Supporting Information

Synthesis and SAR of Benzisothiazole- and Indolizine-β-D-glucopyranoside Inhibitors of SGLT2

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Chemistry General Methods. Reagents were obtained from commercial sources and were used directly. Reactions involving air- or moisture-sensitive reagents were carried out under a nitrogen atmosphere. If not specified, reactions were carried out at ambient temperature. Silica gel was used for chromatographic purification unless otherwise indicated. 1H NMR spectra were recorded on a Varian spectrometer operating at 400 MHz; chemical shifts are reported in parts per million (ppm) relative to TMS. LCMS analysis was conducted on a Waters Acquity BEH C18 column (2x50mm, 1.7m) operating at 40 ^{o}C. The gradient employed was mobile phase A: Water + 0.20% v/v Formic Acid and mobile phase B: Acetonitrile + 0.15% v/v Formic Acid. UV detection was provided by summed absorbance signal from 210 to 350nm scanning at 40Hz. Mass spectrometry utilized Waters Acquity system operating in alternating positive/negative electrospray mode.

Transduction with Bacmam Virus. Cos-7 cells were harvested with 0.25% trypsin (Invitrogen) and plated in growth media in 24-well white with clear bottom tissue culture plates (Wallac) at 100,000 cells per well in a total volume of 500 µl with 5% human SGLT2 Bacmam baculovirus or 10% human SGLT1 Bacmam baculovirus. The plates were returned to the incubator for 48 hours.

Transport inhibition assay. The test compound was dissolved in DMSO at a final concentration of 10 mM and then diluted in assay buffer 1:1000. An 8 point 1:10 serial dilution was then carried out using 37°C assay buffer in test tubes. Transduced cells were washed two times with 37°C wash buffer. Warm assay buffer (250 ul) containing inhibitor were added to the wells. The cells were incubated in a water bath for 2 h for SGLT2 and 1h for SGLT1 during drug treatment. The cells were then washed 3 times with wash buffer. After washing was complete 1 ml of Optiphase Supermix (Perkin Elmer 1200-439) was added to each well. The cells were put on a plate shaker for 1 hour at room temperature, after which the plates were read on a Wallac 1450 Microbeta (PerkinElmer) for CPMs. Basal Buffer was 2 mM KCl, 1 mM MgCl2, 1 mM CaCl2, 10 mM HEPES, 5 mM Tris pH 7.4. Wash Buffer was basal buffer plus 140 mM Choline Chloride. Assay buffer was basal buffer plus 140 mM NaCl and 6 ul/ml (0.3 Ci/well) Alpha D (U-14C) Gluco pyranoside (Amersham). The data was converted to percent of maximum and plotted using the curve fitting software Robosage version 7.31 fitted to the equation Y=((vmax*x^n)/(K^n + x^n)) + Y2. Each treatment was done in triplicate. The assay was performed at least twice and the pIC50s are reported in Table 1.

Pharmacokinetics Studies. All pharmacokinetics studies were conducted using non-fasted male Sprague-Dawley rats (n=2 per treatment group, Charles River Laboratories, Raleigh, NC) containing jugular cannulas. For intravenous pharmacokinetics studies, animals received a single intravenous bolus of **16b** or **16c** (2 mg/kg) formulated in 2% DMSO in 20% hydroxypropyl-β-cyclodextrin (4 mL/kg) via jugular cannula. Blood samples were collected at 0.083, 0.25, 0.5, 1, 2, 4, 8 and 24 hrs post-dose. Plasma was separated immediately via centrifugation and stored at -20°C until liquid chromatography/tandem mass spectrometry (LC-

MS/MS) analysis. For oral pharmacokinetics studies, animals received a single oral dose of **16b** or **16c** (10 mg/kg) formulated as homogenous suspensions in 0.5% hydroxypropyl methylcellulose (HPMC)/0.1% polyoxyethylene sorbitan monooleate (Tween™ 80) via oral gavage (10 mL/kg). Blood samples were collected at 0.25, 0.5, 1, 2, 4, 8, and 24 hr post-dose. Plasma samples were prepared and stored as described previously. Non-compartmental pharmacokinetic parameters were calculated based on the individual plasma concentration-time data using WinNonlin Professional 4.1 (Pharsight, Mountain View, CA). LC-MS/MS Analysis. Plasma samples (40 uL) were extracted by protein precipitation with acetonitrile (160 uL) containing an appropriate internal standard. After the samples were vortex-mixed and centrifuged, an aliquot (60 uL) of each supernatant was removed and added to 120 uL deionized water containing 0.1% formic acid. LC-MS/MS analysis was performed using an Agilent 1100 Series binary pump and a Sciex API-4000 QTrap hybrid triple-quadropole linear ion trap mass spectrometer equipped with a TurboIonSpray source. Chromatographic separation was achieved using a Waters Atlantis dC18 column (2.1 x 30 mm, 3 um). The mobile phase consisted of water containing 0.1% formic acid (solvent A) and acetonitrile containing 0.1% formic acid (solvent B). The gradient began with 25% solvent B from 0 to 0.5 min, then solvent B was increased linearly to 95% over the next 1 minute. These conditions were held for 0.5 minutes, then the system was returned to the initial conditions and allowed to equilibrate for 1 minute before the next injection. The transitions for multiple reaction monitoring were 416.1 to 310.0 (9b) and 430.2 to 310.0 (9c). The linear range for both assays was 1-10,000 ng/mL with a limit of quantification of 1 ng/mL.

Synthesis of Compounds 10 - 21

5-bromo-*N*-methyl-*N*-(methyloxy)-1,2-benzisothiazole-3-carboxamide (10). To a solution of 1,2-Benzisothiazole-3-carboxylic acid **9** (13 g, 72.5 mmol) in nitric acid (60 ml), sulfuric acid (12 ml) and acetic acid (200 ml) was added bromine (5.61 ml, 109 mmol). The reaction was stirred at 70 ^{0}C for about 3 h. LC-MS or HPLC was used to follow the reaction and exact duration of the reaction varied. The reaction was cooled down to RT and water was added. The solution was extracted with ethyl acetate three times. Combined organic layer was washed once with brine and dried over magnesium sulfate. Solvent was removed and the solid was dried on a high vacuum pump overnight to remove residue of water and acetic acid to give a solid as a mixture of 5-bromo-1,2-benzisothiazole-3-carboxylic acid and 7-bromo-1,2-benzisothiazole-3-carboxylic acid with almost quantitative yield. LC-MS for the solid showed 5-bromo-1,2-benzisothiazole-3-carboxylic acid and 7-bromo-1,2-benzisothiazole-3-carboxylic acid in 2:1 ratio with a little of starting material **9** (<4%).

To a solution of compounds 5-bromo-1,2-benzisothiazole-3-carboxylic acid and 7-bromo-1,2-benzisothiazole-3-carboxylic acid (18.5 g, 71.7 mmol) in 200 ml of DMF were added N,O-dimethylhydroxylamine hydrochloride (10.5 g, 108 mmol), Hunig's base (50.1 ml, 287 mmol)

and HATU (54.5 g, 143 mmol) at RT. The reaction was stirred at RT overnight. DMF was removed and dichloromethane was added. The organic solution was washed with water once, brine once and dried over magnesium sulfate. TLC was checked with ethyl acetate/hexane=1/4 and two spots with R_f=0.48 and 5.0 were visible under UV. The bigger upper spot was the desired product. Column chromatography with 0-30% ethyl acetate in hexane provided 10.5 g of **10** in 49% yield. Purity (LCMS): >95%. LCMS (*m/z*): 301 (M+H, isotope for Br) and 303 (M+H, isotope for Br). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (br, 1H), 7.79 (d, *J*=8.6 Hz, 1H), 7.63 (dd, *J*=8.6 and 1.7 Hz, 1H), 3.8 (s, 3H), 3.46 (s, 3H).

(5-bromo-1,2-benzisothiazol-3-yl)[4-(1,1-dimethylethyl)phenyl]methanone (11d). To a solution of **10** (1 g, 3.32 mmol) in THF (20 ml) was added 2M of p-t-butylphenyl magnesium bromide (2.2 ml, 4.32 mmol) at 0 ^{0}C. The reaction was stirred at 0 ^{0}C for 15 min and then RT for another 15 min. Reaction was quenched with saturated ammonium chloride and extracted with ethyl acetate three times. Combined organic solution was washed with brine once and dried over magnesium sulfate. Column chromatography with 0-10% ethyl acetate in hexane provided 1.1 g of **11d** in 89% yield. Purity (LCMS): >95%. LCMS (*m/z*): 374 (M+H, isotope for Br) and 376 (M+H, isotope for Br). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, *J*=1.7 Hz, 1H), 8.15 (d, *J*=8.6 Hz, 2H), 7.84 (d, *J*=8.6 Hz, 1H), 7.66 (dd. *J*=8.6 and 1.7 Hz, 1H), 7.53 (d, *J*=8.6 Hz, 2H), 1.35 (s, 9H).

