Enantioselective construction of quaternary stereocenters via organocatalytic arylation of isoxazolin-5-ones with *o*-quinone diimides

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Experimental Procedures

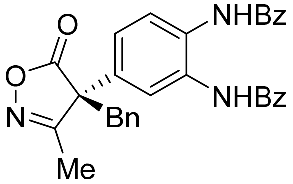
Materials and methods

All reagents were purchased from commercial suppliers and used without further purification. All solvents employed in the reactions were distilled from appropriate drying agents prior to use. Reactions were monitored by TLC analysis using Merck Silica Gel 60 F-254 thin layer plates. Flash column chromatography was performed on Merck silica gel 60, 0.040-0.063 mm. Melting points were determined in capillary tubes. NMR spectra were run at 300 MHz for 1H and at 75 MHz for 13C NMR using residual nondeuterated solvent (CHCl3) as internal standard (δ 7.26 and 77.0 ppm, respectively). Chemical shifts are given in ppm. The carbon type was determined by DEPT experiments. High resolution mass spectra (ESI) were recorded on a Q-TOF spectrometer equipped with an electrospray source with a capillary voltage of 3.3 kV (ESI). Specific optical rotations were measured using sodium light (D line 589 nm). Chiral HPLC analyses were performed in a chromatograph equipped with a UV diode-array detector using chiral stationary phase columns from Daicel or Phenomenex. Isoxazolinones **1**[1] and quinone diimides **2**[2] were prepared according to literature procedures.

General procedure for the enantioselective arylation of isoxazolin-5-ones 1 with quinone diimides 2.

Isoxazolin-5-one **1** (0.11 mmol, 1.1 eq), diimide **2** (0.10 mmol, 1 eq), and squaramide **SQ-3** (6.0 mg, 0.01 mmol) were introduced in a round bottom flask. Dichloromethane (10 mL) was added, and the mixture was stirred at – 20 ºC until completion (TLC). After this time, the reaction mixture was directly chromatographed on silica gel eluting with hexane:EtOAc mixtures to give compound **3**.

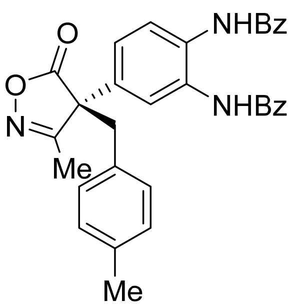
(*R*)-*N,N′*-(4-(4-Benzyl-3-methyl-5-oxo-4,5-dihydroisoxazol-4-yl)-1,2-phenylene)dibenzamide (3aa)



46.4 mg (92%) of **3aa** were obtained from **1a** (19.5 mg) and **2a** (31.4 mg). The enantiomeric excess (93%) was determined using chiral HPLC (Lux i-Amylose-1), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 27.1 min, minor enantiomer: t_r = 53.3 min.

White solid; **m.p.** 111.2-114.0 ºC; **[*α*]$_D^{25}$** -48.5 (*c* 0.27, $CHCl_3$); **^{1}H NMR** (300 MHz, DMSO-*d*$_6$) *δ* 10.24 (1H, s, NH), 10.14 (1H, s, NH), 8.00-7.95 (4H, m, Ar), 7.88 (1H, d, *J* = 8.7 Hz, Ar), 7.67 (1H, d, *J* = 2.4 Hz, Ar), 7.61-7.50 (6H, m, Ar), 7.42-7.25 (6H, m, Ar), 3.78 (1H, d, *J* = 13.5 Hz, CH-Ph), 3.61 (1H, d, *J* = 13.5 Hz, CH-Ph), 2.13 (3H, s, Me); **^{13}C NMR** (75 MHz, DMSO-*d*$_6$) *δ* 178.7 (C), 168.9 (C), 165.8 (C), 165.5 (C), 134.1 (C), 134.0 (C), 133.9 (C), 132.0 (C), 132.03 (C), 131.9 (CH), 131.8 (CH), 130.6 (C), 129.50 (CH), 128.63 (CH), 128.63 (CH), 128.58 (CH), 127.69 (CH), 127.68 (CH), 127.6 (CH), 126.7 (CH), 123.9 (CH), 123.6 (CH), 61.1 (C), 37.5 (CH_2), 12.6 (CH_3); **HRMS** (ESI) *m/z*: 504.1903 $[M+H]^+$, $C_{31}H_{26}N_3O_4^+$ requires 504.1918.

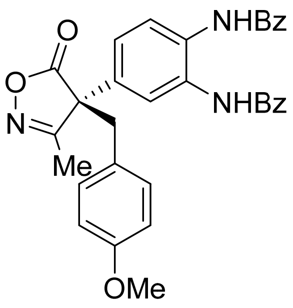
(*R*)-*N,N′*-(4-(3-Methyl-4-(4-methylbenzyl)-5-oxo-4,5-dihydroisoxazol-4-yl)-1,2-phenylene)dibenzamide (3ba)



48.7 mg (94%) of **3ba** were obtained from **1b** (22.3 mg) and **2a** (31.4 mg). The enantiomeric excess (95%) was determined using chiral HPLC (Lux i-Amylose-1), hex:^{i}PrOH 80:20, 1.5 mL min^{-1}, major enantiomer: t_r = 13.5 min, minor enantiomer: t_r = 44.5 min.

White solid; **m.p.** 119.7-121.3ºC; **$[\alpha]_D^{25}$** -55.7 (*c* 0.47, $CHCl_3$); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 10.22 (1H, s, NH), 10.12 (1H, s, NH), 7.99-7.94 (4H, m, Ar), 7.85 (1H, d, J = 8.6 Hz, Ar), 7.65-7.51 (8H, m, Ar), 7.38 (1H, dd, J = 8.4, 2.4 Hz, Ar), 7.17-7.11 (4H, m, Ar), 3.72 (1H, d, J = 13.5 Hz, CH-Ar), 3.55 (1H, d, J = 13.5 Hz, CH-Ar), 2.29 (3H, s, CH_3), 2.11 (3H, s, CH_3); **^{13}C NMR** (75 MHz, DMSO-d_6) δ 179.2 (C), 169.4 (C), 166.2 (C), 166.0 (C), 137.3 (C), 134.52 (C), 134.49 (C), 134.48 (CH), 134.4 (C), 132.48 (C), 132.3 (C), 131.3 (C), 131.1 (C), 129.8 (CH), 129.7 (CH), 129.1 (CH), 129.0 (CH), 128.1 (CH), 128.0 (CH), 127.1 (CH), 124.3 (CH), 61.6 (C), 37.6 (CH_2), 21.1 (CH_3), 13.0 (CH_3); **HRMS** (ESI) *m/z*: 518.2063 $[M+H]^+$, $C_{32}H_{28}N_3O_4^+$ requires 518.2074.

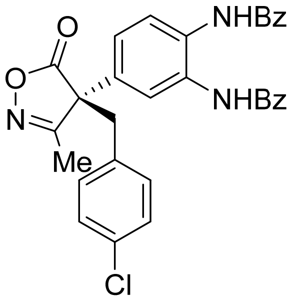
(*R*)-*N,N′*-(4-(4-(4-Methoxybenzyl)-3-methyl-5-oxo-4,5-dihydroisoxazol-4-yl)-1,2-phenylene)dibenzamide (3ca)



50.1 mg (95%) of **3ca** were obtained from **1c** (24.1 mg) and **2a** (31.4 mg). The enantiomeric excess (96%) was determined using chiral HPLC (Lux Cellulose-2), hex:^{i}PrOH 75:25, 1 mL min^{-1}, major enantiomer: t_r = 49.3 min, minor enantiomer: t_r = 42.0 min.

White solid; **m.p.** 116.0-117.0ºC; **$[\alpha]_D^{25}$** -49.1 (*c* 0.54, $CHCl_3$); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 10.21 (1H, s, NH), 10.12 (1H, s, NH), 7.98-7.94 (4H, m, Ar), 7.85 (1H, d, J = 8.7 Hz, Ar), 7.64-7.51 (7H, m, Ar), 7.37 (1H, dd, J = 8.55, 2.4 Hz, Ar), 7.16 (2H, d, J = 8.7 Hz, Ar), 6.90 (2H, d, J = 8.7 Hz, Ar), 3.75 (3H, s, OCH_3), 3.72 (1H, d, J = 16.2 Hz, CH-Ar), 3.53 (1H, d, J = 13.8 Hz, CH-Ar), 2.12 (3H, s, CH_3); **^{13}C NMR** (75 MHz, DMSO-d_6) δ 178.8 (C), 169.0 (C), 165.8 (C), 165.5 (C), 158.7 (C), 134.1 (C), 134.0 (C), 132.0 (CH), 131.9 (C), 131.8 (C), 130.7 (C), 130.6 (CH), 128.62 (CH), 128.57 (CH), 127.7 (CH), 127.6 (CH), 126.7 (CH), 125.6 (C), 123.9 (CH), 123.6 (CH), 114.0 (CH), 61.2 (C), 55.0 (CH_3), 36.8 (CH_2), 12.5 (CH_3); **HRMS** (ESI) *m/z*: 534.2009 $[M+H]^+$, $C_{32}H_{28}N_3O_5^+$ requires 534.2023.

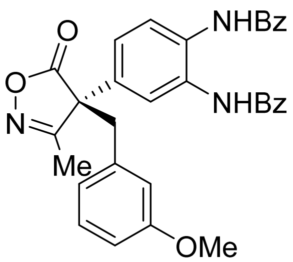
(*R*)-*N,N'*-(4-(4-(4-Chlorobenzyl)-3-methyl-5-oxo-4,5-dihydroisoxazol-4-yl)-1,2-phenylene)dibenzamide (3da)



39.2 mg (74%) of **3da** were obtained from **1d** (24.5 mg) and **2a** (31.4 mg). The enantiomeric excess (93%) was determined using chiral HPLC (Lux Cellulose-2), hex:^{i}PrOH 75:25, 1 mL min^{-1}, major enantiomer: t_r = 35.7 min, minor enantiomer: t_r = 27.7 min.

White solid; **m.p.** 157.3-158.4 ºC; **[*α*]$_D^{25}$** -49.2 (*c* 0.67, $CHCl_3$); **^{1}H NMR** (300 MHz, DMSO-d$_6$) *δ* 10.21 (1H, s, NH), 10.13 (1H, s, NH), 7.96 (4H, ws, Ar), 7.86 (1H, d, *J* = 8.4 Hz, Ar) 7.65-7.53 (8H, m, Ar), 7.44-7.37 (3H, m, Ar), 7.28-7.25 (2H, m, Ar), 3.79 (1H, d, *J* = 13.2 Hz, CH-Ar), 3.60 (1H, d, *J* = 13.2 Hz, CH-Ar), 2.13 (3H, s, CH_3); **^{13}C NMR** (75 MHz, DMSO-d$_6$) *δ* 178.6 (C), 168.9 (C), 165.8 (C), 165.2 (C), 134.1 (C), 133.9 (C), 133.0 (C), 132.6 (C), 132.0 (CH), 131.89 (C), 131.84 (C), 131.4 (CH), 130.3 (C), 128.7 (CH), 128.62 (CH), 128.57 (CH), 127.7 (CH), 127.6 (CH), 126.7 (CH), 124.0 (CH), 123.6 (CH), 61.0 (C), 36.6 (CH_2), 12.5 (CH_3); **HRMS** (ESI) *m/z*: 538.1513 $[M+H]^+$, $C_{31}H_{25}ClN_3O_4^+$ requires 538.1528.

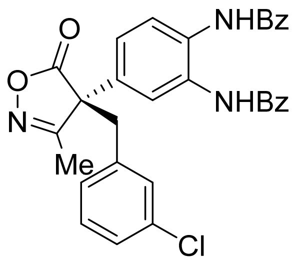
(*R*)-*N,N'*-(4-(4-(3-Methoxybenzyl)-3-methyl-5-oxo-4,5-dihydroisoxazol-4-yl)-1,2-phenylene)dibenzamide (3ea)



51.6 mg (97%) of **3a** were obtained from **1g** (24.1 mg) and **2a** (31.4 mg). The enantiomeric excess (94%) was determined using chiral HPLC (Lux i-Amylose-1), hex:^{i}PrOH 70:30, 1 mL min^{-1}, major enantiomer: t_r = 15.43 min, minor enantiomer: t_r = 50.00 min.

Pink solid; **m.p.** 151.9-154.0ºC; **[*α*]$_D^{25}$** -48.4 (*c* 0.83, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* 9.71 (1H, s, NH), 9.53 (1H, s, NH), 8.08 (4H, m, Ar), 7.53 (8H, m, Ar), 7.16 (1H, dd, *J* = 8.4, 7.3 Hz, Ar), 6.79 (1H, ddd, *J* = 8.4, 2.4, 1.0 Hz, Ar), 6.70 (1H, dd, *J* = 8.5, 2.2 Hz, Ar), 6.53 (2H, m, Ar), 3.74 (3H, s, CH_3O), 3.33 (1H, d, *J* = 13.3 Hz, CH-Ph), 2.97 (1H, d, *J* = 13.3 Hz, CH-Ph), 1.66 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) *δ* 178.5 (C), 167.6 (C), 166.59 (C), 166.55 (C), 159.6 (C), 134.4 (C), 132.9 (C), 132.6 (CH), 131.7 (C), 131.5 (C), 131.4 (C), 129.8 (CH), 128.9 (CH), 127.8 (CH), 127.7 (CH), 126.9 (CH), 124.1 (CH), 123.3 (CH), 121.3 (CH), 115.0 (CH), 113.2 (CH), 60.7 (C), 55.1 (CH_3), 37.9 (CH_2), 12.6 (CH_3); **HRMS** (ESI) *m/z*: 534.2027 $[M+H]^+$, $C_{32}H_{27}N_3O_5^+$ requires 534.2023.

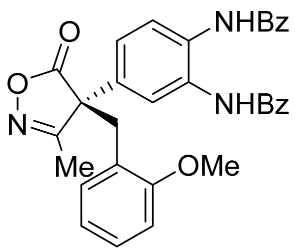
(*R*)-*N,N′*-(4-(4-(3-Chlorobenzyl)-3-methyl-5-oxo-4,5-dihydroisoxazol-4-yl)-1,2-phenylene)dibenzamide (3fa)



51.5 mg (96%) of **3fa** were obtained from **1f** (24.5 mg) and **2a** (31.4 mg). The enantiomeric excess (92%) was determined using chiral HPLC (Lux i-Amylose-1), hex:^{i}PrOH 70:30, 1 mL min^{-1}, major enantiomer: t_r = 13.26 min, minor enantiomer: t_r = 47.45 min.

Pink solid; **m.p.** 104.4-105.3ºC; **[*α*]$_D^{25}$** -41.1 (*c* 0.85, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* 9.79 (1H, s, NH), 9.58 (1H, s, NH), 8.11 (4H, ddt, *J* = 19.7, 6.0, 1.5 Hz, Ar), 7.55 (8H, m, Ar), 7.21 (2H, m, Ar), 6.82 (2H, m, Ar), 6.62 (1H, dd, *J* = 8.5, 2.2 Hz, Ar), 3.24 (1H, d, *J* = 13.3 Hz, CH-Ph), 2.89 (1H, d, *J* = 13.4 Hz, CH-Ph), 1.61 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) *δ* 178.0 (C), 167.3 (C), 166.7 (C), 134.8 (C), 134.5 (C), 132.8 (CH), 132.7 (C), 131.8 (C), 131.6 (C), 131.2 (C), 130.1 (CH), 129.3 (CH), 128.93 (CH), 128.90 (CH), 128.3 (CH), 127.9 (CH), 127.8 (CH), 127.3 (CH), 127.1 (CH), 124.0 (CH), 123.1 (CH), 60.5 (C), 37.3 (CH_2), 12.5 (CH_3); **HRMS** (ESI) *m/z*: 538.1523 $[M+H]^+$, $C_{31}H_{25}ClN_3O_4^+$ requires 538.1528..

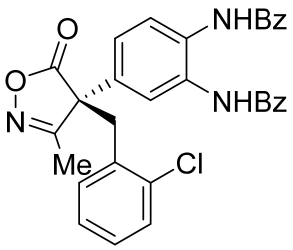
(*R*)-*N,N′*-(4-(4-(2-Methoxybenzyl)-3-methyl-5-oxo-4,5-dihydroisoxazol-4-yl)-1,2-phenylene)dibenza-mide (3ga)



46.5 mg (88%) of **3ga** were obtained from **1g** (24.1 mg) and **2a** (31.4 mg). The enantiomeric excess (90%) was determined using chiral HPLC (Lux Cellulose-2), hex:^{i}PrOH 75:25, 1 mL min^{-1}, major enantiomer: t_r = 43.1 min, minor enantiomer: t_r = 34.9 min.

White solid; **m.p.** 216.3-217.5ºC; **[*α*]$_D^{25}$** -72.0 (*c* 1.00, $CHCl_3$); **^{1}H NMR** (300 MHz, DMSO-d_6) *δ* 10.24 (1H, s, NH), 10.13 (1H, s, NH), 8.00-7.94 (4H, m, Ar), 7.86 (1H, d, *J* = 8.4 Hz, Ar), 7.66-7.52 (7H, m, Ar), 7.38 (1H, dd, *J* = 8.55, 2.4 Hz, Ar), 7.21 (1H, t, *J* = 7.8 Hz, Ar), 7.17 (1H, d, *J* = 7.5 Hz, Ar), 7.03 (1H, d, *J* = 7.8 Hz, Ar), 6.92 (1H, t, *J* = 7.5 Hz, Ar), 3.82 (1H, d, *J* = 13.5 Hz, CH-Ph), 3.78 (3H, s, OCH_3), 3.53 (1H, d, *J* = 13.5 Hz, CH-Ph), 2.01 (3H, s, CH_3); **^{13}C NMR** (75 MHz, DMSO-d_6) *δ* 178.6 (C), 169.1 (C), 165.8 (C), 165.5 (C), 157.3 (C), 134.1 (C), 133.9 (C), 132.03 (CH), 132.00 (CH), 131.8 (C), 131.7 (C), 131.5 (CH), 131.4 (C), 129.3 (CH), 128.62 (CH), 128.57 (CH), 127.7 (CH), 127.5 (CH), 126.7 (CH), 123.9 (CH), 123.6 (CH), 121.9 (C), 120.4 (CH), 60.1 (C), 54.9 (CH), 52.6 (CH_2), 30.7 (CH_3), 12.5 (CH_3); **HRMS** (ESI) *m/z*: 534.2027 $[M+H]^+$, $C_{32}H_{27}N_3O_5^+$ requires 534.2023.

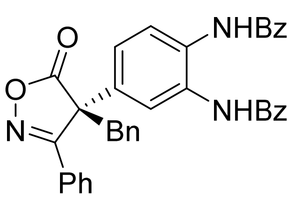
(*R*)-*N,N'*-(4-(4-(2-Chlorobenzyl)-3-methyl-5-oxo-4,5-dihydroisoxazol-4-yl)-1,2-phenylene)dibenzamide (3ha)



51.1 mg (95%) of **3ha** were obtained from **1h** (24.5 mg) and **2a** (31.4 mg). The enantiomeric excess (93%) was determined using chiral HPLC (Lux i-Amylose-1), hex:^{i}PrOH 80:20, 1 mL min^{-1}, major enantiomer: t_r = 19.87 min, minor enantiomer: t_r = 41.84 min.

White solid; **m.p.** 174.0-175.5ºC; **[*α*]$_D^{25}$** -69.9 (*c* 0.89, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* 9.58 (1H, s, NH), 9.45 (1H, s, NH), 8.04 (4H, m, Ar), 7.52 (8H, m, Ar), 7.34 (1H, m, Ar), 7.17 (2H, m, Ar), 7.05 (1H, dd, *J* = 7.3, 2.1 Hz, Ar), 6.84 (1H, dd, *J* = 8.6, 2.2 Hz, Ar), 3.64 (1H, d, *J* = 14.0 Hz, CH-Ph), 3.34 (1H, d, *J* = 14.1 Hz, CH-Ph), 1.83 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) *δ* 178.7 (C), 168.0 (C), 166.69 (C), 166.65 (C), 134.0 (C), 133.02 (C), 132.96 (C), 132.5 (CH), 131.8 (C), 131.7 (C), 131.5 (C), 131.2 (C), 130.6 (CH), 130.0 (CH), 129.3 (CH), 128.8 (CH), 127.8 (CH), 127.7 (CH), 127.4 (CH), 126.8 (CH), 124.0 (CH), 123.4 (CH), 60.1 (C), 34.7 (CH_2), 13.0 (CH_3); **HRMS** (ESI) *m/z*: 538.1525 $[M+H]^+$, $C_{31}H_{25}ClN_3O_4^+$ requires 538.1528.

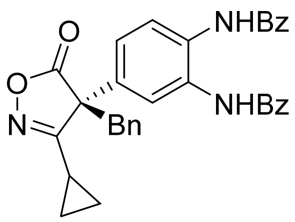
(*R*)-*N,N'*-(4-(4-Benzyl-5-oxo-3-phenyl-4,5-dihydroisoxazol-4-yl)-1,2-phenylene)dibenzamide (3ia)



46.7 mg (83%) of **3ia** were obtained from **1i** (27.6 mg) and **2a** (31.4 mg). The enantiomeric excess (89%) was measured by chiral HPLC (Lux i-Amylose-1), hex:^{i}PrOH 85:15, 1 mL min^{-1}, major enantiomer: t_r = 22.85 min, minor enantiomer: t_r = 28.20 min.

White solid; **m.p.** 151.4-152.3 ºC; **[*α*]$_D^{25}$** -29.2 (*c* 0.94, $CHCl_3$); **^{1}H NMR** (300 MHz, DMSO-d_6) *δ* 10.23 (1H, s, NH), 10.11 (1H, s, NH). 7.97-7.93 (4H, m, Ar), 7.88 (1H, d, *J* = 9 Hz, Ar), 7.80 (1H, d, *J* = 3 Hz, Ar), 7.60-7.46 (12H, m, Ar), 7.26-7.18 (3H, m, Ar), 6.85-6.82 (2H, m, Ar), 3.92 (2H, ws, CH_2-Ph); **^{13}C NMR** (75 MHz, DMSO-d_6) *δ* 178.6 (C), 166.8 (C), 165.8 (C), 165.5 (C), 134.1 (C), 133.9 (C), 133.6 (C), 132.2 (CH), 132.1 (C), 132.02 (CH), 131.98 (CH), 131.2 (C), 129.5 (CH), 129.3 (CH), 128.6 (CH), 128.5 (CH), 127.8 (CH), 127.7 (CH), 127.5 (CH), 127.1 (CH), 127.0 (CH), 126.9 (C), 123.42 (CH), 123.35 (CH), 59.8 (C), 38.2 (CH_2); **HRMS** (ESI) *m/z*: 566.2082 $[M+H]^+$, $C_{36}H_{28}N_3O_4^+$ requires 566.2074.

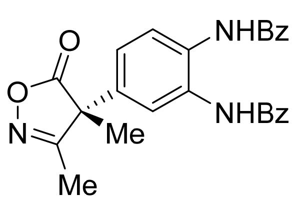
(*R*)-*N,N'*-(4-(4-Benzyl-3-cyclopropyl-5-oxo-4,5-dihydroisoxazol-4-yl)-1,2-phenylene)dibenzamide (3ja)



43.5 mg (82%) of **3ja** were obtained from **1j** (23.6 mg) and **2a** (31.4 mg). The enantiomeric excess (91%) was measured by chiral HPLC (Lux i-Amylose-1), hex:^{i}PrOH 80:20, 1 mL min^{-1}, major enantiomer: t_r = 19.0 min, minor enantiomer: t_r = 53.5 min.

Yellow oil; **[*α*]$_D^{25}$** -17.5 (*c* 0.87, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* 9.78 (1H, s, NH), 9.59 (1H, s, NH), 8.11 (4H, ddt, *J* = 13.0, 6.8, 1.6 Hz, Ar), 7.70 (1H, d, *J* = 2.3 Hz), 7.53 (7H, m, Ar), 7.24 (3H, dd, *J* = 6.6, 2.9 Hz, Ar), 7.03 (2H, m, Ar), 6.81 (1H, dd, *J* = 8.5, 2.2 Hz, Ar), 3.37 (1H, d, *J* = 13.3 Hz, CH-Ph), 3.10 (1H, d, *J* = 13.2 Hz, CH-Ph), 0.79 (5H, m); **^{13}C NMR** (75 MHz, $CDCl_3$) *δ* 178.6 (C), 173.0 (C), 166.6 (C), 166.5 (C), 133.09 (C), 132.97 (C), 132.94 (C) 132.6 (CH), 132.5 (CH), 132.2 (C), 131.7 (C), 131.4 (C), 129.6 (CH), 128.9 (CH), 128.5 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 126.6 (CH), 124.4 (CH), 123.5 (CH), 39.0 (CH3), 11.8 (CH_2), 11.0 (CH_2), 8.3 (CH); **HRMS** (ESI) *m/z*: 530.2077 $[M+H]^+$, $C_{33}H_{28}N_3O_4^+$ requires 530.2074.

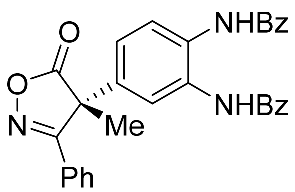
(*R*)-*N,N'*-(4-(3,4-Dimethyl-5-oxo-4,5-dihydroisoxazol-4-yl)-1,2-phenylene)dibenzamide (3ka)



15.3 mg (37%) of **3ka** were obtained from **1k** (12.4 mg) and **2a** (31.4 mg). The enantiomeric excess (71%) was determined using chiral HPLC (Lux i-Amylose-1), hex:^{i}PrOH 80:20, 1 mL min^{-1}, major enantiomer: t_r = 19.6 min, minor enantiomer: t_r = 28.6 min.

Pink solid; **m.p.** 223.2-223.5 ºC; **[*α*]$_D^{25}$** -70.1 (*c* 0.40, $CHCl_3$); **^{1}H NMR** (300 MHz, DMSO-d$_6$) *δ* 10.21 (1H, s, NH), 10.09 (1H, s, NH), 7.95 (4H, m, Ar), 7.81 (1H, d, *J* = 8.5 Hz, Ar), 7.55 (7H, m, Ar), 7.23 (1H, *J* = 8.5, 2.3 Hz, Ar), 2.01 (3H, s, CH_3), 1.78 (3H, s, CH_3); **^{13}C NMR** (75 MHz, DMSO-d$_6$) *δ* 179.6 (C), 170.6 (C), 165.8 (C), 165.5 (C), 134.1 (C), 133.9 (C), 132.0 (CH), 131.9 (CH), 131.8 (C), 131.7 (C), 130.9 (C), 128.6 (CH), 128.5 (CH), 127.7 (CH), 127.5 (CH), 126.7 (CH), 123.4 (CH), 123.2 (CH), 53.8 (C), 18.0 (CH_3), 11.7 (CH_3); **HRMS** (ESI) *m/z*: 428.1609 $[M+H]^+$, $C_{25}H_{23}N_3O_4^+$ requires 428.1605.

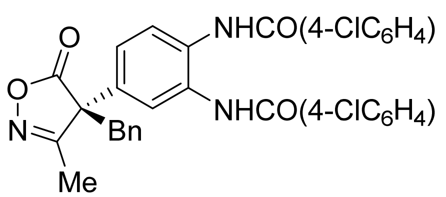
(*R*)-*N,N'*-(4-(4-Methyl-5-oxo-3-phenyl-4,5-dihydroisoxazol-4-yl)-1,2-phenylene)dibenzamide (3la)



45.6 mg (93%) of **3la** were obtained from from **1l** (19.2 mg) and **2a** (31.4 mg). The enantiomeric excess (80%) was measured by chiral HPLC (Chiralpak ADH), hex:^{i}PrOH 80:20, 1 mL min^{-1}, major enantiomer: t_r = 20.9 min, minor enantiomer: t_r = 15.7 min.

White solid; **m.p.** 116.2-117.6 ºC; **[*α*]$_D^{25}$** -19.1 (*c* 0.96, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* 9.45 (1H, s, NH), 9.43 (1H, s, NH), 7.98 (4H, m, Ar), 7.50 (11H, m, Ar), 7.22 (2H, m, Ar), 6.93 (1H, dd, *J*= 8.5, 2.2 Hz, Ar), 1.75 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) *δ* 179.1 (C), 168.4 (C), 166.7 (C), 166.6 (C), 133.3 (C), 133.1 (C), 132.4 (C), 132.34 (CH), 132.28 (CH), 131.8 (C), 131.7 (CH), 131.6 (C), 129.0 (CH), 128.7 (CH), 127.7 (CH), 127.6 (CH), 127.2 (CH), 126.8 (CH), 126.4 (C), 124.0 (CH), 122.9 (CH), 52.8 (C), 19.9 (CH_3); **HRMS** (ESI) *m/z*: 490.1769 $[M+H]^+$, $C_{30}H_{24}N_3O_4^+$ requires 490.1761.

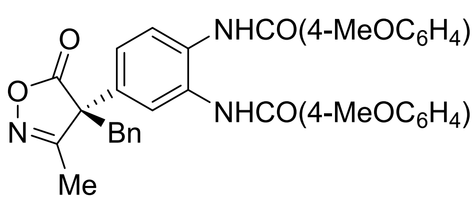
(*R*)-*N,N′*-(4-(4-Benzyl-3-methyl-5-oxo-4,5-dihydroisoxazol-4-yl)-1,2-phenylene)bis(4-chlorobenzamide) (3ab)



50.4 mg (89%) of **3ab** were obtained from **1a** (19.5 mg) and **2b** (38.3 mg). The enantiomeric excess (95%) was measured by chiral HPLC (Chiralpak IC), hex:^{i}PrOH 80:20, 1 mL min^{-1}, major enantiomer: t_r = 24.3 min, minor enantiomer: t_r = 53.1 min.

White solid; **m.p.** 232.6-233.4 ºC; $[\alpha]_D^{25}$ -52.3 (*c* 0.47, $CHCl_3$); **^{1}H NMR** (300 MHz, DMSO-d$_6$) δ 10.23 (1H, s, NH), 10.14 (1H, s NH), 8.00-7.95 (4H, m, Ar), 7.84 (1H, d, J = 6 Hz, Ar), 7.62 (1H, d, J = 9 Hz, Ar), 7.41-7.30 (4H, m, Ar), 7.26-7.23 (2H, m, Ar), 3.78 (1H, d, J = 15 Hz, CH-Ph), 3.59 (1H, d, J = 12 Hz, CH-Ph), 2.12 (3H, s, CH_3); **^{13}C NMR** (75 MHz, DMSO-d$_6$) δ 178.7 (C), 168.9 (C), 164.7 (C), 164.6 (C), 136.8 (C), 136.7 (C), 133.9 (C), 133.0 (C), 132.9 (C), 131.8 (C), 130.7 (C), 129.7 (CH), 129.6 (CH), 129.5 (CH), 128.64 (CH), 128.60 (CH), 127.7 (CH), 126.9 (CH), 124.1 (CH), 123.7 (CH), 61.1 (C), 37.4 (CH_2), 12.6 (CH_3); **HRMS** (ESI) *m/z*: 572.1141 $[M+H]^+$, $C_{31}H_{24}Cl_2N_3O_4^+$ requires 572.1138.

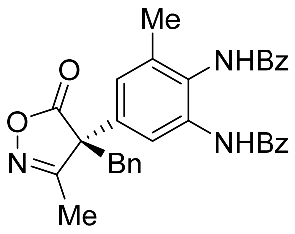
(*R*)-*N,N′*-(4-(4-Benzyl-3-methyl-5-oxo-4,5-dihydroisoxazol-4-yl)-1,2-phenylene)bis(4-methoxybenza-mide) (3ac)



26.3 mg (47%) of **3ac** were obtained from **1a** (19.5 mg) and **2c** (37.4 mg). Enantiomeric excess could not be determined.

Yellow oil; $[\alpha]_D^{25}$ -33.0 (*c* 0.88, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.78 (1H, s, NH), 9.56 (1H, s NH), 8.15 (2H, d, J = 8.9 Hz, Ar), 8.05 (2H, d, J = 8.9 Hz, Ar), 7.51 (1H, d, J = 8.5 Hz, Ar), 7.46 (1H, d, J = 2.3 Hz, Ar), 7.24 (3H, dd, J= 5.0, 1.9 Hz, Ar), 7.06-6,93 (4H, m, Ar), 6.91-6.81 (2H, m, Ar), 7.84 (1H, d, J = 8.5, 2.3 Hz, Ar), 3.82 (3H, s, CH_3O), 3.80 (3H, s, CH_3O), 3.22 (1H, d, J = 13.3 Hz, CH-Ph), 2.80 (1H, d, J = 13.3 Hz, CH-Ph), 1.55 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 178.2 (C), 167.6 (C), 166.2 (C), 163.1 (C), 132.9 (C), 131.9 (C), 131.7 (C), 131.2 (C), 130.1 (CH), 129.8 (CH), 129.7 (CH), 129.2 (CH+C), 128.8 (CH), 128.7 (CH+C), 127.9 (93), 127.1 (CH), 125.0 (C), 124.0 (CH), 123.1 (CH), 114.1 (CH), 114.0 (CH), 60.7 (C), 55.44 (CH_3), 55.40 (CH_3), 37.7 (CH_2), 12.4 (CH_3); **HRMS** (ESI) *m/z*: 564.2129 $[M+H]^+$, $C_{33}H_{30}N_3O_6^+$ requires 564.2129.

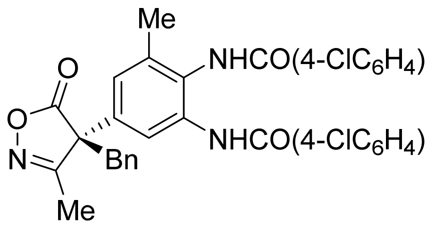
(*R*)-*N,N′*-(5-(4-Benzyl-3-methyl-5-oxo-4,5-dihydroisoxazol-4-yl)-3-methyl-1,2-phenylene)dibenzamide (3ad)



40.0 mg (78%) of **3ad** were obtained from **1a** (19.5 mg) and **2d** (32.8 mg). The enantiomeric excess (93%) was determined using HPLC (Chiralpak IC), hex:^{i}PrOH 80:20, 1 mL min^{-1}, major enantiomer: t_r = 15.1 min, minor enantiomer: t_r = 27.1 min.

White solid; **m.p.** 131.0-133.2 ºC; **[*α*]$_D^{25}$** -86.7 (*c* 0.47, $CHCl_3$); **^{1}H NMR** (300 MHz, DMSO-d$_6$) δ 10.02 (1H, s, NH), 9.84 (1H, s, NH), 8.00 (2H, d, J = 6.9 Hz, Ar), 7.90 (2H, d, J = 6.9 Hz, Ar), 7.61-7.47 (7H, m, Ar), 7.37-7.26 (6H, m, Ar), 3.80 (1H, d, J = 13.5 Hz, CH-Ph), 3.63 (1H, d, J = 13.5 Hz, CH-Ph), 2.37 (3H, s, CH_3), 2.14 (3H, s, CH_3); **^{13}C NMR** (75 MHz, DMSO-d$_6$) δ 178.7 (C), 168.9 (C), 165.6 (C), 165.3 (C), 137.9 (C), 135.2 (C), 134.2 (C) 134.01 (C), 133.96 (C), 131.9 (CH), 131.8 (CH), 130.5 (C), 129.5 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 125.0 (CH), 120.7 (CH), 61.2 (C), 37.4 (CH_2), 18.6 (CH_3), 12.6 (CH_3); **HRMS** (ESI) *m/z*: 518.2090 [M+H]$^+$, $C_{32}H_{28}N_3O_4^+$ requires 518.2074.

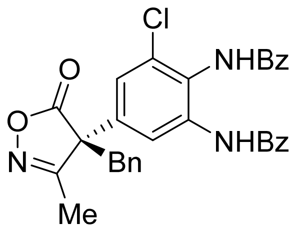
(*R*)-*N,N′*-(5-(4-Benzyl-3-methyl-5-oxo-4,5-dihydroisoxazol-4-yl)-3-methyl-1,2-phenylene)bis(4-chlorobenzamide) (3ae)



50.0 mg (85%) of **3ae** were obtained from **1ae** (12.4 mg) and **3e** (31.4 mg). The enantiomeric excess (95%) was measured by chiral HPLC (Lux i-Celulose-5), hex:^{i}PrOH 80:20, 1 mL min^{-1}, major enantiomer: t_r = 21.5 min, minor enantiomer: t_r = 42.1 min.

White solid; **m.p.** 242.0-242.4 ºC **[*α*]$_D^{25}$** -49.9 (*c* 0.85, $CHCl_3$); **^{1}H NMR** (500 MHz, DMSO-d$_6$) 10.08 (1H, s, NH), 9.87 (1H, s, NH), 8.31 (1H, s, Ar), 7.98 (2H, d, J = 8.5 Hz Ar), 7.90 (2H, d, J = 8.5 Hz Ar), 7.60 (2H, d, J = 8.6 Hz Ar), 7.56 (2H, d, J = 8.6 Hz Ar), 7.53 (1H, s, Ar), 7.38-7.30 (3H, m, Ar), 7.30 (1H, unresolved d, Ar), 7.25 (2H, d, J = 6.5 Hz Ar), 3.77 (1H, d, J = 13.5 Hz, CH_2-Ph), 3.61 (1H, J = 13.5 Hz, CH_2-Ph), 2.32 (3H, s, CH_3), 2.12 (3H, s, CH_3); **^{13}C NMR** (75 MHz, DMSO-d$_6$) δ 178.7 (C), 168.9 (C), 164.7 (C), 164.2 (C), 137.9 (C), 136.7 (C), 136.6 (C), 135.2 (C), 134.0 (C), 133.0 (C), 132.9 (C), 131.9 (C), 130.6 (C), 129.6 (CH), 129.5 (CH), 128.7 (CH), 128.59 (CH), 128.55 (CH), 127.7 (CH), 125.1 (CH), 121.0 (CH), 61.1 (C), 37.4 (CH_2), 18.6 (CH_3), 12.6 (CH_3); **HRMS** (ESI) *m/z*: 586.1294 [M+H]$^+$, $C_{32}H_{26}Cl_2N_3O_4^+$ requires 586.1295.

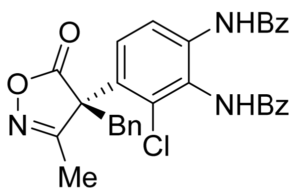
(*R*)-*N,N'*-(5-(4-Benzyl-3-methyl-5-oxo-4,5-dihydroisoxazol-4-yl)-3-chloro-1,2-phenylene)dibenza-mide (3af) and (*R*)-*N,N'*-(4-(4-Benzyl-3-methyl-5-oxo-4,5-dihydroisoxazol-4-yl)-3-chloro-1,2-phenylene)dibenza-mide (3'af)



31.7 mg (62%) of **3af** and 10.8 mg (18%) of **3'af** were obtained from **1a** (19.5 mg) and **2f** (34.8 mg).

