

Design of N-Benzoxaborole Benzofuran GSK8175 – Optimization of Human**Pharmacokinetics Inspired by Metabolites of a Failed Clinical HCV Inhibitor**

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I. Purities of Final Compounds**Immediate Processing Quality Control Protocol (IPQC)**

All compounds underwent IPQC to confirm identity and determine relative purity immediately before processing in the replicon or NS5B Polymerase assays (described below). Analysis is by UPLC-MS with UV diode array detection to determine purity and MS used to confirm molecular weight. A Waters Acquity UPLC system comprising Binary Solvent manager, Sample Manager, PDA Detector, Waters ZQ or SQD mass spectrometer, Waters Acquity Evaporative Light Scattering Detector or Polymer Laboratories Evaporative Light Scattering Detector were employed. Mobile phases: acetonitrile + 0.1% formic acid; water + 0.1% formic acid. Wash solution : strong wash 100% acetonitrile + 0.1% formic acid; weak wash 50:50 acetonitrile:water + 0.1% formic acid.

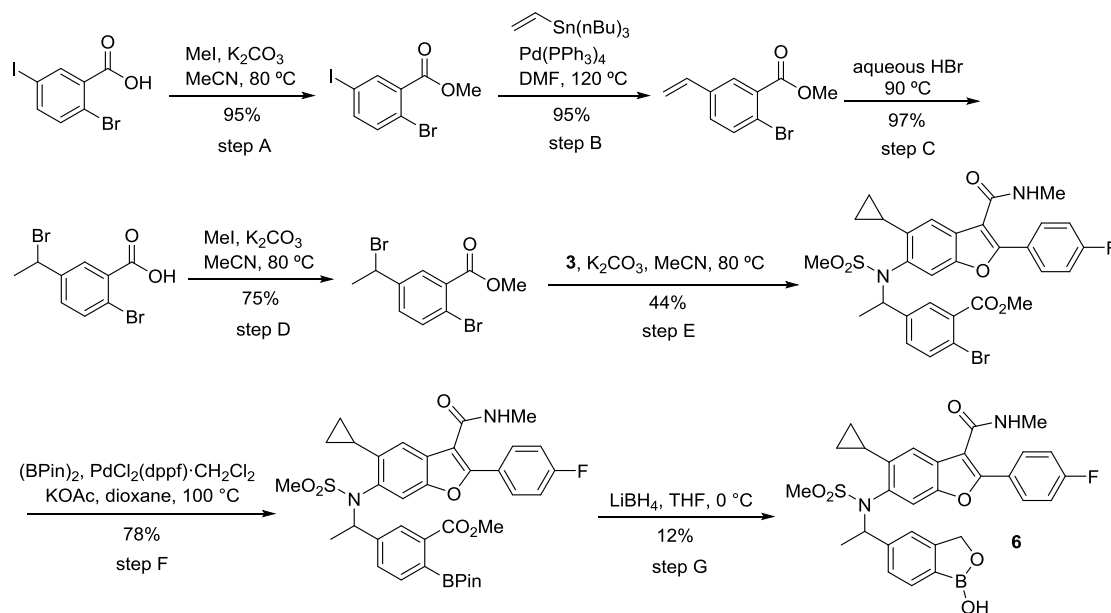
Table SI-1: IPQC Purity Ranges for New Compounds

Cmpd.	Purity (%)	Cmpd.	Purity (%)	Cmpd.	Purity (%)
1	96-100	23	100	45	100
5	98-100	24	100	46	99-100
6	100	25	100	47	97-100
7	100	26	100	48	100
8	100	31	100	49	98-100
9	100	32	100	SI-1	100
10	100	33	100	SI-2	96-100
11	100	34	100	SI-3	98
19	100	35	94-100	SI-4	100
20	100	36	98		
21	100	37	100		
22	100	44	100		

II. Chemical Syntheses of Final Compounds

All commercially obtained solvents and reagents were used as received. ¹H NMR spectra were taken on a Varian (Agilent) Inova 400 NMR spectrometer. Chemical shifts are reported in parts per million (ppm, δ) using the residual solvent line as a reference. Splitting patterns are designated using the following abbreviations: s, singlet; d, doublet; t, triplet; dd, doublet of doublet; m, multiplet; br, broad. Coupling constants (*J*) are reported in hertz (Hz). Mass spectrometric analyses and compound purity determinations were conducted on a Waters Acquity UPLC system (Phenomenex Kinetex column at 40 °C, mobile phase of water with 0.2% v/v formic acid and MeCN with 0.15% v/v formic acid) and Waters Acquity SQD with alternating positive/negative electrospray ionization scanning from 125 to 1000 amu, with a scan time of 105 ms and an interscan delay of 20 ms. High resolution mass spectrometric analysis was performed on a Waters qTOF Premiere mass spectrometer using flow injection operating in W mode. Reverse phase HPLC purifications were performed on an Agilent 1100 preparative system. Chiral analytical SFC chromatography was performed on a Berger analytical SFC system. Chiral preparative SFC chromatography was performed on a Novasep Supersep C20/30 preparative SFC system. Chiral analytical HPLC was performed on an Agilent 1100 analytical system.

5-Cyclopropyl-2-(4-fluorophenyl)-6-(N-(1-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yl)ethyl)methylsulfonamido)-N-methylbenzofuran-3-carboxamide (6).



(A) **Methyl 2-bromo-5-iodobenzoate.** A solution of 2-bromo-5-iodobenzoic acid (2.0 g, 5.5 mmol), K₂CO₃ (1.50 g, 11.0 mmol), and methyl iodide (0.82 g, 5.8 mmol) in MeCN was heated at 80 °C for 48 h. The reaction mixture was poured into water and then extracted with EtOAc. The separated organic solution was dried over Na₂SO₄ and concentrated to dryness at reduced pressure to afford the title compound (2.20 g, 95%).

(B) **Methyl 2-bromo-5-vinylbenzoate.** A solution of methyl 2-bromo-5-iodobenzoate (1.5 g, 4.4 mmol), vinyltributyltin (1.81 g, 5.30 mmol) and Pd(Ph₃)₄ (0.51 g, 0.44 mmol) in DMF (100 mL) was heated to 120 °C for 12 h and then cooled to RT. The reaction mixture was partitioned between water and EtOAc and the phases separated. The EtOAc solution was washed with brine (2x200 ml), dried over Na₂SO₄, and concentrated to dryness at reduced pressure. The crude material was purified by flash chromatography to afford the title compound (1.37 g, 95%) as a colorless oil.

(C) **2-Bromo-5-(1-bromoethyl)benzoic acid**. A solution of methyl 2-bromo-5-vinylbenzoate (1.37 g, 4.28 mmol) in 48% aqueous HBr (20 mL) was heated to 90 °C for 2h and then poured into ice water (200 mL). The resulting mixture was extracted with DCM (3x100 mL). The combined DCM solutions were dried over Na₂SO₄ and concentrated to dryness at reduced pressure. The crude product was subjected to flash chromatography to afford the title compound (1.50 g, 97%) as a yellow oil.

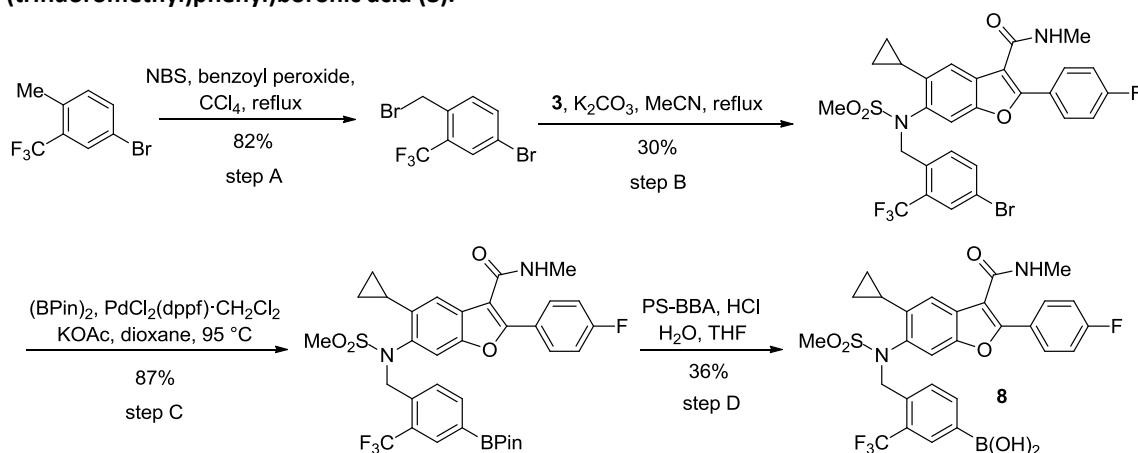
(D) **Methyl 2-bromo-5-(1-bromoethyl)benzoate**. A solution of 2-bromo-5-(1-bromoethyl)benzoic acid (1.20 g, 3.92 mmol), K₂CO₃ (1.08 g, 7.84 mmol), and methyl iodide (0.56 g, 3.9 mmol) in MeCN (50 mL) was heated to 80 °C for 24h and then cooled to RT. The reaction mixture was diluted with water and extracted with EtOAc (3x50 mL). The combined extracts were washed with water (2x50 mL), dried over Na₂SO₄, and concentrated to dryness at reduced pressure. The crude product was purified by flash chromatography to afford the title compound (0.950 g, 75%) as a yellow solid.

(E) **Methyl 2-bromo-5-(1-(N-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)ethyl)benzoate**. A solution of methyl 2-bromo-5-(1-bromoethyl)benzoate (0.950 g, 2.97 mmol), 5-cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-(methylsulfonamido)benzofuran-3-carboxamide (**3**, 1.18 g, 2.96 mmol, prepared as described in WO2013028371), and K₂CO₃ (0.819 g, 5.94 mmol) in MeCN (10 mL) was heated to 80 °C for 3h and then cooled to RT. The mixture was diluted with water (200 mL) and extracted with EtOAc (3x100 mL). The combined EtOAc extracts were dried over Na₂SO₄, and concentrated to dryness at reduced pressure. The crude product was purified by flash chromatography (silica gel, 2:1 petroleum ether/EtOAc) to afford the title compound (0.850 g, 44%) as a white solid.

(F) **Methyl 5-(1-(N-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)ethyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate**. A solution of methyl 2-bromo-5-(1-(N-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)ethyl)benzoate (0.850 g, 1.32 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (78.5 mg, 0.07 mmol), bis(pinacolato)diboron (0.223 g, 0.88 mmol), and KOAc (0.364 g, 2.64 mmol) in dioxane (50 mL) under a nitrogen atmosphere was heated at 100 °C overnight and then cooled to RT. The solution was diluted with ice water (100 mL) and extracted with EtOAc (3x100 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated to dryness at reduced pressure. The crude material was subjected to flash chromatography (silica gel, 3:1 petroleum ether/EtOAc) to afford the title compound (0.650 g, 78%) as a white solid.

(G) **5-Cyclopropyl-2-(4-fluorophenyl)-6-(N-(1-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yl)ethyl)methylsulfonamido)-N-methylbenzofuran-3-carboxamide (6)**. To a solution of methyl 5-(1-(N-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)ethyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (0.650 g, 1.02 mmol) in THF (10 mL) at 0 °C was added 1M LiBH₄/THF (2.0 mL, 2.0 mmol). The resulting solution was stirred at RT for 2h and then poured into ice water (100 mL). The mixture was extracted with EtOAc (3x100 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated to dryness at reduced pressure. The residue was purified by reverse phase HPLC to afford **6** (50 mg, 12%) as a white solid. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 7.89 - 7.98 (m, 2 H), 7.74 (s, 1 H), 7.55 - 7.69 (m, 1 H), 7.16 - 7.32 (m, 3 H), 6.89 (s, 1 H), 5.66 - 5.71 (m, 1H), 4.95 - 5.14 (m, 2 H), 3.18 (s, 2 H), 2.94 - 2.96 (d, 3 H), 2.86 (s, 1 H), 2.51 - 2.56 (m, 1 H), 1.76 - 1.78 (d, 2 H), 1.56 - 1.58 (d, 1 H), 1.15 - 1.17 (m, 1 H), 0.43 - 0.85 (m, 2 H), 0.02 - 0.17 (m, 1 H). ES-LCMS *m/z*: 567 (M+1), 100% purity.

(4-((N-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)methyl)-3-(trifluoromethyl)phenyl)boronic acid (8).



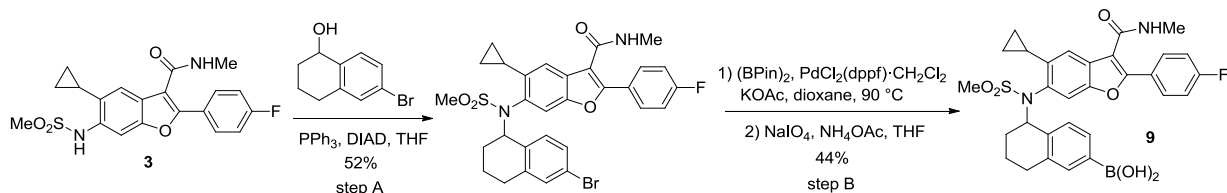
(A) **4-Bromo-1-(bromomethyl)-2-(trifluoromethyl)benzene**. A solution of 4-bromo-1-methyl-2-(trifluoromethyl)benzene (0.460 g, 1.92 mmol), NBS (0.379 g, 2.13 mmol), and benzoyl peroxide (48 mg, 0.19 mmol) in CCl_4 (10 mL) was heated to reflux for 24h and then cooled to RT. The solution was diluted with water and extracted with DCM. The DCM solution was washed with brine, dried over Na_2SO_4 , and concentrated to dryness at reduced pressure. The crude product was purified by flash chromatography (silica gel, 50:1 petroleum ether/EtOAc) to afford the title compound (0.500 g, 82%) as a colorless oil.

(B) **6-(N-(4-bromo-2-(trifluoromethyl)benzyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide**. A mixture of 4-bromo-1-(bromomethyl)-2-(trifluoromethyl)benzene (0.500 g, 1.57 mmol), 5-cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-(methylsulfonamido)benzofuran-3-carboxamide (**3**), 0.632 g, 1.57 mmol, prepared as described in WO2013028371), and K_2CO_3 (0.651 g, 4.71 mmol) in MeCN (20 mL) was stirred at reflux for 12h and then cooled to RT. The mixture was diluted with water and extracted with EtOAc. The EtOAc solution was washed with brine, dried over Na_2SO_4 , and concentrated to dryness at reduced pressure. The residue was subjected to flash chromatography (silica gel, 1:1 petroleum ether/EtOAc) to give the title compound (0.300 g, 30%) as a white solid.

(C) **5-Cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-(N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)benzyl)methylsulfonamido)benzofuran-3-carboxamide**. A solution of 6-(N-(4-bromo-2-(trifluoromethyl)benzyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.300 g, 0.470 mmol), bis(pinacolato)diboron (0.180 g, 0.710 mmol), KOAc (0.138 g, 1.41 mmol), and $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ (17 mg, 0.023 mmol) in 1,4-dioxane (10 mL) was sparged with nitrogen and heated to 95 °C overnight. After cooling to RT the mixture was partitioned between EtOAc and water and the phases separated. The organic phase was washed with brine, dried over Na_2SO_4 , and concentrated at reduced pressure. The crude material was purified by flash chromatography (silica gel, 1:1 petroleum ether/EtOAc) to give the title compound (0.280 g, 87%) as a white solid.

(D) **(4-((N-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)methyl)-3-(trifluoromethyl)phenyl)boronic acid (8)**. To a solution of 5-cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-(N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)benzyl)methylsulfonamido)benzofuran-3-carboxamide (0.280 g, 0.410 mmol) in THF (10 mL) was added PS-BBA (polymer-supported benzenboronic acid, 0.720 g, 1.85 mmol) followed by 5M aqueous HCl (0.25 mL, 1.23 mmol). After stirring at RT for 12 h, the mixture was filtered, the filtrate partitioned between EtOAc and water, and the phases separated. The EtOAc solution was washed with brine and concentrated to dryness at reduced pressure. The crude residue was purified by RP-HPLC to afford **8** (90 mg, 36%) as a white solid. ^1H NMR (400 MHz, $\text{MeOH}-d_4$): δ 7.85 - 8.07 (m, 5 H), 7.71 (s, 1 H), 7.26 - 7.36 (m, 2 H), 7.08 (s, 1 H), 5.11 - 5.39 (m, 2 H), 3.27 (s, 3 H), 2.99 (s, 3 H), 2.28 - 2.39 (m, 1 H), 0.77 - 1.15 (m, 3 H), 0.33 - 0.46 (m, 1 H). ES-LCMS m/z : 605 ($\text{M}+1$), 100% purity.

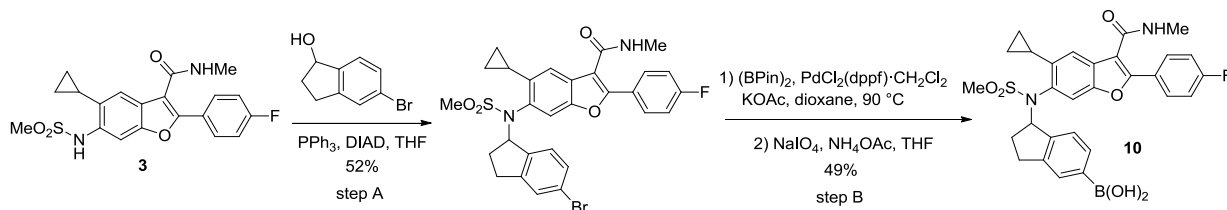
(5-(N-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)-5,6,7,8-tetrahydronaphthalen-2-yl)boronic acid (9).



(A) 6-(N-(6-Bromo-1,2,3,4-tetrahydronaphthalen-1-yl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide. To a stirred suspension of 5-cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-(methylsulfonamido)benzofuran-3-carboxamide (**3**, 0.600 g, 1.49 mmol, prepared as described in WO2013028371), 5-bromo-2,3-dihydro-1H-inden-1-ol (0.401 g, 1.77 mmol), and triphenylphosphine (0.978 g, 3.73 mmol) in THF (7 mL) at 0 °C was added DIAD (0.580 mL, 2.98 mmol) by dropwise addition. The resulting solution was warmed to RT. After 18h the solution was diluted with EtOAc. The solution was washed with saturated aqueous NaHCO₃, saturated aqueous brine, dried over Na₂SO₄ and concentrated to dryness at reduced pressure. The crude product was purified by flash chromatography (silica gel, 0-50% EtOAc/hexane) to afford the title compound (0.471 g, 52%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.63 - 7.94 (m, 3 H), 6.60 - 7.47 (m, 6 H), 5.51 - 5.93 (m, 2 H), 3.02 - 3.14 (m, 3 H), 2.95 (d, *J* = 4.89 Hz, 3 H), 2.05 - 2.60 (m, 4 H), 1.46 - 1.83 (m, 3 H), 0.20 - 1.20 (m, 4 H). ¹H NMR shows evidence of rotamers. ES-LCMS *m/z*: 611 (M+1).

(B) (5-(N-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)-5,6,7,8-tetrahydronaphthalen-2-yl)boronic acid (9). A solution of 6-(N-(6-bromo-1,2,3,4-tetrahydronaphthalen-1-yl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.210 g, 0.344 mmol), bis(pinacolato)diboron (0.175 g, 0.688 mmol), KOAc (0.135 g, 1.38 mmol), and PdCl₂(dppf)·CH₂Cl₂ (28 mg, 0.034 mmol) in 1,4-dioxane (4 mL) was sparged with nitrogen and heated to 90 °C. After 18h LCMS indicated complete conversion of starting material to the expected pinacol boronate ester with a small amount of hydrolysis to the free boronic acid. The solution was cooled to RT, diluted with EtOAc, filtered through Celite[®], and concentrated to dryness at reduced pressure to afford a brown oil. This material was dissolved in THF (10 mL). The solution was diluted with 0.2M aqueous ammonium acetate (7 mL) and treated with sodium periodate (0.589 g, 2.75 mmol). After 18h LCMS indicated nearly complete conversion of the pinacol boronate ester intermediate to the free boronic acid. The solution was partitioned between water and EtOAc, and the phases separated. The aqueous solution was extracted with two additional portions of EtOAc. The combined EtOAc solutions were washed with saturated aqueous brine (1x), dried over Na₂SO₄ and concentrated to dryness at reduced pressure. The crude material was subjected to flash chromatography [silica gel, 0-50% (9:1 MeOH/DCM)/EtOAc] to give **9** (86 mg, 43%) as a light brown solid. ¹H NMR (400 MHz, MeOH-*d*₄): δ 7.67 - 8.02 (m, 3 H), 7.13 - 7.61 (m, 4 H), 6.99 (s, 1 H), 6.69 - 6.76 (m, 1 H), 5.94 (t, *J* = 6.4 Hz, 1 H), 3.17 - 3.22 (m, 3 H), 2.90 (s, 3 H), 2.13 - 2.61 (m, 5 H), 1.55 - 1.65 (m, 2 H), 1.11 - 1.23 (m, 2 H), 0.80 - 0.93 (m, 2 H). ¹H NMR shows evidence of rotamers. ES-LCMS *m/z*: 577 (M+1), 100% purity. HRMS *m/z* calcd for C₃₀H₃₀BFN₂O₆S: 577.1988. Found: 577.1979.

(1-(N-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)-2,3-dihydro-1H-inden-5-yl)boronic acid (10).

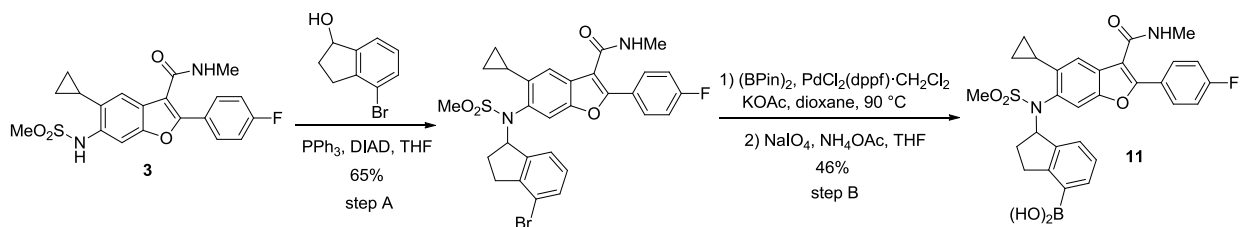


(A) 6-(N-(5-Bromo-2,3-dihydro-1H-inden-1-yl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide. To a stirred suspension of 5-cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-

(methylsulfonamido)benzofuran-3-carboxamide (**3**, 0.600 g, 1.49 mmol, prepared as described in WO2013028371), 5-bromo-2,3-dihydro-1H-inden-1-ol (0.381 g, 1.79 mmol), and triphenylphosphine (0.978 g, 3.73 mmol) in THF (7 mL) at 0 °C was added DIAD (0.580 mL, 2.98 mmol) by dropwise addition. The resulting solution was warmed to RT. After 18h the solution was diluted with EtOAc. The solution was washed with saturated aqueous NaHCO₃, saturated aqueous brine, dried over Na₂SO₄ and concentrated to dryness at reduced pressure. The crude product was purified by flash chromatography (silica gel, 0-50% EtOAc/hexane) to afford the title compound (0.459 g, 52%) as an off-white foam. ¹H NMR (400 MHz, CDCl₃): δ 7.74 - 7.82 (m, 3 H), 7.48 (d, *J* = 8.19 Hz, 1 H), 7.11 - 7.30 (m, 4 H), 6.89 (s, 1 H), 5.94 (dd, *J* = 8.19, 5.66 Hz, 1 H), 5.75 - 5.83 (m, 1 H), 3.06 (s, 3 H), 2.96 (d, *J* = 4.88 Hz, 3 H), 2.54 - 2.65 (m, 1 H), 2.34 - 2.50 (m, 1 H), 2.21 - 2.31 (m, 1 H), 2.08 - 2.20 (m, 1 H), 1.23 - 1.30 (m, 1 H), 1.12 - 1.20 (m, 2 H), 0.82 - 0.96 (m, 2 H). ¹H NMR shows evidence of rotamers. ES-LCMS *m/z*: 597 (M+1).

(B) **(1-(N-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)-2,3-dihydro-1H-inden-5-yl)boronic acid (10)**. A solution of 6-(N-(5-bromo-2,3-dihydro-1H-inden-1-yl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.252 g, 0.422 mmol), bis(pinacolato)diboron (0.215 g, 0.845 mmol), KOAc (0.166 g, 1.69 mmol), and PdCl₂(dppf)·CH₂Cl₂ (34 mg, 0.042 mmol) in 1,4-dioxane (4 mL) was sparged with nitrogen and heated to 90 °C. After 18h LCMS indicated complete conversion of starting material to the expected pinacol boronate ester with a small amount of hydrolysis to the free boronic acid. The solution was cooled to RT, diluted with EtOAc, filtered through Celite®, and concentrated to dryness at reduced pressure to afford a brown oil. This material was dissolved in THF (10 mL). The solution was diluted with 0.2M aqueous ammonium acetate (7 mL) and treated with sodium periodate (0.632 g, 2.96 mmol). After stirring the solution as RT for 4h an additional portion of sodium periodate (0.200 g) was added. After 18h LCMS indicated nearly complete conversion of the pinacol boronate ester intermediate to the free boronic acid. The solution was partitioned between water and EtOAc, and the phases separated. The aqueous solution was extracted with two additional portions of EtOAc. The combined EtOAc solutions were washed with saturated aqueous brine (1x), dried over Na₂SO₄ and concentrated to dryness at reduced pressure. The crude material was subjected to flash chromatography [silica gel, 0-40% (9:1 MeOH/DCM)/EtOAc] to give **10** (0.117 g, 49%) as a light brown solid. ¹H NMR (400 MHz, MeOH-*d*₄): δ 7.53 - 7.94 (m, 4 H), 7.09 - 7.49 (m, 3 H), 7.01 (s, 1 H), 6.69 - 6.79 (m, 1 H), 5.94 (dd, *J* = 8.10, 4.59 Hz, 1 H), 3.18 (s, 3 H), 2.89 - 2.91 (m, 3 H), 2.35 - 2.65 (m, 3 H), 2.01 - 2.30 (m, 2 H), 1.17 (dd, *J* = 5.85, 2.34 Hz, 2 H), 0.80 - 0.93 (m, 2 H). ¹H NMR shows evidence of rotamers. ES-LCMS *m/z*: 563 (M+1), 100% purity. HRMS *m/z* calcd for C₂₉H₂₈BFN₂O₆S: 563.1823. Found: 563.1818.

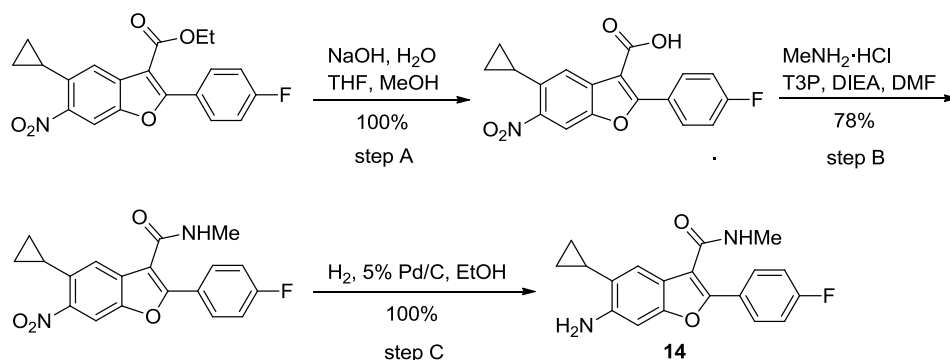
(1-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(methylsulfonamido)benzofuran-7-yl)-2,3-dihydro-1H-inden-4-yl)boronic acid (11).



(A) **6-(N-(4-Bromo-2,3-dihydro-1H-inden-1-yl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide**. To a stirred suspension of 5-cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-(methylsulfonamido)benzofuran-3-carboxamide (**3**, 0.600 g, 1.49 mmol, prepared as described in WO2013028371), 4-bromo-2,3-dihydro-1H-inden-1-ol (0.381 g, 1.79 mmol), and triphenylphosphine (0.978 g, 3.73 mmol) in THF (7 mL) at 0 °C was added DIAD (0.580 mL, 2.98 mmol) by dropwise addition. The resulting solution was warmed to RT. After 18h the solution was diluted with EtOAc. The solution was washed with saturated aqueous NaHCO₃, saturated aqueous brine, dried over Na₂SO₄ and concentrated to dryness at reduced pressure. The crude product was purified by flash chromatography (silica gel, 0-50% EtOAc/hexane) to afford the title compound (0.580 g, 65%) as a white foam. ¹H NMR (400 MHz, CDCl₃): δ 7.52 - 7.89 (m, 3 H), 7.02 - 7.45 (m, 5 H), 6.90 (s, 1 H), 5.94 (t, *J* = 7.20 Hz, 1 H), 5.75 - 5.88 (m, 1 H), 3.05 (s, 3 H), 2.94 (d, *J* = 4.70 Hz, 3 H), 2.27 - 2.69 (m, 5 H), 1.97 - 2.15 (m, 2 H), 1.10 - 1.18 (m, 2 H), 0.81 - 0.97 (m, 2 H). ¹H NMR shows evidence of rotamers. ES-LCMS *m/z*: 563 (M+1).

(B) **(1-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(methylsulfonamido)benzofuran-7-yl)-2,3-dihydro-1H-inden-4-yl)boronic acid (11)**. A solution of 6-(N-(4-bromo-2,3-dihydro-1H-inden-1-yl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.247 g, 0.413 mmol), bis(pinacolato)diboron (0.210 g, 0.827 mmol), KOAc (0.162 g, 1.65 mmol), and PdCl₂(dppf)·CH₂Cl₂ (34 mg, 0.042 mmol) in 1,4-dioxane (4 mL) was sparged with nitrogen and heated to 90 °C. After 18h LCMS indicated complete conversion of starting material to the expected pinacol boronate ester with a small amount of hydrolysis to the free boronic acid. The solution was cooled to RT, diluted with EtOAc, filtered through Celite[®], and concentrated to dryness at reduced pressure to afford a brown oil. This material was dissolved in THF (10 mL). The solution was diluted with 0.2M aqueous ammonium acetate (7 mL) and treated with sodium periodate (0.707 g, 3.31 mmol). After 18h LCMS indicated nearly complete conversion of the pinacol boronate ester intermediate to the free boronic acid. The solution was partitioned between water and EtOAc, and the phases separated. The aqueous solution was extracted with two additional portions of EtOAc. The combined EtOAc solutions were washed with saturated aqueous brine (1x), dried over Na₂SO₄ and concentrated to dryness at reduced pressure. The crude material was subjected to flash chromatography [silica gel, 0-50% (9:1 MeOH/DCM)/EtOAc] to give **11** (0.106 g, 46%) as a light brown solid. ¹H NMR (400 MHz, MeOH-*d*₄): δ 7.83 - 7.92 (m, 1 H), 7.68 - 7.80 (m, 2 H), 7.30 - 7.41 (m, 1 H), 7.12 - 7.25 (m, 3 H), 7.01 (s, 1 H), 6.57 (s, 1 H), 5.88 - 5.96 (m, 1 H), 3.16 (s, 3 H), 2.86 - 2.92 (m, 3 H), 2.24 - 2.59 (m, 3 H), 1.88 - 2.10 (m, 2 H), 1.13 - 1.20 (m, 2 H), 0.80 - 0.93 (m, 2 H). ¹H NMR shows evidence of rotamers. ES-LCMS *m/z*: 563 (M+1), 100% purity. HRMS *m/z* calcd for C₂₉H₂₈BFN₂O₆S: 563.1826. Found: 563.1823.

Synthesis of intermediate 6-amino-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (14).



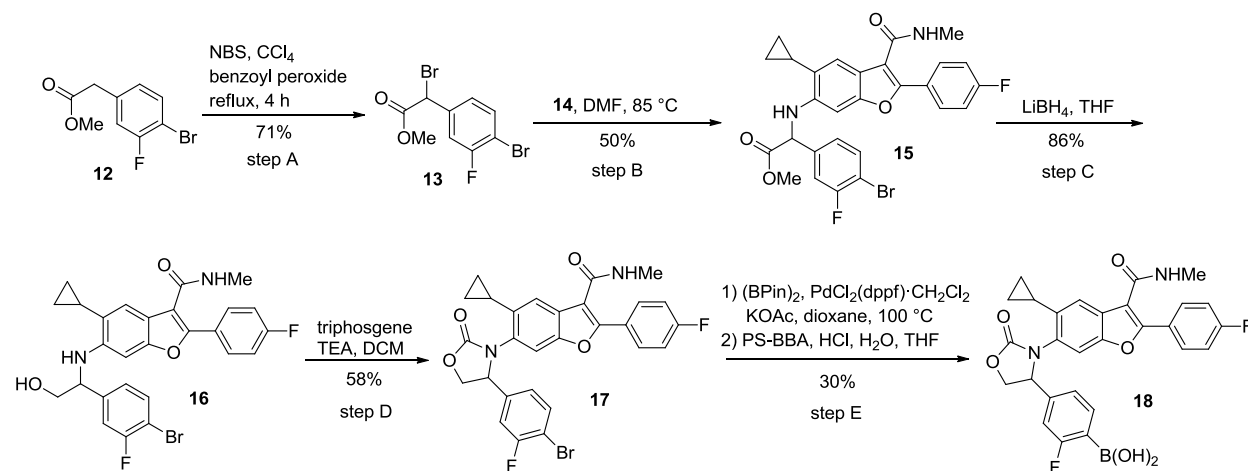
(A) **5-Cyclopropyl-2-(4-fluorophenyl)-6-nitrobenzofuran-3-carboxylic acid**. To a stirred solution of ethyl 5-cyclopropyl-2-(4-fluorophenyl)-6-nitrobenzofuran-3-carboxylate (4.00 g, 10.8 mmol, prepared as described in WO2013028371) in 150 mL of 7:3 THF/MeOH was added 1N aqueous NaOH (54 mL, 54 mmol). The resulting red-orange solution was stirred at RT. After 18h LCMS indicated complete reaction. The solution was concentrated to half volume by rotary evaporation at which point a solid began to precipitate. The suspension was then stirred with addition of 1N aqueous HCl (60 mL, 60 mmol) which produced a light yellow suspension. After stirring for 2h the solid was collected by filtration. The filter cake was washed with water (2x), suction air dried for 1 hour and then dried *in vacuo* to afford the title compound (3.70 g, 100%) as a tan powder. ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.49 (s, 1 H), 8.35 (s, 1 H), 8.03 - 8.14 (m, 2 H), 7.87 (s, 1 H), 7.35 - 7.47 (m, 2 H), 2.26 - 2.41 (m, 1 H), 0.95 - 1.06 (m, 2 H), 0.61 - 0.73 (m, 2 H). ES-LCMS *m/z*: 340 (M-1).

