Supporting Information

Cytotoxic Sugar Analogues of an Optimized Novobiocin Scaffold

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3-(((benzyloxy)carbonyl)amino)-8-methyl-2-oxo-2H-chromen-7-yl acetate (2): A solution of coumarin 1 (182 mg, 0.56 mmol) in pyridine (4.2 mL) at rt was treated with acetic anhydride (1.4 mL). After 12 h, the solvent was concentrated and the residue purified via column chromatography (SiO₂, 40:1 CH₂Cl₂:Acetone) to afford 2 as a colorless amorphous solid (203 mg, 99%): ¹H NMR (CDCl₃, 400 MHz) δ 8.32 (s, 1H), 7.61 (s, 1H), 7.43-7.34 (m, 6H), 7.03 (d, J = 8.8 Hz, 1H), 5.26 (s, 2H), 2.39 (s, 3H), 2.30 (s, 3H); ¹³C NMR (CDCl₃, 500 MHz) δ 168.9, 158.3, 153.1, 149.8 (2C), 148.5, 135.4, 128.7, 128.6, 128.3 (2C), 125.1, 123.4, 121.1, 119.2, 119.0, 117.6, 67.6, 20.8, 9.0; HRMS (ESI⁺) m/z: [M + Na]⁺ calcd for C₂₀H₁₇NNaO₆, 390.0954; found, 390.0957.

3-(3',6-dimethoxy-[1,1'-biphenyl]-3-ylcarboxamido)-8-methyl-2-oxo-2H-chromen-7-yl acetate (3): Palladium on carbon (10%, 160 mg) was added to 2 (1.6 g, 4.36 mmol) in anhydrous THF (50 mL) and the solution was placed under an atmosphere of H₂. After
12 h, the solution was filtered through SiO₂ (40:1 CH₂Cl₂:Acetone) and the eluent was concentrated to afford a yellow solid, which was used without further purification (1.01 g, 99%).

A solution of 3’,6-dimethoxy-[1,1’-biphenyl]-3-carbonyl chloride² (1.2 g, 4.36 mmol), in anhydrous THF (25 mL), was added to a solution of the amine (1.01 g, 4.31 mmol) and anhydrous triethylamine (6.0 mL, 8.72 mmol) in anhydrous THF (25 mL). After 12 h, the solvent was concentrated and the residue purified via column chromatography (SiO₂, 40:1 CH₂Cl₂:Acetone) to afford 3 as a colorless amorphous solid (1.68 g, 81%): ¹H NMR (CDCl₃, 500 MHz) δ 8.84 (s, 1H), 8.76 (s, 1H), 7.93 (dd, J = 8.5, 2.5 Hz, 1H), 7.90 (d, J = 2.5 Hz, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.37 (t, J = 8.0 Hz, 1H), 7.14-7.12 (m, 1H), 7.10-7.09 (m, 2H), 7.07-7.03 (m, 1H), 6.95-6.93 (m, 1H) 3.91 (s, 3H), 3.86 (s, 3H), 2.37 (s, 3H), 2.31 (s, 3H); ¹³C NMR (CDCl₃, 500 MHz) δ 168.9, 165.6, 159.9, 159.3, 159.0, 150.0, 148.7, 138.5, 131.1, 130.0, 129.2, 128.3, 125.8, 125.5, 123.6, 123.2, 122.0, 119.3, 119.0, 117.8, 115.2, 113.2, 111.0, 55.9, 55.3, 20.8, 9.1; HRMS (ESI⁺) m/z: [M + Na]⁺ calcd for C₂₇H₂₃NNaO₇, 496.1372; found, 496.1338.

N-(7-hydroxy-8-methyl-2-oxo-2H-chromen-3-yl)-3’,6-dimethoxy-[1,1’-biphenyl]-3-carboxamide (4): A solution of 3 (1.68 g, 3.55 mmol) in methanol (36 mL) at rt was treated with triethylamine (3.6 mL, 10%). After 12 h, the solvent was concentrated and the residue purified via column chromatography (SiO₂, 10:1 CH₂Cl₂:Acetone) to afford 4 as a yellow amorphous solid (1.45 g, 93%): ¹H NMR (CDCl₃, 500 MHz) δ 8.80 (s, 1H), 8.69 (s, 1H), 7.92 (dd, J = 8.5, 2.0 Hz, 1H), 7.89 (d, J = 2.5 Hz, 1H), 7.37 (t, J = 8.5 Hz, 1H), 7.28 (s, 1H), 7.12 (d, J = 8.5 Hz, 1H), 7.10-7.07 (m, 2H), 6.93 (dd, J = 8.5, 2.0 Hz,
1H), 6.82 (d, J = 8.5 Hz, 1H), 5.31 (s, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 2.36 (s, 3H); 13C NMR (CDCl3, 500 MHz) δ 165.6, 159.8, 159.5, 159.3, 155.5, 149.5, 138.6, 131.0, 130.0, 129.2, 128.2, 126.0, 125.9, 124.6, 122.0, 121.5, 115.2, 113.4, 113.2, 113.0, 111.7, 111.0, 55.9, 55.3, 7.9; HRMS (ESI+) m/z: [M + H]+ calcd for C25H22NO6, 432.1447; found, 432.1443. [M + Na]+ calcd for C25H21NNaO6, 454.1267; found, 454.1232.

