Supporting Information

Discovery of Aryl Sulfonamides as Isoform-Selective Inhibitors of $Na_V1.7$ with Efficacy in Rodent Pain Models

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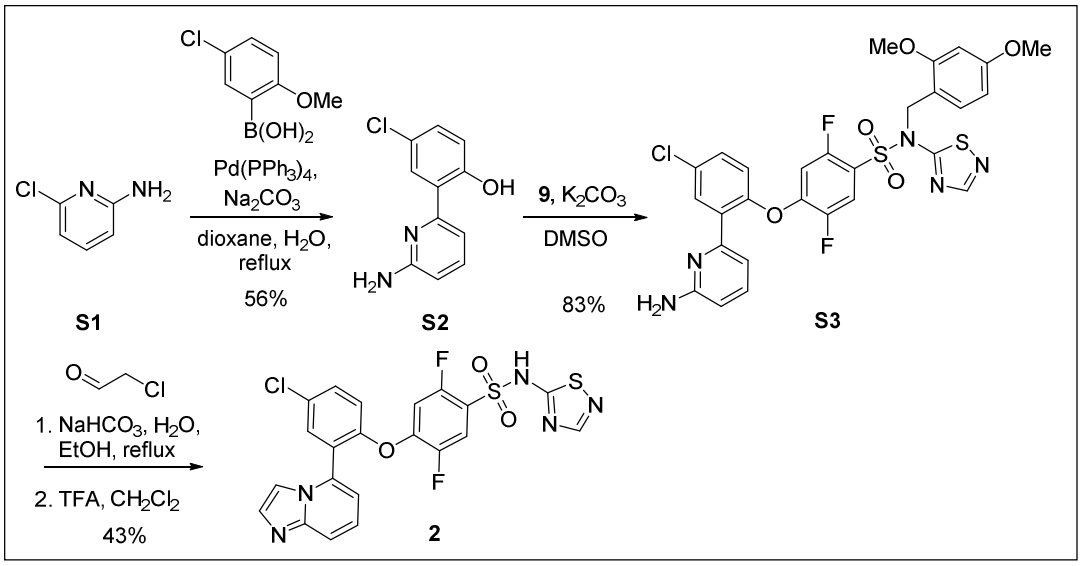
1. Chemistry

1.1 General Information.

Unless otherwise stated, commercially available reagents and solvents were used without purification. Yields were not optimized. Melting points were determined on a Büchi hot-stage apparatus and are uncorrected. NMR spectra were recorded on a Bruker Avance 300 spectrometer with chemical shifts (δ) reported in parts-per-million

(ppm) relative to the residual signal of the deuterated solvent. ^{1}H NMR, ^{19}F and ^{13}C NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet and br = broad), coupling constant in Hz, and number of protons, fluorine or carbon atoms. Mass spectra were obtained using a Waters 2795/Micromass Quattro LC/MS system (Waters Corporation). Purity was determined by HPLC analysis on Agilent 1100, 1200, or 1260 systems (Agilent Technologies) using a XBridge C-18 column (5 µm, 4.6 x 50 mm, Waters Corporation) with a 5−95% gradient over 5 min of CH_3CN in water containing 0.1% TFA at a flow rate of 1.0 mL/min at 25 ºC. Peaks were detected at a wavelength of 254 or 280 nm with an Agilent photodiode array detector. All compounds reported herein with biological data exhibited spectral data consistent with their proposed structures and had purities >95% as determined by HPLC unless otherwise stated. Preparative HPLC was performed on Water HPLC systems using a XBridge Prep C18 column (5 µm, 30 x 50 mm, Waters Corporation), a XSelect CSH Prep column (5 µm, 30 x 50 mm, Waters Corporation), or a Gemini-NX C18 column (5 µm, 150 x 50 mm, Phenomenex) with a 5−95% gradient of CH_3CN in water containing 0.1% TFA or formic acid, respectively. Elemental analyses were performed by Canadian Microanalysis Services Ltd. (Delta, BC, Canada). Chemical names were generated using ChemBioDraw version 14 by CambridgeSoft.

1.2 Synthesis of Compound 2.



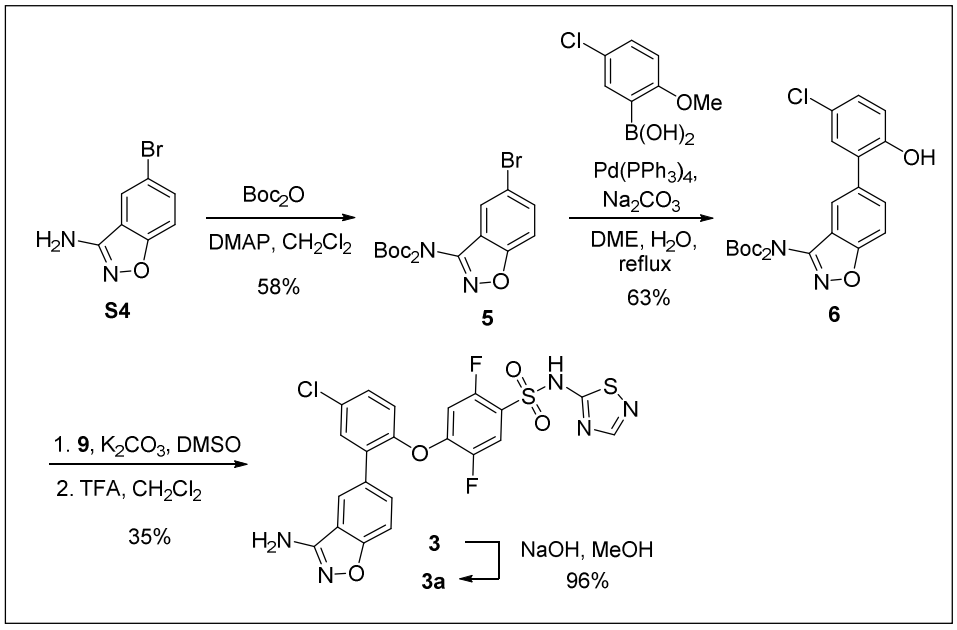
*2-(6-Aminopyridin-2-yl)-4-chlorophenol (**S2**).* To a stirred mixture of 2-amino-6-chloropyridine (0.26 g, 2.0 mmol), 5-chloro-2-hydroxyphenylboronic acid (0.35 g, 2.0 mmol) and 2 M aqueous Na_2CO_3 (3 mL, 6 mmol) in dioxane (6 mL) was added $Pd(PPh_3)_4$ (0.10 g, 0.086 mmol). The mixture was heated at 85 ℃ for 16 h, allowed to cool to ambient temperature and diluted with EtOAc (50 mL) and water (20 mL). The organic layer was separated, washed with brine, and dried over anhydrous Na_2SO_4.

After concentration *in vacuo*, the residue was purified by column chromatography (25-50% ethyl acetate in hexanes) to afford the title compound as a yellowish solid in 56 % yield (0.25 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 2.4 Hz, 1H), 7.57 (dd, J = 7.8, 7.8 Hz, 1H), 7.22–7.13 (m, 2H), 6.89 (d, J = 8.7 Hz, 1H), 6.46 (d, J = 8.4 Hz, 1H), 4.53 (s, 2H), (OH not observed).

*4-(2-(6-Aminopyridin-2-yl)-4-chlorophenoxy)-N-(2,4-dimethoxybenzyl)-2,5-difluoro-N-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (**S3**).* To a stirred mixture of **9** (0.41 g, 0.93 mmol) and K_2CO_3 (0.38 g, 2.8 mmol) in anhydrous DMSO (4 mL) was added phenol **S2** (0.19 g, 0.93 mmol). The reaction mixture was stirred at ambient temperature for 16 h and diluted with ethyl acetate (50 mL) and water (20 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (20-50% EtOAc in hexanes) to afford the title compound as a yellowish oil in 83% yield (0.49 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.84 (d, J = 2.7 Hz, 1H), 7.51–7.34 (m, 3H), 7.14 (d, J = 8.7 Hz, 1H), 7.01 (d, J = 8.7 Hz, 1H), 6.97 (d, J = 7.5 Hz, 1H), 6.42–6.26 (m, 3H), 6.17 (d, J = 2.4 Hz, 1H), 5.25 (s, 2H), 4.39 (s, 2H), 3.75 (s, 3H), 3.63 (s, 3H); LRMS *m/z* calcd for $C_{28}H_{23}ClF_2N_5O_5S_2$ $(M+H)^+$ 646.1, found 645.6.

*4-(4-Chloro-2-(imidazo[1,2-a]pyridin-5-yl)phenoxy)-2,5-difluoro-N-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (**2**).* To a stirred solution of **S3** (2.43 g, 3.75 mmol) in EtOH (75 mL) and water (9 mL) was added $NaHCO_3$ (0.41 g, 4.9 mmol) and chloroacetaldehyde (50% w/w in water, 0.63 mL, 4.9 mmol) at ambient temperature. The mixture was heated at reflux for 16 h, allowed to cool to ambient temperature and diluted with CH_2Cl_2 (200 mL) and water (20 mL). The organic layer washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 mL) and TFA (2 mL) was added. The reaction mixture was stirred for 5 h at ambient temperature and concentrated *in vacuo*. Purification of the residue by column chromatography (0-10% methanol in EtOAc) afforded the title compound as a pale yellow solid in 43% yield (0.84 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.14 (s, 1H), 7.93 (d, J = 1.5 Hz, 2H), 7.87–7.78 (m, 2H), 7.76–7.66 (m, 2H), 7.62–7.52 (m, 1H), 7.42–7.30 (m, 3H), (sulfonamide NH not observed); HRMS *m/z* calcd for $C_{21}H_{13}ClF_2N_5O_3S_2$ $(M+H)^+$ 520.0111, found 520.0118.

1.3 Synthesis of Compounds 3 and 3a.



Di-tert-butyl (5-bromo-1,2-benzoxazol-3-yl)imido-dicarbonate (**5**). To a solution of 5-bromobenzo[d]isoxazol-3-amine (**S4**) (5.5 g, 26 mmol) in THF (50 mL) was added DMAP (0.63 g, 5.2 mmol) and Boc_2O (11.8 g, 54.5 mmol). The reaction mixture was stirred at ambient temperature for 18 h and concentrated *in vacuo*. The residue was diluted with EtOAc (60 mL), washed with water (2 x 30 mL), and dried over anhydrous sodium sulfate. Evaporation *in vacuo* yielded a solid residue which was triturated in a mixture of Et_2O and hexanes to afford **5** as a colorless solid in 58% yield (6.2 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.68–7.63 (m, 2H), 7.47 (d, J = 8.7 Hz, 1H), 1.40 (s, 18H); LRMS *m/z* calcd for $C_{17}H_{22}BrN_2O_5$ $(M+H)^+$ 413.1, found 412.9.

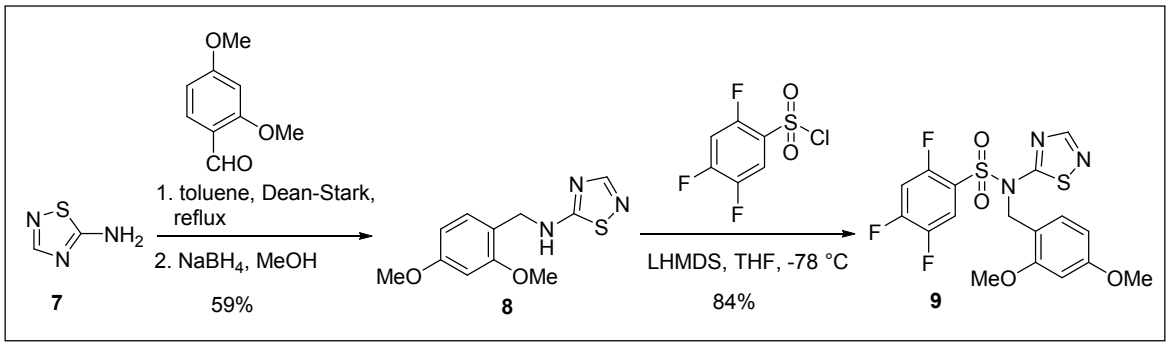
Di-tert-butyl (5-(5-chloro-2-hydroxyphenyl)-1,2-benzoxazol-3-yl)imidodicarbonate (**6**). To a solution of **5** (3.9 g, 9.3 mmol) in DME (100 mL) was added (5-chloro-2-hydroxyphenyl)boronic acid (1.6 g, 9.3 mmol), $Pd(PPh_3)_4$ (1.1 g, 0.9 mmol) and 2 M aqueous Na_2CO_3 (9.3 mL, 18.6 mmol). The mixture was heated at reflux for 5 h, allowed to cool to ambient temperature and concentrated *in vacuo*. The residue was diluted with EtOAc (75 mL), washed with water (2 x 40 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography (10-50% EtOAc in hexanes) to **6** as a colorless solid in 63% yield (2.69 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.66 (m, 2H), 7.47–7.45 (s, 1H), 7.22–7.19 (m, 3H), 6.90–6.87 (m, 1H), 1.41 (s, 18H); LRMS *m/z* calcd for $C_{23}H_{26}ClN_2O_6$ $(M+H)^+$ 461.1, found 460.9.

*4-(2-(3-Aminobenzo[d]isoxazol-5-yl)-4-chlorophenoxy)-2,5-difluoro-N-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (**3**).* Step 1. To a mixture of **6** (2.07 g, 4.49 mmol) and **9** (2.0

g, 4.49 mmol) in anhydrous DMSO (20 mL) was added K_2CO_3 (0.75 g, 5.39 mmol) and the reaction mixture was stirred for 16 h at ambient temperature. The mixture was diluted with EtOAc (200 mL) and water (50 mL), and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by column chromatography (10-25% EtOAc in hexanes) afforded the adduct as a colorless solid in 55% yield (2.23 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.15 (s, 1H), 7.67–7.57 (m, 3H), 7.47–7.39 (m, 3H), 7.13 (m, 1H), 7.00 (m, 1H), 6.32–6.30 (m, 2H), 6.19 (s, 1H), 5.24 (s, 2H), 3.73 (s, 3H), 3.64 (s, 3H), 1.36 (s, 18H); LRMS *m/z* calcd for $C_{40}H_{39}ClF_2N_5O_{10}S_2$ $(M+H)^+$ 886.2, found 885.6. Step 2. To a solution of the product from step 1 (1.70 g, 1.92 mmol) in CH_2Cl_2 (25 mL) was added TFA (10 mL). The reaction mixture was stirred at ambient temperature for 4 h and concentrated *in vacuo*. The residue was taken up in MeOH (15 mL) and filtered. After concentration of the filtrate *in vacuo*, the residue was triturated with CH_2Cl_2/Et_2O (2:1, 15 mL) to afford **3** as a colorless solid in 63% yield (0.65 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.53 (s, 1H), 7.99 (s, 1H), 7.72 (dd, *J* = 9.7, 6.6 Hz, 1H), 7.67–7.59 (m, 2H), 7.54–7.43 (m, 2H), 7.29 (d, *J* = 8.6 Hz, 1H), 7.14 (dd, *J* = 10.3, 6.5 Hz, 1H), 6.48 (s, 2H), (sulfonamide NH not observed); ^{19}F NMR (282 MHz, DMSO-*d*6) δ -110.3 (d, *J* = 15.8 Hz, 1F), -135.3 (d, *J* = 15.8 Hz, 1F); HRMS *m/z* calcd for $C_{21}H_{13}ClF_2N_5O_4S_2$ $(M+H)^+$ 536.0060, found 536.0061.

Sodium ((4-(2-(3-aminobenzo[d]isoxazol-5-yl)-4-chlorophenoxy)-2,5-difluorophenyl)-sulfonyl) (1,2,4-thiadiazol-5-yl)amide (**3a**). To a suspension of **3** (2.19 g, 4.1 mmol) in a 1:1 mixture of MeOH and water (50 mL) was added a solution of NaOH (0.17 g, 4.2 mmol) in water (4.3 mL). The reaction mixture was stirred at ambient temperature for 16 h and slowly turned into a clear solution The solution was filtered, concentrated *in vacuo* to a volume of approximately 5 mL, and then lyophilized to give **3a** as an off-white solid in 96% yield (2.19 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.00 (d, *J* = 1.0 Hz, 1H), 7.90 (s, 1H), 7.66 (dd, *J* = 8.7, 1.5 Hz, 1H), 7.61–7.54 (m, 2H), 7.47 (d, *J* = 8.9 Hz, 1H), 7.45 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.16 (d, *J* = 8.7 Hz, 1H), 7.08 (dd, *J* = 9.9, 6.5 Hz, 1H), 6.47 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 185.4, 161.4, 158.9, 158.5, 154.3 (dd, *J* = 251.2, 2.2 Hz), 150.9, 147.5 (dd, *J* = 246.0, 3.2 Hz), 145.9 (dd, *J* = 12.8, 10.2 Hz), 133.5, 130.8 (2C), 129.3, 129.1, 129.0, 127.9 (dd, *J* = 18.9, 4.5 Hz), 122.3, 120.6, 117.2, 116.6 (dd, *J* = 22.2, 3.0 Hz), 109.3, 109.1 (d, *J* = 28.0 Hz); ^{19}F NMR (282 MHz, DMSO-d_6) δ -110.5 (d, *J* = 16.4 Hz, 1F), -136.4 (d *J* = 16.4 Hz, 1F); LRMS *m/z* calcd for $C_{21}H_{13}ClF_2N_5O_4S_2$ $(M+H)^+$ 536.0, found 535. 9 $(M+H)^+$.

1.4 Synthesis of Compound 9.

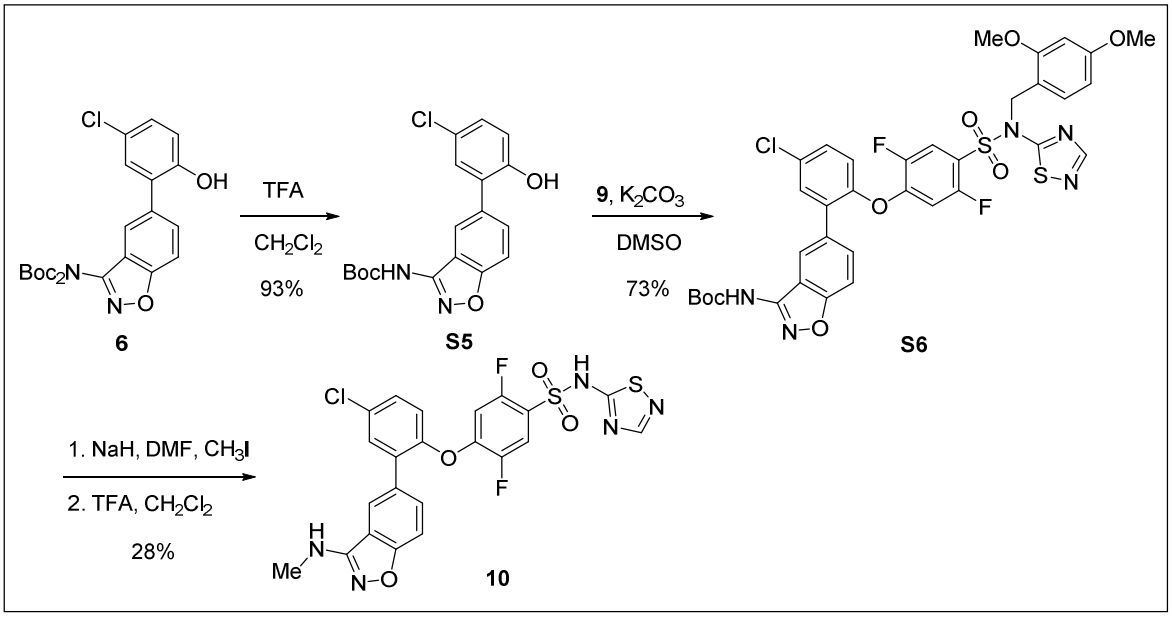


N-(2,4-Dimethoxybenzyl)-1,2,4-thiadiazol-5-amine (**8**). Step 1. To a solution of 1,2,4-thiadiazol-5-amine (**7**) (27.8 g, 274.6 mmol) in toluene (830 mL) was added 2,4-dimethoxybenzaldehyde (50.5 g, 303.8 mmol) and the reaction mixture was heated for 16 h under reflux and azeotropic removal of water using a Dean-Stark apparatus. After cooling to ambient temperature, the reaction mixture was concentrated *in vacuo*. The residue was triturated in boiling hexanes to provide (*E*)-*N*-(2,4-dimethoxybenzylidene)-1,2,4-thiadiazol-5-amine as a yellow solid in 57% yield (42.9 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.32 (s, 1H), 8.46 (s, 1H), 8.20 (d, J = 8.8 Hz, 1H), 6.61 (dd, J = 8.8, 2.1 Hz, 1H), 6.45 (d, J = 2.2 Hz, 1H), 3.91–3.90 (m, 6H). Step 2. To a mixture of the intermediate from step 1 (42.9 g, 172.1 mmol) in MeOH (430 mL) was slowly added $NaBH_4$ (9.8 g, 258 mmol) at 0 ℃. The mixture was allowed to warm to ambient temperature and stirred for 16 h. After concentration of all volatiles, water (200 mL) was added to the residue, and the mixture was extracted with EtOAc (3×200 mL). The combined organic phase was washed with water (1×200 mL), brine (1×200 mL), and dried over anhydrous $MgSO_4$. Concentration *in vacuo* and trituration of the residue with a small volume of diethyl ether afforded **8** as an off-white solid in 53% yield (23.0 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.19 (d, J = 8.1 Hz, 1H), 6.81 (br s, 1H), 6.47–6.42 (m, 2H), 4.35 (d, J = 5.8 Hz, 2H), 3.82–3.80 (m, 6H).

