SUPPORTING INFORMATION

Chimeric Agents Derived from the Functionalized Amino Acid, Lacosamide, and α-AminoAmide, Safinamide: Evaluation of their Inhibitory Actions on Voltage-gated Sodium Channels, and Antiseizure and Anti-nociception Activities and Comparison with Lacosamide and Safinamide

Ki Duk Park,[1,a] Xiao-Fang Yang,[2] Erik T. Dustrude,[3] Yuying Wang,[2] Matthew S. Ripsch,[4] Fletcher A. White,[4] Rajesh Khanna,[2,*] and Harold Kohn[1,5,6,*]

From the [1]Division of Chemical Biology and Medicinal Chemistry, UNC Eshelman School of Pharmacy and the [6]Department of Chemistry, University of North Carolina, Chapel Hill, NC 27599, United States

[2]Department of Pharmacology, College of Medicine, University of Arizona, Tucson, Arizona 85742, United States

[3]Program in Medical Neuroscience, Paul and Carole Stark Neurosciences Research Institute, [4]Department of Anesthesia, Indiana University School of Medicine, Indianapolis, IN 46202

[5]NeuroGate Therapeutics, Inc., 150 Fayetteville Street, Suite 2300, Raleigh, NC 27601

*Corresponding authors

Table S1. Elemental Analyses for New Compounds

Cmpd	Molecular Formula	Calculated (%)	Found (%)
(*R*)-**7**	$C_{20}H_{23}ClN_2O_4$	C, 61.46; H, 5.93; Cl, 9.07; N, 7.17	C, 61.55; H, 5.97; Cl, 8.89; N, 7.17
(*R*)-**8**	$C_{20}H_{23}ClN_2O_4$	C, 61.46; H, 5.93; Cl, 9.07; N, 7.17	C, 61.75; H, 5.86; Cl, 9.15; N, 7.11
(*R*)-**9**	$C_{21}H_{23}F_3N_2O_5$	C, 57.27; H, 5.26; F, 12.94; N, 6.36	C, 57.08; H, 5.20; F, 12.88; N, 6.30
(*R*)-**10**	$C_{21}H_{23}F_3N_2O_5$	C, 57.27; H, 5.26; F, 12.94; N, 6.36	C, 57.35; H, 5.28; F, 12.78; N, 6.38
(*R*)-**25**	$C_{22}H_{27}ClN_2O_5$	C, 60.76; H, 6.26; Cl, 8.15; N, 6.44	C, 60.79; H, 6.29; Cl, 7.98; N, 6.40
(*R*)-**26**	$C_{22}H_{27}ClN_2O_5$	C, 60.76; H, 6.26; Cl, 8.15; N, 6.44	C, 60.85; H, 6.31; Cl, 8.06; N, 6.40
(*R*)-**27**	$C_{23}H_{27}F_3N_2O_6$	C, 57.02; H, 5.62; F, 11.76; N, 5.78	C, 57.06; H, 5.61; F, 11.65; N, 5.75
(*R*)-**28**	$C_{23}H_{27}F_3N_2O_6$	C, 57.02; H, 5.62; F, 11.76; N, 5.78	C, 57.10; H, 5.68; F, 11.63; N, 5.76
(*R*)-**29**	$C_{23}H_{29}ClN_2O_5$	C, 61.53; H, 6.51; Cl, 7.90; N, 6.24	C, 61.67; H, 6.57; Cl, 7.73; N, 6.32
(*R*)-**30**	$C_{23}H_{29}ClN_2O_5$	C, 61.53; H, 6.51; Cl, 7.90; N, 6.24	C, 61.26; H, 6.47; Cl, 7.80; N, 6.17
(*R*)-**31**	$C_{24}H_{29}F_3N_2O_6$	C, 57.83; H, 5.86; F, 11.43; N, 5.62	C, 57.74; H, 5.92; F, 11.18; N, 5.58
(*R*)-**32**	$C_{24}H_{29}F_3N_2O_6$	C, 57.83; H, 5.86; F, 11.43; N, 5.62	C, 58.00; H, 5.95; F, 11.32; N, 5.56

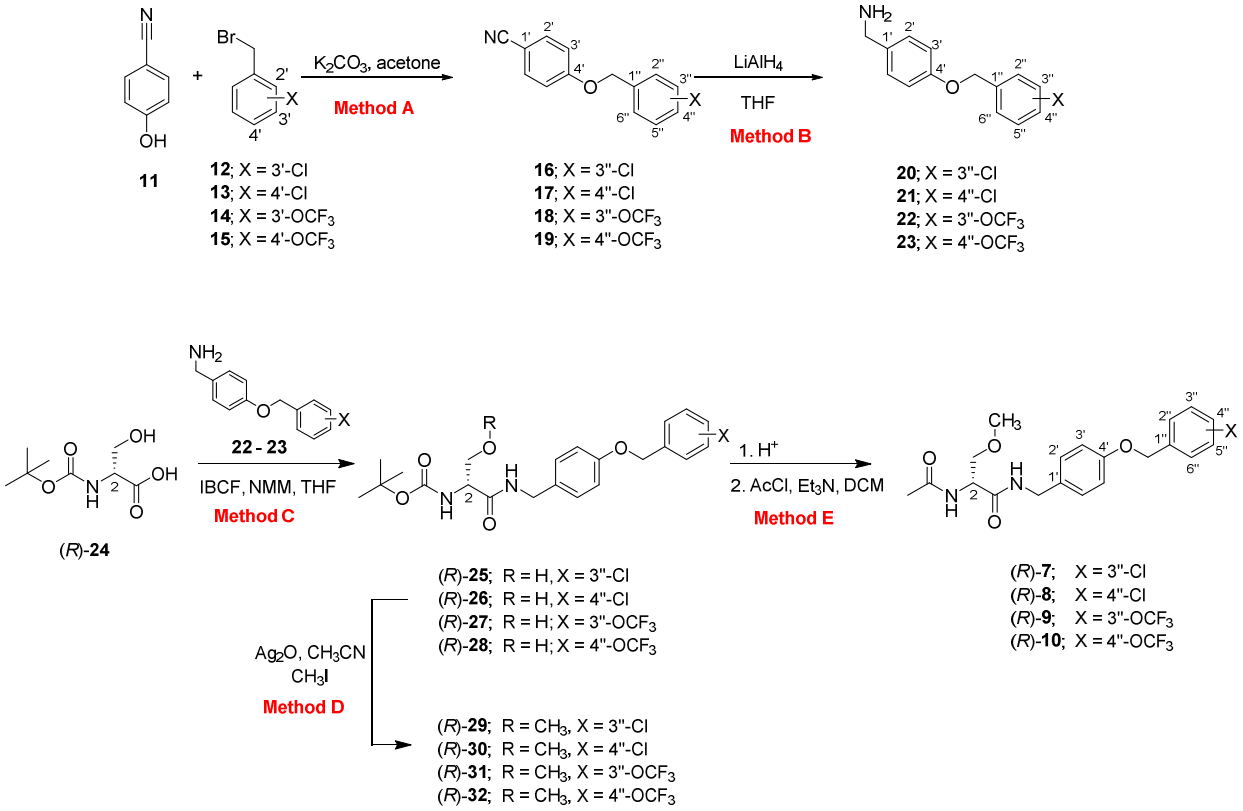
Table S2. High Mass Spectrometry (ESI^+)

Cmpd	Molecular Formula	Found	Calculated
(*R*)-**16**	$C_{14}H_{10}ClNO$	266.0357 $[M + Na]^+$	266.0349
(*R*)-**17**	$C_{14}H_{10}ClNO$	Not observed	266.0349
(*R*)-**18**	$C_{15}H_{10}F_3NO_2$	316.0573 $[M + Na]^+$	316.0561
(*R*)-**19**	$C_{15}H_{10}F_3NO_2$	316.0549 $[M + Na]^+$	316.0561
(*R*)-**20**	$C_{14}H_{14}ClNO$	270.0666 $[M + Na]^+$	270.0662
(*R*)-**21**	$C_{14}H_{14}ClNO$	248.0863 $[M + H]^+$	248.0842
(*R*)-**22**	$C_{15}H_{14}F_3NO_2$	298.1070 $[M + H]^+$	298.1055
(*R*)-**23**	$C_{15}H_{14}F_3NO_2$	298.1034 $[M + H]^+$	298.1055

EXPERIMENTAL SECTION

General Methods. Melting points were determined in open capillary tubes using a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra (IR) were run on an ATI Mattson Genesis FT-IR spectrometer. Absorption values are expressed in wavenumbers (cm^{-1}). Optical rotations were obtained on a Jasco P-1030 polarimeter at the sodium D line (589 nm) using a 1 dm path length cell. NMR spectra were obtained at 400 MHz (^{1}H) and 100 MHz (^{13}C) using TMS as an internal standard. Chemical shifts (δ) are reported in parts per million (ppm) from tetramethylsilane. Low-resolution mass spectra were obtained with a BioToF-II-Bruker Daltonics spectrometer by Dr. S. Habibi at the University of North Carolina Department of Chemistry. The high-resolution mass spectrum was performed on a Bruker Apex-Q 12 Telsa FTICR spectrometer by Dr. S. Habibi. Microanalyses were performed by Atlantic Microlab, Inc. (Norcross, GA). Reactions were monitored by analytical thin-layer chromatography (TLC) plates (Aldrich, Cat # Z12272-6) and analyzed with 254 nm light. The reactions were purified by flash column chromatography using silica gel (Dynamic Adsorbents Inc., Cat # 02826-25). All chemicals and solvents were reagent grade and used as obtained from commercial sources without further purification. Yields reported are for purified products and were not optimized. Compounds were checked by TLC, ^{1}H and ^{13}C NMR, MS, and elemental analyses. The analytical results are within ±0.40% of the theoretical value. The TLC, NMR and the analytical data confirmed the purity of the products was ≥95%.

Scheme 1. Synthesis of (*R*)-**7** - (*R*)-**10**



General Procedure for the Preparation of 4-(Benzyloxy)benzonitrile Derivatives (Method A). A mixture of the desired benzylbromide (5–10 g), 4-cyanophenol (**11**) (1.0–1.2 equiv) and K_2CO_3 (4.0 equiv) was heated in acetone (200–400 mL) at reflux (5 h). The volatiles were evaporated and the residue was diluted in CH_2Cl_2 (300 mL), and then washed with H_2O (2×300 mL), dried (Na_2SO_4), and concentrated in vacuo to give the product as either a white solid or clear oil that was used without further purification.