(5-bromo-1,2-benzisothiazol-3-yl)(4-methylphenyl)methanone (11a). This compound was prepared from **10** and p-methylphenyl magnesium bromide following the procedure in preparation of **11d** in 82% yield. Purity (LCMS): >95%. LCMS (*m/z*): 332 (M+H, isotope for Br) and 334 (M+H, isotope for Br). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (d, *J*=1.6 Hz, 1H), 8.12 (d, *J*=8.1 Hz, 2H), 7.84 (d, *J*=8.6 Hz, 1H), 7.66 (dd. *J*=8.6 and 1.6 Hz, 1H), 7.31 (d, *J*=8.1Hz, 2H), 2.43 (s, 3H).

(5-bromo-1,2-benzisothiazol-3-yl)(4-ethylphenyl)methanone (11b). This compound was prepared from **10** and p-ethylphenyl magnesium bromide following the procedure in preparation of **11d** in 87% yield. Purity (LCMS): >95%. LCMS (*m/z*): 346 (M+H, isotope for Br) and 348 (M+H, isotope for Br).

(5-bromo-1,2-benzisothiazol-3-yl)[4-(1-methylethyl)phenyl]methanone (11c). This compound was prepared from **10** and p-isopropylphenyl magnesium bromide following the procedure in preparation of **11d** in 88% yield. Purity (LCMS): >95%. LCMS (*m/z*): 360 (M+H, isotope for Br) and 362 (M+H, isotope for Br). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (d, *J*=1.7 Hz, 1H), 8.15 (d, *J*=8.3 Hz, 2H), 7.84 (d, J=8.6 Hz, 1H), 7.66 (dd. *J*=8.6 and 1.7 Hz, 1H), 7.36 (d, *J*=8.3 Hz, 2H), 2.98 (m, 1H), 1.28 (d, *J*=7.0 Hz, 6H).

4-biphenylyl(5-bromo-1,2-benzisothiazol-3-yl)methanone (11e). This compound was prepared from **10** and p-biphenyl magnesium bromide following the procedure in preparation of **11d** in 99% yield. Purity (LCMS): >95%. LCMS (*m/z*): 394 (M+H, isotope for Br) and 396 (M+H, isotope for Br). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, *J*=1.7 Hz, 1H), 8.31 (d, *J*=8.4 Hz, 2H), 7.86 (d, *J*=8.6 Hz, 1H), 7.73 (d. *J*=8.4 Hz, 2H), 7.68 (d, *J*=8.6 and 1.7 Hz, 1H), 7.65 (d, *J*=8.4 Hz, 2H), 7.39-7.48 (m, 3H).

(5-bromo-1,2-benzisothiazol-3-yl)(4-chlorophenyl)methanone (11f). This compound was prepared from **10** and p-chlorophenyl magnesium bromide following the procedure in preparation of **11d** in 85% yield. Purity (LCMS): >95%. LCMS (*m/z*): 352 (M+H, isotope for Br and Cl), 354 (M+H, isotope for Br and Cl) and 356 (M+H, isotope for Br and Cl).

(5-bromo-1,2-benzisothiazol-3-yl)(3-methylphenyl)methanone (11g). This compound was prepared from **10** and m-methylphenyl magnesium bromide following the procedure in preparation of **11d** in 91% yield. Purity (LCMS): >95%. LCMS (*m/z*): 332 (M+H, isotope for Br) and 334 (M+H, isotope for Br). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (d, *J*=1.7 Hz, 1H), 7.99 (d, *J*=6.3 Hz, 2H), 7.85 (d, *J*=8.6 Hz, 1H), 7.67 (dd. *J*=8.6 and 1.7 Hz, 1H), 7.37-7.44 (m, 2H), 2.43 (s, 3H).

(5-bromo-1,2-benzisothiazol-3-yl)(3,4-dimethylphenyl)methanone (11h). This compound was prepared from **10** and 3,4-dimethylphenyl magnesium bromide following the procedure in preparation of **11d** in 96% yield.

(5-bromo-1,2-benzisothiazol-3-yl)[4-(methyloxy)phenyl]methanone (11i). This compound was prepared from **10** and p-methoxylphenyl magnesium bromide following the procedure in preparation of **11d** in 95% yield. Purity (LCMS): >95%. LCMS (*m/z*): 348 (M+H, isotope for Br) and 350 (M+H, isotope for Br). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J*=1.6 Hz, 1H), 7.76 (dd, *J*=7.0 and 2.0 Hz, 2H), 7.34 (d, *J*=8.6 Hz, 1H), 7.16 (dd. *J*=8.6 and 1.6 Hz, 1H), 6.48 (dd, *J*=7.0 and 2.0 Hz, 2H), 3.38 (s, 3H).

(5-bromo-1,2-benzisothiazol-3-yl)[4-(ethyloxy)phenyl]methanone (11j). This compound was prepared from **10** and p-ethoxylphenyl magnesium bromide following the procedure in preparation of **11d** in 83% yield. Purity (LCMS): 83%. LCMS (*m/z*): 362 (M+H, isotope for Br) and 364 (M+H, isotope for Br).

5-bromo-3-{[4-(1,1-dimethylethyl)phenyl]methyl}-1,2-benzisothiazole (12d). To a solution of **11d** (1.1 g, 2.94 mmol) in 15 ml of trfluoroacetic acid was added triethylsilane (1.87 ml, 11.76 mmol) at 0 ^{0}C. The reaction was stirred at RT. for 6 h. TFA was removed and the residue was dissolved in ethyl acetate. The organic solution was washed with saturated sodium bicarbonate once, brine once and dried over magnesium sulfate. Column chromatography with 0-10% ethyl acetate in hexane provided 1 g of **12d** in 94% yield. Purity (LCMS): >95%. LCMS (*m/z*): 360 (M+H, isotope for Br) and 362 (M+H, isotope for Br). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J*=1.6 Hz, 1H), 7.75 (d, *J*=8.6 Hz, 1H), 7.54 (dd, *J*=8.6 and 1.6 Hz, 1H), 7.30 (d. *J*=8.2 Hz, 2H), 7.20 (d, *J*=8.2 Hz, 2H), 4.38 (s, 2H), 1.26 (s, 9H).

5-bromo-3-[(4-methylphenyl)methyl]-1,2-benzisothiazole (12a). This compound was prepared from **11a** following the procedure in preparation of **12d** in 92% yield. Purity (LCMS): 95%. LCMS (*m/z*): 318 (M+H, isotope for Br) and 320 (M+H, isotope for Br).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J*=1.5 Hz, 1H), 7.74 (d, *J*=8.6 Hz, 1H), 7.54 (dd, *J*=8.6 and 1.5 Hz, 1H), 7.16 (d. *J*=7.9 Hz, 2H), 7.09 (d, *J*=7. 9 Hz, 2H), 4.37 (s, 2H), 2.29 (s, 3H).

5-bromo-3-[(4-ethylphenyl)methyl]-1,2-benzisothiazole (12b). This compound was prepared from **11b** following the procedure in preparation of **12d** in 88% yield. Purity (LCMS): >95%. LCMS (*m/z*): 332 (M+H, isotope for Br) and 334 (M+H, isotope for Br). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J*=1.5 Hz, 1H), 7.76 (d, *J*=8.6 Hz, 1H), 7.55 (dd, *J*=8.6 and 1.5 Hz, 1H), 7.20 (d. *J*=8.0 Hz, 2H), 7.13 (d, *J*=8.0 Hz, 2H), 4.39 (s, 2H), 2.60 (q, *J*=7.5 Hz, 2H), 1.20 (t, *J*=7.5 Hz, 3H).

