

Bifunctional Brønsted Base Catalyzed Inverse-Electron-Demand Aza-Diels–Alder Reactions of Saccharin-Derived 1-Azadienes with Azlactones

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1. General Information

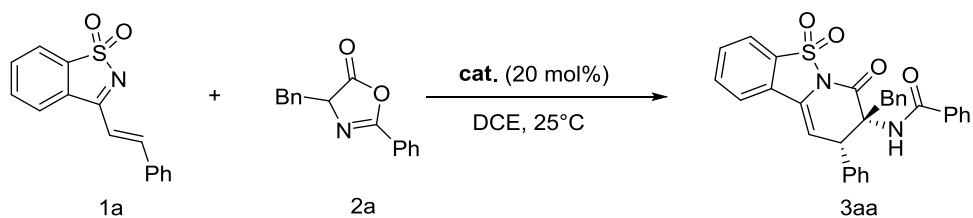
Chemicals and solvents were either purchased from commercial suppliers or purified by standard techniques. Analytical thin-layer chromatography (TLC) was performed on silicycle silica gel plates with F-254 indicator and compounds were visualized by irradiation with UV light. Flash chromatography was carried out utilizing silica gel 200-300 mesh. ^1H NMR, ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer (400 MHz ^1H , 100 MHz ^{13}C). The spectra were recorded in CDCl_3 as the solvent at room temperature, ^1H and $^{13}\text{CNMR}$ chemical shifts are reported in ppm relative to either the residual solvent peak (^{13}C) ($\delta = 77.00$ ppm) or TMS (^1H) ($\delta = 0$ ppm) as an internal standard. Data for ^1H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, dd = double doublet, br = broad), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported as chemical shift. HRMS were performed on Bruker Apex II mass instrument (ESI). Enantiomeric excess values were determined by HPLC with a Daicel Chirapak ID-3 /IA column on Agilent 1260 series with i-PrOH and n-hexane. Optical rotation was measured on the Perkin Elmer 341 polarimeter with $[\alpha]_D$ values reported in degrees. Concentration (c) is in g/100 mL. Saccharin-derived 1-azadienes **1** were prepared according to the literature procedures.¹ Azlactones **2** were also prepared according to the literature procedures.²

(1) Qian-Ru Zhang, Ji-Rong Huang, Wei Zhang, and Lin Dong. *Org. Lett.*, **2014**, *16*, 1684–1687.

(2) Eider Badiola, Bárbara Fiser, Enrique Gómez-Bengoá, Antonia Mielgo, Iurre Olaizola, Iñaki Urruzuno, Jesús M. García, José M. Odriozola, Jesús Razkin, Mikel Oiarbide, and Claudio Palomo. *J. Am. Chem. Soc.*, **2014**, *136*, 17869–17881

2. Preliminary Optimization of the IEDDA Reaction

Table S1 Catalyst Evaluation



entry ^a	catalyst	Yield (%) ^b	dr ^c	ee (%) ^d
1	1	89	>20:1	60
2	2	96	>20:1	67
3	3	79	>20:1	77
4	4	88	>20:1	67
5	5	90	>20:1	60
6	6	Trace	-	-
7	7	98	>20:1	84
8	8	Trace	-	-
9	9	96	>20:1	15
10	10	90	>20:1	46
11	11	Trace	-	-
12	12	88	>20:1	11
13	13	95	>20:1	40
14	14	Trace	-	-
15	15	89	>20:1	27
16	16	92	>20:1	7
17	17	93	>20:1	86

^aConditions: Reactions performed with 1a (0.1 mmol), 2a (0.1 mmol), cat. (20 mol%) in DCE (1 mL) at 25 °C. ^bIsolated yield. ^cDetermined by ¹H NMR analysis of the crude products. ^dDetermined by chiral-phase HPLC analysis.

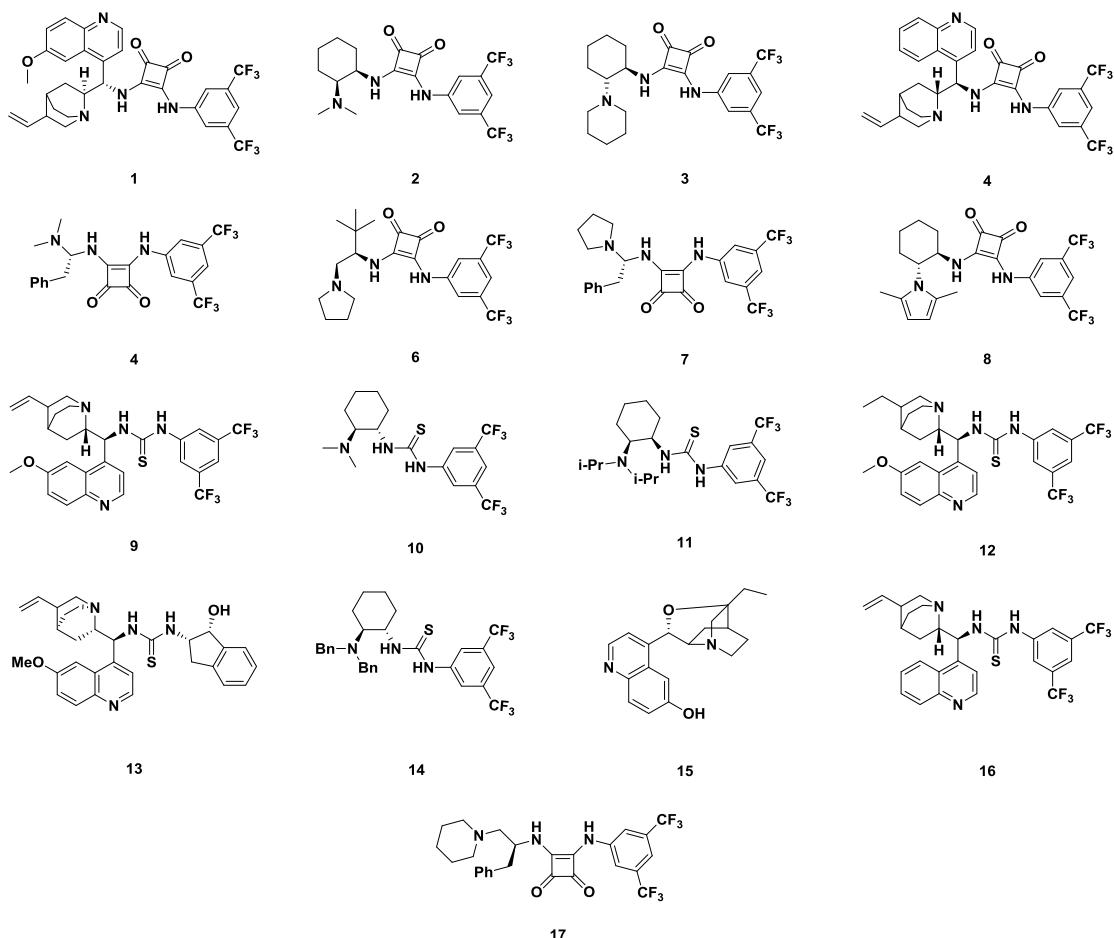
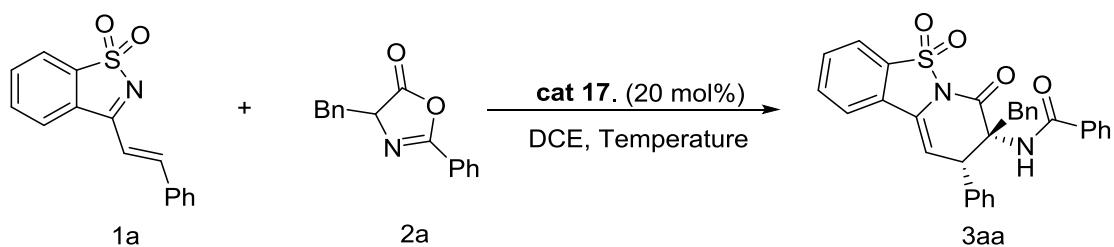


Table S2 Effect of Temperature



entry ^a	Temperature	Yield (%) ^b	dr ^c	ee (%) ^d
1	0 °C	71	> 20:1	90
2	-10 °C	55	> 20:1	91
3	-20 °C	76	> 20:1	92
4	-30 °C	68	> 20:1	92

^aConditions: Reactions performed with **1a** (0.1 mmol), **2a** (0.1 mmol), cat. (20 mol%) in DCE (1 mL). ^bIsolated yield. ^cDetermined by ¹H NMR analysis of the crude products. ^dDetermined by chiral-phase HPLC analysis.

Table S3 Effect of Solvent

entry ^a	solvent	Yield (%) ^b	dr ^c	ee (%) ^d
1	DCE	76	>20:1	92
2	DCM	75	>20:1	91
3	THF	81	>20:1	86
4	EA	60	>20:1	81
5	Toluene	19	>20:1	81
6	Acetone	65	>20:1	86
7	CHCl ₃	74	>20:1	92

^aConditions: Reactions performed with 1a (0.1 mmol), 2a (0.1 mmol), cat. (20 mol%) in solvent (1 mL). ^bIsolated yield. ^cDetermined by ¹H NMR analysis of the crude products. ^dDetermined by chiral-phase HPLC analysis.

Table S4 Additional Optimization of Reaction

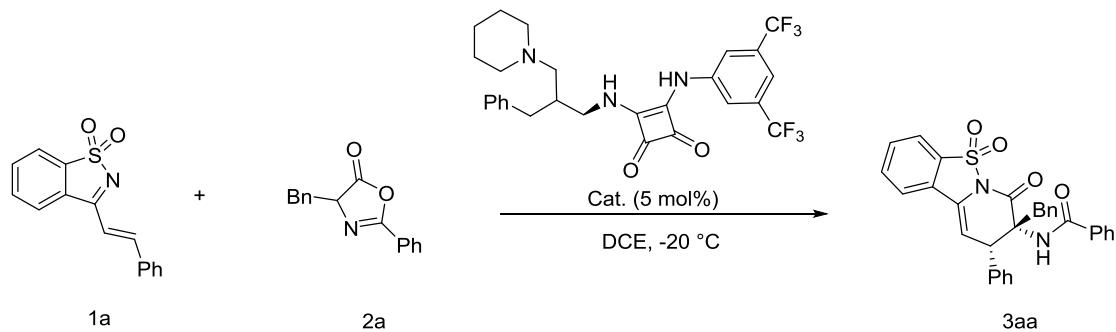
entry ^a	1a (mmol)	2a (mmol)	DCE	cat.17	Yield (%) ^b	dr ^c	ee (%) ^d
1	1.2	1	1 mL	20 mol%	83	>20:1	92
2	1.5	1	1 mL	20 mol%	89	>20:1	92
3	2	1	1 mL	20 mol%	84	>20:1	92
4	1	1.5	1 mL	20 mol%	65	>20:1	92

5	1	2	1 mL	20 mol%	69	>20:1	92
6	1.5	1	1 mL	10 mol%	88	>20:1	92
7	1.5	1	1 mL	5 mol%	89	>20:1	92
8	1.5	1	2 mL	5 mol%	85	>20:1	91
9	1.5	1	0.5 mL	5 mol%	95	>20:1	92
10 ^e	1.5	1	0.5 mL	5 mol%	94	>20:1	90

^aConditions: Reactions performed with 1a, 2a, cat.17. in DCE at - 20 °C. ^bIsolated yield. ^cDetermined by ¹H NMR analysis of the crude products. ^dDetermined by chiral-phase HPLC analysis.^e50 mg 4 Å MS was added.

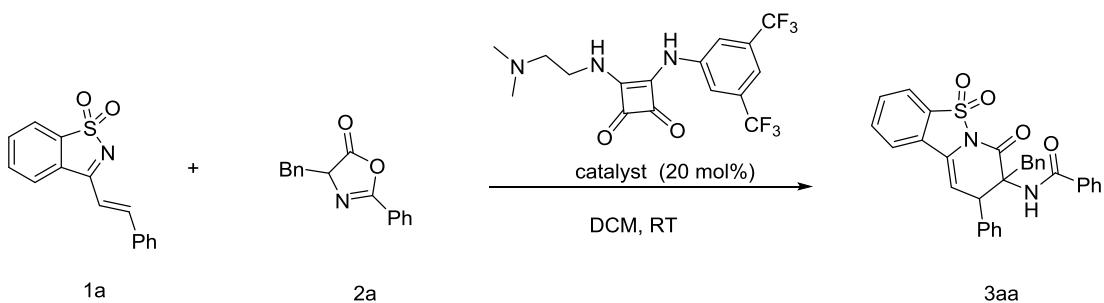
3. General Procedure and Analytical Data of Products

3.1 General Procedure for the Synthesis of Compounds 3



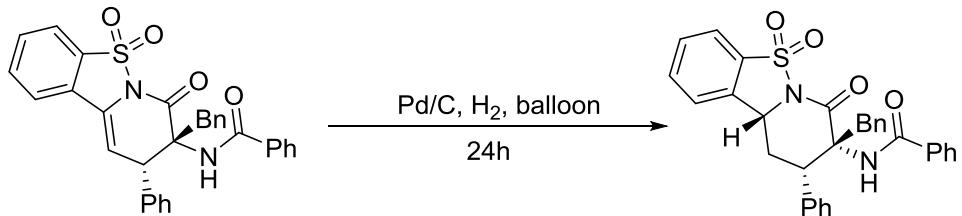
To a flame dried vessel were successively added 1-azadienes **1a** (40.3 mg, 0.15 mmol), azlactones **2a** (25.1 mg, 0.1 mmol), catalyst (2.6 mg, 0.005 mmol) and dried DCE (0.5 mL) at -20 °C. When the reaction was completed, the solvent was evaporated under reduced pressure and the residue was purified by silica gel flash column chromatography (petroleumether/EtOAc = 3:1) to give the corresponding compound **3aa** (49.4 mg, 95% yield) as white solid. The procedures of the asymmetric synthesis of compounds **3ba-3aj** and the gram-scale synthesis of **3aa** (0.98 g, 95% yield) were the same.

3.2 General Procedure for the Synthesis of Racemic Products 3



To a flame dried vessel were successively added 1-azadienes **1a** (26.9 mg, 0.1 mmol), azlactones **2a** (25.1 mg, 0.1 mmol), catalyst (7.9 mg, 0.02 mmol) and dried DCM (1 mL) at RT. When the reaction was completed, the solvent was evaporated under reduced pressure and the residue was purified by silica gel flash column chromatography (petroleumether/EtOAc = 3:1) to give the racemic compounds **3aa**. The procedures of racemic products **3ba-3aj** were the same.

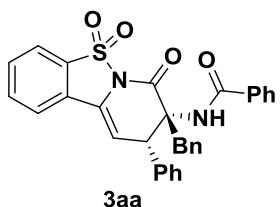
3.3 General Procedure for the Synthesis of Compounds 4



To a stirred solution of **3aa** (52.0 mg, 0.1 mmol) in 1 mL of MeOH was added Pd/C in one portion at room temperature. The mixture was degassed before stirring under a hydrogen atmosphere at room temperature. After the substrate conversion completely, Pd/C was filtered and organic layer was concentrated under reduced pressure and purification by flash column chromatography to get the product **4aa** as a white solid.

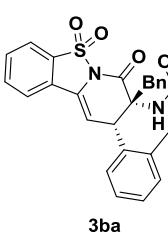
3.4 Analytical Data of Compounds 3 and 4

N-((8*R*,9*S*)-8-benzyl-5,5-dioxido-7-oxo-9-phenyl-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-a]pyridin-8-yl)benzamide (3aa)



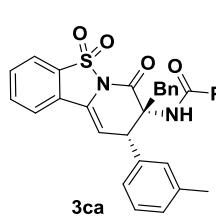
White solid. 95% yield (49.4 mg). m. p.: 130–132 °C. $[\alpha]_D^{20} = 238$ (*c* 1.0, CH₂Cl₂, 92% ee). ¹H NMR (400 MHz, CDCl₃): δ = 7.93 (d, *J* = 7.8 Hz, 1H), 7.74–7.80 (m, 1H), 7.67–7.70 (m, 1H), 7.37–7.41 (m, 1H), 7.27–7.31 (m, 4H), 7.23–7.25 (m, 3H), 7.18–7.20 (m, 7H), 6.77 (s, 1H), 6.38 (d, *J* = 6.6 Hz, 1H), 5.14 (d, *J* = 6.6 Hz, 1H), 4.21 (d, *J* = 13.8 Hz, 1H), 3.42 (d, *J* = 13.8 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 167.9, 166.4, 136.6, 135.0, 134.4, 134.1, 132.6, 131.4, 131.2, 130.3, 128.9, 128.4, 128.2, 128.1, 128.0, 127.95, 127.3, 126.4, 126.3, 121.9, 121.6, 107.1, 66.1, 48.5, 40.1. The enantiomeric excess was determined by HPLC with an ID-3 column (*n*-hexane:*i*-PrOH = 50:50), 1 mL/min. minor enantiomer *t_R* = 21.54 min, major enantiomer *t_R* = 32.45 min. HRMS (ESI): [M+H]⁺ calcd for [C₃₁H₂₅N₂O₄S]: 521.1530, found: 521.1539.

N-((8*R*,9*S*)-8-benzyl-5,5-dioxido-7-oxo-9-(o-tolyl)-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-a]pyridin-8-yl)benzamide(3ba)



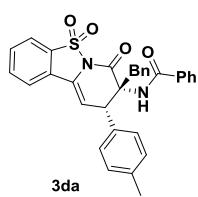
Yellow solid. 80% yield (42.7 mg). m. p.: 239–241 °C. $[\alpha]_D^{20} = 272$ (*c* 1.0, CH₂Cl₂, 86% ee). ¹H NMR (400 MHz, CDCl₃): δ = 7.90 (d, *J* = 7.7 Hz, 1H), 7.65–7.71 (m, 3H), 7.38 (t, *J* = 6.6 Hz, 1H), 7.28–7.30 (m, 3H), 7.25–7.26 (m, 1H), 7.19–7.21 (m, 5H), 7.04–7.10 (m, 3H), 6.99 (d, *J* = 6.8 Hz, 1H), 6.91 (s, 1H), 6.28 (d, *J* = 6.4 Hz, 1H), 5.40 (d, *J* = 6.4 Hz, 1H), 4.20 (d, *J* = 13.7 Hz, 1H), 3.44 (d, *J* = 13.7 Hz, 1H), 2.59 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 167.5, 167.1, 136.5, 136.1, 134.9, 134.3, 133.9, 132.3, 131.3, 131.2, 131.0, 130.5, 128.4, 128.2, 127.5, 127.4, 126.9, 126.7, 126.5, 126.4, 121.8, 121.6, 106.7, 64.7, 45.2, 40.9, 19.6. The enantiomeric excess was determined by HPLC with an IA column (*n*-hexane:*i*-PrOH = 50:50), 1 mL/min. minor enantiomer *t_R* = 7.23 min, major enantiomer *t_R* = 5.95 min. HRMS (ESI): [M+H]⁺ calcd for [C₃₂H₂₇N₂O₄S]: 535.1686, found: 535.1691

N-((8R,9S)-8-benzyl-5,5-dioxido-7-oxo-9-(m-tolyl)-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-8-yl)benzamide(3ca)



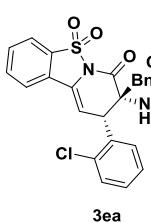
Yellow solid. 86% yield (45.9 mg). m. p.: 119-121 °C. $[\alpha]_D^{20} = 253$ (*c* 1.0, CH₂Cl₂, 92% ee). ¹H NMR (400 MHz, CDCl₃): $\delta = 7.94$ (d, *J* = 7.8Hz, 1H), 7.76-7.81 (m, 2H), 7.68-7.72 (m, 1H), 7.38-7.42 (m, 1H), 7.27-7.33 (m, 4H), 7.16-7.21 (m, 5H), 7.05-7.11 (m, 2H), 6.97-7.02 (m, 2H), 6.74 (S, 1H), 6.36 (d, *J* = 6.6Hz, 1H), 5.09 (d, *J* = 6.6Hz, 1H), 4.21 (d, *J* = 13.8Hz, 1H), 3.42 (d, *J* = 13.8Hz, 1H), 2.18 (S, 3H). ¹³C NMR (100 MHz, CDCl₃): $\delta = 168.0, 166.4, 138.6, 136.4, 135.1, 134.4, 134.2, 132.8, 131.4, 131.2, 130.4, 129.0, 128.9, 128.5, 128.2, 128.1, 127.4, 126.5, 124.9, 121.9, 121.7, 107.2, 66.2, 48.4, 40.0, 21.3$. The enantiomeric excess was determined by HPLC with an ID-3 column (*n*-hexane:*i*-PrOH = 50:50), 1 mL/min. minor enantiomer *t_R* = 23.45 min, major enantiomer *t_R* = 40.23 min. HRMS (ESI): [M+H]⁺ calcd for [C₃₂H₂₇N₂O₄S]: 535.1686, found: 535.1685

N-((8R,9S)-8-benzyl-5,5-dioxido-7-oxo-9-(p-tolyl)-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-8-yl)benzamide(3da)



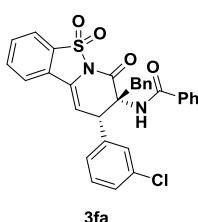
Yellow solid. 93% yield (49.7 mg). m. p.: 236-238 °C. $[\alpha]_D^{20} = 352$ (*c* 1.0, CH₂Cl₂, 93% ee). ¹H NMR (400 MHz, CDCl₃): $\delta = 7.93$ (d, *J* = 7.8Hz, 1H), 7.74-7.80 (m, 2H), 7.67-7.71 (m, 1H), 7.38-7.42 (m, 1H), 7.27-7.34 (m, 4H), 7.15-7.24 (m, 5H), 7.12 (d, *J* = 8.1Hz, 2H), 7.00 (d, *J* = 8.0Hz, 2H), 6.78 (S, 1H), 6.36 (d, *J* = 6.6Hz, 1H), 5.11 (d, *J* = 6.6Hz, 1H), 4.19 (d, *J* = 13.8Hz, 1H), 3.41 (d, *J* = 3.8Hz, 1H), 2.21 (S, 3H). ¹³C NMR (100 MHz, CDCl₃): $\delta = 167.8, 166.5, 137.9, 135.1, 134.4, 134.2, 133.4, 132.6, 131.4, 131.2, 130.4, 129.6, 128.4, 128.2, 127.9, 127.9, 127.3, 126.5, 126.4, 121.9, 121.6, 107.4, 66.2, 48.1, 40.1, 21.0$. The enantiomeric excess was determined by HPLC with an ID-3 column (*n*-hexane:*i*-PrOH = 50:50), 1 mL/min. minor enantiomer *t_R* = 26.29 min, major enantiomer *t_R* = 41.15 min. HRMS (ESI): [M+H]⁺ calcd for [C₃₂H₂₇N₂O₄S]: 535.1686, found: 535.1688

N-((8R,9S)-8-benzyl-9-(2-chlorophenyl)-5,5-dioxido-7-oxo-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-8-yl)benzamide(3ea)



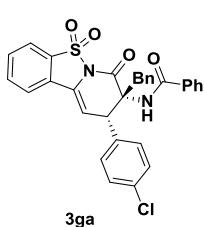
White solid. 83% yield (46.0 mg). m. p.: 217-219 °C. $[\alpha]_D^{20} = 292$ (c 1.0, CH₂Cl₂, 90% ee). ¹H NMR (400 MHz, CDCl₃): δ = 7.90 (d, J = 7.8Hz, 1H), 7.72-7.50 (m, 2H), 7.64-7.68 (m, 1H), 7.38-7.41 (m, 3H), 7.25-7.33 (m, 3H), 7.09-7.21 (m, 8H), 7.03 (S, 1H), 6.33 (br, 1H), 5.81 (br, 1H), 4.15 (d, J = 13.0Hz, 1H), 3.43 (d, J = 13.7Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 166.9, 135.2, 134.6, 134.3, 133.8, 133.7, 132.3, 131.5, 131.2, 130.6, 130.2, 128.8, 128.5, 128.3, 127.5, 126.6, 126.4, 121.9, 121.6, 63.7, 41.2. The enantiomeric excess was determined by HPLC with an IA column (*n*-hexane:*i*-PrOH= 50:50), 1 mL/min. minor enantiomer t_R = 12.38 min, major enantiomer t_R = 7.06min. HRMS (ESI): [M+H]⁺ calcd for [C₃₁H₂₄ClN₂O₄S]: 555.1140, 557.1111, found: 555.1140, 557.1110

N-((8R,9S)-8-benzyl-9-(3-chlorophenyl)-5,5-dioxido-7-oxo-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-8-yl)benzamide(3fa)



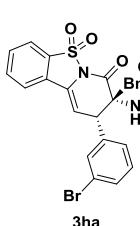
White solid. 74% yield (41.0 mg). m. p.: 216–218 °C. $[\alpha]_D^{20} = 363$ (c 1.0, CH₂Cl₂, 92% ee). ¹H NMR (400 MHz, CDCl₃): δ = 7.96 (d, J = 7.8Hz, 1H), 7.78-7.83 (m, 2H), 7.71-7.75 (m, 1H), 7.41-7.45 (m, 1H), 7.36-7.38 (m, 2H), 7.29-7.34 (m, 3H), 7.20-7.22 (m, 3H), 7.11-7.16 (m, 4H), 7.07-7.09 (m, 1H), 6.79 (S, 1H), 6.34 (d, J = 6.6Hz, 1H), 5.13 (d, J = 6.6Hz, 1H), 4.18 (d, J = 13.8Hz, 1H), 3.41 (d, J = 13.8Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 168.1, 166.1, 138.6, 134.8, 134.6, 134.5, 133.9, 132.8, 131.6, 131.5, 130.4, 130.2, 128.7, 128.6, 128.5, 128.4, 128.3, 127.5, 126.5, 126.2, 125.8, 122.0, 121.8, 106.2, 66.0, 48.0, 40.1. The enantiomeric excess was determined by HPLC with an IA column (*n*-hexane:*i*-PrOH= 50:50), 1 mL/min. minor enantiomer t_R = 11.22 min, major enantiomer t_R = 15.34 min. HRMS (ESI): [M+H]⁺ calcd for [C₃₁H₂₄ClN₂O₄S]: 555.1140, 557.1111, found: 555.1141, 557.1110

N-((8R,9S)-8-benzyl-9-(4-chlorophenyl)-5,5-dioxido-7-oxo-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-8-yl)benzamide(3ga)



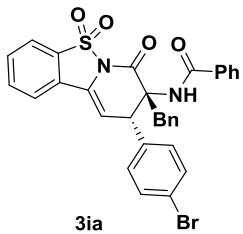
Yellow solid. 98% yield (54.3 mg). m. p.: 134–136 °C. $[\alpha]_D^{20} = 251$ (*c* 1.0, CH₂Cl₂, 90% ee). ¹H NMR (400 MHz, CDCl₃): $\delta = 7.96$ (d, *J* = 7.8Hz, 1H), 7.78-7.82 (m, 2H), 7.70-7.74 (m, 1H), 7.42-7.45 (m, 1H), 7.30-7.36 (m, 4H), 7.19-7.20 (m, 3H), 7.17 (S, 4H), 7.13-7.15 (m, 2H), 6.81 (S, 1H), 6.35 (d, *J* = 6.6Hz, 1H), 5.15 (d, *J* = 6.6Hz, 1H), 4.16 (d, *J* = 13.8Hz, 1H), 3.41 (d, *J* = 6.6Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): $\delta = 167.9, 166.2, 135.2, 134.7, 134.5, 134.0, 133.9, 132.7, 131.7, 131.4, 130.3, 129.5, 129.1, 128.6, 128.3, 127.5, 126.5, 126.2, 122.0, 121.8, 106.5, 66.0, 47.8, 40.1$. The enantiomeric excess was determined by HPLC with an ID-3 column (*n*-hexane:*i*-PrOH = 50:50), 1 mL/min. minor enantiomer *t_R* = 23.97 min, major enantiomer *t_R* = 27.24 min. HRMS (ESI): [M+H]⁺ calcd for [C₃₁H₂₄ClN₂O₄S]: 555.1140, found: 555.1141, 557.1111

N-((8R,9S)-8-benzyl-9-(3-bromophenyl)-5,5-dioxido-7-oxo-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-8-yl)benzamide(3ha)



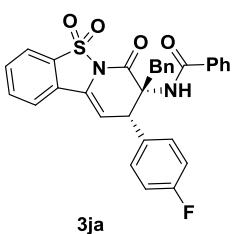
White solid. 98% yield. (58.6 mg). m. p.: 132–134 °C. $[\alpha]_D^{20} = 202$ (*c* 1.0, CH₂Cl₂, 91% ee). ¹H NMR (400 MHz, CDCl₃): 7.95(d, *J* = 7.8Hz, 1H), 7.77-7.83 (m, 2H), 7.70-7.74 (m, 1H), 7.41-7.46 (m, 2H), 7.36-7.38 (m, 2H), 7.29-7.34 (m, 3H), 7.20-7.22 (m, 3H), 7.11-7.16 (m, 3H), 7.07-7.08 (m, 1H), 6.79 (S, 1H), 6.34 (d, *J* = 6.8Hz, 1H), 5.12(d, *J* = 6.6Hz, 1H), 4.17(d, *J* = 13.8Hz, 1H), 3.41 (d, *J* = 13.8Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): $\delta = 168.1, 166.0, 138.8, 134.8, 134.5, 133.9, 132.7, 131.6, 131.5, 131.5, 131.3, 130.5, 130.3, 128.6, 128.3, 127.5, 126.5, 126.1, 126.1, 122.7, 122.0, 121.7, 106.1, 66.0, 47.9., 40.0$. The enantiomeric excess was determined by HPLC with an IA column (*n*-hexane:*i*-PrOH = 50:50), 1 mL/min. minor enantiomer *t_R* = 16.01 min, major enantiomer *t_R* = 12.10 min. HRMS (ESI): [M+H]⁺ calcd for [C₃₁H₂₄BrN₂O₄S]: 599.0635, 601.0615, found: 599.0649, 601.0614

N-((8R,9S)-8-benzyl-9-(4-bromophenyl)-5,5-dioxido-7-oxo-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-8-yl)benzamide(3ia)



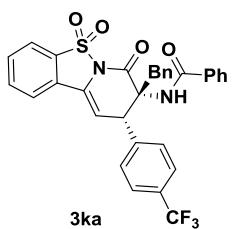
Yellow solid. 97% yield (58.0 mg). m. p.: 124–126 °C. $[\alpha]_D^{20} = 263$ (*c* 1.0, CH₂Cl₂, 90% ee). ¹H NMR (400 MHz, CDCl₃): δ = 7.94 (d, *J* = 7.8 Hz, 1H), 7.76–7.82 (m, 2H), 7.69–7.73 (m, 1H), 7.41–7.45 (m, 1H), 7.30–7.37 (m, 6H), 7.18–7.20 (m, 3H), 7.10–7.15 (m, 4H), 6.82 (s, 1H), 6.35 (d, *J* = 6.6 Hz, 1H), 5.13 (d, *J* = 6.6 Hz, 1H), 4.16 (d, *J* = 13.8 Hz, 1H), 3.41 (d, *J* = 13.8 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 167.9, 161.2, 135.7, 134.7, 134.5, 133.9, 132.7, 132.0, 131.6, 131.4, 130.3, 129.8, 128.6, 128.3, 127.4, 126.5, 126.2, 122.1, 122.0, 121.7, 106.4, 65.9, 47.9, 40.1. The enantiomeric excess was determined by HPLC with an ID-3 column (*n*-hexane:*i*-PrOH = 50:50), 1 mL/min. minor enantiomer *t_R* = 28.66 min, major enantiomer *t_R* = 30.49 min. HRMS (ESI): [M+H]⁺ calcd for [C₃₁H₂₄BrN₂O₄S]: 599.0635, 601.0615, found: 599.0649, 601.0614

N-((8R,9S)-8-benzyl-9-(4-fluorophenyl)-5,5-dioxido-7-oxo-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-8-yl)benzamide(3ja)



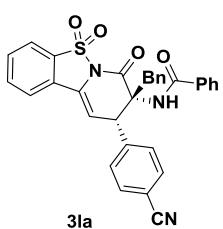
Yellow solid. 92% yield (49.5 mg). m. p.: 130–132 °C. $[\alpha]_D^{20} = 252$ (*c* 1.0, CH₂Cl₂, 88% ee). ¹H NMR (400 MHz, CDCl₃): δ = 7.96 (d, *J* = 7.8 Hz, 1H), 7.78–7.83 (m, 2H), 7.70–7.74 (m, 1H), 7.43 (t, *J* = 6.8 Hz, 1H), 7.29–7.36 (m, 4H), 7.19–7.23 (m, 5H), 7.14–7.16 (m, 2H), 6.89 (t, *J* = 8.6 Hz, 1H), 6.80 (s, 1H), 6.37 (d, *J* = 6.6 Hz, 1H), 5.15 (d, *J* = 6.6 Hz, 1H), 4.17 (d, *J* = 13.8 Hz, 1H), 3.41 (d, *J* = 13.8 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 167.9, 166.3, 162.3 (*J*_{C-F} = 245.9 Hz), 134.8, 134.5, 134.0, 132.7, 132.4 (*J*_{C-F} = 3.0 Hz), 131.6, 131.4, 130.3, 129.8 (*J*_{C-F} = 8.2 Hz), 128.6, 128.3, 128.1, 127.4, 126.5, 126.3, 121.9 (*J*_{C-F} = 24.4 Hz), 115.3 (*J*_{C-F} = 21.3 Hz) 106.8, 66.1, 47.7, 40.0. The enantiomeric excess was determined by HPLC with an ID-3 column (*n*-hexane: *i*-PrOH = 50:50), 1 mL/min. minor enantiomer *t_R* = 17.47 min, major enantiomer *t_R* = 22.50 min. HRMS (ESI): [M+H]⁺ calcd for [C₃₁H₂₄FN₂O₄S]: 539.1435, found: 539.1440

N-((8R,9S)-8-benzyl-5,5-dioxido-7-oxo-9-(4-(trifluoromethyl)phenyl)-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-8-yl)benzamide(3ka)



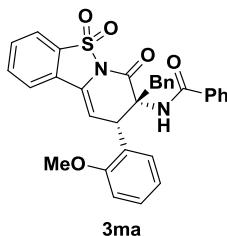
Yellow solid. 79% yield (46.5 mg). m. p.: 124–126 °C. $[\alpha]_D^{20} = 280$ (*c* 1.0, CH₂Cl₂, 84% ee). ¹H NMR (400 MHz, CDCl₃): δ = 7.97 (d, *J* = 7.8 Hz, 1H), 7.78–7.83 (m, 2H), 7.72–7.76 (m, 1H), 7.47 (d, *J* = 8.3 Hz, 2H), 7.41–7.45 (m, 1H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.30–7.32 (m, 4H), 7.20–7.21 (m, 3H), 7.13–7.16 (m, 2H), 6.82 (s, 1H), 6.36 (d, *J* = 6.6 Hz, 1H), 5.25 (d, *J* = 6.6 Hz, 1H), 4.18 (d, *J* = 13.8 Hz, 1H), 3.44 (d, *J* = 13.8 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 168.0, 166.1, 140.9, 134.6, 134.5, 133.8, 132.8, 131.7, 131.6, 130.4, 130.3 (*J*_{C-F} = 32.4 Hz), 128.6, 128.5, 128.4, 127.6, 126.5, 126.1, 125.8 (*J*_{C-F} = 3.6 Hz), 123.7 (*J*_{C-F} = 270.6 Hz), 122.0, 121.8, 106.0, 65.9, 48.2, 40.2. The enantiomeric excess was determined by HPLC with an IA column (*n*-hexane:*i*-PrOH = 50:50), 1 mL/min. minor enantiomer *t*_R = 22.98 min, major enantiomer *t*_R = 12.69 min. HRMS (ESI): [M+H]⁺ calcd for [C₃₂H₂₄F₃N₂O₄S]: 589.1403, found: 589.1408

N-((8R,9S)-8-benzyl-9-(4-cyanophenyl)-5,5-dioxido-7-oxo-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-8-yl)benzamide(3la)



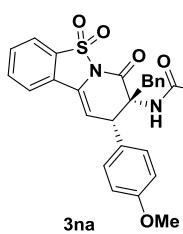
Yellow solid. 84% yield (45.8 mg). m. p.: 252–254 °C. $[\alpha]_D^{20} = 211$ (*c* 1.0, CH₂Cl₂, 76% ee). ¹H NMR (400 MHz, CDCl₃): δ = 7.97 (d, *J* = 7.8 Hz, 1H), 7.78–7.84 (m, 2H), 7.72–7.77 (m, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.43–7.46 (m, 1H), 7.32–7.37 (m, 6H), 7.19–7.20 (m, 3H), 7.12–7.14 (m, 2H), 6.83 (s, 1H), 6.33 (d, *J* = 6.6 Hz, 1H), 5.24 (d, *J* = 6.6 Hz, 1H), 4.15 (d, *J* = 13.8 Hz, 1H), 3.43 (d, *J* = 13.8 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 167.8, 165.9, 142.3, 134.6, 134.3, 133.6, 132.7, 132.6, 131.9, 131.7, 130.3, 128.9, 128.8, 128.7, 128.3, 127.6, 126.4, 126.0, 122.1, 121.8, 118.2, 112.0, 105.4, 65.7, 48.4, 40.1. The enantiomeric excess was determined by HPLC with an IA-3 column (*n*-hexane:*i*-PrOH = 50:50), 1 mL/min. minor enantiomer *t*_R = 10.40 min, major enantiomer *t*_R = 35.96 min. HRMS (ESI): [M+H]⁺ calcd for [C₃₂H₂₄N₃O₄S]: 546.1482, found: 546.1481

N-((8R,9S)-8-benzyl-9-(2-methoxyphenyl)-5,5-dioxido-7-oxo-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-8-yl)benzamide (3ma)



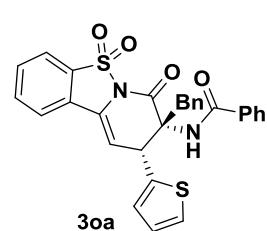
Yellow solid. 96% yield (52.8 mg). m. p.: 230-232 °C. $[\alpha]_D^{20} = 252$ (*c* 1.0, CH₂Cl₂, 88% ee). ¹H NMR (400 MHz, CDCl₃): $\delta = 7.90$ (d, *J* = 7.8Hz, 1H), 7.68-7.74 (m, 2H), 7.62-7.66 (m, 1H), 7.35-7.39(m, 3H), 7.24-7.28 (m, 4H), 7.13-7.20 (m, 6H), 6.91 (s, 1H), 6.85 (td, *J*₁ = 7.48Hz, *J*₂ = 0.96Hz), 6.74 (d, *J* = 8.0 Hz, 1H), 6.0 (d, *J* = 5.8Hz, 1H), 4.98 (s, 1H), 4.17 (d, *J* = 13.6Hz, 1H), 3.7(s, 3H), 3.32 (d, *J* = 13.6Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): $\delta = 167.5, 166.3, 157.6, 135.2, 134.3, 134.0, 132.6, 132.5, 131.1, 130.7, 130.6, 129.3, 128.4, 128.0, 127.22, 127.19, 126.8, 126.3, 125.0, 121.7, 121.4, 120.6, 110.0, 103.7, 63.8, 54.3, 50.6, 41.2$. The enantiomeric excess was determined by HPLC with an ID-3 column (*n*-hexane:*i*-PrOH= 50:50), 1 mL/min. minor enantiomer *t*_R = 38.51 min, major enantiomer *t*_R = 53.56 min. HRMS (ESI): [M+H]⁺ calcd for [C₃₂H₂₇N₂O₅S]:551.1635, found: 551.1634.