General Procedure for the Preparation (4-(Benzyloxy)phenyl)methanamine Derivatives (Method B). A THF (30 mL) solution of the 4-(benzyloxy)benzonitrile derivative (5–10 g) was

added dropwise to a $LiAlH_4$ (3.0 equiv) suspension in THF (400 mL) at 0 °C. The mixture was stirred at room temperature (16 h) and H_2O (4 mL) was added dropwise at 0 °C followed by an aqueous NaOH solution (2 mL, 15% w/w), and then H_2O (4 mL). The mixture was stirred at room temperature (2 h), and the precipitate filtered over a Celite® pad and washed with either CH_2Cl_2 or EtOAc. The combined filtrates were concentrated in vacuo to obtain the desired product that was used without further purification.

General Procedure for the Mixed Anhydride Coupling Reaction (Method C). To a cooled anhydrous THF solution (–78 °C, dry ice acetone bath) of (*R*)-*t*-Boc-D-serine ((*R*)-**24**) ([C] ~ 0.1 M) were successively added *N*-methylmorpholine (NMM) (1.0–1.5 equiv), stirred for 2 min, isobutylchloroformate (IBCF) (1.1–1.3 equiv), stirred for 5 min, and then the desired benzylamine (1.0–1.2 equiv) in anhydrous THF. Upon addition the reaction mixture was allowed to warm to room temperature and further stirred (2–3 h). The salts were filtered over a Celite® pad and rinsed with THF and the filtrate was concentrated in vacuo. The residue obtained was purified by column chromatography on SiO_2 giving the desired product as a white solid.

General Procedure for the Preparation of (*R*)-Substituted *N*-Benzyl 2-*N*-(*tert.*-Butoxycarbonyl)amino-3-methoxypropionamide Derivatives (Method D). To a CH_3CN solution of the 2-*N*-(*tert.*-butoxycarbonyl)amino-3-hydroxypropionamide derivative ([C] ~0.05–0.5 M) was successively added Ag_2O (5 equiv) and MeI (10 equiv) at room temperature. The reaction mixture was vigorously stirred at room temperature (2–3 d) under Ar while kept in the dark and then filtered through Celite® pad and the filtrate evaporated in vacuo. The residue was purified by column chromatography on SiO_2 to give the desired product.

General Procedure for the Deprotection and Acetylation of (*R*)-Substituted *N*-Benzyl 2-*N*-(*tert.*-Butoxycarbonyl)amino-3-methoxypropionamide Derivatives (Method E). A CH_2Cl_2 solution (0.1–0.3 M) of the *N*-(*tert.*-butoxycarbonyl compound was treated with 4 M HCl in dioxane (3–4 equiv) at room temperature (2–12 h). The reaction mixture was evaporated in vacuo. The resulting residue was dissolved in CH_2Cl_2 (0.1–0.3 M) and then triethylamine (2–3 equiv) and acetyl chloride (1.0–1.2 equiv) were carefully added at 0 °C and the resulting solution was stirred at room temperature (2–16 h). The resulting solution was washed with an aqueous 10% citric acid solution followed by a saturated $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 and/or recrystallized with EtOAc/hexanes.

Preparation of 4-(3'-Chlorobenzyloxy)benzonitrile[1] (16). Using Method A, 3-(chloro)benzylbromide (**12**) (9.00 g, 43.8 mmol), 4-cyanophenol (**11**) (6.26 g, 52.6 mmol) and K_2CO_3 (24.21 g, 175.2 mmol) gave **16** as a white solid (10.43 g, 98%): R_f = 0.45 (hexanes/EtOAc 9/1); mp 88-89 °C (lit.[1] mp 91 °C); IR (nujol) 2927, 2860, 2215, 1596, 1462, 1376, 1297, 1247, 1092, 997, 906, 833, 728 cm^{-1}; ^1H NMR (DMSO-d_6) δ5.23 (s, C**H$_2$**O), 7.18–7.22 (m, 2 Ar**H**), 7.42–7.54 (m, 4 Ar**H**), 7.77–7.81 (m, 2 Ar**H**); ^{13}C NMR (DMSO-d_6) δ68.7 (**C**H_2O), 103.2, 115.8 (Ar**C**), 119.0 (**C**N), 126.2, 127.4, 128.0, 130.4, 133.2, 134.2, 138.7, 161.5 (Ar**C**); HRMS (ESI^+) 266.0357 $[M + Na]^+$ (calcd for $C_{14}H_{10}ClNONa^+$ 266.0349).

Preparation of 4-(4'-Chlorobenzyloxy)benzonitrile[1] (17). Using Method A, 4-(chloro)benzylbromide (**13**) (10.00 g, 48.7 mmol), **11** (6.96 g, 58.4 mmol) and K_2CO_3 (26.92 g, 194.8 mmol) gave **17** as a white solid (11.60 g, 98%): R_f = 0.45 (hexanes/EtOAc 9/1); mp 99-100

°C (lit.[1] mp 101 °C); IR (nujol) 2923, 2865, 2212, 1587, 1469, 1368, 1282, 1102, 987, 838, 722 cm^{-1}; ^1H NMR (DMSO-d_6) δ5.22 (s, C**H$_2$**O), 7.19 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.42–7.56 (m, 4 Ar**H**), 7.78 (d, *J* = 8.0 Hz, 2 Ar**H**); ^{13}C NMR (DMSO-d_6) δ68.8 (**C**H_2O), 103.2, 115.8 (Ar**C**), 119.0 (**C**N), 128.5, 129.6, 132.7, 134.1, 135.1, 161.5 (Ar**C**); HRMS (ESI^+) no signal detected.

Preparation of 4-(3'-Trifluoromethoxybenzyloxy)benzonitrile (18). Using Method A, 3-(trifluoromethoxy)benzylbromide (**14**) (5.00 g, 19.6 mmol), **11** (2.80 g, 23.5 mmol) and K_2CO_3 (10.84 g, 78.4 mmol) gave **18** as a clear oil (5.65 g, 98%): R_f = 0.45 (hexanes/EtOAc 9/1); IR (nujol) 2927, 2854, 2216, 1598, 1463, 1384, 1252, 1175, 942, 841, 726 cm^{-1}; ^1H NMR (DMSO-d_6) δ5.29 (s, C**H$_2$**O), 7.21 (d, *J* = 8.8 Hz, 2 Ar**H**), 7.35 (d, *J* = 7.6 Hz, 1 Ar**H**), 7.48–7.58 (m, 3 Ar**H**), 7.80 (d, *J* = 8.8 Hz, 2 Ar**H**); ^{13}C NMR (DMSO-d_6) δ68.6 (**C**H_2O), 103.3, 115.9 (Ar**C**), 119.0 (**C**N), 120.1 (d, *J* = 254.9 Hz, O**C**F_3), 120.1, 120.5, 126.7, 130.6, 134.2, 139.0, 148.5, 161.5 (Ar**C**); HRMS (ESI^+) 316.0573 $[M + Na]^+$ (calcd for $C_{15}H_{10}F_3NO_2Na^+$ 316.0561).

Preparation of 4-(4'-Trifluoromethoxybenzyloxy)benzonitrile (19). Using Method A, 4-(trifluoromethoxy)benzylbromide (**15**) (5.00 g, 19.6 mmol), **11** (2.80 g, 23.5 mmol) and K_2CO_3 (10.84 g, 78.4 mmol) gave **19** as a white solid (5.49 g, 96%): R_f = 0.45 (hexanes/EtOAc 9/1); mp 48-49 °C (lit.[2] mp 59-61 °C); IR (nujol) 2921, 2860, 2219, 1601, 1505, 1457, 1378, 1258, 1171, 1031, 923, 835, 716 cm^{-1}; ^1H NMR (DMSO-d_6) δ5.26 (s, C**H$_2$**O), 7.21 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.41 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.61 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.80 (d, *J* = 8.4 Hz, 2 Ar**H**); ^{13}C NMR (DMSO-d_6) δ 68.7 (**C**H_2O), 103.2, 115.8 (Ar**C**), 119.0 (**C**N), 120.1 (d, *J* = 254.2 Hz, O**C**F_3), 121.1, 129.7, 134.2, 135.7, 148.0, 161.6 (Ar**C**); HRMS (ESI^+) 316.0549 $[M + Na]^+$ (calcd for $C_{15}H_{10}F_3NO_2Na^+$ 316.0561).

Preparation of (4-(3'-Chlorobenzyloxy)phenyl)methanamine (20). Using Method B, 4-(3'-chlorobenzyloxy)benzonitrile (**16**) (10.00 g, 41.0 mmol) and $LiAlH_4$ (4.67 g, 123.1 mmol) gave **20** as a white solid (8.04 g, 79%): R_f = 0.00 (hexanes/EtOAc 9/1); mp 55-56 °C; IR (nujol) 3355, 3262, 2919, 2860, 1605, 1510, 1464, 1378, 1299, 1241, 1173, 1075, 922, 839, 788 cm^{-1}; ^1H NMR (DMSO-d_6) δ1.73 (br s, N**H**$_2$), 3.65 (s, $NH_2C\mathbf{H}_2$), 5.23 (s, C**H**$_2$O), 6.94 (d, J = 8.4 Hz, 2 Ar**H**), 7.24 (d, J = 8.4 Hz, 2 Ar**H**), 7.36–7.50 (m, 4 Ar**H**); ^{13}C NMR (DMSO-d_6) δ45.1 ($NH_2\mathbf{C}H_2$), 68.2 (**C**H_2O), 114.4, 126.0, 127.1, 127.6, 128.1, 130.3, 133.1, 136.8, 139.9, 156.5 (Ar**C**); HRMS (ESI^+) 270.0666 $[M + Na]^+$ (calcd for $C_{14}H_{14}ClNONa^+$ 270.0662).

Preparation of (4-(4'-Chlorobenzyloxy)phenyl)methanamine (21). Using Method B, 4-(4'-chlorobenzyloxy)benzonitrile (**17**) (10.00 g, 41.0 mmol) and $LiAlH_4$ (4.67 g, 123.1 mmol) gave **21** as a white solid (9.88 g, 97%): R_f = 0.00 (hexanes/EtOAc 9/1); mp 72-73 °C; IR (nujol) 3362, 3270, 2922, 2862, 1604, 1508, 1459, 1380, 1251, 1071, 928, 829, 776 cm^{-1}; ^1H NMR (DMSO-d_6) δ1.84 (br s, N**H**$_2$), 3.65 (s, $NH_2C\mathbf{H}_2$), 5.07 (s, C**H**$_2$O), 6.93 (d, J = 8.4 Hz, 2 Ar**H**), 7.24 (d, J = 8.4 Hz, 2 Ar**H**), 7.42–7.47 (m, 4 Ar**H**); ^{13}C NMR (DMSO-d_6) δ45.1 ($NH_2\mathbf{C}H_2$), 68.3 (**C**H_2O), 114.4, 128.1, 128.4, 129.3, 132.3, 136.3, 136.7, 156.6 (Ar**C**); HRMS (ESI^+) 248.0863 $[M + H]^+$ (calcd for $C_{14}H_{14}ClNOH^+$ 248.0842).

