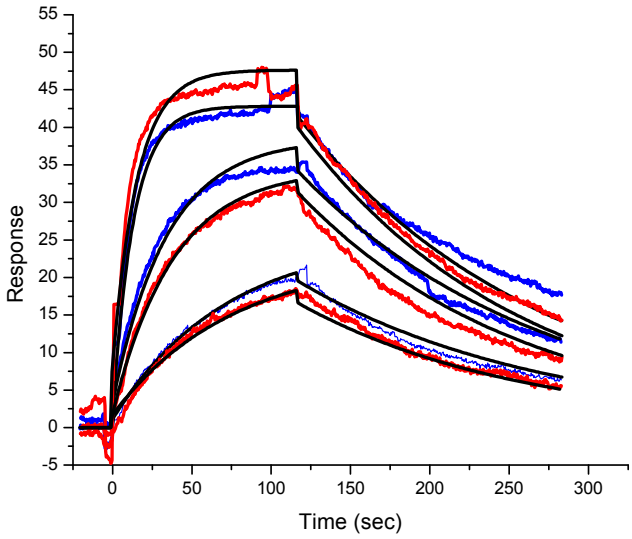
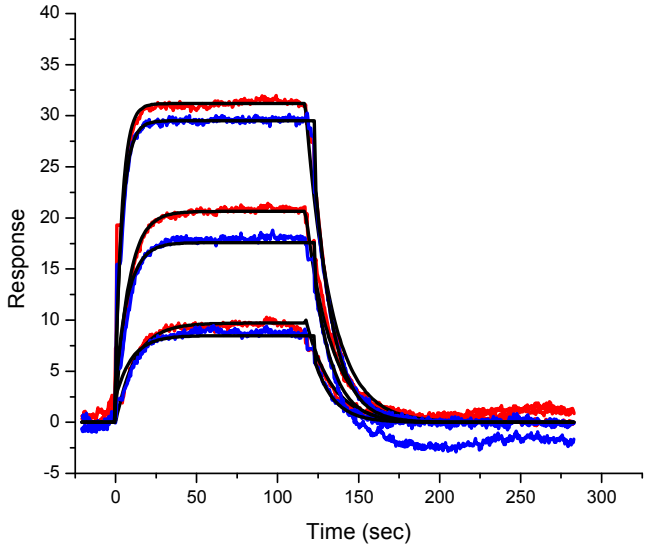
Supplementary Material

Figure S1 - SPR binding sensorgrams obtained at 3 concentrations and in duplicate are shown for two GKAs from Table 1 with different off rate kinetics, dissociative half-lives and hypoglycemic outcomes. (A) Sensorgrams overlaid for compound **6** at concentrations of 164nM, 55nM and 18nM in duplicate. Dissociative $t_{1/2}$, k_{on}, k_{off} and K_D were determined to be 105.5 sec, 3.76 x10^5 ($M^{-1}s^{-1}$), 6.57 x10^{-3} (s^{-1}) and 17.5 nM respectively; (B) Sensorgrams overlaid for compound **15** at concentrations of 500nM, 167nM and 56nM in duplicate. Dissociative $t_{1/2}$, k_{on}, k_{off} and K_D were determined to be 9.7 sec, 3.79 x10^5 ($M^{-1}s^{-1}$), 72.7 x10^{-3} (s^{-1}) and 189.2 nM respectively.



(A)



(B)

Figure S2 – Correlation plot of the logarithmic values of K_D vs. EC_{50} for compounds in Table 1. The K_D is determined by SPR in the presence of 50mM glucose while the EC_{50} is determined using a matrix bioassay at 22 different activator concentrations and 16 different glucose concentrations and is defined as the ligand concentration required to show a half maximal reduction in K_m as previously described.[9]

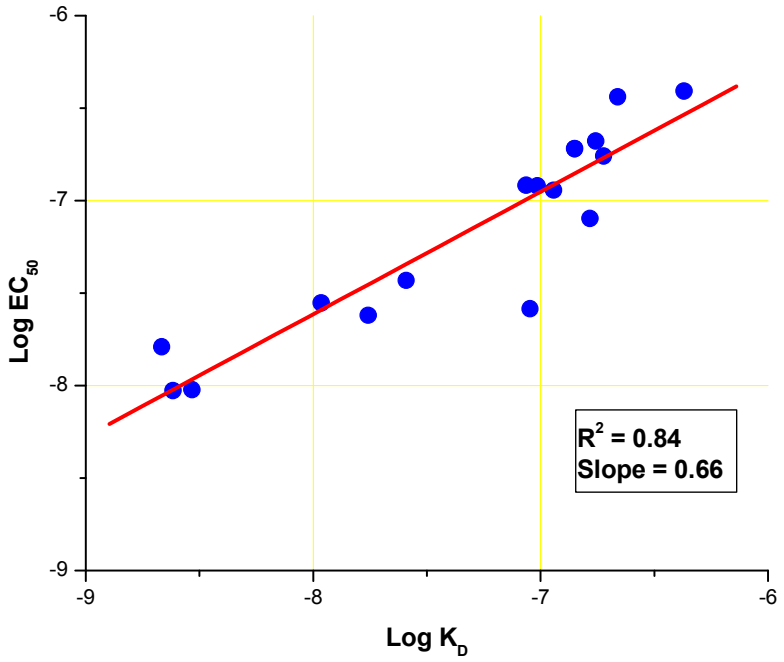


Table S1 – Comparison of off rates for human recombinant and rat recombinant glucokinase for compounds **6**, **7** and **15** as determined by SPR. Off rates for activators against human glucokinase were determined at 3 concentrations (164nM, 55nM and 18nM for cpd **6**, 1uM, 333nM and 111nM for cpd **7** and 500nM, 167nM and 56nM for cpd **15)** in duplicate. Off rates for activators against rat glucokinase were determined at 3 concentrations (164nM, 55nM and 18nM for cpd **6**, 1.48uM, 493nM and 164nM for cpd **7** and 500nM, 167nM and 56nM for cpd **15**) and N=1.