N-((8R,9S)-8-benzyl-9-(4-methoxyphenyl)-5,5-dioxido-7-oxo-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-8-yl)benzamide(3na)



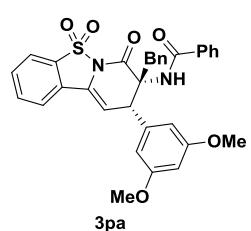
Yellow solid. 94% yield (51.7 mg). m. p.: 118–120 °C. $[\alpha]_D^{20} = 203$ (*c* 1.0, CH₂Cl₂, 86% ee). ¹H NMR (400 MHz, CDCl₃): $\delta = 7.95$ (d, *J* = 7.8Hz, 1H), 7.77-7.82 (m, 2H), 7.69-7.73 (m, 1H), 7.42 (t, *J* = 7.1Hz, 1H), 7.28-7.36 (m, 4H), 7.19-7.20 (m, 3H), 7.14-7.16 (m, 4H), 6.79 (S, 1H), 6.73 (d, *J*=8.7Hz, 1H), 6.37 (d, *J* = 6.6Hz, 1H), 5.10 (d, *J* = 6.6Hz, 1H), 4.18 (d, *J* =13.8Hz, 1H). 3.68 (s, 3H), 3.41 (d, *J* = 13.8Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): $\delta = 167.9, 166.5, 159.3, 135.0, 134.4, 134.2, 132.7, 131.4, 131.2, 130.3, 129.2, 128.5, 128.3, 128.3, 127.8, 127.4, 126.6, 126.5, 121.9, 121.7, 114.3, 107.5, 66.4, 55.1, 47.7, 40.0$. The enantiomeric excess was determined by HPLC with an ID-3 column (*n*-hexane:*i*-PrOH= 50:50), 1 mL/min. minor enantiomer *t*_R = 42.82 min, major enantiomer *t*_R = 32.01 min. HRMS (ESI): [M+H]⁺ calcd for [C₃₂H₂₇N₂O₅S]:551.1635, found: 551.1636

N-((8R,9R)-8-benzyl-5,5-dioxido-7-oxo-9-(thiophen-2-yl)-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-8-yl)benzamide(3oa)



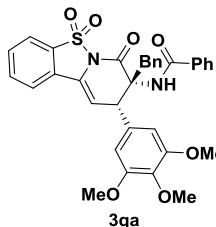
Yellow solid. 99% yield (52.2 mg). m. p.: 140–142 °C. $[\alpha]_D^{20} = 239$ (*c* 1.0, CH₂Cl₂, 92% ee). ¹H NMR (400 MHz, CDCl₃): $\delta = 7.95$ (d, *J* = 7.7 Hz, 1H), 7.78–7.85 (m, 2H), 7.70–7.74 (m, 1H), 7.44–7.46 (m, 3H), 7.32–7.36 (m, 2H), 7.19 (s, 3H), 7.10–7.15 (m, 3H), 6.94 (s, 1H), 6.84–6.84 (m, 2H), 6.46 (d, *J* = 6.6 Hz, 1H), 5.5 (d, *J* = 6.5 Hz, 1H), 4.13 (d, *J* = 13.8 Hz, 1H), 3.40 (d, *J* = 13.8 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): $\delta = 168.0, 165.9, 138.4, 134.9, 134.5, 134.1, 132.7, 131.6, 131.4, 130.3, 128.6, 128.3, 128.2, 127.4, 127.1, 127.0, 127.0, 126.7, 126.1, 125.7, 122.0, 121.7, 106.6, 66.7, 42.6, 39.4$. The enantiomeric excess was determined by HPLC with an ID-3 column (*n*-hexane:*i*-PrOH = 50:50), 1 mL/min. minor enantiomer *t_R* = 22.26 min, major enantiomer *t_R* = 25.34 min. HRMS (ESI): [M+H]⁺ calcd for [C₂₉H₂₃N₂O₄S₂]:527.1094, found: 527.1093

N-((8R,9S)-8-benzyl-9-(3,5-dimethoxyphenyl)-5,5-dioxido-7-oxo-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-8-yl)benzamide(3pa)



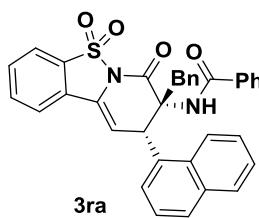
Yellow solid. 87% yield (50.5 mg). m. p.: 137–139 °C. $[\alpha]_D^{20} = 241$ (*c* 1.0, CH₂Cl₂, 86% ee). ¹H NMR (400 MHz, CDCl₃): $\delta = 7.96$ (d, *J* = 7.8 Hz, 1H), 7.78–7.84 (m, 2H), 7.70–7.74 (m, 1H), 7.41–7.45 (m, 1H), 7.37–7.39 (m, 2H), 7.29–7.33 (m, 2H), 7.18–7.23 (m, 3H), 7.13–7.15 (m, 2H), 6.76–6.81 (m, 3H), 6.68 (d, *J* = 8.9 Hz, 1H), 6.41 (d, *J* = 6.7 Hz, 1H), 5.09 (d, *J* = 6.6 Hz, 1H), 4.18 (d, *J* = 13.8 Hz, 1H), 3.75 (s, 3H), 3.68 (s, 3H), 3.42 (d, *J* = 13.8 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): $\delta = 167.8, 166.5, 148.9, 148.6, 134.8, 134.4, 134.2, 132.8, 131.6, 131.2, 130.3, 128.5, 128.3, 128.1, 127.4, 126.6, 126.4, 122.0, 121.7, 120.2, 111.2, 107.5, 66.5, 55.7, 47.8, 39.8$. The enantiomeric excess was determined by HPLC with an ID-3 column (*n*-hexane: *i*-PrOH = 50:50), 1 mL/min. minor enantiomer *t_R* = 29.18 min, major enantiomer *t_R* = 34.64 min. HRMS (ESI): [M+H]⁺ calcd for [C₃₃H₂₉N₂O₆S]:581.1741, found: 581.1752

N-((8R,9S)-8-benzyl-5,5-dioxido-7-oxo-9-(3,4,5-trimethoxyphenyl)-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-8-yl)benzamide(3qa)



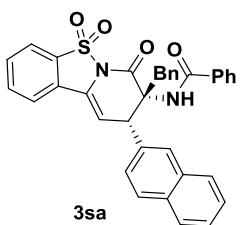
Yellow solid. 92% yield (56.1 mg). m. p.: 128–130 °C. $[\alpha]_D^{20} = 327$ (*c* 1.0, CH₂Cl₂, 91% ee). ¹H NMR (400 MHz, CDCl₃): $\delta = 7.95$ (d, *J* = 7.8 Hz, 1H), 7.80–7.87 (m, 2H), 7.71–7.75 (m, 1H), 7.43–7.47 (m, 1H), 7.38–7.40 (m, 2H), 7.31–7.35 (m, 2H), 7.20–7.21 (m, 3H), 7.13–7.15 (m, 2H), 6.81 (s, 1H), 6.47 (s, 1H), 6.44 (d, *J* = 6.7 Hz, 1H), 5.08 (d, *J* = 6.7 Hz, 1H), 4.19 (d, *J* = 13.8 Hz, 1H), 3.73 (s, 3H), 3.64 (s, 6H), 3.41 (d, *J* = 13.8 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): $\delta = 167.8, 166.4, 153.2, 137.4, 134.7, 134.5, 134.2, 132.9, 131.7, 131.7, 131.3, 130.2, 128.6, 128.5, 128.3, 127.4, 126.6, 126.3, 122.1, 121.7, 107.3, 104.6, 66.5, 60.6, 55.9, 48.1, 39.7$. The enantiomeric excess was determined by HPLC with an IA column (*n*-hexane:*i*-PrOH = 50:50), 1 mL/min. minor enantiomer *t_R* = 10.04 min, major enantiomer *t_R* = 11.34 min. HRMS (ESI): [M+H]⁺ calcd for [C₃₄H₃₁N₂O₇S]: 611.1846, found: 611.1843

N-((8R,9S)-8-benzyl-9-(naphthalen-1-yl)-5,5-dioxido-7-oxo-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-8-yl)benzamide(3ra)



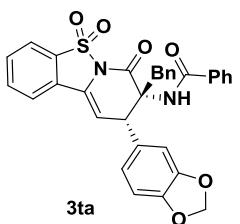
Yellow solid. 91% yield (51.9 mg). m. p.: 157–159 °C. $[\alpha]_D^{20} = 280$ (*c* 1.0, CH₂Cl₂, 86% ee). ¹H NMR (400 MHz, CDCl₃): $\delta = 8.47$ (d, *J* = 8.6 Hz, 1H), 7.90 (d, *J* = 7.3 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.59–7.68 (m, 5H), 7.46 (t, *J* = 7.6 Hz, 1H) 7.24–7.35 (m, 2H), 7.19–7.24 (m, 6H), 7.17 (d, *J* = 4.4 Hz, 4H), 6.93 (s, 1H), 6.42 (d, *J* = 6.6 Hz, 1H), 6.12 (d, *J* = 6.5 Hz, 1H), 4.37 (d, *J* = 13.7 Hz, 1H), 3.57 (d, *J* = 13.7 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): $\delta = 167.4, 167.1, 134.6, 134.3, 134.0, 133.9, 133.7, 132.3, 131.3, 131.1, 131.0, 130.5, 128.8, 128.3, 128.3, 127.5, 127.0, 126.5, 126.5, 126.4, 125.8, 125.6, 124.5, 123.3, 121.8, 121.6, 107.3, 64.9, 43.7, 40.7$. The enantiomeric excess was determined by HPLC with an ID-3 column (*n*-hexane:*i*-PrOH = 50:50), 1 mL/min. minor enantiomer *t_R* = 63.26 min, major enantiomer *t_R* = 34.97 min. HRMS (ESI): [M+H]⁺ calcd for [C₃₅H₂₇N₂O₄S]: 571.1686, found: 571.1700

N-((8R,9S)-8-benzyl-9-(naphthalen-2-yl)-5,5-dioxido-7-oxo-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-8-yl)benzamide(3sa)



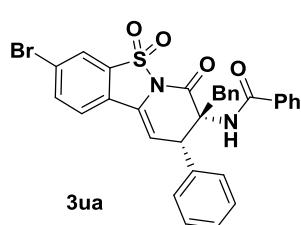
Yellow solid. 95% yield (54.2 mg). m. p.: 144–146 °C. $[\alpha]_D^{20} = 254$ (*c* 1.0, CH₂Cl₂, 92% ee). ¹H NMR (400 MHz, CDCl₃): $\delta = 7.95$ (d, *J* = 7.8Hz, 1H), 7.74-7.80 (m, 2H), 7.66-7.71 (m, 4H), 7.36-7.38 (m, 2H), 7.30-7.33 (m, 2H), 7.24-7.28 (m, 2H), 7.17-7.21 (m, 7H), 6.79 (s, 1H), 6.40 (d, *J* = 6.6Hz, 1H), 5.32 (d, *J* = 6.6Hz, 1H), 4.25 (d, *J* = 13.8Hz, 1H), 3.47 (d, *J* = 13.8Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): $\delta = 168.0, 166.4, 134.9, 134.4, 134.1, 133.9, 133.3, 132.9, 132.8, 131.4, 131.3, 130.4, 128.8, 128.4, 128.3, 128.2, 128.0, 127.5, 127.4, 127.4, 126.5, 126.2, 126.2, 125.4, 122.0, 121.7, 107.1, 66.2, 48.6, 40.1$. The enantiomeric excess was determined by HPLC with an ID-3 column (*n*-hexane:*i*-PrOH = 50:50), 1 mL/min. minor enantiomer *t*_R = 46.19 min, major enantiomer *t*_R = 51.80 min. HRMS (ESI): [M+H]⁺ calcd for [C₃₅H₂₇N₂O₄S]: 571.1686, found: 571.1705

N-((8R,9S)-9-(benzo[d][1,3]dioxol-5-yl)-8-benzyl-5,5-dioxido-7-oxo-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-8-yl)benzamide(3ta)



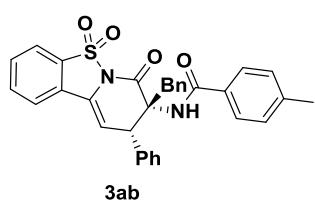
Yellow solid. 88% yield (49.6 mg). m. p.: 246–248 °C. $[\alpha]_D^{20} = 270$ (*c* 1.0, CH₂Cl₂, 90% ee). ¹H NMR (400 MHz, CDCl₃): $\delta = 7.95$ (d, *J* = 7.8Hz, 1H), 7.76-7.82 (m, 2H), 7.69-7.73 (m, 1H), 7.38-7.45 (m, 3H), 7.30-7.34 (m, 2H), 7.19-7.21 (m, 3H), 7.14-7.16 (m, 2H), 6.82 (s, 1H), 6.70-6.74 (m, 2H), 6.61 (d, *J* = 8.0Hz, 1H), 6.35 (d, *J* = 6.6Hz, 1H), 5.82(dd, *J* = 1.2Hz, 12.8Hz, 2H), 5.06 (d, *J* = 6.6Hz, 1H), 4.17 (d, *J* = 13.8Hz, 1H), 3.39 (d, *J* = 13.8Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): $\delta = 167.9, 166.4, 147.9, 147.3, 135.1, 134.4, 134.2, 132.7, 131.5, 131.3, 130.4, 130.0, 128.5, 128.3, 128.0, 127.4, 126.6, 126.4, 121.9, 121.8, 121.7, 108.5, 108.3, 107.1, 101.1, 66.3, 48.2, 40.1$. The enantiomeric excess was determined by HPLC with an IA-3 column (*n*-hexane:*i*-PrOH = 50:50), 1 mL/min. minor enantiomer *t*_R = 24.88 min, major enantiomer *t*_R = 28.79 min. HRMS (ESI): [M+H]⁺ calcd for [C₃₂H₂₅N₂O₆S]: 565.1428, found: 565.1437

N-((8R,9S)-8-benzyl-3-bromo-5,5-dioxido-7-oxo-9-phenyl-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-8-yl)benzamide(3ua)



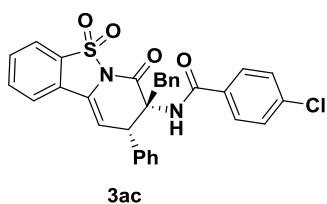
White solid. 60% yield (35.8 mg). m. p.: 138–140 °C. $[\alpha]_D^{20}$ = 169 (*c* 1.0, CH₂Cl₂, 83% ee). ¹H NMR (400 MHz, CDCl₃): δ = 8.08 (d, *J* = 1.6 Hz, 1H), 7.88 (dd, *J* = 1.7 Hz, *J* = 1.7 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.38-7.43 (m, 1H), 7.28-7.29 (m, 4H), 7.19-7.20 (m, 8H), 7.13-7.16 (m, 2H), 6.74 (s, 1H), 6.37 (d, *J* = 6.6 Hz, 1H), 5.13 (d, *J* = 6.6 Hz, 1H), 4.20 (d, *J* = 13.8 Hz, 1H), 3.39 (d, *J* = 13.8 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 168.0, 166.4, 137.7, 136.4, 135.0, 134.0, 131.5, 130.3, 129.0, 128.5, 128.3, 128.1, 127.5, 127.4, 126.5, 125.2, 125.1, 124.8, 123.3, 107.8, 66.1, 48.6, 40.2. The enantiomeric excess was determined by HPLC with an IA-3 column (*n*-hexane:*i*-PrOH = 50:50), 1 mL/min. minor enantiomer *t_R* = 10.42 min, major enantiomer *t_R* = 12.74 min. HRMS (ESI): [M+H]⁺ calcd for [C₃₁H₂₄BrN₂O₄S]: 599.0635, 601.0615, found: 599.0635, 601.0614.

N-((8R,9S)-8-benzyl-5,5-dioxido-7-oxo-9-phenyl-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-8-yl)-4-methylbenzamide(3ab)



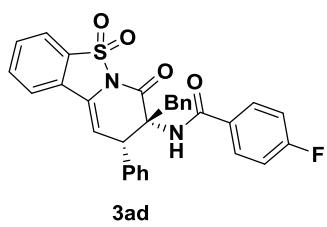
White solid. 97% yield (51.8 mg). m. p.: 136–138 °C. $[\alpha]_D^{20}$ = 240 (*c* 1.0, CH₂Cl₂, 90% ee). ¹H NMR (400 MHz, CDCl₃): δ = 7.95 (d, *J* = 7.8 Hz, 1H), 7.76-7.81 (m, 2H), 7.68-7.72 (m, 1H), 7.21-7.25 (m, 5H), 7.14-7.20 (m, 7H), 7.08 (d, *J* = 8.0 Hz, 1H), 6.75 (s, 1H), 6.37 (d, *J* = 6.6 Hz, 1H), 5.13 (d, *J* = 6.6 Hz, 1H), 4.21 (d, *J* = 13.8 Hz, 1H), 3.41 (d, *J* = 13.8 Hz, 1H), 2.31 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 167.8, 166.5, 141.9, 136.7, 134.4, 134.2, 132.7, 132.2, 131.2, 130.4, 129.1, 128.9, 128.2, 128.1, 128.0, 127.3, 126.54, 126.45, 121.9, 121.7, 107.2, 66.1, 48.6, 40.2, 21.3. The enantiomeric excess was determined by HPLC with an IA-3 column (*n*-hexane:*i*-PrOH = 50:50), 1 mL/min. minor enantiomer *t_R* = 27.74 min, major enantiomer *t_R* = 45.31 min. HRMS (ESI): [M+H]⁺ calcd for [C₃₂H₂₇N₂O₄S]: 535.1686, found: 535.1683

N-((8R,9S)-8-benzyl-5,5-dioxido-7-oxo-9-phenyl-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-8-yl)-4-chlorobenzamide(3ac)



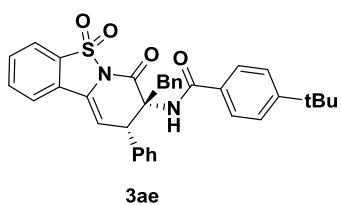
White solid. 98% yield (54.3 mg). m. p.: 127–129 °C.
 $[\alpha]_D^{20} = 255$ (*c* 1.0, CH₂Cl₂, 88% ee). ¹H NMR (400 MHz, CDCl₃): δ = 7.96 (d, *J* = 7.8Hz, 1H), 7.77-7.81 (m, 2H), 7.69-7.73 (m, 1H), 7.24-7.27 (m, 4H), 7.18-7.22 (m, 8H), 7.13-7.15 (m, 2H), 6.73 (s, 1H), 6.37 (d, *J* = 6.6Hz, 1H), 5.10 (d, *J* = 6.6Hz, 1H), 4.16 (d, *J* = 13.9Hz, 1H), 3.43 (d, *J* = 13.8Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 166.8, 166.4, 137.7, 136.6, 134.4, 134.1, 133.3, 132.7, 131.3, 130.3, 129.0, 128.8, 128.3, 128.2, 128.05, 127.95, 127.5, 126.4, 122.0, 121.8, 107.0, 66.2, 48.6, 40.2. The enantiomeric excess was determined by HPLC with an IA-3 column (*n*-hexane:*i*-PrOH = 50:50), 1 mL/min. minor enantiomer *t*_R = 22.46 min, major enantiomer *t*_R = 36.91 min. HRMS (ESI): [M+H]⁺ calcd for [C₃₁H₂₄ClN₂O₄S]: 555.1140, found: 555.1151, 557.1110

N-((8R,9S)-8-benzyl-5,5-dioxido-7-oxo-9-phenyl-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-8-yl)-4-fluorobenzamide(3ad)



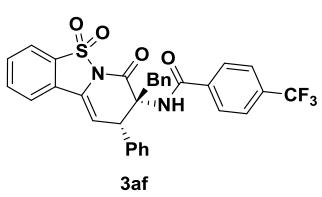
Yellow solid. 98% yield (52.7 mg). m. p.: 125–127 °C.
 $[\alpha]_D^{20} = 221$ (*c* 1.0, CH₂Cl₂, 90% ee). ¹H NMR (400 MHz, CDCl₃): δ = 7.96 (d, *J* = 7.8Hz, 1H), 7.77-7.81 (m, 2H), 7.69-7.73 (m, 1H), 7.31 (dd, *J* = 5.3Hz, 8.8Hz, 2H), 7.17-7.23 (m, 8H), 7.14-7.16 (m, 2H), 6.95 (t, *J* = 8.6Hz, 2H), 6.71 (s, 1H), 6.37 (d, *J* = 6.6Hz, 1H), 5.11 (d, *J* = 6.6Hz, 1H), 4.18 (d, *J* = 13.8Hz, 1H), 3.43 (d, *J* = 13.9Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 166.8, 166.4, 164.6 (*J*_{C-F} = 250 Hz), 136.7, 134.4, 134.1, 132.8, 131.3, 131.17 (*J*_{C-F} = 3.1 Hz), 130.3, 129.0, 128.8 (*J*_{C-F} = 8.9 Hz), 128.3, 128.2, 128.1, 127.4, 126.4, 121.8 (*J*_{C-F} = 19.8 Hz), 115.5 (*J*_{C-F} = 21.8 Hz), 107.0, 66.2, 48.6, 40.2. The enantiomeric excess was determined by HPLC with an IA-3 column (*n*-hexane:*i*-PrOH = 50:50), 1 mL/min. minor enantiomer *t*_R = 19.52 min, major enantiomer *t*_R = 27.93 min. HRMS (ESI): [M+H]⁺ calcd for [C₃₁H₂₄FN₂O₄S]: 539.1435, found: 539.1437

N-((8R,9S)-8-benzyl-5,5-dioxido-7-oxo-9-phenyl-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-8-yl)-4-(tert-butyl)benzamide(3ae)



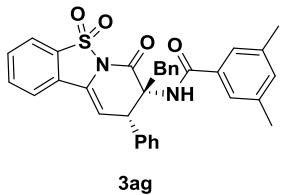
Yellow solid. 96% yield (55.3 mg). m. p.: 137–139 °C.
 $[\alpha]_D^{20} = 244$ (*c* 1.0, CH₂Cl₂, 86% ee). ¹H NMR (400 MHz, CDCl₃): δ = 7.94 (d, *J* = 7.8Hz, 1H), 7.75-7.81 (m, 2H), 7.67-7.72 (m, 1H), 7.26-7.33 (m, 4H), 7.22-7.24 (m, 3H), 7.15-7.20 (m, 7H), 6.76 (s, 1H), 6.37 (d, *J* = 6.6Hz, 1H), 5.14 (d, *J* = 6.6Hz, 1H), 4.21 (d, *J* = 13.8Hz, 1H), 3.41 (d, *J* = 13.8Hz, 1H), 1.27 (s, 9H). ¹³C NMR (100 MHz, CDCl₃): δ = 167.9, 166.5, 154.8, 136.7, 134.4, 134.2, 132.7, 132.3, 131.2, 130.4, 129.2, 129.0, 128.9, 128.2, 128.1, 128.0, 127.3, 126.42, 126.35, 125.4, 121.9, 121.7, 107.2, 66.1, 48.6, 40.1, 34.8, 31.0. The enantiomeric excess was determined by HPLC with an IA-3 column (*n*-hexane:*i*-PrOH = 50:50), 1 mL/min. minor enantiomer *t*_R = 20.45 min, major enantiomer *t*_R = 30.58 min. HRMS (ESI): [M+H]⁺ calcd for [C₃₅H₃₂N₂O₄S]: 577.2156, found: 577.2165

N-((8R,9S)-8-benzyl-5,5-dioxido-7-oxo-9-phenyl-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-8-yl)-4-(trifluoromethyl)benzamide(3af)



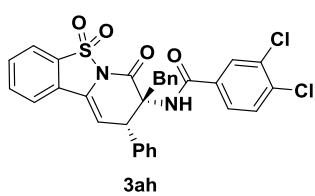
Yellow solid. 96% yield (56.4 mg). m. p.: 120–122 °C.
 $[\alpha]_D^{20} = 196$ (*c* 1.0, CH₂Cl₂, 74% ee). ¹H NMR (400 MHz, CDCl₃): δ = 7.96 (d, *J* = 7.8Hz, 1H), 7.80-7.81 (m, 2H), 7.70-7.74 (m, 1H), 7.55 (d, *J* = 8.3Hz, 2H), 7.38 (d, *J* = 8.2Hz, 2H), 7.20-7.25 (m, 8H), 7.14-7.17 (m, 2H), 6.79 (s, 1H), 6.38 (d, *J* = 6.6Hz, 1H), 5.11 (d, *J* = 6.6Hz, 1H), 4.17 (d, *J* = 13.8Hz, 1H), 3.45 (d, *J* = 13.8Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 166.6, 166.3, 138.2, 136.6, 134.5, 134.0, 133.2 (*J*_{C-F} = 32.34Hz), 132.7, 131.4, 130.3, 129.0, 128.4, 128.3, 128.1, 128.0, 127.5, 127.0, 126.4, 125.6 (*J*_{C-F} = 3.7Hz), 123.5 (*J*_{C-F} = 270.8Hz), 122.0, 121.8, 106.9, 66.2, 48.6, 40.3. The enantiomeric excess was determined by HPLC with an IA-3 column (*n*-hexane:*i*-PrOH = 50:50), 1 mL/min. minor enantiomer *t*_R = 13.03 min, major enantiomer *t*_R = 18.10 min. HRMS (ESI): [M+H]⁺ calcd for [C₃₂H₂₄F₃N₂O₄S]: 589.1403, found: 589.1414

N-((8R,9S)-8-benzyl-5,5-dioxido-7-oxo-9-phenyl-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-8-yl)-3,5-dimethylbenzamide(3ag)



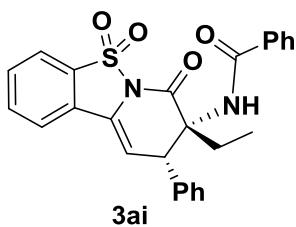
White solid. 95% yield (52.1 mg). m. p.: 127–129 °C. $[\alpha]_D^{20} = 199$ (*c* 1.0, CH₂Cl₂, 87% ee). ¹H NMR (400 MHz, CDCl₃): $\delta = 7.94$ (d, *J* = 7.8Hz, 1H), 7.76-7.81 (m, 2H), 7.68-7.72 (m, 1H), 7.15-7.25 (m, 10H), 7.02 (s, 1H), 6.89 (s, 2H), 6.76 (s, 1H), 6.37 (d, *J* = 6.6Hz, 1H), 5.12 (d, *J* = 6.6Hz, 1H), 4.21 (d, *J* = 13.8Hz, 1H), 3.42 (d, *J* = 13.8Hz, 1H), 2.22 (s, 6H). ¹³C NMR (100 MHz, CDCl₃): $\delta = 168.3$, 166.6, 138.2, 136.7, 135.0, 134.4, 134.2, 133.1, 132.7, 131.2, 130.4, 129.2, 129.0, 128.2, 128.13, 128.06, 128.0, 127.4, 126.4, 124.3, 121.9, 121.7, 107.2, 66.1, 48.6, 40.2, 21.1. The enantiomeric excess was determined by HPLC with an IA-3 column (*n*-hexane:*i*-PrOH = 50:50), 1 mL/min. minor enantiomer *t_R* = 15.76 min, major enantiomer *t_R* = 23.32 min. HRMS (ESI): [M+H]⁺ calcd for [C₃₃H₂₉N₂O₄S]:549.1843, found: 549.1852

N-((8R,9S)-8-benzyl-5,5-dioxido-7-oxo-9-phenyl-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-8-yl)-3,4-dichlorobenzamide(3ah)



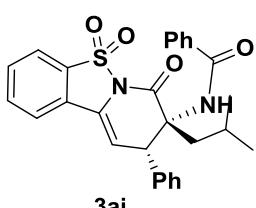
White solid. 97% yield (57.0 mg). m. p.: 130–132 °C. $[\alpha]_D^{20} = 185$ (*c* 1.0, CH₂Cl₂, 77% ee). ¹H NMR (400 MHz, CDCl₃): $\delta = 7.95$ (d, *J* = 7.8Hz, 1H), 7.79-7.80 (m, 2H), 7.68-7.75 (m, 1H), 7.42 (d, *J* = 2.0Hz, 1H), 7.33 (d, *J* = 8.3Hz, 1H), 7.20-7.25 (m, 8H), 7.12-7.14 (m, 2H), 7.03(dd, *J* = 2.0Hz, 8.3Hz, 1H), 6.73 (s, 1H), 6.37 (d, *J* = 6.6Hz, 1H), 5.07 (d, *J* = 6.6Hz, 1H), 4.13 (d, *J* = 13.9Hz, 1H), 3.43 (d, *J* = 13.8Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): $\delta = 166.3$, 165.5, 136.5, 136.0, 134.6, 134.5, 133.9, 133.0, 132.7, 131.3, 130.5, 130.2, 129.0, 128.9, 128.33, 128.29, 128.0, 127.5, 126.3, 125.4, 122.0, 121.7, 106.9, 66.2, 48.6, 40.2. The enantiomeric excess was determined by HPLC with an IA-3 column (*n*-hexane:*i*-PrOH = 50:50), 1 mL/min. minor enantiomer *t_R* = 16.36 min, major enantiomer *t_R* = 31.48 min. HRMS (ESI): [M+H]⁺ calcd for [C₃₁H₂₃Cl₂N₂O₄S]:589.1750, 591.0722, 593.0690, found: 589.0759, 591.0721, 593.0691

N-((8R,9S)-8-ethyl-5,5-dioxido-7-oxo-9-phenyl-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-8-yl)benzamide(3ai)



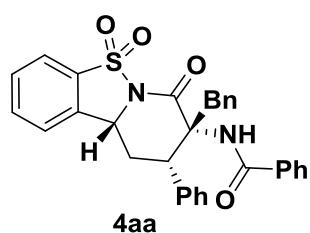
White solid. 89% yield (40.8 mg). m. p.: 214–216 °C. $[\alpha]_D^{20} = 476$ (*c* 1.0, CH₂Cl₂, 85% ee). ¹H NMR (400 MHz, CDCl₃): $\delta =$ 7.91 (d, *J* = 7.8Hz, 1H), 7.76–7.77 (m, 2H), 7.66–7.71 (m, 1H), 7.41–7.43 (m, 3H), 7.30–7.34 (m, 2H), 7.19 (s, 5H), 7.02 (s, 1H), 6.29 (d, *J* = 6.7Hz, 1H), 4.93 (d, *J* = 6.6Hz, 1H), 2.95–3.05 (m, 1H), 2.11–2.20 (m, 1H), 0.95 (t, *J* = 7.4Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): $\delta =$ 167.4, 167.2, 136.9, 134.7, 134.3, 132.6, 131.5, 131.1, 128.9, 128.5, 128.1, 128.0, 127.9, 126.6, 126.5, 121.8, 121.7, 107.1, 65.7, 48.5, 27.2, 8.2. The enantiomeric excess was determined by HPLC with an ID-3 column (*n*-hexane:*i*-PrOH = 50:50), 1 mL/min. minor enantiomer *t*_R = 12.39 min, major enantiomer *t*_R = 27.05 min. HRMS (ESI): [M+H]⁺ calcd for [C₂₆H₂₃N₂O₄S]:459.1373, found: 459.1377

N-((8R,9S)-8-isobutyl-5,5-dioxido-7-oxo-9-phenyl-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-8-yl)benzamide(3aj)



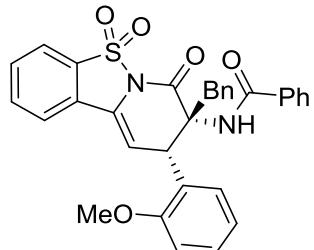
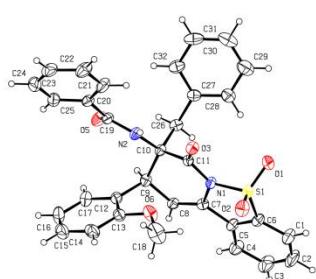
Yellow solid. 86% yield (41.8 mg). m. p.: 231–233 °C. $[\alpha]_D^{20} = 254$ (*c* 1.0, CH₂Cl₂, 74% ee). ¹H NMR (400 MHz, CDCl₃): $\delta =$ 7.91 (d, *J* = 7.8Hz, 1H), 7.76–7.77 (m, 2H), 7.66–7.70 (m, 1H), 7.39–7.44 (m, 3H), 7.30–7.34 (m, 2H), 7.18 (s, 5H), 7.08 (s, 1H), 6.28 (d, *J* = 6.6Hz, 1H), 4.90 (d, *J* = 6.6Hz, 1H), 2.96 (dd, *J* = 6.5Hz, 14.6Hz, 1H), 2.03 (dd, *J* = 5.6Hz, 14.6Hz, 1H), 1.78–1.88 (m, 1H), 0.92 (dd, *J* = 6.7Hz, 11Hz, 6H). ¹³C NMR (100 MHz, CDCl₃): $\delta =$ 168.1, 167.2, 136.7, 135.0, 134.3, 132.7, 131.4, 131.1, 128.9, 128.5, 128.1, 128.0, 126.5, 121.9, 121.7, 107.4, 64.9, 49.3, 42.2, 24.5, 23.9, 23.8. The enantiomeric excess was determined by HPLC with an ID-3 column (*n*-hexane:*i*-PrOH = 50:50), 1 mL/min. minor enantiomer *t*_R = 16.85 min, major enantiomer *t*_R = 28.15 min. HRMS (ESI): [M+H]⁺ calcd for [C₂₈H₂₇N₂O₄S]:487.1686, found: 487.1694

N-((8R,9S,10aR)-8-benzyl-5,5-dioxido-7-oxo-9-phenyl-8,9,10a-tetrahydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-8-yl)benzamide (4aa)



White solid. 95% yield (49.6 mg). m. p.: 152–154 °C.
[α]_D²⁰ = -68 (*c* 1.0, CH₂Cl₂, 92% ee). ¹H NMR (400 MHz, CDCl₃): δ=7.91 (d, *J* = 7.8Hz, 1H), 7.71 (t, *J* = 7.48Hz, 1H), 7.63(t, *J* = 7.56Hz, 1H), 7.41(d, *J* = 7.92Hz, 1H), 7.36-7.40(m, 1H), 7.31-7.32(m, 4H), 7.26-7.28(m, 5H), 7.13-7.22(m, 5H), 6.55(s, 1H), 5.14(d, *J* = 8.0Hz, 1H), 4.27(t, *J* = 8.0Hz, 1H), 4.17(d, *J* = 13.5Hz, 1H), 3.29(d, *J* = 13.5Hz, 1H), 2.94-2.97(m, 1H), 2.68(dd, *J* = 11.8Hz, 12.9Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 168.7, 167.4, 140.9, 134.5, 134.41, 134.36, 134.1, 133.5, 131.4, 130.4, 130.2, 128.8, 128.6, 128.4, 128.3, 127.8, 127.3, 126.6, 123.6, 122.0, 65.2, 56.1, 46.6, 41.3, 35.4. The enantiomeric excess was determined by HPLC with an ID-3 column (*n*-hexane:*i*-PrOH = 50:50), 1 mL/min. minor enantiomer *t*_R = 57.84 min, major enantiomer *t*_R = 28.15 min. HRMS (ESI): [M+H]⁺ calcd for [C₃₁H₂₈N₂O₄S]: 523.1686, found: 523.1685

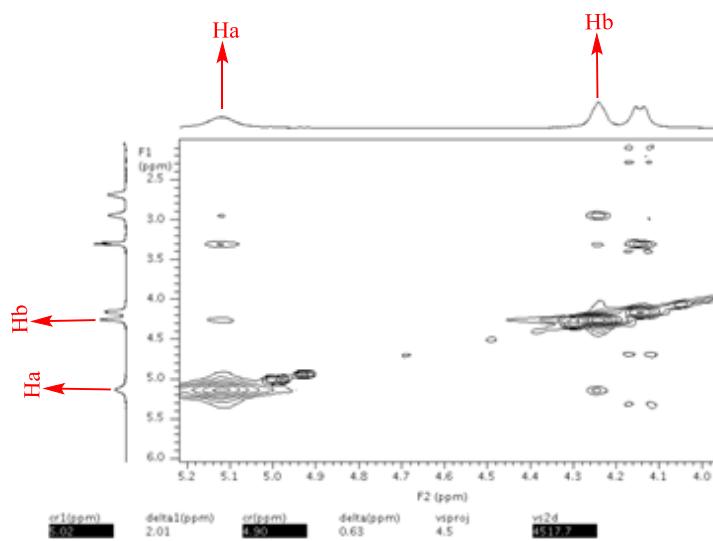
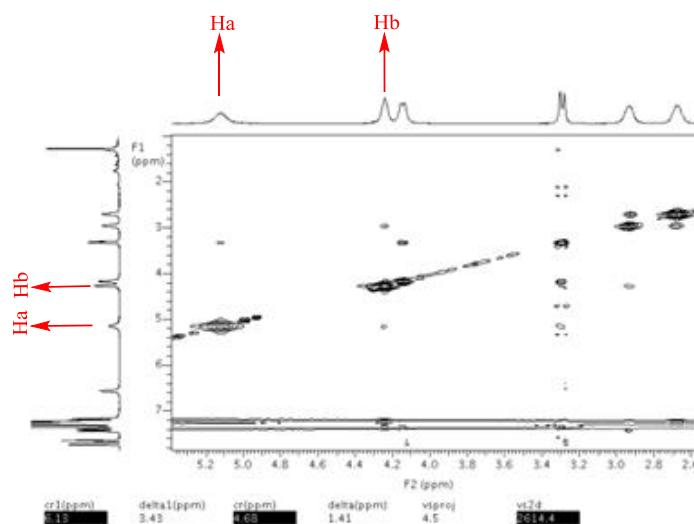
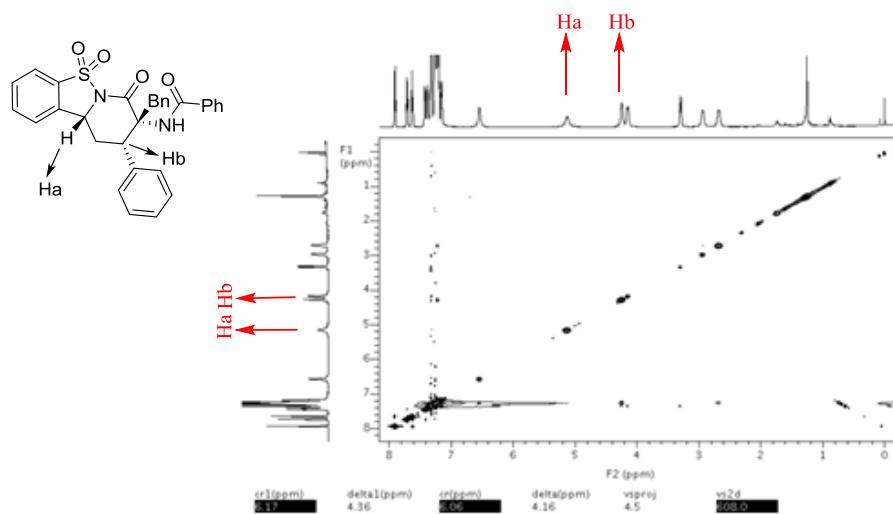
4. X-ray Crystallographic Data of Compound 3ma



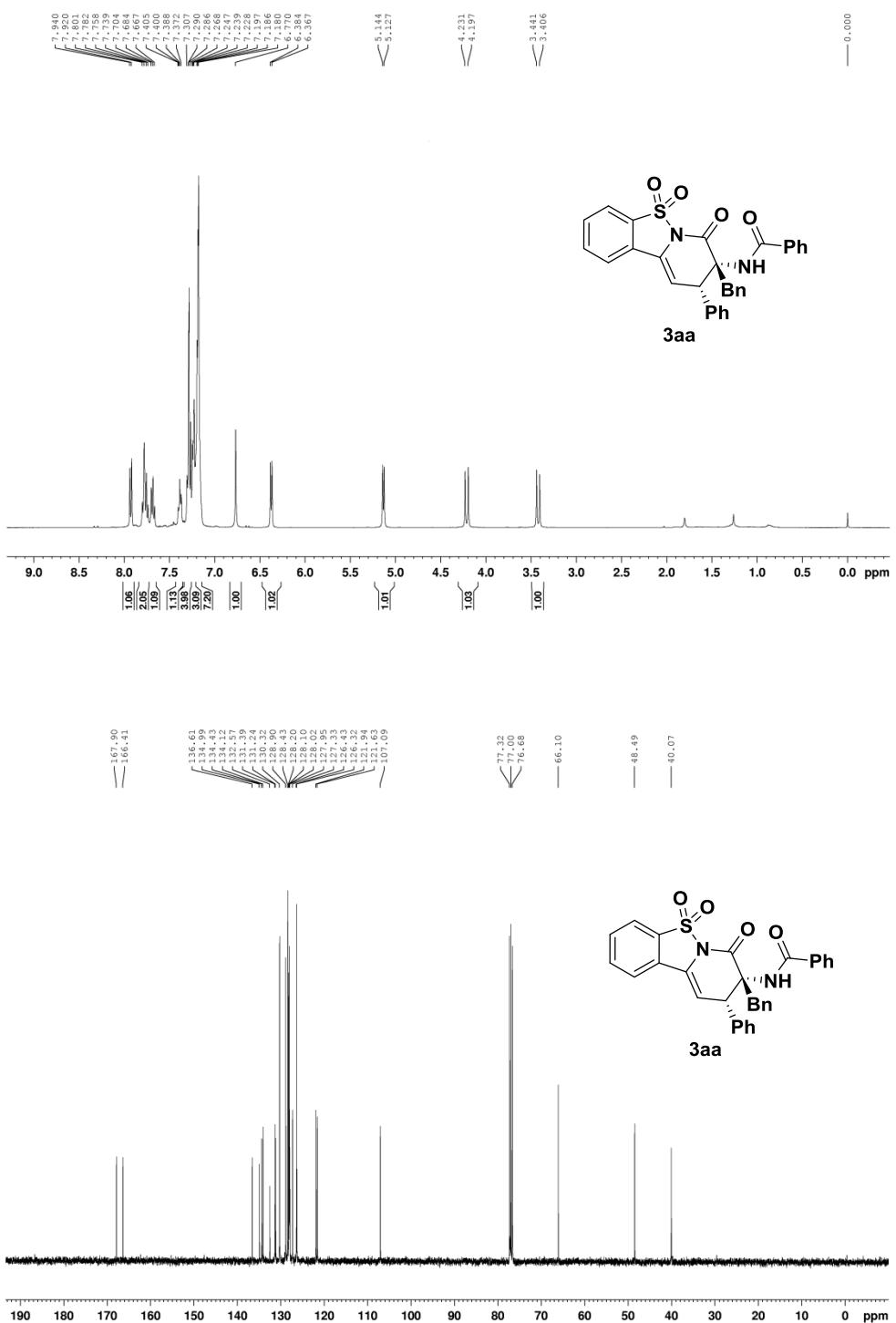
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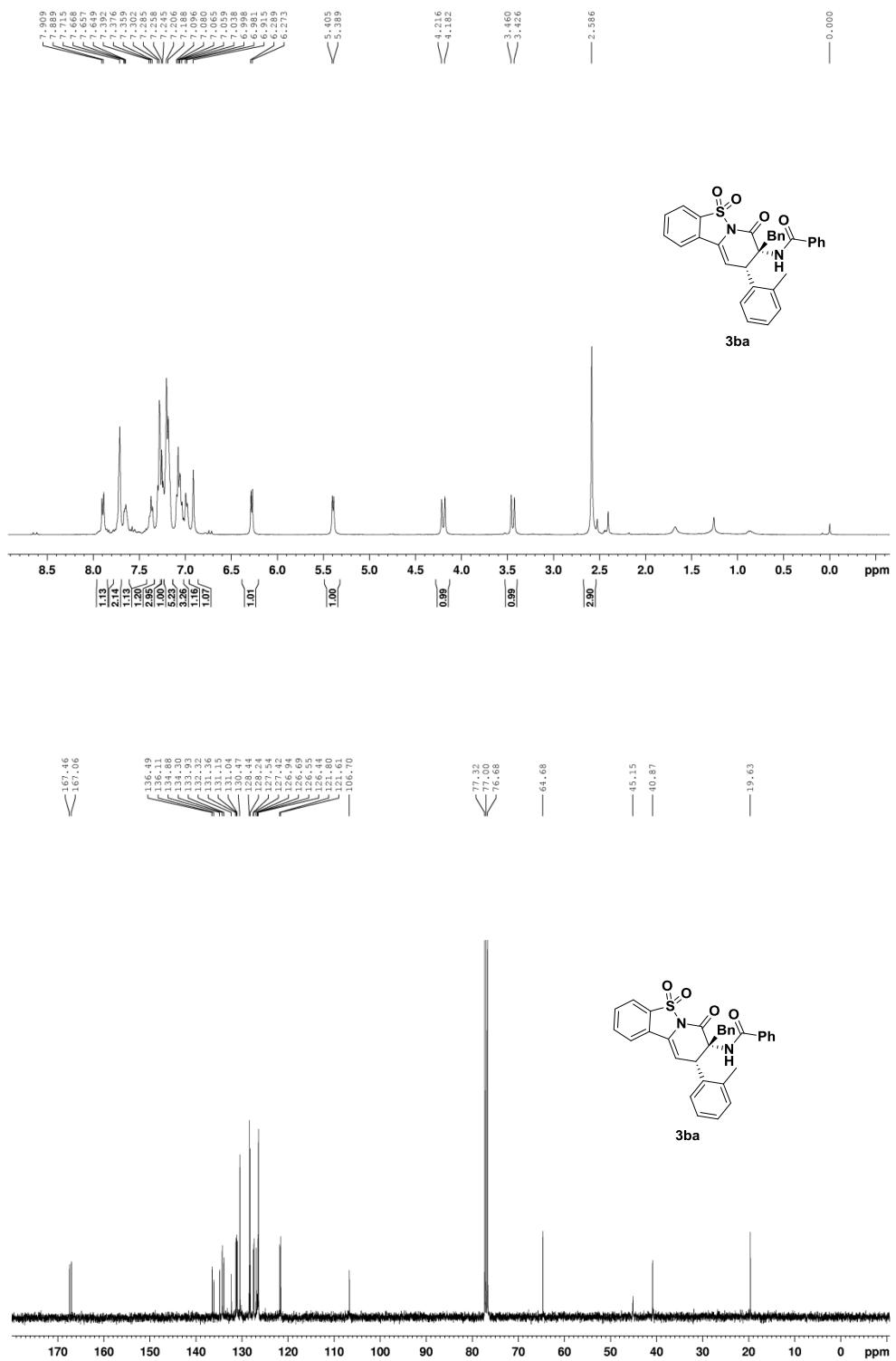
Bond precision:	C-C = 0.0058 Å	Wavelength=0.71073
Cell:	a=10.9357(5)	b=11.7723(6)
	Alpha=90	Beta=90
Temperature:	293 K	
	Calculated	Reported
Volume	3204.7(2)	3204.7(2)
Space group	P 21 21 21	P 21 21 21
Hall group	P 2ac 2ab	P 2ac 2ab
Moiety formula	C ₃₂ H ₂₆ N ₂ O ₅ S, CHCl ₃	C ₃₂ H ₂₆ N ₂ O ₅ S, CHCl ₃
Sum formula	C ₃₃ H ₂₇ Cl ₃ N ₂ O ₅ S	C ₃₃ H ₂₇ Cl ₃ N ₂ O ₅ S
Mr	669.98	669.98
Dx,g cm ⁻³	1.389	1.389
Z	4	4
Mu (mm ⁻¹)	0.395	0.395
F000	1384.0	1384.0
F000'	1386.82	
h, k, lmax	13,14,30	13,14,30
Nref	6315[3558]	6210
Tmin,Tmax	0.945,0.973	0.658,1.000
Tmin'	0.942	
Correction method=	# Reported T	Limits: Tmin=0.658 Tmax=1.000
AbsCorr =	MULTI-SCAN	
Data completeness=	1.75/0.98	Theta(max)= 26.020
R(reflections)=	0.0560(4721)	wR2(reflections)= 0.1352(6210)
S =	1.048	Npar= 429

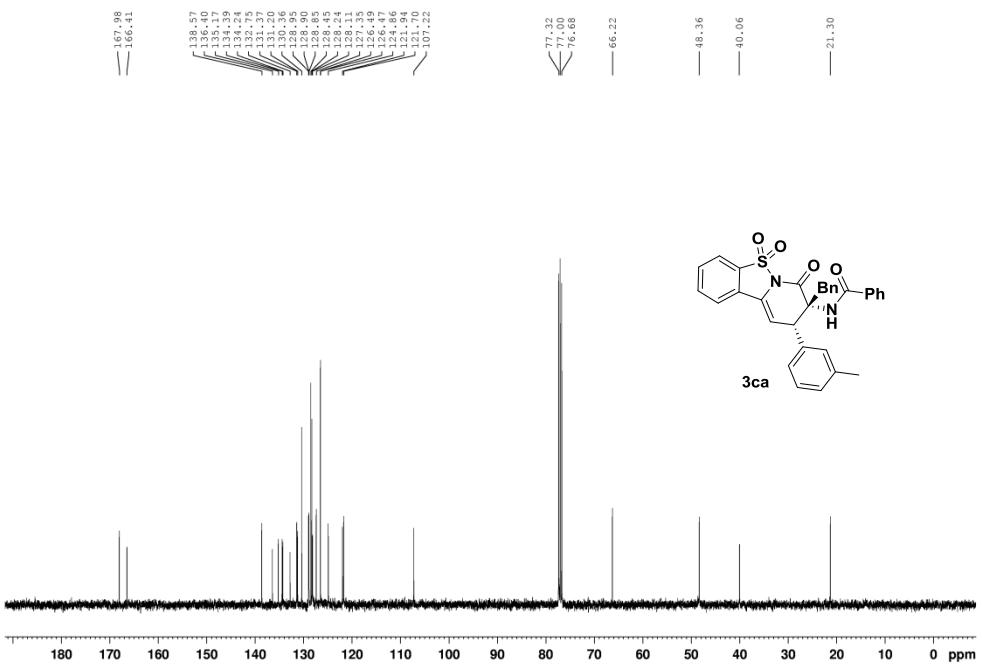
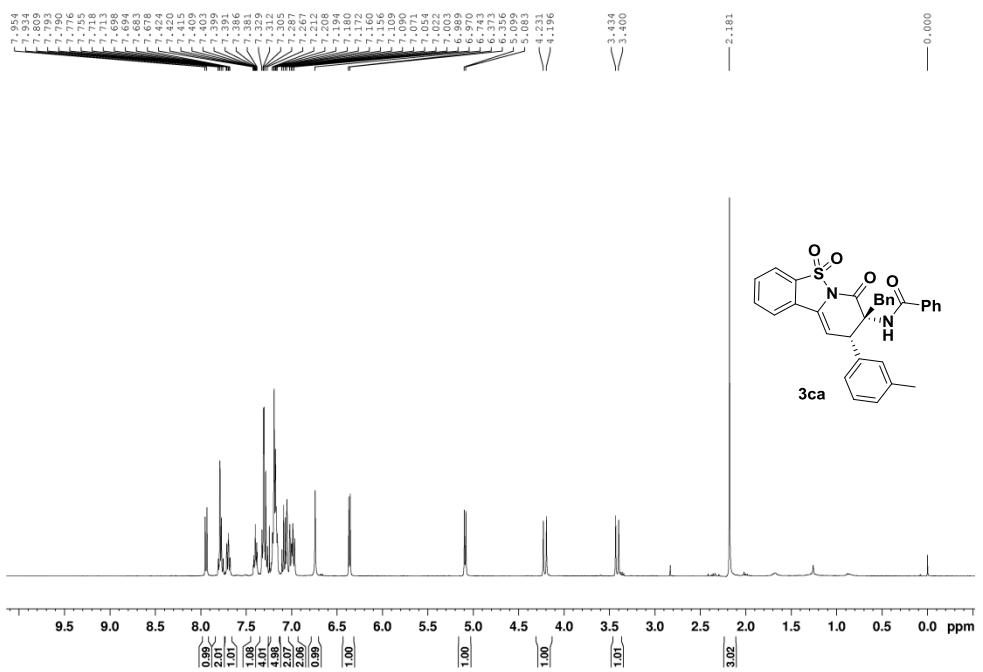
5. NOESY Spectra for the Determination of the Newly Formed Stereocenter.