3-(3',6-dimethoxy-[1,1'-biphenyl]-3-ylcarboxamido)-8-methyl-2-oxo-2H-chromen-7-yl methylcarbamate (5): A solution of 4 (30 mg, 0.070 mmol) in a 1:1 mixture of anhydrous CH2Cl2 (1.6 mL) and anhydrous pyridine (1.6 mL) at rt was treated with methylcarbamic chloride (9.8 mg, 0.10 mmol). After 12 h, the solvent was concentrated and the residue purified via column chromatography (SiO2, 40:1 CH2Cl2:Acetone) to afford 5 as a yellow amorphous solid (33 mg, 99%): 1H NMR (CDCl3, 500 MHz) δ 8.80 (s, 1H), 8.69 (s, 1H), 7.92 (dd, J = 2.5, 8.8 Hz, 1H), 7.89 (d, J = 2.5 Hz, 1H), 7.37 (t, J = 8.0 Hz, 1H), 7.27 (d, J = 8.5 Hz, 1H), 7.12 (dd, J = 1.0, 7.5 Hz, 1H) 7.10-7.07 (m, 2H), 6.94 (td, J = 0.5, 2.5 Hz, 1H), 6.82 (d, J = 8.5 Hz, 1H), 5.32 (brs, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.37 (s, 3H), 2.36 (s, 3H); 13C NMR (CDCl3, 500 MHz) δ 165.6, 159.8, 159.5, 159.3, 155.5, 149.5, 138.6, 131.0, 130.0, 129.2, 128.2, 126.0, 125.9, 124.5, 122.0, 121.5, 115.2, 113.4, 113.2, 113.0, 111.7 (2C), 111.0, 55.9, 55.3, 29.7, 7.9; HRMS (ESI+) m/z: [M + H]+ calcd for C27H25N2O7, 489.1662; found, 489.1674.

3-(3',6-dimethoxy-[1,1'-biphenyl]-3-ylcarboxamido)-8-methyl-2-oxo-2H-chromen-7-yl methanesulfonate (6): Methanesulfonyl chloride (22 µL, 0.28 mmol) was added to
4 (30 mg, 0.070 mmol) in anhydrous pyridine (0.4 mL) at 0°C. The resulting solution was warmed to rt and stirred overnight, then diluted with H2O. The desired product was extracted with EtOAc (3 × 10 mL); combined organic fractions were dried (Na2SO4), filtered, and concentrated. The residue was purified via column chromatography (SiO2, 40:1 CH2Cl2:Acetone) to afford 6 as a yellow amorphous solid (35 mg, 99%): 1H NMR (CDCl3, 500 MHz) δ 8.85 (s, 1H), 8.78 (s, 1H), 7.93 (dd, J = 8.5, 2.5 Hz, 1H), 7.89 (d, J = 2.5 Hz, 1H), 7.44 (d, J = 8.5 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.31 (d, J = 8.5 Hz, 1H), 7.13 (dd, J = 1.5, 1.0 Hz, 1H), 7.12-7.08 (m, 2H), 6.95 (dd, J = 2.5, 0.5 Hz, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 3.27 (s, 3H), 2.49 (s, 3H); 13C NMR (CDCl3, 500 MHz) δ 165.7, 160.0, 159.3, 158.7, 148.7, 147.7, 138.5, 131.1, 130.0, 129.2, 128.3, 125.8, 125.6, 124.2, 122.5, 122.0, 120.4, 119.3, 118.9, 115.3, 113.1, 111.0, 55.9, 55.3, 38.5, 9.7; HRMS (ESI+) m/z: [M + Na]+ calcd for C26H23NNaO8S, 532.1042; found, 532.1031.

