Molecular Pharmacology

Supplemental Data

Synthesis and Evaluation of Potent KCNQ2/3-specific Channel Activators

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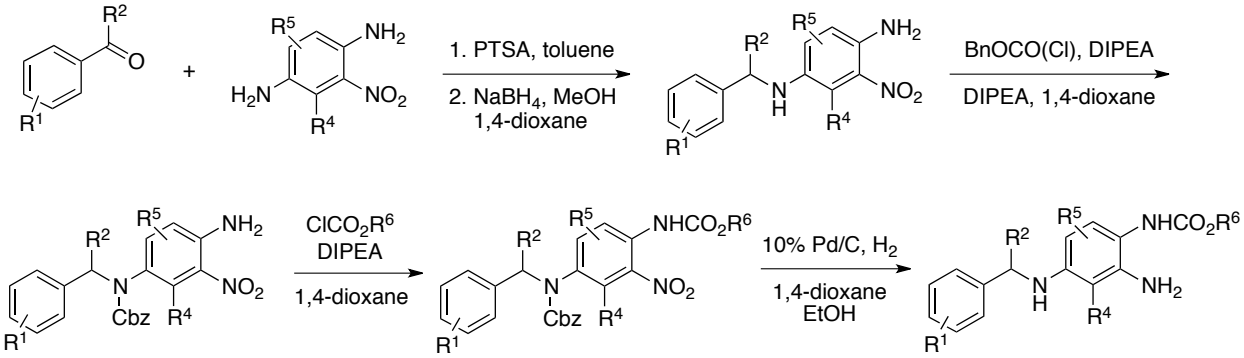
Synthetic Route A:



Synthetic Route B:

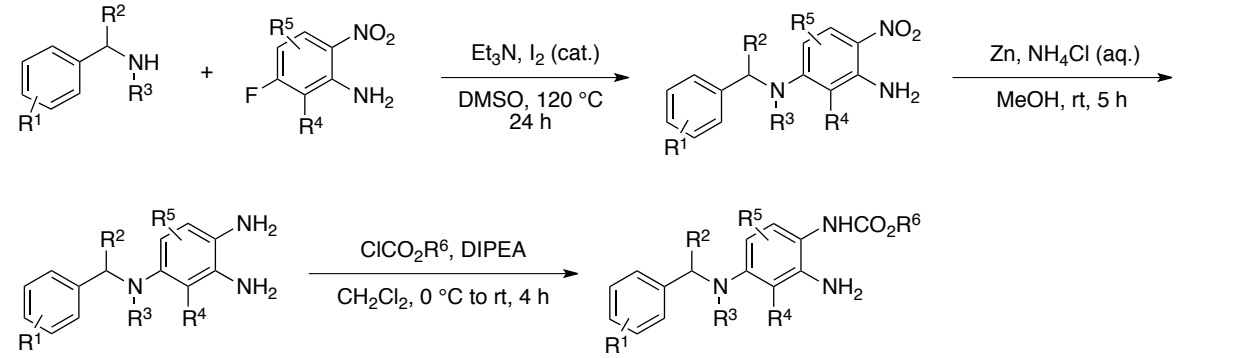


Figure S1.

Figure S1. General synthetic scheme for the analog synthesis.

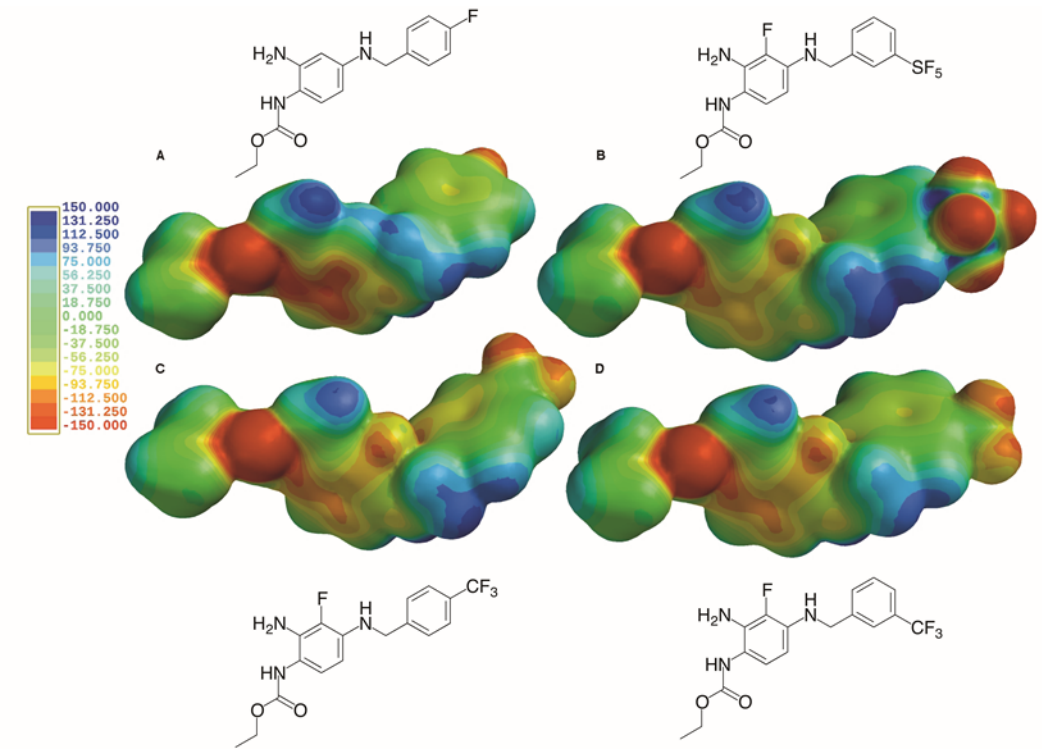


Figure S2.

Figure S2. Combined steric and electronic features of retigabine and new KCNQ2/3-specific channel activators, illustrating the effects of fluorinations on the aromatic rings and their substituents. A: retigabine; **B:** RL673_02; **C:** RL648_81; **D:** RL648_73. The color coding on the electron-density surface reflects the electrostatic potential experienced by a positive probe charge (red=attractive to blue=repulsive). Electron-density surfaces encoded with electrostatic potential maps were calculated in Spartan 10 (Wave Function, Inc., Irvine, CA) with PM6 parametrization. Compared to retigabine (Fig. S2A), RL648_81 (Fig. S2C) has an electron-depleted aniline aromatic system, which also influences the electron density in the attached three nitrogen atoms, decreasing their negative partial charges. The CF_3-substituent in RL648_81 is a stronger deactivator of the benzylamine π-system, but, in particular, increases steric bulk at this

terminus of the molecule and would be expected to pose a steeper steric barrier to cytochrome P450-induced arene hydroxylation and compound metabolism. The electrostatic potential maps for RL673_02 (Fig. S2B) and RL648_73 (Fig. S2D) are also shown for comparison. Both are closely related to that of RL648_81 at the carbamate termini, but show steric and electronic differences in the benzylamine region. The SF_5-substituent in RL673_02 provides the largest steric barrier and electronic deactivation in this series.

Compound	**KCNQ2/3**		**KCNQ4 Max $\Delta V_{1/2}$ (mV)**	**KCNQ5 Max $\Delta V_{1/2}$ (mV)**
	EC50 (μM)	**$\Delta V_{1/2}$ (mV)**		
Retigabine	3.3 ± .08	33.9 ± 1.5	Not Tested (NT)	NT
SF0034	0.06 ± 0.6	50.1 ± 1.6	NT	NT
NR561_40	0.91 ± .08	50.9 ± 3.1	12.7 ± .75	29.7 ± 3.5
NR561_50	0.74 ± .07	39.6 ± 1.7	2.7 ± .85	5.6 ± 1.6
NR561_29	0.76 ± .17	27.8 ± 1.7	19.4 ± 1.7	9.5 ± 1.7
NR561_45	1.34 ± .17	34.1 ± 2.9	NT	NT
NR579_38	2.55 ± .46	13.7 ± 3.9	NT	NT
NR579_46	3.53 ± .54	46.7 ± 2.6	NT	NT
NR561_87	4.03 ± 1.2	32.8 ± 4.9	NT	NT
NR579_04	Not Shifted (NS)	(NS)	NT	NT
NR561_62	1.48 ± .18	34.7 ± .74	NT	NT
NR579_45	4.49 ± 1.0	26.9 ± 1.1	NT	NT
NR579_36	NS	NS	NT	NT
RL673_02	0.88 ± .28	42.5 ± 4.5	9.7 ± .25	7.4 ± 1.3
RL648_86	0.34 ± .07	49.9 ± 2.5	2.6 ± .65	3.6 ± 1.4
RL648_73	0.30 ± .05	47.0 ± 4.1	4.3 ± .71	5.4 ± 1.5
RL648_81	0.19 ± .02	51.1 ± 3.5	5.1 ± 1.3	6.7 ± 1.5

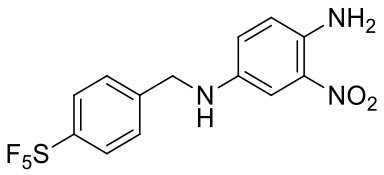
Table S1

Table S1. Summary values of EC_{50} and maximal (Max) $\Delta V_{1/2}$ for all compounds tested. EC_{50} is the concentration of the compound that produces a half-maximal shift in $V_{1/2}$. Maximal (max) $\Delta V_{1/2}$ is the shift in $V_{1/2}$ at 10 μM concentrations of the compound. NS: $V_{1/2}$ was not shifted by this compound. NT: (Max) $\Delta V_{1/2}$ was not tested for this compound.

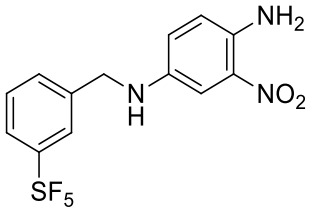
Synthesis: The synthesis of these compounds followed the general routes A and B shown in Figure S1. Briefly, in route A we performed a reductive amination to link the benzylic amine portion with the aniline moiety. After selective introduction of the benzyloxycarbonyl (Cbz) protective group, the *ortho*-nitroaniline was acylated and the Cbz group was removed concomitantly with the reduction of the nitro group to generate the desired analogs. In synthetic route B, we added suitably substituted benzylic amines to *para*-nitrofluorobenzenes under S_NAr conditions, followed by reduction of the nitro group with zinc and ammonium chloride, and selective N-acylation of the resulting *para*-aminoaniline.

General Experimental Details. All reactions were performed under an N_2 atmosphere and all glassware was dried in an oven at 130 ^oC for at least 2 h prior to use and allowed to cool under an atmosphere of dry N_2 or Ar. Reactions carried out below 0 ^oC employed a dry ice/acetone or a low-temperature automated cooler and an acetone bath. THF and Et_2O were distilled over sodium/benzophenone ketyl radical anion; CH_2Cl_2 and toluene were distilled over CaH_2, and 1,4-dioxane, and MeOH, and MeCN were dried over 3 Å molecular sieves unless otherwise noted. Et_3N and other volatile amines were distilled from CaH_2 and stored over KOH. Concentration under reduced pressure refers to the use of a rotary evaporator connected to a PIAB Lab Vac

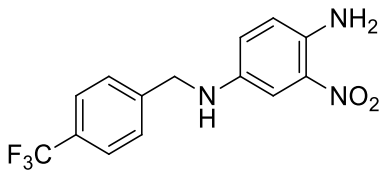
H40 line to remove solvent, and drying under high vacuum refers to the use of a Fischer Scientific Maxima C *Plus* vacuum pump (0.5-4 mmHg) to remove traces of solvent. All chromatography was performed on normal phase SiO_2 (Silicycle, 40-63 μm particle size) using literature conditions [Still, W. C.; Kahn, M.; Mitra, A. Rapid chromatographic technique for preparative separations with moderate resolution. *J. Org. Chem.* **1978**, *43*, 2923-2925] unless stated otherwise. Reactions were monitored by thin-layer chromatography (Merck pre-coated silica gel 60 F_{254} plates, 250 μm layer thickness) and visualization was accomplished with a 254 nm UV light, by staining with a $KMnO_4$ solution (prepared by dissolving 1.5 g of $KMnO_4$ and 1.5 g of K_2CO_3 in 100 mL of a 0.1% NaOH solution), or by staining with *p*-anisaldehyde solution (2.5 mL of *p*-anisaldehyde, 2 mL of AcOH, and 3.5 mL of conc. H_2SO_4 in 100 mL of 95% EtOH). Melting points were obtained using a Laboratory Devices Mel-Temp II with open capillaries and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained on Bruker Avance 300, 400, 500, 600, or 700 MHz instruments as indicated in $CDCl_3$ solution unless otherwise noted. Chemical shifts were reported in parts per million with the residual solvent peak used as an internal standard. ^{1}H NMR spectra were obtained and are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, dd = double of doublets, dt = doublet of triplets, m = multiplet, br = broad, app = apparent), number of protons, and coupling constant(s). ^{13}C NMR were recorded at 75, 100, 125, or 175 MHz as specified using a proton-decoupled pulse sequence and tabulated by observed peak. Infrared spectra were measured on ATR-IR instruments. High resolution mass spectra were obtained on a Thermo Fisher Exactive Orbitrap LC-MS using heated electrospray ionization (HESI).



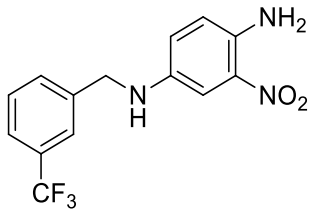
(4-Amino-3-nitro)phenyl-[(4-(pentafluorothio)phenyl)methyl]amine. To a solution of 2-nitro-*p*-phenylenediamine (0.751 g, 4.66 mmol) and PTSA (0.045 g, 0.24 mmol) in toluene (25 mL) was added 4-(pentafluorothio)-benzaldehyde (1.115 g, 4.707 mmol). The resulting solution was heated to reflux with a Dean-Stark trap for 21 h, the mixture was filtered through a Buchner funnel packed with a thin pad of SiO_2, and the filtrate was stirred and allowed to cool to rt. The solvent was removed under reduced pressure to give the crude imine (1.10 g) as a bright orange-red solid that was suspended in a mixture of 1,4-dioxane (5.2 mL) and MeOH (1.3 mL), and $NaBH_4$ (0.120 g, 3.14 mmol) was added in 3 portions at 15 min intervals. The solution was allowed to stir at rt for 3 h, quenched with H_2O (25 mL) and the resulting solid was collected by filtration. The crude product was washed with H_2O (500 mL) and dried under high vacuum to give (4-amino-3-nitro)phenyl-[(4-(pentafluorothio)phenyl)methyl]amine (1.09 g, 2.95 mmol, 63%) as a dark purple powder: Mp 129-130 ^oC (H_2O); IR (ATR) 3522.9, 3397.9, 1576.9, 1531.8, 1327.7, 1216.3 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.73 (d, 2 H, J = 8.4 Hz), 7.61 (d, 2 H, J = 8.4 Hz), 7.27 (d, 1 H, 2.8 Hz), 6.84 (dd, 1 H, J = 9.2, 2.8 Hz), 6.71 (d, 1 H, J = 8.8 Hz), 5.74 (br s, 2 H), 4.37 (s, 2 H), 3.92 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.2 (app. t, J = 17.5 Hz), 143.0, 138.9, 138.5, 132.6, 127.7, 126.5 (quint., J = 4.6 Hz), 125.3, 120.4, 106.2, 48.1; HRMS (HESI) *m/z* calcd for $C_{13}H_{13}N_3O_2F_5S$ $[M+H]^+$ 370.0643, found 370.0645.