Preparation of (4-(3'-Trifluoromethoxybenzyloxy)phenyl)methanamine (22). Using Method B, 4-(3'-trifluoromethoxybenzyloxy)benzonitrile (**18**) (5.50 g, 18.8 mmol) and $LiAlH_4$ (2.14 g, 56.3 mmol) gave **22** as a clear oil (4.46 g, 80%): R_f = 0.00 (hexanes/EtOAc 9/1); IR (nujol) 3357, 3281, 2932, 2858, 1603, 1511, 1467, 1239, 1165, 1032, 939, 837, 742 cm^{-1}; ^1H NMR (DMSO-d_6) δ1.70 (br s, N**H**$_2$), 3.64 (s, $NH_2C\mathbf{H}_2$), 5.15 (s, C**H**$_2$O), 6.95 (d, J = 8.2 Hz, 2 Ar**H**), 7.24 (d, J = 8.2 Hz, 2 Ar**H**),

7.31 (d, *J* = 7.6 Hz, 1 Ar**H**), 7.43–7.53 (m, 3 Ar**H**); ^{13}C NMR (DMSO-d_6) δ45.0 (NH_2**C**H_2), 68.2 (**C**H_2O), 114.4, 119.7 (Ar**C**), 120.1 (q, *J* = 254.9 Hz, O**C**F_3), 120.1, 126.4, 128.1, 130.4, 136.9, 140.2, 148.4, 156.5 (Ar**C**); HRMS (ESI$^+$) 298.1070 $[M + H]^+$ (calcd for $C_{15}H_{14}F_3NO_2H^+$ 298.1055).

Preparation of (4-(4'-Trifluoromethoxybenzyloxy)phenyl)methanamine (23). Using Method B, 4-(4'-trifluoromethoxybenzyloxy)benzonitrile (**19**) (5.50 g, 18.8 mmol) and $LiAlH_4$ (2.14 g, 56.3 mmol) gave **23** as a white solid (4.52 g, 81%): R_f = 0.00 (hexanes/EtOAc 9/1); mp 77-78 °C; IR (nujol) 3364, 3280, 2927, 2862, 1605, 1513, 1459, 1379, 1228, 1173, 1079, 1017, 924, 823, 754 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ1.75 (br s, N**H**$_2$), 3.64 (s, NH_2C**H**$_2$), 5.12 (s, C**H**$_2$O), 6.94 (d, *J* = 8.8 Hz, 2 Ar**H**), 7.24 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.38 (d, *J* = 8.8 Hz, 2 Ar**H**), 7.57 (d, *J* = 8.4 Hz, 2 Ar**H**); ^{13}C NMR (DMSO-d_6) δ45.1 (NH_2**C**H_2), 68.2 (**C**H_2O), 114.4 (Ar**C**), 120.1 (q, *J* = 254.9 Hz, O**C**F_3), 120.1, 128.1, 129.4, 136.8, 136.8, 147.8, 156.6 (Ar**C**); HRMS (ESI$^+$) 298.1034 $[M + H]^+$ (calcd for $C_{15}H_{14}F_3NO_2H^+$ 298.1055).

Preparation of (*R*)-*N*-4'-(3"-Chlorobenzyloxy)benzyl 2-*N*-(*tert.*-Butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-25). Using Method C, **20** (7.24 g, 29.3 mmol), (*R*)-**24** (5.00 g, 24.4 mmol), NMM (4.02 mL, 36.6 mmol), and IBCF (4.02 mL, 30.7 mmol) gave (*R*)-**25** as a white solid (8.82 g, 83%): R_f = 0.40 (hexanes/EtOAc 1/2); mp 83-84 °C; $[\alpha]^{26}_D$ +16.5° (*c* 1.3, $CHCl_3$); IR (nujol) 3324, 2951, 2861, 1690, 1650, 1526, 1458, 1376, 1243, 1170, 1011, 778, 679 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ1.39 (s, (C**H**$_3$)$_3$), 3.53-3.61 (br m, C**H**$_2$OH), 3.98–4.02 (br m, C**H**), 4.17–4.29 (m, C**H**$_2$N), 4.84 (t, *J* = 5.8 Hz, O**H**), 5.11 (s, OC**H**$_2$), 6.63 (d, *J* = 8.0 Hz, N**H**CH), 6.93 (d, *J* = 8.8 Hz, 2 Ar**H**), 7.18 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.36–7.49 (m, 4 Ar**H**), 8.21–8.24 (br m, N**H**CH_2); ^{13}C NMR (DMSO-d_6) δ28.2 ((**C**H_3)$_3$), 41.7 (N**C**H_2), 57.0 (OCH_2**C**H), 61.9 (O**C**H_2CH), 68.2 (O**C**H_2), 78.2

(**C**$(CH_3)_3$), 114.5, 126.0, 127.1, 127.6, 128.3, 130.3, 131.8, 133.1, 139.8 (Ar**C**), 155.2 (N**C**(O)O), 156.9 (Ar**C**), 170.3 (**C**(O)); LRMS (ESI^+) 435.1 $[M + H]^+$ (calcd for $C_{22}H_{27}ClN_2O_5H^+$ 435.1); Anal. Calcd. for $C_{22}H_{27}ClN_2O_5$: C, 60.76; H, 6.26; Cl, 8.15; N, 6.44. Found: C, 60.79; H, 6.29; Cl, 7.98; N, 6.40.

Preparation of (*R*)-*N*-4'-(4"-Chlorobenzyloxy)benzyl 2-*N*-(*tert.*-Butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-26). Using Method C, **21** (4.36 g, 17.6 mmol), (*R*)-**24** (3.00 g, 14.7 mmol), NMM (2.42 mL, 22.0 mmol), and IBCF (2.42 mL, 18.6 mmol) gave (*R*)-**26** as a white solid (5.60 g, 88%): R_f = 0.40 (hexanes/EtOAc 1/2); mp 119-121 °C; $[\alpha]^{26}_D$ +16.4° (*c* 1.1, $CHCl_3$); IR (nujol) 3319, 2938, 2859, 1656, 1538, 1466, 1347, 1241, 1173, 1009, 834, 769, 683 cm^{-1}; ^1H NMR (DMSO-d_6) δ1.39 (s, (C**H**$_3$)$_3$), 3.57-3.62 (br m, C**H**$_2$OH), 3.97–4.03 (br m, C**H**), 4.13–4.28 (m, C**H**$_2$N), 4.83 (t, *J* = 5.6 Hz, O**H**), 5.09 (s, OC**H**$_2$), 6.63 (d, *J* = 8.0 Hz, N**H**CH), 6.92 (d, *J* = 8.8 Hz, 2 Ar**H**), 7.17 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.42–7.47 (m, 4 Ar**H**), 8.20–8.24 (br m, N**H**CH$_2$); ^{13}C NMR (DMSO-d_6) δ28.2 ((**C**H$_3$)$_3$), 41.5 (N**C**H$_2$), 57.0 (OCH$_2$**C**H), 61.9 (O**C**H$_2$CH), 68.3 (O**C**H$_2$), 78.2 (**C**$(CH_3)_3$), 114.5, 128.3, 128.4, 129.3, 131.7, 132.3, 136.3 (Ar**C**), 155.2 (N**C**(O)O), 157.0 (Ar**C**), 170.3 (**C**(O)); LRMS (ESI^+) 435.2 $[M + H]^+$ (calcd for $C_{22}H_{27}ClN_2O_5H^+$ 435.2); Anal. Calcd. for $C_{22}H_{27}ClN_2O_5$: C, 60.76; H, 6.26; Cl, 8.15; N, 6.44. Found: C, 60.85; H, 6.31; Cl, 8.06; N, 6.40.

Preparation of (*R*)-*N*-4'-(3"-Trifluoromethoxybenzyloxy)benzyl 2-*N*-(*tert.*-Butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-27). Using Method C, **22** (4.40 g, 14.8 mmol), (*R*)-**24** (2.50 g, 12.2 mmol), NMM (2.01 mL, 18.3 mmol), and IBCF (2.01 mL, 15.5 mmol) gave (*R*)-**27** as a white solid (4.96 g, 83%): R_f = 0.40 (hexanes/EtOAc 1/2); mp 97-98 °C; $[\alpha]^{26}_D$ +16.8° (*c* 1.0, $CHCl_3$); IR (nujol) 3326, 2945, 2866, 1691, 1645, 1537, 1455, 1378, 1289, 1174,

1029, 839, 734, 645 cm^{-1}; ^1H NMR (DMSO-d_6) δ1.39 (s, (C**H**$_3$)$_3$), 3.57-3.63 (br m, C**H**$_2$OH), 3.98–4.03 (br m, C**H**), 4.18–4.30 (m, C**H**$_2$N), 4.84 (t, *J* = 5.6 Hz, O**H**), 5.16 (s, OC**H**$_2$), 6.64 (d, *J* = 8.0 Hz, N**H**CH), 6.95 (d, *J* = 8.0 Hz, 2 Ar**H**), 7.19 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.31 (d, *J* = 7.6 Hz, 1 Ar**H**), 7.43–7.55 (m, 3 Ar**H**), 8.21–8.25 (br m, N**H**CH$_2$); ^{13}C NMR (DMSO-d_6) δ28.1 ((**C**H$_3$)$_3$), 41.5 (N**C**H$_2$), 57.0 (OCH$_2$**C**H), 61.9 (O**C**H$_2$CH), 68.2 (O**C**H$_2$), 78.2 (**C**(CH$_3$)$_3$), 114.6, 118.8 (Ar**C**), 120.1 (q, *J* = 254.9 Hz, O**C**F$_3$), 120.1, 126.4, 128.3, 130.4, 131.9, 140.2, 148.5 (Ar**C**), 155.2 (N**C**(O)O), 156.9 (Ar**C**), 170.4 (**C**(O)); LRMS (ESI$^+$) 485.2 [M + H]$^+$ (calcd for $C_{23}H_{27}F_3N_2O_6H^+$ 485.2); Anal. Calcd. for $C_{23}H_{27}F_3N_2O_6$: C, 57.02; H, 5.62; F, 11.76; N, 5.78. Found: C, 57.06; H, 5.61; F, 11.65; N, 5.75.