3-(3',6-dimethoxy-[1,1'-biphenyl]-3-ylcarboxamido)-8-methyl-2-oxo-2H-chromen-7-yl 4-methylbenzenesulfonate (7): 4-methylbenzene-1-sulfonyl chloride (53 mg, 0.28 mmol) was added to 4 (30 mg, 0.070 mmol) in anhydrous pyridine (0.4 mL) at 0°C. The resulting solution was warmed to rt and stirred overnight, then diluted with H2O. The desired product was extracted with EtOAc (3 × 10 mL); combined organic fractions were dried (Na2SO4), filtered, and concentrated. The residue was purified via column chromatography (SiO2, 40:1 CH2Cl2:Acetone) to afford 7 as a colorless amorphous solid (40 mg, 99%): 1H NMR (CDCl3, 500 MHz) δ 8.81 (s, 1H), 8.75 (s, 1H), 7.92 (dd, J = 9.0, 2.5 Hz, 1H), 7.88 (d, J = 2.0 Hz, 1H), 7.75 (dd, J = 6.5, 1.5 Hz, 2H), 7.39-7.33 (m, 4H), 7.13-7.11 (m, 1H), 7.09-7.05 (m, 3H), 6.95-6.93 (m, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 2.48
tert-Butyl 5-(3-(3’,6-dimethoxybiphenyl-3-ylcarboxamido)-8-methyl-2-oxo-2H-chromen-7-yloxy)-5,6-dihydropyridine-1(2H)-carboxylate (9):

Diisopropylazodicarboxylate (DIAD, 1.31 g, 6.48 mmol) was added to a solution of allylic alcohol 8 (0.65 g, 3.24 mmol), phenol 4 (1.40 g, 3.24 mmol) and triphenylphosphine (1.70 g, 6.48 mmol) in anhydrous THF (30 mL). After 2 h, the solvent was concentrated and the residue purified via column chromatography (SiO₂, 100:1 CH₂Cl₂:Acetone) to afford compound 9 as a colorless amorphous solid (1.57 g, 79%). ¹H NMR (400 MHz, CDCl₃) δ 8.81 (s, 1H), 8.72 (s, 1H), 7.94-7.90 (m, 2H), 7.39-7.34 (m, 2H), 7.14-7.07 (m, 3H), 6.95-6.92 (m, 2H), 6.02-5.97 (m, 2H), 4.86 (m, 1H), 4.20-3.99 (m, 2H), 3.91 (s, 3H), 3.87 (s, 3H), 3.77-3.42 (m, 2H), 2.32 (s, 3H), 1.49 (brs, 3H), 1.41 (brs, 6H); ¹³C NMR (500 MHz, CDCl₃) δ 165.6, 159.9, 159.6, 159.5, 157.1, 154.7, 149.5, 138.7, 131.1, 130.1, 129.3, 128.9, 128.3, 126.2, 125.7, 125.4, 124.5, 124.3, 122.1, 121.9, 115.4, 113.9, 113.3, 111.1, 110.2, 80.3, 70.2, 56.0, 55.5, 45.0, 43.9, 28.5 (3C), 8.5; HRMS (ESI⁺) m/z: calcd for [M + H⁺] C₃₅H₇₇N₂O₈, 613.2550; found: 613.2533.

tert-butyl 3-(3-(3’,6-dimethoxybiphenyl-3-ylcarboxamido)-8-methyl-2-oxo
2H-chromen-7-yloxy)piperidine-1-carboxylate (10): Palladium on carbon (10%, 5 mg) was added to 9 (40 mg, 0.06 mmol) in anhydrous THF (5 mL) and the solution was placed under an atmosphere of H₂. After 12 h, the solution was filtered through SiO₂ and the eluent was concentrated to afford 10 as a colorless amorphous solid (36 mg, 90%). ¹H NMR (400 MHz, CDCl₃) δ 8.82 (s, 1H), 8.73 (s, 1H), 7.95-7.91 (m, 2H) 7.41-7.35 (m, 2H), 7.16-7.08 (m, 3H), 6.97-6.94 (m, 2H), 4.42 (m, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.74-3.40 (m, 4H), 2.33 (s, 3H), 2.07-1.92 (m, 3H), 1.62-1.58 (m, 1H), 1.48 (brs, 3H), 1.28 (brs, 6H); ¹³C NMR (500 MHz, CDCl₃) 165.5, 159.8, 159.5, 159.3, 156.8, 154.7, 149.4, 138.6, 131.0, 130.0, 129.2, 128.2, 126.1, 125.6, 124.3, 122.0, 121.7, 115.2, 115.0, 113.5, 113.2, 111.0, 109.9, 79.8, 77.3, 55.9, 55.3, 47.3, 43.8, 29.9, 28.3 (3C), 21.8, 8.3; HRMS (ESI⁺) m/z: calcd for [M + Na⁺] C₃₅H₃₈N₂NaO₈, 637.2526; found 637.2524.

