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Supporting Information

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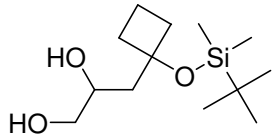
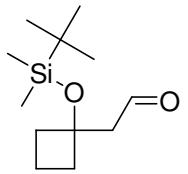
General Information: All reactions were performed in purchased solvent without any further purification, drying, or distillation. Thin layer chromatography was performed on TLC Silica Gel 60 F254 plates. Flash chromatography was performed on Silica Gel 60 (230 – 400 mesh ASTM). One dimensional NMR spectra were recorded in the indicated solvent using 300 or 400 MHz spectrometers. Chemical shifts are reported relative to internal tetramethylsilane (TMS) (δ 0.00 ppm) for 1H. Exact mass data were acquired on a Fourier-Transform Ion Cyclotron Resonance Mass Spectrometer (FTICR-MS) (Bruker Daltonics Inc.) operating at 7 tesla. Samples were introduced to the mass spectrometer by electrospray ionization (analyte concentration ~10 uM) from a 49.5:49.5:1.0 % methanol:water:formic acid solution. The instrument was externally calibrated with a PEG300/600 solution using the standard Francel equation. The calculated mass error for each calibrant ion was less than 1.0 ppm from the measured value. For each spectra 512 k data points were collected using a 1.25 MHz sweep width of detection (86 Da mass cutoff). The time domain data were not processed prior to performing a magnitude mode Fourier transform and frequency to mass conversion. Assay Conditions are described in: *J. Med. Chem.*, **2011**, *54* (16), pp 5836–5857.

Experimentals and Characterization:



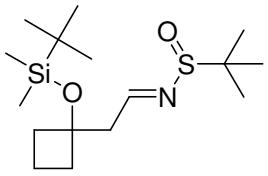
3-(1-(tert-butyldimethylsilyloxy)cyclobutyl)propane-1,2-diol, 6. To a solution of commercially available cyclobutanone (12.55 g, 179 mmol) and THF (1200 mL) that was cooled to -78°C was added allylmagnesium bromide, 1M in ether (196 ml, 196 mmol) via an addition funnel over 30 minutes. The reaction was allowed to stir for a further 30 minutes, then 30 mL of MeOH was added and the cooling bath removed. After stirring for a further 10 minutes. 0.5M HCl (500 mL) was added and the reaction was extracted with ether (2 X 1 L). The organics were dried over $MgSO_4$ and carefully concentrated in vacuo to ~100 mL (Note: Volatile Product). The final ~100 mL of concentrate was redissolved in 400 mL of ether and dried over $MgSO_4$. The solution was diluted with Cl_2Cl_2 (1 L) and the cooled in ice bath. Triethylamine (61.5 ml, 442 mmol) was added followed by TBS triflate (61.0 ml, 266 mmol). After 30 minutes the reaction was quenched with 0.5M HCl (500 mL) and the aqueous layer was extracted with 600 mL of ether. The combined organic layers were dried over $MgSO_4$ and carefully concentrated in vacuo (Note: Product is volatile). The resulting oil is loaded onto a 600 mL Frit almost full of silica gel and eluted with 1400 mL of hexane. The hexane filtrate was then cautiously concentrated in vacuo to give (1-allylcyclobutoxy)(tert-butyl)dimethylsilane, **5**, as a colorless oil that was carried forward without further purification. ^{1}H NMR (300 MHz, CD_3OD) δ 0.10 (s, 6H), 0.88 (s, 9H), 1.43-1.56 (m, 1H), 1.64-1.74 (m, 1H), 2.00-2.17 (m, 4H), 2.34 (d, *J*=7.16 Hz, 2H), 5.05 (d, *J*=13.00 Hz, 2H), 5.82-5.96 (m, 1H).

To a solution of **5** (35.00 g, 155 mmol), H_2O/*t*-BuOH (1:1, 1 L), THF (15 mL), and NMO (32.61 g, 278 mmol) was added a solution of osmium tetroxide (1.00 g, 3.93 mmol) in THF (2 mL). After stirring for 2 hours at room temperature, water (500 mL) and sodium sulfite (39.0 g, 309 mmol) were added to the reaction and stirring continued for an additional hour. The aqueous solution was extracted with ether (2 X 1 L). The combined organics were dried over MgSO4 and concentrated in vacuo to give **6** as a light green oil that was carried forward without further purification or characterization.

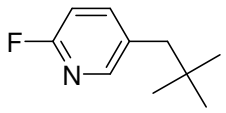


2-(1-(tert-butyldimethylsilyloxy)cyclobutyl)acetaldehyde, 7. To a solution of **6** (40.0 g, 154 mmol) and THF/*t*-BuOH/H_2O (1:1:2, 1 L) was added Sodium periodate (59.00 g, 276 mmol). After addition, the solution became yellow and thickened. After 1.5 hours, water (300 mL) was added and the aqueous solution was extracted with ether (3 X 600 mL). The combined organics were dried over $MgSO_4$ and carefully concentrated in vacuo (Note: volatile product). The resulting yellow oil was azeotroped with benzene (3 X 100 mL). The oil was then loaded onto a plug of silica gel (600 mL frit) and eluted with 4% EtOAc/Hexane

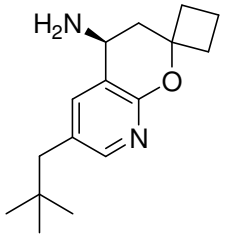
to give **7** (30 g, 131 mmol, 86% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.12 (s, 6H), 0.87 (s, 9H), 1.50-1.61 (m, 1H), 1.71-1.83 (m, 1H), 2.11-2.19 (m, 2H), 2.24-2.35 (m, 2H), 2.62 (d, *J*=2.83 Hz, 2H), 9.82 (t, *J*=3.01 Hz, 1H).



(R,E)-N-(2-(1-(tert-butyldimethylsilyloxy)cyclobutyl)ethylidene)-2-methylpropane-2-sulfinamide, 8. To a solution of **7** (3.57 g, 15.6 mmol) and Cl_2Cl_2 (20 mL) was added $CuSO_4$ (6.22 g, 39.0 mmol) and (R)-2-methylpropane-2-sulfinamide (2.13 g, 17.6 mmol). The reaction was stirred at room temperature for 16 hours, then filtered through celite and the filtrate concentrated in vacuo. The crude oil was eluted through a plug of silica gel using 10%EtOAc/Hexane and the resulting filtrate concentrated in vacuo to give **8** (5.10 g, 98.4% yield) as light blue oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.11 (s, 6H), 0.87 (s, 9H), 1.21 (s, 9H), 1.48-1.62 (m, 1H), 1.68-1.81 (m, 1H), 2.05-2.31 (m, 4H), 2.79 (d, *J*=5.09 Hz, 2H), 8.16 (t, *J*=5.46 Hz, 1H). MS (ESI) *m/z* 332.2 (MH+).