N-(2,4-Dimethoxybenzyl)-2,4,5-trifluoro-N-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (**9**). To a mixture of **8** (5.04 g, 20.1 mmol) in THF (67 mL) was added LHMDS (20 mL of a 1 M solution in THF, 20 mmol) at -78 ºC. The reaction mixture was stirred at -78 ºC for 30 min, warmed to ambient temperature and stirred for additional 5 min. The mixture was cooled to -78 ºC, and 2,4,5-trifluorobenzene-1-sulfonyl chloride (2.7 mL, 19.4 mmol) was slowly added to it. The reaction mixture was allowed to warm to ambient temperature, stirred for 3 h, and quenched by addition of saturated NH_4Cl solution (100 mL). The mixture was extracted with EtOAc (3×200 mL). The combined organic phase was washed with brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Trituration with methanol provided the title compound as an off-white solid in 75% yield (6.48 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.64–7.57

(m, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 6.97–6.89 (m, 1H), 6.36 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.22 (d, *J* = 2.3 Hz, 1H), 5.34 (s, 2H), 3.75 (s, 3H), 3.69 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -107.5 (dd, *J* = 15.2, 10.5 Hz, 1F), -122.4 (dd, *J* = 22.5, 10.5 Hz, 1F), -139.7 (dd, *J* = 22.5, 15.1 Hz, 1F).

1.5 Synthesis of Compound 10.



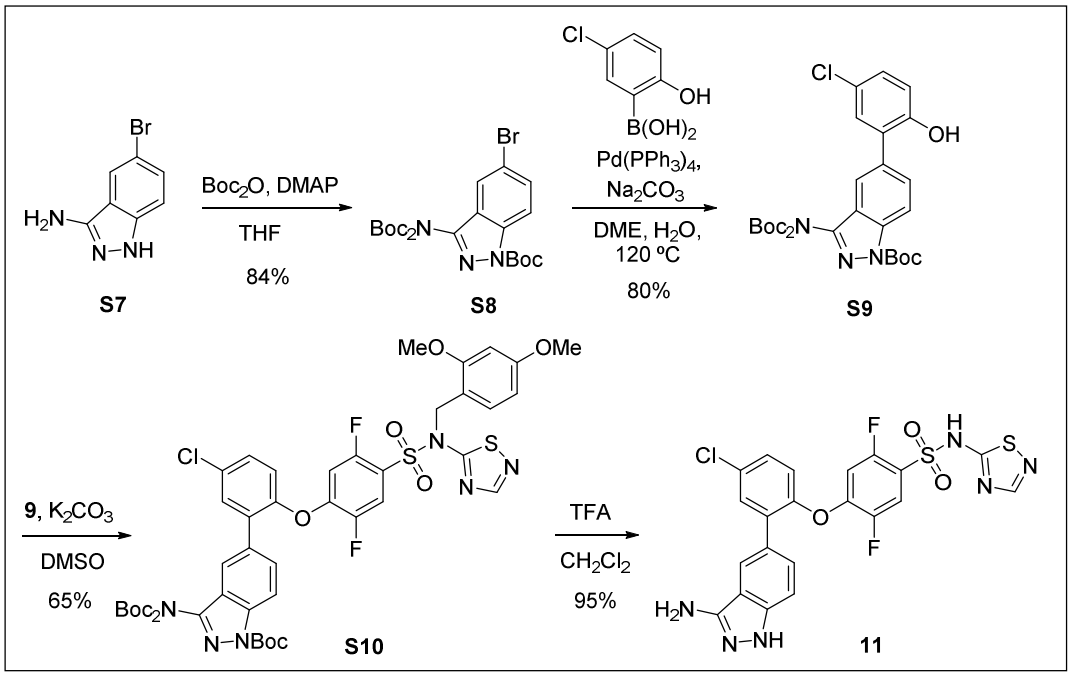
*tert-Butyl (5-(5-chloro-2-hydroxyphenyl)benzo[d]isoxazol-3-yl)carbamate (**S5**)*. To a cold (0 ºC) mixture of **6** (1.29 g, 2.8 mmol) in CH_2Cl_2 (10 mL) was added TFA (0.56 mL, 5.6 mmol), and the reaction mixture was allowed to warm to ambient temperature and stirred to 2 h. Saturated $NaHCO_3$ solution (20 mL) was added and the mixture was diluted with CH_2Cl_2 (100 mL). The organic phase was washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Concentration *in vacuo* provided a residue which was purified by column chromatography, (0-50% EtOAc in hexanes) to afford **S5** as a colorless solid in 93% yield (0.94 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.49 (s, 1H), 9.98 (s, 1H), 8.19 (d, *J* = 1.4 Hz, 1H), 7.82 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.32 (d, *J* = 2.6 Hz, 1H), 7.24 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.99 (d, *J* = 8.6 Hz, 1H), 1.50 (s, 9H).

*tert-Butyl (5-(5-chloro-2-(4-(N-(2,4-dimethoxybenzyl)-N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2,5-difluorophenoxy)phenyl)benzo[d]isoxazol-3-yl)carbamate (**S6**)*. Following the procedure as described for **S3**, making non-critical variations to replace **S2** with **S5**, **S6** was obtained as a colorless solid in 73% yield (1.49 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.19–8.13 (m, 1H), 7.64–7.60 (m, 1H), 7.47-7.41 (m, 5H), 7.14 (d, *J* = 8.2 Hz, 1H), 6.97 (dd, *J* = 8.6, 1.3 Hz, 1H), 6.38 (ddd, *J* = 10.1, 6.2, 1.2 Hz, 1H), 6.31 (d, *J* = 8.4 Hz, 1H), 6.10 (s, 1H), 5.25 (s, 2H), 3.73 (s, 3H), 3.59 (s, 3H), 1.51 (s, 9H); ^{19}F NMR

(282 MHz, $CDCl_3$) δ -107.4 (d, *J* = 15.0 Hz, 1F), -134.98 (d, *J* = 15.1 Hz, 1F); LRMS *m/z* calcd for $C_{35}H_{31}ClF_2N_5O_8S_2$ $(M+H)^+$ 786.1, found 785.6 $(M+H)^+$.

*4-(4-Chloro-2-(3-(methylamino)benzo[d]isoxazol-5-yl)phenoxy)-2,5-difluoro-N-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (**10**).* Step 1. To a solution of **S6** (1.09 g, 1.39 mmol) in DMF (3 mL) was added NaH (0.061 g of a 60% dispersion in mineral oil, 1.53 mmol) and the reaction mixture was stirred for 10 minutes at ambient temperature. MeI (87 µL, 1.39 mmol) was added and the reaction mixture for stirred for 30 minutes at ambient temperature. The reaction mixture was diluted with EtOAc (100 mL) and saturated aqueous NH_4Cl solution (10 mL) was added. The organic phase was washed with water (2 x 5 mL) and brine (10 mL) dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (0-50% EtOAc in hexanes) to afford *tert-butyl* (5-(5-chloro-2-(4-(*N*-(2,4-dimethoxybenzyl)-*N*-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2,5-difluorophenoxy)-phenyl)-benzo[*d*]isoxazol-3-yl)(methyl)carbamate as a colorless foam in 37 % yield (0.41 g). Step 2. The foam was dissolved in CH_2Cl_2 (10 mL) and TFA (5 mL) was added to it. The reaction mixture was stirred for 4 h at ambient temperature and then concentrated *in vacuo*. The residue was suspended in methanol (20 mL), the suspension filtered, and the filtrate concentrated *in vacuo*. Purification purified by column chromatography (20-100% EtOAc in hexanes) provided **10** as a white solid in 75% yield (0.21 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.52 (s, 1H), 7.95 (d, *J* = 1.1 Hz, 1H), 7.72 (dd, *J* = 9.9, 6.5 Hz, 1H), 7.65 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.61 (d, *J* = 2.6 Hz, 1H), 7.52–7.46 (m, 2H), 7.28 (d, *J* = 8.7 Hz, 1H), 7.14 (dd, *J* = 10.4, 6.5 Hz, 1H), 7.04–6.97 (m, 1H), 2.86 (s, 3H), (sulfonamide NH not observed); ^{13}C NMR (300 MHz, DMSO-d_6) δ 178.7, 161.5, 159.0, 154.7 (dd, *J* = 252.8, 1.7 Hz), 150.2, 148.2 (dd, *J* = 12.4, 10.6 Hz), 147.7, 147.6 (dd, *J* = 246.8, 2.2 Hz), 133.9, 131.0, 130.8, 129.7, 129.2, 129.1, 123.9 (dd, *J* = 17.7, 5.2 Hz), 121.9, 121.6, 116.7, 116.5 (dd, *J* = 23.1, 1.6 Hz), 109.4, 108.7 (d, *J* = 27.4 Hz), 29.2; ^{19}F NMR (282 MHz, DMSO-d_6) δ -110.3 (d, *J* = 15.8 Hz, 1F), -135.3 (d, *J* = 15.8 Hz, 1F); LRMS *m/z* calcd for $C_{22}H_{15}ClF_2N_5O_4S_2$ $(M+H)^+$ 550.0, found 549.6.

1.6 Synthesis of Compound 11.



*tert-Butyl 3-[bis(tert-butoxycarbonyl)amino]-5-bromo-1H-indazole-1-carboxylate (**S8**).* To a mixture of 5-bromo-1*H*-indazol-3-amine (**S7**) (1.5 g, 7.1 mmol) in THF was added di-*tert*-butyl dicarbonate (4.8 g, 22.1 mmol) and 4-(*N,N*-dimethylamino)pyridine (0.17 g, 1.4 mmol) and the reaction mixture was stirred for 16 h at ambient temperature. After concentration *in vacuo*, the residue was purified by column chromatography (0-20% EtOAc in hexanes) to afford **S8** as a white solid in 84% yield (3.06 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 8.8 Hz, 1H), 7.72–7.68 (m, 1H), 7.67–7.60 (m, 1H), 1.72 (s, 9H), 1.44 (s, 18H); LRMS *m/z* calcd for $C_{22}H_{31}BrN_3O_6$ $(M+H)^+$ 512.1, found 511.9 $(M+H)^+$.

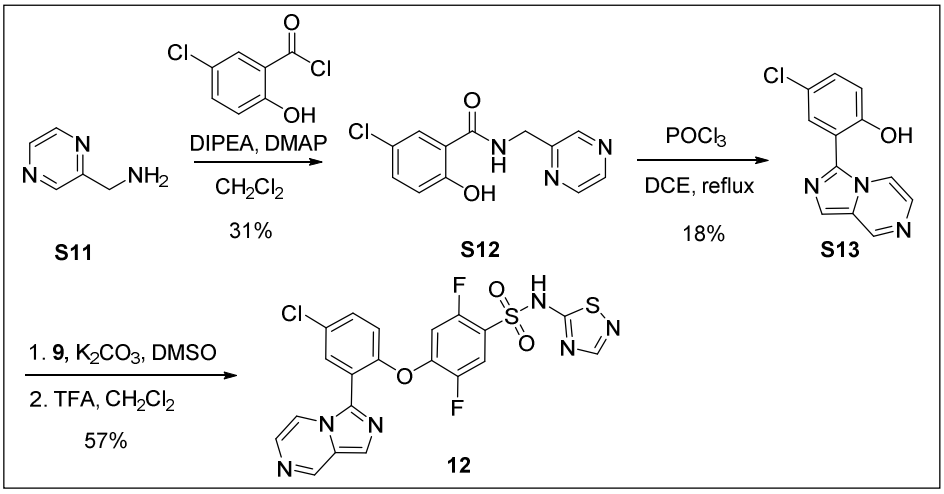
*tert-Butyl 3-[bis(tert-butoxycarbonyl)amino]-5-(5-chloro-2-hydroxyphenyl)-1H-indazole-1-carboxylate (**S9**).* Following the procedure as described for **S2** and making non-critical variations to replace 6-chloropyridin-2-amine (**S1**) with **S8**, **S9** was obtained as a yellowish solid in 80% yield (2.57 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, J = 7.8 Hz, 1H), 7.62-7.59 (m, 2H), 7.46 (s, 1H), 6.90-6.86 (m, 2H), 5.33 (br s, 1H), 1.72 (s, 9H), 1.42 (s, 18H); LRMS *m/z* calcd for $C_{28}H_{35}ClN_3O_7$ $(M+H)^+$ 560.2, found 560.0 $(M+H)^+$.

*tert-Butyl 3-[bis(tert-butoxycarbonyl)amino]-5-(5-chloro-2-{4-[(2,4-dimethoxybenzyl)-(1,2,4-thiadiazol-5-yl)sulfamoyl]-2,5-difluorophenoxy}phenyl)-1H-indazole-1-carboxylate (**S10**).* To a mixture of **9** (0.93 g, 2.1 mmol) and potassium carbonate (0.35 g, 2.51 mmol) in DMSO (10 mL) was added **S9** (1.1 g, 2.1 mmol) and the mixture was stirred at ambient temperature for 5 h. After dilution with EtOAc (150 mL), the organic phase was washed with water (2x20 mL), brine (15 mL), and dried over Na_2SO_4. Concentration *in*

vacuo provided a residue which was purified by column chromatography (0-50% EtOAc in hexanes) to afford **S10** as a colorless solid in 65% yield (1.3 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.15-8.11 (m, 2H), 7.63–7.55 (m, 2H), 7.49–7.38 (m, 3H), 7.14–7.10 (m, 1H), 7.02–6.99 (m, 1H), 6.32–6.19 (m, 3H), 5.23–5.22 (m, 2H), 3.74 (s, 3H), 3.64 (s, 3H), 1.54 (s, 9H), 1.38 (s, 18H); LRMS *m/z* calcd for $C_{45}H_{48}ClF_2N_6O_{11}S_2$ $(M+H)^+$ 985.2, found 985.1.

*4-(2-(3-Amino-1H-indazol-5-yl)-4-chlorophenoxy)-2,5-difluoro-N-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (**11**)*. To a mixture of **S10** (1.3 g, 1.32 mmol) in CH_2Cl_2 (20 mL) was added TFA (10 mL) and the reaction mixture was stirred for 3 at ambient temperature. After concentration *in vacuo*, the residue was triturated in methanol (20 mL) and filtered. The filtrate was concentrated *in vacuo* and the residue was triturated in MeOH (20 mL). The solid was filtered off to provide the *2,2,2-trifluoroacetic acid salt* of **11** as an off-white solid in 95% yield (0.82 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.61–8.62 (br s, 5H), 8.52 (s, 1H), 8.00 (d, J = 0.8 Hz, 1H), 7.72 (dd, J = 9.9, 6.4 Hz, 1H), 7.59 (d, J = 2.6 Hz, 1H), 7.55 (dd, J = 8.8, 1.6 Hz, 1H), 7.48 (dd, J = 8.7, 2.6 Hz, 1H), 7.36 (d, J = 8.7 Hz, 1H), 7.28 (d, J = 8.7 Hz, 1H), 7.09 (dd, J = 10.4, 6.5 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 178.8, 154.8 (dd, J = 252.6, 2.1 Hz), 158.6 (q, J = 35.3 Hz, CF_3COOH), 150.1, 147.8, 147.6 (dd, J = 247.4, 2.8 Hz), 148.4 (dd, J = 12.4, 10.6 Hz), 146.9, 141.1, 134.7, 130.8, 130.0, 129.8, 128.9, 126.5, 123.7 (dd, J = 17.7, 5.2 Hz), 121.9, 121.7, 116.5 (d, J = 23.3 Hz), 116.1 (br q, J = 291.5 Hz, CF_3COOH), 113.0, 110.4, 108.4 (d, J = 27.5 Hz); ^{19}F NMR (282 MHz, DMSO-d_6) δ -74.5 (s, 3F), -110.4 (d, J = 15.8 Hz, 1F), -135.6 (d, J = 15.8 Hz, 1F); LRMS *m/z* calcd for $C_{21}H_{14}ClF_2N_6O_3S_2$ $(M+H)^+$ 535.0, found 534.6.

1.7 Synthesis of Compound 12.



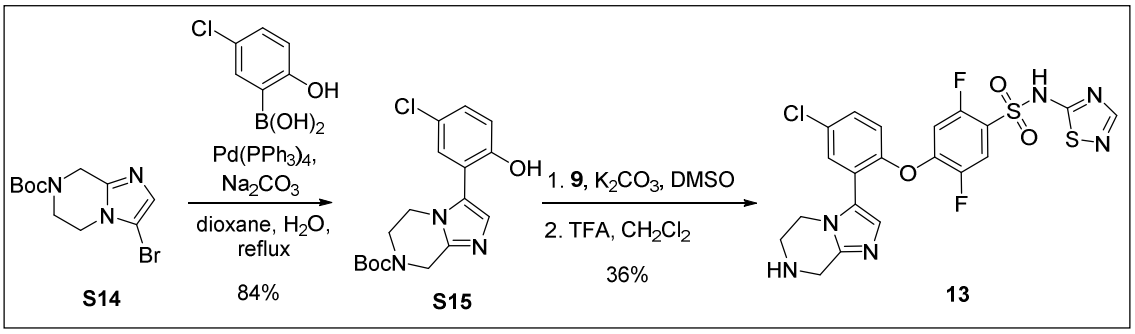
*5-Chloro-2-hydroxy-N-(pyrazin-2-ylmethyl)benzamide (**S12**)*. To a suspension of 5-chlorosalicylic acid (0.96 g, 5.6 mmol) in CH_2Cl_2 (13 mL) was added thionyl chloride (2

mL, 28 mmol) and DMF (~3 drops). The reaction mixture was heated at reflux for 1 h, at which point a clear solution was obtained. The mixture was allowed to cool to ambient temperature and was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL), and pyrazin-2-ylmethanamine (**S11**) (0.80 g, 4.6 mmol), *N*,*N*-diisopropylethylamine (1.6 mL, 9.3 mmol), and 4-(*N,N*-dimethylamino)pyridine (0.056 m, 0.5 mmol) were added. The reaction mixture was stirred at ambient temperature for 16 h, diluted with CH_2Cl_2 (70 mL) and washed with 1 N hydrochloric acid (2 x 7 mL), water (2 x 7 mL) and brine (10 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (10-60% EtOAc in hexanes) to afford **S12** as a yellow solid in 31% yield (0.379 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.10 (s, 1H), 8.67 (s, 1H), 8.57 (s, 2H), 7.57 (br s, 1H), 7.46 (d, *J* = 2.1 Hz, 1H), 7.34 (dd, *J* = 8.9, 1.8 Hz, 1H), 6.93 (d, *J* = 8.9 Hz, 1H), 4.78 (d, *J* = 4.8 Hz, 2H); LRMS *m/z* calcd for $C_{12}H_{11}ClN_3O_2$ $(M+H)^+$ 264.1, found 264.0.

*4-Chloro-2-(imidazo[1,5-a]pyrazin-3-yl)phenol (**S13**)*. A suspension of **S12** (0.38 g, 1.4 mmol) in a mixture of 1,2-dichloroethane (6 mL) and phosphoryl chloride (6 mL) was heated at reflux for 2 h, allowed to cool to ambient temperature and concentrated *in vacuo*. The residue was suspended in water (10 mL), and the pH was adjusted to 6-7 with 1 N aqueous sodium hydroxide. The aqueous phase was extracted with EtOAc (3 x 30 mL) followed by CH_2Cl_2 (3 x 40 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (0-10% methanol in CH_2Cl_2) to afford **S13** as a pale yellow solid in 18% yield (0.064 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.13 (s, 1H), 8.34 (br s, 1H), 7.99 (s, 1H), 7.83 (d, *J* = 4.0 Hz, 1H), 7.57 (d, *J* = 4.6 Hz, 1H), 7.50 (d, *J* = 1.9 Hz, 1H), 7.42 (d, *J* = 8.3 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H); LRMS *m/z* calcd for $C_{12}H_9ClN_3O$ $(M+H)^+$ 246.0, found 246.1.