(4-Amino-3-nitro)phenyl-[(3-(pentafluorothio)phenyl)methyl]amine. A solution of 2-nitro-*p*-phenylenediamine (0.756 g, 4.69 mmol) and PTSA (0.054 g, 0.28 mmol) in toluene (25 mL) was treated with 3-(pentafluorothio)benzaldehyde (1.10 g, 4.56 mmol) via syringe and the resulting solution was heated to reflux with a Dean-Stark trap for 5 h. The mixture was filtered through a Buchner funnel packed with a thin pad of SiO_2 and the filtrate was stirred and allowed to cool to rt. The solvent was removed under reduced pressure to give the crude imine (1.571 g) as a bright orange-red solid that was suspended in a mixture of 1,4-dioxane (5.2 mL) and MeOH (1.3 mL), and $NaBH_4$ (0.126 g, 3.30 mmol) was added in 3 portions at 15 min intervals. The solution was allowed to stir at rt for 3 h, quenched with H_2O (25 mL), and extracted from brine with CH_2Cl_2 (3 x 200 mL). The solvent was removed under reduced pressure and the resulting residue dried under high vacuum at 60 ^oC for 12 h to give (4-amino-3-nitro)phenyl-[(3-(pentafluorothio)phenyl)methyl]amine (1.36 g, 3.69 mmol, 79%) as a dark red-purple powder: Mp 128-129 ^oC (CH_2Cl_2); IR (ATR) 3477.6, 3422.5, 3360.7, 3110.0, 1574.8, 1515.2, 1206.6; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.77 (s, 1 H), 7.68 (d, 1 H, J = 8.4 Hz), 7.53 (d, 1 H, 7.6 Hz), 7.47-7.43 (m, 1 H), 7.30 (d, 1 H, J = 2.8 Hz), 6.86 (dd, 1 H, J = 8.8, 2.8 Hz), 6.72 (d, 1 H, J = 8.8 Hz), 5.75 (br s, 2 H), 4.37 (s, 2 H), 3.89 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) 154.4 (quint., J = 18.0 Hz), 140.3, 139.0, 138.5, 132.6, 130.7, 129.3, 125.4, 125.3-125.1 (overlapping quint.), 120.4, 106.4, 48.6; HRMS (HESI) *m/z* calcd for $C_{13}H_{13}N_3O_2F_5S$ $[M+H]^+$ 370.0643, found 370.0641.

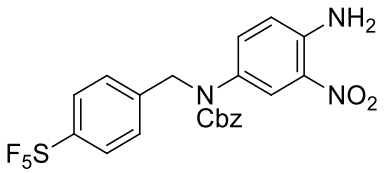


(4-Amino-3-nitro)phenyl{[4-(trifluoromethyl)phenyl]methyl}amine. A solution of 2-nitro-*p*-phenylenediamine (0.754 g, 4.68 mmol) and PTSA (0.054 g, 0.28 mmol) in toluene (25 mL) was treated via syringe with 4-(trifluoromethyl)benzaldehyde (0.640 mL, 4.69 mmol). The mixture was heated at reflux with a Dean-Stark trap for 5 h, filtered through a Buchner funnel packed with a thin pad of SiO_2, and the filtrate was stirred and allowed to cool to rt. The solvent was removed under reduced pressure to give the crude imine (1.23 g) as a bright orange-red solid that was suspended in a mixture of 1,4-dioxane (5.2 mL) and MeOH (1.3 mL), and $NaBH_4$ (0.120 g, 3.14 mmol) was added in 3 portions at 15 min intervals. The resulting solution was allowed to stir at rt for 3 h, quenched with H_2O (25 mL) and extracted from brine with CH_2Cl_2 (3 x 200 mL). The solvent was removed under reduced pressure and the residue dried under high vacuum at 60 ^oC to give (4-amino-3-nitro)phenyl{[4-(trifluoromethyl)phenyl]methyl}amine (1.141 g, 3.666 mmol, 78%) as a dark purple oil: IR (CH_2Cl_2) 3483.6, 3370.0, 1573.9, 1521.1, 1325.0 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.60 (d, 2 H, J = 8.0 Hz), 7.48 (d, 2 H, J = 8.0 Hz), 7.28 (d, 1 H, J = 2.8 Hz), 6.85 (dd, 1 H, J = 8.8, 2.8 Hz), 6.71 (d, 1 H, J = 8.8 Hz), 5.47 (br s, 2 H), 4.37 (s, 2 H), 3.92 (br s, 1 H); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 143.1, 139.1, 138.4, 132.6, 129.9 (q, J = 32.1 Hz), 127.8, 125.8 (q, J = 3.6 Hz), 125.3, 124.2 (q, J = 270.0 Hz), 120.3, 106.1, 48.5; HRMS (HESI) *m/z* calcd for $C_{14}H_{13}N_3O_2F_3$ $[M+H]^+$ 312.0954, found 312.0955.



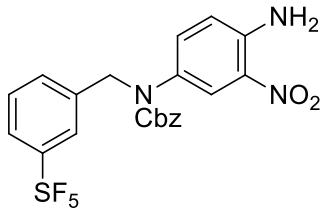
(4-Amino-3-nitro)phenyl{[3-(trifluoromethyl)phenyl]methyl}amine. A solution of 2-nitro-*p*-phenylenediamine (0.753 g, 4.67 mmol) and PTSA (0.050 g, 0.26 mmol) in toluene (25 mL) was treated via syringe with 3-(trifluoromethyl)benzaldehyde (0.620 mL, 4.64 mmol). The resulting

solution was heated to reflux with a Dean-Stark trap for 5 h, filtered through a Buchner funnel packed with a thin pad of SiO_2, and allowed to cool to rt. The solvent was removed under reduced pressure to give the crude imine (1.203 g) as bright orange solid, that was suspended in a mixture of 1,4-dioxane (3.7 mL) and MeOH (0.90 mL) and $NaBH_4$ (0.117 g, 0.655 mmol) was added in 3 portions at 15 minute intervals. The resulting solution was allowed to stir at rt for 3 h, quenched with H_2O (25 mL), and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and the solvent evaporated under reduced pressure to give crude product (1.141 g). Purification by chromatography on SiO_2 (70% CH_2Cl_2 in hexanes) gave (4-amino-3-nitro)phenyl{[3-(trifluoromethyl)phenyl]methyl}amine (1.10 g, 3.35 mmol, 72%) as a dark purple powder: Mp 95-96 ^oC (CH_2Cl_2); IR (ATR) 3456.00, 3396.7, 3330.7, 1515.1, 1323.5 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.64 (s, 1 H), 7.55 (m, 2 H), 7.47 (m, 1 H), 7.29 (d, 1 H, J = 2.8 Hz), 6.86 (dd, 1 H, J = 8.8, 2.8 Hz), 6.71 (d, 1 H, J = 8.8 Hz), 5.74 (br s, 2 H), 4.36 (s, 2 H), 3.89 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.0, 139.16, 138.5, 132.6, 131.2 (q, J = 32 Hz), 131.0, 129.3, 125.4, 124.5 (q, J = 3.7 Hz), 124.4 (q, J = 3.8 Hz), 124.2 (q, J = 271 Hz), 120.3, 106.2, 48.6; HRMS (ESI) *m/z* calcd for $C_{14}H_{13}N_2O_3F_3$ $[M+H]^+$ 312.0954, found 312.0947.

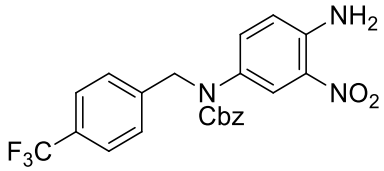


***N*-(4-Amino-3-nitro)phenyl-(phenylmethoxy)-*N*-{[4-(pentafluorothio)phenyl]methyl}carboxamide**. A solution of (4-amino-3-nitro)phenyl-[(4-(pentafluorothio)phenyl)methyl]amine (0.207 g, 0.544 mmol) and DIPEA (0.110 mL, 0.665 mmol) in 1,4-dioxane (2.8 mL) at rt was treated dropwise via syringe with benzyl chloroformate

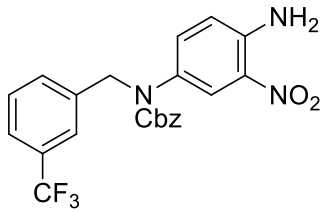
(0.100 mL, 0.682 mmol). The resulting solution was allowed to stir for 18 h and was then quenched with H_2O:CH_2Cl_2 (1:1, 6.5 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and the solvent evaporated to give crude *N*-(4-amino-3-nitro)phenyl-(phenylmethoxy)-*N*-{[4-(pentafluorothio)phenyl]methyl}carboxamide (0.280 g) as an orange foam that was used without further purification.



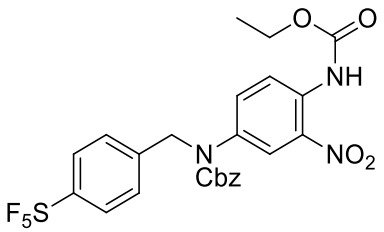
***N*-(4-Amino-3-nitro)phenyl(phenylmethoxy)-*N*-{[3-(pentafluorothio)phenyl]methyl}carboxamide**. A solution of (4-amino-3-nitro)phenyl-[(3-(pentafluorothio)phenyl)methyl]amine (0.202 g, 0.531 mmol) and DIPEA (0.090 mL, 0.54 mmol) in 1,4-dioxane (2.8 mL) at rt was treated dropwise via syringe with benzyl chloroformate (0.080 mL, 0.55 mmol). The reaction mixture was stirred for 3 h and then quenched with 6.50 mL of H_2O:CH_2Cl_2 (1:1). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and the solvent was evaporated to give crude *N*-(4-amino-3-nitrophenyl)(phenylmethoxy)-*N*-{[3-(pentafluorothio)phenyl]methyl}carboxamide (0.309 g) as an orange oil which was used without further purification.



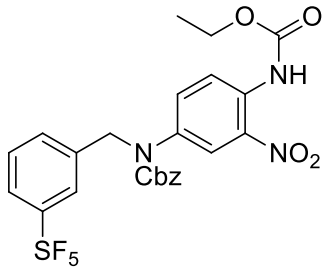
***N*-(4-Amino-3-nitro)phenyl(phenylmethoxy)-*N*-{[4-(trifluoromethyl)phenyl]methyl}carboxamide**. A solution of (4-amino-3-nitro)phenyl{[4-(trifluoromethyl)phenyl]methyl}amine (0.199 g, 0.639 mmol) and DIPEA (0.110 mL, 0.666 mmol) in 1,4-dioxane (3.2 mL) at rt was treated dropwise via syringe with benzyl chloroformate (0.100 mL, 0.682 mmol). The resulting solution was allowed to stir for 4 h and was then quenched with H_2O:CH_2Cl_2 (1:1, 6.5 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and the solvent was evaporated to give crude *N*-(4-amino-3-nitro)phenyl(phenylmethoxy)-*N*-{[4-(trifluoromethyl)phenyl]methyl}carboxamide (0.328 g) as a dark orange oil which was used without further purification.



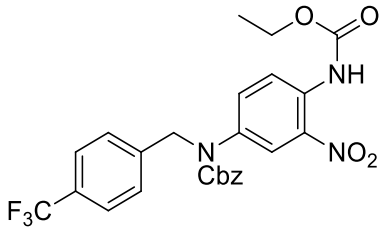
***N*-(4-Amino-3-nitro)phenyl(phenylmethoxy)-*N*-{[3-(trifluoromethyl)phenyl]methyl}carboxamide**. A solution of (4-amino-3-nitro)phenyl{[3-(trifluoromethyl)phenyl]methyl}amine (0.205 g, 0.659 mmol) and DIPEA (0.115 mL, 0.696 mmol) in 1,4-dioxane (3.5 mL) at rt was treated dropwise via syringe with benzyl chloroformate (0.100 mL, 0.682 mmol). The resulting solution was allowed to stir for 4 h at rt and was then quenched with H_2O:CH_2Cl_2 (1:1, 10 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic phases were washed with H_2O and brine, dried (Na_2SO_4), filtered, and the solvent was evaporated to give crude *N*-(4-amino-3-nitro)phenyl(phenylmethoxy)-*N*-{[3-(trifluoromethyl)phenyl]methyl}carboxamide (0.331 g) as an orange oil which was used without further purification.



Benzyl (4-((ethoxycarbonyl)amino)-3-nitrophenyl)[4-(pentafluorothio)benzyl]carbamate. A solution of crude *N*-(4-amino-3-nitro)phenyl-(phenylmethoxy)-*N*-{[4-(pentafluorothio)phenyl]methyl}carboxamide (0.050 g, 0.099 mmol) and DIPEA (0.050 mL, 0.30 mmol) in 1,4-dioxane (1.0 mL) at rt was treated dropwise via syringe with ethyl chloroformate (0.030 mL, 0.31 mmol). The resulting solution was allowed to stir at 70 ^{o}C for 24 h and was then quenched with H_2O:CH_2Cl_2 (1:1, 5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with H_2O and brine, dried ($MgSO_4$), filtered, and the solvent was evaporated under reduced pressure to give crude product (0.050 g) as an orange oil. The oil was purified by chromatography on SiO_2 (30% EtOAc in hexanes) to give benzyl (4-((ethoxycarbonyl)amino)-3-nitrophenyl)[4-(pentafluorothio)benzyl]carbamate (0.036 g, 0.063 mmol, 63%, 82% based on recovered starting material) as an orange oil: IR (CH_2Cl_2) 3365.8, 2094.7, 1738.1, 1706.7, 1515.2 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.77 (s, 1 H), 8.54 (d, 1 H, *J* = 9.2 Hz), 8.04 (br s, 1 H), 7.68 (d, 2 H, *J* = 8.8 Hz), 7.33-7.27 (m, 5 H), 7.24-7.22 (m, 2 H), 5.19 (s, 2 H), 4.92 (s, 2 H), 4.26 (q, 2 H, *J* = 7.2 Hz), 1.34 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.2, 153.4 (quint., *J* = 18.0 Hz),153.2, 153.2, 141.0, 135.8, 135.7, 134.2, 128.8, 128.8, 128.2, 127.9, 126.6 (app. t, *J* = 4.6 Hz), 123.6, 121.4, 68.5, 62.3, 53.4, 14.5; HRMS (HESI) *m/z* calcd for $C_{24}H_{23}N_3O_6F_5S$ $[M+H]^+$ 576.1222, found 576.1221.

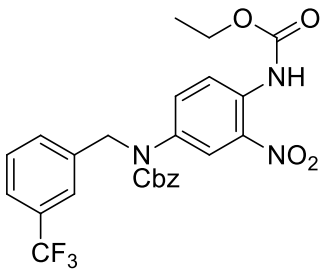


Benzyl (4-((ethoxycarbonyl)amino)-3-nitrophenyl)[3-(pentafluorothio)benzyl]carbamate. A solution of crude *N*-(4-amino-3-nitrophenyl)(phenylmethoxy)-*N*-{[3-(pentafluorothio)phenyl]methyl}carboxamide (0.326 g), DIPEA (0.280 mL, 1.69 mmol), and DMAP (0.003 g, 0.02 mmol) in 1,4-dioxane (4 mL) at rt was treated dropwise via syringe with ethyl chloroformate (0.155 mL, 1.58 mmol). The resulting solution was allowed to stir at 70 ^{o}C for 2 d and was then quenched by the addition of H_2O:CH_2Cl_2 (1:1, 10 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with H_2O, 1 M aq. HCl, and brine, dried ($MgSO_4$), filtered, and the solvent was evaporated under reduced pressure to give crude product (0.340 g) as an orange oil. The crude residue was purified by chromatography on SiO_2 (20% EtOAc in hexanes) to give benzyl (4-((ethoxycarbonyl)amino)-3-nitrophenyl)[3-(pentafluorothio)benzyl]carbamate (0.052 g) as a yellow oil which was used without further purification.