CPD	Human k_{off} (s^{-1}) x 10^{-3}	Rat k_{off} (s^{-1}) x 10^{-3}
6	**6.57**	**9.4**
7	**7.01**	**6.8**
15	**72.7**	**107**

Supporting Information

Surface Plasmon Resonance (SPR) Experimental Method

SPR experiments were performed to characterize the binding affinity of activators to human recombinant glucokinase and on a small group of activators to rat recombinant glucokinase. Measurements were conducted on a Biacore^{TM} 3000 instrument (GE Healthcare). Biotinylated glucokinase was expressed in *E. Coli*, and purified as previously described.[8,10] SPR binding experiments were carried out in duplicate at 3 ligand concentrations and in the presence of 50mM glucose and 10mM HEPES, pH 7.4, 150mM NaCl, 0.5mM TCEP, 0.05% P20, 1mg/mL BSA and 1% DMSO at 25ºC. Initially, human recombinant biotinylated glucokinase (3.7 mg/mL) was diluted 1:1000 in assay buffer and injected (flow rate 5 mL/min, contact time 100s) onto a streptavidin sensor chip to capture levels of protein ranging from 5000-6000 response units. Subsequently samples of glucokinase activators (300 mL) from Table 1, dimethyl sulfoxide (DMSO) standard curve samples and buffer blanks were transferred to a 96 deep well plate. All samples were injected at a flow rate of 50 mL/min and 120 s contact time. Data for the activators was collected in duplicate on the same chip surface. Binding responses were processed using Scrubber 2 (BioLogic Software Pty Ltd) to zero, x-align, double reference and correct for excluded volume effects of DMSO in the data. Kinetic parameters were obtained from global fits of the data to a simple 1:1 interaction model using Biaeval (GE Healthcare).

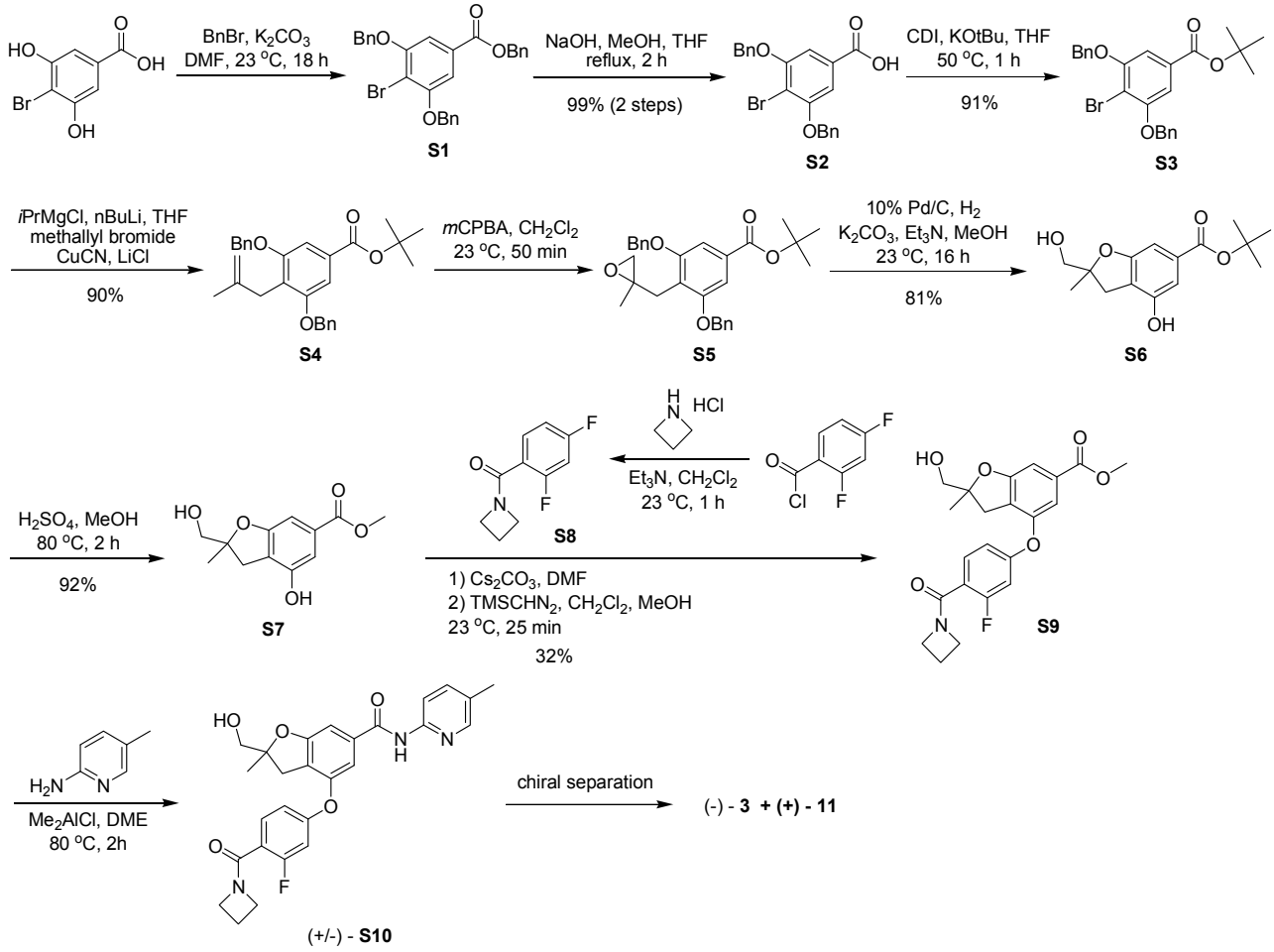
All procedures performed on any animals were in accordance with regulations and established guidelines and were reviewed and approved by a Pfizer Institutional Animal Care and Use Committee.

