

Supporting Information

Optimizing Ligand Efficiency of Selective Androgen Receptor Modulators (SARMs).

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Table of Contents

1. Chemistry General Methods	S2
2. Analytical Chemistry Methods.	S2
3. Androgen receptor activation Assay.	S2
4. Pharmacokinetics Studies	S3
5. CLND solubility assay	S3
6. Synthesis of Compounds 5 – 121.	S4

Chemistry General Methods. Reagents were obtained from commercial sources and were used directly. Reactions involving air- or moisture-sensitive reagents were carried out under a nitrogen atmosphere. If not specified, reactions were carried out at ambient temperature. Silica gel was used for chromatographic purification unless otherwise indicated. All final products were tested as racemic mixtures.

Analytical Chemistry Methods. ^1H NMR spectra were recorded on a Bruker or Varian spectrometer operating at 400 MHz; chemical shifts are reported in parts per million (ppm) relative to TMS. LCMS analysis was conducted on a Waters Acquity BEH C18 column (2x50mm, 1.7m) operating at 40 °C. The gradient employed was mobile phase A: Water + 0.20% v/v Formic Acid and mobile phase B: Acetonitrile + 0.15% v/v Formic Acid. UV detection was provided by summed absorbance signal from 210 to 350nm scanning at 40Hz. Mass spectrometry utilized Waters Acquity system operating in alternating positive/negative electrospray mode. Gas chromatography mass specrometry (GCMS) was carried out using an Agilent Technologies 5975 inert GC/mass selective detector system operating in mid-temperature mode (start at 125 °C, heat rate 30 °C/min, 7 min run time) and using a Phenomenex Capillary GC column ZB-5MS (10 m length, 0.1 mm ID, 0.1 mm film thickness). High-resolution mass spectrometry (HRMS) samples were analyzed on an Agilent 6210 qTOF using ESI ionization in negative ion mode with resolving power up to 15,000. Samples were introduced by flow injection using an Agilent 1200 HPLC stack. Data was processed using the Agilent Mass Hunter software B.04.00. All samples have passed accurate mass determination (< or = 5mDa error).

Androgen receptor activation assay.

Plasmids. To generate pAR, a plasmid containing the C-terminus of the human AR gene (a 154 residue N-terminal truncation) was obtained from ATCC. The N-terminal region of the AR gene was cloned by PCR from a human liver cDNA library. These C-terminus and N-terminus pieces were joined together by PCR and subcloned into the pSG5 vector (Stratagene) at the BamHI site along with a Kozak sequence. To generate pMMTV Luciferase, pMSG (Pharmacia) was digested with HindIII, blunt ended, and then digested with XhoI to excise the mouse mammary tumor virus long terminal repeat (MMTV LTR), a glucocorticoid-inducible promoter. The MMTV-LTR fragment was then ligated to the SmaI and XhoI sites of pGL3-Basic (Promega), a luciferase expression vector. The integrity of each construct was confirmed by diagnostic restriction digestion and by sequencing. Plasmid DNA was prepared using Qiagen Maxi-Prep kits.

Cell-based luciferase assay. African Green Monkey kidney cell line CV-1 (ATCC CCL-70) was maintained at 5% CO₂ and 37°C in Dulbecco's Modified Eagle's Medium (D-MEM) containing 10% fetal bovine serum, 2 mM glutamine, and 1% penicillin/streptomycin. In preparation for luciferase assays, CV-1 cells were grown in D-MEM/F-12 medium supplemented with 5% dextran-treated/charcoal-stripped (CS) fetal bovine serum and 2 mM glutamine. CS fetal bovine serum was purchased from Hyclone; all other cell culture reagents were from Invitrogen. CV-1 cells were transiently transfected with FuGENE 6 (Roche) according to the manufacturer's protocol. Briefly, 14 million CV-1 cells (~80% confluence, T-175 cm² flask) were transfected with a 1:3 ratio of DNA mix to FuGENE 6 (25 ug of mix DNA and 75 ul of FuGENE 6). The DNA mix (1.4 ug pAR, 2.5 ug pMMTV Luciferase and 18.75 ug pBluescript filler DNA per T-175 cm²) was incubated with FuGENE 6 in 5 mL OptimEM-1 for 30 min and then diluted up to

Supporting Information

20 mL in transfection media (DMEM/F12 containing 5% CS fetal bovine serum) prior to addition to the cells. After 24h, cells were washed with PBS, detached from the flask using 0.25% trypsin, and then frozen in 90% DMSO/10% CS fetal bovine serum.

Assay-ready frozen cells were thawed and centrifuged to remove the DMSO then diluted in assay media (DMEM containing 5% CS fetal bovine serum, 2mM glutamine, and 25mM HEPES). Approximately 7.5 x 10³ cells were dispensed to each well of white 384-well plates (Nunc catalog #164610) containing compound at the required concentrations. After 24h, 10 μ l of Steady Glo (Promega) was added to each well of the plates. Plates were incubated in the dark for 10 min before reading on a Viewlux (Perkin Elmer). All results were normalized to the mean of 16 high (agonist GSK232420A) and 16 low (DMSO) control wells on each plate. A four parameter curve fit model was then applied.

Pharmacokinetics Studies. All laboratory animal use and care protocols were reviewed and approved by the GSK Institutional Animal Care and Use Committee (IUCUC). All pharmacokinetics studies were conducted using non-fasted male Wistar Han rats (n=2 per treatment group, Charles River Laboratories, Raleigh, NC) containing jugular and femoral vein cannulas. For intravenous pharmacokinetics studies, animals received a single intravenous bolus of test compound (0.5 mg/kg) formulated in 30% Solutol® HS-15 (1 mL/kg) via a femoral cannula. For oral pharmacokinetics studies, animals received a single oral dose of test compound (5 mg/kg) formulated as a solution in 30% Solutol® HS-15 via oral gavage (10 mL/kg). Blood samples were collected via a jugular cannula at 0.083 (IV only), 0.25, 0.5, 1, 2, 4, 8 and 24 hours post-dose. Whole blood was diluted 1:1 in 5%EDTA water solution, briefly vortexed and stored at -80°C until analyzed by liquid chromatography/tandem mass spectrometry (LC-MS/MS) analysis. Non-compartmental pharmacokinetic parameters were calculated based on the individual blood concentration-time data using Phoenix™ WinNonlin® (Certara, Princeton, NJ).

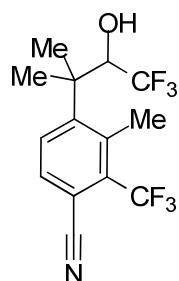
Ex.	Oral bioavailability (rat at 10 mg/Kg)	Oral half-life (h)
9	37%	10
12	70%	83
14	86%	20
25	80%	18
43	83%	8
51	100%	5.5

CLND solubility

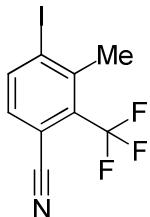
Kinetic aqueous solubility determinations were carried out using chemiluminescent nitrogen detection (CLND). A 5 μ l of 10 mM DMSO stock solution of the test compound was diluted to

100 μ l with pH 7.4 phosphate buffered saline, equilibrated for 1 hour at room temperature, and filtered through Millipore Multiscreen_{HTS}-PCF filter plates (MSSL BPC). The filtrate was quantified by suitably calibrated flow injection CLND.

Synthesis of Compounds 5 – 121.

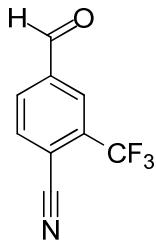


3-methyl-4-(4,4,4-trifluoro-3-hydroxy-2-methylbutan-2-yl)-2-(trifluoromethyl)benzonitrile (5). To a solution of ethyl 2-(4-cyano-2-methyl-3-(trifluoromethyl)phenyl)-2-methylpropanoate (128 mg, 0.428 mmol) in tetrahydrofuran (THF) (4 mL) was added lithium borohydride (0.855 mL, 1.711 mmol) as a 2M solution in THF dropwise. The mixture was heated stirred at 60 °C for 2 h. An additional 1 mL (2 mmol) of the lithium borohydride solution was added and the reaction was stirred at 60 °C for 72 h. The reaction was quenched with water and saturated NH₄Cl. Once bubbling had subsided the reaction mixture was extracted with ethyl acetate twice. The organic extracts were washed with brine and concentrated in vacuo to afford a clear residue. This material was dissolved in dichloromethane (5 mL) and then Dess-Martin periodinane (99 mg, 0.233 mmol) was added in 3 portions over 5 min. The reaction mixture was stirred at RT for 2 h. After completion 5 mL of 1M Na₂SO₃ (aq) was added and the mixture stirred at RT for 30 min. The organic layer was separated and washed with saturated NaHCO₃, water, and brine before drying over Na₂SO₄, filtering and conc. in vacuo to afford a clear oil. The product from the previous step was dissolved in tetrahydrofuran (THF) (2.5 mL). To this solution was added Ruppert's reagent, TMS-CF₃ (0.056 mL, 0.360 mmol) dropwise. Cesium fluoride (54.8 mg, 0.360 mmol) was added in one portion. After stirring for 30 min tetrabutylammonium fluoride, TBAF (0.180 mL, 0.180 mmol) as a solution in THF (1M) was added dropwise and the mixture was stirred for 10 min. The reaction was quenched with satd NH₄Cl and then extracted with ethyl acetate twice. The organic extracts were concentrated in vacuo and the product was purified through a short plug of silica gel to afford a clear oil that solidified upon standing to give the title product, 23.2 mg, 0.071 mmol, 17% yield). LCMS AUC at 240 nm showed 95% purity. ESIMS (M+H) = 326. HRMS calcd for C₁₆H₁₃O₃NF₉ (M-H+TFA) 438.07462. Found 438.07532. Loss of H and the formation of trifluoroacetic acid adduct occurred during ionization in the high resolution mass spectrometer. ¹H NMR (400 MHz, DMSO-d₆) δ 7.81-7.97 (m, 2H), 6.61 (d, *J*=7.22 Hz, 1H), 4.48-4.64 (m, 1H), 2.63 (d, *J*=2.34 Hz, 3H), 1.51 (d, *J*=7.80 Hz, 6H).



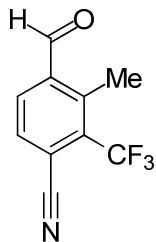
4-iodo-3-methyl-2-(trifluoromethyl)benzonitrile (110b).

The title compound was prepared from 4-amino-3-methyl-2-(trifluoromethyl)benzonitrile in 87% yield using the procedure outlined in J. A. Van Camp et al. / Bioorg. Med. Chem. Lett. 17 (2007) 5529–5532. ¹H NMR (400 MHz, CDCl₃) δ 8.21 (d, *J*=8.03 Hz, 1H), 7.35 (d, *J*=8.28 Hz, 1H), 2.70 (d, *J*=1.76 Hz, 3H).



4-formyl-2-(trifluoromethyl)benzonitrile (111a).

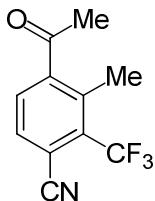
To a solution of 4-iodo-2-(trifluoromethyl)benzonitrile (594 mg, 2 mmol, Sigma Aldrich, Inc.) in tetrahydrofuran (THF) (8 mL) at 0 °C is added dropwise isopropylmagnesium chloride lithium chloride (1.846 mL, 2.400 mmol) 1.3 M solution in THF. The reaction mixture was stirred for 45 min at 0 °C. To the reaction mixture at 0 °C was added piperidine-1-carbaldehyde (0.267 mL, 2.400 mmol). The mixture was stirred at 0 °C for 90 min. TLC showed that starting material was consumed. The reaction was quenched by addition of NH₄Cl solution (10 ml). Then MTBE (20 ml) was added and the solution transferred to separatory funnel. The organic layer was washed with brine and the aqueous layer was extracted twice with MTBE. The product was purified via silica gel column. The product eluted at 25% EtOAc / hexane. The desired product was isolated as a white crystalline solid (needles) 4-formyl-2-(trifluoromethyl)benzonitrile (145 mg, 0.728 mmol, 36.4 % yield ESIMS (M+45) = 244 (negative ion mode). ¹H NMR (400 MHz, CDCl₃) δ 10.17 (s, 1H), 8.33 (s, 1H), 8.18-8.27 (m, 1H), 8.09 (d, *J*=7.78 Hz, 1H).



4-formyl-3-methyl-2-(trifluoromethyl)benzonitrile (111d).

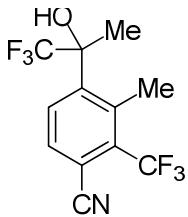
Supporting Information

The title compound was prepared from **110b** using the procedure outlined for **111a**. ESIMS (M-H) = 212. ¹H NMR (400 MHz, CDCl₃) δ 10.47 (s, 1H), 8.09 (d, *J*=8.06 Hz, 1H), 7.85 (d, *J*=7.92 Hz, 1H), 2.85 (s, 4H).



4-acetyl-3-methyl-2-(trifluoromethyl)benzonitrile (87).

To a solution of 4-iodo-3-methyl-2-(trifluoromethyl)benzonitrile **110b**, (0.875 g, 2.81 mmol) in DMF (23 mL) was added acetic anhydride (1.50 g, 14.69 mmol) followed by lithium chloride (0.69, 16.28 mmol) and Hunig's base (1.20 g, 9.28 mmol). The resulting solution was then purged with a heavy bubbling stream of nitrogen for 2 min. The catalyst Pd₂(dba)₃ (0.074 g, 0.081 mmol) was added followed by another nitrogen purge cycle. The reaction vessel was capped and then heated to 100 °C. Heating afforded a pale yellow homogeneous solution. The reaction's color changed to dark yellow with time. LCMS and TLC after 6 h showed some conversion to the desired product, but a significant amount of starting material remaining. The reaction was boosted with 74 mgs more catalyst and heating was continued overnight. LCMS and TLC after 26 h of heating showed no remaining starting material. The reaction was diluted with EtOAc and water and extracted. The combined organic portions were dried over Na₂SO₄ and then concentrated to a brown oil. This oil was purified by column chromatography (ISCO 80 g silica, 0-60% hexane/EtOAc) to afford the desired product in excellent purity as a brown oil (274 mg, 1.21 mmol, 43% yield). ¹H NMR (400 MHz, DMSO-d₆) δ 8.06 (d, *J*=8.01 Hz, 1H), 8.00 (d, *J*=8.01 Hz, 1H), 2.57 (s, 3H), 2.39 (d, *J*=2.35 Hz, 3H).

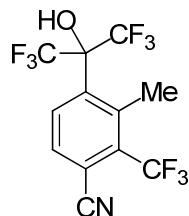


3-methyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)-2-(trifluoromethyl)benzonitrile (6).

To a solution of **87**, 4-acetyl-3-methyl-2-(trifluoromethyl)benzonitrile (0.174 mmol) in THF (3 ml) was added cesium fluoride (29.1 mg, 0.192 mmol). The suspension was sonicated briefly to dissolve the CsF. The mixture was cooled to 0 °C. Ruppert's reagent, trimethyl(trifluoromethyl)silane, (0.103 mL, 0.696 mmol) was added. The reaction was stirred 30 min at 0 °C and then 30 min at RT. TBAF (1 M in THF, 0.192 ml, 0.192 mmol) was added and the mixture stirred for 15 min. Workup: The reaction mixture was diluted with EtOAc (10 ml) and transferred to a separatory funnel. The solution was washed with brine 3X. The

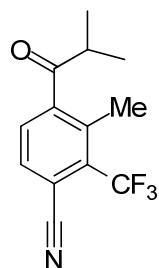
Supporting Information

organic layer was dried over Na_2SO_4 and concentrated. The product was purified on an Isco normal-phase silica gel column (12 g). Gradient was hexane to 100 % DCM. The product eluted at 45% DCM/hexane. The product was isolated as a white solid, (41 mg, 0.138 mmol, 79 % yield). LCMS AUC showed 98% purity and ESIMS ($\text{M}-\text{H}$) = 296 and ($\text{M}+\text{formate}$) = 342. HRMS calcd for $\text{C}_{12}\text{H}_9\text{F}_6\text{NO}$ ($\text{M}-\text{H}$) 296.0508, found 296.0499. ^1H NMR (400 MHz, DMSO-d_6) δ 7.94 (s, 2H), 7.03 (s, 1H), 2.69 (d, $J=2.15$ Hz, 3H), 1.81 (s, 3H).



