Supplemental Info

Liver Microsomal Clearance assay

For determination of CYP-mediated metabolic stability, test compounds (1 μM), were incubated with 0.5 mg/mL of rat or human liver microsomes suspended in 50 mM potassium phosphate buffer, pH 7.4 supplemented with 2 mM $MgCl_2$. CYP cofactor, NADPH (1 mM), was added to initiate bulk reactions (300 μL final volume). Following 0, 5, 20 and 30 min of incubation at 37 °C, 50 μL aliquots were removed in singlet and reactions were terminated using an equal volume of acetonitrile/H_20 (80:20) containing 0.4 μM glyburide as LC-MS/MS internal standard. The quenched reactions were centrifuged for 10 min at 3400x*g* to pellet precipitated protein, and supernatant was submitted for LC-MS/MS quantification of parent compound remaining at each time point. The *in vitro* clearance half-life, t(1/2), was determined essentially as described elsewhere based on the natural logarithm-linear transformation of % parent remaining versus time [Obach 1999].

Biotransformation

For metabolite ID, compound was incubated with rat liver microsomes for 30 min using similar conditions as the CYP stability test. Samples were precipitated with 1.5 x volumes of 100% acetonitrile followed by 10 min centrifugation at 4000g. 10μl of supernatant was analyzed by LC/MS/MS in a TSQ Quantum Ultra® Mass Spectrometer (Thermo Fisher Scientific, Waltham MA) in H-ESI positive mode. A Waters XTerra® MS C18 5μM particle size 4.6x150 mm with MS C18 5μM Waters Sentry® Guard Column was used for separation of parent and metabolites. The following reverse phase LC conditions were used: mobile phase A = H_2O+0.1% formic acid; mobile phase B = acetonitrile + 0.1% formic acid; flow = 1 mL/min; gradient ramp from 5% B at 1 min to 95% B over 21 min (25 min total run time). Authentic standards were used to develop specific SRM methods for parent compounds, as well as putative metabolites. Specific retention time, UV absorption spectra and product ion spectra of compounds and metabolites (authentic standards and assay produced metabolites) were analyzed to confirm compound identities.

CYP Inhibition

Reversible and time-dependent CYP inhibition (TDI) was assessed with human liver microsomes in an "IC_{50}-shift" approach [Obach et al, 2007]. Briefly, test compounds were first pre-incubated at 37 ^{o}C, with human liver microsomes (0.1 mg/mL) suspended in 100 mM potassium phosphate buffer, pH 7.4, supplemented with 5 mM $MgCl_2$ plus or minus 1 mM NADPH. Each compound was examined at 7 concentrations, ranging from 0.14 to 100 µM in the pre-incubation to evaluate the dose-response. After 30 min, all pre-incubations were then combined with an equal volume of 100 mM phosphate buffer, pH 7.4, containing 1 mM NADPH and selective CYP 3A4/5 probe substrate, midazolam (2 µM). This dilution step generated a final incubation mixture of 0.05 mg/mL human liver micosomes, 0.07-50 µM test compound and 1 µM midazolam that was incubated an additional 10 min at 37 ^{o}C. This final reaction (100 µL) was terminated through addition of 185 µL of acetonitrile containing [$^{13}C_3$]-1'-hydroxymidazolam as MS internal standard and supernatants were prepared for bioanalysis essentially as described above. Bioanalysis of 1'-hydroxymidazolam formation in each reaction well was determined as previously reported [Brown et al, 2009].

Each IC_{50} was derived from an 8-point dose-response (including a 0 µM reference incubation) tested in singlet, and % CYP 3A4/5 inhibition for each reaction was determined relative to a 0 µM reference incubation used to define 100% of midazolam 1'-hydroxylation activity. A linear-log transformation of % inhibition versus test article concentration was fit with a 4-parameter, one-site dose-response curve using XLFit. The IC_{50} that is derived from the pre-incubation lacking NADPH is taken as the measure of competitive, reversible CYP inhibition. For each compound, the ratio of IC_{50} derived from pre-incubations lacking NADPH versus pre-incubations containing NADPH was used as an indicator of CYP 3A4/5 TDI, where a ratio >2 is indicative of TDI.

[Obach RS (1999)] Prediction of human clearance of twenty-nine drugs from hepatic microsomal intrinsic clearance data: An examination of *in vitro* half-life approach and nonspecific binding to microsomes. *Drug Metab. Dispos.*; **27**:1350-1359.

[Obach RS, Walsky RL, Venkatakrishnan (2007)] Mechanism-Based Inactivation of Human Cytochrome P450 Enzymes and the Prediction of Drug-Drug Interactions. *Drug Metab. Dispos.*; **35**: 246-255.

[Brown A, Bickford S, Hatsis P, Amin J, Bell L, Harriman S (2010)] High-throughput analysis of in vitro cytochrome p450 inhibition samples using mass spectrometry

coupled with an integrated liquid chromatography/autosampler system. *Rapid Commun. Mass Spectrom.* **24**:1207-1210.

CYP Reaction Phenotyping

The Cytochrome P450 (CYP) Reaction Phenotyping (RP) Assay is designed to assess the relative metabolic clearance contribution of five major human CYP drug-metabolizing isoforms (3A, 2D6, 2C9, 1A2 and 2C19) to the metabolism of new chemical entities (NCEs) in Human Liver Microsomes (HLM). These five isoforms contribute to the biotransformation of about 90% marketed drugs subjected to human CYP metabolism [Guengerich, 2004]. The assay described here uses the parent depletion approach [Lau 2002, Obach 1999, Obach 1997]. The condition for achieving isoform-selective inhibition is through addition in combination of selective chemical inhibitors and/or monoclonal antibodies (mAb) to knock out individual CYP activities to inhibit each of the five major CYPs isoforms (3A, 2D6, 2C9, 1A2, 2C19) by >90% while generating <20% “off-target” CYP inhibition. The contribution of each of the major CYPs to microsomal clearance of a new chemical entity (NCE) can be measured. This is done by evaluating the reduction in intrinsic clearance (CL_{int}) observed in selectively inhibited CYP incubations relative to the uninhibited control CL_{int}, reported as a “% Clearance Inhibition” (%CL Inh) for each of the five major CYP isoforms outlined above. The observation of a high %CL Inh associated with a particular CYP isoform is indicative of a high contribution from that CYP isoform in the NCE metabolism.