Synthesis of Compounds 3, 5, 6 and 11

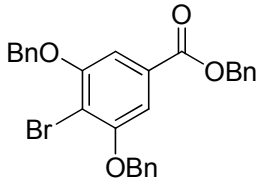
Acknowledgements: David J. Edmonds (Cambridge), Jianwei Bian (Groton), Martha Minich (Groton), Ru Zhou (La Jolla)

Experimental Section

All reagents and solvents were used as received from commercial sources. 1H-NMR spectra were recorded on a Varian 400 MHz Nuclear Magnetic Resonance Spectrometer. 1H-NMR spectra were recorded in $CDCl_3$ or CD_3OD 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, dd = doublet of doublets, m = multiplet, br. s = broad singlet. Mass spectral analysis was conducted on a Waters Micromass ZQ instrument. Achiral purification was done by 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 methanol in ethyl acetate, or isopropanol in ethyl acetate, or similar instrument. Purity was determined by LCMS and/or NMR integration and in all cases was >95%, except where otherwise noted. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Reaction conditions and yields were not optimized.

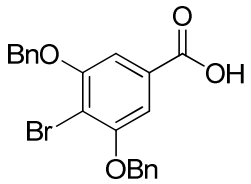


Benzyl 3,5-bis(benzyloxy)-4-bromobenzoate (S1)



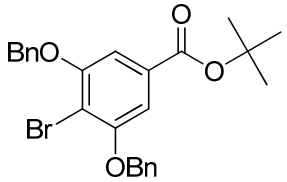
4-Bromo-3,5-dihydroxybenzoic acid (25.5 g, 109.4 mmol, 1.0 eq.) was dissolved in DMF. K_2CO_3 (76.4 g, 438 mmol, 5.0 eq.) was added in one portion causing some gas evolution. The reaction mixture was placed under an N_2 atmosphere and benzyl bromide (53.2 mL, 438 mmol, 4.0 eq.) was added over 5 min. The reaction was stirred at room temperature for 17 h. At this point additional DMF (50 mL) was added to improve stirring. TLC indicated incomplete reaction and so additional benzyl bromide (6.7 mL, 55 mmol, 0.5 eq.) was added and the reaction was warmed to 50 °C. After 1 h, the reaction was cooled to room temperature and poured into water (~400 mL). This was stirred for 15 min and then the solid was collected by filtration. The solid was dissolved in CH_2Cl_2 (1.2 L) and washed with water and brine. The organic layer was dried over $MgSO_4$ and concentrated to an off white solid which was dried under vacuum overnight with gentle warming. This provided desired material **S1** (59.2 g, theoretical maximum amount 55 g) still wet with solvent, which was carried onto the next step. **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.47 (d, J = 6.83 Hz, 4H), 7.27 - 7.42 (m, 13H), 5.33 (s, 2H), 5.19 (s, 4H).

3,5-Bis(benzyloxy)-4-bromobenzoic acid (S2)



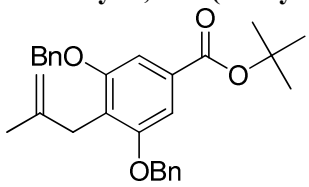
S1 (59.2 g crude weight, theoretically 55.0 g, 109.3 mmol, 1.0 eq.) was suspended in THF (200 mL) and MeOH (100 mL). A solution of NaOH (22.3 g, 546 mmol, 5.0 eq.) in water (100 mL) was added and the reaction mixture refluxed for 2 h. The mixture was cooled to room temperature and water (100 mL) was added. The organics were removed *in vacuo* and the resulting mixture extracted with petroleum ether. The aqueous layer was diluted with additional water (50 mL) and acidified to pH 1 with 6 N HCl. The solid was collected by filtration, washing with ethyl acetate. The solid was dissolved in a mixture of 2-MeTHF and ethyl acetate and washed with half brine/half water, followed by brine. The initial aqueous layer was further extracted with ethyl acetate (3 x 300 mL). All combined organics were dried over Na_2SO_4 and concentrated to give **S2** as a white solid (44.8 g, 99% over two steps). **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.49 (d, J = 7.22 Hz, 4H), 7.28 - 7.44 (m, 8H), 5.22 (s, 4H). **MS** *m/z* (–ESI) 411,413 $[M–H]^–$.

***tert*-Butyl 3,5-bis(benzyloxy)-4-bromobenzoate (S3)**



S2 (4.50 g, 10.9 mmol, 1.0 eq.) was suspended in THF (15 mL) and 1,1'-carbonyl diimidazole (1.80 g, 10.9 mmol, 1.0 eq.) was added. Gas evolved and the reaction became a solution. At 15 min, a second portion of 1,1'-carbonyl diimidazole (0.90 g, 5.5 mmol, 0.5 eq.) was added and the mixture stirred for 1 h. KO*t*Bu (1.93 g, 16.3 mmol, 1.5 eq.) was added and the mixture stirred at 50 °C for 80 min before cooling to room temperature. Water was added and the product extracted into MTBE. The organic layer was washed with 1 N HCl and brine, and dried over $MgSO_4$. The crude material was purified by silica gel flash chromatography (ethyl acetate / heptane) to afford **S3** (4.65 g, 91%) as a white solid. **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.46 - 7.51 (m, 4H), 7.35 - 7.41 (m, 4H), 7.28 - 7.34 (m, 2H), 7.23 (s, 2H), 5.19 (s, 4H), 1.56 (s, 9H).

