Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications

Supporting Information

Designing Glucokinase Activators with Reduced Hypoglycemia Risk: Discovery of *N,N*-dimethyl-5-(2-methyl-6-((5-methylpyrazin-2-yl)-carbamoyl)benzofuran-4-yloxy)pyrimidine-2-carboxamide as a Clinical Candidate for the Treatment of Type 2 Diabetes Mellitus.

Experimental Section

All reagents and solvents were used as received from commercial sources. All experiments were conducted under an inert nitrogen atmosphere unless otherwise noted. ^{1}H-NMR spectra were recorded on a Varian 400 MHz , Jeol 300 MHz, or Bruker 300MHz Nuclear Magnetic Resonance Spectrometer. ^{1}H-NMR spectra were recorded in $CDCl_3$, CD_3OD or DMSO-d_6 and chemical shifts are reported relative to the residual solvent peak. The following abbreviations were used to assign spectra: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet. Mass spectral analysis was conducted on a Waters Micromass ZQ instrument.

HPLC analysis was conducted according to one of the following or similar methods with the retention time (t_R) expressed in min at UV detection of 254 or 215 nM. HPLC Method 1: Waters Acquity UPLC with chromatography performed on an Acquity UPLC BEH C18 Column, 2.1 x 50 mm, 1.7 μm, with mobile phase gradient of 5 – 95 % acetonitrile in water with each containing 0.05% trifluoroacetic acid. HPLC Method 2: Agilent 1100 Series HPLC with chromatography performed on an Xbridge 150 x 4.6 mm, 5 μm C18 column with mobile phase gradient of 5 – 95 % acetonitrile in water with each containing 0.1% trifluoroacetic acid and flow rate of 1.5 mL/min. Method 3: As Method 2 with chromatography performed on a Waters 3.0 x 50 mm 3 μm C18 column with mobile phase gradient of 10 – 80% acetonitrile in water with each containing 0.0675% trifluoroacetic acid. Method 4: As Method 2 with chromatography performed on Halo 4.6 x 30mm, 2.7 μm C18 column with mobile phase gradient of 5 – 95 % acetonitrile in water with each containing 0.05% trifluoroacetic acid and flow rate of 1.5 mL/min. Method 5: As Method 2 with chromatography performed on an Xbridge 4.6 x 50 mm, 3.5 μm C18 column with mobile phase gradient of 5 – 95% acetonitrile in water with each containing 0.03% ammonium hydroxide and flow rate of 2 mL/min.

Purification was done by either silica gel flash chromatography with a Teledyne Isco CombiFlash Rf with RediSep Flash Columns using a gradient of ethyl acetate in heptanes or methanol in dichloromethane, or similar instrument, or reverse phase preparatory HPLC with either (Method 6) an Xbridge 19 x 50 mm, 5 μm C18 column with gradient of acetonitrile in water each containing 0.03% ammonium hydroxide at a flow rate of 25 mL/min; or (Method 7) a Phenomenex Luna (2) 21.2 x 150mm, 5μm C18 column using a gradient of 5 - 95% acetonitrile each with 0.1% formic acid; or (Method 8) a Kromasil Eternity-5-C18 150 x 30mm x 5 μm column with mobile phase gradient of 18 - 45% acetonitrile in water each containing 0.225% formic acid.

Purity was determined by HPLC and in all cases was >95%, except where otherwise noted. The synthesis of compounds noted to follow Method A either were carried out explicitly as shown for Method A or a minor variation of Method A due to functional group compatibility or ease of synthesis. Reaction conditions and yields were not optimized.

For experiments involving the use of animals, all procedures were carried out in compliance with the NIH Guide for the Care and Use of Laboratory Animals under a protocol approved by the Institutional (Pfizer Worldwide Research and Development) Animal Care and Use Committee.

Typical Procedure (Method A) Featuring an SNAr Mechanistic Step for Formation of Biaryl Ether. (E)-3-(Ethoxycarbonyl)-4-(5-methylfuran-2-yl)but-3-enoic acid (11). To a vigorously stirred solution of 5-methyl-2-furaldehyde (264 mL, 2.65 mol) and diethyl succinate (840 mL, 5.05 mol) in ethanol (1.82 L) at room temperature was added sodium ethoxide (0.93 L of a 21 weight % solution in ethanol) in one portion. The reaction mixture was then heated at reflux for 13 hours. After cooling to room temperature, the mixture was concentrated *in vacuo*. The resulting residue was partitioned between ethyl acetate (1 L) and hydrochloric acid (1 L of a 2M aqueous solution). After separation, the aqueous layer was extracted with ethyl acetate (2 x 1 L). The combined organic extracts were then extracted with sodium hydrogen carbonate (2 x 1 L of a saturated aqueous solution). These aqueous extracts were combined and adjusted to pH 2 with hydrochloric acid (2 M aqueous solution) then extracted with ethyl acetate (2 x 1 L). These organic extracts were combined and concentrated *in vacuo* to afford desired product (34.3g, 5% yield). The original organic extract was extracted with sodium hydroxide (2 L of a 2 M aqueous solution). This aqueous extract was adjusted to pH 2 with hydrochloric acid (2 M aqueous solution) then extracted with ethyl acetate (2 x 1 L). These organic extracts were combined and concentrated *in vacuo* to give additional desired material (395 g, 63%) as a red liquid. ^{1}H NMR (400MHz, DMSO-d_6) δ 12.30 (br. s, 1H), 7.38 (s, 1H), 6.85 (d, J = 3.2 Hz, 1H), 6.29 (d, J = 3.2 Hz, 1H), 4.18-4.13 (m, 2H), 4.07-3.99 (q, J = 7.2 Hz, 2H), 1.25-1.20 (m, 3H), 1.16 (t, J = 7.2 Hz, 3H); MS(ES$^+$): *m/z* 261 (M+Na).