2-fluoro-5-neopentylpyridine, 9. To an Ar degassed solution of commercially available 5-bromo-2-fluoropyridine (25.3 g, 144 mmol) and A-Phos (2.04 g, 2.88 mmol) in 1,4-dioxane (250 mL) was added neopentylmagnesium chloride (200 mL, 200 mmol) dropwise over 15 min. Ether self refluxes during addition so the temperature was moderated using a water bath slightly chilled with ice. The mixture turned from a yellow slurry to a very thick tan mixture. After the addition was complete the mixture was stirred for 45 min then quenched by the slow addition of H_2O (500 mL). Et_2O (500 mL) was added and the layers separated, the aqueous layer washed with Et_2O (500 mL), the combined organic layers washed with brine (300 mL), dried over $MgSO_4$, and concentrated in vacuo to give a dark brown oil. The crude product was purified by vacuum distillation through a short path [high vacuum line, bp = 60-65 °C] to give **9**, (20.90 g, 86.9% yield) as a clear, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (s, 9H), 2.48 (s, 2H), 6.83 (dd, *J*=8.22, *J*=2.93 Hz, 1H), 7.53 (td, *J*=8.02, *J*=2.54 Hz, 1H), 7.96 (s, 1H).

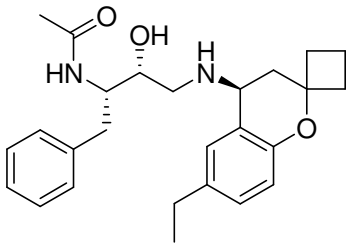


(S)-6'-neopentyl-3',4'-dihydrospiro[cyclobutane-1,2'-pyrano[2,3-b]pyridin]-4'-amine, 12. To a -78°C cooled solution of 2,2,6,6-tetramethylpiperidine (12 ml, 71 mmol) in dry THF (200 mL) was added n-butyllithium (22 ml, 55 mmol, 2.5M in toluene) dropwise, maintaining the internal temperature below -65°C. The reaction was allowed to warm to 0°C for 15 minutes. A solution of **9** (7.9 g, 47 mmol) in dry THF (35 ml) was added dropwise, then stirred for 30 minutes at 0°C. The solution was then cooled to -78°C. A solution of **8** (13.0 g, 39 mmol) in dry THF (55 ml) was added dropwise, maintaining the internal temperature below -65°C. The reaction was then stirred at -10°C for 30 minutes, then warmed to 0°C and quenched with sat'd NH_4Cl. The reaction was extracted with EtOAc (3X). The combined organic fractions were dried over $MgSO_4$, concentrated in vacuo and purified by flash chromatography, eluting with 10-40% EtOAc/hexanes to give (S)-N-((S)-2-(1-(tert-butyldimethylsilyloxy)cyclobutyl)-1-(2-fluoro-5-neopentylpyridin-3-yl)ethyl)-2-methylpropane-2-sulfinamide, **10,** (12 g, 61% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.14 (s, 3H), 0.20 (s, 3H), 0.90 (s, 9H), 0.93 (s, 9H), 1.17 (s, 9H), 1.43-1.55 (m, 1H), 1.60-1.74 (m, 2H), 1.93-2.07 (m, 2H), 2.11 (dd, *J*=14.48, 8.41 Hz, 1H), 2.19-2.32 (m, 2H), 2.47 (s, 2H), 4.36 (d, *J*=2.74 Hz, 1H), 4.87-4.93 (m, 1H), 7.54 (dd, *J*=9.19, 2.35 Hz, 1H), 7.86 (s, 1H).

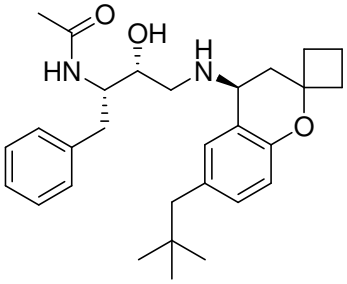
To a solution of **10** (41.0g , 82 mmol) in DMSO (100 mL) was added CsF (14 g, 90 mmol). After stirring for 15 hours at 120°C, the reaction was allowed to cool to room temperature, then poured into ice water (300 mL). The aqueous solution was extracted with DCM (2 X 100 mL). The combined organics were dried over $MgSO_4$, concentrated in vacuo. The crude product was purified by flash chromatography, eluting with 20-100% EtOAc/hexanes to give (R)-2-methyl-N-((S)-6'-neopentyl-3',4'-dihydrospiro[cyclobutane-1,2'-pyrano[2,3-b]pyridine]-4'-yl)propane-2-sulfinamide (19 g, 63%) as a yellow foam.

To a solution of (R)-2-methyl-N-((S)-6'-neopentyl-3',4'-dihydrospiro[cyclobutane-1,2'-pyrano[2,3-b]pyridine]-4'-yl)propane-2-sulfinamide (18 g, 49 mmol) and DCM (100 mL) was added HCl (4M, 25 mL, 100 mmol) slowly to maintain the temperature below 25°C. The HCl salt came out of solution over ~1 hour. The solids were filtered and washed with DCM. The HCl salt was dissolved in water and nuetralized with sodium hydroxide. The precipitate was filtered and dried to give **12** (8.0 g, 62% yield) as a white solid. (>99%ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (s, 9H), 1.66-1.81 (m, 2H), 1.88-2.00 (m, 1H), 2.05-2.13 (m, 1H), 2.15-2.24 (m, 1H), 2.28-2.40 (m, 2H), 2.41 (s, 2H), 2.55 (q,

J=9.78 Hz, 1H), 4.04 (dd, *J*=10.76, 5.48 Hz, 1H), 7.56 (d, *J*=1.37 Hz, 1H), 7.86 (d, *J*=2.15 Hz, 1H).



