Supporting Information

Synthesis and Structure-Activity Relationships for Extended Side Chain Analogues of the Antitubercular Drug (6*S*)-2-Nitro-6-{[4-(trifluoromethoxy)benzyl]oxy}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (PA-824)

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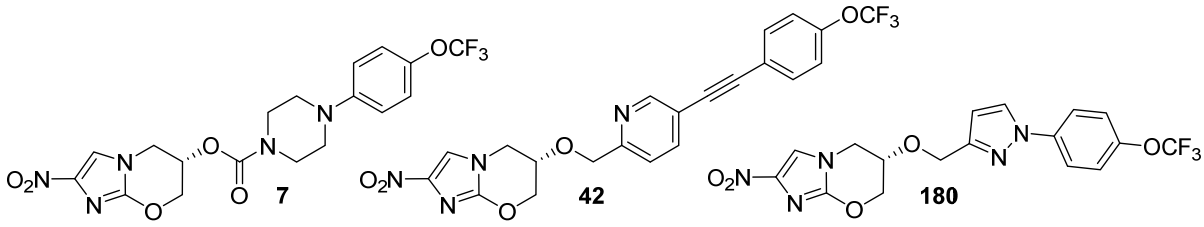
Table S1. Metabolite formation data for selected compounds



	HLM (% **95**)[a]				MLM (% **95**)[a]			
compd	0 h	0.5 h	1 h	2 h	0 h	0.5 h	1 h	2 h
7	0.13	0.34	0.39	0.23	0.36	0.89	1.17	0.63
42	0.09	0.14	0.17	0.17	0.09	0.13	0.16	0.15
180[b]	0.07	0.54	0.67	0.72	0.06	1.24	1.75	1.85

[a]Percent of test compound (at 5 μM) isolated as alcohol metabolite **95** following incubation with human or mouse liver microsomes.
[b]Compound **180** was the lead candidate from an earlier SAR study and is included here for comparison with **42** (see ref. 24 of manuscript)

Figure S1. Comparative concentration-time profiles for **4**, **35**, and **42** in CD-1 mice following a single oral dose of 40 mg/kg

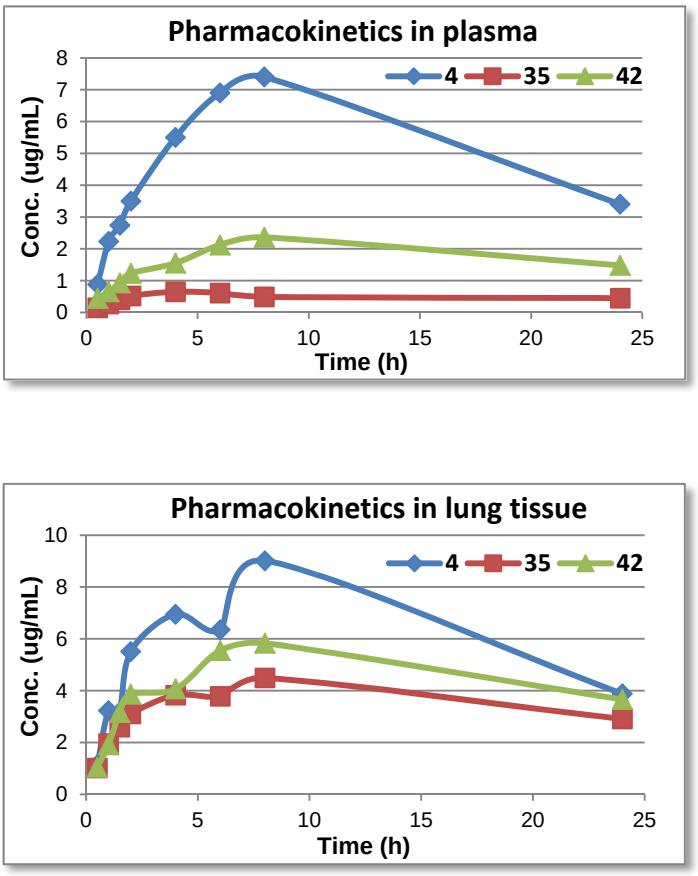
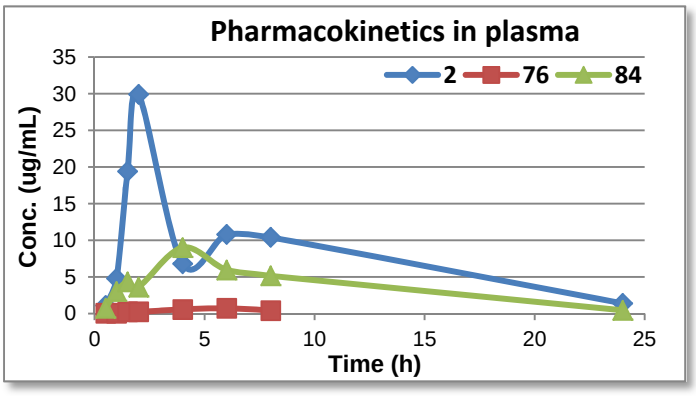
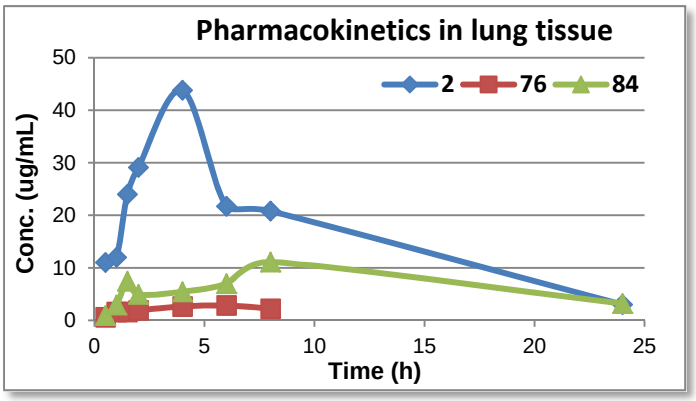


Figure S2. Comparative concentration-time profiles for **2**, **76**, and **84** in CD-1 mice following a single oral dose of 40 mg/kg





Compounds of Table 1

Synthesis of 12 (Scheme 1A):

Methyl 4-(4-fluorobenzyl)benzoate (92b). Reaction of methyl 4-(bromomethyl)benzoate (**91**) with 4-fluorophenylboronic acid, using procedure A, gave **92b** (82%) as a clear oil; ^{1}H NMR ($CDCl_3$) δ 7.96 (br d, *J* = 8.4 Hz, 2 H), 7.23 (br d, *J* = 8.6 Hz, 2 H), 7.12 (br dd, *J* = 8.7, 5.4 Hz, 2 H), 6.98 (br t, *J* = 8.7 Hz, 2 H), 4.00 (s, 2 H), 3.90 (s, 3 H); HREIMS calcd for $C_{15}H_{13}FO_2$ *m*/*z* (M^+) 244.0900, found 244.0908.

[4-(4-Fluorobenzyl)phenyl]methanol (93b). Reduction of ester **92b** with $LiAlH_4$, using procedure B for 2 h, gave **93b**[1] (97%) as a white solid: mp 53-56 °C (lit.[1] mp 62 °C); ^{1}H NMR ($CDCl_3$) δ 7.29 (br d, *J* = 8.1 Hz, 2 H), 7.16 (br d, *J* = 8.1 Hz, 2 H), 7.13 (br dd, *J* = 8.7, 5.5 Hz, 2 H), 6.96 (br t, *J* = 8.7 Hz, 2 H), 4.66 (d, *J* = 5.6 Hz, 2 H), 3.95 (s, 2 H), 1.56 (t, *J* = 5.9 Hz, 1 H); HREIMS calcd for $C_{14}H_{13}FO$ *m*/*z* (M^+) 216.0950, found 216.0953.

1-(Bromomethyl)-4-(4-fluorobenzyl)benzene (94b). Bromination of alcohol **93b** with PBr_3, using procedure C, gave **94b** (54%) as a clear oil; ^{1}H NMR ($CDCl_3$) δ 7.31 (br d, *J* = 8.1 Hz, 2 H), 7.15-7.09 (m, 4 H), 6.97 (br t, *J* = 8.7 Hz, 2 H), 4.48 (s, 2 H), 3.94 (s, 2 H); HREIMS calcd for $C_{14}H_{12}BrF$ *m*/*z* (M^+) 280.0086, 278.0106, found 280.0082, 278.0105.

(6*S*)-6-{[4-(4-Fluorobenzyl)benzyl]oxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (12). Reaction of (6*S*)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-ol[2] (**95**) with bromide **94b** and NaH, using procedure D, gave **12** (82%) as a white solid: mp 150-151 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.00 (s, 1 H), 7.26-7.17 (m, 6 H), 7.08 (br t, *J* = 8.9 Hz, 2 H), 4.63 (dt, *J* = 11.9, 2.2 Hz, 1 H), 4.61 (d, *J* = 11.8 Hz, 1 H), 4.57 (d, *J* = 11.8 Hz, 1 H), 4.45 (br d, *J* = 11.9 Hz, 1 H), 4.28-4.17 (m, 3 H), 3.91 (s, 2 H). Anal. ($C_{20}H_{18}FN_3O_4$) C, H, N.

Synthesis of 13 (Scheme 1A):

Methyl 4-[4-(trifluoromethyl)benzyl]benzoate (92c). Reaction of bromide **91** with 4-(trifluoromethyl)phenylboronic acid, using procedure A, gave **92c**[3] (76%) as a clear oil; ^{1}H NMR ($CDCl_3$) δ 7.97 (br d, *J* = 8.3 Hz, 2 H), 7.55 (br d, *J* = 8.1 Hz, 2 H), 7.28 (br d, *J* = 8.0 Hz, 2 H), 7.24 (br d, *J* = 8.4 Hz, 2 H), 4.08 (s, 2 H), 3.90 (s, 3 H); HREIMS calcd for $C_{16}H_{13}F_3O_2$ *m*/*z* (M^+) 294.0868, found 294.0864.

{4-[4-(Trifluoromethyl)benzyl]phenyl}methanol (93c). Reduction of ester **92c** with $LiAlH_4$, using procedure B for 1.5 h, gave **93c**[4] (100%) as a white solid: mp 50-51 °C; ^{1}H NMR ($CDCl_3$) δ 7.53 (br d, *J* = 8.1 Hz, 2 H), 7.31 (br d, *J* = 8.5 Hz, 2 H), 7.29 (br d, *J* = 8.5 Hz, 2 H), 7.17 (br d, *J* = 8.1 Hz, 2 H), 4.67 (d, *J* = 5.0 Hz, 2 H), 4.03 (s, 2 H), 1.59 (t, *J* = 5.6 Hz, 1 H); HREIMS calcd for $C_{15}H_{13}F_3O$ *m*/*z* (M^+) 266.0919, found 266.0918.

1-(Bromomethyl)-4-[4-(trifluoromethyl)benzyl]benzene (94c). Bromination of alcohol **93c** with PBr_3, using procedure C, gave **94c** (67%) as a white solid: mp (EtOAc/hexane) 41-43 °C; ^{1}H NMR ($CDCl_3$) δ 7.54 (br d, *J* = 8.1 Hz, 2 H), 7.33 (br d, *J* = 8.1 Hz, 2 H), 7.28 (br d, *J* = 8.0 Hz, 2 H), 7.14 (br d, *J* = 8.1 Hz, 2 H), 4.48 (s, 2 H), 4.02 (s, 2 H); HREIMS calcd for $C_{15}H_{12}BrF_3$ *m*/*z* (M^+) 330.0054, 328.0075, found 330.0055, 328.0070.

(6*S*)-2-Nitro-6-({4-[4-(trifluoromethyl)benzyl]benzyl}oxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (13). Reaction of alcohol **95** with bromide **94c** and NaH, using procedure D for 2 h, gave **13** (65%) as a white solid: mp 141-143 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.00 (s, 1 H),

7.62 (br d, *J* = 8.0 Hz, 2 H), 7.43 (br d, *J* = 8.0 Hz, 2 H), 7.25 (br d, *J* = 8.5 Hz, 2 H), 7.22 (br d, *J* = 8.5 Hz, 2 H), 4.64 (dt, *J* = 11.9, 2.2 Hz, 1 H), 4.62 (d, *J* = 11.7 Hz, 1 H), 4.58 (d, *J* = 11.8 Hz, 1 H), 4.45 (br d, *J* = 11.9 Hz, 1 H), 4.28-4.17 (m, 3 H), 4.03 (s, 2 H). Anal. ($C_{21}H_{18}F_3N_3O_4$) C, H, N.

Synthesis of 14 (Scheme 1A):

Methyl 4-{[6-(trifluoromethyl)pyridin-3-yl]methyl}benzoate (92d). Reaction of bromide **91** with 6-(trifluoromethyl)pyridin-3-ylboronic acid, using procedure A, gave **92d** (80%) as a white solid: mp (EtOAc/hexane) 62-63 °C; ^{1}H NMR ($CDCl_3$) δ 8.61 (br s, 1 H), 8.00 (br d, *J* = 8.4 Hz, 2 H), 7.64-7.58 (m, 2 H), 7.25 (br d, *J* = 8.4 Hz, 2 H), 4.11 (s, 2 H), 3.91 (s, 3 H); HREIMS calcd for $C_{15}H_{12}F_3NO_2$ *m*/*z* (M^+) 295.0820, found 295.0824.

(4-{[6-(Trifluoromethyl)pyridin-3-yl]methyl}phenyl)methanol (93d). Reduction of ester **92d** with $LiAlH_4$, using procedure B for 2 h, gave **93d** (100%) as a clear oil; ^{1}H NMR ($CDCl_3$) δ 8.60 (br s, 1 H), 7.62 (br dd, *J* = 8.0, 1.5 Hz, 1 H), 7.58 (br d, *J* = 8.1 Hz, 1 H), 7.33 (br d, *J* = 8.0 Hz, 2 H), 7.17 (br d, *J* = 8.0 Hz, 2 H), 4.68 (s, 2 H), 4.05 (s, 2 H), 1.60 (br s, 1 H); HREIMS calcd for $C_{14}H_{12}F_3NO$ *m*/*z* (M^+) 267.0871, found 267.0873.

5-[4-(Bromomethyl)benzyl]-2-(trifluoromethyl)pyridine (94d). Bromination of alcohol **93d** with PBr_3, using procedure C, gave **94d** (75%) as a white solid: mp (EtOAc/hexane) 78-80 °C; ^{1}H NMR ($CDCl_3$) δ 8.60 (br s, 1 H), 7.62 (br dd, *J* = 8.2, 1.7 Hz, 1 H), 7.59 (dd, *J* = 8.1, 0.9 Hz, 1 H), 7.35 (br d, *J* = 8.1 Hz, 2 H), 7.15 (br d, *J* = 8.2 Hz, 2 H), 4.47 (s, 2 H), 4.05 (s, 2 H); HREIMS calcd for $C_{14}H_{11}BrF_3N$ *m*/*z* (M^+) 331.0007, 329.0027, found 330.9998, 329.0019.

(6*S*)-2-Nitro-6-[(4-{[6-(trifluoromethyl)pyridin-3-yl]methyl}benzyl)oxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (14). Reaction of alcohol **95** with bromide **94d** and NaH, using procedure D, gave **14** (36%) as a white solid: mp 88-90 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.69 (br d, *J* = 1.6 Hz, 1 H), 8.00 (s, 1 H), 7.88 (dd, *J* = 8.1, 1.6 Hz, 1 H), 7.80 (d, *J* = 8.0 Hz, 1 H), 7.26 (s, 4 H), 4.64 (dt, *J* = 11.9, 2.2 Hz, 1 H), 4.62 (d, *J* = 11.9 Hz, 1 H), 4.58 (d, *J* = 11.9 Hz, 1 H), 4.45 (br d, *J* = 11.9 Hz, 1 H), 4.28-4.17 (m, 3 H), 4.08 (s, 2 H). Anal. ($C_{20}H_{17}F_3N_4O_4 \cdot 0.25H_2O$) C, H, N.

Synthesis of 16 and 17 (Scheme 1B):

(6*S*)-6-{[4-(4-Fluorophenoxy)benzyl]oxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (16). Reaction of alcohol **95** with 1-(bromomethyl)-4-(4-fluorophenoxy)benzene[5] (**99b**) [prepared from 4-fluorobenzaldehyde (**96**) using procedures E, F, and C] and NaH (1.3 equiv), using procedure D for 2.5 h, gave **16** (70%) as a white solid: mp 141-143 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.01 (s, 1 H), 7.32 (br d, *J* = 8.6 Hz, 2 H), 7.21 (br t, *J* = 8.8 Hz, 2 H), 7.04 (br dd, *J* = 9.1, 4.5 Hz, 2 H), 6.96 (br d, *J* = 8.6 Hz, 2 H), 4.65 (dt, *J* = 11.9, 2.3 Hz, 1 H), 4.63 (d, *J* = 11.4 Hz, 1 H), 4.59 (d, *J* = 11.7 Hz, 1 H), 4.46 (br d, *J* = 11.9 Hz, 1 H), 4.29-4.19 (m, 3 H). Anal. ($C_{19}H_{16}FN_3O_5$) C, H, N.

(6*S*)-2-Nitro-6-({4-[4-(trifluoromethyl)phenoxy]benzyl}oxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (17). Reaction of alcohol **95** with 1-(bromomethyl)-4-[4-(trifluoromethyl)phenoxy]benzene[5] (**99c**) [prepared from **96** using procedures E, F, and C] and NaH (3.1 equiv), using procedure D, gave **17** (26%) as a white solid: mp 150-152 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.02 (s, 1 H), 7.72 (br d, *J* = 8.7 Hz, 2 H), 7.40 (br d, *J* = 8.6 Hz, 2 H), 7.16-7.08 (m, 4 H), 4.70-4.61 (m, 3 H), 4.48 (br d, *J* = 11.8 Hz, 1 H), 4.31-4.21 (m, 3 H). Anal. ($C_{20}H_{16}F_3N_3O_5$) C, H, N.

Synthesis of 18 (Scheme 1B):

4-{[6-(Trifluoromethyl)pyridin-3-yl]oxy}benzaldehyde (97d). Reaction of 4-fluorobenzaldehyde (**96**) with 6-(trifluoromethyl)pyridin-3-ol, using procedure E, gave **97d**[6] (59%) as a white solid: mp (EtOAc/hexane) 44-46 °C; ^{1}H NMR ($CDCl_3$) δ 9.99 (s, 1 H), 8.54 (d, *J* = 2.7 Hz, 1 H), 7.95 (br d, *J* = 8.7 Hz, 2 H), 7.72 (d, *J* = 8.6 Hz, 1 H), 7.49 (dd, *J* = 8.6, 2.7 Hz, 1 H), 7.18 (br d, *J* = 8.7 Hz, 2 H); HRFABMS calcd for $C_{13}H_9F_3NO_2$ *m*/*z* $[M + H]^+$ 268.0585, found 268.0588.

(4-{[6-(Trifluoromethyl)pyridin-3-yl]oxy}phenyl)methanol (98d). Reduction of aldehyde **97d** with $NaBH_4$, using procedure F, gave **98d** (97%) as a clear oil; ^{1}H NMR ($CDCl_3$) δ 8.46 (d, *J* = 2.7 Hz, 1 H), 7.62 (d, *J* = 8.6 Hz, 1 H), 7.43 (br d, *J* = 8.6 Hz, 2 H), 7.33 (dd, *J* = 8.6, 2.7 Hz, 1 H), 7.07 (br d, *J* = 8.6 Hz, 2 H), 4.73 (s, 2 H), 1.74 (br s, 1 H); HREIMS calcd for $C_{13}H_{10}F_3NO_2$ *m*/*z* (M^+) 269.0664, found 269.0661.

5-[4-(Bromomethyl)phenoxy]-2-(trifluoromethyl)pyridine (99d). Bromination of alcohol **98d** with PBr_3, using procedure C for 3 h, gave **99d** (84%) as a clear oil; ^{1}H NMR ($CDCl_3$) δ 8.48 (d, *J* = 2.7 Hz, 1 H), 7.64 (d, *J* = 8.6 Hz, 1 H), 7.45 (br d, *J* = 8.5 Hz, 2 H), 7.36 (dd, *J* = 8.6, 2.7 Hz, 1 H), 7.04 (br d, *J* = 8.5 Hz, 2 H), 4.51 (s, 2 H); HRCIMS (NH_3) calcd for $C_{13}H_{10}BrF_3NO$ *m*/*z* $[M + H]^+$ 333.9877, 331.9898, found 333.9876, 331.9902.

(6*S*)-2-Nitro-6-[(4-{[6-(trifluoromethyl)pyridin-3-yl]oxy}benzyl)oxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (18). Reaction of alcohol **95** with bromide **99d** and NaH, using procedure D for 2.5 h, gave **18** (81%) as a white solid: mp 149-151 °C; ^{1}H NMR [$(CD_3)_2SO$]) δ 8.53 (d, *J* = 2.8 Hz, 1 H), 8.03 (s, 1 H), 7.87 (d, *J* = 8.7 Hz, 1 H), 7.52 (dd, *J* = 8.6, 2.7 Hz, 1 H), 7.42 (br d, *J* = 8.6 Hz, 2 H), 7.18 (br d, *J* = 8.6 Hz, 2 H), 4.71-4.62 (m, 3 H), 4.48 (br d, *J* = 11.8 Hz, 1 H), 4.32-4.21 (m, 3 H). Anal. ($C_{19}H_{15}F_3N_4O_5$) C, H, N.

Synthesis of 21 (Scheme 1C):

[5-(4-Fluorophenoxy)pyridin-2-yl]methanol (104b). Reaction of 5-fluoropyridine-2-carbaldehyde (**102**) with 4-fluorophenol, using procedure J at 110 °C for 20 h, followed by reduction of the resulting aldehyde **103b** with $NaBH_4$, using procedure G, gave **104b** (10% over 2 steps) as a colourless oil; ^{1}H NMR ($CDCl_3$) δ 8.31 (d, *J* = 2.3 Hz, 1 H), 7.32 (dd, *J* = 8.5, 2.6 Hz, 1 H), 7.26 (br d, *J* = 8.4 Hz, 1 H), 7.07 (br dd, *J* = 9.2, 8.0 Hz, 2 H), 7.00 (br dd, *J* = 9.2, 4.5 Hz, 2 H), 4.76 (s, 2 H), one exchangeable proton not evident; HREIMS calcd for $C_{12}H_{10}FNO_2$ *m*/*z* (M^+) 219.0696, found 219.0691.

(6*S*)-6-{[5-(4-Fluorophenoxy)pyridin-2-yl]methoxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (21). Bromination of alcohol **104b** with NBS and PPh_3, using procedure H for 3 h, followed by reaction of the resulting bromide **105b** with alcohol **95** and NaH, using procedure I for 3 h, gave **21** (21% over 2 steps) as a pale yellow solid: mp (CH_2Cl_2/pentane) 170-172 °C; ^{1}H NMR ($CDCl_3$) δ 8.30 (br d, *J* = 2.8 Hz, 1 H), 7.37 (s, 1 H), 7.30 (br d, *J* = 8.6 Hz, 1 H), 7.24 (dd, *J* = 8.5, 2.8 Hz, 1 H), 7.08 (br dd, *J* = 9.1, 8.0 Hz, 2 H), 7.00 (br dd, *J* = 9.2, 4.5 Hz, 2 H), 4.77 (d, *J* = 12.5 Hz, 1 H), 4.72 (d, *J* = 12.5 Hz, 1 H), 4.65 (ddd, *J* = 12.2, 3.6, 1.6 Hz, 1 H), 4.36 (dd, *J* = 12.1, 1.4 Hz, 1 H), 4.29-4.16 (m, 3 H). Anal. ($C_{18}H_{15}FN_4O_5$) C, H, N.

Synthesis of 22 (Scheme 1C):

5-[4-(Trifluoromethyl)phenoxy]pyridine-2-carbaldehyde (103c). Reaction of aldehyde **102** with 4-(trifluoromethyl)phenol, using procedure J at 110 °C for 19 h, gave crude **103c**

(99%) as a colourless oil; ^{1}H NMR ($CDCl_3$) δ 10.04 (d, *J* = 0.8 Hz, 1 H), 8.55 (dd, *J* = 2.6, 0.4 Hz, 1 H), 7.99 (dd, *J* = 8.6, 0.5 Hz, 1 H), 7.70 (br d, *J* = 8.4 Hz, 2 H), 7.41 (ddd, *J* = 8.6, 2.7, 0.8 Hz, 1 H), 7.19 (br d, *J* = 8.4 Hz, 2 H); HRESIMS calcd for $C_{13}H_9F_3NO_2$ *m/z* $[M + H]^+$ 268.0580, found 268.0580.

{5-[4-(Trifluoromethyl)phenoxy]pyridin-2-yl}methanol (104c). Reduction of crude aldehyde **103c** with $NaBH_4$, using procedure G for 1 h, gave **104c** (88%) as a colourless oil; ^{1}H NMR ($CDCl_3$) δ 8.39 (br d, *J* = 2.5 Hz, 1 H), 7.61 (br d, *J* = 8.5 Hz, 2 H), 7.39 (dd, *J* = 8.5, 2.7 Hz, 1 H), 7.31 (br d, *J* = 8.5 Hz, 1 H), 7.07 (br d, *J* = 9.0 Hz, 2 H), 4.78 (d, *J* = 5.2 Hz, 2 H), 3.33 (t, *J* = 5.3 Hz, 1 H); HRESIMS calcd for $C_{13}H_{11}F_3NO_2$ *m/z* $[M + H]^+$ 270.0736, found 270.0740.

2-(Bromomethyl)-5-[4-(trifluoromethyl)phenoxy]pyridine (105c). Bromination of alcohol **104c** with NBS and PPh_3, using procedure H for 3 h, gave **105c** (85%) as a colourless oil that was used directly in the next step; ^{1}H NMR ($CDCl_3$) δ 8.38 (br d, *J* = 2.8 Hz, 1 H), 7.63 (br d, *J* = 8.5 Hz, 2 H), 7.46 (br d, *J* = 8.5 Hz, 1 H), 7.33 (dd, *J* = 8.5, 2.8 Hz, 1 H), 7.10 (br d, *J* = 8.4 Hz, 2 H), 4.57 (s, 2 H); APCI MS *m/z* 334, 332 $[M + H]^+$.

(6*S*)-2-Nitro-6-({5-[4-(trifluoromethyl)phenoxy]pyridin-2-yl}methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (22). Reaction of alcohol **95** with bromide **105c** (1.1 equiv) and NaH, using procedure I for 3 h, gave **22** (74%) as a cream solid: mp (CH_2Cl_2/pentane) 130-131 °C; ^{1}H NMR ($CDCl_3$) δ 8.37 (dd, *J* = 2.2, 1.2 Hz, 1 H), 7.63 (br d, *J* = 8.5 Hz, 2 H), 7.39 (s, 1 H), 7.38 (d, *J* = 8.5 Hz, 1 H), 7.36 (dd, *J* = 8.5, 2.2 Hz, 1 H), 7.08 (br d, *J* = 8.4 Hz, 2 H), 4.81 (d, *J* = 12.6 Hz, 1 H), 4.75 (d, *J* = 12.6 Hz, 1 H), 4.68 (ddd, *J* = 12.2, 3.4, 1.5 Hz, 1 H), 4.38 (dd, *J* = 12.2, 1.5 Hz, 1 H), 4.31-4.19 (m, 3 H). Anal. ($C_{19}H_{15}F_3N_4O_5$) C, H, N.

Synthesis of 23 (Scheme 1C):

(5-{[6-(Trifluoromethyl)pyridin-3-yl]oxy}pyridin-2-yl)methanol (104d). Reaction of aldehyde **102** with 6-(trifluoromethyl)pyridin-3-ol, using procedure J at 110 °C for 20 h, followed by reduction of the resulting aldehyde **103d** with $NaBH_4$, using procedure G, gave **104d** (53% over 2 steps) as a colourless oil; ^{1}H NMR ($CDCl_3$) δ 8.50 (d, *J* = 2.7 Hz, 1 H), 8.43 (d, *J* = 2.6 Hz, 1 H), 7.67 (d, *J* = 8.7 Hz, 1 H), 7.43 (dd, *J* = 8.5, 2.7 Hz, 1 H), 7.40-7.32 (m, 2 H), 4.80 (d, *J* = 5.1 Hz, 2 H), 3.31 (t, *J* = 5.3 Hz, 1 H); HRESIMS calcd for $C_{12}H_{10}F_3N_2O_2$ *m/z* $[M + H]^+$ 271.0689, found 271.0695.

2-(Bromomethyl)-5-{[6-(trifluoromethyl)pyridin-3-yl]oxy}pyridine (105d). Bromination of alcohol **104d** with NBS and PPh_3, using procedure H for 3 h, gave **105d** (85%) as a light red oil that was used directly in the next step; ^{1}H NMR ($CDCl_3$) δ 8.51 (d, *J* = 2.7 Hz, 1 H), 8.42 (d, *J* = 2.7 Hz, 1 H), 7.69 (d, *J* = 8.6 Hz, 1 H), 7.51 (d, *J* = 8.4 Hz, 1 H), 7.41 (br dd, *J* = 8.7, 2.8 Hz, 1 H), 7.38 (dd, *J* = 8.5, 2.8 Hz, 1 H), 4.58 (s, 2 H); APCI MS *m/z* 335, 333 $[M + H]^+$.

(6*S*)-2-Nitro-6-[(5-{[6-(trifluoromethyl)pyridin-3-yl]oxy}pyridin-2-yl)methoxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (23). Reaction of alcohol **95** with bromide **105d** and NaH, using procedure I for 2 h, gave **23** (62%) as a pale yellow solid: mp (CH_2Cl_2/pentane) 121-123 °C; ^{1}H NMR ($CDCl_3$) δ 8.49 (d, *J* = 2.7 Hz, 1 H), 8.40 (dd, *J* = 2.0, 1.4 Hz, 1 H), 7.69 (d, *J* = 8.6 Hz, 1 H), 7.45-7.36 (m, 4 H), 4.83 (d, *J* = 12.7 Hz, 1 H), 4.77 (d, *J* = 12.7 Hz, 1 H), 4.70 (ddd, *J* = 12.2, 3.3, 1.3 Hz, 1 H), 4.39 (dd, *J* = 12.2, 1.2 Hz, 1 H), 4.32-4.20 (m, 3 H). Anal. ($C_{18}H_{14}F_3N_5O_5$) C, H, N.

Synthesis of 24 (Scheme 1D):

6-[4-(Trifluoromethoxy)phenoxy]pyridine-3-carbaldehyde (108a). Reaction of 6-fluoropyridine-3-carbaldehyde (**106**) with 4-(trifluoromethoxy)phenol, using procedure J at 102 °C for 15 h, followed by chromatography of the product on silica gel (50 g), eluting with 0-40% CH_2Cl_2/petroleum ether (foreruns) and then with 40-60% CH_2Cl_2/petroleum ether, gave **108a**[7] (70%) as a colourless oil; ^{1}H NMR ($CDCl_3$) δ 10.00 (s, 1 H), 8.62 (d, *J* = 2.3 Hz, 1 H), 8.21 (dd, *J* = 8.6, 2.3 Hz, 1 H), 7.29 (br d, *J* = 9.0 Hz, 2 H), 7.20 (br d, *J* = 9.1 Hz, 2 H), 7.08 (d, *J* = 8.5 Hz, 1 H); HREIMS calcd for $C_{13}H_8F_3NO_3$ *m*/*z* (M^+) 283.0456, found 283.0464.

{6-[4-(Trifluoromethoxy)phenoxy]pyridin-3-yl}methanol (109a). Reduction of aldehyde **108a** with $NaBH_4$, using procedure G, gave **109a**[8] (90%) as a colourless oil; ^{1}H NMR ($CDCl_3$) δ 8.16 (br d, *J* = 2.4 Hz, 1 H), 7.76 (dd, *J* = 8.4, 2.5 Hz, 1 H), 7.24 (br d, *J* = 9.0 Hz, 2 H), 7.15 (br d, *J* = 9.1 Hz, 2 H), 6.95 (d, *J* = 8.4 Hz, 1 H), 4.68 (d, *J* = 5.7 Hz, 2 H), 1.70 (t, *J* = 5.7 Hz, 1 H); HREIMS calcd for $C_{13}H_{10}F_3NO_3$ *m*/*z* (M^+) 285.0613, found 285.0613.

5-(Bromomethyl)-2-[4-(trifluoromethoxy)phenoxy]pyridine (110a). Bromination of alcohol **109a** with NBS and PPh_3, using procedure H for 2 h, gave **110a** (92%) as a colourless oil; ^{1}H NMR ($CDCl_3$) δ 8.17 (d, *J* = 2.4 Hz, 1 H), 7.76 (dd, *J* = 8.5, 2.5 Hz, 1 H), 7.25 (m, 2 H), 7.16 (br d, *J* = 9.1 Hz, 2 H), 6.94 (d, *J* = 8.5 Hz, 1 H), 4.46 (s, 2 H); HREIMS calcd for $C_{13}H_9BrF_3NO_2$ *m*/*z* (M^+) 348.9748, 346.9769, found 348.9747, 346.9763.