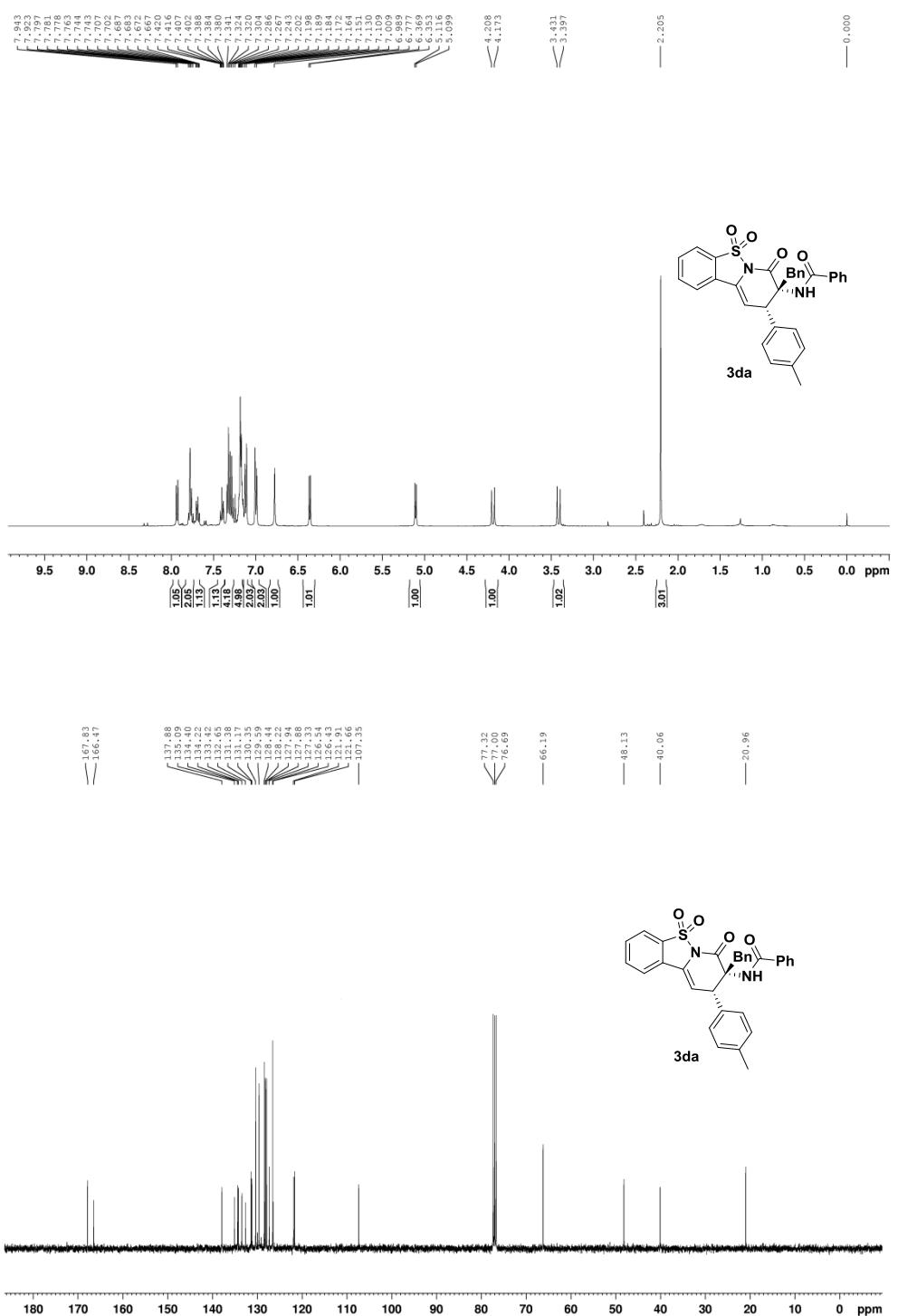


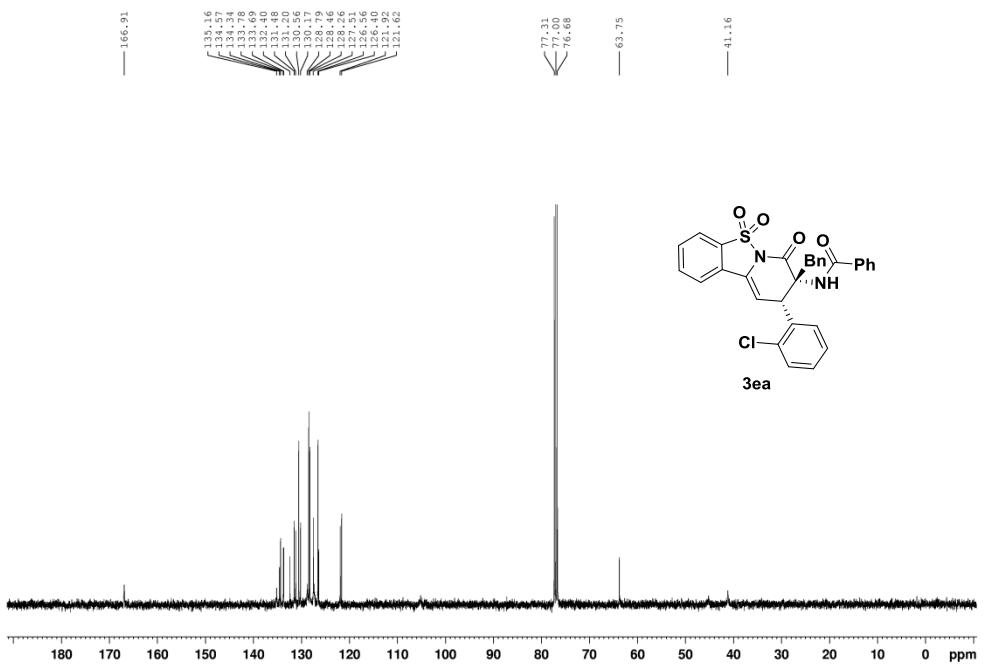
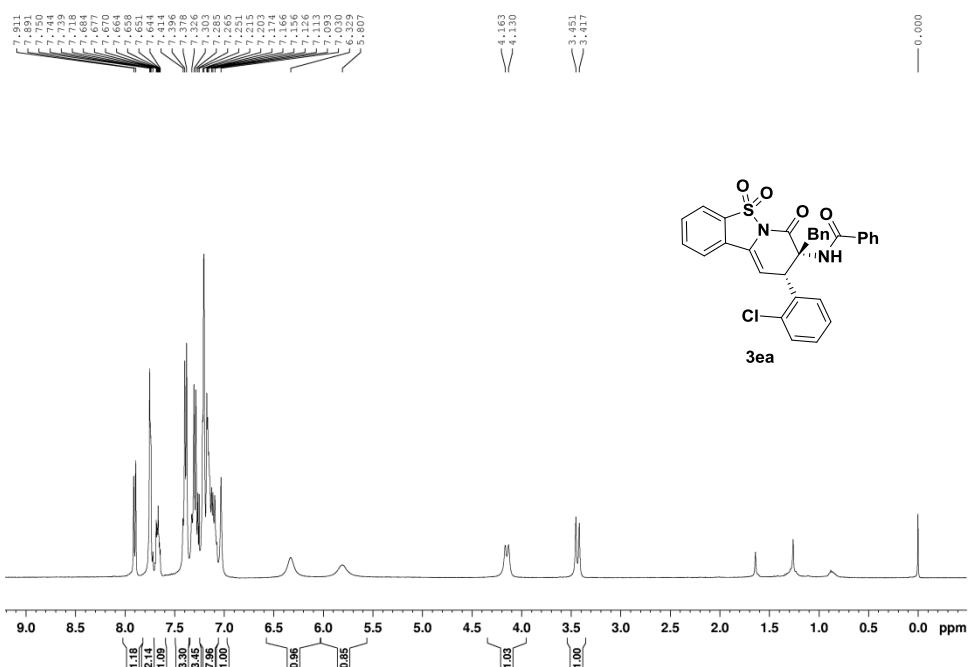
6. Copies of NMR Spectra

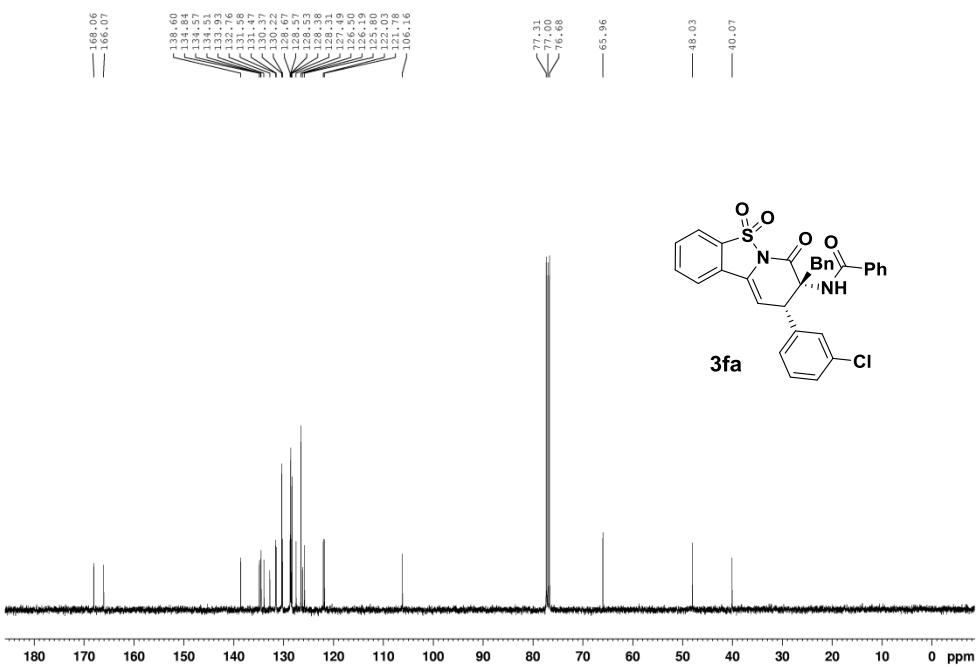
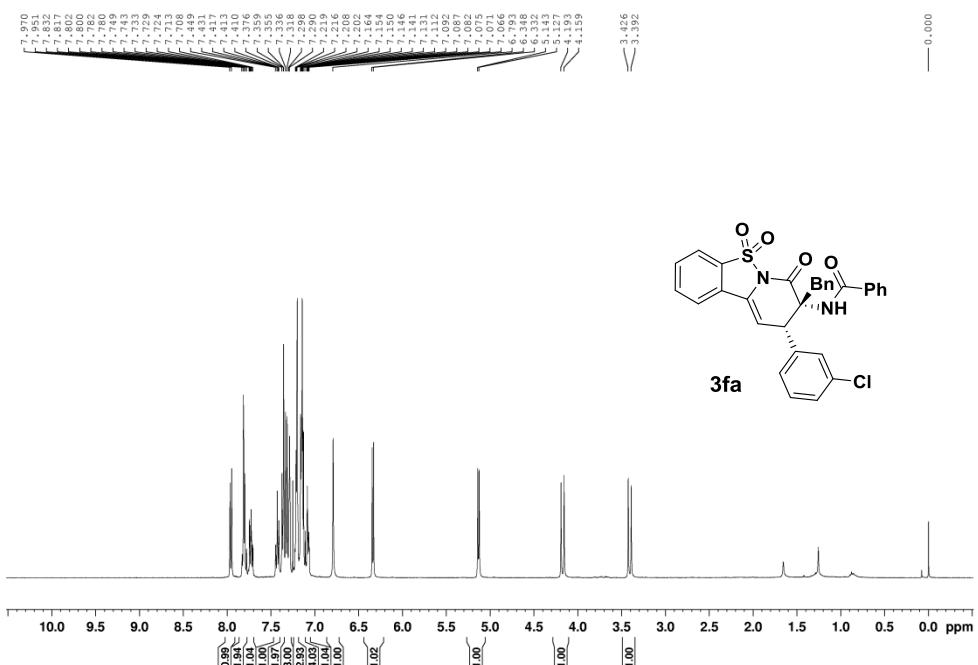


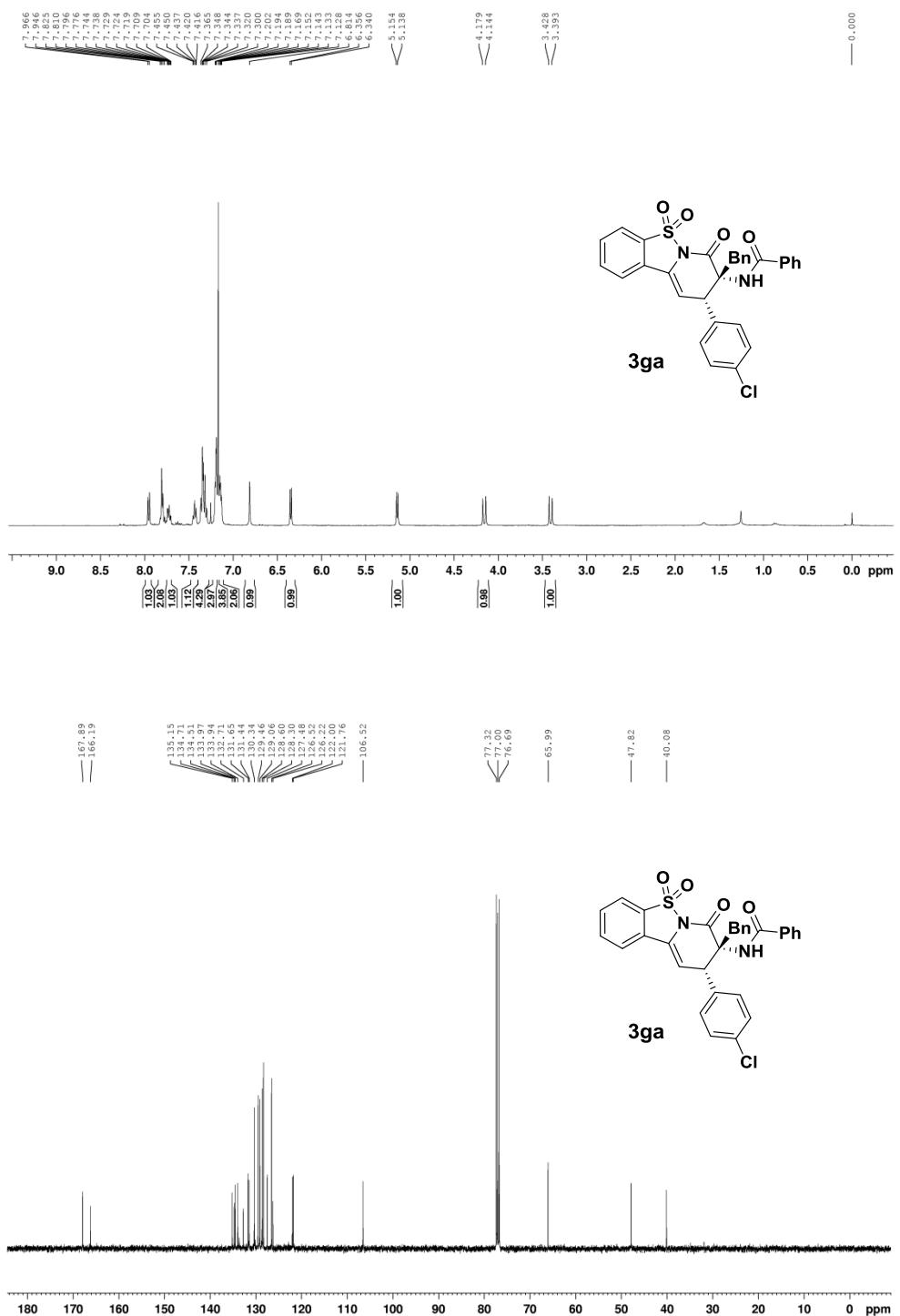


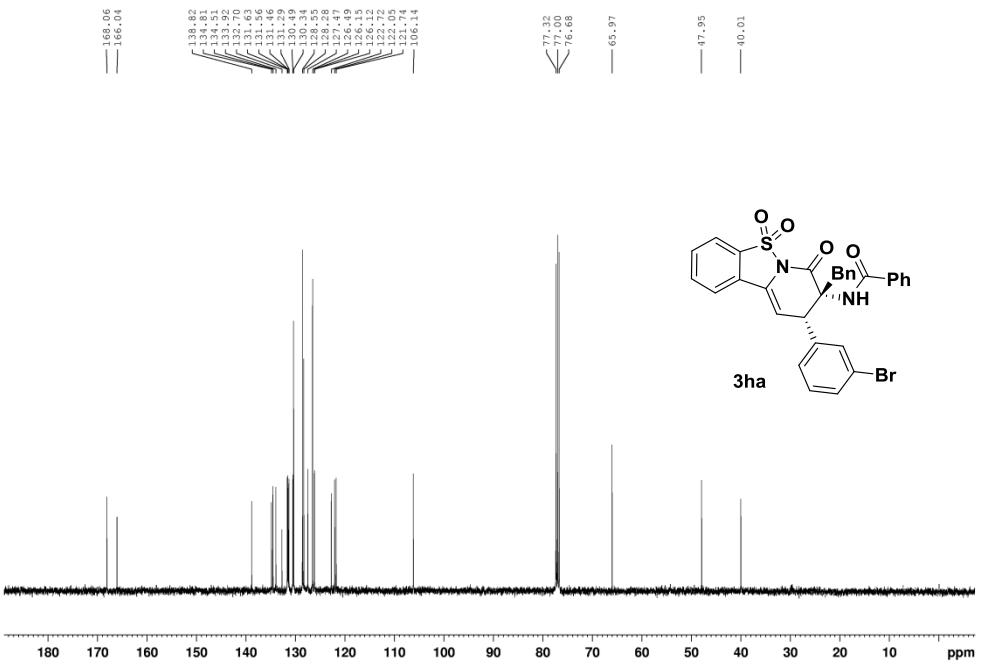
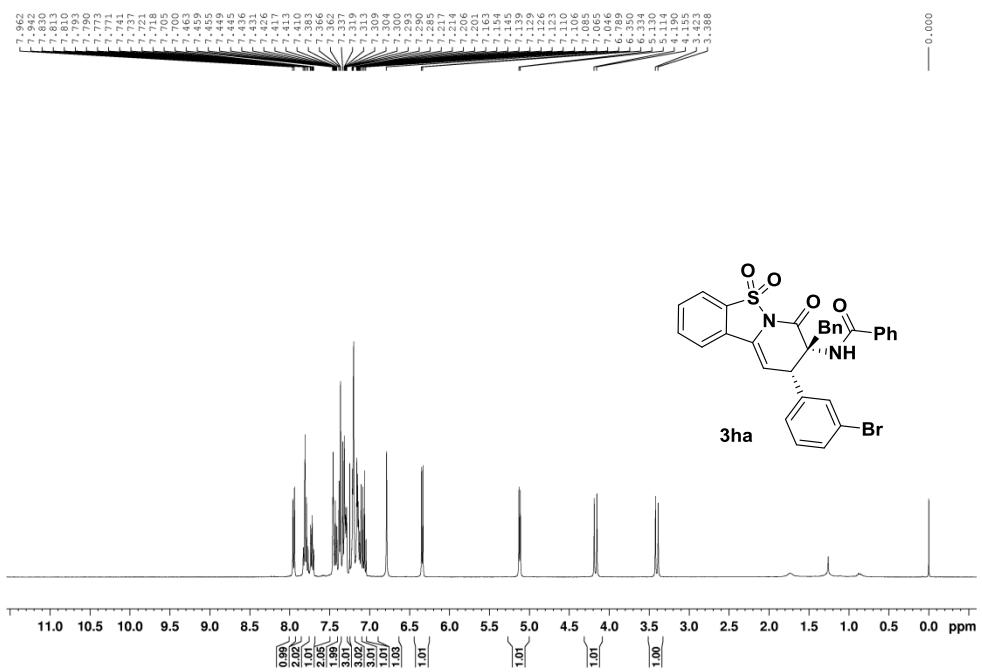


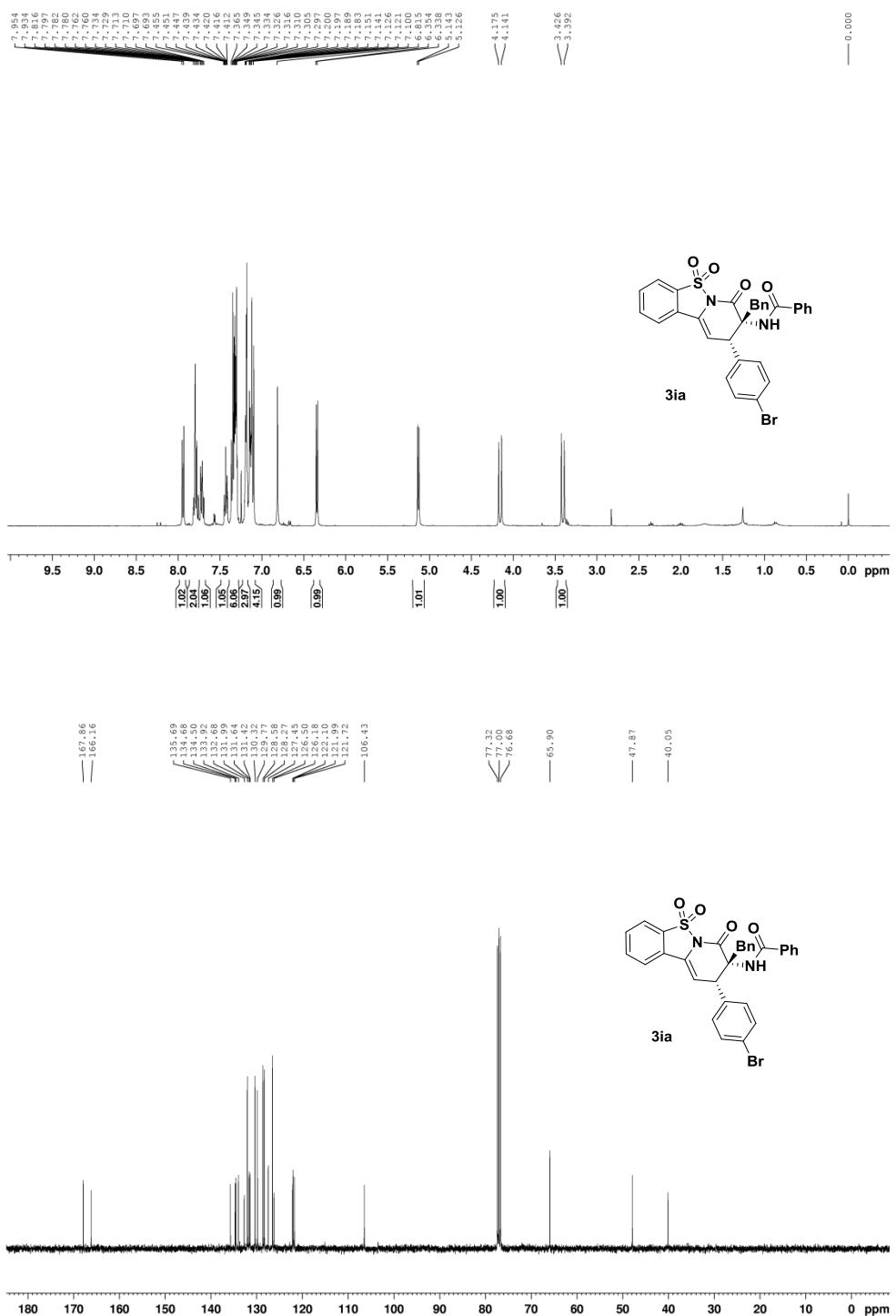


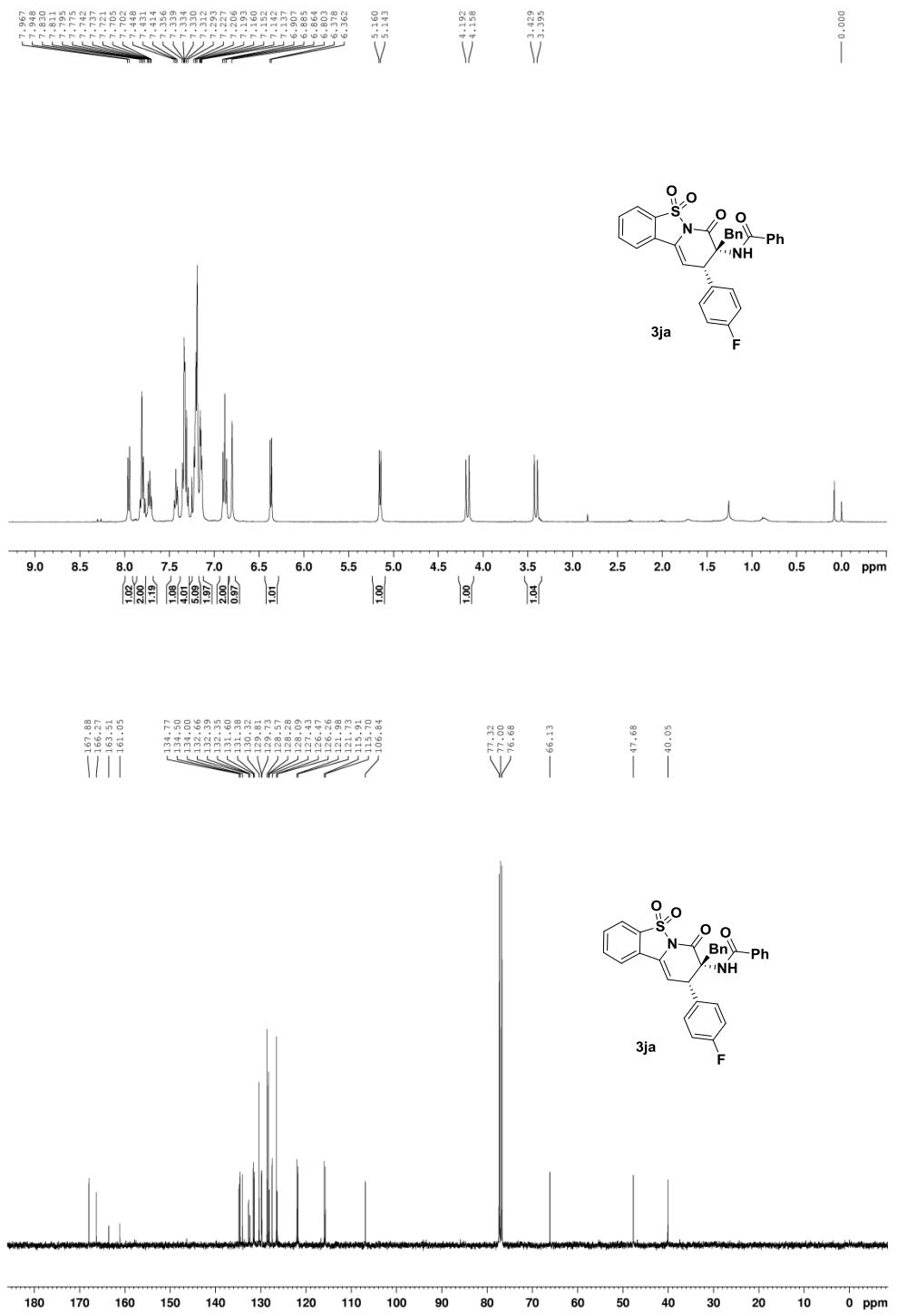


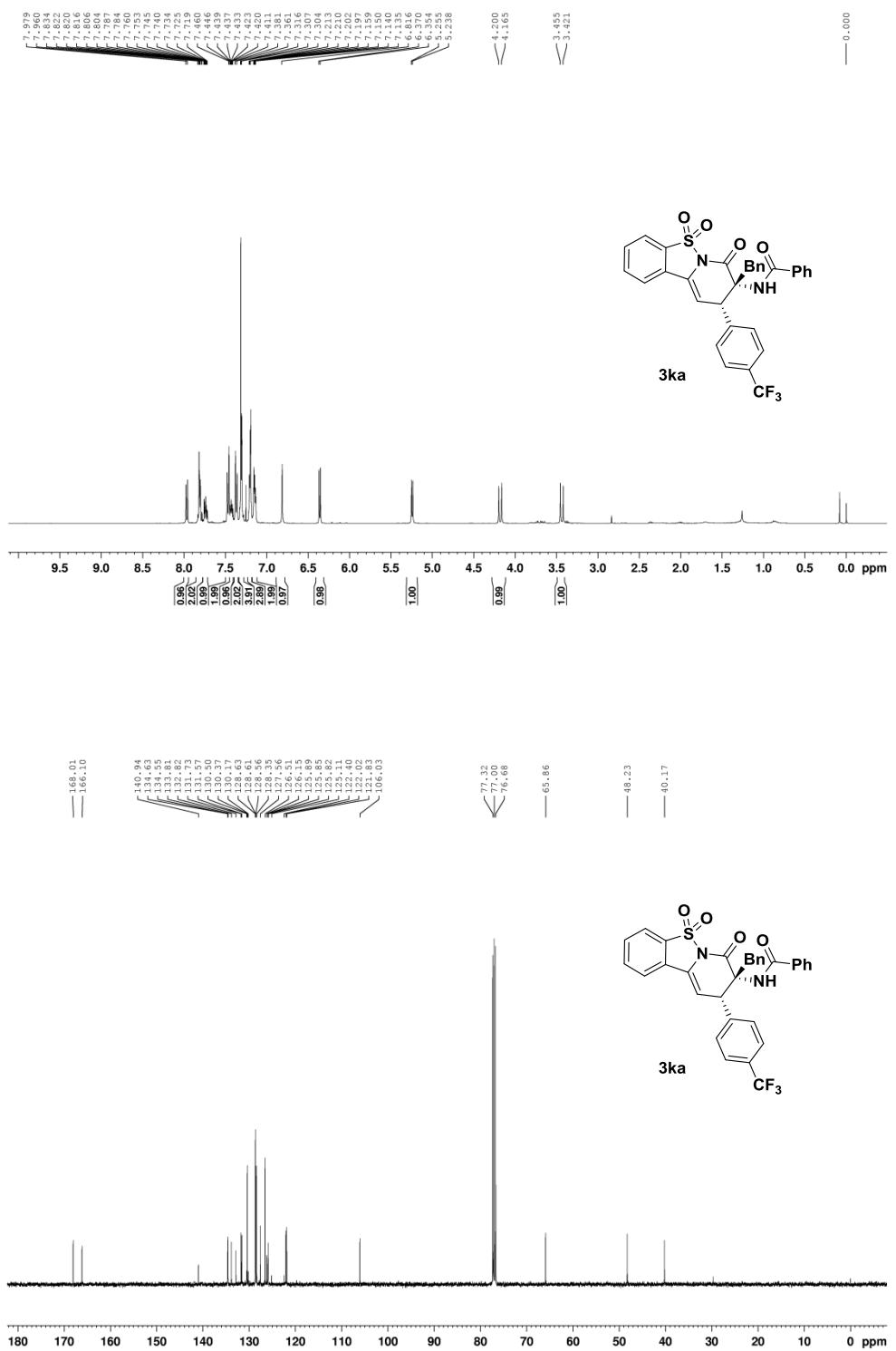


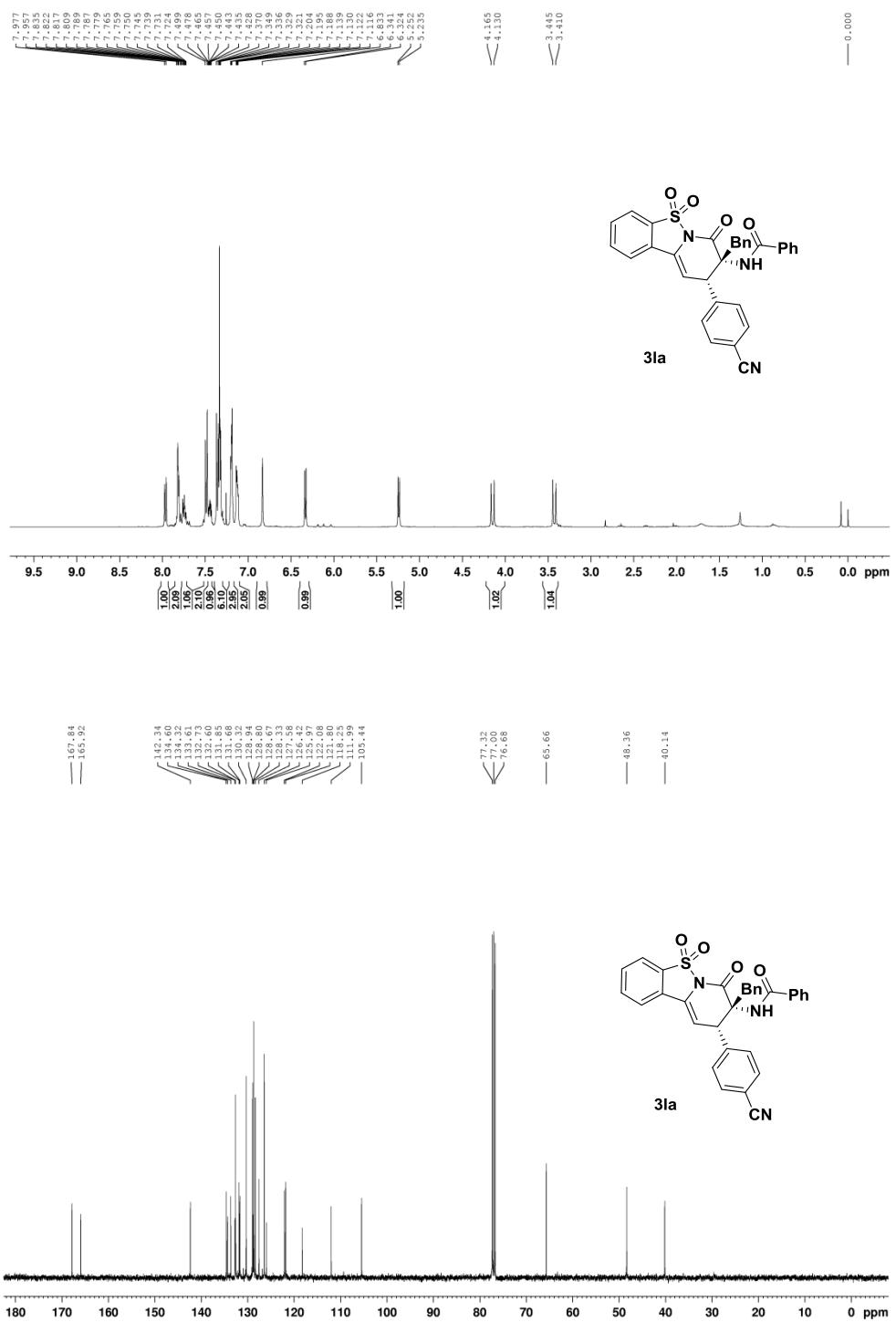


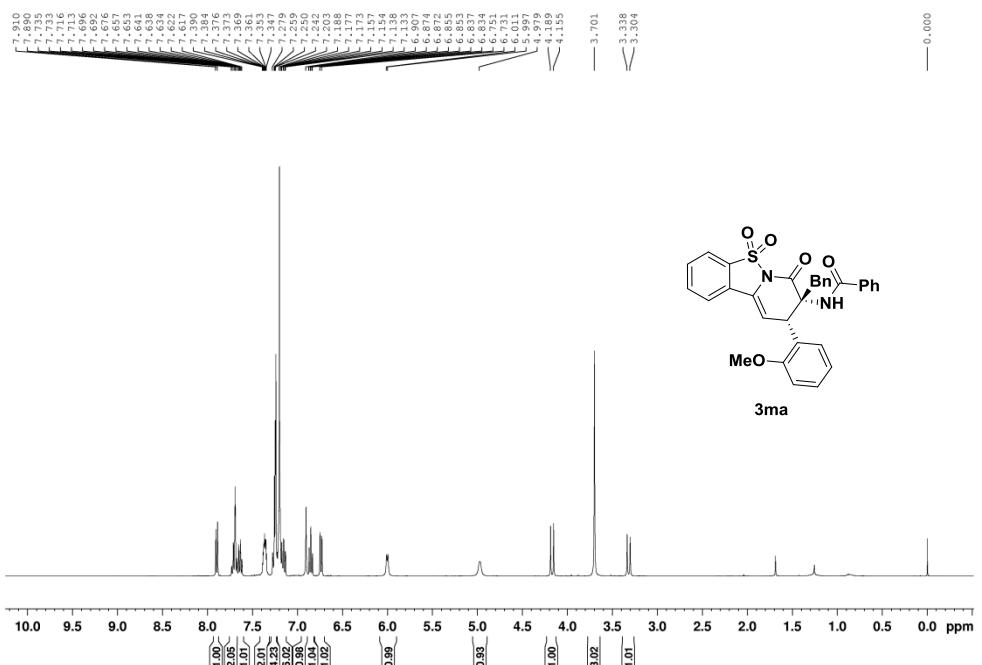




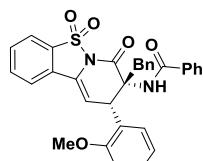
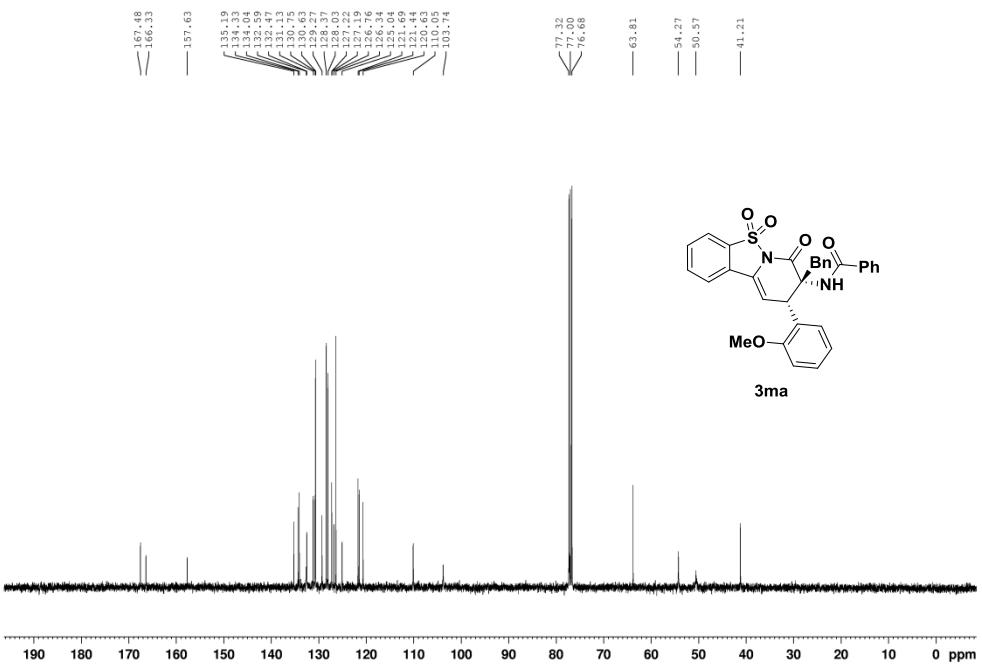




