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Cu-diamine Ligand-Controlled Asymmetric Henry Reactions and Its Application in a Concise Total Syntheses of Linezolid and Rivaroxaban

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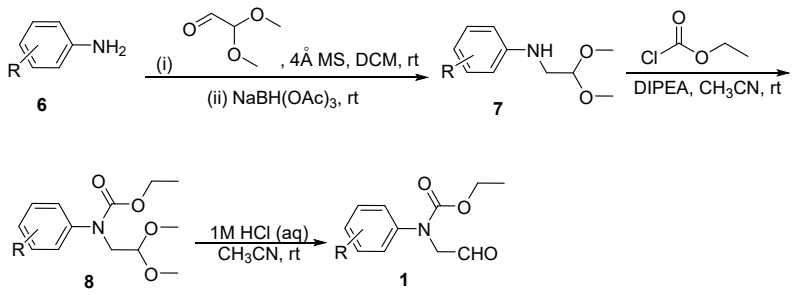
1. General information

All commercially provided reagents were used directly without further purification. Tetrahydrofuran and toluene were dried and distilled before use. Column chromatography was carried out via using 200−300 mesh silica gel. The structure of new compounds were analyzed by ^{1}H NMR, ^{13}C NMR and HRMS. NMR spectra results were collected by a 400 MHz NMR spectrometer. Reference values for residual organic solvents were regarded as δ = 7.26 ppm for ^{1}H NMR, and δ = 77.0 ppm for ^{13}C NMR ($CDCl_3$), δ = 2.51 ppm for ^{1}H NMR, and δ =39.98 ppm for ^{13}C NMR (DMSO-d6). Coupling constants (*J*) are expressed in Hz and are uncorrected, and multiplicities for coupled signals were represented as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad signal and dd = double doublet etc. High-resolution mass spectra (HRMS) were measured by a Bruker TOF Premier with electron spray ionization (ESI). The melting point (m.p.) values were collected by an SRS-optic melting point apparatus. Optical rotations were recorded on an automatic polarimeter (Rudolph Research Analytical Autopol VI). Chiral HPLC was carried out using the Daicel chiral analytical column (CHIRALCEL AS-H, IC, AD-H, and OD-H). Unless otherwise stated, all products are isolated yields.

2. General procedure for the asymmetric Henry reactions

In the test tube with a Teflon stir bar, CuOAc (0.02 mmol, 2.4 mg) was added into a solution of absolute EtOH (0.6 mL) containing **L1** (0.02 mmol, 15.2 mg) and the mixture reacted for 1 h at room temperature. Nitromethane **2a** (2.0 mmol), aldehyde **1** (0.2 mmol) and pyridine (0.2 mmol, 16.1 μL) was added to the resulting blue solution and the mixture reacted at room temperature for another 48-72 h. The reaction process was monitored by TLC. After the reaction ended, removing the solvent under reduced pressure, then the crude product was further purified via flash chromatography (DCM/MeOH = 100:2 as eluent), and the corresponding **3** was obtained.

3. General synthesis of aldehyde 1

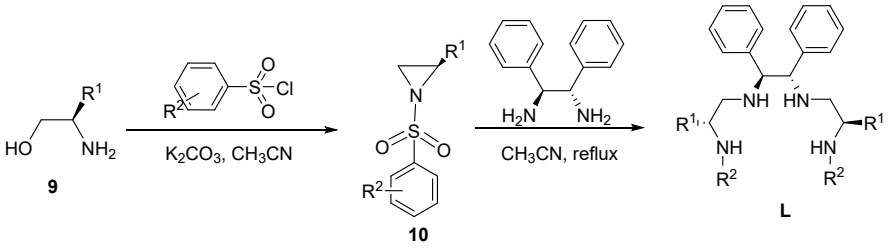


To a solution of **6** (10.0 mmol) in dichloroethane (40 mL), dimethoxyacetaldehyde (60% wt in water, 1.5 eq, 15.0 mmol, 2.26 mL) was added. 4Å molecular sieves (1.0 g) were added and the mixture was maintained under magnetic stirring at room temperature for 1 h. After this time, $NaBH(OAc)_3$ (1.5 eq, 15 mmol, 3.16 g) was added portion wise and the solution was stirred for 1 hour at room temperature. The mixture was filtrate and the residue was washed with dichloroethane. Evaporated in vacuo and the residue was chromatographed giving compound **7**.

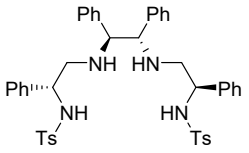
To a solution of **7** (10.0 mmol) in acetonitrile (40 mL), DIPEA (1.0 eq, 10.0 mmol, 1.65 mL) and ethyl chloroformate (1.5 eq, 15.0 mmol, 1.15 mL) were added. After 24 h under stirring at room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and evaporated in vacuo. The residue was chromatographed giving compound **8**.

To a solution of **8** (10.0 mmol) in acetonitrile (75 mL), 20% HCl aq. (10 mL) was added. After 24 h under stirring at room temperature, the reaction mixture was neutralized with a saturated solution of $NaHCO_3$ and extracted whit ethyl acetate. The organic layer was dried over Na_2SO_4, evaporated in vacuo and the compound **1** was purified by flash chromatography.

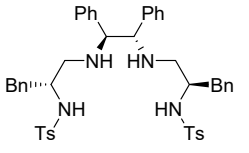
4. General preperation of bis(sulfonamide)-diamine ligand



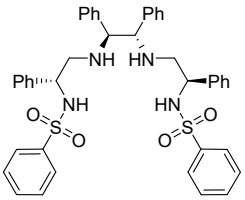
R^2 substituted benzoyl chloride (2.2 eq, 22.0 mmol) was added portion wise at room temperature to a stirred mixture of **9** (1.0 eq, 10.0 mmol), K_2CO_3 (4.0 eq, 40.0 mmol) and acetonitrile (20 mL). After 24 h, ethyl acetate (10 mL) was added, the solid was filtered off and the solvents evaporated, leaving the corresponding aziridine **10** as a white solid. (*S*,*S*)-1,2-Diamine (1.0 eq, 2.0 mmol) and the corresponding aziridine **10** (2.2 eq, 4.4 mmol) were dissolved in dry acetonitrile (14 mL), and the mixture was stirred under reflux for 3 days. The solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography.



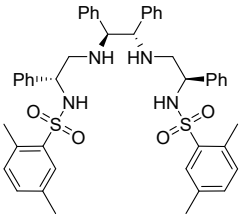
***N*,*N'*-((1*R*,1'*R*)-(((1*S*,2*S*)-1,2-diphenylethane-1,2-diyl)bis(azanediyl))bis(1-phenylethane-2,1-diyl))bis(4-methylbenzenesulfonamid) (L1):** The NMR spectra of compounds **L1** is in accord with the reported spectra.[1] **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.59 (d, *J* = 7.6 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.24-7.11 (m, 10H), 7.09-7.07 (m, 3H), 7.04-6.99 (m, 5H), 6.85-6.81 (m, 4H), 6.74-6.72 (m, 2H), 5.76 (s, 1H), 5.14 (s, 1H), 4.33 (t, *J* = 5.6 Hz, 1H), 3.42 (d, *J* = 8.8 Hz, 1H), 3.23-3.19 (m, 2H), 2.97-2.86 (m, 2H), 2.64 (dd, J_1 = 12.0 Hz, J_2 = 6.0 Hz, 1H), 2.46 (dd, J_1 = 12.0 Hz, J_2 = 5.2 Hz, 1H), 2.36 (s, 3H), 2.31 (s, 3H).



***N*,*N*'-((2*R*,2'*R*)-(((1*S*,2*S*)-1,2-diphenylethane-1,2-diyl)bis(azanediyl))bis(3-phenylpropane-1,2-diyl))bis(4-methylbenzenesulfonamide) (L2):** White solid (75% yield), m.p. 148.0-150.0°C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.51 (d, *J* = 8.4 Hz, 4H), 7.17-7.08 (m, 16H), 6.98-6.96 (m, 4H), 6.92-6.89 (m, 4H), 5.36 (br, 2H), 3.55 (s, 2H), 3.48 (t, *J* = 6.0 Hz, 2H), 2.74-2.70 (m, 4H), 2.46 (d, *J* = 4.8 Hz, 1H), 2.43 (d, *J* = 4.4 Hz, 1H), 2.37 (s, 6H), 2.33 (d, *J* = 5.2 Hz, 1H), 2.30 (d, *J* = 5.6 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 142.8, 140.8, 137.7, 137.3, 129.5, 129.2, 128.5, 128.0, 127.8, 127.0, 126.8, 126.4, 69.1, 55.4, 49.7, 39.4, 21.5 ppm. **HRMS** (ESI) m/z calcd for $C_{46}H_{50}N_4O_4S_2$ $[M + Na]^+$: 809.3171, found: 809.3168. **$[\alpha]_D^{25}$** = +54.87 (c = 0.39, EtOH).

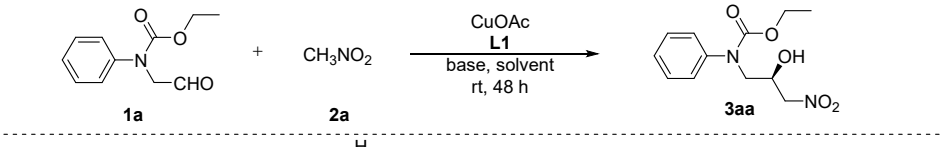
***N*,*N*'-((1*R*,1'*R*)-(((1*S*,2*S*)-1,2-diphenylethane-1,2-diyl)bis(azanediyl))bis(1-phenylethane-2,1-diyl))dibenzenesulfonamide (L3):** 

White solid (65% yield), m.p. 82.0-84.0°C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.72-7.69 (m, 2H), 7.56-7.54 (m, 2H), 7.50 (t, J = 7.6 Hz, 1H), 7.40-7.37 (m, 3H), 7.26-7.17 (m, 8H), 7.12-7.09 (m, 5H), 7.05-7.03 (m, 3H), 6.87-6.83 (m, 4H), 6.75 (dd, J_1 = 6.0 Hz, J_2 = 2.4 Hz, 2H), 4.37 (t, J = 5.6 Hz, 1H), 3.44 (d, J = 9.2 Hz, 1H), 3.24-3.20 (m, 2H), 2.99 (t, J = 13.2 Hz, 1H), 2.91 (dd, J_1 = 12.8 Hz, J_2 = 4.8 Hz, 1H), 2.65 (dd, J_1 = 12.4 Hz, J_2 = 6.4 Hz, 1H), 2.49 (dd, J_1 =12.0 Hz, J_2 = 5.2 Hz, 1H), 2.18 (br, 2H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ: 140.49, 140.44, 139.6, 139.1, 132.5, 132.2, 129.1, 128.8, 128.7, 128.4, 128.2, 128.1, 127.9, 127.9, 127.6, 127.5, 127.25, 127.20, 127.1, 127.0, 126.9, 126.7, 69.0, 65.2, 58.7, 57.3, 52.4, 49.3 ppm. **HRMS** (ESI) m/z calcd for $C_{42}H_{42}N_4O_4S_2$ [M + Na]$^+$: 753.2545, found: 753.2552, **$[\alpha]_D^{25}$** = +24.7 (c = 0.66, EtOH).

***N*,*N*'-((1*R*,1'*R*)-(((1*S*,2*S*)-1,2-diphenylethane-1,2-diyl)bis(azanediyl))bis(1-phenylethane-2,1-diyl))bis(2,5-dimethylbenzenesulfonamide)(L4):** 

White solid (70% yield), m.p. 86.0-96.0°C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.70 (d, J = 1.6 Hz, 1H), 7.49 (d, J = 1.6 Hz, 1H), 7.27-7.25 (m, 3H), 7.20 (dd, J_1 = 7.6 Hz, J_2 = 2.0 Hz, 1H), 7.15-7.09 (m, 8H), 7.04-6.97 (m, 6H), 6.92-6.86 (m, 4H), 6.77-6.74 (m, 2H), 5.53 (s, 1H), 5.04 (s, 1H), 4.33 (t, J = 6.0 Hz, 1H), 3.50 (d, J = 8.8 Hz, 1H), 3.37-3.33 (m, 1H), 3.28 (d, J = 8.8 Hz, 1H), 2.96-2.89 (m, 2H), 2.68-2.61 (m, 2H), 2.47 (s, 3H), 2.40 (s, 3H), 2.31 (s, 3H), 2.20 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ: 140.3, 140.1, 140.0, 139.0, 138.0, 137.1, 136.0, 135.6, 133.7, 133.6, 133.4, 133.1, 132.4, 132.1, 130.0, 129.8, 128.8, 128.3, 128.2, 128.0, 127.9, 127.8, 127.6, 127.5, 127.24, 127.22, 127.1, 126.7, 69.2, 65.2, 58.6, 57.6, 52.9, 49.1, 20.8, 20.7, 19.77, 19.75 ppm. **HRMS** (ESI) m/z calcd for $C_{46}H_{50}N_4O_4S_2$ [M + Na]$^+$: 809.3137, found: 809.3130, **$[\alpha]_D^{25}$** = +27.5 (c = 0.61, EtOH).

5. Optimization of other conditions for Henry reaction[a]

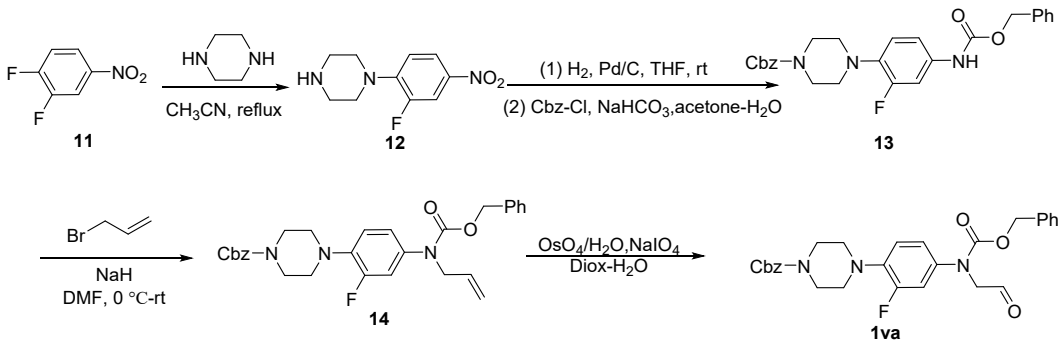


Entry	1a:2a	Base	Solvent	Yield (%)[b]	*ee* (%)[c]
1	1:10	Pyridine	Et_2O	85	87
2	1:10	Pyridine	CH_3CN	80	89
3	1:10	Pyridine	EtOH (0.4 mL)	95	93
4	1:10	Pyridine	EtOH (0.8 mL)	92	95
5	1:7.5	Pyridine	EtOH	93	94
6	1:5.0	Pyridine	EtOH	85	93
7	1:10	-	EtOH	25	93
8	1:10	DIPEA	EtOH	67	34
9	1:10	KF	EtOH	37	56
10	1:10	**B1**	EtOH	90	60

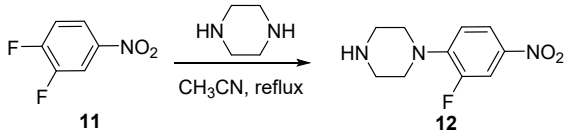
11	1:10	**B2**	EtOH	85	53

[a] Reaction conditions unless specified otherwise: 0.2 mmol of **1a**, 10.0 eq of **2a**, 10.0 mol % of **L1**, 10.0 mol % of CuOAc, 1.0 eq of base, 0.6 mL of solvent, room temperature, 48 h. [b] Isolated yield. [c] *ee* values were determined by chiral HPLC.

6. Total synthesis of aldehyde 1va

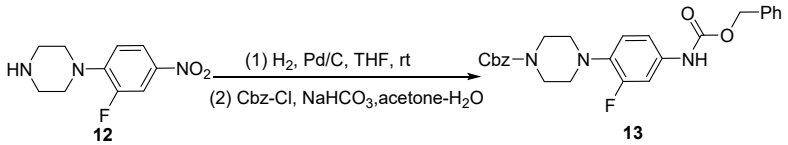


Preperation of 1-(2-Fluoro-4-nitrophenyl)piperazine (12)



A solution of 15.91 g (100 mmol) of 3,4-difluoronitrobenzene **11** in 200 mL of acetonitrile was treated with 21.54 g (250 mmol) of piperazine followed by warming at reflux for 3 h. The solution was cooled to room temperature and concentrated in vacuo. The resulting residue was diluted with 200 mL of water and extracted with ethyl acetate (3×250 mL). The combined organic layers were extracted with water (200 mL) and saturated sodium chloride solution (200 mL) followed by drying on sodium sulfate. The solution was concentrated in vacuo to afford crude product. The material was purified by flash column chromatography (DCM: MeOH= 10:1) to get yellow solid **12** (19.81g, 80% yield). The NMR spectra of compounds **12** is in accord with the reported spectra.[2] **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.90 (dd, J_1 = 8.8 Hz, J_2 =2.4 Hz, 1H), 7.82 (dd, J_1 = 13.2 Hz, J_2 =2.4 Hz, 1H), 6.84 (t, J = 8.8 Hz, 1H), 3.19 (t, J = 4.8 Hz, 1H), 2.98 (t, J = 4.8 Hz, 1H) ppm.

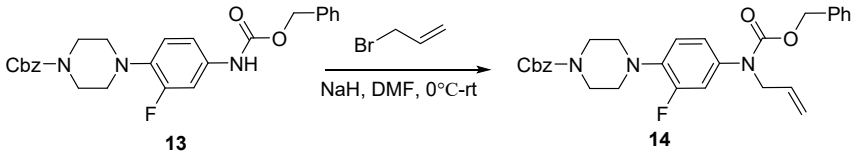
Preperation of benzyl 4-(4-(((benzyloxy)carbonyl)amino)-2-fluorophenyl)piperazine-1-carboxylate (13)



A mixture of 11.25 g (50.0 mmol) of **12** and 1.69 g of 10% palladium on carbon in 100 mL of THF was stirred under 40 psi of H_2 for 1.5 h, while maintaining the reaction at room temperature. The reaction mixture was filtered through diatomaceous earth and the pad washed with 2 × 50 mL of THF. The filtrate was concentrated, and the crude product was azeotroped with 50 mL of acetone. The crude amine was immediately dissolved in 69 mL of acetone and added to a 500 mL reaction flask equipped with a

mechanical stirrer, containing 125 mL of 10% aqueous sodium carbonate. The mixture was cooled to 0℃, and 14.05 mL (100 mmol) of benzylchloroformate was added dropwise over 20 min while maintaining the temperature of 0℃. The mixture was then stirred for 1 h at 0℃ and then allowed to stir overnight at room temperature. The mixture was decanted, and the product was extracted with chloroform (3×50 mL) and dried over sodium sulfate then dried in vacuo, and then was decolorized by activated charcoal in hot methanol and filtrated to give white solid compound **13** (14.13g, 61% yield).[2]

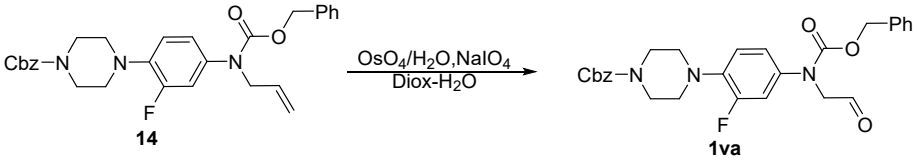
Preperation of benzyl 4-(4-(allyl((benzyloxy)carbonyl)amino)-2-fluorophenyl)piperazine-1-carboxylate (14)



13 **14**

NaH (60 wt %, 880 mg, 22.0 mmol) was added to a solution of **13** (9.26 g, 20.0 mmol) in DMF (150 mL) at 0℃. The reaction mixture was stirred for 30 minutes at room temperature. After an addition of allyl bromide (5.19 mL, 60.0 mmol) at room temperature, the reaction mixture was stirred for additional 3 h at the same temperature. The reaction was quenched with saturated aqueous NH_4Cl solution and the organic materials were extracted with EtOAc two times. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure after filtration. The residue was purified by silica gel column chromatography (PE : EtOAc = 2.5:1) to afford yellow oil **14** (9.06 g, 93% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.29 (d, J = 4.4 Hz, 4H), 7.21-7.18 (m, 6H), 6.90-6.85 (m, 2H), 6.77 (t, J = 8.8 Hz, 1H), 5.82-5.76 (m, 1H), 5.08-5.06 (m, 5H), 5.04-5.01 (m, 1H), 4.14 (dt, J_1 = 6.0 Hz, J_2 =1.6 Hz, 2H), 3.59 (t, J = 4.8 Hz, 4H), 2.94 (t, J = 5.2 Hz, 4H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ: 155.2, 155.1, 155.0 (d, J = 245.8 Hz), 138.1, 136.6, 136.4, 135.5, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 122.5, 118.8 (d, J = 3.8 Hz),117.3, 115.1, 67.4, 67.3, 53.2, 50.4, 43.9 ppm. **HRMS** (ESI) m/z calcd for $C_{29}H_{30}FN_3O_4$ $[M + Na]^+$: 526.2118, found: 526.2139.

Preperation of benzyl 4-(4-(((benzyloxy)carbonyl)(2-oxoethyl)amino)-2-fluorophenyl) piperazine-1-carboxylate (1va)

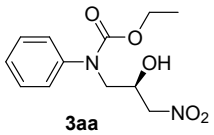


14 **1va**

2,6-Lutidine (3.24 mL, 31.12 mmol), OsO_4 (4% solution in H_2O, 0.99 mL), and $NaIO_4$ (13.31 g, 62.24; mmol) were added to a solution of **14** (7.83g, 15.56 mmol) in dioxane (117 mL) and water (39 mL) at room temperature. After the reaction was complete in about 5 h, water (100 mL) and CH_2Cl_2 (200 mL) were added. After the separation of the organic layer and aqueous layer, the aqueous layer was extracted by CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo after filtration. The residue was purified by silica gel column chromatography (PE : EtOAc = 2.5:1) to afford yellow oil **1va** (6.29 g, 80% yield). **^{1}H NMR** (400 MHz, DMSO) δ: 9.61 (s, 1H), 7.39-7.28 (m, 10H), 7.18 (dd, J_1 = 13.6 Hz, J_2 =2.8 Hz, 1H), 7.08 (dd, J_1 = 8.4 Hz, J_2 =2.8 Hz, 1H), 7.00 (t, J = 9.2 Hz, 1H), 5.13 (s, 4H), 4.51 (s, 2H), 3.56 (t, J = 4.8 Hz, 4H), 2.97 (t, J = 4.8 Hz, 4H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO) δ: 199.3, 155.0, 154.8, 154.5 (d, J = 243.9 Hz), 138.4, 137.3, 136.8,

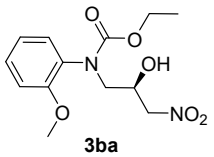
128.9, 128.8, 128.3, 128.0, 127.8, 119.6 (d, J = 14.8 Hz), 67.4, 66.8, 60.4, 50.4, 43.9 ppm. **HRMS** (ESI) m/z calcd for $C_{28}H_{28}FN_3O_5$ $[M + Na]^+$: 528.1911, found: 528.1905.

7. Analytical data (3aa~3va)



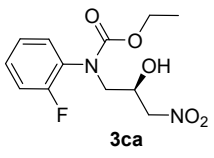
3aa

Ethyl (*R*)-(2-hydroxy-3-nitropropyl)(phenyl)carbamate (**3aa**): Prepared according to the general method from **1a** (41.42 mg, 0.2 mmol) with 10 mol% catalyst, and purified as a yellow oil (50.94 mg, 95%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.32-7.29 (m, 2H), 7.21 (t, J = 7.6 Hz, 1H), 7.15-7.13 (m, 2H), 4.48-4.42 (m, 1H), 4.38-4.32 (m, 2H), 4.07 (q, J = 7.2 Hz, 2H), 3.81 (dd, J_1 = 14.8 Hz, J_2 = 6.8 Hz, 1H), 3.72 (dd, J_1 = 14.8 Hz, J_2 = 4.8 Hz, 1H), 1.11 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ: 157.0, 141.7, 129.3, 127.3, 127.0, 78.7, 68.0, 62.5, 53.7, 14.4 ppm; **HRMS** (ESI) calcd. for $C_{12}H_{16}N_2O_5$ + Na: 291.0957, found: 291.0961; **$[\alpha]_D^{25}$** = +28.81 (c = 0.59, EtOH); **Chiral HPLC**: 95% *ee* of **3aa** (CHIRALCEL AS-H, 220 nm, *n*-hexane/2-propanol = 80/20, flow rate 0.8 mL/min, T = 30 °C), t_R = 14.5 min (minor), 16.9 min (major).



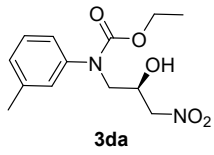
3ba

Ethyl (*R*)-(2-hydroxy-3-nitropropyl)(2-methoxyphenyl)carbamate (**3ba**): Prepared according to the general method from **1b** (47.50 mg, 0.2 mmol) with 10 mmol% catalyst, and purified as a yellow oil (55.45 mg, 93%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.31 (td, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H), 7.14 (d, J = 7.6 Hz, 1H), 6.97 (dd, J_1 = 14.0 Hz, J_2 = 7.6 Hz, 2H), 4.59 (s, 3H), 4.22-3.93 (m, 3H), 3.85 (s, 3H), 3.55 (t, J = 18.8 Hz, 1H), 1.11 (t, J = 6.8 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ: 156.0, 153.7, 129.3, 128.1, 127.6, 120.3, 110.8, 77.7, 66.6, 61.2, 54.6, 52.8, 13.4 ppm; **HRMS** (ESI) calcd. for $C_{13}H_{18}N_2O_6$ + Na: 321.1063, found: 321.1067; **$[\alpha]_D^{25}$** = +34.02 (c = 0.24, EtOH); **Chiral HPLC**: 94% *ee* of **3ba** (CHIRALCEL IC, 220 nm, *n*-hexane/2-propanol = 80/20, flow rate 0.8 mL/min), T = 30 °C, t_R = 16.3 min (minor), 36.1 min (major).



3ca

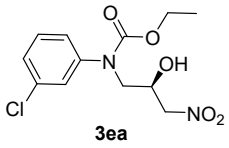
Ethyl (*R*)-(2-fluorophenyl)(2-hydroxy-3-nitropropyl)carbamate (**3ca**): Prepared according to the general method from **1c** (45.04 mg, 0.2 mmol) with 10 mmol% catalyst, and purified as a yellow oil (48.64 mg, 85%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.34-7.24 (m, 2H), 7.19-7.12 (m, 2H), 4.56-4.45 (m, 3H), 4.14 (q, J = 7.2 Hz, 2H), 3.83-3.80 (m, 2H), 3.68 (br, 1H), 1.16 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ: 158.0 (d, J = 230.2 Hz), 156.6, 129.4, 129.39, 129.30 (d, J = 43.2 Hz), 124.8 (d, J = 3.8 Hz), 116.5 (d, J = 20.4 Hz), 78.4, 68.1, 62.8, 53.6, 14.3 ppm; **HRMS** (ESI) calcd. for $C_{12}H_{15}FN_2O_5$ + Na: 309.0863, found: 309.0863; **$[\alpha]_D^{25}$** = +20.93 (c = 0.43, EtOH); **Chiral HPLC**: 90% *ee* of **3ca** (CHIRALCEL AS-H, 220 nm, *n*-hexane/2-propanol = 80/20, flow rate 0.8 mL/min, T = 30 °C), t_R = 16.7 min (minor), 19.7 min (major).



3da

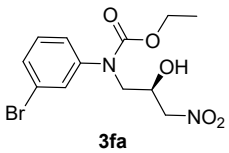
Ethyl (*R*)-(2-hydroxy-3-nitropropyl)(m-tolyl)carbamate (**3da**): Prepared according to the general method from **1d** (44.26 mg, 0.2 mmol) with 10 mmol% catalyst, and purified as a yellow oil (51.91 mg, 92%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.26 (t, J = 7.6 Hz, 1H), 7.10 (d, J = 7.6 Hz, 1H), 7.01-6.99 (m, 2H), 4.55-4.49 (m, 1H), 4.45-4.43 (m, 2H), 4.14 (q, J = 7.2 Hz, 2H), 3.88 (dd, J_1 = 14.8 Hz, J_2 = 6.8 Hz, 1H), 3.78 (dd, J_1 = 14.8 Hz, J_2 = 4.8 Hz, 1H), 2.36 (s, 3H), 1.19 (t, J = 7.2 Hz, 3H);

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 157.1, 141.6, 139.4, 129.1, 128.1, 127.5, 124.0, 78.7, 68.1, 62.5, 53.8, 21.3, 14.4 ppm; **HRMS** (ESI) calcd. for $C_{13}H_{18}N_2O_5$ + Na: 305.1113, found: 305.1116; **$[\alpha]_D^{25}$** = +23.59 (c = 0.76, EtOH); **Chiral HPLC**: 94% *ee* of **3da** (CHIRALCEL AS-H, 220nm, *n*-hexane/2-propanol = 90/10, flow rate 0.8 mL/min, *T* = 30 °C), t_R = 27.0 min (minor), 32.4 min (major).



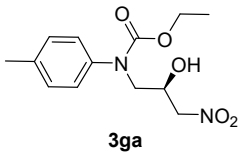
3ea

Ethyl (*R*)-(3-chlorophenyl)(2-hydroxy-3-nitropropyl)carbamate (**3ea**): Prepared according to the general method from **1e** (48.21 mg, 0.2 mmol) with 10 mol% catalyst, and purified as a yellow oil (51.35 mg, 85%). **^1H NMR** (400 MHz, $CDCl_3$) δ: 7.33-7.26 (m, 3H), 7.13 (dt, J_1 = 7.6 Hz, J_2 = 2.0 Hz, 1H), 4.60-4.52 (m, 1H), 4.50-4.41 (m, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.86 (dd, J_1 = 14.4 Hz, J_2 = 6.8 Hz, 1H), 3.79 (dd, J_1 = 14.8 Hz, J_2 = 4.8 Hz, 1H), 3.61 (br, 1H), 1.21 (t, *J* = 6.8 Hz, 3H); **$^{13}C\{^1H\}$ NMR** (100 MHz, $CDCl_3$) δ: 156.5, 142.9, 134.6, 130.2, 127.5, 127.4, 125.3, 78.5, 67.9, 62.8, 53.6, 14.4 ppm; **HRMS** (ESI) calcd. for $C_{12}H_{15}ClN_2O_5$ + Na: 325.0567, found: 325.0563; **$[\alpha]_D^{25}$** = +13.92 (c = 0.54, EtOH); **Chiral HPLC**: 92% *ee* of **3ea** (CHIRALCEL AS-H, 220nm, *n*-hexane/2-propanol = 80/20, flow rate 0.8 mL/min, *T* = 30 °C), t_R = 32.8 min (minor), 43.2 min (major).



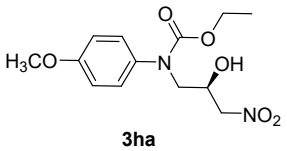
3fa

Ethyl (*R*)-(3-bromophenyl)(2-hydroxy-3-nitropropyl)carbamate (**3fa**): Prepared according to the general method from **1f** (57.23 mg, 0.2 mmol) with 10 mmol% catalyst, and purified as a yellow oil (56.75 mg, 82%). **^1H NMR** (400 MHz, $CDCl_3$) δ: 7.43-7.39 (m, 2H), 7.28-7.23 (m, 1H), 7.19(dt, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 4.55-4.49 (m, 1H), 4.47-4.41 (m, 2H), 4.16 (q, *J* = 6.8 Hz, 2H), 3.85 (dd, J_1 = 14.8 Hz, J_2 = 7.2 Hz, 1H), 3.78 (dd, J_1 = 14.4 Hz, J_2 = 4.8 Hz, 1H), 3.69 (br, 1H), 1.21 (t, *J* = 7.2 Hz, 3H); **$^{13}C\{^1H\}$ NMR** (100 MHz, $CDCl_3$) δ: 156.5, 143.0, 130.5, 130.4, 130.2, 125.9, 122.4, 78.5, 67.8, 62.8, 53.6, 14.4 ppm; **HRMS** (ESI) calcd. for $C_{12}H_{15}BrN_2O_5$ + Na: 369.0062, found: 369.0071; **$[\alpha]_D^{25}$** = +15.3 (c = 0.88, EtOH); **Chiral HPLC**: 91% *ee* of **3fa** (CHIRALCEL AS-H, 220nm, *n*-hexane/2-propanol = 80/20, flow rate 0.8 mL/min, *T* = 30 °C), t_R = 16.3 min (minor), 19.9 min (major)



3ga

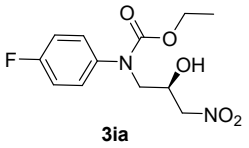
Ethyl (*R*)-(2-hydroxy-3-nitropropyl)(p-tolyl)carbamate(**3ga**): Prepared according to the general method from **1g** (44.26 mg, 0.2 mmol) with 10 mol% catalyst, and purified as a yellow oil (51.91 mg, 94%). **^1H NMR** (400 MHz, $CDCl_3$) δ: 7.17 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 4.54-4.49 (m, 1H), 4.44-4.42 (m, 2H), 4.13 (q, *J* = 6.8 Hz, 2H), 3.87 (dd, J_1 = 14.8 Hz, J_2 = 6.8 Hz, 1H), 3.76 (dd, J_1 = 14.8 Hz, J_2 = 4.8 Hz, 1H), 2.35 (s, 3H), 1.18 (t, *J* = 7.2 Hz, 3H); **$^{13}C\{^1H\}$ NMR** (100 MHz, $CDCl_3$) δ: 157.3, 139.1, 137.2, 130.0, 126.8, 78.7, 68.1, 62.5, 53.8, 21.0, 14.4 ppm; **HRMS** (ESI) calcd. for $C_{13}H_{18}N_2O_5$ + Na: 305.1113, found: 305.1108; $[\alpha]_D^{25}$ = +21.02 (c = 0.85, EtOH); **Chiral HPLC**: 94% *ee* of **3ga** (CHIRALCEL AS-H, 220 nm, *n*-hexane/2-propanol = 80/20, flow rate 0.8 mL/min, *T* = 30 °C), t_R = 14.2 min (minor), 17.4 min (major).



3ha

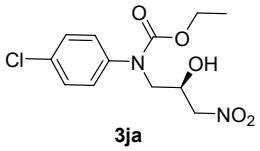
Ethyl (*R*)-(2-hydroxy-3-nitropropyl)(4-methoxyphenyl)carbamate (**3ha**): Prepared according to the general method from **1h** (47.46 mg, 0.2 mmol) with 10 mol% catalyst, and purified as a yellow oil (53.66 mg, 90%). **^1H NMR** (400 MHz, $CDCl_3$) δ: 7.11 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 4.55-4.49 (m, 1H), 4.45-4.43 (m, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.87-3.82 (m, 1H), 3.80 (s, 3H), 3.73 (dd, J_1 = 14.4 Hz, J_2 = 4.8 Hz, 1H), 1.17 (t, *J* = 7.2 Hz, 3H); **$^{13}C\{^1H\}$ NMR** (100 MHz, $CDCl_3$) δ

157.4, 133.4, 127.2, 113.5, 77.7, 67.1, 61.5, 54.4, 53.0, 13.4 ppm; **HRMS** (ESI) calcd. for $C_{13}H_{18}N_2O_6$ + Na: 321.1063, found: 321.1059; $[\alpha]_D^{25}$ = +39.79 (c = 0.78, EtOH); **Chiral HPLC**: 89% *ee* of **3ha** (CHIRALCEL AS-H, 220nm, *n*-hexane/2-propanol = 80/20, flow rate 0.8 mL/min, T = 30 °C), t_R = 21.6 min (minor), 25.5 min (major)



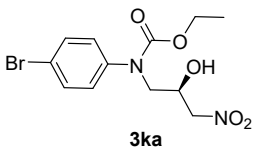
3ia

Ethyl (*R*)-(4-fluorophenyl)(2-hydroxy-3-nitropropyl)carbamate (**3ia**): Prepared according to the general method from **1i** (45.02 mg, 0.2 mmol) with 10 mol% catalyst, and purified as a yellow oil (46.95 mg, 82%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.19 (dd, J_1 = 8.8 Hz, J_2 = 4.8 Hz, 2H), 7.08-7.00 (m, 2H), 4.53–4.43 (m, 3H), 4.12 (q, J = 7.2 Hz, 2H), 3.83 (dd, J_1 = 14.4 Hz, J_2 = 7.2 Hz, 1H), 3.74 (dd, J_1 = 14.8 Hz, J_2 = 4.8 Hz, 1H), 1.17 (t, J = 7.6 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ: 161.3 (d, J = 245.8 Hz), 157.0, 137.7 (d, J = 3.2 Hz), 128.9 (d, J = 8.6 Hz), 116.2 (d, J = 22.6 Hz), 78.6, 67.9, 62.6, 53.8, 14.4 ppm; **HRMS** (ESI) calcd. for $C_{12}H_{15}FN_2O_5$ + Na: 309.0863, found: 309.0860; $[\alpha]_D^{25}$ = +15.68 (c = 0.17, EtOH); **Chiral HPLC**: 94% *ee* of **3ia** (CHIRALCEL AS-H, 220 nm, *n*-hexane/2-propanol = 95/5, flow rate 0.8 mL/min, T = 30 °C), t_R = 55.7 min (minor), 59.0 min (major).



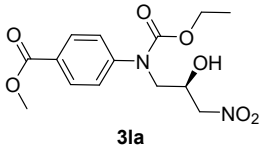
3ja

Ethyl (*R*)-(4-chlorophenyl)(2-hydroxy-3-nitropropyl)carbamate (**3ja**): Prepared according to the general method from **1j** (48.21 mg, 0.2 mmol) with 10 mol% catalyst, and purified as a yellow oil (48.33 mg, 80%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.36-7.32 (m, 2H), 7.18-7.15 (m, 2H), 4.55-4.52 (m, 1H), 4.50-4.42 (m, 2H), 4.15 (q, J = 6.8 Hz, 2H), 3.85 (dd, J_1 = 14.4 Hz, J_2 = 6.8 Hz, 1H), 3.77 (dd, J_1 = 14.4 Hz, J_2 = 4.4 Hz, 1H), 3.63 (bra, 1H), 1.19 (t, J = 6.4 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ: 156.6, 140.3, 132.9, 129.5, 128.4, 78.5, 67.9, 62.7, 53.7, 14.3 ppm; **HRMS** (ESI) calcd. for $C_{12}H_{15}ClN_2O_5$ + Na^+: 325.0567, found: 325.0558; $[\alpha]_D^{25}$ = +12.59 (c = 0.09, EtOH); **Chiral HPLC**: 89% *ee* of **3ja** (CHIRALCEL AS-H, 220nm, *n*-hexane/2-propanol = 95/5, flow rate 1 mL/min, T = 30 °C), t_R = 58.3 min (minor), 63.9 min (major).