5-bromo-3-{[4-(1-methylethyl)phenyl]methyl}-1,2-benzisothiazole (12c). This compound was prepared from **11c** following the procedure in preparation of **12d** in 84% yield. Purity (LCMS): >95%. LCMS (*m/z*): 346 (M+H, isotope for Br) and 348 (M+H, isotope for Br). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J*=1.7 Hz, 1H), 7.76 (d, *J*=8.6 Hz, 1H), 7.55 (dd, *J*=8.6 and 1.7 Hz, 1H), 7.21 (d. *J*=8.2 Hz, 2H), 7.16 (d, *J*=8.2 Hz, 2H), 2.86 (m, 1H), 1.21 (d, *J*=6.8 Hz, 6H).

3-(4-biphenylylmethyl)-5-bromo-1,2-benzisothiazole (12e). This compound was prepared from **11e** following the procedure in preparation of **12d** in 88% yield**.** Purity (LC-MS): 93%**.** LCMS (*m/z*): 380 (M+H, isotope for Br) and 382 (M+H, isotope for Br). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J*=1.6 Hz, 1H), 7.77 (d, *J*=8.6 Hz, 1H), 7.51-7.57 (m, 5H), 7.30-7.41 (m, 5H), 4.46 (s, 2H).

5-bromo-3-[(4-chlorophenyl)methyl]-1,2-benzisothiazole (12f). This compound was prepared from **11f** following the procedure in preparation of **12d** in 73% yield. Purity (LCMS): >95%. LCMS (*m/z*): 338 (M+H, isotope for Br and Cl) 340 (M+H, isotope for Br and Cl) and 342 (M+1, isotope for Br and Cl). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.97 (d, *J*=1.7 Hz, 1H), 7.76 (d, *J*=8.6 Hz, 1H), 7.56 (dd, *J*=8.6 and 1.7 Hz, 1H), 7.26 (d. *J*=8.6 Hz, 2H), 7.19 (d, *J*=8.6 Hz, 2H), 4.37 (s, 2H).

5-bromo-3-[(3-methylphenyl)methyl]-1,2-benzisothiazole (12g). This compound was prepared from **11g** following the procedure in preparation of **12d** in 70% yield. Purity (LC-MS): 95%. LCMS (*m/z*): 318 (M+H, isotope for Br) and 320 (M+H, isotope for Br). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J*=1.5 Hz, 1H), 7.72 (d, *J*=8.6 Hz, 1H), 7.53 (dd, *J*=8.6 and 1.5 Hz, 1H), 7.20 (t. *J*=7.5 Hz, 1H), 7.10 (d, *J*=7.5 Hz, 1H), 7.05 (d, *J*=7.5 Hz, 1H), 4.39 (s, 2H), 2.32 (s, 3H).

5-bromo-3-[(3,4-dimethylphenyl)methyl]-1,2-benzisothiazole (12h). This compound was prepared from **11h** following the procedure in preparation of **12d** in 93% yield. Purity (LCMS): >95%. LCMS (*m/z*): 332 (M+H, isotope for Br) and 334 (M+H, isotope for Br).

5-bromo-3-{[4-(methyloxy)phenyl]methyl}-1,2-benzisothiazole (12i). This compound was prepared from **11i** following the procedure in preparation of **12d**. Purity (LCMS): >95%. LCMS (*m/z*): 334 (M+H, isotope for Br) and 336 (M+H, isotope for Br). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J*=1.7 Hz, 1H), 7.76 (d, *J*=8.6 Hz, 1H), 7.56 (dd, *J*=8.6 and 1.7 Hz, 1H), 7.20 (d. *J*=8.6 Hz, 2H), 6.83 (d, *J*=8.6 Hz, 2H), 4.37 (s, 2H), 3.76 (s, 3H).

5-bromo-3-{[4-(ethyloxy)phenyl]methyl}-1,2-benzisothiazole (12j). This compound was prepared from **11j** following the procedure in preparation of **12d** in 85% yield. Purity (LCMS): >95%. LCMS (*m/z*): 348 (M+H, isotope for Br) and 350 (M+H, isotope for Br).

6-bromo-3-[(4-methylphenyl)methyl]indolizine (12k). To a mixture of aluminum chloride (2.1 g, 16 mmol) and sodium borohydride (1.2 g, 32 mmol) in 30 ml of THF was added (6-bromo-3-indolizinyl)(4-methylphenyl)methanone **19k** (2 g, 6.4 mmol) at 0 ^{0}C. The reaction was stirred at 0 ^{0}C for 30 min and then 50 ^{0}C for another 30 min. The mixture was cooled, poured to iced water and extracted with ether 3 times. Combined ether solution was washed with brine once and dried over magnesium sulfate. Column chromatography with 100% petroleum ether provided 1.2 g of **12k** as a yellow solid in 63% yield. Purity (LCMS): >95%. LCMS (*m/z*): 300 (M+H, isotope for Br) and 302 (M+H, isotope for Br). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 1H), 7.42 (d, *J*=9.6 Hz, 1H), 7.10 (s, 4H), 6.72 (d. *J*=9.6 Hz, 1H), 6.58 (d, *J*=3.6 Hz, 1H), 6.48 (d, *J*=3.6 Hz, 1H), 4.22 (s, 2H), 2.26 (s, 3H).

6-bromo-3-{[4-(methyloxy)phenyl]methyl}indolizine (12l). This compound was prepared from (6-bromo-3-indolizinyl)(4-methoxyphenyl)methanone **19l** following the procedure in preparation of **12k**. Purity (LCMS): >95%**.** LCMS (*m/z*): 316 (M+H, isotope for Br) and 318 (M+H, isotope for Br). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.27 (d, *J*=9.6 Hz, 1H), 7.07 (d. *J*=8.8 Hz, 2H), 6.74 (d, *J*=8.8 Hz, 2H), 6.66 (d, *J*=9.6 Hz, 1H), 6.54 (s, 2H), 4.12 (s, 2H), 3.79 (s, 3H).

6-bromo-3-[(4-fluorophenyl)methyl]indolizine (12m). This compound was prepared from (6-bromo-3-indolizinyl)(4-fluorophenyl)methanone **19m** following the procedure in preparation of **12k**. Purity (LCMS): >95%**.** LCMS (*m/z*): 304 (M+H, isotope for Br) and 306 (M+H, isotope for Br). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.31 (d, *J*=9.2 Hz, 1H), 7.14 (m, 2H), 7.02 (t. *J*=8.4 Hz, 2H), 6.71 (d, *J*=9.2 Hz, 1H), 6.57 (s, 1H), 6.49 (s, 1H), 4.18 (s, 2H).

6-bromo-3-[(4-chlorophenyl)methyl]indolizine (12n). This compound was prepared from (6-bromo-3-indolizinyl)(4-chlorophenyl)methanone **19n** following the procedure in preparation of **12k.** Purity (LCMS): >95%. LCMS (*m/z*): 320 (M+H, isotope for Br and Cl), 322 (M+H, isotope for Br and Cl) and 324 (M+H, isotope for Br and Cl). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.43 (d, *J*=9.2 Hz, 1H), 7.36 (d, *J*=8.4 Hz, 2H), 7.23 (d, *J*=8.4 Hz, 2H), 6.74 (d, *J*=9.2 Hz, 1H), 6.59 (d, *J*=3.6 Hz, 1H), 6.49 (d, *J*=3.6 Hz, 1H), 4.28 (s, 2H).

6-bromo-3-{[4-(trifluoromethyl)phenyl]methyl}indolizine (12o). This compound was prepared from (6-bromo-3-indolizinyl)(4-trifluoromethylphenyl)methanone **19o** following the procedure in preparation of **12k**. Purity (LCMS): >95%**.** LCMS (*m/z*): 354 (M+H, isotope for Br) and 356 (M+H, isotope for Br). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.59 (d, *J*=7.6 Hz, 2H), 7.31 (m, 3H), 6.73 (d, *J*=9.6 Hz, 1H), 6.57 (d, *J*=3.6 Hz, 1H), 6.51 (d, *J*=3.6 Hz, 1H), 4.27 (s, 2H).