Preparation of (*R*)-*N*-4'-(4"-Trifluoromethoxybenzyloxy)benzyl 2-*N*-(*tert.*-Butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-28). Using Method C, **23** (4.15 g, 14.0 mmol), (*R*)-**24** (2.50 g, 12.2 mmol), NMM (2.01 mL, 18.3 mmol), and IBCF (2.01 mL, 15.5 mmol) gave (*R*)-**28** as a white solid (4.45 g, 75%): R_f = 0.40 (hexanes/EtOAc 1/2); mp 96-97 °C; $[\alpha]^{26}_D$ +16.5° (*c* 1.2, $CHCl_3$); IR (nujol) 3339, 2912, 2861, 1684, 1639, 1524, 1457, 1377, 1294, 1242, 1169, 1046, 824, 721, 627 cm^{-1}; ^1H NMR (DMSO-d_6) δ1.39 (s, (C**H**$_3$)$_3$), 3.56-3.61 (br m, C**H**$_2$OH), 3.98–4.03 (br m, C**H**), 4.17–4.29 (m, C**H**$_2$N), 4.84 (t, *J* = 5.6 Hz, O**H**), 5.13 (s, OC**H**$_2$), 6.63 (d, *J* = 8.0 Hz, N**H**CH), 6.94 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.19 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.37 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.57 (d, *J* = 8.4 Hz, 2 Ar**H**), 8.21–8.25 (br m, N**H**CH$_2$); ^{13}C NMR (DMSO-d_6) δ28.1 ((**C**H$_3$)$_3$), 41.5 (N**C**H$_2$), 57.0 (OCH$_2$**C**H), 61.9 (O**C**H$_2$CH), 68.2 (O**C**H$_2$), 78.2 (**C**(CH$_3$)$_3$), 114.5 (Ar**C**), 120.1 (q, *J* = 254.9 Hz, O**C**F$_3$), 121.0, 128.3, 129.4, 131.8, 136.8, 147.8 (Ar**C**), 155.2 (N**C**(O)O), 157.0 (Ar**C**), 170.3 (**C**(O)); LRMS (ESI$^+$) 485.2 [M + H]$^+$ (calcd for $C_{23}H_{27}F_3N_2O_6H^+$ 485.2); Anal. Calcd. for $C_{23}H_{27}F_3N_2O_6$: C, 57.02; H, 5.62; F, 11.76; N, 5.78. Found: C, 57.10; H, 5.68; F, 11.63; N, 5.76.

Preparation of (*R*)-*N*-4'-(3"-Chlorobenzyloxy)benzyl 2-*N*-(*tert.*-Butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-29). Using Method D, (*R*)-**25** (8.60 g, 19.8 mmol), Ag_2O (22.95 g, 99.0 mmol) and CH_3I (12.36 mL, 198.1 mmol) gave (*R*)-**29** as a white solid (8.34 g, 94%): R_f = 0.45 (hexanes/EtOAc 1/1); mp 110-111 °C; $[\alpha]^{26}_D$ –16.1° (*c* 1.1, $CHCl_3$); IR (nujol) 3310, 2950, 2856, 1646, 1527, 1457, 1375, 1247, 1169, 1091, 1049, 859, 777, 682 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.38 (s, (C**H**$_3$)$_3$), 3.23 (s, OC**H**$_3$), 3.45-3.49 (br m, C**H**$_2$OH), 4.15–4.27 (m, C**H**, C**H**$_2$N), 5.11 (s, OC**H**$_2$), 6.82 (d, *J* = 8.0 Hz, N**H**CH), 6.94 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.17 (d, *J* = 8.0 Hz, 2 Ar**H**), 7.36–7.49 (m, 4 Ar**H**), 8.33 (t, *J* = 5.8 Hz, N**H**CH$_2$); ^{13}C NMR (DMSO-d_6) δ28.1 ((**C**H$_3$)$_3$), 41.5 (N**C**H$_2$), 54.3 (OCH$_2$**C**H), 58.1 (O**C**H$_3$), 68.2 (O**C**H$_2$), 72.0 (O**C**H$_2$CH), 78.2 (**C**(CH$_3$)$_3$), 114.5, 126.0, 127.1, 127.6, 128.3, 130.3, 131.7, 133.1, 139.8 (Ar**C**), 155.2 (N**C**(O)O), 156.9 (Ar**C**), 169.8 (**C**(O)); LRMS (ESI^+) 471.2 $[M + Na]^+$ (calcd for $C_{23}H_{29}ClN_2O_5Na^+$ 471.2); Anal. Calcd. for $C_{23}H_{29}ClN_2O_5$: C, 61.53; H, 6.51; Cl, 7.90; N, 6.24. Found: C, 61.67; H, 6.57; Cl, 7.73; N, 6.32.

Preparation of (*R*)-*N*-4'-(4"-Chlorobenzyloxy)benzyl 2-*N*-(*tert.*-Butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-30). Using Method D, (*R*)-**26** (5.40 g, 12.4 mmol), Ag_2O (14.41 g, 62.2 mmol) and CH_3I (7.76 mL, 124.4 mmol) gave (*R*)-**30** as a white solid (5.14 g, 92%): R_f = 0.45 (hexanes/EtOAc 1/1); mp 95-96 °C; $[\alpha]^{26}_D$ –17.5° (*c* 1.0, $CHCl_3$); IR (nujol) 3321, 2959, 2864, 1650, 1531, 1454, 1378, 1259, 1178, 1087, 934, 829, 754, 667 cm^{-1}; ^1H NMR (DMSO-d_6) δ1.38 (s, (C**H**$_3$)$_3$), 3.23 (s, OC**H**$_3$), 3.45-3.49 (br m, C**H**$_2$OCH$_3$), 4.15–4.26 (m, C**H**, C**H**$_2$N), 5.08 (s, OC**H**$_2$), 6.81 (d, *J* = 8.0 Hz, N**H**CH), 6.92 (d, *J* = 7.6 Hz, 2 Ar**H**), 7.16 (d, *J* = 8.0 Hz, 2 Ar**H**), 7.42–7.47 (m, 4 Ar**H**), 8.32 (t, *J* = 5.8 Hz, N**H**CH$_2$); ^{13}C NMR (DMSO-d_6) δ28.1 ((**C**H$_3$)$_3$), 41.5 (N**C**H$_2$), 54.3 (OCH$_2$**C**H), 58.1 (O**C**H$_3$), 68.3 (O**C**H$_2$), 72.0 (O**C**H$_2$CH), 78.2 (**C**(CH$_3$)$_3$), 114.6, 128.3, 128.4, 129.3, 131.6, 132.3, 136.2 (Ar**C**), 155.2 (N**C**(O)O), 157.0 (Ar**C**), 169.8 (**C**(O)); LRMS (ESI^+) 449.2 $[M + H]^+$ (calcd for

$C_{23}H_{29}ClN_2O_5H^+$ 449.2); Anal. Calcd. for $C_{23}H_{29}ClN_2O_5$: C, 61.53; H, 6.51; Cl, 7.90; N, 6.24. Found: C, 61.26; H, 6.47; Cl, 7.80; N, 6.17.

Preparation of (*R*)-*N*-4'-(3"-Trifluoromethoxybenzyloxy)benzyl 2-*N*-(*tert.*-Butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-31). Using Method D, (*R*)-**27** (4.80 g, 9.9 mmol), Ag_2O (11.50 g, 49.6 mmol) and CH_3I (6.19 mL, 99.2 mmol) gave (*R*)-**31** as a white solid (4.65 g, 94%): R_f = 0.45 (hexanes/EtOAc 1/1); mp 84-86 °C; $[\alpha]^{26}_D$ −15.3° (*c* 1.1, $CHCl_3$); IR (nujol) 3307, 2964, 2859, 1654, 1521, 1457, 1387, 1222, 1169, 1063, 872, 767, 691 cm^{-1}; ^1H NMR (DMSO-d_6) δ1.39 (s, $(CH_3)_3$), 3.24 (s, OCH_3), 3.47-3.51 (br m, CH_2OCH_3), 4.16–4.28 (m, CH, CH_2N), 5.16 (s, OCH_2), 6.82 (d, *J* = 8.0 Hz, NHCH), 6.95 (d, *J* = 7.6 Hz, 2 ArH), 7.18 (d, *J* = 8.4 Hz, 2 ArH), 7.31 (d, *J* = 8.0 Hz, 1 ArH), 7.43–7.55 (m, 3 ArH), 8.34 (t, *J* = 5.8 Hz, $NHCH_2$); ^{13}C NMR (DMSO-d_6) δ28.1 ($(CH_3)_3$), 41.5 (NCH_2), 54.3 (OCH_2CH), 58.1 (OCH_3), 68.2 (OCH_2), 72.0 (OCH_2CH), 78.2 ($C(CH_3)_3$), 114.6, 119.7 (ArC), 120.1 (q, *J* = 254.9 Hz, OCF_3), 120.1, 126.4, 128.3, 130.4, 131.8, 140.1, 148.5 (ArC), 155.2 (NC(O)O), 156.9 (ArC), 169.9 (C(O)); LRMS (ESI^+) 449.3 $[M + H]^+$ (calcd for $C_{24}H_{29}F_3N_2O_6H^+$ 449.3); Anal. Calcd. for $C_{24}H_{29}F_3N_2O_6$: C, 57.83; H, 5.86; F, 11.43; N, 5.62. Found: C, 57.74; H, 5.92; F, 11.18; N, 5.58.

Preparation of (*R*)-*N*-4'-(4"-Trifluoromethoxybenzyloxy)benzyl 2-*N*-(*tert.*-Butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-32). Using Method D, (*R*)-**28** (4.30 g, 8.9 mmol), Ag_2O (10.29 g, 44.4 mmol) and CH_3I (5.54 mL, 88.8 mmol) gave (*R*)-**32** as a white solid (3.84 g, 87%): R_f = 0.45 (hexanes/EtOAc 1/1); mp 97-98 °C; $[\alpha]^{26}_D$ −15.8° (*c* 1.5, $CHCl_3$); IR (nujol) 3322, 3027, 2928, 2846, 1658, 1519, 1442, 1378, 1235, 1178, 1079, 1054, 839, 747, 679 cm^{-1}; ^1H NMR (DMSO-d_6) δ1.38 (s, $(CH_3)_3$), 3.23 (s, OCH_3), 3.44-3.51 (br m, CH_2OCH_3), 4.14–4.27 (m,

C**H**, C**H**$_2$N), 5.13 (s, OC**H**$_2$), 6.82 (d, *J* = 8.0 Hz, N**H**CH), 6.94 (d, *J* = 8.8 Hz, 2 Ar**H**), 7.17 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.38 (d, *J* = 8.0 Hz, 2 Ar**H**), 7.56 (d, *J* = 8.4 Hz, 2 Ar**H**), 8.33 (t, *J* = 6.0 Hz, N**H**CH$_2$); ^{13}C NMR (DMSO-d_6) δ28.1 ((**C**H$_3$)$_3$), 41.5 (N**C**H$_2$), 54.3 (OCH$_2$**C**H), 58.1 (O**C**H$_3$), 68.2 (O**C**H$_2$), 72.0 (O**C**H$_2$CH), 78.2 (**C**(CH$_3$)$_3$), 114.5 (Ar**C**), 120.1 (q, *J* = 254.9 Hz, O**C**F$_3$), 121.0, 128.3, 129.4, 131.6, 136.7, 147.8 (Ar**C**), 155.2 (N**C**(O)O), 157.0 (Ar**C**), 169.8 (**C**(O)); LRMS (ESI$^+$) 449.2 [M + H]$^+$ (calcd for $C_{24}H_{29}F_3N_2O_6H^+$ 449.2); Anal. Calcd. for $C_{24}H_{29}F_3N_2O_6$: C, 57.83; H, 5.86; F, 11.43; N, 5.62. Found: C, 58.00; H, 5.95; F, 11.32; N, 5.56.

