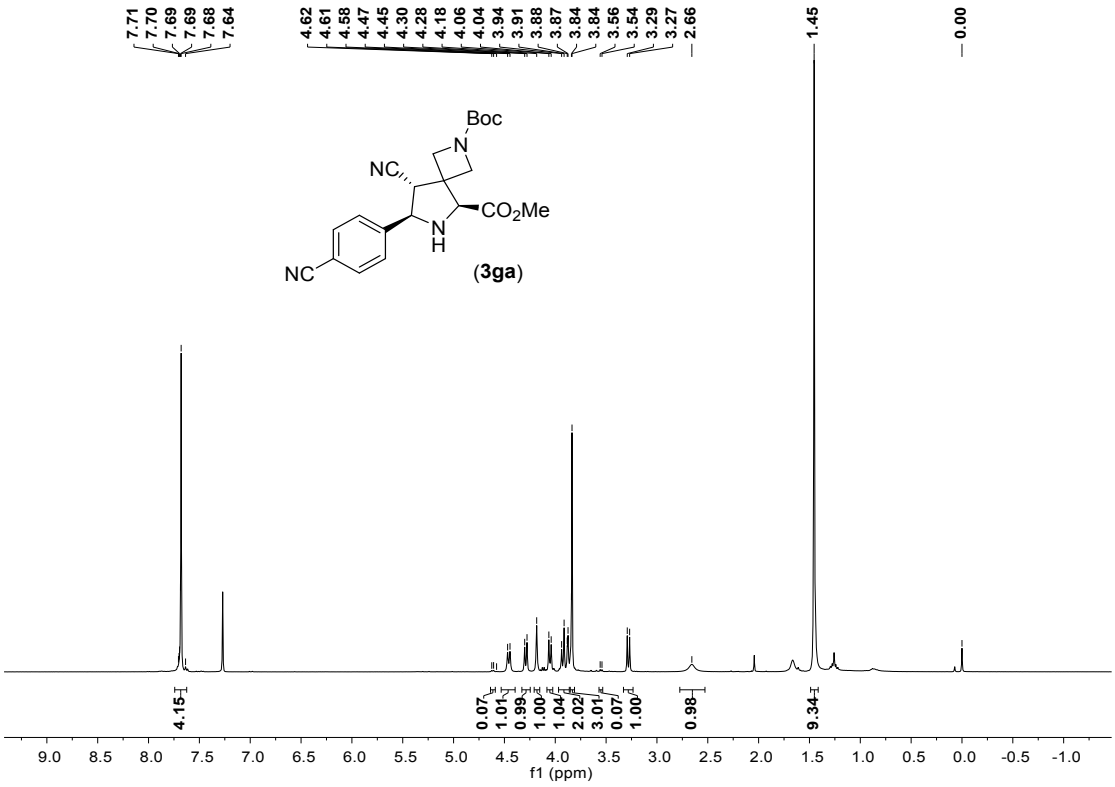
^{1}H NMR spectrum of compound **3fa** ($CDCl_3$)



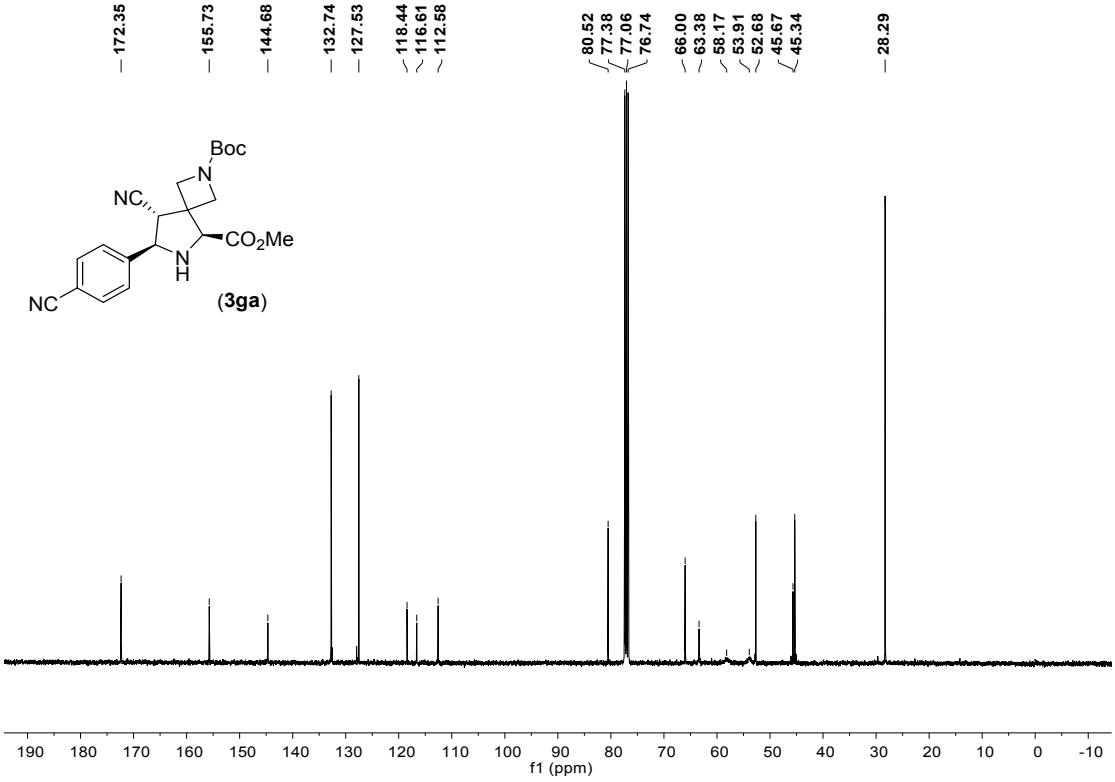
^{13}C NMR spectrum of compound **3fa** ($CDCl_3$)



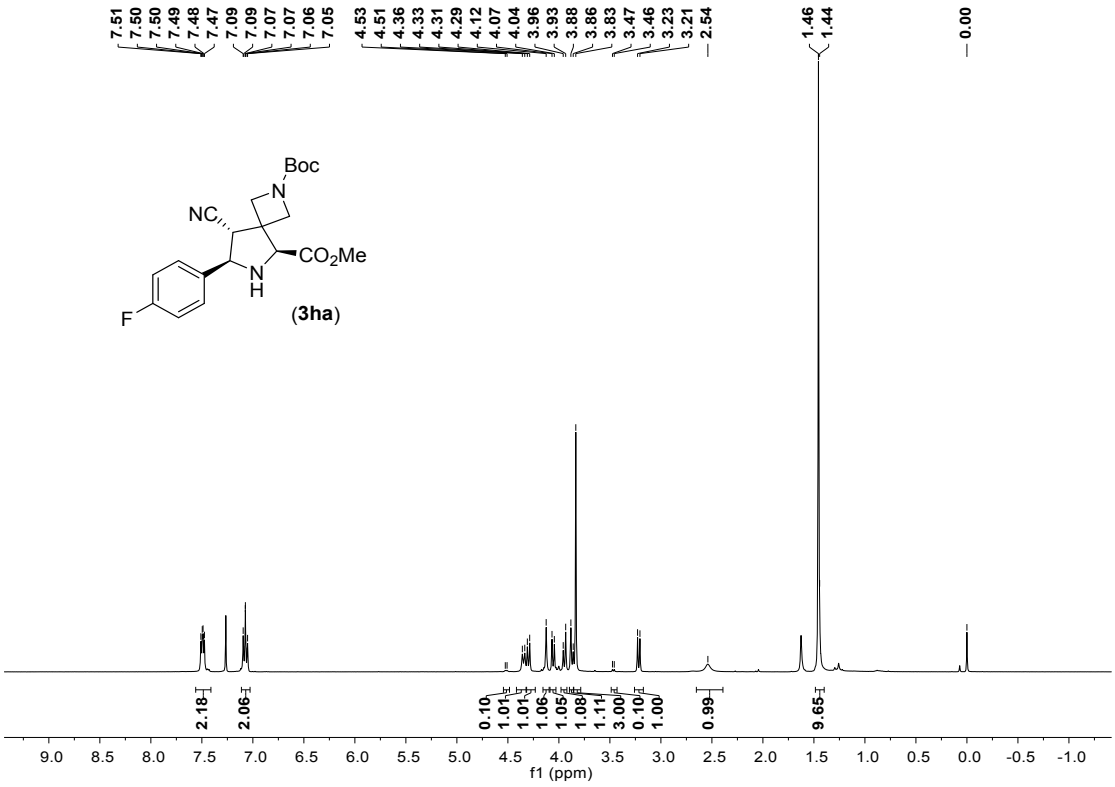
^{1}H NMR spectrum of compound **3ga** ($CDCl_3$)



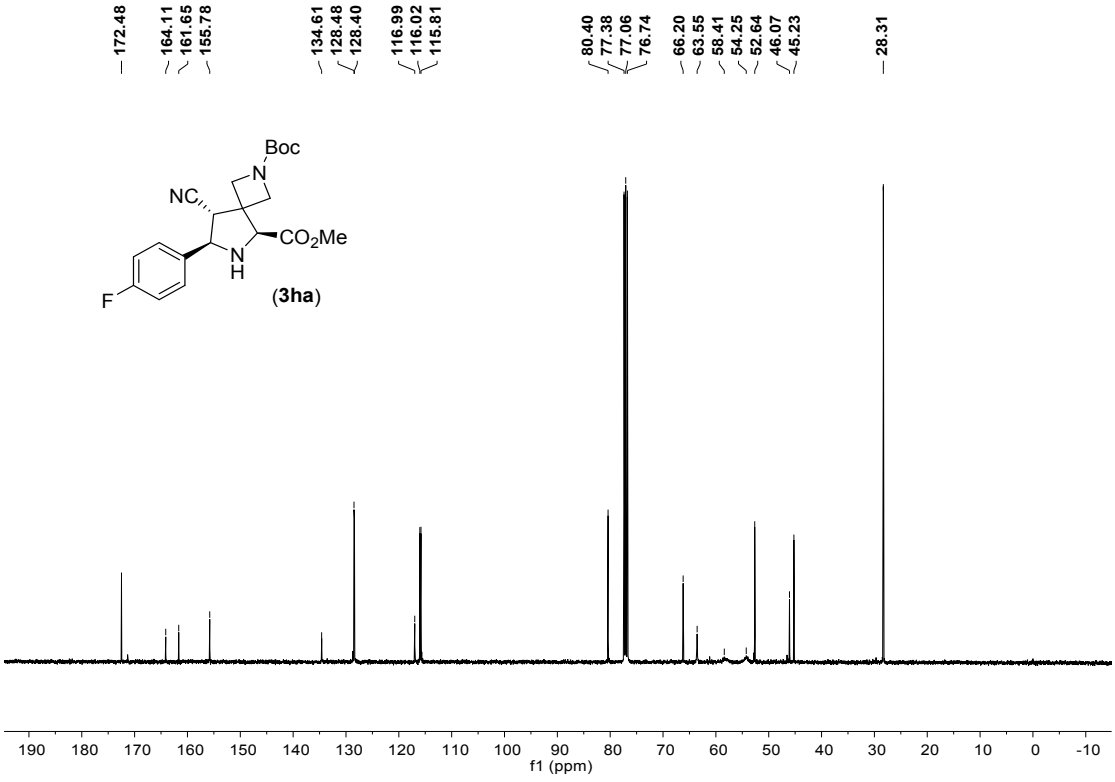
^{13}C NMR spectrum of compound **3ga** ($CDCl_3$)



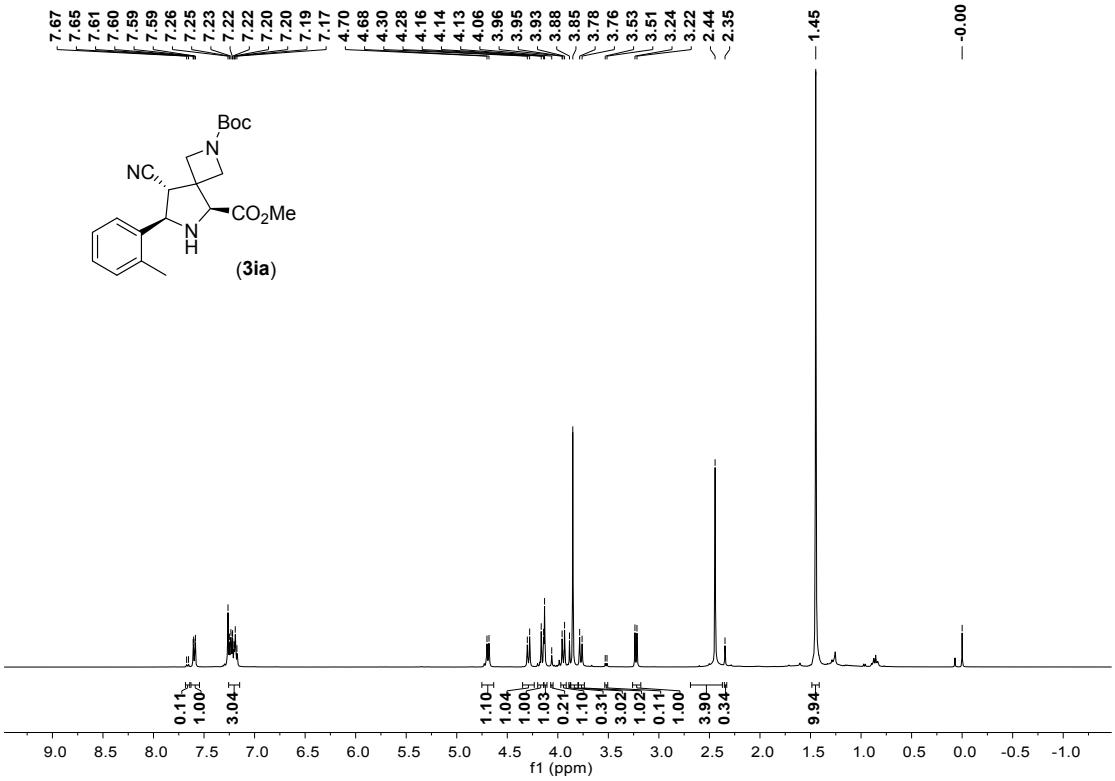
^{1}H NMR spectrum of compound **3ha** ($CDCl_3$)



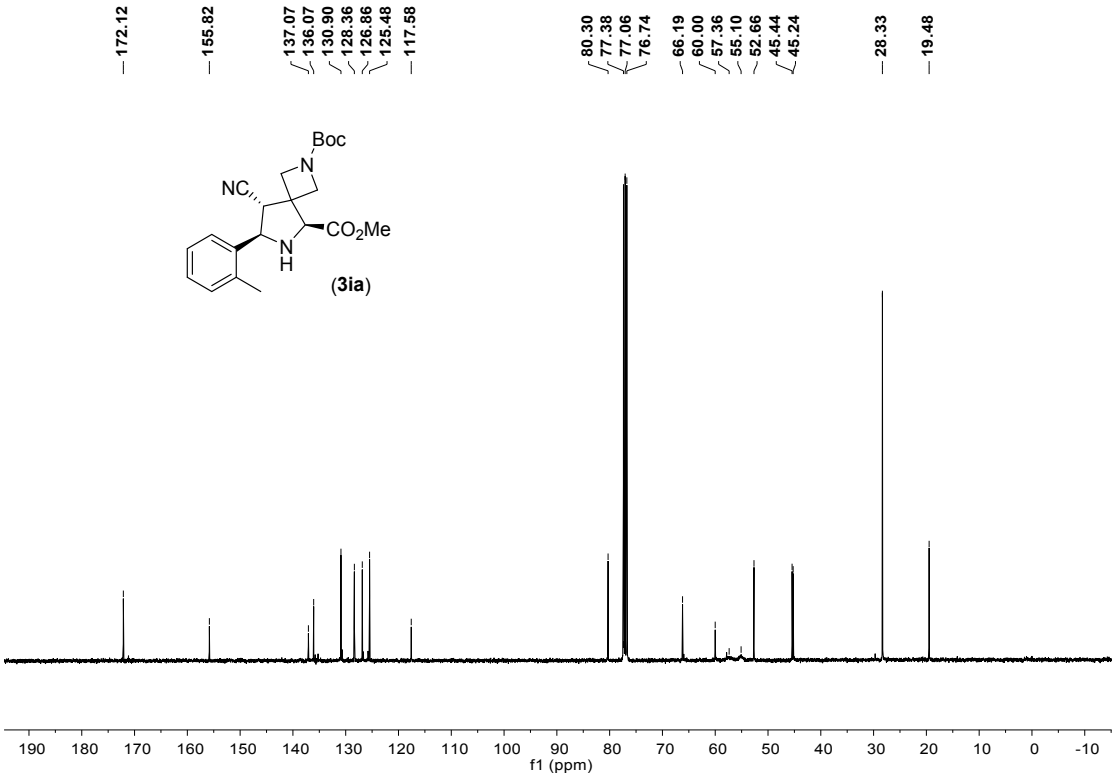
^{13}C NMR spectrum of compound **3ha** ($CDCl_3$)



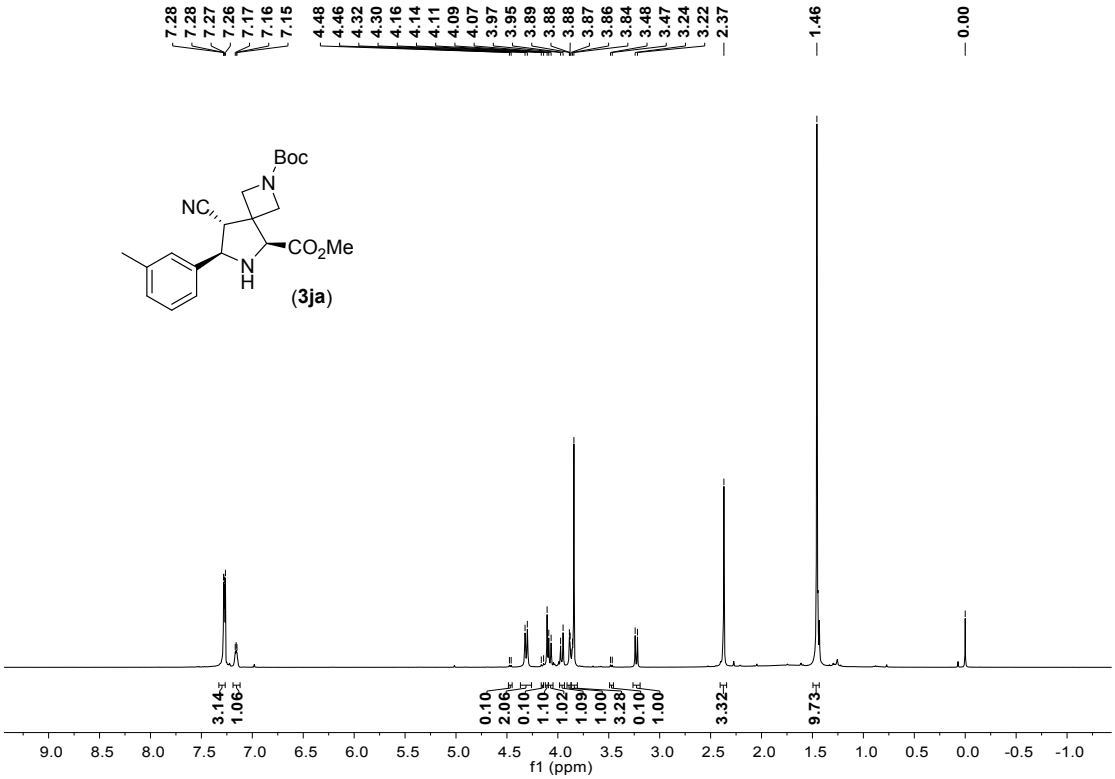
^{1}H NMR spectrum of compound **3ia** ($CDCl_3$)