6-bromo-3-{[4-(methyloxy)phenyl]methyl}imidazo[1,2-a]pyridine (12p)

TFA (16.8 mL, 218 mmol) was cooled to 0 °C in a dry flask under nitrogen. To this sodium borohydride (0.763 g, 20.17 mmol) was added portionwise, gas evolution was observed. After bubbling had ceased the newly formed reducing agent was added to a suspension of (6-bromoimidazo[1,2-a]pyridin-3-yl)[4-(methyloxy)phenyl]methanol **21** (1.12 g, 3.36 mmol) in dichloromethane (15 mL). Upon complete addition the suspension turned homogeneous and the light pink color persisted. After stirring for 1h the reaction was quenched with saturated bicarbonate and the organics isolated. They were rewashed 3 times with saturated bicarbonate to remove any residual acid. The organics were dried over sodium sulfate, filtered and concentrated to a brown oil, with traces of white solids. Upon suspending the oil in ethyl acetate the solids were precipitated out with hexane and filtered off. The filtrate was reconcentrated and purified by reverse-phase column chromatography with 0-100% acetonitrile in water to give 400mg of **12p** in 38% yield. LCMS (*m/z*): 317 (M+H, isotope for Br) and 319 (M+H, isotope for Br). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.96 (s, 1H), 7.81-7.95 (m, 2H), 7.77 (s, 1H), 7.26 (d, *J*=8.70 Hz, 2H), 6.92 (d, *J*=8.70 Hz, 2H), 4.31 (s, 2H), 3.73 (s, 3H).

5-((4a*R*,8*R*,8a*R*)-2,2-bis(1,1-dimethylethyl)-8-{[tris(1-methylethyl)silyl]oxy}-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasilin-6-yl)-3-{[4-(1,1-dimethylethyl)phenyl]methyl}-1,2-benzisothiazole (14d). To a solution of **12d** (1 g, 2.78 mmol) and (4aR,8R,8aR)-2,2-bis(1,1-dimethylethyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-{[tris(1-methylethyl)silyl]oxy}-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3,2]dioxasilin **13** (2.76 g, 4.86 mmol, WO 2005/012326, *Chem Abstr* **2005**, *142*, 219491) in 40 ml of 1,2-dimethoxyethane were added 2 M of sodium carbonate (15 ml) and bis(triphenylphosphine) palladium(II) chloride (390 mg, 0.56 mmol). The mixture was heated at 85 ^{0}C for 30 min and then cooled down. Ethyl acetate was added and the organic layer was isolated. The organic layer was washed with brine once and dried over magnesium sulfate. Column chromatography with 0-10% ethyl acetate in hexane provided **14d** as an oil in quantitative yield, which proceeded directly to the next step.

5-((4a*R*,8*R*,8a*R*)-2,2-bis(1,1-dimethylethyl)-8-{[tris(1-methylethyl)silyl]oxy}-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasilin-6-yl)-3-[(4-methylphenyl)methyl]-1,2-benzisothiazole (14a). This compound was prepared from **12a** and **13** following the procedure in preparation of **14d** in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.80 (d, *J*=8.6 Hz, 1H), 7.59 (d, *J*=8.6 Hz, 1H), 7.16 (d. *J*=8.0 Hz, 2H), 7.07 (d, *J*=8.0 Hz, 2H), 5.24 (d, *J*=2.3 Hz, 1H), 4.57 (dd, *J*=6.8 and 2.3 Hz, 1H), 4.40 (s, 2H), 4.32 (dd, *J*=10.5 and 4.8 Hz, 1H), 4.11 (m, 2H), 4.00 (m, 1H), 2.28 (s, 3H), 0.8-1.9 (m, 39H).

5-((4a*R*,8*R*,8a*R*)-2,2-bis(1,1-dimethylethyl)-8-{[tris(1-methylethyl)silyl]oxy}-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasilin-6-yl)-3-[(4-ethylphenyl)methyl]-1,2-benzisothiazole (14b). This compound was prepared from **12b** and **13** following the procedure in preparation of **14d** in 99% yield**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.80 (d, *J*=8.6 Hz, 1H), 7.59 (d, *J*=8.6 Hz, 1H), 7.19 (d. *J*=8.0 Hz, 2H), 7.10 (d, *J*=8.0 Hz, 2H), 5.25 (d, *J*=2.4 Hz, 1H), 4.57 (dd, *J*=6.7 and 2.3 Hz, 1H), 4.40 (s, 2H), 4.32 (m, 1H), 4.09 (m, 2H), 4.00 (m, 1H), 2.58 (q, *J*=7.6 Hz, 2H), 0.8-1.9 (m, 42H).

5-((4a*R*,8*R*,8a*R*)-2,2-bis(1,1-dimethylethyl)-8-{[tris(1-methylethyl)silyl]oxy}-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasilin-6-yl)-3-{[4-(1-methylethyl)phenyl]methyl}-1,2-benzisothiazole (14c). This compound was prepared from **12c** and **13** following the procedure in preparation of **14d** in quantitative yield**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.80 (d, *J*=8.6 Hz, 1H), 7.59 (d, *J*=8.6 Hz, 1H), 7.20 (d. *J*=8.0 Hz, 2H), 7.12 (d, *J*=8.0 Hz, 2H), 5.25 (d, *J*=2.3 Hz, 1H), 4.57 (dd, *J*=6.8 and 2.2 Hz, 1H), 4.40 (s, 2H), 4.32 (m, 1H), 4.10 (m, 2H), 4.00 (m, 1H), 2.83 (m, 1H), 0.8-1.9 (m, 45H).

5-((4a*R*,8*R*,8a*R*)-2,2-bis(1,1-dimethylethyl)-8-{[tris(1-methylethyl)silyl]oxy}-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasilin-6-yl)-3-[(4-chlorophenyl)methyl]-1,2-benzisothiazole (14f). This compound was prepared from **12f** and **13** following the procedure in preparation of **14d** in quantitative yield**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.83 (d, *J*=8.5 Hz, 1H), 7.62 (d, *J*=8.5 Hz, 1H), 7.25 (d. *J*=8.4 Hz, 2H), 7.20 (d, *J*=8.4 Hz, 2H), 5.25 (d, *J*=2.3 Hz, 1H), 4.58 (dd, *J*=6.6 and 2.2 Hz, 1H), 4.42 (s, 2H), 4.31 (dd, *J*=10.4 and 4.8 Hz, 1H), 4.11 (m, 2H), 4.01 (m, 1H), 0.8-1.9 (m, 39H).

5-((4a*R*,8*R*,8a*R*)-2,2-bis(1,1-dimethylethyl)-8-{[tris(1-methylethyl)silyl]oxy}-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasilin-6-yl)-3-{[4-(methyloxy)phenyl]methyl}-1,2-benzisothiazole (14i). This compound was prepared from **12i** and **13** following the procedure in preparation of **14d** in 85% yield**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.80 (d, *J*=8.4 Hz, 1H), 7.59 (d, *J*=8.4 Hz, 1H), 7.19 (d. *J*=8.6 Hz, 2H), 7.07 (d, *J*=8.6 Hz, 2H), 5.24 (d, *J*=2.3 Hz, 1H), 4.57 (dd, *J*=6.6 and 2.3 Hz, 1H), 4.37 (s, 2H), 4.32 (m, 1H), 4.10 (m, 2H), 4.00 (m, 1H), 3.74 (s, 3H), 0.8-1.9 (m, 39H).

5-((4a*R*,8*R*,8a*R*)-2,2-bis(1,1-dimethylethyl)-8-{[tris(1-methylethyl)silyl]oxy}-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasilin-6-yl)-3-{[4-(ethyloxy)phenyl]methyl}-1,2-benzisothiazole (14j). This compound was prepared from **12j** and **13** following the procedure in preparation of **14d** in 88% yield**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.80 (d, *J*=8.6 Hz, 1H), 7.60 (d, *J*=8.6 Hz, 1H), 7.17 (d. *J*=8.5 Hz, 2H), 6.79 (d, *J*=8.5 Hz, 2H), 5.24 (d, *J*=2.4 Hz, 1H), 4.57 (dd, *J*=6.7 and 2.3 Hz, 1H), 4.37 (s, 2H), 4.32 (m, 1H), 4.11 (m, 2H), 3.98 (m, 3H), 0.8-1.9 (m, 42H).

6-((4a*R*,8*R*,8a*R*)-2,2-bis(1,1-dimethylethyl)-8-{[tris(1-methylethyl)silyl]oxy}-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasilin-6-yl)-3-[(4-fluorophenyl)methyl]indolizine (14m). This compound was prepared from **12m** and **13** following the procedure in preparation of **14d** in 91% yield**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.29 (d, *J*=9.4 Hz, 1H), 7.12 (m, 2H), 6.96 (t. *J*=8.7 Hz, 2H), 6.70 (d, *J*=9.4 Hz, 1H), 6.55 (d, *J*=3.7 Hz, 1H), 6.38 (d, *J*=3.7 Hz, 1H), 5.08 (d, *J*=2.3 Hz, 1H), 4.53 (dd, *J*=6.9 and 2.2 Hz, 1H), 4.23 (m, 1H), 4.15 (s, 2H), 4.07 (m, 2H), 3.92 (m, 1H), 0.8-1.9 (m, 39H).