(6*S*)-2-Nitro-6-({6-[4-(trifluoromethoxy)phenoxy]pyridin-3-yl}methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (24). Reaction of alcohol **95** with bromide **110a** and NaH, using procedure I for 3 h, gave **24** (75%) as a pale yellow solid: mp (MeOH/CH_2Cl_2/hexane) 179-181 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.11 (br d, *J* = 2.3 Hz, 1 H), 8.03 (s, 1 H), 7.83 (dd, *J* = 8.4, 2.4 Hz, 1 H), 7.40 (br d, *J* = 9.0 Hz, 2 H), 7.24 (br d, *J* = 9.1 Hz, 2 H), 7.08 (br d, *J* = 8.5 Hz, 1 H), 4.66 (dt, *J* = 12.1, 2.5 Hz, 1 H), 4.66 (d, *J* = 12.0 Hz, 1 H), 4.62 (d, *J* = 11.8 Hz, 1 H), 4.47 (br d, *J* = 11.8 Hz, 1 H), 4.30-4.19 (m, 3 H); ^{13}C NMR [$(CD_3)_2SO$] δ 162.3, 152.6, 147.1, 146.7, 144.6 (q, $J_{C\text{-}F}$ = 1.6 Hz), 142.1, 140.4, 128.8, 122.8 (2 C), 122.5 (2 C), 120.1 (q, $J_{C\text{-}F}$ = 256.0 Hz), 118.0, 111.5, 67.8, 66.7, 66.4, 46.8. Anal. ($C_{19}H_{15}F_3N_4O_6$) C, H, N. HPLC purity: 100%.

Synthesis of 25 (Scheme 1D):

5-Bromo-2-(4-fluorophenoxy)pyridine (107b). Reaction of 5-bromo-2-fluoropyridine (**111**) with 4-fluorophenol, using procedure K, gave **107b**[7] (84%) as a white solid: mp (pentane) 50-51 °C; ^{1}H NMR ($CDCl_3$) δ 8.20 (br d, *J* = 2.6 Hz, 1 H), 7.77 (dd, *J* = 8.7, 2.6 Hz, 1 H), 7.08 (m, 4 H), 6.83 (br d, *J* = 8.7 Hz, 1 H); HREIMS calcd for $C_{11}H_7BrFNO$ *m*/*z* (M^+) 268.9675, 266.9695, found 268.9682, 266.9692.

6-(4-Fluorophenoxy)pyridine-3-carbaldehyde (108b). *n*BuLi (0.82 mL of a 2.5M solution in hexanes, 2.05 mmol) was added dropwise to a stirred solution of bromide **107b** (500 mg, 1.87 mmol) in anhydrous THF (10 mL) under N_2 at -78 °C. After 1 h at -78 °C, anhydrous DMF (0.50 mL, 6.46 mmol) was added, and the mixture was stirred at -78 °C for 40 min, slowly warmed to 20 °C (over 1.5 h), and then quenched with aqueous citric acid (9 mL of a 0.25 M solution, 2.25 mmol). Water (40 mL) was added and the mixture was extracted with EtOAc (3 x 50 mL). The extracts were washed with brine (50 mL) and then concentrated under reduced pressure, and the residue was chromatographed on silica gel (30 g). Elution with 0-40% CH_2Cl_2/petroleum ether first gave foreruns, and then further elution with 40-70% CH_2Cl_2/petroleum ether gave **108b**[7] (269 mg, 66%) as a white solid: mp (CH_2Cl_2/pentane) 100-101 °C; ^{1}H NMR ($CDCl_3$) δ 9.98 (d, *J* = 0.4 Hz, 1 H), 8.61 (dd, *J* = 2.3, 0.4 Hz, 1 H),

8.19 (dd, *J* = 8.6, 2.4 Hz, 1 H), 7.17-7.09 (m, 4 H), 7.04 (br d, *J* = 8.6 Hz, 1 H); HREIMS calcd for $C_{12}H_8FNO_2$ *m/z* (M^+) 217.0539, found 217.0534.

[6-(4-Fluorophenoxy)pyridin-3-yl]methanol (109b). Reduction of aldehyde **108b** with $NaBH_4$, using procedure G, gave **109b** (89%) as a white solid: mp (CH_2Cl_2/pentane) 74-76 °C; ^{1}H NMR ($CDCl_3$) δ 8.14 (d, *J* = 2.2 Hz, 1 H), 7.74 (dd, *J* = 8.4, 2.5 Hz, 1 H), 7.13-7.04 (m, 4 H), 6.91 (d, *J* = 8.4 Hz, 1 H), 4.67 (d, *J* = 5.7 Hz, 2 H), 1.66 (t, *J* = 5.7 Hz, 1 H); HREIMS calcd for $C_{12}H_{10}FNO_2$ *m/z* (M^+) 219.0696, found 219.0687.

5-(Bromomethyl)-2-(4-fluorophenoxy)pyridine (110b). Bromination of alcohol **109b** with NBS and PPh_3, using procedure H for 3 h, gave **110b** (82%) as a white solid that was used directly in the next step; ^{1}H NMR ($CDCl_3$) δ 8.16 (d, *J* = 2.5 Hz, 1 H), 7.73 (dd, *J* = 8.5, 2.5 Hz, 1 H), 7.13-7.05 (m, 4 H), 6.90 (d, *J* = 8.5 Hz, 1 H), 4.45 (s, 2 H); APCI MS *m/z* 284, 282 $[M + H]^+$.

(6*S*)-6-{[6-(4-Fluorophenoxy)pyridin-3-yl]methoxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (25). Reaction of alcohol **95** with bromide **110b** and NaH, using procedure I for 3 h, gave **25** (72%) as a cream solid: mp (CH_2Cl_2/hexane) 149-150 °C; ^{1}H NMR ($CDCl_3$) δ 8.09 (d, *J* = 2.3 Hz, 1 H), 7.66 (dd, *J* = 8.5, 2.5 Hz, 1 H), 7.39 (s, 1 H), 7.11-7.04 (m, 4 H), 6.93 (d, *J* = 8.5 Hz, 1 H), 4.67 (d, *J* = 11.6 Hz, 1 H), 4.62 (ddd, *J* = 12.2, 3.7, 2.2 Hz, 1 H), 4.57 (d, *J* = 11.6 Hz, 1 H), 4.36 (dd, *J* = 12.2, 1.3 Hz, 1 H), 4.21 (br dd, *J* = 13.2, 4.3 Hz, 1 H), 4.16-4.09 (m, 2 H). Anal. ($C_{18}H_{15}FN_4O_5$) C, H, N.

Synthesis of 26 (Scheme 1D):

6-[4-(Trifluoromethyl)phenoxy]pyridine-3-carbaldehyde (108c). Reaction of aldehyde **106** with 4-(trifluoromethyl)phenol, using procedure J at 100 °C for 9 h, followed by chromatography of the product on silica gel (30 g), eluting with 0-5% Et_2O/petroleum ether (foreruns) and then with 6% Et_2O/petroleum ether, gave **108c**[8] (56%) as a colourless oil; ^{1}H NMR ($CDCl_3$) δ 10.00 (d, *J* = 0.4 Hz, 1 H), 8.62 (dd, *J* = 2.3, 0.5 Hz, 1 H), 8.24 (dd, *J* = 8.6, 2.3 Hz, 1 H), 7.71 (br d, *J* = 8.4 Hz, 2 H), 7.30 (br d, *J* = 8.4 Hz, 2 H), 7.11 (br d, *J* = 8.6 Hz, 1 H); HRESIMS calcd for $C_{13}H_9F_3NO_2$ *m/z* $[M + H]^+$ 268.0580, found 268.0579.

{6-[4-(Trifluoromethyl)phenoxy]pyridin-3-yl}methanol (109c). Reduction of aldehyde **108c** with $NaBH_4$, using procedure G, gave **109c**[9] (78%) as a white solid: mp (pentane) 65-67 °C; ^{1}H NMR ($CDCl_3$) δ 8.18 (d, *J* = 2.3 Hz, 1 H), 7.79 (dd, *J* = 8.4, 2.4 Hz, 1 H), 7.65 (br d, *J* = 8.7 Hz, 2 H), 7.23 (br d, *J* = 8.6 Hz, 2 H), 6.99 (d, *J* = 8.4 Hz, 1 H), 4.70 (d, *J* = 5.6 Hz, 2 H), 1.71 (t, *J* = 5.7 Hz, 1 H); HRESIMS calcd for $C_{13}H_{11}F_3NO_2$ *m/z* $[M + H]^+$ 270.0736, found 270.0742.

5-(Bromomethyl)-2-[4-(trifluoromethyl)phenoxy]pyridine (110c). Bromination of alcohol **109c** with NBS and PPh_3, using procedure H for 3 h, gave **110c** (98%) as a white solid that was used directly in the next step; ^{1}H NMR ($CDCl_3$) δ 8.18 (br d, *J* = 2.5 Hz, 1 H), 7.79 (dd, *J* = 8.5, 2.5 Hz, 1 H), 7.66 (br d, *J* = 8.4 Hz, 2 H), 7.25 (m, 2 H), 6.98 (br d, *J* = 8.5 Hz, 1 H), 4.46 (s, 2 H); APCI MS *m/z* 334, 332 $[M + H]^+$.

(6*S*)-2-Nitro-6-({6-[4-(trifluoromethyl)phenoxy]pyridin-3-yl}methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (26). Reaction of alcohol **95** with bromide **110c** and NaH (1.3 equiv), using procedure I for 3 h, gave **26** (81%) as a pale yellow solid: mp (CH_2Cl_2/hexane) 162-164 °C; ^{1}H NMR ($CDCl_3$) δ 8.11 (br d, *J* = 2.3 Hz, 1 H), 7.71 (dd, *J* = 8.4, 2.5 Hz, 1 H), 7.66 (br d, *J* = 8.5 Hz, 2 H), 7.40 (s, 1 H), 7.23 (br d, *J* = 8.3 Hz, 2 H), 7.00 (d, *J* = 8.4 Hz, 1 H), 4.70 (d, *J* = 11.6 Hz, 1 H), 4.64 (ddd, *J* = 12.3, 3.6, 2.3 Hz, 1 H), 4.60 (d, *J* = 11.6 Hz, 1

H), 4.37 (dd, *J* = 12.2, 1.4 Hz, 1 H), 4.22 (br dd, *J* = 13.3, 4.3 Hz, 1 H), 4.19-4.11 (m, 2 H). Anal. ($C_{19}H_{15}F_3N_4O_5$) C, H, N.

Synthesis of 27 (Scheme 1D):

6-{[6-(Trifluoromethyl)pyridin-3-yl]oxy}pyridine-3-carbaldehyde (108d). Reaction of aldehyde **106** with 6-(trifluoromethyl)pyridin-3-ol, using procedure J at 102 °C for 15 h, followed by chromatography of the product on silica gel (40 g), eluting with 0-60% CH_2Cl_2/petroleum ether (foreruns) and then with 75-80% CH_2Cl_2/petroleum ether and CH_2Cl_2, gave **108d** (67%) as a colourless oil; ^{1}H NMR ($CDCl_3$) δ 10.03 (s, 1 H), 8.64 (d, *J* = 2.3 Hz, 1 H), 8.60 (d, *J* = 2.1 Hz, 1 H), 8.28 (dd, *J* = 8.6, 2.3 Hz, 1 H), 7.79 (br d, *J* = 8.0 Hz, 1 H), 7.75 (dd, *J* = 8.6, 2.4 Hz, 1 H), 7.19 (d, *J* = 8.6 Hz, 1 H); HREIMS calcd for $C_{12}H_7F_3N_2O_2$ *m/z* (M^+) 268.0460, found 268.0460.

(6-{[6-(Trifluoromethyl)pyridin-3-yl]oxy}pyridin-3-yl)methanol (109d). Reduction of aldehyde **108d** with $NaBH_4$, using procedure G, gave **109d** (69%) as a colourless oil; ^{1}H NMR ($CDCl_3$) δ 8.59 (d, *J* = 2.4 Hz, 1 H), 8.14 (br d, *J* = 2.3 Hz, 1 H), 7.83 (dd, *J* = 8.4, 2.4 Hz, 1 H), 7.72 (br d, *J* = 8.2 Hz, 1 H), 7.68 (dd, *J* = 8.7, 2.2 Hz, 1 H), 7.06 (d, *J* = 8.4 Hz, 1 H), 4.71 (d, *J* = 5.6 Hz, 2 H), 1.77 (t, *J* = 5.6 Hz, 1 H); HRCIMS (NH_3) calcd for $C_{12}H_{10}F_3N_2O_2$ *m/z* $[M + H]^+$ 271.0694, found 271.0697.

5-(Bromomethyl)-2-{[6-(trifluoromethyl)pyridin-3-yl]oxy}pyridine (110d). Bromination of alcohol **109d** with NBS and PPh_3, using procedure H for 3 h, gave **110d** (71%) as a colourless oil that was used directly in the next step; ^{1}H NMR ($CDCl_3$) δ 8.60 (d, *J* = 2.4 Hz, 1 H), 8.15 (d, *J* = 2.4 Hz, 1 H), 7.83 (dd, *J* = 8.5, 2.5 Hz, 1 H), 7.73 (br d, *J* = 8.5 Hz, 1 H), 7.70 (dd, *J* = 8.6, 2.4 Hz, 1 H), 7.05 (d, *J* = 8.5 Hz, 1 H), 4.47 (s, 2 H); APCI MS *m/z* 335, 333 $[M + H]^+$.

(6*S*)-2-Nitro-6-[(6-{[6-(trifluoromethyl)pyridin-3-yl]oxy}pyridin-3-yl)methoxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (27). Reaction of alcohol **95** with bromide **110d** and NaH (1.6 equiv), using procedure I, gave **27** (74%) as a light yellow solid: mp (CH_2Cl_2/pentane) 158-160 °C; ^{1}H NMR ($CDCl_3$) δ 8.59 (d, *J* = 2.5 Hz, 1 H), 8.08 (d, *J* = 2.1 Hz, 1 H), 7.75 (dd, *J* = 8.4, 2.5 Hz, 1 H), 7.73 (br d, *J* = 8.9 Hz, 1 H), 7.68 (dd, *J* = 8.6, 2.4 Hz, 1 H), 7.40 (s, 1 H), 7.07 (d, *J* = 8.4 Hz, 1 H), 4.71 (d, *J* = 11.5 Hz, 1 H), 4.66 (ddd, *J* = 12.3, 3.5, 2.3 Hz, 1 H), 4.61 (d, *J* = 11.6 Hz, 1 H), 4.38 (dd, *J* = 12.2, 1.1 Hz, 1 H), 4.24 (dd, *J* = 13.3, 4.3 Hz, 1 H), 4.19-4.12 (m, 2 H). Anal. ($C_{18}H_{14}F_3N_5O_5$) C, H, N.

Synthesis of 29 (Scheme 2A):

Methyl 4-[(*E*)-2-(4-fluorophenyl)ethenyl]benzoate (114b). Reaction of 4-fluorobenzaldehyde (**113b**) with [4-(methoxycarbonyl)benzyl]triphenylphosphonium bromide (**112**), using procedure L, gave **114b**[10] (42%) as white flakes: mp (petroleum ether) 145-146 °C (lit.[10] mp 144 °C); ^{1}H NMR ($CDCl_3$) δ 8.02 (br d, *J* = 8.4 Hz, 2 H), 7.55 (br d, *J* = 8.4 Hz, 2 H), 7.50 (br dd, *J* = 8.8, 5.4 Hz, 2 H), 7.17 (d, *J* = 16.3 Hz, 1 H), 7.07 (br t, *J* = 8.7 Hz, 2 H), 7.04 (d, *J* = 16.4 Hz, 1 H), 3.92 (s, 3 H); APCI MS *m/z* 257 $[M + H]^+$.

{4-[(*E*)-2-(4-Fluorophenyl)ethenyl]phenyl}methanol (115b). Reduction of ester **114b** with $LiAlH_4$ (1.0 equiv), using procedure M for 1 h, gave **115b** (89%) as a white solid: mp 168-170 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.64 (dd, *J* = 8.8, 5.6 Hz, 2 H), 7.54 (br d, *J* = 8.2 Hz, 2 H), 7.32 (br d, *J* = 8.2 Hz, 2 H), 7.26-7.14 (m, 4 H), 5.15 (t, *J* = 5.7 Hz, 1 H), 4.50 (d, *J* = 5.7 Hz, 2 H); APCI MS *m/z* 211 $[M + H - H_2O]^+$.

1-(Bromomethyl)-4-[(*E*)-2-(4-fluorophenyl)ethenyl]benzene (116b). Bromination of alcohol **115b** with PBr_3, using procedure N, gave **116b**[11] (75%) as a white solid: mp 111-113 °C (lit.[11] mp 111 °C); ^{1}H NMR ($CDCl_3$) δ 7.51-7.44 (m, 4 H), 7.38 (br d, *J* = 8.2 Hz, 2 H), 7.11-6.96 (m, 4 H), 4.51 (s, 2 H); APCI MS *m*/*z* 211 $[M + H - HBr]^+$.

(6*S*)-6-({4-[(*E*)-2-(4-Fluorophenyl)ethenyl]benzyl}oxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (29). Reaction of alcohol **95** with bromide **116b** (1.0 equiv) and NaH (1.5 equiv), using procedure O, gave **29** (74%) as a white solid: mp 248-250 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.02 (s, 1 H), 7.64 (br dd, *J* = 8.8, 5.6 Hz, 2 H), 7.57 (br d, *J* = 8.2 Hz, 2 H), 7.32 (br d, *J* = 8.2 Hz, 2 H), 7.28-7.15 (m, 4 H), 4.69-4.60 (m, 3 H), 4.47 (br d, *J* = 11.9 Hz, 1 H), 4.31-4.20 (m, 3 H). Anal. ($C_{21}H_{18}FN_3O_4$) C, H, N.

Synthesis of 30 (Scheme 2A):

Methyl 4-{(*E*)-2-[4-(trifluoromethyl)phenyl]ethenyl}benzoate (114c). Reaction of 4-(trifluoromethyl)benzaldehyde (**113c**) with phosphonium salt **112**, using procedure L, gave **114c**[12] (46%) as white flakes: mp (petroleum ether) 158-160 °C (lit.[12] mp 157-158 °C); ^{1}H NMR ($CDCl_3$) δ 8.05 (br d, *J* = 8.5 Hz, 2 H), 7.62 (s, 4 H), 7.59 (br d, *J* = 8.5 Hz, 2 H), 7.22 (s, 2 H), 3.93 (s, 3 H); APCI MS *m*/*z* 307 $[M + H]^+$.

(4-{(*E*)-2-[4-(Trifluoromethyl)phenyl]ethenyl}phenyl)methanol (115c). Reduction of ester **114c** with $LiAlH_4$ (1.0 equiv), using procedure M for 1 h, gave **115c** (91%) as a white solid: mp 188-191 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.81 (br d, *J* = 8.2 Hz, 2 H), 7.72 (br d, *J* = 8.3 Hz, 2 H), 7.61 (d, *J* = 8.2 Hz, 2 H), 7.42 (d, *J* = 16.5 Hz, 1 H), 7.38-7.29 (m, 3 H), 5.18 (t, *J* = 5.7 Hz, 1 H), 4.52 (d, *J* = 5.7 Hz, 2 H); APCI MS *m*/*z* 261 $[M + H - H_2O]^+$.

1-(Bromomethyl)-4-{(*E*)-2-[4-(trifluoromethyl)phenyl]ethenyl}benzene (116c). Bromination of alcohol **115c** with PBr_3, using procedure N, gave **116c**[11] (73%) as a white solid: mp 107-110 °C; ^{1}H NMR ($CDCl_3$) δ 7.63-7.57 (m, 4 H), 7.50 (br d, *J* = 8.3 Hz, 2 H), 7.40 (br d, *J* = 8.2 Hz, 2 H), 7.18 (d, *J* = 16.4 Hz, 1 H), 7.12 (d, *J* = 16.4 Hz, 1 H), 4.51 (s, 2 H); APCI MS *m*/*z* 261 $[M + H - HBr]^+$.

(6*S*)-2-Nitro-6-[(4-{(*E*)-2-[4-(trifluoromethyl)phenyl]ethenyl}benzyl)oxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (30). Reaction of alcohol **95** with bromide **116c** (1.0 equiv) and NaH (1.6 equiv), using procedure O, gave **30** (73%) as a white solid: mp 267-270 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.03 (s, 1 H), 7.81 (br d, *J* = 8.2 Hz, 2 H), 7.72 (br d, *J* = 8.3 Hz, 2 H), 7.63 (br d, *J* = 8.2 Hz, 2 H), 7.42 (d, *J* = 16.5 Hz, 1 H), 7.37-7.30 (m, 3 H), 4.71-4.62 (m, 3 H), 4.48 (d, *J* = 11.9 Hz, 1 H), 4.31-4.20 (m, 3 H). Anal. ($C_{22}H_{18}F_3N_3O_4$) C, H, N.

Synthesis of 31 (Scheme 2A):

Methyl 4-{(*E*)-2-[6-(trifluoromethyl)pyridin-3-yl]ethenyl}benzoate (114d). Reaction of 6-(trifluoromethyl)pyridine-3-carbaldehyde (**113d**) (1.1 equiv) with phosphonium salt **112**, using procedure L, gave **114d** (30%) as white flakes: mp (petroleum ether) 128-130 °C; ^{1}H NMR ($CDCl_3$) δ 8.84 (d, *J* = 1.7 Hz, 1 H), 8.07 (d, *J* = 8.4 Hz, 2 H), 7.99 (dd, *J* = 8.2, 2.0 Hz, 1 H), 7.69 (d, *J* = 8.2 Hz, 1 H), 7.61 (d, *J* = 8.3 Hz, 2 H), 7.29 (d, *J* = 16.5 Hz, 1 H), 7.21 (d, *J* = 16.4 Hz, 1 H), 3.94 (s, 3 H); APCI MS *m*/*z* 308 $[M + H]^+$.

(4-{(*E*)-2-[6-(Trifluoromethyl)pyridin-3-yl]ethenyl}phenyl)methanol (115d). Reduction of ester **114d** with $LiAlH_4$ (1.0 equiv), using procedure M for 1 h, gave **115d** (67%) as a white solid: mp 145-147 °C; ^{1}H NMR ($CDCl_3$) δ ^{1}H NMR [$(CD_3)_2SO$] δ 8.96 (d, *J* = 1.6 Hz, 1 H), 8.29 (dd, *J* = 8.2, 1.7 Hz, 1 H), 7.89 (d, *J* = 8.2 Hz, 1 H), 7.63 (d, *J* = 8.2 Hz, 2 H), 7.56

(d, *J* = 16.6 Hz, 1 H), 7.40-7.32 (m, 3 H), 5.20 (t, *J* = 5.7 Hz, 1 H), 4.52 (d, *J* = 5.7 Hz, 2 H); APCI MS *m*/*z* 280 $[M + H]^+$.

5-{(*E*)-2-[4-(Chloromethyl)phenyl]ethenyl}-2-(trifluoromethyl)pyridine (116d). A solution of alcohol **115d** (89 mg, 0.319 mmol) in MeOH (5 mL) was treated with a solution of HCl in MeOH (0.5 mL of 1.25 M, 0.63 mmol). The mixture was stirred at 20 °C for 5 min and then the solvent was removed. The residue was treated with $SOCl_2$ (0.12 mL, 1.65 mmol) in $CHCl_3$ (10 mL), stirring at 20 °C for 20 h. The solvent was removed and the residue was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The organic portion was dried and evaporated, and the residue was chromatographed on silica gel. Elution with 5% EtOAc/CH_2Cl_2 gave **116d** (72 mg, 76%) as a white solid: mp 115-118 °C; ^{1}H NMR ($CDCl_3$) δ 8.82 (br d, *J* = 1.4 Hz, 1 H), 7.97 (dd, *J* = 8.1, 1.7 Hz, 1 H), 7.67 (d, *J* = 8.2 Hz, 1 H), 7.54 (br d, *J* = 8.2 Hz, 2 H), 7.42 (d, *J* = 8.2 Hz, 2 H), 7.25 (d, *J* = 16.4 Hz, 1 H), 7.12 (d, *J* = 16.4 Hz, 1 H), 4.61 (s, 2 H); APCI MS *m*/*z* 298, 300 $[M + H]^+$.

(6*S*)-2-Nitro-6-[(4-{(*E*)-2-[6-(trifluoromethyl)pyridin-3-yl]ethenyl}benzyl)oxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (31). Reaction of alcohol **95** with chloride **116d** (1.0 equiv) and NaH (1.5 equiv), using procedure O at 0 °C for 1 h and then at 20 °C for 3 h, gave **31** (19%) as a white solid: mp 214-216 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.96 (d, *J* = 1.4 Hz, 1 H), 8.29 (dd, *J* = 8.3, 1.6 Hz, 1 H), 8.03 (s, 1 H), 7.89 (d, *J* = 8.3 Hz, 1 H), 7.64 (br d, *J* = 8.2 Hz, 2 H), 7.57 (d, *J* = 16.6 Hz, 1 H), 7.42-7.34 (m, 3 H), 4.72-4.63 (m, 3 H), 4.48 (br d, *J* = 11.9 Hz, 1 H), 4.32-4.21 (m, 3 H). Anal. ($C_{21}H_{17}F_3N_4O_4$) C, H, N.

Synthesis of 33-36 (Scheme 2B):

(6*S*)-6-({4-[(4-Fluorophenyl)ethynyl]benzyl}oxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (33). Reaction of (6*S*)-6-[(4-ethynylbenzyl)oxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (**119**) and 1-fluoro-4-iodobenzene (1.6 equiv) under the Sonogashira coupling conditions described in procedure Q gave **33** (81%) as a white solid: mp 227-229 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.02 (s, 1 H), 7.61 (br dd, *J* = 8.9, 5.4 Hz, 2 H), 7.53 (br d, *J* = 8.2 Hz, 2 H), 7.36 (br d, *J* = 8.3 Hz, 2 H), 7.27 br t, *J* = 8.9 Hz, 2 H), 4.73-4.61 (m, 3 H), 4.48 (br d, *J* = 11.9 Hz, 1 H), 4.32-4.21 (m, 3 H). Anal. ($C_{21}H_{16}FN_3O_4 \cdot 0.25H_2O$) C, H, N.

(6*S*)-2-Nitro-6-[(4-{[4-(trifluoromethyl)phenyl]ethynyl}benzyl)oxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (34). Reaction of alkyne **119** and 1-iodo-4-(trifluoromethyl)benzene (1.3 equiv) under the Sonogashira coupling conditions described in procedure Q gave **34** (77%) as a white solid: mp 262-265 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.03 (s, 1 H), 7.81-7.75 (m, 4 H), 7.58 (br d, *J* = 8.2 Hz, 2 H), 7.39 (br d, *J* = 8.3 Hz, 2 H), 4.75-4.64 (m, 3 H), 4.48 (br d, *J* = 11.9 Hz, 1 H), 4.32-4.21 (m, 3 H). Anal. ($C_{22}H_{16}F_3N_3O_4$) C, H, N.

(6*S*)-2-Nitro-6-[(4-{[6-(trifluoromethyl)pyridin-3-yl]ethynyl}benzyl)oxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (35). Reaction of alkyne **119** and 5-bromo-2-(trifluoromethyl)pyridine (1.6 equiv) under the Sonogashira coupling conditions described in procedure Q (but at 50 °C for 30 min) gave **35** (61%) as a white solid: mp 229-231 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.94 (d, *J* = 1.4 Hz, 1 H), 8.26 (dd, *J* = 8.2, 1.6 Hz, 1 H), 8.03 (s, 1 H), 7.97 (d, *J* = 8.2 Hz, 1 H), 7.62 (br d, *J* = 8.2 Hz, 2 H), 7.41 (br d, *J* = 8.2 Hz, 2 H), 4.76-4.65 (m, 3 H), 4.49 (br d, *J* = 11.9 Hz, 1 H), 4.32-4.21 (m, 3 H). Anal. ($C_{21}H_{15}F_3N_4O_4$) C, H, N. HPLC purity: 98.4%.

(6*S*)-2-Nitro-6-[(4-{[5-(trifluoromethyl)pyridin-2-yl]ethynyl}benzyl)oxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (36). Reaction of alkyne **119** and 2-iodo-5-(trifluoromethyl)pyridine (1.6 equiv) under the Sonogashira coupling conditions described in procedure Q gave **36** (64%) as a white solid: mp 248-250 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.99 (br d, *J* = 2.2 Hz, 1 H), 8.27 (dd, *J* = 8.4, 2.2 Hz, 1 H), 8.03 (s, 1 H), 7.87 (d, *J* = 8.3 Hz, 1 H), 7.64 (br d, *J* = 8.2 Hz, 2 H), 7.42 (br d, *J* = 8.2 Hz, 2 H), 4.76-4.65 (m, 3 H), 4.49 (br d, *J* = 11.8 Hz, 1 H), 4.32-4.21 (m, 3 H). Anal. ($C_{21}H_{15}F_3N_4O_4$) C, H, N.

Synthesis of 37-41 (Scheme 2B):

(6*S*)-6-[(3-Ethynylbenzyl)oxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (120). Reaction of (6*S*)-6-[(3-iodobenzyl)oxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine[13] (**118**) and ethynyl(trimethylsilane) under the Sonogashira coupling conditions described in procedure P, followed by desilylation of the crude product with TBAF, as described in procedure P, gave **120** (69%) as a cream solid: mp 136-138 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.01 (s, 1 H), 7.42-7.33 (m, 4 H), 4.69-4.60 (m, 3 H), 4.47 (br d, *J* = 12.0 Hz, 1 H), 4.31-4.20 (m, 3 H), 4.15 (s, 1 H). Anal. ($C_{15}H_{13}N_3O_4$) C, H, N.

(6*S*)-2-Nitro-6-[(3-{[4-(trifluoromethoxy)phenyl]ethynyl}benzyl)oxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (37). Reaction of alkyne **120** and 1-iodo-4-(trifluoromethoxy)benzene under the Sonogashira coupling conditions described in procedure Q gave **37** (73%) as a white solid: mp 180-181 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.01 (s, 1 H), 7.68 (br d, *J* = 8.8 Hz, 2 H), 7.52-7.47 (m, 2 H), 7.45-7.35 (m, 4 H), 4.72-4.63 (m, 3 H), 4.48 (br d, *J* = 11.8 Hz, 1 H), 4.32-4.21 (m, 3 H). Anal. ($C_{22}H_{16}F_3N_3O_5$) C, H, N.

(6*S*)-6-({3-[(4-Fluorophenyl)ethynyl]benzyl}oxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (38). Reaction of alkyne **120** and 1-fluoro-4-iodobenzene (1.2 equiv) under the Sonogashira coupling conditions described in procedure Q gave **38** (91%) as a white solid: mp 153-155 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.01 (s, 1 H), 7.61 (br dd, *J* = 8.9, 5.5 Hz, 2 H), 7.50-7.45 (m, 2 H), 7.43-7.33 (m, 2 H), 7.27 (br t, *J* = 8.9 Hz, 2 H), 4.71-4.63 (m, 3 H), 4.48 (br d, *J* = 11.9 Hz, 1 H), 4.32-4.21 (m, 3 H). Anal. ($C_{21}H_{16}FN_3O_4$) C, H, N.

(6*S*)-2-Nitro-6-[(3-{[4-(trifluoromethyl)phenyl]ethynyl}benzyl)oxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (39). Reaction of alkyne **120** and 1-iodo-4-(trifluoromethyl)benzene (1.3 equiv) under the Sonogashira coupling conditions described in procedure Q gave **39** (75%) as a white solid: mp 193-196 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.01 (s, 1 H), 7.80 (br d, *J* = 8.8 Hz, 2 H), 7.76 (br d, *J* = 8.7 Hz, 2 H), 7.55-7.50 (m, 2 H), 7.46-7.37 (m, 2 H), 4.73-4.64 (m, 3 H), 4.48 (br d, *J* = 11.8 Hz, 1 H), 4.32-4.21 (m, 3 H). Anal. ($C_{22}H_{16}F_3N_3O_4$) C, H, N.

(6*S*)-2-Nitro-6-[(3-{[6-(trifluoromethyl)pyridin-3-yl]ethynyl}benzyl)oxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (40). Reaction of alkyne **120** and 5-bromo-2-(trifluoromethyl)pyridine (1.6 equiv) under the Sonogashira coupling conditions described in procedure Q (but at 50 °C for 16 h with double quantities of each catalyst) gave **40** (62%) as a white solid: mp 160-162 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.93 (d, *J* = 1.5 Hz, 1 H), 8.26 (dd, *J* = 8.1, 1.5 Hz, 1 H), 8.01 (s, 1 H), 7.98 (d, *J* = 8.2 Hz, 1 H), 7.59-7.54 (m, 2 H), 7.50-7.40 (m, 2 H), 4.74-4.64 (m, 3 H), 4.49 (br d, *J* = 11.9 Hz, 1 H), 4.32-4.21 (m, 3 H). Anal. ($C_{21}H_{15}F_3N_4O_4$) C, H, N.