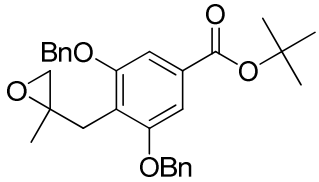
***tert*-Butyl 3,5-bis(benzyloxy)-4-(2-methylallyl)benzoate (S4)**



To a solution of *i*PrMgCl (2.0 M in THF, 7.4 mL, 9.88 mmol, 1.50 eq.) in THF (30 mL) at 0 °C was added nBuLi (2.5 M in hexanes, 11.9 mL, 29.7 mmol, 3.0 eq.). The mixture was stirred for 10 min and then cooled to –78 °C. After an additional 10 min, **S3** (4.64 g, 9.88 mmol, 1.0 eq.) was added, and the solution stirred for 40 mins. Methallyl bromide (5.14 mL, 49.4 mmol, 5.0 eq) was added neat, followed by copper (I) cyanide (0.274 g, 3.06 mmol, 0.31 eq.) and lithium chloride (0.254 g, 5.93 mmol, 0.6 eq.). After 10 min, the reaction was warmed to 0 °C before being quenched with sat. aq. NH_4Cl that was previously adjusted to pH 8 with NH_4OH. This was stirred at room temperature for 20 min and then extracted into MTBE. The organic layer was washed with additional pH 8 sat. aq. NH_4Cl, and brine, and dried over Na_2SO_4. This was combined with the crude material from a second reaction performed using 3.45 g **S3** and purified by silica gel flash chromatography (ethyl acetate / heptane) to give **S4** (6.86 g, 90% combined yield) as a light orange oil. **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.41 - 7.46 (m, 4H), 7.35 - 7.40 (m,

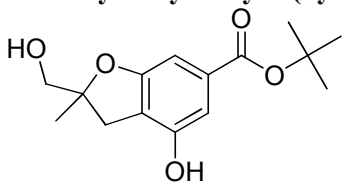
4H), 7.28 - 7.34 (m, 2H), 7.27 (s, 2H), 5.11 (s, 4H), 4.67 - 4.71 (m, 1H), 4.49 (s, 1H), 3.49 (s, 2H), 1.75 (s, 3H), 1.59 (s, 9H).

***tert*-Butyl 3,5-bis(benzyloxy)-4-((2-methyloxiran-2-yl)methyl)benzoate (S5)**



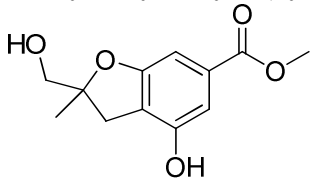
To a solution of **S4** (500 mg, 1.12 mmol, 1.0 eq.) in CH_2Cl_2 (5 mL) at room temperature was added *m*CPBA (388 mg, 1.69 mmol, 1.5 eq.) portionwise. The mixture was stirred for 30 min before another portion of *m*CPBA (240 mg, 0.54 mmol, 0.72 eq.) was added. After 20 min the reaction was diluted with MTBE (100 mL) and washed sequentially with portions of 10% $NaHSO_3$, 1:1 10% $NaHSO_3$: 5% Na_2CO_3, 5% Na_2CO_3 (x 2), and brine. The solution was dried over Na_2SO_4 and concentrated to give crude **S5** (540 mg, theoretical yield 518 mg) as a pale yellow oil which contained residual MTBE. **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.28 - 7.46 (m, 10H), 7.26 (s, 2H), 5.09 (s, 4H), 3.37 (dd, *J* = 12.98, 0.68 Hz, 1H), 2.78 (d, *J* = 13.08 Hz, 1H), 2.58 (d, *J* = 5.07 Hz, 1H), 2.40 (dd, *J* = 5.07, 0.78 Hz, 1H), 1.57 (s, 9H), 1.23 (s, 3H). **MS** *m/z* (+ESI) 461.5 $(M+H)^+$.

***tert*-Butyl 4-hydroxy-2-(hydroxymethyl)-2-methyl-2,3-dihydrobenzofuran-6-carboxylate (S6)**



To a solution of **S5** (3.48 g, 7.56 mmol, 1.0 eq.) in methanol under nitrogen was added K_2CO_3 (1.16 g, 8.31 mmol, 1.1 eq.) followed by 10% Pd on carbon (wet form, 1.1 g, 1.0 mmol, 0.14 eq.). The vessel was evacuated and purged with H_2 (40 psi) and shaken on a Parr shaker at room temperature. After 16 h, the reaction was diluted with ethyl acetate (100 mL) and filtered through celite. This filtrate was combined with that from a similar reaction done using 3.12 g **S5**. The combined filtrates were concentrated to a volume of ~20 mL, diluted with water (180 mL), and neutralized with 1 N HCl. This was extracted with ethyl acetate (5 x 200 mL) and the combined organics were sequentially washed with 0.5 N HCl (2 x 80 mL), sat. aq. $NaHCO_3$ (80 mL), and brine. The organics were dried over Na_2SO_4, concentrated, and combined with material from a third reaction performed using 0.250 g **S5**. This material was purified by silica gel flash chromatography (heptane / ethyl acetate) to give **S6** (3.37 g, 81% combined yield) as a white solid. **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.00 - 7.07 (m, 1H), 6.97 (s, 1H), 5.22 (br. s., 1H), 3.69 (dd, *J* = 11.90, 5.90 Hz, 1H), 3.61 (dd, *J* = 11.90, 7.20 Hz, 1H), 3.21 (d, *J* = 16.20 Hz, 1H), 2.86 (d, *J* = 16.00 Hz, 1H), 1.85 (t, 1H), 1.54 (s, 9H), 1.43 (s, 3H). **MS** *m/z* (+ESI) 281.4 $(M+H)^+$, (–ESI) 279.2 $(M–H)^–$.