6-((4a*R*,8*R*,8a*R*)-2,2-bis(1,1-dimethylethyl)-8-{[tris(1-methylethyl)silyl]oxy}-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasilin-6-yl)-3-{[4-(trifluoromethyl)phenyl]methyl}indolizine (14o). This compound was prepared from **12o** and **13** following the procedure in preparation of **14d** in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.52 (d, *J*=8.1 Hz, 2H), 7.29 (d, *J*=9.4 Hz, 1H), 7.24 (d, *J*=8.1 Hz, 2H), 6.70 (d, *J*=9.4 Hz, 1H), 6.55 (d, *J*=3.8 Hz, 1H), 6.39 (d, *J*=3.8 Hz, 1H), 5.08 (d, *J*=2.3 Hz, 1H), 4.52 (dd, *J*=6.8 and 2.3 Hz, 1H), 4.23 (s, 2H), 4.20 (m, 1H), 4.06 (m, 2H), 3.92 (m, 1H), 0.8-1.9 (m, 39H).

6-((4aR,8R,8aR)-2,2-bis(1,1-dimethylethyl)-8-{[tris(1-methylethyl)silyl]oxy}-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3,2]dioxasilin-6-yl)-3-{[4-(methyloxy)phenyl]methyl}imidazo[1,2-a]pyridine (14p). This compound was prepared from **12p** and **13** following the procedure in preparation of **14d** in 63% yield. LCMS (*m/z*) 679 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.51 (d, *J*=9.4 Hz, 1H), 7.38 (s, 1H), 7.20 (dd, *J*=9.4 and 1.7 Hz, 1H), 7.09 (d, *J*=8.6 Hz, 2H), 6.81 (d, *J*=8.6 Hz, 2H), 5.14 (d, *J*=2.4 Hz, 1H), 4.53 (dd, *J*=6.9 and 2.3 Hz, 1H), 4.24 (dd, *J*=10.2 and 4.8 Hz, 1H), 3.8-4.1(m, 8H with contaminants), 0.8-1.2 (m, 39H with comtaminants).

(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-bis(1,1-dimethylethyl)-6-(3-{[4-(1,1-dimethylethyl)phenyl]methyl}-1,2-benzisothiazol-5-yl)-8-{[tris(1-methylethyl)silyl]oxy}hexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol (15d). To a solution of **14d** (from last step) in 20 ml of THF was added 1 M of borane-tetrahydrofuran complex (8.31 ml, 8.31 mmol) in THF at 0 ^{0}C. The reaction was maintained at 0 ^{0}C for 3 h and then stirred at RT overnight. Hydrogen peroxide (30%, 20 ml) and 20 ml of 3 M sodium hydroxide were added at 0 ^{0}C and the mixture was stirred at RT. After 30 min, 30 ml of 20% sodium thiosulfate was added carefully at 0 ^{0}C. The mixture was extracted with ethyl acetate three times, and the combined organic layer was washed with brine once and dried over magnesium sulfate. Column chromatography with 0-10% ethyl acetate in hexane provided 770 mg of **15d** in 38% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.88 (d, *J*=8.6 Hz, 1H), 7.51 (d, *J*=8.6 Hz, 1H), 7.28 (d. *J*=8.2 Hz, 2H), 7.21 (d, *J*=8.2 Hz, 2H), 4.42 (s, 2H), 4.36 (d, *J*=9.6 Hz, 1H), 4.17 (dd, *J*=10.2 and 4.9 Hz, 1H), 3.88 (m, 3H), 3.58 (m, 1H), 3.45 (m, 1H), 1.2 (m, 3H), 1.0-1.05 (m, 46H).

(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-bis(1,1-dimethylethyl)-6-{3-[(4-methylphenyl)methyl]-1,2-benzisothiazol-5-yl}-8-{[tris(1-methylethyl)silyl]oxy}hexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol (15a). This compound was prepared from **14a** following the procedure in preparation of **15d** in 37% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.88 (d, *J*=9.4 Hz, 1H), 7.52 (d, *J*=9.4 Hz, 1H), 7.18 (d. *J*=8.0 Hz, 2H), 7.08 (d, *J*=8.0 Hz, 2H), 4.44 (s, 2H), 4.36 (d, *J*=9.6 Hz, 1H), 4.18 (dd, *J*=10.1 and 4.9 Hz, 1H), 3.88 (m, 3H), 3.58 (m, 1H), 3.45 (m, 1H), 2.29 (s, 3H), 2.00 (s,1H), 0.80-1.3 (m, 39H).

(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-bis(1,1-dimethylethyl)-6-{3-[(4-ethylphenyl)methyl]-1,2-benzisothiazol-5-yl}-8-{[tris(1-methylethyl)silyl]oxy}hexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol (15b). This compound was prepared from **14b** following the procedure in preparation of **15d** in 39% yield ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.88 (d, *J*=8.4 Hz, 1H), 7.52 (d, *J*=8.4 Hz, 1H), 7.20 (d. *J*=8.0 Hz, 2H), 7.11 (d, *J*=8.0 Hz, 2H), 4.43 (s, 2H), 4.36 (d, *J*=9.4 Hz, 1H), 4.18 (m, 1H), 3.89 (m, 3H), 3.59 (m, 1H), 3.46 (m, 1H), 2.58 (q, *J*=7.6 Hz, 2H), 0.8-1.3 (m, 43H).

(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-bis(1,1-dimethylethyl)-6-(3-{[4-(1-methylethyl)phenyl]methyl}-1,2-benzisothiazol-5-yl)-8-{[tris(1-methylethyl)silyl]oxy}hexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol (15c). This compound was prepared from **14c** following the procedure in preparation of **15d** in 38% yield**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.87 (d, *J*=8.4 Hz, 1H), 7.51 (d, *J*=8.4 Hz, 1H), 7.20 (d. *J*=8.0 Hz, 2H), 7.12 (d, *J*=8.0 Hz, 2H), 4.42 (s, 2H), 4.35 (d, *J*=9.6 Hz, 1H), 4.16 (dd, *J*=10.1 and 4.9 Hz, 1H), 3.87 (m, 3H), 3.58 (m, 1H), 3.45 (m, 1H), 2.83 (m, 1H), 0.8-1.2 (m, 46H).

(4a*R*,6*S*,7*S*,8*R*,8a*R*)-6-[3-(4-biphenylylmethyl)-1,2-benzisothiazol-5-yl]-2,2-bis(1,1-dimethylethyl)-8-{[tris(1-methylethyl)silyl]oxy}hexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol (15e). This compound was prepared from **14e** following the procedure in preparation of **15d** in 40% yield**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.90 (d, *J*=8.4 Hz, 1H), 7.52 (m, 5H), 7.34 (m, 5H), 4.49 (s, 2H), 4.37 (d, *J*=9.6 Hz, 1H), 4.17 (m, 1H), 3.89 (m, 3H), 3.58 (m, 1H), 3.48 (m, 1H), 0.8-1.2 (m, 40H).

(4a*R*,6*S*,7*S*,8*R*,8a*R*)-6-{3-[(4-chlorophenyl)methyl]-1,2-benzisothiazol-5-yl}-2,2-bis(1,1-dimethylethyl)-8-{[tris(1-methylethyl)silyl]oxy}hexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol (15f). This compound was prepared from **14f** following the procedure in preparation of **15d** in 33% yield**.** ^{1}H NMR (400MHz, $CDCl_3$) δ 7.89 (d, *J*=8.5 Hz, 1H), 7.86 (s, 1H), 7.56 (d, *J*=8.5 Hz, 1H), 7.25 (d, *J*=8.5 Hz, 2H), 7.21 (d, *J*=8.5 Hz, 2H), 4.40 (s, 2H), 4.38 (d, *J*=9.6 Hz, 1H), 4.18 (m, 1H), 3.00 (m, 3H), 3.61 (m, 1H), 3.49 (m, 1H), 0.8-1.2 (m, 40H).