[Guengerich FP (2004)] Cytochrome P450: What Have We Learned and What Are the Future Issues? *Drug Metab. Rev.;* **36**, **No. 2**: 159–197.

[Lau YY, Krishna G, Yumibe NP, Grotz DE, Sapidou E, Norton L, Chu I, Chen C, Soares AD, Lin CC (2002)] The use of *in vitro* metabolic stability for rapid selection of compounds in early discovery based on their expected hepatic extraction ratios. *Pharm. Res.;* **19**:1606-1610.

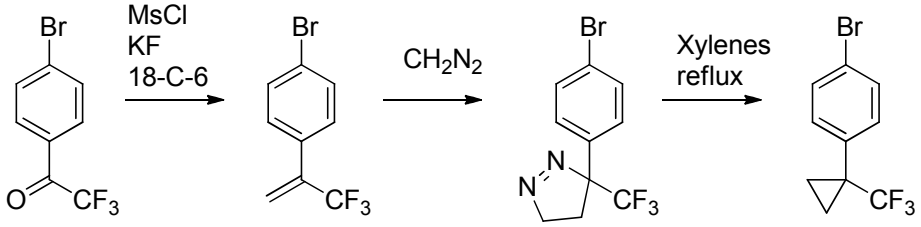
[Obach RS, Baxter JG, Liston TE, Silber BM, Jones BC, MacIntyre F, Rance DJ, Wastall P (1997)] The prediction of human pharmacokinetic parameters from preclinical and *in vitro* metabolism data. *J. Pharmacol. Exp. Ther.;* **283**:46-58.

[Obach RS (1999)] Prediction of human clearance of twenty-nine drugs from hepatic microsomal intrinsic clearance data: An examination of *in vitro* half-life approach and nonspecific binding to microsomes. *Drug Metab. Dispos.;* **27**:1350-1359.

In Vivo Clearance Studies in Sprague-Dawley Rats. The in-life portion of this study was conducted at Novartis Institutes for Biomedical Research (Cambridge, MA) in accordance with Institutional Animal Care and Use Committee (IACUC) protocols. For each Novartis compound, male Sprague-Dawley rats (n=3) with dual jugular veins cannulated were administered an intravenous ≤ 1 mg/kg dose of the compound, formulated as a solution. Blood samples were collected at 0.083, 0.25, 0.5, 1, 2, 4 and 7 h post dose and centrifuged to obtain plasma. Plasma was stored at -80°C until bioanalysis.

Spectral data

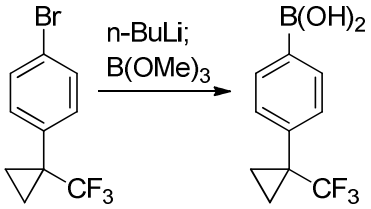
Analytic HPLC method: Atlantis 4.6x150 mm 0-95% acetonitrile/water 0.1% trifluoroacetic acid in 19 min. Purity by HPLC UV was >99% for all products.
LCMS method: 3 mm x 33 mm Intersil C8-3 reverse phase, 3.0 µm particle size running a gradient of 5-95% MeCN/water (5 mM ammonium formate) over a period of 2 min at a flow rate of 4 mL/min at 40 °C; DAD-UV detection, 220-600 nm.
HRMS data was collected using a Waters LCT Premier mass spectrometer with dual electrospray ionization source and Waters Acquity UPLC. The resolution of the MS system was approximately 12000 (FWHM definition).



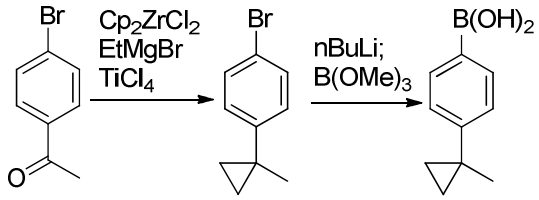
1-bromo-4-(3,3,3-trifluoroprop-1-en-2-yl)benzene was prepared as described in Nader, B. S.; Cordova, J. A.; Reese, K. E.; Powell, C. L. *J. Org. Chem.* **1994**, 2898-2901.

3-(4-Bromo-phenyl)-3-trifluoromethyl-4,5-dihydro-3*H*-pyrazole was prepared analogous to a literature procedure (*Eur. Pat. Appl.* **1999**, EP0933363A1) from 1-(4-bromo-phenyl)-2,2,2-trifluoro-ethanone as a pale-yellow oil.

1-Bromo-4-(1-trifluoromethyl-cyclopropyl)-benzene was prepared analogous to a literature procedure (*Eur. Pat. Appl.* **1999**, EP0933363A1) from 3-(4-bromo-phenyl)-3-trifluoromethyl-4,5-dihydro-3*H*-pyrazole as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (m, 2H), 7.24 (d, *J* = 8 Hz, 2H), 1.25-1.28 (m, 2H), 0.90-0.93 (m, 2H).



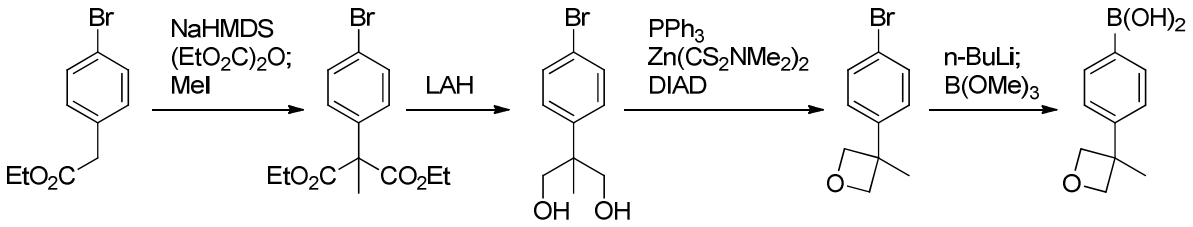
4-(1-(trifluoromethyl)cyclopropyl)phenylboronic acid: To 1-bromo-4-(1-(trifluoromethyl)cyclopropyl)benzene (5.0 g, 19 mmol) in THF (50 mL) at -78 °C was added butyllithium (13 mL, 21 mmol). After stirring 1h, trimethylborate (3.15 mL, 28.3 mmol) was added. After warming to room temp, the THF was removed *in vacuo*. The solid residue was taken up in water and extracted with ether to remove non-polar impurities. The aqueous layer was acidified and extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride, dried over sodium sulfate, filtered and concentrated to dryness to afford pure 4-(1-(trifluoromethyl)cyclopropyl)phenylboronic acid (3.12 g, 72%). ^{1}H NMR (400 MHz, MeOD) δ 7.60 (d, *J* = 8 Hz, 2H), 7.46 (d, *J* = 8 Hz, 2H), 1.34 (m, 2H), 1.06 (m, 2H);
ES- M-H (-) 229.3.



