Asymmetric Construction of a Multi-Pharmacophore-Containing Dispirotriheterocyclic Scaffold and Identification of a Human Carboxylesterase 1 Inhibitor

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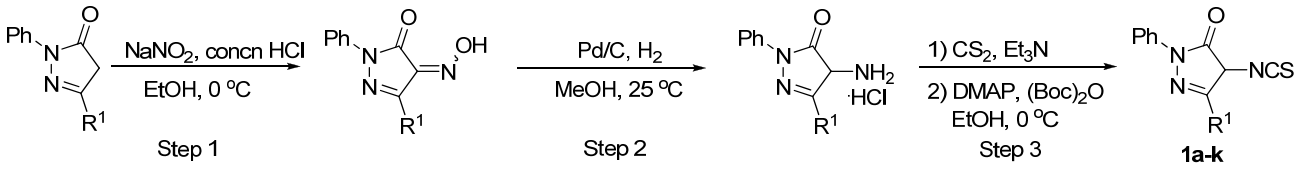
1. General information

Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. Column chromatography was performed on silica gel (200~300 mesh). Enantiomeric excesses (*ee*) were determined by HPLC using corresponding commercial chiral columns as stated at 30 °C with UV detector at 254 nm. Optical rotations were reported as follows: $[\alpha]^{T}_{D}$ (*c* g/100 mL, solvent). All ^{1}H NMR and ^{19}F NMR spectra were recorded on a Bruker Avance Ⅱ 400 MHz and Bruker Avance Ⅲ 471 MHz respectively, ^{13}C NMR spectra were recorded on a Bruker Avance Ⅱ 101 MHz or Bruker Avance Ⅲ 126 MHz with chemical shifts reported as ppm (in $CDCl_3$, TMS as an internal standard). Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad singlet, dd = double doublet, coupling constants in Hz, integration). HRMS (ESI) was obtained with a HRMS/MS instrument (LTQ Orbitrap XL TM). The absolute configuration of **3af** and ***ent-6*** were assigned by the X-ray analysis.

N-Boc ketimines **2a-j** were prepared from isatin according to the literature.[1] Catalyst **Q5** was synthesized according to the literature procedure.[2] The racemic products were synthesized using quinine/quinidine = 1:1 as the catalyst.

2. General procedure and characterization of 4-isothiocyanato pyrazolone 1

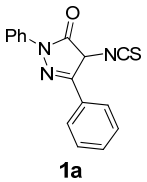


Step 1: To a round bottom flask equipped with a magnetic stir bar was charged with pyrazolone (4.0 mmol, 1.0 equiv) and EtOH (15.0 mL). After cooling to 0 °C, concentrated HCl aqueous (0.5 mL, 6 mmol, 1.5 equiv) was added dropwise. To the resulting solution was added a solution of $NaNO_2$ (0.414 g, 6.0 mmol, 1.5 equiv) in 1.5 mL of water slowly. The resulting mixture was stirred at 0 °C for 0.5 h. The precipitation (water could be added if there was no precipitation) was filtrated, washed with water (15 mL) and EtOH (5.0 mL). The solid was dried under vacuum to yield the 4-hydroxyimino pyrazolone as orange or yellow solid in 85-95% yield, and used directly to the next step without further purification.

Step 2: To a round bottom flask equipped with a magnetic stir bar was charged with 4-hydroxyimino pyrazolone (4.0 mmol, 1.0 equiv) and MeOH (40.0 mL), under argon. After the addition of (10% Pd/C) (5% w/w), the reaction mixture was exchanged with H_2, and stirred overnight at rt till the consumption of the starting material. After that, 6.0 mL of concentrated HCl aqueous was added to the reaction mixture and stirred at rt for 0.5 h. The Pd/C was removed through celite pad, washed with MeOH. The filtrate was concentrated and dried under vacuum. The 4-amino pyrazolone hydrochloride was used directly for the next step without any further purification.

Step 3: To a suspension of 4-amino pyrazolone hydrochloride (4.0 mmol, 1.0 equiv) in EtOH (10 mL) were added CS_2 (3.05 g, 40.0 mmol, 10.0 equiv) and Et_3N (1.62 g, 16.0 mmol, 4.0 equiv), under argon. The reaction mixture was stirred for 45 min at room temperature and then cooled on an ice bath. Then a solution of Boc_2O (0.87 g, 4.0 mmol, 1.0 equiv) and DMAP (10 mol %) in 3 mL EtOH was added slowly. The reaction mixture was kept in the ice bath for 5 min, and then stirred for another 15 min at room temperature. Then the reaction mixture was quenched with 10% HCl aqueous (10 mL), and the mixture was extracted with DCM. The combined organic layers were dried over Na_2SO_4, concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 6:1) or recrystallization (dichloromethane/hexane) to obtain the 4-isothiocyanato pyrazolone **1a-k** in 40-70% yields.

4-isothiocyanato-1,3-diphenyl-1*H*-pyrazol-5-ol (**1a**)

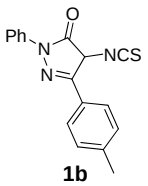


1a

Prepared according to the general procedure as white solid (purified by recrystallization, 0.76 g, 65% yield). mp 225.0-227.4 °C; ^{1}H NMR (400 MHz, DMSO d_6) δ 7.80 (t, J = 7.1 Hz, 4H), 7.55-7.43 (m, 5H), 7.36 (t, J = 7.4 Hz, 1H); ^{13}C NMR (101 MHz, DMSO d_6) δ 145.0, 138.2, 129.6, 129.4, 127.2, 126.8,

122.1; HRMS (ESI) m/z Calcd. for $C_{16}H_{12}N_3OS$ ([M+H]$^+$) 294.0696, Found 294.0698.

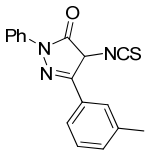
4-isothiocyanato-1-phenyl-3-*p*-tolyl-1*H*-pyrazol-5-ol (**1b**)



1b

Prepared according to the general procedure as off-white solid (purified by recrystallization, 0.86 g, 70% yield). mp 231.0-234.4 °C; ^{1}H NMR (400 MHz, DMSO d_6) δ 7.78 (d, J = 7.8 Hz, 2H), 7.69 (d, J = 8.0 Hz, 2H), 7.51 (t, J = 7.8 Hz, 2H), 7.34 (t, J = 8.7 Hz, 3H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, DMSO d_6) δ 145.0, 139.4, 138.1, 123.0, 129.6, 127.1, 126.7, 121.9, 21.4; HRMS (ESI) m/z Calcd. for $C_{17}H_{14}N_3OS$ ([M+H]$^+$) 308.0852, Found 308.0858.

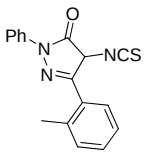
4-isothiocyanato-1-phenyl-3-*m*-tolyl-1*H*-pyrazol-5-ol (**1c**)



1c

Prepared according to the general procedure as white solid (purified by recrystallization, 0.83 g, 67% yield). mp 205.6-208.4 °C; ^{1}H NMR (400 MHz, DMSO d_6) δ 7.82-7.70 (m, 2H), 7.63 (s, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.55-7.49 (m, 2H), 7.41 (t, J = 7.7 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.28 (d, J = 7.7 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (101 MHz, DMSO d_6) δ 145.2, 138.6, 138.2, 130.3, 129.6, 129.3, 127.3, 127.2, 123.9, 122.0, 21.6; HRMS (ESI) m/z Calcd. for $C_{17}H_{14}N_3OS$ ([M+H]$^+$) 308.0852, Found 308.0857.

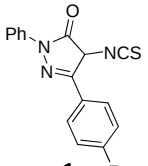
4-isothiocyanato-1-phenyl-3-*o*-tolyl-1*H*-pyrazol-5-ol (**1d**)



1d

Prepared according to the general procedure as white solid (purified by recrystallization, 0.49 g, 40% yield). mp 188.0-190.4 °C; ^{1}H NMR (400 MHz, DMSO d_6) δ 7.78 (d, J = 7.8 Hz, 2H), 7.52 (t, J = 7.9 Hz, 2H), 7.45 (d, J = 7.4 Hz, 1H), 7.41-7.30 (m, 4H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, DMSO d_6) δ 147.0, 138.2, 137.1, 131.2, 130.1, 129.7, 129.6, 127.1, 126.4, 121.9, 20.3; HRMS (ESI) m/z Calcd. for $C_{17}H_{14}N_3OS$ ([M+H]$^+$) 308.0852, Found 308.0857.

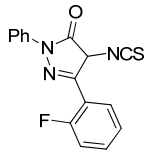
3-(4-fluorophenyl)-4-isothiocyanato-1-phenyl-1*H*-pyrazol-5-ol (**1e**)



1e

Prepared according to the general procedure as off-white solid (purified by recrystallization, 0.69 g, 55% yield). mp 208.4-210.5 °C; ^{1}H NMR (400 MHz, DMSO d_6) δ 7.88-7.75 (m, 4H), 7.52 (t, J = 8.0 Hz, 2H), 7.41-7.32 (m, 3H); ^{19}F NMR (377 MHz, DMSO d_6) δ -125.37; ^{13}C NMR (101 MHz, DMSO d_6) δ 162.9 (d, J = 247.3 Hz), 144.1, 138.1, 129.6, 128.9 (d, J = 8.5 Hz), 127.3, 122.1, 116.4 (d, J = 21.7 Hz); HRMS (ESI) m/z Calcd. for $C_{16}H_{11}FN_3OS$ ([M+H]$^+$) 312.0601, Found 312.0607.

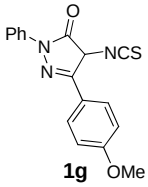
3-(2-fluorophenyl)-4-isothiocyanato-1-phenyl-1*H*-pyrazol-5-ol (**1f**)



1f

Prepared according to the general procedure as off-white solid (purified by column chromatography, 0.49 g, 40% yield). mp 170.6-172.7 °C; ^{1}H NMR (400 MHz, DMSO d_6) δ 7.78 (d, J = 8.0 Hz, 2H), 7.69 (t, J = 7.5 Hz, 1H), 7.57-7.48 (m, 3H), 7.34-7.33 (m, 3H); ^{19}F NMR (377 MHz, DMSO d_6) δ -114.81; ^{13}C NMR (101 MHz, DMSO d_6) δ 159.9 (d, J = 249.6 Hz), 149.8, 142.3, 138.2, 134.3, 132.0 (d, J = 7.7 Hz), 131.0 (d, J = 2.9 Hz), 129.6, 127.4, 125.4, 122.3, 119.0, 116.6 (d, J = 21.7 Hz); HRMS (ESI) m/z Calcd. for $C_{16}H_{11}FN_3OS$ ([M+H]$^+$) 312.0601, Found 312.0606.

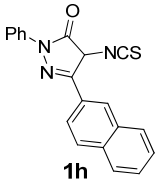
4-isothiocyanato-3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-5-ol (**1g**)



1g

Prepared according to the general procedure as grey solid (purified by recrystallization, 0.91 g, 70% yield). mp 213.0-216.4 °C; ^{1}H NMR (400 MHz, DMSO d_6) δ 7.82-7.71 (m, 4H), 7.51 (t, J = 7.8 Hz, 2H), 7.34 (t, J = 7.3 Hz, 1H), 7.10 (d, J = 8.7 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (101 MHz, DMSO d_6) δ 160.6, 144.6, 138.0, 129.6, 128.3, 127.0, 121.7, 114.9, 55.8; HRMS (ESI) m/z Calcd. for $C_{17}H_{14}N_3O_2S$ ([M+H]$^+$) 324.0801, Found 324.0803.

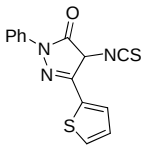
4-isothiocyanato-3-(naphthalen-2-yl)-1-phenyl-1*H*-pyrazol-5-ol (**1h**)



1h

Prepared according to the general procedure as grey solid (purified by recrystallization, 0.96 g, 70% yield). mp 230.5-232.7 °C; ^{1}H NMR (400 MHz, DMSO d_6) δ 8.33 (s, 1H), 8.06 (d, J = 8.7 Hz, 1H), 8.01-7.94 (m, 3H), 7.84 (d, J = 7.7 Hz, 2H), 7.61-7.57 (m, 2H), 7.54 (t, J = 7.9 Hz, 2H), 7.38 (t, J = 7.4 Hz, 1H); ^{13}C NMR (101 MHz, DMSO d_6) δ 145.0, 138.2, 133.4, 133.2, 129.6, 129.0, 128.8, 128.5, 128.2, 127.4, 127.3, 126.0, 124.3, 122.1; HRMS (ESI) m/z Calcd. for $C_{20}H_{14}N_3OS$ ([M+H]$^+$) 344.0852, Found 344.0857.

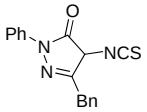
4-isothiocyanato-1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-5-ol (**1i**)



1i

Prepared according to the general procedure as white solid (purified by column chromatography, 0.60 g, 50% yield). mp 207.8-209.9 °C; ^{1}H NMR (400 MHz, DMSO d_6) δ 7.75 (d, J = 7.7 Hz, 2H), 7.72-7.65 (m, 1H), 7.55-7.47 (m, 3H), 7.36 (t, J = 7.4 Hz, 1H), 7.23 (dd, J = 5.0, 3.6 Hz, 1H); ^{13}C NMR (101 MHz, DMSO d_6) δ 150.8, 141.0, 138.1, 133.2, 129.6, 128.5, 127.5, 127.3, 125.8, 122.2, 93.0; HRMS (ESI) m/z Calcd. for $C_{14}H_{10}N_3OS_2$ ([M+H]$^+$) 300.0260, Found 300.0265.

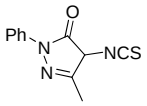
3-benzyl-4-isothiocyanato-1-phenyl-1*H*-pyrazol-5-ol (**1j**)



1j

Prepared according to the general procedure as light yellow solid (purified by recrystallization, 0.63 g, 51% yield). mp 159.5-161.0 °C; ^{1}H NMR (400 MHz, DMSO d_6) δ 7.70 (d, J = 7.8 Hz, 2H), 7.48 (t, J = 7.6 Hz, 2H), 7.38-7.23 (m, 5H), 3.94 (s, 2H); ^{13}C NMR (101 MHz, DMSO d_6) δ 147.7, 138.1, 137.8, 129.5, 129.1, 128.9, 127.1, 126.8, 121.7, 33.0; HRMS (ESI) m/z Calcd. for $C_{17}H_{14}N_3OS$ ([M+H]$^+$) 308.0852, Found 308.0857.

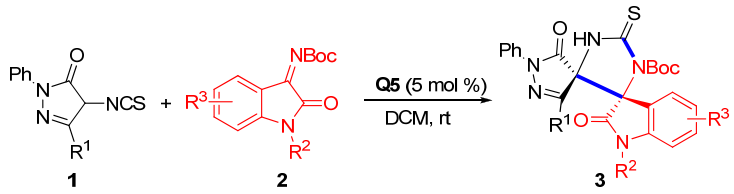
4-isothiocyanato-3-methyl-1-phenyl-1*H*-pyrazol-5-ol (**1k**)



1k

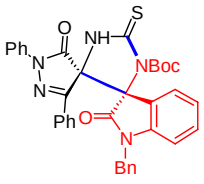
Prepared according to the general procedure as light yellow solid (purified by recrystallization, 0.38 g, 41% yield). mp 201.3-203.7 °C; ^{1}H NMR (400 MHz, DMSO d_6) δ 7.68 (d, J = 7.7 Hz, 2H), 7.47 (t, J = 7.9 Hz, 2H), 7.29 (t, J = 7.4 Hz, 1H), 2.22 (s, 3H); ^{13}C NMR (101 MHz, DMSO d_6) δ 144.7, 137.8, 129.5, 126.5, 121.1, 11.8; HRMS (ESI) m/z Calcd. for $C_{11}H_{10}N_3OS$ ([M+H]$^+$) 232.0539, Found 232.0540.

3. Experimental procedures and characterization of compounds 3-10



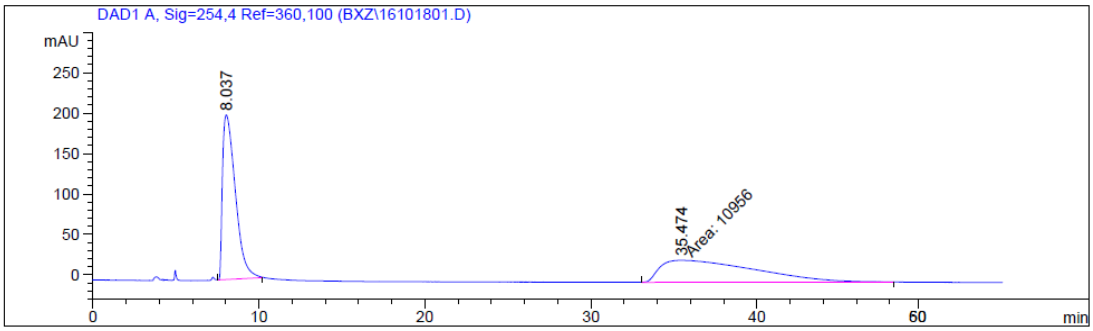
A Schlenk tube equipped with a magnetic stir bar was charged with 4-isothiocyanato pyrazolone **1** (0.2 mmol), **Q5** (0.01 mmol), and DCM (2 mL). After stirring for 5 min, isatin derived ketimine **2** (0.24 mmol) was added in one portion. The reaction was detected by TLC. After 5-24 h, the mixture was purified by column chromatography on silica gel (unless otherwise noticed, petroleum ether/EtOAc = 6:1 was used as the eluent) directly to give the product **3**.

Compound 3aa

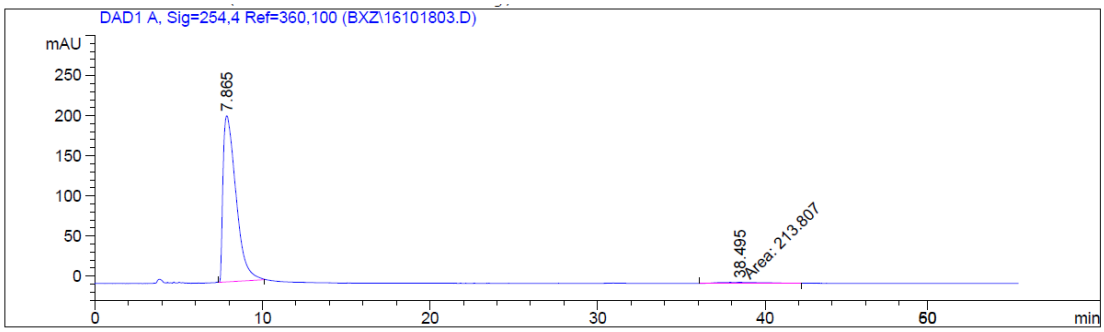


3aa

Prepared according to the procedure within 5 h as off-white solid (120.0 mg, 96% yield, dr > 20:1). mp 171.2-174.6 °C; $[\alpha]_D^{17}$ = -190.3 (c 0.79, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.84-7.72 (m, 2H), 7.36-7.30 (m, 2H), 7.25-7.11 (m, 11H), 6.93 (td, J = 7.8, 1.1 Hz, 1H), 6.87 (d, J = 7.5 Hz, 1H), 6.53 (d, J = 7.8 Hz, 1H), 6.43 (t, J = 7.6 Hz, 1H), 5.28 (d, J = 15.3 Hz, 1H), 4.08 (d, J = 15.3 Hz, 1H), 1.12 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.0, 169.2, 168.7, 153.2, 147.6, 141.6, 136.9, 135.0, 131.5, 130.7, 130.0, 128.9, 128.8, 128.4, 128.0, 127.7, 126.9, 125.9, 125.6, 123.4, 122.5, 119.3, 108.7, 84.9, 74.1, 72.0, 44.6, 27.5; HRMS (ESI) m/z Calcd. for $C_{36}H_{31}N_5NaO_4S$ ([M+Na]$^+$) 652.1989, Found 652.1997; Enantiomeric excess was determined to be 96% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.8 mL/min, t_{major} = 7.9 min, t_{minor} = 38.5 min).

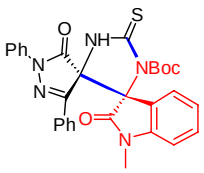


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.037	BB	0.8176	1.09525e4	203.59567	49.9921
2	35.474	MM	6.6658	1.09560e4	27.39341	50.0079



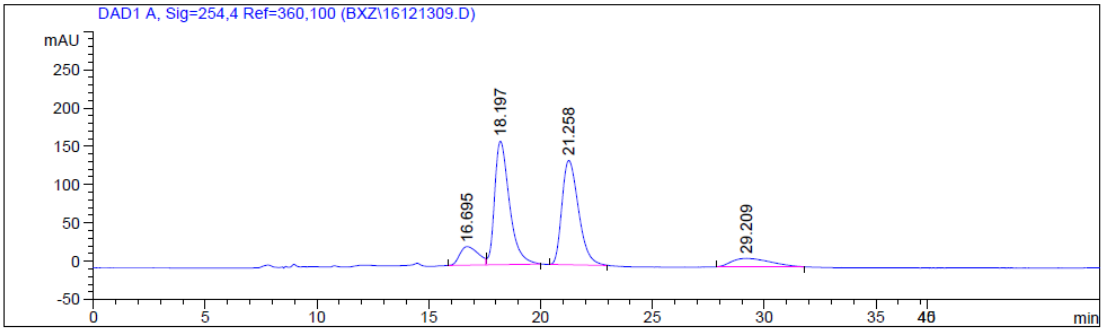
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.865	BB	0.8386	1.11261e4	207.17055	98.1146
2	38.495	MM	3.1260	213.80688	1.13993	1.8854

Compound 3ab

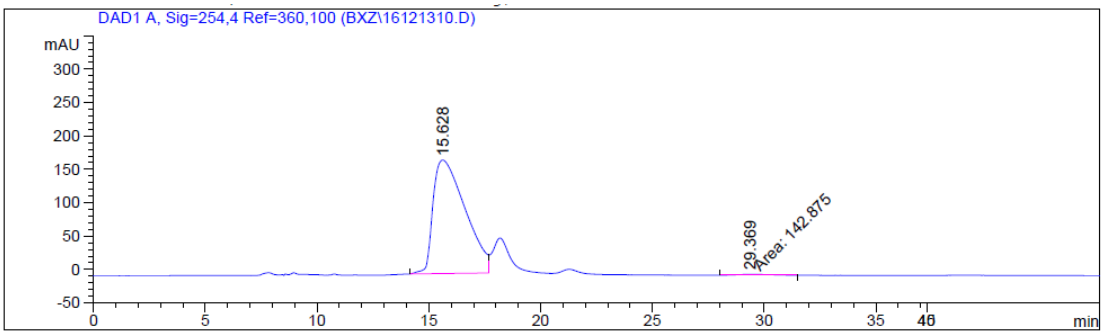


3ab

Prepared according to the procedure within 5 h as white solid (104.6 mg, 94% yield, dr = 10:1). mp 182.3-184.5 °C; $[\alpha]_D^{17}$ = -178.4 (*c* 0.40, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (brs, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 7.2 Hz, 2H), 7.38-7.23 (m, 5H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.06 (t, *J* = 7.7 Hz, 1H), 6.84 (d, *J* = 7.5 Hz, 1H), 6.60 (d, *J* = 7.8 Hz, 1H), 6.49 (t, *J* = 7.6 Hz, 1H), 3.06 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.0, 169.2, 168.6, 153.6, 147.5, 142.5, 136.9, 131.5, 130.9, 130.2, 128.9, 128.6, 126.9, 126.0, 125.5, 123.3, 122.4, 119.6, 107.8, 84.7, 74.4, 72.0, 27.4, 26.8; HRMS (ESI) m/z Calcd. for $C_{30}H_{27}N_5NaO_4S$ ($[M+Na]^+$) 576.1676, Found 576.1683; Enantiomeric excess was determined to be 98% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.4 mL/min, t_{major} = 15.6 min, t_{minor} = 29.4 min).

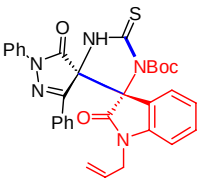


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.695	BV	0.6840	1392.92456	24.25619	8.0933
2	18.197	VB	0.6955	7453.23291	161.17281	43.3055
3	21.258	BB	0.7968	7038.64600	136.23125	40.8966
4	29.209	BB	1.4063	1326.01465	11.06386	7.7045



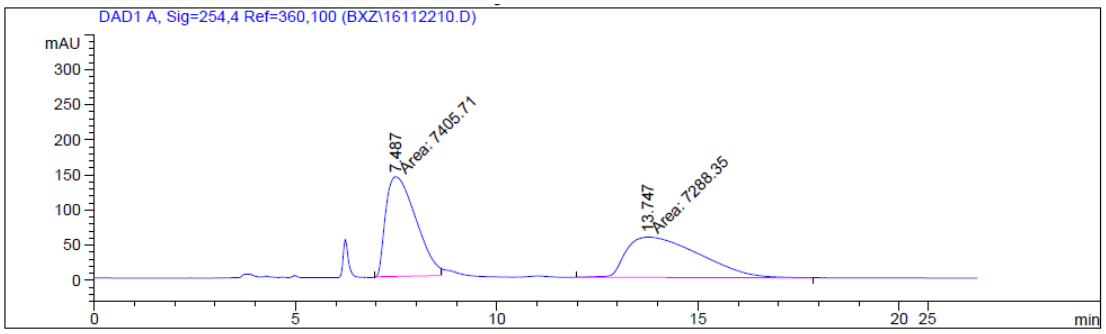
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.628	BV	1.1883	1.70077e4	169.83354	99.1669
2	29.369	MM	1.6663	142.87515	1.42907	0.8331

Compound 3ac

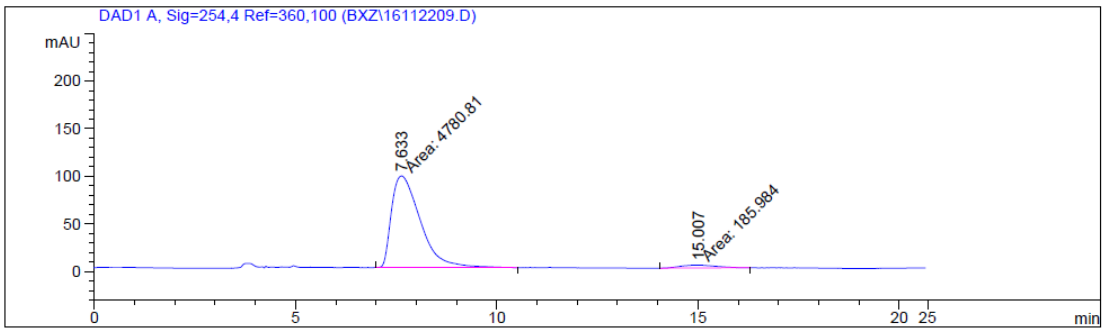


3ac

Prepared according to the procedure within 5 h as white solid (107.6 mg, 93% yield, dr > 20:1). mp 153.2-155.6 °C; $[\alpha]_D^{18}$ = -158.6 (*c* 0.88, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (brs, 1H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 7.2 Hz, 2H), 7.34-7.23 (m, 5H), 7.15 (t, *J* = 7.3 Hz, 1H), 7.00 (t, *J* = 7.8 Hz, 1H), 6.84 (d, *J* = 7.4 Hz, 1H), 6.59 (d, *J* = 7.9 Hz, 1H), 6.44 (t, *J* = 7.6 Hz, 1H), 5.69-5.57 (m, 1H), 5.19 (d, *J* = 17.2 Hz, 1H), 5.08 (d, *J* = 10.3 Hz, 1H), 4.63-4.49 (m, 1H), 3.66 (dd, *J* = 16.1, 6.0 Hz, 1H), 1.07 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.9, 168.9, 168.8, 153.7, 147.5, 141.7, 137.0, 131.6, 130.7, 130.6, 130.1, 128.8, 128.5, 126.9, 125.8, 125.5, 123.4, 122.3, 119.4, 118.2, 108.5, 84.8, 74.2, 72.3, 42.9, 27.4; HRMS (ESI) m/z Calcd. for $C_{32}H_{29}N_5NaO_4S$ ($[M+Na]^+$) 602.1832, Found 602.1828; Enantiomeric excess was determined to be 93% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.8 mL/min, t_{major} = 7.6 min, t_{minor} = 15.0 min).

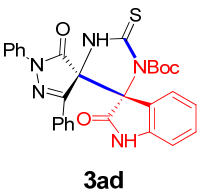


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.487	MM	0.8690	7405.71191	142.03740	50.3994
2	13.747	MM	2.1124	7288.34863	57.50378	49.6006



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.633	MM	0.8286	4780.80859	96.16181	96.2555
2	15.007	MM	1.0258	185.98378	3.02163	3.7445

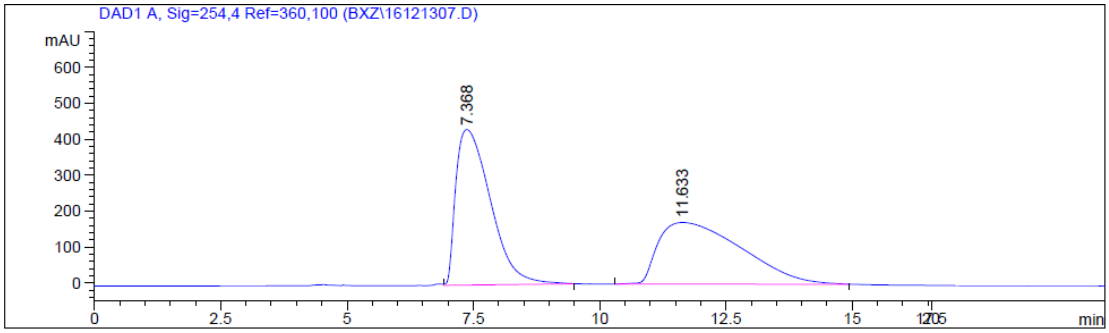
Compound 3ad



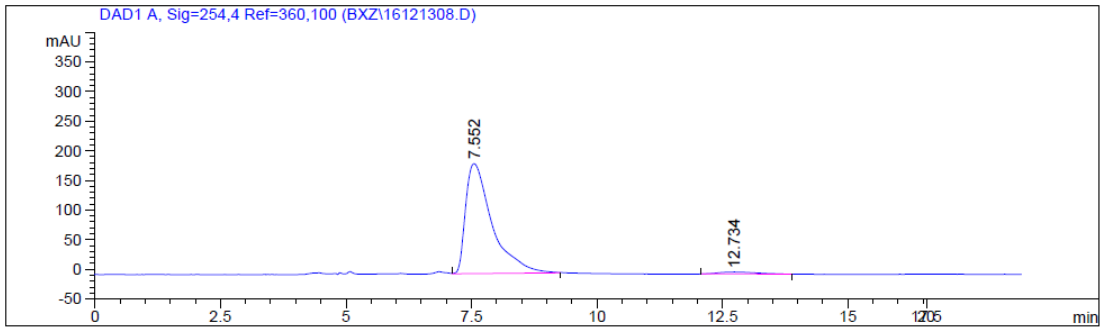
3ad

Prepared according to the procedure within 24 h as white solid (petroleum ether/EtOAc = 4:1, 97.0 mg, 90% yield, dr > 20:1). mp 197.5-199.9 °C; $[\alpha]_D^{18}$ = -147.8 (*c* 0.60, CH_2Cl_2); ^1H NMR (400 MHz,

acetone d_6) δ 9.73 (s, 1H), 9.00 (brs, 1H), 7.83-7.73 (m, 2H), 7.59-7.52 (m, 2H), 7.47 -7.37 (m, 3H), 7.33 (t, J = 7.3 Hz, 2H), 7.25 (t, J = 7.4 Hz, 1H), 7.06 (td, J = 7.8, 1.1 Hz, 1H), 6.81 (d, J = 3.0 Hz, 1H), 6.80 (d, J = 2.8 Hz, 1H), 6.53-6.46 (m, 1H), 1.21 (s, 9H); ^{13}C NMR (101 MHz, acetone d_6) δ 182.8, 170.3, 168.6, 153.8, 147.7, 141.2, 137.5, 132.1, 130.7, 130.1, 128.9, 128.4, 126.8, 125.6, 125.3, 124.3, 121.6, 118.9, 109.9, 84.1, 74.4, 72.0, 26.78; HRMS (ESI) m/z Calcd. for $C_{29}H_{25}N_5NaO_4S$ ([M+Na]$^+$) 562.1519, Found 562.1521; Enantiomeric excess was determined to be 94% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.7 mL/min, t_{major} = 7.6 min, t_{minor} = 12.7 min).

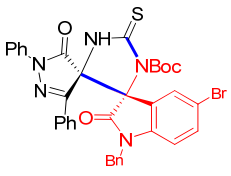


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.368	VB	0.7668	2.06864e4	433.45871	51.1780
2	11.633	BB	1.5554	1.97341e4	171.63237	48.8220



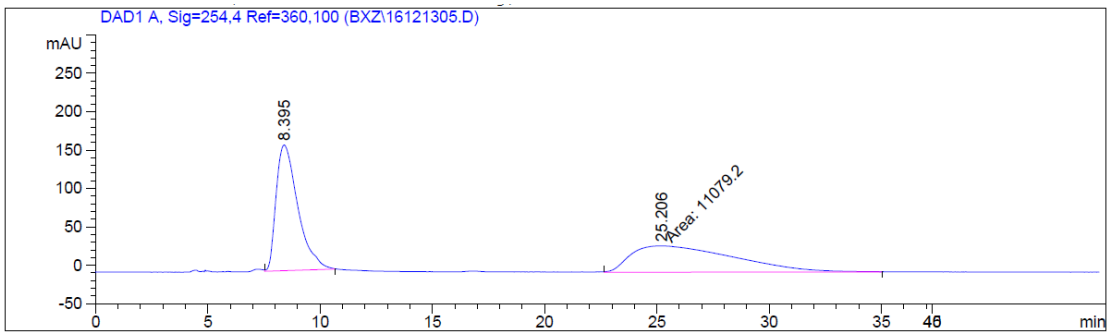
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.552	VB	0.5465	6821.73145	185.74582	97.3837
2	12.734	BB	0.6382	183.26932	3.40365	2.6163

Compound 3ae

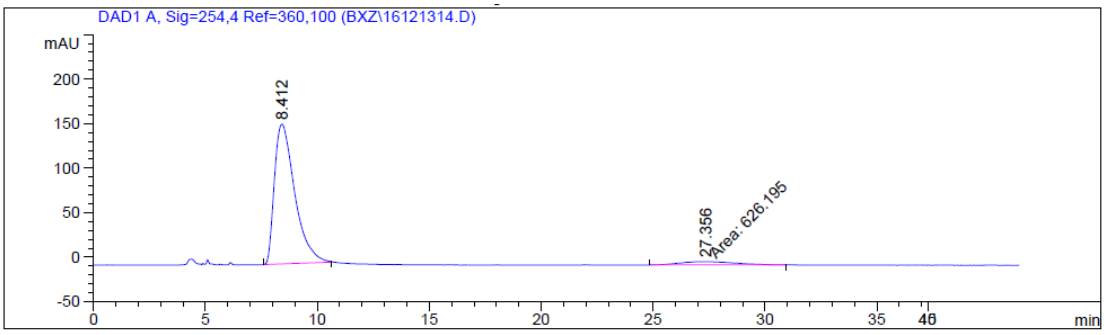


3ae

Prepared according to the procedure within 5 h as white solid (131.5 mg, 93% yield, dr > 20:1). mp 172.8-176.0 °C; $[\alpha]_D^{18}$ = -224.1 (c 0.72, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.77 (d, J = 8.0 Hz, 2H), 7.36-7.27 (m, 3H), 7.25-7.13 (m, 10H), 7.03-6.97 (m, 2H), 6.40 (d, J = 8.4 Hz, 1H), 5.25 (d, J = 15.2 Hz, 1H), 4.08 (d, J = 15.3 Hz, 1H), 1.19 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.7, 168.6, 168.5, 152.7, 147.5, 140.5, 136.8, 134.6, 133.5, 131.0, 130.5, 129.0, 128.9, 128.5, 128.2, 127.7, 126.7, 126.0, 125.2, 119.3, 115.5, 110.2, 85.4, 73.5, 71.8, 44.7, 27.6; HRMS (ESI) m/z Calcd. for $C_{36}H_{30}BrN_5NaO_4S$ ([M+Na]$^+$) 730.1094, Found 730.1101; Enantiomeric excess was determined to be 88% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.7 mL/min, t_{major} = 8.4 min, t_{minor} = 27.4 min).

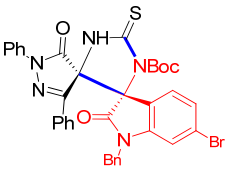


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.395	VB	0.9964	1.10370e4	163.74792	49.9046
2	25.206	MM	5.3677	1.10792e4	34.40055	50.0954



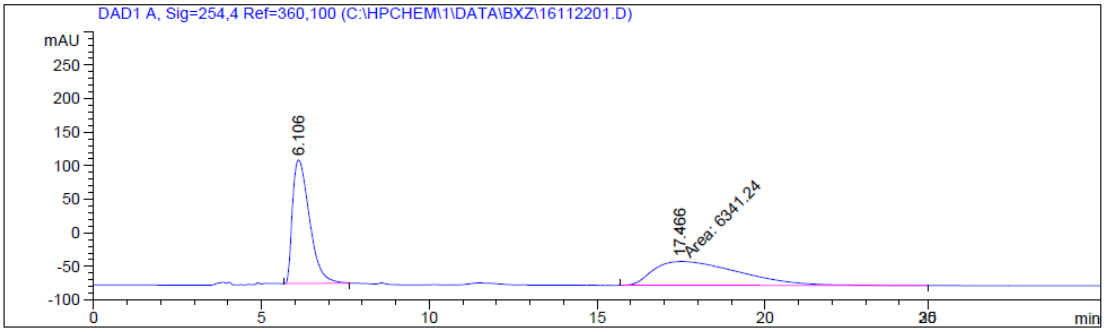
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.412	PB	0.9721	9907.38281	157.01772	94.0552
2	27.356	MM	2.8341	626.19513	3.68247	5.9448

Compound 3af

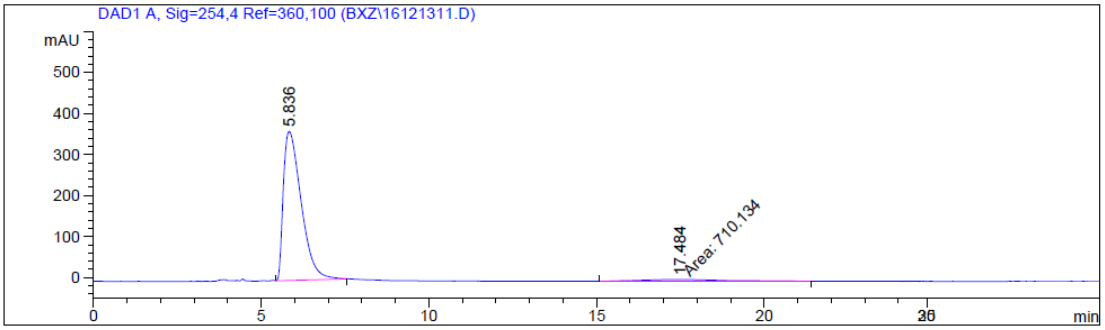


3af

Prepared according to the procedure within 5 h as white solid (134.1 mg, 95% yield, dr > 20:1). mp 173.4-177.1 °C; $[\alpha]_D^{18}$ = -164.6 (*c* 0.72, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.74 (d, *J* = 7.9 Hz, 2H), 7.35-7.28 (m, 3H), 7.22-7.12 (m, 10H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.66 (d, *J* = 1.4 Hz, 1H), 6.50 (dd, *J* = 8.0, 1.3 Hz, 1H), 5.22 (d, *J* = 15.4 Hz, 1H), 4.04 (d, *J* = 15.3 Hz, 1H), 1.17 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.8, 167.0, 168.5, 153.2, 147.5, 142.7, 136.9, 134.4, 131.4, 130.1, 129.0, 128.5, 128.2, 127.6, 127.0, 126.7, 126.0, 125.3, 124.5, 122.3, 119.3, 112.0, 85.4, 73.5, 72.1, 44.8, 27.6; HRMS (ESI) m/z Calcd. for $C_{36}H_{30}BrN_5NaO_4S$ ($[M+Na]^+$) 730.1094, Found 730.1085; Enantiomeric excess was determined to be 90% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.8 mL/min, t_{major} = 5.8 min, t_{minor} = 17.5 min).

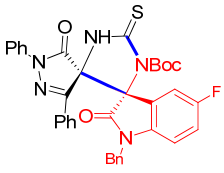


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.106	PB	0.5524	6482.09521	184.26427	50.5492
2	17.466	MM	2.9675	6341.23828	35.61535	49.4508



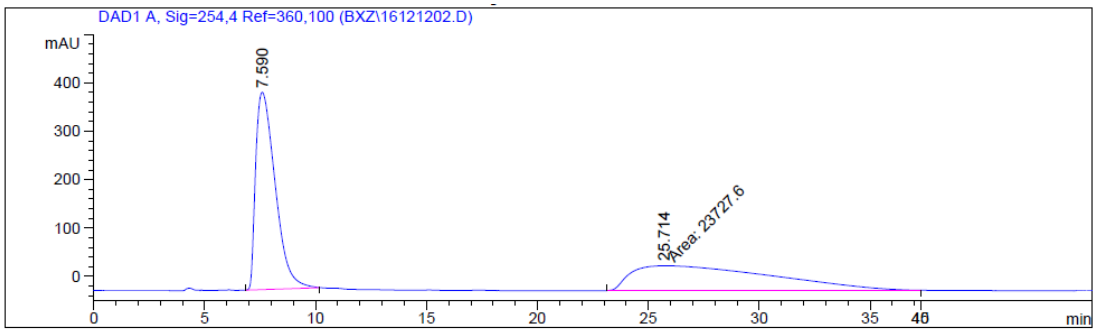
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.836	VB	0.5672	1.34190e4	363.10400	94.9740
2	17.484	MM	2.6991	710.13361	4.38492	5.0260

Compound 3ag

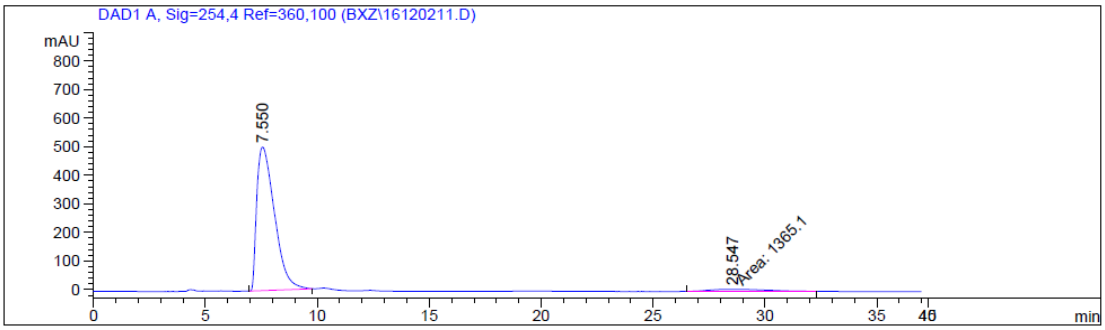


3ag

Prepared according to the procedure within 5 h as white solid (117.5 mg, 91% yield, dr > 20:1). mp 173.1-175.5 °C; $[\alpha]_D^{15}$ = -191.3 (*c* 1.03, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.32 (t, *J* = 7.8 Hz, 2H), 7.26-7.12 (m, 11H), 6.66-6.58 (m, 2H), 6.46 (dd, *J* = 8.2, 3.8 Hz, 1H), 5.24 (d, *J* = 15.3 Hz, 1H), 4.06 (d, *J* = 15.3 Hz, 1H), 1.16 (s, 9H); ^{19}F NMR (377 MHz, $CDCl_3$) δ -119.48; ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.8, 168.9, 168.6, 158.3 (d, *J* = 244.9 Hz), 152.9, 147.5, 137.6, 136.9, 134.7, 131.3, 130.3, 128.9, 128.4, 128.1, 127.7, 126.9, 125.9, 125.0 (d, *J* = 8.1 Hz), 119.3, 117.1 (d, *J* = 23.6 Hz), 113.9 (d, *J* = 25.8 Hz), 109.7 (d, *J* = 7.7 Hz), 85.3, 73.7, 71.9, 44.8, 27.5; HRMS (ESI) m/z Calcd. for $C_{36}H_{30}FN_5NaO_4S$ ($[M+Na]^+$) 670.1895, Found 670.1886; Enantiomeric excess was determined to be 91% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.7 mL/min, t_{major} = 7.6 min, t_{minor} = 28.5 min).

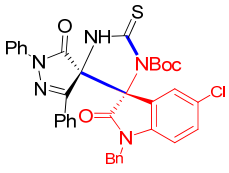


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.590	PB	0.9350	2.49422e4	408.14102	51.2478
2	25.714	MM	7.5669	2.37276e4	52.26214	48.7522



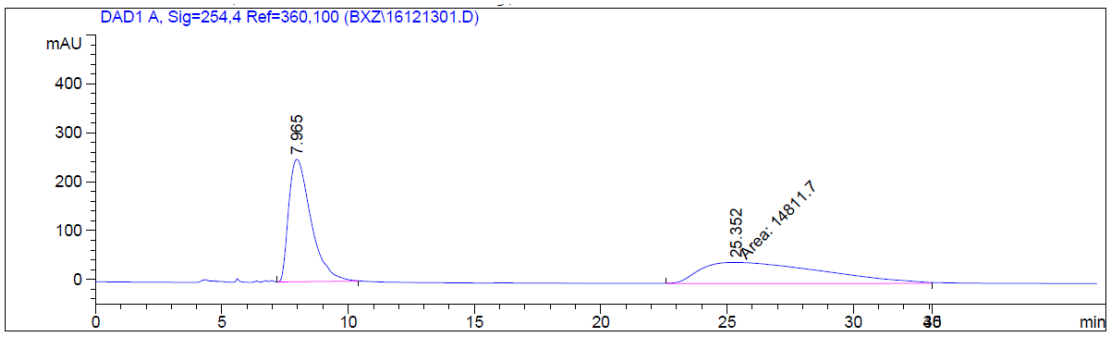
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.550	PB	0.8501	2.76379e4	502.17505	95.2932
2	28.547	MM	2.9422	1365.10156	7.73290	4.7068

Compound 3ah

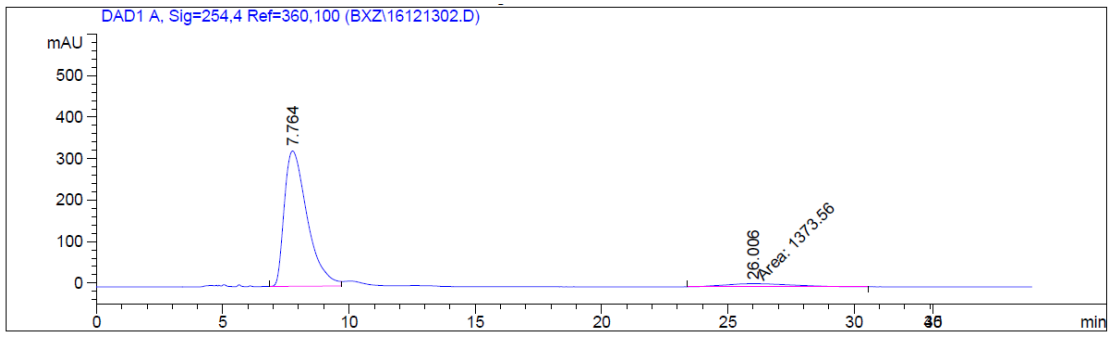


3ah

Prepared according to the procedure within 5 h as white solid (123.0 mg, 92% yield, dr > 20:1). mp 175.4-178.4 °C; $[\alpha]_D^{15}$ = -236.6 (*c* 1.13, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.32 (t, *J* = 7.8 Hz, 2H), 7.25-7.11 (m, 11H), 6.86 (d, *J* = 7.3 Hz, 2H), 6.46 (d, *J* = 9.0 Hz, 1H), 5.23 (d, *J* = 15.3 Hz, 1H), 4.07 (d, *J* = 15.2 Hz, 1H), 1.16 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.8, 168.6, 152.8, 147.5, 140.1, 136.8, 134.6, 131.1, 130.6, 130.4, 128.9, 128.9, 128.4, 128.2, 127.7, 126.8, 126.3, 126.0, 124.9, 119.3, 109.8, 85.4, 73.5, 71.9, 44.7, 27.6; HRMS (ESI) m/z Calcd. for $C_{36}H_{30}ClN_5NaO_4S$ ($[M+Na]^+$) 686.1599, Found 686.1594; Enantiomeric excess was determined to be 88% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.7 mL/min, t_{major} = 7.8 min, t_{minor} = 26.0 min).

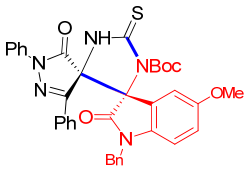


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.965	VB	0.9301	1.53764e4	250.52432	50.9354
2	25.352	MM	5.6687	1.48117e4	43.54807	49.0646



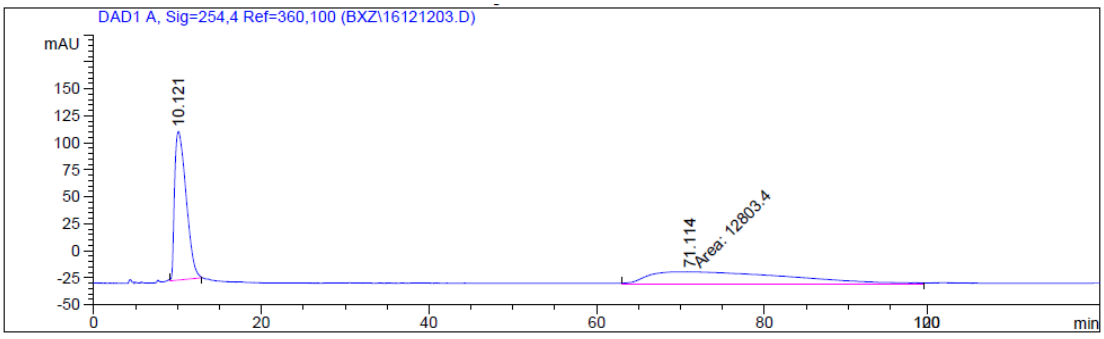
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.764	BB	0.9443	2.06554e4	326.40100	93.7647
2	26.006	MM	3.1289	1373.56360	7.31649	6.2353

Compound 3ai

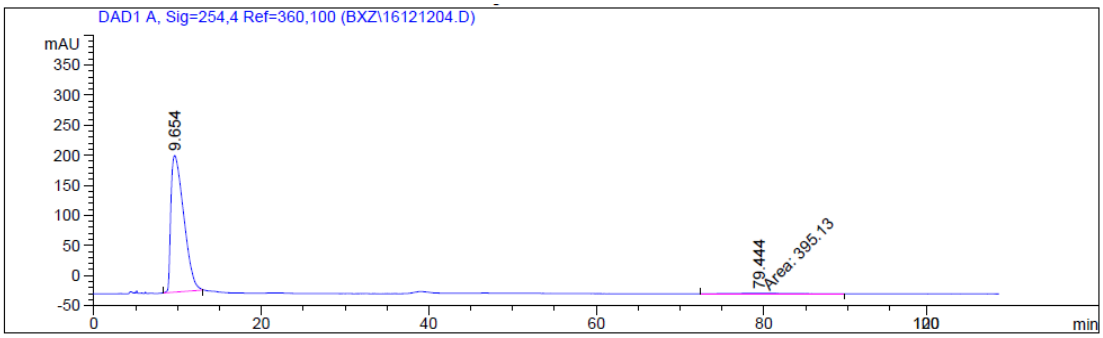


3ai

Prepared according to the procedure within 5 h as white solid (125.0 mg, 95% yield, dr > 20:1). mp 168.4-170.9 °C; $[\alpha]_D^{18}$ = -225.1 (*c* 1.20, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.24-7.12 (m, 11H), 6.45 (d, *J* = 12.3 Hz, 2H), 6.44 (s, 1H), 5.24 (d, *J* = 15.1 Hz, 1H), 4.02 (d, *J* = 15.2 Hz, 1H), 3.44 (s, 3H), 1.13 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.2, 168.9, 155.4, 153.3, 147.5, 136.9, 135.1, 134.8, 131.5, 129.8, 128.9, 128.8, 128.3, 128.0, 127.8, 127.0, 125.9, 124.5, 119.4, 116.1, 111.6, 109.6, 84.9, 74.2, 72.2, 55.4, 44.7, 27.5; HRMS (ESI) m/z Calcd. for $C_{37}H_{33}N_5NaO_5S$ ([M+Na]$^+$) 682.2095, Found 682.2089; Enantiomeric excess was determined to be 97% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.7 mL/min, t_{major} = 9.7 min, t_{minor} = 79.4 min).