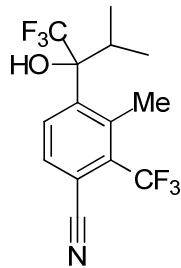
4-(1,1,1,3,3-hexafluoro-2-hydroxypropan-2-yl)-3-methyl-2-(trifluoromethyl)benzonitrile (7).

The title compound was prepared from methyl 4-cyano-2-methyl-3-(trifluoromethyl)benzoate via intermediate trifluoromethyl ketone **88** using the procedure outlined for **6**. LCMS AUC showed 97% purity and ESIMS ($\text{M}-\text{H}$) = 350. HRMS calcd for $\text{C}_{12}\text{H}_6\text{F}_9\text{NO}$ ($\text{M}-\text{H}$) 350.0226, found 350.0265. ^1H NMR (400 MHz, DMSO-d_6) δ 9.33 (s, 1H), 8.07 (d, $J=8.60$ Hz, 1H), 7.97 (br. s., 1H), 2.73 (br. s., 3H).



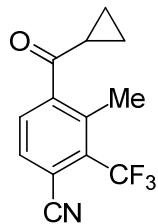
4-isobutyryl-3-methyl-2-(trifluoromethyl)benzonitrile (89).

The title compound was prepared from **110b** and isobutyraldehyde using the procedure for **59**. ^1H NMR (400 MHz, CDCl_3) δ 7.76 (d, $J=8.03$ Hz, 1H), 7.54 (d, $J=8.03$ Hz, 1H), 3.15 (td, $J=6.84, 13.93$ Hz, 1H), 2.46 (q, $J=2.01$ Hz, 3H), 1.21 (d, $J=7.03$ Hz, 6H).



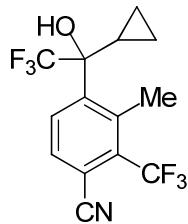
3-methyl-4-(1,1,1-trifluoro-2-hydroxy-3-methylbutan-2-yl)-2-(trifluoromethyl)benzonitrile (8).

Following the procedure for **6**, ketone **89** was converted to the title product in 77% yield. LCMS AUC showed 97% purity. ESIMS (M-H) = 324. HRMS calcd for C₁₄H₁₃F₆NO (M-H) 324.0821, found 324.0839. ¹H NMR (400 MHz, METHANOL-d₄) δ 8.03 (br. s., 1H), 7.82 (d, J=8.53 Hz, 1H), 2.78 (br. s., 4H), 1.07-1.26 (m, 3H), 0.80 (d, J=6.78 Hz, 3H).



4-(cyclopropanecarbonyl)-3-methyl-2-(trifluoromethyl)benzonitrile (90).

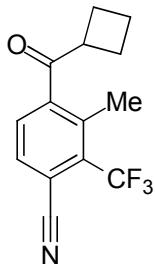
The title compound was prepared from **111d** 4-formyl-3-methyl-2-(trifluoromethyl)benzonitrile and cyclopropylmagnesium iodide according to the procedure for **58**. ¹H NMR (400 MHz, DMSO-d₆) δ 8.08 (d, J=8.01 Hz, 1H), 7.92 (d, J=8.01 Hz, 1H), 2.39-2.47 (m, 4H), 1.08-1.22 (m, 4H).



4-(1-cyclopropyl-2,2,2-trifluoro-1-hydroxyethyl)-3-methyl-2-(trifluoromethyl)benzonitrile (9).

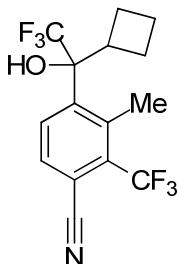
Following the procedure for **6**, ketone **90** was converted to the title product in 65% yield. LCMS AUC showed 100% purity. ESIMS (M-H) = 322. HRMS calcd for C₁₄H₁₁F₆NO (M-H) 322.0665, found 322.0674. ¹H NMR (400 MHz, DMSO-d₆) δ 8.23 (d, J=8.40 Hz, 1H), 7.96 (d,

J=8.40 Hz, 1H), 6.43 (s, 1H), 2.62-2.83 (m, 3H), 1.75-1.92 (m, 1H), 0.82 (qd, *J*=4.98, 9.67 Hz, 1H), 0.54-0.68 (m, 1H), 0.41-0.54 (m, 1H), 0.15-0.30 (m, 1H).



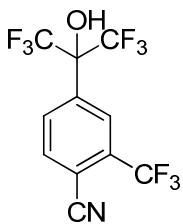
4-(cyclobutanecarbonyl)-3-methyl-2-(trifluoromethyl)benzonitrile (91).

The title compound was prepared from **110b** and cyclobutanecarbaldehyde using the procedure for **59**. ¹H NMR (400 MHz, CDCl₃) δ 7.75 (d, *J*=8.03 Hz, 1H), 7.54 (d, *J*=8.03 Hz, 1H), 3.78 (dquin, *J*=1.00, 8.47 Hz, 1H), 2.52 (q, *J*=2.18 Hz, 3H), 2.34-2.49 (m, 2H), 2.18-2.34 (m, 2H), 2.03-2.18 (m, 1H), 1.88-2.02 (m, 1H).



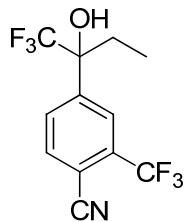
4-(1-cyclobutyl-2,2,2-trifluoro-1-hydroxyethyl)-3-methyl-2-(trifluoromethyl)benzonitrile (10).

Following the procedure for **6**, ketone **91** was converted to the title product in 73% yield. LCMS AUC showed 100% purity. ESIMS (M-H) = 336. HRMS calcd for C₁₅H₁₃F₆NO (M-H) 336.0821, found 336.0844. ¹H NMR (400 MHz, CDCl₃) δ 7.63-7.83 (m, 1H), 7.57 (d, *J*=14.31 Hz, 1H), 3.54 (br. s., 1H), 2.82 (br. s., 4H), 2.09-2.26 (m, 2H), 1.89-2.09 (m, 1H), 1.64-1.89 (m, 3H).



4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-(trifluoromethyl)benzonitrile (11).

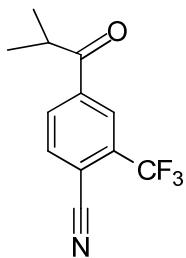
Methyl 4-cyano-3-(trifluoromethyl)benzoate (99 mg, 0.432 mmol) was dissolved in toluene (4 mL) and treated with Ruppert's reagent, trimethyl(trifluoromethyl)silane (92 mg, 96 μ L, 0.648 mmol). The mixture was cooled in an ice bath and tetrabutylammonium acetate (6.5 mg, 0.022 mmol) was added. The reaction was allowed to warm to ambient temperature. LCMS after 2.0 h showed good consumption of the starting material and conversion to a single nonpolar product. THF (2 mL) was added followed by 2 mL of 1N HCl. LCMS after stirring overnight showed the same profile as before. The reaction was diluted with EtOAc and water and extracted. The combined organic portions were dried over Na_2SO_4 , and then concentrated to a yellow oil. The trifluoromethyl ketone (**55**) from the preceding step was dissolved in THF (2 mL) and then treated with Ruppert's reagent, CF_3SiMe_3 (96 μ L, 0.648 mmol). The mixture was then cooled to 0° C and treated with CsF (32.8 mg, 0.216 mmol). The icebath was removed and the mixture was left to warm to ambient temperature. The mixture was stirred for 2.0 h. TLC confirmed that no starting material remained and conversion to a more polar product. The reaction was next treated with 1 equiv of TBAF (1 M, 0.216 mL, 0.216 mmol). After 20 min, the reaction was quenched with water. The mixture was extracted three times with ethyl acetate. The combined organic portions were dried over Na_2SO_4 and then concentrated to a light brown oil that was purified by chromatography (ISCO, 24 g silica, hex/EtOAc, 0-50%, monitor at 230 and 254 nm) to afford the desired product in excellent purity as a very pale yellow solid, 4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-(trifluoromethyl)benzonitrile, 49.9 mg, 0.141, 65.1 % yield). LCMS AUC showed 95% purity. ESIMS (M-H) = 336. HRMS calcd for $\text{C}_{11}\text{H}_4\text{F}_9\text{NO}$ (M-H) 336.0069, found 336.011. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.13 (s, 1 H) 8.18 (d, J =8.21 Hz, 1 H) 8.37 (d, J =8.40 Hz, 1 H) 9.61 (s, 1 H).



4-(1,1,1-trifluoro-2-hydroxybutan-2-yl)-2-(trifluoromethyl)benzonitrile (12).

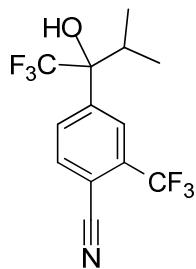
4-Formyl-2-(trifluoromethyl)benzonitrile, **111a**, was treated with ethylmagnesium bromide to give 4-(1-hydroxypropyl)-2-(trifluoromethyl)benzonitrile (22 mg, 0.096 mmol). This material was dissolved in CH_2Cl_2 (1 mL) and the resulting homogeneous solution was then treated with PCC (62 mg, 0.288 mmol). TLC after 3 h showed very little starting material remaining and good conversion to a less polar product. After another 2 h, the reaction was filtered through celite and the brown solid was rinsed with EtOAc. The filtrate was concentrated to a solid and chromatographed (ISCO, 12 g SiO_2 , monitored at 230/254 nm, hexane/EtOAc, 0 to 50%) to afford the intermediate ethyl ketone (**56**) as a white solid. The material from the preceding step was dissolved in THF (4 mL) and then treated with CsF (14.6 mg, 0.096 mmol). The resulting heterogeneous solution was then cooled to 0° C and treated with CF_3SiMe_3 (41 mg, 0.288 mmol). The icebath was removed and the mixture was left to warm to ambient temperature. After 1.0 h LCMS showed that no starting material remained and was converted to a non-polar product. The

reaction was treated with 1 equiv of TBAF (1M in THF, 0.096 mmol). LCMS after ca. 10 min showed conversion to the desired product. After another 10 min the reaction was quenched with saturated aqueous NH₄Cl and then extracted with EtOAc. The combined organic portions were dried over Na₂SO₄. The drying agent was filtered away and concentrated affording an offwhite solid that was purified by chromatography (ISCO, 12 g silica, hex/EtOAc, 0-30%, monitor at 230 and 254 nm) to afford the desired product in excellent purity as a very pale yellow solid (21.5 mg, 0.072 mmol 75% yield). LCMS AUC showed 100% purity. ESIMS (M-H) = 296. HRMS calcd for C₁₂H₉F₆NO (M-H) 296.0508, found 296.051. ¹H NMR (400 MHz, DMSO-d₆) δ 8.24 (d, *J*=8.01 Hz, 1H), 8.00-8.15 (m, 2H), 7.04 (s, 1H), 2.24-2.41 (m, 1H), 2.04 (dd, *J*=7.23, 14.27 Hz, 1H), 0.63 (t, *J*=7.33 Hz, 3H).



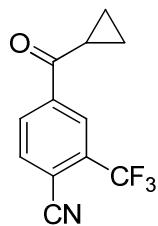
4-isobutyl-2-(trifluoromethyl)benzonitrile (57).

To a solution of **111a**, 4-formyl-2-(trifluoromethyl)benzonitrile (145 mg, 0.728 mmol) in tetrahydrofuran (THF) (4 mL) at 0 °C was added dropwise isopropylmagnesium chloride (0.546 mL, 1.092 mmol) 2.0 M solution in THF. The reaction mixture was stirred for 30 minutes, The ice bath was removed and the mixture was allowed to stir at RT 2h. LCMS showed that starting material was consumed and a new peak for product (M + 45 at 288 in negative ion scan) was formed. To the reaction mixture was added NH₄Cl (2 ml) to quench. The solution was transferred to a separatory funnel and extracted with MTBE (10 ml) 3X. The organics were dried over Na₂SO₄, filtered and concentrated. The residue was dissolved in Dichloromethane (DCM) (4.00 mL). Dess-Martin periodinane (309 mg, 0.728 mmol) was added at RT. The reaction mixture was stirred at RT one hour. Workup: Saturated aqueous NaHCO₃ (10 ml) was added to the mixture and stirring was continued for 15 minutes. The biphasic mixture was separated and the aqueous layer was extracted 3X with CH₂Cl₂. The combined organic layers were washed with brine, dried over Na₂SO₄ and filtered. The product was purified on an Isco silica gel column (24 g). The product eluted at 15% EtOAc / hexane. The fractions were concentrated to give 4-isobutyl-2-(trifluoromethyl)benzonitrile (46 mg, 0.191 mmol, 26.2 % yield). GCMS showed 100% purity and strong molecular ion at 241. ¹H NMR (400 MHz, CDCl₃) Shift 8.35 (s, 1H), 8.17-8.29 (m, 1H), 8.00 (d, *J*=8.03 Hz, 1H), 3.55 (td, *J*=6.87, 13.62 Hz, 1H), 1.28 (d, *J*=6.78 Hz, 6H).



4-(1,1,1-trifluoro-2-hydroxy-3-methylbutan-2-yl)-2-(trifluoromethyl)benzonitrile (13).

To a solution of **57**, 4-isobutryl-2-(trifluoromethyl)benzonitrile, (42 mg, 0.174 mmol) in THF (3 ml) was added cesium fluoride (29.1 mg, 0.192 mmol). The suspension was sonicated briefly to dissolve the CsF. The mixture was cooled to 0 °C. Ruppert's reagent, trimethyl(trifluoromethyl)silane, (0.103 mL, 0.696 mmol) was added. The reaction was stirred 30 min at 0 °C and then 30 min at RT. TBAF (1 M in THF, 0.192 mL, 0.192 mmol) was added and the mixture stirred for 15 min. Workup: The reaction mixture was diluted with EtOAc (10 mL) and transferred to a separatory funnel. The solution was washed with brine 3X. The organic layer was dried over Na₂SO₄ and concentrated. The product was purified on an Isco normal-phase silica gel column (12 g). Gradient was hexane to 100 % DCM. The product eluted at 45% DCM/hexane. The product was isolated as a white solid, 4-(1,1,1-trifluoro-2-hydroxy-3-methylbutan-2-yl)-2-(trifluoromethyl)benzonitrile (43 mg, 0.138 mmol, 79 % yield). LCMS AUC showed 100% purity. ESIMS (M-H) = 310 and (M+formate) = 356. HRMS calcd for C₁₃H₁₁F₆NO (M-H) 310.0665, found 310.0683. ¹H NMR (400 MHz, CDCl₃) δ 8.05 (s, 1H), 7.90 (s, 2H), 2.70 (s, 1H), 2.56 (td, *J*=6.81, 13.74 Hz, 1H), 1.19 (dd, *J*=1.51, 6.78 Hz, 3H), 0.72 (d, *J*=6.78 Hz, 3H).

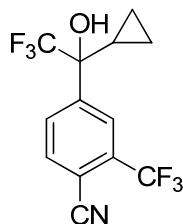


4-(cyclopropanecarbonyl)-2-(trifluoromethyl)benzonitrile (58).