3ka

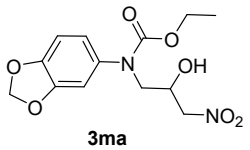
Ethyl (*R*)-(4-bromophenyl)(2-hydroxy-3-nitropropyl)carbamate(**3ka**): Prepared according to the general method from **1k** (57.00 mg, 0.2 mmol) with 10 mol% catalyst, and purified as a yellow oil (55.36 mg, 80%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.50 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 4.55-4.51 (m, 1H), 4.50-4.41 (m, 2H), 4.15 (q, J = 7.2 Hz, 2H), 3.85 (dd, J_1 = 14.4 Hz, J_2 = 6.8 Hz, 1H), 3.78 (dd, J_1 = 14.4 Hz, J_2 = 4.4 Hz, 1H), 3.53 (bra, 1H), 1.20 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 140.9, 132.5, 128.7, 120.9, 78.4, 68.0, 62.7, 53.7, 14.4 ppm; **HRMS** (ESI) calcd. for $C_{12}H_{15}BrN_2O_5$ + Na: 369.0062, found: 369.0047; $[\alpha]_D^{25}$ = +12.3 (c = 0.87, EtOH); **Chiral HPLC**: 87% *ee* of **3ka** (CHIRALCEL AS-H, 220nm, *n*-hexane/2-propanol = 95/5, flow rate 1 mL/min, T = 30 °C), t_R = 63.2 min (minor), 69.4 min (major).



3la

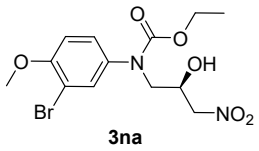
Methyl (*R*)-4-((ethoxycarbonyl)(2-hydroxy-3-nitropropyl)amino)benzoate (**3la**): Prepared according to the general method from **1l** (53.06 mg, 0.2 mmol) with 10 mol% catalyst, and purified as a yellow oil (57.39 mg, 88%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.01 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.8 Hz, 2H), 4.57-4.52 (m, 1H), 4.49-4.40 (m, 2H), 4.16 (q, J = 7.2 Hz, 2H), 3.91 (s, 3H), 3.89-3.85 (m, 2H), 3.67 (bra, 1H), 1.19 (t, J = 7.2, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ: 166.3, 156.3, 145.9, 130.7, 128.6,

126.6, 78.5, 67.9, 62.8, 53.4, 52.3, 14.3 ppm; **HRMS** (ESI) calcd. for $C_{14}H_{18}N_2O_7$ + Na: 349.1012, found: 349.1011; **$[\alpha]_D^{25}$** = +86.11 (c = 0.24, EtOH); **Chiral HPLC**: 94% *ee* of **3la** (CHIRALCEL AS-H, 220 nm, *n*-hexane/2-propanol = 80/20, flow rate 0.8 mL/min, *T* = 30 °C), t_R = 33.9 min (minor), 51.0 min (major).



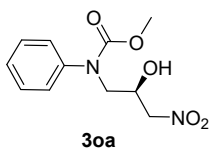
3ma

Ethyl (*R*)-benzo[d][1,3]dioxol-5-yl(2-hydroxy-3-nitropropyl)carbamate (**3ma**): Prepared according to the general method from **1m** (50.20 mg, 0.2 mmol) with 10 mmol% catalyst, and purified as a yellow oil (53.06 mg, 85%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 6.77 (d, *J* = 8.4 Hz, 1H), 6.69-6.65 (m, 2H), 5.99 (s, 2H), 4.53-4.51 (m, 1H), 4.50-4.44 (m, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.83 (dd, J_1 = 14.8 Hz, J_2 = 7.2 Hz, 1H), 3.70 (dd, J_1 = 14.4 Hz, J_2 = 4.4 Hz, 1H), 1.19 (t, *J* = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ: 157.5, 148.1, 146.7, 135.5, 120.5, 108.4, 108.3, 101.7, 78.6, 68.0, 62.6, 54.1, 14.4 ppm; **HRMS** (ESI) calcd. for $C_{13}H_{17}N_2O_7$ + Na: 335.0855, found: 335.0848; **$[\alpha]_D^{25}$** = +17.27 (c = 0.39, EtOH); **Chiral HPLC**: 92% *ee* of **3ma** (CHIRALCEL IC, 220 nm, *n*-hexane/2-propanol = 80/20, flow rate 1 mL/min, *T* = 30 °C), t_R = 18.5 min (minor), 31.2 min (major).



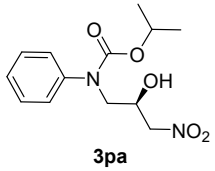
3na

Ethyl (*R*)-(3-bromo-4-methoxyphenyl)(2-hydroxy-3-nitropropyl)carbamate (**3na**): Prepared according to the general method from **1n** (63.24 mg, 0.2 mmol) with 10 mmol% catalyst, and purified as a yellow oil (61.67 mg, 85%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.42 (s, 1H), 7.15 (d, *J* = 7.2 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 1H), 4.53-4.49 (m, 1H), 4.48-4.40 (m, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.90 (s, 3H), 3.82 (dd, J_1 = 14.8 Hz, J_2 = 7.2 Hz, 1H), 3.71 (dd, J_1 = 14.8 Hz, J_2 = 4.4 Hz, 1H), 1.18 (t, *J* = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ: 155.0, 135.2, 132.0, 127.4, 111.8, 111.5, 78.6, 67.9, 62.7, 56.4, 53.9, 14.4 ppm; **HRMS** (ESI) calcd. for $C_{13}H_{17}BrN_2O_6$ + Na: 399.0168, found: 399.0156; **$[\alpha]_D^{25}$** = +14.87 (c = 0.50, EtOH); **Chiral HPLC**: 89% *ee* of **3na** (CHIRALCEL AS-H, 220 nm, *n*-hexane/2-propanol = 80/20, flow rate 0.8 mL/min, *T* = 30 °C), t_R = 26.8 min (minor), 30.1 min (major).



3oa

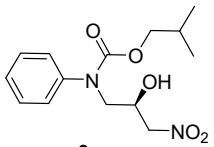
Methyl (*R*)-(2-hydroxy-3-nitropropyl)(phenyl)carbamate (**3oa**): Prepared according to the general method from **1o** (38.61 mg, 0.2 mmol) with 10 mmol% catalyst, and purified as a yellow oil (47.41 mg, 93%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.39 (t, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 2H), 4.55-4.51 (m, 1H), 4.49-4.39 (m, 2H), 3.89 (dd, J_1 = 14.4 Hz, J_2 = 6.8 Hz, 1H), 3.79 (dd, J_1 = 14.8 Hz, J_2 = 4.8 Hz, 1H), 3.68 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ: 157.5, 141.6, 129.4, 127.5, 127.1, 78.6, 68.0, 53.8, 53.5 ppm; **HRMS** (ESI) calcd. for $C_{11}H_{14}N_2O_5$ + Na: 277.0800, found: 277.0810; **$[\alpha]_D^{25}$** = +17.27 (c = 0.39, EtOH); **Chiral HPLC**: 87% *ee* of **3oa** (CHIRALCEL IC, 220 nm, *n*-hexane/2-propanol = 80/20, flow rate 1 mL/min, *T* = 30 °C), t_R = 12.3 min (minor), 22.4 min (major).



3pa

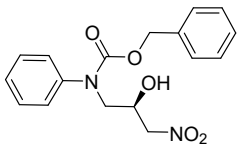
Isopropyl (*R*)-(2-hydroxy-3-nitropropyl)(phenyl)carbamate (**3pa**): Prepared according to the general procedure from **1p** (44.22 mg, 0.2 mmol) with 10 mmol% catalyst, and purified as a yellow oil (51.91 mg, 92%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.30 (t, *J* = 7.6 Hz, 2H), 7.22-7.18 (m, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 4.89-4.83 (m, 1H), 4.45 (, 1H), 4.47- 4.43 (m, 2H), 3.82 (dd, J_1 = 14.8 Hz, J_2 = 6.8

Hz, 1H), 3.73 (dd, J_1 = 14.8 Hz, J_2 = 4.8 Hz, 1H), 1.11 (d, J = 6.0 Hz, 6H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ: 156.8, 141.8, 129.3, 127.1, 126.9, 78.7, 70.4, 68.2, 53.7, 21.89, 21.85 ppm; **HRMS** (ESI) calcd. for $C_{13}H_{18}N_2O_5$ + Na: 305.1113, found: 305.1108; **$[\alpha]_D^{25}$** = +20.40 (c = 0.42, EtOH); **Chiral HPLC**: 94% *ee* of **3pa** (CHIRALCEL IC, 220 nm, *n*-hexane/2-propanol = 80/20, flow rate 1 mL/min, *T* = 30 °C), t_R = 12.9 min (minor), 14.3 min (major).



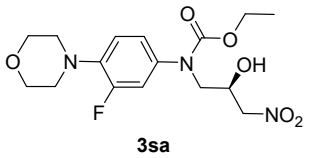
3qa

Isobutyl (*R*)-(2-hydroxy-3-nitropropyl)(phenyl)carbamate (**3qa**): Prepared according to the general method from **1q** (47.02 mg, 0.2 mmol) with 10 mmol% catalyst, and purified as a yellow oil (52.71 mg, 93%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.38 (t, J = 8.0 Hz, 2H), 7.28 (t, J = 7.6 Hz, 1H), 7.21 (d, J = 7.6 Hz, 2H), 4.56-4.51 (m, 1H), 4.48- 4.41 (m, 2H), 3.92-3.84 (m, 3H), 3.79 (dd, J_1 = 14.8 Hz, J_2 = 4.8 Hz, 1H), 1.84- 1.76 (m, 1H), 0.79 (d, J = 6.8 Hz, 6H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ: 157.2, 141.7, 129.3, 127.4, 127.1, 78.7, 72.5, 68.1, 53.7, 27.8, 18.8 ppm; **HRMS** (ESI) calcd. for $C_{14}H_{20}N_2O_5$ + Na: 335.0855, found: 335.0848; **$[\alpha]_D^{25}$** = +18.64 (c = 0.44, EtOH); **Chiral HPLC**: 93% *ee* of **3qa** (CHIRALCEL AD-H, 220 nm, *n*-hexane/2-propanol = 90/10, flow rate 0.8 mL/min, *T* = 30 °C), t_R = 14.7 min (minor), 16.3 min (major).



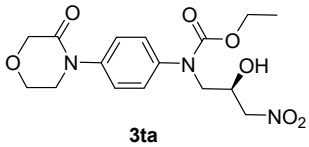
3ra

Benzyl (*R*)-(2-hydroxy-3-nitropropyl)(phenyl)carbamate (**3ra**): Prepared according to the general method from **1r** (53.82 mg, 0.2 mmol) with 10 mmol% catalyst, and purified as a yellow oil (61.04 mg, 93%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.32-7.28 (m, 2H), 7.24-7.19 (m, 4H), 7.17-7.11 (m, 4H), 5.05 (s, 2H), 4.48-4.42 (m, 1H), 4.38-4.30 (m, 2H), 3.81 (dd, J_1 = 14.8 Hz, J_2 = 7.2 Hz, 1H), 3.72 (dd, J_1 = 14.4 Hz, J_2 = 4.8 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ: 156.8, 141.5, 135.9, 129.4, 128.5, 128.1, 127.5, 127.1, 78.6, 67.9, 53.8 ppm; **HRMS** (ESI) calcd. for $C_{17}H_{18}N_2O_5$ + Na: 353.1113, found: 353.1114; **$[\alpha]_D^{25}$** = +17.27 (c = 0.39, EtOH); **Chiral HPLC**: 94% *ee* of **3ra** (CHIRALCEL IC, 220 nm, *n*-hexane/2-propanol = 80/20, flow rate 0.8 mL/min, *T* = 30 °C), t_R = 15.0 min (minor), 22.0 min (major).



3sa

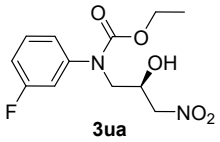
Ethyl (*R*)-(3-fluoro-4-morpholinophenyl)(2-hydroxy-3-nitropropyl)carbamate (**3sa**): Prepared according to the general method from **1s** (62.02 mg, 0.2 mmol) with 10 mmol% catalyst, and purified as a white solid (68.27 mg, 92%). m.p. 116.3-117.3°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 6.96-6.87 (m, 3H), 4.55-4.41 (m, 1H), 4.49-4.43 (m, 2H), 4.15 (q, J = 7.2 Hz, 2H), 3.88-3.81 (m, 5H), 3.74 (dd, J_1 = 14.4 Hz, J_2 = 4.8 Hz, 1H), 3.61 (bra, 1H), 3.10 (t, J = 4.4 Hz, 4H), 1.21 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ: 156.9, 155.0 (d, J = 246.8 Hz), 139.1 (d, J = 8.3 Hz), 135.9 (d, J = 9.5 Hz), 123.0 (d, J = 3.2 Hz), 118.6 (d, J = 4.0 Hz), 115.4 (d, J = 22.1 Hz), 78.5, 68.0, 66.9, 62.7, 50.75, 50.71, 14.4 ppm; **HRMS** (ESI) calcd. for $C_{16}H_{22}FN_3O_6$ + Na: 394.1390, found: 394.1384; **$[\alpha]_D^{25}$** = +17.27 (c = 0.39, EtOH); **Chiral HPLC**: 94% *ee* of **3sa** (CHIRALCEL AS-H, 220 nm, *n*-hexane/2-propanol = 70/30, flow rate 0.6 mL/min, *T* = 30 °C), t_R = 16.1 min (minor), 19.7 min (major).



3ta

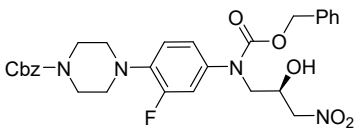
Ethyl (*R*)-(2-hydroxy-3-nitropropyl)(4-(3-oxomorpholino)phenyl)carbamate (**3ta**): Prepared according to the general method from **1t** (61.22 mg, 0.2 mmol) with 10 mmol% catalyst,

and isolated as a yellow oil (70.71 mg, 94%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.27 (d, *J* = 8.4 Hz, 2H), 7.20-7.18 (m, 2H), 4.43-4.40 (m, 1H), 4.38-4.30 (m, 2H), 4.25 (s, 2H), 4.08 (q, *J* = 7.2 Hz, 2H), 3.98-3.95 (m, 2H), 3.74-3.69 (m, 4H), 3.08 (bra, 1H), 1.13 (t, *J* = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ: 166.9, 156.5, 140.3, 139.8, 127.8, 126.0, 78.7, 68.4, 67.8, 64.0, 62.5, 53.6, 49.5, 14.4 ppm; **HRMS** (ESI) calcd. for $C_{16}H_{21}N_3O_7$ + Na: 390.1277, found: 390.1273; **$[\alpha]_D^{25}$** = +17.27 (c = 0.39, EtOH); **Chiral HPLC**: 95% *ee* of **3ta** (CHIRALCEL IC, 220 nm, *n*-hexane/2-propanol = 65/35, flow rate 0.7 mL/min, *T* = 30 °C), t_R = 40.4 min (minor), 51.9 min (major).



3ua

Ethyl (*R*)-(3-fluorophenyl)(2-hydroxy-3-nitropropyl)carbamate (**3ua**): Prepared according to the general method from **1u** (45.02 mg, 0.2 mmol) with 10 mol% catalyst, and purified as a yellow oil (48.06 mg, 84%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.34 (dd, J_1 = 14.8 Hz, J_2 = 7.6 Hz, 1H), 7.03-6.97 (m, 3H), 4.54-4.44 (m, 3H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.87 (dd, J_1 = 14.4 Hz, J_2 = 6.8 Hz, 1H), 3.80 (dd, J_1 = 14.8 Hz, J_2 =4.8 Hz, 1H), 3.59 (br, 1H), 1.20 (t, *J* = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ: 162.7 (d, *J* = 246.3 Hz), 156.6, 143.2 (d, *J* = 9.7 Hz), 130.4 (d, *J* = 9.1 Hz) , 122.6 (d, *J* = 3.3 Hz), 114.6 (d, *J* = 22.6 Hz), 114.3 (d, *J* = 20.8 Hz), 78.5, 67.9, 62.8, 53.6, 14.3 ppm; **HRMS** (ESI) calcd. for $C_{12}H_{15}FN_2O_5$ + Na: 309.0863, found: 309.0852; **$[\alpha]_D^{25}$** = +22.74 (c 0.27, EtOH); **Chiral HPLC**: 90% *ee* of **3ua** (CHIRALCEL AS-H, 220 nm, *n*-hexane/2-propanol = 90/10, flow rate 0.8 mL/min, *T* = 30 °C), t_R = 30.7 min (minor), 39.9 min (major).

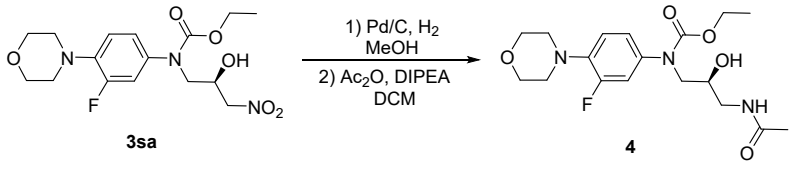


3va

Benzyl(*R*)-4-(4-(((benzyloxy)carbonyl)(2-hydroxy-3-nitropropyl)amino)-2-fluorophenyl)piperazine-1-carboxylate (**3va**): Prepared according to the general method from **1v** (41.42 mg, 0.2 mmol) with 10 mol% catalyst, and purified as a yellow oil (101.92 mg, 90%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.35-7.33 (m, 4H), 7.32-7.24 (m, 4H), 7.22-7.20 (m, 2H), 7.00-6.94 (m, 2H), 6.85-6.81 (m, 1H), 5.12-5.09 (m, 4H), 4.53-4.49 (m, 1H), 4.41-4.33 (m, 2H), 4.12 (d, *J* = 5.6 Hz, 1H), 3.72 (d, *J* = 6.4 Hz, 2H), 3.60 (t, *J* = 4.8 Hz, 4H), 2.98 (t, *J* = 5.2 Hz, 4H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ: 155.3, 155.0 (d, *J* = 246.4 Hz), 138.9 (d, *J* = 8.3 Hz), 136.2 (d, *J* = 6.2 Hz), 135.9, 128.6, 128.5, 128.25, 128.20, 128.0, 127.7, 123.3, 119.1 (d, *J* = 3.9 Hz), 115.6 (d, *J* = 22.0 Hz), 78.9, 67.9, 67.5, 67.4, 53.7, 50.2, 43.8 ppm; **HRMS** (ESI) calcd. for $C_{29}H_{31}FN_4O_7$ + Na: 589.2074, found: 589.2078; **$[\alpha]_D^{25}$** = +6.58 (c 2.70, EtOH); **Chiral HPLC**: 92% *ee* of **3va** (CHIRALCEL OD-H, 254 nm, *n*-hexane/2-propanol = 75/25, flow rate 0.8 mL/min, *T* = 30 °C), t_R = 53.0 min (minor), 61.8 min (major)

8. Asymmetric total synthesis of linezolid

Synthesis of ethyl (*S*)-(3-acetamido-2-hydroxypropyl)(3-fluoro-4-morpholinophenyl)carbamate (4)

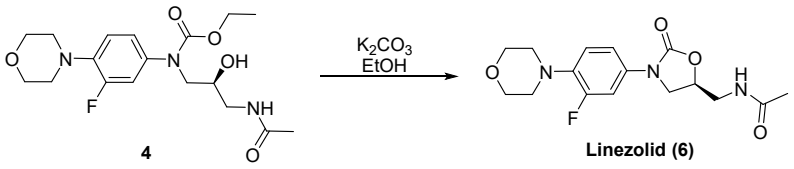


3sa **4**

3sa (2.5 mmol, 929.30 mg) in an oven-dried 250-mL high pressure reactor, and Pd/C (10% wt, 180

mg) in MeOH (50 mL) were stirred at room temperature for 24 h under H_2 (20 bar). After the reaction ended, the mixture was filtered through a Celite pad and washed with MeOH (25 mL). The filtrate was evaporated *in vacuo* to provide the crude product, which was used directly in next step. Then Ac_2O (1.0 eq, 2.5 mmol, 0.24 mL) was slowly added to a mixture of the above residue and DIPEA (1.1 eq, 2.75 mmol, 0.46 mL) in dry DCM (50 mL) at 0 °C. The resulting mixture was further stirred at 25 °C for 5 h. The reaction mixture was quenched by adding a saturated $NaHCO_3$ solution (40 mL). The organic layer was dried with Na_2SO_4, filtered subsequently, and then concentrated *in vacuo*. The residue was purified via column chromatography with an eluent of EA/Hex to afford the desired compound **4**, which was finally obtained as yellow oil (670.9 mg, 70% yield).The NMR spectra of compound **4** is consistent with the reported spectra.[3] **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 6.89-6.84 (m, 3H), 6.77-6.72 (m, 1H), 4.35 (br., 1H), 3.98 (q, *J* = 7.2 Hz, 2H),3.71-3.69 (m, 5H), 3.53-3.49 (m, 2H), 3.37-3.31 (m, 1H), 3.02-2.92 (m, 5H), 1.82 (s, 3H), 1.05 (t, *J* = 7.2 Hz, 3H) ppm.

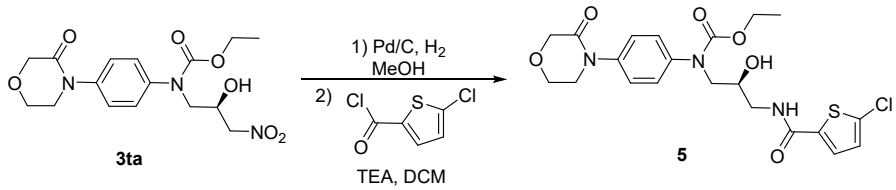
Synthesis of linezolid (6)



Compound **4** (0.5 mmol, 191.60 mg) in an oven-dried 25-mL flask, and K_2CO_3 (1.50 mmol, 206.85 mg) in absolute EtOH (2.5 mL) were stirred at 25 °C for 12 h. The mixture was quenched with water (10 mL), subsequently neutralized with 1M HCl aq. and then extracted with EA (25 mL). The organic layer was dried with Na_2SO_4, followed by filtered, and evaporated *in vacuo*. The residue was crystallized from isopropanol, affording Linezolid **6** as white solid (155.2 mg, 92% yield). m.p. 181.2-182.7 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.41 (dt, J_1 = 14.4 Hz, J_2 =3.2 Hz, 1H), 7.06-7.03 (m, 1H), 6.95-6.89 (m, 1H), 6.60-6.48 (m, 1H), 4.79-4.73 (m, 1H), 4.00 (t, *J* = 8.8 Hz, 1H), 3.87-3.84 (m, 4H), 3.76-3.72 (m, 1H), 3.66-3.61 (m, 2H), 3.05-3.02 (m, 4H), 2.00 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ: 170.3, 154.4 (d, *J* = 244.9 Hz), 153.4, 135.3 (d, 5.8 Hz), 131.9 (d, 10.1 Hz), 117.9 (d, 4.2 Hz), 112.9 (d, 3.3 Hz), 106.5 (d, 26.1 Hz), 71.0, 65.8, 49.9 (d, 3.2 Hz), 46.6 (d, 4.0 Hz), 40.8, 22.0; **^{19}F NMR** (100 MHz, $CDCl_3$) δ: -120.125 ppm; **HRMS** (ESI) calcd. for $C_{16}H_{20}FN_3O_4$ + Na: 360.1336, found: 360.1340; **$[\alpha]_D^{20}$** = —8.7 (c 0.73, $CHCl_3$).

9. Asymmetric total synthesis of rivaroxaban

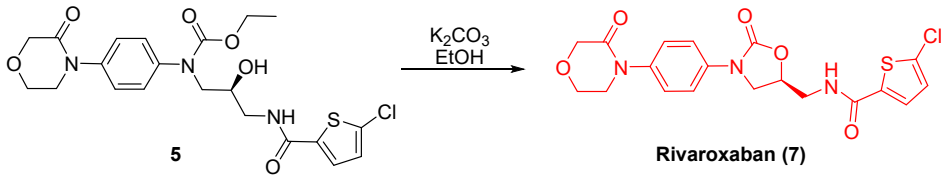
Synthesis of ethyl (*S*)-(3-(5-chlorothiophene-2-carboxamido)-2-hydroxypropyl)(4-(3-oxomorpholino)phenyl) carbamate (5)



Nitroalcohol **3ta** (881.14 mg, 2.4 mmol) in an oven-dried 250-mL high pressure reactor, and Pd/C (10% wt, 180 mg) in MeOH (50 mL) were stirred at room temperature for 24 h under H_2 (20 bar). After

reaction ended, the mixture was filtered through a Celite pad and washed with MeOH (50 mL). The filtrate was evaporated *in vacuo* to prepare the crude product, which was used in next step without further purification. 5-Chlorothiophene-2-carbonyl chloride (0.29 mL, 2.4 mmol) was slowly added to a mixture of the above residue and triethylamine (0.37 mL, 2.64 mmol) in dry DCM (40 mL) at 0 °C. The resulting mixture was kept stirring at 25 °C for 4 h. The reaction mixture was quenched with water (40 mL). The organic layer was dried with Na_2SO_4, subsequently filtered, and then concentrated *in vacuo*. The residue was purified via column chromatography with an eluent of acetone/CH_2Cl_2 1/5 to yield the desired compound **5** as yellow oil (867.5mg, 75% yield). The NMR spectra of compound **5** is in accord with the reported data.[4] **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.32-7.30 (m, 3H), 7.24-7.17 (m, 3H), 6.87 (d, J = 4.0 Hz, 1H), 4.32 (s, 2H), 4.13 (q, J = 6.8 Hz, 2H), 4.04-4.01 (m, 2H), 3.93-3.87 (m, 1H), 3.80-3.74 (m, 3H), 3.71-3.68 (m, 2H), 3.29-3.25 (m, 1H), 1.18 (t, J = 7.2 Hz, 3H) ppm.

Synthesis rivaroxaban (7)

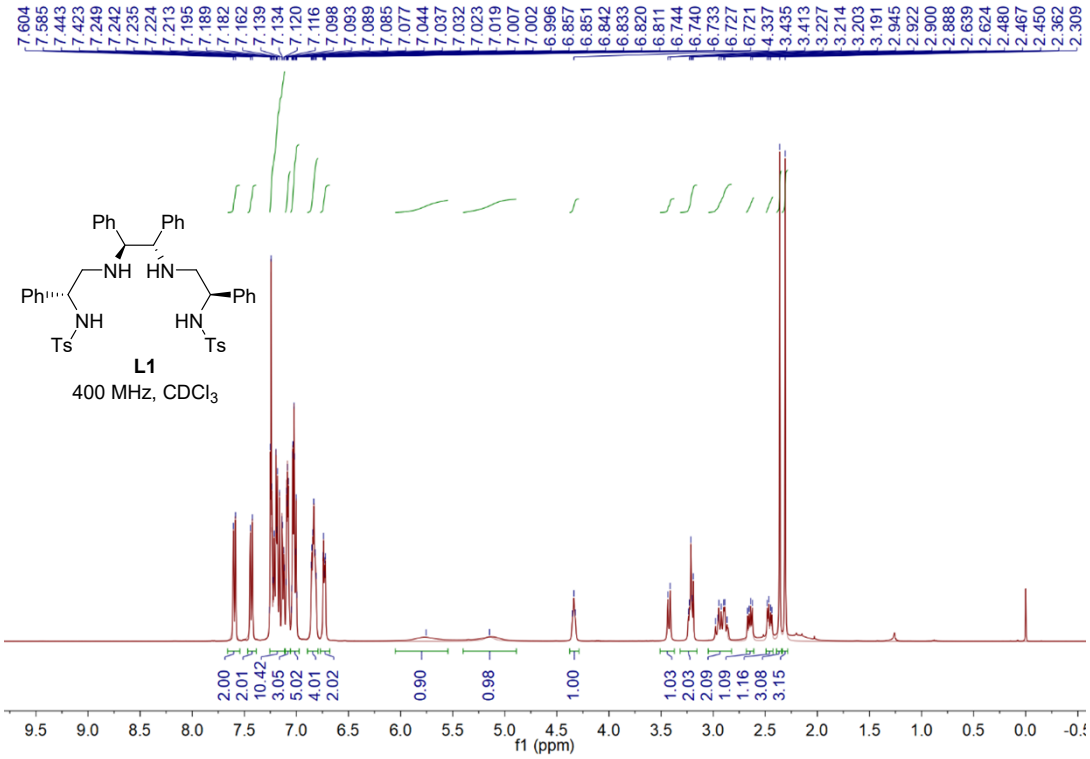


Compound **5** (360.80 mg, 0.75 mmol) in an oven-dried 25-mL flask, and anhydrous K_2CO_3 (310.30 mg, 2.25 mmol) in absolute EtOH (15 mL) were stirred at 25 °C for 24 h. The reaction process was monitored by TLC. The formed suspension was filtered off, and then washed with n-hexane (2 × 15 mL), followed by washed with water (2 × 15 mL), and dried in vacuo to obtain rivaroxaban (**7**) as white crystalline solid (310.6 mg, 95% yield). m.p. 206.0-208.3 °C; **^{1}H NMR** (400 MHz, DMSO) δ: 8.97 (t, J = 6.0 Hz, 1H), 7.70 (d, J = 4.4 Hz, 1H), 7.56 (dd, J_1 = 6.8 Hz, J_2 =2.0 Hz, 2H), 7.41 (dd, J_1 = 6.8 Hz, J_2 =2.0 Hz, 2H), 7.19 (d, J = 4.0 Hz, 1H), 4.88-4.81 (m, 1H), 4.21-4.17 (m, 3H), 3.98-3.96 (m, 2H), 3.85 (dd, J_1 = 9.2 Hz, J_2 =6.4 Hz, 1H), 3.72-3.70 (m, 2H), 3.61 (t, J = 5.6 Hz, 2H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO) δ: 166.4, 161.2, 154.5, 138.9, 137.5, 136.9, 133.7, 128.9, 128.6, 126.4, 118.8, 71.8, 68.2, 63.9, 49.4, 47.9, 42.6 ppm; **HRMS** (ESI) calcd. for $C_{19}H_{18}ClN_3O_5S$ + Na: 458.0553, found: 458.0547; $[\alpha]_D^{20}$ = −40.2 (c 0.34, DMSO).

10. NMR spectra

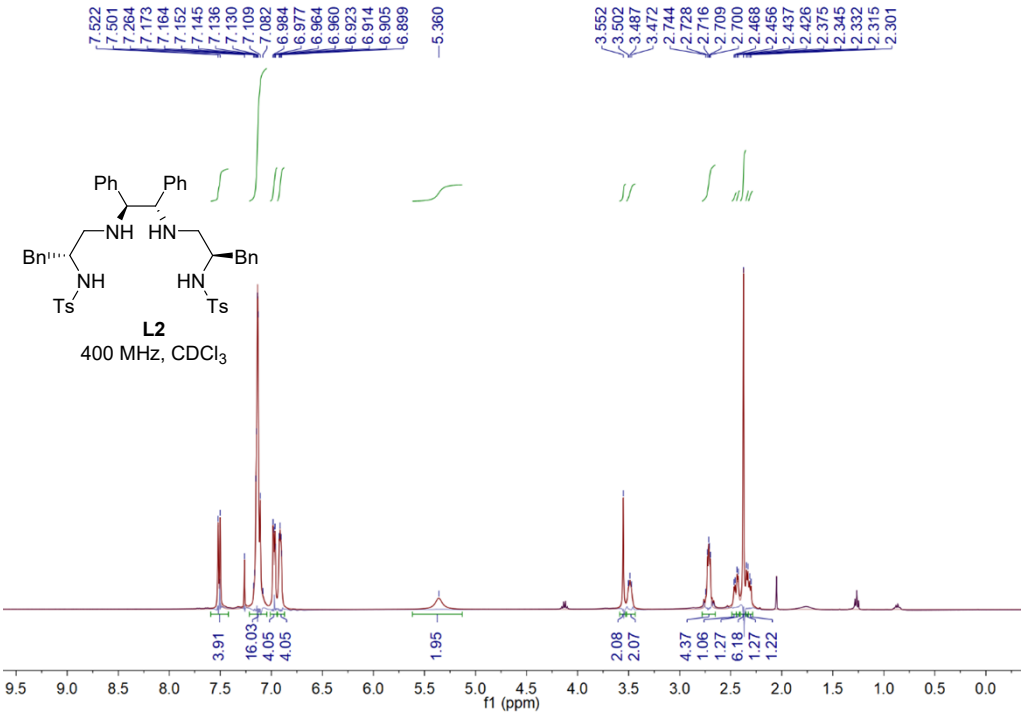
***N*,*N*'-((1*R*,1'*R*)-(((1*S*,2*S*)-1,2-diphenylethane-1,2-diyl)bis(azanediyl))bis(1-phenylethane-2,1-diyl))bis(4-methylbenzenesulfonamide) (L1)**

^{1}H NMR of **L1** (400 MHz, $CDCl_3$)

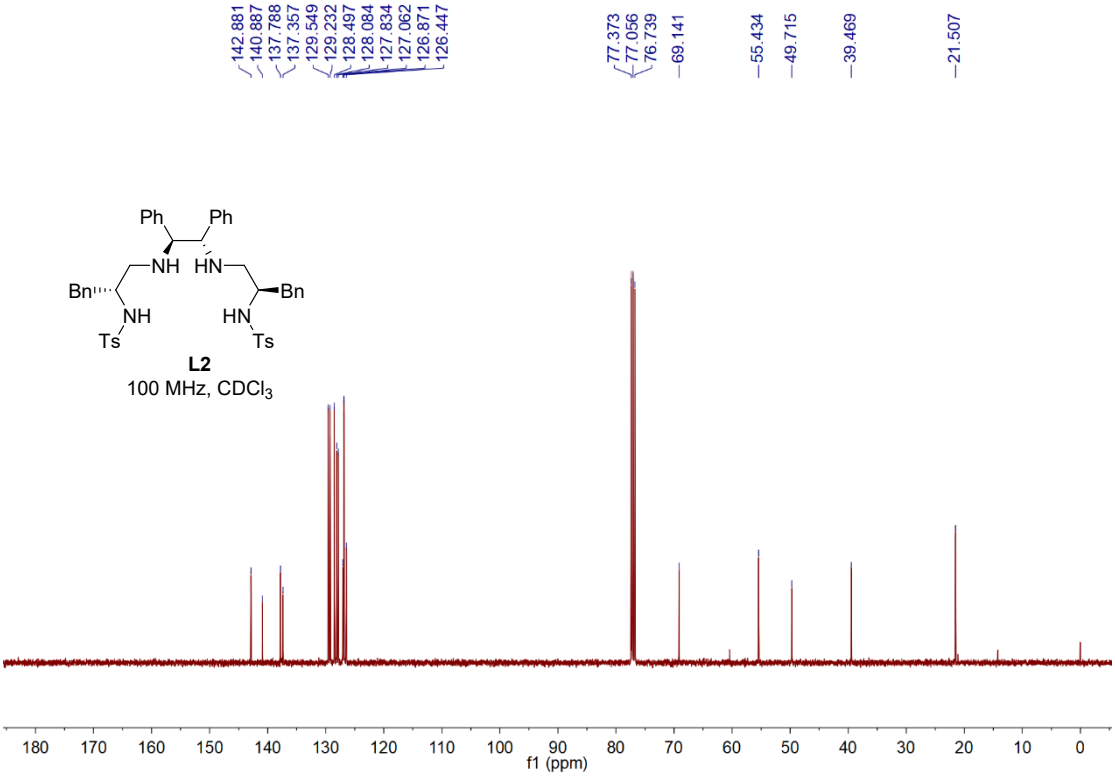


***N*,*N*'-((2*R*,2'*R*)-(((1*S*,2*S*)-1,2-diphenylethane-1,2-diyl)bis(azanediyl))bis(3-phenylpropane-1,2-diyl))bis(4-methylbenzenesulfonamide)**

^{1}H NMR of **L2** (400 MHz, $CDCl_3$)

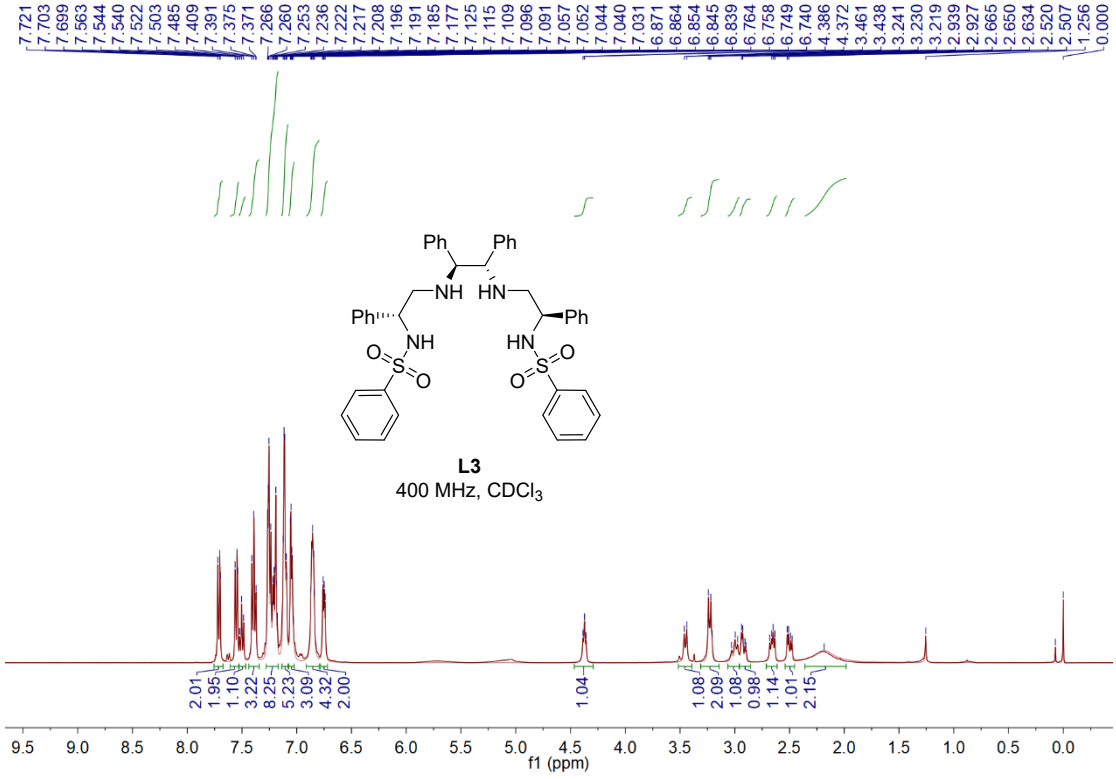


$^{13}C\{^{1}H\}$ NMR of **L2** (100 MHz, $CDCl_3$)