1-Bromo-4-(1-methyl-cyclopropyl)-benzene was prepared from 1-(4-bromo-phenyl)-ethanone according to a literature procedure (*Eur. J. Org. Chem.* **2000**, 3713-3719) with

the following notes. In stage 2, $TiCl_4$ was used for the ring contraction. After workup as described in that paper, silica gel flash chromatography eluted with straight heptane gave the title compound as a colorless oil.

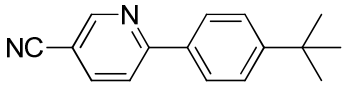
4-(1-methyl-cyclopropyl)phenylboronic acid was prepared by the procedure for 4-(1-(trifluoromethyl)cyclopropyl)phenylboronic acid.



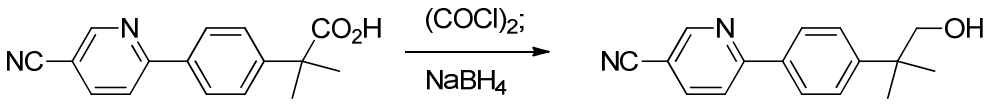
3-(4-bromophenyl)-3-methyloxetane was prepared according to Brodney, M. A. **2006** PCT Int. Appl., 2006000912.

(4-(3-methyloxetan-3-yl)phenyl)boronic acid was prepared by the procedure for 4-(1-(trifluoromethyl)cyclopropyl)phenylboronic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.76 (m, 2H), 7.13-7.35 (m, 2H), 4.96 (d, *J* = 6 Hz, 2H), 4.63 (d, *J* = 6 Hz, 2H) 1.68 (s, 3H); ES- M-H (-) 191.3.

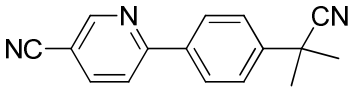
General procedure for the synthesis of compounds 1-10, 19-22: The arylboronic acid was stirred with 1 eq of the aryl halide, 0.06 eq of dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (SPhos), 0.03 eq of $Pd(OAc)_2$ and 3 eq potassium phosphate in THF until the reaction was judged complete by LCMS, then filtered and purified by HPLC (acetonitrile/water with 0.1% ammonium hydroxide).



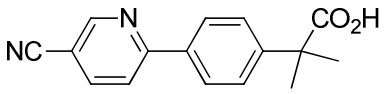
6-(4-tert-butylphenyl)nicotinonitrile (1): Yield 69%; ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.93 (dd, *J* = 0.88, 2.15 Hz, 1H), 7.96 - 8.04 (m, 3H), 7.83 (dd, *J* = 0.88, 8.46 Hz, 1H), 7.51 - 7.56 (m, 3H), 1.37 (s, 9H); ^{13}C NMR (400 MHz, CHLOROFORM-d) δ 160.48, 154.19, 152.46, 139.72, 134.56, 127.14, 126.07, 119.64, 117.13, 107.47, 34.89, 31.20 ppm; HPLC rt 16.50 min, LCMS rt 1.61 min , ES+ M+H (+) 237.3; HRMS $[M+H]^+$ 237.1391, calcd 237.1386.



6-(4-(1-hydroxy-2-methylpropan-2-yl)phenyl)nicotinonitrile (2): 2-(4-(5-cyanopyridin-2-yl)phenyl)-2-methylpropanoic acid (20 mg, 0.075 mmol) was stirred in methylene chloride (1 mL) and oxalyl chloride (1 mL) for 3 hr, then evaporated to dryness. The residue was dissolved in THF (1 mL), cooled to 0 °C, and sodium borohydride (14 mg, 0.37 mmol) was added. The reaction mixture was stirred at 23 °C for 1 hr. The reaction was judged complete by LCMS, quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered, evaporated and purified by HPLC (acetonitrile/water with 0.1% ammonium hydroxide) to afford 6-(4-(1-hydroxy-2-methylpropan-2-yl)phenyl)nicotinonitrile (11 mg, 0.044 mmol, 58% yield). ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.96 (dd, *J* = 0.76, 2.27 Hz, 1H), 7.99 - 8.08 (m, 3H), 7.86 (dd, *J* = 0.76, 8.34 Hz, 1H), 7.53 - 7.60 (m, 2H), 3.70 (d, *J* = 4.55 Hz, 2H), 1.41 (s, 6H). 1.29 (br. s., 1H) ppm; ^{13}C NMR (400 MHz, CHLOROFORM-d) δ 160.25, 152.51, 149.51, 139.85, 135.30, 127.42, 127.08, 119.79, 117.08, 107.69, 72.90, 40.32, 25.29 ppm; HPLC rt 12.46 min, LCMS rt 1.37 min, ES+ M+H (+) 253.3; HRMS $[M+H]^{+}$ 253.1341, calcd 252.1335.

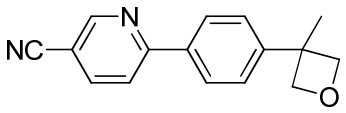


6-(4-(2-cyanopropan-2-yl)phenyl)nicotinonitrile (3): Yield 77%; ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.97 (dd, *J* = 0.88, 2.15 Hz, 1H), 8.08 - 8.13 (m, 2H), 8.05 (dd, *J* = 2.02, 8.34 Hz, 1H), 7.88 (dd, *J* = 1.01, 8.34 Hz, 1H), 7.61 - 7.68 (m, 2H), 1.80 (s, 6H) ppm; ^{13}C NMR (400 MHz, CHLOROFORM-d) δ 159.55, 152.54, 143.93, 140.02, 136.95, 127.96, 125.90, 124.11, 119.97, 116.89, 108.19, 37.20, 29.06 ppm; HPLC rt 12.68 min, LCMS rt 1.44 min, ES+ M+H (+) 248.4; HRMS $[M+H]^{+}$ 248.1185, calcd 248.1182.