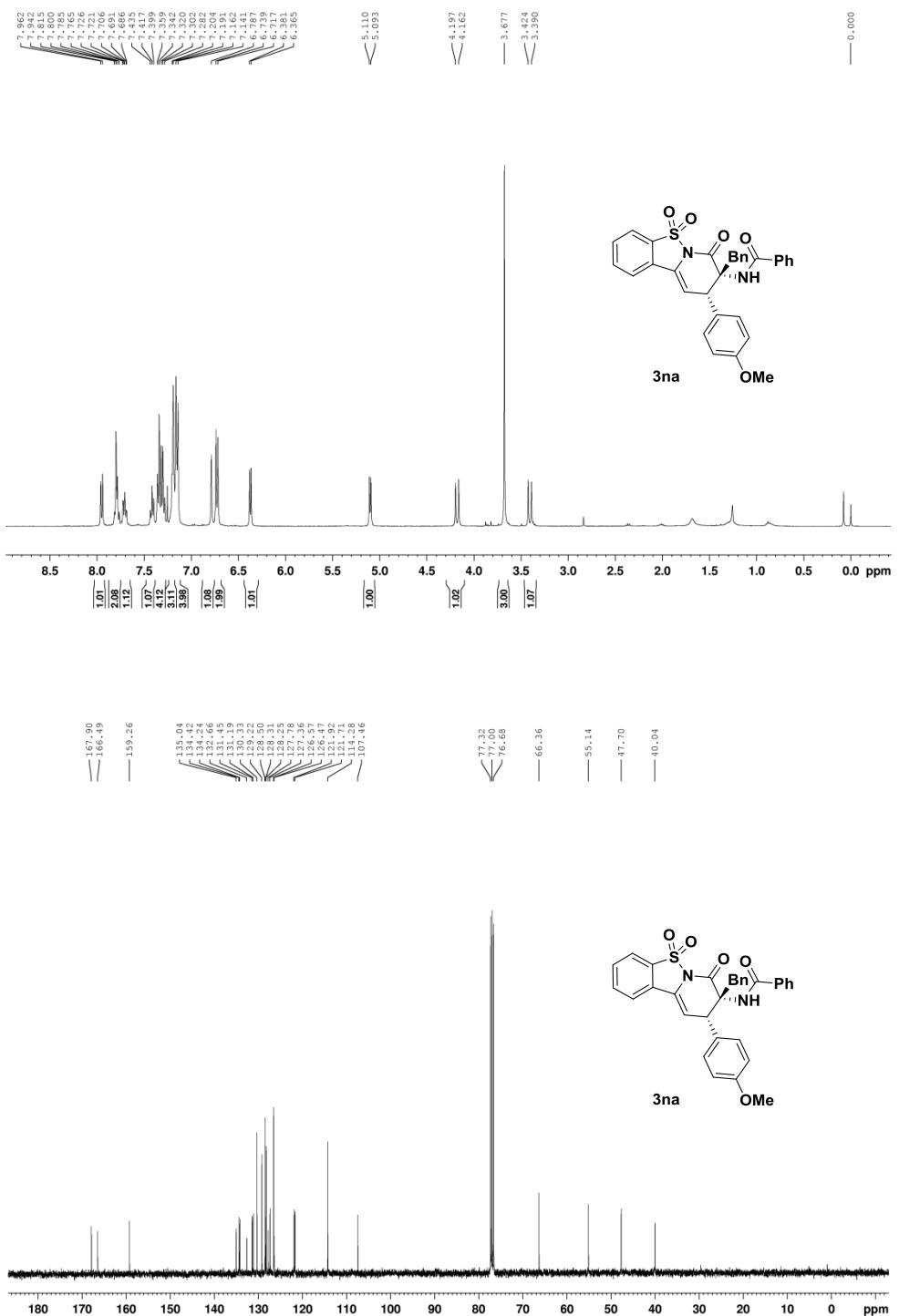


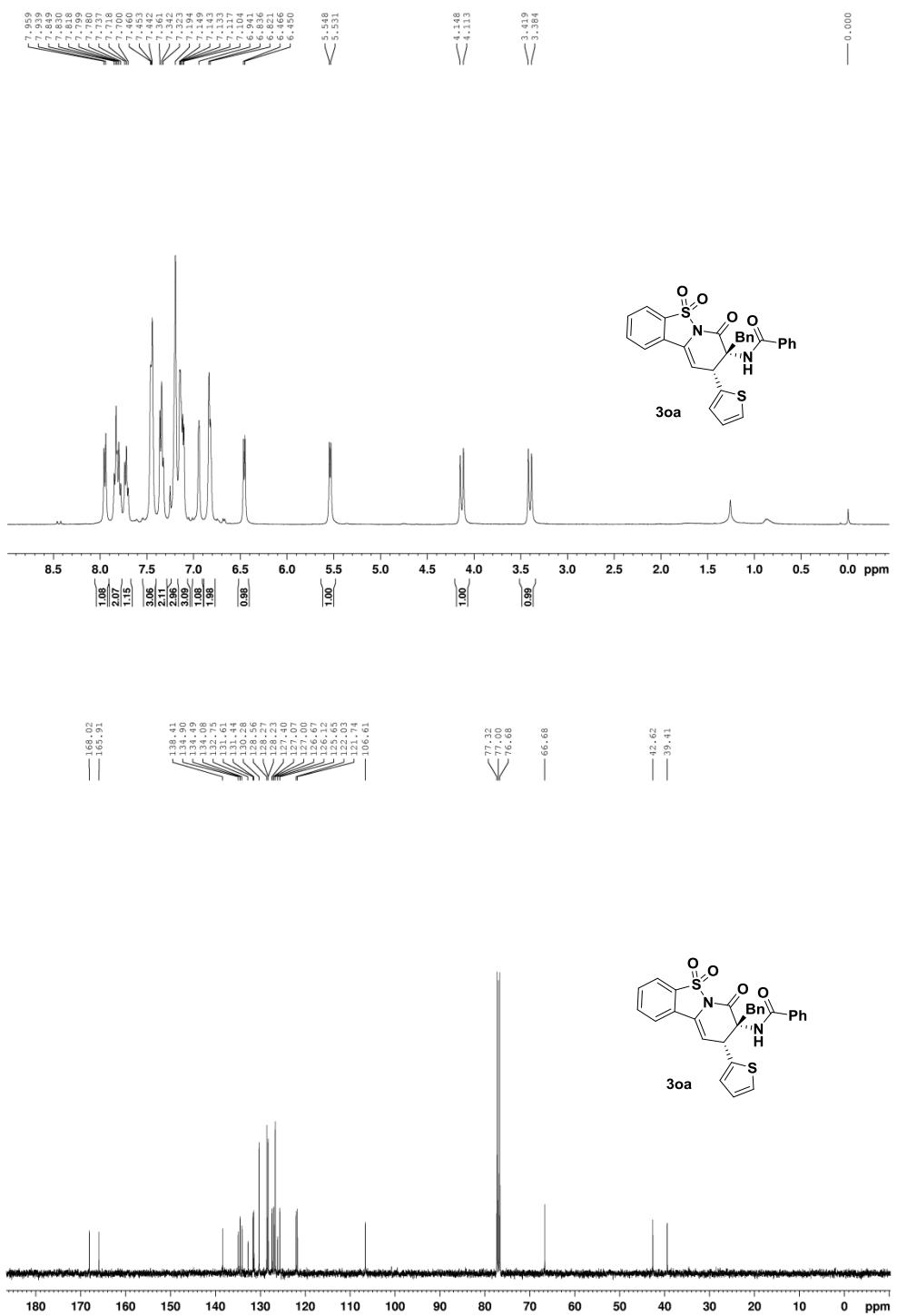


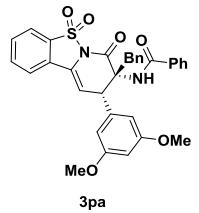
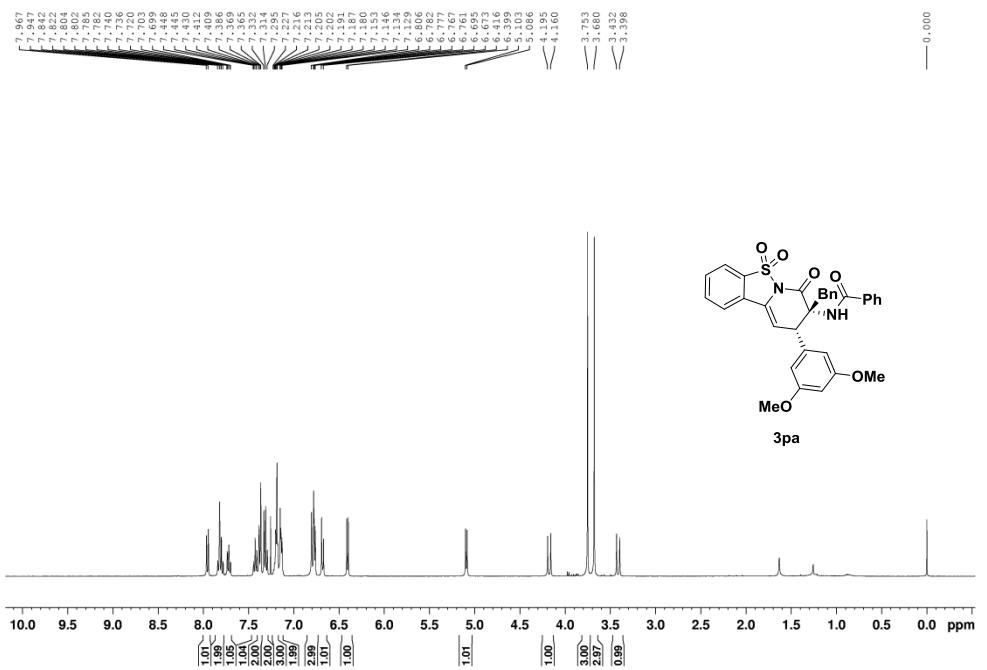
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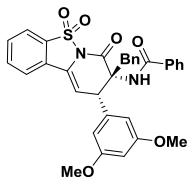
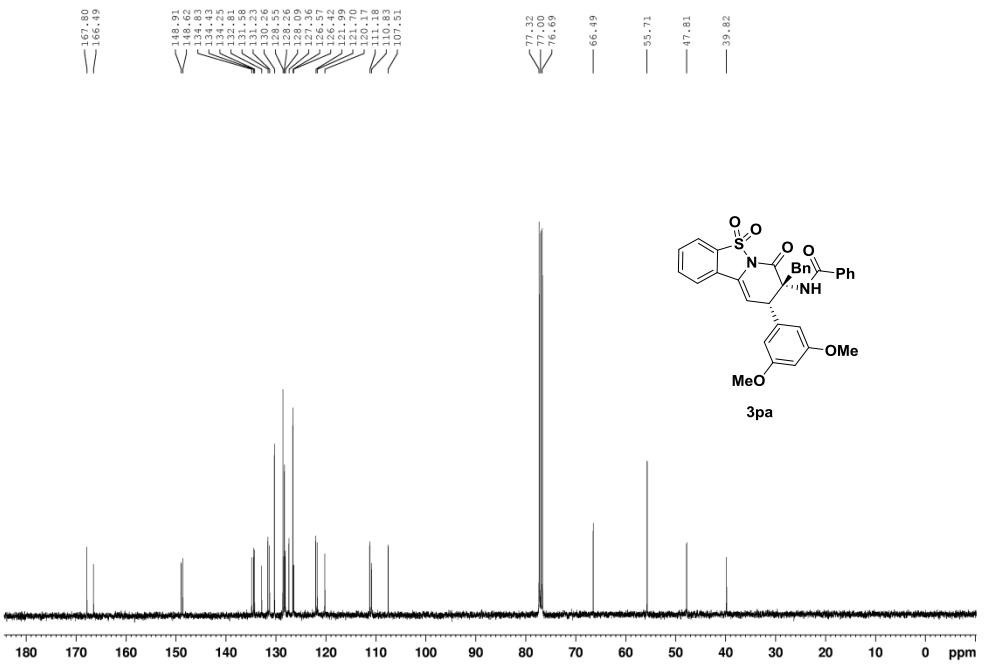
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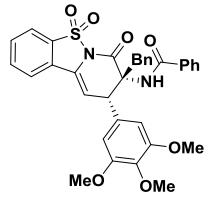
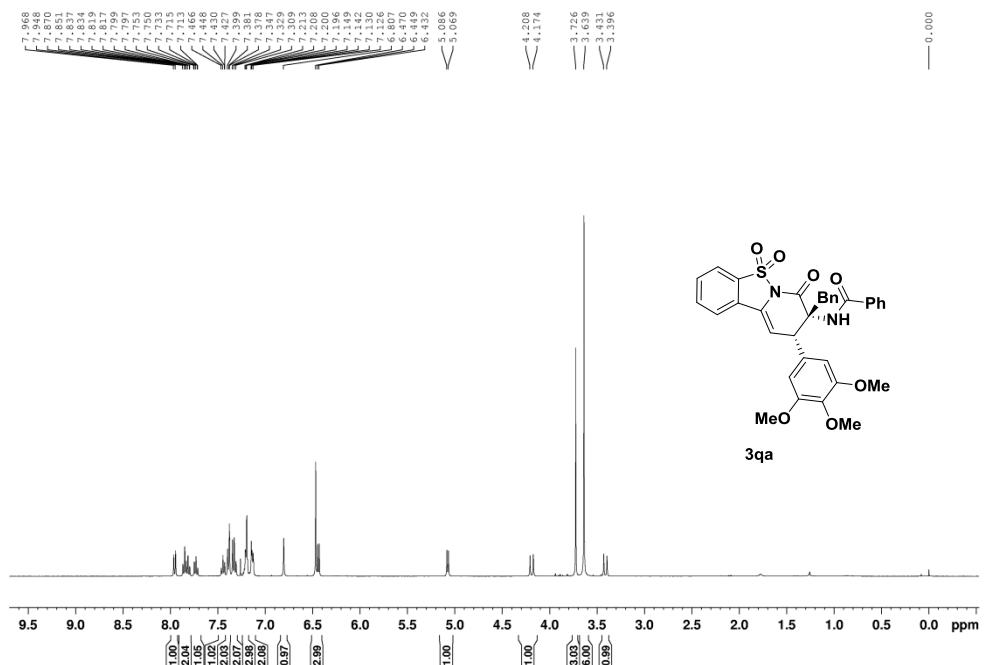




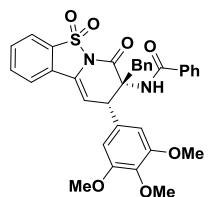
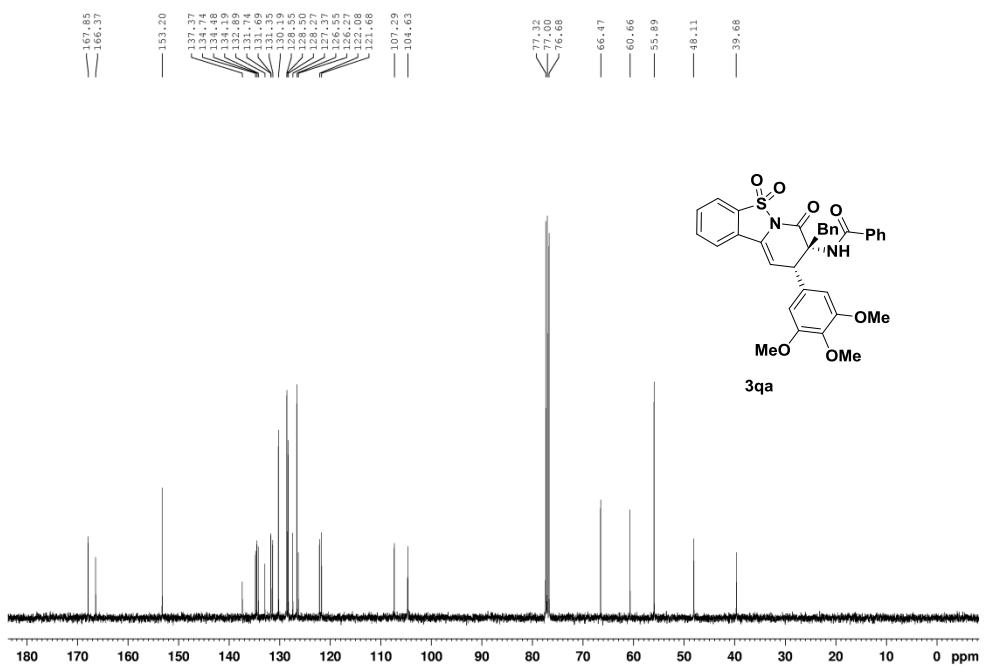
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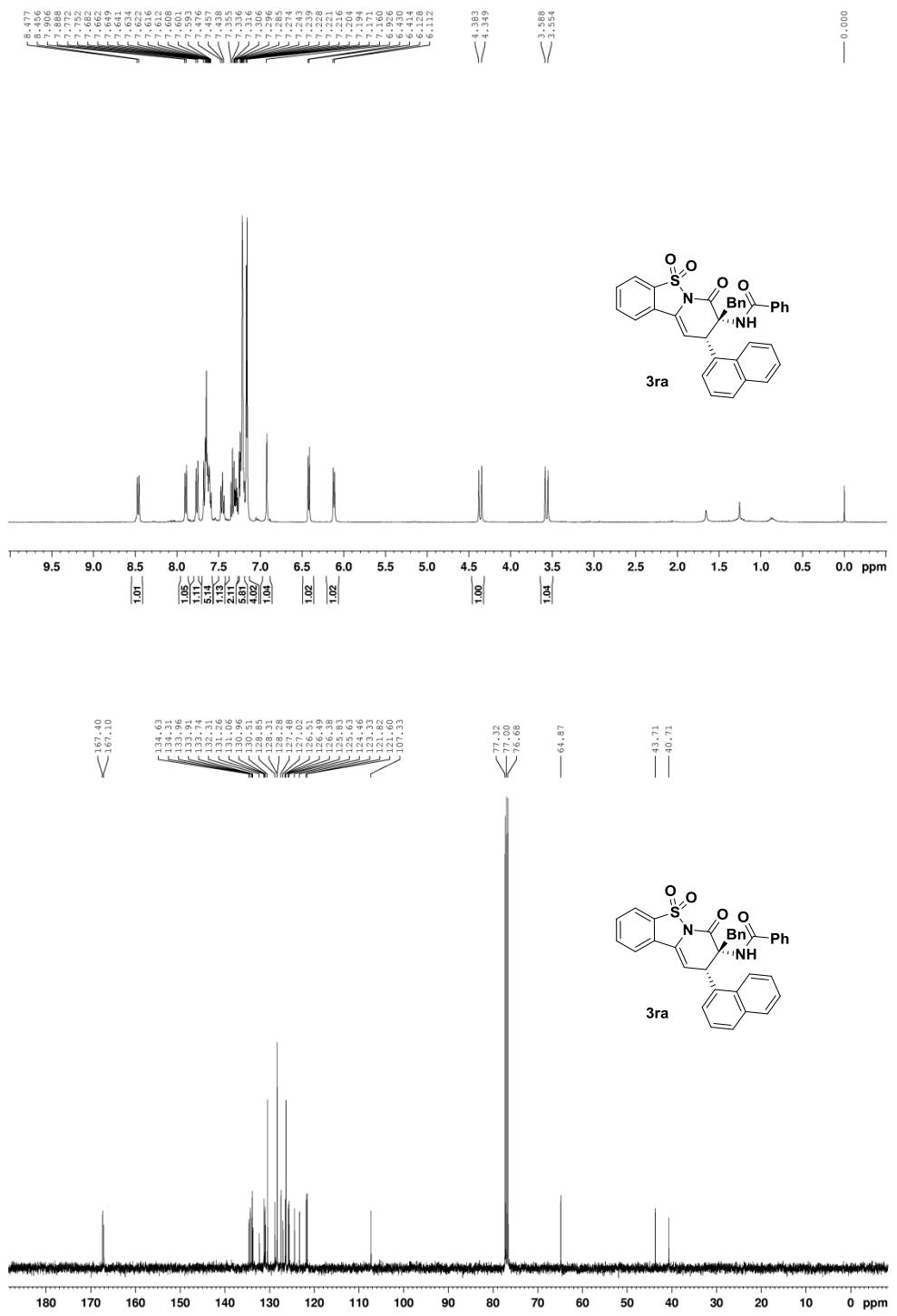
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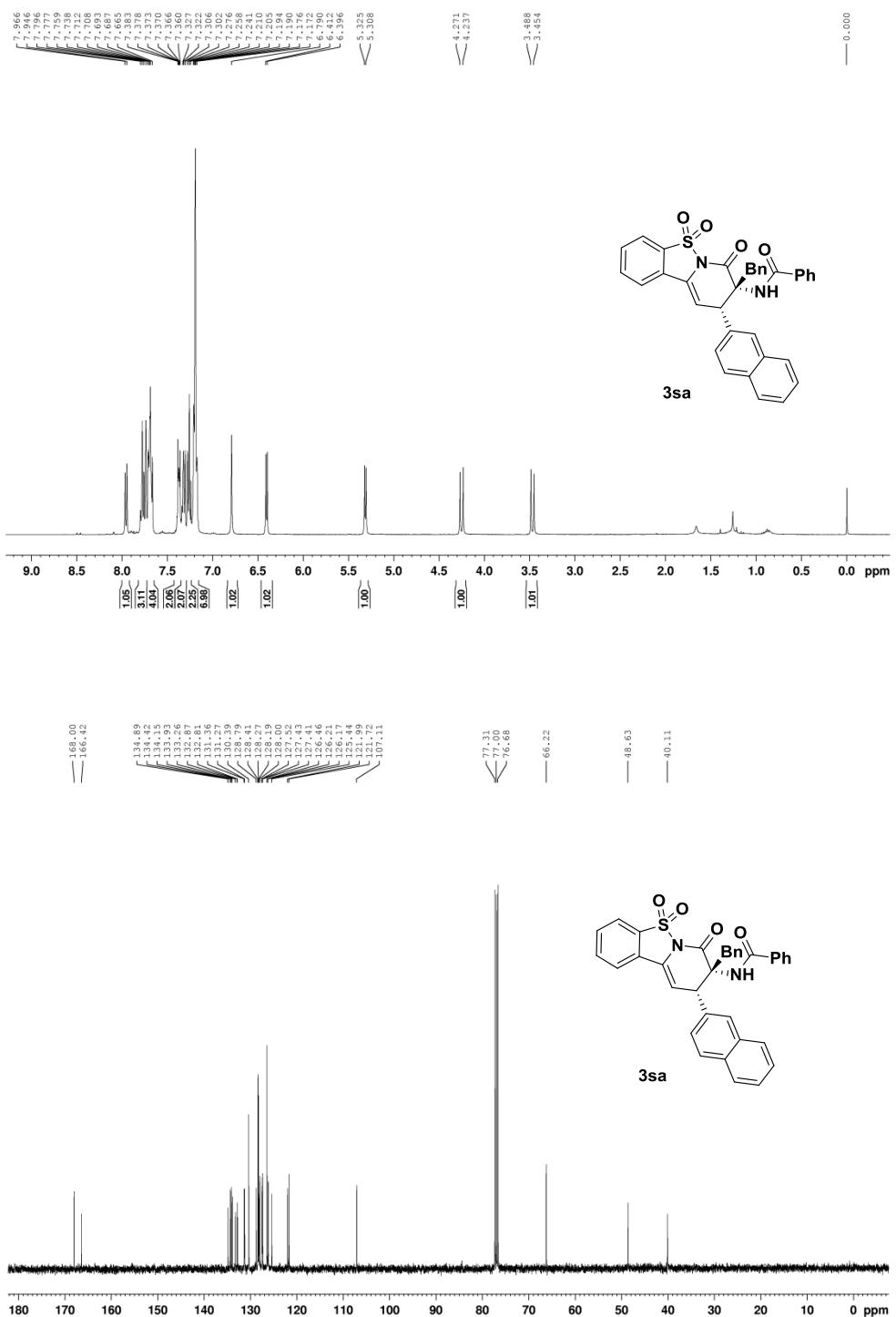


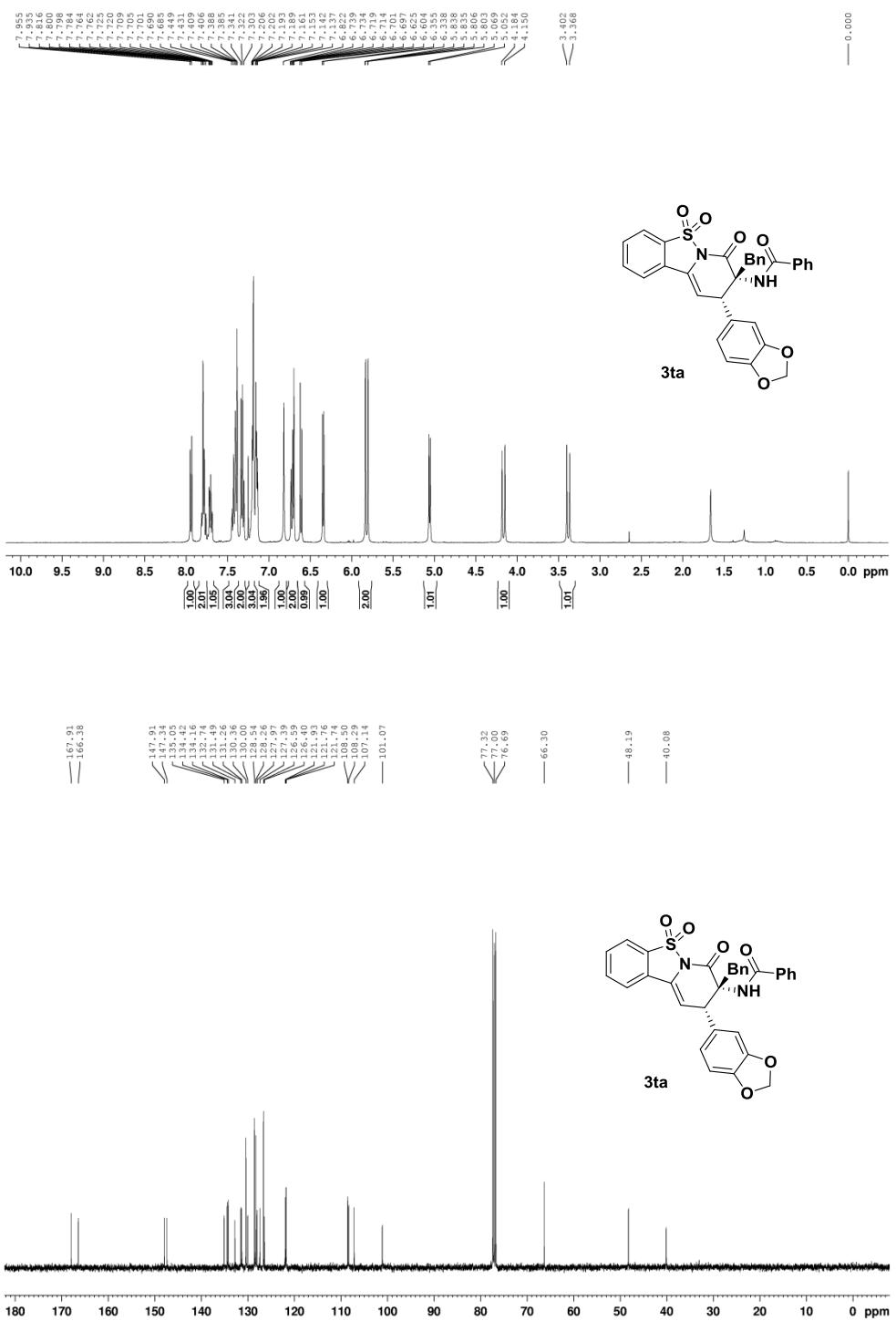
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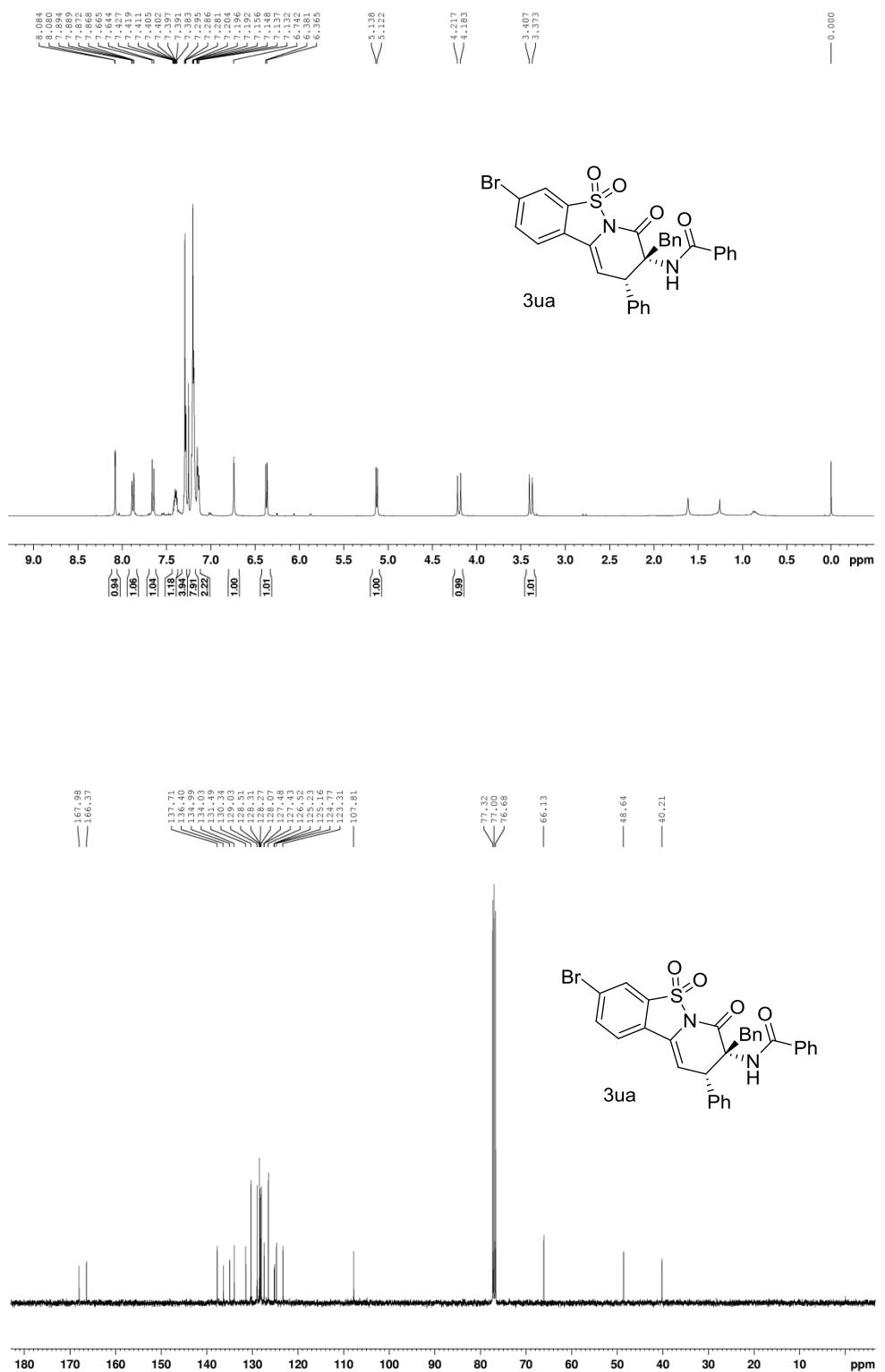


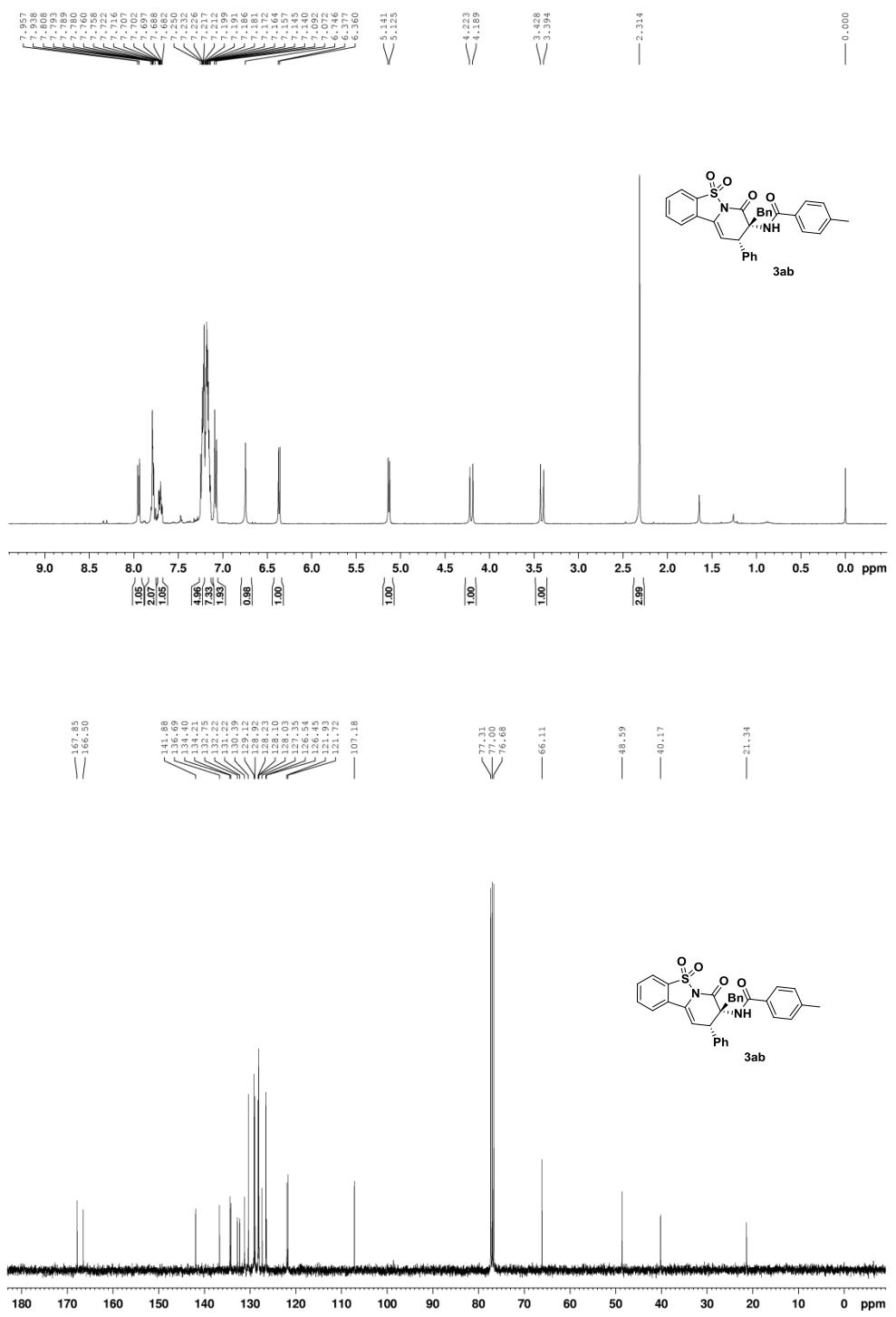
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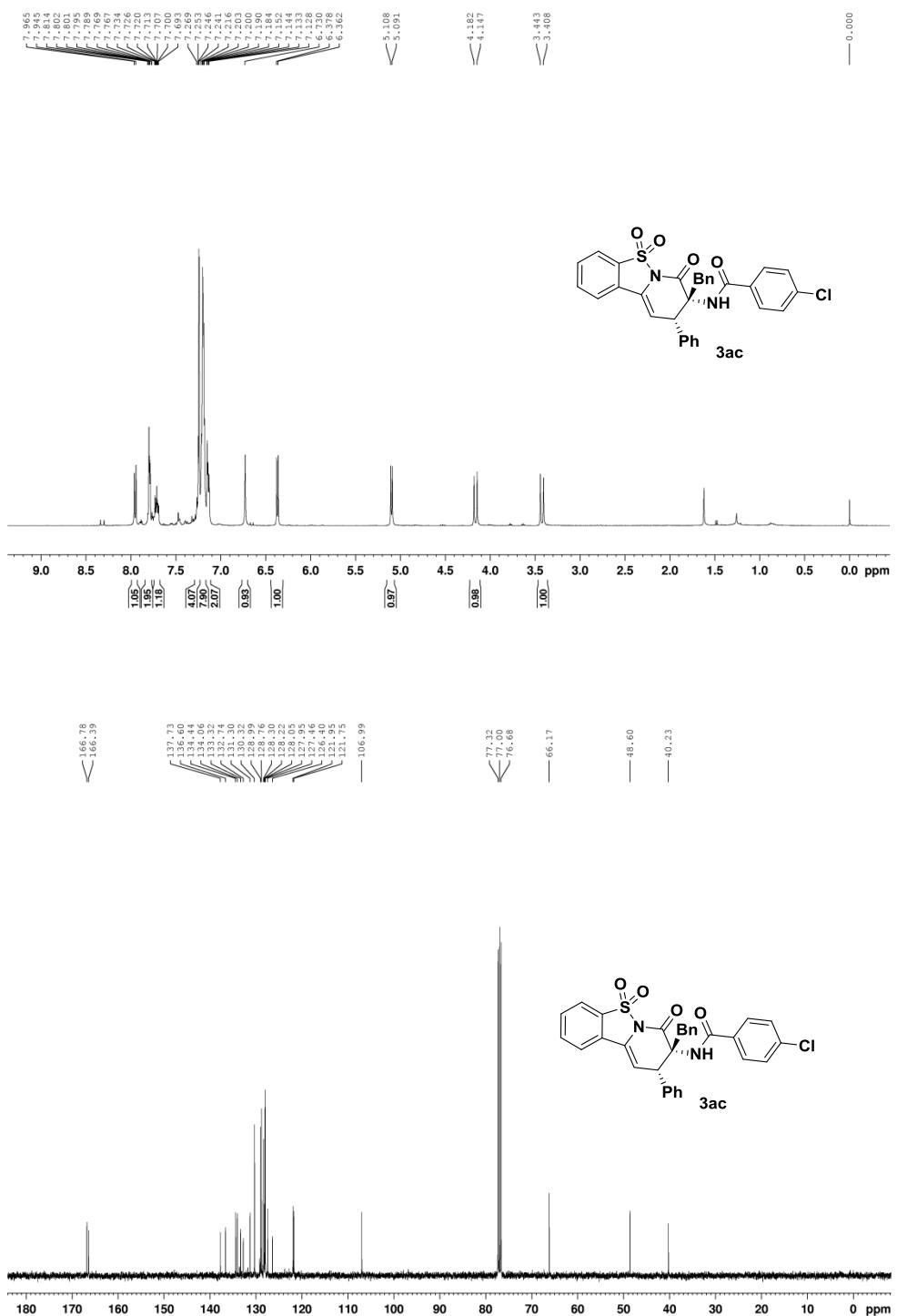