4-formyl-2-(trifluoromethyl)benzonitrile **111a** (226 mg, 1.135 mmol) was dissolved in THF (8 mL) and the resulting homogeneous solution was cooled to -5°C. The cyclopropylmagnesium iodide (0.5 M in THF, 340 μ L, 1.70 mmol) was added slowly causing the reaction mixture to turn pale yellow. TLC after 5 min showed conversion to a more polar product and some starting material remaining. The reaction was quenched with sat aq NH₄Cl and left to warm to ambient temperature. The mixture was diluted with EtOAc and water and then extracted with EtOAc. The combined organic portions were dried over Na₂SO₄ and then concentrated. Column chromatography (ISCO, 40 g silica, 254 and 230 nm detection, 0-60% hex/EtOAc) afforded the intermediate carbinol as a light brown solid. The material from the preceding step was dissolved in CH₂Cl₂ (8 mL) and then treated with the PCC (0.402 g, 1.866 mmol) and silica gel (0.5 g). TLC after 3 h showed conversion to a less polar product. The reaction mixture was filtered

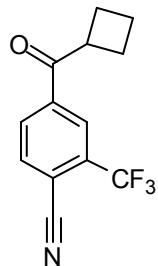
Supporting Information

through celite and the resulting yellow filtrate was concentrated to a yellow solid. This solid was then partially dissolved in a mixture of CH_2Cl_2 and EtOAc and chromatographed (ISCO, 40 g silica to afford the desired product as a pale yellow oil in excellent purity (65 mg, 24% yield). ^1H NMR (400 MHz, DMSO-d_6) δ 8.51 (d, $J=8.01$ Hz, 1H), 8.29-8.45 (m, 2H), 2.95-3.10 (m, 1H), 1.03-1.26 (m, 4H).



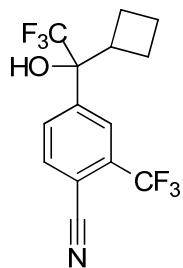
4-(1-cyclopropyl-2,2,2-trifluoro-1-hydroxyethyl)-2-(trifluoromethyl)benzonitrile (14).

4-(cyclopropanecarbonyl)-2-(trifluoromethyl)benzonitrile **58** (65 mg, 0.272 mmol) was dissolved in THF (4 mL) and then treated with CsF (41.3 mg, 0.272 mmol). The resulting suspension was sonicated for 60 s to solvate the CsF. The resulting heterogeneous solution was then cooled to 0° C and treated with Ruppert's reagent, CF_3SiMe_3 (0.120 ml, 0.815 mmol). The icebath was removed and the mixture was left to warm to ambient temperature. After 0.5 h TLC confirmed that no sm remained and was converted to a less polar product. The reaction was treated with 1 equiv of TBAF (1 M in THF, 0.272 mmol). LCMS after 10 min showed very clean conversion to the desired product. After another 10 min, the reaction was quenched with saturated aqueous NH_4Cl and then extracted with EtOAc. The combined organic portions were dried over Na_2SO_4 and then concentrated to a light brown oil that was purified by chromatography (ISCO, 24 g silica, hex/EtOAc, 0-60%, monitor at 230 and 254 nm) to afford the desired product in excellent purity as a gummy pale yellow solid. Recrystallization from hex/ CH_2Cl_2 afforded the desired product as a white solid in excellent purity (83.4 mg, 0.270 mmol, 99% yield). LCMS AUC showed 100% purity. ESIMS (M-H) = 308. HRMS calcd for $\text{C}_{13}\text{H}_9\text{F}_6\text{NO}$ (M-H) 308.0508, found 308.0508. ^1H NMR (400 MHz, DMSO-d_6) δ 8.22-8.32 (m, 1H), 8.07-8.22 (m, 2H), 6.69 (s, 1H), 1.73-1.90 (m, 1H), 0.74-0.92 (m, 1H), 0.51-0.63 (m, 1H), 0.30-0.43 (m, 1H), 0.12-0.30 (m, 1H)



4-(cyclobutanecarbonyl)-2-(trifluoromethyl)benzonitrile (59)

To a solution of 4-iodo-2-(trifluoromethyl)benzonitrile **110A** (297 mg, 1 mmol, Sigma Aldrich, Inc.) in Tetrahydrofuran (THF) (7 mL) at -78 °C was added dropwise n-butyllithium 2.5 M in hexane (0.520 mL, 1.300 mmol). The solution was stirred for 10 minutes. To the reaction mixture at -78 °C was added cyclobutanecarbaldehyde (118 mg, 1.400 mmol) dissolved in 1 mL THF. The dry ice was allowed to evaporate and the mixture was stirred overnight at RT. TLC showed that starting material was consumed and single new spot appeared with lower R_f. LCMS showed single peak for carbinol intermediate (MW = 255) with MH⁺ at 256 and strong M+formate at 300. The reaction was quenched by addition of NH₄Cl solution (5 mL). MTBE (10 mL) was added and the reaction mixture was transferred to a separatory funnel. The organic layer was washed with brine. The aqueous layer was extracted twice with MTBE. The organics were dried over Na₂SO₄ and concentrated. Carry on to oxidation step. The residue from the previous step was dissolved in dichloromethane (DCM) (7.00 mL). Dess-Martin periodinane (467 mg, 1.100 mmol) was added and the reaction was stirred at RT 30 min. Workup: Saturated aqueous NaHCO₃ was added to the mixture and stirring was continued for 15 minutes. The biphasic mixture was separated and the aqueous layer was extracted 3X with CH₂Cl₂. The combined organic layers were washed with brine, dried over Na₂SO₄ and filtered. The product was purified on an Isco silica gel column (24 g). The product eluted at 15% EtOAc / hexane. The fractions were concentrated to give a pale yellow solid, 4-(cyclobutanecarbonyl)-2-(trifluoromethyl)benzonitrile (180 mg, 0.711 mmol, 71.1 % yield). LCMS AUC showed 96% purity and MH⁺ at 254 and M-H at 252. ¹H NMR (400 MHz, CDCl₃) Shift 8.29 (s, 1H), 8.09-8.23 (m, 1H), 7.97 (d, J=8.03 Hz, 1H), 3.93-4.11 (m, 1H), 2.27-2.54 (m, 4H), 2.07-2.27 (m, 1H), 1.83-2.06 (m, 1H).

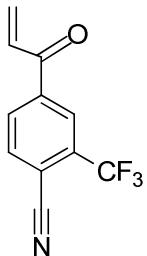


4-(1-cyclobutyl-2,2,2-trifluoro-1-hydroxyethyl)-2-(trifluoromethyl)benzonitrile (15).

To a solution of 4-(cyclobutanecarbonyl)-2-(trifluoromethyl)benzonitrile **59** (180 mg, 0.711 mmol) in tetrahydrofuran (THF) (8 mL) was added CsF (119 mg, 0.782 mmol). The suspension was sonicated briefly to dissolve the CsF. The suspension was cooled to 0 °C. Ruppert's reagent, trimethyl(trifluoromethyl)silane (0.420 mL, 2.84 mmol) was added. The solution was stirred 2 min at 0 °C and then 5 min at RT. TBAF solution (1 M, 0.78 mmol) was added to the solution stirred 10 min at RT. Workup: The reaction mixture was diluted with EtOAc and transferred to separatory funnel. The solution was washed with brine 3 times. The organic layer was dried over Na₂SO₄ and concentrated. The product was purified with a silica gel normal-phase column (12 g). Gradient was hexane to 80 % DCM/hexane. Desired product eluted at 70% DCM/hexane. Isolate product as an off-white solid, 4-(1-cyclobutyl-2,2,2-trifluoro-1-hydroxyethyl)-2-(trifluoromethyl)benzonitrile (168 mg, 0.520 mmol, 73.1 % yield) ESIMS (M-H) = 322. LCMS AUC showed 100% purity. HRMS calcd for C₁₄H₁₁F₆NO (M-H) 322.0665,

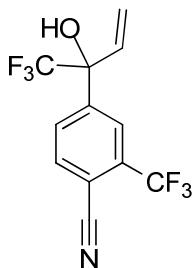
Supporting Information

found 322.068. ^1H NMR (400 MHz, CDCl_3) δ 8.04 (s, 1H), 7.89 (s, 2H), 3.30 (t, $J=8.53$ Hz, 1H), 2.91 (s, 1H), 2.10-2.25 (m, 2H), 1.89-2.02 (m, 1H), 1.72-1.86 (m, 2H), 1.45-1.60 (m, 1H).



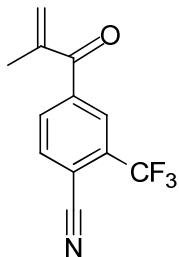
4-acryloyl-2-(trifluoromethyl)benzonitrile (61).

Following the procedure for **58** 4-formyl-2-(trifluoromethyl)benzonitrile **111a** was reacted with vinylmagnesium chloride to give 4-acryloyl-2-(trifluoromethyl)benzonitrile (98 mg, 0.435 mmol, 57.0 % yield). GCMS showed 100% purity and strong molecular ion at 225. ^1H NMR (400 MHz, CDCl_3) Shift 8.33 (s, 1H), 8.22 (d, $J=8.03$ Hz, 1H), 8.01 (d, $J=8.03$ Hz, 1H), 7.14 (dd, $J=10.67, 17.19$ Hz, 1H), 6.54 (dd, $J=1.13, 17.19$ Hz, 1H), 6.14 (dd, $J=1.00, 10.54$ Hz, 1H).



4-(1,1,1-trifluoro-2-hydroxybut-3-en-2-yl)-2-(trifluoromethyl)benzonitrile (16).

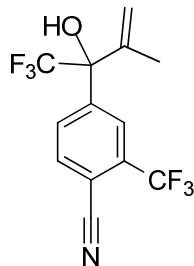
Using the procedure for **13**, ketone **61** was converted to 4-(1,1,1-trifluoro-2-hydroxybut-3-en-2-yl)-2-(trifluoromethyl)benzonitrile (63 mg, 0.213 mmol, 49.0 % yield). LCMS AUC showed 100% purity; ESIMS ($\text{M}-\text{H}$) = 294. HRMS calcd for $\text{C}_{12}\text{H}_7\text{F}_6\text{NO}$ ($\text{M}-\text{H}$) 294.0352, found 294.0372. ^1H NMR (400 MHz, CDCl_3) δ 8.07 (s, 1H), 7.83-7.98 (m, 2H), 6.45 (dd, $J=10.92, 17.19$ Hz, 1H), 5.56-5.76 (m, 2H), 2.92 (s, 1H).



4-methacryloyl-2-(trifluoromethyl)benzonitrile (60).

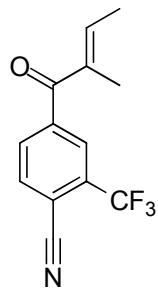
Supporting Information

Following the procedure for **58**, 4-formyl-2-(trifluoromethyl)benzonitrile **111a** was reacted with prop-1-en-2-ylmagnesium chloride to give 4-methacryloyl-2-(trifluoromethyl)benzonitrile (78 mg, 0.326 mmol, 50.0 % yield). GCMS showed 100% purity and strong molecular ion at 239. NMR N28696-96-1 showed clean product: olefin protons clearly seen at 6.09 and 5.62 ppm. Also isolated N28696-96-2 (aldehyde). ¹H NMR (400 MHz, CDCl₃) Shift 8.10 (s, 1H), 7.88-8.03 (m, 2H), 6.12 (d, J=1.51 Hz, 1H), 5.65 (s, 1H), 2.12 (s, 3H).



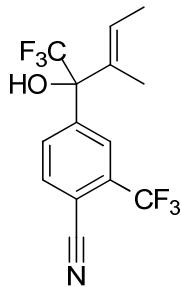
4-(1,1,1-trifluoro-2-hydroxy-3-methylbut-3-en-2-yl)-2-(trifluoromethyl)benzonitrile (17).

Using the procedure for **13**, ketone **60** was converted to 4-(1,1,1-trifluoro-2-hydroxy-3-methylbut-3-en-2-yl)-2-(trifluoromethyl)benzonitrile (81 mg, 0.262 mmol, 80 % yield). LCMS AUC showed 100% purity; ESIMS (M-H) = 308. HRMS calcd for C₁₃H₉F₆NO (M-H) 308.0508, found 308.0534. ¹H NMR (400 MHz, CDCl₃) δ 8.06 (s, 1H), 7.91 (s, 2H), 5.45-5.60 (m, 1H), 5.65 (s, 1H), 2.22 (s, 3H).



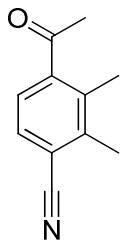
(E)-4-(2-methylbut-2-enoyl)-2-(trifluoromethyl)benzonitrile (62).

Using the procedure for **59**, 4-iodo-2-(trifluoromethyl)benzonitrile **110a** (216 mg, 0.727 mmol) was converted to (E)-4-(2-methylbut-2-enoyl)-2-(trifluoromethyl)benzonitrile (131 mg, 0.517 mmol, 71.1 % yield) . LCMS AUC showed 100% purity; ESIMS (M-H) = 254. ¹H NMR (400 MHz, CDCl₃) δ 7.98 (s, 1H), 7.92 (d, J=8.03 Hz, 1H), 7.80-7.89 (m, 1H), 6.39 (dd, J=1.25, 6.78 Hz, 1H), 1.98-2.07 (m, 3H), 1.96 (dd, J=1.00, 6.78 Hz, 3H).



(E)-4-(1,1,1-trifluoro-2-hydroxy-3-methylpent-3-en-2-yl)-2-(trifluoromethyl)benzonitrile (18).

Using the procedure for **13**, ketone **62**, (E)-4-(2-methylbut-2-enoyl)-2-(trifluoromethyl)benzonitrile (131 mg, 0.517 mmol), was converted to (E)-4-(1,1,1-trifluoro-2-hydroxy-3-methylpent-3-en-2-yl)-2-(trifluoromethyl)benzonitrile (114 mg, 0.353 mmol, 68.2 % yield) LCMS AUC showed 98% purity; ESIMS (M-H) = 322. HRMS calcd for C₁₄H₁₁F₆NO (M-H) 322.0665, found 322.0688. ¹H NMR (400 MHz, CDCl₃) Shift 8.02 (s, 1H), 7.87 (s, 2H), 5.98-6.15 (m, 1H), 2.75 (s, 1H), 1.78 (dd, J=0.88, 6.65 Hz, 3H), 1.52 (s, 3H).

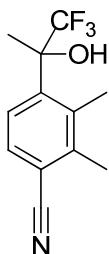


4-acetyl-2,3-dimethylbenzonitrile (63).

To a solution of 1-(4-methoxy-2,3-dimethylphenyl)ethanone (2.0 g, 11.22 mmol) in DCM (20 ml) at -78 °C was added via dropping funnel BBr₃ (28.1 ml, 28.1 mmol) slowly. The reaction mixture was allowed to slowly warm to RT and stirred overnight. The reaction mixture was added slowly to an ice slurry of NaHCO₃ aqueous solution. The mixture was stirred for 30 min and then extracted 3x with MTBE. The organic layer was separated and dried over Na₂SO₄ and concentrate to give a tan solid. The phenol intermediate was dissolved in DCM (25 ml). To the solution was added triethylamine (1.877 ml, 13.47 mmol). Dropwise trifluoromethanesulfonic anhydride (2.085 ml, 12.34 mmol) was added. The reaction was stirred at RT for 1 hour. The reaction mixture was concentrated by rotary evaporation and the intermediate triflate was purified by column chromatography: silica gel 40 gram column. The triflate eluted at 15% EtOAc / hexane. The triflate intermediate was dissolved in DMF (14 ml) in a sealed tube. To the DMF solution was added Zinc Cyanide (0.206 g, 1.755 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.390 g, 0.338 mmol). The suspension was purged with nitrogen under stirring for 5 minutes. The tube was sealed and placed in a heat block at 110 °C for 90 min. Workup: The reaction mixture was partitioned between brine and MTBE and the organic layer was washed twice with brine. The aqueous washes were extracted twice with MTBE. The organics were dried over Na₂SO₄ and filtered. The product was purified on a silica gel column (24 g). The desired product eluted at 45% EtOAc / hexane giving a pale yellow crystalline solid, 4-acetyl-2,3-dimethylbenzonitrile (0.528 g, 3.05 mmol, 27 % yield).