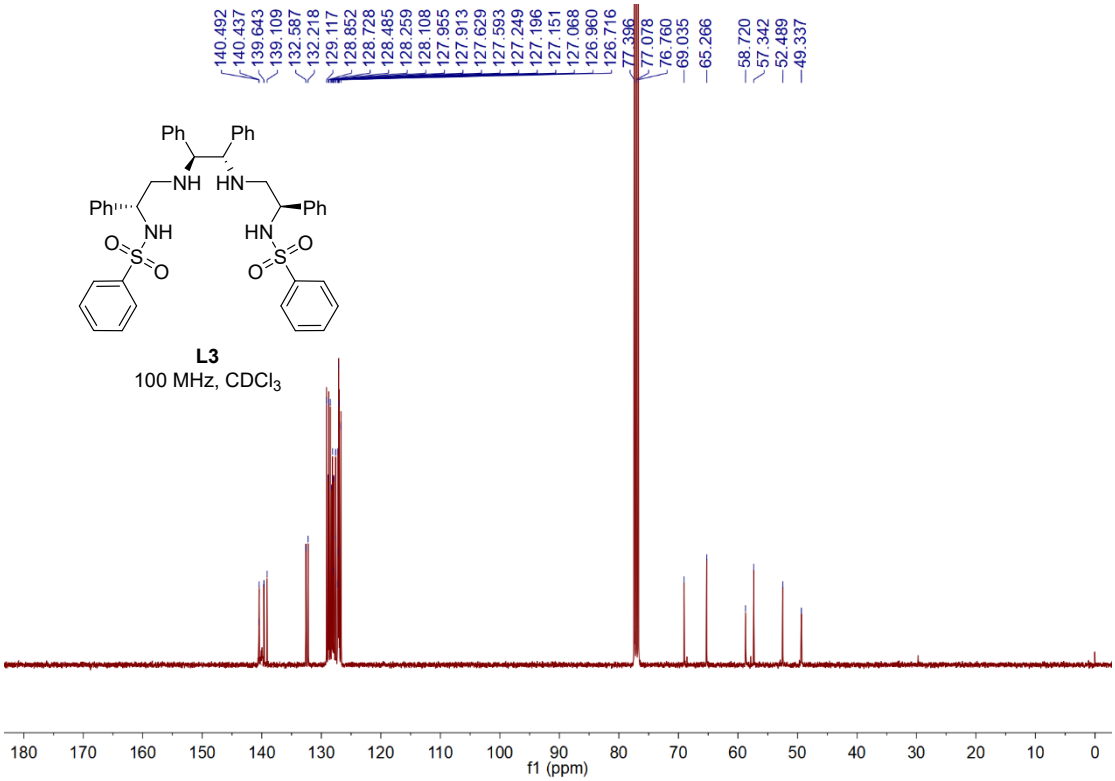


***N*,*N*'-((1*R*,1'*R*)-(((1*S*,2*S*)-1,2-diphenylethane-1,2-diyl)bis(azanediyl))bis(1-phenylethane-2,1-diyl))dibenzenesulfonamide (L3)**

^{1}H NMR of **L3** (400 MHz, $CDCl_3$)

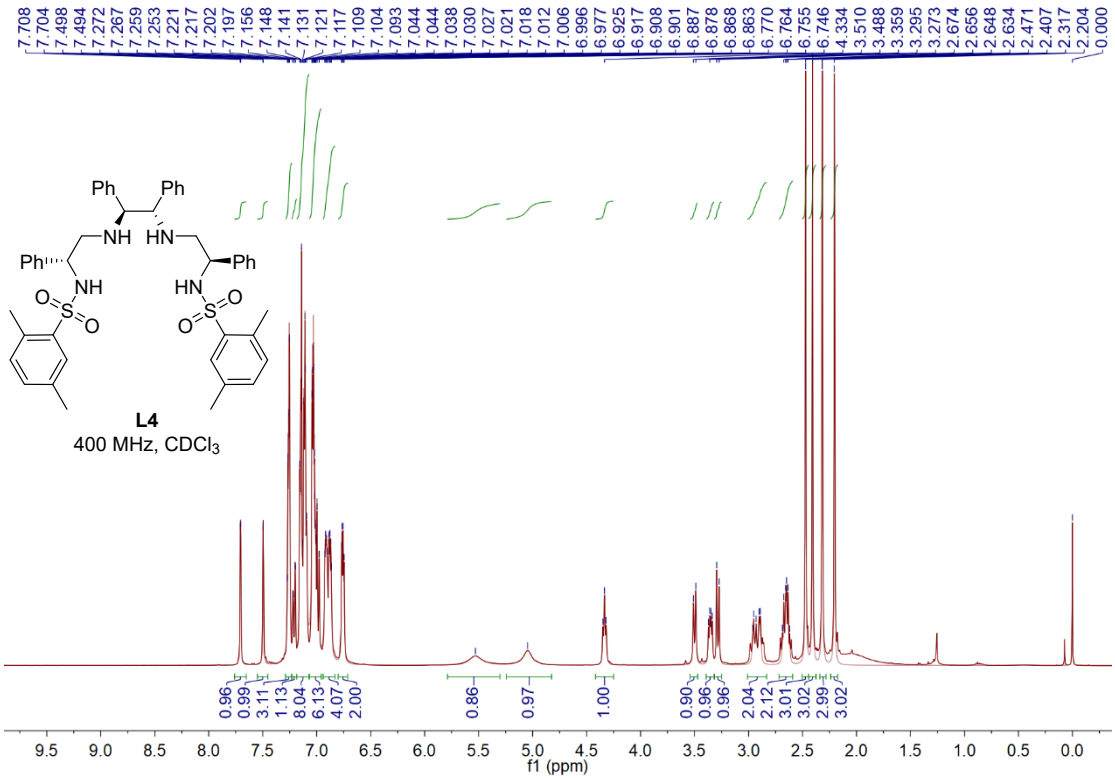


$^{13}C\{^{1}H\}$ NMR of **L3** (100 MHz, $CDCl_3$)

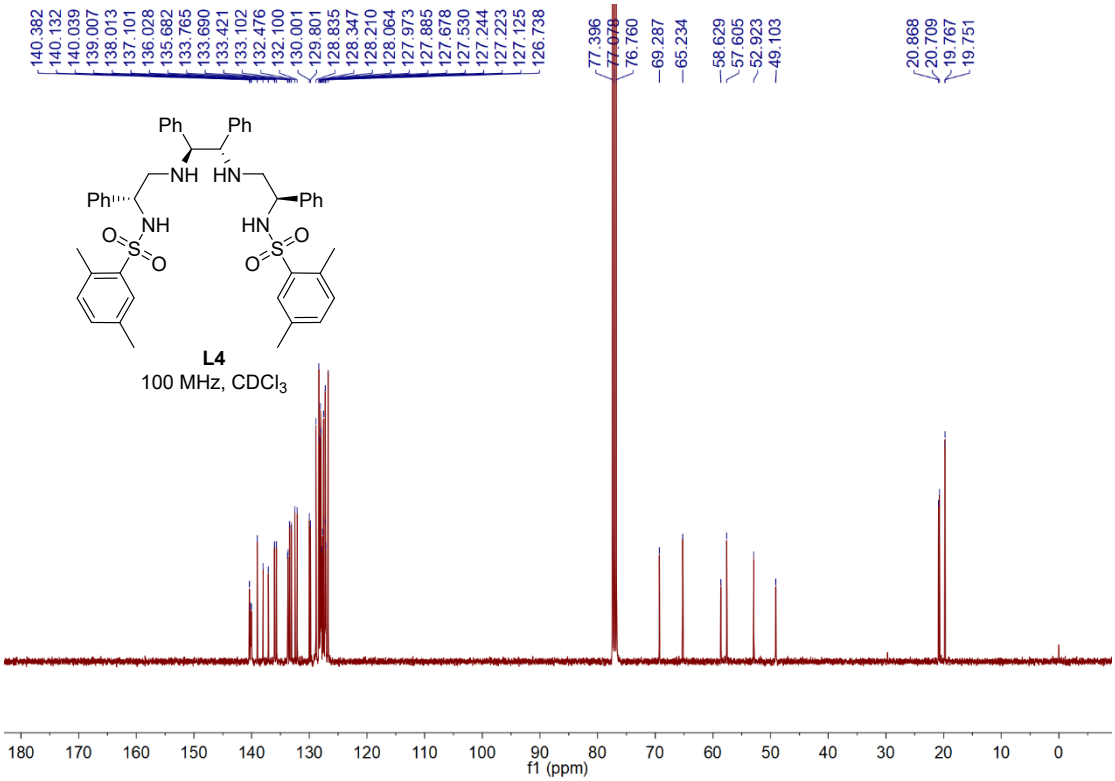


***N*,*N*'-((1*R*,1'*R*)-(((1*S*,2*S*)-1,2-diphenylethane-1,2-diyl)bis(azanediyl))bis(1-phenylethane-2,1-diyl))bis(2,5-dimethylbenzenesulfonamide) (L4)**

^{1}H NMR of **L4** (400 MHz, $CDCl_3$)

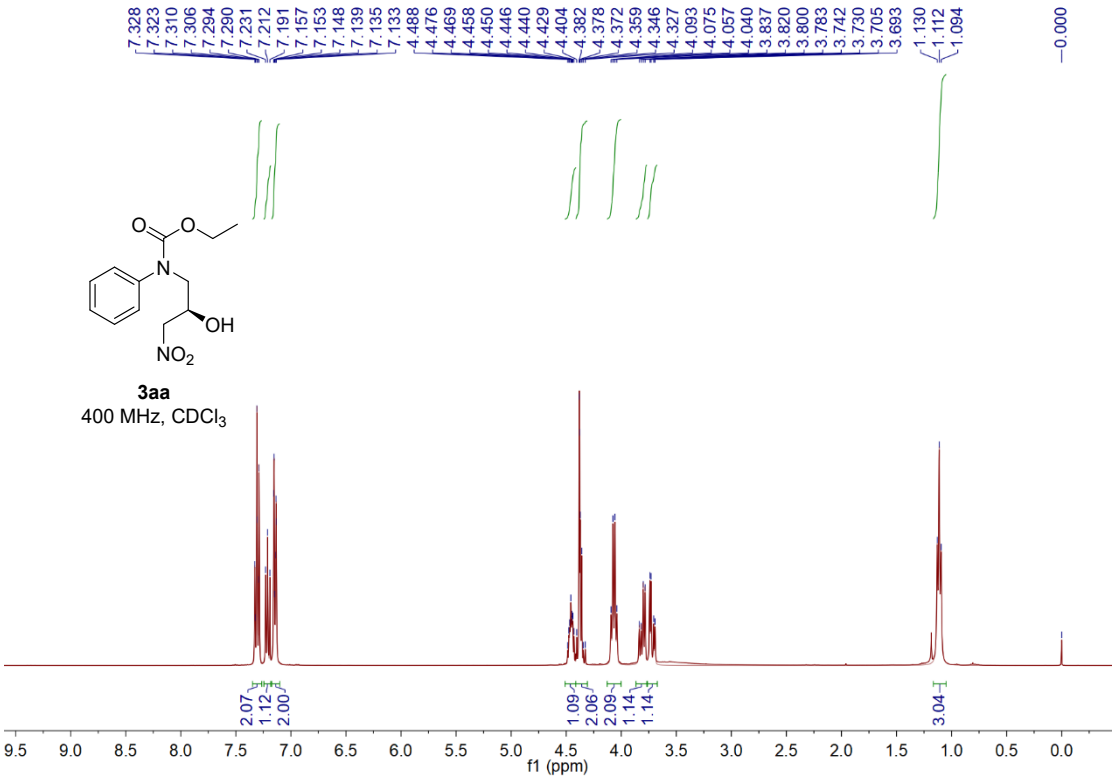


$^{13}C\{^{1}H\}$ NMR of **L4** (100 MHz, $CDCl_3$)

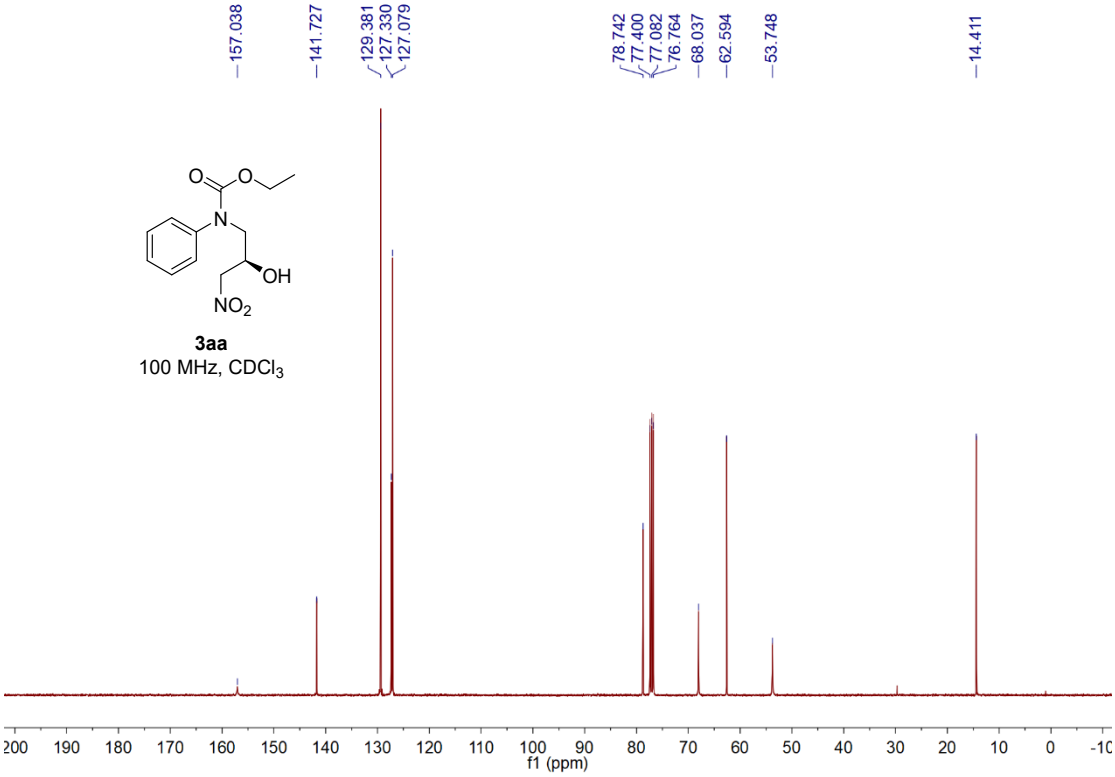


Ethyl (*R*)-(2-hydroxy-3-nitropropyl)(phenyl)carbamate (3aa)

^{1}H NMR of **3aa** (400 MHz, $CDCl_3$)

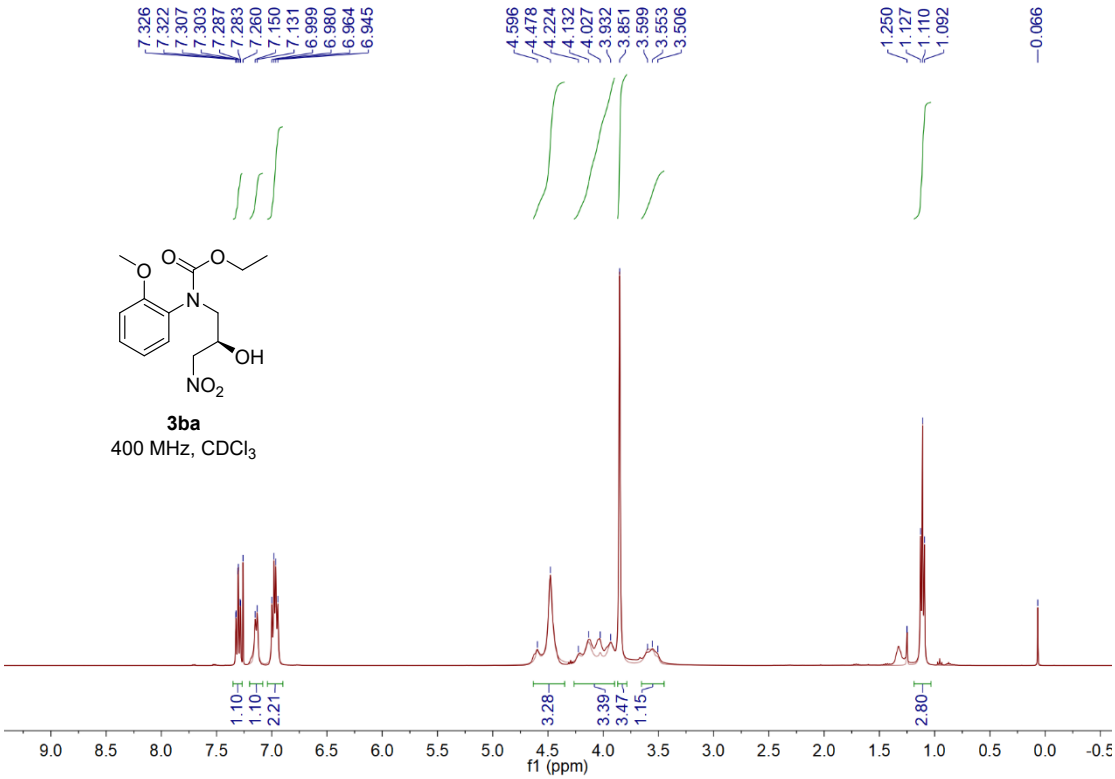


$^{13}C\{^{1}H\}$ NMR of **3aa** (100 MHz, $CDCl_3$)

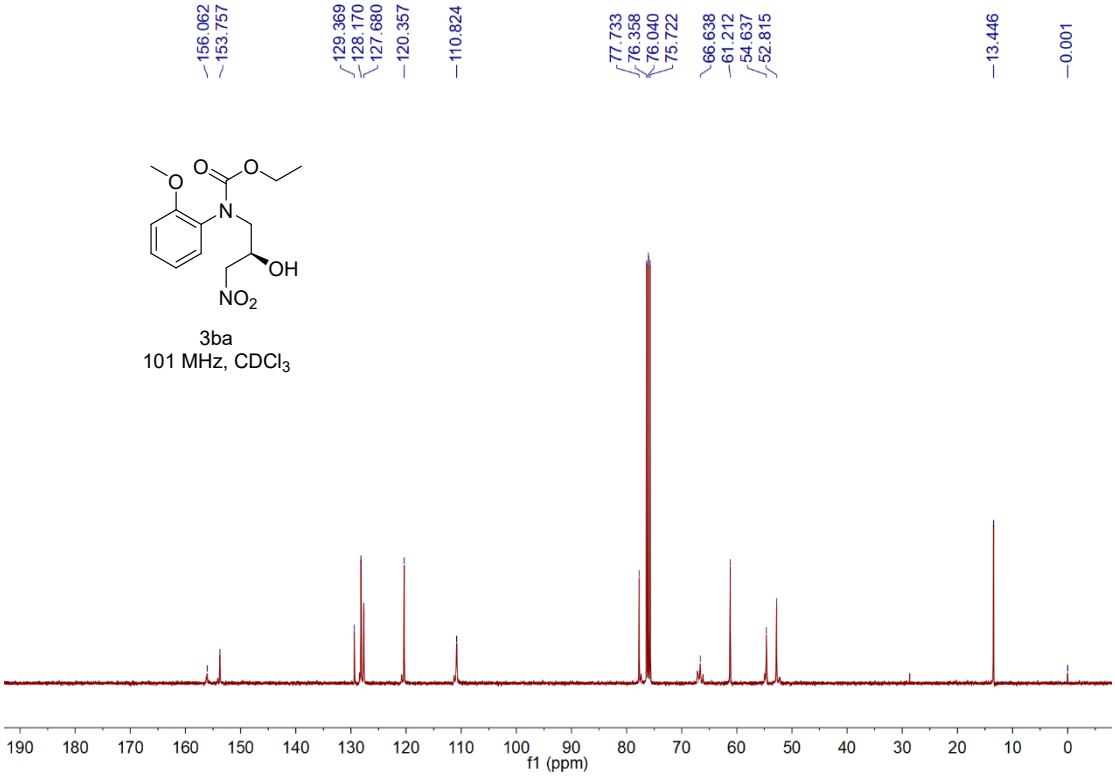


Ethyl (*R*)-(2-hydroxy-3-nitropropyl)(2-methoxyphenyl)carbamate (3ba)

^{1}H NMR of **3ba** (400 MHz, $CDCl_3$)

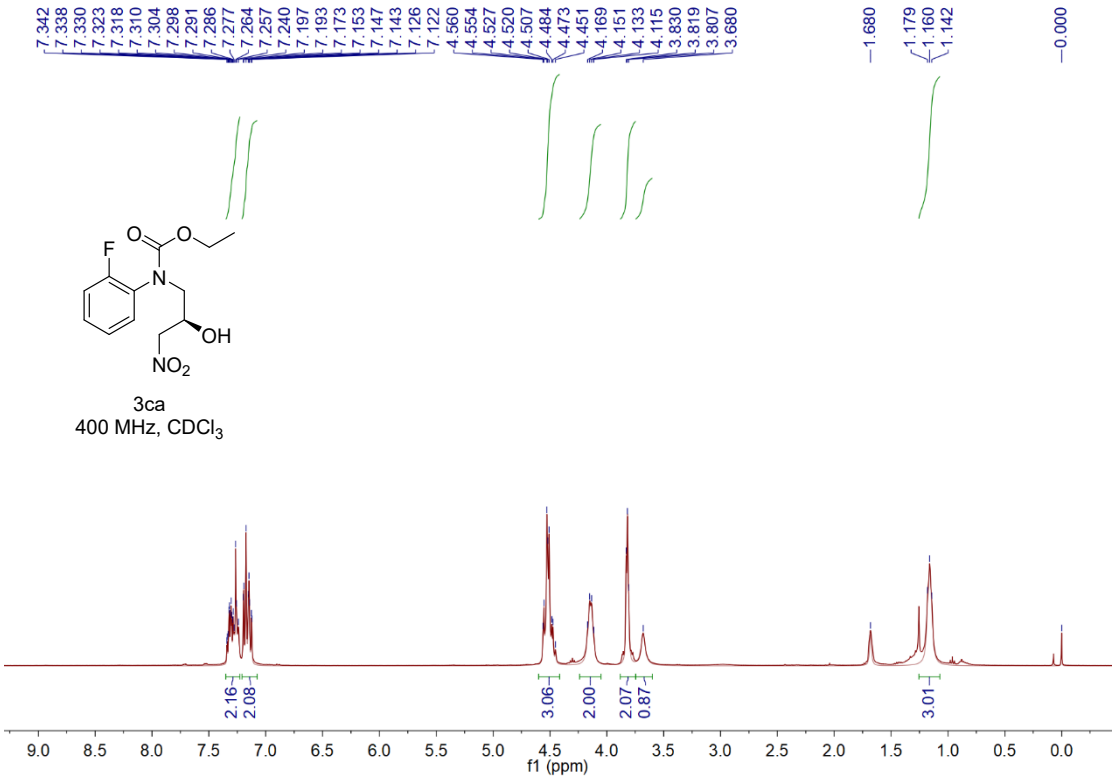


$^{13}C\{^{1}H\}$ NMR of **3ba** (100 MHz, $CDCl_3$)

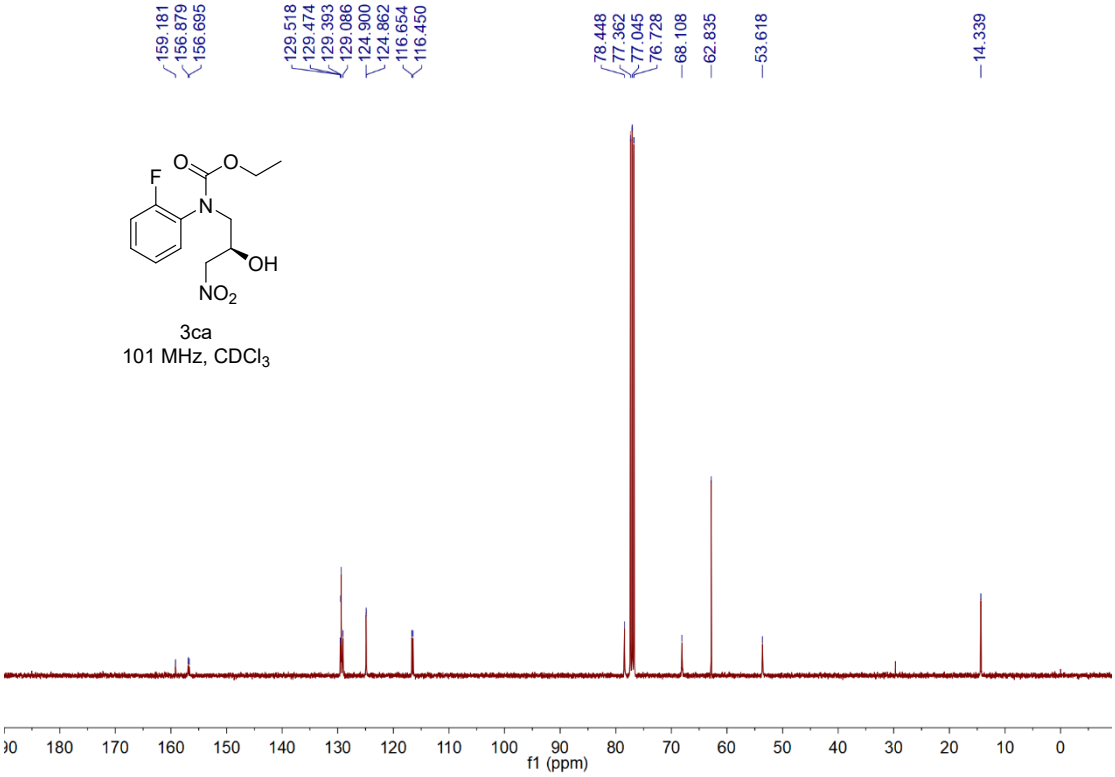


Ethyl (*R*)-(2-fluorophenyl)(2-hydroxy-3-nitropropyl)carbamate (3ca)

^{1}H NMR of **3ca** (400 MHz, $CDCl_3$)

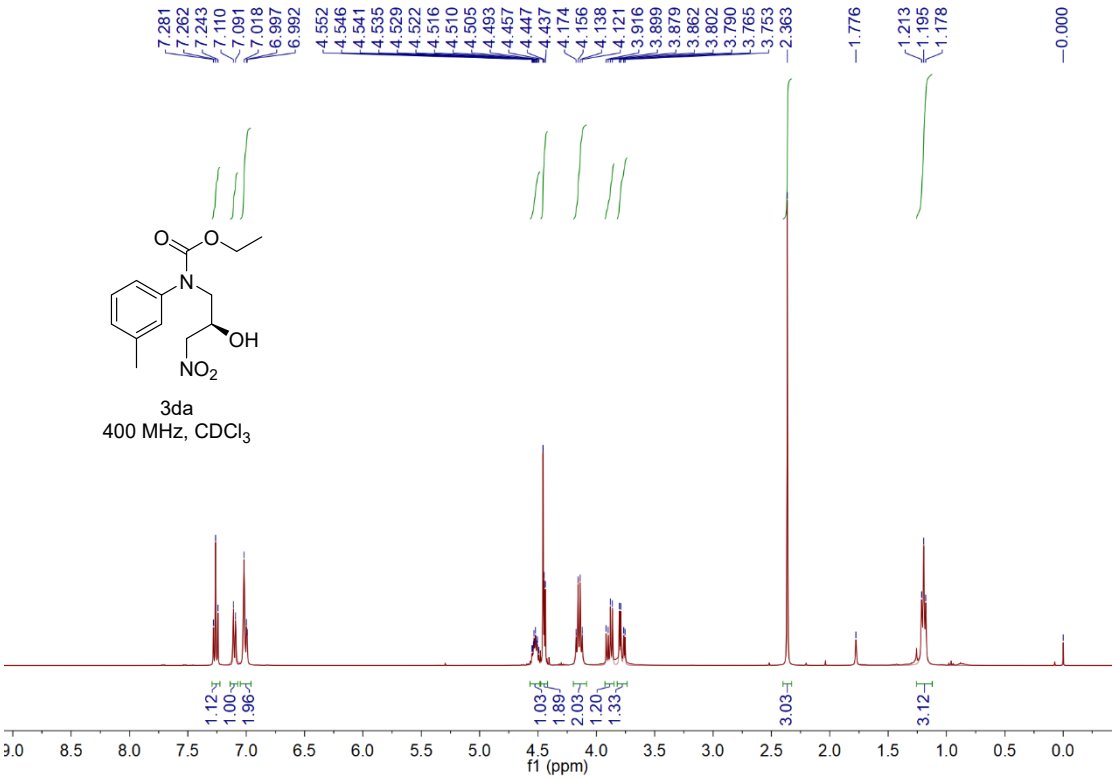


$^{13}C\{^{1}H\}$ NMR of **3ca** (100 MHz, $CDCl_3$)

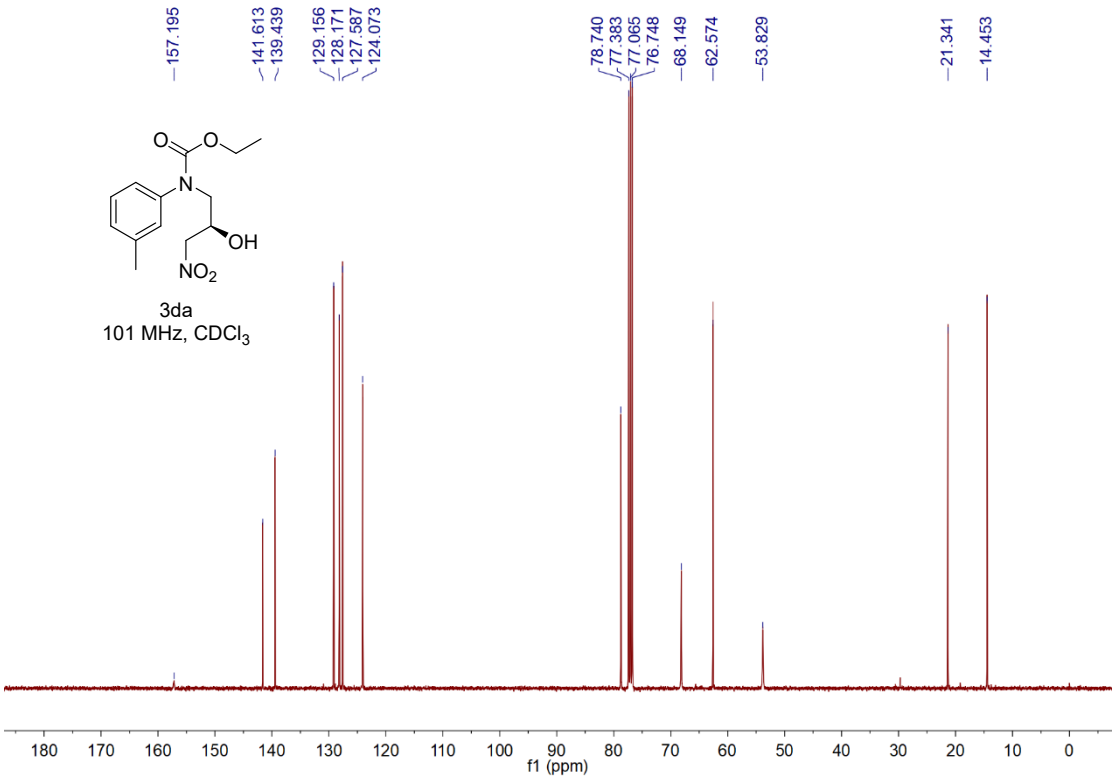


Ethyl (*R*)-(2-hydroxy-3-nitropropyl)(m-tolyl)carbamate (3da)

^{1}H NMR of **3da** (400 MHz, $CDCl_3$)

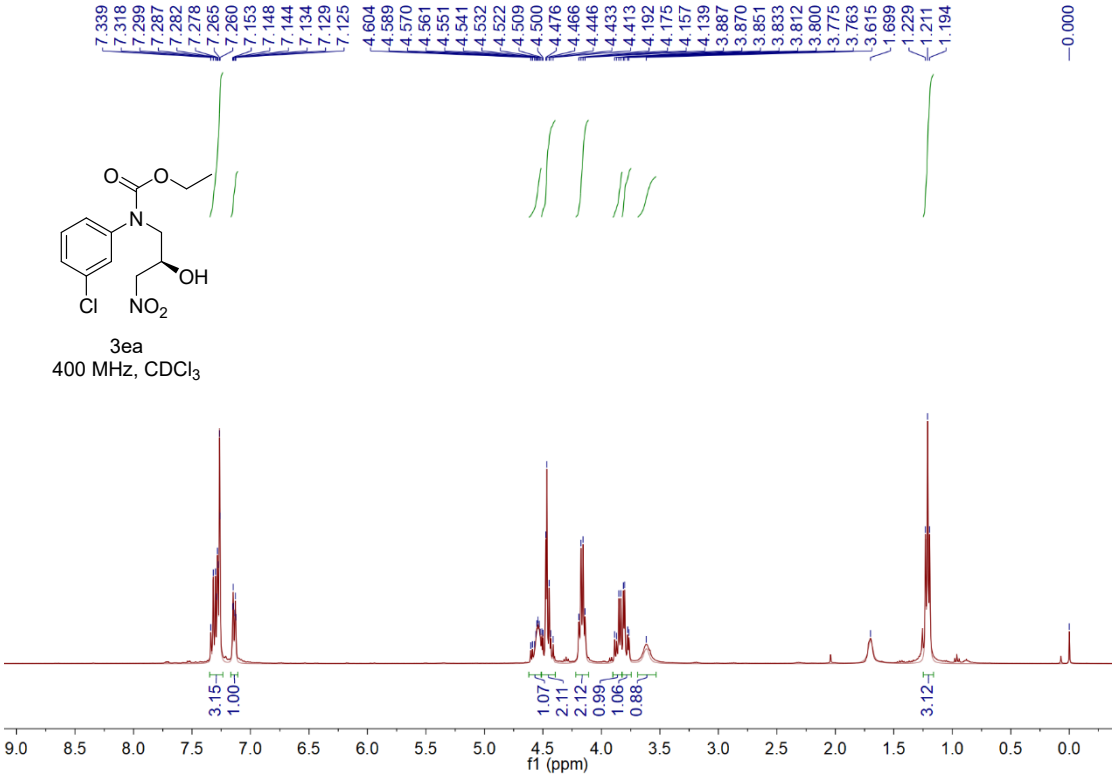


$^{13}C\{^{1}H\}$ NMR of **3da** (100 MHz, $CDCl_3$)

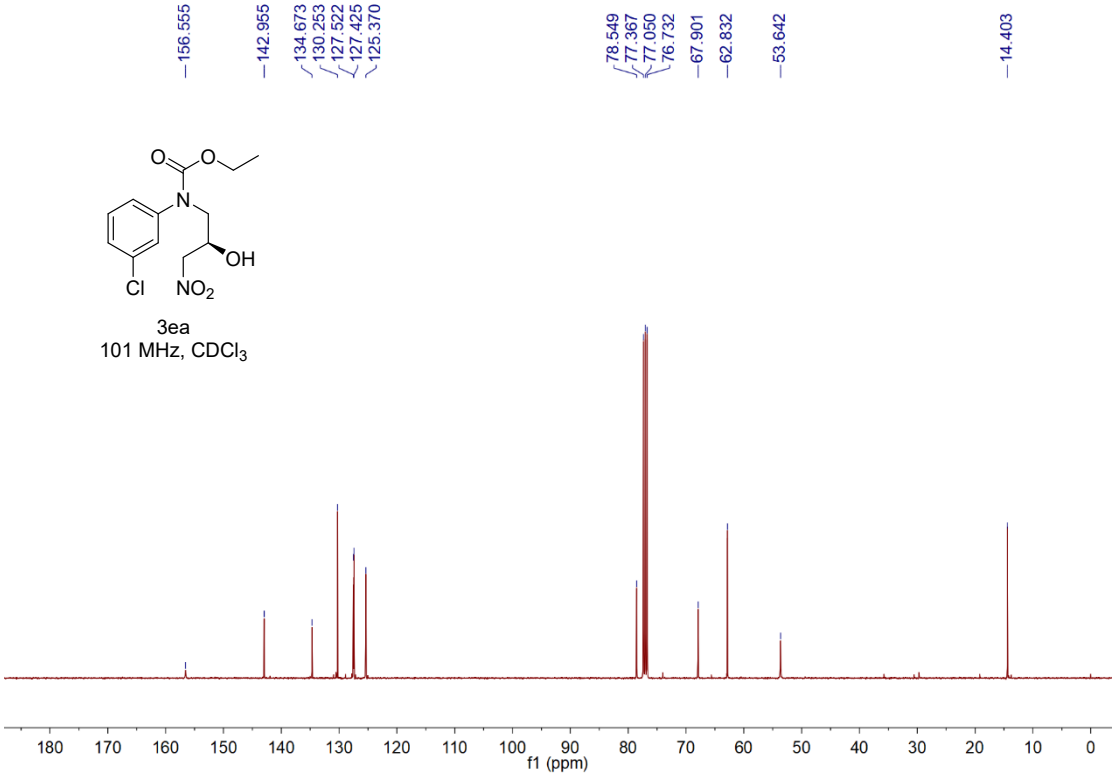


Ethyl (*R*)-(3-chlorophenyl)(2-hydroxy-3-nitropropyl)carbamate (3ea)

^{1}H NMR of **3ea** (400 MHz, $CDCl_3$)

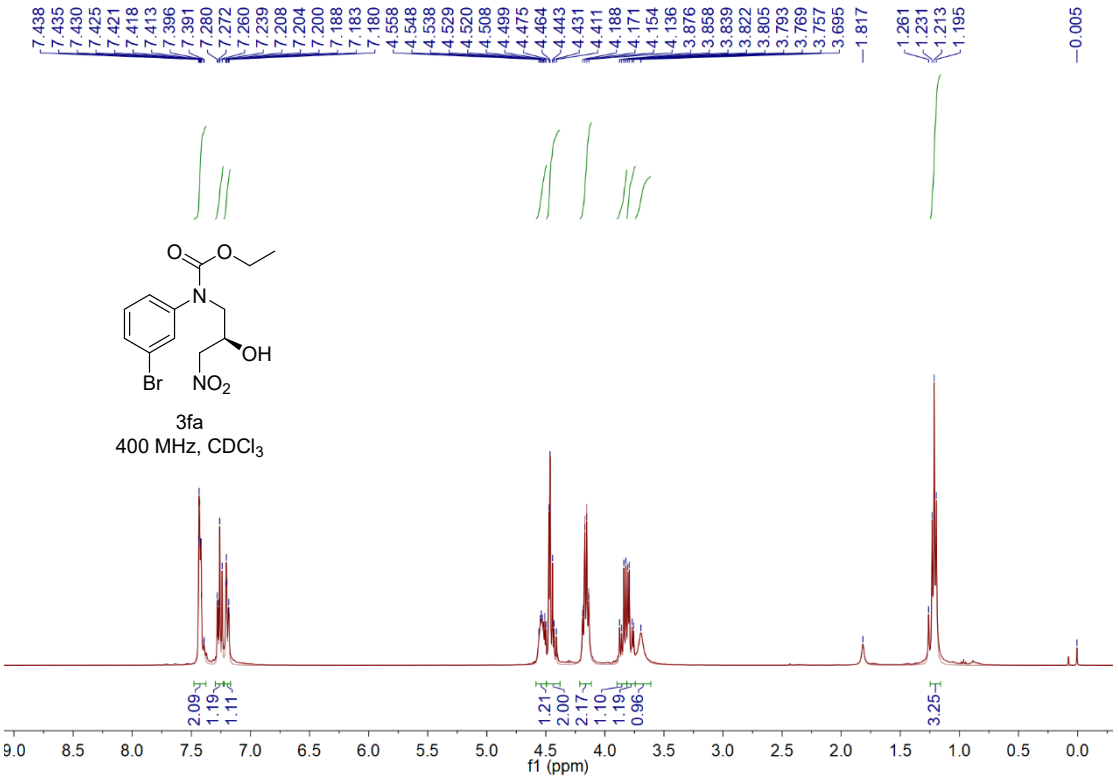


$^{13}C\{^{1}H\}$ NMR of **3ea** (100 MHz, $CDCl_3$)