*4-(4-Chloro-2-(imidazo[1,5-a]pyrazin-3-yl)phenoxy)-2,5-difluoro-N-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (**12**).* Following the procedure as described for **3** and making non-critical variations to replace phenol **6** with **S13**, **12** was obtained as a yellow solid containing trace amounts of trifluoroacetic acid in 57% yield over 2 steps (0.075 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.14 (s, 1H), 8.52 (s, 1H), 8.10 (d, *J* = 4.6 Hz, 1H), 8.02 (s, 1H), 7.80 (s, 1H), 7.71–7.56 (m, 3H), 7.35 (d, *J* = 8.9 Hz, 1H), 7.29 (dd, *J* = 10.3, 6.2 Hz, 1H) (NH not observed); ^{13}C NMR (75 MHz, DMSO-d_6) δ 178.9, 154.6 (dd, *J* = 252.4, 2.1 Hz), 151.7, 147.8, 147.7 (dd, *J* = 247.9, 3.1 Hz), 147.0 (dd, *J* = 12.7, 10.7 Hz), 145.7, 134.1, 131.8 (2C), 129.3, 127.7, 126.8, 126.1, 124.7 (dd, *J* = 17.8, 5.3 Hz), 121.6, 120.9, 116.6 (d, *J* = 22.8 Hz), 115.8, 109.5 (d, *J* = 27.5 Hz); ^{19}F NMR (282 MHz, DMSO-d_6) δ -74.6 (s, 1F, 0.3·CF_3COOH), -110.4 (d, *J* = 16.0 Hz, 1F), -134.7 (d, *J* = 16.0 Hz, 1F); LRMS *m/z* calcd for $C_{20}H_{12}ClF_2N_6O_3S_2$ $(M+H)^+$ 521.0, found 520.7 $(M+H)^+$.

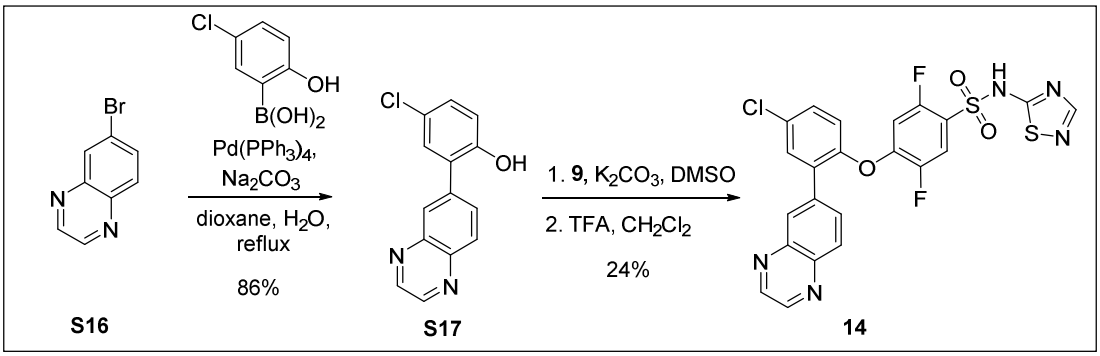
1.8 Synthesis of Compound 13.



*tert-Butyl 3-(5-chloro-2-hydroxyphenyl)-5,6-dihydroimidazo[1,2-a]pyrazine-7(8H)-carboxylate (**S15**)*. Following the procedure as described for **S2** and making non-critical variations to replace 6-chloropyridin-2-amine (**S1**) with *tert*-butyl 3-bromo-5,6-dihydroimidazo[1,2-*a*]pyrazine-7(8*H*)-carboxylate (**S14**), **S15** was obtained as a colorless solid in 84% yield (0.126 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.16 (s, 1H), 7.27 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.21 (d, *J* = 2.3 Hz, 1H), 6.98-6.92 (m, 2H), 4.58 (br s, 2H), 3.87-3.79 (m, 2H), 3.74-3.67 (m, 2H), 1.44 (s, 9H); LRMS *m/z* calcd for $C_{17}H_{21}ClN_3O_3$ $(M+H)^+$ 350.1, found 349.5.

*4-(4-Chloro-2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl)phenoxy)-2,5-difluoro-N-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (**13**).* Following the procedure as described for the synthesis of **3** and making non-critical variations using **S15** to replace phenol **6**, the trifluoroacetic acid salt of **13** was obtained as a colorless solid in 36% yield over 2 steps (0.080 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.45 (s, 1H), 7.84–7.75 (m, 1H), 7.60–7.52 (m, 2H), 7.35–7.21 (m, 3H), 4.45 (s, 2H), 4.19–4.09 (m, 2H), 3.82–3.50 (m, 3H) (NH and CF_3COOH not observed); ^{13}C NMR (75 MHz, DMSO-d_6) δ 180.2, 155.2 (d, *J* = 253.9 Hz), 159.1 (q, *J* = 33.1, 32.8 Hz, CF_3COOH), 152.1, 149.7, 148.5 (dd, *J* = 247.6, 3.0 Hz), 147.2 (dd, *J* = 12.6, 10.6 Hz), 139.1, 132.0, 131.4, 129.4, 127.0, 126.8, 125.9 (dd, *J* = 17.9, 5.1 Hz), 121.2, 120.6, 117.3 (d, *J* = 22.6 Hz), 117.0 (br q, *J* = 298.5 Hz, CF_3COOH), 110.3 (d, *J* = 27.2 Hz), 56.0 (br), 55.9 (br), 30.1; ^{19}F NMR (282 MHz, DMSO-d_6) δ -74.2 (s, 3F, CF_3COOH), -110.2 (d, *J* = 16.0 Hz, 1F), -134.4 (d, *J* = 16.0 Hz, 1F); LRMS *m/z* calcd for $C_{20}H_{16}ClF_2N_6O_3S_2$ $(M+H)^+$ 525.0, found 524.7.

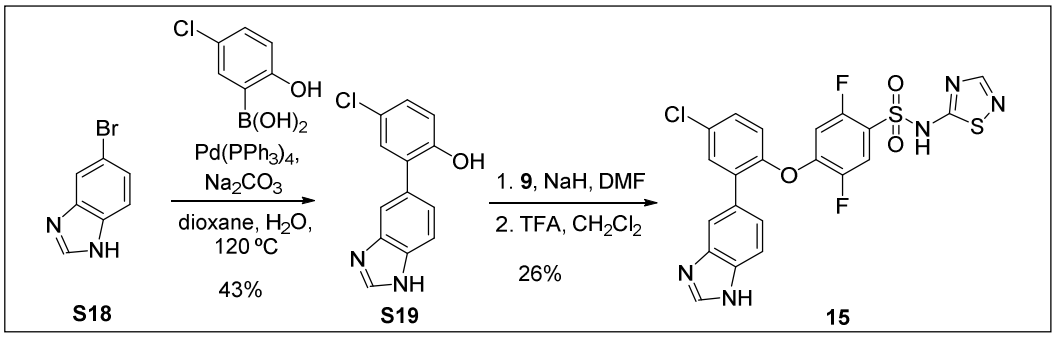
1.9 Synthesis of Compound 14.



*4-Chloro-2-(quinoxalin-6-yl)phenol (**S17**).* Following the procedure as described for **S2** and making non-critical variations to replace 6-chloropyridin-2-amine (**S1**) with 6-bromoquinoxaline (**S16**), **S17** was obtained as a beige solid in 86% yield (4.2 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.18 (s, 1H), 8.98–8.94 (m, 2H), 8.25 (d, J = 1.1 Hz, 1H), 8.12 (d, J = 8.7 Hz, 1H), 8.07 (dd, J = 8.8, 1.6 Hz, 1H), 7.50 (d, J = 2.6 Hz, 1H), 7.30 (dd, J = 8.7, 2.6 Hz, 1H), 7.04 (d, J = 8.7 Hz, 1H); LRMS *m/z* calcd for $C_{14}H_8ClN_2O$ $(M-H)^-$ 255.0, found 255.1.

*4-(4-Chloro-2-(quinoxalin-6-yl)phenoxy)-2,5-difluoro-N-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (**14**).* Following the procedure as described for the synthesis of **3** and making non-critical variations using **S17** to replace phenol **6**, **14** was obtained as a colorless solid in 24% yield over 2 steps (0.15 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.95 (s, 2H), 8.54 (s, 1H), 8.22 (d, J = 1.6 Hz, 1H), 8.12 (d, J = 8.7 Hz, 1H), 7.99 (dd, J = 8.7, 1.8 Hz, 1H), 7.79 (d, J = 2.5 Hz, 1H), 7.71 (dd, J = 9.9, 6.4 Hz, 1H), 7.57 (dd, J = 8.8, 2.5 Hz, 1H), 7.34 (d, J = 8.8 Hz, 1H), 7.25 (dd, J = 10.4, 6.5 Hz, 1H), (NH not observed); ^{13}C NMR (75 MHz, DMSO-d_6) δ 178.7, 154.7 (dd, J = 252.5, 2.4 Hz), 150.3, 148.2 (dd, J = 12.4, 10.6 Hz), 147.6, 147.5 (dd, J = 247.3, 2.9 Hz), 146.3, 146.2, 141.8, 141.6, 136.8, 133.1, 131.2, 131.0, 130.1, 129.9, 129.2, 129.1, 123.9 (dd, J = 17.7, 5.3 Hz), 121.7, 116.5 (d, J = 22.9 Hz), 108.8 (d, J = 27.4 Hz); ^{19}F NMR (282 MHz, DMSO-d_6) δ -110.2 (d, J = 15.9 Hz, 1F), -135.6 (d, J = 15.9 Hz, 1F); HRMS *m/z* calcd for $C_{22}H_{13}ClF_2N_5O_3S_2$ $(M+H)^+$ 532.0111, found 532.0115.

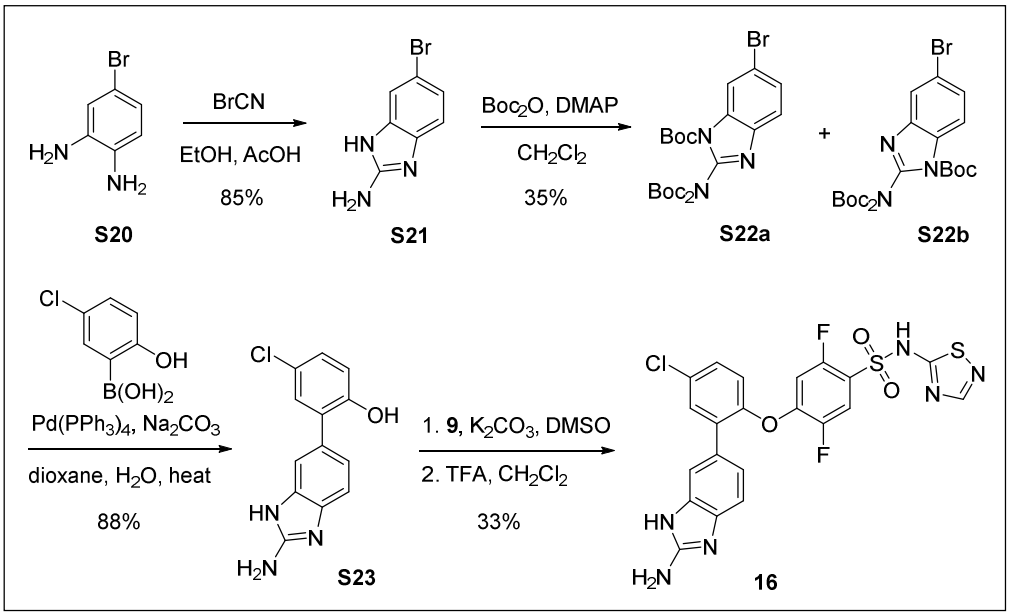
1.10 Synthesis of Compound 15.



*2-(1H-Benzo[d]imidazol-5-yl)-4-chlorophenol (**S18**).* Following the procedure as described for the synthesis of **S2** and making non-critical variations to replace 6-chloropyridin-2-amine (**S1**) with 6-bromo-1*H*-benzo[*d*]imidazole hydrochloride salt (**S18**), **S19** was obtained as a beige solid in 43% yield (0.110 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.48 (s, 1H), 9.80 (s, 1H), 8.24 (s, 1H), 7.74 (s, 1H), 7.60 (d, *J* = 8.3 Hz, 1H), 7.36 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.30 (d, *J* = 2.5 Hz, 1H), 7.18 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.96 (d, *J* = 8.6 Hz, 1H); LRMS *m/z* calcd for $C_{13}H_{10}ClN_2O$ $(M+H)^+$ 245.0, found 245.1.

*4-(2-(1H-Benzo[d]imidazol-5-yl)-4-chlorophenoxy)-2,5-difluoro-N-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (**15**)*. Following the procedure as described for the synthesis of **3** and making non-critical variations using **S19** to replace phenol **6**, the trifluoroacetic acid salt of **15** was obtained as a colorless solid in 24% yield over 2 steps (0.15 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.11 (s, 1H), 8.37 (s, 1H), 7.84 (s, 1H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.64 (dd, *J* = 10.2, 6.5 Hz, 1H), 7.62 (d, *J* = 2.6 Hz, 1H), 7.54 (d, *J* = 8.3 Hz, 1H), 7.49 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.27 (d, *J* = 8.7 Hz, 1H), 7.11 (dd, *J* = 10.4, 6.5 Hz, 1H), (2 NH and CF_3COOH not observed); ^{13}C NMR (75 MHz, DMSO-d_6) δ 179.9, 154.7 (d, *J* = 252.3 Hz), 150.2, 149.8, 148.1 (dd, *J* = 12.3, 10.6 Hz), 147.4 (dd, *J* = 247.0, 2.6 Hz), 141.9, 134.2, 132.6, 132.3, 131.8, 131.2, 129.8, 129.5, 126.0, 124.4 (dd, *J* = 17.8, 4.8 Hz), 121.8, 116.5 (d, *J* = 22.9 Hz), 115.0, 114.7, 108.4 (d, *J* = 27.4 Hz) (CH_3COOH peaks not observed); ^{19}F NMR (282 MHz, DMSO-d_6) δ -76.6 (s, 3F), -113.0 (d, *J* = 15.8 Hz, 1F), -139.0 (d, *J* = 15.9 Hz, 1F); LRMS *m/z* calcd for $C_{21}H_{13}ClF_2N_5O_3S_2$ $(M+H)^+$ 520.0, found 519.7.

1.11 Synthesis of Compound 16.



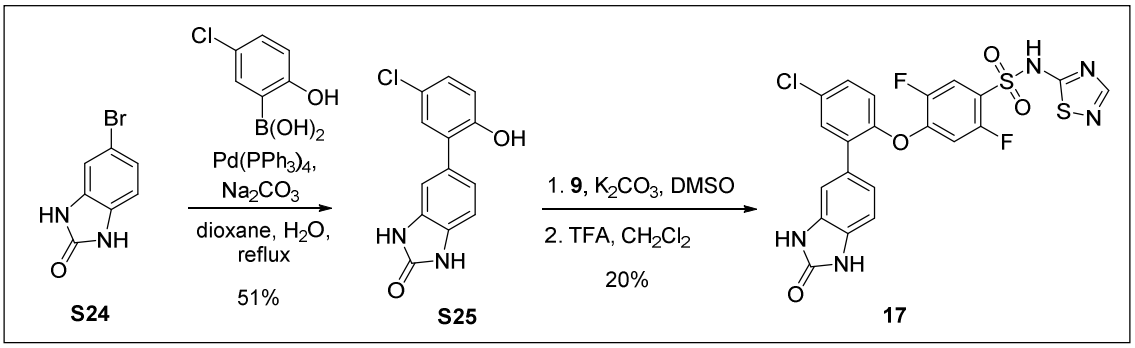
*5-Bromo-1H-benzo[d]imidazol-2-amine hydrobromide (**S21**).* To a solution of 4-bromo-1,2-diaminobenzene (**S20**) (3.0 g, 16 mmol) in a mixture of ethanol and acetic acid (1:1 v/v, 180 mL) was added cyanogen bromide (2.56 g, 24.0 mmol) and the reaction mixture was stirred at ambient temperature for 16 h. Concentration *in vacuo* and trituration of the residue in EtOAc (200 mL) provided **S21** as a tannish solid in 85% yield (3.98 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.49 (br s, 2H), 8.61 (s, 2H), 7.50 (s, 1H), 7.38–7.23 (m, 2H); LRMS *m/z* calcd for $C_7H_7BrN_3$ $(M+H)^+$ 212.0, found 211.9.

*tert-Butyl 2-[bis(tert-butoxycarbonyl)amino]-5-bromo-1H-benzimidazole-1-carboxylate and tert-butyl 2-[bis(tert-butoxycarbonyl)amino]-6-bromo-1H-benzimidazole-1-carboxylate (**S22a** and **S22b**).* To a solution of **S21** (2.21 g, 7.54 mmol) in CH_2Cl_2 (100 mL) was added Boc_2O (4.94 g, 22.6 mmol) and DMAP (0.921 g, 7.54 mmol) and the reaction mixture was stirred for 16 h at ambient temperature. Concentration *in vacuo* and purification of the residue by column chromatography (gradient of 10-20% EtOAc in hexanes) afforded a 1:1 mixture of **S22a** and **S22b** in 35% yield (1.37 g). LRMS *m/z* calcd for $C_{22}H_{31}BrN_3O_6$ $(M+H)^+$ 512.1, found 511.8.

2-(2-Amino-1H-benzo[d]imidazol-5-yl)-4-chlorophenol (**S23**). Following the procedure as described for the synthesis of **S2** and making non-critical variations to replace 6-chloropyridin-2-amine (**S1**) with a mixture of **S22a** and **S22b**, **S23** was obtained as a yellow solid in 88% yield (0.61 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.81 (br s, 1H), 7.58 (br s, 2H), 7.42 (s, 1H), 7.27–7.10 (m, 5H), 6.92 (d, J = 8.6 Hz, 1H); LRMS *m/z* calcd for $C_{13}H_{11}ClN_3O$ $(M+H)^+$ 260.1, found 260.0.

*4-(2-(2-Amino-1H-benzo[d]imidazol-5-yl)-4-chlorophenoxy)-2,5-difluoro-N-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (**16**).* Following the procedure as described for the synthesis of **3** and making non-critical variations using **S23** to replace phenol **6** followed by preparative HPLC purification (Gemini NX, C18, 5µm, 30 x 150 mm, 20-60% CH_3CN in water containing 0.1% NH_4OH) **16** was obtained as an off-white solid in 33% yield over 2 steps (0.57 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.36 (s, 2H), 7.92 (s, 1H), 7.59-7.52 (m, 2H), 7.48-7.42 (m, 2H), 7.33 (d, J = 8.2 Hz, 1H), 7.28 (dd, J = 8.3, 1.3 Hz, 1H), 7.21 (d, J = 8.7 Hz, 1H), 7.00 (dd, J = 10.0, 6.5 Hz, 1H), (two NH not observed); ^{13}C NMR (75 MHz, DMSO-d_6) δ 185.1, 158.6, 154.3 (dd, J = 251.7, 1.7 Hz), 151.1, 150.4, 147.1 (dd, J = 245.8, 3.1 Hz), 146.6 (dd, J = 12.6, 10.2 Hz), 134.2, 130.8, 130.0, 130.0, 129.9, 129.3, 129.1, 127.0 (dd, J = 19.0, 4.3 Hz), 123.8, 121.5, 111.6, 116.5 (dd, J = 22.2, 2.7 Hz), 111.3, 108.3 (d, J = 27.8 Hz); ^{19}F NMR (282 MHz, DMSO-d_6) δ -110.4 (d, J = 16.9 Hz), -137.2 (d, J = 16.9 Hz); HRMS *m/z* calcd for $C_{21}H_{14}ClF_2N_6O_3S_2$ $(M+H)^+$ 535.0220, found 535.0227.

1.12 Synthesis of Compound 17.

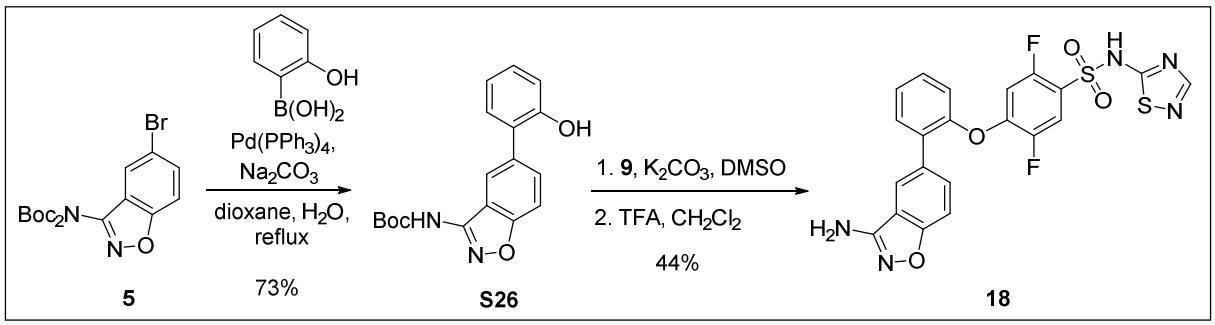


*5-(5-Chloro-2-hydroxyphenyl)-1H-benzo[d]imidazol-2(3H)-one (**S25**).* Following the procedure as described for the synthesis of **S2** and making non-critical variations to replace 6-chloropyridin-2-amine (**S1**) with 5-bromo-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (**S24**) and purification by trituration in CH_2Cl_2, **S25** was obtained as a tan solid in 51% yield (0.198 g) ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.62 (s, 1H), 10.60 (s, 1H), 9.73 (s, 1H), 7.19 (d, J = 2.6 Hz, 1H), 7.15–7.08 (m, 2H), 7.05 (dd, J = 8.1, 1.3 Hz, 1H), 6.94–6.86 (m, 2H); LRMS *m/z* calcd for $C_{13}H_{10}ClN_2O_2$ $(M+H)^+$ 261.0, found 260.9.