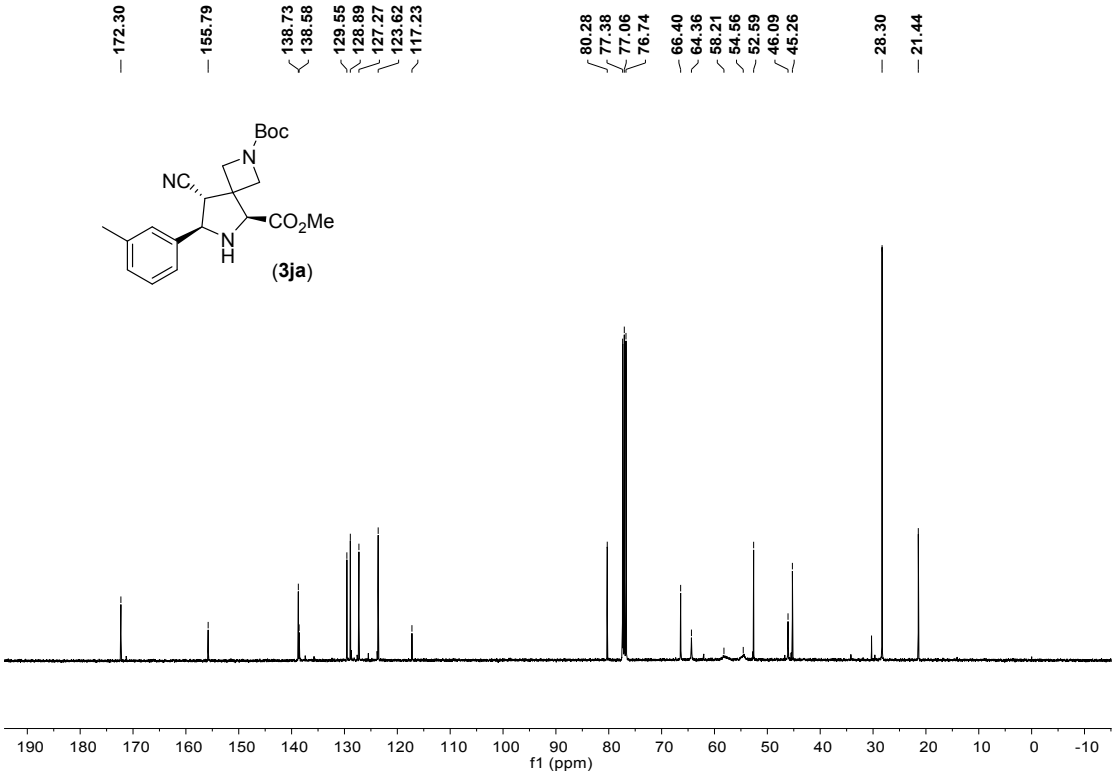
^{13}C NMR spectrum of compound **3ia** ($CDCl_3$)



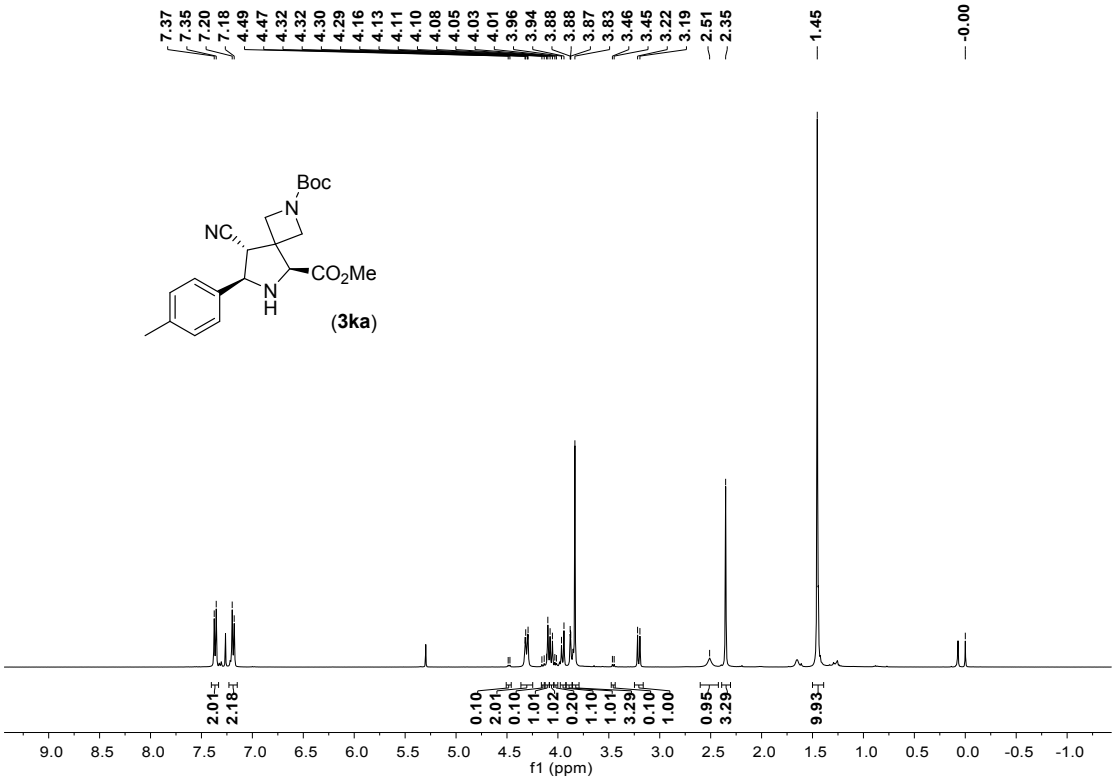
^{1}H NMR spectrum of compound **3ja** ($CDCl_3$)



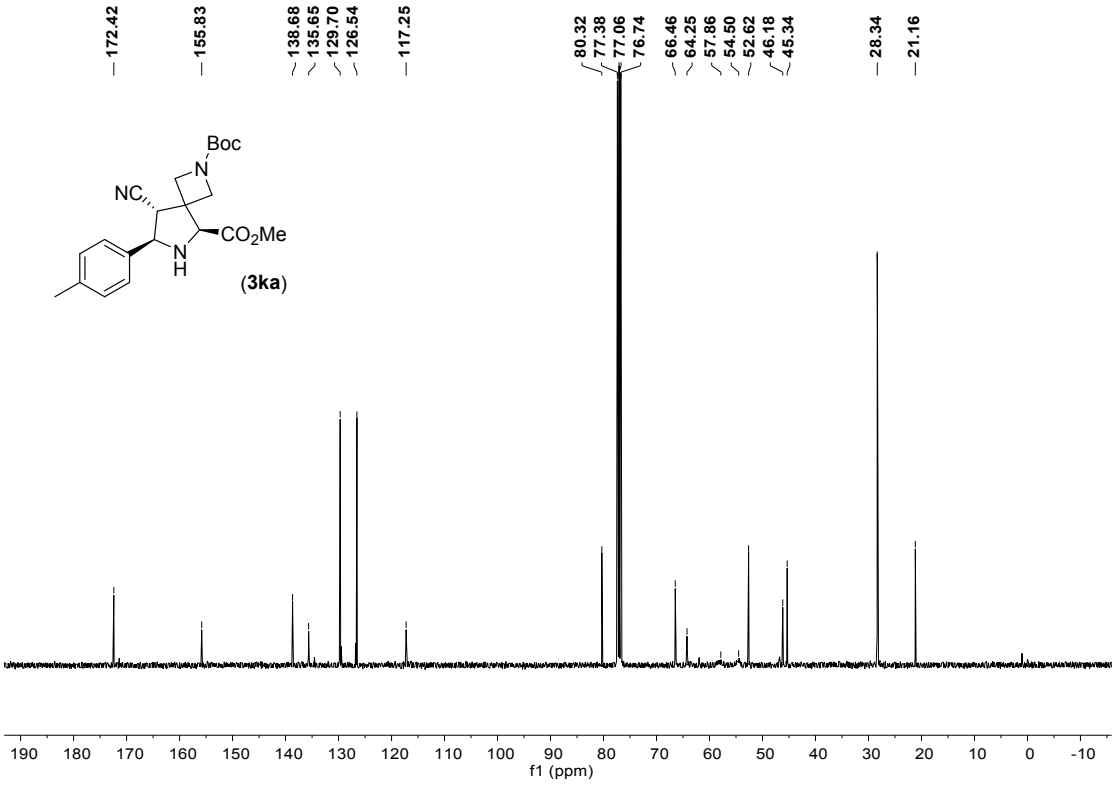
^{13}C NMR spectrum of compound **3ja** ($CDCl_3$)



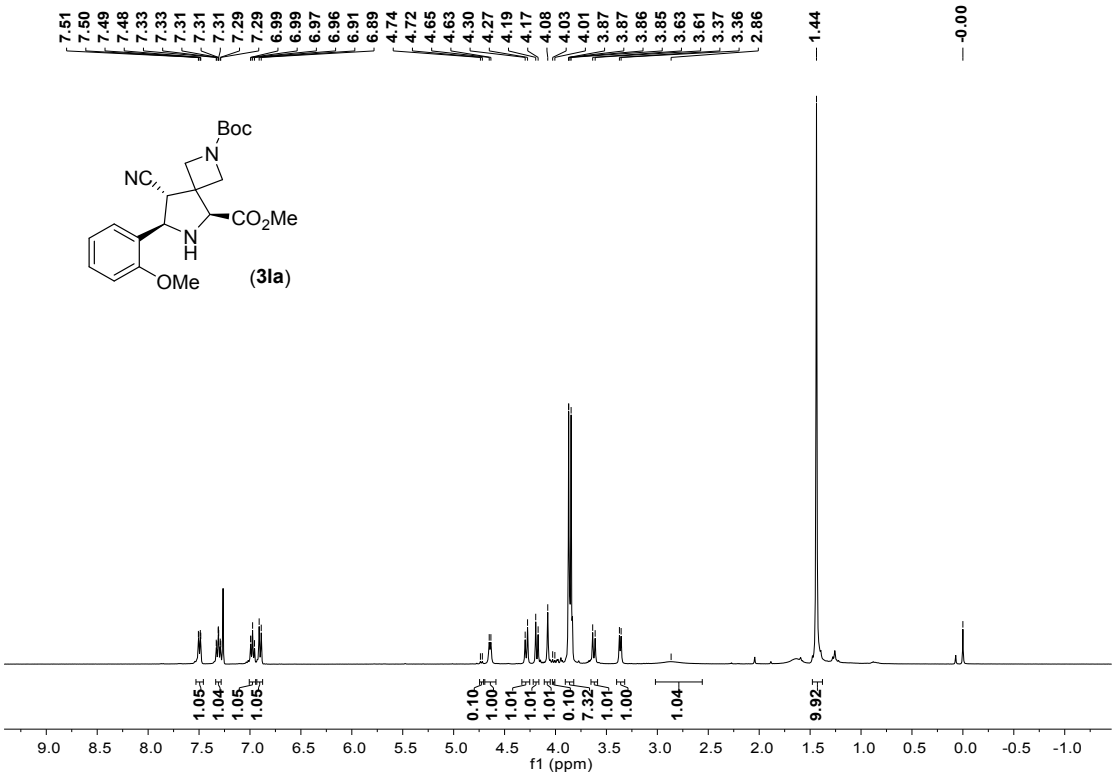
^{1}H NMR spectrum of compound **3ka** ($CDCl_3$)



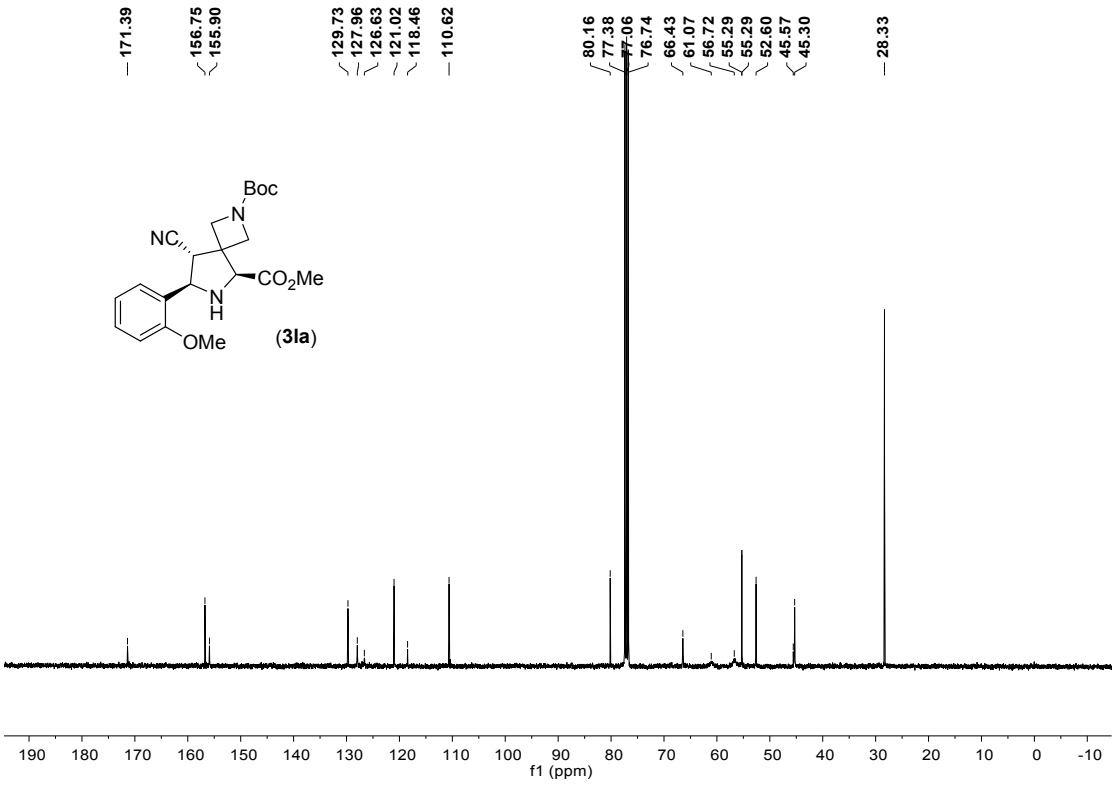
^{13}C NMR spectrum of compound **3ka** ($CDCl_3$)



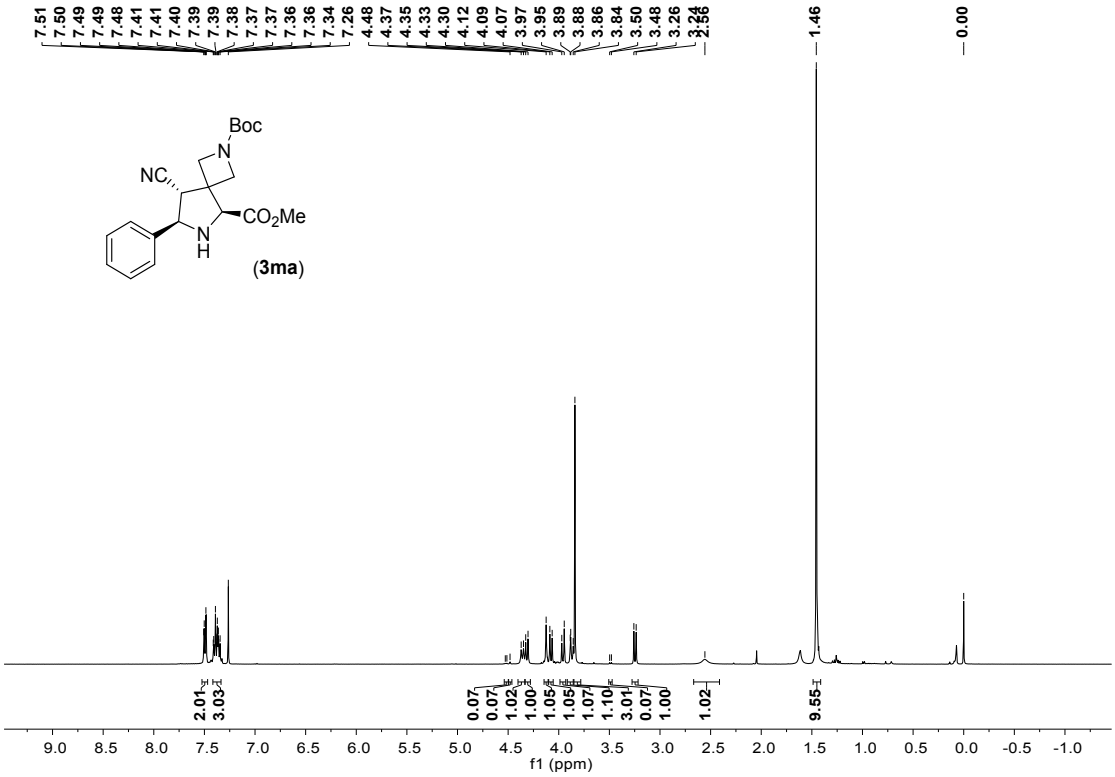
^{1}H NMR spectrum of compound **3la** ($CDCl_3$)



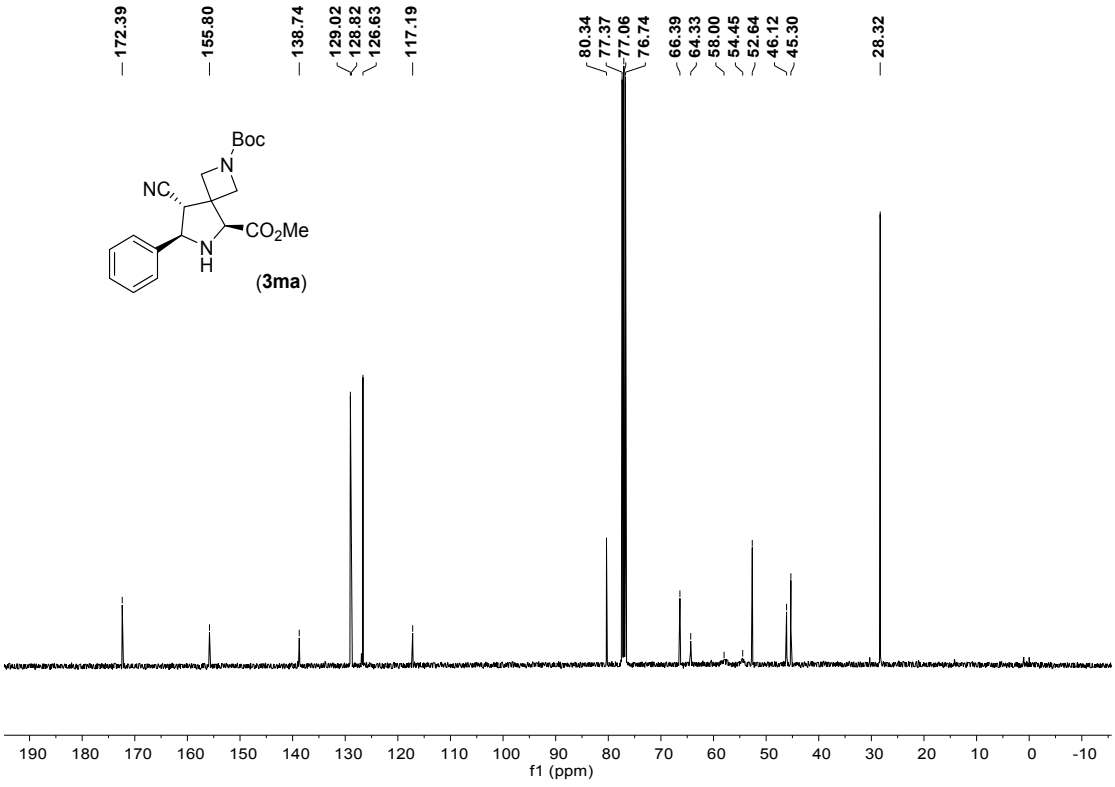
^{13}C NMR spectrum of compound **3la** ($CDCl_3$)