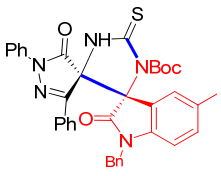


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.121	BB	1.3092	1.31379e4	137.69460	50.6447
2	71.114	MM	19.2830	1.28034e4	11.06621	49.3553



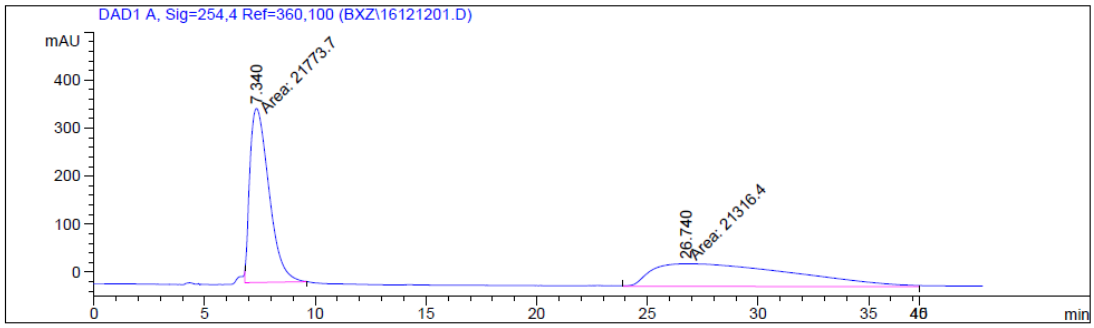
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.654	BB	1.4593	2.41756e4	227.22186	98.3919
2	79.444	MM	8.0720	395.13025	8.15846e-1	1.6081

Compound 3aj

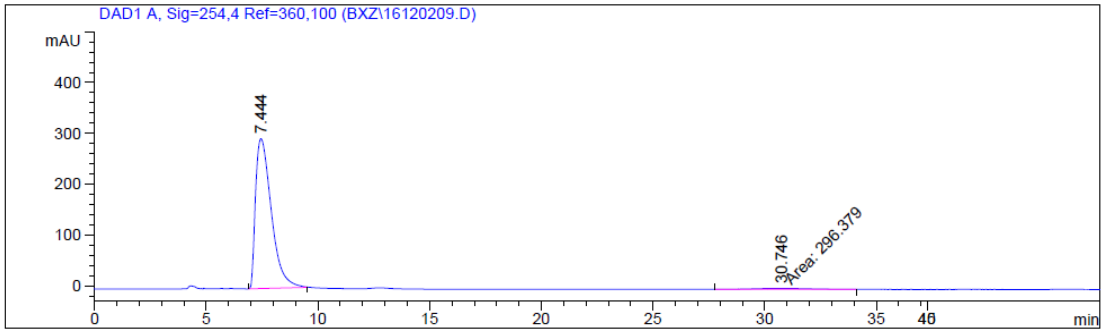


3aj

Prepared according to the procedure within 5 h as white solid (124.5 mg, 97% yield, dr > 20:1). mp 167.1-170.4 °C; $[\alpha]_D^{19}$ = -239.7 (*c* 1.20, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.86-7.71 (m, 2H), 7.34-7.28 (m, 2H), 7.22-7.10 (m, 11H), 6.68 (d, *J* = 6.4 Hz, 1H), 6.67 (s, 1H), 6.42 (d, *J* = 8.4 Hz, 1H), 5.24 (d, *J* = 15.3 Hz, 1H), 4.04 (d, *J* = 15.3 Hz, 1H), 1.84 (s, 3H), 1.12 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.2, 169.1, 168.9, 153.3, 147.6, 139.0, 136.9, 135.1, 132.3, 131.5, 130.9, 129.8, 128.9, 128.8, 128.1, 127.9, 127.7, 126.9, 126.6, 125.8, 123.4, 119.4, 108.5, 84.8, 73.9, 72.2, 44.6, 27.5, 20.5; HRMS (ESI) m/z Calcd. for $C_{37}H_{33}N_5NaO_4S$ ($[M+Na]^+$) 666.2145, Found 666.2130; Enantiomeric excess was determined to be 96% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.7 mL/min, t_{major} = 7.4 min, t_{minor} = 30.7 min).

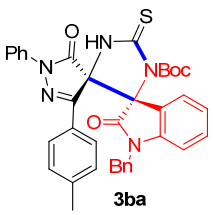


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.340	MM	1.0008	2.17737e4	362.59988	50.5307
2	26.740	MM	7.4917	2.13164e4	47.42223	49.4693



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.444	PB	0.7674	1.44442e4	294.92801	97.9894
2	30.746	MM	2.7502	296.37943	1.79613	2.0106

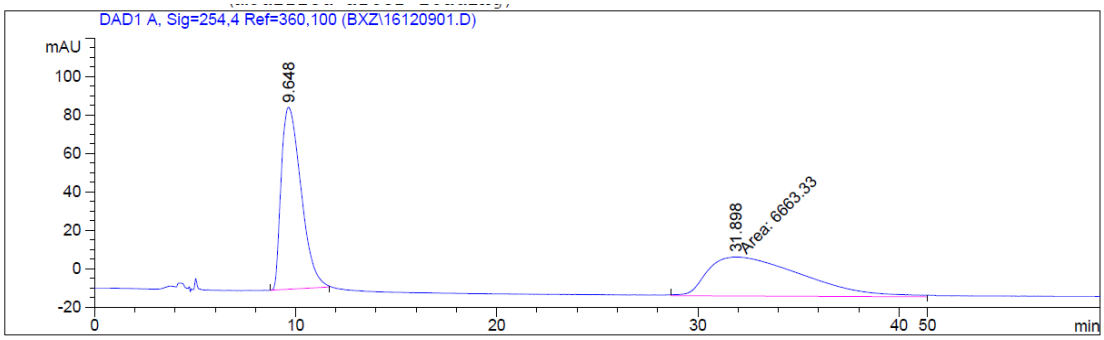
Compound 3ba



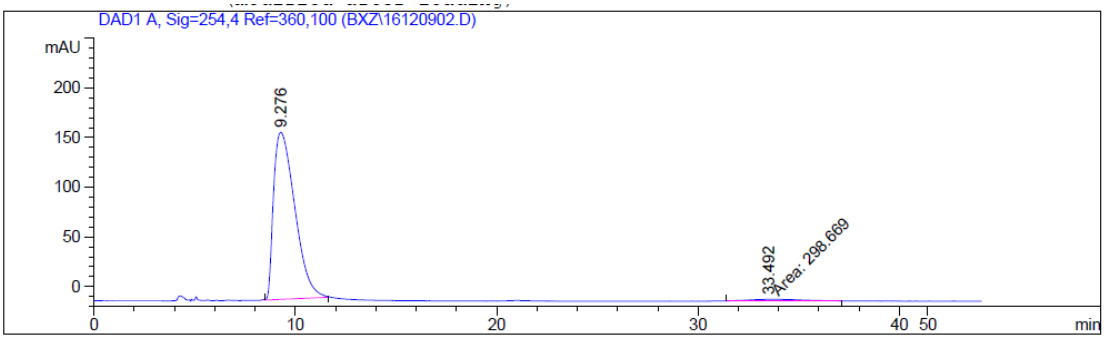
3ba

Prepared according to the procedure within 5 h as light yellow solid (122.1 mg, 95% yield, dr > 20:1). mp 170.6-173.3 °C; $[\alpha]_D^{16}$ = -132.1 (*c* 1.10, CH_2Cl_2); ***ent*-3ba** was prepared according to the procedure with quinine **Q2** as the catalyst within 24 h (115.8 mg, 90% yield, dr > 20:1, 93% ee);

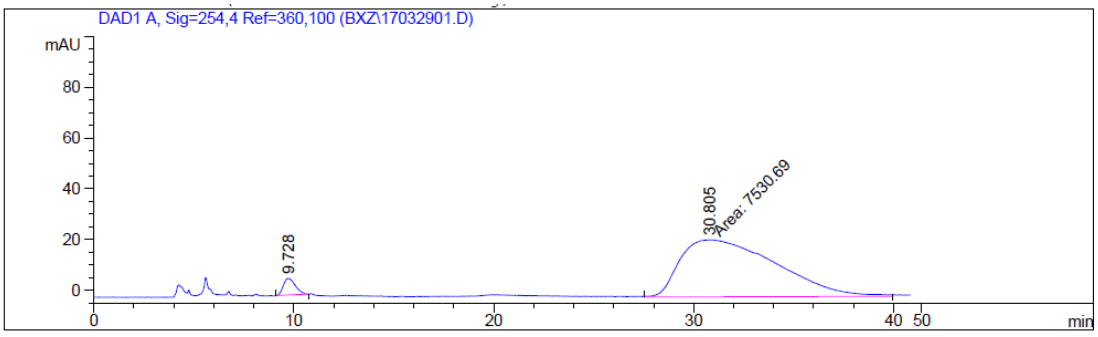
mp 173.8-176.4 °C; $[\alpha]_D^{19}$ = +131.0 (*c* 0.46, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.29 (t, *J* = 7.9 Hz, 2H), 7.22-7.09 (m, 8H), 6.98-6.92 (m, 3H), 6.86 (d, *J* = 7.4 Hz, 1H), 6.51 (d, *J* = 7.9 Hz, 1H), 6.46 (t, *J* = 7.6 Hz, 1H), 5.23 (d, *J* = 15.3 Hz, 1H), 4.07 (d, *J* = 15.2 Hz, 1H), 2.26 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.0, 169.4, 168.4, 153.5, 147.6, 141.8, 140.4, 137.1, 134.9, 130.6, 129.1, 128.8, 128.7, 127.9, 127.7, 127.0, 125.7, 123.3, 122.4, 119.2, 108.7, 84.8, 74.2, 72.0, 44.6, 27.4, 21.4; HRMS (ESI) m/z Calcd. for $C_{37}H_{33}N_5NaO_4S$ ($[M+Na]^+$) 666.2145, Found 666.2140; Enantiomeric excess was determined to be 95% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.7 mL/min, t_{major} = 9.3 min, t_{minor} = 33.5 min). For ***ent*-3ba**, enantiomeric excess was determined to be 93% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.7 mL/min, t_{major} = 30.8 min, t_{minor} = 9.7 min).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.648	PB	0.9911	6496.43359	94.60829	49.3659
2	31.898	MM	5.4808	6663.33057	20.26255	50.6341

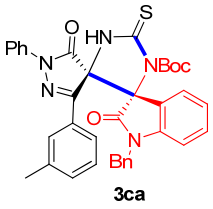


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.276	BB	1.0446	1.23226e4	168.22624	97.6336
2	33.492	MM	2.9375	298.66949	1.69460	2.3664



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.728	BP	0.4969	271.84299	6.56785	3.4840
2	30.805	MM	5.5825	7530.69287	22.48298	96.5160

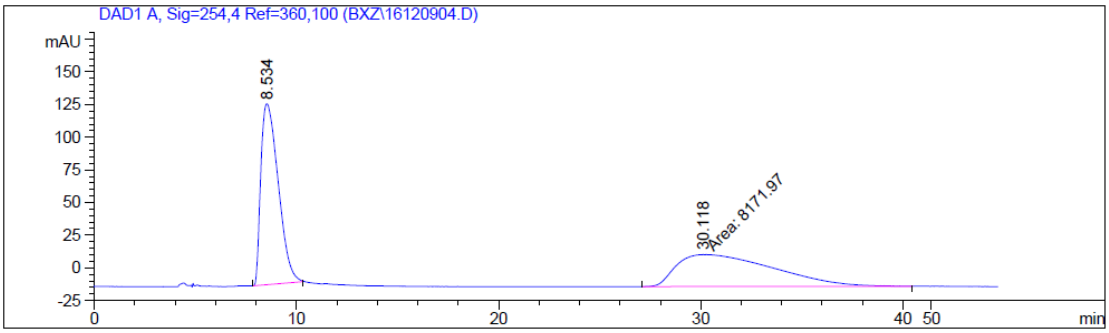
Compound 3ca



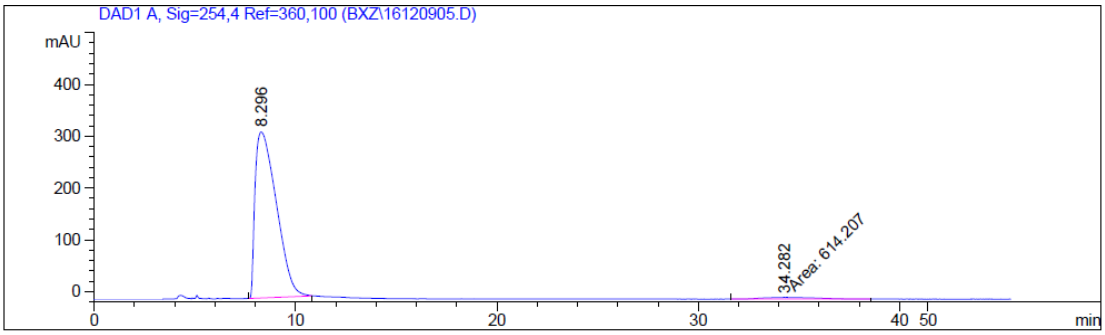
3ca

Prepared according to the procedure within 5 h as white solid (120.9 mg, 94% yield, dr > 20:1). mp 171.8-174.6 °C; $[\alpha]_D^{16}$ = -179.8 (*c* 1.20, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.31 (t, *J* = 7.9 Hz, 2H), 7.22-7.12 (m, 7H), 7.07 (t, *J* = 7.7 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 6.92 (t, *J* = 7.8 Hz, 1H), 6.85 (d, *J* = 7.5 Hz, 1H), 6.70 (s, 1H), 6.55 (d, *J* = 7.9 Hz,

1H), 6.41 (t, J = 7.7 Hz, 1H), 5.26 (d, J = 15.2 Hz, 1H), 4.06 (d, J = 15.1 Hz, 1H), 2.10 (s, 3H), 1.11 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.1, 169.1, 168.7, 153.4, 147.6, 141.6, 137.9, 137.0, 135.0, 131.3, 130.7, 130.5, 128.9, 128.8, 128.3, 128.0, 127.5, 125.8, 125.5, 124.4, 123.3, 122.4, 119.3, 108.5, 84.8, 74.0, 72.1, 44.5, 27.4, 21.1; HRMS (ESI) m/z Calcd. for $C_{37}H_{33}N_5NaO_4S$ ([M+Na]$^+$) 666.2145, Found 666.2124; Enantiomeric excess was determined to be 95% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.7 mL/min, t_{major} = 8.3 min, t_{minor} = 34.3 min).

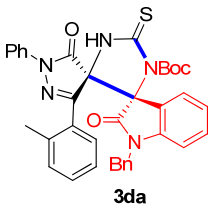


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.534	PB	0.9102	8290.27637	138.53622	50.3593
2	30.118	MM	5.5473	8171.97363	24.55253	49.6407



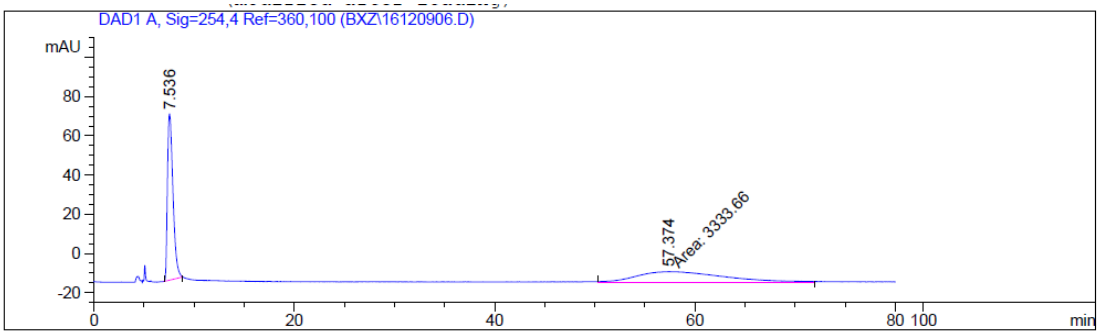
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.296	PB	1.0908	2.35018e4	320.74686	97.4531
2	34.282	MM	3.1618	614.20734	3.23761	2.5469

Compound 3da

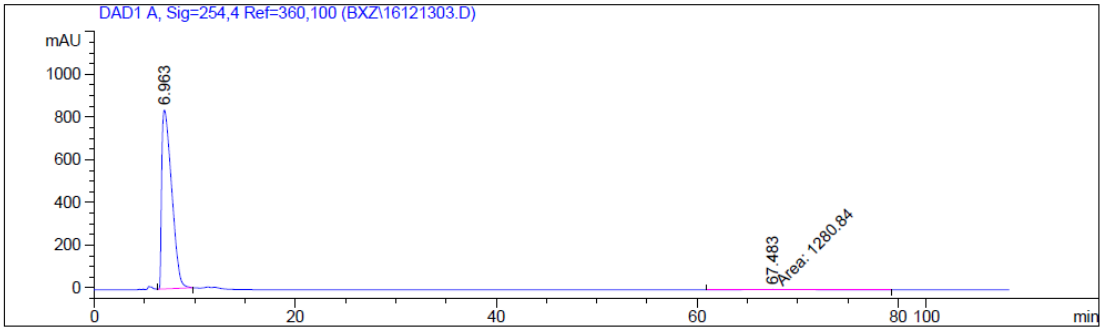


3da

Prepared according to the procedure within 24 h as white solid (60.1 mg, 47% yield, dr > 20:1 after recrystallization by ether/hexane). mp 166.0-169.7 °C; $[\alpha]_D^{16}$ = -270.7 (c 0.36, CH_2Cl_2); ^{1}H NMR (400 MHz, DMSO d_6) δ 10.32 (brs, 1H), 7.78 (d, J = 7.9 Hz, 2H), 7.58 (t, J = 7.9 Hz, 2H), 7.48 (d, J = 7.5 Hz, 1H), 7.34 (t, J = 7.3 Hz, 1H), 7.29 (d, J = 7.4 Hz, 2H), 7.16 (t, J = 7.4 Hz, 2H), 7.12-7.03 (m, 3H), 6.94 (t, J = 7.7 Hz, 2H), 6.76 (d, J = 7.5 Hz, 1H), 6.50 (d, J = 7.4 Hz, 1H), 6.36-6.27 (m, 1H), 5.16 (d, J = 14.8 Hz, 1H), 4.41 (d, J = 14.8 Hz, 1H), 1.15 (s, 3H), 1.11 (s, 9H); ^{13}C NMR (101 MHz, DMSO d_6) δ 182.1, 169.3, 168.5, 152.1, 147.7, 141.6, 137.3, 136.2, 136.2, 131.3, 130.8, 130.4, 129.7, 129.1, 128.8, 128.4, 128.2, 126.2, 125.5, 124.2, 123.5, 122.5, 118.9, 109.7, 84.4, 72.8, 72.7, 44.1, 27.5, 19.5; HRMS (ESI) m/z Calcd. for $C_{37}H_{33}N_5NaO_4S$ ([M+Na]$^+$) 666.2145, Found 666.2128; Enantiomeric excess was determined to be 96% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.7 mL/min, t_{major} = 7.0 min, t_{minor} = 67.5 min).

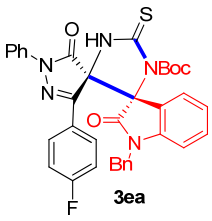


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.536	PB	0.5902	3246.47461	84.89344	49.3375
2	57.374	MM	10.1296	3333.65942	5.48503	50.6625

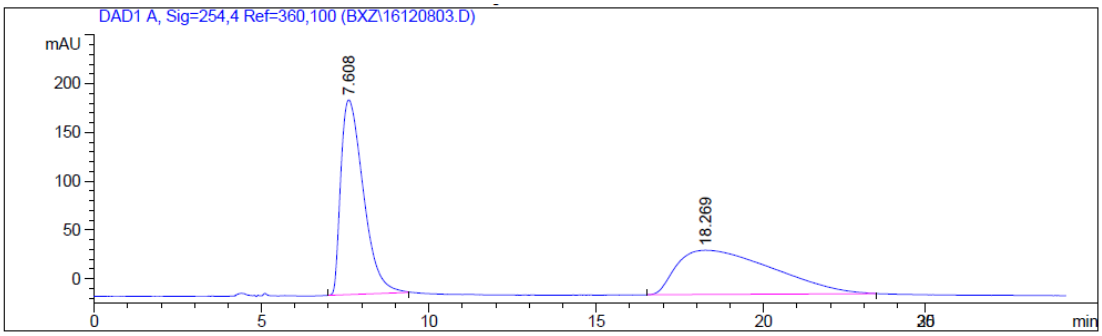


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.963	PB	0.9739	5.75361e4	837.11377	97.8223
2	67.483	MM	8.2598	1280.83826	2.58447	2.1777

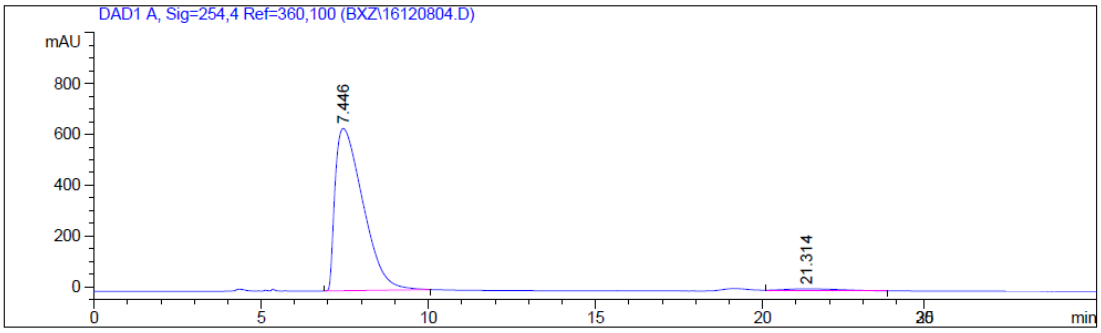
Compound 3ea



Prepared according to the procedure within 5 h as white solid (116.5 mg, 90% yield, dr > 20:1). mp 168.1-170.9 °C; $[\alpha]_D^{16}$ = -176.5 (*c* 1.10, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.33-7.11 (m, 10H), 6.97 (t, *J* = 7.7 Hz, 1H), 6.89 (d, *J* = 7.4 Hz, 1H), 6.83 (t, *J* = 8.6 Hz, 2H), 6.58-6.48 (m, 2H), 5.24 (d, *J* = 15.2 Hz, 1H), 4.06 (d, *J* = 15.2 Hz, 1H), 1.11 (s, 9H); ^{19}F NMR (377 MHz, $CDCl_3$) δ -109.72; ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.2, 169.2, 168.7, 163.6 (d, *J* = 252.6 Hz), 152.4, 147.5, 141.5, 136.8, 134.9, 130.8, 129.3 (d, *J* = 8.5 Hz), 128.9, 128.8, 128.0, 127.8, 126.0, 125.6, 123.4, 122.6, 119.4, 115.5 (d, *J* = 22.1 Hz), 108.8, 85.0, 73.4, 72.1, 44.6, 27.4; HRMS (ESI) m/z Calcd. for $C_{36}H_{30}FN_5NaO_4S$ ($[M+Na]^+$) 670.1895, Found 670.1877; Enantiomeric excess was determined to be 95% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.7 mL/min, t_{major} = 7.4 min, t_{minor} = 21.3 min).

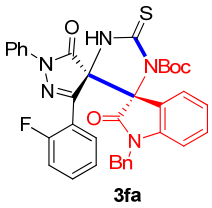


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.608	BB	0.7360	9339.68359	199.55956	50.6262
2	18.269	BB	2.3542	9108.62012	45.48783	49.3738



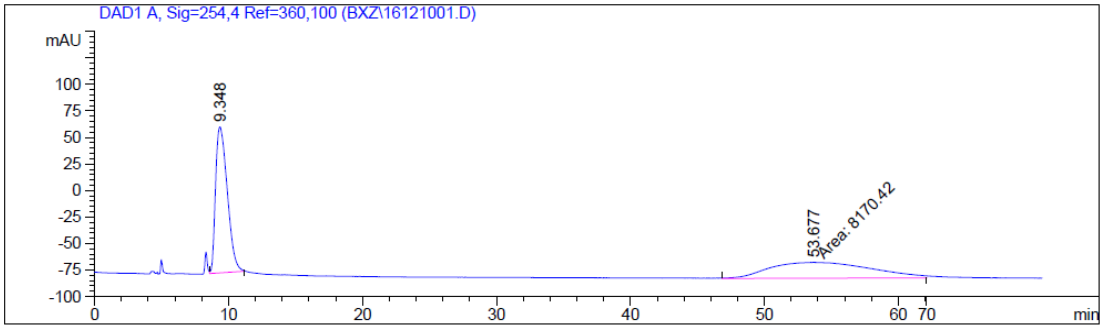
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.446	BB	0.8555	3.69697e4	638.46674	97.3314
2	21.314	VB	1.4643	1013.60626	8.14281	2.6686

Compound 3fa

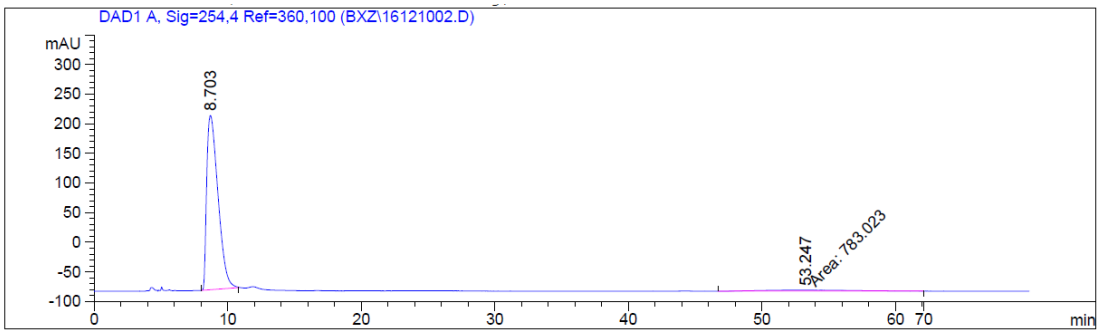


3fa

Prepared according to the procedure within 8 h as off-white solid (120.1 mg, 93% yield, dr > 20:1). mp 115.1-117.3 °C; $[\alpha]_D^{19}$ = -151.2 (*c* 0.49, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8 8.67 (s, 1H), 7.84 (d, *J* = 7.9 Hz, 2H), 7.42 (t, *J* = 8.0 Hz, 2H), 7.25-7.12 (m, 7H), 6.98 (t, *J* = 7.9 Hz, 1H), 6.89 (d, *J* = 7.4 Hz, 1H), 6.82-6.65 (m, 4H), 6.37 (t, *J* = 7.5 Hz, 1H), 5.33 (d, *J* = 15.2 Hz, 1H), 4.16 (d, *J* = 15.2 Hz, 1H), 1.20 (s, 9H); ^{19}F NMR (377 MHz, $CDCl_3$) δ -111.03; ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.4, 168.8, 168.7, 159.0 (d, *J* = 253.6 Hz), 148.7, 147.7, 141.4, 136.9, 134.5, 131.3 (d, *J* = 8.1 Hz), 130.7, 129.7, 129.0, 128.7, 128.0, 127.9, 125.9, 124.2, 124.01, 123.7, 122.6, 119.7, 119.1, 115.7 (d, *J* = 21.7 Hz), 108.78, 84.8, 73.2, 72.2, 44.7, 27.6; HRMS (ESI) m/z Calcd. for $C_{36}H_{30}FN_5NaO_4S$ ($[M+Na]^+$) 670.1895, Found 670.1877; Enantiomeric excess was determined to be 95% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.7 mL/min, t_{major} = 8.7 min, t_{minor} = 53.2 min).

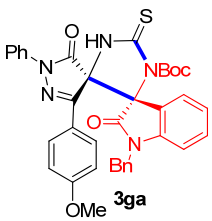


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.348	VB	0.8842	8383.75586	137.71667	50.6444
2	53.677	MM	9.0605	8170.41895	15.02932	49.3556



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.703	PB	0.8929	1.72678e4	294.14673	95.6621
2	53.247	MM	7.6113	783.02258	1.71460	4.3379

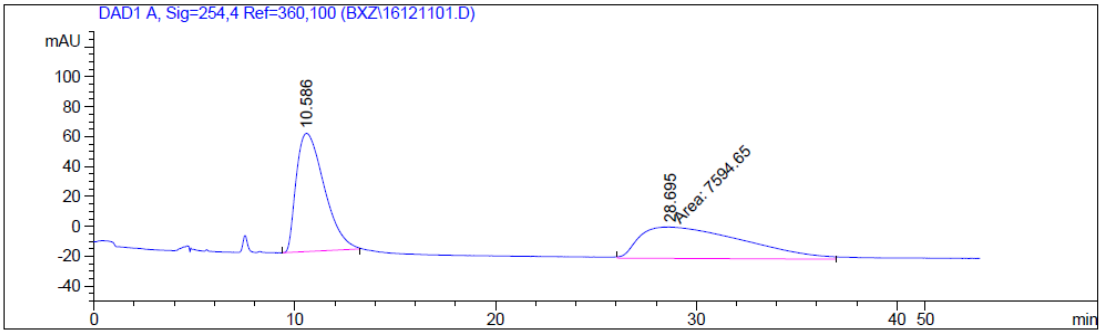
Compound 3ga



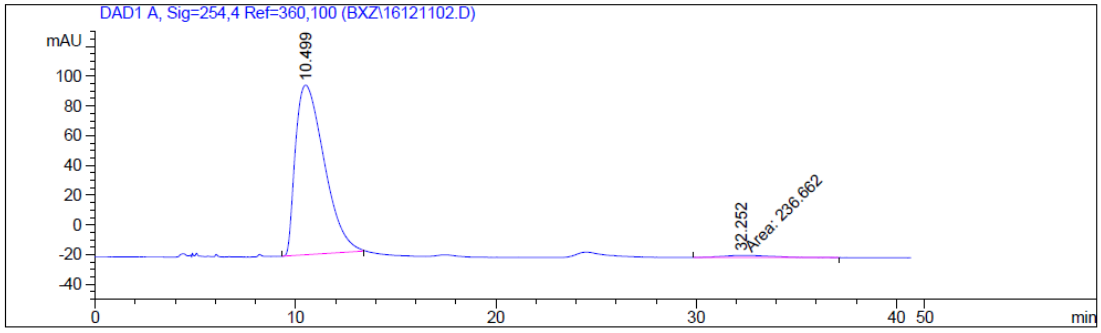
3ga

Prepared according to the procedure within 24 h as white solid (125.1 mg, 95% yield, dr > 20:1). mp 170.2-172.9 °C; $[\alpha]_D^{19}$ = -119.3 (*c* 1.04, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H),

7.73 (d, J = 8.2 Hz, 2H), 7.37-7.28 (m, 4H), 7.21-7.08 (m, 6H), 6.97 (t, J = 7.8 Hz, 1H), 6.86 (d, J = 7.7 Hz, 1H), 6.72 (d, J = 8.8 Hz, 2H), 6.52 (t, J = 7.1 Hz, 2H), 5.23 (d, J = 15.3 Hz, 1H), 4.07 (d, J = 15.4 Hz, 1H), 3.77 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.0, 169.5, 168.1, 161.1, 153.4, 147.6, 141.9, 137.1, 134.9, 130.7, 128.8, 128.7, 127.9, 127.7, 125.7, 124.2, 123.3, 122.4, 119.3, 114.0, 108.8, 84.8, 74.4, 72.0, 55.5, 44.6, 27.4; HRMS (ESI) m/z Calcd. for $C_{37}H_{33}N_5NaO_5S$ ([M+Na]$^+$) 682.2095, Found 682.2073; Enantiomeric excess was determined to be 96% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.7 mL/min, t_{major} = 10.5 min, t_{minor} = 32.3 min).

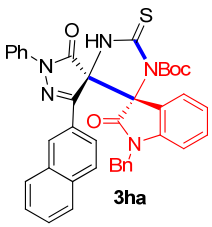


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.586	PB	1.1665	7640.50977	78.99114	50.1505
2	28.695	MM	6.0405	7594.64893	20.95490	49.8495



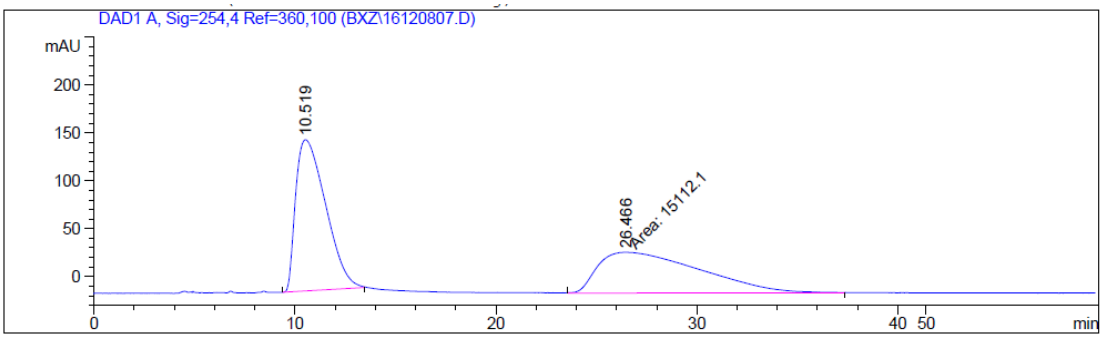
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.499	BB	1.3471	1.13645e4	113.99376	97.9600
2	32.252	MM	2.8453	236.66209	1.38628	2.0400

Compound 3ha

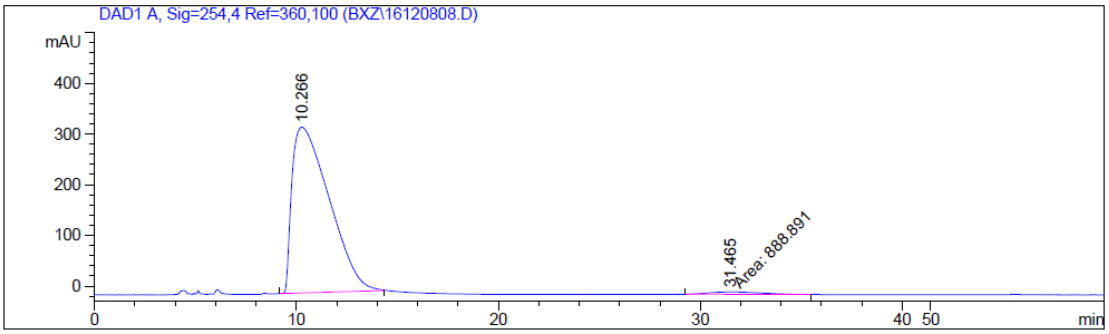


3ha

Prepared according to the procedure within 5 h as white solid (129.1 mg, 95% yield, dr > 20:1). mp 180.3-183.4 °C; $[\alpha]_D^{14}$= -64.8 (c 1.14, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.83-7.68 (m, 5H), 7.61 (d, J = 8.7 Hz, 1H), 7.50-7.41 (m, 3H), 7.31 (t, J = 7.9 Hz, 2H), 7.25-7.11 (m, 6H), 6.83 (d, J = 7.5 Hz, 1H), 6.68 (t, J = 7.7 Hz, 1H), 6.46 (d, J = 7.9 Hz, 1H), 6.17 (t, J = 7.6 Hz, 1H), 5.23 (d, J = 15.2 Hz, 1H), 4.06 (d, J = 14.9 Hz, 1H), 1.04 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.2, 169.4, 168.1, 153.4, 147.6, 141.8, 137.1, 135.0, 133.7, 132.5, 130.6, 129.1, 128.9, 128.8, 128.7, 128.2, 128.0, 127.7, 127.5, 127.4, 126.6, 125.8, 125.6, 123.8, 123.0, 122.3, 119.2, 108.8, 84.8, 74.4, 72.1, 44.6, 27.4; HRMS (ESI) m/z Calcd. for $C_{40}H_{33}N_5NaO_4S$ ([M+Na]$^+$) 702.2145, Found 702.2135; Enantiomeric excess was determined to be 96% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.7 mL/min, t_{major} = 10.3 min, t_{minor} = 31.5 min).

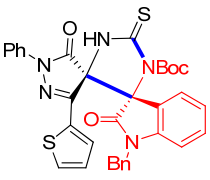


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.519	PB	1.4447	1.63283e4	157.87151	51.9341
2	26.466	MM	5.9034	1.51121e4	42.66488	48.0659



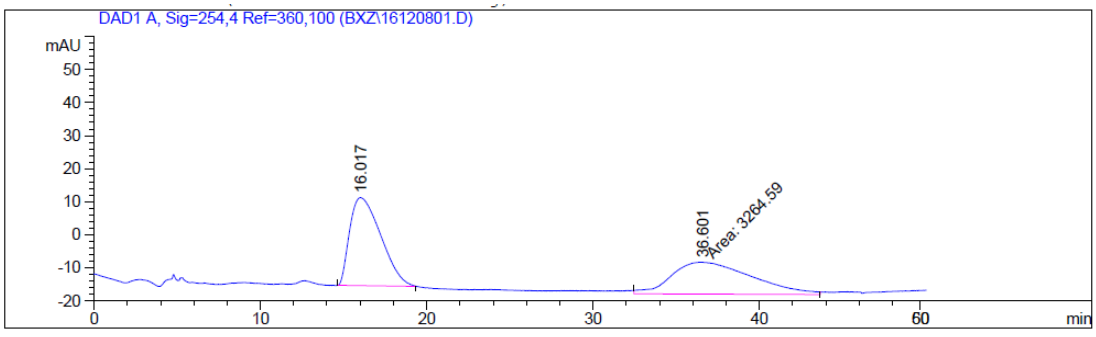
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.266	BB	1.7044	4.17993e4	327.19830	97.9177
2	31.465	MM	3.0006	888.89093	4.93730	2.0823

Compound 3ia

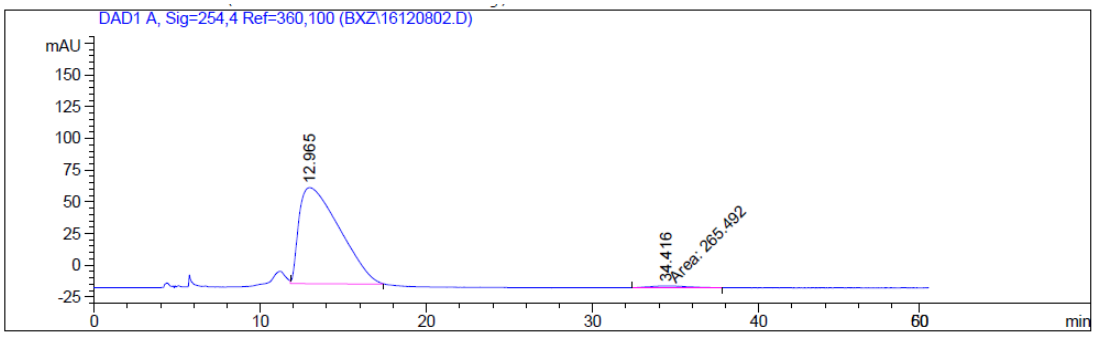


3ia

Prepared according to the procedure within 5 h as yellow solid (120.7 mg, 96% yield, dr > 20:1). mp 181.3-183.0 °C; $[\alpha]_D^{14}$= +10.88 (*c* 0.62, CH_2Cl_2); ^{1}H NMR (400 MHz, DMSO d_6) δ 10.29 (s, 1H), 7.85 (d, *J* = 4.6 Hz, 1H), 7.51-7.17 (m, 13H), 6.87 (d, *J* = 7.8 Hz, 1H), 6.81 (t, *J* = 7.4 Hz, 1H), 6.71 (d, *J* = 7.3 Hz, 1H), 5.11 (d, *J* = 15.6 Hz, 1H), 4.50 (d, *J* = 15.3 Hz, 1H), 0.99 (s, 9H); ^{13}C NMR (101 MHz, DMSO d_6) δ 182.2, 170.1, 166.6, 151.6, 147.7, 143.4, 136.9, 135.9, 133.8, 131.7, 131.5, 129.7, 129.1, 128.9, 128.3, 128.1, 126.6, 124.9, 122.7, 122.2, 119.3, 110.3, 84.5, 74.4, 71.8, 44.2, 27.4; HRMS (ESI) m/z Calcd. for $C_{34}H_{29}N_5NaO_4S_2$ ([M+Na]$^+$) 658.1553, Found 658.1536; Enantiomeric excess was determined to be 96% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.7 mL/min, t_{major} = 13.0 min, t_{minor} = 34.4 min).

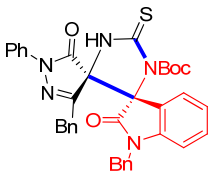


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.017	PB	1.5357	3466.48608	26.68300	51.4997
2	36.601	MM	5.6329	3264.59009	9.65937	48.5003



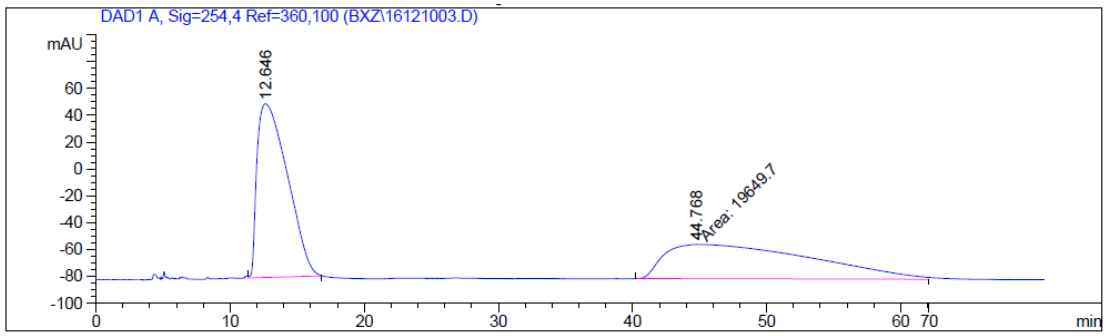
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.965	VB	1.9898	1.28469e4	75.78008	97.9753
2	34.416	MM	2.8897	265.49194	1.53127	2.0247

Compound 3ja

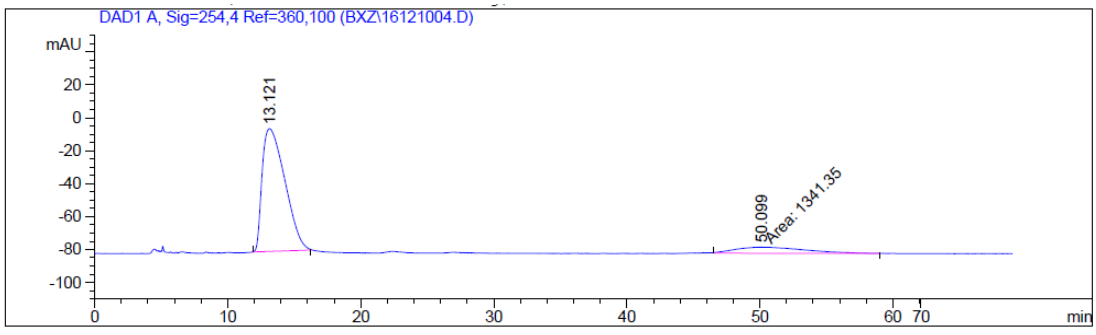


3ja

Prepared according to the procedure within 5 h as white solid (122.0 mg, 95% yield, dr > 20:1). mp 158.5-160.8 °C; $[\alpha]_D^{19}$ = -115.0 (*c* 1.06, CH_2Cl_2); ^1H NMR (400 MHz, acetone d_6) δ 8.76 (s, 1H), 7.64 (t, *J* = 8.2 Hz, 3H), 7.44 (t, *J* = 7.7 Hz, 1H), 7.36 (t, *J* = 7.4 Hz, 4H), 7.27-7.14 (m, 8H), 7.06-6.99 (m Hz, 3H), 5.28 (d, *J* = 15.6 Hz, 1H), 4.57 (d, *J* = 15.6 Hz, 1H), 3.56 (d, *J* = 17.2 Hz, 1H), 3.07 (d, *J* = 17.2 Hz, 1H), 1.26 (s, 9H); ^{13}C NMR (101 MHz, acetone d_6) δ 182.6, 169.1, 167.9, 156.5, 147.9, 142.8, 137.6, 135.6, 134.5, 131.5, 129.6, 128.8, 128.7, 128.2, 127.7, 127.6, 126.8, 125.3, 124.5, 124.2, 123.0, 118.4, 110.2, 84.0, 73.5, 72.1, 44.0, 35.8, 27.0; HRMS (ESI) m/z Calcd. for $C_{37}H_{33}N_5NaO_4S$ ([M+Na]$^+$) 666.2145, Found 666.2137; Enantiomeric excess was determined to be 74% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.7 mL/min, t_{major} = 13.1 min, t_{minor} = 50.1 min).

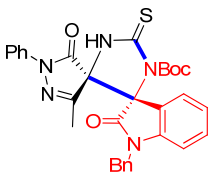


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.646	VB	1.8541	2.03196e4	129.53482	50.8380
2	44.768	MM	12.7871	1.96497e4	25.61145	49.1620



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.121	BB	1.3981	8843.31934	74.54319	86.8297
2	50.099	MM	5.9973	1341.34631	3.72765	13.1703

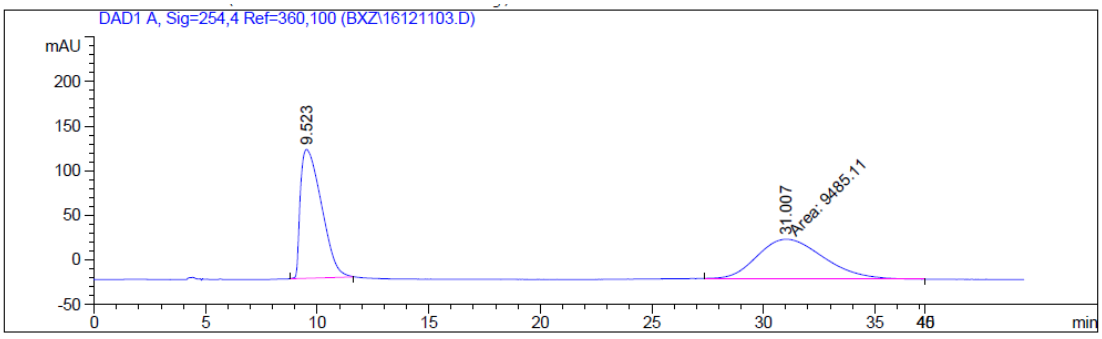
Compound 3ka



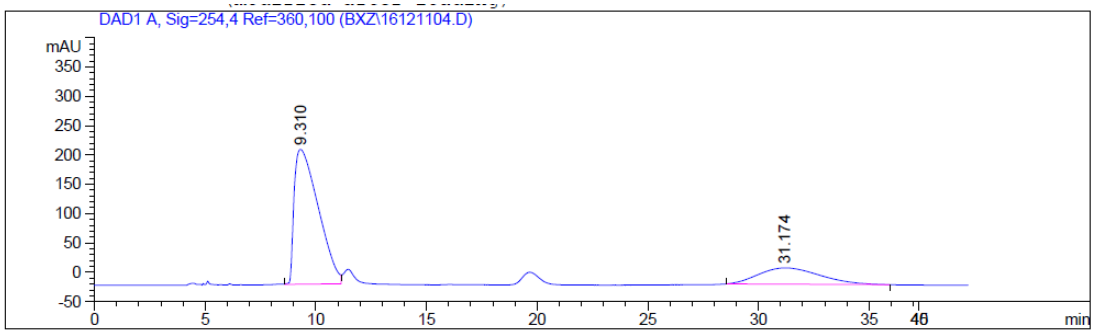
3ka

Prepared according to the procedure within 5 h as white solid (107.5 mg, 95% yield, dr = 13:1). mp 159.1-162.3 °C; $[\alpha]_D^{19}$ = -91.9 (*c* 1.00, CH_2Cl_2); ^1H NMR (400 MHz, acetone d_6) δ 8.72 (s, 1H),

7.72 (d, J = 8.2 Hz, 2H), 7.54 (d, J = 7.4 Hz, 1H), 7.41 (t, J = 8.0 Hz, 3H), 7.36 (d, J = 6.7 Hz, 2H), 7.26-7.15 (m, 5H), 6.99 (d, J = 7.8 Hz, 1H), 5.25 (d, J = 15.6 Hz, 1H), 4.56 (d, J = 15.7 Hz, 1H), 1.73 (s, 3H), 1.24 (s, 9H); ^{13}C NMR (101 MHz, acetone d_6) δ 182.6, 169.1, 167.7, 155.0, 147.9, 142.7, 137.5, 135.6, 131.3, 128.8, 128.6, 127.6, 125.3, 124.3, 124.1, 122.9, 118.4, 101.0, 84.0, 73.2, 71.9, 44.0, 27.0, 15.3; HRMS (ESI) m/z Calcd. for $C_{31}H_{29}N_5NaO_4S$ ([M+Na]$^+$) 590.1832, Found 590.1826; Enantiomeric excess was determined to be 52% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.7 mL/min, t_{major} = 9.3 min, t_{minor} = 31.2 min).

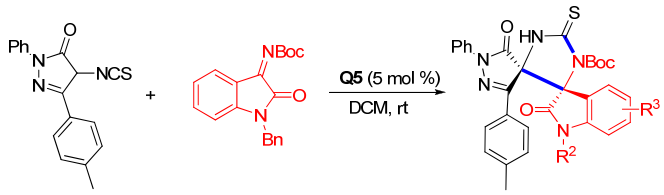


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.523	BB	0.9272	9485.48535	144.62839	50.0010
2	31.007	MM	3.5128	9485.11328	45.00229	49.9990



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.310	BV	1.0935	1.73789e4	230.00601	76.2438
2	31.174	BB	2.2706	5414.95654	27.92067	23.7562

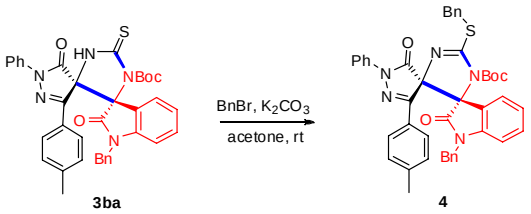
Gram scale synthesis of the product 3ba



To a Schlenk tube equipped with a magnetic stir bar was charged with 4-isothiocyanato pyrazolone **1b** (553 mg, 1.8 mmol, 1.0 equiv) and **Q5** (53.7 mg, 0.09 mmol, 0.05 equiv), followed with DCM (18 mL). After stirred for 5 min, isatin derivatived ketimine **2a** (665 mg, 1.98 mmol, 1.1 equiv) was added in one portion. The reaction was detected by TLC. After 5 h, the solvent was removed under vacuum, the residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 6:1) directly to give the product **3ba** 1.16 g as light-yellow solid (yield 96%, ee 95%, dr > 20:1).

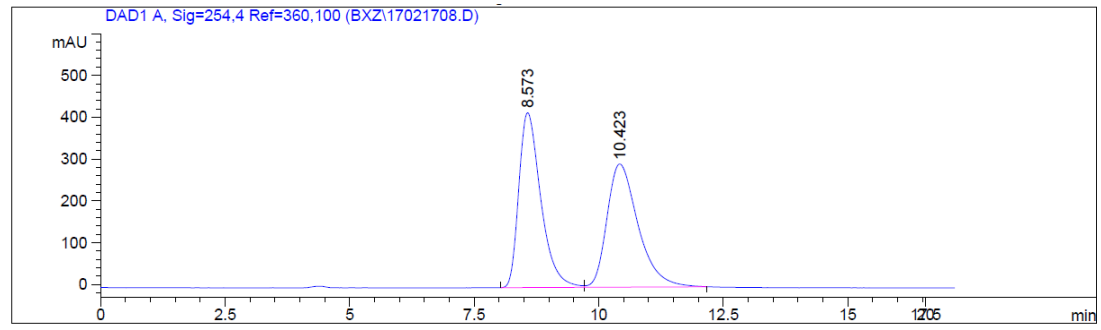
The procedure for the synthesis of compounds 4-10.

Synthesis of compound 4

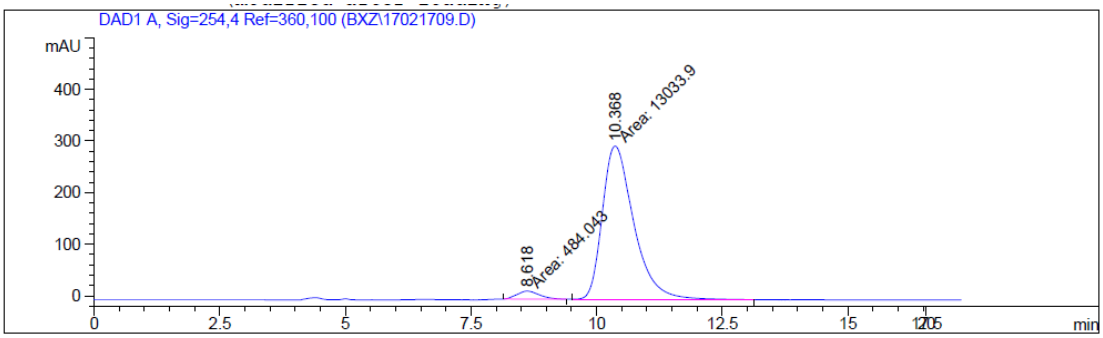


3ba 4

To a solution of **3ba** (64.3 mg, 0.1 mmol, 1.0 equiv) in acetone (2.0 mL) was added K_2CO_3 (16.6 mg, 0.12 mmol, 1.2 equiv) and benzyl bromide (20.5 mg, 0.12 mmol, 1.2 equiv) in sequence. The reaction mixture was stirred at rt for 1 h. The solvent was evaporated, and then the crude mixture was purified by silica gel column chromatography (EtOAc/petroleum ether = 1/6) to give **4** as white solid (66.8 mg, 91% yield). mp 173.7-176.0 °C; $[\alpha]_D^{15}$ = -181.2 (*c* 0.25, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 7.3 Hz, 2H), 7.39-7.28 (m, 5H), 7.21-7.08 (m, 6H), 7.01 (d, *J* = 8.0 Hz, 2H), 6.88 (t, *J* = 7.7 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 2H), 6.46 (d, *J* = 7.7 Hz, 2H), 6.28 (t, *J* = 7.6 Hz, 1H), 5.37 (d, *J* = 15.3 Hz, 1H), 4.59 (d, *J* = 13.6 Hz, 1H), 4.40 (d, *J* = 13.7 Hz, 1H), 4.04 (d, *J* = 15.8 Hz, 1H), 2.26 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 168.4, 155.9, 141.6, 139.7, 137.7, 136.6, 135.1, 130.1, 129.9, 129.3, 128.8, 128.7, 128.6, 127.8, 127.4, 127.3, 126.6, 125.2, 124.9, 124.5, 121.6, 119.0, 108.3, 75.0, 44.4, 37.2, 27.4, 21.4; HRMS (ESI) m/z Calcd. for $C_{44}H_{39}N_5NaO_4S$ ([M+Na]$^+$) 756.2615, Found 756.2601; Enantiomeric excess was determined to be 93% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.7 mL/min, t_{major} = 10.4 min, t_{minor} = 8.6 min).