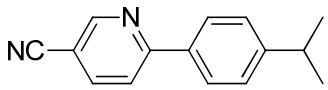


2-(4-(5-cyanopyridin-2-yl)phenyl)-2-methylpropanoic acid (4): Yield 78%; ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 11 (br. s., 1H), 8.97 (dd, *J* = 0.76, 2.02 Hz, 1H), 8.02-8.09 (m, 3H) 7.81 - 7.89 (m, 1H), 7.51 - 7.63 (m, 2H), 1.67 (s, 6H) ppm; ^{13}C NMR (400 MHz, CHLOROFORM-d) δ 180.43, 160.04, 152.46, 146.68, 139.96, 135.98, 127.52,

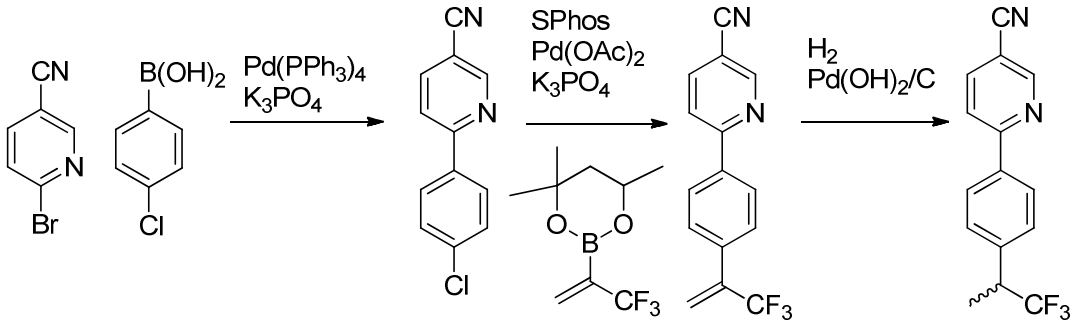
126.66, 119.99, 116.96, 107.91, 77.22, 26.24 ppm; HPLC rt 12.52 min, LCMS rt 1.17 min, ES+ M+H (+) 267.1; HRMS $[M+H]^+$ 267.1140, calcd 267.1128.



6-(4-(3-methyloxetan-3-yl)phenyl)nicotinonitrile (5): Yield 70%; ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.96 (dd, *J* = 0.88, 2.15 Hz, 1H), 8.00 - 8.11 (m, 3H), 7.84 - 7.92 (m, 1H), 7.35 - 7.41 (m, 2H), 5.02 (d, *J* = 5.56 Hz, 2H), 4.71 (d, *J* = 5.56 Hz, 2H), 1.79 (s, 3H) ppm; ^{13}C NMR (400 MHz, CHLOROFORM-d) δ 160.07, 152.51, 149.25, 139.91, 135.51, 127.67, 125.88, 119.81, 117.02, 107.82, 83.54, 43.46, 27.64 ppm; HPLC rt 11.87 min, LCMS rt 1.45 min, ES+ M+H (+) 251.0; HRMS $[M+H]^+$ 251.1182, calcd 251.1179.



6-(4-isopropylphenyl)nicotinonitrile (6): Yield 84%; ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.92 (dd, *J* = 0.76, 2.27 Hz, 1H), 7.94 - 8.02 (m, 3H), 7.82 (dd, *J* = 0.76, 8.34 Hz, 1H), 7.34 - 7.40 (m, 2H), 2.99 (sept, *J* = 6.95 Hz, 1H), 1.25 - 1.32 (m, 6H) ppm; ^{13}C NMR (400 MHz, CHLOROFORM-d) δ 160.55, 152.45, 151.95, 139.78, 134.95, 127.43, 127.24, 119.69, 117.16, 107.44, 34.06, 23.82 ppm; HPLC rt 14.85 min, LCMS rt 1.64 min, ES+ M+H (+) 223.4; HRMS $[M+H]^+$ 223.1230, calcd 223.1230.



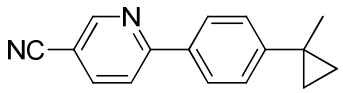
6-(4-(1,1,1-trifluoropropan-2-yl)phenyl)nicotinonitrile (7)

A. 6-(4-chlorophenyl)nicotinonitrile: To 4-chlorophenylboronic acid (64.1 mg, 0.410 mmol), 2-bromo-5-cyanopyridine (75 mg, 0.41 mmol), and potassium phosphate (261 mg, 1.23 mmol) in THF (0.5 mL) under nitrogen was added tetrakis(triphenylphosphine)palladium(0) (23.7 mg, 0.0205 mmol) in THF (0.5 mL) under

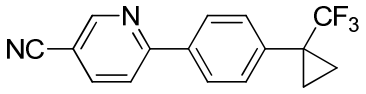
nitrogen. The reaction mixture was stirred at 100 °C until it was judged complete by LCMS, and then filtered and purified by HPLC to afford 19 mg (22%) 6-(4-chlorophenyl)nicotinonitrile.

B. 6-(4-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)nicotinonitrile: To a mixture of 6-(4-chlorophenyl)nicotinonitrile (16.4 mg, 0.0764 mmol), 4,4,6-trimethyl-2-(3,3,3-trifluoroprop-1-en-2-yl)-1,3,2-dioxaborinane (33.9 mg, 0.153 mmol), and potassium phosphate (48.7 mg, 0.229 mmol) in THF (1 mL) was added a premixed solution of SPhos (1.9 mg, 4.6 µmol) and palladium acetate (0.5 mg, 2 µmol). The reaction mixture was stirred at 120 °C with microwave irradiation for 20 min. After the reaction mixture was judged complete by LCMS, it was filtered and purified by HPLC to afford 6 mg (29%) 6-(4-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)nicotinonitrile.