(B) **5-Cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-nitrobenzofuran-3-carboxamide**. A solution of 5-cyclopropyl-2-(4-fluorophenyl)-6-nitrobenzofuran-3-carboxylic acid (2.01 g, 5.89 mmol) and methylamine hydrochloride (0.90 g, 13.3 mmol) in DMF (20 mL) was cooled in an ice water bath. To the solution was added DIEA (4.12 mL, 23.6 mmol) followed by 50% propylphosphonic anhydride/EtOAc (5.60 mL, 8.84 mmol) by slow addition over 3 min. The resulting solution was stirred at 0 °C for 30 min and then allowed to warm to RT. After 2h the solution was diluted with EtOAc. The resulting solution was washed with water (2x), 10% aqueous citric acid (1x), 10% aqueous sodium carbonate (2x), and brine (1x). At this point a solid began precipitating from the solution. The mixture was concentrated nearly to dryness by rotary evaporation. The residue was suspended in

water and the suspension stirred for 30 min. The solid was collected by filtration. The filter cake was washed with water (2x), suction air dried for 1 hour and then dried *in vacuo* overnight to afford the title compound (1.62 g, 78%) as a tan powder. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.52 - 8.60 (m, 1 H), 8.34 (s, 1 H), 7.93 - 8.06 (m, 2 H), 7.34 - 7.54 (m, 3 H), 2.85 (d, *J* = 4.30 Hz, 3 H), 2.27 - 2.37 (m, 1 H), 0.94 - 1.05 (m, 2 H), 0.69 - 0.78 (m, 2 H). ES-LCMS *m/z*: 355 (M+1).

(C) **6-Amino-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (14)**. A suspension of 5-cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-nitrobenzofuran-3-carboxamide (1.00 g, 2.82 mmol) in EtOH (70 mL) was subjected to hydrogenation at 40 psi in the presence of 5% Pd/C (100 mg). Over a five hour period the solid starting material appeared to largely dissolve and then another solid formed. After another 5h LCMS indicated the reaction to be 95% complete. The mixture was purged with nitrogen and diluted with 25 mL of THF which dissolved all of the solids. After treatment with a 50 mg portion of 10% Pd/C, the mixture was again subjected to hydrogenation at 40 psi. After 2h LCMS indicated no remaining starting material. The reaction vessel was purged with nitrogen, catalyst removed by filtration through Celite[®] and the filtrate concentrated at reduced pressure to afford **14** (0.91, 100%) as a tan powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.29 (d, *J* = 4.10 Hz, 1 H), 7.85 (dd, *J* = 8.01, 5.86 Hz, 2 H), 7.30 (t, *J* = 8.69 Hz, 2 H), 7.05 (s, 1 H), 6.80 (s, 1 H), 5.32 (br s, 2 H), 2.81 (d, *J* = 4.30 Hz, 3 H), 1.65 - 1.75 (m, 1 H), 0.84 - 0.94 (m, 2 H), 0.48 - 0.56 (m, 2 H). ES-LCMS *m/z*: 325 (M+1).

(4-(3-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)-2-oxooxazolidin-4-yl)-2-fluorophenyl)boronic acid (18).



(A) **Methyl 2-bromo-2-(4-bromo-3-fluorophenyl)acetate (13)**. A solution of methyl 2-(4-bromo-3-fluorophenyl)acetate (**12**, 2.20 g, 9.09 mmol), NBS (1.94 g, 10.9 mmol) and benzoyl peroxide (0.436 g, 1.80 mmol) in CCl₄ (10 mL) was heated at reflux for 4h and then cooled to RT. The mixture was concentrated to dryness and the residue purified by flash chromatography (silica gel, petroleum ether/EtOAc) to afford **13** (2.10 g, 71%) as an oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.67 (t, *J* = 7.80 Hz, 1 H), 7.34 (dd, *J* = 9.95, 1.56 Hz, 1 H), 7.11 (d, *J* = 8.20 Hz, 1 H), 3.76 (s, 3 H), 3.35 (s, 1 H).

(B) **Methyl 2-(4-bromo-3-fluorophenyl)-2-((5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)amino)acetate (15)**. A solution of 6-amino-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (**14**, 2.40 g, 7.40 mmol) and methyl 2-bromo-2-(4-bromo-3-fluorophenyl)acetate (4.82 g, 14.8 mmol) in DMF (30 mL) was stirred at 85 °C for 18h and then cooled to RT. The reaction mixture was diluted with water and extracted with EtOAc (3x). The combined EtOAc extracts were washed with water (1x), brine (1x), dried over Na₂SO₄, and concentrated to dryness at reduced pressure. The crude product was subjected to flash chromatography (silica gel, EtOAc/hexanes) to afford **15** (2.10 g, 50%) as a yellow solid. ES-LCMS *m/z*: 569 (M+1).

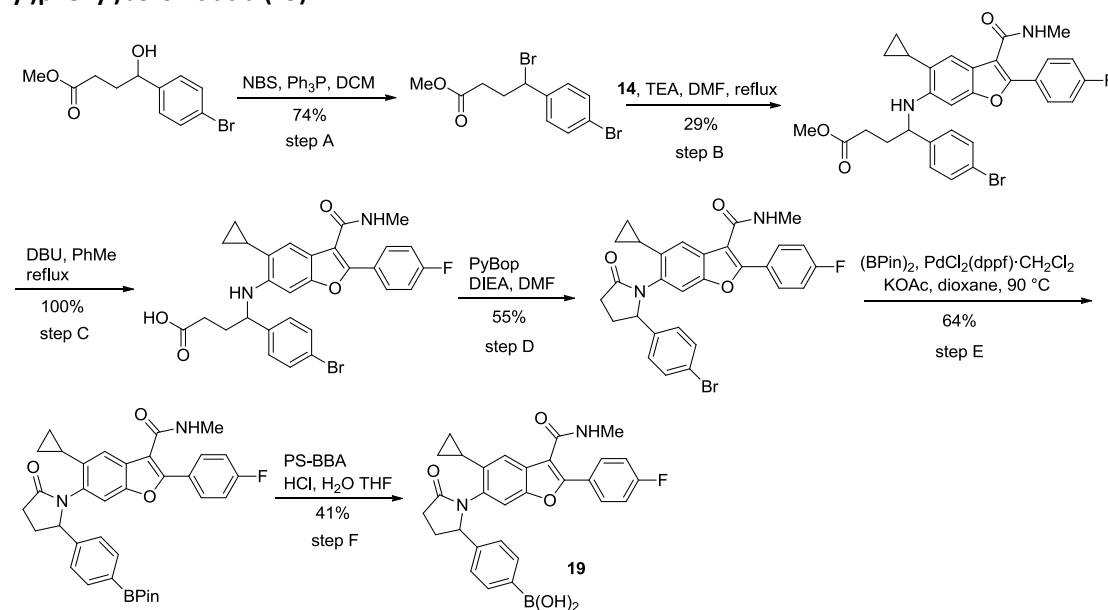
(C) **6-((1-(4-Bromo-3-fluorophenyl)-2-hydroxyethyl)amino)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (16)**. To a stirred solution of methyl 2-(4-bromo-3-fluorophenyl)-2-((5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)amino)acetate (**15**, 2.20 g, 3.86 mmol) in THF

(20 mL) at 0 °C was added LiBH₄ (0.253 g, 11.6 mmol). The solution was allowed to warm to RT and stirred for 2 h. The reaction mixture was quenched with aqueous NH₄Cl and extracted with EtOAc. The EtOAc solution was washed with brine, dried over Na₂SO₄ and concentrated to dryness at reduced pressure. The crude material was purified by flash chromatography (silica gel, EtOAc/hexanes) to afford **16** (1.80 g, 86%) as a white solid. ES-LCMS *m/z*: 541 (M+1).

(D) **6-(4-(4-Bromo-3-fluorophenyl)-2-oxooxazolidin-3-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (17)**. To a stirred solution of 6-((1-(4-bromo-3-fluorophenyl)-2-hydroxyethyl)amino)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (**16**, 2.15 g, 3.97 mmol) in DCM (30 mL) at 0 °C was added TEA (2.77 mL, 19.9 mmol) followed by triphosgene (2.36 g, 7.94 mmol). The solution was stirred at 0 °C for 1 hour and then allowed to warm to RT. After 18h the solution was concentrated to dryness at reduced pressure and the residue subjected to flash chromatography (silica gel, 0-80% EtOAc/hexanes) to afford racemic **17** (1.30 g, 58%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.36 - 8.44 (m, 1 H), 7.93 (dd, *J* = 8.78, 5.46 Hz, 2 H), 7.63 - 7.72 (m, 3 H), 7.28 - 7.42 (m, 3 H), 7.12 (br s, 1 H), 5.73 (t, *J* = 8.29 Hz, 1 H), 4.93 (t, *J* = 8.68 Hz, 1 H), 4.42 (t, *J* = 8.39 Hz, 1 H), 2.82 (d, *J* = 4.49 Hz, 3 H), 2.13 - 2.22 (m, 1 H), 0.72 - 1.13 (m, 4 H). ES-LCMS *m/z*: 567 (M+1).

(E) **5-Cyclopropyl-6-(4-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2-oxooxazolidin-3-yl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (18)**. A solution of 6-(4-(4-bromo-3-fluorophenyl)-2-oxooxazolidin-3-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (**17**, 0.210 g, 0.370 mmol), bis(pinacolato)diboron (1.40 g, 5.55 mmol), KOAc (0.109 g, 1.11 mmol), and PdCl₂(dppf)·CH₂Cl₂ (30 mg, 0.040 mmol) in 1,4-dioxane (5 mL) was sparged with nitrogen and heated to 100 °C. After 18h the solution was cooled to RT, filtered, and concentrated to dryness at reduced pressure. The residue was purified by flash chromatography (silica gel, petroleum ether/EtOAc) to afford a yellow solid (0.230 g). This material was dissolved in THF (10 mL) and the solution treated with PS-BBA (polymer-supported benzeneboronic acid, 0.720 g, 1.85 mmol) followed by 1N aqueous HCl (5.00 mL, 5.00 mmol). After stirring the mixture at RT for 18h the solid was removed by filtration. The filtrate was concentrated to dryness at reduced pressure. The residue was purified by RP-HPLC to give **18** (60 mg, 30%) as a white solid. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 7.80 - 7.90 (m, 2 H), 7.14 - 7.44 (m, 7 H), 5.62 (t, *J* = 7.91 Hz, 1 H), 4.98 (t, *J* = 8.89 Hz, 1 H), 4.54 (t, *J* = 8.11 Hz, 1 H), 2.91 (s, 3 H), 2.08 - 2.18 (m, 1 H), 0.95 - 1.17 (m, 2 H), 0.61 - 0.84 (m, 2 H). ES-LCMS *m/z*: 533 (M+1), 100% purity. HRMS *m/z* calcd for C₂₈H₂₃BF₂N₂O₆: 533.1695. Found: 533.1696.

(4-(1-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)-5-oxopyrrolidin-2-yl)phenyl)boronic acid (19)



(A) **Methyl 4-bromo-4-(4-bromophenyl)butanoate**. A solution of methyl 4-(4-bromophenyl)-4-hydroxybutanoate (2.73 g, 10.0 mmol) and triphenylphosphine (5.24 g, 0.020 mmol) in DCM (20 mL) was cooled to 0 °C and treated with NBS (3.57 g, 0.02 mmol) in portions. After warming to RT and stirring overnight the solution was diluted with DCM (30 mL), washed with 10% aqueous potassium carbonate (50 mL), brine (50 mL), dried over Na₂SO₄, and concentrated to dryness at reduced pressure. The residue was subjected to flash chromatography (silica gel, petroleum ether/EtOAc) (silica gel, 30:1 petroleum ether/EtOAc) to afford the title compound (2.50 g, 74%) as a colorless oil.

(B) **Methyl 4-(4-bromophenyl)-4-((5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)amino)butanoate**. A solution of methyl 4-bromo-4-(4-bromophenyl)butanoate (1.56 g, 4.63 mmol), 6-amino-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (**14**, 0.500 g, 1.54 mmol), and TEA (1.30 mL, 9.26 mmol) in DMF (3 mL) was heated to reflux for 48h and then cooled to RT. The mixture was partitioned between EtOAc and water and the phases separated. The aqueous solution was extracted with EtOAc (2x). The combined EtOAc solutions were washed with brine, dried over Na₂SO₄, and concentrated to dryness at reduced pressure. The crude product was purified by flash chromatography (silica gel, 20:1 DCM/EtOAc) to give the title compound (0.260 g, 29%) as a brown solid.

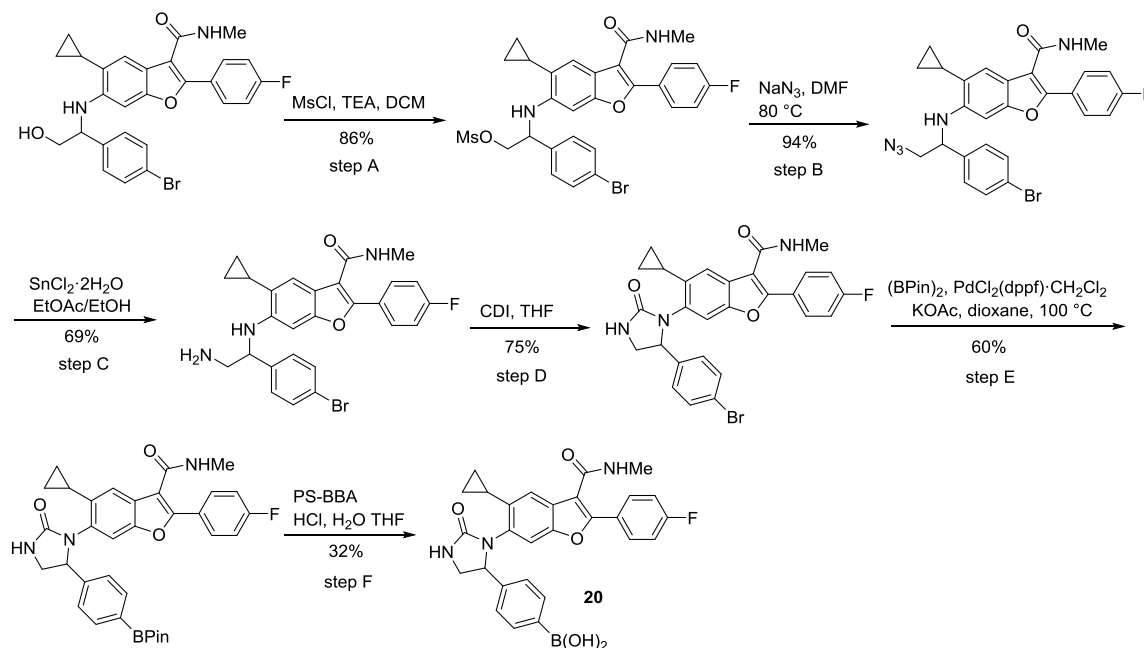
(C) **4-(4-Bromophenyl)-4-((5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)amino)butanoic acid**. A solution of methyl 4-(4-bromophenyl)-4-((5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)amino)butanoate (0.200 g, 0.345 mmol) and DBU (3 mL) in toluene (3 mL) was heated to reflux overnight and then cooled to RT. The mixture was partitioned between EtOAc and water and the phases separated. The aqueous solution was extracted with EtOAc (2x). The combined EtOAc solutions were washed with 1N aqueous HCl (1x), dried over Na₂SO₄ and concentrated to dryness at reduced pressure to give the title compound as a brown solid in quantitative yield. The material was used in the next step without further purification.

(D) **6-(2-(4-Bromophenyl)-5-oxopyrrolidin-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide**. A solution of 4-(4-bromophenyl)-4-((5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)amino)butanoic acid (0.150 g, 0.265 mmol), PyBOP (0.207 g, 0.398 mmol), and DIEA (0.139 mL, 0.796 mmol) in DMF (10 mL) was stirred at 50 °C overnight and then cooled to RT. The mixture was diluted with EtOAc (60 mL), washed with 1N aqueous HCl (1x30 mL), water (2x30 mL), brine (1x30 mL), dried over Na₂SO₄ and concentrated to dryness at reduced pressure. The residue was subjected to flash chromatography (silica gel, petroleum ether/ EtOAc) to afford the title compound (80 mg, 55%) as a yellow solid.

(E) **5-Cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-(2-oxo-5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidin-1-yl)benzofuran-3-carboxamide**. A solution of 6-(2-(4-bromophenyl)-5-oxopyrrolidin-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.100 g, 0.183 mmol), bis(pinacolato)diboron (0.232 g, 0.914 mmol), KOAc (54 mg, 0.54 mmol), and PdCl₂(dppf)·CH₂Cl₂ (45 mg, 0.055 mmol) in 1,4-dioxane (4 mL) was sparged with nitrogen and heated to 90°C. After 18h the solution was cooled to RT and concentrated to dryness at reduced pressure. The crude residue was subjected to flash chromatography (silica gel, 1:2 petroleum ether/EtOAc) to give the title compound (70 mg, 64%) as an off white solid.

(F) **4-(1-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)-5-oxopyrrolidin-2-yl)phenyl)boronic acid (**19**)**. A solution of 5-cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-(2-oxo-5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidin-1-yl)benzofuran-3-carboxamide (0.200 g, 0.336 mmol) in 5 mL of THF was treated with PS-BBA (polymer-supported benzenboronic acid, 0.640 g, 1.68 mmol) followed by 5N aqueous HCl (0.35 mL, 1.75 mmol). After stirring the mixture at RT overnight the solid was removed by filtration. The filtrate was diluted with EtOAc, washed with water (1x), brine (1x), dried over Na₂SO₄, and concentrated to dryness at reduced pressure. The residue was purified by RP-HPLC to give **19** (70 mg, 41%) as a white solid. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 7.82 (dd, *J* = 8.70, 5.40 Hz, 2 H), 7.52 (d, *J* = 6.78 Hz, 2 H), 7.34 (d, *J* = 7.51 Hz, 2 H), 7.13 - 7.24 (m, 4 H), 5.33 (t, *J* = 6.59 Hz, 1 H), 2.67 - 2.93 (m, 6 H), 2.22 - 2.38 (m, 1 H), 1.93 - 2.06 (m, 1 H), 0.63 - 1.14 (m, 4 H). ES-LCMS *m/z*: 513 (M+1), 100% purity. HRMS *m/z* calcd for C₂₉H₂₆BFN₂O₅: 513.1997. Found: 513.1999.

(4-(3-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)-2-oxoimidazolidin-4-yl)phenyl)boronic acid (20).



(A) 2-(4-Bromophenyl)-2-((5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)amino)ethyl methanesulfonate. To a stirred solution of 6-((1-(4-bromophenyl)-2-hydroxyethyl)amino)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.625 g, 1.20 mmol) in DCM (50 mL) at 0 °C was added TEA (0.361 mL, 2.60 mmol) followed by MsCl (0.138 g, 1.20 mmol). After stirring at 0 °C for 1 hour the solution was washed with water (2x), dried over Na₂SO₄, and concentrated to dryness at reduced pressure. The crude material was purified by flash chromatography (silica gel, petroleum ether/EtOAc) to give the title compound (0.620 g, 86%) as a white solid.

(B) 6-((2-Azido-1-(4-bromophenyl)ethyl)amino)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide. A mixture of 2-(4-bromophenyl)-2-((5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)amino)ethyl methanesulfonate (0.620 g, 1.03 mmol) and sodium azide (0.136 g, 2.06 mmol) in DMF (30 mL) was heated to 80 °C for 18 h. The mixture was cooled to RT and diluted with water (50 mL). The resulting mixture was extracted with EtOAc (3x50 mL). The combined EtOAc extracts were washed with water (1x50 mL), brine (1x50 mL), dried over Na₂SO₄, and evaporated to dryness. The residue was subjected to flash chromatography (silica gel, petroleum ether/EtOAc) to give the title compound (0.530 g, 94%) as a light yellow solid.

(C) 6-((2-Amino-1-(4-bromophenyl)ethyl)amino)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide. To a stirred solution of 6-((2-azido-1-(4-bromophenyl)ethyl)amino)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.530 g, 0.968 mmol) in 1:1 EtOAc/EtOH (50 mL) was added SnCl₂·2H₂O (0.650 g, 2.91 mmol). The solution was heated to 80 °C for 2 h, cooled to RT, and then concentrated to dryness at reduced pressure. The residue was partitioned between EtOAc and 10% aqueous sodium carbonate and the phases separated. The EtOAc solution was washed with 10% aqueous sodium carbonate (2x), dried over Na₂SO₄ and concentrated to dryness. The crude material was purified by flash chromatography (silica gel, petroleum ether/EtOAc) to give the title compound (0.350 g, 69%) as a light yellow solid.

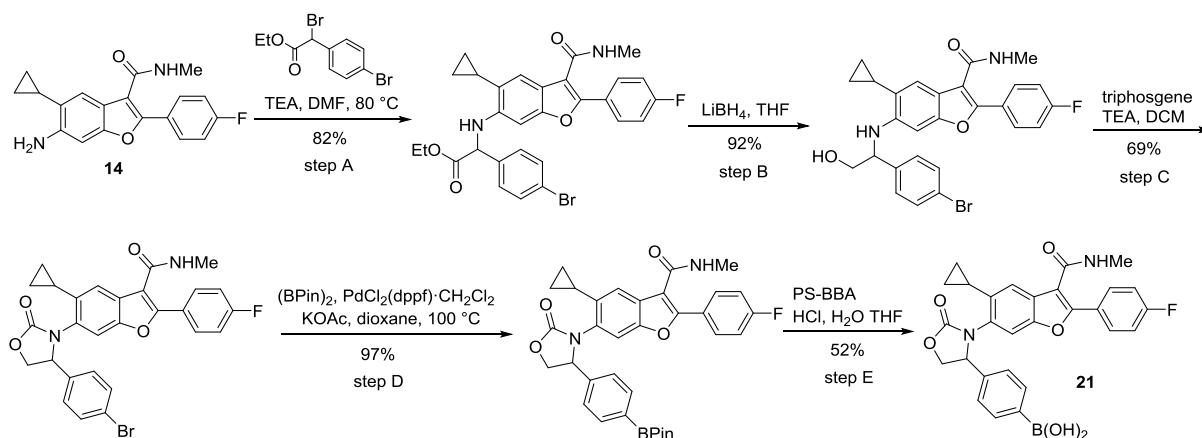
(D) 6-(5-(4-Bromophenyl)-2-oxoimidazolidin-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide. To a stirred solution of 6-((2-amino-1-(4-bromophenyl)ethyl)amino)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.295 g, 0.560 mmol) in THF (50 mL) at 0 °C was added a solution of CDI (92 mg, 0.56 mmol) in 5 mL by dropwise addition. The resulting solution was allowed to warm to RT. After 18h the solution was diluted with brine (50 mL) and the mixture extracted with EtOAc (3x50 mL). The combined EtOAc solutions were dried over Na₂SO₄ and concentrated to dryness at reduced pressure.

The residue was subjected to flash chromatography (silica gel, petroleum ether/EtOAc) to give the title compound (0.230 g, 75%) as a white solid.

(E) **5-Cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-(2-oxo-5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)imidazolidin-1-yl)benzofuran-3-carboxamide**. A solution of 6-(5-(4-bromophenyl)-2-oxoimidazolidin-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.230 g, 0.394 mmol), bis(pinacolato)diboron (0.300 g, 1.18 mmol), KOAc (0.116 g, 1.18 mmol), and PdCl₂(dppf)·CH₂Cl₂ (33 mg, 0.040 mmol) in 1,4-dioxane (30 mL) was sparged with nitrogen and heated to 100 °C. After 18h the solution was cooled to RT and concentrated to dryness at reduced pressure. The crude residue was subjected to flash chromatography (silica gel, petroleum ether/EtOAc) to give the title compound (0.143 g, 60%) as a light yellow solid.

(F) **(4-(3-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)-2-oxoimidazolidin-4-yl)phenyl)boronic acid (20)**. A solution of 5-cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-(2-oxo-5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)imidazolidin-1-yl)benzofuran-3-carboxamide (0.143 g, 0.240 mmol) in 20 mL of THF was treated with PS-BBA (polymer-supported benzenboronic acid, 0.460 g, 1.20 mmol) followed by 5N aqueous HCl (0.33 mL, 1.68 mmol). After stirring the mixture at RT overnight the solid was removed by filtration. The filtrate was concentrated to dryness at reduced pressure. The residue was purified by RP-HPLC to give **20** (40 mg, 32%) as a white solid. ¹H NMR (300 MHz, METHANOL-*d*₄) δ 7.90 - 7.98 (m, 2 H) 7.66 (d, *J* = 7.92 Hz, 2 H) 7.53 (d, *J* = 7.92 Hz, 2 H) 7.23 - 7.35 (m, 4 H) 5.53 (t, *J* = 8.25 Hz, 1 H) 4.13 (t, *J* = 9.24 Hz, 1 H) 3.66 - 3.77 (m, 1 H) 3.01 (s, 3 H) 2.20 - 2.32 (m, 1 H) 1.02 - 1.27 (m, 2 H) 0.72 - 0.91 (m, 2 H). ES-LCMS *m/z*: 514 (M+1), 100% purity. HRMS *m/z* calcd for C₂₈H₂₅BFN₃O₅: 514.1950. Found: 514.1953.

(4-(3-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)-2-oxooxazolidin-4-yl)phenyl)boronic acid (21).



(A) **Ethyl 2-(4-bromophenyl)-2-((5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)amino)acetate**. To a solution of 6-amino-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (**14**, 0.500 g, 1.54 mmol) and ethyl 2-bromo-2-(4-bromophenyl)acetate (0.546 g, 1.70 mmol) in DMF (25 mL) was added TEA (0.59 mL, 4.62 mmol). After stirring at 80 °C overnight the solution was cooled to RT and diluted with water (30 mL). The resulting mixture was extracted with EtOAc (3x). The combined EtOAc extracts were washed with water (1x), brine (1x), dried over Na₂SO₄ and concentrated to dryness at reduced pressure. The crude material was purified by flash chromatography to afford the title compound (0.720 g, 82%) as a white solid.

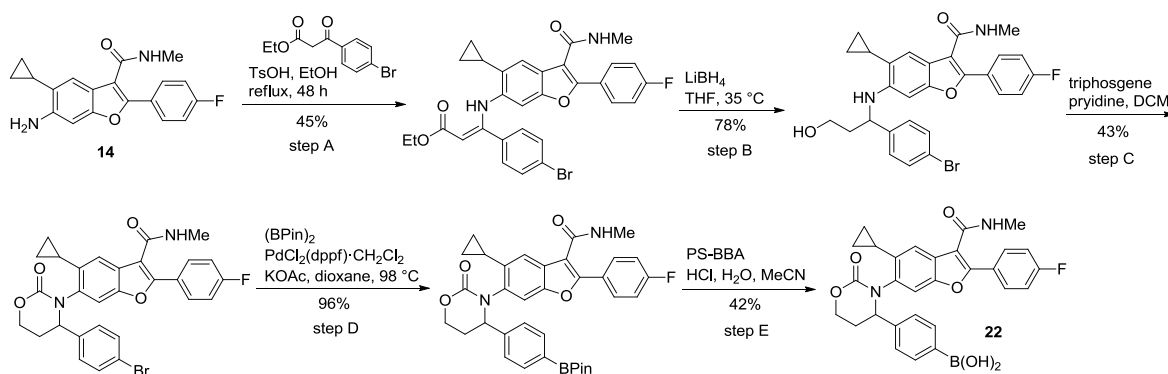
(B) **6-((1-(4-Bromophenyl)-2-hydroxyethyl)amino)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide**. To a stirred solution of ethyl 2-(4-bromophenyl)-2-((5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)amino)acetate (0.720 g, 1.27 mmol) in THF (30 mL) at 0 °C was added 2M LiBH₄/THF (1.91 mL, 3.82 mmol). The solution was allowed to warm to RT and stirred for an additional 1 hour. The solution was quenched with water (50 mL) and extracted with EtOAc (3x50 mL). The combined EtOAc extracts were washed with brine (1x), dried over Na₂SO₄, and concentrated to dryness at reduced pressure. The residue was subjected to flash chromatography (silica gel, EtOAc/petroleum ether) to afford the title compound (0.610 g, 92%) as an off white solid.

(C) **6-(4-(4-Bromophenyl)-2-oxooxazolidin-3-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide**. A solution of 6-((1-(4-bromophenyl)-2-hydroxyethyl)amino)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.200 g, 0.380 mmol) and TEA (0.266 mL, 1.90 mmol) in DCM (20 mL) was cooled to -78 °C and was treated with triphosgene (0.114 g, 0.38 mmol). The solution was then allowed to warm to RT. After 18h the solution was washed with water (3x), dried over Na₂SO₄, and concentrated to dryness at reduced pressure. The residue was subjected to flash chromatography to give the title compound (0.145 g, 69%) as a light yellow solid.

(D) **5-Cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-(2-oxo-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)oxazolidin-3-yl)benzofuran-3-carboxamide**. A solution of 6-(4-(4-bromophenyl)-2-oxooxazolidin-3-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.145 g, 0.26 mmol), bis(pinacolato)diboron (0.201 g, 0.780 mmol), KOAc (76 mg, 0.78 mmol), and PdCl₂(dppf)·CH₂Cl₂ (21 mg, 0.026 mmol) in 1,4-dioxane (10 mL) was sparged with nitrogen and heated to 100 °C. After 18h the solution was cooled to RT, filtered to remove solids, and the filtrate concentrated to dryness at reduced pressure. The crude residue was purified by flash chromatography to afford the title compound (0.150 g, 97%) as a yellow solid.

(E) **(4-(3-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)-2-oxooxazolidin-4-yl)phenyl)boronic acid (21)**. A solution of 5-cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-(2-oxo-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)oxazolidin-3-yl)benzofuran-3-carboxamide (0.150 g, 0.250 mmol) in 10 mL of THF was treated with PS-BBA (polymer-supported benzenboronic acid, 0.48 g, 1.25 mmol) followed by 5N aqueous HCl (0.35 mL, 1.75 mmol). After stirring the mixture at RT overnight the solid was removed by filtration and the filtrate concentrated to dryness at reduced pressure. The residue was purified by RP-HPLC to give **21** (66 mg, 52%) as a white solid. ¹H NMR (300 MHz, METHANOL-*d*₄) δ 7.94 (dd, *J* = 8.58, 5.35 Hz, 2 H), 7.70 (d, *J* = 7.62 Hz, 2 H), 7.54 (d, *J* = 7.77 Hz, 2 H), 7.23 - 7.41 (m, 4 H), 5.68 (t, *J* = 7.77 Hz, 1 H), 5.08 (t, *J* = 8.80 Hz, 1 H), 4.59 - 4.70 (m, 1 H), 3.01 (s, 3 H), 2.15 - 2.28 (m, 1 H), 1.03 - 1.29 (m, 2 H), 0.73 - 0.92 (m, 2 H). ES-LCMS *m/z*: 515 (M+1), 100% purity. HRMS *m/z* calcd for C₂₈H₂₄BFN₂O₆: 515.1790. Found: 515.1793.

(4-(3-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)-2-oxo-1,3-oxazinan-4-yl)phenyl)boronic acid (22).



(A) **(Z)-Ethyl 3-(4-bromophenyl)-3-(((5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)amino)acrylate**. A mixture of 6-amino-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (**14**, 1.70 g, 5.25 mmol), ethyl 3-(4-bromophenyl)-3-oxopropanoate (2.13 g, 7.87 mmol), and *p*-toluenesulfonic acid (90 mg, 0.53 mmol) in EtOH (15 mL) was heated at reflux for 48 h. The mixture was then cooled and stored in a refrigerator for 3 h. The solid product was collected by filtration. The filter cake was washed with EtOH (2x) and dried *in vacuo* to give the title compound (1.40 g, 45%) as a yellow solid.