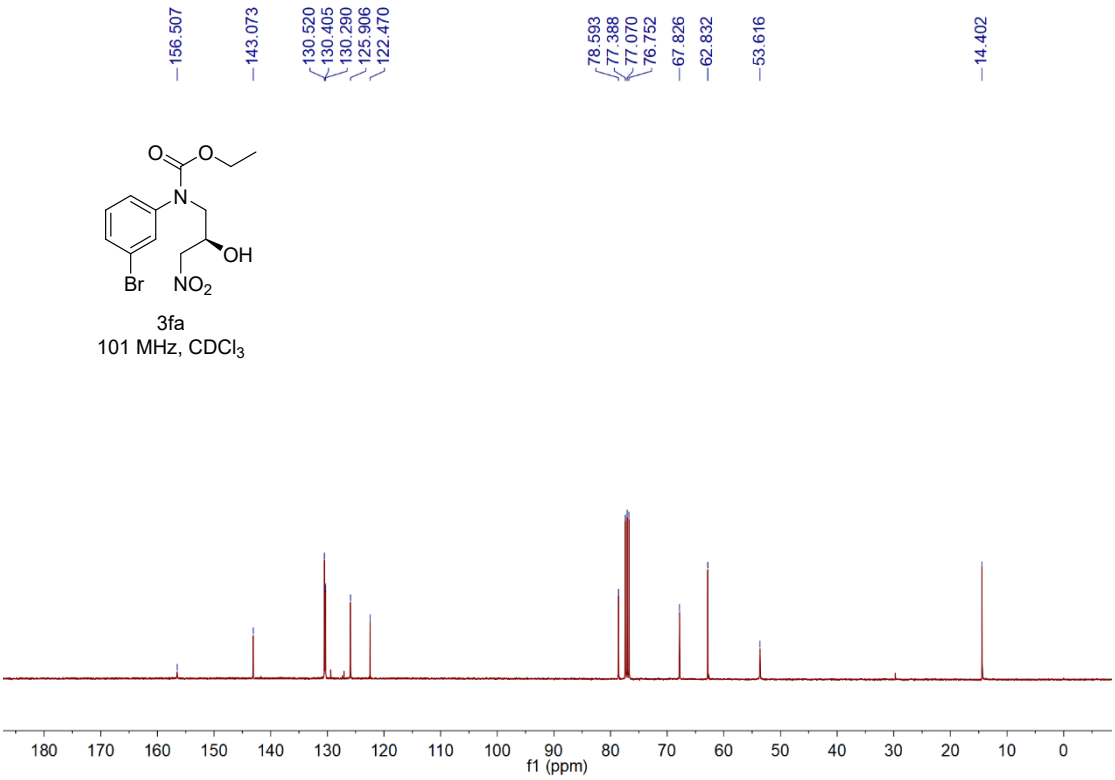


Ethyl (*R*)-(3-bromophenyl)(2-hydroxy-3-nitropropyl)carbamate (3fa)

^{1}H NMR of **3fa** (400 MHz, $CDCl_3$)

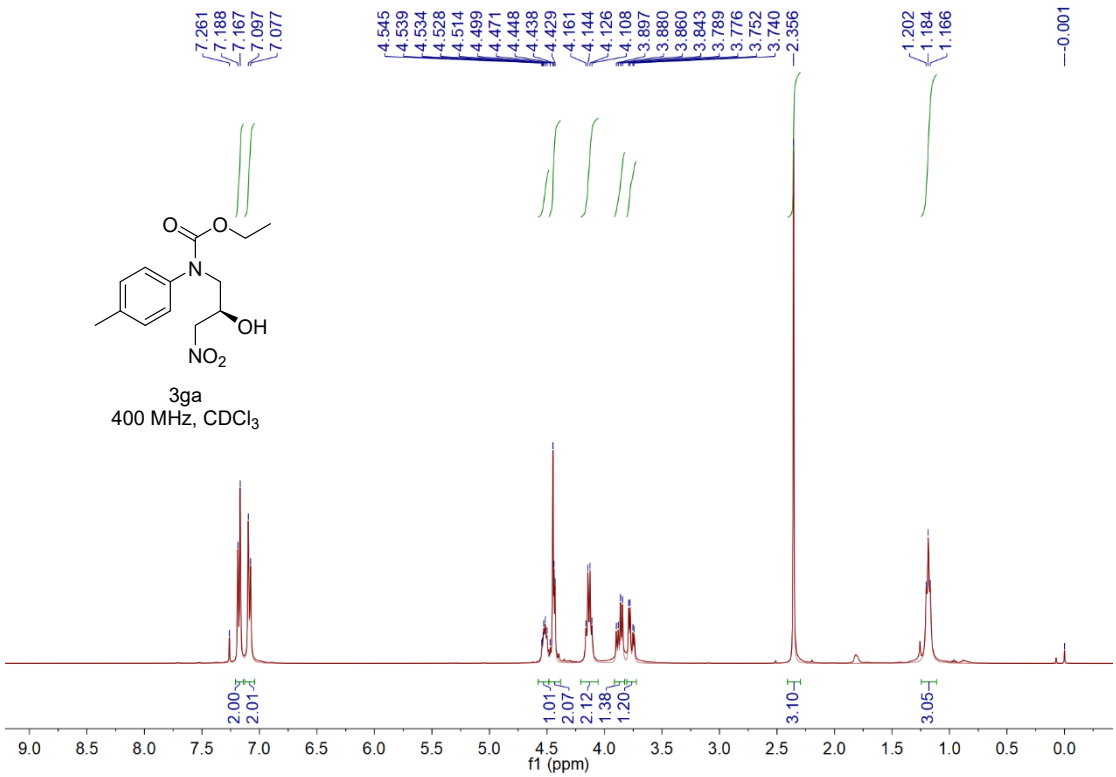


$^{13}C\{^{1}H\}$ NMR of **3fa** (100 MHz, $CDCl_3$)

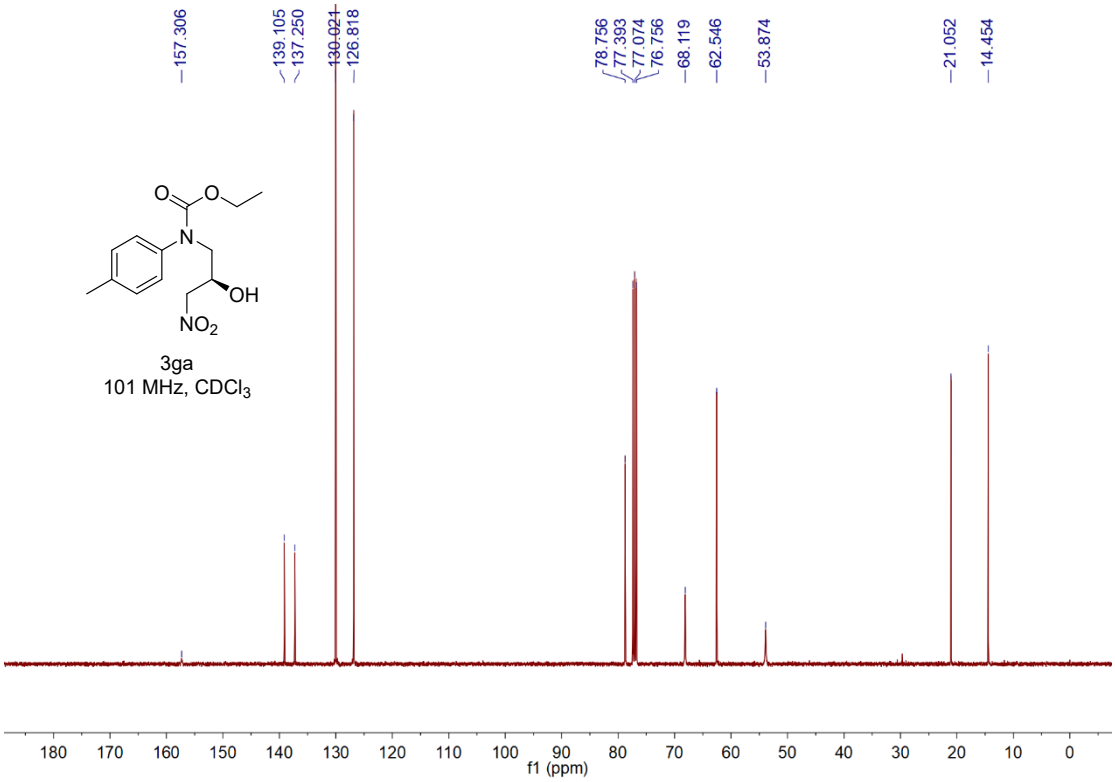


Ethyl (*R*)-(2-hydroxy-3-nitropropyl)(p-tolyl)carbamate(3ga)

^{1}H NMR of **3ga** (400 MHz, $CDCl_3$)

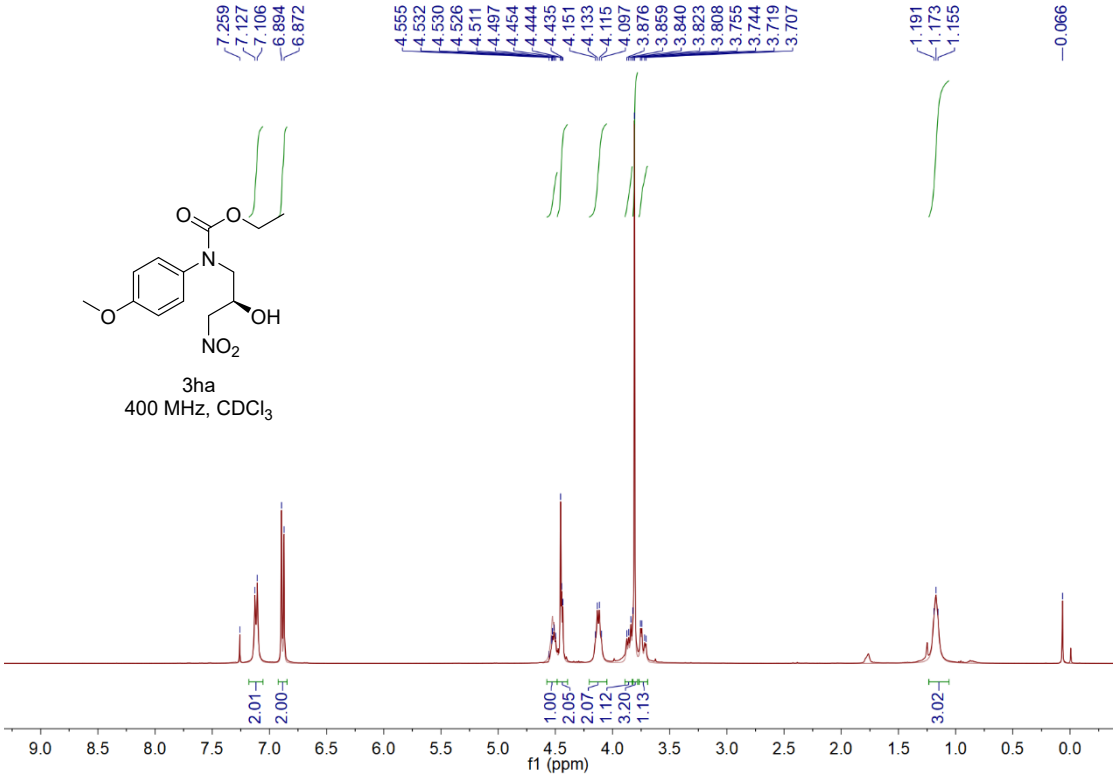


$^{13}C\{^{1}H\}$ NMR of **3ga** (100 MHz, $CDCl_3$)

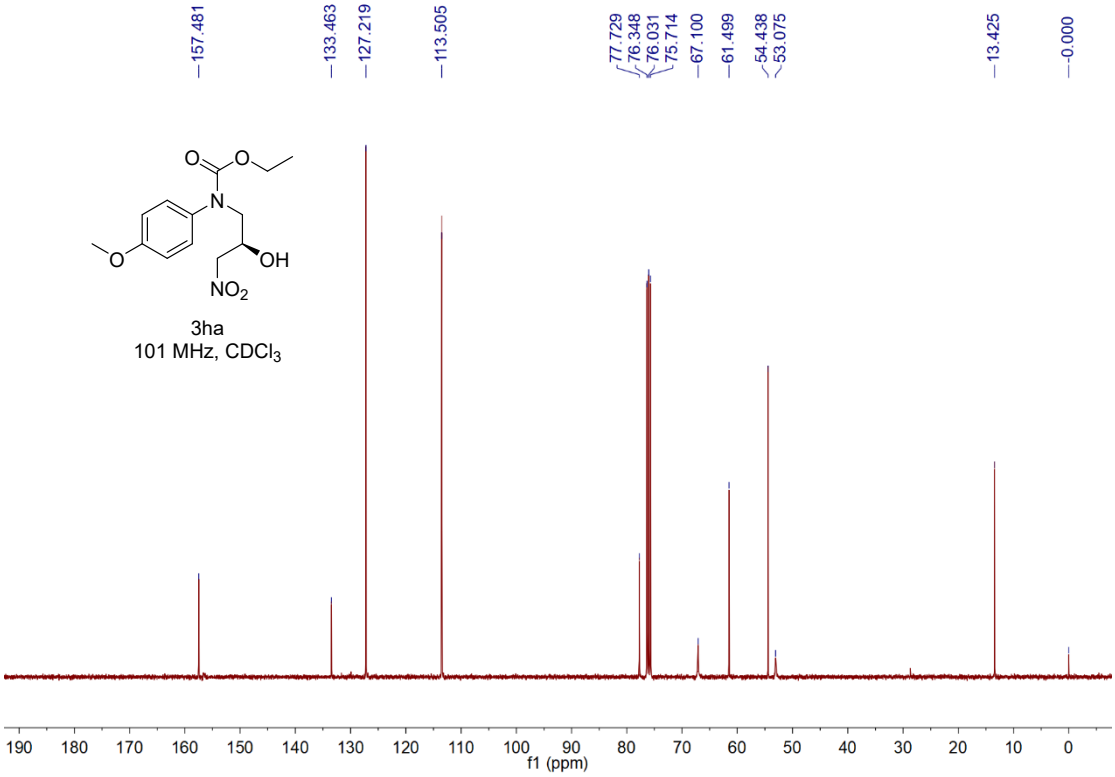


Ethyl (*R*)-(2-hydroxy-3-nitropropyl)(4-methoxyphenyl)carbamate (3ha)

^{1}H NMR of **3ha** (400 MHz, $CDCl_3$)

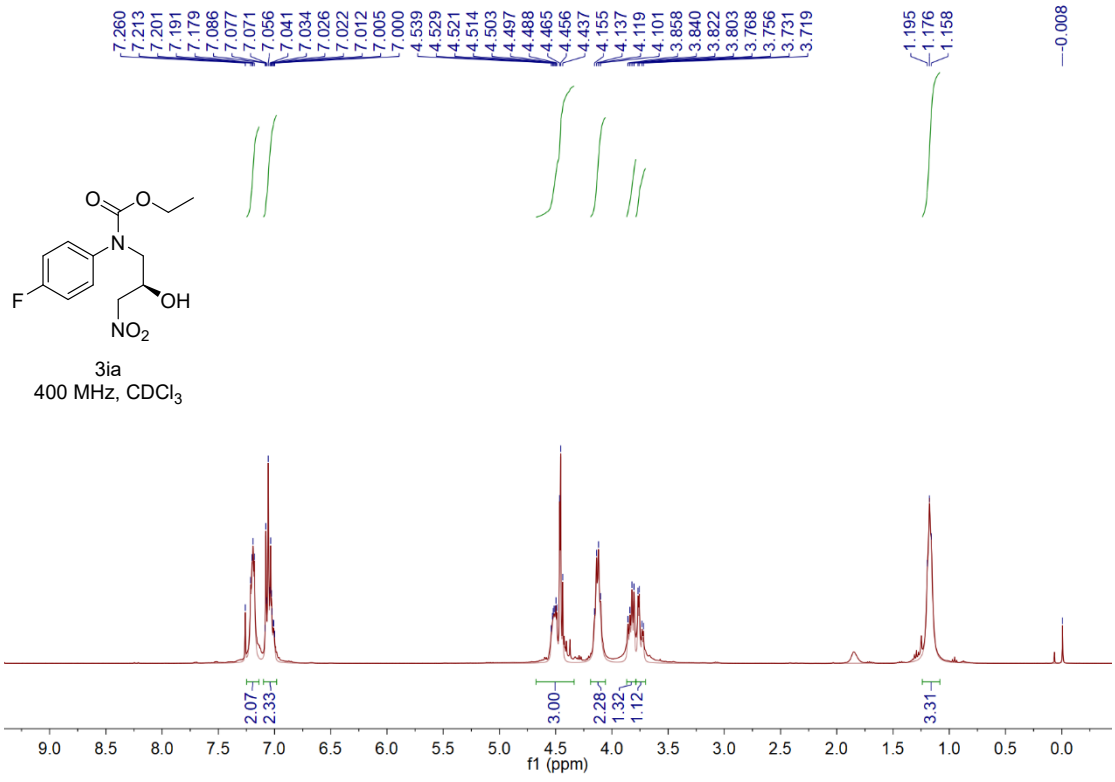


$^{13}C\{^{1}H\}$ NMR of **3ha** (100 MHz, $CDCl_3$)

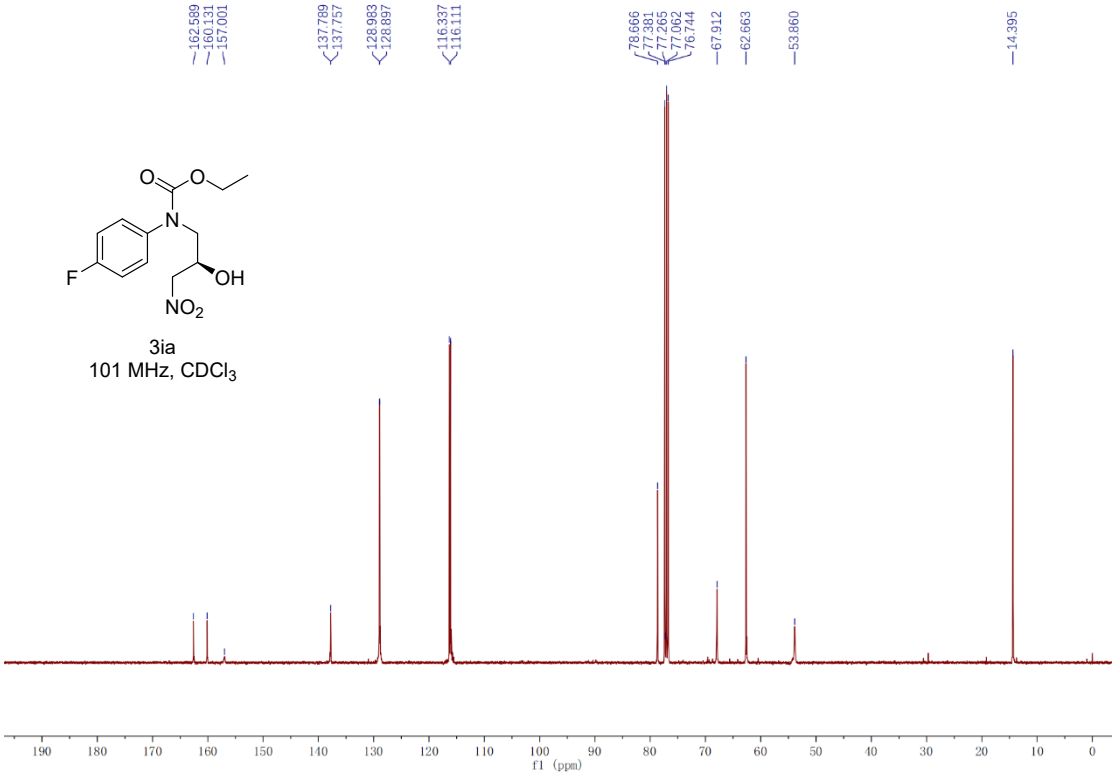


Ethyl (*R*)-(4-fluorophenyl)(2-hydroxy-3-nitropropyl)carbamate (3ia)

^{1}H NMR of **3ia** (400 MHz, $CDCl_3$)

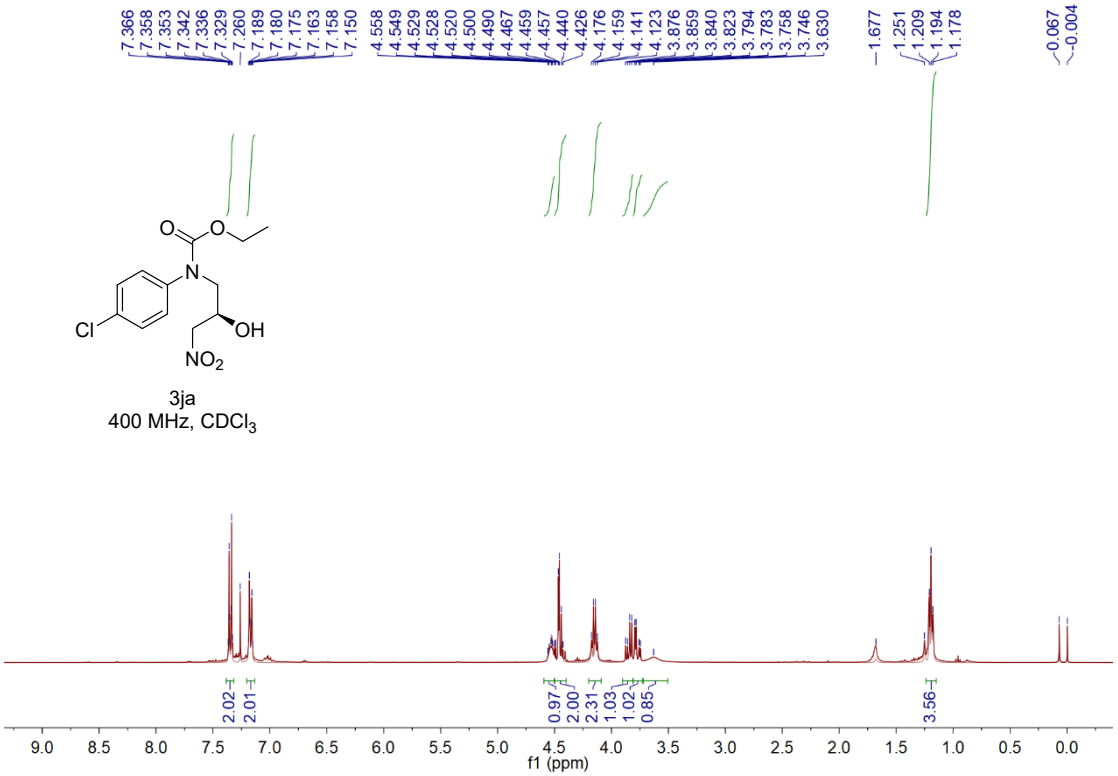


$^{13}C\{^{1}H\}$ NMR of **3ia** (100 MHz, $CDCl_3$)

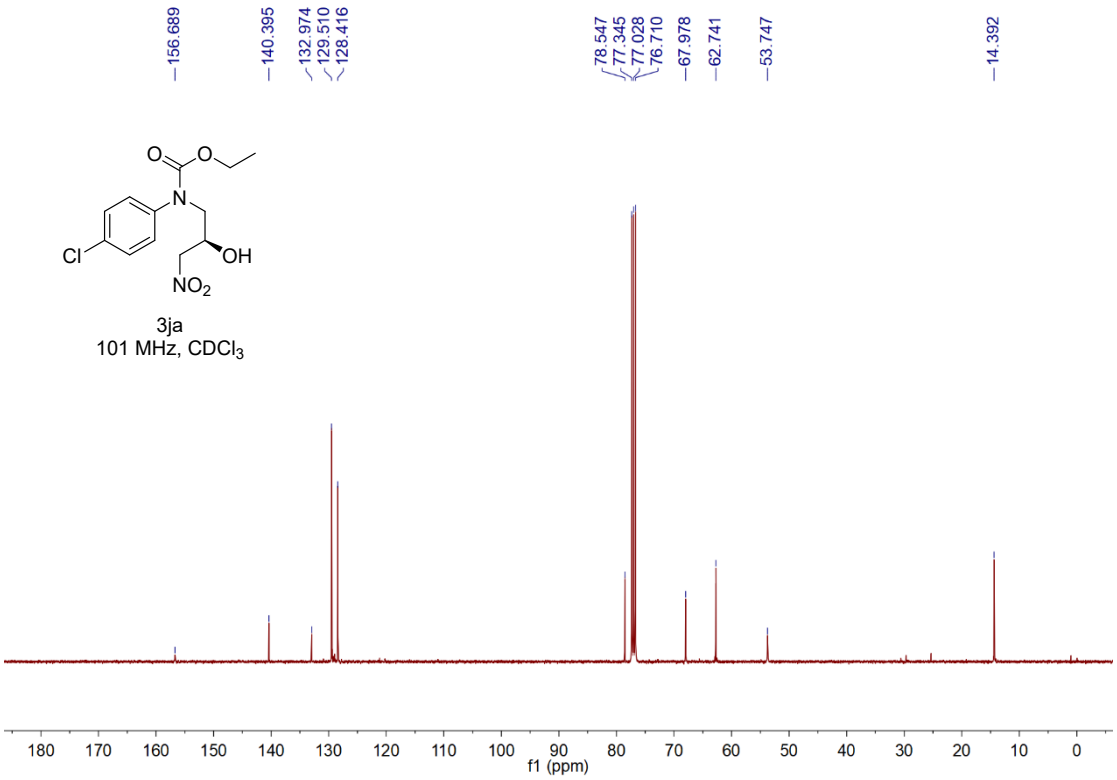


Ethyl (*R*)-(4-chlorophenyl)(2-hydroxy-3-nitropropyl)carbamate (3ja)

^{1}H NMR of **3ja** (400 MHz, $CDCl_3$)

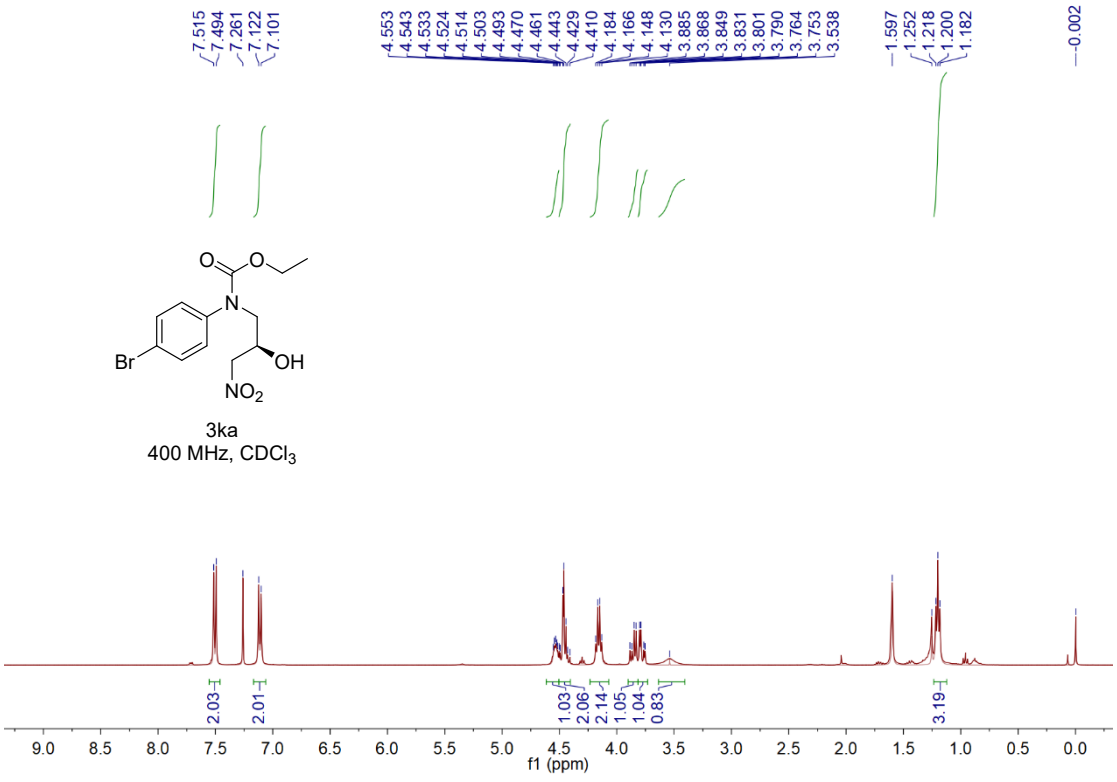


$^{13}C\{^{1}H\}$ NMR of **3ja** (100 MHz, $CDCl_3$)

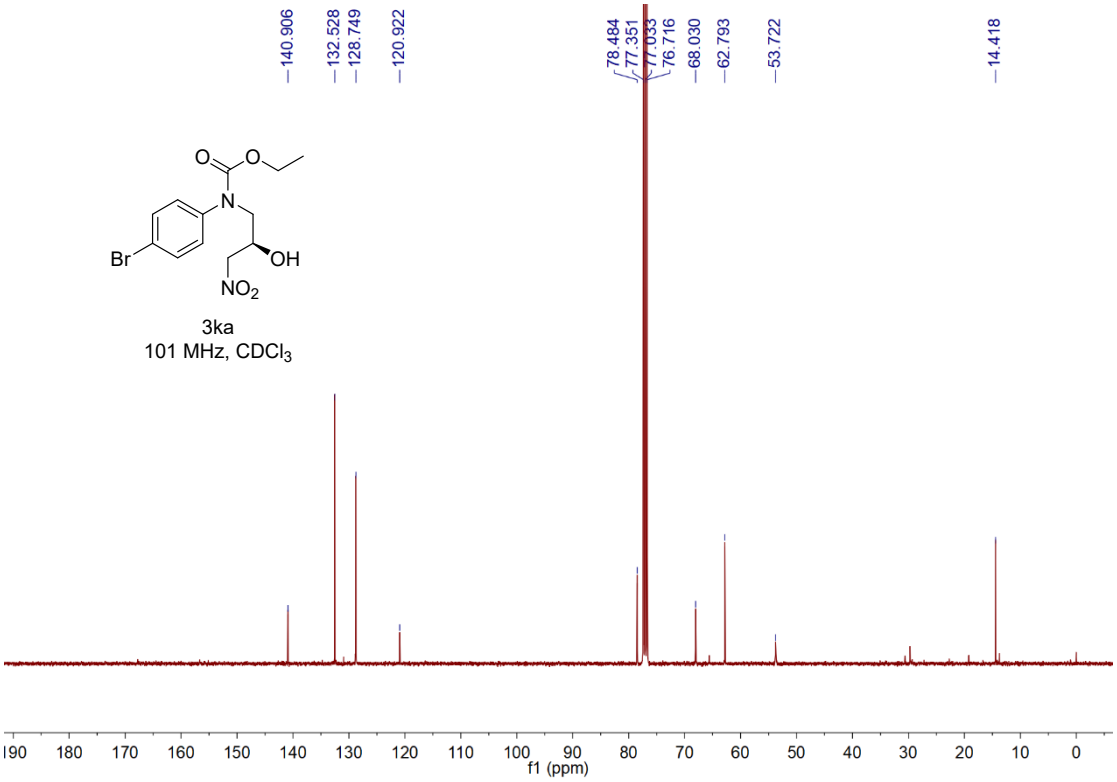


Ethyl (*R*)-(4-bromophenyl)(2-hydroxy-3-nitropropyl)carbamate(3ka)

^{1}H NMR of **3ka** (400 MHz, $CDCl_3$)

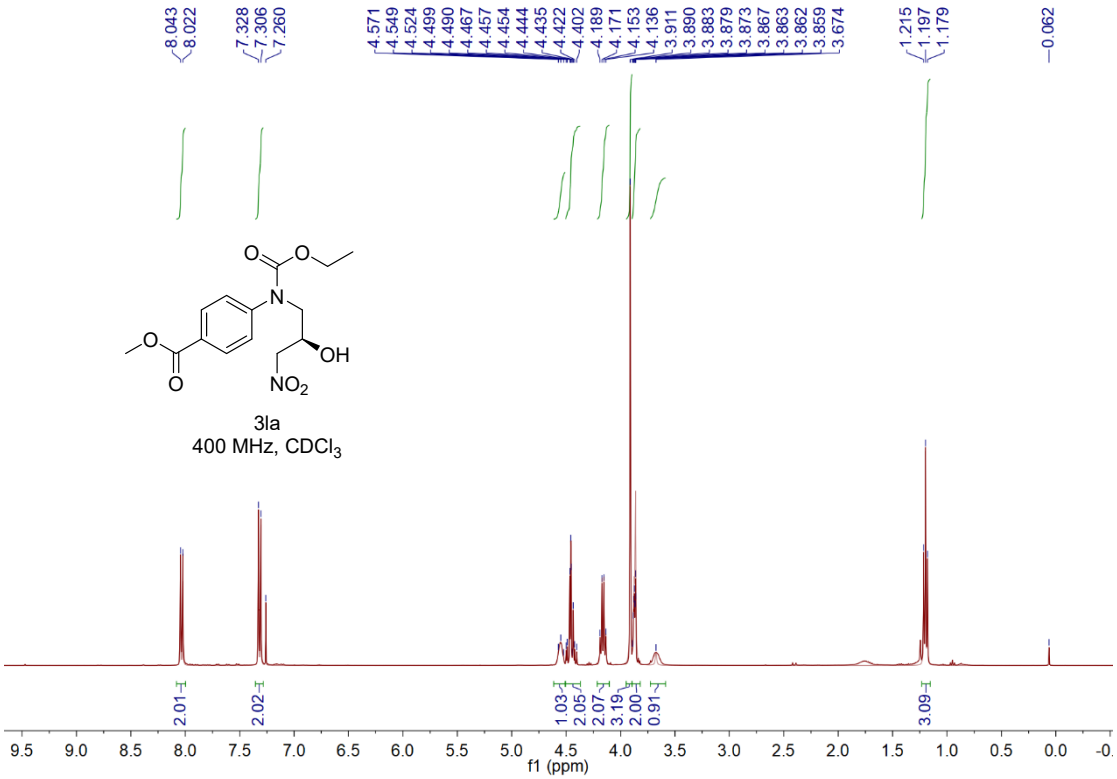


$^{13}C\{^{1}H\}$ NMR of **3ka** (100 MHz, $CDCl_3$)

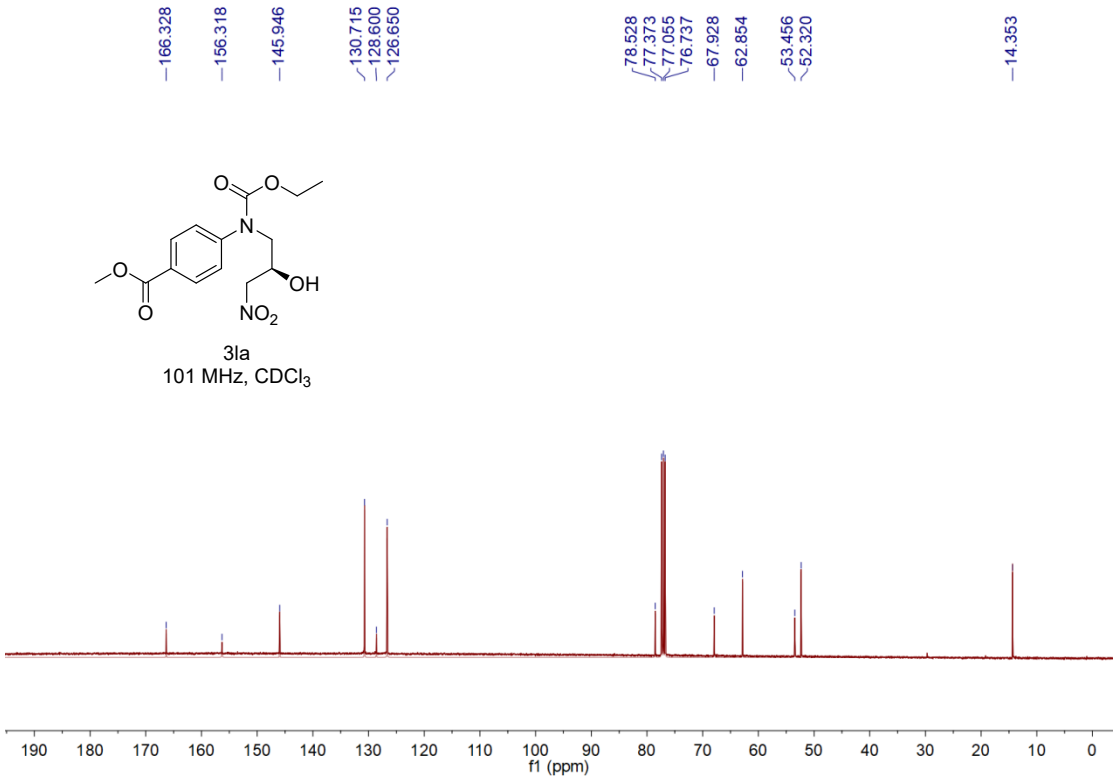


Methyl (*R*)-4-((ethoxycarbonyl)(2-hydroxy-3-nitropropyl)amino)benzoate (3la)

^{1}H NMR of **3la** (400 MHz, $CDCl_3$)