(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-bis(1,1-dimethylethyl)-6-{3-[(3-methylphenyl)methyl]-1,2-benzisothiazol-5-yl}-8-{[tris(1-methylethyl)silyl]oxy}hexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol (15g). This compound was prepared from **14g** following the procedure in preparation of **15d** in 30% yield**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.87 (d, *J*=9.2 Hz, 1H), 7.51 (d, *J*=9.2 Hz, 1H), 7.15 (t. *J*=7.4 Hz, 1H), 7.09 (s, 1H), 7.07 (d, *J*=7.4 Hz, 1H), 7.00 (d, *J*=7.4 Hz, 1H), 4.41 (s, 2H), 4.35 (d, *J*=9.4 Hz, 1H), 4.17 (m, 1H), 3.87 (m, 3H), 3.57 (m, 1H), 3.44 (m, 1H), 2.27 (s, 3H), 2.00 (s,1H), 0.80-1.3 (m, 39H).

(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-bis(1,1-dimethylethyl)-6-{3-[(3,4-dimethylphenyl)methyl]-1,2-benzisothiazol-5-yl}-8-{[tris(1-methylethyl)silyl]oxy}hexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol (15h). This compound was prepared from **14h** following the procedure in preparation of **15d** in 32% yield**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.88 (d, *J*=8.4 Hz, 1H), 7.50 (d, *J*=8.4 Hz, 1H), 7.03 (d. *J*=13.5 Hz, 2H), 7.02 (s, 1H), 4.38 (s, 2H), 4.35 (d, *J*=9.6 Hz, 1H), 4.17 (m, 1H), 3.88 (m, 3H), 3.58 (m, 1H), 3.45 (m, 1H), 2.18 (s, 6H), 0.80-1.3 (m, 40H).

(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-bis(1,1-dimethylethyl)-6-(3-{[4-(methyloxy)phenyl]methyl}-1,2-benzisothiazol-5-yl)-8-{[tris(1-methylethyl)silyl]oxy}hexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol (15i). This compound was prepared from **14i** following the procedure in preparation of **15d** in 41% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J*=9.4 Hz, 1H), 7.88 (s, 1H), 7.53 (d, *J*=9.4 Hz, 1H), 7.20 (d. *J*=8.6 Hz, 2H), 6.81 (d, *J*=8.6 Hz, 2H), 4.40 (s, 2H), 4.36 (d, *J*=9.6 Hz, 1H), 4.18 (m, 1H), 3.89 (m, 3H), 3.75 (s, 3H), 3.60 (m, 1H), 3.47 (m, 1H), 2.00 (s, 1H), 0.80-1.3 (m, 39H).

(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-bis(1,1-dimethylethyl)-6-(3-{[4-(ethyloxy)phenyl]methyl}-1,2-benzisothiazol-5-yl)-8-{[tris(1-methylethyl)silyl]oxy}hexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol (15j). This compound was prepared from **14j** following the procedure in preparation of **15d** in 25% yield**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (m, 2H), 7.53 (d, *J*=8.8 Hz, 1H), 7.18 (d. *J*=8.6 Hz, 2H), 6.80 (d, *J*=8.6 Hz, 2H), 4.39 (s, 2H), 4.36 (d, *J*=9.5 Hz, 1H), 4.18 (m, 1H), 3.97 (q, *J*=7.0 Hz, 2H), 3.88 (m, 3H), 3.59 (m, 1H), 3.48 (m, 1H), 2.00 (s, 1H), 0.80-1.3 (m, 39H).

(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-bis(1,1-dimethylethyl)-6-(3-{[4-(methyloxy)phenyl]methyl}-6-indolizinyl)-8-{[tris(1-methylethyl)silyl]oxy}hexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol (15l). This compound was prepared from **14l** following the procedure in preparation of **15d** in 23% yield**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.36 (d, *J*=9.3 Hz, 1H), 7.04 (d, *J*=8.6 Hz, 2H), 6.80 (d. *J*=8.6 Hz, 2H), 6.65 (d, *J*=9.3 Hz, 1H), 6.49 (d, *J*=3.9 Hz, 1H), 6.37 (d, *J*=3.9 Hz, 1H), 4.11 (d, *J*=8.8 Hz, 1H), 4.10 (m, 3H), 3.83 (m, 2H), 3.75 (s, 3H), 2.00 (s, 1H), 0.80-1.3 (m, 39H).

(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-bis(1,1-dimethylethyl)-6-{3-[(4-fluorophenyl)methyl]-6-indolizinyl}-8-{[tris(1-methylethyl)silyl]oxy}hexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol (15m). This compound was prepared from **14m** following the procedure in preparation of **15d** in 32% yield**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.35 (d, *J*=9.2 Hz, 1H), 7.09 (m, 2H), 6.96 (t. *J*=8.7 Hz, 2H), 6.68 (d, *J*=9.2 Hz, 1H), 6.51 (d, *J*=3.8 Hz, 1H), 6.39 (d, *J*=3.8 Hz, 1H), 3.4-4.2 (m, 9H), 1.99 (s, 1H), 0.80-1.3 (m, 39H).

(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-bis(1,1-dimethylethyl)-6-(3-{[4-(trifluoromethyl)phenyl]methyl}-6-indolizinyl)-8-{[tris(1-methylethyl)silyl]oxy}hexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol (15o). This compound was prepared from **14o** following the procedure in preparation of **15d** in 31% yield**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.53 (d, *J*=8.0 Hz, 2H), 7.23-7.4 (m, 3H), 6.69 (d, *J*=9.4 Hz, 1H), 6.52 (d, *J*=3.8 Hz, 1H), 6.40 (d, *J*=3.8 Hz, 1H), 3.3-4.3 (m, 9H), 1.99 (s, 1H), 0.80-1.3 (m, 39H).

(4aR,7S,8R,8aR)-2,2-bis(1,1-dimethylethyl)-6-(3-{[4-(methyloxy)phenyl]methyl}imidazo[1,2-a]pyridin-6-yl)-8-{[tris(1-

methylethyl)silyl]oxy}hexahydropyrano[3,2-d][1,3,2]dioxasilin-7-ol (15p). This compound was prepared from **14p** following the procedure in preparation of **15d** and was taken directly to the next step. LCMS (*m/z*) 697 (M+H).

(1*S*)-1,5-anhydro-1-(3-{[4-(1,1-dimethylethyl)phenyl]methyl}-1,2-benzisothiazol-5-yl)-D-glucitol (16d). To a solution of **15d** (280 mg, 0.378 mmol) in 5 ml of THF was added triethylamine trihydrofluoride (0.308 ml, 1.891 mmol) and the reaction is stirred at 60 ^{0}C for 4 days. Solvent was removed and the residue was purified by column chromatography with 0-20% methanol in dichloromethane to give an oil. The oil was further purified by reverse-phase column chromatography with 0-80% acetonitrile in water to provide 80 mg of **16d** in 47% yield.

Purity (LCMS): >95%. HRMS calcd for $C_{24}H_{30}NO_5S$ (M+H) 444.1845, found 444.1847. ^{1}H NMR (400 MHz, CD_3OD) δ 8.09 (s, 1H), 7.95 (d, *J*=8.6 Hz, 1H), 7.64 (d, *J*=8.6 Hz, 1H), 7.27 (d. *J*=8.3 Hz, 2H), 7.20 (d, *J*=8.3 Hz, 2H), 4.42 (s, 2H), 4.27 (d, *J*=9.4 Hz, 1H), 3.87 (dd, *J*=11.9 and 1.4 Hz, 1H), 3.71 (dd, *J*=12.0 and 5.0 Hz, 1H), 3.44 (m, 3H), 3.33 (m, 1H), 1.24 (s, 9H).

(1*S*)-1,5-anhydro-1-{3-[(4-methylphenyl)methyl]-1,2-benzisothiazol-5-yl}-D-glucitol (16a). This compound was prepared from **15a** following the procedure in preparation of **16d** in 9% yield. Purity (LCMS): >95%. HRMS calcd for $C_{21}H_{24}NO_5S$ (M+H) 402.1375, found 402.1372. ^{1}H NMR (400 MHz, CD_3OD) δ 8.05 (s, 1H), 7.92 (d, *J*=8.6 Hz, 1H), 7.62 (d, *J*=8.6 Hz, 1H), 7.14 (d. *J*=7.8 Hz, 2H), 7.03 (d, *J*=7.8 Hz, 2H), 4.39 (s, 2H), 4.25 (d, *J*=9.6 Hz, 1H), 3.87 (dd, *J*=11.9 and 1.8 Hz, 1H), 3.71 (dd, *J*=11.9 and 5.0Hz, 1H), 3.45 (m, 3H), 3.33 (m, 1H), 2.22(s, 3H).