(B) **6-((1-(4-Bromophenyl)-3-hydroxypropyl)amino)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide**. To a solution of (Z)-ethyl 3-(4-bromophenyl)-3-(((5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)amino)acrylate (1.37 g, 2.37 mmol) in anhydrous THF (30 mL) at 0 °C was added 2M LiBH₄/THF (14 mL, 28.5 mmol). The solution was then stirred at 35 °C for 18 h. The solution was poured into ice water and the mixture extracted with EtOAc (3x). The combined EtOAc extracts were

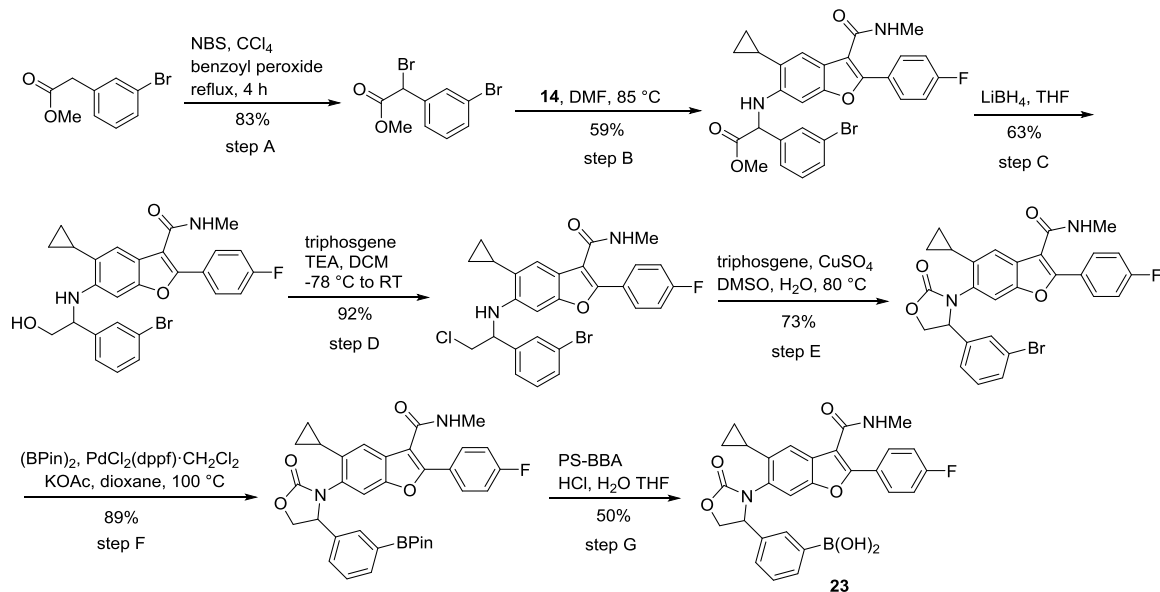
concentrated and the residue subjected to flash chromatography (silica gel, petroleum ether/EtOAc) to afford the title compound (0.990 g, 78%) as a brown solid.

(C) **6-(4-(4-Bromophenyl)-2-oxo-1,3-oxazinan-3-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide**. To a stirred solution of 6-((1-(4-bromophenyl)-3-hydroxypropyl)amino)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.250 g, 0.465 mmol) and pyridine (0.220 g, 2.79 mmol) in DCM (60 mL) at -78 °C was added a solution of triphosgene (0.414 g, 1.40 mmol) in DCM (5 mL). The solution was warmed to around -45 °C and stirred for 2h at which point TLC indicated complete reaction. The solution was diluted with saturated aqueous NaHCO₃ (10 mL) and extracted with DCM (2x20 mL). The combined DCM extracts were dried over Na₂SO₄ and concentrated to dryness at reduced pressure. The crude residue was purified by flash chromatography (silica gel, petroleum ether/EtOAc) to afford the title compound (0.112 g, 43%) as a brown solid.

(D) **5-Cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-(2-oxo-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1,3-oxazinan-3-yl)benzofuran-3-carboxamide**. A solution of 6-(4-(4-Bromophenyl)-2-oxo-1,3-oxazinan-3-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (90 mg, 0.16 mmol), bis(pinacolato)diboron (0.122 g, 0.480 mmol), KOAc (47 mg, 0.48 mmol), and PdCl₂(dppf)·CH₂Cl₂ (13 mg, 0.016 mmol) in 1,4-dioxane (10 mL) was sparged with nitrogen and heated to 98 °C. After 12h the solution was cooled to RT, filtered to remove solids, and the filtrate concentrated to dryness at reduced pressure. The crude residue was purified by flash chromatography (silica gel, petroleum ether/EtOAc) to afford the title compound (95 mg, 96%) as a brown solid.

(E) **(4-(3-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)-2-oxo-1,3-oxazinan-4-yl)phenyl)boronic acid (22)**. A solution of 5-cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-(2-oxo-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1,3-oxazinan-3-yl)benzofuran-3-carboxamide (95 mg, 0.156 mmol) in MeCN (10 mL) was treated with PS-BBA (polymer-supported benzenboronic acid, 0.300 g, 0.78 mmol) followed by 5N aqueous HCl (0.50 mL, 2.50 mmol). After stirring the mixture at RT for 48h the solid was removed by filtration and the filtrate concentrated to dryness at reduced pressure. The residue was purified by RP-HPLC to give **22** (35 mg, 42%) as a white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.38 (q, *J* = 4.43 Hz, 1 H), 8.02 (s, 2 H), 7.85 - 7.93 (m, 2 H), 7.80 (d, *J* = 8.04 Hz, 2 H), 7.43 (d, *J* = 8.04 Hz, 2 H), 7.29 - 7.36 (m, 2 H), 7.24 (s, 1 H), 7.18 (s, 1 H), 5.04 (t, *J* = 4.72 Hz, 1 H), 4.32 - 4.45 (m, 2 H), 2.81 (d, *J* = 4.64 Hz, 3 H), 2.60 - 2.71 (m, 1 H), 2.05 - 2.13 (m, 2 H), 1.08 - 1.17 (m, 1 H), 0.95 - 1.04 (m, 1 H), 0.82 - 0.91 (m, 1 H), 0.66 - 0.76 (m, 1 H). ES-LCMS *m/z*: 529 (M+1), 100% purity. HRMS *m/z* calcd for C₂₉H₂₆BFN₂O₆: 529.1946. Found: 529.1946.

(3-(3-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)-2-oxooxazolidin-4-yl)phenyl)boronic acid (23).



(A) **Methyl 2-bromo-2-(3-bromophenyl)acetate**. A solution of methyl 2-(3-bromophenyl)acetate (2.00 g, 8.73 mmol), NBS (2.02 g, 11.4 mmol), and benzoyl peroxide (0.317 g, 1.31 mmol) in CCl₄ (10 mL) was heated to reflux with stirring for 4h and then cooled to RT. The mixture was concentrated to dryness at reduced pressure and the residue subjected to flash chromatography (silica gel, EtOAc/petroleum ether) to afford the title compound (2.20 g, 83%) as an oil.

(B) **Methyl 2-(3-bromophenyl)-2-((5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)amino)acetate**. A solution of methyl 6-amino-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (**14**, 0.800 g, 2.46 mmol) and methyl 2-bromo-2-(3-bromophenyl)acetate (1.12 g, 3.70 mmol) in DMF (10 mL) was heated to 85 °C overnight and then cooled to RT. The solution was diluted with water and extracted with EtOAc. The EtOAc solution was concentrated to dryness at reduced pressure and the residue subjected to flash chromatography (silica gel, 3:1 petroleum ether/EtOAc) to afford the title compound (0.800 g, 59%) as a yellow solid.

(C) **6-((1-(3-Bromophenyl)-2-hydroxyethyl)amino)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide**. A solution of methyl 2-(3-bromophenyl)-2-((5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)amino)acetate (0.780 g, 1.42 mmol) in THF (8 mL) at 0 °C was treated with LiBH₄ (93 mg, 4.2 mmol). After stirring at 0 °C for 3h the reaction mixture was quenched by addition of aqueous NH₄Cl. The resulting mixture was extracted with EtOAc. The EtOAc solution was concentrated to dryness and the residue subjected to flash chromatography (silica gel, 3:1 petroleum ether/EtOAc) to afford the title compound (0.470 g, 63%) as a yellow solid.

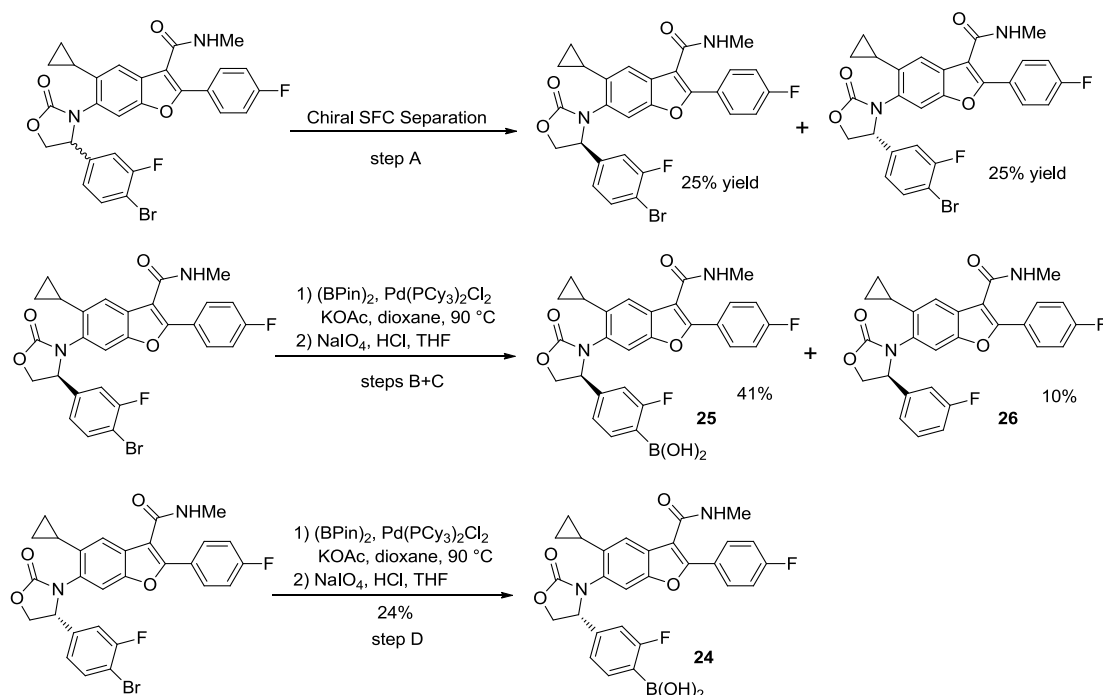
(D) **6-((1-(3-Bromophenyl)-2-chloroethyl)amino)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide**. To a stirred solution of 6-((1-(3-bromophenyl)-2-hydroxyethyl)amino)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.470 g, 0.900 mmol) and TEA (0.454 g, 4.50 mmol) in DCM (5 mL) at -78 °C was added triphosgene (0.294 g, 0.990 mmol). After stirring the solution at -78 °C for 3h the solution was allowed to warm to RT. After another 18h the solution was quenched with aqueous NH₄Cl and extracted with DCM. The DCM solution was dried over Na₂SO₄ and concentrated at reduced pressure to afford the title compound (0.470 g, 92%) as a yellow solid.

(E) **6-(4-(3-Bromophenyl)-2-oxooxazolidin-3-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide**. A solution of 6-((1-(3-bromophenyl)-2-chloroethyl)amino)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.470 g, 0.830 mmol), CuSO₄ (0.416 g, 1.66 mmol), and triphosgene (0.282 g, 0.83 mmol) in 3:2 DMSO/H₂O (12.5 mL) was heated to 80 °C for 3h and then cooled to RT. The solution was diluted with water and extracted with EtOAc. The EtOAc solution was concentrated and the residue purified by flash chromatography (silica gel, 3:1 petroleum ether/EtOAc) to give the title compound (0.330 g, 73%) as a yellow solid.

(F) **5-Cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-(2-oxo-4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)oxazolidin-3-yl)benzofuran-3-carboxamide**. A solution of 6-(4-(3-bromophenyl)-2-oxooxazolidin-3-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.330 g, 0.600 mmol), bis(pinacolato)diboron (2.29 g, 9.00 mmol), KOAc (0.176 g, 1.80 mmol), and PdCl₂(dppf)·CH₂Cl₂ (49 mg, 0.060 mmol) in 1,4-dioxane (5 mL) was sparged with nitrogen and heated to 100 °C. After 18h the solution was cooled to RT, filtered to remove solids, and the filtrate concentrated to dryness at reduced pressure. The crude material was subjected to flash chromatography (silica gel, 1:1 petroleum ether/EtOAc) to afford the title compound (0.320 g, 89%) as a yellow solid.

(G) **(3-(3-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)-2-oxooxazolidin-4-yl)phenyl)boronic acid (23)**. A solution of 5-cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-(2-oxo-4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)oxazolidin-3-yl)benzofuran-3-carboxamide (0.320 g, 0.530 mmol) in 10 mL of THF was treated with PS-BBA (polymer-supported benzenboronic acid, 0.500 g, 2.65 mmol) followed by 1N aqueous HCl (5.00 mL, 5.00 mmol). After stirring the mixture at RT for 18h the solid was removed by filtration. The filtrate was concentrated to dryness at reduced pressure. The residue was purified by RP-HPLC to give **23** (0.150 g, 50%) as a white solid. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 7.82 (dd, *J* = 8.79, 5.31 Hz, 2 H), 7.61 (s, 1 H), 7.51 (dd, *J* = 17.49, 7.23 Hz, 2 H), 7.10 - 7.39 (m, 5 H), 5.50 - 5.62 (m, 1 H), 4.96 (t, *J* = 8.88 Hz, 1 H), 4.55 (t, *J* = 7.97 Hz, 1 H), 2.89 (s, 3 H), 2.04 - 2.16 (m, 1 H), 1.06 - 1.16 (m, 1 H), 0.94 - 1.04 (m, 1 H), 0.62 - 0.79 (m, 2 H). ES-LCMS *m/z*: 515 (M+1), 100% purity. HRMS *m/z* calcd for C₂₈H₂₄BFN₂O₆: 515.1790. Found: 515.1785.

(R)- and (S)-4-(3-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)-2-oxooxazolidin-4-yl)-2-fluorophenyl)boronic acid (24 and 25) and (S)-5-cyclopropyl-2-(4-fluorophenyl)-6-(4-(3-fluorophenyl)-2-oxooxazolidin-3-yl)-N-methylbenzofuran-3-carboxamide (26).



(A) (S)- and (R)-6-(4-(4-bromo-3-fluorophenyl)-2-oxooxazolidin-3-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide. Racemic 6-(4-(4-bromo-3-fluorophenyl)-2-oxooxazolidin-3-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (1.30 g, 2.29 mmol, for preparation see **18**, step D) was subjected to chiral supercritical fluid chromatography [ChiralPak AS-H column (30x250mm, 5 μm), isocratic at 3:1:6 MeOH/CHCl₃/CO₂, 100 bars, 40 °C] to afford (S)-6-(4-(4-bromo-3-fluorophenyl)-2-oxooxazolidin-3-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.560 g, 25%) and (R)-6-(4-(4-bromo-3-fluorophenyl)-2-oxooxazolidin-3-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.560 g, 25%). The chemical purities were determined at >98% for both enantiomers by LCMS. The enantiopurities were determined to be >98% for both enantiomers by chiral analytical SFC chromatography [ChiralPak AS-H column (4.6x250mm, 5 μm), isocratic at 3:1:6 MeOH/CHCl₃/CO₂, 100 bars, 40 °C] with t_R=3.70 and 5.48 min for the S and R enantiomers respectively. The absolute configurations were assigned by VCD spectroscopy (see supporting information for details).

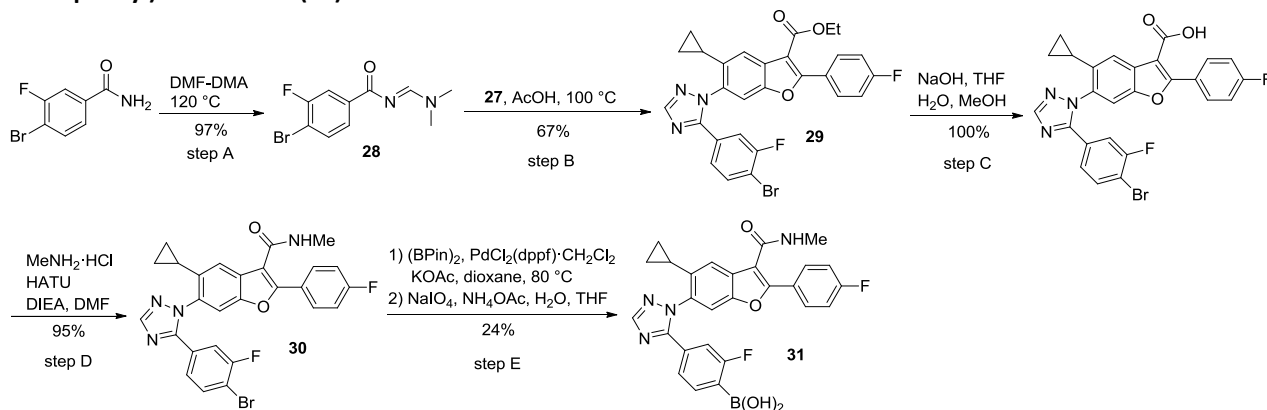
(B) (S)-5-Cyclopropyl-6-(4-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2-oxooxazolidin-3-yl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide. A solution of (S)-6-(4-(4-bromo-3-fluorophenyl)-2-oxooxazolidin-3-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.500 g, 0.881 mmol), bis(pinacolato)diboron (0.671 g, 2.64 mmol), KOAc (0.346 g, 3.52 mmol), and Pd(PCy₃)₂Cl₂ (64 mg, 0.088 mmol) in 1,4-dioxane (12 mL) was sparged with nitrogen and heated to 90 °C. After 18h LCMS indicated complete reaction accompanied by the formation of 19% of the bromo-reduction by-product (S)-5-cyclopropyl-2-(4-fluorophenyl)-6-(4-(3-fluorophenyl)-2-oxooxazolidin-3-yl)-N-methylbenzofuran-3-carboxamide. The solution was cooled to RT, filtered, and concentrated to dryness at reduced pressure. The residue was subjected to flash chromatography (silica gel, 0-70% EtOAc/hexanes) to afford the pinacol boronate ester intermediate as a mixture with the bromo-reduction by-product.

(C) (S)-4-(3-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)-2-oxooxazolidin-4-yl)-2-fluorophenyl)boronic acid (25) and (S)-5-cyclopropyl-2-(4-fluorophenyl)-6-(4-(3-fluorophenyl)-2-oxooxazolidin-3-yl)-N-methylbenzofuran-3-carboxamide (26). The mixture from step B was dissolved in THF (10 mL) and cooled to 0 °C. To the solution was added 1M aqueous HCl (10.0 mL, 10.0 mmol) followed by NaIO₄ (1.74

g, 8.14 mmol). After warming to RT, the solution was stirred for an additional 18h. The reaction mixture was diluted with EtOAc, washed with 5% aqueous sodium bisulfite (1x), brine (1x), dried over Na₂SO₄ and concentrated to dryness at reduced pressure. The crude material was purified by flash chromatography (silica gel, 0-100% EtOAc/DCM over 12 min, then 0-3.5% MeOH/DCM over 5 min) to afford **25** (0.193 g, 41%) and **26** (41 mg, 10%), both as off-white solids. Data for **25**: ¹H NMR (400 MHz, METHANOL-*d*₄) δ 7.80 - 7.90 (m, 2 H), 7.14 - 7.44 (m, 7 H), 5.62 (t, *J* = 7.91 Hz, 1 H), 4.98 (t, *J* = 8.89 Hz, 1 H), 4.54 (t, *J* = 8.11 Hz, 1 H), 2.91 (s, 3 H), 2.08 - 2.18 (m, 1 H), 0.95 - 1.17 (m, 2 H), 0.61 - 0.84 (m, 2 H). ES-LCMS *m/z*: 533 (M+1), 100% purity. HRMS *m/z* calcd for C₂₈H₂₃BF₂N₂O₆: 533.1695. Found: 533.1695. Enantiopurity determined to be >99% by chiral analytical SFC chromatography [ChiralPak AS-H column (4.6x250mm, 5 μm), isocratic at 25% iPrOH/CO₂, 140 bars, 40 °C] with *t*_R=3.87 min. Data for **26**: ¹H NMR (400 MHz, METHANOL-*d*₄) δ 7.81 - 7.91 (m, 2 H), 7.17 - 7.41 (m, 7 H), 7.01 - 7.08 (m, 1 H), 5.62 (t, *J* = 8.01 Hz, 1 H), 4.98 (t, *J* = 8.89 Hz, 1 H), 4.54 (dd, *J* = 8.89, 7.33 Hz, 1 H), 2.91 (s, 3 H), 2.03 - 2.18 (m, 1 H), 1.09 - 1.18 (m, 1 H), 0.97 - 1.07 (m, 1 H), 0.64 - 0.83 (m, 2 H). ES-LCMS *m/z*: 489 (M+1), 100% purity. HRMS *m/z* calcd for C₂₈H₂₂F₂N₂O₄: 489.1626. Found: 489.1628.

(D) **(R)-(4-(3-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)-2-oxooxazolidin-4-yl)-2-fluorophenyl)boronic acid (24)**. The title compound was prepared from (*R*)-6-(4-(4-bromo-3-fluorophenyl)-2-oxooxazolidin-3-yl)-5-cyclopropyl-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide as described above for the synthesis of **25**. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 7.80 - 7.90 (m, 2 H), 7.14 - 7.44 (m, 7 H), 5.62 (t, *J* = 7.91 Hz, 1 H), 4.98 (t, *J* = 8.89 Hz, 1 H), 4.54 (t, *J* = 8.11 Hz, 1 H), 2.91 (s, 3 H), 2.08 - 2.18 (m, 1 H), 0.95 - 1.17 (m, 2 H), 0.61 - 0.84 (m, 2 H). ES-LCMS *m/z*: 533 (M+1), 100% purity. HRMS *m/z* calcd for C₂₈H₂₃BF₂N₂O₆: 533.1695. Found: 533.1694. Enantiopurity determined to be >99% by chiral analytical SFC chromatography [ChiralPak AS-H column (4.6x250mm, 5 μm), isocratic at 25% iPrOH/CO₂, 140 bars, 40 °C] with *t*_R=12.47 min.

(4-(1-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)-1H-1,2,4-triazol-5-yl)-2-fluorophenyl)boronic acid (31).



(A) **(E)-4-Bromo-N-((dimethylamino)methylene)-3-fluorobenzamide (28)**. A solution of 4-bromo-3-fluorobenzamide (2.75 g, 12.6 mmol) in DMF-DMA (20 mL, 149 mmol) was heated to 120 °C for 3h and then cooled to RT. The solution was evaporated to dryness at reduced pressure. The resulting solid was triturated with ether and isolated by filtration to give **28** (3.34 g, 97%) as an off-white solid. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 8.65 (s, 1 H), 8.03 (dd, *J* = 9.56, 1.76 Hz, 1 H), 7.94 (dd, *J* = 8.39, 1.56 Hz, 1 H), 7.60 (dd, *J* = 8.10, 6.93 Hz, 1 H), 3.24 (s, 3 H), 3.23 (s, 3 H).

(B) **Ethyl 6-(5-(4-bromo-3-fluorophenyl)-1H-1,2,4-triazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylate (29)**. A solution of (*E*)-4-bromo-*N*-((dimethylamino)methylene)-3-fluorobenzamide (0.424 g, 1.55 mmol) and ethyl 5-cyclopropyl-2-(4-fluorophenyl)-6-hydrazinylbenzofuran-3-carboxylate hydrochloride (**27**, 0.500 g, 1.28 mmol, for preparation see example **33**, step B) in glacial AcOH (3 mL) was heated to 100 °C for 4h and then cooled to RT. The solution was concentrated to dryness at reduced pressure and the residue dissolved in EtOAc. The solution was washed with saturated aqueous NaHCO₃, washed with brine, dried over Na₂SO₄, and evaporated. The residue was subjected to flash chromatography (silica gel, 0-40% EtOAc/hexanes) to afford **29** (0.535 g, 67%) as a white foam. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 8.18 (s, 1 H), 8.07 (dd, *J* = 8.70, 5.37 Hz, 2 H), 7.82 (s, 1 H), 7.51 (s, 1 H), 7.47 (t, *J* = 7.72 Hz, 1 H), 7.37 (dd, *J* = 9.58, 1.76 Hz, 1 H),

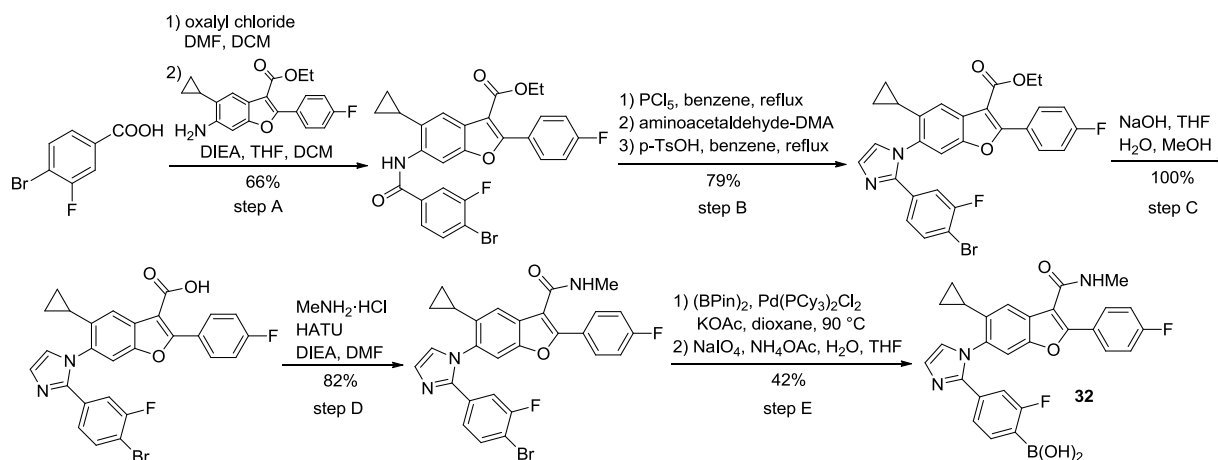
7.11 - 7.24 (m, 3 H), 4.44 (q, $J = 7.04$ Hz, 2 H), 1.37 - 1.49 (m, 4 H), 0.72 (br s, 3 H), 0.43 (br s, 1 H). ES-LCMS m/z : 564 (M+1).

(C) **6-(5-(4-Bromo-3-fluorophenyl)-1H-1,2,4-triazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylic acid**. The title compound was prepared from ethyl 6-(5-(4-bromo-3-fluorophenyl)-1H-1,2,4-triazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylate in 100% yield as described herein for the synthesis of **33**, step D. ES-LCMS m/z : 536 (M+1).

(D) **6-(5-(4-Bromo-3-fluorophenyl)-1H-1,2,4-triazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (30)**. Compound **30** was prepared from 6-(5-(4-bromo-3-fluorophenyl)-1H-1,2,4-triazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylic acid in 95% yield as described herein for the synthesis of **33**, step E. ^1H NMR (400 MHz, CHLOROFORM- d) δ 8.18 (s, 1 H), 7.91 (dd, $J = 8.58, 5.27$ Hz, 2 H), 7.62 (s, 1 H), 7.44 - 7.52 (m, 2 H), 7.39 (dd, $J = 9.37, 1.76$ Hz, 1 H), 7.23 (t, $J = 8.59$ Hz, 2 H), 7.12 (dd, $J = 8.39, 1.37$ Hz, 1 H), 5.78 - 5.89 (m, 1 H), 3.04 (d, $J = 4.88$ Hz, 3 H), 1.34 - 1.47 (m, 1 H), 0.73 (br s, 3 H) 0.45 (br s, 1 H).

(E) **(4-(1-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)-1H-1,2,4-triazol-5-yl)-2-fluorophenyl)boronic acid (31)**. A solution of 6-(5-(4-bromo-3-fluorophenyl)-1H-1,2,4-triazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.200 g, 0.364 mmol), bis(pinacolato)diboron (0.277 g, 1.09 mmol), KOAc (0.143 g, 1.46 mmol), and $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ (30 mg, 0.036 mmol) in 1,4-dioxane (5 mL) was sparged with nitrogen and heated to 80 °C. After 3h the solution was cooled to RT, diluted with THF (10 mL), and treated with 1M aqueous NH_4OAc (7 mL) followed by NaIO_4 (0.779 g, 3.64 mmol). After stirring at RT for 3 days the mixture was diluted with water and extracted with EtOAc. The EtOAc solution was washed with saturated aqueous sodium thiosulfate (1x), brine (1x), dried over Na_2SO_4 , and concentrated to dryness at reduced pressure. The residue was subjected to RP-HPLC purification (C18, 5-100% MeCN/ H_2O with 0.1% formic acid) to afford **31** (45 mg, 24%) as a white solid. ^1H NMR (400 MHz, METHANOL- d_4) δ 8.28 (s, 1 H), 7.94 (dd, $J = 8.78, 5.27$ Hz, 2 H), 7.76 (s, 1 H), 7.34 - 7.43 (m, 2 H), 7.16 - 7.30 (m, 4 H), 2.95 (s, 3 H), 1.31 - 1.44 (m, 1 H), 0.69 (br s, 3 H), 0.39 (br s, 1 H). ES-LCMS m/z : 515 (M+1), 100% purity. HRMS m/z calcd for $\text{C}_{27}\text{H}_{21}\text{BF}_2\text{N}_4\text{O}_4$: 515.1702. Found: 515.1705.

(4-(1-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)-1H-imidazol-2-yl)-2-fluorophenyl)boronic acid (32)



(A) **Ethyl 6-(4-bromo-3-fluorobenzamido)-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylate**. To a stirred suspension of 4-bromo-3-fluorobenzoic acid (1.00 g, 4.57 mmol) in DCM (15 mL) was added 2M oxalyl chloride/DCM (2.40 mL, 4.79 mmol) followed by a few drops of DMF. After 18h LCMS indicated the reaction to be incomplete and solid starting material remained. THF (10 mL) was added followed by an additional portion of 2M oxalyl chloride/DCM (2.40 mL, 4.79 mmol). After 1 hour the solution was concentrated to dryness at reduced pressure. The residue was dissolved in 1:1 DCM/THF and the solution treated with ethyl 6-amino-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylate (1.55 g, 4.57 mmol, prepared as described in WO2012067663) followed by DIEA (1.60 mL, 9.13 mmol). After several min a gold solid had precipitated. Additional DCM was added to aid in stirring. After another 1 hour LCMS indicated nearly complete reaction. The mixture was diluted with water and

extracted with DCM (3x). The DCM phases contained a considerable amount of solid which was collected by filtration and dried *in vacuo* to afford the title compound (0.481 g, 20%). The filtrate was concentrated to dryness. The solid residue was suspended in DCM, the mixture stirred briefly, and the solid collected by filtration and dried *in vacuo* to give an additional (1.15 g, 46%) of the title compound as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.19 (s, 1 H), 8.04 - 8.11 (m, 2 H), 7.91 - 8.01 (m, 2 H), 7.87 (s, 1 H), 7.81 - 7.85 (m, 1 H), 7.69 (s, 1 H), 7.37 - 7.44 (m, 2 H), 4.35 (q, *J* = 7.03 Hz, 2 H), 2.08 - 2.25 (m, 1 H), 1.34 (t, *J* = 7.03 Hz, 3 H), 0.89 - 1.03 (m, 2 H), 0.55 - 0.69 (m, 2 H). ES-LCMS *m/z*: 540 (M+1).

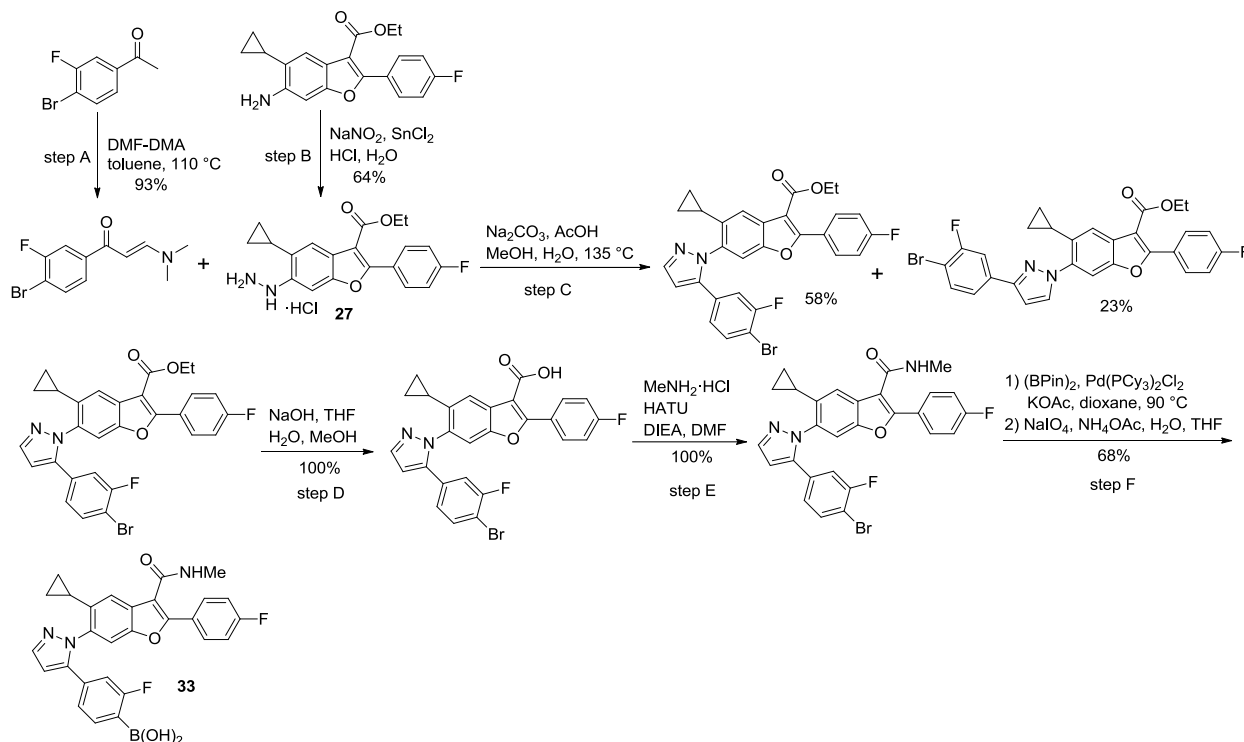
(B) **Ethyl 6-(2-(4-bromo-3-fluorophenyl)-1H-imidazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylate**. A suspension of ethyl 6-(4-bromo-3-fluorobenzamido)-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylate (1.15 g, 2.13 mmol) in benzene (25 mL) was treated with PCl₅ and heated to reflux with stirring. After 2h the solution was cooled to RT and concentrated to dryness at reduced pressure. The residue was dissolved in THF (20 mL) and the solution cooled to 0 °C. To the solution was added a solution of aminoacetaldehyde dimethyl acetal (0.464 mL, 4.26 mmol) in THF (10 mL) by slow addition. The solution was allowed to slowly warm to RT with melting of the ice bath and then stirred at RT overnight. The solution was diluted with ether and filtered to remove the small amount of suspended solid. The filtrate was concentrated at reduced pressure and the residue redissolved in benzene (45 mL). The solution was treated with *p*-TsOH (0.810 g, 4.26 mmol) and heated to reflux. After 1 hour the solution was concentrated to dryness at reduced pressure. The crude residue was subjected to flash chromatography (silica gel, 0-100% EtOAc/hexanes) to give the title compound (0.95 g, 79%) as an off-white foam. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.05 - 8.12 (m, 2 H), 7.96 (s, 1 H), 7.66 (s, 1 H), 7.60 (t, *J* = 8.03 Hz, 1 H), 7.52 (d, *J* = 1.00 Hz, 1 H), 7.42 (t, *J* = 8.91 Hz, 2 H), 7.35 (dd, *J* = 10.29, 1.76 Hz, 1 H), 7.30 (d, *J* = 1.00 Hz, 1 H), 7.03 (dd, *J* = 8.53, 2.01 Hz, 1 H), 4.31 - 4.40 (m, 2 H), 1.28 - 1.37 (m, 4 H), 0.71 - 0.81 (m, 1 H), 0.59 - 0.70 (m, 2 H), 0.31 - 0.39 (m, 1 H). ES-LCMS *m/z*: 563 (M+1).