(6*S*)-2-Nitro-6-[(3-{[5-(trifluoromethyl)pyridin-2-yl]ethynyl}benzyl)oxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (41). Reaction of alkyne **120** and 2-iodo-5-(trifluoromethyl)pyridine (1.2 equiv) under the Sonogashira coupling conditions described in

procedure Q gave **41** (66%) as a white solid: mp 191-194 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.00 (br d, *J* = 2.2 Hz, 1 H), 8.28 (dd, *J* = 8.3, 2.1 Hz, 1 H), 8.01 (s, 1 H), 7.87 (d, *J* = 8.2 Hz, 1 H), 7.62-7.57 (m, 2 H), 7.50-7.42 (m, 2 H), 4.74-4.65 (m, 3 H), 4.48 (br d, *J* = 11.8 Hz, 1 H), 4.32-4.21 (m, 3 H). Anal. ($C_{21}H_{15}F_3N_4O_4$) C, H, N.

Synthesis of 42-46 (Scheme 2C):

(6*S*)-6-[(5-Ethynylpyridin-2-yl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (123). Reaction of (6*S*)-6-[(5-bromopyridin-2-yl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine[14] (**121**) and ethynyl(trimethylsilane) (5.0 equiv) under the Sonogashira coupling conditions described in procedure P (but at 50 °C for 17 h in a sealed tube), followed by desilylation of the crude product with TBAF, as described in procedure P, gave **123** (70%) as a tan solid: mp 141-144 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.61 (br d, *J* = 2.0 Hz, 1 H), 8.02 (s, 1 H), 7.90 (dd, *J* = 8.1, 2.1 Hz, 1 H), 7.38 (d, *J* = 8.2 Hz, 1 H), 4.78 (d, *J* = 13.7 Hz, 1 H), 4.74 (d, *J* = 13.7 Hz, 1 H), 4.69 (dt, *J* = 12.0, 2.6 Hz, 1 H), 4.49 (br d, *J* = 12.0 Hz, 1 H), 4.40 (s, 1 H), 4.35-4.29 (m, 2 H), 4.25 (dd, *J* = 13.7, 3.5 Hz, 1 H). Anal. ($C_{14}H_{12}N_4O_4$) C, H, N.

(6*S*)-2-Nitro-6-[(5-{[4-(trifluoromethoxy)phenyl]ethynyl}pyridin-2-yl)methoxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (42). Reaction of alkyne **123** and 1-iodo-4-(trifluoromethoxy)benzene (1.2 equiv) under the Sonogashira coupling conditions described in procedure Q gave **42** (73%) as a white solid: mp 213 °C (dec); ^{1}H NMR [$(CD_3)_2SO$] δ 8.72 (d, *J* = 2.0 Hz, 1 H), 8.05 (s, 1 H), 7.99 (dd, *J* = 8.1, 2.2 Hz, 1 H), 7.73 (d, *J* = 8.9 Hz, 2 H), 7.47-7.41 (m, 3 H), 4.81 (d, *J* = 13.9 Hz, 1 H), 4.77 (d, *J* = 13.9 Hz, 1 H), 4.71 (dt, *J* = 12.0, 2.5 Hz, 1 H), 4.50 (br d, *J* = 11.9 Hz, 1 H), 4.37-4.31 (m, 2 H), 4.26 (dd, *J* = 13.7, 3.5 Hz, 1 H); ^{13}C NMR [$(CD_3)_2SO$] δ 157.7, 151.0, 148.5 (q, J_{C-F} = 1.4 Hz), 147.1, 142.1, 139.4, 133.6 (2 C), 121.4 (2 C), 121.1, 121.0, 120.0 (q, J_{C-F} = 256.4 Hz), 118.0, 117.8, 90.6, 87.0, 70.6, 68.0, 67.2, 46.7. Anal. ($C_{21}H_{15}F_3N_4O_5$) C, H, N. HPLC purity: 100%.

(6*S*)-6-({5-[(4-Fluorophenyl)ethynyl]pyridin-2-yl}methoxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (43). Reaction of alkyne **123** and 1-fluoro-4-iodobenzene (1.2 equiv) under the Sonogashira coupling conditions described in procedure Q gave **43** (46%) as a white solid: mp 200-203 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.70 (br d, *J* = 1.5 Hz, 1 H), 8.03 (s, 1 H), 7.97 (dd, *J* = 8.1, 2.2 Hz, 1 H), 7.65 (br dd, *J* = 8.9, 5.5 Hz, 2 H), 7.43 (d, *J* = 8.1 Hz, 1 H), 7.29 (br t, *J* = 8.9 Hz, 2 H), 4.80 (d, *J* = 13.7 Hz, 1 H), 4.76 (d, *J* = 13.7 Hz, 1 H), 4.71 (dt, *J* = 12.0, 2.5 Hz, 1 H), 4.50 (br d, *J* = 11.9 Hz, 1 H), 4.37-4.31 (m, 2 H), 4.26 (dd, *J* = 13.7, 3.5 Hz, 1 H). Anal. ($C_{20}H_{15}FN_4O_4$) C, H, N.

(6*S*)-2-Nitro-6-[(5-{[4-(trifluoromethyl)phenyl]ethynyl}pyridin-2-yl)methoxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (44). Reaction of alkyne **123** and 1-iodo-4-(trifluoromethyl)benzene (1.2 equiv) under the Sonogashira coupling conditions described in procedure Q gave **44** (70%) as a white solid: mp 231-235 °C (dec); ^{1}H NMR [$(CD_3)_2SO$] δ 8.75 (br d, *J* = 1.6 Hz, 1 H), 8.05-7.99 (m, 2 H), 7.81 (s, 4 H), 7.45 (d, *J* = 8.2 Hz, 1 H), 4.82 (d, *J* = 13.9 Hz, 1 H), 4.78 (d, *J* = 13.8 Hz, 1 H), 4.71 (dt, *J* = 12.0, 2.5 Hz, 1 H), 4.51 (br d, *J* = 11.9 Hz, 1 H), 4.38-4.31 (m, 2 H), 4.26 (dd, *J* = 13.8, 3.5 Hz, 1 H). Anal. ($C_{21}H_{15}F_3N_4O_4$) C, H, N.

(6*S*)-2-Nitro-6-[(5-{[6-(trifluoromethyl)pyridin-3-yl]ethynyl}pyridin-2-yl)methoxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (45). Reaction of alkyne **123** and 5-bromo-2-(trifluoromethyl)pyridine (1.2 equiv) under the Sonogashira coupling conditions described in procedure Q (but at 50 °C for 16 h) gave **45** (77%) as a white solid: mp 229-232 °C; ^{1}H NMR

[$(CD_3)_2SO$] δ 8.97 (br d, *J* = 1.3 Hz, 1 H), 8.78 (d, *J* = 1.4 Hz, 1 H), 8.30 (dd, *J* = 8.1, 1.5 Hz, 1 H), 8.06 (dd, *J* = 8.1, 2.2 Hz, 1 H), 8.04 (s, 1 H), 8.00 (d, *J* = 8.2 Hz, 1 H), 7.47 (d, *J* = 8.1 Hz, 1 H), 4.83 (d, *J* = 13.9 Hz, 1 H), 4.79 (d, *J* = 13.9 Hz, 1 H), 4.72 (dt, *J* = 12.0, 2.5 Hz, 1 H), 4.51 (br d, *J* = 11.9 Hz, 1 H), 4.38-4.32 (m, 2 H), 4.26 (dd, *J* = 13.8, 3.5 Hz, 1 H). Anal. ($C_{20}H_{14}F_3N_5O_4$) C, H, N. HPLC purity: 99.8%.

(6*S*)-2-Nitro-6-[(5-{[5-(trifluoromethyl)pyridin-2-yl]ethynyl}pyridin-2-yl)methoxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (46). Reaction of alkyne **123** and 2-iodo-5-(trifluoromethyl)pyridine (1.2 equiv) under the Sonogashira coupling conditions described in procedure Q gave **46** (60%) as a white solid: mp 231-235 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.02 (br s, 1 H), 8.80 (br d, *J* = 1.5 Hz, 1 H), 8.31 (dd, *J* = 8.5, 2.2 Hz, 1 H), 8.09 (dd, *J* = 8.1, 2.2 Hz, 1 H), 8.04 (s, 1 H), 7.92 (d, *J* = 8.2 Hz, 1 H), 7.48 (d, *J* = 8.3 Hz, 1 H), 4.83 (d, *J* = 14.0 Hz, 1 H), 4.79 (d, *J* = 14.0 Hz, 1 H), 4.72 (dt, *J* = 12.0, 2.5 Hz, 1 H), 4.51 (br d, *J* = 12.0 Hz, 1 H), 4.38-4.32 (m, 2 H), 4.27 (dd, *J* = 13.8, 3.6 Hz, 1 H). Anal. ($C_{20}H_{14}F_3N_5O_4$) C, H, N.

Synthesis of 47-51 (Scheme 2C):

(6*S*)-6-[(6-Ethynylpyridin-3-yl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (124). Reaction of (6*S*)-6-[(6-bromopyridin-3-yl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine[14] (**122**) and ethynyl(trimethylsilane) (5.0 equiv) under the Sonogashira coupling conditions described in procedure P (but at 20 °C for 18 h in a sealed tube), followed by desilylation of the crude product with TBAF, as described in procedure P, gave **124** (57%) as a white solid: mp 168-170 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.51 (d, *J* = 1.7 Hz, 1 H), 8.02 (s, 1 H), 7.74 (dd, *J* = 8.0, 2.2 Hz, 1 H), 7.54 (br d, *J* = 8.2 Hz, 1 H), 4.73 (d, *J* = 12.6 Hz, 1 H), 4.70 (d, *J* = 12.6 Hz, 1 H), 4.67 (dt, *J* = 12.0, 2.4 Hz, 1 H), 4.47 (br d, *J* = 11.9 Hz, 1 H), 4.31-4.20 (m, 4 H). Anal. ($C_{14}H_{12}N_4O_4$) C, H, N.

(6*S*)-2-Nitro-6-[(6-{[4-(trifluoromethoxy)phenyl]ethynyl}pyridin-3-yl)methoxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (47). Reaction of alkyne **124** and 1-iodo-4-(trifluoromethoxy)benzene (1.2 equiv) under the Sonogashira coupling conditions described in procedure Q gave **47** (55%) as a white solid: mp 235-238 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.57 (d, *J* = 1.7 Hz, 1 H), 8.03 (s, 1 H), 7.79 (dd, *J* = 8.0, 2.2 Hz, 1 H), 7.75 (br d, *J* = 8.8 Hz, 2 H), 7.66 (d, *J* = 7.9 Hz, 1 H), 7.45 (br d, *J* = 8.0 Hz, 2 H), 4.76 (d, *J* = 12.7 Hz, 1 H), 4.72 (d, *J* = 12.7 Hz, 1 H), 4.69 (dt, *J* = 12.0, 2.4 Hz, 1 H), 4.49 (br d, *J* = 11.9 Hz, 1 H), 4.33-4.22 (m, 3 H); ^{13}C NMR [$(CD_3)_2SO$] δ 149.4, 148.7 (q, J_{C-F} = 1.5 Hz), 147.1, 142.1, 141.2, 136.0, 133.8 (2 C), 133.5, 127.1, 121.4 (2 C), 120.7, 120.0 (q, J_{C-F} = 257.4 Hz), 118.0, 89.6, 86.9, 67.8, 67.0, 66.8, 46.7. Anal. ($C_{21}H_{15}F_3N_4O_5$) C, H, N.

(6*S*)-6-({6-[(4-Fluorophenyl)ethynyl]pyridin-3-yl}methoxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (48). Reaction of alkyne **124** and 1-fluoro-4-iodobenzene (1.2 equiv) under the Sonogashira coupling conditions described in procedure Q gave **48** (26%) as a white solid: mp 209-211 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.55 (br s, 1 H), 8.03 (s, 1 H), 7.78 (dd, *J* = 8.0, 2.1 Hz, 1 H), 7.67 (br dd, *J* = 8.9, 5.5 Hz, 2 H), 7.63 (br d, *J* = 8.0 Hz, 1 H), 7.30 (br t, *J* = 8.9 Hz, 2 H), 4.76 (d, *J* = 12.6 Hz, 1 H), 4.72 (d, *J* = 12.6 Hz, 1 H), 4.68 (dt, *J* = 11.9, 2.3 Hz, 1 H), 4.49 (br d, *J* = 11.9 Hz, 1 H), 4.32-4.21 (m, 3 H). Anal. ($C_{20}H_{15}FN_4O_4$) C, H, N.

(6*S*)-2-Nitro-6-[(6-{[4-(trifluoromethyl)phenyl]ethynyl}pyridin-3-yl)methoxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (49). Reaction of alkyne **124** and 1-iodo-4-(trifluoromethyl)benzene (1.2 equiv) under the Sonogashira coupling conditions described in procedure Q gave **49** (65%) as a white solid: mp 262-265 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.58 (br d, *J* = 1.6 Hz, 1 H), 8.03 (s, 1 H), 7.85-7.79 (m, 5 H), 7.69 (br d, *J* = 8.0 Hz, 1 H), 4.77 (d, *J*

= 12.7 Hz, 1 H), 4.73 (d, *J* = 12.7 Hz, 1 H), 4.69 (dt, *J* = 12.0, 2.4 Hz, 1 H), 4.49 (br d, *J* = 11.9 Hz, 1 H), 4.33-4.22 (m, 3 H). Anal. ($C_{21}H_{15}F_3N_4O_4$) C, H, N.

(6*S*)-2-Nitro-6-[(6-{[6-(trifluoromethyl)pyridin-3-yl]ethynyl}pyridin-3-yl)methoxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (50). Reaction of alkyne **124** and 5-bromo-2-(trifluoromethyl)pyridine (1.2 equiv) under the Sonogashira coupling conditions described in procedure Q (but at 50 °C for 18 h) gave **50** (40%) as a white solid: mp 242-245 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.00 (d, *J* = 1.4 Hz, 1 H), 8.60 (d, *J* = 1.6 Hz, 1 H), 8.34 (dd, *J* = 8.1, 1.7 Hz, 1 H), 8.03 (s, 1 H), 8.00 (d, *J* = 8.2 Hz, 1 H), 7.83 (dd, *J* = 8.0, 2.1 Hz, 1 H), 7.74 (d, *J* = 8.0 Hz, 1 H), 4.78 (d, *J* = 12.8 Hz, 1 H), 4.75 (d, *J* = 12.7 Hz, 1 H), 4.69 (dt, *J* = 12.0, 2.4 Hz, 1 H), 4.49 (br d, *J* = 11.9 Hz, 1 H), 4.33-4.22 (m, 3 H). Anal. ($C_{20}H_{14}F_3N_5O_4$) C, H, N.

(6*S*)-2-Nitro-6-[(6-{[5-(trifluoromethyl)pyridin-2-yl]ethynyl}pyridin-3-yl)methoxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (51). Reaction of alkyne **124** and 2-iodo-5-(trifluoromethyl)pyridine (1.2 equiv) under the Sonogashira coupling conditions described in procedure Q gave **51** (66%) as a white solid: mp 243-246 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.04 (br s, 1 H), 8.62 (d, *J* = 1.4 Hz, 1 H), 8.31 (dd, *J* = 8.3, 2.0 Hz, 1 H), 8.03 (s, 1 H), 7.94 (d, *J* = 8.2 Hz, 1 H), 7.84 (dd, *J* = 8.0, 2.1 Hz, 1 H), 7.76 (d, *J* = 8.0 Hz, 1 H), 4.79 (d, *J* = 12.8 Hz, 1 H), 4.75 (d, *J* = 12.8 Hz, 1 H), 4.69 (dt, *J* = 12.0, 2.3 Hz, 1 H), 4.49 (d, *J* = 12.0 Hz, 1 H), 4.33-4.22 (m, 3 H). Anal. ($C_{20}H_{14}F_3N_5O_4$) C, H, N.

Synthesis of 53 (Scheme 3A):

1-Fluoro-4-(4-iodophenoxy)benzene (129b). Reaction of 1-fluoro-4-iodobenzene (**126**) (0.25 equiv) with 4-fluorophenol, using procedure R at 100 °C for 51 h, gave **129b**[15] (16%) as a white solid: mp (petroleum ether) 41-42 °C; ^{1}H NMR ($CDCl_3$) δ 7.60 (br d, *J* = 8.9 Hz, 2 H), 7.04 (br dd, *J* = 9.1, 8.1 Hz, 2 H), 6.97 (br dd, *J* = 9.2, 4.5 Hz, 2 H), 6.73 (br d, *J* = 8.9 Hz, 2 H); HREIMS calcd for $C_{12}H_8FIO$ *m*/*z* (M^+) 313.9604, found 313.9607.

(6*S*)-6-{[4'-(4-Fluorophenoxy)[1,1'-biphenyl]-4-yl]methoxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (53). Reaction of (6*S*)-2-nitro-6-[(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyloxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine[13] (**133**) and iodide **129b** (2.0 equiv) under the Suzuki coupling conditions described in procedure S gave **53** (41%) as a pale yellow solid: mp (CH_2Cl_2/pentane) 172-174 °C; ^{1}H NMR ($CDCl_3$) δ 7.56 (br d, *J* = 8.3 Hz, 2 H), 7.53 (br d, *J* = 8.7 Hz, 2 H), 7.37 (br d, *J* = 8.1 Hz, 2 H), 7.37 (s, 1 H), 7.09-6.98 (m, 6 H), 4.77 (d, *J* = 12.0 Hz, 1 H), 4.66 (d, *J* = 12.1 Hz, 1 H), 4.62 (ddd, *J* = 12.0, 3.6, 2.2 Hz, 1 H), 4.35 (br d, *J* = 11.9 Hz, 1 H), 4.21-4.09 (m, 3 H); HRFABMS calcd for $C_{25}H_{21}FN_3O_5$ *m*/*z* $[M + H]^+$ 462.1465, found 462.1460. HPLC purity: 96.2%.

Synthesis of 54, 56, and 57 (Scheme 3A):

1-Bromo-4-[4-(trifluoromethyl)phenoxy]benzene (129c). Reaction of 1-chloro-4-(trifluoromethyl)benzene (**131**) with 4-bromophenol, using procedure R at 160 °C for 3 d, gave **129c**[16] (62%) as a colourless oil that was used directly in the next step; ^{1}H NMR ($CDCl_3$) δ 7.58 (br d, *J* = 8.8 Hz, 2 H), 7.49 (br d, *J* = 8.8 Hz, 2 H), 7.04 (br d, *J* = 8.7 Hz, 2 H), 6.93 (br d, *J* = 8.8 Hz, 2 H).

4,4,5,5-Tetramethyl-2-{4-[4-(trifluoromethyl)phenoxy]phenyl}-1,3,2-dioxaborolane (130c). A stirred mixture of bis(pinacolato)diboron (170 mg, 0.670 mmol), KOAc (197 mg, 2.01 mmol) and Pd(dppf)Cl_2 (23.6 mg, 0.032 mmol) in anhydrous DMSO (3.8 mL) was degassed for 10 min (vacuum pump) and then N_2 was added. Bromide **129c** (206 mg, 0.650 mmol) was added by syringe and the stirred mixture was again degassed for 5 min, and then

N_2 was added. The resulting mixture was stirred at 90 °C for 140 min, and then cooled, diluted with water (50 mL), and extracted with EtOAc (3 x 50 mL). The extracts were washed with water and then concentrated under reduced pressure, and the residue was chromatographed on silica gel (20 g). Elution with 0-10% CH_2Cl_2/petroleum ether first gave foreruns, and then further elution with 15-50% CH_2Cl_2/petroleum ether and CH_2Cl_2 gave **130c**[17] (201 mg, 85%) as a pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.83 (br d, *J* = 8.5 Hz, 2 H), 7.58 (br d, *J* = 8.6 Hz, 2 H), 7.06 (br d, *J* = 8.5 Hz, 2 H), 7.03 (br d, *J* = 8.6 Hz, 2 H), 1.35 (s, 12 H); HRFABMS calcd for $C_{19}H_{20}BF_3O_3$ *m*/*z* (M^+) 364.1458, 363.1494, found 364.1466, 363.1469.

(6*S*)-2-Nitro-6-({4'-[4-(trifluoromethyl)phenoxy][1,1'-biphenyl]-4-yl}methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (54). Reaction of boronate ester **130c** and (6*S*)-6-[(4-iodobenzyl)oxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine[13] (**117**) (0.63 equiv) under the Suzuki coupling conditions described in procedure S gave **54** (71%) as a cream solid: mp (CH_2Cl_2/pentane) 207-210 °C; ^{1}H NMR ($CDCl_3$) δ 7.63-7.55 (m, 6 H), 7.39 (br d, *J* = 8.4 Hz, 2 H), 7.38 (s, 1 H), 7.12 (br d, *J* = 8.8 Hz, 2 H), 7.10 (m, 2 H), 4.78 (d, *J* = 12.0 Hz, 1 H), 4.67 (d, *J* = 12.1 Hz, 1 H), 4.63 (ddd, *J* = 12.1, 3.8, 2.5 Hz, 1 H), 4.36 (br d, *J* = 12.0 Hz, 1 H), 4.22-4.11 (m, 3 H). Anal. ($C_{26}H_{20}F_3N_3O_5$) C, H, N.

(6*S*)-2-Nitro-6-[(4-{6-[4-(trifluoromethoxy)phenoxy]pyridin-3-yl}benzyl)oxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (56). Reaction of boronate ester **133** and 5-bromo-2-[4-(trifluoromethoxy)phenoxy]pyridine[7] (**107a**) (1.7 equiv) under the Suzuki coupling conditions described in procedure S for 2 h (but using 0.25 equiv catalyst) gave **56** (66%) as a pale yellow solid: mp (CH_2Cl_2/pentane) 184-187 °C; ^{1}H NMR ($CDCl_3$) δ 8.39 (br d, *J* = 2.5 Hz, 1 H), 7.90 (dd, *J* = 8.5, 2.6 Hz, 1 H), 7.53 (br d, *J* = 8.3 Hz, 2 H), 7.40 (br d, *J* = 8.3 Hz, 2 H), 7.38 (s, 1 H), 7.26 (m, 2 H), 7.20 (br d, *J* = 9.2 Hz, 2 H), 7.03 (br d, *J* = 8.5 Hz, 1 H), 4.78 (d, *J* = 12.0 Hz, 1 H), 4.67 (d, *J* = 12.2 Hz, 1 H), 4.63 (ddd, *J* = 12.1, 3.6, 2.1 Hz, 1 H), 4.36 (br dd, *J* = 12.1, 1.4 Hz, 1 H), 4.22-4.11 (m, 3 H). Anal. ($C_{25}H_{19}F_3N_4O_6$) C, H, N.

(6*S*)-6-({4-[6-(4-Fluorophenoxy)pyridin-3-yl]benzyl}oxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (57). Reaction of boronate ester **133** and 5-bromo-2-(4-fluorophenoxy)pyridine[7] (**107b**) (1.6 equiv) under the Suzuki coupling conditions described in procedure S for 2 h (but using 0.24 equiv catalyst) gave **57** (71%) as a pale yellow-orange solid: mp (CH_2Cl_2/pentane) 179-181 °C; ^{1}H NMR ($CDCl_3$) δ 8.37 (br d, *J* = 2.5 Hz, 1 H), 7.88 (dd, *J* = 8.5, 2.6 Hz, 1 H), 7.52 (br d, *J* = 8.3 Hz, 2 H), 7.40 (br d, *J* = 8.2 Hz, 2 H), 7.38 (s, 1 H), 7.17-7.06 (m, 4 H), 6.99 (br d, *J* = 8.5 Hz, 1 H), 4.77 (d, *J* = 12.0 Hz, 1 H), 4.66 (d, *J* = 12.2 Hz, 1 H), 4.63 (ddd, *J* = 12.1, 3.6, 2.1 Hz, 1 H), 4.36 (br d, *J* = 12.1 Hz, 1 H), 4.22-4.10 (m, 3 H). Anal. ($C_{24}H_{19}FN_4O_5$) C, H, N.

Synthesis of 58 (Scheme 3C):

[4'-({[(6*S*)-2-Nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy}methyl)[1,1'-biphenyl]-4-yl][4-(trifluoromethoxy)phenyl]methanone (58). Reaction of boronate ester **133** and (4-bromophenyl)[4-(trifluoromethoxy)phenyl]methanone[18] (**137**) (1.15 equiv) under the Suzuki coupling conditions described in procedure S gave **58** (68%) as a pale yellow solid: mp (CH_2Cl_2/hexane) 219-220 °C; ^{1}H NMR ($CDCl_3$) δ 7.90 (br d, *J* = 8.8 Hz, 2 H), 7.88 (br d, *J* = 8.3 Hz, 2 H), 7.70 (br d, *J* = 8.4 Hz, 2 H), 7.65 (br d, *J* = 8.2 Hz, 2 H), 7.43 (br d, *J* = 8.2 Hz, 2 H), 7.39 (s, 1 H), 7.34 (br d, *J* = 8.8 Hz, 2 H), 4.80 (d, *J* = 12.1 Hz, 1 H), 4.69 (d, *J* = 12.1 Hz, 1 H), 4.65 (ddd, *J* = 12.2, 3.5, 2.1 Hz, 1 H), 4.37 (br d, *J* = 11.9 Hz, 1 H), 4.24-4.12 (m, 3 H). Anal. ($C_{27}H_{20}F_3N_3O_6$) C, H, N.

Synthesis of 59 (Scheme 3D):

(6*S*)-2-Nitro-6-[(4'-{[4-(trifluoromethoxy)phenoxy]methyl}[1,1'-biphenyl]-4-yl)methoxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (59). Reaction of 4-{[4-(trifluoromethoxy)phenoxy]methyl}phenylboronic acid (**140**) and iodide **117** (0.78 equiv) under the Suzuki coupling conditions described in procedure S for 20 min, followed by chromatography of the product on silica gel, eluting with 50% EtOAc/petroleum ether (foreruns) and then with 90% EtOAc/petroleum ether, gave **59** (91%) as a pink solid: mp 208-210 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.03 (s, 1 H), 7.68 (br d, *J* = 8.3 Hz, 2 H), 7.66 (br d, *J* = 8.3 Hz, 2 H), 7.53 (br d, *J* = 8.3 Hz, 2 H), 7.41 (br d, *J* = 8.3 Hz, 2 H), 7.30 (br d, *J* = 9.0 Hz, 2 H), 7.12 (br d, *J* = 9.2 Hz, 2 H), 5.17 (s, 2 H), 4.73-4.64 (m, 3 H), 4.48 (br d, *J* = 11.9 Hz, 1 H), 4.33-4.21 (m, 3 H). Anal. ($C_{27}H_{22}F_3N_3O_6$) C, H, N.

Synthesis of 63 (Scheme 4B):

***tert*-Butyl [4-(bromomethyl)phenyl]sulfonyl[4-(trifluoromethoxy)benzyl]carbamate (149).** 4-(Trifluoromethoxy)benzyl amine (0.56 mL, 3.67 mmol) was added to a solution of 4-(bromomethyl)benzenesulfonyl chloride (**146**) (0.50 g, 1.86 mmol) and DMAP (20 mg, 0.16 mmol) in anhydrous CH_2Cl_2 (10 mL) at 5 °C, and the mixture was stirred at this temperature for 5 min, and then at 20 °C for 1 h. The resulting mixture was diluted with CH_2Cl_2, washed with water and 1 N HBr, and then dried and concentrated under reduced pressure to give the crude sulfonamide **148** (0.79 g, 100%) as a low melting solid, which was used directly. A solution of **148** (3.00 g, 7.07 mmol), di-*tert*-butyl dicarbonate (2.30 g, 10.5 mmol) and DMAP (0.17 g, 1.39 mmol) in anhydrous THF (60 mL) was stirred at 20 °C for 20 min. The resulting mixture was diluted with water and extracted with EtOAc. The extracts were washed with water, dried, and concentrated under reduced pressure to give **149** (3.54 g, 95%) as a white solid: mp 56-60 °C; ^{1}H NMR ($CDCl_3$) δ 7.65 (br d, *J* = 8.5 Hz, 2 H), 7.48-7.42 (m, 4 H), 7.20 (br d, *J* = 8.0 Hz, 2 H), 5.03 (s, 2 H), 4.47 (s, 2 H), 1.32 (s, 9 H). Anal. ($C_{20}H_{21}BrF_3NO_5S$) H, N. C: calcd, 45.81; found, 46.30.

4-({[(6*S*)-2-Nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy}methyl)-*N*-[4-(trifluoromethoxy)benzyl]benzenesulfonamide (63). Reaction of alcohol **95** with bromide **149** and NaH (2.0 equiv) for 30 min, using procedure U, gave an oily product, which was dissolved in 3:1 CH_2Cl_2/TFA (40 mL) and stirred at 20 °C for 1 h. The solvents were removed under reduced pressure and the residue was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic portion was dried and concentrated under reduced pressure, and the residue was chromatographed on silica gel. Elution with 50% EtOAc/petroleum ether first gave foreruns, and then further elution with 5% MeOH/EtOAc gave **63** (19%) as a light yellow solid: mp 79-83 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.18 (t, *J* = 6.3 Hz, 1 H), 8.03 (s, 1 H), 7.76 (br d, *J* = 8.4 Hz, 2 H), 7.48 (br d, *J* = 8.5 Hz, 2 H), 7.36 (br d, *J* = 8.8 Hz, 2 H), 7.26 (br d, *J* = 7.9 Hz, 2 H), 4.78-4.65 (m, 3 H), 4.49 (br d, *J* = 11.9 Hz, 1 H), 4.35-4.22 (m, 3 H), 3.99 (d, *J* = 6.3 Hz, 2 H). Anal. ($C_{21}H_{19}F_3N_4O_7S{\cdot}0.25Et_2O$) C, H, N.

Synthesis of 65 (Scheme 4A):

***N*-[4-({[(6*S*)-2-Nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy}methyl)phenyl]-4-(trifluoromethoxy)benzamide (65).** Reaction of 2-[4-({[(6*S*)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy}methyl)phenyl]-1*H*-isoindole-1,3(2*H*)-dione (**144**) with hydrazine monohydrate, followed by reaction of the crude aniline **145** with 4-(trifluoromethoxy)benzoyl chloride at 50 °C for 1 h, using procedure V, gave **65** (48%) as a light yellow solid: mp 181-183 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.35 (br s, 1 H), 8.07 (br d, *J* =

8.9 Hz, 2 H), 8.02 (s, 1 H), 7.74 (br d, *J* = 8.6 Hz, 2 H), 7.52 (br d, *J* = 8.8 Hz, 2 H), 7.31 (br d, *J* = 8.6 Hz, 2 H), 4.68-4.58 (m, 3 H), 4.47 (br d, *J* = 11.8 Hz, 1 H), 4.30-4.19 (m, 3 H); ^{13}C NMR [$(CD_3)_2SO$] δ 164.3, 150.4, 147.1, 142.1, 138.5, 134.0, 133.0, 130.0 (2 C), 128.2 (2 C), 120.7 (2 C), 120.2 (2 C), 120.0 (q, J_{C-F} = 257.1 Hz), 118.0, 69.4, 67.9, 66.2, 46.8; HRFABMS calcd for $C_{21}H_{18}F_3N_4O_6$ *m*/*z* $[M + H]^+$ 479.1178, found 479.1169. HPLC purity: 95.8%.

Synthesis of 67 (Scheme 5A):

[4-({[6-(Trifluoromethyl)pyridin-3-yl]amino}methyl)phenyl]methanol (152b). Reaction of methyl 4-(aminomethyl)benzoate (**150**) and 5-bromo-2-(trifluoromethyl)pyridine (1.1 equiv) under the Buchwald-Hartwig coupling conditions described in procedure W for 1 h, followed by reduction of the crude product with $LiAlH_4$ (2.1 equiv), as described in procedure W, gave **152b** (17%) as a colourless oil; ^{1}H NMR ($CDCl_3$) δ 8.10 (d, *J* = 2.8 Hz, 1 H), 7.43 (d, *J* = 8.6 Hz, 1 H), 7.38 (br d, *J* = 8.2 Hz, 2 H), 7.33 (br d, *J* = 8.2 Hz, 2 H), 6.88 (dd, *J* = 8.6, 2.8 Hz, 1 H), 4.70 (d, *J* = 5.1 Hz, 2 H), 4.52 (br s, 1 H), 4.40 (d, *J* = 5.6 Hz, 2 H), one exchangeable proton not evident; HREIMS calcd for $C_{14}H_{13}F_3N_2O$ *m*/*z* (M^+) 282.0980, found 282.0981.

***N*-[4-({[(6*S*)-2-Nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy}methyl)benzyl]-6-(trifluoromethyl)pyridin-3-amine (67).** Bromination of alcohol **152b** with HBr for 1 h, followed by reaction of the resulting crude bromide **153b** with alcohol **95** and NaH, using procedure X, gave **67** (16%) as a cream solid: mp 92 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.06 (d, *J* = 2.7 Hz, 1 H), 8.01 (s, 1 H), 7.48 (d, *J* = 8.7 Hz, 1 H), 7.33 (br d, *J* = 8.2 Hz, 2 H), 7.28 (br d, *J* = 8.2 Hz, 2 H), 7.25 (t, *J* = 5.9 Hz, 1 H), 6.94 (dd, *J* = 8.6, 2.6 Hz, 1 H), 4.65 (dt, *J* = 11.9, 2.3 Hz, 1 H), 4.63 (d, *J* = 11.8 Hz, 1 H), 4.59 (d, *J* = 11.8 Hz, 1 H), 4.45 (br d, *J* = 11.7 Hz, 1 H), 4.35 (d, *J* = 6.0 Hz, 2 H), 4.28-4.17 (m, 3 H); HRFABMS calcd for $C_{20}H_{19}F_3N_5O_4$ *m*/*z* $[M + H]^+$ 450.1389, found 450.1391. HPLC purity: 96.9%.