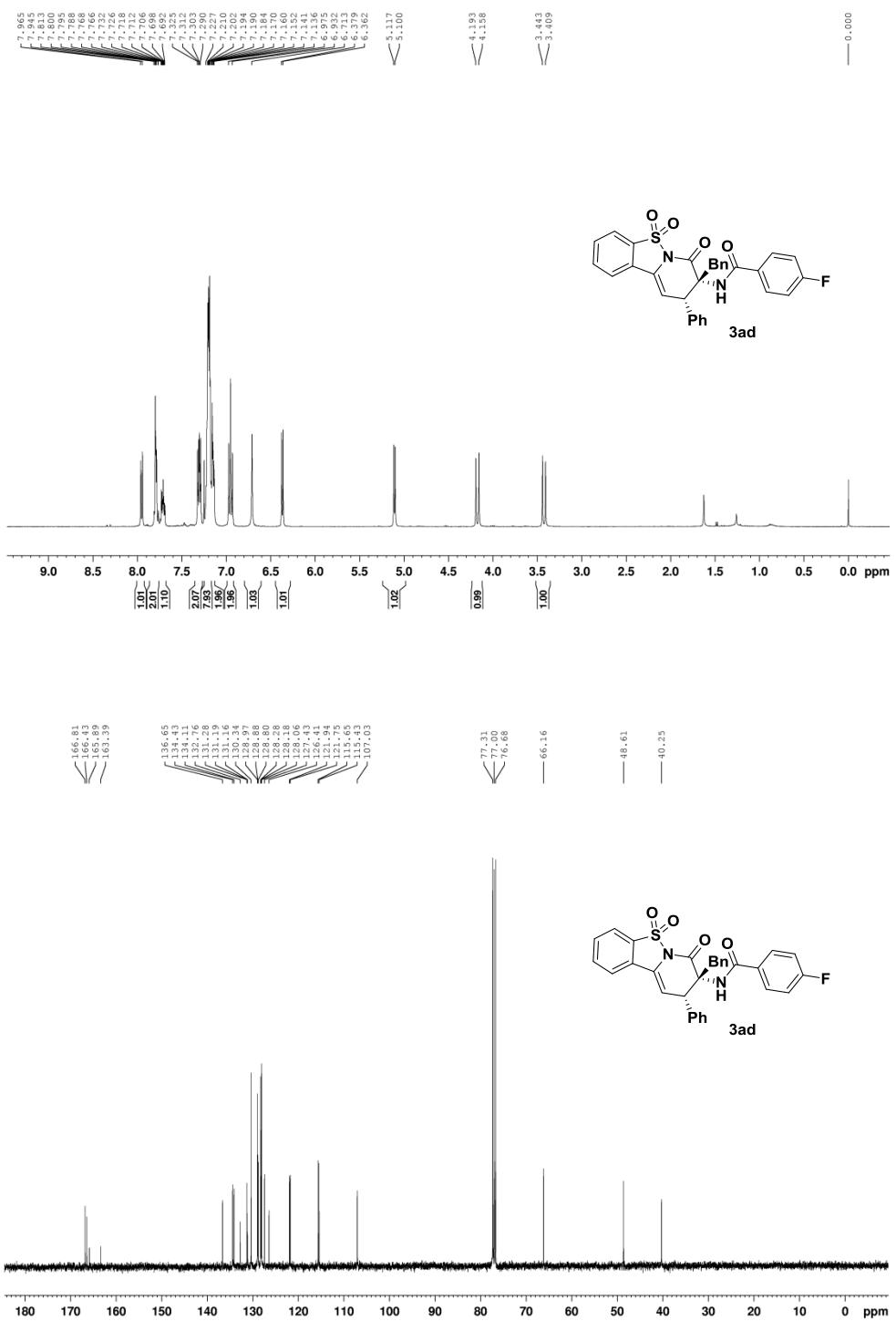


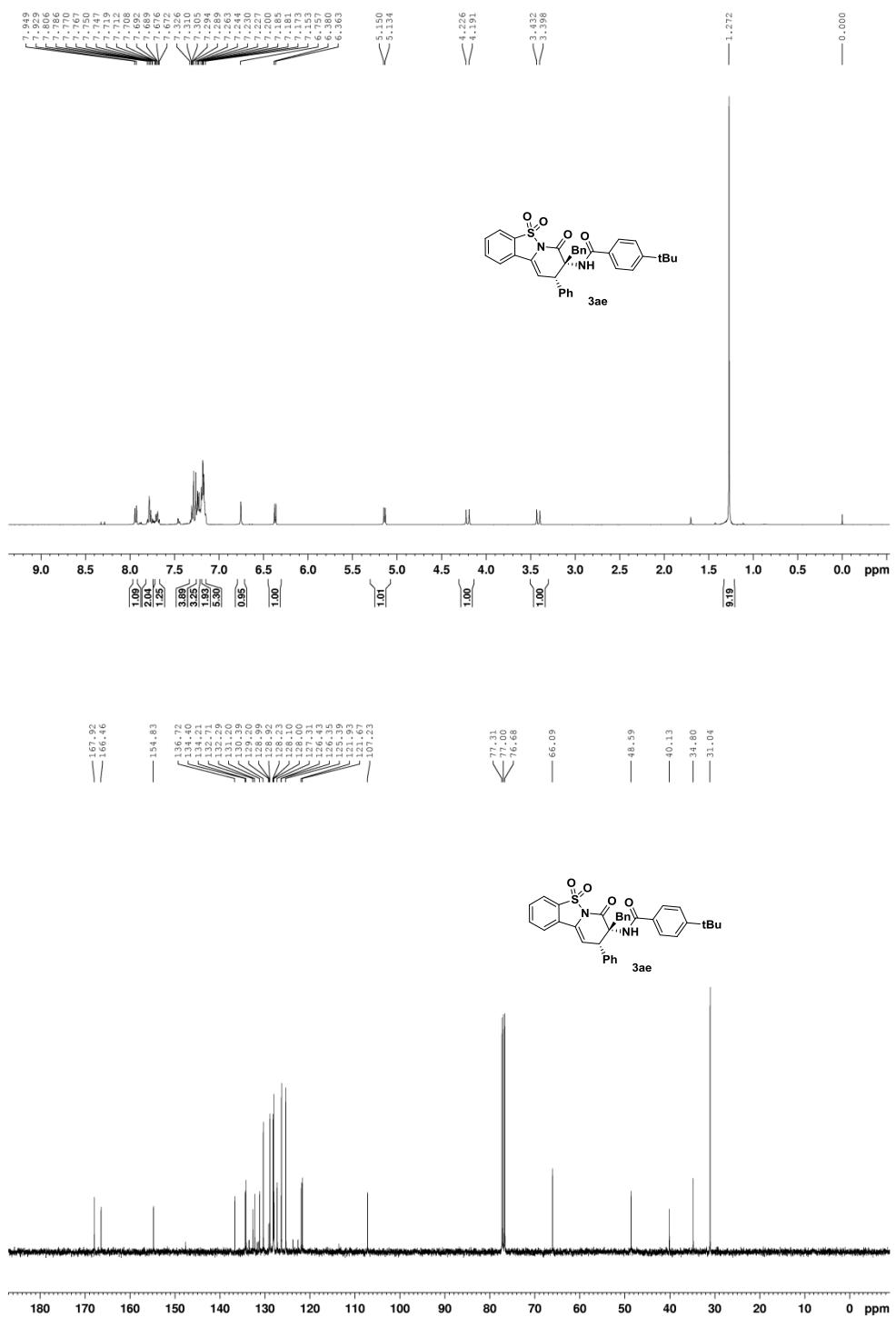


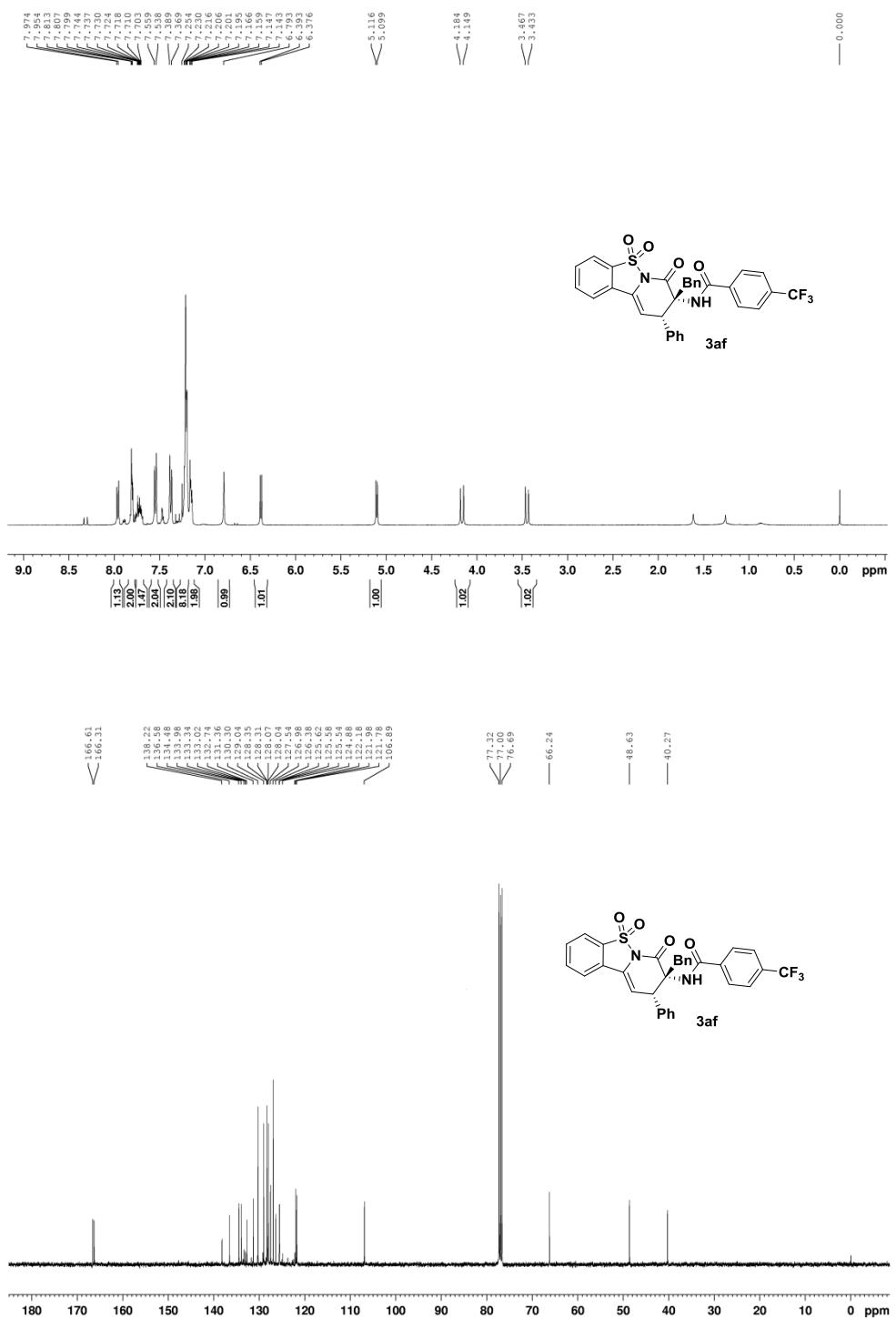


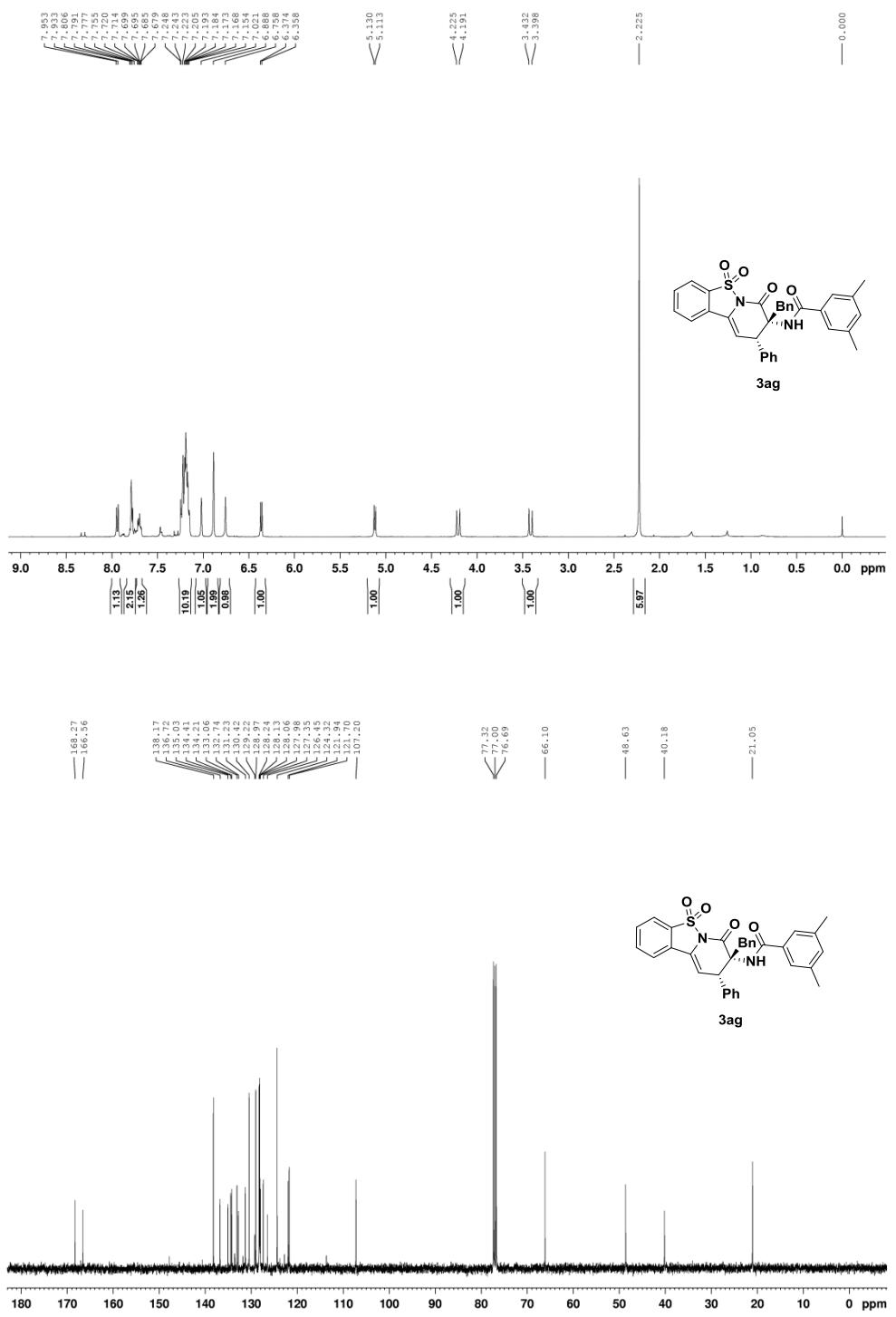


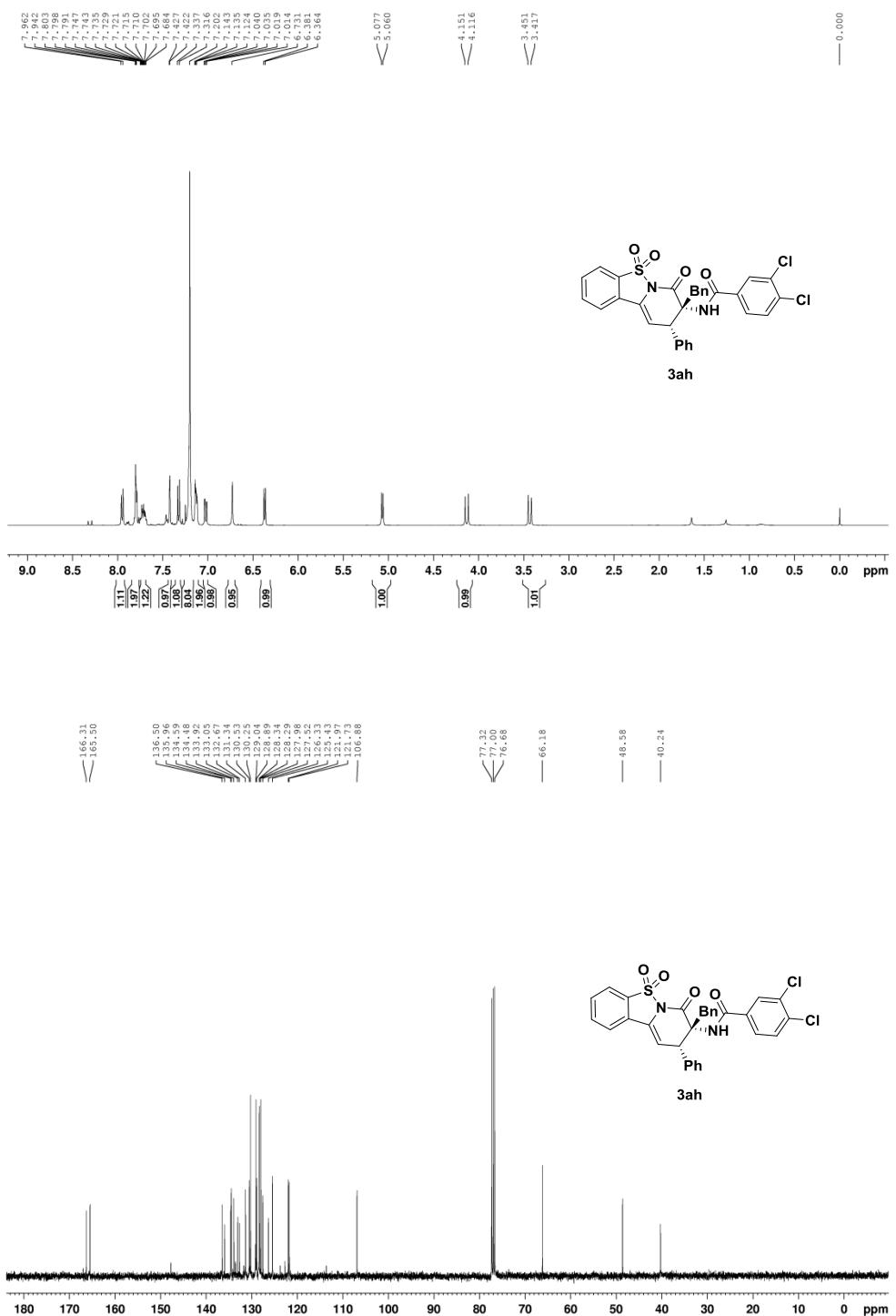


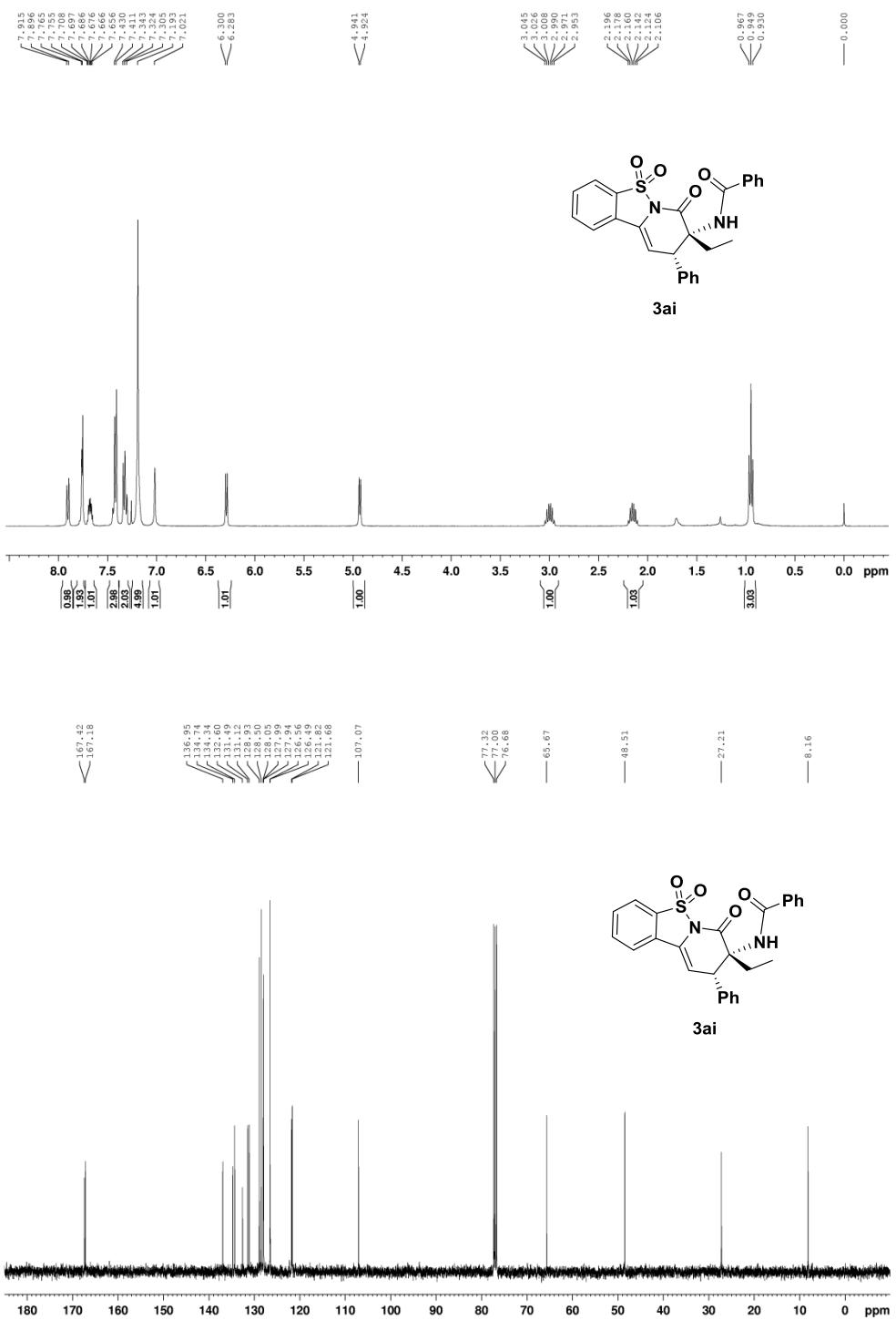


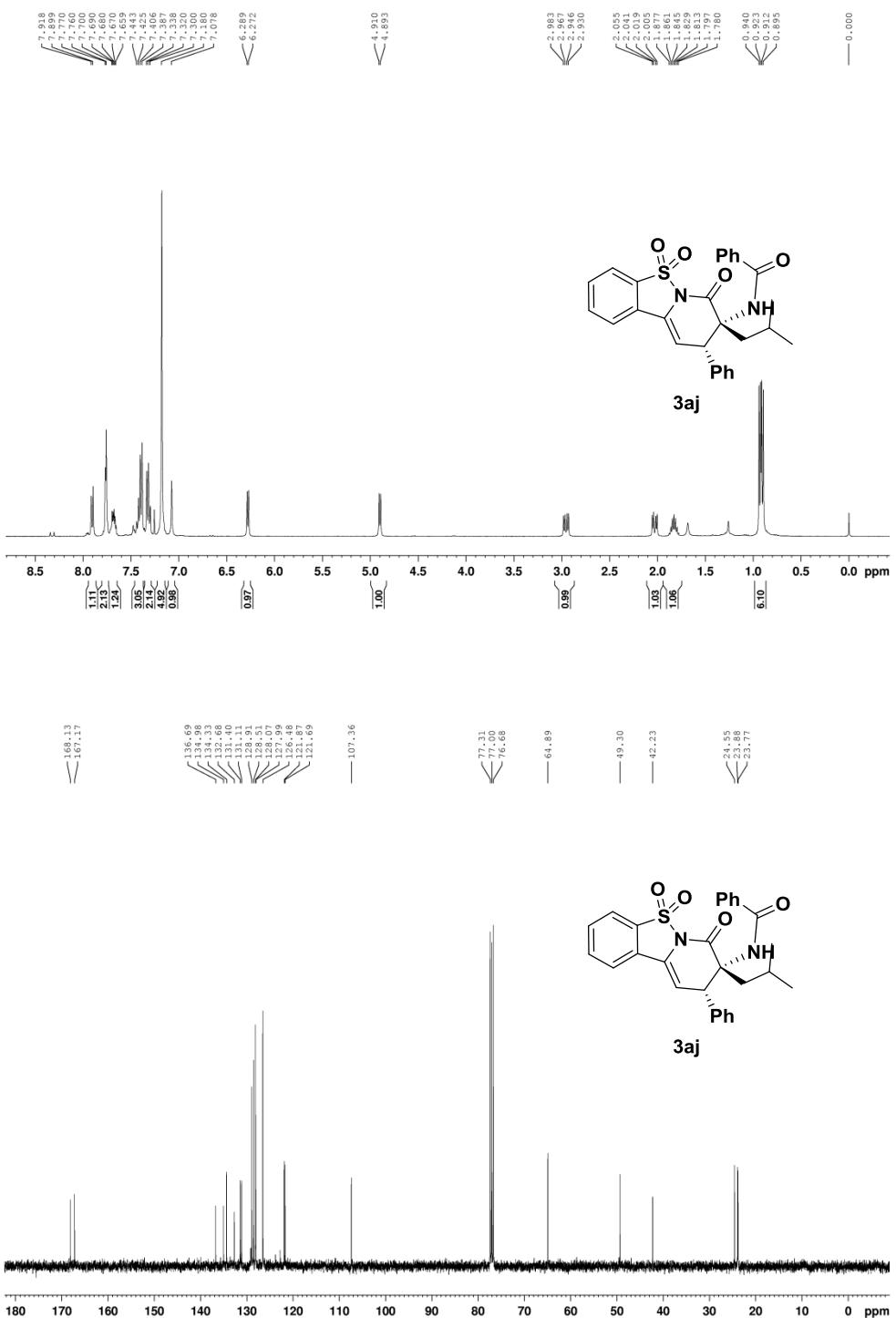


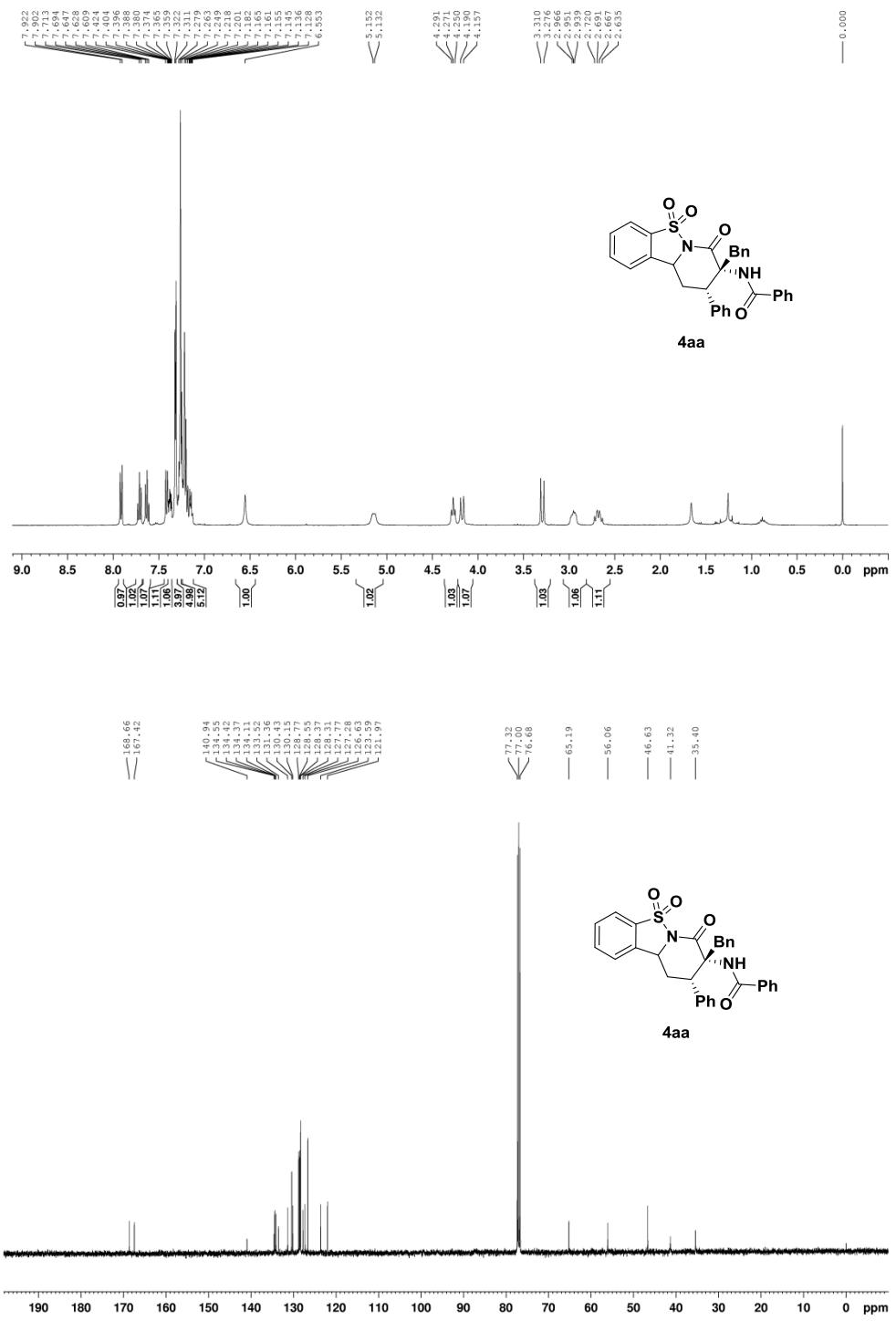






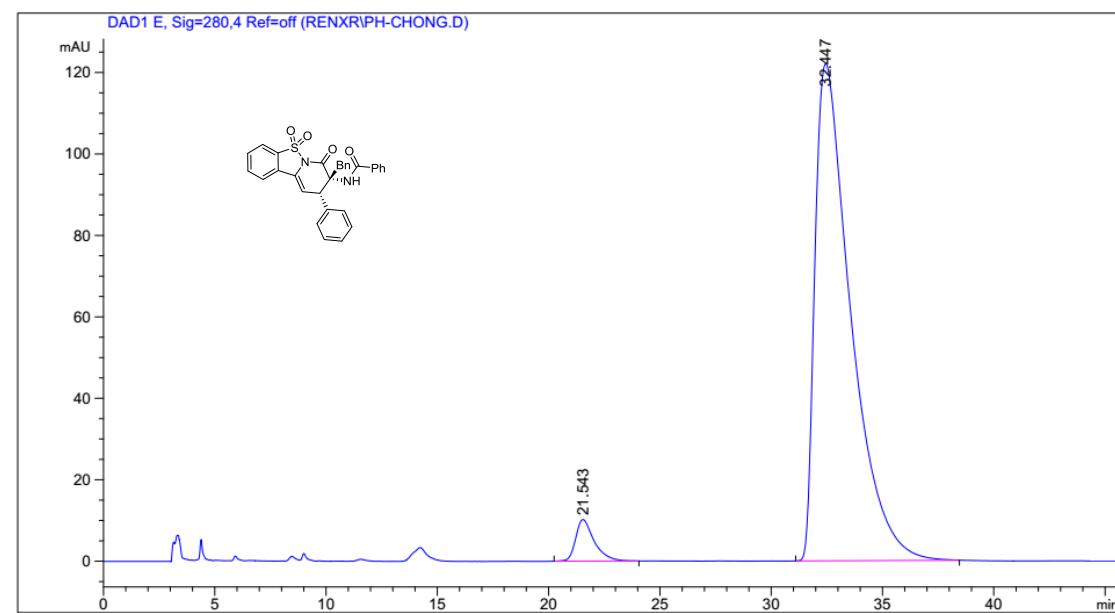
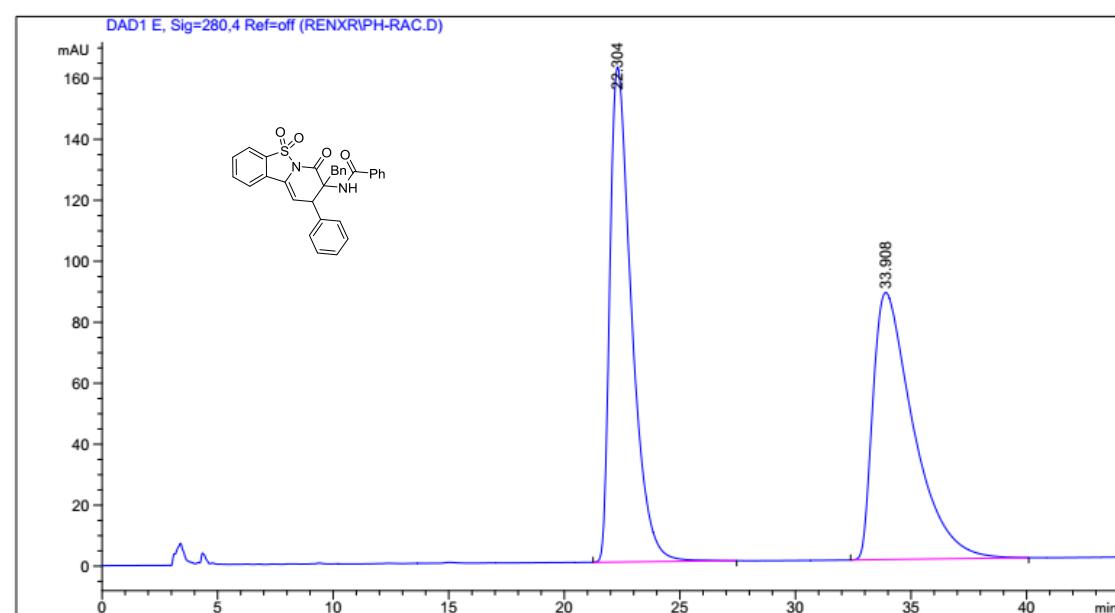




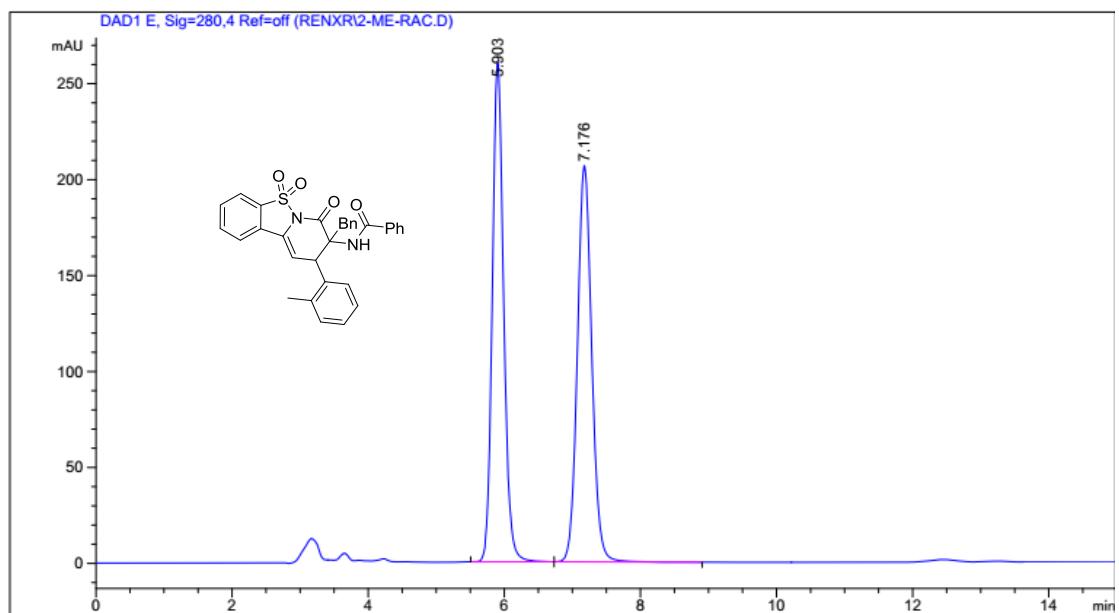


7.HPLC Data

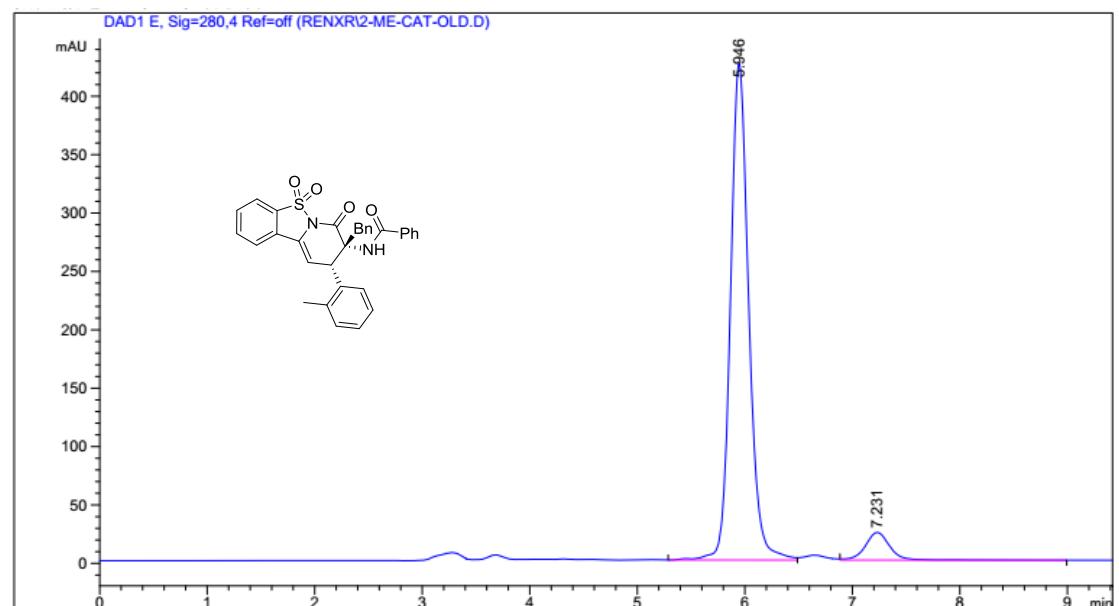
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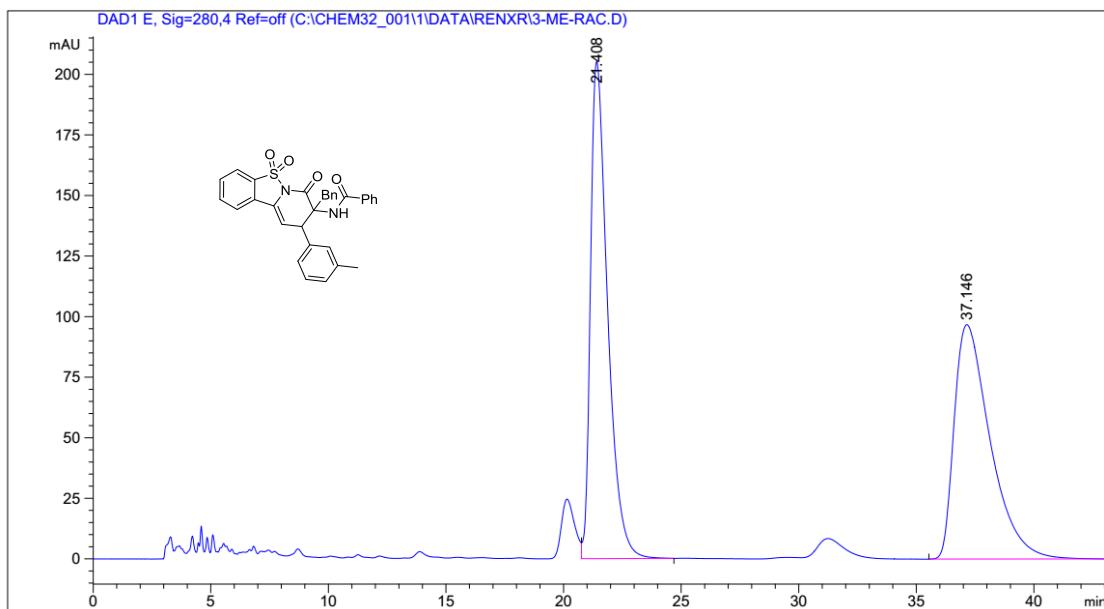


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	5.903	3010.49341	260.13449	49.8875
2	DAD 280,4nm	7.176	3024.07422	206.57803	50.1125

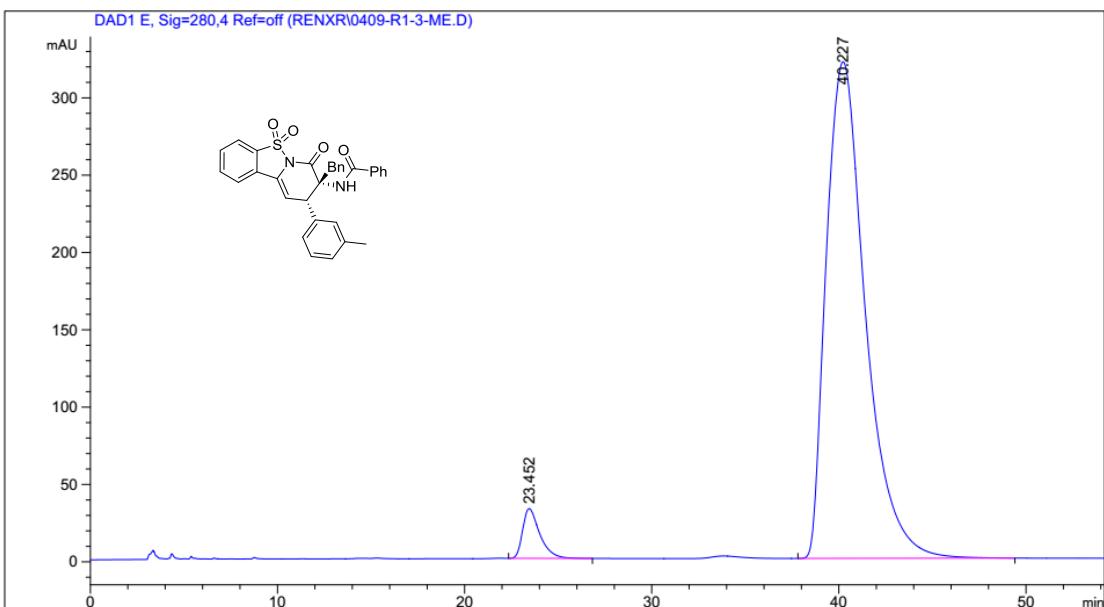


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	5.946	5022.41064	425.09317	92.9899
2	DAD 280,4nm	7.231	378.62015	23.71989	7.0101

3ca

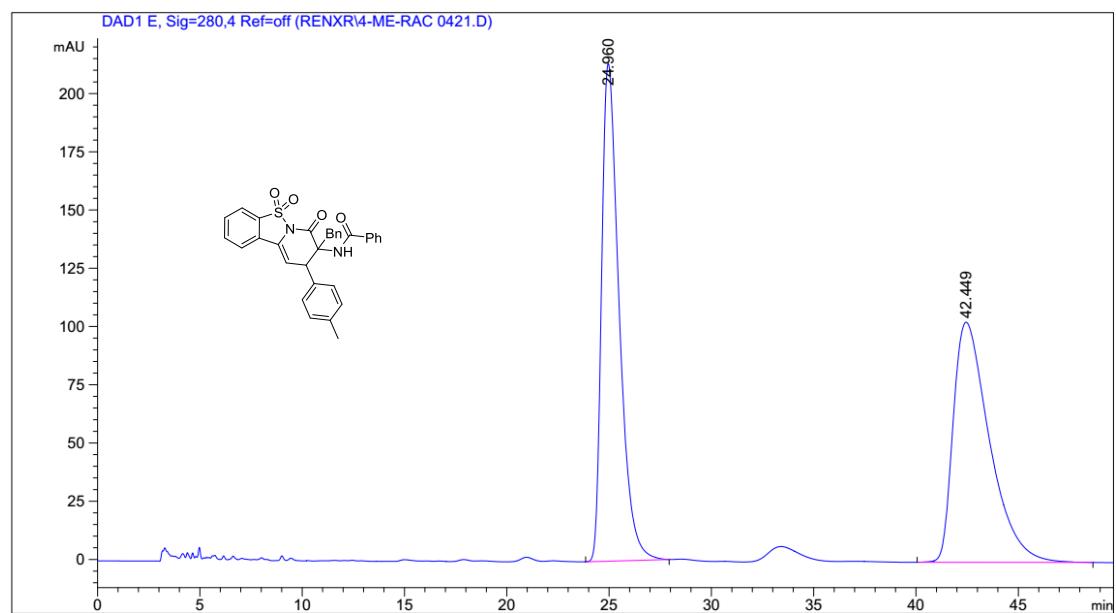


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	21.408	1.03472e4	205.18503	50.1854
2	DAD 280,4nm	37.146	1.02708e4	96.75040	49.8146