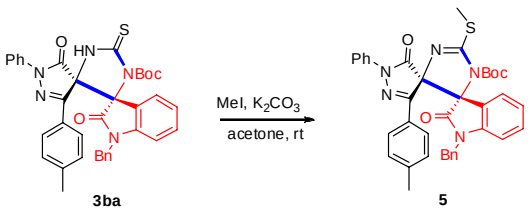


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.573	BB	0.4684	1.28473e4	418.17871	50.0503
2	10.423	BB	0.6595	1.28214e4	294.75699	49.9497



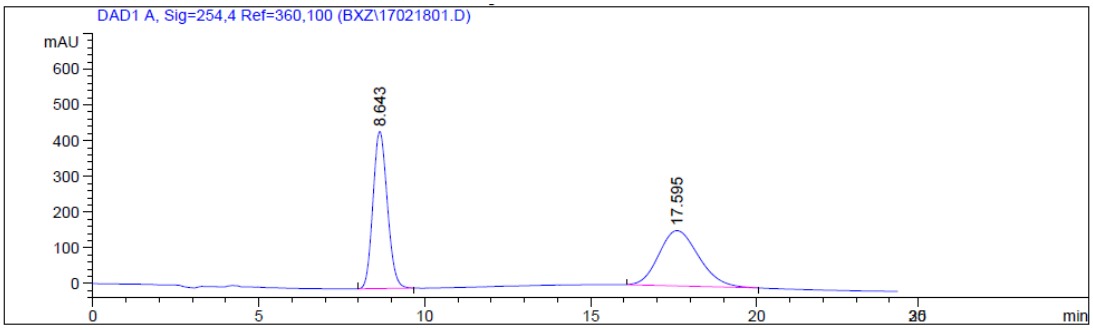
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.618	MM	0.5175	484.04263	15.58978	3.5808
2	10.368	MM	0.7294	1.30339e4	297.81952	96.4192

Synthesis of compound 5

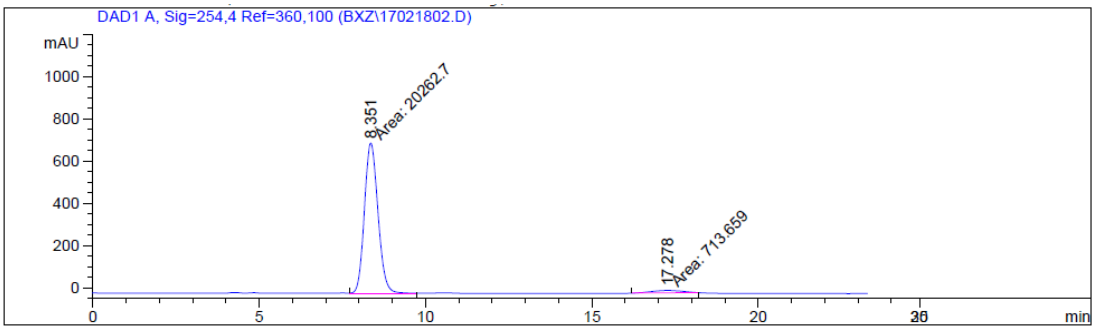


3ba 5

To a solution of **3ba** (64.3 mg, 0.1 mmol, 1.0 equiv) in acetone (2.0 mL) was added K_2CO_3 (16.6 mg, 0.12 mmol, 1.2 equiv) and methyl iodide (17.0 mg, 0.12 mmol, 1.2 equiv) in sequence. The reaction mixture was stirred at rt for 1 h. The solvent was evaporated, and then the crude mixture was purified by silica gel column chromatography (EtOAc/petroleum ether = 1/6) to give **5** as white solid (64.4 mg, 98% yield). mp 186.7-188.3 °C; $[\alpha]_D^{15}$ = -202.0 (*c* 0.39, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.7 Hz, 2H), 7.35 (t, *J* = 8.0 Hz, 2H), 7.22-7.08 (m, 8H), 6.98-6.85 (m, 3H), 6.55 (d, *J* = 6.9 Hz, 1H), 6.48 (d, *J* = 7.8 Hz, 1H), 6.33 (t, *J* = 7.5 Hz, 1H), 5.36 (d, *J* = 15.3 Hz, 1H), 4.06 (d, *J* = 14.6 Hz, 1H), 2.67 (s, 3H), 2.28 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 168.4, 155.9, 148.9, 141.7, 139.9, 137.6, 135.1, 130.3, 130.0, 128.8, 128.7, 127.8, 127.4, 126.6, 125.2, 124.9, 124.5, 121.6, 119.0, 108.5, 84.2, 83.5, 75.3, 44.4, 27.4, 21.4, 15.8; HRMS (ESI) m/z Calcd. for $C_{38}H_{35}N_5NaO_4S$ ($[M+Na]^+$) 680.2302, Found 680.2306; Enantiomeric excess was determined to be 93% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.7 mL/min, t_{major} = 8.4 min, t_{minor} = 17.3 min).

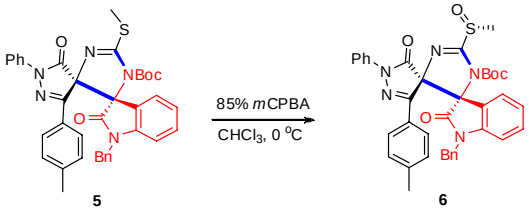


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.643	PB	0.4691	1.32318e4	439.67575	50.5019
2	17.595	BB	1.1936	1.29688e4	155.09041	49.4981



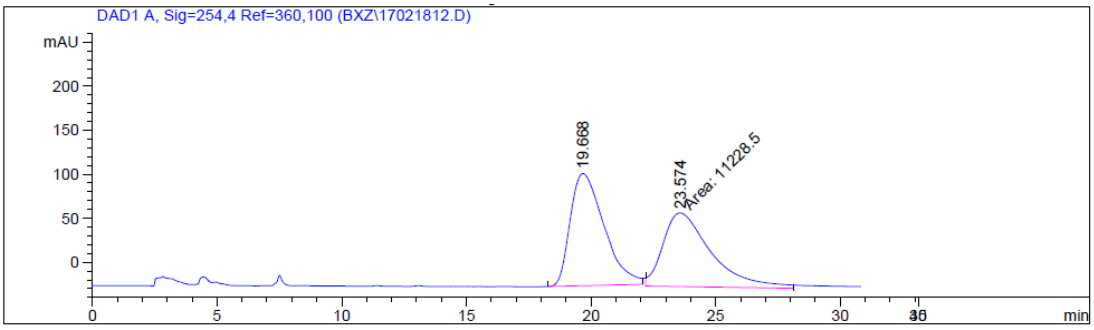
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.351	MM	0.4742	2.02627e4	712.15131	96.5978
2	17.278	MM	0.7481	713.65887	11.27620	3.4022

Synthesis of compound 6



To a solution of **5** (65.8 mg, 0.1 mmol, 1.0 equiv) in $CHCl_3$ (2.0 mL) was added 85% *m*CPBA (21.3 mg, 0.105 mmol, 1.05 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. And then the mixture was diluted with DCM (10 mL) and quenched with saturated $NaHCO_3$ aqueous (5 mL). The organic phase was separated and washed with saturated $NaHCO_3$ aqueous and brine, dried over Na_2SO_4, concentrated. The crude mixture was purified by silica gel column chromatography (EtOAc/petroleum ether = 1/2) to give **6** as white solid (61.2 mg, 91% yield, dr > 20:1). mp 121.0-123.4 °C; $[\alpha]_D^{15}$ = -198.2 (*c* 0.49, CH_2Cl_2); ***ent*-6** (60.6 mg, 90% yield, dr > 20:1, 93% ee); mp 125.3-128.5 °C; $[\alpha]_D^{19}$= +190.6 (*c* 0.36, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.8 Hz, 2H), 7.38 (t, *J* = 8.0 Hz, 2H),

7.23-7.16 (m, 6H), 7.12 (d, J = 8.0 Hz, 2H), 6.93 (t, J = 7.7 Hz, 1H), 6.87 (d, J = 8.0 Hz, 2H), 6.71 (d, J = 7.3 Hz, 1H), 6.52 (d, J = 7.8 Hz, 1H), 6.35 (t, J = 7.6 Hz, 1H), 5.37 (d, J = 15.3 Hz, 1H), 4.07 (d, J = 15.3 Hz, 1H), 3.40 (s, 3H), 2.24 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8, 169.4, 166.2, 155.1, 141.0, 140.1, 137.2, 134.8, 130.7, 129.5, 128.9, 128.8, 128.8, 128.0, 127.6, 127.3, 126.8, 125.7, 124.8, 123.1, 122.1, 119.4, 108.6, 85.7, 83.5, 76.2, 44.4, 42.7, 27.3, 21.4; HRMS (ESI) m/z Calcd. for $C_{38}H_{35}N_5NaO_5S$ ([M+Na]$^+$) 696.2251, Found 696.2272; Enantiomeric excess was determined to be 95% (determined by HPLC using chiral OD-H column, hexane/2-propanol = 90/10, λ = 254 nm, 30 °C, 0.7 mL/min, t_{major} = 18.4 min, t_{minor} = 23.5 min). For ***ent*-6**, enantiomeric excess was determined to be 93% (determined by HPLC using chiral OD-H column, hexane/2-propanol = 90/10, λ = 254 nm, 30 °C, 0.7 mL/min, t_{major} = 23.1 min, t_{minor} = 19.6 min).



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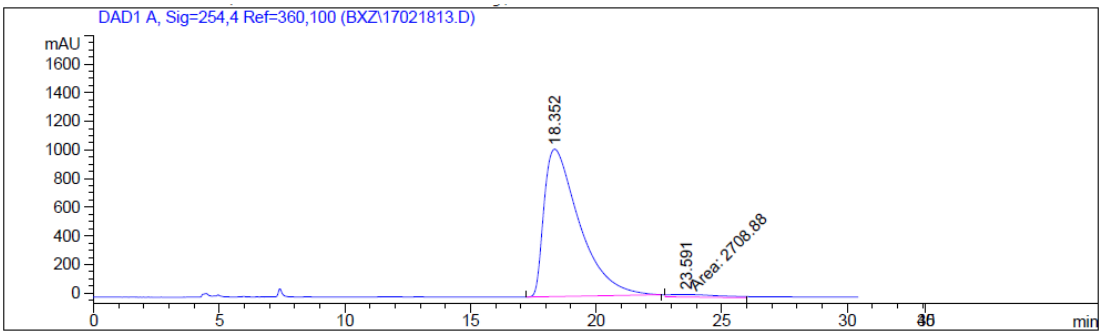

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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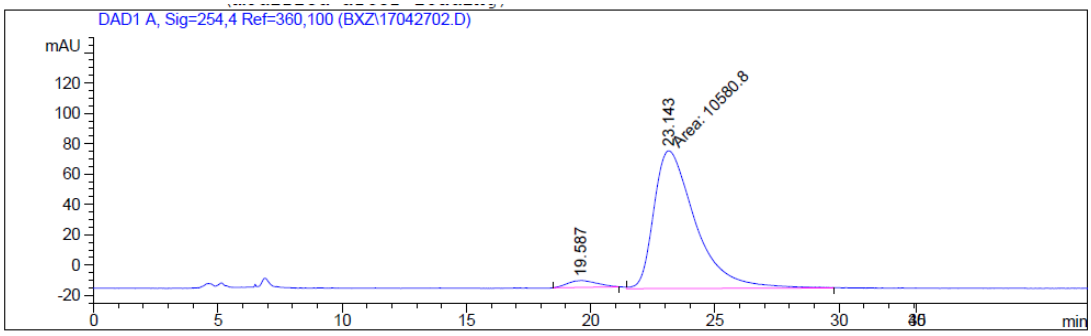
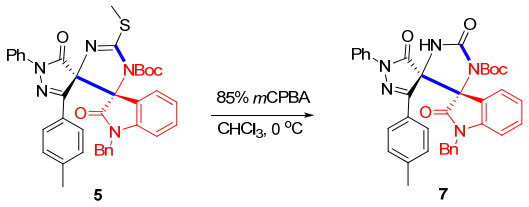


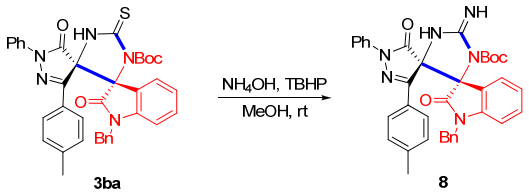
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.587	BB	0.9678	372.63620	4.53895	3.4020
2	23.143	MM	1.9437	1.05808e4	90.72580	96.5980

Synthesis of compound 7

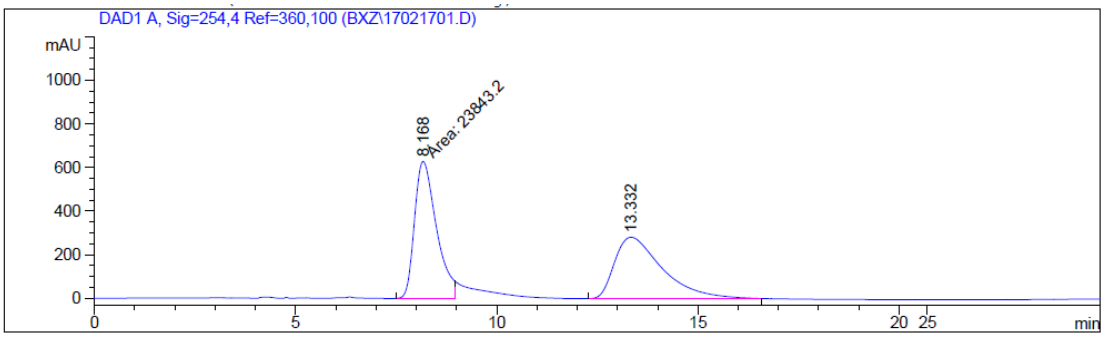


To a solution of **5** (65.8 mg, 0.1 mmol, 1.0 equiv) in $CHCl_3$ (2.0 mL) was added 85% *m*CPBA (42.6 mg, 0.21 mmol, 2.1 equiv.) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. And then the mixture was diluted with DCM (10 mL) and quenched with saturated $NaHCO_3$ aqueous (5 mL). The organic phase was separated and washed with saturated $NaHCO_3$ aqueous and brine, dried over Na_2SO_4, concentrated. The crude mixture was purified by silica gel column chromatography (EtOAc/petroleum ether = 1/2) to give **7** as white solid (58.9 mg, 94% yield). mp 159.3-162.3 °C; $[\alpha]_D^{15}$ = -176.2 (*c* 0.30, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.2 Hz, 2H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.22-7.09 (m, 8H), 6.92 (d, *J* = 8.0 Hz, 4H), 6.51 (d, *J* = 8.0 Hz, 1H), 6.44 (t, *J* = 7.7 Hz, 1H), 6.25 (s, 1H), 5.30 (d, *J* = 15.2 Hz, 1H), 4.10 (d, *J* = 15.3 Hz, 1H), 2.27 (s, 3H), 1.12 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 169.6, 155.7, 154.0, 147.5, 141.9, 140.2, 137.2, 135.0, 130.3, 129.0, 128.9, 128.7, 127.9, 127.6, 126.7, 125.6, 125.6, 124.0, 122.3, 119.1, 108.5, 84.1, 69.9, 68.4, 44.6, 27.5, 21.4; HRMS (ESI) m/z Calcd. for $C_{37}H_{33}N_5NaO_5$ ($[M+Na]^+$) 650.2374, Found 650.2377.

Synthesis of compound 8



To a solution of **3ba** (64.3 mg, 0.1 mmol, 1.0 equiv) in MeOH (1.5 mL) was added 30% ammonium hydroxide (0.5 ml) and 60% *tert*-butyl hydroperoxide (69 mg, 0.5 mmol, 5.0 equiv), the resulting mixture was stirred at rt overnight. And then the mixture was diluted with DCM (10 mL) and water (5 mL), extracted with DCM (10 mL × 2). The organic phase was washed with brine, dried over Na_2SO_4, concentrated. The crude mixture was purified by silica gel column chromatography (EtOAc/petroleum ether = 1/2) to give **8** as white solid (59.5 mg, 95% yield). mp 176.1-178.9 °C; $[\alpha]_D^{14}$ = -169.0 (*c* 0.40, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.9 Hz, 2H), 7.34 (dd, *J* = 16.4, 7.9 Hz, 4H), 7.21-7.09 (m, 6H), 6.94-6.87 (m, 3H), 6.75 (brs, 1H), 6.59 (d, *J* = 7.0 Hz, 1H), 6.46 (d, *J* = 7.9 Hz, 1H), 6.33 (t, *J* = 7.5 Hz, 1H), 5.39 (d, *J* = 15.4 Hz, 1H), 4.03 (d, *J* = 15.3 Hz, 1H), 2.27 (s, 3H), 1.03 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 170.6, 158.7, 156.9, 150.4, 141.8, 139.5, 137.9, 135.1, 130.5, 129.7, 128.7, 128.7, 127.7, 127.4, 126.8, 125.0, 124.9, 121.5, 119.0, 108.3, 84.1, 80.2, 73.9, 44.4, 27.4, 21.4; HRMS (ESI) m/z Calcd. For $C_{37}H_{35}N_6O_4$ ($[M+H]^+$) 627.2714, Found 627.2711; Enantiomeric excess was determined to be 95% (determined by HPLC using chiral OD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.7 mL/min, t_{major} = 8.1 min, t_{minor} = 13.8 min).



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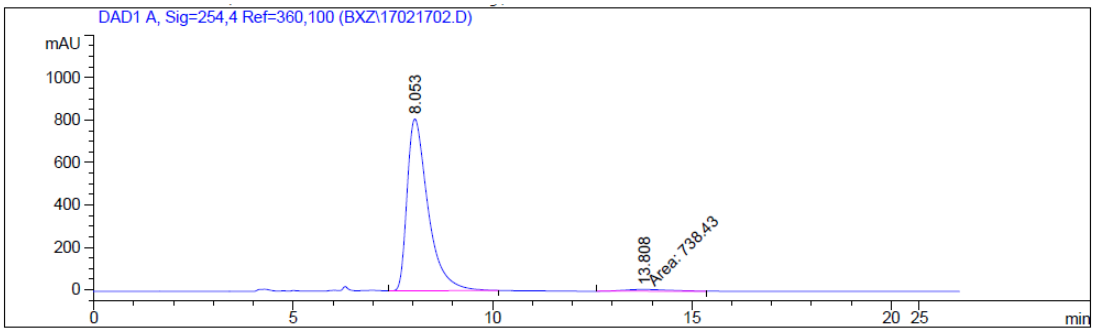
2	13.332	BB	1.1925	2.31749e4	281.49997	49.2894



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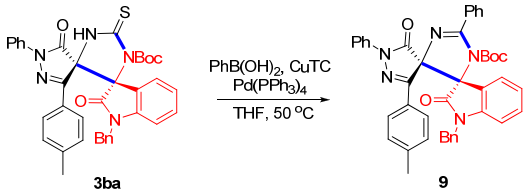
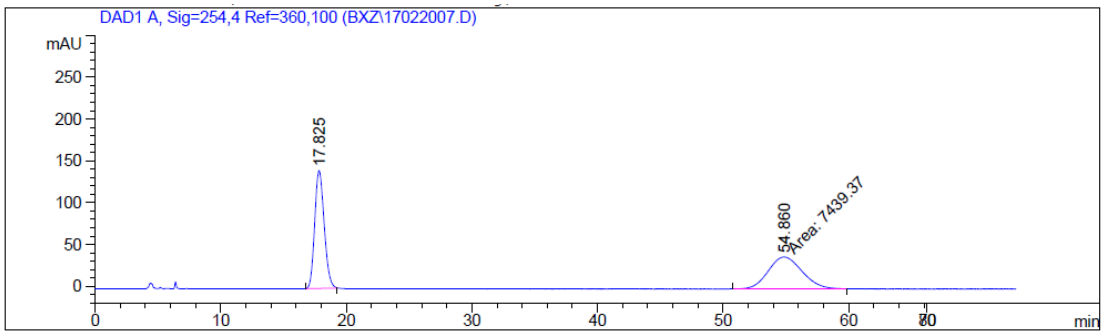
1	8.053	VB	0.5541	2.95720e4	809.63879	97.5638
2	13.808	MM	1.4345	738.42981	8.57938	2.4362

Synthesis of compound 9



To a solution of **3ba** (64.3 mg, 0.1 mmol, 1.0 equiv) and phenylboronic acid (24.3 mg, 0.2 mmol, 2.0 equiv) in anhydrous THF (2.0 mL) was added copper(I) thiophene-2-carboxylate (57.0 mg, 0.3 mmol, 3.0 equiv) and $Pd(PPh_3)_4$ (11.5 mg, 0.01 mmol, 0.1 equiv) in sequence, under argon. The resulting mixture was heated at 50 °C for 6 h. After cooling to rt, DCM (10 mL) and water (5 mL) were added to the mixture, extracted with DCM (10 mL × 2). The organic phase was washed with saturated $NaHCO_3$ aqueous and brine, dried over Na_2SO_4, concentrated. The crude mixture was purified by silica gel column chromatography (EtOAc/petroleum ether = 1/6) to give **9** as white solid (35.8 mg, 52% yield). mp 109.1-112.3 °C; $[\alpha]_D^{15}$ = -159.0 (*c* 0.30, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.8 Hz, 2H), 7.83-7.76 (m, 2H), 7.57-7.48 (m, 3H), 7.40-7.36 (m, 2H), 7.25-7.15 (m, 8H), 6.96-6.88 (m, 3H), 6.72 (d, *J* = 7.0 Hz, 1H), 6.51 (d, *J* = 7.9 Hz, 1H), 6.37 (t, *J* = 7.4 Hz, 1H), 5.36 (d, *J* = 15.4 Hz, 1H), 4.22 (d, *J* = 15.3 Hz, 1H), 2.27 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 167.8, 166.3, 155.9, 148.0, 141.5, 139.8, 137.6, 135.2, 130.8, 130.2, 130.0, 128.8, 128.7, 128.0, 127.8, 127.4, 126.7, 125.3, 124.8, 124.6, 121.7, 119.2, 108.7, 83.7, 83.1, 75.1, 44.5, 27.4, 21.4; HRMS (ESI) m/z Calcd. for $C_{43}H_{38}N_5O_4$ ($[M+H]^+$) 688.2918, Found 688.2903; Enantiomeric excess was determined to be 96% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 90/10, λ = 254 nm, 30 °C, 0.7 mL/min, t_{major} = 17.5 min, t_{minor} = 54.9 min).



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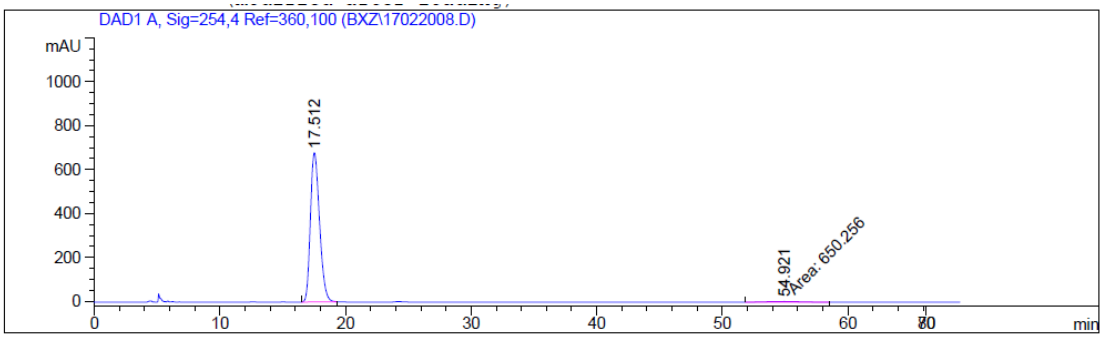
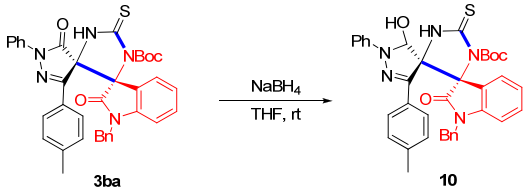
2	54.860	MM	3.2026	7439.36670	38.71470	50.0961

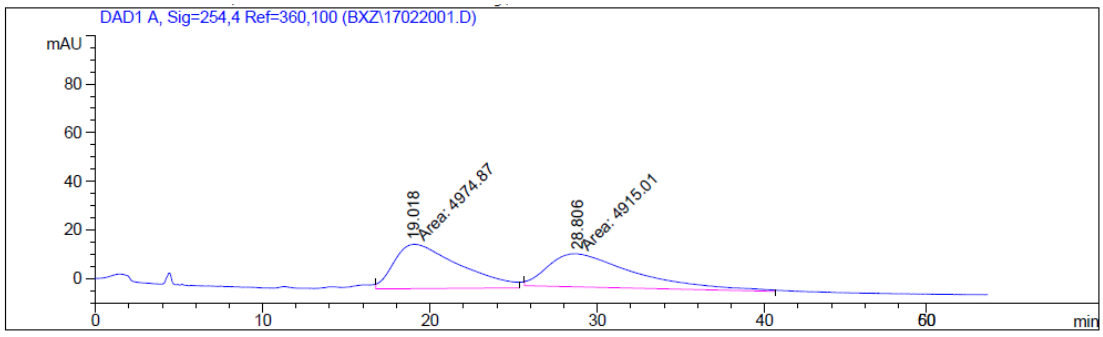


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.512	BB	0.7771	3.43100e4	679.42786	98.1400
2	54.921	MM	3.4668	650.25641	3.12614	1.8600

Synthesis of compound 10



To a solution of **3ba** (64.3 mg, 0.1 mmol, 1.0 equiv) in MeOH (2.0 mL) was added sodium borohydride (3.8 mg, 0.1 mmol, 1.0 equiv) at °0 C. After 10 min, the solvent was removed under vacuum, the residue was purified by silica gel column chromatography (EtOAc/petroleum ether = 1/6) to give **10** as light yellow solid (61.4 mg, 95% yield, >20:1 dr). Decomposed at 165 °C; $[\alpha]_D^{16}$ = -264.2 (*c* 0.54, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.52 (d, *J* = 7.7 Hz, 2H), 7.45 (d, *J* = 6.8 Hz, 2H), 7.41-7.26 (m, 6H), 7.08-7.00 (m, 3H), 6.94-6.84 (m, 3H), 6.79 (d, *J* = 7.4 Hz, 1H), 6.50 (d, *J* = 7.8 Hz, 1H), 6.34 (t, *J* = 7.5 Hz, 1H), 5.45 (d, *J* = 15.4 Hz, 1H), 5.43 (d, *J* = 12.0 Hz, 1H), 4.23 (d, *J* = 15.4 Hz, 1H), 2.24 (s, 3H), 1.18 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.2, 174.7, 147.7, 147.2, 145.3, 141.3, 138.6, 134.4, 130.4, 130.2, 129.0, 128.9, 128.8, 128.1, 127.6, 126.2, 125.2, 124.5, 123.0, 122.6, 117.8, 109.0, 97.6, 85.1, 73.3, 45.2, 27.6, 21.3; HRMS (ESI) m/z Calcd. for $C_{37}H_{35}N_5NaO_4S$ ($[M+Na]^+$) 668.2302, Found 668.2283; Enantiomeric excess was determined to be 95% (determined by HPLC using chiral OD-H column, hexane/2-propanol = 90/10, λ = 254 nm, 30 °C, 0.7 mL/min, t_{major} = 18.7 min, t_{minor} = 31.4 min).



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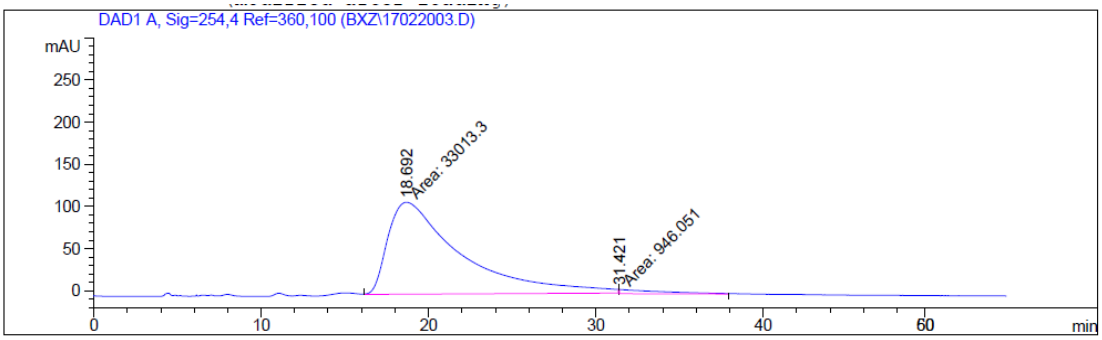
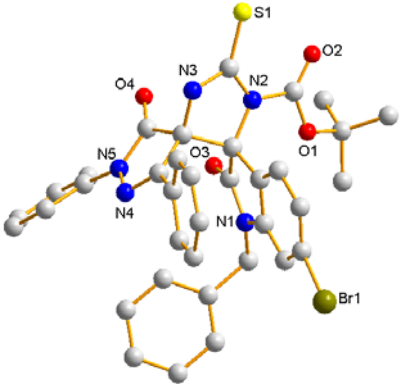
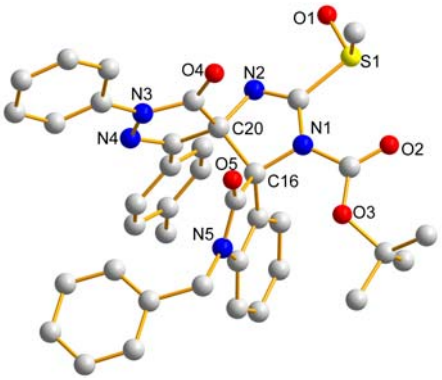


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.692	MM	5.0387	3.30133e4	109.19875	97.2142
2	31.421	MM	3.1132	946.05090	5.06468	2.7858

4. X-ray structures of 3af and *ent*-6



X-ray structure of 3af



X-ray structure of *ent*-6

5. Evaluation of the inhibitory activity to hCE1

Chemicals and reagents

Bis-*p*-nitrophenyl phosphate (BNPP) and bavachininwere were purchased from TCI (Tokyo, Japan). D-Luciferin methyl ester (DME) was synthesized by Dr. Liwei Zou from Shanghai University of Traditional Chinese Medicine and used as a specific probe substrate for hCE1 in human liver preparations.[3] Luciferin detection reagent (LDR) was obtained from Promega Biotech (Madison, USA). The pooled human liver microsomes (HLM) from 50 donors were obtained from RILD Co. Ltd. (Shanghai, China), as the enzyme source for human carboxylesterases1 (hCE1) inhibition assays. The stock solutions of all compounds were dissolved by LC grade DMSO (Tedia, USA). Phosphate saline buffer (100 mM, pH 6.5) was prepared by using Millipore water and stored at 4 °C until use. LC grade acetonitrile (Tedia, USA) was used to stop all incubations in this study.

General procedure for inhibition assays of hCE1-mediated DME hydrolysis

The inhibitory effects against human carboxylesterase1 (hCE1) were investigated using D-Luciferin methyl ester (DME) as the probe substrate, while Bis-*p*-nitrophenyl phosphate (BNPP) and bavachinin were used as positive control.[3] In brief, the incubation mixture with a total volume of 100 μL mL was consisted of PBS (pH 6.5), HLM (10 μg/mL, final concentration), and each inhibitor. After 10 min pre-incubation at 37 °C, the reaction was started by the addition of DME (3 μM, near the Km value of DME in HLM, final concentration), with the final concentration of DMSO at 1% (v/v, without loss of the catalytic activity). After incubation at 37 °C for 10 min in a shaking bath, LDR (equal volume of incubation mixture, 50 μL) was added to terminate the reaction. The mixture was then taken for luminescence measurements by a Synergy H1 Multi-Mode Reader (Biotek, USA). The lumines-

cent product of D-Luciferin (the hydrolytic metabolite of DME) was quantified with the excitation wavelength of 600 nm, while the emission wavelength was 662 nm. The gain value was set at 60. The residual activities of hCE1 were calculated with the following formula: the residual activity (%) = (the florescence intensity in the presence of inhibitor)/the florescence intensity in negative control (without any inhibitor) × 100%. All assays were conducted in triplicate, and the data were shown as mean ± SD.

6. Table *S*-1 and Figure *S*-1

Table S-1. The Preliminary Evaluation of the Activity to Inhibit hCE1[a]

entry	compound	IC_{50} (μM)	entry	compound	IC_{50} (μM)
1	**3aa**	>100	6	***r*-3ia**	>100
2	***r*-3aa**	>100	7	**3ba**	>100
3	**3ad**	>100	8	***r*-3ba**	52.62 ± 6.40
4	***r*-3ad**	>100	9[b]	**Bavachinin**	3.42 ± 0.81
5	**3ia**	>100	10[c]	**BNPP**	0.035 ± 0.003

[a]All data presented are averages of at least three separate experiments. [b]Bavachinin, a positive inhibitor against hCE1. [c]Bis-*p*-nitrophenyl phosphate (BNPP), a positive inhibitor against hCE1.

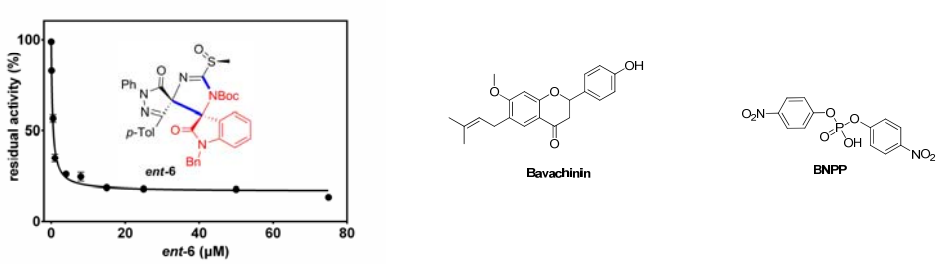


Figure *S*-1. The Inhibition Curve of *ent*-6 and the Structures of Positive Inhibitors.

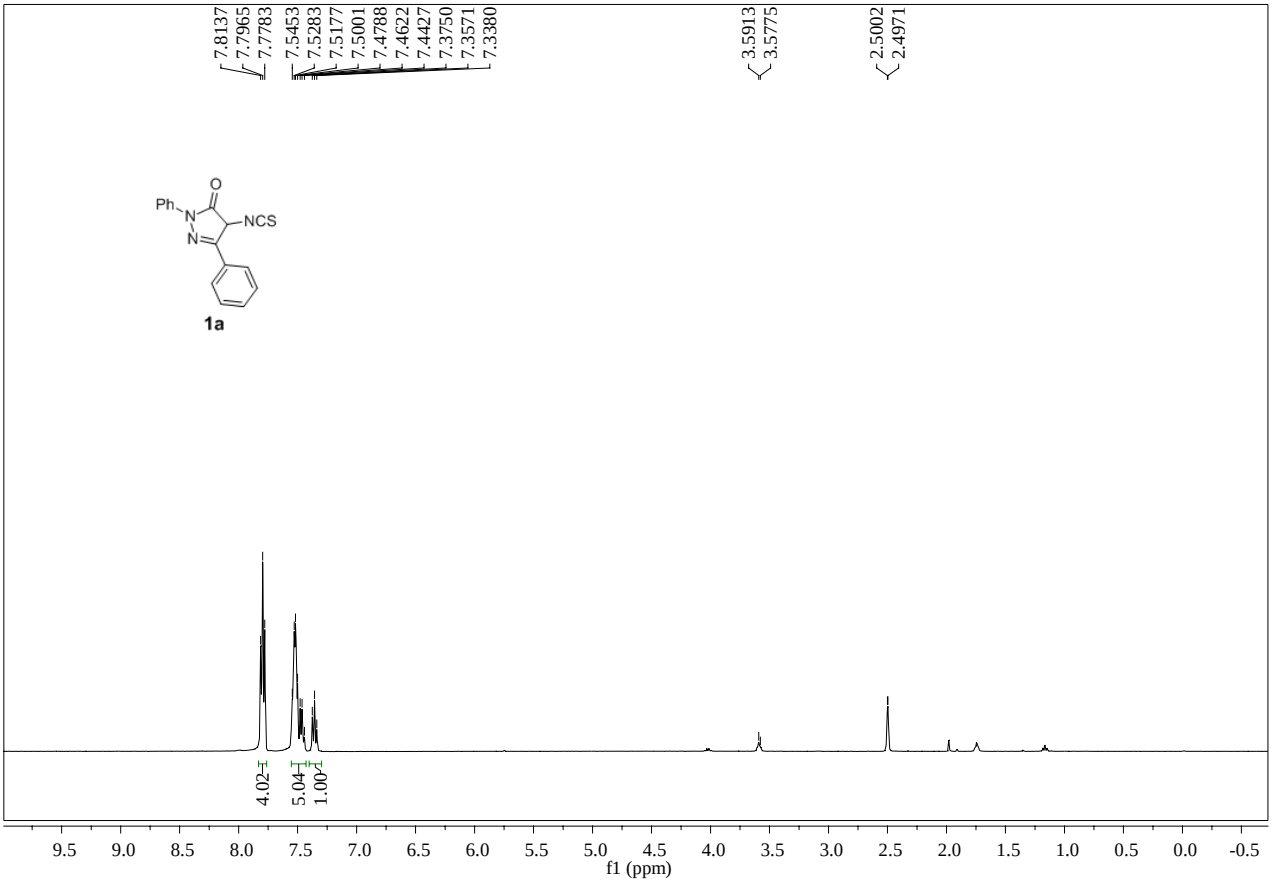
7. Reference

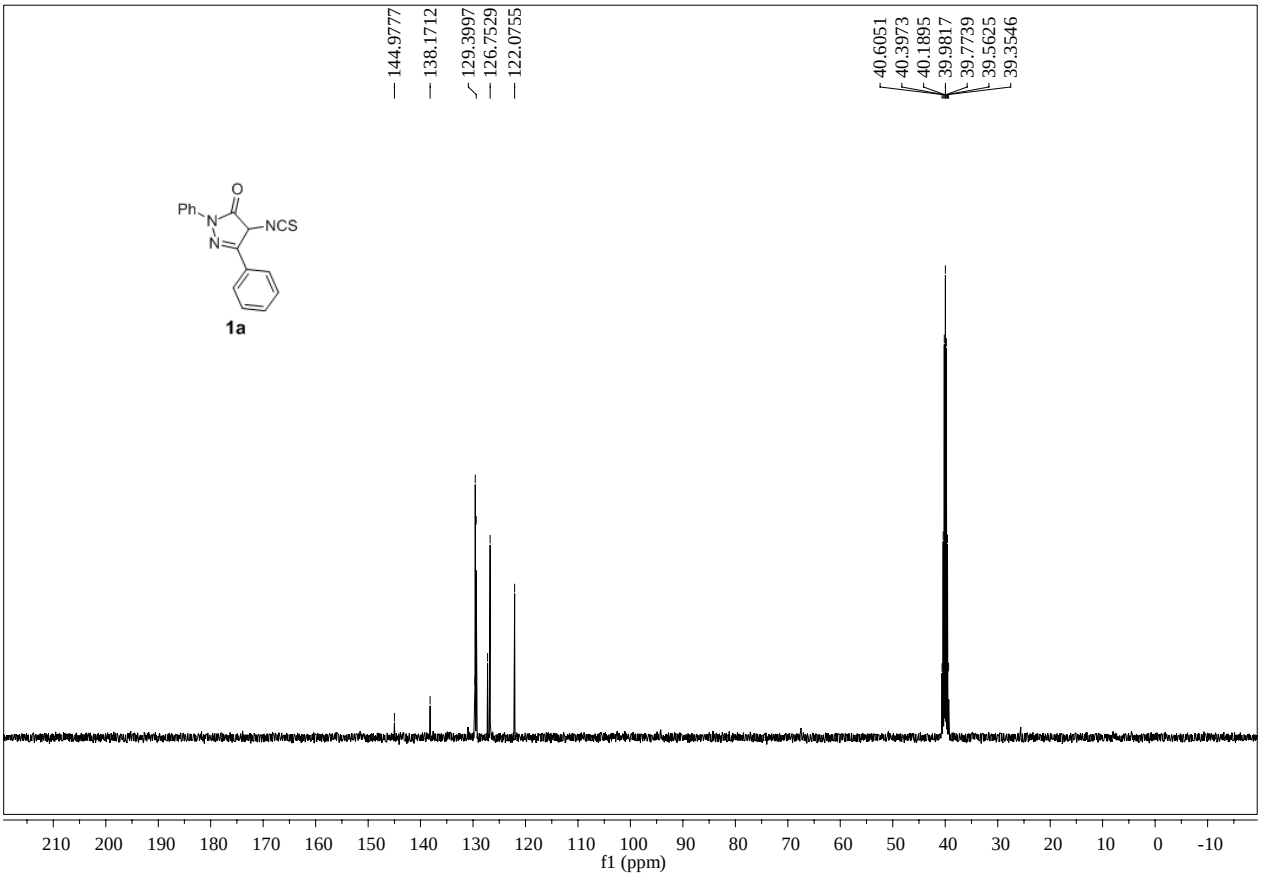
[1] Yan, W.; Wang, D.; Feng, J.; Li, P.; Zhao, D.; Wang, R. *Org. Lett.* **2012**, *14*, 2512.

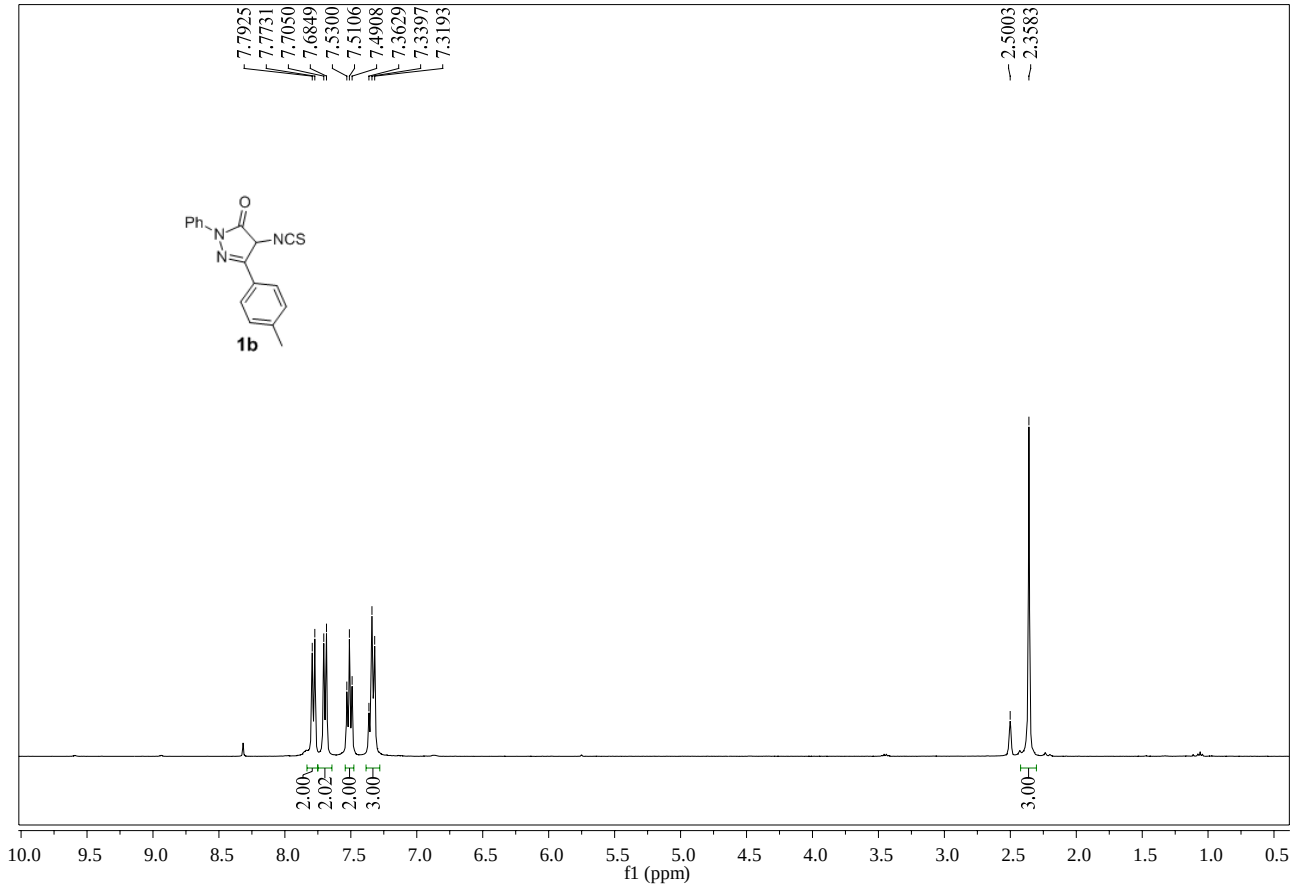
[2] Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967.

[3] Wang, D.-D.; Jin, Q.; Zou, L.-W.; Hou, J.; Lv, X.; Lei, W.; Cheng, H.-L.; Ge, G.-B.; Yang, L. *Chem. Commun.* **2016**, *52*, 3183.

