Small Molecule Disruptors of the Glucokinase-Glucokinase Regulatory Protein Interaction: 5. A Novel Aryl Sulfones Series, Optimization through Conformational Analysis

Nuria A. Tamayo,[*†] Mark H. Norman,[†] Michael D. Bartberger,[‡] Fang-Tsao Hong,[†] Yunxin Bo,[†] Longbin Liu,[†] Nobuko Nishimura,[†] Kevin C. Yang,[†] Seifu Tadesse,[†] Christopher Fotsch,[†] Jie Chen,[ǀ] Samer Chmait,[‡] Rod Cupples,[§] Clarence Hale,[§] Steven R. Jordan,[‡] David J. Lloyd,[§] Glenn Sivits,[§] Gwyneth Van,[⊥] and David J. St. Jean, Jr.[†]

Amgen, Inc., One Amgen Center Drive, Thousand Oaks, California, 91320-1799
[†]Department of Therapeutic Discovery—Medicinal Chemistry
[‡]Department of Therapeutic Discovery—Molecular Structure and Characterization
[§]Department of Metabolic Disorders, [ǀ]Department of Pharmacokinetics and Drug Metabolism
[⊥]Department of Pathology

ntamayo@amgen.com

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1,1,1-Trifluoro-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-ol (8). A solution of 2-(4-bromophenyl)-1,1,1-trifluoropropan-2-ol (2.68 g, 9. 96 mmol), bis(pinacolato)diboron (2.53 g, 9.96 mmol), $PdCl_2$(dppf) (0.41 g, 0.5 mmol), KOAc (2.93 g, 30 mmol) in dioxane (20 mL), and H_2O (2 mL) was heated at 100 °C for 18 h. The reaction mixture was allowed to cool to rt and passed through a short path of Celite. The filter cake was washed with EtOAc (15 mL x 3) and the combined organics were concentrated under reduced pressure to give the crude residue. The crude material was purified by silica gel chromatography (20% EtOAc/hexanes) to provide the title

compound (1.82 g, 58%) as a white solid. MS (ESI positive ion): m/z calcd for $C_{15}H_{20}BF_3O_3$ 316, found 317 (M + H).

1,1,1,3,3,3-Hexafluoro-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-ol (96). A glass vessel was charged with 2-(4-bromophenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (5.0 g, 15.48 mmol), bis(pinacolato)diboron (4.72 g, 18.57 mmol), $PdCl_2$(dppf) (0.63 g, 0.77 mmol), KOAc (4.56 g, 46.4 mmol, and dioxane (25 mL). The reaction mixture was heated at 100 °C for 3 h. The reaction mixture was allowed to cool to rt and passed through a short path of Celite. The filter cake was washed with EtOAc (15 mL x 3) and the combined organics were concentrated under reduced pressure to give the crude residue. The crude material was purified by silica gel chromatography (0-25% EtOAc/hexanes) to provide the title compound (3.50 g, 61%) as a white solid. MS (ESI positive ion): m/z calcd for $C_{15}H_{17}BF_6O_3$ 370, found 371(M + H).

1,1,1-Trifluoro-2-(6-(trimethylstannyl)pyridin-3-yl)propan-2-ol (16). To a stirred mixture of 2-(6-bromo-3-pyridinyl)-1,1,1-trifluoro-2-propanol (0.53 g, 1.96 mmol), $Pd(Ph_3P)_4$ (0.113 g, 0.098 mmol), LiCl (0.42 g, 9.81 mmol) in dioxane (3 mL) was added hexamethylditin (0.61 mL, 2.94 mmol). The reaction mixture was stirred at 90 °C for 18 h. After cooling to rt, the reaction mixture was passed through a short path of Celite. The filter cake was washed with EtOAc (15 mL x 3) and the combined organic phases were concentrated concentrated under reduced pressure to give the title compound (0.66 g, 94%) as a brown semi-solid. MS (ESI positive ion): m/z calcd for $C_{11}H_{16}F_3NOSn$ 355, found 356 (M + H).

***tert*-Butyl (5-mercaptopyridin-2-yl)carbamate (31).** To a stirred solution of *tert*-butyl (5-(chlorosulfonyl)pyridin-2-yl)carbamate (2.89 g, 9.87 mmol) in THF (14 mL) was

added triphenylphosphine (9.06 g, 34.6 mmol). The reaction mixture was stirred at room temperature for 30 min and then concentrated under reduced pressure to give the crude residue. The crude material was purified by silica gel chromatography (10-70% DCM/hexanes) to provide the title compound (1.02 g, 46%) as a white solid. MS (ESI positive ion): m/z calcd for $C_{10}H_{14}N_2O_2S$ 226, found 227 (M + H).