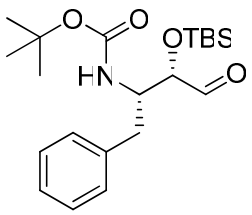
N-((2S,3R)-4-((S)-6-ethylspiro[chroman-2,1'-cyclobutane]-4-ylamino)-3-hydroxy-1-phenylbutan-2-yl)acetamide, 2. To a solution of (2R,3S)-3-amino-1-((S)-6-ethylspiro[chroman-2,1'-cyclobutane]-4-ylamino)-4-phenylbutan-2-ol dihydrochloride (100 mg, 0.22 mmol), DIPEA (0.1 ml, 0.7 mmol), and DMF (3 mL) was added 1-(1H-imidazol-1-yl)ethanone (30 mg, 0.27 mmol) in one portion. The solution was allowed to stir at room temperature for 14 h. The reaction mixture was diluted with MeOH and then purified via Varian HPLC to give **2** (80 mg, 86%) as a TFA salt. ^{1}H NMR (300 MHz, CD_3OD) δ 1.23 (t, *J*=7.72 Hz, 3H), 1.74 - 1.87 (m, 4H), 1.88 - 2.28 (m, 5H), 2.41 – 2.51 (m, 1H), 2.56 - 2.72 (m, 4H), 2.92 – 3.02 (m, 1H), 3.20 (dt, *J*=10.55, 3.96 Hz, 2H), 3.93 (dt, *J*=8.86, 2.64 Hz, 1H), 4.04 (m, 1H), 4.75 (dd, *J*=10.74, 6.97 Hz, 1H), 6.84 (d, *J*=8.48 Hz, 1H), 7.10 – 7.33 (m, 7H). HRMS (TOF) calcd for [$C_{26}H_{34}N_2O_3$ + H] 423.26338 found 423.26394, error = -1.33 ppm. Purity: 100.0%.



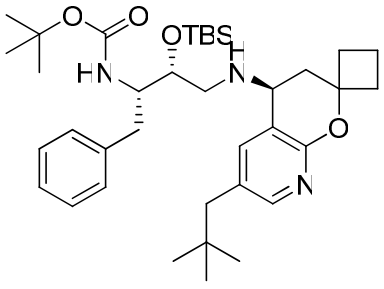
N-((2S,3R)-3-hydroxy-4-((S)-6-neopentylspiro[chroman-2,1'-cyclobutane]-4-ylamino)-1-phenylbutan-2-yl)acetamide, 3. To a solution of (S)-6-bromospiro[chroman-2,1'-cyclobutan]-4-amine (1.00 g, 3.73 mmol), (1s,5s)-9-neopentyl-9-bora-bicyclo[3.3.1]nonane (1.00 g, 5.22 mmol), and 5N NaOH (1.86 mL, 9.32 mmol) in toluene (15 mL) was added $Pd(PPh_3)_4$ (0.43 g, 0.37 mmol). The solution was heated at 80°C for 24 hours. The mixture was allowed to cool to room temperature and diluted with ether. The organic layer was separated and dried over MgSO4, concentrated in vacuo, and purified by silica gel chromatography (5% i-PrOH/CH_2Cl_2) to give (S)-6-neopentylspiro[chroman-2,1'-cyclobutan]-4-amine (268 mg, 28%) as a light yellow oil. MS (ESI) *m/z* 243.2 (M-NH_2).

To a solution of tert-butyl (S)-1-((S)-oxiran-2-yl)-2-phenylethyl-carbamate (0.286 g, 1.08 mmol, Anaspec), (S)-6-neopentylspiro[chroman-2,1'-cyclobutan]-4-amine (0.268 g, 1.03 mmol), and dioxane (8 mL) was added lithium perchlorate (0.011 g, 0.103 mmol). The solution was stirred at 80 °C for 16 hours. The mixture was allowed to cool and concentrated in vacuo. The residue was taken up in dioxane and 4M HCl in p-dioxane (3 mL) and stirred at room temperature overnight. The mixture was concentrated in vacuo and taken up in H_2O. The aqueous solution was neutralized with 5N NaOH, then extracted with CH_2Cl_2 (3X). The combined organic layers were dried over $MgSO_4$, concentrated in vacuo, and purified by silica gel chromatography using 10% MeOH in CH_2Cl_2 as the eluent to give (2R,3S)-3-amino-1-((S)-6-neopentylspiro[chroman-2,1'-cyclobutane]-4-ylamino)-4-phenylbutan-2-ol (150 mg, 34%) as a light yellow solid. MS (ESI) *m/z* 423.5 (MH+).

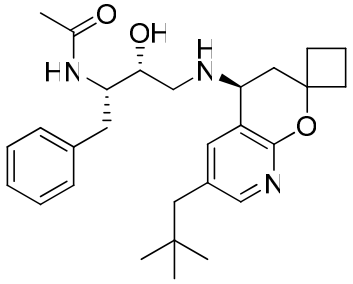
Following the same procedure used in the final step for compound **2**, (2R,3S)-3-amino-1-((S)-6-neopentylspiro[chroman-2,1'-cyclobutane]-4-ylamino)-4-phenylbutan-2-ol gave **3,** as an off white solid. HRMS (TOF) calcd for [$C_{29}H_{40}N_2O_3$ + H] 465.31018 found 465.31124, error = -2.29 ppm. Purity: 100.0%.



tert-butyl (2S,3S)-3-(tert-butyldimethylsilyloxy)-4-oxo-1-phenylbutan-2-ylcarbamate, 14. To a solution of tert-butyl (2S,3S)-3-(tert-butyldimethylsilyloxy)-4-hydroxy-1-phenylbutan-2-ylcarbamate (360 mg, 0.87 mmol, **13**), DCM (30 mL), and sodium carbonate (219 mg, 2.61 mmol) was added Dess-Martin Periodinane (480 mg, 1.1 mmol). The solution was stirred at room temperature. After 2 hours, the reaction mixture was loaded directly to a silica gel column and eluted with 20% EtOAc in hexanes to give **14** (300 mg, 84% yield), as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.10 (s, 6H), 0.89 (s, 9H), 1.38 (s, 9H), 2.63 - 2.85 (m, 2H), 4.18 – 4.30 (m, 2H), 4.50 – 4.58 (m, 1H), 6.97 (t, *J*=8.85 Hz, 2H), 7.14 (dd, *J*=8.48, 5.46 Hz, 2H), 9.39 (s, 1H).