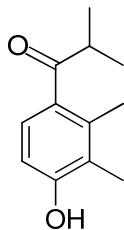
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LCMS AUC showed 95% purity and weak MH^+ for product at 174. GCMS showed high purity and strong molecular ion peak at 173. ^1H NMR (400 MHz, CDCl_3) δ 7.55 (d, $J=8.03$ Hz, 1H), 7.39 (d, $J=8.03$ Hz, 1H), 2.56 (s, 3H), 2.59 (s, 3H), 2.37 (s, 3H).



2,3-dimethyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzonitrile (19).

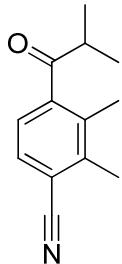
The 4-acetyl-2,3-dimethylbenzonitrile **63** (57 mg, 0.329 mmol) was converted to the title product using the procedure for **13** affording a white crystalline solid, 2,3-dimethyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzonitrile (66 mg, 0.271 mmol, 82 % yield). LCMS AUC showed 95% purity, ESIMS ($\text{M}+\text{H}$) = 244 and strong ($\text{M}+\text{formate}$) at 288. GCMS showed molecular ion at 243. HRMS calcd for $\text{C}_{12}\text{H}_{12}\text{F}_3\text{NO}$ ($\text{M}-\text{H}$) 242.0791, found 242.0791. ^1H NMR (400 MHz, METHANOL- d_4) δ 7.52 (s, 2H), 2.62 (s, 3H), 2.54 (s, 3H), 1.85 (s, 3H).



1-(4-hydroxy-2,3-dimethylphenyl)-2-methylpropan-1-one (105a).

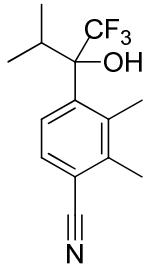
To a solution of 1-methoxy-2,3-dimethylbenzene **104a** (1.66 g, 12.19 mmol) in DCM (10 ml) was added aluminium chloride (2.113 g, 15.85 mmol) anhydrous powder. To the suspension was added isobutyrylchloride (1.353 mL, 14.63 mmol) (in 4ml DCM). The reaction was stirred overnight at RT. TLC showed complete reaction. The reaction mixture was added to an ice-water slurry (75 ml). The solution was extracted three times with MTBE. The organic layer was washed with brine and sodium bicarbonate and dried over Na_2SO_4 . The organics were concentrated to give a pale amber oil, 1-(4-methoxy-2,3-dimethylphenyl)-2-methylpropan-1-one (2.52 g, 12.22 mmol, 100 % yield). LCMS AUC showed 98% purity. ESIMS ($\text{M}+\text{H}$) = 207. The intermediate was carried on to demethylation without further purification. To a solution of the material from the preceding step (0.66 g, 3.20 mmol) in heptane in a vial was added aluminium chloride (1.280 g, 9.60 mmol). The suspension was heated for 20 minutes in a heat block at 105 °C. The vial was allowed cool to RT. To the vial was added 3 ml water and 5 ml MTBE. The resulting solution was extracted twice with MTBE. The organic extracts were dried over Na_2SO_4 and concentrated. The product was purified using silica gel column chromatography using a gradient up to 40% EtOAc/ hexane. Isolate product the desired product 1-(4-hydroxy-2,3-dimethylphenyl)-2-methylpropan-1-one (0.49 g, 2.55 mmol, 80 % yield) LCMS AUC showed 100% purity. ESIMS ($\text{M}+\text{H}$) = 193. ^1H NMR (400 MHz, CDCl_3) δ 7.25-7.35 (d,

$J=8.28$ Hz, 1H), 6.68 (d, $J=8.28$ Hz, 1H), 5.42 (s, 1H), 3.32 (td, $J=6.81, 13.74$ Hz, 1H), 2.33 (s, 3H), 2.22 (s, 3H), 1.18 (d, $J=6.78$ Hz, 6H).



4-isobutryl-2,3-dimethylbenzonitrile (64).

To a solution of **105a**, 1-(4-hydroxy-2,3-dimethylphenyl)-2-methylpropan-1-one (0.53 g, 2.76 mmol) in DCM (10 ml) was added triethylamine (0.461 mL, 3.31 mmol). Dropwise triflic anhydride (0.512 mL, 3.03 mmol) was added. The reaction was stirred at RT for 1 hour. The reaction mixture was concentrated by rotary evaporation. The intermediate triflate was purified using a silica gel 40 gram column. The intermediate eluted in a single peak at 15% EtOAc / hexane affording an amber oil, 4-isobutryl-2,3-dimethylphenyl trifluoromethanesulfonate (0.843 g, 2.60 mmol, 94 % yield). LCMS AUC showed 100% purity. ESIMS (M+H) = 325. To a DMF (5 ml) solution of the triflate from the previous step (0.356 g, 1.098 mmol) in a sealed tube was added Zinc Cyanide (0.067 g, 0.571 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.127 g, 0.110 mmol). The tube was purged with nitrogen under stirring for 5 minutes. The tube was sealed and placed in a heat block at 110 °C for 90 min. LCMS showed that the starting material was completely consumed and a new peak was apparent. The reaction mixture was partitioned between brine and MTBE. The organics were washed twice with brine. The aqueous washes were extracted twice with MTBE. The organic extracts were dried over Na₂SO₄ and filtered. The product was purified on a silica gel column (12 g). The desired product eluted at 10% EtOAc / hexane. The title product was isolated as a colorless oil, 4-isobutryl-2,3-dimethylbenzonitrile (170 mg, 0.845 mmol, 77 % yield). LCMS AUC showed 100% purity. ESIMS (M+H) = 202. ¹H NMR (400 MHz, CDCl₃) δ 7.47 (d, $J=7.82$ Hz, 1H), 7.18 (d, $J=8.01$ Hz, 1H), 3.03-3.21 (m, 1H), 2.48 (s, 3H), 2.21 (s, 3H), 1.13 (d, $J=6.84$ Hz, 6H).

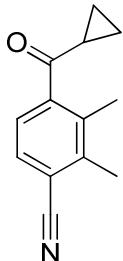


2,3-dimethyl-4-(1,1,1-trifluoro-2-hydroxy-3-methylbutan-2-yl)benzonitrile (20).

Ketone **64** was converted to the title product using the procedure for **13** affording a colorless glass, 2,3-dimethyl-4-(1,1,1-trifluoro-2-hydroxy-3-methylbutan-2-yl)benzonitrile (62.3 mg, 0.230 mmol, 92 % yield). LCMS AUC showed 100% purity, ESIMS (M-H) = 270 and (M + formate) = 316. HRMS calcd for C₁₄H₁₆F₃NO (M-H) 270.1104, found 270.1078. ¹H NMR

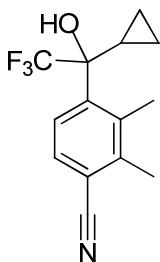
Supporting Information

(400 MHz, METHANOL-d₄) δ 7.62 (br. s., 1H), 7.50 (d, J =8.28 Hz, 1H), 2.76 (br. s., 1H), 2.59 (br. s., 3H), 2.54 (s, 3H), 1.13 (d, J =6.27 Hz, 3H), 0.82 (d, J =6.02 Hz, 3H).



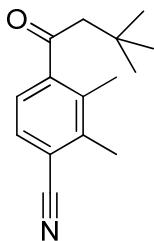
4-(cyclopropanecarbonyl)-2,3-dimethylbenzonitrile (65).

Following the procedures for **105a** and **64**, 1-methoxy-2,3-dimethylbenzene **104a** was converted to the title product in 46% overall yield. LCMS AUC showed 100% purity. ESIMS (M+H) = 200. ¹H NMR (400 MHz, CDCl₃) δ 7.55 (d, J =7.78 Hz, 1H), 7.41 (d, J =8.03 Hz, 1H), 2.56 (s, 3H), 2.37 (s, 3H), 2.22-2.35 (m, 1H), 1.33 (quin, J =3.76 Hz, 2H), 1.15 (qd, J =3.60, 7.53 Hz, 2H).



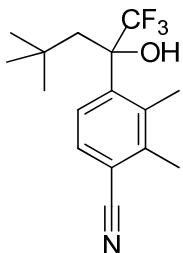
4-(1-cyclopropyl-2,2,2-trifluoro-1-hydroxyethyl)-2,3-dimethylbenzonitrile (21).

Following the procedure for **13**, 4-(cyclopropanecarbonyl)-2,3-dimethylbenzonitrile **65** (110 mg, 0.552 mmol) was converted to the title product (106 mg, 0.394 mmol, 71.3 % yield). LCMS showed 100% purity. ESIMS (M+H) = 270 and (M-H) = 268. HRMS calcd for C₁₄H₁₄F₃NO (M-H) 268.0947, found 268.0914. ¹H NMR (400 MHz, METHANOL-d₄) δ 7.82 (d, J =8.53 Hz, 1H), 7.53 (d, J =8.53 Hz, 1H), 2.63 (s, 3H), 2.54 (s, 3H), 1.71-1.88 (m, 1H), 0.90 (dd, J =4.89, 9.91 Hz, 1H), 0.53-0.75 (m, 2H), 0.29 (dd, J =4.52, 10.04 Hz, 1H).



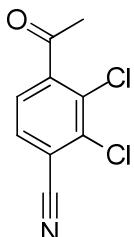
4-(3,3-dimethylbutanoyl)-2,3-dimethylbenzonitrile (66).

Following the procedures for **105a** and **64**, 1-methoxy-2,3-dimethylbenzene **104a** (1.362 g, 10 mmol) was reacted with 3,3-dimethylbutanoyl chloride (1.667 mL, 12.00 mmol) and subsequently converted to the benzonitrile giving the title compound in 77% overall yield. LCMS AUC showed 100% purity. ESIMS (M-H) = 228 and (M+H) = 230. GCMS showed molecular ion at 229. ¹H NMR (400 MHz, CDCl₃) δ 7.52 (d, *J*=8.03 Hz, 1H), 7.28 (d, *J*=7.78 Hz, 1H), 2.76 (s, 2H), 2.54 (s, 3H), 2.32 (s, 3H), 1.08 (s, 9H).



2,3-dimethyl-4-(1,1,1-trifluoro-2-hydroxy-4,4-dimethylpentan-2-yl)benzonitrile (22).

Following the procedure for **13**, ketone **66** was converted to the title product affording a colorless glass, 88 mg, 0.294 mmol, 94 % yield . LCMS AUC showed 98% purity, ESIMS (M-H) = 298 and (M + formate) = 344. HRMS calcd for C₁₆H₂₀F₃NO (M-H) 298.1417, found 298.1432. ¹H NMR (400 MHz, METHANOL-d₄) δ 7.50 (d, *J*=7.28 Hz, 2H), 2.60 (br. s., 2H), 2.54 (s, 6H), 2.02 (d, *J*=15.06 Hz, 1H), 0.84 (s, 9H).

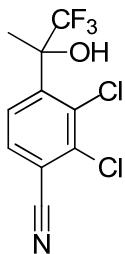


4-acetyl-2,3-dichlorobenzonitrile (67).

To a solution of 1,2-dichloro-3-methoxybenzene **104b** (2.145 g, 12.12 mmol) in DCM (15 ml) was added aluminium chloride (2.100 g, 15.75 mmol) anhydrous powder. A solution of acetyl chloride (0.991 mL, 14.54 mmol) in 5 ml DCM was added dropwise and the mixture was allowed to stir overnight at RT. The reaction was quenched by the addition of an ice-water slurry (75 ml). The resulting solution was extracted with MTBE three times. The organic layer

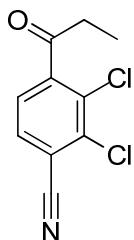
Supporting Information

was washed with brine and sodium bicarbonate, dried over sodium sulfate and concentrated. The intermediate purified by column chromatography giving a white crystalline solid, 1-(2,3-dichloro-4-methoxyphenyl)ethanone (1.94 g, 8.86 mmol, 73.1 % yield). To a solution of the intermediate from the preceding step (1.06 g, 4.84 mmol) in heptane (50 ml) was added aluminium chloride (1.936 g, 14.52 mmol) and the suspension was refluxed for one hour in a heat block at 135 °C. Following an aqueous workup, the phenol intermediate was purified by silica gel column chromatography giving 1-(2,3-dichloro-4-hydroxyphenyl)ethanone (0.263 g, 1.283 mmol, 26.5 % yield). To the material from the preceding step, 1-(2,3-dichloro-4-hydroxyphenyl)ethanone (0.26 g, 1.268 mmol) in DCM (6 ml) was added triethylamine (0.212 mL, 1.522 mmol) followed by dropwise addition of triflic anhydride (0.236 mL, 1.395 mmol). The reaction mixture was stirred at RT for 1 hour. The mixture was concentrated by rotary evaporation. The intermediate was purified by column chromatography using an Isco silica gel 40 gram column. The intermediate eluted in a single peak with 15% EtOAc / hexane giving 4-acetyl-2,3-dichlorophenyl trifluoromethanesulfonate (0.352 g, 1.044 mmol, 82 % yield). To a DMF (5 ml) solution of the triflate (352 mg, 1.044 mmol) in a sealed tube was added Zinc Cyanide (63.8 mg, 0.543 mmol) and tetrakis(triphenylphosphine)palladium(0) (121 mg, 0.104 mmol). The suspension was purged with nitrogen for five minutes, sealed under nitrogen and placed in a heat block at 110 °C for 90 min. Following a standard aqueous workup, the product was purified on an Isco silica gel column (12 g). The desired product eluted at 10% EtOAc / hexane giving 4-acetyl-2,3-dichlorobenzonitrile (172 mg, 0.804 mmol, 77 % yield) as a crystalline solid. LCMS AUC showed 100% purity. GCMS gave strong molecular ion at 213, 215. ¹H NMR (400 MHz, CDCl₃) δ 7.70 (d, *J*=7.78 Hz, 1H), 7.44 (d, *J*=7.78 Hz, 1H), 2.67 (s, 3H).



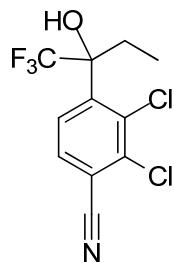
2,3-dichloro-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzonitrile (28).

Following the procedure for **13**, 4-acetyl-2,3-dichlorobenzonitrile **67** (55 mg, 0.257 mmol) was converted to the title product in 93 % yield. LCMS AUC showed 96% purity. ESIMS (M-H) = 282 and (M + formate) = 328. HRMS calcd C₁₀H₆Cl₂F₃NO (M-H) 281.9699, found 281.9673. ¹H NMR (400 MHz, methanol-d4) δ 8.25 (d, *J*=7.78 Hz, 1H), 7.60 (d, *J*=7.78 Hz, 1H), 2.07 (s, 3H).

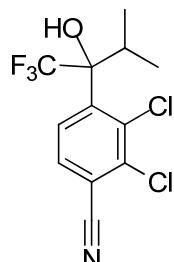


2,3-dichloro-4-propionylbenzonitrile (68).

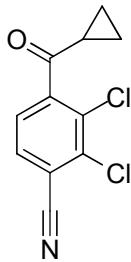
1,2-dichloro-3-methoxybenzene **104b** was converted to the title product in 57% overall yield using the procedure for **67**. LCMS AUC showed 97% purity. GCMS showed high purity and strong molecular ion at 227/229. ¹H NMR (400 MHz, CDCl₃) δ 7.69 (d, *J*=7.78 Hz, 1H), 7.35 (d, *J*=8.03 Hz, 1H), 2.93 (q, *J*=7.28 Hz, 2H), 1.25 (t, *J*=7.28 Hz, 3H).

**2,3-dichloro-4-(1,1,1-trifluoro-2-hydroxybutan-2-yl)benzonitrile (29).**

Following the procedure for **13**, 2,3-dichloro-4-propionylbenzonitrile **68**, was converted to the title product in 32% yield. LCMS AUC showed 100% purity, ESIMS (M-H = 296/298. HRMS calcd for C₁₁H₈C₁₂F₃NO (M-H) 295.9855, found 295.982. ¹H NMR (400 MHz, METHANOL-d₄) δ 8.20 (d, *J*=8.53 Hz, 1H), 7.85 (d, *J*=8.53 Hz, 1H), 3.10 (dd, *J*=7.40, 14.68 Hz, 1H), 2.08 (dd, *J*=7.40, 14.68 Hz, 1H), 0.84 (t, *J*=7.28 Hz, 3H).