*4-(4-Chloro-2-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)phenoxy)-2,5-difluoro-N-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (**17**).* Following the procedure as described for the synthesis of **3** and making non-critical variations using **S25** to replace phenol **6** and purification by column chromatography (0-20% methanol in CH_2Cl_2), **17** was obtained as a colorless solid in 20% yield over 2 steps (0.081 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.67 (s, 1H), 10.64 (s, 1H), 8.49 (s, 1H), 7.69 (dd, J = 9.9, 6.4 Hz, 1H), 7.50 (d, J = 2.5 Hz, 1H), 7.40 (dd, J = 8.7, 2.6 Hz, 1H), 7.22 (d, J = 8.7 Hz, 1H), 7.05–

6.98 (m, 3H), 6.90 (d, *J* = 7.9 Hz, 1H), (sulfonamide NH not observed); ^{13}C NMR (75 MHz, DMSO-d_6) δ 178.6, 155.3, 154.8 (dd, *J* = 252.5, 2.0 Hz), 149.8, 148.7 (dd, *J* = 12.3, 10.5 Hz), 147.6, 147.4 (dd, *J* = 246.9, 2.8 Hz), 135.3, 130.9, 129.8, 129.7 (2C), 128.6, 127.3, 123.3 (dd, *J* = 17.7, 5.2 Hz), 122.1, 121.4, 116.4 (d, *J* = 22.9 Hz), 108.7, 107.9 (d, *J* = 27.4 Hz), 108.4; ^{19}F NMR (282 MHz, DMSO-d_6) δ -110.3 (d, *J* = 15.7 Hz, 1F), -136.1 (d, *J* = 15.8 Hz, 1F); LRMS *m/z* calcd for $C_{21}H_{11}ClF_2N_5O_4S_2$ $(M-H)^-$ 534.0, found 533.8.

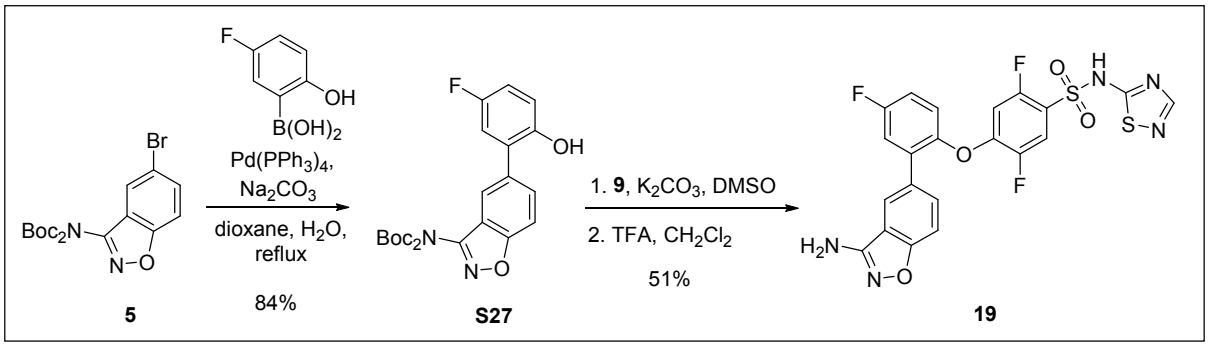
1.13 Synthesis of Compound 18.



*tert-Butyl (5-(2-hydroxyphenyl)benzo[d]isoxazol-3-yl)carbamate (**S26**).* Following the procedure as described for the synthesis of **9** and making non-critical variations to replace (5-chloro-2-hydroxyphenyl)boronic acid with phenylboronic acid, **S26** was obtained as a pale yellow solid in 73% yield (0.36 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.50 (s, 1H), 9.64 (s, 1H), 8.16–8.15 (m, 1H), 7.79 (dd, *J* = 8.8, 1.7 Hz, 1H), 7.65 (d, *J* = 8.8 Hz, 1H), 7.28 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.23–7.16 (m, 1H), 6.97 (d, *J* = 8.1 Hz, 1H), 6.91 (t, *J* = 7.4 Hz, 1H), 1.50 (s, 9H); LRMS *m/z* calcd for $C_{18}H_{17}N_2O_4$ $(M-H)^-$ 325.1, found 325.1.

*4-(2-(3-Aminobenzo[d]isoxazol-5-yl)phenoxy)-2,5-difluoro-N-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (**18**).* Following the procedure as described for the synthesis of **3** and making non-critical variations using **S26** to replace phenol **6**, **18** was obtained as a colorless solid in 44% yield (0.185 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.52 (s, 1H), 7.95 (d, *J* = 1.17 Hz, 1H), 7.71 (dd, *J* = 10.0, 6.5 Hz, 1H), 7.62 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.55 (dd, *J* = 7.3, 1.9 Hz, 1H), 7.51–7.36 (m, 3H), 7.24 (dd, *J* = 7.8, 1.1 Hz, 1H), 6.98 (dd, *J* = 10.4, 6.4 Hz, 1H), 6.45 (br s, 2H) (sulfonamide NH not observed); ^{13}C NMR (75 MHz, DMSO-d_6) δ 178.6, 161.2, 158.5, 154.7 (dd, *J* = 252.3, 2.3 Hz), 151.2, 148.7 (dd, *J* = 12.4, 10.5 Hz), 147.7 (dd, *J* = 247.3, 2.9 Hz), 147.6, 132.3, 131.7, 130.8, 130.4, 129.6, 126.0, 123.4 (dd, *J* = 17.6, 5.2 Hz), 122.0, 119.8, 117.1, 116.5 (dd, *J* = 22.9, 1.6 Hz), 109.2, 108.2 (d, *J* = 27.3 Hz); ^{19}F NMR (282 MHz, DMSO-d_6) δ -110.5 (d, *J* = 15.7 Hz, 1F), -135.5 (d, *J* = 15.8 Hz, 1F); LRMS *m/z* calcd for $C_{21}H_{14}F_2N_5O_4S_2$ $(M+H)^+$ 502.0, found 501.6.

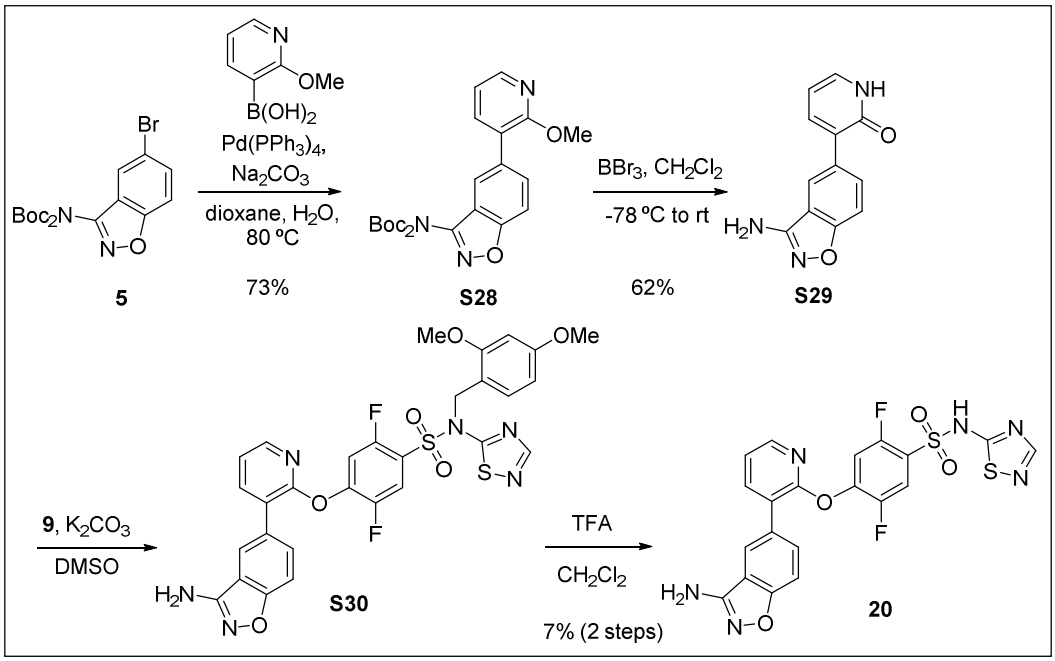
1.14 Synthesis of Compound 19.



*di-tert-Butyl (5-(5-fluoro-2-hydroxyphenyl)-1,2-benzoxazol-3-yl)imidodicarbonate (**S27**).* Following the procedure as described for the synthesis of **6** and making non-critical variations to replace (5-chloro-2-hydroxyphenyl)boronic acid with (fluoro-2-hydroxyphenyl)boronic acid, compound **S27** was obtained as a colorless solid in 84% yield (10.8 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.74 (s, 1H), 7.94–7.86 (m, 2H), 7.81 (d, J = 8.9 Hz, 1H), 7.16 (dd, J = 9.7, 3.1 Hz, 1H), 7.00 (dd, J = 8.2, 3.1 Hz, 1H), 6.96–6.90 (m, 1H), 1.34 (s, 18H); LRMS *m/z* calcd for $C_{23}H_{24}FN_2O_6$ $(M-H)^-$ 443.2, found 443.1.

*4-(2-(3-Aminobenzo[d]isoxazol-5-yl)-4-fluorophenoxy)-2,5-difluoro-N-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (**19**).* Following the procedure as described for the synthesis of **3** and making non-critical variations using **S27** to replace phenol **6**, compound **19** was obtained as an off-white solid in 51% yield over 2 steps (0.188 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.47 (s, 1H), 7.95–7.94 (m, 1H), 7.65 (dd, J = 10.0, 6.5 Hz, 1H), 7.59 (dd, J = 8.7, 1.8 Hz, 1H), 7.43 (d, J = 8.7 Hz, 1H), 7.43–7.37 (m, 1H), 7.34–7.24 (m, 2H), 6.94 (dd, J = 10.5, 6.5 Hz, 1H), 6.43 (br s, 2H), (sulfonamide NH not observed); ^{13}C NMR (75 MHz, DMSO-d_6) δ 178.8, 161.4, 159.4 (d, J = 242.7 Hz), 158.5, 154.7 (dd, J = 252.3, 2.3 Hz), 148.9 (dd, J = 12.0, 10.7 Hz), 147.9, 147.3 (dd, J = 248.5, 2.7 Hz), 147.2 (d, J = 2.4 Hz), 134.5 (d, J = 8.5 Hz), 130.7, 129.4 (d, J = 1.1 Hz), 123.4 (dd, J = 17.8, 5.2 Hz), 122.5, 122.3, 118.0 (d, J = 23.9 Hz), 117.2, 116.7-115.9 (m, 2C), 109.3, 107.7 (d, J = 27.4 Hz); ^{19}F NMR (282 MHz, DMSO-d_6) δ -110.4 (d, J = 15.7 Hz, 1F), -116.6 (s, 1F), -136.0 (d, J = 15.8 Hz, 1F); HRMS *m/z* calcd for $C_{21}H_{13}F_3N_5O_4S_2$ $(M+H)^+$ 520.0356, found 520.0363.

1.15 Synthesis of Compound 20.



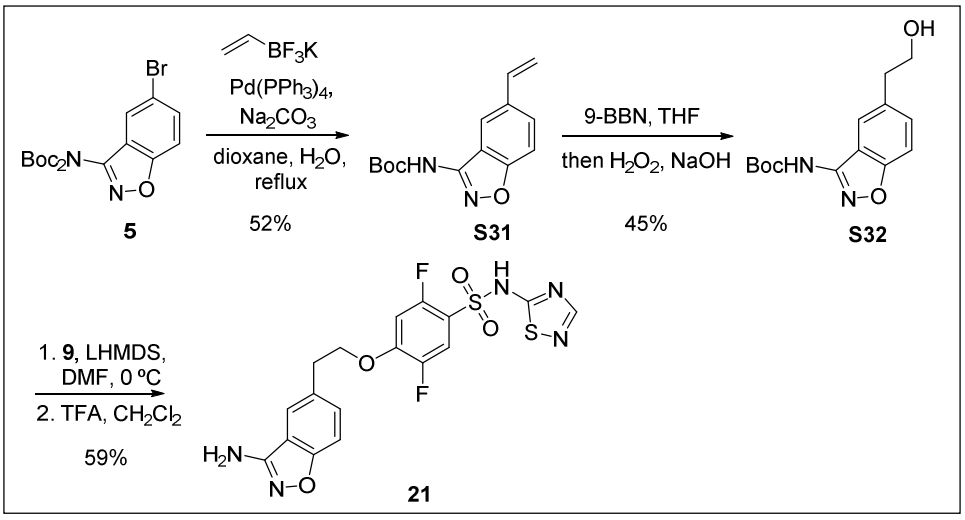
*di-tert-Butyl [5-(2-methoxypyridin-3-yl)-1,2-benzoxazol-3-yl]imidodicarbonate (**S28**).* Following the procedure as described for the synthesis of **6** and making non-critical variations to replace (5-chloro-2-hydroxyphenyl)boronic acid with (2-methoxypyridin-3-yl)boronic acid, **S28** was obtained as a tan solid in 71% yield (0.47 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (dd, J = 5.0, 1.7 Hz, 1H), 7.74-7.68 (m, 2H), 7.62-7.55 (m, 2H), 6.97 (dd, J = 7.3, 5.0 Hz, 1H), 3.92 (s, 3H), 1.37 (s, 18H); LRMS *m/z* calcd for $C_{23}H_{28}N_3O_6$ $(M+H)^+$ 442.2, found 442.1.

*3-(3-Aminobenzo[d]isoxazol-5-yl)pyridin-2(1H)-one (**S29**).* To a mixture of **S28** (0.235 g, 0.53 mmol) in acetic acid (3 mL) was added 48% hydrobromic acid (1 mL), the reaction mixture stirred at ambient temperature 16 h, and subsequently heated to 75 ºC for 6 h. After cooling to ambient temperature, the reaction mixture was concentrated *in vacuo*. The residue was partitioned between water (100 mL) and EtOAc (50 mL), and the aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic phase was washed with brine (25 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to afford **S29** as a brownish solid in 62% yield (0.075 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.87 (br s, 1H), 8.18 (d, J = 1.2 Hz, 1H), 7.84 (dd, J = 8.7, 1.8 Hz, 1H), 7.64 (dd, J = 6.9, 2.1 Hz, 1H), 7.46–7.38 (m, 2H), 6.43 (br s, 2H), 6.32 (dd, J = 6.7, 6.7 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.2, 161.1, 158.6, 138.6, 134.5, 130.9, 130.3, 129.6, 121.3, 116.7, 108.6, 105.4; LRMS *m/z* calcd for $C_{12}H_{10}N_3O_2$ $(M+H)^+$ 228.1, found 228.0.

*4-((3-(3-Aminobenzo[d]isoxazol-5-yl)pyridin-2-yl)oxy)-N-(2,4-dimethoxybenzyl)-2,5-difluoro-N-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (**S30**).* To a mixture of **S29** (0.075 g, 0.33 mmol) and potassium carbonate (0.065 g, 0.50 mmol) in anhydrous DMSO (2 mL) was added **9** (0.147 g, 0.33 mmol) and the reaction mixture was stirred at ambient temperature for 16 h. After dilution with EtOAc (80 mL), the mixture was washed with water (2 x 10 mL), brine (10 mL), and dried over anhydrous $MgSO_4$. Concentration *in vacuo* provided a residue which was purified by column chromatography (20-70% EtOAc in hexanes) to afford **S30** as first eluting compound and 4-(3-(3-aminobenzo[*d*]isoxazol-5-yl)-2-oxopyridin-1(2*H*)-yl)-*N*-(2,4-dimethoxybenzyl)-2,5-difluoro-*N*-(1,2,4-thiadiazol-5-yl)benzenesulfonamide as second eluting compound. Data for **S30**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.21 (s, 1H), 8.12 (dd, *J* = 4.9, 1.8 Hz, 1H), 7.87–7.82 (m, 2H), 7.72 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.53 (d, *J* = 8.7 Hz, 1H), 7.42 (dd, *J* = 9.4, 6.2 Hz, 1H), 7.25–7.20 (m, 2H), 6.99 (dd, *J* = 9.8, 5.8 Hz, 1H), 6.38 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.20 (d, *J* = 2.3 Hz, 1H), 5.36 (s, 2H), 4.68 (s, 2H), 3.73 (s, 3H), 3.64 (s, 3H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -108.70 (d, *J* = 15.3 Hz, 1F), -129.26 (d, *J* = 15.3 Hz, 1F); LRMS *m/z* calcd for $C_{29}H_{23}F_2N_6O_6S_2$ $(M+H)^+$ 653.1, found 652.7. Data for 4-(3-(3-aminobenzo[*d*]isoxazol-5-yl)-2-oxopyridin-1(2*H*)-yl)-*N*-(2,4-dimethoxybenzyl)-2,5-difluoro-*N*-(1,2,4-thiadiazol-5-yl)benzenesulfonamide: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.22 (s, 1H), 8.02–7.98 (m, 1H), 7.72 (dd, *J* = 8.8, 1.7 Hz, 1H), 7.64–7.52 (m, 2H), 7.40 (d, *J* = 8.8 Hz, 1H), 7.29–7.15 (m, 3H), 6.44 (dd, *J* = 7.1, 7.1 Hz, 1H), 6.36 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.21 (d, *J* = 2.3 Hz, 1H), 5.37 (s, 2H), 4.60 (s, 2H), 3.73 (s, 3H), 3.67 (s, 3H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -109.48 (d, *J* = 16.8 Hz, 1F), -121.85 (d, *J* = 16.9 Hz, 1F); LRMS *m/z* calcd for $C_{29}H_{23}F_2N_6O_6S_2$ $(M+H)^+$ 653.1, found 652.7.

*4-((3-(3-Aminobenzo[d]isoxazol-5-yl)pyridin-2-yl)oxy)-2,5-difluoro-N-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (**20**).* To a solution of **S30** in CH_2Cl_2 (10 mL) was added TFA (1 mL). The mixture was stirred at ambient temperature for 5 min and then concentrated *in vacuo*. The residue was triturated in methanol (15 mL), filtered, and the filtrate concentrated to afford **20** as a colorless solid in 7% yield over 2 steps from **S29** (0.011 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.44 (s, 1H), 8.16–8.11 (m, 2H), 8.02 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.83 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.78 (dd, *J* = 9.6, 6.4 Hz, 1H), 7.66 (dd, *J* = 10.1, 6.1 Hz, 1H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.36 (dd, *J* = 7.5, 4.9 Hz, 1H), 6.52 (br s, 2H), (sulfonamide NH not observed); HRMS *m/z* calcd for $C_{20}H_{13}F_2N_6O_4S_2$ $(M+H)^+$ 503.0402, found 503.0409.

1.16 Synthesis of Compound 21.

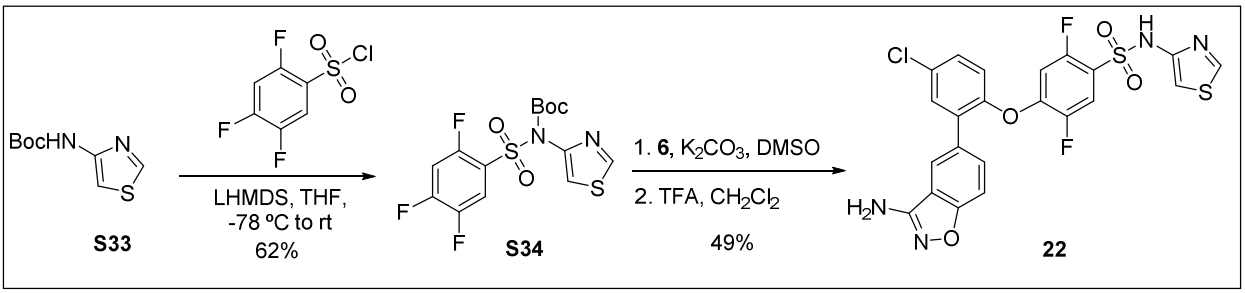


*tert-Butyl (5-vinylbenzo[d]isoxazol-3-yl)carbamate (**S31**)*. To a mixture of di-*tert*-butyl (5-bromo-1,2-benzoxazol-3-yl)imidodicarbonate (**8**) (0.827 g, 2.0 mmol), potassium vinyltrifluoroborate (0.402 g, 3.0 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.232 g, 0.2 mmol) in dioxane (12 mL) was added 2 M sodium carbonate (3.0 mL, 6.0 mmol). The reaction mixture was degassed by passing argon through it and then heated to 120 ºC for 16 h. After cooling to ambient temperature, the mixture was diluted with EtOAc (50 mL) and filtered over Na_2SO_4. Concentration of the filtrate *in vacuo* provided a residue which was purified by column chromatography (0-20% EtOAc in hexanes) to afford **S31** as a yellowish oil in 52% yield (0.27 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.65 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.46–7.36 (m, 2H), 6.81 (dd, *J* = 17.5, 10.9 Hz, 1H), 5.74 (d, *J* = 17.6 Hz, 1H), 5.26 (d, *J* = 10.9 Hz, 1H), 1.55 (s, 9H).