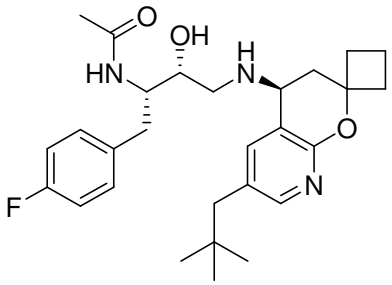


tert-butyl (2S,3R)-3-(tert-butyldimethylsilyloxy)-4-((S)-6'-neopentyl-3',4'-dihydrospiro[cyclobutane-1,2'-pyrano[2,3-b]pyridine]-4'-ylamino)-1-phenylbutan-2-ylcarbamate, 15. To a solution of **12** (330 mg, 1.27 mmol), **14** (522 mg, 1.27 mmol), and DCE (10 mL) was added trimethyl orthoformate (3.7 ml, 31.7 mmol). The solution was stirred at room temperature for 30 min., then sodium triacetoxyborohydride (1.07 g, 5.07 mmol) was added. After stirring for 12 h, then quenched by the addition of DCM (75 mL) and aqueous sodium carbonate (10%, 75 mL). The quenched reaction was allowed to stir for 3 h and then extracted with DCM (4 x 50 mL). The combined organics were washed with brine, dried with sodium sulfate, filtered through a plug of silica el and eluted with EtOAc and concentrated to give **15** (831 mg, 100% yield), as a white solid. MS (ESI) *m/z* 655.9 (MH+).

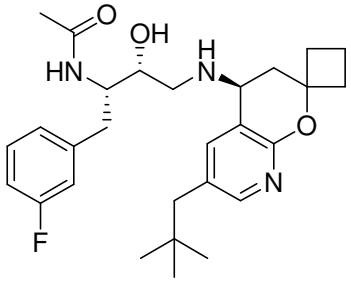


N-((2S,3R)-3-hydroxy-4-((S)-6'-neopentyl-3',4'-dihydrospiro[cyclobutane-1,2'-pyrano[2,3-b]pyridine]-4'-ylamino)-1-phenylbutan-2-yl)acetamide, 4. To a solution of **15** (1385 mg, 2111 µmol and MeOH (20 mL) was added HCl (4.0 M in dioxane, 60 mL). After stirring for 12h at room temperature, LC-MS showed complete deprotection. The reaction was concentrated in vacuo to give a pink oil. The oil was dissolved in EtOAc and MeOH and concentrated to about 12 mL and loaded onto a short silica gel column. The column was eluted with 500 mL of 50% EtOAc in hexanes and then flush with 10% MeOH (2M in NH_3) in DCM (250 mL). The MeOH and DCM fractions were concentrated and subjected to high vacuum for 1 h to give (2R,3S)-3-amino-1-((S)-6'-neopentyl-3',4'-dihydrospiro[cyclobutane-1,2'-pyrano[2,3-b]pyridine]-4'-ylamino)-4-phenylbutan-2-ol (1024 mg, 110%), as an off-white solid. MS (ESI) *m/z* 424.2 (MH+).

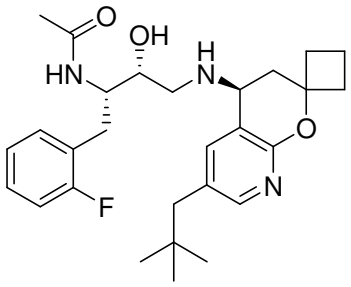
Following the same procedure used in the final step for compound **2**, (2R,3S)-3-amino-4-(4-fluorophenyl)-1-((S)-6'-neopentyl-3',4'-dihydrospiro[cyclobutane-1,2'-pyrano[2,3-b]pyridine]-4'-ylamino)butan-2-ol gave **4**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (s, 9H), 1.70-1.84 (m, 1H), 1.88 (s, 3H), 1.93-2.18 (m, 3H), 2.19–2.35 (m, 2H), 2.46 (s, 2H), 2.53-2.69 (m, 2H), 2.71-2.85 (m, 2H), 2.90-3.01 (m, 1H), 3.07 (d, *J*=12.13 Hz, 1H), 4.00-4.11 (m, 2H), 4.73-4.82 (m, 1H), 6.41-6.48 (m, 1H), 7.07-7.14 (m, 2H), 7.20-7.29 (m, 3H), 8.00-8.06 (m, 2H). HRMS (TOF) calcd for [$C_{28}H_{39}N_3O_3$ + H] 466.30548 found 466.30609, error = -1.32 ppm. Purity: 98.1%.



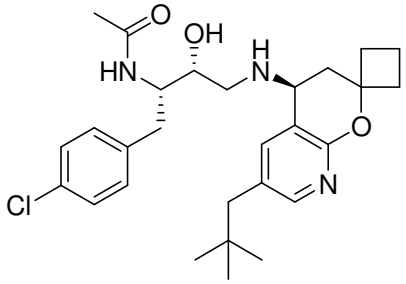
N-((2S,3R)-1-(4-fluorophenyl)-3-hydroxy-4-((S)-6'-neopentyl-3',4'-dihydrospiro[cyclobutane-1,2'-pyrano[2,3-b]pyridine]-4'-ylamino)butan-2-yl)acetamide, 16. Following the same procedure used in the final step for compound **2**, (2R,3S)-3-amino-4-(4-fluorophenyl)-1-((S)-6'-neopentyl-3',4'-dihydrospiro[cyclobutane-1,2'-pyrano[2,3-b]pyridine]-4'-ylamino)butan-2-ol gave **16**. ^{1}H NMR (300 MHz, CD_3OD) δ 0.89 (s, 9H), 1.71-1.85 (m, 5H), 1.88-2.01 (m, 1H), 2.10–2.31 (m, 3H), 2.42-2.53 (m, 4H), 2.63 (dd, *J*=13.94, 10.55 Hz, 1H), 2.72-2.77 (m, 2H), 3.10 (dd, *J*=15.01, 3.75 Hz, 1H), 3.62–3.70 (m, 1H), 3.98-4.13 (m, 2H), 6.97 (t, *J*=8.85 Hz, 2H), 7.22 (m, 2H), 7.76 (m, 2H). HRMS (TOF) calcd for [$C_{28}H_{38}FN_3O_3$ + H] 484.29608 found 484.29702, error = -1.95 ppm.



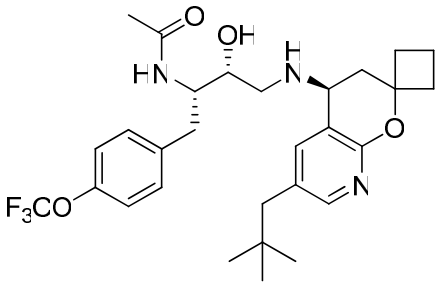
N-((2S,3R)-1-(3-fluorophenyl)-3-hydroxy-4-((S)-6'-neopentyl-3',4'-dihydrospiro[cyclobutane-1,2'-pyrano[2,3-b]pyridine]-4'-ylamino)butan-2-yl)acetamide, 17. Following the same procedure used in the final step for compound **2**, gave **17**. ^{1}H NMR (300 MHz, CD_3OD) δ 0.93 (s, 9H), 1.80 - 1.91 (m, 4H), 1.92 - 2.38 (m, 5H), 2.53 (s, 2H), 2.55 - 2.80 (m, 3H), 3.04 (dd, *J*=12.62, 9.04 Hz, 1H), 3.20 (dd, *J*=13.94, 3.20 Hz, 1H), 3.33 – 3.37 (m, 1H), 3.91 – 4.09 (m, 2H), 4.82 – 4.89 (m, 1H), 6.90 – 7.08 (m, 3H), 7.24 -7.33 (m, 1H), 7.90 (s, 1H), 8.00 (m, 1H). HRMS (TOF) calcd for [$C_{28}H_{38}FN_3O_3$ + H] 484.29608 found 484.29725, error = -2.42 ppm.