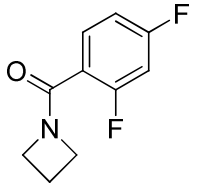
Methyl 4-hydroxy-2-(hydroxymethyl)-2-methyl-2,3-dihydrobenzofuran-6-carboxylate (S7)



S6 (1.25 g, 4.46 mmol, 1.0 eq.) was dissolved in anhydrous methanol (20 mL) and concentrated sulfuric acid (0.50 mL, 9.2 mmol, 2.1 eq.) was added. The mixture was stirred at 80 °C for 2 h before cooling and then solid $NaHCO_3$ was slowly added until gas evolution ceased. The mixture was diluted with water (~20 mL) and the methanol was removed *in vacuo*. The aqueous mixture was adjusted to pH 8 and

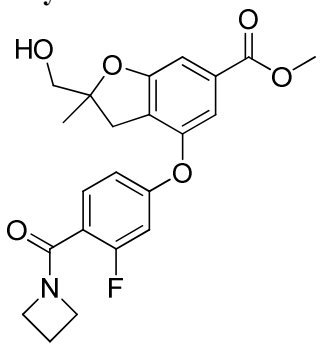
extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. Purification of the crude material by silica gel flash chromatography (heptane / ethyl acetate), followed by trituration with CH_2Cl_2 provided **S7** (0.974 g, 92%) as a white solid. **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.22 (br. s., 1H), 7.01 (s, 1H), 6.86 (s, 1H), 3.83 (s, 3H), 3.71 (d, *J* = 11.91 Hz, 1H), 3.60 (dd, *J* = 10.54, 5.66 Hz, 1H), 3.21 (d, *J* = 16.39 Hz, 1H), 3.01 (br. s., 1H), 2.83 (d, *J* = 16.20 Hz, 1H), 1.39 (s, 3H). **MS** *m/z* (+ESI) 239 $(M+H)^+$, (–ESI) 237 $(M–H)^–$.

Azetidin-1-yl(2,4-difluorophenyl)methanone (S8)



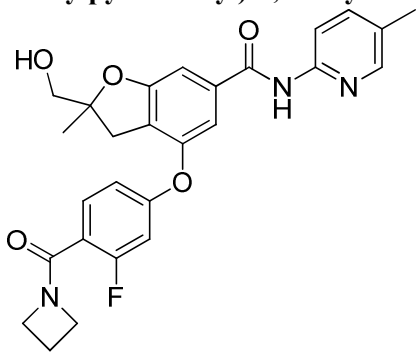
To a solution of 2,4-difluorobenzoyl chloride (1.14 g, 6.46 mmol, 1.0 eq.) in CH_2Cl_2 was added azetidine hydrochloride (1.46 g, 15.6 mmol, 2.4 eq.) and triethylamine (2.70 mL, 19.4 mmol, 3.0 eq.). The reaction was stirred at room temperature for 1 h before partitioning between dichloromethane (100 mL) and water (100 mL). The aqueous layer was back extracted with dichloromethane (100 mL) and the combined organics dried over $MgSO_4$ and concentrated to **S8** (0.896 g, 70%) as an off-white solid which was used without further purification. **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.52 - 7.59 (m, 1H) 6.91 - 6.98 (m, 1H) 6.81 - 6.87 (m, 1H) 4.21 (t, *J* = 7.71 Hz, 2H) 4.11 (t, *J* = 7.71 Hz, 2H) 2.30 - 2.38 (m, 2H).

Methyl 4-(4-(azetidine-1-carbonyl)-3-fluorophenoxy)-2-(hydroxymethyl)-2-methyl-2,3-dihydrobenzofuran-6-carboxylate (S9)



S7 (100 mg, 0.420 mmol, 1.0 eq.), **S8** (91 mg, 0.462 mmol, 1.1 eq.), and cesium carbonate (276 mg, 0.840 mmol, 2.0 eq.) were combined in a vial and DMF (0.6 mL) was added. The vial was purged with N_2, sealed and heated to 120 °C for 19 h. The reaction was cooled and water and ethyl acetate were added. The aqueous layer was acidified with 1 N HCl and extracted with ethyl acetate (x 6). The combined organics were washed with a mixture of brine and 1 N HCl, and then with brine. This was dried over Na_2SO_4 and concentrated *in vacuo*. LCMS of this crude product showed that mostly the carboxylic acid was present and so the material was dissolved in methanol (3 mL) and CH_2Cl_2 (3 mL) and TMS-diazomethane (2 M in hexanes, 0.21 mL, 0.420 mmol, 1.0 eq.) was added. After 25 min a few drops of trifluoroacetic acid were added and the reaction was concentrated. Purification by silica gel flash chromatography (heptane / ethyl acetate) afforded **S9** (55 mg, 32%) as a gum. **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.50 (dd, *J* = 8.49, 7.90 Hz, 1H), 7.23 - 7.24 (m, 1H), 7.19 (d, *J* = 1.37 Hz, 1H), 6.75 (dd, *J* = 8.59, 2.34 Hz, 1H), 6.64 (dd, *J* = 11.13, 2.34 Hz, 1H), 4.18 (t, *J* = 7.81 Hz, 2H), 4.08 - 4.14 (m, 2H), 3.85 (s, 3H), 3.68 (dd, *J* = 11.91, 5.66 Hz, 1H), 3.57 (dd, *J* = 11.81, 7.32 Hz, 1H), 3.14 (d, *J* = 16.79 Hz, 1H), 2.76 (d, *J* = 16.59 Hz, 1H), 2.26 - 2.35 (m, 2H), 1.98 - 2.04 (m, 1H), 1.41 (s, 3H). **MS** *m/z* (+ESI) 416 $(M+H)^+$.