*tert-Butyl (5-(2-hydroxyethyl)benzo[d]isoxazol-3-yl)carbamate (**S32**).* To a cold (0 ºC) mixture of **S31** (0.270 g, 1.04 mmol) in anhydrous THF (5 mL) was added 9-borabicyclo[3.3.1]nonane (10.4 mL of a 0.5 M solution in THF, 5.2 mmol). The reaction mixture was allowed to warm to ambient temperature and stirred for 16 h. The mixture was then diluted with methanol (10 mL), cooled to 0 ºC , and 1 M sodium hydroxide (6.2 mmol) followed by 32% hydrogen peroxide (0.59 mL, 6.2 mmol) was added. The reaction mixture was stirred for 2 h at 0 ºC. The mixture was extracted with CH_2Cl_2 (3 x 15 mL), and the combined organic phase was washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by column chromatography (0-20% EtOAc in hexanes) afforded **S32** as a colorless solid in 45% yield (0.13 g). ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD) δ 7.74 (s, 1H), 7.33–7.32 (m, 2H), 3.76 (t, *J* = 6.7, 6.7 Hz, 2H), 2.87 (t, *J* = 6.6, 6.6 Hz, 2H), 1.47 (s, 9H) (NH and OH not observed); LRMS *m/z* calcd for $C_{14}H_{18}N_2NaO_4$ $(M+Na)^+$ 301.1, found 301.0.

*4-(2-(3-Aminobenzo[d]isoxazol-5-yl)ethoxy)-2,5-difluoro-N-(1,2,4-thiadiazol-5-yl)-benzenesulfonamide (**21**).* Step 1. To a cold (0 ºC) mixture of **S32** (0.120 g, 0.43 mmol) in anhydrous DMF (3 mL) was added a 1.0 M solution of LHMDS in THF (1.3 mL, 1.3 mmol). The reaction mixture was stirred for 1 h at 0 ºC and then allowed to warm to ambient temperature. To it was then added sulfonamide **9** (0.211 g, 0.47 mmol) in one portion. The reaction mixture was stirred for 1 h at ambient temperature and then quenched by addition of saturated NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 x 20 mL), and the organic phase was washed with water (2 x 5 mL), brine (2 x 5 mL), and dried over anhydrous Na_2SO_4. After concentration *in vacuo*, the obtained residue was purified by column chromatography (10-100% EtOAc in hexanes) to afford *tert*-butyl (5-(2-(4-(*N*-(2,4-dimethoxybenzyl)-*N*-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2,5-difluorophenoxy)ethyl)benzo[*d*]isoxazol-3-yl)carbamate as an off-white solid in 84% yield (0.256 g). LRMS *m/z* calcd for $C_{31}H_{32}F_2N_5O_8S_2$ $(M+H)^+$ 704.2, found 703.9. Step 2. To a mixture of the product from step 1 in CH_2Cl_2 (4 mL) was added TFA (0.4 mL) and the reaction mixture was stirred at ambient temperature for 2 h. Concentration *in vacuo* provided a residue which was purified by column chromatography (0-20% MeOH in CH_2Cl_2) followed by lyophilization from water to afford **21** as an off-white solid in 70% yield (0.115 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.35 (s, 1H), 7.68 (d, J = 0.9 Hz, 1H), 7.54 (dd, J = 10.5, 6.7 Hz, 1H), 7.45 (dd, J = 8.6, 1.7 Hz, 1H), 7.38–7.30 (m, 2H), 6.31 (br s, 2H), 4.33 (t, J = 6.8 Hz, 2H), 3.12 (t, J = 6.7 Hz, 2H), (sulfonamide NH not oberved); ^{13}C NMR (75 MHz, DMSO-d_6) δ 179.7, 160.9, 158.3, 155.2 (dd, J = 250.3, 2.2 Hz), 150.7 (dd, J = 11.9, 10.9 Hz), 149.8, 146.5 (dd, J = 244.2, 2.7 Hz), 131.3, 131.0, 121.5, 120.7 (dd, J = 17.9, 5.2 Hz), 116.9, 115.2 (dd, J = 22.9, 2.4 Hz), 109.2, 104.3 (d, J = 27.7 Hz), 70.3, 34.0. ^{19}F NMR (282 MHz, DMSO-d_6) δ -110.6 (d, J = 15.2 Hz, 1F), -138.4 (d, J = 15.3 Hz, 1F); HRMS *m/z* calcd for $C_{17}H_{14}F_2N_5O_4S_2$ $(M+H)^+$ 454.0450, found 454.0457.

1.17 Synthesis of Compound 22.

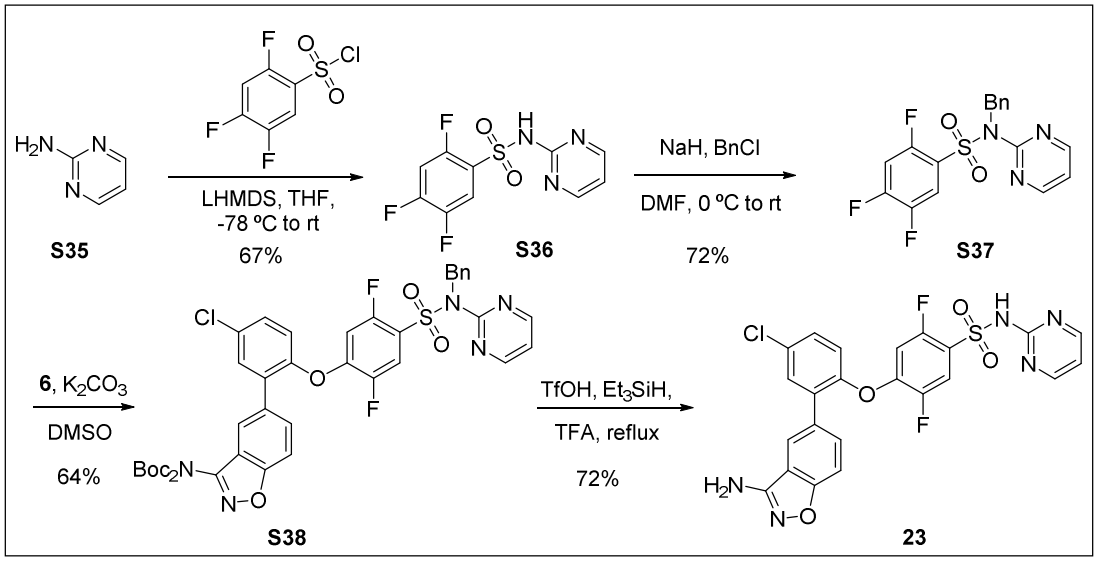


*tert-Butyl thiazol-4-yl((2,4,5-trifluorophenyl)sulfonyl)carbamate (**S34**).* A cold (at -78 ºC) solution of *tert-butyl* thiazol-4-ylcarbamate *(**S33**)* (3.46 g, 17.3 mmol) in anhydrous THF (150 mL) was treated with a 1.0 M solution of LHMDS in THF (20.8 mL, 20.8 mmol). The resulting mixture was stirred at -78 ºC for 0.5 h, allowed to warm to ambient

temperature and stirred for a further 0.5 h. The reaction mixture was cooled to -78 ºC, and a solution of 2,4,5-trifluorobenzene-1-sulfonyl chloride (3.99 g, 17.3 mmol) in anhydrous THF (30 mL) was added to it. The resulting mixture was stirred at -78 ºC for 4 h, allowed to warm to ambient temperature and stirred for 16 h. The reaction mixture was diluted with EtOAc (300 mL), washed with saturated aqueous NH_4Cl solution (2 x 150 mL), brine (2 x 150 mL), and dried over anhydrous Na_2SO_4. Concentration *in vacuo* provided a residue which was purified by column chromatography (EtOAc in hexanes) to afford **S34** as a beige solid in 62% yield (4.23 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79–8.75 (m, 1H), 8.06–7.96 (m, 1H), 7.53–7.48 (m, 1H), 7.15–7.04 (m, 1H), 1.34 (s, 9H); LRMS *m/z* calcd for $C_{14}H_{14}F_3N_2O_4S_2$ $(M+H)^+$ 395.0, found 394.7.

*4-(2-(3-Aminobenzo[d]isoxazol-5-yl)-4-chlorophenoxy)-2,5-difluoro-N-(thiazol-4-yl)benzenesulfonamide (**22**).* Following the procedure as described for the synthesis of **3** and making non-critical variations using **S34** to replace sulfonamide **9**, compound **22** was obtained as a colorless solid in 49% yield over 2 steps (0.35 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.36 (br s, 1H), 8.82 (d, *J* = 1.9 Hz, 1H), 7.94 (d, *J* = 1.3 Hz, 1H), 7.67 (dd, *J* = 10.1, 6.4 Hz, 1H), 7.61-7.55 (m, 2H), 7.48 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.41 (d, *J* = 8.8 Hz, 1H), 7.26 (d, *J* = 8.8 Hz, 1H), 7.05 (dd, *J* = 10.7, 6.4 Hz, 1H), 6.98 (d, *J* = 2.0 Hz, 1H), 6.44 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.3, 158.5, 154.6 (dd, *J* = 253.7, 2.4 Hz), 153.2, 149.9, 148.7 (dd, *J* = 12.4, 10.6 Hz), 147.3 (dd, *J* = 247.2, 2.9 Hz), 146.5, 134.1, 131.0, 130.6, 129.8, 129.2, 128.9, 122.2, 122.2-122.0 (m), 121.9, 117.9 (d, *J* = 22.7 Hz), 117.1, 109.2, 108.2 (d, *J* = 27.2 Hz), 104.3; HRMS *m/z* calcd for $C_{22}H_{14}ClF_2N_4O_4S_2$ $(M+H)^+$ 535.0108, found 535.0115.

1.18 Synthesis of Compound 23.



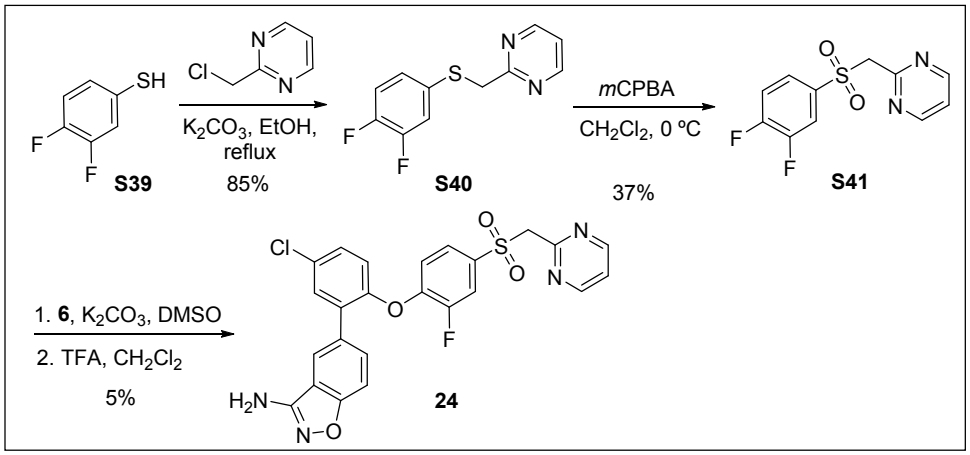
*2,4,5-Trifluoro-N-(pyrimidin-2-yl)benzenesulfonamide (**S36**).* To a cold (0^0 C) solution of 2-aminopyrimidine (**S35**) (10.1 g, 10.5 mmol) in anhydrous THF (150 mL) was added a 1.0 M solution of LHMDS in THF (15 mL, 15 mmol) and the reaction mixture was stirred for 0.5 h. The reaction mixture was cooled to -78 ^{0}C, and a solution of 2,4,5-trifluorobenzene-1-sulfonyl chloride (10.1 mmol) in anhydrous THF (100 mL) was added to it. The reaction mixture was allowed to warm to ambient temperature and stirred for 16 h. The mixture was diluted with EtOAc (150 mL), washed with NH_4Cl solution (3 x 50 mL), brine (3 x 50 mL), and dried over Na_2SO_4. After concentration *in vacuo*, the residue was triturated with Et_2O to afford **S36** as pale yellow solid in 67% yield (19.5 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.88 (br s, 1H), 8.51 (d, J = 5.0 Hz, 2H), 8.00 (ddd, J = 9.6, 8.9, 6.6 Hz, 1H), 7.76 (ddd, J = 10.2, 10.2, 6.3 Hz, 1H), 7.03 (t, J = 5.0 Hz, 1H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -111.1 (dd, J = 15.7, 8.6 Hz,1F), -126.3–126.6 (m, 1F), -141.2 (dd, J = 22.4, 15.8 Hz,1F); LRMS *m/z* calcd for $C_{10}H_7F_3N_3O_2S$ $(M+H)^+$ 290.0, found 290.1.

*N-Benzyl-2,4,5-trifluoro-N-(pyrimidin-2-yl)benzenesulfonamide (**S37**).* To a cold (0 °C) solution of **S36** (1.00 g, 3.46 mmol) in anhydrous DMF (10 mL) was added NaH (0.20 g, 5.19 mmol, 60% dispersion in oil), the reaction mixture was stirred for 0.5 h, and benzyl chloride (0.65 g, 5.1 mmol) was added to it. The reaction mixture was allowed to warm to ambient temperature, and stirred for 16 h. The mixture was diluted with EtOAc (100 mL), washed with brine (3 x 25 mL), and dried over anhydrous Na_2SO_4. After concentration *in vacuo*, the residue was triturated with Et_2O to afford the **S37** as beige solid in 72% yield (0.95 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.53–8.51 (m, 2H), 8.18–8.09 (m, 1H), 7.89–7.81 (m, 1H), 7.41–7.28 (m 4H), 7.26–7.18 (m, 1H), 7.14–7.11 (m, 1H), 5.37 (s, 2H); LRMS *m/z* calcd for $C_{17}H_{13}F_3N_3O_2S$ $(M+H)^+$ 380.1, found 380.0.

*di-tert-Butyl (5-(2-(4-(N-benzyl-N-(pyrimidin-2-yl)sulfamoyl)-2,5-difluorophenoxy)-5-chlorophenyl)benzo[d]isoxazol-3-yl)imidodicarbonate (**S38**).* To a mixture of phenol **6** (1.99 g, 4.32 mmol) and sulfonamide **S37** (1.90 g, 5.01 mmol) in anhydrous DMSO (15 mL) was added potassium carbonate (1.20 g, 8.68 mmol) and the reaction mixture was stirred at ambient temperature for 5 h. Saturated $NaHCO_3$ solution (50 mL) was added to it, and the mixture was extracted with Et_2O (2 x 200 mL). The combined organic phase was dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by column chromatography (0-30% EtOAc in hexanes) to afford **S38** as a colorless, amorphous solid in 64% yield (2.27 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ8.31–8.29 (m, 2H), 7.84 (dd, J = 6.4, 9.8 Hz, 1H), 7.67–7.63 (m, 2H), 7.52–7.49 (m, 1H), 7.46–7.42 (m, 3H), 7.40–7.36 (m, 1H), 7.31–7.29 (m, 1H), 7.26–7.22 (m, 2H), 7.05 (d, J = 8.6 Hz, 1H), 6.88–6.85 (m, 1H), 6.38 (dd, J = 6.2, 10.2 Hz, 1H), 5.39 (s, 2H), 1.38 (s, 18H); LRMS *m/z* calcd for $C_{40}H_{37}ClF_2N_5O_8S$ $(M+H)^+$ 820.2, found 819.7.

*4-(2-(3-Aminobenzo[d]isoxazol-5-yl)-4-chlorophenoxy)-2,5-difluoro-N-(pyrimidin-2-yl)benzenesulfonamide (**23**).* To a solution of **S38** (2.03 g, 2.47 mmol) in TFA (50 mL) was added triethylsilane (2.0 mL, 13 mmol) and trifluoromethanesulfonic acid (0.5 mL) and the reaction mixture was heated at reflux for 5 h. After cooling to ambient temperature and concentrating the mixture *in vacuo*, the obtained residue was triturated in Et_2O (40 mL) to afford **23** as an off-white solid in 72% yield (0.95 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.38 (d, J = 5.1 Hz, 2H), 7.92 (m, 1H), 7.75 (dd, J = 10.2, 6.5 Hz, 1H), 7.60-7.56 (m, 2H), 7.48 (dd, J =8.7, 2.7 Hz, 1H), 7.38 (d, J = 8.7 Hz, 1H), 7.27 (d, J = 8.7 Hz, 1H), 7.00-6.93 (m, 2H), 6.47-6.36 (m, 2H), (sulfonamide NH not observed); ^{19}F NMR (282 MHz, DMSO-d_6) δ -112.4 (d, J = 16.4 Hz, 1F), -137.9 (d, J = 16.4 Hz, 1F); HRMS *m/z* calcd for $C_{23}H_{15}ClF_2N_5O_4S$ $(M+H)^+$ 530.0496, found 530.0502.

1.19 Synthesis of Compound 24.



*2-(((3,4-Difluorophenyl)thio)methyl)pyrimidine (**S40**).* To a mixture of 2-(chloromethyl)pyrimidine hydrochloride (12.2 g, 73.9 mmol) and K_2CO_3 (27.9 g, 201.6 mmol) in anhydrous ethanol (150 mL) was added with 3,4-difluorobenzenethiol (**S39**) (7.4 mL, 67.2 mmol) and the reaction mixture was heated under reflux for 18 h. After cooling to ambient temperature, the solid was filtered off and the filtrate was concentrated *in vacuo*. The residue was dissolved in EtOAc (250 mL), washed with saturated ammonium chloride (2 x 75 mL), brine (75 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. Purification by column chromatography (0-75% EtOAc in hexanes) provided **S40** as a colorless oil in 85% yield (13.6 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (d, J = 5.1 Hz, 2H), 7.26–7.18 (m, 1H), 7.15 (dd, J = 5.0 Hz, 1H), 7.11–7.05 (m, 1H), 7.05–9.95 (m, 1H), 4.29 (s, 2H); LRMS *m/z* calcd for $C_{11}H_9F_2N_2S$ $(M+H)^+$ 239.0, found 239.0.

*2-(((3,4-Difluorophenyl)sulfonyl)methyl)pyrimidine (**S41**).* To a cold (0 ºC) solution of **S40** (11.6 g, 48.7 mmol) in CH_2Cl_2 (250 mL) was added 77% *m*-chloroperoxybenzoic acid (16.4 g, 73.1 mmol). The resulting mixture was stirred for 18 h and then

concentrated *in vacuo*. The residue was diluted with ethyl acetate (250 mL), washed with 1 M sodium hydroxide (3 x 100 mL), brine (3 x 75 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified by flash chromatography (15-100% EtOAc in hexanes) to afford **S41** as a colorless solid in 37% yield (4.9 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (d, J = 5.1 Hz, 2H), 7.60–4.86 (m, 2H), 7.31–7.21 (m, 2H), 4.72 (s, 2H); LRMS *m/z* calcd for $C_{11}H_9F_2N_2O_2S$ $(M+H)^+$ 271.0, found 271.0.

5-(5-Chloro-2-(2-fluoro-4-((pyrimidin-2-ylmethyl)sulfonyl)phenoxy)phenyl)benzo[d]isoxazol-3-amine (**24**). A mixture of **S41** (0.18 g, 0.65 mmol), **6** (0.30 g, 0.65 mmol) and potassium carbonate (0.27 g, 1.95 mmol) in anhydrous dimethylformamide (4.0 mL) was heated to 80 ºC for 3 h. The reaction mixture was diluted with ethyl acetate (50 mL), washed with saturated ammonium chloride (2 x 30 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (5 mL) and TFA (5 mL) was added to it. The resulting mixture was stirred at ambient temperature for 2 h and then concentrated *in vacuo*. The residue was purified by preparative HPLC (Waters XBridge, C18, 5 µm, 30 x 50 mm, 15-95% CH_3CN in water containing 0.1% TFA) to provide **24** as a colorless solid in 5% yield (0.017 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.58 (d, J = 4.8 Hz, 2H), 7.98–7.96 (m, 1H), 7.71–7.60 (m, 3H), 7.53 (dd, J = 8.6, 2.5 Hz, 1H), 7.46 (d, J = 8.9 Hz, 1H), 7.39–7.30 (m, 2H), 7.22 (d, J = 8.8 Hz, 1H), 7.00–6.93 (m, 1H), 6.47 (br s, 2H), 4.88 (s, 2H); LRMS *m/z* calcd for $C_{24}H_{17}ClFN_4O_4S$ $(M+H)^+$ 511.1, found 510.8.

1.20 HPLC Purity Check of Final Compounds

Purity was determined by HPLC analysis on Agilent 1100, 1200, or 1260 systems (Agilent Technologies) using an Xbridge C-18 column (5 µm, 4.6 x 50 mm, Waters Corporation) with a gradient of CH_3CN in water containing 0.1% TFA at a flow rate of 1.0 mL/min at 25 ºC: 5% CH_3CN for 1 min, 5% to 95% CH_3CN over 5 min, 95% CH_3CN for 3 min. Peaks were detected at a wavelength of 254 or 280 nm with an Agilent photodiode array detector. The retention times vary by about 0.1 min between the different HPLC systems (Agilent 1100, 1200, or 1260).