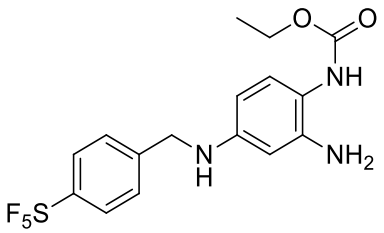
Benzyl (4-((ethoxycarbonyl)amino)-3-nitrophenyl)[4-(trifluoromethyl)benzyl]carbamate. A solution of crude *N*-(4-amino-3-nitro)phenyl(phenylmethoxy)-*N*-{[4-(trifluoromethyl)phenyl]methyl}carboxamide (0.310 g) and DIPEA (0.670 mL, 4.05 mmol) in

1,4-dioxane (5.2 mL) at rt was treated dropwise via syringe with ethyl chloroformate (0.395 mL, 4.03 mmol). The resulting solution was allowed to stir at 70 ^{o}C for 3 d and was then quenched by the addition of H_2O:CH_2Cl_2 (1:1, 10 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4), filtered, and the solvent was evaporated under reduced pressure to give crude product **(**0.350 g) as an orange solid. The crude solid was purified by chromatography on SiO_2 (20% EtOAc in hexanes) to give benzyl (4-((ethoxycarbonyl)amino)-3-nitrophenyl)[4-(trifluoromethyl)benzyl]carbamate (0.194 g, 0.375 mmol, 59% over 2 steps) as an orange oil: IR (CH_2Cl_2) 3365.8, 2983.2, 1738.2, 1706.4, 1514.4, 1323.3 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz, 353 K) δ 9.50 (br s, 1 H), 7.96 (d, 1 H, *J* = 2.4 Hz), 7.77 (d, 1 H, *J* = 8.8 Hz), 7.64 (d, 1 H, *J* = 8.4 Hz), 7.60 (dd, 1 H, *J* = 8.8, 2.4 Hz), 7.48 (d, 1 H, *J* = 8.0 Hz), 7.33-7.26 (m, 7 H), 5.19 (s, 2 H), 5.05 (s, 2 H), 4.15 (q, 2 H, *J* = 7.2 Hz), 1.24 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz, 353 K) δ 154.2, 152.9, 141.8, 140.0, 136.8, 135.8, 131.8, 130.3, 128.0, 127.9, 127.7, 127.5, 127.1, 124.9 (q, *J* = 3.7 Hz), 123.8 (q, *J* = 270.3 Hz), 123.8, 122.5, 67.0, 60.8, 52.3, 13.8; HRMS (HESI) *m/z* calcd for $C_{25}H_{21}N_3O_6F_3$ (M-H) 516.1377, found 516.1372.



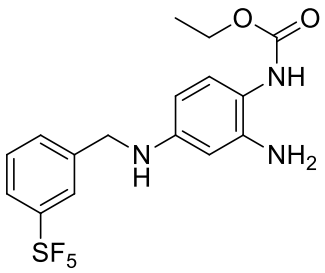
Benzyl (4-((ethoxycarbonyl)amino)-3-nitrophenyl)[3-(trifluoromethyl)benzyl]carbamate. A solution of crude *N*-(4-amino-3-nitro)phenyl(phenylmethoxy)-*N*-{[3-(trifluoromethyl)phenyl]methyl}carboxamide (0.330 g) and DIPEA (0.545 mL, 3.30 mmol) in 1,4-dioxane (5 mL) at rt was treated dropwise via syringe with ethyl chloroformate (0.160 mL,

1.63 mmol). The resulting solution was allowed to stir at 70 ^{o}C for 2 d and was then quenched by the addition of 1:1 H_2O:CH_2Cl_2 (10 mL), the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with H_2O (2 x 20 mL) and brine (2 x 10 mL), dried ($MgSO_4$), filtered, and the solvent was evaporated under reduced pressure to give crude product (0.310 g) as an orange oil. The crude oil was purified by chromatography on SiO_2 (20% EtOAc in hexanes) to give benzyl (4-((ethoxycarbonyl)amino)-3-nitrophenyl)[3-(trifluoromethyl)benzyl]carbamate (0.113 g) as a yellow oil which was carried on without further purification.

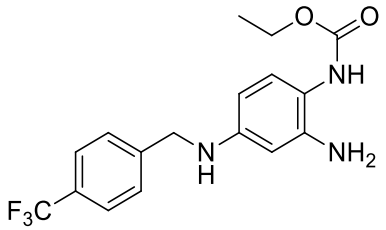


***N*-[2-Amino-4-({[4-(pentafluorothio)phenyl]methyl}amino)phenyl]ethoxycarboxamide (NR561_29)**. A solution of benzyl (4-((ethoxycarbonyl)amino)-3-nitrophenyl)[4-(pentafluorothio)benzyl]carbamate (0.047 g, 0.082 mmol) and 10% Pd/C (0.010 g, 0.009 mmol, 10 mol%) in a mixture of 1,4-dioxane (0.46 mL) and EtOH (0.24 mL) was allowed to stir for 21 h at rt under an H_2 atmosphere (balloon). The reaction mixture was diluted with Et_2O (5 mL) and filtered through a pad of Celite. The organic phase was concentrated under reduced pressure to give crude product (0.037 g) as an orange oil. The crude oil was purified by chromatography on SiO_2 (50% EtOAc in hexanes) to give NR561_29 (0.018 g, 0.044 mmol, 54%) as a light brown solid: Mp 146-147 ^{o}C (CH_2Cl_2); IR (ATR) 3377.6, 2925.7, 1697.8, 1620.9, 1525.7 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (d, 2 H, *J* = 8.4 Hz), 7.43 (d, 2 H, *J* = 8.4 Hz), 6.92 (d, 1 H, *J* = 8.4 Hz), 6.02 (dd, 1 H, *J* = 8.4, 2.4 Hz), 5.95 (d, 1 H, *J* = 2.4 Hz), 4.35 (s, 2 H), 4.18 (q, 2 H, *J* =

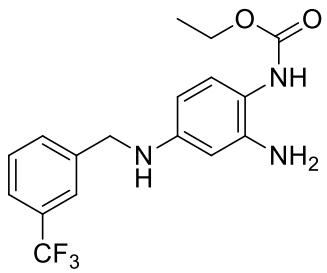
7.2 Hz), 3.90 (br s, 2 H), 1.28 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.6, 152.9 (quint., *J* = 13.5 Hz), 147.4, 143.9, 142.2, 128.1, 127.3, 126.4 (quint., *J* = 4.0 Hz), 114.5, 104.5, 100.8, 61.5, 47.6, 14.7; HRMS (HESI) *m/z* calcd for $C_{16}H_{19}N_3O_2F_5S$ 412.1113, found 412.1111.



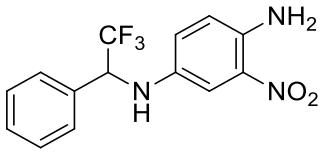
***N*-[2-Amino-4-({[3-(pentafluorothio)phenyl]methyl}amino)phenyl]ethoxycarboxamide (NR561_45)**. A mixture of benzyl (4-((ethoxycarbonyl)amino)-3-nitrophenyl)[3-(pentafluorothio)benzyl]carbamate (0.050 g, 0.087 mmol) and 10% Pd/C (0.010 g, 0.010 mmol) in 1,4-dioxane (0.46 mL) and EtOH (0.24 mL) was allowed to stir under an H_2 atmosphere (balloon) for 18 h. The reaction mixture was diluted with Et_2O (5 mL) and filtered through a pad of Celite. The solvent was removed under reduced pressure to give crude product (0.049 g) as an orange oil. The crude residue was purified by chromatography on SiO_2 (50% EtOAc in hexanes) to give NR561_45 (0.027 g, 0.066 mmol, 76%) as a light brown oil that solidified on standing: Mp 52-53 ^{o}C (CH_2Cl_2); IR (ATR) 3355.4, 2931.1, 1699.4, 1623.1, 1525.2, 1229.4 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73 (s, 1 H), 7.65 (d, 1 H, *J* = 8.0 Hz), 7.50 (d, 1 H, *J* = 7.6 Hz), 7.42 (app. t, 1 H, *J* = 7.8 Hz), 6.92 (d, 1 H, *J* = 8.4 Hz), 6.04 (dd, 1 H, *J* = 8.0, 2.0 Hz), 5.98 (d, 1 H, *J* = 2.0 Hz), 4.34 (s, 2 H), 4.18 (q, 2 H, *J* = 7.1 Hz), 3.85 (br s, 2 H), 1.28 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 175 MHz) δ 155.6, 154.4 (quint., *J* = 16.8 Hz), 147.4, 143.1, 141.1, 130.4, 129.1, 128.0, 124.9 (quint., *J* = 4.2 Hz), 124.8 (quint., *J* = 4.4 Hz), 114.5, 104.5, 100.9, 61.5, 48.1, 14.7; HRMS (HESI) *m/z* calcd for $C_{16}H_{19}N_3O_2F_5S$ $[M+H]^+$ 412.1113, found 412.1101.



***N*-[2-Amino-4-({[4-(trifluoromethyl)phenyl]methyl}amino)phenyl]ethoxycarboxamide (NR561_40)**. A mixture of benzyl (4-((ethoxycarbonyl)amino)-3-nitrophenyl)[4-(trifluoromethyl)benzyl]carbamate (0.090 g, 0.174 mmol) and 10% Pd/C (0.018 g, 0.017 mmol) in a mixture of 1,4-dioxane (1 mL) and EtOH (0.50 mL) was allowed to stir at rt for 18 h under an H_2 atmosphere (balloon). The reaction mixture was diluted with Et_2O (5 mL) and filtered through a pad of Celite. The organic phase was concentrated under reduced pressure to give crude product (0.051 g) as a light brown solid. The crude solid was purified by chromatography on SiO_2 (50% EtOAc in hexanes) to give NR561_40 (0.044 g, 0.12 mmol, 72%) as a grey solid: Mp 171-172 ^{o}C (CH_2Cl_2); IR (ATR) 3279.6, 2980.6, 1677.2, 1527.0 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.59 (d, 2 H, *J* = 8.4 Hz), 7.46 (d, 2 H, *J* = 8.0 Hz), 6.92 (d, 1 H, *J* = 8.4 Hz), 6.05 (dd, 1 H, *J* = 8.4, 2.4 Hz), 5.98 (d, 1 H, *J* = 2.4 Hz), 4.37 (s, 2 H), 4.19 (q, 2 H, *J* = 7.2 Hz), 4.06 (br s, 1 H), 3.74 (br s, 2 H), 1.28 (t, 3 H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz δ 155.7, 147.6, 143.9, 143.2, 129.6 (q, *J* = 32.0 Hz), 128.1, 127.5, 125.7 (q, *J* = 3.7 Hz), 124.3 (q, *J* = 270.2 Hz), 114.3, 104.5, 100.6, 61.5, 48.0, 14.8; HRMS (HESI) *m/z* calcd for $C_{17}H_{19}N_3O_2F_3$ $[M+H]^+$ 354.1424, found 354.1425.

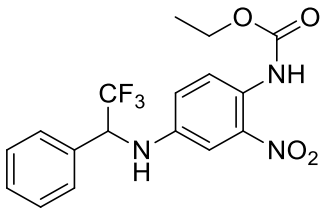


***N*-[2-Amino-4-({[3-(trifluoromethyl)phenyl]methyl}amino)phenyl]ethoxycarboxamide (NR561_50)**. A mixture of crude benzyl (4-((ethoxycarbonyl)amino)-3-nitrophenyl)[3-(trifluoromethyl)benzyl]carbamate (0.100 g, 0.193 mmol) and 10% Pd/C (0.020 g, 0.018 mmol, 10 mol%) in 1,4-dioxane (1 mL) and EtOH (0.50 mL) was allowed to stir at rt for 18 h under an H_2 atmosphere (balloon). The reaction mixture was diluted with Et_2O, filtered through a pad of Celite, and the solvent removed under reduced pressure to give crude product (0.067 g) as a dark brown oil, which was purified by chromatography on SiO_2 (50% EtOAc in hexanes) to give NR561_50 (0.056 g, 0.16 mmol, 24% over 3 steps) as an off-white solid: Mp 103-104 ^oC (CH_2Cl_2); IR (ATR) 3335.1, 2987.6, 1723.5, 1679.8, 1535.3 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.61 (s, 1 H), 7.53 (app. t, 2 H, *J* = 7.0 Hz), 7.46-7.42 (m, 1 H), 6.92 (d, 1 H, *J* = 8.0 Hz), 6.05 (dd, 1 H, *J* = 8.4, 2.4 Hz), 5.98 (d, 1 H, *J* = 2.4 Hz), 4.34 (s, 2 H), 4.19 (q, 2 H, *J* = 7.2 Hz), 3.76 (br s, 2 H), 1.28 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.6, 147.6, 143.2, 140.8, 131.1 (q, *J* = 32.0 Hz), 130.7, 129.2, 128.0, 124.3 (q, *J* = 270.9 Hz), 124.2-124.1 (overlapping q.), 114.3, 104.5, 100.8, 61.5, 48.1, 14.7; HRMS (HESI) *m/z* calcd for $C_{17}H_{19}N_3O_2F_3$ $[M+H]^+$ 354.1424, found 354.1421.



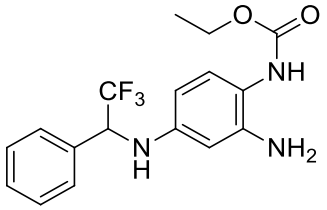
(4-Amino-3-nitrophenyl)(2,2,2-trifluoro-1-phenylethyl)amine. A solution of 2-nitro-*p*-phenylenediamine (0.504 g, 3.13 mmol) and PTSA (0.034 g, 0.17 mmol) in toluene (15 mL) at rt was treated with 2,2,2-trifluoroacetophenone (0.544 g, 3.09 mmol). The reaction mixture was stirred at reflux for 24 h with a Dean-Stark trap, and filtered through a pad of SiO_2. The solvent was evaporated under reduced pressure to give the crude imine (0.170 g), which was suspended

in 1,4-dioxane (4 mL) and MeOH (1 mL), and $NaBH_4$ (0.125 g, 3.27 mmol) was added in 3 portions at 15-min intervals. The resulting solution was allowed to stir at rt for 3 h, quenched with H_2O (25 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The organic phase was dried (Na_2SO_4), filtered, and the solvent was evaporated under reduced pressure. Further drying under high vacuum gave (4-amino-3-nitrophenyl)(2,2,2-trifluoro-1-phenylethyl)amine (0.120 g, 0.386 mmol, 12%) as a dark red solid: Mp 126-127 ^oC (CH_2Cl_2); IR (ATR) 3436.0, 3388.0, 333.4, 1581.3, 1514.4, 1326.1, 1237.6; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.44-7.38 (m, 5 H), 7.33 (d, 1 H, J = 2.8 Hz), 6.89 (dd, 1 H, J = 9.2, 2.8 Hz), 6.69 (d, 1 H, J = 8.8 Hz), 5.75 (br s, 2 H), 4.84 (m, 1 H), 4.13 (d, 1 H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.2, 136.6, 133.6, 132.3, 129.51, 129.2, 128.0, 126.0, 125.1 (q, J = 280.3 Hz), 120.3, 108.6, 61.4 (q, J = 30.0 Hz); HRMS (HESI) *m/z* calcd for $C_{14}H_{13}N_3O_2F_3$ $[M+H]^+$ 312.0954, found 312.0953.