(+/–)-4-(4-(Azetidine-1-carbonyl)-3-fluorophenoxy)-2-(hydroxymethyl)-2-methyl-*N*-(5-methylpyridin-2-yl)-2,3-dihydrobenzofuran-6-carboxamide (+/–) S10



5-Methylpyridin-2-amine (3.42 g, 31.6 mmol, 3.0 eq.) was dissolved in 1,2-dimethoxyethane (105 mL) and dimethylaluminum chloride (1.0 M in hexanes, 52.7 mL, 52.7 mmol, 5.0 eq.) was added. The mixture was stirred at room temperature for 20 min, at which point a solution of **S9** (4.375 g, 10.53 mmol, 1.0 eq.) in 1,2-dimethoxyethane (40 mL) was added. The mixture was heated to 80 ^{o}C for 2 h before cooling and quenching with sat. Rochelle's salt (50 mL). MTBE (100 mL) was added and stirred overnight at room temperature. The layers were separated and the aqueous layer extracted with ethyl acetate (200 mL x 7) and CH_2Cl_2 (200 mL). The combined organics were washed sequentially with brine adjusted to pH 4-5 with 10% citric acid, 1 N NaOH (100 mL x 3), sat. Rochelle's salt adjusted to pH 6 with HCl, and brine (100 mL x 2). This was dried over Na_2SO_4 and concentrated. Purification by silica gel flash chromatography (heptane / ethyl acetate) gave (+/–)-**S10** (4.71 g, corresponds to 4.31 g pure or 83% yield) as a white foam still wet with ethyl acetate (2 wt%) and CH_2Cl_2 (6 wt%) by NMR. **^{1}H NMR** (400 MHz; $CDCl_3$) δ 8.37 (s, 1 H), 8.19 (d, J=8.39 Hz, 1 H), 8.08 (dd, J=1.46, 0.88 Hz, 1 H), 7.53 (dd, J=8.39, 2.34 Hz, 1 H), 7.51 (dd, J=8.49, 7.90 Hz, 1 H), 7.10 (d, J=1.37 Hz, 1 H), 7.06 (d, J=1.37 Hz, 1 H), 6.76 (dd, J=8.59, 2.34 Hz, 1 H), 6.66 (dd, J=11.13, 2.34 Hz, 1 H), 4.19 (t, J=7.90 Hz, 2 H), 4.13 (t, J=7.22 Hz, 2 H), 3.71 (dd, J=11.81, 3.61 Hz, 1 H), 3.59 (dd, J=11.71, 6.05 Hz, 1 H), 3.15 (d, J=16.59 Hz, 1 H), 2.76 (d, J=16.59 Hz, 1 H), 2.26 - 2.36 (m, 5 H), 2.09 (t, J=5.37 Hz, 1 H), 1.43 (s, 3H). **MS** *m/z* (+ESI) 492.6 $(M+H)^+$, (–ESI) 490.6 $(M–H)^–$.

(+/–)-**S10** was purified by chiral SFC (Chiralpak1 AD-H, 21x250, 60:40 CO_2:EtOH, flow 65 mL/min, 180 Bar back pressure) to provide each enantiomer (Compounds **3** and **11**).

(–)-4-(4-(azetidine-1-carbonyl)-3-fluorophenoxy)-2-(hydroxymethyl)-2-methyl-*N*-(5-methylpyridin-2-yl)-2,3-dihydrobenzofuran-6-carboxamide (3)

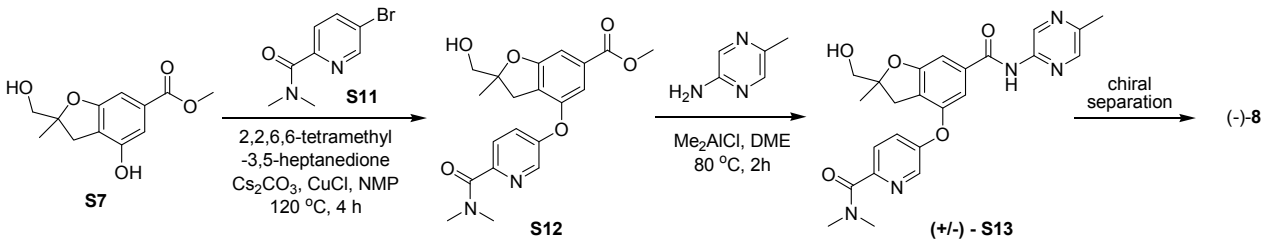
Peak 1 (R_t = 6.48 min; Chiralpak AD-H 4.6 mm x 25 cm, 60:40 CO_2:EtOH, flow 2.5 mL/min) corresponds to (–)-**3** (2.02 g with 0.4 eq. EtOH, >99%ee).

Optical rotation: $[\alpha]_D^{22}$ = –6.8 (c = 1.0, MeOH) and $[\alpha]_D^{22}$ = –9.3 (c = 1.0, $CHCl_3$).

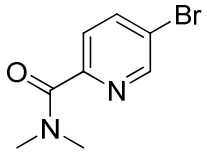
(+)-4-(4-(azetidine-1-carbonyl)-3-fluorophenoxy)-2-(hydroxymethyl)-2-methyl-*N*-(5-methylpyridin-2-yl)-2,3-dihydrobenzofuran-6-carboxamide (11)

Peak 2 (R_t = 7.87 min; Chiralpak AD-H 4.6 mm x 25 cm, 60:40 CO_2:EtOH, flow 2.5 mL/min) corresponds to (+)-**3** (1.94 g with 0.6 eq. EtOH, 98%ee).

Optical rotation: $[\alpha]_D^{22}$ = +9.3 (c = 1.0, MeOH) and $[\alpha]_D^{22}$ = +10.5 (c = 1.0, $CHCl_3$).