Compound	RT (min)	Purity (%)
2	4.59	98
3	5.62	97
10	5.95	95
11	4.97	99
12	4.85	>99
13	4.56 (broad)	97
14	5.92	>99
15	4.93	>99
16	4.94	>99
17	5.34	99
18	5.30	98
19	5.54	98
20	5.17	96
21	5.06	91
22	5.90	>99
23	5.45	96
24	5.49	97

For selected compounds, purity check was also performed using a high pH method: Gemini NX C-18 column (3 µm, 4.6 x 150 mm, Phenomenex) with a gradient of CH_3CN in water containing 0.1% NH_4OH at a flow rate of 1.0 mL/min at 25 ºC: 10% CH_3CN for 2 min, 10% to 80% CH_3CN over 16 min, 95% CH_3CN for 4 min.

Compound	RT (min)	Purity (%)
13	8.98	96

Compounds that were used for advanced profiling and *in vivo* studies were checked for purity by a longer HPLC method using a Gemini NX C-18 column (5 µm, 4.6 x 150 mm, Phenomenex) with a gradient of CH_3CN in water containing 0.1% TFA at a flow rate of 1.0 mL/min at 25 ºC: 5% CH_3CN for 2 min, 5% to 95% CH_3CN over 40 min.

Compound	RT (min)	Purity (%)
3a	24.86	98
16	23.04	99

2. Voltage-Clamp Whole Cell Recordings and Cell Lines

$Na_V1.x$ cell lines: cDNA sequences encoding the full-length human sodium channel α-subunit were cloned into an expression vector and permanently transfected into human embryonic kidney cells (HEK) and grown in culture media containing 10% FBS, 1%

PSG, and 0.5 mg/mL G418 at 37 ℃ with 5% CO_2. The human sodium channel β1 subunit was co-expressed in all these cell lines except $Na_V1.8$ (which was co-expressed with the human sodium channel β3 subunit). The neuronal CAD cell was used to assess endogenous mouse NaV1.7 currents.[1] Macroscopic sodium currents were recorded in the whole-cell configuration using either the PatchXpress® (PX, Molecular Devices, Sunnyvale, CA) or QPatch HT (Sophion A/S, Copenhagen, Denmark) automated voltage clamp device.

For the majority of Na_V cell line studies (except $Na_V1.8$), the intracellular solution comprised 5 mM NaCl, 10 mM CsCl, 120 mM CsF, 0.1 mM $CaCl_2$, 2 mM $MgCl_2$, 10 mM HEPES, 10 mM EGTA (adjusted to pH 7.2 with CsOH), while the extracellular solution comprised 140 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM HEPES (adjusted to pH 7.4 with NaOH). Generally, the external sodium was reduced by equimolar replacement with choline.

For $Na_V1.8$ studies, a flipped Na^+ gradient was used where the intracellular solution comprised 115 mM NaF, 15 mM $CsCl_2$, 5 mM CsF, 3 mM Na_2ATP, 0.3 mM Na_2GTP, 2mM $MgCl_2 \cdot H_2O$, 0.1 mM $CaCl_2$, 10 mM EGTA, 10 mM HEPES (pH 7.2 with CsOH), while the extracellular solution comprised 5 mM NaCl, 125 mM Choline chloride, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$ and 10 mM HEPES (adjusted to pH 7.4 with NaOH).

Osmolarity in the internal and external solutions was adjusted to 300 mOsm/kg and 310 mOsm/kg with glucose, respectively. Currents were recorded at 40 kHz sampling frequency, filtered at 5 Hz, and analyzed either with DataXpress software (DX2, Molecular Devices, Sunnyvale, CA) or with QPatch Assay Software (Sophion A/S, Copenhagen, Denmark). Series resistance compensation was applied at 60-80%.

The membrane potential was maintained at a holding voltage (V_{hold}) where inactivation of the channel was complete. Specifically, for inactivated state block, general holding voltages were -60 mV ($Na_V1.7$ and $Na_V1.5$), -35 mV ($Na_V1.2$, and $Na_V1.6$), -40 mV ($Na_V1.1$), -50 mV ($Na_V1.3$), and -20 mV ($Na_V1.8$). Once every second, the voltage was then stepped back to a very negative (V_{hold} = -150mV) voltage for 20 ms and then a test pulse is applied to quantify the drug block. Compound inhibition was fitted to the hill equation $Y = C^h/(IC_{50}{}^h+C^h)$ to estimate the half maximal inhibition concentration (IC_{50} value); where Y is the normalized inhibition relative to the control, C the test compound concentration, IC_{50} the concentration of test compound to inhibit the currents 50%, and h the Hill coefficient.

Table 1-3 data by automated voltage clamp device:

Cmpd	Voltage clamp device	$hNa_V1.7$ IC_{50} [nM]	Voltage clamp device	$hNa_V1.5$ IC_{50} [nM]
2	PatchXpress®[a]	17 ± 6	PatchXpress®[a]	>10,000
3	PatchXpress®[a]	0.4 ± 0.2	PatchXpress®[a]	1,380 ± 668
10	PatchXpress®[a]	0.5 ± 0.0	PatchXpress®[a]	230 ± 42
11	PatchXpress®[a]	5.3 ± 2.1	QPatch HT[b]	>10,000
12	PatchXpress®[a]	2,300 ± 870	N/A	nd
13	PatchXpress®[a]	222 ± 54	QPatch HT[b]	>10,000
14	PatchXpress®[a]	3.6 ± 2.0	PatchXpress®[a]	>10,000
15	PatchXpress®[a]	1.7 ± 0.9	QPatch HT[b]	>10,000
16	PatchXpress®[a]	0.3 ± 0.2	PatchXpress®[a]	>10,000
17	PatchXpress®[a]	1.7 ± 0.5	PatchXpress®[a]	>10,000
18	PatchXpress®[a]	3.0 ± 0.8	N/A	nd
19	PatchXpress®[a]	1.7 ± 0.4	N/A	nd
20	PatchXpress®[a]	51 ± 11	N/A	nd
21	PatchXpress®[a]	241 ± 122	N/A	nd
22	PatchXpress®[a]	8.7 ± 3.6	N/A	nd
23	PatchXpress®[a]	4.4 ± 0.9	N/A	nd
24	QPatch HT[b]	5,200	N/A	nd

[a] IC_{50} values are reported as average values of two or more determinations ± SD, generated from a 5-point concentration response curve on an automated voltage-clamp platform; nd: not determined. [b] IC50 generated from the fit of pooled data; average and SD do not apply in this case.

Table 4 and text data by automated voltage clamp device:

$Na_V1.x$		Cmpd 3	Cmpd 16	Cmpd 14
		IC_{50} [nM]	IC_{50} [nM]	IC_{50} [nM]
hNa_V 1.1	PatchXpress®[a]	3,080 ± 1850	6,380 ± 3900	-
hNa_V 1.2	PatchXpress®[a]	4.2 ± 2.3	0.2 ± 0.0	-
hNa_V 1.3	PatchXpress®[a]	nd	9,330 ± 4590	-
hNa_V 1.4	QPatch HT[b]	nd	>10,000	-
hNa_V 1.5	PatchXpress®[a] / QPatch HT[b]	1,380 ± 668 / 5,660	>10,000	-
hNa_V 1.6	PatchXpress®[a]	11 ± 4	0.8 ± 0.7	-
hNa_V 1.7	PatchXpress®[a] / QPatch HT[b]	0.4 ± 0.2 / 0.2	0.3 ± 0.2 / 0.1	3.6 ± 2.0 / 2.2
hNa_V 1.7	Manual, -150 mV [c]	-	495 ± 23	-
hNa_V 1.8	Manual [c]	nd	3,850 ± 930	-
$rNa_V1.7$	PatchXpress®[a] / QPatch HT[b]	26 ± 10 / -	nd	- / 740
$mNa_V1.7$	PatchXpress®[a]	0.2 ± 0.1	nd	-

[a] IC_{50} values are reported as average values of two or more determinations, generated from a 5-point concentration response curve on an automated voltage-clamp platform; nd: not determined. [b] IC50 generated from the fit of pooled data; average and SD do not apply in this case. [c] Determined by manual voltage-clamp.

3. In Vitro Predicated Hepatic Clearance Data with Hepatocytes

The oxidative and conjugative metabolism of compounds were evaluated in cryopreserved hepatocytes from CD-1 mice (n=10), Sprague-Dawley rats (n=3), (Invitrogen Corporation, Carlsbad, CA), and humans (n=10; Celsis, Baltimore, MD). The cells were seeded at a density of 0.5 x 10^6 cells/mL, reactions were initiated with the addition of compound to make the final substrate concentration of 1 µM. Samples were incubated at 37 ℃ in 5% carbon dioxide with s aturating humidity, and aliquots were sampled at 0, 1, 2 and 3 hours. Reactions were quenched with acetonitrile containing internal standard at each timepoint. Samples were centrifuged at 2000 g for 10 minutes. Supernatant was diluted with water (1:2 ratio) and the percentage of compound remaining was determined by LC/MS/MS. Using the t=0 peak area ratio values as 100%, the *in vitro* CL_{int} and scaled hepatic CL were determined as described:[2-4] Standard deviation not applicable.

$CL_{hep} = \frac{Q_{Liver}*CL_{int}}{Q_{Liver}+CL_{int}}$, where Q_{Liver} is the liver blood flow.

4. In Vitro MDCK Cell Permeability

The MDCKI (Madin-Darby Canine Kidney) cell line was acquired from American Type Culture Collection (Manassas, VA). The cells were seeded at a density of 1.3 x 10^5 cells/mL in Costar Transwell® plates (12-well, polyester membrane, 0.4 µm pore size, 1.0 cm2 growth area). Cells were cultured with Eagle's Minimum Essential Medium (Earle's BSS, 0.1% non essential amino acids, 1 mM sodium pyruvate, 2 mM L-glutamine, 1.5 g/L sodium bicarbonate, 10% FBS) for 5 days at 37 ℃ with 5% CO_2 and 95% humidity. Compound was added to either the apical or basolateral side of the monolayer at an initial concentration of 10 µM, and incubated at 37 ℃ for 2 hours. Transepithelial electrical resistance (TEER) and lucifer yellow (LY) permeability were used to monitor monolayer integrity at the beginning and the end of the experiments, respectively. The apparent permeability P_{app}, in the apical to basolateral (A-B) and basolateral to apical (B-A) directions, was calculated as:

$P_{app} = (dQ/dt)•(1/A•C_0)$

Where: dQ/dt = rate of compound appearance in the receiver compartment; A = Surface area of the insert; C_0= Initial substrate concentration at T_0. Standard deviation not available.

5. In Vitro Pgp (MDR1) and BCRP Transport Assays

Madin-Darby canine kidney (MDCK) cells heterologously expressing either human Pgp or mouse Bcrp1 were used to determine if a compound was a substrate of these transporters. MDR1-MDCKI cells were licensed from the National Cancer Institute

Bethesda, MD), whereas Bcrp1-MDCKII cells were obtained from the Netherlands Cancer Institutes (Amsterdam, The Netherlands). For transport studies, cells were seeded on 12-well Costar Transwell plates 4 days before use (polyester membrane, 0.4 µm pore size; Corning Life Sciences, Lowell, MA) at a seeding density of 1.3 x 105 cells/mL. Compounds were tested at 10 µM in the MDR1 assay, and at 5 µM in the Bcrp1 assay in the apical-to-basolateral (A-B) and basolateral-to-apical (B-A) directions. The compound was dissolved in transport buffer consisting of Hank's balanced salt solution and 10 mM HEPES (Invitrogen Corporation, Grand Island, NY). Lucifer Yellow (Sigma-Aldrich) was used as the paracellular marker. The efflux ratio (ER) was calculated as ER = $\frac{P_{app,B-A.}}{P_{app,A-B}}$; Standard deviation not available.

6. Plasma Protein Binding Incubations

Plasma protein binding in rat plasma was determined using 96-well equilibrium dialysis method (DIALYZER^{TM}). The percent of drug bound to protein was determined by measuring the amount of free drug that couldn pass through a semi-permeable membrane that retained plasma proteins. The test compound was prepared at a final 10µM (0.01% v/v with DMSO) in rat plasma. 200µL of the 10µM test compound plasma was added to the plasma side of the equilibrium dialysis membrane and 200µL of phosphate buffer (pH 7.4) was added to the opposite side. The dialysis plate was sealed and incubated with rotation at 37 ℃ in a 5% CO_2 incubator for 20 hours, at which time equilibrium had been reached. 100µL of the plasma and buffer samples were removed from each side of the dialysis wells into a new 96-deep well plate. To eliminate matrix effect on HPLC-MS/MS quantiation, equal volume of blank plasma and blank buffer were added to the plasma and buffer samples, respecitvely. 500µL acetonitrile with internal standard was then added to all samples. The plate was centrifuged at 4000 rpm for 20 minutes at 4℃. The amount of the parent analyte in the supernatants was then quantified in HPLC-MS/MS. All experiments were done in triplicate.

The percentage of bound drug was calculated using this equation:

% Protein Binding = (Plasma – Buffer)/(Plasma)*100%

Note: Under othwerwise similar conditions, using a shorter equibliration time (4 h) and a RED (rapid equilibrium dialysis) device, higher PPB (99.9%) was observed.

7. Cytochrome P450 (CYP) inhibition Assays

Test compounds were incubated with 0.2 mg/mL human liver microsomes (150 donor pool, BD Biosciences, San Jose, CA) together with NADPH cofactor and the specific probe substrate for each CYP tested: CYP1A2 (phenacetin), CYP2C9 (warfarin),

CYP2C19 (mephenytoin), CYP2D6 (dextromethorphan), and CYP3A4 (testosterone and midazolam). The reactions were terminated after 30 min by addition of cold acetonitrile/formic acid (94:6 v/v) containing an internal standard. Inhibition was determined through conversion of the probes substrates by CYP's as determined by LC/MS/MS analysis. Five concentrations of each test compound were tested (0.1, 1, 5, and 10 µM, as well as a solvent control) to generate IC_{50} values. IC_{50}'s obtained from single experiments, SD not applicable.

8. UV-metric pKa method

The dissociation constant (pKa) of the test compound was determined by using Spectrophotometric titration method, a UV-metric pKa method. The analysis was performed using an automatic titration instrument, Sirius T3, manufactured by Sirius Analytical Ltd. The acid/base titration was performed in the titration cell with an in-situ UV probe to measure the UV absorbance profile of the compound at each pH point during the titration. 5 µL of 10mM DMSO stock compound was dissolved by acid (0.5M HCl) and base (0.5M KOH) to make 100uM concentration. The available titration pH range was 2 to 11. The changes of UV absorbance with each pH were recorded as the compound undergoes ionization. A mathematical technique (Target Factor Analysis) was applied to this set of data to produce molar absorption profiles and to plot the proportion of each species varies with pH values. The pKa values were then determined by the combination of molar absorption profile, pH titration curve, and TFA best fit. The report pKa value was the average from three duplicate titrations. Standard deviation not available.

9. Pharmacokinetic Studies in Rats

All studies performed were approved by the Institutional Animal Care and Use Committee at Genentech, Inc. (South San Francisco, CA). Jugular and femoral vein canulated male Sprague-Dawley rats (Charles River Laboratories, Hollister, CA) were assigned to the IV group and only jugular vein canulaed rats were assigned to the PO group. At the initiation of the study, the rats weighed from 250 to 300 g. Three rats were given a single IV dose in 10% DMSO, 50% polyethylene glycol 400 and 40% phosphate buffered saline as a solution via a femoral vein canulae. Three additional rats were given a single PO dose in 0.5% methylcellulose with 0.2% Tween 80 (MCT). Blood samples (approximately 0.2 mL per sample) were drawn from each animal via the jugular vein cannulae at 0.033, 0.083, 0.25, 0.5, 1, 2, 4, 6, and 8 hours post-dose. Plasma samples were collected and analyzed.

10. Formalin- and Aconitine-Induced Pain Model in Rats

Compound **3** was dosed intraperitoneally (IP) in 0.9% saline 2 hours prior to the subcutaneous injection of formalin (50 µL; 2.5% v/v in saline) or aconitine (50 µL; 39 µM in saline) into the dorsal hindpaw to initiate the pain response. Rats were acclimatized to the test chamber for 30 minutes prior to formalin or aconitine injection. Following the injection, rats were immediately placed on the recording platform of the automated nociception analyzer (University of California San Diego, Department of Anesthesiology) where paw flinches were captured for 60 minutes using the associated data analysis software. Following data acquisition, animals were euthanized and blood was withdrawn by cardiac puncture. Plasma was then harvested and stored frozen at -80 ℃ until analyzed for the presence of test compound. The aconitine pain model was validated using the unselective sodium channel blockers mexiletine, carbamazepine, and lamotrigine.

11. CFA-Induced Cold Allodynia Pain Model in Mice

Mice were injected subcutaneously with 20 µL of Complete Freund's Adjuvant (CFA) into the ventral left hindpaw. On Day 2 post-CFA, the mice were dosed IP (10 ml/kg) with test compound formulated in saline 1 hour before inducing cold allodynia with acetone. Acclimation to the test environment was provided for 30-45 minutes prior to the application of acetone (100 ul to the plantar surface of the ipsilateral hind paw). Commencing 15 sec post acetone, the time spent flinching, licking and lifting the paw is scored for 120 sec. As detailed above for the formalin and aconitine assays, terminal plasma samples were harvested for subsequent analysis of test compound,

12. Analysis of Plasma and Brain Samples

Plasma samples (50uL) previously generated by centrifugation of blood samples collected at each time point and extracted by protein precipitation with CH_3CN after addition of an appropriate internal standard, centrifuged for 20 min and the supernatants collected for analysis. Individual rat brains were homogenized and extracted in 4 mL of 1:1 water: CH_3CN and centrifuged to collect the supernatant. A sample (50uL) of the supernatant was spiked with the appropriate internal standard and readied for analysis. All samples were analyzed by ultra-high pressure liquid chromatography (UHPLC) using gradient elution with 0.1% (v/v) formic acid in water (A) and 0.1% (v/v) formic acid in acetonitrile (B) starting at 50% B and ending at 100% B in 2 minutes on a Acquity C18, 2.5 x 50 mm, 1.7 um column. Analytes were detected by tandem mass spectrometry (MS/MS) using Waters Premier XE mass spectrometer as detector.

13. References

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(2) Obach, R. S.; Baxter, J. G.; Liston, T. E.; Silber, B. M.; Jones, B. C.; MacIntyre, F.; Rance, D. J.; Wastall, P. The Prediction of Human Pharmacokinetic Parameters from Preclinical and In Vitro Metabolism Data. *J. Pharmacol. Exp. Ther.* **1997**, *283*, 46–58.