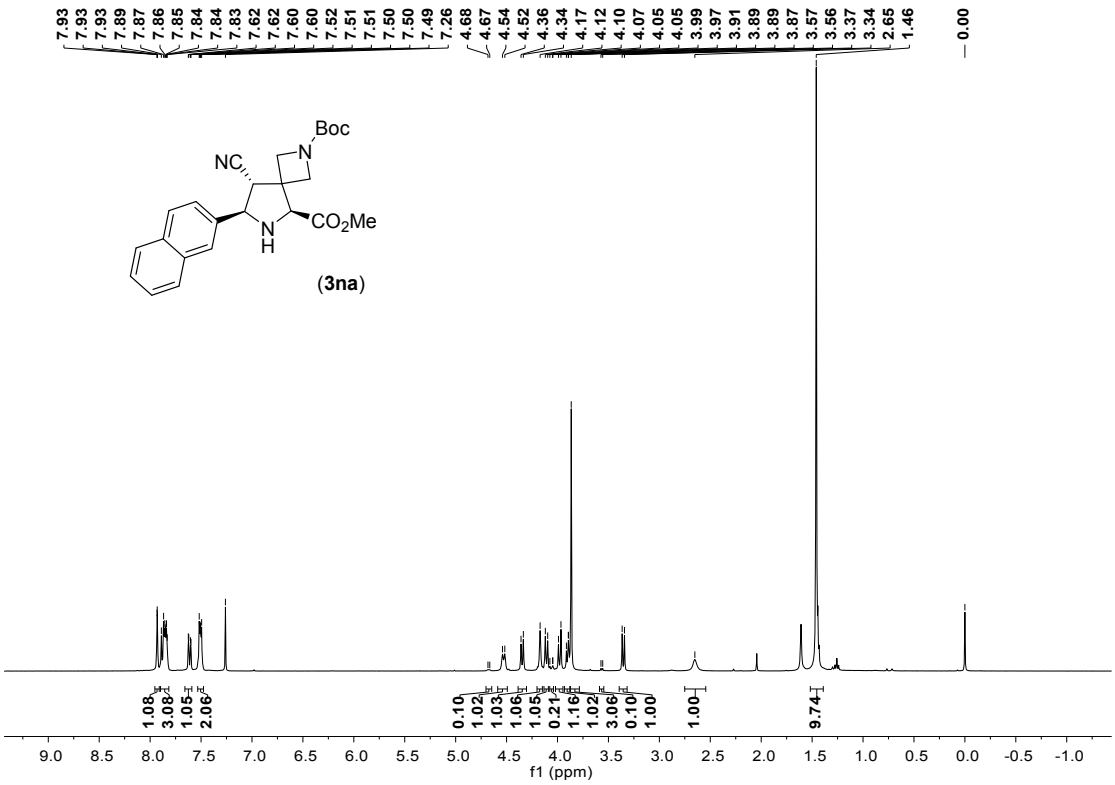
^{1}H NMR spectrum of compound **3ma** ($CDCl_3$)



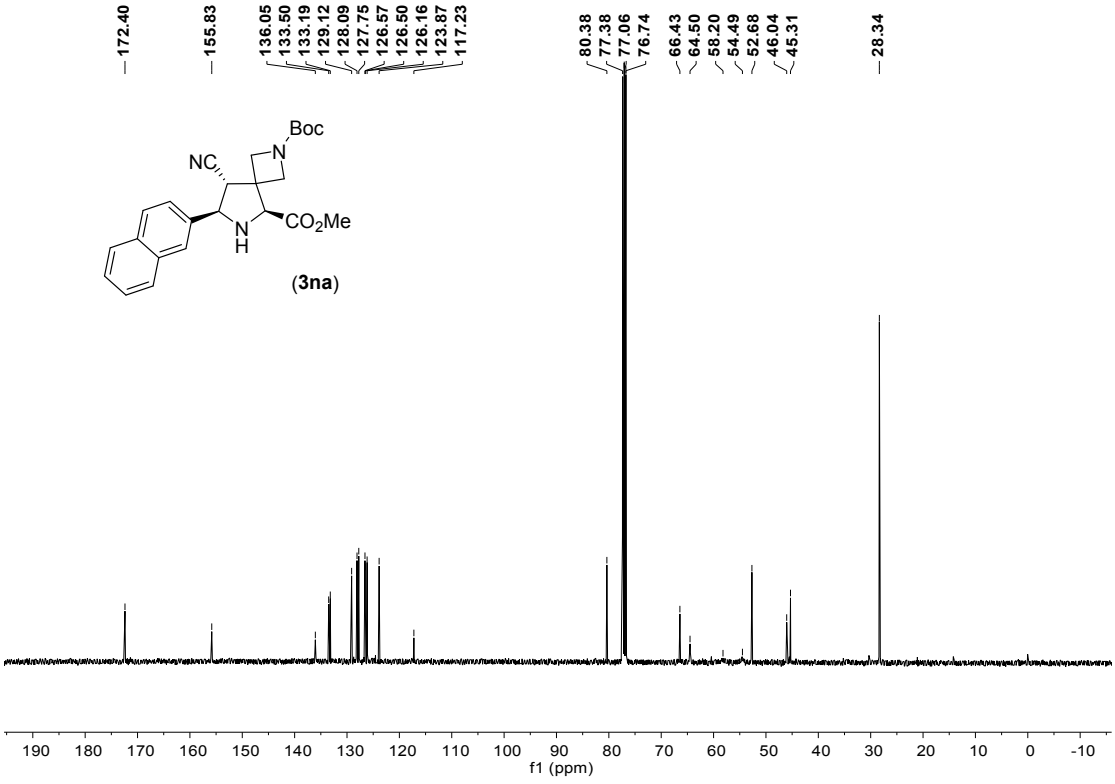
^{13}C NMR spectrum of compound **3ma** ($CDCl_3$)



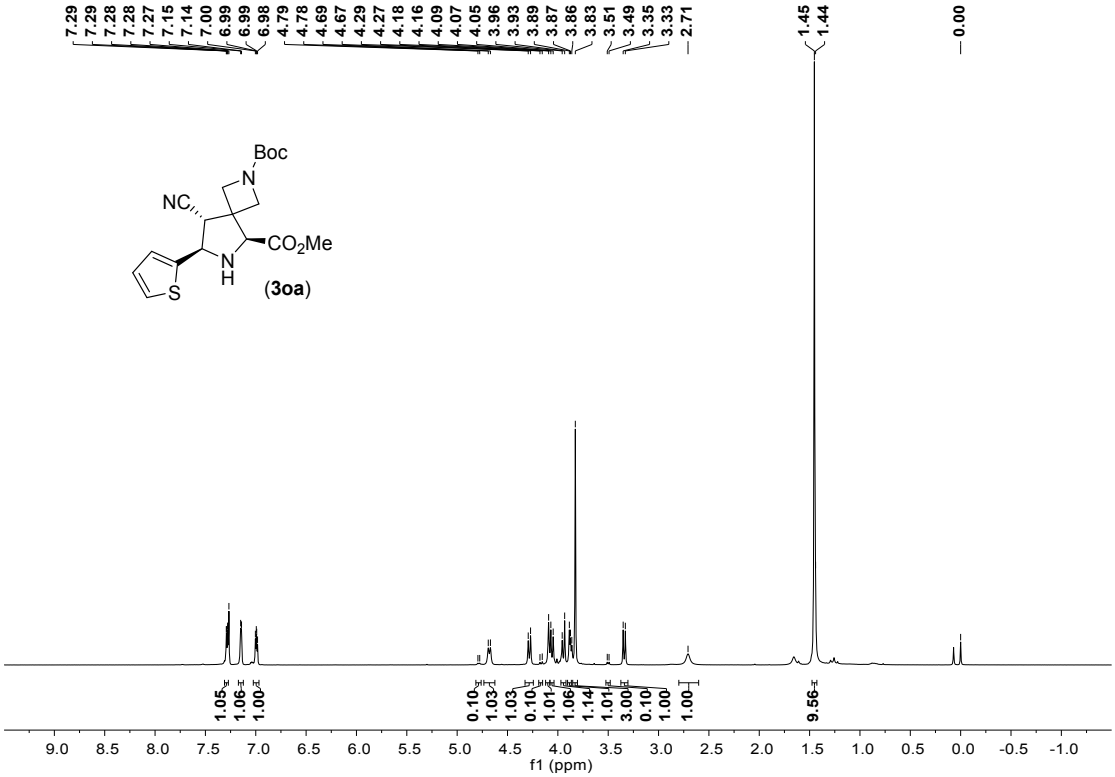
^{1}H NMR spectrum of compound **3na** ($CDCl_3$)



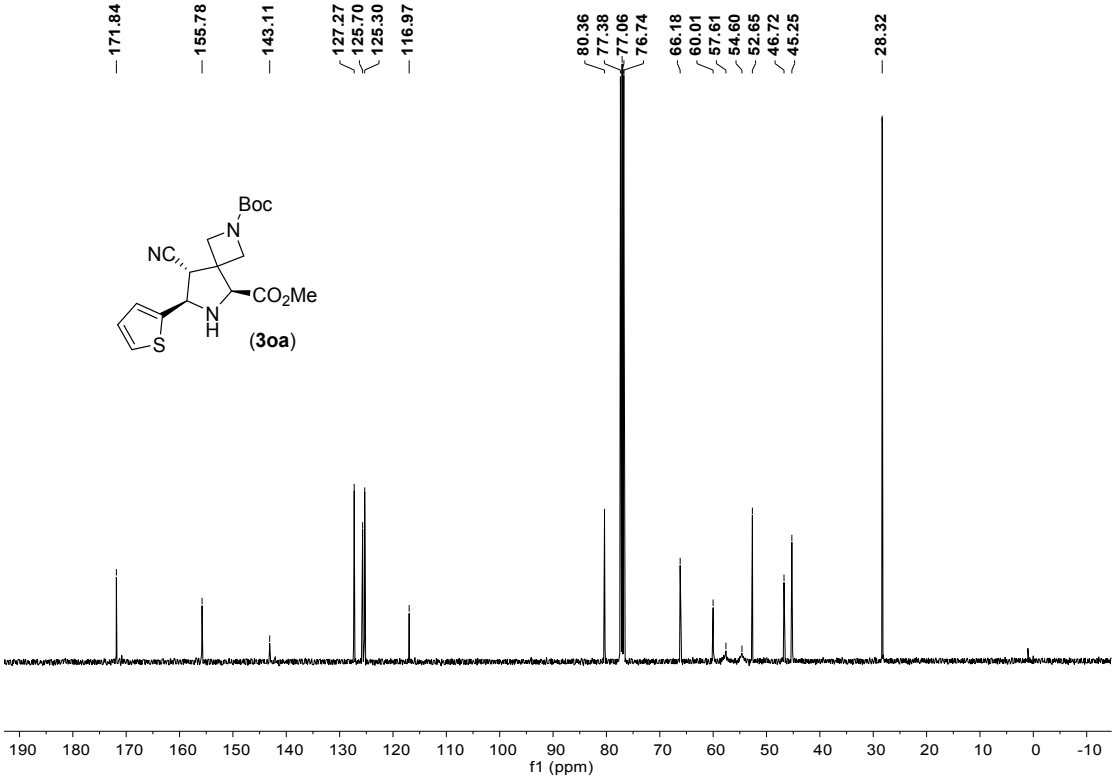
^{13}C NMR spectrum of compound **3na** ($CDCl_3$)



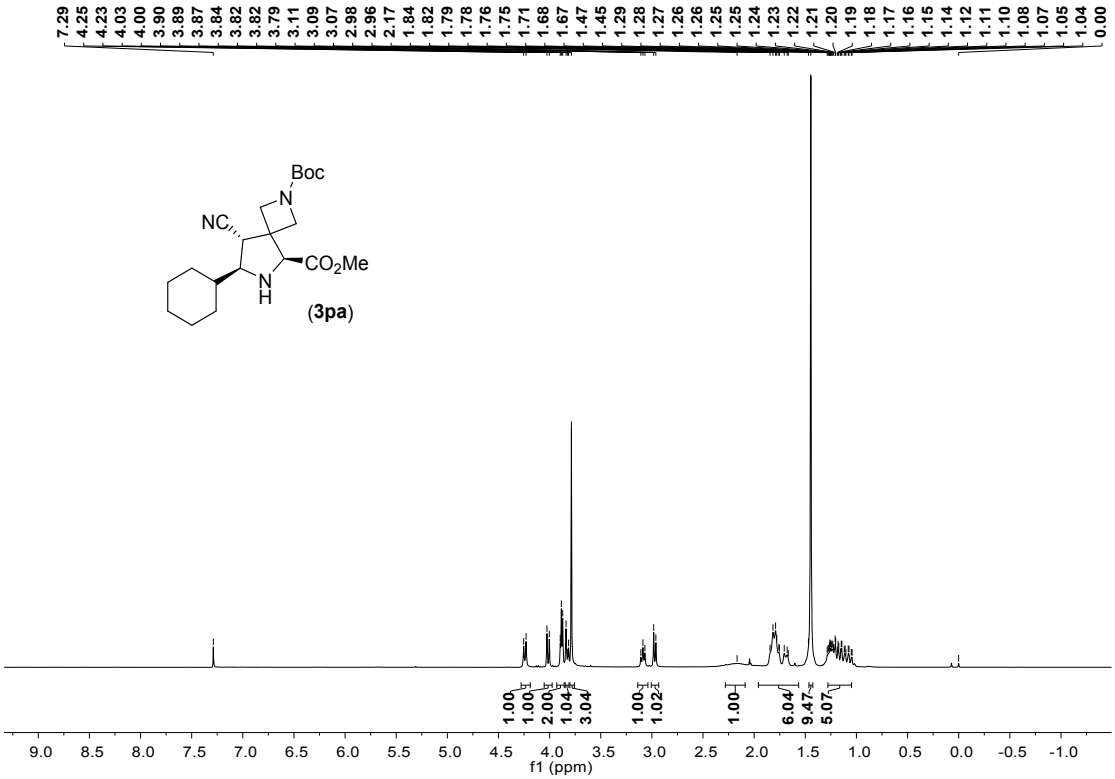
^{1}H NMR spectrum of compound **3oa** ($CDCl_3$)



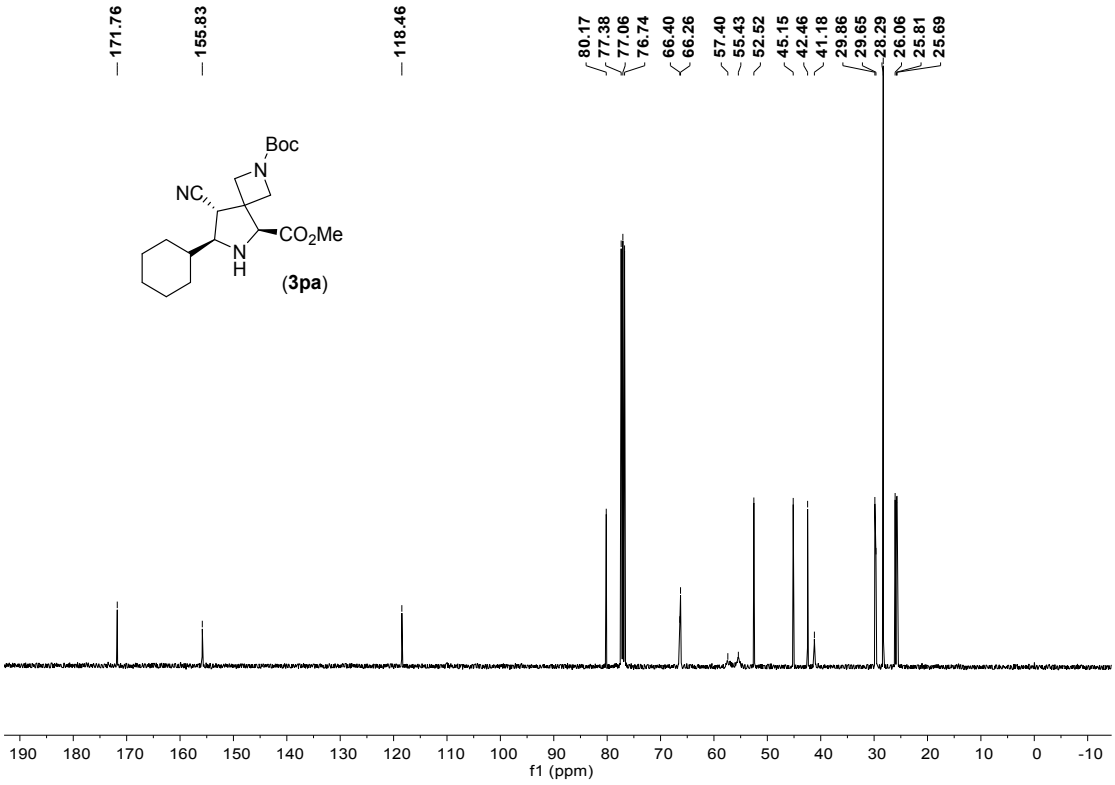
^{13}C NMR spectrum of compound **3oa** ($CDCl_3$)



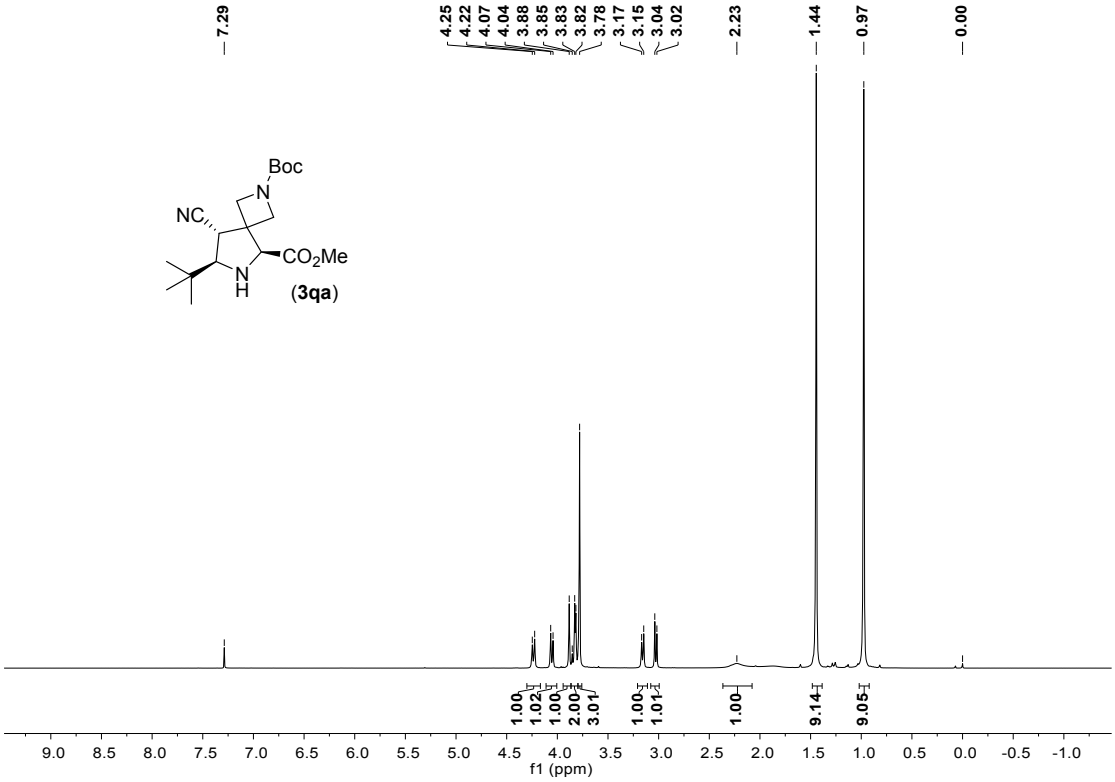
^{1}H NMR spectrum of compound **3pa** ($CDCl_3$)