Ethyl 4-acetoxy-2-methylbenzofuran-6-carboxylate (12). To a vigorously stirred solution of **11** (327 g, 1.37 mol) in acetic anhydride (1.77 L, 18.7 mol) at room temperature was added sodium acetate (193 g, 2.35 mol) in one portion. The reaction mixture was then heated at reflux for 2.5 h. After cooling to room temperature, the mixture was concentrated *in vacuo*. The resulting residue was suspended in DCM (1.5 L) and filtered, washing the solids with DCM (3 x 500 mL). The combined filtrate and washings were then washed with sat. aq. $NaHCO_3$ (2 x 1 L) and brine (2 L), then concentrated *in vacuo* to give desired material (549 g) in quantitative yield. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.63 (s, 1H), 6.31 (s, 1H), 4.40-4.35 (q, J = 7.2 Hz, 2H), 2.47 (s, 3H), 2.37 (s, 3H), 1.39 (t, J = 7.2 Hz, 3H); MS(ES$^+$): *m/z* 263 (M+1).

Ethyl 4-hydroxy-2-methylbenzofuran-6-carboxylate (13). To a stirred solution of **12** (549 g, 1.37 mol) in ethanol (4.00 L) at room temperature was added potassium carbonate (266 g, 1.92 mol) in one portion. The reaction mixture was then heated at 60 °C for 3 h. Potassium carbonate (100 g, 0.720 mol) was then added in one portion and the reaction mixture was heated at 60 °C for a further 3 h. After cooling to room temperature the mixture was diluted with DCM (2 L) and the suspension filtered, washing the solids with DCM (2 x 1 L). The combined filtrate and washings were then washed with citric acid (2.5 L of a 1 M aqueous solution), then concentrated *in vacuo* and the resulting residue purified by flash chromatography (hexane then 2:1

hexane:ethyl acetate). All fractions containing the desired product were combined and concentrated *in vacuo*. The resulting residue, which solidified upon standing, was slurried with cold toluene and filtered. The solids were then stirred with hot toluene and decolorizing charcoal for 1 h, followed by filtration of the hot mixture through a pad of celite. The filtrate was allowed to cool and the resulting precipitate isolated by filtration to give desired material as orange powder (360 g) in 90% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.42 (s, 1H), 6.50 (s, 1H), 6.11 (s, 1H), 4.41-4.35 (q, J = 7.2 Hz, 2H), 2.46 (s, 3H), 1.39 (t, J = 7.2 Hz, 3H); MS(ES^+): *m/z* 221.1 (M+1).

5-Chloropyrazine-2-carbonyl chloride (15). 5-chloropyrazine-2-carboxylic acid (**14**) (1.00 g, 6.31 mmol) in DCM (30 mL) was treated with a catalytic amount of DMF, followed by $(COCl)_2$ (0.85 mL, 9.46 mmol). The resulting mixture was stirred for 18 h. The reaction was concentrated *in vacuo* to give desired material as solid (1.05 g) in quantitative yield.

5-Chloro-*N*,*N*-dimethylpyrazine-2-carboxamide (16). 15 (2.13 g, 12.1 mmol) and dimethylamine hydrochloride (1.06 g, 12.7 mmol) were suspended in DCM (50 mL) with stirring. Triethylamine (5.04 mL, 36.2 mmol) in DCM (25 mL) was added dropwise at 0 ºC to the reaction mixture. The combined solution was warmed up to ambient temperature and stirred for 4 h. The reaction was diluted with DCM, washed with 1N HCl, water, and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash chromatography (gradient of 30 to 80% ethyl acetate in heptane) to provide desired material (2.24g) in 85% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.74 (d, J = 1.37 Hz, 1H), 8.53 (d, J = 1.37 Hz, 1H) 3.15 (s, 3H) 3.12 (s, 3H); MS($APCI^+$): *m/z* 186.1 (M+1).

Ethyl 4-(5-(dimethylcarbamoyl)pyrazin-2-yloxy)-2-methylbenzofuran-6-carboxylate (17). A flask was charged with **13** (6.07 g, 27.6 mmol), **16** (5.06 g, 27.3 mmol), and cesium carbonate (9.78 g, 30 mmol) and then the solids were dissolved in DMF (60 mL). The reaction was heated to 90 ºC for 3 h before cooling to room temperature and removing the DMF *in vacuo*. The crude reaction mixture was partitioned between ethyl acetate (100 mL) and water (30 mL). The aqueous layer was extracted with ethyl acetate (50 mL). The combined organic layer was washed with water and then brine, dried over sodium sulfate, and concentrated *in vacuo*. The crude product was purified by silica gel flash chromatography (30 to 80 % gradient of ethyl acetate in heptane) to give desired material as a light brown solid (8.3 g) in 95% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.48 (d, J = 1.17 Hz, 1H) 8.41 (d, J = 0.98 Hz, 1H) 8.04 (t, J = 1.07 Hz, 1H) 7.71 (d, J = 1.17 Hz, 1H) 6.16 - 6.21 (m, 1H) 4.38 (q, J = 7.22 Hz, 2H) 3.17 (s, 3H) 3.14 (s, 3H) 2.45 (d, J = 1.17 Hz, 3H) 1.38 (t, J = 7.12 Hz, 3H); MS(ES^+): *m/z* 370.1 (M+1).