(C) **6-(2-(4-Bromo-3-fluorophenyl)-1H-imidazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylic acid**. The title compound was prepared from ethyl 6-(2-(4-bromo-3-fluorophenyl)-1H-imidazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylate in 100% yield as described herein for the synthesis of **33**, step D. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.34 (br s, 1 H), 8.05 - 8.12 (m, 2 H), 7.94 (s, 1 H), 7.68 (s, 1 H), 7.61 (t, *J* = 7.91 Hz, 1 H), 7.54 (s, 1 H), 7.30 - 7.45 (m, 4 H), 7.03 (dd, *J* = 8.41, 1.88 Hz, 1 H), 1.27 - 1.36 (m, 1 H), 0.71 - 0.79 (m, 1 H), 0.58 - 0.69 (m, 2 H), 0.29 - 0.39 (m, 1 H). ES-LCMS *m/z*: 535 (M+1).

(D) **6-(2-(4-Bromo-3-fluorophenyl)-1H-imidazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide**. The title compound was prepared from 6-(2-(4-bromo-3-fluorophenyl)-1H-imidazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylic acid in 82% yield as described herein for the synthesis of **33**, step E. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.42 - 8.50 (m, 1 H), 7.93 - 7.99 (m, 2 H), 7.89 (s, 1 H), 7.57 - 7.64 (m, 1 H), 7.49 (d, *J* = 1.00 Hz, 1 H), 7.32 - 7.45 (m, 3 H), 7.26 - 7.31 (m, 2 H), 7.05 (dd, *J* = 8.41, 1.88 Hz, 1 H), 2.85 (d, *J* = 4.52 Hz, 3 H), 1.22 - 1.32 (m, 1 H), 0.55 - 0.76 (m, 3 H), 0.33 - 0.44 (m, 1 H). ES-LCMS *m/z*: 548 (M+1).

(E) **(4-(1-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)-1H-imidazol-2-yl)-2-fluorophenyl)boronic acid (32)**. Compound **32** was prepared from 6-(2-(4-bromo-3-fluorophenyl)-1H-imidazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide in 42% yield as described herein for the synthesis of **33**, step F. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 7.90 - 7.96 (m, 2 H), 7.68 (s, 1 H), 7.40 (s, 1 H), 7.35 (s, 1 H), 7.23 - 7.32 (m, 4 H), 7.08 - 7.19 (m, 2 H), 2.95 (s, 3 H), 1.33 - 1.43 (m, 1 H), 0.60 - 0.82 (m, 3 H), 0.39 - 0.48 (m, 1 H). ES-LCMS *m/z*: 514 (M+1), 100% purity. HRMS *m/z* calcd for C₂₈H₂₂BF₂N₃O₄: 514.1750. Found: 514.1754.

(4-(1-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)-1H-pyrazol-5-yl)-2-fluorophenyl)boronic acid (33).



(A) **(E)-1-(4-Bromo-3-fluorophenyl)-3-(dimethylamino)prop-2-en-1-one.** To a stirred solution of 1-(4-bromo-3-fluorophenyl)ethanone (1.00 g, 4.38 mmol) in toluene (3.5 mL) was added DMF-DMA (0.837 mL, 6.13 mmol). The resulting solution was heated to 110 °C overnight and cooled to RT. The mixture was concentrated at reduced pressure and the residue triturated with hexanes. The solid was collected by filtration and dried *in vacuo* to afford the title compound (1.11 g, 93%) as a tan solid. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 7.88 (d, *J* = 12.10 Hz, 1 H), 7.64 - 7.69 (m, 1 H), 7.54 - 7.63 (m, 2 H), 5.64 (d, *J* = 12.29 Hz, 1 H), 3.20 (br s, 3 H), 2.97 (br s, 3 H). ES-LCMS *m/z*: 272 (M+1).

(B) **Ethyl 5-cyclopropyl-2-(4-fluorophenyl)-6-hydrazinylbenzofuran-3-carboxylate hydrochloride (27).** A solution of NaNO₂ (0.122 g, 1.77 mmol) in water (1 mL) was added to a mixture of ethyl 6-amino-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylate (0.500 g, 1.47 mmol, prepared as described in WO2012067663) in concentrated HCl (11.0 mL, 134 mmol) at 0 °C in an ice bath. This resulted in the formation of a thick slurry. The mixture was stirred at 0 °C for 30 min, then a solution of SnCl₂ (0.855 g, 4.42 mmol) in concentrated HCl (1.00 mL, 12.2 mmol) was added dropwise. The stirring stopped due to precipitation. Another 40 mL of concentrated HCl was added. The reaction mixture was allowed to warm up to RT and stirred at RT for 2 h. The solid was collected by filtration, washed with ether, and air dried to give **27** (0.528 g, 64%) as a tan solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.99 - 8.12 (m, 4 H), 7.64 (s, 1 H), 7.36 - 7.44 (m, 3 H), 7.27 (s, 1 H), 4.34 (q, *J* = 6.89 Hz, 2 H), 1.88 - 2.00 (m, 1 H), 1.34 (t, *J* = 6.90 Hz, 3 H), 0.95 - 1.06 (m, 2 H), 0.54 - 0.68 (m, 2 H).

(C) **Ethyl 6-(5-(4-bromo-3-fluorophenyl)-1H-pyrazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylate.** To a stirred solution of ethyl 5-cyclopropyl-2-(4-fluorophenyl)-6-hydrazinylbenzofuran-3-carboxylate hydrochloride (**27**, 0.404 g, 0.889 mmol), (E)-1-(4-bromo-3-fluorophenyl)-3-(dimethylamino)prop-2-en-1-one (0.220 g, 0.808 mmol) and Na₂CO₃ (60.0 mg, 0.566 mmol) in 5:1 MeOH/water (6 mL) was added glacial AcOH (0.5 mL, 8.74 mmol). The resulting mixture was heated to 135 °C for 4 h and then cooled to RT. The mixture was diluted with water and extracted with DCM. The combined DCM extracts were washed with water, brine, dried over Na₂SO₄ and concentrated at reduced pressure to give a dark brown oil. The crude product was subjected to flash chromatography (silica gel, 0-20% EtOAc/hexanes) to afford the title compound (0.266 g, 58%) as a tan foam. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 8.04 - 8.10 (m, 2 H), 7.83 (d, *J* = 1.95 Hz, 1 H), 7.70 (s, 1 H), 7.50 (s, 1 H), 7.42

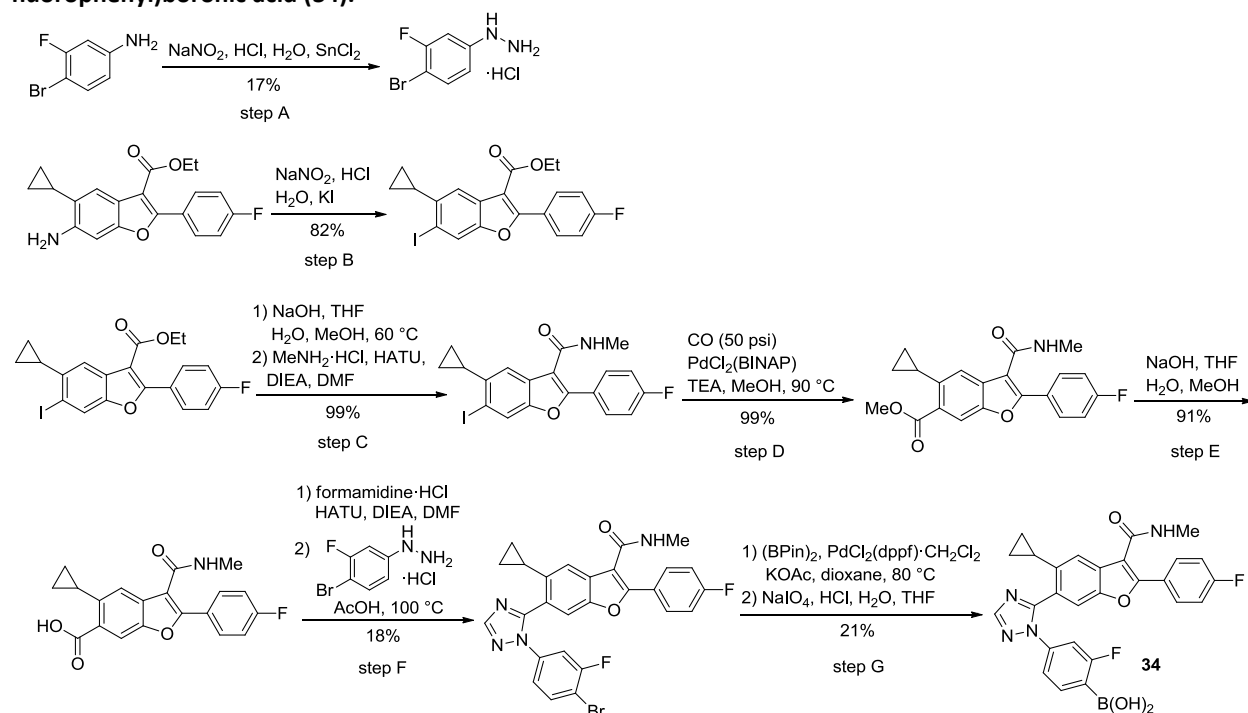
(dd, $J = 8.19, 7.22$ Hz, 1 H), 7.15 - 7.24 (m, 2 H), 6.98 - 7.04 (m, 1 H), 6.88 (dd, $J = 8.39, 1.95$ Hz, 1 H), 6.65 (d, $J = 1.95$ Hz, 1 H), 4.43 (q, $J = 7.02$ Hz, 2 H), 1.39 - 1.52 (m, 4 H), 0.64 - 0.87 (m, 3 H), 0.43 (br s, 1 H). ES-LCMS m/z : 563 (M+1). The minor, higher Rf regioisomer ethyl 6-(3-(4-bromo-3-fluorophenyl)-1H-pyrazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylate was isolated in 23% yield.

(D) **6-(5-(4-Bromo-3-fluorophenyl)-1H-pyrazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylic acid**. To a stirred solution of ethyl 6-(5-(4-bromo-3-fluorophenyl)-1H-pyrazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylate (0.264 g, 0.469 mmol) in THF (4 mL), MeOH (3 mL) and water (2 mL) was added 1M aqueous NaOH (1.41 mL, 1.41 mmol). The resulting solution was heated to 60 °C for 2.5h and then cooled to RT. The solution was acidified to pH 2 by addition of 1M aqueous HCl and the mixture extracted with EtOAc (2x). The combined EtOAc extracts were washed with brine, dried over Na₂SO₄, and concentrated at reduced pressure to afford the title compound (0.251 g, 100%) as a beige foam. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 8.12 (dd, $J = 8.88, 5.37$ Hz, 2 H), 7.81 (d, $J = 1.95$ Hz, 1 H), 7.72 (s, 1 H), 7.66 (s, 1 H), 7.51 (t, $J = 7.80$ Hz, 1 H), 7.24 (t, $J = 8.88$ Hz, 2 H), 7.17 (dd, $J = 9.85, 1.85$ Hz, 1 H), 6.99 (dd, $J = 8.39, 1.76$ Hz, 1 H), 6.81 (d, $J = 1.95$ Hz, 1 H), 1.31 - 1.42 (m, 1 H), 0.71 (br s, 3 H), 0.37 (br s, 1 H). ES-LCMS m/z : 535 (M+1).

(E) **6-(5-(4-Bromo-3-fluorophenyl)-1H-pyrazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide**. To a stirred solution of 6-(5-(4-bromo-3-fluorophenyl)-1H-pyrazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylic acid (0.251 g, 0.469 mmol), methylamine hydrochloride (38.0 mg, 0.563 mmol) and HATU (0.267 g, 0.703 mmol) in DMF (5 mL) at 0 °C was added DIEA (0.246 mL, 1.41 mmol) by dropwise addition. The mixture was stirred at RT for 3h and the product precipitated by addition of water. The solid was collected by vacuum filtration. The filter cake was washed with saturated aqueous NaHCO₃, water, and then air dried to afford the title compound (0.256 g, 100%) as an off-white solid. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 7.93 (dd, $J = 8.78, 5.27$ Hz, 2 H) 7.81 (d, $J = 1.76$ Hz, 1 H) 7.67 (s, 1 H) 7.50 (t, $J = 7.90$ Hz, 1 H) 7.21 - 7.31 (m, 3 H) 7.14 (dd, $J = 9.85, 1.85$ Hz, 1 H) 7.01 (dd, $J = 8.29, 1.66$ Hz, 1 H) 6.80 (d, $J = 1.95$ Hz, 1 H) 2.94 (s, 3 H) 1.25 - 1.39 (m, 1 H) 0.71 (br s, 3 H) 0.37 (br s, 1 H). ES-LCMS m/z : 548 (M+1).

(F) **(4-(1-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)-1H-pyrazol-5-yl)-2-fluorophenyl)boronic acid (33)**. A mixture of 6-(5-(4-bromo-3-fluorophenyl)-1H-pyrazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.240 g, 0.438 mmol), KOAc (0.172 g, 1.75 mmol), bis(pinacolato)diboron (0.227 g, 0.875 mmol) and dichlorobis(tricyclohexylphosphine)palladium (II) (34.0 mg, 0.044 mmol) in 1,4-dioxane (5 mL) was maintained at 90 °C in a sealed pressure tube under N₂ for 23h and then cooled to RT. The mixture was diluted with EtOAc, filtered through a pad of Celite[®], washed with brine and dried over Na₂SO₄, filtered and concentrated to give 5-cyclopropyl-6-(5-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-pyrazol-1-yl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.510 g) as a brown oil. This material was dissolved in THF (10 mL) and the solution treated with 0.2 N aqueous NH₄OAc followed by sodium periodate (0.936 g, 4.38 mmol). After stirring at RT for 2.5 days, the mixture was diluted with brine and extracted with EtOAc (2x). The combined EtOAc extracts were washed with 5% aqueous NaHSO₃ (3x) followed by brine. The solution was dried over Na₂SO₄ and concentrated at reduced pressure. The crude material was purified by flash chromatography (silica gel, 0-100% EtOAc over 12 min, then switch solvents to A=DCM and B=9:1 DCM/MeOH; 0-35% B/A over 5 min) to afford **33** (0.153 g, 68%) as an off-white solid. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 7.93 (dd, $J = 8.88, 5.37$ Hz, 2 H), 7.81 (d, $J = 1.95$ Hz, 1 H), 7.65 (s, 1 H), 7.21 - 7.31 (m, 4 H), 7.09 (d, $J = 7.61$ Hz, 1 H), 6.98 (d, $J = 10.15$ Hz, 1 H), 6.79 (d, $J = 1.76$ Hz, 1 H), 2.94 (s, 3 H), 1.31 - 1.41 (m, 1 H), 0.71 (br s, 3 H), 0.36 (br s, 1 H). ES-LCMS m/z : 514 (M+1), 100% purity. HRMS m/z calcd for C₂₈H₂₂BF₂N₃O₄: 514.1750. Found: 514.1753.

(4-(5-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)-1H-1,2,4-triazol-1-yl)-2-fluorophenyl)boronic acid (34).



(A) (4-Bromo-3-fluorophenyl)hydrazine hydrochloride. To a stirred suspension of 4-bromo-3-fluoroaniline (1.00 g, 5.26 mmol) in 6N aqueous HCl (4 mL) at 0 °C was added sodium nitrite (0.726 g, 10.5 mmol). After 30 minutes, a solution of SnCl₂ (2.99 g, 15.8 mmol) in concentrated HCl (45 mL) was added dropwise. The mixture was warmed to RT and stirred for 15 min. The resulting solid was collected by filtration. The filter cake was washed with water followed by ether, and then air dried overnight to give the title compound (0.215 g, 17%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.37 (br s, 3 H), 8.72 (br s, 1 H), 7.59 (t, *J* = 8.29 Hz, 1 H), 6.99 (dd, *J* = 11.02, 2.44 Hz, 1 H), 6.77 (dd, *J* = 8.78, 2.15 Hz, 1 H). ES-LCMS *m/z*: 205 (M+1).

(B) (A) Ethyl 5-cyclopropyl-2-(4-fluorophenyl)-6-iodobenzofuran-3-carboxylate. To a stirred suspension of ethyl 6-amino-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylate (10.0 g, 29.5 mmol), prepared as described in WO2013028371) in 6N aqueous HCl at -3 °C (ice water/brine bath) was added a solution of NaNO₂ (4.07 g, 58.9 mmol) in water (25 mL) over a 15 minute period. After 75 minutes the solution was poured into a rapidly stirred, bi-phasic solution of KI (48.9 g, 295 mmol) in water (250 mL) and EtOAc (250 mL). After 15 minutes the mixture was transferred to a separatory funnel and the phases separated. The aqueous phase was extracted with EtOAc (1x). The EtOAc solution was washed with saturated aqueous sodium thiosulfate (2x), 10% aqueous Na₂CO₃ (1x) and brine (1x). The solution was dried over Na₂SO₄ and concentrated at reduced pressure. The crude product was purified by flash chromatography (silica gel, 0-60% DCM/hexanes) to afford the title compound (10.8 g, 82%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.24 (s, 1 H), 8.00 - 8.07 (m, 2 H), 7.63 (s, 1 H), 7.35 - 7.44 (m, 2 H), 4.33 (q, *J* = 7.03 Hz, 2 H), 2.00 - 2.12 (m, 1 H), 1.32 (t, *J* = 7.03 Hz, 3 H), 1.03 - 1.11 (m, 2 H), 0.61 - 0.69 (m, 2 H). ES-LCMS *m/z*: 451 (M+1).

(C) 5-Cyclopropyl-2-(4-fluorophenyl)-6-iodo-N-methylbenzofuran-3-carboxamide. A solution of ethyl 5-cyclopropyl-2-(4-fluorophenyl)-6-iodobenzofuran-3-carboxylate (2.40 g, 5.33 mmol) in 4:3:2 THF/MeOH/H₂O was added 1M aqueous NaOH (26.7 mL, 26.7 mmol). The solution was stirred at 60 °C for 2h and then cooled to RT. The solution was acidified to pH 2 by addition of 1N aqueous HCl. The resulting cloudy solution was extracted with EtOAc (2x). The combined EtOAc extracts were washed with brine (1x), dried over Na₂SO₄ and concentrated to dryness at reduced pressure to give the carboxylic acid intermediate as a tan solid. This material was dissolved in DMF (18 mL). The solution was treated with methylamine hydrochloride (0.432 g, 6.40 mmol), HATU (3.04 g, 8.00 mmol) and DIEA (2.79 mL, 16.0 mmol). A solid precipitated from the solution immediately. An additional 30 mL of DMF was added to facilitate stirring. After 1h the reaction mixture was diluted with water. After stirring the

suspension for 10 minutes the solid was collected by filtration, washed with aqueous NaHCO₃, water, and then air dried overnight to give the title compound (2.29 g, 99%) as an off-white solid. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 8.03 (s, 1 H), 7.89 (dd, *J* = 8.59, 5.27 Hz, 2 H), 7.50 (s, 1 H), 7.20 (t, *J* = 8.59 Hz, 2 H), 5.79 (br s, 1 H), 3.02 (d, *J* = 4.88 Hz, 3 H), 2.00 - 2.12 (m, 1 H), 1.02 - 1.11 (m, 2 H), 0.68 - 0.77 (m, 2 H). ES-LCMS *m/z*: 436 (M+1).

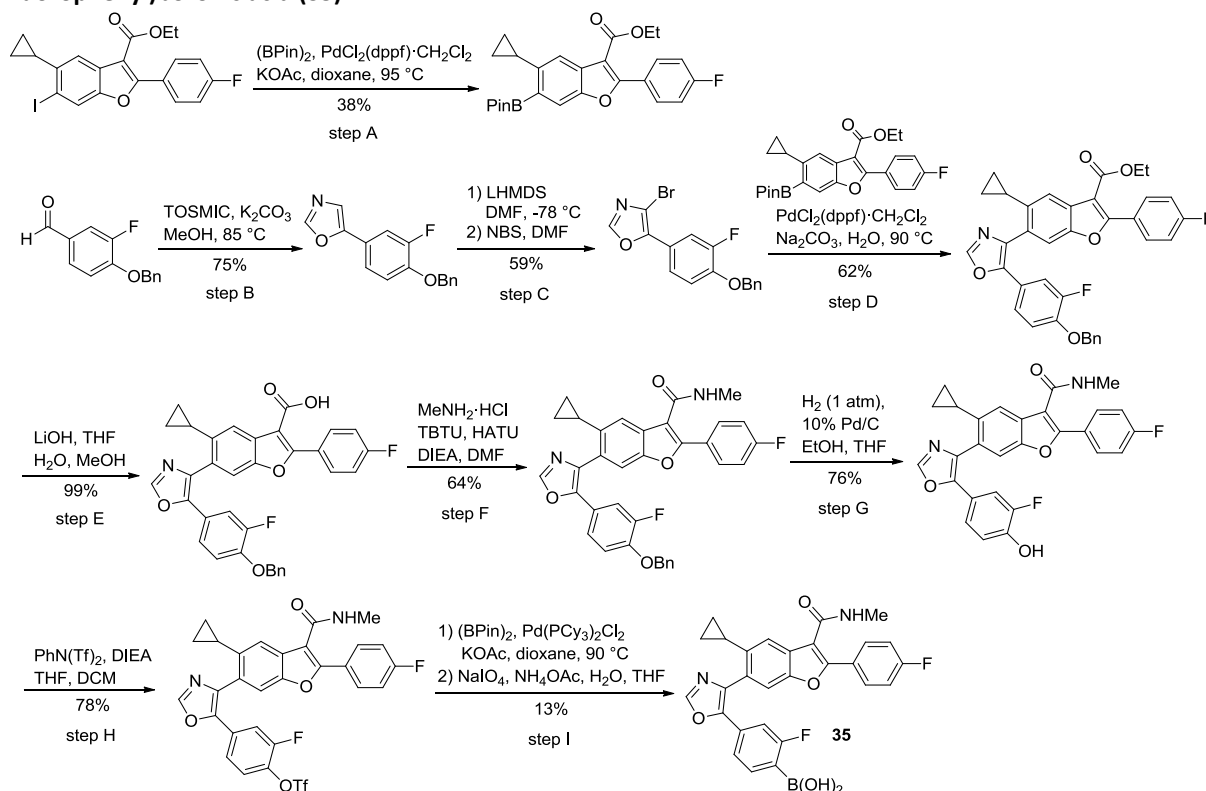
(D) **Methyl 5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-carboxylate**. A solution of 5-cyclopropyl-2-(4-fluorophenyl)-6-iodo-N-methylbenzofuran-3-carboxamide (1.00 g, 2.30 mmol), TEA (0.416 mL, 2.99 mmol), and PdCl₂(BINAP) (92 mg, 0.12 mmol) in MeOH (25 mL) was heated to 90 °C under CO (50 psi) for 18h and then cooled to RT. The solution was evaporated to dryness and the residue subjected to flash chromatography (silica gel, 0-50% EtOAc/hexanes) to give the title compound (0.833 g, 99%) as a brown solid. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 8.01 (s, 1 H), 7.90 - 7.97 (m, 2 H), 7.56 (s, 1 H), 7.21 (t, *J* = 8.59 Hz, 2 H), 5.81 (br s, 1 H), 3.97 (s, 3 H), 3.04 (d, *J* = 4.88 Hz, 3 H), 2.61 - 2.73 (m, 1 H), 0.97 - 1.07 (m, 2 H), 0.68 - 0.78 (m, 2 H). ES-LCMS *m/z*: 368 (M+1).

(E) **5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-carboxylic acid**. A solution of methyl 5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-carboxylate (0.833 g, 2.27 mmol) in 4:3:2 THF/MeOH/H₂O was treated with 1M aqueous NaOH (11.3 mL, 11.3 mmol) and the resulting solution heated 60 °C. After 2h the solution was cooled to RT and acidified to pH 2 by addition of 1N aqueous HCl (15 mL). The solid was collected by filtration, washed with water, and then dried *in vacuo* to give the title compound (0.731 g, 91%) as a light grey solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.03 (s, 1 H), 8.48 (d, *J* = 4.68 Hz, 1 H), 7.89 - 8.05 (m, 3 H), 7.41 (t, *J* = 8.88 Hz, 2 H), 7.26 (s, 1 H), 2.85 (d, *J* = 4.49 Hz, 3 H), 2.63 - 2.77 (m, 1 H), 0.93 - 1.03 (m, 2 H), 0.63 - 0.78 (m, 2 H). ES-LCMS *m/z*: 354 (M+1).

(F) **6-(1-(4-Bromo-3-fluorophenyl)-1H-1,2,4-triazol-5-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide**. To a stirred solution of 5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-carboxylic acid (0.300 g, 0.849 mmol), formamidinium hydrochloride (89 mg, 1.1 mmol), and HATU (0.355 g, 0.934 mmol) in DMF (4.5 mL) was added DIEA (0.445 mL, 2.55 mmol). The mixture was stirred at RT for 1h and then treated with (4-bromo-3-fluorophenyl)hydrazine hydrochloride (0.214 g, 0.886 mmol) followed by glacial AcOH (0.729 mL, 12.7 mmol). The solution was heated to 90 °C at which point a suspension developed. The mixture was treated with an additional 1.5 mL of AcOH, heated to 100 °C overnight, and then cooled to RT. The reaction mixture was partitioned between aqueous NaHCO₃ and EtOAc and the phases separated. The EtOAc solution was washed with brine, dried over Na₂SO₄, and concentrated to dryness at reduced pressure. The residue was subjected to flash chromatography (silica gel, 0-50% EtOAc/hexanes) to afford the title compound (85 mg, 18%). ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 8.17 (s, 1 H), 7.88 (dd, *J* = 7.80, 5.46 Hz, 2 H), 7.40 - 7.51 (m, 3 H), 7.15 - 7.25 (m, 3 H), 6.90 (dd, *J* = 8.68, 0.88 Hz, 1 H), 6.08 (br s, 1 H) 3.01 (d, *J* = 4.88 Hz, 3 H), 1.45 - 1.57 (m, 1 H), 0.63 - 0.72 (m, 2 H), 0.47 - 0.57 (m, 2 H). ES-LCMS *m/z*: 549 (M+1).

(G) **(4-(5-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)-1H-1,2,4-triazol-1-yl)-2-fluorophenyl)boronic acid (34)**. The title compound was prepared from 6-(1-(4-bromo-3-fluorophenyl)-1H-1,2,4-triazol-5-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide in 21% yield as described herein for the synthesis of **37**, step C. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 8.31 (s, 1 H), 7.89 - 7.97 (m, 2 H), 7.71 (s, 1 H), 7.32 - 7.42 (m, 2 H), 7.26 (t, *J* = 8.78 Hz, 2 H), 7.08 - 7.20 (m, 2 H), 2.95 (s, 3 H), 1.41 - 1.52 (m, 1 H), 0.64 - 0.72 (m, 2 H), 0.46 - 0.56 (m, 2 H). ES-LCMS *m/z*: 515 (M+1), 100% purity. HRMS *m/z* calcd for C₂₇H₂₁BF₂N₄O₄: 515.1702. Found: 515.1698.

(4-(4-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)oxazol-5-yl)-2-fluorophenyl)boronic acid (35).



(A) **Ethyl 5-cyclopropyl-2-(4-fluorophenyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-3-carboxylate.** A suspension of ethyl 5-cyclopropyl-2-(4-fluorophenyl)-6-iodobenzofuran-3-carboxylate (1.50 g, 3.33 mmol, preparation described in **34**, step B), bis(pinacolato)diboron (2.54 g, 9.99 mmol), KOAc (0.981 g, 9.99 mmol) and PdCl₂(dppf)·CH₂Cl₂ (0.136 g, 0.167 mmol) in 1,4-dioxane (12 mL) was heated to 95 °C for 45 min, cooled to RT, and stirred overnight. The reaction mixture was filtered through Celite[®] washing with EtOAc (60 mL). The filtrate was concentrated at reduced pressure and the crude residue subjected to flash chromatography (silica gel, 0-5% EtOAc/hexanes) to afford the title compound (0.601 g, 38%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.03 - 8.10 (m, 2 H), 7.82 (s, 1 H), 7.53 (s, 1 H), 7.41 (t, *J* = 8.88 Hz, 2 H), 4.33 (q, *J* = 7.15 Hz, 2 H), 2.62 - 2.74 (m, 1 H), 1.28 - 1.39 (m, 15 H), 0.96 - 1.05 (m, 2 H), 0.62 - 0.70 (m, 2 H). ES-LCMS *m/z*: 451 (M+1).

(B) **5-(4-(Benzyloxy)-3-fluorophenyl)oxazole.** A mixture of 4-(benzyloxy)-3-fluorobenzaldehyde (2.30 g, 10.0 mmol), TOSMIC (2.15 g, 11.0 mmol) and K₂CO₃ (2.76 g, 20.0 mmol) in MeOH (50 mL) in a sealed tube was heated to 85 °C for 18h and cooled to RT. The solution was concentrated to dryness and the residue dissolved in EtOAc (150 mL). The solution was washed with saturated aqueous NH₄Cl (1x50 mL), brine (1x50 mL), dried over Na₂SO₄, and concentrated at reduced pressure. The crude product was purified by flash chromatography (silica gel, 0-30% EtOAc/hexanes) to afford the title compound (2.00 g, 75%) as a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.42 (s, 1 H), 7.60 - 7.68 (m, 2 H), 7.32 - 7.54 (m, 7 H), 5.24 (s, 2 H). ES-LCMS *m/z*: 270 (M+1).

(C) **5-(4-(Benzyloxy)-3-fluorophenyl)-4-bromooxazole.** To a stirred solution of 5-(4-(benzyloxy)-3-fluorophenyl)oxazole (2.00 g, 7.46 mmol) in DMF (7.1 mL) at -15 °C (ice-MeOH bath) was added 1M LHMDS/THF (7.84 mL, 7.84 mmol) over 8 min. After stirring at -15 °C for 30 min, the mixture was cooled to -78 °C which afforded a thick slurry. To this was added a solution of NBS (1.33 g, 7.46 mmol) in DMF (3 mL) by dropwise addition. After 40 min at -78 °C the mixture was quenched with saturated aqueous NH₄Cl (20 mL) and allowed to warm to RT. The mixture was diluted with EtOAc (200 mL) and the phases separated. The EtOAc solution was washed with brine, dried over Na₂SO₄, and concentrated to dryness at reduced pressure. The crude material was subjected to flash chromatography (silica gel, 0-20% EtOAc/hexanes) to afford the title compound (1.52 g, 59%) as

a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.57 (s, 1 H), 7.61 - 7.74 (m, 2 H), 7.29 - 7.56 (m, 6 H), 5.27 (s, 2 H). ES-LCMS m/z : 348 (M+1).

(D) Ethyl 6-(5-(4-(benzyloxy)-3-fluorophenyl)oxazol-4-yl)-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylate. A suspension of 5-(4-(benzyloxy)-3-fluorophenyl)-4-bromooxazole (0.580 g, 1.67 mmol), ethyl 5-cyclopropyl-2-(4-fluorophenyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-3-carboxylate (0.600 g, 1.33 mmol), 2M aqueous Na_2CO_3 (2.00 mL, 4.00 mmol), and $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ (0.109 g, 0.133 mmol) in 1,4-dioxane (6 mL) was heated to 90 °C with stirring. After 3h the reaction mixture was cooled to RT, diluted with EtOAc, filtered to remove solids, and the filtrate concentrated to dryness at reduced pressure. The crude product was subjected to flash chromatography (silica gel, 0-50% EtOAc/hexanes) to give the title compound (0.510 g, 62%) as a foam. ^1H NMR (400 MHz, DMSO- d_6) δ 8.60 (s, 1 H), 8.04 - 8.11 (m, 2 H), 7.67 (s, 2 H), 7.31 - 7.45 (m, 7 H), 7.27 (t, J = 8.78 Hz, 1 H), 7.19 (dd, J = 12.39, 1.85 Hz, 1 H), 7.08 (d, J = 8.59 Hz, 1 H), 5.17 (s, 2 H), 4.36 (q, J = 7.22 Hz, 2 H), 1.74 - 1.90 (m, 1 H), 1.35 (t, J = 7.12 Hz, 3 H), 0.68 - 0.79 (m, 2 H), 0.51 - 0.64 (m, 2 H). ES-LCMS m/z : 592 (M+1).