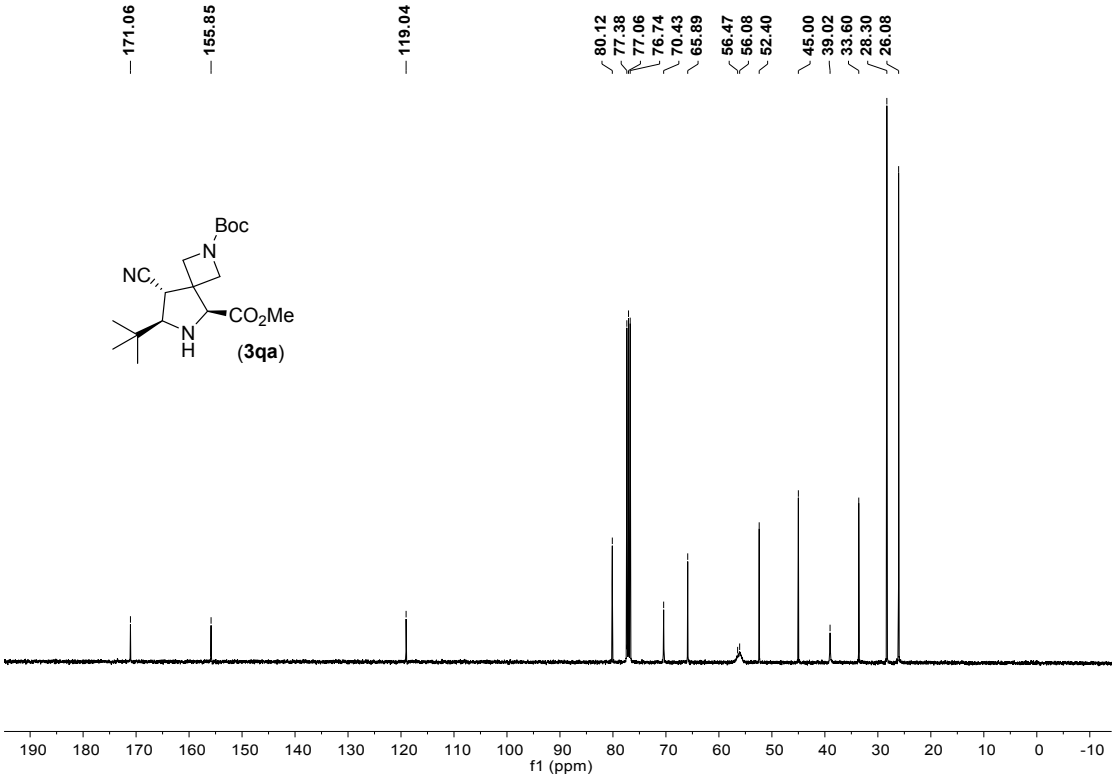
^{13}C NMR spectrum of compound **3pa** ($CDCl_3$)



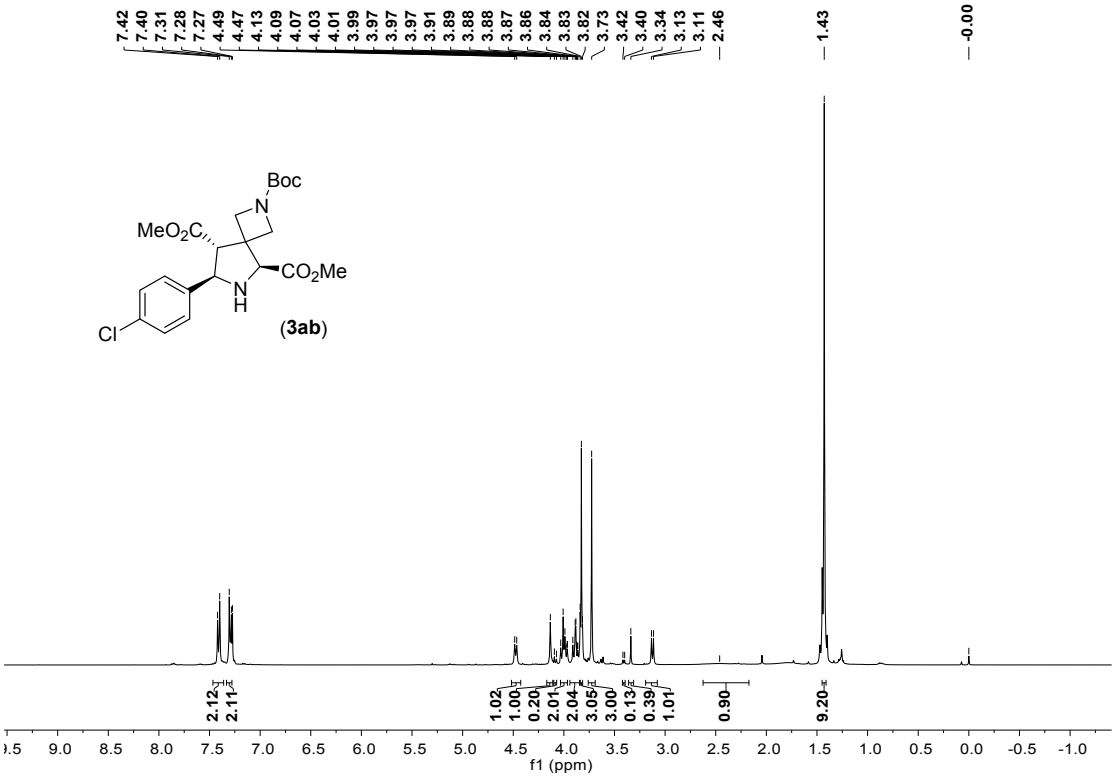
^{1}H NMR spectrum of compound **3qa** ($CDCl_3$)



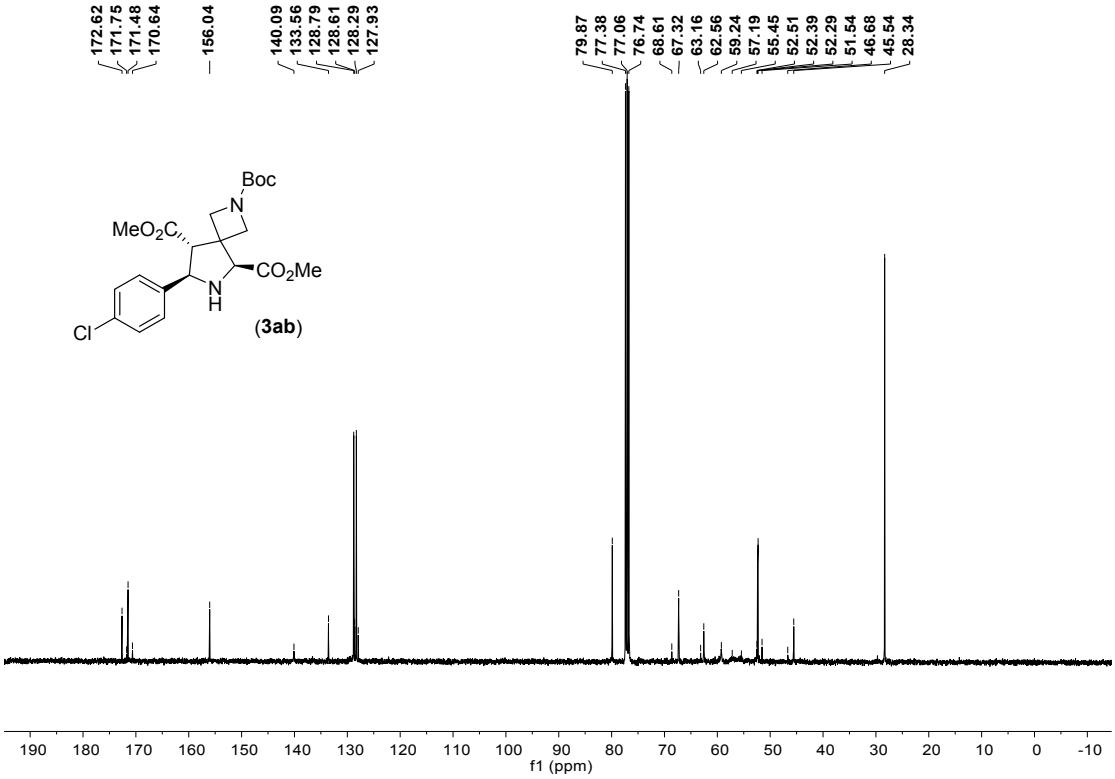
^{13}C NMR spectrum of compound **3qa** ($CDCl_3$)



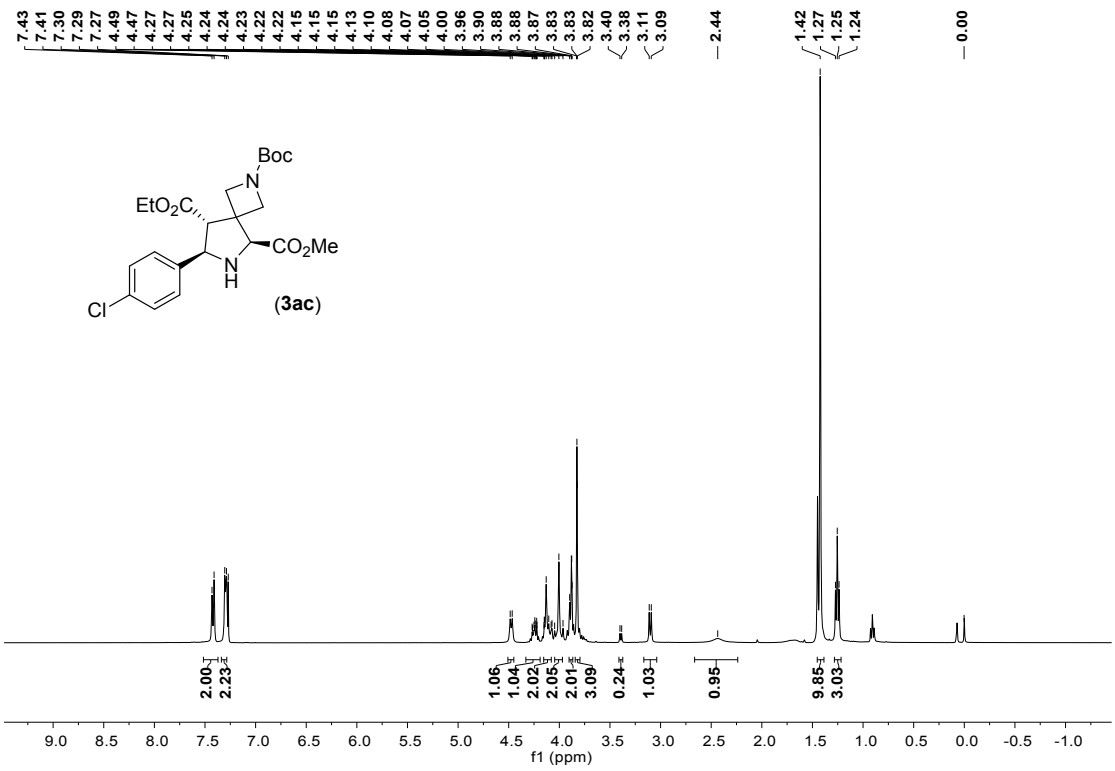
^{1}H NMR spectrum of compound **3ab** ($CDCl_3$)



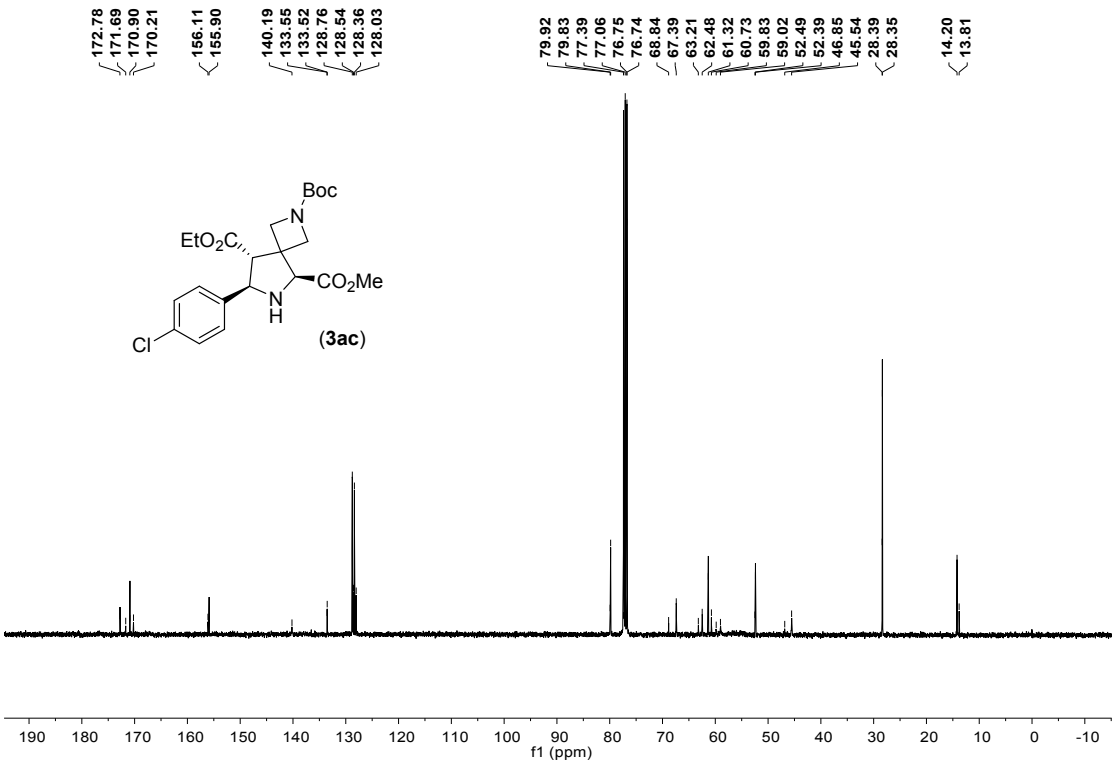
^{13}C NMR spectrum of compound **3ab** ($CDCl_3$)



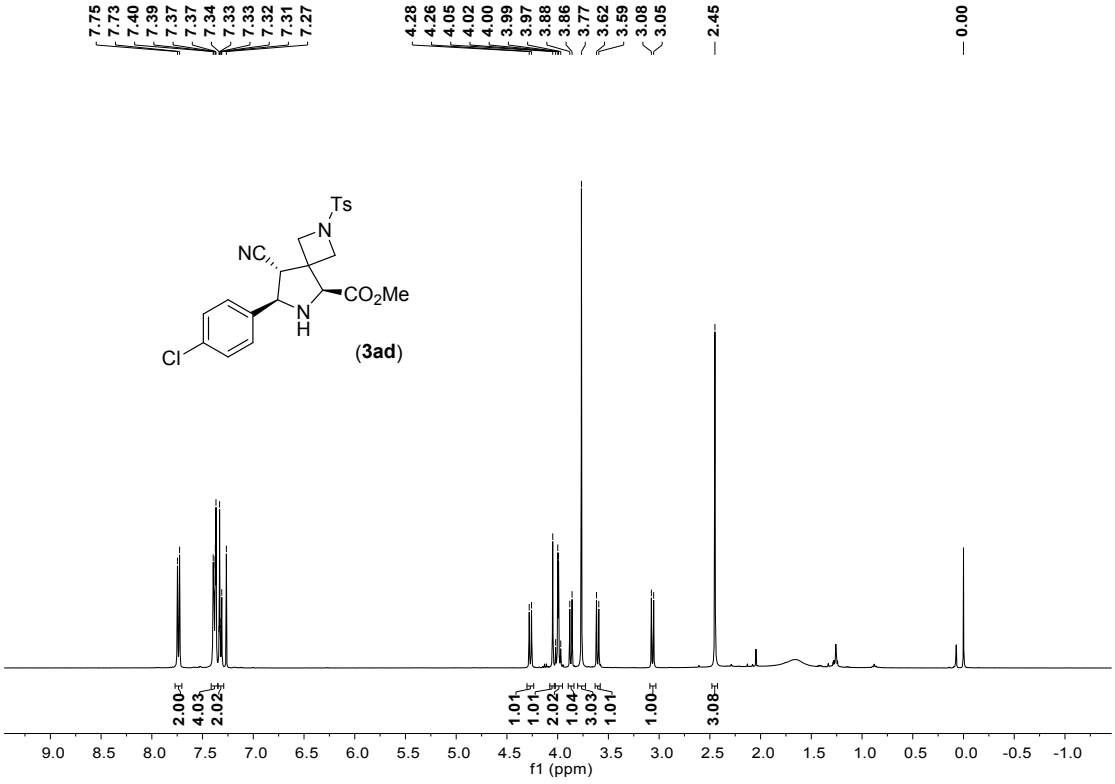
^{1}H NMR spectrum of compound **3ac** ($CDCl_3$)