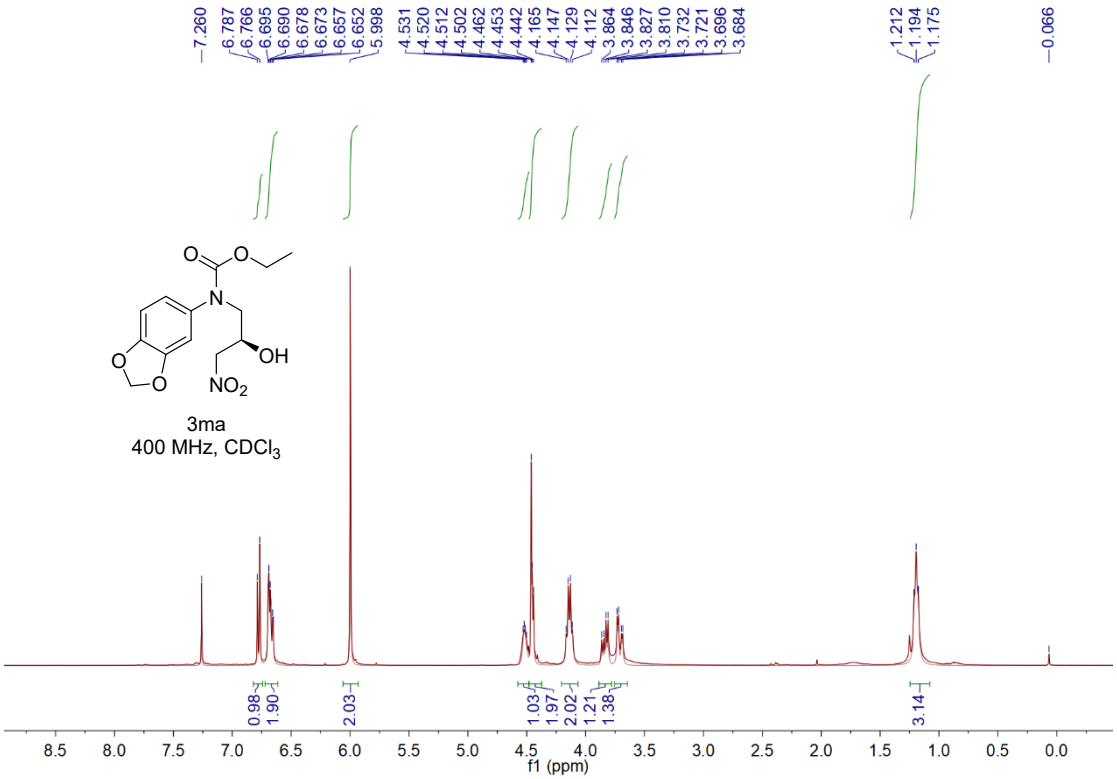


$^{13}C\{^{1}H\}$ NMR of **3la** (100 MHz, $CDCl_3$)

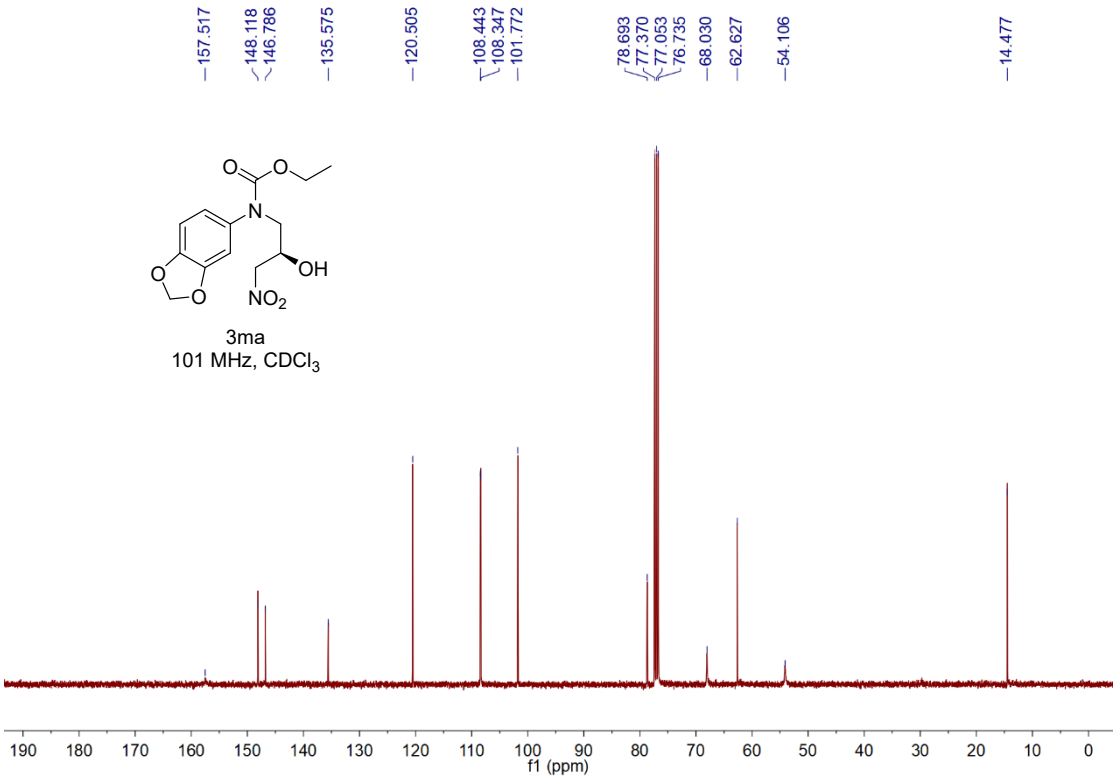


Ethyl (*R*)-benzo[d][1,3]dioxol-5-yl(2-hydroxy-3-nitropropyl)carbamate (3ma)

^{1}H NMR of **3ma** (400 MHz, $CDCl_3$)

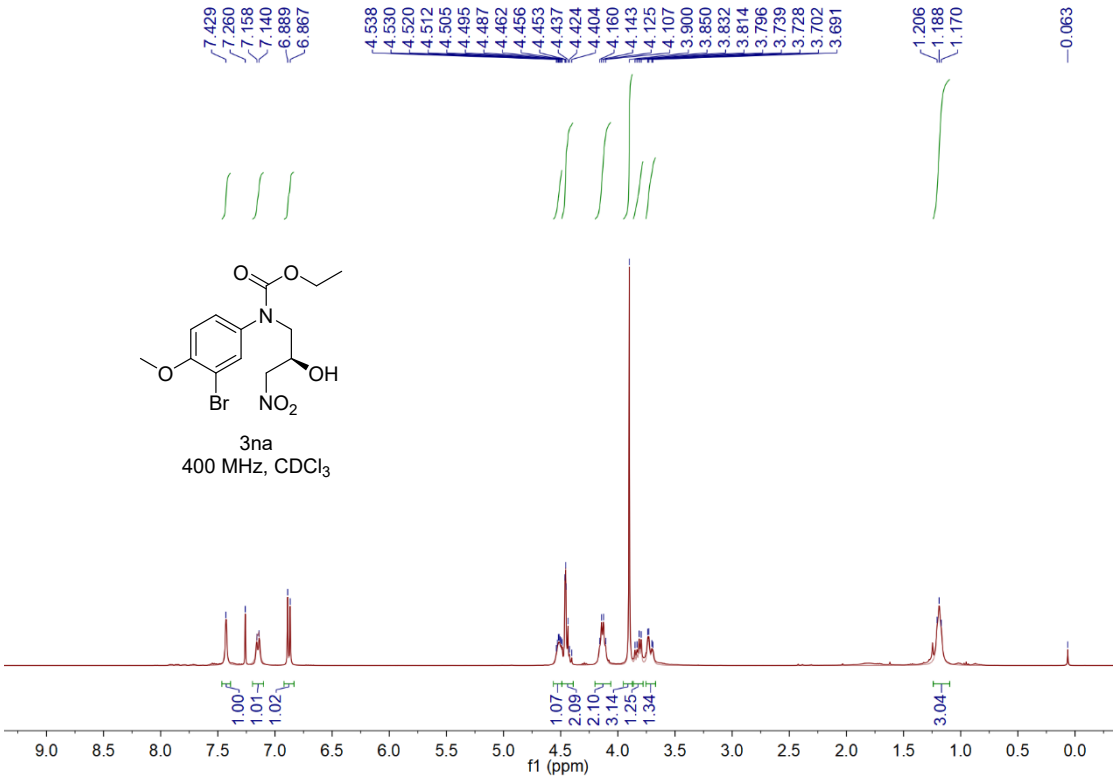


$^{13}C\{^{1}H\}$ NMR of **3ma** (100 MHz, $CDCl_3$)

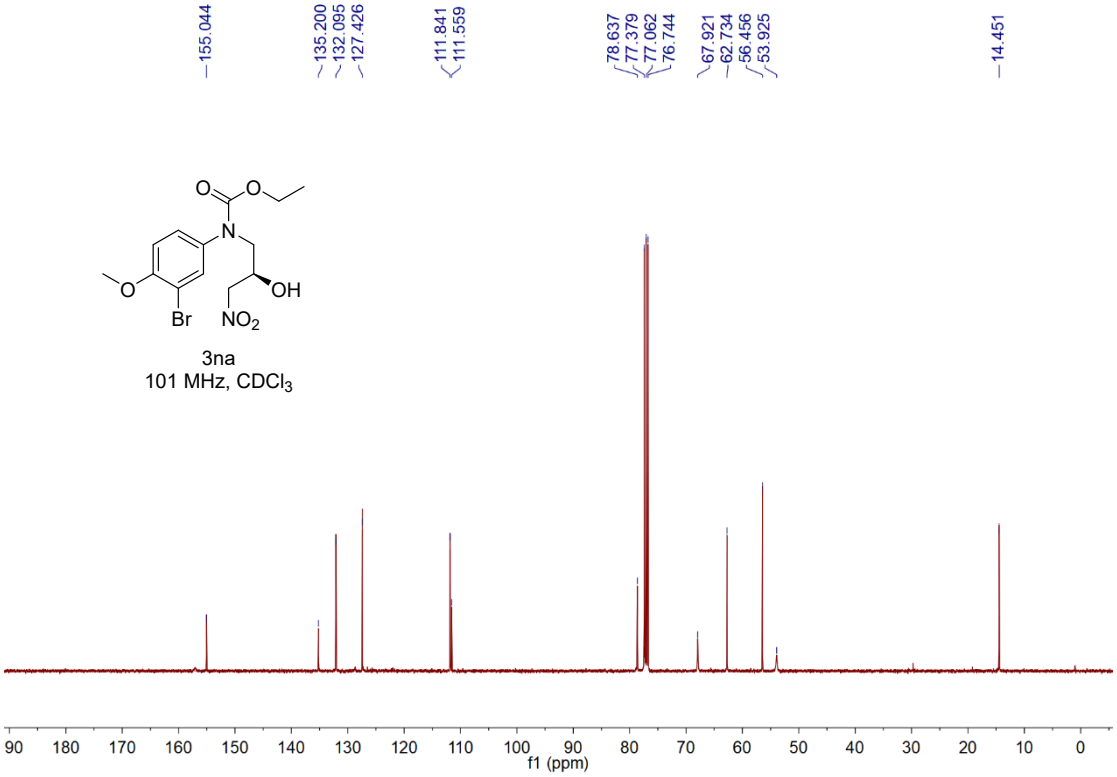


Ethyl (*R*)-(3-bromo-4-methoxyphenyl)(2-hydroxy-3-nitropropyl)carbamate (3na)

^{1}H NMR of **3na** (400 MHz, $CDCl_3$)

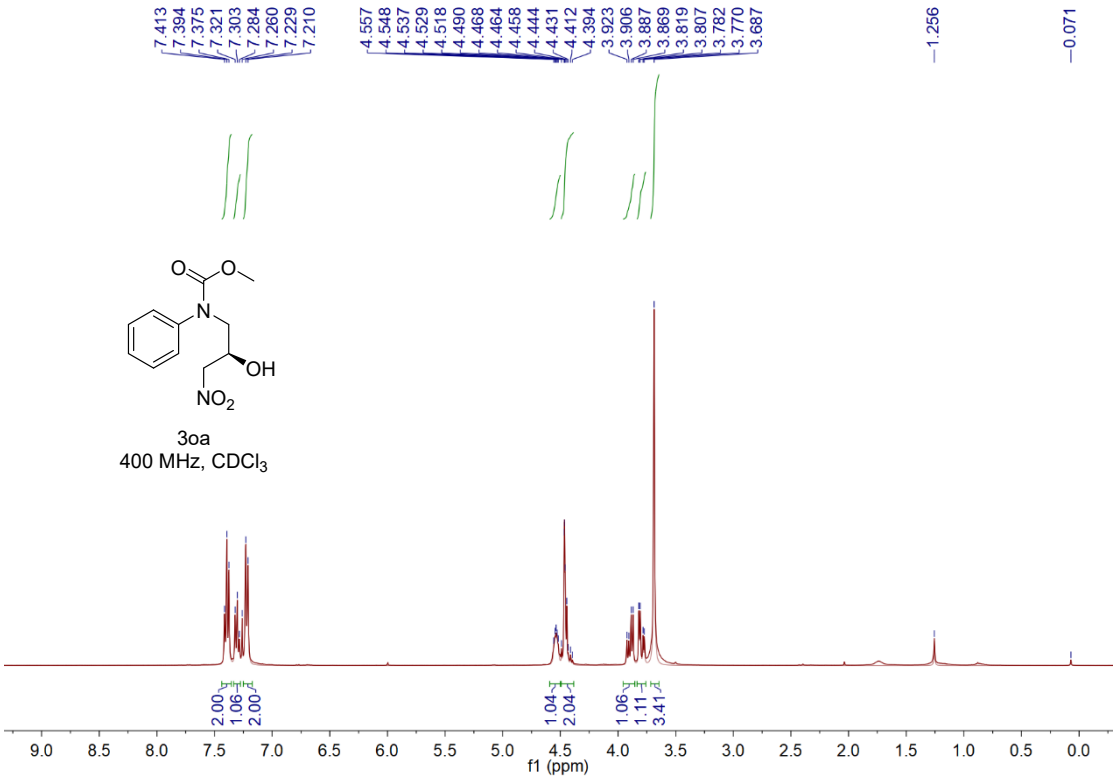


$^{13}C\{^{1}H\}$ NMR of **3na** (100 MHz, $CDCl_3$)

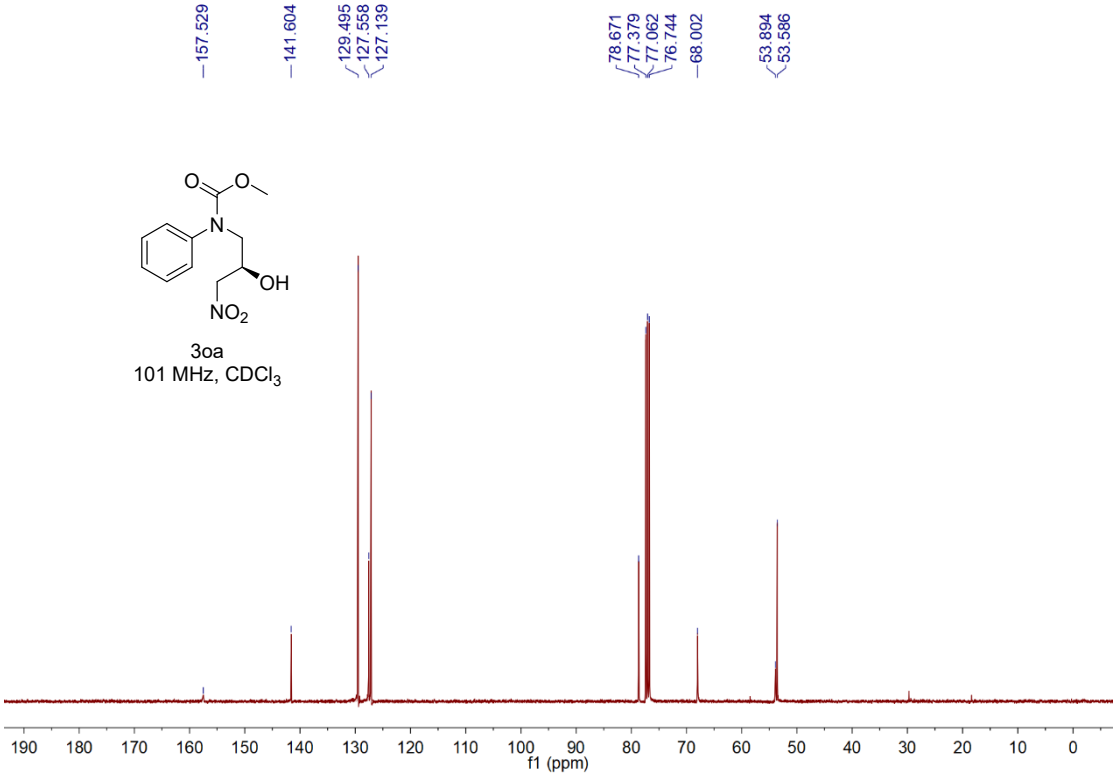


Methyl (*R*)-(2-hydroxy-3-nitropropyl)(phenyl)carbamate (3oa)

^{1}H NMR of **3oa** (400 MHz, $CDCl_3$)

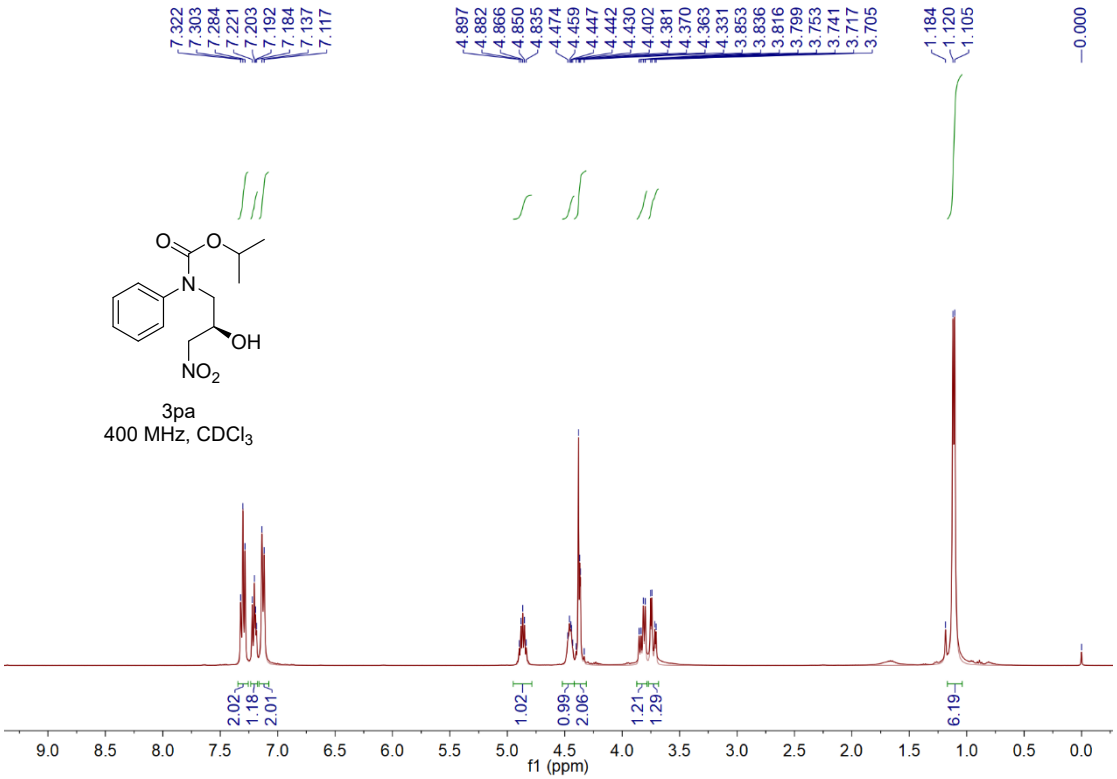


$^{13}C\{^{1}H\}$ NMR of **3oa** (100 MHz, $CDCl_3$)

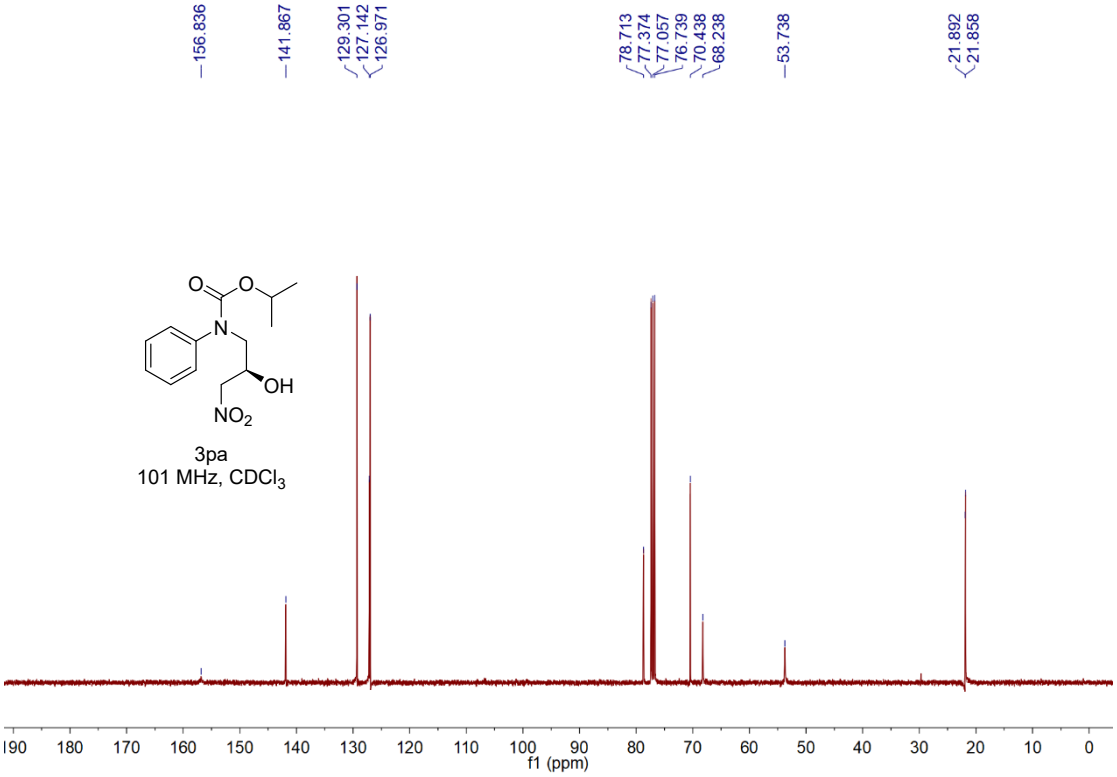


Isopropyl (*R*)-(2-hydroxy-3-nitropropyl)(phenyl)carbamate (3pa)

^{1}H NMR of **3pa** (400 MHz, $CDCl_3$)

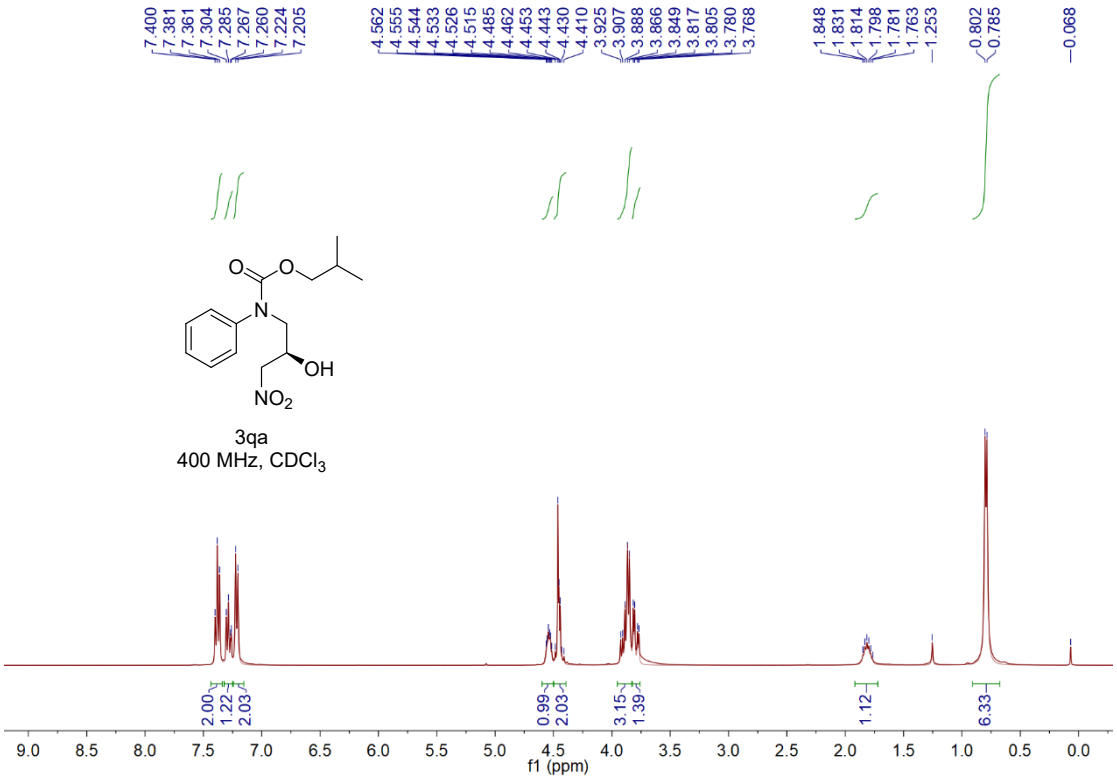


$^{13}C\{^{1}H\}$ NMR of **3pa** (100 MHz, $CDCl_3$)

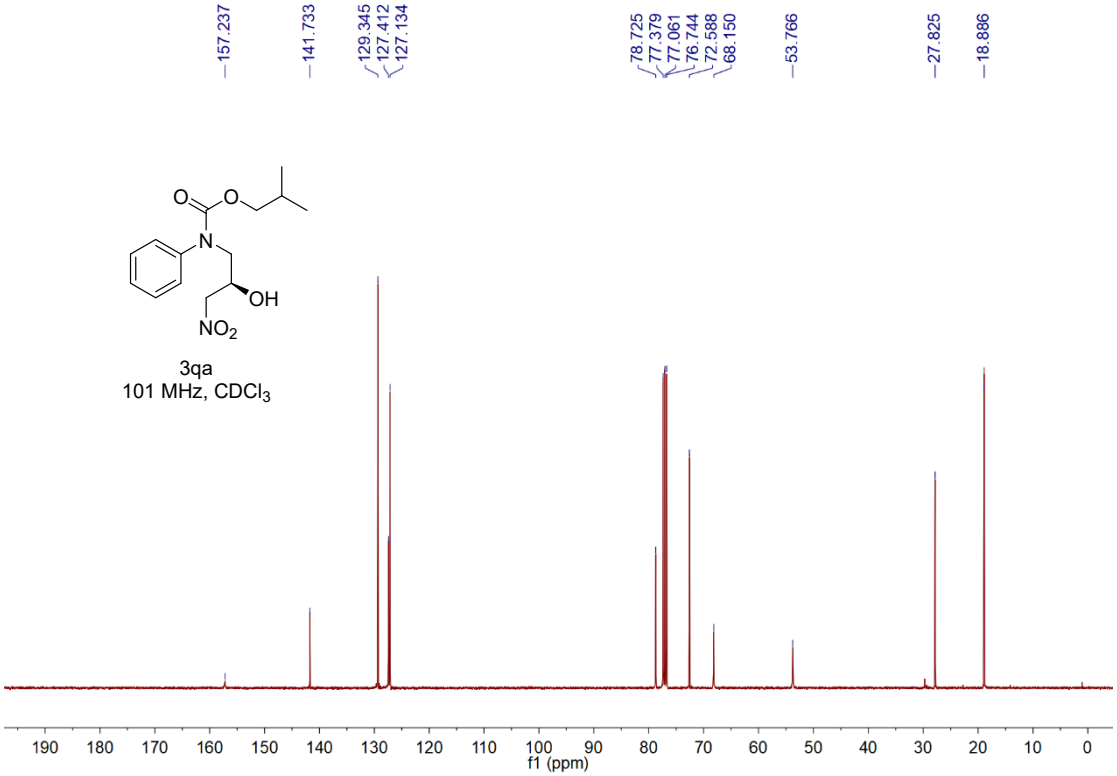


Isobutyl (*R*)-(2-hydroxy-3-nitropropyl)(phenyl)carbamate (3qa)

^{1}H NMR of **3qa** (400 MHz, $CDCl_3$)

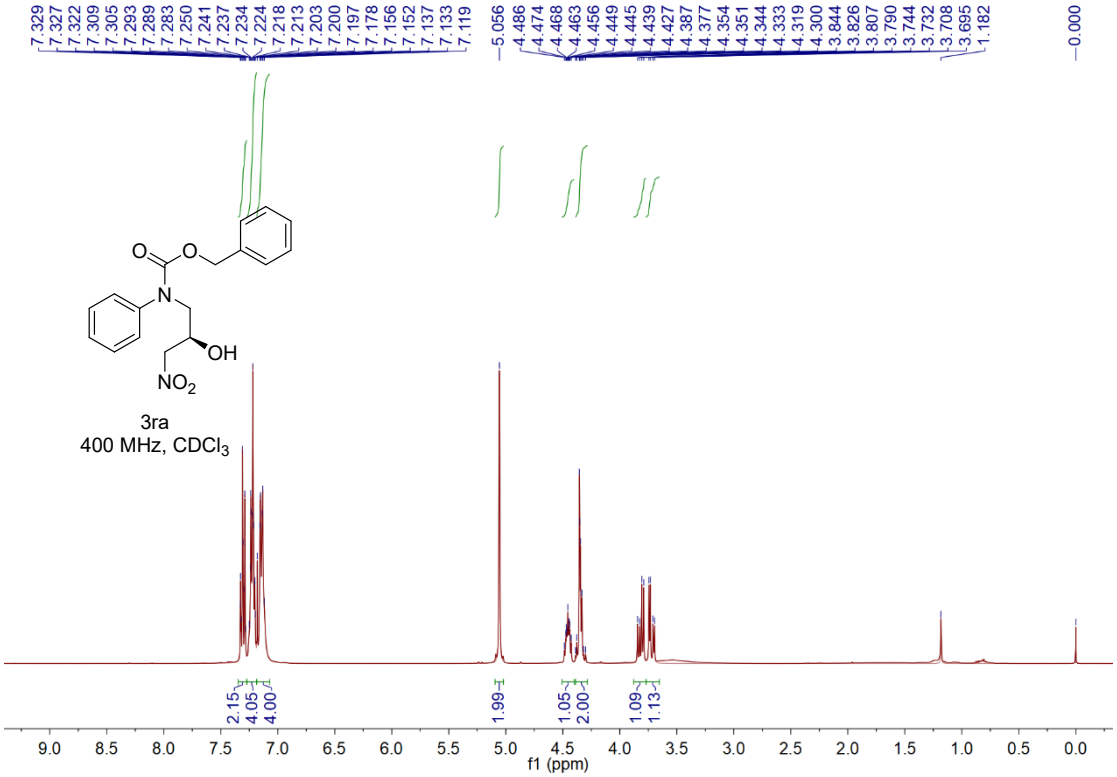


$^{13}C\{^{1}H\}$ NMR of **3qa** (100 MHz, $CDCl_3$)

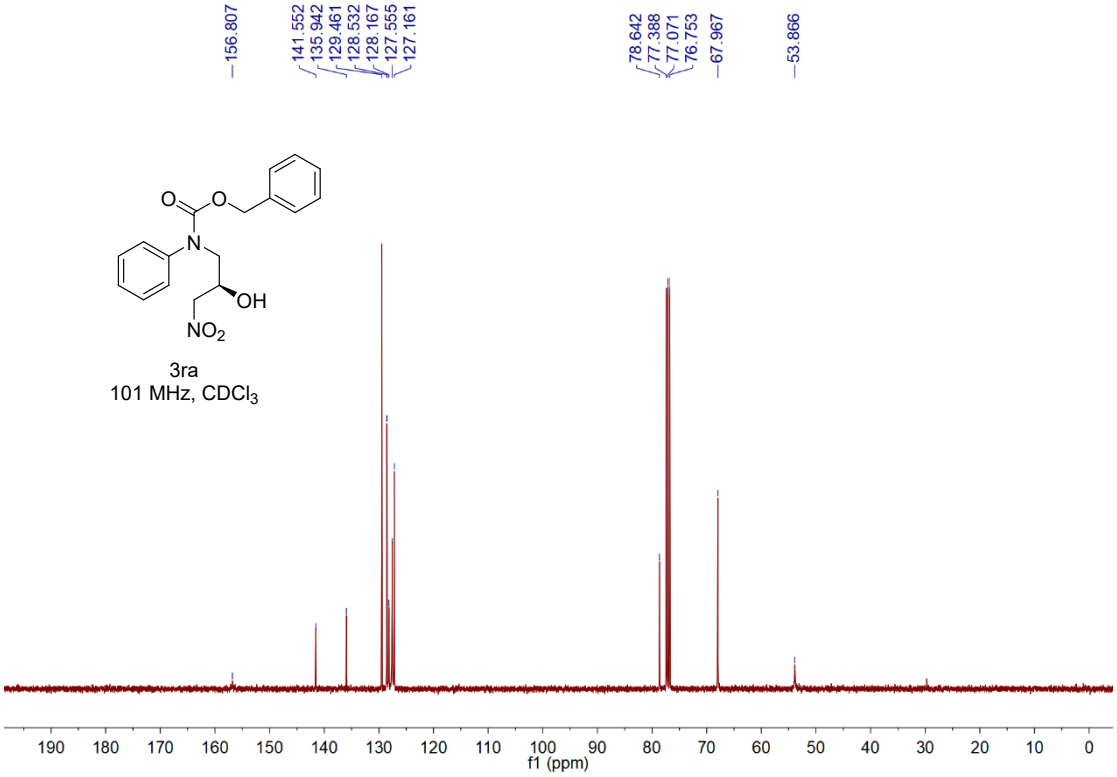


Benzyl (*R*)-(2-hydroxy-3-nitropropyl)(phenyl)carbamate (3ra)

^{1}H NMR of **3ra** (400 MHz, $CDCl_3$)

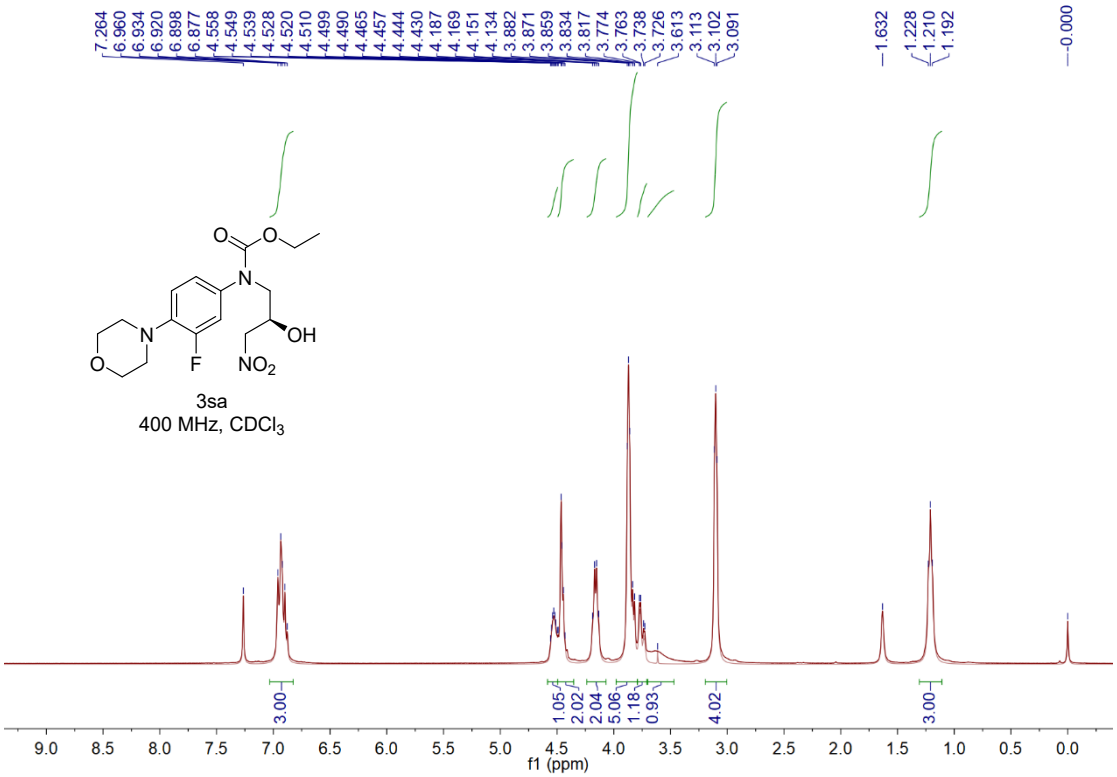


$^{13}C\{^{1}H\}$ NMR of **3ra** (100 MHz, $CDCl_3$)

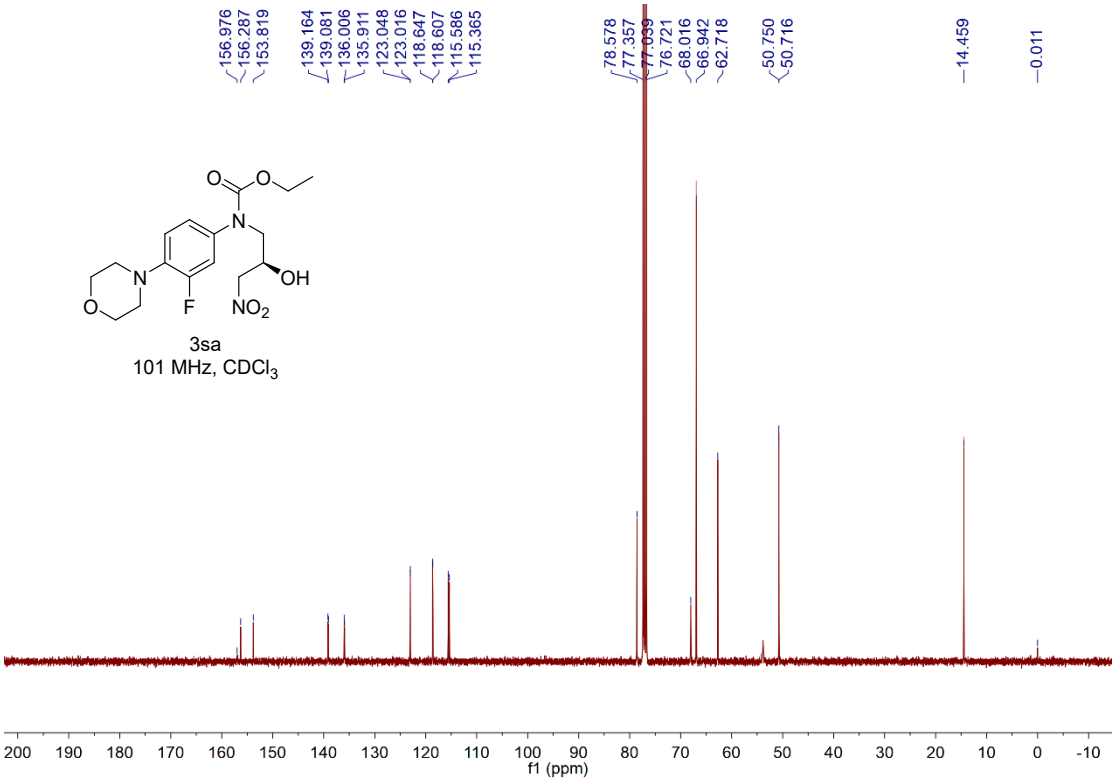


Ethyl (*R*)-(3-fluoro-4-morpholinophenyl)(2-hydroxy-3-nitropropyl)carbamate (**3sa**)

^{1}H NMR of **3sa** (400 MHz, $CDCl_3$)