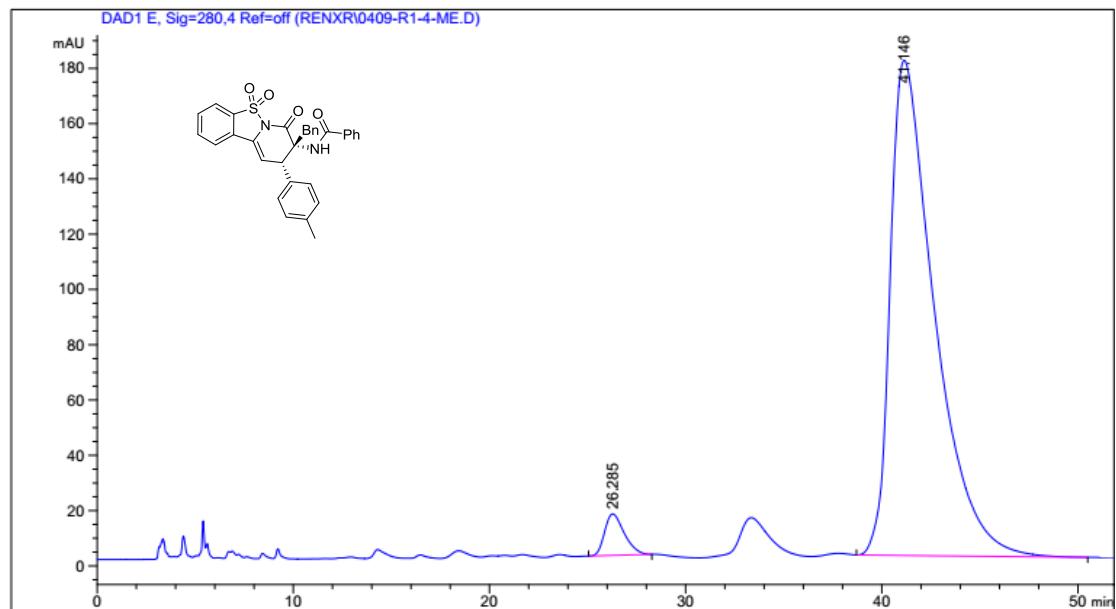


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	23.452	2044.08459	32.16880	4.1952
2	DAD 280,4nm	40.227	4.66805e4	321.09293	95.8048

3da

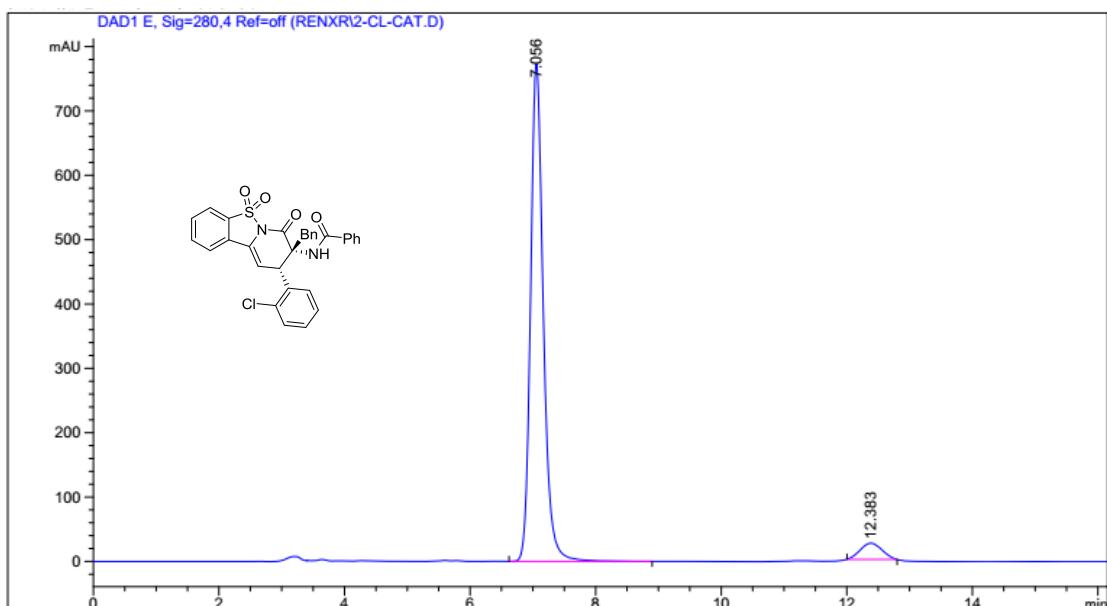
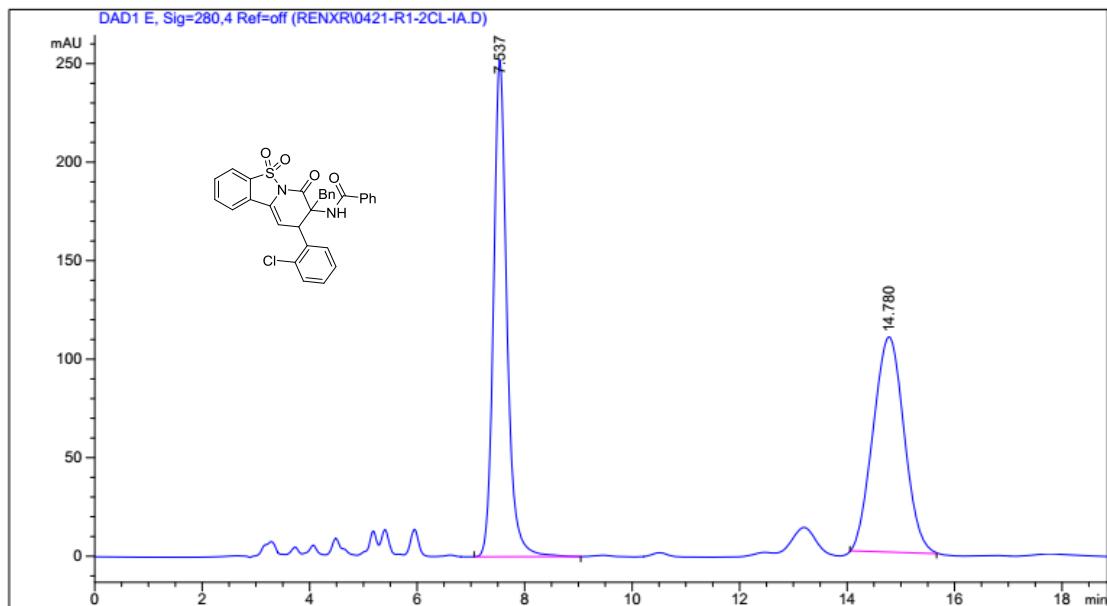


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	24.960	1.26692e4	213.64732	50.0174
2	DAD 280,4nm	42.449	1.26603e4	103.05259	49.9826



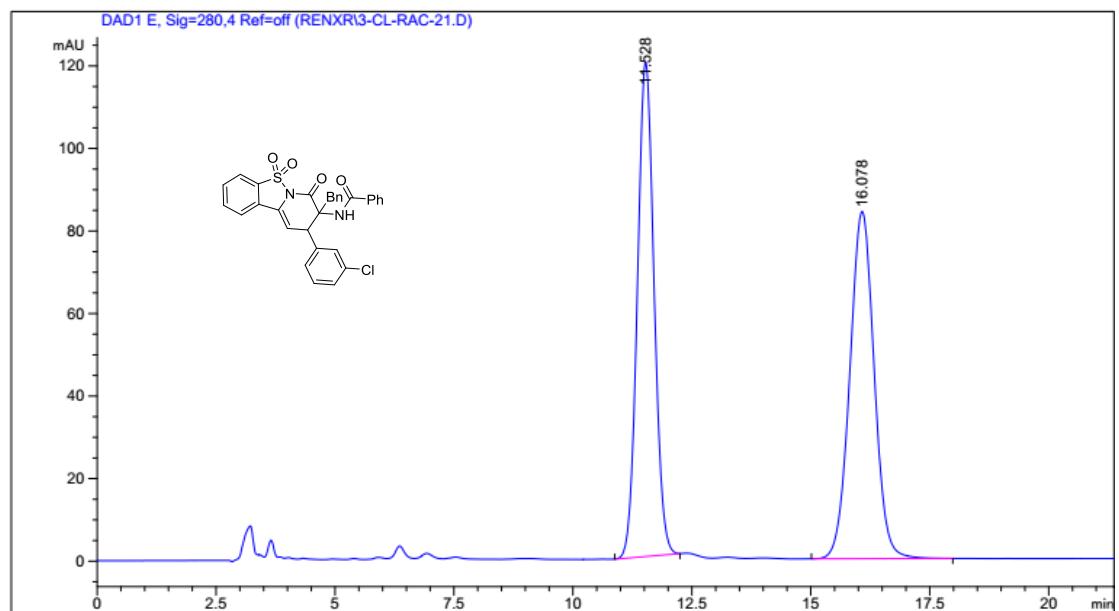
Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	26.285	1040.70435	15.00699	3.5834
2	DAD 280,4nm	41.146	2.80016e4	179.10585	96.4166

3ea

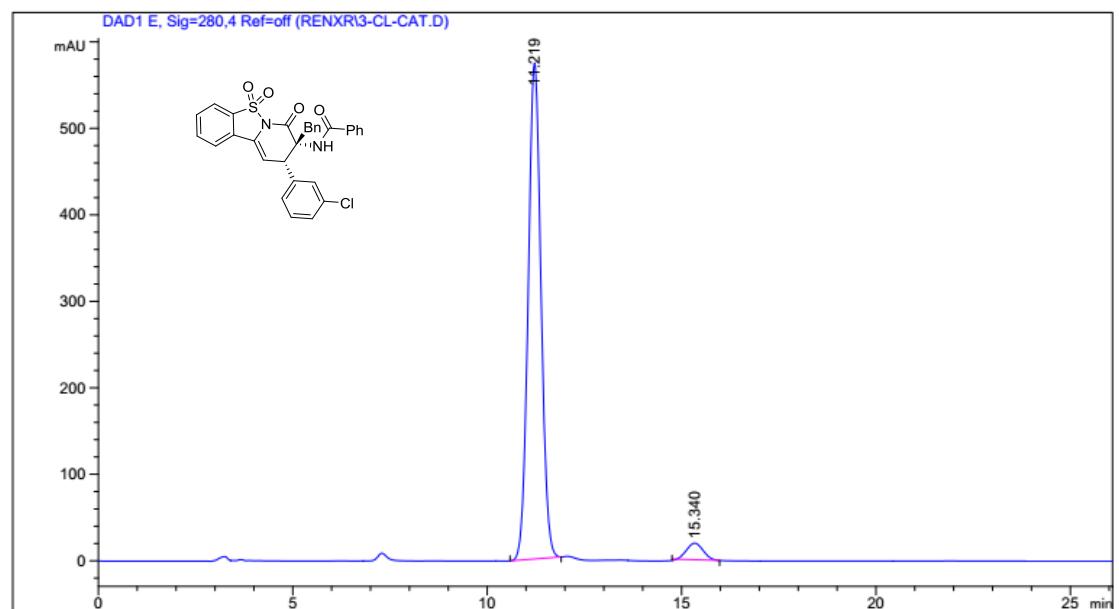


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	7.056	1.08840e4	773.75391	94.7452
2	DAD 280,4nm	12.383	603.65515	25.15029	5.2548

3fa

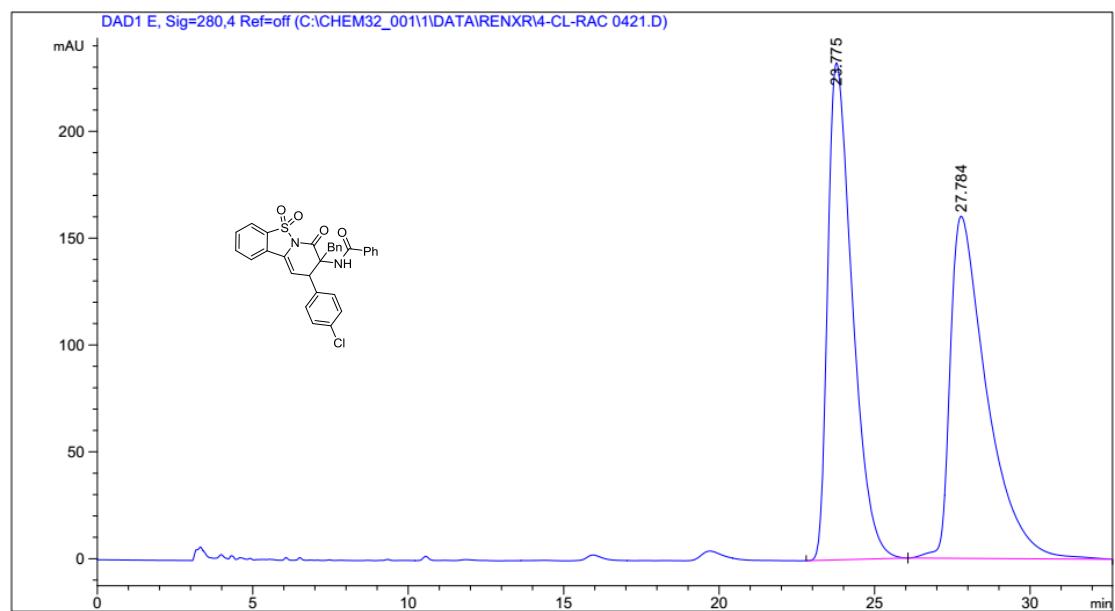


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	11.528	2912.44482	119.73755	49.3534
2	DAD 280,4nm	16.078	2988.75952	84.16077	50.6466

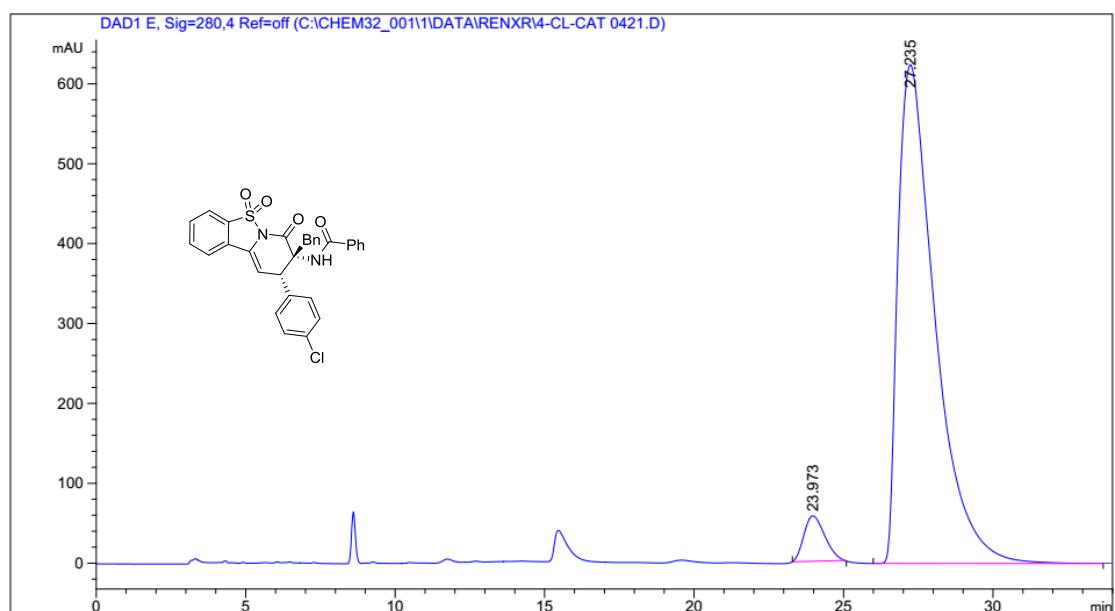


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	11.219	1.30681e4	573.23590	95.8643
2	DAD 280,4nm	15.340	563.77618	19.09134	4.1357

3ga

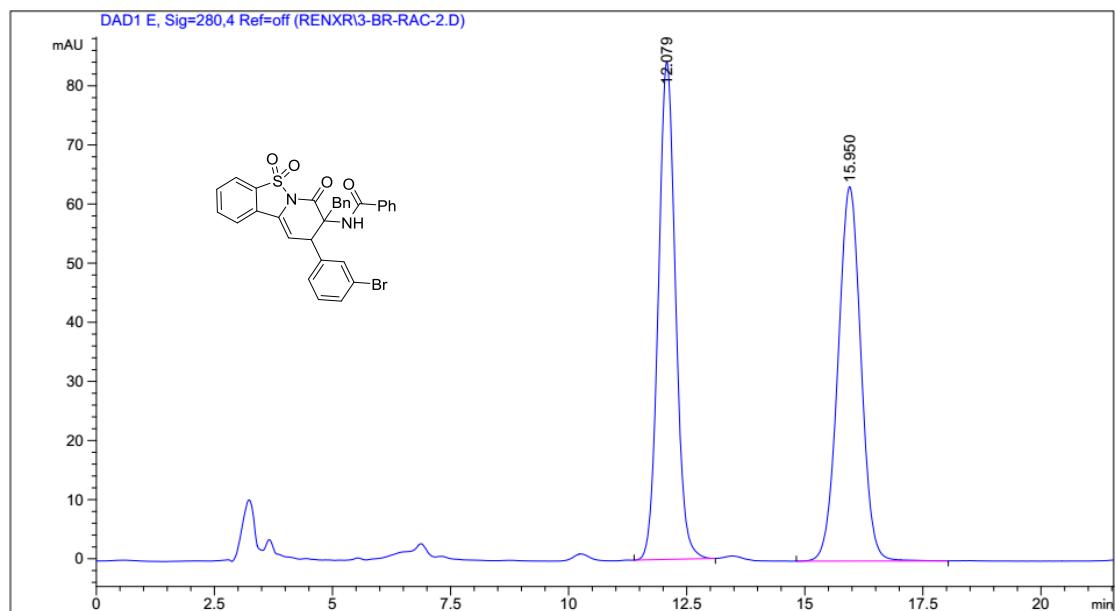


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	23.775	1.28021e4	232.60614	49.5014
2	DAD 280,4nm	27.784	1.30600e4	160.11501	50.4986

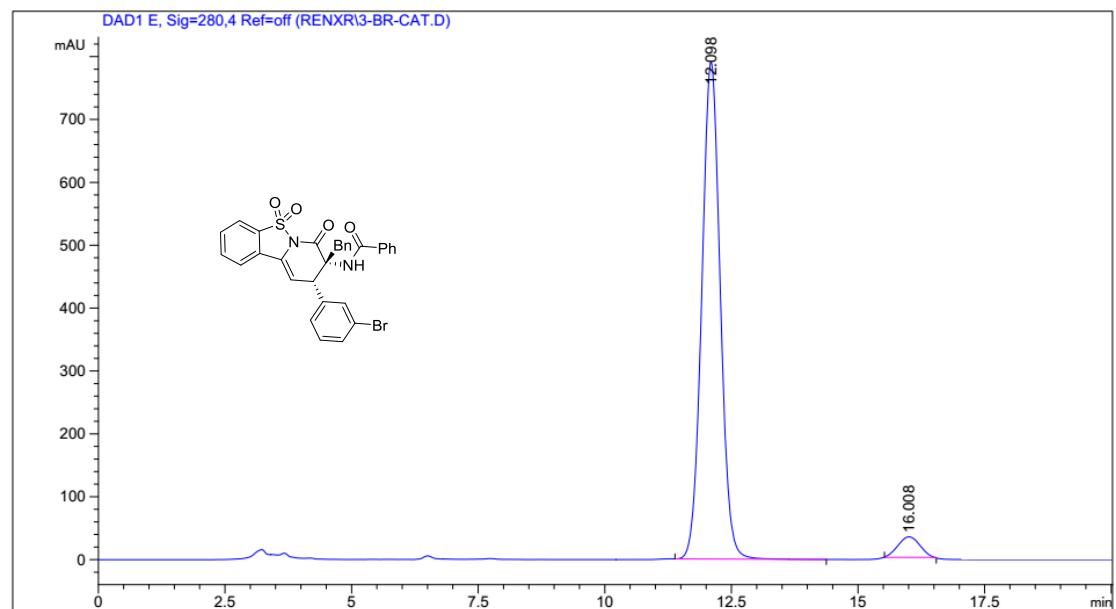


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	23.973	2760.12036	56.88066	4.9006
2	DAD 280,4nm	27.235	5.35622e4	624.01514	95.0994

3ha

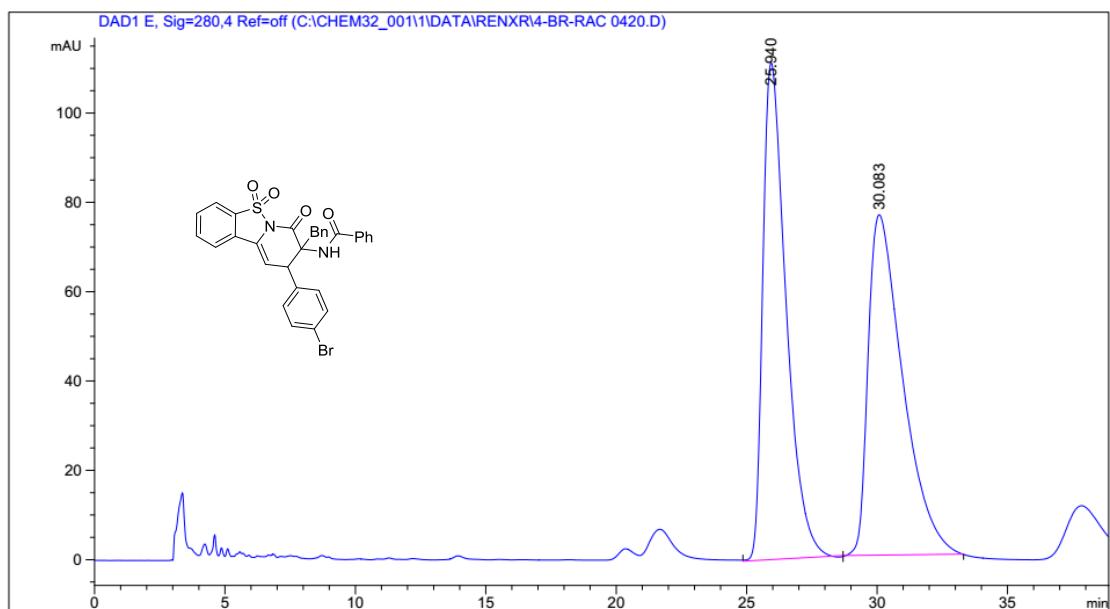


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	12.079	2120.97485	84.16270	49.8336
2	DAD 280,4nm	15.950	2135.13672	63.32970	50.1664

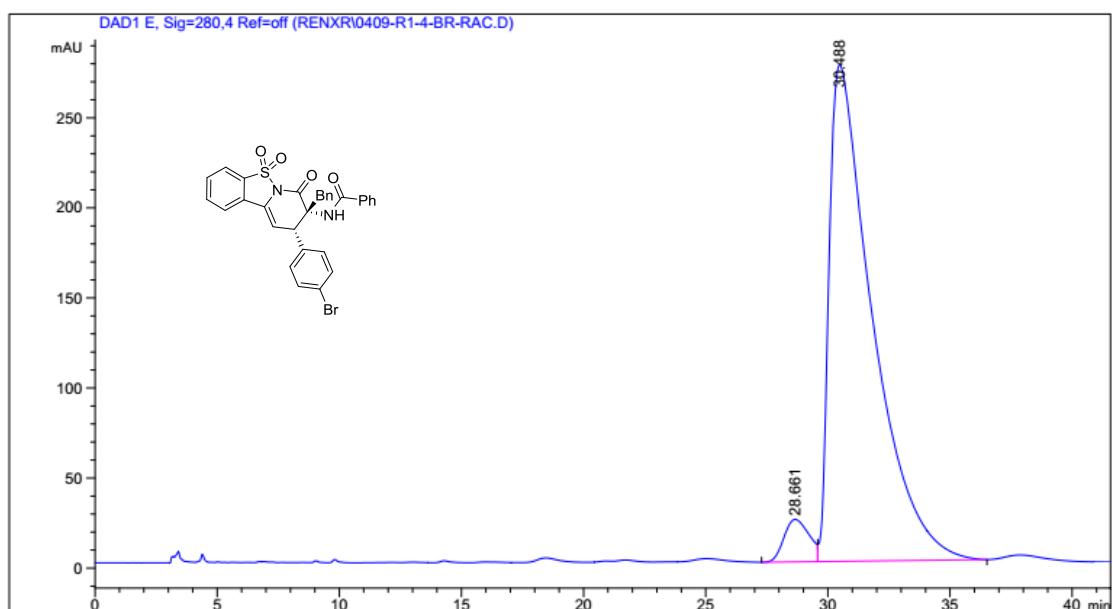


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	12.098	1.99703e4	790.63483	95.3403
2	DAD 280,4nm	16.008	976.03387	32.74494	4.6597

3ia

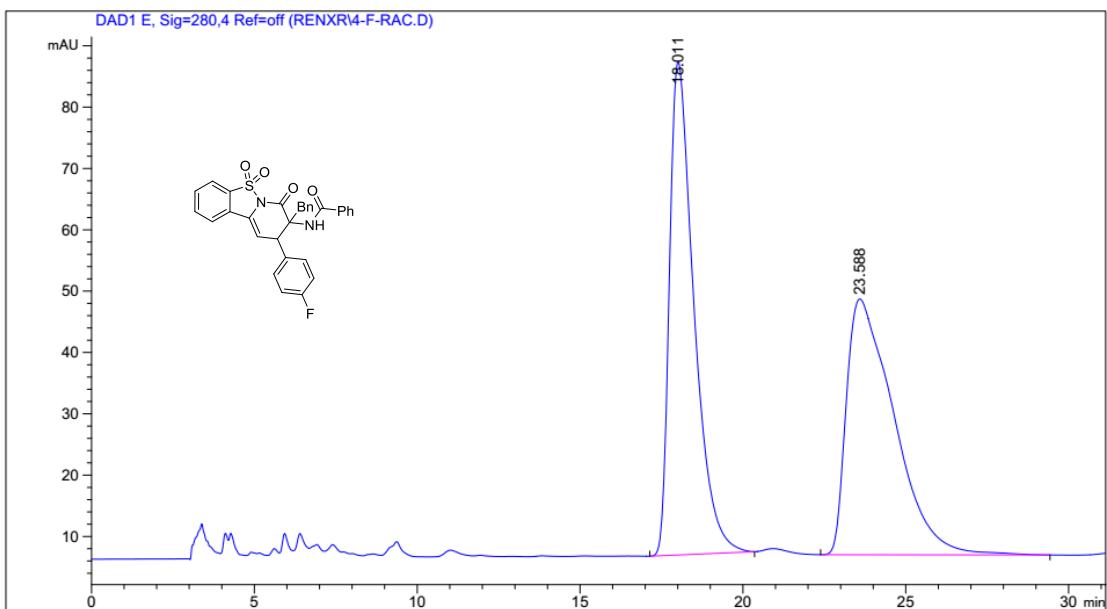


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	25.940	6871.95508	111.22198	49.5086
2	DAD 280,4nm	30.083	7008.37305	76.21506	50.4914

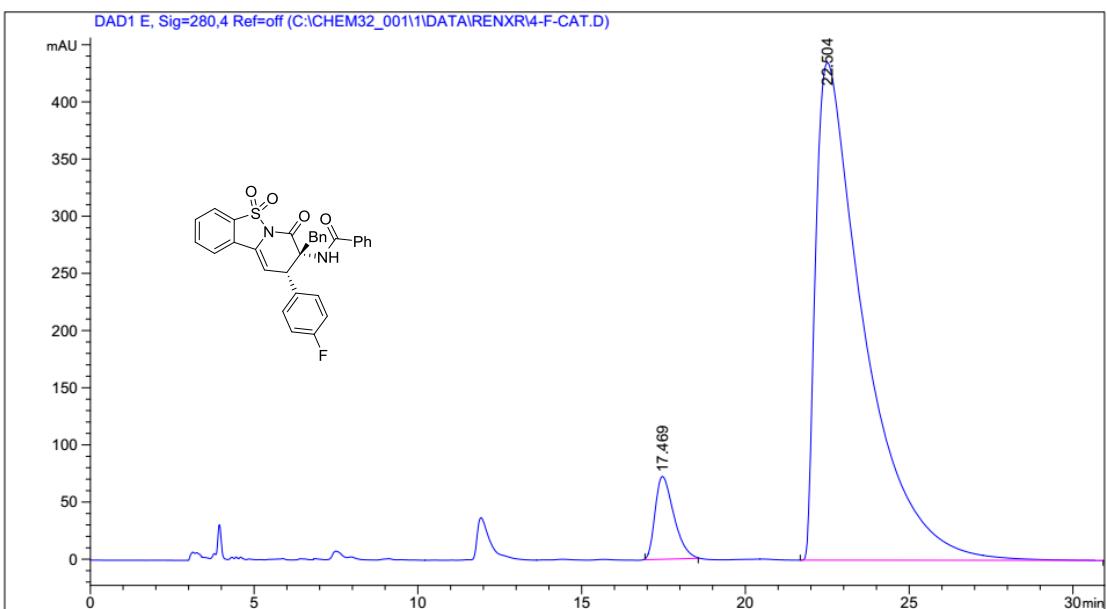


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	28.661	1682.51660	23.55353	4.7419
2	DAD 280,4nm	30.488	3.37998e4	275.67023	95.2581

3ja

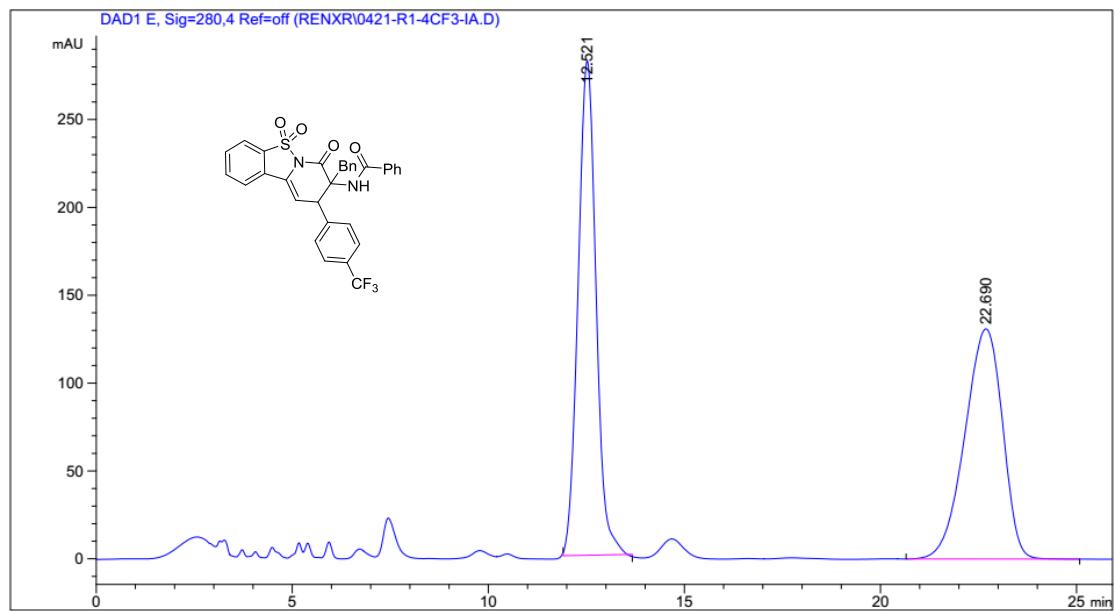


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	18.011	4182.62549	80.41293	49.7133
2	DAD 280,4nm	23.588	4230.87256	41.71724	50.2867

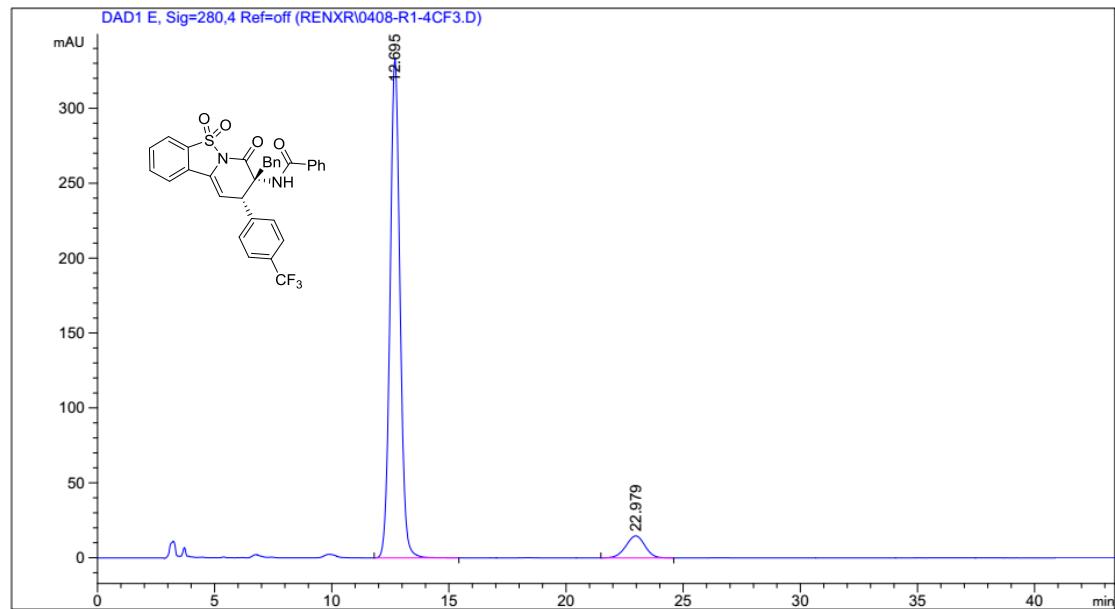


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	17.469	2882.14795	72.44197	6.0948
2	DAD 280,4nm	22.504	4.44066e4	435.05081	93.9052

3ka

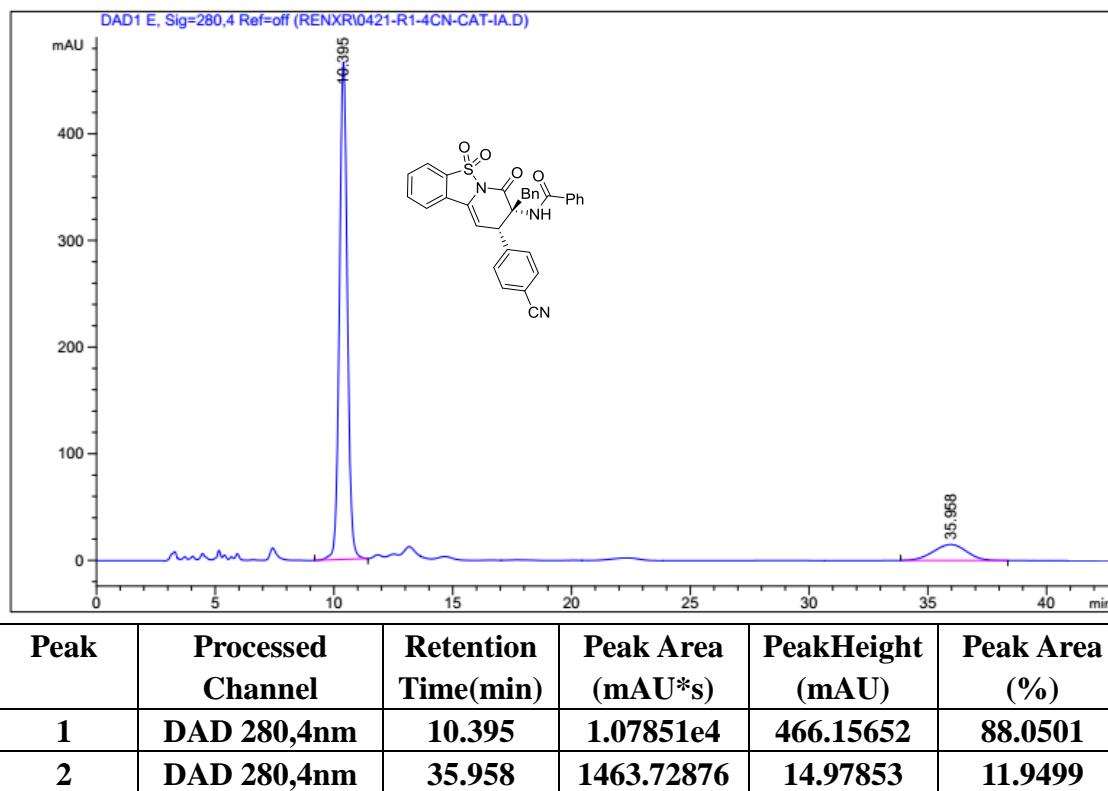
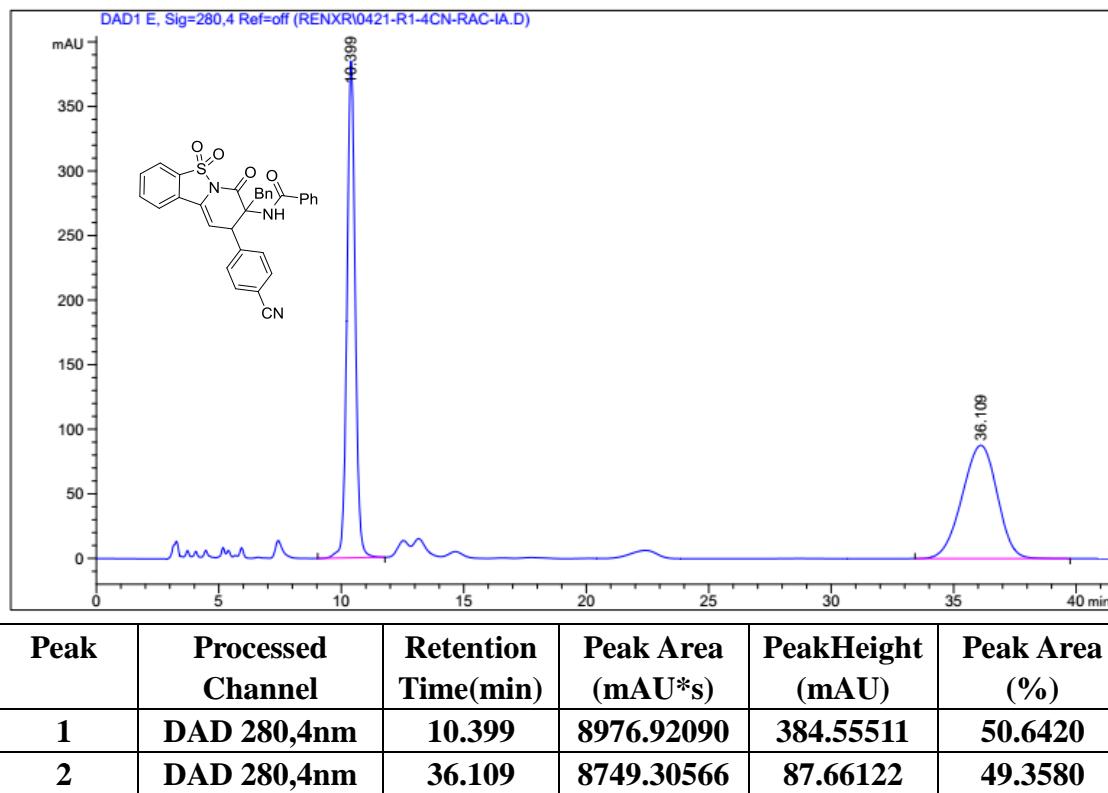


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	12.521	8939.76367	281.38528	50.5255
2	DAD 280,4nm	22.690	8753.81738	130.97723	49.4745

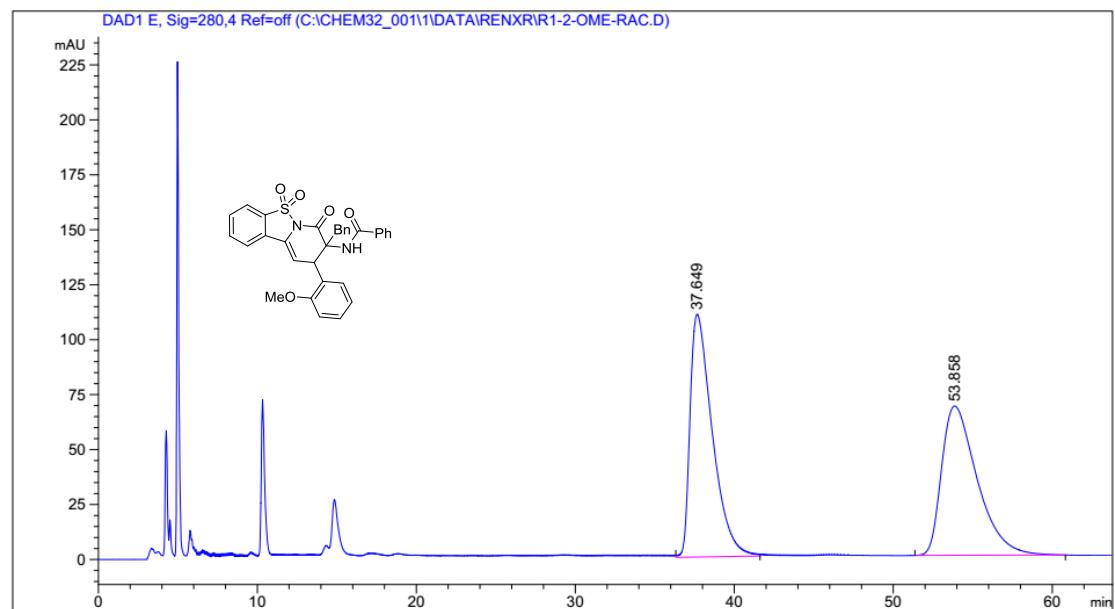


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	12.695	9786.53418	332.93295	92.1796
2	DAD 280,4nm	22.979	830.27289	14.67468	7.8204