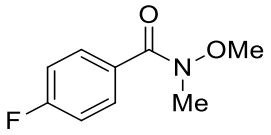
Ethyl (2-nitro-4-((2,2,2-trifluoro-1-phenylethyl)amino)phenyl)carbamate. A solution of (4-amino-3-nitrophenyl)(2,2,2-trifluoro-1-phenylethyl)amine (0.060 g, 0.19 mmol) and DIPEA (0.065 mL, 0.39 mmol) in 1,4-dioxane (1.3 mL) at rt was treated dropwise via syringe with ethyl chloroformate (0.020 mL, 0.20 mmol). The resulting solution was allowed to stir at 50 ^oC for 18 h and was then quenched by the addition of 1:1 H_2O:CH_2Cl_2 (10 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were washed with H_2O (2 x 10 mL) and brine (2 x 10 mL), dried (Na_2SO_4), filtered, and the solvent was evaporated under reduced pressure to give crude product (0.100 g) as an orange-red oil that was purified by chromatography on SiO_2 (40-60% CH_2Cl_2 in hexanes) to give ethyl (2-

nitro-4-((2,2,2-trifluoro-1-phenylethyl)amino)phenyl)carbamate (0.054 g, 0.14 mmol, 73%) as a red oil: IR (CH_2Cl_2) 3373.0, 2983.9, 1719.0, 1523.1, 1324.1 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 9.39 (s, 1 H), 8.30 (d, 1 H, *J* = 9.0 Hz), 7.46-7.40 (m, 6 H), 6.98 (dd, 1 H, *J* = 9.5, 2.2 Hz), 4.91 (m, 1 H), 4.56 (br d, 1 H, *J* = 7.0 Hz), 4.22 (q, 2 H, *J* = 7.0 Hz), 1.31 (t, 3 H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.6, 140.7, 137.0, 133.1, 129.6, 129.3, 128.0, 127.7, 124.9 (q, *J* = 280.5 Hz), 122.7, 122.6, 121.5, 108.8, 61.9, 60.6 (q, *J* = 30.4 Hz), 14.5; HRMS (HESI) *m/z* calcd for $C_{17}H_{17}N_3O_4F_3$ $[M+H]^+$ 384.1166, found 384.1163.

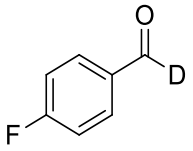


***N*-{2-Amino-4-[(2,2,2-trifluoro-1-phenylethyl)amino]phenyl}ethoxycarboxamide**.

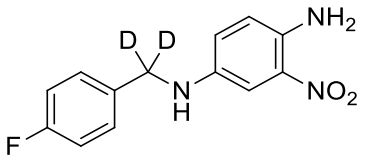
(**NR579_04**) A suspension of ethyl (2-nitro-4-((2,2,2-trifluoro-1-phenylethyl)amino)phenyl)carbamate (0.050 g, 0.13 mmol) and 10% Pd/C (0.014 g, 0.013 mmol) was allowed to stir under an H_2 atmosphere (balloon) for 18 h. The reaction mixture was diluted with Et_2O, filtered through Celite, and the solvent evaporated under reduced pressure to give crude product (0.066 g) as a gray oil that was purified by chromatography on SiO_2 (0-10% EtOAc in CH_2Cl_2) to give NR579_04 (0.041 g, 0.12 mmol, 89%) as a clear, colorless oil that solidified upon standing: Mp 51-52 ^oC (CH_2Cl_2); IR (ATR) 3346.1, 2984.8, 1696.0, 1524.2 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.42-7.37 (m, 5 H), 6.90 (d, 1 H, *J* = 8.0 Hz), 6.05 (app. d, 1 H, *J* = 8.4 Hz), 6.01 (app. s, 1 H), 4.84 (m, 1 H), 4.28 (d, 1 H, *J* = 7.2 Hz), 4.17 (q, 2 H, *J* = 7.1 Hz), 3.72 (br s, 2 H), 1.27 (t, 3 H, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.5, 145.3, 143.0, 134.2, 129.2, 129.0, 128.0, 125.1 (q, *J* = 280.2 Hz), 115.5, 105.2, 102.1, 61.5, 60.7 (q, *J* = 29.8 Hz), 14.7; HRMS (HESI) *m/z* calcd for $C_{17}H_{19}N_3O_2F_3$ $[M+H]^+$ 354.1424, found 354.1422.



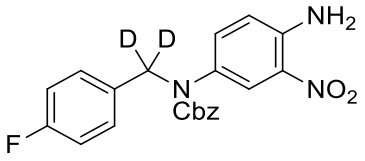
4-Fluoro-*N*-methoxy-*N*-methylbenzamide. A solution of methoxymethylamine hydrochloride (0.634 g, 6.37 mmol) and Et_3N (0.860 mL, 6.12 mmol) in CH_2Cl_2 (3.75 mL) at 0 ^oC was treated dropwise via syringe with 4-fluorobenzoyl chloride (0.370 mL, 3.07 mmol) over 30 min. The reaction mixture was allowed to stir at rt for 2 h, poured into H_2O and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and the solvent was removed under reduced pressure. Further drying under high vacuum gave crude 4-fluoro-*N*-methoxy-*N*-methylbenzamide (0.672 g, 2.63 mmol, quant.) which was used without further purification: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.74 (m, 2 H), 7.08 (m, 2 H), 3.53 (s, 3 H), 3.36 (s, 3 H); HRMS (HESI) *m/z* calcd for $C_9H_{11}NO_2F$ $[M+H]^+$ 184.0768, found 184.0768.



4-Fluoro[*formyl*-^{2}H]benzaldehyde. To a solution of 4-fluoro-*N*-methoxy-*N*-methylbenzamide (0.062 g, 0.338 mmol) in THF (1.9 mL) at -78 ^oC was added $LiAlD_4$ (0.018 g, 0.42 mmol) portionwise. The reaction mixture was stirred for 2 h at -78 ^oC, quenched with H_2O at the same temperature, treated with Et_2O, and the precipitate was removed by filtration through a pad of Celite. The filtrate was washed with H_2O and brine, dried (Na_2SO_4), and concentrated under reduced pressure. Further drying under high vacuum for 1 h gave crude 4-fluoro[*formyl*-^{2}H]benzaldehyde (0.032 g, 0.26 mmol) as a pale yellow oil that was used without further purification.

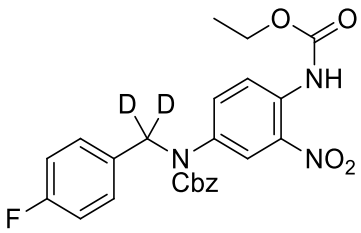


(4-Amino-3-nitrophenyl)[$^2H_2$(4-fluorophenyl)methyl]amine. A solution of 2-nitro-*p*-phenylenediamine (0.602 g, 3.73 mmol), PTSA (0.040 g, 0.21 mmol) and crude 4-fluoro[*formyl*-^{2}H]benzaldehyde (0.273 g) was heated to reflux with a Dean-Stark trap for 18 h. The solution was filtered through a thin pad of SiO_2 and the solvent was evaporated under reduced pressure to give a crude imine (0.328 g) which was suspended in 1,4-dioxane (4 mL) and MeOH (1 mL). After addition of $NaBD_4$ (0.111 g, 2.60 mmol) in 3 portions at 15-min intervals, the reaction mixture was stirred at rt for 3 h, quenched with H_2O (25 mL), and filtered to give (4-amino-3-nitrophenyl)[$^2H_2$(4-fluorophenyl)methyl]amine (0.241 g, 0.915 mmol, 42% over 2 steps) as a dark purple powder: Mp 113-114 ^oC (H_2O); IR (ATR) 3517.2, 3497.0, 3371.2, 1577.4, 1502.5, 1329.5 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.34-7.27 (m, 3 H), 7.28 (d, 1 H, J = 2.4 Hz), 7.03 (t, 2 H, J = 8.6 Hz), 6.84 (dd, 1 H, J = 8.8, 2.4 Hz), 5.75 (br s, 2 H), 3.80 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.3 (d, J = 244.0 Hz), 139.4, 138.3, 134.5 (d, J = 3.0 Hz), 132.5, 129.3 (d, J = 8.0 Hz), 125.5, 120.2, 115.7 (d, J = 21.3 Hz), 105.9, 47.7 (t, J = 20.6 Hz); HRMS (HESI) *m/z* calcd for $C_{13}H_{11}D_2N_3O_2F$ $[M+H]^+$ 264.1112, found 264.1110.



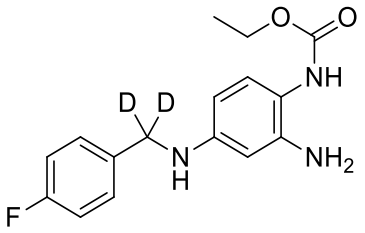
***N*-(4-Amino-3-nitrophenyl)-*N*-[$^2H_2$(4-fluorophenyl)methyl](phenylmethoxy)carboxamide**. A solution of (4-amino-3-nitrophenyl)[$^2H_2$(4-fluorophenyl)methyl]amine (0.100 g, 0.380 mmol)

and DIPEA (0.095 mL, 0.58 mmol) in 1,4-dioxane (1.9 mL) at rt was treated dropwise via syringe with benzyl chloroformate (0.060 mL, 0.41 mmol). The resulting solution was allowed to stir at rt for 18 h and was then quenched by the addition of H_2O/CH_2Cl_2 (1:1, 10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with H_2O (2 x 10 mL) and brine (2 x 10 mL), dried (Na_2SO_4), filtered, and the solvent was evaporated under reduced pressure to give crude *N*-(4-amino-3-nitrophenyl)-*N*-[$^2H_2$(4-fluorophenyl)methyl](phenylmethoxy)carboxamide (0.220 g) as an orange-yellow oil that was used without further purification.



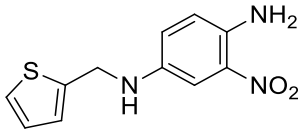
Benzyl (4-((ethoxycarbonyl)amino)-3-nitrophenyl)[$^2H_2$(4-fluorobenzyl)]carbamate. A solution of crude *N*-(4-amino-3-nitrophenyl)-*N*-[$^2H_2$(4-fluorophenyl)methyl](phenylmethoxy)carboxamide (0.220 g) and DIPEA (0.190 mL, 1.15 mmol) in 1,4-dioxane (3.5 mL) at rt was treated dropwise via syringe with ethyl chloroformate (0.090 mL, 0.92 mmol). The reaction mixture was stirred at 70 ^oC for 2 d and quenched by addition of H_2O/CH_2Cl_2 (1:1, 20 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic phases were washed with 1 M aq. HCl (2 x 10 mL) and brine (2 x 10 mL), dried ($MgSO_4$), filtered, and the filtrate was concentrated under reduced pressure. Further drying under high vacuum gave crude product (0.320 g) as an orange-yellow solid that was purified by chromatography on SiO_2 (20% EtOAc in hexanes) to give benzyl (4-((ethoxycarbonyl)amino)-3-nitrophenyl)[$^2H_2$(4-

fluorobenzyl)]carbamate (0.100 g, 0.213 mmol, 56%) as a yellow oil: IR (CH_2Cl_2) 3364.5, 2981.5, 1738.4, 1702.4, 1509.8, 1331.4; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.77 (s, 1 H), 8.51 (d, 1 H, *J* = 8.8 Hz), 7.99 (br s, 1 H), 7.36-7.30 (m, 4 H), 7.27-7.25 (m, 2 H), 7.17-7.13 (m, 2 H), 6.96 (tt, 2 H, *J* = 8.6, 2.3 Hz), 5.19 (s, 2 H), 4.26 (q, 2 H, *J* = 7.0 Hz), 1.34 (t, 3 H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.4 (d, *J* = 245.0 Hz), 155.2, 153.1, 136.0, 135.7, 134.7, 134.0, 132.6 (d, *J* = 3.2 Hz), 129.7, 128.7, 128.4, 128.1, 123.9, 121.1, 115.7 (d, *J* = 21.3 Hz), 68.1, 62.2, 52.8 (br), 14.5; HRMS (HESI) *m/z* calcd for $C_{24}H_{19}D_2N_3O_6F$ [M-H] 468.1534, found 468.1545.

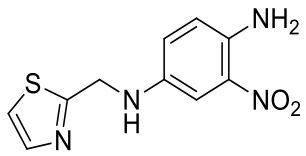


***N*-[2-Amino-4-({[^{2}H$_2$(4-fluorophenyl)]methyl}amino)phenyl]ethoxycarboxamide (NR561_87)**. A suspension of benzyl (4-((ethoxycarbonyl)amino)-3-nitrophenyl)[^{2}H$_2$(4-fluorobenzyl)]carbamate (0.095 g, 0.196 mmol) and 10% Pd/C (0.022 g, 0.020 mmol) in 1,4-dioxane (1.1 mL) and EtOH (0.60 mL) was allowed to stir at rt under an H_2 atmosphere (balloon) for 18 h. The solution was diluted with Et_2O (5 mL), filtered through a pad of Celite, and the solvent was evaporated under reduced pressure to give crude product (0.078 g) as a light brown oil that was purified by chromatography on SiO_2 (55% EtOAc in hexanes) to give NR561_87 (0.045 g, 0.147 mmol, 75%) as a light brown solid: Mp 142-143 ^{o}C (CH_2Cl_2); IR (ATR) 3394.7, 3342.6, 2987.4, 1675.6, 1506.2 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32-7.28 (m, 2 H), 7.01 (app. t, 2 H, *J* = 8.6 Hz), 6.91 (d, 1 H, *J* = 8.4 Hz), 6.04 (dd, 1 H, *J* = 8.4, 2.4 Hz), 5.98 (d, 1 H, *J* = 2.4 Hz), 4.18 (q, 2 H, *J* = 7.0 Hz), 3.78 (br s, 2 H), 1.28 (t, 3 H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.1 (d, *J* = 243.0 Hz), 155.7, 147.8, 143.1, 135.1 (d, *J* = 3.0 Hz), 129.0 (d, *J* = 8.0

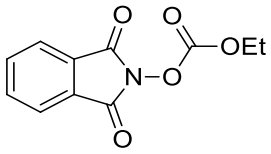
Hz), 128.0, 115.5 (d, J = 21.2 Hz), 114.1, 104.4, 100.8, 61.5, 47.1 (t, J = 20.6 Hz), 14.7; HRMS (HESI) *m/z* calcd for $C_{16}H_{17}D_2N_3O_2F$ $[M+H]^+$ 306.1581, found 306.1584.



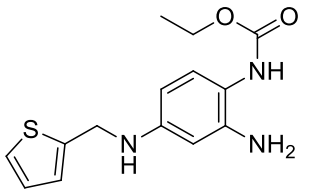
(4-Amino-3-nitrophenyl)(2-thienylmethyl)amine (1-37). A mixture of thiophene-2-carboxaldehyde (0.125 mL, 1.34 mmol), 2-nitro-*p*-phenylenediamine (0.210 g, 1.30 mmol), PTSA (0.035 g, 0.18 mmol), and 4 Å mol. sieves (1.063 g) in CH_2Cl_2 (3.1 mL) and MeOH (3.1 mL) was allowed to stir at rt for 5 h. The reaction mixture was filtered through Celite and the solvent removed under reduced pressure to give a dark brown solid that was dissolved in CH_2Cl_2 (20 mL), filtered through a thin pad of SiO_2 (CH_2Cl_2), and concentrated under reduced pressure to give crude imine (0.250 g) as a bright orange solid. The solid was suspended in 1,4-dioxane (1.5 mL) and MeOH (0.50 mL) and treated with $NaBH_4$ (0.070 g, 1.83 mmol) in 3 portions at 15 min intervals. The solution was allowed to stir at rt for 20 h and quenched by the addition of H_2O/CH_2Cl_2 (1:1, 30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with H_2O (2 x 10 mL) and brine (2 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Further drying of the residue under high vacuum at 50 ^oC gave (4-amino-3-nitrophenyl)(2-thienylmethyl)amine (0.230 g, 0.923 mmol, 71%) as a dark red solid: Mp 103-105 ^oC (CH_2Cl_2); IR (ATR) 3506.5, 3380.5, 3116.0, 1576.6, 1518.9, 1332.9 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.37 (d, 1 H, J = 2.8 Hz), 7.23 (dd, 1 H, J = 4.8, 1.2 Hz), 7.03-7.02 (m, 1 H), 6.97 (dd, 1 H, J = 5.2, 3.6 Hz), 6.88 (dd, 1 H, J = 8.8, 2.8 Hz), 6.71 (d, 1 H, J = 8.8 Hz), 5.74 (br s, 2 H), 4.48 (s, 2 H), 3.83 (br s, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.2, 139.0, 138.5, 132.6, 127.1, 125.6, 125.6, 125.0, 120.2, 106.6, 44.2; HRMS (HESI) *m/z* calcd for $C_{11}H_{12}N_3O_2S$ $[M+H]^+$ 250.0645, found 250.0644.