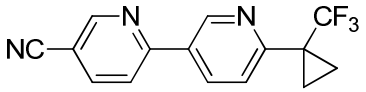
C. 6-(4-(1,1,1-trifluoropropan-2-yl)phenyl)nicotinonitrile: To 6-(4-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)nicotinonitrile (6 mg, 0.02 mmol) in EtOAc (1 mL) and THF (1 mL) a was added 5 mg $Pd(OH)_2/C$. The reaction vessel was evacuated and flushed with hydrogen. The reaction mixture was stirred until it was judged complete by LCMS. The reaction mixture was filtered and purified by HPLC to afford 3.4 mg (56%) 6-(4-(1,1,1-trifluoropropan-2-yl)phenyl)nicotinonitrile. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.94 (s, 1H), 7.97 - 8.09 (m, 3H), 7.85 (d, *J* = 8.34 Hz, 1H), 7.47 (d, *J* = 7.58 Hz, 2H), 3.51 (td, *J* = 8.08, 16.17 Hz, 1H), 1.56 (d, *J* = 7.33 Hz, 3H) ppm; ^{13}C NMR (400 MHz, CHLOROFORM-d) δ 159.89, 152.52, 139.93, 139.04, 138.92, 137.19, 129.26, 128.85, 127.62, 119.94, 108.1, 44.08 (q, *J* = 27.81 Hz), 14.57 ppm; HPLC rt 15.91 min LCMS rt 1.61 min, ES+ M+H (+) 277.2; HRMS $[M+H]^+$ 277.0952, calcd 277.0947.



6-(4-(1-methylcyclopropyl)phenyl)nicotinonitrile (8): Yield 62%; ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.92 (dd, *J* = 0.76, 2.27 Hz, 1H), 7.92 - 8.02 (m, 3H), 7.82 (dd, *J* = 0.76, 8.34 Hz, 1H), 7.33 - 7.41 (m, 2H), 1.46 (s, 3H), 0.89 - 0.99 (m, 2H), 0.76 - 0.89 (m, 2H) ppm; ^{13}C NMR (400 MHz, CHLOROFORM-d) δ 160.39, 152.45, 150.29, 139.74, 134.39, 127.20, 127.02, 119.61, 117.1, 107.38, 25.07, 19.47, 16.52 ppm; HPLC rt 15.44 min, LCMS rt 1.73 min, ES+ M+H (+) 235.2; HRMS $[M+H]^+$ 235.1240, calcd 235.1230.

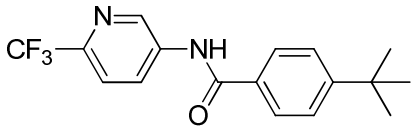


6-(4-(1-(trifluoromethyl)cyclopropyl)phenyl)nicotinonitrile (9): Yield 81%; ^{1}H NMR (400 MHz, ACETONITRILE-d_3) δ 9.10 - 9.16 (m, 1H), 8.33 (dd, *J* = 2.30, 8.59 Hz, 1H), 8.29 (d, *J* = 8.21 Hz, 2H), 8.19 (dd, *J* = 0.57, 8.40 Hz, 1H), 7.81 (d, *J* = 8.34 Hz, 2H), 1.54 - 1.63 (m, 2H), 1.32 (s, 2H); ^{13}C NMR (400 MHz, CHLOROFORM-d) δ 159.86, 152.50, 139.96, 138.68, 137.33, 131.92, 127.37, 120.04, 116.92, 108.08, 28.09, 9.98 ppm; HPLC rt 16.09 min, LCMS rt 1.57, ES+ M+H (+) 289.1; HRMS $[M+H]^+$ 289.0955, calcd 289.0947.

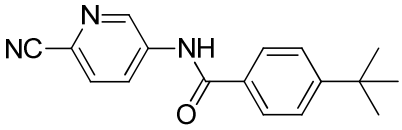


6'-(1-(trifluoromethyl)cyclopropyl)-2,3'-bipyridine-5-carbonitrile (10)
5-bromo-2-(1-(trifluoromethyl)cyclopropyl)pyridine (69 mg, 0.26 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (66 mg, 0.26 mmol), $PdCl_2$(dppf).CH_2Cl_2 adduct (6.4 mg, 7.8 µmol) and potassium acetate (76 mg, 0.78 mmol) were heated at 125 °C with microwave irradiation for 35 min. Potassium carbonate (0.52 mL, 1.0 mmol) and 6-bromonicotinonitrile (47.5 mg, 0.259 mmol) were added, and the reaction mixture was heated at 125 °C with microwave irradiation for 35 min. The reaction mixture was filtered and purified by HPLC to afford 2.5 mg (3%) 6'-(1-(trifluoromethyl)cyclopropyl)-2,3'-bipyridine-5-carbonitrile; ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 9.14 - 9.21 (m, 1H), 8.97 - 9.02 (m, 1H), 8.36 (dd, *J* = 2.53, 8.34 Hz, 1H), 8.08 (dd, *J* = 2.15, 8.21 Hz, 1H), 7.89 (dd, *J* = 0.76, 8.34 Hz, 1H), 7.74 (d, *J* = 8.34 Hz, 1H), 1.45 - 1.61 (m, 6H) ppm; ^{13}C NMR (400 MHz, CHLOROFORM-d) δ 157.65, 157.25, 152.75, 148.07, 140.19, 135.07, 131.36, 126.37 (q, *J* = 274 Hz) 122.98, 119.86, 116.66, 108.69, 28.99, 13.27 ppm; HPLC rt 12.72 min, LCMS rt 1.21 min, ES+ M+H (+) 290.1; HRMS $[M+H]^+$ 290.0911, calcd 290.0900.

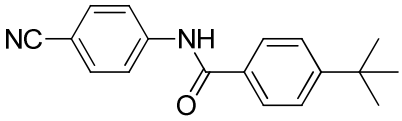
General procedure for preparation of compounds 11, 13, 15, 17.
To the arylamine and 1 eq diisopropylethylamine at 0.18 M in acetonitrile was added 4-*tert*-butylbenzoyl chloride. The reaction mixture was stirred at 23 ºC until complete as judged by LCMS, then diluted with water. The precipitate was collected to afford pure product.