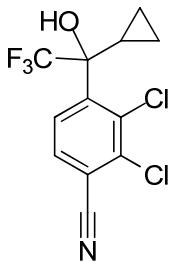
**2,3-dichloro-4-(1,1,1-trifluoro-2-hydroxy-3-methylbutan-2-yl)benzonitrile (30).**

2,3-dichloro-4-isobutyrylbenzonitrile, **70**, was converted to the title product in 30 % yield following the procedure for **13**. LCMS AUC showed 95% purity. ESIMS (M-H) = 310, 312. HRMS calcd for C₁₂H₁₀C₁₂F₃NO (M-H) 310.0012, found 310.0029. ¹H NMR (400 MHz, DMSO-d₆) δ 8.05 (s, 2H), 6.95 (s, 1H), 3.16-3.29 (m, 1H), 1.09 (d, *J*=6.45 Hz, 3H), 0.61 (d, *J*=6.84 Hz, 3H).



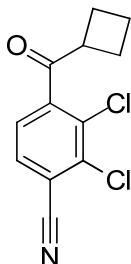
2,3-dichloro-4-(cyclopropanecarbonyl)benzonitrile (69).

1,2-Dichloro-3-methoxybenzene **104b** was converted to the title product in 25% overall yield using the procedure for **67**. LCMS AUC showed 94% purity. ESIMS (M+H) = 245/247. ¹H NMR (400 MHz, CDCl₃) δ 7.69 (d, *J*=8.03 Hz, 1H), 7.44 (d, *J*=8.03 Hz, 1H), 2.26-2.50 (m, 1H), 1.33-1.52 (m, 2H), 1.12-1.33 (m, 2H).



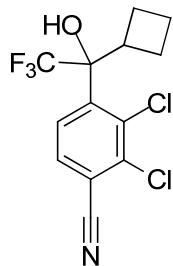
2,3-dichloro-4-(1-cyclopropyl-2,2,2-trifluoro-1-hydroxyethyl)benzonitrile (31).

2,3-dichloro-4-(cyclopropanecarbonyl)benzonitrile, **69**, was converted to the title product in 52% yield using the procedure for **13**. LCMS AUC showed 100% purity. ESIMS (M-H) = 308/310. HRMS calcd for C₁₂H₈C₁₂F₃NO (M-H) 307.9855, found 307.9872. ¹H NMR (400 MHz, METHANOL-d₄) δ 8.11 (d, *J*=8.53 Hz, 1H), 7.82 (d, *J*=8.53 Hz, 1H), 2.12-2.29 (m, 1H), 0.88-1.10 (m, 1H), 0.63-0.82 (m, 1H), 0.47-0.62 (m, 1H), 0.16-0.33 (m, 1H).



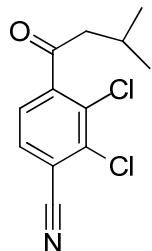
2,3-dichloro-4-(cyclobutanecarbonyl)benzonitrile (71).

1,2-dichloro-3-methoxybenzene **104b** was converted to the title product in 22% overall yield using the procedure for **67**. LCMS AUC showed 99% purity. GCMS showed 100% purity and molecular ion at 253/255. ¹H NMR (400 MHz, CDCl₃) δ 7.67 (d, *J*=7.78 Hz, 1H), 7.34 (d, *J*=8.03 Hz, 1H), 3.86 (quin, *J*=8.47 Hz, 1H), 2.33-2.51 (m, 2H), 2.17-2.32 (m, 2H), 1.87-2.16 (m, 2H).



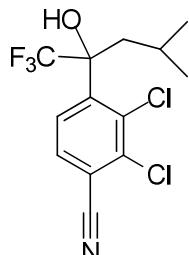
2,3-dichloro-4-(1-cyclobutyl-2,2,2-trifluoro-1-hydroxyethyl)benzonitrile (32).

2,3-Dichloro-4-(cyclobutanecarbonyl)benzonitrile **71**, was converted to the title product in 25% yield following the procedure for **13**. LCMS AUC showed 96% purity. ESIMS (M-H) = 322, 324. HRMS calcd for $C_{13}H_{10}Cl_2F_3NO$ (M-H) 322.0012, found 322.0023. 1H NMR (400 MHz, METHANOL-d₄) δ 8.19 (br, s., 1H), 7.83 (d, J =8.53 Hz, 1H), 4.12 (br, s, 1H), 2.33-2.60 (m, 1H), 1.87-2.12 (m, 2H), 1.58-1.87 (m, 2H).



2,3-dichloro-4-(3-methylbutanoyl)benzonitrile (72).

1,2-Dichloro-3-methoxybenzene **104b** was converted to the title product in 28% overall yield using the procedure for **67**. LCMS AUC showed 97% purity. GCMS showed 100% purity and strong molecular ion at 255/257. 1H NMR (400 MHz, DMSO-d₆) δ 8.10 (d, J =8.03 Hz, 1H), 7.76 (d, J =8.03 Hz, 1H), 2.84 (d, J =6.78 Hz, 2H), 2.12 (td, J =6.65, 13.30 Hz, 1H), 0.94 (d, J =6.78 Hz, 6H).

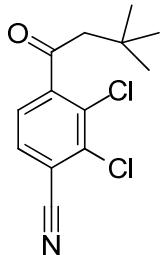


2,3-dichloro-4-(1,1,1-trifluoro-2-hydroxy-4-methylpentan-2-yl)benzonitrile (33).

2,3-Dichloro-4-(3-methylbutanoyl)benzonitrile **72**, was converted to the title product in 43% yield following the procedure for **13**. LCMS AUC showed 98% purity. ESIMS (M-H) = 324/326, (M + formate) = 370/372. GCMS showed high purity and molecular ion at 325/327. HRMS calcd for $C_{13}H_{12}Cl_2F_3NO$ (M-H) 324.0168, found 324.0182. 1H NMR (400 MHz,

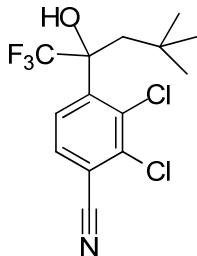
Supporting Information

DMSO-d₆) δ 8.17 (d, *J*=8.53 Hz, 1H), 8.07 (d, *J*=8.53 Hz, 1H), 7.07 (s, 1H), 2.90 (dd, *J*=3.64, 14.43 Hz, 1H), 1.83 (dd, *J*=9.41, 14.68 Hz, 1H), 1.37-1.57 (m, 1H), 0.82 (t, *J*=6.53 Hz, 6H).



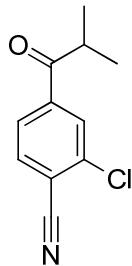
2,3-dichloro-4-(3,3-dimethylbutanoyl)benzonitrile (73).

1,2-dichloro-3-methoxybenzene **104b** was converted to the title product in 22% overall yield using the procedure for **67**. LCMS AUC showed 100% purity. GCMS showed high purity and molecular ion at 269/271. ¹H NMR (400 MHz, CDCl₃) δ 7.68 (d, *J*=7.78 Hz, 1H), 7.33 (d, *J*=7.78 Hz, 1H), 2.84 (s, 2H), 1.10 (s, 9H).



2,3-dichloro-4-(1,1,1-trifluoro-2-hydroxy-4,4-dimethylpentan-2-yl)benzonitrile (34).

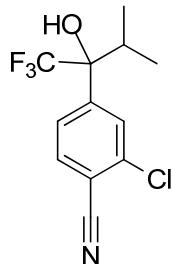
2,3-Dichloro-4-(3,3-dimethylbutanoyl)benzonitrile, **73** was converted to the title product in 55% yield following the procedure for **13**. LCMS AUC showed 99% purity. ESIMS (M-H) = 338/340 and (M+formate) = 384/386. HRMS calcd for C₁₄H₁₄Cl₂F₃NO (M-H) 338.0325, found 338.0348. ¹H NMR (400 MHz, METHANOL-d₄) δ 8.31 (d, *J*=8.03 Hz, 1H), 7.86 (d, *J*=8.53 Hz, 1H), 3.19 (d, *J*=14.05 Hz, 1H), 1.97 (d, *J*=15.06 Hz, 1H), 0.73-0.96 (m, 9H).



2-chloro-4-isobutyrylbenzonitrile (74).

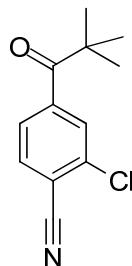
1-Chloro-2-methoxybenzene **104c** was converted to the title product in 54% overall yield following the procedure for **67**. LCMS AUC showed 100% purity. GCMS showed 100% purity and molecular ion at 207/209. ¹H NMR (400 MHz, CDCl₃) δ 8.03 (d, *J*=1.37 Hz, 1H),

7.88 (dd, $J=1.37$, 8.01 Hz, 1H), 7.78 (d, $J=8.01$ Hz, 1H), 3.46 (td, $J=6.84$, 13.68 Hz, 1H), 1.21 (d, $J=6.84$ Hz, 6H).



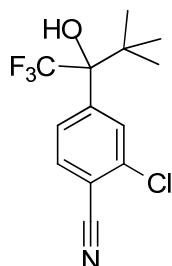
2-chloro-4-(1,1,1-trifluoro-2-hydroxy-3-methylbutan-2-yl)benzonitrile (23).

2-Chloro-4-isobutyrylbenzonitrile, **74** was converted to the title product in 75% yield using the procedure for **13**. LCMS AUC showed 100% purity. ESIMS ($\text{M}+\text{H}$) = 278/280, ($\text{M}-\text{H}$) = 276/278, ($\text{M}+\text{formate}$) = 322/324. HRMS calcd for $\text{C}_{12}\text{H}_{11}\text{ClF}_3\text{NO}$ ($\text{M}-\text{H}$) 276.0401, found 276.0389. ^1H NMR (400 MHz, CDCl_3) δ 7.75 (s, 1H), 7.69 (d, $J=8.21$ Hz, 1H), 7.54 (d, $J=8.21$ Hz, 1H), 2.57 (s, 1H), 2.47 (td, $J=6.84$, 13.68 Hz, 1H), 1.13 (d, $J=6.45$ Hz, 3H), 0.69 (d, $J=6.84$ Hz, 3H).



2-chloro-4-pivaloylbenzonitrile (75).

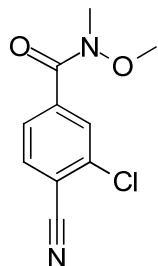
Following the procedure for **58**, 2-chloro-4-formylbenzonitrile **111b** was converted to the title product in 33% yield. LCMS AUC showed 100% purity. ESIMS ($\text{M}+\text{H}$) = 222/224. GCMS showed molecular ion at 221/223. ^1H NMR (400 MHz, CDCl_3) δ 7.68-7.80 (m, 2H), 7.55-7.66 (m, 1H), 1.35 (s, 9H).



2-chloro-4-(1,1,1-trifluoro-2-hydroxy-3,3-dimethylbutan-2-yl)benzonitrile (24).

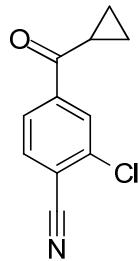
Supporting Information

2-Chloro-4-pivaloylbenzonitrile **75**, was converted to the title product in 81% yield using the procedure for **13**. LCMS AUC showed 100% purity. ESIMS (M-H) = 290/292 and (M+H) = 292/294. HRMS calcd for C₁₃H₁₃ClF₃NO (M-H) 290.0558, found 290.0586. ¹H NMR (400 MHz, CDCl₃) δ 7.74-7.94 (m, 1H), 7.70 (d, *J*=8.03 Hz, 1H), 7.63 (br. s., 1H), 2.86 (s, 1H), 0.99-1.16 (m, 9H).



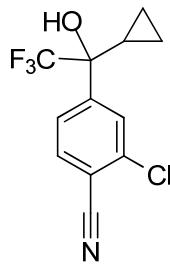
3-chloro-4-cyano-N-methoxy-N-methylbenzamide (108).

To a solution of 3-chloro-4-cyanobenzoic acid **107** (0.726 g, 4 mmol) and N,O-dimethylhydroxylamine hydrochloride (0.429 g, 4.40 mmol) in N,N-Dimethylformamide (DMF) (12 mL) was added Hunig's base (1.537 mL, 8.80 mmol) and HATU (1.673 g, 4.40 mmol). The reaction mixture was stirred at RT for 2.5 h. The mixture was partitioned between MTBE and 0.5 M HCl. The biphasic mixture was extracted three times with MTBE. The organic extracts were washed with brine. The organic extracts were dried and concentrated. The product was purified by silica gel column chromatography. The product eluted at 40% EtOAc / hexane giving a white solid (0.79 g, 3.51 mmol, 88% yield). LCMS AUC showed 100% purity. ESIMS (M+H) = 225/227. ¹H NMR (400 MHz, CDCl₃) δ 7.85 (s, 1H), 7.63-7.80 (m, 2H), 3.57 (s, 3H), 3.40 (s, 3H).



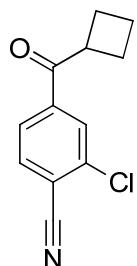
2-chloro-4-(cyclopropanecarbonyl)benzonitrile (76).

To a solution of **108**, 3-chloro-4-cyano-N-methoxy-N-methylbenzamide (180 mg, 0.801 mmol), in THF at -78 °C was added cyclopropylmagnesium bromide (9.62 mL, 4.81 mmol). The mixture was stirred at -78 °C for 1 h. The reaction was quenched at -78 °C by the addition of 1 ml NH₄Cl solution. The ice bath was removed and 10 ml more NH₄Cl solution was added. The mixture was allowed to warm to RT and then was extracted three times with MTBE. The product was purified by silica gel column chromatography. The product eluted at 10% EtOAc / hexane giving a white solid, 2-chloro-4-(cyclopropanecarbonyl)benzonitrile (98 mg, 0.477 mmol, 59.5 % yield). LCMS AUC showed 99% purity and no molecular ion. ¹H NMR (400 MHz, CDCl₃) δ 8.13 (s, 1H), 7.99 (d, *J*=7.78 Hz, 1H), 7.83 (d, *J*=8.03 Hz, 1H), 2.53-2.69 (m, 1H), 1.28-1.42 (m, 2H), 1.19 (qd, *J*=3.63, 7.43 Hz, 2H).



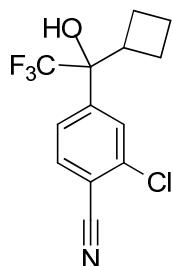
2-chloro-4-(1-cyclopropyl-2,2,2-trifluoro-1-hydroxyethyl)benzonitrile (25).

2-Chloro-4-(cyclopropanecarbonyl)benzonitrile **76**, was converted to the title product in 81% yield using the procedure for **13**. LCMS AUC showed 100% purity. ESIMS (M-H) = 274/276 and (M+ formate) = 320/322. HRMS calcd for C₁₂H₉ClF₃NO (M-H) 274.0245, found 274.0249. ¹H NMR (400 MHz, METHANOL-d₄) δ 7.93 (s, 1H), 7.70-7.90 (m, 2H), 1.55-1.76 (m, 1H), 0.77-0.95 (m, 1H), 0.58-0.76 (m, 1H), 0.38-0.56 (m, 1H), 0.32 (td, *J*=5.11, 10.10 Hz, 1H).



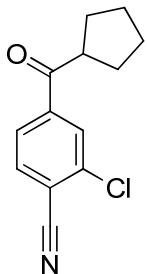
2-chloro-4-(cyclobutanecarbonyl)benzonitrile (77).