(E) 6-(5-(4-(Benzyloxy)-3-fluorophenyl)oxazol-4-yl)-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylic acid. To a stirred solution of ethyl 6-(5-(4-(benzyloxy)-3-fluorophenyl)oxazol-4-yl)-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylate (0.506 g, 0.855 mmol) in 3:1 THF/MeOH (20 mL) was added a solution of LiOH (61.4 mg, 2.57 mmol) in water (5 mL). After stirring overnight at RT, the solution was cooled and treated with 1N aqueous HCl (4.28 mL, 4.28 mmol). The organic solvents were removed by rotary evaporation and the remaining aqueous mixture extracted with EtOAc (2x). The combined EtOAc solutions were dried over MgSO_4 and concentrated to dryness at reduced pressure to afford the title compound (0.560 g, 99%) as a foam. ^1H NMR (400 MHz, DMSO- d_6) δ 8.59 (s, 1 H), 8.05 - 8.13 (m, 2 H), 7.69 (s, 1 H), 7.64 (s, 1 H), 7.31 - 7.46 (m, 7 H), 7.27 (t, J = 8.78 Hz, 1 H), 7.19 (dd, J = 12.29, 1.95 Hz, 1 H), 7.08 (d, J = 8.59 Hz, 1 H), 5.16 (s, 2 H), 1.75 - 1.88 (m, 1 H), 0.68 - 0.76 (m, 2 H), 0.52 - 0.59 (m, 2 H). ES-LCMS m/z : 564 (M+1).

(F) 6-(5-(4-(Benzyloxy)-3-fluorophenyl)oxazol-4-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide. A solution of 6-(5-(4-(benzyloxy)-3-fluorophenyl)oxazol-4-yl)-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylic acid (0.555 g, 0.985 mmol) and $\text{MeNH}_2\cdot\text{HCl}$ (0.100 g, 1.48 mmol) in DMF (5 mL) was treated with TBTU (0.348 g, 1.08 mmol) followed by DIEA (0.860 mL, 4.92 mmol). After stirring at RT for 5h, LCMS indicated incomplete reaction. The solution was then treated with HATU (37.4 mg, 0.098 mmol). After 18h, the solution was added dropwise to a solution of 10 mL of saturated aqueous NaHCO_3 in 40 mL of water. This afforded a white suspension. After stirring for 30 min the solid was collected by filtration and dried *in vacuo*. The crude product was purified by flash chromatography (silica gel, 2% DCM/EtOAc) to give the title compound (0.361 g, 64%) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.59 (s, 1 H), 8.48 - 8.55 (m, 1 H), 7.96 (dd, J = 8.88, 5.37 Hz, 2 H), 7.61 (s, 1 H), 7.33 - 7.46 (m, 7 H), 7.24 - 7.30 (m, 2 H), 7.19 (dd, J = 12.49, 1.95 Hz, 1 H), 7.09 (d, J = 8.58 Hz, 1 H), 5.16 (s, 2 H), 2.86 (d, J = 4.49 Hz, 3 H), 1.75 - 1.85 (m, 1 H), 0.65 - 0.74 (m, 2 H), 0.56 - 0.64 (m, 2 H). ES-LCMS m/z : 577 (M+1).

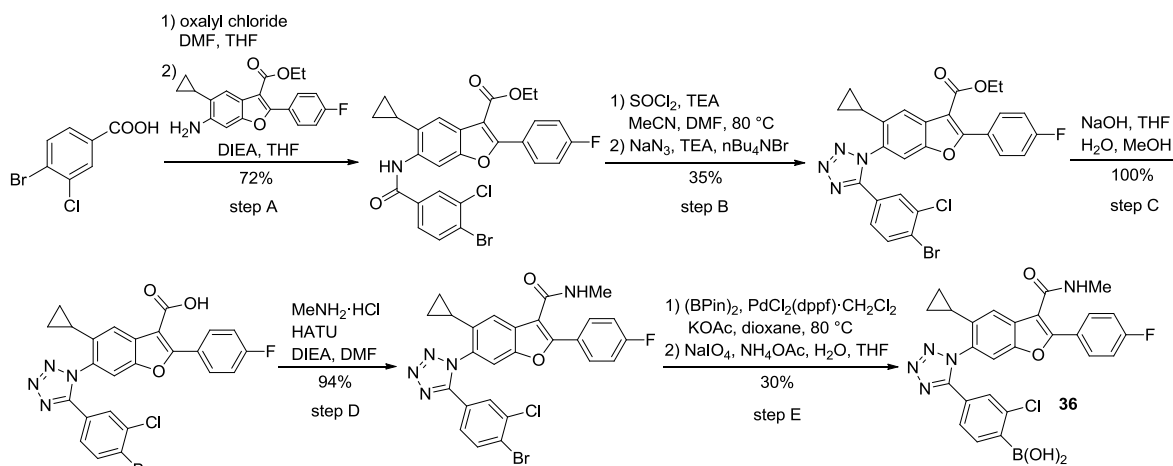
(G) 5-Cyclopropyl-6-(5-(3-fluoro-4-hydroxyphenyl)oxazol-4-yl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide. A suspension of 6-(5-(4-(benzyloxy)-3-fluorophenyl)oxazol-4-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.359 g, 0.623 mmol) in 1:1 THF/EtOH (20 mL) was subjected to hydrogenation (1 atm, balloon) in the presence of 10% Pd/C (66 mg, Degussa type). After 18h, the reaction vessel was purged with nitrogen, catalyst removed by filtration, and the filtrate concentrated at reduced pressure. The residue was subjected to flash chromatography (silica gel, 3-5% THF/DCM) to afford the title compound (0.230 g, 76%) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 10.29 (br s, 1 H), 8.54 (s, 1 H), 8.47 - 8.53 (m, 1 H), 7.97 (dd, J = 8.78, 5.46 Hz, 2 H), 7.60 (s, 1 H), 7.39 (t, J = 8.88 Hz, 2 H), 7.27 (s, 1 H), 7.09 (dd, J = 12.29, 1.95 Hz, 1 H), 7.01 (dd, J = 8.60, 1.80 Hz, 1 H), 6.90 - 6.96 (m, 1 H), 2.87 (d, J = 4.49 Hz, 3 H), 1.73 - 1.88 (m, 1 H), 0.66 - 0.73 (m, 2 H), 0.57 - 0.64 (m, 2 H). ES-LCMS m/z : 487 (M+1).

(H) 4-(4-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)oxazol-5-yl)-2-fluorophenyl trifluoromethanesulfonate. To a solution of 5-cyclopropyl-6-(5-(3-fluoro-4-hydroxyphenyl)oxazol-4-yl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.227 g, 0.467 mmol) in 3:2 DCM/THF was added DIEA (0.407 mL, 2.33 mmol) followed by $\text{PhN}(\text{Tf})_2$ (0.292 g, 0.817 mmol). After stirring at RT for 18h, LCMS indicated the reaction to be 81% complete. The solution was treated with additional portions of DIEA (0.163 mL, 0.933 mmol) and $\text{PhN}(\text{Tf})_2$ (0.167 g, 0.467 mmol). After another 8h, the solution was concentrated to dryness at reduced pressure and the residue redissolved in EtOAc (100 mL). The solution was washed with saturated aqueous NaHCO_3 (1x15 mL), brine (1x15 mL), dried over Na_2SO_4 , and concentrated to dryness. The crude residue was subjected to

flash chromatography (silica gel, 5-20% EtOAc/DCM) to afford the title compound (0.225 g, 78%) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.74 (s, 1 H), 8.46 - 8.54 (m, 1 H), 7.97 (dd, J = 8.88, 5.37 Hz, 2 H), 7.67 - 7.76 (m, 2 H), 7.56 (dd, J = 11.32, 1.76 Hz, 1 H), 7.40 (t, J = 8.88 Hz, 2 H), 7.21 - 7.31 (m, 2 H), 2.86 (d, J = 4.49 Hz, 3 H), 1.71 - 1.83 (m, 1 H), 0.53 - 0.72 (m, 4 H). ES-LCMS m/z : 619 (M+1).

(I) **(4-(4-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)oxazol-5-yl)-2-fluorophenyl)boronic acid (35)**. Compound **35** was prepared from 4-(4-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)oxazol-5-yl)-2-fluorophenyl trifluoromethanesulfonate in 13% yield as described herein for the synthesis of **33**, step F. ^1H NMR (400 MHz, METHANOL- d_4) δ 8.40 (s, 1 H), 7.86 - 7.93 (m, 2 H), 7.52 (s, 1 H), 7.37 (s, 1 H), 7.27 - 7.35 (m, 1 H), 7.14 - 7.25 (m, 3 H), 7.04 (d, J = 9.96 Hz, 1 H), 2.93 (s, 3 H), 1.72 - 1.83 (m, 1 H), 0.54 - 0.71 (m, 4 H). ES-LCMS m/z : 515 (M+1), 100% purity. HRMS m/z calcd for $\text{C}_{28}\text{H}_{21}\text{BF}_2\text{N}_2\text{O}_5$: 515.1590. Found: 515.1592.

(2-Chloro-4-(1-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)-1H-tetrazol-5-yl)phenyl)boronic acid (36).



(A) Ethyl 6-(4-bromo-3-chlorobenzamido)-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylate.

The title compound was prepared from 4-bromo-3-chlorobenzoic acid and ethyl 6-amino-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylate (prepared as described in WO2012067663) in 72% yield as described herein for the synthesis of **32**, step A. ES-LCMS m/z : 556 (M+1).

(B) Ethyl 6-(5-(4-bromo-3-chlorophenyl)-1H-tetrazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylate. To a stirred mixture of ethyl 6-(4-bromo-3-chlorobenzamido)-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylate (0.500 g, 0.898 mmol) in MeCN (4 mL) was added DMF (21 μL , 0.269 mmol) followed by TEA (0.138 mL, 0.988 mmol). After stirring the mixture for 5 min at RT, thionyl chloride (85 μL , 1.17 mmol) was added slowly keeping the temperature below 25 $^{\circ}\text{C}$. The mixture was stirred at RT for 6 h, heated to 80 $^{\circ}\text{C}$ for an additional 4 h, and then cooled to 10 $^{\circ}\text{C}$ in an ice bath. TEA (0.375 mL, 2.69 mmol) was added followed by NaN_3 (0.128 g, 1.98 mmol) and tetrabutylammonium bromide (43.4 mg, 0.135 mmol). The mixture was warmed to RT and stirred overnight. The mixture was diluted with water and extracted with DCM (2x). The combined DCM solutions were washed with brine, dried over Na_2SO_4 , and concentrated at reduced pressure. The residue was subjected to flash chromatography (silica gel, 5-100% DCM/hexanes) to afford the title compound (0.184 g, 35%) as a tan solid. ^1H NMR (400 MHz, CHLOROFORM- d) δ 8.05 - 8.12 (m, 2 H), 7.93 (s, 1 H), 7.90 (d, J = 2.15 Hz, 1 H), 7.59 (d, J = 8.40 Hz, 1 H), 7.54 (s, 1 H), 7.17 - 7.25 (m, 3 H), 4.45 (q, J = 7.23 Hz, 2 H), 1.45 (t, J = 7.13 Hz, 3 H), 1.29 - 1.38 (m, 1 H), 0.52 - 0.76 (m, 4 H). ES-LCMS m/z : 581 (M+1).

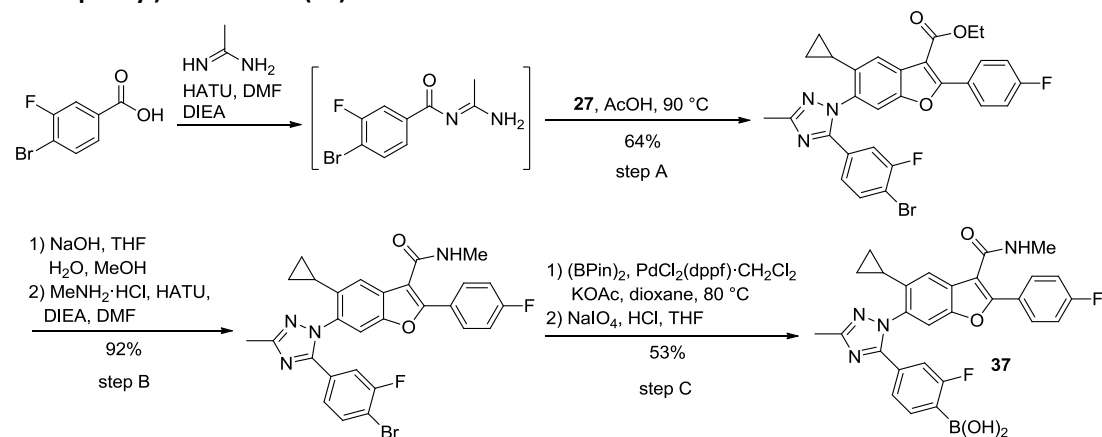
(C) 6-(5-(4-Bromo-3-chlorophenyl)-1H-tetrazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylic acid. The title compound was prepared from ethyl 6-(5-(4-bromo-3-chlorophenyl)-1H-tetrazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylate in 100% yield as described herein for the synthesis of **33**, step D. ^1H NMR (400 MHz, METHANOL- d_4) δ 8.12 - 8.19 (m, 2 H), 7.94 (s, 1 H), 7.88 (s, 1 H), 7.87 (d, J = 2.15 Hz, 1

H), 7.75 (d, $J = 8.40$ Hz, 1 H), 7.32 (dd, $J = 8.50, 2.05$ Hz, 1 H), 7.23 - 7.30 (m, 2 H), 1.27 - 1.36 (m, 1 H), 0.40 - 0.78 (m, 4 H). ES-LCMS m/z : 553 (M+1).

(D) **6-(5-(4-Bromo-3-chlorophenyl)-1H-tetrazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide**. The title compound was prepared from 6-(5-(4-bromo-3-chlorophenyl)-1H-tetrazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylic acid in 94% yield as described herein for the synthesis of **33**, step E. ^1H NMR (400 MHz, METHANOL- d_4) δ 7.93 - 7.99 (m, 2 H), 7.90 (s, 1 H), 7.85 (d, $J=1.95$ Hz, 1 H), 7.74 (d, $J=8.39$ Hz, 1 H), 7.53 (s, 1 H), 7.34 (dd, $J=8.39, 1.95$ Hz, 1 H), 7.24 - 7.32 (m, 2 H), 2.97 (s, 3 H), 1.20 - 1.37 (m, 1 H), 0.47 - 0.77 (m, 4 H). ES-LCMS m/z : 566 (M+1).

(E) **(2-Chloro-4-(1-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)-1H-tetrazol-5-yl)phenyl)boronic acid (36)**. Compound **36** was prepared from 6-(5-(4-bromo-3-chlorophenyl)-1H-tetrazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide in 30% yield as described herein for the synthesis of **31**, step E. ^1H NMR (400 MHz, METHANOL- d_4) δ 7.93 - 8.00 (m, 2 H), 7.90 (s, 1 H), 7.69 (s, 1 H), 7.52 (s, 1 H), 7.35 - 7.45 (m, 2 H), 7.28 (t, $J = 8.78$ Hz, 2 H), 2.97 (s, 3 H), 1.23 - 1.38 (m, 1 H), 0.45 - 0.77 (m, 4 H). ES-LCMS m/z : 532 (M+1), 98% purity. HRMS m/z calcd for $\text{C}_{26}\text{H}_{20}\text{BClF}_5\text{O}_4$: 532.1359. Found: 532.1360.

(4-(1-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)-3-methyl-1H-1,2,4-triazol-5-yl)-2-fluorophenyl)boronic acid (37).



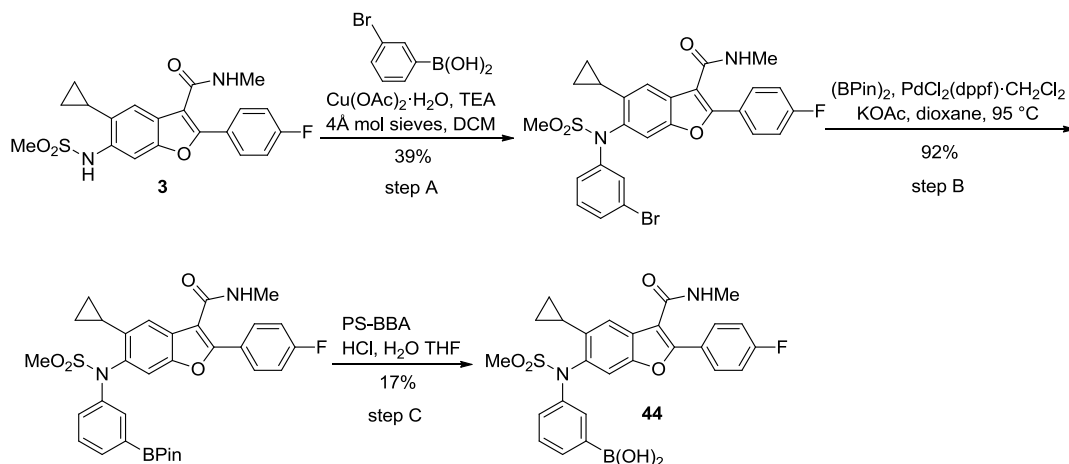
(A) **Ethyl 6-(5-(4-bromo-3-fluorophenyl)-3-methyl-1H-1,2,4-triazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylate**. To a stirred solution of 4-bromo-3-fluorobenzoic acid (0.300 g, 1.37 mmol), acetimidamide (0.194 g, 2.06 mmol), and HATU (0.625 g, 1.64 mmol) in DMF (5 mL) at RT was added DIEA (0.718 mL, 4.11 mmol). After 1.5h, LCMS indicated complete conversion of starting material to (E)-N-(1-aminoethylidene)-4-bromo-3-fluorobenzamide. The solution was then treated with ethyl 5-cyclopropyl-2-(4-fluorophenyl)-6-hydrazinylbenzofuran-3-carboxylate hydrochloride (**27**, 0.400 g, 1.02 mmol, for preparation see example **33**, step B) followed by glacial AcOH (0.80 mL, 14.0 mmol). The solution was heated to 90 °C for 2.5h and cooled to RT. The mixture was diluted with EtOAc, washed with saturated aqueous NaHCO_3 (1x), brine (1x), dried over Na_2SO_4 , and concentrated at reduced pressure. The crude material was purified by flash chromatography (silica gel, 0-40% EtOAc/hexanes) to afford the title compound (0.380 g, 64%) as a yellow foam. ^1H NMR (400 MHz, CHLOROFORM- d) δ 8.05 - 8.11 (m, 2 H), 7.79 (s, 1 H), 7.51 (s, 1 H), 7.46 (dd, $J = 8.19, 7.22$ Hz, 1 H), 7.36 (dd, $J = 9.56, 1.95$ Hz, 1 H), 7.18 - 7.25 (m, 2 H), 7.13 (dd, $J = 8.39, 1.56$ Hz, 1 H), 4.45 (q, $J = 7.22$ Hz, 2 H), 2.56 (s, 3 H), 1.40 - 1.53 (m, 4 H), 0.62 - 0.90 (m, 3 H), 0.42 (br s, 1 H). ES-LCMS m/z : 578 (M+1).

(B) **6-(5-(4-Bromo-3-fluorophenyl)-3-methyl-1H-1,2,4-triazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide**. A solution of ethyl 6-(5-(4-bromo-3-fluorophenyl)-3-methyl-1H-1,2,4-triazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylate (0.380 g, 0.657 mmol) in 4:3:2 THF/MeOH/ H_2O (10 mL) was treated with 1M aqueous NaOH (3.29 mL, 3.29 mmol). The resulting solution was stirred at 60 °C for 2h and then cooled to RT. The solution was acidified to pH 2 by addition of 1M aqueous HCl and extracted with EtOAc (2x). The combined EtOAc extracts were washed with brine (1x), dried over Na_2SO_4 , and concentrated to dryness at reduced pressure to give the carboxylic acid intermediate. This material was dissolved in DMF (3 mL). To the solution was added methylamine hydrochloride (53 mg, 0.79 mmol), HATU (0.375 g, 0.986 mmol) and DIEA (0.344

mL, 1.97 mmol). The solution was stirred at RT for 1 hour at which point LCMS indicated the reaction to be complete. The solution was diluted with H₂O which induced precipitation. After stirring the suspension for 10 min, the solid was collected by filtration, washed with aqueous NaHCO₃ (1x), water (1x), and then air dried overnight to afford the title compound (0.340 g, 92%) as an off-white solid. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 7.90 (dd, *J* = 8.49, 5.37 Hz, 2 H), 7.57 (s, 1 H), 7.41 - 7.51 (m, 2 H), 7.36 (d, *J* = 9.37 Hz, 1 H), 7.23 (t, *J* = 8.49 Hz, 2 H), 7.10 (d, *J* = 7.61 Hz, 1 H), 5.77 - 5.88 (m, 1 H), 3.03 (d, *J* = 4.88 Hz, 3 H), 2.55 (s, 3 H), 1.40 - 1.52 (m, 1 H), 0.59 - 0.87 (m, 3 H), 0.41 (br s, 1 H). ES-LCMS *m/z*: 563 (M+1).

(C) **(4-(1-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)-3-methyl-1H-1,2,4-triazol-5-yl)-2-fluorophenyl)boronic acid (37)**. A solution of 6-(5-(4-bromo-3-fluorophenyl)-3-methyl-1H-1,2,4-triazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.200 g, 0.355 mmol), bis(pinacolato)diboron (0.270 g, 1.07 mmol), KOAc (0.139 g, 1.42 mmol), and PdCl₂(dppf)·CH₂Cl₂ (29 mg, 0.035 mmol) in 1,4-dioxane (4 mL) was sparged with nitrogen and heated to 80 °C. After 4h the reaction mixture was cooled to RT, partitioned between EtOAc and water and the phases separated. The EtOAc solution was washed with brine (1x), dried over Na₂SO₄, and evaporated to dryness. The residue was dissolved in THF (10 mL). The solution was treated with 1M aqueous HCl (7 mL) followed by NaIO₄ (0.759 g, 3.55 mmol). After stirring at RT for 1h LCMS indicated complete reaction. The solution was diluted with water and extracted with EtOAc. The EtOAc solution was washed with brine (1x), dried over Na₂SO₄, and concentrated to dryness at reduced pressure. The residue was subjected to RP-HPLC purification (C18, 5-100% MeCN/H₂O with 0.1% formic acid) to afford **37** (99 mg, 53%) as a white solid. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 7.89 - 7.97 (m, 2 H), 7.74 (s, 1 H), 7.40 (s, 1 H), 7.17 - 7.30 (m, 5 H), 2.95 (s, 3 H), 2.51 (s, 3 H), 1.35 - 1.46 (m, 1 H), 0.59 - 0.88 (m, 3 H), 0.37 (br s, 1 H). ES-LCMS *m/z*: 529 (M+1), 100% purity. HRMS *m/z* calcd for C₂₈H₂₃BF₂N₄O₄: 529.1859. Found: 529.1860.

(3-(N-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)phenyl)boronic acid (44).



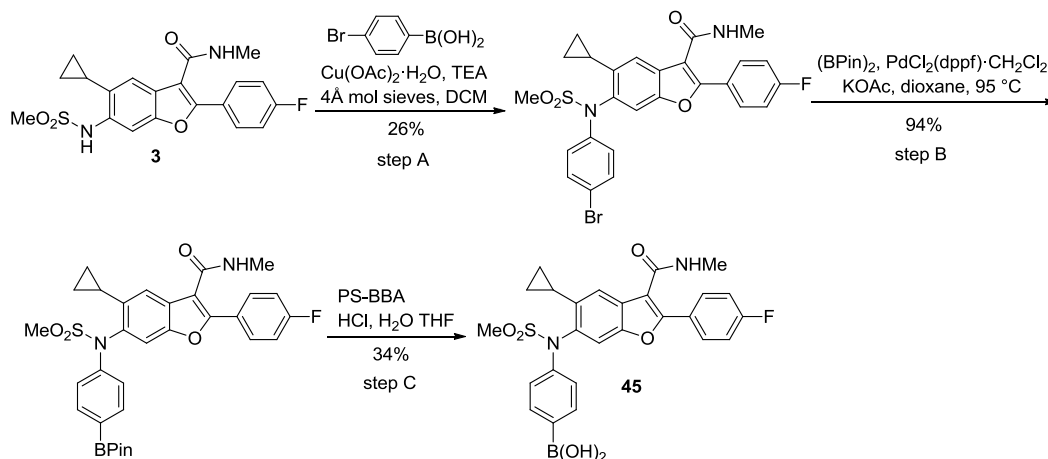
(A) **6-(N-(3-Bromophenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide**. A solution of 5-cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-[(methylsulfonyl)amino]-1-benzofuran-3-carboxamide (**3**, 0.500 g, 1.24 mmol, prepared as described in WO2013028371), 3-bromophenylboronic acid (1.50 g, 7.46 mmol), Cu(OAc)₂·H₂O (0.372 g, 1.87 mmol), TEA (0.252 g, 2.49 mmol), and activated 4 Å molecular sieves (1.0 g) in DCE (160 mL) was stirred at RT for 2 days. The solution was filtered, taken to a residue under reduced pressure, and the residue purified by flash chromatography to afford the title compound (0.270 g, 39%) as a brown solid. ES-LCMS *m/z*: 557 (M+1).

(B) **5-Cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-(N-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methylsulfonamido)benzofuran-3-carboxamide**. A suspension of 6-(N-(3-bromophenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.240 g, 0.430 mmol), KOAc (0.128 g, 1.29 mmol), bis(pinacolato)diboron (0.328 g, 1.29 mmol), and PdCl₂(dppf)·CH₂Cl₂ (35 mg, 0.043 mmol) in 1,4-dioxane (20 mL) was maintained at 95 °C with stirring overnight. The solution was cooled

to room temperature, filtered, taken to a residue under reduced pressure, and the residue purified by flash chromatography to afford the title compound (0.269 g, 92%) as a brown solid. ES-LCMS m/z : 605 (M+1).

(C) **3-(N-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)phenylboronic acid (44)**. Compound **44** was prepared from 5-cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-(N-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methylsulfonamido)benzofuran-3-carboxamide in 17% yield as described herein for the synthesis of **45**, step C. ^1H NMR (METHANOL- d_4) δ 7.99 - 7.95 (m, 2 H), 7.94 (s, 1 H), 7.77 - 7.38 (m, 4 H), 7.32 - 7.25 (m, 3 H), 3.32 (s, 3 H), 2.98 (s, 3 H), 2.29 - 2.25 (m, 1 H), 1.10 - 0.37 (m, 4 H). ES-LCMS m/z : 523 (M+1), 100% purity. HRMS m/z calcd for $\text{C}_{26}\text{H}_{24}\text{BFN}_2\text{O}_6\text{S}$: 523.1510. Found: 523.1512.

(4-(N-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)phenyl)boronic acid (45).



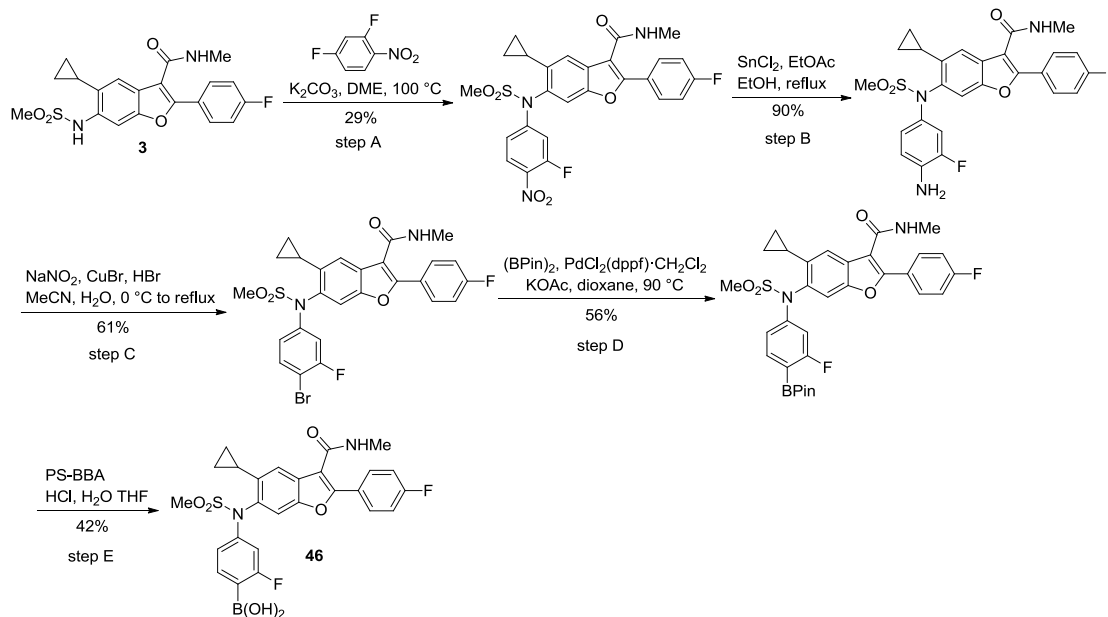
(A) **6-(N-(4-Bromophenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide**. A solution of 5-cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-[(methylsulfonyl)amino]-1-benzofuran-3-carboxamide (**3**, 0.500 g, 1.24 mmol, prepared as described in WO2013028371), 4-bromophenylboronic acid (1.50 g, 7.46 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (0.372 g, 1.87 mmol), TEA (0.252 g, 2.49 mmol), and activated 4 Å molecular sieves (1.0 g) in DCM (160 mL) was stirred at RT for 2 days. The solution was filtered, concentrated under reduced pressure, and the residue purified by flash chromatography to afford the title compound (0.180 g, 26%) as a brown solid. ^1H NMR (METHANOL- d_4) δ 7.89 (d, $J = 8.7$ Hz, 1 H), 7.87 (d, $J = 8.7$ Hz, 1 H), 7.62 (s, 1 H), 7.46 (s, 1 H), 7.43 (d, $J = 8.7$ Hz, 2 H), 7.29 (s, 1 H), 7.21 (d, $J = 8.7$ Hz, 2 H), 7.17 (s, 1 H), 3.23 (s, 3 H), 3.00 (d, $J = 4.8$ Hz, 3 H), 1.26 - 1.25 (m, 3 H), 0.88 - 0.85 (m, 2 H). ES-LCMS m/z : 557 (M+1).

(B) **5-Cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-(N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methylsulfonamido)benzofuran-3-carboxamide**. A suspension of 6-(N-(4-bromophenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.150 g, 0.269 mmol), KOAc (80.0 mg, 0.807 mmol), bis(pinacolato)diboron (0.205 g, 0.807 mmol), and $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$ (22 mg, 0.027 mmol) in 1,4-dioxane (20 mL) was maintained at 95 °C with stirring overnight. The solution was cooled to RT, filtered, taken to a residue under reduced pressure, and the residue purified by flash chromatography to afford the title compound (0.152 g, 94%) as a brown solid. ES-LCMS m/z : 605 (M+1).

(C) **4-(N-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)phenylboronic acid (45)**. A suspension of 5-cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-(N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methylsulfonamido)benzofuran-3-carboxamide (0.152 g, 0.251 mmol), PS-BBA (polymer-supported benzenboronic acid, 0.480 g, 1.26 mmol), and 5N aqueous HCl (0.350 mL, 1.76 mmol) in THF (15 mL) was stirred at room temperature for 48 h. The solution was filtered, taken to a residue under reduced pressure, and the residue purified by RP-HPLC to afford **45** (45 mg, 34%) as a white solid. ^1H NMR (METHANOL- d_4) δ 7.98 (d, $J = 9.0$ Hz, 1 H), 7.96 (d, $J = 9.0$ Hz, 1 H), 7.87 (s, 1 H), 7.66 (d, $J = 8.4$ Hz, 2 H), 7.46

(d, $J = 8.4$ Hz, 2 H), 7.32 - 7.26 (m, 3 H), 3.33 (s, 3 H), 2.99 (s, 3 H), 2.22 - 2.18 (m, 1 H), 1.10 - 0.37 (m, 4 H). ES-LCMS m/z : 523 (M+1), 100% purity. HRMS m/z calcd for $C_{26}H_{24}BFN_2O_6S$: 523.1510. Found: 523.1509.

(4-(N-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)-2-fluorophenyl)boronic acid (46).



(A) **5-Cyclopropyl-6-(N-(3-fluoro-4-nitrophenyl)methylsulfonamido)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide.** A suspension of 2,4-difluoro-1-nitrobenzene (0.261 g, 1.64 mmol) and 5-cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-[(methylsulfonyl)amino]-1-benzofuran-3-carboxamide (**3**, 0.600, 1.49 mmol), prepared as described in WO2013028371) in DME (0.8 mL) and water (0.2 mL) was treated with K_2CO_3 (0.616 g, 4.47 mmol) and maintained at 100 °C for 24 h. The suspension was cooled to RT, concentrated, and the residue purified by flash chromatography to afford the title compound (0.230 g, 29%) as a yellow powder. ES-LCMS m/z : 542 (M+1).