The enantiomeric excess (90%) of **3af** was determined using chiral HPLC (Chiralpak IC), hex:^{i}PrOH 80:20, 1.5 mL min^{-1}, major enantiomer: t_r = 8.4 min, minor enantiomer: t_r = 14.3 min.

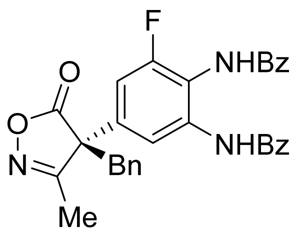
White solid; **m.p.** 215.3-216.1 ºC; **$[\alpha]_D^{25}$** -75.7 (*c* 0.47, $CHCl_3$); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 10.10 (1H, s, NH), 10.05 (1H, s, NH), 8.00-7.97 (2H, m, Ar), 7.88-7.86 (2H, m, Ar), 7.74 (1H, d, J = 3.0 Hz, Ar), 7.65 (1H, d, J = 3.0 Hz, Ar), 7.61-7.46 (6H, m, Ar), 7.36-7.31 (3H, m, Ar), 7.26-7.24 (2H, m, Ar), 3.84 (1H, d, J = 15 Hz, CH-Ph), 3.7 (1H, d, J = 12 Hz), 2.17 (3H, s, CH_3); **^{13}C NMR** (75 MHz, DMSO-d_6) δ 178.3 (C), 168.5 (C), 165.8 (C), 165.4 (C), 137.3 (C), 134.0 (C), 133.74 (C), 133.68 (C), 133.6 (C), 133.2 (C), 132.04 (CH), 132.01 (CH), 129.5 (CH), 129.3 (C), 128.6 (CH), 128.53 (CH), 128.50 (CH), 127.8 (CH), 127.7 (CH), 124.0 (CH), 121.8 (CH), 61.1 (CH), 37.3 (CH_2), 12.6 (CH_3); **HRMS** (ESI) *m/z*: 538.1519 $[M+H]^+$, $C_{31}H_{25}ClN_3O_4^+$ requires 538.1528.



The enantiomeric excess (>99%) of **3'af** was determined using chiral HPLC (Chiralpak IC), hex:^{i}Pr 80:20, 1.5 mL min^{-1}, major enantiomer: t_r = 58.47 min, minor enantiomer: t_r = 33.63 min.

Yellow oil; **$[\alpha]_D^{25}$** +5.5 (*c* 0.43, $CHCl_3$); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 10.10 (1H, s, NH), 10.00 (1H, s, NH), 8.09 (1H, d, J = 9.0 Hz, Ar), 8.00-7.97 (2H, m, Ar), 7.94 (1H, d, J = 9.0 Hz), 7.88-7.85 (2H, m, Ar), 7.59-7.47 (6H, m, Ar), 7.36-7.33 (3H, m, Ar), 7.21-7.18 (2H, m, Ar), 3.94 (1H, d, J = 12 Hz, CH-Ph), 3.53 (1H, d, J = 12 Hz, CH-Ph), 2.01 (3H, s, CH_3); **^{13}C NMR** (75 MHz, DMSO-d_6) δ 177.9 (C), 166.3 (C), 165.7 (C), 165.4 (C), 137.5 (C), 134.1 (C), 133.5 (C), 132.7 (C), 132.5 (C), 132.0 (CH), 122.0 (C), 130.1 (CH), 129.4 (C), 128.6 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 127.9 (CH), 127.8 (CH), 127.6 (CH), 123.5 (CH), 60.6 (C), 39.3 (CH_2), 12.2 (CH_3)

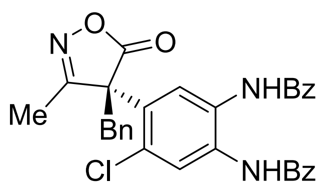
(*R*)-*N,N'*-(5-(4-benzyl-3-methyl-5-oxo-4,5-dihydroisoxazol-4-yl)-3-fluoro-1,2-phenylene)dibenza-mide (3ag)



28.1 mg (54%) of **3ag** were obtained from from **1a** (19.5 mg) and **2g** (33.2 mg). The enantiomeric excess (97%) was determined using HPLC (Chiralpak IC), hex:^{i}PrOH 80:20, 1 mL min^{-1}, major enantiomer: t_r = 16.4 min, minor enantiomer: t_r = 25.5 min.

Yellow oil; **[α]$_D^{25}$** -60.8 (*c* 0.26, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.84 (1H, s, NH), 8.40 (1H, s, NH), 7.99 (4H, dt, J = 8.6 Hz, J = 1.5 Hz, Ar), 7.86 (1H, t, $J_{H\text{-}F}$ = 1.8 Hz, $J_{H\text{-}H}$ = 1.8 Hz, Ar), 7.64-7.46 (7H, m, Ar), 7.32-7.27 (3H, m, Ar), 7.14-7.09 (2H, m, Ar), 6.91 (1H, dd, $J_{H\text{-}F}$ = 10.7 Hz, $J_{H\text{-}H}$ = 2.2 Hz, Ar), 3.61 (1H, d, J = 13.4 Hz, CH-Ph), 3.32 (1H, d, J = 13.4 Hz, CH-Ph), 2.05 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 178.1 (C), 167.3 (C), 167.1 (C), 165.9 (C), 170.4 (C, d, $J_{C\text{-}F}$ = 265 Hz), 154.9 (C), 134.8 (C), 134.7 (C), 133.5 (C), 133.1 (CH), 133.2 (C), 132.8 (C), 132.5 (C, d, $J_{C\text{-}F}$ = 8 Hz), 132.4 (CH), 129.2 (CH), 129.1 (CH), 129.0 (CH), 128.8 (CH), 128.2 (CH), 127.7 (CH), 127.5 (CH), 119.1 (CH, d, $J_{C\text{-}F}$ = 4 Hz), 110.3 (CH, d, $J_{C\text{-}F}$ = 22 Hz), 60.9 (C), 39.0 (CH_2), 13.1 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -119.80 (1F, s); **HRMS** (ESI) *m/z*: 522.1826 [M+H]$^+$, $C_{31}H_{25}FN_3O_4^+$ requires 522.1824.

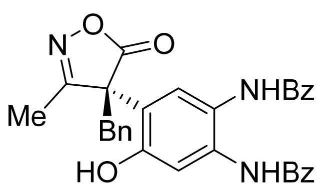
(*R*)-*N,N′*-(4-(4-Benzyl-3-methyl-5-oxo-4,5-dihydroisoxazol-4-yl)-5-chloro-1,2-phenylene)dibenzamide (3ah)



47.3 mg (88%) of **3ah** were obtained from **1a** (19.5 mg) and **2h** (34.8 mg). The enantiomeric excess (98%) was measured using chiral HPLC (Chiralpak IC), hex:^{i}PrOH 80:20, 1 mL min^{-1}, major enantiomer: t_r = 11.3 min, minor enantiomer: t_r = 17.5 min.

White solid; **m.p.** 253.5-255.2 ºC; **[α]$_D^{25}$** -16.7 (*c* 0.30, $CHCl_3$); **^{1}H NMR** (300 MHz, DMSO-d$_6$) δ 10.30 (1H, s, NH), 10.22 (1H, s, NH), 8.20 (1H, s, Ar), 8.03-7.94 (6H, m, Ar), 7.63-7.54 (6H, m, Ar), 7.35-7.33 (3H, m, Ar), 7.21-7.18 (2H, m, Ar), 3.90 (1H, d, J = 12 Hz, CH-Ph), 3.43 (1H, d, J = 12 Hz, CH-Ph), 2.04 (3H, s, CH_3); **^{13}C NMR** (75 MHz, DMSO-d$_6$) δ 177.9 (C), 166.2 (C), 166.0 (C), 165.7 (C), 133.91 (C), 133.90 (C), 133.4 (C), 132.4 (C), 132.2 (CH), 132.2 (CH), 130.4 (C), 130.0 (CH), 128.8 (CH), 128.7 (C), 128.63 (CH), 128.60 (CH), 128.4 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.5 (CH), 127.4 (CH), 127.3 (C), 126.5 (CH), 60.1 (C), 39.1 (CH_3), 12.3 (CH_2); **HRMS** (ESI) *m/z*: 538.1527 [M+H]$^+$, $C_{31}H_{25}ClN_3O_4^+$ requires 538.1528.

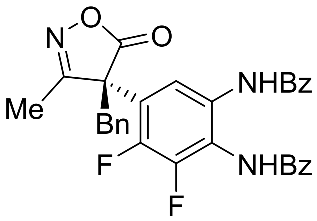
(*R*)-*N,N′*-(4-(4-Benzoyl-3-methyl-5-oxo-4,5-dihydroisoxazol-4-yl)-5-hydroxy-1,2-phenylene)dibenzamide (3ai)



44.2 mg (85%) of **3ai** were obtained from **1a** (19.5 mg) and **2i** (33.0 mg). The enantiomeric excess (70%) was measured by chiral HPLC (Lux i-Amylose-1), hex:^{i}PrOH 80:20, 1 mL min^{-1}, major enantiomer: t_r = 15.4 min, minor enantiomer: t_r = 20.0 min.

White solid; **m.p.** 223.2-223.5 ºC; **[α]$_D^{25}$** -70.1 (*c* 0.40, $CHCl_3$); **^{1}H NMR** (300 MHz, DMSO-d$_6$) 10.15 (1H, s, NH), 10.01 (1H, s, NH), 8.02 (2H, m , Ar), 7.93 (1H, m, Ar), 7.76 (1H, s, Ar), 7.56 (6H, m, Ar), 7.45 (1H, m, Ar), 7.32 (3H, m, Ar), 7.19 (2H, m, Ar), 3.76 (1H, d, J = 12.9 Hz, CH_2-Ph), 3.31 (1H, J = 12.8 Hz, CH_2-Ph), 1.95 (3H, s, CH_3); **^{13}C NMR** (75 MHz, DMSO-d$_6$) δ 179.2 (C), 166.3 (C), 166.0 (C), 165.2 (C), 152.7 (C), 134.3 (C), 134.1 (C), 133.6 (C), 133.4 (C), 132.0 (CH), 131.9 (CH), 129.9 (CH), 128.7 (CH), 128.6 (CH), 128.3 (CH), 127.6 (CH), 127.4 (CH), 126.1 (CH), 122.2 (C), 117.6 (C), 110.9 (CH), 57.7 (C), 37.7 (CH_2), 12.2 (CH_3); **HRMS** (ESI) *m/z*: 520.1869 $[M+H]^+$, $C_{31}H_{26}N_3O_5^+$ requires 520.1867.

(*R*)-*N,N'*-(5-(4-Benzyl-3-methyl-5-oxo-4,5-dihydroisoxazol-4-yl)-3,4-difluoro-1,2-phenylene)dibenzamide (3aj)



26.9 mg (54%) were obtained from **1a** (19.5 mg) and **2j** (35.0 mg). The enantiomeric excess (97%) was determined using HPLC (Chiralpak IC), hex:^{i}PrOH 90:10, 1 mL min^{-1}, major enantiomer: t_r = 32.9 min, minor enantiomer: t_r = 41.6 min.

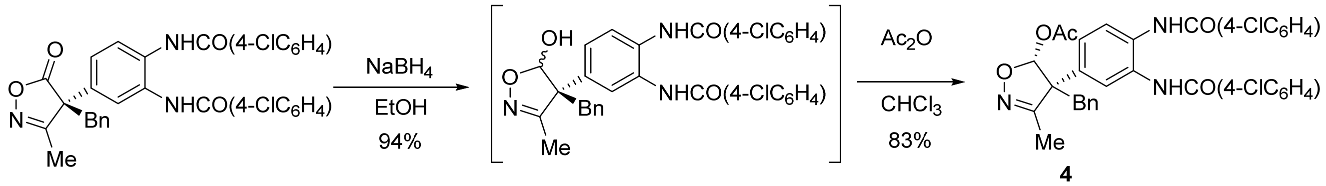
Yellow oil; $[\alpha]_D^{25}$ -57.3 (*c* 0.35, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.85 (1H, NH, Ar), 8.95 (1H, NH, Ar), 8.06 (4H, m, Ar), 7.56 (8H, m, Ar), 7.27 (4H, m, Ar), 6.91 (2H, m, Ar), 3.26 (1H, d, J = 12.9 Hz, CH-Ph), 3.16 (1H, d, J = 12.9 Hz, CH-Ph), 1.64 (3H, s, CH_3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 177.3 (C), 166.7 (C), 166.3 (C), 164.9 (C), 145.9 (C, dd, $J_{C\text{-}F}$ = 249, 13 Hz), 145.3 (C, dd, $J_{C\text{-}F}$ = 250, 14 Hz), 133.4 (CH), 132.8 (CH), 132.5 (C), 131.8 (C), 131.2 (C), 129.8 (br, C), 129.5 (CH), 129.2 (CH), 128.9 (CH), 128.7 (CH), 128.4 (CH), 127.9 (CH), 127.6 (CH), 121.9 (C, d, $J_{C\text{-}F}$ = 10 Hz), 121.3 (C, d, $J_{C\text{-}F}$ = 11 Hz), 118.5 (CH), 57.0 (C), 38.0 (CH_2), 12.3 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -138.71 (1F, d, $J_{F\text{-}F}$ = 20.5 Hz), -139.99 (1F, bd); **HRMS** (ESI) *m/z*: 540.1727 $[M+H]^+$, $C_{31}H_{24}F_2N_3O_4^+$ requires 540.1729.

One mmol scale synthesis of compound 3aa

Isoxazolin-5-one **1a** (131 mg, 1.1 mmol), diimide **2a** (314 mg, 1.0 mmol), and squaramide **SQ-3** (60 mg, 0.1 mmol) were introduced in a round bottom flask and dissolved in dichloromethane (100 mL). The mixture was stirred at – 20 ºC overnight. The solvent was removed under reduced pressure and the mixture chromatographed over silica gel eluting with hexane:EtOAc (8:2 to 6:4) to give 500 mg (99%) of compound **3aa** with identical spectroscopic features as those reported above and with 93% ee.

Synthetic transformations

(4*R*,5*R*)-4-Benzyl-4-(3,4-bis(4-chlorobenzamido)phenyl)-3-methyl-4,5-dihydroisoxazol-5-yl acetate and (4*R*,5*S*)-4-benzyl-4-(3,4-bis(4-chlorobenzamido)phenyl)-3-methyl-4,5-dihydroisoxazol-5-yl acetate (4)



3ab, 95% ee

4
dr: 87:13,
93% ee/99% ee

Isoxazol-5-one **3ab** (115 mg, 0.2 mmol, 1 eq) was added in portions to a solution of $NaBH_4$ (3 8 mg, 1 mmol, 5 eq) in a 1:1 mixture of EtOH:CH_2Cl_2 (2 mL). The solution was stirred at room temperature for 24 h and quenched with water (1 mL). The phases were separated and the aqueous layer was extracted with dichloromethane (3×15mL). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure to obtain 109 mg (94%) of a mixture of lactols that were used in the next step without further purification.

The previously obtained lactol mixture was introduced in a round bottom flask and dissolved in $CHCl_3$ (5 mL). Acetic anhydride (26 µL, 0.27 mmol, 1.5 eq) and pyridine (78 µL, 0.97 mmol, 5.4 eq) were added dropwise and the reaction was stirred at room temperature for 24h. Then, the mixture was purified by flash column chromatography using mixtures of hexane:EtOAc as eluent to give 91.6 mg (83%) of compound 4 as a ca. 87:13 diastereomer mixture. Pure samples of each diastereomer could be obtained by sem-prepartive HPLC.

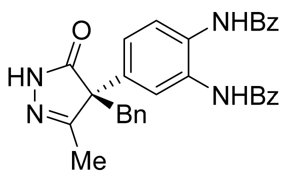
Major diastereoisomer (4*R*,5*S*)-4: The enantiomeric excess (93%) was measured by chiral HPLC (Chiralpak IC), hex:^{i}PrOH 80:20, 1 mL min^{-1}, major enantiomer: t_r = 29.3 min, minor enantiomer: t_r = 20.3 min.

Yellow oil; $[\alpha]_D^{25}$ +43.3 (*c* 0.98, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.53 (1H, s, NH), 9.37 (1H, s, NH), 7.98 (4H, dd, *J* = 12.5, 8.6 Hz, Ar), 7.55-7.43 (6H, m, Ar), 7.28-7.24 (3H, m, Ar), 7.01 (2H, dd, *J* = 6.6, 2.8 Hz, Ar), 6.96 (1H, dd, *J* = 8.6, 2.1 Hz, Ar), 6.49 (1H, s, Ar), 3.40 (1H, d, *J* = 13.6 Hz, CH-Ph), 2.94 (1H, d, *J* = 13.6 Hz, CH-Ph), 1.59 (3H, s, CH_3), 1.55 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.1 (C), 165.4 (C), 165.2 (C), 159.4 (C), 139.3 (C), 139.1 (C), 134.0 (C), 132.7 (C), 131.3 (C), 130.5 (C), 130.3 (C), 129.8 (CH), 129.24 (CH), 129.20 (CH), 129.1 (CH), 128.9 (CH), 128.6 (CH), 127.9 (CH), 127.6 (CH), 125.8 (CH), 124.9 (CH), 100.5 (CH), 67.2 (C), 38.4 CH_2), 20.5 (CH_3), 11.1 (CH_3); **HRMS** (ESI) *m/z*: 654.0940 $[M+K]^+$, $C_{33}H_{27}Cl_2KN_3O_5^+$ requires 654.0959.

Minor diastereoisomer (4*R*,5*R*)-4: The enatiomeric excess (99%) was measured by chiral HPLC (Chiralpak IC), hex:^{i}PrOH 80:20, 1 mL min^{-1}, major enantiomer: t_r = 48.3 min, minor enantiomer: t_r = 54.4 min.

Yellow oil; **[*α*]$_D^{25}$** -142.5 (*c* 0.53, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* 9.23 (1H, s, NH), 8.78 (1H, s, NH), 7.87 (4H, dd, *J* = 8.6, 2.8 Hz, Ar), 7.72 (1H, d, *J* = 8.6 Hz, Ar), 7.53 (1H, d, *J* = 2.2 Hz, Ar), 7.46 (4H, dd, *J* = 8.6, 5.1 Hz, Ar), 7.29 (1H, dd, *J* = 8.6, 2.3 Hz, Ar), 7.20-7.12 (3H, m, Ar), 6.97 (2H, dd, *J* = 7.5, 2.1 Hz, Ar), 6.93 (1H, s, Ar), 3.71 (1H, d, *J* = 16.4 Hz, CH-Ph), 3.43 (1H, d, *J* = 16.4 Hz, CH-Ph), 1.95 (3H, s, CH_3), 1.78 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) *δ* 169.1 (C), 165.9 (C), 165.0 (C), 162.3 (C), 139.0 (C), 138.7 (C), 136.1 (C), 135.1 (C), 132.1 (C), 131.6 (C), 131.1 (C), 130.6 (C), 129.2 (CH), 128.9 (CH), 128.8 (CH), 128.6 (CH), 128.54 (CH), 126.53 (CH), 126.1 (C), 124.6 (CH), 123.3 (CH), 64.2 (C), 33.8 (CH_2), 20.5 (CH_3), 10.1 (CH_3); **HRMS** (ESI) *m/z*: 654.0940 $[M+K]^+$, $C_{33}H_{27}Cl_2KN_3O_5^+$ requires 654.0959.

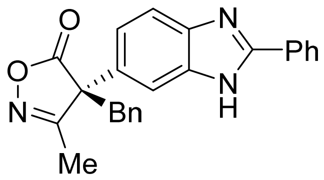
(*R*)-*N,N′*-(4-(4-benzyl-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl)-1,2-phenylene)dibenzamide (5).



In a round bottom flask, compound **3aa** (47.3 mg, 0.094 mmol) was dissolved in absolute EtOH (1 mL) under nitrogen atmosphere. Then, 98% $N_2H_4·H_2O$ (45.8 μL, 0.94 mmol) was added and the reaction mixture was stirred at 80 ºC for 16h. After this time, the reaction was concentrated under reduced pressure, dissolved in EtOAc (75 mL), washed with brine (2 ×10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford 39.6 mg (84%) of compound **5**. The enantiomeric excess (92%) was determined using chiral HPLC (ADH), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 35.9 min, minor enantiomer: t_r = 17.0 min.

Yellow oil; **[*α*]$_D^{25}$** 17.8 (*c* 0.29, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* 9.33 (1H, s, NH), 9.31 (1H, s, NH), 8.17 (1H, s, NH), 8.00 (1H, d, *J* = 6.8 Hz, Ar), 7.61-7.45 (8H, m, *J* = Ar), 7.24-7.22 (3H, m, Ar), 7.13-7.10 (2H, m, Ar), 6.98 (1H, dd, *J* = 8.5, 2.2 Hz, Ar), 3.55 (1H, d, *J* = 13.2 Hz, CH-Ph), 3.21 (1H, d, *J* = 13.2 Hz, CH-Ph), 1.93 (3H, s, Me); **^{13}C NMR** (75 MHz, $CDCl_3$) *δ* 177.9 (C), 166.5 (C), 162.5 (C), 134.1 (C), 133.54 (C), 133.48 (C), 133.3 (C), 132.34 (CH), 132.28 (CH), 131.4 (C), 130.8 (C), 129.3 (CH), 128.80 (CH), 128.78 (C), 128.5 (CH), 127.63 (CH), 127.61 (C), 127.5 (CH), 126.4 (CH), 124.2 (CH), 123.6 (CH), 61.8 (C), 38.5 (CH_2), 15.0 (CH_3); **HRMS** (ESI) *m/z*: 503.2082 $[M+H]^+$, $C_{31}H_{27}N_4O_3^+$ requires 503.2078.

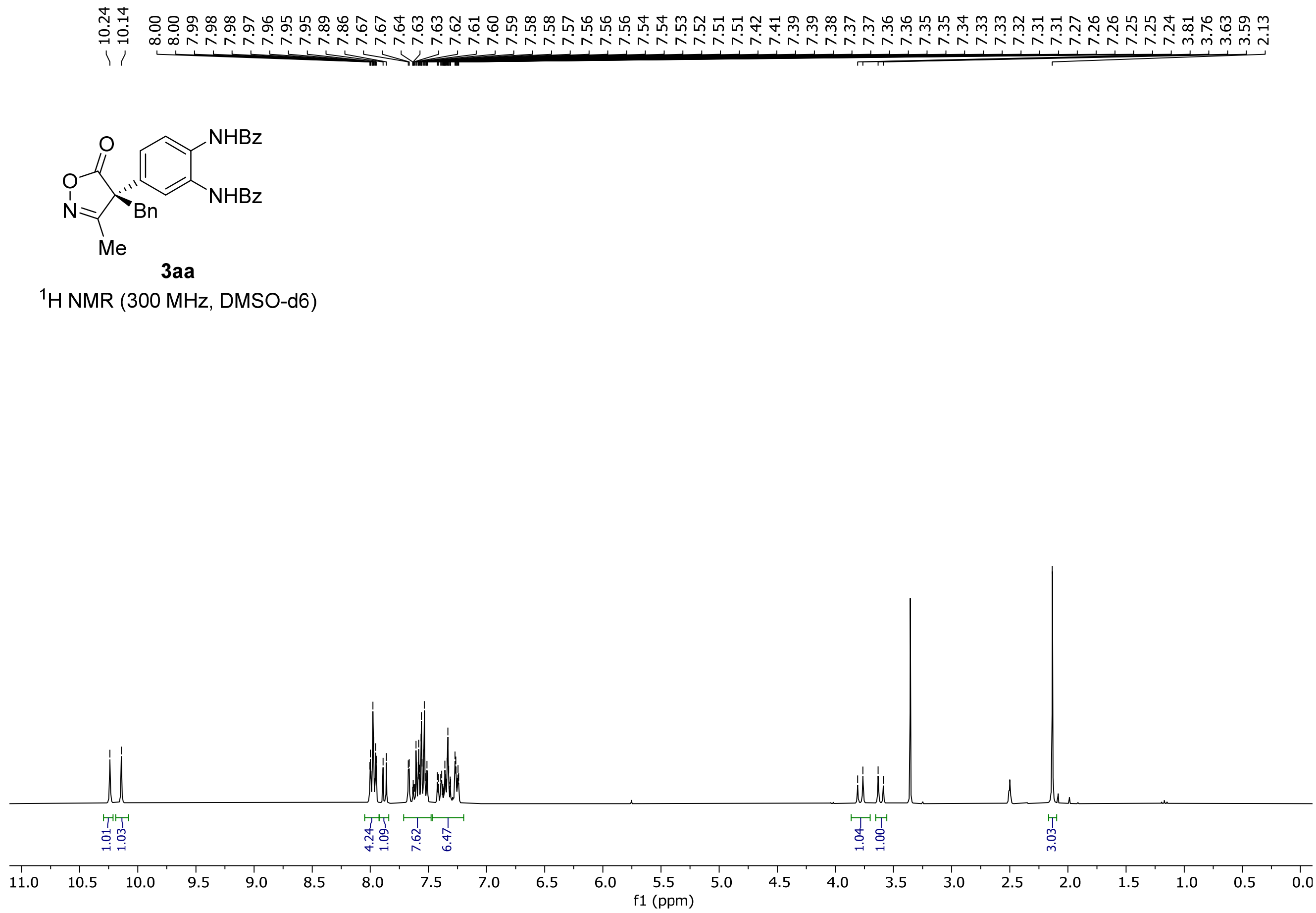
(*R*)-4-Benzyl-3-methyl-4-(2-phenyl-1*H*-benzo[d]imidazol-6-yl)isoxazol-5(4*H*)-one (6)



A solution of compound **3aa** (30 mg, 0.06 mmol) and *p*-TsOH·H_2O (23 mg (0.12 mmol) in xylenes (1 mL) was stirred at 100 ºC for 72h. Then, the mixture was cooled to room temperature, diluted with EtOAc (30 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried and concentrated under reduced pressure. Flash column chromatography using mixtures of hexane:EtOAc (8:2 to 5:5) gave 13.2 mg (58%) of compound **6**. The enantiomeric excess (91%) was determined using chiral HPLC (IC), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 22.0 min, minor enantiomer: t_r = 15.1 min.

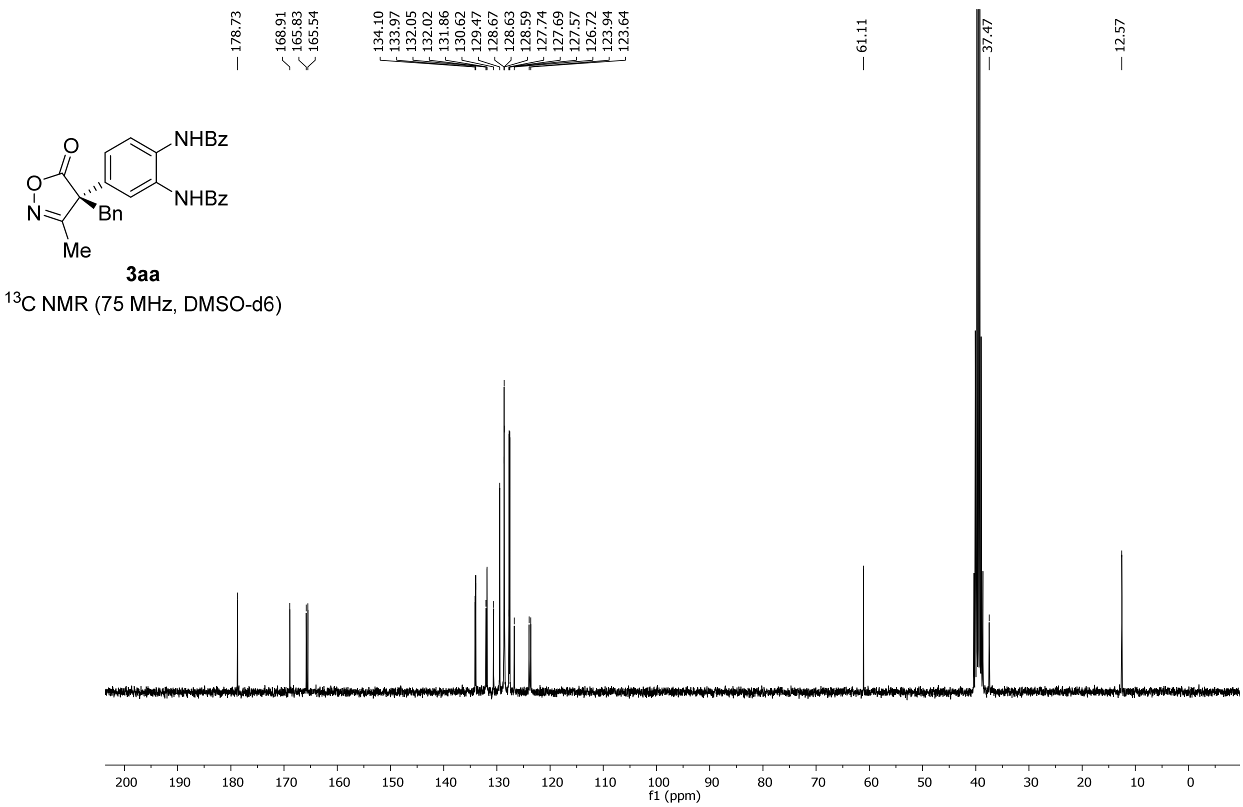
Yellow solid; **m.p.** 140.2-142.4 ºC; **[*α*]$_D^{25}$** -55.3 (*c* 0.27, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* 8.09-8.06 (2H, m, Ar), 7.84-7.67 (1H, m, Ar), 7.51-7.49 (4H, m, Ar), 7.33-7.30 (3H, m, Ar), 7.21-7.18 (2H, m, Ar), 7.08 (1H, bs, NH), 3.73 (1H, d, *J* = 13.4 Hz, CH-Ph), 3.43 (1H, d, *J* = 13.4 Hz, CH-Ph), 2.00 (3H, s, Me); **^{13}C NMR** (75 MHz, $CDCl_3$) *δ* 179.7 (C), 168.5 (C), 153.2 (C), 136.5 (C), 133.4 (C), 130.7 (CH), 129.3 (C), 129.2 (CH), 129.0 (CH), 128.3 (C), 128.1 (CH), 126.7 (CH), 120.9 (C), 61.6 (C), 38.6 (CH_2), 13.0 (CH_3); **HRMS** (ESI) *m/z*: 382.1552 [M+H]$^+$, $C_{24}H_{20}N_3O_2^+$ requires 382.1550.

NMR spectra for compounds 3-6



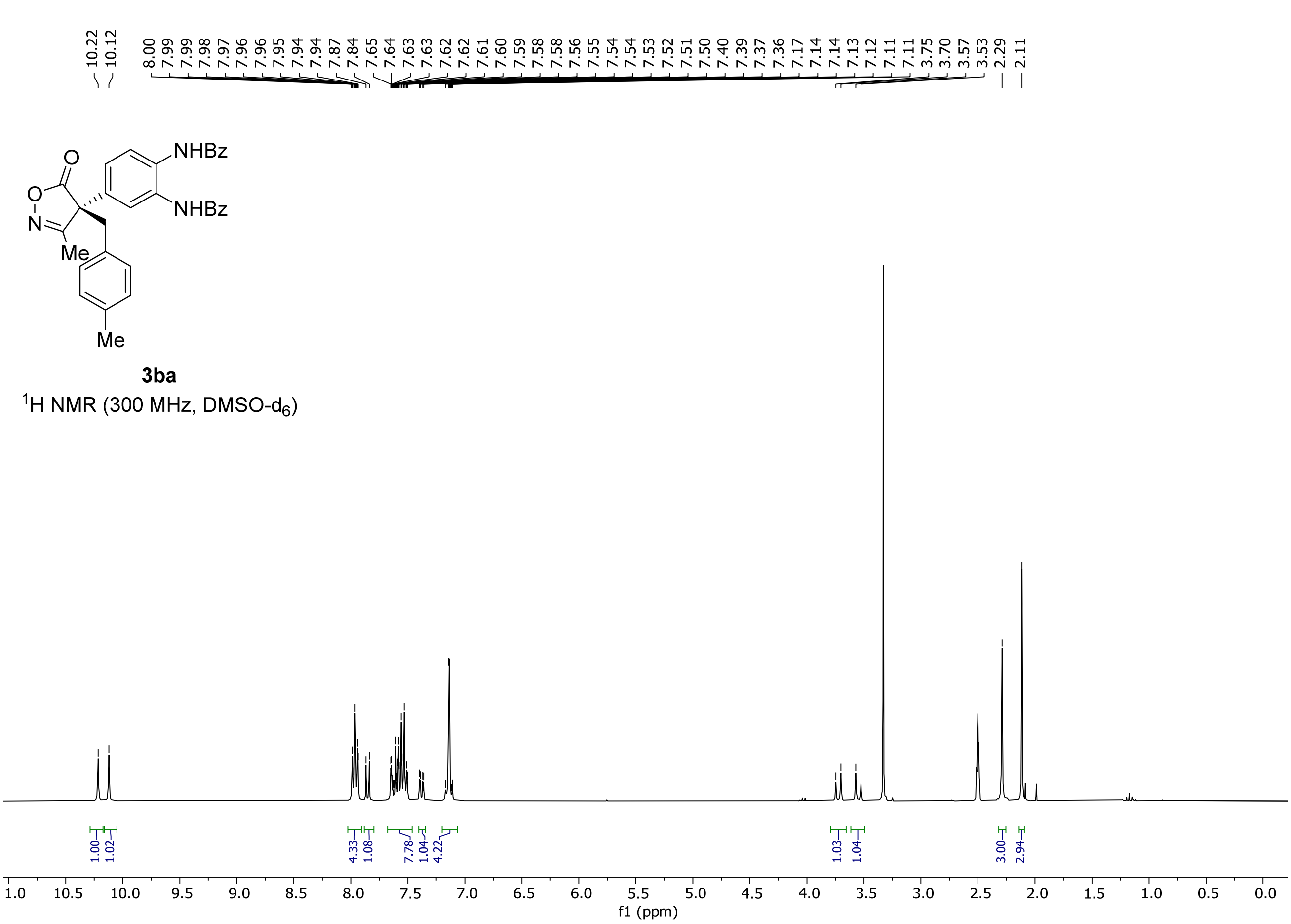
3aa

^{1}H NMR (300 MHz, DMSO-d6)



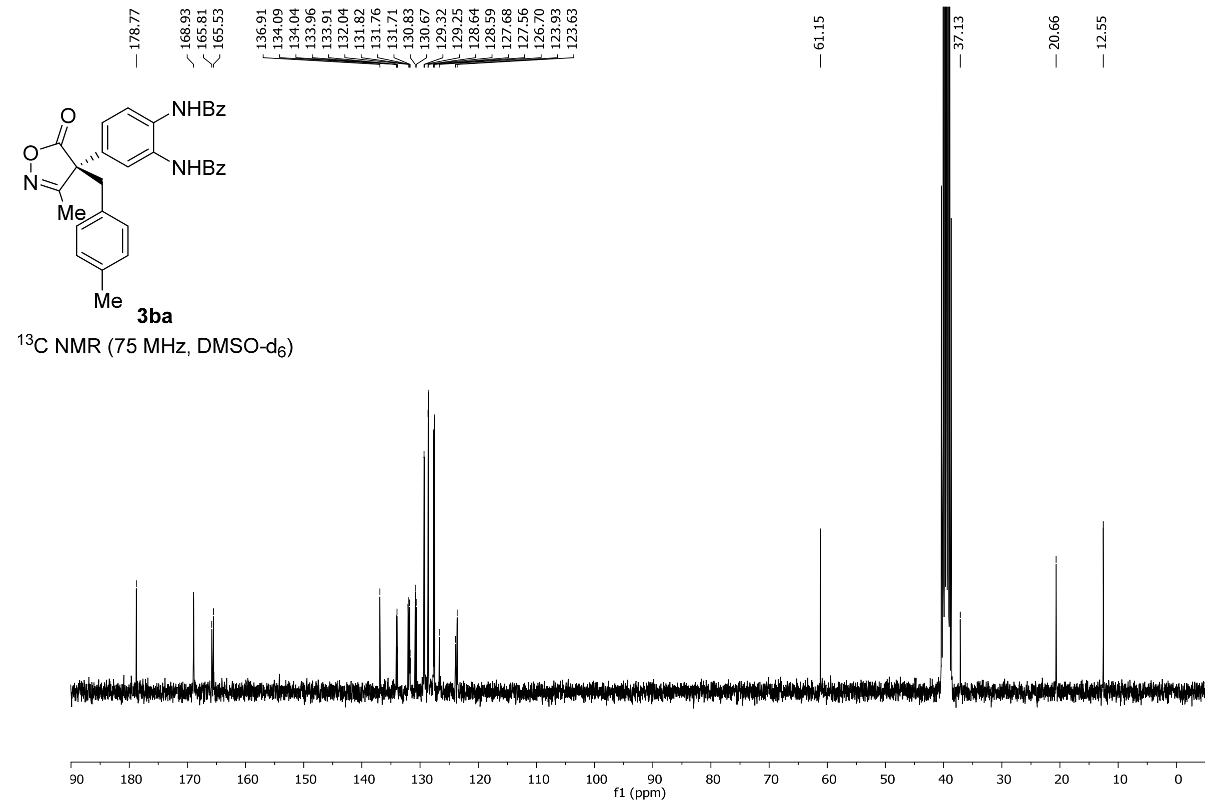
3aa

^{13}C NMR (75 MHz, DMSO-d6)