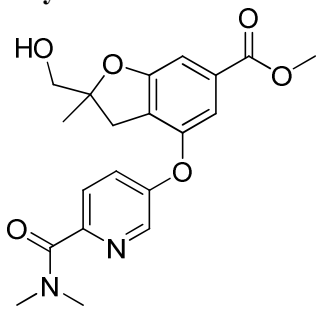


5-Bromo-*N*,*N*-dimethylpicolinamide (S11)



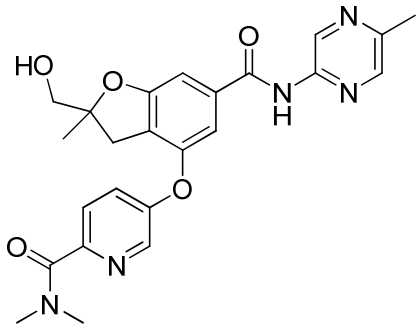
The synthesis of **S11** has been published previously.[9]

Methyl 4-(6-(dimethylcarbamoyl)pyridin-3-yloxy)-2-(hydroxymethyl)-2-methyl-2,3-dihydrobenzofuran-6-carboxylate (S12)



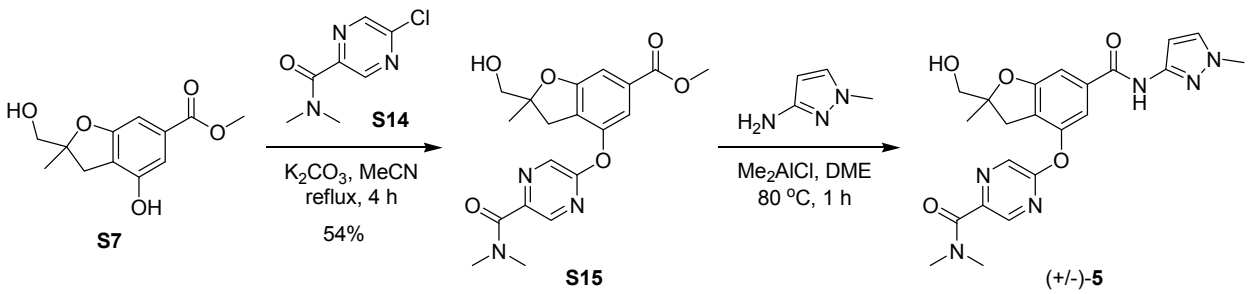
S7 (300 mg, 1.26 mmol, 1.0 eq.), **S11** (317 mg, 1.38 mmol, 1.1 eq.), and cesium carbonate (621 mg, 1.89 mmol, 1.5 eq.) were added to a vial followed by 1-methyl-2-pyrrolididone (2 mL). The vial was purged with N_2 and then 2,2,6,6-tetramethyl 3,5-heptanedione (0.134 mL, 0.629 mmol, 0.5 eq.) was added. Copper (I) chloride (62.9 mg, 0.629 mmol, 0.5 eq.) was added and the mixture heated at 120 °C. At 3 h, additional **S11** (58 mg, 0.252 mmol, 0.2 eq.) was added. After 1 h, the reaction was cooled and 1 N HCl was added. This was extracted with MTBE and the organic layer was washed with brine and dried over Na_2SO_4. Purification by silica gel flash chromatography (heptane / ethyl acetate) gave product that still contained NMP. The residue was placed on the Genevac which removed some of the solvent to then provide **S12** (340 mg, containing 0.72 eq. NMP by NMR) still with NMP which was utilized without additional purification. **^{1}H NMR** (400 MHz; $CDCl_3$) δ 8.31 (d, *J* = 2.73 Hz, 1H), 7.68 (d, *J*= 8.59 Hz, 1H), 7.30 (dd, *J* = 8.69, 2.83 Hz, 1H), 7.25 (d, *J* = 1.17 Hz, 1H), 7.17 (d, *J* = 1.17 Hz, 1H) 3.85 (s, 3H), 3.71 (d, *J* = 11.42 Hz, 1H), 3.59 (d, *J* = 12.49 Hz, 1H), 3.19 (d, *J* = 16.59 Hz, 1H), 3.13 (s, 3H), 3.12 (s, 3H), 2.81 (d, *J* = 16.59 Hz, 1H), 1.92 (br. s., 1H), 1.43 (s, 3H).

(+/–)-5-(2-(Hydroxymethyl)-2-methyl-6-(5-methylpyrazin-2-ylcarbamoyl)-2,3-dihydrobenzofuran-4-yloxy)-*N*,*N*-dimethylpicolinamide (+/–) – S13