Synthesis of 68 (Scheme 5A):

[4-({[5-(Trifluoromethyl)pyridin-3-yl]amino}methyl)phenyl]methanol (152c). Reaction of amine **150** and 3-bromo-5-(trifluoromethyl)pyridine (1.1 equiv) under the Buchwald-Hartwig coupling conditions described in procedure W for 30 min, followed by reduction of the crude product with $LiAlH_4$ (2.3 equiv), as described in procedure W, gave **152c** (36%) as a white solid: mp 86 °C; ^{1}H NMR ($CDCl_3$) δ 8.21 (d, *J* = 0.8 Hz, 1 H), 8.18 (d, *J* = 2.7 Hz, 1 H), 7.38 (br d, *J* = 8.4 Hz, 2 H), 7.34 (br d, *J* = 8.3 Hz, 2 H), 7.03 (br t, *J* = 2.1 Hz, 1 H), 4.71 (d, *J* = 4.7 Hz, 2 H), 4.37 (br s, 3 H), 1.75 (br t, *J* = 5.5 Hz, 1 H); HREIMS calcd for $C_{14}H_{13}F_3N_2O$ *m*/*z* (M^+) 282.0980, found 282.0977.

***N*-[4-({[(6*S*)-2-Nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy}methyl)benzyl]-5-(trifluoromethyl)pyridin-3-amine (68).** Bromination of alcohol **152c** with HBr, followed by reaction of the resulting crude bromide **153c** with alcohol **95** and NaH for 30 min, using procedure X, gave **68** (12%) as a light yellow solid: mp (EtOAc/Et_2O) 140-141 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.21 (d, *J* = 2.6 Hz, 1 H), 8.04 (d, *J* = 0.9 Hz, 1 H), 8.00 (s, 1 H), 7.35 (br d, *J* = 8.1 Hz, 2 H), 7.29 (br d, *J* = 8.1 Hz, 2 H), 7.12 (br t, *J* = 1.9 Hz, 1 H), 6.97 (br t, *J* = 6.0 Hz, 1 H), 4.66-4.57 (m, 3 H), 4.45 (br d, *J* = 11.9 Hz, 1 H), 4.36 (d, *J* = 5.9 Hz, 2 H), 4.28-4.18 (m, 3 H). Anal. ($C_{20}H_{18}F_3N_5O_4$) C, H, N.

Synthesis of 73 (Scheme 5C):

Methyl 4-({[6-(trifluoromethyl)pyridin-3-yl]oxy}methyl)benzoate (157b). Reaction of methyl 4-(bromomethyl)benzoate (**91**) with 6-(trifluoromethyl)pyridin-3-ol, using procedure Y for 33 h, gave **157b** (91%) as a white solid: mp (CH_2Cl_2/pentane) 115-117 °C; ^{1}H NMR ($CDCl_3$) δ 8.46 (d, *J* = 2.8 Hz, 1 H), 8.08 (br d, *J* = 8.4 Hz, 2 H), 7.61 (d, *J* = 8.7 Hz, 1 H), 7.50 (br d, *J* = 8.6 Hz, 2 H), 7.33 (dd, *J* = 8.7, 2.7 Hz, 1 H), 5.23 (s, 2 H), 3.93 (s, 3 H); HRESIMS calcd for $C_{15}H_{13}F_3NO_3$ *m/z* $[M + H]^+$ 312.0842, found 312.0842.

[4-({[6-(Trifluoromethyl)pyridin-3-yl]oxy}methyl)phenyl]methanol (158b). Reduction of ester **157b** with $LiAlH_4$ (1.1 equiv), using procedure Z, gave **158b** (97%) as a white solid: mp (CH_2Cl_2/pentane) 99-101 °C; ^{1}H NMR ($CDCl_3$) δ 8.45 (d, *J* = 2.8 Hz, 1 H), 7.60 (d, *J* = 8.7 Hz, 1 H), 7.42 (s, 4 H), 7.33 (dd, *J* = 8.7, 2.8 Hz, 1 H), 5.17 (s, 2 H), 4.73 (d, *J* = 5.9 Hz, 2 H), 1.67 (t, *J* = 5.9 Hz, 1 H); HRESIMS calcd for $C_{14}H_{13}F_3NO_2$ *m/z* $[M + H]^+$ 284.0893, found 284.0893.

5-{[4-(Iodomethyl)benzyl]oxy}-2-(trifluoromethyl)pyridine (159b). Iodination of alcohol **158b** with I_2, imidazole, and PPh_3, using procedure T for 2 h, gave **159b** (77%) as a white solid that was used directly in the next step; ^{1}H NMR ($CDCl_3$) δ 8.44 (d, *J* = 2.8 Hz, 1 H), 7.61 (d, *J* = 8.7 Hz, 1 H), 7.42 (br d, *J* = 8.2 Hz, 2 H), 7.35 (br d, *J* = 8.2 Hz, 2 H), 7.33 (dd, *J* = 8.8, 2.8 Hz, 1 H), 5.13 (s, 2 H), 4.46 (s, 2 H); APCI MS *m/z* 394 $[M + H]^+$.

(6*S*)-2-Nitro-6-{[4-({[6-(trifluoromethyl)pyridin-3-yl]oxy}methyl)benzyl]oxy}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (73). Reaction of alcohol **95** with iodide **159b** and NaH, using procedure I for 80 min, gave **73** (91%) as a cream solid: mp (MeOH/CH_2Cl_2/hexane) 140-141 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.50 (d, *J* = 2.8 Hz, 1 H), 8.01 (s, 1 H), 7.84 (d, *J* = 8.8 Hz, 1 H), 7.66 (dd, *J* = 8.7, 2.8 Hz, 1 H), 7.46 (br d, *J* = 8.1 Hz, 2 H), 7.35 (br d, *J* = 8.1 Hz, 2 H), 5.28 (s, 2 H), 4.71-4.61 (m, 3 H), 4.47 (d, *J* = 11.9 Hz, 1 H), 4.31-4.19 (m, 3 H). Anal. ($C_{20}H_{17}F_3N_4O_5 \cdot 0.75CH_2Cl_2$) C, H, N. HPLC purity: 100%.

Synthesis of 75 (Scheme 5D):

(4-{[4-(Trifluoromethoxy)benzyl]oxy}phenyl)methanol (167). Reaction of 1-(bromomethyl)-4-(trifluoromethoxy)benzene (**166**) and 4-(hydroxymethyl)phenol (0.97 equiv), using procedure Y for 3 d, followed by chromatography of the product on silica gel (12 g), eluting with CH_2Cl_2, gave **167** (81%) as a white solid: mp (CH_2Cl_2/pentane) 80-81 °C; ^{1}H NMR ($CDCl_3$) δ 7.46 (br d, *J* = 8.8 Hz, 2 H), 7.30 (br d, *J* = 8.7 Hz, 2 H), 7.23 (br d, *J* = 8.8 Hz, 2 H), 6.95 (br d, *J* = 8.7 Hz, 2 H), 5.07 (s, 2 H), 4.63 (d, *J* = 5.8 Hz, 2 H), 1.53 (t, *J* = 5.8 Hz, 1 H); HRESIMS calcd for $C_{15}H_{13}F_3NaO_3$ *m/z* $[M + Na]^+$ 321.0709, found 321.0717.

(6*S*)-2-Nitro-6-[(4-{[4-(trifluoromethoxy)benzyl]oxy}benzyl)oxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (75). Bromination of alcohol **167** with NBS and PPh_3, using procedure H for 4.5 h, followed by reaction of the resulting bromide **168** with alcohol **95** (1.1 equiv) and NaH (1.9 equiv), using procedure I, gave **75** (30%, 2 steps) as a pale yellow solid: mp (CH_2Cl_2/pentane) 140-141 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.02 (s, 1 H), 7.57 (br d, *J* = 8.7 Hz, 2 H), 7.38 (br d, *J* = 8.0 Hz, 2 H), 7.25 (br d, *J* = 8.6 Hz, 2 H), 6.98 (br d, *J* = 8.7 Hz, 2 H), 5.13 (s, 2 H), 4.67.4.60 (m, 1 H), 4.58 (d, *J* = 11.5 Hz, 1 H), 4.54 (d, *J* = 11.5 Hz, 1 H), 4.45 (br d, *J* = 11.9 Hz, 1 H), 4.28-4.15 (m, 3 H); ^{13}C NMR [$(CD_3)_2SO$] δ 157.8, 147.8 (q, J_{C-F} = 1.6 Hz), 147.1, 142.1, 136.6, 130.0, 129.5 (2 C), 129.4 (2 C), 121.0 (2 C), 120.1 (q, J_{C-F} = 256.1 Hz), 118.0, 114.6 (2 C), 69.3, 68.2, 67.9, 66.0, 46.8. Anal. ($C_{21}H_{18}F_3N_3O_6$) C, H, N.

Compounds of Table 2

Synthesis of 77 (Scheme 6A):

1-(4-{[(Tetrahydro-2*H*-pyran-2-yl)oxy]methyl}phenyl)-4-[5-(trifluoromethyl)pyridin-2-yl]piperazine (171b). Reaction of 2-[(4-bromobenzyl)oxy]tetrahydro-2*H*-pyran[19] (**169**) and 1-[5-(trifluoromethyl)pyridin-2-yl]piperazine (**170b**) under the Buchwald-Hartwig coupling conditions described in procedure AA for 22 h gave **171b** (54%) as a white solid: mp 100-101 °C; ^{1}H NMR ($CDCl_3$) δ 8.42 (m, 1 H), 7.65 (dd, *J* = 9.0, 2.5 Hz, 1 H), 7.29 (br d, *J* = 8.6 Hz, 2 H), 6.94 (br d, *J* = 8.6 Hz, 2 H), 6.68 (d, *J* = 9.0 Hz, 1 H), 4.71 (d, *J* = 11.7 Hz, 1 H), 4.70-4.67 (m, 1 H), 4.44 (d, *J* = 11.6 Hz, 1 H), 3.96-3.88 (m, 1 H), 3.85-3.77 (m, 4 H), 3.58-3.50 (m, 1 H), 3.33-3.25 (m, 4 H), 1.91-1.47 (m, 6 H). Anal. ($C_{22}H_{26}F_3N_3O_2$) C, H, N.

(6*S*)-2-Nitro-6-[(4-{4-[5-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}benzyl)oxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (77). Bromination of THP ether **171b** with 48% HBr, followed by reaction of the resulting bromide **172b** with alcohol **95** (2.0 equiv) and NaH (6 equiv) for 45 min, using procedure BB, gave **77** (3%) as a yellow-brown solid: mp 200-202 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.43 (m, 1 H), 8.00 (s, 1 H), 7.81 (dd, *J* = 9.1, 2.5 Hz, 1 H), 7.19 (br d, *J* = 8.7 Hz, 2 H), 7.01 (d, *J* = 9.1 Hz, 1 H), 6.96 (br d, *J* = 8.7 Hz, 2 H), 4.62 (br d, *J* = 11.7 Hz, 1 H), 4.55 (d, *J* = 11.5 Hz, 1 H), 4.51 (d, *J* = 11.4 Hz, 1 H), 4.44 (d, *J* = 11.5 Hz, 1 H), 4.23-4.15 (m, 3 H), 3.81-3.73 (m, 4 H), 3.28-3.20 (m, 4 H); HRFABMS calcd for $C_{23}H_{24}F_3N_6O_4$ *m*/*z* $[M + H]^+$ 505.1811, found 505.1810. HPLC purity: 97.1%.

Synthesis of 79 (Scheme 6A):

1-(5-{[(Tetrahydro-2*H*-pyran-2-yl)oxy]methyl}pyridin-2-yl)-4-[5-(trifluoromethyl)pyridin-2-yl]piperazine (174b). Reaction of 2-bromo-5-[(tetrahydro-2*H*-pyran-2-yloxy)methyl]pyridine[20] (**173**) and 1-[5-(trifluoromethyl)pyridin-2-yl]piperazine (**170b**) under the Buchwald-Hartwig coupling conditions described in procedure CC for 3 h gave **174b** (63%) as a white solid: mp (hexane) 121 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.43 (br d, *J* = 1.6 Hz, 1 H), 8.09 (d, *J* = 2.2 Hz, 1 H), 7.82 (dd, *J* = 9.1, 2.5 Hz, 1 H), 7.54 (dd, *J* = 8.7, 2.4 Hz, 1 H), 6.99 (d, *J* = 9.1 Hz, 1 H), 6.87 (d, *J* = 8.7 Hz, 1 H), 4.65-4.61 (m, 1 H), 4.54 (d, *J* = 11.5 Hz, 1 H), 4.33 (d, *J* = 11.5 Hz, 1 H), 3.82-3.71 (m, 5 H), 3.66-3.58 (m, 4 H), 3.50-3.43 (m, 1 H), 1.76-1.40 (m, 6 H). Anal. ($C_{21}H_{25}F_3N_4O_2$) C, H, N.

(6*S*)-2-Nitro-6-[(6-{4-[5-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}pyridin-3-yl)methoxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (79). Bromination of THP ether **174b** with 48% HBr at 20 °C for 48 h, followed by reaction of the resulting crude bromide **175b** with alcohol **95** and NaH for 30 min, using procedure BB, gave **79** (3%) as a cream solid: mp 244 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.43 (br d, *J* = 1.7 Hz, 1 H), 8.10 (d, *J* = 2.2 Hz, 1 H), 8.00 (s, 1 H), 7.81 (dd, *J* = 9.2, 2.5 Hz, 1 H), 7.52 (dd, *J* = 8.7, 2.4 Hz, 1 H), 6.99 (d, *J* = 9.1 Hz, 1 H), 6.86 (d, *J* = 8.7 Hz, 1 H), 4.65-4.58 (m, 1 H), 4.54 (d, *J* = 11.5 Hz, 1 H), 4.50 (d, *J* = 11.5 Hz, 1 H), 4.44 (d, *J* = 11.8 Hz, 1 H), 4.24-4.16 (m, 3 H), 3.78-3.71 (m, 4 H), 3.66-3.59 (m, 4 H); HRFABMS calcd for $C_{22}H_{23}F_3N_7O_4$ *m*/*z* $[M + H]^+$ 506.1764, found 506.1770. HPLC purity: 96.1%.

Synthesis of 80 (Scheme 6B):

2-Bromo-4-[(tetrahydro-2*H*-pyran-2-yloxy)methyl]pyridine (177). Pyridinium *p*-toluenesulfonate (0.20 g, 0.796 mmol) was added to a solution of (2-bromopyridin-4-yl)methanol (**176**) (3.10 g, 0.0165 mol) and dihydropyran (15 mL, 0.164 mol) in CH_2Cl_2 (30 mL) and the mixture was stirred at 20 °C for 16 h. After being diluted with CH_2Cl_2, the

solution was successively washed with saturated aqueous $NaHCO_3$ and water, dried, and concentrated under reduced pressure to give **177** (4.31 g, 96%) as an oil, which was used directly; ^{1}H NMR [$(CD_3)_2SO$] δ 8.35 (d, *J* = 5.1 Hz, 1 H), 7.58 (m, 1 H), 7.42-7.39 (m, 1 H), 4.72 (d, *J* = 14.4 Hz, 1 H), 4.69 (m, 1 H), 4.53 (d, *J* = 14.4 Hz, 1 H), 3.79-3.71 (m, 1 H), 3.50-3.41 (m, 1 H), 1.82-1.40 (m, 6 H); APCI MS *m*/*z* 274, 272 $[M + H]^+$.

1-(4-{[(Tetrahydro-2*H*-pyran-2-yl)oxy]methyl}pyridin-2-yl)-4-[4-(trifluoromethoxy)phenyl]piperazine (178a). Reaction of bromopyridine **177** and 1-[4-(trifluoromethoxy)phenyl]piperazine[21] (**170a**) under the Buchwald-Hartwig coupling conditions described in procedure CC for 3 h gave **178a** (82%) as a white solid: mp (petroleum ether) 65-66 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.09 (d, *J* = 5.1 Hz, 1 H), 7.21 (br d, *J* = 9.0 Hz, 2 H), 7.06 (br d, *J* = 9.2 Hz, 2 H), 6.82 (br s, 1 H), 6.66 (d, *J* = 5.0 Hz, 1 H), 4.69-4.65 (m, 1 H), 4.62 (d, *J* = 13.4 Hz, 1 H), 4.43 (d, *J* = 13.4 Hz, 1 H), 3.82-3.74 (m, 1 H), 3.67-3.59 (m, 4 H), 3.52-3.43 (m, 1 H), 3.31-3.23 (m, 4 H), 1.82-1.38 (m, 6 H). Anal. ($C_{22}H_{26}F_3N_3O_3$) C, H, N.

(6*S*)-2-Nitro-6-[(2-{4-[4-(trifluoromethoxy)phenyl]-1-piperazin-1-yl}pyridin-4-yl)methoxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (80). Bromination of THP ether **178a** with HBr in CH_2Cl_2 for 16 h, followed by reaction of the resulting crude bromide **179a** with alcohol **95** and NaH (4 equiv) for 30 min, using procedure X, gave **80** (20%) as a yellow solid: mp 189-191 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.08 (d, *J* = 5.1 Hz, 1 H), 8.03 (s, 1 H), 7.21 (br d, *J* = 8.5 Hz, 2 H), 7.05 (br d, *J* = 9.2 Hz, 2 H), 6.74 (br s, 1 H), 6.60 (br d, *J* = 5.1 Hz, 1 H), 4.69-4.63 (m, 1 H), 4.63 (d, *J* = 13.4 Hz, 1 H), 4.59 (d, *J* = 13.4 Hz, 1 H), 4.48 (br d, *J* = 11.9 Hz, 1 H), 4.31-4.20 (m, 3 H), 3.63-3.57 (m, 4 H), 3.27-3.21 (m, 4 H). Anal. ($C_{23}H_{23}F_3N_6O_5 \cdot 0.25Et_2O$) C, H, N. HPLC purity: 98.1%.

Synthesis of 81 (Scheme 6B):

1-(4-{[(Tetrahydro-2*H*-pyran-2-yl)oxy]methyl}pyridin-2-yl)-4-[5-(trifluoromethyl)pyridin-2-yl]piperazine (178b). Reaction of bromopyridine **177** and 1-[5-(trifluoromethyl)pyridin-2-yl]piperazine (**170b**) under the Buchwald-Hartwig coupling conditions described in procedure CC for 3 h gave **178b** (81%) as a white solid: mp (petroleum ether) 107-108 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.43 (br s, 1 H), 8.09 (d, *J* = 5.1 Hz, 1 H), 7.82 (dd, *J* = 9.1, 2.3 Hz, 1 H), 6.99 (d, *J* = 9.1 Hz, 1 H), 6.80 (s, 1 H), 6.66 (d, *J* = 5.1 Hz, 1 H), 4.69-4.65 (m, 1 H), 4.62 (d, *J* = 13.4 Hz, 1 H), 4.43 (d, *J* = 13.4 Hz, 1 H), 3.82-3.72 (m, 5 H), 3.66-3.58 (m, 4 H), 3.51-3.44 (m, 1 H), 1.83-1.42 (m, 6 H). Anal. ($C_{21}H_{25}F_3N_4O_2$) H, N. C: calcd, 59.71; found, 60.14.

(6*S*)-2-Nitro-6-[(2-{4-[5-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}pyridin-4-yl)methoxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (81). Bromination of THP ether **178b** with 48% HBr (at 92 °C for 48 h), followed by reaction of the resulting bromide **179b** with alcohol **95** and NaH for 30 min, using procedure BB, gave **81** (22%) as a light yellow solid: mp 209-211 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.43 (br d, *J* = 1.5 Hz, 1 H), 8.08 (d, *J* = 5.1 Hz, 1 H), 8.02 (s, 1 H), 7.82 (dd, *J* = 9.1, 2.5 Hz, 1 H), 6.98 (d, *J* = 9.1 Hz, 1 H), 6.72 (s, 1 H), 6.60 (d, *J* = 5.1 Hz, 1 H), 4.69-4.56 (m, 3 H), 4.48 (d, *J* = 11.9 Hz, 1 H), 4.31-4.20 (m, 3 H), 3.77-3.70 (m, 4 H), 3.63-3.56 (m, 4 H); HRFABMS calcd for $C_{22}H_{23}F_3N_7O_4$ *m*/*z* $[M + H]^+$ 506.1764, found 506.1764. HPLC purity: 96.0%.

Synthesis of 82 (Scheme 6A):

1-(4-{[(Tetrahydro-2*H*-pyran-2-yl)oxy]methyl}phenyl)-4-[4-(trifluoromethoxy)benzyl]piperazine (171c). Reaction of bromide **169** and 1-[4-

(trifluoromethoxy)benzyl]piperazine (**170c**) under the Buchwald-Hartwig coupling conditions described in procedure AA for 16 h gave **171c** (45%) as a waxy solid: mp 51-53 °C; ^{1}H NMR ($CDCl_3$) δ 7.38 (br d, *J* = 8.6 Hz, 2 H), 7.25 (br d, *J* = 8.6 Hz, 2 H), 7.17 (br d, *J* = 7.9 Hz, 2 H), 6.89 (br d, *J* = 8.7 Hz, 2 H), 4.69 (d, *J* = 11.6 Hz, 1 H), 4.69-4.65 (m, 1 H), 4.41 (d, *J* = 11.6 Hz, 1 H), 3.96-3.88 (m, 1 H), 3.55 (s, 2 H), 3.55-3.49 (m, 1 H), 3.22-3.16 (m, 4 H), 2.62-2.56 (m, 4 H), 1.91-1.79 (m, 1 H), 1.75-1.66 (m, 1 H), 1.66-1.45 (m, 4 H). Anal. ($C_{24}H_{29}F_3N_2O_3$) C, H, N.

(6*S*)-2-Nitro-6-[(4-{4-[4-(trifluoromethoxy)benzyl]piperazin-1-yl}benzyl)oxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (82). Bromination of THP ether **171c** with 48% HBr (at 55 °C for 2.5 h), followed by reaction of the resulting bromide **172c** with alcohol **95** (1.5 equiv) and NaH, using procedure BB, gave **82** (4%) as a light yellow solid: mp 130-132 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.00 (s, 1 H), 7.46 (br d, *J* = 8.6 Hz, 2 H), 7.32 (br d, *J* = 7.9 Hz, 2 H), 7.15 (d, *J* = 8.6 Hz, 2 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 4.63-4.56 (m, 1 H), 4.53 (d, *J* = 11.4 Hz, 1 H), 4.49 (d, *J* = 11.4 Hz, 1 H), 4.43 (d, *J* = 11.6 Hz, 1 H), 4.22-4.13 (m, 3 H), 3.55 (s, 2 H), 3.32-3.26 (m, 4 H), 3.16-3.09 (m, 4 H). Anal. ($C_{25}H_{26}F_3N_5O_5$) C, H, N.

Synthesis of 83 (Scheme 6A):

1-(4-{[(Tetrahydro-2*H*-pyran-2-yl)oxy]methyl}phenyl)-4-{[4-(trifluoromethoxy)phenyl]sulfonyl)piperazine (171d). Reaction of bromide **169** and 1-{[4-(trifluoromethoxy)phenyl]sulfonyl}piperazine[22] (**170d**) under the Buchwald-Hartwig coupling conditions described in procedure AA for 16 h gave **171d** (88%) as colorless plates: mp (MeOH) 130-132 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.92 (br d, *J* = 8.9 Hz, 2 H), 7.66 (br d, *J* = 8.8 Hz, 2 H), 7.17 (br d, *J* = 8.6 Hz, 2 H), 6.88 (br d, *J* = 8.7 Hz, 2 H), 4.63-4.58 (m, 1 H), 4.54 (d, *J* = 11.6 Hz, 1 H), 4.31 (d, *J* = 11.6 Hz, 1 H), 3.81-3.73 (m, 1 H), 3.48-3.40 (m, 1 H), 3.24-3.16 (m, 4 H), 3.10-3.02 (m, 4 H), 1.76-1.38 (m, 6 H). Anal. ($C_{23}H_{27}F_3N_2O_5S$) C, H, N.

(6*S*)-2-Nitro-6-{[4-(4-{[4-(trifluoromethoxy)phenyl]sulfonyl}piperazin-1-yl)benzyl]oxy}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (83). Bromination of THP ether **171d** with 48% HBr (at 45 °C for 90 min), followed by reaction of the resulting bromide **172d** with alcohol **95** (0.67 equiv) and NaH (2.0 equiv), using procedure BB, gave **83** (11%) as a light yellow-orange solid: mp 119-123 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.99 (s, 1 H), 7.92 (br d, *J* = 8.9 Hz, 2 H), 7.65 (br d, *J* = 8.9 Hz, 2 H), 7.15 (br d, *J* = 8.7 Hz, 2 H), 6.88 (br d, *J* = 8.7 Hz, 2 H), 4.62-4.56 (m, 1 H), 4.52 (d, *J* = 11.6 Hz, 1 H), 4.48 (d, *J* = 11.5 Hz, 1 H), 4.42 (br d, *J* = 11.5 Hz, 1 H), 4.21-4.12 (m, 3 H), 3.23-3.16 (m, 4 H), 3.08-3.00 (m, 4 H); HRFABMS calcd for $C_{24}H_{25}F_3N_5O_7S$ *m*/*z* $[M + H]^+$ 584.1427, found 584.1421. HPLC purity: 98.1%.

Synthesis of 84 (Scheme 6A):

1-(4-{[(Tetrahydro-2*H*-pyran-2-yl)oxy]methyl}phenyl)-4-[4-(trifluoromethoxy)phenoxy)piperidine (171e). Reaction of bromide **169** and 4-[4-(trifluoromethoxy)phenoxy]piperidine[23] (**170e**) under the Buchwald-Hartwig coupling conditions described in procedure AA for 16 h gave **171e** (26%) as a white solid: mp 69-71 °C; ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 2 H), 7.14 (d, *J* = 8.9 Hz, 2 H), 6.96-6.88 (m, 4 H), 4.70 (d, *J* = 11.5 Hz, 1 H), 4.69 (t, *J* = 3.5 Hz, 1 H), 4.46-4.38 (m, 1 H), 4.42 (d, *J* = 11.5 Hz, 1 H), 3.96-3.88 (m, 1 H), 3.58-3.45 (m, 3 H), 3.14-3.05 (m, 2 H), 2.14-2.02 (m, 2 H), 1.98-1.79 (m, 3 H), 1.76-1.45 (m, 5 H). Anal ($C_{24}H_{28}F_3NO_4$) C, H, N.

6*S*)-2-Nitro-6-[(4-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}benzyl)oxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (84). Bromination of THP ether **171e** with 48%

HBr, followed by reaction of the resulting bromide **172e** with alcohol **95** (1.5 equiv) and NaH (3 equiv) for 1 h, using procedure BB, gave **84** (18%) as a light yellow-orange solid: mp 131-134 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.01 (s, 1 H), 7.27 (br d, *J* = 8.5 Hz, 2 H), 7.16 (br d, *J* = 8.7 Hz, 2 H), 7.08 (br d, *J* = 9.2 Hz, 2 H), 6.93 (br d, *J* = 8.7 Hz, 2 H), 4.64-4.46 (m, 4 H), 4.44 (d, *J* = 11.7 Hz, 1 H), 4.23-4.14 (m, 3 H), 3.55-3.46 (m, 2 H), 3.09-3.00 (m, 2 H), 2.07-1.97 (m, 2 H), 1.75-1.64 (m, 2 H); ^{13}C NMR [$(CD_3)_2SO$] δ 155.9, 150.4, 147.1, 142.1, 141.7, 129.1 (2 C), 127.3, 122.6 (2 C), 120.2 (q, J_{C-F} = 255.3 Hz), 118.0, 117.0 (2 C), 115.5 (2 C), 72.6, 69.5, 67.9, 65.8, 46.8, 45.8 (2 C), 29.8 (2 C). Anal ($C_{25}H_{25}F_3N_4O_6$) C, H, N. HPLC purity: 99.7%.

Synthesis of 85 (Scheme 6A):

5-{[1-(4-{[(Tetrahydro-2*H*-pyran-2-yl)oxy]methyl}phenyl)piperidin-4-yl]oxy}-2-(trifluoromethyl)pyridine (171f). Reaction of bromide **169** and 5-(piperidin-4-yloxy)-2-(trifluoromethyl)pyridine[24] (**170f**) under the Buchwald-Hartwig coupling conditions described in procedure AA gave **171f** (41%) as a yellow oil; ^{1}H NMR ($CDCl_3$) δ 8.39 (d, *J* = 2.8 Hz, 1 H), 7.61 (d, *J* = 8.7 Hz, 1 H), 7.32 (dd, *J* = 8.7, 2.8 Hz, 1 H), 7.28 (br d, *J* = 8.6 Hz, 2 H), 6.94 (br d, *J* = 8.6 Hz, 2 H), 4.71 (d, *J* = 11.6 Hz, 1 H), 4.69-4.67 (m, 1 H), 4.61-4.56 (m, 1 H), 4.42 (d, *J* = 11.6 Hz, 1 H), 3.96-3.90 (m, 1 H), 3.57-3.47 (m, 3 H), 3.18-3.11 (m, 2 H), 2.19-2.11 (m, 2 H), 2.02-1.93 (m, 2 H), 1.90-1.80 (m, 1 H), 1.77-1.67 (m, 1 H), 1.67-1.48 (m, 4 H); HRFABMS calcd for $C_{23}H_{27}F_3N_2O_3$ *m*/*z* (M^+) 436.1974, found 436.1970.

(6*S*)-2-Nitro-6-{[4-(4-{[6-(trifluoromethyl)pyridin-3-yl]oxy}piperidin-1-yl)benzyl]oxy}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (85). Bromination of THP ether **171f** with 48% HBr, followed by reaction of the resulting bromide **172f** with alcohol **95** (2.0 equiv) and NaH (6 equiv) for 45 min, using procedure BB, gave **85** (10%) as a pale brown solid: mp 115-118 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.47 (d, *J* = 2.8 Hz, 1 H), 8.02 (s, 1 H), 7.83 (d, *J* = 8.7 Hz, 1 H), 7.69 (dd, *J* = 8.7, 2.8 Hz, 1 H), 7.17 (br d, *J* = 8.7 Hz, 2 H), 6.94 (br d, *J* = 8.7 Hz, 2 H), 4.84-4.77 (m, 1 H), 4.62 (br d, *J* = 11.8 Hz, 1 H), 4.54 (d, *J* = 11.4 Hz, 1 H), 4.50 (d, *J* = 11.4 Hz, 1 H), 4.44 (br d, *J* = 11.6 Hz, 1 H), 4.23-4.15 (m, 3 H), 3.55-3.49 (m, 2 H), 3.13-3.05 (m, 2 H), 2.12-2.03 (m, 2 H), 1.81-1.71 (m, 2 H); ^{13}C NMR [$(CD_3)_2SO$] δ 155.7, 150.3, 147.1, 142.1, 139.7, 138.3 (q, J_{C-F} = 34.3 Hz), 129.2 (2 C), 127.4, 122.6, 122.0 (q, J_{C-F} = 272.8 Hz), 121.9 (q, J_{C-F} = 2.5 Hz), 118.0, 115.5 (2 C), 73.2, 69.5, 67.9, 65.8, 46.8, 45.7 (2 C), 29.5 (2 C); HRFABMS calcd for $C_{24}H_{25}F_3N_5O_5$ *m*/*z* $[M + H]^+$ 520.1808, found 520.1801. HPLC purity: 99.4%.

Synthesis of 86 (Scheme 6A):

5-{[(Tetrahydro-2*H*-pyran-2-yl)oxy]methyl}-2-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}pyridine (174e). Reaction of bromopyridine **173** and 4-[4-(trifluoromethoxy)phenoxy]piperidine[23] (**170e**) under the Buchwald-Hartwig coupling conditions described in procedure CC (but at 85 °C for 3 h) gave **174e** (42%) as a yellow solid: mp (hexane) 60-62 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.06 (d, *J* = 2.2 Hz, 2 H), 7.50 (dd, *J* = 8.7, 2.4 Hz, 1 H), 7.27 (br d, *J* = 9.0 Hz, 2 H), 7.08 (br d, *J* = 9.2 Hz, 2 H), 6.86 (d, *J* = 8.7 Hz, 1 H), 4.69-4.60 (m, 2 H), 4.53 (d, *J* = 11.4 Hz, 1 H), 4.31 (d, *J* = 11.4 Hz, 1 H), 4.00-3.93 (m, 2 H), 3.82-3.75 (m, 1 H), 3.50-3.44 (m, 1 H), 3.37-3.31 (m, 2 H), 2.03-1.94 (m, 2 H), 1.77-1.40 (m, 7 H). Anal. ($C_{23}H_{27}F_3N_2O_4$) C, H, N.