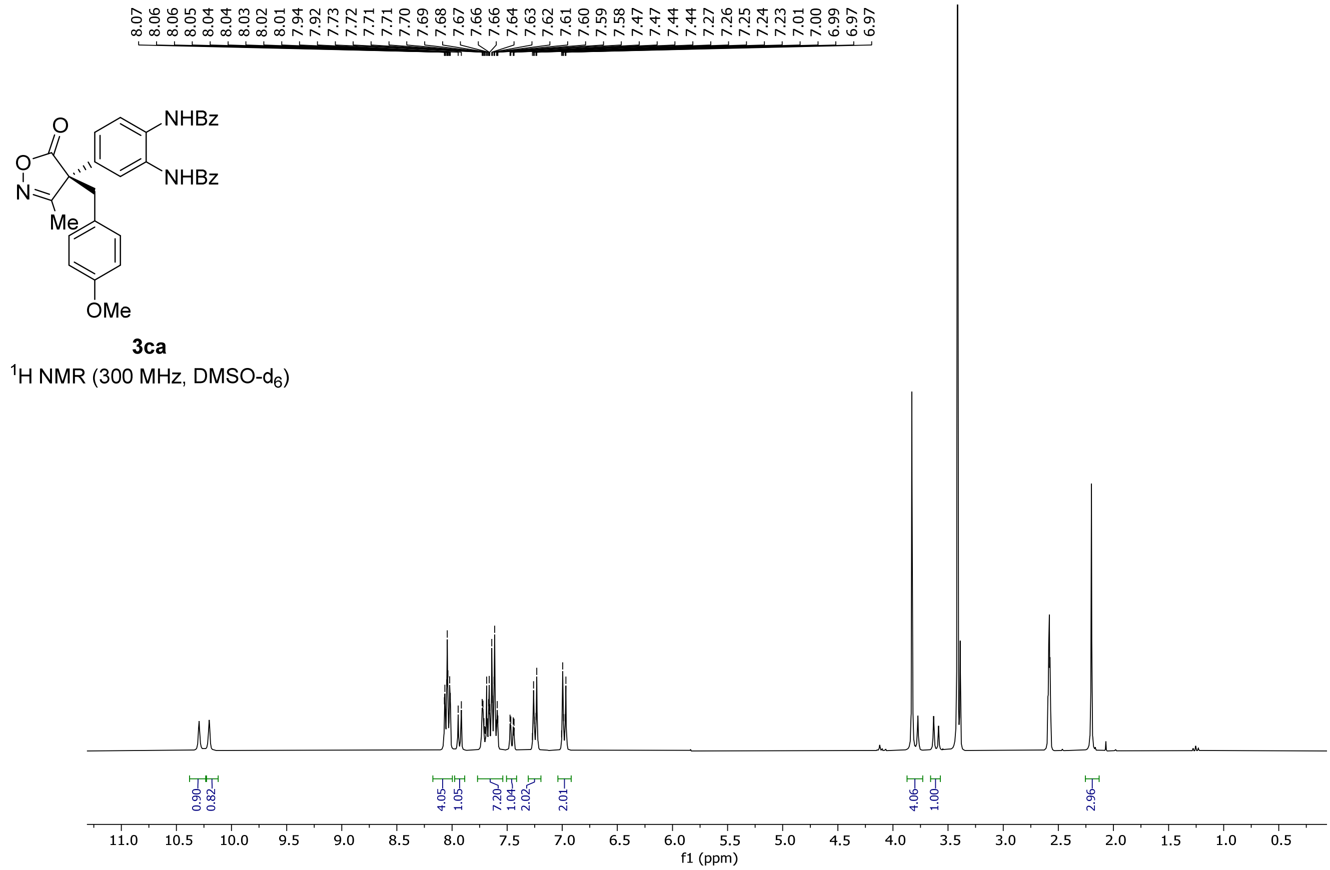
3ba

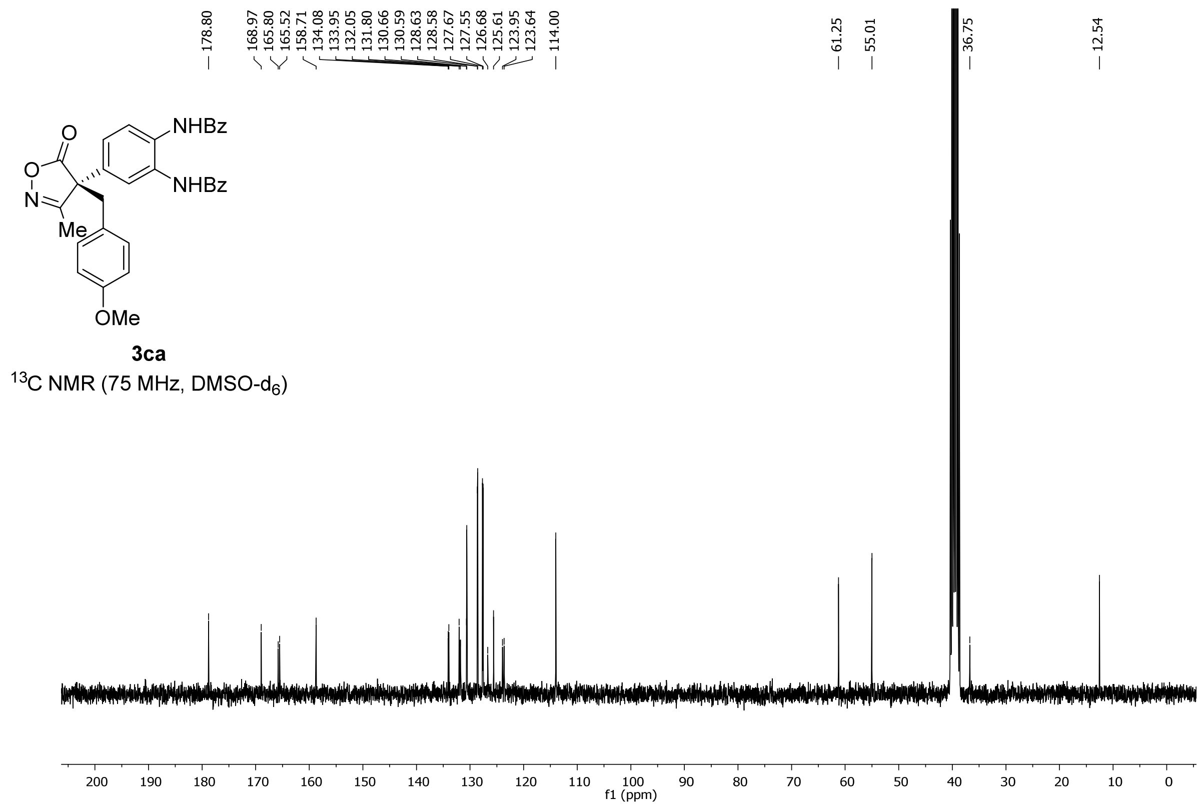
^{1}H NMR (300 MHz, DMSO-d$_6$)

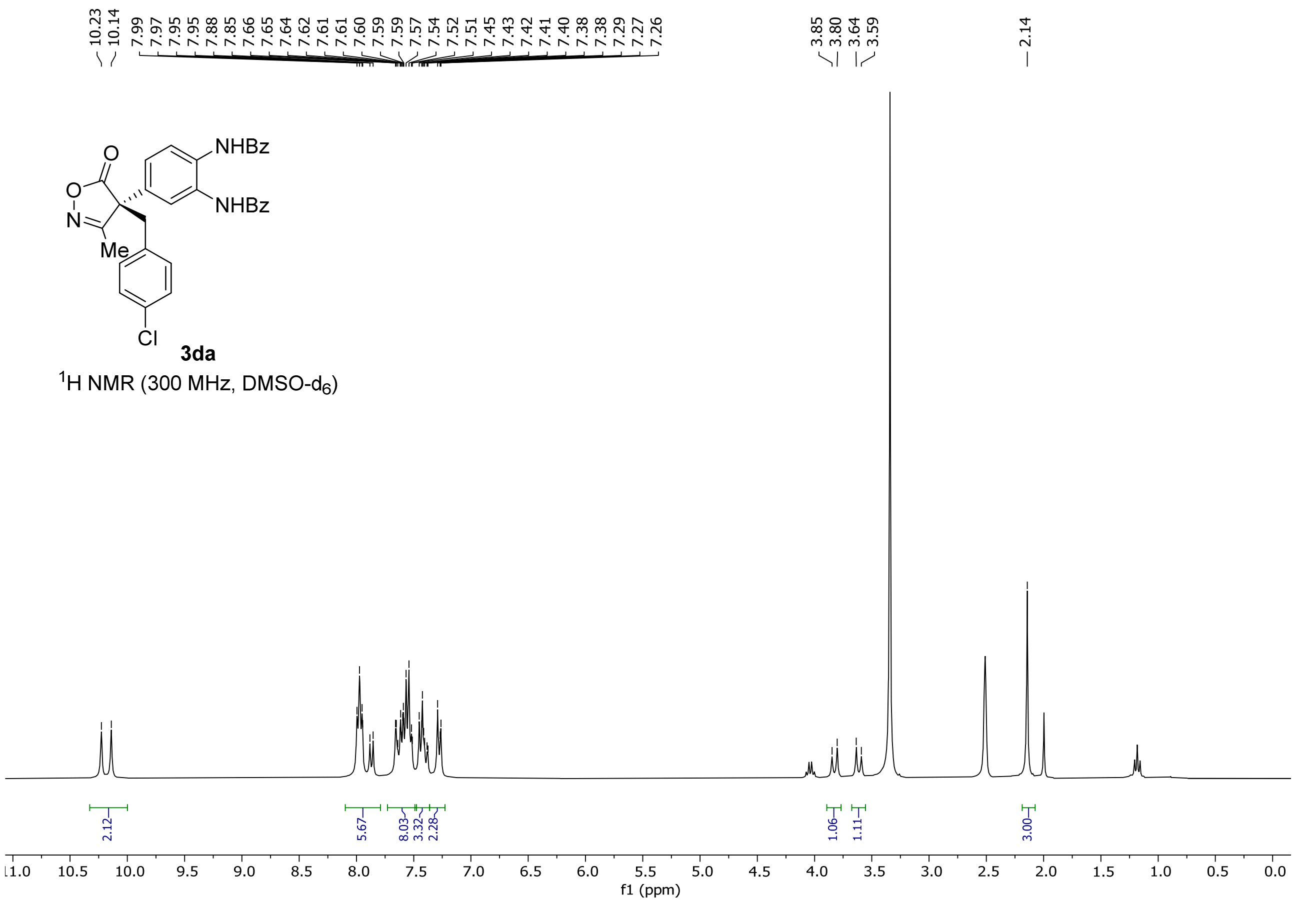


3ba

^{13}C NMR (75 MHz, DMSO-d$_6$)

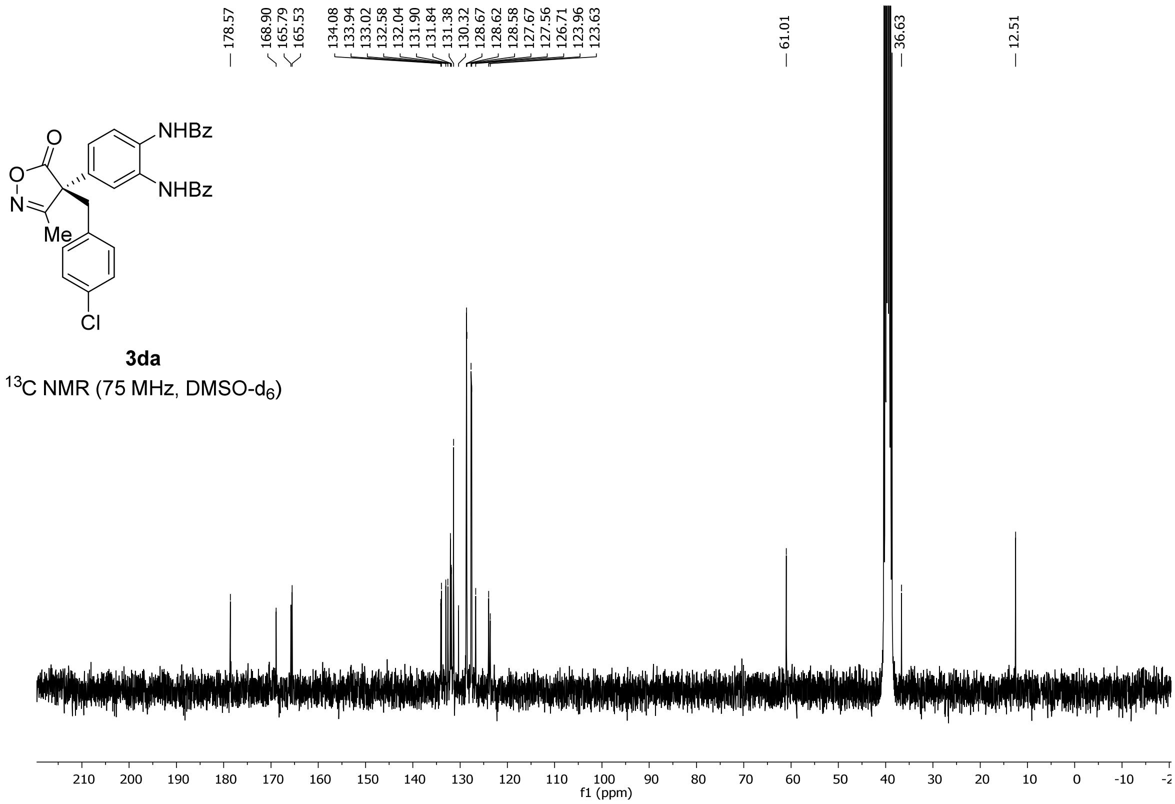

NHBz
NHBz
Me
OMe
3ca
^{1}H NMR (300 MHz, DMSO-d$_6$)
f1 (ppm)


NHBz
NHBz
Me
OMe
3ca
^{13}C NMR (75 MHz, DMSO-d$_6$)
f1 (ppm)



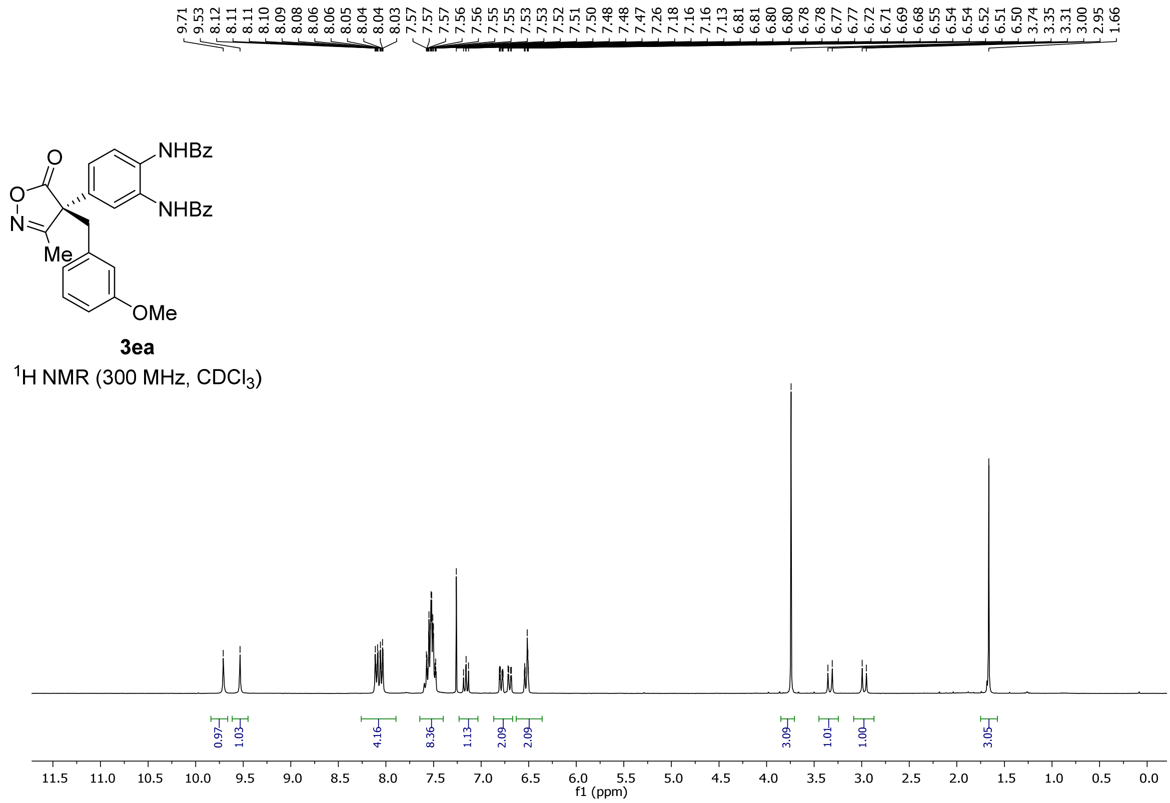
3da

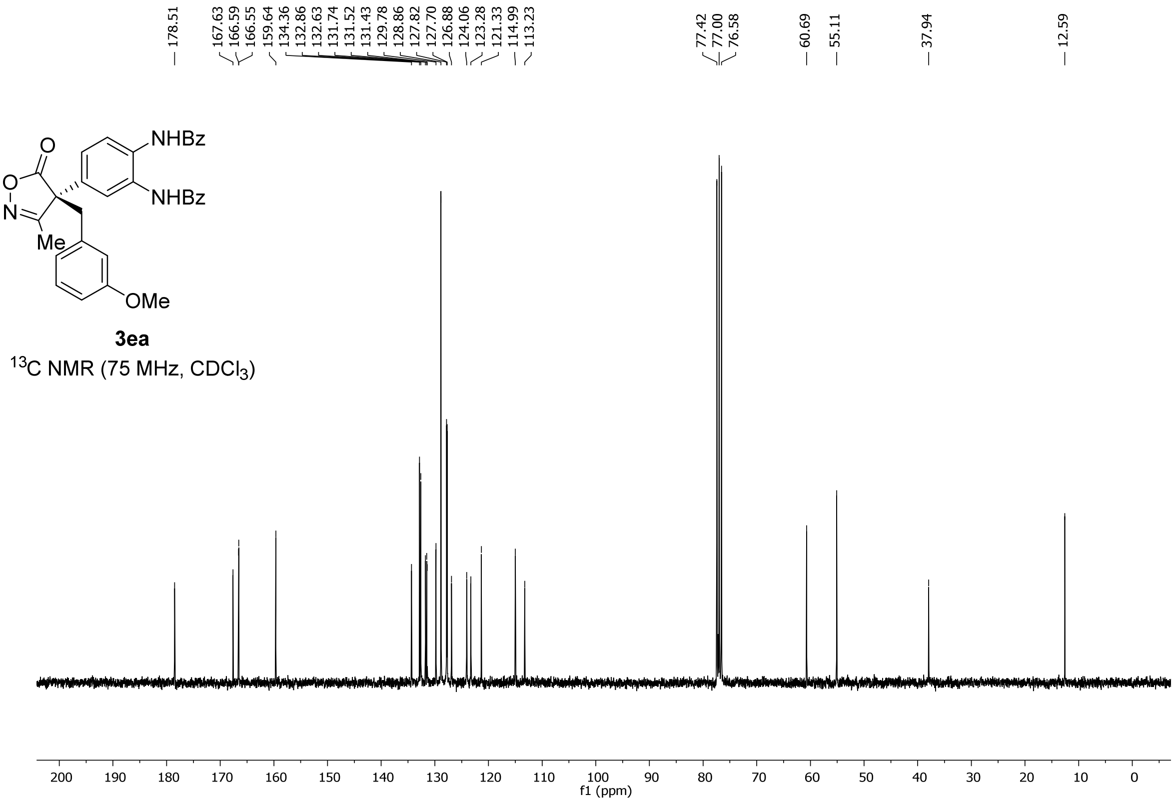
^1H NMR (300 MHz, DMSO-d_6)

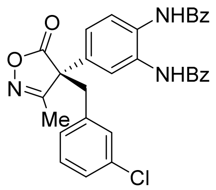


3da

^{13}C NMR (75 MHz, DMSO-d_6)

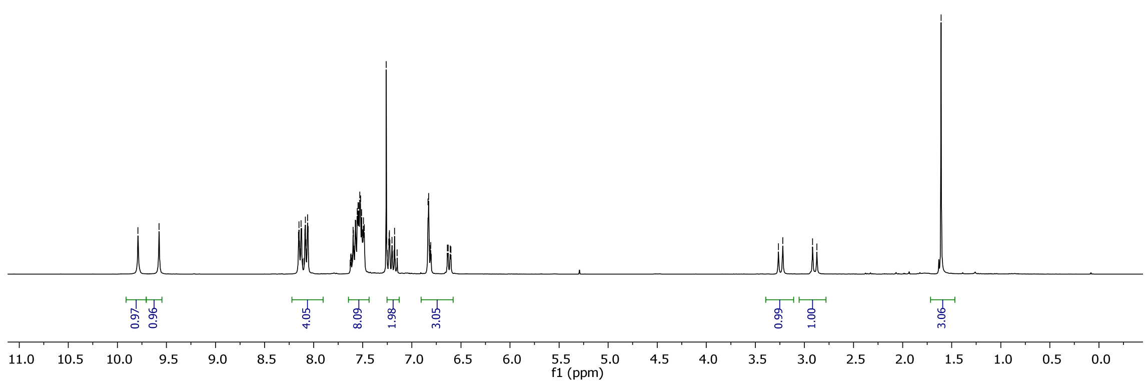

NHBz
NHBz
O
O
N
Me
OMe
3ea
^{1}H NMR (300 MHz, CDCl$_3$)
f1 (ppm)

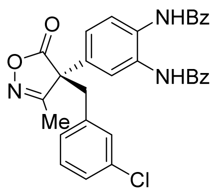

NHBz
NHBz
O
O
N
Me
OMe
3ea
^{13}C NMR (75 MHz, CDCl$_3$)
f1 (ppm)



3fa

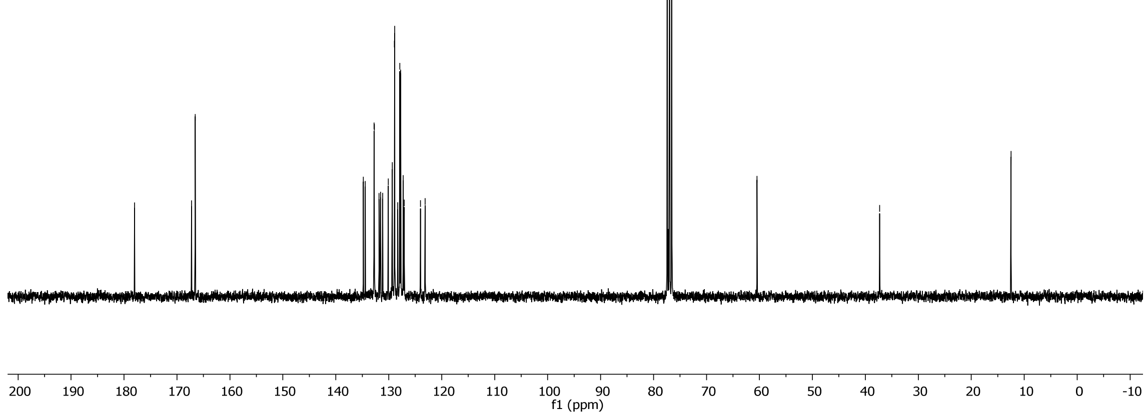
^{1}H NMR (300 MHz, CDCl$_3$)

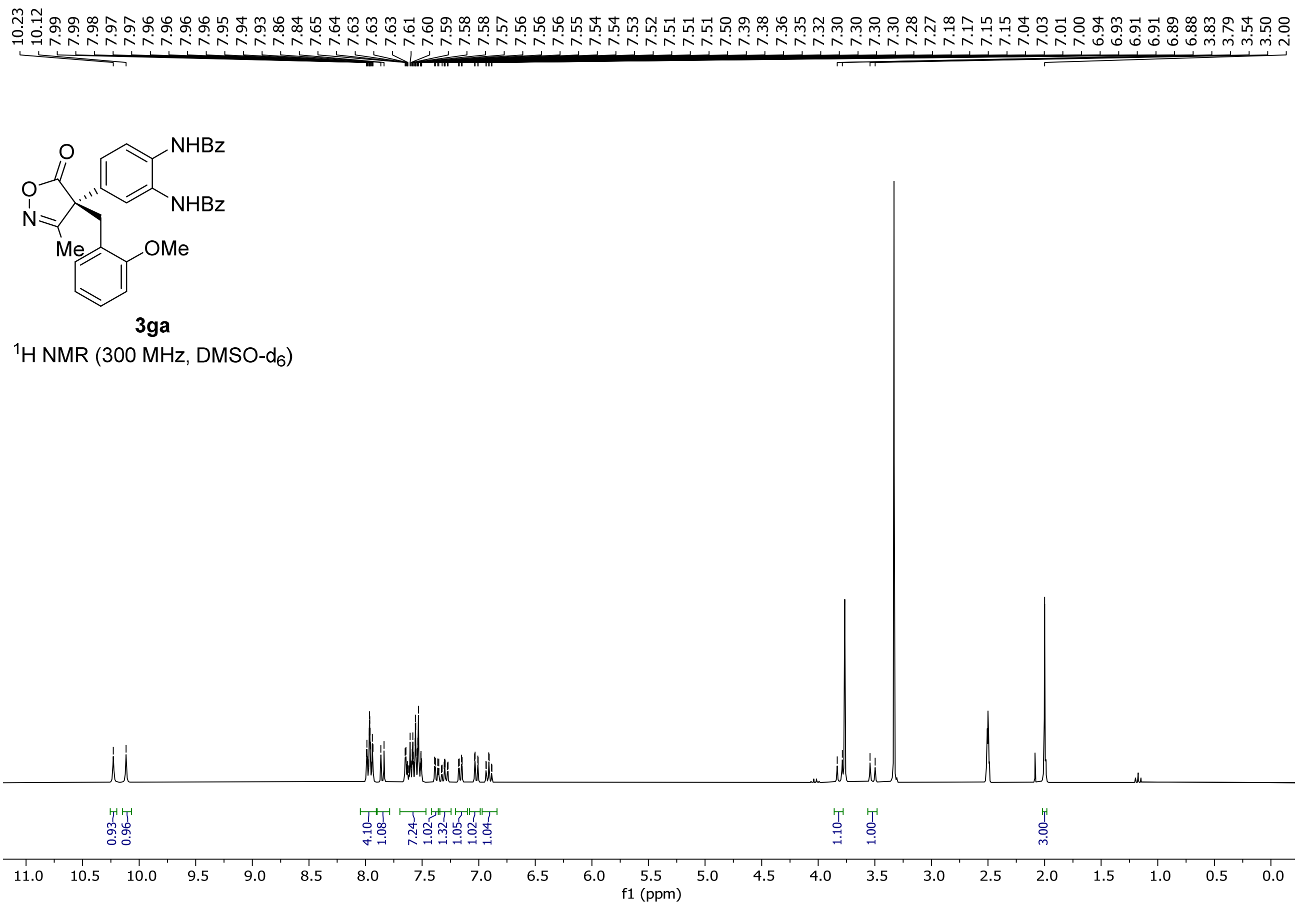




3fa

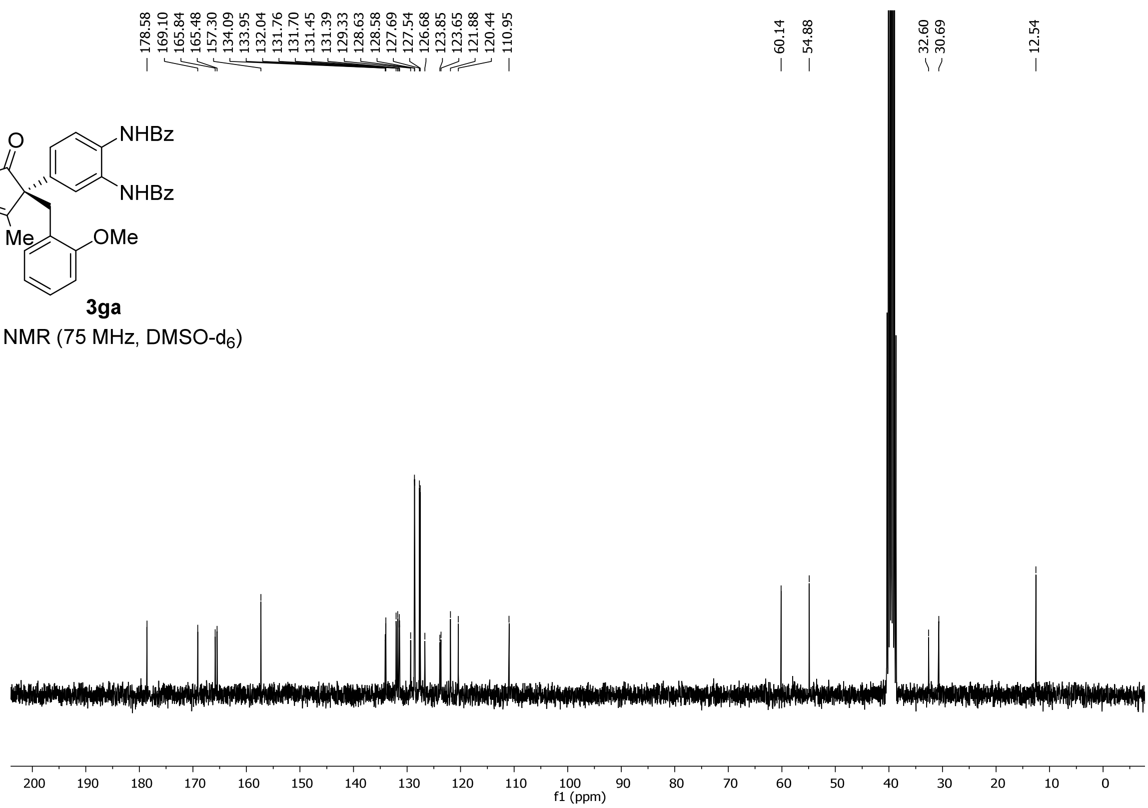
^{13}C NMR (75 MHz, CDCl$_3$)





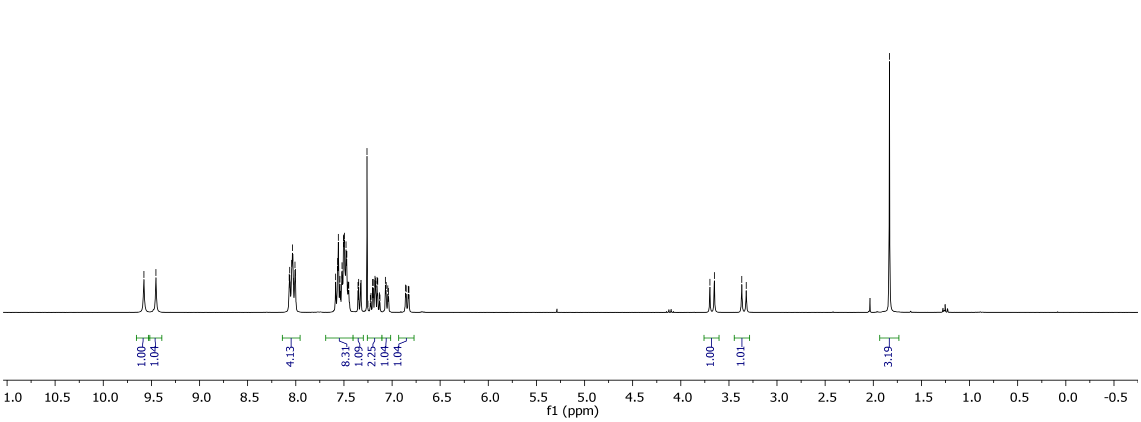
3ga

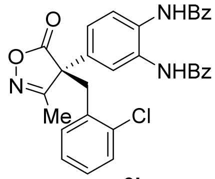
^{1}H NMR (300 MHz, DMSO-d_6)



3ga

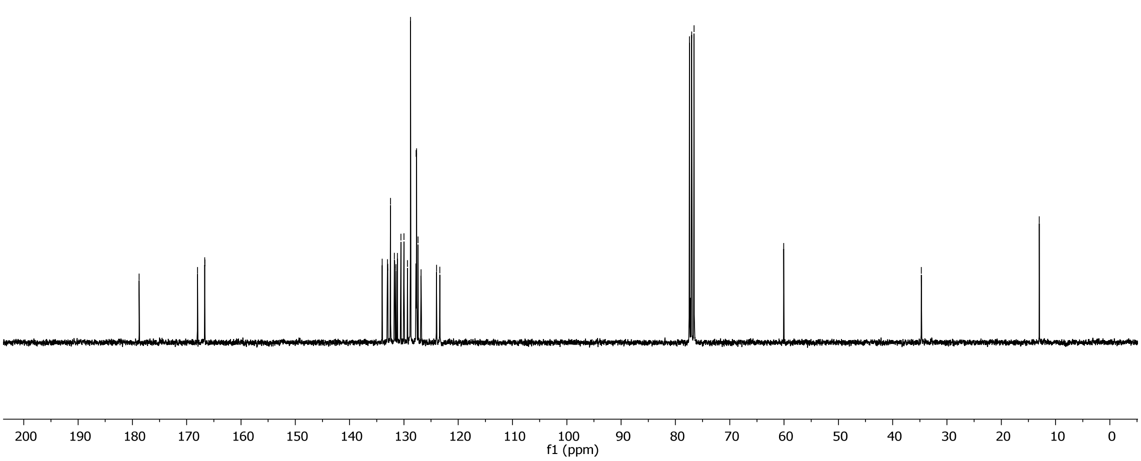
^{13}C NMR (75 MHz, DMSO-d_6)

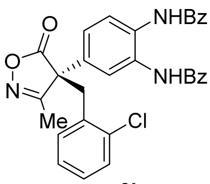




3ha

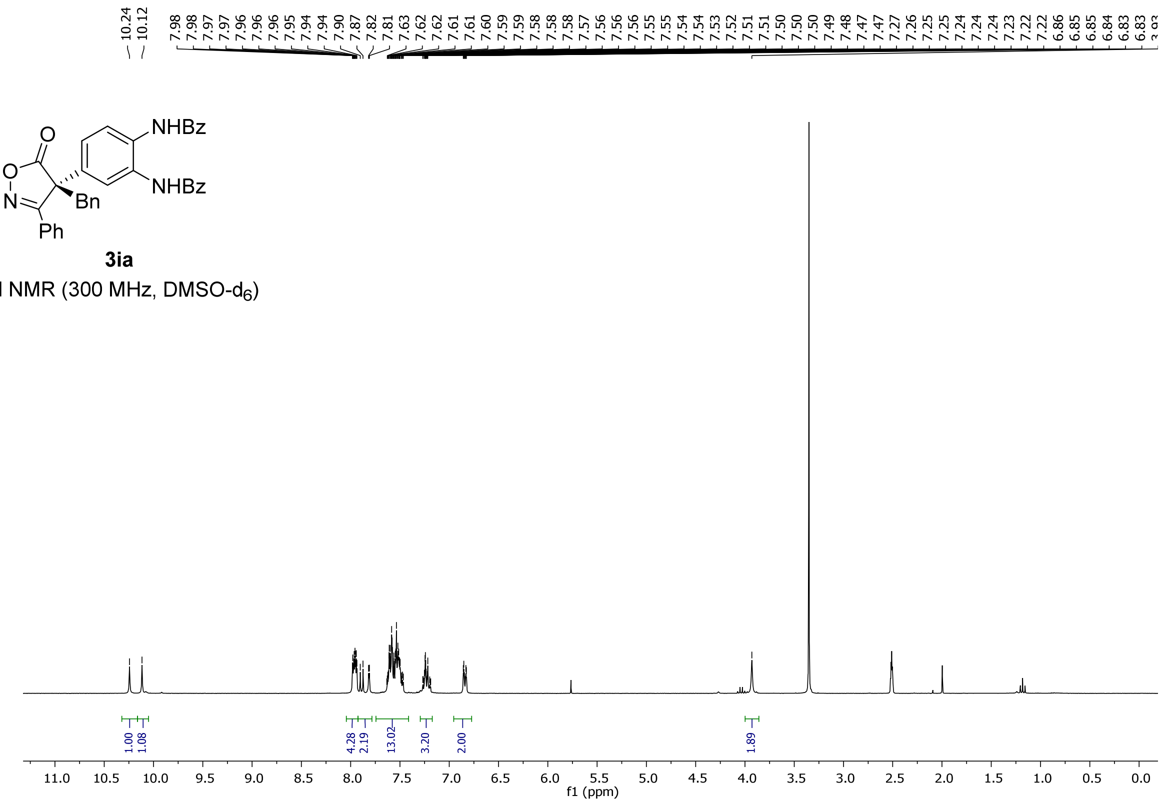
^{1}H NMR (300 MHz, $CDCl_3$)





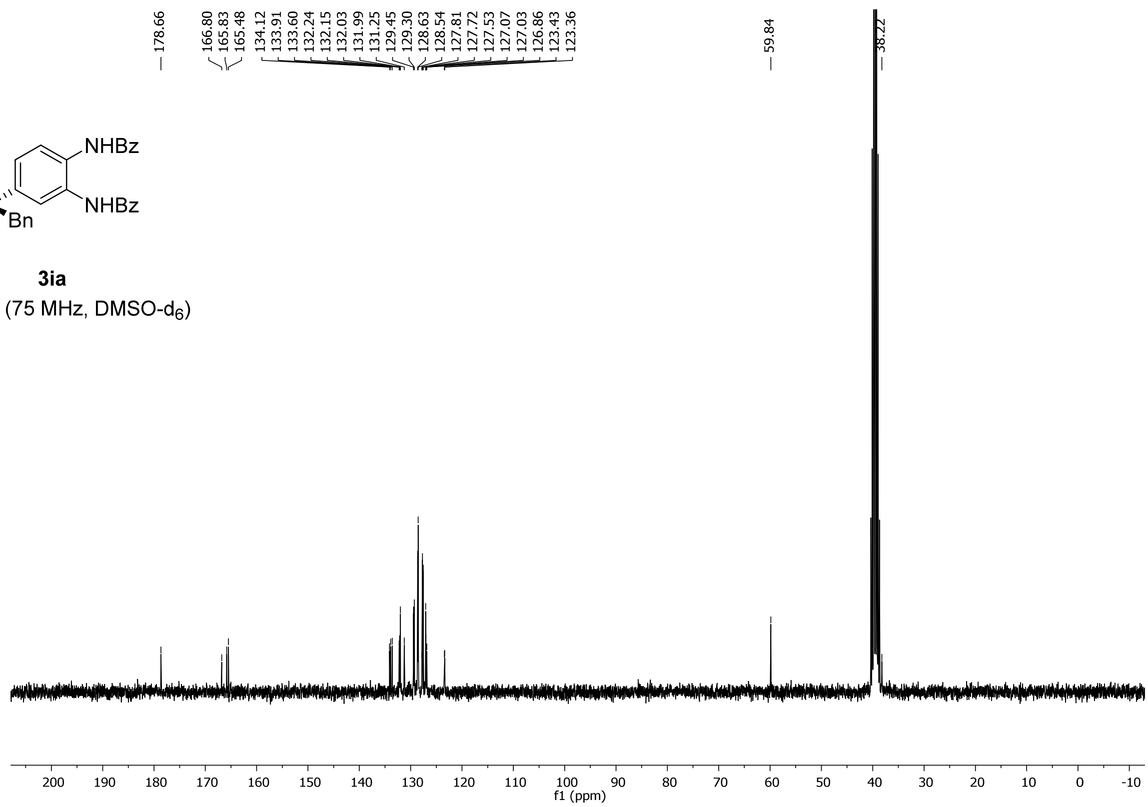
3ha

^{13}C NMR (75 MHz, $CDCl_3$)