1-chloro-2-methoxybenzene **104c** was converted to the title product in 62% overall yield following the procedure for **67**. LCMS AUC showed 100% purity. ESIMS (M + formate) = 264/266. ¹H NMR (400 MHz, CDCl₃) δ 7.98 (s, 1H), 7.69-7.91 (m, 2H), 3.93 (quin, *J*=8.45 Hz, 1H), 2.24-2.53 (m, 5H), 2.02-2.19 (m, 1H), 1.82-2.02 (m, 1H).



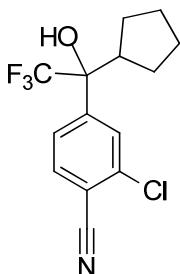
2-chloro-4-(1-cyclobutyl-2,2,2-trifluoro-1-hydroxyethyl)benzonitrile (26).

2-Chloro-4-(cyclobutanecarbonyl)benzonitrile **77**, was converted to the title product in 78% yield using the procedure for **13**. LCMS AUC showed 98% purity. ESIMS (M+formate) = 334/336, (M-H) = 288/290. HRMS calcd for C₁₃H₁₁ClF₃NO (M-H) 288.0401, found 288.0391. ¹H NMR (400 MHz, CDCl₃) δ 7.74 (s, 1H), 7.67 (d, *J*=8.21 Hz, 1H), 7.53 (d, *J*=8.21 Hz, 1H), 3.21 (quin, *J*=8.65 Hz, 1H), 2.74 (s, 1H), 2.01-2.22 (m, 2H), 1.84-2.00 (m, 1H), 1.65-1.83 (m, 2H), 1.42-1.63 (m, 2H).



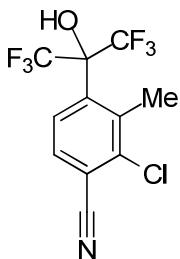
2-chloro-4-(cyclopentanecarbonyl)benzonitrile (78).

1-chloro-2-methoxybenzene **104c** was converted to the title product in 37% overall yield following the procedure for **67**. LCMS AUC showed 100% purity. ESIMS ($M + H$) = 234/236. GCMS showed a single peak with molecular ion at 233/235. 1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J =1.51 Hz, 1H), 7.94 (dd, J =1.63, 8.16 Hz, 1H), 7.81 (d, J =8.28 Hz, 1H), 3.57-3.73 (m, 1H), 1.81-2.05 (m, 4H), 1.64-1.81 (m, 4H).



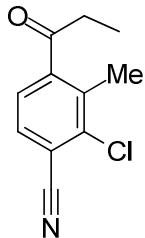
2-chloro-4-(1-cyclopentyl-2,2,2-trifluoro-1-hydroxyethyl)benzonitrile (27).

2-Chloro-4-(cyclopentanecarbonyl)benzonitrile **78**, was converted to the title product in 76% yield using the procedure for **13**. LCMS AUC showed 97% purity. ESIMS ($M + formate$) = 348/350, ($M - H$) = 302/304. HRMS calcd for $C_{14}H_{13}ClF_3NO$ ($M - H$) 302.0558, found 302.0536. 1H NMR (400 MHz, $CDCl_3$) δ 7.78-7.87 (m, 1H), 7.72 (d, J =8.28 Hz, 1H), 7.55-7.66 (m, 1H), 2.60-2.79 (m, 2H), 1.89-2.08 (m, 1H), 1.61-1.87 (m, 3H), 1.45-1.60 (m, 3H), 1.15-1.34 (m, 2H).



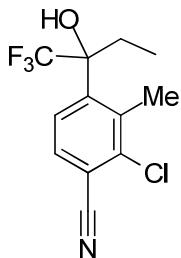
2-chloro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-3-methylbenzonitrile (35).

Following the procedure for **11**, methyl 3-chloro-4-cyano-2-methylbenzoate was converted to ketone **79** and then to the title compound in 71% yield. LCMS AUC showed 90% purity. ESIMS ($M - H$) = 316/318. HRMS calcd for $C_{11}H_6ClF_6NO$ ($M - H$) 315.9962, found 315.9978. 1H NMR (400 MHz, $DMSO-d_6$) δ 9.22 (s, 1H), 7.95 (d, J =8.59 Hz, 1H), 7.67 (d, J =7.03 Hz, 1H), 2.62 (s, 3H).



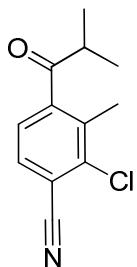
2-chloro-3-methyl-4-propionylbenzonitrile (80).

Following the procedure for **58**, 2-chloro-4-formyl-3-methylbenzonitrile was reacted with ethylmagnesium bromide to give the title compound. LCMS AUC showed 99% purity. ESIMS (M+H) = 208/210.



2-chloro-3-methyl-4-(1,1,1-trifluoro-2-hydroxybutan-2-yl)benzonitrile (36).

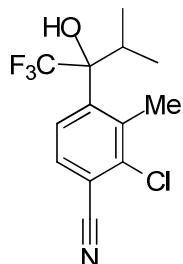
To a solution of 2-chloro-3-methyl-4-propionylbenzonitrile **80** (40 mg, 0.193 mmol) in tetrahydrofuran (THF) (25 mL) at 0 °C was added trimethyl(trifluoromethyl)silane (0.222 mL, 1.156 mmol) followed by cesium fluoride (88 mg, 0.578 mmol). After stirring at 0 °C for 30 min., TLC (25% ethyl acetate/hexanes) showed a higher R_f spot indicative of the silyl ether intermediate. Next, TBAF (0.193 mL, 0.193 mmol) was added and stirring was continued for 15 additional min at 0 °C. At this time, the reaction was judged complete by TLC (25% ethyl acetate/hexanes) by a lower R_f product indicating removal of the TMS group. The reaction was adsorbed onto silica gel and purified by LC (5-25% ethyl acetate/hexanes) to provide the desired product (25 mg, 47%). ESIMS (M+H)⁺ = 278. HRMS calcd for C₁₂H₁₁ClF₃NO (M-H) 276.0401, found 276.0413. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.90 (t, *J*=7.46 Hz, 3 H) 1.97 - 2.10 (m, 1 H) 2.31 (s, 1 H) 2.48 - 2.60 (m, 1 H) 2.69 (s, 3 H) 7.48 - 7.57 (m, 2 H)



2-chloro-4-isobutyryl-3-methylbenzonitrile (81).

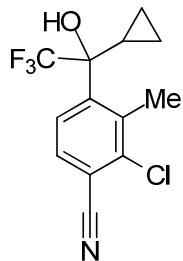
To a solution of 2-chloro-4-formyl-3-methylbenzonitrile **111c** (200 mg, 1.114 mmol) in Tetrahydrofuran (THF) (25 mL) at -78C under nitrogen was added isopropylmagnesium

chloride (3.34 mL, 6.68 mmol). After stirring for 30 min at this temperature, the reaction was warmed to room temperature and stirred for 3 hrs. TLC (20% ethyl acetate/hexanes) showed complete reaction. The reaction was quenched by pouring into a stirring mixture of ethyl acetate (50 ml) and saturated NH₄Cl (50 ml). The organic layer was adsorbed to silica gel and the product was purified by column chromatography (5-25% ethyl acetate/hexane) over 30 min giving the carbinol intermediate (150 mg, 0.671 mmol, 60% yield). To the intermediate from the preceding step (100mg, 0.447 mmol) in dichloromethane (DCM) (10 ml) was added PCC (482 mg, 2.235 mmol). After stirring at room temperature overnight, TLC (30% ethyl acetate/hexanes) showed reaction complete. The contents were adsorbed to silica gel and purified by silica gel column chromatography (5-25% ethyl acetate/hexanes) over 30 min to give the title product (92 mg, 0.415 mmol, 93% yield). LCMS ESIMS (M+H) = 224.



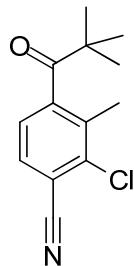
2-chloro-3-methyl-4-(1,1,1-trifluoro-2-hydroxy-3-methylbutan-2-yl)benzonitrile (37).

To a solution of 2-chloro-4-isobutyryl-3-methylbenzonitrile **81** (80 mg, 0.361 mmol) in Tetrahydrofuran (THF) (25 mL) at 0 °C was added trimethyl(trifluoromethyl)silane (0.416 mL, 2.165 mmol) followed by cesium fluoride (164 mg, 1.083 mmol). After stirring at 0 °C for 30 min., TLC (25% ethyl acetate/hexanes) showed a higher R_f spot indicative of the silyl ether intermediate. Next, TBAF (0.361 mL, 0.361 mmol) was added and stirring was continued for 15 additional min at 0 °C. At this time, the reaction was judged complete by TLC (25% ethyl acetate/hexanes) by a lower R_f product indicating removal of the TMS group. The reaction was adsorbed to silica gel and purified by LC (5-25% ethyl acetate/hexanes) to afford the alcohol (50 mg, 48%). ESIMS (M+H)⁺ = 292. HRMS calcd for C₁₃H₁₃ClF₃NO (M-H) 290.0558, found 290.0559. ¹H NMR (CDCl₃) okay.= 292. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.69 (d, *J*=6.61 Hz, 3 H) 1.02 (d, *J*=6.44 Hz, 3 H) 2.62 (s, 3 H) 2.65 - 2.75 (m, 1 H) 6.51 - 6.61 (m, 1 H) 7.68 (br. s., 1 H) 7.81 (d, *J*=8.53 Hz, 1 H).



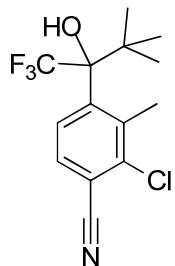
2-chloro-4-(1-cyclopropyl-2,2,2-trifluoro-1-hydroxyethyl)-3-methylbenzonitrile (38).

Following the procedure for **37**, 2-chloro-4-(cyclopropanecarbonyl)-3-methylbenzonitrile **82** was converted to the title product in 39% yield. LCMS AUC showed 97% purity. ESIMS (M-H) = 288/290. HRMS calcd for C₁₃H₁₁ClF₃NO (M-H) 288.0401, found 288.0425. ¹H NMR (400 MHz, DMSO-d₆) δ 7.93 (d, *J*=8.60 Hz, 1H), 7.84 (d, *J*=8.40 Hz, 1H), 6.34 (s, 1H), 2.64 (s, 3H), 2.43-2.50 (m, 5H).



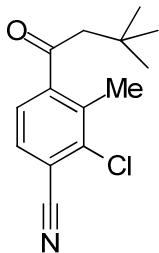
2-chloro-3-methyl-4-pivaloylbenzonitrile (83).

Following the procedure for **58**, 2-chloro-4-formyl-3-methylbenzonitrile was reacted with tert-butyldimagnesium chloride to give the title compound in 32% yield. LCMS AUC showed 100% purity and no molecular ion. GCMS showed high purity and strong molecular ion at 235/237. ¹H NMR (400 MHz, CDCl₃) δ 7.57 (d, *J*=8.03 Hz, 1H), 7.13 (d, *J*=8.03 Hz, 1H), 2.29 (s, 3H), 1.26 (s, 10H).



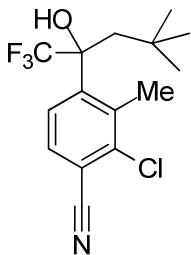
2-chloro-3-methyl-4-(1,1,1-trifluoro-2-hydroxy-3,3-dimethylbutan-2-yl)benzonitrile (39).

Following the procedure for **13**, ketone **83** was converted to the title product in 74% yield. LCMS AUC showed 100% purity. ESIMS (M+H) = 306/308 and (M-H) = 304/306. GCMS showed 100% purity and molecular ion at 305/307. HRMS calcd for C₁₄H₁₅ClF₃NO (M-H) 304.0714, found 304.073. ¹H NMR (400 MHz, CDCl₃) δ 7.49 (d, *J*=3.26 Hz, 2H), 2.74-2.88 (m, 4H), 1.02-1.17 (m, 9H).



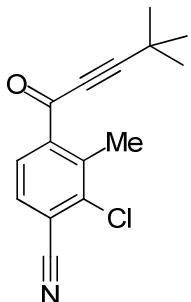
2-chloro-4-(3,3-dimethylbutanoyl)-3-methylbenzonitrile (84).

Following the procedure for **58**, 2-chloro-4-formyl-3-methylbenzonitrile was reacted neopentylmagnesium chloride (1M in THF) to give the title compound in 59% yield. LCMS AUC showed 98% purity. GCMS showed 100% purity and strong molecular ion at 249/251. ¹H NMR (400 MHz, CDCl₃) δ 7.61 (d, *J*=8.03 Hz, 1H), 7.37 (d, *J*=8.03 Hz, 1H), 2.77 (s, 2H), 2.47 (s, 3H), 1.09 (s, 9H).



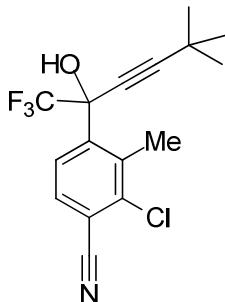
2-chloro-3-methyl-4-(1,1,1-trifluoro-2-hydroxy-4,4-dimethylpentan-2-yl)benzonitrile (40).

Following the procedure for **13**, ketone **84** was converted to the title product in 83% yield. LCMS AUC showed 100% purity. ESIMS (M-H) = 318/320 and (M+formate) = 364/366. GCMS showed molecular ion at 319/321. HRMS calcd for C₁₅H₁₇ClF₃NO (M-H) 318.0871, found 318.0887. ¹H NMR (400 MHz, DMSO-d₆) δ 7.82 (br. s., 2H), 6.59 (br. s., 1H), 2.68 (br. s., 3H), 1.97 (d, *J*=14.81 Hz, 2H), 0.78 (s, 9H).



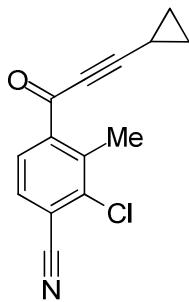
2-chloro-4-(4,4-dimethylpent-2-ynoyl)-3-methylbenzonitrile (85).

Following the procedure for **84**, 2-chloro-4-formyl-3-methylbenzonitrile **111c** was reacted with 3,3-dimethylbut-1-yne to give the title product in 62% yield. LCMS AUC showed 100% purity. GCMS showed 100% purity and strong ions at 244/246 for (M-Me) radical cation and weaker molecular ions at 259/260. ¹H NMR (400 MHz, CDCl₃) δ 7.91 (d, *J*=8.01 Hz, 1H), 7.62 (d, *J*=8.01 Hz, 1H), 2.63 (s, 3H), 1.34 (s, 9H).



2-chloro-3-methyl-4-(1,1,1-trifluoro-2-hydroxy-5,5-dimethylhex-3-yn-2-yl)benzonitrile (41).

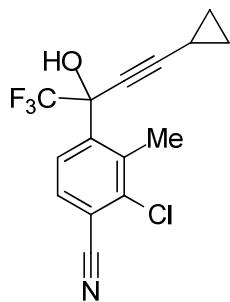
Following the procedure for **13**, ketone **85** was converted to the title product in 68% yield. LCMS AUC showed 100% purity. ESIMS (M-H) = 328/330 and (M+formate) = 374/376. HRMS calcd for C₁₆H₁₅ClF₃NO (M-H) 328.0714, found 328.071. ¹H NMR (400 MHz, CDCl₃) δ 7.87 (d, *J*=8.40 Hz, 1H), 7.55 (d, *J*=8.40 Hz, 1H), 2.70 (s, 3H), 1.18-1.37 (m, 9H).



2-chloro-4-(3-cyclopropylpropioloyl)-3-methylbenzonitrile (86).