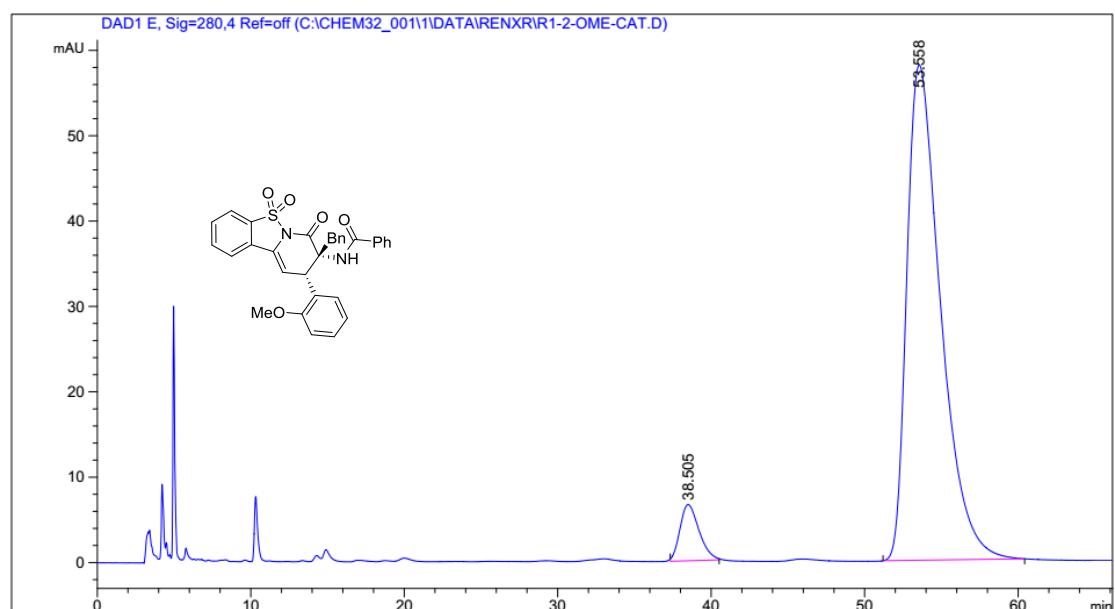
3la



3ma

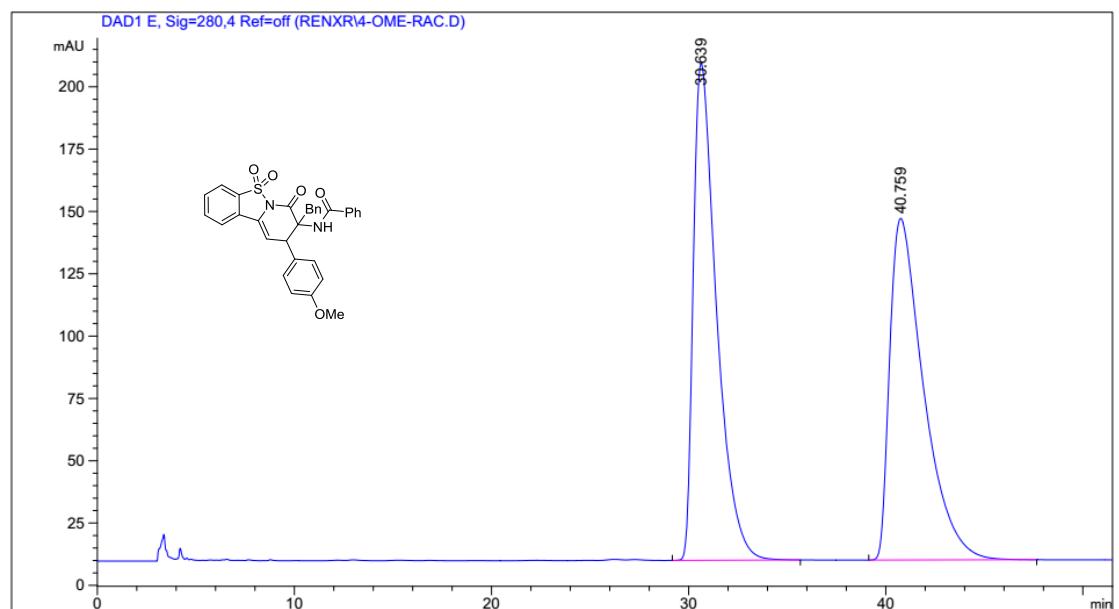


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	37.649	1.07466e4	110.49342	50.4612
2	DAD 280,4nm	53.858	1.05502e4	67.90972	49.5388

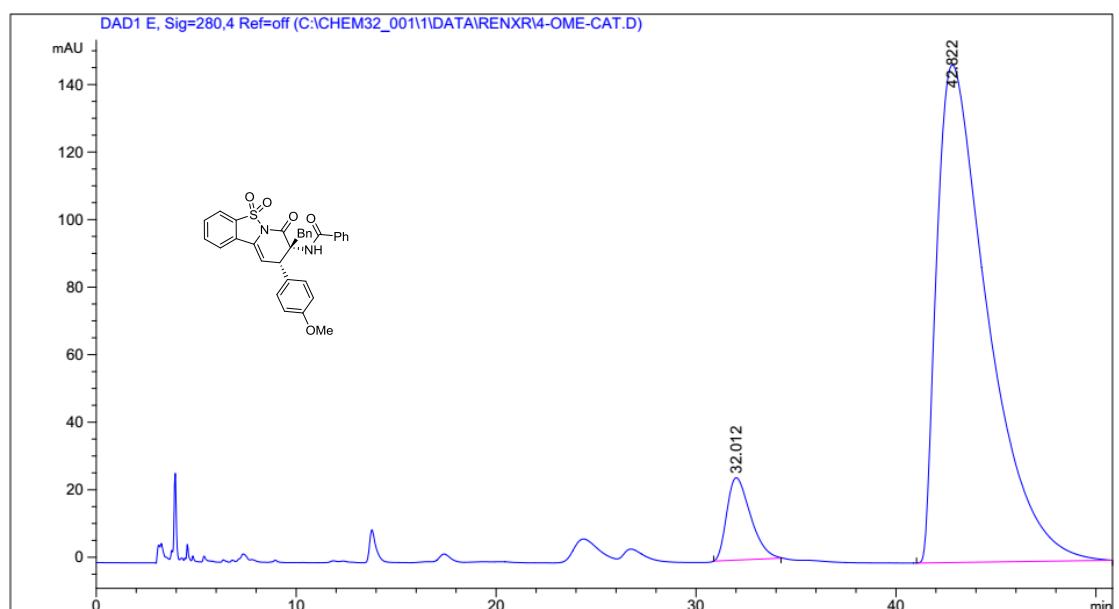


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	38.505	568.51874	6.58195	6.0362
2	DAD 280,4nm	53.558	8850.00293	58.00994	93.9638

3na

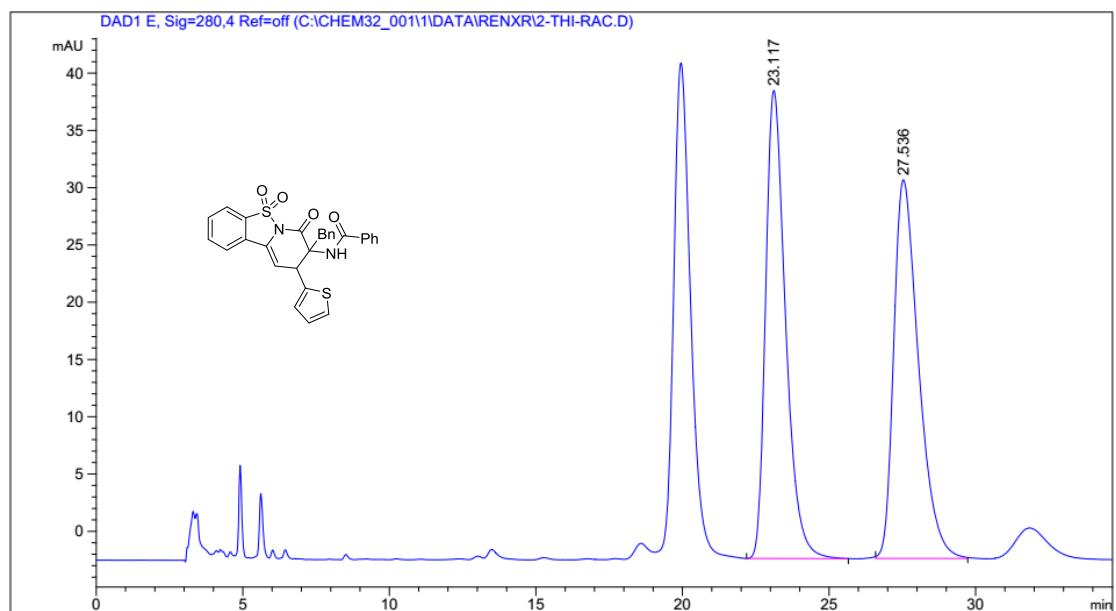


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	30.639	1.63203e4	199.49008	49.9529
2	DAD 280,4nm	40.759	1.63511e4	137.02501	50.0471

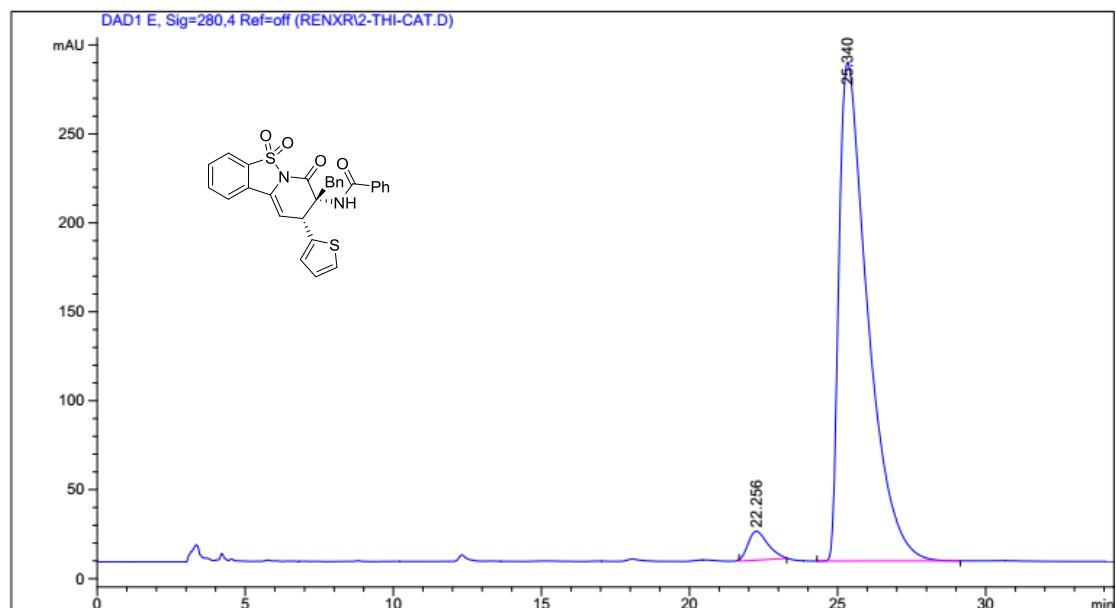


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	32.012	2007.73816	24.38774	7.1669
2	DAD 280,4nm	42.822	2.60065e4	147.34763	92.8331

3oa

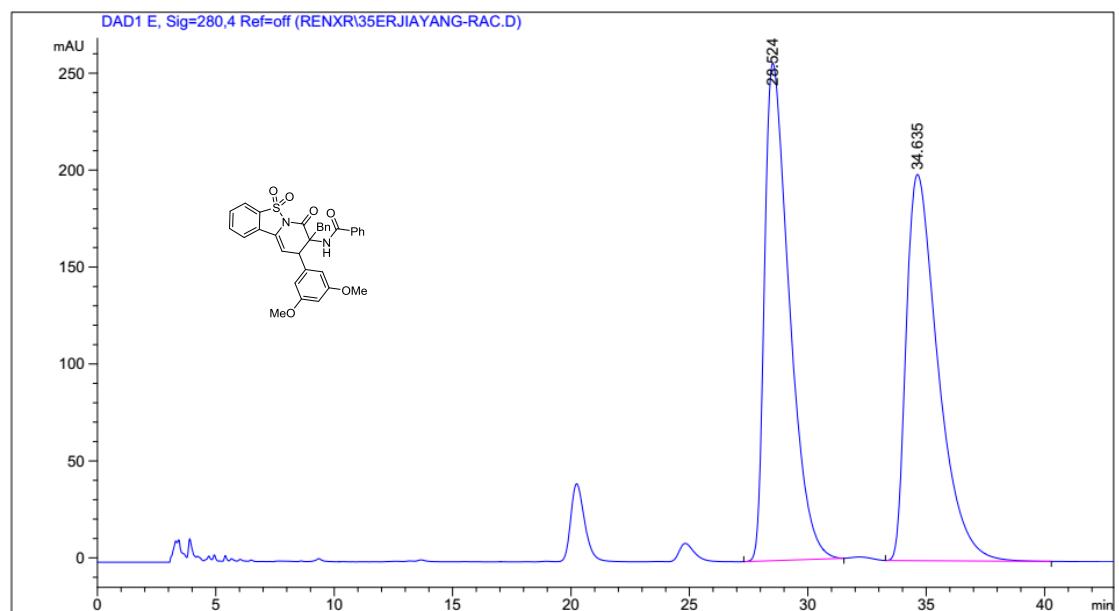


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	23.117	1922.94446	40.87045	49.7997
2	DAD 280,4nm	27.536	1938.41663	33.05637	50.2003

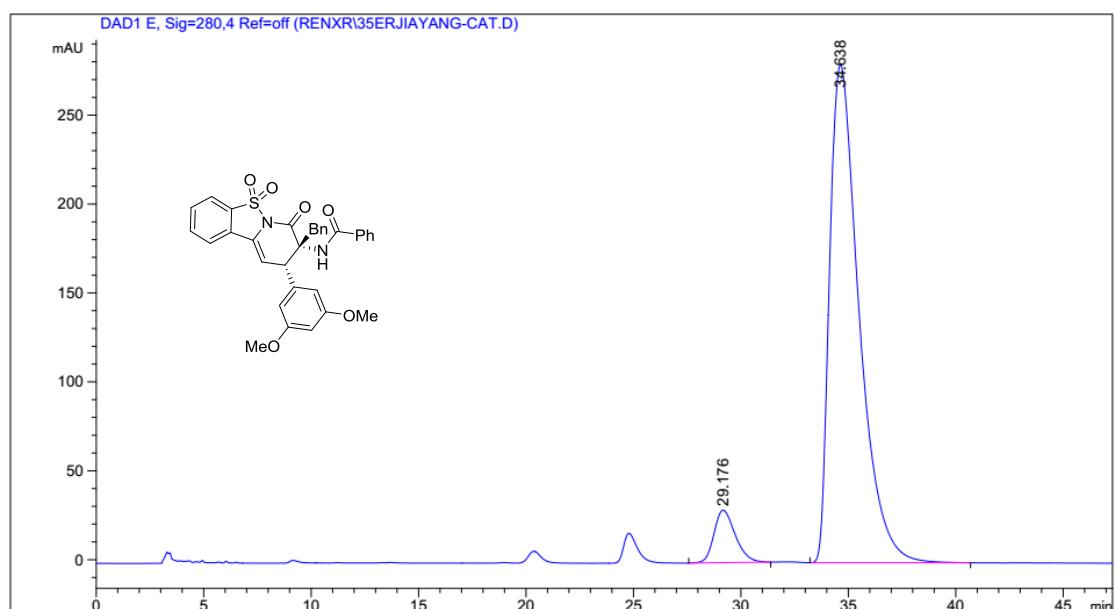


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	22.256	751.70264	16.22500	3.8346
2	DAD 280,4nm	25.340	1.88514e4	280.31644	96.1654

3pa

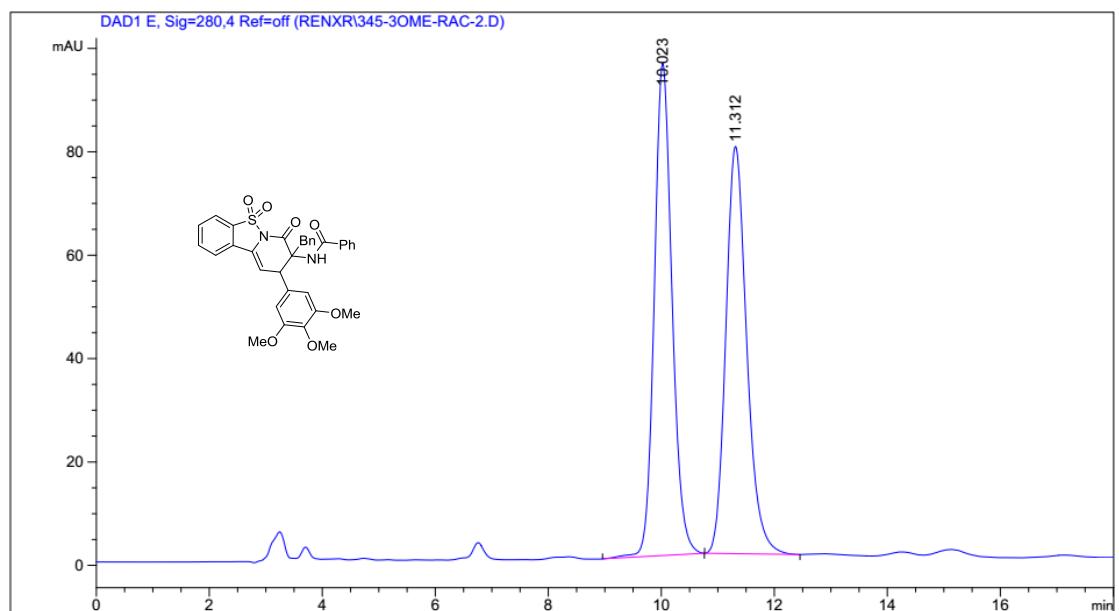


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	28.524	1.86076e4	256.66373	49.9973
2	DAD 280,4nm	34.635	1.86096e4	199.20345	50.0027

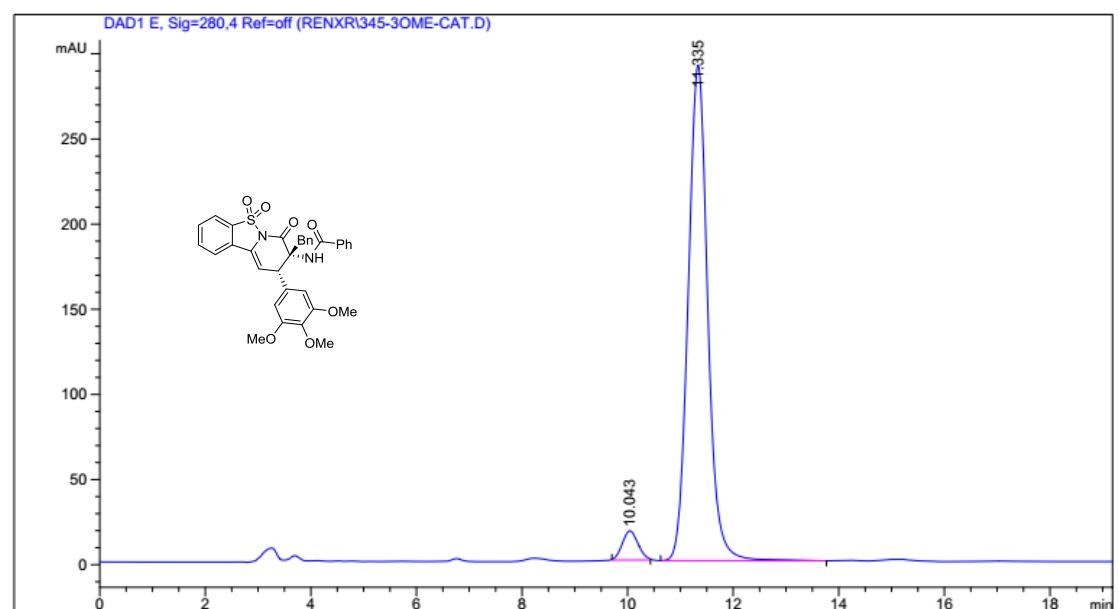


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	29.176	2024.39075	29.47186	7.0567
2	DAD 280,4nm	34.638	2.66633e4	279.92307	92.9433

3qa

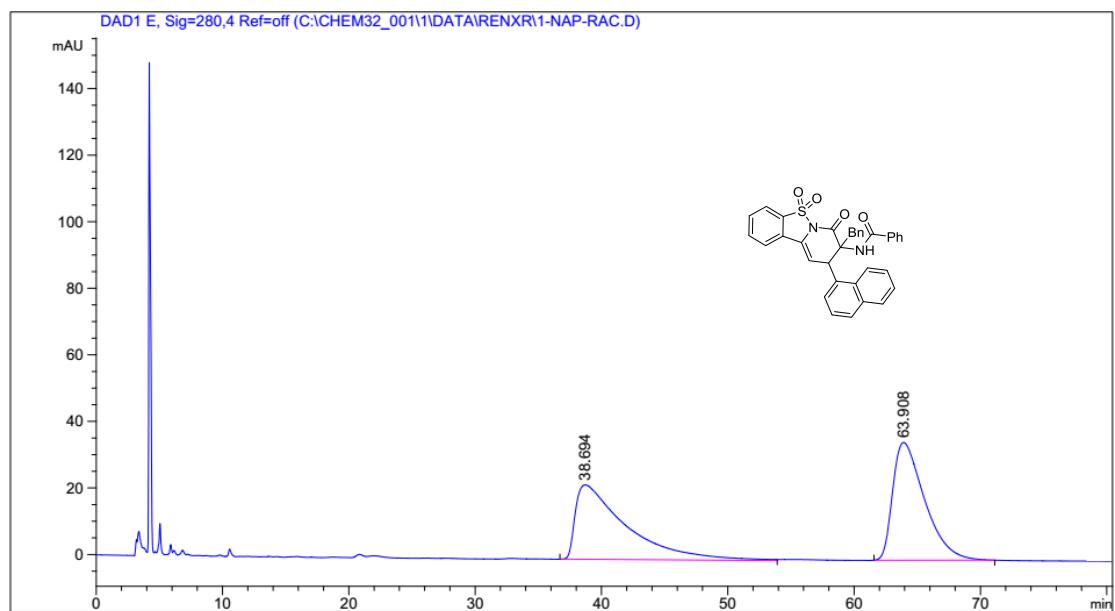


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	10.023	2074.41650	95.28205	50.6401
2	DAD 280,4nm	11.312	2021.97607	78.78347	49.3599

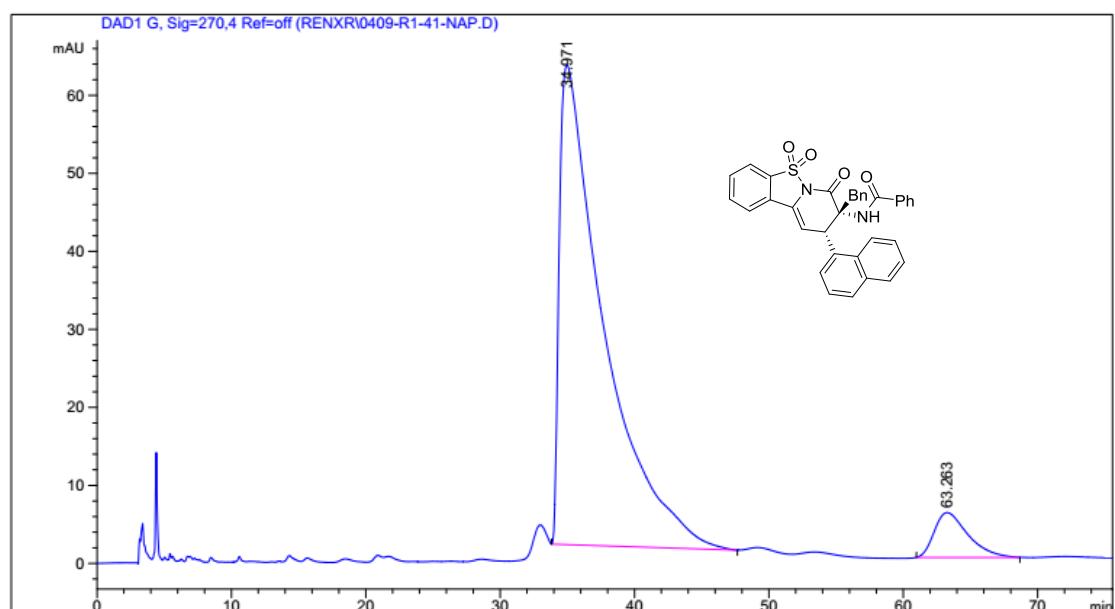


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	10.043	354.03128	17.12081	4.5265
2	DAD 280,4nm	11.335	7467.35645	290.99557	95.4735

3ra

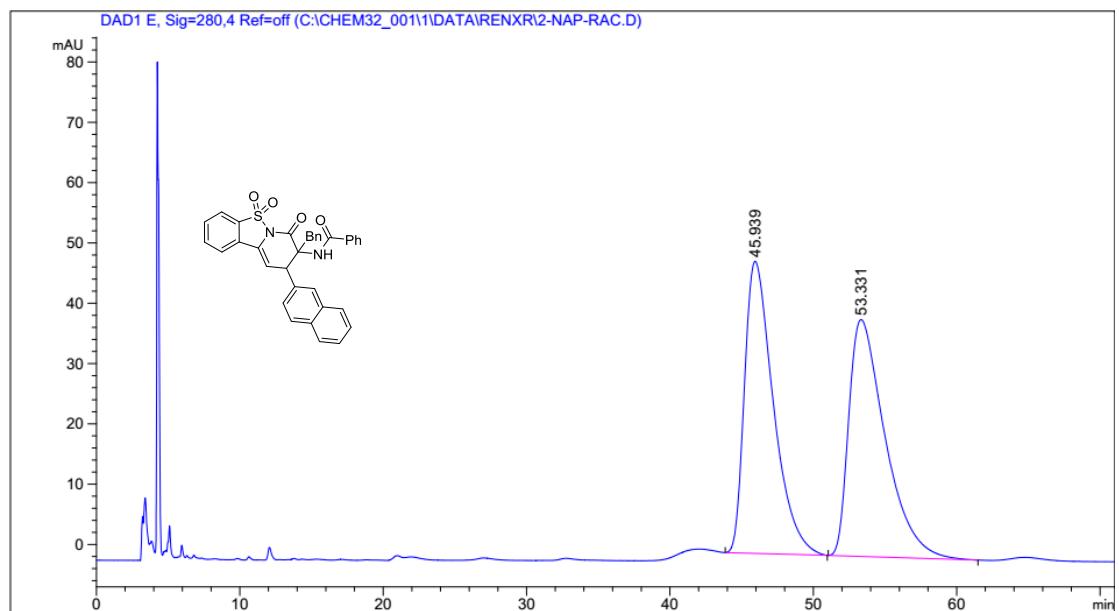


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	38.694	6239.47705	22.35515	50.1291
2	DAD 280,4nm	63.908	6207.34521	35.36945	49.8709

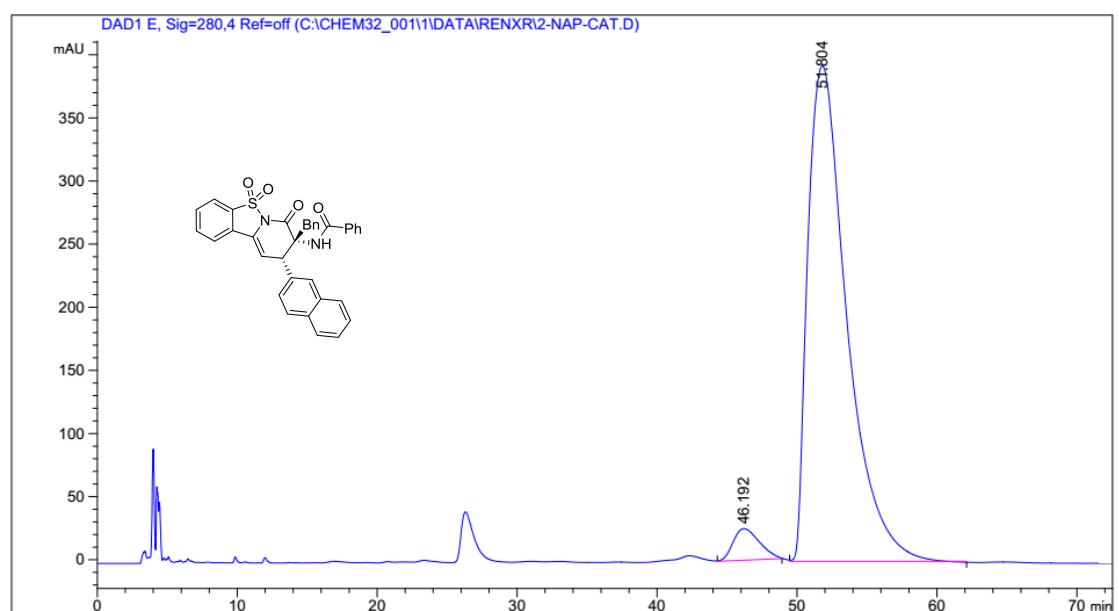


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	34.971	1.40508e4	61.44172	93.3211
2	DAD 280,4nm	63.263	1005.60724	5.75503	6.6789

3sa

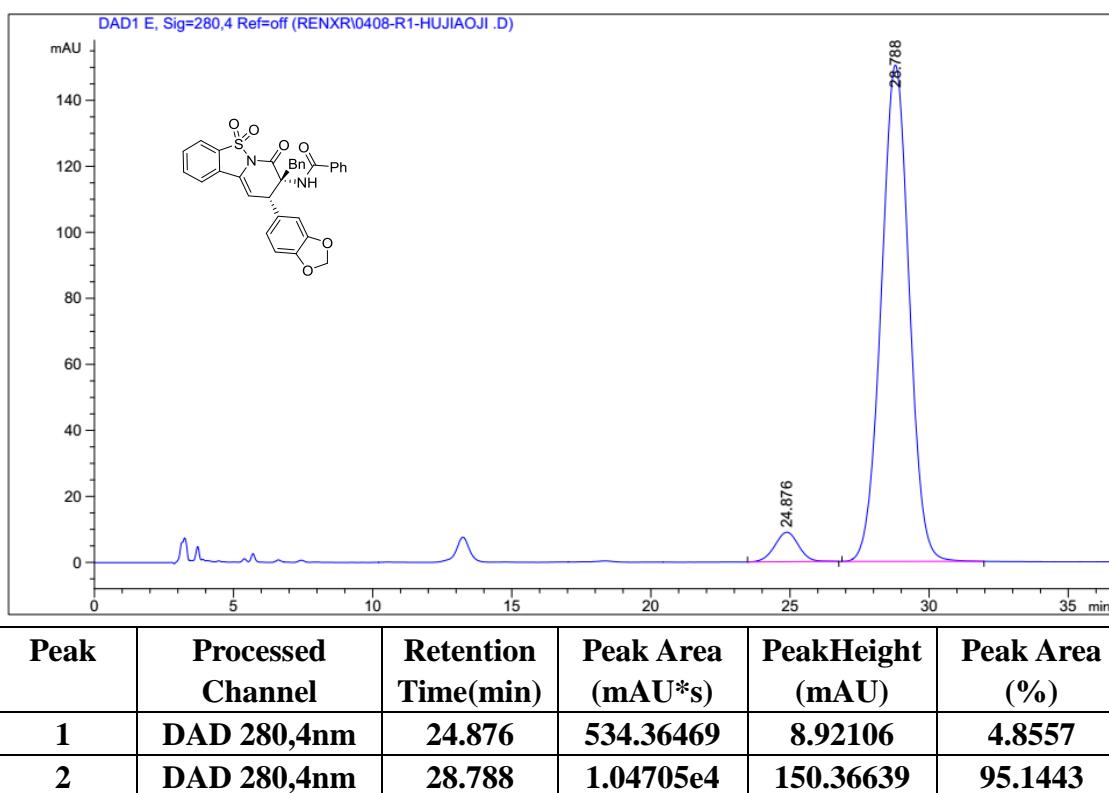
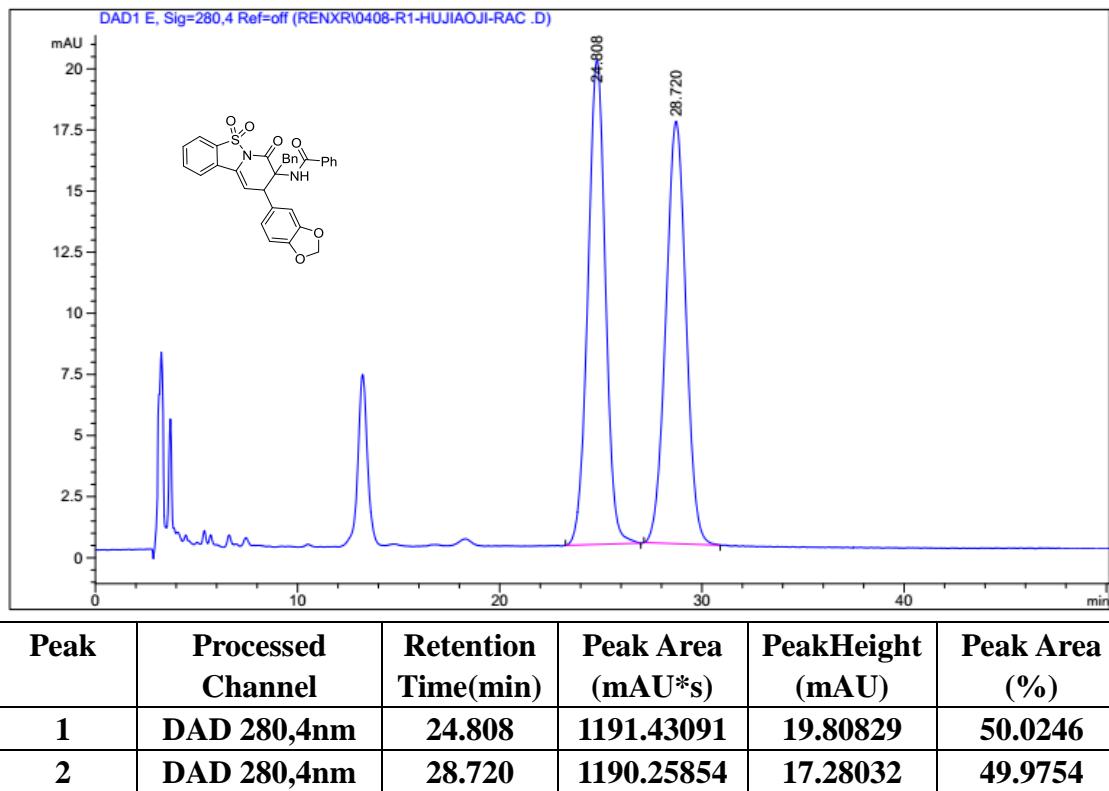


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	45.939	6765.58105	48.43176	49.5157
2	DAD 280,4nm	53.331	6897.93115	39.27061	50.4843

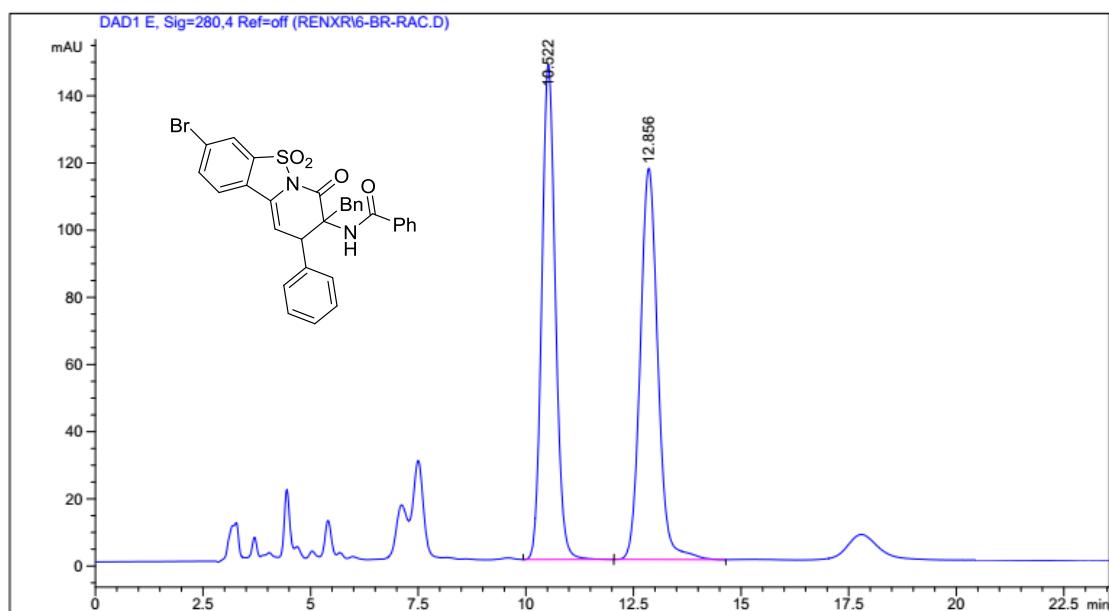


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	46.192	3257.75781	24.98763	4.1139
2	DAD 280,4nm	51.804	7.59313e4	392.57556	95.8861

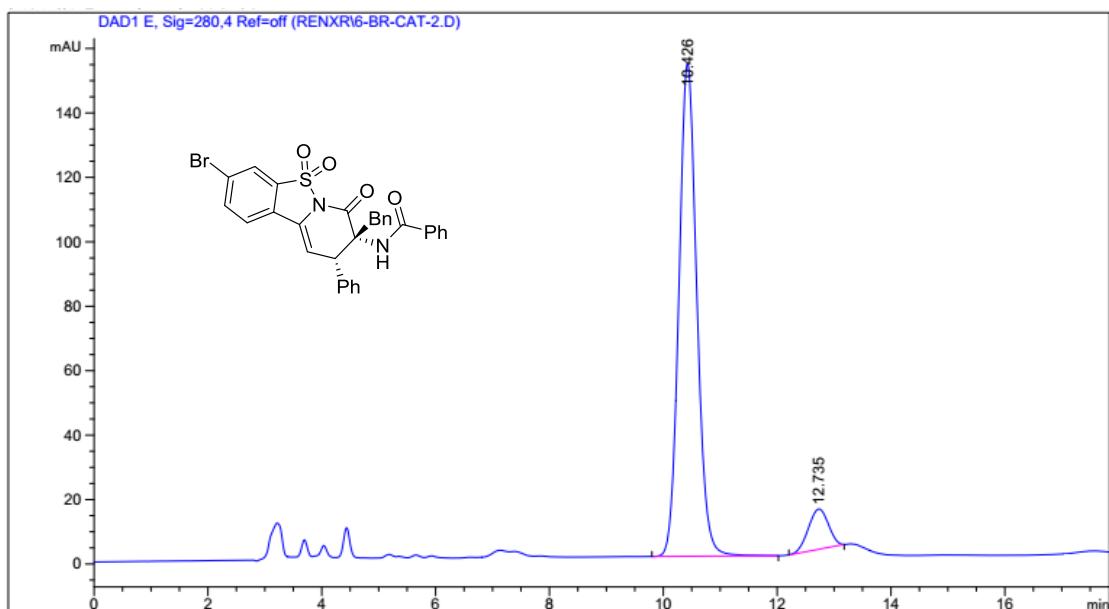
3ta



3ua

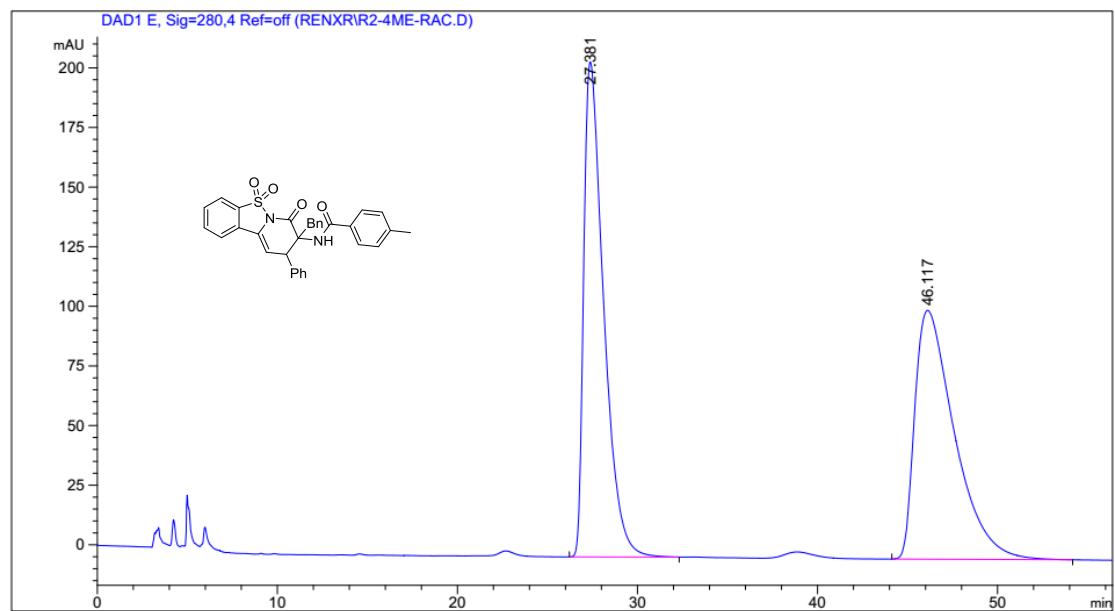


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	10.522	3228.31812	147.47612	49.5115
2	DAD 280,4nm	12.856	3292.02100	116.52240	50.4885