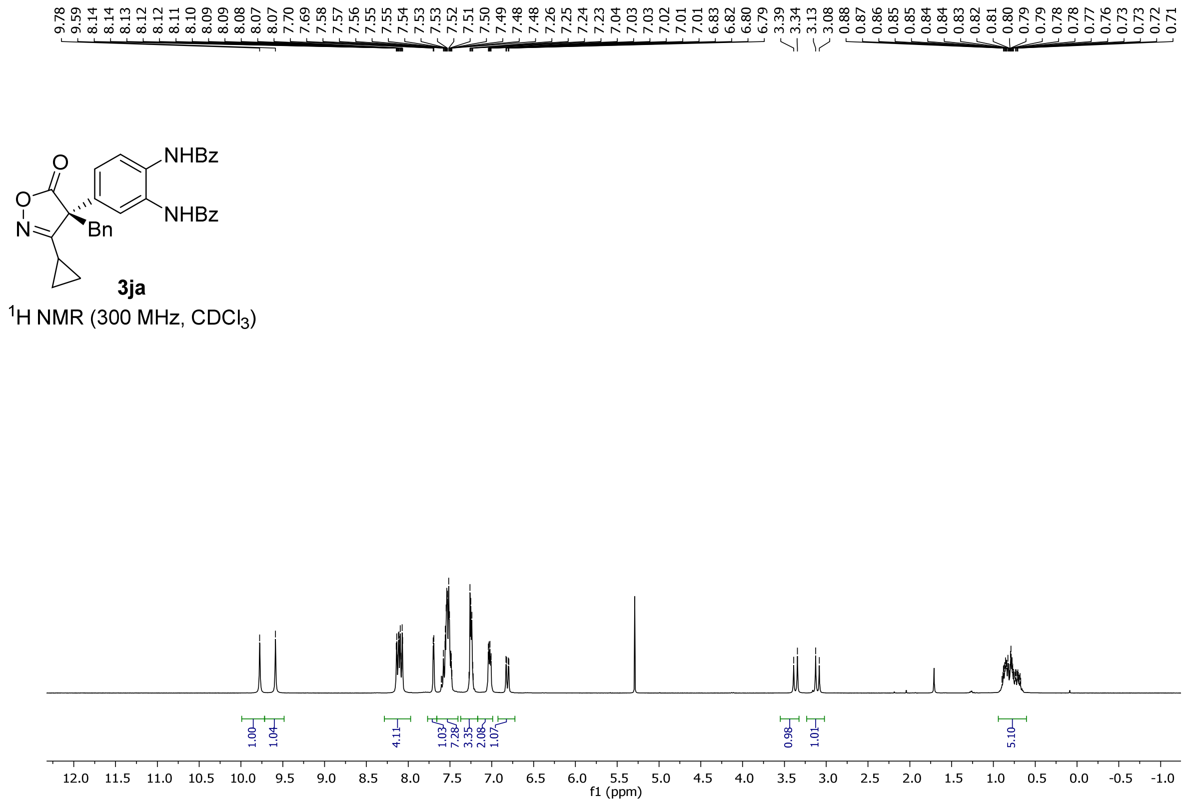
3ia

^{1}H NMR (300 MHz, DMSO-d$_6$)



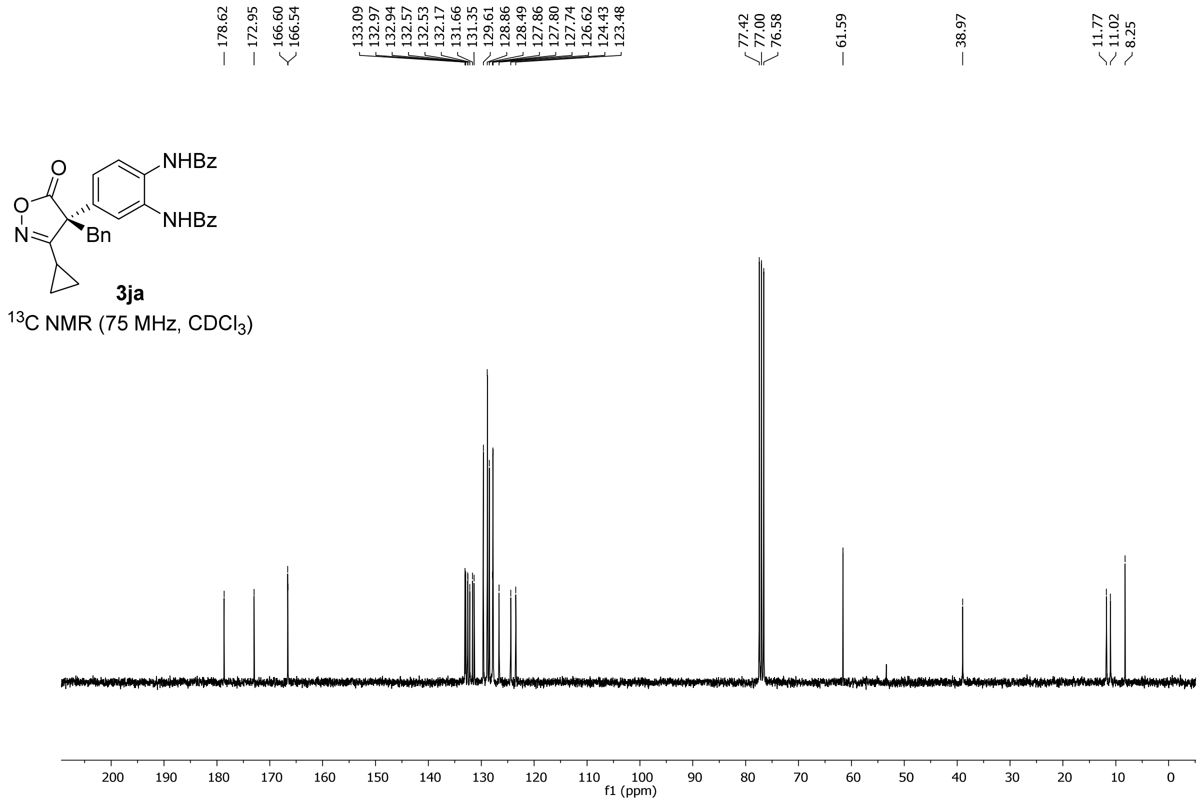
3ia

^{13}C NMR (75 MHz, DMSO-d$_6$)



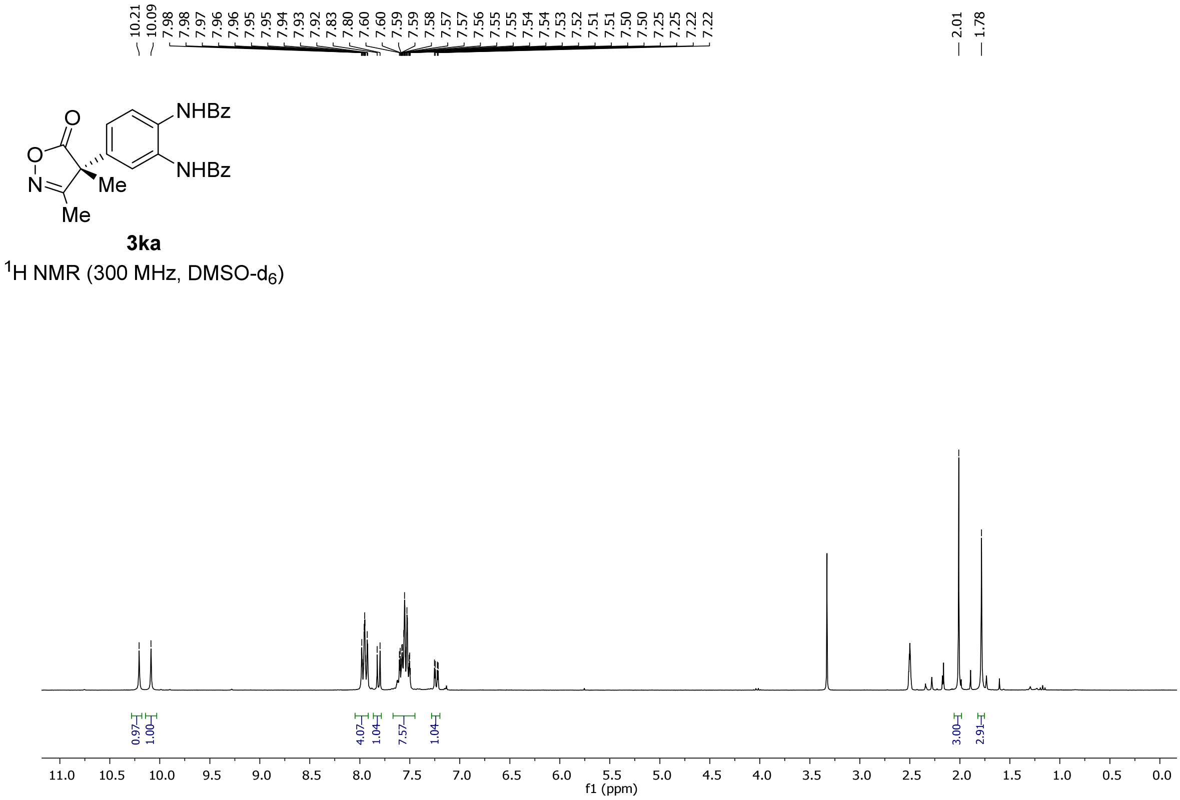
3ja

^{1}H NMR (300 MHz, $CDCl_3$)



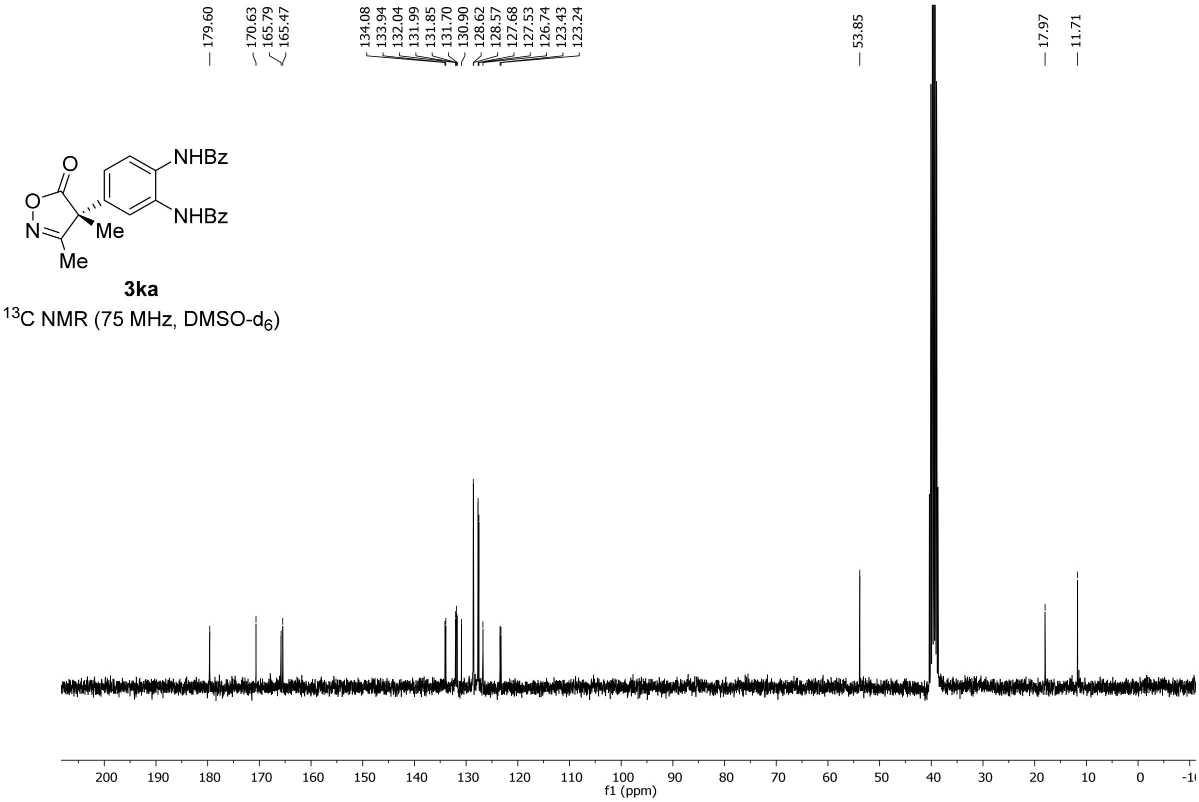
3ja

^{13}C NMR (75 MHz, $CDCl_3$)



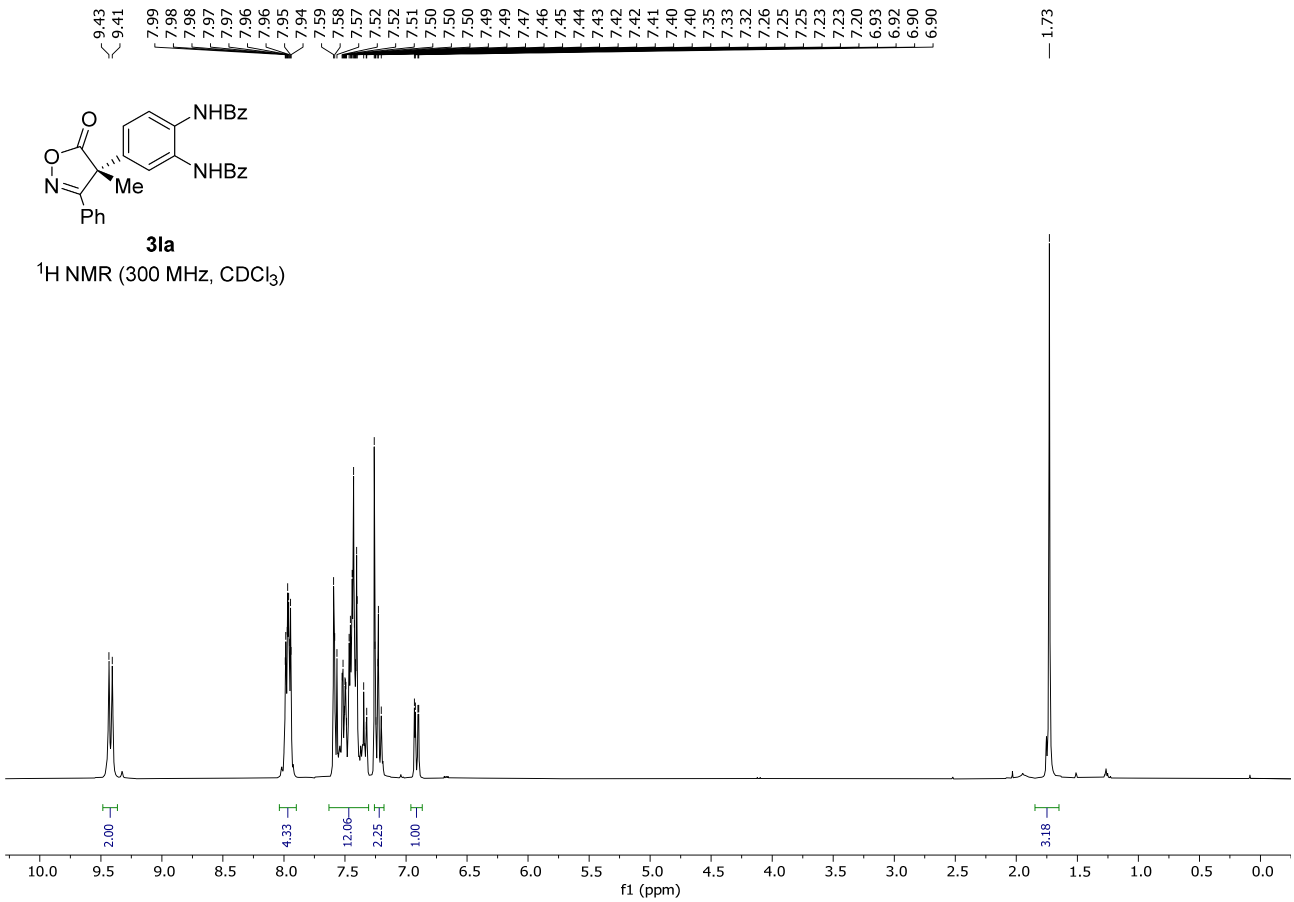
3ka

^{1}H NMR (300 MHz, DMSO-d$_6$)



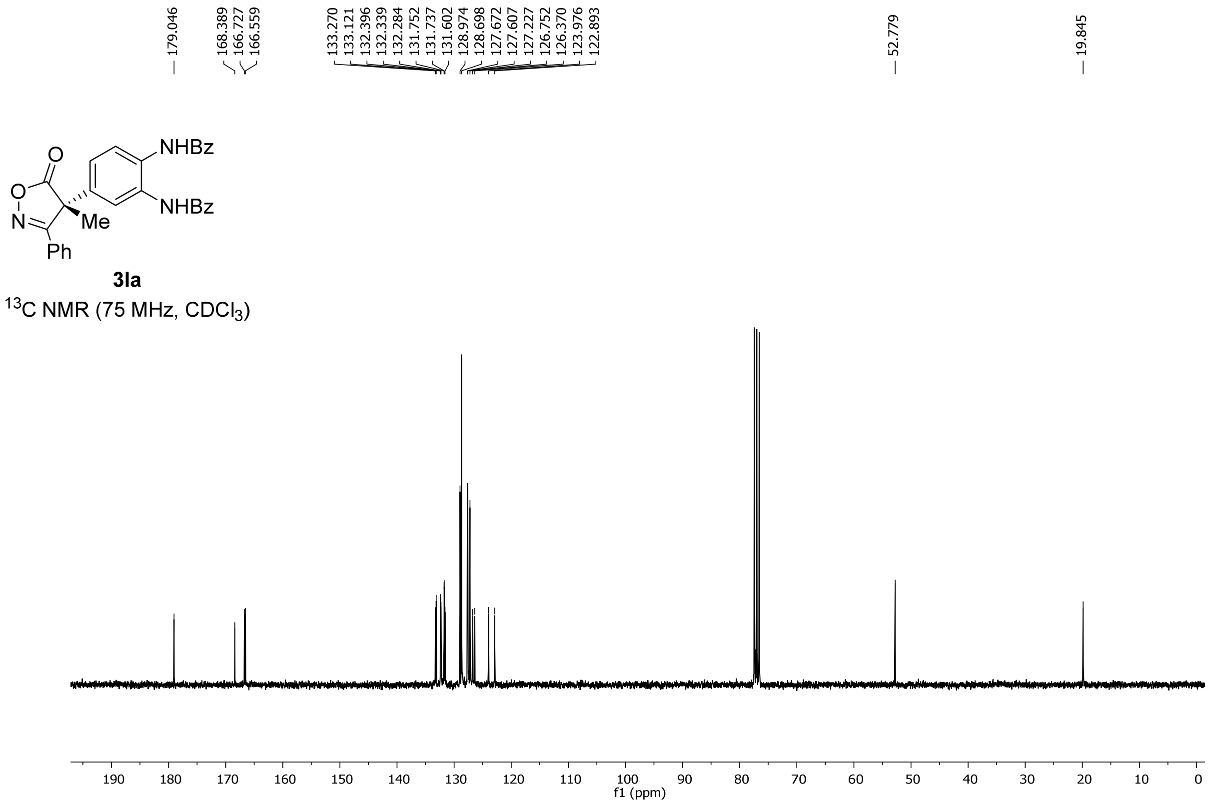
3ka

^{13}C NMR (75 MHz, DMSO-d$_6$)



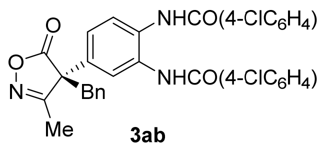
3la

^{1}H NMR (300 MHz, $CDCl_3$)



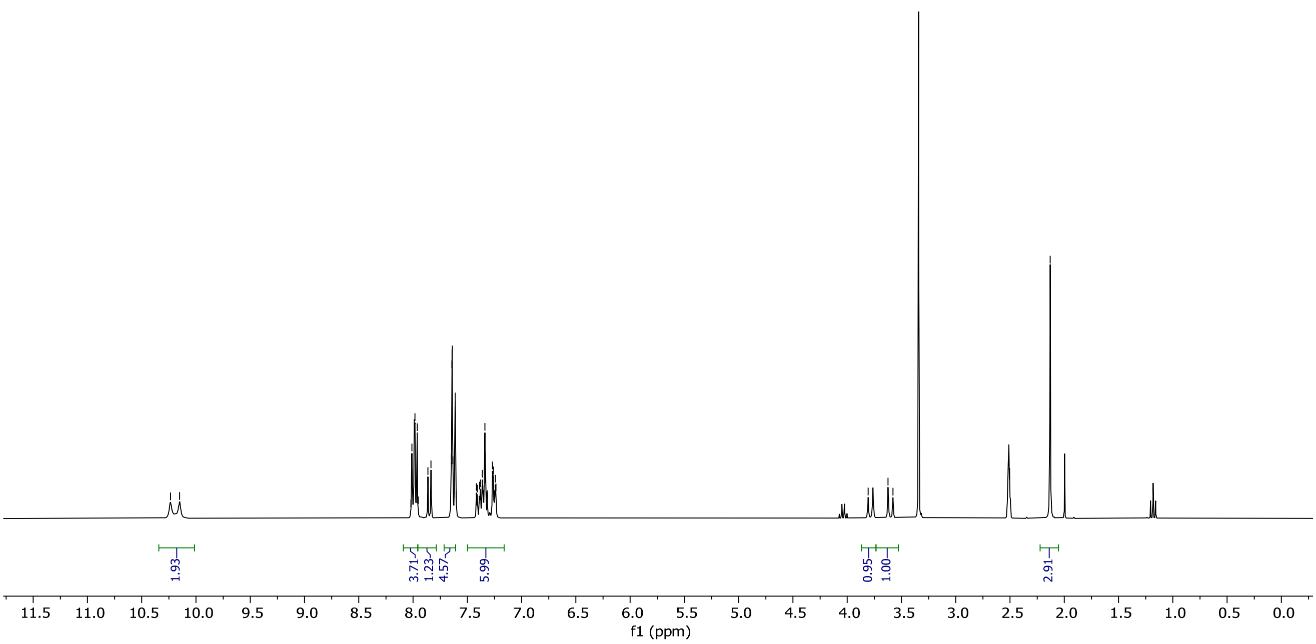
3la

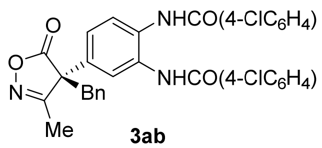
^{13}C NMR (75 MHz, $CDCl_3$)



3ab

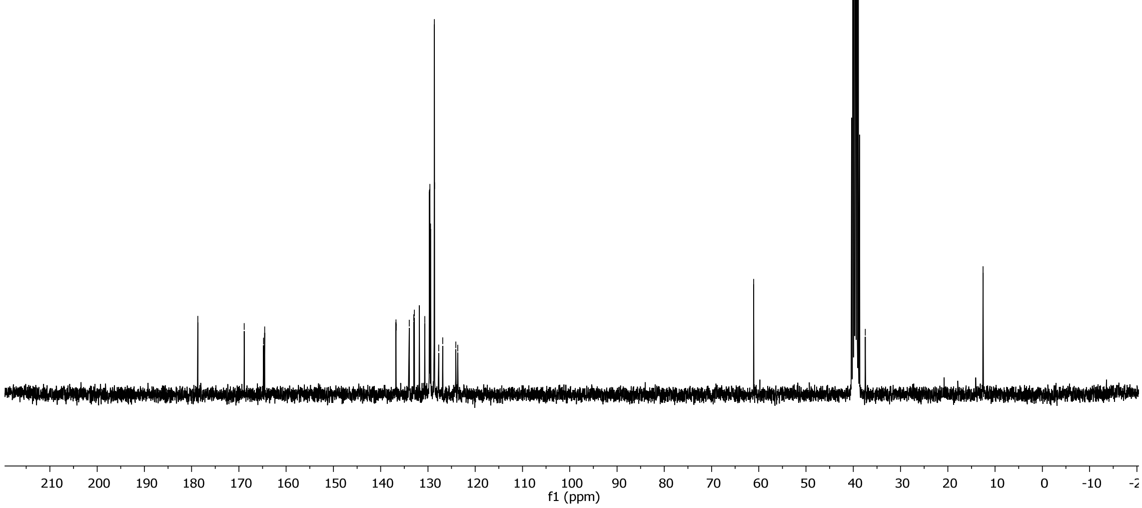
^{1}H NMR (300 MHz, DMSO-d_6)

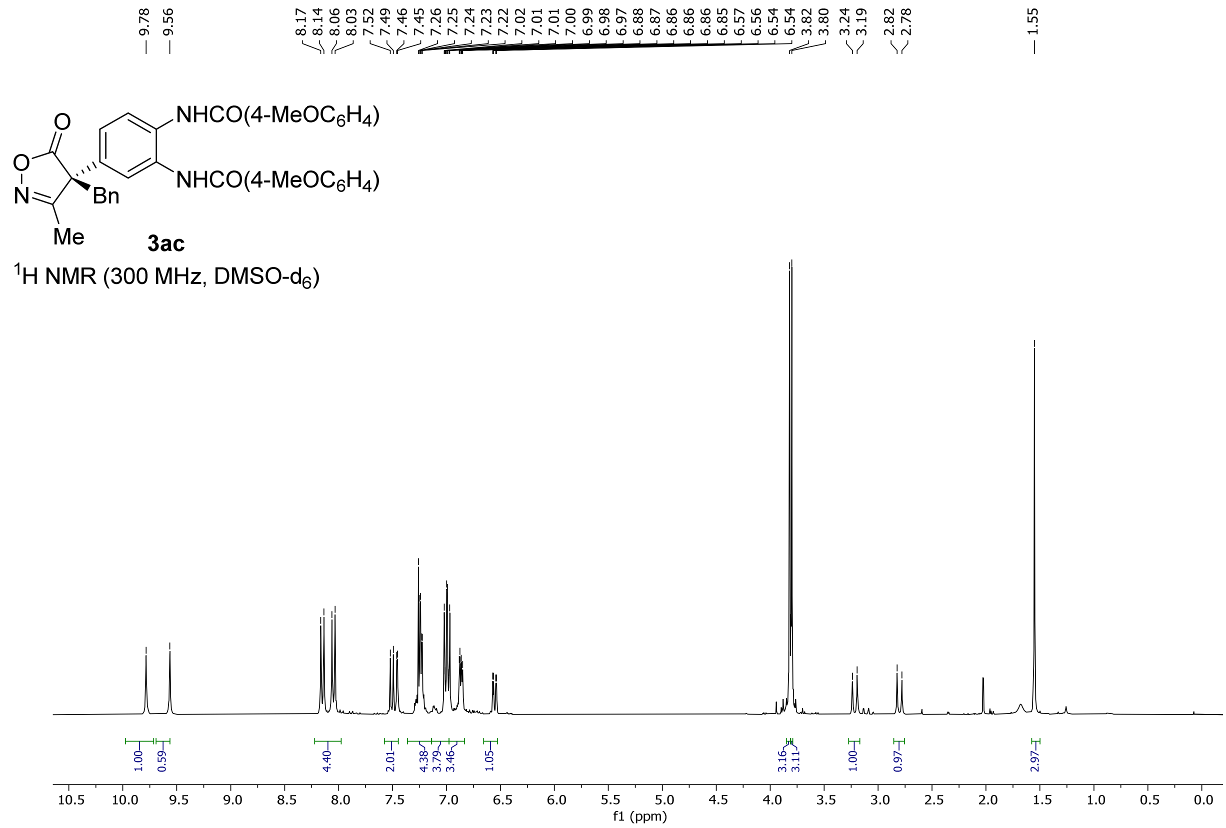


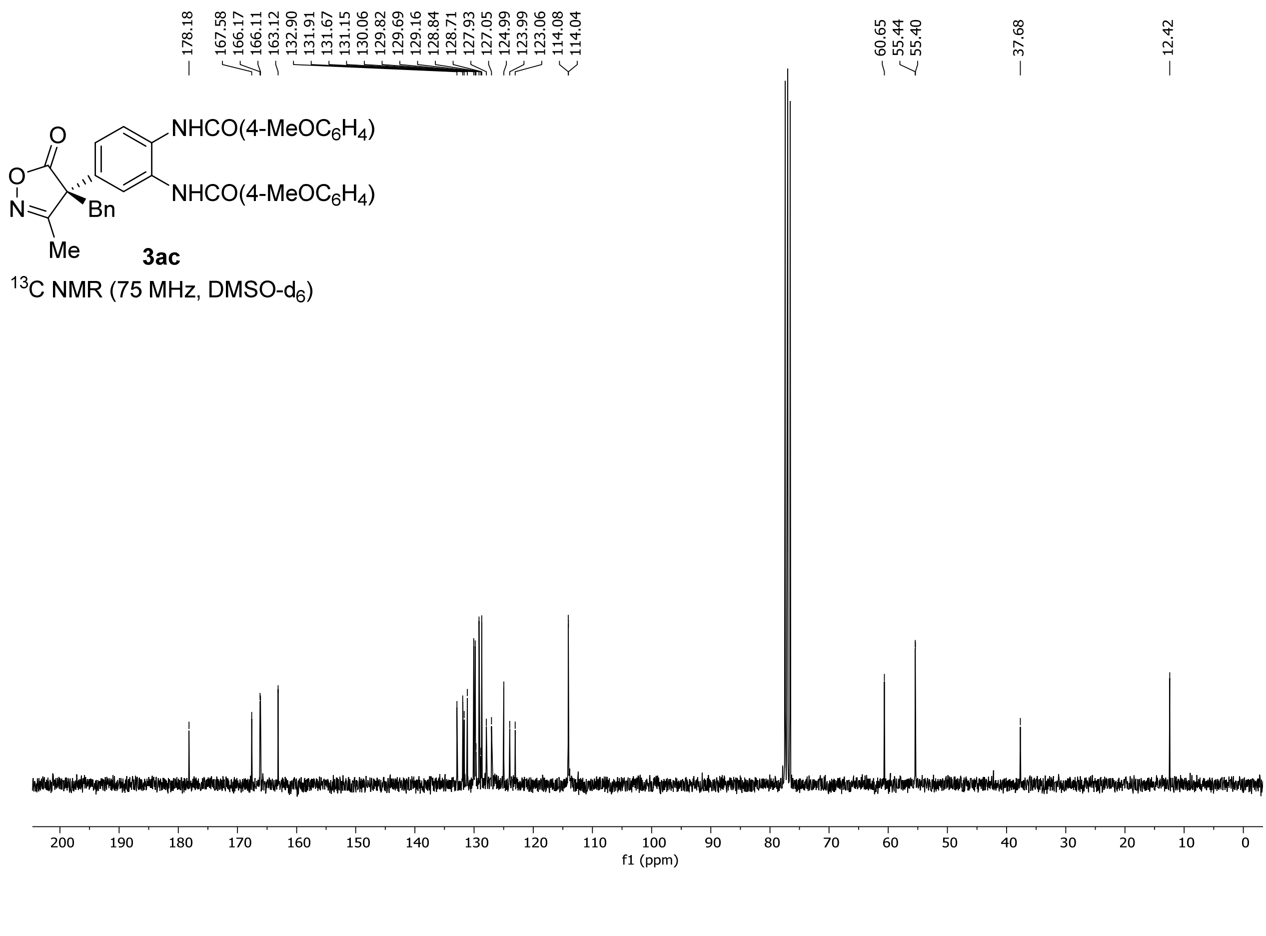


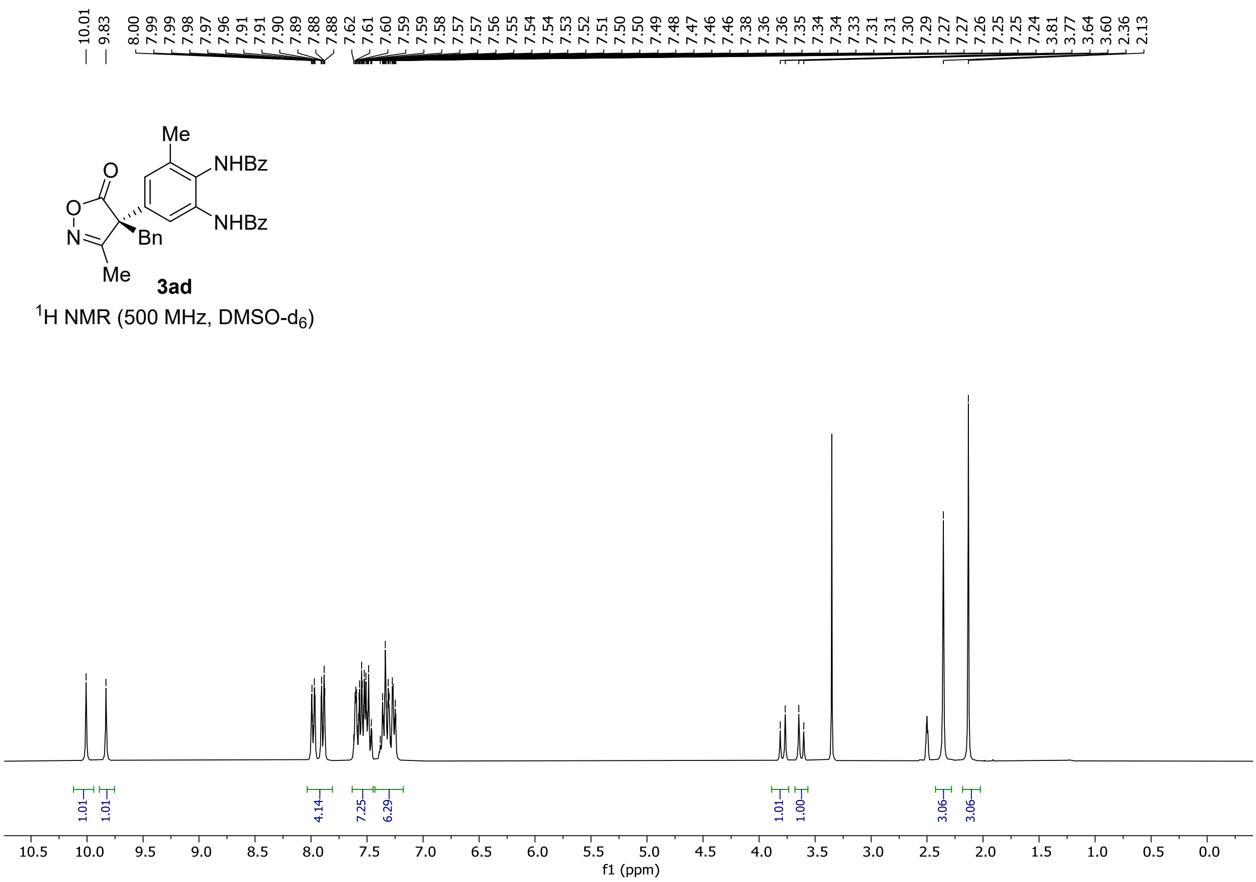
3ab

^{13}C NMR (75 MHz, DMSO-d_6)



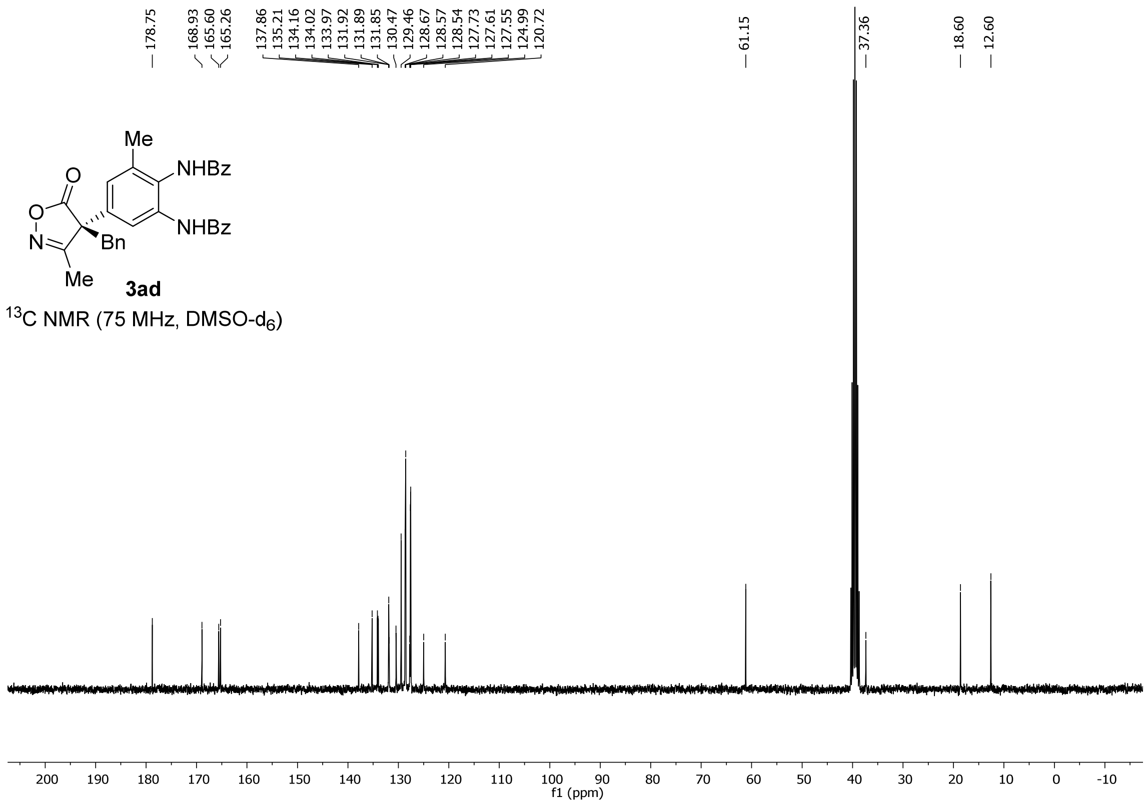

NHCO(4-MeOC6H4)
NHCO(4-MeOC6H4)
O
O
N
Bn
Me
3ac
1H NMR (300 MHz, DMSO-d6)
f1 (ppm)


NHCO(4-MeOC6H4)
NHCO(4-MeOC6H4)
O
O
N
Bn
Me
3ac
13C NMR (75 MHz, DMSO-d6)
f1 (ppm)



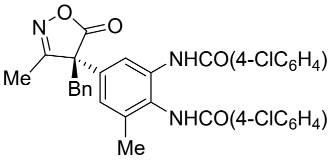
3ad

^{1}H NMR (500 MHz, DMSO-d_6)