(6*S*)-2-Nitro-6-[(6-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}pyridin-3-yl)methoxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (86). Bromination of THP ether **174e** with 48% HBr (at 20 °C for 24 h), followed by reaction of the resulting bromide **175e**

with alcohol **95** and NaH for 30 min, using procedure BB, gave **86** (3%) as a yellow solid: mp 140-141 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.06 (d, *J* = 2.2 Hz, 1 H), 8.01 (s, 1 H), 7.48 (dd, *J* = 8.8, 2.4 Hz, 1 H), 7.28 (br d, *J* = 9.0 Hz, 2 H), 7.07 (br d, *J* = 9.2 Hz, 2 H), 6.85 (d, *J* = 8.8 Hz, 1 H), 4.68-4.58 (m, 2 H), 4.52 (d, *J* = 11.4 Hz, 1 H), 4.48 (d, *J* = 11.4 Hz, 1 H), 4.44 (d, *J* = 12.1 Hz, 1 H), 4.24-4.16 (m, 3 H), 4.00-3.91 (m, 2 H), 3.37-3.30 (m, 2 H), 2.04-1.93 (m, 2 H), 1.64-1.54 (m, 2 H); HRFABMS calcd for $C_{24}H_{25}F_3N_5O_6$ *m*/*z* $[M + H]^+$ 536.1757, found 536.1767. HPLC purity: 96.9%.

Synthesis of 87 (Scheme 6A):

5-{[(Tetrahydro-2*H*-pyran-2-yl)oxy]methyl}-2-(4-{[6-(trifluoromethyl)pyridin-3-yl]oxy}piperidin-1-yl)pyridine (174f). Reaction of bromopyridine **173** and 5-(piperidin-4-yloxy)-2-(trifluoromethyl)pyridine[24] (**170f**) under the Buchwald-Hartwig coupling conditions described in procedure CC (but at 90 °C for 3 h) gave **174f** (82%) as a colourless oil; ^{1}H NMR [$(CD_3)_2SO$] δ 8.47 (d, *J* = 2.8 Hz, 1 H), 8.07 (d, *J* = 2.2 Hz, 1 H), 7.83 (d, *J* = 8.7 Hz, 1 H), 7.69 (dd, *J* = 8.7, 2.7 Hz, 1 H), 7.51 (dd, *J* = 8.7, 2.4 Hz, 1 H), 6.87 (d, *J* = 8.8 Hz, 1 H), 4.90-4.82 (m, 1 H), 4.65-4.62 (m, 1 H), 4.53 (d, *J* = 11.4 Hz, 1 H), 4.32 (d, *J* = 11.4 Hz, 1 H), 4.03-3.95 (m, 2 H), 3.82-3.75 (m, 1 H), 3.51-3.43 (m, 1 H), 3.39-3.29 (m, 2 H), 2.08-1.99 (m, 2 H), 1.76-1.40 (m, 8 H); HRFABMS calcd for $C_{22}H_{27}F_3N_3O_3$ *m*/*z* $[M + H]^+$ 438.2005, found 438.2012.

(6*S*)-2-Nitro-6-{[6-(4-{[6-(trifluoromethyl)pyridin-3-yl]oxy}piperidin-1-yl)pyridin-3-yl]methoxy}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (87). Bromination of THP ether **174f** with HBr in CH_2Cl_2 for 24 h, followed by reaction of the resulting crude bromide **175f** with alcohol **95** (2.0 equiv) and NaH (6 equiv) for 30 min, using procedure X, gave **87** (5%) as a pale yellow-orange solid: mp 142 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.46 (d, *J* = 2.8 Hz, 1 H), 8.07 (d, *J* = 2.2 Hz, 1 H), 8.01 (s, 1 H), 7.83 (d, *J* = 8.7 Hz, 1 H), 7.68 (dd, *J* = 8.7, 2.8 Hz, 1 H), 7.49 (dd, *J* = 8.8, 2.4 Hz, 1 H), 6.87 (d, *J* = 8.7 Hz, 1 H), 4.90-4.84 (m, 1 H), 4.65-4.59 (m, 1 H), 4.52 (d, *J* = 11.4 Hz, 1 H), 4.48 (d, *J* = 11.4 Hz, 1 H), 4.44 (br d, *J* = 11.9 Hz, 1 H), 4.23-4.17 (m, 3 H), 4.10-3.94 (m, 2 H), 3.39-3.30 (m, 2 H), 2.07-1.98 (m, 2 H), 1.69-1.59 (m, 2 H); HRFABMS calcd for $C_{23}H_{24}F_3N_6O_5$ *m*/*z* $[M + H]^+$ 521.1760, found 521.1760. HPLC purity: 99.6%.

Synthesis of 88 (Scheme 6B):

4-{[(Tetrahydro-2*H*-pyran-2-yl)oxy]methyl}-2-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}pyridine (178e). Reaction of bromopyridine **177** and 4-[4-(trifluoromethoxy)phenoxy]piperidine[23] (**170e**) under the Buchwald-Hartwig coupling conditions described in procedure CC for 3 h gave **178e** (85%) as a white solid: mp (petroleum ether) 52-54 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.06 (d, *J* = 5.0 Hz, 1 H), 7.28 (br d, *J* = 9.1 Hz, 2 H), 7.09 (br d, *J* = 9.2 Hz, 2 H), 6.79 (s, 1 H), 6.61 (d, *J* = 5.1 Hz, 1 H), 4.67-4.62 (m, 2 H), 4.60 (d, *J* = 13.3 Hz, 1 H), 4.40 (d, *J* = 13.3 Hz, 1 H), 3.99-3.90 (m, 2 H), 3.80-3.74 (m, 1 H), 3.52-3.45 (m, 1 H), 3.37-3.28 (m, 2 H), 2.04-1.95 (m, 2 H), 1.82-1.44 (m, 8 H). Anal. ($C_{23}H_{27}F_3N_2O_4$) C, H, N.

(6*S*)-2-Nitro-6-[(2-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}pyridin-4-yl)methoxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (88). Bromination of THP ether **178e** with HBr-saturated dioxane (at 20 °C for 3 d), followed by reaction of the resulting crude bromide **179e** with alcohol **95** and NaH (4 equiv) for 30 min, using procedure X, gave **88** (52%) as a yellow-orange solid: mp 78-82 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.05 (d, *J* = 5.0 Hz, 1 H), 8.02 (s, 1 H), 7.28 (br d, *J* = 8.4 Hz, 2 H), 7.08 (br d, *J* = 9.1 Hz, 2 H), 6.71 (s, 1 H),

6.55 (d, *J* = 5.1 Hz, 1 H), 4.68-4.60 (m, 2 H), 4.61 (d, *J* = 13.3 Hz, 1 H), 4.56 (d, *J* = 13.3 Hz, 1 H), 4.46 (d, *J* = 11.9 Hz, 1 H), 4.30-4.20 (m, 3 H), 3.96-3.88 (m, 2 H), 3.33-3.26 (m, 2 H), 2.02-1.94 (m, 2 H), 1.64-1.54 (m, 2 H); HRFABMS calcd for $C_{24}H_{25}F_3N_5O_6$ *m*/*z* $[M + H]^+$ 536.1757, found 536.1753. HPLC purity: 98.0%.

Synthesis of 89 (Scheme 6B):

4-{[(Tetrahydro-2*H*-pyran-2-yl)oxy]methyl}-2-(4-{[6-(trifluoromethyl)pyridin-3-yl]oxy}piperidin-1-yl)pyridine (178f). Reaction of bromopyridine **177** and 5-(piperidin-4-yloxy)-2-(trifluoromethyl)pyridine[24] (**170f**) under the Buchwald-Hartwig coupling conditions described in procedure CC gave **178f** (67%) as a white solid: mp (petroleum ether) 81-82 °C; ^{1}H NMR $[(CD_3)_2SO]$ δ 8.47 (d, *J* = 2.8 Hz, 1 H), 8.07 (d, *J* = 5.1 Hz, 1 H), 7.83 (d, *J* = 8.8 Hz, 1 H), 7.69 (dd, *J* = 8.7, 2.8 Hz, 1 H), 6.81 (s, 1 H), 6.61 (d, *J* = 5.0 Hz, 1 H), 4.90-4.83 (m, 1 H), 4.68-4.65 (m, 1 H), 4.62 (d, *J* = 13.3 Hz, 1 H), 4.40 (d, *J* = 13.3 Hz, 1 H), 4.01-3.93 (m, 2 H), 3.80-3.74 (m, 1 H), 3.50-3.44 (m, 1 H), 3.38-3.31 (m, 2 H), 2.09-2.00 (m, 2 H), 1.82-1.42 (m, 8 H). Anal. ($C_{22}H_{26}F_3N_3O_3$) C, H, N.

(6*S*)-2-Nitro-6-{[2-(4-{[6-(trifluoromethyl)pyridin-3-yl]oxy}piperidin-1-yl)pyridin-4-yl]methoxy}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (89). Bromination of THP ether **178f** with 48% HBr (at 90 °C for 16 h), followed by reaction of the resulting bromide **179f** with alcohol **95** and NaH for 30 min, using procedure BB, gave **89** (10%) as a yellow-orange solid: mp 75 °C; ^{1}H NMR $[(CD_3)_2SO]$ δ 8.47 (d, *J* = 2.7 Hz, 1 H), 8.06 (d, *J* = 5.1 Hz, 1 H), 8.02 (s, 1 H), 7.83 (d, *J* = 8.7 Hz, 1 H), 7.69 (dd, *J* = 8.7, 2.7 Hz, 1 H), 6.72 (s, 1 H), 6.56 (d, *J* = 5.0 Hz, 1 H), 4.90-4.83 (m, 1 H), 4.69-4.62 (m, 1 H), 4.62 (d, *J* = 13.4 Hz, 1 H), 4.57 (d, *J* = 13.4 Hz, 1 H), 4.47 (d, *J* = 11.9 Hz, 1 H), 4.30-4.20 (m, 3 H), 3.99-3.90 (m, 2 H), 3.35-3.29 (m, 2 H), 2.07-1.97 (m, 2 H), 1.69-1.58 (m, 2 H); HRFABMS calcd for $C_{23}H_{24}F_3N_6O_5$ *m*/*z* $[M + H]^+$ 521.1760, found 521.1762. HPLC purity: 95.6%.

Synthesis of 90 (Scheme 6A):

***N*-Methyl-1-(4-{[(tetrahydro-2*H*-pyran-2-yl)oxy]methyl}phenyl)-*N*-[4-(trifluoromethoxy)benzyl]piperidin-4-amine (171g) (Scheme 6A).** Reaction of bromide **169** and *N*-methyl-*N*-[4-(trifluoromethoxy)benzyl]piperidin-4-amine[24] (**170g**) under the Buchwald-Hartwig coupling conditions described in procedure AA for 16 h gave **171g** (18%) as a cream solid: mp 49-52 °C; ^{1}H NMR ($CDCl_3$) δ 7.35 (br d, *J* = 8.5 Hz, 2 H), 7.25 (br d, *J* = 8.7 Hz, 2 H), 7.15 (br d, *J* = 8.1 Hz, 2 H), 6.91 (br d, *J* = 8.6 Hz, 2 H), 4.68 (d, *J* = 11.6 Hz, 1 H), 4.68-4.67 (m, 1 H), 4.41 (d, *J* = 11.6 Hz, 1 H), 3.96-3.88 (m, 1 H), 3.78-3.72 (m, 2 H), 3.59 (s, 2 H), 3.57-3.50 (m, 1 H), 2.76-2.67 (m, 2 H), 2.62-2.52 (m, 1 H), 2.21 (s, 3 H), 1.95-1.49 (m, 10 H); HREIMS calcd for $C_{26}H_{33}F_3N_2O_3$ *m*/*z* (M^+) 478.2443, found 478.2439.

***N*-Methyl-1-[4-({[(6*S*)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy}methyl)phenyl]-*N*-[4-(trifluoromethoxy)benzyl]piperidin-4-amine (90).** Bromination of THP ether **171g** with 48% HBr (at 50 °C for 3 h), followed by reaction of the resulting bromide **172g** with alcohol **95** (2.0 equiv) and NaH (6 equiv) for 1 h, using procedure BB, followed by chromatography of the product on silica gel, eluting with 7% MeOH/CH_2Cl_2, gave **90** (5%) as a white solid: mp 131-133 °C; ^{1}H NMR $[(CD_3)_2SO]$ δ 8.00 (s, 1 H), 7.43 (br d, *J* = 8.7 Hz, 2 H), 7.29 (br d, *J* = 8.7 Hz, 2 H), 7.14 (br d, *J* = 8.7 Hz, 2 H), 6.90 (br d, *J* = 8.8 Hz, 2 H), 4.64-4.58 (m, 1 H), 4.52 (d, *J* = 11.4 Hz, 1 H), 4.47 (d, *J* = 11.4 Hz, 1 H), 4.43 (br d, *J* = 11.2 Hz, 1 H), 4.22-4.14 (m, 3 H), 3.78-3.72 (m, 2 H), 3.59 (s, 2 H), 2.68-2.62 (m, 2 H), 2.59-2.46 (m, 1 H), 2.11 (s, 3 H), 1.87-1.79 (m, 2 H), 1.66-1.55 (m,

2 H); HRFABMS calcd for $C_{27}H_{31}F_3N_5O_5$ *m*/*z* $[M + H]^+$ 562.2277, found 562.2266. HPLC purity: 97.3%.

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Table S2. Combustion analyses for the new compounds of Table 1.

No	Formula	Calculated			Found		
		C	**H**	**N**	**C**	**H**	**N**
11	$C_{21}H_{18}F_3N_3O_5$	56.13	4.04	9.35	56.35	4.02	9.35
12	$C_{20}H_{18}FN_3O_4$	62.66	4.73	10.96	62.51	4.65	11.12
13	$C_{21}H_{18}F_3N_3O_4$	58.20	4.19	9.70	58.03	4.29	9.76
14	$C_{20}H_{17}F_3N_4O_4 \cdot 0.25H_2O$	54.73	4.02	12.77	54.80	4.04	12.80
15	$C_{20}H_{16}F_3N_3O_6$	53.22	3.57	9.31	53.44	3.48	9.39
16	$C_{19}H_{16}FN_3O_5$	59.22	4.19	10.90	59.28	4.09	10.98
17	$C_{20}H_{16}F_3N_3O_5$	55.18	3.70	9.65	55.09	3.76	9.60
18	$C_{19}H_{15}F_3N_4O_5$	52.30	3.46	12.84	52.41	3.65	12.68
19	$C_{19}H_{15}F_3N_4O_5$	52.30	3.46	12.84	52.46	3.53	12.87
20	$C_{19}H_{15}F_3N_4O_6$	50.45	3.34	12.39	50.50	3.31	12.37
21	$C_{18}H_{15}FN_4O_5$	55.96	3.91	14.50	55.72	4.00	14.45
22	$C_{19}H_{15}F_3N_4O_5$	52.30	3.46	12.84	52.59	3.54	12.92
23	$C_{18}H_{14}F_3N_5O_5$	49.43	3.23	16.01	49.71	3.27	16.14
24	$C_{19}H_{15}F_3N_4O_6$	50.45	3.34	12.39	50.56	3.31	12.40
25	$C_{18}H_{15}FN_4O_5$	55.96	3.91	14.50	55.99	3.86	14.51
26	$C_{19}H_{15}F_3N_4O_5$	52.30	3.46	12.84	52.30	3.49	13.05
27	$C_{18}H_{14}F_3N_5O_5$	49.43	3.23	16.01	49.36	3.26	16.15
28	$C_{22}H_{18}F_3N_3O_5$	57.27	3.93	9.11	57.53	3.98	9.18
29	$C_{21}H_{18}FN_3O_4$	63.79	4.59	10.63	63.90	4.54	10.63
30	$C_{22}H_{18}F_3N_3O_4$	59.33	4.07	9.43	59.41	4.04	9.47
31	$C_{21}H_{17}F_3N_4O_4$	56.50	3.84	12.55	56.45	3.87	12.51
32	$C_{22}H_{16}F_3N_3O_5$	57.52	3.51	9.15	57.52	3.68	9.23
33	$C_{21}H_{16}FN_3O_4 \cdot 0.25H_2O$	63.39	4.18	10.56	63.58	4.31	10.70
34	$C_{22}H_{16}F_3N_3O_4$	59.60	3.64	9.48	59.45	3.81	9.54

35	$C_{21}H_{15}F_3N_4O_4$	56.76	3.40	12.61	56.46	3.54	12.53
36	$C_{21}H_{15}F_3N_4O_4$	56.76	3.40	12.61	56.73	3.61	12.66
37	$C_{22}H_{16}F_3N_3O_5$	57.52	3.51	9.15	57.41	3.44	9.13
38	$C_{21}H_{16}FN_3O_4$	64.12	4.10	10.68	64.15	4.01	10.81
39	$C_{22}H_{16}F_3N_3O_4$	59.60	3.64	9.48	59.24	3.80	9.54
40	$C_{21}H_{15}F_3N_4O_4$	56.76	3.40	12.61	56.49	3.42	12.54
41	$C_{21}H_{15}F_3N_4O_4$	56.76	3.40	12.61	56.76	3.39	12.75
42	$C_{21}H_{15}F_3N_4O_5$	54.79	3.28	12.17	54.68	3.46	12.16
43	$C_{20}H_{15}FN_4O_4$	60.91	3.83	14.21	60.62	3.85	14.08
44	$C_{21}H_{15}F_3N_4O_4$	56.76	3.40	12.61	56.58	3.46	12.40
45	$C_{20}H_{14}F_3N_5O_4$	53.94	3.17	15.73	53.86	3.30	15.53
46	$C_{20}H_{14}F_3N_5O_4$	53.94	3.17	15.73	53.70	3.24	15.51
47	$C_{21}H_{15}F_3N_4O_5$	54.79	3.28	12.17	54.73	3.45	12.08
48	$C_{20}H_{15}FN_4O_4$	60.91	3.83	14.21	60.64	3.86	14.16
49	$C_{21}H_{15}F_3N_4O_4$	56.76	3.40	12.61	56.75	3.44	12.70
50	$C_{20}H_{14}F_3N_5O_4$	53.94	3.17	15.73	53.67	3.21	15.80
51	$C_{20}H_{14}F_3N_5O_4$	53.94	3.17	15.73	53.96	3.24	15.79
52	$C_{26}H_{20}F_3N_3O_6$	59.21	3.82	7.97	59.48	3.93	7.98
54	$C_{26}H_{20}F_3N_3O_5$	61.06	3.94	8.22	61.20	3.95	8.35
55	$C_{25}H_{19}F_3N_4O_5$	58.60	3.74	10.93	58.75	3.83	10.96
56	$C_{25}H_{19}F_3N_4O_6$	56.82	3.62	10.60	56.83	3.56	10.53
57	$C_{24}H_{19}FN_4O_5$	62.34	4.14	12.12	62.35	4.12	11.99
58	$C_{27}H_{20}F_3N_3O_6$	60.11	3.74	7.79	60.26	3.78	7.73
59	$C_{27}H_{22}F_3N_3O_6$	59.89	4.10	7.76	60.03	4.20	7.88
60	$C_{21}H_{16}F_3N_3O_6$	54.43	3.48	9.07	54.50	3.32	8.94
61	$C_{21}H_{17}F_3N_4O_6 \cdot 0.25H_2O$	52.23	3.65	11.60	52.11	3.62	11.29
63	$C_{21}H_{19}F_3N_4O_7S \cdot 0.25Et_2O$	48.31	3.96	10.24	48.36	3.78	10.17
64	$C_{20}H_{17}F_3N_4O_7S \cdot 0.25Et_2O$	47.33	3.69	10.51	47.54	3.53	10.24

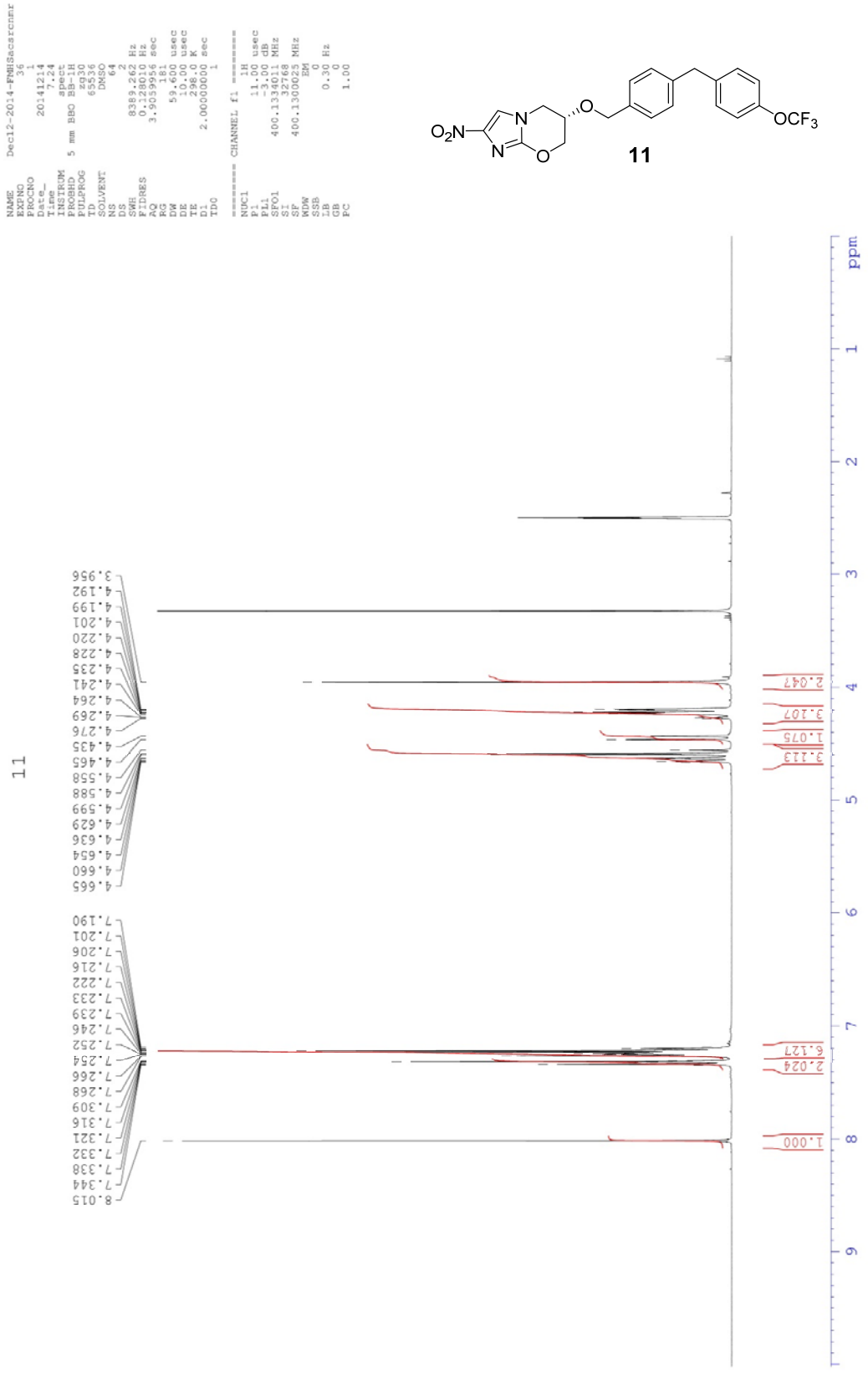
66	$C_{21}H_{19}F_3N_4O_5$	54.31	4.12	12.06	54.69	4.21	11.94
68	$C_{20}H_{18}F_3N_5O_4$	53.45	4.04	15.58	53.48	4.13	15.53
69	$C_{22}H_{21}F_3N_4O_5$	55.23	4.42	11.71	55.13	4.37	11.63
70	$C_{22}H_{21}F_3N_4O_5$	55.23	4.42	11.71	55.26	4.47	11.70
71	$C_{23}H_{23}F_3N_4O_5$	56.10	4.71	11.38	56.29	4.61	11.46
72	$C_{21}H_{18}F_3N_3O_6$	54.20	3.90	9.03	54.39	3.92	9.09
73	$C_{20}H_{17}F_3N_4O_5 \cdot 0.75CH_2Cl_2$	48.48	3.63	10.90	48.09	3.72	10.61
74	$C_{20}H_{17}F_3N_4O_6$	51.51	3.67	12.01	51.76	3.86	12.15
75	$C_{21}H_{18}F_3N_3O_6$	54.20	3.90	9.03	54.40	4.05	9.08

Table S3. Combustion analyses for the new compounds of Table 2

No	Formula	Calculated			Found		
		C	**H**	**N**	**C**	**H**	**N**
76	$C_{24}H_{24}F_3N_5O_5$	55.49	4.66	13.48	55.66	4.59	13.26
80	$C_{23}H_{23}F_3N_6O_5 \cdot 0.25Et_2O$	53.48	4.77	15.59	53.46	4.67	15.50
82	$C_{25}H_{26}F_3N_5O_5$	56.28	4.91	13.13	56.00	5.16	12.89
84	$C_{25}H_{25}F_3N_4O_6$	56.18	4.71	10.48	56.05	4.82	10.53