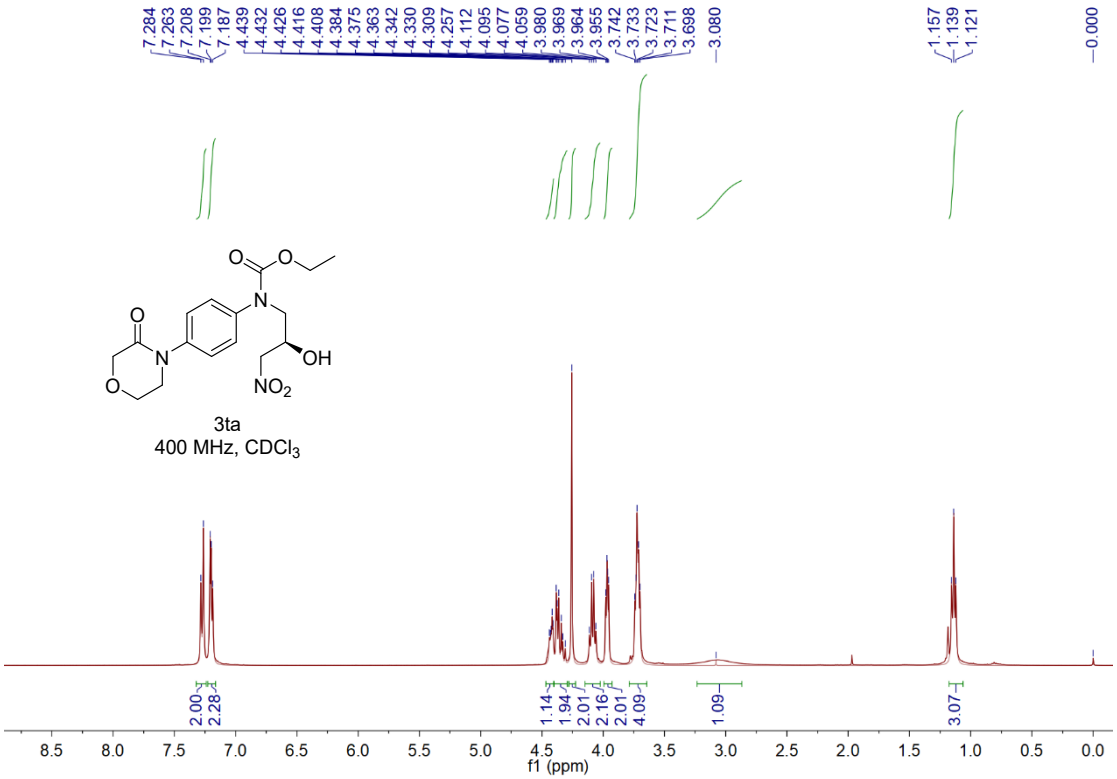


$^{13}C\{^{1}H\}$ NMR of **3sa** (100 MHz, $CDCl_3$)

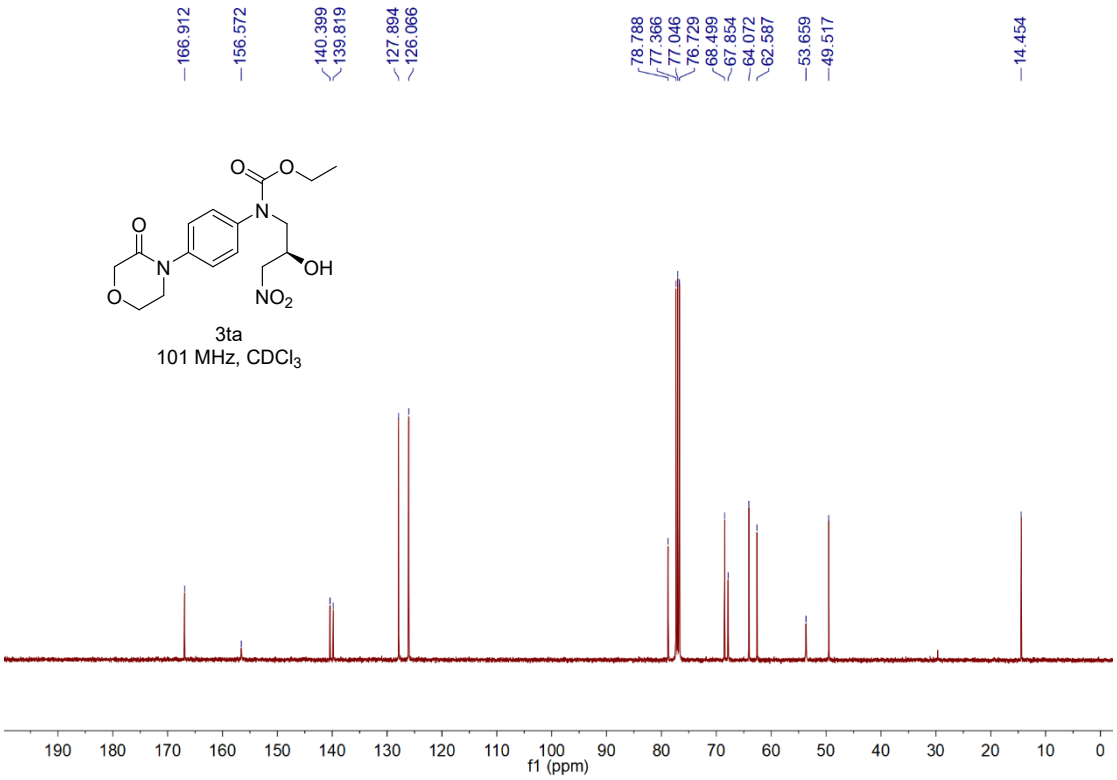


Ethyl (*R*)-(2-hydroxy-3-nitropropyl)(4-(3-oxomorpholino)phenyl)carbamate (3ta)

^{1}H NMR of **3ta** (400 MHz, $CDCl_3$)

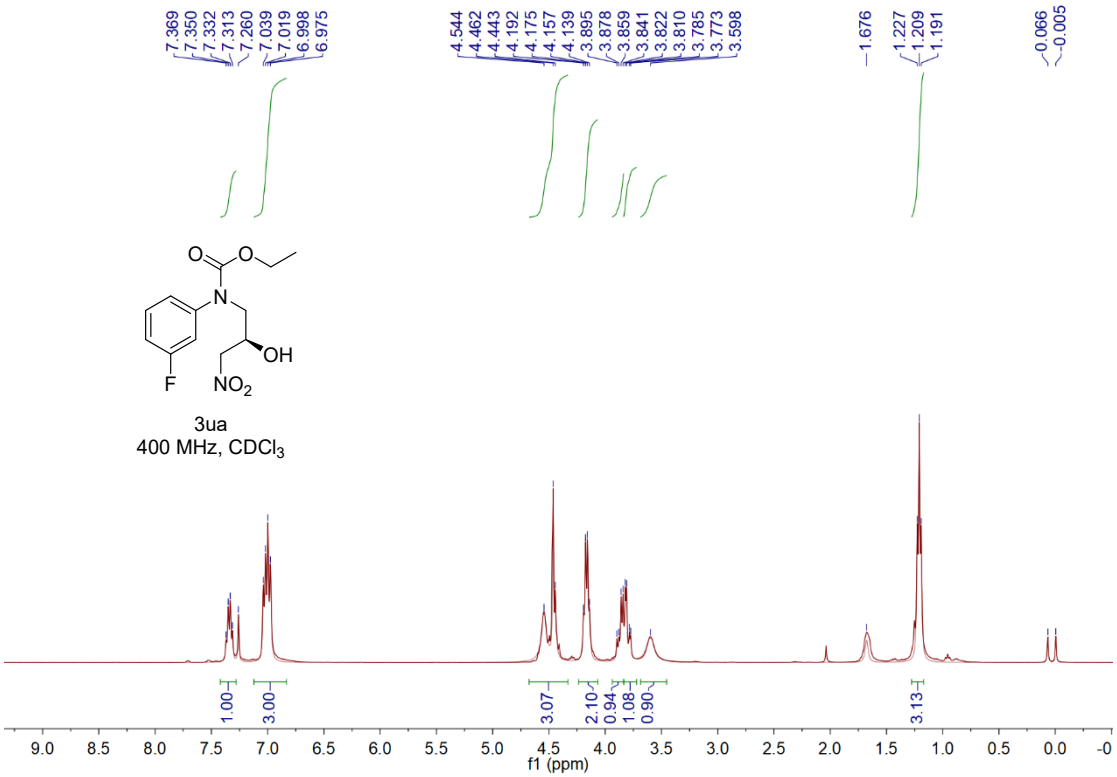


$^{13}C\{^{1}H\}$ NMR of **3ta** (100 MHz, $CDCl_3$)

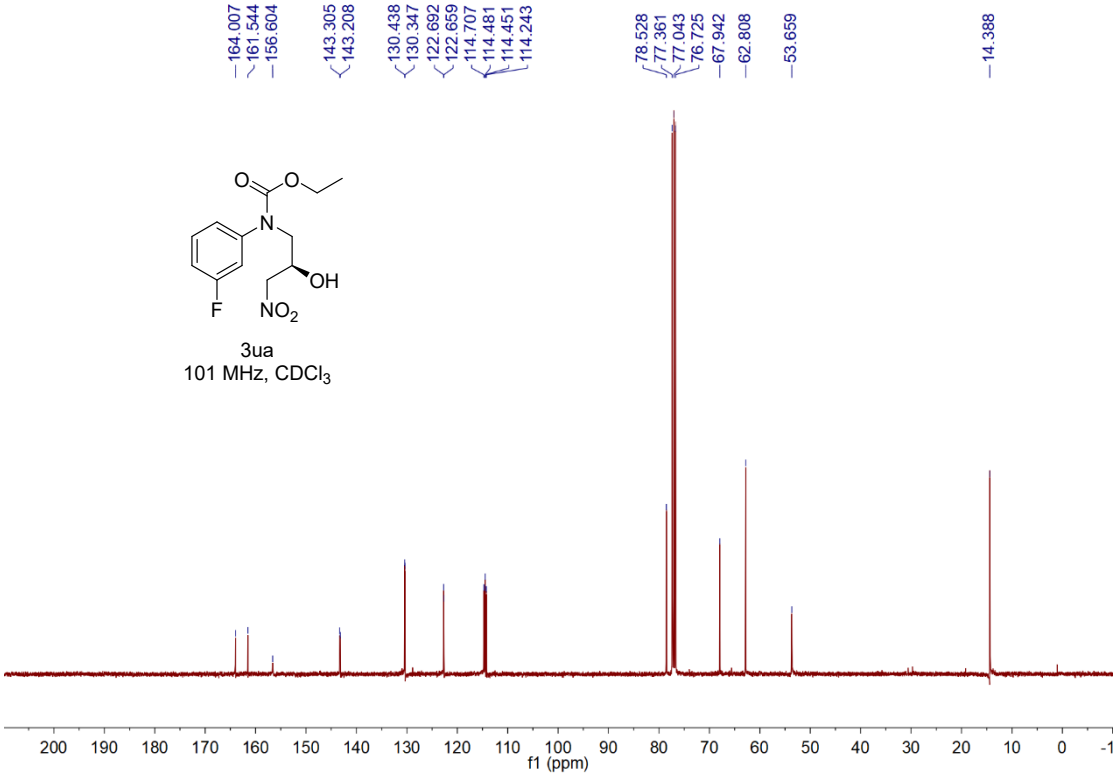


Ethyl (*R*)-(3-fluorophenyl)(2-hydroxy-3-nitropropyl)carbamate (3ua)

^{1}H NMR of **3ua** (400 MHz, $CDCl_3$)

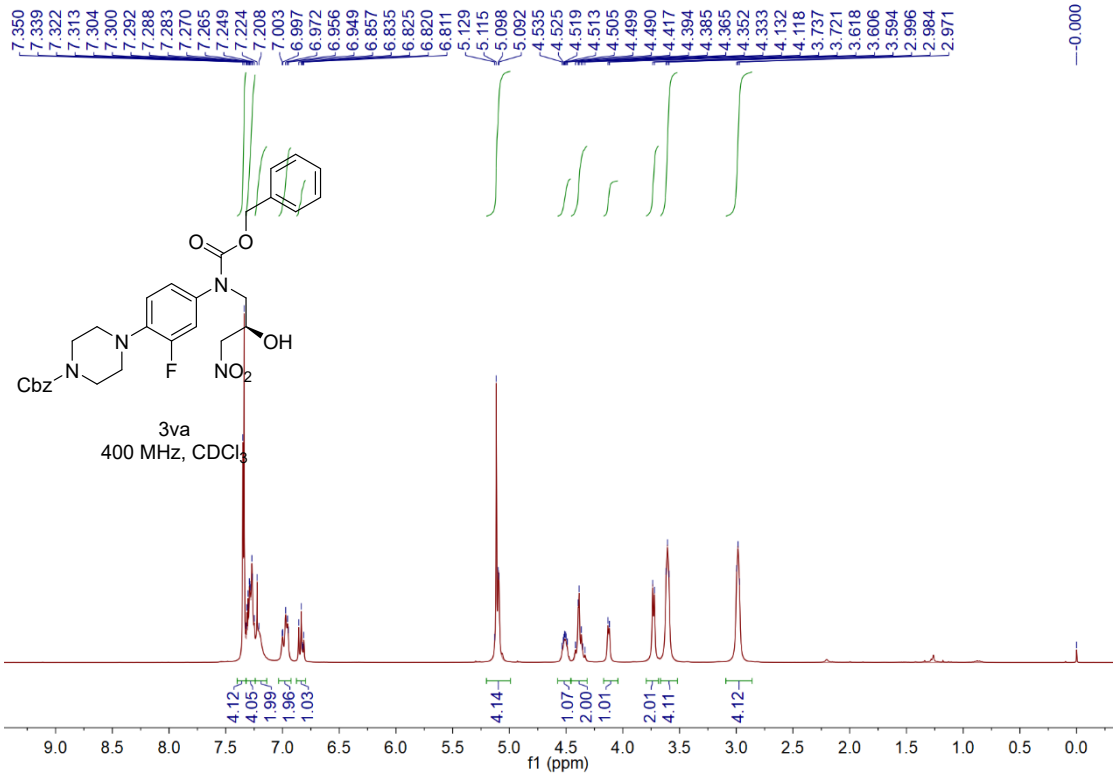


$^{13}C\{^{1}H\}$ NMR of **3ua** (100 MHz, $CDCl_3$)

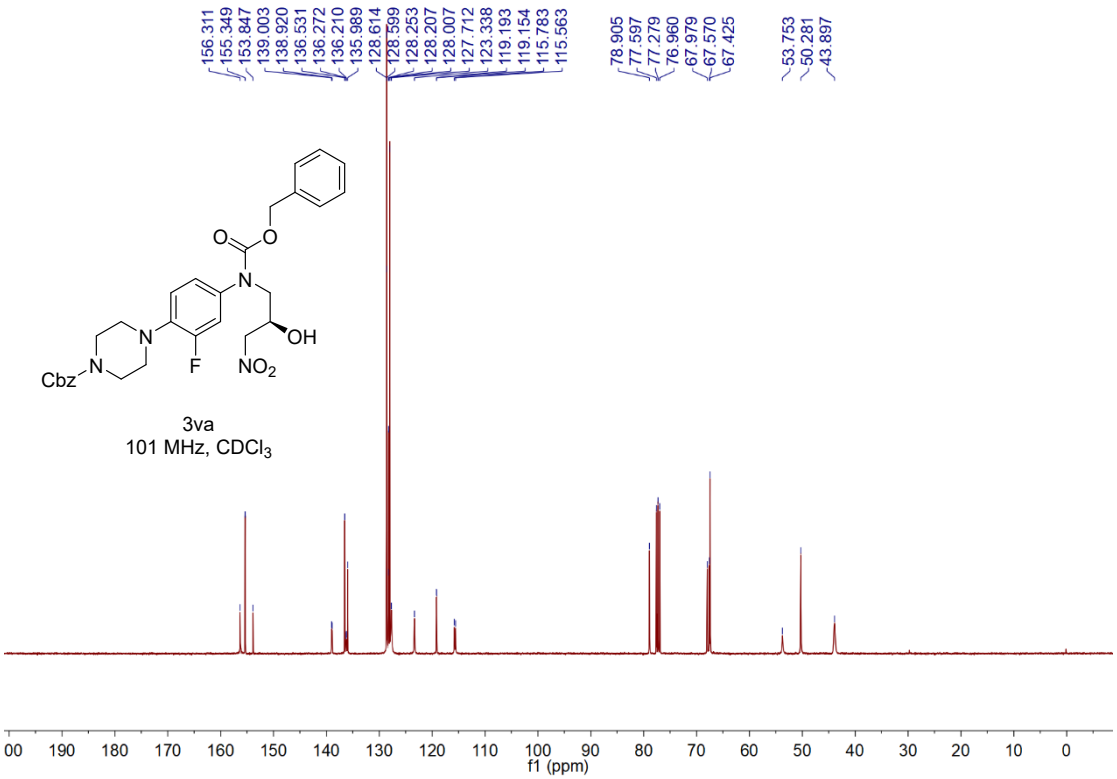


Benzyl(*R*)-4-(4-(((benzyloxy)carbonyl)(2-hydroxy-3-nitropropyl)amino)-2-fluorophenyl)piperazine-1-carboxylate (3va)

^{1}H NMR of **3va** (400 MHz, $CDCl_3$)

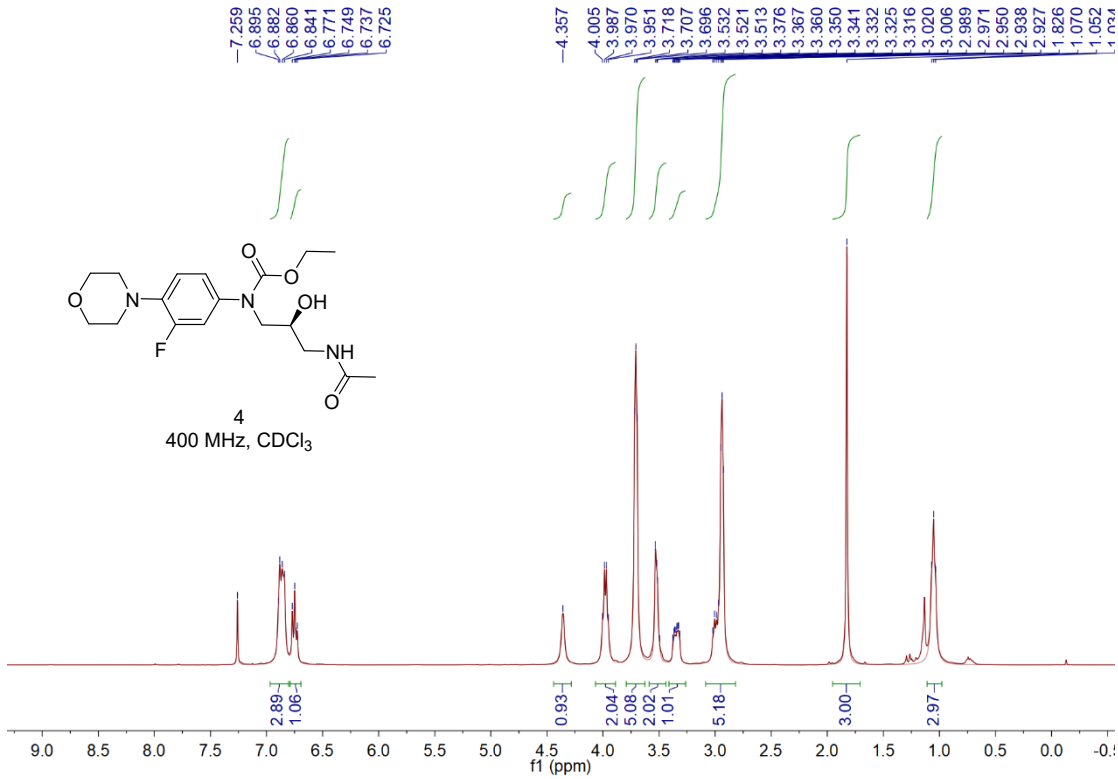


$^{13}C\{^{1}H\}$ NMR of **3va** (100 MHz, $CDCl_3$)



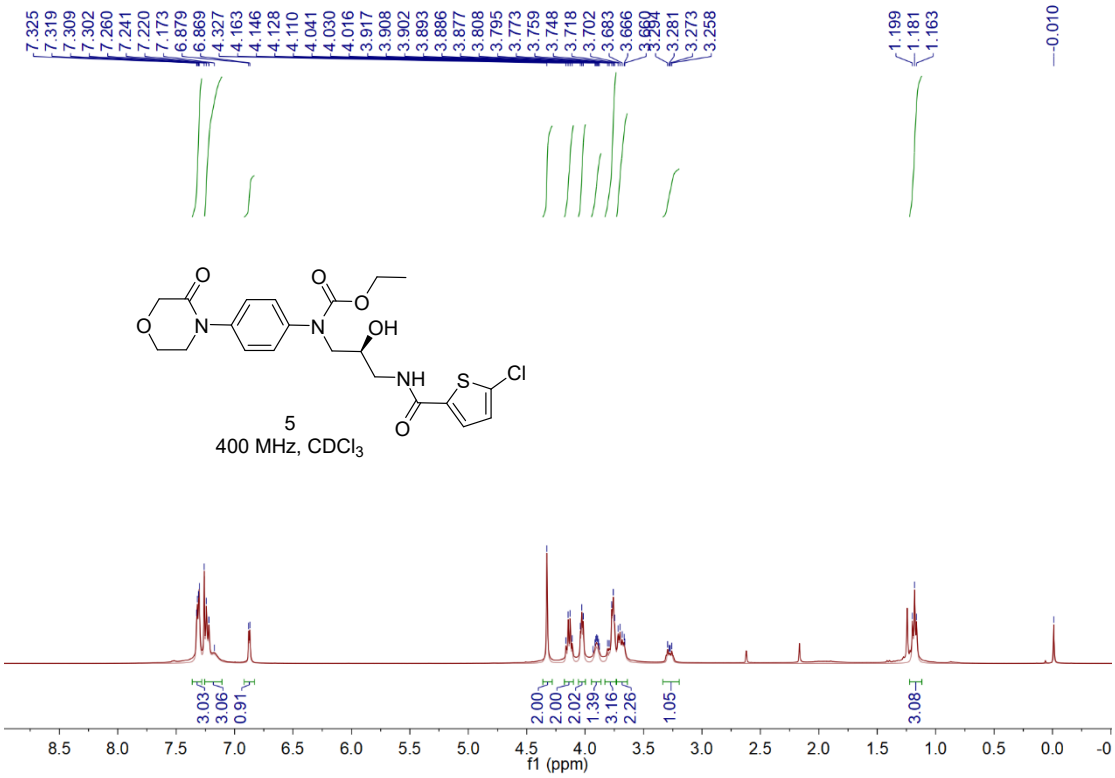
Ethyl (*S*)-(3-acetamido-2-hydroxypropyl)(3-fluoro-4-morpholinophenyl)carbamate (4)

^{1}H NMR of **4** (400 MHz, $CDCl_3$)



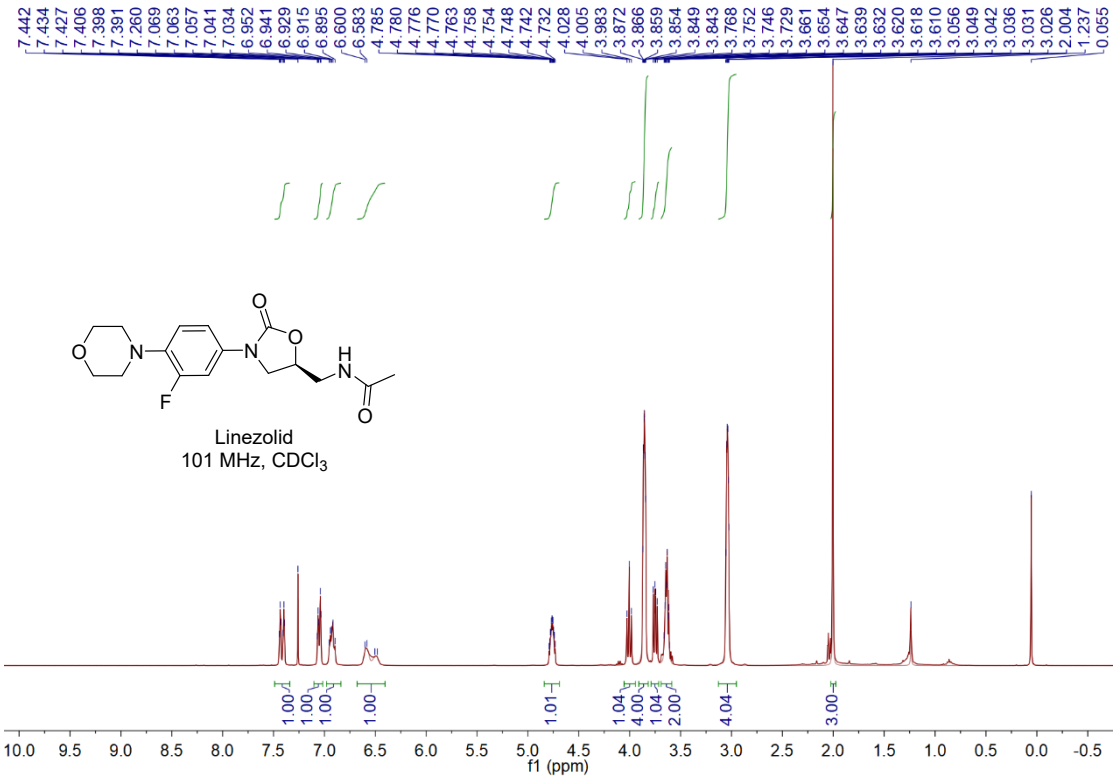
Ethyl (*S*)-(3-(5-chlorothiophene-2-carboxamido)-2-hydroxypropyl)(4-(3-oxomorpholino)phenyl) carbamate(5)

^{1}H NMR of **5** (400 MHz, $CDCl_3$)

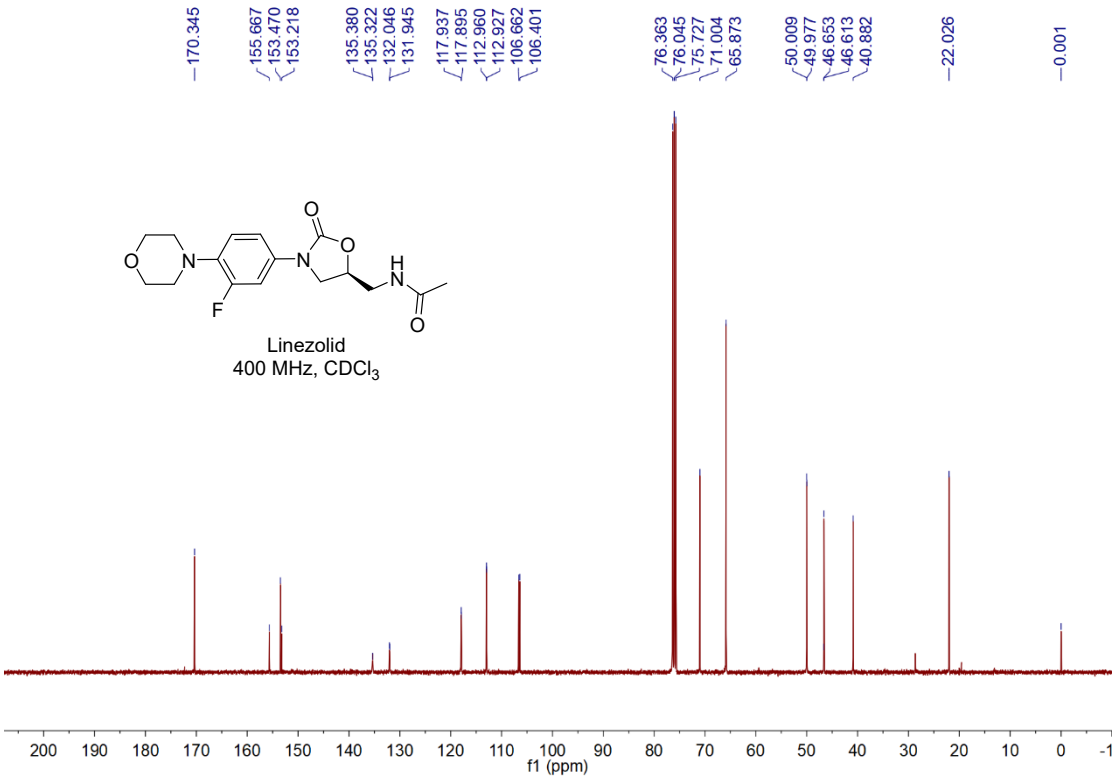


Linezolid (6)

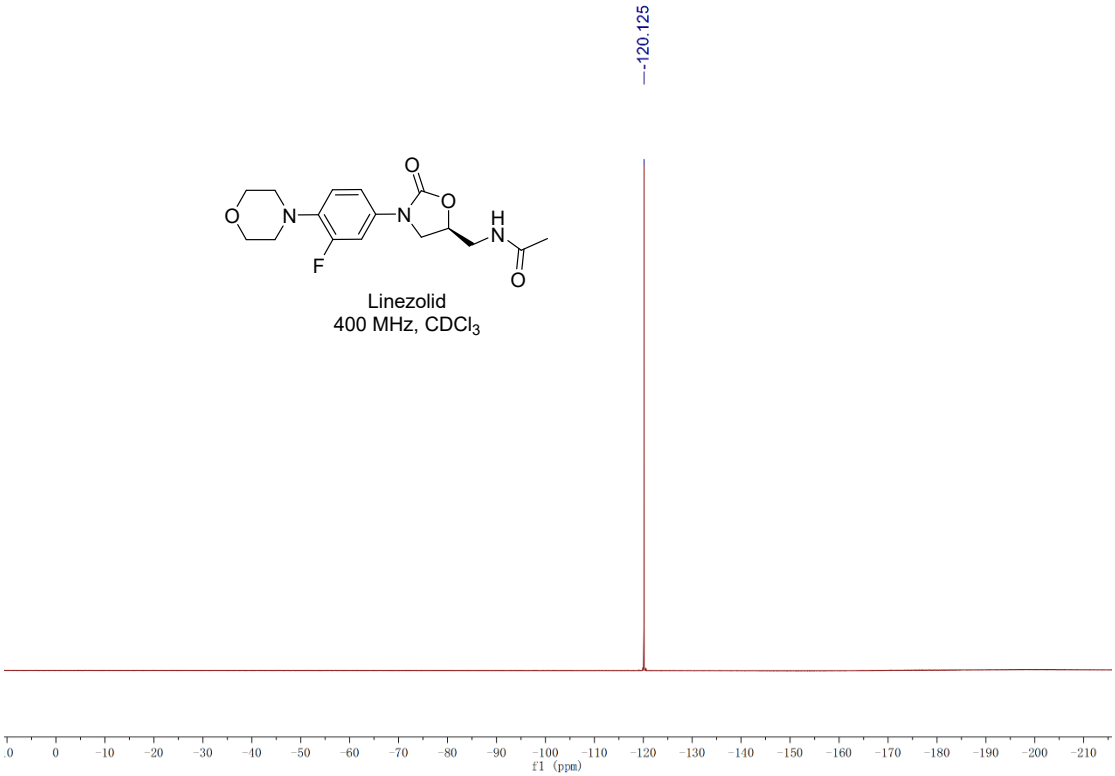
^{1}H NMR of **6** (400 MHz, $CDCl_3$)



$^{13}C\{^{1}H\}$ NMR of **6** (100 MHz, $CDCl_3$)

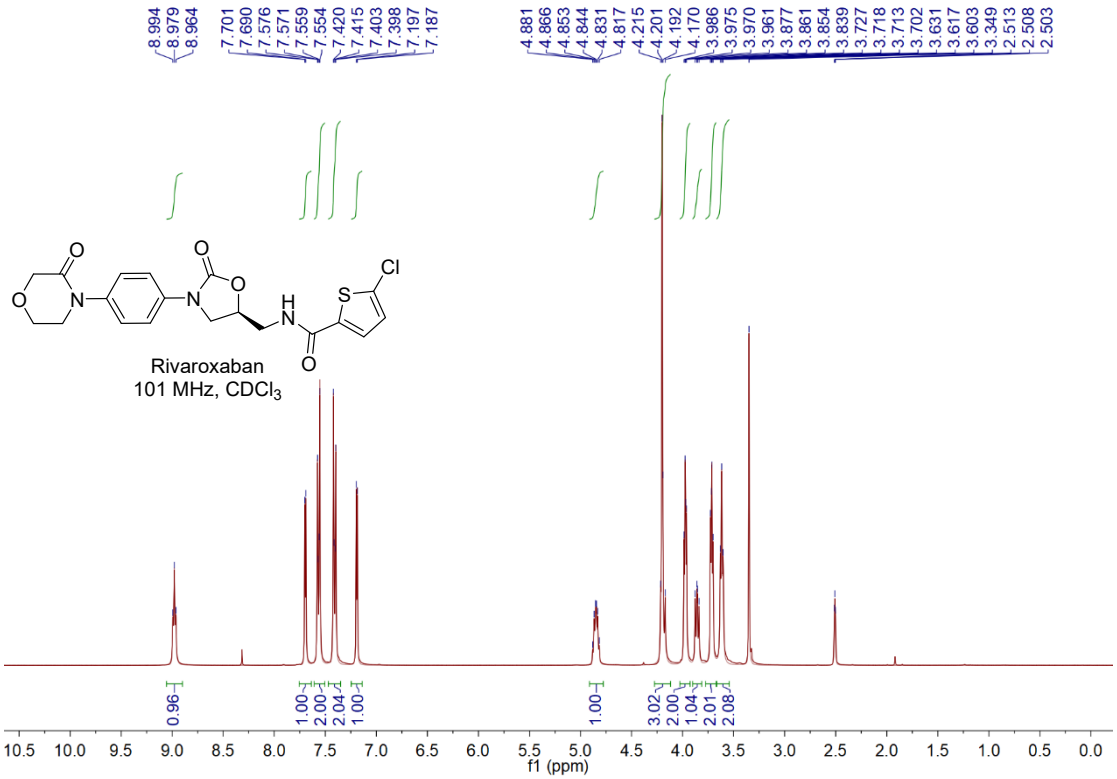


^{19}F NMR of **6** (100 MHz, $CDCl_3$)

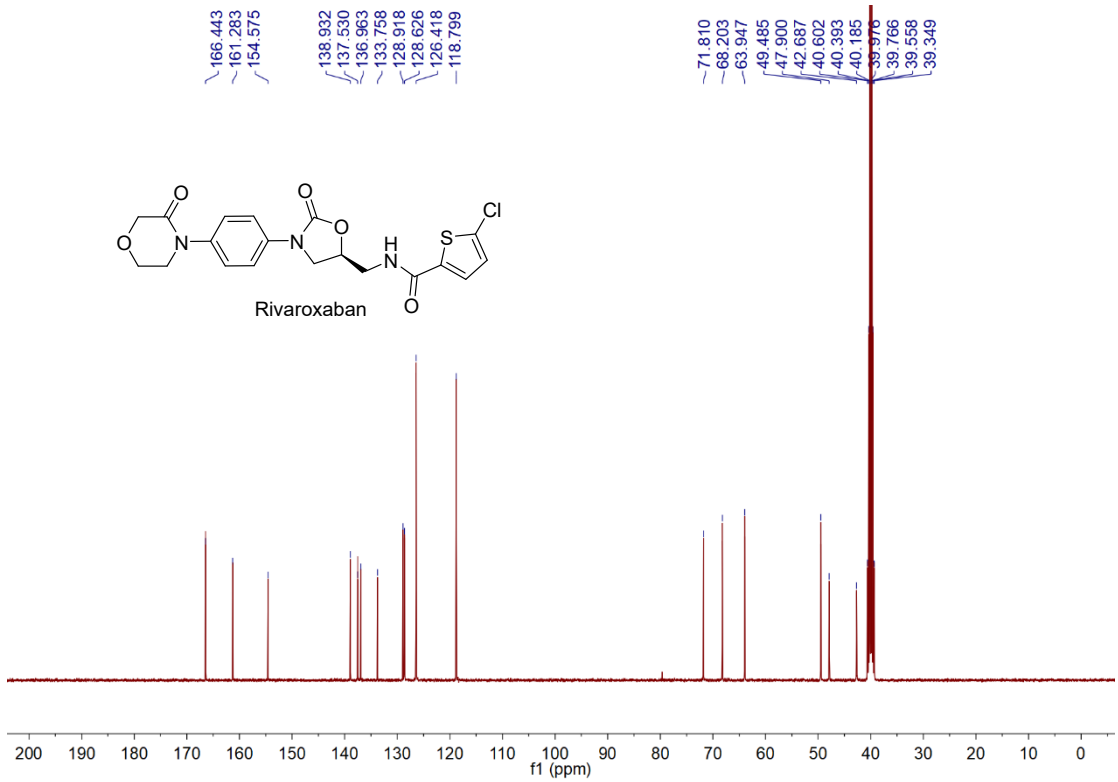


Rivaroxaban (7)

^{1}H NMR of **7** (400 MHz, $CDCl_3$)

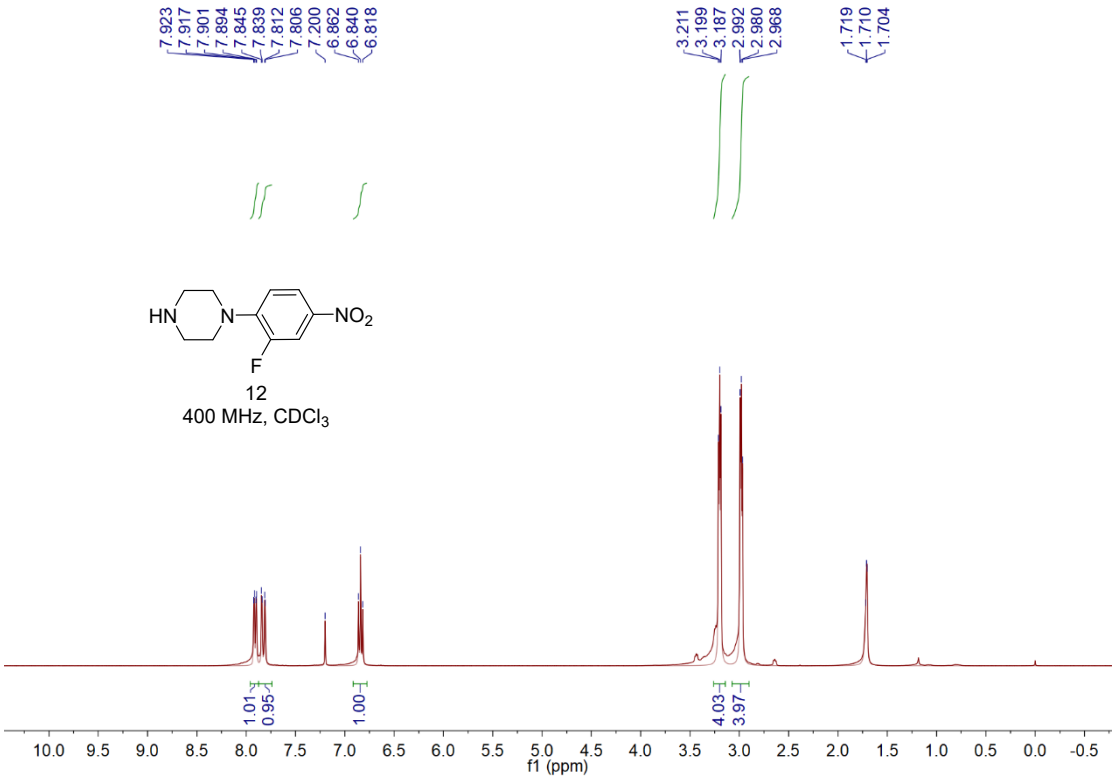


^{13}C{^{1}H} NMR of **7** (100 MHz, $CDCl_3$)



