Supplemental Methods

Synthetic Procedures and Compound Characterization

Reagents and solvents were obtained from commercial sources and were used without further purification unless otherwise stated. All reactions were performed in flame-dried glassware under an argon atmosphere unless otherwise stated and monitored by TLC using solvent mixtures appropriate to each reaction. All column chromatography was performed on silica gel (40-63µm). Nuclear magnetic resonance spectra were recorded on a Bruker 400 MHz instrument. Chemical shifts are reported as δ values in ppm referenced to $CDCl_3$ (^{1}H NMR = 7.26 and ^{13}C NMR = 77.16) or CD_3OD (^{1}H NMR = 3.31 and ^{13}C NMR = 49.00). Multiplicity is indicated as follows: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublet of doublets); ddd (doublet of doublet of doublets); td (triplet of doublets); m (multiplet); br (broad). All carbon peaks are rounded to one decimal place.

ethyl 3-((3-chloro-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[*c,f*][1,2]thiazepin-11-yl)amino)propanoate (1a). To a mixture of 3,11-dichloro-6-methyl-6,11-dihydrodibenzo[*c,f*][1,2]thiazepine 5,5-dioxide (328 mg, 1.00 mmol) and β-alanine ethyl ester hydrochloride (184 mg, 1.20 mmol) was added nitromethane (2.0 mL) followed by triethylamine (335 µL, 243 mg, 2.40 mmol). The resulting mixture was warmed to 60 °C, stirred for 1 h, and then concentrated to give a sticky, colorless solid. This material was purified directly by column chromatography (20:1 CH_2Cl_2:Et_2O, 3 column volumes → 7:3 CH_2Cl_2:Et_2O, 3 column volumes) to provide the pure ester **1a** as an extremely viscous, colorless oil (393 mg,

96%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.96 – 7.94 (m, 1H), 7.49 – 7.43 (m, 2H), 7.41 – 7.33 (m, 3H), 7.32 – 7.26 (m, 1H), 5.05 (s, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.39 (s, 3H), 2.82 – 2.69 (m, 2H), 2.60 – 2.40 (m, 3H), 1.24 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.7, 140.6, 138.8, 138.6, 136.9, 134.5, 132.4, 131.1, 129.9, 129.5, 128.5, 128.3, 128.1, 65.9, 60.7, 43.6, 38.6, 34.9, 14.3.

ethyl 5-((3-chloro-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[*c,f*][1,2]thiazepin-11-yl)amino)pentanoate (1b). To a mixture of 3,11-dichloro-6-methyl-6,11-dihydrodibenzo[*c,f*][1,2]thiazepine 5,5-dioxide (328 mg, 1.00 mmol) and ethyl 5-aminovalerate hydrochloride (218 mg, 1.20 mmol) was added nitromethane (2.0 mL) followed by triethylamine (335 µL, 243 mg, 2.40 mmol). The resulting mixture was warmed to 60 °C, stirred for 1 h, and then concentrated to give a sticky, colorless solid. To this material was added water (20 mL) and the mixture was extracted with Et_2O (2 x 20 mL). The combined organics were washed with water (10 mL) and 10% NH_4OH (10 mL), dried over Na_2SO_4, and concentrated to give a viscous, pale-yellow oil. This material was purified by column chromatography (40:1 CH_2Cl_2:Et_2O, 4 column volumes → 20:1 CH_2Cl_2:Et_2O, 2 column volumes → 7:3 CH_2Cl_2:Et_2O, 2 column volumes) to provide the pure ester **1b** as an extremely viscous, nearly colorless oil (256 mg, 59%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.96 (d, *J* = 2.1 Hz, 1H), 7.48 – 7.33 (m, 5H), 7.32 – 7.27 (m, 1H), 5.00 (s, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.36 (s, 3H), 2.48 (t, *J* = 7.0 Hz, 2H), 2.27 (t, *J* = 7.3 Hz, 2H), 2.08 (br s, 1H), 1.70 – 1.58 (m, 2H), 1.58 – 1.44 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 173.6, 140.5, 138.7, 137.0, 134.4, 132.3, 131.3, 130.3, 129.5, 128.6, 128.2, 128.1, 66.3, 60.4, 47.8, 38.8, 34.2, 29.6, 22.8, 14.4.

3-((3-chloro-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[*c,f*][1,2]thiazepin-11-yl)amino)propanoic acid hydrochloride (2a = MC3). To ester **1a** (364 mg, 0.890 mmol) was added 0.5 M aqueous HCl (20 mL), and the mixture was stirred vigorously for 4.5 h at 80 °C. The solution was then concentrated *in vacuo* with heating to provide a foamy, colorless glass. In order to remove residual HCl (causes esterification during NMR in CD_3OD), this residue was re-dissolved in a small quantity of water and concentrated again *in vacuo* with heating. This procedure was repeated once more to provide the pure hydrochloride salt **2a**, free from residual HCl, as a foamy, colorless glass (364 mg, 98%, white solid when crushed). **^{1}H NMR (400 MHz, CD_3OD)** δ 8.09 (d, *J* = 2.2 Hz, 1H), 7.94 (d, *J* = 8.3 Hz, 1H), 7.87 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.77 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.68 – 7.63 (m, 1H), 7.60 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.49 (td, *J* = 7.6, 1.4 Hz, 1H), 6.02 (s, 1H), 3.33 – 3.26 (m, 1H), 3.28 (s, 3H), 3.17 – 3.06 (m, 1H), 2.83 – 2.68 (m, 2H); **^{13}C NMR (101 MHz, CD_3OD)** δ 174.2, 142.3, 142.1, 139.0, 137.1, 135.1, 134.7, 133.6, 129.5, 129.3, 128.3, 127.8, 127.4, 68.1, 44.3, 39.4, 30.7.

5-((3-chloro-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[*c,f*][1,2]thiazepin-11-yl)amino)pentanoic acid hydrochloride (2b = MC5). To ester **1b** (243 mg, 0.556 mmol) was added 0.5 M aqueous HCl (13 mL), and the mixture was stirred vigorously for 3 h at 80 °C. The solution was then concentrated *in vacuo* with heating to provide a foamy, nearly colorless glass. In order to remove residual HCl (causes esterification during NMR in CD_3OD), this residue was re-dissolved in a small quantity of water and concentrated again *in vacuo* with heating. This procedure was repeated once more to provide the pure hydrochloride salt **2b**, free from residual HCl, as a foamy, nearly colorless glass (243 mg, 98%, off-white solid when crushed). **^{1}H**

NMR (400 MHz, CD_3OD) δ 8.09 (d, *J* = 2.1 Hz, 1H), 7.92 (d, *J* = 8.2 Hz, 1H), 7.87 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.74 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.68 – 7.62 (m, 1H), 7.58 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.49 (td, *J* = 7.6, 1.4 Hz, 1H), 5.98 (s, 1H), 3.24 (s, 3H), 3.00 (ddd, *J* = 12.3, 9.6, 5.9 Hz, 1H), 2.86 (ddd, *J* = 12.3, 9.6, 6.3 Hz, 1H), 2.31 (t, *J* = 7.0 Hz, 2H), 1.82 – 1.64 (m, 2H), 1.64 – 1.54 (m, 2H); **^{13}C NMR (101 MHz, CD_3OD)** δ 176.7, 142.5, 141.9, 138.8, 137.1, 135.2, 134.8, 133.5, 129.4, 129.2, 128.5, 127.9, 127.1, 67.6, 48.1, 39.7, 33.8, 26.4, 22.7.