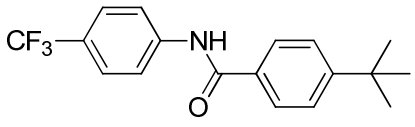
4-tert-butyl-N-(6-(trifluoromethyl)pyridin-3-yl)benzamide (11): Yield 99%; ^{1}H NMR (400 MHz, ACETONITRILE-d_3) δ 9.22 (br. s., 1H), 9.16 (d, *J* = 2.40 Hz, 1H), 8.59 (dd, *J* = 2.27, 8.59 Hz, 1H), 8.02 - 8.09 (m, 2H), 7.92 (d, *J* = 8.59 Hz, 1H), 7.75 (m, 2H), 1.51 (s, 9H); ^{13}C NMR (400 MHz, CHLOROFORM-d) δ 165.81, 155.63, 141.58, 141.36, 138.28, 130.80, 127.20, 127.11, 125.31, 122.99, 120.62, 34.36, 29.98 ppm; HPLC rt 14.96 min, LCMS rt 1.58 min, ES+ M+H (+) 323.1; HRMS $[M+H]^+$ 323.1368, calcd 323.1366.



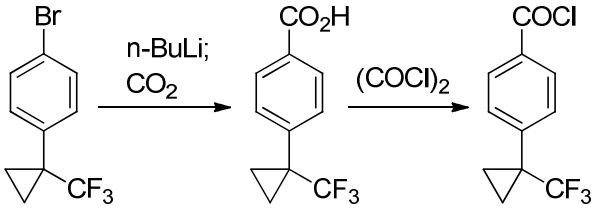
4-tert-butyl-N-(6-cyanopyridin-3-yl)benzamide (13): Yield 85%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.80 (s, 1H), 9.08 (d, *J* = 2.53 Hz, 1H), 8.45 (dd, *J* = 2.53, 8.59 Hz, 1H), 8.04 (d, *J* = 8.59 Hz, 1H), 7.93 (d, *J* = 8.59 Hz, 2H), 7.59 (d, *J* = 8.59 Hz, 2H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 166.25, 155.27, 142.69, 139.20, 130.93, 129.42, 127.71, 126.58, 125.99, 117.64, 34.69, 30.76 ppm; HPLC rt 14.96 min, LCMS rt 1.46 min, ES+ M+H (+) 280.3; HRMS $[M+H]^+$ 280.1458, calcd 280.1444.



4-tert-butyl-N-(4-cyanophenyl)benzamide (15): Yield 89%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.57 (s, 1H), 7.99 (d, *J* = 8.72 Hz, 2H), 7.89 (d, *J* = 8.59 Hz, 2H), 7.82 (d, *J* = 8.84 Hz, 2H), 7.57 (d, *J* = 8.59 Hz, 2H), 1.3 (s, 9H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 166.11, 154.96, 143.56, 133.10, 131.63, 127.69, 125.26, 120.03, 119.08, 105.14, 34.72, 30.86; HPLC rt 14.77 min, LCMS rt 1.54 min, ES+ M+H (+) 279.2; HRMS $[M+H]^+$ 279.1505, calcd 279.1492.



4-tert-butyl-N-(4-trifluoromethylphenyl)benzamide (17): Yield 84%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 8.01 (d, *J* = 8.59 Hz, 2H), 7.91 (d, *J* = 8.59 Hz, 2H), 7.73 (d, *J* = 8.46 Hz, 2H), 7.57 (d, *J* = 8.46 Hz, 2H), 1.33 (s, 9H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 165.96, 154.81, 142.88, 131.75, 127.65, 125.90, 125.87, 125.23, 123.26, 119.95, 34.70, 30.88 ppm; HPLC rt 16.82 min, LCMS rt 1.68 min, ES+ M+H (+) 322.1; HRMS $[M+H]^+$ 322.1423, calcd 322.1413.

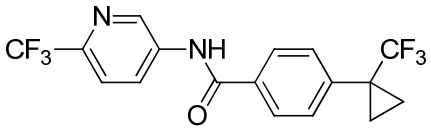


4-(1-(trifluoromethyl)cyclopropyl)benzoic acid: To a -78 °C solution of 1-bromo-4-(1-(trifluoromethyl)cyclopropyl)benzene (5.0 g, 19 mmol) in THF (50 mL) was added butyllithium (13 mL, 21 mmol). The reaction mixture was stirred for 1h, then a fast stream of carbon dioxide was bubbled through the reaction mixture. The THF was removed *in vacuo*. The solid residue was taken up in water and extracted with ether to remove non-polar impurities. The aqueous layer was acidified and extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride, dried over sodium sulfate, filtered and concentrated to dryness to afford pure 4-(1-(trifluoromethyl)cyclopropyl)benzoic acid (3.06 g, 70%).

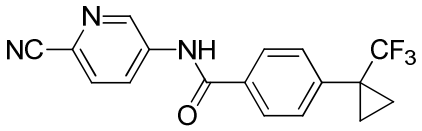
4-(1-(trifluoromethyl)cyclopropyl)benzoyl chloride: To 4-(1-(trifluoromethyl)cyclopropyl) benzoic acid (240 mg, 1.04 mmol) in 1 mL methylene chloride was added 2 mL of oxalyl chloride. The reaction mixture was stirred overnight, then evaporated to dryness to afford pure 4-(1-(trifluoromethyl)cyclopropyl)benzoyl chloride (259 mg, 100%).

General procedure for preparation of compounds 12, 14, 16, 18.

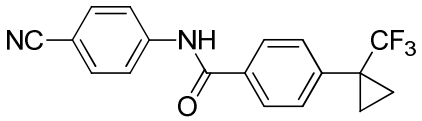
To the arylamine and 2 eq diisopropylethylamine at 0.3 M in acetonitrile was added 4-(1-(trifluoromethyl)cyclopropyl)benzoyl chloride as a 0.3 M acetonitrile solution. The reaction mixture was stirred at 23 ºC until complete as judged by LCMS, then diluted with acetonitrile, filtered and purified by HPLC (acetonitrile/water with 0.1% ammonium hydroxide).