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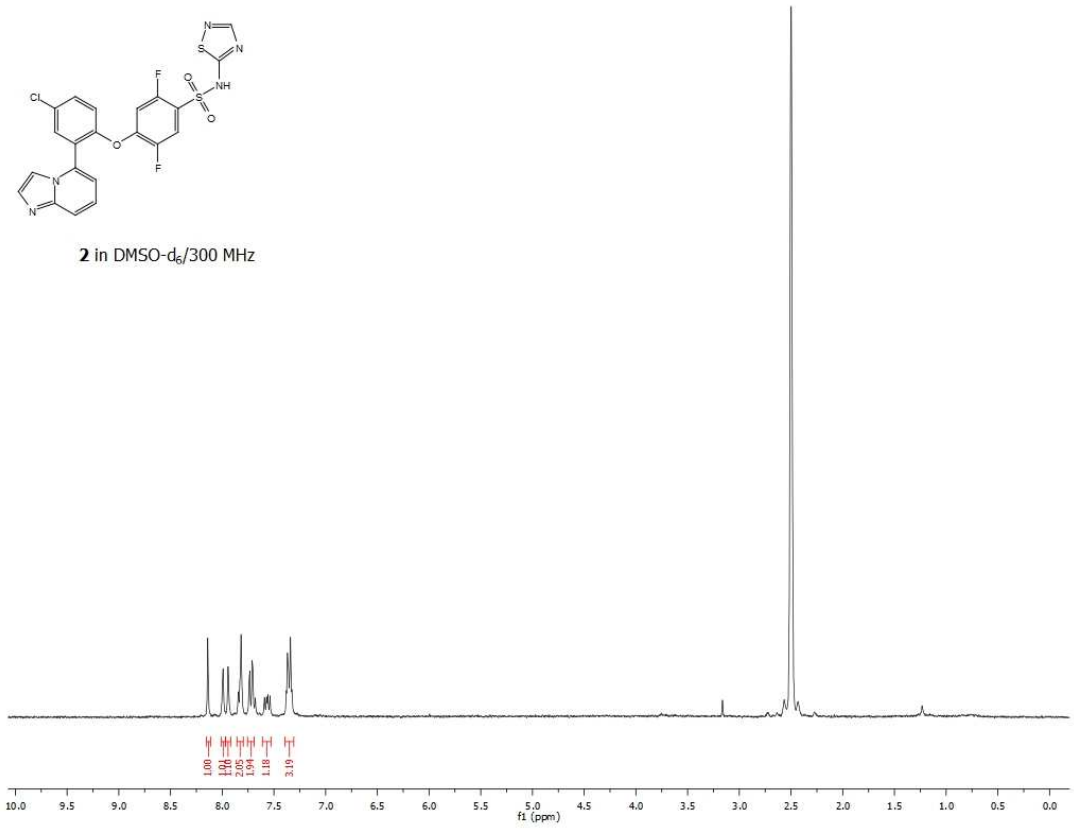
14. NMR Spectra



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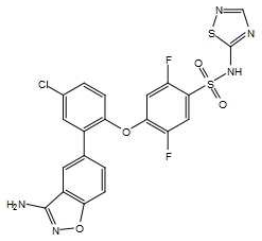

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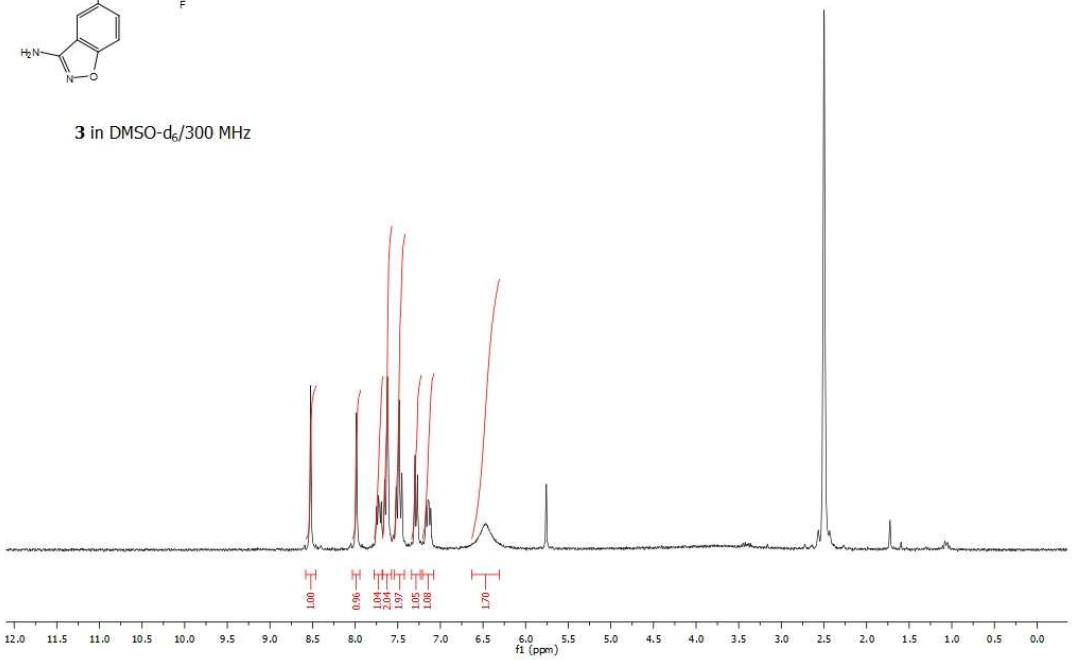

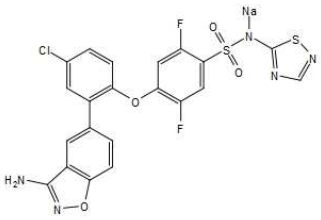

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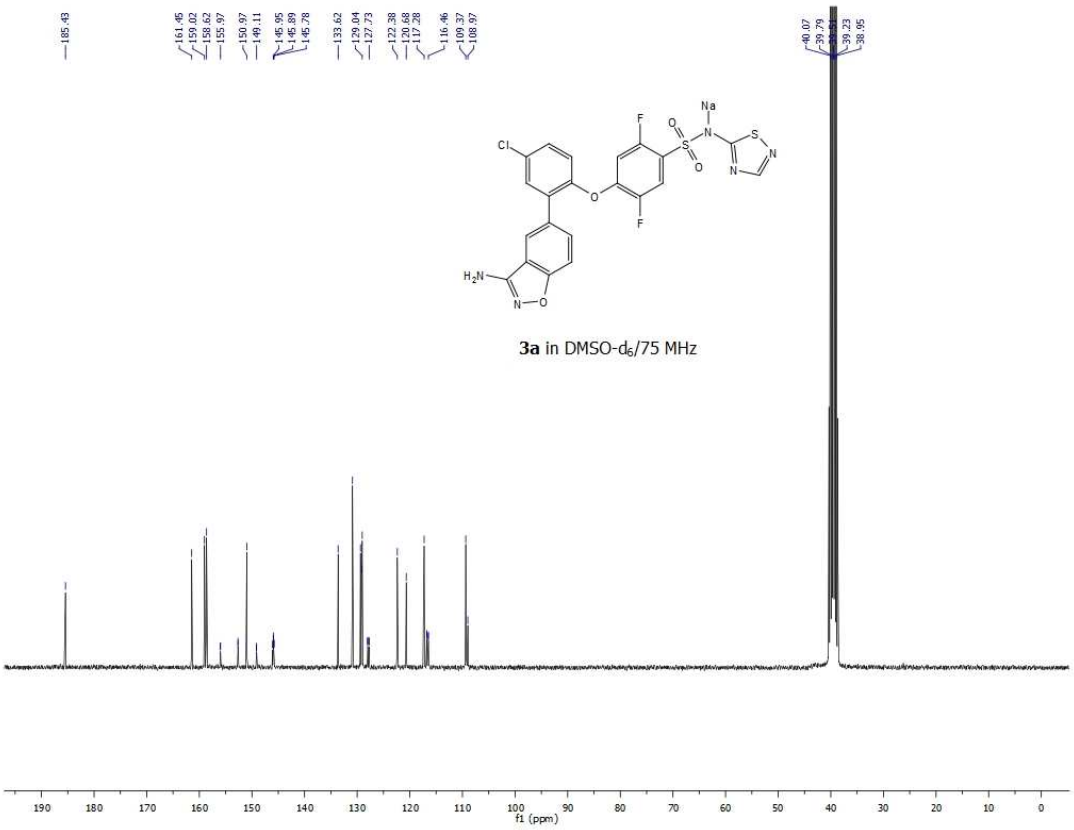

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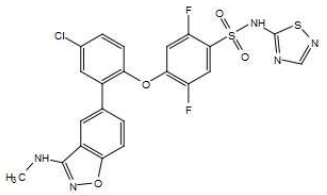

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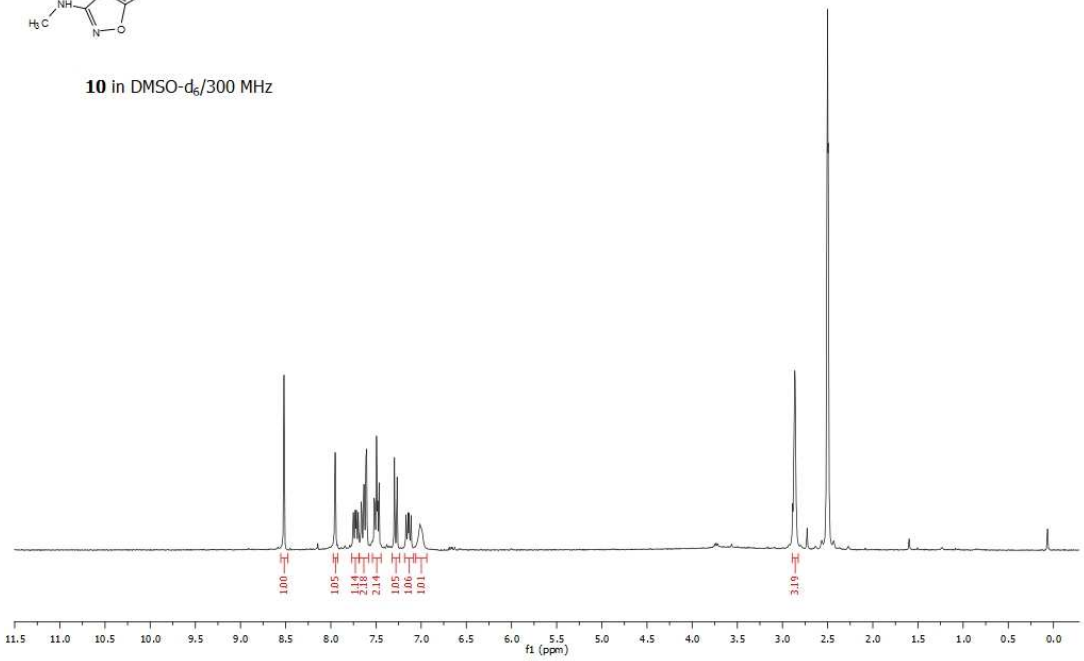

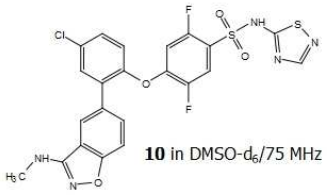

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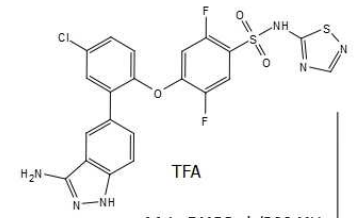

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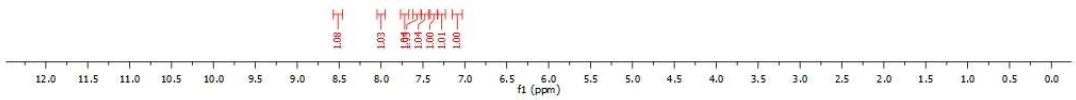

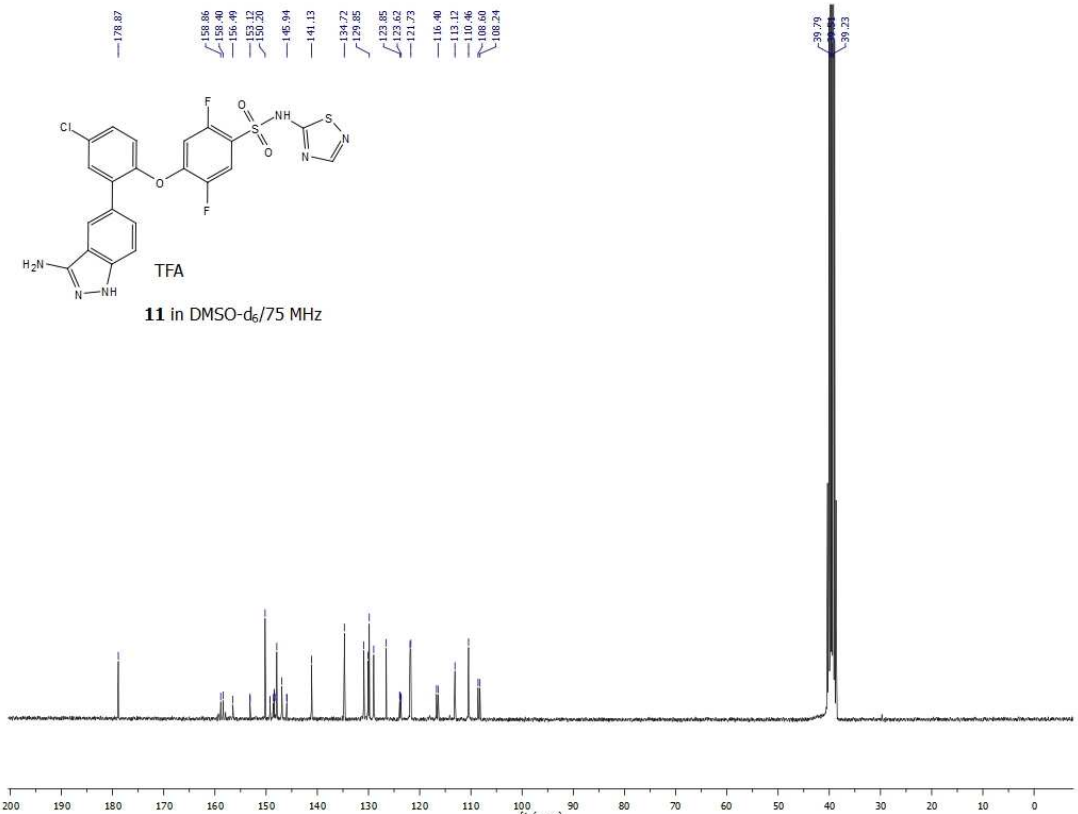

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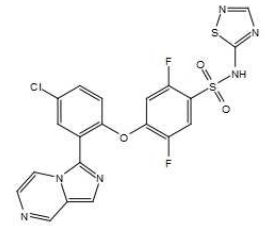

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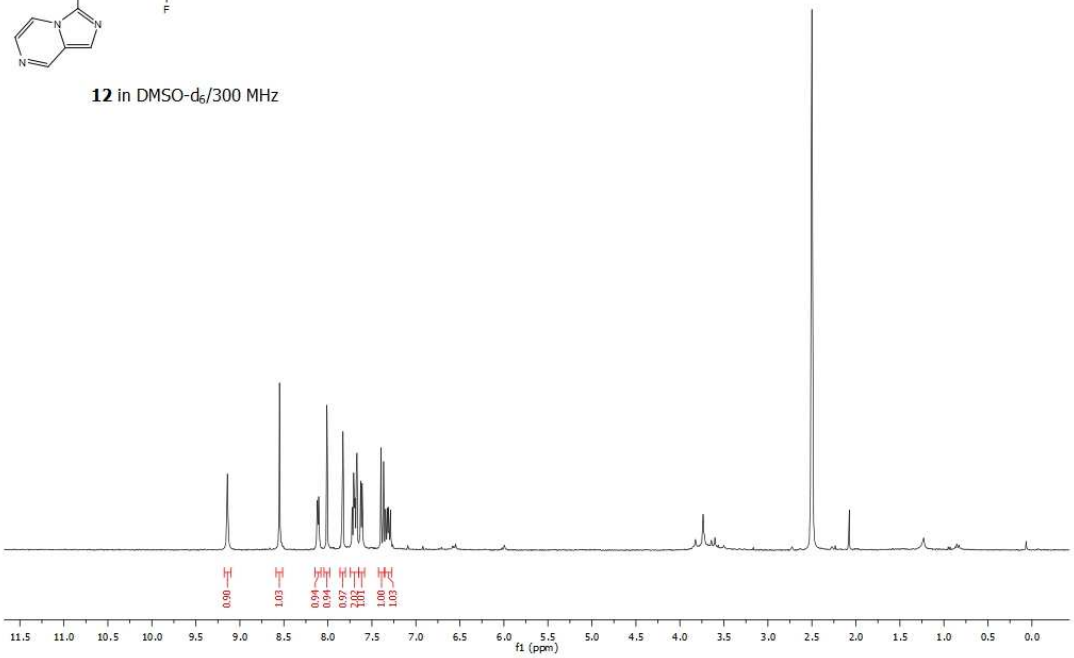

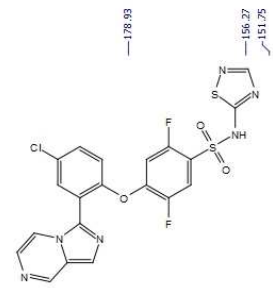

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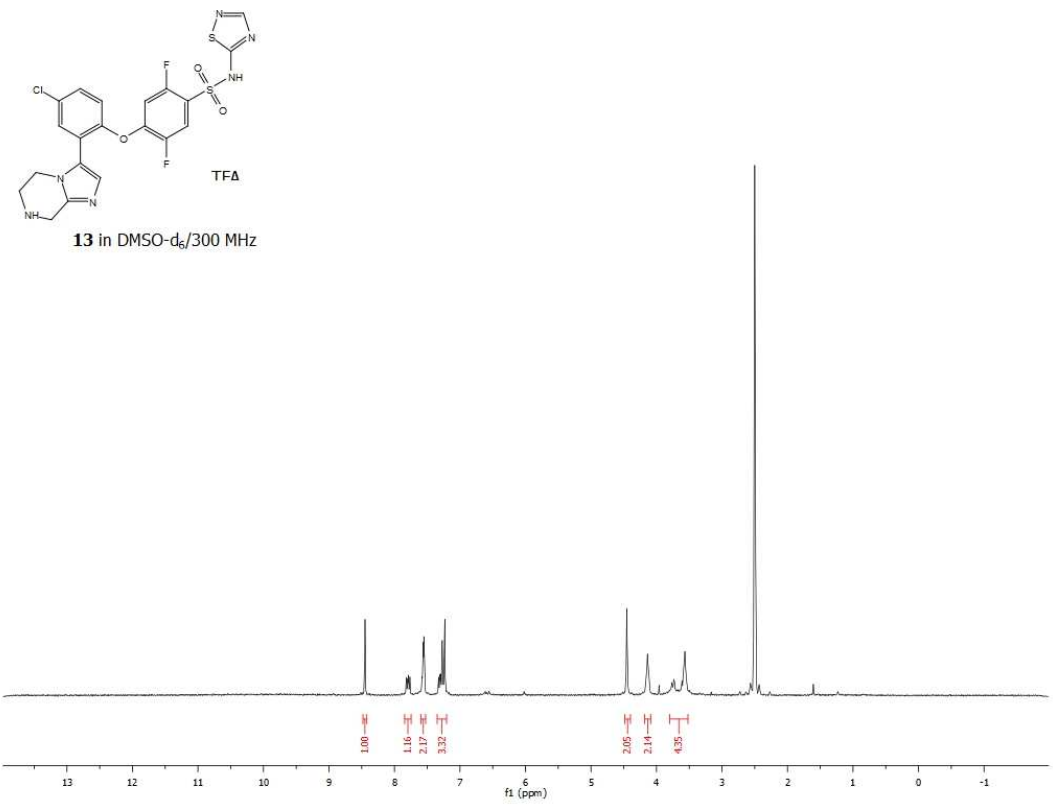

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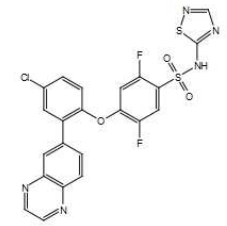

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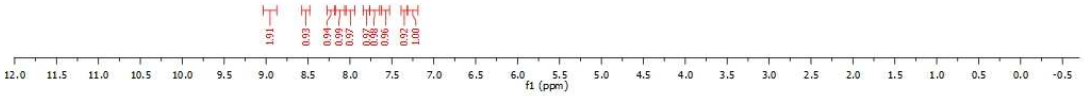

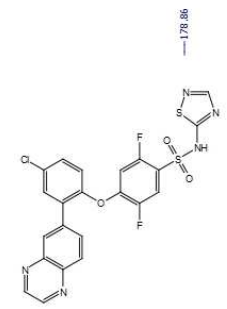

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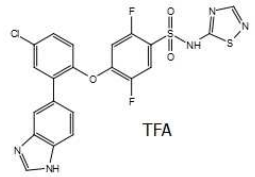

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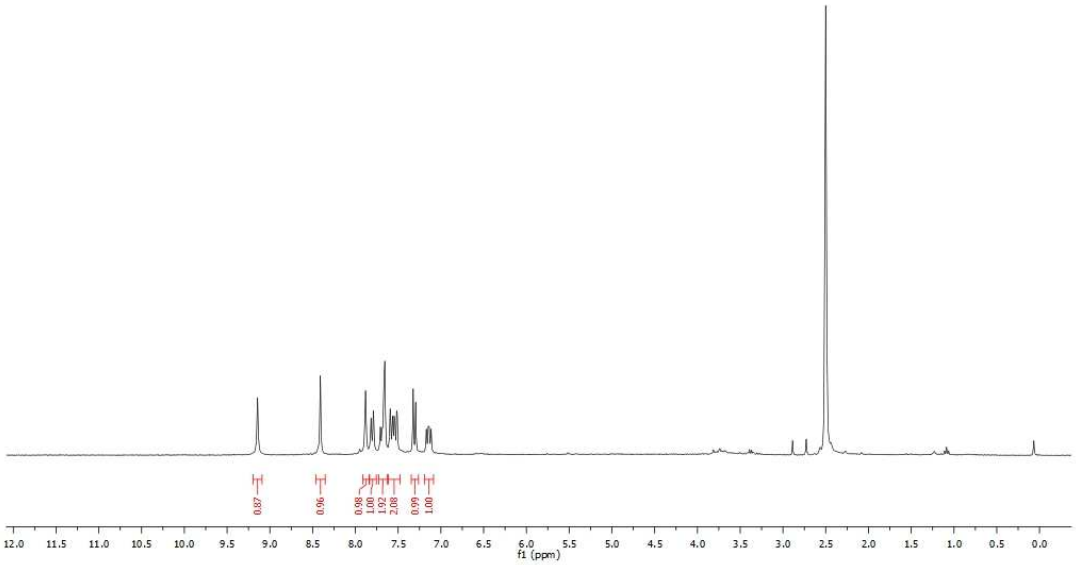