4-(5-(Azetidine-1-carbonyl)pyrazin-2-yloxy)-2-methyl-*N*-(5-methylpyrazin-2-yl)benzofuran-6-carboxamide (18). 2-amino-5-methylpyrazine (6.86 g, 62.8 mmol) was taken up in dimethoxyethane (70 mL) and cooled to 0 ºC. Dimethylaluminium chloride (131 mL, 131 mmol, 1 M in hexane) was added dropwise. The resulting mixture was warmed up to ambient temperature and stirred for 30 min. **17** (10.1 g, 27.3 mmol) in dimethoxyethane (70 mL) was then added to the activated amine solution *via* cannula. The combined solution was heated to reflux for 18 h. The reaction was then cooled in an ice bath and slowly quenched by the dropwise addition of aqueous Rochelle's salt (concentrated, 300 mL). The mixture was stirred for 20 min and then the layers separated. The organic layer was washed with aqueous Rochelle's salt (30 mL), 1N HCl (30 mL), and brine (30 mL), and then dried over sodium sulfate, and

concentrated *in vacuo*. The crude product was purified by silica gel flash chromatography (gradient of ethyl acetate from 50-100% in heptane) to give desired material as a solid (8.5 g) in 72% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ 9.57 (d, *J* = 1.37 Hz, 1H) 8.49 (d, *J* = 1.37 Hz, 1H) 8.45 (d, *J* = 1.37 Hz, 1H) 8.42 (s, 1H) 8.14 (dd, *J* = 1.56, 0.59 Hz, 1H) 7.91 - 7.94 (m, 1H) 7.62 (d, *J* = 1.37 Hz, 1H) 6.22 (t, *J* = 0.98 Hz, 1H) 3.18 (s, 3H) 3.15 (s, 3H) 2.55 (s, 3H) 2.48 (d, *J* = 1.17 Hz, 3H); MS(ES$^+$): *m/z* 433.1 (M+1), MS(ES$^-$): *m/z* 431.1 (M-1).

Typical Procedure (Method B) Featuring Palladium-mediated Formation of Biaryl Ether. 5-Bromopicolinoyl chloride (20). To a room temperature suspension of 5-bromopicolinic acid (**19**) (10.0 g, 49.5 mmol) in DCM (50 mL), oxalyl chloride (6.68 mL, 74.3 mmol) was added followed by 2 drops of DMF. The reaction was stirred for 18 h before concentrating under reduced pressure and drying overnight on the vacuum pump. This gave a greater than theoretical amount (11.02 g) of **20** as an oil, which was carried on as is. A small amount dissolved in MeOH shows the methyl ester mass: MS(ES$^+$): *m/z* 216.1 (M+1) for methyl ester.

5-Bromo-*N*,*N*-dimethylpicolinamide (21). 20 (actual 5.51 g, theoretical 5.46 g, 24.7 mmol) was dissolved in DCM (25 mL) and Et_3N (10.5 mL, 75.0 mmol) was added followed by portionwise dimethylamine hydrochloride (2.06 g, 25.0 mmol). The reaction was stirred at room temperature for 4 h before diluting with DCM and washing with water and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to provide **21** (3.64 g) in 64% two-step yield. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.64 (d, *J* = 1.6 Hz, 1H), 7.92 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.57 (d, *J* = 8.2 Hz, 1H), 3.12 (s, 3H), 3.09 (s, 3H); MS(ES$^+$): *m/z* 229.1 (M+1).

Ethyl 4-(6-(dimethylcarbamoyl)pyridin-3-yloxy)-2-methylbenzofuran-6-carboxylate (25). **21** (1.11 g, 4.85 mmol) was combined with **13** (1.12 g, 5.08 mmol), $Pd(OAc)_2$ (112 mg, 0.484 mmol), 2-di-tert-butylphosphino-2',4',6'-triisopropylbiphenyl (212 mg, 0.484 mmol), K_3PO_4 (2.09 g, 9.67 mmol), and toluene (20 mL) and refluxed for 24 h. After cooling, the contents were filtered through a pad of celite, washing with ethyl acetate. The filtrate was concentrated under reduced pressure and purified by silica gel flash chromatography (ethyl acetate/heptane) to afford **25** (144 mg) as a yellow solid in 8% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.34 (d, *J* = 2.34 Hz, 1H); 7.95 - 8.02 (m, 1H), 7.65 (d, *J* = 8.59 Hz, 1H), 7.57 (d, *J* = 1.17 Hz, 1H), 7.22 - 7.33 (m, 1H), 6.23 (t, *J* = 0.98 Hz, 1H), 4.37 (q, *J* = 7.03 Hz, 2H), 3.09 - 3.17 (m, 6H), 2.44 (d, *J* = 0.98 Hz, 3H), 1.37 (t, *J* = 7.12 Hz, 3H); MS(ES$^+$): *m/z* 369.3 (M+1).