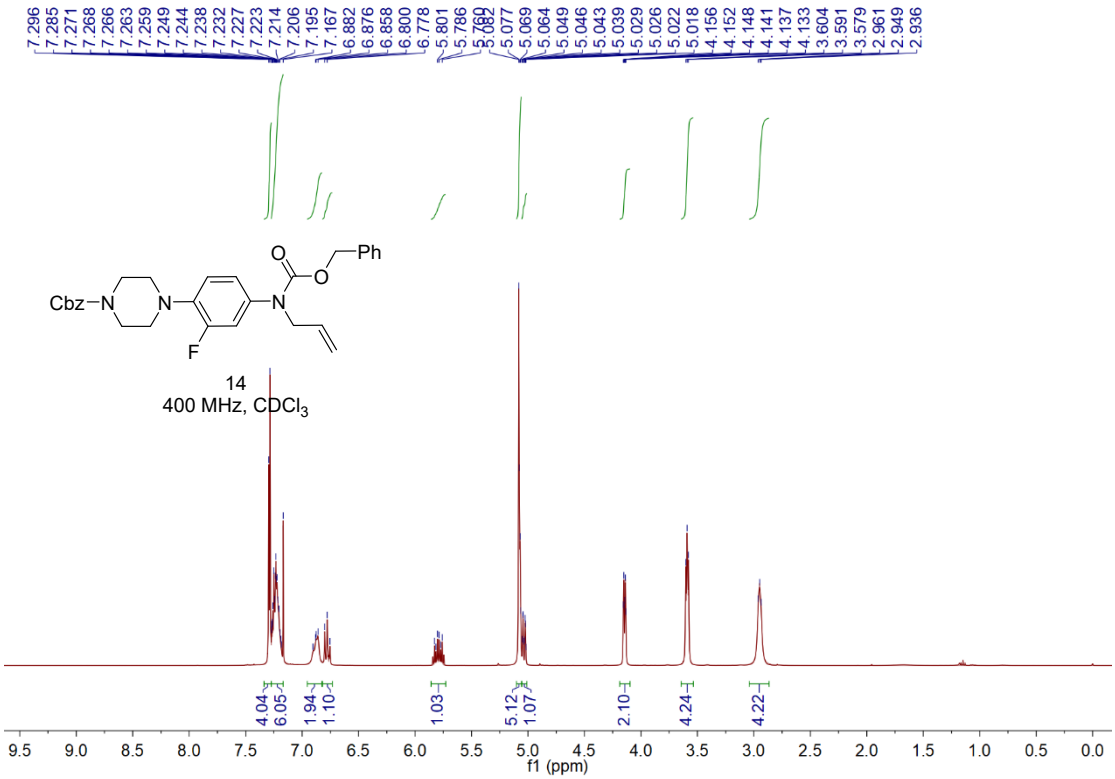
1-(2-Fluoro-4-nitrophenyl)piperazine (12)

^{1}H NMR of **12** (400 MHz, $CDCl_3$)

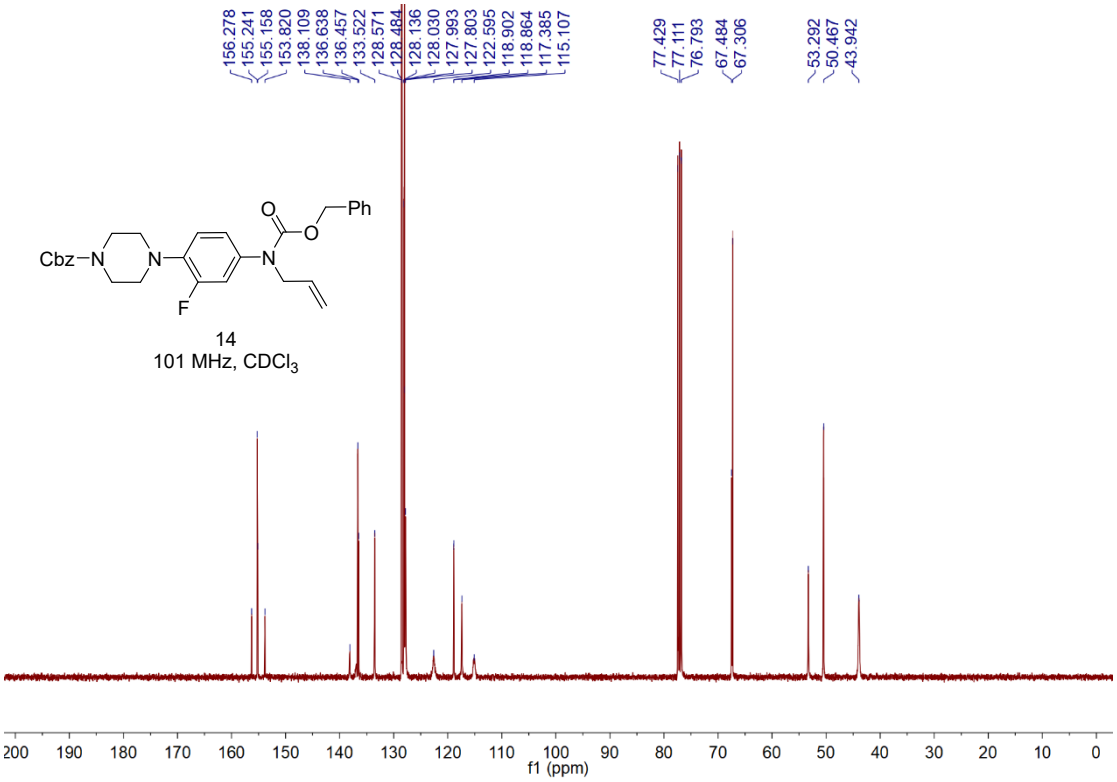


Benzyl 4-(4-(allyl((benzyloxy)carbonyl)amino)-2-fluorophenyl)piperazine-1- carboxylate (14)

^{1}H NMR of **14** (400 MHz, $CDCl_3$)

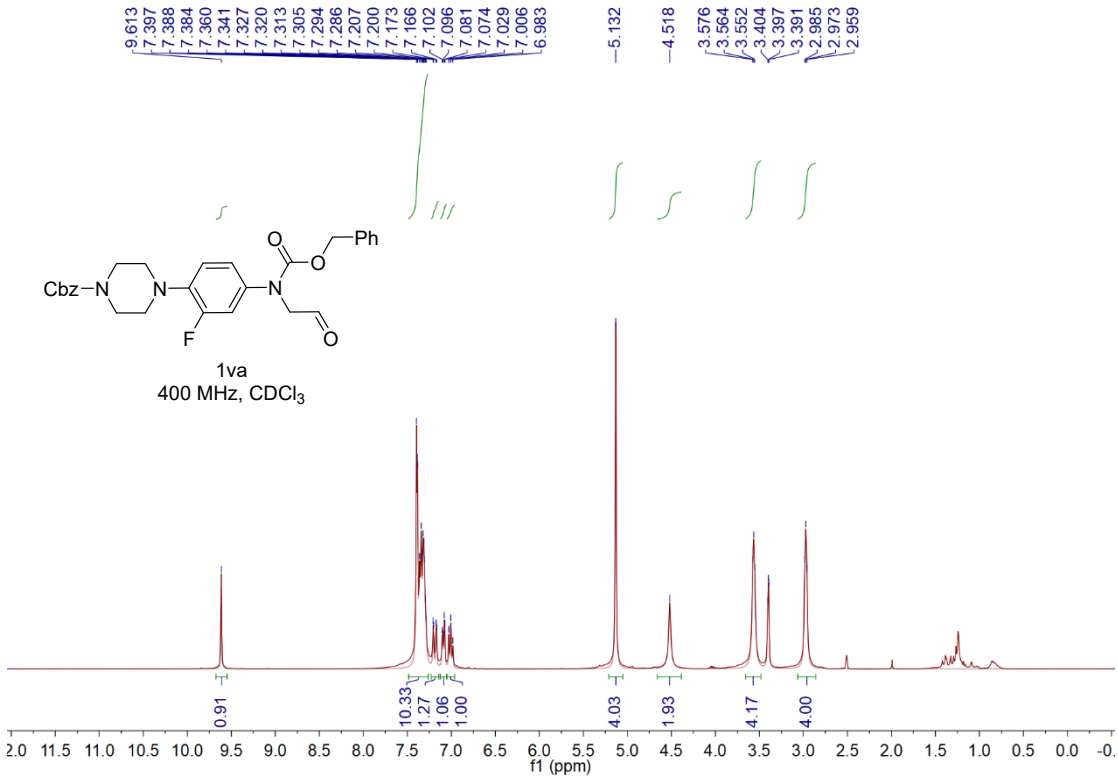


$^{13}C\{^{1}H\}$ NMR of **14** (100 MHz, $CDCl_3$)

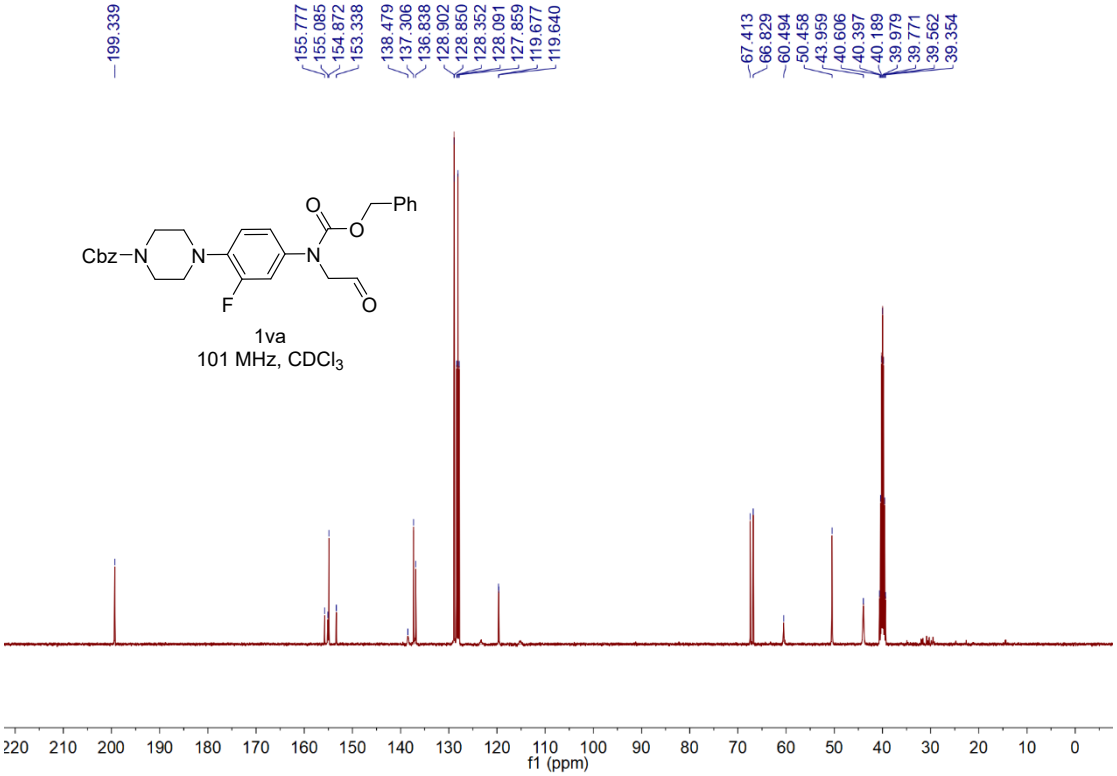


Benzyl 4-(4-(((benzyloxy)carbonyl)(2-oxoethyl)amino)-2-fluorophenyl) piperazine-1-carboxylate (1va)

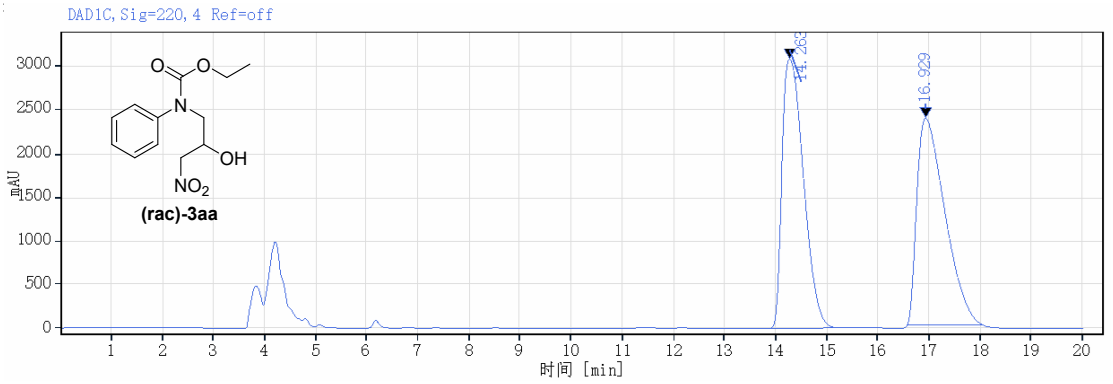
^{1}H NMR of **1va** (400 MHz, $CDCl_3$)



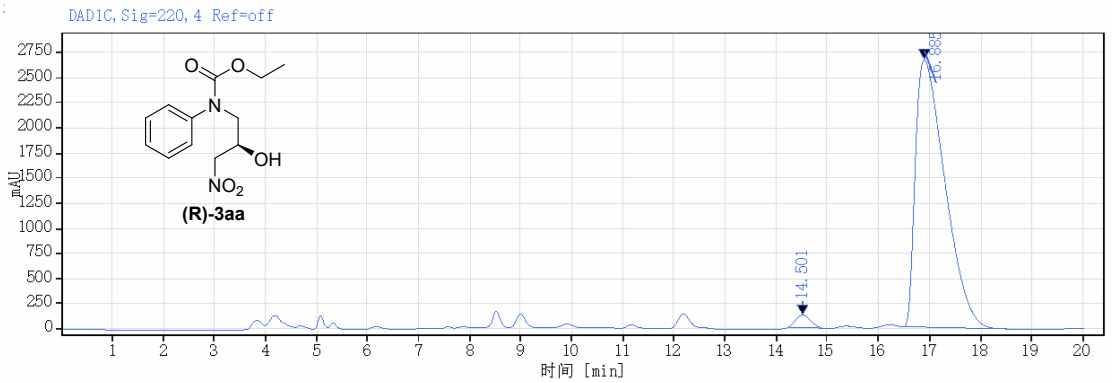
$^{13}C\{^{1}H\}$ NMR of **1va** (100 MHz, $CDCl_3$)



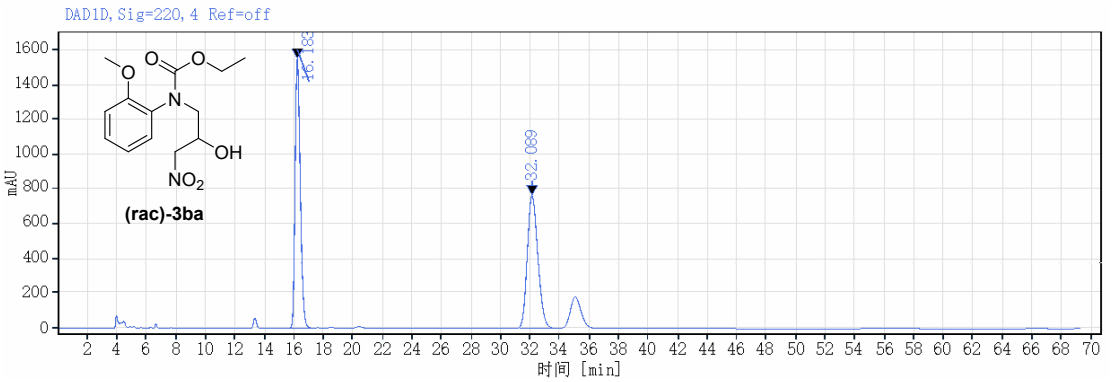
11. HPLC spectra



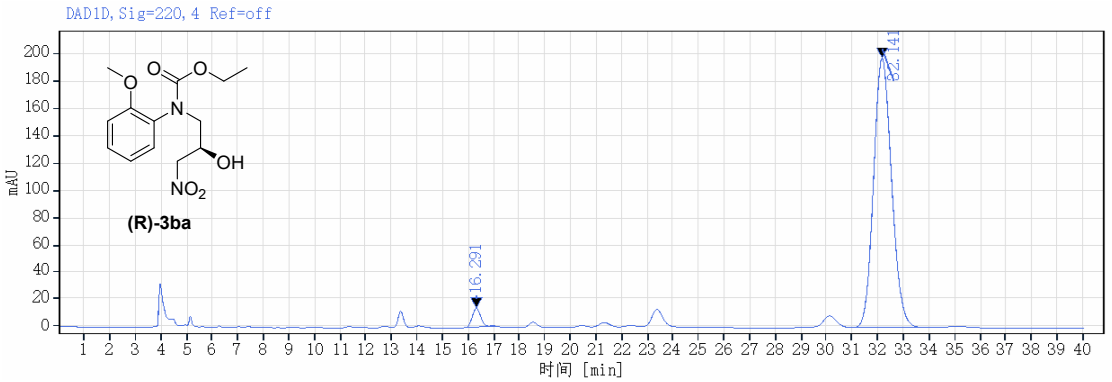
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
14.263	MM m	0.46	90038.19	3086.99	49.83
16.929	MM m	0.60	90646.65	2371.74	50.17



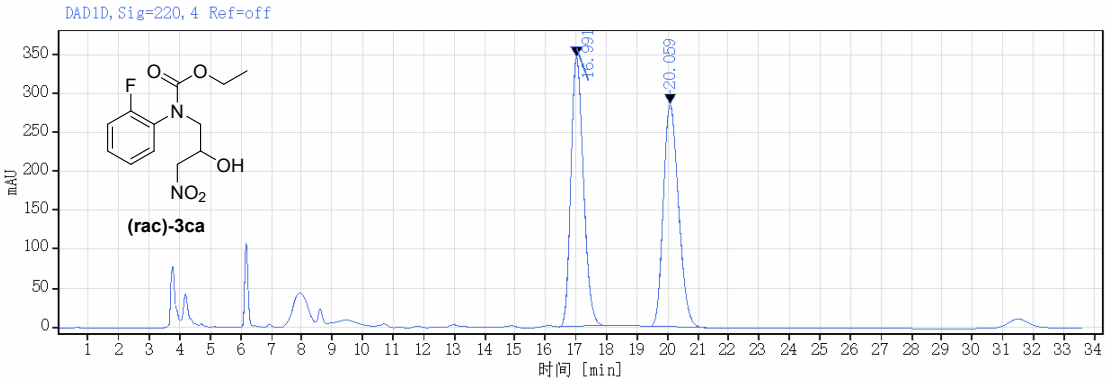
Time [min]	Type	Width [min]	Area [Mau * s]	Height [Mau]	Area%
14.501	MM m	0.33	2491.70	123.49	2.28
16.885	MM m	0.63	106931.46	2658.88	97.72



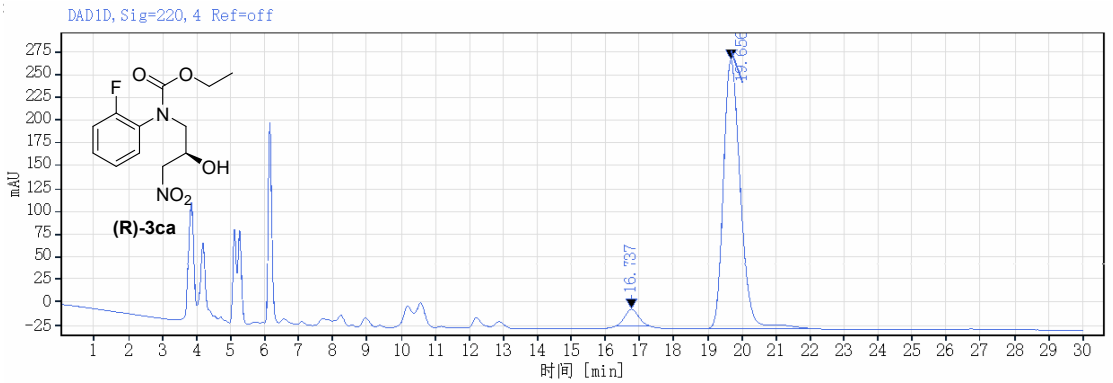
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
16.183	MM m	0.38	37709.09	1549.70	49.97
32.089	MM m	0.77	37757.73	763.83	50.03



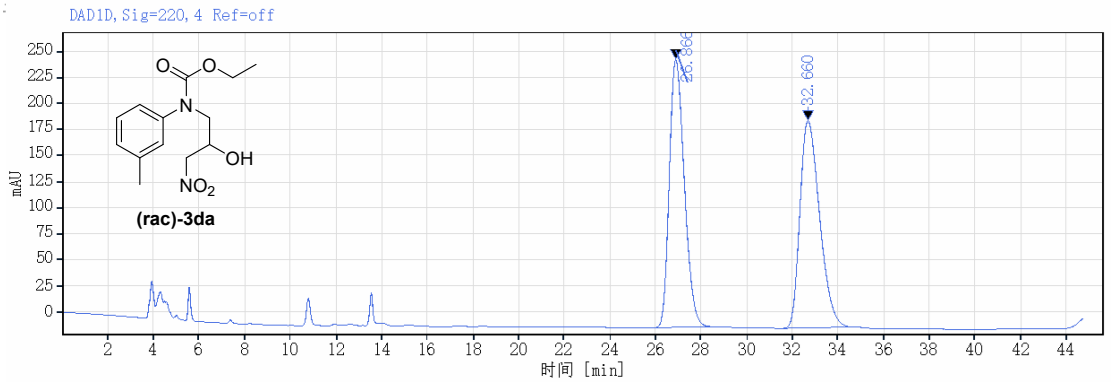
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
16.291	MM m	0.36	311.39	13.48	3.12
32.141	MM m	0.76	9666.55	197.26	96.88



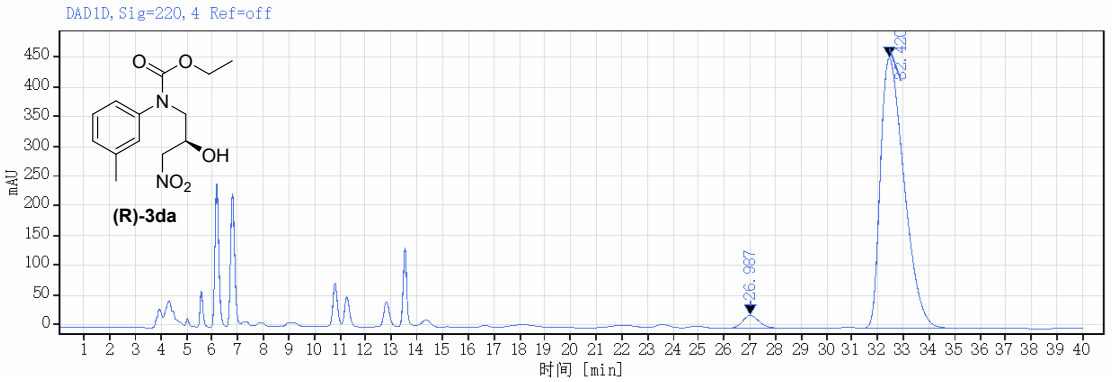
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
16.991	MM m	0.45	9866.44	344.53	50.00
20.059	MM m	0.54	9867.66	284.88	50.00



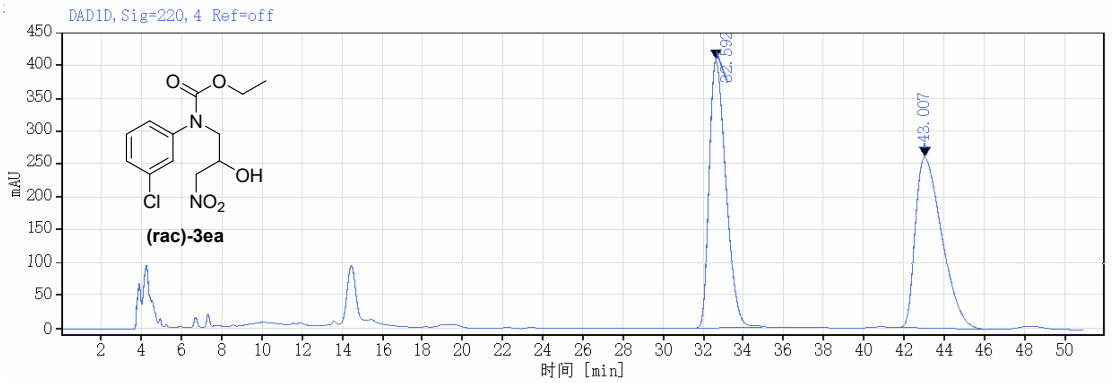
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
16.737	MM m	0.44	522.65	18.35	4.86
19.656	MM m	0.54	10223.25	294.72	95.14



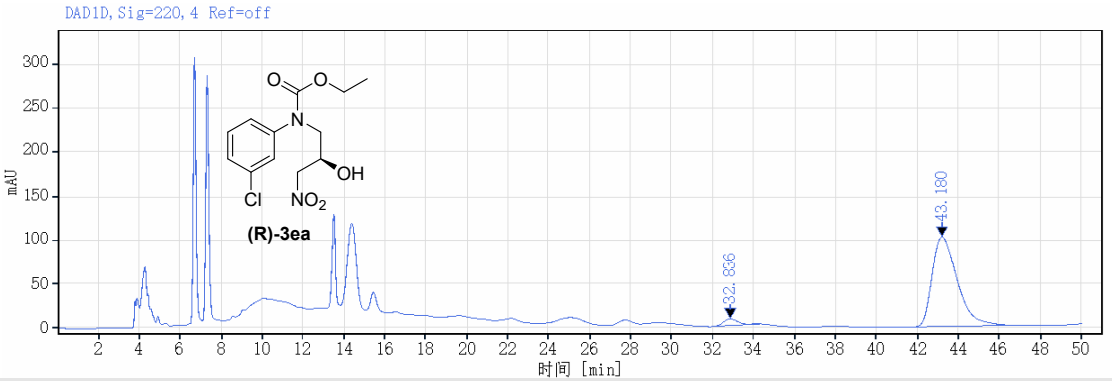
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
26.866	MM m	0.71	11733.86	256.75	49.67
32.660	MM m	0.93	11890.64	198.73	50.33



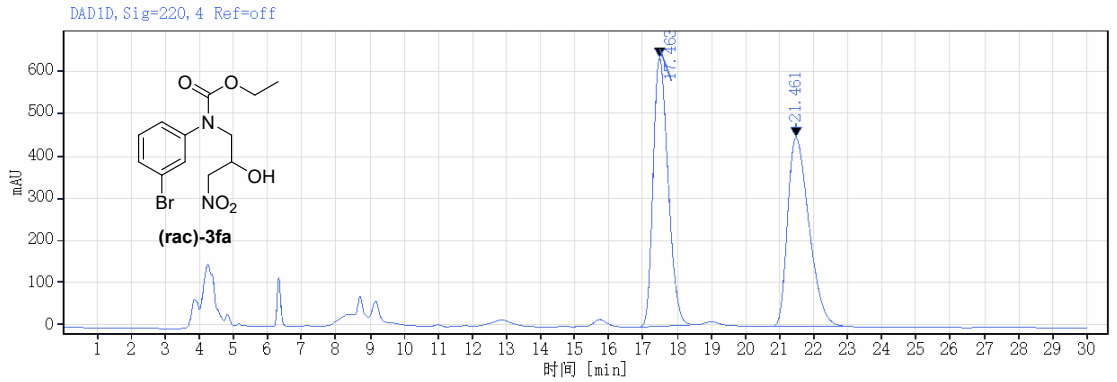
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
26.987	MM m	0.69	946.05	21.34	3.13
32.420	MM m	1.00	29255.13	455.57	96.87



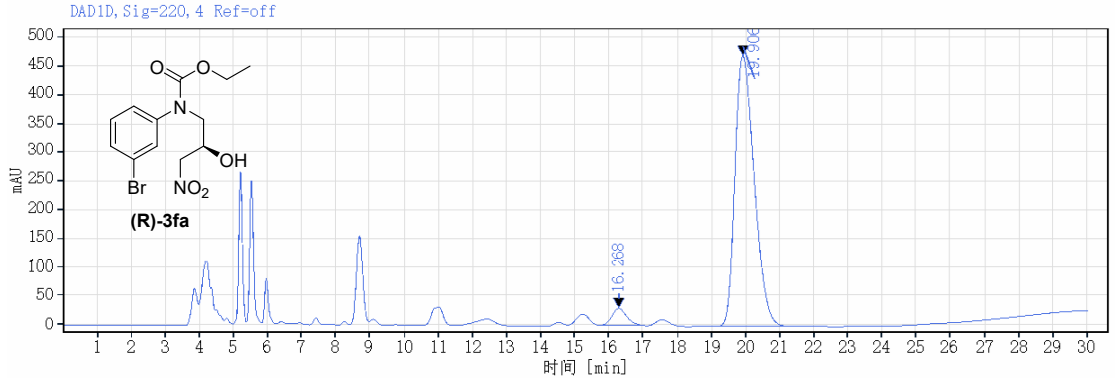
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
32.592	MM m	0.91	23605.50	406.92	49.83
43.007	MM m	1.44	23762.94	258.98	50.17



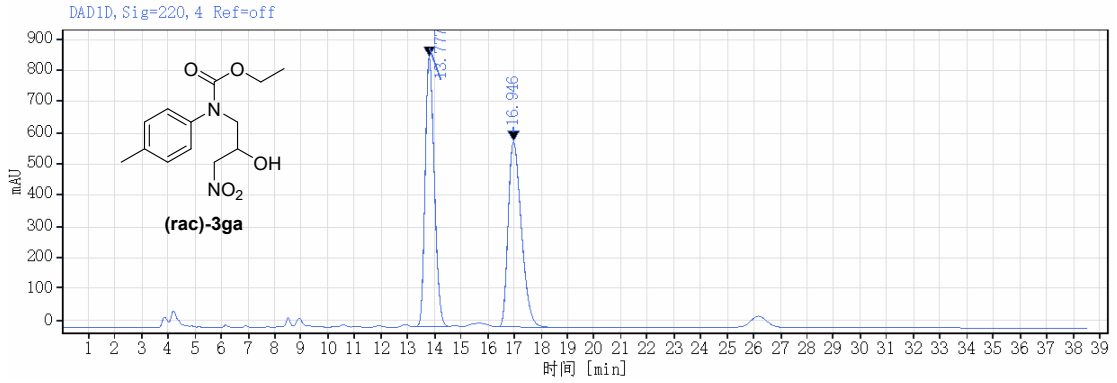
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
32.836	MM m	0.72	365.09	7.39	4.04
43.180	MM m	1.29	8675.63	102.42	95.96



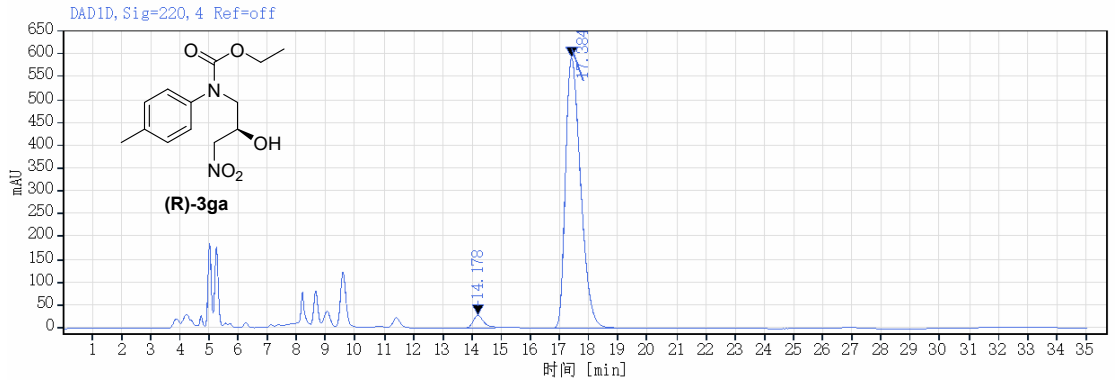
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
17.463	MM m	0.48	19372.90	634.92	49.94
21.461	MM m	0.68	19422.21	447.26	50.06



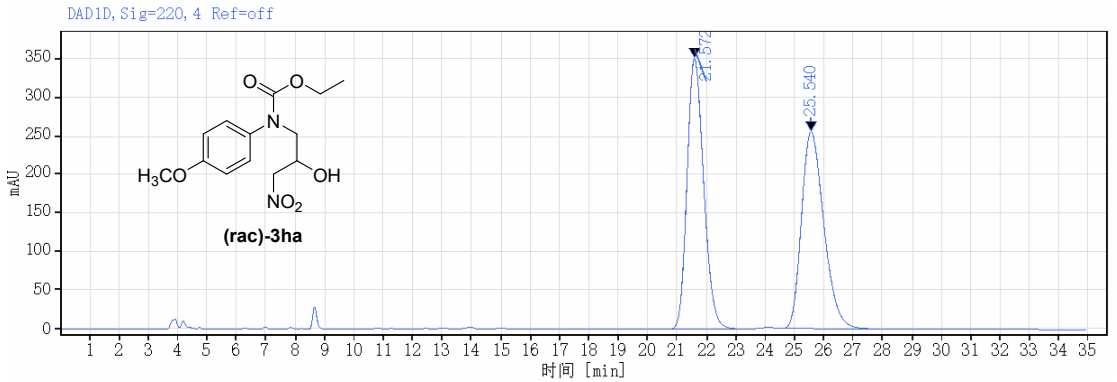
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
16.268	MM m	0.45	827.68	28.76	4.28
19.906	MM m	0.61	18519.70	471.64	95.72



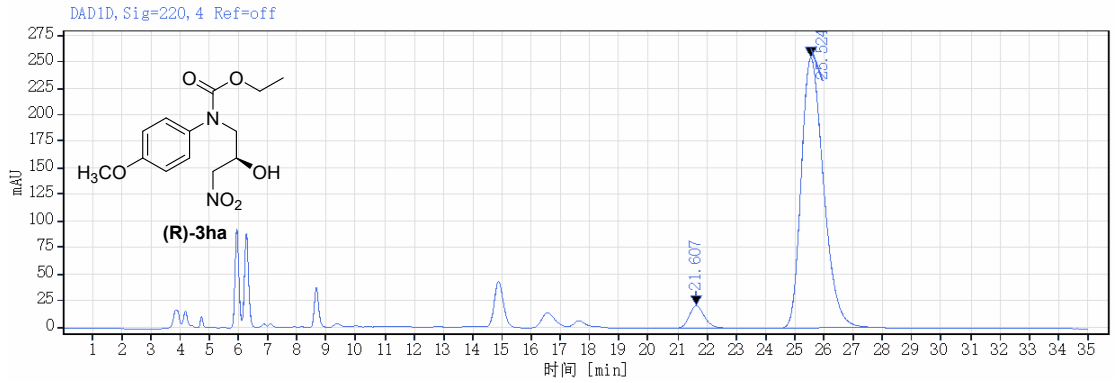
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
13.777	MM m	0.37	20664.34	864.34	50.20
16.946	MM m	0.54	20502.05	594.41	49.80



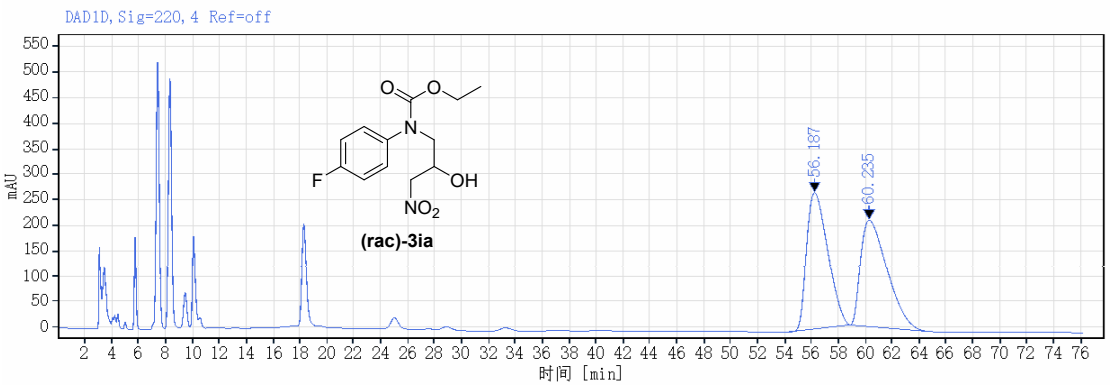
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
14.178	MM m	0.39	703.15	27.61	3.20
17.384	MM m	0.56	21290.10	591.52	96.80



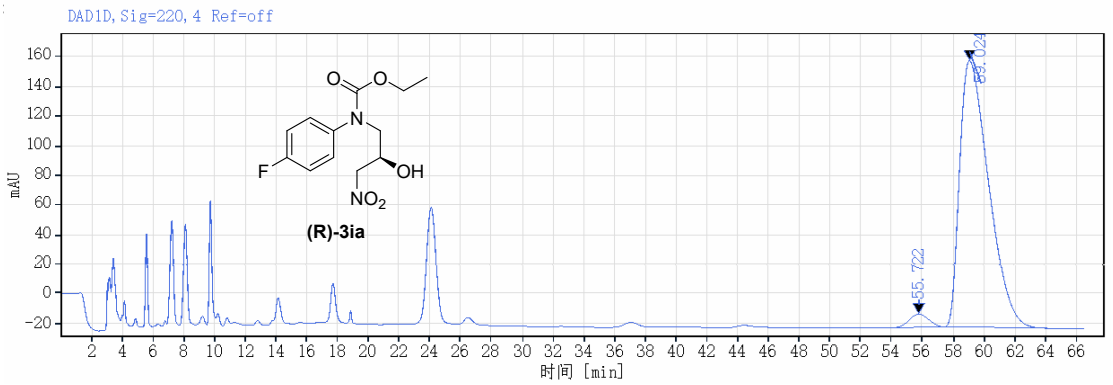
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
21.572	MM m	0.61	13771.76	350.20	50.56
25.540	MM m	0.82	13468.56	255.06	49.44