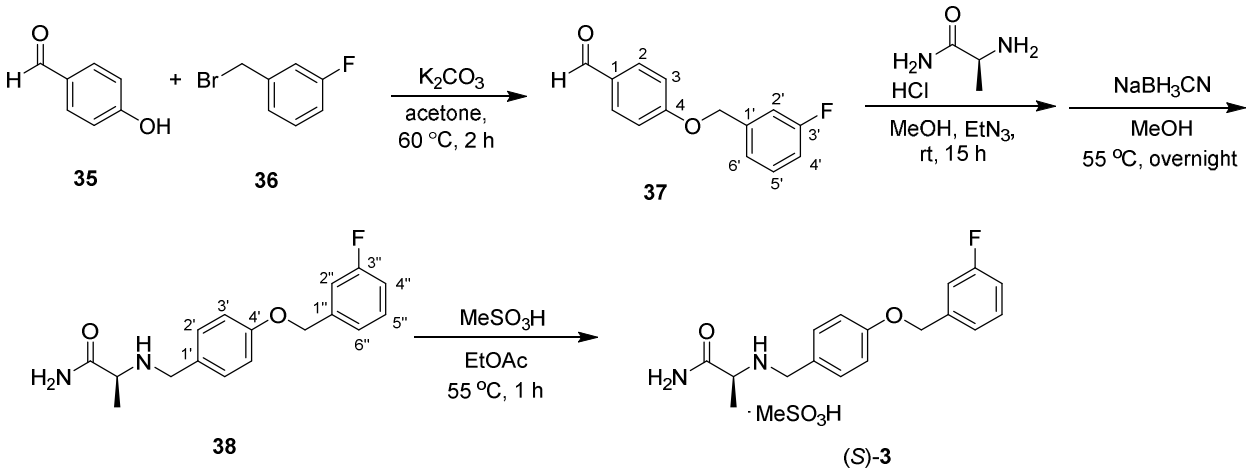
Preparation of (*R*)-*N*-4'-(3"-Chlorobenzyloxy)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-7). Using Method E, (*R*)-**29** (8.18 g, 18.26 mmol) and 4 M HCl (15.98 mL, 63.9 mmol), followed by Et$_3$N (5.60 mL, 40.2 mmol) and AcCl (1.42 mL, 20.1 mmol) gave (*R*)-**7** as a white solid (5.86 g, 82%): R_f = 0.40 (MeOH/CH$_2$Cl$_2$ 1/20); mp 170-172 °C; $[\alpha]^{26}_D$ −18.1° (*c* 1.2, CHCl$_3$); IR (nujol) 3282, 3082, 2923, 2860, 1634, 1551, 1456, 1378, 1246, 1130, 1058, 980, 777, 716 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ2.00 (s, C(O)C**H**$_3$), 3.35 (s, OC**H**$_3$), 3.42–3.46 (m, C**H**H'OCH$_3$), 3.77 (dd, *J* = 4.0, 9.0 Hz, CH**H'**OCH$_3$), 4.32–4.43 (m, C**H**$_2$N), 4.53–4.58 (m, C**H**), 5.01 (s, OC**H**$_2$), 6.55 (d, *J* = 6.4 Hz, N**H**CH), 6.83–6.91 (m, 2 Ar**H**, N**H**CH$_2$), 7.18 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.26–7.42 (m, 4 Ar**H**), addition of excess (*R*)-(−)-mandelic acid to a CDCl$_3$ solution of (*R*)-**7** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR (CDCl$_3$) δ23.4 (C(O)**C**H$_3$), 43.2 (N**C**H$_2$), 52.6 (OCH$_2$**C**H), 59.2 (O**C**H$_3$), 69.4 (O**C**H$_2$), 72.0 (O**C**H$_2$CH), 115.2, 125.5, 127.6, 128.3, 129.1, 130.1, 130.8, 134.7, 139.2, 158.0 (Ar**C**), 170.1, 170.5 (2 **C**(O)); LRMS (ESI$^+$) 413.2 [M + Na]$^+$ (calcd for $C_{20}H_{23}ClN_2O_4Na^+$ 413.2); Anal. Calcd. for $C_{20}H_{23}ClN_2O_4$: C, 61.46; H, 5.93; Cl, 9.07; N, 7.17. Found: C, 61.55; H, 5.97; Cl, 8.89; N, 7.17.

Preparation of (*R*)-*N*-4'-(4"-Chlorobenzyloxy)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-8). Using Method E, (*R*)-**30** (4.80 g, 10.7 mmol) and 4 M HCl (9.38 mL, 37.5 mmol), followed by Et_3N (3.28 mL, 23.5 mmol) and AcCl (0.83 mL, 11.8 mmol) gave (*R*)-**8** as a white solid (3.65 g, 87%): R_f = 0.40 (MeOH/CH_2Cl_2 1/20); mp 180-181 °C; $[\alpha]^{26}_D$ –17.9° (*c* 1.1, $CHCl_3$); IR (nujol) 3280, 3103, 2924, 2859, 1635, 1553, 1458, 1375, 1240, 1098, 1047, 815, 727, 608 cm^{-1}; ^1H NMR ($CDCl_3$) δ1.99 (s, C(O)C**H**$_3$), 3.35 (s, OC**H**$_3$), 3.42–3.46 (m, C**H**H'OCH_3), 3.76 (dd, *J* = 4.0, 9.0 Hz, CH**H'**OCH_3), 4.31–4.42 (m, C**H**$_2$N), 4.54–4.59 (m, C**H**), 5.00 (s, OC**H**$_2$), 6.58 (d, *J* = 6.4 Hz, N**H**CH), 6.85–6.92 (m, 2 Ar**H**, N**H**CH_2), 7.17 (d, *J* = 8.0 Hz, 2 Ar**H**), 7.34 (s, 4 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-**8** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ23.3 (C(O)**C**H_3), 43.2 (N**C**H_2), 52.6 (OCH_2**C**H), 59.2 (O**C**H_3), 69.4 (O**C**H_2), 72.1 (O**C**H_2CH), 115.2, 128.9, 128.9, 129.0, 130.7, 133.9, 135.6, 158.1 (Ar**C**), 170.1, 170.5 (2 **C**(O)); LRMS (ESI^+) 391.2 $[M + H]^+$ (calcd for $C_{20}H_{23}ClN_2O_4H^+$ 391.2); Anal. Calcd. for $C_{20}H_{23}ClN_2O_4$: C, 61.46; H, 5.93; Cl, 9.07; N, 7.17. Found: C, 61.75; H, 5.86; Cl, 9.15; N, 7.11.

Preparation of (*R*)-*N*-4'-(3"-Trifluoromethoxybenzyloxy)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-9). Using Method E, (*R*)-**31** (4.50 g, 9.0 mmol) and 4 M HCl (7.90 mL, 31.6 mmol), followed by Et_3N (2.77 mL, 19.9 mmol) and AcCl (0.70 mL, 9.9 mmol) gave (*R*)-**9** as a white solid (3.50 g, 88%): R_f = 0.40 (MeOH/CH_2Cl_2 1/20); mp 139-140 °C; $[\alpha]^{26}_D$ –15.1° (*c* 1.0, $CHCl_3$); IR (nujol) 3281, 3081, 2924, 2860, 1632, 1550, 1456, 1381, 1281, 1141, 1060, 974, 822, 710, 618 cm^{-1}; ^1H NMR ($CDCl_3$) δ1.98 (s, C(O)C**H**$_3$), 3.35 (s, OC**H**$_3$), 3.43–3.47 (m, C**H**H'OCH_3), 3.76 (dd, *J* = 4.0, 9.2 Hz, CH**H'**OCH_3), 4.32–4.43 (m, C**H**$_2$N), 4.56–4.61 (m, C**H**), 5.04 (s, OC**H**$_2$), 6.63 (d, *J* = 6.8 Hz, N**H**CH), 6.89–6.97 (m, 2 Ar**H**, N**H**CH_2), 7.18 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.29–7.42 (m,

4 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-**9** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ23.3 (C(O)**C**H_3), 43.1 (N**C**H_2), 52.7 (OCH_2**C**H), 59.2 (O**C**H_3), 69.2 (O**C**H_2), 72.1 (O**C**H_2CH), 115.2, 119.3, 120.4 (Ar**C**), 120.6 (q, *J* = 256.4 Hz, O**C**F_3), 125.6, 129.1, 130.1, 130.9, 139.5, 149.6, 158.0 (Ar**C**), 170.1, 170.5 (2 **C**(O)); LRMS (ESI^+) 441.1 $[M + H]^+$ (calcd for $C_{21}H_{23}F_3N_2O_5H^+$ 441.1); Anal. Calcd. for $C_{21}H_{23}F_3N_2O_5$: C, 57.27; H, 5.26; F, 12.94; N, 6.36. Found: C, 57.08; H, 5.20; F, 12.88; N, 6.30.

Preparation of (*R*)-*N*-4'-(4"-Trifluoromethoxybenzyloxy)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-10). Using Method E, (*R*)-**32** (3.68 g, 7.4 mmol) and 4 M HCl (6.47 mL, 25.9 mmol), followed by Et_3N (2.27 mL, 16.3 mmol) and AcCl (0.58 mL, 8.1 mmol) gave (*R*)-**10** as a white solid (3.10 g, 95%): R_f = 0.40 (MeOH/CH_2Cl_2 1/20); mp 172-173 °C; $[\alpha]^{26}_D$ –16.0° (*c* 1.1, $CHCl_3$); IR (nujol) 3281, 3102, 2923, 2860, 1635, 1552, 1457, 1378, 1275, 1233, 1148, 1021, 835, 730, 609 cm^{-1}; ^1H NMR ($CDCl_3$) δ1.99 (s, C(O)C**H**$_3$), 3.35 (s, OC**H**$_3$), 3.43–3.47 (m, C**H**H'OCH_3), 3.76 (dd, *J* = 4.0, 9.2 Hz, CH**H'**OCH_3), 4.32–4.43 (m, C**H**$_2$N), 4.56–4.60 (m, C**H**), 5.03 (s, OC**H**$_2$), 6.61 (d, *J* = 6.4 Hz, N**H**CH), 6.89–6.94 (m, 2 Ar**H**, N**H**CH_2), 7.18 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.22 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.44 (d, *J* = 8.4 Hz, 2 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-**10** gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ23.3 (C(O)**C**H_3), 43.1 (N**C**H_2), 52.7 (OCH_2**C**H), 59.2 (O**C**H_3), 69.3 (O**C**H_2), 72.0 (O**C**H_2CH), 115.1 (Ar**C**), 120.6 (q, *J* = 255.7 Hz, O**C**F_3), 121.3, 129.0, 129.1, 130.8, 135.8, 149.0, 158.1 (Ar**C**), 170.1, 170.5 (2 **C**(O)); LRMS (ESI^+) 441.1 $[M + H]^+$ (calcd for $C_{21}H_{23}F_3N_2O_5H^+$ 441.1); Anal. Calcd. for $C_{21}H_{23}F_3N_2O_5$: C, 57.27; H, 5.26; F, 12.94; N, 6.36. Found: C, 57.35; H, 5.28; F, 12.78; N, 6.38.