8. NMR spectra for compounds



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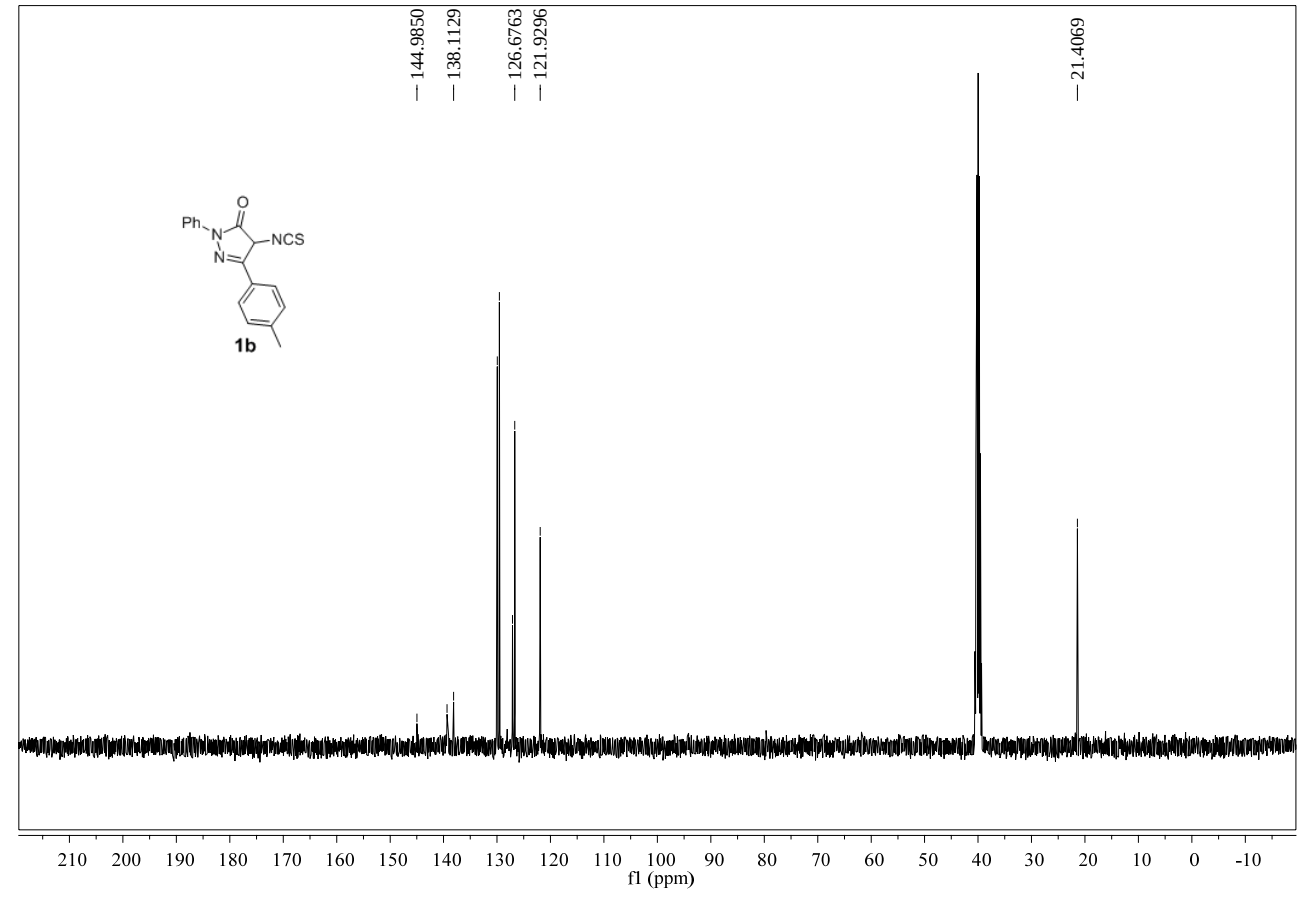
7.7731
7.7050
7.6849
7.5300
7.5106
7.4908
7.3629
7.3397
7.3193
2.5003
2.3583
Ph
N
N
O
NCS
1b
2.00
2.02
2.00
3.00
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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O
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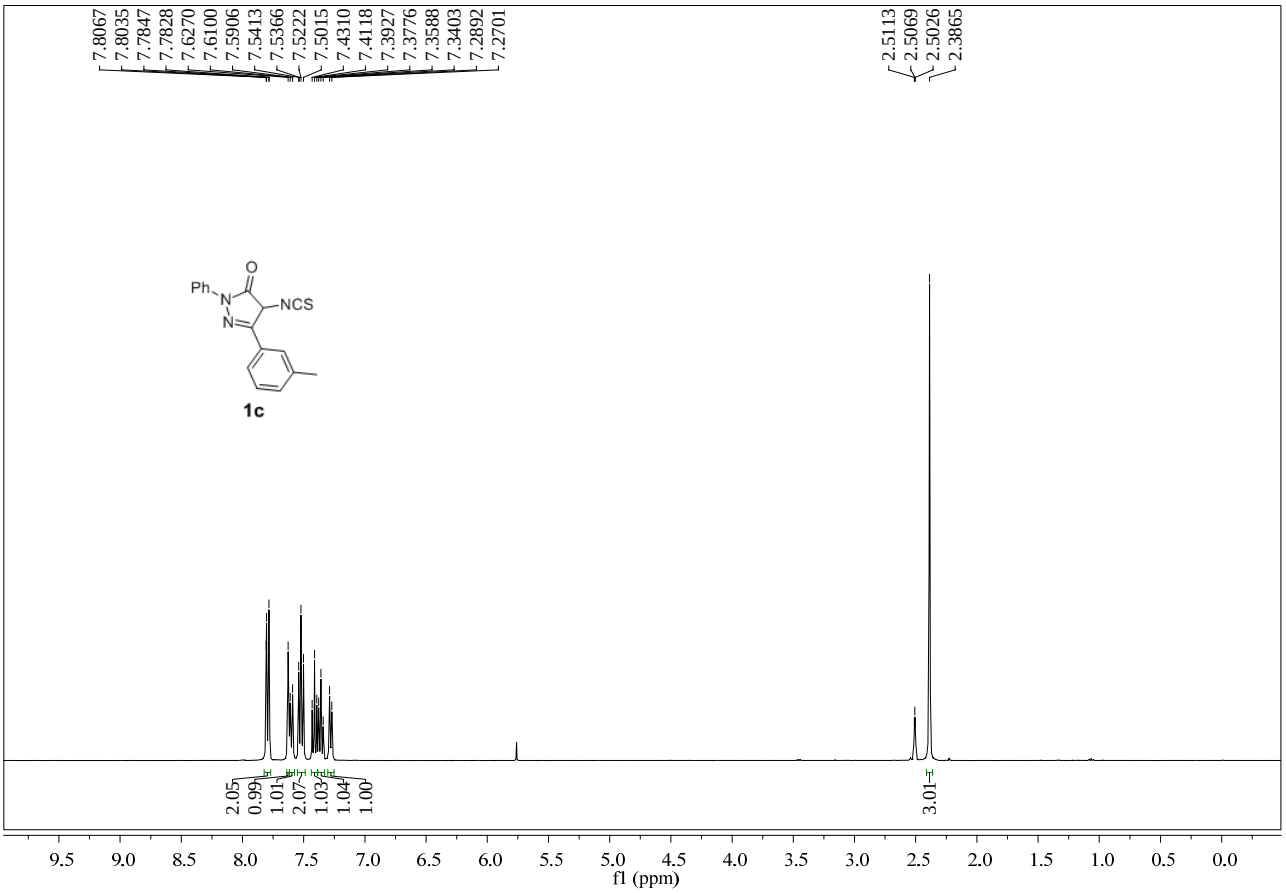
1b
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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7.5906
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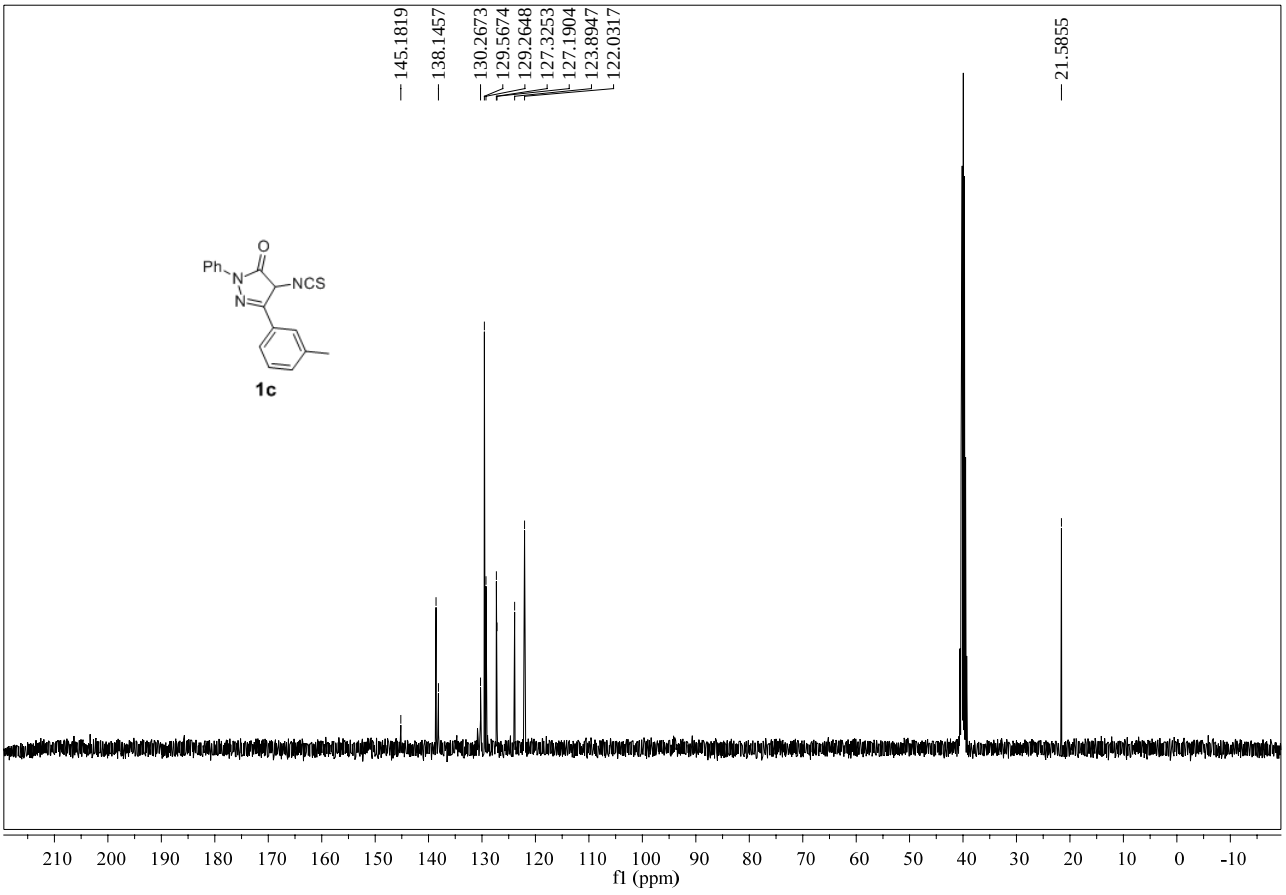
7.5015
7.4310
7.4118
7.3927
7.3776
7.3588
7.3403
7.2892
7.2701
2.5113
2.5069
2.5026
2.3865
Ph
N
N
O
NCS
1c
2.05
0.99
1.01
2.07
1.03
1.04
1.00
3.01
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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138.1457
130.2673
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129.2648
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127.1904
123.8947
122.0317
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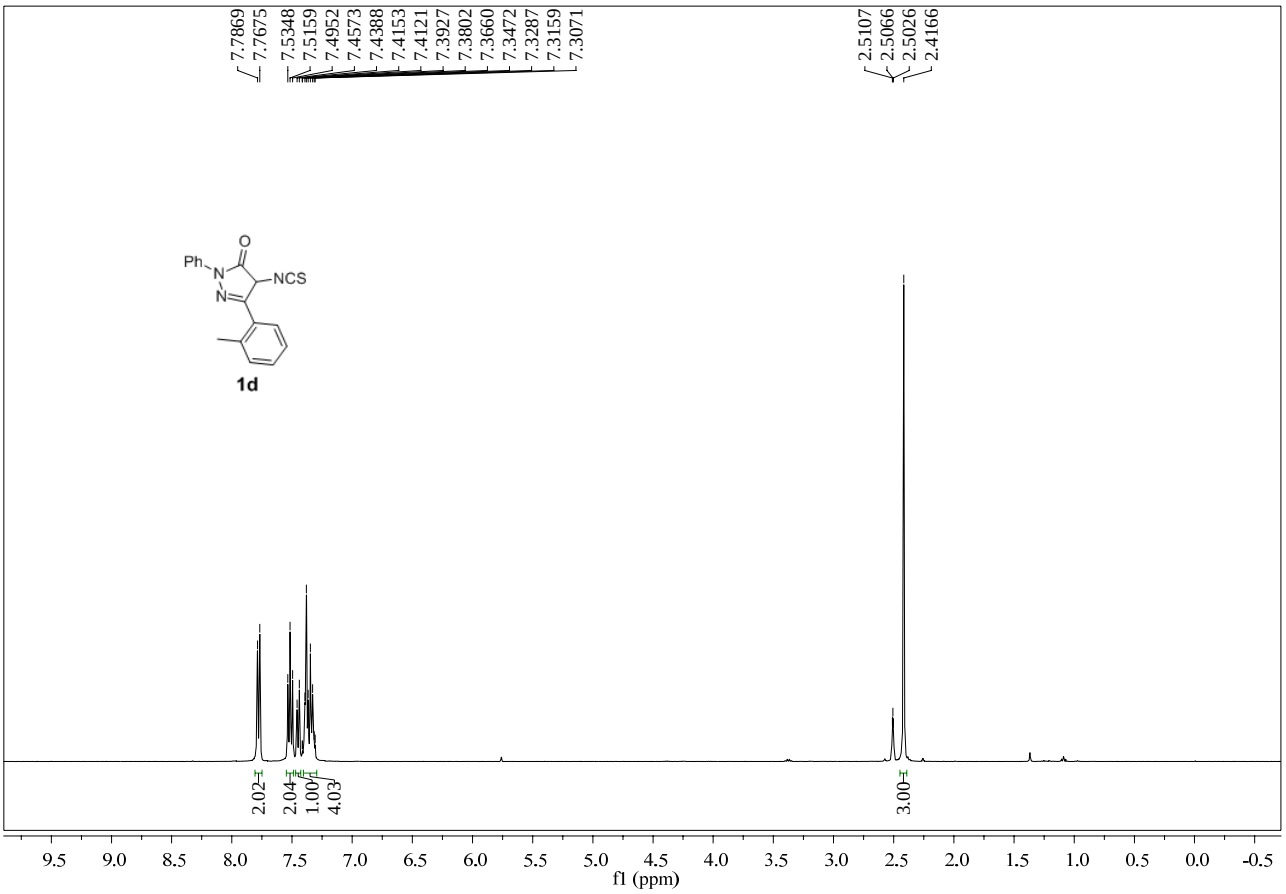
N
O
NCS
1c
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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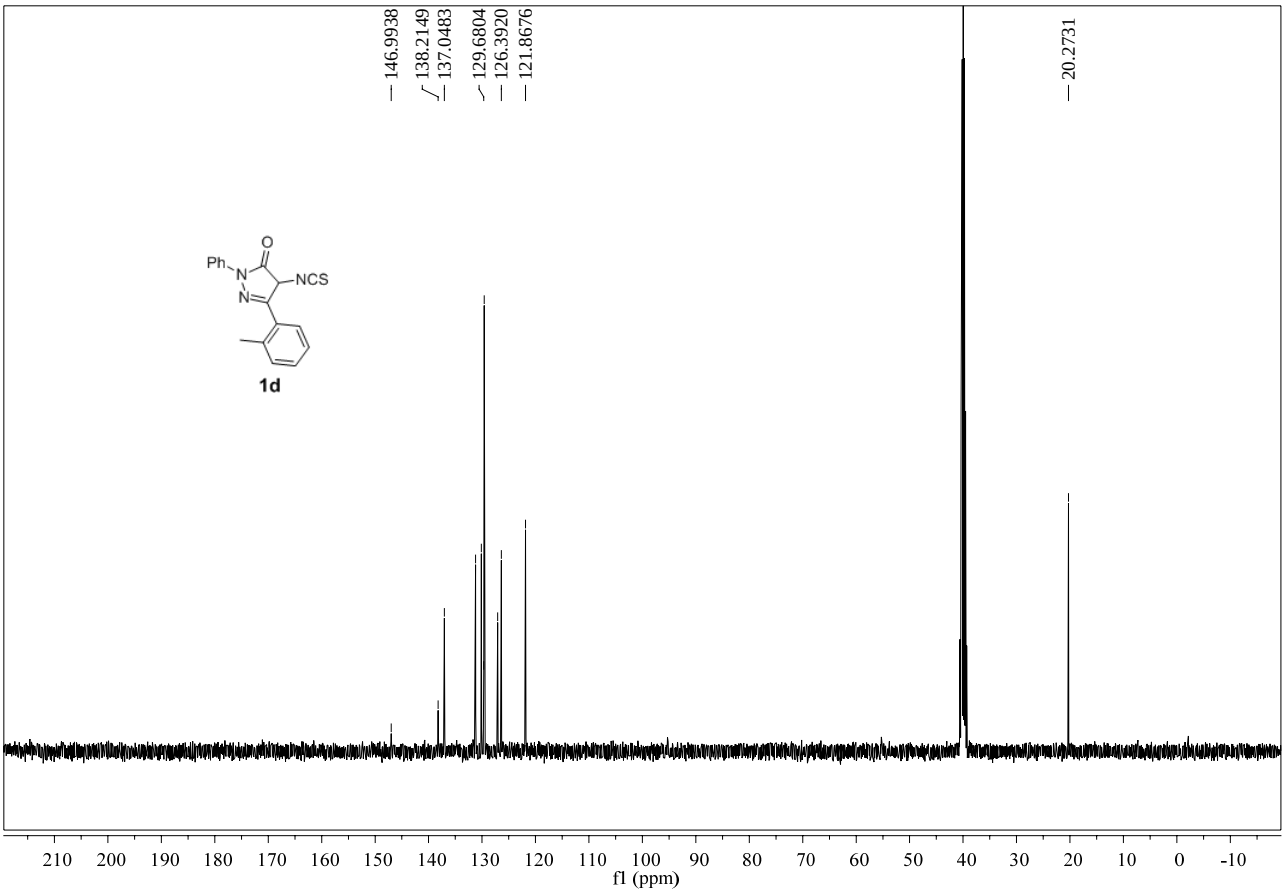
7.3802
7.3660
7.3472
7.3287
7.3159
7.3071
2.5107
2.5066
2.5026
2.4166
Ph
N
N
O
NCS
1d
2.02
2.04
1.00
4.03
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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126.3920
121.8676
20.2731
Ph
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N
O
NCS
1d
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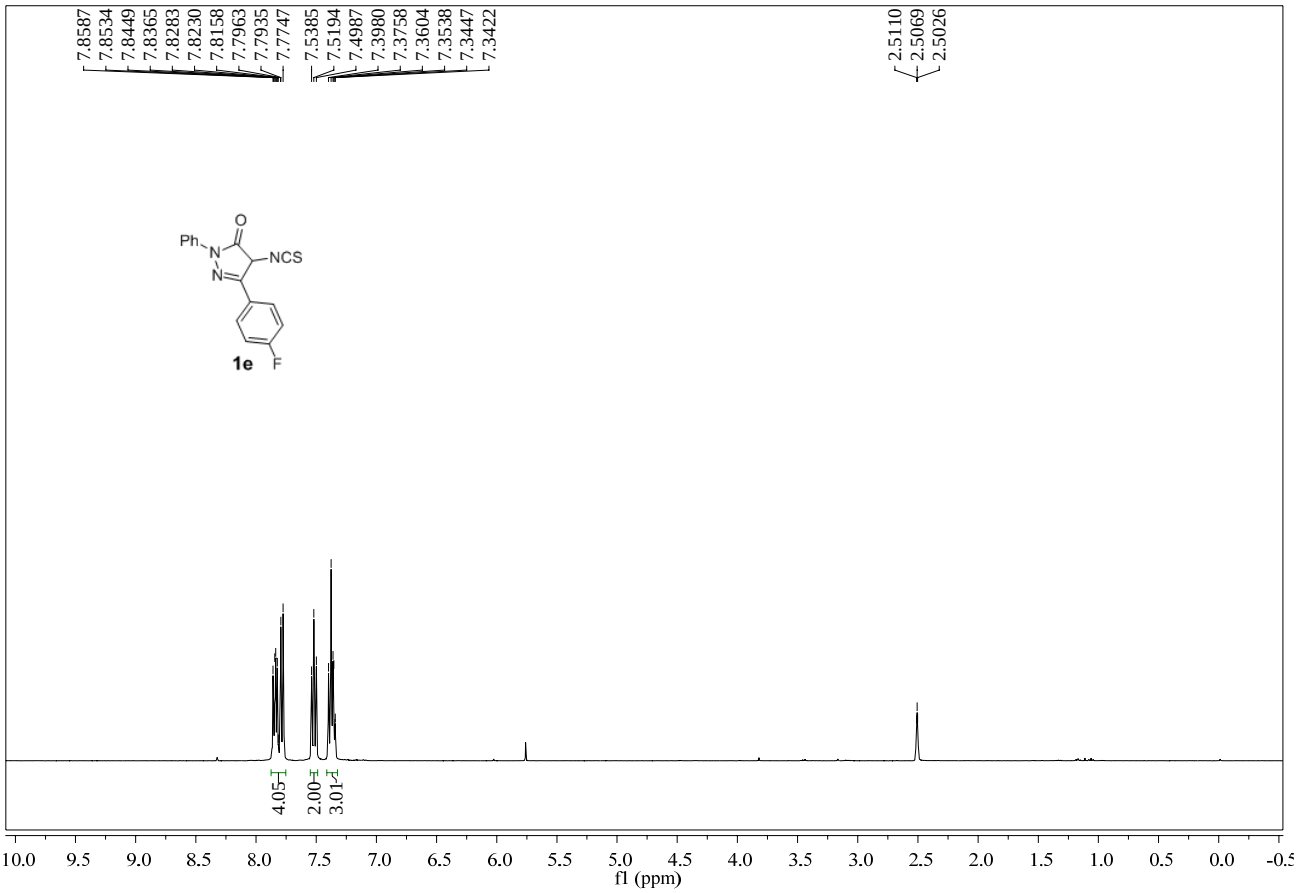
f1 (ppm)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7.7935
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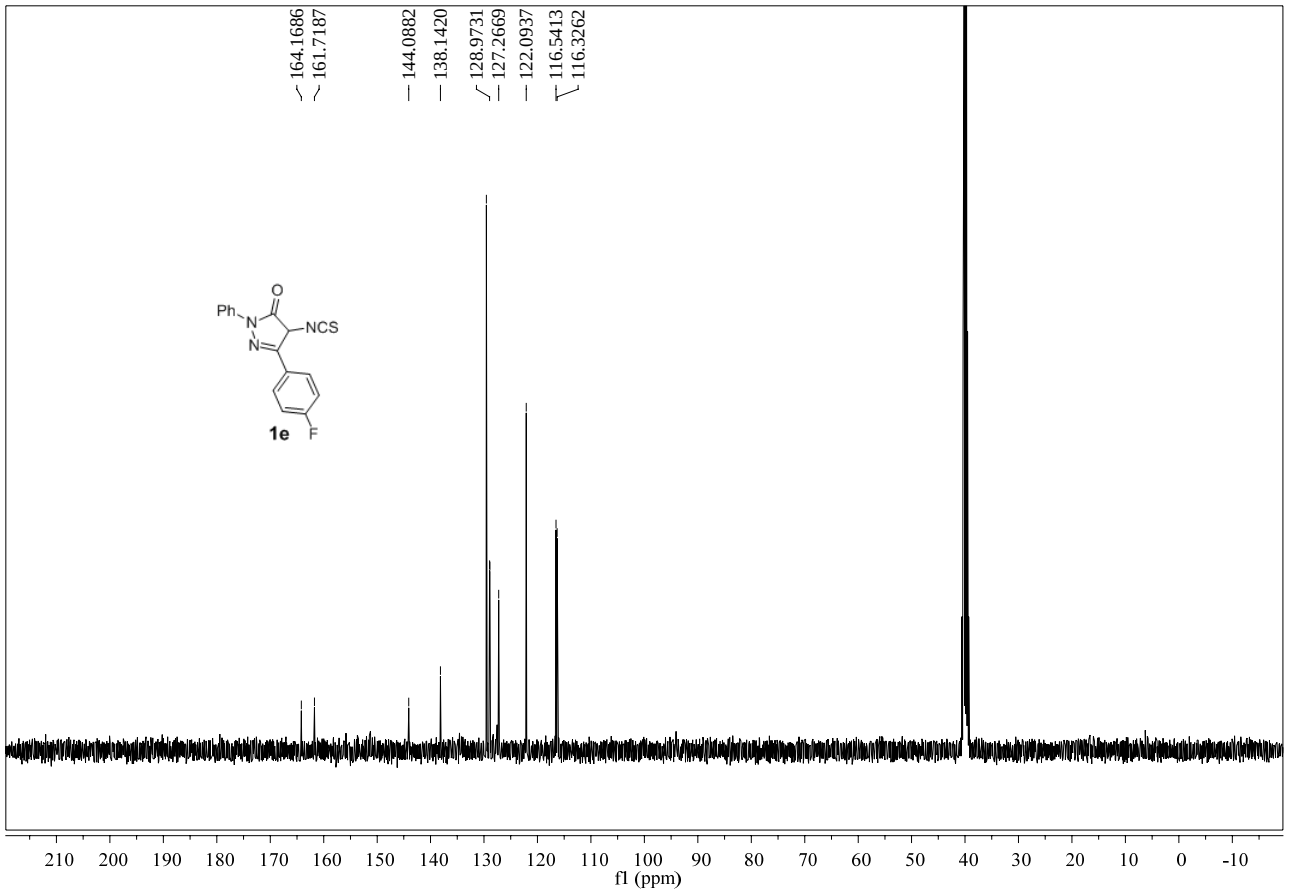
7.5385
7.5194
7.4987
7.3980
7.3758
7.3604
7.3538
7.3447
7.3422
2.5110
2.5069
2.5026
Ph
N
N
O
NCS
F
1e
4.05
2.00
3.01
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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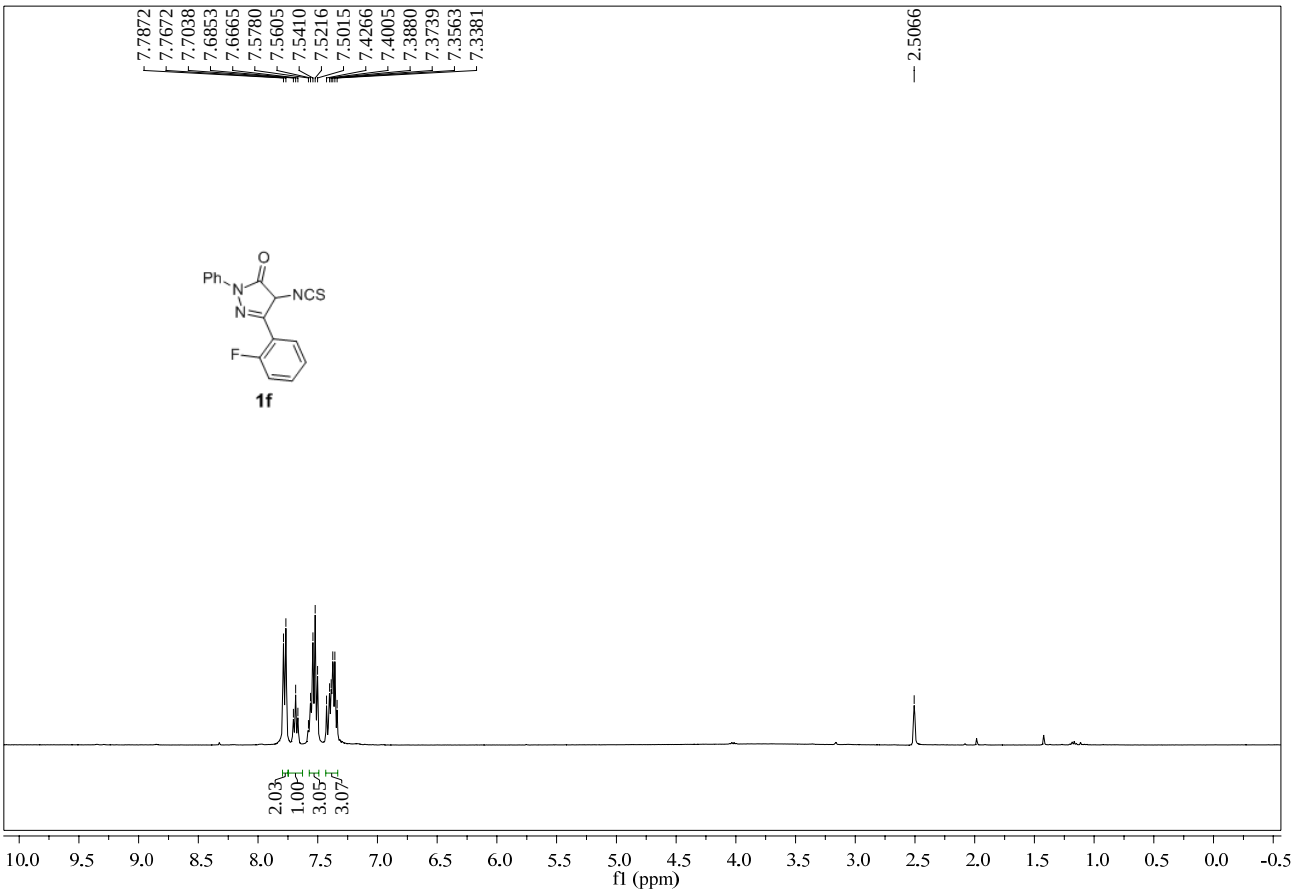
N
O
NCS
F
1e
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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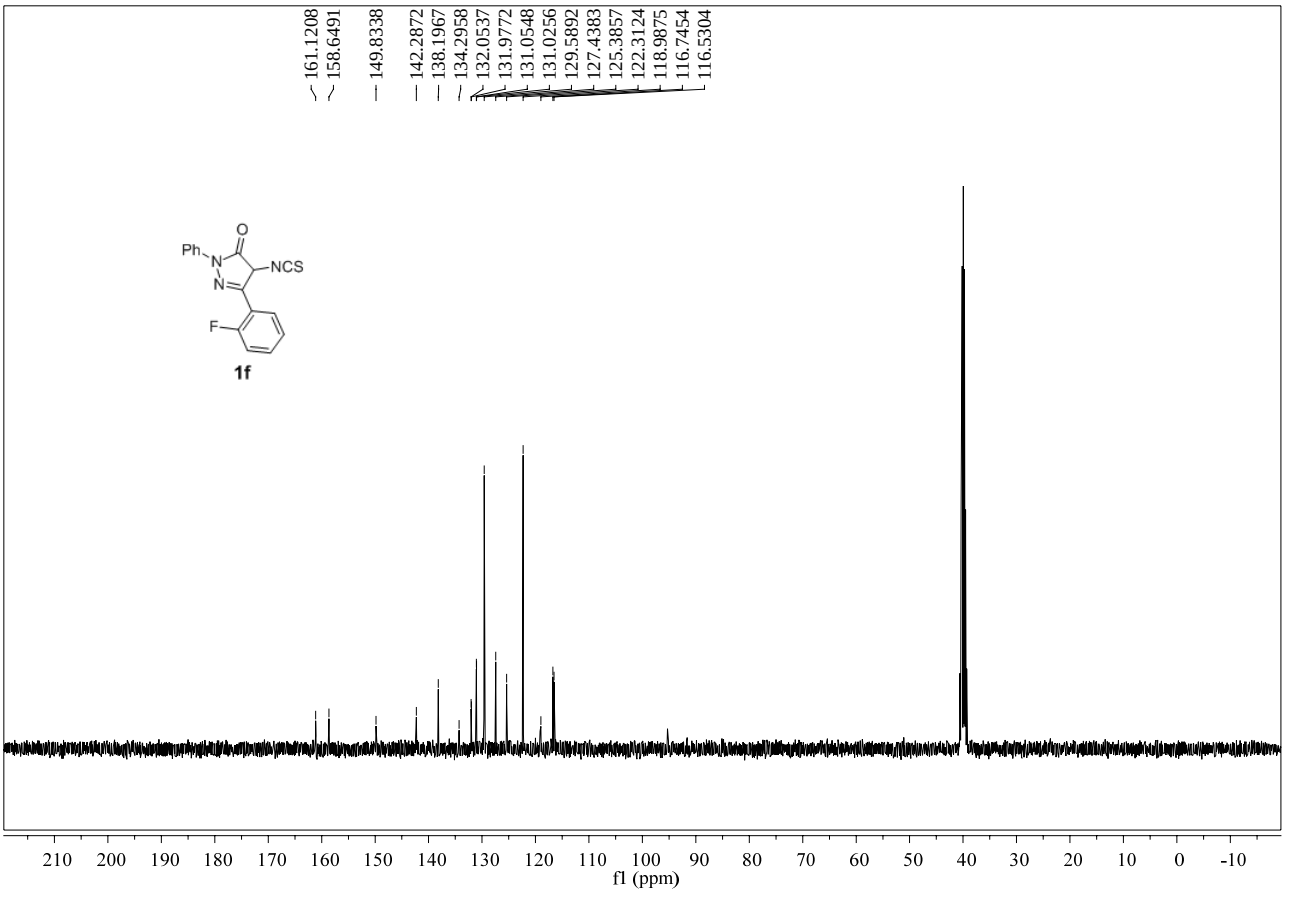
7.6665
7.5780
7.5605
7.5410
7.5216
7.5015
7.4266
7.4005
7.3880
7.3739
7.3563
7.3381
2.5066
Ph
N
N
O
NCS
F
1f
2.03
1.00
3.05
3.07
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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158.6491
149.8338
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138.1967
134.2958
132.0537
131.9772
131.0548
131.0256
129.5892
127.4383
125.3857
122.3124
118.9875
116.7454
116.5304
Ph
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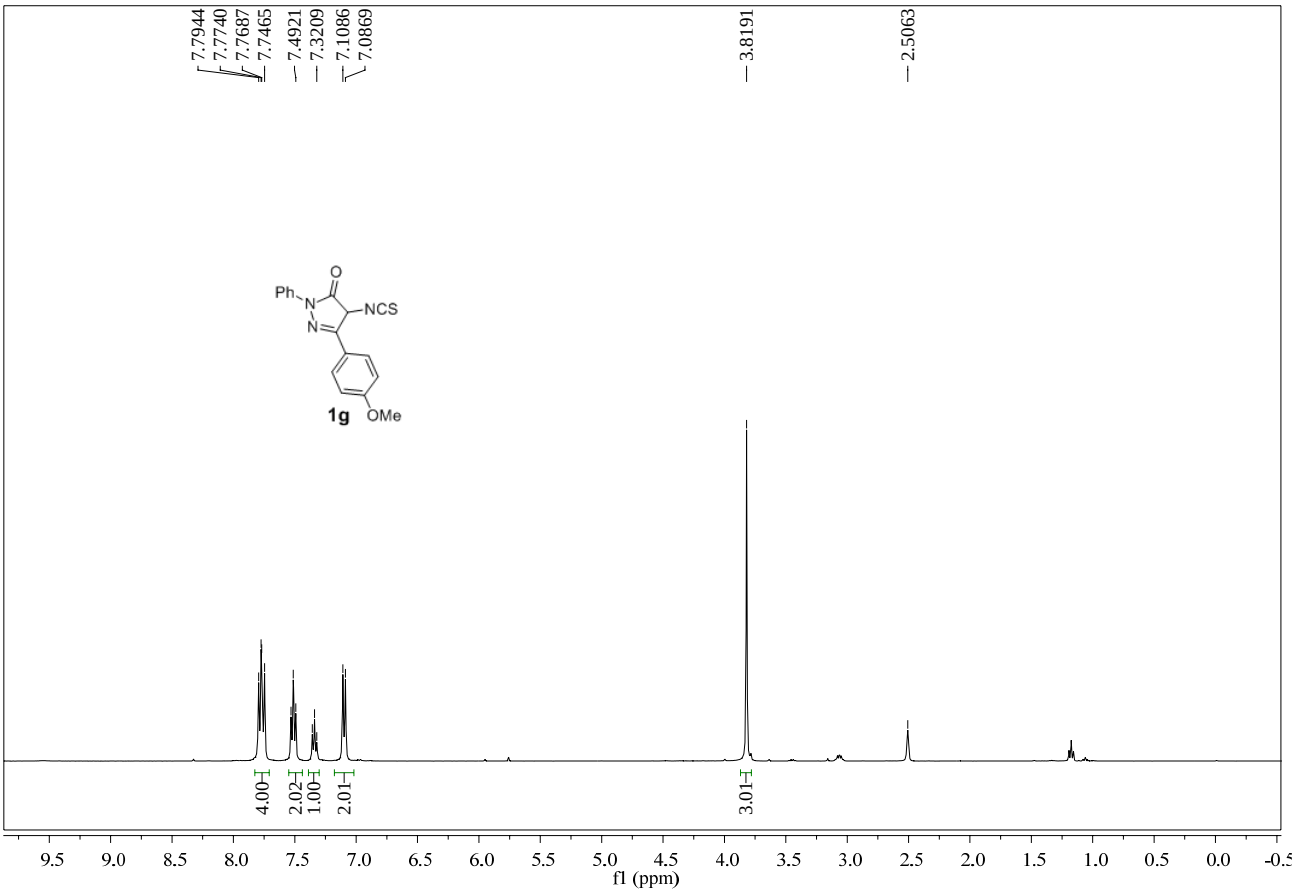
N
O
NCS
F
1f
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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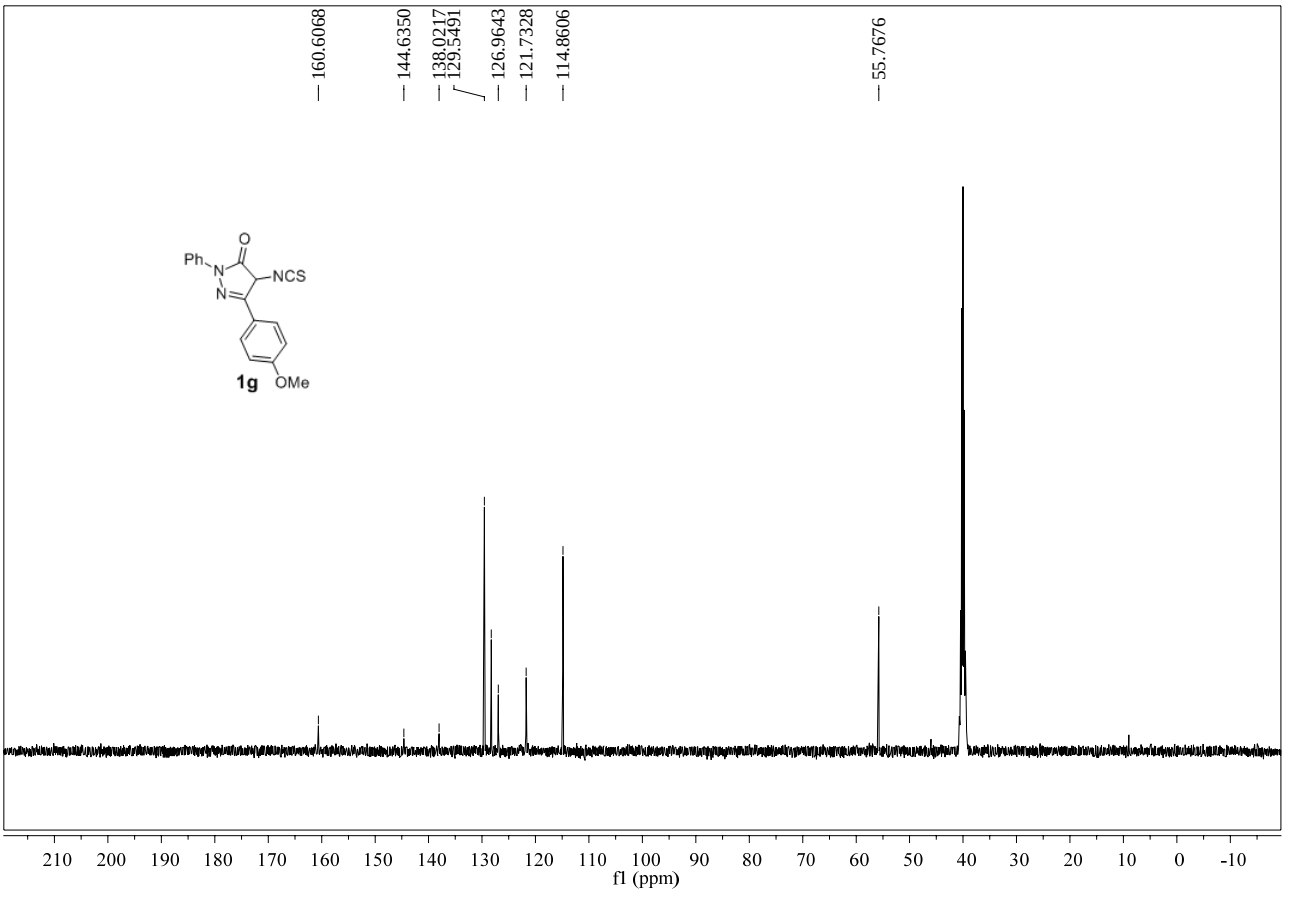
7.7687
7.7465
7.4921
7.3209
7.1086
7.0869
3.8191
2.5063
Ph
N
N
O
NCS
OMe
1g
4.00
2.02
1.00
2.01
3.01
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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138.0217
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126.9643
121.7328
114.8606
55.7676
Ph
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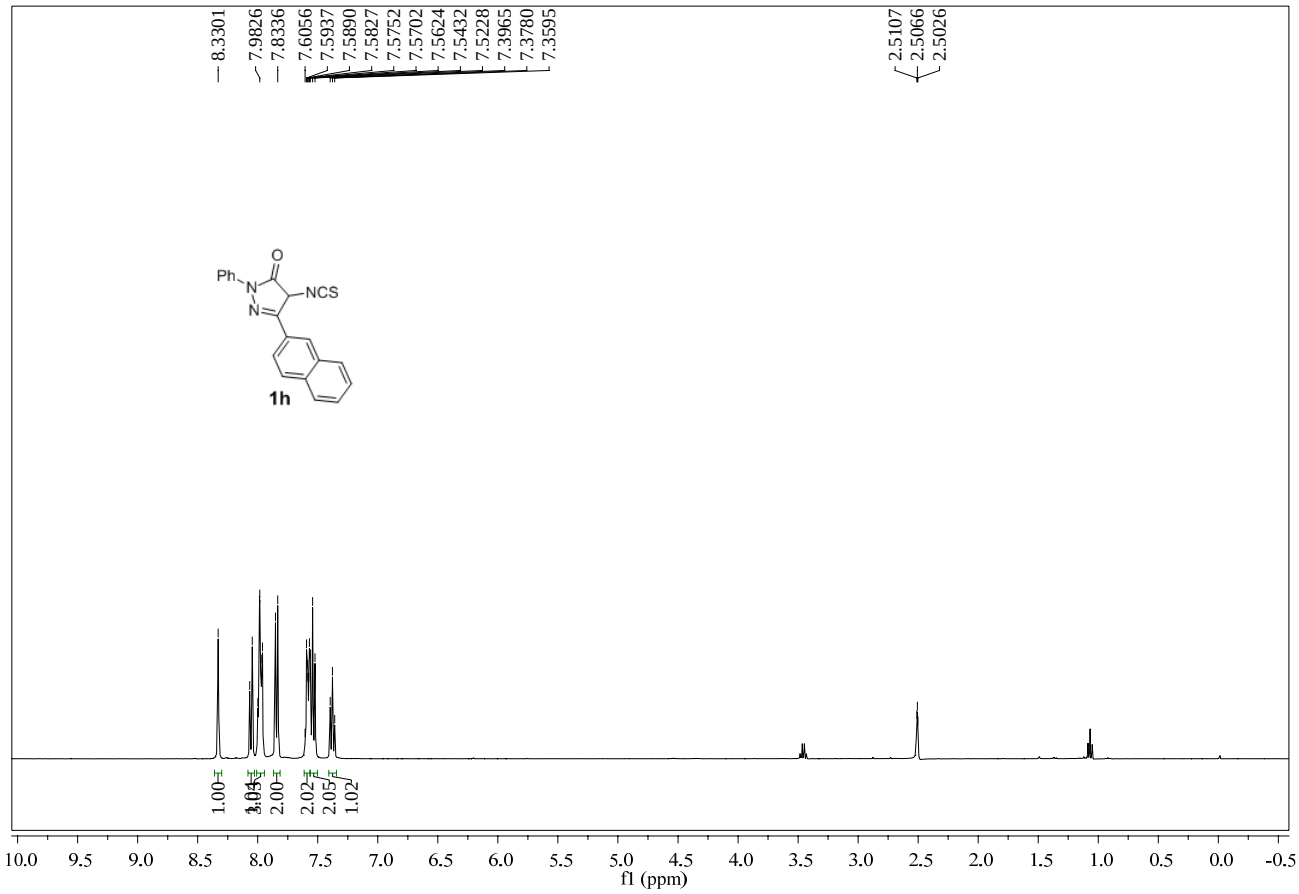
N
O
NCS
OMe
1g
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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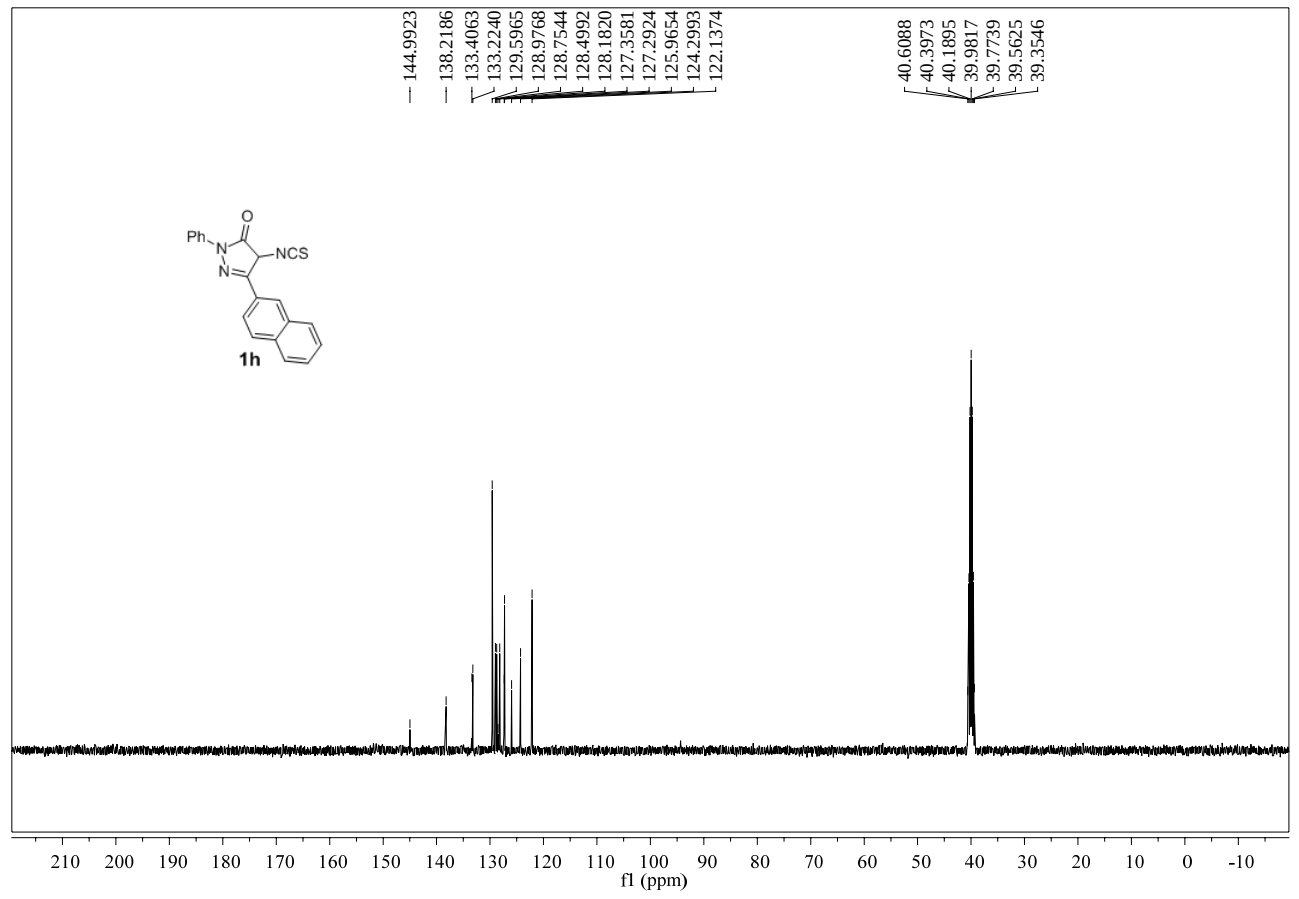
7.5432
7.5228
7.3965
7.3780
7.3595
2.5107
2.5066
2.5026
Ph
N
N
O
NCS
1h
1.00
2.00
2.02
2.05
1.02
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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128.1820
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127.2924
125.9654
124.2993
122.1374
40.6088
40.3973
40.1895
39.9817
39.7739
39.5625
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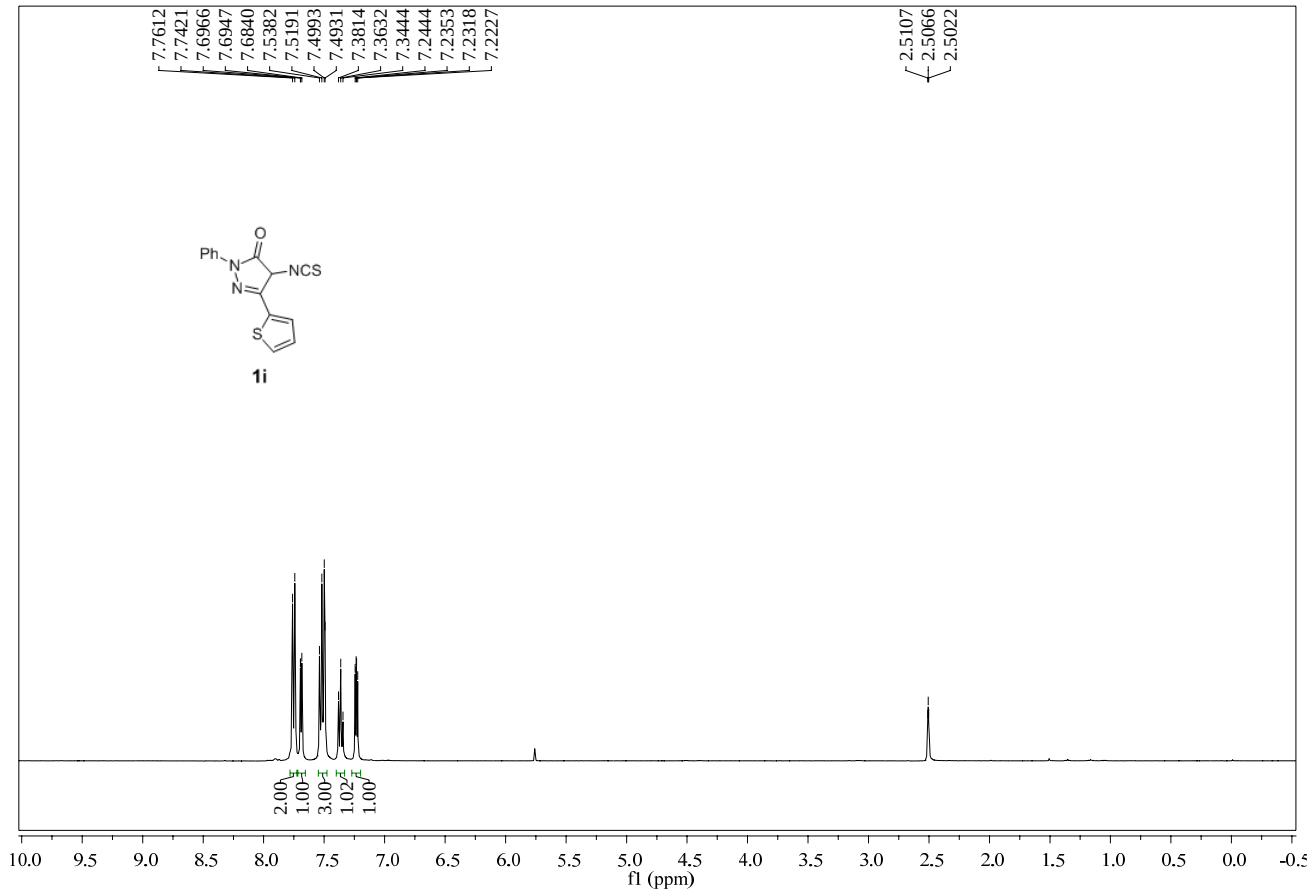
Ph
N
N
O
NCS
1h
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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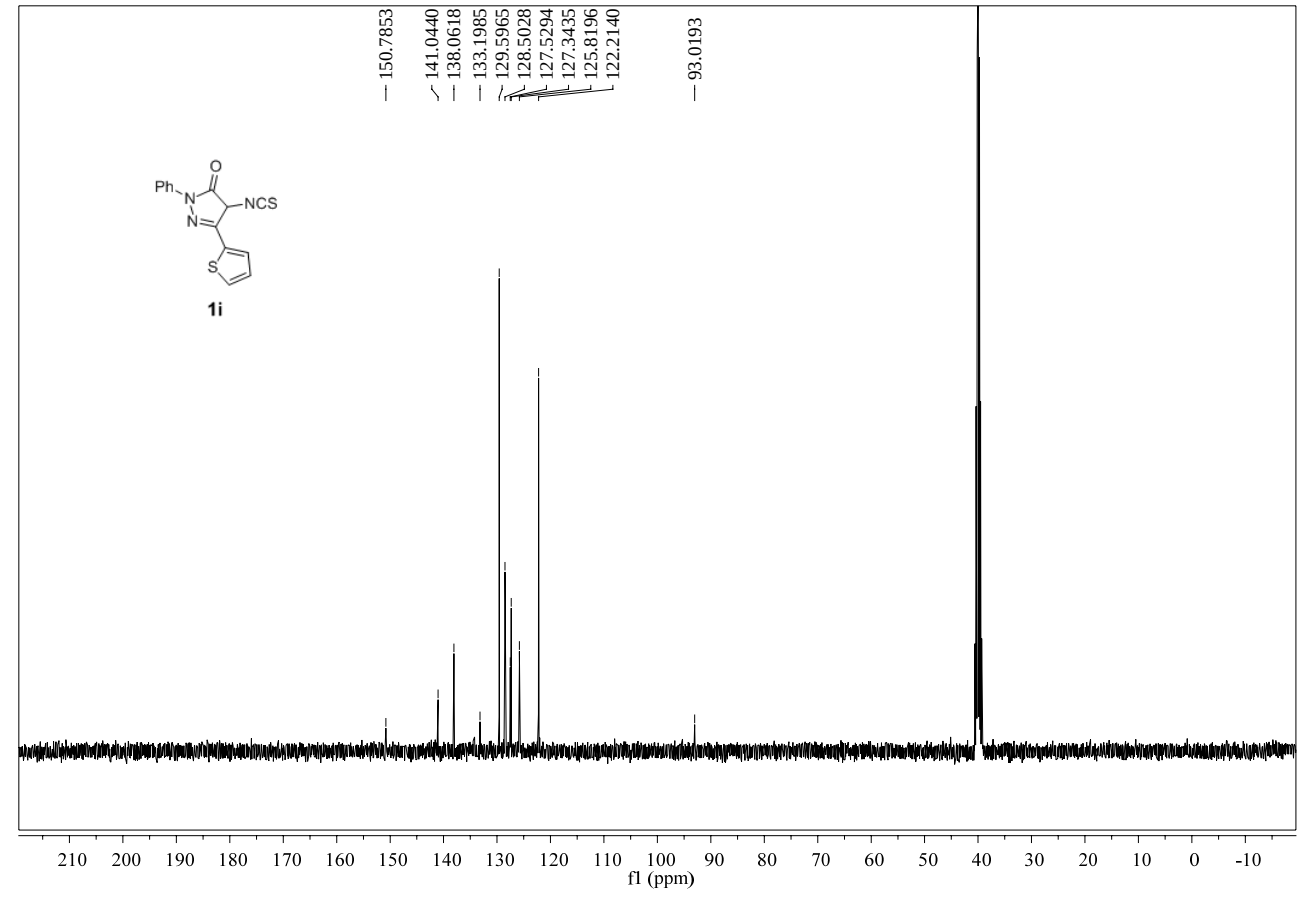
7.3632
7.3444
7.2444
7.2353
7.2318
7.2227
2.5107
2.5066
2.5022
Ph
N
N
O
NCS
S
1i
2.00
1.00
3.00
1.02
1.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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125.8196
122.2140
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Ph
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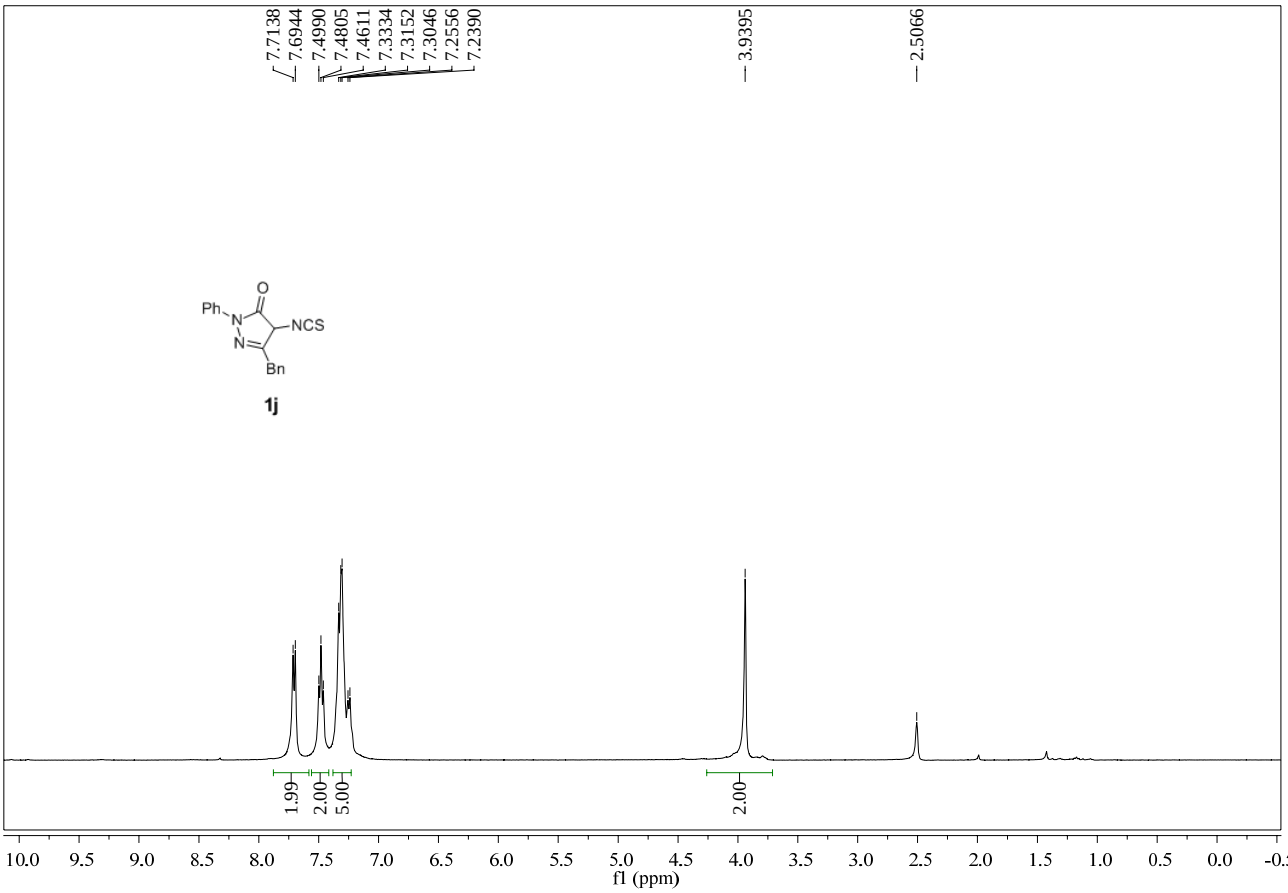
N
O
NCS
S
1i
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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7.2556
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3.9395
2.5066
Ph
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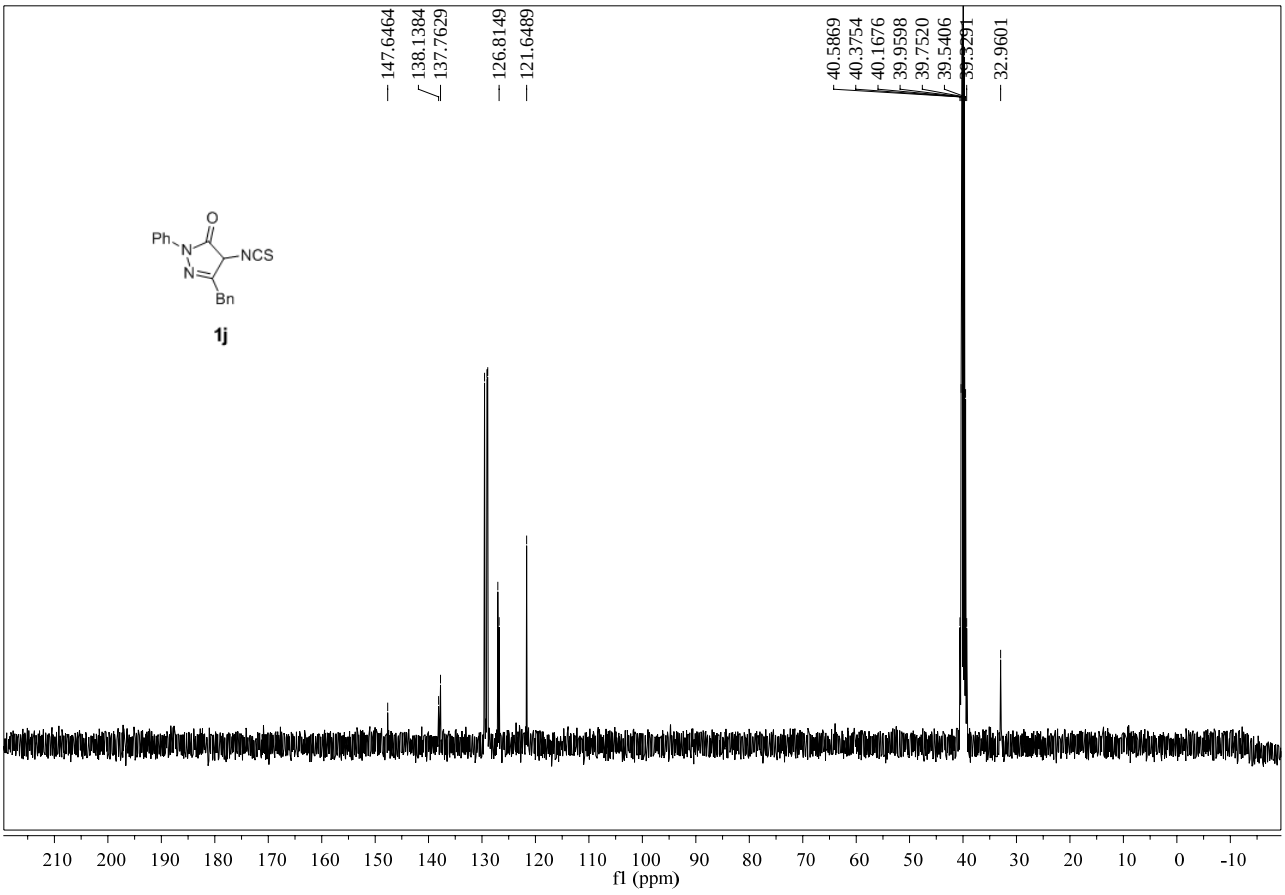