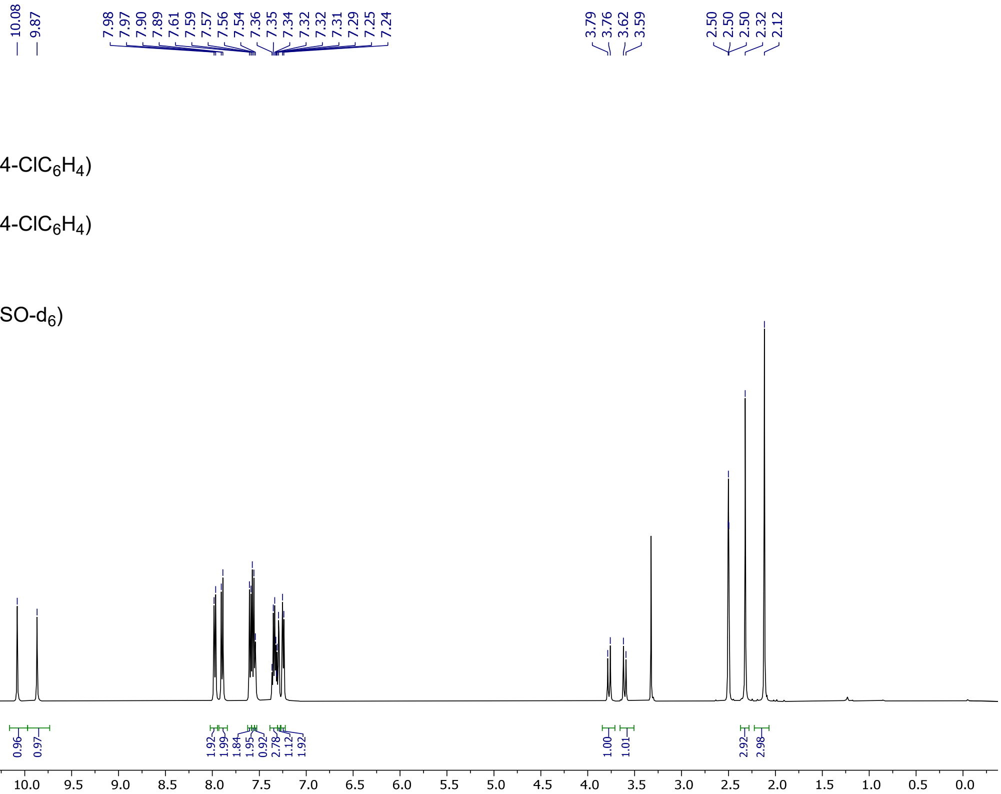
3ad

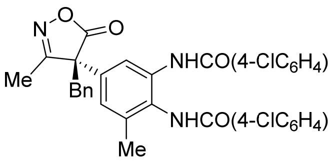
^{13}C NMR (75 MHz, DMSO-d_6)



3ae

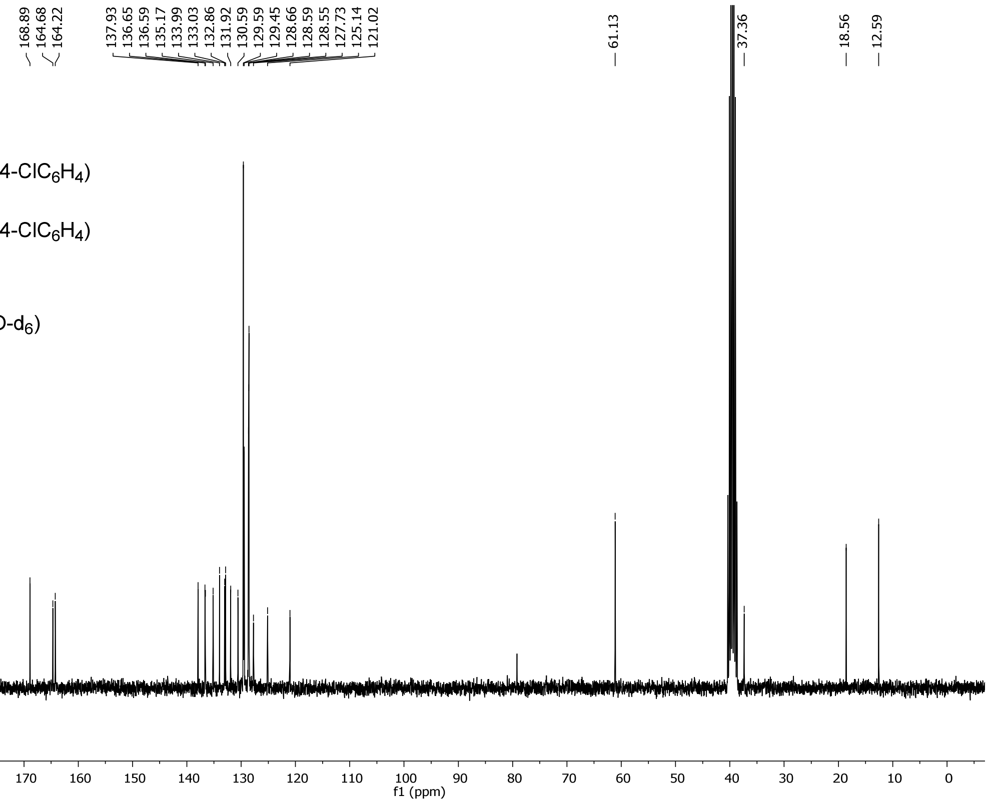
^{1}H NMR (300 MHz, DMSO-d$_6$)

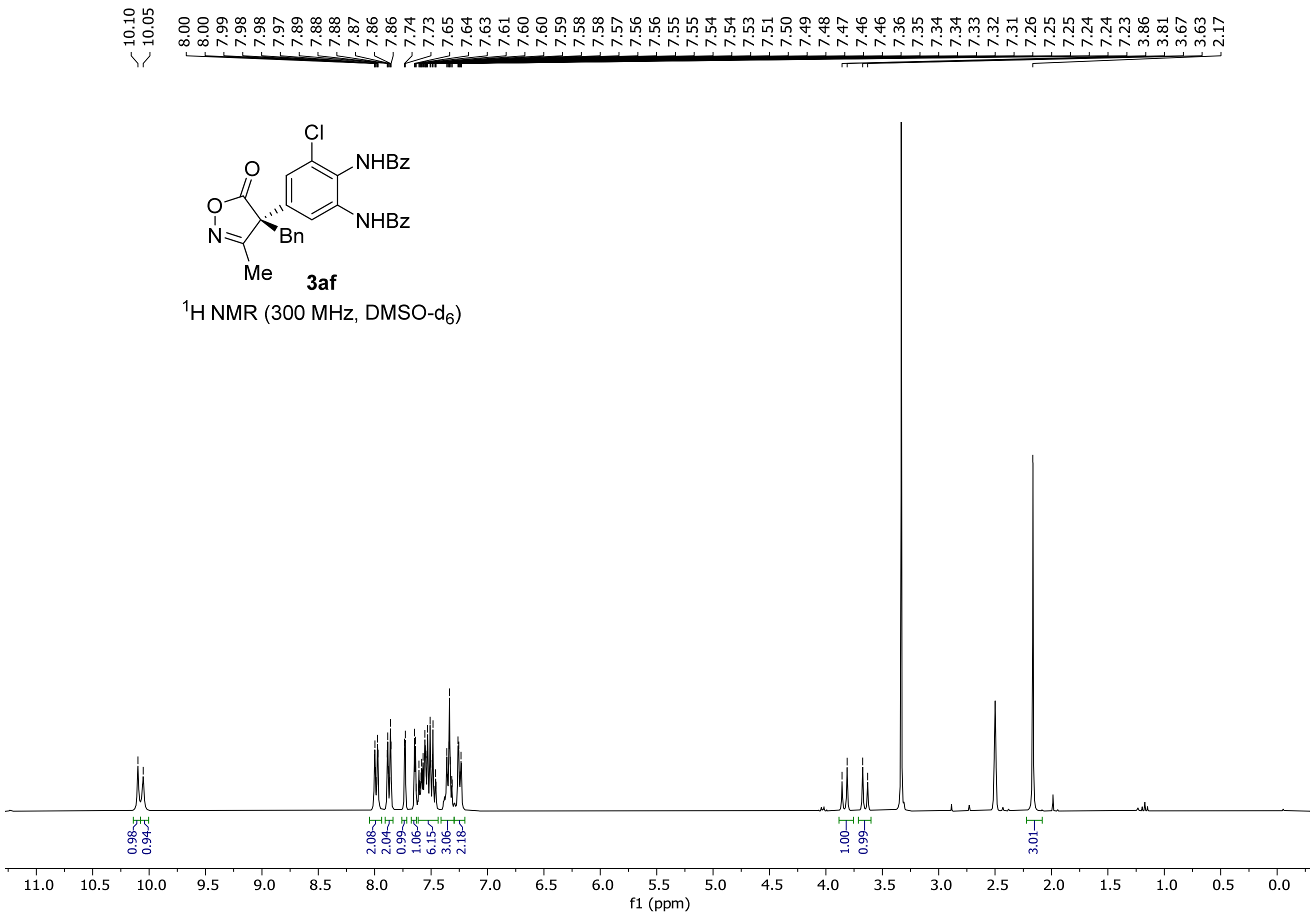


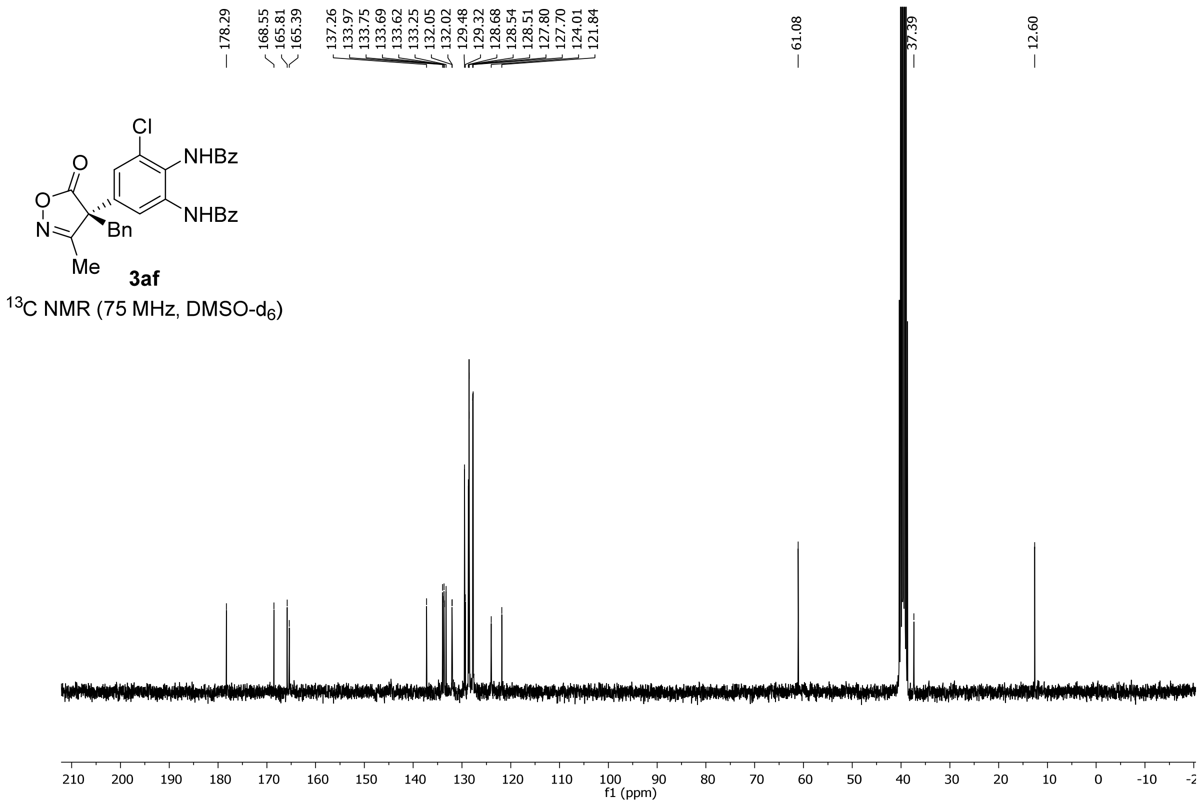


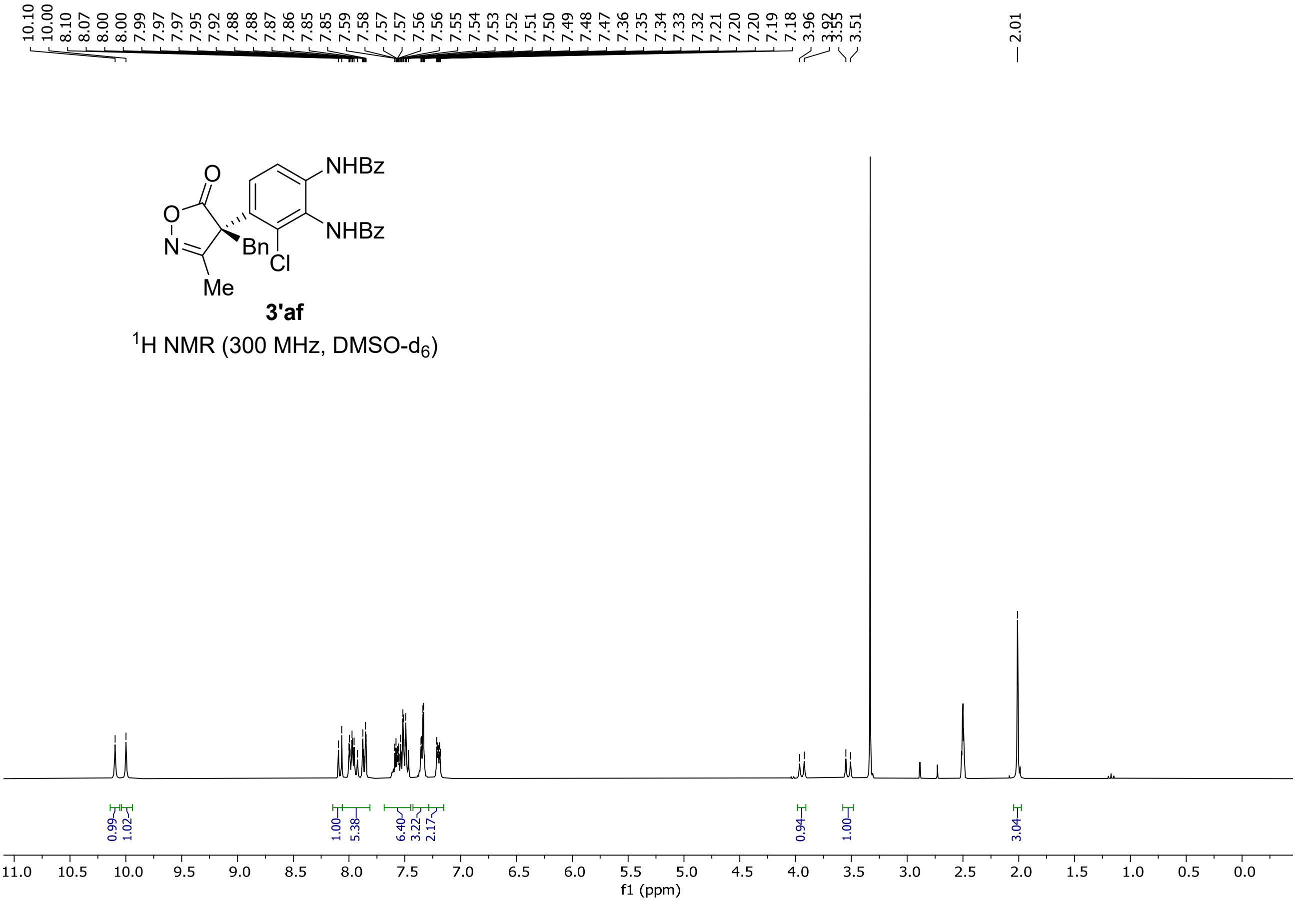
3ae

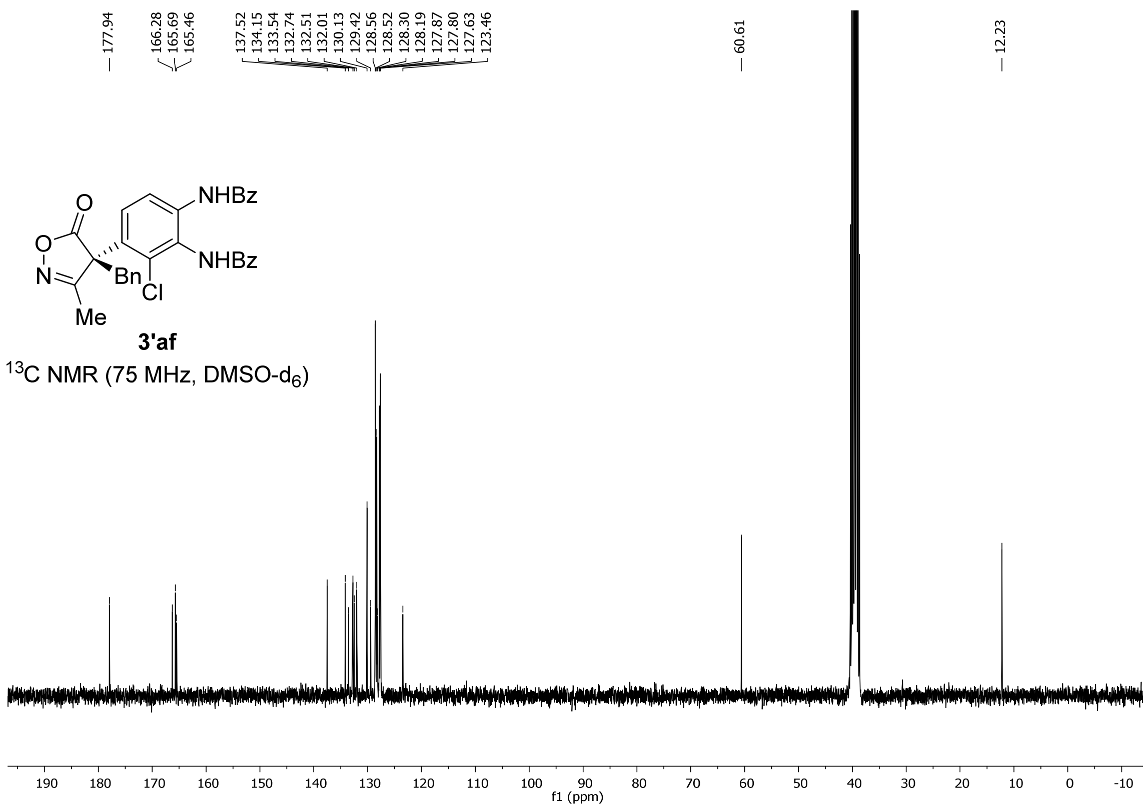
^{13}C NMR (75 MHz, DMSO-d$_6$)

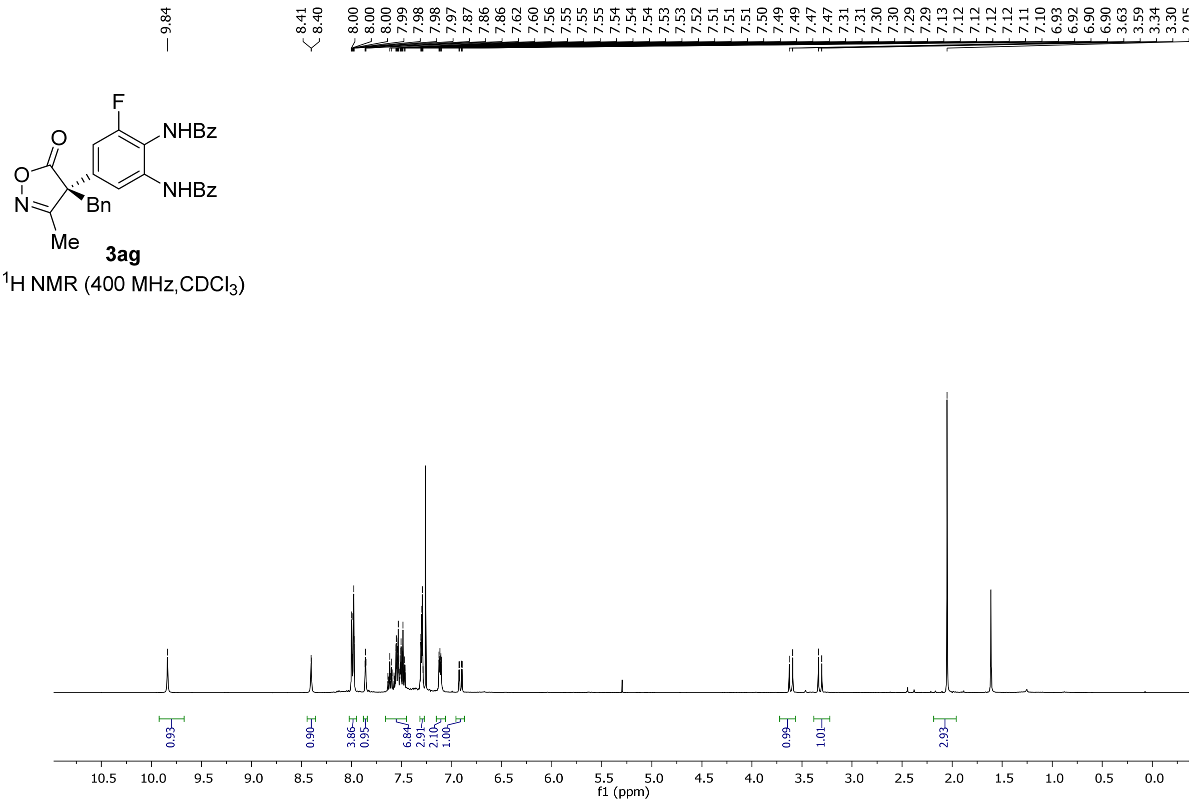



Cl
NHBz
NHBz
O
O
N
Bn
Me
3af
^{1}H NMR (300 MHz, DMSO-d$_6$)
10.10
10.05
8.00
7.86
7.74
7.23
3.86
3.81
3.67
3.63
2.17
f1 (ppm)


Cl
NHBz
NHBz
O
O
N
Bn
Me
3af
^{13}C NMR (75 MHz, DMSO-d$_6$)
178.29
168.55
165.81
165.39
137.26
133.97
133.75
133.69
133.62
133.25
132.05
132.02
129.48
129.32
128.68
128.54
128.51
127.80
127.70
124.01
121.84
61.08
37.39
12.60
f1 (ppm)

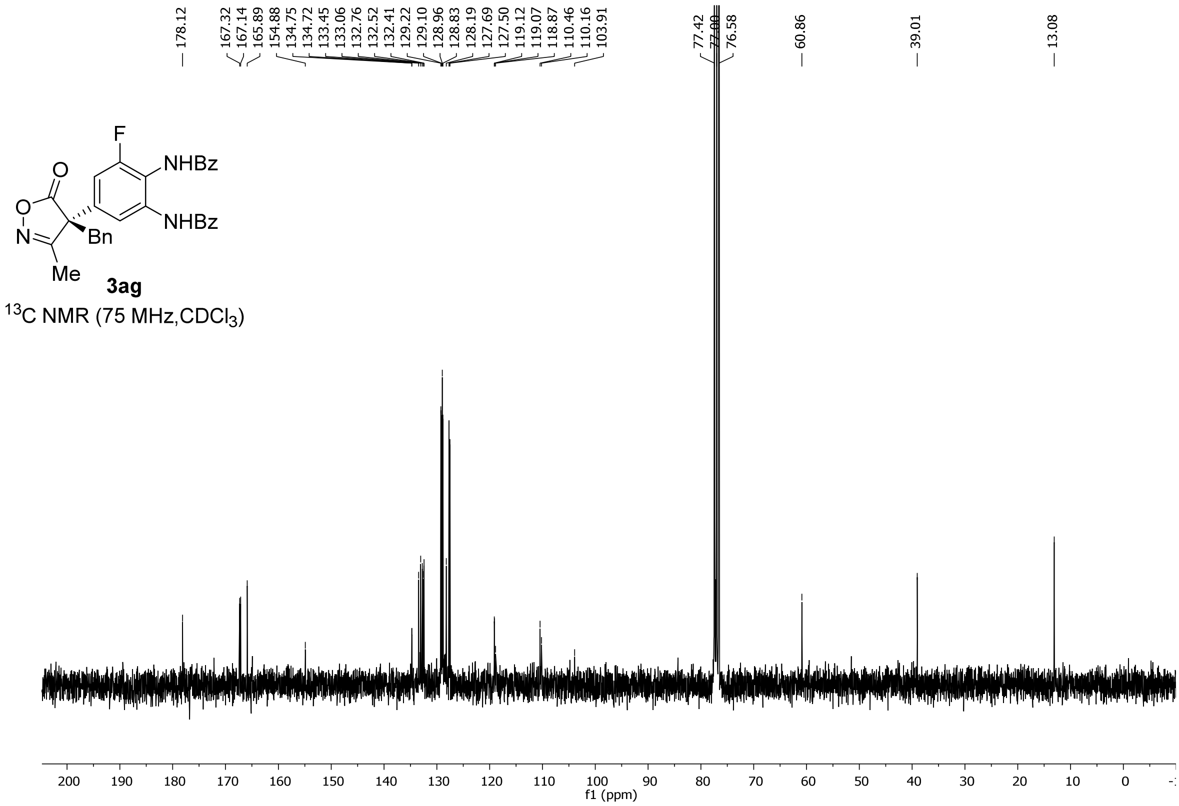

10.10
10.00
8.10
8.07
8.00
8.00
7.99
7.97
7.97
7.95
7.92
7.88
7.88
7.87
7.86
7.85
7.85
7.59
7.58
7.57
7.57
7.56
7.56
7.55
7.54
7.53
7.52
7.51
7.50
7.49
7.48
7.47
7.36
7.35
7.34
7.33
7.32
7.21
7.20
7.20
7.19
7.18
3.96
3.92
3.55
3.51
2.01
NHBz
NHBz
O
O
N
Bn
Cl
Me
3'af
^{1}H NMR (300 MHz, DMSO-d$_6$)
0.99
1.02
1.00
5.38
6.40
3.22
2.17
0.94
1.00
3.04
11.0 10.5 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)


177.94
166.28
165.69
165.46
137.52
134.15
133.54
132.74
132.51
132.01
130.13
129.42
128.56
128.52
128.30
128.19
127.87
127.80
127.63
123.46
60.61
12.23
NHBz
NHBz
O
O
N
Bn
Cl
Me
3'af
^{13}C NMR (75 MHz, DMSO-d$_6$)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



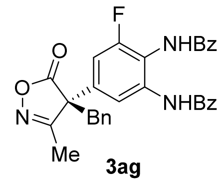
3ag

^{1}H NMR (400 MHz,$CDCl_3$)



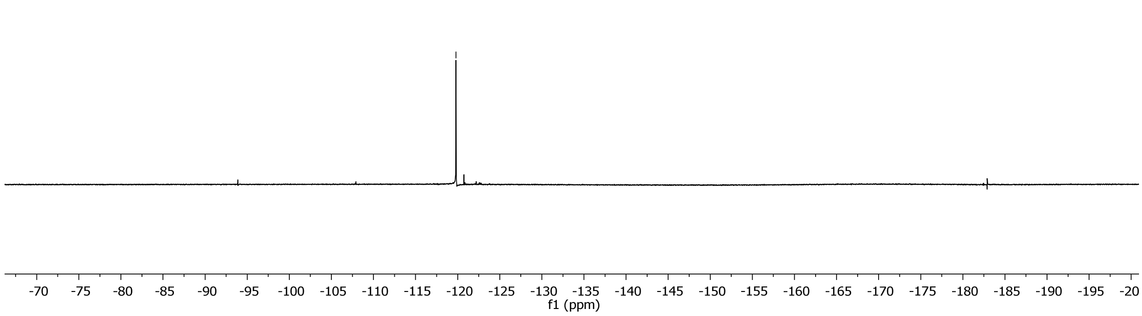
3ag

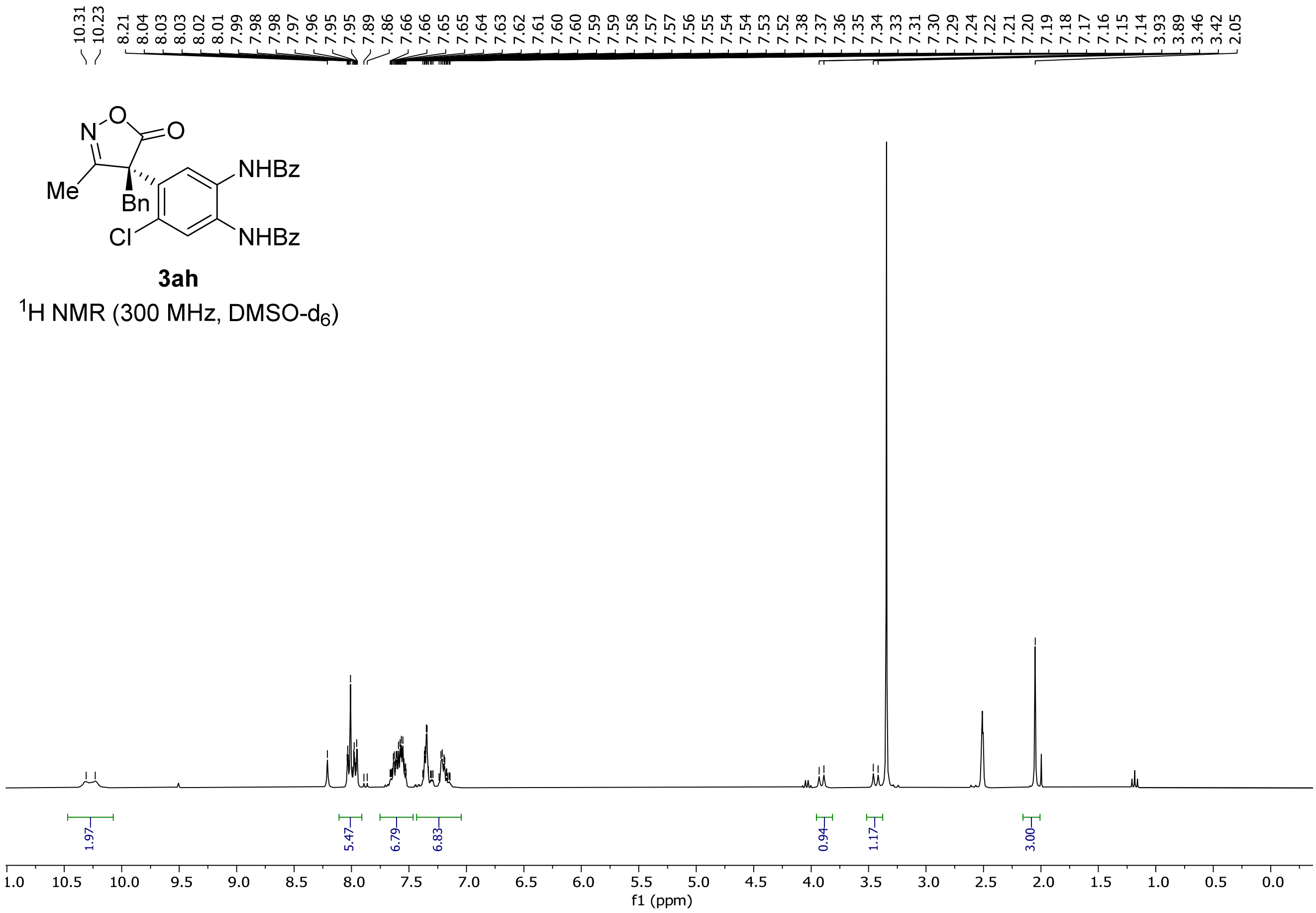
^{13}C NMR (75 MHz,$CDCl_3$)



3ag

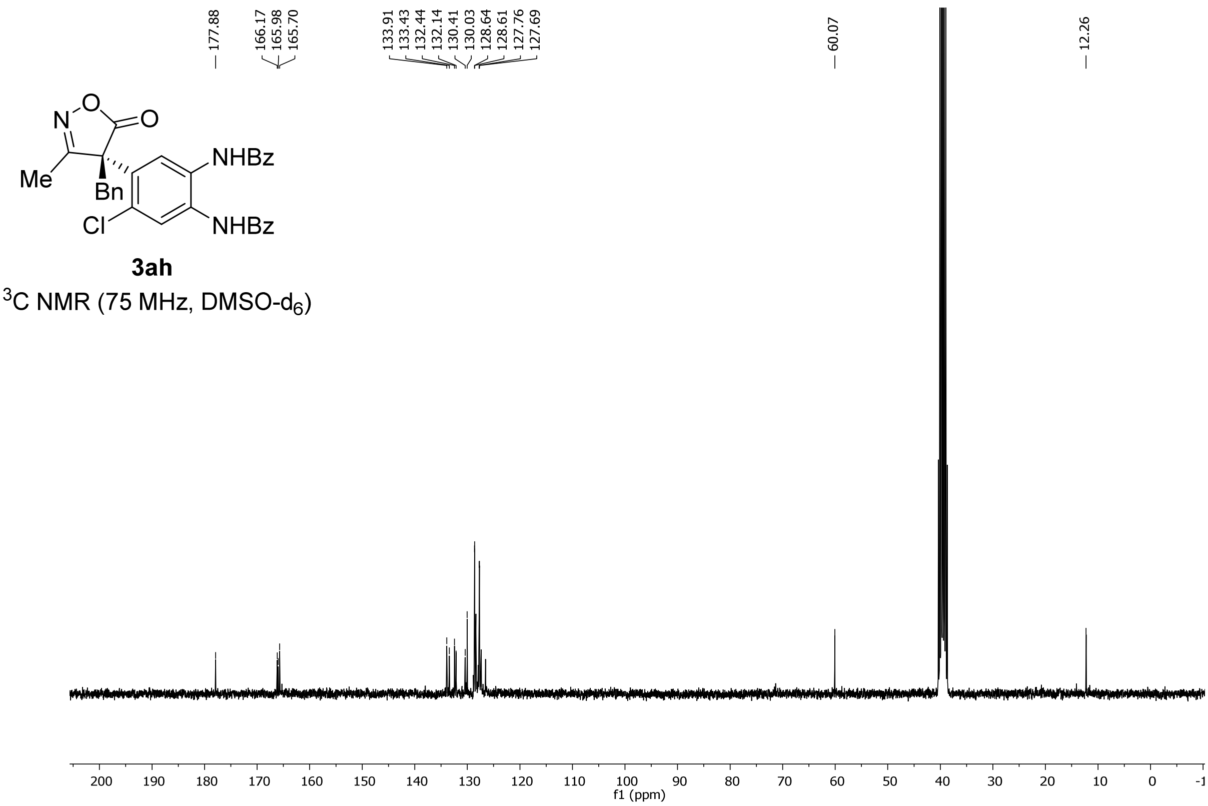
^{19}F NMR (282 MHz,CDCl$_3$)





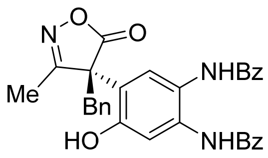
3ah

^{1}H NMR (300 MHz, DMSO-d$_6$)



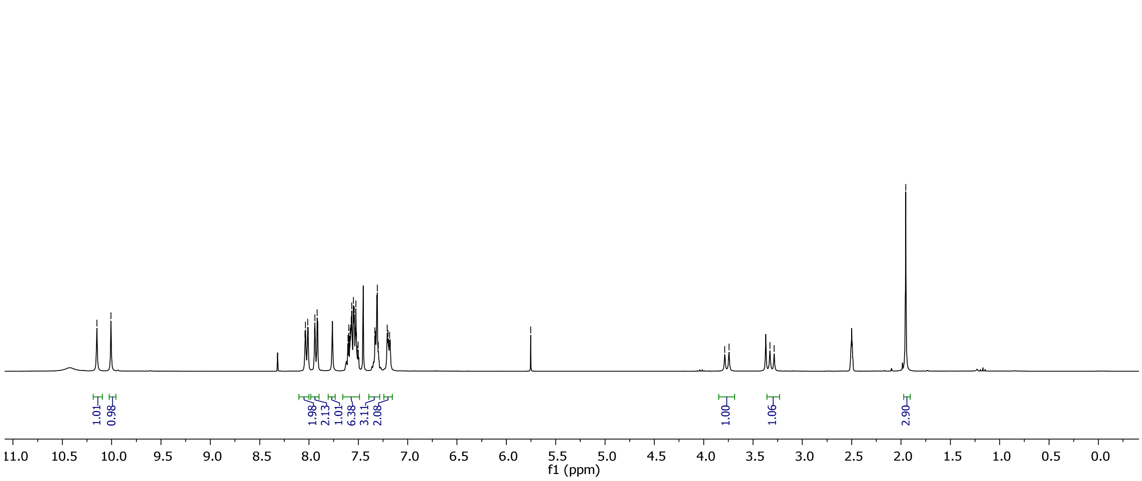
3ah

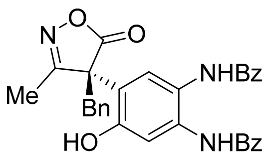
^{13}C NMR (75 MHz, DMSO-d$_6$)



3ai

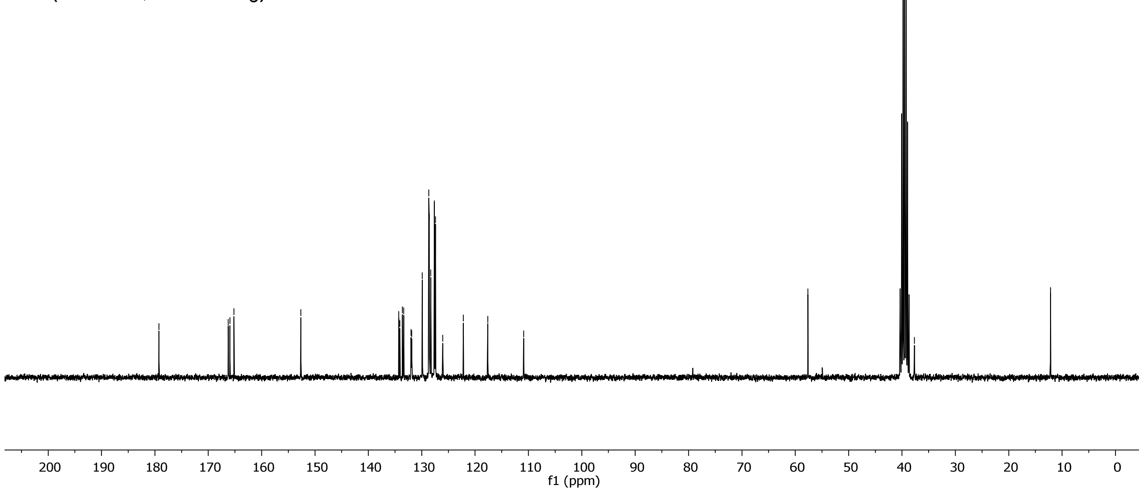
^{1}H NMR (300 MHz, $DMSO-d_6$)