(1*S*)-1,5-anhydro-1-{3-[(4-ethylphenyl)methyl]-1,2-benzisothiazol-5-yl}-D-glucitol (16b). This compound was prepared from **15b** following the procedure in preparation of **16d** in 19% yield**.** Purity (LCMS): >95%**.** HRMS calcd for $C_{22}H_{26}NO_5S$ (M+H) 416.1532, found 416.1534. ^{1}H NMR (400 MHz, CD_3OD) δ 8.07 (s, 1H), 7.96 (d, *J*=8.5 Hz, 1H), 7.64 (d, *J*=8.5 Hz, 1H), 7.18 (d. *J*=8.0 Hz, 2H), 7.07 (d, *J*=8.0 Hz, 2H), 4.42 (s, 2H), 4.26 (d, *J*=9.4 Hz, 1H), 3.88 (d, *J*=12.5 Hz, 1H), 3.71 (dd, *J*=12.0 and 5.0 Hz, 1H), 3.44 (m, 3H), 3.32 (m, 1H), 2.55 (q, *J*=7.6 Hz, 2H), 1.15 (t, *J*=7.6 Hz, 3H).

(1*S*)-1,5-anhydro-1-(3-{[4-(1-methylethyl)phenyl]methyl}-1,2-benzisothiazol-5-yl)-D-glucitol (16c). This compound was prepared from **15c** following the procedure in preparation of **16d** in 20% yield**.** Purity (LCMS): >95%**.** HRMS calcd for $C_{23}H_{28}NO_5S$ (M+H) 430.1688, found 430.1691. ^{1}H NMR (400 MHz, CD_3OD) δ 8.11 (s, 1H), 7.97 (d, *J*=8.6 Hz, 1H), 7.67 (d, *J*=8.6 Hz, 1H), 7.22 (d. *J*=8.2 Hz, 2H), 7.13 (d, *J*=8.2 Hz, 2H), 4.44 (s, 2H), 4.29 (d, *J*=9.4 Hz, 1H), 3.91 (dd, *J*=11.9 and 1.6 Hz, 1H), 3.71 (dd, *J*=11.9 and 5.1 Hz, 1H), 3.48 (m, 3H), 3.37 (m, 1H), 2.83 (m, 1H), 1.19 (d, *J*=6.8 Hz, 6H).

(1*S*)-1,5-anhydro-1-[3-(4-biphenylylmethyl)-1,2-benzisothiazol-5-yl]-D-glucitol (16e). This compound was prepared from **15e** following the procedure in preparation of **16d** in 60% yield. Purity (LCMS): >95%. HRMS calcd for $C_{26}H_{26}NO_5S$ (M+H) 464.1532, found 464.1532. ^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (s, 1H), 7.91 (d, *J*=8.5 Hz, 1H), 7.63 (dd, *J*=8.5 and 1.0 Hz,

1H), 7.46 (m, 4H), 7.32 (m, 4H), 7.23 (m, 1H), 4.44 (s, 2H), 4.28 (d, *J*=9.4 Hz, 1H), 3.87 (dd, *J*=11.9 and 2.0 Hz, 1H), 3.72 (dd, *J*=12.0 and 5.4 Hz, 1H), 3.49 (m, 3H), 3.36 (m, 1H).

(1*S*)-1,5-anhydro-1-{3-[(4-chlorophenyl)methyl]-1,2-benzisothiazol-5-yl}-D-glucitol (16f). This compound was prepared from **15f** following the procedure in preparation of **16d** in 42% yield**.** Purity (LCMS): >95%**.** HRMS calcd for $C_{20}H_{21}NO_5SCl$ (M+H) 422.0829, found 422.0826. ^{1}H NMR (400 MHz, CD_3OD) δ 8.06 (s, 1H), 7.92 (d, *J*=8.5 Hz, 1H), 7.64 (d, *J*=8.5 Hz, 1H), 7.24 (d. *J*=8.6 Hz, 2H), 7.20 (d, *J*=8.6 Hz, 2H), 4.39 (s, 2H), 4.27 (d, *J*=9.5 Hz, 1H), 3.88 (dd, *J*=12.0 and 1.9 Hz, 1H), 3.73 (dd, *J*=12.0 and 5.2 Hz, 1H), 3.47 (m, 3H), 3.34 (m, 1H).

(1*S*)-1,5-anhydro-1-{3-[(3-methylphenyl)methyl]-1,2-benzisothiazol-5-yl}-D-glucitol (16g). This compound was prepared from **15g** following the procedure in preparation of **16d** in 19% yield**.** Purity (LCMS): >95%**.** HRMS calcd for $C_{21}H_{24}NO_5S$ (M+H) 402.1375, found 401.1376. ^{1}H NMR (400 MHz, CD_3OD) δ 8.08 (s, 1H), 7.95 (d, *J*=8.4 Hz, 1H), 7.64 (d, *J*=8.4 Hz, 1H), 7.08 (m, 3H), 6.97 (d, *J*=7.4 Hz, 1H), 4.41 (s, 2H), 4.27 (d, *J*=9.5 Hz, 1H), 3.89 (dd, *J*=11.9 and 1.8 Hz, 1H), 3.72 (dd, *J*=11.9 and 5.1 Hz, 1H), 3.44 (m, 3H), 3.29 (m, 1H), 2.24 (s, 3H).

(1*S*)-1,5-anhydro-1-{3-[(3,4-dimethylphenyl)methyl]-1,2-benzisothiazol-5-yl}-D-glucitol (16h). This compound was prepared from **15h** following the procedure in preparation of **16d** in 36% yield. Purity (LCMS): >95%. HRMS calcd for $C_{22}H_{26}NO_5S$ (M+H) 416.1532, found 416.1535. ^{1}H NMR (400 MHz, CD_3OD) δ 8.05 (s, 1H), 7.89 (d, *J*=8.4 Hz, 1H), 7.61 (d, *J*=8.4 Hz, 1H), 7.01 (s, 1H), 6.95 (s, 2H), 4.33 (s, 2H), 4.25 (d, *J*=9.4 Hz, 1H), 3.88 (dd, *J*=12.0 and 1.8

Hz, 1H), 3.72 (dd, *J*=11.9 and 5.2 Hz, 1H), 3.48 (m, 3H), 3.33 (m, 1H), 2.13 (s, 3H), 2.12 (s, 3H).

(1*S*)-1,5-anhydro-1-(3-{[4-(methyloxy)phenyl]methyl}-1,2-benzisothiazol-5-yl)-D-glucitol (16i). This compound was prepared from **15i** following the procedure in preparation of **16d** in 10% yield**.** Purity (LCMS): >95%**.** HRMS calcd for $C_{21}H_{24}NO_6S$ (M+H) 418.1324, found 418.1320. ^{1}H NMR (400 MHz, CD_3OD) δ 8.05 (s, 1H), 7.93 (d, *J*=8.4 Hz, 1H), 7.63 (d, *J*=8.4 Hz, 1H), 7.18 (d. *J*=8.6 Hz, 2H), 6.78 (d, *J*=8.6 Hz, 2H), 4.37 (s, 2H), 4.26 (d, *J*=9.4 Hz, 1H), 3.87 (dd, *J*=11.8 and 1.6 Hz, 1H), 3.71 (m, 1H), 3.69 (s, 3H), 3.45 (m, 3H), 3.32 (m, 1H).

(1*S*)-1,5-anhydro-1-(3-{[4-(ethyloxy)phenyl]methyl}-1,2-benzisothiazol-5-yl)-D-glucitol (16j). This compound was prepared from **15j** following the procedure in preparation of **16d** in 26% yield. Purity (LCMS): >95%**.** HRMS calcd for $C_{22}H_{26}NO_6S$ (M+H) 432.1481, found 432.1482. ^{1}H NMR (400 MHz, CD_3OD) δ 8.06 (s, 1H), 7.95 (d, *J*=8.4 Hz, 1H), 7.64 (d, *J*=8.4 Hz, 1H), 7.17 (d. *J*=8.6 Hz, 2H), 6.77 (d, *J*=8.6 Hz, 2H), 4.38 (s, 2H), 4.26 (d, *J*=9.5 Hz, 1H), 3.95 (q, *J*=7.0 Hz, 2H), 3.88 (d, *J*=11.3 Hz, 1H), 3.71 (dd, *J*=11.9 and 5.1 Hz, 1H), 3.44 (m, 3H), 3.33 (m, 1H), 1.31 (t, *J*=7.0 Hz, 3H).