N
O
NCS
Bn
1j
1.99
2.00
5.00
2.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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39.5406
39.3291
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Ph
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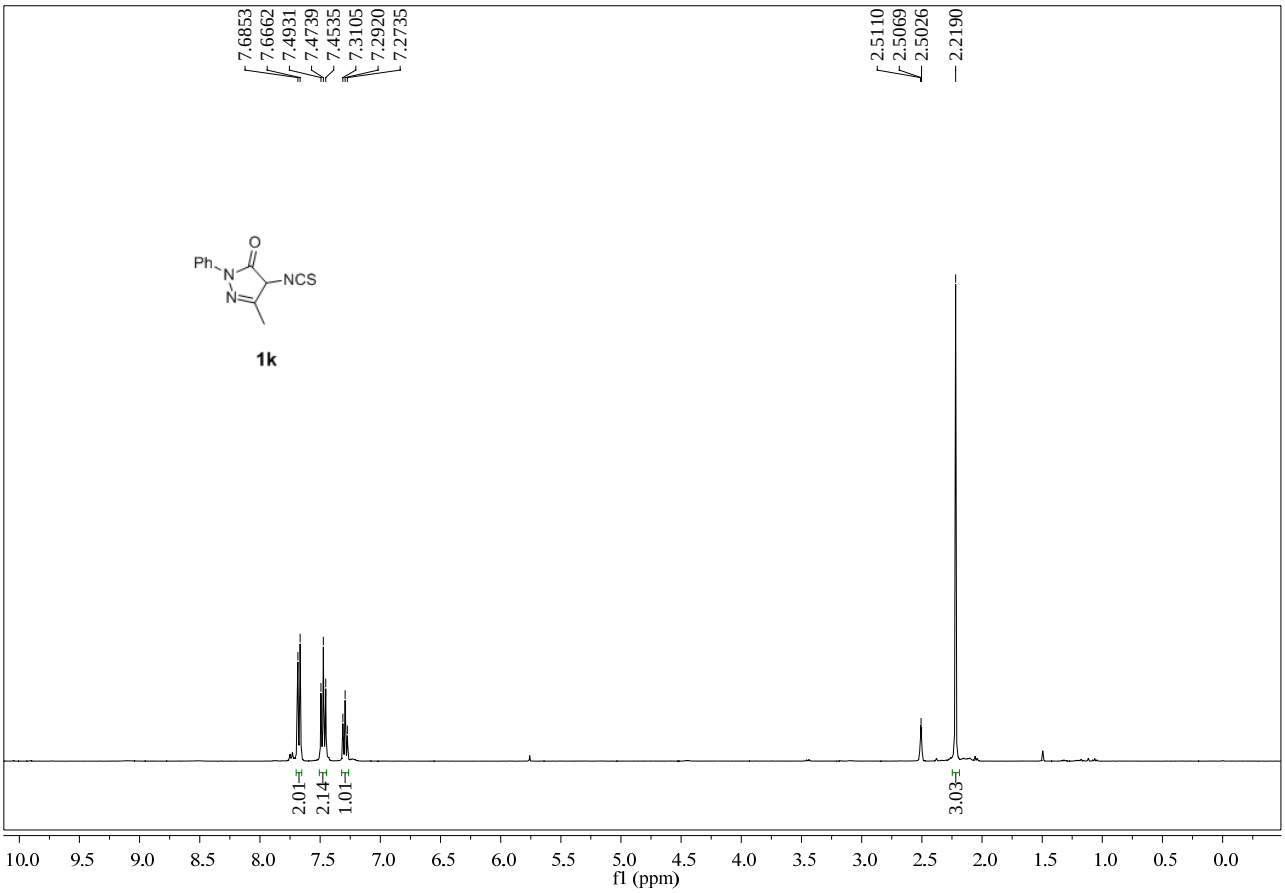
O
NCS
Bn
1j
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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7.2920
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2.5069
2.5026
2.2190
Ph
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N
O
NCS
1k
2.01
2.14
1.01
3.03
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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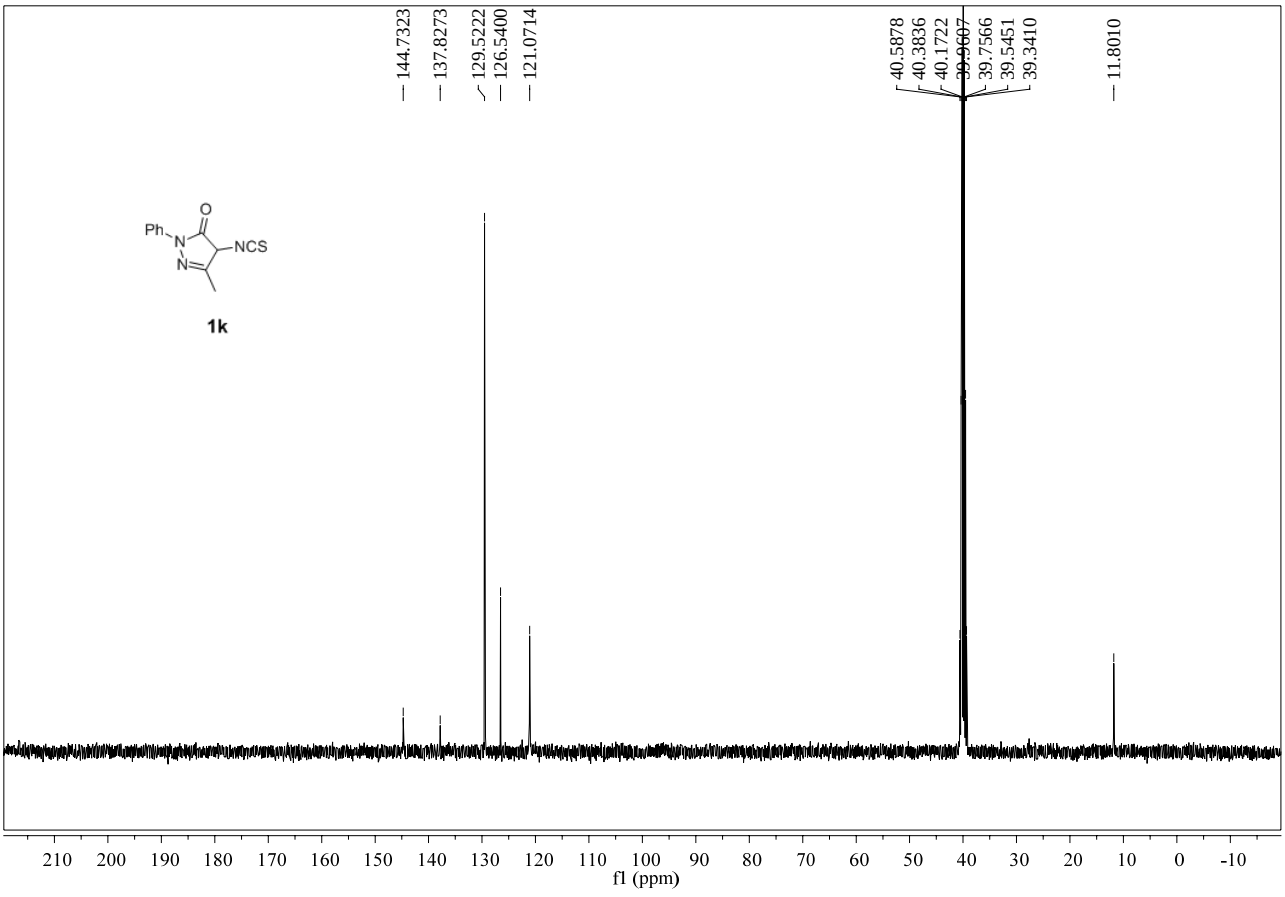
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39.5451
39.3410
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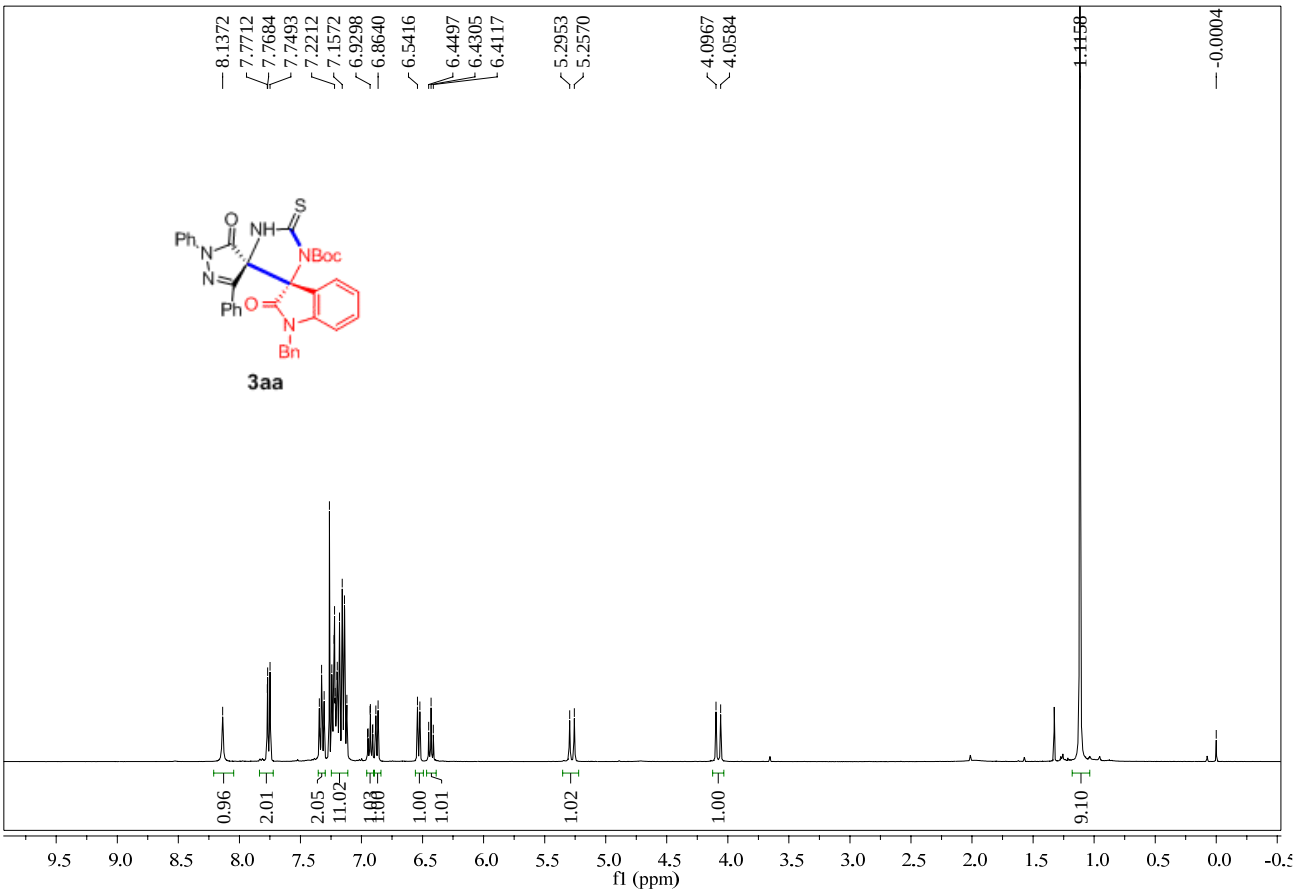
N
O
NCS
1k
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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6.4305
6.4117
5.2953
5.2570
4.0967
4.0584
1.1158
-0.0004
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2.01
2.05
11.02
1.00
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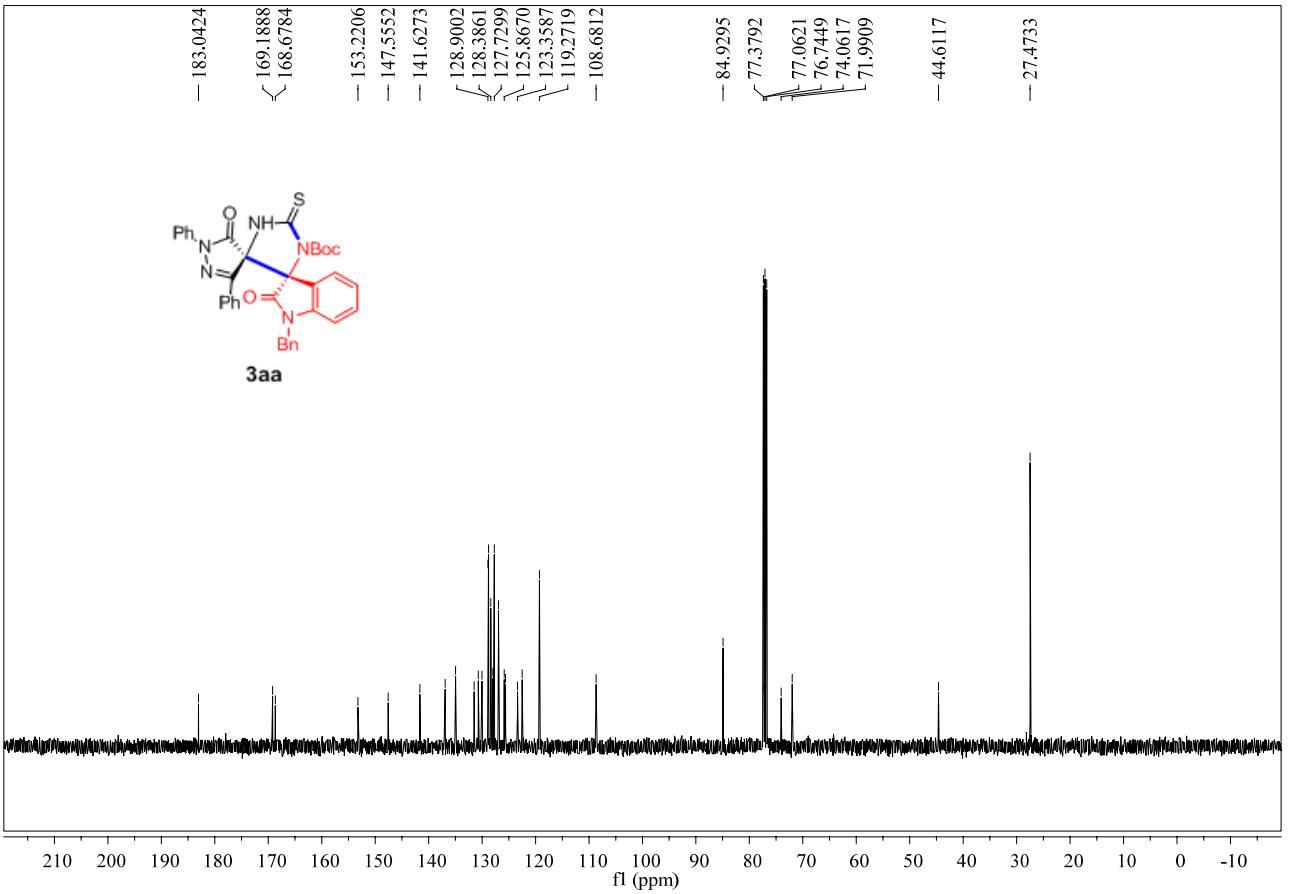
9.10
Ph
NH
S
NBoc
N
Ph
O
N
Bn
3aa
f1 (ppm)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77.3792
77.0621
76.7449
74.0617
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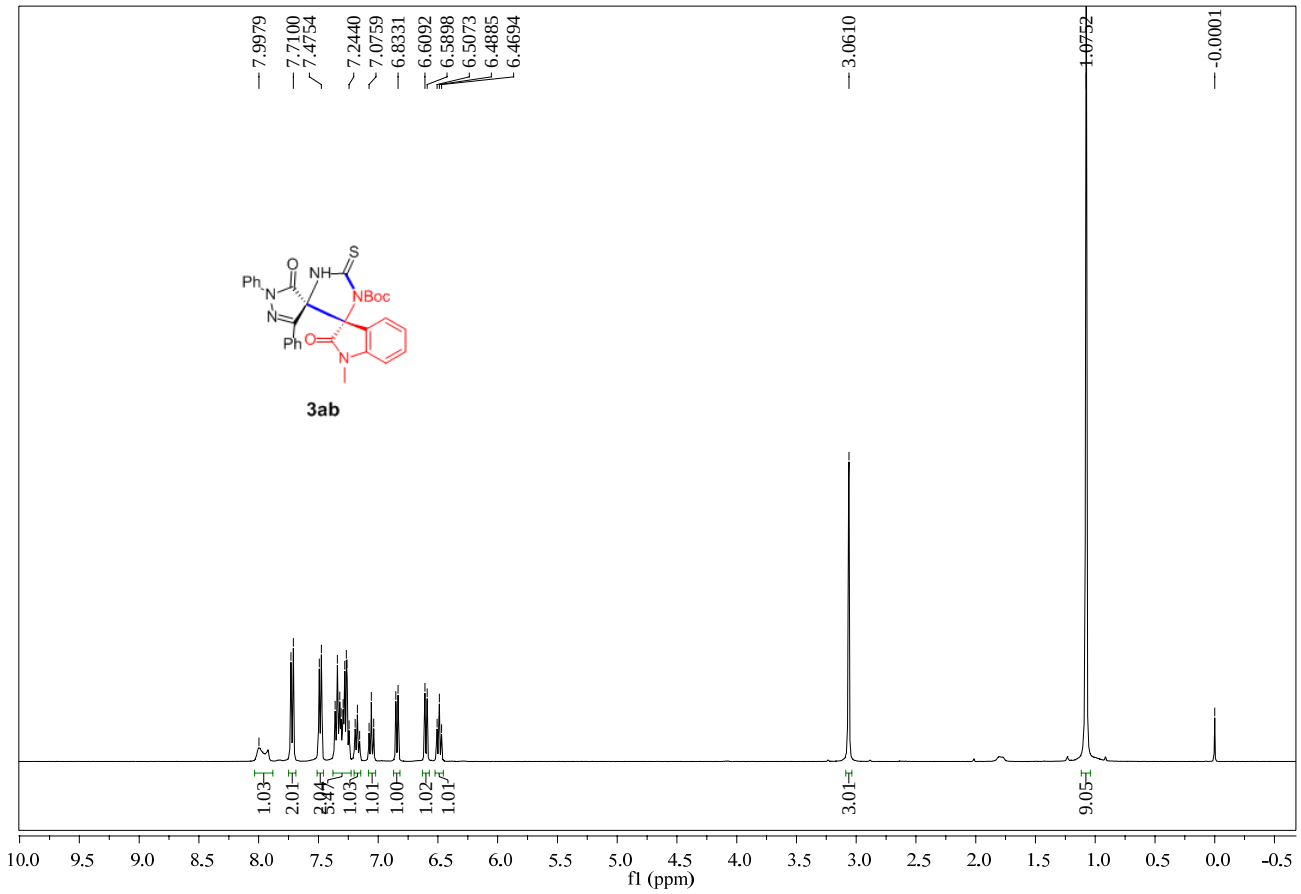
Ph
O
N
Bn
3aa
f1 (ppm)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6.4694
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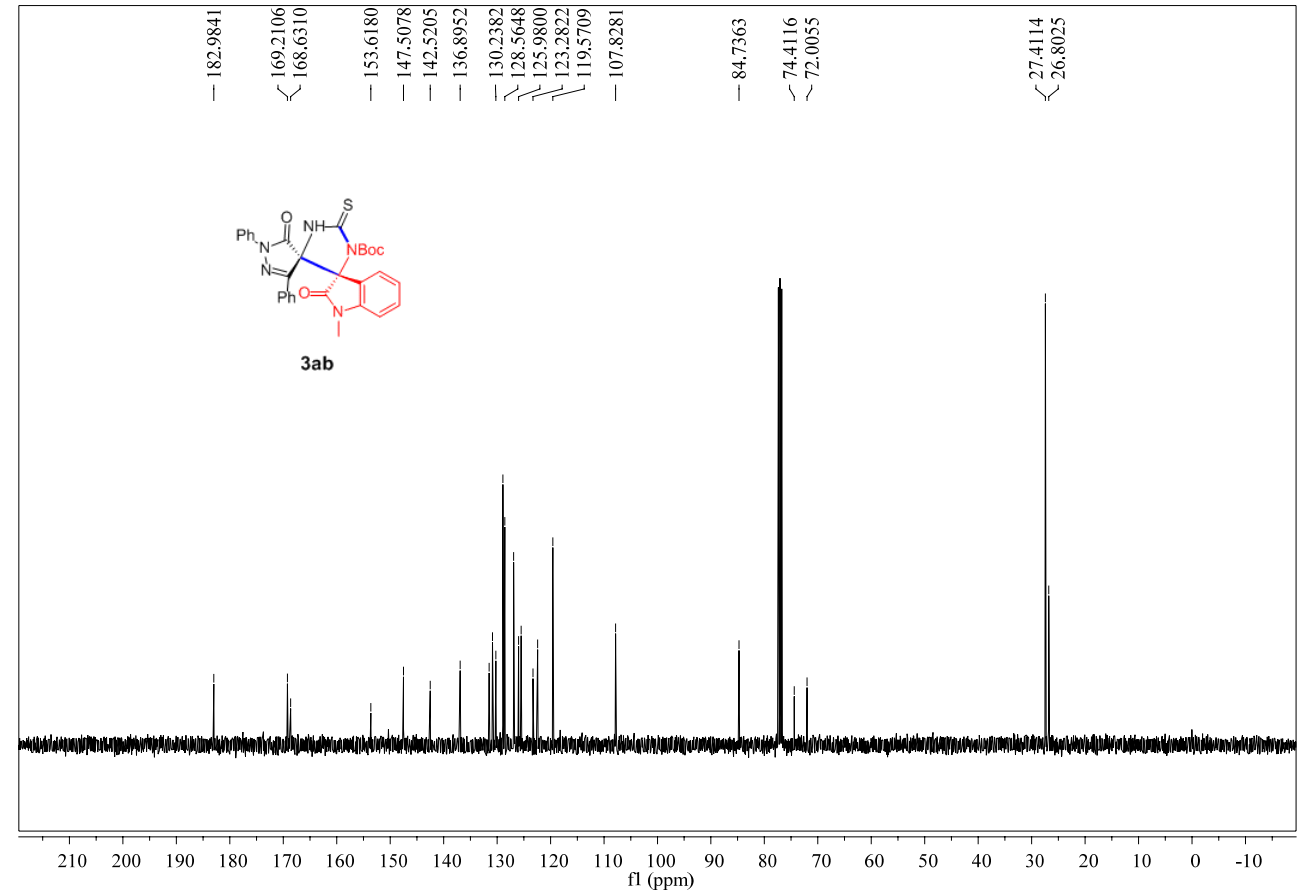
2.01
2.04
1.03
1.01
1.00
1.02
1.01
3.01
9.05
Ph
N
N
O
NH
S
NBoc
Ph
O
N
3ab
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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123.2822
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107.8281
84.7363
74.4116
72.0055
27.4114
26.8025
Ph
N
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S
NBoc
Ph
O
N
3ab
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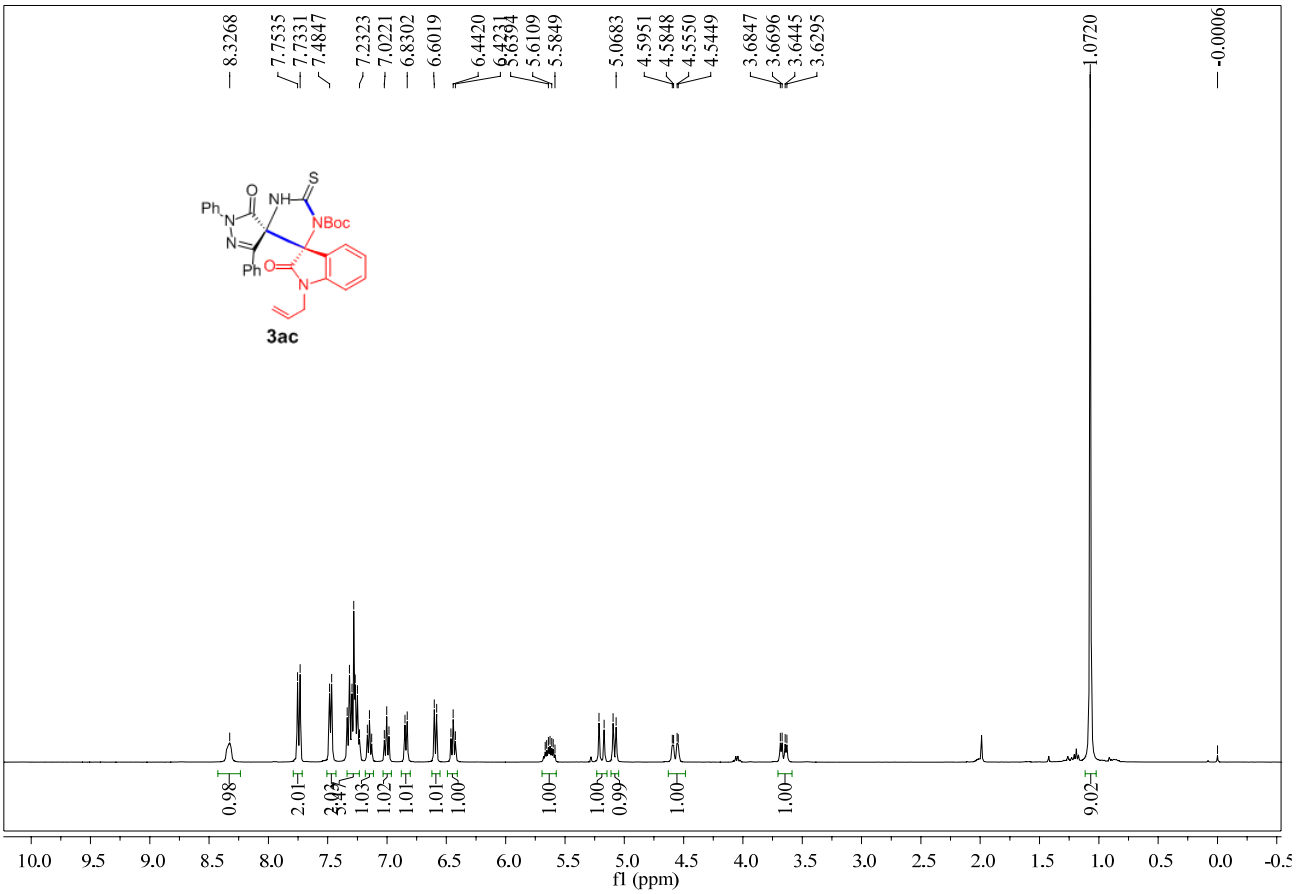
f1 (ppm)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5.6109
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5.0683
4.5951
4.5848
4.5550
4.5449
3.6847
3.6696
3.6445
3.6295
1.0720
-0.0006
0.98
2.01
2.03
3.44
1.03
1.02
1.01
1.01
1.00
1.00
1.00
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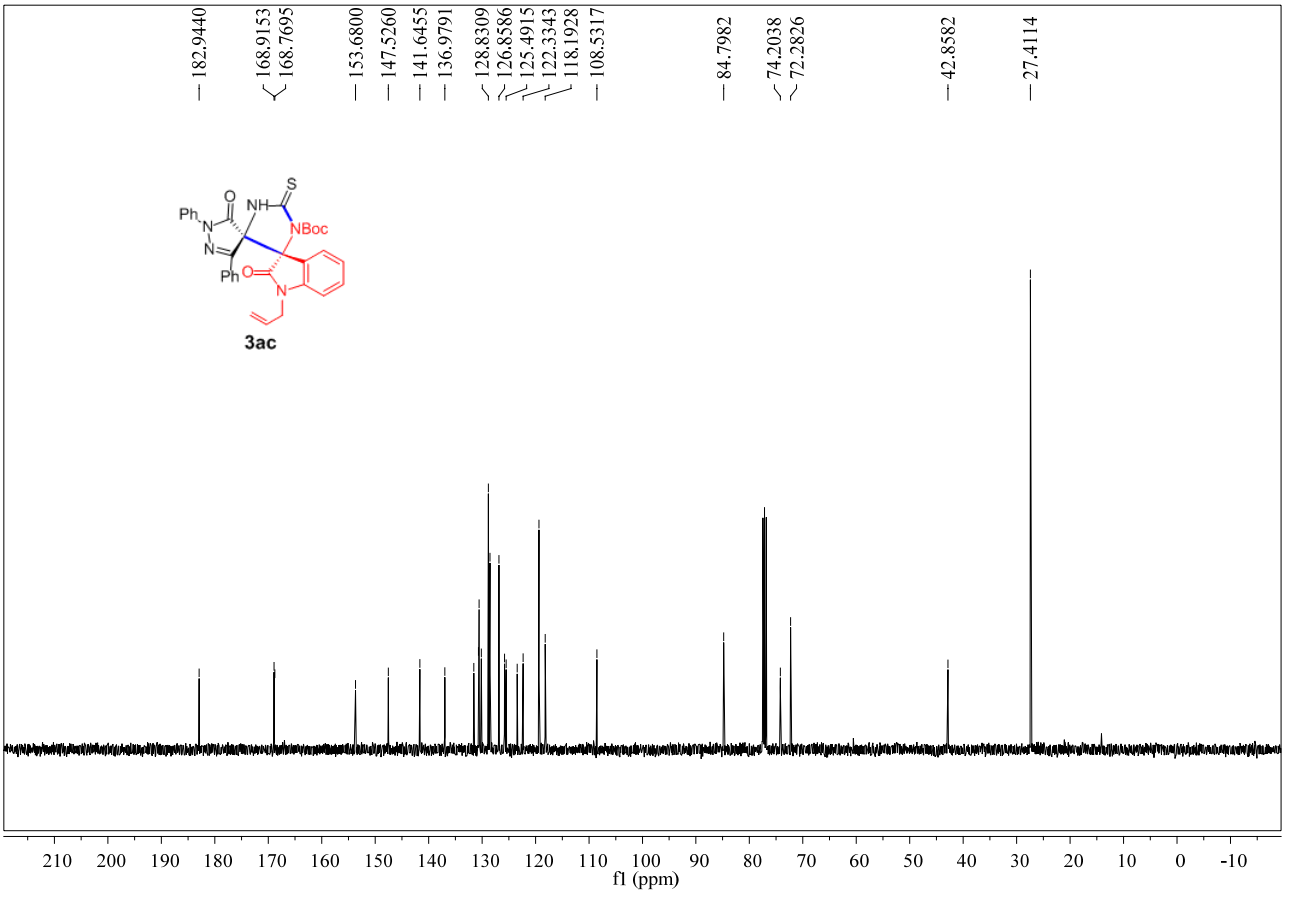
1.00
1.00
9.02
3ac
f1 (ppm)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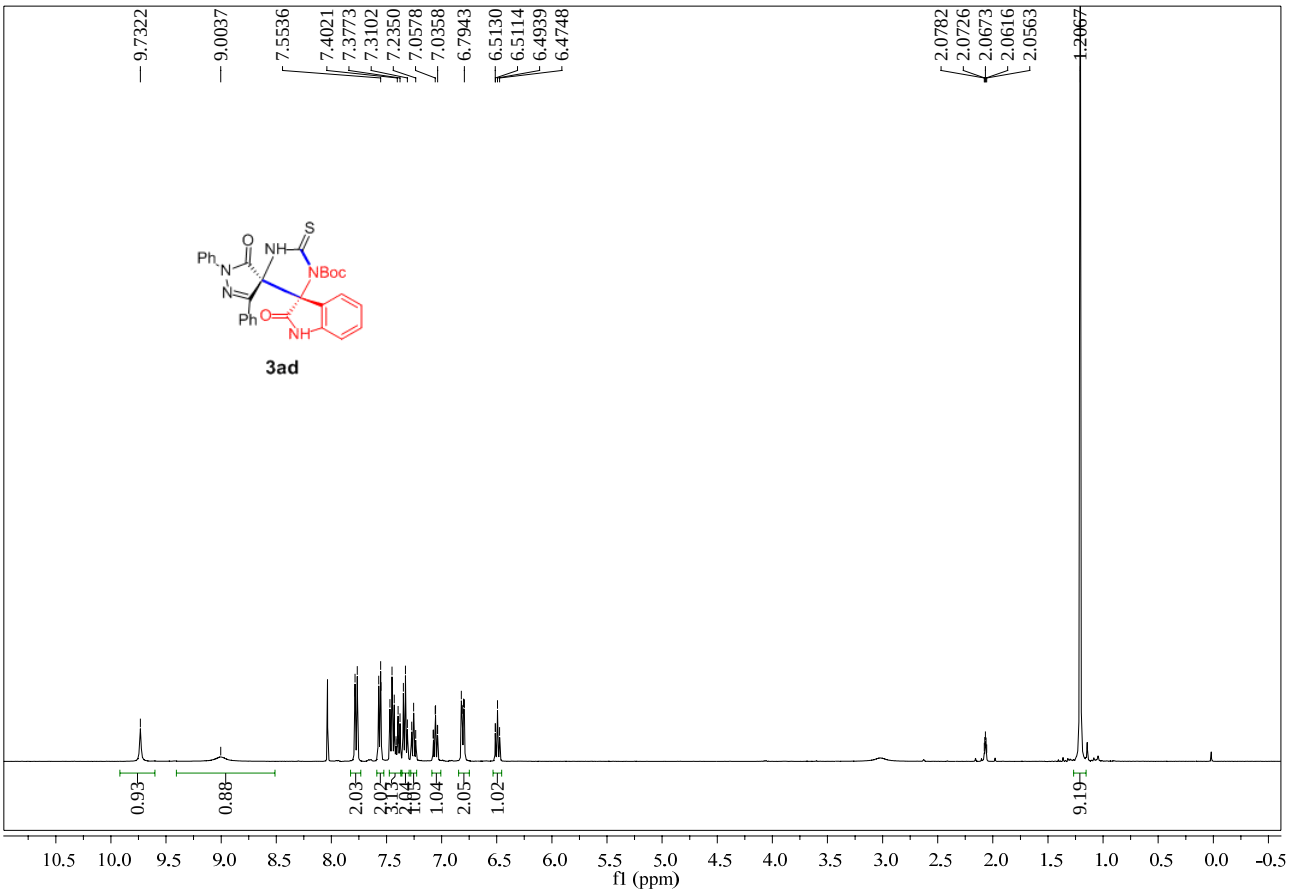
42.8582
27.4114
3ac
f1 (ppm)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6.5130
6.5114
6.4939
6.4748
2.0782
2.0726
2.0673
2.0616
2.0563
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2.04
1.04
2.05
1.02
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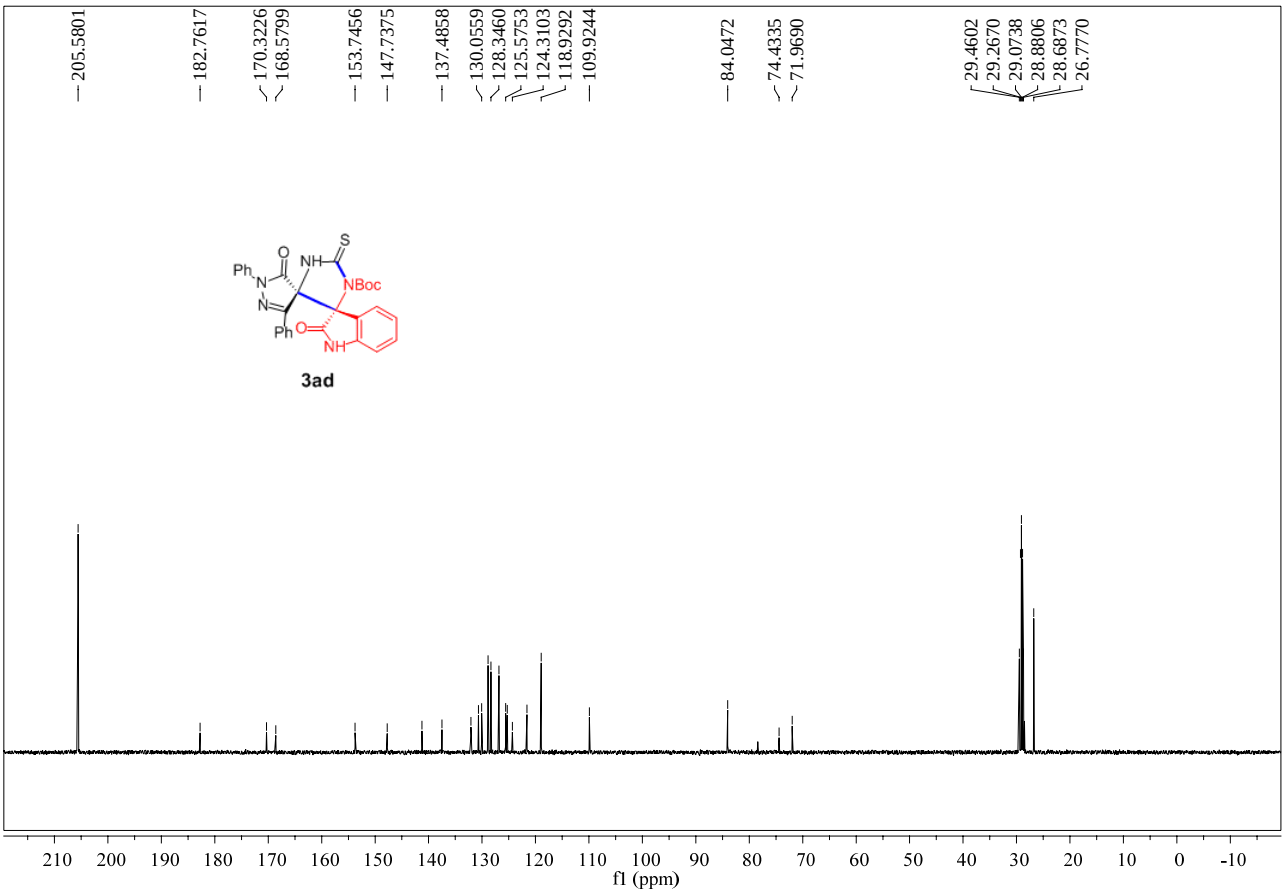
3ad
f1 (ppm)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153.7456
147.7375
137.4858
130.0559
128.3460
125.5753
124.3103
118.9292
109.9244
84.0472
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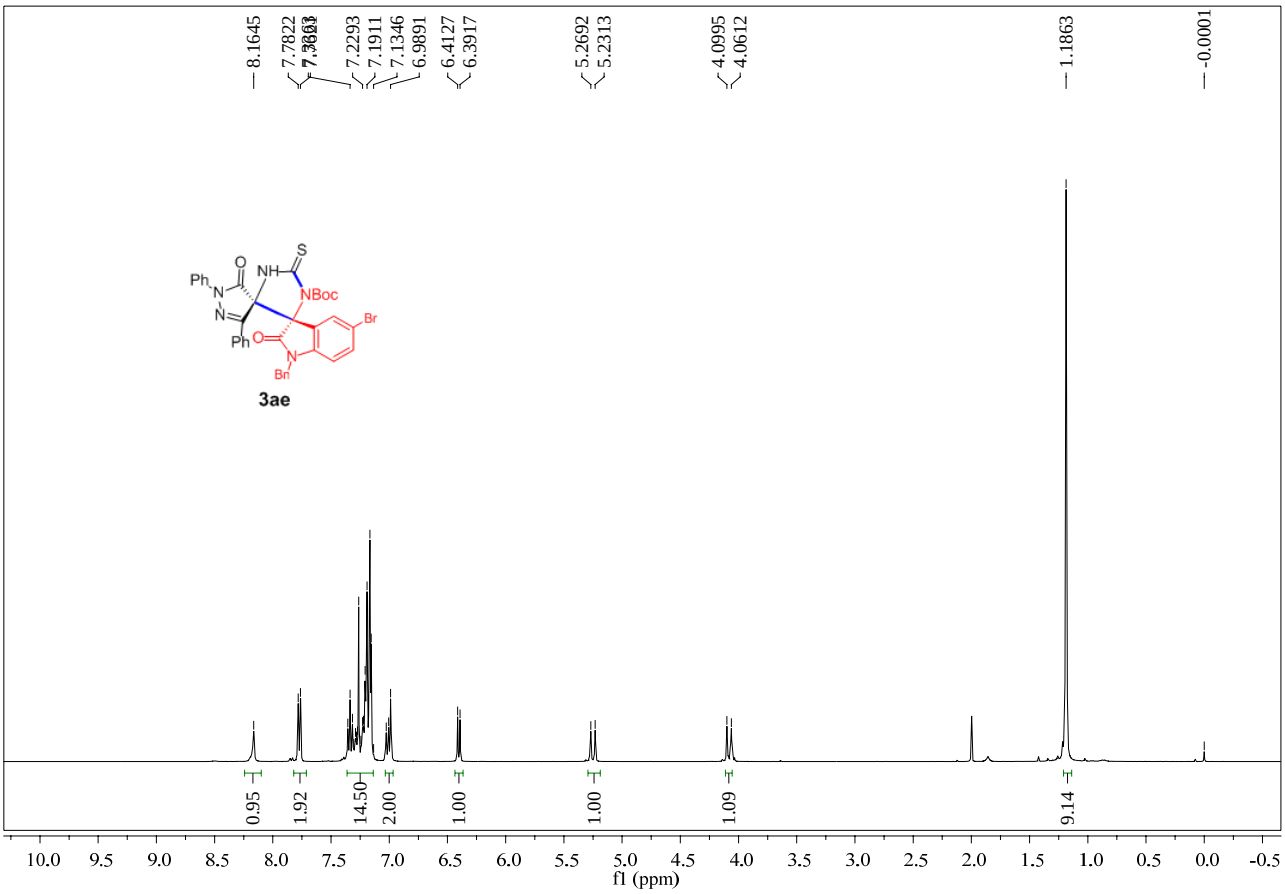
29.4602
29.2670
29.0738
28.8806
28.6873
26.7770
3ad
f1 (ppm)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7.2293
7.1911
7.1346
6.9891
6.4127
6.3917
5.2692
5.2313
4.0995
4.0612
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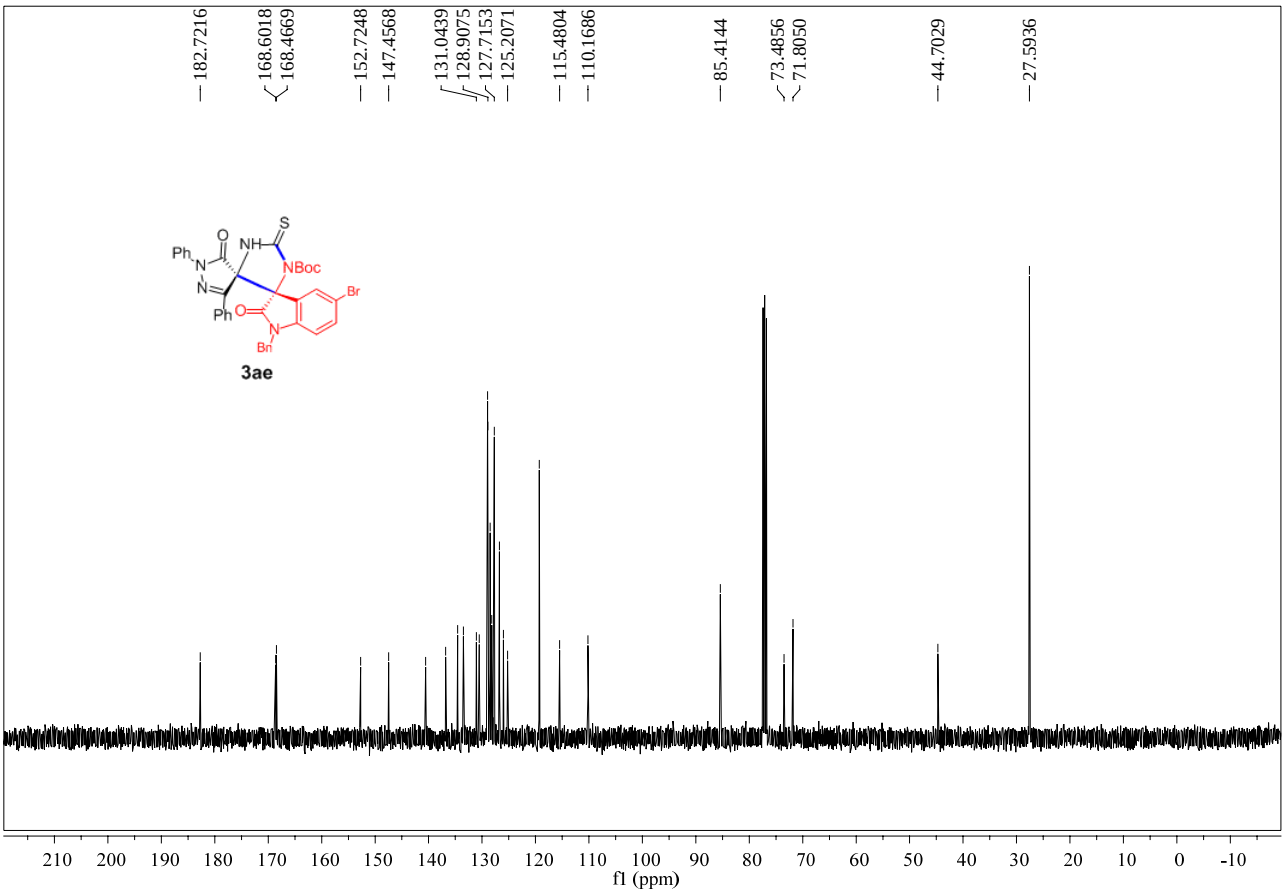
1.92
14.50
2.00
1.00
1.00
1.09
9.14
f1 (ppm)
3ae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147.4568
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127.7153
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110.1686
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73.4856
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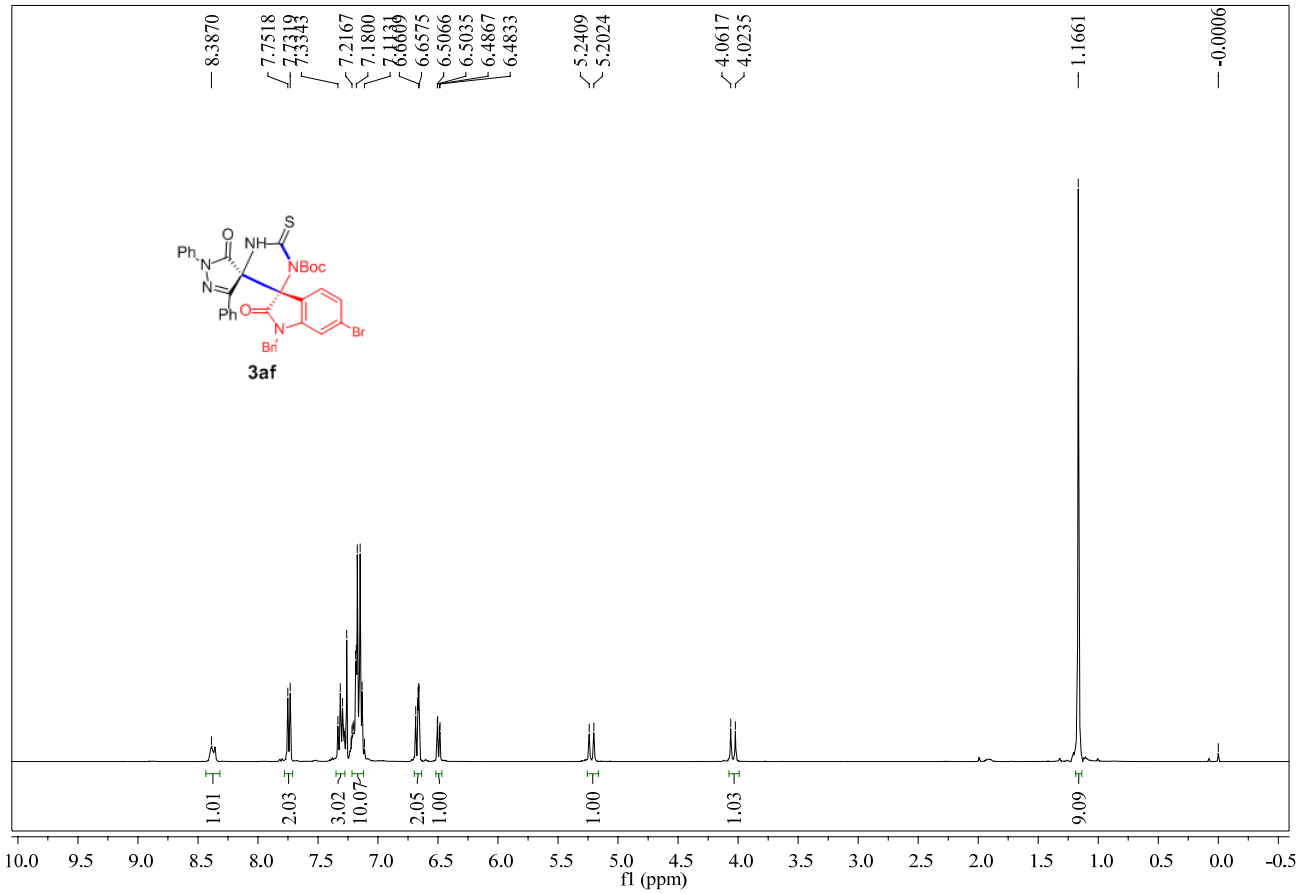
44.7029
27.5936
f1 (ppm)
3ae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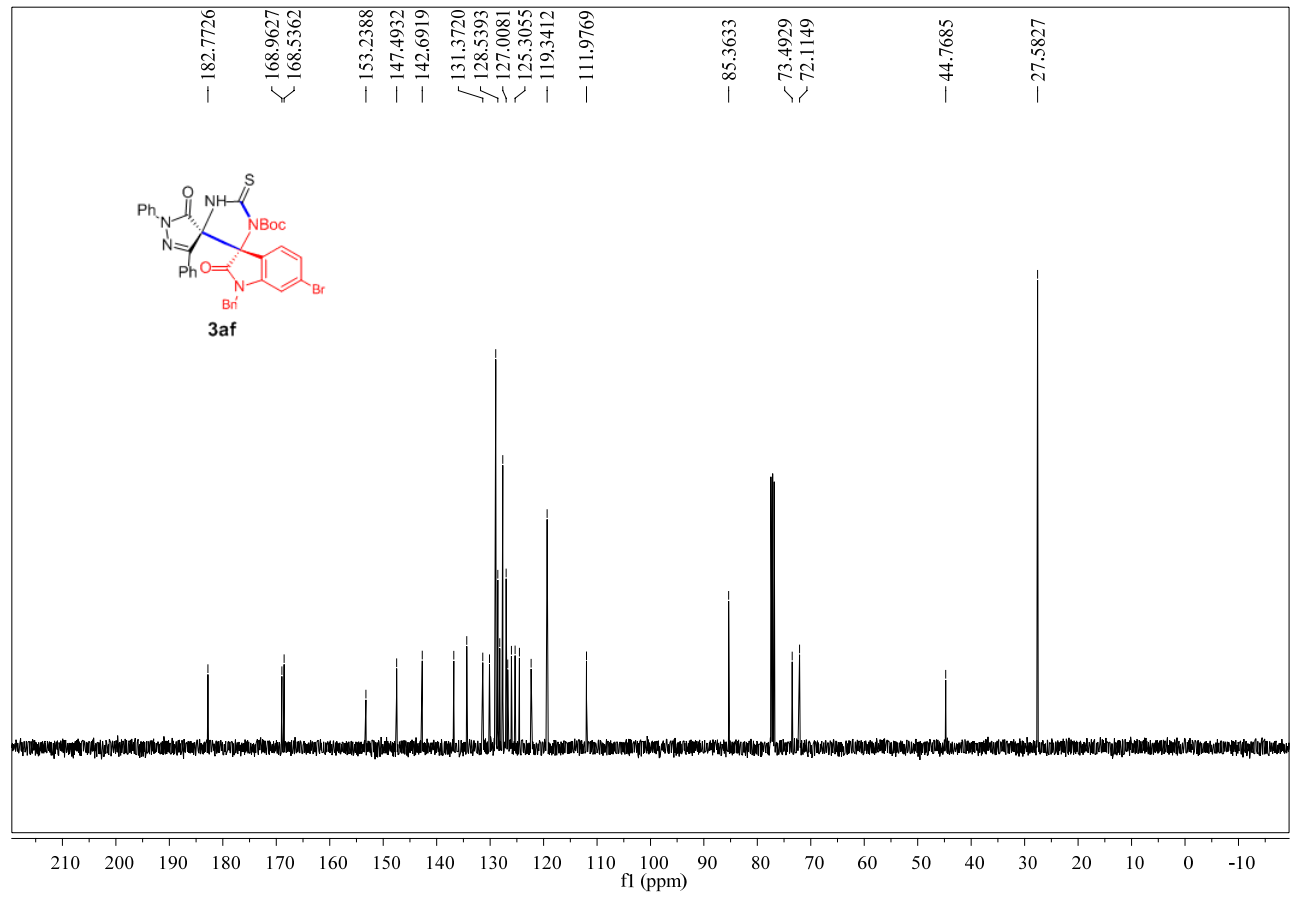
6.5035
6.4867
6.4833
5.2409
5.2024
4.0617
4.0235
1.1661
-0.0006
1.01
2.03
3.02
10.07
2.05
1.00
1.00
1.03
9.09
fl (ppm)
3af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168.5362
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147.4932
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131.3720
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127.0081
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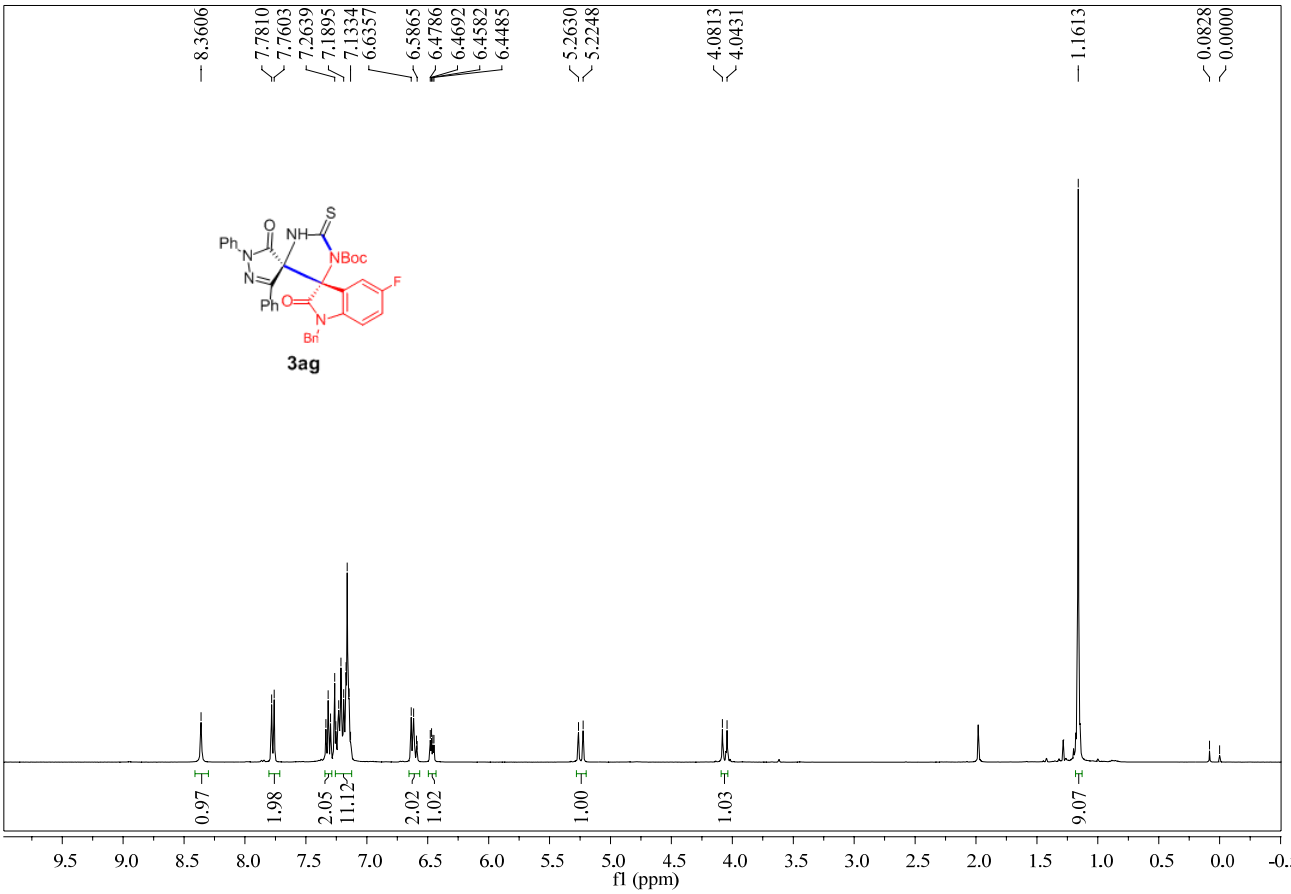
111.9769
85.3633
73.4929
72.1149
44.7685
27.5827
fl (ppm)
3af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6.6357
6.5865
6.4786
6.4692
6.4582
6.4485
5.2630
5.2248
4.0813
4.0431
1.1613
0.0828
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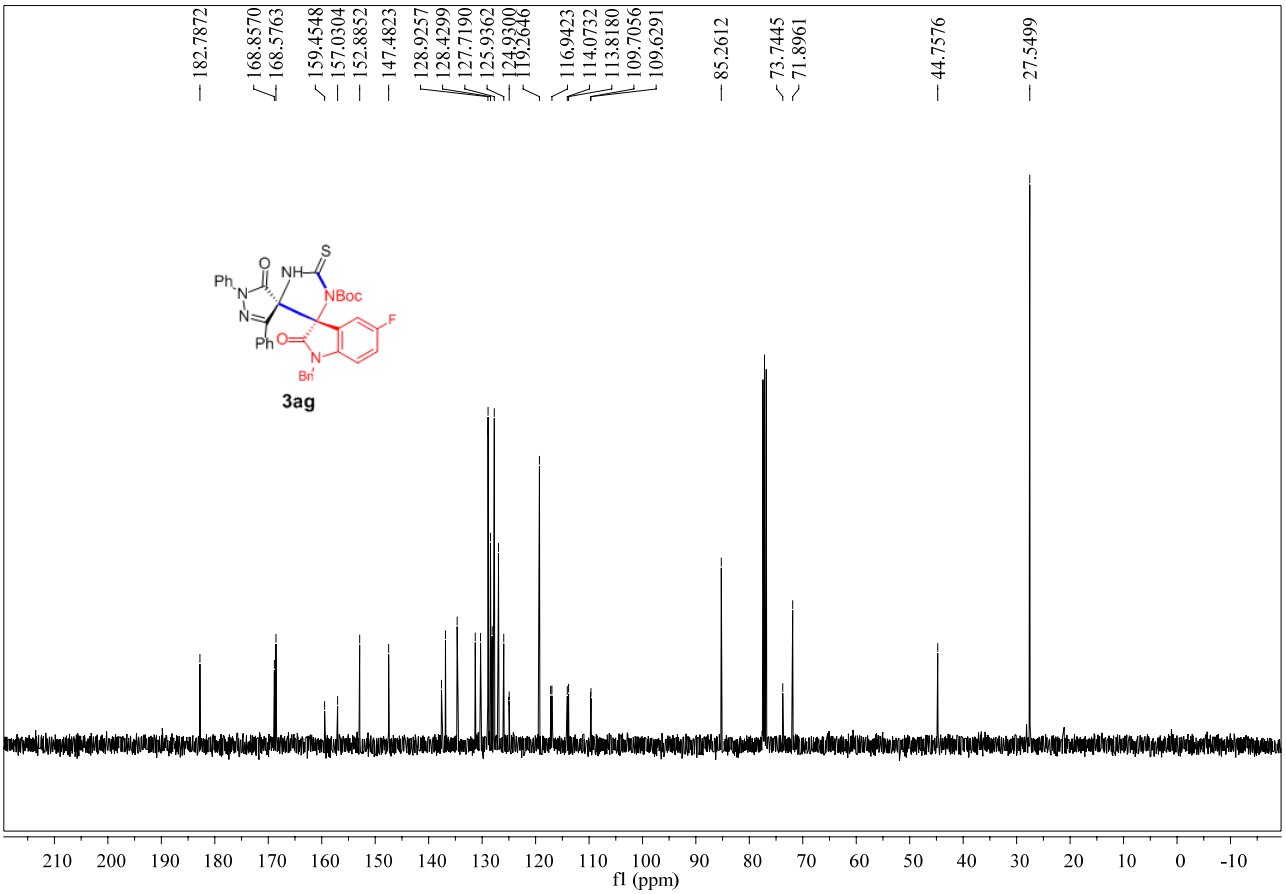
0.97
1.98
2.05
11.12
2.02
1.02
1.00
1.03
9.07
fl (ppm)