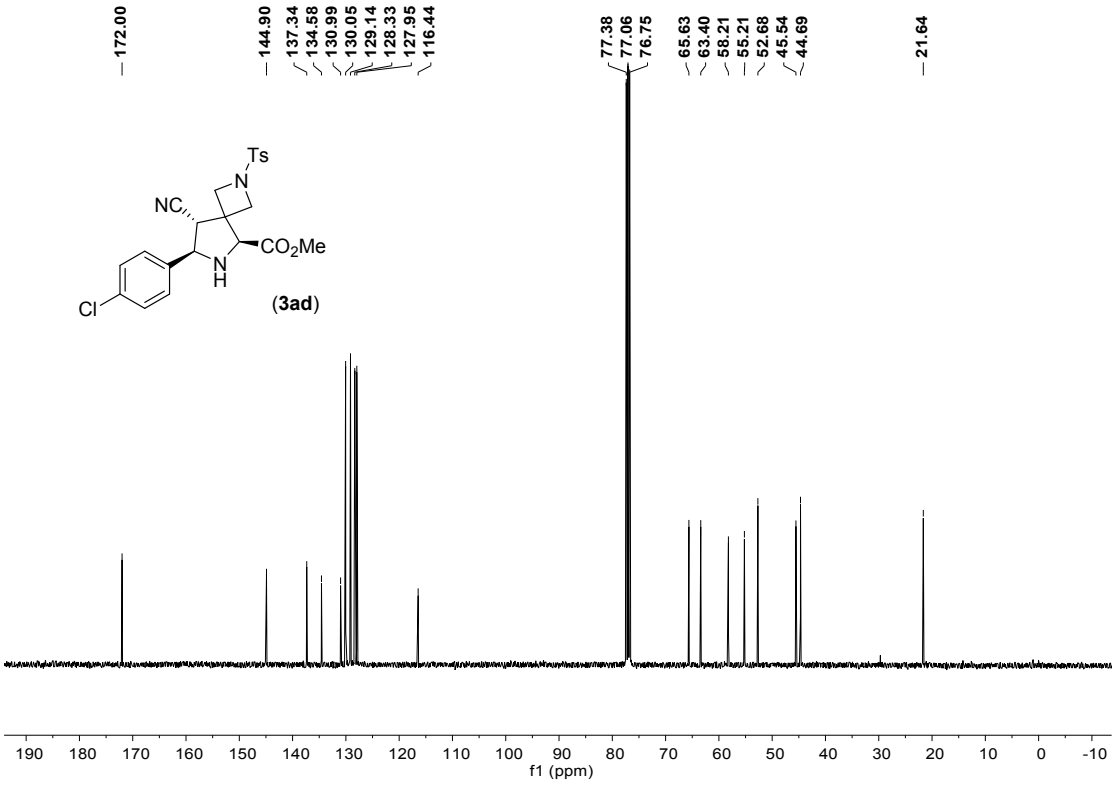
^{13}C NMR spectrum of compound **3ac** ($CDCl_3$)



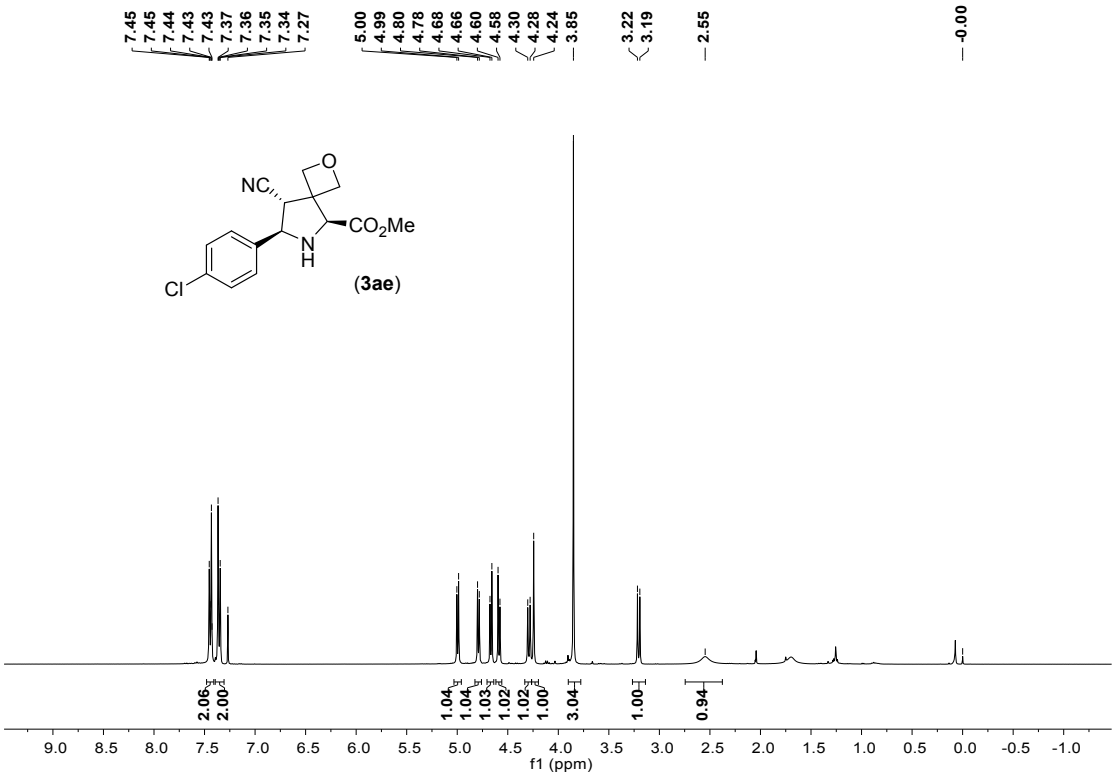
^{1}H NMR spectrum of compound **3ad** ($CDCl_3$)



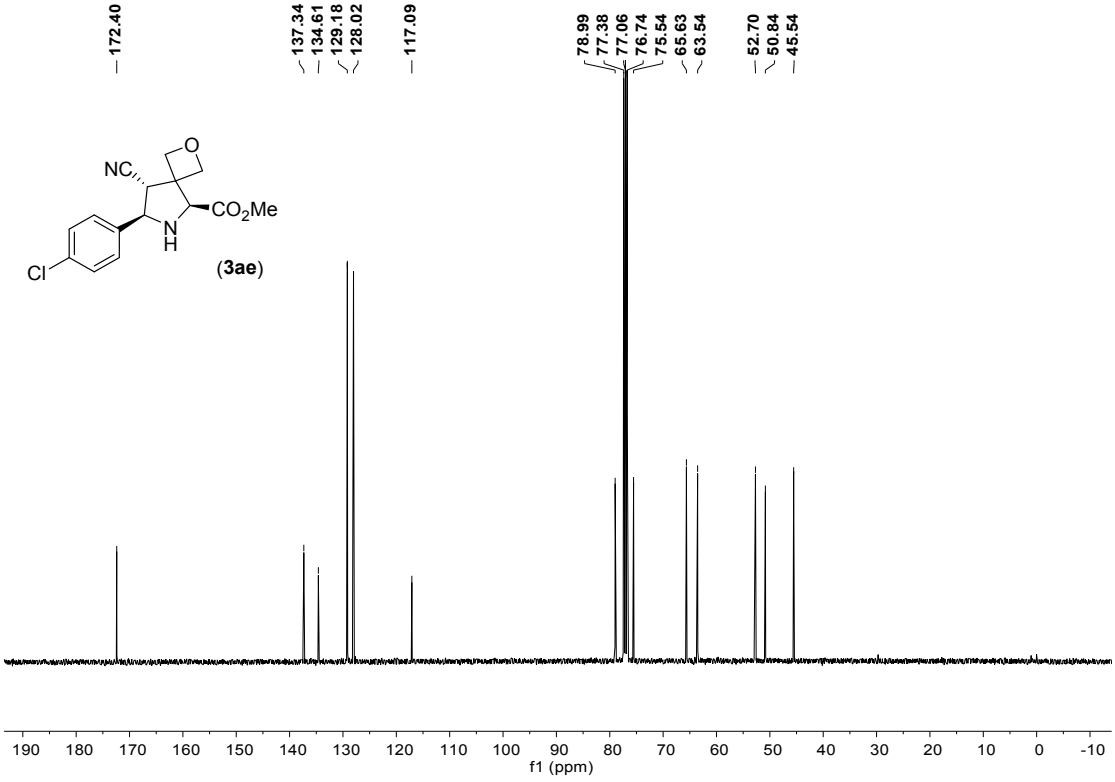
^{13}C NMR spectrum of compound **3ad** ($CDCl_3$)



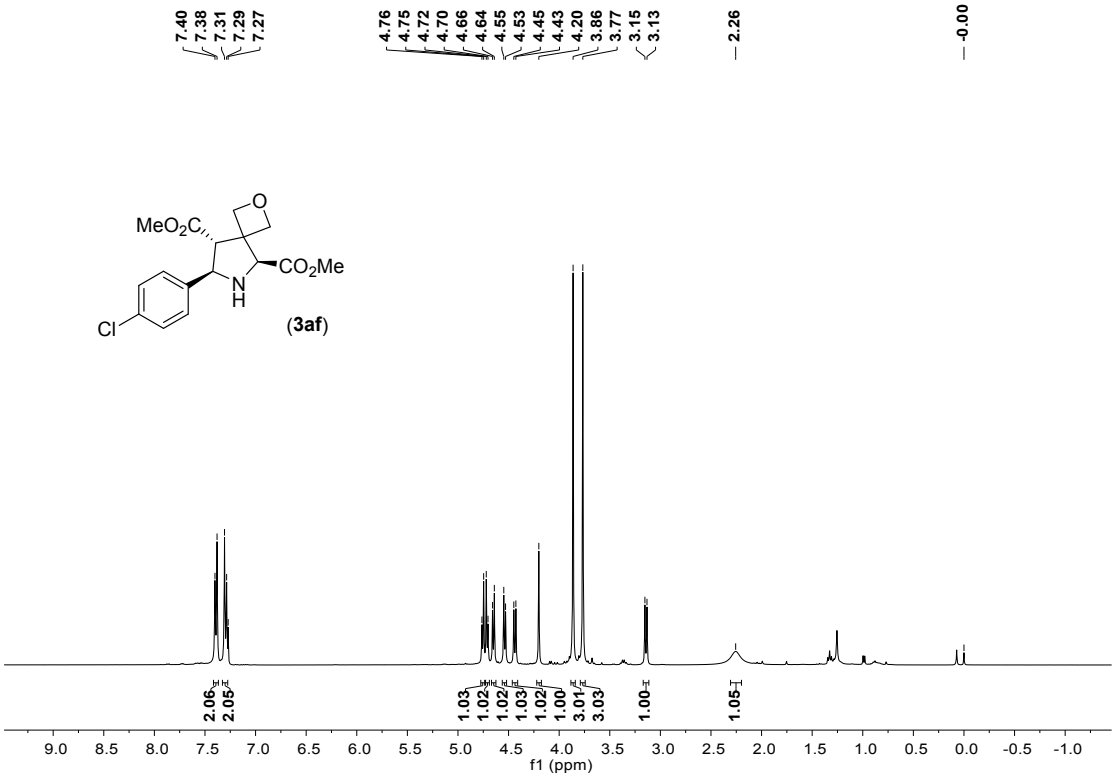
^{1}H NMR spectrum of compound **3ae** ($CDCl_3$)



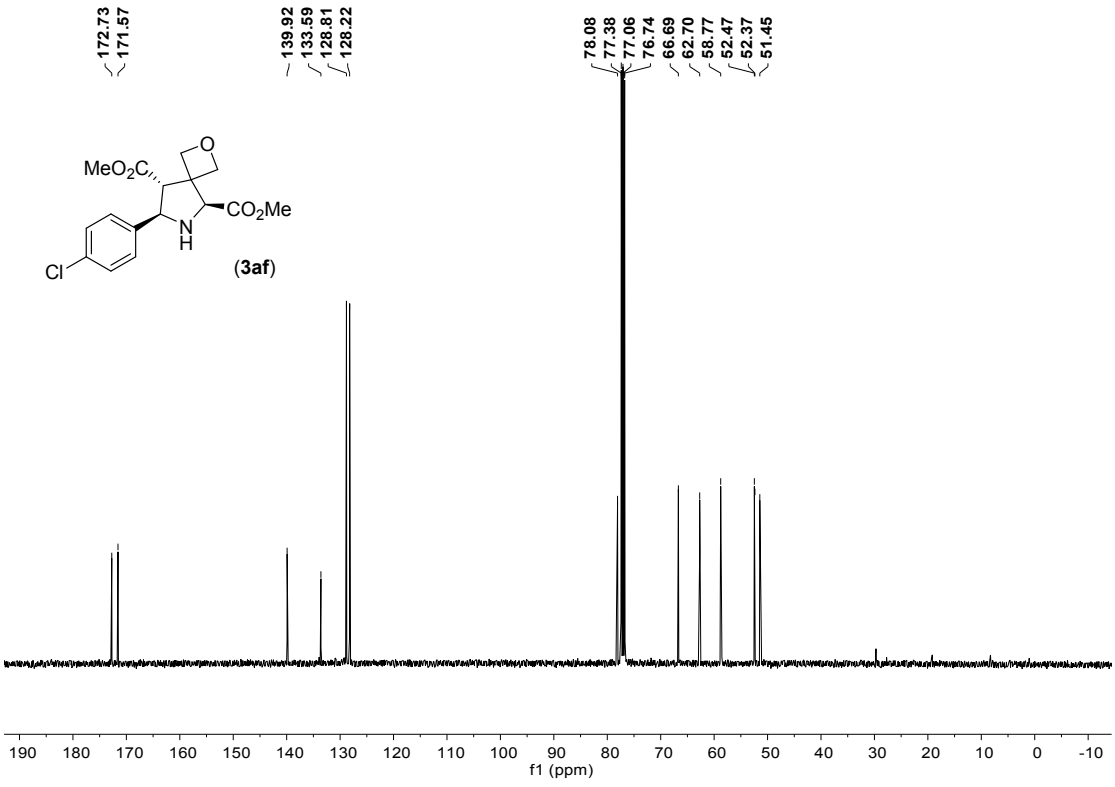
^{13}C NMR spectrum of compound **3ae** ($CDCl_3$)



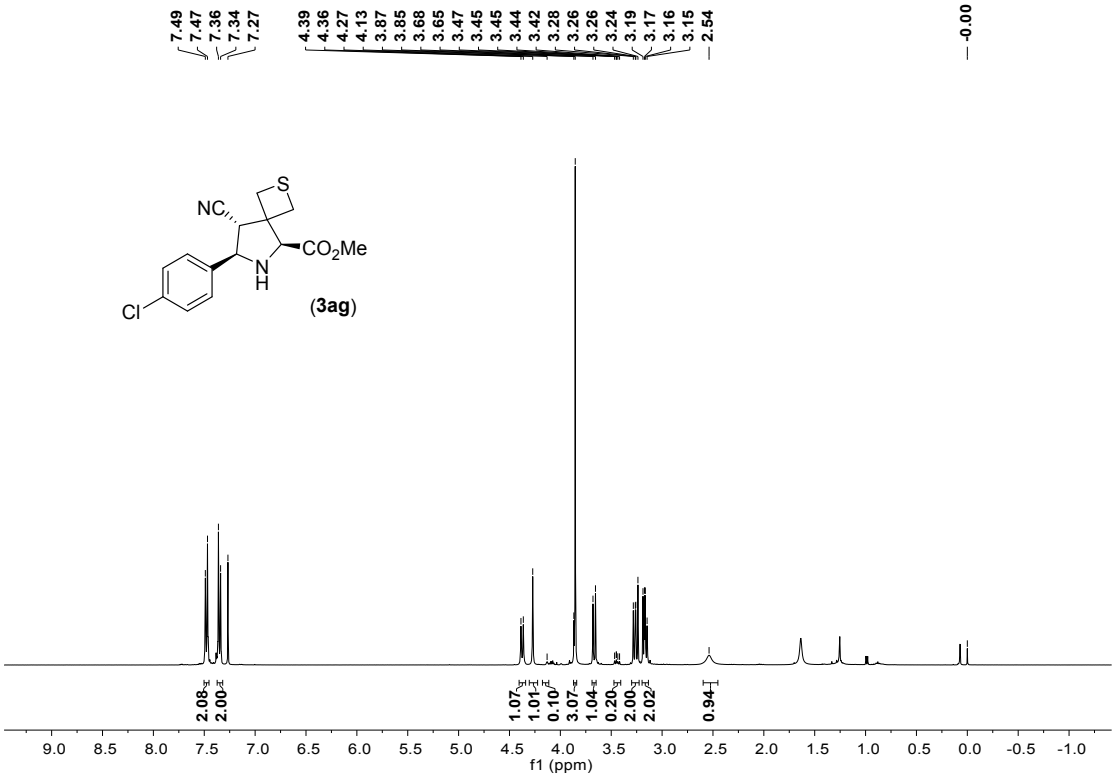
^{1}H NMR spectrum of compound **3af** ($CDCl_3$)



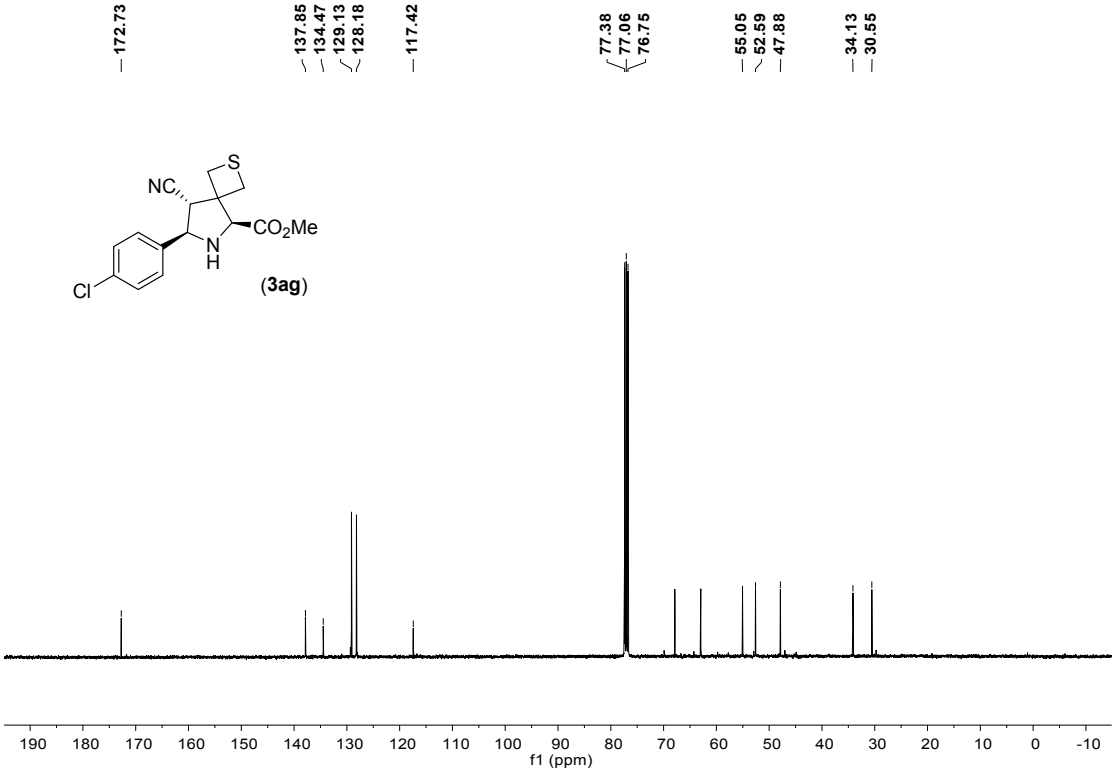
^{13}C NMR spectrum of compound **3af** ($CDCl_3$)