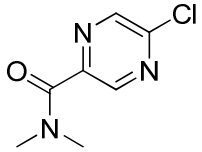


To a solution of 5-methylpyrazin-2-amine (123 mg, 1.12 mmol, 3.0 eq.) in 1,2-dimethoxyethane (3.75 mL) was added dimethylaluminum chloride (1.0 M in hexanes, 1.88 mL, 1.88 mmol, 5.0 eq.). This was stirred at room temperature for 40 min before adding a solution of **S12** (145 mg, 0.375 mmol, 1.0 eq.) in 1,2-dimethoxyethane. The mixture was heated to 80 ^{o}C for 2 h before cooling and slowly adding sat. Rochelle's salt (5 mL). This was stirred overnight before extracting with ethyl acetate (x 5). The combined organics were washed with brine that was adjusted to pH 3 with 10% citric acid (x 3) and then dried over Na_2SO_4. Purification by silica gel flash chromatography (isopropanol / ethyl acetate) gave product still contaminated with NMP. This was re-chromatographed (methanol / CH_2Cl_2) to afford desired product (+/–) - **S13** (175 mg) as a white solid. **^{1}H NMR** (400 MHz; $CDCl_3$) δ 9.44 (d, *J* = 1.56 Hz, 1H), 8.58 (s, 1H), 8.29 (d, *J* = 2.93 Hz, 1H), 8.07 (d, *J* = 0.98 Hz, 1H), 7.65 (d, *J* = 8.59 Hz, 1H), 7.29 (dd, *J* = 8.69, 2.83 Hz, 1H), 7.08 (d, *J* = 1.37 Hz, 1H), 7.04 (d, *J* = 1.37 Hz, 1H), 3.72 (dd, *J* = 12.00, 5.56 Hz, 1H), 3.57 (dd, *J* = 12.10, 7.42 Hz, 1H), 3.20 (d, *J* = 16.59 Hz, 1H), 3.11 (s, 3H), 3.09 (s, 3H), 2.88 (t, *J* = 6.54 Hz, 1H), 2.78 (d, *J* = 16.39 Hz, 1H), 2.50 (s, 3H), 1.42 (s, 3H). **MS** *m/z* (+ESI) 464.6 $(M+H)^+$, (– ESI) 462.6 $(M–H)^–$.
(+/–) - **S13** (110 mg) was purified by chiral SFC (Chiralcel OJ-H, 10 x 250, 75:25 CO_2:EtOH, flow 10 mL/min, 120 Bar back pressure) to provide each enantiomer.

(–)-5-(2-(Hydroxymethyl)-2-methyl-6-(5-methylpyrazin-2-ylcarbamoyl)-2,3-dihydrobenzofuran-4-yloxy)-*N*,*N*-dimethylpicolinamide (8)
Peak 2 (R_t = 5.30 min; Chiralcel OJ-H 4.6 mm x 25 cm, 75:25 CO_2:EtOH, flow 2.5 mL/min) corresponds to (–)-**8** (42.2 mg, >99%ee). **Optical rotation**: $[\alpha]_D^{22}$ = –16.0 (c = 1.06, MeOH).

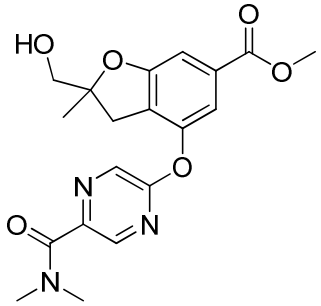


5-Chloro-*N*,*N*-dimethylpyrazine-2-carboxamide (S14)



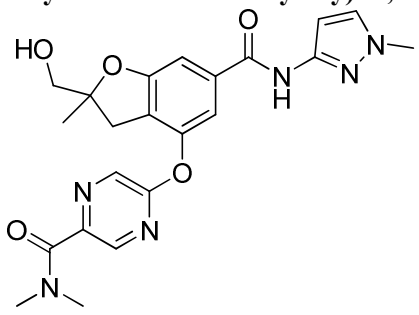
The synthesis of **S14** has been published previously.[9]

Methyl 4-(5-(dimethylcarbamoyl)pyrazin-2-yloxy)-2-(hydroxymethyl)-2-methyl-2,3-dihydrobenzofuran-6-carboxylate (S15)



To a solution of **S7** (150 mg, 0.535 mmol, 1.0 eq.) in anhydrous acetonitrile (5 mL) was added **S14** (104 mg, 0.562 mmol, 1.05 eq.) followed by potassium carbonate (747 mg, 5.35 mmol, 10 eq.) The mixture was refluxed for 4 h before cooling and filtering. The solid was washed with acetonitrile and the combined filtrates were concentrated and purified by silica gel flash chromatography (ethyl acetate) to afford **S15** (112 mg, 54%) as a white glass. **^{1}H NMR** (400 MHz; $CDCl_3$) δ 8.50 (s, 1H) 8.35 (s, 1H) 7.36 (s, 1H) 7.33 (s, 1H) 3.87 (s, 3H) 3.57-3.72 (AB, 2H) 3.16 (s, 3H), 3.14 (s, 3H), 2.75-3.12 (AB, 2H) 1.81-1.84 (m, 1H) 1.43 (s, 3H). **MS** *m/z* (+ESI) 387.8 $(M+H)^+$.

(+/–)-5-(2-(Hydroxymethyl)-2-methyl-6-(1-methyl-1*H*-pyrazol-3-ylcarbamoyl)-2,3-dihydrobenzofuran-4-yloxy)-*N*,*N*-dimethylpyrazine-2-carboxamide (+/–)-5



To a solution of 1-methyl-1*H*-pyrazol-3-amine (28 mg, 0.288 mmol, 3.0 eq.) in 1,2-dimethoxyethane (1 mL) was added dimethylaluminum chloride (1.0 M in hexanes, 0.480 mL, 0.480 mL, 5.0 eq.). This was stirred at room temperature for 40 min before adding a solution of **S15** (37 mg, 0.096 mmol, 1.0 eq.) in 1,2-dimethoxyethane. The mixture was heated to 80 ^{o}C for 1 h before cooling and sat. Rochelle's salt was slowly added. Additional ethyl acetate was added and the mixture stirred overnight. The mixture was transferred into a separatory funnel with water, ethyl acetate, a small amount of ethanol, and additional sat. Rochelle's salt. The organic layer was separated and filtered through an Alltech filter before concentrating and purifying by silica gel flash chromatography (methanol / ethyl acetate) to afford (+/–)-**5** (12.1 mg). **^{1}H NMR** (400 MHz; CD_3OD) δ 8.46 (s, 1H) 8.41 (s, 1H) 7.46 (s, 1H) 7.26 (s, 1H) 7.21 (s, 1H) 6.55 (s, 1H) 3.80 (s, 3H) 3.52-3.63 (AB, 2H) 3.11-3.15 (m, 7H) 2.74-2.78 (m, 1H) 1.41 (s, 3H). **MS** *m/z* (+ESI) 452.9 $(M+H)^+$.