3',6-dimethoxy-N-(8-methyl-2-oxo-7-(piperidin-3-yloxy)-2H-chromen-3-yl)-[1,1'-biphenyl]-3-carboxamide (11): Trifluoroacetic acid (0.2 mL) was added to a solution of 10 (35 mg, 0.057 mmol) in dichloromethane (2 mL). After 12 h, the solvent was concentrated and the residue purified via column chromatography (SiO₂, 10:1 CH₂Cl₂:MeOH) to afford compound 11 as a colorless amorphous solid (23 mg, 79%). ¹H NMR (500 MHz, CDCl₃) δ 8.74 (s, 1H), 8.68 (s, 1H), 7.91-7.88 (m, 2H), 7.38-7.32 (m, 2H), 7.13-6.92 (m, 5H), 4.87 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.58-3.56 (m, 1H), 3.31 (m, 1H), 3.17-3.15 (m, 2H), 2.36 (s, 3H), 2.16-2.14 (m, 2H), 2.01-1.99 (m, 1H), 1.91-1.85 (m, 1H); ¹³C NMR (500 MHz, CDCl₃) δ 165.7, 160.0, 159.5, 159.4, 155.7, 149.5, 138.8, 131.2, 130.2, 129.4, 128.4, 126.2, 125.9, 123.9, 122.4, 122.2, 115.8, 115.4, 114.5,
113.3, 111.2, 110.4, 69.3, 56.1, 55.5, 46.9, 43.9, 28.2, 19.6, 8.8; HRMS (ESI+) m/z: calced for [M + H+] C_{30}H_{31}N_{2}O_{6}, 515.2182; found 515.2182.

3',6-Dimethoxy-N-(8-methyl-2-oxo-7-(1,2,3,6-tetrahydropyridin-3-yloxy)-2H-chromen-3-yl)biphenyl-3-carboxamide (12): Trifluoroacetic acid (2.0 mL) was added to a solution 9 (0.47 g, 0.78 mmol) in dichloromethane (20 mL). After 12 h, the solvent was concentrated and the residue purified via column chromatography (SiO\textsubscript{2}, 10:1 CH\textsubscript{2}Cl\textsubscript{2}:MeOH) to afford compound 12 as a colorless amorphous solid (0.35 g, 88%).

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 8.77 (s, 1H), 8.72 (s, 1H), 7.92-7.90 (m, 2H), 7.38-7.29 (m, 2H), 7.14-7.04 (m, 3H), 6.94-6.88 (m, 2H), 6.10-5.99 (m, 2H), 4.70 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.46-3.31 (m, 2H), 2.32 (m, 2H), 2.32 (s, 3H); \textsuperscript{13}C NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 165.4, 159.7, 159.4, 159.3, 157.2, 149.4, 138.6, 133.4, 130.9, 130.0, 129.2, 128.2, 126.1, 125.6, 124.4, 124.2, 122.0, 121.7, 115.3, 115.1, 113.6, 113.1, 111.0, 110.5, 69.4, 55.9, 55.3, 47.7, 44.8, 8.5; HRMS (ESI+) m/z: calced for [M + H+] C_{30}H_{29}N_{2}O_{6}, 513.2026; found 513.2024.

N-(7-((1-acetyl-1,2,3,6-tetrahydropyridin-3-yl)oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (13): A solution of 12 (45 mg, 0.088 mmol) in pyridine (3.0 mL) at rt was treated with acetic anhydride (1.0 mL). After 2 h, the solvent was concentrated and the residue purified via column chromatography (SiO\textsubscript{2}, 4:1 CH\textsubscript{2}Cl\textsubscript{2}:Acetone) to afford 13 as a colorless amorphous solid (43 mg, 88%).

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 8.81 (s, 1H), 8.72 (s, 1H), 7.90-7.89 (m, 2H), 7.38-7.34 (m, 2H), 7.13-7.06 (m, 3H), 6.98-6.90 (m, 2H), 6.10-5.94 (m, 2H), 4.90-4.87 (m, 1H), 4.50-
N-(7-(1-acetylpiperidin-3-yloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (14): Palladium on carbon (10%, 5 mg) was added to 13 (36 mg, 0.07 mmol) in anhydrous THF (3 mL) and the solution was placed under an atmosphere of H₂. After 12 h, the solution was filtered through SiO₂ and the eluent was concentrated to afford 14 as a colorless amorphous solid (32 mg, 89%). 