(4-Amino-3-nitrophenyl)(1,3-thiazol-2-ylmethyl)amine. A suspension of 2-thiazolecarboxaldehyde (0.115 mL, 1.27 mmol), 2-nitro-*p*-phenylenediamine (0.209 g, 1.30 mmol), PTSA (0.025 g, 0.13 mmol) and 4 Å molecular sieves (1.15 g) in CH_2Cl_2 (3.1 mL) and MeOH (3.1 mL) was stirred for 18 h at rt and filtered through Celite. The solvent was removed under reduced pressure to give a dark brown residue that was suspended in CH_2Cl_2 (20 mL), filtered through a thin pad of SiO_2 (CH_2Cl_2), concentrated under reduced pressure to give crude imine (0.205 g) as a bright orange solid. The solid was suspended in 1,4-dioxane (2 mL) and MeOH (0.75 mL) and $NaBH_4$ (0.035 g, 0.92 mmol) were added. The reaction mixture was stirred at rt for 8 h and quenched by the addition of H_2O/CH_2Cl_2 (1:1, 15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with H_2O (2 x 10 mL) and brine (2 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Further drying under high vacuum at 50 ^oC overnight gave (4-amino-3-nitrophenyl)(1,3-thiazol-2-ylmethyl)amine (0.194 g, 0.775 mmol, 61%) as a dark red solid: Mp 161-162 ^oC (CH_2Cl_2); IR (ATR) 3469.8, 3380.2, 3349.8, 1584.1, 1518.8, 1384.3, 1330.6 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 7.74 (d, 1 H, *J* = 3.0 Hz), 7.58 (d, 1 H, *J* = 3.0 Hz), 7.04 (br s, 2 H), 7.02 (d, 1 H, *J* = 3.0 Hz), 6.99 (d, 1 H, *J* = 2.5 Hz), 6.90 (d, 1 H, *J* = 9.0 Hz), 6.39 (t, 1 H, *J* = 6.0 Hz), 4.54 (d, 2 H, *J* = 6.0 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 171.8, 142.4, 140.1, 138.2, 129.9, 126.5, 120.4, 119.9, 103.0, 45.6; HRMS (HESI) *m/z* calcd for $C_{10}H_{11}N_4O_2S$ $[M+H]^+$ 251.0597, found 251.0595.

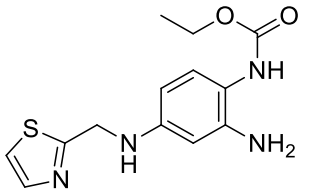


Ethyl (1,3-dioxobenzo[*c*]azolidin-2-yloxy)formate. A suspension of diphthalimidyl carbonate (0.382 g, 1.08 mmol) and EtOH (0.065 mL, 1.1 mmol) in THF (2.5 mL) was treated with Et_3N (0.150 mL, 1.07 mmol). Upon addition of base, the suspension turned yellow, progressing to orange over 30 min. The reaction mixture was stirred for 5 h and the solvent was evaporated. The residue was dissolved in EtOAc (25 mL) and washed with sat. aq. $NaHCO_3$ (5 x 10 mL) until the organic layer became clear. The combined aqueous washings were extracted with EtOAc (2 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent was evaporated under reduced pressure. Further drying under high vacuum gave ethyl (1,3-dioxobenzo[*c*]azolidin-2-yloxy)formate (0.230 g, 0.978 mmol, 90%) as a light yellow solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.90-7.84 (m, 2 H), 7.81-7.76 (m, 2 H), 4.40 (q, 2 H, *J* = 7.2 Hz), 1.40 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.6, 152.4, 135.0, 128.8, 124.1, 67.7, 14.1.



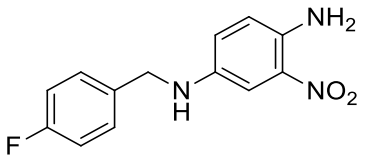
***N*-{2-Amino-4-[(2-thienylmethyl)amino]phenyl}ethoxycarboxamide (NR579_46)**. A suspension of (4-amino-3-nitrophenyl)(2-thienylmethyl)amine (0.104 g, 0.334 mmol, 80% purity) and 10% Pd/C (0.035 g, 0.032 mmol) in 1,4-dioxane (1.7 mL) and EtOH (0.70 mL) was allowed to stir at rt for 16 h under an H_2 atmosphere. The reaction mixture was diluted with Et_2O, filtered through a pad of Celite, and concentrated under reduced pressure. Further drying

under high vacuum gave the crude triamine (0.093 g) as a dark yellow oil. A solution of this oil (0.093 g) and Et_3N (0.080 mL, 0.57 mmol) in CH_2Cl_2 (1.2 mL) at rt was treated dropwise via syringe over 15 min with a solution of ethyl (1,3-dioxobenzo[*c*]azolidin-2-yloxy)formate (0.050 g, 0.21 mmol) in CH_2Cl_2 (1.2 mL). The reaction mixture was allowed to stir at rt for 18 h and concentrated under reduced pressure. The crude residue was dissolved in EtOAc (20 mL) and washed with sat. aq. $NaHCO_3$ (5 x 10 mL). The aqueous washes were extracted with EtOAc (2 x 20 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give crude product (0.200 g) as a brown-green oil, which was purified by chromatography on SiO_2 (5-10% EtOAc in CH_2Cl_2) to give NR579_46 (0.037 g, 0.13 mmol, 60%) as a gray oil that solidified upon standing: Mp 95-96 ^oC (CH_2Cl_2); IR (ATR) 3403.4, 3287.9, 1677.0, 1518.6 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.20 (dd, 1 H, *J* = 5.0, 1.5 Hz), 6.99 (app. d, 1 H, *J* = 2.5 Hz), 6.96 (dd, 1 H, *J* = 5.0, 3.5 Hz), 6.93 (d, 1 H, *J* = 8.5 Hz), 6.09 (dd, 1 H, *J* = 8.3, 2.5 Hz), 6.04 (d, 1 H, *J* = 2.5 Hz), 4.44 (s, 2 H), 4.19 (q, 2 H, *J* = 7.0 Hz), 3.82 (br s, 3 H), 1.28 (t, 3 H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.6, 147.4, 143.1, 127.8, 127.0, 125.1, 124.7, 114.5, 104.7, 101.2, 61.5, 43.7, 14.7; HRMS (HESI) *m/z* calcd for $C_{14}H_{18}N_3O_2S$ $[M+H]^+$ 292.1120, found 292.1109.



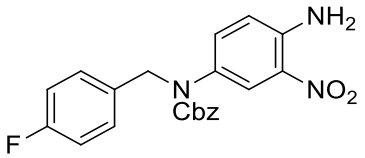
***N*-{2-Amino-4-[(1,3-thiazol-2-ylmethyl)amino]phenyl}ethoxycarboxamide (NR579_38)**. A suspension of (4-amino-3-nitrophenyl)(1,3-thiazol-2-ylmethyl)amine (0.072 g, 0.29 mmol) and Pd/C (0.028 g, 0.026 mmol) was stirred under an H_2 atmosphere (balloon) for 18 h, diluted with Et_2O (10 mL) and filtered through a pad of Celite. The solvent was removed under reduced

pressure to give the crude triamine (0.076 g) as a dark red oil which was used without further purification. A solution of this oil (0.076 g) and Et_3N (0.075 mL, 0.53 mmol) in CH_2Cl_2 (1 mL) at rt was treated dropwise via syringe over 10 min with a solution of ethyl (1,3-dioxobenzo[*c*]azolidin-2-yloxy)formate (0.061 g, 0.26 mmol) in CH_2Cl_2 (1.10 mL). The reaction mixture was stirred for 18 h, concentrated under reduced pressure, resuspended in EtOAc (20 mL), and washed with sat aq. $NaHCO_3$ (4 x 20 mL) until the washes were clear. The aqueous layers were extracted with EtOAc (2 x 20 mL) and the combined organic fractions were washed with H_2O (2 x 20 mL) and brine (2 x 20 mL), dried ($MgSO_4$), filtered, and the solvent evaporated under reduced pressure to give crude product (0.060 g) as a brown-red oil that was purified by chromatography on SiO_2 (70% EtOAc in hexanes) to give NR579_38 (0.045 g, 0.15 mmol, 59% over 2 steps) as a blue-green oil that solidified upon standing: Mp 46-47 ^oC (CH_2Cl_2); IR (CH_2Cl_2) 3352.87, 2981.3, 1696.9, 1621.1, 1523.2 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.72 (d, 1 H, *J* = 3.2 Hz), 7.24 (d, 1 H, *J* = 3.2 Hz), 6.91 (d, 1 H, *J* = 8.4 Hz), 6.16 (br s, 1 H), 6.08 (dd, 1 H, *J* = 8.4, 2.4 Hz), 6.02 (d, 1 H, *J* = 2.4 Hz), 4.59 (s, 2 H), 4.17 (q, 2 H, *J* = 7.2 Hz), 3.81 (br s, 2 H), 1.27 (t, 3 H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 171.6, 155.7, 146.8, 143.1, 142.7, 127.9, 119.2, 114.8, 104.7, 101.2, 61.5, 46.5, 14.7; HRMS (HESI) *m/z* calcd for $C_{13}H_{17}N_4O_2S$ $[M+H]^+$ 293.1067, found 293.1063.



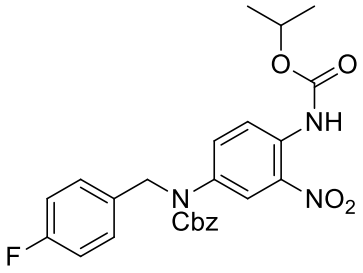
(4-Amino-3-nitrophenyl)[(4-fluorophenyl)methyl]amine. A mixture of 2-nitro-*p*-phenylenediamine (0.998 g, 6.19 mmol) and 3 Å molecular sieves (3 g) in xylenes (30 mL) was heated to 90 ^oC and treated with 4-fluorobenzaldehyde (0.690 mL, 6.27 mmol). The reaction

mixture was allowed to stir for 20 h, filtered through a short pad of SiO_2, and allowed to cool for 6 h. A solid precipitate was filtered off and dried in vacuo to give crude imine (0.719 g), that was dissolved in 1,4-dioxane (4 mL) and MeOH (1 mL) and treated with $NaBH_4$ (0.157 g, 4.11 mmol) in 3 batches at 15 min intervals. The solution was stirred for 10 h, and quenched with H_2O (25 mL). The solid precipitated was filtered and dried to give colorless (4-amino-3-nitrophenyl)[(4-fluorophenyl)methyl]amine (0.573 g, 2.19 mmol, 35%): Mp 113-114 ^oC; IR (ATR) 3518.0, 3497.9, 3395.8, 3372.6, 1578.7, 1503.2, 1406.7, 1330.0 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.33 (app. dd, 2 H, *J* = 5.4, 2.2 Hz), 7.30 (d, 1 H, *J* = 2.8 Hz), 7.04 (app. t, 2 H, *J* = 8.6 Hz), 6.84 (dd, 1 H, *J* = 8.8, 2.8 Hz), 6.70 (d, 1 H, *J* = 8.8 Hz), 5.73 (br s, 2 H), 4.26 (d, 2 H, *J* = 4.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.3 (d, *J* = 245.0 Hz), 139.4, 138.3, 134.6 (d, *J* = 2.9 Hz), 132.6, 129.4 (d, *J* = 8.0 Hz), 125.4, 120.2, 115.7 (d, *J* = 22.0 Hz), 106.1, 48.4; HRMS (HESI) *m/z* calcd for $C_{13}H_{13}N_3O_2F$ $[M+H]^+$ 262.0986, found 262.0981.



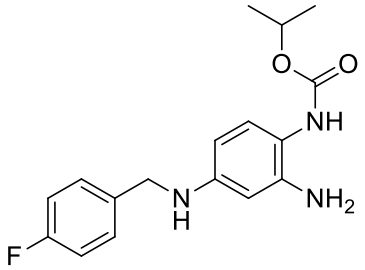
***N*-(4-Amino-3-nitrophenyl)-N-[(4fluorophenyl)methyl](phenylmethoxy)carboxamide**. A solution of (4-amino-3-nitrophenyl)[(4-fluorophenyl)methyl]amine (0.207 g, 0.792 mmol) and DIPEA (0.140 mL, 0.848 mmol) in 1,4-dioxane (4 mL) at rt was treated dropwise via syringe with benzyl chloroformate (0.120 mL, 0.819 mmol). The reaction mixture was allowed to stir at rt for 5 h and was then quenched with H_2O/CH_2Cl_2 (1:1, 6.5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give crude *N*-(4-amino-3-

nitrophenyl)-N-[(4fluorophenyl)methyl](phenylmethoxy)carboxamide (0.420 g) as an orange oil that was used without further purification.

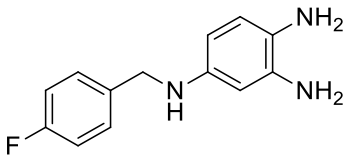


***O*-Benzyl *N*-(4-fluorobenzyl)-*N*-(4-((isopropoxycarbonyl)amino)-3-nitrophenyl)carbamate**. A solution of crude *N*-(4-amino-3-nitrophenyl)-N-[(4fluorophenyl)methyl](phenylmethoxy)-carboxamide (0.415 g) and DIPEA (0.390 mL, 2.36 mmol) in 1,4-dioxane (6.00 mL) at rt was treated dropwise via syringe with a solution of isopropyl chloroformate in toluene (1.95 mL, 1.95 mmol, 1.0 M). The reaction mixture was stirred at 70 ^{o}C for 2 d and quenched by the addition of H_2O/CH_2Cl_2 (1:1, 10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give crude product (0.410 g) as a dark orange oil that was purified by chromatography on SiO_2 (10% EtOAc in hexanes) to give *O*-benzyl *N*-(4-fluorobenzyl)-*N*-(4-((isopropoxycarbonyl)amino)-3-nitrophenyl)carbamate (0.097 g) as a yellow oil along with recovered starting material (0.140 g). The starting material was recycled through the reaction procedure again to give *O*-benzyl *N*-(4-fluorobenzyl)-*N*-(4-((isopropoxycarbonyl)amino)-3-nitrophenyl)carbamate (0.050 g, 0.147 g total, 0.305 mmol, 39% over two steps) as a yellow oil: IR (CH_2Cl_2) 3367.4, 2982.2, 1735.0, 1705.4, 1510.6, 1338.3 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.72 (s, 1 H), 8.52 (d, 1 H, *J* = 8.8 Hz), 7.98 (br s, 1 H), 7.36-7.25 (m, 5 H), 7.15 (app. t, 2 H, *J* = 6.8 Hz), 6.96 (t, 2 H, *J* = 8.8 Hz), 5.19 (s, 2 H), 5.08-4.96 (m, 2 H), 4.84 (s, 2 H), 1.32 (d, 6 H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.4 (d, *J* =

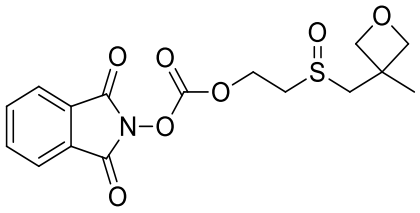
245.0 Hz), 155.3, 152.8, 136.0, 135.7, 134.7, 134.2, 132.8 (d, *J* = 3.2 Hz), 129.8, 128.7, 128.4, 128.1, 124.0, 121.1, 115.8 (d, *J* = 21.3 Hz); HRMS (HESI) *m/z* calcd for $C_{25}H_{24}N_3O_6F$ $[M-H]^-$ 480.1565, found 480.1575.