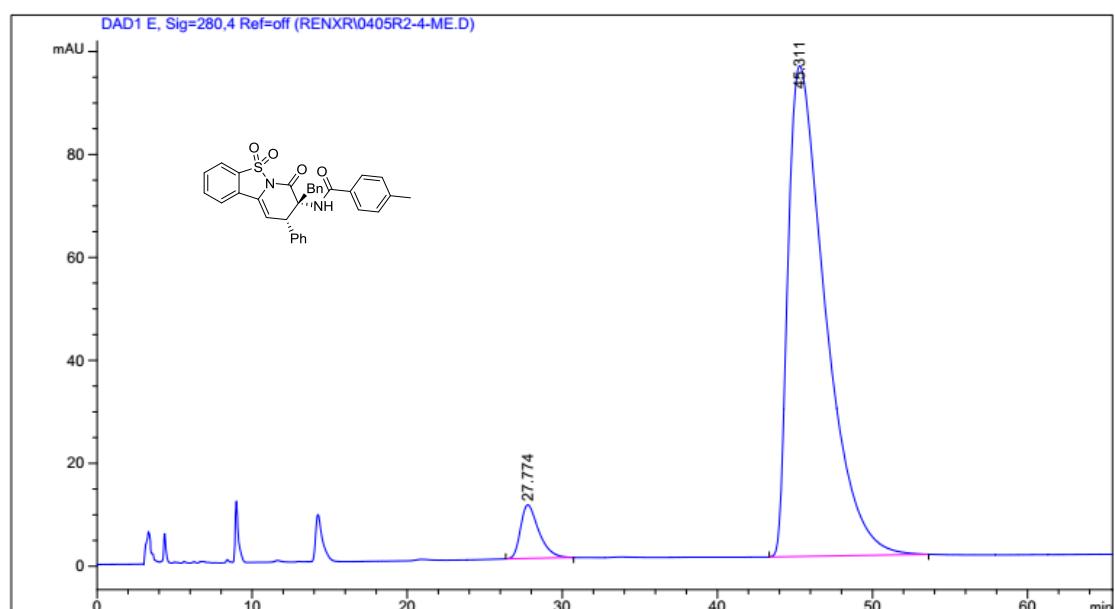


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	10.426	3329.45630	152.94992	91.6063
2	DAD 280,4nm	12.735	305.07315	12.48556	8.3937

3ab

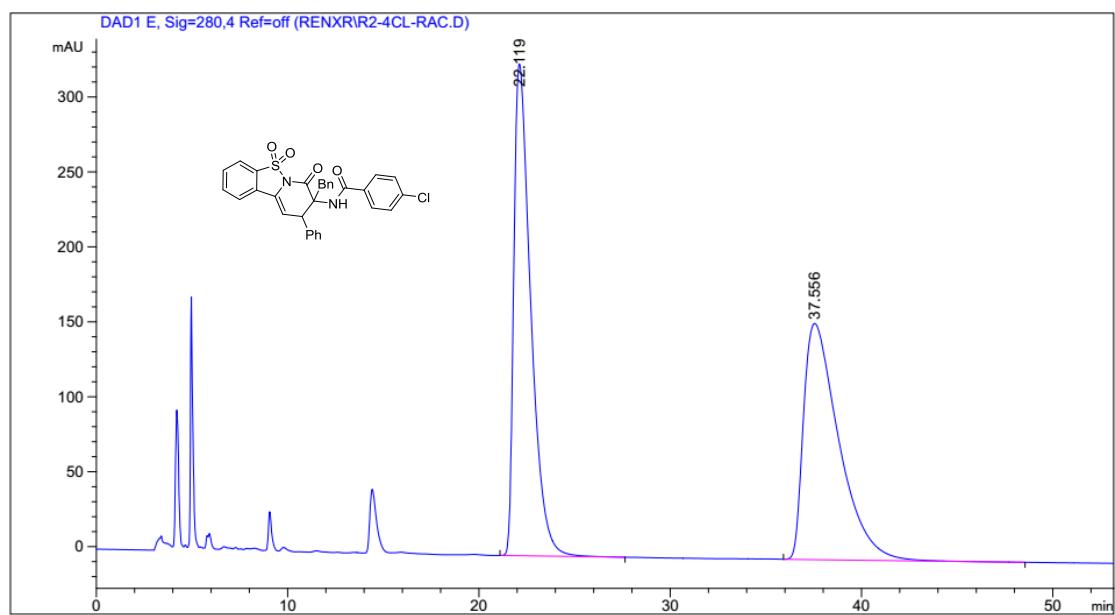


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	27.381	1.59060e4	207.56673	49.9435
2	DAD 280,4nm	46.117	1.59420e4	104.35244	50.0565

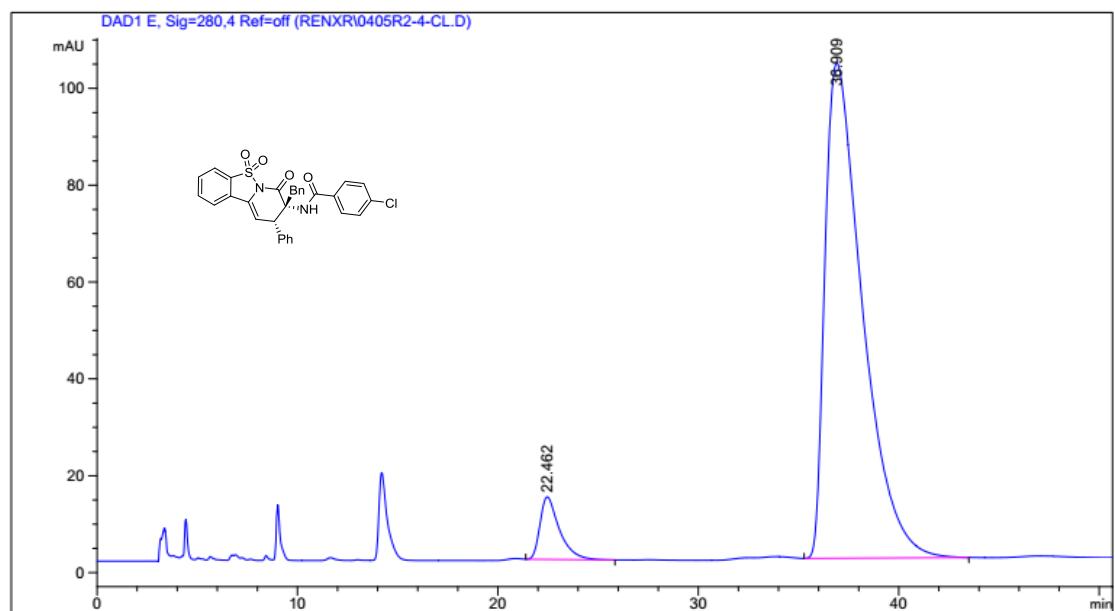


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	27.774	852.71924	10.39601	5.1094
2	DAD 280,4nm	45.311	1.58364e4	95.31211	94.8906

3ac

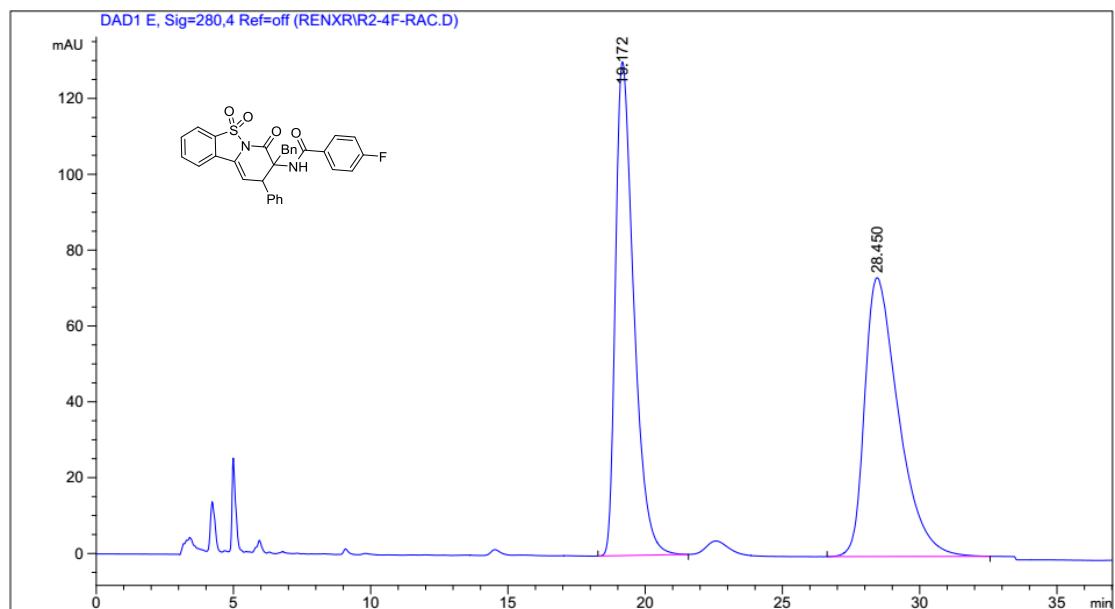


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	22.119	2.01633e4	328.11826	49.9808
2	DAD 280,4nm	37.556	2.01788e4	157.54744	50.0192

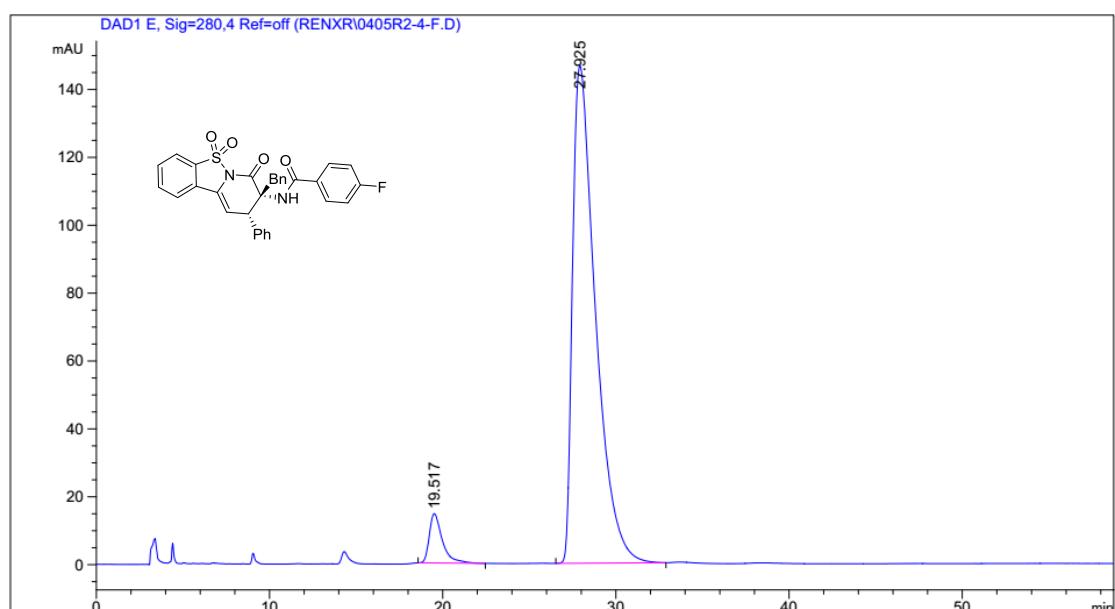


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	22.462	867.33453	12.90907	6.1427
2	DAD 280,4nm	36.909	1.32525e4	102.22998	93.8573

3ad

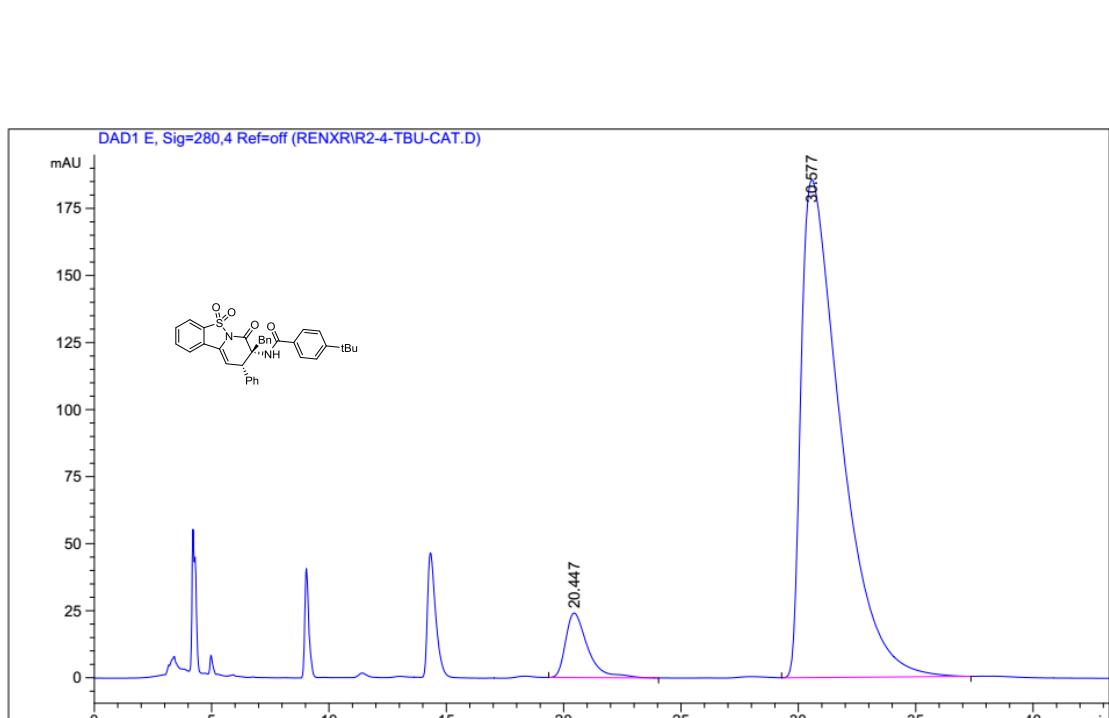
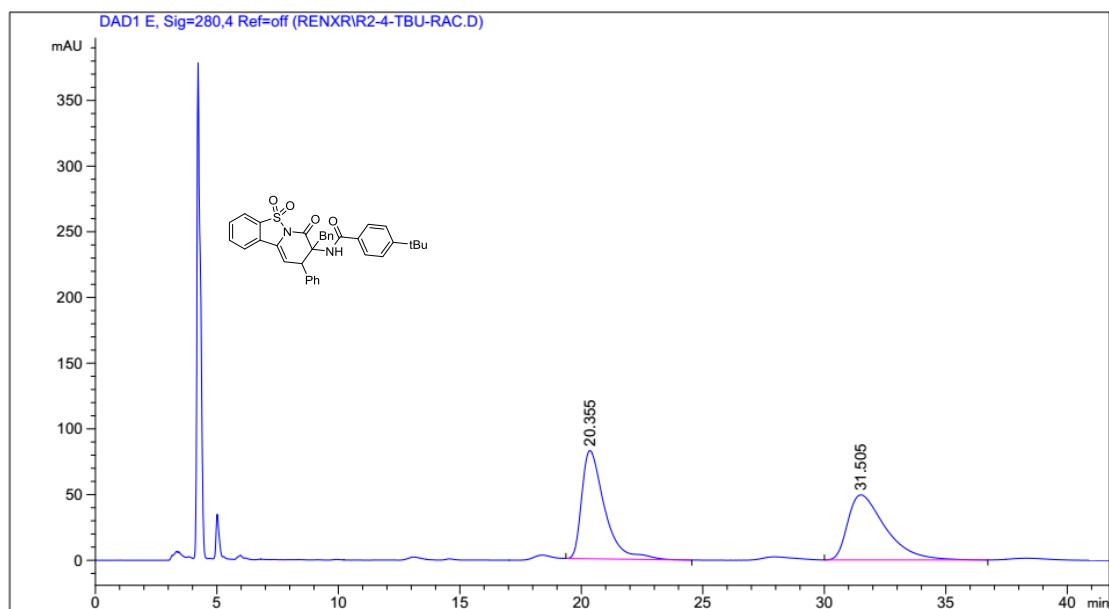


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	19.172	6025.26465	130.23244	48.8319
2	DAD 280,4nm	28.450	6313.52637	73.53452	51.1681

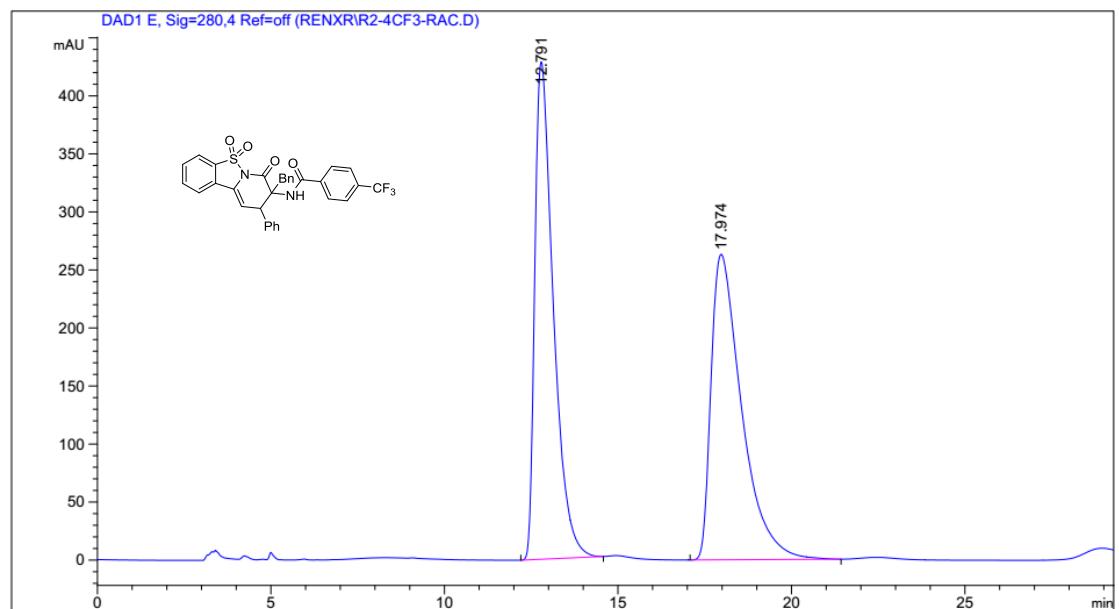


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	19.517	759.27161	14.52846	5.3421
2	DAD 280,4nm	27.925	1.34538e4	146.52672	94.6579

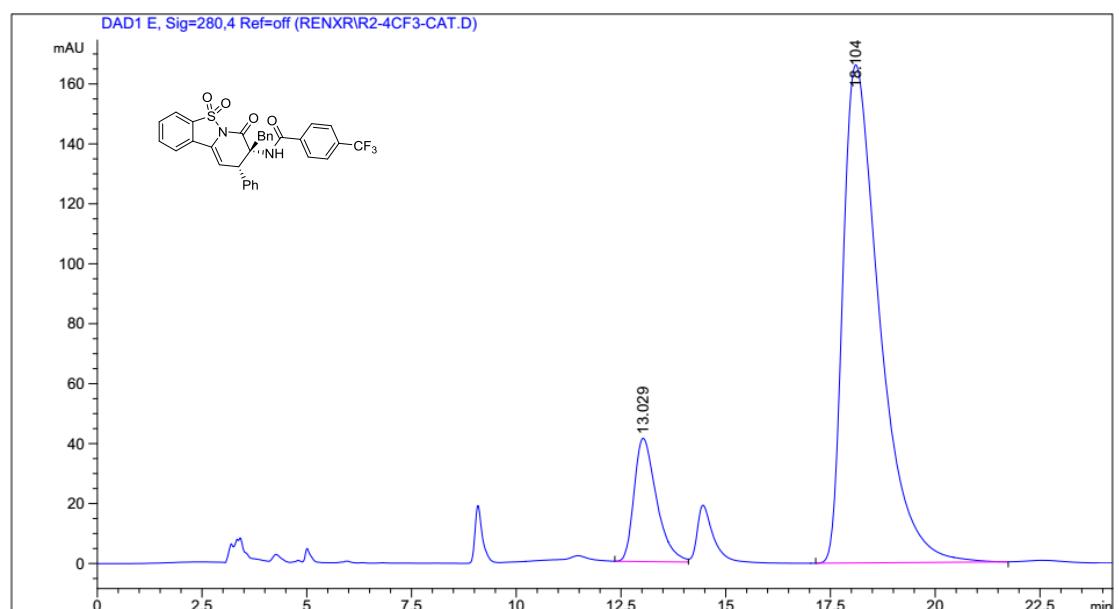
3ae



3af

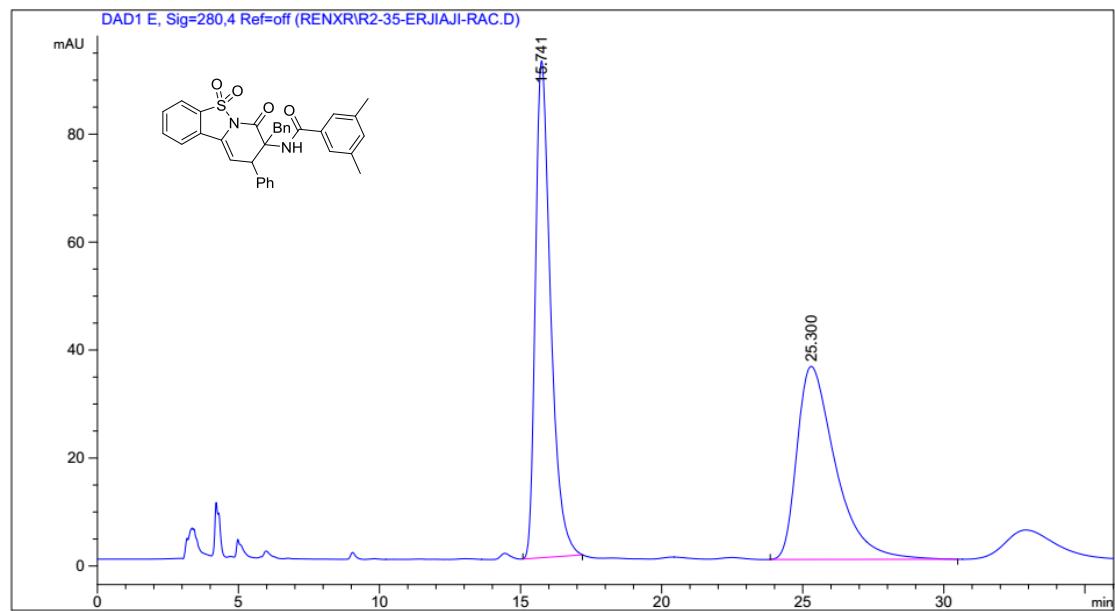


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	12.791	1.58305e4	428.54779	49.5611
2	DAD 280,4nm	17.974	1.61109e4	263.23816	50.4389

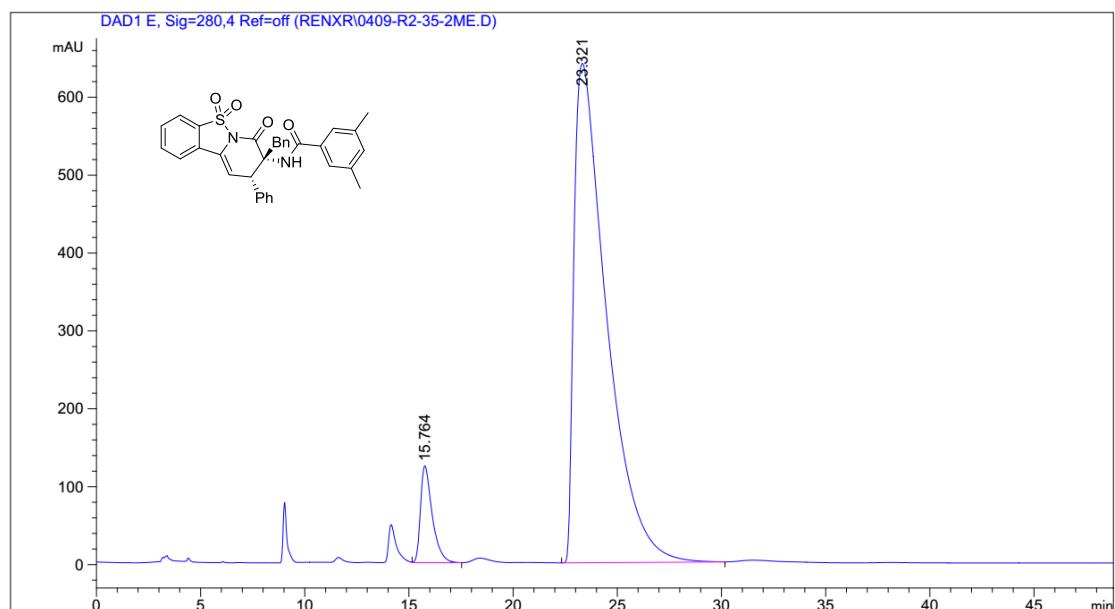


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	13.029	1527.36414	41.15207	13.1845
2	DAD 280,4nm	18.104	1.00572e4	166.20166	86.8155

3ag

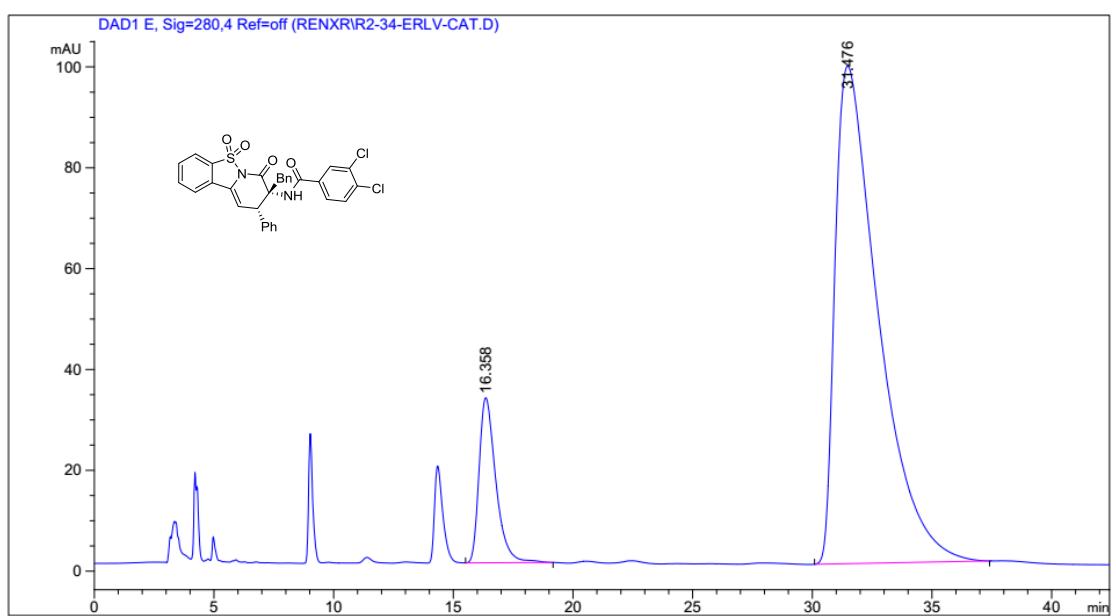
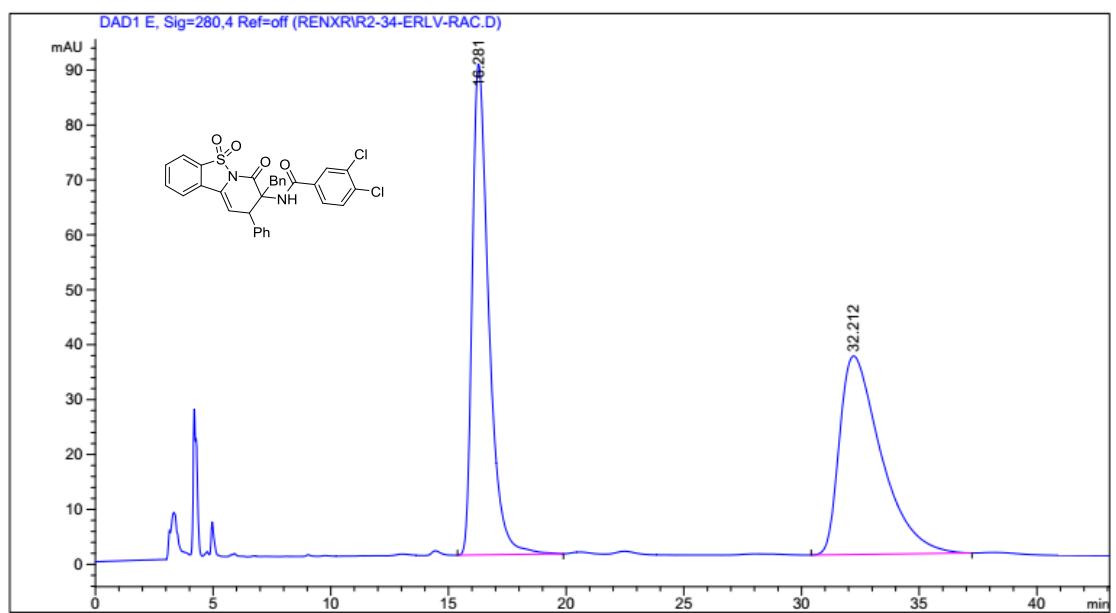


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	15.741	3454.99609	92.03073	50.5048
2	DAD 280,4nm	25.300	3385.93506	35.75331	49.4952



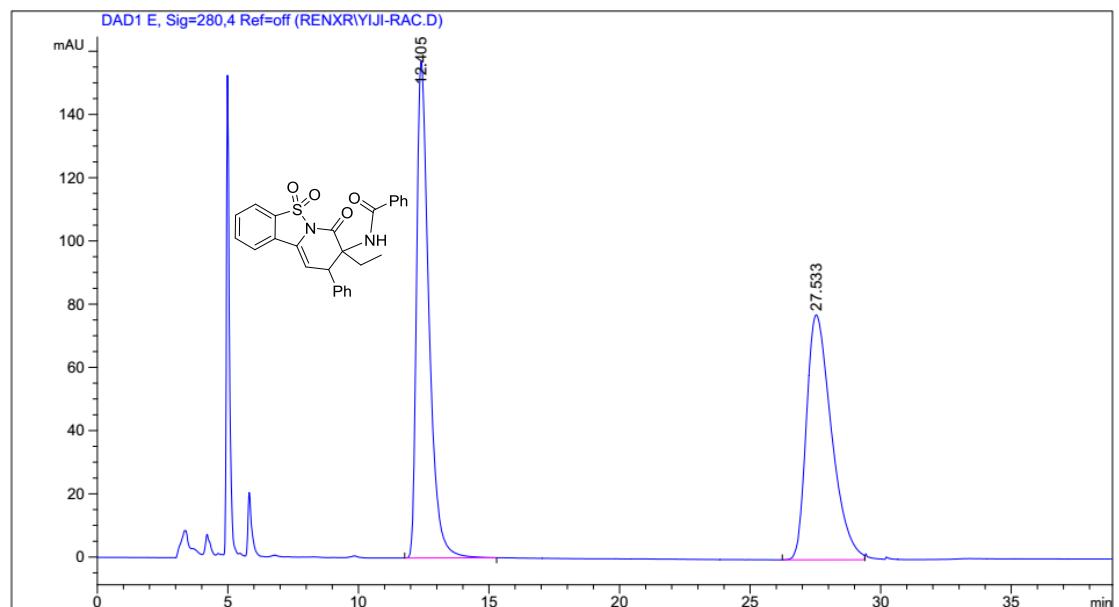
Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	15.764	4851.64551	124.27473	6.5225
2	DAD 280,4nm	23.321	6.95310e4	641.10840	93.4775

3ah

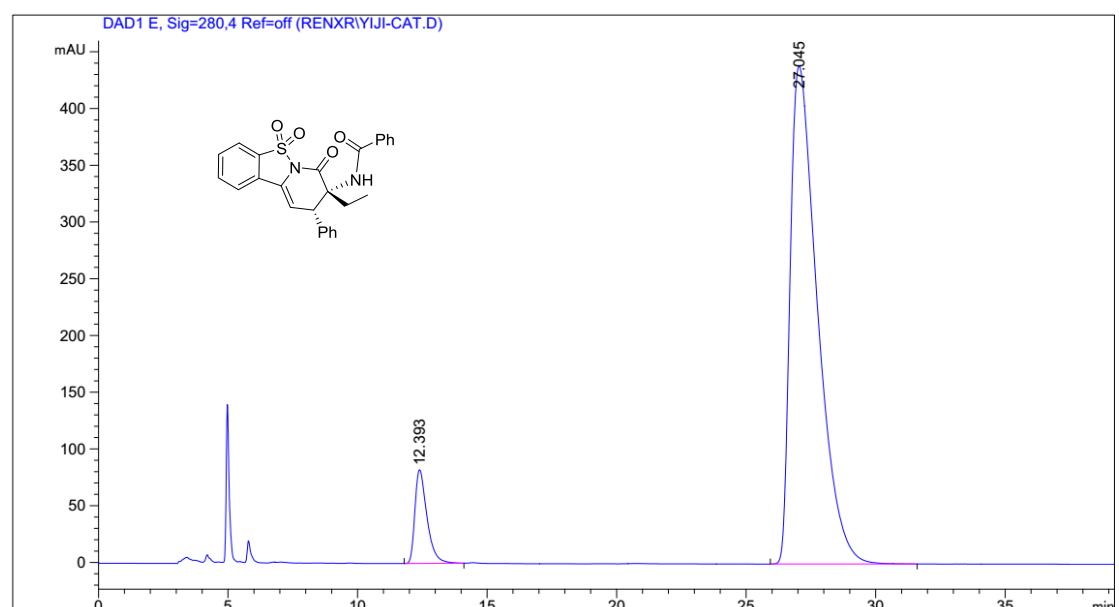


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	16.358	1592.76489	32.73678	11.4145
2	DAD 280,4nm	31.476	1.23611e4	98.67574	88.5855

3ai

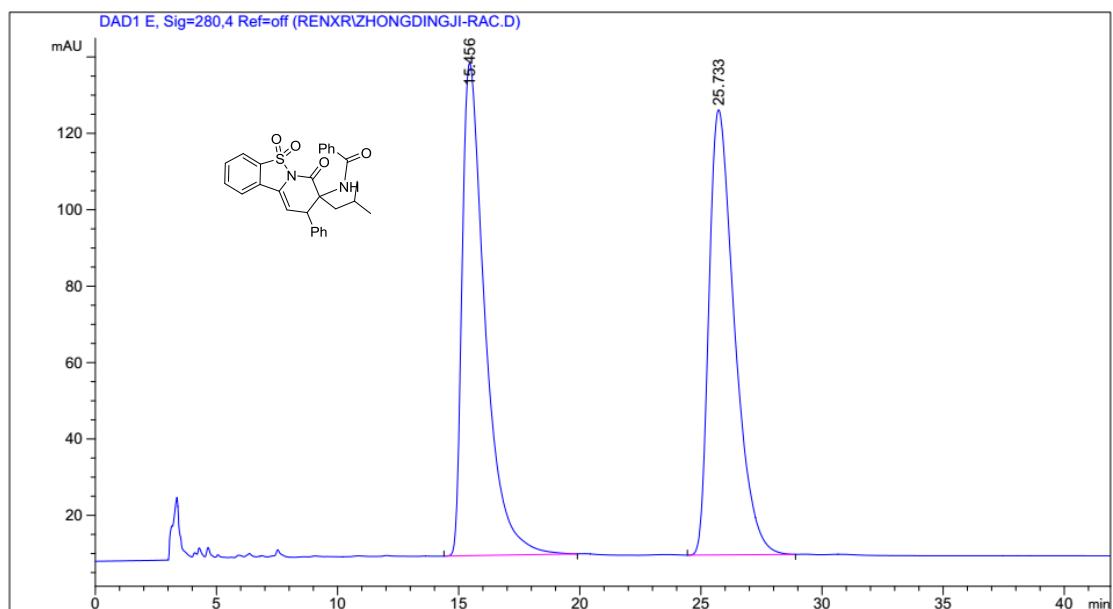


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	12.405	5161.64795	156.93698	50.0551
2	DAD 280,4nm	27.533	5150.28955	77.43819	49.9449

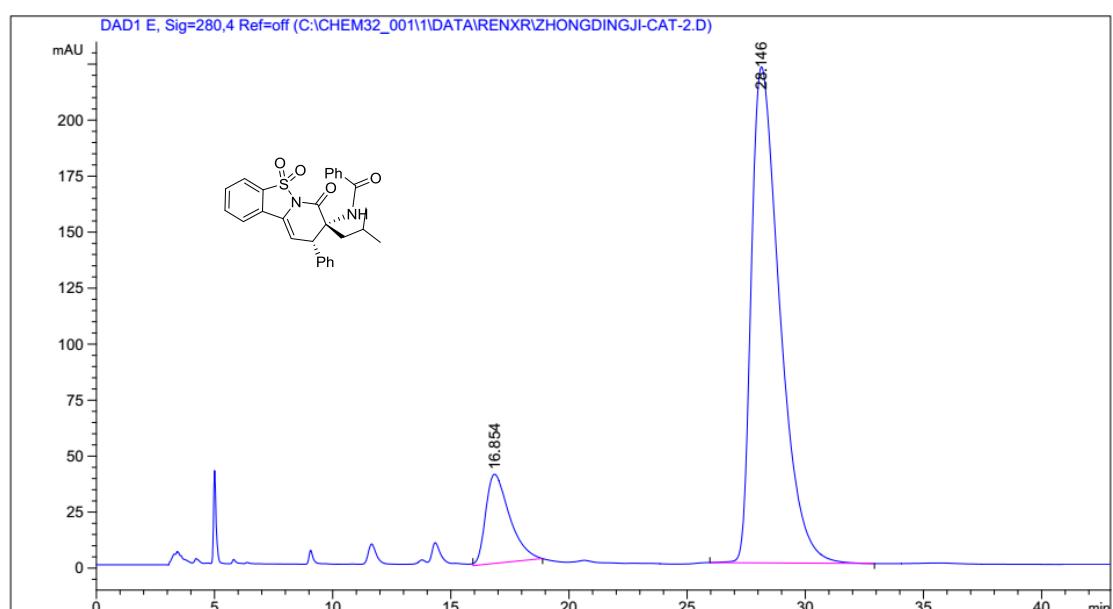


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	12.393	2665.35254	82.52624	7.7077
2	DAD 280,4nm	27.045	3.19149e4	439.01831	92.2923

3aj

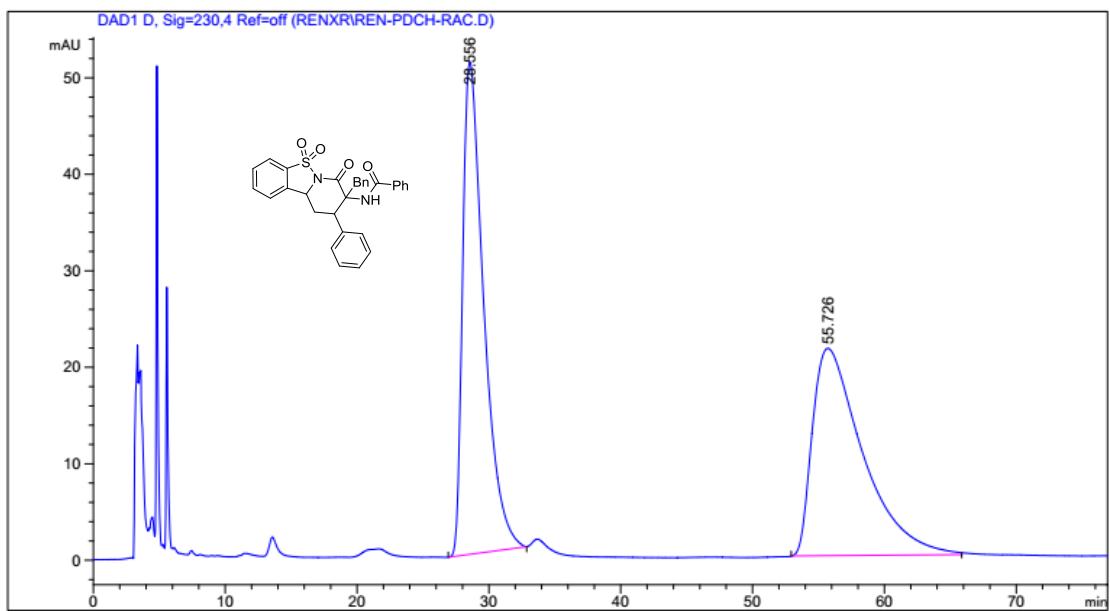


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	15.456	8472.29004	129.00008	49.8400
2	DAD 280,4nm	25.733	8526.69727	116.54206	50.1600

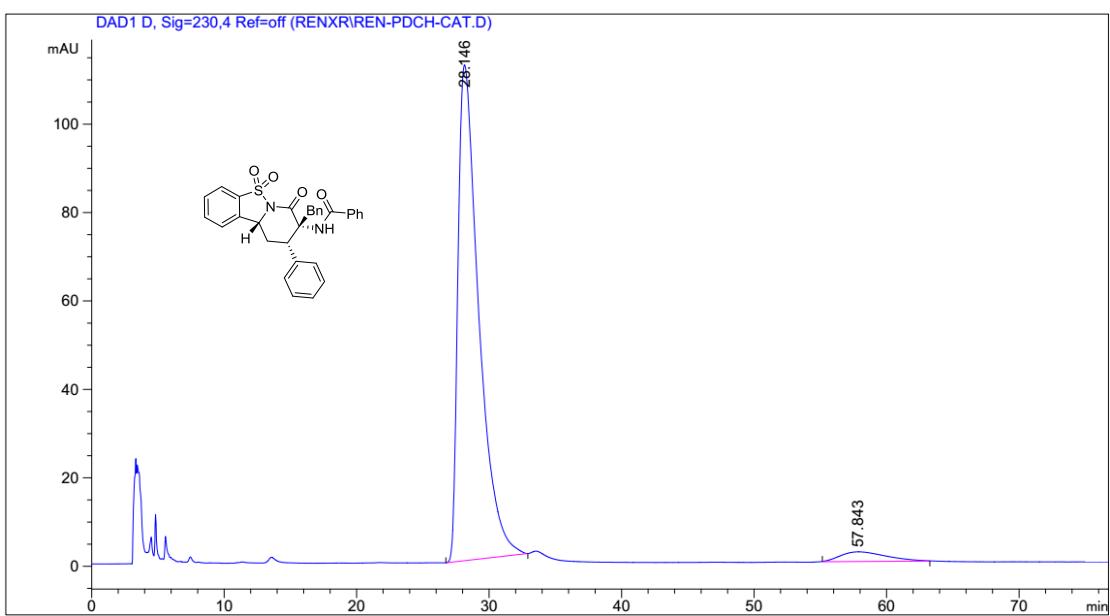


Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 280,4nm	16.854	2787.08423	39.81051	13.0775
2	DAD 280,4nm	28.146	1.85249e4	221.45209	86.9225

4aa



Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 230,4nm	28.556	5665.26465	51.00072	49.8691
2	DAD 230,4nm	55.726	5695.01465	21.48969	50.1309



Peak	Processed Channel	Retention Time(min)	Peak Area (mAU*s)	PeakHeight (mAU)	Peak Area (%)
1	DAD 230,4nm	28.146	1.21621e4	112.13569	95.8904
2	DAD 230,4nm	57.843	521.23407	2.18615	4.1096