3ag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168.5763
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124.9300
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116.9423
114.0732
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109.6291
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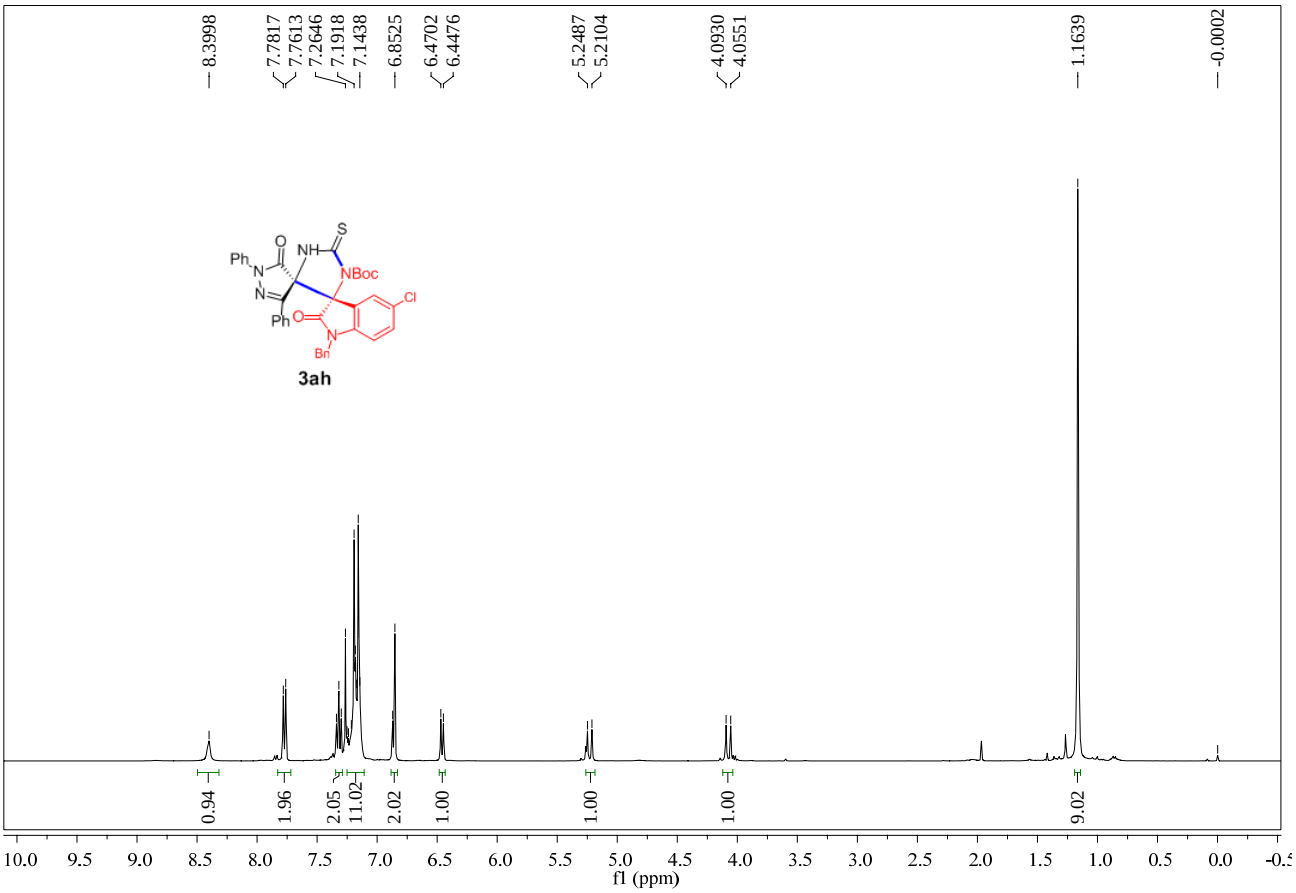
73.7445
71.8961
44.7576
27.5499
fl (ppm)