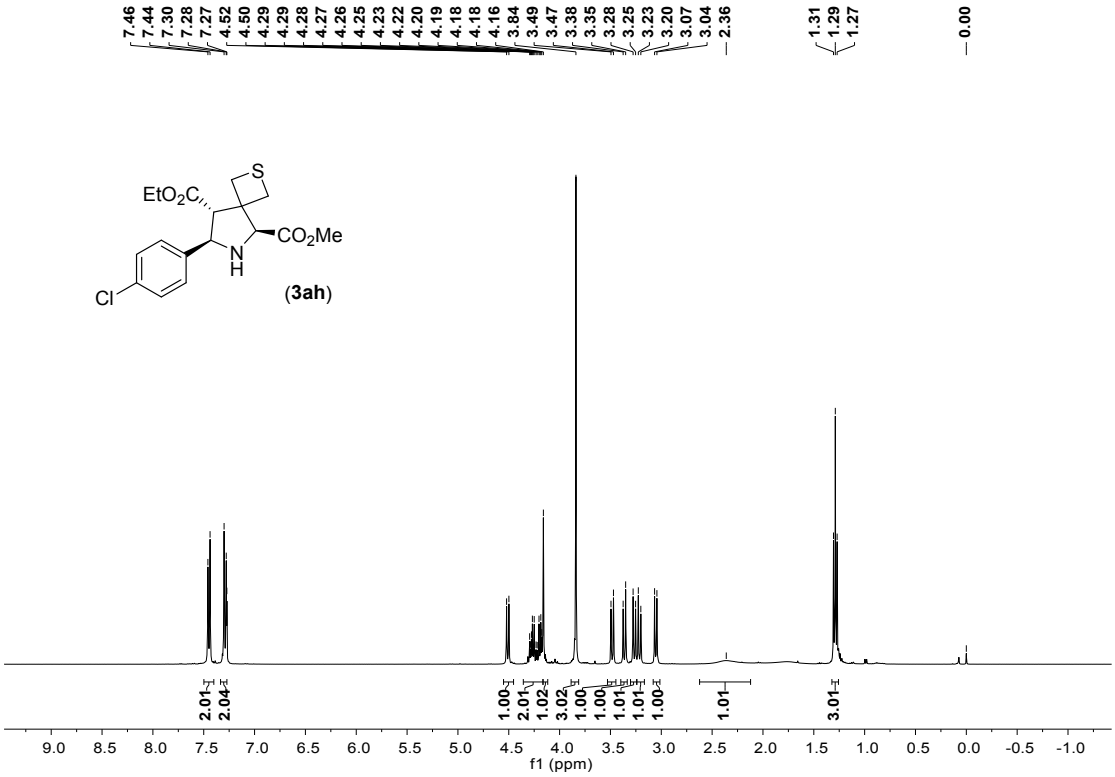
^{1}H NMR spectrum of compound **3ag** ($CDCl_3$)



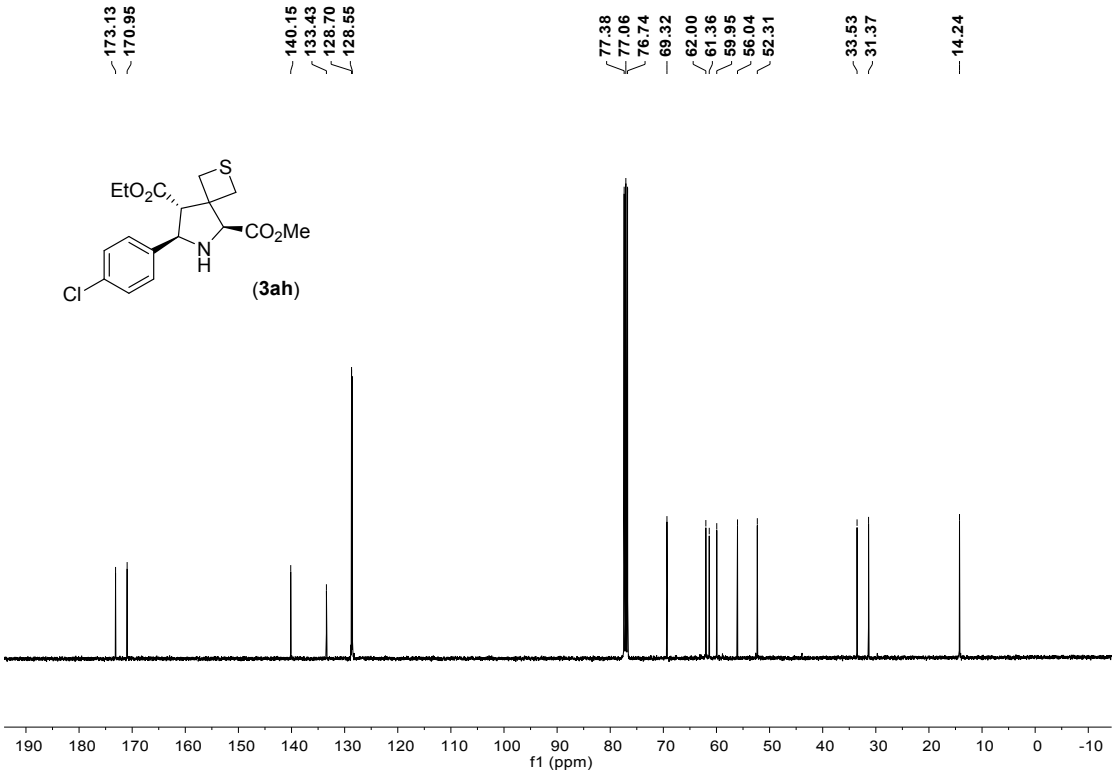
^{13}C NMR spectrum of compound **3ag** ($CDCl_3$)



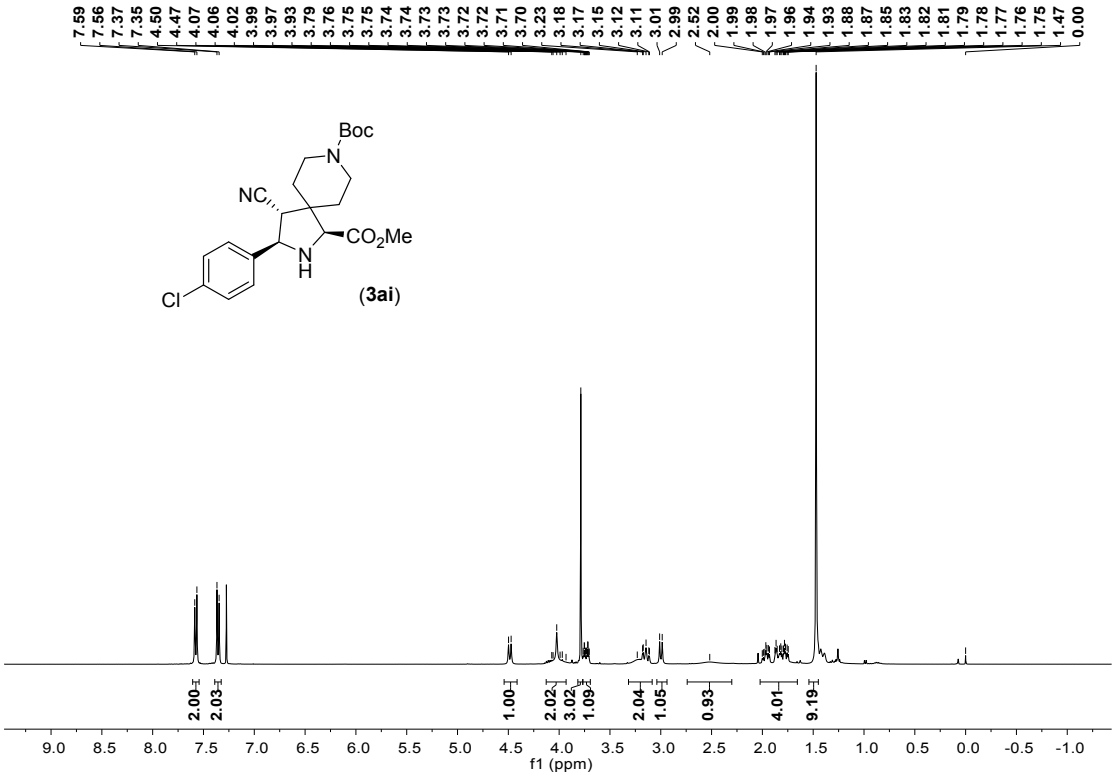
^{1}H NMR spectrum of compound **3ah** ($CDCl_3$)



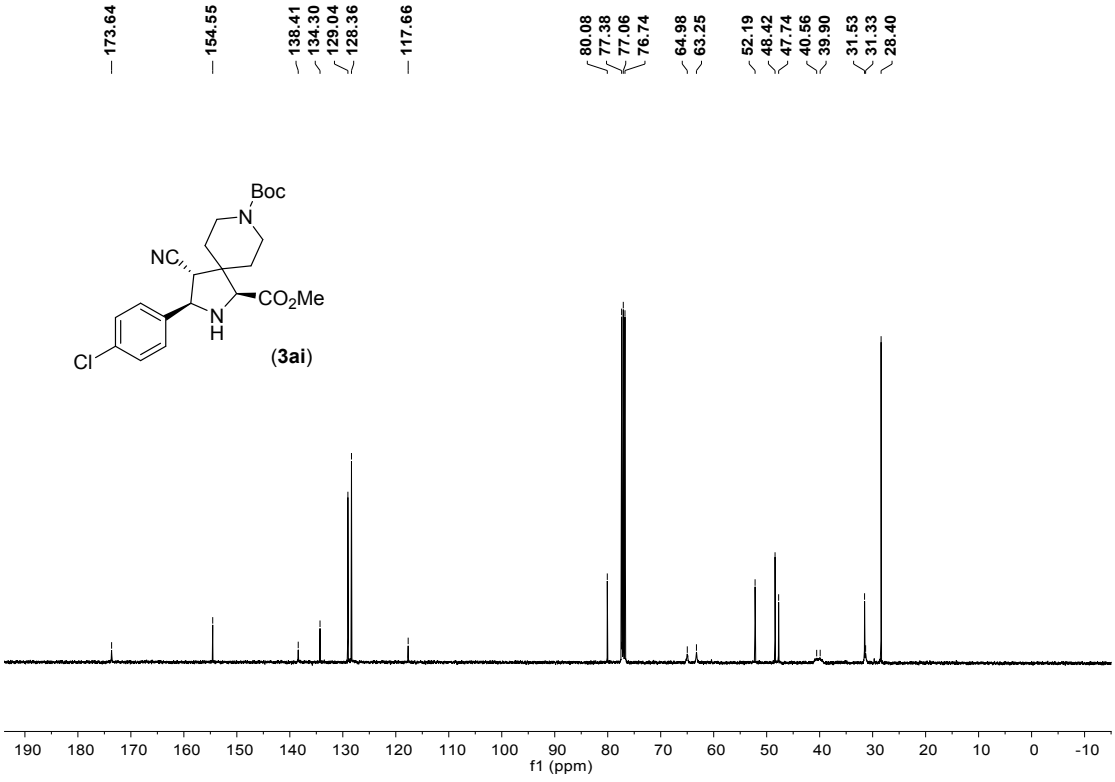
^{13}C NMR spectrum of compound **3ah** ($CDCl_3$)



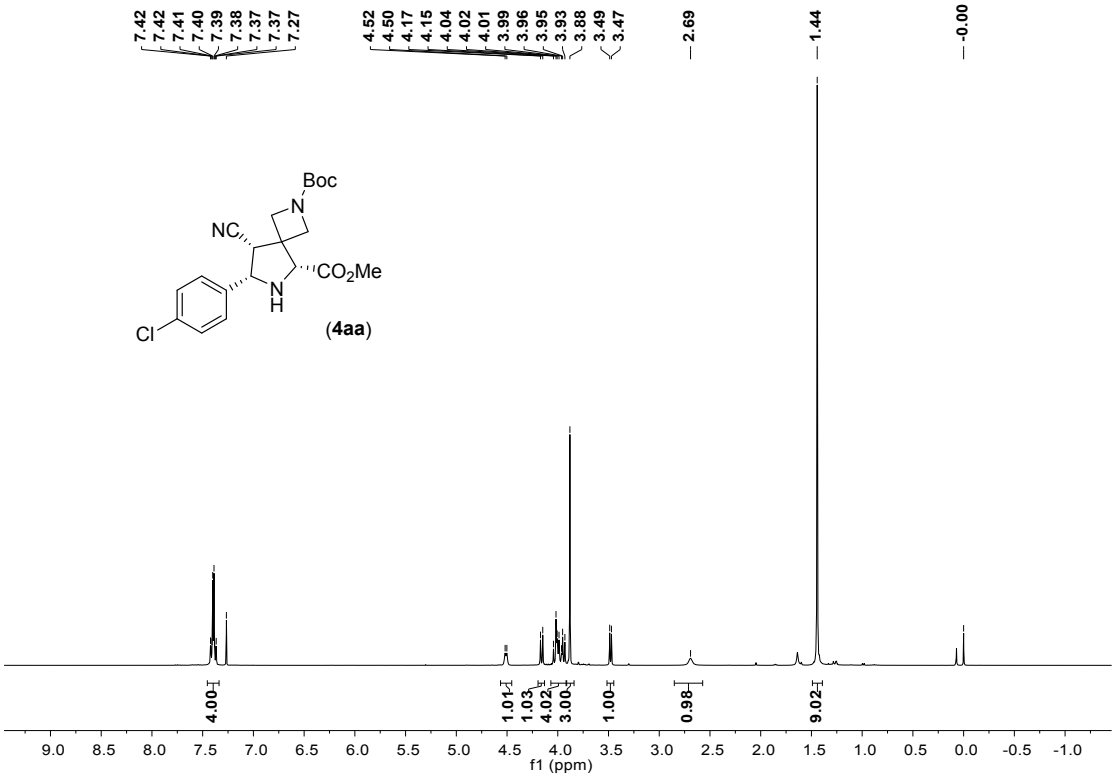
^{1}H NMR spectrum of compound **3ai** ($CDCl_3$)



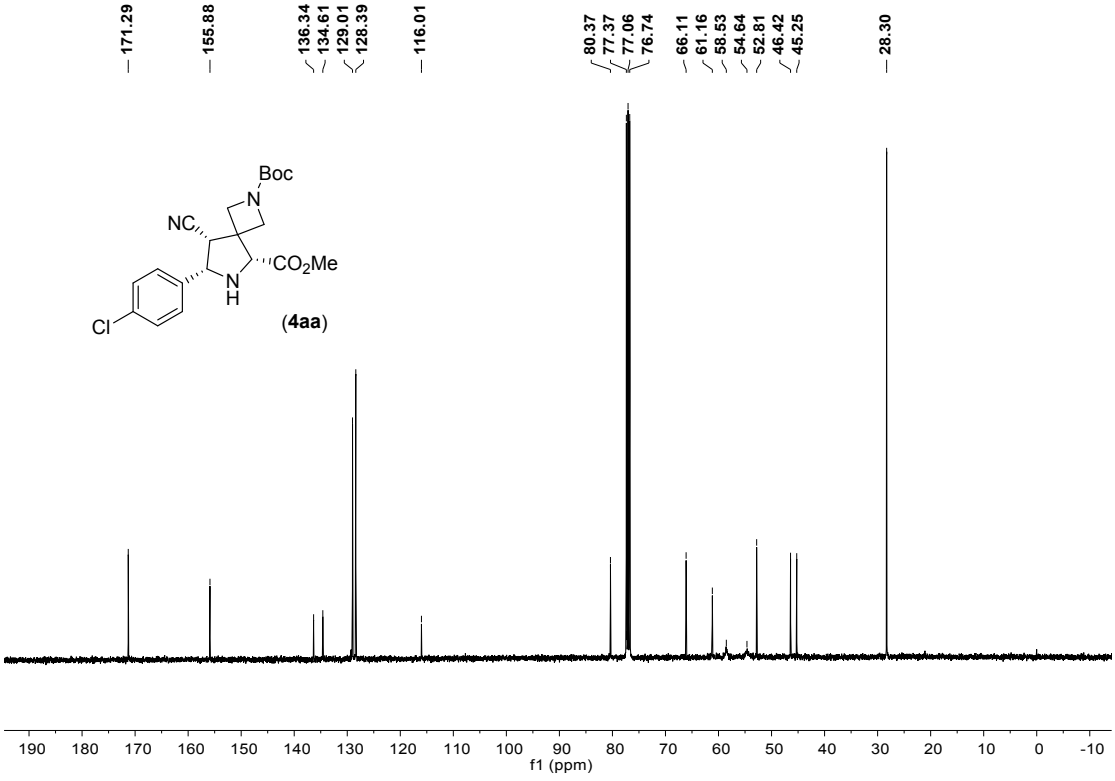
^{13}C NMR spectrum of compound **3ai** ($CDCl_3$)



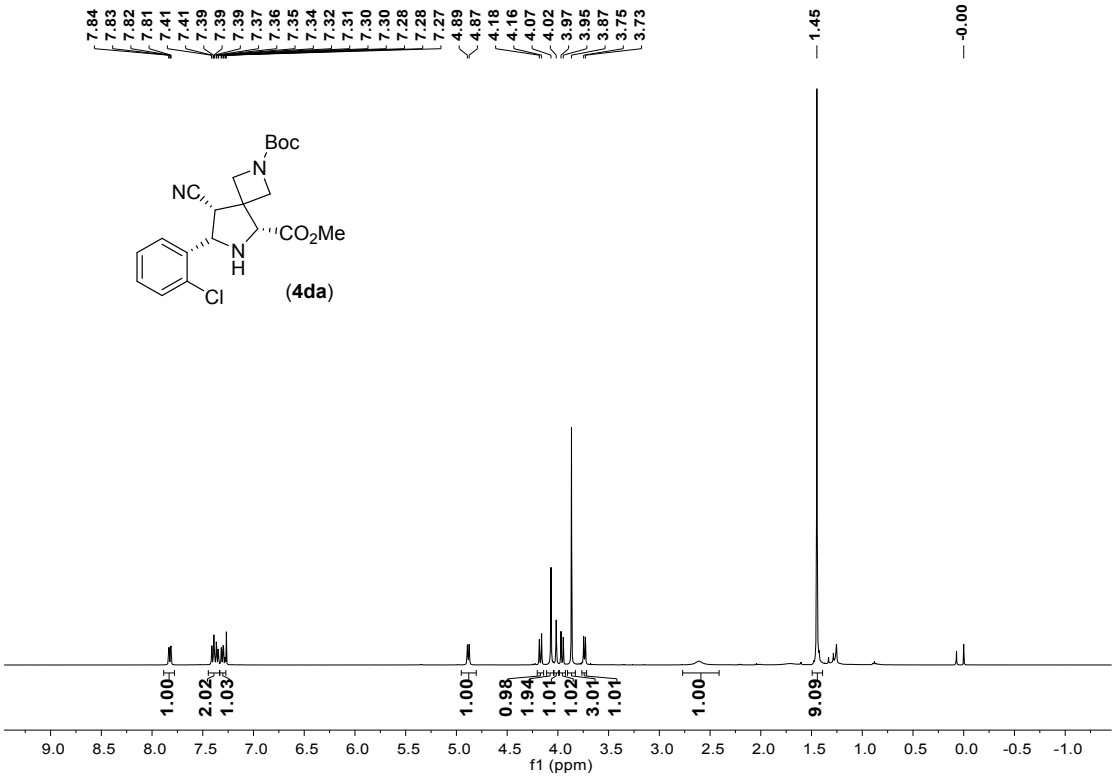
^{1}H NMR spectrum of compound **4aa** ($CDCl_3$)