***N*-(2-Amino-4-{[(4-fluorophenyl)methyl]amino}phenyl)(1-methylethoxy)carboxamide (NR561_62)**. A suspension of *O*-benzyl *N*-(4-fluorobenzyl)-*N*-(4-((isopropoxycarbonyl)amino)-3-nitrophenyl)carbamate (0.049 g, 0.10 mmol) and 10% Pd/C (0.013 g, 0.012 mmol, 10 mol%) in 1,4-dioxane (0.60 mL) and EtOH (0.30 mL) was allowed to stir at rt for 18 h under an H_2 atmosphere (balloon). The reaction mixture was diluted with Et_2O (5 mL), filtered through Celite, and the solvent was evaporated under reduced pressure to give crude product (0.033 g) as a brown oil that was purified by chromatography on SiO_2 (50% EtOAc in hexanes) to give NR561_62 (0.024 g, 0.076 mmol, 74%) as an off-white solid: Mp 171-172 ^oC (CH_2Cl_2); IR (ATR) 3396.4, 3342.9, 3289.3, 2981.7, 1674.8; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.31 (app. dd, 2 H, *J* = 8.4, 5.6 Hz), 7.01 (app. t, 2 H, *J* = 10.2 Hz), 6.92 (d, 1 H, *J* = 8.0 Hz), 6.06 (dd, 1 H, *J* = 8.4, 2.4 Hz), 6.00 (d, 1 H, *J* = 2.4 Hz), 4.97 (m, 1 H), 4.25 (s, 2 H), 3.81 (br s, 2 H), 1.27 (d, 6 H, *J* = 6.4 Hz); 13C NMR ($CDCl_3$, 100 MHz) δ 162.2 (d, *J* = 244.0 Hz), 155.3, 147.7, 143.1, 135.3 (d, *J* = 2.9 Hz), 129.1 (d, *J* = 7.9 Hz), 127.8, 115.6 (d, *J* = 21.2 Hz), 114.4, 104.5, 100.8, 68.9, 47.8, 22.3; HRMS (HESI) *m/z* calcd for $C_{17}H_{21}N_3O_2F$ $[M-H]^-$ 318.1612, found 318.1611.

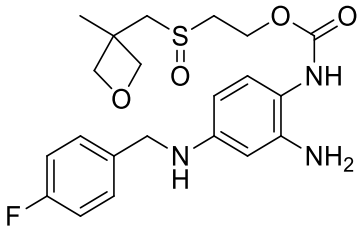


(3,4-Diaminophenyl)[(4-fluorophenyl)methyl]amine. A suspension of (4-amino-3-nitrophenyl)[(4-fluorophenyl)methyl]amine (0.101 g, 0.321 mmol) and 10% Pd/C (0.035 g, 0.032 mmol) in 1,4-dioxane (1.6 mL) and EtOH (0.80 mL) was allowed to stir at rt under an H_2 atmosphere (balloon) for 18 h. The reaction mixture was diluted with Et_2O (10 mL), filtered through a pad of celite, and concentrated under reduced pressure. Further drying under high vacuum gave crude (3,4-diaminophenyl)[(4-fluorophenyl)methyl]amine (0.077 g) as a brown oil which was used without further purification.



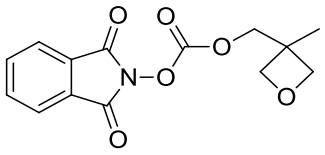
2-{[(3-Methyloxetan-3-yl)methyl]sulfinyl}ethyl(1,3-dioxobenzo[c]azolidin-2-yloxy)formate. A suspension of diphthalimidyl carbonate (0.380 g, 1.08 mmol) and MMS-350 sulfoxide alcohol (Sprachman et al., **2012**, *10*, 269-277) (0.195 g, 1.09 mmol) in THF (5 mL) was treated with Et_3N (0.145 mL, 1.03 mmol). Upon addition of base, the suspension turned yellow, eventually progressing to a clear orange solution after 20 min. The reaction mixture was stirred for 2 h, concentrated under reduced pressure, dissolved in EtOAc (25 mL) and washed with saturated aqueous $NaHCO_3$ (5 x 3 mL) until the organic layer became clear. The combined aqueous washings were extracted with EtOAc (2 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give 1-2-{[(3-methyloxetan-3-

yl)methyl]sulfinyl}ethyl(1,3-dioxobenzo[c]azolidin-2-yloxy)formate (0.265 g, 0.721 mmol, 66%) as a foaming solid which was used without further purification.

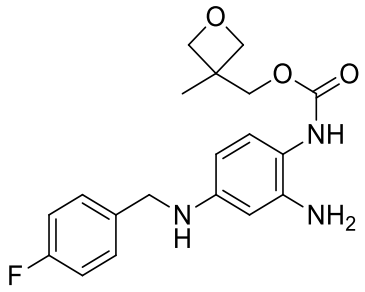


2-(((3-Methyloxetan-3-yl)methyl)sulfinyl)ethyl (2-amino-4-((4-fluorobenzyl)amino)phenyl)carbamate (NR579_36). A solution of crude (3,4-diaminophenyl)[(4-fluorophenyl)methyl]amine (0.062 g, 0.27 mmol) and Et_3N (0.070 mL, 0.50 mmol) in CH_2Cl_2 (1.00 mL) was treated dropwise via syringe over 10 min with a solution of crude 1-2-{[(3-methyloxetan-3-yl)methyl]sulfinyl}ethyl(1,3-dioxobenzo[c]azolidin-2-yloxy)formate (0.095 g, 0.26 mmol) in CH_2Cl_2 (1.00 mL). The reaction mixture was stirred for 18 h at rt, concentrated under reduced pressure, dissolved in EtOAc (20 mL), and washed with sat. aq. $NaHCO_3$ (3 x 10 mL). The combined aqueous layers were extracted with EtOAc (2 x 20 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give crude product (0.090 g) as a dark green oil that was purified by chromatography on SiO_2 (3-5% MeOH in CH_2Cl_2) to give NR579_36 (0.041 g, 0.094 mmol, 39% over two steps) as a light brown oil: IR (CH_2Cl_2) 3362.9, 2257.0, 1712.8, 1619.2, 1525.3, 1508.3 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz, 323 K) δ 7.99 (br s, 1 H), 7.38-7.35 (m, 2 H), 7.09 (t, 2 H, J = 8.8 Hz), 6.73 (d, 1 H, J = 8.5 Hz), 5.99 (d, 1 H, J = 2.0 Hz), 5.88 (dd, 1 H, J = 8.5, 2.5 Hz), 5.56 (s, 1 H), 4.64 (d, 1 H, J = 5.5 Hz), 4.55 (d, 1 H, J = 5.5 Hz), 4.45-4.31 (m, 5 H), 4.24 (d, 1 H, J = 6.0 Hz), 4.19 (d, 2 H, J = 4.5 Hz), 3.19-3.13 (m, 2 H), 3.03-3.00 (m, 2 H), 1.49 (s, 3 H); ^{13}C NMR (DMSO-d_6, 125 MHz, 323 K) δ 160.7 (d, J = 240.0 Hz), 154.2, 147.1, 143.2,

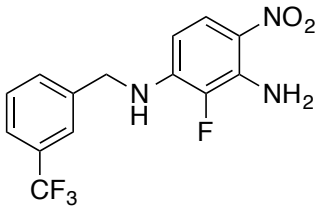
136.4, 128.5 (d, J = 7.5 Hz), 126.9, 114.3 (d, J = 21.3 Hz), 112.7, 101.7, 98.9, 90.0, 80.6, 59.8, 56.7, 51.7, 45.9, 37.6, 23.0; HRMS (HESI) *m/z* calcd for $C_{21}H_{27}N_3O_4FS$ $[M+H]^+$ 436.1701, found 436.1698.



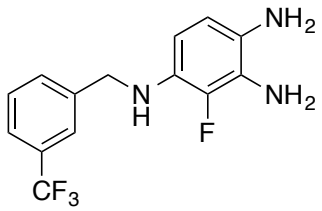
(3-Methyloxetan-3-yl)methyl(1,3-dioxobenzo[*c*]azolidin-2-yloxy)formate. A suspension of diphthalimidyl carbonate (0.381 g, 1.08 mmol) and 3-methyl-3-oxetanemethanol (0.110 mL, 1.08 mmol) in THF (5 mL) was treated with Et_3N (0.160 mL, 1.14 mmol). Upon addition of base, the suspension turned yellow, progressing to orange over 2 h. The reaction mixture was stirred for 14 h, concentrated under reduced pressure, dissolved in EtOAc (25 mL) and washed with sat. aq. $NaHCO_3$ (5 x 10 mL) until the organic layer became clear. The combined aqueous washings were extracted with EtOAc (2 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Further drying under high vacuum gave (3-methyloxetan-3-yl)methyl(1,3-dioxobenzo[*c*]azolidin-2-yloxy)formate (0.255 g, 0.876 mmol, 81%) as a clear, light yellow oil: IR (CH_2Cl_2) 2965.4, 2875.7, 1811.8, 1788.7, 1742.0 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.91-7.88 (m, 2 H), 7.81-7.79 (m, 2 H), 4.54 (d, 2 H, J = 6.4 Hz), 4.47 (s, 2 H), 4.43 (d, 2 H, J = 6.0 Hz), 1.41 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) 161.5, 152.7, 135.1, 128.8, 124.3, 79.1, 75.4, 39.5, 20.8; HRMS (HESI) *m/z* calcd for $C_{14}H_{14}NO_6$ $[M+H]^+$ 292.0816, found 292.0819.



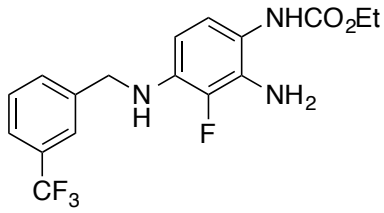
***N*-(2-Amino-4-{[(4-fluorophenyl)methyl]amino}phenyl)[(3-methyloxetan-3-yl)methoxy] carboxamide (NR579_45)**. A solution of crude (3,4-diaminophenyl)[(4-fluorophenyl)methyl]amine (0.077 g) and Et_3N (0.090 mL, 0.64 mmol) in CH_2Cl_2 (1.30 mL) at rt was treated dropwise via syringe over 15 min with a solution of (3-methyloxetan-3-yl)methyl(1,3-dioxobenzo[*c*]azolidin-2-yloxy)formate (0.101 g, 0.347 mmol) in CH_2Cl_2 (1.30 mL). The reaction mixture was allowed to stir for 18 h, concentrated under reduced pressure, dissolved in EtOAc (20 mL), and washed with sat. aq. $NaHCO_3$ (3 x 10 mL). The combined aqueous washes were extracted with EtOAc (2 x 20 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and the solvent evaporated under reduced pressure to give crude product (0.110 g) as an olive green oil that was purified by chromatography on SiO_2 (40-50% EtOAc in hexanes) to give NR579_45 (0.033 g, 0.092 mmol, 29% over 2 steps) as a dark brown oil: IR (CH_2Cl_2) 3346.5, 2960.4, 2877.0, 1701.7, 1619.5, 1524.5, 1508.1 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.30 (dd, 2 H, *J* = 8.2, 5.4 Hz), 7.02 (app. t, 2 H, *J* = 8.6 Hz), 6.93 (d, 1 H, *J* = 7.6 Hz), 6.21 (br s, 1 H), 6.06 (d, 1 H, *J* = 8.4 Hz), 6.00 (s, 1 H), 4.58 (app. br s, 2 H), 4.39 (app. br s, 2 H), 4.25 (s, 2 H), 4.20 (s, 2 H), 3.80 (br s, 3 H), 1.35 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.2 (d, *J* = 243.0 Hz), 155.5, 147.9, 143.1, 135.2 (d, *J* = 3.0 Hz), 129.0 (d, *J* = 8.0 Hz), 127.9, 115.6 (d, *J* = 21.0 Hz), 113.9, 104.6, 100.8, 79.6, 69.4, 47.7, 39.5, 21.3; HRMS (HESI) *m/z* calcd for $C_{19}H_{23}N_3O_3F$ $[M+H]^+$ 360.1723, found 360.1712.



2-Fluoro-4-nitro-*N*^{1}-(3-(trifluoromethyl)benzyl)benzene-1,3-diamine. To a stirred solution of 2,3-difluoro-6-nitroaniline (0.200 g, 1.11 mmol, 1.00 equiv) in dry DMSO (4.6 mL) were added 3-(trifluoromethyl)benzylamine (0.195 mL, 1.34 mmol, 1.2 equiv) followed by Et_3N (0.135 g, 1.34 mmol, 1.2 equiv) and I_2 (cat. 2 mg). The reaction mixture was heated to 120 °C for 24 h, cooled to room temperature, diluted with water (25 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (EtOAc/hexanes, 1:10 to 1:4 to 1:3) to afford 2-fluoro-4-nitro-*N*^{1}-(3-(trifluoromethyl)benzyl)benzene-1,3-diamine as a yellow solid (0.280 g, 76%): Mp 156.0-157.2 °C; IR (ATR) 3495.2, 3383.4, 1627.4, 1480.1, 1411.1, 1275.1, 1250.8, 1120.3, 1070.0, 797.8 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 9.6, 1.6 Hz, 1 H), 7.59-7.57 (m, 2 H), 7.54-7.47 (m, 2 H), 6.15-6.00 (m, 3 H), 4.93 (br, 1 H), 4.54 (d, *J* = 6.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9 (d, *J* = 9.5 Hz), 138.9, 138.0 (d, *J* = 228.6 Hz), 135.2 (d, *J* = 12.9 Hz), 131.5 (q, *J* = 32.5 Hz), 130.5, 129.6, 125.6 (d, *J* = 3.5 Hz), 124.9 (q, *J* = 3.7 Hz), 124.1 (q, *J* = 272.4 Hz), 124.0 (q, *J* = 3.7 Hz), 123.7 (d, *J* = 2.9 Hz), 100.7 (d, *J* = 2.9 Hz), 46.8; ^{19}F NMR (471 MHz , $CDCl_3$) δ -62.7 (s, 3 F), -160.6 (s, 1 F); HRMS (HESI) *m/z* calcd for $C_{14}H_{12}N_3O_2F_4$ $[M+H]^+$ 330.0860, found 330.0858.

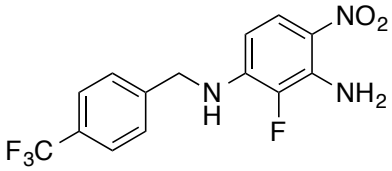


3-Fluoro-N^4-(3-(trifluoromethyl)benzyl)benzene-1,2,4-triamine. To a stirred solution of 2-fluoro-4-nitro-N^1-(3-(trifluoromethyl)benzyl)benzene-1,3-diamine (0.280 g, 0.85 mmol) in MeOH (2 mL) was added zinc powder (0.278 g, 4.25 mmol) followed by the dropwise addition of saturated ammonium chloride (0.80 mL). The reaction mixture was stirred vigorously at room temperature overnight, diluted with EtOAc (2 mL) and water (1 mL), and filtered through Celite. The Celite was washed with EtOAc and the solution was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to afford crude product as a dark red solid (0.190 g, 75%) that was used in the next step without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1 H), 7.56 (d, 1 H, J = 7.6 Hz), 7.52 (d, 1 H, J = 7.6 Hz), 7.44 (t, 1 H, J = 7.6 Hz), 6.37 (dd, 1 H, J = 8.4, 2.0 Hz), 5.99 (t, 1 H, J = 8.8 Hz), 4.36 (s, 2 H), 3.98 (br s, 1 H), 3.52 (br s, 2 H), 3.10 (br s, 2 H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.5 (s, 3 F), -155.8 (s, 1 F).