3ag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7.1918
7.1438
6.8525
6.4702
6.4476
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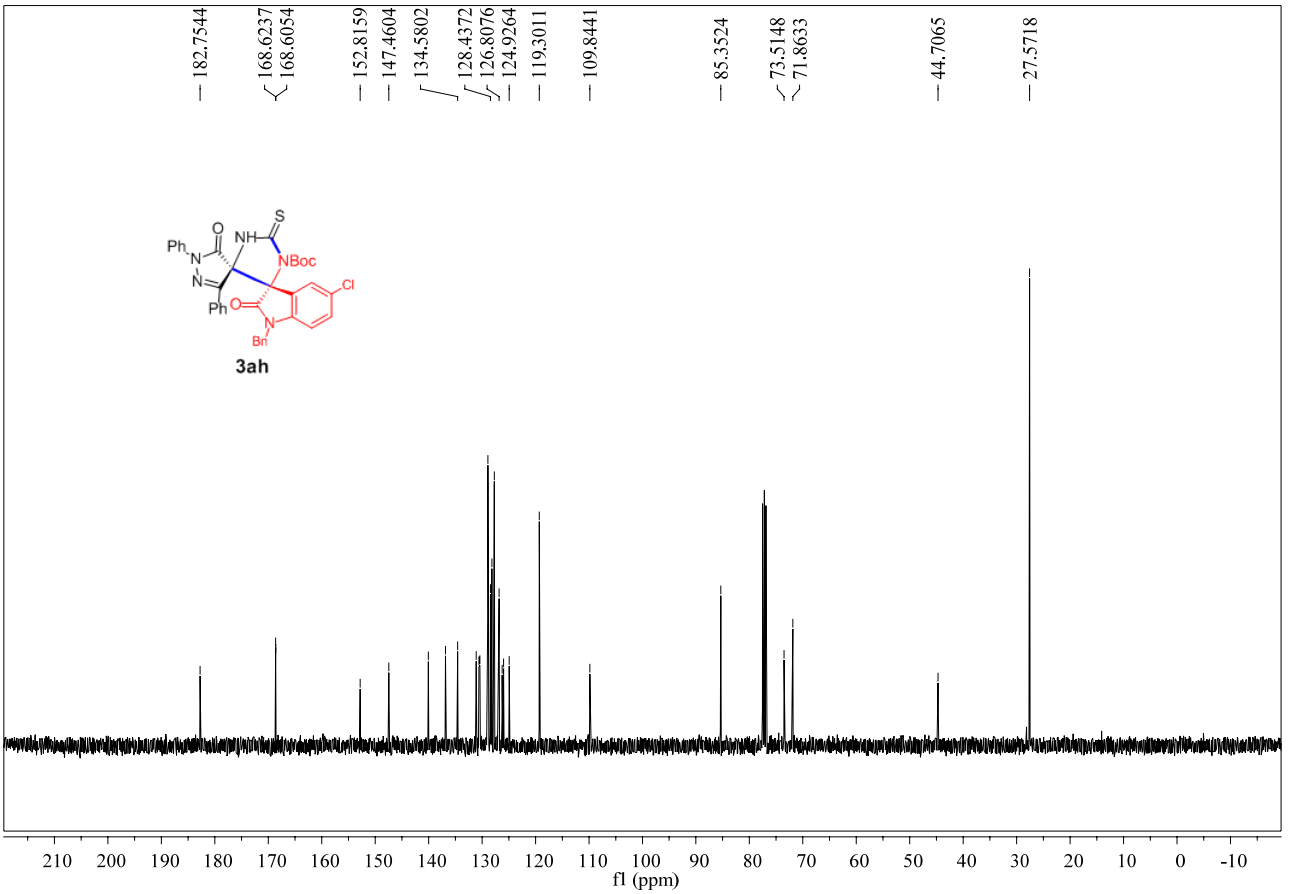
5.2104
4.0930
4.0551
1.1639
-0.0002
0.94
1.96
2.05
11.02
2.02
1.00
1.00
1.00
9.02
f1 (ppm)
3ah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168.6054
152.8159
147.4604
134.5802
128.4372
126.8076
124.9264
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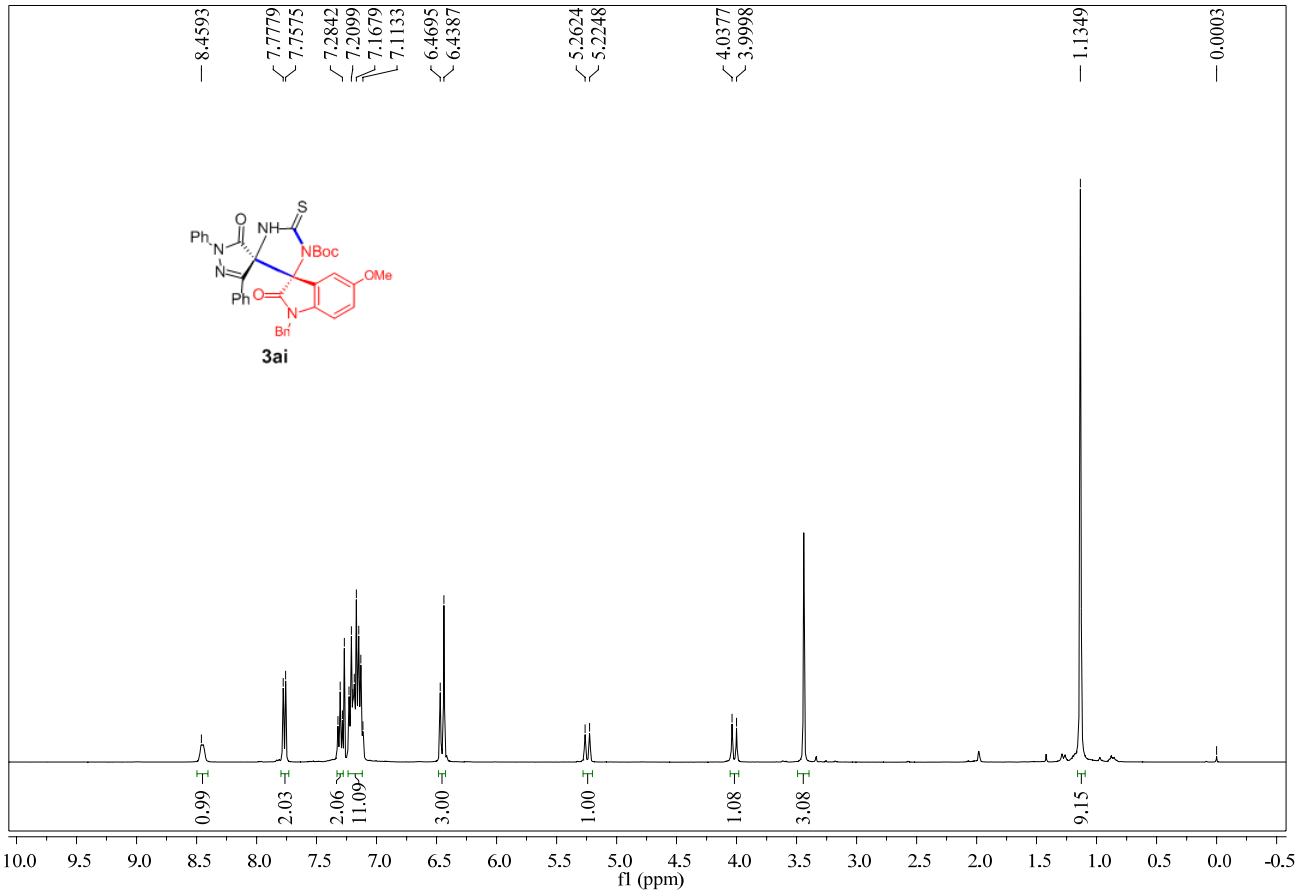
109.8441
85.3524
73.5148
71.8633
44.7065
27.5718
f1 (ppm)
3ah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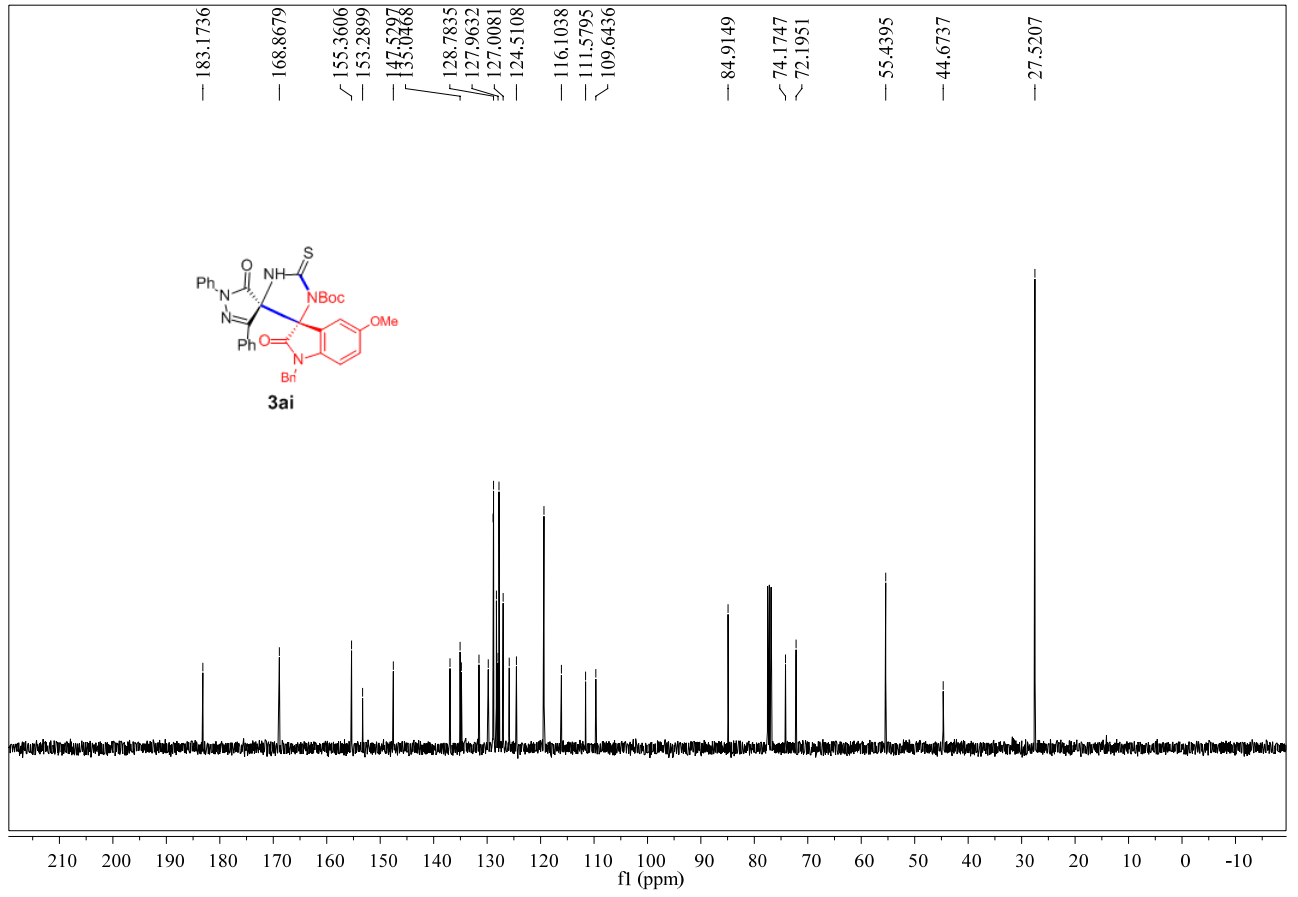
7.7575
7.2842
7.2099
7.1679
7.1133
6.4695
6.4387
5.2624
5.2248
4.0377
3.9998
1.1349
0.0003
0.99
2.03
2.06
11.09
3.00
1.00
1.08
3.08
9.15
fl (ppm)
3ai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128.7835
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124.5108
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84.9149
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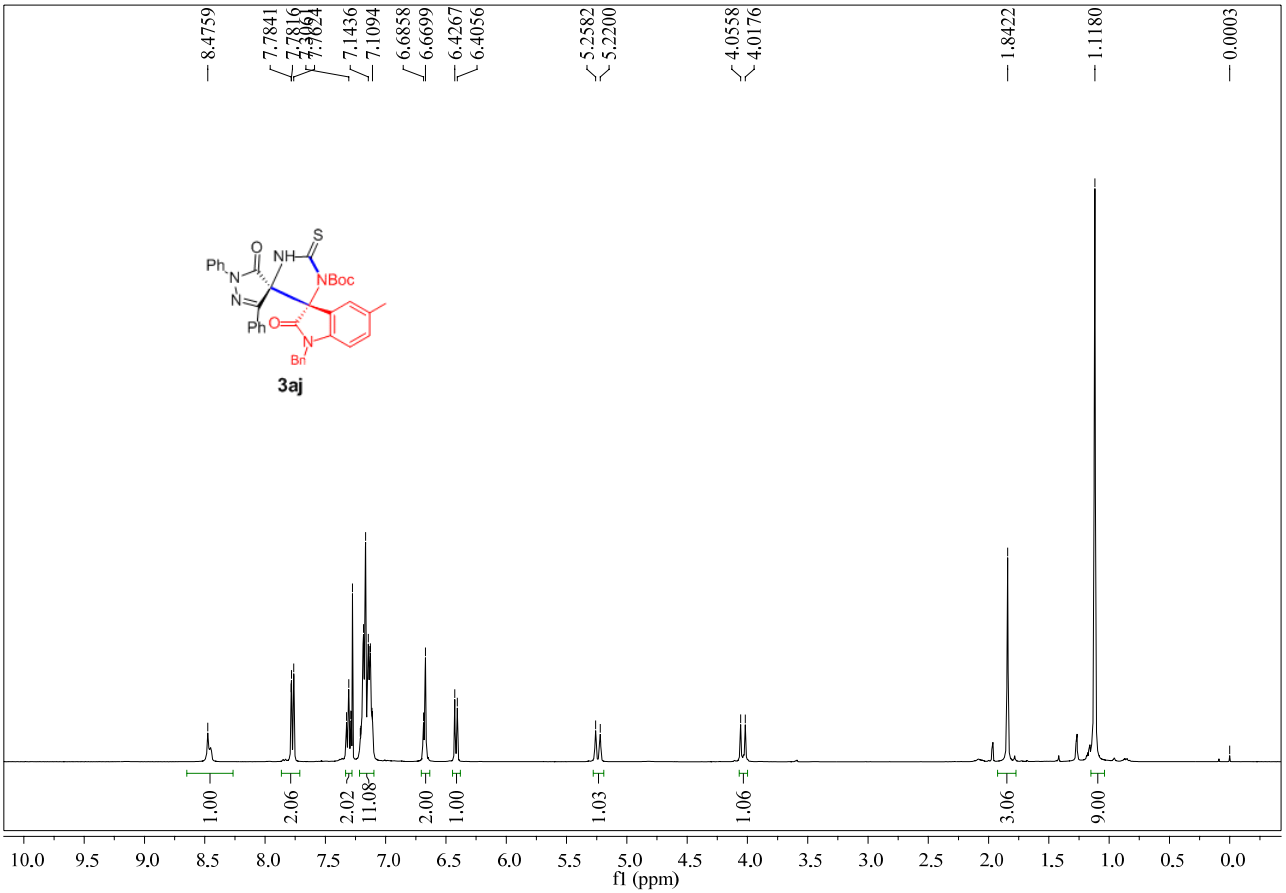
72.1951
55.4395
44.6737
27.5207
fl (ppm)
3ai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7.1094
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6.6699
6.4267
6.4056
5.2582
5.2200
4.0558
4.0176
1.8422
1.1180
0.0003
1.00
2.06
2.02
11.08
2.00
1.00
1.03
1.06
3.06
9.00
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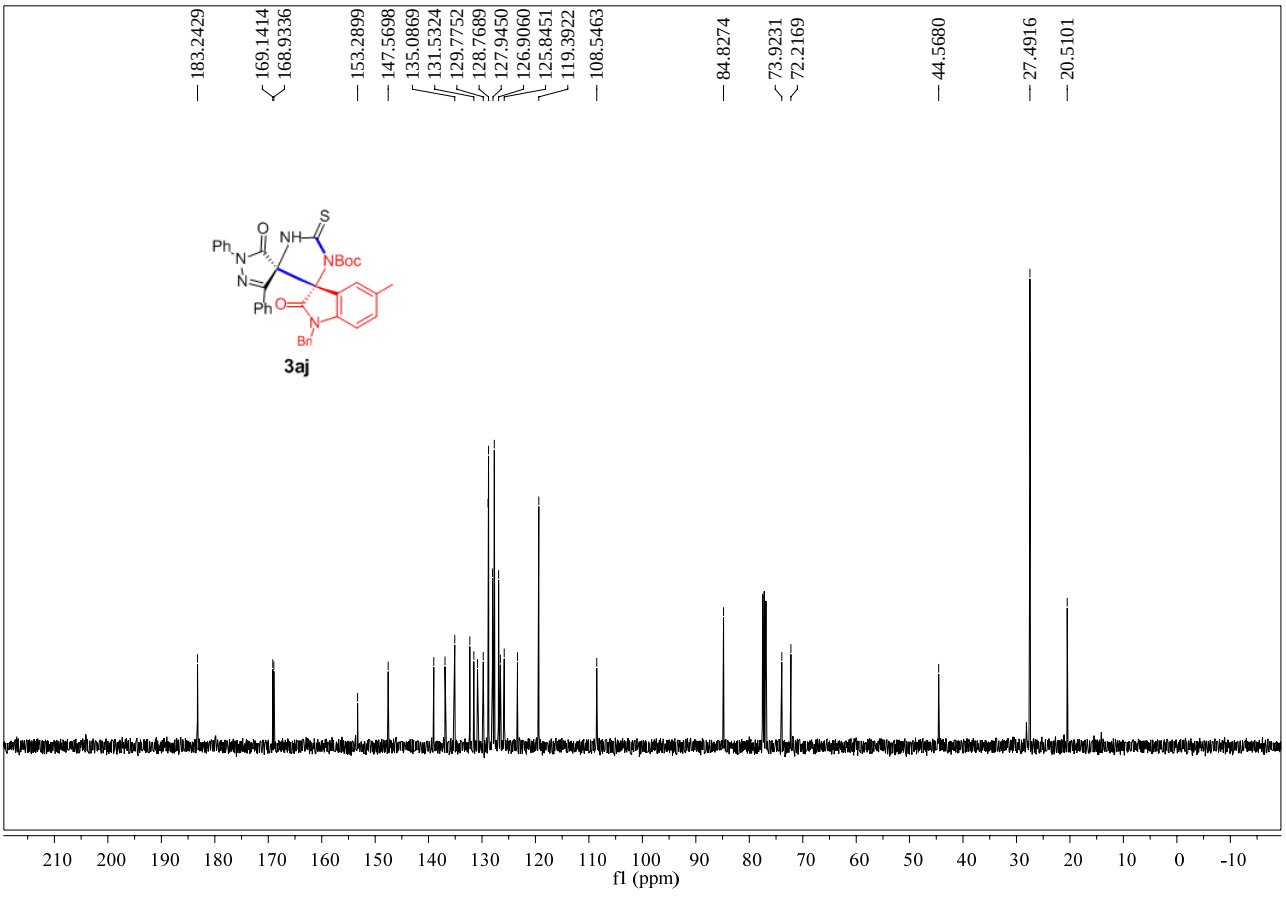
f1 (ppm)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125.8451
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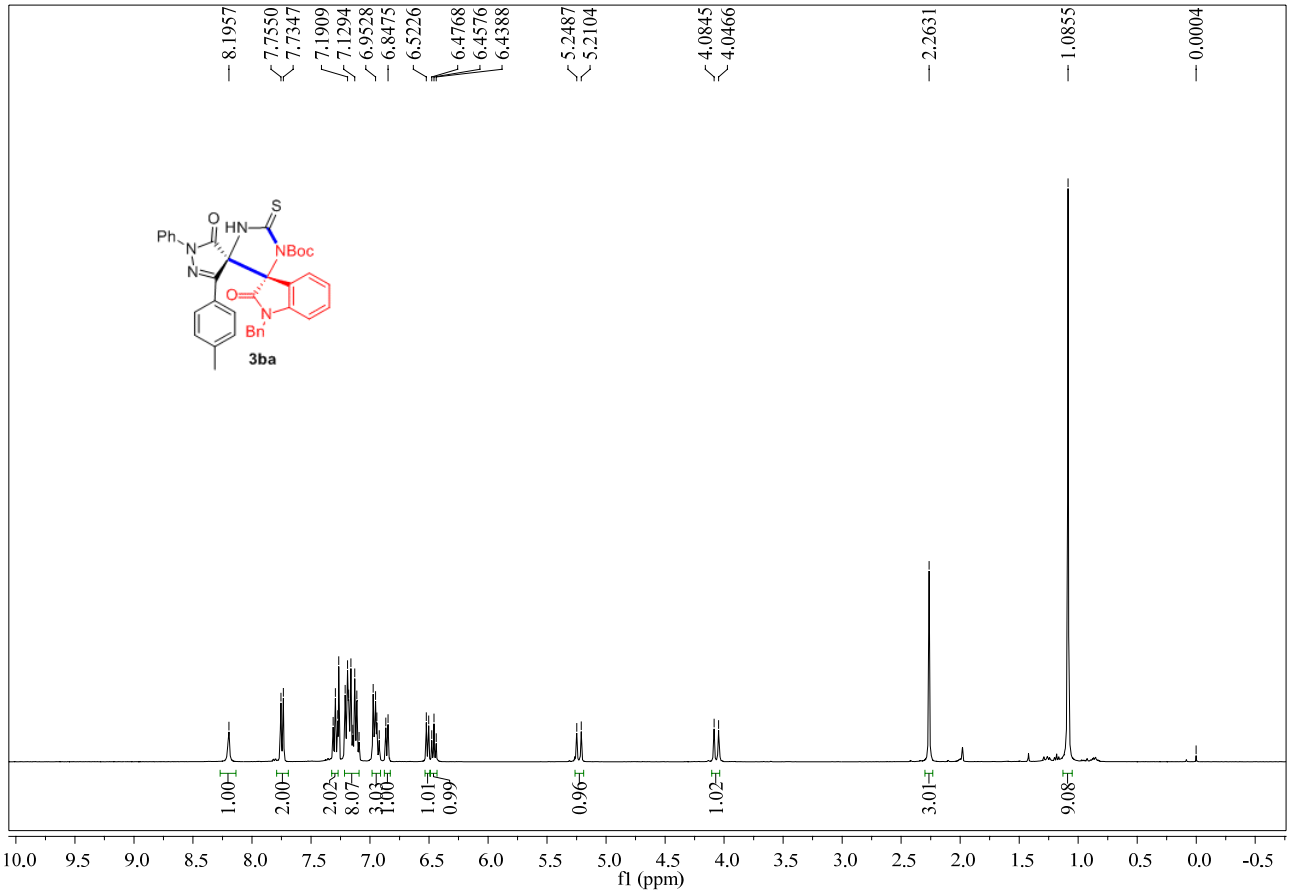
f1 (ppm)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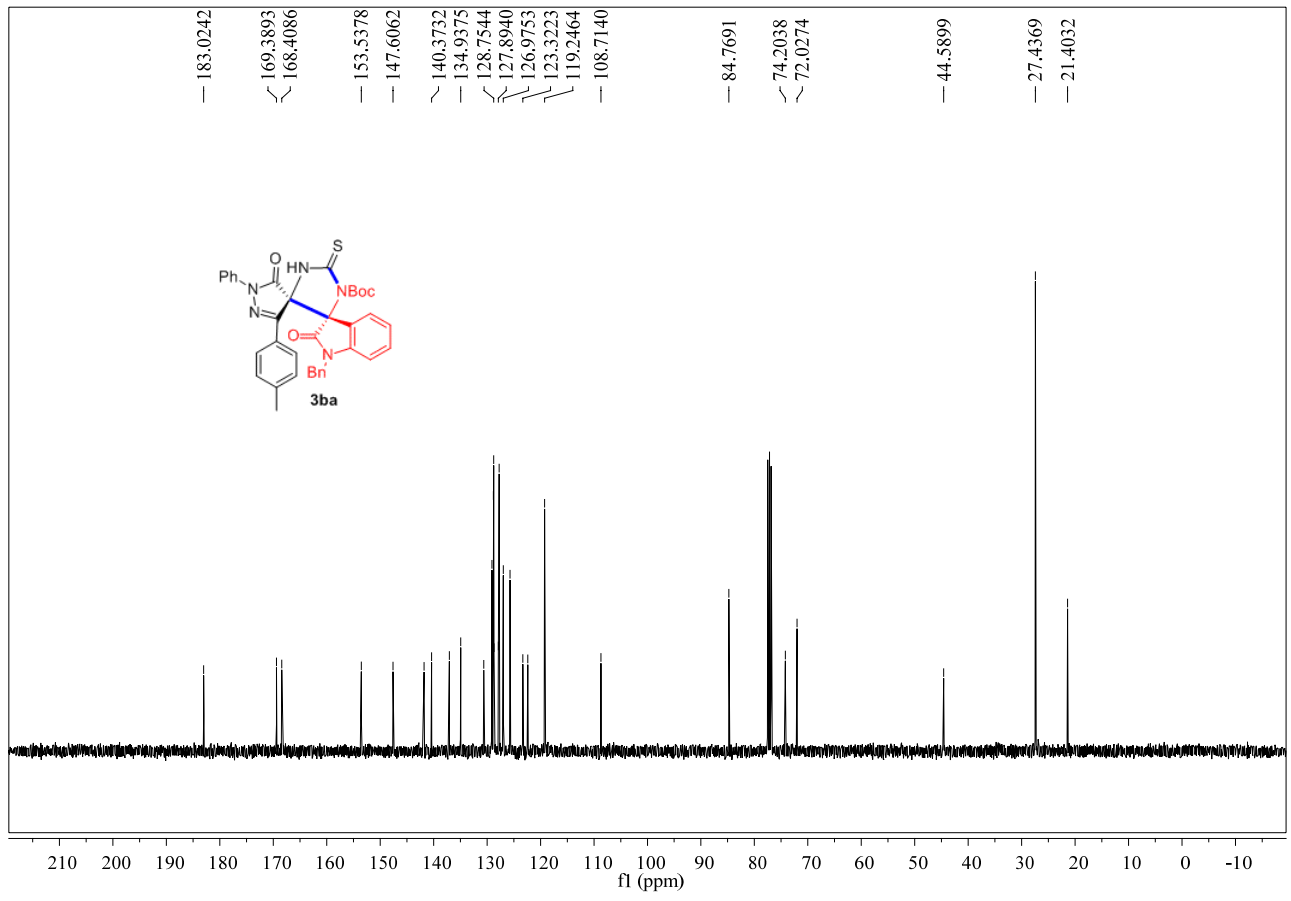
6.4388
5.2487
5.2104
4.0845
4.0466
2.2631
1.0855
0.0004
1.00
2.00
2.02
8.07
3.03
1.00
1.01
0.99
0.96
1.02
3.01
9.08
Ph
HN
S
O
NBoc
N
Bn
3ba
fl (ppm)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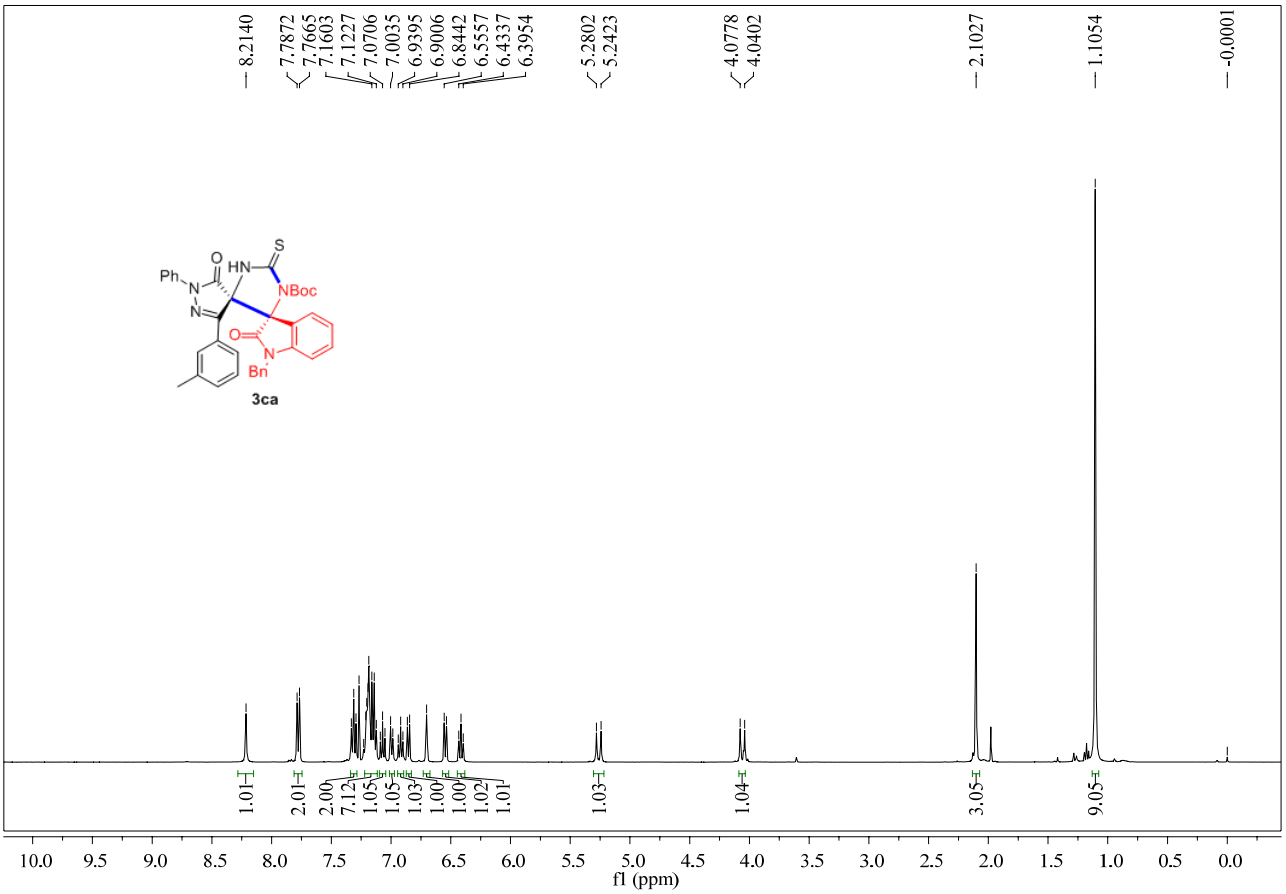
21.4032
Ph
HN
S
O
NBoc
N
Bn
3ba
fl (ppm)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7.0035
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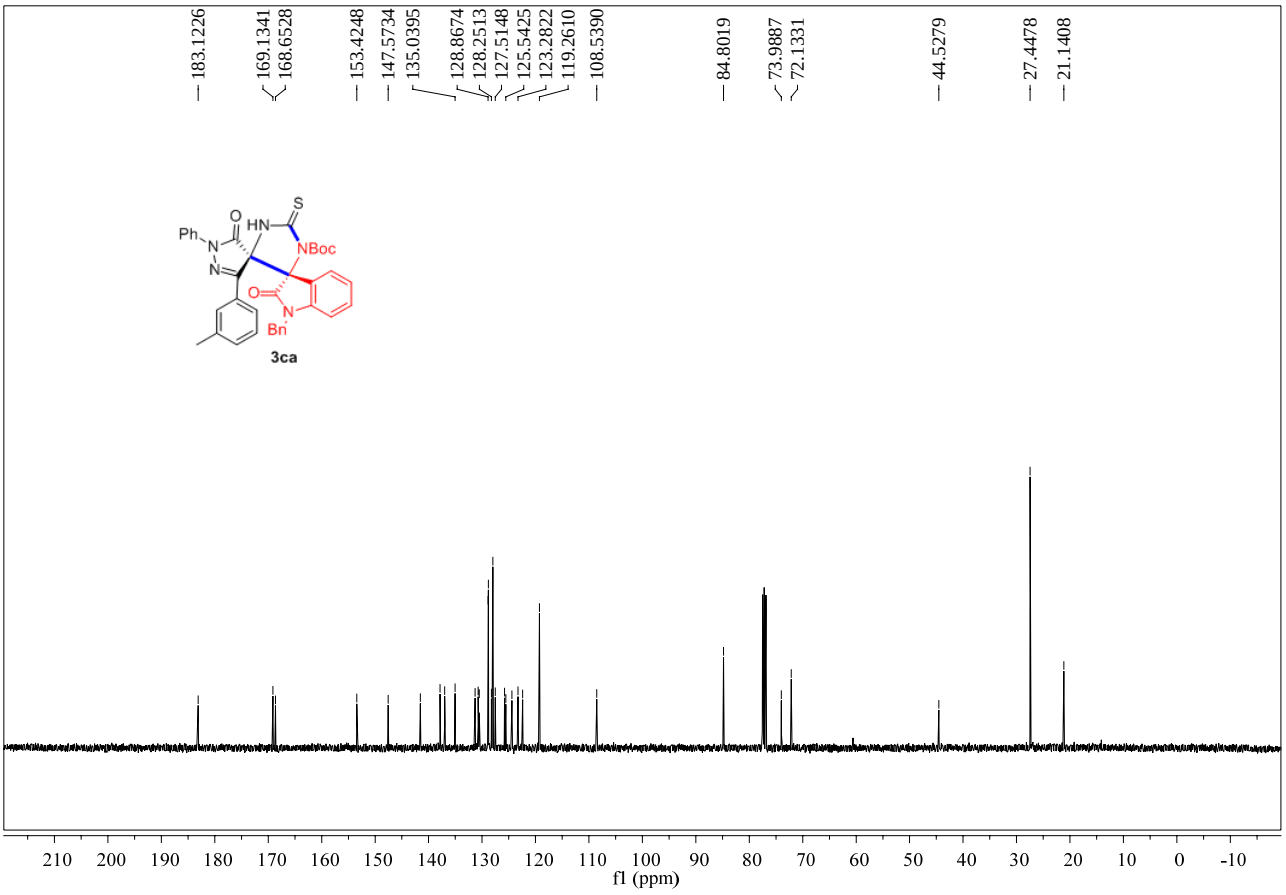
6.4337
6.3954
5.2802
5.2423
4.0778
4.0402
2.1027
1.1054
-0.0001
1.01
2.01
2.00
7.12
1.05
1.05
1.03
1.00
1.00
1.02
1.01
1.03
1.04
3.05
9.05
Ph
N
N
O
HN
S
NBoc
O
N
Bn
3ca
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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119.2610
108.5390
84.8019
73.9887
72.1331
44.5279
27.4478
21.1408
Ph
N
N
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HN
S
NBoc
O
N
Bn
3ca
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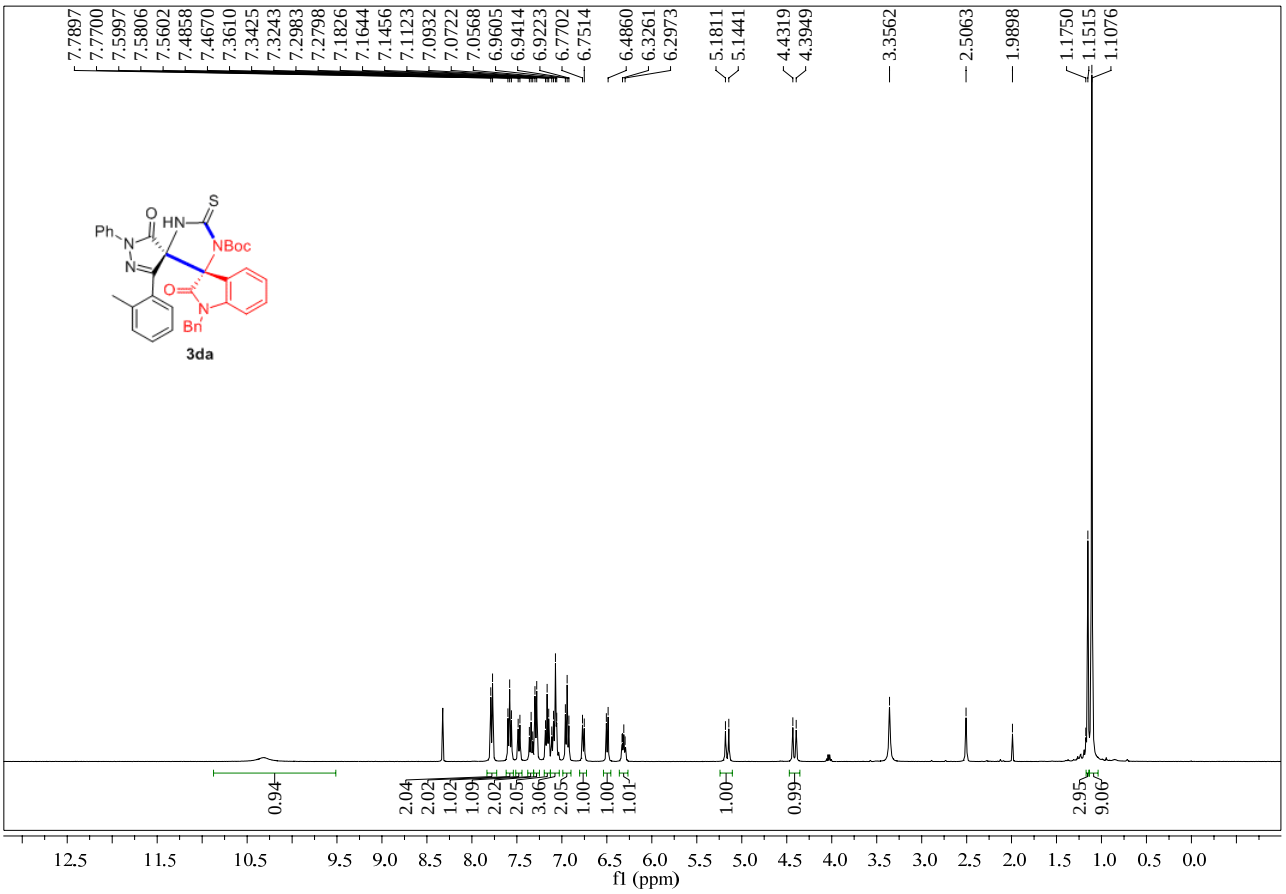
f1 (ppm)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7.2798
7.1826
7.1644
7.1456
7.1123
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7.0722
7.0568
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6.9414
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6.7702
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6.4860
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6.2973
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5.1441
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4.3949
3.3562
2.5063
1.9898
1.1750
1.1515
1.1076
Ph
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NBoc
O
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Bn
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2.02
1.02
1.09
2.02
2.05
3.06
2.05
1.00
1.00
1.01
1.00
0.99
2.95
9.06
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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3.0
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1.0
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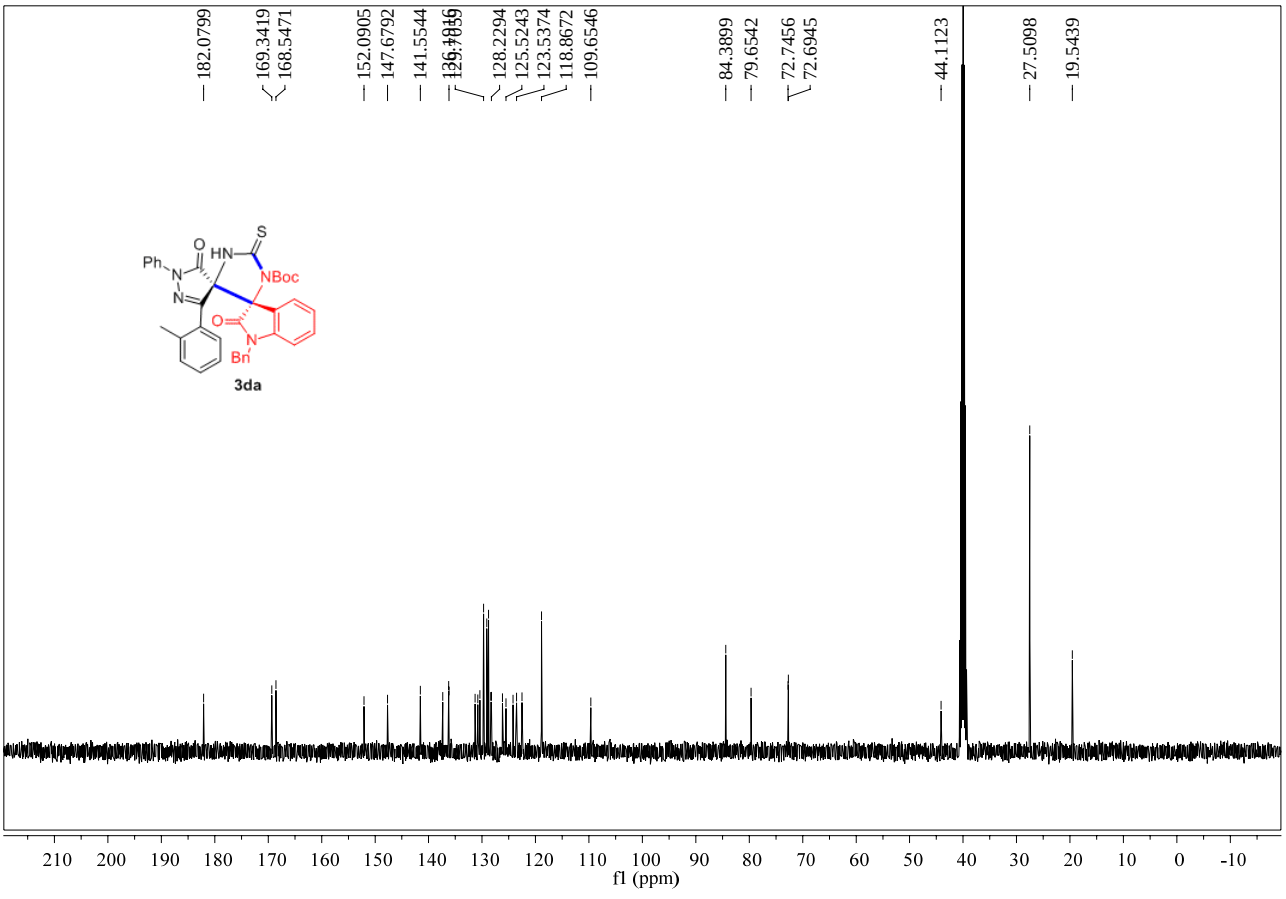
f1 (ppm)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109.6546
84.3899
79.6542
72.7456
72.6945
44.1123
27.5098
19.5439
Ph
N
N
O
HN
S
NBoc
O
N
Bn
3da
210
200
190
180
170
160
150
140
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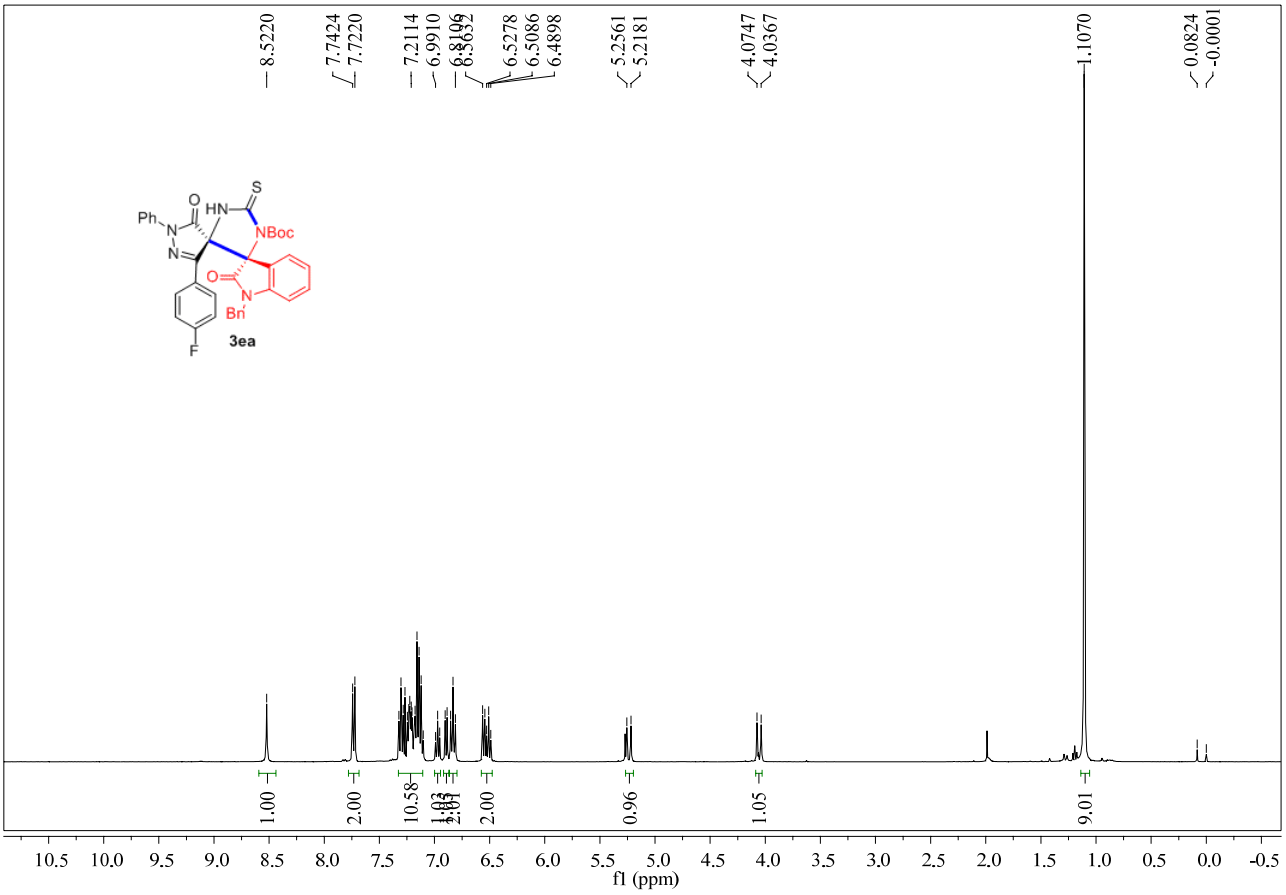
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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5.2181
4.0747
4.0367
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1.00
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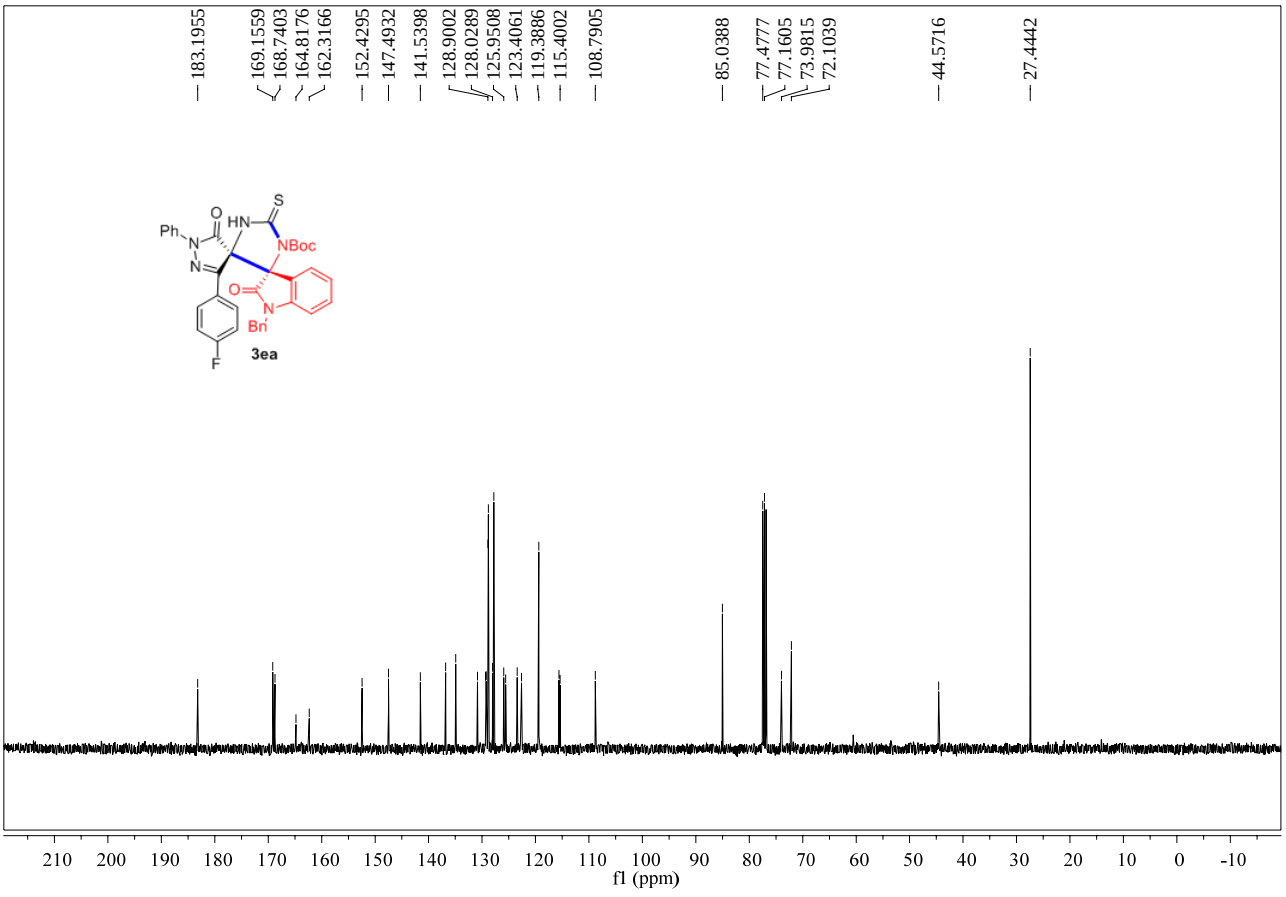
2.00
0.96
1.05
9.01
fl (ppm)
3ea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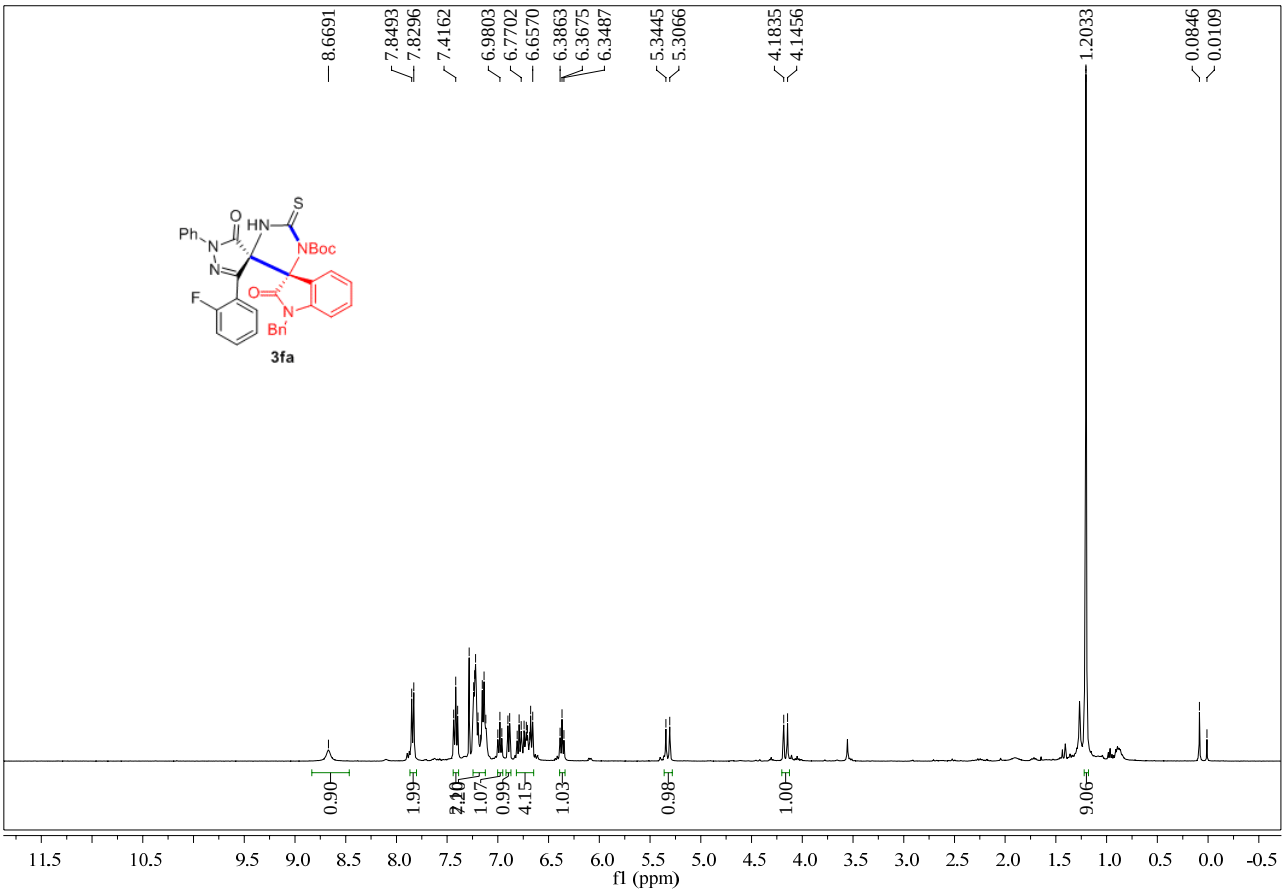
fl (ppm)
3ea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4.1456
1.2033
0.0846
0.0109
0.90
1.99
2.10
1.07
0.99
4.15
1.03
0.98
1.00
9.06
11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)
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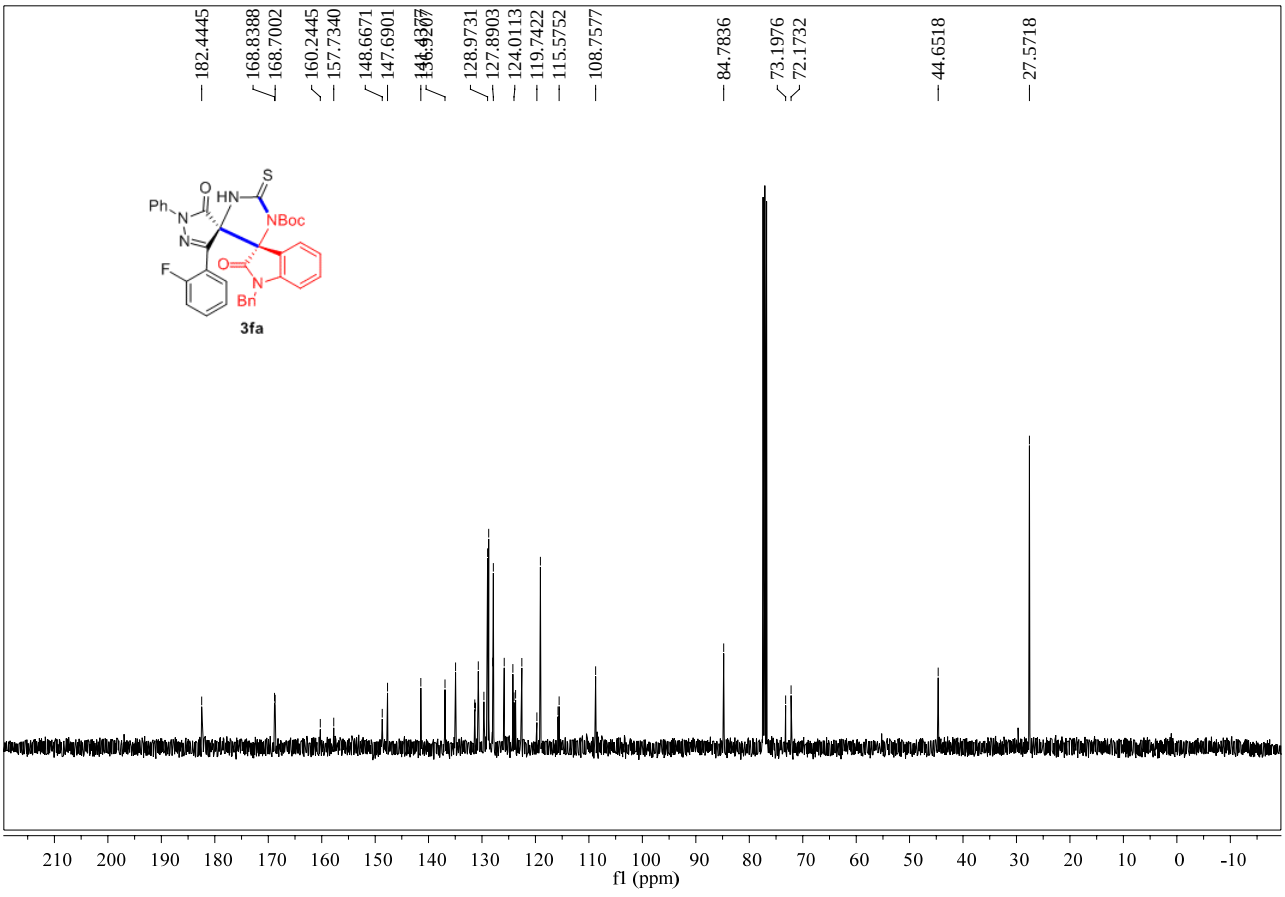
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115.5752
108.7577
84.7836
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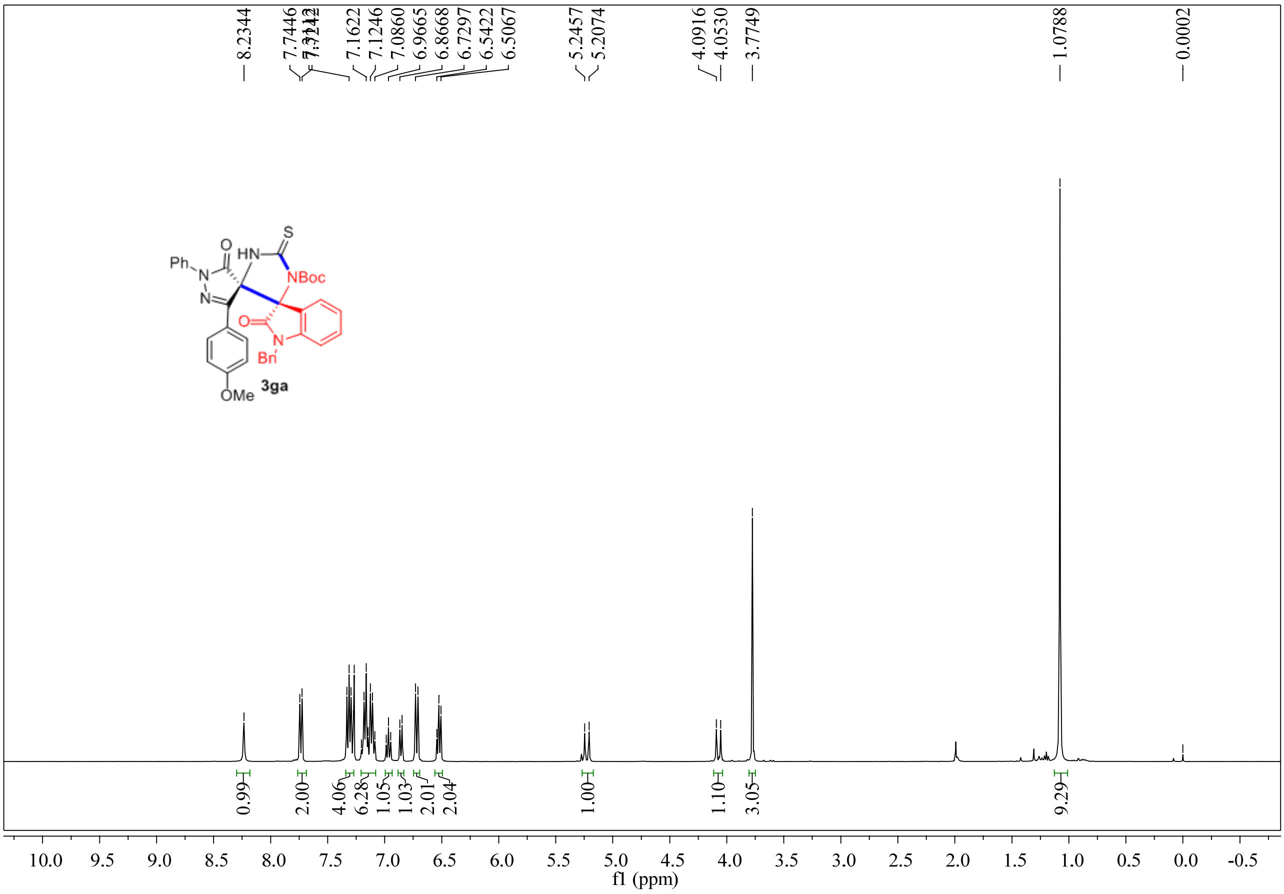
44.6518
27.5718
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)
3fa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5.2074
4.0916
4.0530
3.7749
1.0788
0.0002
Ph
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O
HN
S
NBoc
O
N
Bn
OMe
3ga
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1.03
2.01
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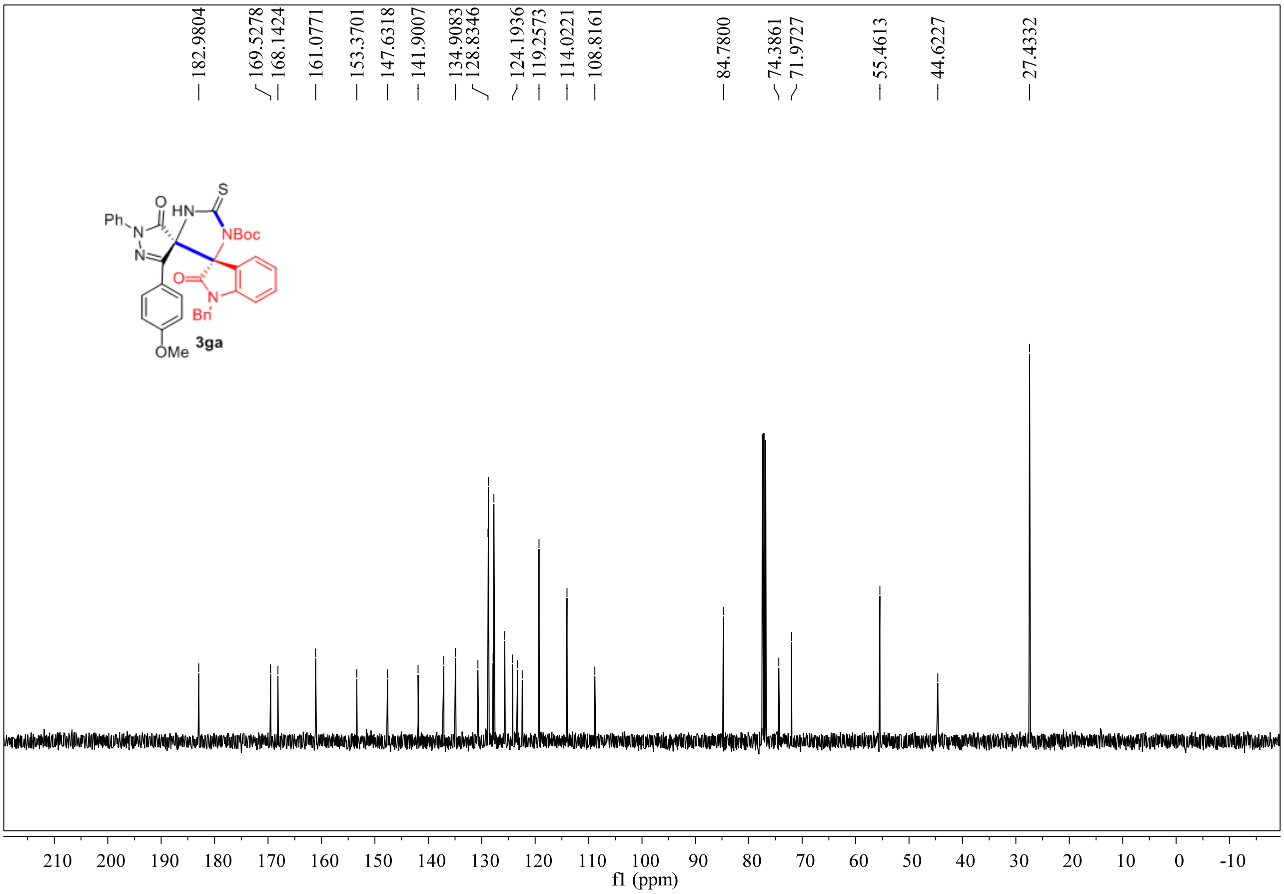
1.00
1.10
3.05
9.29
f1 (ppm)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108.8161
84.7800
74.3861
71.9727
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Ph
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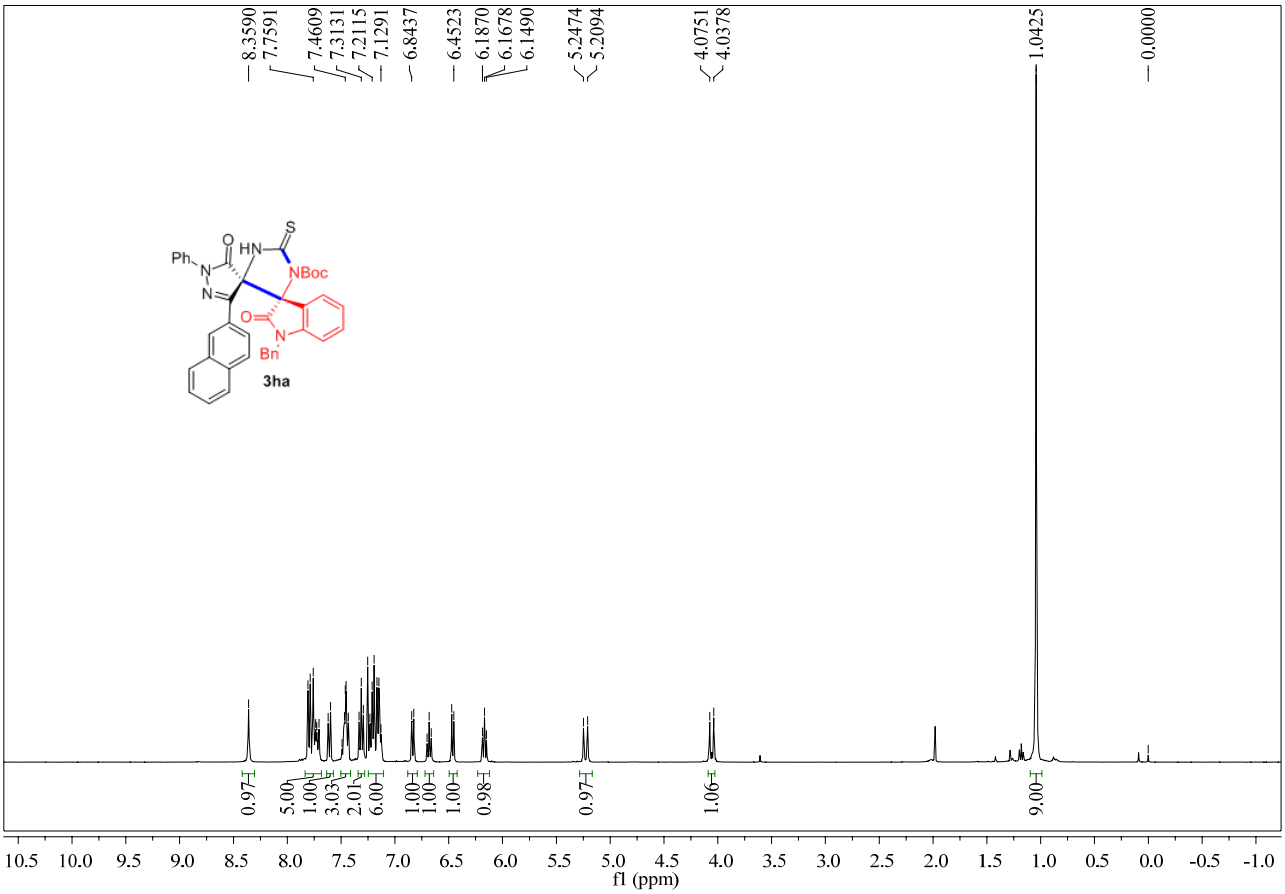
HN
S
NBoc
O
N
Bn
OMe
3ga
f1 (ppm)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5.2094
4.0751
4.0378
1.0425
0.0000
0.97
5.00
1.00
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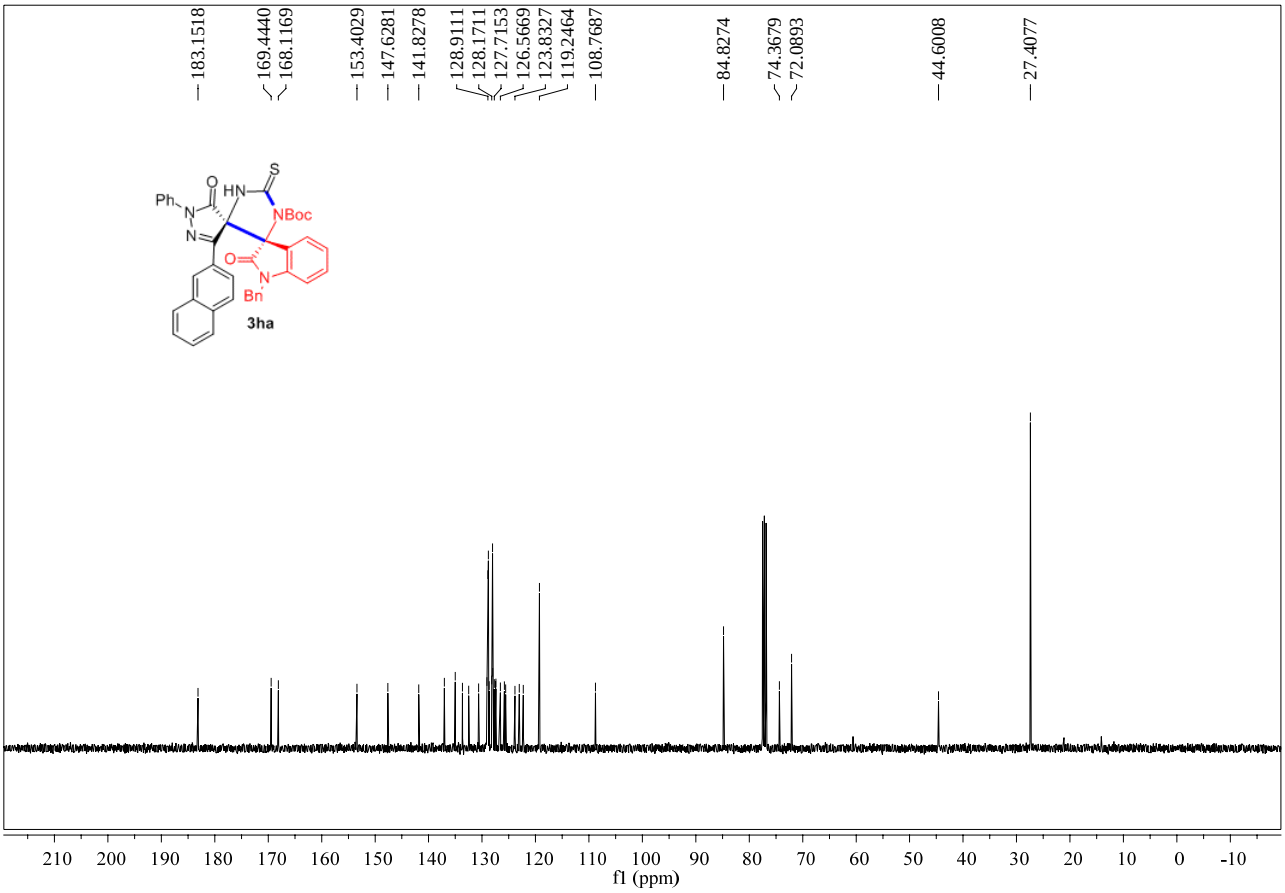
1.00
1.00
1.00
0.98
0.97
1.06
9.00
f1 (ppm)
3ha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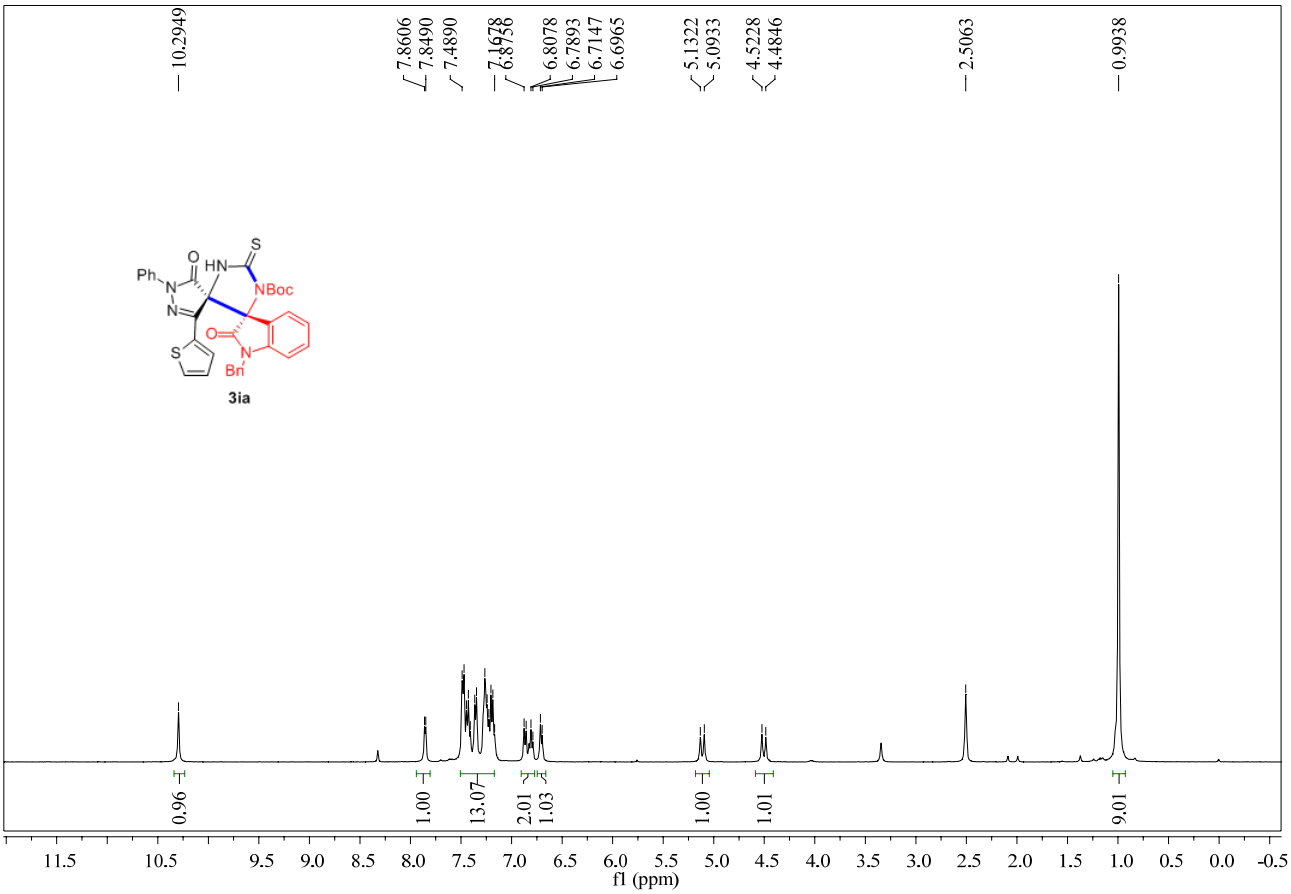
108.7687
84.8274
74.3679
72.0893
44.6008
27.4077
f1 (ppm)
3ha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6.7147
6.6965
5.1322
5.0933
4.5228
4.4846
2.5063
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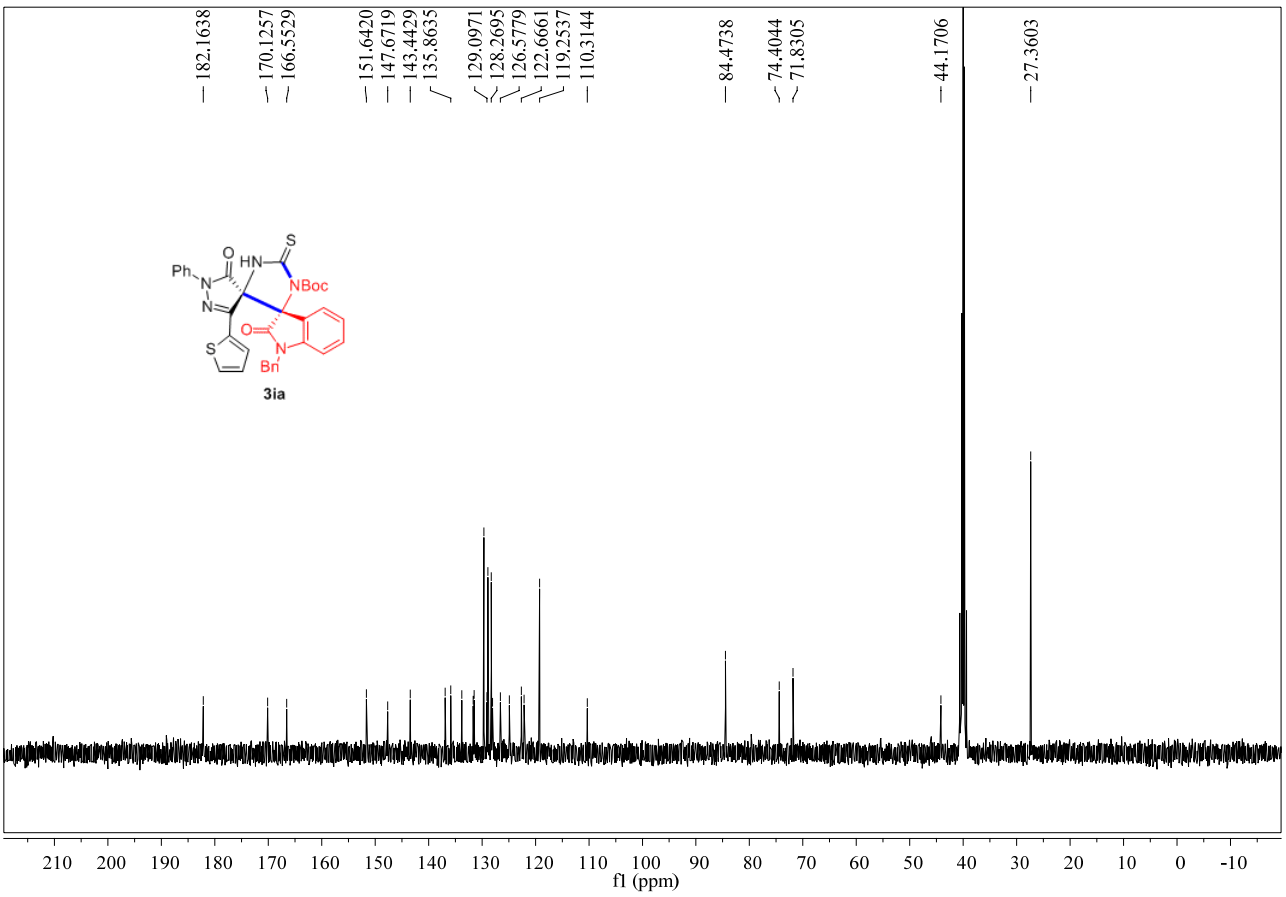
0.96
1.00
13.07
2.01
1.03
1.00
1.01
9.01
3ia
f1 (ppm)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166.5529
151.6420
147.6719
143.4429
135.8635
129.0971
128.2695
126.5779
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110.3144
84.4738
74.4044
71.8305
44.1706
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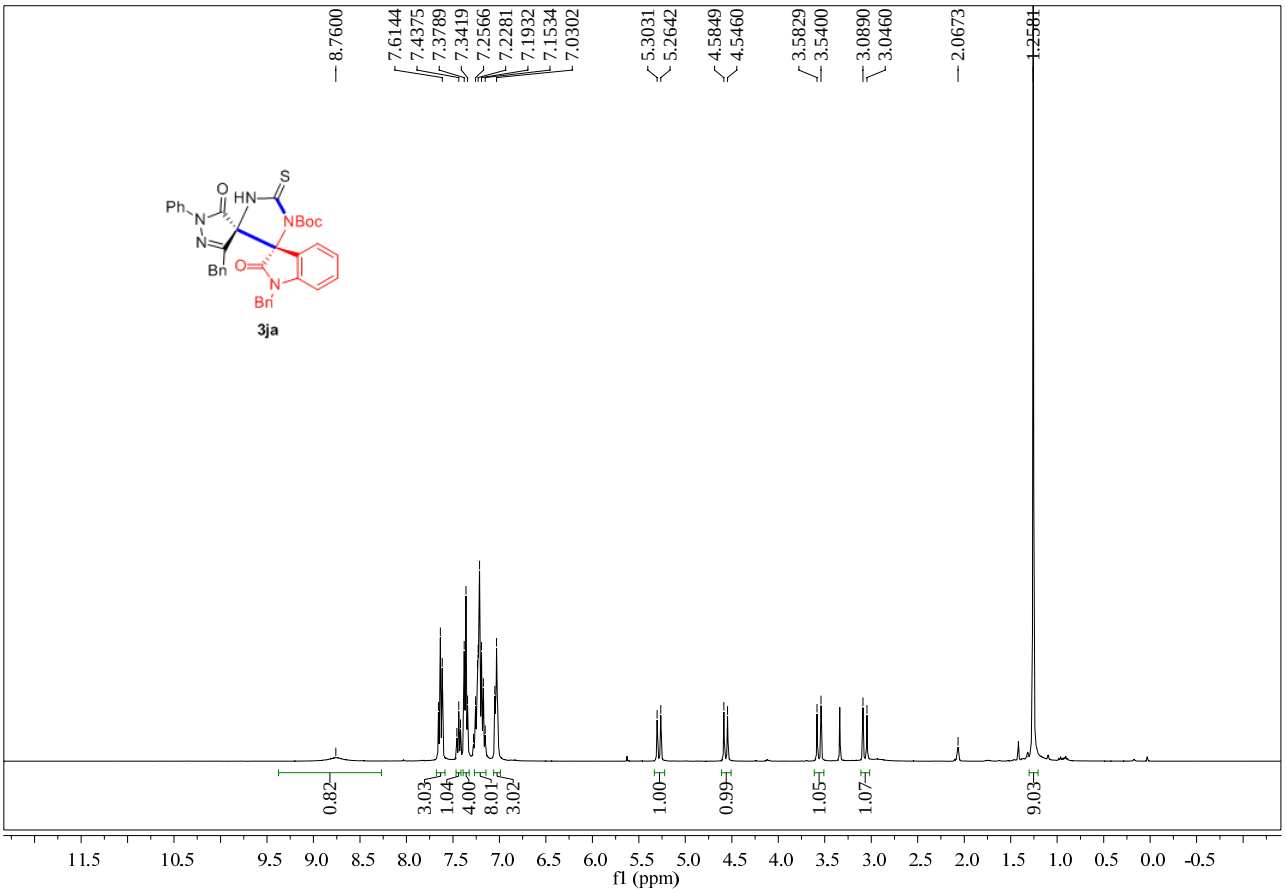
f1 (ppm)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7.2566
7.2281
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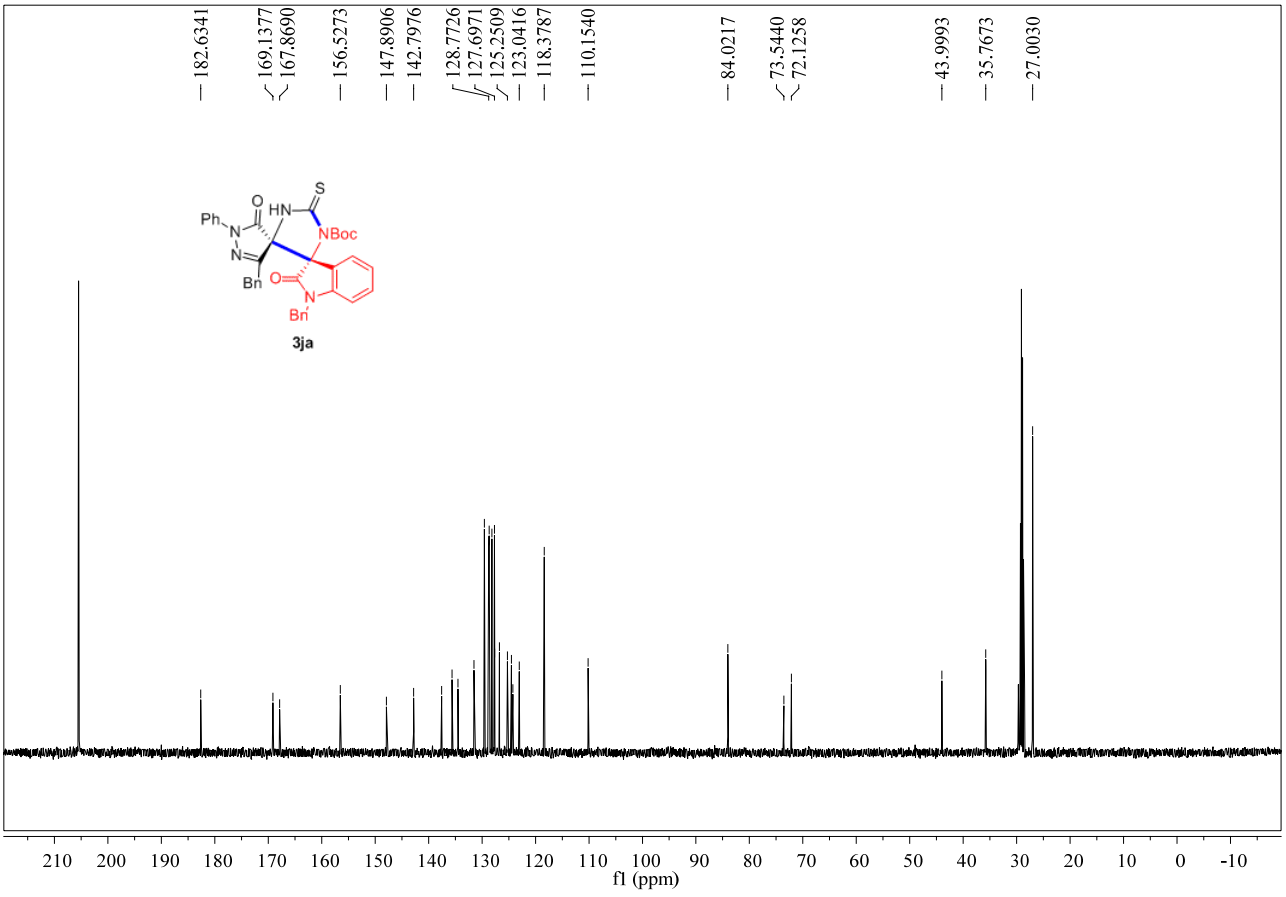
7.1534
7.0302
5.3031
5.2642
4.5849
4.5460
3.5829
3.5400
3.0890
3.0460
2.0673
1.2581
0.82
3.03
1.04
4.00
8.01
3.02
1.00
0.99
1.05
1.07
9.03
3ja
f1 (ppm)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167.8690
156.5273
147.8906
142.7976
128.7726
127.6971
125.2509
123.0416
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84.0217
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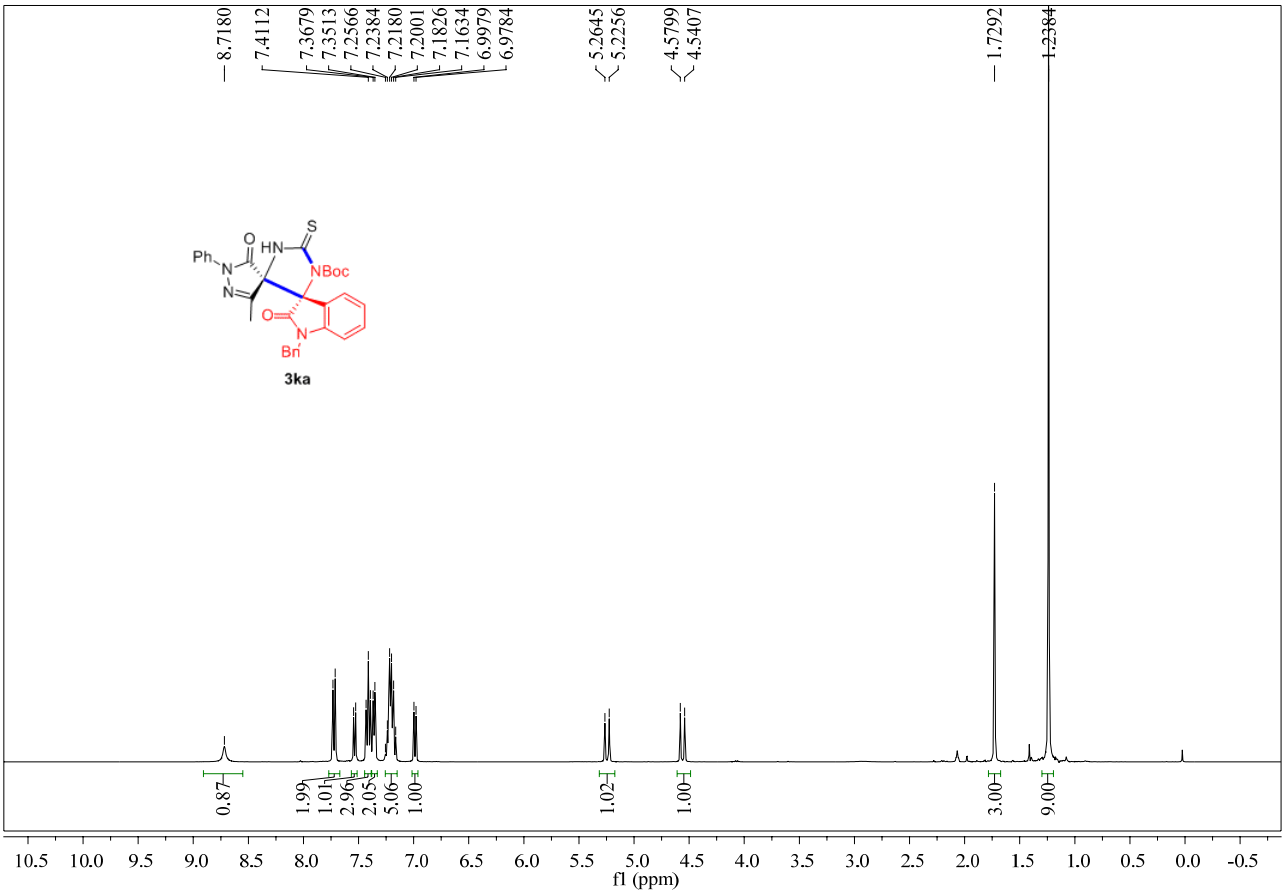
72.1258
43.9993
35.7673
27.0030
3ja
f1 (ppm)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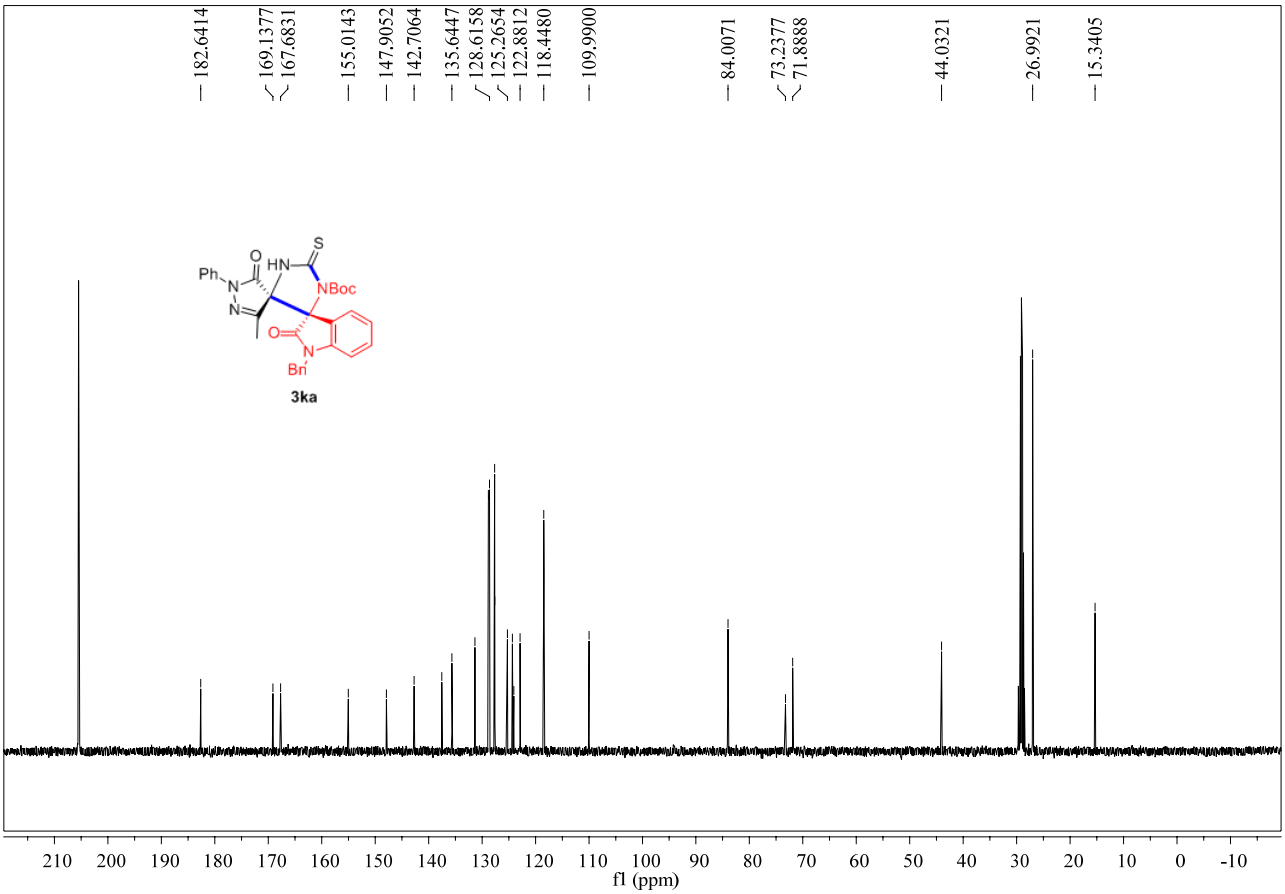
7.2566
7.2384
7.2180
7.2001
7.1826
7.1634
6.9979
6.9784
5.2645
5.2256
4.5799
4.5407
1.7292
1.2384
0.87
1.99
1.01
2.96
2.05
5.06
1.00
1.02
1.00
3.00
9.00
fl (ppm)
3ka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167.6831
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147.9052
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135.6447
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125.2654
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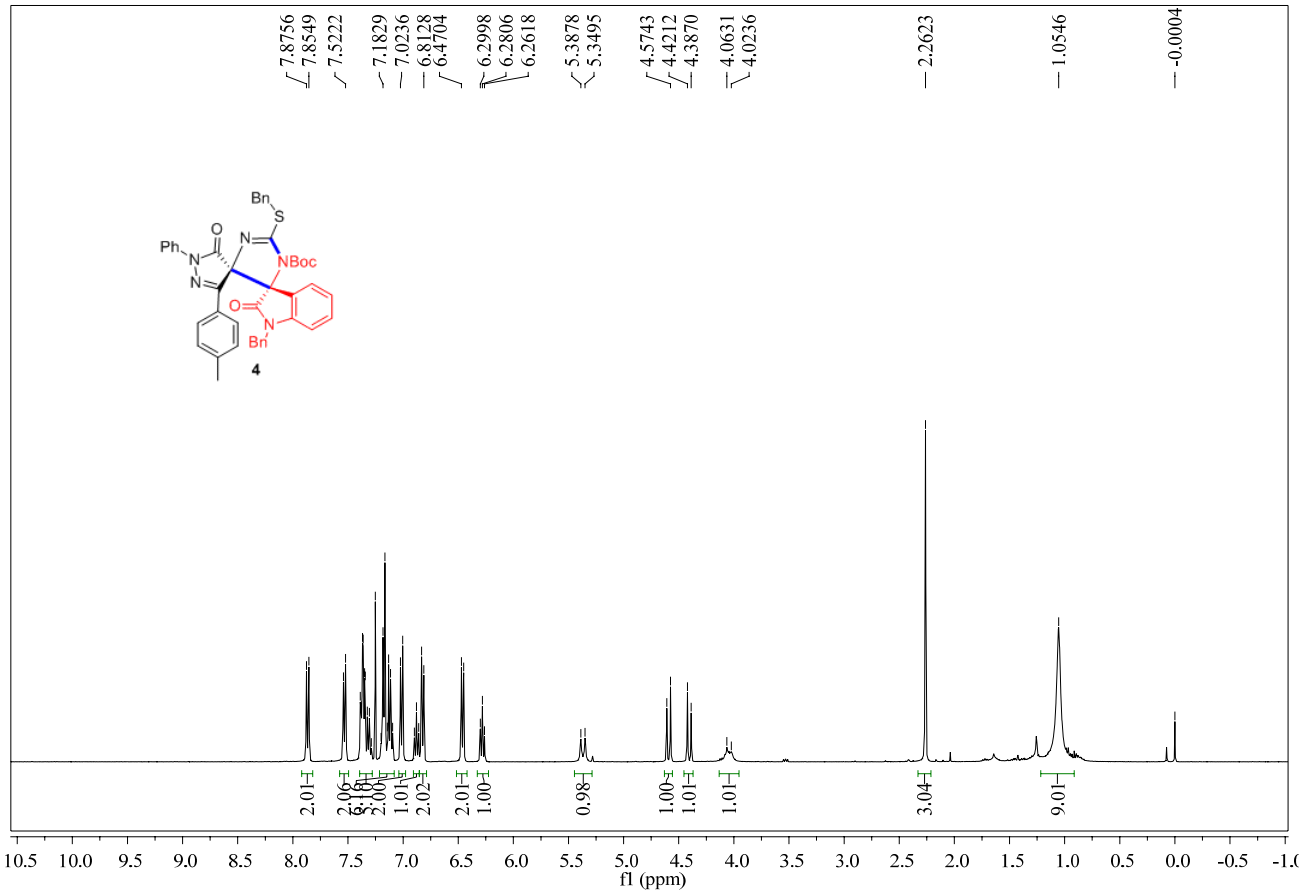
71.8888
44.0321
26.9921
15.3405
fl (ppm)
3ka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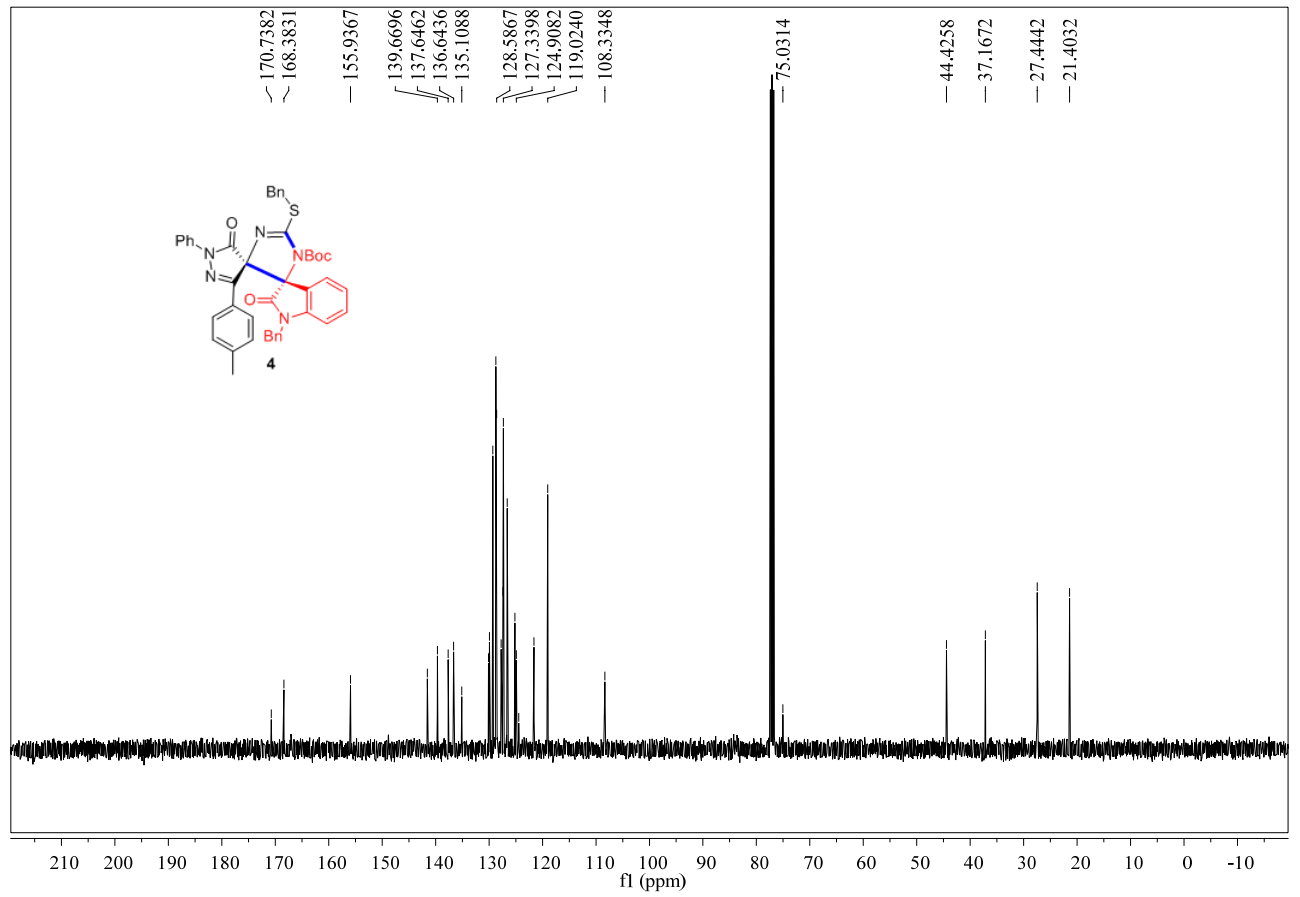
7.1829
7.0236
6.8128
6.4704
6.2998
6.2806
6.2618
5.3878
5.3495
4.5743
4.4212
4.3870
4.0631
4.0236
2.2623
1.0546
-0.0004
Bn
S
Ph
N
O
NBoc
Bn
4
2.01
2.06
1.01
2.02
2.01
1.00
0.98
1.00
1.01
1.01
3.04
9.01
fl (ppm)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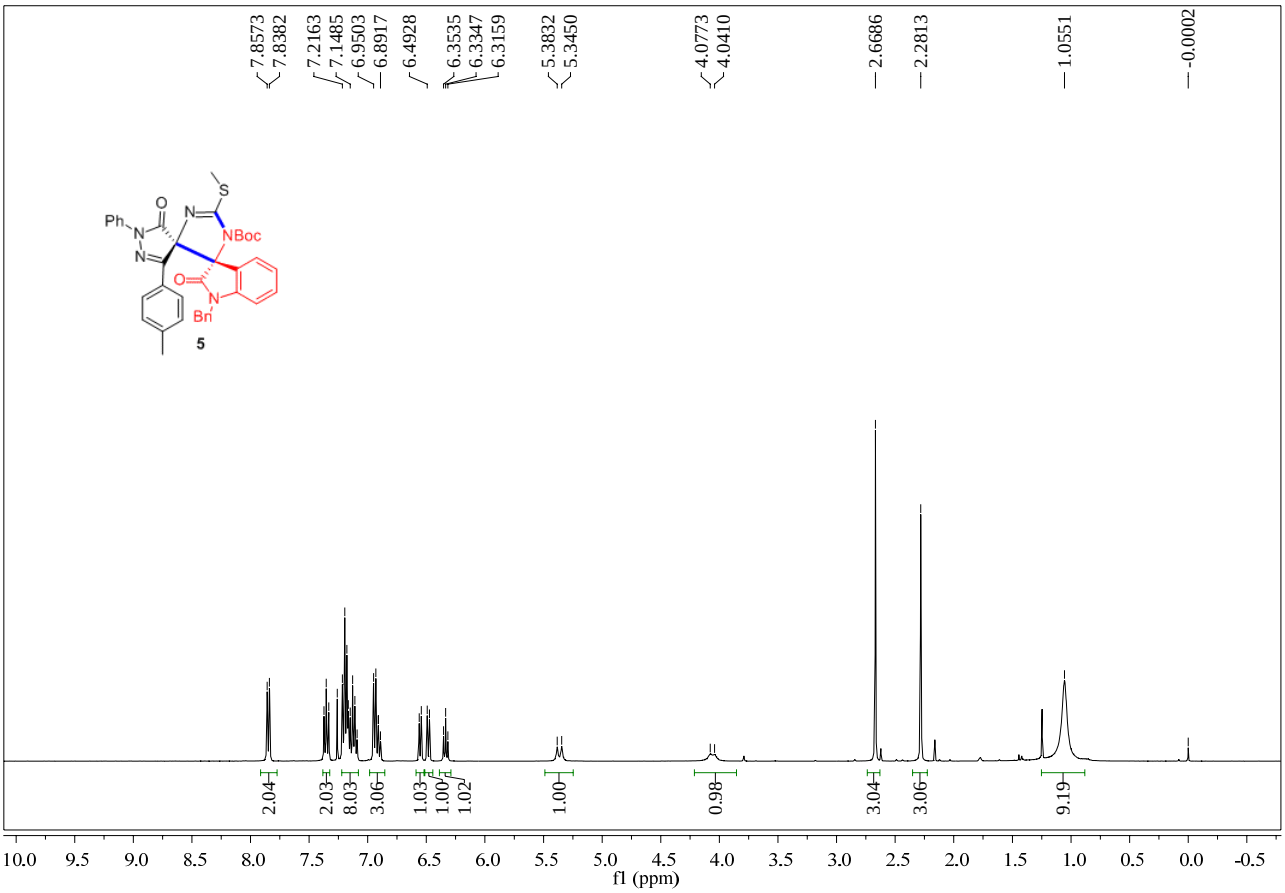
155.9367
139.6696
137.6462
136.6436
135.1088
128.5867
127.3398
124.9082
119.0240
108.3348
75.0314
44.4258
37.1672
27.4442
21.4032
Bn
S
Ph
N
O
NBoc
Bn
4
fl (ppm)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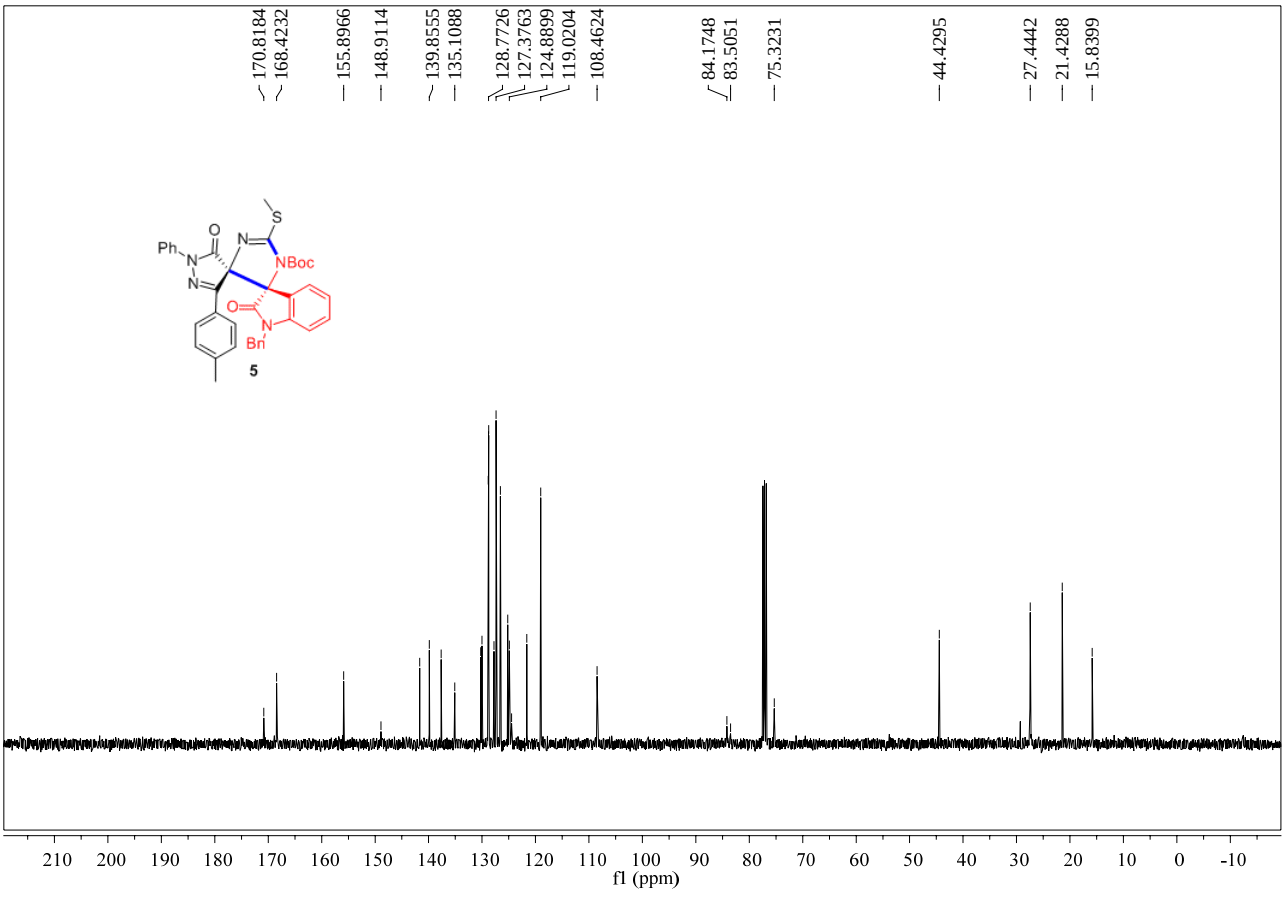
7.8382
7.2163
7.1485
6.9503
6.8917
6.4928
6.3535
6.3347
6.3159
5.3832
5.3450
4.0773
4.0410
2.6686
2.2813
1.0551
-0.0002
2.04
2.03
8.03
3.06
1.03
1.00
1.02
1.00
0.98
3.04
3.06
9.19
Ph
N
O
S
NBoc
Bn
5
f1 (ppm)