1H NMR (400 MHz, CDCl₃) δ 8.80 (s, 1H), 8.72 (s, 1H), 7.94-7.90 (m, 2H), 7.40-7.34 (m, 2H), 7.15-7.07 (m, 3H), 6.99-6.86 (m, 2H), 4.60-4.30 (m, 1H), 4.25-3.95 (m, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.76-3.39 (m, 3H), 2.32-2.30 (3H), 2.19-2.04 (3H), 1.98-1.82 (m, 3H), 1.70-1.50 (m, 1H); 

13C NMR (500 MHz, CDCl₃) δ 169.5, 169.4, 165.5 (2C), 159.8, 159.7, 159.5, 159.4, 159.3, 156.7, 156.1, 149.5, 149.4, 138.6 (2C), 131.0, 130.0, 129.2, 128.2, 126.1, 126.0, 125.7, 124.3, 124.0, 122.0, 121.7, 115.4, 115.3, 115.2, 113.8, 113.7, 113.2, 113.1, 111.0, 110.5, 109.8, 72.0, 71.4, 55.9, 55.3, 50.3, 46.6, 45.5, 42.0, 30.0, 28.8, 23.3, 21.5, 21.4, 21.2, 8.3; HRMS (ESI⁺) m/z: calced for [M + H⁺] C₃₂H₃₅N₂O₇, 557.2288; found 557.2291.
tert-butyl 4-((3-(3',6-dimethoxy-[1,1'-biphenyl]-3-ylcarboxamido)-8-methyl-2-oxo-2H-chromen-7-yl)oxy)piperidine-1-carboxylate (16): Diisopropylazodicarboxylate (202 mg, 1.0 mmol) was added to a solution of allylic alcohol 15 (100 mg, 0.50 mmol), phenol 4 (217 mg, 0.50 mmol) and triphenylphosphine (262 mg, 1.0 mmol) in anhydrous THF (30 mL). After 2 h, the solvent was concentrated and the residue purified via column chromatography (SiO2, 100:1 CH2Cl2:Acetone) to afford compound 16 as a colorless amorphous solid (220 mg, 72%). 1H NMR (400 MHz, CDCl3) δ 8.77 (s, 1H), 8.70 (s, 1H), 7.91-7.89 (m, 2H), 7.38-7.28 (m, 2H), 7.14-7.04 (m, 3H), 6.94-6.86 (m, 2H), 4.60 (m, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.67-3.63 (m, 2H), 3.47-3.46 (m, 2H), 2.33 (s, 3H), 1.93-1.81 (m, 4H), 1.49 (s, 9H); 13C NMR (500 MHz, CDCl3) δ 165.5, 159.8, 159.5, 159.4, 156.7, 154.9, 149.5, 138.7, 131.0, 130.0, 129.2, 128.2, 126.1, 125.7, 124.2, 122.1, 121.8, 115.3 (2C), 113.6, 113.2, 111.1, 110.5, 79.8, 77.6, 72.8, 56.0, 55.4, 30.6, 28.5 (3C), 22.0, 21.8, 8.4; HRMS (ESI+) m/z: calcd for [M + Na+] C35H38N2NaO8, 637.2526; found 637.2523.

3',6-dimethoxy-N-(8-methyl-2-oxo-7-(piperidin-4-yloxy)-2H-chromen-3-yl)-[1,1'-biphenyl]-3-carboxamide (17). Trifluoroacetic acid (0.2 mL) was added to a solution 16 (72 mg, 0.12 mmol) in dichloromethane (2 mL). After 12 h, the solvent was concentrated and the residue purified via column chromatography (SiO2, 10:1 CH2Cl2:MeOH) to afford compound 17 as a colorless amorphous solid (41 mg, 68%). 1H NMR (400 MHz, CDCl3) δ 8.81 (s, 1H), 8.73 (s, 1H), 7.95-7.91 (m, 2H), 7.41-7.35 (m, 2H), 7.15-7.08 (m, 3H), 6.96-6.88 (m, 2H), 4.66 (m, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.28-3.26 (m, 2H), 3.05-3.04 (m, 2H), 2.38 (s, 3H), 2.19-2.16 (m, 2H), 1.99-1.93 (m, 2H); 13C NMR (500 MHz,
CDCl₃ δ 165.7, 160.0, 159.6, 159.5, 156.4, 149.6, 138.8, 131.2, 130.2, 129.4, 128.4, 126.2, 125.8, 124.3, 122.2, 122.0, 115.5, 115.4, 113.9, 113.3, 111.2, 110.5, 77.4, 56.1, 55.5, 42.0 (2C), 29.8 (2C), 8.6; HRMS (ESI⁺) m/z: calcd for [M + H⁺] C₃₀H₃₁N₂O₆, 515.2182; found 515.2189.