***N*,*N*-Dimethyl-5-(2-methyl-6-((5-methylpyrazin-2-yl)carbamoyl)benzofuran-4-yloxy)picolinamide (27).** 2-Amino-5-methylpyrazine (42.6 mg, 0.390 mmol) was dissolved in dimethoxyethane (1 mL). The temperature was brought to 0 °C and dimethylaluminum chloride (0.974 mL, 0.974 mmol, 1 M in hexanes) was added. The resulting mixture was warmed to room temperature and stirred for 30 min. This solution was then added to a solution of **25** (72 mg, 0.20 mmol) in dimethoxyethane (2 mL) and then this was refluxed for 18 h. The solution was then cooled to room temperature and quenched by the slow addition of 1 M aq. Rochelle's salt. After stirring for 15 min, the product was extracted into two portions of ethyl acetate. The combined organic layers were washed with 1 M citric acid and brine, and then dried over $MgSO_4$. After concentrating under reduced pressure, the crude material was purified by reverse phase preparatory HPLC (Method 7) to afford desired material (19.5 mg) as an oil in 23% yield.

^{1}H NMR (400MHz, $CDCl_3$) δ 9.57 (d, *J* = 1.0 Hz, 1H), 8.54 (s, 1H), 8.39 (d, *J* = 2.7 Hz, 1H), 8.15 (s, 1H), 7.89 (s, 1H), 7.70 (d, *J* = 8.6 Hz, 1H), 7.49 (s, 1H), 7.33 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.28 (s, 1H), 3.17 (s, 3H), 3.15 (s, 3H), 2.57 (s, 3H), 2.49 (s, 3H); MS(ES^+): *m/z* 432.4 (M+1), MS(ES^-): *m/z* 430.3 (M-1).

Procedure Featuring Copper-mediated Formation of Biaryl Ether. 5-Bromopyrimidine-2-carbonyl chloride (23). Oxalyl chloride (32.0 mL, 369 mmol) was added to a suspension of 5-bromo-pyrimidine-2-carboxylic acid (**22**) (50 g, 250 mmol) in DCM (820 mL) at room temperature followed by 2 drops of DMF. The reaction mixture was stirred under nitrogen for 2 h. Additional DMF (0.8 mL) was added to the reaction mixture. The acid dissolved completely after 30 min. The solvent was removed *in vacuo* to afford the crude desired material (55 g) in quantitative yield. A small amount dissolved in MeOH shows the methyl ester mass: MS(ES^+): *m/z* 217.1 (M+1) for methyl ester.

5-Bromo-*N*,*N*-dimethylpyrimidine-2-carboxamide (24). 23 (55 g, 250 mmol) was dissolved in THF (830 mL) and dimethylamine (2.0 M solution in THF) (373 mL, 745 mmol) was added portionwise at room temperature. The reaction was stirred at room temperature under nitrogen for 16 h before diluting with ethyl acetate (500 mL) and washing with water (500 mL). The aqueous layer was further extracted with DCM (5 x 500 mL). The combined organics were dried over $MgSO_4$, concentrated *in vacuo* and then suspended in mtbe (650 mL). The solution was then heated to reflux. The hot solution was allowed to cool overnight to afford a pink solid. The solid was filtered and washed with cold mtbe (100 mL). The solid was dried in a vacuum oven at 55 ^oC for 12 h to afford the desired material as a pink solid (44g) in 77% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.85 (s, 2H), 3.13 (s, 3H), 2.94 (s, 3H); MS(ES^+): *m/z* 230.1 (M+1).

Ethyl 4-(2-(dimethylcarbamoyl)pyrimidin-5-yloxy)-2-methylbenzofuran-6-carboxylate (26). A mixture of Cs_2CO_3 (62.1 g, 191 mmol), **24** (24 g, 104 mmol), and **13** (20 g, 91 mmol); 1,10-phenanthroline (1.64 g, 9.07 mmol) and copper iodide (864 mg, 4.54 mmol) in DMF (200 mL) was purged with N_2 gas and then heated to 90 °C with mechanical stirring. At 18 h, the heterogeneous reaction mixture was cooled to 35 ^oC and diluted with ethyl acetate (300 mL). The mixture was filtered to remove any cesium carbonate. The filtrate was then partitioned between water (500 mL) and ethyl acetate (500 mL); however, no separation was observed. Concentrated HCl (20 mL) was added to the mixture. When the aqueous phase was about pH 1, the phases separated. The organic layer was removed and the aqueous layer re-extracted with ethyl acetate (2 x 500 mL). All organics were combined and back extracted with water (200 mL) and then brine (500mL). The organic layer was treated with activated charcoal (10 g) and magnesium sulfate. The mixture was allowed to stir for 10 min and then filtered through a plug of celite to afford a crude yellow solution. The filter cake was washed with ethyl acetate (100 mL). The combined organics were concentrated *in vacuo* to afford a crude solid this was dried under high vacuum for 4 d. The dry crude solid was triturated using methanol (80 mL). The solids were dispersed into a fine light orange powder with a red liquor. The solids were isolated by filtration and rinsed with methanol (20 mL). The solid was dried in the vacuum oven at 55 ^oC for 12 h to afford desired material as a yellow solid (18.2 g) in 54% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.50 (s, 2H), 8.06 (s, 1H), 7.62 (d, *J* = 1.17 Hz, 1H), 6.29 (s, 1H), 4.41 (d, *J* = 7.22 Hz, 2H), 3.17 (s, 3H), 3.00 (s, 3H), 2.50 (d, *J* = 0.98 Hz, 3H), 1.41 (t, *J* = 7.12 Hz, 3H); MS(ES^+): *m/z* 370.4 (M+1).