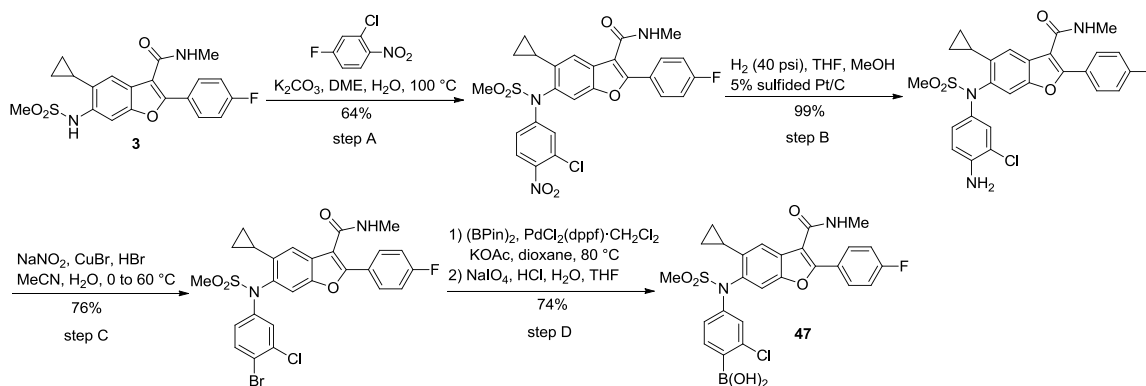
(B) **6-(N-(4-Amino-3-fluorophenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide.** A mixture of 5-cyclopropyl-6-(N-(3-fluoro-4-nitrophenyl)methylsulfonamido)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.230 g, 0.430 mmol) and $SnCl_2$ (0.291 g, 1.29 mmol) in EtOAc (5 mL) and EtOH (5 mL) was maintained at reflux for 3 h. The mixture was cooled to room temperature and partitioned between EtOAc and water. The organic layer was dried over Na_2SO_4 and concentrated to dryness at reduced pressure. The residue was subjected to flash chromatography to afford the title compound (0.200 g, 90%) as a yellow powder. ES-LCMS m/z : 512 (M+1).

(C) **6-(N-(4-Bromo-3-fluorophenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide.** A suspension of 6-(N-(4-amino-3-fluorophenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.200 g, 0.390 mmol) in MeCN (5 mL) and 48% aqueous HBr (5 mL) was treated with an aqueous solution of $NaNO_2$ (29.6 mg, 0.430 mmol) and maintained at 0 °C with stirring for 30 min. $CuBr$ (64.3 mg, 0.450 mmol) was then added and the reaction mixture was heated to reflux for 2 h. The solution was cooled to RT and partitioned between ethyl acetate and water. The organic layer was dried over Na_2SO_4 , and concentrated to dryness at reduced pressure. The residue was purified by flash chromatography to afford the title compound (0.140 g, 61%) as a white solid. ES-LCMS m/z : 577 (M+1).

(D) **5-Cyclopropyl-6-(N-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methylsulfonamido)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide.** The title compound was prepared from 6-(N-(4-bromo-3-fluorophenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide in 56% yield as described herein for the synthesis of **45**, step B. ES-LCMS m/z : 623 (M+1).

(E) **4-(N-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)-2-fluorophenylboronic acid (46)**. Compound **46** was prepared from 5-cyclopropyl-6-(N-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methylsulfonamido)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide in 42% yield as described herein for the synthesis of **45**, step C. ¹H NMR (300 MHz, METHANOL-*d*₄) δ 7.96 (dd, *J* = 8.9, 5.3 Hz, 2 H), 7.83 (s, 1H), 7.45 - 7.15 (m, 6 H), 3.43 (s, 3 H), 2.96 (s, 3 H), 2.12 (m, 1 H), 1.01 - 0.52 (m, 4 H). ES-LCMS *m/z*: 541 (M+1), 100% purity. HRMS *m/z* calcd for C₂₆H₂₃BF₂N₂O₆S: 541.1416. Found: 541.1416.

(2-Chloro-4-(N-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)phenyl)boronic acid (47).



(A) **6-(N-(3-Chloro-4-nitrophenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide**. A mixture of 5-cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-(methylsulfonamido)benzofuran-3-carboxamide (**3**, 12.5 g, 31.1 mmol, prepared as described in WO2013028371), 2-chloro-4-fluoronitrobenzene (10.9 g, 62.1 mmol) and K₂CO₃ (12.9 g, 93.0 mmol) in 4:1 DME/water (130 mL) in a sealed flask was heated to 100 °C with stirring. An identical 12.5 g scale reaction was set up in a second sealed vessel. The reaction vessels were maintained at 100 °C for 70 h, cooled to RT, and stirred for an additional 18 h. The combined reaction mixtures were partitioned between EtOAc (300 mL) and water (600 mL), and the phases separated. The aqueous solution was extracted with two additional 150 mL portions of EtOAc. The combined EtOAc solutions were washed with half saturated brine (1x), saturated brine (1x), dried over Na₂SO₄ and concentrated to dryness at reduced pressure. The resulting yellow-brown solid was recrystallized from EtOAc/ether to give the title compound (22.3 g, 64%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.47 - 8.54 (m, 1 H), 8.08 - 8.14 (m, 1 H), 8.04 - 8.08 (m, 1 H), 7.97 (dd, *J* = 8.6, 5.5 Hz, 2 H), 7.47 - 7.52 (m, 1 H), 7.30 - 7.44 (m, 3 H), 7.24 - 7.29 (m, 1 H), 3.59 (s, 3 H), 2.84 (d, *J* = 4.4 Hz, 3 H), 1.91 - 2.02 (m, 1 H), 0.67 - 1.02 (m, 3 H), 0.41 - 0.54 (m, 1 H). ES-LCMS *m/z*: 558 (M+1).

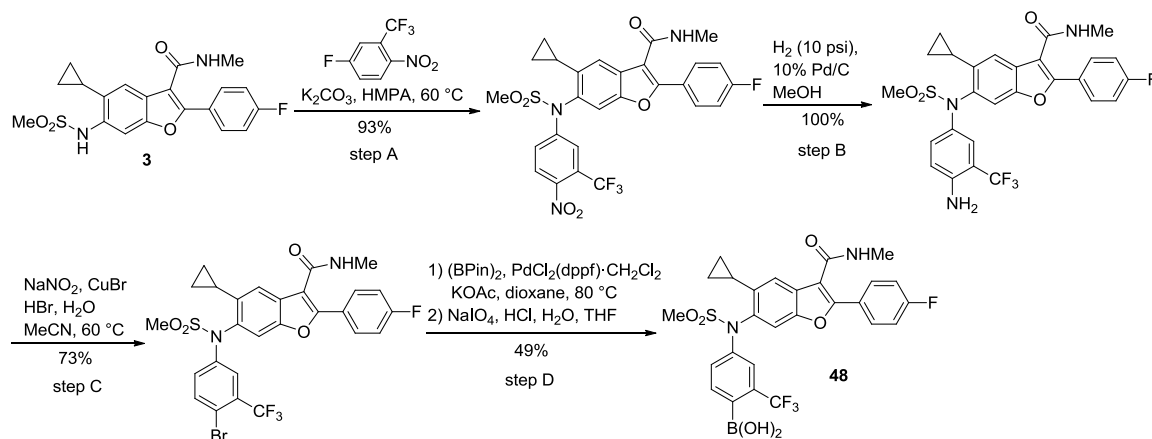
(B) **6-(N-(4-Amino-3-chlorophenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide**. A solution of 6-(N-(3-chloro-4-nitrophenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (11.0 g, 19.7 mmol) in 1:1 THF/MeOH (75 mL) was subjected to hydrogenation at 40 psi in the presence of 5% sulfided Pt/C (0.560 g). After 4h an additional portion of catalyst was added (0.250 g). After another 16h the reaction vessel was purged with nitrogen, catalyst removed by filtration through Celite[®], and the filtrate concentrated to dryness at reduced pressure. The residue was recrystallized from hexane/EtOAc to afford the title compound (10.3 g, 99%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.43 (q, *J* = 4.4 Hz, 1 H), 8.15 (s, 1 H), 7.96 (dd, *J* = 9.0, 5.5 Hz, 2 H), 7.49 (d, *J* = 2.5 Hz, 1 H), 7.29 - 7.43 (m, 3 H), 7.11 (s, 1 H), 6.76 (d, *J* = 8.7 Hz, 1 H), 5.55 (s, 2 H), 3.33 (s, 3 H), 2.81 (d, *J* = 4.6 Hz, 3 H), 2.26 - 2.36 (m, 1 H), 0.76 - 1.09 (m, 3 H), 0.45 (br s, 1 H). ES-LCMS *m/z*: 528 (M+1).

(C) **6-(N-(4-Bromo-3-chlorophenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide**. To a 1 L 3-necked flask equipped with a mechanical stirrer was added 6-(N-(4-amino-3-chlorophenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (10.0 g, 18.9 mmol) followed by MeCN (200 mL) and then 48% aqueous HBr (200 mL). A thick, lumpy suspension resulted which was stirred vigorously for 30 min to afford a more uniform suspension. The reaction vessel was cooled in an ice water bath for 30 min and the mixture treated with a solution of NaNO₂ (1.96 g, 28.4 mmol) in

water (20 mL) via addition funnel over 5 min. The resulting yellow suspension was stirred in the ice bath for 1.5h and then treated with CuBr (4.1 g, 28.4 mmol) in small portions over 5 min. This afforded a dark brown solution that was warmed to 60 °C (internal temperature) with continued stirring. After 40 min at elevated temperature the mixture was cooled to RT and poured into a rapidly stirred mixture of 5% aqueous sodium bisulfite (600 mL) and EtOAc (800 mL). The phases were separated and the aqueous solution extracted with two additional 150 mL portions of EtOAc. The combined EtOAc solutions were washed with 5% aqueous sodium bisulfite (2x150 mL), saturated aqueous NaHCO₃ (2x300 mL), saturated brine (1x200 mL), dried over Na₂SO₄ and concentrated to dryness at reduced pressure to give a yellow foam. This material was subjected to flash chromatography (silica gel, 10-100% EtOAc/hexanes). During concentration of the pure fractions a white solid crystallized out. After concentrating down to a thick suspension the mixture was diluted with 150 mL of hexane and the mixture stirred at RT overnight. The solid was collected by filtration in a medium fritted funnel and dried *in vacuo* to afford the title compound (8.55 g, 76%) as a white crystalline solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.44 - 8.51 (m, 1 H), 8.12 (s, 1 H), 7.93 - 8.00 (m, 2 H), 7.76 (d, *J* = 8.8 Hz, 1 H), 7.63 (d, *J* = 2.6 Hz, 1 H), 7.40 (t, *J* = 8.9 Hz, 2 H), 7.29 (dd, *J* = 8.8, 2.7 Hz, 1 H), 7.20 (s, 1 H), 3.44 (s, 3 H), 2.83 (d, *J* = 4.6 Hz, 3 H), 2.02 - 2.14 (m, 1 H), 0.70 - 1.05 (m, 3 H), 0.43 (br s, 1 H). ES-LCMS *m/z*: 591 (M+1).

(D) **(2-Chloro-4-(N-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)phenyl)boronic acid (47)**. To a 350 mL screw capped flask equipped with a magnetic stirrer was added 6-(N-(4-bromo-3-chlorophenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (8.54 g, 14.4 mmol), bis(pinacolato)diboron (18.3 g, 72.1 mmol), KOAc (7.08 g, 72.1 mmol), PdCl₂(dppf)·CH₂Cl₂ (0.589 g, 0.721 mmol) and anhydrous 1,4-dioxane (150 mL). The mixture was sparged with nitrogen for 10 min. The vessel was sealed and heated in an 80 °C oil bath with stirring. After 4h the mixture was cooled to RT and diluted with EtOAc (400 mL). The resulting black solution was washed with water (2x), saturated brine (1x), and dried over Na₂SO₄. While stirring with Na₂SO₄, Celite[®] was added to facilitate removal of the insoluble black material that remained suspended in solution. The mixture was filtered through a medium frit to afford a golden-brown filtrate that was concentrated to dryness at reduced pressure. The residue was dissolved in 300 mL of THF and the solution cooled in an ice water bath. The solution was treated with 1N aqueous HCl (120 mL) followed by NaIO₄ (46.3 g, 216 mmol). The mixture was stirred at 0 °C for 10 min and then allowed to warm to RT. After 18h the mixture was partitioned between water and EtOAc and the phases separated. The aqueous solution was extracted with EtOAc (2x). The combined EtOAc solutions were washed with 5% aqueous sodium bisulfite (4x), saturated brine (2x), dried over Na₂SO₄ and concentrated to dryness at reduced pressure. The residue was subjected to flash chromatography (silica gel, 2-part gradient: DCM to EtOAc over 15 min, then 0-6.5% MeOH/DCM over 4 min, followed by 6.5% MeOH/DCM isocratic for 15 min) to give a light tan foam (7.28 g). This material was dissolved in MeCN (75 mL) and the solution stirred with rapid dropwise addition of 0.25 N aqueous HCl (175 mL) over a 20 minute period. A white suspension was produced which was stirred at RT. After 2h the solid was collected by filtration in a medium fritted funnel. The filter cake was washed with water (2x), suction air dried for 30 min, and then dried *in vacuo* overnight to afford **47** (5.90 g, 74%) as a white solid. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 7.90 - 7.97 (m, 2 H), 7.85 (s, 1 H), 7.29 - 7.41 (m, 4 H), 7.26 (t, *J* = 8.8 Hz, 2 H), 3.34 (s, 3 H), 2.95 (s, 3 H), 2.07 - 2.17 (m, 1 H), 0.69 - 1.08 (m, 3 H), 0.49 (br s, 1 H). ES-LCMS *m/z*: 557 (M+1), 100% purity. HRMS *m/z* calcd for C₂₆H₂₃BClFN₂O₆S: 557.1121. Found: 557.1121.

(4-(N-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)-2-(trifluoromethyl)phenyl)boronic acid (48).



(A) 5-Cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-(N-(4-nitro-3-(trifluoromethyl)phenyl)methylsulfonamido)benzofuran-3-carboxamide. A solution of 5-cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-(methylsulfonamido)benzofuran-3-carboxamide (**3**, 1.00 g, 2.49 mmol, prepared as described in WO2013028371), 4-fluoro-1-nitro-2-(trifluoromethyl)benzene (1.04 g, 4.97 mmol), K_2CO_3 (1.03 g, 7.45 mmol) in HMPA (6.2 mL) was stirred at 60 °C for 15 h. The reaction mixture was diluted with EtOAc and water. The organic layer was washed with brine, dried (Na_2SO_4), filtered, evaporated and purified by flash chromatography (silica gel, 0-50% EtOAc/hexanes) to afford the title compound (1.37 g, 93%) as an orange solid. 1H NMR (400 MHz, $CHLOROFORM-d$) δ 7.85 - 7.97 (m, 3 H), 7.69 (d, $J = 2.34$ Hz, 1 H), 7.53 - 7.62 (m, 3 H), 7.23 (t, $J = 8.59$ Hz, 2 H), 5.74 - 5.85 (m, 1 H), 3.35 (s, 3 H), 3.02 (d, $J = 4.88$ Hz, 3 H), 1.85 - 1.98 (m, 1 H), 0.73 - 1.13 (m, 3 H), 0.58 (br s, 1 H). ES-LCMS m/z : 592 (M+1).

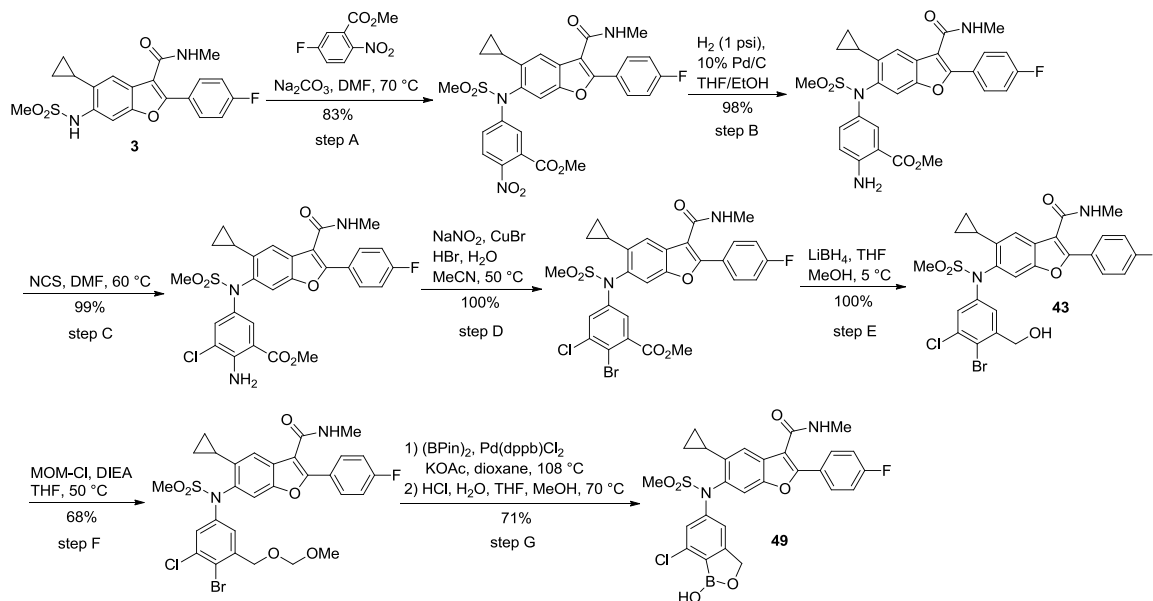
(B) 6-(N-(4-Amino-3-(trifluoromethyl)phenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide. A solution of 5-cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-(N-(4-nitro-3-(trifluoromethyl)phenyl)methylsulfonamido)benzofuran-3-carboxamide (1.37 g, 2.31 mmol) and 10% Pd/C (catalytic) in MeOH (23 mL) was stirred under a hydrogen atmosphere (10 psi) for 1 h. The reaction mixture was filtered through celite, evaporated, and purified by flash chromatography (silica gel, 0-50% EtOAc/hexanes) to afford the title compound (1.30 g, 100%) as a white solid. 1H NMR (400 MHz, $CHLOROFORM-d$) δ 7.86 - 7.93 (m, 2 H), 7.71 (s, 1 H), 7.57 (d, $J = 2.34$ Hz, 1 H), 7.51 (dd, $J = 8.78, 2.34$ Hz, 1 H), 7.44 (s, 1 H), 7.20 (t, $J = 8.59$ Hz, 2 H), 6.72 (d, $J = 8.78$ Hz, 1 H), 5.74 - 5.85 (m, 1 H), 4.26 (br s, 2 H), 3.19 (s, 3 H), 3.00 (d, $J = 4.88$ Hz, 3 H), 2.16 - 2.27 (m, 1 H), 0.45 - 1.14 (m, 4 H). ES-LCMS m/z : 562 (M+1).

(C) 6-(N-(4-Bromo-3-(trifluoromethyl)phenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide. Sodium nitrite (0.18 g, 2.55 mmol) was added to a 0 °C solution of 6-(N-(4-amino-3-(trifluoromethyl)phenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (1.3 g, 2.32 mmol) in MeCN (14 mL) and aqueous HBr (48%) (14 mL). The reaction mixture was stirred for 30 min at 0 °C and copper (I) bromide (0.40 g, 2.78 mmol) was added. The reaction mixture was stirred at 60 °C for 1 h and diluted with EtOAc and water. The organic layer was washed with brine, dried (Na_2SO_4), filtered, evaporated and purified by flash chromatography (silica gel, 0-50% EtOAc/hexanes) to afford the title compound (1.06 g, 73%) as a white foam. 1H NMR (400 MHz, $CHLOROFORM-d$) δ 7.89 (dd, $J = 8.60, 5.28$ Hz, 2 H), 7.61 - 7.69 (m, 3 H), 7.50 (s, 1 H), 7.43 (dd, $J = 8.70, 2.64$ Hz, 1 H), 7.21 (t, $J = 8.60$ Hz, 2 H), 5.72 - 5.81 (m, 1 H), 3.26 (s, 3 H), 3.00 (d, $J = 4.89$ Hz, 3 H), 1.96 - 2.06 (m, 1 H), 0.69 - 1.12 (m, 3 H), 0.53 (br s, 1 H). ES-LCMS m/z : 625 (M+1).

(D) (4-(N-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)-2-(trifluoromethyl)phenyl)boronic acid (48). A solution of 6-(N-(4-bromo-3-(trifluoromethyl)phenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.20 g, 0.32 mmol), KOAc (0.13 g, 1.28 mmol), $PdCl_2(dppf) \cdot CH_2Cl_2$ adduct (0.026 g, 0.032 mmol), bis(pinacolato)diboron (0.24 g, 0.96 mmol) in 1,4-dioxane (4 mL) was degassed, purged with nitrogen and heated at 80 °C for 4 h. The reaction mixture was diluted with EtOAc and water, filtered through celite, and evaporated. The

brown residue was dissolved in 10 mL THF, and 5 mL 1M HCl. NaIO₄ (0.64 g, 3.20 mmol) was added and the suspension was stirred for 3h and diluted with EtOAc and water. The organic layer was washed with water, brine, dried (Na₂SO₄), filtered, evaporated and purified by reverse phase chromatography (C18, 5-100% MeCN/H₂O with 0.1% formic acid) to afford **48** (92 mg, 49%) as a white solid. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 7.86 - 7.96 (m, 3 H), 7.61 - 7.70 (m, 2 H), 7.47 (d, *J* = 8.00 Hz, 1 H), 7.32 (s, 1 H), 7.25 (t, *J* = 8.78 Hz, 2 H), 3.35 (s, 3 H), 2.94 (s, 3 H), 2.06 - 2.18 (m, 1 H), 0.65 - 1.13 (m, 3 H), 0.41 (br s, 1 H). ES-LCMS *m/z*: 591 (M+1), 100% purity. HRMS *m/z* calcd for C₂₇H₂₃BF₄N₂O₆S: 591.1384. Found: 591.1382.

6-(N-(7-Chloro-1-hydroxy-1,3-dihydrobenzo[*c*][1,2]oxaborol-5-yl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (49).



(A) **Methyl 5-(N-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)-2-nitrobenzoate (40)**. A mixture of 5-cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-(methylsulfonamido)benzofuran-3-carboxamide (**3**⁷, 55.0 g, 123 mmol), methyl 5-fluoro-2-nitrobenzoate (36.7 g, 184 mmol) and Na₂CO₃ (39.1 g, 369 mmol) in DMF (400 mL) was heated to 70 °C with vigorous stirring. After 72h LCMS indicated nearly complete reaction. The mixture was cooled to RT, diluted with EtOAc (300 mL), and filtered through a bed of Celite® to remove solids. The filter cake was washed with EtOAc until the filtrate ran colorless which gave a total filtrate volume of 1.2 L. The filtrate was transferred to a separatory funnel, partitioned with 1.4 L of 5% aqueous NaCl, and the phases separated. The aqueous solution was extracted with two additional 300 mL portions of EtOAc. The combined EtOAc solutions were washed with 5% aqueous NaCl (2x), saturated aqueous NaCl (1x), dried over Na₂SO₄ and concentrated to approximately 200 mL by rotary evaporation. At this point a solid began to crystallize. The suspension was diluted with 200 mL of DCM and the suspension stirred overnight. The suspension was then cooled in an ice water bath for 2h and the solid collected by vacuum filtration. The filter cake was washed twice with cold 1:1 EtOAc/DCM, suction air dried for 30 min and then dried *in vacuo* overnight to afford the title compound (59.6 g, 83%) as a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.52 (q, *J* = 4.42 Hz, 1 H), 8.13 (d, *J* = 9.07 Hz, 1 H), 8.08 (s, 1 H), 7.93 - 8.01 (m, 2 H), 7.57 (d, *J* = 2.63 Hz, 1 H), 7.53 (dd, *J* = 9.07, 2.73 Hz, 1 H), 7.38 - 7.46 (m, 2 H), 7.29 (s, 1 H), 3.83 (s, 3 H), 3.60 (s, 3 H), 2.85 (d, *J* = 4.59 Hz, 3 H), 1.87 - 2.04 (m, 1 H), 0.87 (m, 2 H), 0.73 (m, 1 H), 0.46 (m, 1 H). ES-LCMS *m/z*: 582 (M+1).

(B) **Methyl 2-amino-5-(N-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)benzoate (41)**. A stirred suspension of methyl 5-(N-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)-2-nitrobenzoate (**40**, 59.5 g, 102 mmol) and 10% Pd/C (6.00 g) in 2:1 THF/EtOH (1.2 L) was saturated with hydrogen by bubbling hydrogen gas through for 10 min and then subjected to hydrogenation (1 atm) at RT. After 24h the mixture was purged with nitrogen, catalyst removed

by filtration through Celite[®], and the filtrate concentrated to dryness at reduced pressure to give the title compound (55.2 g, 98%) as a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.46 (q, *J* = 4.42 Hz, 1 H), 8.16 (s, 1 H), 7.91 - 8.00 (m, 3 H), 7.61 (dd, *J* = 8.98, 2.73 Hz, 1 H), 7.41 (t, *J* = 8.88 Hz, 2 H), 7.15 (s, 1 H), 6.76 - 6.86 (m, 3 H), 3.79 (s, 3 H), 3.28 (s, 3 H), 2.83 (d, *J* = 4.68 Hz, 3 H), 2.25 - 2.38 (m, 1 H), 0.82 - 1.10 (m, 3 H), 0.42 (m, 1 H). ES-LCMS *m/z*: 552 (M+1).

(C) **Methyl 2-amino-3-chloro-5-(N-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)benzoate**. A suspension of methyl 2-amino-5-(N-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)benzoate (**41**, 55.0 g, 100 mmol) in DMF (320 mL) was heated to 60 °C. The resulting yellow solution was treated with NCS (14.0 g, 105 mmol) in one portion. The solution quickly darkened. After 5 min LCMS indicated complete conversion of the starting material to the desired chloro compound. The solution was cooled to RT and diluted with EtOAc (1 L). The resulting solution was washed with 5% aqueous NaCl (1x1L), 5% aqueous sodium bisulfite (2x200 mL), saturated aqueous NaHCO₃ (3x200 mL), and saturated aqueous NaCl (1x200mL). The solution was dried over Na₂SO₄ and concentrated to dryness at reduced pressure to afford the title compound (58.0 g, 99%) as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.46 (q, *J* = 4.42 Hz, 1 H), 8.25 (s, 1 H), 7.94 - 8.04 (m, 3 H), 7.90 (d, *J* = 2.63 Hz, 1 H), 7.34 - 7.46 (m, 2 H), 7.18 (s, 1 H), 6.93 (br s, 2 H), 3.83 (s, 3 H), 3.33 (s, 3 H), 2.84 (d, *J* = 4.59 Hz, 3 H), 2.26 - 2.36 (m, 1 H), 0.84 - 1.11 (m, 3 H), 0.40 (br s, 1 H). ES-LCMS *m/z*: 586 (M+1).

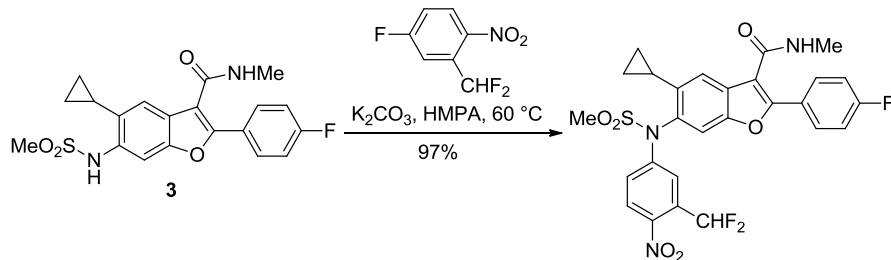
(D) **Methyl 2-bromo-3-chloro-5-(N-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)benzoate**. To a 1 L 3-necked flask equipped with a magnetic stirrer was added methyl 2-amino-3-chloro-5-(N-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)benzoate (58.0 g, 99.0 mmol) followed by MeCN (500 mL) and 48% aqueous HBr (500 mL). The dark brown solution was cooled to 0 °C in an ice water/brine bath and treated with a solution of NaNO₂ (8.20 g, 119 mmol) in water (50 mL) over a 5 min period. After 30 min LCMS indicated complete consumption of the starting material. The solution was then treated with CuBr (18.5 g, 129 mmol) over 2 min and warmed to 50 °C. After 30 min at 50 °C LCMS indicated complete conversion to the desired bromo compound. The solution was cooled to RT and partitioned between EtOAc (1 L) and water (1.5 L). The phases were separated and the aqueous solution extracted with EtOAc (2x200 mL). The combined EtOAc solutions were washed with 5% aqueous NaCl (1x1L), 5% aqueous sodium bisulfite (2x300 mL), saturated aqueous NaHCO₃ (2x300 mL), saturated aqueous NaCl (1x300 mL), and dried over Na₂SO₄. The drying agent was removed by filtration through a pad of silica gel and the filtrate concentrated to dryness at reduced pressure to afford the title compound (64.3 g, quantitative) as a reddish-brown foam. The crude product was carried forward without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.50 (q, *J* = 4.29 Hz, 1 H), 8.16 (s, 1 H), 7.92 - 8.03 (m, 2 H), 7.79 (d, *J* = 2.73 Hz, 1 H), 7.65 (d, *J* = 2.73 Hz, 1 H), 7.41 (t, *J* = 8.93 Hz, 2 H), 7.24 (s, 1 H), 3.81 - 3.89 (m, 3 H), 3.45 - 3.53 (m, 3 H), 2.85 (d, *J* = 4.59 Hz, 3 H), 2.04 - 2.16 (m, 1 H), 0.71 - 1.07 (m, 3 H), 0.40 (br s, 1 H). ES-LCMS *m/z*: 649 (M+1).

(E) **6-(N-(4-Bromo-3-chloro-5-(hydroxymethyl)phenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (43)**. A solution of methyl 2-bromo-3-chloro-5-(N-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)benzoate (54.3 g, 84.0 mmol) in anhydrous THF (351 mL) and anhydrous MeOH (39 mL) was cooled in an ice water/brine bath to -5 °C (internal temperature). To the stirred solution was added 2M LiBH₄/THF (125 mL, 250 mmol) via addition funnel at a rate so as to maintain the temperature below 5 °C. The addition required 35 min. The brine bath was then replaced with an ice water bath and stirring of the solution continued. After another 1.5h LCMS indicated complete reaction. The solution was diluted with saturated aqueous NaHCO₃ (200 mL) followed by water (400 mL) and then EtOAc (600 mL). The mixture was stirred vigorously for 30 min and then transferred to a separatory funnel. After the phases separated, solid remained in the aqueous phase so an additional 200 mL portion of water was added and the mixture shaken, and the phases again separated. The aqueous solution was extracted with EtOAc (2x200 mL). The combined EtOAc solutions were washed with 5% aqueous NaCl (1x), saturated aqueous NaCl (1x), dried over Na₂SO₄ and concentrated to dryness at reduced pressure to afford the title compound (54.5 g, quantitative) as an orange-brown foam. The crude material was carried forward to the next step without purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.45 - 8.54 (m, 1 H), 8.12 (s, 1 H), 7.98 (dd, *J* = 8.93, 5.41 Hz, 2 H), 7.59 (d, *J* = 2.73 Hz, 1 H), 7.54 (d, *J* = 2.63 Hz, 1 H), 7.41 (t, *J* = 8.88 Hz, 2 H), 7.22 (s, 1 H), 5.64 (t, *J* = 5.56 Hz, 1 H), 4.48 (d, *J* = 5.56 Hz, 2 H), 3.45 (s, 3 H), 2.84 (d, *J* = 4.59 Hz, 3 H), 2.06 - 2.17 (m, 1 H), 0.75 - 1.06 (m, 3 H), 0.47 (br s, 1 H). ES-LCMS *m/z*: 623 (M+1).

(F) **6-(N-(4-Bromo-3-chloro-5-((methoxymethoxy)methyl)phenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide**. A solution of 6-(N-(4-bromo-3-chloro-5-(hydroxymethyl)phenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (**43**, 50.0 g, 80.0 mmol) in THF (500 mL) was treated with DIEA (42.1 mL, 241 mmol) followed by MOM-Cl (15.3 mL, 201 mmol). The resulting solution was heated to 50 °C with stirring. After 18h LCMS indicated complete reaction. The solution was cooled to RT and diluted with EtOAc (600 mL) followed by water (600 mL). After stirring vigorously for 10 min the mixture was transferred to a separatory funnel and the phases separated. The aqueous phase was extracted with EtOAc (1x200 mL). The combined EtOAc solutions were washed with an aqueous solution of 5% citric acid and 5% NaCl (3x300 mL), saturated aqueous NaHCO₃ (2x300 mL), saturated brine (1x300 mL), and dried over Na₂SO₄. The drying agent was removed by filtration and the filtrate concentrated to dryness at reduced pressure to give an orange-brown foam. This material was dissolved in EtOAc (250 mL) and the solution heated to reflux with stirring. To the solution was added hexane (375 mL) over a 5 min period maintaining reflux temperature. The solution was then allowed to cool to RT with stirring during which time a light tan solid crystallized. After 2h the solution was cooled in an ice water bath and stirred for an additional 2h. The solid was collected by filtration in a medium fritted funnel. The filter cake was washed with cold 3:2 hexane/EtOAc (250 mL), dried by suction filtration for 30 min, and then dried *in vacuo* to afford the title compound (36.4 g, 68% over 3 steps) as a light tan solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.49 (q, *J* = 4.30 Hz, 1 H), 8.14 (s, 1 H), 7.93 - 8.00 (m, 2 H), 7.62 (d, *J* = 2.74 Hz, 1 H), 7.52 (d, *J* = 2.74 Hz, 1 H), 7.40 (t, *J* = 8.94 Hz, 2 H), 7.21 (s, 1 H), 4.68 (s, 2 H), 4.57 (s, 2 H), 3.44 (s, 3 H), 3.24 (s, 3 H), 2.83 (d, *J* = 4.59 Hz, 3 H), 2.06 - 2.19 (m, 1 H), 0.74 - 1.05 (m, 3 H), 0.44 (br s, 1 H). ES-LCMS *m/z*: 665 (M+1).