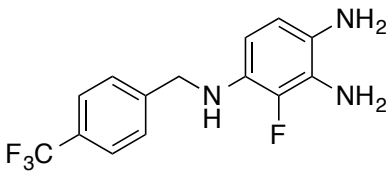
Ethyl (2-amino-3-fluoro-4-((3-(trifluoromethyl)benzyl)amino)phenyl)carbamate (RL648_73). An oven-dried 5-mL round bottomed flask equipped with a magnetic stir bar under argon was charged at 0 °C with 3-fluoro-N^4-(3-(trifluoromethyl)benzyl)benzene-1,2,4-triamine (0.06 g, 0.20 mmol), CH_2Cl_2 (1 mL) and DIPEA (0.043 mL, 0.25 mmol). Ethyl chloroformate (0.02 mL, 0.20 mmol) was added dropwise via syringe at 0 °C. The resulting mixture was stirred for 1 h at 0 °C and for 3 h at room temperature, and quenched by addition of water. The aqueous layer was extracted with CH_2Cl_2 (3 x 2 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was purified by chromatography on

SiO_2 (EtOAc/hexanes, 4:1 to 3:1) to afford RL648_73 as a dark red solid (0.045 g, 60%). Recrystallization from CH_2Cl_2/hexanes gave colorless crystals: Mp 129.3-129.7 °C; IR (ATR) 3405.8, 3290.2, 1675.9, 1452.2, 1329.1, 1246.2, 1159.5, 1112.9, 1071.9, 915.3, 700.9 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1 H), 7.54 (app t, 2 H, *J* = 7.2 Hz), 7.45 (t, 1 H, *J* = 7.6 Hz), 6.74 (dd, 1 H, *J* = 8.4, 1.2 Hz), 6.11 (br s, 1 H), 6.02 (t, 1 H, *J* = 8.8 Hz), 4.41 (d, 2 H, *J* = 5.2 Hz), 4.30 (br s, 1 H), 4.20 (q, 2 H, *J* = 7.2 Hz), 3.86 (br s, 2 H), 1.28 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 156.0, 143.1, 141.8 (d, *J* = 227.9 Hz), 135.5 (d, *J* = 9.7 Hz), 132.4, 131.8, 130.9 (q, *J* = 31.8 Hz), 130.1, 125.5 (q, *J* = 271.5 Hz), 124.5 (q, *J* = 3.9 Hz), 124.3 (q, *J* = 3.9 Hz), 122.3, 116.5, 101.3, 61.2, 47.4, 15.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.6 (s, 3 F), -155.5 (s, 1 F); HRMS (HESI) *m/z* calcd for $C_{17}H_{18}N_3O_2F_4$ $[M+H]^+$ 372.1330, found 372.1328.

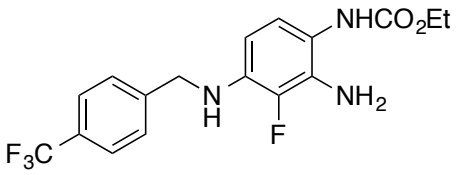


2-Fluoro-4-nitro-*N*^{1}-(4-(trifluoromethyl)benzyl)benzene-1,3-diamine. A solution of 2,3-difluoro-6-nitroaniline (0.100 g, 0.557 mmol, 1.00 equiv) in dry DMSO (4.6 mL) was treated with 4-(trifluoromethyl)benzylamine (0.081 mL, 0.557 mmol, 1.00 equiv) followed by Et_3N (0.09 mL, 0.669 mmol, 1.20 equiv) and I_2 (cat. 1 mg). The reaction mixture was heated to 120 °C for 24 h, cooled to room temperature, diluted with water (25 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (EtOAc/hexanes,1:10 to 1:5 to 1:3) to afford the 2-fluoro-4-nitro-*N*^{1}-(4-(trifluoromethyl)benzyl)benzene-1,3-diamine (0.120 g, 65 %) as a yellow solid: Mp 165.4-166.7

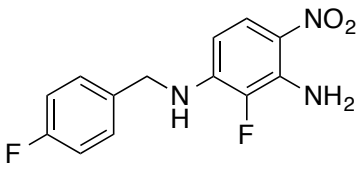
°C; IR (ATR) 3487.3, 3377.3, 1629.0, 1548.9, 1479.9, 1410.9, 1328.9, 1274.9, 1235.7, 1200.3, 1178.0, 1153.7, 1090.4, 1066.1, 1015.8, 786.5, 754.9 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (dd, 1H, *J* = 9.5, 1.0 Hz), 7.63 (d, 2 H, *J* = 8.0 Hz), 7.44 (d, 2 H, *J* = 8.0 Hz), 6.00-6.12 (m, 3H), 4.94 (br s, 1 H), 4.55 (d, *J* = 6.0 Hz, 2 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 144.2 (d, *J* = 1.0 Hz), 141.5 (d, *J* = 9.0 Hz), 137.6 (d, *J* = 227.0 Hz), 135.8 (d, *J* = 13.0 Hz), 128.8 (q, *J* = 32.0 Hz), 127.6, 125.4 (q, *J* = 4.0 Hz), 124.5 (d, *J* = 4.0 Hz), 124.5 (q, *J* = 269.0 Hz), 122.9 (d, *J* = 2.0 Hz), 100.7 (d, *J* = 4.0 Hz), 45.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.9 (s, 3 F), -160.7 (s, 1 F); HRMS (HESI) *m/z* calcd for $C_{14}H_{12}N_3O_2F_4$ $[M+H]^+$ 330.0860, found 330.0858.



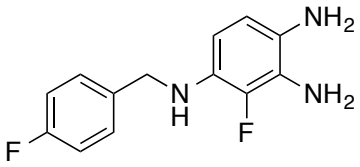
3-Fluoro-*N*^{4}-(4-(trifluoromethyl)benzyl)benzene-1,2,4-triamine. To a solution of 2-fluoro-4-nitro-*N*^{1}-(4-(trifluoromethyl)benzyl)benzene-1,3-diamine (0.066 g, 0.2 mmol) in MeOH (0.5 mL) was added zinc powder (0.066 g, 1.00 mmol) followed by the dropwise addition of a solution of saturated ammonium chloride (0.19 mL). The reaction mixture was stirred vigorously at room temperature for 5 h and filtered through Celite. The Celite was washed with EtOAc and the aqueous solution was extracted with EtOAc (3 x 2 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to afford 3-fluoro-*N*^{4}-(4-(trifluoromethyl)benzyl)benzene-1,2,4-triamine (0.060 g, 100%) as a dark red solid that was used in the next step without further purification: ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, 2 H, *J* = 8.0 Hz), 7.47 (d, 2 H, *J* = 8.0 Hz), 6.35 (dd, 1 H, *J* = 8.4, 1.6 Hz), 5.99 (t, 1 H, *J* = 8.4 Hz), 4.37 (s, 2 H), 4.02 (br s, 1 H), 3.52 (br s, 2 H), 3.13 (br s, 2 H); HRMS (HESI) *m/z* calcd for $C_{14}H_{14}N_3F_4$ $[M+H]^+$ 300.1118, found 300.1113.



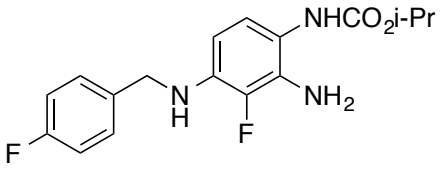
Ethyl (2-amino-3-fluoro-4-((4-(trifluoromethyl)benzyl)amino)phenyl)carbamate (RL648_81). An oven-dried 5-mL round bottomed flask equipped with a magnetic stir bar under argon was charged at 0 °C with 3-fluoro-N^4-(4-(trifluoromethyl)benzyl)benzene-1,2,4-triamine (0.06 g, 0.20 mmol), CH_2Cl_2 (1 mL) and DIPEA (0.043 mL, 0.25 mmol). Ethyl chloroformate (0.02 mL, 0.20 mmol) was added dropwise via syringe at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and then for 3 h at room temperature, quenched with water, and extracted with CH_2Cl_2 (3 x 2 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (EtOAc/hexanes, 4:1 to 3:1) to afford a dark red solid. Recrystallization from CH_2Cl_2/hexanes gave RL648_81 (0.035 g, 47%) as colorless crystals: Mp 171.4-172.2 °C; IR (ATR) 3399.7, 3338.2, 3299.0, 1675.6, 1643.9, 1617.8, 1528.4, 1489.2, 1478.0, 1442.6, 1323.3, 1248.8, 1157.5, 1112.7, 1103.4, 825.7, 781.0, 775.4, 767.9, 672.9 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, 2 H, J = 8.0 Hz), 7.46 (d, 2 H, J = 8.0 Hz), 6.73 (d, 1 H, J = 8.4 Hz), 6.13 (br s, 1 H), 5.99 (t, 1 H, J = 8.8 Hz), 4.42 (s, 2 H), 4.33 (br s, 1 H), 4.19 (q, 2 H, J = 7.2 Hz), 3.86 (br s, 2 H), 1.29 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 156.0, 146.4, 141.7 (d, J=227.7 Hz), 135.4, 132.5, 129.3 (q, J = 32.0 Hz), 128.5, 126.1 (q, J = 3.9 Hz), 125.5 (q, J = 271.0 Hz), 122.3, 116.4, 101.3, 61.2, 47.4, 15.0; ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.5 (s, 3 F), -156.1 (s ,1 F); HRMS (HESI) *m/z* calcd for $C_{17}H_{18}N_3O_2F_4$ $[M+H]^+$ 372.1330, found 372.1327.



2-Fluoro-*N*^{1}-(4-fluorobenzyl)-4-nitrobenzene-1,3-diamine. A solution of 2,3-difluoro-6-nitroaniline (1.00 g, 5.57 mmol, 1.00 equiv) in dry DMSO (6 mL) was treated with 4-fluorobenzylamine (0.79 mL, 6.68 mmol, 1.20 equiv) followed by Et_3N (0.93 mL, 6.68 mmol, 1.2 equiv) and I_2 (cat. 5 mg). The reaction mixture was heated to 120 °C for 24 h, cooled to room temperature, quenched with water (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was treated with a small amount of Et_2O (5 mL), sonicated, and filtered. The filter cake was washed with Et_2O (3 x 3 mL) to afford product (1.20 g) as a yellow solid. The filtrate was concentrated in vacuo and the residue was purified by chromatography on SiO_2 (EtOAc/hexanes/Et_3N, 1:4:0.1 to 1:3:0.1) to afford additional product (0.2 g) which was combined with the earlier fraction to provide 2-fluoro-*N*^{1}-(4-fluorobenzyl)-4-nitrobenzene-1,3-diamine (1.40 g, 90%) as a yellow solid: Mp 195.0-195.7 °C; IR (ATR) 3504.6, 3387.1, 3329.3, 3070.2, 2950.9, 1625.5, 1601.3, 1578.9, 1549.1, 1506.2, 1483.8, 1267.6, 1239.6, 1174.4, 1086.8, 991.7, 848.2, 837.0, 820.2, 805.3, 751.2 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, 1 H, *J* = 9.6, 2.0 Hz), 7.33 (dd, 2 H, *J* = 8.4, 5.2 Hz), 7.12-7.06 (m, 2 H), 6.12 (dd, 1 H, *J* = 9.6, 8.0 Hz), 6.07 (br s, 2 H), 4.86 (br s, 1 H), 4.47 (s, 2 H); ^{13}C NMR (125 MHz, acetone-d_6) δ 163.0 (d, *J* = 243.2 Hz), 142.6 (d, *J* = 9.3 Hz), 138.5 (d, *J* = 228.2 Hz), 136.7 (d, *J* = 13.4 Hz), 136.2 (d, *J* = 3.4 Hz), 129.9 (d, *J* = 8.2 Hz), 125.4, 123.9 (d, *J* = 2.6 Hz), 116.1 (d, *J* = 21.6 Hz), 101.8 (d, *J* = 3.5 Hz), 46.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.3 (s, 1 F), -161.1 (s, 1 F); HRMS (HESI) *m/z* calcd for $C_{13}H_{12}N_3O_2F_2$ $[M+H]^+$ 280.0892, found 280.0890.

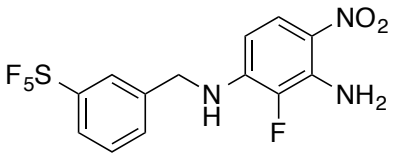


3-Fluoro-*N*^{4}-(4-fluorobenzyl)benzene-1,2,4-triamine. A stirred solution of 2-fluoro-*N*^{1}-(4-fluorobenzyl)-4-nitrobenzene-1,3-diamine (0.200 g, 0.716 mmol) in MeOH (2 mL) was treated with zinc powder (0.230 g, 3.58 mmol) followed by the dropwise addition of a solution of saturated ammonium chloride (0.68 mL). The reaction mixture was stirred vigorously at room temperature overnight, and filtered through Celite. The Celite was washed with EtOAc and the filtrate was extracted with EtOAc (3 x 3 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford 3-fluoro-*N*^{4}-(4-fluorobenzyl)benzene-1,2,4-triamine (0.120 g, 67%) as a dark red solid that was used in the next step without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (dd, 2 H, *J* = 8.5, 5.5 Hz), 7.04-6.98 (m, 2H), 6.38 (d, 1 H, *J* = 8.5 Hz), 6.03 (t, 1 H, *J* = 8.5 Hz), 4.26 (s, 2 H), 3.21 (br, 5 H); ^{19}F NMR (471 MHz, $CDCl_3$) δ -115.7 (s, 1 F), -155.8 (s, 1 F); HRMS (HESI) *m/z* calcd for $C_{13}H_{14}N_3F_2$ $[M+H]^+$ 250.1150, found 250.1148.



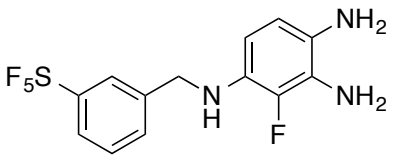
Isopropyl (2-amino-3-fluoro-4-((4-fluorobenzyl)amino)phenyl)carbamate (RL648_86). An oven-dried 5-mL round bottomed flask equipped with a magnetic stir bar under argon was charged at 0 °C with 3-fluoro-*N*^{4}-(4-fluorobenzyl)benzene-1,2,4-triamine (0.120 g, 0.48 mmol), CH_2Cl_2 (2.5 mL) and DIPEA (0.10 mL, 0.60 mmol). Isopropyl chloroformate (1 M in toluene, 0.48 mL) was added dropwise via syringe at 0 °C. The reaction mixture was stirred for 1 h at 0

°C, for 3 h at room temperature, and quenched by addition of water. The aqueous layer was extracted with CH_2Cl_2 (3 x 4 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (EtOAc/hexanes, 4:1 to 3:1) to give a light red solid, which was washed with a small amount of Et_2O to afford RL648_86 (0.035 g, 21%) as a colorless solid: Mp 177.5-178.2 °C; IR (ATR) 3407.6, 3338.7, 3295.8, 1675.9, 1646.0, 1618.1, 1532.3, 1487.6, 1442.8, 1323.5, 1284.4, 1263.9, 1249.0, 1155.8, 1112.9, 1101.7, 1066.3, 823.9, 781.1 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.21 (dd, 2 H, *J* = 8.5, 5.5 Hz), 7.02 (app t, 2 H, *J* = 8.5 Hz), 6.74 (d, 1 H, *J* = 8.5 Hz), 6.11 (br s, 1 H), 6.06 (t, 1 H, *J* = 8.5 Hz), 4.98 (sept, 1 H, *J* = 6.0 Hz), 4.31 (d, 2 H, *J* = 3.0 Hz), 4.19 (br s, 1 H), 3.86 (br s, 2 H), 1.28 (d, 6 H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.2 (d, *J* = 245.2 Hz), 155.1, 141.4 (d, *J* = 233.8 Hz), 135.1 (d, *J* = 10.4 Hz), 135.0 (d, *J* = 3.1 Hz), 130.8 (d, *J* = 11.4 Hz), 129.0 (d, *J* = 8.1 Hz), 121.6, 115.6 (d, *J* = 21.5 Hz), 115.5, 102.0, 69.2, 47.4, 22.2; ^{19}F NMR (471 MHz, $CDCl_3$) δ -115.5 (s, 1 F), -156.2 (s,1 F); HRMS (HESI) m/z calcd for $C_{17}H_{20}N_3O_2F_2$ $[M+H]^+$ 336.1518, found 336.1518.