***N*,*N*-Dimethyl-5-(2-methyl-6-((5-methylpyrazin-2-yl)carbamoyl)-benzofuran-4-yloxy)pyrimidine-2-carboxamide (28).** To a solution of the 5-methyl-2-aminopyrazine (38.9 g, 356 mmol) in dimethoxyethane (315 mL) in a 3-neck flask equipped with overhead stirring and a condenser at 0 ^{o}C was added Me_2AlCl (1 M solution in hexanes) (715 mL). The mixture was warmed to room temperature and stirred for 1.5 h. In a separate flask, **26** (52.6 g, 142.5 mmol) was dissolved in dimethoxyethane (210 mL). This mixture was then added to the amine mixture. A gum precipitated and upon scratching the flask it dissipated into a solid. The reaction was refluxed for 3.5 h. Aq. Rochelle's salt (5 L) and 2-MeTHF (2 L) was added to the mixture and this was allowed to stir with overhead stirring for 14 h, after which time, a yellow solid precipitated. The solid was collected by filtration, washing with 2-MeTHF. The resulting solid was dried in a vacuum oven overnight to afford the desired material (50.0g) in 81% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ 9.54 (d, J = 1.56 Hz, 1H), 8.50 (s, 2H), 8.37 (s, 1H), 8.14 (d, J = 0.78 Hz, 1H), 7.88 - 7.92 (m, 1H), 7.52 (d, J = 1.37 Hz, 1H), 6.28 (t, J = 0.98 Hz, 1H), 3.14 (s, 3H), 2.98 (s, 3H), 2.55 (s, 3H), 2.49 (d, J = 1.17 Hz, 3H); MS(ES^+): *m/z* 433.4 (M+1), MS(ES^-): *m/z* 431.3 (M-1).

2-Methyl-*N*-(5-methylpyrazin-2-yl)-4-(*p*-tolyloxy)benzofuran-6-carboxamide (29). Preparation of this compound followed Method B. ^{1}H NMR (400MHz, $CDCl_3$) δ 9.56 (d, J = 1.2 Hz, 1H), 8.42 (s, 1H), 8.12 (s, 1H), 7.76 (s, 1H), 7.17 (d, J = 8.2 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 6.34 (s, 1H), 2.55 (s, 3H), 2.48 (s, 3H), 2.36 (s, 3H); MS(ES^+): *m/z* 374.3 (M+1).

2-Methyl-*N*-(5-methylpyrazin-2-yl)-4-(4-(methylsulfonyl)phenoxy)benzofuran-6-carboxamide (30). Preparation of this compound followed Method A. ^{1}H NMR (400MHz, $CDCl_3$) δ 9.58 (s, 1H), 8.40 (s, 1H), 8.16 (s, 1H), 7.84 - 8.00 (m, 3H), 7.51 (d, J = 1.0 Hz, 1H), 7.13 (d, J = 8.8 Hz, 2H), 6.27 (s, 1H), 3.09 (s, 3H), 2.57 (s, 3H), 2.50 (s, 3H); MS(ES^+): *m/z* 438.3 (M+1).

4-(4-Cyanophenoxy)-2-methyl-*N*-(5-methylpyrazin-2-yl)benzofuran-6-carboxamide (31). Preparation of this compound followed Method A. ^{1}H NMR (400MHz, $CDCl_3$) δ 9.58 (s, 1H), 8.40 (s, 1H), 8.16 (s, 1H), 7.90 (s, 1H), 7.64 (d, J = 8.8 Hz, 2H), 7.49 (s, 1H), 7.05 (d, J = 8.8 Hz, 2H), 6.24 (s, 1H), 2.57 (s, 3H), 2.49 (s, 3H); MS(ES^+): *m/z* 384.8 (M+1).

4-(4-(Dimethylcarbamoyl)phenoxy)-2-methyl-*N*-(5-methylpyrazin-2-yl)benzofuran-6-carboxamide (32). Preparation of this compound followed Method A. ^{1}H NMR (400MHz, MeOD-d_4) δ 9.33 (s, 1H), 8.32 (s, 1H), 7.99 (s, 1H), 7.54 (s, 1H), 7.48 (d, J = 8.5 Hz, 2H), 7.11 (d, J = 8.5 Hz, 2H), 6.35 (s, 1H), 3.10 (s, 3H), 3.06 (s, 3H), 2.53 (s, 3H), 2.48 (s, 3H); MS(ES^+): *m/z* 453.2 (M+Na).

***N*,*N*-Dimethyl-2-(2-methyl-6-((5-methylpyrazin-2-yl)carbamoyl)benzofuran-4-yloxy)pyrimidine-5-carboxamide (33).** Preparation of this compound followed Method A. ^{1}H NMR (400MHz, $CDCl_3$) δ 9.59 (d, J = 1.0 Hz, 1H), 8.69 (s, 2H), 8.52 (s, 1H), 8.15 (s, 1H), 7.96 (s, 1H), 7.66 (d, J = 1.0 Hz, 1H), 6.30 (s, 1H), 3.14 (s, 3H), 3.11 (s, 3H), 2.57 (s, 3H), 2.49 (s, 3H); MS(ES^+): *m/z* 433.5 (M+1), MS(ES^-): *m/z* 431.4 (M-1).