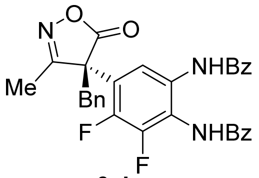




3ai

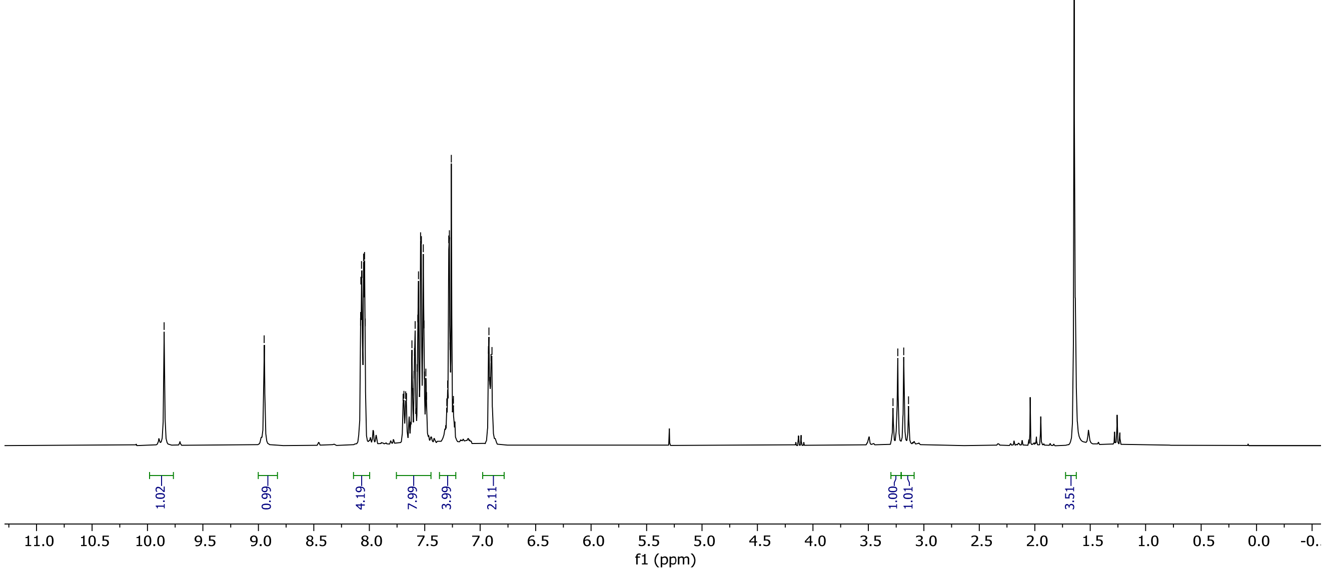
^{13}C NMR (75 MHz, $DMSO-d_6$)

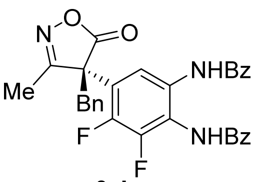




3aj

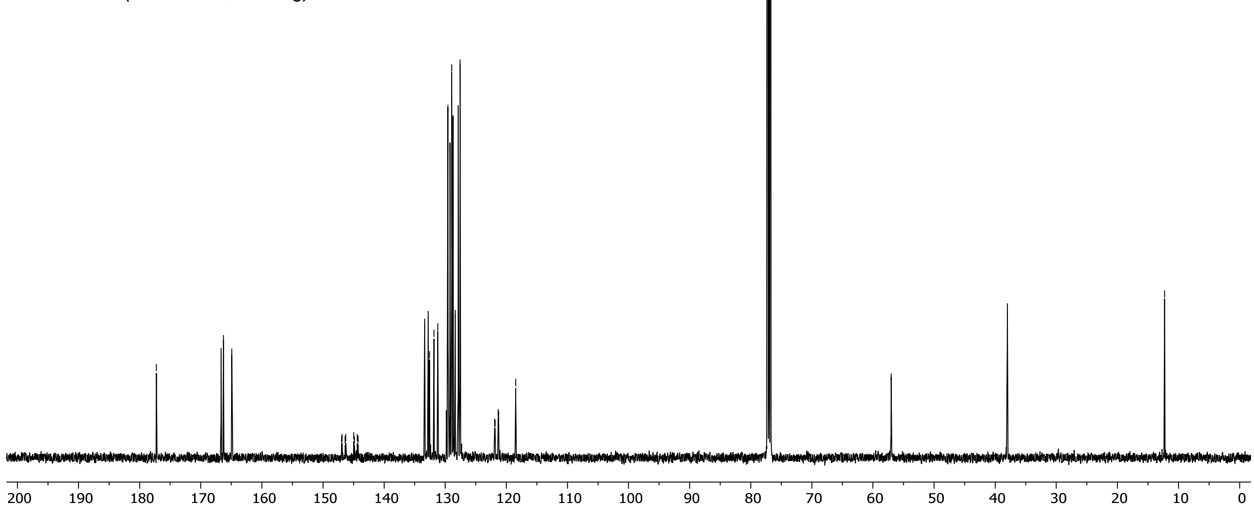
^{1}H NMR (300 MHz, $CDCl_3$)

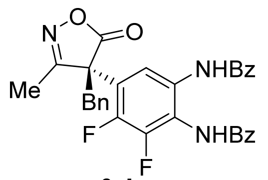




3aj

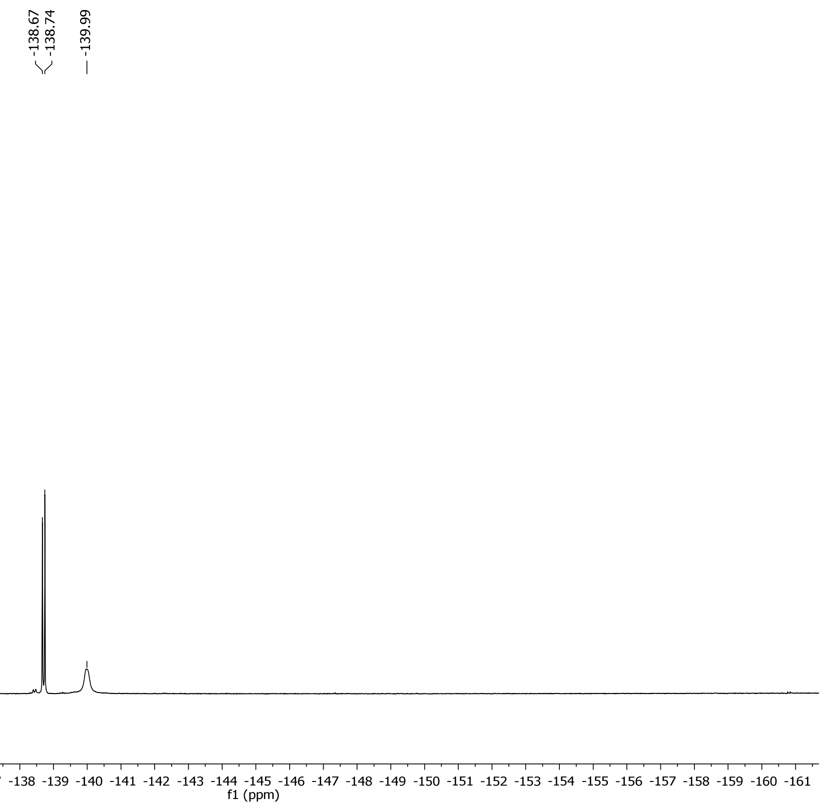
^{13}C NMR (125 MHz, $CDCl_3$)

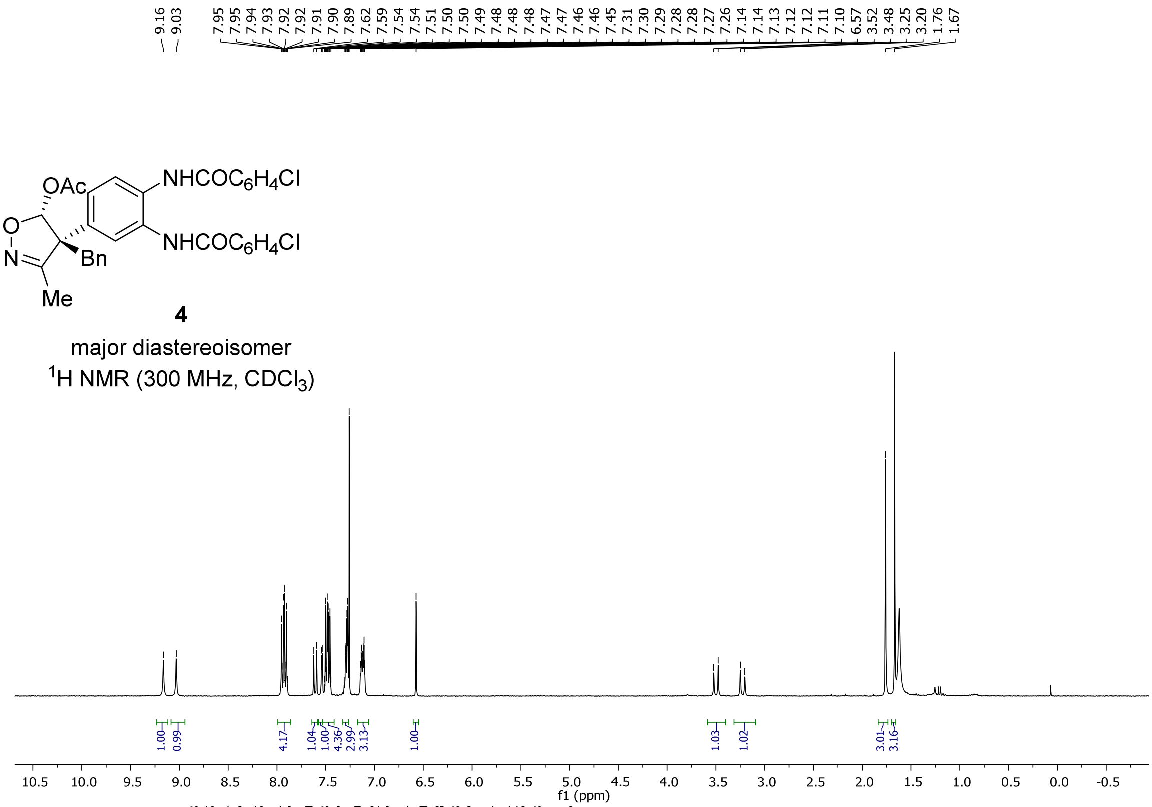




3aj

^{19}F NMR (282 MHz, $CDCl_3$)

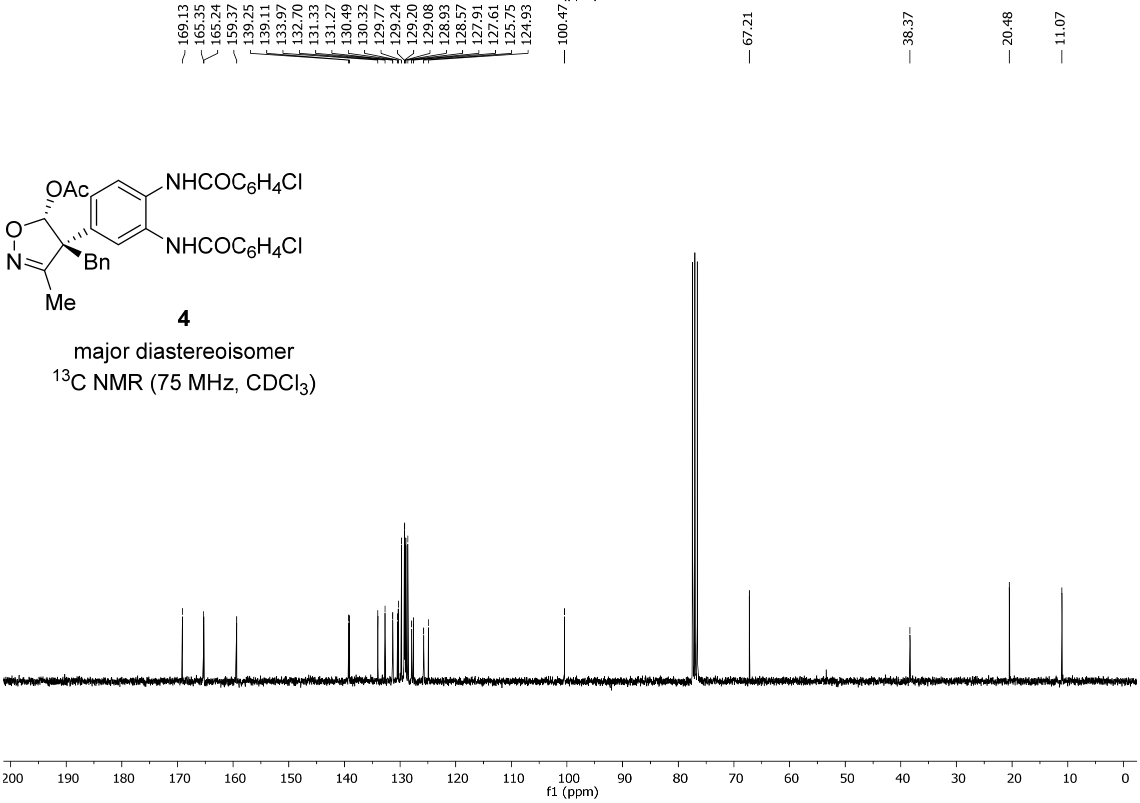




4

major diastereoisomer

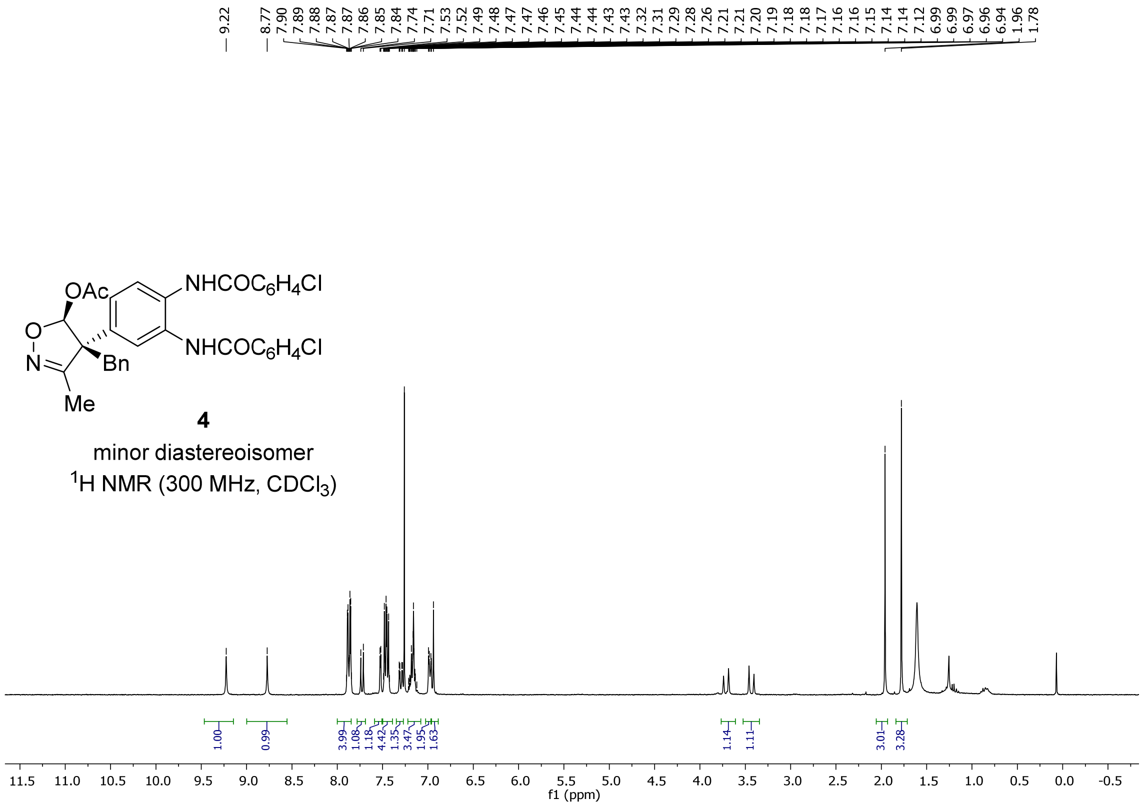
^{1}H NMR (300 MHz, $CDCl_3$)

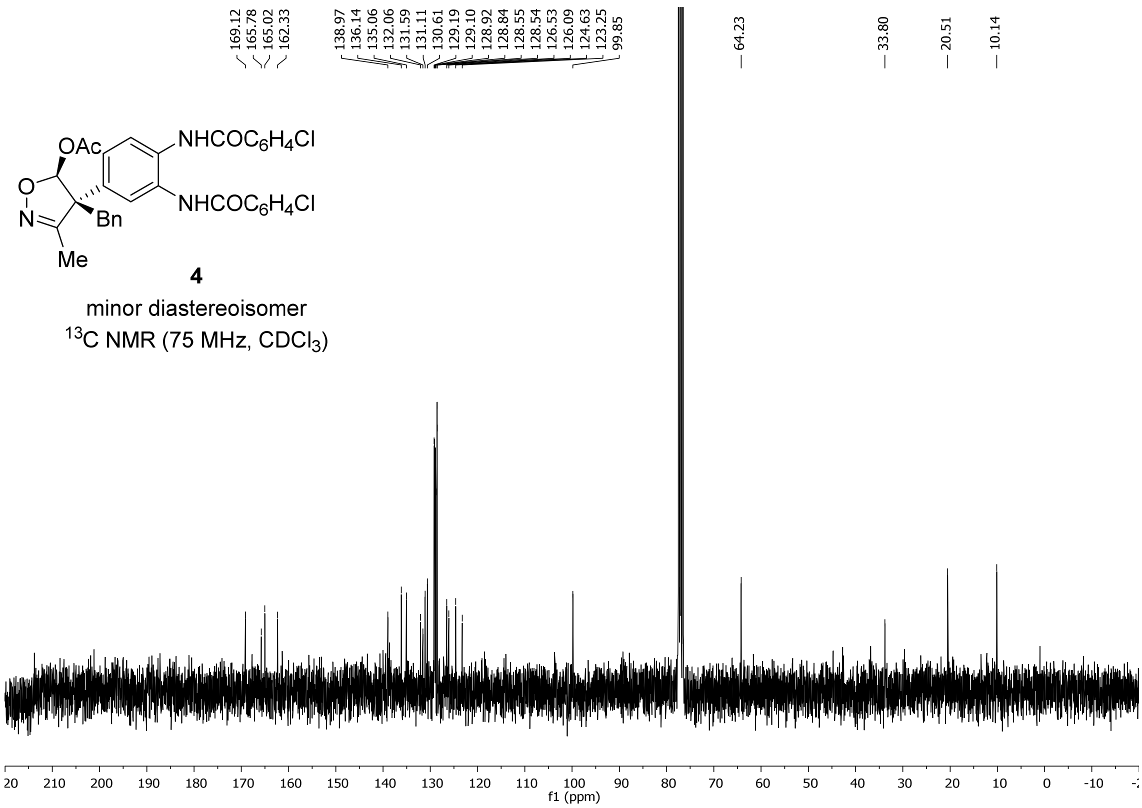


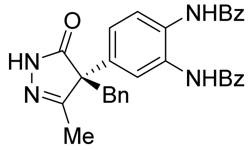
4

major diastereoisomer

^{13}C NMR (75 MHz, $CDCl_3$)

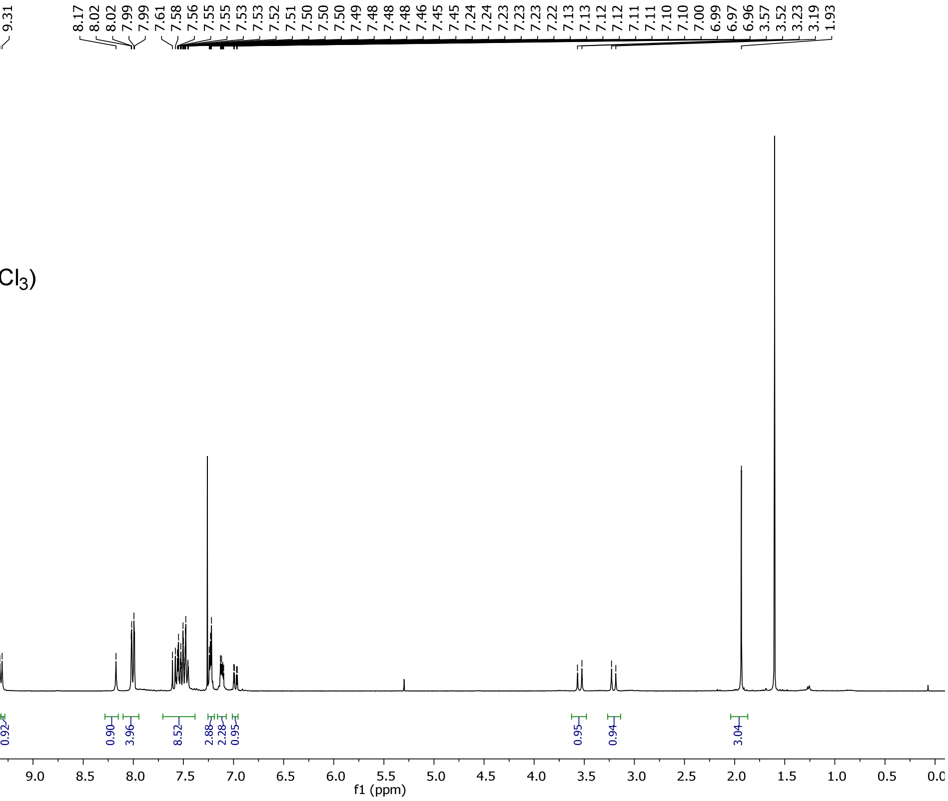

NHCOC6H4Cl
NHCOC6H4Cl
OAc
O
N
Bn
Me
4
minor diastereoisomer
1H NMR (300 MHz, CDCl3)
f1 (ppm)

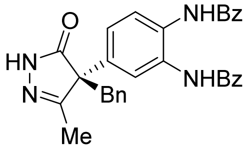

NHCOC6H4Cl
NHCOC6H4Cl
OAc
O
N
Bn
Me
4
minor diastereoisomer
13C NMR (75 MHz, CDCl3)
f1 (ppm)



5

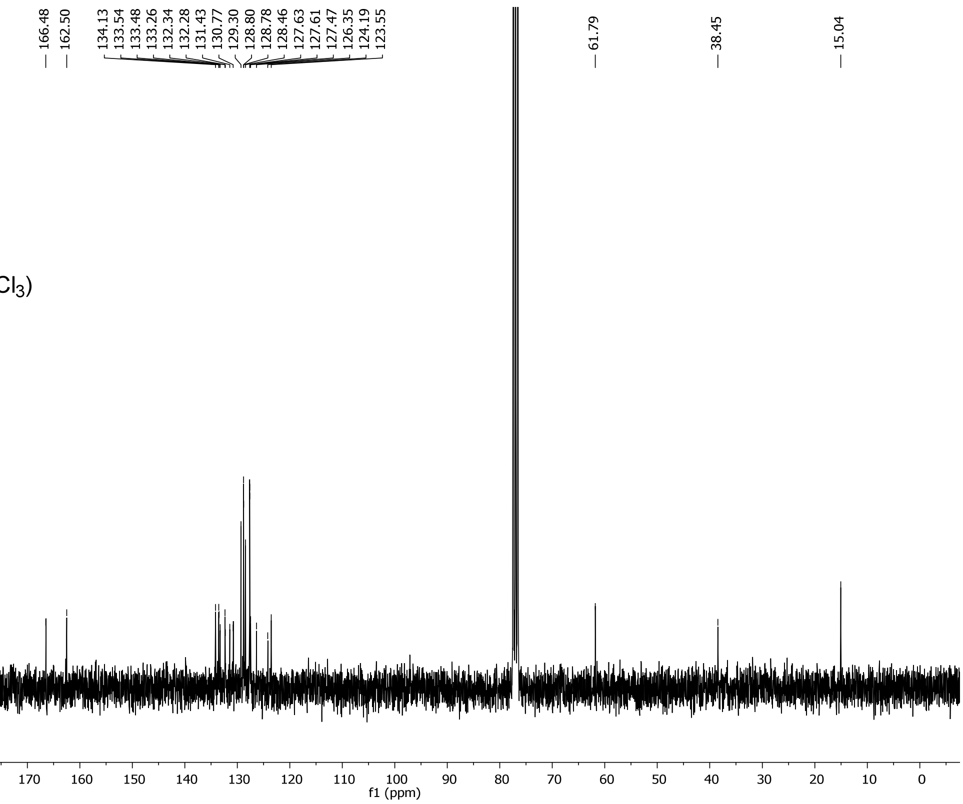
^{1}H NMR (300 MHz, $CDCl_3$)

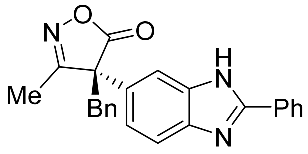




5

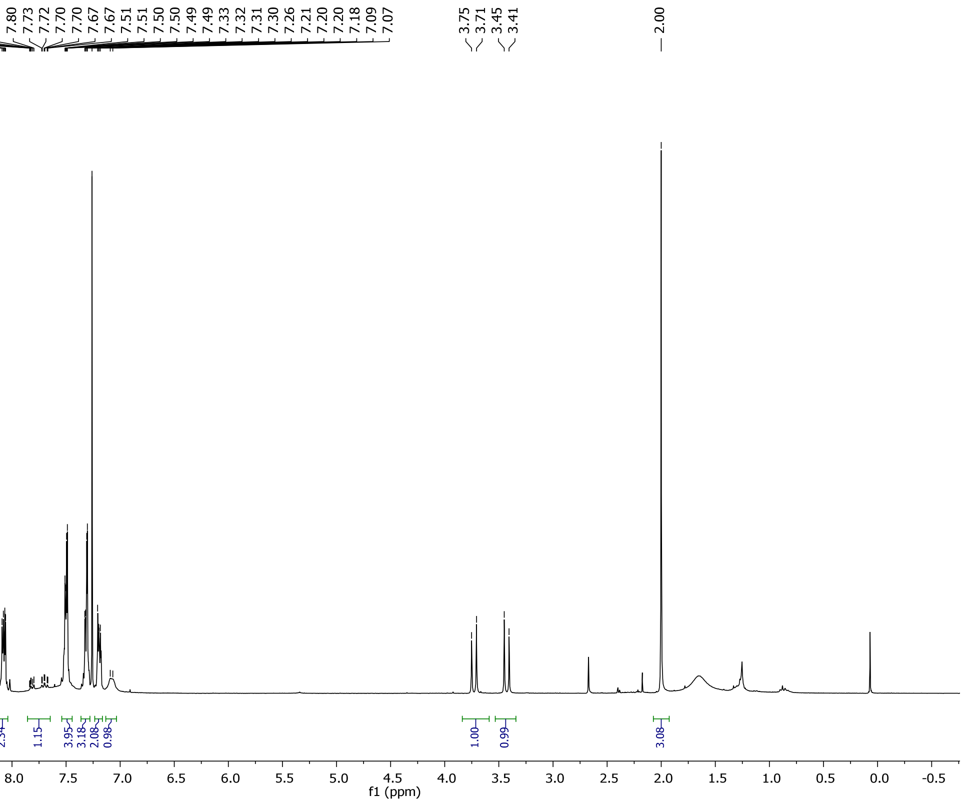
^{13}C NMR (75 MHz, $CDCl_3$)

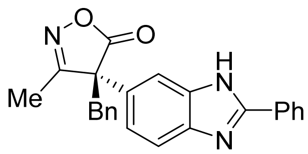




6

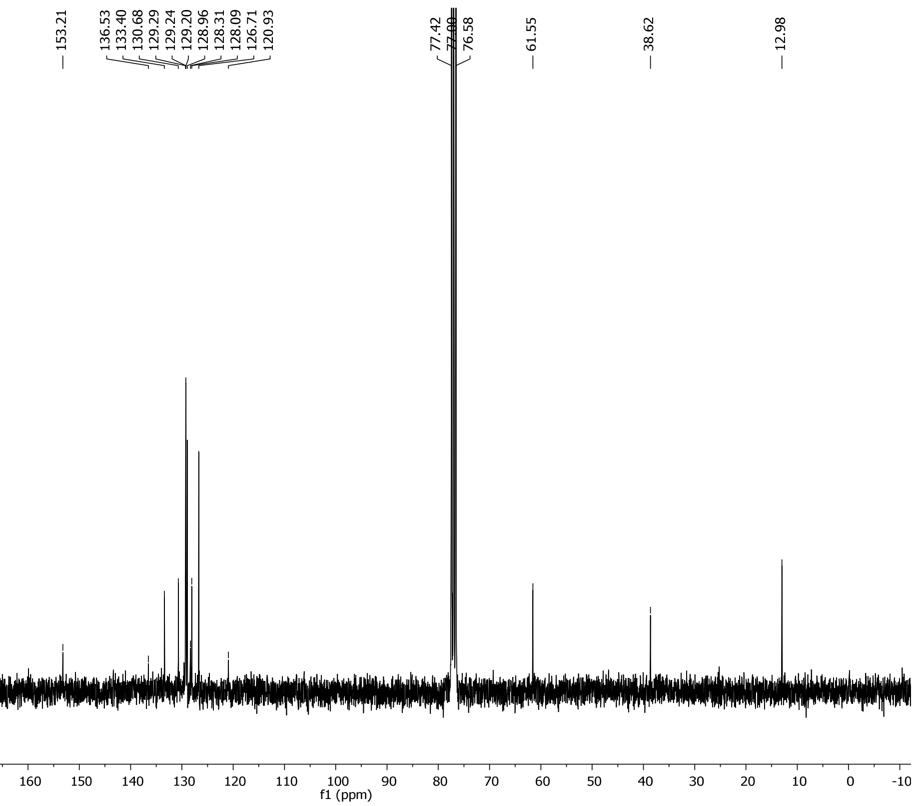
^{1}H NMR (300 MHz, $CDCl_3$)



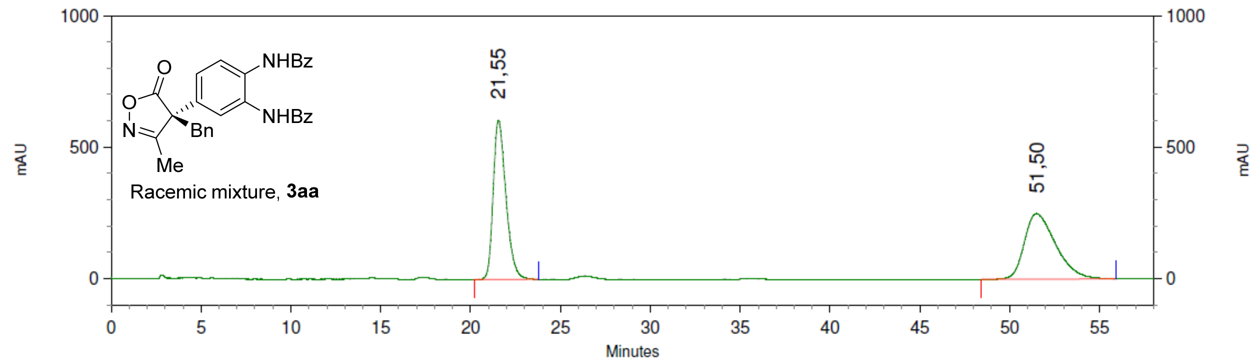


6

^{13}C NMR (75 MHz, $CDCl_3$)