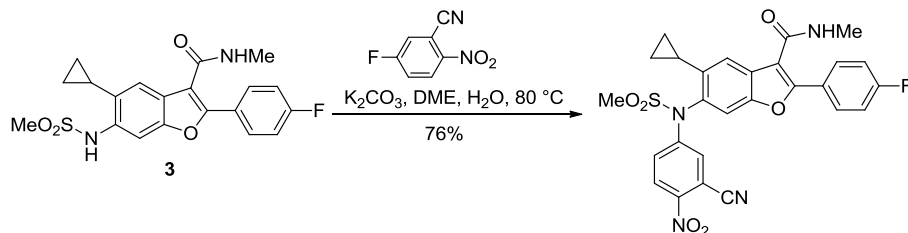
(G) **6-(N-(7-Chloro-1-hydroxy-1,3-dihydrobenzo[*c*][1,2]oxaborol-5-yl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (49)**. A mixture of 6-(N-(4-bromo-3-chloro-5-((methoxymethoxy)methyl)phenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (46.4 g, 69.7 mmol), bis(pinacolato)diboron (44.2 g, 174 mmol), KOAc (27.4 g, 279 mmol), and Pd(dppb)Cl₂ (2.10 g, 3.48 mmol) in 1,4-dioxane (350 mL) was sparged with nitrogen for 15 min and then heated to 108 °C under nitrogen. After 22h LCMS showed complete conversion of starting material to an 84:16 mixture of desired product / protio by-product (replacement of bromine by hydrogen). The mixture was cooled to RT, combined with the crude reaction mixture from a 1 g scale pilot reaction and diluted with 500 mL of EtOAc. The mixture was filtered through a pad of silica gel to remove solids and the filtrate was concentrated at reduced pressure to give a light tan solid. This material was dissolved in THF (437 mL) and the solution diluted with MeOH (87 mL) followed by 1 M aqueous HCl (440 mL). A tan solid rapidly precipitated. The mixture was heated to 70 °C. The solid slowly dissolved affording a yellow solution. After 18h LCMS indicated complete reaction. The solution was cooled to approximately 40 °C and poured into a rapidly stirred mixture of water (1 L) and MTBE (1 L). To the mixture was added 1 M aqueous NaOH (440 mL). The pH was then adjusted to approximately 12 by addition of 3 M aqueous NaOH. The mixture was transferred to a separatory funnel and the phases separated. The aqueous phase was washed with MTBE (3x250 mL) and then treated with concentrated HCl to a pH of approximately 2. The resulting cloudy solution was extracted with EtOAc (4x500 mL). The combined EtOAc extracts were washed with 5% aqueous NaCl (1x), saturated aqueous NaCl (1x), and dried over Na₂SO₄. The drying agent was removed by filtration through a pad of Celite®. The light yellow filtrate was concentrated to dryness at reduced pressure to give a tan foam (39.0 g). This material was dissolved in MeCN (400 mL). The solution was stirred with slow addition of 0.1 M aqueous HCl (800 mL) *via* addition funnel over a 40 min period. Early in the addition the solution was seeded with a small amount of previously prepared, crystalline **49** which induced vigorous crystallization. The suspension was stirred overnight at RT. The solid was collected by vacuum filtration rinsing with 2:1 MeCN/water. The material was suction air dried for 1h and then dried to constant weight *in vacuo* to afford **49** (28.8 g, 71%) as an off-white powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.18 (s, 1 H), 8.50 (q, *J* = 4.42 Hz, 1 H), 8.09 (s, 1 H), 7.93 - 8.02 (m, 2 H), 7.37 - 7.46 (m, 3 H), 7.28 (d, *J* = 1.56 Hz, 1 H), 7.22 (s, 1 H), 4.97 (s, 2 H), 3.48 (s, 3 H), 2.85 (d, *J* = 4.59 Hz, 3 H), 2.02 - 2.14 (m, 1 H), 0.92 - 1.04 (m, 1 H), 0.82 (br s, 2 H), 0.49 (br s, 1 H). ES-LCMS *m/z*: 569 (M+1), 100% purity. HRMS *m/z* calcd for C₂₇H₂₃BClFN₂O₆S: 569.1121. Found: 569.1121.

S_NAr Reaction of compound **3 with 2-(difluoromethyl)-4-fluoro-1-nitrobenzene**



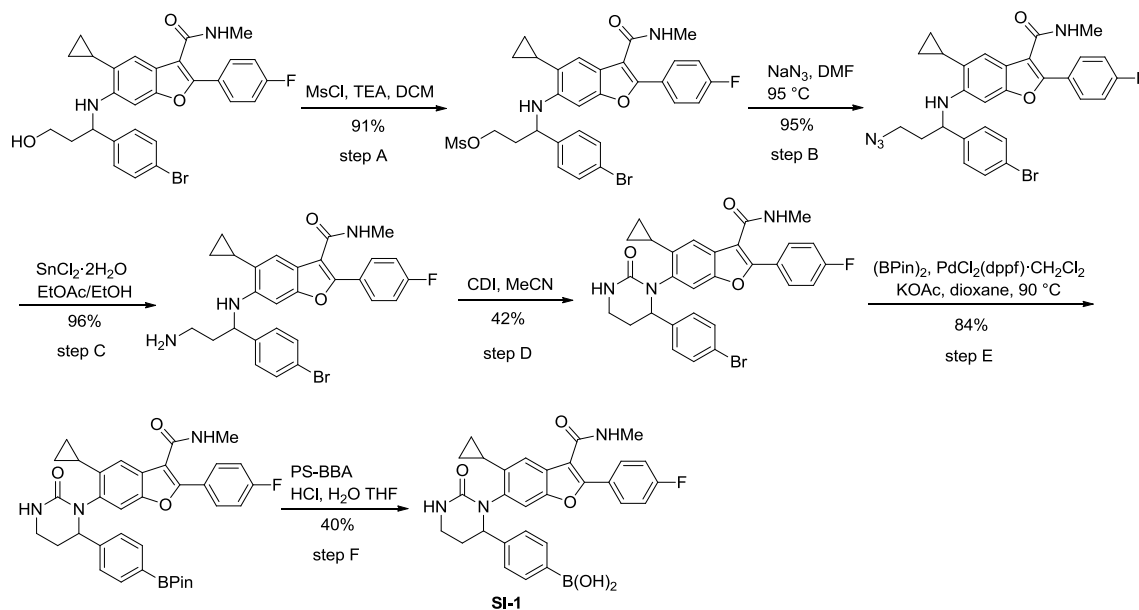
5-Cyclopropyl-6-(N-(3-(difluoromethyl)-4-nitrophenyl)methylsulfonamido)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide. A mixture of **3** (1.00 g, 2.49 mmol), 2-(difluoromethyl)-4-fluoro-1-nitrobenzene (1.13 g, 5.91 mmol) and K_2CO_3 (0.850 g, 6.15 mmol) in HMPA (6.2 mL) was stirred at 60 °C for 15 h. The reaction mixture was cooled to RT and partitioned between EtOAc and water. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated to dryness. The crude material was purified by flash chromatography (silica gel, 0-80% EtOAc/hexanes) to afford the title compound (1.45 g, 97%) as a yellow solid. 1H NMR (400 MHz, CHLOROFORM-*d*) δ 8.17 (d, $J = 9.17$ Hz, 1 H), 7.86 - 7.93 (m, 2 H), 7.70 (d, $J = 2.15$ Hz, 1 H), 7.49 - 7.59 (m, 3 H), 7.40 (s, 1 H), 7.18 - 7.27 (m, 2 H), 5.75 - 5.86 (m, 1 H), 3.36 (s, 3 H), 3.02 (d, $J = 4.88$ Hz, 3 H), 1.86 - 1.98 (m, 1 H), 0.87 - 1.08 (m, 2 H), 0.79 (br s, 1 H), 0.58 (br s, 1 H). ES-LCMS m/z : 574 (M+1).

S_NAr Reaction of compound **3 with 5-fluoro-2-nitrobenzonitrile**



6-(N-(4-Amino-3-cyanophenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (X=CN). A mixture of 5-fluoro-2-nitrobenzonitrile (1.28 mL, 11.2 mmol), **3** (3.00 g, 7.45 mmol) and K_2CO_3 (3.09 g, 22.4 mmol) in DME (30 mL) and water (7.5 mL) in a seal tube was heated to 80 °C overnight. The mixture was cooled down to room temperature, diluted with EtOAc, filtered and the off-white solid was washed with water and then dried *in vacuo* to give the title compound (3.90 g, 76%) as a yellow solid. 1H NMR (400 MHz, DMSO-*d*₆) δ 8.48 - 8.56 (m, 1 H), 8.37 (d, $J = 9.37$ Hz, 1 H), 8.09 (s, 1 H), 7.99 (dd, $J = 8.88, 5.37$ Hz, 2 H), 7.90 (d, $J = 2.73$ Hz, 1 H), 7.60 (dd, $J = 9.27, 2.63$ Hz, 1 H), 7.43 (t, $J = 8.88$ Hz, 2 H), 7.31 (s, 1 H), 3.66 (s, 3 H), 2.86 (d, $J = 4.68$ Hz, 3 H), 1.88 - 2.00 (m, 1 H), 0.68 - 1.02 (m, 3 H), 0.47 (br s, 1 H). ES-LCMS m/z : 549 (M+1).

(4-(3-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)-2-oxohexahydropyrimidin-4-yl)phenyl)boronic acid (SI-1).



(A) 3-(4-Bromophenyl)-3-((5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)amino)propyl methanesulfonate. To a stirred solution of 6-((1-(4-bromophenyl)-3-hydroxypropyl)amino)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.990 g, 1.84 mmol, for preparation see **22**, step B) and TEA (0.64 mL, 4.60 mmol) in anhydrous DCM at 0 °C was added MsCl (0.316 g, 2.76 mmol). The resulting solution was warmed to RT. After 15 minutes the solution was washed with water and concentrated to dryness at reduced pressure. The residue was purified by flash chromatography (silica gel, petroleum ether/EtOAc) to afford the title compound (1.03 g, 91%) as a brown solid.

(B) 6-((3-Azido-1-(4-bromophenyl)propyl)amino)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide. A solution of 3-(4-bromophenyl)-3-((5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)amino)propyl methanesulfonate (1.33 g, 2.16 mmol) and NaN₃ (0.281 g, 4.32 mmol) in DMF (60 mL) was stirred at 95 °C for 2 hours and then cooled to RT. The mixture was poured into water and the resulting solid isolated by filtration. The crude solid was subjected to flash chromatography (silica gel, petroleum ether/EtOAc) to give the title compound (1.20 g, 95%) as a brown solid.

(C) 6-((3-Amino-1-(4-bromophenyl)propyl)amino)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide. A solution of 6-((3-azido-1-(4-bromophenyl)propyl)amino)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.760 g, 1.35 mmol) and SnCl₂·H₂O (1.18 g, 2.00 mmol) in 10:10:1 EtOAc/EtOH/H₂O (70 mL) was stirred at 80 °C for 2 hours and then cooled to RT. The solution was concentrated to dryness at reduced pressure and the residue subjected to flash chromatography (silica gel, petroleum ether/EtOAc) to give the title compound (0.700 g, 96%) as a brown solid.

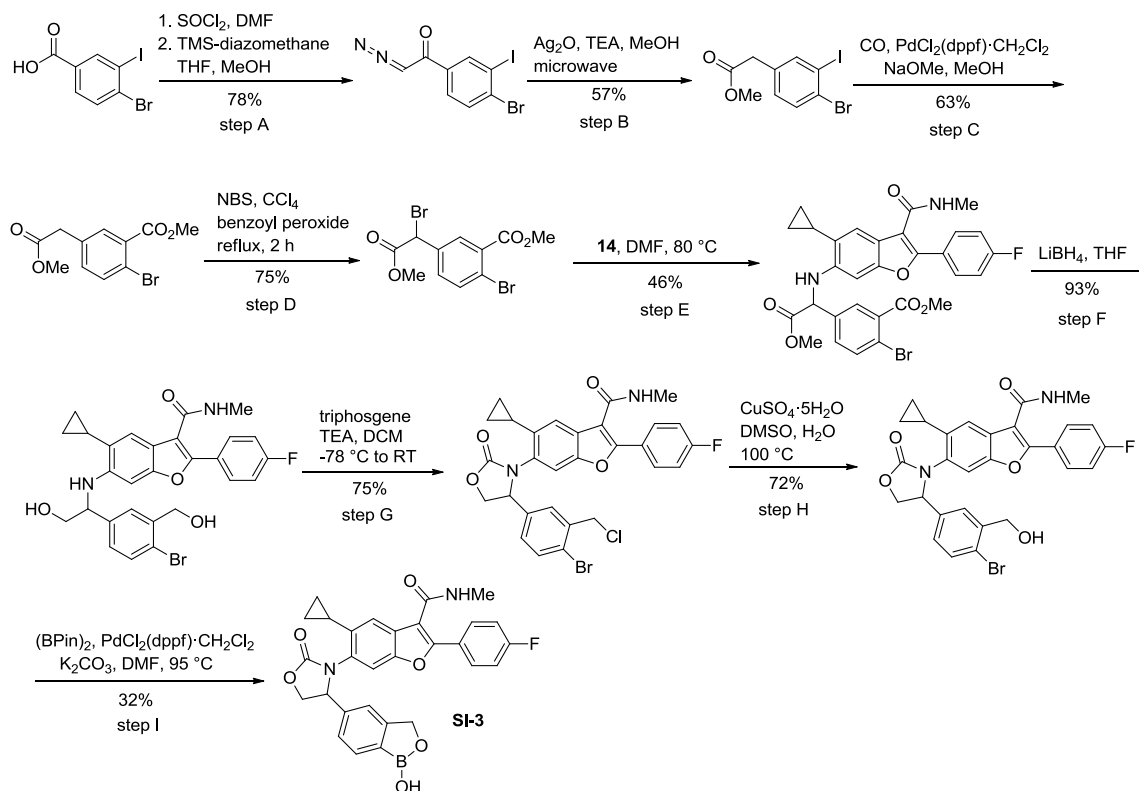
(D) 6-(6-(4-Bromophenyl)-2-oxotetrahydropyrimidin-1(2H)-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide. A solution of 6-((3-amino-1-(4-bromophenyl)propyl)amino)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.300 g, 0.560 mmol) and CDI (0.180 g, 1.10 mmol) in MeCN (50 mL) was heated to reflux for 30 minutes and then cooled to RT. The solution was concentrated to dryness at reduced pressure and the residue purified by flash chromatography (silica gel, petroleum ether/EtOAc) to afford the title compound (0.132 g, 42%) as a brown solid.

(E) 5-Cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-(2-oxo-6-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)phenyl)tetrahydropyrimidin-1(2H)-yl)benzofuran-3-carboxamide. A solution of 6-(6-(4-bromophenyl)-2-oxotetrahydropyrimidin-1(2H)-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.132 g, 0.240 mmol), bis(pinacolato)diboron (0.179 g, 0.710 mmol), KOAc (69 mg, 0.71 mmol), and PdCl₂(dppf)·CH₂Cl₂ (19 mg, 0.024 mmol) in 1,4-dioxane (15 mL) was sparged with nitrogen and heated to 90 °C. After 16 hours the

solution was cooled to RT, filtered to remove solids, and the filtrate concentrated to dryness at reduced pressure. The crude material was subjected to flash chromatography (silica gel, 5:1 petroleum ether/EtOAc) to afford the title compound (0.120 g, 84%) as a brown solid.

(F) **(4-(3-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)-2-oxohexahydropyrimidin-4-yl)phenyl)boronic acid (SI-1)**. A solution of 5-cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-(2-oxo-6-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)tetrahydropyrimidin-1(2H)-yl)benzofuran-3-carboxamide (0.120 g, 0.200 mmol) in 15 mL of THF was treated with PS-BBA (polymer-supported benzenboronic acid, 0.380 g, 0.99 mmol) followed by 5N aqueous HCl (0.60 mL, 1.38 mmol). After stirring the mixture at RT for 48 hours the solid was removed by filtration. The filtrate was concentrated to dryness at reduced pressure. The residue was purified by RP-HPLC to give **SI-1** (42 mg, 40%) as a white solid. ^1H NMR (300 MHz, METHANOL- d_4) δ 7.93 (dd, J = 8.65, 5.42 Hz, 2 H), 7.79 (d, J = 7.92 Hz, 2 H), 7.51 (d, J = 7.62 Hz, 2 H), 7.42 (s, 1 H), 7.28 (t, J = 8.80 Hz, 2 H), 7.19 (s, 1 H), 5.00 - 5.07 (m, 1 H), 3.03 (s, 3 H), 2.59 - 2.76 (m, 1 H), 2.07 - 2.26 (m, 2 H), 1.36 - 1.47 (m, 1 H), 0.98 - 1.28 (m, 4 H), 0.70 - 0.85 (m, 1 H). ES-LCMS m/z : 528 (M+1), 100% purity. HRMS m/z calcd for $\text{C}_{29}\text{H}_{27}\text{BFN}_3\text{O}_5$: 528.2106. Found: 528.2111.

5-Cyclopropyl-2-(4-fluorophenyl)-6-(4-(1-hydroxy-1,3-dihydrobenzo[*c*][1,2]oxaborol-5-yl)-2-oxooxazolidin-3-yl)-N-methylbenzofuran-3-carboxamide (SI-3).



(A) **1-(4-Bromo-3-iodophenyl)-2-diazoethanone**. To a stirred solution of 4-bromo-3-iodobenzoic acid (5.00 g, 15.3 mmol) in THF (30 mL) was added SOCl_2 (5.46 g, 45.9 mmol) followed by DMF (0.223 g, 3.06 mmol). The resulting solution was stirred at 80 °C for 2 hs, cooled to RT, and concentrated to dryness at reduced pressure. The residue was dissolved in MeOH (30 mL) and the solution cooled to 0 °C. To the solution was added 2M TMS-diazomethane/THF (9.18 mL, 18.4 mmol) by dropwise addition. After stirring at 0 °C for 2 hs, the solution was concentrated to dryness at reduced pressure. The residue was dissolved in EtOAc (50 mL). The solution was washed with aqueous AcOH (1x), water (1x), brine (1x), dried over Na_2SO_4 and concentrated to dryness. The crude material was purified by flash chromatography (petroleum ether/EtOAc) to afford the title compound (4.19 g, 78%) as an off white solid.

(B) **Methyl 2-(4-bromo-3-iodophenyl)acetate**. A mixture of 1-(4-bromo-3-iodophenyl)-2-diazoethanone (1.4 g, 4.00 mmol), TEA (8.10 g, 80.0 mmol), and Ag₂O (4.60 g, 20.0 mmol) in MeOH (50 mL) was subjected to microwave heating for 1 h. The mixture was filtered and the filtrate concentrated to dryness. The residue was dissolved in EtOAc (100 mL). The solution was washed with 2N aqueous HCl (50 mL), water (50 mL), brine (50 mL), dried over Na₂SO₄ and concentrated to dryness at reduced pressure. The residue was combined with the crude products from two identical reactions and purified by flash chromatography (silica gel, petroleum ether/EtOAc) to give the title compound (0.807 g, 57%) as a light yellow oil.

(C) **Methyl 2-bromo-5-(2-methoxy-2-oxoethyl)benzoate**. A solution of methyl 2-(4-bromo-3-iodophenyl)acetate (2.10 g, 5.90 mmol), 1M NaOMe (8.85 mL, 8.85 mmol), and PdCl₂(dppf)·CH₂Cl₂ (0.960 g, 1.18 mmol) in MeOH (50 mL) was subjected to carbonylation (1 atm CO) at RT for 3 hs. The reaction vessel was purged with nitrogen, solids removed by filtration, and the filtrate concentrated to dryness at reduced pressure. The residue was subjected to flash chromatography (silica gel, petroleum ether/EtOAc) to give the title compound (1.07 g, 63%) as a colorless oil.

(D) **Methyl 2-bromo-5-(1-bromo-2-methoxy-2-oxoethyl)benzoate**. A mixture of methyl 2-bromo-5-(2-methoxy-2-oxoethyl)benzoate (1.06 g, 3.70 mmol), NBS (0.724 g, 4.07 mmol), and benzoyl peroxide (45 mg, 0.19 mmol) in CCl₄ (25 mL) was heated to 80 °C with stirring for 2h and then cooled to RT. Solids were removed by filtration and the filtrate concentrated to dryness at reduced pressure. The crude material was purified by flash chromatography (silica gel, petroleum ether/EtOAc) to give the title compound (1.02 g, 75%) as a colorless oil.

(E) **Methyl 2-bromo-5-(1-((5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)amino)-2-methoxy-2-oxoethyl)benzoate**. A solution of 6-amino-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (**14**, 0.800 g, 2.47 mmol), methyl 2-bromo-5-(1-bromo-2-methoxy-2-oxoethyl)benzoate (1.02 g, 2.79 mmol), and TEA (0.748 g, 7.41 mmol) in DMF (30 mL) was heated to 80 °C for 5h and then cooled to RT. The mixture was diluted with water and extracted with EtOAc. The EtOAc solution was washed with water, brine, dried over Na₂SO₄, and concentrated to dryness at reduced pressure. The crude material was subjected to flash chromatography (silica gel, petroleum ether/EtOAc) to give the title compound (0.700 g, 46%) as a yellow solid.

(F) **6-((1-(4-Bromo-3-(hydroxymethyl)phenyl)-2-hydroxyethyl)amino)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide**. To a stirred solution of methyl 2-bromo-5-(1-((5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)amino)-2-methoxy-2-oxoethyl)benzoate (0.700 g, 1.15 mmol) in anhydrous THF (50 mL) at 0 °C was added LiBH₄ (0.152 g, 6.90 mmol). The resulting solution was warmed to RT and then stirred overnight. The solution was quenched with water and extracted with EtOAc (3x). The combined EtOAc extracts were dried over Na₂SO₄ and concentrated to dryness at reduced pressure. The crude material was purified by flash chromatography (silica gel, petroleum ether/EtOAc) to give the title compound (0.590 g, 93%) as a white solid.

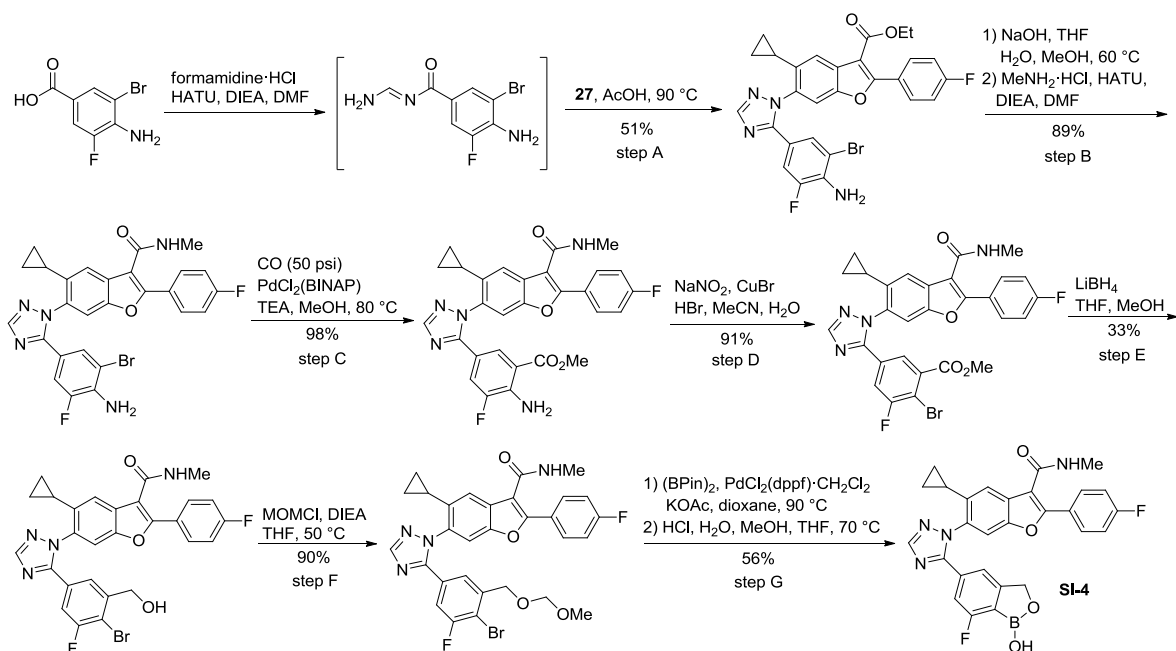
(G) **6-(4-(4-Bromo-3-(chloromethyl)phenyl)-2-oxooxazolidin-3-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide**. To a stirred solution of 6-((1-(4-bromo-3-(hydroxymethyl)phenyl)-2-hydroxyethyl)amino)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.520 g, 0.96 mmol) in DCM (50 mL) at -78 °C was added TEA (0.500 g, 4.70 mmol). This was followed by addition of a solution of triphosgene (0.297 g, 0.94 mmol) in DCM (10 mL) by dropwise addition. The resulting solution was warmed to RT and stirred overnight. The solution was washed with water, dried over Na₂SO₄, and concentrated to dryness at reduced pressure. The residue was subjected to flash chromatography (silica gel, petroleum ether/EtOAc) to give the title compound (0.440 g, 75%) as a white solid.

(H) **6-(4-(4-Bromo-3-(hydroxymethyl)phenyl)-2-oxooxazolidin-3-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide**. A solution of 6-(4-(4-bromo-3-(chloromethyl)phenyl)-2-oxooxazolidin-3-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.430 g, 0.72 mmol) in 1:1 DMSO/H₂O (30 mL) was treated with CuSO₄·5H₂O (0.180 g, 0.720 mmol) and heated to 100 °C for 6 hs. After cooling to RT the solution was partitioned between water and EtOAc and the phases separated. The EtOAc solution was washed with water, brine, dried over Na₂SO₄, and concentrated to dryness at reduced pressure. The residue was subjected to flash chromatography (silica gel, petroleum ether/EtOAc) to give the title compound (0.300 g, 72%) as a white solid.

(I) **5-Cyclopropyl-2-(4-fluorophenyl)-6-(4-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yl)-2-oxooxazolidin-3-yl)-N-methylbenzofuran-3-carboxamide (SI-3)**. A solution of 6-(4-(4-bromo-3-(hydroxymethyl)phenyl)-2-oxooxazolidin-3-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.240 g, 0.414 mmol), bis(pinacolato)diboron (0.315 g, 1.24 mmol), potassium carbonate (0.171 g,

1.24 mmol), and PdCl₂(dppf)·CH₂Cl₂ (67 mg, 0.083 mmol) in 1,4-dioxane (20 mL) was sparged with nitrogen and heated to 95 °C. After 1h the solution was cooled to RT, diluted with water, and extracted with EtOAc (3x). The combined EtOAc solutions were washed with water (1x), brine (1x), dried over Na₂SO₄, and concentrated to dryness at reduced pressure. The residue was purified by RP-HPLC to give **SI-3** (70 mg, 32%) as an off-white solid. ¹H NMR (300 MHz, METHANOL-*d*₄) δ 7.87 - 7.99 (m, 2 H), 7.74 (d, *J* = 7.62 Hz, 1 H), 7.50 - 7.62 (m, 2 H), 7.22 - 7.42 (m, 4 H), 5.74 (t, *J* = 7.92 Hz, 1 H), 5.03 - 5.16 (m, 3 H), 4.65 (dd, *J* = 8.87, 7.11 Hz, 1 H), 3.00 (s, 3 H), 2.16 - 2.31 (m, 1 H), 1.04 - 1.29 (m, 2 H), 0.67 - 0.94 (m, 2 H). ES-LCMS *m/z*: 527 (M+1), 100% purity. HRMS *m/z* calcd for C₂₉H₂₄BFN₂O₆: 527.1790. Found: 527.1790.

5-Cyclopropyl-6-(5-(7-fluoro-1-hydroxy-1,3-dihydrobenzo[*c*][1,2]oxaborol-5-yl)-1H-1,2,4-triazol-1-yl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (SI-4).



(A) **Ethyl 6-(5-(4-amino-3-bromo-5-fluorophenyl)-1H-1,2,4-triazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylate.** To a stirred solution of 4-amino-3-bromo-5-fluorobenzoic acid (1.00 g, 4.27 mmol), formamidine hydrochloride (0.516 g, 6.41 mmol) and HATU (1.95 g, 5.13 mmol) in DMF (14 mL) was added DIEA (2.24 mL, 12.8 mmol). After stirring at RT for 1h the solution was treated with ethyl 5-cyclopropyl-2-(4-fluorophenyl)-6-hydrazinylbenzofuran-3-carboxylate hydrochloride (**27**, 1.00 g, 2.56 mmol, for preparation see example **33**, step B) followed by glacial AcOH (1.90 mL, 33.3 mmol). The solution was heated to 90 °C for 3h and then cooled to RT. The reaction mixture was diluted with EtOAc, washed with saturated aqueous NaHCO₃ (1x), brine (1x), dried over Na₂SO₄, and concentrated to dryness at reduced pressure. The residue was subjected to flash chromatography (silica gel, 0-40% EtOAc/hexanes) to afford the title compound (0.758 g, 51%) as a yellow solid. ES-LCMS *m/z*: 579 (M+1).

(B) **6-(5-(4-Amino-3-bromo-5-fluorophenyl)-1H-1,2,4-triazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide.** The title compound was prepared from ethyl 6-(5-(4-amino-3-bromo-5-fluorophenyl)-1H-1,2,4-triazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylate in 89% yield as described herein for the synthesis of **31**, steps C and D. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 8.11 (s, 1 H), 7.86 - 7.96 (m, 2 H), 7.56 - 7.65 (m, 2 H), 7.49 (s, 1 H), 7.17 - 7.26 (m, 2 H), 6.97 (d, *J* = 11.53 Hz, 1 H), 5.85 (br s, 1 H), 4.34 (br s, 2 H), 3.03 (d, *J* = 4.89 Hz, 3 H), 1.38 - 1.51 (m, 1 H), 0.71 (br s, 3 H), 0.48 (br s, 1 H).

(C) **Methyl 2-amino-5-(1-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)-1H-1,2,4-triazol-5-yl)-3-fluorobenzoate.** The title compound was prepared from 6-(5-(4-amino-3-bromo-5-fluorophenyl)-1H-1,2,4-triazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide in 98%

yield as described herein for the synthesis of **34**, step D. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 8.13 (s, 1 H), 7.84 - 7.96 (m, 3 H), 7.60 (s, 1 H), 7.50 (s, 1 H), 7.19 - 7.26 (m, 3 H), 6.03 (br s, 2 H), 5.78 - 5.90 (m, 1 H), 3.74 (s, 3 H), 3.04 (d, *J* = 4.88 Hz, 3 H), 1.42 - 1.54 (m, 1 H), 0.62 - 0.87 (m, 3 H), 0.47 (br s, 1 H). ES-LCMS *m/z*: 544 (M+1).

(D) **Methyl 2-bromo-5-(1-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)-1H-1,2,4-triazol-5-yl)-3-fluorobenzoate**. To a stirred solution of methyl 2-amino-5-(1-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)-1H-1,2,4-triazol-5-yl)-3-fluorobenzoate (1.23 g, 2.26 mmol) in MeCN (9 mL) and 48% aqueous HBr (9 mL) at 0 °C was added NaNO₂ (0.171 g, 2.48 mmol). After stirring at 0 °C for 30 min the solution was treated with CuBr (0.389 g, 2.71 mmol), heated to 50 °C for 30 min, and then cooled to RT. The reaction mixture was partitioned between EtOAc and water and the phases separated. The EtOAc solution was washed with brine (1x), dried over Na₂SO₄, and concentrated at reduced pressure. The residue was subjected to flash chromatography (silica gel, 0-50% EtOAc/hexanes) to give the title compound (1.24 g, 91%) as a yellow foam. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 8.21 (s, 1 H), 7.87 - 7.96 (m, 3 H), 7.63 (s, 1 H), 7.50 (s, 1 H), 7.32 (dd, *J* = 8.98, 2.15 Hz, 1 H), 7.19 - 7.27 (m, 2 H), 5.78 - 5.90 (m, 1 H), 3.86 (s, 3 H), 3.04 (d, *J* = 4.88 Hz, 3 H), 1.37 - 1.48 (m, 1 H), 0.61 - 0.89 (m, 3 H), 0.45 (br s, 1 H). ES-LCMS *m/z*: 607 (M+1).

(E) **6-(5-(4-Bromo-3-fluoro-5-(hydroxymethyl)phenyl)-1H-1,2,4-triazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide**. To a stirred solution of methyl 2-bromo-5-(1-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)-1H-1,2,4-triazol-5-yl)-3-fluorobenzoate (1.24 g, 2.05 mmol) in THF (16 mL) and MeOH (1.58 mL) at 0 °C was added 2M LiBH₄/THF (3.07 mL, 6.14 mmol) by dropwise addition. After 1h at 0 °C the solution was partitioned between water and EtOAc and the phases separated. The aqueous phase was extracted with additional EtOAc (2x). The combined EtOAc solutions were washed with brine (1x), dried over Na₂SO₄, and concentrated at reduced pressure. The residue was subjected to flash chromatography (silica gel, 0-80% EtOAc/hexanes) to afford the title compound (0.391 g, 33%) as a white solid. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 8.18 (s, 1 H), 7.86 - 7.94 (m, 2 H), 7.58 - 7.62 (m, 2 H), 7.49 (s, 1 H), 7.22 (t, *J* = 8.60 Hz, 2 H), 7.15 (dd, *J* = 8.99, 1.76 Hz, 1 H), 5.80 - 5.89 (m, 1 H), 4.67 (s, 2 H), 3.03 (d, *J* = 4.89 Hz, 3 H), 1.36 - 1.48 (m, 1 H), 0.71 (br s, 3 H), 0.46 (br s, 1 H). ES-LCMS *m/z*: 579 (M+1).