(1*S*)-1,5-anhydro-1-{3-[(4-methylphenyl)methyl]-6-indolizinyl}-D-glucitol (16k). This compound was prepared from **15k** following the procedure in preparation of **16d** in 13% yield**.** Purity (LCMS): >95%**.** HRMS calcd for $C_{22}H_{26}NO_5$ (M+H) 384.1811, found 384.1814. ^{1}H NMR (400 MHz, CD_3OD) δ 7.78 (s, 1H), 7.31 (d, *J*=9.3 Hz, 1H), 7.02 (m, 4H), 6.72 (d. *J*=9.3 Hz, 1H),

6.47 (d, *J*=3.8 Hz, 1H), 6.32 (d, *J*=3.8 Hz, 1H), 4.17 (d, *J*=16.4 Hz, 1H), 4.12 (d, *J*=16.4 Hz, 1H), 3.96 (d, *J*=8.8 Hz, 1H), 3.84 (d, *J*=10.5 Hz, 1H), 3.65 (m, 1H), 3.38 (m, 4H), 2.25 (s, 3H).

(1*S*)-1,5-anhydro-1-(3-{[4-(methyloxy)phenyl]methyl}-6-indolizinyl)-D-glucitol (16l). This compound was prepared from **15l** following the procedure in preparation of **16d** in 12% yield**.** Purity (LCMS): >95%**.** HRMS calcd for $C_{22}H_{26}NO_6$ (M+H) 400.1760, found 400.1757. ^{1}H NMR (400 MHz, CD_3OD) δ 7.78 (s, 1H), 7.31 (d, *J*=9.4 Hz, 1H), 7.05 (d, *J*=8.4 Hz, 2H), 6.78 (d. *J*=8.4 Hz, 2H), 6.72 (d, *J*=9.4 Hz, 1H), 6.46 (d, *J*=3.8 Hz, 1H), 6.31 (d, *J*=3.8 Hz, 1H), 4.15 (d, *J*=16.4 Hz, 1H), 4.10 (d, *J*=16.4 Hz, 1H), 3.96 (d, *J*=9.0 Hz, 1H), 3.84 (d, *J*=11.0 Hz, 1H), 3.70 (s, 3H), 3.66 (m, 1H), 3.37 (m, 4H).

(1*S*)-1,5-anhydro-1-{3-[(4-fluorophenyl)methyl]-6-indolizinyl}-D-glucitol (16m). This compound was prepared from **15m** following the procedure in preparation of **16d** in 14% yield**.** Purity (LCMS): >95%**.** HRMS calcd for $C_{21}H_{23}NO_5F$ (M+H) 388.1560, found 388.1559. ^{1}H NMR (400 MHz, CD_3OD) δ 7.79 (s, 1H), 7.32 (d, *J*=9.4 Hz, 1H), 7.13 (m, 2H), 6.93 (t, J=8. 8Hz, 2H), 6.72 (d. *J*=9.4 Hz, 1H), 6.47 (d, *J*=3.8 Hz, 1H), 6.32 (d, *J*=3.8 Hz, 1H), 4.19 (d, *J*=17.0 Hz, 1H), 4.15 (d, *J*=17.0 Hz, 1H). 3.97 (d, *J*=9.2 Hz, 1H), 3.83 (d, *J*=12.0 Hz, 1H), 3.65 (m, 1H), 3.38 (m, 4H).

(1*S*)-1,5-anhydro-1-{3-[(4-chlorophenyl)methyl]-6-indolizinyl}-D-glucitol (16n). This compound was prepared from **15n** following the procedure in preparation of **16d** in 11% yield. Purity (LCMS): >95%**.** HRMS calcd for $C_{21}H_{23}NO_5Cl$ (M+H) 404.1265, found 404.1262. ^{1}H NMR (400 MHz, CD_3OD) δ 7.79 (s, 1H), 7.33 (d, *J*=9.4 Hz, 1H), 7.23 (d, *J*=8.3 Hz, 2H), 7.12

(d, *J*=8.3 Hz, 2H), 6.75 (d. *J*=9.4 Hz, 1H), 6.51 (s, 1H), 4.22 (d, *J*=16.9 Hz, 1H), 4.17 (d, *J*=16.9 Hz, 1H), 3.99 (d, *J*=9.2 Hz, 1H), 3.84 (d, *J*=12.0 Hz, 1H), 3.66 (m, 1H), 3.39 (m, 4H).

(1*S*)-1,5-anhydro-1-(3-{[4-(trifluoromethyl)phenyl]methyl}-6-indolizinyl)-D-glucitol (16o). This compound was prepared from **15o** following the procedure in preparation of **16d** in 5% yield**.** Purity (LCMS): >95%**.** HRMS calcd for $C_{22}H_{23}NO_5F_3$ (M+H) 438.1528, found 438.1530. ^{1}H NMR (400 MHz, CD_3OD) δ 7.82 (s, 1H), 7.55 (d, *J*=8.3 Hz, 2H), 7.35 (d, *J*=8.8 Hz, 3H), 6.77 (d. *J*=8.3 Hz, 1H), 6.55 (d, *J*=3.8 Hz, 1H), 6.36 (d, *J*=3.8 Hz, 1H), 4.36 (d, *J*=17.9 Hz, 1H), 4.32 (d, *J*=17.9 Hz, 1H), 3.99 (d, *J*=9.2 Hz, 1H), 3.85 (d, *J*=10.9 Hz, 1H), 3.66 (m, 1H), 3.38 (m, 4H)

1,5-anhydro-1-(3-{[4-(methyloxy)phenyl]methyl}imidazo[1,2-*a*]pyridin-6-yl)-D-glucitol (16p). 15p (535 mg, 0.768 mmol) and 1 M TBAF in THF (2.456 ml, 2.456 mmol) were combined and stirred for 1.5 h at RT. No starting material remained. The reaction was diluted with water (20 mL) and washed with dichloromethane twice. The aqueous layer was concentrated to 1/2 volume to remove any excess THF, then eluted down a 5 g plug of C18 silica gel (which had been conditioned with acetonitrile and water). After washing with water to remove salts the product was eluted with 50:50 MeOH/CH_3CN. The filtrate was concentrated to give about 450 mg of crude material as a mixture of solids and yellow oil. The material was redissolved in MeOH and purified by reverse-phase column chromatography with 0-90% acetonitrile in water to give 10mg of **16p** in 3% yield. Purity (LCMS): 93%. HRMS calcd for $C_{21}H_{25}N_2O_6$ (M+H) 401.1713, found: 401.1713. ^{1}H NMR (400 MHz, CD_3OD) δ 8.61 (s, 1H), 8.07 (d, *J*=9.3 Hz, 1H), 7.85 (d, *J*=9.3 Hz, 1H), 7.64 (s, 1H), 7.25 (d, *J*=8.5 Hz, 2H), 6.89 (d, *J*=8.6 Hz, 2H), 4.29-4.36 (m, 2H), 3.88 (d, *J*=11.4 Hz, 1H), 3.75 (br, 3H), 3.41-3.53 (m, 3H), 3.27 (br, 3H), 3.19-3.32 (m, 3H).

(6-bromoimidazo[1,2-a]pyridin-3-yl)[4-(methyloxy)phenyl]methanol (21)

bromo[4-(methyloxy)phenyl]magnesium (8.89 mL, 4.44 mmol) was cooled to -30 °C and a solution of 6-bromoimidazo[1,2-a]pyridine-3-carbaldehyde **20** (1.0 g, 4.44 mmol) in THF (9 mL) was added. After 15 min at -30 °C the reaction was complete. The reaction was removed from the bath and quenched with water and brine. The product was extracted with ethyl acetate, dried over sodium sulfate, filtered, concentrated and dried under high vacuum to give 1.32 g of **21** as a solid in 89% yield. LCMS (*m/z*): 332 (M+H, isotope for Br) and 334 (M+H, isotope for Br). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (s, 2H), 7.57 (d, *J*=9.6 Hz, 1H), 7.33-7.41 (m, 3H), 7.13 (s, 1H), 6.95 (d, *J*=8.7 Hz, 2H), 6.14 (s, 2H), 3.76 (s, 3H).