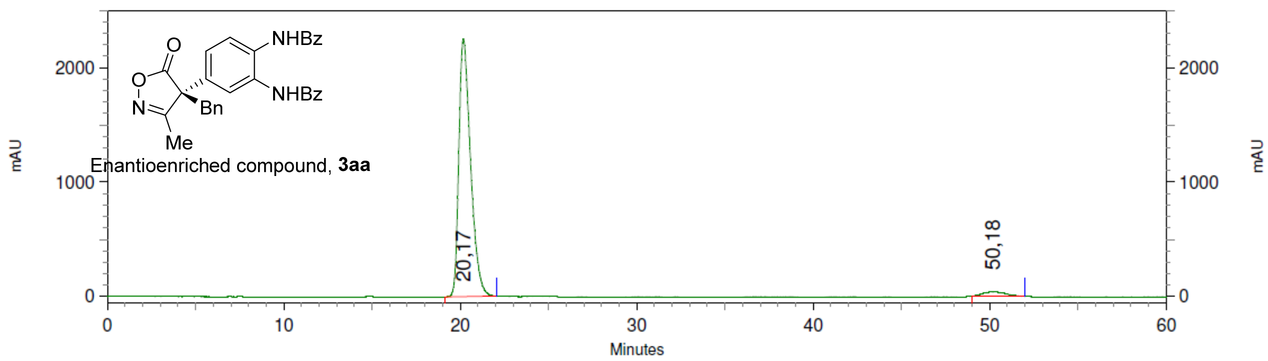


HPLC traces for compounds 3-6



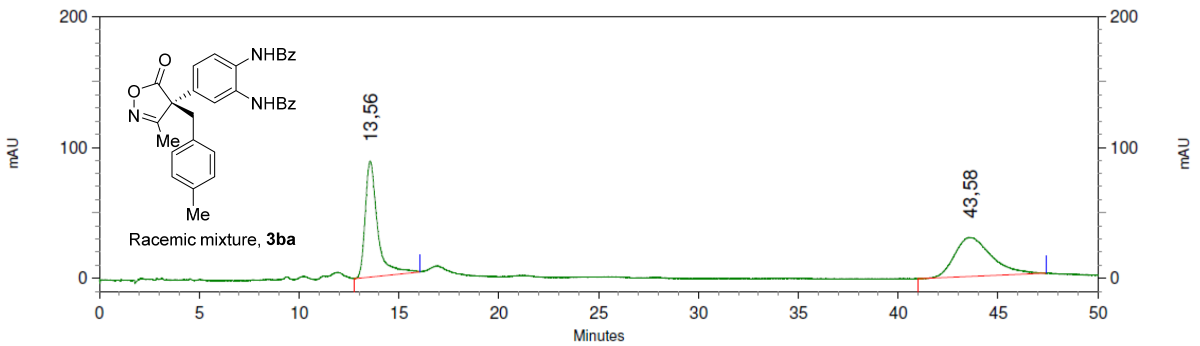
34: 250 nm, 4 nm
Results

Retention Time	Area	Area Percent
21,55	119772187	49,759
51,50	120931288	50,241



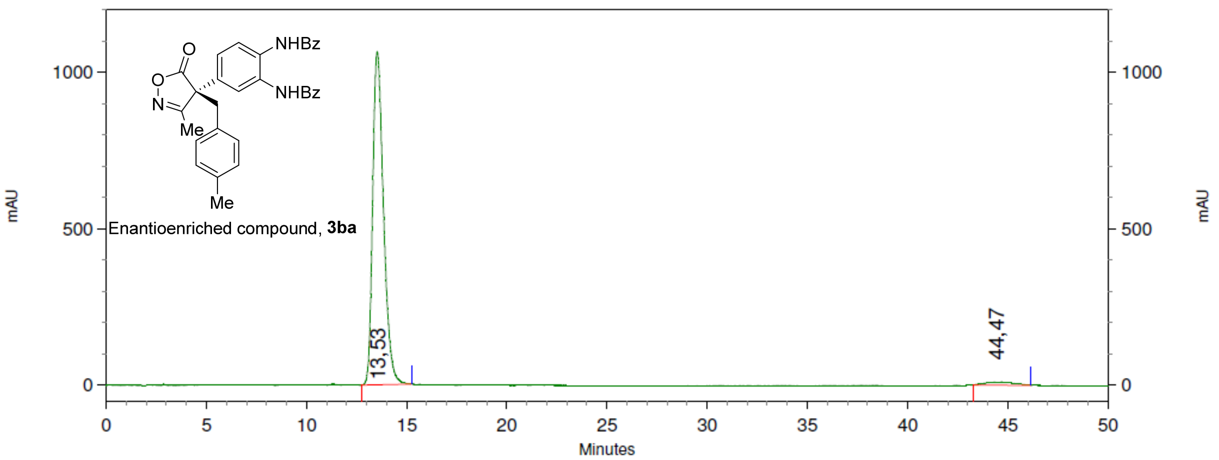
34: 250 nm, 4 nm
Results

Retention Time	Area	Area Percent
20,17	416474475	96,527
50,18	14949349	3,465



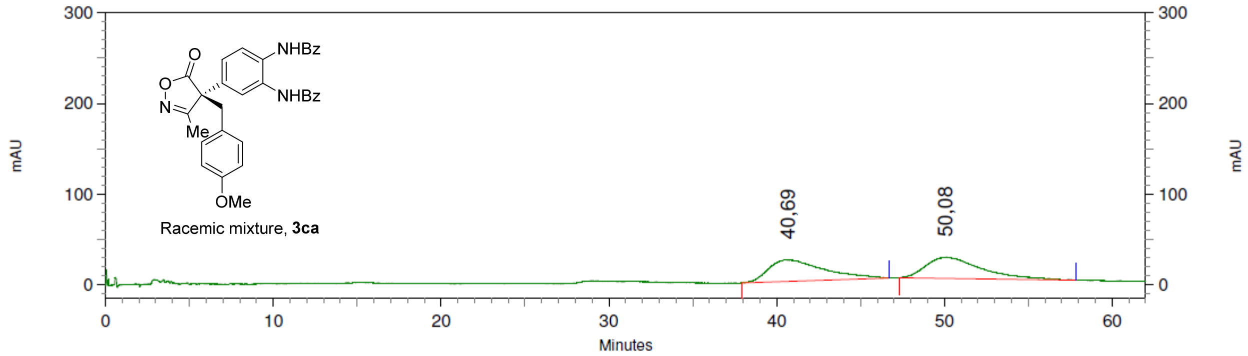
34: 250 nm, 4 nm
Results

Retention Time	Area	Area Percent
13,56	15217717	49,984
43,58	15227194	50,016



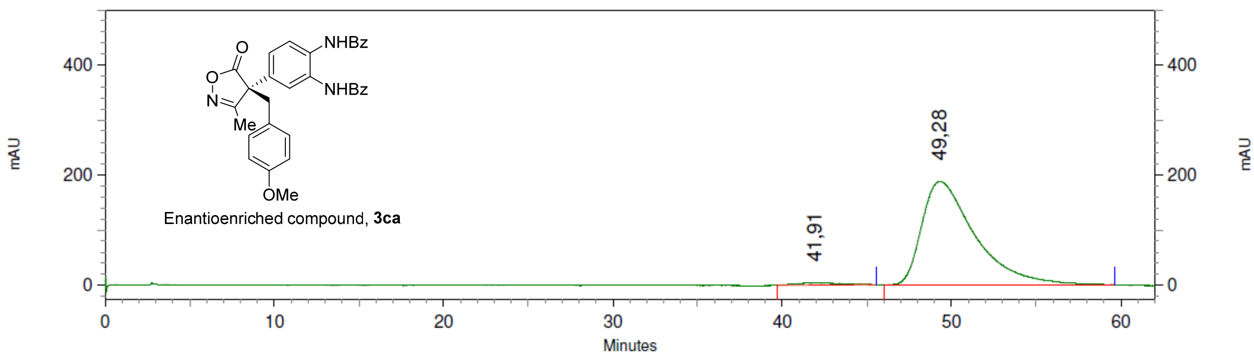
10: 250 nm, 4 nm
Results

Retention Time	Area	Area Percent
13,53	160022221	97,649
44,47	3853050	2,351



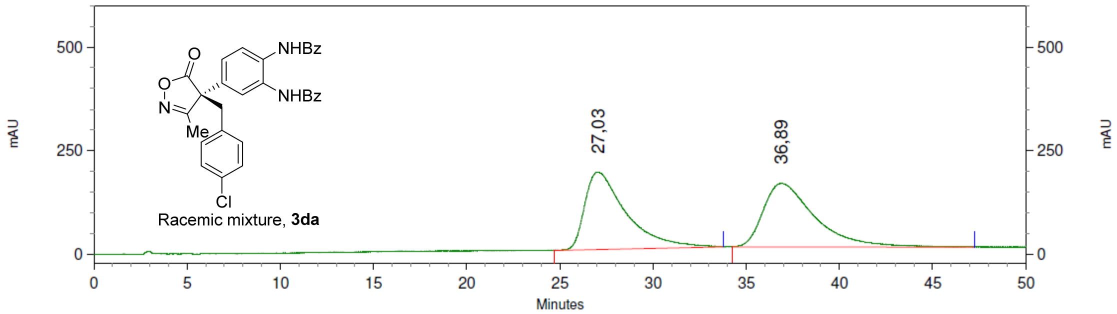
2: 250 nm, 4 nm Results

Retention Time	Area	Area Percent
40,69	21542445	50,244
50,08	21333517	49,756



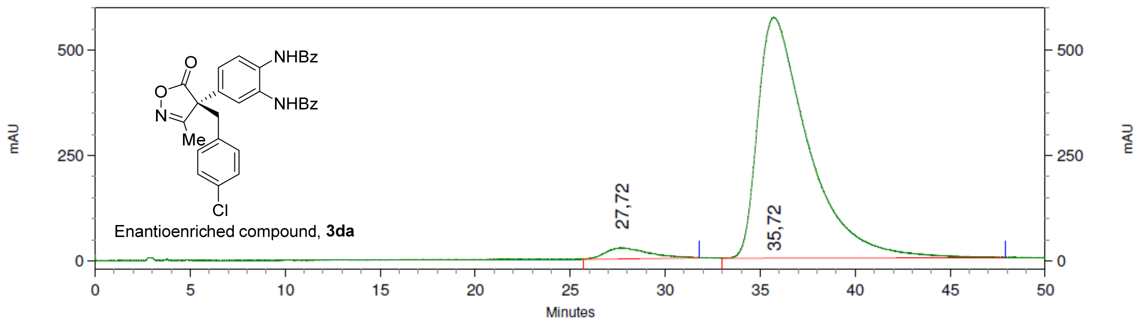
34: 250 nm, 4 nm
Results

Retention Time	Area	Area Percent
41,91	3013357	1,795
49,28	164889339	98,205



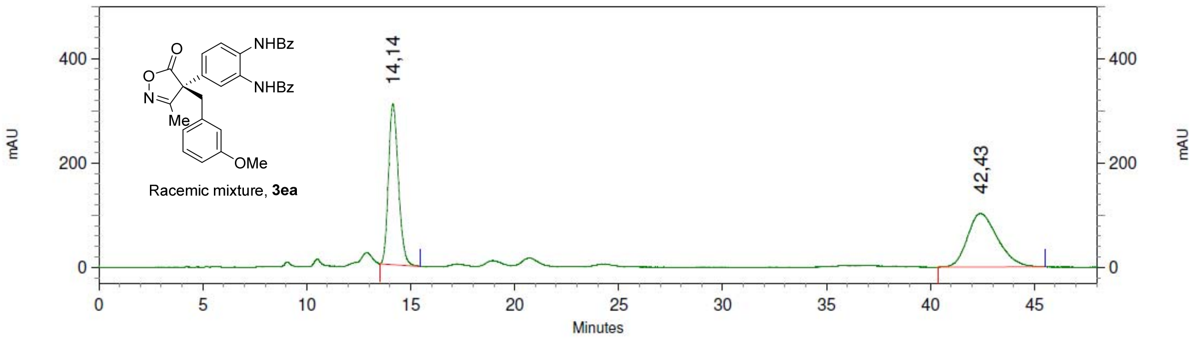
13: 230 nm, 4 nm
Results

Retention Time	Area	Area Percent
27,03	115352062	49,407
36,89	118122321	50,593



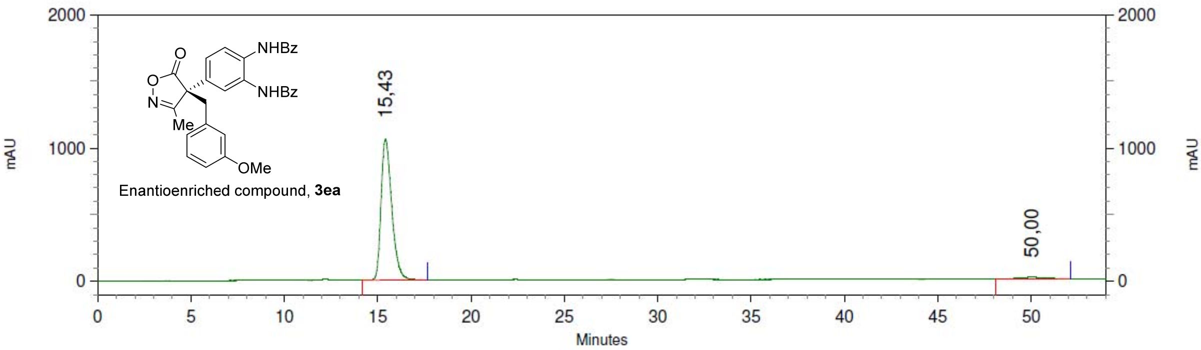
6: 230 nm, 4 nm Results

Retention Time	Area	Area Percent
27,72	16323625	3,724
35,72	421997215	96,276



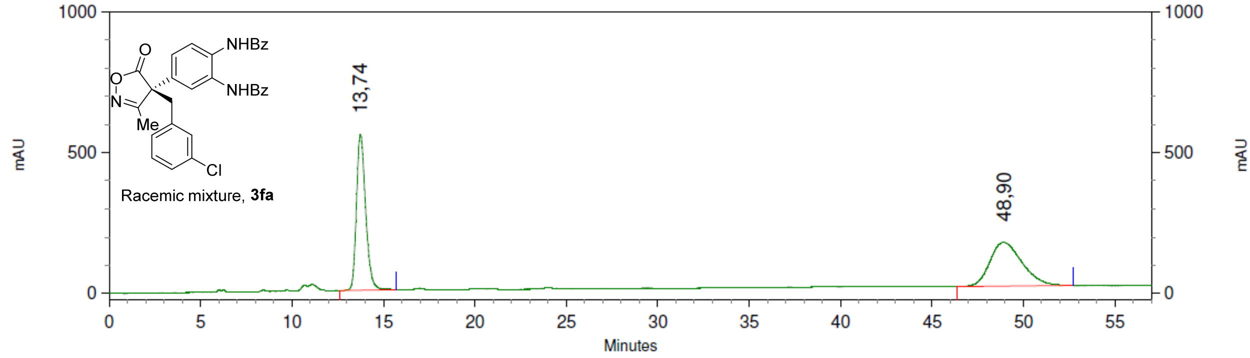
6: 274 nm, 4 nm Results

Retention Time	Area	Area Percent
14,14	40760069	49,716
42,43	41226510	50,284



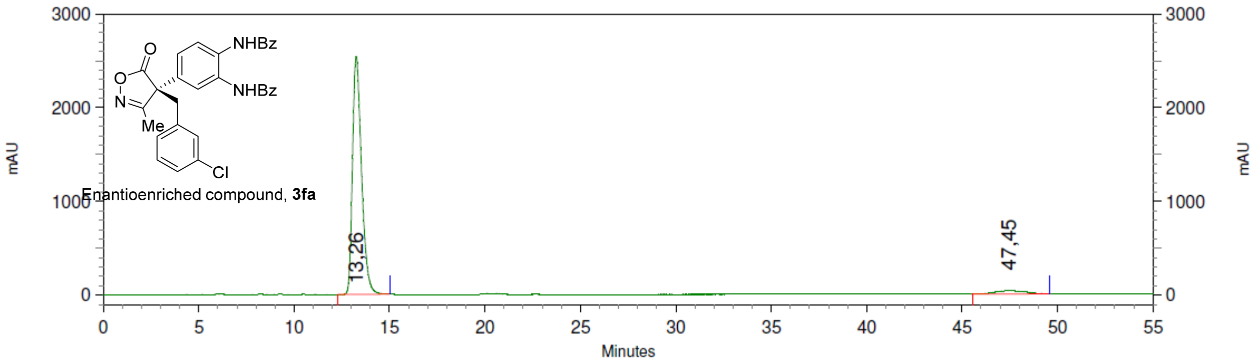
6: 274 nm, 4 nm Results

Retention Time	Area	Area Percent
15,43	168653655	96,957
50,00	5293816	3,043



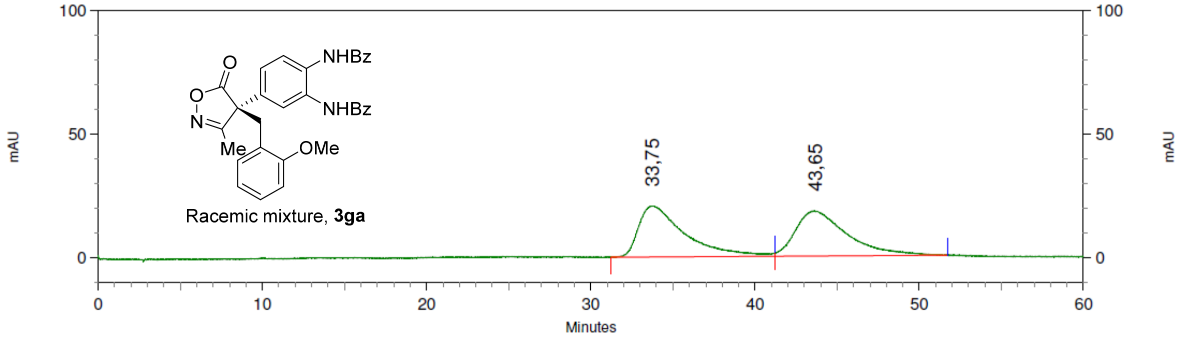
5: 258 nm, 4 nm Results

Retention Time	Area	Area Percent
13,74	77745321	50,532
48,90	76108570	49,468



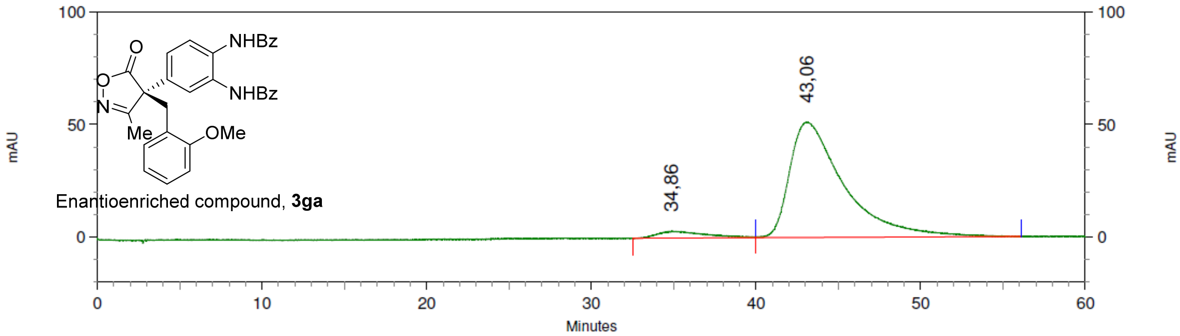
5: 258 nm, 4 nm Results

Retention Time	Area	Area Percent
13,26	334410522	95,726
47,45	14932429	4,274



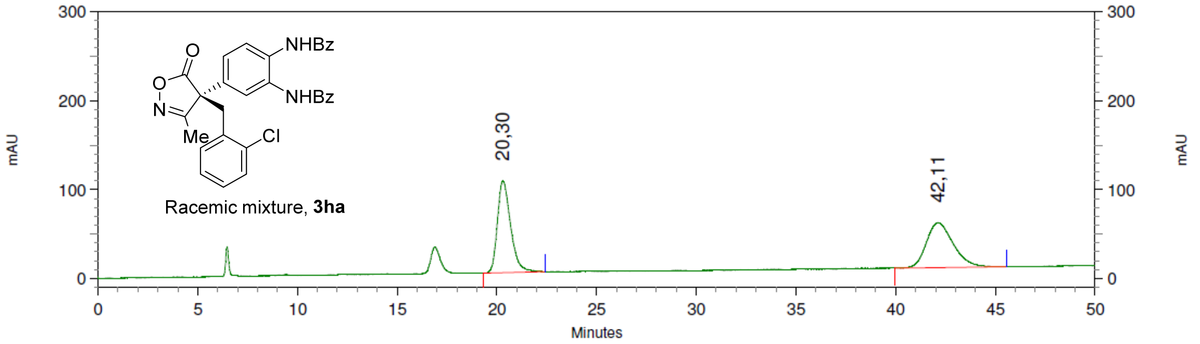
8: 300 nm, 4 nm Results

Retention Time	Area	Area Percent
33,75	16089537	50,418
43,65	15822833	49,582



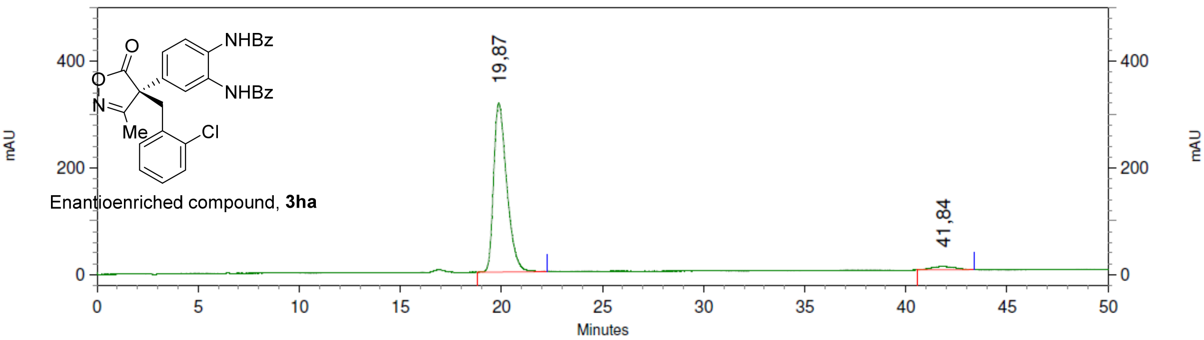
8: 300 nm, 4 nm Results

Retention Time	Area	Area Percent
34,86	2474679	4,989
43,06	47126753	95,011



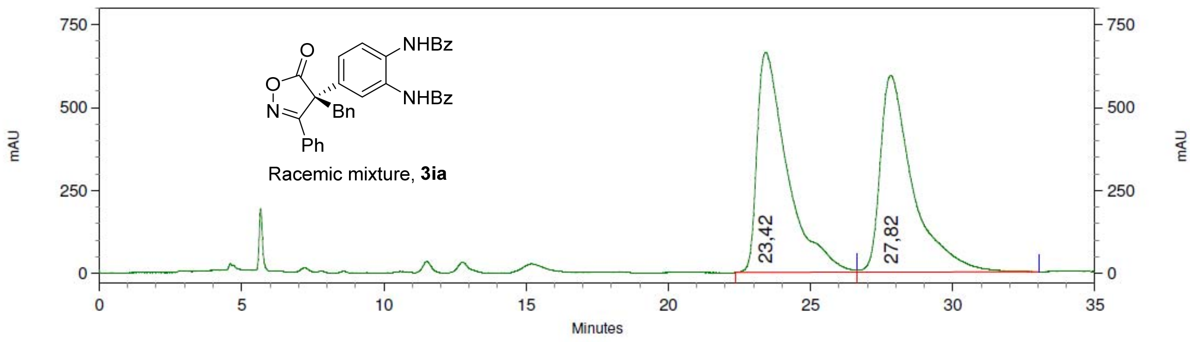
60: 292 nm, 4 nm
Results

Retention Time	Area	Area Percent
20,30	19039349	49,934
42,11	19090022	50,066



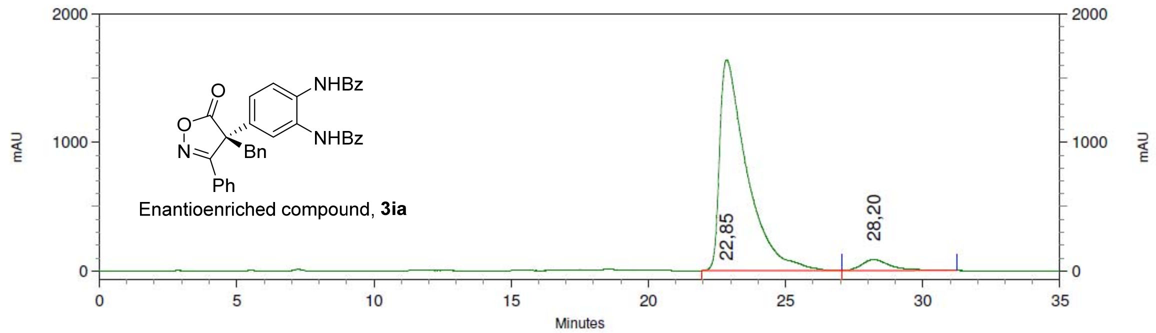
60: 292 nm, 4 nm
Results

Retention Time	Area	Area Percent
19,87	56968349	96,600
41,84	2004829	3,400



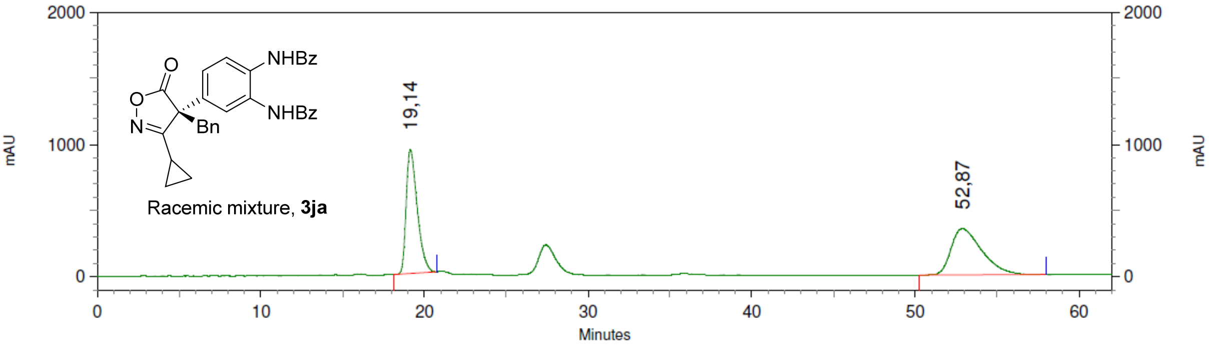
13: 260 nm, 4 nm
Results

Retention Time	Area	Area Percent
23,42	196474641	50,929
27,82	189310414	49,071



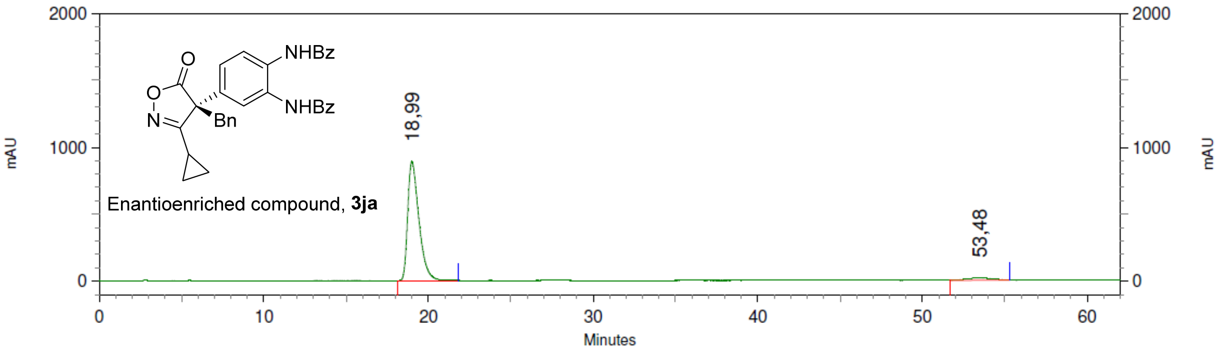
13: 260 nm, 4 nm
Results

Retention Time	Area	Area Percent
22,85	454488490	94,653
28,20	25675268	5,347



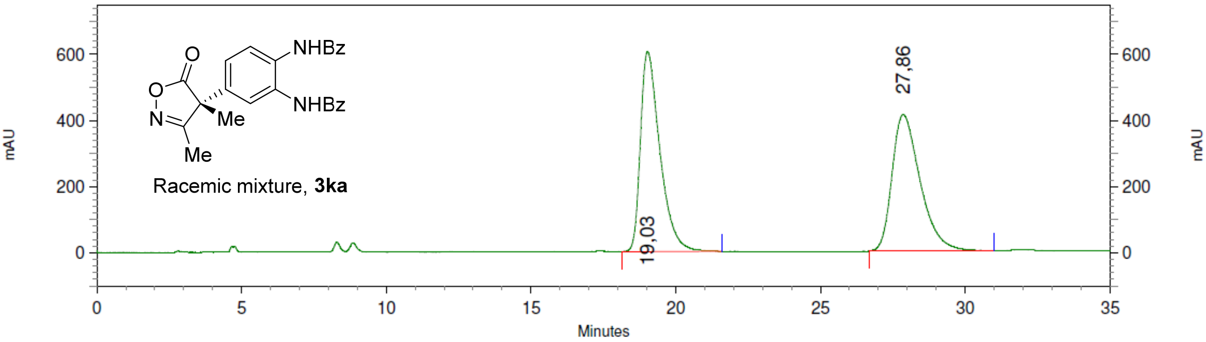
2: 229 nm, 4 nm Results

Retention Time	Area	Area Percent
19,14	176536963	49,052
52,87	183360544	50,948



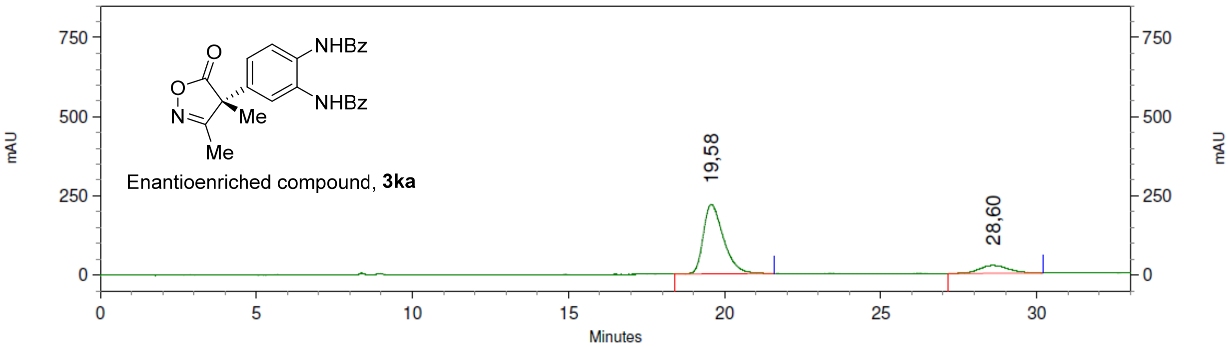
2: 229 nm, 4 nm Results

Retention Time	Area	Area Percent
18,99	168341233	95,363
53,48	8185635	4,637



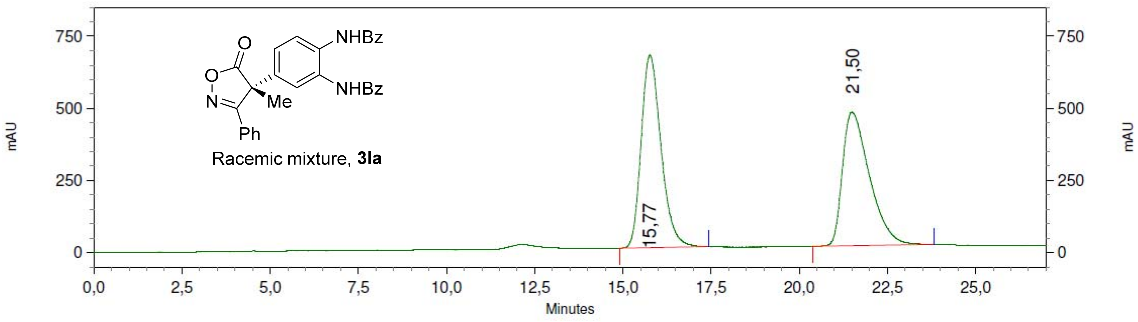
34: 250 nm, 4 nm
Results

Retention Time	Area	Area Percent
19,03	113044558	50,345
27,86	111494769	49,655



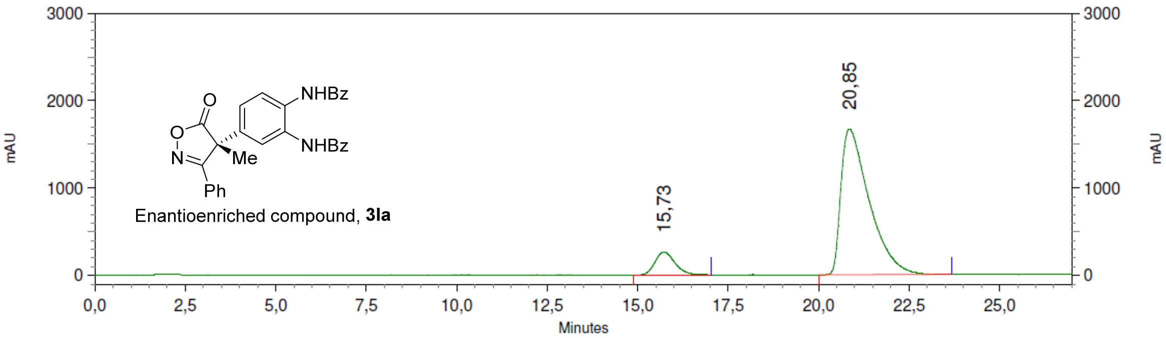
34: 250 nm, 4 nm
Results

Retention Time	Area	Area Percent
19,58	39579031	85,741
28,60	6582371	14,259



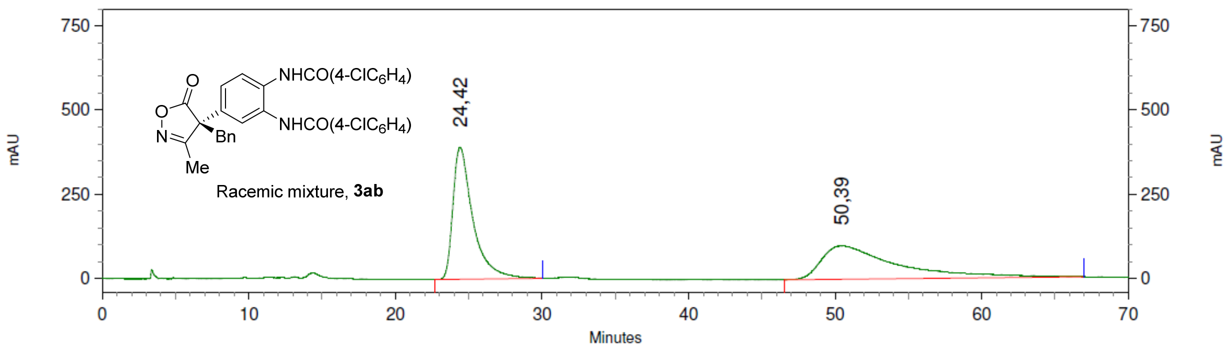
38: 258 nm, 4 nm
Results

Retention Time	Area	Area Percent
15,77	104568023	51,534
21,50	98343557	48,466



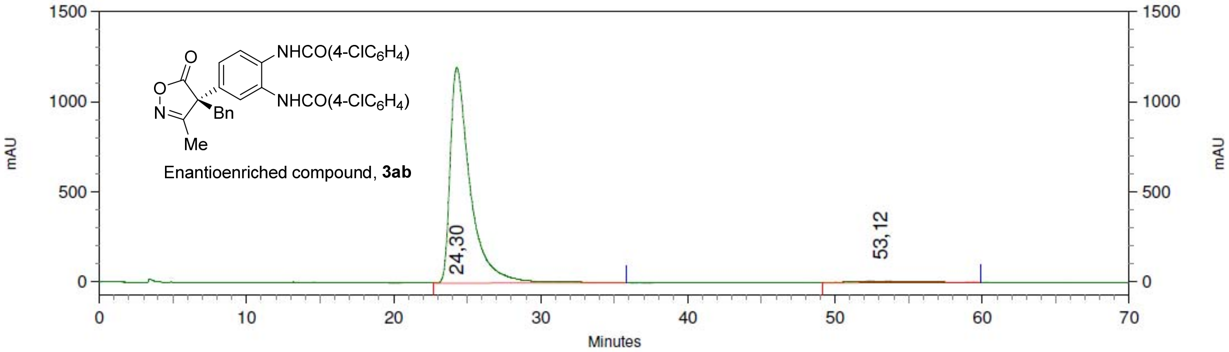
38: 258 nm, 4 nm
Results

Retention Time	Area	Area Percent
15,73	40183605	9,972
20,85	362767420	90,028



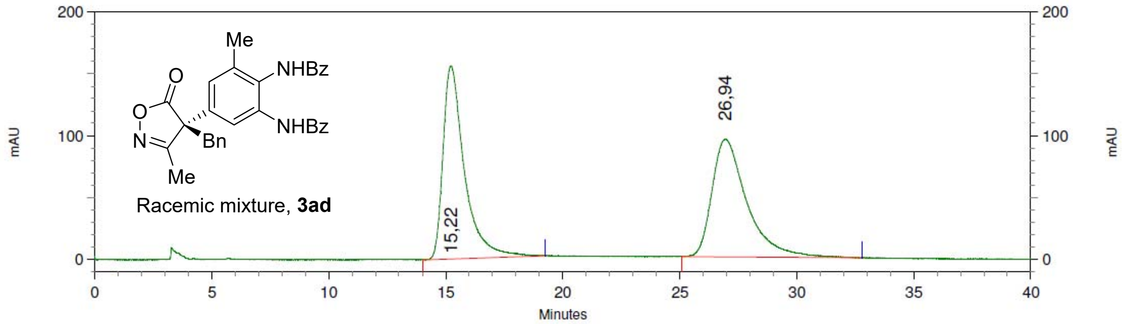
23: 220 nm, 4 nm
Results

Retention Time	Area	Area Percent
24,42	149318466	51,492
50,39	140665267	48,508



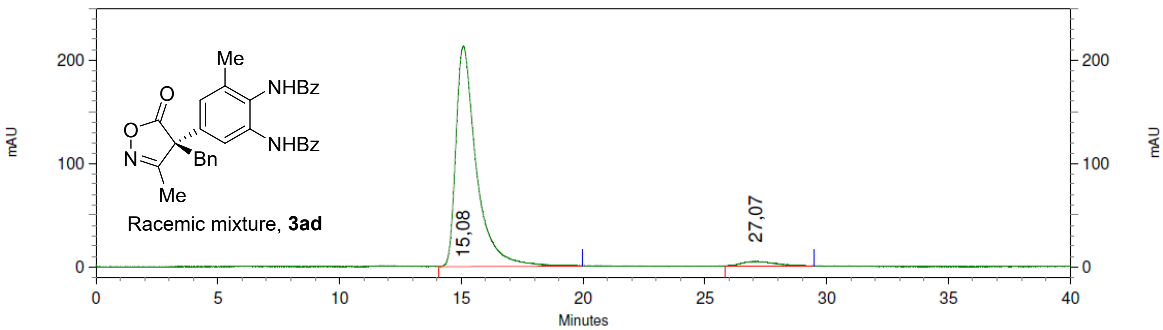
17: 220 nm, 4 nm
Results

Retention Time	Area	Area Percent
24,30	456368688	97,654
53,12	10961900	2,346



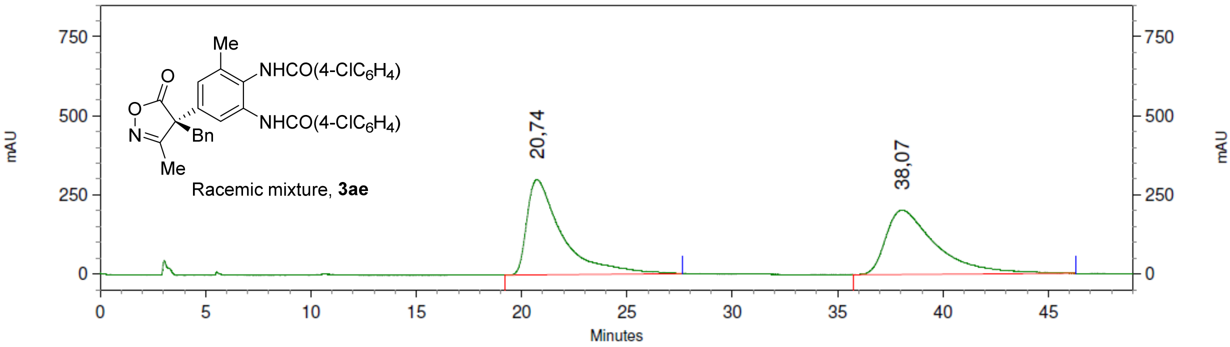
34: 250 nm, 4 nm
Results

Retention Time	Area	Area Percent
15,22	39814586	50,180
26,94	39528260	49,820



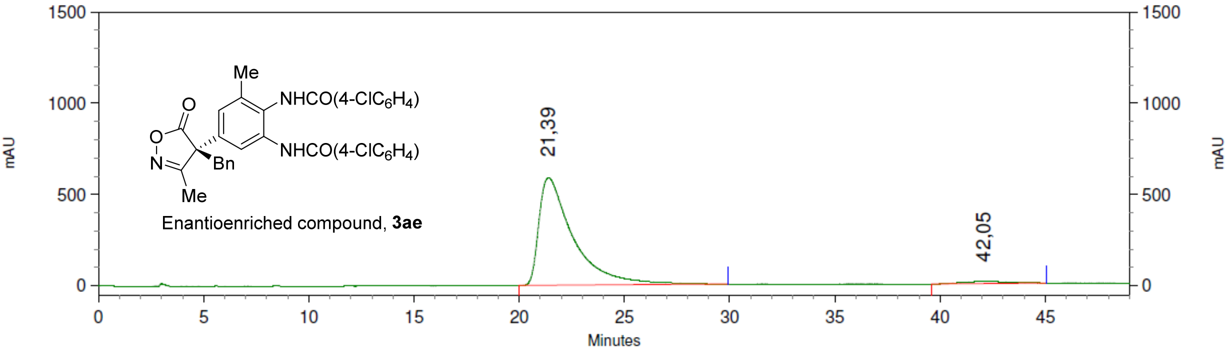
40: 290 nm, 4 nm
Results

Retention Time	Area	Area Percent
15,08	49876237	96,409
27,07	1857980	3,591



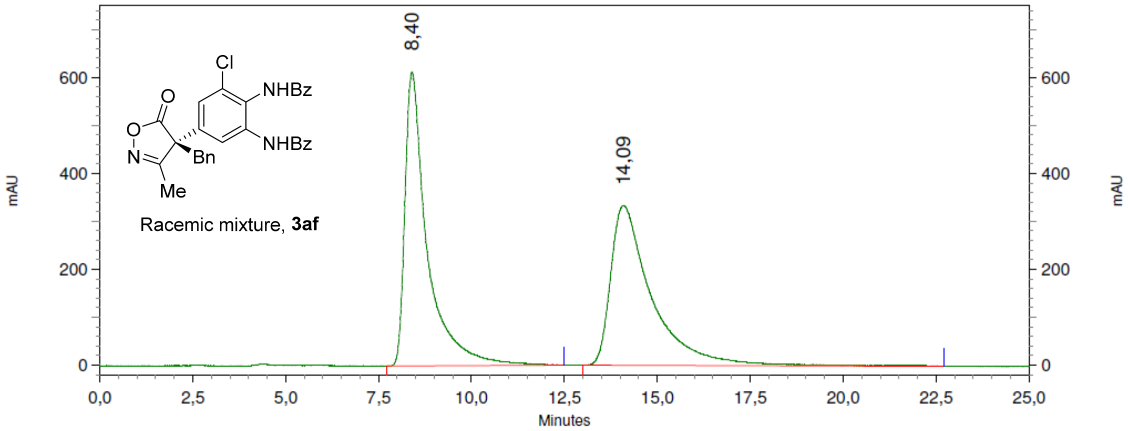
14: 245 nm, 4 nm
Results

Retention Time	Area	Area Percent
20,74	139491358	50,927
38,07	134412784	49,073



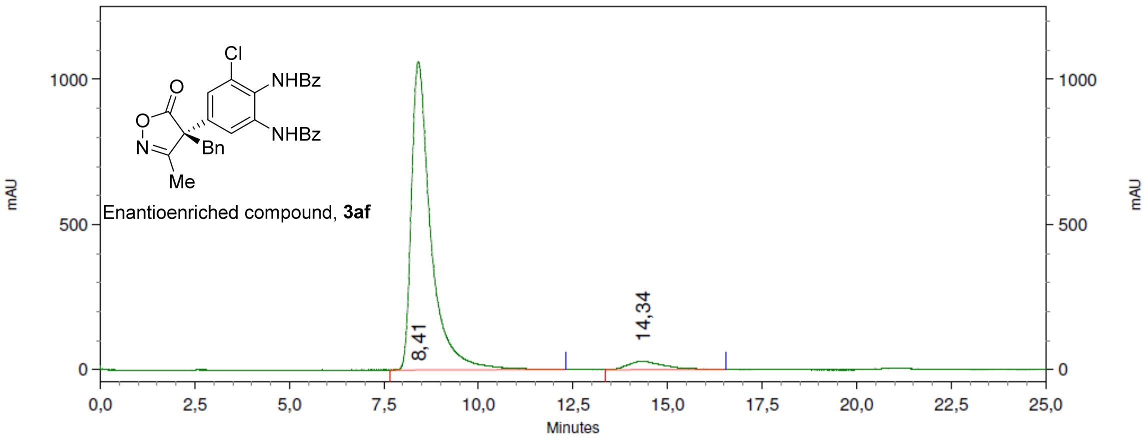
14: 245 nm, 4 nm
Results

Retention Time	Area	Area Percent
21,39	269250356	97,415
42,05	7145338	2,585



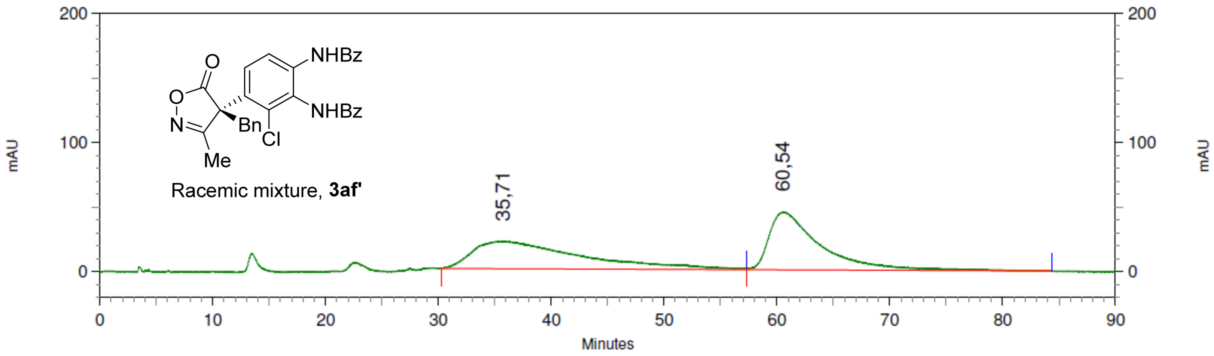
10: 250 nm, 4 nm
Results

Retention Time	Area	Area Percent
8,40	102041483	49,850
14,09	102655688	50,150



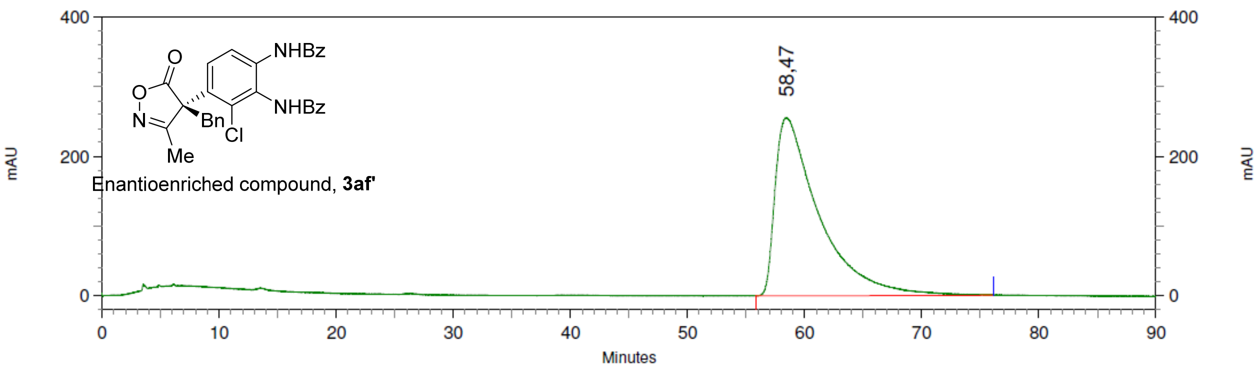
10: 250 nm, 4 nm
Results

Retention Time	Area	Area Percent
8,41	151736132	95,177
14,34	7689047	4,823



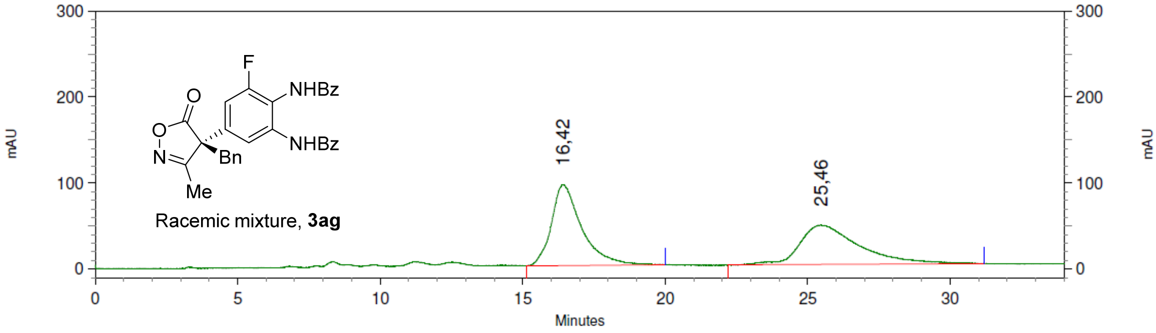
34: 250 nm, 4 nm
Results

Retention Time	Area	Area Percent
35,71	56649854	49,885
60,54	56910792	50,115



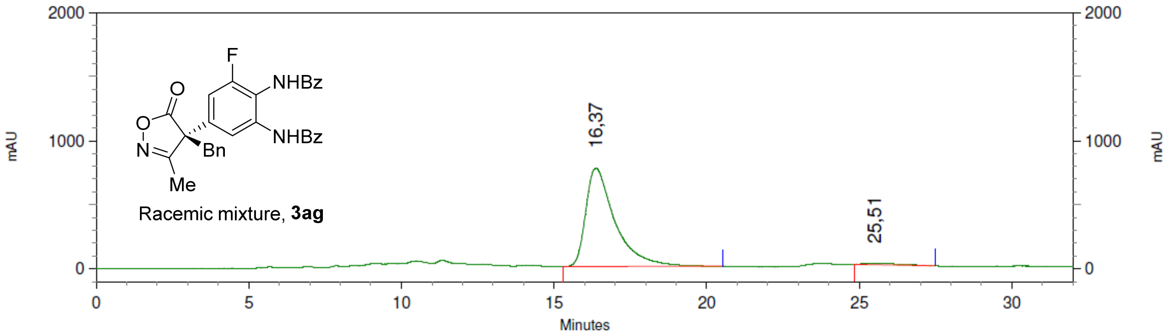
34: 250 nm, 4 nm
Results

Retention Time	Area	Area Percent
58,47	267720471	100,000



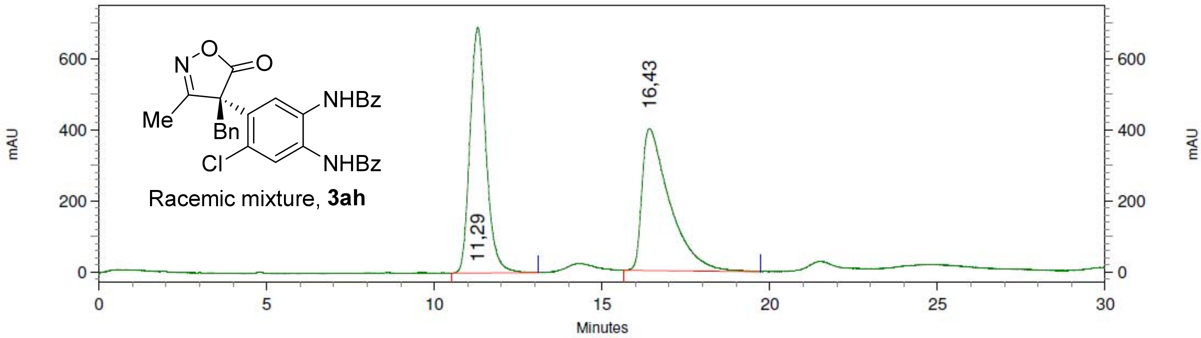
34: 250 nm, 4 nm