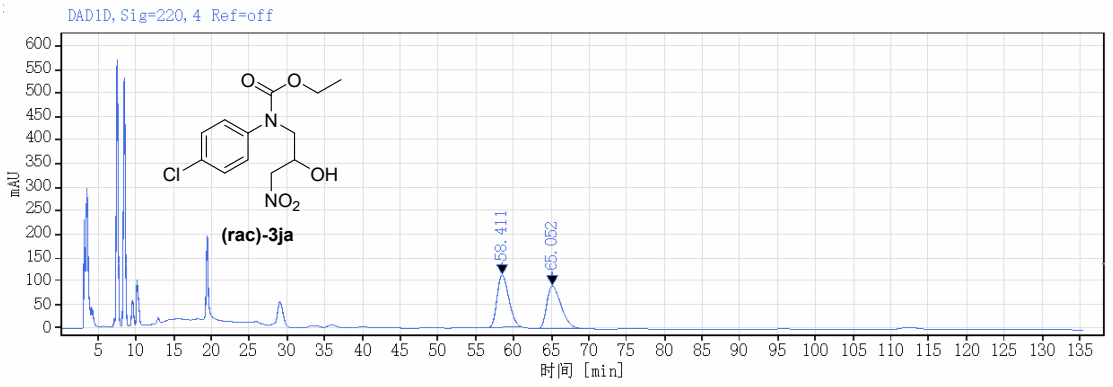
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
21.607	MM m	0.55	752.99	21.03	5.31
25.524	MM m	0.82	13440.54	254.13	94.69



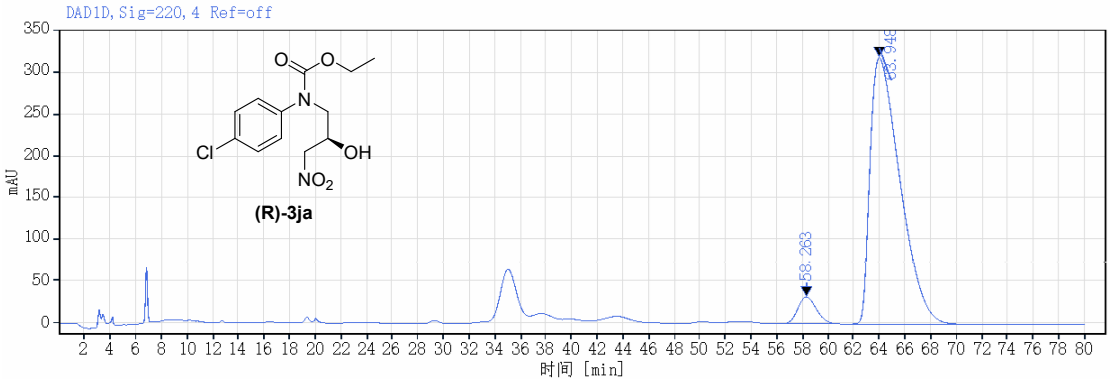
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
56.187	MM m	1.70	29172.06	267.33	50.41
60.235	MM m	2.03	28699.58	209.25	49.59



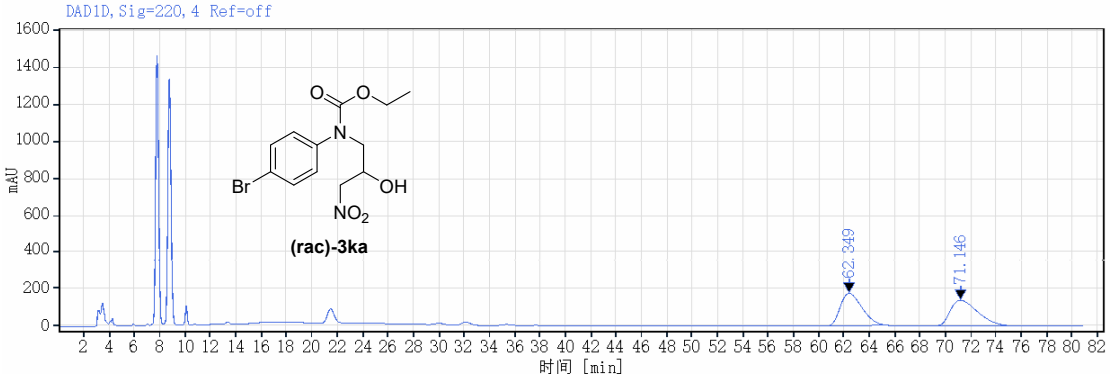
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
55.722	MM m	1.03	748.12	8.65	3.08
59.024	MM m	1.95	23552.23	180.05	96.92



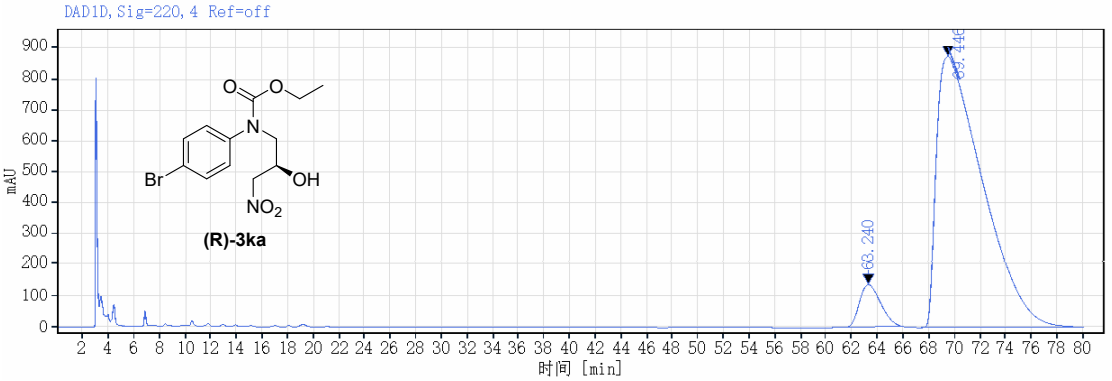
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
58.411	MM m	1.67	11701.24	109.34	49.98
65.052	MM m	1.90	11709.18	89.16	50.02



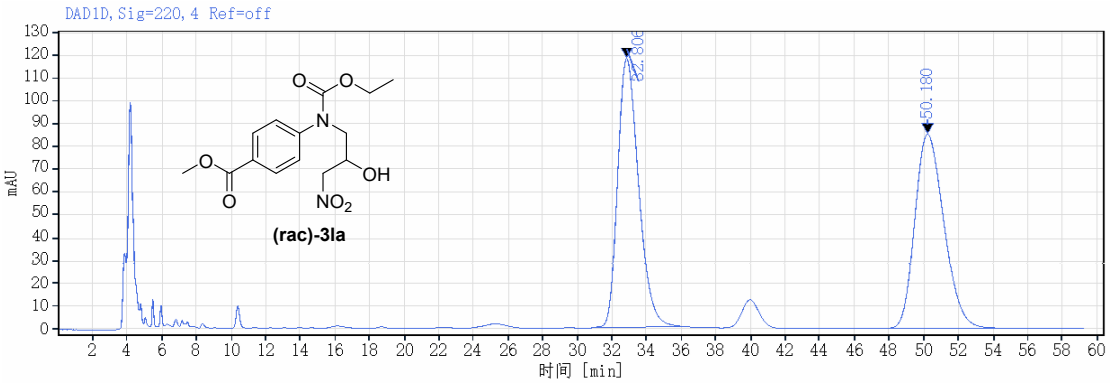
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
58.263	MM m	1.46	3156.04	31.64	5.75
63.948	MM m	2.46	51743.04	319.88	94.25



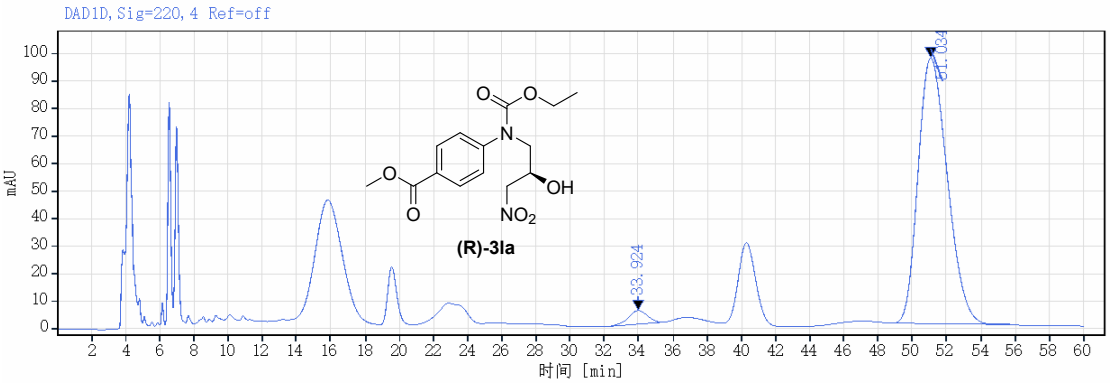
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
62.349	MM m	1.80	20653.05	173.78	49.96
71.146	MM m	2.19	20683.60	137.87	50.04



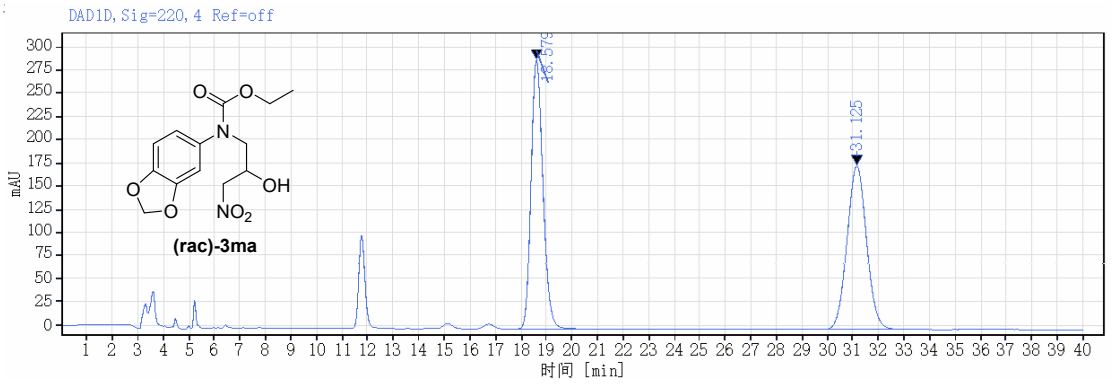
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
63.240	MM m	1.79	15430.45	134.64	6.61
69.446	MM m	3.31	217936.20	875.65	93.39



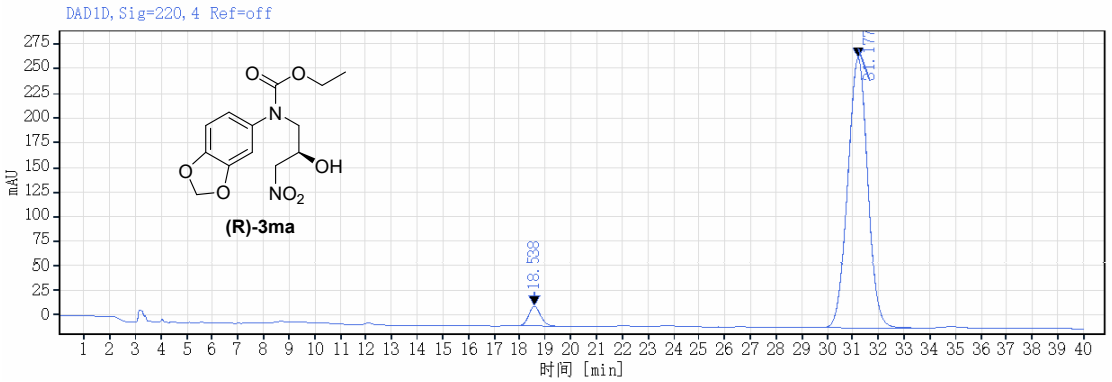
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
32.806	MM m	1.29	9879.94	117.74	49.97
50.180	MM m	1.75	9892.83	85.05	50.03



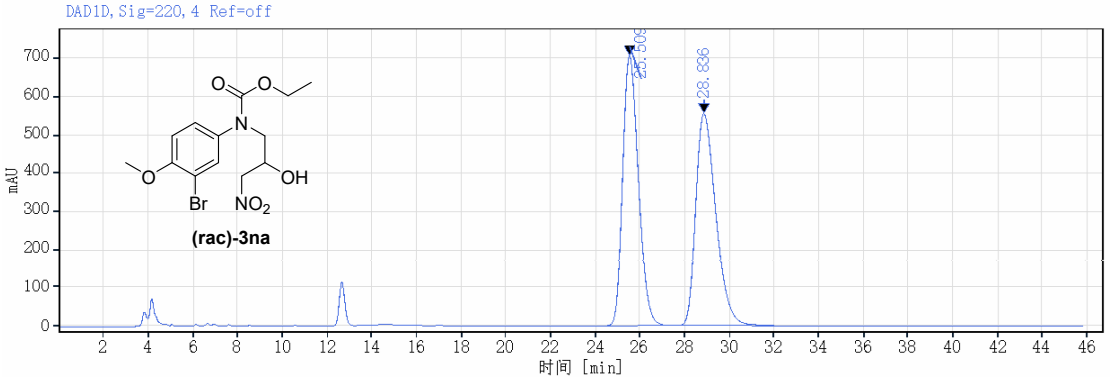
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
33.924	MM m	0.94	384.48	4.92	3.23
51.034	MM m	1.81	11504.01	96.46	96.77



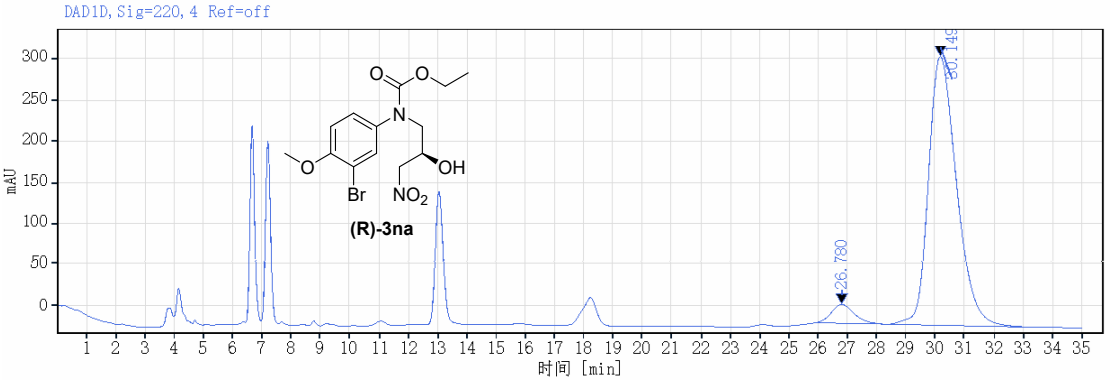
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
18.579	MM m	0.50	9356.84	290.06	49.92
31.125	MM m	0.82	9385.20	176.88	50.08



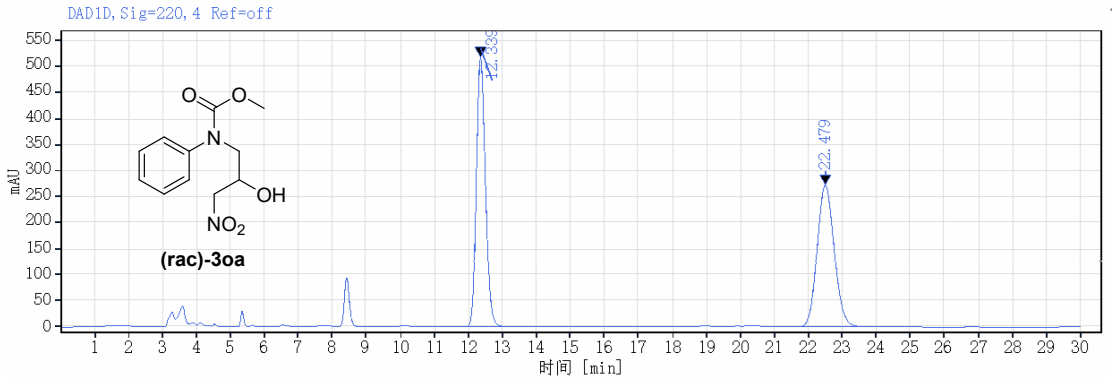
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
18.538	MM m	0.49	627.90	19.62	4.06
31.177	MM m	0.85	14850.09	273.81	95.94



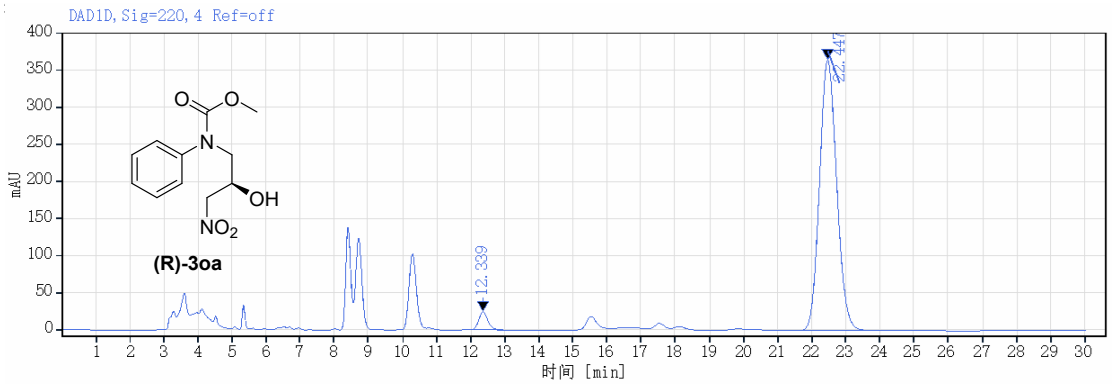
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
25.509	MM m	0.76	34531.15	706.81	49.93
28.836	MM m	0.96	34629.41	554.86	50.07



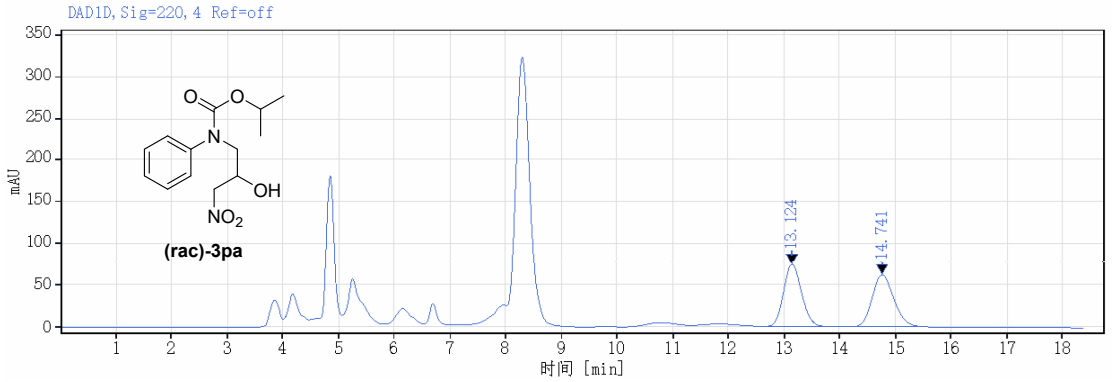
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
26.780	MM m	0.82	1221.76	22.45	5.29
30.149	MM m	1.03	21857.90	327.49	94.71



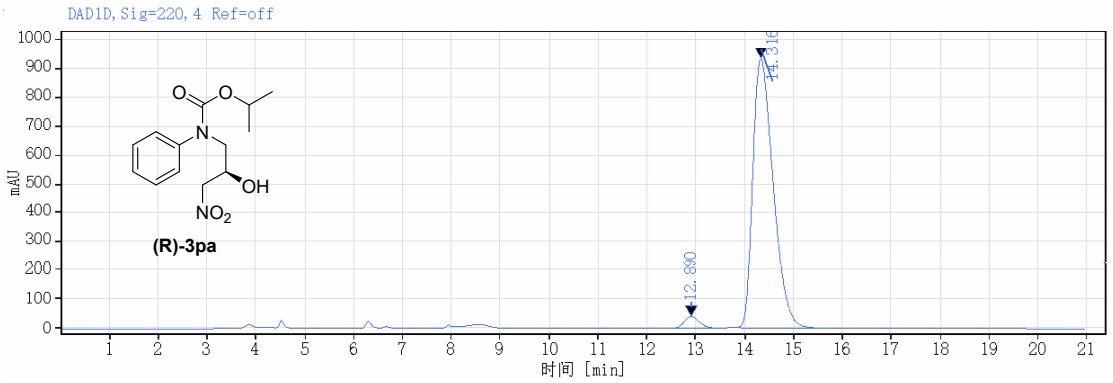
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
12.339	MM m	0.28	9505.44	517.08	50.00
22.479	MM m	0.54	9505.68	272.65	50.00



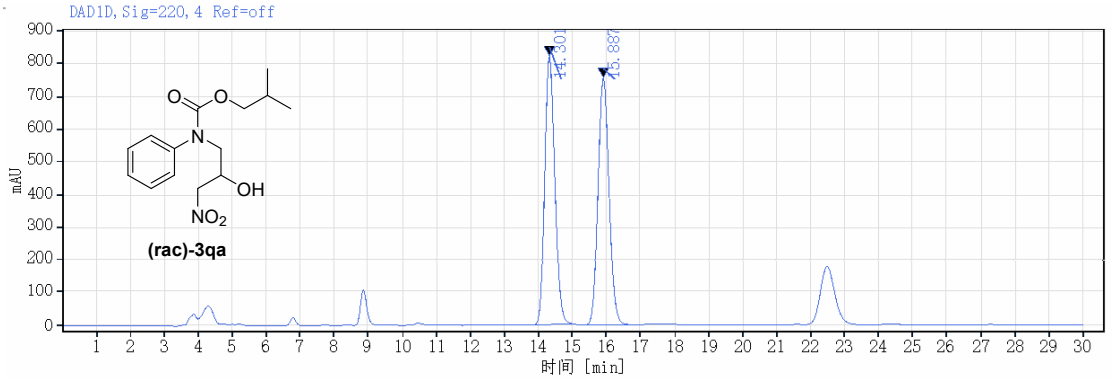
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
12.339	MM m	0.29	444.48	23.95	3.37
22.447	MM m	0.54	12760.75	364.71	96.63



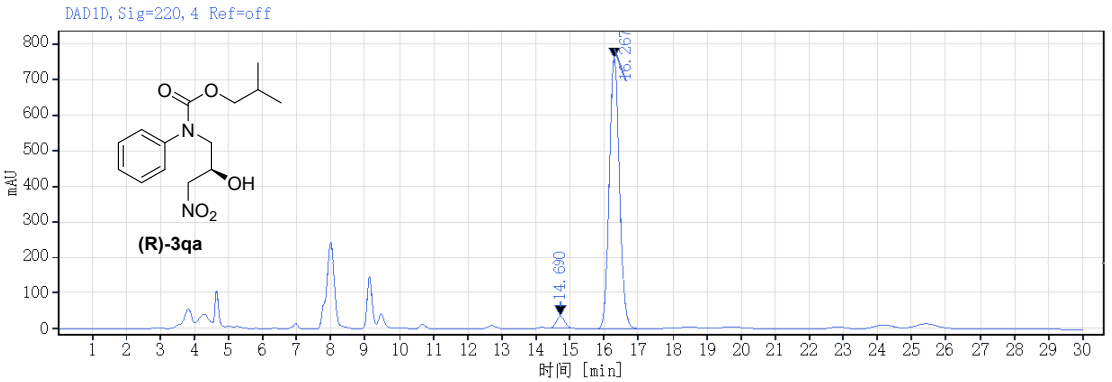
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
13.124	MM m	0.35	1650.02	74.04	50.02
14.741	MM m	0.42	1648.67	61.49	49.98



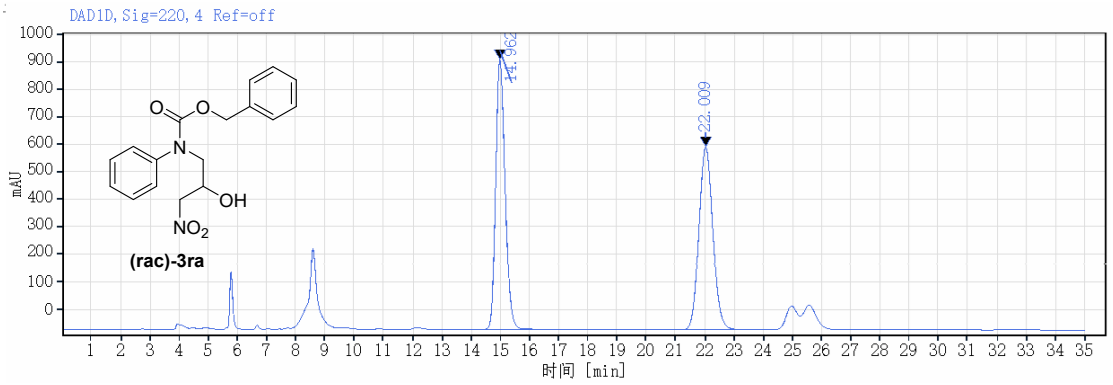
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
12.890	MM m	0.33	855.84	39.93	3.06
14.316	MM m	0.45	27073.89	934.06	96.94



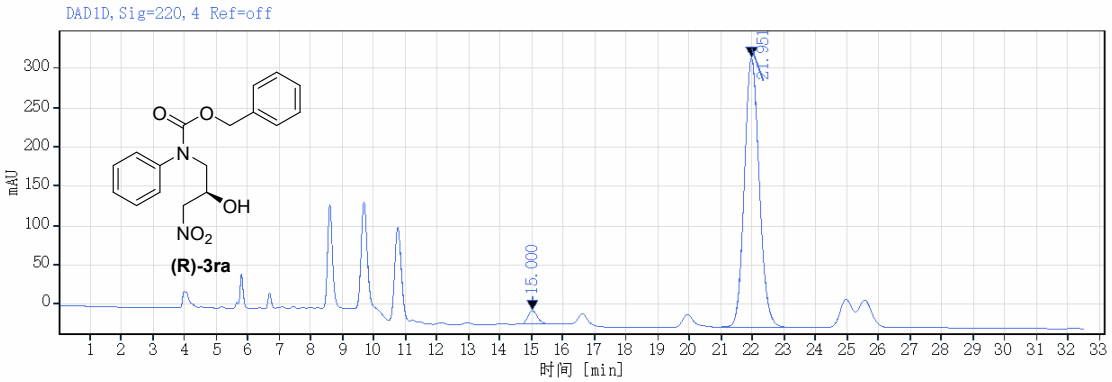
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
14.301	MM m	0.32	16918.19	822.64	49.91
15.887	MM m	0.35	16980.45	756.27	50.09



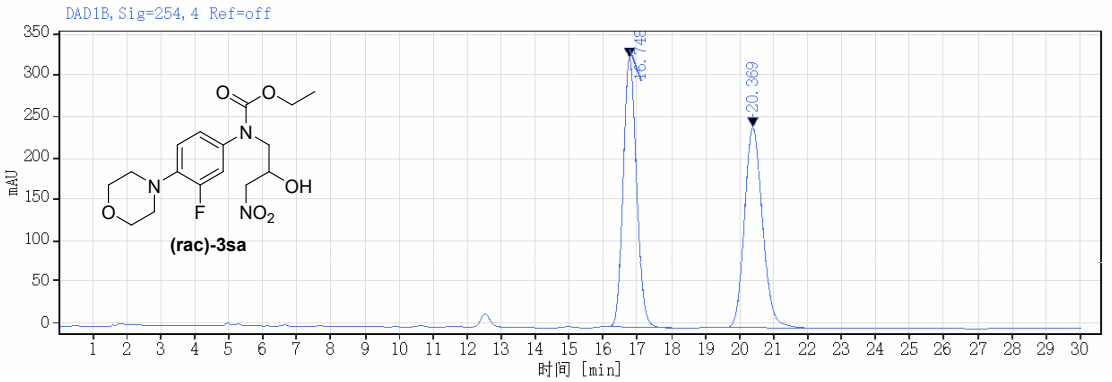
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
14.690	MM m	0.27	584.64	33.40	3.57
16.267	MM m	0.32	15789.92	760.69	96.43



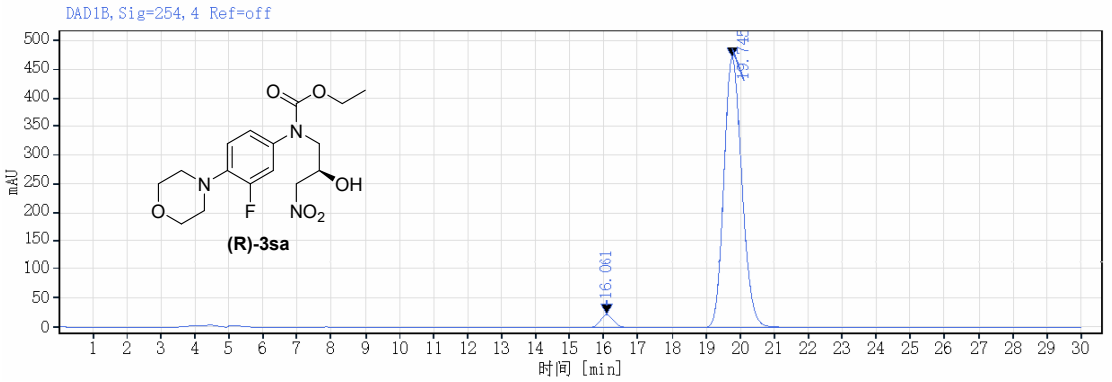
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
14.962	MM m	0.34	21832.34	979.97	49.94
22.009	MM m	0.51	21885.37	664.02	50.06



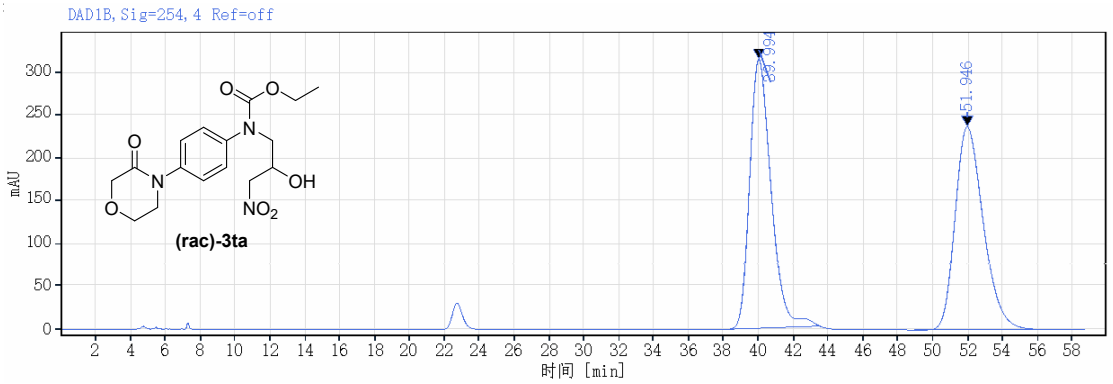
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
15.000	MM m	0.33	357.15	17.05	3.08
21.951	MM m	0.51	11249.89	343.09	96.92



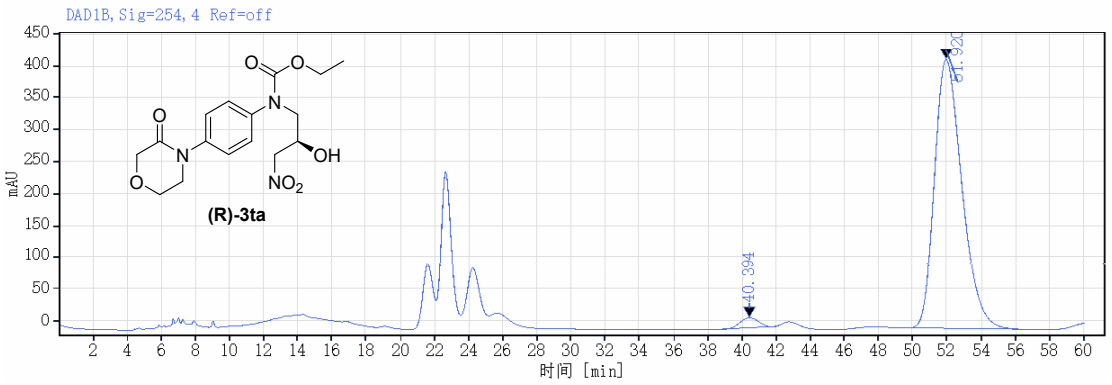
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
16.748	MM m	0.42	8867.21	325.62	49.92
20.369	MM m	0.57	8896.05	242.41	50.08



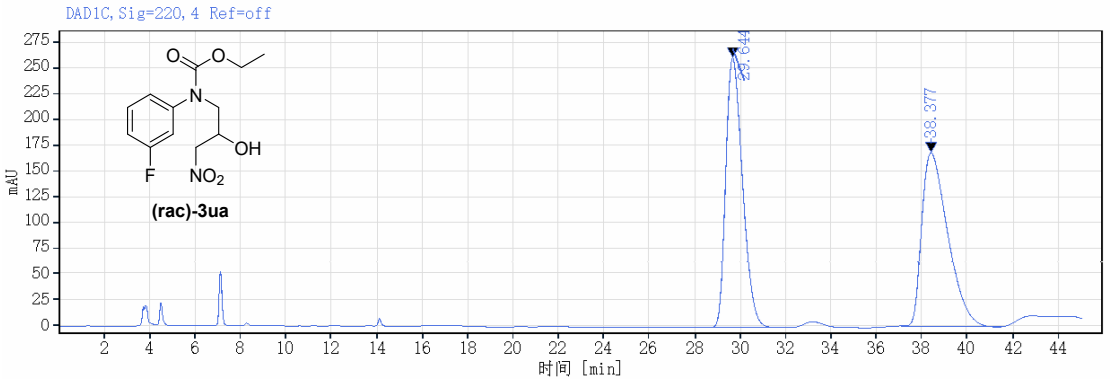
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
16.061	MM m	0.41	565.56	21.40	3.15
19.745	MM m	0.57	17385.10	472.58	96.85



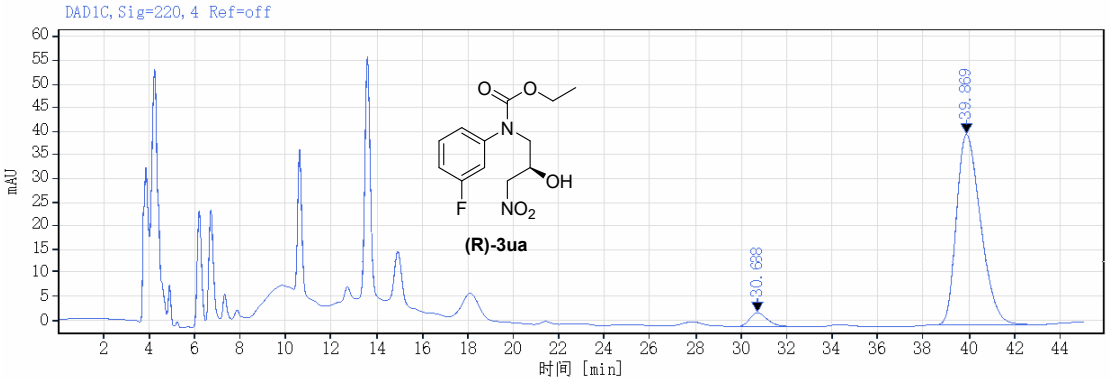
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
39.994	MM m	1.31	26945.46	315.61	50.15
51.946	MM m	1.72	26785.31	238.56	49.85



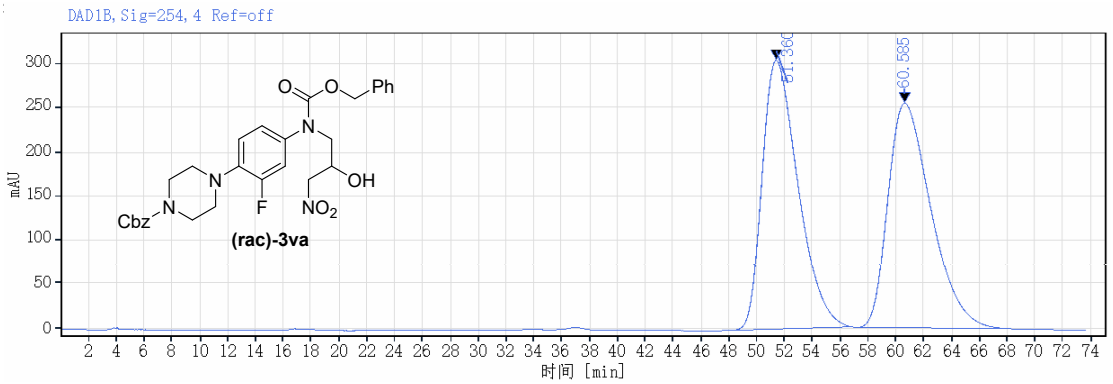
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
40.394	MM m	1.08	1089.61	15.30	2.26
51.920	MM m	1.73	47031.94	420.98	97.74



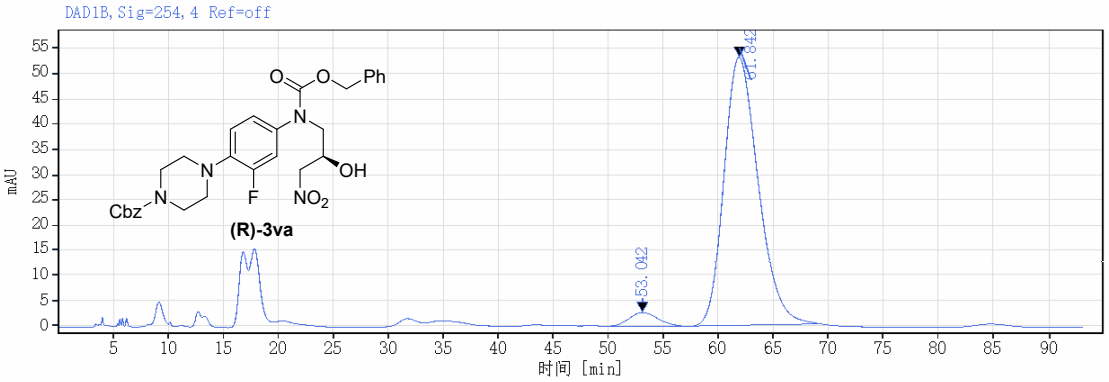
Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
29.644	MM m	0.80	13436.61	262.18	50.09
38.377	MM m	1.21	13388.14	168.81	49.91



Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
30.688	MM m	0.66	157.01	2.91	5.00
39.869	MM m	1.12	2983.67	40.45	95.00



Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
51.360	MM m	2.65	54771.27	305.91	50.01
60.585	MM m	3.02	54756.56	255.56	49.99



Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
53.042	MM m	2.08	469.91	2.64	3.93
61.842	MM m	2.54	11501.01	53.18	96.07

12. References

(1) Jin, W.; Li, X. C.; Huang,Y. B.; Wu, F.; Wan, B. S. *Chem. Eur. J.* **2010**, *16*, 8259-8261.

(2) Khalaj, A.; Nakhjiri, M.; Negahbani, A. S.; Samadizadeh, M.; Firoozpour, L.; Rajabalian, S.; Samadi, N.; Faramarzi, M. A.; Adibpour, N.; Shafiee, A.; Foroumadi, A. *Eur. J. Med. Chem.* **2011,** *46*, 65-70.

(3) Piccionello, A. P.; Pierro, P.; Accardo, A.; Buscemi, S.; Pace, A. *RSC Adv.* **2013**, *3*, 24946-24951.

(4) Drabina, P.; Feixova, V.; Sedlak, M. *Tetrahedron Lett.* **2019**, *60*, 99-101.