Scheme S1. Synthesis of Safinamide ((*S*)-**3**).

Preparation of 4-((3'-Fluoro)benzyloxy)benzaldehyde (37).[3] To an acetone solution (250 mL) of 4-hydroxybenzaldehyde (**35**) (4.00 g, 32.5 mmol) was added 3-fluorobenzylbromide (**36**) (4.24 mL, 34.1 mmol) and K_2CO_3 (17.96 g, 129.9 mmol), and stirred at reflux (60 °C, 2 h). The reaction mixture was concentrated in vacuo, and then H_2O (50 mL) and CH_2Cl_2 (50 mL) were added, and the mixture was extracted with CH_2Cl_2 (3 X 50 mL)). The combined organic layers were dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash liquid chromatography on SiO_2 (EtOAc/hexanes 1/9) to yield **37** as a white solid (6.18 g, 83%): R_f = 0.50 (EtOAc/hexanes, 1/5); mp 45–46 °C (lit.[3] mp 40–41 °C); ^{1}H NMR ($CDCl_3$) δ 5.15 (s, OC**H**$_2$, 2H), 7.00-7.22 (m, 5 Ar**H**), 7.30-7.40 (m, 1 Ar**H**), 7.80-7.90 (m, 2 Ar**H**), 9.90 (s, C(O)**H**, 1H); ^{13}C NMR ($CDCl_3$) δ 69.5 (**C**H_2O), 114.4 (d, J = 22.1 Hz, Ar**C**), 115.2 (Ar**C**), 115.3 (d, J (est) = 17.6 Hz, one peak is overlapped with near peak, Ar**C**), 122.9, 130.5, 130.5 (d, J = 7.8 Hz, Ar**C**), 132.2, 138.6 (d, J = 7.2 Hz, Ar**C**), 163.1 (d, J = 245.1 Hz, Ar**C**), 163.5 (Ar**C**), 190.9 (**C**(O)H).

Preparation of (*S*)-2-((4'-(3"-fluorobenzoxy)benzyl)amino)propanamide (38). To a MeOH solution of L-alanine amide hydrochloride (0.32 g, 2.61 mmol) was added EtN_3 (453 μL, 3.26

mmol) and **37** (0.5 g, 2.17 mmol) successively. The reaction solution was allowed to stir at room temperature (2 h) and concentrated in vacuo. The residue was dissolved in EtOAc (100 mL) and washed with H_2O (3 X 100 mL), and then dried over anhydrous Na_2SO_4. The organic layer was concentrated in vacuo and dissolved in MeOH (25 mL). The resulting solution was treated with sodium cyanoborohydride ($NaBH_3CN$) (215.5 mg, 3.26 mmol) at 0 °C and allowed to stir at room temperature (16 h). The resulting solution was concentrated in vacuo, disoolved in EtOAc (100 mL), and washed with H_2O (3 X 100 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash liquid chromatography on SiO_2 (EtOAc) to yield **38** as a white solid (0.39 g, 60%); R_f = 0.10 (EA); mp 123-125 °C; ^{1}H NMR (DMSO-d_6) δ 1.11 (dd, *J* = 5.6, 1.3 Hz, C**H$_3$**), 2.26 (br s, N**H**), 2.99 (q, *J* = 6.4 Hz, C**H**), 3.46 (d, *J* = 13.2 Hz, NHC**H**H'), 3.60 (d, *J* = 13.2 Hz, NHCH**H'**), 5.11 (s, OC**H$_2$**), 6.93-7.29 (m, 7 Ar**H,** N**H$_2$**), 7.40-7.47 (m, 1 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 19.7 (**C**H$_3$), 51.9 (NH**C**H$_2$), 57.6 (C(O)**C**HNH$_2$), 69.2 (O**C**H$_2$), 114.2 (d, *J* = 21.9 Hz, Ar**C**), 114.8 (d, *J* = 21.0 Hz, Ar**C**), 114.9 (Ar**C**), 122.7 (d, *J* = 2.8 Hz, Ar**C**), 129.3 (Ar**C**), 130.2 (d, *J* = 8.2 Hz, Ar**C**), 132.3 (Ar**C**), 139.7 (d, *J* = 7.2 Hz, Ar**C**), 163.0 (d, *J* = 244.7 Hz, Ar**C**), 178.4 (**C**(O)), the remaining signal was not detected and is believed to overlap with nearby peaks

Preparation of (*S*)-2-((4'-(3"-Fluorobenzoxy)benzyl)amino)propanamide, methanesulfonate ((*S*)-3). To an EtOAc solution (10 mL) of **38** (0.30 g, 1.0 mmol) was added methanesulfonic acid (78 μL, 1.2 mmol) at 50 °C (1 h). The reaction mixture was cooled down to room temperature and filtered. The solid was washed with EtOAc (100 mL) and dried in vacuo to yield (*S*)-**3** as a white solid (0.36 g, 90%); mp 213 °C (dec) (lit.[4] mp 210 °C (dec)); $[\alpha]^{26}_D$ +12.9° (*c* 1.0, acetic acid (lit.[4] $[\alpha]^{25}_D$ +12.9°(*c* 1.1, acetic acid); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.42 (d, *J* = 6.9 Hz, CHC**H$_3$**),

2.31 (s, C**H**$_3$SO$_3$H), 3.68–3.75 (m, C**H**CH$_3$), 3.97–4.07 (m, C**H**$_2$NH), 5.17 (s, OC**H**$_2$), 7.06–7.09 (m, 2 Ar**H**), 7.13–7.20 (m, 1 Ar**H**), 7.26–7.30 (m, 2 Ar**H**), 7.39–7.48 (m, 3 Ar**H**), 7.63 (s, C(O)N**H**H'), 7.90 (s, C(O)NH**H**'), 8.98 (br s, N**H**$_2$); ^{13}C NMR (300 MHz, DMSO-d_6) δ16.4 (CH**C**H$_3$), 48.5 (**C**H$_2$NH), 54.8 (**C**HCH$_3$), 68.8 (O**C**H$_2$), 114.6 (d, *J* = 21.7 Hz, Ar**C**), 115.0 (d, *J* = 20.8 Hz, Ar**C**), 115.4 (Ar**C**), 123.9 (d, *J* = 2.6 Hz, Ar**C**), 124.4 (Ar**C**), 131.0 (d, *J* = 8.3 Hz, Ar**C**), 132.1 (Ar**C**), 140.3 (d, *J* = 7.4 Hz, Ar**C**), 159.0 (Ar**C**), 162.7 (d, *J* = 242.2 Hz, Ar**C**-F), 171.0 (**C**(O)), the remaining signal was not detected and is believed to overlap with the DMSO-d_6 peaks.

Footnotes and Author Current Address

[a]Center for Neuro-Medicine, Korea Institute of Science and Technology, Seoul, Korea

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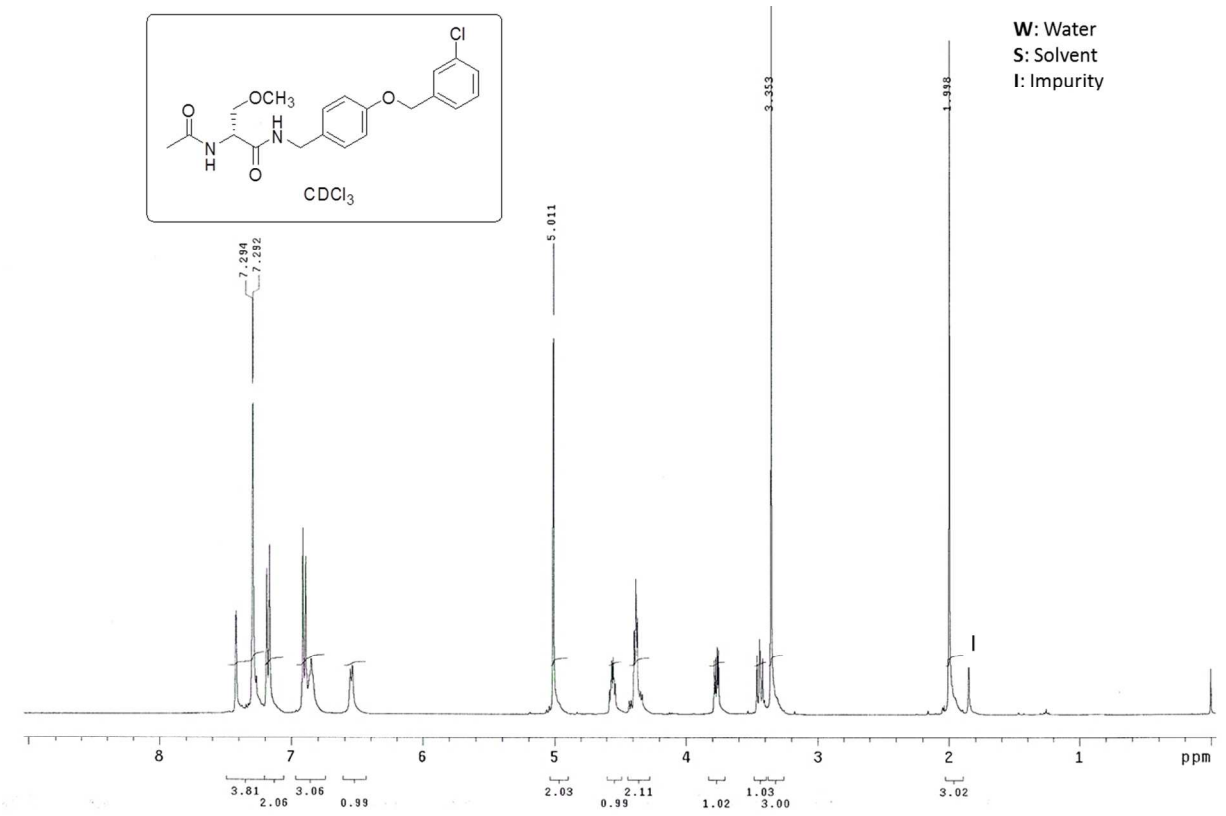
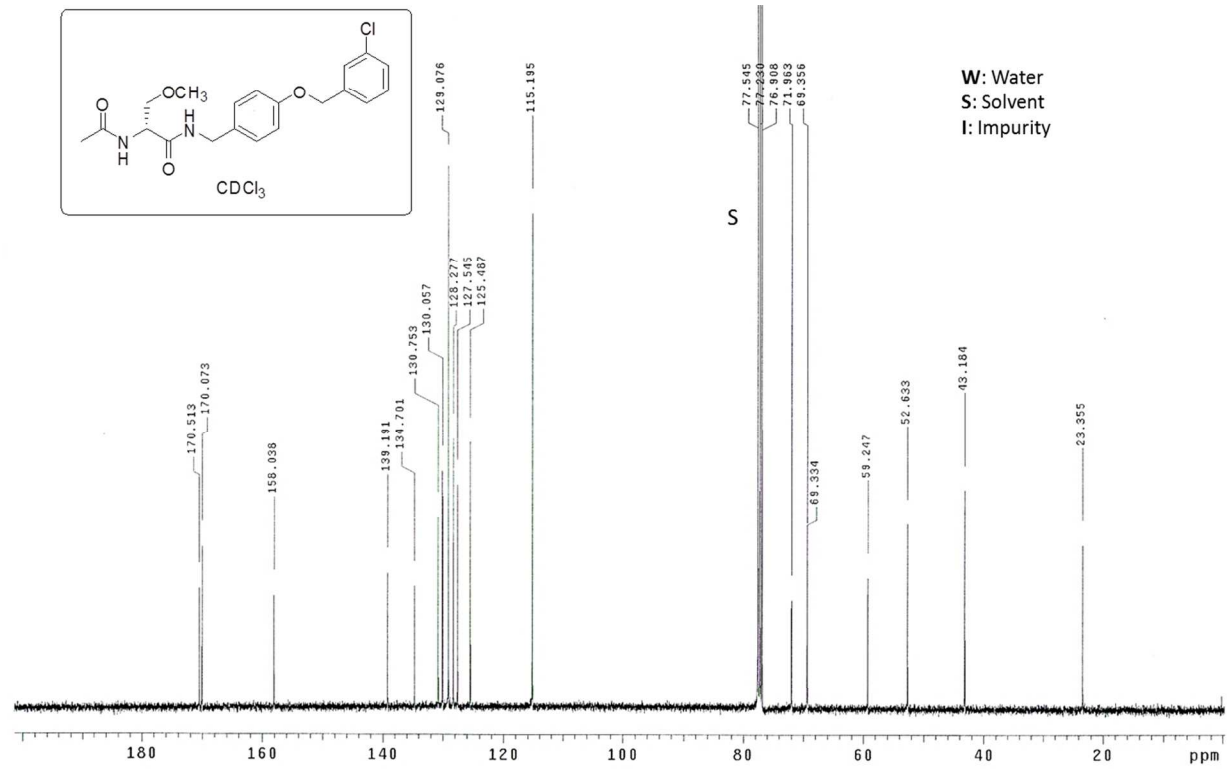
(*R*)-*N*-(4'-(3"-Chlorobenzyloxy)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-7)