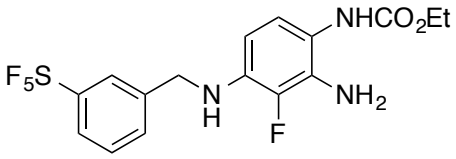
2-Fluoro-4-nitro-*N*^{1}-(3-(pentafluoro-λ^6-sulfanyl)benzyl)benzene-1,3-diamine. A suspension of 2,3-difluoro-6-nitroaniline (0.500 g, 2.78 mmol, 1.00 equiv) in dry DMSO (5 mL) was treated with 3-(pentafluorosulfanyl)benzylamine (0. 714 g, 3.06 mmol, 1.1 equiv) followed by Et_3N (0.43 mL, 3.06 mmol, 1.1 equiv) and I_2 (cat. 5 mg). The reaction mixture was heated to 120 °C for 24 h, cooled to room temperature, diluted with water (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and

concentrated under reduced pressure. To resulting residue was treated with a small amount of Et_2O (2 mL), sonicated, and filtered, and the filter cake was again washed with Et_2O (3 x 3 mL) to afford a yellow solid (0.51 g). The filtrate was concentrated in vacuo and the residue was purified by chromatography on SiO_2 (acetone/hexanes, 1:10 to 1:4 to 1:3) to afford additional product (0.17 g). The fractions were combined to yield 2-fluoro-4-nitro-*N*^{1}-(3-(pentafluoro-λ^6-sulfanyl)benzyl)benzene-1,3-diamine (0.68 g, 63%) as a yellow solid: Mp 169.5-170.0 °C; IR (neat) 3494.7, 3384.8, 1630.9, 1548.9, 1481.8, 1412.8, 1286.1, 1273.0, 1239.5, 1205.9, 1176.1, 1140.7, 1105.3, 1086.6, 890.9, 859.2, 820.1, 795.9, 775.4, 751.1, 687.8 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, 1 H, *J* = 9.6, 1.6 Hz), 7.72-7.68 (m, 2 H), 7.50-7.46 (m, 2 H), 6.07 (br s, 2 H), 6.02 (dd, 1 H, *J* = 9.6, 8.0 Hz), 4.50 (br s, 1 H), 4.54 (d, 2 H, *J* =1.5 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 153.9 (t, *J* = 16.1 Hz), 141.3 (d, *J* = 9.4 Hz), 141.3, 137.6 (d, *J* = 228.7 Hz), 135.8 (d, *J* = 13.3 Hz), 135.7, 130.8, 129.5, 124.6 (t, *J* = 4.7 Hz), 124.4 (t, *J* = 4.7 Hz), 122.9 (d, *J* = 2.8 Hz), 100.7 (d, *J* = 3.0 Hz), 45.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ 84.0 (quint, *J* = 150.4 Hz, 1 F), 62.7 (d, *J* = 150.4 Hz, 4 F), -160.4 (s, 1 F); HRMS (HESI) *m/z* calcd for $C_{13}H_{12}N_3O_2F_2S$ $[M+H]^+$ 388.0549, found 388.0549.



3-Fluoro-*N*^{4}-(3-(pentafluoro-λ^6-sulfanyl)benzyl)benzene-1,2,4-triamine. A stirred solution of 2-fluoro-4-nitro-*N*^{1}-(3-(pentafluoro-λ^6-sulfanyl)benzyl)benzene-1,3-diamine (0.500 g, 1.29 mmol) in MeOH (4 mL) was treated with zinc powder (0.422 g, 6.45 mmol) followed by dropwise addition of a solution of saturated ammonium chloride (1.22 mL). The reaction mixture was stirred vigorously at room temperature overnight, and filtered through Celite. The Celite was

washed with EtOAc and the filtrate was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried (Na_2SO_4), and concentrated under reduced pressure to afford 3-fluoro-N^4-(3-(pentafluoro-λ^6-sulfanyl)benzyl)benzene-1,2,4-triamine (0.390 g, 85%) as a red solid that was used in the next step without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1 H), 7.64 (d, J = 8.4 Hz, 1 H), 7.51 (d, J =7.6 Hz, 1 H), 7.41 (t, J = 8.0 Hz, 1 H), 6.39 (d, J = 7.6 Hz, 1 H), 5.98 (t, J = 8.4 Hz, 1 H), 4.35 (s, 2 H), 3.32 (br, 5 H).



Ethyl (2-amino-3-fluoro-4-((3-(pentafluoro-λ^6-sulfanyl)benzyl)amino)phenyl)carbamate (RL673_02). An oven-dried 5-mL round bottomed flask equipped with a magnetic stir bar was charged under argon at 0 °C with 3-fluoro-N^4-(3-(pentafluoro-λ^6-sulfanyl)benzyl)benzene-1,2,4-triamine (0.20 g, 0.56 mmol), CH_2Cl_2 (3 mL) and DIPEA (0.12 mL, 0.7 mmol). Ethyl chloroformate (0.055 mL, 0.56 mmol) was added dropwise via syringe at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, then 3 h at room temperature, quenched with water and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and purified by chromatography on SiO_2 (EtOAc/hexanes, 5:1 to 4:1 to 3:1) to afford the product as a yellow solid. Recrystallization from CH_2Cl_2/hexanes afford RL673_02 (0.123 g, 44%) as a colorless solid: Mp 141.3-142.1 °C; IR (ATR) 3420.2, 3375.41, 2985.9, 1688.7, 1636.5, 1524.6, 1483.6, 1287.9, 1254.4, 1241.3, 829.4, 816.4, 786.5, 688.7 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1 H), 7.65 (d, 1 H, J = 8.0 Hz), 7.50 (d, 1 H, J = 7.6 Hz), 7.42 (t, 1 H, J = 8.0 Hz), 6.74 (d, 1 H, J = 7.6 Hz), 6.24 (br s, 1 H), 6.00 (t, 1 H, J = 8.8 Hz), 4.40 (s, 2 H), 4.19 (q, 2 H, J = 7.2 Hz), 3.98 (br s, 3 H), 1.28 (t, 3 H, J = 7.2 Hz); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 155.5, 154.4 (quint, *J* = 16.9 Hz), 141.3 (d, *J* = 233.6 Hz), 140.7, 134.7 (d, *J* = 9.8 Hz), 130.9, 130.3, 129.2, 125.0 (t, *J* = 4.6 Hz), 124.8 (t, *J* = 4.6 Hz), 121.7, 115.6, 101.9, 61.7, 47.6, 14.6; ^{19}F NMR (565 MHz, $CDCl_3$) δ 84.5 (quint, *J* = 146.9 Hz, 1 F), 62.8 (d, *J* = 146.9 Hz, 4 F), -155.8 (s, 1 F); HRMS (HESI) *m/z* calcd for $C_{16}H_{18}N_3O_2F_6S$ $[M+H]^+$ 430.1018, found 430.1015.

Detailed values for main figures

Figure 3C. Retigabine: control (-29.5 ± 0.9; n=11), 100 nM (-30.43 ± 1.2; n=4), 1 μM (-39.35 ± 1.2; n=4) and 10 μM (-53.47 ± 0.9; n=4) and **SF0034:** control (-32.65 ± 0.9; n=21), 100 nM (-39.67 ± 0.9; n=4), 1 μM (-56.62 ± 0.5; n=5) and 10 μM (-73.21 ± 2.8; n=5).

Figure 3D. Retigabine: EC_{50} 3.3± 0.8 μM, $\Delta V_{1/2\ max}$ = 41 mV, slope = 0.93, n= 4-11; **SF0034:** EC_{50} 0.60 ± 0.06 μM, $\Delta V_{1/2\ max}$ = 50 mV, slope = 0.92, n= 5-21.

Figure 4A$_3$. NR561_40: Control (-32.82 ± 1.1; n=8), 100 nM (-38.71 ± 0.6; n=4), 1 μM (-60.45 ± 1.5; n=4) and 10 μM (-75.21 ± 1.7; n=4).

Figure 4B$_3$. NR561_50: Control (-27.75 ± 1.5; n=9), 100 nM (-34.91 ± 1.9; n=5), 1 μM (-48.56 ± 2.3; n=5) and 10 μM (-69.71 ± 1.7; n=4).

Figure 4C$_3$. NR579_04: Control (-29.35 ± 2.4; n=9), 100 nM (-31.25 ± 2.3; n=4), 1 μM (-31.77 ± 2.1; n=4) and 10 μM (-35.65 ± 2.1; n=4).

Figure 4D$_3$. NR561_62: Control (-27.99 ± 1.2; n=9), 100 nM (-33.52 ± 1.6; n=5), 1 μM (-43.15 ± 2.3; n=5) and 10 μM (-66.84 ± 2.4; n=4)].

Figure 4A$_4$. NR561_40: EC_{50} 0.91 ± 0.08 μM, $\Delta V_{1/2\ max}$ = 51 mV, slope = 0.83, n= 4-8.

Figure 4B$_4$. NR561_50: EC_{50} 0.74 ± 0.07 μM, $\Delta V_{1/2\ max}$ = 40 mV, slope = 1.1, n= 4-9.

Figure 4C$_4$. NR579_04: EC_{50} NA, $\Delta V_{1/2\ max}$ = NA, slope = NA, n= 4-9.

Figure 4D$_4$. NR561_62: EC_{50} 1.48 ± 0.18 μM, $\Delta V_{1/2\ max}$ = 35 mV, slope = 1.2, n= 4-9.

Figure 5. Retigabine: EC_{50} 3.3 ± 0.8 μM; max $\Delta V_{1/2}$ 33.88 ± 1.46 (n= 4-11), **SF0034:** EC_{50} 0.60 ± 0.06 μM; max $\Delta V_{1/2}$ 50.04 ± 1.56 (n= 5-21), **NR561_40:** EC_{50} 0.91 ± 0.08 μM; max $\Delta V_{1/2}$ 50.90 ± 3.1 (n= 4-8), **NR561_50:** EC_{50} 0.74 ± 0.07 μM; max $\Delta V_{1/2}$ 39.6 ± 1.7 (n= 4-9), **NR561_29:** EC_{50} 0.76 ± 0.17 μM; max $\Delta V_{1/2}$ 27.81 ± 1.72 (n= 4-10), **NR561_45:** EC_{50} 1.34 ± 0.17 μM; max $\Delta V_{1/2}$ 34.1 ± 3.05 (n= 4-9), **NR579_38:** EC_{50} 2.55 ± 0.46 μM; max $\Delta V_{1/2}$ 13.74 ± 3.9 (n= 4-5), **NR579_46:** EC_{50} 3.53 ± 0.84 μM; max $\Delta V_{1/2}$ 46.67 ± 2.67 (n= 4-8), **NR561_87:** EC_{50} 4.03 ± 1.21 μM; max $\Delta V_{1/2}$ 32.78 ± 5.0 (n= 4-7), **NR579_04:** EC_{50} NA ; max $\Delta V_{1/2}$ NA (n= 4-9), **NR561_62:** EC_{50} 1.48 ± 0.18 μM; max $\Delta V_{1/2}$ 34.74 ± 0.74 (n= 4-9), **NR579_45:** EC_{50} 4.49 ± 1.05 μM; max $\Delta V_{1/2}$ 26.91 ± 0.99 (n= 4-5) and **NR579_36:** EC_{50} NA ; max $\Delta V_{1/2}$ NA (n= 4-5).

Figure 6A$_3$. NR561_50: Control (-39.07 ± 1.23; n=5), 100 nM (-38.65 ± 0.85; n=5) and 1 μM (-42.35 ± 1.2; n=4).

Figure 6B$_3$ NR561_50: Control (-48.8 ± 2.96; n=4), 100 nM (-53.52 ± 3.5; n=4) and 1 μM (-59.16 ± 5.0; n=4).

Figure 6C$_3$. NR561_40: Control (-39.38 ± 3.1; n=6), 100 nM (-42.22 ± 2.0; n=6) and 1 μM (-52.04 ± 1.5; n=6).

Figure 6D$_3$. NR561_40: Control (-45.80 ± 2.0; n=4), 100 nM (-66.8 ± 3.1; n=4) and 1 μM (-79.15 ± 2.5; n=4).

Figure 6E$_3$. NR561_29: Control (-45.99 ± 1.4; n=4), 100 nM (-48.50 ± 1.52; n=4) and 1 μM (-64.5 ± 1.2; n=4).

Figure 6F$_3$. NR561_29: Control (-53.37 ± 1.8; n=4), 100 nM (-60.5 ± 2.5; n=4) and 1 μM (-65.2 ± 0.92; n=4).

Figure 8A$_3$. Control (-32.67 ± 1.3; n=5), 100 nM (-50.31 ± 1.44; n=5), 1 μM (-73.9 ± 2.3; n=5) and 10 μM (-90.31 ± 1.29; n=5).

Figure 8A$_4$. RL648_81: EC_{50} 0.19 ± 0.02 μM, $\Delta V_{1/2\ max}$ = 52 mV, slope = 0.74, n= 5; **SF0034:** EC_{50} 0.60 ± 0.06 μM, $\Delta V_{1/2\ max}$ = 50 mV, slope = 0.92, n= 5-21.

Figure 8B$_3$. RL648_81: Control (-50.43 ± 2.69; n=7), 100 nM (-54.43 ± 2.7; n=7), 1 μM (-55.4 ± 2.5; n=4) and 10 μM (-58.1 ± 2.6; n=4)

Figure 8C$_3$. RL648_81: Control (-53.95 ± 4.5; n=5), 100nM (-56.92 ± 3.8; n=5), 1μM (-64.4 ± 3.5; n=5) and 10 μM (-63.4 ± 1.8; n=4).

Figure 8D. SF0034: EC_{50} 0.60 ± 0.06 μM; max $\Delta V_{1/2}$ 50.04 ± 1.56 (n= 5-21), **RL648_81:** EC_{50} 0.19 ± 0.02 μM; max $\Delta V_{1/2}$ 51.12 ± 3.5 (n= 5), **RL648_73:** EC_{50} 0.30 ± 0.05 μM; max $\Delta V_{1/2}$ 47.0 ± 3.9 (n= 4-6), **RL648_86:** EC_{50} 0.34 ± 0.07 μM; max $\Delta V_{1/2}$ 49.9 ± 2.5 (n= 4-5), **NR573_02:** EC_{50} 0.88 ± 0.28 μM; max $\Delta V_{1/2}$ 42.5 ± 4.5 (n= 4-11).

Figure 8E. RL648_73: control (-44.52 ± 2.0; n=4), 100 nM (-43.53 ± 1.1; n=4), 1μM (-48.8 ± 3.0; n=4) and 10 μM (-49.8 ± 1.7; n=3), **RL648_86:** control (-44.51 ± 4.0; n=5), 100 nM (-45.93 ± 4.1; n=4), 1μM (-52.4 ± 3.9; n=4) and 10 μM (-49.7 ± 2.4; n=4) and **RL673_02:** control (-

42.5 ± 2.9; n=4), 100 nM (-41.7 ± 3.0; n=4) and 1μM (-42.8 ± 2.4; n=4) and 10 μM (-55.7 ± 2.5; n=4).

Figure 8F. RL648_73: control (-53.92 ± 4.1; n=4), 100nM (-59.5 ± 2.5; n=4), 1μM (-61.4 ± 2.6; n=4) and 10 μM (-60.4 ± 2.3; n=4), **RL648_86:** control (-54.84 ± 1.5; n=4), 100nM (-55.14 ± 1.4; n=4), 1μM (-58.4 ± 2.5; n=4) and 10 μM (-60.2 ± 2.9; n=3) and **RL673_02:** control (-64.35 ± 3.8; n=4), 100nM (-67.5 ± 5.5; n=4), 1μM (-74.4 ± 4.5; n=4) and 10 μM (-75.2 ± 1.8; n=4)

Figure 9A$_3$. RL648_81: Control (-40.5 ± 2; n=5), 100 nM (-47.7 ± 1.3; n=4), 1 μM (-61.57 ± 1.4; n=4) and 10 μM (-64.9 ± 1.3; n=4).

Figure 9B$_3$. RL648_81: Control (-43.5 ± 0.8; n=4), 100 nM (-43.1 ± 2.5; n=4), 1 μM (-42.75 ± 2.7; n=4) and 10 μM (-41.1 ± 2; n=4).