Table S4. Combustion analyses for intermediates

No	Formula	Calculated			Found		
		C	**H**	**N**	**C**	**H**	**N**
119	$C_{15}H_{13}N_3O_4$	60.20	4.38	14.04	59.91	4.58	13.88
120	$C_{15}H_{13}N_3O_4$	60.20	4.38	14.04	59.90	4.28	14.00
123	$C_{14}H_{12}N_4O_4$	56.00	4.03	18.66	55.85	4.20	18.47
124	$C_{14}H_{12}N_4O_4$	56.00	4.03	18.66	56.07	4.05	18.46
141	$C_{15}H_{15}N_3O_6$	54.05	4.54	12.61	54.08	4.63	12.33
144	$C_{21}H_{16}N_4O_6$	60.00	3.84	13.33	60.24	4.07	13.05
149	$C_{20}H_{21}BrF_3NO_5S$	45.81	4.04	2.67	46.30	4.36	2.73
171a	$C_{23}H_{27}F_3N_2O_3$	63.29	6.24	6.42	63.51	6.36	6.31
171b	$C_{22}H_{26}F_3N_3O_2$	62.70	6.22	9.97	62.91	6.19	9.67
171c	$C_{24}H_{29}F_3N_2O_3$	63.99	6.49	6.22	64.39	6.48	6.07
171d	$C_{23}H_{27}F_3N_2O_5S$	55.19	5.44	5.60	55.22	5.60	5.64
171e	$C_{24}H_{28}F_3NO_4$	63.85	6.25	3.10	63.58	6.23	2.97
174a	$C_{22}H_{26}F_3N_3O_3$	60.40	5.99	9.61	60.54	5.75	9.50
174b	$C_{21}H_{25}F_3N_4O_2$	59.71	5.96	13.26	59.79	5.90	13.38
174e	$C_{23}H_{27}F_3N_2O_4$	61.05	6.01	6.19	61.34	6.20	6.14
178a	$C_{22}H_{26}F_3N_3O_3$	60.40	5.99	9.61	60.71	6.02	9.68
178b	$C_{21}H_{25}F_3N_4O_2$	59.71	5.96	13.26	60.14	5.83	13.06
178e	$C_{23}H_{27}F_3N_2O_4$	61.05	6.01	6.19	61.02	5.86	6.18
178f	$C_{22}H_{26}F_3N_3O_3$	60.40	5.99	9.61	60.49	5.90	9.45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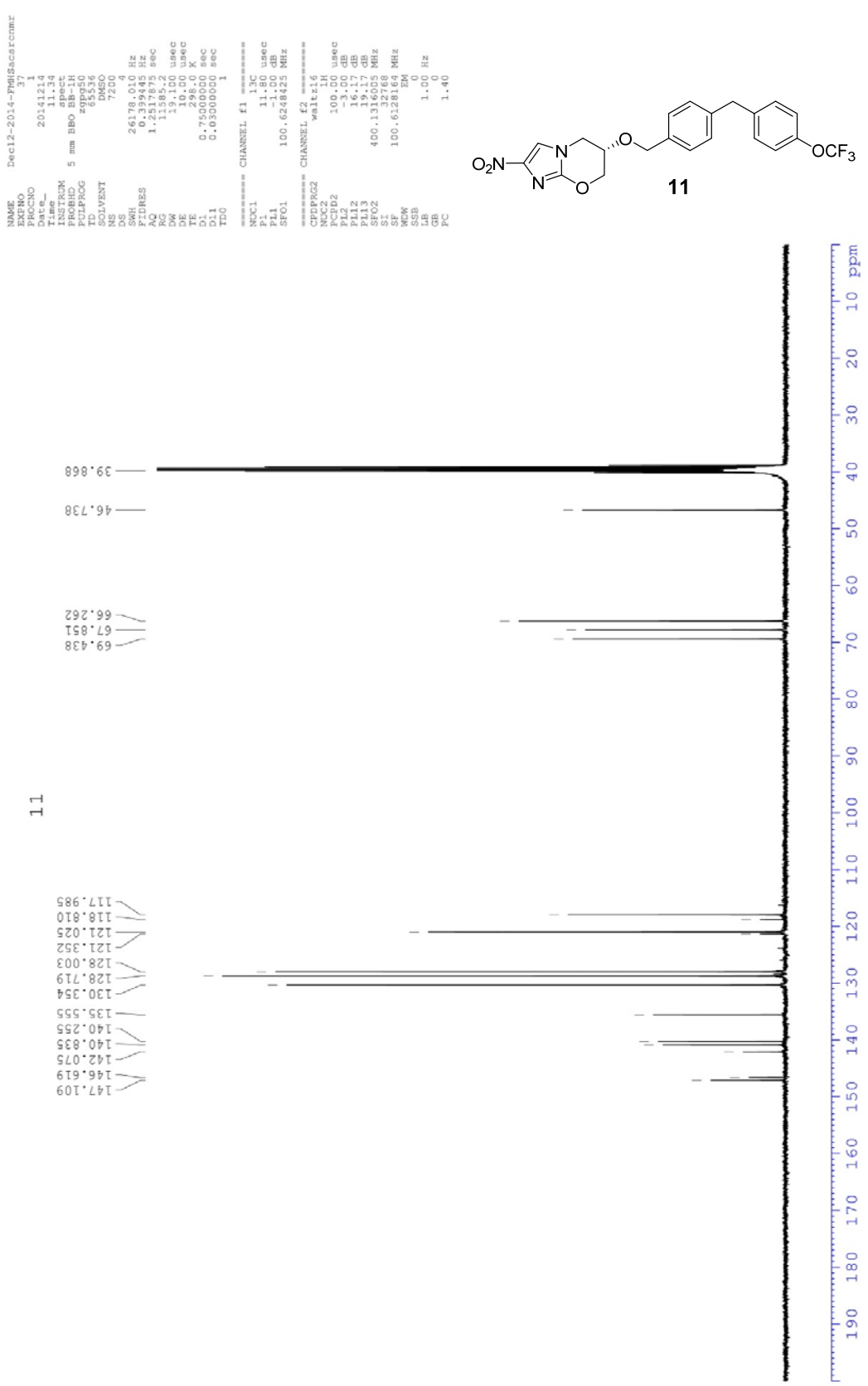
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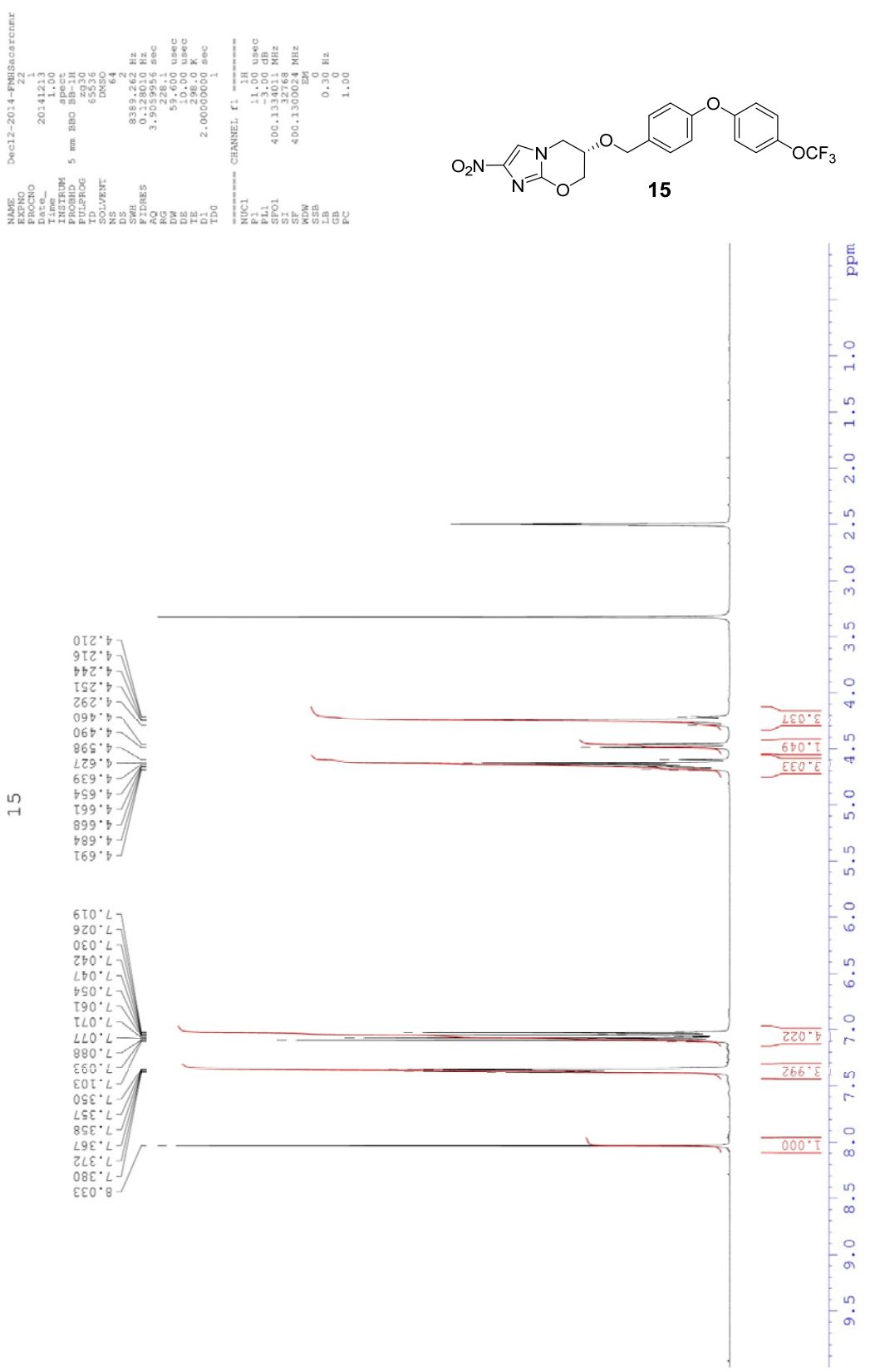
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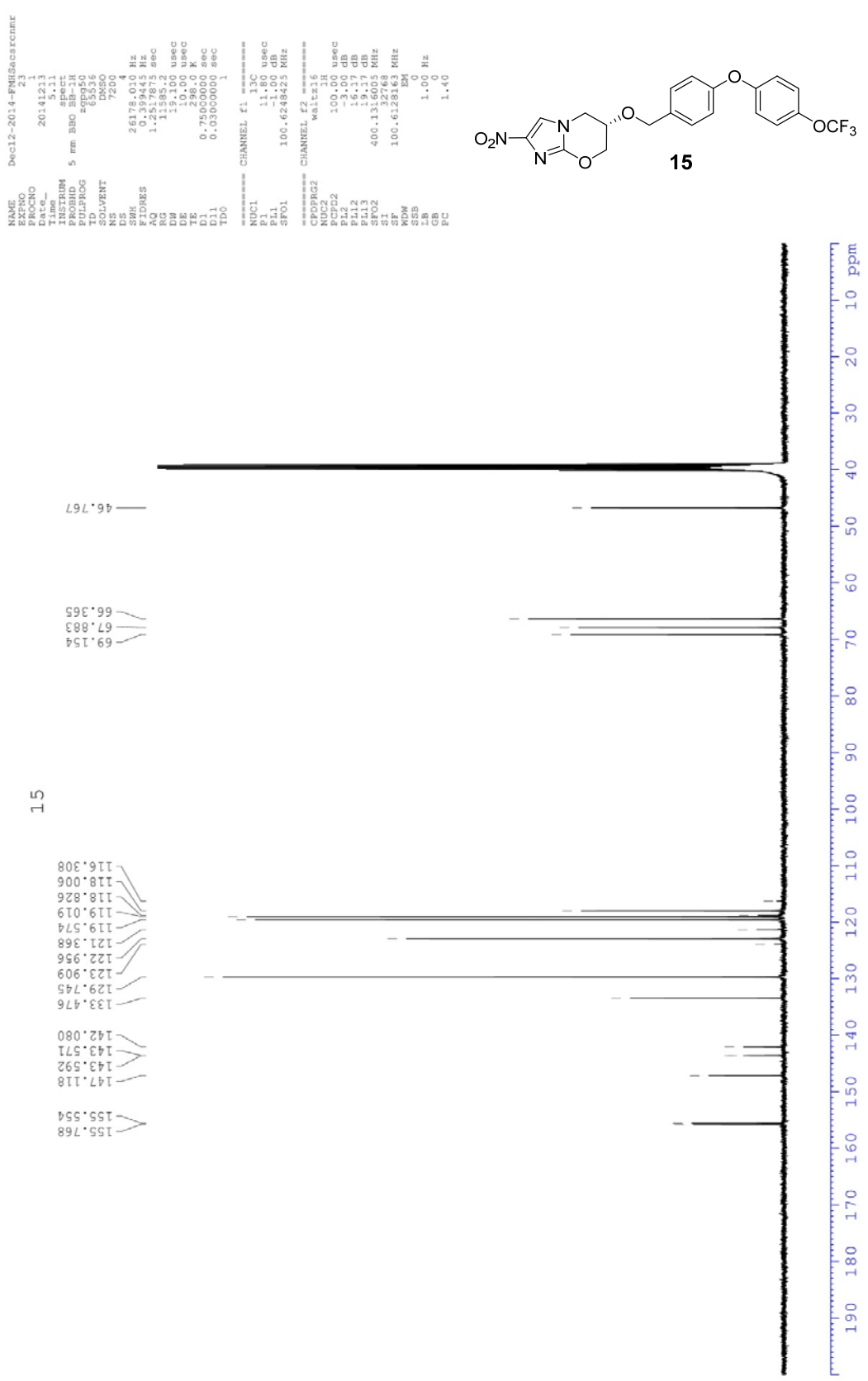
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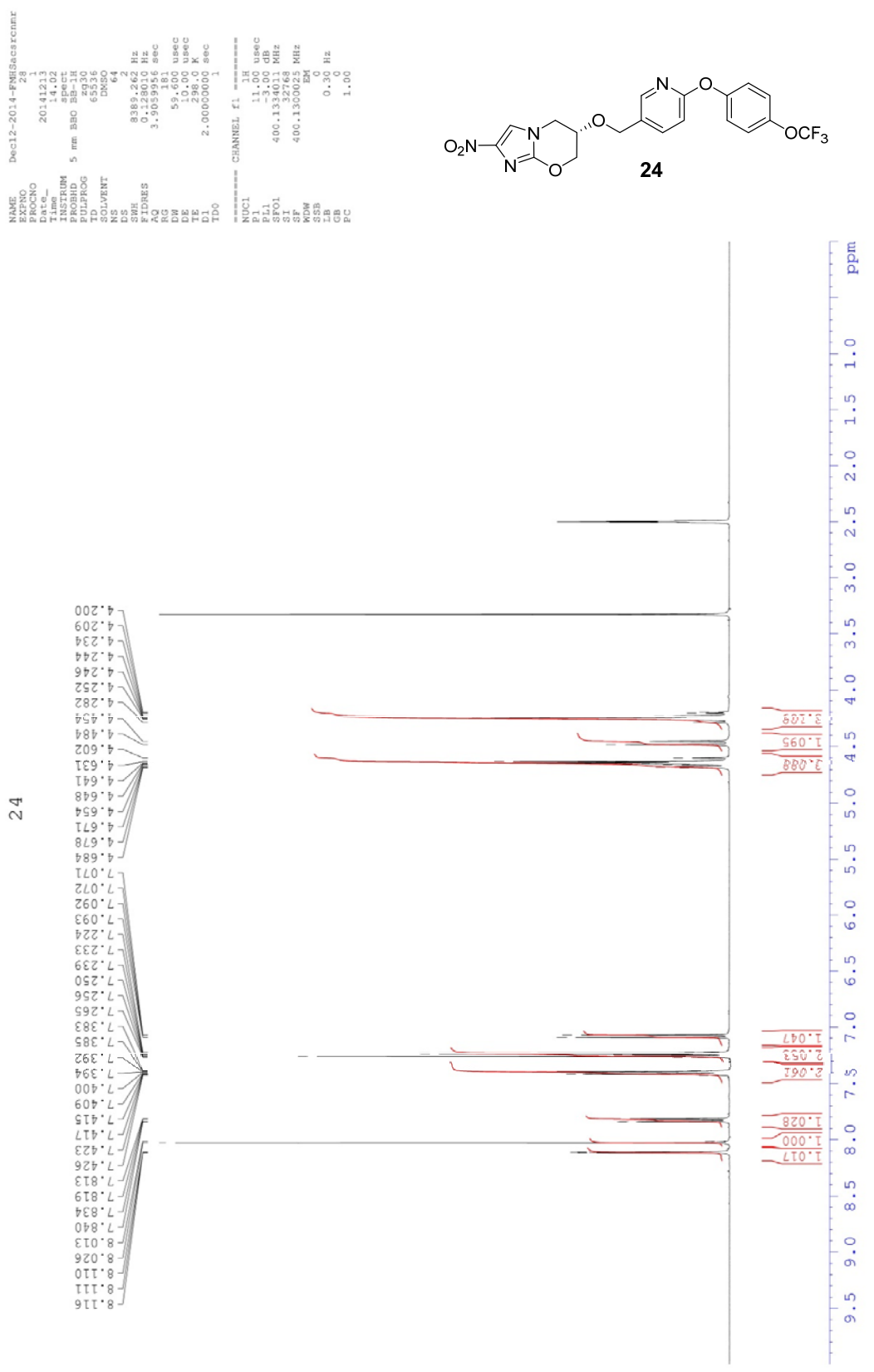

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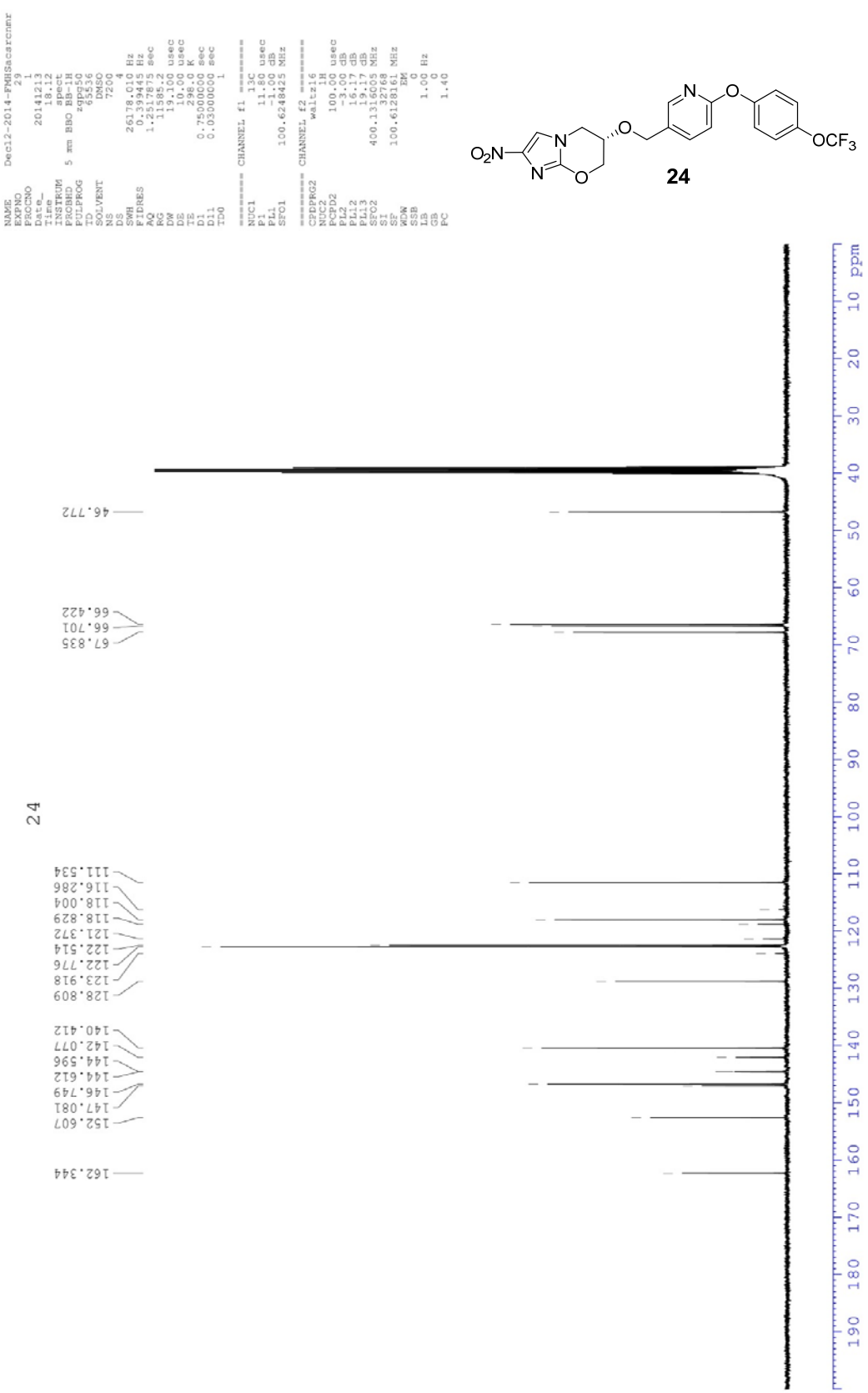
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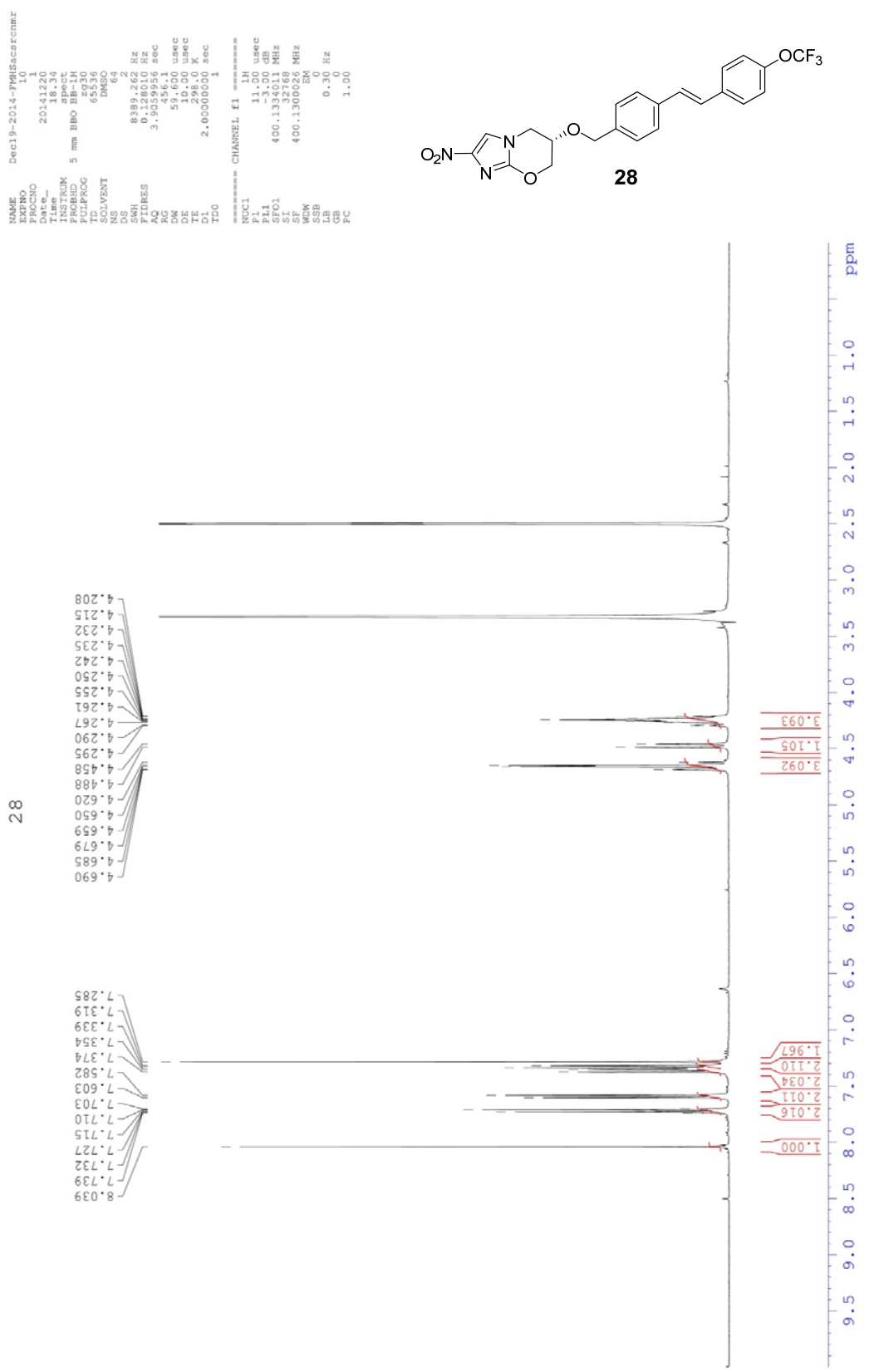
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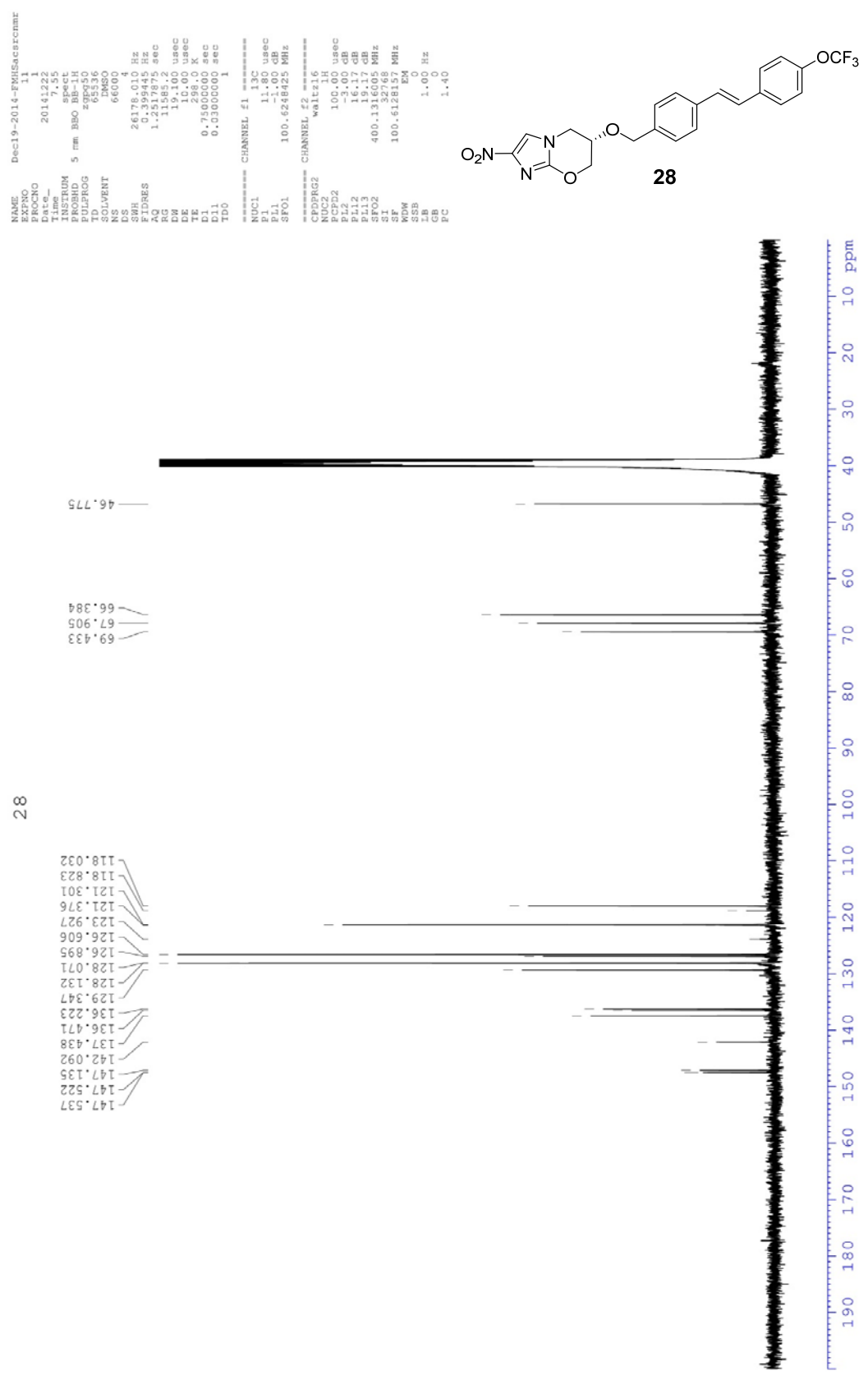
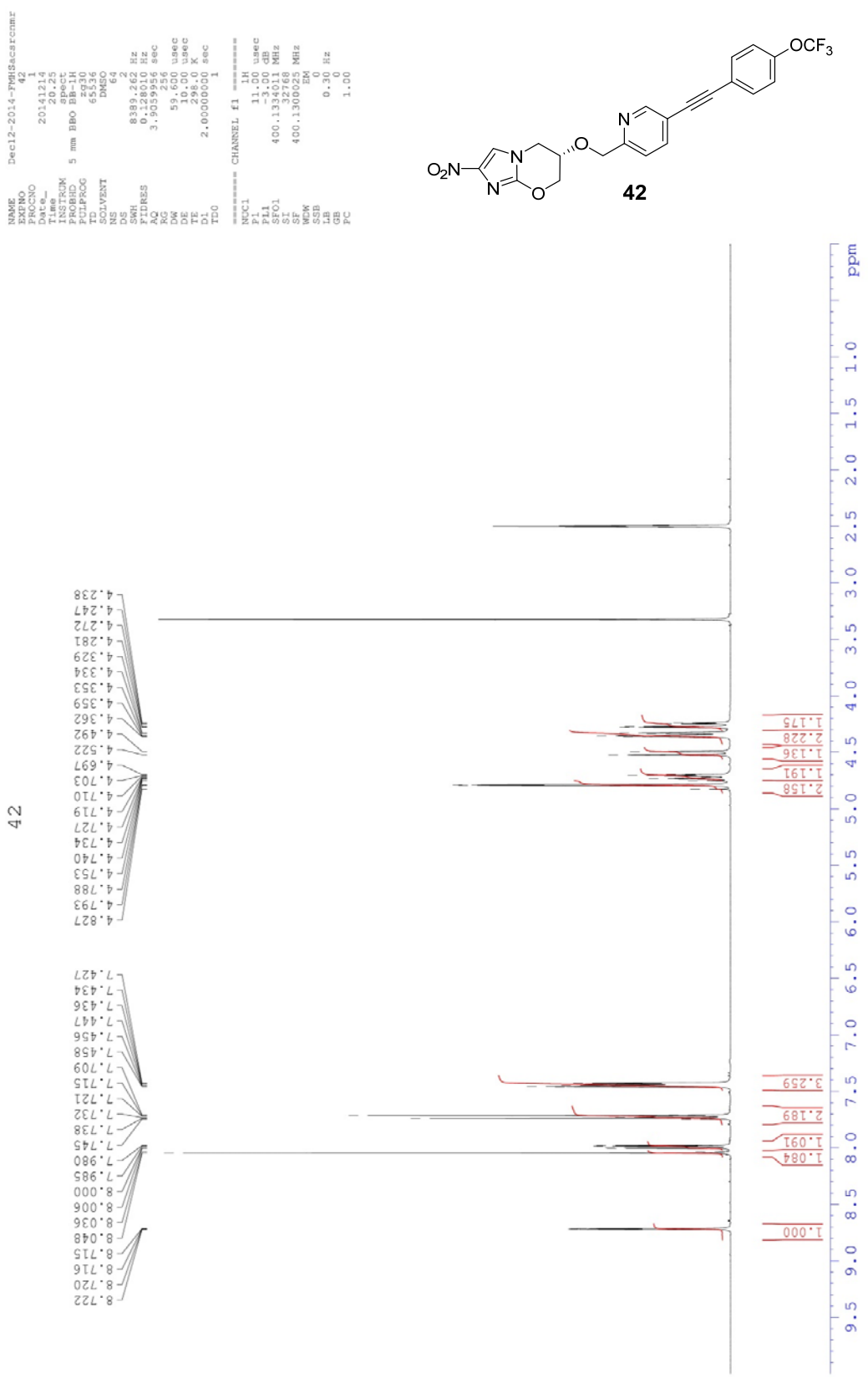
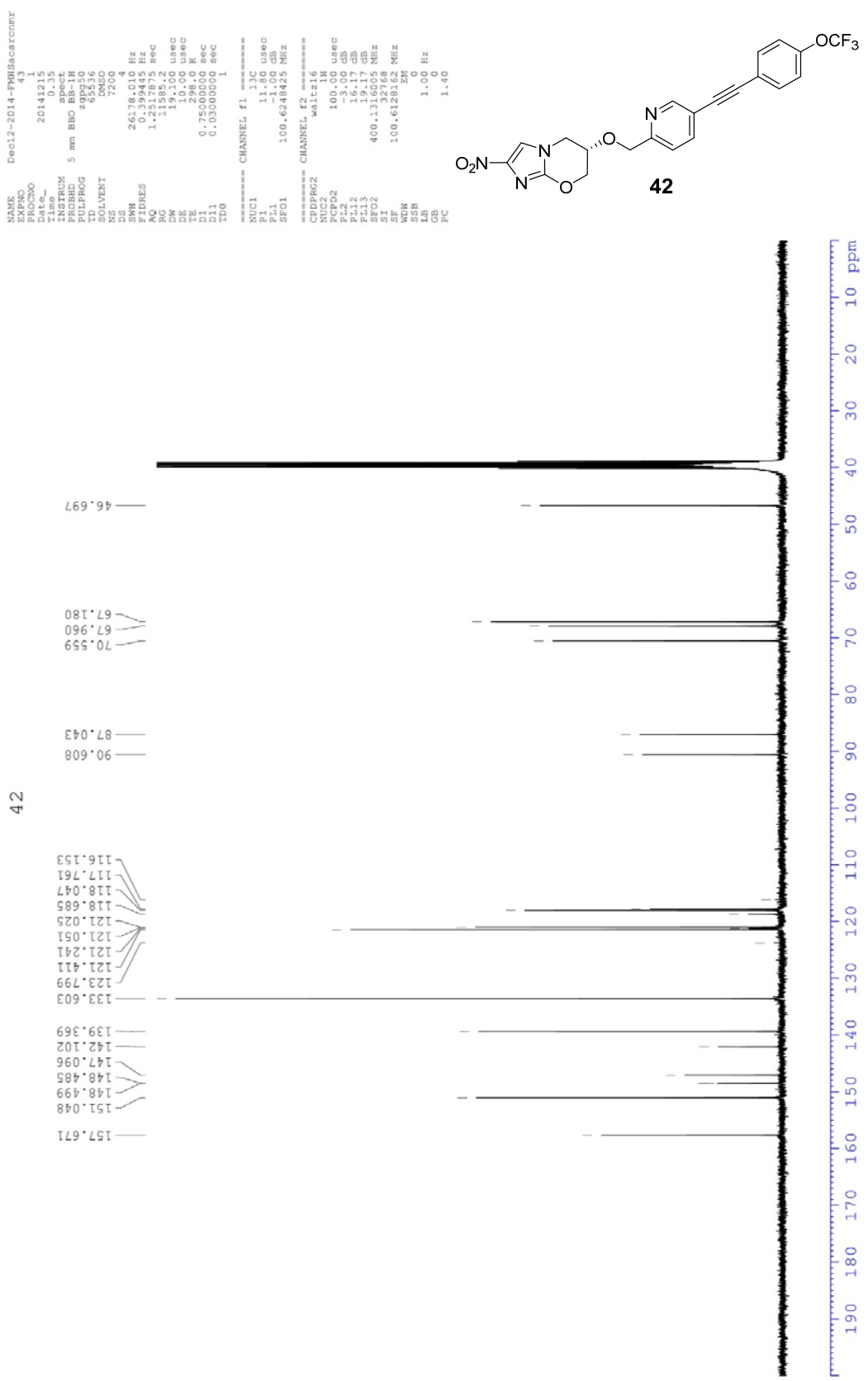
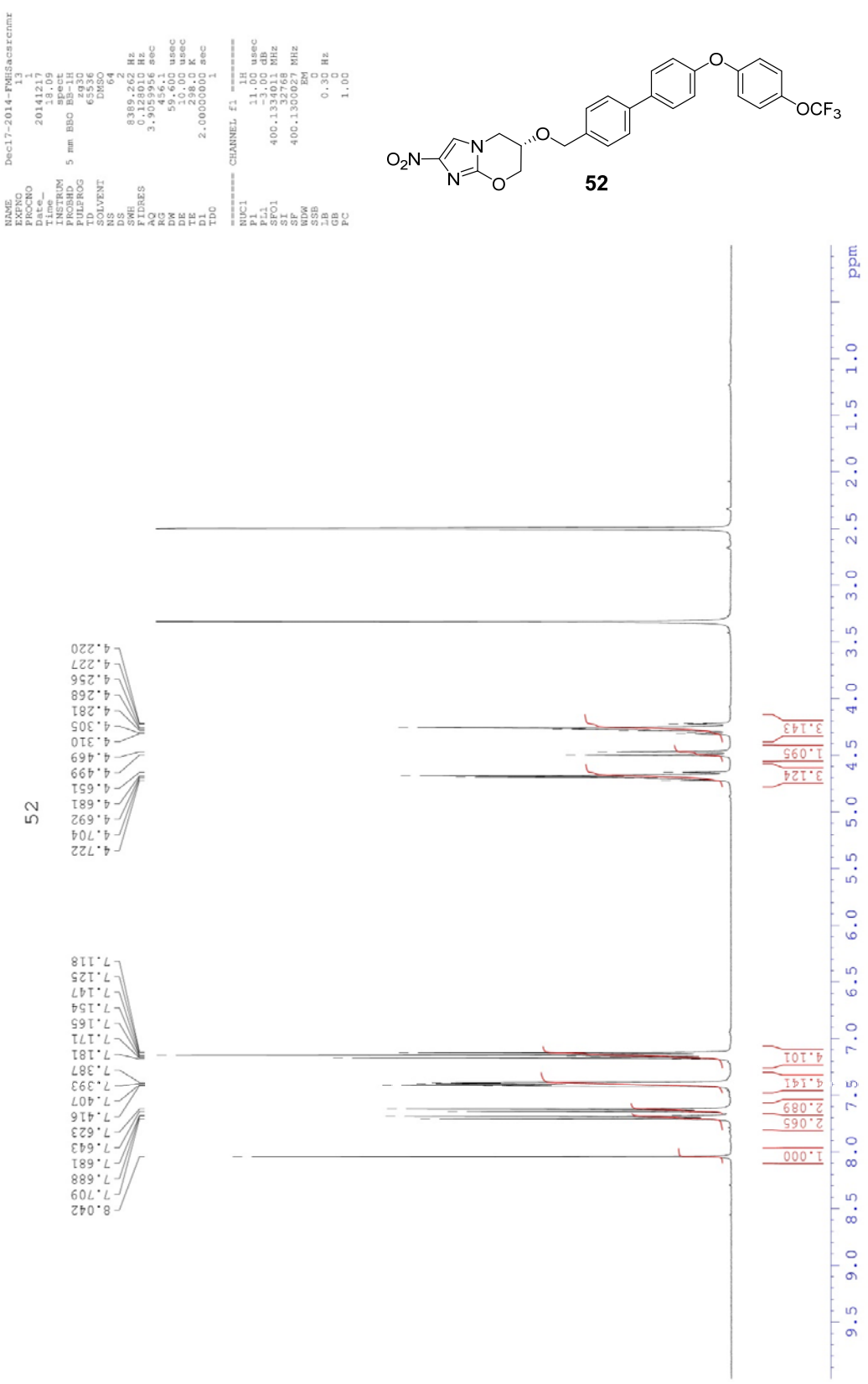
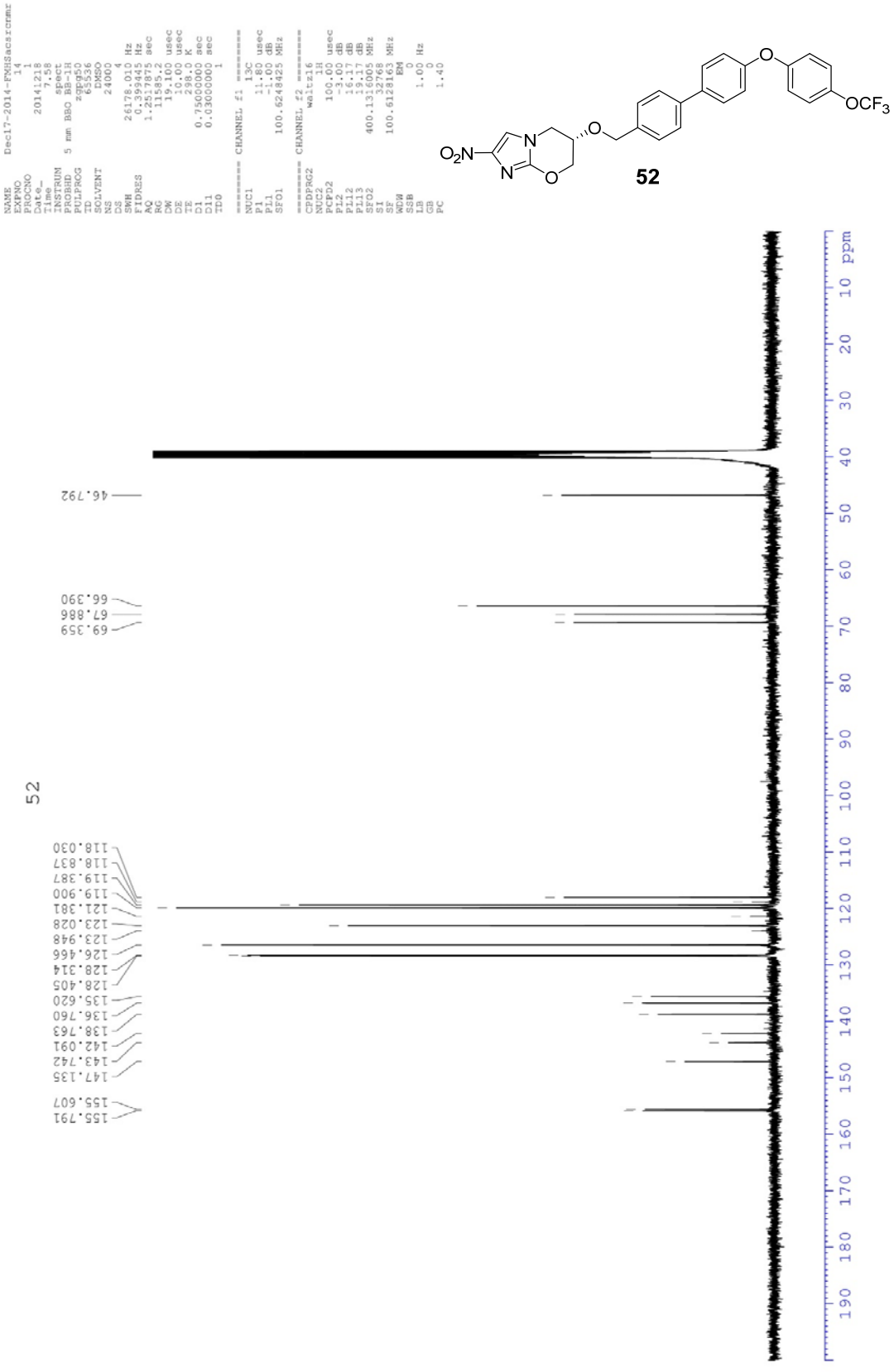
4.208
8.039
7.739
7.732
7.727
7.715
7.710
7.703
7.603
7.582
7.374
7.354
7.339
7.319
7.285
1.000
2.016
2.011
2.034
2.110
1.967
3.092
1.105
3.093
ppm
28