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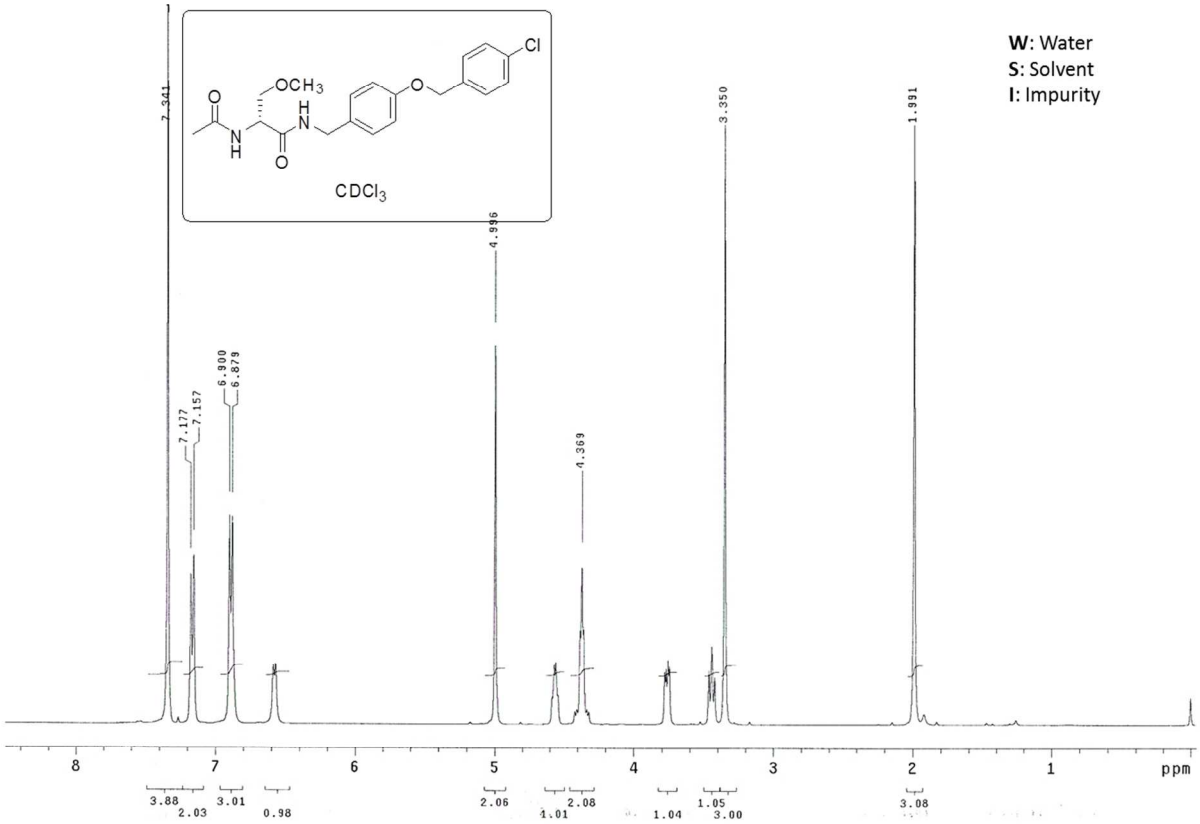