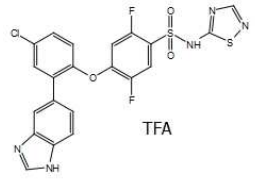

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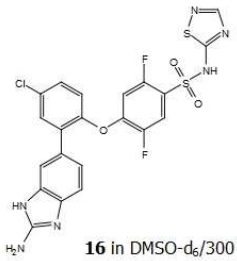

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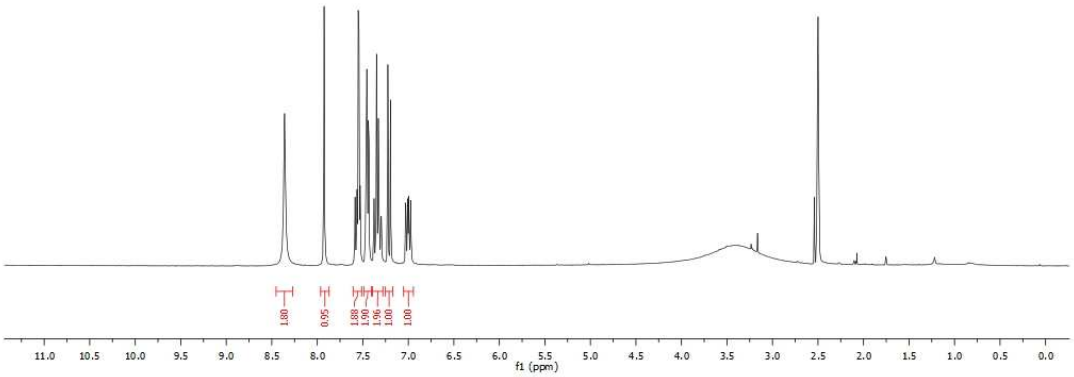

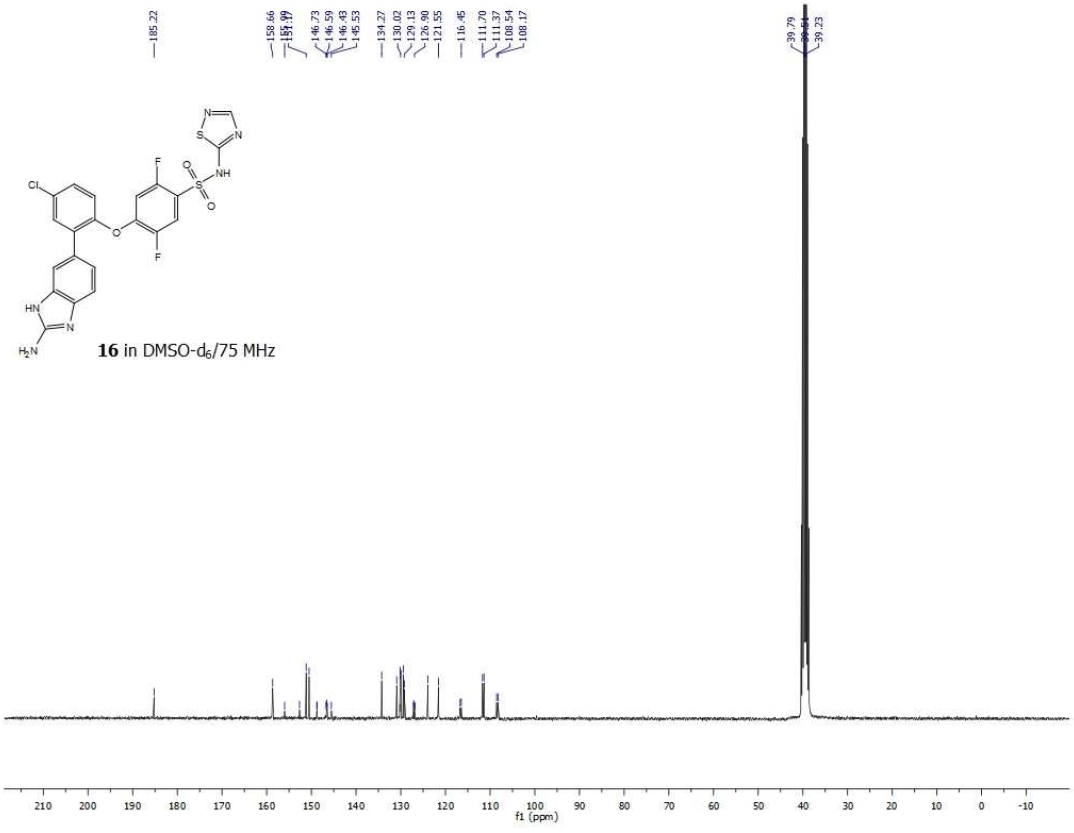

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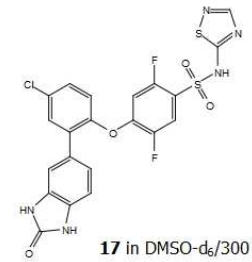

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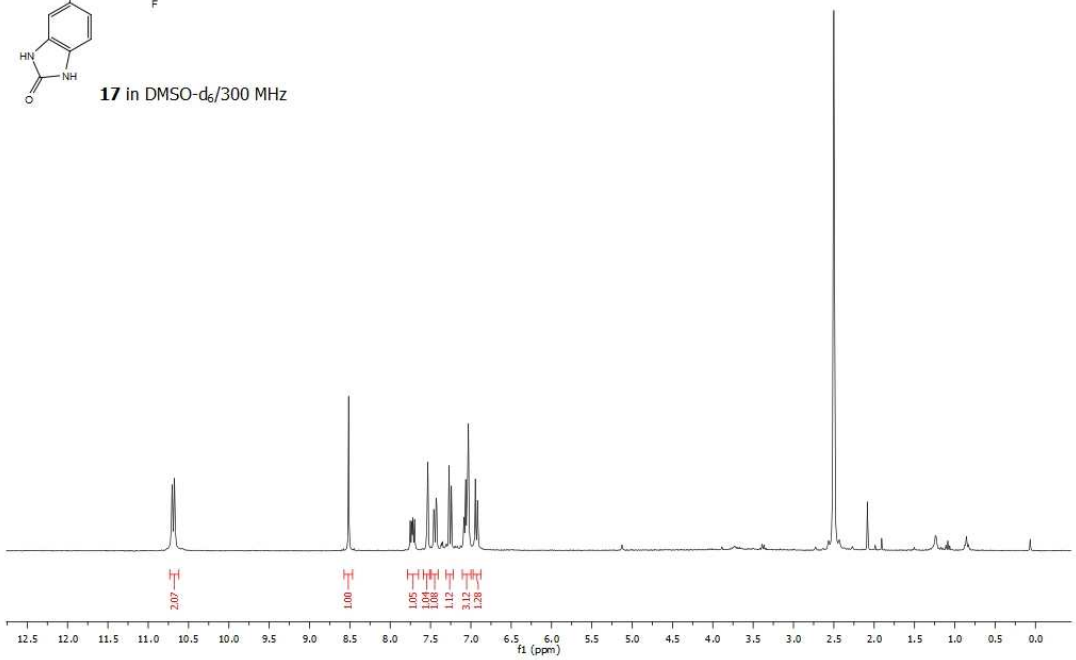

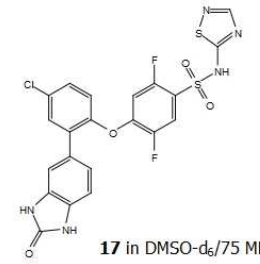

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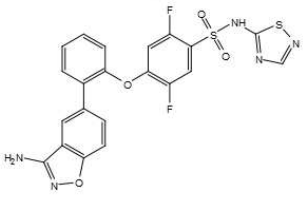

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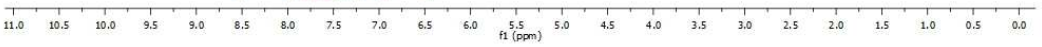

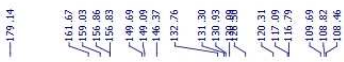

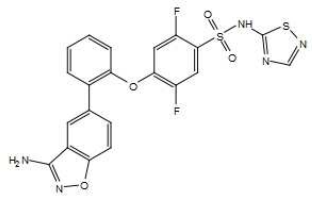

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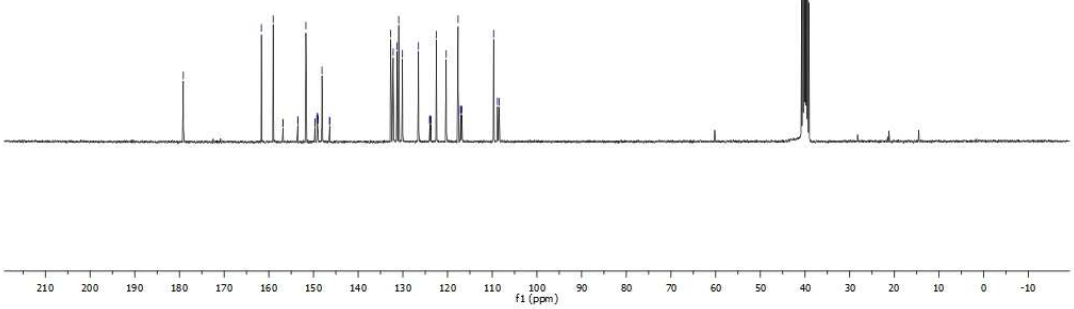

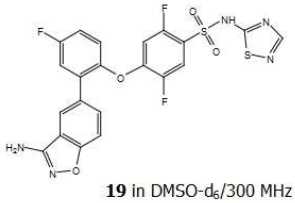

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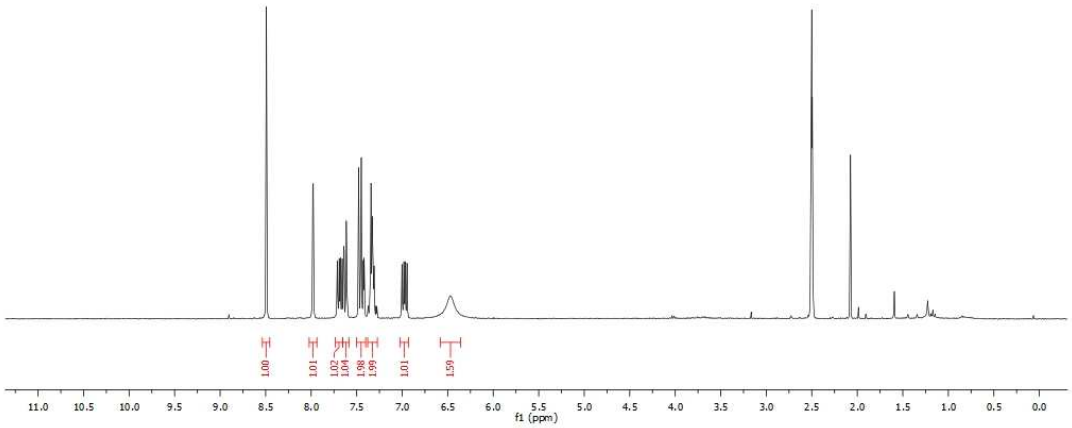

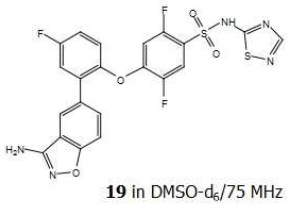

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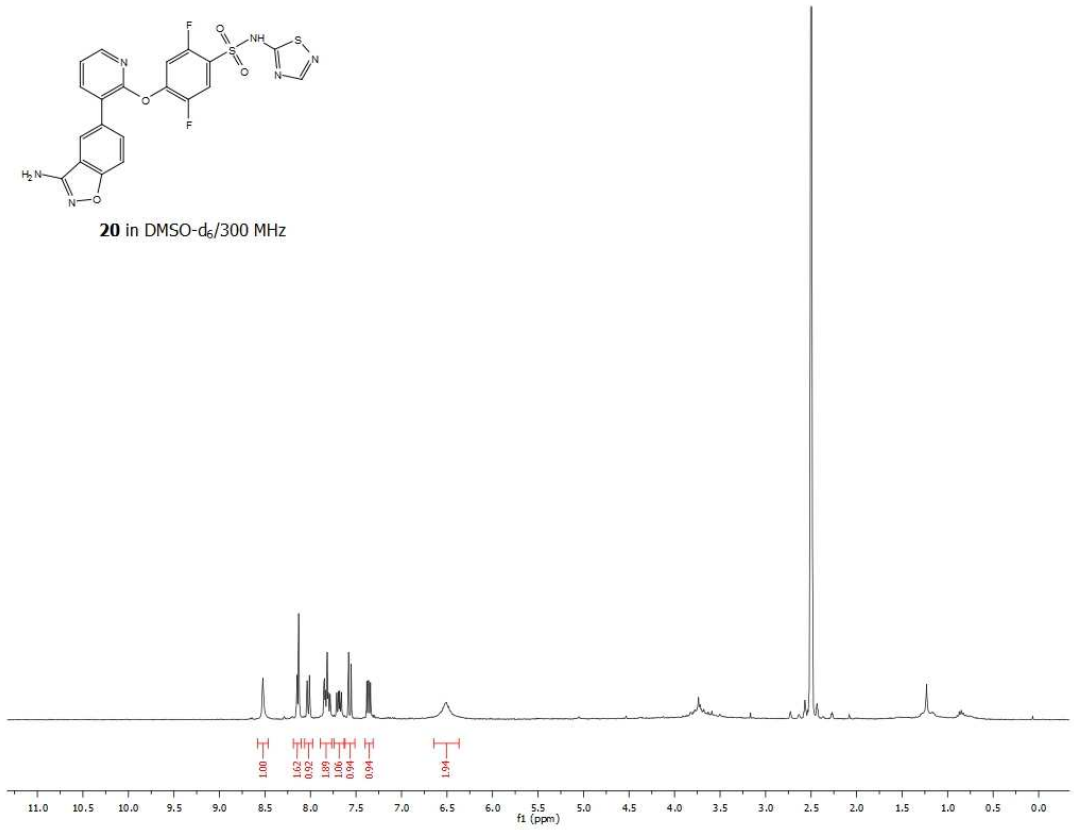

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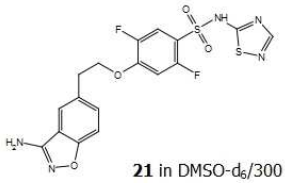

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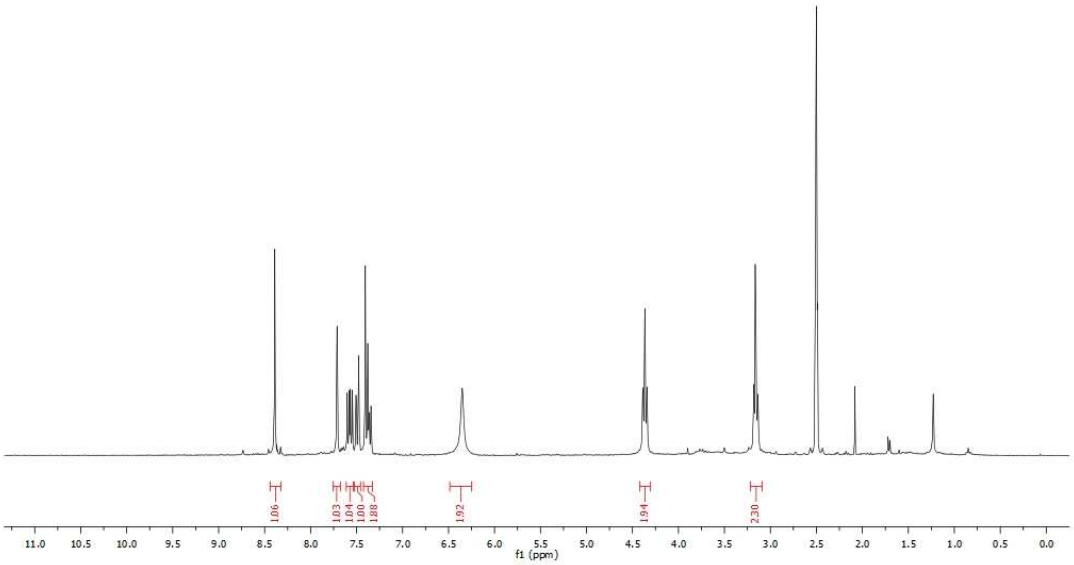

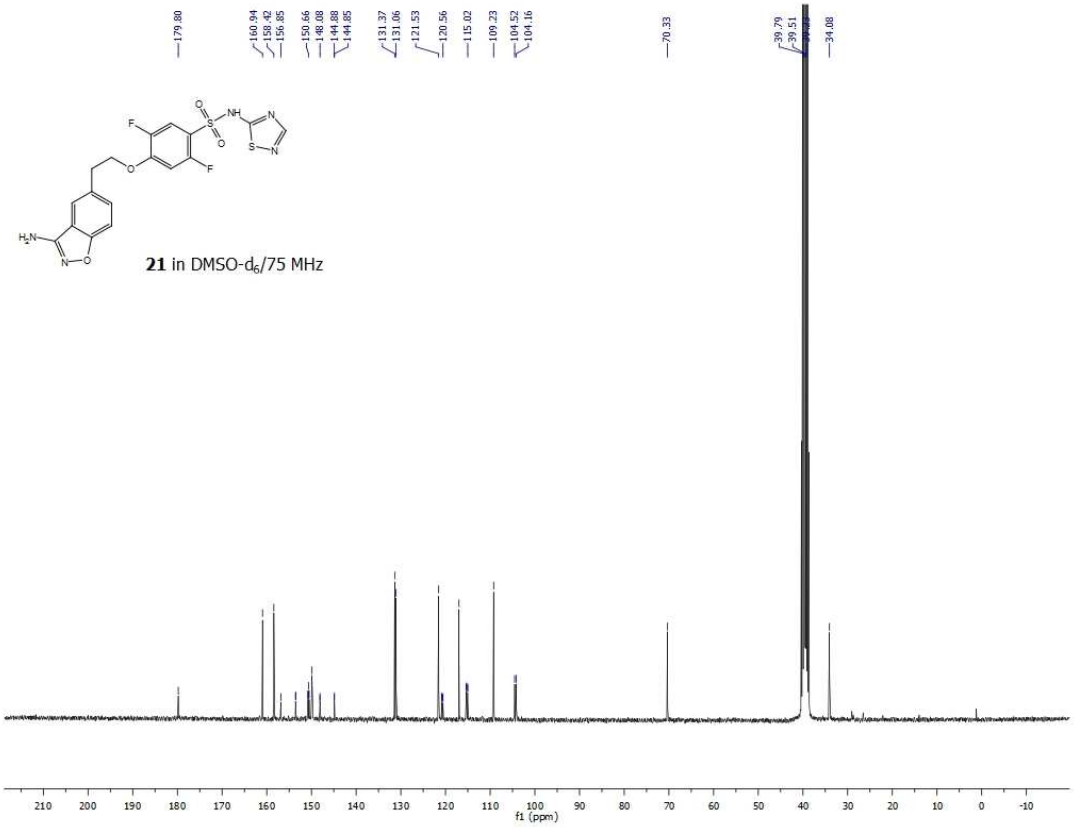

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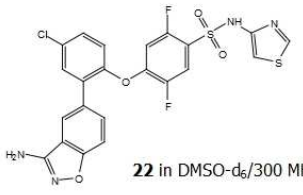

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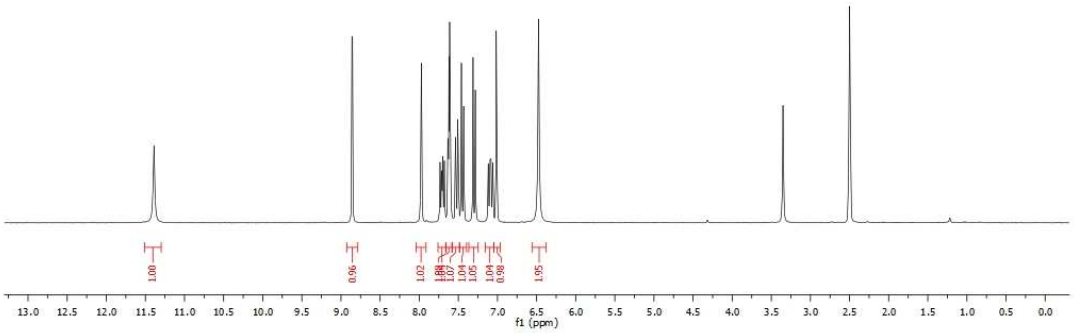

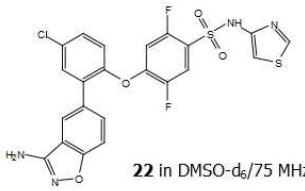

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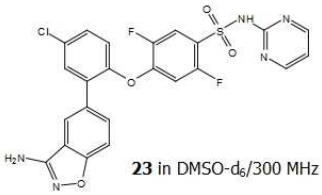

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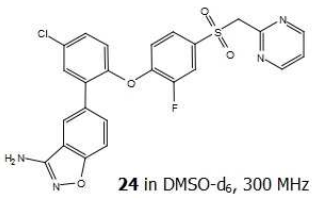

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