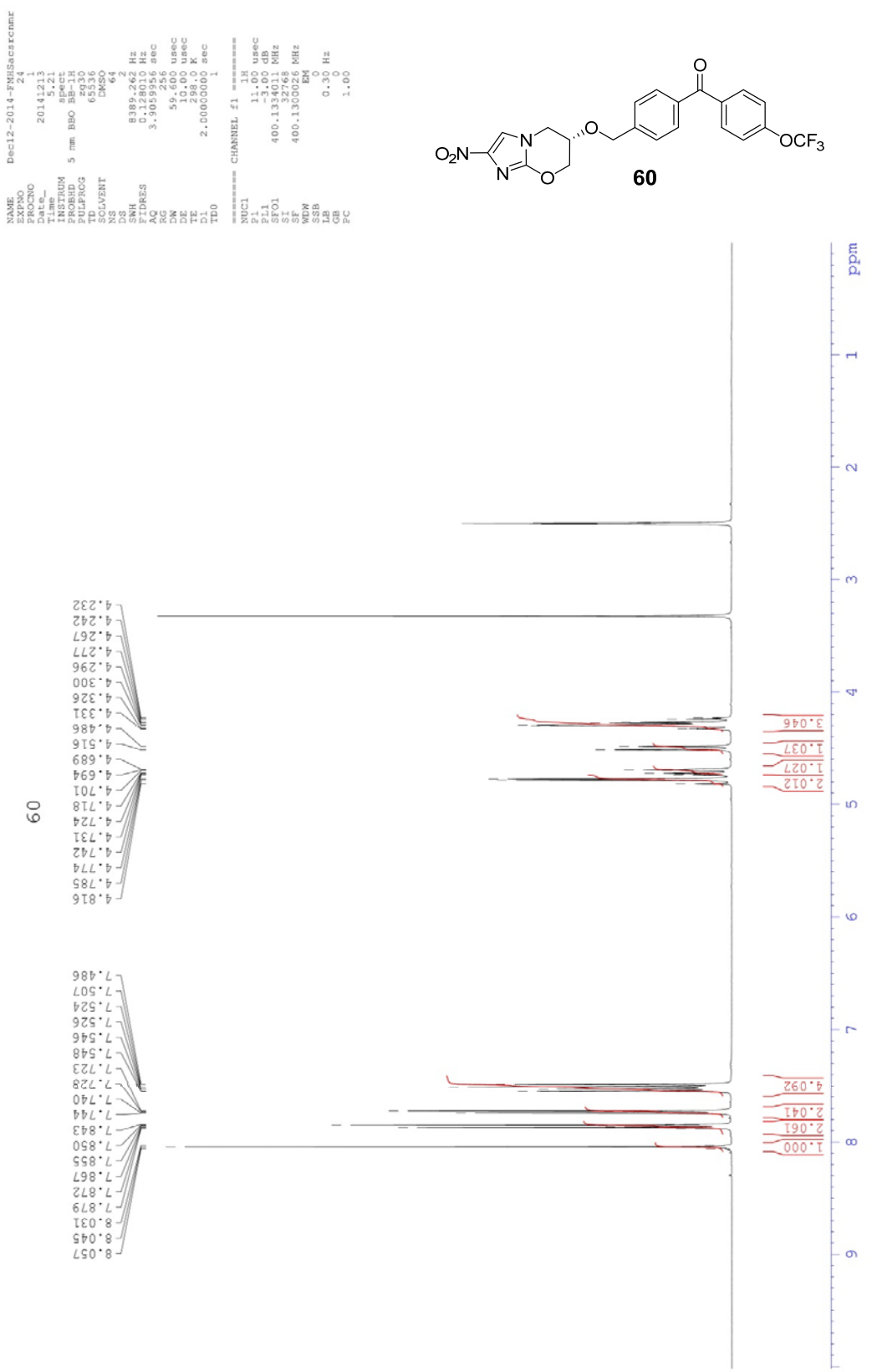

28
46.775
66.384
67.905
69.433
118.032
118.823
121.301
121.376
123.927
126.606
126.895
128.071
128.132
129.347
136.223
136.471
137.438
142.092
147.135
147.522
147.537
ppm

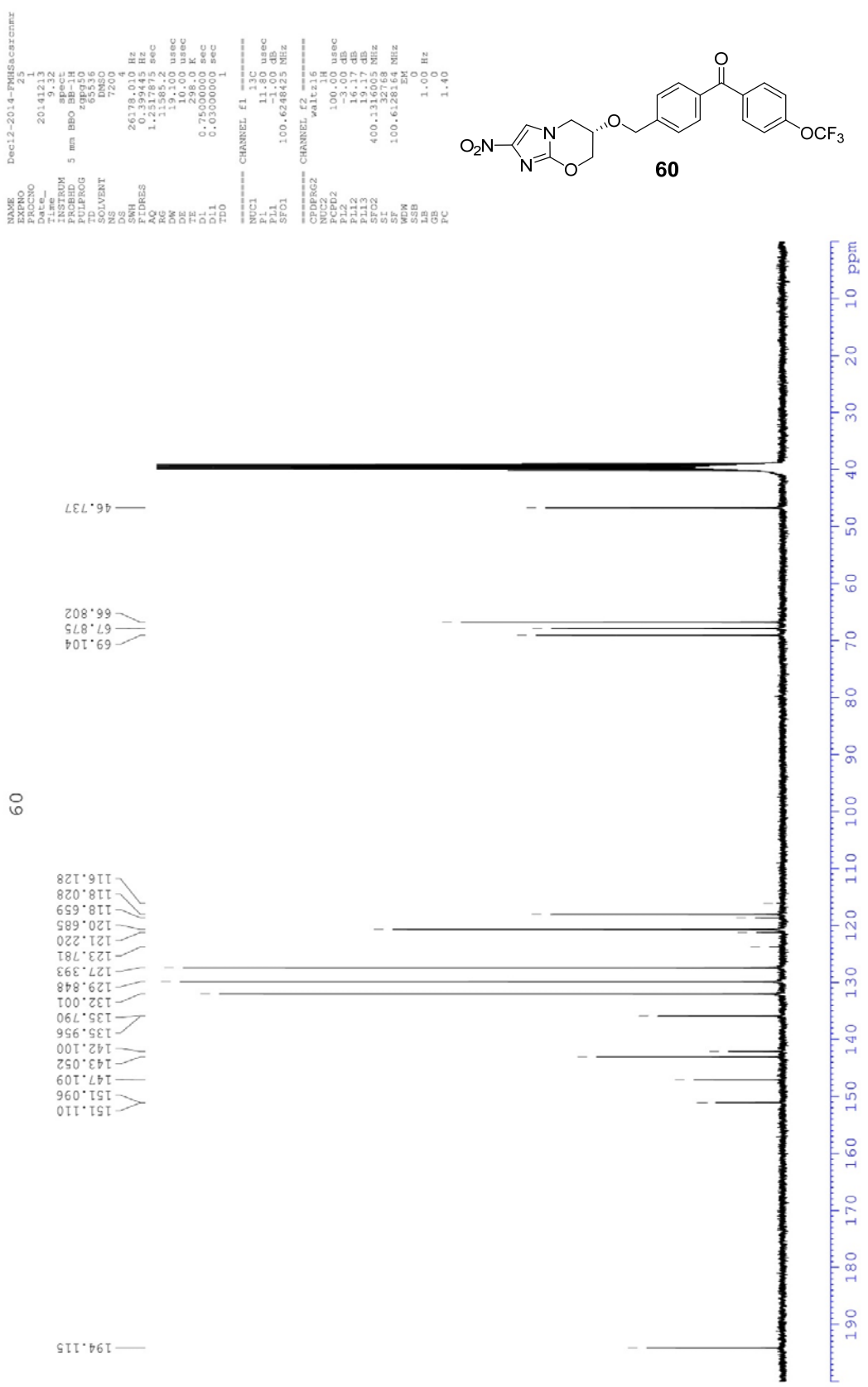

NAME Dec12-2014-PMHSacrcmmr
EXPNO 42
PROCNO 1
Date_ 20141214
Time 20.25
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 64
DS 2
SWH 8389.262 Hz
FIDRES 0.128010 Hz
AQ 3.9059956 sec
RG 256
DW 59.600 usec
DE 19.00 usec
TE 298.1 K
D1 2.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 11.00 usec
PL1 3.00 dB
SFO1 400.1334011 MHz
SI 32768
SF 400.1300025 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
42
OCF3
N
O
N
O2N
N
O
42
ppm
1.000
1.084
1.091
2.189
3.259
2.158
1.191
1.136
2.228
1.175

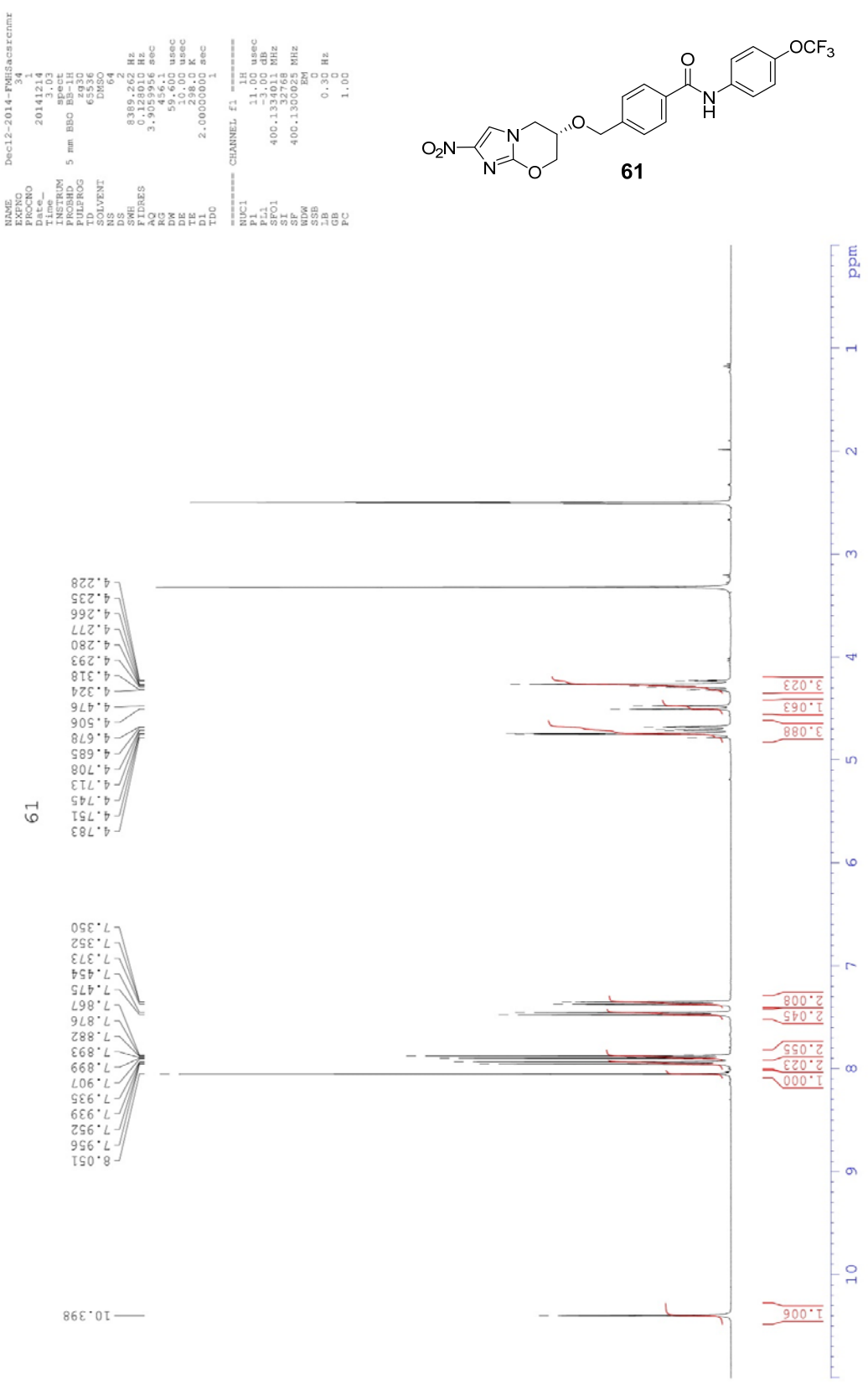

42
157.671
151.048
148.499
148.485
147.096
142.102
139.369
133.603
123.799
121.411
121.241
121.051
121.025
118.685
118.047
117.761
116.153
90.608
87.043
70.559
67.960
67.180
46.697
10 ppm
42


52
ppm


52
155.791
155.607
147.135
143.742
142.091
138.763
136.760
135.620
128.405
128.314
126.466
123.948
123.028
121.381
119.900
119.387
118.837
118.030
69.359
67.886
66.390
46.792
52

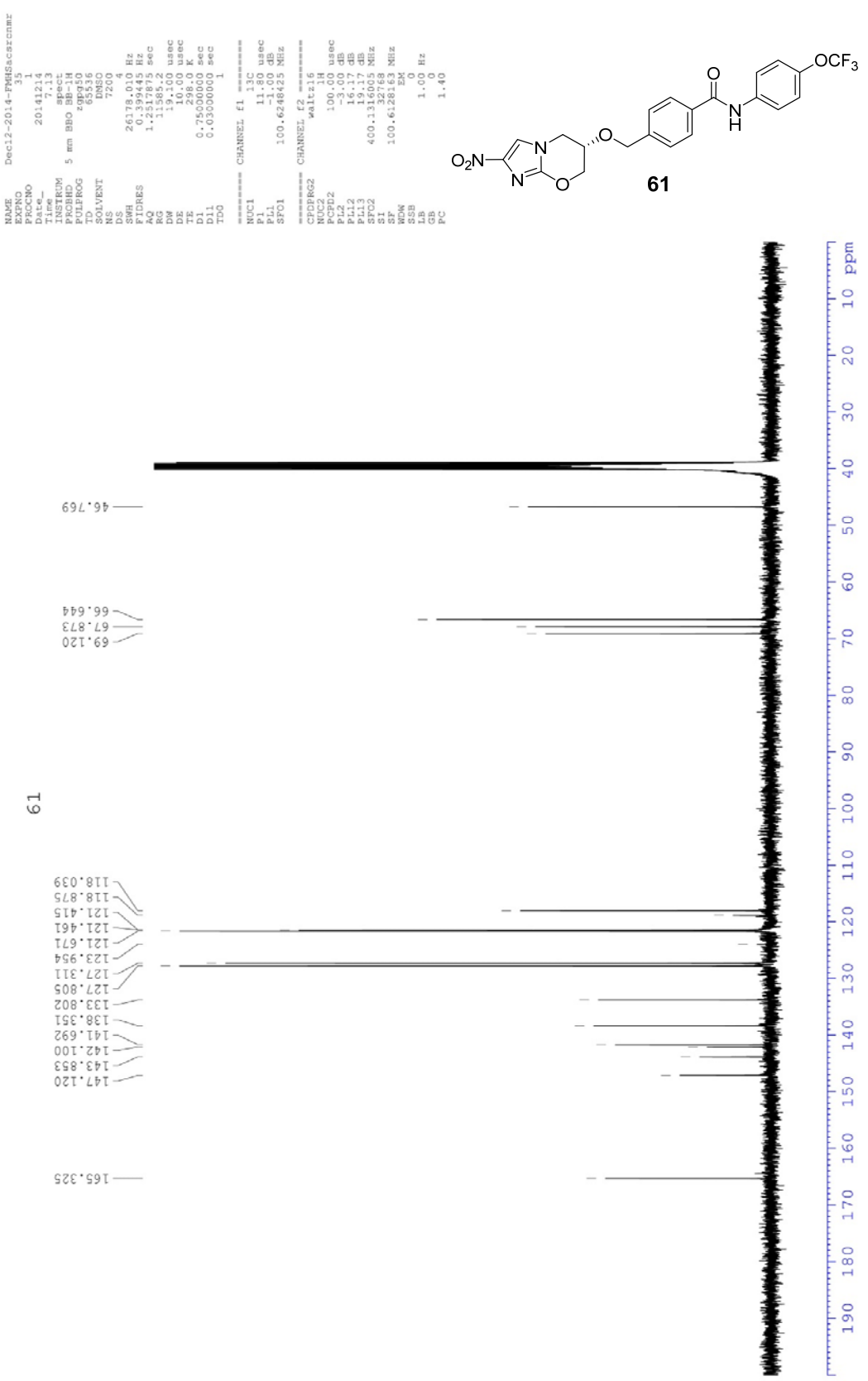

NAME Dec12-2014-FMHSacsfcrmr
EXPNO 24
PROCNO 1
Date_ 20141213
Time 5.21
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 64
DS 4
SWH 8389.262 Hz
FIDRES 0.128010 Hz
AQ 3.9059956 sec
RG 256
DW 59.600 usec
DE 10.00 usec
TE 298.0 K
D1 2.00000001 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 11.00 usec
PL1 3.00 dB
SFO1 400.1330011 MHz
SI 32768
SF 400.1300026 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
O2N
N
N
O
O
O
OCF3
60
60
ppm
1
2
3
4
5
6
7
8
9
4.232
4.242
4.267
4.277
4.296
4.300
4.326
4.331
4.486
4.516
4.689
4.694
4.701
4.718
4.724
4.731
4.742
4.774
4.785
4.816
7.486
7.507
7.524
7.526
7.546
7.548
7.723
7.728
7.740
7.744
7.843
7.850
7.855
7.867
7.872
7.879
8.031
8.045
8.057
3.046
1.037
1.027
2.012
4.092
2.041
2.061
1.000

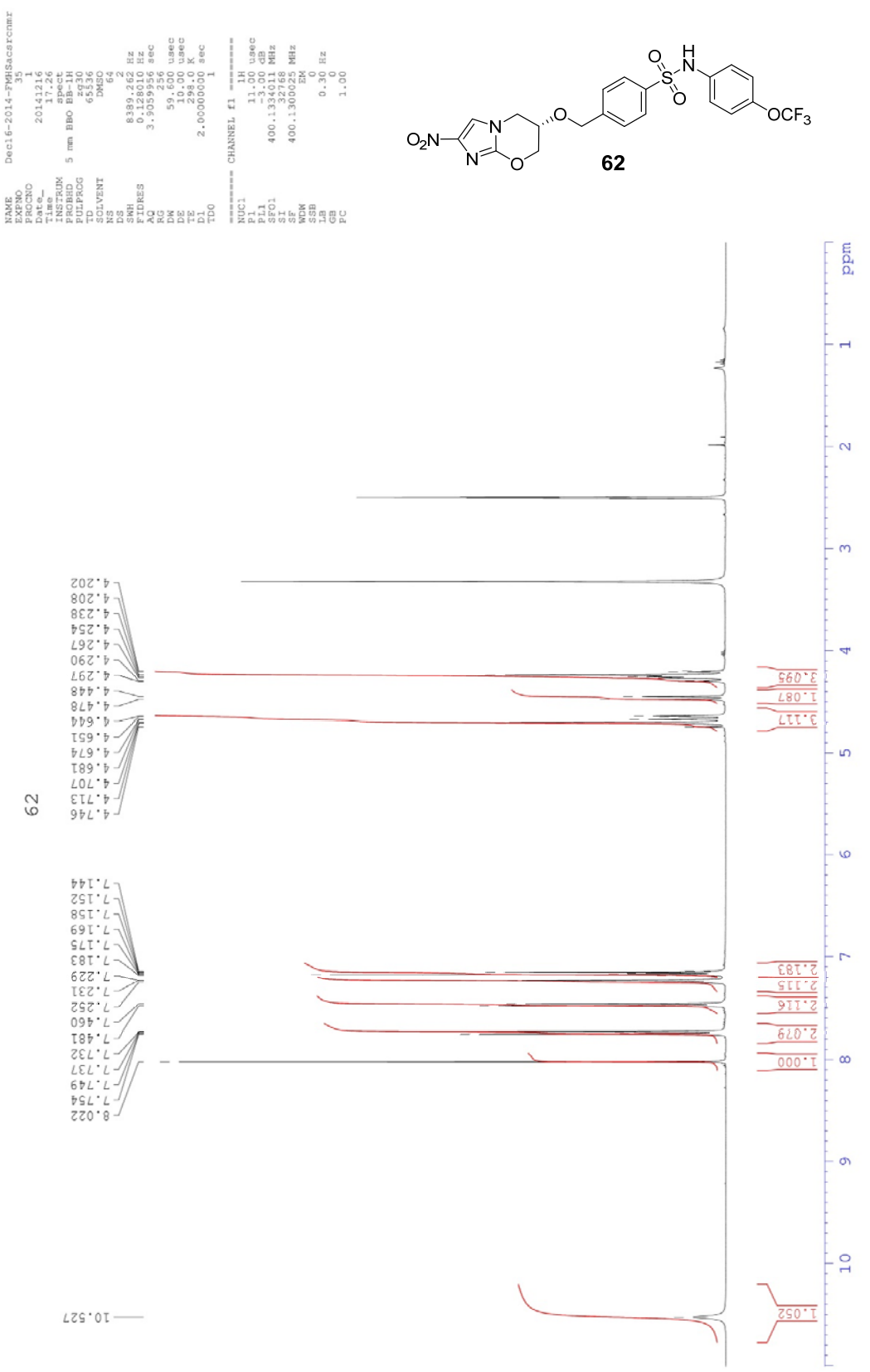

NAME Dec12-2014-PMHSacrcmr
EXPNO 25
PROCNO 1
Date_ 20141213
Time 9.32
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 720
DS 4
SWH 26178.010 Hz
FIDRES 0.399445 Hz
AQ 1.2511787 sec
RG 11585.2
DW 19.100 usec
DE 10.00 usec
TE 298.1 K
D1 0.75000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 11.00 usec
PL1 1.00 dB
SFO1 100.6248425 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -3.00 dB
PL12 16.17 dB
PL13 19.17 dB
SFO2 400.1316005 MHz
SI 32768
SF 100.6128164 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
60
46.737
66.802
67.875
69.104
116.128
118.028
118.659
120.685
121.220
123.781
127.393
129.848
132.001
135.790
135.956
142.100
143.052
147.109
151.096
151.110
194.115
10 ppm


61
10.398
8.051
7.956
7.952
7.939
7.935
7.907
7.899
7.893
7.882
7.876
7.867
7.475
7.454
7.373
7.352
7.350
4.783
4.751
4.745
4.713
4.708
4.685
4.678
4.506
4.476
4.324
4.318
4.293
4.280
4.277
4.266
4.235
4.228
3.023
1.063
3.088
2.008
2.045
2.055
2.023
1.000
1.006
ppm

O2N
N
N
O
O
O
N
H
OCF3

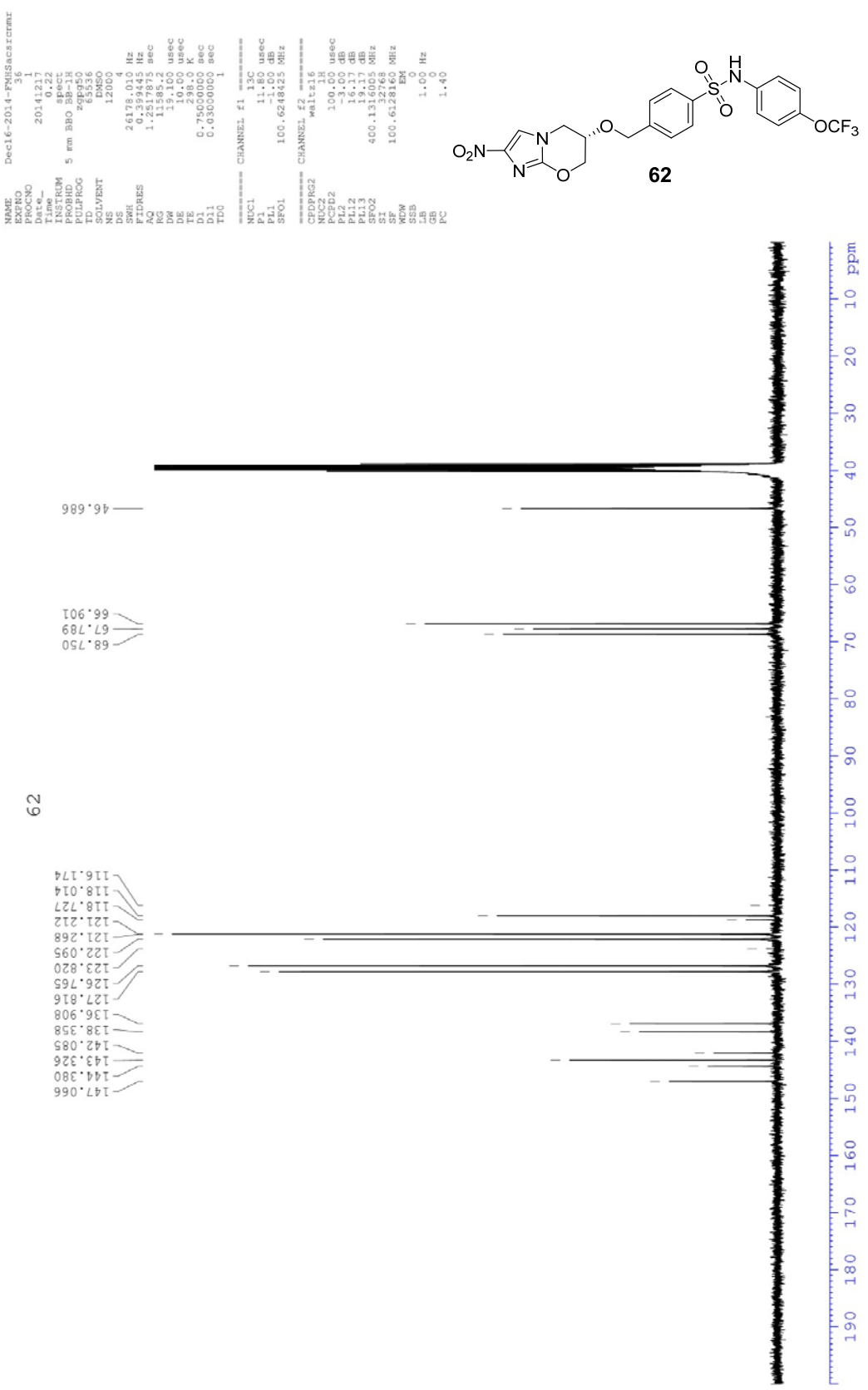
61

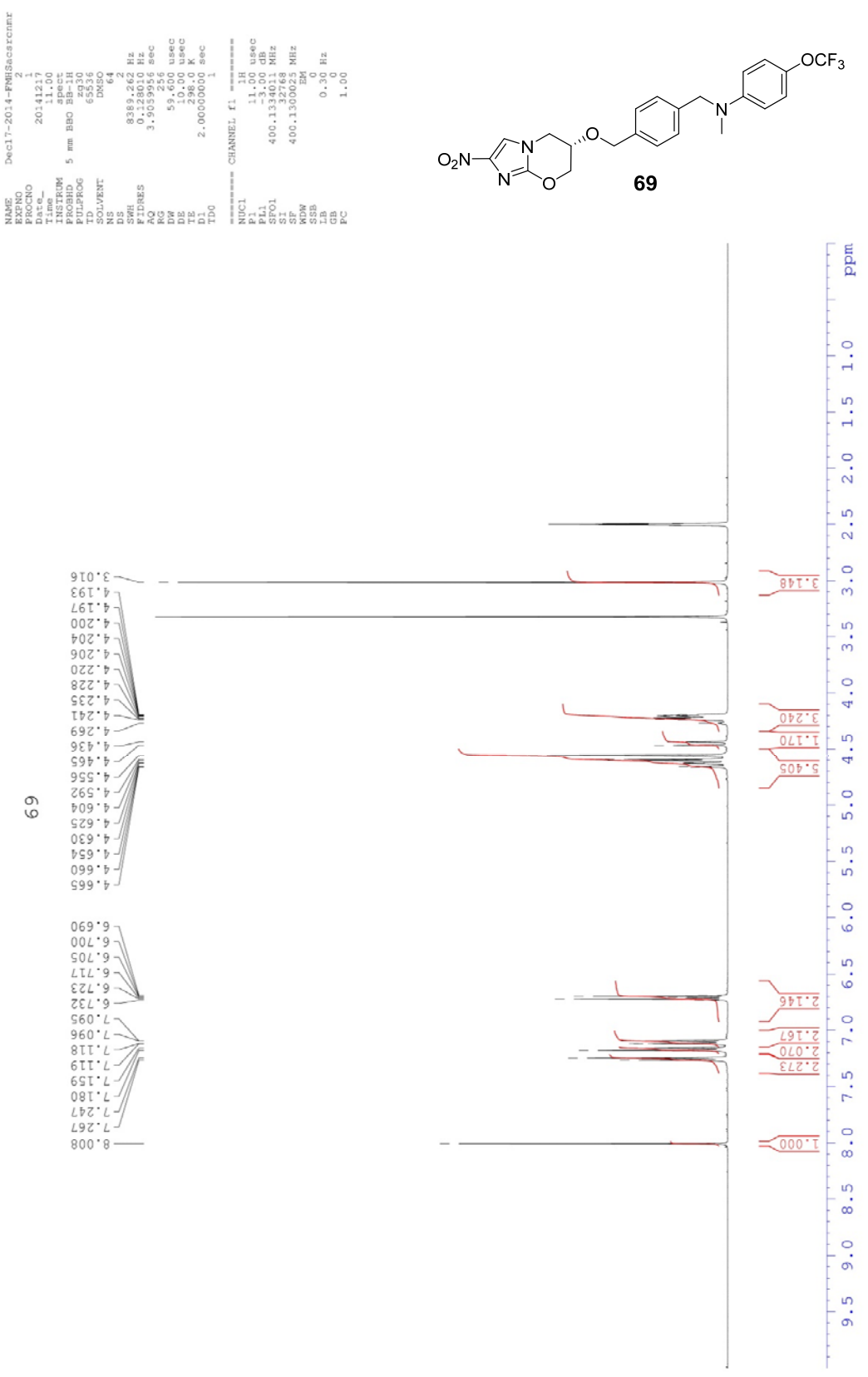

61
46.769
66.644
67.873
69.120
118.039
118.875
121.415
121.461
121.671
123.954
127.311
127.805
133.802
138.351
141.692
142.100
143.853
147.120
165.325
10 ppm