170.8184
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155.8966
148.9114
139.8555
135.1088
128.7726
127.3763
124.8899
119.0204
108.4624
84.1748
83.5051
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27.4442
21.4288
15.8399
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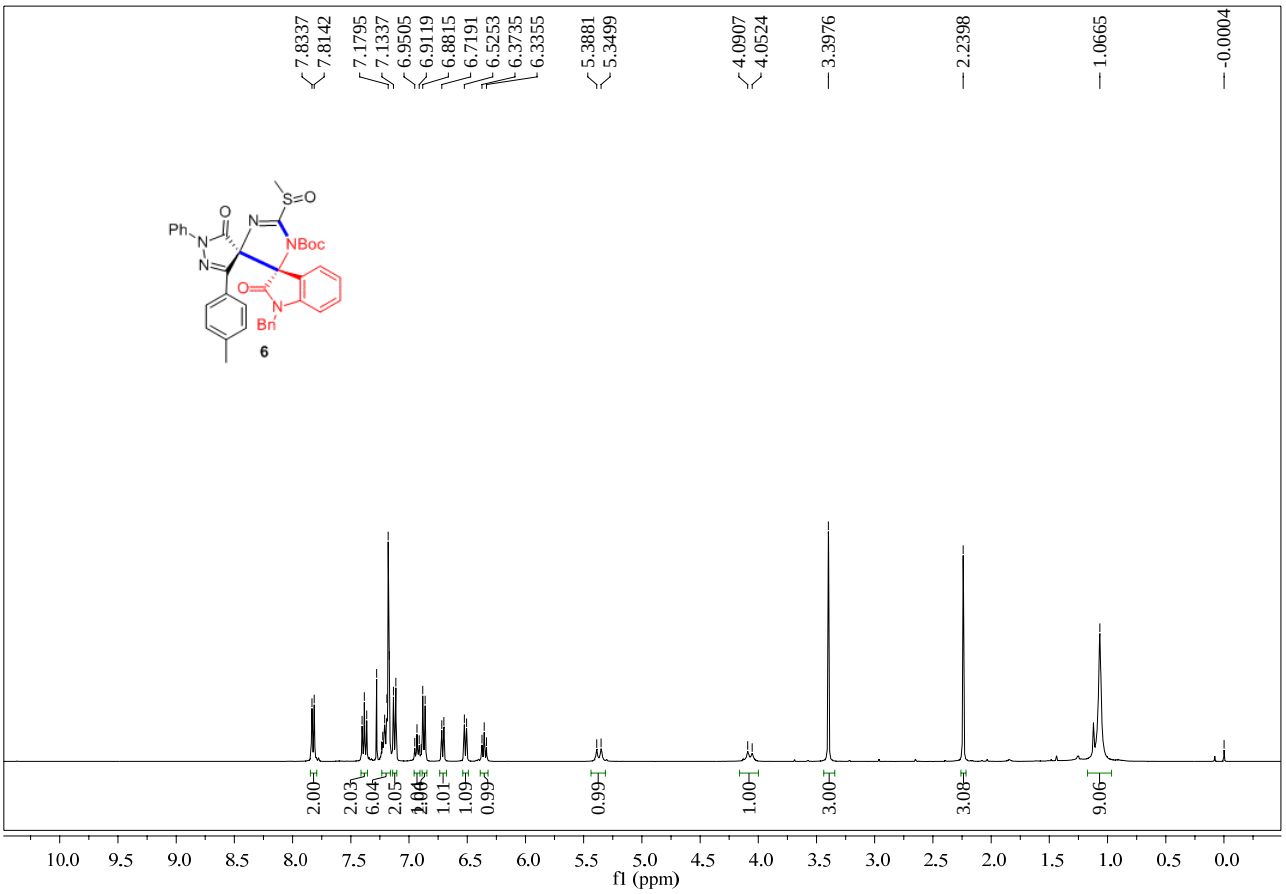
O
S
NBoc
Bn
5
f1 (ppm)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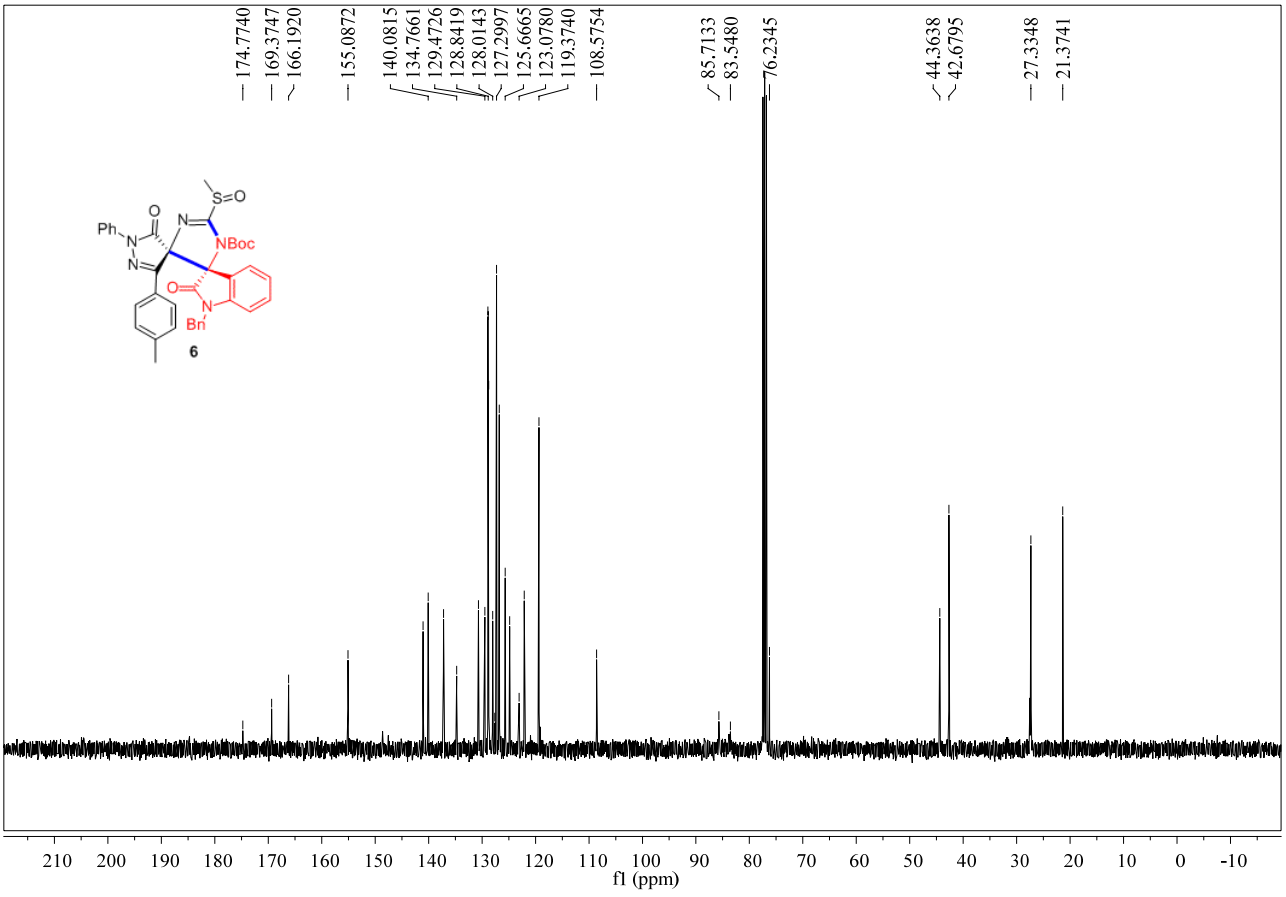
7.8142
7.1795
7.1337
6.9505
6.9119
6.8815
6.7191
6.5253
6.3735
6.3355
5.3881
5.3499
4.0907
4.0524
3.3976
2.2398
1.0665
-0.0004
Ph
N
O
S=O
NBoc
Bn
6
2.00
2.03
6.04
2.05
1.01
1.09
0.99
0.99
1.00
3.00
3.08
9.06
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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140.0815
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129.4726
128.8419
128.0143
127.2997
125.6665
123.0780
119.3740
108.5754
85.7133
83.5480
76.2345
44.3638
42.6795
27.3348
21.3741
Ph
N
O
S=O
NBoc
Bn
6
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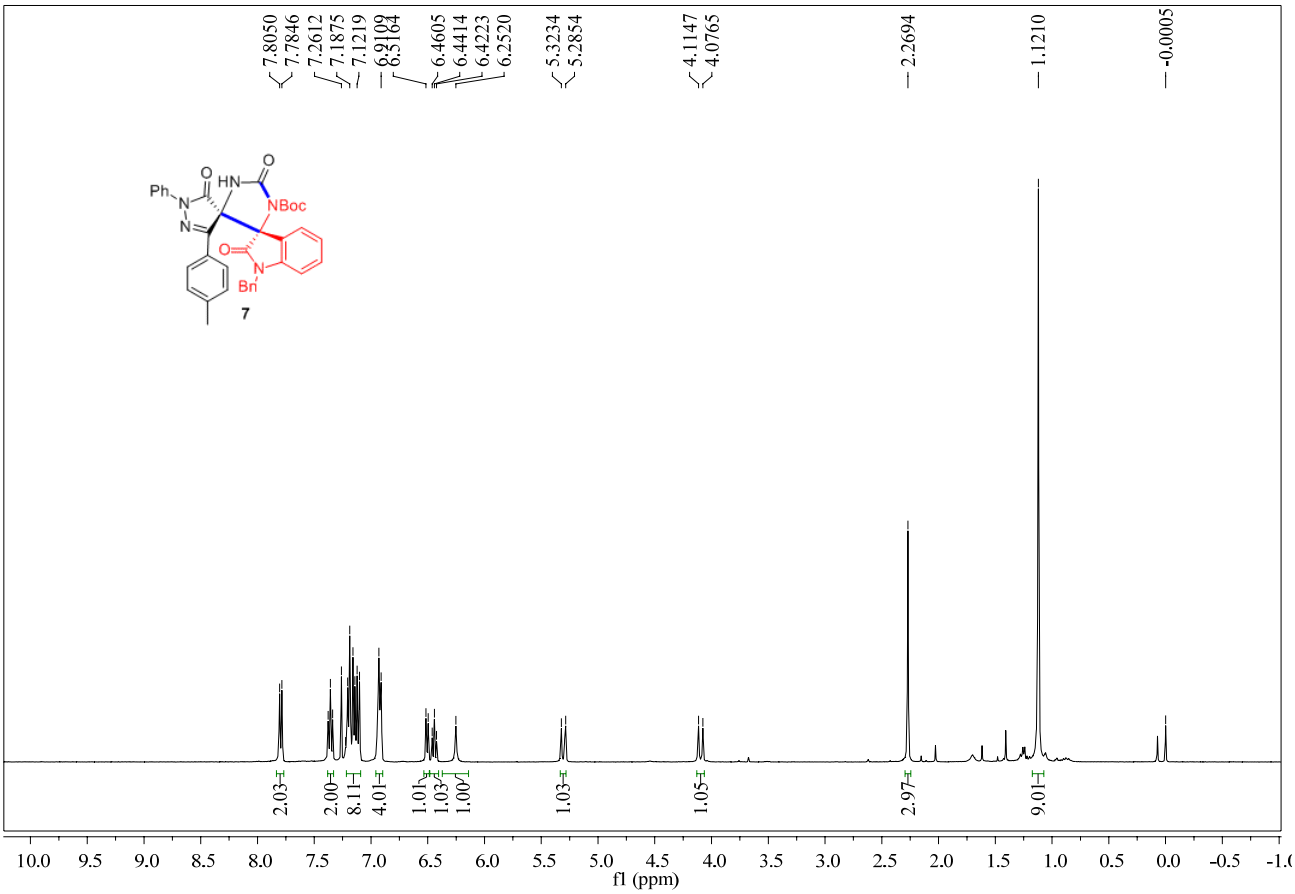
f1 (ppm)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7.2612
7.1875
7.1219
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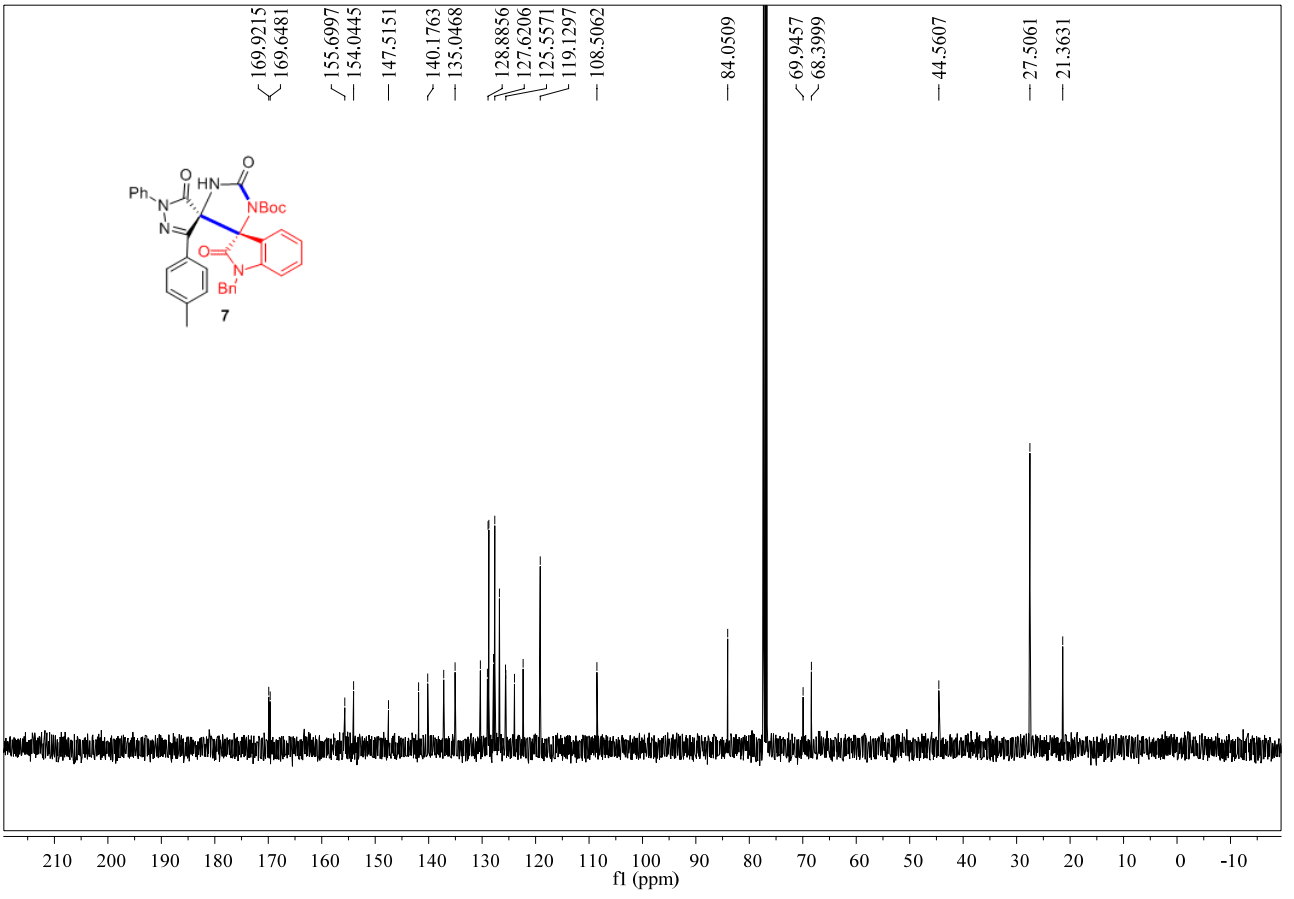
6.4414
6.4223
6.2520
5.3234
5.2854
4.1147
4.0765
2.2694
1.1210
-0.0005
2.03
2.00
8.11
4.01
1.01
1.03
1.00
1.03
1.05
2.97
9.01
Ph
HN
NBoc
Bn
7
f1 (ppm)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140.1763
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125.5571
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108.5062
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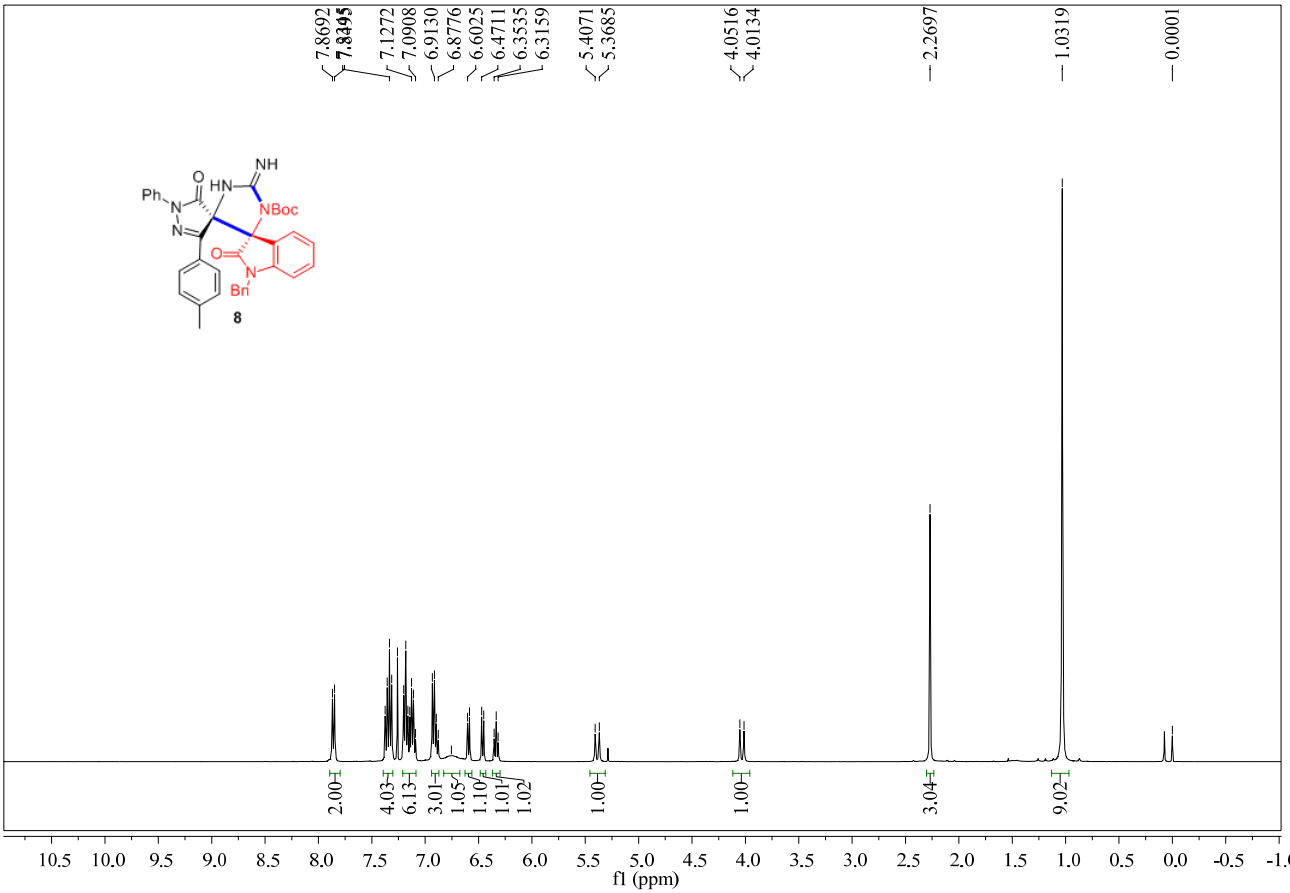
27.5061
21.3631
Ph
HN
NBoc
Bn
7
f1 (ppm)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6.6025
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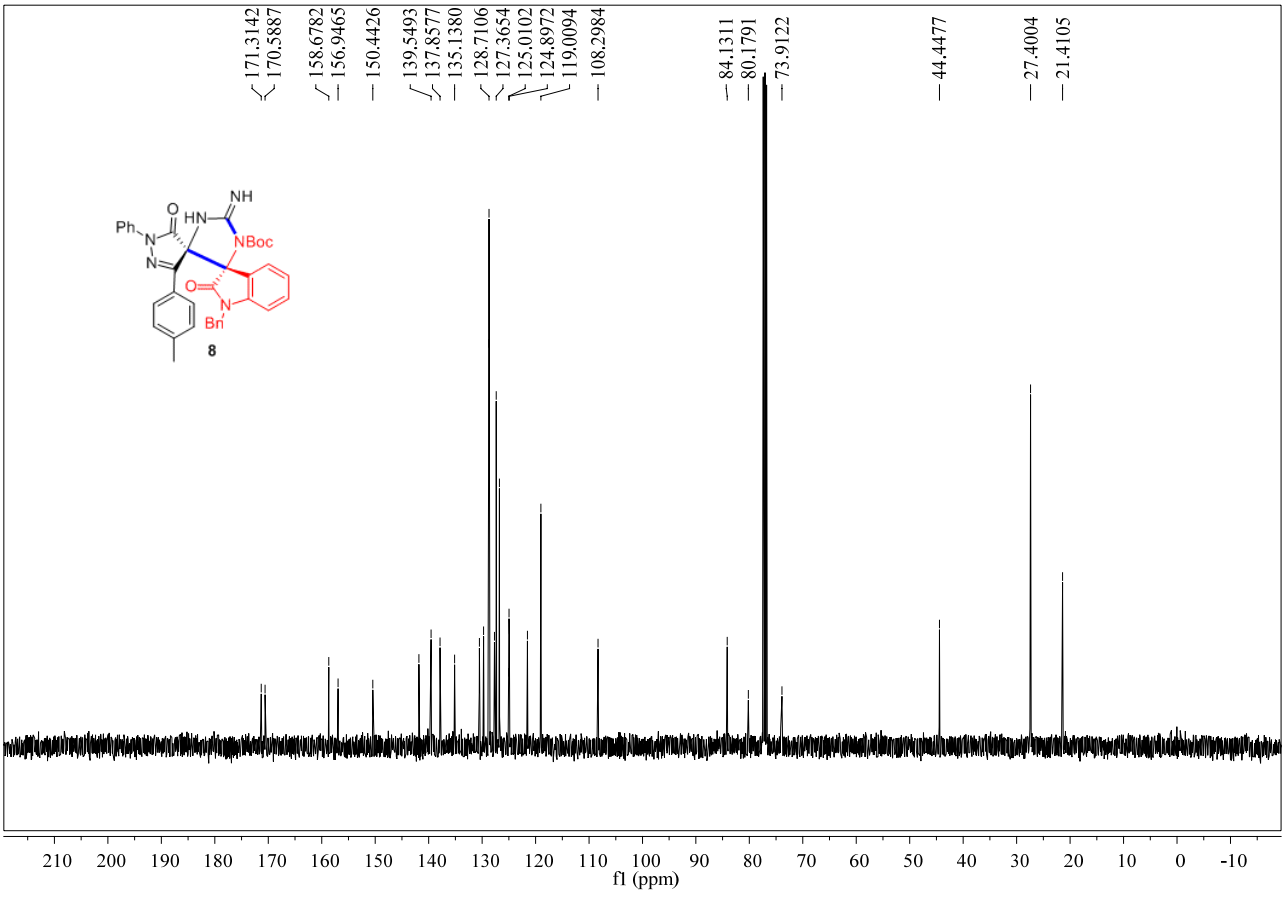
6.3535
6.3159
5.4071
5.3685
4.0516
4.0134
2.2697
1.0319
0.0001
2.00
4.03
6.13
3.01
1.05
1.10
1.01
1.02
1.00
1.00
3.04
9.02
fl (ppm)
8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84.1311
80.1791
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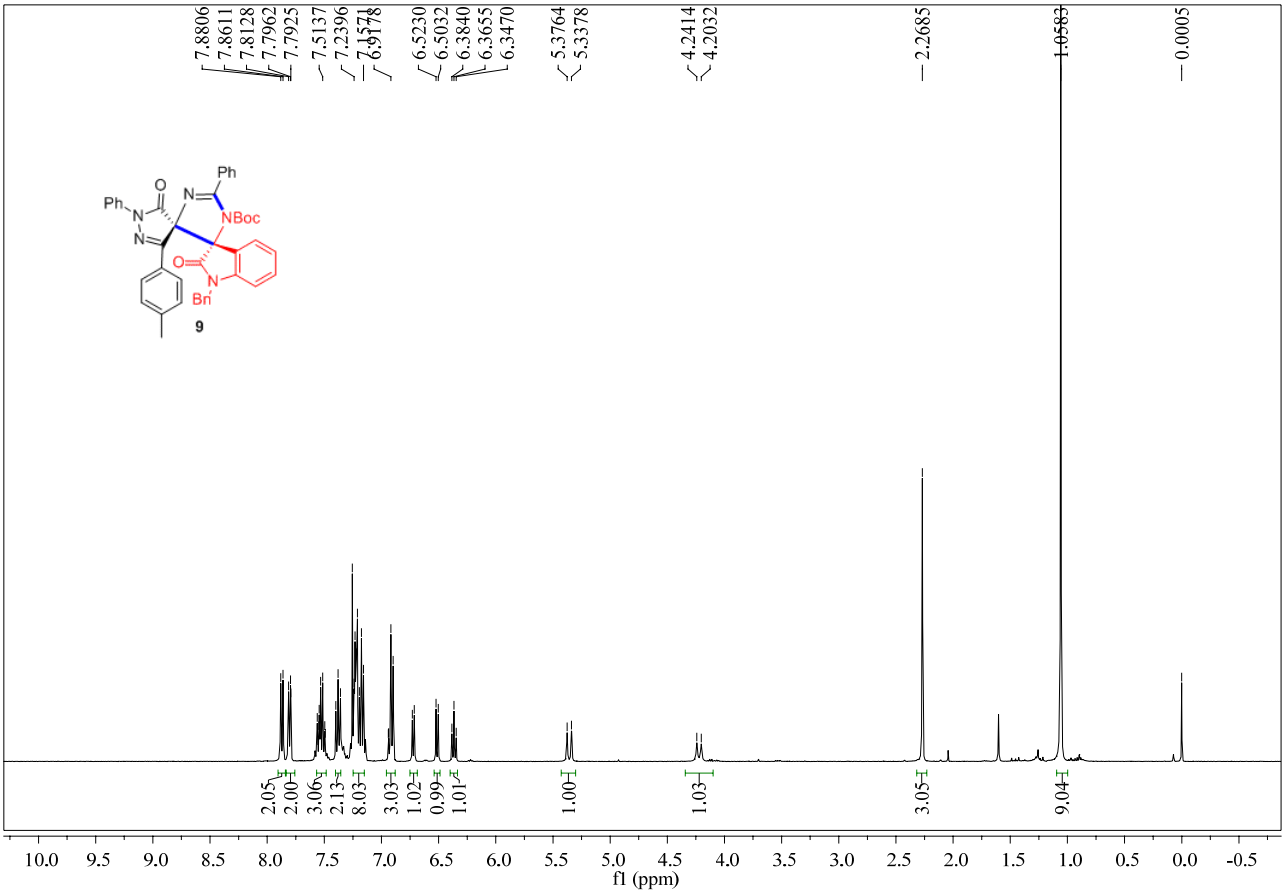
21.4105
fl (ppm)
8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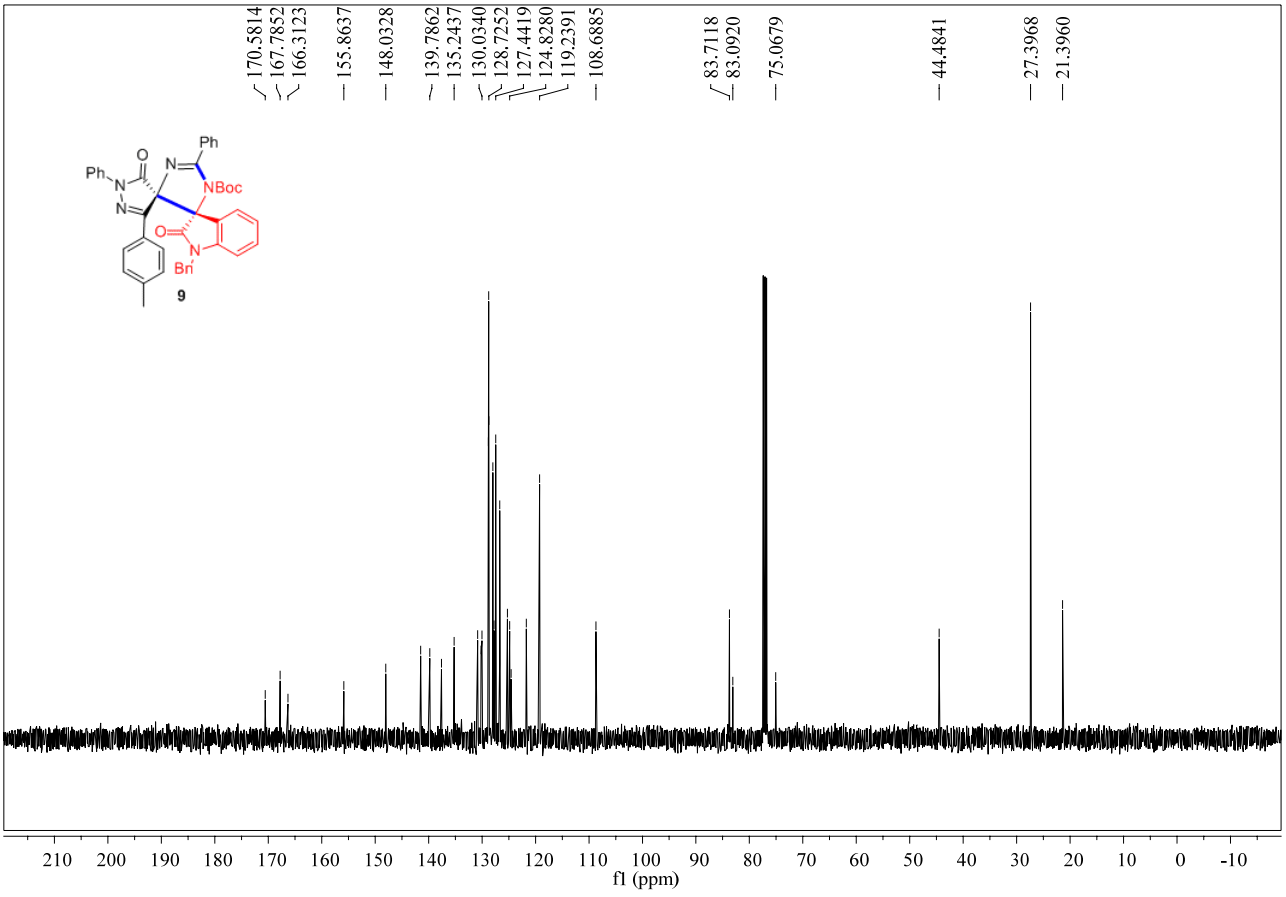
6.5032
6.3840
6.3655
6.3470
5.3764
5.3378
4.2414
4.2032
2.2685
1.0583
0.0005
2.05
2.00
3.06
2.13
8.03
3.03
1.02
0.99
1.01
1.00
1.03
3.05
9.04
Ph
N
NBoc
O
Ph
N
N
O
N
Bn
9
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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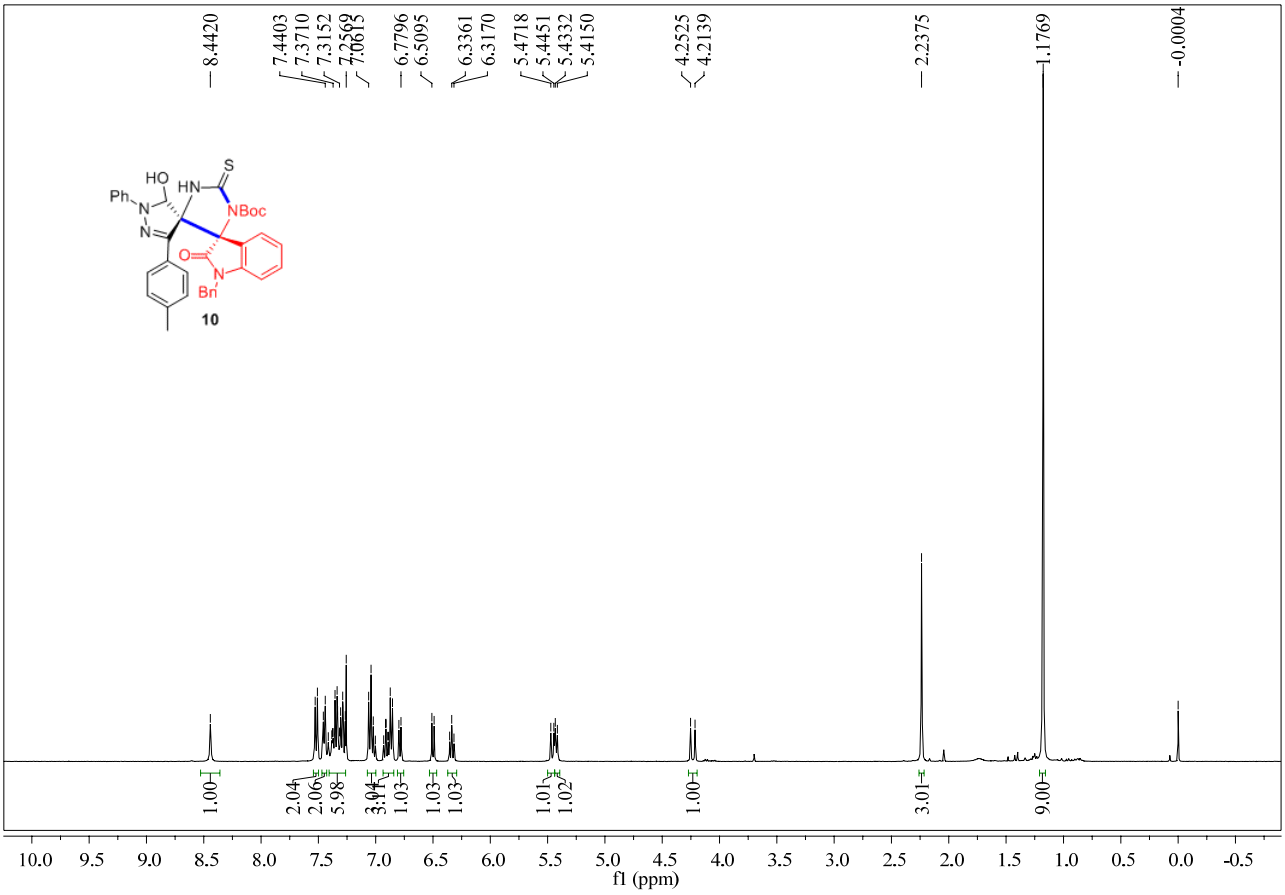
127.4419
124.8280
119.2391
108.6885
83.7118
83.0920
75.0679
44.4841
27.3968
21.3960
Ph
N
NBoc
O
Ph
N
N
O
N
Bn
9
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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7.3152
7.2569
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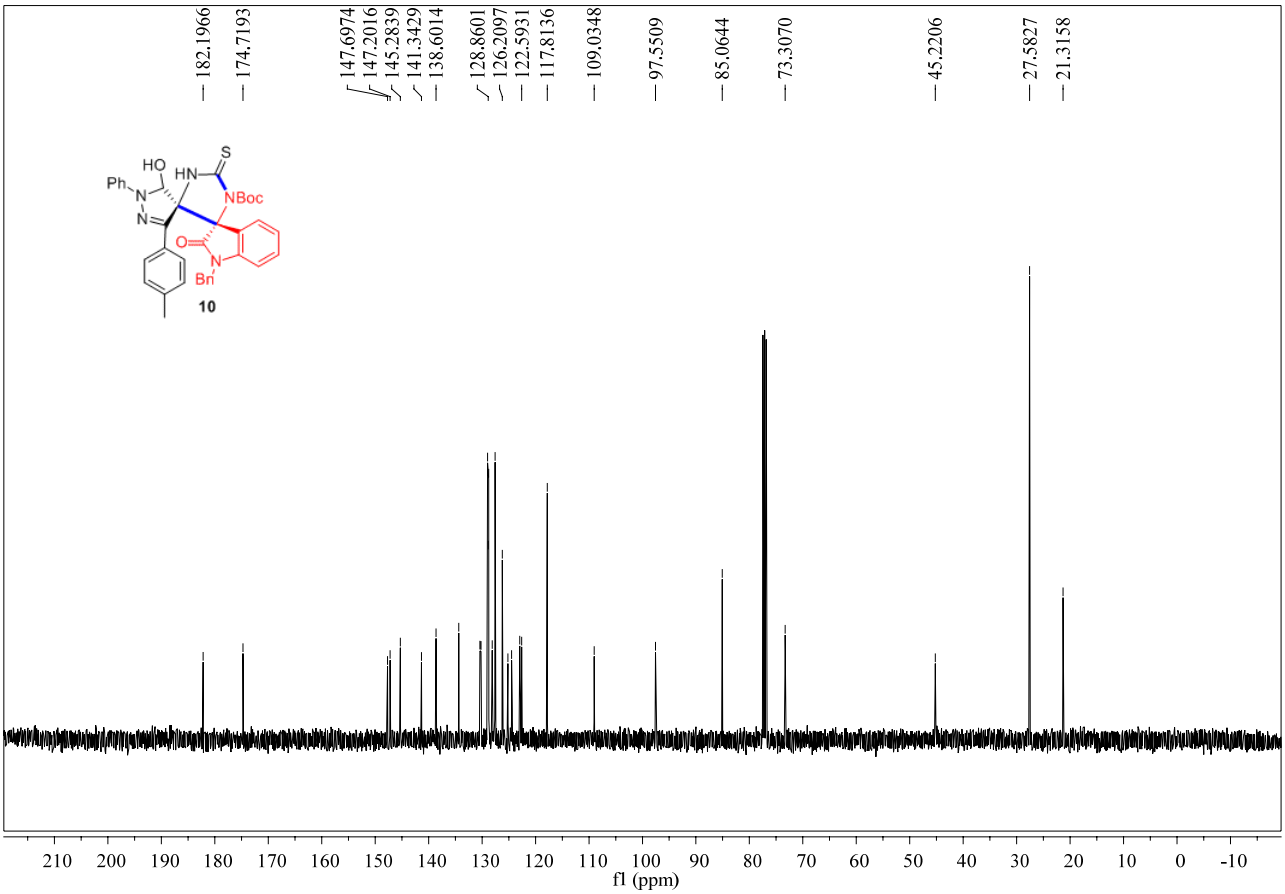
6.7796
6.5095
6.3361
6.3170
5.4718
5.4451
5.4332
5.4150
4.2525
4.2139
2.2375
1.1769
-0.0004
HO
HN
S
Ph
N
N
NBoc
O
N
Bn
10
1.00
2.04
2.06
5.98
3.04
3.11
1.03
1.03
1.03
1.01
1.02
1.00
3.01
9.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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126.2097
122.5931
117.8136
109.0348
97.5509
85.0644
73.3070
45.2206
27.5827
21.3158
HO
HN
S
Ph
N
N
NBoc
O
N
Bn
10
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)