***N*-Ethyl-*N*-methyl-5-(2-methyl-6-((5-methylpyrazin-2-yl)carbamoyl)-benzofuran-4-yloxy)pyrazine-2-carboxamide (34).** Preparation of this compound followed Method A. ^{1}H

NMR (400MHz, $CDCl_3$) [mixture of rotomers at 23 °C] δ 9.58 (d, *J* = 1.2 Hz, 1H), 8.54 (s, 1H), 8.42 - 8.52 (m, 2H), 8.14 (s, 1H), 7.95 (s, 1H), 7.64 (s, 1H), 6.23 (s, 1H), 3.51 - 3.62 (m, 2H), 3.12 – 3.15 (m, 3H), 2.56 (s, 3H), 2.49 (s, 3H), 1.27 (t, *J* = 6.9 Hz, 3H); MS(APCI$^+$): *m/z* 447.3 (M+1), MS(APCI$^-$): *m/z* 445.4 (M-1).

***N*-Methyl-5-(2-methyl-6-((5-methylpyrazin-2-yl)carbamoyl)benzofuran-4-yloxy)pyrazine-2-carboxamide (35).** Preparation of this compound followed Method A. ^{1}H NMR (400MHz, $CDCl_3$) δ 9.59 (s, 1H), 8.90 (s, 1H), 8.44 (br. s., 1H), 8.42 (s, 1H), 8.16 (s, 1H), 7.96 (s, 1H), 7.65 (s, 2H), 6.20 (s, 1H), 3.06 (d, *J* = 5.1 Hz, 3H), 2.57 (s, 3H), 2.49 (s, 3H); MS(APCI$^+$): *m/z* 418.9 (M+1), MS(APCI$^-$): *m/z* 416.9 (M-1).

4-(5-(Azetidine-1-carbonyl)pyrazin-2-yloxy)-2-methyl-*N*-(5-methylpyrazin-2-yl)benzofuran-6-carboxamide (36). Preparation of this compound followed Method A. ^{1}H NMR (400MHz, $CDCl_3$) δ 9.56 (s, 1H), 8.82 (s, 1H), 8.68 (s, 1H), 8.40 (s, 1H), 8.11 (s, 1H), 7.95 (s, 1H), 7.64 (s, 1H), 6.17 (s, 1H), 4.69 (t, *J* = 7.7 Hz, 2H), 4.25 (t, *J* = 7.7 Hz, 2H), 2.54 (s, 3H), 2.46 (s, 3H), 2.38 (quin, 2H); MS(ES$^+$): *m/z* 445.4 (M+1), MS(ES$^-$): *m/z* 443.3 (M-1).

2-Methyl-*N*-(5-methylpyrazin-2-yl)-4-(5-(pyrrolidine-1-carbonyl)pyrazin-2-yloxy)benzofuran-6-carboxamide (37). Preparation of this compound followed Method A. ^{1}H NMR (400MHz, $CDCl_3$) δ 9.59 (s, 1H), 8.69 (s, 1H), 8.46 (s, 2H), 8.16 (s, 1H), 7.95 (s, 1H), 7.63 (s, 1H), 6.22 (s, 1H), 3.84 (t, *J* = 6.3 Hz, 2H), 3.71 (t, *J* = 6.4 Hz, 2H), 2.57 (s, 3H), 2.49 (s, 3H), 1.89 - 2.05 (m, 4H); MS(ES$^+$): *m/z* 459.1 (M+1), MS(ES$^-$): *m/z* 457.1 (M-1).

2-Methyl-*N*-(5-methylpyrazin-2-yl)-4-(5-(piperidine-1-carbonyl)pyrazin-2-yloxy)benzofuran-6-carboxamide (38). Preparation of this compound followed Method A. ^{1}H NMR (400MHz, $CDCl_3$) δ 9.59 (s, 1H), 8.40 - 8.51 (m, 3H), 8.16 (s, 1H), 7.95 (s, 1H), 7.64 (s, 1H), 6.25 (s, 1H), 3.75 (br. s., 2H), 3.56 (br. s., 2H), 2.57 (s, 3H), 2.50 (s, 3H), 1.50 - 1.81 (m, 6H); MS(APCI$^+$): *m/z* 472.8 (M+1), MS(APCI$^-$): *m/z* 470.9 (M-1).

2-Methyl-4-(5-(3-methylazetidine-1-carbonyl)pyrazin-2-yloxy)-*N*-(pyrazin-2-yl)benzofuran-6-carboxamide (39). Preparation of this compound followed Method A. ^{1}H NMR (400MHz, $CDCl_3$) δ 9.72 (d, *J* = 1.2 Hz, 1H), 8.84 (d, *J* = 1.2 Hz, 1H), 8.51 (s, 1H), 8.43 (d, *J* = 1.2 Hz, 1H), 8.40 (d, *J* = 2.3 Hz, 1H), 8.26 - 8.33 (m, 1H), 7.96 (s, 1H), 7.65 (d, *J* = 1.2 Hz, 1H), 6.20 (s, 1H), 4.80 (t, *J* = 9.2 Hz, 1H), 4.36 (t, *J* = 9.4 Hz, 1H), 4.25 (dd, *J* = 10.2, 5.6 Hz, 1H), 3.81 (dd, *J* = 10.4, 5.6 Hz, 1H), 2.74 - 2.90 (m, 1H), 2.49 (s, 3H), 1.32 (d, 3H); MS(ES$^+$): *m/z* 445.4 (M+1), MS(ES$^-$): *m/z* 443.3 (M-1).