3',6-dimethoxy-N-(8-methyl-7-((1-methylpiperidin-4-yl)oxy)-2-oxo-2H-chromen-3-yl)-[1,1'-biphenyl]-3-carboxamide (18): Potassium carbonate (28 mg, 0.20 mmol) was added to 17 (21 mg, 0.04 mmol) in THF (3 mL) at 0°C. After 10 min, iodomethane (3.05 µL, 0.05 mmol) was added and the solution was warmed to rt. After 4h, the reaction was quenched with saturated ammonium chloride solution and extracted with dichloromethane (3 × 10 mL); combined organic fractions were dried (MgSO₄), filtered, and concentrated. The residue was purified by column chromatography (SiO₂, 10:1 CH₂Cl₂:MeOH) to afford 18 as a colorless amorphous solid (13 mg, 59%). ¹H NMR (400 MHz, CDCl₃) δ 8.70 (s, 1H), 8.61 (s, 1H), 7.86-7.80 (m, 2H), 7.31-7.27 (m, 2H), 7.05-7.02 (m, 3H), 6.87-6.83 (m, 2H), 4.48 (m, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 2.74-2.70 (m, 2H), 2.51 (m, 2H), 2.34 (s, 3H), 2.26 (s, 3H), 2.13-2.07 (m, 2H), 1.91-1.86 (m, 2H); ¹³C NMR (500 MHz, CD₂Cl₂) δ 165.1, 159.7, 159.4, 159.3, 157.0, 149.4, 138.9, 130.8 (2C), 129.8, 128.1, 126.1, 125.5, 123.9, 121.9, 121.7, 115.3, 115.0, 113.2, 112.8, 111.0, 110.5, 73.1, 55.8, 55.3, 52.5, 46.0 (2C), 30.9 (2C), 8.1; HRMS (ESI⁺) m/z: calcd for [M + H⁺] C₃₁H₃₃N₂O₆, 529.2339; found 529.2334.

(R)-2-((3-(3',6-dimethoxy-[1,1'-biphenyl]-3-ylcarboxamido)-8-methyl-2-oxo-2H-chromen-7-yl)oxy)tetrahydro-2H-pyran-3-yl benzoate (20):
Diisopropylazodicarboxylate (90 µl, 0.46 mmol) was added to a solution of a mixture of sugars 19 (62 mg, 0.28 mmol), phenol 4 (100 mg, 0.23 mmol) and triphenylphosphine (122 mg, 0.46 mmol) in anhydrous THF (2 mL). After 2 h, the reaction was quenched with H₂O and extracted with EtOAc (3 x 10 mL); combined organic fractions were dried (Na₂SO₄), filtered, and concentrated. The residue was purified by column chromatography (SiO₂, 100:1 CHCl₃:MeOH) to afford a mixture of diastereomers 20 as a colorless amorphous solid (101 mg, 68%).

N-(7-((2S,3R)-3-hydroxytetrahydro-2H-pyran-2-yl-oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (21): Sodium metal (18 mg, 0.79 mmol) was added to a solution of diastereomers 20 (100 mg, 0.16 mmol) in MeOH (3 mL) at 0 °C. After 5 min, the reaction was quenched with H₂O and extracted with EtOAc (3 x 10 mL); combined organic fractions were dried (Na₂SO₄), filtered, and concentrated. The residue was purified by column chromatography (SiO₂, 100:1 CH₂Cl₂:MeOH) to afford 21 as a colorless amorphous solid (71 mg, 86%). ¹H NMR (500 MHz, CDCl₃) δ: 8.81 (s, 1H), 8.71 (s, 1H), 7.92 (dd, J = 2.4, 8.6 Hz, 1H), 7.89 (d, J = 2.4 Hz, 1H), 7.36 (t, J = 7.9 Hz, 1H), 7.35 (d, J = 8.6 Hz, 1H), 7.14 (d, J = 8.7 Hz, 1H), 7.12 (m, 1H), 7.09 (m, 1H), 7.07 (d, J = 8.5 Hz, 1H), 6.93 (ddd, J = 0.8, 2.5, 8.5 Hz, 1H), 5.55 (t, J = 3.4 Hz, 1H), 4.15 (m, 2H), 3.90 (s, 3H), 3.86 (s, 3H), 3.64 (dt, J = 4.4, 12.1 Hz, 1H), 2.86 (d, J = 6.4 Hz, 1H), 2.37 (s, 3H), 2.23 (dt, J = 3.6, 14.1 Hz, 1H), 2.10 (m, 1H), 1.99 (m, 1H), 1.77 (m, 1H); ¹³C NMR (500 MHz, CDCl₃) δ: 165.7, 159.9, 159.5, 159.4, 156.2, 149.1, 138.7, 131.2, 130.1, 129.3, 128.3, 126.1, 125.9, 124.1, 122.3, 122.1, 115.4,
114.9, 114.7, 113.3, 112.0, 111.1, 97.6, 64.1, 57.3, 56.0, 55.5, 37.2, 32.7, 8.7; HRMS (FAB) m/z: [M + Na]^+ calcd for C_{30}H_{29}NNaO_{8}, 554.1791; found 554.1838.