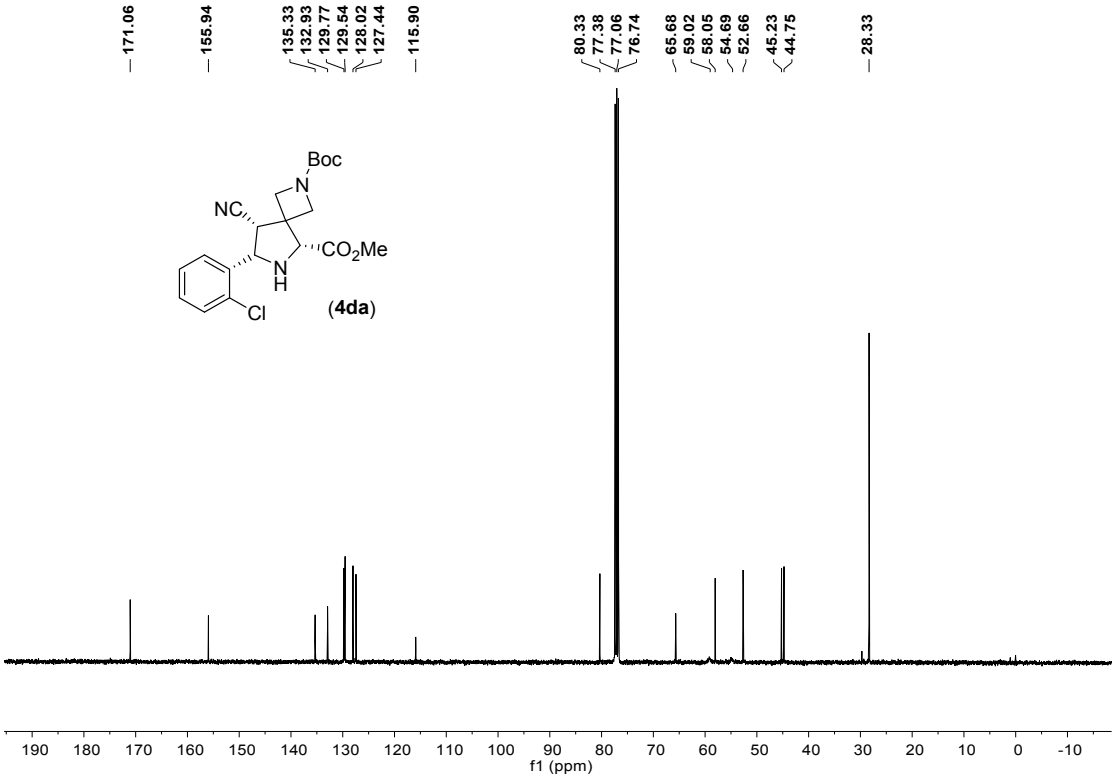
^{13}C NMR spectrum of compound **4aa** ($CDCl_3$)



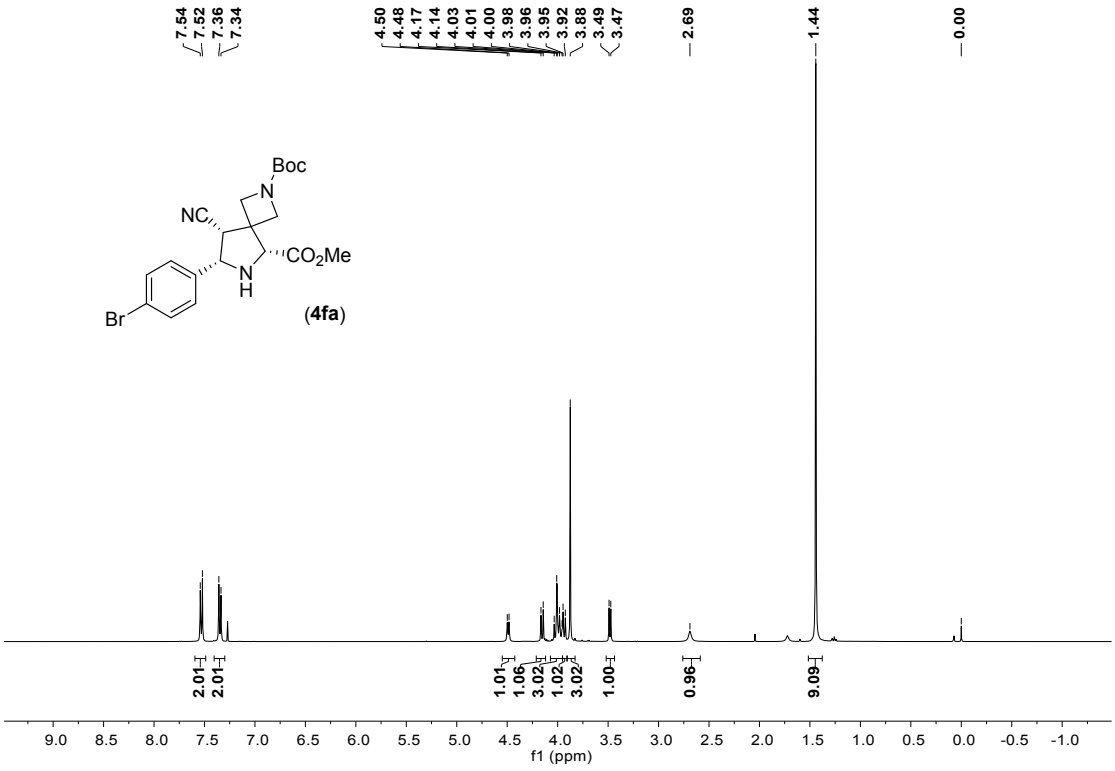
^{1}H NMR spectrum of compound **4da** ($CDCl_3$)



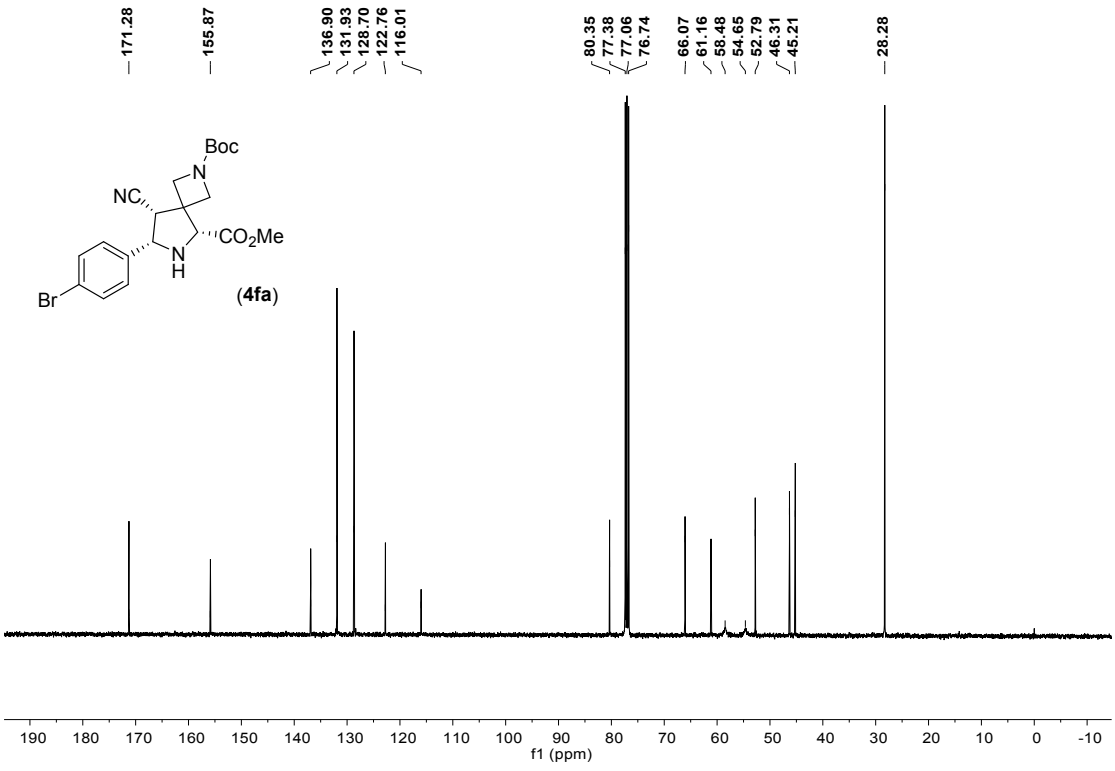
^{13}C NMR spectrum of compound **4da** ($CDCl_3$)



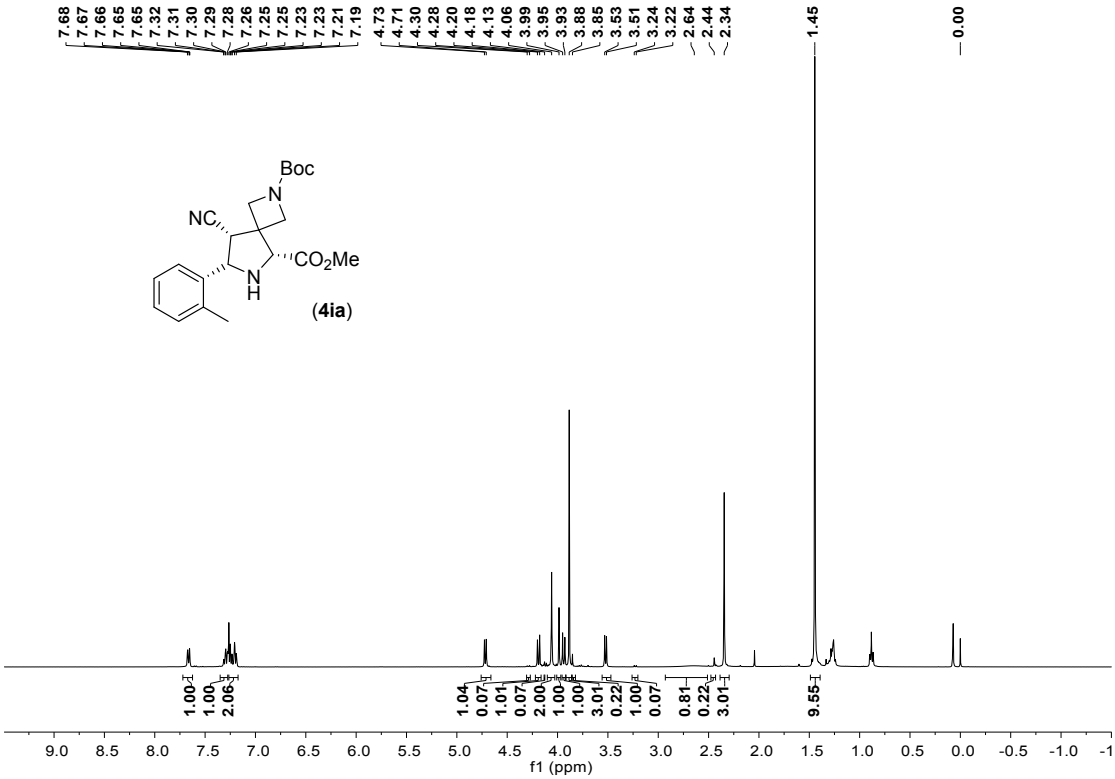
^{1}H NMR spectrum of compound **4fa** ($CDCl_3$)



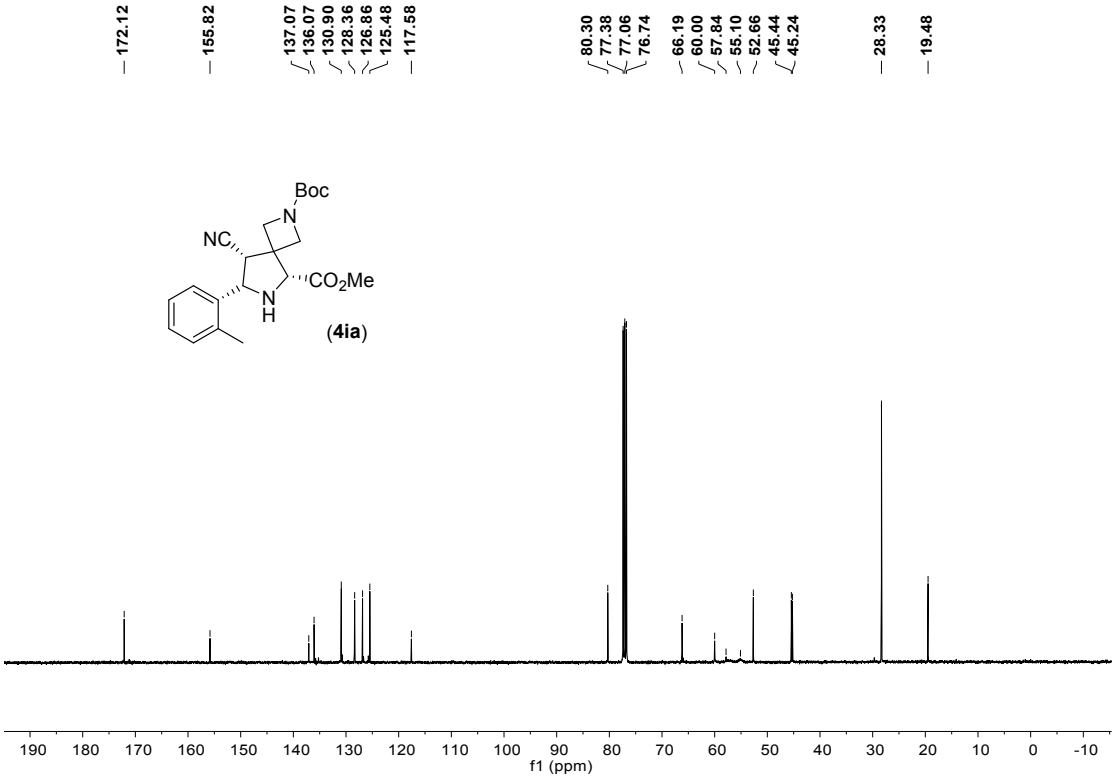
^{13}C NMR spectrum of compound **4fa** ($CDCl_3$)



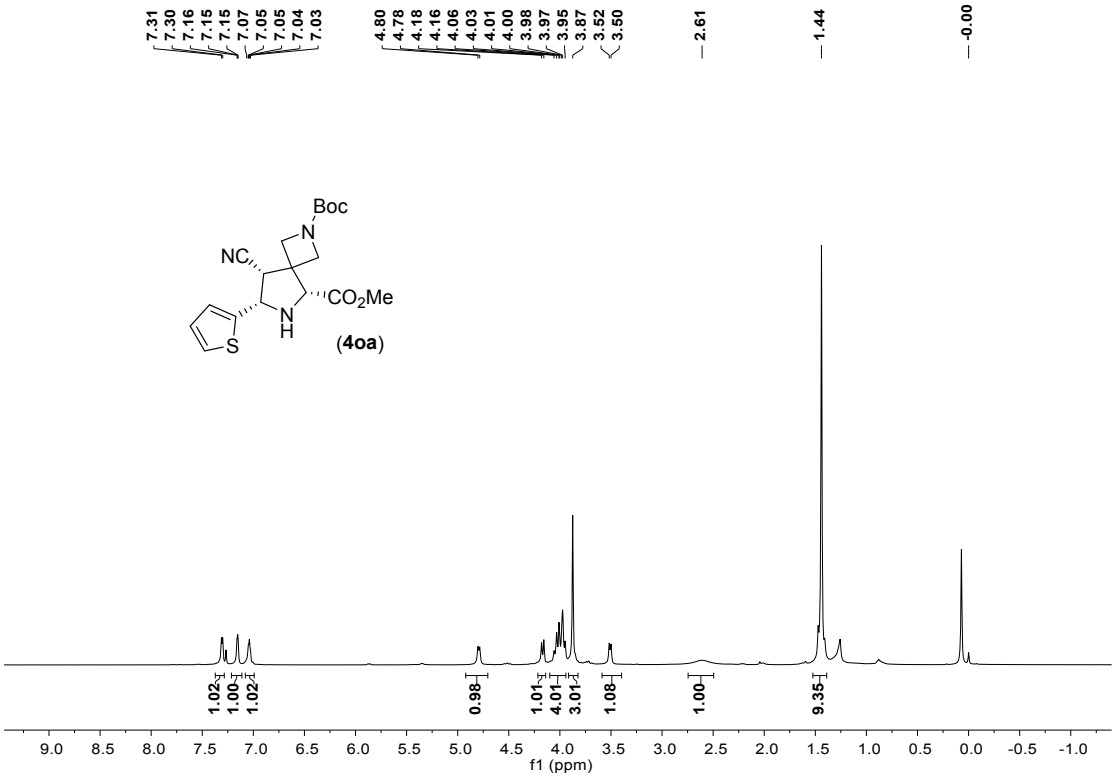
^{1}H NMR spectrum of compound **4ia** ($CDCl_3$)



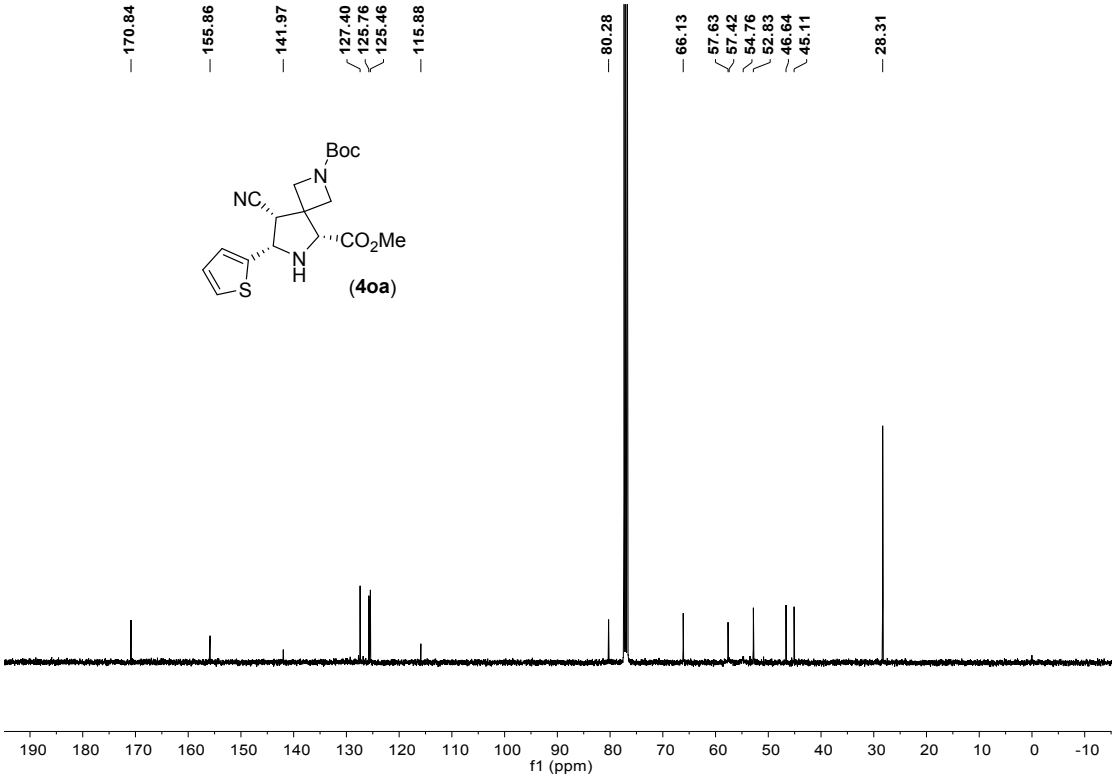
^{13}C NMR spectrum of compound **4ia** ($CDCl_3$)