Results

Retention Time	Area	Area Percent
16,42	27947589	51,120
25,46	26722443	48,880



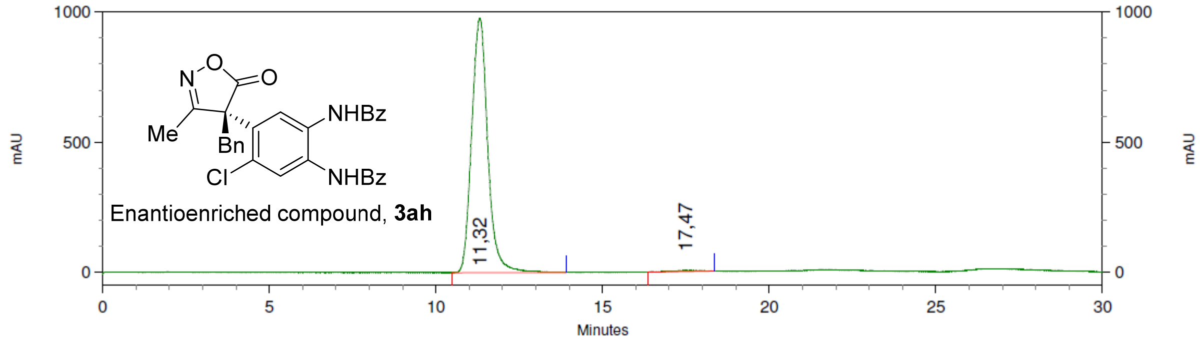
31: 250 nm, 4 nm
Results

Retention Time	Area	Area Percent
16,37	204935692	98,232
25,51	3687584	1,768



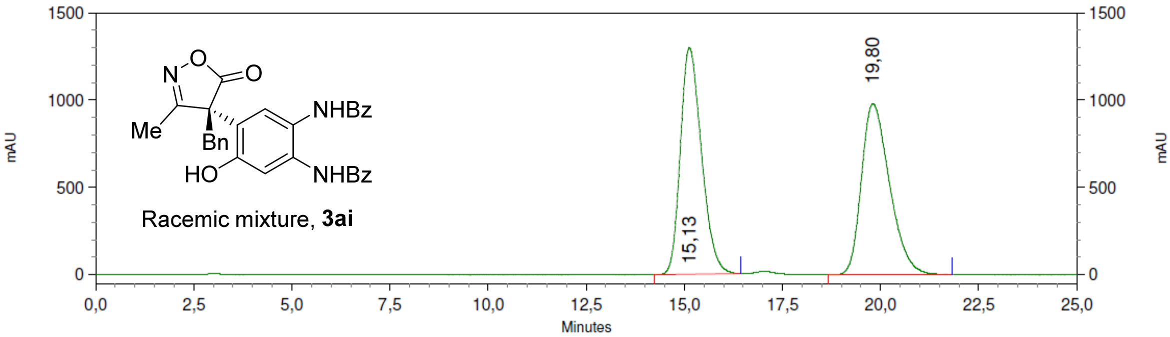
8: 250 nm, 4 nm Results

Retention Time	Area	Area Percent
11,29	91820114	49,970
16,43	91929849	50,030



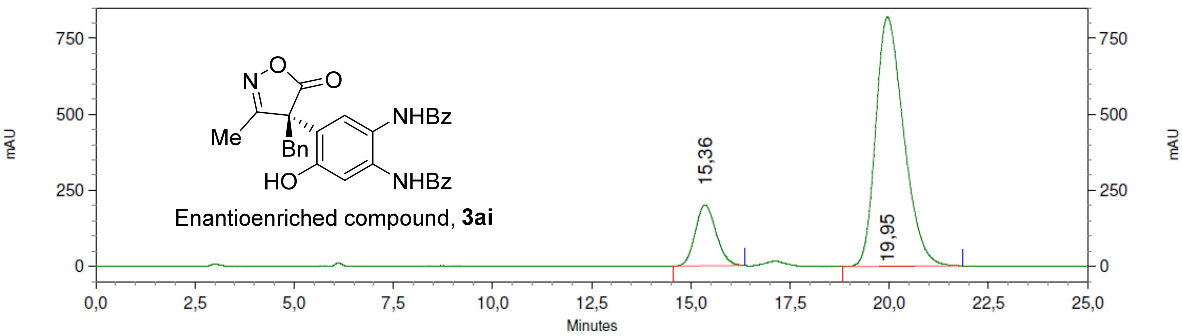
8: 250 nm, 4 nm Results

Retention Time	Area	Area Percent
11,32	131154393	99,129
17,47	1152837	0,871



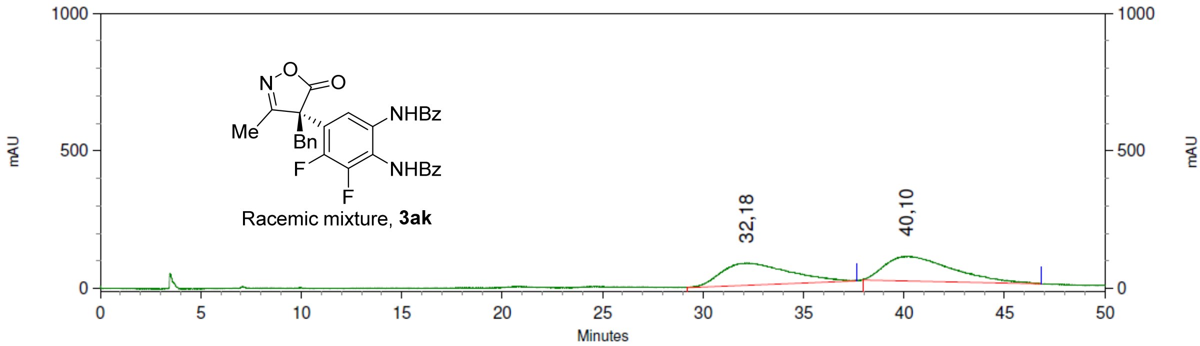
6: 230 nm, 4 nm Results

Retention Time	Area	Area Percent
15,13	193931848	49,863
19,80	194994879	50,137



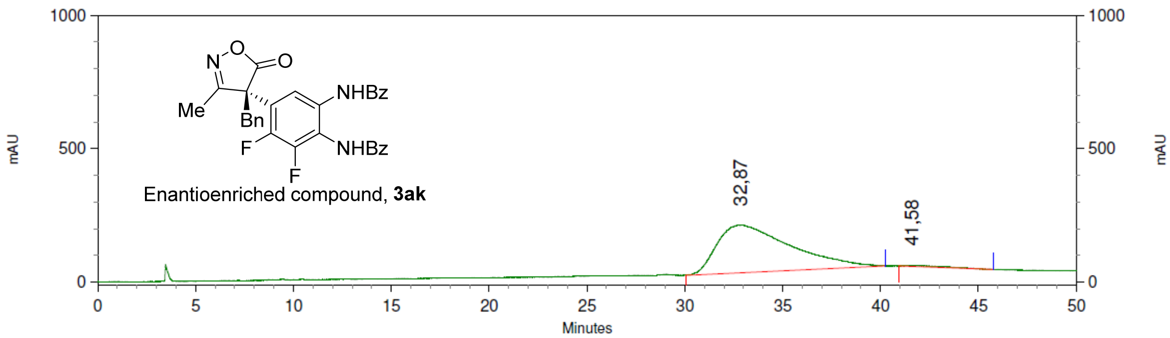
6: 230 nm, 4 nm Results

Retention Time	Area	Area Percent
15,36	29322456	15,403
19,95	161041216	84,597



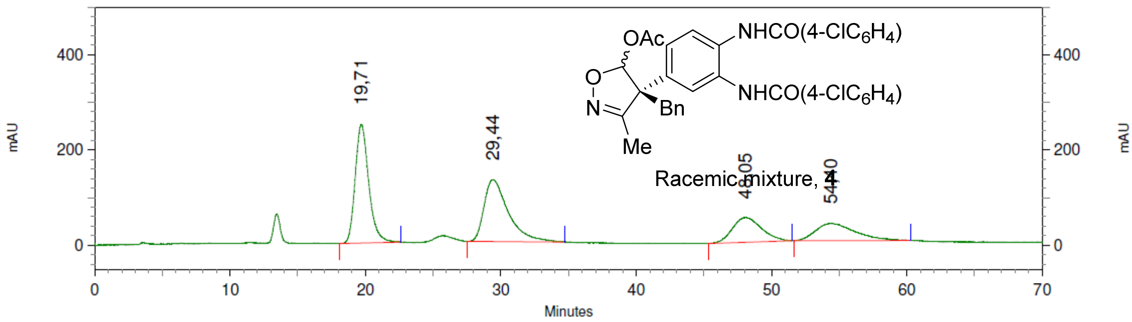
31: 209 nm, 4 nm
Results

Retention Time	Area	Area Percent
32,18	74894989	47,233
40,10	83668450	52,767



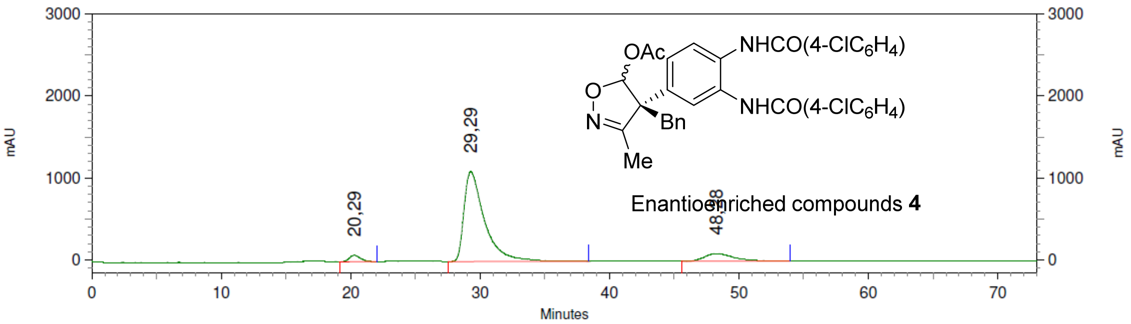
31: 209 nm, 4 nm
Results

Retention Time	Area	Area Percent
32,87	185520717	98,600
41,58	2634328	1,400



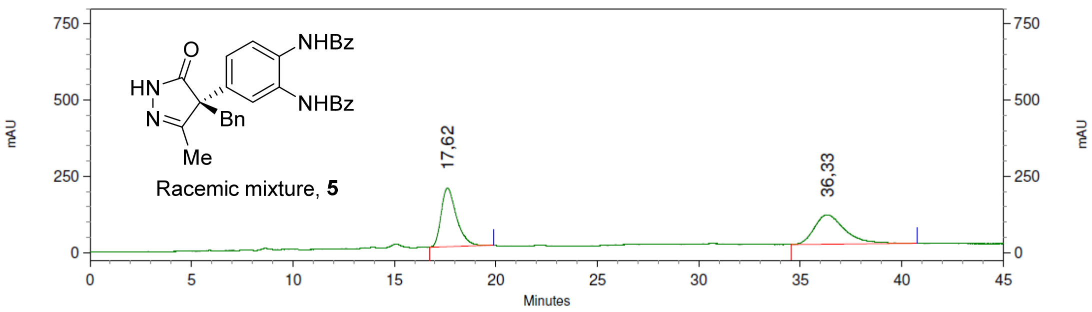
12: 248 nm, 4 nm
Results

Retention Time	Area	Area Percent
19,71	69702963	35,573
29,44	65140759	33,244
48,05	31280648	15,964
54,40	29820377	15,219



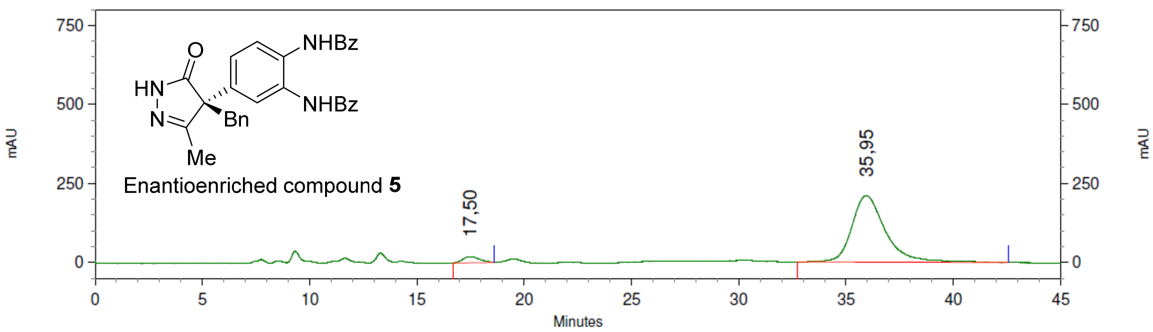
12: 248 nm, 4 nm
Results

Retention Time	Area	Area Percent
20,29	18956358	3,379
29,29	483909310	86,265
48,28	58093035	10,356



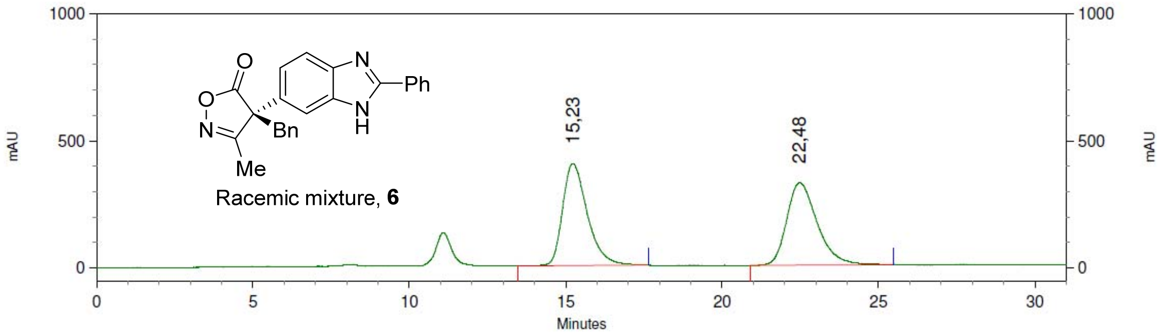
30: 266 nm, 4 nm
Results

Retention Time	Area	Area Percent
17,62	40520209	49,814
36,33	40822821	50,186



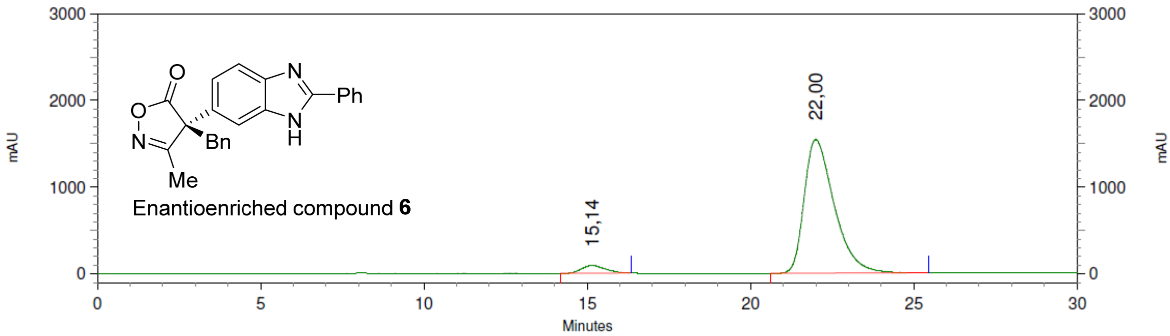
30: 266 nm, 4 nm
Results

Retention Time	Area	Area Percent
17,50	4105407	4,257
35,95	92342778	95,743



35: 306 nm, 4 nm
Results

Retention Time	Area	Area Percent
15,23	88266750	50,173
22,48	87658124	49,827

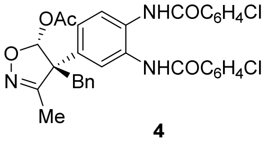


35: 306 nm, 4 nm
Results

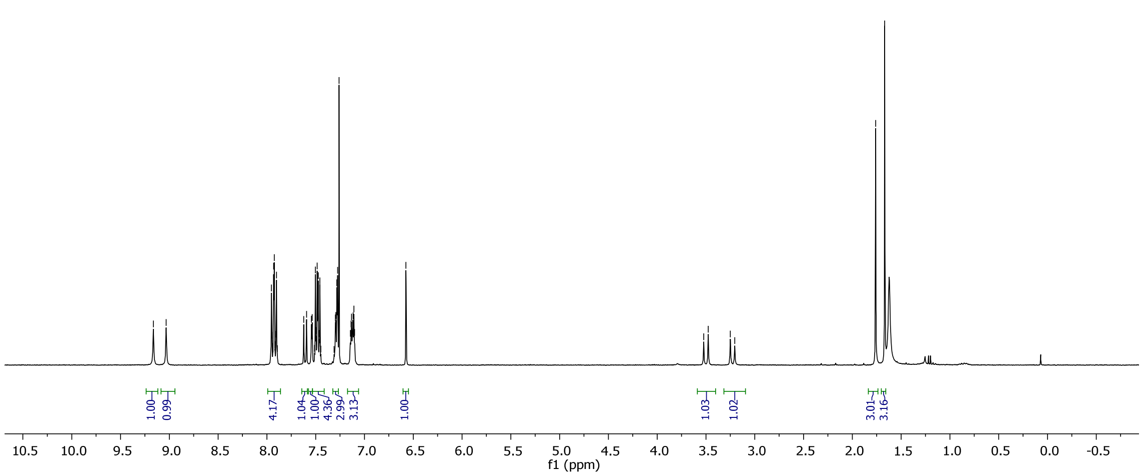
Retention Time	Area	Area Percent
15,14	17990991	4,359
22,00	394742947	95,641

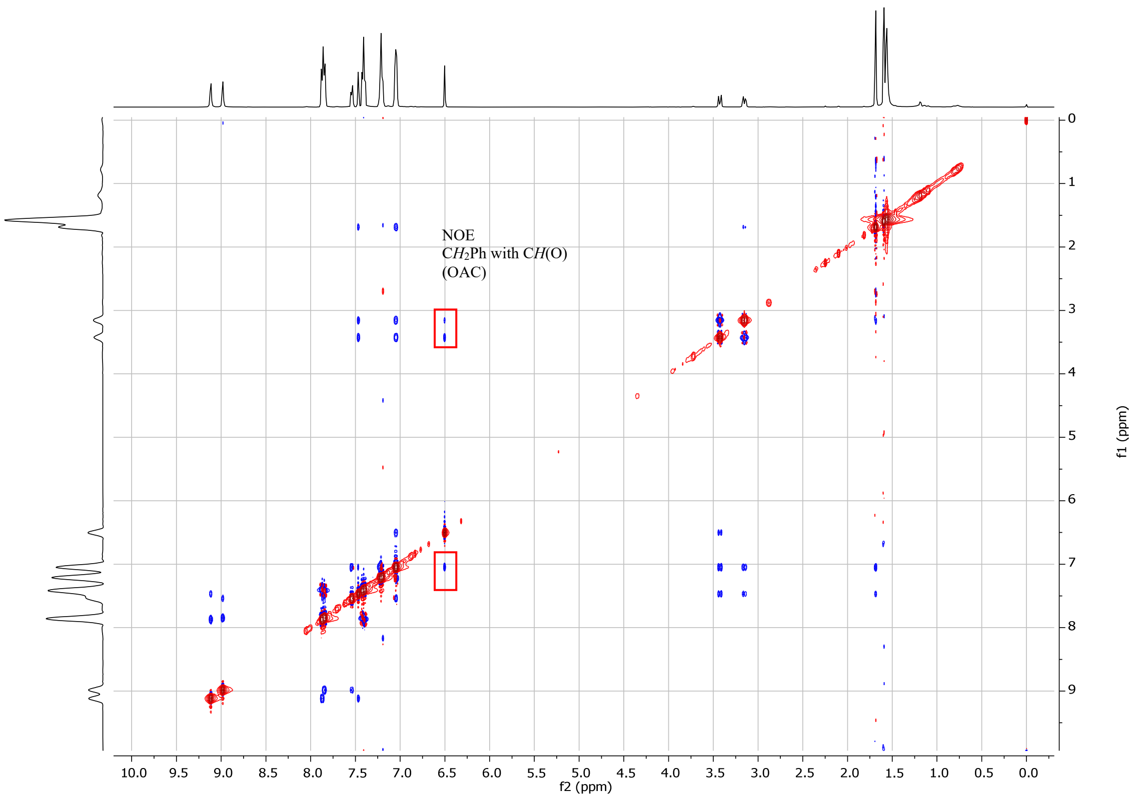
Determination of the relative stereochemistry of compounds 4

The relative stereochemistry of lactols 4 ws determine by NOESY experiments. Major diastereoisomer showed interaction between tha CH_2 of the Bn group (3.23 and 3.50 ppm) and lactol CH at 6.57 ppm

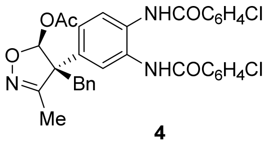


4
major diastereoisomer



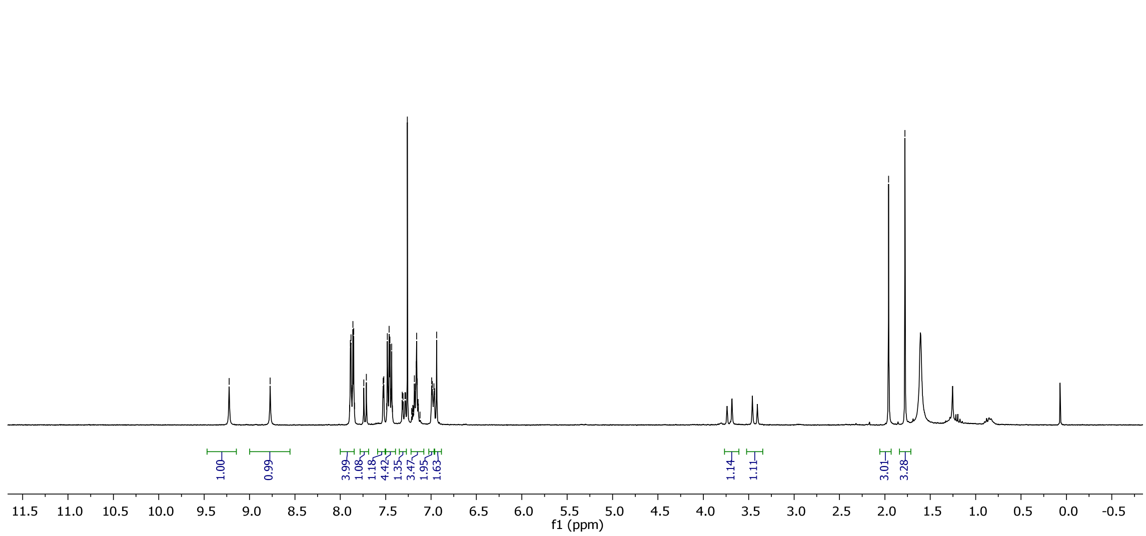


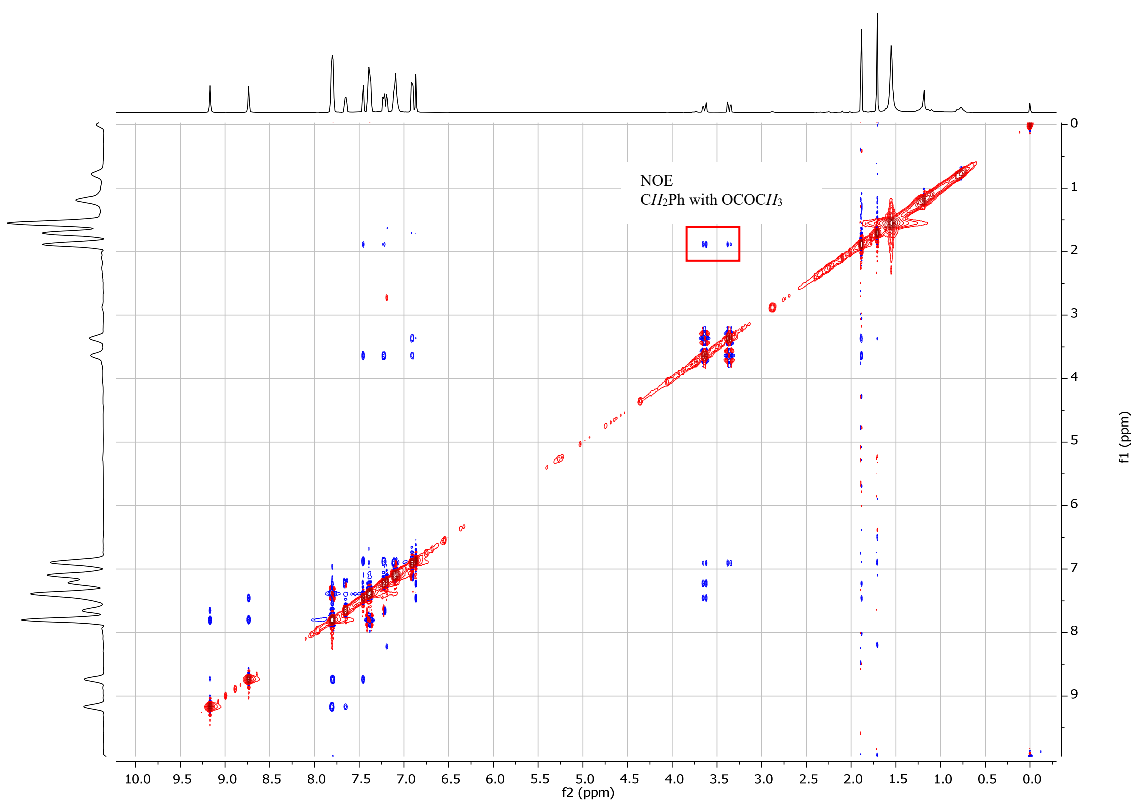
On the other hand the minor diastereoisomer showed interaction between the CH_2 of the Bn group (3.47 and 3.70 ppm) and the methyl group of the acetate at 1.96 ppm.



4

minor diastereoisomer





X-Ray structure of compound 3ha. CCDC 2292242

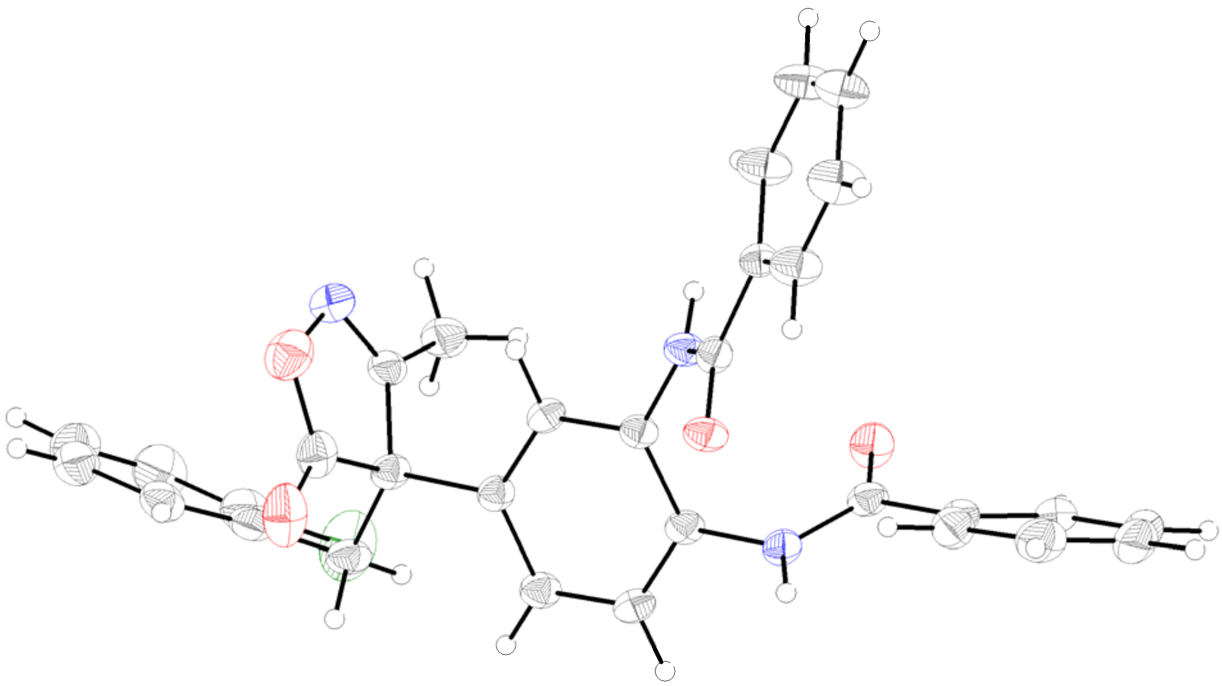


Figure S1. Ortep plot for compound **3ha**. Ellipsoids drawn at 50% probability level. Flack parameter 0.042(10).

Structural determination of compounds 3ad-3ag.

The structural determination of compounds **3ad-3ag** (regiochemistry) was carried out by analyzing the coupling constants (*J*) of the two aromatic hydrogens within the tetrasubstituted aryl ring.

In the NMR spectrum of compound **3ad,** signals corresponding to these protons were overlapped with those of the aromatic hydrogens of the thre other aromatic rings. Consequently, he structural assignment of 3ad was made based on its similarity to compound **3ae**, which exhibited a singlet signal at δ 7.53 (1H) and an unresolved doublet at δ 7.30 (1H) consistent with a 1,2,3,5-tetrasubstituted ring.

The differentiation between the structures of regioisomers **3af** and **3'af** followed a similar approach. The major regioisomer **3af** displayed two signals at 7.74 (1H, d, J = 3.0 Hz) and 7.65 (1H, d, J = 3.0 Hz) ppm, with a *meta* coupling value, indicating a 1,2,3,5-tetrasubstituted aryl ring. Conversely, the minor regioisomer **3'af** exhibited two doublets at 8.09 (1H, d, J = 9.0 Hz, Ar) and 7.94 (1H, d, J = 9.0 Hz, Ar) confirming the *ortho* disposition of both hydrogens, in line with a 1,2,3,4-tetrasubstituted aryl ring.

Finally, the fluorinated compound **3ag** displayed a partially resolved double doublet at 7.86 (1H) with $J_{H\text{-}F}$ = 1.8 Hz (*para* H-F coupling) and $J_{H\text{-}H}$ = 2.0 Hz (*meta* H-H coupling) along with a double doublet at 6.91 (1H) with $J_{H\text{-}F}$ = 10.7 Hz (*ortho* H-F coupling) and $J_{H\text{-}H}$ = 2.2 Hz (*meta* H-H coupling). These findings indicated the *meta* disposition of both hydrogens in a 1,2,3,5-tetrasubstituted aryl ring featuring a fluorine atom at position 3.

References

[1] a) N. Capreti, I. D. Jurberg *Org. Lett.* 2015, **17**, 2490-2493; b) A. A. G. Fernandes, M. L. Stivanin, I. D. Jurberg *Chem. Select.* 2019, **4**, 3360. c) H. Zhang, B. Wang, L. Cui, X. Bao, J. Qu, Y. Song, *Eur. J. Org. Chem.* 2015, 2143; d) R. Torán, C. Vila, A. Sanz-Marco, M. C. Muñoz, J. R. Pedro, G. Blay, *Eur. J. Org. Chem.* 2020, 627.

[2] A. Lavios, P. Martinez-Pardo, A. Sanz-Marco, C. Vila, Jose R. Pedro, G. Blay, *Org. Lett.* 2023, **25**, 5608.