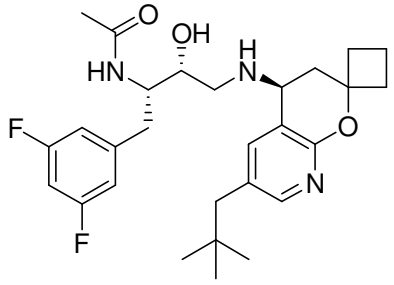
N-((2S,3R)-1-(2-fluorophenyl)-3-hydroxy-4-((S)-6'-neopentyl-3',4'-dihydrospiro[cyclobutane-1,2'-pyrano[2,3-b]pyridine]-4'-ylamino)butan-2-yl)acetamide, 18. Following the same procedure used in the final step for compound **2**, gave 18. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (s, 9H), 1.65-1.85 (m, 2H), 1.88 (s, 3H), 1.91-2.12 (m, 3H), 2.14-2.27 (m, 2H), 2.27-2.38 (m, 2H), 2.40 (s, 2H), 2.48-2.61 (m, 1H), 2.66 (dd, *J*=12.24, 4.14 Hz, 1H), 2.81-2.92 (m, 2H), 3.13 (dd, *J*=14.32, 3.58 Hz, 1H), 3.56 (ddd, *J*=6.73, 4.62, 4.47 Hz, 1H), 3.93 (dd, *J*=10.64, 5.37 Hz, 1H), 4.06 (ddd, *J*=6.31, 2.73 Hz, 1H), 5.79 (d, *J*=8.48 Hz, 1H), 6.98-7.13 (m, 2H), 7.17-7.26 (m, 2H), 7.56 (d, *J*=1.51 Hz, 1H), 7.85 (d, *J*=2.07 Hz, 1H). MS (ESI) *m/z* 483.9 (MH+). No HRMS data. Purity: 98.5%



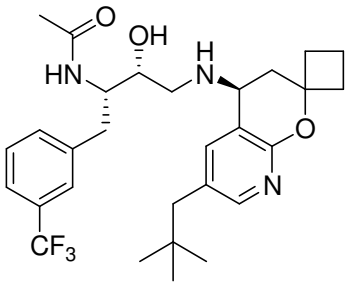
N-((2S,3R)-1-(4-chlorophenyl)-3-hydroxy-4-((S)-6'-neopentyl-3',4'-dihydrospiro[cyclobutane-1,2'-pyrano[2,3-b]pyridine]-4'-ylamino)butan-2-yl)acetamide, 19. Following the same procedure used in the final step for compound **2**, gave **19**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (s, 9H), 1.65-1.84 (m, 2H), 1.89 (s, 3H), 1.90-2.11 (m, 3H), 2.20 (ddd, *J*=16.22, 7.89, 3.51 Hz, 1H), 2.26-2.32 (m, 1H), 2.32 (dd, *J*=13.30, 5.41 Hz, 1H), 2.40 (s, 2H), 2.47-2.59 (m, 1H), 2.63 (dd, *J*=12.28, 3.95 Hz, 1H), 2.75-2.88 (m, 2H), 3.06 (dd, 1H), 3.52 (dt, *J*=6.87, 4.38 Hz, 2H), 3.92 (dd, *J*=10.67, 5.41 Hz, 1H), 4.11 (ddd, *J*=15.93, 8.77, 4.53 Hz, 1H), 5.75 (d, *J*=8.92 Hz, 1H), 7.15 (d, *J*=8.33 Hz, 2H), 7.27 (d, *J*=8.33 Hz, 2H), 7.54 (d, *J*=1.61 Hz, 1H), 7.83 (d, *J*=2.05 Hz, 1H). HRMS (TOF) calcd for [$C_{28}H_{38}ClN_3O_3$ + H] 500.26658 found 500.26682, error = -0.49 ppm. Purity: 96.7%.



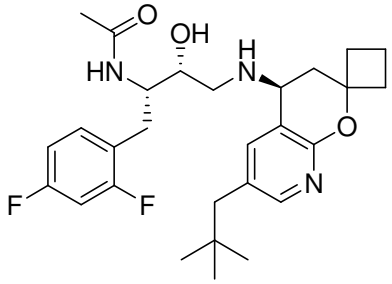
N-((2S,3R)-3-hydroxy-4-((S)-6'-neopentyl-3',4'-dihydrospiro[cyclobutane-1,2'-pyrano[2,3-b]pyridine]-4'-ylamino)-1-(4-(trifluoromethoxy)phenyl)butan-2-yl)acetamide, 20. Following the same procedure used in the final step for compound **2**, gave **20**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (s, 9H), 1.65-1.79 (m, 2H), 1.82 (br s, 3H), 1.87-2.00 (m, 4H), 2.00-2.13 (m, 1H), 2.15-2.26 (m, 1H), 2.34 (d, *J*=5.26 Hz, 1H), 2.41 (s, 2H), 2.48-2.62 (m, 1H), 2.68 (dd, 1H), 2.79 (dd, *J*=12.42, 5.12 Hz, 1H), 2.83-2.93 (m, 1H), 3.08 (dd, *J*=14.18, 3.95 Hz, 1H), 3.52-3.64 (m, 1H), 3.94-4.06 (m, 1H), 4.07-4.20 (m, 1H), 5.66 (d, *J*=8.92 Hz, 1H), 7.08-7.19 (m, 2H), 7.18-7.30 (m, 2H), 7.57 (br s, 1H), 7.86 (br s, 1H). HRMS (TOF) calcd for [$C_{29}H_{38}F_3N_3O_4$ + H] 550.28778 found 550.28856, error = -1.42 ppm. Purity: 96.5%