4-(5-(3,3-Dimethylazetidine-1-carbonyl)pyrazin-2-yloxy)-2-methyl-N-(pyrazin-2-yl)benzofuran-6-carboxamide (40). Preparation of this compound followed Method A. ^{1}H NMR (400MHz, MeOD-d_4) δ 9.50 (d, *J* = 1.4 Hz, 1H), 8.68 (d, *J* = 1.2 Hz, 1H), 8.55 (d, *J* = 1.2 Hz, 1H), 8.39 - 8.46 (m, 1H), 8.34 (d, *J* = 2.5 Hz, 1H), 8.10 (s, 1H), 7.76 (d, *J* = 1.2 Hz, 1H), 6.35 (s, 1H), 4.41 (s, 2H), 3.88 (s, 2H), 2.48 (s, 3H), 1.34 (s, 6H); MS(ES$^+$): *m/z* 459.3 (M+1), MS(ES$^-$): *m/z* 457.4 (M-1).

4-(5-(3-Methoxyazetidine-1-carbonyl)pyrazin-2-yloxy)-2-methyl-*N*-(pyrazin-2-yl)benzofuran-6-carboxamide (41). Preparation of this compound followed Method A. ^{1}H

NMR (400MHz, $CDCl_3$) δ 9.72 (d, *J* = 1.2 Hz, 1H), 8.85 (d, *J* = 1.2 Hz, 1H), 8.53 (s, 1H), 8.44 (d, *J* = 1.2 Hz, 1H), 8.40 (d, *J* = 2.5 Hz, 1H), 8.26 - 8.33 (m, 1H), 7.97 (s, 1H), 7.65 (d, *J* = 1.2 Hz, 1H), 6.20 (s, 1H), 4.86 (ddd, *J* = 11.2, 6.2, 1.3 Hz, 1H), 4.51 - 4.59 (m, 1H), 4.36 - 4.45 (m, 1H), 4.25 - 4.34 (m, 1H), 4.12 (dt, *J* = 11.1, 1.9 Hz, 1H), 3.36 (s, 3H), 2.50 (s, 3H); MS(ES^+): *m/z* 461.3 (M+1), MS(ES^-): *m/z* 459.3 (M-1).

4-(5-(3-Hydroxy-3-methylazetidine-1-carbonyl)pyrazin-2-yloxy)-2-methyl-*N*-(pyrazin-2-yl)benzofuran-6-carboxamide (42). Preparation of this compound followed Method A. ^1H NMR (400MHz, $CDCl_3$) δ 9.72 (d, *J* = 1.2 Hz, 1H), 8.86 (d, *J* = 1.2 Hz, 1H), 8.53 (s, 1H), 8.44 (d, *J* = 1.2 Hz, 1H), 8.40 (d, *J* = 2.5 Hz, 1H), 8.27 - 8.33 (m, 1H), 7.96 (s, 1H), 7.65 (d, *J* = 1.0 Hz, 1H), 6.20 (s, 1H), 4.62 (s, 2H), 4.18 (s, 2H), 2.49 (s, 3H), 1.62 (s, 3H); MS(ES^+): *m/z* 461.3 (M+1), MS(ES^-): *m/z* 459.3 (M-1). HPLC purity = 88% (Method 2, t_R = 0.41 min).

2-Methyl-4-[5-(2-oxa-6-aza-spiro[3.3]heptane-6-carbonyl)-pyrazin-2-yloxy]-benzofuran-6-carboxylic acid pyrazin-2-ylamide (43). Preparation of this compound followed Method A. ^1H NMR (400MHz, DMSO-d_6) δ 11.16 (s, 1H), 9.42 (d, *J* = 1.1 Hz, 1H), 8.69 (d, *J* = 1.1 Hz, 1H), 8.62 (s, 1H), 8.48 (d, *J* = 1.6 Hz, 1H), 8.42 (d, *J* = 2.4 Hz, 1H), 8.24 (s, 1H), 7.83 (d, *J* = 1.0 Hz, 1H), 6.50 (s, 1H), 4.70 (s, 6H), 4.26 (s, 2H), 2.47 (s,3H); MS(ES^+): *m/z* 472.9 (M+1).

***N*,*N*-Dimethyl-5-(2-methyl-6-((5-methylpyridin-2-yl)carbamoyl)benzofuran-4-yloxy)pyrazine-2-carboxamide (44).** Preparation of this compound followed Method A. ^1H NMR (400MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.49 (d, *J* = 1.13 Hz, 1H), 8.44 (d, *J* = 1.13 Hz, 1H), 8.28 (d, *J* = 8.48 Hz, 1H), 8.09 (s, 1H), 7.95 (s, 1H), 7.63 (d, *J* = 0.94 Hz, 1H), 7.57 (dd, *J* = 8.48, 1.13 Hz, 1H), 6.21 (s, 1H), 3.18 (s, 3H), 3.14 (s, 3H), 2.47 (s, 3H), 2.31 (s, 3H); MS(ES^+): *m/z* 432.0 (M+1).