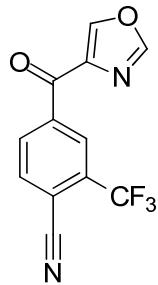
To a solution of 2-chloro-4-formyl-3-methylbenzonitrile **111c** (216 mg, 1.2 mmol) and zinc chloride (245 mg, 1.800 mmol) in toluene (4 ml) and DCM (2 ml) at RT was added ethynylcyclopropane (0.112 mL, 1.320 mmol) and then triethylamine (0.251 mL, 1.800 mmol). The mixture was sonicated for 5 min. The solution was stirred overnight at RT. The reaction was quenched by addition of 10 ml NH₄Cl solution at RT. The reaction mixture was filtered to remove solids. The filtrate was transferred to a separatory funnel and extracted with MTBE. The organic layer was washed with brine. The aqueous layer was extracted two more times with MTBE. The organic layer was dried and concentrated. The intermediate carbinol was purified via silica gel column chromatography. The intermediate eluted at 30% EtOAc/hexane and concentrated to give a white solid, 2-chloro-4-(3-cyclopropyl-1-hydroxyprop-2-yn-1-yl)-3-methylbenzonitrile (233 mg, 0.948 mmol, 79 % yield). The material from the preceding step

was dissolved in DCM (10 ml). 2 g silica gel was added followed by PCC (470 mg, 2.181 mmol) powder and The mixture was stirred at RT 4 h. The reaction mixture was filtered through a silica gel pad. The filtrate was evaporated. The product was purified by silica gel chromatography. Desired product eluted at 10% EtOAc / hexane. The title product was isolated as a highly crystalline solid (90.7 mg, 0.372 mmol, 39.2 % yield). LCMS AUC showed 100% purity. GCMS showed 100% purity and strong ions at 242/244 consistent with one chlorine atom. ¹H NMR (400 MHz, CDCl₃) δ 7.93 (d, *J*=8.28 Hz, 1H), 7.64 (d, *J*=8.03 Hz, 1H), 2.64 (s, 3H), 1.43-1.65 (m, 1H), 0.94-1.18 (m, 4H).



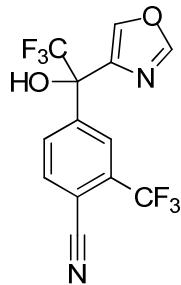
2-chloro-4-(4-cyclopropyl-1,1,1-trifluoro-2-hydroxybut-3-yn-2-yl)-3-methylbenzonitrile (42).

Following the procedure for **13**, ketone **86** was converted to the title product in 71% yield. LCMS AUC showed 95% purity. ESIMS (M-H) = 312/314. HRMS calcd for C₁₅H₁₁ClF₃NO (M-H) 312.0401, found 312.0432. ¹H NMR (400 MHz, CDCl₃) δ 7.88 (d, *J*=8.53 Hz, 1H), 7.58 (d, *J*=8.28 Hz, 1H), 3.10 (s, 1H), 2.72 (s, 3H), 1.30-1.49 (m, 1H), 0.87-1.03 (m, 2H), 0.72-0.87 (m, 2H).



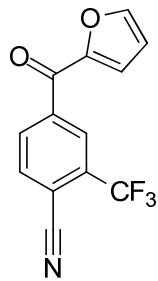
4-(oxazole-4-carbonyl)-2-(trifluoromethyl)benzonitrile (92).

Following the procedure for **59**, oxazole-4-carbaldehyde was converted to the title product in 28% yield. LCMS AUC showed 93% purity. ESIMS (M+H) = 267 and (M + formic acid) = 312. ¹H NMR (400 MHz, CDCl₃) δ 8.83 (s, 1H), 8.73 (dd, *J*=1.25, 8.03 Hz, 1H), 8.55 (d, *J*=1.00 Hz, 1H), 7.97-8.14 (m, 2H).



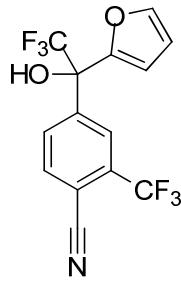
4-(2,2,2-trifluoro-1-hydroxy-1-(oxazol-4-yl)ethyl)-2-(trifluoromethyl)benzonitrile (43).

Intermediate **92** was converted to the title product in 73% yield using the procedure for **15**. LCMS AUC showed 100% purity. ESIMS ($M+H$) = 337 and ($M-H$) = 335. HRMS calcd for $C_{13}H_6F_6N_2O_2$ ($M-H$) 335.0253, found 335.0295. 1H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.80-8.07 (m, 4H), 4.60 (s, 1H).



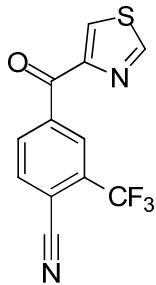
4-(furan-2-carbonyl)-2-(trifluoromethyl)benzonitrile (93).

Following the procedure for **59**, furan-2-carbaldehyde was converted to the title product in 25% yield. LCMS AUC showed 91% purity. ESIMS ($M+H$) = 266. 1H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.32 (d, $J=8.01$ Hz, 1H), 8.01 (d, $J=8.01$ Hz, 1H), 7.77 (s, 1H), 7.40 (d, $J=3.32$ Hz, 1H), 6.65-6.76 (m, 1H).



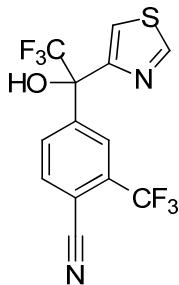
4-(2,2,2-trifluoro-1-(furan-2-yl)-1-hydroxyethyl)-2-(trifluoromethyl)benzonitrile (44).

Ketone **93** was converted to the title product in 38% yield using the procedure for **15**. LCMS AUC showed 100% purity. ESIMS ($M-H$) = 334. HRMS calcd for $C_{14}H_7F_6NO_2$ ($M-H$) 334.0301, found 334.0345. 1H NMR (400 MHz, $CDCl_3$) Shift 8.09 (s, 1H), 7.86-7.94 (m, 2H), 7.51 (d, $J=1.25$ Hz, 1H), 6.62 (d, $J=3.26$ Hz, 1H), 6.51 (dd, $J=1.88, 3.39$ Hz, 1H), 3.41 (s, 1H).



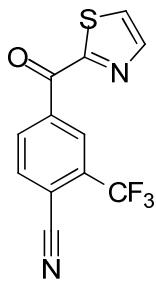
4-(thiazole-4-carbonyl)-2-(trifluoromethyl)benzonitrile (94).

Following the procedure for **59**, thiazole-4-carbaldehydewas converted to the title product in 59% yield. LCMS AUC showed 100% purity. ESIMS (M+H) = 283. ¹H NMR (400 MHz, CDCl₃) δ 8.97 (d, *J*=2.26 Hz, 1H), 8.77 (s, 1H), 8.67 (dd, *J*=1.25, 8.03 Hz, 1H), 8.57 (d, *J*=2.26 Hz, 1H), 8.02 (d, *J*=8.03 Hz, 1H).



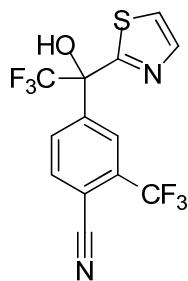
4-(2,2,2-trifluoro-1-hydroxy-1-(thiazol-4-yl)ethyl)-2-(trifluoromethyl)benzonitrile (45).

Ketone **94** was converted to the title product in 42% yield using the procedure for **15**. LCMS AUC showed 100% purity. ESIMS (M+H) = 353 and (M-H) = 351. HRMS calcd for C₁₃H₆F₆N₂OS (M-H) 351.0025, found 351.0069. ¹H NMR (400 MHz, METHANOL-d₄) δ 9.04 (d, *J*=2.01 Hz, 1H), 8.26 (s, 1H), 7.98-8.13 (m, 2H), 7.92 (d, *J*=1.25 Hz, 1H).



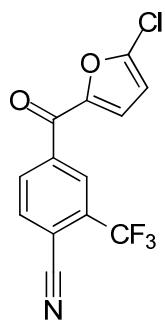
4-(thiazole-2-carbonyl)-2-(trifluoromethyl)benzonitrile (95).

Following the procedure for **59**, thiazole-2-carbaldehydewas converted to the title product in 17% yield. LCMS AUC showed 85% purity. ESIMS (M+H) = 283. ¹H NMR (400 MHz, CDCl₃) δ 8.99 (s, 1H), 8.84-8.93 (m, 1H), 8.19 (d, *J*=3.01 Hz, 1H), 8.05 (d, *J*=8.03 Hz, 1H), 7.88 (d, *J*=3.01 Hz, 1H).



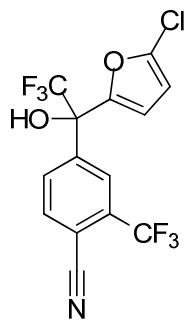
4-(2,2,2-trifluoro-1-hydroxy-1-(thiazol-2-yl)ethyl)-2-(trifluoromethyl)benzonitrile (46).

Ketone **95** was converted to the title product in 18% yield using the procedure for **15**. LCMS AUC showed 100% purity. ESIMS ($M+H$) = 353. HRMS calcd for $C_{13}H_6F_6N_2OS$ ($M-H$) 351.0025, found 351.0032. 1H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.20 (d, $J=8.28$ Hz, 1H), 7.87-7.99 (m, 2H), 7.59 (d, $J=3.26$ Hz, 1H), 5.44 (s, 1H).



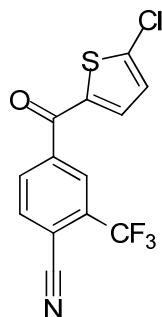
4-(5-chlorofuran-2-carbonyl)-2-(trifluoromethyl)benzonitrile (96).

Following the procedure for **59**, 5-chlorofuran-2-carbaldehyde was converted to the title product in 21% yield. LCMS AUC showed 100% purity. ESIMS ($M+H$) = 300/302. 1H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 8.32 (d, $J=8.03$ Hz, 1H), 8.05 (d, $J=8.03$ Hz, 1H), 7.40 (d, $J=3.51$ Hz, 1H), 6.54 (d, $J=3.76$ Hz, 1H).



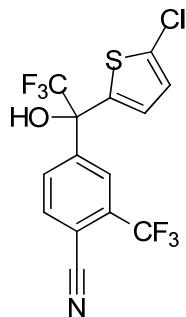
4-(1-(5-chlorofuran-2-yl)-2,2,2-trifluoro-1-hydroxyethyl)-2-(trifluoromethyl)benzonitrile (47).

Ketone **96** was converted to the title product in 76% yield using the procedure for **15**. LCMS AUC showed 100% purity. ESIMS (M-H) = 368. HRMS calcd for $C_{14}H_6ClF_6NO_2$ (M-H) 367.9911, found 367.9907. 1H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.91 (q, $J=8.45$ Hz, 2H), 6.55-6.71 (m, 1H), 6.29 (d, $J=3.51$ Hz, 1H), 3.49 (s, 1H).



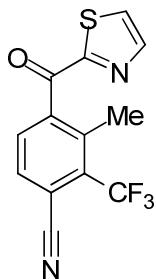
4-(5-chlorothiophene-2-carbonyl)-2-(trifluoromethyl)benzonitrile (97).

Following the procedure for **59**, 5-chlorothiophene-2-carbaldehyde was converted to the title product in 33% yield. LCMS AUC showed 100% purity. ESIMS (M+H) = 316/318. 1H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 8.12 (d, $J=8.03$ Hz, 1H), 8.03 (d, $J=7.78$ Hz, 1H), 7.41 (d, $J=4.27$ Hz, 1H), 7.09 (d, $J=4.27$ Hz, 1H).



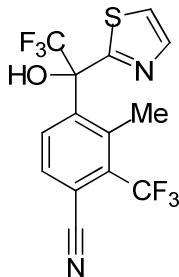
4-(1-(5-chlorothiophen-2-yl)-2,2,2-trifluoro-1-hydroxyethyl)-2-(trifluoromethyl)benzonitrile (48).

Ketone **97** was converted to the title product in 31% yield using the procedure for **15**. LCMS AUC showed 90% purity. ESIMS (M-H) = 384/386. HRMS calcd for $C_{14}H_6ClF_6NOS$ (M-H) 383.9683, found 383.9692. 1H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.91 (s, 2H), 7.03-7.14 (m, 1H), 6.91 (d, $J=3.76$ Hz, 1H), 3.51 (s, 1H).



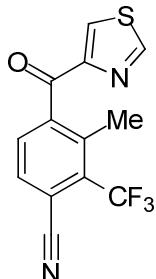
3-methyl-4-(thiazole-2-carbonyl)-2-(trifluoromethyl)benzonitrile (98).

Following the procedure for **59**, **110b** was reacted with thiazole-2-carbaldehyde to give the title product in 30% yield. LCMS AUC showed 100% purity. ESIMS (M+H) = 297. ¹H NMR (400 MHz, CDCl₃) δ 8.10 (d, *J*=3.01 Hz, 1H), 7.89 (d, *J*=3.01 Hz, 1H), 7.75-7.87 (m, 2H), 2.53 (q, *J*=2.18 Hz, 3H).



3-methyl-4-(2,2,2-trifluoro-1-hydroxy-1-(thiazol-2-yl)ethyl)-2-(trifluoromethyl)benzonitrile (49).

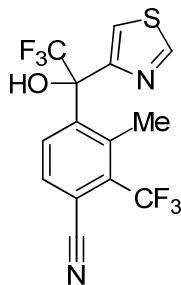
Ketone **98** was converted to the title product in 37% yield using the procedure for **15**. LCMS AUC showed 95% purity. ESIMS (M+H) = 367. HRMS calcd for C₁₄H₈F₆N₂OS (M-H) 365.0182, found 365.0223. ¹H NMR (400 MHz, CDCl₃) δ 8.07 (d, *J*=8.28 Hz, 1H), 7.92 (d, *J*=3.26 Hz, 1H), 7.82 (d, *J*=8.53 Hz, 1H), 7.59 (d, *J*=3.26 Hz, 1H), 5.19 (s, 1H), 2.22 (d, *J*=2.26 Hz, 3H).



3-methyl-4-(thiazole-4-carbonyl)-2-(trifluoromethyl)benzonitrile (99).

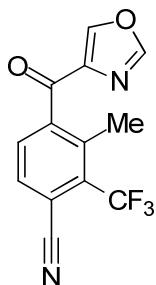
Supporting Information

Following the procedure for **59**, **110b** was reacted thiazole-4-carbaldehyde to give the title product in 31% yield. LCMS AUC showed 100% purity. ESIMS (M+H) = 297. ^1H NMR (400 MHz, CDCl_3) δ 8.88 (d, $J=2.01$ Hz, 1H), 8.48 (d, $J=2.01$ Hz, 1H), 7.81 (d, $J=7.78$ Hz, 1H), 7.67 (d, $J=8.03$ Hz, 1H), 2.48 (q, $J=2.18$ Hz, 3H).



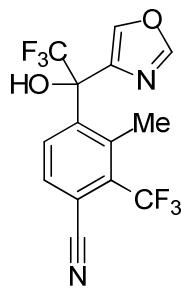
3-methyl-4-(2,2,2-trifluoro-1-hydroxy-1-(thiazol-4-yl)ethyl)-2-(trifluoromethyl)benzonitrile (50).

Ketone **99** was converted to the title product in 70% yield using the procedure for **15**. LCMS AUC showed 100% purity. ESIMS (M+H) = 367. HRMS calcd for $\text{C}_{14}\text{H}_8\text{F}_6\text{N}_2\text{OS}$ (M-H) 365.0182, found 365.0231. ^1H NMR (400 MHz, CDCl_3) δ 8.83-8.99 (m, 1H), 8.04 (d, $J=8.28$ Hz, 1H), 7.79 (d, $J=8.53$ Hz, 1H), 7.16 (s, 1H), 5.06 (s, 1H), 2.06-2.27 (m, 3H).



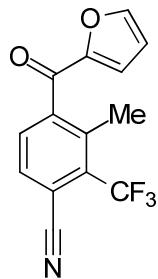
3-methyl-4-(oxazole-4-carbonyl)-2-(trifluoromethyl)benzonitrile (100).