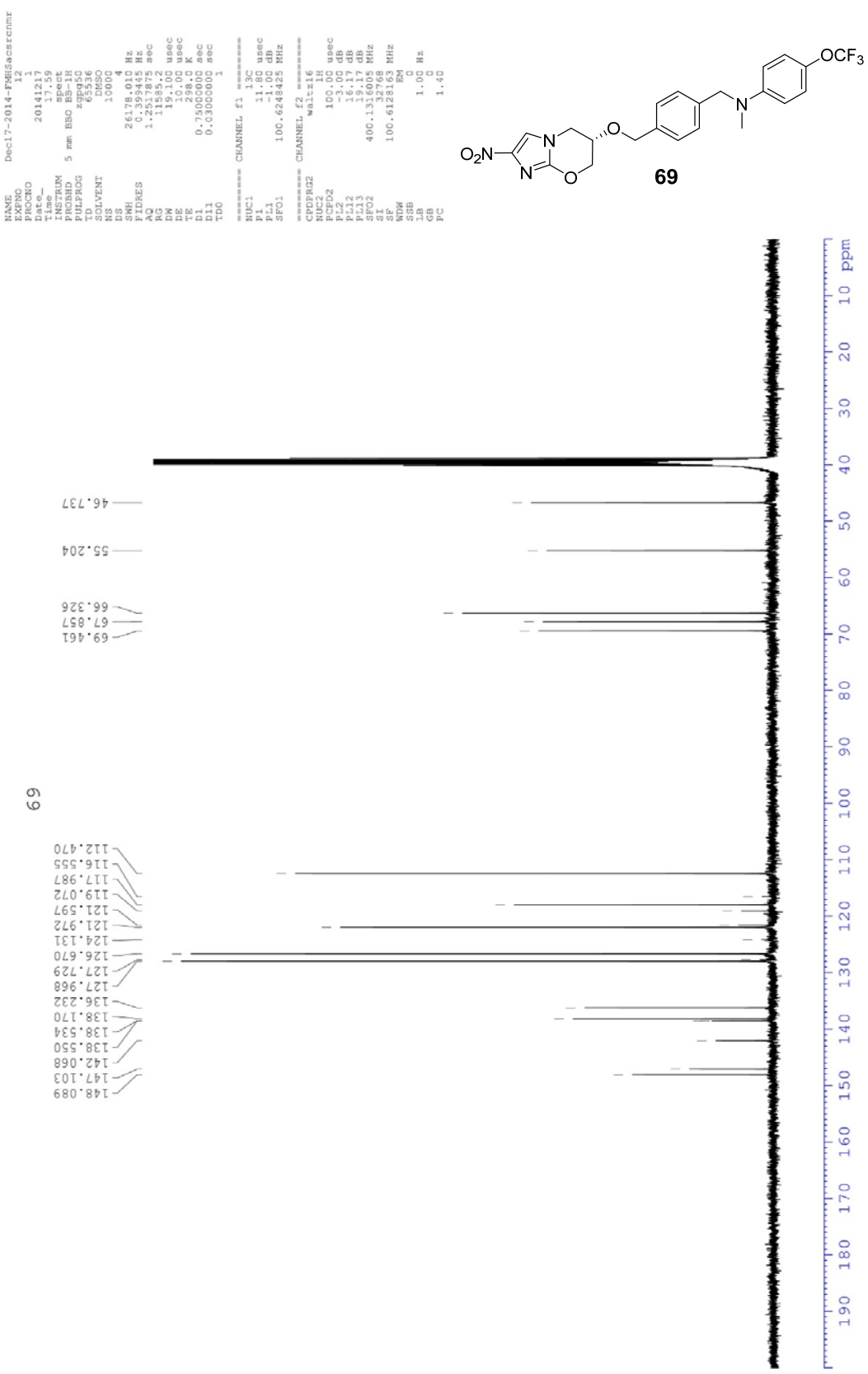

62
10.527
8.022
7.754
7.749
7.737
7.732
7.481
7.460
7.252
7.231
7.229
7.183
7.175
7.169
7.158
7.152
7.144
4.746
4.713
4.707
4.681
4.674
4.651
4.644
4.478
4.448
4.297
4.290
4.267
4.254
4.238
4.208
4.202
3.095
1.087
3.117
2.183
2.115
2.116
2.079
1.000
1.052
ppm

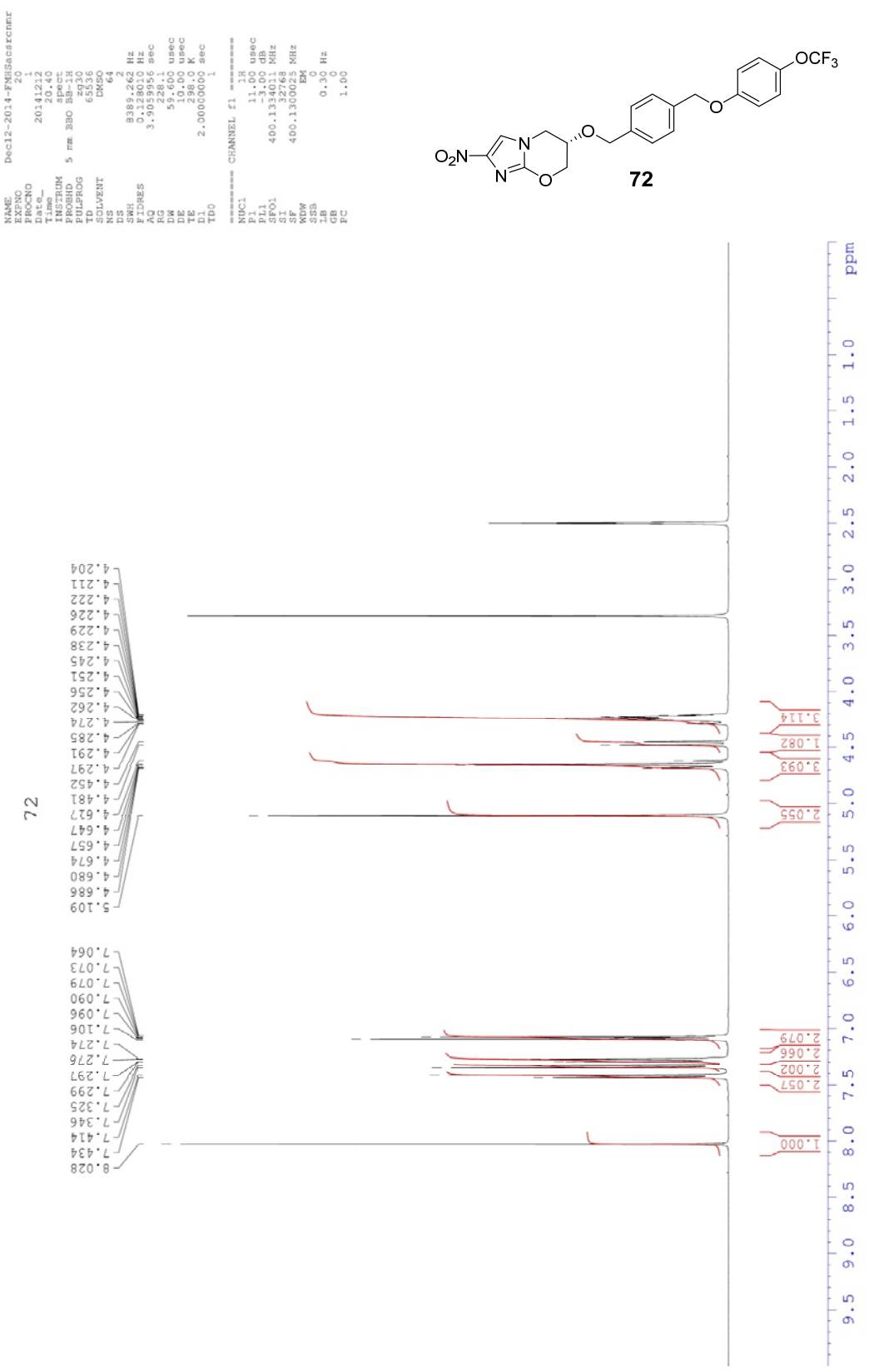
O2N
N
N
O
O
S
O
H
N
OCF3

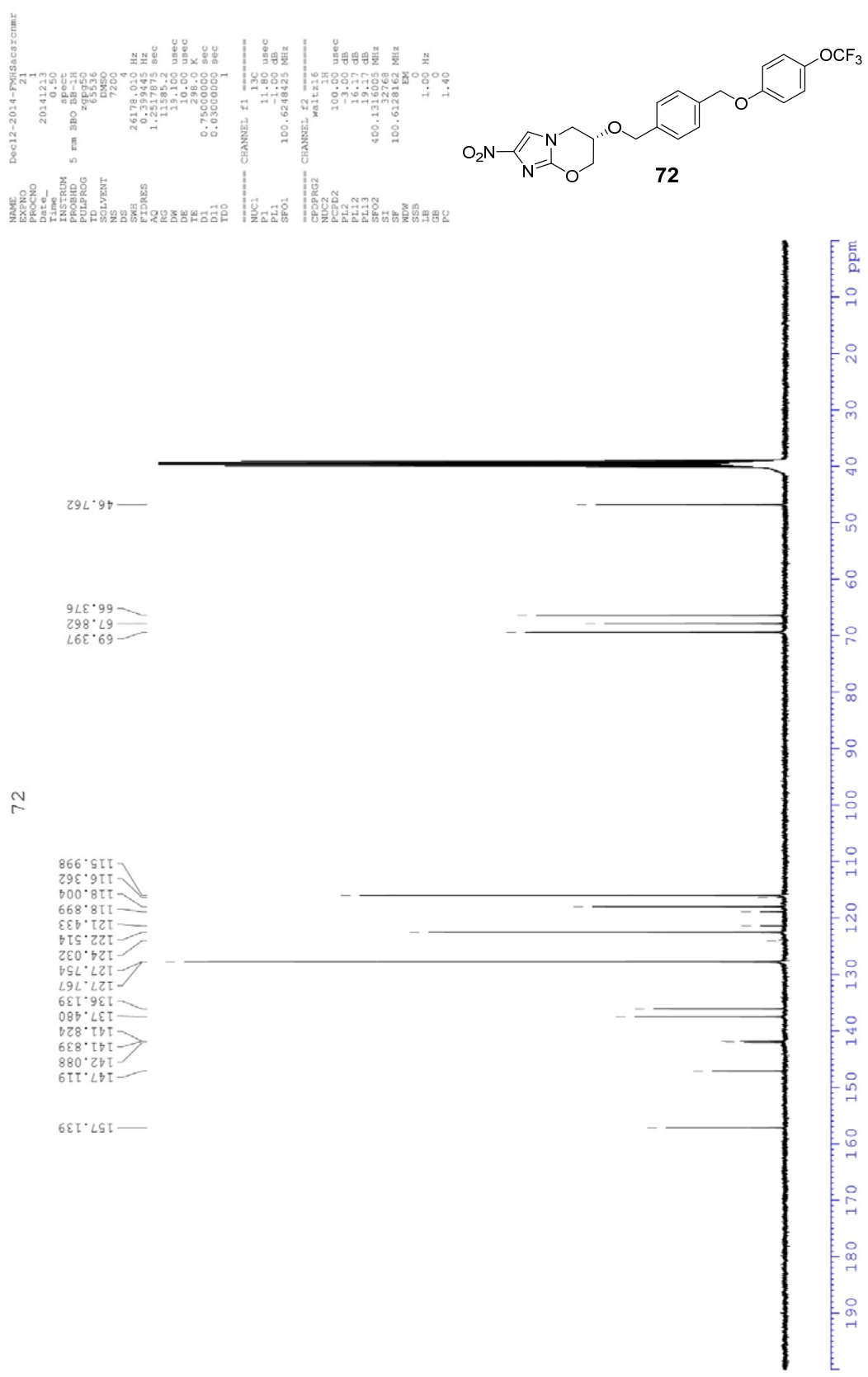
62

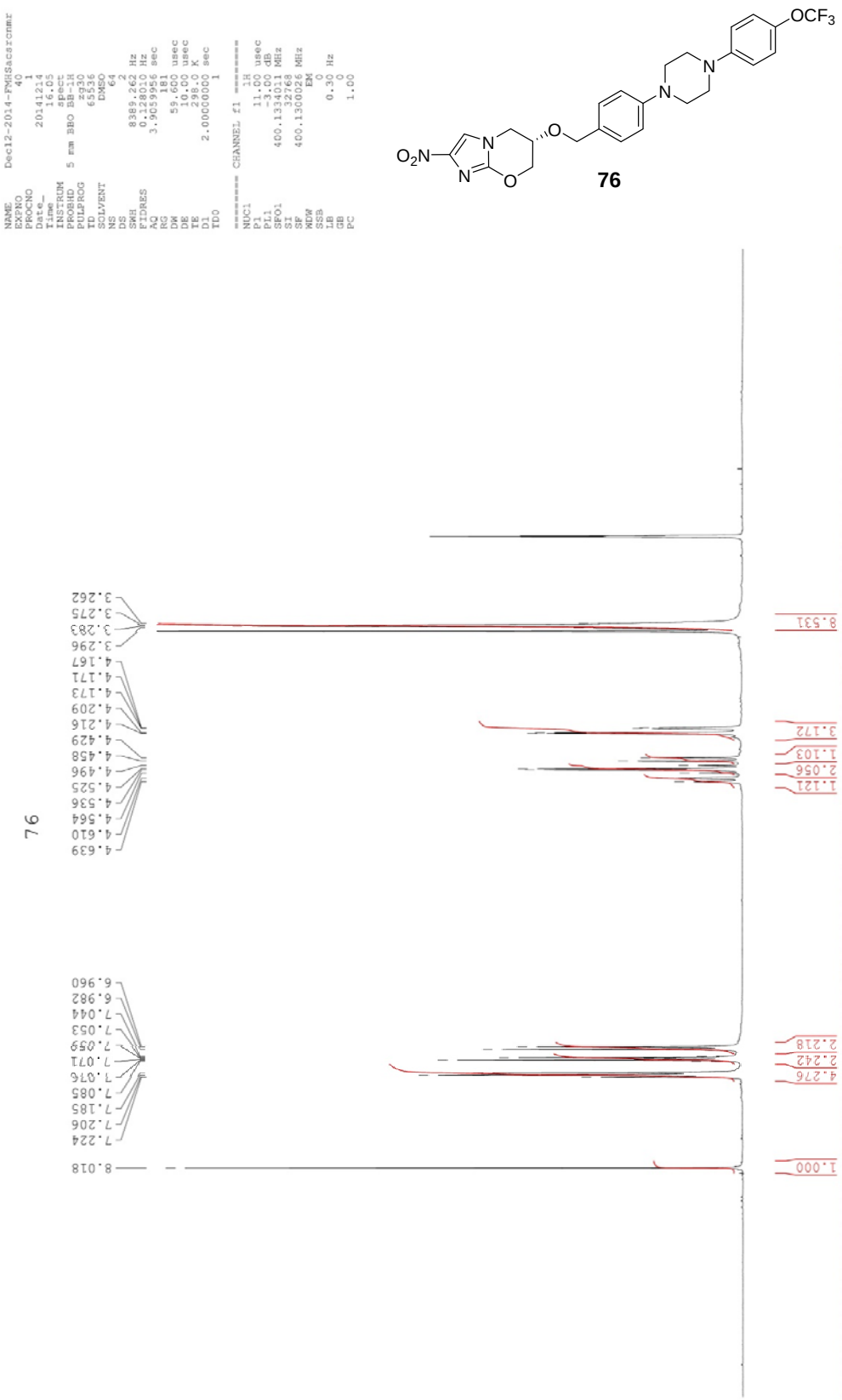

62
147.066
144.380
143.326
142.085
138.358
136.908
127.816
126.765
123.820
122.095
121.268
121.212
118.727
118.014
116.174
66.901
67.789
68.750
46.686
ppm

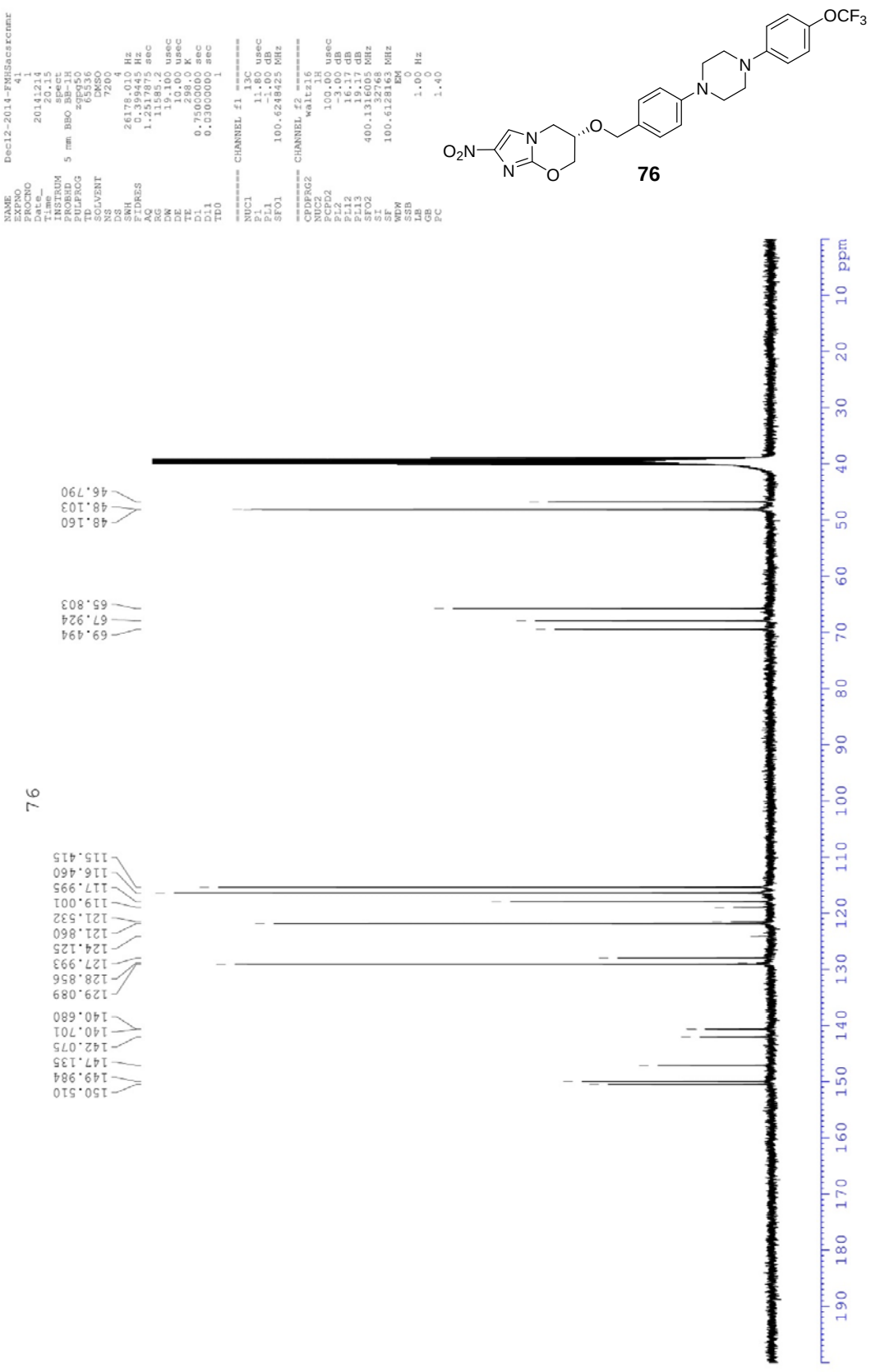

NAME Dec17-2014-FMHSacramnr
EXPNO 2
PROCNO 1
Date_ 20141217
Time 11.00
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 64
DS 4
SWH 8389.262 Hz
FIDRES 0.128010 Hz
AQ 3.9059956 sec
RG 256
DW 59.600 usec
DE 10.00 usec
TE 298.2 K
D1 2.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 11.00 usec
PL1 -3.00 dB
SFO1 400.1330013 MHz
SI 32768
SF 400.1300025 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
69
OCF3
O2N
N
O
N
O
N
69
ppm
1.000
2.146
2.167
2.070
2.273
5.405
1.170
3.240
3.148

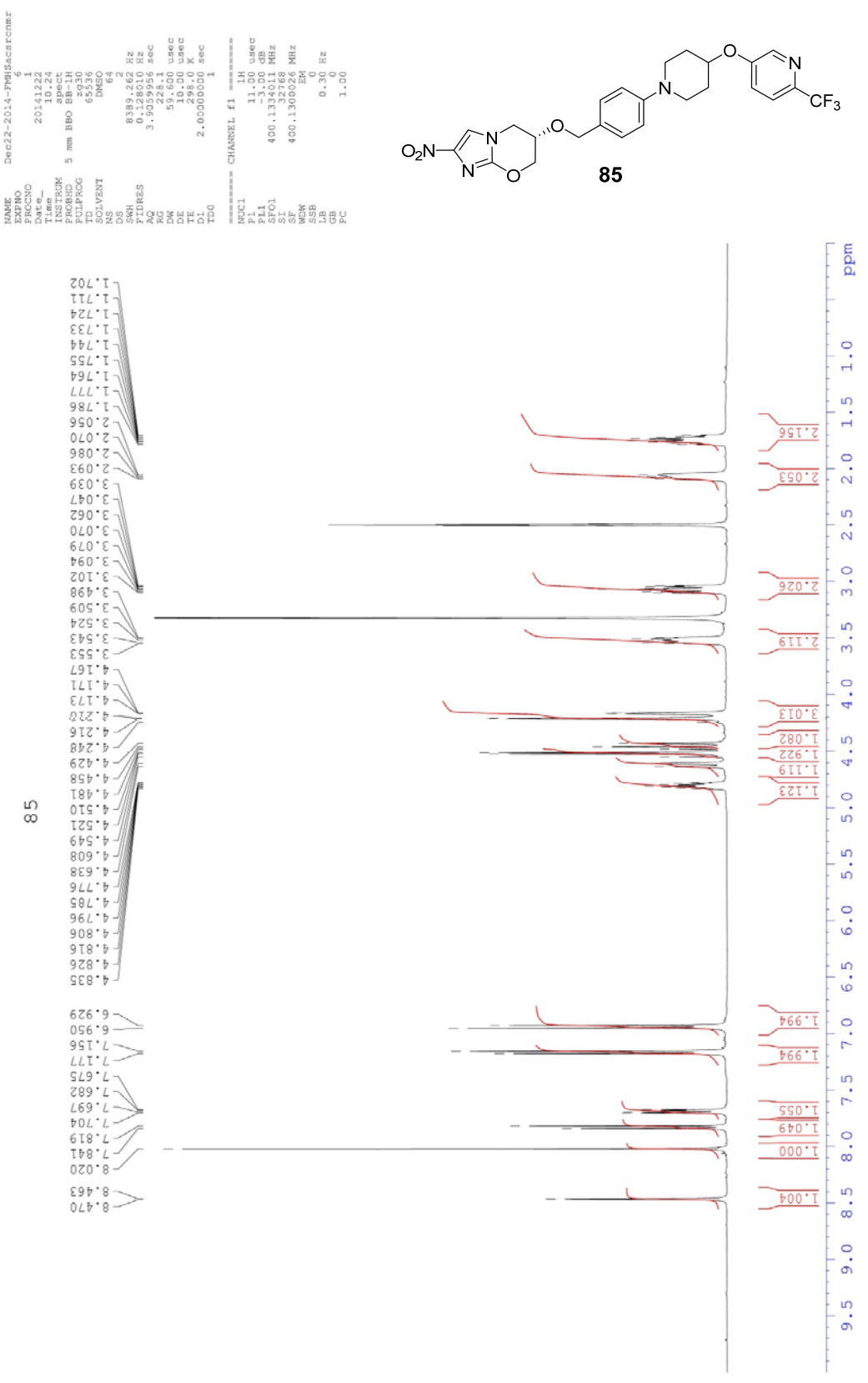

NAME Dec17-2014-FMHSaszrenmr
EXPNO 12
PROCNO 1
Date_ 20141217
Time 17.59
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 10000
DS 4
SWH 26178.010 Hz
FIDRES 0.399445 Hz
AQ 1.2517875 sec
RG 11585.2
DW 19.100 usec
DE 10.00 usec
TE 298.0 K
D1 0.75000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 11.80 usec
PL1 -1.00 dB
SFO1 100.6248425 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -1.00 dB
PL12 16.17 dB
PL13 19.17 dB
SFO2 400.1316005 MHz
SI 32768
SF 100.6128163 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
69
46.737
55.204
66.326
67.857
69.461
112.470
116.555
117.987
119.072
121.597
121.972
124.131
126.670
127.729
127.968
136.232
138.170
138.534
138.550
142.068
147.103
148.089
69
O2N
N
N
O
O
N
OCF3
69
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 ppm


NAME Dec12-2014-FMHSaszrcmnr
EXPNO 20
PROCNO 1
Date_ 20141212
Time 20.40
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 64
DS 2
SWH 8389.262 Hz
FIDRES 0.128010 Hz
AQ 3.9059956 sec
RG 228.1
DW 59.600 usec
DE 10.00 usec
TE 298.0 K
D1 2.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 11.00 usec
PL1 -3.00 dB
SFO1 400.1334011 MHz
SI 32768
SF 400.1300025 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OCF3
O2N
72
ppm
72
3.114
1.082
3.093
2.055
2.079
2.066
2.002
2.057
1.000


NAME Dec12-2014-PMHSaczcrmr
EXPNO 21
PROCNO 1
Date_ 20141213
Time 0.50
INSTRUM spec
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 7200
DS 4
SWH 26178.010 Hz
FIDRES 0.399445 Hz
AQ 1.2517875 sec
RG 11585.2
DW 19.100 usec
DE 10.00 usec
TE 298.0 K
D1 0.75000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 11.80 usec
PL1 1.00 dB
SFO1 100.6248425 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -3.00 dB
PL12 16.17 dB
PL13 16.17 dB
SFO2 400.1316005 MHz
SI 32768
SF 100.6128162 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
72
46.762
66.376
67.862
69.397
115.998
116.362
118.004
118.899
121.433
122.514
124.032
127.754
127.767
136.139
137.480
141.824
141.839
142.088
147.119
157.139
O_2N
N
N
O
O
O
O
OCF_3
72
10 ppm

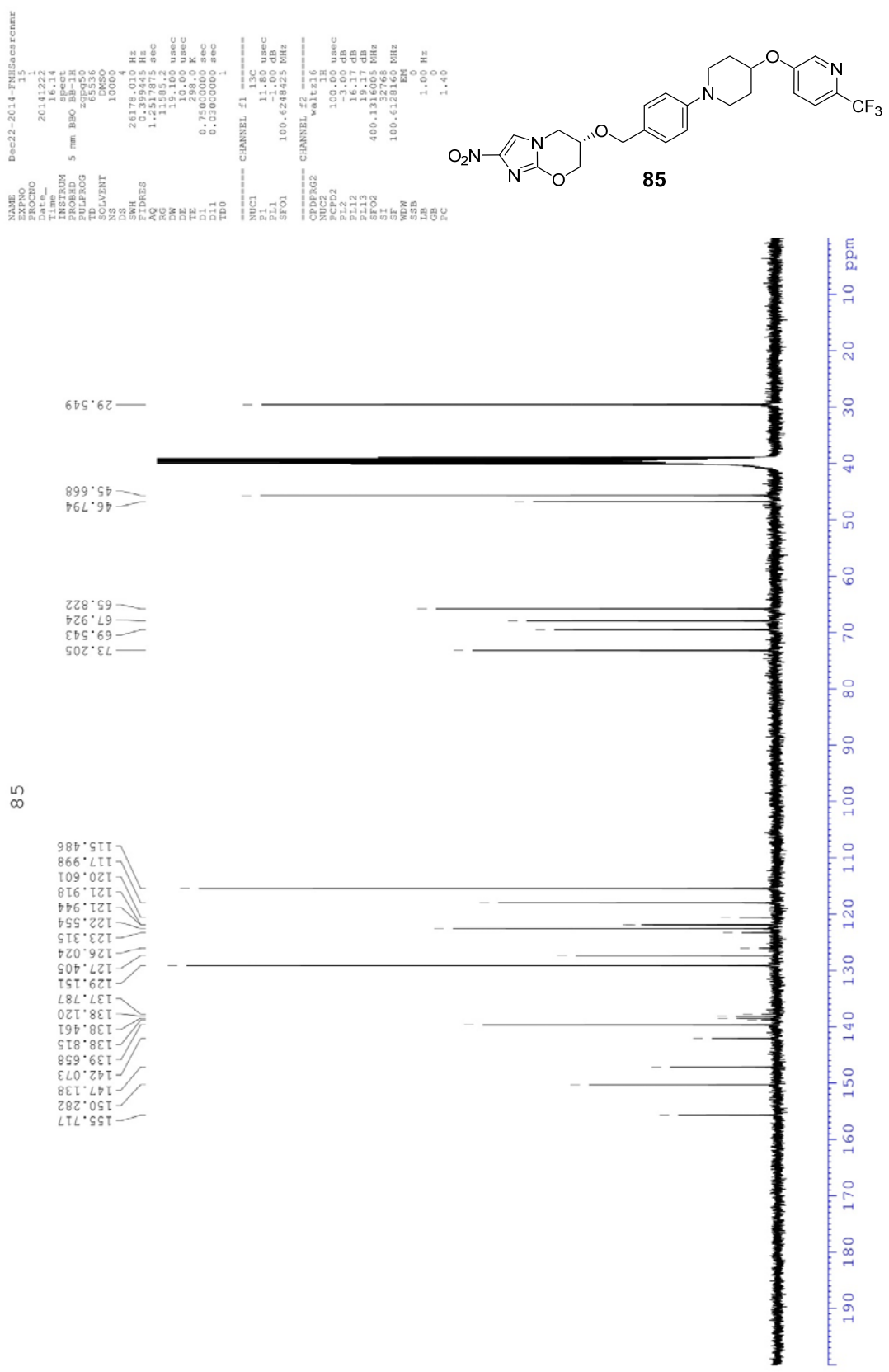

NAME Dec12-2014-PMHSaczcrmx
EXPNO 40
PROCNO 1
Date_ 20141214
Time 16.05
INSTRUM spec
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 64
DS 2
SWH 8389.262 Hz
FIDRES 0.128010 Hz
AQ 3.9059956 sec
RG 181
DW 59.600 usec
DE 10.00 usec
TE 298.0 K
D1 2.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 11.00 usec
PL1 -3.00 dB
SFO1 400.1334021 MHz
SI 32768
SF 400.1300026 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OCF3
O2N
76
ppm
8.531
3.172
1.103
2.056
1.121
2.218
2.242
4.276
1.000
3.262
3.275
3.283
3.296
4.167
4.171
4.173
4.209
4.216
4.429
4.458
4.496
4.525
4.536
4.564
4.610
4.639
6.960
6.982
7.044
7.053
7.059
7.071
7.076
7.085
7.185
7.206
7.224
8.018


76
46.790
48.103
48.160
65.803
67.924
69.494
115.415
116.460
117.995
119.001
121.532
121.860
124.125
127.993
128.856
129.089
140.680
140.701
142.075
147.135
149.984
150.510
10 ppm
76


NAME Dec22-2014-FMHSacrcmnr
EXPNO 6
PROCNO 1
Date_ 20141222
Time 10.24
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 64
DS 2
SWH 8389.262 Hz
FIDRES 0.128010 Hz
AQ 3.9059956 sec
RG 228.1
DW 59.600 usec
DE 10.00 usec
TE 298.0 K
D1 2.00000001 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 11.00 usec
PL1 -3.00 dB
SFO1 400.1330771 MHz
SI 32768
SF 400.1300026 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
85
ppm

O2N
N
O
N
O
N
O
N
CF3

85


85
29.549
45.668
46.794
65.822
67.924
69.543
73.205
115.486
117.998
120.601
121.918
121.944
122.554
123.315
126.024
127.405
129.151
137.787
138.120
138.461
138.815
139.658
142.073
147.138
150.282
155.747
85
O2N
N
O
N
O
N
O
N
CF3
NAME Dec22-2014-FMHSaesfcnmr
EXPNO 15
PROCNO 1
Date_ 20141222
Time 16.14
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgpg50
TD 65536
SOLVENT DMSO
NS 10000
DS 4
SWH 26178.010 Hz
FIDRES 0.399445 Hz
AQ 1.2517875 sec
RG 11585.2
DW 19.100 usec
DE 10.00 usec
TE 298.0 K
D1 0.75000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 11.80 usec
PL1 1.00 dB
SFO1 100.6248425 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 3.00 dB
PL12 16.17 dB
PL13 19.17 dB
SFO2 400.1316005 MHz
SI 32768
SF 100.6128160 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
10 ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190