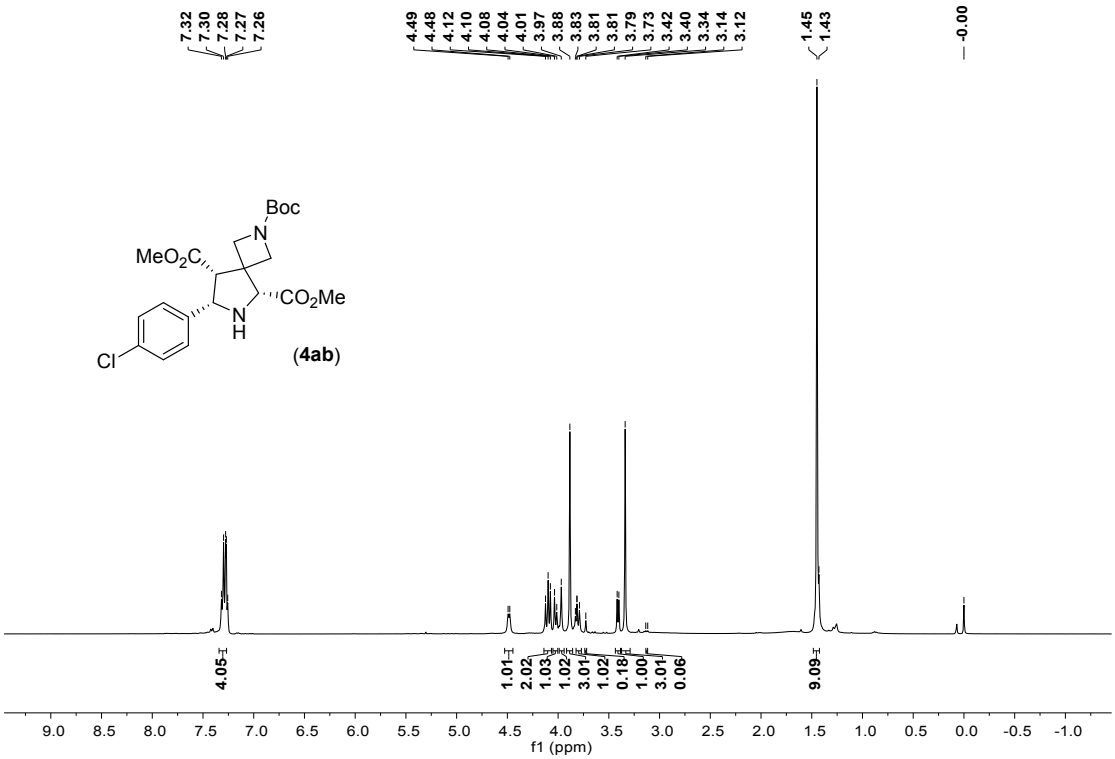
^{1}H NMR spectrum of compound **4oa** ($CDCl_3$)



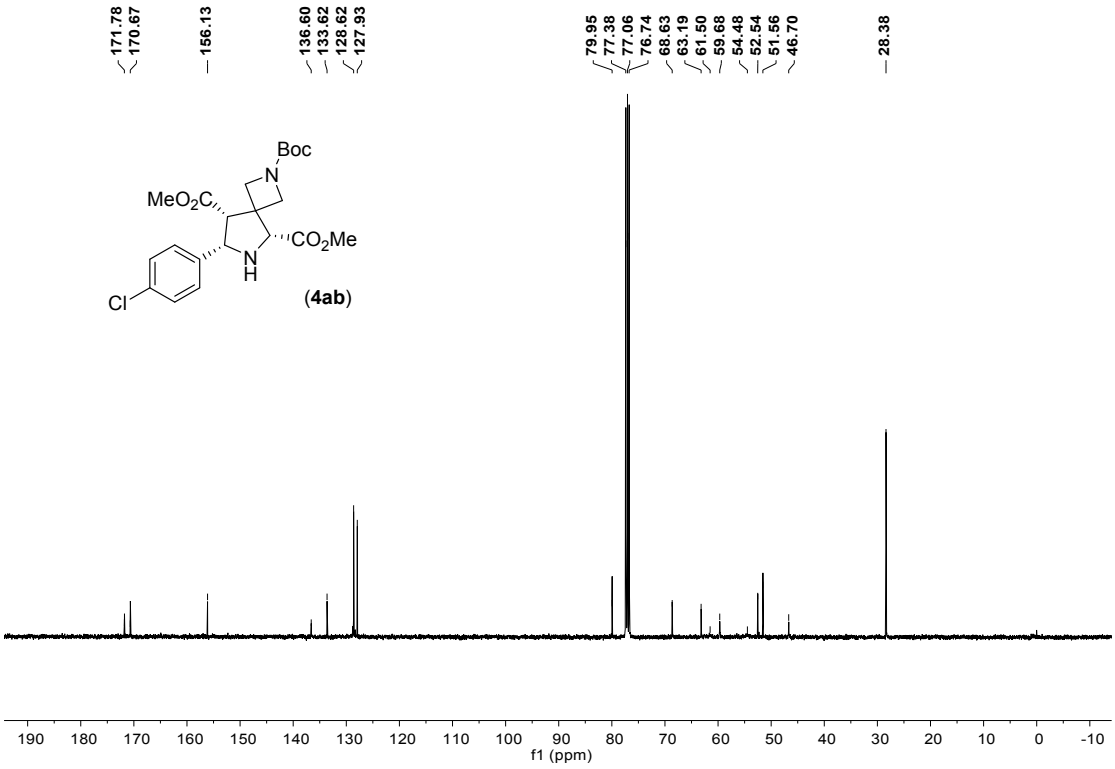
^{13}C NMR spectrum of compound **4oa** ($CDCl_3$)



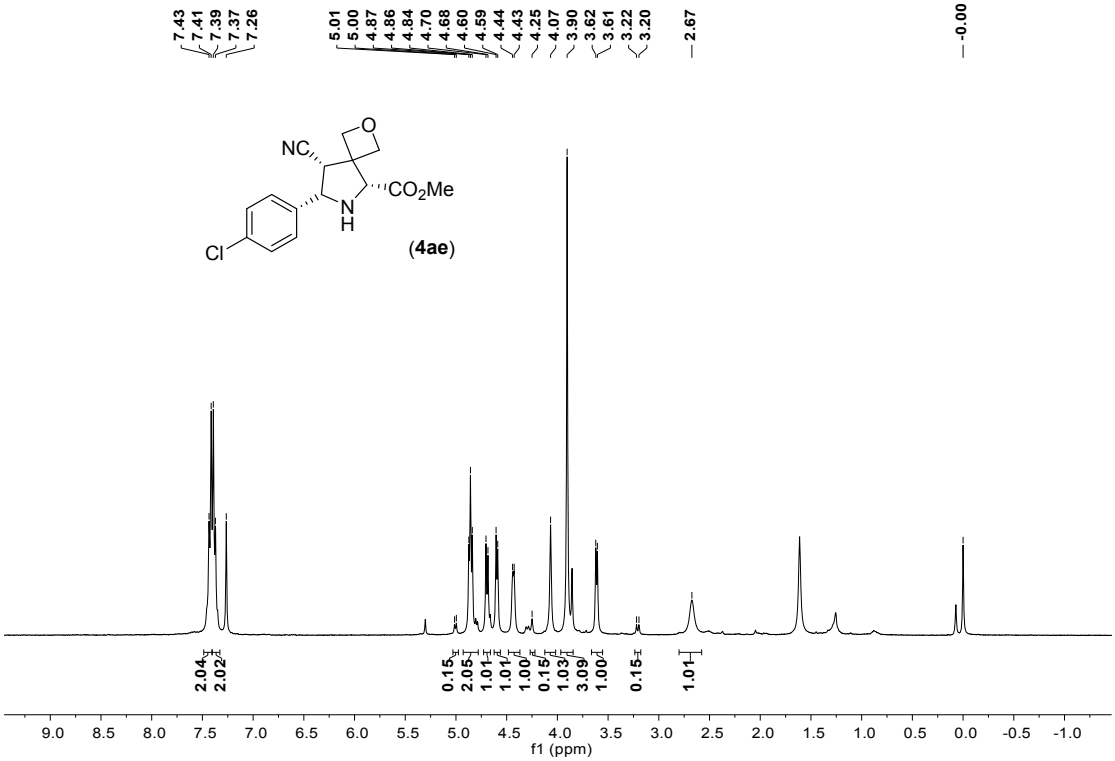
^{1}H NMR spectrum of compound **4ab** ($CDCl_3$)



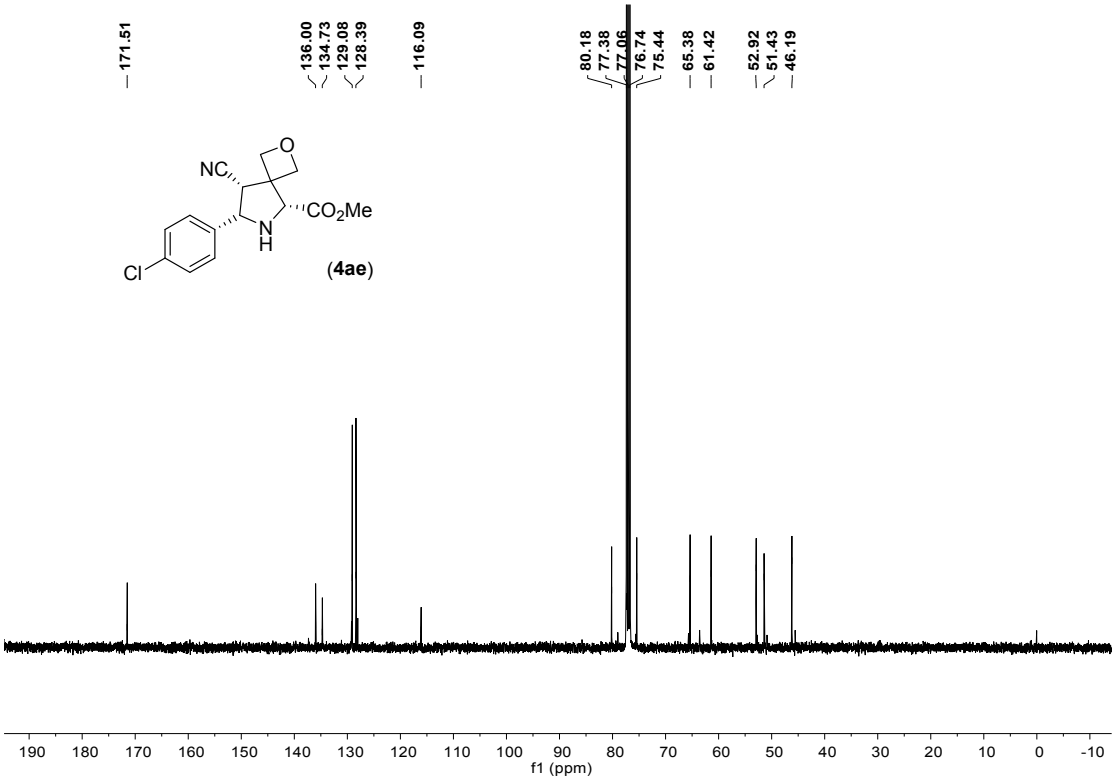
^{13}C NMR spectrum of compound **4ab** ($CDCl_3$)



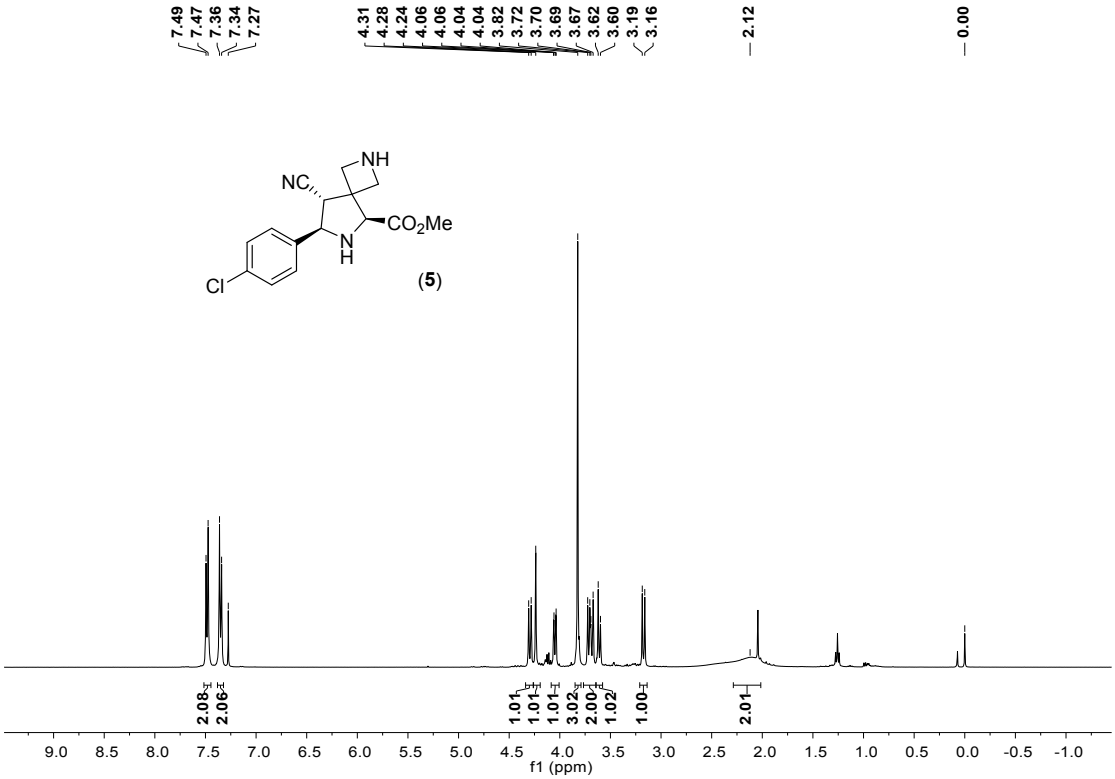
^{1}H NMR spectrum of compound **4ae** ($CDCl_3$)



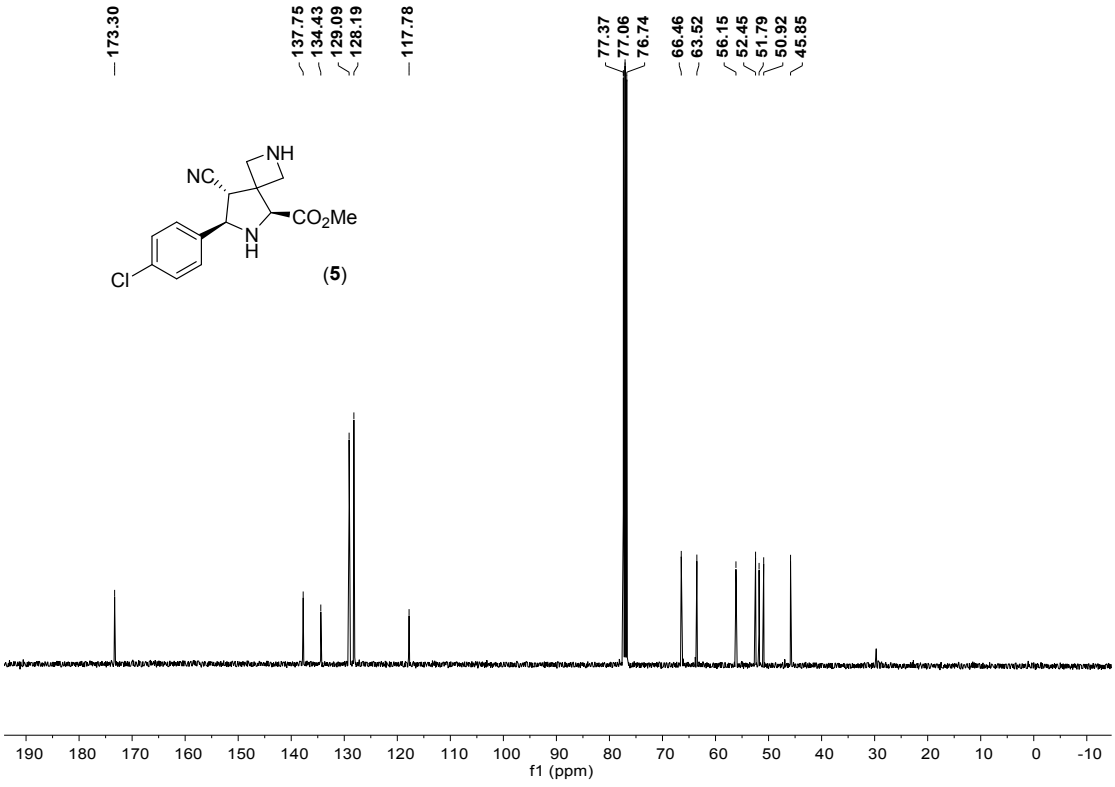
^{13}C NMR spectrum of compound **4ae** ($CDCl_3$)



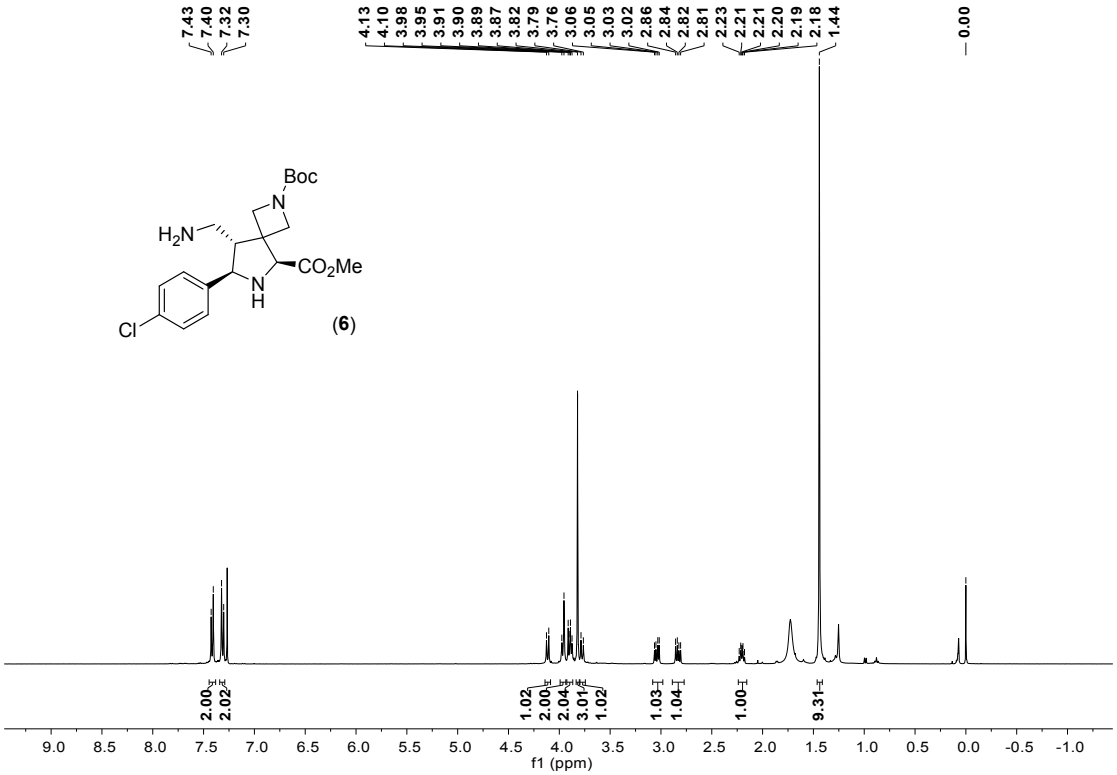
^{1}H NMR spectrum of compound **5** ($CDCl_3$)



^{13}C NMR spectrum of compound **5** ($CDCl_3$)



^{1}H NMR spectrum of compound **6** ($CDCl_3$)



^{13}C NMR spectrum of compound **6** ($CDCl_3$)