***N*,*N*-Dimethyl-5-(2-methyl-6-(pyrazin-2-ylcarbamoyl)benzofuran-4-yloxy)pyrazine-2-carboxamide (45).** Preparation of this compound followed Method A. ^1H NMR (400MHz, $CDCl_3$) δ 9.72 (s, 1H), 8.44 - 8.57 (m, 3H), 8.41 (d, *J* = 2.1 Hz, 1H), 8.30 (s, 1H), 7.96 (s, 1H), 7.65 (s, 1H), 6.25 (s, 1H), 3.20 (s, 3H), 3.17 (s, 3H), 2.50 (s, 3H); MS(ES^+): *m/z* 419.1 (M+1), MS(ES^-): *m/z* 417.1 (M-1).

5-(6-((5-Methoxypyrazin-2-yl)carbamoyl)-2-methylbenzofuran-4-yloxy)-*N*,*N*-dimethylpyrazine-2-carboxamide (46). Preparation of this compound followed Method A. ^1H NMR (400MHz, $CDCl_3$) δ 9.21 (d, *J* = 1.2 Hz, 1H), 8.51 (d, *J* = 1.2 Hz, 1H), 8.46 (d, *J* = 1.4 Hz, 1H), 8.36 (s, 1H), 7.96 (d, *J* = 1.2 Hz, 1H), 7.94 (s, 1H), 7.63 (d, *J* = 1.2 Hz, 1H), 6.24 (s, 1H), 4.00 (s, 3H), 3.20 (s, 3H), 3.17 (s, 3H), 2.50 (s, 3H); MS($APCI^+$): *m/z* 448.9 (M+1), MS($APCI^-$): *m/z* 446.9 (M-1).

***N*,*N*-Dimethyl-5-(2-methyl-6-((5-(trifluoromethyl)pyrazin-2-yl)carbamoyl)benzofuran-4-yloxy)pyrazine-2-carboxamide (47).** Preparation of this compound followed Method A. ^1H NMR (400MHz, $CDCl_3$) δ 9.81 (s, 1H), 8.75 (s, 1H), 8.65 (s, 1H), 8.51 (d, *J* = 1.2 Hz, 1H), 8.49 (d, *J* = 1.2 Hz, 1H), 7.98 (s, 1H), 7.66 (d, *J* = 1.2 Hz, 1H), 6.26 (s, 1H), 3.21 (s, 3H), 3.17 (s, 3H), 2.51 (s, 3H); MS(ES^+): *m/z* 487.4 (M+1), MS(ES^-): *m/z* 485.4 (M-1).

5-(6-((5-Ethylpyrazin-2-yl)carbamoyl)-2-methylbenzofuran-4-yloxy)-*N*,*N*-dimethylpyrazine-2-carboxamide (48). Preparation of this compound followed Method A. ^{1}H NMR (400MHz, $CDCl_3$) δ 9.61 (d, *J* = 1.2 Hz, 1H), 8.51 (d, *J* = 1.2 Hz, 1H), 8.47 (d, *J* = 1.2 Hz, 1H), 8.44 (s, 1H), 8.17 (s, 1H), 7.95 (s, 1H), 7.64 (d, *J* = 1.2 Hz, 1H), 6.24 (s, 1H), 3.20 (s, 3H), 3.17 (s, 3H), 2.86 (q, *J* = 7.6 Hz, 2H), 2.50 (s, 3H), 1.35 (t, 3H); MS(ES$^+$): *m/z* 447.3 (M+1), MS(ES$^-$): *m/z* 445.4 (M-1).

***N*,*N*-Dimethyl-5-(2-methyl-6-((1-methyl-1*H*-pyrazol-3-yl)carbamoyl)benzofuran-4-yloxy)pyrazine-2-carboxamide (49).** Preparation of this compound followed Method A. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.50 (d, *J* = 1.2 Hz, 1H), 8.44 (d, *J* = 1.2 Hz, 1H), 7.89 (s, 1H), 7.58 (d, *J* = 1.0 Hz, 1H), 7.30 (d, *J* = 2.1 Hz, 1H), 6.83 (d, *J* = 2.1 Hz, 1H), 6.22 (s, 1H), 3.81 (s, 3H), 3.20 (s, 3H), 3.16 (s, 3H), 2.48 (s, 3H); MS(ES$^+$): *m/z* 421.2 (M+1).

***N*,*N*-Dimethyl-5-(2-methyl-6-(pyrimidin-2-ylcarbamoyl)benzofuran-4-yloxy)pyrazine-2-carboxamide (50).** Preparation of this compound followed Method A. ^{1}H NMR (400MHz, $CDCl_3$) δ 9.72 (d, *J* = 1.4 Hz, 1H), 8.54 (s, 1H), 8.51 (d, *J* = 1.4 Hz, 1H), 8.47 (d, *J* = 1.2 Hz, 1H), 8.40 (d, *J* = 2.5 Hz, 1H), 8.24 - 8.33 (m, 1H), 7.96 (s, 1H), 7.65 (d, *J* = 1.2 Hz, 1H), 6.25 (s, 1H), 3.20 (s, 3H), 3.17 (s, 3H), 2.50 (s, 3H); MS(APCI$^+$): *m/z* 419.0 (M+1), MS(APCI$^-$): *m/z* 417.0 (M-1).