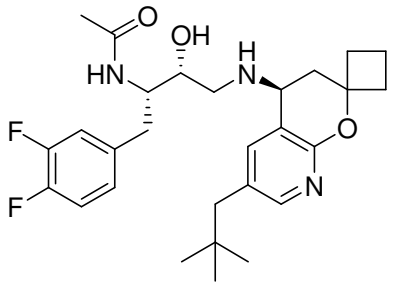
N-((2S,3R)-1-(3,5-difluorophenyl)-3-hydroxy-4-((S)-6'-neopentyl-3',4'-dihydrospiro[cyclobutane-1,2'-pyrano[2,3-b]pyridine]-4'-ylamino)butan-2-yl)acetamide, 21. Following the same procedure used in the final step for compound **2**, gave **21**. ^{1}H NMR (400 MHz, CD_3OD) δ 0.94 (s, 9H), 1.81-1.92 (m, 4H), 1.96-2.06 (m, 1H), 2.08–2.27 (m, 3H), 2.28-2.37 (m, 1H), 2.54 (s, 2H), 2.55-2.78 (m, 3H), 3.07 (dd, *J*=12.52, 8.61 Hz, 1H), 3.06 (dd, *J*=14.28, 3.13 Hz, 1H), 3.33–3.37 (m, 1H), 3.94 (dt, *J*=8.61, 2.54 Hz, 1H), 4.00–4.08 (m, 1H), 6.77–6.90 (m, 3H), 7.86 (s, 1H), 8.00 (m, 1H). HRMS (TOF) calcd for [$C_{28}H_{37}F_2N_3O_3$ + H] 502.28668 found 502.28709, error = -0.82 ppm. Purity: 97.8%.



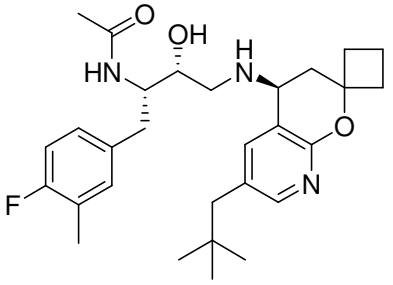
N-((2S,3R)-3-hydroxy-4-((S)-6'-neopentyl-3',4'-dihydrospiro[cyclobutane-1,2'-pyrano[2,3-b]pyridine]-4'-ylamino)-1-(3-(trifluoromethyl)phenyl)butan-2-yl)acetamide, 22. Following the same procedure used in the final step for compound **2**, gave **22**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (s, 9H), 1.65-1.77 (m, 1H), 1.78-1.87 (m, 1H), 1.88 (s, 3H), 1.90-1.99 (m, 1H), 1.99-2.11 (m, 1H), 2.14-2.26 (m, 1H), 2.26-2.37 (m, 2H), 2.41 (s, 2H), 2.47-2.61 (m, 1H), 2.67 (dd, *J*=12.15, 3.86 Hz, 2H), 2.77-2.86 (m, 2H), 2.86-2.95 (m, 1H), 3.19 (dd, *J*=14.32, 4.14 Hz, 1H), 3.51-3.59 (m, 1H), 3.94 (dd, *J*=10.55, 5.46 Hz, 1H), 4.07-4.19 (m, 1H), 5.69 (d, *J*=8.85 Hz, 1H), 7.42 (d, *J*=4.14 Hz, 2H), 7.45 (br s, 1H), 7.47-7.52 (m, 1H), 7.54 (d, *J*=1.51 Hz, 1H), 7.85 (d, *J*=2.07 Hz, 1H). HRMS (TOF) calcd for [$C_{29}H_{38}F_3N_3O_3$ + H] 534.29288 found 534.29345, error = -1.07 ppm. Purity: 97.6%



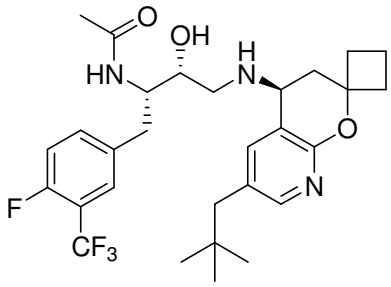
N-((2S,3R)-1-(2,4-difluorophenyl)-3-hydroxy-4-((S)-6'-neopentyl-3',4'-dihydrospiro[cyclobutane-1,2'-pyrano[2,3-b]pyridine]-4'-ylamino)butan-2-yl)acetamide, 23. Following the same procedure used in the final step for compound **2**, gave **23**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (s, 9H), 1.65-1.84 (m, 2H), 1.89 (s, 3H), 1.99-2.12 (m, 1H), 2.26-2.38 (m, 1H), 2.40 (s, 2H), 2.52 (t, *J*=10.08 Hz, 1H), 2.67 (dd, *J*=12.24, 3.96 Hz, 1H), 2.75-2.89 (m, 2H), 3.09 (dd, *J*=14.41, 3.11 Hz, 1H), 3.43-3.50 (m, 2H), 3.45-3.49 (m, 2H), 3.56 (dt, *J*=6.64, 4.50 Hz, 1H), 3.94 (dd, *J*=10.46, 5.18 Hz, 1H), 3.98-4.12 (m, 2H), 5.90 (d, *J*=8.85 Hz, 1H), 6.70-6.87 (m, 2H), 7.11-7.26 (m, 1H), 7.55 (d, *J*=1.88 Hz, 1H), 7.84 (d, *J*=2.07 Hz, 1H). HRMS (TOF) calcd for [$C_{28}H_{37}F_2N_3O_3$ + H] 502.28668 found 502.28725, error = -1.14 ppm. Purity: 95.2%.



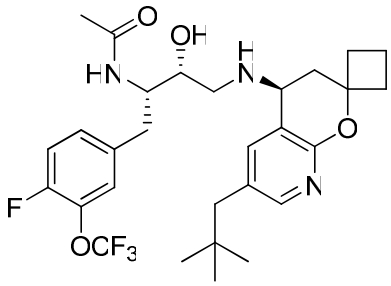
N-((2S,3R)-1-(3,4-difluorophenyl)-3-hydroxy-4-((S)-6'-neopentyl-3',4'-dihydrospiro[cyclobutane-1,2'-pyrano[2,3-b]pyridine]-4'-ylamino)butan-2-yl)acetamide, 24. Following the same procedure used in the final step for compound **2**, gave **24**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (s, 9H), 1.65-1.84 (m, 2H), 1.91 (s, 3H), 1.93-1.99 (m, 1H), 1.99-2.12 (m, 2H), 2.14-2.26 (m, 1H), 2.26-2.37 (m, 2H), 2.41 (s, 2H), 2.48-2.60 (m, 1H), 2.65 (dd, *J*=12.34, 3.86 Hz, 1H), 2.74-2.85 (m, 2H), 3.07 (dd, *J*=14.41, 4.05 Hz, 1H), 3.46-3.56 (m, 2H), 3.94 (dd, *J*=10.45, 5.37 Hz, 1H), 4.02-4.16 (m, 1H), 5.74 (d, *J*=8.85 Hz, 1H), 6.86-6.97 (m, 1H), 6.97-7.15 (m, 2H), 7.55 (s, 1H), 7.84 (d, *J*=1.51 Hz, 1H). HRMS (TOF) calcd for [$C_{28}H_{37}F_2N_3O_3$ + H] 502.28668 found 502.28762, error = -1.88 ppm. Purity: 96.1%