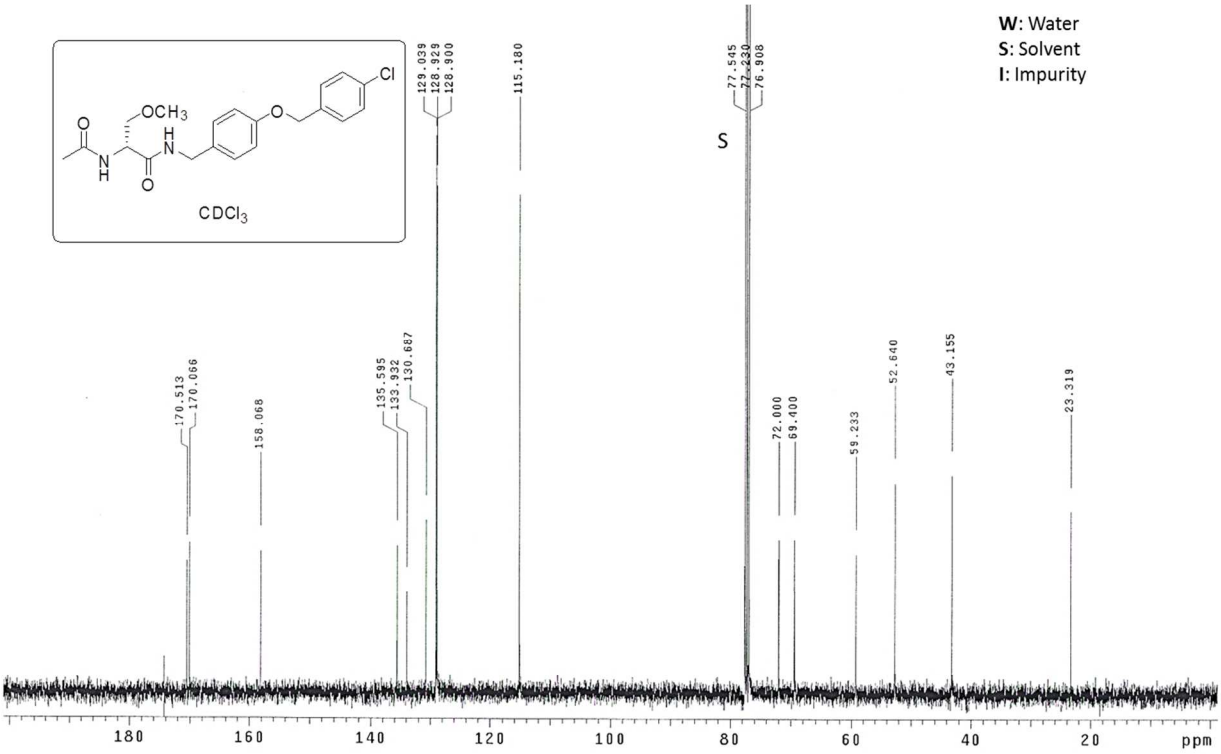

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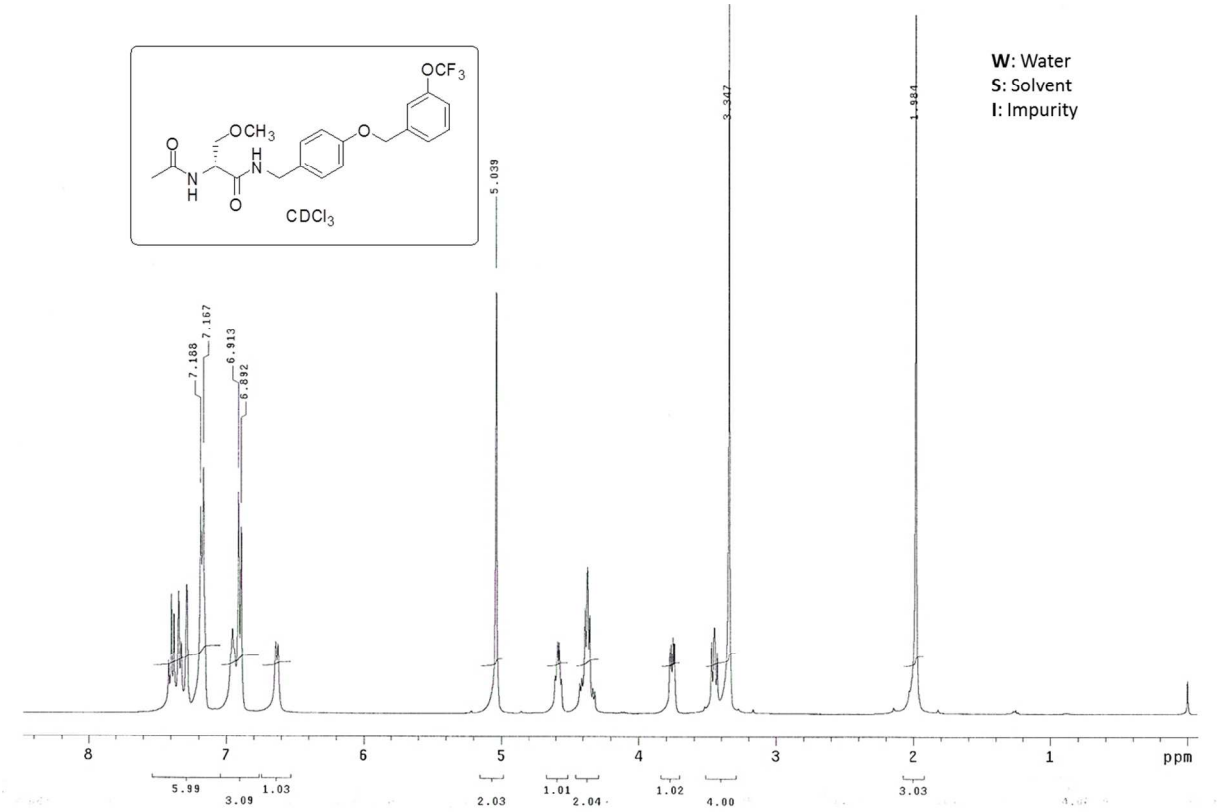

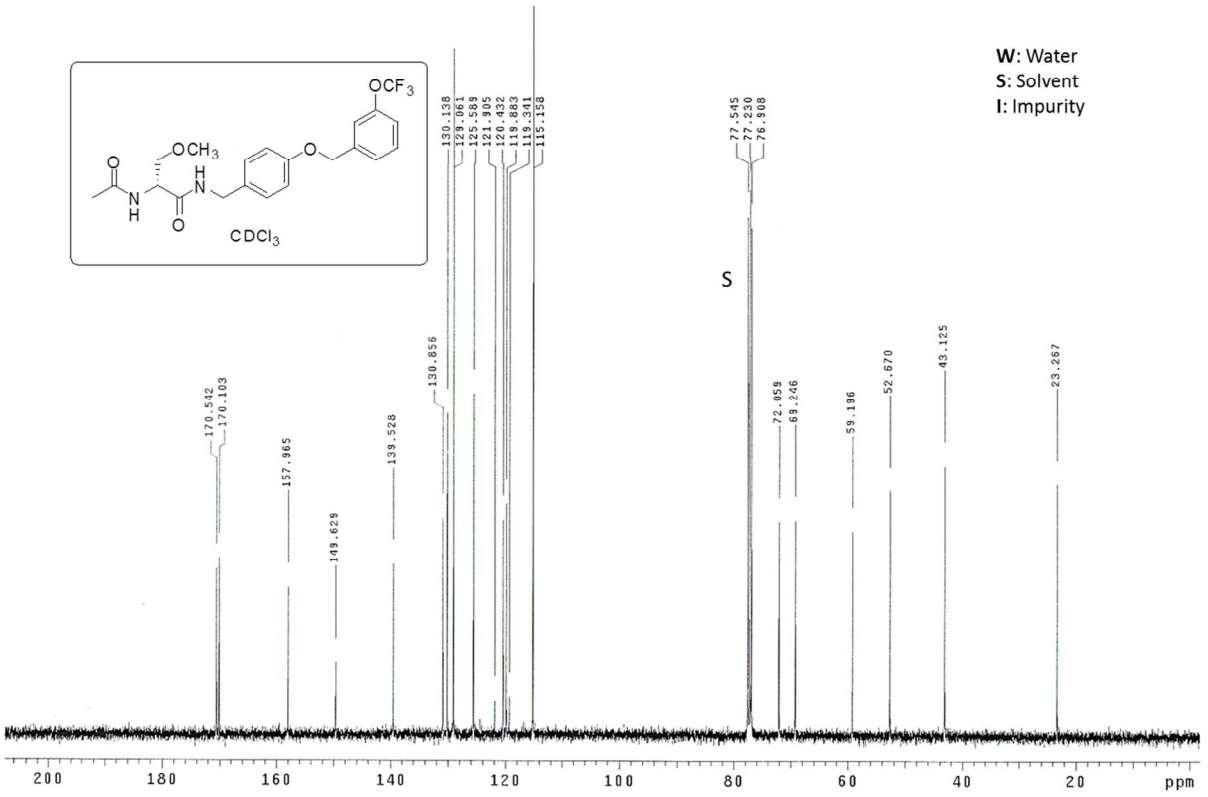

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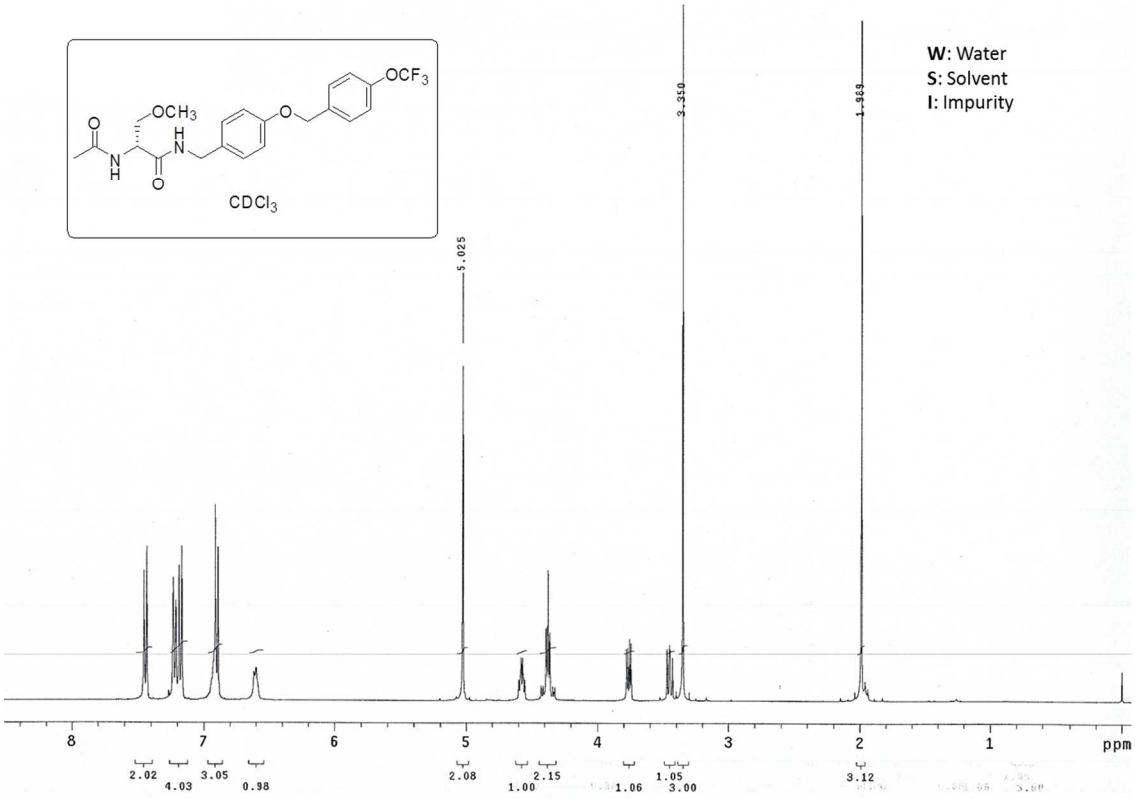

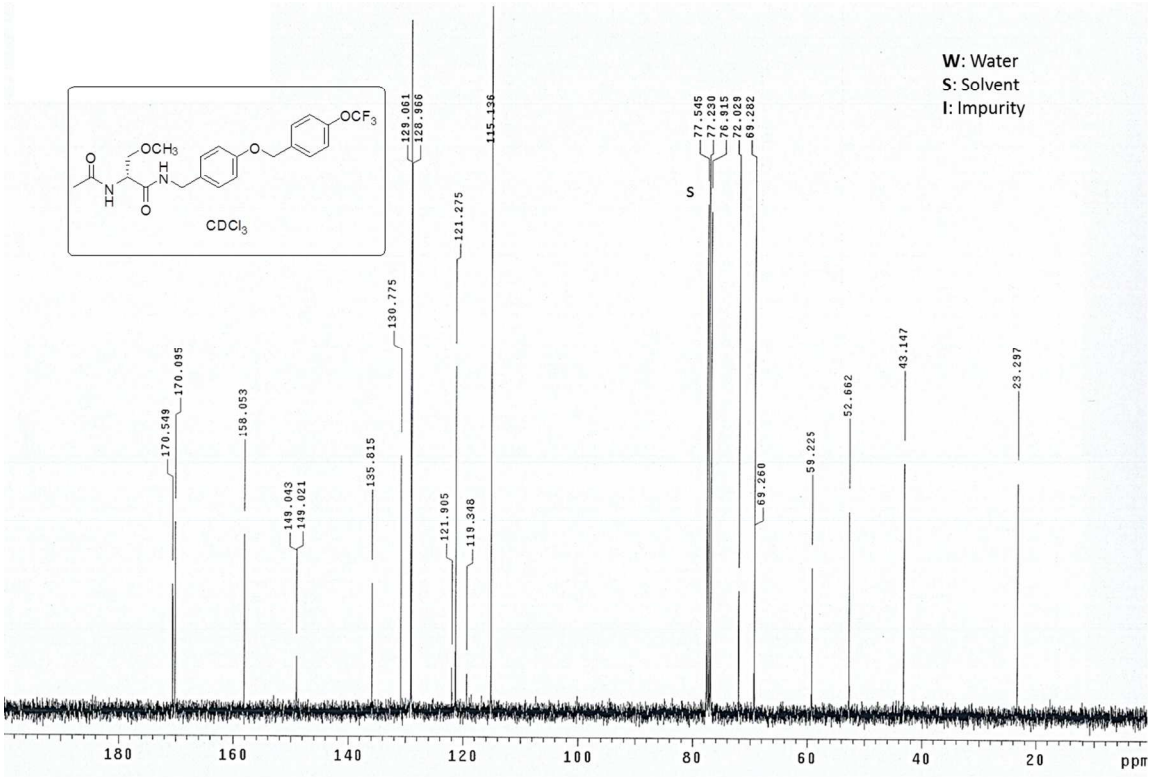

(*S*)-2-((4'-(3"-fluorobenzoxy)benzyl)amino)propanamide, methanesulfonate ((*S*)-3)