(F) **6-(5-(4-Bromo-3-fluoro-5-((methoxymethoxy)methyl)phenyl)-1H-1,2,4-triazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide**. A solution of 6-(5-(4-bromo-3-fluoro-5-(hydroxymethyl)phenyl)-1H-1,2,4-triazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.391 g, 0.676 mmol) in THF (6.27 mL) was treated with DIEA (0.354 mL, 2.027 mmol) followed by MOM-Cl (0.128 mL, 1.69 mmol) and the resulting solution heated to 50 °C. After 18h the solution was cooled to RT, partitioned between saturated aqueous NaHCO₃ and EtOAc and the phases separated. The aqueous phase was extracted with EtOAc (2x). The combined EtOAc extracts were washed with brine (1x), dried over Na₂SO₄, and concentrated to dryness at reduced pressure. The crude product was purified by flash chromatography (silica gel, 0-50% EtOAc/hexanes) to afford the title compound (0.378 g, 90%) as an off-white foam. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 8.18 (s, 1 H), 7.87 - 7.94 (m, 2 H), 7.59 (s, 1 H), 7.48 (s, 1 H), 7.46 (s, 1 H), 7.26 - 7.30 (m, 1 H), 7.22 (t, *J* = 8.70 Hz, 2 H), 5.83 - 5.93 (m, 1 H), 4.52 (s, 4 H), 3.25 (s, 3 H), 3.03 (d, *J* = 4.89 Hz, 3 H), 1.39 - 1.49 (m, 1 H), 0.58 - 0.86 (m, 3 H), 0.46 (br s, 1 H). ES-LCMS *m/z*: 623 (M+1).

(G) **5-Cyclopropyl-6-(5-(7-fluoro-1-hydroxy-1,3-dihydrobenzo[*c*][1,2]oxaborol-5-yl)-1H-1,2,4-triazol-1-yl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (SI-4)**. A stirred solution of 6-(5-(4-bromo-3-fluoro-5-((methoxymethoxy)methyl)phenyl)-1H-1,2,4-triazol-1-yl)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.379 g, 0.607 mmol), KOAc (0.238 g, 2.43 mmol), bis(pinacolato)diboron (0.462 g, 1.82 mmol), and PdCl₂(dppf)·CH₂Cl₂ (50 mg, 0.061 mmol) in 1,4-dioxane (6.1 mL) was purged with nitrogen and heated 90 °C. After 18h the mixture was cooled to RT, diluted with EtOAc, and filtered through Celite® to remove solids. The filtrate was washed with brine, dried over Na₂SO₄, and concentrated to dryness at reduced pressure. The resulting brown oil was dissolved in 1:1 THF/MeOH, and the solution diluted with 1M aqueous HCl. The solution was heated to 70 °C for 3h and cooled to RT. The mixture was diluted with brine and extracted with EtOAc. The EtOAc solution was dried over Na₂SO₄, and concentrated at reduced pressure. The crude product was purified by flash chromatography (silica gel, 0-100% EtOAc/DCM followed by 0-10% MeOH/DCM) to afford **SI-4** (0.178 g, 56%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.39 (s, 1 H), 8.47 - 8.55 (m, 1 H), 8.38 (s, 1 H), 7.92 - 8.02 (m, 3 H), 7.48 (s, 1 H), 7.40 (t, *J* = 8.89 Hz, 2 H), 7.32 (s, 1 H), 7.01 (d, *J* = 8.79 Hz, 1 H), 4.96 (s, 2 H), 2.84 (s, 3 H), 1.23 - 1.34 (m, 1 H), 0.49 - 0.79 (m, 3 H), 0.34 (br s, 1 H). ES-LCMS *m/z*: 527 (M+1), 100% purity. HRMS *m/z* calcd for C₂₈H₂₁BF₂N₄O₄: 527.1702. Found: 527.1701.

III. EC₅₀/pEC₅₀ Determination Methods and Replicon Assay Protocols

EC₅₀/pEC₅₀ Determination

The data for dose responses were plotted as % inhibition versus compound concentration following normalization using the formula $100-100*(U-C2)/(C1-C2)$, where U was the unknown value, C1 was the average of the negative (0% inhibition) control wells and C2 was the average of the positive (100% inhibition) control wells. Curve fitting was performed with ActivityBase XE (ID Business Solutions Ltd., Guilford, UK) using equation 1.

$$y = A + [B - A]/[1 + [(10^x/10^C)^D]] \quad (\text{equation 1})$$

A was the minimum response, B was the maximum response, C was the log(EC₅₀) and D was the Hill slope. The results for each test compound were recorded as pEC₅₀ values (C in the above equation) from which the EC₅₀ values reported throughout the paper were calculated.

HCV Replicon Activity Assays

The assay protocols described below were originally reported in reference 8 within the manuscript [Voitenleitner *et. al.* In vitro characterization of GSK2485852, a novel hepatitis C virus polymerase inhibitor. *Antimicrob. Agents Chemother.* **2013**, 57, 5216–5224].

Stable replicon cell lines were seeded at a density of 2×10^4 cells per well in a final volume of 200 μ l of assay medium (DMEM supplemented with 5% FBS, penicillin-streptomycin, and nonessential amino acids) in 96-well assay plates containing compounds or dimethyl sulfoxide (DMSO). Alternatively, stable replicon cell lines were seeded at a density of 5×10^3 cells per well in a final volume of 50 μ l of assay medium (DMEM supplemented with 5% FBS, penicillin-streptomycin, and nonessential amino acids) in 384-well assay plates containing compounds or DMSO. Cells were then incubated at 37°C and 5% CO₂ for 48 h. HCV replication was monitored by determining firefly luciferase activity using Steady-Glo (Promega) and measurement of luminescence in an EnVision 2103 Multilabel Reader (PerkinElmer) or ViewLux (PerkinElmer). Cytotoxicity was measured on parallel plates using CellTiter-Glo (Promega). Replicon 50% effective concentrations (EC_{50s}) and CC_{50s} (the concentration of compound required to inhibit 50% of the assay response), were calculated by curve fitting data to the Hill equation, using XLFit for the 96-well assays. ActivityBase (IDBS Software) with XE Runner for curve fitting was used to plot the curve of percentage of inhibition against compound concentration and derive the 50% effective concentration (EC₅₀) for the compounds assayed in the 384-well format.

It is worth noting for GT1b WT and 316N stable replicon assays that two closely related assay formats were developed to meet the demand for higher throughput. The authors decided to report the data separately (as opposed to averaging) to preserve the integrity of the data and account for any subtle variation on assay conditions that might impact IC₅₀ determination. The 2 methods are denoted by the appended descriptor _PTS format or _DPU format in Table SI-2b.

Transient-transfection assays used plasmid constructs containing wild-type, mutant, or chimeric replicons as the templates for *in vitro* transcription reactions using the T7 Express kit (Promega). The *in vitro* transcripts were aliquoted and stored at -80°C before use. For genotype 1a constructs, 15 μ g of RNA was electroporated into 5×10^6 Huh7 Lunet cells in Cytomix supplemented with 2 mM ATP and 5 mM glutathione. Electroporation was in 0.4-cm cuvettes using a Bio-Rad Gene Pulser II at 270 V, 950 μ F, and infinite resistance. Transient transfections with genotype 1b constructs were performed similarly, except that 5 μ g of RNA was electroporated into 5×10^6 ET cured cells in phosphate-buffered saline (PBS). Electroporated cells were resuspended in growth medium, and 2×10^4 cells were transferred to wells of a 96-well plate containing compounds or DMSO. Cells were incubated at 37°C and 5% CO₂ for 3 days, and inhibition of HCV replication was measured as for the stable replicon cells.

IV. Replicon Data for Cmpds 1, 5-11, 19-26, 31-37, 44-49, and SI-1-4

Table SI-2a. Replicon data, 95% Confidence Intervals, assay replicates (n), and cytotoxicity data for transient transfection assays for GT1a replicons

Cmpd	Transient Replicon Assay (nM)								Huh7 CC ₅₀ (nM)
	GT 1a WT				GT 1A C316Y				
	Mean EC50	UCL	LCL	N	Mean EC50	UCL	LCL	N	
1	0.9	1.1	0.7	21	3.2	4.5	2.3	8	>50,000
5	1.3	2.3	0.8	4	165.0	261.6	104.1	4	>50,000
6	n.t.				n.t.				>50,000
7	1.5	3.2	0.7	2	117.5	225.4	61.2	2	>50,000
8	n.t.				n.t.				>50,000
9	28.3	47.6	16.9	4	5011.9			3	6500
10	9.2	15.5	5.5	4	4365.2	10968.7	1737.2	1	9100
11	10.8	18.2	6.5	4	1220.9	2078.2	717.2	3	>50,000
19	n.t.				n.t.				>50,000
20	n.t.				n.t.				>50,000
21	8.3	17.3	4.0	2	1995.3	3827.8	1040.0	2	>50,000
22	55.6	115.8	26.7	2	309.0	592.9	161.1	2	>50,000
23	n.t.				n.t.				>50,000
24	142.9	240.1	85.1	4	5011.9			4	>50,000
25	2.6	4.3	1.5	4	24.3	38.5	15.3	4	>50,000
26	291.7	607.6	140.1	2	5011.9			2	>50,000
31	1.1	1.7	0.7	6	45.5	66.3	31.3	6	>50,000
32	18.2	51.4	6.4	1	2041.7	3917.0	1064.3	2	17000
33	2.3	3.1	1.7	12	20.4	26.6	15.6	12	>50,000
34	1.2	2.5	0.6	2	24.5	47.1	12.8	2	>50,000
35	3.4	7.1	1.6	2	29.5	56.6	15.4	2	23000
36	3.8	7.8	1.8	2	660.7	1267.5	344.4	2	3600
37	6.0	10.1	3.6	4	631.0	1074.1	370.7	3	>50,000
44	2.2	4.6	1.1	2	1949.8	3740.7	1016.4	2	>50,000
45	0.9	1.8	0.4	2	288.4	553.3	150.3	2	>50,000
46	1.0	1.4	0.7	10	39.4	52.8	29.5	10	>50,000
47	1.2	1.6	1.0	19	10.9	13.4	8.9	20	>50,000
48	1.1	2.3	0.5	2	16.8	32.2	8.8	2	>50,000
49	1.3	1.5	1.0	30	31.9	46.4	21.9	6	>50,000
SI-1	n.t.				n.t.				>50,000
SI-2	2.8	4.7	1.7	4	189.5	300.3	119.5	4	>50,000
SI-3	11.4	23.6	5.4	2	3845.9	7378.2	2004.7	2	>50,000
SI-4	3.5	5.3	2.3	6	426.6	621.4	292.8	6	>50,000

Upper and lower 95% CI interval limits (UCL and LCL, respectively) were calculated using the pooled variance for each assay.

CC₅₀ – 50% cellular cytotoxicity concentration

Table SI-2b. Replicon data, 95% Confidence Intervals, and assay replicates (n) for stable replicon assays for GT1b WT and 316N

Cmpd	Stable Replicon Assay (nM)															
	GT1b WT_PTS format ^a				GT1b WT_DPU format ^b				GT1b 316N_PTS format ^a				GT1b 316N_DPU format ^b			
	Mean EC50	UCL	LCL	N	Mean EC50	UCL	LCL	N	Mean EC50	UCL	LCL	N	Mean EC50	LCL	UCL	N
1	2.0	2.2	1.8	80	1.6	2.2	1.1	11	n.t.				1.9	2.1	1.7	26
5	n.t.				2.7	3.9	1.8	8	n.t.				15.8	22.1	11.4	3
6	25.1	49.3	12.8	2	21.4	45.8	10.0	2	n.t.				831.8	1248.8	554.0	2
7	3.2	6.2	1.6	2	2.5	4.0	1.5	5	12.6	26.9	5.9	2	12.0	16.8	8.6	3
8	5.0	9.8	2.6	2	5.1	11.0	2.4	2	n.t.				18.6	28.0	12.4	2
9	100.0	259.7	38.5	1	n.t.				251.2	733.7	86.0	1				
10	50.1	130.2	19.3	1	n.t.				501.2	1463.8	171.6	1				
11	39.8	103.4	15.3	1	n.t.				316.2	923.6	108.3	1				
19	63.1	163.9	24.3	1	n.t.				794.3	1474.9	427.8	3				
20	251.2	652.4	96.7	1	n.t.				3162.3	9236.2	1082.7	1				
21	15.8	27.5	9.1	3	n.t.				199.5	425.7	93.5	2				
22	50.1	80.8	31.1	4	n.t.				398.1	680.4	232.9	4				
23	100.0	259.7	38.5	1	n.t.				1584.9	3381.8	742.8	2				
24	199.5	391.8	101.6	2	n.t.				1584.9	3381.8	742.8	2				
25	2.0	3.9	1.0	2	n.t.				5.0	10.7	2.3	2				
26	1584.9	4116.2	610.3	1	n.t.				5011.9	0.0	0.0	1				
31	2.0	5.2	0.8	1	n.t.				6.3	18.4	2.2	1				
32	50.1	130.2	19.3	1	n.t.				398.1	1162.8	136.3	1				
33	4.0	10.3	1.5	1	n.t.				7.9	23.2	2.7	1				
34	2.0	5.2	0.8	1	n.t.				4.0	11.6	1.4	1				
35	4.0	10.3	1.5	1	n.t.				6.3	18.4	2.2	1				
36	5.0	13.0	1.9	1	n.t.				39.8	116.3	13.6	1				
37	12.6	32.7	4.8	1	n.t.				398.1	1162.8	136.3	1				
44	6.3	8.7	4.6	9	n.t.				63.1	184.3	21.6	1				
45	2.5	3.3	1.9	11	n.t.				6.3	18.4	2.2	1				
46	2.0	2.6	1.5	12	n.t.				3.2	6.7	1.5	2				
47	2.5	3.2	2.0	17	n.t.				4.0	6.8	2.3	4				
48	4.0	5.4	2.9	10	n.t.				7.9	23.2	2.7	1				
49	2.5	3.7	1.7	6	n.t.				2.5	4.3	1.5	4				
SI-1	5011.9	13016	1929.8	1	n.t.				2511.9	7336.5	860.0	1				
SI-2	3.2	3.4	2.9	183	4.8	6.4	3.6	14	12.6	13.9	11.4	119	12.9	15.4	10.7	10
SI-3	10.0	26.0	3.9	1	n.t.				199.5	582.8	68.3	1				
SI-4	4.0	5.9	2.7	6	n.t.				50.1	77.6	32.4	6				

^aStable replicon assay format adapted for higher throughput (PTS refers to the GSK department conducting the assay).

^bStable replicon assay format initially developed with lower throughput (DPU refers to the GSK department conducting the assay).

Upper and lower 95% CI interval limits (UCL and LCL, respectively) were calculated using the pooled variance for each assay.

V. In Vivo/In Vitro DMPK Profiling

All studies were conducted after review by the Institutional Animal Care and Use Committee at GSK (or at the institution where the work was performed, if not at GSK) and in accordance with the GSK Policy on the Care, Welfare and Treatment of Laboratory Animals.

In Vivo Pharmacokinetics

Male CD-1 mice (n=3, ~ 30 g body weight), Sprague-Dawley (n=3, ~300 g body weight) or Han Wistar rats (typical n=2, 200-300 g body weight) from Charles River Labs, Raleigh, NC or BioDuro, Beijing, China, beagle dogs (n=3, ~10 kg body weight) from Marshall Farms, North Rose, NY and cynomolgus monkeys (n=3, 3-4 kg body weight) Covance Laboratories, Alice, TX were typically dosed intravenously at 1 mg/kg and orally at 5 mg/kg for low dose pharmacokinetic evaluations. Blood samples were collected at various time points into EDTA tubes or centrifuged for plasma. PK samples were generally stored at -70°C until sample analysis. Samples were protein precipitated with an organic solvent and then analyzed by LC/MS/MS. Non-fasted animals were used for rodents and fasted animals were used for the dog and cynomolgus PK studies.

Non-compartmental blood pharmacokinetic parameters such as terminal blood half-life ($t_{1/2}$), maximum concentration (C_{max}), time of maximum concentration (T_{max}), total clearance (CL), steady-state volume of distribution (V_{ss}), area under the concentration-time curve extrapolated to infinite time ($AUC_{0-\infty}$), and area under the blood concentration time curve up to 24 h (AUC_{0-24}) were calculated based on the individual blood concentration-time data using Phoenix WinNonlin version 6.1 (Pharsight, Mountain View CA). Oral bioavailability (F) was calculated using the following equation: $F (\%) = [(AUC_{0-\infty, oral}/Oral\ Dose)/(AUC_{0-\infty, IV}/IV\ Dose)] * 100$ where $AUC_{0-\infty, PO}$ was the individual animal $AUC_{0-\infty}$ following PO dose administration and $AUC_{0-\infty, IV}$ was the average $AUC_{0-\infty}$ after intravenous administration.

Direct CYP450 inhibition

Test compounds were incubated with pooled, mixed-gender human liver microsomes (catalogue number H0610) from Xenotec LLC (Lenexa, KS) to assess direct inhibition of CYP1A2, 2C9, 2C19, 2D6, and 3A4. In a 96 well plate, a 3 mM DMSO stock of test compound was serially diluted 1:3 for 7 concentrations ranging from 33 μ M to 33 nM. Duplicate microsomal incubations containing 0.1 mg/mL microsomal protein were incubated with the probe cocktails (either 3 CYP3A4 substrates including atorvastatin, nifedipine and midazolam or substrates such as phenacetin, diclofenac, s-mephenytoin and bufuralol for CYP1A2, 2C9, 2C19, and 2D6, respectively) along with dilutions of test compound for 7 minutes (CYP3A4 cocktail) or 10 minutes (CYP1A2, 2C9, 2C19, and 2D6 cocktail). Incubations were initiated with 50 μ L of an NADPH regenerating system (containing 1.7 mg NADP, 7.8 mg glucose-6-phosphate and 6 units of glucose-6-phosphate dehydrogenase per mL of 2% w/v sodium bicarbonate). Incubations were quenched with an equal volume of acetonitrile/methanol. The amount of the metabolites formed from each substrate in the probe cocktail was quantified by LC/MS/MS analysis. Enzyme activity in the presence of test compound was normalized for the enzyme activity in the absence of test compounds and expressed as percent control activity. Percent control activity versus concentrations plots were fitted and IC50 curves were generated using XLFit software (IDBS, Guildford, UK).

In Vitro Hepatocyte stability assay

Hepatocyte incubations were conducted with cryopreserved hepatocytes purchased either from CellDirect (Durham, NC) or Celsis (Baltimore, MD). Cryopreserved hepatocytes were removed from liquid nitrogen and thawed according to XenoTech's guidelines listed in "XenoTech Protocol for Thawing Cryopreserved Hepatocytes" using Hepatocyte Isolation Kit K2000 [12/13/2004]. Hepatocytes were diluted to 1×10^6 cells in 1 mL of Williams E media containing 25 mM HEPES buffer and 2 mM Glutamax. Cell viability was determined using trypan blue exclusion. Hepatocyte incubations were carried out in 96-well plates on an Eppendorf shaker at 350 rpm at 37 °C. Final reaction mixtures consisted of 0.25×10^6 cells and 0.5 μ M test compound (0.05% final DMSO concentration) in a final volume of 0.5 mL. An initial time-point (t_0) was collected and subsequent aliquots were removed at 15, 30, 60, 90, and 120 min. Reactions were terminated by mixing 50 μ L of the incubation mixture with 100 μ L of an ice cold mixture acetonitrile and methanol. After centrifugation and the resultant supernatant was injected for

LC/MS/MS analysis. Drug-free matrix control and 2 positive QC standards (phenacetin and propranolol) were included in each experiment and treated in the same manner along with the test compound. Intrinsic clearance determined from hepatocyte incubations (Clint, mL/min/kg body weight) was calculated from the half-life values using the following equations [RS, Obach, J. Pharmacol. Exp Ther. **1997**, 283: 46-58, The prediction of human pharmacokinetic parameters from preclinical and in vitro metabolism data]

$$\text{Clint} = 0.693/t_{1/2}(\text{min}) * (\text{mL incubation})/\#\text{cells} * C * B$$

Where $t_{1/2}$ is calculated using the parent depletion method, B = g liver/kg body wt [B, Davis and T, Morris, Pharm. Res. **1993**, 10:1093-1095, Physiological parameters in laboratory animals and humans], C = # cells/g liver [T, Iwatsubo, Pharmacol. Ther. **1997**, 73: 147-171, Prediction of in vivo drug metabolism in the human liver from in vitro metabolism data]: 1.2×10^8 cells/g for rat and human, 2.4×10^8 cells/g for dog, C = 40 gm liver/kg body wt for rat, 32 gm liver/kg body wt for dog and 26 gm liver/kg body wt for human.

Table SI-3: In Vitro metabolic stability in cryopreserved human hepatocytes

Cmpd	T1/2 (h)	Clint (mL/min/kg BW)
1 ^a	~1	77
49 ^b	>6	n.d. ^c

^a Human hepatocytes (mixed gender) were purchased from CellzDirect (Cat.#: HMCH-P10; Lot# HuP88)

^b Human hepatocytes (mixed gender) were purchased from Celsis (Cat.#: X008000; Lot#000)

^c Not determined due to no significant parent loss

Table SI-4: In vivo rat pharmacokinetic profiles of compounds 7 and 8

Cmpd	i.v.			p.o.	
	Cl (mL/min/kg)	Vdss (L/kg)	t1/2 (h)	AUC (ng*hr/mL)	F (%)
7 ^a	36	5.0	3.3	15	3
8 ^b	3.5	1.2	4.3	3280	14

^a Dosed IV and PO (n=2/per arm) at 1 mg/kg in DMSO/4% cyclodextrin with 0.05% acetic acid (5/95) to male CD rats and plasma sample were collected

^b Dosed IV at 1 mg/kg and PO (n=1/per arm) at 5 mg/kg in DMSO/20% hydroxypropyl-β-cyclodextrin (10/90) to Han Wistar rats and whole blood was collected

Table SI-5: In vivo pharmacokinetic profiles of compound 49 in preclinical species.

Species	i.v. ^a			p.o. ^b	
	Cl (mL/min/kg)	Vdss (L/kg)	t1/2 (h)	AUC(0-∞) (ng*hr/mL)	F (%)
Mouse	0.7	0.5	8.4	65000	57
Rat	6.9	0.9	2.8	5400	43
Dog	1.2	0.6	6.9	57000	82
Cyno	5.7	1.2	3.7	ND ^c	ND

^a Blood clearance was used.

^b Typically dosed i.v. at 1 mg/kg and PO at 5 mg/kg in DMSO/20% hydroxypropyl-β-cyclodextrin (10/90, pH adjusted)

^c ND: not determined

VI. VCD Analysis for Intermediates En Route to Chiral Compounds 24, 25, and 26

Ab Initio VCD Analysis of N20353-66-1-E1 and N20353-66-1-E2

I. Sample Information:

- ART Requests: 31708 (E1) and 31708-1 (E2)
- Date: July 20, 2011
- Submitter: Jianjun Yu
- Analyst: Doug Minick
- Analytical Reference: N19695-74
- Project: HCV polymerase NS5b inhibitor (hinge-site) - HCV
- Project Code: 17294

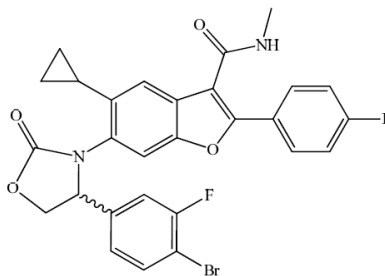
II. Technique: VCD

III. Experiment:

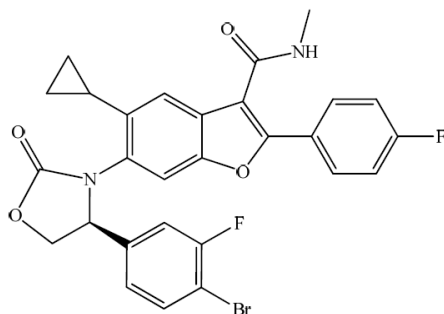
- Determination of absolute stereochemistry

IV. Objective:

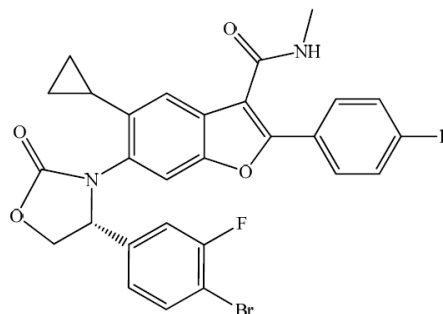
- Assign the absolute configurations for a set of enantiomers with the following general structure:



V. Assigned Structures:



N20353-66-1-E1
(*S*)-6-(4-(4-bromo-3-fluorophenyl)-2-oxooxazolidin-3-yl)-5-cyclopropyl-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide



N20353-66-1-E2
(*R*)-6-(4-(4-bromo-3-fluorophenyl)-2-oxooxazolidin-3-yl)-5-cyclopropyl-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide

VI. Comments:

- Input as required.

VII. Theoretical Analysis:

- Model(s):



Full-Structure Model with (S)-configuration

- Conformational Search: MOE stochastic csearch using MMFF94x force field
- Model Chemistry: # opt freq=(noraman,vcd) b3lyp/dgdzvp
- Conformational Analysis: Fractional populations estimated using Boltzmann statistics
- Lorentzian band width: 8 cm^{-1}
- Frequency scale factor: 0.980
- Estimation of Confidence Limit: CompareVOA (BioTools, Inc.) analysis (Section IX)

VIII. Experimental:

- Spectrometer: BioTools Chiral/IR VCD spectrometer operated at 4 cm^{-1}
- Frequency Range: 2000-800 cm^{-1}
- PEM Calibration: PEM calibrated at 1400 cm^{-1}
- PEM Retardation Settings: PEM1 = 0.250* λ ; PEM2 = 0.260* λ
- Scan Method: single block scan [2 min. DC scan + 360 min. AC scan]
- Solvent: CDCl_3
- Concentrations: ~15mg/200ul
- Baseline Correction Method: modified half-difference ($\text{VCD}_{\text{E1}}(\text{corr'd}) = \text{VCD}_{\text{E1}} \text{ minus } \text{VCD}_{\text{E2}}$; $\text{VCD}_{\text{E2}}(\text{corr'd}) = \text{VCD}_{\text{E2}} \text{ minus } \text{VCD}_{\text{E1}}$)
- Additional Processing: Savitsky-Golay 9-point smooth

IX. Results:

- Analysis of Experimental and Calculated Data:
The experimental VCD and IR spectra of N20353-66-1-E1 and N20353-66-1-E2 are compared with calculated data in Figures 1 and 2, respectively. [Note: The green box in the upper panel of each figure highlights the VCD spectral range used to assign the absolute configuration(s) and estimate the level of reliability (Section X). The smaller box inside the larger one designates the region omitted from the VCD analysis (1415-1370 cm^{-1}).]

In the upper panel of Figure 1, the experimental VCD spectrum inside the highlighted box is largely coincident with the calculated VCD spectrum, indicating that the chiral center in this molecule has the same absolute stereochemistry as the model. Therefore, N20353-66-1-E1 was assigned as the (S)-enantiomer.

In the upper panel of Figure 2, the experimental VCD spectrum inside the highlighted box is largely the mirror image of the calculated VCD spectrum, indicating that the chiral center in this molecule is inverted relative to the model. Therefore, N20353-66-1-E2 was assigned as the (R)-enantiomer.

Note: The IR spectrum calculated for the model is in excellent overall agreement with the IR spectra observed for these enantiomers, demonstrating adequate coverage of the conformational space (a requirement for reliable VCD assignments based on full structure models).

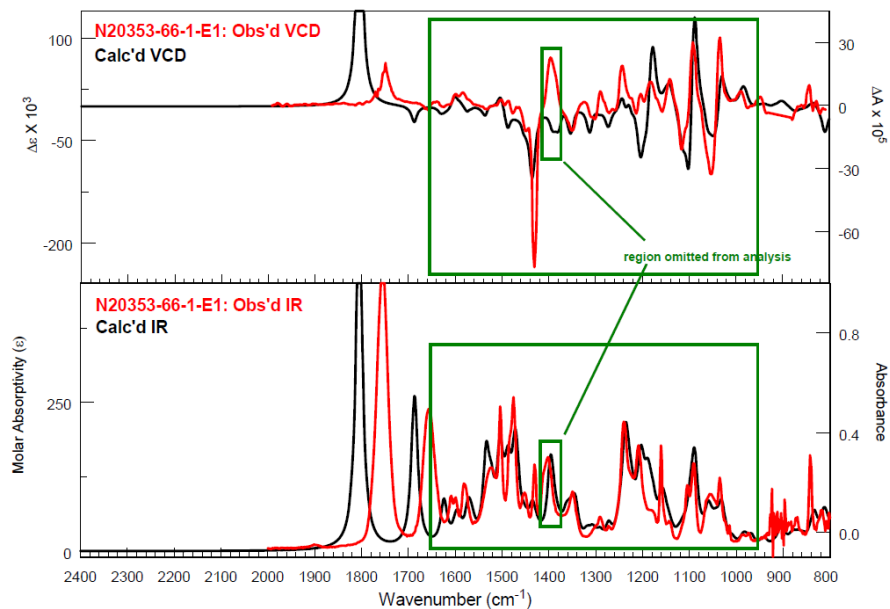


Figure 1. Upper panel: VCD spectrum of N20353-66-1-E1 (red trace) vs calculated VCD spectrum (black trace). Lower panel: IR spectrum of N20353-66-1-E1 (red) vs calculated IR spectrum (black).

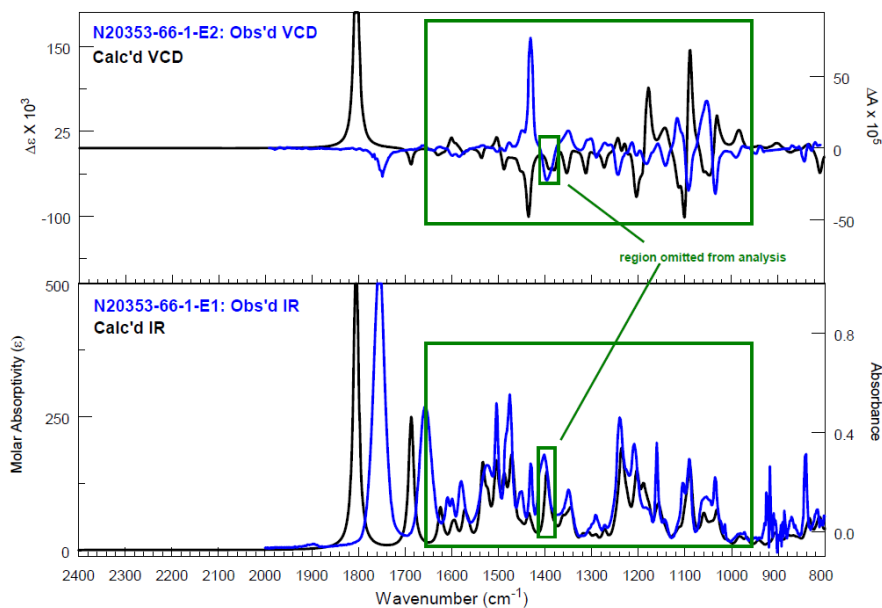


Figure 2. Upper panel: VCD spectrum of N20353-66-1-E2 (blue trace) vs calculated VCD spectrum (black trace). Lower panel: IR spectrum of N20353-66-1-E2 (blue) vs calculated IR spectrum (black).

X. Estimated Level of Reliability

- The confidence limit in this study was estimated using CompareVOATM (BioTools, Inc.), an automated tool for quantifying the level of agreement between two sets of spectral data.

- The degree of reliability (the confidence limit) is assessed using the absolute values of two parameters: total neighborhood similarity for the VCD correlation (TNS (VCD)) and the enantiomeric similarity index (ESI).
- The degrees of reliability based on CompareVOA analysis are as follows:

Reliability	*TNS (VCD) (range)	*ESI (range)	Confidence Limit (CL) (range)
High	≥ 70	≥ 60	> 99 %
Medium	60 - 70	50 - 60	95 – 99 %
Low	50 - 60	40 – 50	90 – 95 %
Unreliable	< 50	< 40	< 90 %

*absolute value

- CompareVOA results for the current study:
 - Spectral range: 1650-955 cm^{-1}
 - Region omitted: 1415-1370 cm^{-1}
 - Range of statistical analysis (minimum 400 cm^{-1}): 650 cm^{-1}
 - Width of triangular weighting function: 20 cm^{-1}
 - TNS (VCD): 68.3 (absolute value)
 - ESI: 68.0 (absolute value)
 - Optimized scale factor: 0.983
- *Level of Reliability:* ***High-Medium (CL ~ 99%)***

XI. Optical Rotation Data:

- Not measured.

VII. Crystal Structures and PDB ID Numbers

Protein isolation, crystallization, data capture and refinement procedures have been described previously *J. Med. Chem.*, **2014**, *57*, 1902–1913 (Supporting Information, pp20-23).

Authors will release the atomic coordinates and experimental data upon article publication.

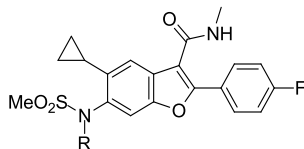
Table SI-6: Resolution and PDB ID for Figure 4 and Figure 5

Figure #	Resolution (Å)	PDB ID
4a	2.3	4KAI
4b	2.3	6MVK
4c	2.14	6MVQ
4d	2.00	6MVP
5	1.95	6MVO

VIII. Potentiometric pKa Determination Protocol Using Co-Solvent

The Sirius T3 (Sirius Analytical Inc, UK) instrument was used for pKa determination of compounds. The pH-metric method with co-solvent (pKa) was used. The assay is performed using various concentrations of co-solvent, usually 80:20 methanol: ISA water, but other solvents are suitable. Three titrations are performed increasing the aqueous proportion of the solution. The pKa in water is calculated by utilising the Yasuda-Shedlovsky extrapolation.

Table SI-7. Measured pKa values for sulfonamide-N-phenyl or benzyl boronic acids



Cmpd	R	pKa
1		7.9
45		8.4
49		5.4
SI-5		6.5
SI-6		7.9

IX. pH-Solubility Profile of Compound 49 (GSK8175)