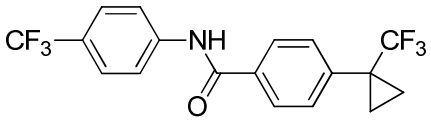
4-(1-(trifluoromethyl)cyclopropyl)-N-(6-(trifluoromethyl)pyridin-3-yl)benzamide (12): Yield 73%; ^{1}H NMR (400 MHz, ACETONITRILE-d_3) δ 9.25 (br. s., 1H), 9.12 (d, *J* = 2.27 Hz, 1H), 8.54 (dd, *J* = 2.40, 8.59 Hz, 1H), 8.50 - 8.53 (m, 1H), 8.07 (d, *J* = 8.21 Hz, 2H), 7.89 (d, *J* = 8.72 Hz, 1H), 7.77 (d, *J* = 8.34 Hz, 2H), 1.42 - 1.63 (m, 2H), 1.17 - 1.34 (m, 2H); ^{13}C NMR (400 MHz, ACETONITRILE-d_3) δ 165.54, 141.89, 141.55, 140.08, 138.35, 133.96, 131.19, 127.73, 127.57, 123.00, 120.66, 120.48, 27.74, 9.27 ppm; HPLC rt 15.82 min, LCMS rt 1.55, ES+ M+H (+) 375.0; HRMS $[M+H]^+$ 375.0925, calcd 375.0927.



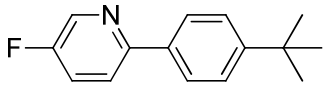
N-(6-cyanopyridin-3-yl)-4-(1-(trifluoromethyl)cyclopropyl)benzamide (14): Yield 70%; ^{1}H NMR (400 MHz, ACETONITRILE-d_3) δ 9.29 (br. s., 1H), 9.09 (d, *J* = 2.40 Hz, 1H), 8.52 (dd, *J* = 2.53, 8.59 Hz, 1H), 8.07 (d, *J* = 8.34 Hz, 2H), 7.93 (d, *J* = 8.59 Hz, 1H), 7.78 (d, *J* = 8.21 Hz, 2H), 2.26 (s, 2H), 1.50 - 1.60 (m, 3H), 1.21 - 1.35 (m, 3H); ^{13}C NMR (400 MHz, CHLOROFORM-d) δ 142.30, 141.11, 137.66, 133.40, 131.91, 130.05, 129.16, 128.39, 127.35, 126.72, 125.81, 117.20, 28.16, 9.98 ppm; HPLC rt 14.82 min, LCMS rt 1.43, ES+ M+H (+) 332.0; HRMS $[M+H]^+$ 332.1010, calcd 332.1005.



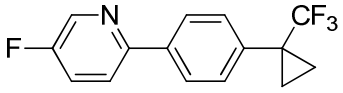
N-(4-cyanophenyl)-4-(1-(trifluoromethyl)cyclopropyl)benzamide (16): Yield 73%; ^{1}H NMR (400 MHz, ACETONITRILE-d_3) δ 9.09 - 9.21 (m, 1H), 8.06 (d, *J* = 8.10 Hz, 2H), 8.02 (d, *J* = 8.10 Hz, 2H), 7.83 (d, *J* = 8.72 Hz, 2H), 7.76 (d, *J* = 8.21 Hz, 2H), 1.46 - 1.64 (m, 2H), 1.22 - 1.34 (m, 2H) ppm; ^{13}C NMR (400 MHz, CHLOROFORM-d) δ 159.79, 152.46, 139.91, 138.56, 137.23, 133.37, 131.80, 127.27, 119.97, 116.94, 108.05, 28.17, 9.97 ppm; HPLC rt 15.48 min, LCMS rt 1.36, ES+ M+H (+) 331.3; HRMS $[M+H]^+$ 331.1061, calcd 331.1053.



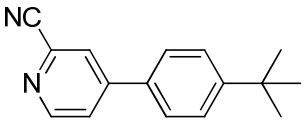
4-(1-(trifluoromethyl)cyclopropyl)-N-(4-(trifluoromethyl)phenyl)benzamide (18): Yield 82%; ^{1}H NMR (400 MHz, ACETONITRILE-d_3) δ 9.08 (br. s, 1H), 7.99 - 8.09 (m, 4H), 7.76 - 7.86 (m, 4H), 1.49 - 1.61 (m, 2H), 1.19 - 1.36 (m, 2H); ^{13}C NMR (400 MHz, CHLOROFORM-d) δ 165.27, 140.71, 140.51, 134.46, 131.80, 127.14, 126.43, 126.04, 124.66, 122.7, 119.73, 28.34, 9.97 ppm; HPLC rt 16.84 min, LCMS rt 1.63, ES+ M+H (+) 374.0; HRMS $[M+H]^+$ 374.0967, calcd 374.0974.



2-(4-tert-butylphenyl)-5-fluoropyridine (19): Yield 65%; ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.52 (d, *J* = 2.53 Hz, 1H), 7.84 - 7.92 (m, 2H), 7.70 (dd, *J* = 4.29, 8.84 Hz, 1H), 7.39 - 7.55 (m, 3H), 1.36 (s, 9H); ^{13}C NMR (400 MHz, CHLOROFORM-d) δ 158.66 (d, *J* = 255.4 Hz), 153.74, 152.06, 137.52, 126.45, 125.77, 123.45, 123.35, 121.00, 34.67, 31.28; HPLC rt 15.33 min, LCMS rt 1.65, ES+ M+H (+) 230.3; HRMS $[M+H]^+$ 230.1350, calcd 230.1340.

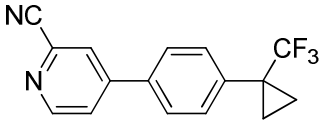


5-fluoro-2-(4-(1-(trifluoromethyl)cyclopropyl)phenyl)pyridine (20): Yield 74%; ^{1}H NMR (400 MHz, Acetone) δ 8.79 (d, *J* = 2.91 Hz, 1H), 8.30 (d, *J* = 8.21 Hz, 2H), 8.20 - 8.24 (m, 1H), 7.92 (dt, *J* = 3.03, 8.65 Hz, 1H), 7.81 (d, *J* = 8.21 Hz, 2H); ^{13}C NMR (400 MHz, CHLOROFORM-d) δ 160.05, 157.43, 152.45, 138.11, 137.52, 136.39, 131.60, 126.40 (q, *J* = 254 Hz), 123.51, 121.57, 27.52, 9.33 ppm; HPLC rt 15.26 min, LCMS rt 1.63 min, ES+ M+H (+) 282.1; HRMS $[M+H]^+$ 282.0893, calcd 282.0900.