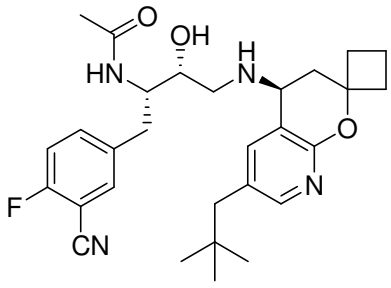
N-((2S,3R)-1-(4-fluoro-3-methylphenyl)-3-hydroxy-4-((S)-6'-neopentyl-3',4'-dihydrospiro[cyclobutane-1,2'-pyrano[2,3-b]pyridine]-4'-ylamino)butan-2-yl)acetamide, 25. Following the same procedure used in the final step for compound **2**, gave **25**. ^{1}H NMR (300 MHz, CD_3OD) δ 0.91 (s, 9H), 1.69-1.84 (m, 5H), 1.87-1.99 (m, 1H), 2.12-2.31 (m, 6H), 2.41-2.51 (m, 4H), 2.58 (dd, *J*=13.75, 10.36Hz, 1H), 2.68-2.79 (m, 2H), 3.07 (dd, *J*=13.94, 3.58 Hz, 1H), 3.63-3.69 (m, 1H), 3.95-4.13 (m, 2H), 6.92 (t, *J*=8.48, 1H), 6.97-7.12 (m, 2H), 7.76 (s, 1H), 7.79 (s, 1H). HRMS (TOF) calcd for [$C_{29}H_{40}FN_3O_3$ + H] 498.31168 found 498.31221, error = -1.07 ppm. Purity: 100.0%



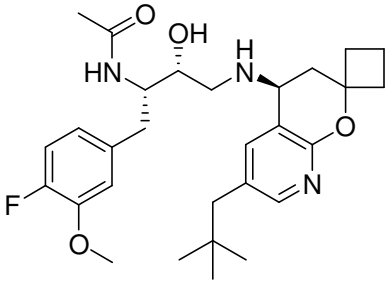
N-((2S,3R)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-3-hydroxy-4-((S)-6'-neopentyl-3',4'-dihydrospiro[cyclobutane-1,2'-pyrano[2,3-b]pyridine]-4'-ylamino)butan-2-yl)acetamide, 26. Following the same procedure used in the final step for compound **2**, gave **26**. ^{1}H NMR (300 MHz, CD_3OD) δ 0.90 (s, 9H), 1.72-1.86 (m, 5H), 1.88-1.99 (m, 1H), 2.13-2.31 (m, 3H), 2.41-2.54 (m, 4H), 2.63-2.79 (m, 3H), 3.18 (dd, *J*=14.03, 3.51 Hz, 1H), 3.63-3.69 (m, 1H), 3.99-4.10 (m, 2H), 7.21 (t, *J*=8.62, 1H), 7.46-7.57 (m, 2H), 7.76 (s, 1H), 7.79 (s, 1H). HRMS (TOF) calcd for [$C_{29}H_{37}F_4N_3O_3$ + H] 552.28348 found 552.28449, error = -1.84 ppm. Purity: 97.3%.



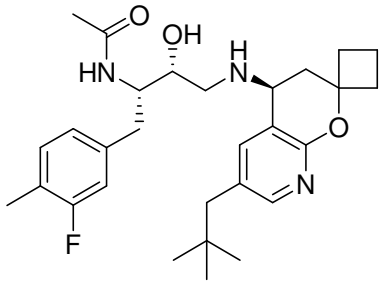
N-((2S,3R)-1-(4-fluoro-3-(trifluoromethoxy)phenyl)-3-hydroxy-4-((S)-6'-neopentyl-3',4'-dihydrospiro[cyclobutane-1,2'-pyrano[2,3-b]pyridine]-4'-ylamino)butan-2-yl)acetamide, 27. Following the same procedure used in the final step for compound **2**, gave **27**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (s, 9H), 1.70-1.83 (m, 2H), 1.93 (s, 3H), 1.96-2.14 (m, 3H), 2.19-2.27 (m, 1H), 2.30-2.35 (m, 1H), 2.44 (s, 2H), 2.54-2.64 (m, 1H), 2.74-2.89 (m, 3H), 3.09 (dd, *J*=14.38, 4.11 Hz, 1H), 3.61 (s, 1H), 4.03-4.19 (m, 2H), 5.52-5.60 (m, 1H), 7.12-7.20 (m, 3H), 7.60 (s, 1H), 7.91 (d, *J*=2.05 Hz, 1H). HRMS (TOF) calcd for [$C_{29}H_{37}F_4N_3O_4$ + H] 568.27838 found 568.27838, error = -0.39 ppm.



N-((2S,3R)-1-(3-cyano-4-fluorophenyl)-3-hydroxy-4-((S)-6'-neopentyl-3',4'-dihydrospiro[cyclobutane-1,2'-pyrano[2,3-b]pyridine]-4'-ylamino)butan-2-yl)acetamide, 28. Following the same procedure used in the final step for compound **2**, gave **28**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (s, 9H), 1.67-1.85 (m, 2H), 1.91 (s, 3H), 1.93-2.10 (m, 3H), 2.16-2.26 (m, 1H), 2.27-2.37 (m, 2H), 2.41 (s, 2H), 2.51-2.60 (m, 1H), 2.67 (dd, *J*=12.32, 3.91 Hz, 1H), 2.73-2.83 (m, 2H), 3.12 (dd, *J*=14.48, 4.11 Hz, 1H), 3.49 (br s, 1H), 3.71 (br s, 1H), 3.91–3.97 (dd, *J*=10.56, 5.48 Hz, 1H), 4.08-4.16 (m, 1H), 5.46 (d, *J*=9.39 Hz, 1H), 7.16 (t, *J*=8.80 Hz, 1H), 7.42–7.53 (m, 3H), 7.87 (d, *J*=2.15 Hz, 1H). HRMS (TOF) calcd for [$C_{29}H_{37}FN_4O_3$ + H] 509.29138 found 509.29195, error = -1.13 ppm. Purity: 100.0%.