(R)-3',6-dimethoxy-N-(8-methyl-2-oxo-7-((4-((triisopropylsilyl)oxy)tetrahydro-2H-pyran-2-yl)oxy)-2H-chromen-3-yl)-[1,1'-biphenyl]-3-carboxamide (23):

Diisopropylazodicarboxylate (180 µl, 0.92 mmol) was added to a solution of a mixture of sugars 22<sup>3</sup> (153 mg, 0.56 mmol), phenol 4 (200 mg, 0.46 mmol) and triphenylphosphine (244 mg, 0.92 mmol) in anhydrous THF (4 mL). After 2 h, the reaction was quenched with H₂O and extracted with EtOAc (3 x 10 mL). The combined organic fractions were washed with saturated aqueous NaCl, dried (Na₂SO₄), filtered, and concentrated. The residue was purified by column chromatography (SiO₂, 100:1 CHCl₃:MeOH) to afford a mixture of diastereomers 23 as a colorless amorphous solid (245 mg, 77%).

N-(7-(((2S,4R)-4-hydroxytetrahydro-2H-pyran-2-yl)oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (24):

Tetrabutylammonium flouride (0.25 mL, 0.250 mmol) was added dropwise to a solution of diastereomers 23 (98 mg, 0.143 mmol) in THF (4 mL) at rt. After 1h, the reaction was quenched with H₂O and extracted with EtOAc (3 x 10 mL); combined organic fractions were dried (Na₂SO₄), filtered, and concentrated. The residue was purified by column chromatography (SiO₂, 100:1 CH₂Cl₂:MeOH) to afford 24 as a colorless amorphous solid (63 mg, 82%). <sup>1</sup>H NMR (500 MHz, CDCl₃) δ: 8.81 (s, 1H), 8.71 (brs, 1H), 7.92 (dd, J = 2.4, 8.6 Hz, 1H), 7.89 (d, J = 2.3 Hz, 1H), 7.37 (t, J = 7.9 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.08-7.14 (m, 3H), 7.07 (d, J = 8.8 Hz, 1H), 6.93 (ddd, J = 0.7, 2.6, 8.3 Hz, 1H),
5.16 (d, \( J = 4.6 \) Hz, 1H), 3.92 (m, 2H), 3.90 (s, 3H), 3.86 (s, 3H), 3.62 (m, 1H), 2.38 (s, 3H), 2.23 (m, 2H), 1.90 (m, 1H), 1.74 (m, 1H), 1.63 (m, 1H); \(^{13}\)C NMR (500 MHz, CDCl\(_3\)) \( \delta \): 165.7, 159.9, 159.5, 159.4, 156.1, 149.2, 138.7, 131.2, 130.1, 129.3, 128.3, 125.9, 124.2, 122.3, 122.1, 115.4, 115.2, 114.7, 113.3, 112.1, 111.1, 100.4, 67.8, 63.4, 56.0, 55.5, 27.5, 22.1, 21.9, 8.6; HRMS (FAB) \( m/\text{z} \): [M + Na]\(^+ \) calcd for C\(_{30}\)H\(_{29}\)N\(_2\)O\(_8\), 554.1791; found 554.1838.