Following the procedure for **59**, **110b** was reacted oxazole-4-carbaldehyde to give the title product in 28% yield. LCMS AUC showed 100% purity. ESIMS (M+H) = 281 and (M-H) = 279. ^1H NMR (400 MHz, CDCl_3) δ 8.39 (d, $J=0.75$ Hz, 1H), 7.94-8.06 (m, 1H), 7.83 (d, $J=8.03$ Hz, 1H), 7.70 (d, $J=8.03$ Hz, 1H), 2.53 (q, $J=2.18$ Hz, 3H).



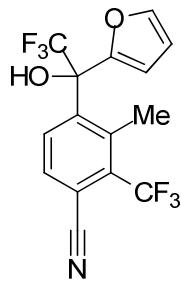
3-methyl-4-(2,2,2-trifluoro-1-hydroxy-1-(oxazol-4-yl)ethyl)-2-(trifluoromethyl)benzonitrile (51).

Ketone **100** was converted to the title product in 41% yield using the procedure for **15**. LCMS AUC showed 100% purity. ESIMS (M+H) = 351 and (M-H) = 349. HRMS calcd for C₁₄H₈F₆N₂O₂ (M-H) 349.0410, found 349.0385. ¹H NMR (400 MHz, METHANOL-d₄) δ 8.21-8.30 (m, 1H), 8.09-8.20 (m, 2H), 7.90 (d, *J*=8.53 Hz, 1H), 2.38 (d, *J*=2.26 Hz, 3H).



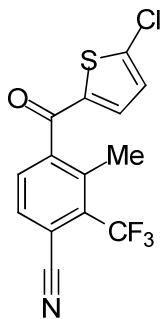
4-(furan-2-carbonyl)-3-methyl-2-(trifluoromethyl)benzonitrile (101).

Following the procedure for **59**, **110b** was reacted furan-2-carbaldehyde to give the title product in 16% yield. ¹H NMR (400 MHz, CDCl₃) δ 7.81 (d, *J*=7.78 Hz, 1H), 7.71-7.78 (m, 1H), 7.66 (d, *J*=8.03 Hz, 1H), 7.14 (d, *J*=3.51 Hz, 1H), 6.66 (dd, *J*=1.63, 3.64 Hz, 1H), 2.51 (d, *J*=2.01 Hz, 3H).



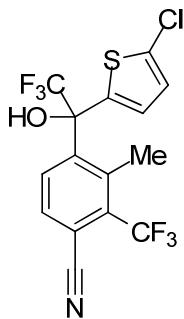
3-methyl-4-(2,2,2-trifluoro-1-(furan-2-yl)-1-hydroxyethyl)-2-(trifluoromethyl)benzonitrile (52).

Ketone **101** was converted to the title product in 66% yield using the procedure for **15**. LCMS AUC showed 91% purity. ESIMS (M-H) = 348. HRMS calcd for C₁₅H₉F₆NO₂ (M-H) 348.0457, found 348.0500. ¹H NMR (400 MHz, CDCl₃) δ 8.14 (d, *J*=8.53 Hz, 1H), 7.78 (d, *J*=8.53 Hz, 1H), 7.44-7.56 (m, 1H), 6.58 (br. s., 1H), 6.52 (dd, *J*=1.88, 3.39 Hz, 1H), 3.24 (s, 1H), 2.11-2.32 (m, 3H).



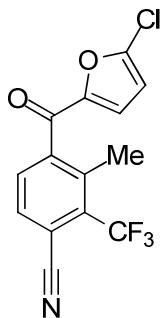
4-(5-chlorothiophene-2-carbonyl)-3-methyl-2-(trifluoromethyl)benzonitrile (102).

Following the procedure for **59**, **110b** was reacted 5-chlorothiophene-2-carbaldehyde to give the title product in 20% yield. LCMS AUC showed 99% purity. ESIMS ($\text{M}+\text{H}$) = 330/332. ^1H NMR (400 MHz, CDCl_3) δ 7.82 (d, $J=7.78$ Hz, 1H), 7.63 (d, $J=7.78$ Hz, 1H), 7.14 (d, $J=4.27$ Hz, 1H), 7.03 (d, $J=4.02$ Hz, 1H), 2.42-2.57 (m, 3H).



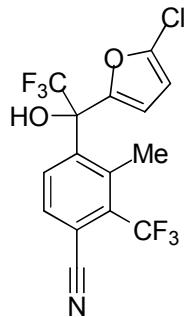
4-(1-(5-chlorothiophen-2-yl)-2,2,2-trifluoro-1-hydroxyethyl)-3-methyl-2-(trifluoromethyl)benzonitrile (53).

Ketone **102** was converted to the title product in 56% yield using the procedure for **15**. LCMS AUC showed 98% purity. ESIMS ($\text{M}-\text{H}$) = 398/400. HRMS calcd for $\text{C}_{15}\text{H}_8\text{ClF}_6\text{NOS}$ ($\text{M}-\text{H}$) 397.9839, found 397.9866. ^1H NMR (400 MHz, CDCl_3) δ 8.05 (d, $J=8.28$ Hz, 1H), 7.78 (d, $J=8.53$ Hz, 1H), 6.86 (d, $J=4.02$ Hz, 1H), 6.76 (d, $J=4.02$ Hz, 1H), 3.27 (s, 1H), 2.43 (d, $J=2.01$ Hz, 3H).



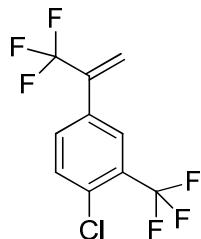
4-(5-chlorofuran-2-carbonyl)-3-methyl-2-(trifluoromethyl)benzonitrile (103).

Following the procedure for **59**, **110b** was reacted 5-chlorofuran-2-carbaldehyde to give the title product in 26% yield. LCMS AUC showed 97% purity. ESIMS ($M+H$) = 314/316. ^1H NMR (400 MHz, CDCl_3) δ 7.82 (d, $J=7.78$ Hz, 1H), 7.65 (d, $J=8.03$ Hz, 1H), 7.10 (d, $J=3.51$ Hz, 1H), 6.48 (d, $J=3.76$ Hz, 1H), 2.43-2.62 (m, 3H).



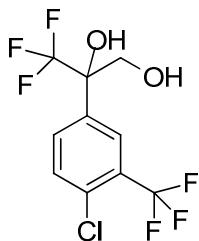
4-(1-(5-chlorofuran-2-yl)-2,2,2-trifluoro-1-hydroxyethyl)-3-methyl-2-(trifluoromethyl)benzonitrile (54).

Ketone **103** was converted to the title product in 64% yield using the procedure for **15**. LCMS AUC showed 100% purity. ESIMS ($M-H$) = 382/384. HRMS calcd for $\text{C}_{15}\text{H}_8\text{ClF}_6\text{NO}_2$ ($M-H$) 382.0068, found 382.0085. ^1H NMR (400 MHz, CDCl_3) δ 8.09 (d, $J=8.53$ Hz, 1H), 7.79 (d, $J=8.53$ Hz, 1H), 6.55 (d, $J=3.01$ Hz, 1H), 6.30 (d, $J=3.51$ Hz, 1H), 3.27 (br. s., 1H), 2.32 (d, $J=2.01$ Hz, 3H).



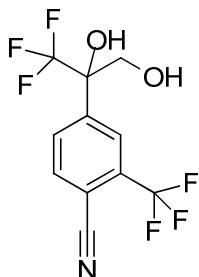
1-chloro-2-(trifluoromethyl)-4-(3,3,3-trifluoroprop-1-en-2-yl)benzene (113).

To a solution of 4-chloro-3-trifluoromethylphenyl boronic acid **112** (0.314 g, 1.399 mmol) and 2-bromo-3,3,3-trifluoropropene (0.245 g, 1.399 mmol) in 1,2-dimethoxyethane (6 ml) and water (2 ml) in a sealed tube were added sodium carbonate (0.237 g, 2.239 mmol) and dichlorobis(triphenylphosphine) palladium (II) (0.05 g) were added. The tube was sealed and stirred at 80 °C for 1 h. The reaction mixture was cooled to room temperature. The organic layer was separated in a separatory funnel, concentrated and the product purified on a silica gel column (12 g). The desired product eluted with 100% hexane. Isolate the desired product as a colorless oil, 0.237 g, 62% yield. GCMS showed very high purity and strong parent molecular ion at 274. ^1H NMR (400 MHz, CDCl_3) δ 7.75 (s, 1H), 7.47-7.61 (m, 2H), 6.07 (s, 1H), 5.83 (s, 1H).



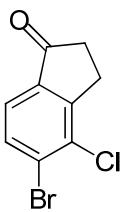
2-(4-chloro-3-(trifluoromethyl)phenyl)-3,3,3-trifluoropropane-1,2-diol (114).

Alkene **113** (0.237 g, 0.863 mmol) was dissolved in acetone (6 ml) and water (2 ml). To the solution was added N-methylmorpholine-N-oxide (0.121 g, 1.036 g) and OsO₄ solution (2.5 wt% in t-BuOH, 0.216 ml, 0.017 mmol) at RT. The reaction was stirred overnight at RT. LCMS after 16 h showed new peak for product plus the starting olefin is still present. To the reaction mixture was added 50 mg N-methylmorpholine-N-oxide and 0.1 ml OsO₄ solution. After stirring for 7 h, LCMS showed complete reaction. The acetone was removed under vacuum and the residue was partitioned between water and EtOAc. The solution was extracted twice with EtOAc and the combined organics were dried over Na₂SO₄ and concentrated. Purify with silica gel column chromatography. Solvent system A: DCM; B: 10% MeOH / DCM. The desired product eluted at 30% B. Isolate product as a colorless oil, 144 mg, 0.467 mmol, 54% yield. LCMS AUC showed 100% purity. ESIMS (M-H) = 307/309. ¹H NMR (400 MHz, CDCl₃) δ 7.88-8.00 (m, 1H), 7.65-7.75 (m, 1H), 7.59 (d, *J*=8.53 Hz, 1H), 4.39 (dd, *J*=5.40, 11.92 Hz, 1H), 3.77-3.95 (m, 2H), 2.02 (dd, *J*=5.52, 7.53 Hz, 1H)



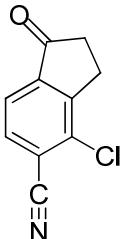
4-(1,1,1-trifluoro-2,3-dihydroxypropan-2-yl)-2-(trifluoromethyl)benzonitrile (115).

To a solution of **114**, 2-(4-chloro-3-(trifluoromethyl)phenyl)-3,3,3-trifluoropropane-1,2-diol (0.104 g, 0.337 mmol) in DMF (3 ml) was added zinc cyanide (0.079 g, 0.674 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.039 g, 0.034 mmol). The reaction flask was purged with nitrogen, then heated at 150 °C for 3.5 h. LCMS showed about 65% product to starting material. Workup: The reaction mixture at RT was partitioned between brine and EtOAc and the organic layer was dried over Na₂SO₄, filtered and concentrated. The product was purified using reverse-phase C18 column. Dry down fractions giving desired product (34.3 mg, 0.115 mmol, 34.0 % yield). LCMS AUC showed 98%. ESIMS (M-H) = 298 and (M+45) = 344. HRMS calcd for C₁₁H₇F₆NO₂ (M-H) 298.0301, found 298.0284. ¹H NMR (400 MHz, METHANOL-d₄) δ 8.22 (s, 1H), 8.00-8.16 (m, 2H), 4.15 (d, *J*=11.80 Hz, 1H), 4.04 (d, *J*=11.80 Hz, 1H).



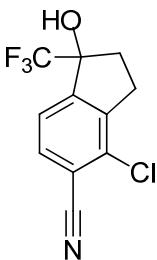
5-bromo-4-chloro-2,3-dihydro-1H-inden-1-one (116).

The title product was prepared from 3-bromo-2-chlorobenzaldehyde using the procedure as outlined in *Tetrahedron*, **2007**, vol. 63(2), p. 389 – 395. LCMS AUC showed high purity (93%) and (M+H) ions at 247, 245 for product. GCMS showed single peak and distinctive molecular ion isotope pattern: 246, 244, 248, 247, 245, 249. ^1H NMR (400 MHz, CDCl_3) δ 7.70 (d, J =8.03 Hz, 1H), 7.54 (d, J =8.28 Hz, 1H), 3.12-3.25 (m, 2H), 2.70-2.84 (m, 2H).



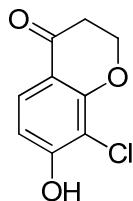
4-chloro-1-oxo-2,3-dihydro-1H-indene-5-carbonitrile (117).

Following the cyanation procedure for **115**, the reaction mixture was heated to 100 °C for 60 min giving the desired product in 76% yield. LCMS AUC showed 100% purity. GCMS showed strong molecular ion at 191/193 for desired product. ^1H NMR (400 MHz, CDCl_3) δ 7.63-7.86 (m, 2H), 3.14-3.32 (m, 2H), 2.72-2.97 (m, 2H).



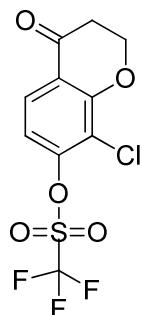
4-chloro-1-hydroxy-1-(trifluoromethyl)-2,3-dihydro-1H-indene-5-carbonitrile (118).

4-Chloro-1-oxo-2,3-dihydro-1H-indene-5-carbonitrile **117**, was converted to the title product following the procedure for **13**. LCMS AUC 100% purity. ESIMS (M-H) = 260/262; (M+H) = 262/264. HRMS calcd for $\text{C}_{11}\text{H}_7\text{ClF}_3\text{NO}$ (M-H) 260.0088, found 260.0071. ^1H NMR (400 MHz, CDCl_3) Shift 7.68 (d, J =8.03 Hz, 1H), 7.54 (d, J =7.78 Hz, 1H), 3.17-3.32 (m, 1H), 3.01-3.17 (m, 1H), 2.72-2.89 (m, 1H), 2.35 (dd, J =1.38, 6.65, 9.07, 14.27 Hz, 3H).



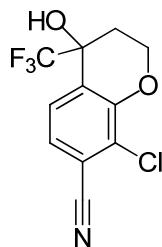
8-chloro-7-hydroxychroman-4-one (119).

The title compound was prepared from 2-chlorobenzene-1,3-diol using the procedures outlined in Bioorganic and Medicinal Chemistry Letters, 2005, vol. 15, # 9 p. 2389 – 2393. LCMS ESIMS (M+H) = 235/237. ^1H NMR (400 MHz, CDCl_3) δ 7.80 (d, $J=8.79$ Hz, 1H), 6.74 (d, $J=8.79$ Hz, 1H), 6.17 (br. s., 1H), 4.65 (t, $J=6.54$ Hz, 2H), 2.81 (t, $J=6.44$ Hz, 2H).



8-chloro-4-oxochroman-7-yl trifluoromethanesulfonate (120).

To a solution of **119**, 8-chloro-7-hydroxychroman-4-one (1.5 g, 7.55 mmol), in DCM (40 ml) was added triethylamine (1.26 ml, 1.2 eq) and trifluoromethanesulfonic anhydride (1.40 ml, 1.1 eq). After 15 min, the solvent was removed under vacuum and the product purified by silica column chromatography giving the title compound in 93% yield. ESIMS (M+H) = 332.



8-chloro-4-hydroxy-4-(trifluoromethyl)chroman-7-carbonitrile (121).

The title compound was prepared from 8-Chloro-4-oxochroman-7-yl trifluoromethanesulfonate **120** following the cyanation procedure for **115** followed by the procedure used to give **13** affording the title product in 31% overall yield for the 2 steps. LCMS AUC showed 100% purity. ESIMS (M-H) = 276. HRMS calcd for $\text{C}_{11}\text{H}_7\text{ClF}_3\text{NO}_2$ (M-H) 276.0037, found 276.0022. ^1H NMR (400 MHz, CDCl_3) δ 7.56-7.71 (m, 1H), 7.25-7.32 (m, 1H), 4.52-4.63 (m, 1H), 4.37-4.52 (m, 1H), 2.49 (ddd, $J=4.02, 8.53, 14.56$ Hz, 1H), 2.25-2.37 (m, 1H), 2.19 (br. s., 1H).