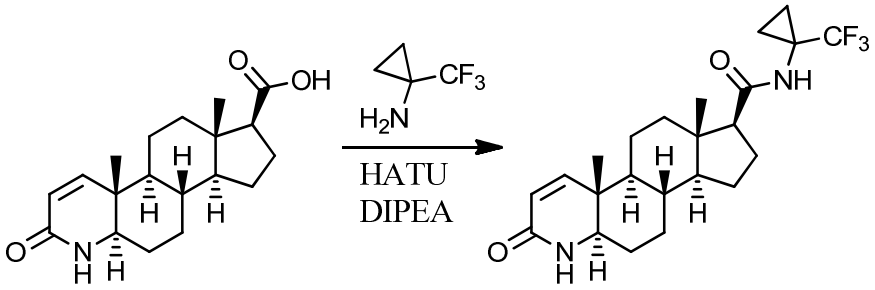


4-(4-tert-butylphenyl)picolinonitrile (21): Yield 37%; ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.73 (dd, *J* = 0.76, 5.31 Hz, 1H), 7.91 (dd, *J* = 0.88, 1.89 Hz, 1H), 7.71 (dd, *J* = 1.77, 5.31 Hz, 1H), 7.51 - 7.61 (m, 4H), 1.37 (s, 9H); ^{13}C NMR (400 MHz,

CHLOROFORM-d) δ 153.79, 151.42, 149.62, 134.47, 132.93, 126.68, 126.52, 126.25, 124.32, 117.45, 34.85, 31.19 ppm; HPLC rt 16.75 min, LCMS rt 1.60 min , ES+ M+H (+) 237.3; HRMS $[M+H]^+$ 237.1389, calcd 237.1386.

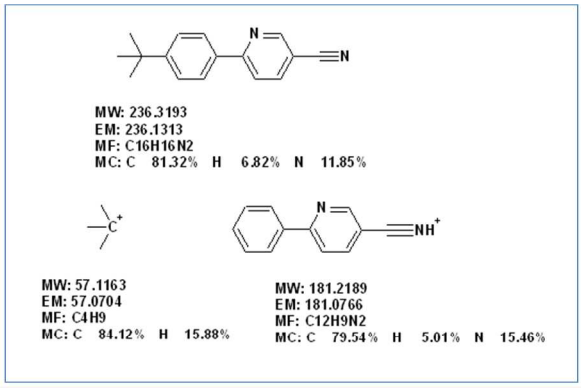


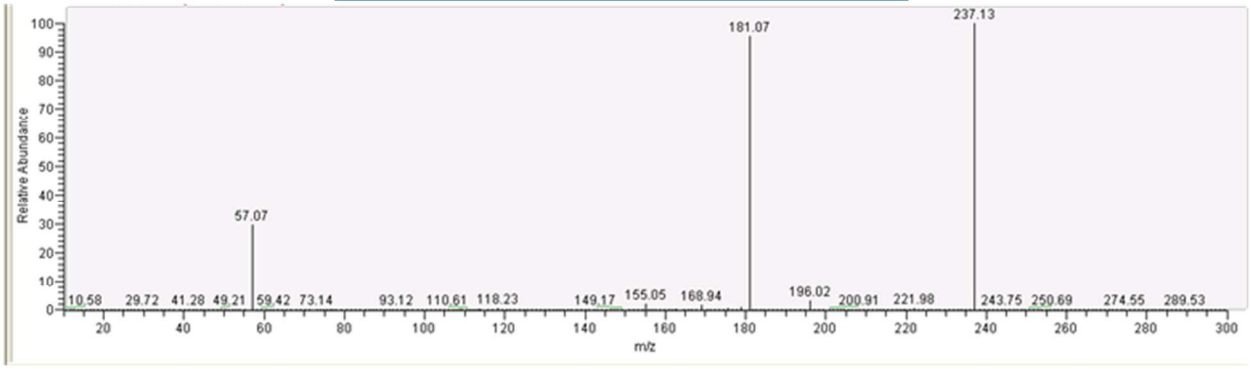
4-(4-(1-(trifluoromethyl)cyclopropyl)phenyl)picolinonitrile (22): Yield 69%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 (d, *J* = 5.18 Hz, 1H), 8.45 (d, *J* = 1.39 Hz, 1H), 8.10 (dd, *J* = 1.83, 5.24 Hz, 1H), 7.93 (d, *J* = 8.34 Hz, 2H), 7.64 (d, *J* = 8.21 Hz, 2H), 1.36 - 1.45 (m, 2H), 1.20 (s, 2H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 151.77, 147.96, 137.34, 135.31, 133.43, 131.90, 127.76, 127.35, 126.51, 124.96, 117.59, 27.34, 9.68 ppm; HPLC rt 14.76 min; LCMS rt 1.56 min, ES+ M+H (+) 289.1; HRMS $[M+H]^+$ 289.0949, calcd 289.0947.



N-(trifluoromethyl)cyclopropyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide (24): To 3-oxo-4-aza-5α-androst-1-ene-17β-carboxylic acid (50 mg, 0.16 mmol) and diisopropylethylamine (0.055 mL, 0.32 mmol) in DMF (1 mL) was added HATU (61 mg, 0.16 mmol). The mixture was stirred for 10 min, then 1-(trifluoromethyl)cyclopropanamine (0.044 mL, 0.47 mmol) was added and the mixture was heated at 80 °C. The mixture was purified by HPLC to afford **24** (21 mg, 31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (d, *J* = 9.96 Hz, 1H), 6.51 (br s, 1H), 5.69 (d, *J* = 9.92 Hz, 1H), 5.50 (s, 1H), 3.19 (dd, J = 11.46, 4.78 Hz, 1H), 1.97-2.08 (m, 1H), 1.94 (t, *J* = 8.86 Hz, 1H), 1.82 (dt, J = 11.86, 3.21 Hz, 1H), 1.54-1.64 (m, 4H), 1.46-1.54 (m, 2H), 1.29-1.33 (m, 2H), 1.19-1.23 (m, 1H), 1.07-1.18 (m, 3H), 0.82-1.07 (m, 5H), 0.81 (s, 3H), 0.52 (s, 3H); LCMS rt 1.14 min, ES+ M+H (+) 245.2; HRMS $[M+H]^+$ 245.2396, calcd 425.2416.

Daughter ion spectra of **1**





Daughter ion spectra of **2**