N-(7-((1R,2R,3R)-2,3-dihydroxycyclohexyloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (27): Diisopropylazodicarboxylate (146 mg, 0.72 mmol) was added to a solution of allylic alcohol 26 (35.7 mg, 0.36 mmol), phenol 4 (157 mg, 0.36 mmol) and triphenylphosphine (189 mg, 0.72 mmol) in anhydrous THF (5 mL). After 2 h, the solvent was concentrated and the residue purified via column chromatography (SiO\(_2\), 100:1 CH\(_2\)Cl\(_2\):Acetone) to afford compound 27 as a colorless amorphous solid (103 mg, 56%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.81 (s, 1H), 8.72 (s, 1H), 7.95-7.92 (m, 2H), 7.40-7.28 (m, 2H), 7.16-7.07 (m, 3H), 6.97-6.93 (m, 2H), 6.03-5.90 (m, 2H), 4.88 (brs, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 2.34 (s, 3H), 2.09-1.89 (m, 5H), 1.76-1.70 (m, 1H); \(^{13}\)C NMR (500 MHz, CDCl\(_3\)) \( \delta \) 165.6, 159.9, 159.7, 159.5, 157.8, 149.6, 138.8, 132.8, 131.1, 130.1, 129.3, 128.3, 126.3, 126.0, 125.7, 124.6, 122.2, 121.6, 115.4, 115.3, 113.4, 113.3, 111.1, 110.8, 72.1, 56.0, 55.5, 28.7, 25.3, 19.1, 8.6; HRMS (ESI\(^+\)) \( m/\text{z} \): calcd for [M + H]\(^+ \) C\(_{31}\)H\(_{30}\)NO\(_6\), 512.2073; found 512.2077.

N-(7-((1R,2R,3R)-2,3-dihydroxycyclohexyloxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3',6-dimethoxybiphenyl-3-carboxamide (28): A solution of 27 (45 mg, 0.09 mmol) in
acetone (3 mL) was treated with N-Methylmorpholine-N-oxide (25.0 mg, 2.4 mmol), followed by an aqueous solution of OsO₄ (4%, 56 μL). After 12 h, the solvent was concentrated and the residue purified via column chromatography (SiO₂, 20:1 CH₂Cl₂:Acetone) to afford compound 28 as a colorless amorphous solid (41 mg, 85%).

1H NMR (400 MHz, CDCl₃) δ 8.78 (s, 1H), 8.72 (s, 1H), 7.95-7.91 (m, 2H), 7.41-7.32 (m, 2H), 7.16-7.08 (m, 3H), 6.98-6.94 (m, 2H), 4.65-4.55 (m, 1H), 4.23-4.22 (m, 1H), 3.92 (s, 3H), 3.86 (s, 3H), 3.85 (brs, 1H), 2.34 (s, 3H), 2.11-1.45 (m, 6H); 13C NMR (500 MHz, CDCl₃) δ 165.7, 160.0, 159.7, 159.6 (2C), 157.4, 149.5, 138.8, 131.3, 130.2, 129.4, 128.4, 126.3, 125.8, 124.4, 122.2, 122.0, 115.5, 114.0, 113.4, 111.2 (2C), 78.5, 74.5, 69.7, 56.1, 55.5, 29.9, 28.6, 18.4, 8.6; HRMS (ESI⁺) m/z: caled for [M + H⁺] C₃₁H₃₂NO₈, 546.2128; found 546.2127.

**Anti-Proliferation Assays.** Cells were maintained in a 1:1 mixture of Advanced DMEM/F12 (Gibco) supplemented with non-essential amino acids, L-glutamine (2 mM), streptomycin (500 μg/mL), penicillin (100 units/mL), and 10% FBS. Cells were grown to confluence in a humidified atmosphere (37° C, 5% CO₂), seeded (2000/well, 100 μL) in 96-well plates, and allowed to attach overnight. Compound or GDA at varying concentrations in DMSO (1% DMSO final concentration) was added, and cells were returned to the incubator for 72 h. At 72 h, the number of viable cells was determined using an MTS/PMS cell proliferation kit (Promega) per the manufacturer’s instructions. Cells incubated in 1% DMSO were used at 100% proliferation, and values were adjusted accordingly. IC₅₀ values were calculated from separate experiments performed in triplicate using GraphPad Prism.
Western Blot Analyses. MCF-7 cells were cultured as described above and treated with various concentrations of drug, GDA in DMSO (1% DMSO final concentration), or vehicle (DMSO) for 24 h. Cells were harvested in cold PBS and lysed in RIPA lysis buffer containing 1 mM PMSF, 2 mM sodium orthovanadate, and protease inhibitors on ice for 1 h. Lysates were clarified at 14000g for 10 min at 4°C. Protein concentrations were determined using the Pierce BCA protein assay kit per the manufacturer’s instructions. Equal amounts of protein (20 μg) were electrophoresed under reducing conditions, transferred to a nitrocellulose membrane, and immunoblotted with the corresponding specific antibodies. Membranes were incubated with an appropriate horseradish peroxidase-labeled secondary antibody, developed with a chemiluminescent substrate, and visualized.

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