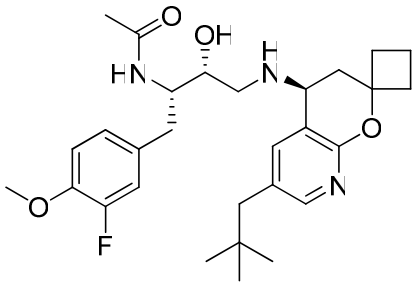


N-((2S,3R)-1-(4-flouro-3-methoxyphenyl)-3-hydroxy-4-((S)-6'-neopentyl-3',4'-dihydrospiro[cyclobutane-1,2'-pyrano[2,3-b]pyridine]-4'-ylamino)butan-2-yl)acetamide, 29. Following the same procedure used in the final step for compound **2**, gave **29**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (s, 9H), 1.70-1.90 (m, 2H), 1.92 (s, 3H), 1.95-2.12 (m, 3H), 2.17-2.27 (m, 1H), 2.27-2.41 (m, 2H), 2.43 (s, 2H), 2.52-2.63 (m, 1H), 2.70 (dd, *J*=12.28, 3.85 Hz, 1H), 2.77-2.90 (m, 2H), 3.05 (dd, *J*=14.52, 4.45 Hz, 1H), 3.57 (br s, 1H), 3.89 (s, 3H), 3.99-4.07 (m, 2H), 4.10-4.19 (m, 1H), 5.56 (m, 1H), 6.69-6.74 (m, 1H), 6.86 (dd, *J*=8.17, 1.91 Hz, 1H), 6.98-7.04 (m, 1H), 7.58 (d, *J*=1.37 Hz, 1H), 7.90 (d, *J*=2.05 Hz, 1H). HRMS (TOF) calcd for [$C_{29}H_{40}FN_3O_4$ + H] 514.30658 found 514.30773, error = -2.24 ppm.

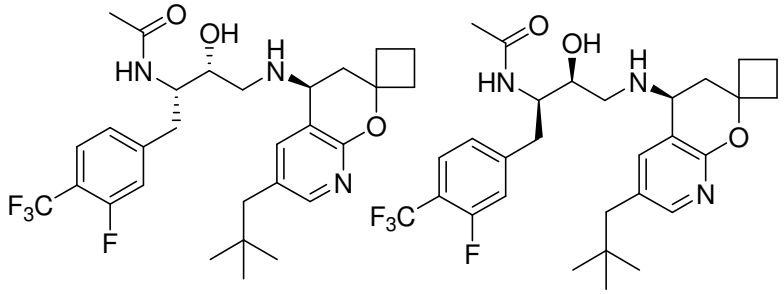


N-((2S,3R)-1-(3-flouro-4-methylphenyl)-3-hydroxy-4-((S)-6'-neopentyl-3',4'-dihydrospiro[cyclobutane-1,2'-pyrano[2,3-b]pyridine]-4'-ylamino)butan-2-yl)acetamide, 30. Following the same procedure used in

the final step for compound **2**, gave **30**. ^{1}H NMR (300 MHz, CD_3OD) δ 0.91 (s, 9H), 1.69-1.85 (m, 5H), 1.87-2.00 (m, 1H), 2.11-2.31 (m, 3H), 2.42-2.54 (m, 4H), 2.58 (dd, *J*=13.94, 10.93, 1H), 2.68-2.80 (m, 2H), 3.10 (dd, *J*=14.13, 2.83 Hz, 1H), 3.63-3.70 (m, 1H), 4.01 (dd, *J*=10.55, 5.46 Hz, 1H), 4.05-4.16 (m, 1H), 6.85-6.96 (m, 2H), 7.10 (t, *J*=8.10 Hz, 1H), 7.76 (s, 1H), 7.79 (s, 1H). HRMS (TOF) calcd for [$C_{29}H_{40}FN_3O_3$ + H] 498.31168 found 498.31263, error = -1.91 ppm.



N-((2S,3R)-1-(3-flouro-4-methoxyphenyl)-3-hydroxy-4-((S)-6'-neopentyl-3',4'-dihydrospiro[cyclobutane-1,2'-pyrano[2,3-b]pyridine]-4'-ylamino)butan-2-yl)acetamide, 31. Following the same procedure used in the final step for compound **2**, gave **31**. ^{1}H NMR (400 MHz, CD_3OD) δ 0.91 (s, 9H), 1.71-1.86 (m, 4H), 1.88-1.99 (m, 1H), 2.12-2.30 (m, 3H), 2.44-2.53 (m, 4H), 2.58 (dd, *J*=14.09, 10.17, 1H), 2.68-2.79 (m, 2H), 3.07 (dd, *J*=14.28, 3.91 Hz, 1H), 3.63-3.69 (m, 1H), 3.82 (s, 3H), 4.00 (dd, *J*=10.76, 5.48 Hz, 1H), 4.05-4.10 (m, 1H), 6.92-6.99 (m, 3H), 7.76 (d, *J*=1.96 Hz, 1H), 7.79 (d, *J*=1.17 Hz, 1H). HRMS (TOF) calcd for [$C_{29}H_{40}FN_3O_4$ + H] 514.30658 found 514.30769, error = -2.17 ppm.



N-((2S,3R)-1-(3-flouro-4-trifluoromethylphenyl)-3-hydroxy-4-((S)-6'-neopentyl-3',4'-dihydrospiro[cyclobutane-1,2'-pyrano[2,3-b]pyridine]-4'-ylamino)butan-2-yl)acetamide and N-((2R,3S)-1-(3-flouro-4-trifluoromethylphenyl)-3-hydroxy-4-((S)-6'-neopentyl-3',4'-dihydrospiro[cyclobutane-1,2'-pyrano[2,3-b]pyridine]-4'-ylamino)butan-2-yl)acetamide, 32. Following the same procedure used in the final step for compound **2**, gave **32**. ^{1}H NMR (400 MHz, CD_3OD) δ 0.94 (s, 9H), 1.81-1.92 (m, 4H), 1.95-2.07 (m, 1H), 2.08-2.37 (m, 4H), 2.51-2.64 (m, 3H), 2.71-2.80 (m, 2H), 3.07 (dd, *J*=12.72, 8.80 Hz, 1H), 3.96 (td,

J=8.80, 2.74 Hz, 1H), 4.04-4.12 (m, 1H), 7.20-7.25 (m, 2H), 7.61 (t, *J*=7.83 Hz, 1H), 7.85 (d, *J*=1.37 Hz, 1H), 8.00 (d, *J*=1.76 Hz, 1H). Some peaks obscured by residual solvent peak. MS (ESI) *m/z* 552.2 (MH+). No HRMS data.